REACHING FOR THE HIGH-HANGING FRUITS IN OLEFIN METATHESIS

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Abstract

■Chapter 1: *E*- and *Z*-, Di- and Trisubstituted Alkenyl Nitriles through Catalytic Cross Metathesis

We have described the development of several catalytic cross-metathesis strategies, which can deliver a considerable range of *Z*- or *E*-disubstituted alkenyl nitriles and their corresponding trisubstituted variants. Through careful examination of the steric and electronic attributes of the starting materials, a Mo-based monoaryloxide pyrrolide or chloride complex may be the optimal choice depending on the reaction type. In the event, equimolar amounts of the two substrates are necessary to maximize reaction efficiency; a pyridine ligand is more desirable than a phosphine ligand, as a stabilizing ligand for a Mo-based complex, for improving reaction stereoselectivity. We also highlighted the utility of this approach with the synthesis of several biologically active compounds, such as LR5182 (Cocaine abuse treatment), alliarinoside (anti-feedant), perhydrohistrionicotoxin (natural product), CC-5079 (anti-cancer) and indatraline (anti-depressant).

■Chapter 2: Traceless Protection for More Broadly Applicable Olefin Metathesis

We have devised an operationally simple *in-situ* protection/deprotection strategy that significantly expands the scope of kinetically controlled catalytic olefin metathesis. Pretreatment of an olefin containing a protic group with commercially available HB(pin) or $HB(trip)_2$ is sufficient for generating the desired product efficiently through the catalytic cross-metathesis reaction. A wide range of stereochemically defined *Z*- and *E*-alkenyl halides and boronates as well as *Z*-trifluoromethyl-substituted alkenes with a hydroxy or carboxylic acid group were prepared. We also discovered that a small amount of HB(pin) may be used for the removal of residual water and impurities, significantly enhancing the efficiency of a multigram-scale olefin metathesis transformation.

■Chapter 3: *E*- and *Z*-Macrocyclic Trisubstituted Alkenes for Natural Product Synthesis and Skeletal Editing

We have introduced a reliable catalytic strategy for the synthesis of a variety of macrocyclic trisubstituted olefins in either stereoisomeric form. This was achieved by overcoming the unexpected difficulties through careful mechanistic studies, including addressing complications arising from pre-metathesis alkene isomerization. Macrocyclic ring-closing metathesis can be performed with a commercially available Mo-based complex and an easily accessible linear diene precursor. Accordingly, we can synthesize a skeletally diverse array of otherwise difficult-to-access macrocyclic alkenes, a critical set of compounds in drug discovery, in either isomeric form. The utility of the method is highlighted in two instances. The first is the near complete reversal of substrate-controlled selectivity in the generation of the macrolactam intermediate, in the total

synthesis of the anti-fungal agent Fluvirucin B_1. The second is an exceptionally stereoselective late-stage formation of a 24-membered macrocyclic *E*-trisubstituted alkene, enabling the completion of the total synthesis of a cytotoxic natural product dolabelide C, which is seven times more efficient than that reported previously.

■Chapter 4: Stereodefined Alkenes with a Fluoro-Chloro Terminus as a Uniquely Enabling Compound Class

We have offered a practical solution for the synthesis of trisubstituted alkenyl fluorides by unveiling a widely applicable strategy for stereodivergent synthesis of olefins bearing a fluoro and chloro terminus. The core transformation is unprecedented: cross-metathesis between two trisubstituted olefins, one of which is a commercially available but scarcely utilized trihalo alkene. Alkenes bearing a fluoro,chloro-terminus are versatile substrates for the generation of otherwise difficult-to-access trisubstituted alkenyl fluorides, through stereospecific catalytic cross-coupling reactions. We also highlighted the utility of the method throguh synthesis of, among others, a fluoro-nematic liquid crystal component, peptide analogs bearing an *E*- or a *Z*-amide bond mimic, and all four stereoisomers of difluoro-rumenic ester (anti-cancer).

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Acknowledgments

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Chapter One

E- and Z-, Di- and Trisubstituted Alkenyl Nitriles through Catalytic Cross-Metathesis

1.1. Introduction

Nitrile-containing compounds are valuable in many branches of scientific research, including chemistry, medicine [1] and materials science. [2] Alkenyl nitrile units are particularly attractive, as these robust and highly polarized alkenes[3] may be the origin of biological activity, or provide a site for irreversible and covalent inhibition.[4] Moreover, alkenyl nitriles may be readily modified at the nitrile moiety and/or the olefin site, through methods including catalytic enantioselective hydrogenation [5] and conjugate addition.[6] *Z*- and *E*-Disubstituted variants can be further functionalized to medicinally relevant compounds through stereoselective transformations, such as the norepinephrine-dopamine inhibitor LR5182[7] (Scheme 1.1.1). A nitrile unit can be the key component in many biologically active molecules, including the anti-HIV reverse transcriptase inhibitors rilpivirine [8] and fosdevirine [9] (Scheme 1.1.1). Stereodefined trisubstituted

(1) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902–7917.
(2) Sugura, J. L.; Martin, N.; Hanack, M. *Eur. J. Org. Chem.* **1999**, 643–651.
(3) Allgäuer, D. S.; Jangra, H.; Asahara, H.; Li, Z.; Chen, Q.; Zipse. H., Ofial, A. R.; Mayr, H. *J. Am. Chem. Soc.* **2017**, *139*, 13318–13329.
(4) Serafimova, I. M.; Pufall, M. A.; Krishnan, S.; Duda, K.; Cohen, M. S.; Maglathlin, R. L.; McFarland, J. M.; Miller, R. M.; Frödin M.; Taunton, J. *Nat. Chem. Biol.* **2012**, *8*, 471–476.
(5) (a) Lee, D.; Kim, D.; Yun, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 2785–2787. (b) Yan, Q.; Kong, D.; Li, M.; Hou, G.; Zi, G. *J. Am. Chem. Soc.* **2015**, *137*, 10177–10181. (c) Müller, M.-A.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 8668–8671.
(6) Lee, J.-E.; Yun, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 145–147.
(7) Deutsch, H. M.; Collard, D. M.; Zhang, L.; Burnham, K. S.; Deshpande, A. K.; Holtzman, S. G.; Schweri, M. M. *J. Med. Chem.* **1999**, *42*, 882–895.
(8) Janssen, P. A. J.; Lewi, P. J.; Arnold, E.; Daeyaert, F.; de Jonge, M.; Heeres, J.; Koymans, L.; Vinkers, M.; Guillemont, J.; Pasquier, E.; Kukla, M.; Ludovici, D.; Andries, K.; de Béthune, M.-P.; Pauwels, R.;

alkenyl nitriles are found within the anticancer agents CC-5079[10], where the *Z*-isomer is a more potent drug candidate than the *E*-isomer, phorboxazoles and their analogues[11], where the alkenyl oxazole moiety may also be generated by the cyclization of a cyano-bearing olefin[12], and calyculin A[13] (Scheme. 1.1.1). Di- and trisubstituted alkenyl nitriles were also often used in the synthesis of bioactive compounds, such as the synthesis of indatraline[14] and perhydro-histrionicotoxin.[15] In our group, we have developed strategies to furnish N–H amines[16] through a sequential addition of two different nucleophiles to an alkenyl nitrile at the CN bond, without the need for oxidation-state adjustments or protection/deprotection schemes.

Despite the significant value of stereodefined di- and trisubstituted alkenyl nitriles, their stereoselective synthesis is not trivial. Because the cyano group is small, development of a highly stereoselective reaction that generates alkenyl nitriles is especially challenging. The energy difference between the isomers of cyano-propene has

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Das, K.; Clark, A. D.; Frenkel, Y. V.; Hughes, S. H.; Medaer, B.; De Knaep, F.; Bohets, H.; De Clerck, F.; Lampo, A.; Williams, P.; Stoffels, P. *J. Med. Chem.* **2005**, *48*, 1901-1909.

(9) Castellino, S.; Groseclose, M. R.; Sigafoos, J.; Wagner, D.; de Serres, M.; Polli, J. W.; Romach, E.; Myer, J.; Hamilton, B. *Chem. Res. Toxicol.* **2013**, *26*, 241−251.

(10) (a) Zhang, L.-H.; Wu, L.; Raymon, H. K.; Chen, R. S.; Corral, L.; Shirley, M. A.; Narla, R. K.; Gamez, J.; Muller, G. W.; Stirling, D. I.; Bartlett, J. B.; Schafer, P. H.; Payvandi, F. *Cancer Res.* **2006**, *66*, 951–959. (b) Ruchelman, A. L.; Man, H. W.; Chen, R.; Liu, W.; Lu, L.; Cedzik, D.; Zhang, L.; Leisten, J.; Collette, A.; Narla, R. K.; Raymon, H. K.; Muller, G. W. *Bioorg. Med. Chem.* **2011**, *19*, 6356–637.

(11) (a) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1998**, *118*, 9422–9423. (b) Dalisay, D. S.; Molinski, T. F. *Org. Lett.* **2009**, *11*, 1967–1970.

(12) (a) Doyle, M. P.; Buhro, W. E.; Davidson, J. G.; Elliott, R. C.; Hoekstra, J. W.; Oppenhuizen, M. *J. Org. Chem.* **1980**, *45*, 18, 3657–3664. (b) Vedejs, E.; Piotrowski, D. W.; Tucci, F. C. *J. Org. Chem.* **2000**, *65*, 5498–5505.

(13) Suganuma, M.; Fujiki, H.; Furuya-Suguri, H.; Yoshizawa, S.; Yasumoto, S.; Kato, Y.; Fusetani, N.; Sugimura, T. *Cancer Res.* **1990**, *50*, 3521–3525.

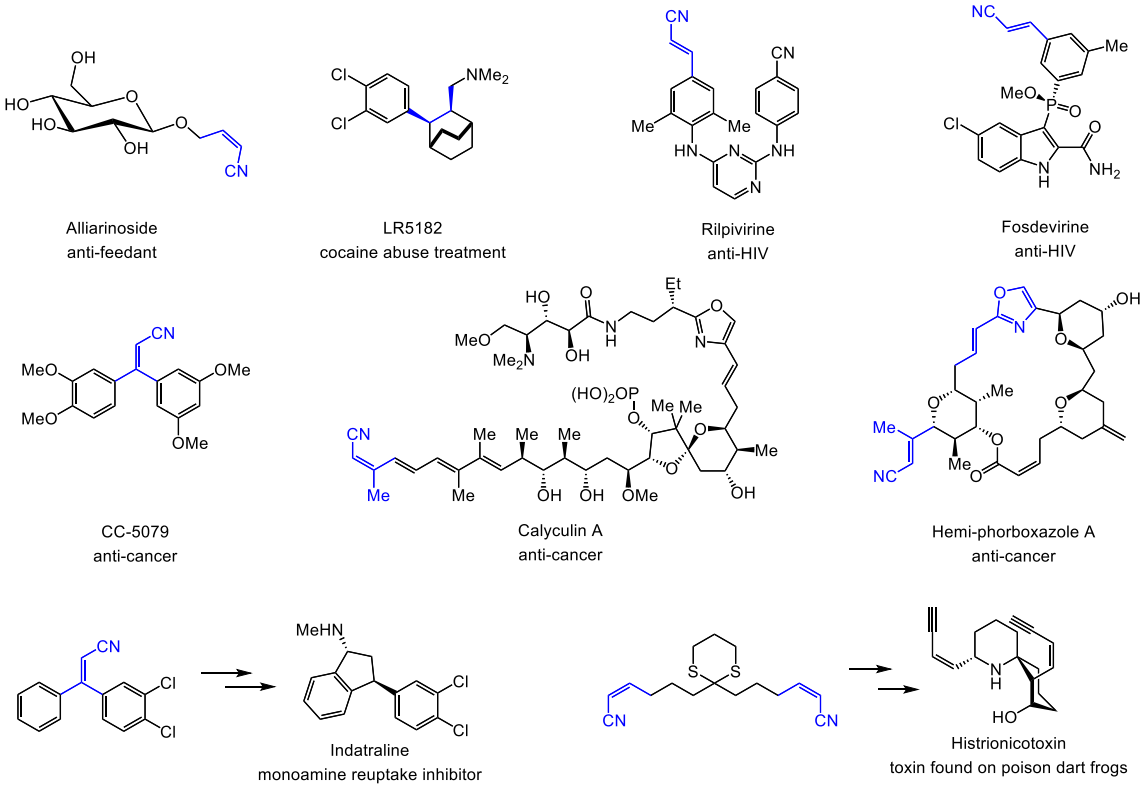
(14) Yan, Q.; Kong, D.; Li, M.; Hou, G.; Zi, G. *J. Am. Chem. Soc.* **2015**, *137*, 10177–10181.

(15) Stockman, R. A.; Sinclair, A.; Arini, L. G.; Szeto, P.; Hughes, D. L. *J. Org. Chem.* **2004**, *69*, 1598–1602.

(16) (a) Jang, H.; Romiti, F.; Torker, S.; Hoveyda, A. H. *Nat. Chem.* **2017**, *9*, 1269–1275. (b) Zhang, S.; del Pozo, J.; Romiti, F.; Mu, Y.; Torker, S.; Hoveyda, A. H. *Science* **2019**, *364*, 45–51.

been calculated by Wiberg *et al.*[17] to be just 0.26 ± 0.04 kcal/mol in favor of the *Z* isomer (61:39 *Z*:*E*).

Scheme 1.1.1. Natural Products and Drug Candidates Containing Alkenyl Nitriles



Alkenyl nitriles have been target molecules for many organic chemists and most of the synthesis of disubstituted alkenyl nitriles has been attempted with palladium-[18] nickel-[19], iron-[20], gallium-[21], copper-[22] or rhodium-based[23] complexes. Major shortcomings still remain to be addressed: (1) toxic[18,19] or costly reagents[20c] or catalysts

(17) Wiberg, K. B.; Wang, Y.; Petersson, G. A.; Bailey, W. F. *J. Chem. Theory Comput.* **2009**, *5*, 1033–1037.
(18) (a) Zhang, Z.; Liebeskind, L. S.; *Org. Lett.* **2006**, *8*, 4331–4333. (b) Powell, K. J.; Han, L.-C.; Sharma, P.; Moses, J. E. *Org. Lett.* **2014**, *16*, 2158–2161.
(19) (a) Nakao, Y.; Yada, A.; Ebata, S.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 2428–2429. (b) Zhang, X.; Xie, X.; Liu, Y. *J. Am. Chem. Soc.* **2018**, *140*, 7385–7389.
(20) Qin, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 15893–15895.
(21) Murai, M.; Hatano, R.; Kitabata, S.; Ohe, K. *Chem. Commun.* **2011**, *47*, 2375–2377.
(22) (a) Wang, Z.; Chang, S. *Org. Lett.* **2013**, *15*, 1990–1993. (b) Pradal, A.; Evano, G. A. *Chem. Commun.* **2014**, *50*, 11907–11910. (c) Gao, D.-W.; Vinogradova, E. B.; Nimmagadda, S. K.; Medina, J. M.; Xiao, Y.; Suciu, R. M.; Cravatt, D. F.; Engle, K. M. *J. Am. Chem. Soc.* **2018**, *140*, 8069–8073.
(23) Ye, F.; Chen, J.; Ritter, T. *J. Am. Chem. Soc.* **2017**, *139*, 7184–7187.

bearing a precious metal[16,21] are often required; (2) some reactions produce hydrogen cyanide as a toxic byproduct[16b,20b,21]; (3) many methods are in limited substrate scope, and methods that furnish alkyl-substituted alkenyl nitriles are uncommon[16b,17,20b,21]; (4) effective control of stereochemistry can be problematic and most strategies can only deliver substrate-controlled product; (5) Wittig-[24] and Peterson-type[25] reactions have been used to obtain *Z*-alkenyl nitriles, but stereoselectivities can be moderate[22a,23a], and stoichiometric amounts of a strong base (*n*-BuLi or NaHMDS) and cryogenic conditions (–78 °C)[22a,23b] are often required. Only two methods for disubstituted alkenyl nitrile synthesis offer access to a cyano-substituted *Z*-olefin selectively[16b,22b], but these approaches require a stereochemically defined *Z*-alkenyl bromide or iodide, the stereoselective synthesis of which is non-trivial.

Stereoselective preparation of trisubstituted alkenyl nitriles are more challenging and therefore less reported. The majority of the nitrile-containing products are confined to aryl- or polyaryl-substituted products[16b,18,26] or demand harsh conditions (≥ 120 °C).[27] In some instances, high loadings of precious transition-metal complexes[28] or excess amounts of a strong Lewis acid additive BCl_3[24c] are needed. In rare cases where aliphatic trisubstituted alkenyl nitriles can be synthesized, slight structural variations in the

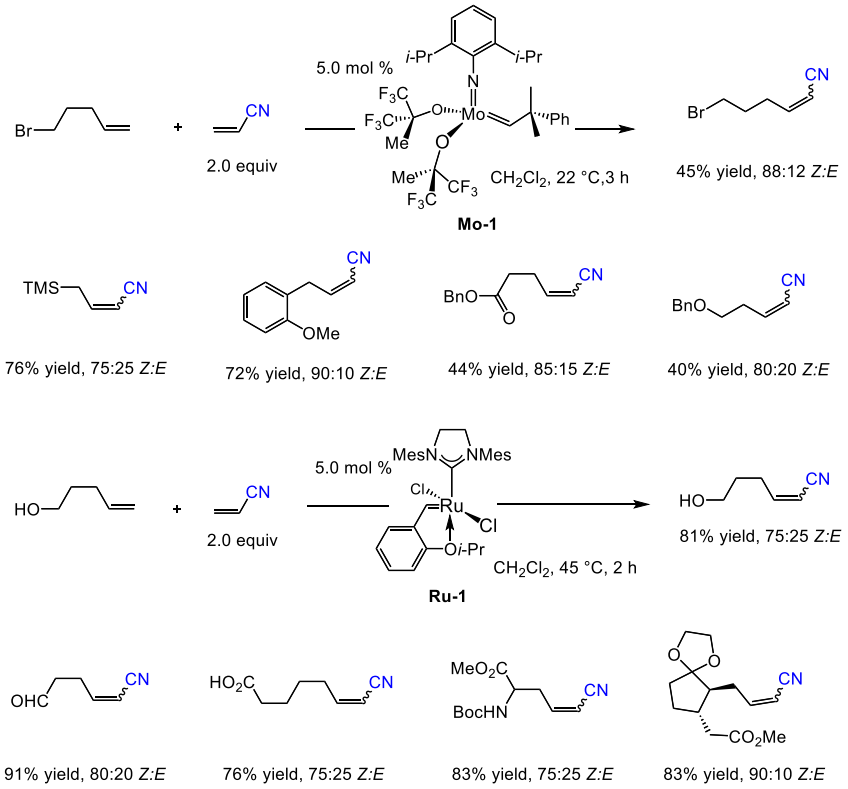
(24) (a) Zhang, T. Y.; O'Toole, J. C.; Dunigan, J. M. *Tetrahedron Lett.* **1998**, *39*, 1461–1464. (b) Fang, F.; Li, Y.; Tian, S. K. *Eur. J. Org. Chem.* **2011**, 1084–1091.
(25) (a) Palomo, C.; Aizpurua, J. M.; Garcia, J. M.; Ganboa, I.; Cossio, F. P.; Lecea, B.; Lopez, C. *J. Org. Chem.* **1990**, *55*, 2498–2503. (b) Kojima, S., Fukuzaki, T., Yamakawa, A. & Murai, Y. *Org. Lett.* **2004**, *6*, 3917–3920.
(26) (a) Chakraborty, S.; Das, U. K.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2017**, *139*, 11710–11713. (b) Yamamoto, Y.; Asatani, T.; Kirai, N. *Adv. Synth. Catal.* **2009**, *351*, 1243–1249. (c) Barrado, A. G.; Zielinski, A.; Goddard, R.; Alcarazo, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 13401–13405. (d) Wang, X.; Studer, A. *Angew. Chem. Int. Ed.* **2018**, *57*, 11792–11796.
(27) Han, Y.-P.; Song, X.-R.; Qiu, Y.-F.; Hao, X.-H.; Wang, J.; Wu, X.-X.; Liu, X.-Y.; Liang, Y. M. *J. Org. Chem.* **2015**, *80*, 9200–9207.
(28) (a) Su, W.; Gong, T.-J.; Xiao, B.; Fu, Y. *Chem. Commun.* **2015**, *51*, 11848–11851. (b) Suginome, M.; Yamamoto, A.; Murakami, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 2380–2382.

substrates can result in low stereoselectivity[20c] or the required starting materials are difficult-to-access stereo-defined trisubstituted alkenyl iodides.[20b]

As a widely used transformation for C-C double bond formation, catalytic cross-metathesis represents an attractive strategy for the preparation of stereodefined alkenyl nitriles. However, few examples have been reported to afford such products through cross-metathesis. The first example was disclosed more than two decades ago by Crowe and Goldberg, where they showed that a Mo bis-alkoxide complex **Mo-1** can be used to synthesize *Z*-disubstituted alkenyl nitriles.[29] Later studies with Ru-based complexes **Ru-1** led to protocols that afford either similar[30] or lower stereoselectivities.[31] Regardless of the catalyst types, *Z*:*E* ratios were mostly substrate-controlled and did not exceed 90:10. The substrate scope is also very limited as only reactions of unhindered *n*-alkyl-substituted olefins were reasonably efficient. Only three trisubstituted alkenyl nitrile compounds have been prepared with similar conditions through cross-metathesis[32], while the approaches are still limited to aliphatic substrates and only minimal stereoselectivity was observed (66:34 *Z*:*E*).

(29) Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162–5163.
(30) (a) Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430–432. (b) Miao, X.; Dixneuf, P. H.; Fischmeister, C.; Bruneau, C. *Green Chem.* **2011**, *13*, 2258–2271.
(31) Gawin, R.; Tracz, A.; Chwalba, M.; Kozakiewicz, A.; Trzaskowski, B.; Skowerski, K. *ACS Catal.* **2017**, *7*, 5443–5449.
(32) (a) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318–9325. (b) Bieniek, M.; Bujok, R.; Cabaj, M.; Lugan, N.; Lavigne, G.; Arlt, D.; Grela, K. *J. Am. Chem. Soc.* **2006**, *128*, 13652–13653. (c) Bai, C.-X.; Lu, X.-B.; He, R.; Zhang, W.-Z.; Feng, X.-J. *Org. Biomol. Chem.* **2005**, *3*, 4139–4142.

Scheme 1.1.2. Previous Reports on Synthesis of *Z*-Disubstituted Alkenyl Nitriles through Catalytic Cross-Metathesis



It should be mentioned that, whereas most cross-metathesis reactions generate thermodynamically more stable *E*-isomers preferentially, cyano-substituted alkenes are formed with low to moderate *Z* selectivity, which was recently attributed to stereoelectronic factors.[33] This observation is consistent with some other cross-metathesis reactions we have explored with Cl-[34], Br-[34] and F_3C-substituted[35] alkenes before. The recent development of new classes of molybdenum complexes by our group allowed us to explore the potential of efficient and stereoselective synthesis for di- and trisubstituted

(33) Torker, S.; Koh, M. J.; Khan, R. K. M.; Hoveyda, A. H. *Organometallics* **2016**, *35*, 543–562.
(34) (a) Koh, M. J.; Nguyen, T. T.; Zhang, H.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2016**, *531*, 459–465. (b) Nguyen, T. T.; Koh, M. J.; Shen, X.; Romiti, F.; Schrock, R. R.; Hoveyda, A. H. *Science* **2016**, *352*, 569–575. (c) Nguyen, T. T.; Koh, M. J.; Mann, T. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *552*, 347–354.
(35) Koh, M. J.; Nguyen, T. T.; Lam, J. K.; Torker, S.; Hyvl, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *542*, 80–85.

alkenyl nitriles in either stereoisomeric form and with safe, easily accessible nitrile-containing cross-partners.

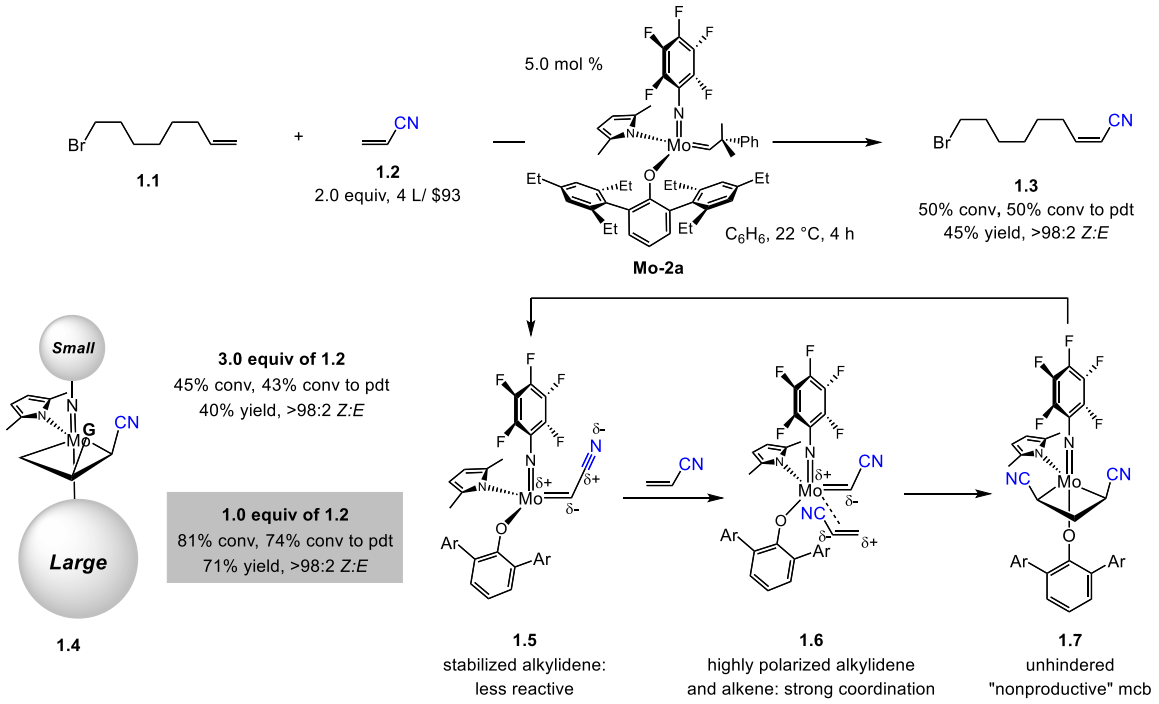
1.2. Stereoselective Synthesis of Z-Disubstituted Alkenyl Nitriles

We began our studies with the transformation between an abundant monosubstituted alkene **1.1** and an inexpensive cross-partner acrylonitrile **1.2**. Among the Mo monoaryloxide pyrrolide (MAP) complexes, **Mo-2a** emerged as the most effective complex to afford the desired *Z*-alkenyl nitrile **1.3** with complete stereochemical control, but there was only 45% consumption of the starting material **1.1** (Scheme 1.2.1). The exceptional selectivity is a significant improvement compared to previously reported cross-metathesis methods. This is achieved due to the size difference within the metallacyclobutane **1.4**, where the bottom larger aryloxide ligand forces the substituents to point towards the smaller pentafluorophenyl imido ligand. Usually, one of the solutions to increase the consumption of the substrate is to add excess amounts of cross-partners[32,33]. However, for this transformation, 3 equivalents of **1.2** actually led to lower conversion to **1.3**. In contrast, with equimolar amounts of substrates, there was 81% conversion to **1.3**, which was isolated in 71% yield as the pure Z isomer.

We propose that this complication originates from the strongly electron-withdrawing nature of a nitrile unit. The major impact of a cyano moiety is stabilization of electron density at the alkylidene carbon in complex **1.5**, which translates to diminished catalyst activity. The small size of a nitrile group and the strongly polarized C=C bond in acrylonitrile further complicate matters, as these factors favor reaction via the electronically matched **1.6**, which is a precursor to the symmetrical metallacyclobutane **1.7**, an intermediate for non-productive self-metathesis pathway.

Therefore, less cross-partner **1.2** would facilitate the productive metathesis with substrate **1.1** by suppressing non-productive processes.

Scheme 1.2.1. Reaction Optimization and Challenges of Non-Productive Metathesis[a]



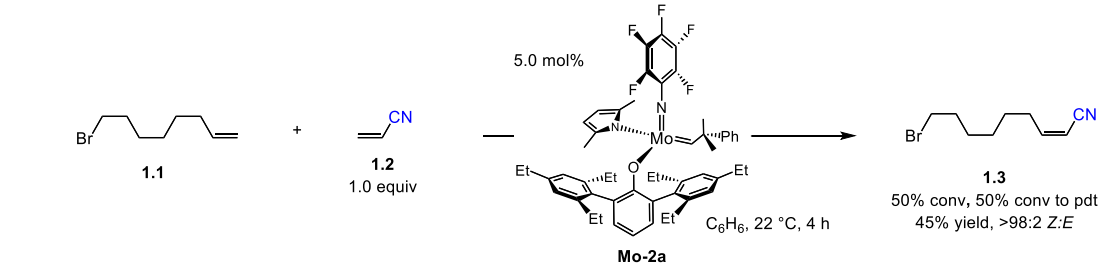
[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details.

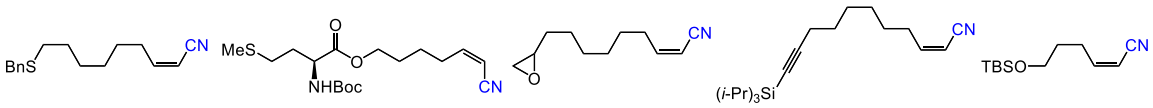
With the optimal cross-metathesis conditions in hand, we set out to examine substrates containing various important functional groups (see Scheme 1.2.2). Nitrile-containing products bearing a sulfide (**1.8**–**1.9**), an epoxide (**1.10**), an alkyne (**1.11**), a silyl ether (**1.12**) or a Lewis basic carbonyl unit (**1.13**–**1.14**) were isolated in 63–86% yield as a single isomer. Reactions with allylic-substituted alkenes with a relatively long C–Si (**1.15**) or C–Sn (**1.16**) bond were similarly efficient and stereoselective. However, bulky and/or electron-withdrawing substituents on the alkene exhibited adverse effects on reaction efficiency. The *tert*-butyl(dimethyl)silyl ether **1.17** was isolated in only 42% yield, while no formation of boronate **1.18** was observed. These data demonstrate the

difficulty of preparing alkenyl nitriles. As in our previous studies towards alkenyl halides, the *Z*-chloro-allyl boronate was afforded efficiently (66% yield, >98:2 *Z*:*E*).[34a] The challenge within this class of transformation is again, due to the unique feature of a cyano-substituted alkylidene and the competitive non-productive process (see Scheme 1.2.1). When the substrate is too bulky or contains an electron-withdrawing group, the self-metathesis of acrylonitrile dominates even with only 1 equivalent of the cross-partner. *β*-Branched secondary homoallylic ether **1.19** and γ-aryl α,*β*-unsaturated nitriles **1.20**–**1.21** were formed in moderate yield. No conversion of the styrene substrate to compound **1.22** was observed, which further underscored the presence of a non-productive cycle.

To address the issue of low efficiency for sterically hindered and/or electron-deficient substrates, the solution could very likely rely on more reactive Mo-based alkylidene complexes. We turned to Mo monoaryloxide chloride (MAC) complexes, which have demonstrated greater reactivity than MAP complexes in our attempts to generate disubstituted CF_3-substituted olefins.[33] During previous studies, MAC complexes decomposed readily in the presence of terminal olefins but exhibited high reactivity with internal *Z*-disubstituted alkenes, which are often prepared by single-vessel operations (e.g., Suzuki cross-coupling of commercially available aryl boronates and alkenyl bromides).

Scheme 1.2.2. Scope of Terminal Alkenyl Nitriles with Acrylonitrile[a]





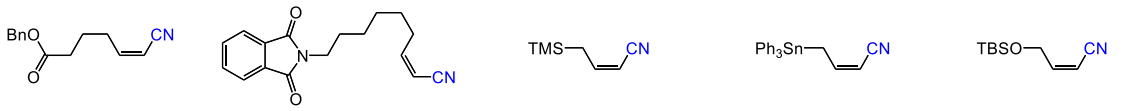
1.8
82% conv, 77% yield
>98:2 *Z*:*E*

1.9
64% conv, 63% yield
>98:2 *Z*:*E*

1.10
80% conv, 70% yield
>98:2 *Z*:*E*

1.11
83% conv, 78% yield
>98:2 *Z*:*E*

1.12
83% conv, 73% yield
>98:2 *Z*:*E*



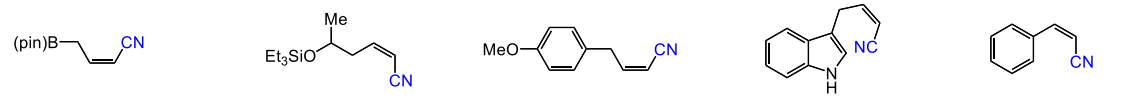
1.13
71% conv, 63% yield
>98:2 *Z*:*E*

1.14
89% conv, 86% yield
>98:2 *Z*:*E*

1.15
84% conv, 71% yield
>98:2 *Z*:*E*

1.16
84% conv, 71% yield
>98:2 *Z*:*E*

1.17
70% conv, 42% yield
>98:2 *Z*:*E*



1.18
< 2% conv

1.19
70% conv, 41% yield
>98:2 *Z*:*E*

1.20
56% conv, 46% yield
>98:2 *Z*:*E*

1.21
75% conv, 69% yield
>98:2 *Z*:*E*

1.22
< 2% conv

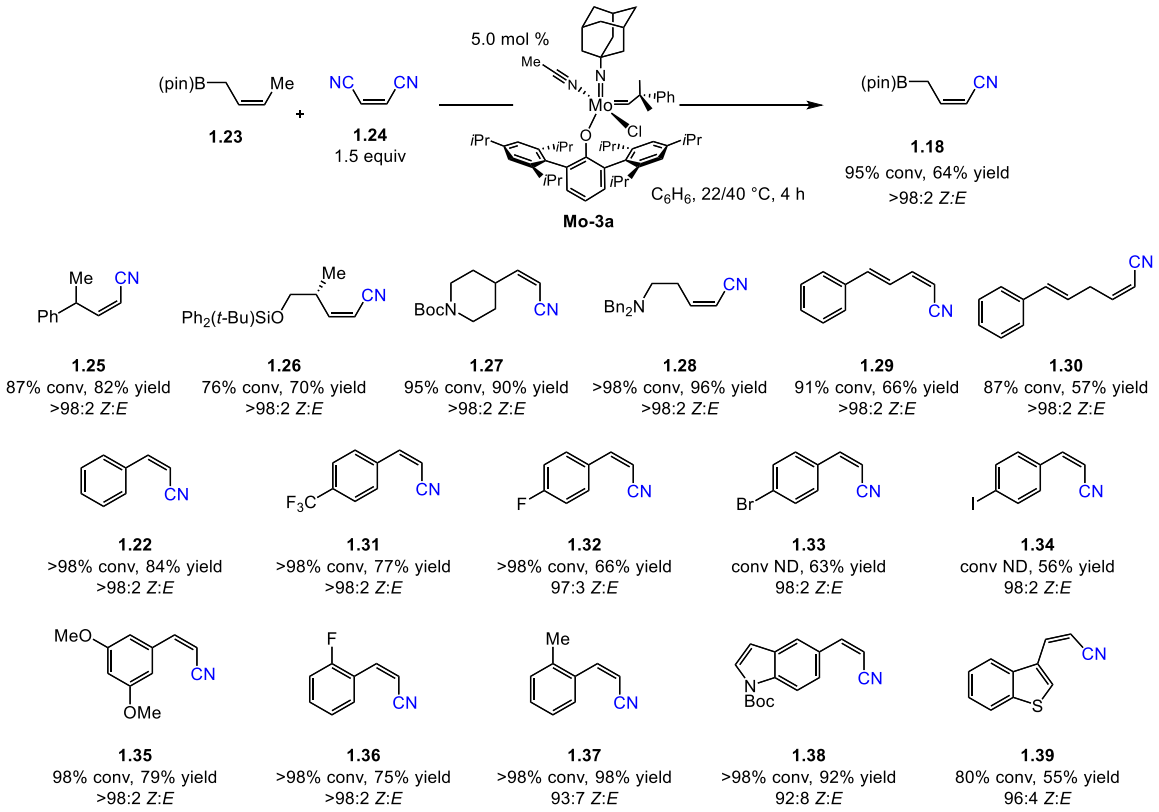
[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details.

As illustrated in Scheme 1.2.3, subjection of MAC complex **Mo-3a** to commercially available *Z*-crotyl–B(pin) **1.23** and 1.5 equivalents of maleonitrile **1.24** afforded cyano-substituted *Z*-allyl–B(pin) product **1.18** in 64% yield and >98:2 *Z*:*E* ratio. This is a significant improvement from previous transformations with MAP complexes, which yielded no product regardless of stereoselectivity. This approach is also applicable to the α-branched alkenes (**1.25**–**1.27**), which are among the most challenging substrates in olefin metathesis. Products containing an amine (**1.28**), a 1,3-diene (**1.29**) and a 1,4-diene (**1.30**) unit were successfully generated. MAP complex **Mo-2a** was not able to afford these valuable alkenyl nitriles due to strong intramolecular N→Mo chelation with

1.28 (<30% conv to product) and alkene regio-selectivity issues for **1.29** and **1.30**, where significant amounts of byproducts arose from cross-metathesis with the internal alkenes.

Equally notable are the transformations that generate different aryl- and hetereoaryl-substituted *Z*-alkenyl nitriles **1.22**, **1.31**–**1.39** (Scheme 1.2.3). For substrates containing aryl substituents at various positions or with different electronic attributes, the desired products were isolated in 55–98% yield and 92:8 to >98:2 *Z*:*E* ratio. For aryl olefin cases, we found that slight heating to 40 °C led to a higher yield, but the duration of all transformations was just 4 h. It is worth to note that with a MAC complex, reaction with unprotected indole-containing substrate (cf. **1.38**) did not lead to any significant generation of the desired product. The products presented in Scheme 1.2.3 are not able to be preapred with any existing cross-metathesis methods, where a more traditional Mo-[27] or Ru-based[28] complex is used. Despite significant steric repulsion within metallacyclobutane for the *ortho*-tolyl-substituted alkenyl nitrile **1.37**, the reaction with the MAC complex can secure the product in 98% yield and 93:7 *Z*:*E* ratio.

Scheme 1.2.3. Scope of *Z*-Disubstituted Alkenyl Nitriles with Maleonitrile[a]



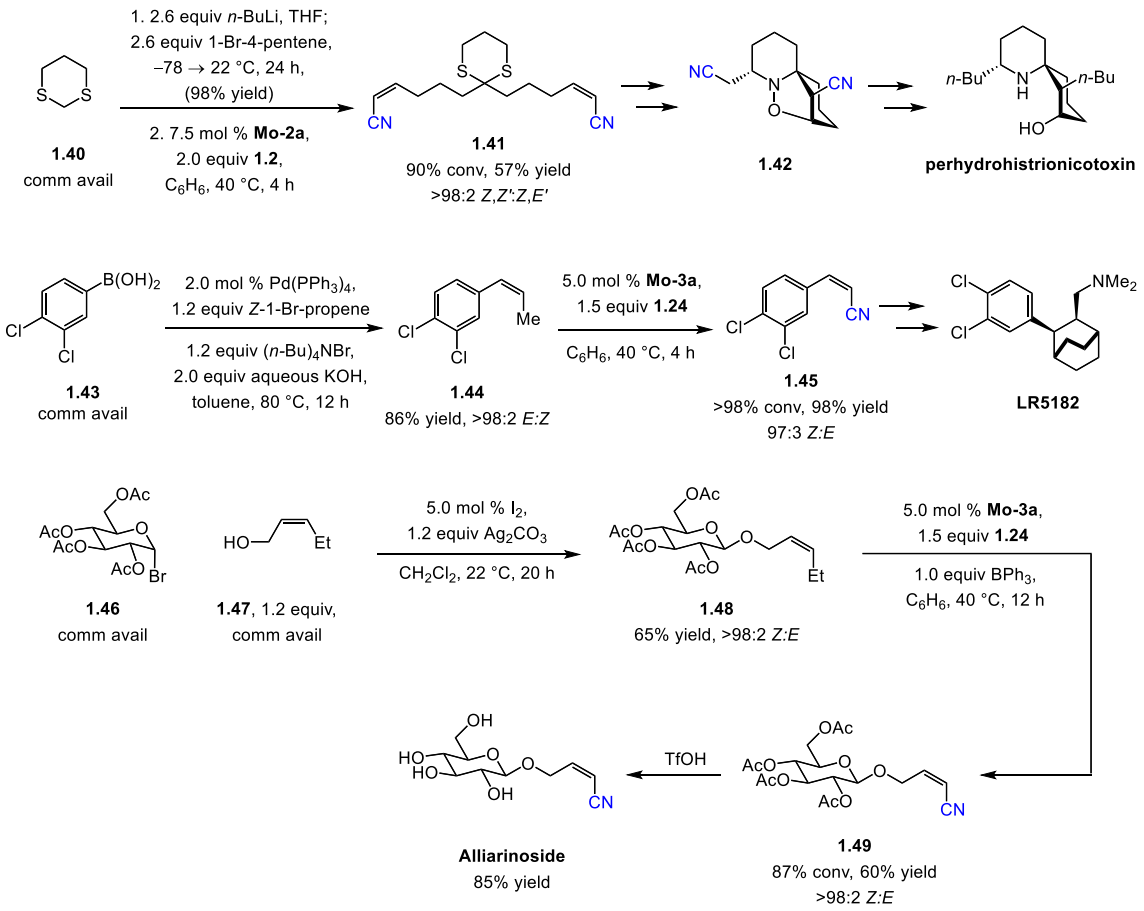
[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details.

The aforementioned advancement in cross-metathesis methods provides a convenient entry to many otherwise hard-to-access *Z*-disubstituted alkenyl nitriles, facilitating the preparation of a wide range of bioactive compounds (Scheme 1.2.4). Firstly, the bis-alkenyl nitrile **1.41** was utilized in the synthesis of perhydrohistrionicotoxin through the [5,5,6]-tricycle **1.42**. It was formerly synthesized by the Horner–Wadsworth–Emmons reaction from a bis-aldehyde, which necessitated an additional acetal removal step and the use of the less desirable hexamethylphosphoramide[15] With this newly developed cross-metathesis strategy, we can start from the commercially available 1,3-dithiane with the Corey-Seebach alkylation to install the bis-terminal alkene in one step, followed by the double cross-metathesis

with the MAP complex **Mo-2a** to afford **1.41** in 57% yield and >98:2 *Z,Z'*:*Z,E'*. Secondly, to complete the synthesis of the drug candidate for cocaine abuse treatment LR5182[7], *Z*-alkenyl nitrile **1.45** was required for a [4+2] cycloaddition. While previous synthesis afforded **1.45** in only 80:20 *Z*:*E* selectivity under harsh conditions (180 ℃), we can efficiently yield the product in almost quantitative yield and >98:2 *Z*:*E* ratio. Finally, to synthesize the anti-feedant natural product Alliarinoside, the reaction between glycosyl bromide **1.46** and allylic alcohol **1.47**, followed by catalytic cross-metathesis delivered **1.49** in 39% overall yield over two steps and >98:2 *Z*:*E* ratio. It is noteworthy that the addition of BPh_3 can improve the efficiency of the cross-metathesis by preventing chelation of the carbohydrate to the Mo-center. Two previously reported protocols on synthesis of Alliarinoside either generated a mixture of alkene isomers through Horner–Wadsworth–Emmons olefination[36], which is hard to separate, or demanded the utilization of a *Z*-alkenyl iodide, requiring at least two additional operations[20b], for further catalytic cross-coupling reactions.

(36) (a) Haribal, M.; Yang, Z.; Attygale, A. B.; Renwick, J. A. A.; Meinwald, J. *J. Nat. Prod.* **2001**, *64*, 440–443. (b) Olsen, C. E.; Møller, B. L.; Motawia, M. S. *Carbohydr. Res.* **2014**, *394*, 13–16.

Scheme 1.2.4. Synthetic Applications of *Z*-Disubstituted Alkenyl Nitriles[a]



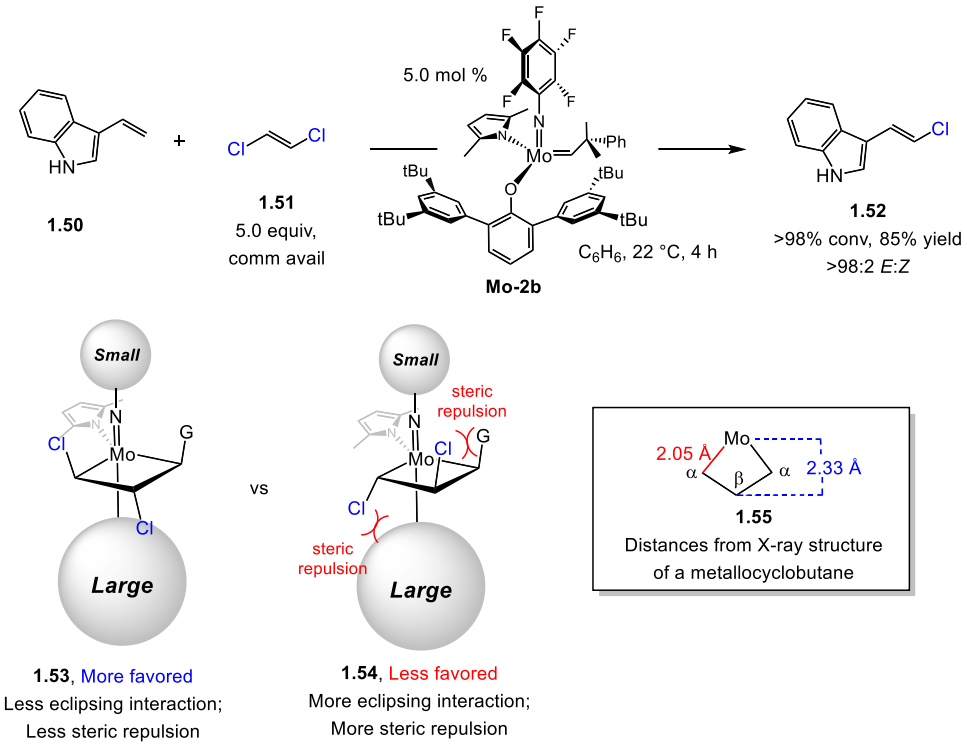
[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details.

1.3. Stereoselective Synthesis of E-Disubstituted Alkenyl Nitriles

We then moved to investigate the generation of *E*-disubstituted alkenyl nitriles. As we learned from previous alkenyl halide cross-metathesis reactions[34,35] (Scheme 1.3.1), *E*-disubstituted alkenes are generally more difficult to form as the metallocyclobutane needs to accommodate a substituent pointing towards the large aryloxide ligand[32b]. Therefore, compared to the vinyl halides (e.g., vinyl chloride) used in stereoselective reactions, *E*-disubstituted cross-partners (e.g., *E*-1,2-dichloroethene **1.51**) were chosen for the stereoretentive transformations. It also required a smaller aryloxide ligand (e.g., 3,5-substituted aryloxide ligand in **Mo-2b** compared to the 2,6-disubstituted

derivative in **Mo-2a**) to allow more space for the substituent at the β-carbon that points towards the large ligand. With the optimal Mo complex **Mo-2b**, *E*-disubstituted alkenyl chloride **1.52** was secured in 85% yield and >98:2 *E*:*Z* ratio.

Scheme 1.3.1. Synthesis of *E*-Disubstituted Alkenyl Halides



We proposed that the >98:2 *E*-selectivity originates from the energy difference between metallacyclobutanes **1.53** and **1.54**, the latter of which involves both eclipsing effects and steric repulsion at the α-carbon. It should be noted that based on the X-ray structure of a metallacyclobutane[37], the β-carbon is further away from the Mo-center than the α-carbon and therefore, less affected by the steric hindrance from the large aryloxide group. As in the past for the synthesis of stereodefined alkenyl halides (Scheme 1.3.1), we chose to focus on the stereoretentive processes to afford *E*-disubstituted alkenyl nitriles (Scheme 1.3.2). We commenced the study of *E*-alkenyl nitriles with commercially

(37) Marinescu, S. C.; Schrock, R. R.; Müller, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 10840–10841.

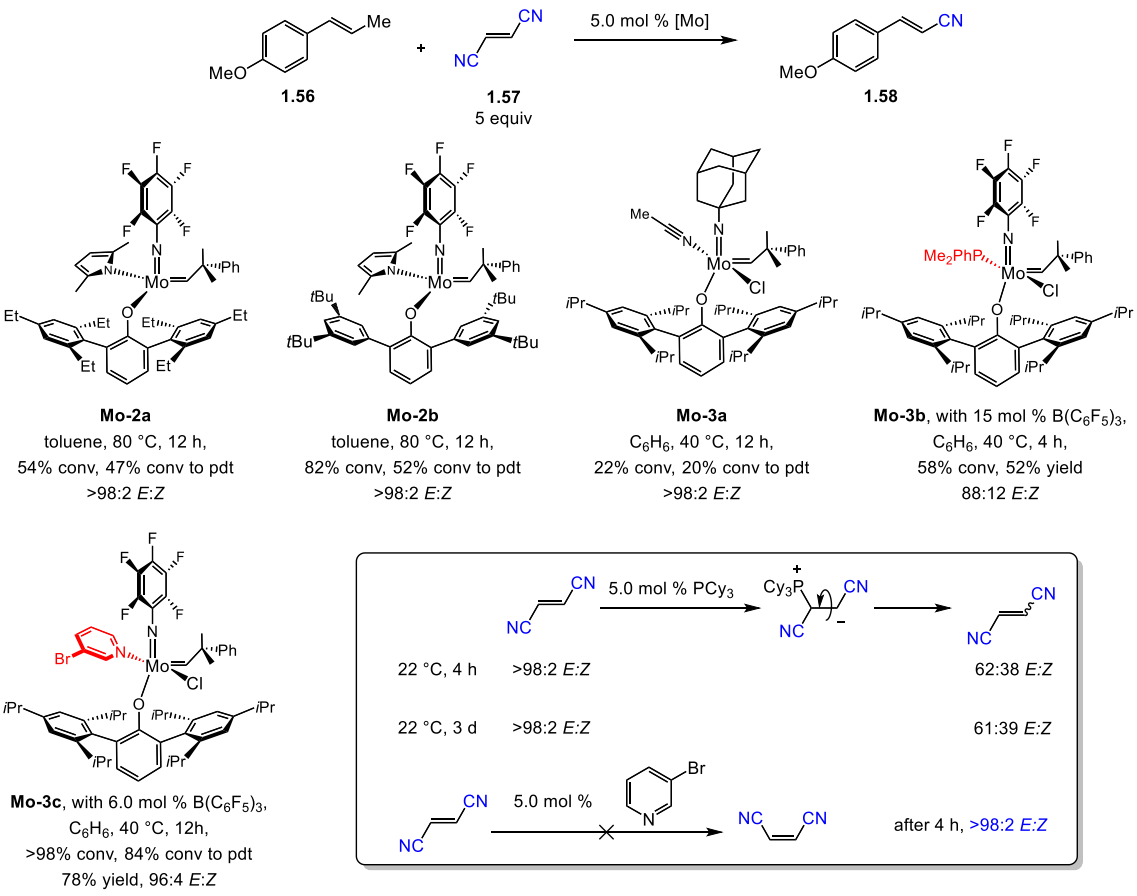
available 4-vinylanisole **1.56** and fumaronitrile **1.57** to test various Mo complexes. The transformation with pentafluorophenyl imido MAP complexes **Mo-2a** and **Mo-2b**, were highly stereoretentive but only moderately efficient, even at the elevated temperatures (47% and 52% conversion to **1.58**, respectively, at 80 ℃). The low reactivity of MAP complexes led us to screen MAC alkylidenes **Mo-3a**, which were effective for *Z*-alkenyl nitrile synthesis but not formerly used for reactions that generate *E*-alkenes. Although there was only 20% conversion to **1.58**, the reaction was completely stereoretentive and minimal conversion to homo-coupling product or any byproduct were observed. We envisioned that incorporating an activating polyfluoroaryl-imido ligand may further improve efficiency because whereas **Mo-2a** and **Mo-2b** are already pentafluoroaryl-imido complexes, **Mo-3a** is an adamantyl-imido derivative. We thus prepared the corresponding complex **Mo-3b**[38], which was often stabilized by a phosphine ligand, and probed the reactivity of this MAC alkylidene for the *E*-disubstituted alkenyl nitrile cross-metathesis reactions. Lewis acid (15 mol % of $B(C_6F_5)_3$) was added to scavenge the stabilizing phosphine ligand to release the active tetra-coordinated complex. A notable boost in reactivity was observed as there was 67% consumption of **1.56** and 49% conversion to **1.58**. However, a significant diminution of selectivity (>98:2 → 88:12 *E*:*Z*) was observed for the stereoretentive transformation and demanded further explorations into these newly developed pentafluoroaryl-imido MAC complexes.

Usually, lower selectivity in a stereoretentive cross-metathesis reaction is owing to the adventitious isomerization of the starting alkene. We surmised that fumaronitrile **1.57**, an exceedingly electrophilic reagent, might interconvert with its similarly favored

(38) Lam, J. K.; Zhu, C.; Bukhryakov, K. V.; Müller, P.; Hoveyda, A. H.; Schrock. R. R. *J. Am. Chem. Soc.* **2016**, *138*, 15774–15783.

Z-isomer through an addition/elimination sequence. Considering the complete retention of stereoselectivity with the acetonitrile complex **Mo-3a**, the likely nucleophilic promoter for this event would be an uncoordinated dimethylphenylphosphine. To support our rationale, we subjected 5.0 mol % PCy_3 (easier to handle than PMe_2Ph in **Mo-3b**) to the solution of **1.57** in C_6H_6, and it indeed became a 62:38 *E*:*Z* mixture after only 4 h. This equilibrium seems to be a fast process as after 3 days, the *E*:*Z* ratio was similar (61:39). Mindful that we have a strong Lewis acid in our catalytic system, we also added 15 mol % $B(C_6F_5)_3$ to the isomerization control experiments. We found that even with the Lewis acid, the phosphine species could dissociate from the 'frustrated' Lewis pair $Cy_3P{\rightarrow}B(C_6F_5)_3$ to isomerize the fumaronitrile from >98:2 to 97:3 *E*:*Z* selectivity. This 3% maleonitrile formation might seem insignificant, but considering that *Z*-alkenes generally react faster with this catalyst class[33], particularly with a larger aryloxide ligand, this could indeed be the source of the 12% loss in stereochemical purity. This discovery directed our study to the identification of the optimal stabilizing ligand. We quickly found that 3-Br-pyridine does not facilitate the fumaronitrile isomerization even in the absence of the strong Lewis acid (Scheme 1.3.2). To confirm our findings, we prepared the MAC complex **Mo-3c**, with which we can isolate the desired product **1.58** in 78% yield and in 96:4 *E*:*Z* stereoselectivity.

Scheme 1.3.2. Reaction Optimization for *E*-Disubstituted Alkenyl Nitriles

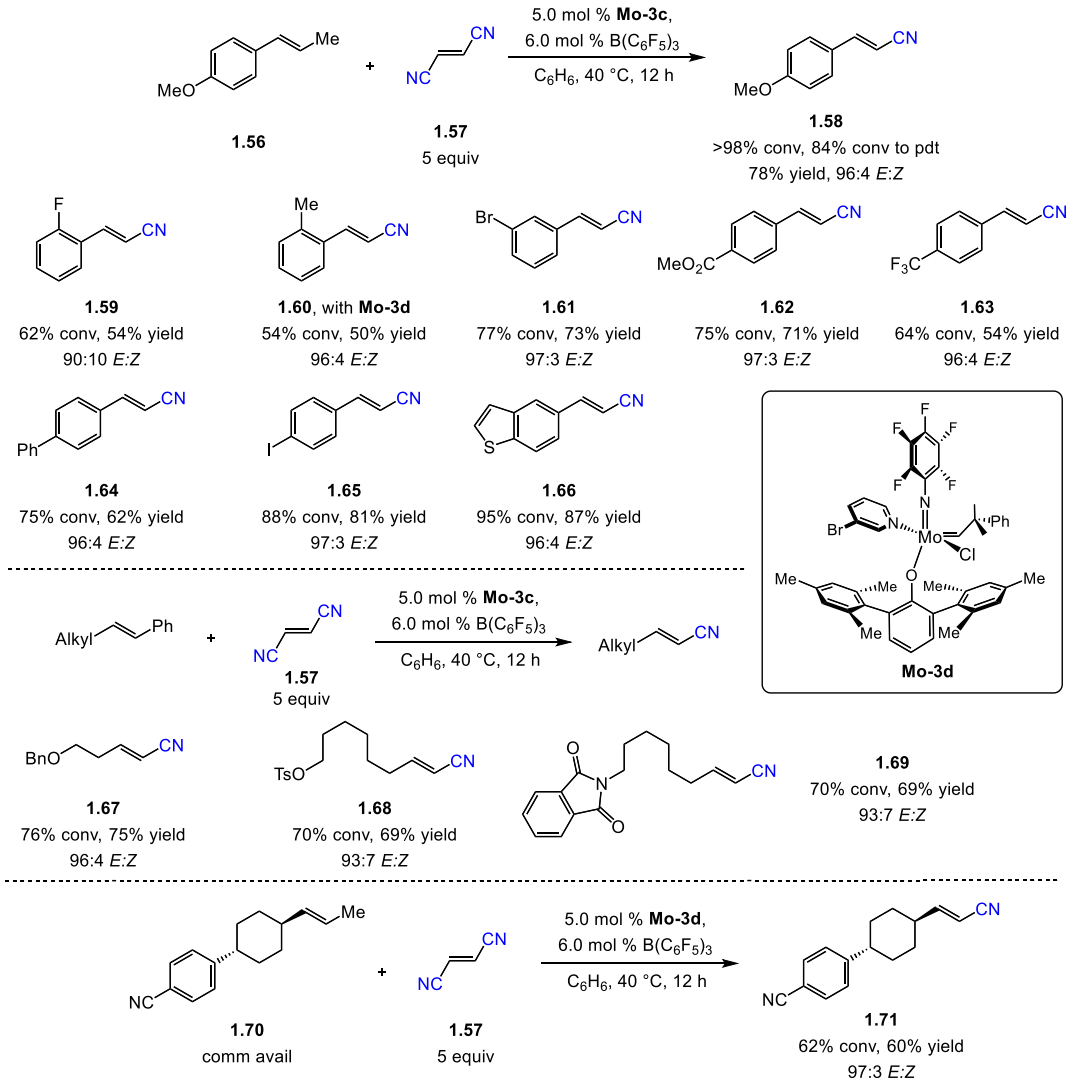


[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details.

This catalytic strategy is able to deliver many *E*-aryl- and hetereoaryl-alkenes with *ortho*- (**1.59** and **1.60**), *meta*- (**1.61**) or *para*-substitutents (**1.58, 1.62**–**1.65**) and with electron-donating (**1.58**, **1.66**) or withdrawing (**1.61**–**1.65**) properties. *E*-Disubstituted nitrile-containing products were obtained in 54% to 87% yield, with stereoselectivity from 90:10 to 97:3 *E*:*Z* ratio (Scheme 1.3.3). In the case of *o*-tolyl-substituted product **1.60**, less sterically demanding **Mo-3d** was employed because when the substrate contains a particularly hindered substituent, the reaction was much less efficient and required a smaller aryloxide ligand to accommodate the *ortho*-substituent.

E-alkenyl nitriles with *n*-alkyl substituents were more challenging, an observation also noticed in our previous synthesis of *E*-disubstituted alkenyl chlorides[32b], due to homo-coupling of the starting alkene and low selectivity. We discovered that with *E*-β-alkyl styrenes instead of monosubstituted alkenes as substrates, maximum efficiency and selectivity can be achieved for *E*-alkene products[32b], where the phenyl group can serve as a handle to help control the stereoselectivity. Indeed, when we applied the same strategy to the *E*-alkenyl nitrile synthesis, products **1.67**–**1.69** can be obtained in 69–75% yield and 93:7–96:4 *E*:*Z* ratio (Scheme 1.3.3). As in the case of sterically hindered **1.60**, the reaction of α-branched alkene **1.70** to generate **1.71** was more efficient with **Mo-3d**. The smaller aryloxide ligand of **Mo-3d** may better accommodate the sizeable alkyl moiety, which would be projected towards the aryloxide ligand in the corresponding metallacyclobutane.

Scheme 1.3.3. Scope of *E*-Disubstituted Alkenyl Nitriles[a]



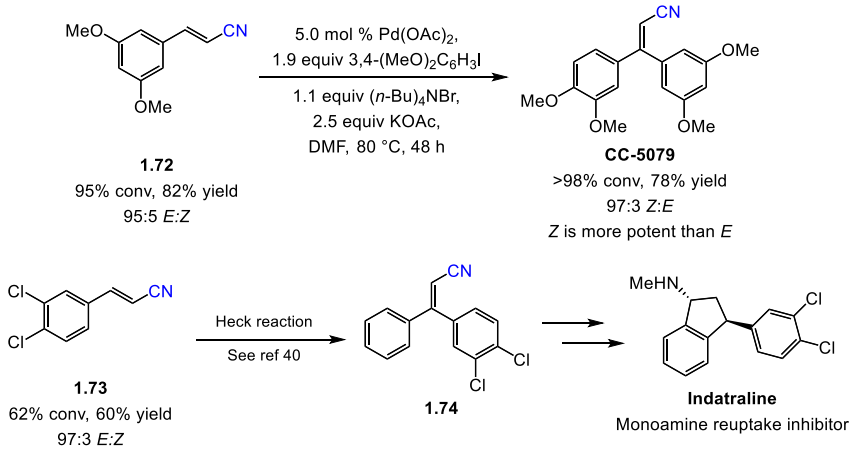
[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details.

The *E*-alkenyl nitriles were widely used in many bioactive molecules synthesis (Scheme 1.3.4). To synthesize the anticancer agent CC-5079, the cross-metathesis reaction can deliver the product **1.72** in 82% yield and 95:5 *E*:*Z* ratio, which can further undergo a catalytic Heck reaction to afford the drug candidate in 78% yield. Two points merit attention for this synthetic sequence: (1) the *Z*-isomer of CC-5079[39] is more potent

(39) Ruchelman, A. L.; Man, H.-W.; Chen, R.; Liu, W.; Lu, L.; Cedzik, D.; Zhang, L.; Leisten, J.; Collette, A.; Narla, R. K.; Raymon, H. K.; Muller, G. W. *Bioorg. Med. Chem.* **2011**, *19*, 6356–6374.

and must therefore be synthesized stereoselectively; (2) the Heck reaction is considerably more efficient with an *E*-alkenyl nitrile[14]. In line with such findings, we were unable to detect any of the desired trisubstituted alkene when *Z*-**1.72** was subjected to the conditions used for the reaction of the corresponding *E*-isomer. Antidepressant indatraline[40] can be synthesized by a similar process via **1.74** from *E*-alkenyl nitrile product **1.73** (60% yield, 97:3 *E*:*Z*), followed by catalytic enantioselective hydrogenation[14]. Furthermore, in previous studies, the requisite 1,2-disubstituted alkenyl nitriles **1.72** and **1.73** could only be generated as 80:20 *E*:*Z* mixtures by Wittig-type reactions[39,14], and the stoichiometric amount of the phosphine-oxide byproduct generated is wasteful and difficult to remove in purification procedures.

Scheme 1.3.4. Synthetic Applications of *E*-Disubstituted Alkenyl Nitriles[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details.

1.4. Stereoselective Synthesis of E- and Z-Trisubstituted Alkenyl Nitriles

We then investigated the development of a catalytic method for stereoretentive synthesis of trisubstituted alkenyl nitriles. In 2017, when we tried to synthesize the stereodefined *E*- and *Z*-trisubstituted alkenyl chlorides[32c], we realized that compared to the reactions

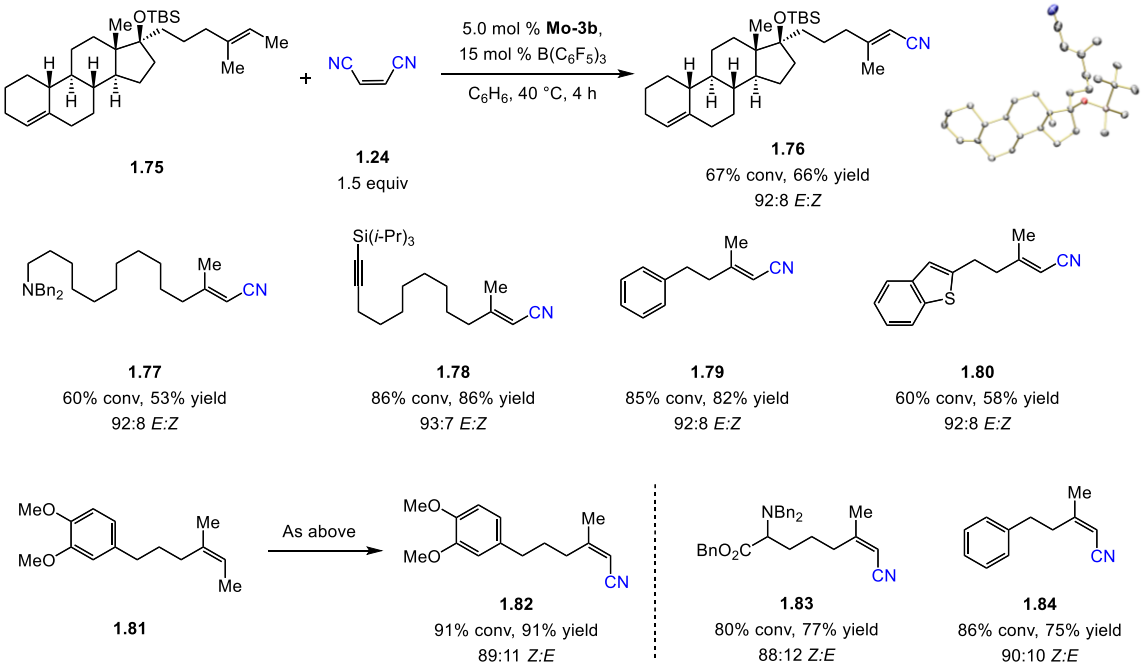
(40) Walton, J. G. A.; Jones, D. C.; Kiuru, P.; Durie, A. J.; Westwood, N. J.; Fairlamb, A. H. *ChemMedChem* **2011**, *6*, 321–328.

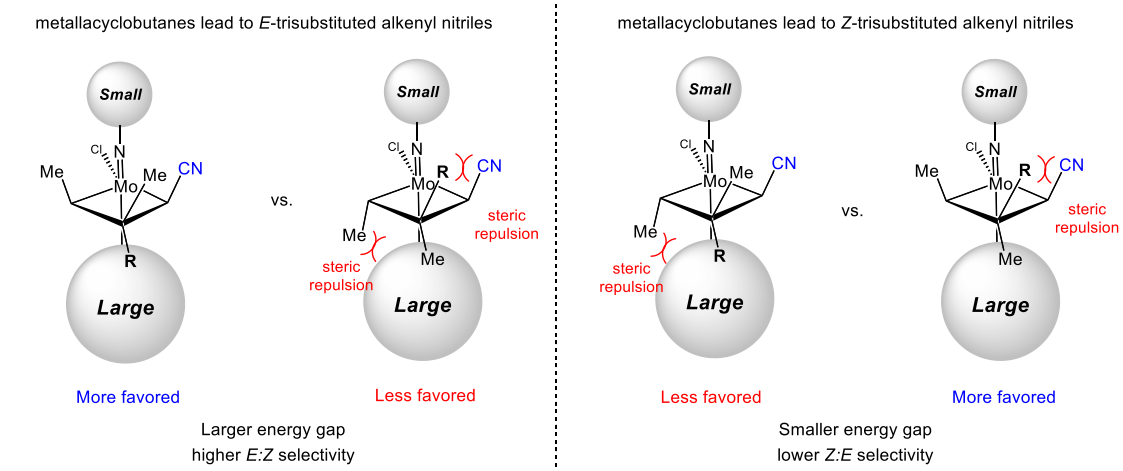
between a 1,1-disubstituted alkene and a terminal olefin that often generated the product in low efficiency and low stereoselectivity, stereoretentive reactions between a *E*- or *Z*-trisubstituted alkene and a 1,2-disubstituted cross-partner were much more efficient and selective. This unique transformation involves a mono-substituted alkylidene exclusively, as opposed to a 1,1-disubstituted variant arising from initial reaction with a trisubstituted olefin or a short-living methylidene[41] arising from a terminal alkene. One of the most important lessons we learned was that with the chloro-substituted *syn*-alkylidene being preferred, the choice of *Z*- or *E*-cross-partner no longer matters because they should lead to the same degree of stereo-purity[32c] through the same *syn*-alkylidene.

These findings drove us to discover the potential of using a stereoretentive process to afford the *E*- and *Z*-trisubstituted alkenyl nitriles. After the examination of different Mo-baed complexes, we identified that the subjection of **Mo-3b** to $(C_6F_5)_3B$, **1.75**, and **1.24** afforded **1.76** in 66% yield and 92:8 *E*:*Z* selectivity (Scheme 1.4.1). The *E*:*Z* ratio was the same with Mo-based complex **Mo-3c**, in line with the cyano-substituted *syn*-alkylidene being the predominant intermediate, regardless of whether **1.24** (maleonitrile) or **1.57** (fumaronitrile) is involved. An assortment of aliphatic *E*-trisubstituted alkenyl nitriles were accessed in 53–86% yield and 92:8–93:7 *E*:*Z* selectivity (**1.77**–**1.80**); an X-ray structure of **1.76** further confirmed the structure of the product. This approach is applicable to the preparation of *Z*-trisubstituted alkenyl nitriles in a similar fashion (see **1.82**–**1.84**). The slightly lower stereochemical control in the formation of the *Z*-isomers was owing to the smaller energy gap between two competing metallacycobutanes as shown in Scheme 1.4.1.

(41) Hoveyda, A. H.; Liu, Z.; Qin, C.; Koengeter, T.; Mu, Y. *Angew. Chem. Int. Ed.* **2020**, *59*, 22324–22348.

Scheme 1.4.1. Scope of Aliphatic Trisubstituted Alkenyl Nitriles[a]



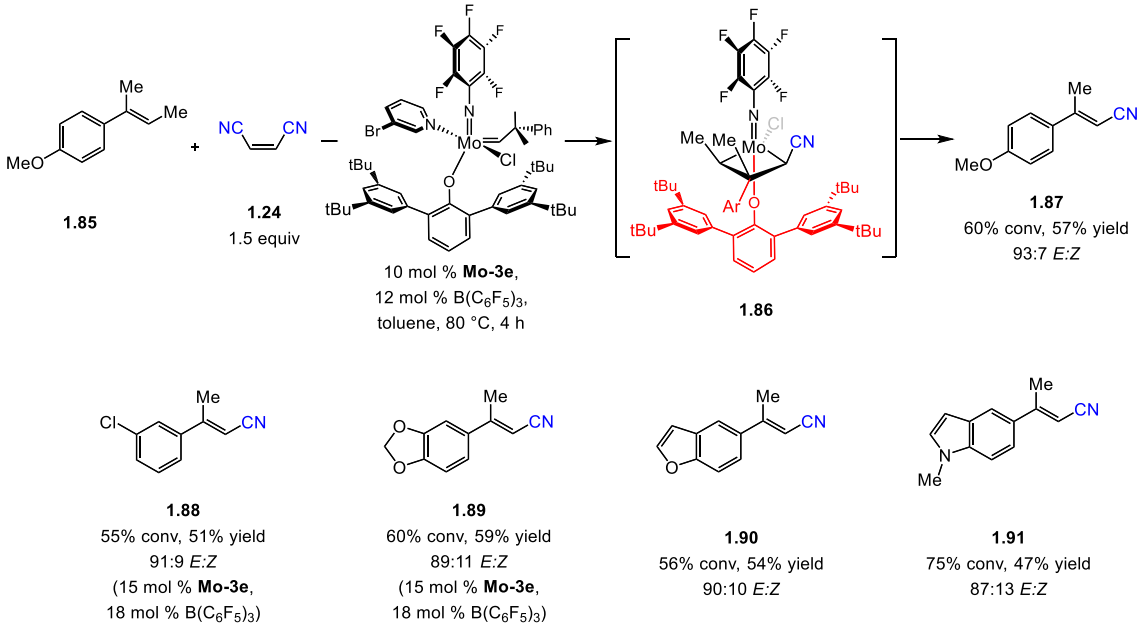


[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details.

Although efficient for aliphatic trisubstituted olefins, the catalytic reaction shown above was not applicable to aryl olefins. This again highlighted the difference between alkenyl nitriles and alkenyl halides, the latter of which were obtained in high yield when MAP complex **Mo-2b** was used. This is due to the formation of a more stabilized/less reactive cyano-substituted alkylidene species compared to chloro-substituted derivatives

(Scheme 1.2.1). There was no **1.87** formation with MAC complex **Mo-3c** or **Mo-3d**. To address this issue, we synthesized **Mo-3e**, which bears an aryloxide with 3,5-di-*t*-butylphenyl groups at its C2 and C6 sites. We expected that the reduced steric pressure in the corresponding metallacyclobutane (**1.86**) would improve the reactivity. With the use of 10 mol % **Mo-2e** and 12 mol % $(C_6F_5)_3B$, we were able to isolate **1.87** in 57% yield and in 93:7 *E*:*Z* selectivity. As illustrated by the synthesis of **1.88**–**1.91**, the approach is compatible with electron-withdrawing aryl and hetereo-aryl alkenes (Scheme 1.4.2). For more challenging electron-deficient substrates (**1.88**–**1.89**), 15 mol % **Mo-3e** is necessary to promote the reaction in moderate yield and selectivity, further demonstrating the difficulty of this set of transformations.

Scheme 1.4.2. Scope of Aryl-Substituted Trisubstituted Alkenyl Nitriles[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details.

Under the same conditions, there was only about 20% conversion to the desired *Z*-trisubstituted aryl-substituted alkenyl nitriles, formed with minimal stereoisomeric purity

(~60:40 *Z*:*E*). Development of a more effective cross-metathesis reaction for this important but difficult class of starting material warrants future investigation.

1.5. Conclusions

We have developed a broadly applicable set of catalytic methods for the preparation of *Z*- and *E*-, di- and trisubstituted alkenyl nitriles in high stereoisomeric purity. Compared to the halides with similar size, cross-metathesis reactions involving nitrile substitutents are more challenging because (1) nitrile is more electron-withdrawing and leads to a more stabilized alkylidene; (2) nitrile is well-known to be a ligand for Mo-based complexes (e.g., **Mo-3a**) and is likely to decrease the reactivity of a Mo-complex intermediate. We have shown that, complexes with different electronic and steric attributes can be chosen to prepare a wide range of stereodefined alkenyl nitriles, including products bearing a linear aliphatic substituent to those containing a hindered α-branched or aryl moiety. Especially noteworthy is that an equimolar amount of the two cross partners is not only sufficient, but also optimal, for achieving high efficiency in a cross-metathesis reaction. The ability to access an alkenyl nitrile isomer with high stereochemical selectivity, for both di- and trisubstituted alkenes, allows for significant improvement in the preparation of these valuable alkenyl nitriles, many of which are biologically active entities.

1.6. Experimental Section

1.6.1. General

Unless otherwise noted, transformations were performed with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum line techniques. Infrared (IR) spectra were recorded on a Bruker FTIR Alpha (ATR Mode) spectrometer, ν_{max} in cm^{-1}. Bands are characterized as

broad (br), strong (s), medium (m), or weak (w). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz), 500 (500 MHz), or 600 (600MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuterium incorporation as the internal standard ($CDCl_3$: δ 7.26 ppm, C_6D_6: δ 7.16 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz), 500 (125 MHz), or 600 (150 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm, C_6D_6: δ 128.00 ppm). ^{19}F NMR spectra were recorded on a Varian Unity INOVA 400 (376 MHz) spectrometer. High-resolution mass spectrometry was performed on a JEOL Accu TOF Dart (positive mode) at the Boston College Mass Spectrometry Facility. Melting points were determined using a Thomas Hoover Uni-melt capillary melting point apparatus. Values for *E*:*Z* ratios of products were determined by ^{1}H NMR analysis of unpurified mixtures.

Solvents:

Solvents (CH_2Cl_2, Et_2O, pentane, benzene and toluene) were purified under a positive pressure of dry argon gas by an Innovative Technologies purification system. Tetrahydrofuran was distilled from Na/benzophenone. Methanol was distilled over Mg. Acetone, *N*,*N*-dimethylformamide (anhydrous), 1,2-dimethoxyethane (anhydrous) and 1,4-dioxane (anhydrous) were used as received. All purification procedures of CM products were carried out with reagent grade solvents (purchased from Fisher) under bench-top conditions.

Reagents:

8-Bromo-1-octene (Aldrich), acrylonitrile (ACROS), 1,2-epoxy-9-decene (Aldrich), allyltrimethylsilane (Aldrich), allyltriphenyl stannane (Aldrich), 4-allylanisole (Aldrich), 3-(2-propenyl)indole (Combi-blocks), (*Z*)-crotylboronic acid pinacol ester (Frontier Scientific), (*Z*)-prop-1-en-1-ylbenzene (TCI America), (*E*)-1-Methoxy-4-(prop-1-en-1-yl)benzene (Aldrich), Fumaronitrile (Combi-blocks), 4-[*trans*-4-[(*E*)-1-propenyl]cyclohexyl]benzonitrile (TCI America), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Oakwood), oleic acid (Aldrich), oleyl alcohol (Aldrich) were either distilled (from CaH_2 or $CaCl_2$) under vacuum or dried by azeotropic distillation (with anhydrous benzene) prior to use.

Benzyl(7-octenyl)sulfane[42], 9-decen-1-ynyltriisopropylsilane[43], benzyl hex-5-enoate[44], 2-(5-hexenyl)isoindoline-1,3-dione[45], triethyl(pent-4-en-2-yloxy)silane[46], (allyloxy)(tert-butyl)dimethylsilane[47], (*Z*)-*tert*-butyl((2-methylpent-3-en-1-yl)oxy)diphenylsilane[33], *tert*-butyl (*Z*)-4-(prop-1-en-1-yl)piperidine-1-carboxylate[33], ((1*E*,3*Z*)-penta-1,3-dien-1-yl)benzene[33], ((1*E*,4*Z*)-hexa-1,4-dien-1-yl)benzene[33], (*Z*)-*N*,*N*-dibenzylhex-3-en-1-amine[33], *tert*-butyl (*Z*)-5-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate[33], *N*,*N*-dibenzyl-10-undecen-1-amine[48], 2-vinylbenzo[*b*]thiophene[49], benzyl 2-(dibenzylamino)pent-4-enoate[50] were prepared in analogy to reported procedures.

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(42) Lin, Y. A.; Chalker, J. M.; Floyd, N.; Bernardes, G. J. L.; Davis, B. G. *J. Am. Chem. Soc.* **2008**, *130*, 9642–9643.
(43) Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461–466.
(44) Xu, C.; Shen, X.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 10919–10928.
(45) Koh, M. J.; Khan, R. K. M.; Torker, S.; Yu, M.; Mikus, M. S.; Hoveyda, A. H. *Nature* **2015**, *517*, 181–186.
(46) Yu, E. C.; Johnson, B. M.; Townsend, E. M.; Schrock, R. R.; Hoveyda, A. H. *Angew.Chem. Int. Ed.* **2016**, *55*, 13210–13214.
(47) Kiesewetter, E. T.; O'Brien, R. V.; Yu, E. C.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2013**, *135*, 6026–6029.
(48) Bélanger, G.; Doré, M.; Ménard, F.; Darsigny, V. *J. Org. Chem.* **2006**, *71*, 7481–7484.

1-(*tert*-Butyldimethylsilyoxy)-4-pentene (from 4-pentene-1-ol (Alfa Aesar)) and allylestrenol *tert*-butyldimethylsilyl ether (from allylestrenol (TCI)) were prepared in analogy to a reported procedure[51].

Hex-5-en-1-yl (*tert*-butoxycarbonyl)-*L*-methioninate (from 5-hexene-1-ol (Aldrich) and *L*-methionine (Advanced Chemtech)) was prepared by esterification in analogy to a reported procedure[52].

(*Z*)-Pent-3-en-2-ylbenzene (from 2-phenylpropanal (Aldrich)), (*Z*)-1-bromo-4-(prop-1-en-1-yl)benzene (from 4-bromobenzaldehyde (Aldrich)) and (*Z*)-1-iodo-4-(prop-1-en-1-yl)benzene (from 4-iodobenzaldehyde (Oakwood)) were prepared by Wittig reaction in analogy to a reported procedure[53].

(*Z*)-1-(Prop-1-en-1-yl)-4-(trifluoromethyl)benzene (from 4-trifluoromethylphenyl boronic acid, pinacol ester (Combi-blocks) and (*Z*)-1-bromo-1-propene (Aldrich)), (*Z*)-1-fluoro-4-(prop-1-en-1-yl)benzene (from 4-fluorophenylboronic acid (Aldrich) and (*Z*)-1-bromo-1-propene (Aldrich)), (*Z*)-1,3-dimethoxy-5-(prop-1-en-1-yl)benzene (from 3,5-dimethoxylphenylboronic acid (Combi-blocks) and (*Z*)-1-bromo-1-propene (Aldrich)), (*Z*)-1-fluoro-2-(prop-1-en-1-yl)benzene (from 2-fluorophenylboronic acid (Combi-blocks) and (*Z*)-1-bromo-1-propene (Aldrich)), (*Z*)-1-methyl-2-(prop-1-en-1-yl)benzene (from 2-methylphenylboronic acid (Aldrich) and (*Z*)-1-bromo-1-propene (Aldrich)), (*Z*)-3-(prop-1-en-1-yl)benzo[*b*]thiophene (from benzo[*b*]thien-3-ylboronic acid (Aldrich) and (*Z*)-1-bromo-1-propene (Aldrich)), (*Z*)-1,2-dichloro-4-(prop-1-en-1-yl)benzene (from

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(49) Falk, A.; Cavalieri, A.; Nichol, G. S.; Vogt, D.; Schmalz, H. *Adv. Synth. Catal.* **2015**, *357*, 3317–3320.
(50) Rodriquez, M.; Bruno, I.; Cini, E.; Marchetti, M.; Taddei, M.; Gomez-Paloma, L. *J. Org. Chem.* **2006**, *71*, 103–107.
(51) Aponick, A.; Li, C.-Y.; Palmes, J. A. *Org. Lett.* **2009**, *11*, 121–124.
(52) Mori, A.; Mizusaki, T.; Kawase, M.; Maegawa, T.; Monguchi, Y.; Takao, S.; Takagi, Y.; Sajiki, H. *Adv. Synth. Catal.* **2008**, *350*, 406–410.
(53) Bess, E. N.; DeLuca, R. J.; Tindall, D. J.; Oderinde, M. S.; Roizen, J. L.; Du Bois, J.; Sigman, M. S. *J. Am. Chem. Soc.* **2014**, *136*, 5783–5789.

3,4-dichlorophenylboronic acid (Combi-blocks) and (*Z*)-1-bromo-1-propene (Aldrich)), (*E*)-1,3-dimethoxy-5-(prop-1-en-1-yl)benzene (from 3,5-dimethoxylphenylboronic acid (Combi-blocks) and (*E*)-1-bromo-1-propene (Aldrich)), (*E*)-1-methyl-2-(prop-1-en-1-yl)benzene (from 2-methylphenylboronic acid (Aldrich) and (*E*)-1-bromo-1-propene (Aldrich)), (*E*)-5-(pent-1-en-1-yl)benzo[*b*]thiophene (from 5-bromo-1-benzothiophene (Combi-blocks) and (*E*)-pent-1-en-1-ylboronic acid (Combi-blocks)), (*E*)-1-(but-2-en-2-yl)-4-methoxybenzene (from 4-methoxyphenylboronic acid (Aldrich) and (*E*)-2-bromo-2-butene (Aldrich)), (*E*)-5-(but-2-en-2-yl)benzofuran (from (*Z*)-but-2-en-2-ylboronic acid[54] and 5-bromobenzofuran (Combi-blocks)), (*E*)-5-(but-2-en-2-yl)-1-methyl-1*H*-indole (from (1-methyl-1*H*-indol-5-yl)boronic acid (Aldrich) and (*E*)-2-bromo-2-butene (Aldrich)), (*E*)-1-(but-2-en-2-yl)-3-chlorobenzene (from (3-chlorophenyl)boronic acid (Oakwood) and (*E*)-2-bromo-2-butene (Aldrich)) and (*E*)-5-(but-2-en-2-yl)benzo[*d*][1,3]dioxole (from 2-(benzo[*d*][1,3]dioxol-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Combi-blocks) and (*E*)-2-bromo-2-butene (Aldrich)) were prepared by cross-coupling in analogy to a reported procedure[55].

(*E*)-1-Fluoro-2-(prop-1-en-1-yl)benzene (95:5 *E*:*Z*) (from 2-fluorobenzaldehyde (Aldrich) and 3-pentanone (Aldrich)), (*E*)-1-bromo-3-(prop-1-en-1-yl)benzene (from 3-bromobenzaldehyde (Aldrich) and 3-pentanone (Aldrich)), methyl (*E*)-4-(prop-1-en-1-yl)benzoate (from methyl 4-formylbenzoate (Aldrich) and 3-pentanone (Aldrich)), (*E*)-1-(prop-1-en-1-yl)-4-(trifluoromethyl)benzene (from 4-trifluoromethylbenzaldehyde (Aldrich) and 3-pentanone (Aldrich)), (*E*)-4-(prop-1-en-1-yl)-1,1'-biphenyl (from biphenyl-4-carboxadehyde (Aldrich) and 3-pentanone (Aldrich)), (*E*)-1-iodo-4-(prop-1-

(54) Bi, H.-Y.; Liu, F.-P.; Liang, C.; Su, G.-F.; Mo, D.-L. *Adv. Synth. Catal.* **2016**, *360*, 1510–1516.
(55) Fristrup, P.; Tanner, D.; Norrby, P.-O. *Chirality* **2003**, *15*, 360–368.

en-1-yl)benzene (from 4-iodobenzaldehyde (Oakwood) and 3-pentanone (Aldrich)), (*E*)-1,2-dichloro-4-(prop-1-en-1-yl)benzene (from 3,4-dichlorobenzaldehyde (Combi-blocks) and 3-pentanone (Aldrich)) were prepared in analogy to a reported procedure[56].

(*E*)-(4-(Benzyloxy)but-1-en-1-yl)benzene (from (*E*)-4-phenylbut-3-en-1-ol[32b] and benzyl bromide (Aldrich)) was prepared in analogy to a reported procedure[57].

(*E*)-8-Phenyloct-7-en-1-yl-4-methylbenzenesulfonate (from (*E*)-8-phenyloct-7-en-1-ol[55] (from iodobenzene and (*E*)-8-(4,4,5,5-petramethyl-1,3,2-dioxaborolan-2-yl)oct-7-en-1-ol[58]) and 4-toluenesulfonyl chloride (Aldrich)) was prepared in analogy to a reported procedure[59].

(*E*)-2-(8-Phenyloct-7-en-1-yl)isoindoline-1,3-dione (from (*E*)-8-phenyloct-7-en-1-ol[55] (from iodobenzene and (*E*)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-7-en-1-ol [59]) and phthalimide (Aldrich)) was prepared in analogy to a reported procedure[46].

tert-Butyldimethyl(((8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-13-methyl-17-((*E*)-4-methylhex-4-en-1-yl)-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)oxy)silane, (*E*)-*N*,*N*-dibenzyl-12-methyltetradec-12-en-1-amine, (*E*)-triisopropyl(11-methyltridec-11-en-1-yn-1-yl)silane, (*E*)-(3-methylpent-3-en-1-yl)benzene, (*E*)-2-(3-methylpent-3-en-1-yl)benzo[*b*]thiophene, (*Z*)-1,2-dimethoxy-4-(4-methylhex-4-en-1-yl)benzene, benzyl (*Z*)-2-(dibenzylamino)-6-methyloct-6-enoate, (*Z*)-(3-methylpent-3-en-1-yl)benzene was prepared in analogy to a reported procedure[32c].

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(56) Kabalka, G. W.; Li, N.-S.; Tejedor, D.; Malladi, R. R.; Trotman, S. *J. Org. Chem.* **1999**, *64*, 3157–3161.
(57) Kim, I. S.; Dong, G. Q.; Jung, Y. H. *J. Org. Chem.* **2007**, *72*, 5424–5426.
(58) Shen, X.; Nguyen, T. T.; Koh, M. J.; Xu, D. M.; Speed, A. W. H.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *541*, 380–385.
(59) Kojima, K.; Koyama, K.; Amemiya, S. *Tetrahedron* **1985**, *41*, 4449–4462.

Maleonitrile (from fumaronitrile (Combi-blocks)) was prepared in analogy to a reported procedure[60].

Styrene (Aldrich), 4-allyl-1,2-dimethoxybenzene (Aldrich), 9-borabicyclo[3.3.1]nonane (Alfa Aesar), tetrakis(triphenylphosphine)palladium(0) (Strem), (*E*)-2-bromo-2-butene (Aldrich), (*Z*)-2-bromo-2-butene (Aldrich), acetobromo-α-D-glucose (Oakwood), (*Z*)-pent-2-en-1-ol (Aldrich), tris(pentafluorophenyl)borane (TCI), triphenylborane (Aldrich), silver carbonate (Strem), iodine (Alfa Aesar), palladium acetate (Strem), 4-iodo-1,2-dimethoxybenzene (Combi-blocks), tetrabutylammonium bromide (Combi-blocks), potassium acetate (Aldrich) were used as received.

1.6.2. Preparation of organometallic complexes

Mo-2a[32a], **Mo-2b**[32b], **Mo-3a**[32c], **Mo-3b**[38] and **Mo-3d**[38] were prepared according to previously reported procedures. Mo complexes were manipulated under an atmosphere of N_2 in a glove box.

General procedure for preparation of Mo-3c for spectroscopic analysis: In a N_2-filled glove box, an oven-dried 8 mL vial equipped with a magnetic stir bar was charged with pentafluorophenylimido Mo bispyrrolide complex [61] (59.8 mg, 0.100 mmol), 2,2",4,4",6,6"-hexaisopropyl-[1,1':3',1"-terphenyl]-2'-ol[33] (49.9 mg, 0.100 mmol) and toluene (1.0 mL), resulting in a dark red solution. The vial was capped and the mixture was allowed to stir for 12 h at 60 °C, after which time it was cooled to room temperature and 3-bromopyridinium chloride (21.4 mg, 0.110 mmol) was added. The resulting dark red solution was allowed to stir for 12 h at 22 °C, after which time it was filtered through

(60) Halter, R. J.; Fimmen, R. L.; McMahon, R. J.; Peebles, S. A.; Kuczkowski, R. L.; Stanton, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 12353–12363.
(61) Yuan, J.; Schrock, R. R.; Müller, P.; Axtell, J. C.; Dobereiner, G. E. *Organometallics* **2012**, *31*, 4650–4653.

a short pad of celite and the filtrate was concentrated to dryness. The resulting yellow oil was dissolved in CH_2Cl_2 (1.0 mL) and hexanes (10 mL) were added carefully to maintain two distinct layers. The biphasic mixture was allowed to stand for 12 h. The clear red supernatant liquid was collected and concentrated to dryness to give **Mo-2c** as yellow viscous oil. Only the diagnostic α proton signal of the *syn*-alkylidene of **Mo-2c** is reported: **^{1}H NMR (600 MHz, C_6D_6)**: δ 12.89 (1H, s).

General procedure for preparation of Mo-3e for spectroscopic analysis: In a N_2-filled glove box, an oven-dried 8 mL vial equipped with a magnetic stir bar was charged with pentafluorophenylimido Mo bispyrrolide complex[62] (59.8 mg, 0.100 mmol), 3,3",5,5"-tetra-*tert*-butyl-[1,1':3',1"-terphenyl]-2'-ol[33] (47.0 mg, 0.100 mmol) and toluene (1.0 mL), resulting in a dark red solution. The vial was capped and the mixture was allowed to stir for 4 h at 22 °C, after which time 3-bromopyridinium chloride (21.4 mg, 0.110 mmol) was added. The resulting dark red solution was allowed to stir for 12 h at 22 °C, after which time it was filtered through a short pad of celite and the filtrate was concentrated to dryness. Pentane (2.0 mL) was added to this oil and the mixture was allowed to stir vigorously for 1 h at 22 °C, at which time the precipitate was collected by filtration to give **Mo-2e** as light yellow solid. Only the diagnostic α proton signal of the *syn*-alkylidene of **Mo-2e** is reported: **^{1}H NMR (600 MHz, C_6D_6)**: δ 12.88 (1H, s).

1.6.3. Cross-Metathesis (CM) Reactions

General Procedure: In a N_2-filled glove box, an oven-dried 8 mL vial equipped with a magnetic stir bar was charged with a terminal, a disubsitituted or a trisubstituted alkene substrate and the corresponding alkenyl nitrile cross partner (acrylonitrile, maleonitrile or fumaronitrile). A solution of **Mo-1a**, **Mo-1b**, **Mo-2a**, **Mo-2b, Mo-2c, Mo-2d** or **Mo-2e** in

benzene was then added, followed by the solution of $B(C_6F_5)_3$ in benzene (only for **Mo-2b, Mo-2c, Mo-2d** and **Mo-2e**). The resulting mixture was allowed to stir for 4 to 12 h at 22 to 80 °C, after which the reaction was quenched by the addition of wet (undistilled) $CDCl_3$ (percent conversion was determined by ^1H NMR analysis of the unpurified mixture). Purification was performed through silica gel chromatography.

(*Z*)-9-Bromonon-2-enenitrile (1.3): Following the general procedure, a solution of **Mo-2a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing acrylonitrile solution (0.36 M, 280 μL, 0.100 mmol) and 8-bromooct-1-ene (19.1 mg, 0.100 mmol). The resulting solution was allowed to stir for 4 h at 22 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 81% consumption of 8-bromooct-1-ene. The resulting red oil was purified by silica gel chromatography (2% Et_2O in pentane) to afford 1.3 in >98:2 *Z*:*E* ratio as colorless oil (15.3 mg, 0.0708 mmol, 71% yield). **IR (neat)**: 2933 (s), 2857 (s), 2219 (s), 1621 (w), 1461 (w), 1438 (w), 1259 (w), 740 (m); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.47 (1H, dt, J = 10.9, 7.7 Hz), 5.32 (1H, dt, J = 10.9, 1.3 Hz), 3.41 (2H, t, J = 6.8 Hz), 2.43 (2H, qd, J = 7.5, 1.3 Hz), 1.86 (2H, dq, J = 7.8, 6.8 Hz), 1.55–1.42 (4H, m), 1.41–1.33 (2H, m); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 155.0, 116.1, 99.9, 33.8, 32.7, 31.8, 28.3, 28.2, 28.0; **HRMS [M+H]$^+$** calcd for $C_9H_{15}BrN$: 216.0388, found: 216.0378.

(*Z*)-9-(Benzylthio)non-2-enenitrile (1.8): Following the general procedure, a solution of **Mo-2a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing acrylonitrile solution (0.36 M, 280 μL, 0.100 mmol) and benzyl(oct-7-en-1-yl)sulfane (23.4 mg, 0.100 mmol). The resulting solution was allowed to stir for 4 h at 22 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the

unpurified mixture revealed 82% consumption of benzyl(oct-7-en-1-yl)sulfane. The resulting red oil was purified by silica gel chromatography (2% Et_2O in pentane) to afford 1.8 in >98:2 *Z*:*E* ratio as colorless oil (20.0 mg, 0.0771 mmol, 77% yield). **IR (neat)**: 3061 (w), 3028 (w), 2928 (s), 2856 (s), 2218 (s), 1621 (w), 1494 (w), 1453 (m), 1239 (w), 1071 (w), 740 (m), 701 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.31 (4H, d, J = 4.3 Hz), 7.25 (1H, dt, J = 8.8, 4.2 Hz), 6.46 (1H, dt, J = 10.9, 7.7 Hz), 5.30 (1H, dtd, J = 10.9, 1.4, 0.6 Hz), 3.70 (2H, s), 2.40 (4H, q, J = 6.7, 6.2 Hz), 1.55 (2H, p, J = 7.8 Hz), 1.45 (2H, p, J = 7.3 Hz), 1.34 (4H, m); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 155.1, 138.7, 128.9, 128.6, 127.0, 116.2, 99.7, 36.4, 31.9, 31.4, 29.1, 28.7, 28.6, 28.2; **HRMS $[M+H]^+$** calcd for $C_{16}H_{22}N$: 260.1473, found: 260.1479.

(*Z*)-6-Cyanohex-5-en-1-yl (*tert*-butoxycarbonyl)-*L*-methioninate (1.9): Following the general procedure, a solution of **Mo-2a** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried vial containing acrylonitrile solution (0.36 M, 140 μL, 0.050 mmol) and hex-5-en-1-yl (*tert*-butoxycarbonyl)-*L*-methioninate (16.6 mg, 0.050 mmol). The resulting solution was allowed to stir for 4 h at 22 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 64% consumption of hex-5-en-1-yl (*tert*-butoxycarbonyl)-*L*-methioninate. The resulting red oil was purified by silica gel chromatography (5% → 10% EtOAc in hexanes) to afford 1.9 in >98:2 *Z*:*E* ratio as colorless oil (11.2 mg, 0.0314 mmol, 63% yield). **IR (neat)**: 3363 (w), 2858 (w), 2220 (w), 1709 (s), 1508 (m), 1445 (w), 1391 (w), 1366 (m), 1250 (m), 1161 (s), 1050 (m), 1024 (m), 740 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 6.47 (1H, dt, J = 10.9, 7.7 Hz), 5.35 (1H, dt, J = 10.9, 1.3 Hz), 5.11 (1H, d, J = 6.2 Hz), 4.39 (1H, d, J = 7.9 Hz), 4.16 (2H, tt, J = 10.7, 5.5 Hz), 2.53 (2H, t, J = 8.0 Hz),

2.47 (2H, q, *J* = 7.1 Hz), 2.10 (3H, s), 1.92 (1H, dq, *J* = 14.5, 7.8 Hz), 1.70 (2H, dt, *J* = 13.1, 6.4 Hz), 1.57 (2H, dq, *J* = 15.3, 7.3, 6.7 Hz), 1.44 (9H, s); **^{13}C NMR (150 MHz, $CDCl_3$)**: *δ* 172.5, 155.5, 154.2, 116.0, 100.4, 80.2, 65.0, 53.0, 32.3, 31.5, 30.1, 28.4, 28.1, 24.8, 15.7; **HRMS [M+H]$^+$** calcd for $C_{17}H_{29}N_2O_4S$: 357.1848, found: 357.1864.

(*Z*)-9-(Oxiran-2-yl)non-2-enenitrile (1.10): Following the general procedure, a solution of **Mo-2a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing acrylonitrile solution (0.36 M, 280 μL, 0.100 mmol) and 2-(oct-7-en-1-yl)oxirane (15.4 mg, 0.100 mmol). The resulting solution was allowed to stir for 4 h at 22 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 80% consumption of 2-(oct-7-en-1-yl)oxirane. The resulting red oil was purified by silica gel chromatography (2% → 10% Et_2O in pentane) to afford 1.10 in >98:2 *Z*:*E* ratio as colorless oil (12.6 mg, 0.0703 mmol, 70% yield). **IR (neat)**: 2927 (s), 2857 (s), 2220 (s), 1733 (w), 1620 (w), 1464 (m), 1260 (w), 914 (w), 835 (m), 740 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 6.47 (1H, dt, *J* = 10.9, 7.7 Hz), 5.31 (1H, dd, *J* = 10.9, 1.5 Hz), 2.90 (1H, dd, *J* = 4.5, 2.2 Hz), 2.83–2.70 (1H, m), 2.55–2.33 (3H, m), 1.50 (6H, m), 1.37 (4H, m); **^{13}C NMR (100 MHz, $CDCl_3$)**: *δ* 155.2, 116.2, 99.7, 52.4, 47.2, 32.5, 31.9, 29.2, 29.0, 28.2, 26.0; **HRMS [M+H]$^+$** calcd for $C_{11}H_{18}NO$: 180.1288, found: 180.1386.

(*Z*)-11-(Triisopropylsilyl)undec-2-en-10-ynenitrile (1.11): Following the general procedure, a solution of **Mo-2a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing acrylonitrile solution (0.36 M, 280 μL, 0.100 mmol) and dec-9-en-1-yn-1-yltriisopropylsilane (26.8 mg, 0.100 mmol). The resulting solution was allowed to stir for 4 h at 22 °C. The reaction was quenched by the addition

of wet $CDCl_3$ and analysis of the unpurified mixture revealed 83% consumption of dec-9-en-1-yn-1-yltriisopropylsilane. The resulting red oil was purified by silica gel chromatography (pentane → 1% Et_2O in pentane) to afford **1.11** in >98:2 *Z*:*E* ratio as colorless oil (23.0 mg, 0.0783 mmol, 78% yield). **IR (neat)**: 2937 (s), 2863 (s), 2221 (s), 2171 (s), 1621 (w), 1462 (m), 995 (m), 883 (m), 740 (m), 676 (s), 661 (s), 521(m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.48 (1H, dtd, J = 10.9, 7.7, 0.7 Hz), 5.31 (1H, dq, J = 10.9, 1.3 Hz), 2.43 (2H, q, J = 7.2 Hz), 2.25 (2H, t, J = 6.7 Hz), 1.49 (6H, m), 1.37 (2H, q, J = 8.4, 7.7 Hz), 1.10–0.98 (21H, m); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 155.2, 116.2, 109.1, 99.7, 80.4, 32.0, 28.8, 28.6, 28.5, 28.3, 19.9, 18.8, 11.4; **HRMS [M+H]$^+$** calcd for $C_{20}H_{36}NSi$: 318.2617, found: 318.2610.

(*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)hex-2-enenitrile (1.12): Following the general procedure, a solution of **Mo-2a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing acrylonitrile solution (0.36 M, 280 μL, 0.100 mmol) and *tert*-butyldimethyl(pent-4-en-1-yloxy)silane (20.0 mg, 0.100 mmol). The resulting solution was allowed to stir for 4 h at 22 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 83% consumption of *tert*-butyldimethyl(pent-4-en-1-yloxy)silane. The resulting oil was purified by silica gel chromatography (1% → 2% Et_2O in pentane) to afford **1.12** in >98:2 *Z*:*E* ratio as colorless oil (16.5 mg, 0.0732 mmol, 73% yield). **IR (neat)**: 2953 (m), 2929 (m), 2857 (m), 2220 (w), 1623 (w), 1472 (m), 1255 (m), 1099 (s), 835 (s), 776 (s), 736 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.53 (1H, dt, J = 10.9, 7.7 Hz), 5.30 (1H, dt, J = 10.9, 1.4 Hz), 3.65 (2H, t, J = 6.1 Hz), 2.50 (2H, qd, J = 7.5, 1.4 Hz), 1.75–1.63 (2H, m), 0.89 (9H,

s), 0.05 (6H, s); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 155.2, 116.1, 99.6, 62.3, 31.5, 28.8, 26.0, 18.4, -5.2; **HRMS [M+H]$^+$** calcd for $C_{12}H_{24}NOSi$: 226.1627, found: 226.1632.

Benzyl (*Z*)-6-cyanohex-5-enoate (1.13): Following the general procedure, a solution of **Mo-2a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing acrylonitrile solution (0.36 M, 280 μL, 0.100 mmol) and benzyl hex-5-enoate (20.4 mg, 0.100 mmol). The resulting solution was allowed to stir for 4 h at 22 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 71% consumption of benzyl hex-5-enoate. The resulting red oil was purified by silica gel chromatography (20% Et_2O in pentane) to afford 1.13 in >98:2 *Z*:*E* ratio as colorless oil (14.5 mg, 0.0632 mmol, 63% yield). **IR (neat)**: 2944 (w), 2219 (m), 1731 (s), 1498 (m), 1419 (w), 1213 (m), 1152 (s), 1082 (w), 1002 (w), 729 (m), 698 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.48–7.27 (5H, m), 6.45 (1H, dt, J = 10.9, 7.7 Hz), 5.32 (1H, dt, J = 10.9, 1.4 Hz), 5.13 (2H, s), 2.48 (2H, qd, J = 7.6, 1.4 Hz), 2.42 (2H, t, J = 7.4 Hz), 1.85 (2H, p, J = 7.5 Hz); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 172.6, 153.6, 135.8, 128.6, 128.30, 128.29, 115.7, 100.5, 66.4, 33.3, 31.1, 23.4; **HRMS [M+H]$^+$** calcd for $C_{14}H_{16}NO_2$: 230.1181, found: 230.1192.

(*Z*)-9-(1,3-Dioxoisoindolin-2-yl)non-2-enenitrile (1.14): Following the general procedure, a solution of **Mo-2a** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried vial containing acrylonitrile solution (0.36 M, 140 μL, 0.050 mmol) and 2-(oct-7-en-1-yl)isoindoline-1,3-dione (12.8 mg, 0.050 mmol). The resulting solution was allowed to stir for 4 h at 22 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 89% consumption of 2-(oct-7-en-1-yl)isoindoline-1,3-dione. The resulting red oil was purified by silica gel

chromatography (5% EtOAc in pentane) to afford 1.14 in >98:2 *Z*:*E* ratio as colorless oil (12.2 mg, 0.0432 mmol, 86% yield). **IR (neat)**: 2932 (w), 2858 (w), 2218 (w), 1772 (w), 1709 (s), 1396 (m), 1369 (w), 1054 (w), 720 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.84 (2H, dd, *J* = 5.4, 3.1 Hz), 7.70 (2H, dd, *J* = 5.5, 3.0 Hz), 6.46 (1H, dt, *J* = 10.9, 7.7 Hz), 5.30 (1H, dt, *J* = 10.9, 1.4 Hz), 3.68 (2H, t, *J* = 7.2 Hz), 2.41 (2H, qd, *J* = 7.5, 1.4 Hz), 1.68 (2H, p, *J* = 7.5 Hz), 1.46 (2H, q, J = 7.0, 6.4 Hz), 1.42–1.34 (4H, m); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 168.6, 155.1, 134.0, 132.3, 123.3, 116.1, 99.8, 38.0, 31.9, 28.7, 28.5, 28.2, 26.6; **HRMS [M+H]$^+$** calcd for $C_{17}H_{19}N_2O_2$: 283.1447, found: 283.1461.

(*Z*)-4-(Trimethylsilyl)but-2-enenitrile (1.15): Following the general procedure, a solution of **Mo-2a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing acrylonitrile solution (0.36 M, 280 μL, 0.100 mmol) and allyltrimethylsilane (11.4 mg, 0.100 mmol). The resulting solution was allowed to stir for 4 h at 22 °C. The reaction was quenched by the addition of wet $CDCl_3$ and consumption of allyltrimethylsilane was not determined due to volatility of the starting material. The resulting red oil was purified by silica gel chromatography (pentane → 2% Et_2O in pentane) to afford 1.15 in >98:2 *Z*:*E* ratio as colorless oil (10.3 mg, 0.0740 mmol, 74% yield). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.54 (1H, dt, *J* = 10.8, 9.1 Hz), 5.15 (1H, dt, *J* = 10.8, 1.1 Hz), 2.01 (2H, dd, *J* = 9.1, 1.1 Hz), 0.11 (9H, d, *J* = 1.0 Hz). The spectral data of this compound is consistent with those previously reported[27].

(*Z*)-4-(Triphenylstannyl)but-2-enenitrile (1.16): Following the general procedure, a solution of **Mo-2a** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried vial containing acrylonitrile solution (0.36 M, 140 μL, 0.050 mmol) and allyltriphenylstannane (19.6 mg, 0.050 mmol). The resulting solution was allowed to stir

for 4 h at 22 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 84% consumption of allyltriphenylstannane. The resulting yellow tar was purified by silica gel chromatography (5% EtOAc in hexanes) to afford **1.16** in >98:2 *Z*:*E* ratio as off-white solid (14.7 mg, 0.0353 mmol, 71% yield). **MP**: 98–100 °C; **IR (neat)**: 3064 (w), 3047 (w), 2211 (w), 1599 (w), 1480 (w), 1429 (m), 1075 (m), 728 (s), 697 (s), 446 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.66–7.48 (6H, m), 7.46–7.39 (9H, m), 6.73 (1H, dt, J = 10.6, 9.4 Hz), 4.97 (1H, dt, J = 10.6, 1.0 Hz), 2.84 (2H, ddd, J = 9.5, 1.0, 0.5 Hz); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 153.8, 137.0, 136.8, 129.7, 129.0, 116.9, 94.2, 19.4; **HRMS [M+H]$^+$** calcd for $C_{22}H_{20}NSn$: 418.0618, found: 418.0634.

(*Z*)-4-((*tert*-Butyldimethylsilyl)oxy)but-2-enenitrile (1.17): Following the general procedure, a solution of **Mo-2a** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried vial containing acrylonitrile solution (0.36 M, 140 μL, 0.050 mmol) and (allyloxy)(*tert*-butyl)dimethylsilane (8.6 mg, 0.050 mmol). The resulting solution was allowed to stir for 4 h at 22 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 70% consumption of (allyloxy)(*tert*-butyl)dimethylsilane. The resulting red oil was purified by silica gel chromatography (pentane → 1% Et_2O in pentane) to afford **1.17** in >98:2 *Z*:*E* ratio as colorless oil (4.1 mg, 0.0208 mmol, 42% yield). **IR (neat)**: 2955 (w), 2929 (m), 2857 (w), 2222 (w), 1472 (w), 1256 (m), 1107 (m), 838 (s), 778 (s), 677 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 6.55 (1H, dt, J = 11.3, 5.6 Hz), 5.37 (1H, dt, J = 11.3, 1.8 Hz), 4.49 (2H, dd, J = 5.6, 1.9 Hz), 0.92 (9H, s), 0.11 (6H, s); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ

153.6, 115.4, 98.8, 62.2, 26.0, 18.5, -5.2; **HRMS [M+H]$^+$** calcd for $C_{10}H_{20}NOSi$: 198.1314, found: 198.1309.

(*Z*)-5-((Triethylsilyl)oxy)hex-2-enenitrile (1.19): Following the general procedure, a solution of **Mo-2a** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried vial containing acrylonitrile solution (0.36 M, 140 μL, 0.050 mmol) and triethyl(pent-4-en-2-yloxy)silane (10.2 mg, 0.050 mmol). The resulting solution was allowed to stir for 4 h at 22 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 70% consumption of triethyl(pent-4-en-2-yloxy)silane. The resulting red oil was purified by silica gel chromatography (pentane → 1% Et_2O in pentane) to afford 1.19 in >98:2 *Z*:*E* ratio as colorless oil (4.6 mg, 0.0204 mmol, 41% yield). **IR (neat)**: 2956 (m), 2877 (m), 2221 (w), 1459 (w), 1378 (w), 1239 (w), 1131 (m), 1099 (m), 1004 (s), 739 (s); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.61 (1H, dt, J = 10.7, 7.5 Hz), 5.40 (1H, dd, J = 10.7, 1.4 Hz), 4.00 (1H, h, J = 5.9 Hz), 2.56 (3H, dt, J = 14.1, 7.7 Hz), 1.19 (3H, d, J = 6.1Hz), 0.96 (9H, t, J = 7.9 Hz), 0.60 (6H, q, J = 7.9 Hz); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 152.1, 116.2, 101.1, 67.2, 41.7, 23.8, 7.0, 5.0; **HRMS [M+H]$^+$** calcd for $C_{12}H_{24}NOSi$: 226.1627, found: 226.1631.

(Z)-4-(4-Methoxyphenyl)but-2-enenitrile (1.20): Following the general procedure, a solution of **Mo-2a** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried vial containing acrylonitrile solution (0.36 M, 140 μL, 0.050 mmol) and 1-allyl-4-methoxybenzene (7.4 mg, 0.050 mmol). The resulting solution was allowed to stir for 4 h at 22 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 56% consumption of (allyloxy)(*tert*-butyl)dimethylsilane. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in

pentane) to afford 1.20 in >98:2 *Z*:*E* ratio as colorless oil (4.0 mg, 0.0231 mmol, 46% yield). **IR (neat)**: 2951 (w), 2921 (W), 2838 (w), 2220 (w), 1610 (w), 1510 (s), 1107 (m), 1463 (w), 1441 (w), 1248 (s), 1178 (m), 1111 (w), 1034 (m), 817 (m), 720 (w), 400 (w); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.17–7.08 (2H, m), 6.90–6.84 (2H, m), 6.58 (1H, dtd, *J* = 10.8, 7.8, 0.9 Hz), 5.38 (1H, dt, *J* = 10.8, 1.3 Hz), 3.80 (3H, s), 3.73–3.64 (2H, m); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 158.8, 153.4, 129.7, 129.0, 116.1, 114.5, 99.6, 55.5, 37.3; **HRMS [M+H]$^+$** calcd for $C_{11}H_{12}NO$: 174.0919, found: 174.0911.

(*Z*)-4-(1*H*-Indol-3-yl)but-2-enenitrile (1.21): Following the general procedure, a solution of **Mo-2a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing acrylonitrile solution (0.36 M, 280 μL, 0.100 mmol) and 3-allyl-1*H*-indole (15.7 mg, 0.100 mmol). The resulting solution was allowed to stir for 4 h at 22 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 75% consumption of 3-allyl-1*H*-indole. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in pentane) to afford 1.21 in >98:2 *Z*:*E* ratio as red oil (12.6 mg, 0.0691 mmol, 69% yield). **IR (neat)**: 3411 (s), 3059 (w), 2854 (w), 2220 (m), 1619 (w), 1457 (m), 1423 (m), 1339 (m), 1230 (m), 1126 (m), 1011 (w), 784 (m), 743 (s), 711 (m); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.07 (1H, s), 7.62 (1H, d, *J* = 7.8 Hz), 7.39 (1H, d, *J* = 8.1 Hz), 7.29–7.20 (1H, m), 7.17 (1H, t, *J* = 7.4 Hz), 7.05 (1H, s), 6.69 (1H, dt, *J* = 10.7, 7.6 Hz), 5.40 (1H, d, *J* = 10.7 Hz), 3.89 (2H, d, *J* = 7.6 Hz); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 153.5, 136.4, 127.0, 122.6, 122.2, 119.9, 118.7, 116.2, 111.4, 99.4, 99.4, 28.1; **HRMS [M+H]$^+$** calcd for $C_{12}H_{11}N_2$: 183.0922, found: 183.0916.

(*Z*)-4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enenitrile (1.18): Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing *Z*-crotylboronic acid pinacol ester (18.2 mg, 0.100 mmol) and maleonitrile (11.7 mg, 0.150 mmol) in 0.30 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 95% consumption of *Z*-crotylboronic acid pinacol ester. The resulting red oil was purified by Kugelrohr distillation (90 ºC, 1 torr) to afford a mixture of **1.18** and initiation product (*Z*)-4-methyl-4-phenylpent-2-enenitrile in >98:2 *Z*:*E* ratio as colorless oil (14.3 mg, 87% purity by weight accounting for the mass of initiation product, 0.0644 mmol, 64% yield). **IR (neat)**: 2931 (m), 2858 (m), 2218 (m), 1602 (m), 1460 (w), 1440 (w), 738 (s); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.60 (1H, dt, *J* = 10.8, 8.4 Hz), 5.28 (1H, dt, *J* = 10.8, 1.4 Hz), 2.13 (2H, d, *J* = 8.1 Hz), 1.26 (12H, s); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 151.8, 99.1, 84.1, 24.9, 24.7. **HRMS [M+H]$^+$** calcd for $C_{10}H_{17}BNO_2$: 194.1347, found: 194.1343.

(*Z*)-4-Phenylpent-2-enenitrile (1.25): Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-pent-3-en-2-ylbenzene (14.6 mg, 0.100 mmol) and maleonitrile (11.7 mg, 0.150 mmol) in 0.30 mL benzene. The resulting solution was allowed to stir for 4 h at 22 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 87% consumption of (*Z*)-pent-3-en-2-ylbenzene. The resulting red oil was purified by silica gel chromatography (1% → 2% Et_2O in hexanes) to afford a 13.6 mg mixture of inseparable 1.25 in >98:2 *Z*:*E* ratio (12.9 mg, 0.0820 mmol, 82% yield) and initiation product (*Z*)-4-methyl-4-phenylpent-2-enenitrile in >98:2

Z:*E* ratio (0.7 mg, 0.00410 mmol, 4.1% yield) as colorless oil. **IR (neat)**: 3063 (w), 3030 (w), 2971 (w), 2929 (w), 2219 (m), 1619 (w), 1600 (w), 1494 (m), 1452 (m), 1014 (m), 743 (s), 698 (s), 510 (m); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.35 (2H, t, J = 7.6 Hz), 7.27 (3H, d, J = 7.5 Hz), 6.54 (1H, td, J = 10.8, 1.0 Hz), 5.29 (1H, dd, J = 10.8, 0.6 Hz), 4.09 (1H, dq, J = 10.2, 7.0 Hz), 1.48 (3H, d, J = 6.9 Hz); initiation product (resolved signals only): δ 5.36 (1H, d, J = 12.2 Hz), 1.64 (6H, s); **^{13}C NMR (150 MHz, $CDCl_3$)**: **2q:** δ 158.6, 142.4, 129.0, 127.3, 127.0, 116.1, 97.8, 42.2, 20.5; initiation product (resolved signals only): δ 28.5; **HRMS [M+H]$^+$** calcd for $C_{11}H_{12}N$: 158.0970, found: 158.0972.

(*Z*)-5-((*tert*-Butyldiphenylsilyl)oxy)-4-methylpent-2-enenitrile (1.26): Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-*tert*-butyl((2-methylpent-3-en-1-yl)oxy)diphenylsilane (16.9 mg, 0.050 mmol) and maleonitrile (5.9 mg, 0.075 mmol) in 0.15 mL benzene. The resulting solution was allowed to stir for 4 h at 22 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 76% consumption of (*Z*)-*tert*-butyl((2-methylpent-3-en-1-yl)oxy)diphenylsilane. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in hexanes) to afford a 12.6 mg mixture of inseparable 1.26 in >98:2 *Z*:*E* ratio (12.3 mg, 0.0350 mmol, 70% yield) and initiation product (*Z*)-4-methyl-4-phenylpent-2-enenitrile in >98:2 *Z*:*E* ratio (0.3 mg, 0.00175 mmol, 3.5% yield) as colorless oil. **IR (neat)**: 3070 (w), 2931 (w), 2858 (w), 2220 (w), 1472 (w), 1428 (m), 1106 (s), 1029 (w), 823 (m), 740 (m), 700 (s), 614 (m), 504 (s); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.65 (4H, ddd, J = 8.0, 3.6, 1.5 Hz), 7.47–7.37 (6H, m), 6.39 (1H, dd, J = 10.9, 10.1 Hz), 5.33 (1H, dd, J = 10.9, 0.7 Hz), 3.65 (1H, dd, J = 10.0, 5.0 Hz), 3.56 (1H, dd, J = 9.9, 6.7 Hz), 3.04 (1H, dtd, J =

10.6, 6.7, 5.4 Hz), 1.06 (12H, s, J = 8.0 Hz); initiation product (resolved signals only): δ 6.54 (1H, d, J = 12.2 Hz), 1.65 (6H, s); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 157.9, 135.7, 133.48, 133.43, 129.91, 129.89, 127.87, 127.86, 116.2, 99.6, 67.4, 39.7, 27.0, 19.4, 16.2; initiation product (resolved peaks only): δ 28.5; **HRMS [M+H]$^+$** calcd for $C_{22}H_{28}NOSi$: 350.1940, found: 350.1957.

***tert*-Butyl (*Z*)-4-(2-cyanovinyl)piperidine-1-carboxylate (1.27)**: Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing *tert*-butyl (*Z*)-4-(prop-1-en-1-yl)piperidine-1-carboxylate (22.5 mg, 0.100 mmol) and maleonitrile (11.7 mg, 0.150 mmol) in 0.30 mL benzene. The resulting solution was allowed to stir for 4 h at 22 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 95% consumption of *tert*-butyl (*Z*)-4-(prop-1-en-1-yl)piperidine-1-carboxylate. The resulting red oil was purified by silica gel chromatography (2% →5% EtOAc in hexanes) to afford **1.27** in >98:2 *Z*:*E* ratio as colorless oil (21.2 mg, 0.0897 mmol, 90% yield). **IR (neat)**: 2975 (w), 2933 (w), 2853 (w), 2219 (w), 1688 (s), 1447 (m), 1393 (m), 1293 (w), 1243 (m), 1168 (s), 1133 (m), 996 (w), 752 (w); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.29 (1H, ddd, J = 10.9, 9.8, 1.3 Hz), 5.29 (1H, dd, J = 10.9, 1.3 Hz), 4.13 (2H, s), 3.11–2.53 (3H, m), 1.69 (2H, d, J = 12.6 Hz), 1.45 (9H, s), 1.36 (2H, qd, J = 12.2, 3.7 Hz); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 157.8, 154.8, 115.9, 98.9, 79.8, 43.1, 39.4, 30.8, 28.6; **HRMS [M+H]$^+$** calcd for $C_{13}H_{21}N_2O_2$: 237.1603, found: 237.1610.

(*Z*)-5-(Dibenzylamino)pent-2-enenitrile (1.28): Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-*N,N*-dibenzylhex-3-en-1-amine (15.8 mg, 0. 050 mmol)

and maleonitrile (5.9 mg, 0.075 mmol) in 0.15 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed >98% consumption of (*Z*)-*N,N*-dibenzylhex-3-en-1-amine. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in Hexanes) to afford **1.28** in >98:2 *Z*:*E* ratio as colorless oil (13.2 mg, 0.0478 mmol, 96% yield). **IR (neat)**: 3062 (w), 3028 (w), 2924 (w), 2802 (w), 2219 (w), 1621 (w), 1494 (m), 1452 (m), 1367 (w), 1128 (w), 1074 (w), 746 (s), 699 (s); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.38–7.29 (8H, m), 7.28–7.23 (2H, m), 6.48–6.41 (1H, m), 5.32 (1H, dd, *J* = 11.0, 1.3 Hz), 3.60 (4H, s), 2.61 (4H, s); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 153.9, 139.3, 129.0, 128.4, 127.2, 116.2, 100.1, 58.3, 51.4, 29.8; **HRMS $[M+H]^+$** calcd for $C_{19}H_{21}N_2$: 277.1705, found: 277.1699.

(2*Z*,4*E*)-5-Phenylpenta-2,4-dienenitrile (1.29): Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing ((1*E*,3*Z*)-penta-1,3-dien-1-yl)benzene (14.4 mg, 0.100 mmol) and maleonitrile (11.7 mg, 0.150 mmol) in 0.30 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 91% consumption of ((1*E*,3*Z*)-penta-1,3-dien-1-yl)benzene. The resulting red oil was purified by silica gel chromatography (1% → 2% Et_2O in Hexanes) to afford a 10.6 mg mixture of inseparable **1.29** in 98:2 *Z*:*E* ratio (10.3 mg, 0.0664 mmol, 66% yield) and initiation product (*Z*)-4-methyl-4-phenylpent-2-enenitrile in >98:2 *Z*:*E* ratio (0.3 mg, 0.00175 mmol, 1.8% yield) as colorless oil. **IR (neat)**: 3064 (w), 3031 (w), 2927 (w), 2211 (s), 1623 (s), 1582 (m), 1494 (w), 1450 (m), 989 (m), 945 (w), 735 (s), 690 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** *Z* isomer (major): δ

7.52 (2H, dt, *J* = 8.4, 2.2 Hz), 7.38 (3H, dddd, *J* = 8.7, 7.0, 5.8, 1.7 Hz), 7.24 (1H, ddd, *J* = 15.5, 11.2, 0.9 Hz), 7.03–6.89 (2H, m), 5.26 (1H, dt, *J* = 10.6, 0.9 Hz); *E* isomer (resolved signals only): *δ* 5.44 (1H, d, *J* = 16.0 Hz); initiation product (resolved signals only): *δ* 6.53 (1H, d, *J* = 12.1 Hz), 5.36 (1H, d, *J* = 12.2 Hz), 1.64 (6H, s); **^{13}C NMR (100 MHz, $CDCl_3$)**: *Z* isomer (major): *δ* 149.4, 141.8, 135.4, 129.9, 129.1, 127.8, 124.3, 116.8, 96.7; **HRMS [M+H]$^+$** calcd for $C_{11}H_{10}N$: 156.0813, found: 156.0815.

(2*Z*,5*E*)-6-Phenylhexa-2,5-dienenitrile (1.30): Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing ((1*E*,4*Z*)-hexa-1,4-dien-1-yl)benzene (15.8 mg, 0.100 mmol) and maleonitrile (11.7 mg, 0.150 mmol) in 0.30 mL benzene. The resulting solution was allowed to stir for 4 h at 22 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 87% consumption of ((1*E*,4*Z*)-hexa-1,4-dien-1-yl)benzene. The resulting red oil was purified by silica gel chromatography (1% → 2% Et_2O in hexanes) to afford a 10.0 mg mixture of inseparable 1.30 in >98:2 *Z*:*E* ratio (9.7 mg, 0.0573 mmol, 57% yield) and initiation product (*Z*)-4-methyl-4-phenylpent-2-enenitrile in >98:2 *Z*:*E* ratio (0.3 mg, 0.00175 mmol, 1.8% yield) as colorless oil. **IR (neat)**: 3060 (w), 3029 (w), 2920 (w), 2219 (m), 1619 (w), 1496 (w), 1448 (w), 966 (m), 74 (s), 693 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 7.38–7.29 (4H, m), 7.28–7.20 (1H, m), 6.55 (1H, dt, *J* = 10.9, 7.6 Hz), 6.49 (1H, dt, *J* = 15.8, 1.6 Hz), 6.15 (1H, dt, *J* = 15.8, 6.7 Hz), 5.42 (1H, dt, *J* = 10.8, 1.4 Hz), 3.34 (2H, ddt, *J* = 8.0, 6.7, 1.5 Hz); initiation product (resolved signals only): *δ* 5.36 (1H, d, *J* = 12.1 Hz), 1.64 (6H, s); **^{13}C NMR (100 MHz, $CDCl_3$)**: *δ* 152.1, 136.9, 133.0, 128.8, 127.8, 126.3, 124.3, 115.9, 100.5, 35.2; **HRMS [M+H]$^+$** calcd for $C_{12}H_{12}N$: 170.0970, found: 170.0964.

(*Z*)-3-Phenylacrylonitrile (1.22): Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing a solution of *cis*-β-methylstyrene (11.8 mg, 0.100 mmol) and maleonitrile (11.7 mg, 0.150 mmol, 1.50 equiv) in 0.30 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed >98% consumption of *cis*-β-methylstyrene. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in hexanes) to afford a 11.4 mg mixture of inseparable **1.22** in >98:2 *Z*:*E* ratio (10.8 mg, 0.0838 mmol, 84% yield) and initiation product (*Z*)-4-methyl-4-phenylpent-2-enenitrile in >98:2 *Z*:*E* ratio (0.6 mg, 0.00335 mmol, 3.4% yield) as colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.84–7.78 (2H, m), 7.48–7.42 (3H, m), 7.13 (1H, d, J = 12.1 Hz), 5.45 (1H, d, J = 12.1 Hz); initiation product (resolved signals only): δ 6.53 (1H, d, J = 12.2 Hz), 5.36 (1H, d, J = 12.1 Hz), 1.64 (6H, s). The spectral data of this compound is consistent with those previously reported[62].

(*Z*)-3-(4-(Trifluoromethyl)phenyl)acrylonitrile (1.31): Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1-(prop-1-en-1-yl)-4-(trifluoromethyl)benzene (18.6 mg, 0.100 mmol) and maleonitrile (11.7 mg, 0.150 mmol, 1.50 equiv) in 0.30 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed >98% consumption of (*Z*)-1-(prop-1-en-1-yl)-4-(trifluoromethyl)benzene. The resulting red oil was purified by silica gel chromatography

(62) Tomioka, T.; Takahashi, Y.; Vaughan, T. G.; Yanase, T. *Org. Lett.* **2010**, *12*, 2171–2173.

(2% → 5% Et_2O in hexanes) to afford 1.31 in >98:2 *Z*:*E* ratio as colorless oil (15.2 mg, 0.0771 mmol, 77% yield). **IR (neat)**: 3070 (w), 2219 (w), 1619 (w), 1418 (w), 1323 (s), 1169 (m), 1124 (m), 1068 (m), 1016 (w), 850 (m), 605(w); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.96–7.87 (2H, m), 7.75–7.68 (2H, m), 7.19 (1H, d, J = 12.1 Hz), 5.61 (1H, d, J = 12.1 Hz); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 147.2, 136.8 (q, $J_{C\text{-}F}$ = 1.5 Hz), 132.5 (q, $J_{C\text{-}F}$ = 32.8 Hz), 129.3, 126.1 (q, $J_{C\text{-}F}$ = 3.8 Hz), 123.8 (q, $J_{C\text{-}F}$ = 272.4 Hz), 116.8, 98.1; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -63.1; **HRMS [M+H]$^+$** calcd for $C_{10}H_7F_3N$: 198.0531, found: 198.0521.

(*Z*)-3-(4-Fluorophenyl)acrylonitrile (1.32): Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1-fluoro-4-(prop-1-en-1-yl)benzene (13.6 mg, 0.100 mmol) and maleonitrile (11.7 mg, 0.150 mmol, 1.50 equiv) in 0.30 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed >98% consumption of (*Z*)-1-fluoro-4-(prop-1-en-1-yl)benzene. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in hexanes) to afford a 10.0 mg mixture of inseparable 1.32 in 97:3 *Z*:*E* ratio (9.7 mg, 0.0659 mmol, 66% yield) and initiation product (*Z*)-4-methyl-4-phenylpent-2-enenitrile in >98:2 *Z*:*E* ratio (0.3 mg, 0.00175 mmol, 1.8% yield) as colorless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** *Z* isomer (major): δ 7.89–7.79 (2H, m), 7.18–7.11 (2H, m), 7.09 (1H, d, J = 12.1 Hz, 1H), 5.43 (1H, dd, J = 12.1, 0.7 Hz); *E* isomer (resolved signals only): δ 5.81 (1H, d, J = 16.7 Hz); initiation product (resolved signals only): δ 6.53 (1H, d, J = 12.2 Hz), 5.35 (1H, d, J = 12.1 Hz), 1.64 (6H, s); **HRMS**

[M+H]$^+$ calcd for C_9H_7FN: 148.0563, found: 148.0568. The spectral data of this compound is consistent with those previously reported[63].

(*Z*)-3-(4-Bromophenyl)acrylonitrile (1.33): Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1-bromo-4-(3-methylbut-1-en-1-yl)benzene (22.5 mg, 0.100 mmol) and maleonitrile (11.7 mg, 0.150 mmol) in 0.30 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$. Consumption of (*Z*)-1-bromo-4-(3-methylbut-1-en-1-yl)benzene was not determined due to overlapping of peaks between starting material and product. The resulting red oil was purified by silica gel chromatography (1% → 2% Et_2O in hexanes) to afford a 13.4 mg mixture of inseparable 1.33 in 98:2 *Z*:*E* ratio (13.2 mg, 0.0634 mmol, 63% yield) and initiation product (*Z*)-4-methyl-4-phenylpent-2-enenitrile in >98:2 *Z*:*E* ratio (0.2 mg, 0.00117 mmol, 1.2% yield) as off-white solid. **M.p.**: 62–64 °C; **IR (neat)**: 3067 (w), 2215 (m), 1614 (m), 1587 (m), 1487 (s), 1391 (w), 1074 (s), 1010 (m), 835 (s), 752 (w), 698 (w), 573 (w), 463 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *Z* isomer (major): δ 7.71–7.65 (2H, m), 7.62–7.55 (2H, m), 7.07 (1H, d, J = 12.1 Hz), 5.49 (1H, d, J = 12.1 Hz); *E* isomer (resolved signals only): δ 5.88 (1H, d, J = 16.7 Hz); initiation product (resolved signals only): δ 6.53 (1H, d, J = 12.2 Hz), 5.35 (1H, d, J = 12.2 Hz), 1.64 (6H, s); **^{13}C NMR (125 MHz, $CDCl_3$)**: **2y:** δ 147.5, 132.5, 132.4, 130.5, 125.5, 117.2, 96.0, 77.4, 77.2, 76.9; **HRMS [M+H]$^+$** calcd for C_9H_7NBr: 207.9762, found: 207.9755.

(*Z*)-3-(4-Iodophenyl)acrylonitrile (1.34): Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried

(63) Fang, F.; Li, Y.; Tian, S.-K. *Eur. J. Org. Chem.* **2011**, *6*, 1084–1091.

vial containing (*Z*)-1-iodo-4-(3-methylbut-1-en-1-yl)benzene (27.2 mg, 0.100 mmol) and maleonitrile (11.7 mg, 0.150 mmol) in 0.30 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$. Consumption of (*Z*)-1-iodo-4-(3-methylbut-1-en-1-yl)benzene was not determined due to overlapping of peaks between starting material and product. The resulting red oil was purified by silica gel chromatography (1% → 2% Et_2O in hexanes) to afford a 14.7 mg mixture of inseparable 1.34 in 98:2 *Z*:*E* ratio (14.4 mg, 0.0564 mmol, 56% yield) and initiation product (*Z*)-4-methyl-4-phenylpent-2-enenitrile in >98:2 *Z*:*E* ratio (0.3 mg, 0.00176 mmol, 1.8% yield) as off-white solid. **M.p.**: 66–68 °C; **IR (neat)**: 3064 (w), 2214 (m), 1612 (m), 1582 (m), 1484 (s), 1389 (w), 1062 (m), 1005 (s), 831 (s), 787 (w), 697 (w), 574 (w), 457 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *Z* isomer (major): δ 7.91–7.75 (2H, m), 7.63–7.48 (2H, m), 7.05 (1H, d, J = 12.1 Hz), 5.48 (1H, d, J = 12.1 Hz); *E* isomer (resolved signals only): δ 5.89 (1H, d, J = 16.6 Hz); initiation product (resolved signals only): δ 6.53 (1H, d, J = 12.2 Hz), 5.35 (1H, d, J = 12.2 Hz), 1.64 (6H, s); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 147.5, 132.5, 132.4, 130.5, 125.5, 117.2, 96.0, 77.4, 77.2, 76.9; **HRMS [M+H]$^+$** calcd for C_9H_7NI: 255.9623, found: 255.9619.

(*Z*)-3-(3,5-Dimethoxyphenyl)acrylonitrile (1.35): Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 120 μL, 12.0 μmol) was transferred by syringe to an oven-dried vial containing a solution of (*Z*)-1,3-dimethoxy-5-(prop-1-en-1-yl)benzene (42.9 mg, 0.241 mmol) and maleonitrile (28.2 mg, 0.361 mmol) in 0.36 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed >98% consumption of (*Z*)-1,3-dimethoxy-5-(prop-1-en-1-yl)benzene. The resulting red oil was

purified by silica gel chromatography (5% → 10% Et_2O in pentane) to afford **1.35** in >98:2 *Z*:*E* ratio as off-white solid (36.1 mg, 0.191 mmol, 79% yield). **IR (in CH_2Cl_2)**: 2961 (w), 2937 (w), 2839 (w), 2211 (w), 1585 (s), 1456 (m), 1426 (m), 1301 (m), 1203 (s), 1156 (s), 1064 (m), 837 (m), 677 (m); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.04 (1H, d, J = 12.1 Hz), 6.96 (2H, d, J = 2.2 Hz), 6.54 (1H, t, J = 2.2 Hz), 5.43 (1H, d, J = 12.1 Hz), 3.82 (6H, s); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 161.1, 148.9, 148.9, 147.1, 135.3, 117.5, 106.9, 103.7, 95.5, 55.6, 55.6; **HRMS $[M+H]^+$** $C_{11}H_{12}NO_2$ calcd 190.0868, found 190.0872.

(*Z*)-3-(2-Fluorophenyl)acrylonitrile (1.36): Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing a solution of (*Z*)-1-fluoro-2-(prop-1-en-1-yl)benzene (13.6 mg, 0.100 mmol) and maleonitrile (11.7 mg, 0.150 mmol) in 0.3 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed >98% consumption of (*Z*)-1-fluoro-2-(prop-1-en-1-yl)benzene. The resulting red oil was purified by silica gel chromatography (pentane → 2% Et_2O in pentane) to afford **1.36** in >98:2 *Z*:*E* ratio as colorless oil (11.0 mg, 0.0748 mmol, 75% yield). **IR (neat)**: 3072 (w), 2870 (w), 2216 (w), 1620 (m), 1484 (s), 1403 (s), 1207 (s), 1184 (m), 832 (m), 765 (s), 712(w); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 8.21 (1H, td, J = 7.7, 1.7 Hz), 7.43 (2H, dd, J = 10.0, 6.0 Hz), 7.31–7.20 (1H, m), 7.12 (1H, ddd, J = 9.8, 8.4, 1.1 Hz), 5.56 (1H, d, J = 12.2 Hz); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 160.7 (d, $J_{C\text{-}F}$ = 253.2 Hz), 140.5 (d, $J_{C\text{-}F}$ = 7.0 Hz), 132.9 (d, $J_{C\text{-}F}$ = 8.7 Hz), 128.4 (d, $J_{C\text{-}F}$ = 1.7 Hz), 124.7 (d, $J_{C\text{-}F}$ = 3.6 Hz), 121.9 (d, $J_{C\text{-}F}$ = 11.3 Hz), 117.0, 116.0 (d, $J_{C\text{-}F}$ = 21.9 Hz), 97.2 (d, $J_{C\text{-}F}$ = 2.2 Hz); **^{19}F NMR (376 MHz,**

$CDCl_3$): δ -115.39 (ddd, J = 10.2, 7.4, 5.3 Hz); **HRMS [M+H]$^+$** C_9H_7FN calcd 148.0563, found 148.0563.

(*Z*)-3-(*o*-Tolyl)acrylonitrile (1.37): Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1-methyl-2-(prop-1-en-1-yl)benzene (13.2 mg, 0.100 mmol) and maleonitrile (11.7 mg, 0.150 mmol) in 0.30 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed >98% consumption of (*Z*)-1-methyl-2-(prop-1-en-1-yl)benzene. The resulting red oil was purified by silica gel chromatography (1% → 2% Et_2O in hexanes) to afford a 14.8 mg mixture of inseparable 1.37 in 93:7 *Z*:*E* ratio (14.0 mg, 0.0977 mmol, 98% yield) and initiation product (*Z*)-4-methyl-4-phenylpent-2-enenitrile in >98:2 *Z*:*E* ratio (0.8 mg, 0.00467 mmol, 4.7% yield) as colorless oil. **IR (neat)**: 3059 (w), 2975 (w), 2865 (w), 2215 (m), 1612 (m), 1486 (m), 1380 (w), 1303 (w), 1105 (w), 1033 (w), 949 (w), 794 (s), 761 (s), 740 (s), 709 (s), 586 (w), 488 (w), 443 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *Z* isomer (major): δ 7.93 (1H, dd, J = 7.5, 1.6 Hz), 7.41 (1H, d, J = 11.9 Hz), 7.31 (2H, dtd, J = 20.7, 7.4, 1.6 Hz), 7.27–7.21 (1H, m), 5.52 (1H, d, J = 11.9 Hz), 2.36 (3H, s); *E* isomer (resolved signals only): δ 7.70 (1H, d, J = 16.5 Hz), 7.46 (1H, d, J = 7.8 Hz), 5.81 (1H, d, J = 16.5 Hz), 2.41 (3H, s); initiation product (resolved signals only): δ 6.54 (1H, d, J = 12.2 Hz), 5.36 (1H, d, J = 12.2 Hz), 1.64 (6H, s); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 147.7, 137.2, 132.8, 130.7, 130.7, 127.8, 126.6, 117.2, 97.1, 19.8; **HRMS [M+H]$^+$** calcd for $C_{10}H_{10}N$: 144.0813, found: 144.0809.

***tert*-Butyl (*Z*)-5-(2-cyanovinyl)-1H-indole-1-carboxylate (1.38)**: Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing *tert*-butyl (*Z*)-5-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate (25.7 mg, 0.100 mmol) and maleonitrile (11.7 mg, 0.150 mmol) in 0.30 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed >98% consumption of *tert*-butyl (*Z*)-5-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate. The resulting red oil was purified by silica gel chromatography (1% → 2% Et_2O in hexanes) to afford 1.38 in 92:8 *Z*:*E* ratio as off-white solid (24.7 mg, 0.0920 mmol, 92% yield). **M.p.**: 56–58 °C; **IR (neat)**: 2978 (w), 2924 (w), 2852 (w), 2210 (w), 1735 (s), 1605 (w), 1467 (w), 1368 (s), 1334 (s), 1258 (m), 1161 (s), 1128 (m), 1084 (m), 1023 (m), 824 (w), 766 (m), 723 (m); **^{1}H NMR (500 MHz, $CDCl_3$):** *Z* isomer (major): δ 8.18 (1H, d, J = 8.6 Hz), 8.08 (1H, d, J = 1.7 Hz), 7.75 (1H, dd, J = 8.8, 1.8 Hz), 7.65 (1H, d, J = 3.8 Hz), 7.20 (1H, d, J = 12.1 Hz), 6.63 (1H, dd, J = 3.7, 0.8 Hz), 5.40 (1H, d, J = 12.1 Hz), 1.69 (9H, s); *E* isomer (resolved signals only): δ 7.49 (1H, d, J = 16.6 Hz), 7.42 (1H, dd, J = 8.6, 1.8 Hz), 6.59 (1H, d, J = 3.7 Hz), 5.87 (1H, d, J = 16.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 149.5, 149.3, 131.0, 128.5, 127.4, 125.6, 122.3, 118.1, 115.6, 107.7, 99.2, 93.2, 84.5, 28.3; **HRMS [M+H]$^+$** calcd for $C_{16}H_{17}N_2O_2$: 269.1290, found: 269.1289.

(*Z*)-3-(Benzo[*b*]thiophen-3-yl)acrylonitrile (1.39): Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-3-(prop-1-en-1-yl)benzo[*b*]thiophene (17.4 mg, 0.100 mmol) and maleonitrile (11.7 mg, 0.150 mmol) in 0.30 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by addition of

wet $CDCl_3$ and analysis of the unpurified mixture revealed 80% consumption of (*Z*)-3-(prop-1-en-1-yl)benzo[*b*]thiophene. The resulting red oil was purified by silica gel chromatography (1% → 2% Et_2O in hexanes) to afford a 10.6 mg mixture of inseparable 1.39 in 96:4 *Z*:*E* ratio (10.2 mg, 0.0551 mmol, 55% yield) and initiation product (*Z*)-4-methyl-4-phenylpent-2-enenitrile in >98:2 *Z*:*E* ratio (0.4 mg, 0.00234 mmol, 2.3% yield) as colorless oil. **IR (neat)**: 3107 (w), 3066 (w), 2212 (m), 1611 (w), 1501 (m), 1426 (m), 1406 (m), 1262 (w), 765 (m), 741 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** *Z* isomer (major): δ 8.57 (1H, d, J = 0.7 Hz), 7.94–7.90 (1H, m), 7.84–7.79 (1H, m), 7.50–7.41 (3H, m), 5.54 (1H, d, J = 11.9 Hz); *E* isomer (resolved signals only): δ 5.97 (1H, d, J = 16.7 Hz); initiation product (resolved signals only): δ 6.53 (1H, d, J = 12.1 Hz), 5.35 (1H, d, J = 12.1 Hz), 1.64 (6H, s); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 139.6, 139.1, 137.9, 129.5, 129.5, 125.4, 125.1, 123.1, 120.9, 118.1, 95.3; **HRMS $[M+H]^+$** calcd for $C_{11}H_8NS$: 186.0377, found: 186.0374.

(2*Z*,2'*Z*)-6,6'-(1,3-Dithiane-2,2-diyl)bis(hex-2-enenitrile) (1.41):: To a flame-dried 250 mL round bottom flask was added 1,3-dithiane (1.20 g, 10.0 mmol) and THF (50 mL) and the resulting solution was allowed to cool to –78 °C. *n*-BuLi (1.30 M in THF, 10.0 mL) was added in a dropwise manner, and the solution was allowed to warm up to 0 °C and stir for 2 h. Then 5-bromopent-1-ene (1.54 mL, 13.0 mmol) was added in a dropwise manner at –78 °C, and the solution was allowed to warm up to 22 °C and stir for 10 h. Without any work-up, second batch of *n*-BuLi (1.30 M in THF, 10.0 mL) was added in a dropwise manner at –78 °C before being warmed up to stir for 2 h at 0 °C. Then 5-bromopent-1-ene (1.54 mL, 13.0 mmol) was added dropwise at –78 °C and the mixture was allowed to warm up to 22 °C and stir for 10 h. The reaction was quenched by the

addition of water (50 mL) and washed with Et_2O (3×50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo to afford light yellow oil, which was purified by silica gel chromatography (2% Et_2O in hexanes) to afford **2,2-di(pent-4-en-1-yl)-1,3-dithiane** as colorless oil (2.51 g, 9.80 mmol, 98% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.81 (2H, ddt, J = 16.9, 10.2, 6.7 Hz), 5.04 (2H, dq, J = 17.1, 1.7 Hz), 4.98 (2H, ddt, J = 10.2, 2.3, 1.3 Hz), 2.87–2.73 (4H, m), 2.12–2.01 (4H, m), 1.99–1.91 (2H, m), 1.91–1.81 (4H, m), 1.58–1.46 (4H, m). The spectral data of this compound is consistent with those previously reported[64].

Following the general procedure, a solution of **Mo-2a** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried vial containing acrylonitrile solution (0.36 M, 280 μL, 0.100 mmol) and **2,2-di(pent-4-en-1-yl)-1,3-dithiane** (12.8 mg, 0.050 mmol). The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 90% consumption of **2,2-di(pent-4-en-1-yl)-1,3-dithiane**. The resulting oil was purified by silica gel chromatography (5% → 10% EtOAc in hexanes) to afford 1.41 in >98:2 *Z*:*E* ratio as colorless oil (8.7 mg, 0.0284 mmol, 57% yield). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 6.49 (2H, dt, J = 10.9, 7.6 Hz), 5.36 (2H, d, J = 10.9 H), 2.86–2.73 (4H, m), 2.46 (4H, qd, J = 7.5, 1.4 Hz), 1.98–1.92 (2H, m), 1.92–1.84 (4H, m), 1.70–1.60 (4H, m); **HRMS [M+H]$^+$** calcd for $C_{16}H_{23}N_2S_2$: 307.1297, found: 307.1289. The spectral data of this compound is consistent with those previously reported[34].

(*Z*)-3-(3,4-Dichlorophenyl)acrylonitrile (1.45): Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an

(64) Song, S.; He, F.; Fu, Z.; Xu, J.; Fan, Z. *Journal of Polymer Science, Part A: Polymer Chemistry* **2016**, *54*, 2468–2475.

oven-dried vial containing (*Z*)-1,2-dichloro-4-(prop-1-en-1-yl)benzene (19.8 mg, 0.100 mmol) and maleonitrile (11.7 mg, 0.150 mmol) in 0.30 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed >98% consumption of (*Z*)-1,2-dichloro-4-(prop-1-en-1-yl)benzene. The resulting red oil was purified by silica gel chromatography (1% → 2% Et_2O in hexanes) to afford 1.45 in 97:3 *Z*:*E* ratio as off-white solid (19.8 mg, 0.100 mmol, >98% yield). **M.p.**: 56–58 °C; **IR (neat)**: 3067 (w), 2921 (w), 2850(w), 2215 (m), 1613 (w), 1549 (w), 1470 (s), 1385 (w), 1284 (w), 1185 (w), 1135 (m), 1031 (m), 884 (m), 825 (s), 753 (w), 695 (m), 605 (w), 436 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** *Z* isomer (major): δ 7.81 (1H, d, J = 2.2 Hz), 7.73 (1H, ddd, J = 8.4, 2.1, 0.6 Hz), 7.53 (1H, d, J = 8.4 Hz), 7.04 (1H, d, J = 12.1 Hz), 5.54 (1H, d, J = 12.1 Hz); *E* isomer (resolved signals only): δ 5.88 (1H, d, J = 16.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 146.1, 135.3, 133.5, 133.4, 131.1, 131.1, 127.8, 116.7, 97.3; **HRMS $[M+H]^+$** calcd for $C_9H_6Cl_2N$: 197.9877, found: 197.9875.

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(((*Z*)-pent-2-en-1-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (1.48): In analogy to a reported procedure[65], a mixture of acetobromo-α-D-glucose (411 mg, 1.00 mmol, 1.0 equiv.), *cis*-2-penten-1-ol (103 mg, 1.20 mmol, 1.20 equiv.), and activated powdered 4Å molecular sieves (100 mg) in 8 mL anhydrous CH_2Cl_2 was allowed to stir under N_2 atm at 22 °C for 30 min. The resulting suspension was treated with a small crystal of I_2 (~15 mg) and Ag_2CO_3 (330 mg, 1.20 mmol 1.20 equiv.), covered with aluminum foil and allowed to stir for 24 h at 22 °C. The reaction mixture was filtered through a pad of celite, concentrated in vacuo and the

(65) Delso, I.; Valero-González, J.; Marca, E.; Tejero, T.; Hurtado-Guerrero, R.; Merino, P. *Chem. Biol. Drug. Des.* **2016**, *87*, 163−170.

yellow residue was purified by silica gel chromatography (30% EtOAc in hexanes) to afford **1.48** in >98:2 *Z*:*E* ratio as colorless viscous oil (270 mg, 0.648 mmol, 65% yield). **IR (neat)**: 2965 (w), 2875 (w), 1746 (s), 1432 (w), 1366 (m), 1213 (s), 1166 (m), 1035 (s), 905 (m); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 5.61 – 5.52 (1H, m), 5.38 – 5.29 (1H, m), 5.11 (1H, t, J = 9.5 Hz), 4.98 (1H, dd, J = 10.0, 9.3 Hz), 4.89 (1H, dd, J = 9.5, 8.0 Hz), 4.47 (1H, d, J = 8.0 Hz), 4.21 – 4.14 (3H, m), 4.05 (1H, dd, J = 12.3, 2.5 Hz), 3.60 (1H, ddd, J = 10.0, 5.0, 2.5 Hz), 2.03 – 1.88 (14H, m), 0.89 (3H, t, J = 7.5 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.5, 170.1, 169.3, 169.2, 136.8, 123.6, 98.8, 72.8, 71.7, 71.2, 68.4, 64.2, 62.0, 20.7, 20.6, 20.6, 20.5, 14.1; **HRMS [M+NH_4]$^+$** $C_{19}H_{32}NO_{10}$ calcd 434.2026, found 434.2019.

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(((*Z*)-3-cyanoallyl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (1.49): Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried vial containing 1.48 (20.8 mg, 0.050 mmol), maleonitrile (5.9 mg, 0.075 mmol) and BPh_3 (12.1 mg, 0.050 mmol) in 0.15 mL benzene. The resulting solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 87% consumption of 1.48. The resulting red oil was purified by silica gel chromatography (30% to 50% EtOAc in hexanes) to afford **1.49** in >98:2 *Z*:*E* ratio as colorless oil (12.5 mg, 0.0299 mmol, 60% yield). **IR (neat)**: 2956 (w), 2222 (w), 1745 (s), 1433 (w), 1367 (m), 1214 (s), 1167 (w), 1036 (s), 906 (w), 731 (w), 599 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 6.57 (1H, ddd, J = 11.0, 6.7, 5.6 Hz), 5.47 (1H, dt, J = 11.0, 1.7 Hz), 5.21 (1H, t, J = 9.5 Hz), 5.08 (1H, t, J = 9.7 Hz), 5.01 (1H, dd, J = 9.6, 7.9 Hz), 4.63–4.44 (3H, m), 4.26 (1H, dd, J = 12.3, 4.9 Hz), 4.16 (1H, dd, J = 12.4,

2.4 Hz), 3.72 (1H, ddd, J = 10.0, 4.9, 2.3 Hz), 2.10 (3H, s), 2.05 (3H, s), 2.03 (3H, s), 2.00 (3H, s); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 170.8, 170.3, 169.5, 169.5, 149.6, 114.9, 101.4, 100.6, 72.9, 72.3, 71.2, 68.4, 67.4, 61.9, 20.9, 20.8, 20.7, 20.7; **HRMS [M+H]$^+$** calcd for $C_{18}H_{24}O_{10}N$: 414.1400, found: 414.1393.

(*E*)-3-(4-Methoxyphenyl)acrylonitrile (1.56): Following the general procedure, a solution of **Mo-3c** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 30 μL, 3.0 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-1-methoxy-4-(prop-1-en-1-yl)benzene (7.4 mg, 0.050 mmol) and fumaronitrile (19.5 mg, 0.250 mmol) in 0.25 mL benzene. The resulting solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed >98% consumption of (*E*)-1-methoxy-4-(prop-1-en-1-yl)benzene and formation of the product in 96:4 *E:Z* ratio. The resulting red oil was purified by silica gel chromatography (2% → 10% Et_2O in hexanes) to afford **1.**56 in >98:2 *E:Z* ratio as off-white solid (6.2 mg, 0.0389 mmol, 78% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.43–7.38 (2H, m), 7.34 (1H, dt, J = 16.6, 0.5 Hz), 6.95–6.89 (2H, m), 5.72 (1H, d, J = 16.6 Hz), 3.85 (3H, s); **HRMS [M+H]$^+$** calcd for $C_{10}H_{10}NO$: 160.0757, found: 160.0764. The spectral data of this compound is consistent with those previously reported[66].

(*E*)-3-(2-Fluorophenyl)acrylonitrile (1.59): Following the general procedure, a solution of **Mo-3c** in benzene (0.1 M, 50 μL, 5.0 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 60 μL, 6.0 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-1-fluoro-2-(prop-1-en-1-yl)benzene (13.6 mg, 0.100 mmol) and fumaronitrile (39.0 mg, 0.500

(66) Ye, F.; Chen, J.; Ritter, T. *J. Am. Chem. Soc.* **2017**, *139*, 7184–7187.

mmol) in 0.50 mL benzene. The resulting solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 62% consumption of (*E*)-1-fluoro-2-(prop-1-en-1-yl)benzene and formation of the product in 90:10 *E:Z* ratio. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in hexanes) to afford a 8.9 mg mixture of inseparable **1.**59 in >98:2 *E:Z* ratio (8.0 mg, 0.0544 mmol, 54% yield) and initiation product (*E*)-4-methyl-4-phenylpent-2-enenitrile in >98:2 *E:Z* ratio (0.9 mg, 0.00526 mmol, 5.3% yield) as colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.49 (1H, d, J = 16.8 Hz), 7.47–7.38 (2H, m), 7.19 (1H, td, J = 7.6, 1.1 Hz), 7.13 (1H, ddd, J = 10.9, 8.3, 1.2 Hz), 6.04 (1H, dd, J = 16.8, 0.9 Hz); initiation product (resolved signals only): δ 6.89 (1H, d, J = 16.6 Hz), 5.29 (1H, d, J = 16.6 Hz), 1.47 (6H, s); **HRMS [M+H]$^+$** calcd for $C_9H_{16}NF$: 148.0557, found: 148.0561. The spectral data of this compound is consistent with those previously reported[67].

(*E*)-3-(*o*-Tolyl)acrylonitrile (1.60): Following the general procedure, a solution of **Mo-3d** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 30 μL, 3.0 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-1-methyl-2-(prop-1-en-1-yl)benzene (6.6 mg, 0.050 mmol) and fumaronitrile (19.5 mg, 0.250 mmol) in 0.25 mL benzene. The resulting solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 54% consumption of (*E*)-1-methyl-2-(prop-1-en-1-yl)benzene and formation of the product in 96:4 *E:Z* ratio. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in hexanes) to afford a 4.0 mg mixture of inseparable

(67) Zhou, W.; Xu, J.; Zhang, L.; Jiao, N. *Org. Lett.* **2010**, *12*, 2888–2891.

1.60 in 97:3 *E:Z* ratio (3.7 mg, 0.0251 mmol, 50% yield) and initiation product (*E*)-4-methyl-4-phenylpent-2-enenitrile in >98:2 *E:Z* ratio (0.3 mg, 0.00175 mmol, 3.5% yield) as colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 7.70 (1H, d, J = 16.5 Hz), 7.50–7.44 (1H, m), 7.33 (1H, td, J = 7.2, 6.8, 1.5 Hz), 7.25–7.19 (2H, m), 5.81 (1H, d, J = 16.5 Hz), 2.41 (3H, s); *Z* isomer (resolved signals only): δ 5.52 (1H, d, J = 12.0 Hz); initiation product (resolved signals only): δ 6.89 (1H, d, J = 16.6 Hz), 5.29 (1H, d, J = 16.6 Hz), 1.47 (6H, s). The spectral data of this compound is consistent with those previously reported[67].

(*E*)-3-(3-Bromophenyl)acrylonitrile (1.61): Following the general procedure, a solution of **Mo-3c** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 30 μL, 3.0 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-1-bromo-3-(prop-1-en-1-yl)benzene (9.9 mg, 0.050 mmol) and fumaronitrile (19.5 mg, 0.250 mmol) in 0.25 mL benzene. The resulting solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 77% consumption of (*E*)-1-bromo-3-(prop-1-en-1-yl)benzene and formation of the product in 97:3 *E:Z* ratio. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in hexanes) to afford a 7.6 mg mixture of inseparable 1.61 in 98:2 *E:Z* ratio (7.6 mg, 0.0365 mmol, 73% yield) and initiation product (*E*)-4-methyl-4-phenylpent-2-enenitrile in >98:2 *E:Z* ratio (0.1 mg, 0.00058 mmol, 1.2% yield) as off-white solid. **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 7.60 (1H, q, J = 1.4 Hz), 7.56 (1H, ddt, J = 7.9, 2.0, 1.0 Hz), 7.40–7.36 (1H, m), 7.33 (1H, d, J = 16.7 Hz), 7.29 (1H, td, J = 7.9, 1.0 Hz), 5.89 (1H, dd, J = 16.7, 1.0 Hz); *Z* isomer (resolved signals only): δ 5.52 (1H, dd, J = 12.1, 1.0 Hz); initiation product (resolved signals only): δ 6.89

(1H, dd, *J* = 16.7, 1.0 Hz), 5.29 (1H, dd, *J* = 16.6, 1.0 Hz), 1.47 (6H, s); **HRMS [M+H]$^+$** calcd for C_9H_7NBr: 207.9756, found: 207.9766. The spectral data of this compound is consistent with those previously reported[68].

Methyl (*E*)-4-(2-cyanovinyl)benzoate (1.62): Following the general procedure, a solution of **Mo-3c** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 30 μL, 3.0 μmol) were transferred by syringe to an oven-dried vial containing methyl (*E*)-4-(prop-1-en-1-yl)benzoate (8.8 mg, 0.050 mmol) and fumaronitrile (19.5 mg, 0.250 mmol) in 0.25 mL benzene. The resulting solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 75% consumption of methyl (*E*)-4-(prop-1-en-1-yl)benzoate and formation of the product in 97:3 *E:Z* ratio. The resulting red oil was purified by silica gel chromatography (100% hexanes → 5% EtOAc in hexanes) to 1.62 in >98:2 *E:Z* ratio as colorless oil (6.6 mg, 0.0353 mmol, 71% yield). **IR (neat)**: 3113 (w), 2957 (w), 2217 (w), 1724 (s), 1623 (w), 1453 (m), 1292 (s), 1187 (w), 1109 (m), 972 (m), 825 (w), 760 (s), 693 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.09–8.05 (2H, m), 7.54–7.49 (2H, m), 7.43 (1H, dt, *J* = 16.6, 0.5 Hz), 5.98 (1H, d, *J* = 16.6 Hz), 3.94 (3H, s); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 166.2, 149.4, 137.6, 132.4, 130.4, 127.4, 117.7, 99.0, 52.6; **HRMS [M+H]$^+$** calcd for $C_{11}H_9N_2O_2$: 188.0706, found: 188.0709.

(*E*)-3-(4-(Trifluoromethyl)phenyl)acrylonitrile (1.63): Following the general procedure, a solution of **Mo-3c** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 30 μL, 3.0 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-1-(prop-1-en-1-yl)-4-(trifluoromethyl)benzene (9.9 mg, 0.050 mmol) and

(68) Zhang, W.; Haskins, C. W.; Yang, Y.; Dai, M. *Org. Biomol. Chem.* **2014**, *12*, 9109–9112.

fumaronitrile (19.5 mg, 0.250 mmol) in 0.25 mL benzene. The resulting solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 64% consumption of (*E*)-1-(prop-1-en-1-yl)-4-(trifluoromethyl)benzene and formation of the product in 96:4 *E:Z* ratio. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in hexanes) to afford 1.63 in >98:2 *E:Z* as off-white solid (5.3 mg, 0.0269 mmol, 54% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.68 (2H, d, J = 8.2 Hz), 7.60–7.53 (2H, m), 7.44 (1H, d, J = 16.7 Hz), 5.99 (1H, d, J = 16.7 Hz); **HRMS [M+H]$^+$** calcd for $C_{10}H_7NF_3$: 198.0525, found: 198.0527. The spectral data of this compound is consistent with those previously reported[69].

(*E*)-3-([1,1'-Biphenyl]-4-yl)acrylonitrile (1.64): Following the general procedure, a solution of **Mo-3c** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 30 μL, 3.0 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-4-(prop-1-en-1-yl)-1,1'-biphenyl (9.7 mg, 0.050 mmol) and fumaronitrile (19.5 mg, 0.250 mmol) in 0.25 mL benzene. The resulting solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 75% consumption of (*E*)-4-(prop-1-en-1-yl)-1,1'-biphenyl and formation of the product in 96:4 *E:Z* ratio. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in hexanes) to afford 1.64 in 98:2 *E:Z* ratio as off-white solid (6.3 mg, 0.0308 mmol, 62% yield). **^{1}H NMR (600 MHz, $CDCl_3$):** *E* isomer (major): δ 7.65 (2H, d, J = 8.1 Hz), 7.63–7.59 (2H, m), 7.53 (2H, d, J = 8.0 Hz), 7.50–7.37 (4H, m), 5.91 (1H, dd, J = 16.6, 1.0 Hz); *Z* isomer (resolved signals only): δ 5.46

(69) Qin, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 15893–15895.

(1H, d, *J* = 12.1 Hz); **HRMS [M+H]$^+$** calcd for $C_{15}H_{12}N$: 206.0964, found: 206.0970. The spectral data of this compound is consistent with those previously reported[67].

(*E*)-3-(4-Iodophenyl)acrylonitrile (1.65): Following the general procedure, a solution of **Mo-3c** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 30 μL, 3.0 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-1-iodo-4-(prop-1-en-1-yl)benzene (12.2 mg, 0.050 mmol) and fumaronitrile (19.5 mg, 0.250 mmol) in 0.25 mL benzene. The resulting solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 88% consumption of (*E*)-1-iodo-4-(prop-1-en-1-yl)benzene and formation of the product in 97:3 *E:Z* ratio. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in hexanes) to a 10.4 mg mixture of inseparable **1.65** in 97:3 *E:Z* ratio (10.3 mg, 0.0404 mmol, 81% yield) and initiation product (*E*)-4-methyl-4-phenylpent-2-enenitrile in >98:2 *E:Z* ratio (0.1 mg, 0.00808 mmol, 1.6% yield) as off-white solid. **M.p.**: 120–122 °C; **IR (neat)**: 3045 (w), 2918 (w), 2211 (m), 1616 (m), 1578 (w), 1474 (w), 1398 (w), 1057 (w), 1004 (w), 1004 (m), 969 (w), 840 (w), 794 (s), 532 (w), 449 (m); **^{1}H NMR (600 MHz, $CDCl_3$):** *E* isomer (major): δ 7.76 (2H, d, *J* = 8.1 Hz), 7.32 (1H, d, *J* = 16.6 Hz), 7.17 (2H, d, *J* = 8.1 Hz), 5.90 (1H, dd, *J* = 16.6, 0.9 Hz); *Z* isomer (resolved signals only): δ 5.49 (1H, dd, *J* = 12.0, 0.9 Hz); initiation product (resolved signals only): δ 6.89 (1H, dd, *J* = 16.6, 0.7 Hz), 5.28 (1H, d, *J* = 16.6 Hz), 1.46 (6H, s); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 149.5, 138.5, 133.1, 128.8, 117.9, 97.9, 97.3; **HRMS [M+H]$^+$** calcd for C_9H_7IN: 255.9618, found: 255.9632.

(*E*)-3-(Benzo[b]thiophen-5-yl)acrylonitrile (1.66): Following the general procedure, a solution of **Mo-3c** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M,

30 μL, 3.0 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-5-(pent-1-en-1-yl)benzo[*b*]thiophene (10.1 mg, 0.050 mmol) and fumaronitrile (19.5 mg, 0.250 mmol) in 0.25 mL benzene. The resulting solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 95% consumption of (*E*)-5-(pent-1-en-1-yl)benzo[*b*]thiophene and formation of the product in 96:4 *E:Z* ratio. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in hexanes) to 1.66 in 98:2 *E:Z* ratio as off-white solid (8.1 mg, 0.0437 mmol, 87% yield). **MP**: 106–108 °C; **IR (neat)**: 3071 (w), 3058 (w), 2212 (s), 1613 (m), 1415 (w), 1330 (m), 971 (s), 954 (m), 902 (m), 805 (s), 757 (m), 703 (s), 465 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 7.90 (1H, dq, *J* = 8.4, 0.6 Hz), 7.87 (1H, d, *J* = 1.8 Hz), 7.53 (1H, dd, *J* = 1.8, 0.5 Hz), 7.51 (1H, dd, *J* = 9.3, 0.5 Hz), 7.44 (1H, ddt, *J* = 8.5, 1.8, 0.5 Hz), 7.37 (1H, dd, *J* = 5.5, 0.8 Hz), 5.94 (1H, d, *J* = 16.6 Hz); *Z* isomer (resolved signals only): δ 5.47 (1H, d, *J* = 12.1Hz); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 151.0, 142.5, 140.1, 130.1, 128.3, 124.2, 123.8, 123.3, 122.1, 118.5, 95.8; **HRMS [M+H]$^+$** calcd for $C_{11}H_8NS$: 186.0372, found: 186.0380.

(*E*)-5-(Benzyloxy)pent-2-enenitrile (1.67): Following the general procedure, a solution of **Mo-3c** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 30 μL, 3.0 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-(4-(benzyloxy)but-1-en-1-yl)benzene (11.9 mg, 0.050 mmol) and fumaronitrile (19.5 mg, 0.250 mmol) in 0.25 mL benzene. The resulting solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 76% consumption of (*E*)-(4-(benzyloxy)but-1-en-1-

yl)benzene and formation of the product in 96:4 *E:Z* ratio. The resulting red oil was purified by silica gel chromatography (5% → 10% Et_2O in hexanes) to **1.67** in 96:4 *E:Z* ratio as colorless oil (7.0 mg, 0.0374 mmol, 75% yield). **IR (neat)**: 3031 (w), 2917 (w), 2858 (w), 2222 (w), 1634 (w), 1454 (w), 1362 (w), 1206 (w), 1100 (s), 1028 (w), 964 (m), 739 (m), 699 (m); **^{1}H NMR (600 MHz, $CDCl_3$):** *E* isomer (major): δ 7.40–7.34 (2H, m), 7.31 (3H, d, J = 7.5 Hz), 6.75 (1H, dtd, J = 16.4, 6.9, 0.9 Hz), 5.42 (1H, dq, J = 16.4, 1.4 Hz), 4.51 (2H, s), 3.57 (2H, td, J = 6.1, 0.9 Hz), 2.52 (2H, tdd, J = 7.7, 6.8, 4.2, 1.2 Hz); *Z* isomer (resolved signals only): δ 6.61 (1H, dt, J = 10.6, 7.5 Hz), 4.53 (2H, s), 3.61 (2H, t, J = 6.1 Hz), 2.73 (2H, q, J = 6.3 Hz); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 152.8, 137.9, 128.6, 128.0, 127.8, 117.5, 101.6, 73.3, 67.7, 33.8; **HRMS $[M+H]^+$** calcd for $C_{12}H_{14}NO$: 188.1070, found: 188.1078.

(*E*)-8-Cyanooct-7-en-1-yl 4-methylbenzenesulfonate (1.68): Following the general procedure, a solution of **Mo-3c** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 30 μL, 3.0 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-8-phenyloct-7-en-1-yl 4-methylbenzenesulfonate (17.9 mg, 0.050 mmol) and fumaronitrile (19.5 mg, 0.250 mmol) in 0.25 mL benzene. The resulting solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 70% consumption of (*E*)-8-phenyloct-7-en-1-yl 4-methylbenzenesulfonate and formation of the product in 93:7 *E:Z* ratio. The resulting red oil was purified by silica gel chromatography (5% → 10% Et_2O in hexanes) to **1.68** in 93:7 *E:Z* ratio as colorless oil (10.6 mg, 0.0345 mmol, 69% yield). **IR (neat)**: 2926 (br), 2856 (br), 2222 (w), 1632 (w), 1598 (w), 1459 (w), 1354 (m), 1173 (s), 1097 (w), 948 (m), 912 (m), 813 (m), 688 (s), 575 (m), 553 (s); **^{1}H NMR (600 MHz,**

$CDCl_3$): *E* isomer (major): δ 7.89–7.73 (2H, m), 7.35 (2H, d, J = 7.9 Hz), 6.68 (1H, ddd, J = 16.4, 7.7, 6.2 Hz), 5.30 (1H, dq, J = 16.4, 1.7 Hz), 4.02 (2H, td, J = 6.3, 1.4 Hz), 2.45 (3H, s), 2.19 (2H, q, J = 7.3 Hz), 1.63 (2H, q, J = 6.8, 6.4 Hz), 1.41 (2H, p, J = 7.3 Hz), 1.33 (2H, tt, J = 8.5, 6.3 Hz), 1.30–1.23 (2H, m); *Z* isomer (resolved signals only): δ 6.45 (1H, dt, J = 11.2, 7.8 Hz), 2.38 (2H, q, J = 7.6 Hz); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 155.8, 144.8, 133.3, 130.0, 128.0, 117.6, 100.0, 70.5, 33.2, 28.8, 28.4, 27.5, 25.2, 21.8; **HRMS $[M+NH_4]^+$** calcd for $C_{16}H_{25}N_2O_3S$: 325.1580, found: 325.1585.

(*E*)-9-(1,3-Dioxoisoindolin-2-yl)non-2-enenitrile (1.69): Following the general procedure, a solution of **Mo-3c** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 30 μL, 3.0 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-2-(8-phenyloct-7-en-1-yl)isoindoline-1,3-dione (16.7 mg, 0.050 mmol) and fumaronitrile (19.5 mg, 0.250 mmol) in 0.25 mL benzene. The resulting solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 70% consumption of (*E*)-2-(8-phenyloct-7-en-1-yl)isoindoline-1,3-dione and formation of the product in 93:7 *E:Z* ratio. The resulting red oil was purified by silica gel chromatography (5% → 10% EtOAc in hexanes) to **1.**69 in 93:7 *E:Z* ratio as colorless oil (9.7 mg, 0.0344 mmol, 69% yield). **IR (neat)**: 2933 (w), 2858 (w), 2222 (w), 1772 (w), 1710 (s), 1437 (w), 1396 (m), 1370 (w), 1053 (w); 720 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 7.84 (2H, dd, J = 5.4, 3.1 Hz), 7.77–7.66 (2H, m), 6.70 (1H, dt, J = 16.4, 6.9 Hz), 5.31 (1H, dt, J = 16.4, 1.7 Hz), 3.67 (2H, t, J = 7.2 Hz), 2.21 (2H, qd, J = 7.0, 1.7 Hz), 1.67 (2H, td, J = 10.7, 8.9, 5.2 Hz), 1.44 (2H, p, J = 7.0 Hz), 1.36 (4H, dq, J = 7.3, 4.1, 3.6 Hz); *Z* isomer (resolved signals only): δ 6.46 (1H, dt, J = 10.9, 7.7 Hz), 2.41 (2H, qd, J = 7.3, 1.3 Hz);

^{13}C NMR (150 MHz, $CDCl_3$): δ 168.6, 156.0, 134.0, 132.2, 123.3, 117.7, 99.9, 37.9, 33.3, 28.6, 28.5, 27.6, 26.6; **HRMS [M+H]$^+$** calcd for $C_{17}H_{19}N_2O_2$: 283.1441, found: 283.1442.

4-(*trans*-4-((*E*)-2-Cyanovinyl)cyclohexyl)benzonitrile (1.71): Following the general procedure, a solution of **Mo-3d** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 30 μL, 3.0 μmol) were transferred by syringe to an oven-dried vial containing 4-(*trans*-4-((*E*)-prop-1-en-1-yl)cyclohexyl)benzonitrile (11.3 mg, 0.050 mmol) and fumaronitrile (19.5 mg, 0.250 mmol) in 0.25 mL benzene. The resulting solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 62% consumption of 4-(*trans*-4-((*E*)-prop-1-en-1-yl)cyclohexyl)benzonitrile and formation of the product in 97:3 *E:Z* ratio. The resulting red oil was purified by silica gel chromatography (5% → 10% EtOAc in hexanes) to 1.7**1** in 98:2 *E:Z* ratio as off-white solid (7.1 mg, 0.0300 mmol, 60% yield). **M.p.**: 152–154 °C; **IR (neat)**: 2924 (s), 2852 (m), 2222 (s), 1626 (m), 1605 (m), 1505 (m), 1446 (m), 1262 (w), 1175 (w), 976 (s), 940 (w), 855 (w), 828 (m), 804 (w), 562 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 7.63–7.54 (2H, m), 7.31–7.27 (2H, m), 6.70 (1H, dd, *J* = 16.5, 6.8 Hz), 5.33 (1H, dd, *J* = 16.5, 1.5 Hz), 2.56 (1H, tt, *J* = 12.2, 3.3 Hz), 2.24 (1H, ddddq, *J* = 11.6, 10.1, 6.7, 3.3, 1.8 Hz), 1.97 (4H, ddt, *J* = 14.8, 12.4, 3.3 Hz), 1.51 (2H, qd, *J* = 13.8, 13.0, 3.5 Hz), 1.34 (2H, td, *J* = 12.9, 12.1, 3.6 Hz); *Z* isomer (resolved signals only): δ 6.34 (1H, dd, *J* = 10.7, 10.1 Hz), 5.28 (1H, d, *J* = 10.9 Hz); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 159.8, 152.1, 132.5, 127.7, 119.1, 117.7, 110.2, 98.4, 43.9, 41.1, 33.0, 31.3; **HRMS [M+H]$^+$** calcd for $C_{16}H_{17}N_2$: 237.1386, found: 237.1375.

(*E*)-3-(3,5-Dimethoxyphenyl)acrylonitrile (1.72): Following the general procedure, a solution of **Mo-3c** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 30 μL, 3.0 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-1,3-dimethoxy-5-(prop-1-en-1-yl)benzene (8.9 mg, 0.050 mmol) and fumaronitrile (19.5 mg, 0.250 mmol) in 0.25 mL benzene. The resulting solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 95% consumption of (*E*)-1,3-dimethoxy-5-(prop-1-en-1-yl)benzene and formation of the product in 95:5 *E:Z* ratio. The resulting red oil was purified by silica gel chromatography (5% → 10% Et_2O in hexanes) to 1.72 in >98:2 *E:Z* ratio as off-white solid (7.7 mg, 0.0412 mmol, 82% yield). **M.p.**: 120–122 °C; **IR (neat)**: 3045 (w), 2918 (w), 2211 (m), 1616 (m), 1578 (w), 1474 (w), 1398 (w), 1057 (w), 1004 (w), 1004 (m), 969 (w), 840 (w), 794 (s), 532 (w), 449 (m); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.32 (1H, dd, J = 16.6, 1.1 Hz), 6.57 (2H, dd, J = 2.3, 1.1 Hz), 6.53 (1H, dt, J = 3.3, 1.6 Hz), 5.85 (1H, dd, J = 16.6, 1.2 Hz), 3.81 (6H, d, J = 1.1 Hz); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 161.3, 150.7, 135.5, 118.1, 105.5, 103.3, 97.0, 55.6; **HRMS $[M+H]^+$** calcd for $C_{11}H_{12}NO_2$: 190.0863, found: 190.0872.

CC-5079: 0.15 mL DMF was added to an oven-dried vial containing $Pd(OAc)_2$ (0.6 mg, 0.0025 mmol), **1.72** (9.5 mg, 0.050 mmol), 4-iodo-1,2-dimethoxybenzene (25.1 mg, 0.095 mmol), KOAc (12.3 mg, 0.125 mmol) and $(n\text{-Bu})_4NBr$ (17.7 mg, 0.055 mmol). The resulting solution was allowed to stir for 48 h at 80 °C. The reaction was quenched by the addition of H_2O (1.0 mL) and the resulting mixture was partitioned with Et_2O (3 × 2.0 mL). The organic layers were combined, dried and concentrated to afford a dark orange oil. The resulting dark orange oil was purified by silica gel chromatography (10%

→ 30% EtOAc in hexanes) to afford CC-5079 in 97:3 *Z:E* ratio as off-white solid (12.7 mg, 0.0390 mmol, 78% yield). **MP**: 108–110 °C; **IR (neat)**: 3005 (w), 2935 (w), 2839 (w), 2210 (w), 1587 (s), 1514 (s), 1455 (m), 1421 (m), 1364 (w), 1333 (w), 1266 (s), 1205 (m), 1156 (s), 1064 (w), 1024 (m), 854 (w), 806 (w), 766 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** *Z* isomer (major): δ 6.90 (1H, dd, J = 8.4, 2.1 Hz), 6.84 (1H, s), 6.83 (1H, d, J = 2.1 Hz), 6.55 (3H, s), 5.66 (1H, s), 3.91 (3H, s), 3.84 (3H, s), 3.80 (6H, s); *E* isomer (resolved signals only): δ 5.60 (1H, s), 3.93 (3H, s), 3.87 (3H, s), 3.77 (3H, s).; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 162.7, 160.8, 151.3, 149.0, 139.1, 131.3, 122.3, 118.1, 111.1, 110.9, 107.8, 102.3, 93.3, 56.2, 56.2, 55.7.; **HRMS [M+H]$^+$** calcd for $C_{19}H_{20}NO_4$: 326.1387, found: 326.1384.

(*E*)-3-(3,4-Dichlorophenyl)acrylonitrile (1.73): Following the general procedure, a solution of **Mo-3c** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 30 μL, 3.0 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-1,2-dichloro-4-(prop-1-en-1-yl)benzene (9.4 mg, 0.050 mmol) and fumaronitrile (19.5 mg, 0.250 mmol) in 0.25 mL benzene. The resulting solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 62% consumption of (*E*)-1,2-dichloro-4-(prop-1-en-1-yl)benzene in 97:3 *E:Z* ratio. The resulting red oil was purified by silica gel chromatography (100% hexanes → 2% Et_2O in hexanes) to afford 1.73 in >98:2 *E:Z* ratio as off-white solid (5.9 mg, 0.0298 mmol, 60% yield). **M.p.**: 92–94 °C; **IR (neat)**: 3057 (w), 2959 (w), 2923 (m), 2852 (w), 2217 (s), 1620 (m), 1534 (w), 1475 (m), 1397 (w), 1272 (w), 1208 (w), 1135 (w), 1033 (w), 969 (s), 914 (w), 674 (w), 435 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.54 (1H, d, J = 2.1 Hz), 7.50 (1H, d, J = 8.4 Hz), 7.35–7.26

(2H, m), 5.89 (1H, d, J = 16.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 148.0, 135.5, 133.8, 133.5, 131.3, 129.1, 126.4, 117.5, 98.6; **HRMS [M+H]$^+$** calcd for $C_9H_6NCl_2$: 197.9872, found: 197.9883.

(*E*)-6-((8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-17-((*tert*-Butyldimethylsilyl)oxy)-13-methyl-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-3-methylhex-2-enenitrile (1.76): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 75 μL, 7.5 μmol) were transferred by syringe to an oven-dried vial containing *tert*-butyldimethyl(((8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-13-methyl-17-((*E*)-4-methylhex-4-en-1-yl)-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)oxy)silane (23.5 mg, 0.050 mmol) and maleonitrile (5.9 mg, 0.075 mmol) in 0.15 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 67% consumption of *tert*-butyldimethyl(((8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-13-methyl-17-((*E*)-4-methylhex-4-en-1-yl)-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)oxy)silane. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in hexanes) to afford a 16.9 mg mixture of inseparable 1.76 in 92:8 *E*:*Z* ratio (15.9 mg, 0.0330 mmol, 66% yield) and aryloxide ligand 2,2",4,4",6,6"-hexaisopropyl-[1,1':3',1"-terphenyl]-2'-ol (1.0 mg, 0.00200 mmol, 4.0% yield) as off-white solid. **M.p.**: 150–152 °C; **IR (neat)**: 2983 (w), 2949 (m), 2930 (s), 2908 (m), 2853 (m), 2832 (w), 2213 (w), 1471 (w), 1256 (m), 1129 (w), 1092 (w), 1072 (s), 903 (w), 832 (s), 802 (m), 774 (m); **^{1}H NMR (600 MHz, $CDCl_3$):** *E* isomer (major): δ 5.38 (1H, s), 5.10 (1H, s), 2.22–2.11 (3H, m), 2.05 (3H, s), 2.03–1.94 (2H, m),

1.91 (2H, d, *J* = 5.5 Hz), 1.84–1.72 (4H, m), 1.71–1.63 (2H, m), 1.62–1.49 (3H, m), 1.46 (1H, d, *J* = 12.2 Hz), 1.40–1.21 (6H, m), 1.21–1.15 (1H, m), 1.10 (3H, ddd, *J* = 22.7, 12.0, 6.4 Hz), 0.87 (9H, s), 0.82 (3H, s), 0.61 (1H, qd, *J* = 10.9, 4.1 Hz), 0.07 (6H, d, *J* = 21.3 Hz); aryloxide ligand (resolved signals only): *δ* 7.12–6.95 (7H, m), 4.52 (1H, s), 3.48 (1H, q, *J* = 7.0 Hz), 2.94 (2H, p, *J* = 6.9 Hz), 2.72 (4H, p, *J* = 6.8 Hz); **^{13}C NMR (100 MHz, $CDCl_3$)**: *δ* 165.7, 140.6, 120.0, 117.5, 95.1, 86.4, 50.5, 48.8, 48.0, 42.2, 42.1, 39.7, 38.4, 35.7, 34.7, 32.2, 32.1, 29.0, 26.3, 26.2, 25.7, 23.8, 22.7, 22.3, 21.2, 18.8, 15.67, -1.41; **HRMS $[M+H]^+$** calcd for $C_{31}H_{52}NOSi$: 482.3818, found: 482.3821.

(*E*)-14-(Dibenzylamino)-3-methyltetradec-2-enenitrile (1.77): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 75 μL, 7.5 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-*N*,*N*-dibenzyl-12-methyltetradec-12-en-1-amine (20.3 mg, 0.050 mmol) and maleonitrile (5.9 mg, 0.075 mmol) in 0.15 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 60% consumption of (*E*)-*N*,*N*-dibenzyl-12-methyltetradec-12-en-1-amine. The resulting red oil was purified by silica gel chromatography (2% → 10% Et_2O in hexanes) to afford 1.77 in 92:8 *E*:*Z* ratio as colorless oil (11.0 mg, 0.0264 mmol, 53% yield). **IR (neat)**: 3027 (w), 2924 (s), 2853 (m), 2795 (w), 2217 (w), 1631 (w), 1494 (w), 1452 (m), 1366 (w), 1251(w), 1128 (w), 1074 (w), 1028 (w), 834 (w), 744 (m), 698 (s); **^{1}H NMR (500 MHz, $CDCl_3$):** *E* isomer (major): *δ* 7.37 (4H, d, *J* = 7.5 Hz), 7.30 (4H, t, *J* = 7.6 Hz), 7.22 (2H, t, *J* = 7.3 Hz), 5.10 (1H, s), 3.55 (4H, s), 2.46–2.35 (2H, m), 2.16 (2H, t, *J* = 7.6 Hz), 2.04 (3H, s), 1.55–1.48 (2H, m), 1.46 (2H, dd, *J* = 12.1, 4.9 Hz), 1.25 (14H, d, *J* = 20.0 Hz); *Z* isomer (resolved

signals only): δ 1.90 (3H, s); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 165.7, 140.2, 128.9, 128.2, 126.8, 117.5, 95.1, 58.4, 53.6, 38.8, 29.7, 29.7, 29.63, 29.61, 29.5, 29.2, 27.4, 27.22, 27.17, 21.1; **HRMS [M+H]$^+$** calcd for $C_{29}H_{41}N_2$: 417.3270, found: 417.3291.

(*E*)-3-Methyl-13-(triisopropylsilyl)tridec-2-en-12-ynenitrile (1.78): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 75 μL, 7.5 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-triisopropyl(11-methyltridec-11-en-1-yn-1-yl)silane (17.4 mg, 0.050 mmol) and maleonitrile (5.9 mg, 0.075 mmol) in 0.15 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 86% consumption of (*E*)-triisopropyl(11-methyltridec-11-en-1-yn-1-yl)silane. The resulting red oil was purified by silica gel chromatography (100% hexanes → 2% Et_2O in hexanes) to afford a 15.9 mg mixture of inseparable 1.78 in 93:7 *E*:*Z* ratio (15.5 mg, 0.0431 mmol, 86% yield) and initiation product (*Z*)-4-methyl-4-phenylpent-2-enenitrile in >98:2 *Z*:*E* ratio (0.4 mg, 0.0215 mmol, 4.3% yield) as colorless oil. **IR (neat)**: 2928 (s), 2862 (s), 2218 (w), 2170 (w), 1631 (w), 1462 (m), 1383 (w), 1072 (w), 995 (w), 883 (m), 676 (s), 661 (s), 621 (m), 457 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 5.09 (1H, s), 2.24 (2H, t, J = 6.8 Hz), 2.20–2.12 (2H, m), 2.04 (3H, s), 1.59–1.25 (12H, m), 1.06 (21H, d, J = 4.5 Hz); *Z* isomer (resolved signals only): δ 1.90 (3H, s); initiation product (resolved signals only): δ 7.39–7.30 (5H, m), 6.53 (1H, d, J = 12.2 Hz), 5.35 (1H, d, J = 12.2 Hz), 1.64 (6H, s); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 165.7, 117.4, 109.3, 95.1, 80.2, 38.8, 29.4, 29.1, 29.0, 28.9, 28.7, 27.2, 21.1, 19.9, 18.8, 11.4; **HRMS [M+H]$^+$** calcd for $C_{23}H_{42}NSi$: 360.3087, found: 360.3098.

(*E*)-3-Methyl-5-phenylpent-2-enenitrile (1.79): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 50 μL, 5.0 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 150 μL, 15.0 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-(3-methylpent-3-en-1-yl)benzene (16.0 mg, 0.100 mmol) and maleonitrile (11.7 mg, 0.150 mmol) in 0.30 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 85% consumption of (*E*)-(3-methylpent-3-en-1-yl)benzene. The resulting red oil was purified by silica gel chromatography (hexanes → 2% Et_2O in hexanes) to afford **1.79** in 92:8 *E*:*Z* ratio as colorless oil (14.0 mg, 0.0818 mmol, 82% yield). **IR (neat)**: 3061 (w), 2920 (w), 2853 (w), 2217 (m), 1632 (w), 1603 (w), 1495 (w), 1454 (m), 1384 (w), 810 (w), 748 (m), 699 (s), 517 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 7.30 (2H, ddd, J = 7.5, 6.3, 1.3 Hz), 7.25–7.19 (1H, m), 7.18–7.13 (2H, m), 5.09 (1H, h, J = 1.2 Hz), 2.82–2.76 (2H, m), 2.54–2.46 (2H, m), 2.09 (3H, d, J = 1.0 Hz); *Z* isomer (resolved signals only): δ 5.12 (1H, q, J =1.5 Hz), 1.92 (3H, d, J =1.5 Hz); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 164.3, 140.2, 128.8, 128.3, 126.6, 117.2, 96.0, 40.4, 33.6, 21.3; **HRMS [M+H]$^+$** calcd for $C_{12}H_{14}N$: 174.1126, found: 174.1120.

(*E*)-5-(Benzo[*b*]thiophen-2-yl)-3-methylpent-2-enenitrile (1.80): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 75 μL, 7.5 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-2-(3-methylpent-3-en-1-yl)benzo[*b*]thiophene (10.8 mg, 0.050 mmol) and maleonitrile (5.9 mg, 0.075 mmol) in 0.15 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 60% consumption of (*E*)-2-(3-

methylpent-3-en-1-yl)benzo[*b*]thiophene. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in hexanes) to afford 1.80 in 92:8 *E*:*Z* ratio as colorless oil (6.6 mg, 0.0290 mmol, 58% yield). **IR (neat)**: 3058 (w), 2924 (m), 2852 (w), 2216 (m), 1632 (w), 1603 (w), 1457 (w), 1436 (m), 1383 (w), 1065 (w), 859 (w), 825 (m), 747 (s), 726 (m), 564 (w); **^{1}H NMR (600 MHz, $CDCl_3$):** *E* isomer (major): δ 7.77 (1H, d, J = 7.9 Hz), 7.68 (1H, d, J = 7.6 Hz), 7.33 (1H, tt, J = 8.0, 1.2 Hz), 7.28 (1H, tt, J = 7.1, 1.2 Hz), 7.01 (1H, s), 5.17 (1H, t, J = 1.2 Hz), 3.09 (2H, t, J = 7.6 Hz), 2.64 (2H, t, J = 7.6 Hz), 2.12 (3H, s); *Z* isomer (resolved signals only): δ 7.07 (1H, s), 3.14 (2H, t, J = 7.7 Hz), 2.87 (2H, t, J = 7.7 Hz), 1.94 (3H, s); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 163.2, 143.6, 140.0, 139.4, 124.5, 124.1, 123.1, 122.3, 121.5, 117.0, 96.6, 39.8, 28.6, 21.2; **HRMS [M+H]$^+$** calcd for $C_{14}H_{14}NS$: 228.0847, found: 228.0836.

(*Z*)-6-(3,4-Dimethoxyphenyl)-3-methylhex-2-enenitrile (1.82): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 75 μL, 7.5 μmol) were transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dimethoxy-4-(4-methylhex-4-en-1-yl)benzene (12.5 mg, 0.050 mmol) and maleonitrile (5.9 mg, 0.075 mmol) in 0.15 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 91% consumption of (*Z*)-1,2-dimethoxy-4-(4-methylhex-4-en-1-yl)benzene. The resulting red oil was purified by silica gel chromatography (2% → 5% EtOAc in hexanes) to afford 1.82 in 89:11 *Z:E* ratio as colorless oil (11.2 mg, 0.0457 mmol, 91% yield). **IR (neat)**: 2923 (m), 2852 (w), 2215 (w), 1590 (w), 1514 (s), 1463 (m), 1418 (w), 1258 (s), 1235 (s), 1155 (m), 1142 (m), 1028 (s), 803 (w), 762 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** *Z* isomer (major): δ 6.80 (1H,

d, J = 8.2 Hz), 6.76–6.66 (2H, m), 5.12 (1H, q, J = 1.5 Hz), 3.88 (3H, s), 3.86 (3H, s), 2.65–2.58 (2H, m), 2.49–2.42 (2H, m), 1.90 (3H, d, J = 1.5 Hz), 1.86–1.76 (2H, m); *E* isomer (resolved signals only): δ 5.11 (1H, dd, J = 2.4, 1.2 Hz), 3.87 (3H, s), 2.58–2.53 (2H, m), 2.23–2.17 (2H, m), 2.05 (3H, d, J = 1.0 Hz); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 165.3, 149.0, 147.5, 134.2, 120.3, 117.1, 111.8, 111.4, 96.0, 56.0, 56.0, 36.2, 35.2, 29.7, 23.0; **HRMS [M+H]$^+$** calcd for $C_{15}H_{20}NO_2$: 246.1489, found: 246.1483.

Benzyl (*Z*)-7-cyano-2-(dibenzylamino)-6-methylhept-6-enoate (1.83): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 75 μL, 7.5 μmol) were transferred by syringe to an oven-dried vial containing benzyl (*Z*)-2-(dibenzylamino)-6-methyloct-6-enoate (22.1 mg, 0.050 mmol) and maleonitrile (5.9 mg, 0.075 mmol) in 0.15 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 80% consumption of benzyl (*Z*)-2-(dibenzylamino)-6-methyloct-6-enoate. The resulting red oil was purified by silica gel chromatography (5% → 10% EtOAc in hexanes) to afford 1.83 in 88:12 *Z:E* ratio as colorless oil (17.5 mg, 0.0387 mmol, 77% yield). **IR (neat)**: 3029 (w), 2922 (m), 2851 (w), 2217 (w), 1727 (m), 1494 (w), 1454 (m), 1377 (w), 1221 (w), 1146 (m), 1074 (w), 1028 (w), 966 (w), 747 (m), 968 (s); **^{1}H NMR (600 MHz, $CDCl_3$):** *Z* isomer (major): δ 7.46–7.35 (5H, m), 7.32–7.27 (8H, m), 7.23 (2H, dt, J = 6.7, 3.6 Hz), 5.31–5.14 (2H, m), 5.06 (1H, s), 3.89 (2H, d, J = 13.8 Hz), 3.53 (2H, d, J = 13.4 Hz), 3.36 (1H, t, J = 7.3 Hz), 2.34–2.20 (2H, m, J = 6.9 Hz), 1.79 (3H, s), 1.76 (2H, t, J = 7.8 Hz), 1.63 (1H, dq, J = 13.7, 7.4 Hz), 1.38 (1H, tt, J = 15.2, 8.2 Hz); *E* isomer (resolved signals only): δ 4.91 (1H, s), 3.87 (2H, d, J = 5.5 Hz), 1.93 (3H, s); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 172.7,

165.0, 139.6, 136.2, 129.0, 128.8, 128.7, 128.5, 128.4, 127.2, 117.0, 96.1, 66.2, 60.8, 54.7, 35.9, 29.1, 24.3, 22.8; **HRMS [M+H]$^+$** calcd for $C_{30}H_{33}N_2O_2$: 453.2536, found: 453.2525.

(*Z*)-(3-Methylpent-3-en-1-yl)benzene (1.84): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 75 μL, 7.5 μmol) were transferred by syringe to an oven-dried vial containing (*Z*)-(3-methylpent-3-en-1-yl)benzene (8.0 mg, 0.050 mmol) and maleonitrile (5.9 mg, 0.075 mmol) in 0.15 mL benzene. The resulting solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 86% consumption of (*Z*)-(3-methylpent-3-en-1-yl)benzene. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in hexanes) to afford 1.84 in 90:10 *Z:E* ratio as colorless oil (6.4 mg, 0.0374 mmol, 75% yield). **IR (neat)**: 3028 (w), 2951 (w), 2862 (w), 2216 (s), 1631 (m), 1603 (w), 1496 (m), 1454 (m), 1379 (w), 1031 (w), 804 (w), 746 (m), 699 (s), 497 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** *Z* isomer (major): δ 7.37–7.26 (2H, m), 7.27–7.18 (3H, m), 5.12 (1H, q, J = 1.6 Hz), 2.83 (2H, dd, J = 9.0, 5.9 Hz), 2.78–2.69 (2H, m), 1.92 (3H, d, J = 1.5 Hz); *E* isomer (resolved signals only): δ 5.09 (1H, q, J = 1.2 H), 2.50 (2H, ddd, J = 8.8, 6.8, 1.3 Hz), 2.09 (3H, d, J = 1.0 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 164.5, 140.2, 128.7, 128.5, 126.5, 116.9, 96.5, 38.0, 34.0, 23.2; **HRMS [M+H]$^+$** calcd for $C_{12}H_{14}N$: 172.1126, found: 172.1130.

(*E*)-3-(4-Methoxyphenyl)but-2-enenitrile (1.87): Following the general procedure, a solution of **Mo-3e** in benzene (0.1 M, 50 μL, 5.0 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 60 μL, 6.0 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-1-(but-2-en-2-yl)-4-methoxybenzene (8.1 mg, 0.050 mmol) and maleonitrile (5.9 mg, 0.075

mmol) in 0.15 mL benzene. The resulting solution was allowed to stir for 4 h at 80 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 60% consumption of (*E*)-1-(but-2-en-2-yl)-4-methoxybenzene. The resulting red oil was purified by silica gel chromatography (5% → 10% Et_2O in hexanes) to afford 1.87 in 93:7 *E:Z* ratio as off-white solid (4.9 mg, 0.0283 mmol, 57% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 7.48–7.39 (2H, m), 6.94–6.88 (2H, m), 5.55 (1H, q, J = 1.0 Hz), 3.84 (3H, s), 2.44 (3H, d, J = 1.0 Hz); *Z* isomer (resolved signals only): δ 7.60–7.54 (2H, m), 5.31 (1H, q, J = 1.5 Hz), 2.26 (3H, d, J = 1.5 Hz); **HRMS [M+H]$^+$** calcd for $C_{11}H_{12}NO$: 174.0913, found: 174.0910. The spectral data of this compound is consistent with those previously reported.[34]

(*E*)-3-(3-Chlorophenyl)but-2-enenitrile (1.88): Following the general procedure, a solution of **Mo-3e** in benzene (0.1 M, 75 μL, 7.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 90 μL, 9.0 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-1-(but-2-en-2-yl)-3-chlorobenzene (8.3 mg, 0.050 mmol) and maleonitrile (5.9 mg, 0.075 mmol) in 0.15 mL benzene. The resulting solution was allowed to stir for 4 h at 80 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 55% consumption of (*E*)-1-(but-2-en-2-yl)-3-chlorobenzene. The resulting red oil was purified by silica gel chromatography (hexanes → 2% Et_2O in hexanes) to afford a 5.5 mg mixture of inseparable 1.88 in 91:9 *E:Z* ratio (4.5 mg, 0.0255 mmol, 51% yield) and initiation product 4-methyl-4-phenylpent-2-enenitrile in 46:54 *E:Z* ratio (1.0 mg, 0.00584 mmol, 12% yield) as colorless oil. **^{1}H NMR (600 MHz, $CDCl_3$):** *E* isomer (major): δ 7.45–7.43 (1H, m), 7.40 (1H, dq, J = 4.5, 2.7 Hz), 7.34 (2H, dd, J = 3.5, 2.0 Hz), 5.62 (1H, s), 2.46 (3H, s); *Z* isomer (resolved signals only): δ 5.44 (1H, s),

2.27 (3H, s); initiation product: *E* isomer isomer (resolved signals only): δ 6.89 (1H, d, J = 16.6 Hz), 5.29 (1H, d, J = 16.6 Hz), 1.46 (6H, s); *Z* isomer (resolved signals only): δ 6.54 (1H, d, J = 12.2 Hz), 5.36 (1H, d, J = 12.2 Hz), 1.64 (6H, s); **HRMS [M+H]$^+$** calcd for $C_{10}H_9NCl$: 178.0418, found: 178.0416. The spectral data of this compound is consistent with those previously reported[70].

(*E*)-3-(Benzo[*d*][1,3]dioxol-5-yl)but-2-enenitrile (1.89): Following the general procedure, a solution of **Mo-3e** in benzene (0.1 M, 75 μL, 7.5 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 90 μL, 9.0 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-5-(but-2-en-2-yl)benzo[*d*][1,3]dioxole (8.8 mg, 0.050 mmol) and maleonitrile (5.9 mg, 0.075 mmol) in 0.15 mL benzene. The resulting solution was allowed to stir for 4 h at 80 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 60% consumption of (*E*)-5-(but-2-en-2-yl)benzo[*d*][1,3]dioxole. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in hexanes) to afford 1.89 in 89:11 *E:Z* ratio as off-white solid (5.5 mg, 0.0294 mmol, 59% yield). **M.p.**: 108–109 ℃; **IR (neat)**: 2918 (w), 2851 (w), 2203 (w), 1595 (w), 1501 (m), 1489 (s), 1431 (m), 1385 (w), 1281 (w), 1246 (s), 1230 (m), 1111 (w), 1037 (s), 931 (w), 873 (w), 807 (s); **^{1}H NMR (500 MHz, $CDCl_3$):** *E* isomer (major): δ 7.00 (1H, dd, J = 8.2, 1.9 Hz), 6.94 (1H, d, J = 1.9 Hz), 6.82 (1H, d, J = 8.2 Hz), 6.01 (2H, s), 5.52 (1H, s), 2.42 (3H, d, J = 1.0 Hz); *Z* isomer (resolved signals only): δ 7.10 (1H, dd, J = 8.1, 1.8 Hz), 7.05 (1H, d, J = 1.8 Hz), 6.85 (1H, d, J = 8.1 Hz), 5.32 (1H, s), 2.23 (3H, d, J = 1.4 Hz); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 159.0, 149.6, 148.4, 132.5,

(70) Müller, M.-A.; Pfaltz, A. *Angew.Chem. Int. Ed.* **2014**, *53*, 8668–8671.

120.7, 118.0, 108.5, 106.1, 101.8, 94.2, 20.4; **HRMS [M+H]$^+$** calcd for $C_{11}H_{10}NO_2$: 188.0706, found: 188.0706.

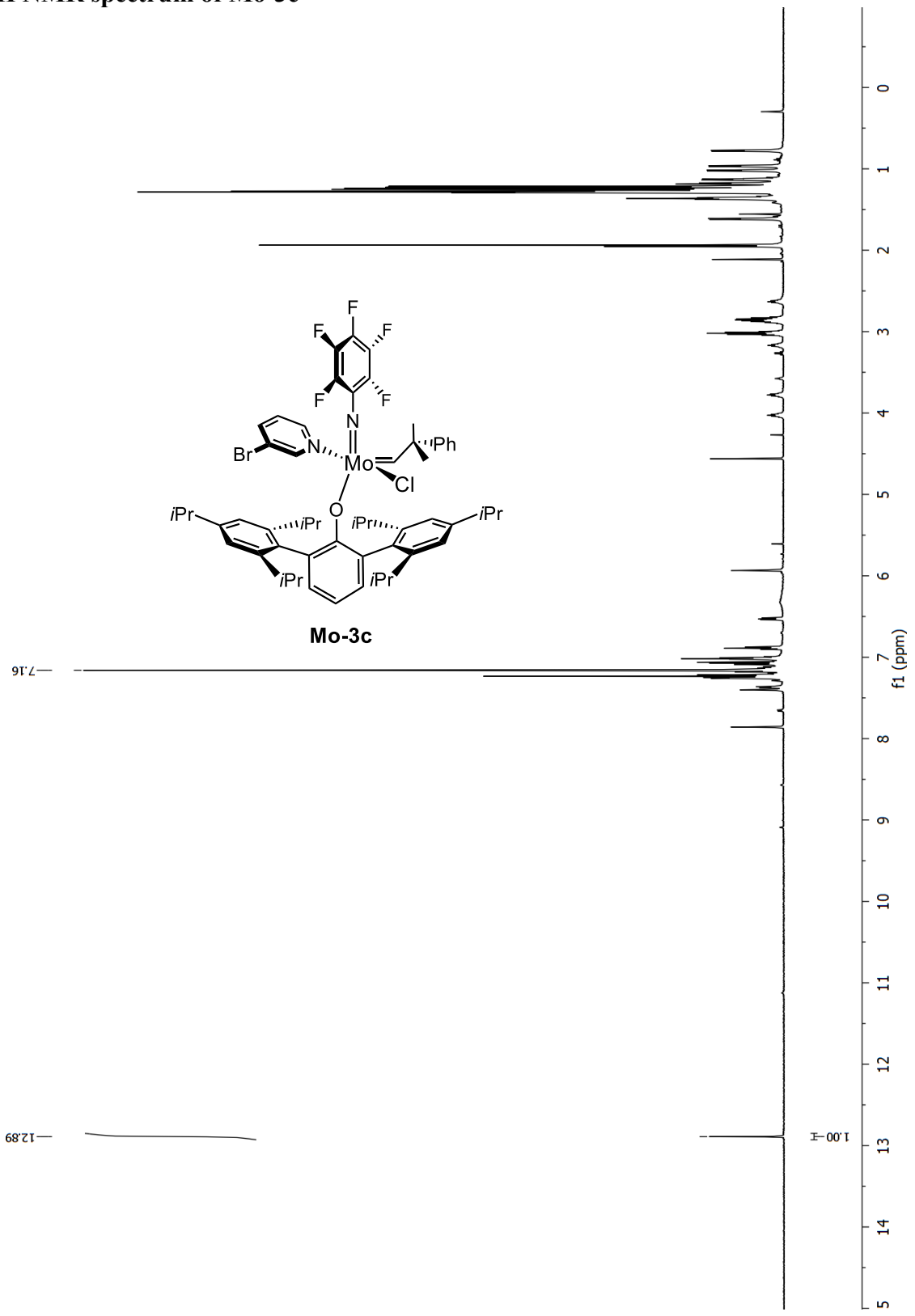
(*E*)-3-(Benzofuran-5-yl)but-2-enenitrile (1.90): Following the general procedure, a solution of **Mo-3e** in benzene (0.1 M, 50 μL, 5.0 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 60 μL, 6.0 μmol) were transferred by syringe to an oven-dried vial containing (*E*)-5-(but-2-en-2-yl)benzofuran (8.6 mg, 0.050 mmol) and maleonitrile (5.9 mg, 0.075 mmol) in 0.15 mL benzene. The resulting solution was allowed to stir for 4 h at 80 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 56% consumption of (*E*)-5-(but-2-en-2-yl)benzofuran. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in hexanes) to afford 1.90 in 90:10 *E:Z* ratio as colorless oil (4.9 mg, 0.0267 mmol, 54% yield). **IR (neat)**: 2920 (w), 2850 (w), 2211 (m), 1603 (w), 1470 (m), 1439 (m), 1381 (w), 1269 (m), 1131 (m), 1113 (m), 1028 (m), 875 (w), 804 (s), 767 (s), 738 (s), 645 (w), 578 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 7.72 (1H, dd, J = 2.0, 0.7 Hz), 7.67 (1H, d, J = 2.2 Hz), 7.51 (1H, dt, J = 8.7, 0.8 Hz), 7.41 (1H, dd, J = 8.7, 2.0 Hz), 6.81 (1H, dd, J = 2.2, 1.0 Hz), 5.63 (1H, q, J = 1.0 Hz), 2.53 (3H, d, J = 1.0 Hz); *Z* isomer (resolved signals only): δ 7.81 (1H, dd, J = 1.9, 0.7 Hz), 5.42 (1H, q, J = 1.5 Hz), 2.34 (3H, d, J = 1.5 Hz); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 160.2, 156.0, 146.4, 133.6, 128.0, 122.5, 119.3, 118.0, 111.9, 107.0, 95.0, 20.8; **HRMS [M+H]$^+$** calcd for $C_{12}H_{10}NO$: 184.0757, found: 184.0760.

(*E*)-3-(1-Methyl-1*H*-indol-5-yl)but-2-enenitrile (1.91): Following the general procedure, a solution of **Mo-3e** in benzene (0.1 M, 50 μL, 5.0 μmol) and $B(C_6F_5)_3$ in benzene (0.1 M, 60 μL, 6.0 μmol) were transferred by syringe to an oven-dried vial

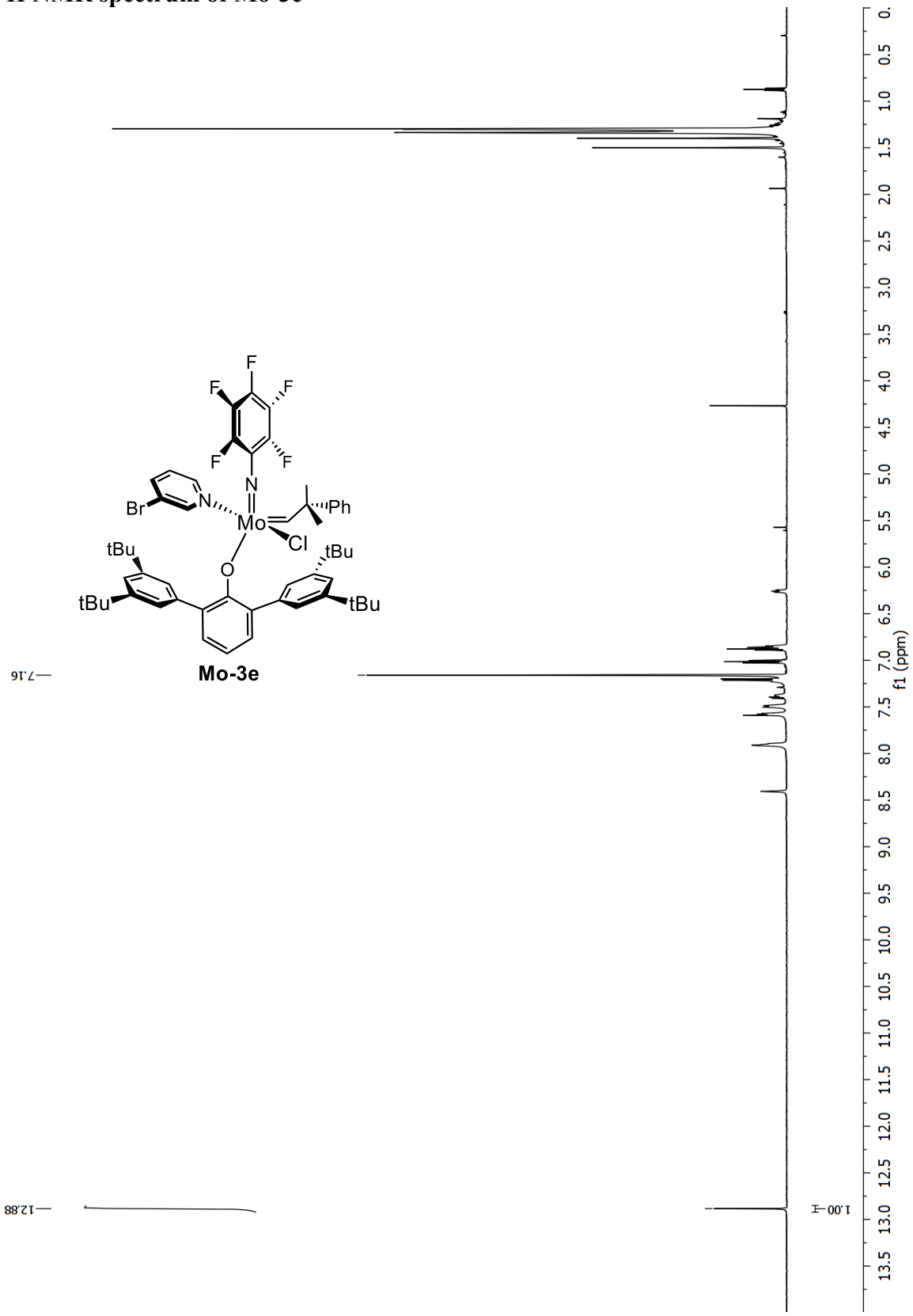
containing (*E*)-5-(but-2-en-2-yl)-1-methyl-1*H*-indole (9.3 mg, 0.050 mmol) and maleonitrile (5.9 mg, 0.075 mmol) in 0.15 mL benzene. The resulting solution was allowed to stir for 4 h at 80 °C. The reaction was quenched by the addition of wet $CDCl_3$ and analysis of the unpurified mixture revealed 75% consumption of (*E*)-5-(but-2-en-2-yl)-1-methyl-1*H*-indole and formation of the product in 87:13 *E:Z* ratio. The resulting red oil was purified by silica gel chromatography (2% → 5% Et_2O in hexanes) to afford 1.91 in 90:10 *E:Z* ratio as off-white solid (4.6 mg, 0.0234 mmol, 47% yield). **M.p.**: 82–84 °C; **IR (neat)**: 2988 (w), 2208 (w), 1594 (w), 1447 (w), 1342 (w), 1275 (m), 1260 (m), 766 (s), 750 (s), 726 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** *E* isomer (major): δ 7.77 (1H, d, J = 1.8 Hz), 7.36 (1H, dd, J = 8.7, 1.8 Hz), 7.31 (1H, d, J = 8.7 Hz), 7.10 (1H, d, J = 3.1 Hz), 6.53 (1H, d, J = 3.2 H), 5.64 (1H, d, J = 1.2 Hz), 3.82 (3H, s), 2.55 (3H, d, J = 1.0 Hz); *Z* isomer (resolved signals only): δ 7.85 (1H, d, J = 1.8 Hz), 7.50 (2H, dd, J = 8.9, 2.1 Hz), 5.35 (1H, d, J = 1.6 Hz), 3.67 (3H, s), 2.35 (3H, d, J = 1.4 Hz); **^{13}C NMR (125 MHz, $CDCl_3$)**: *E* isomer (major): δ 160.9, 137.8, 130.4, 129.7, 128.6, 119.6, 119.3, 118.6, 109.6, 102.3, 93.0, 33.1, 20.6; *Z* isomer (resolved signals only): δ 162.1, 137.5, 130.1, 129.3, 128.4, 121.0, 120.3, 118.7, 109.4, 102.1, 93.4, 33.1, 25.2; **HRMS $[M+H]^+$** calcd for $C_{13}H_{13}N_2$: 197.1073, found: 197.1075.

NMR Spectra

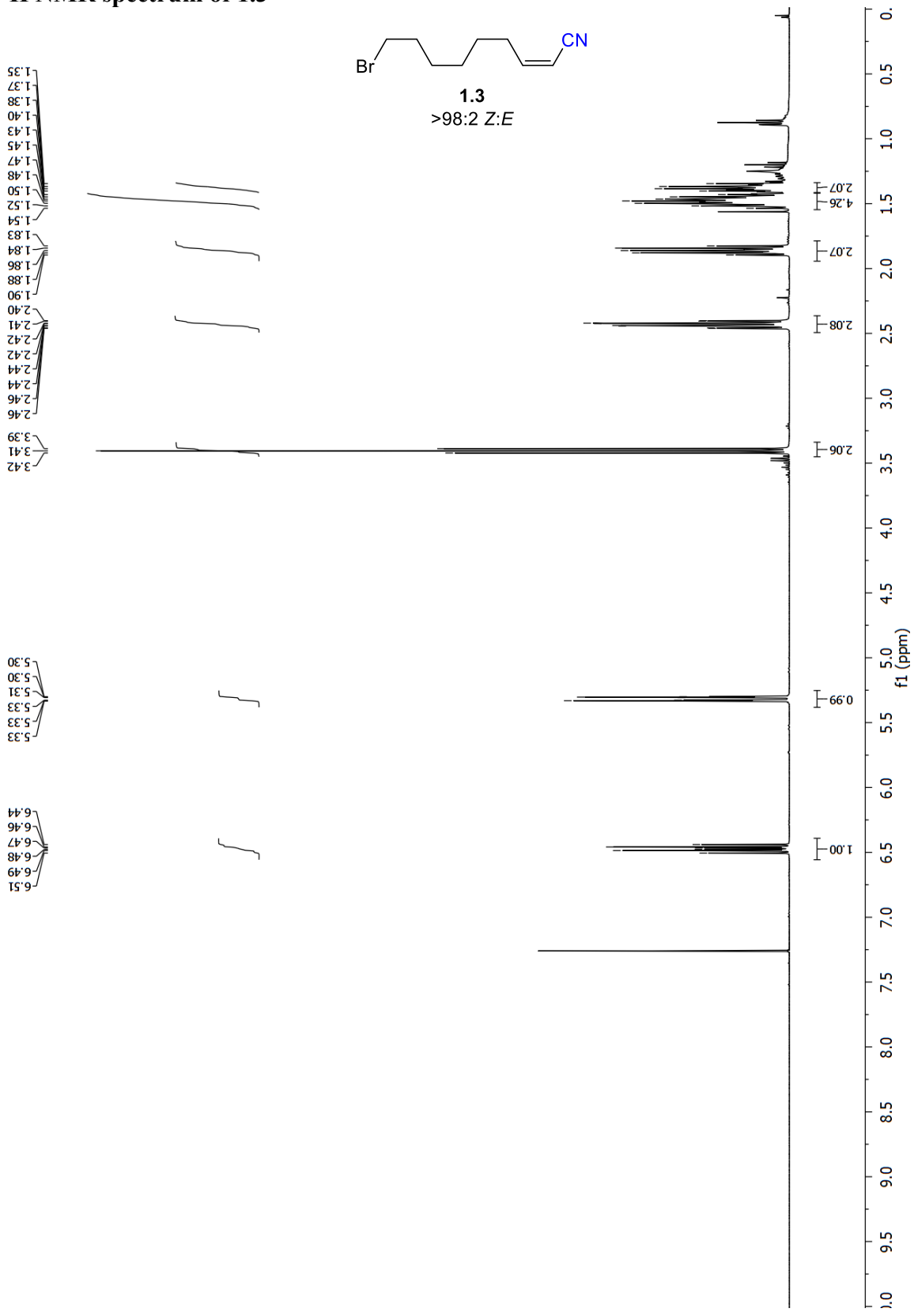
^{1}H NMR spectrum of Mo-3c



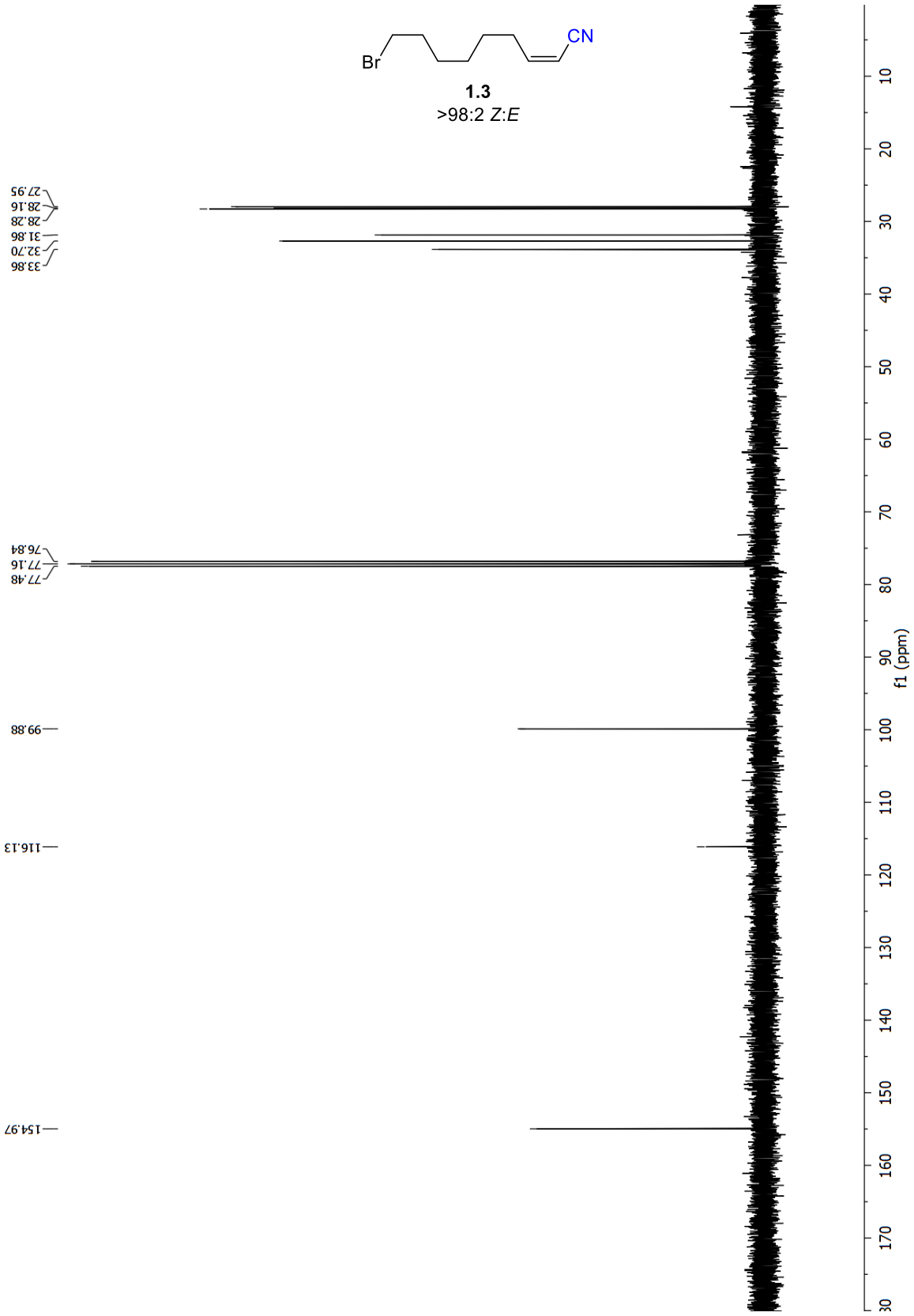
^{1}H NMR spectrum of Mo-3e



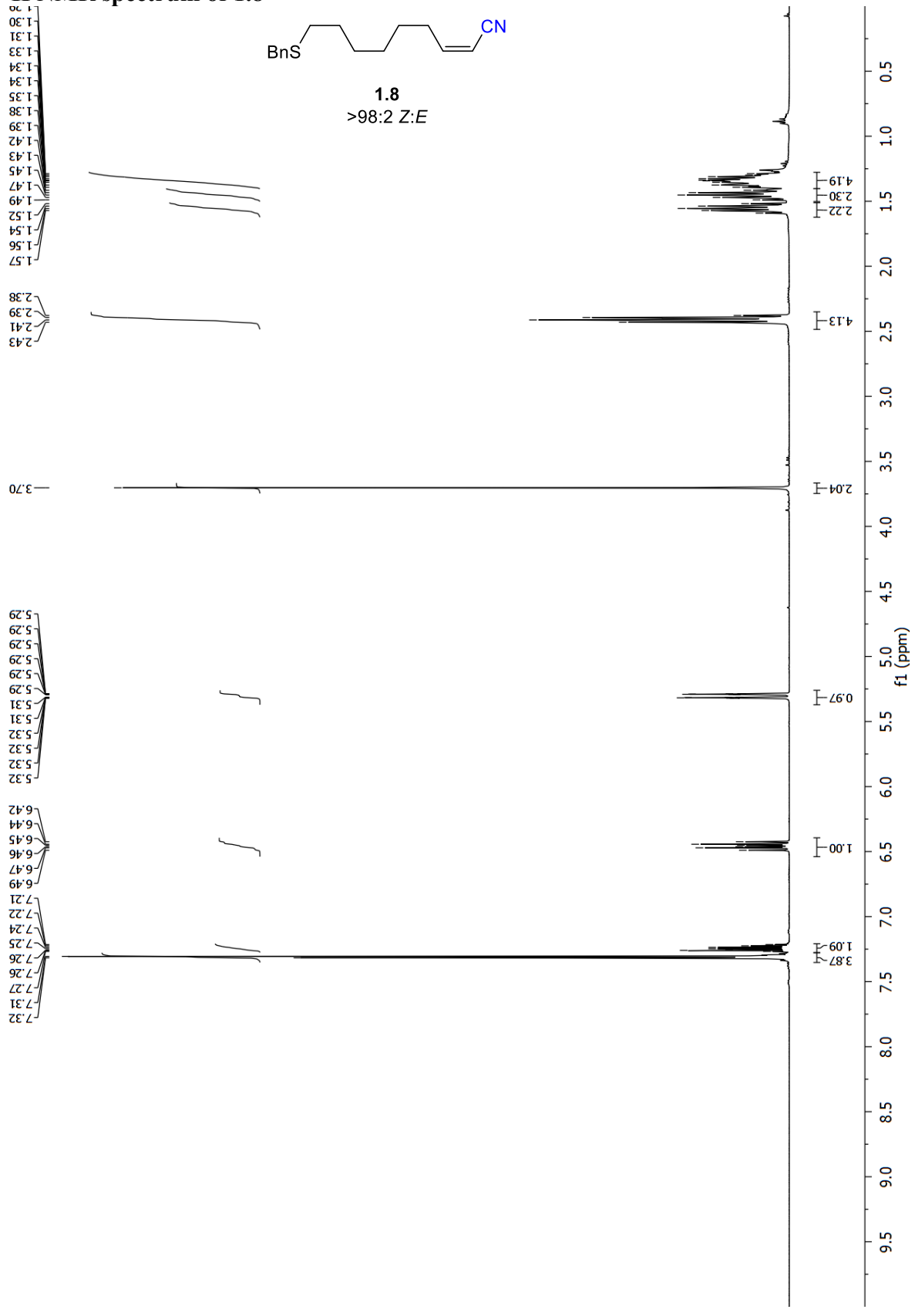
^{1}H NMR spectrum of 1.3



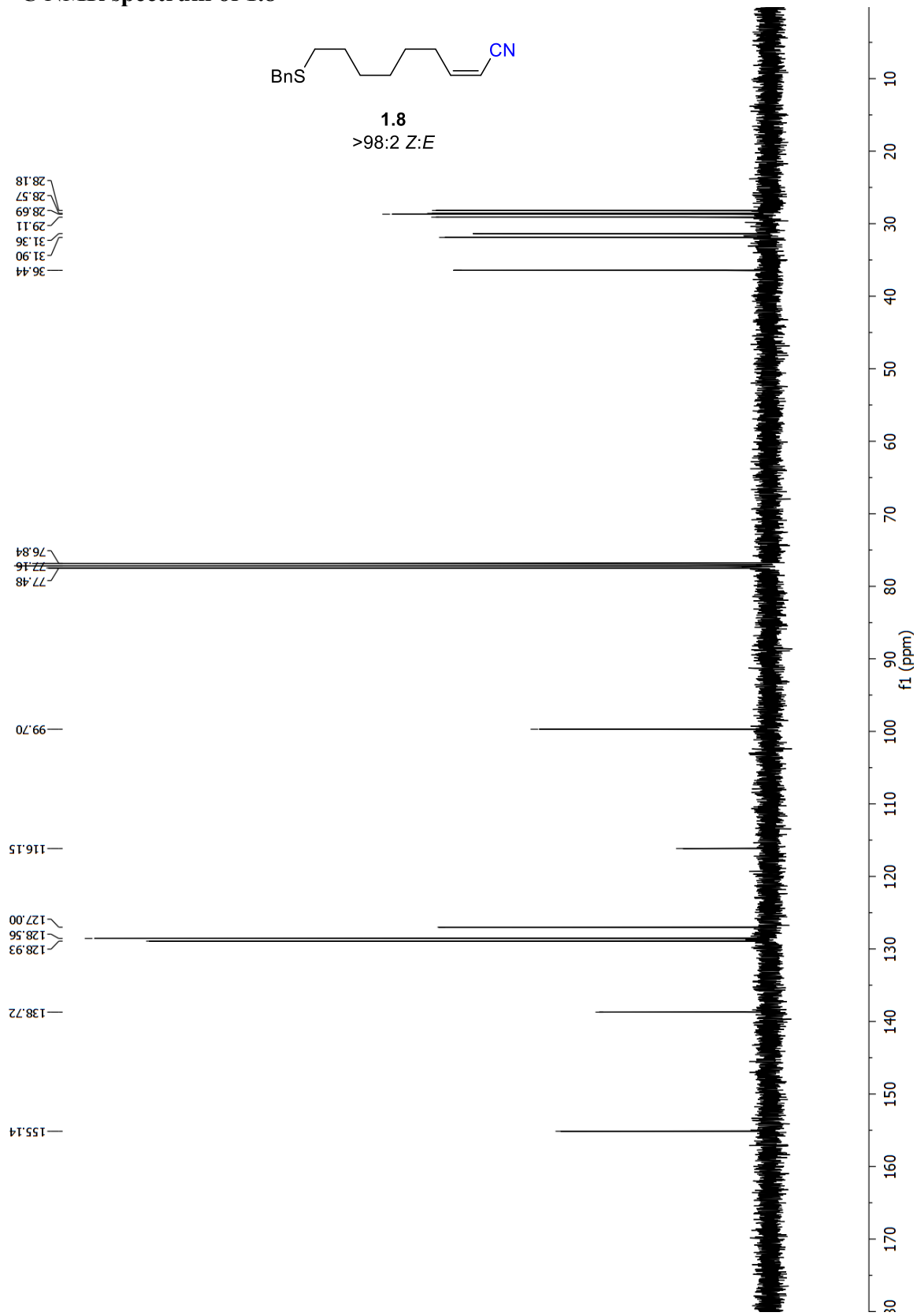
^{13}C NMR spectrum of 1.3



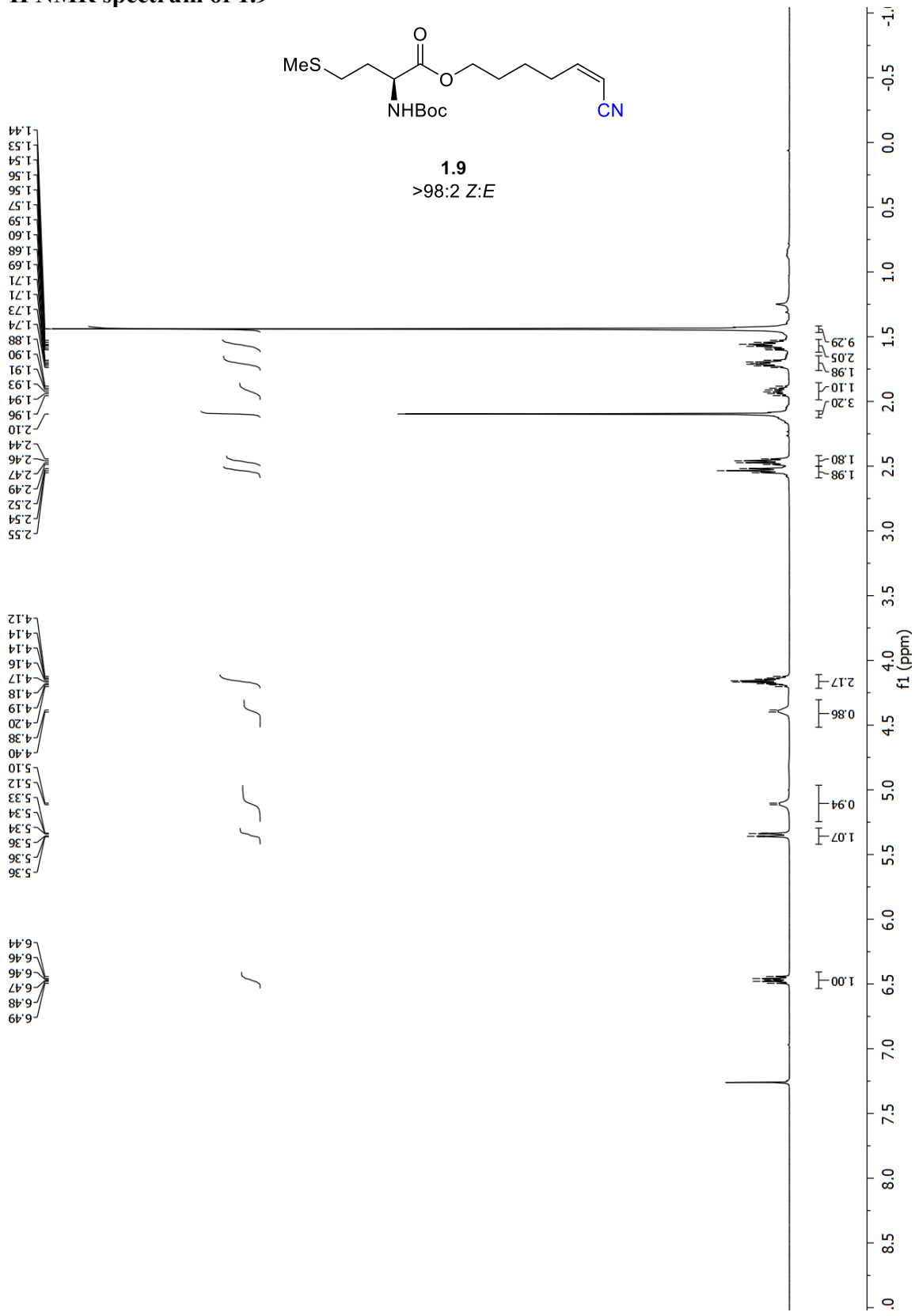
^{1}H NMR spectrum of 1.8



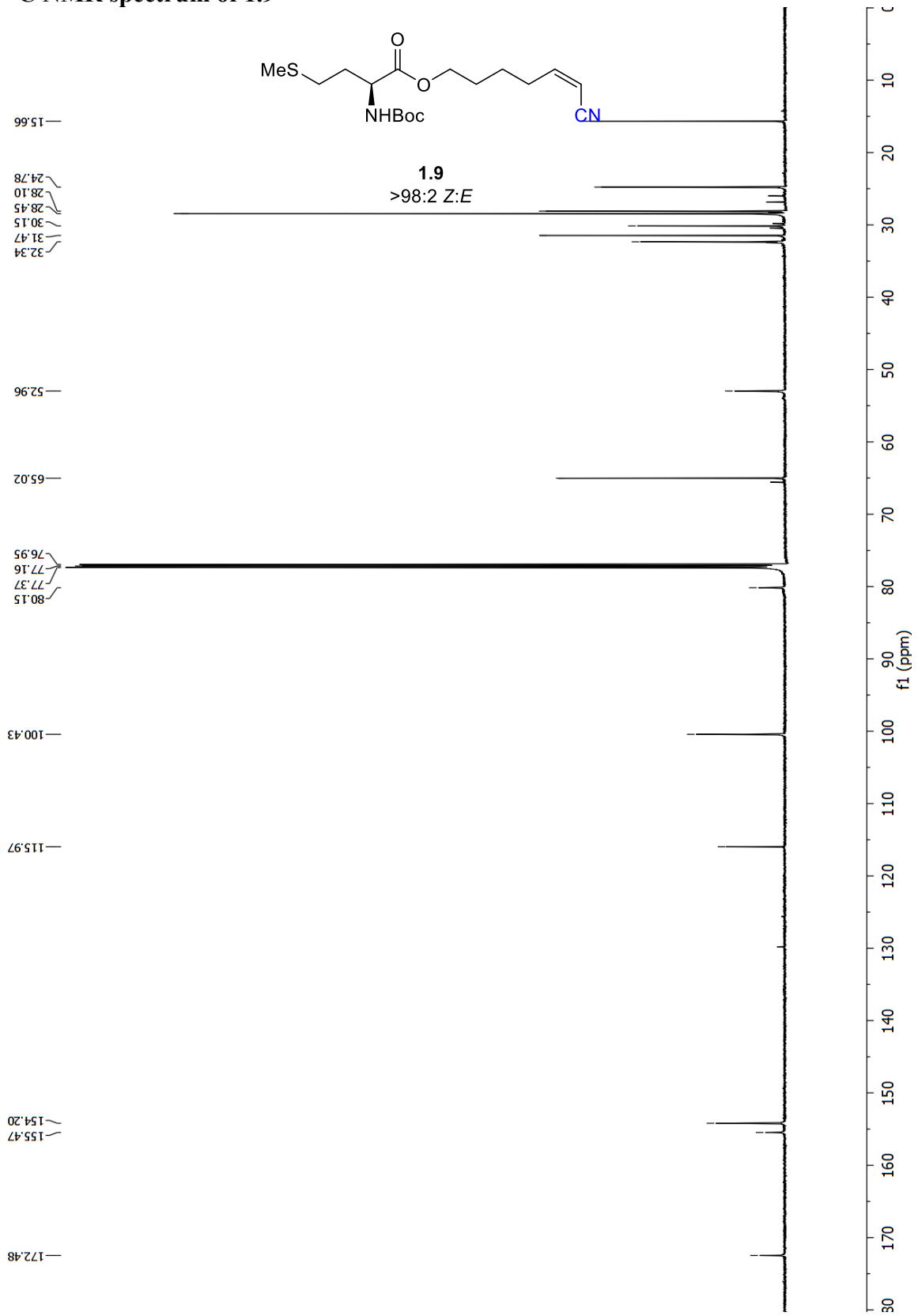
^{13}C NMR spectrum of 1.8



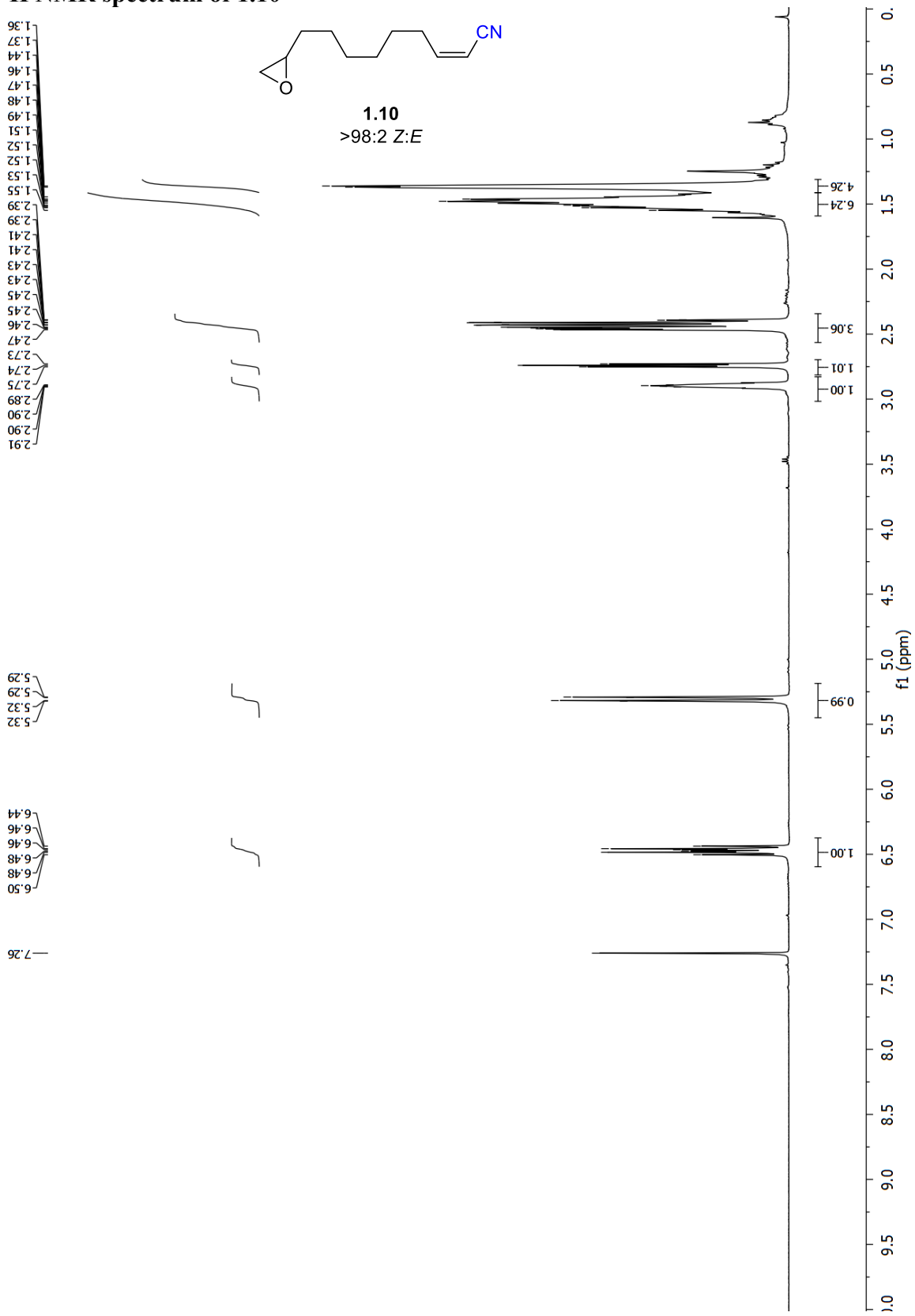
^{1}H NMR spectrum of 1.9



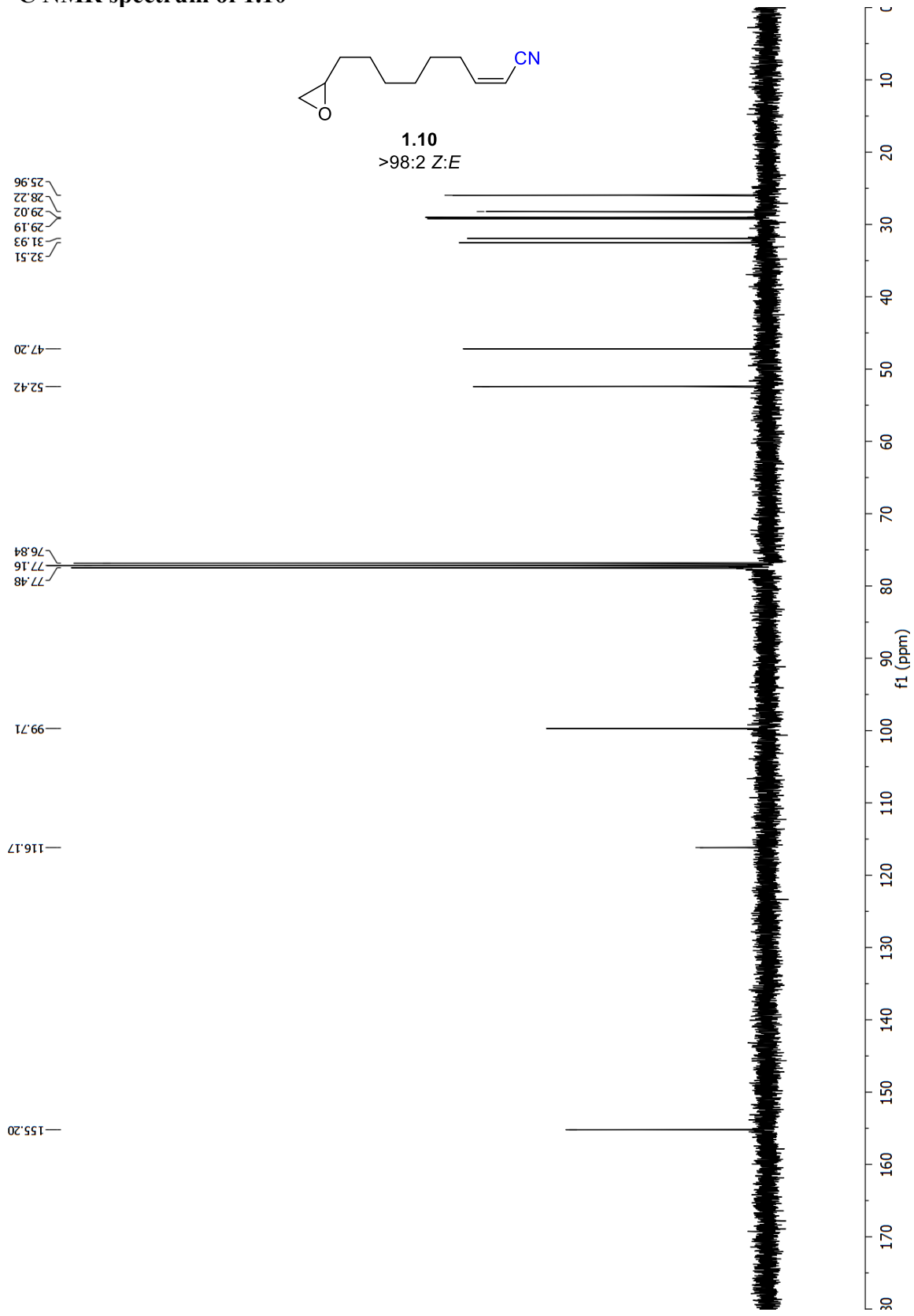
^{13}C NMR spectrum of 1.9



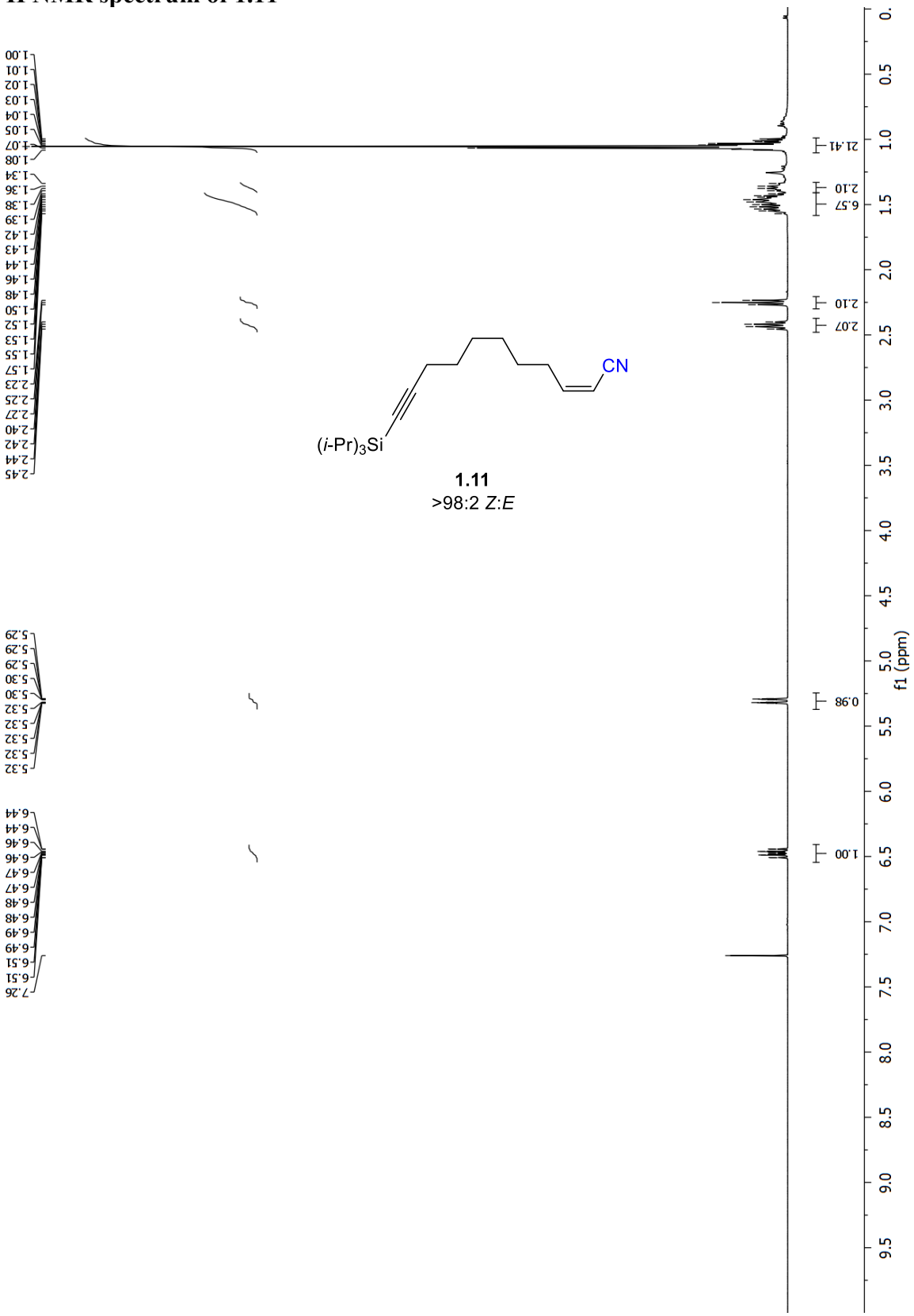
^{1}H NMR spectrum of 1.10



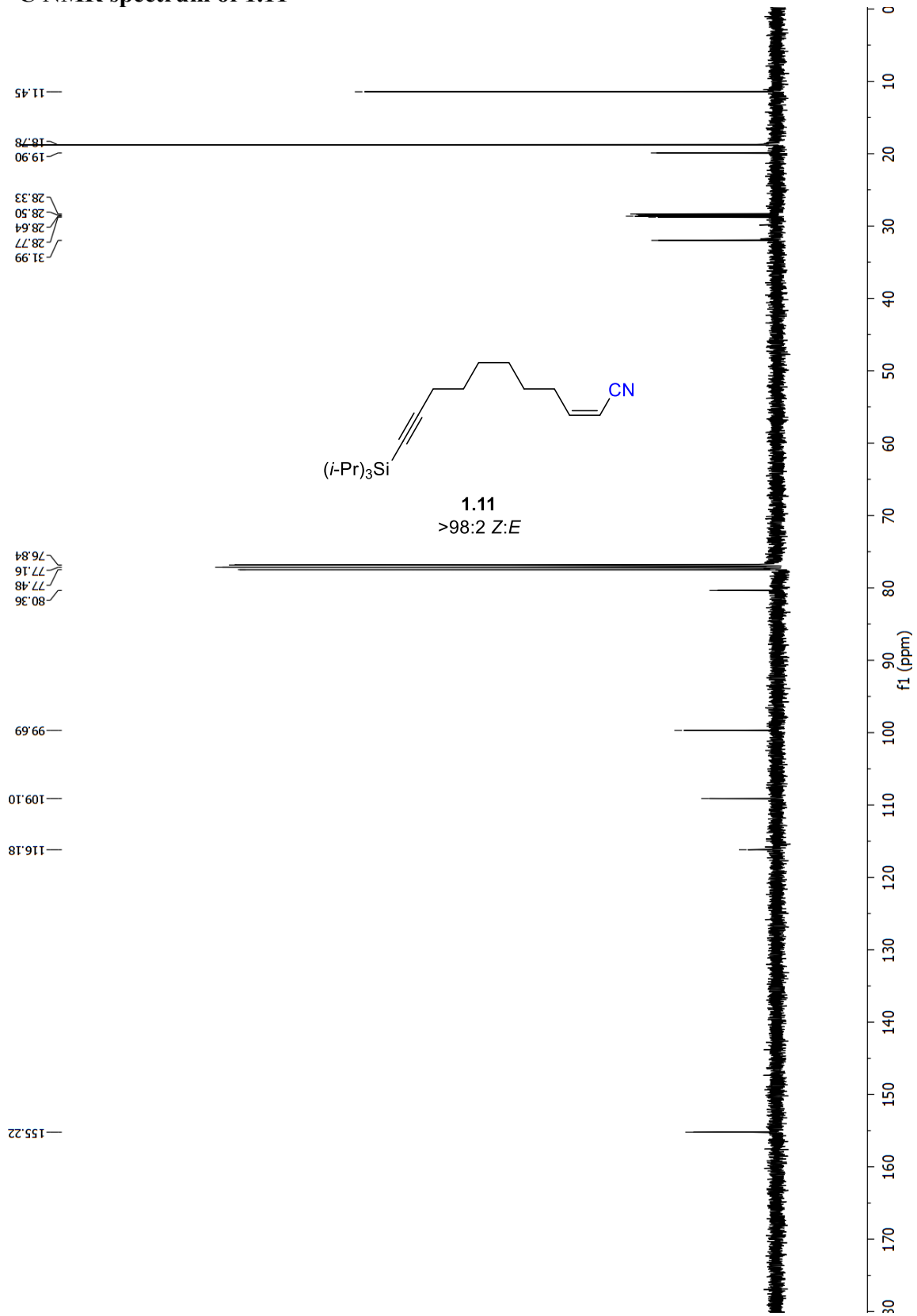
^{13}C NMR spectrum of 1.10



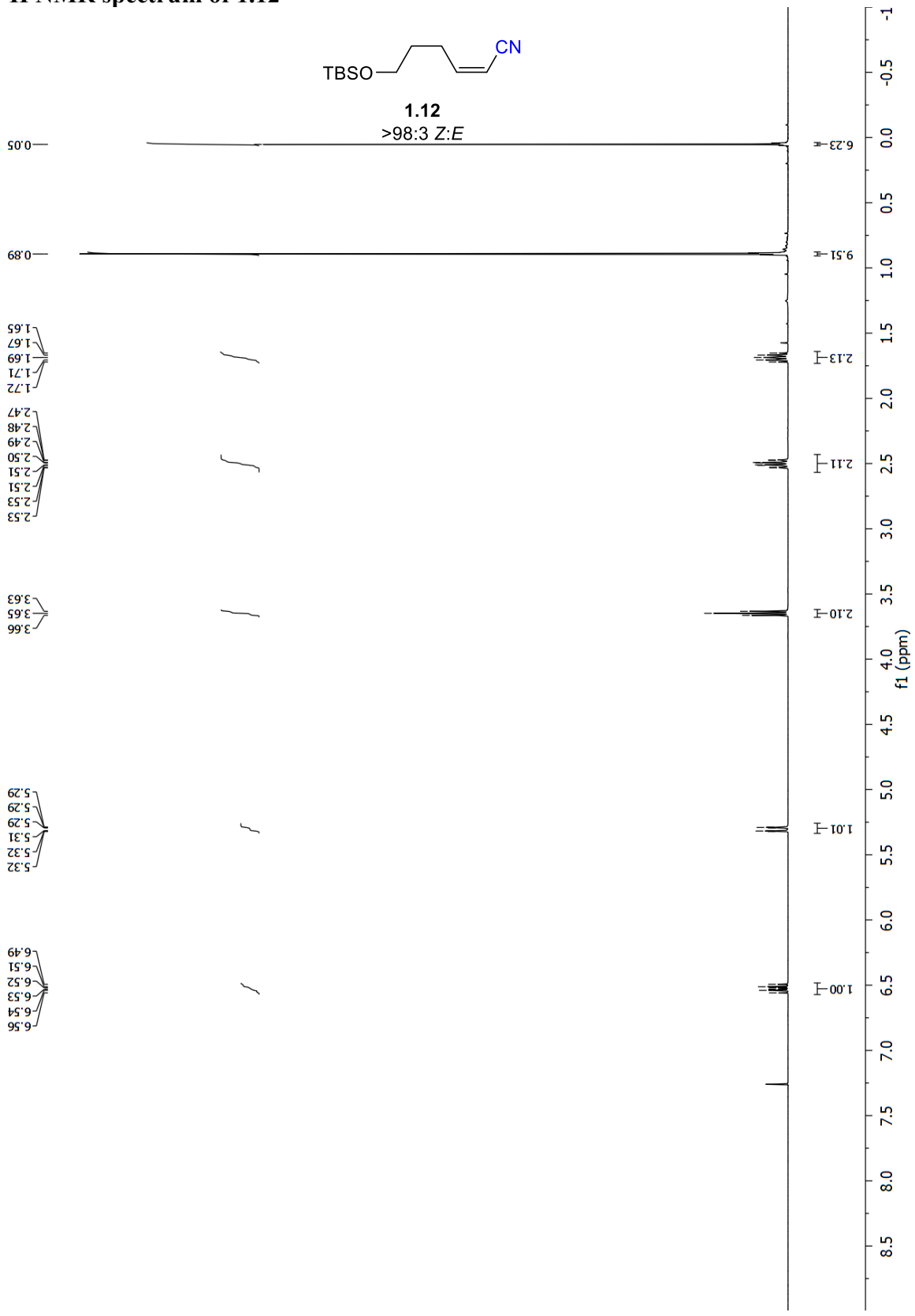
^{1}H NMR spectrum of 1.11



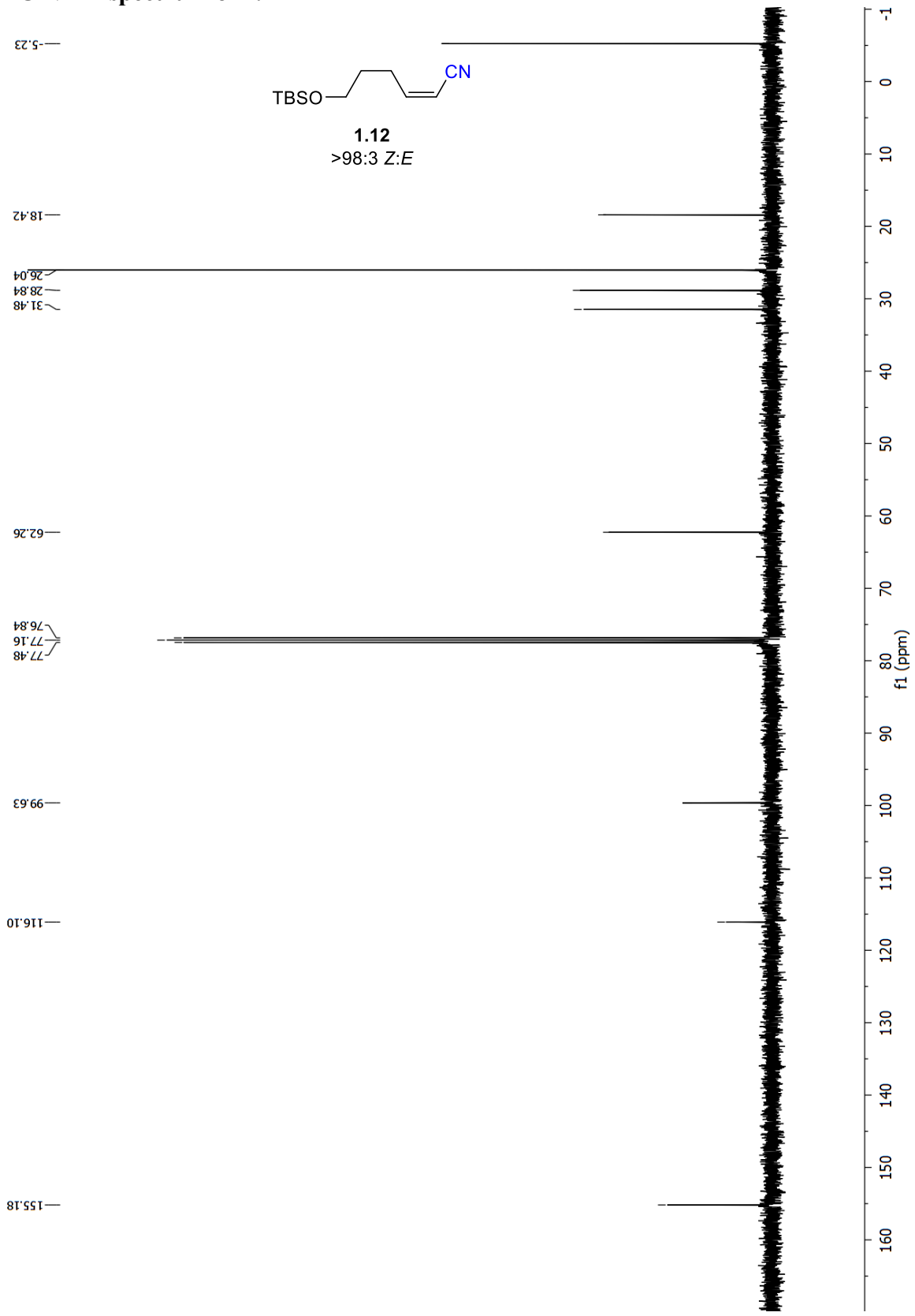
^{13}C NMR spectrum of 1.11



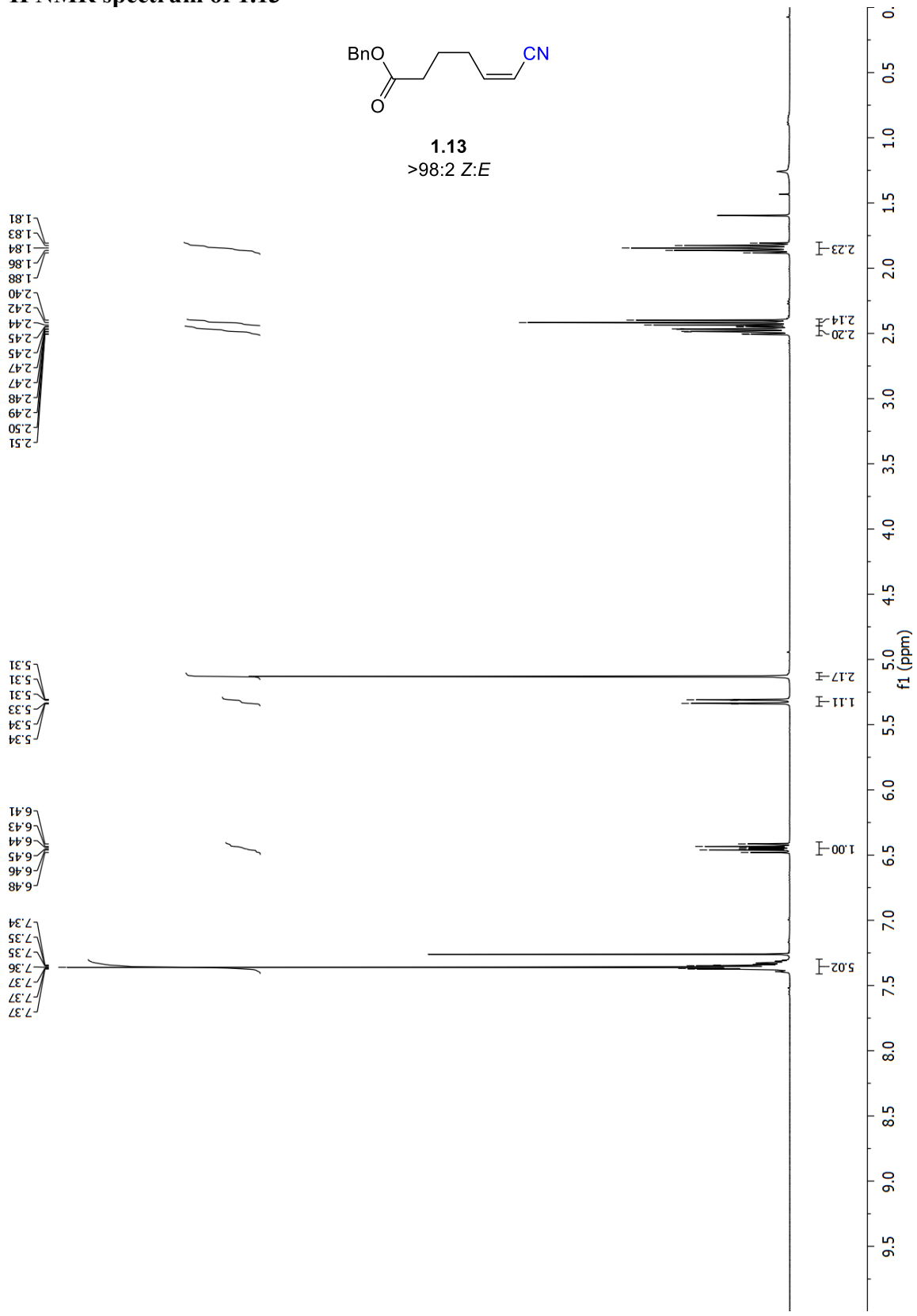
^{1}H NMR spectrum of 1.12



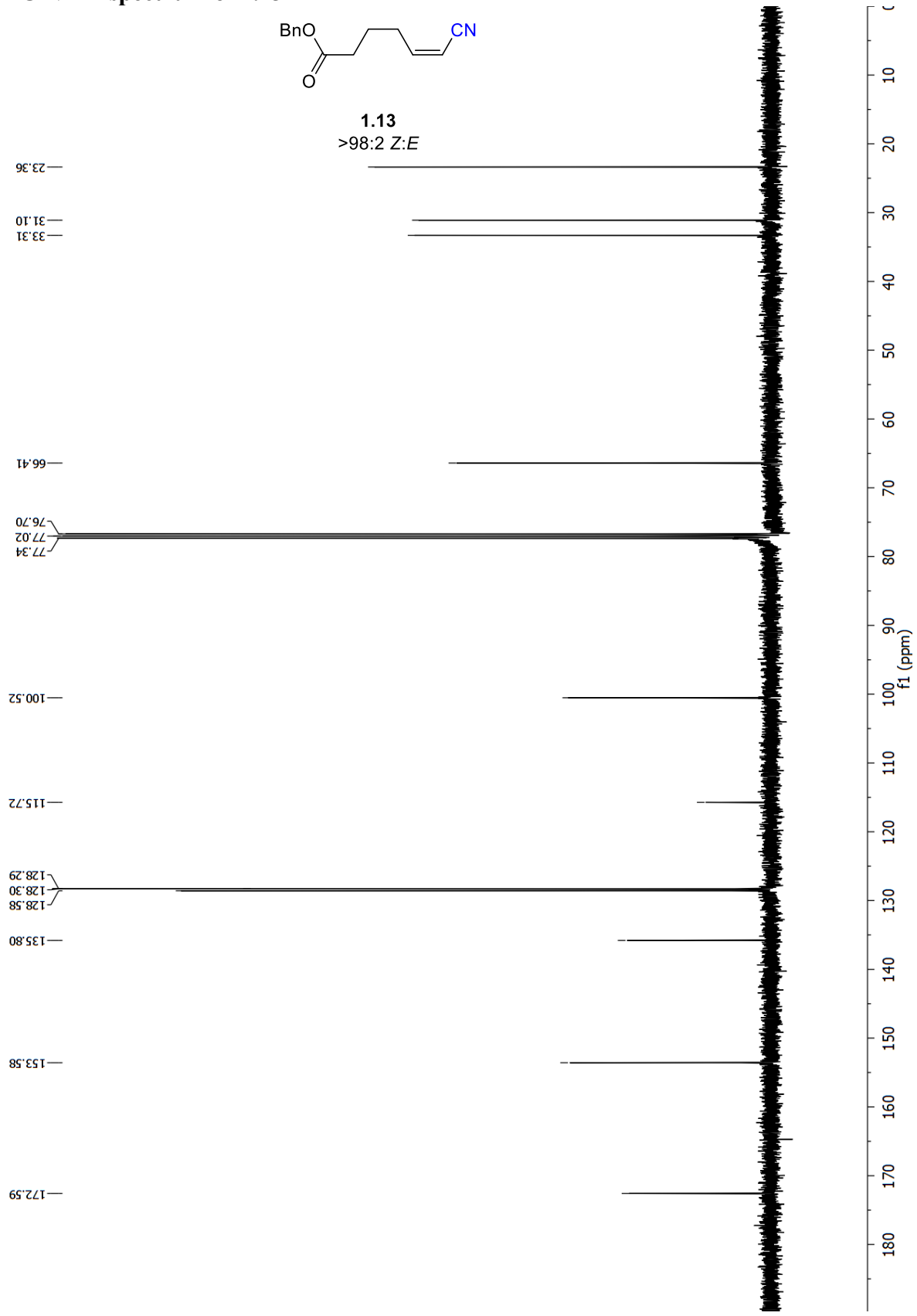
^{13}C NMR spectrum of 1.12



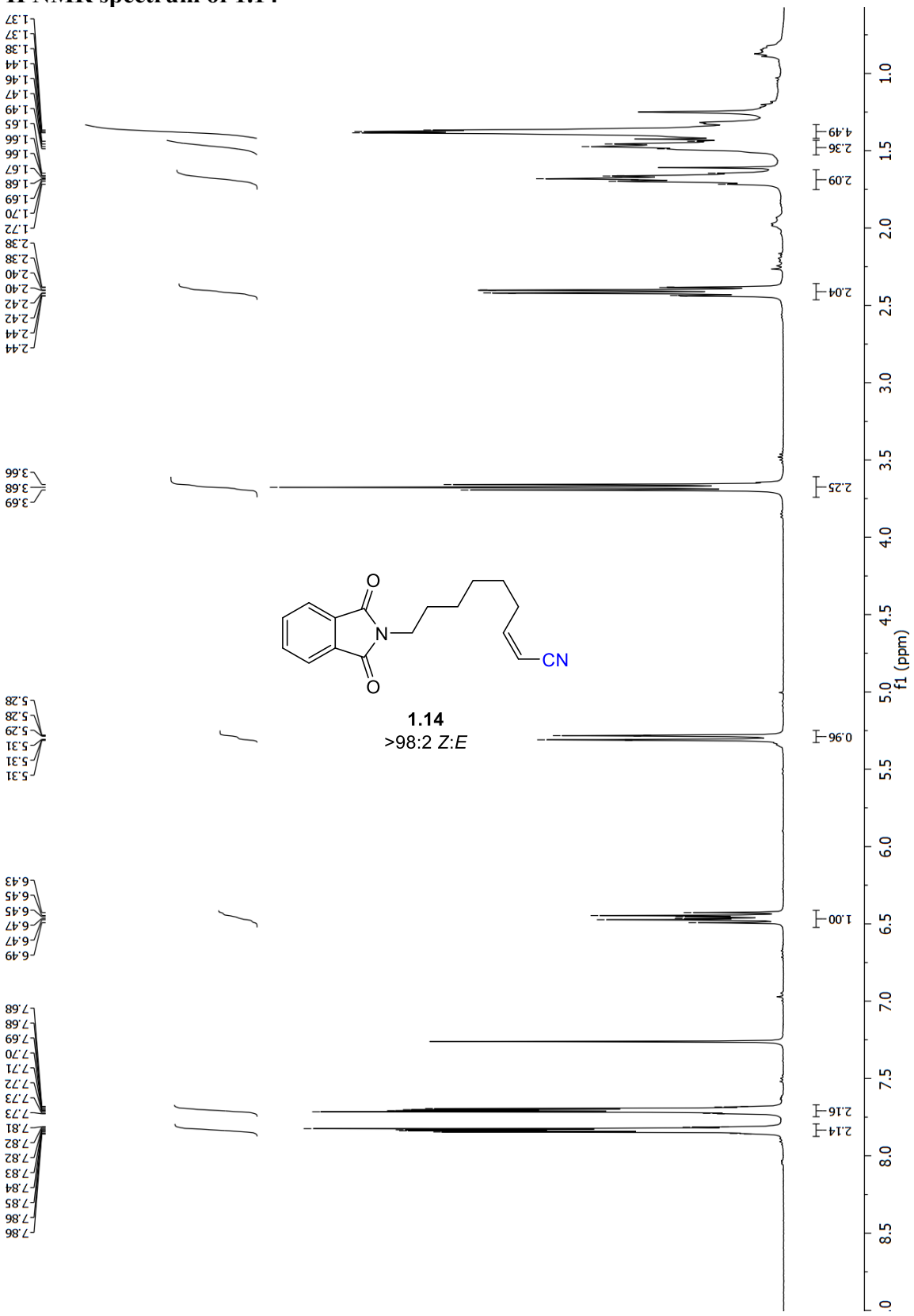
^{1}H NMR spectrum of 1.13



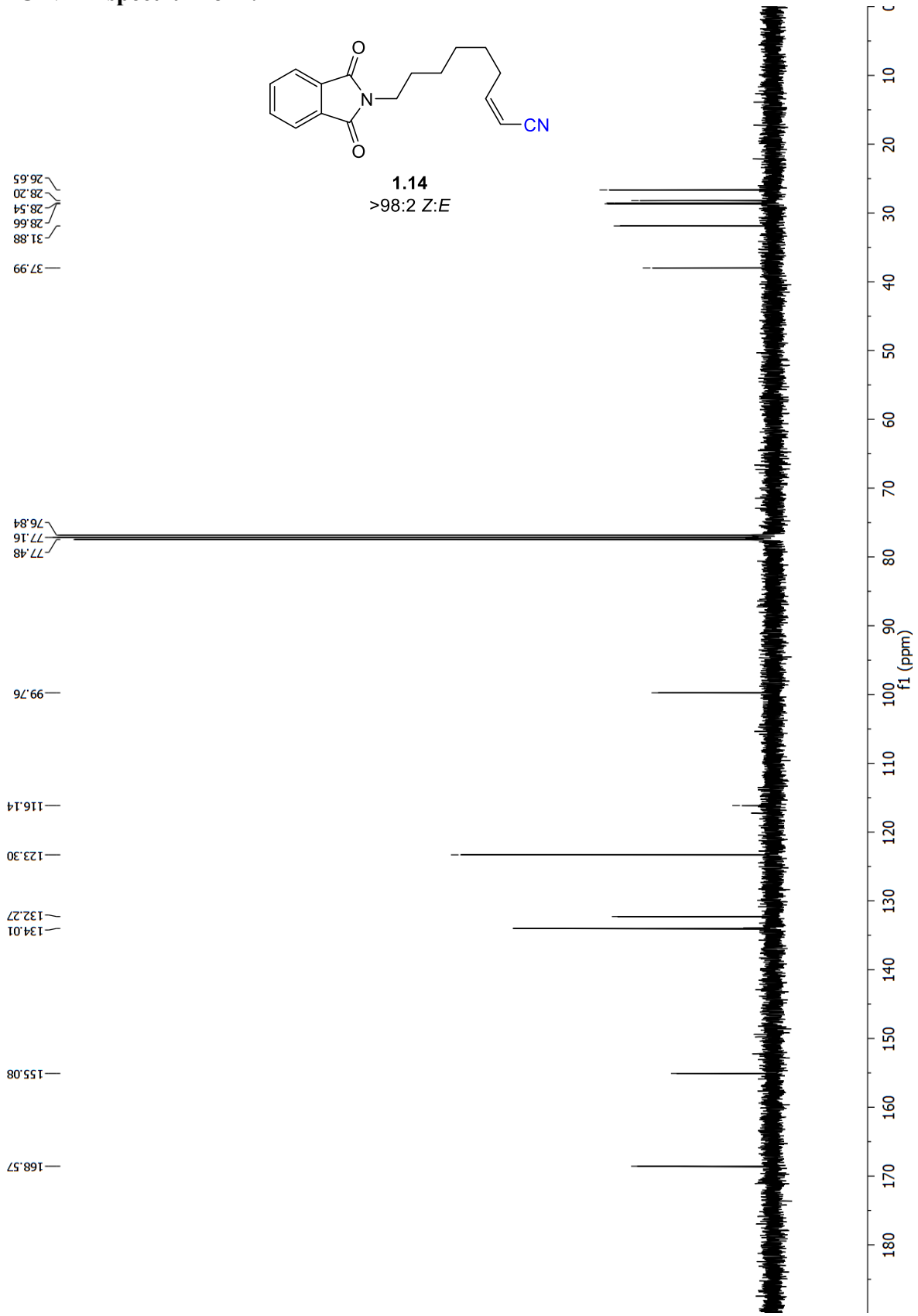
^{13}C NMR spectrum of 1.13



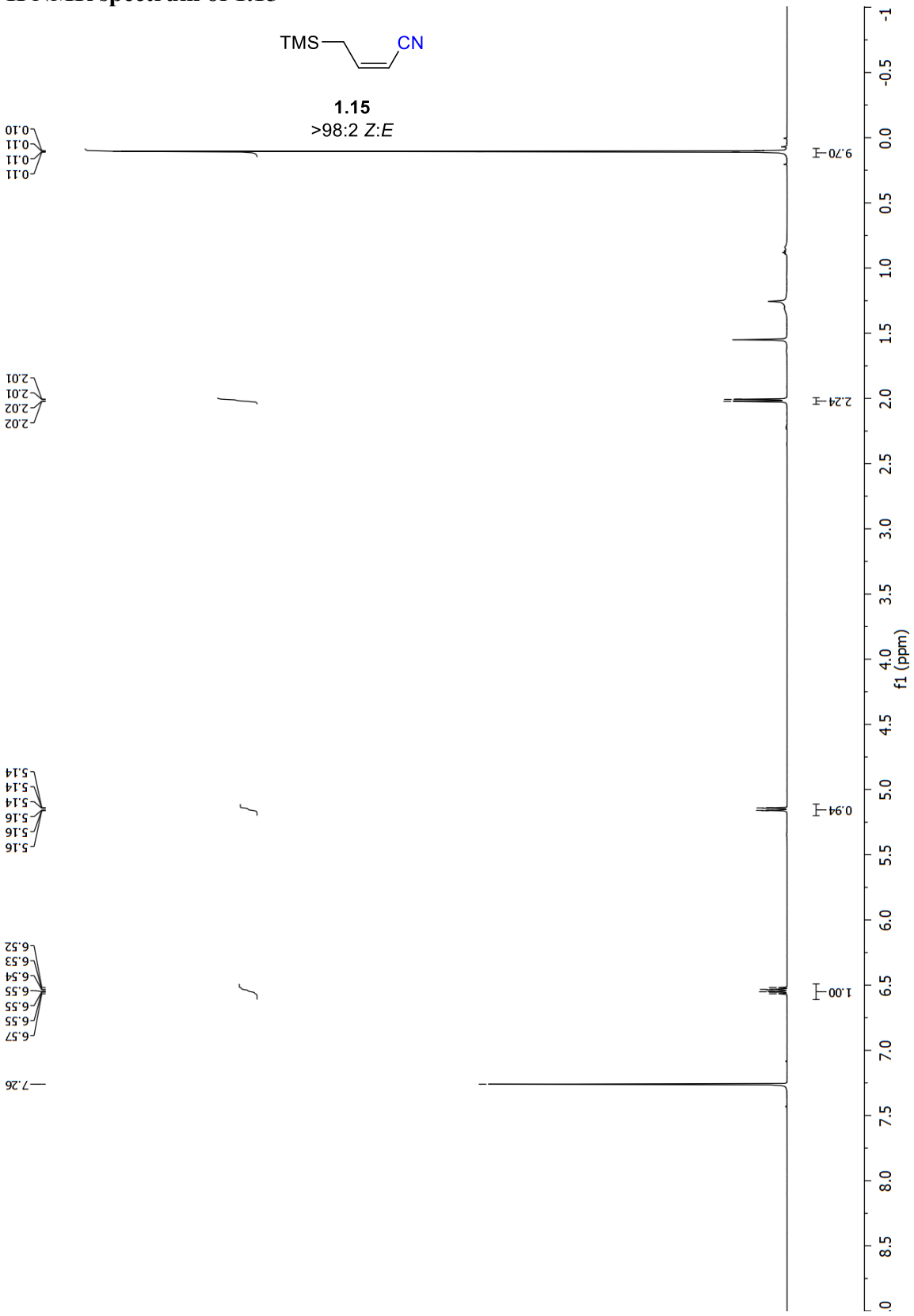
^{1}H NMR spectrum of 1.14



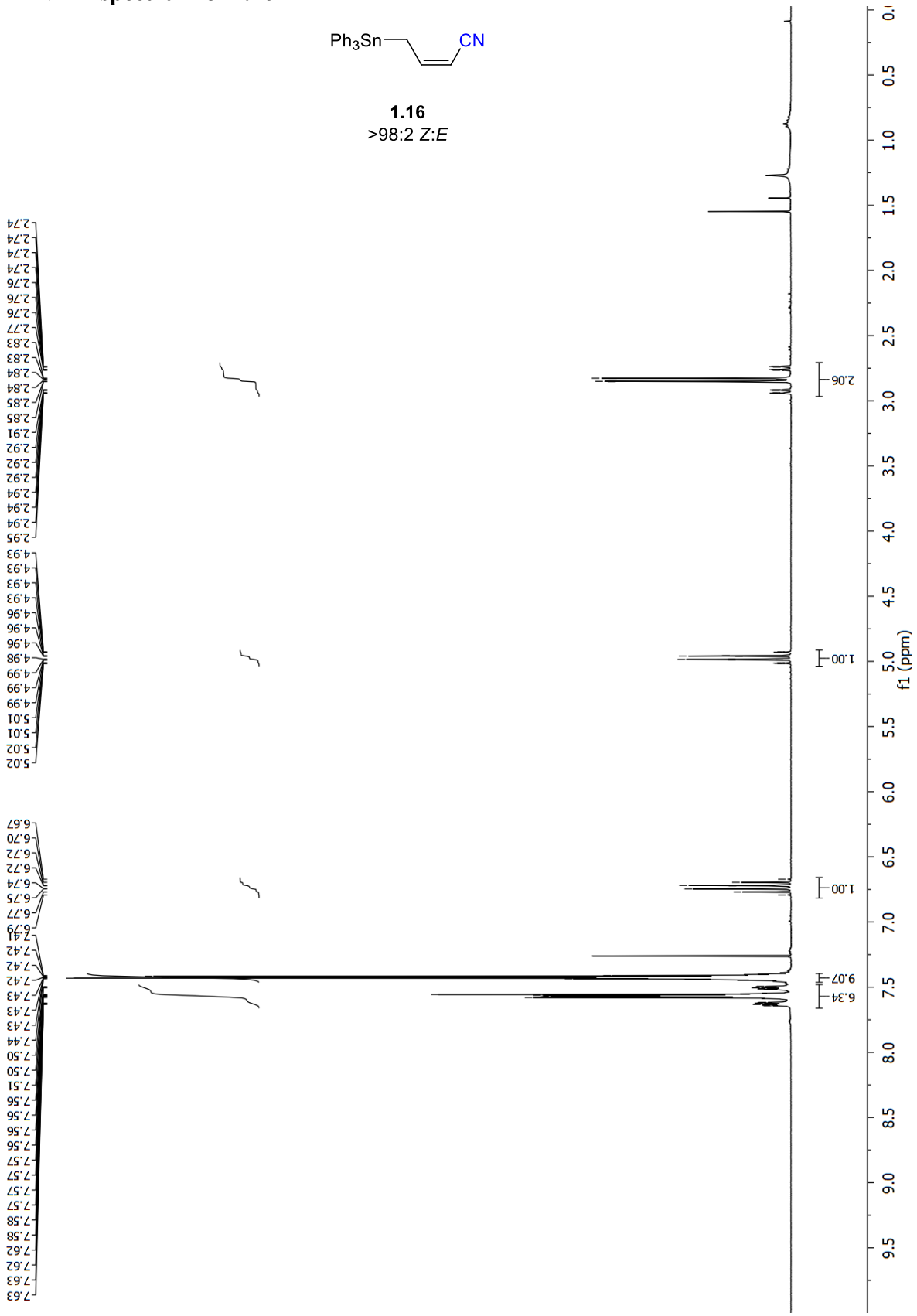
^{13}C NMR spectrum of 1.14



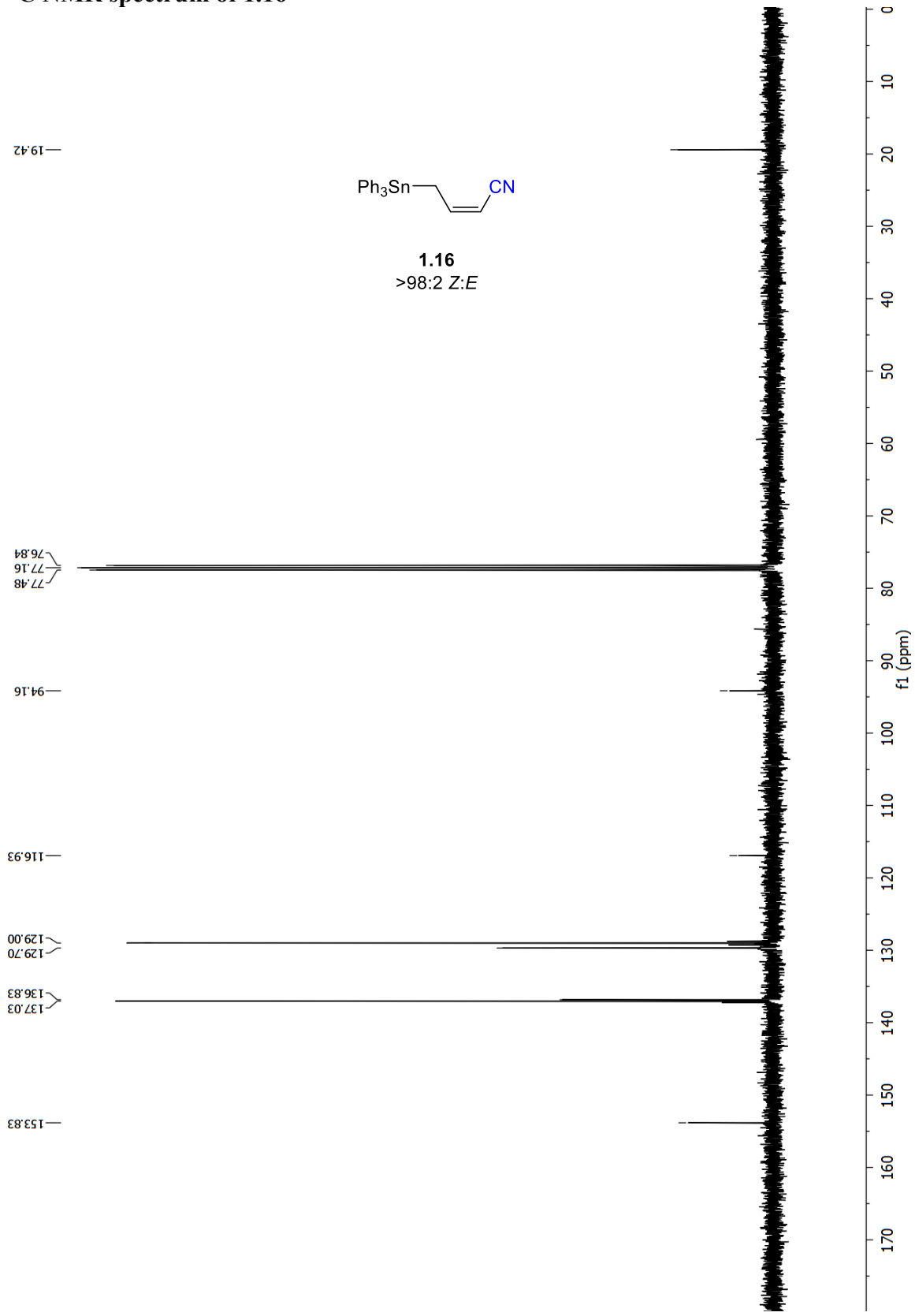
^{1}H NMR spectrum of 1.15



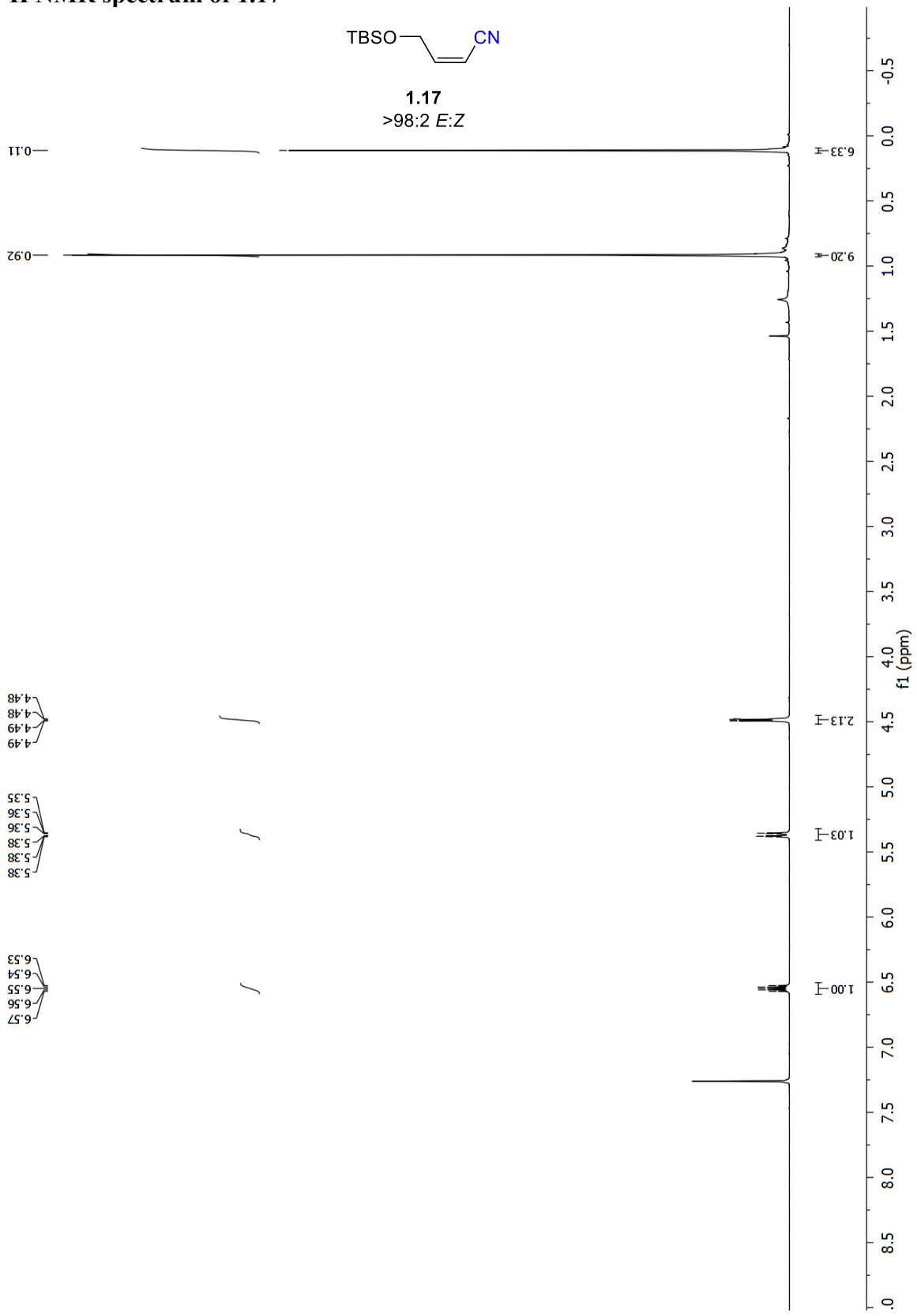
^{1}H NMR spectrum of 1.16



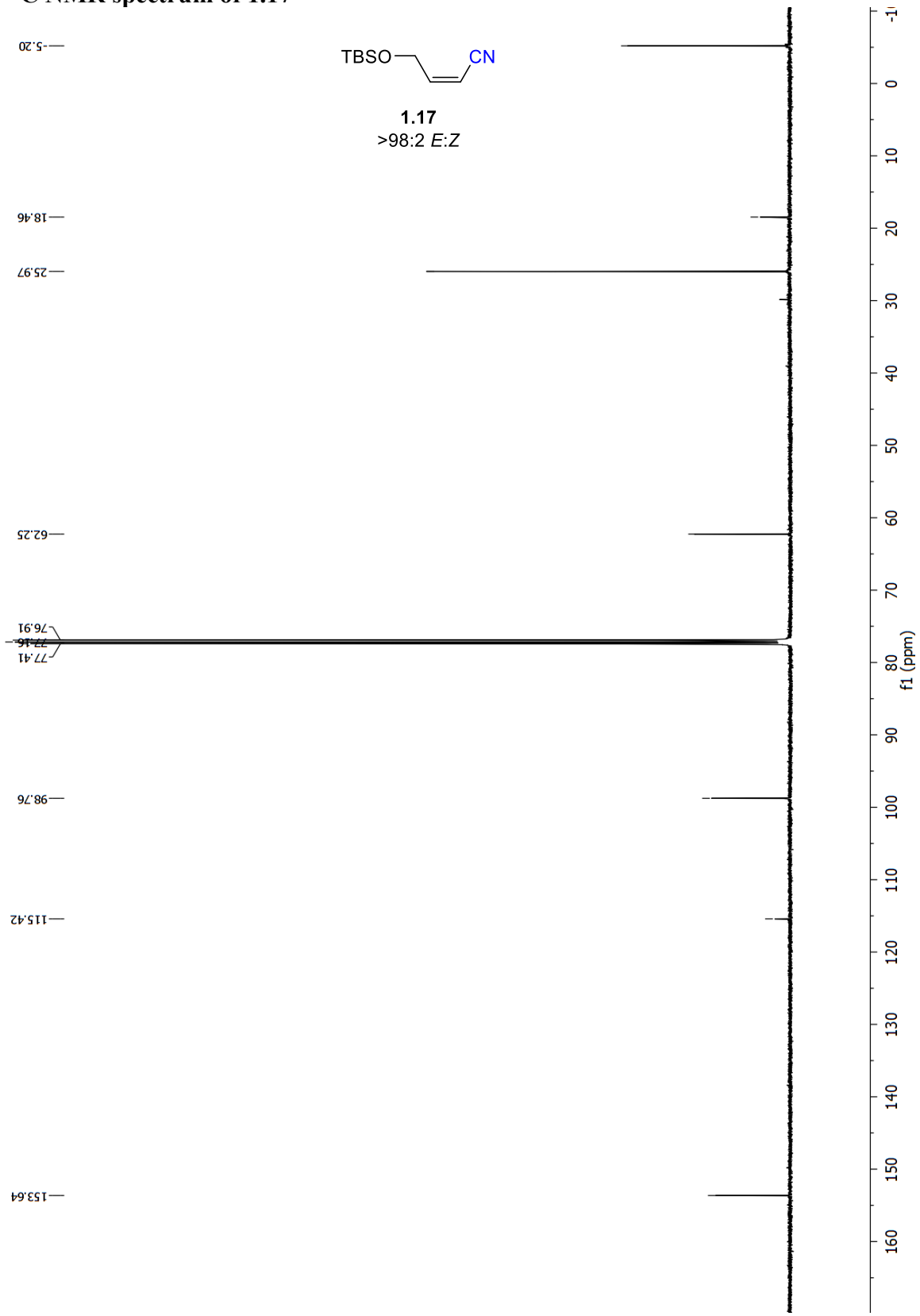
^{13}C NMR spectrum of 1.16



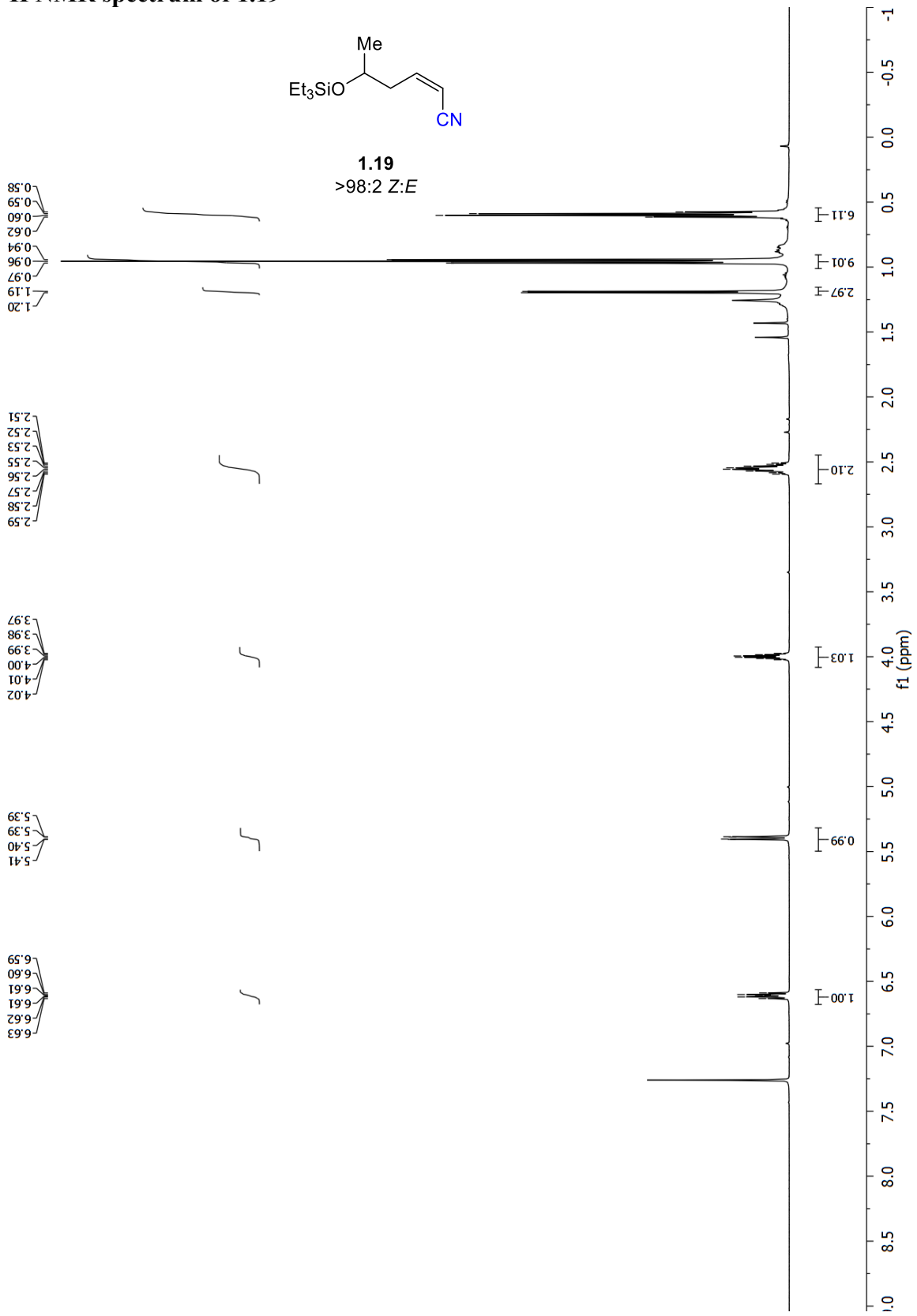
^{1}H NMR spectrum of 1.17



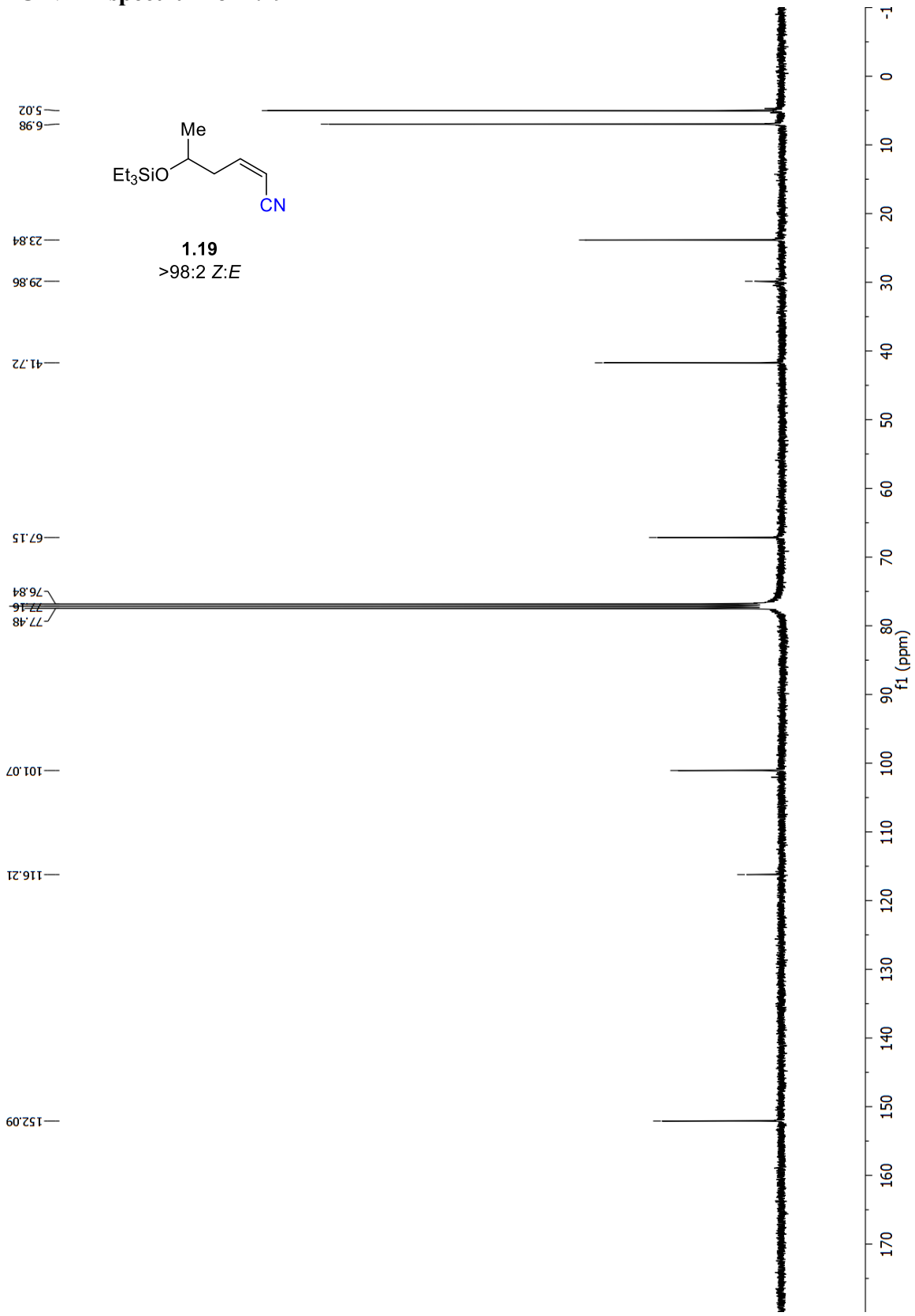
^{13}C NMR spectrum of 1.17



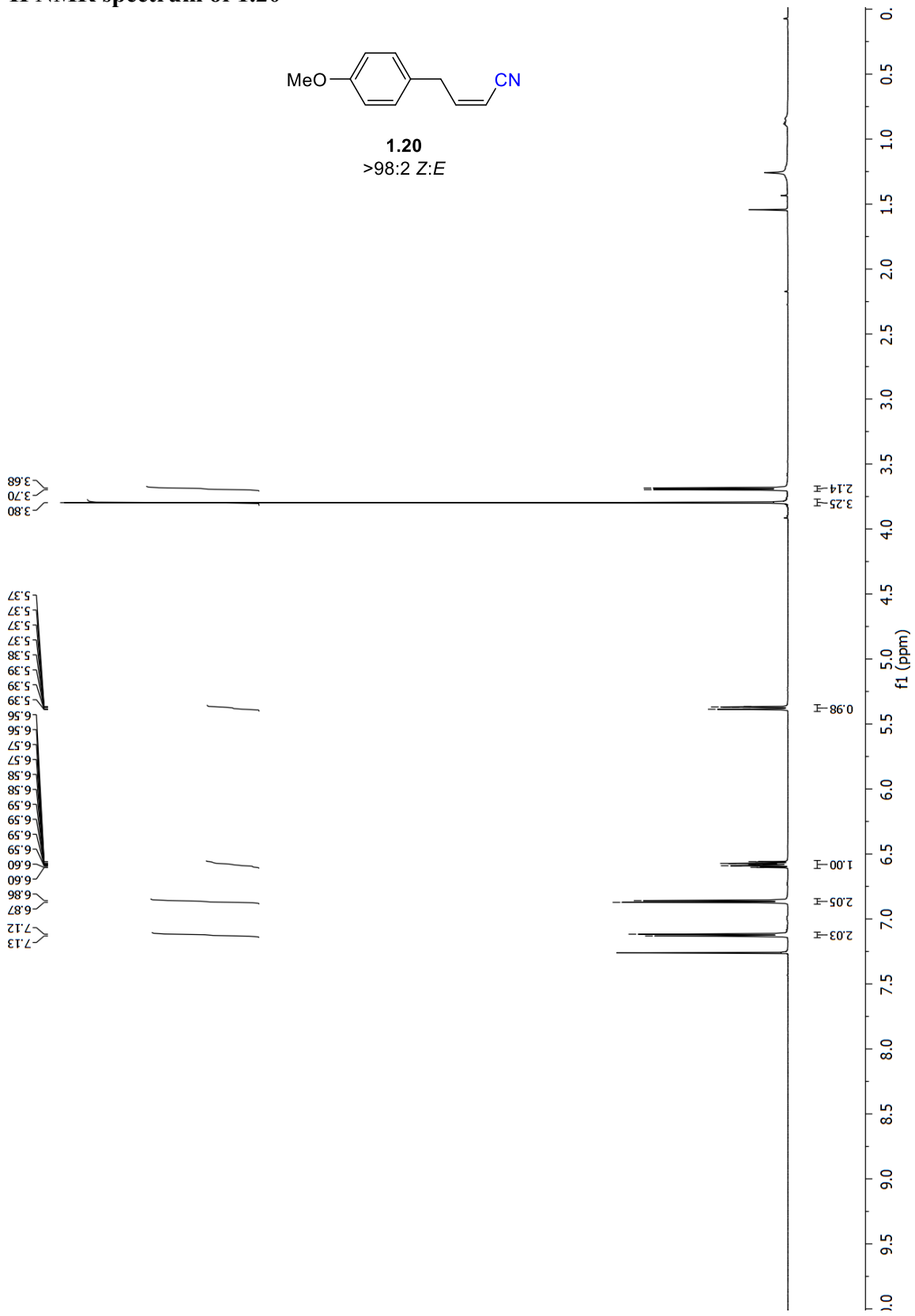
^{1}H NMR spectrum of 1.19



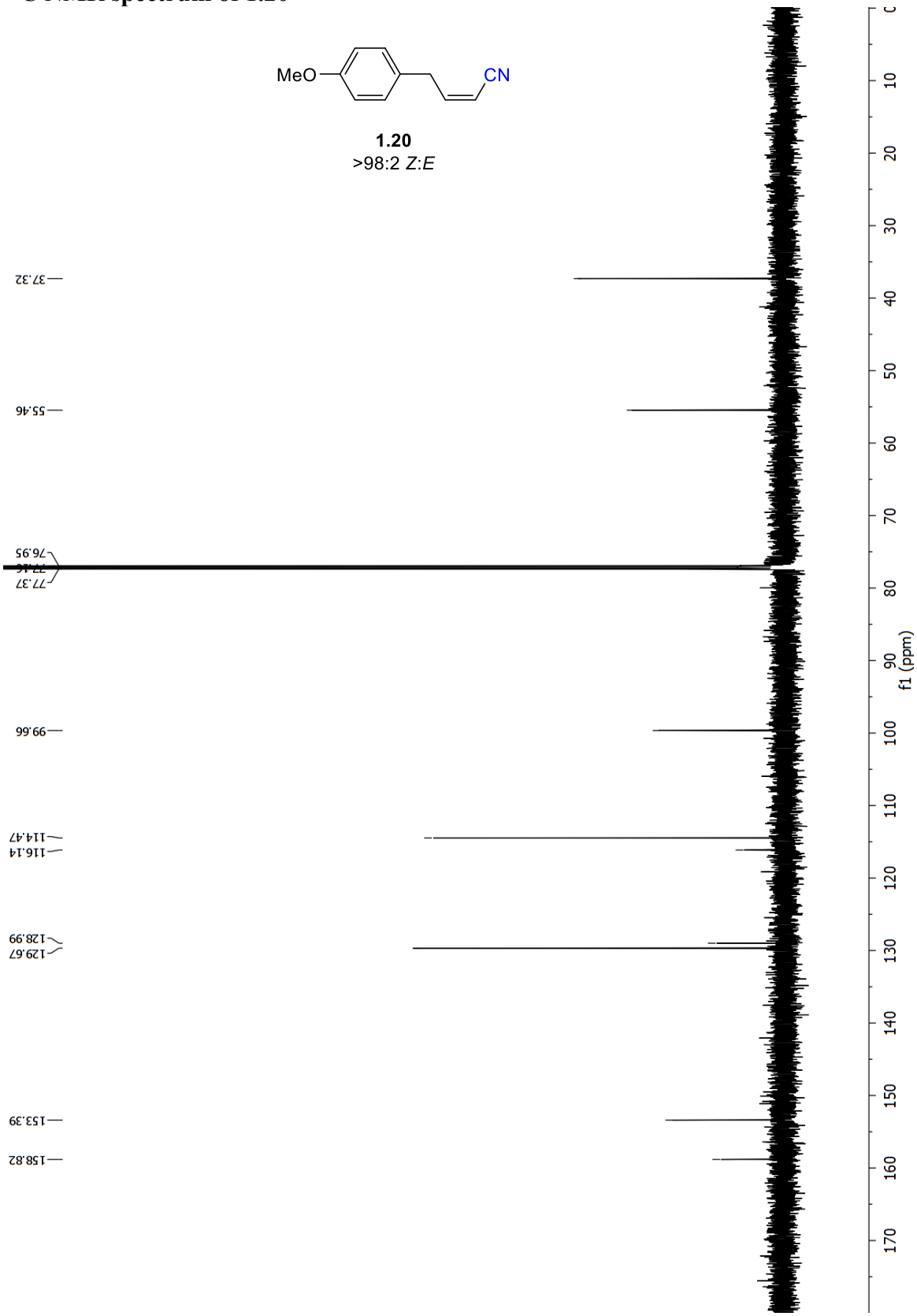
^{13}C NMR spectrum of 1.19



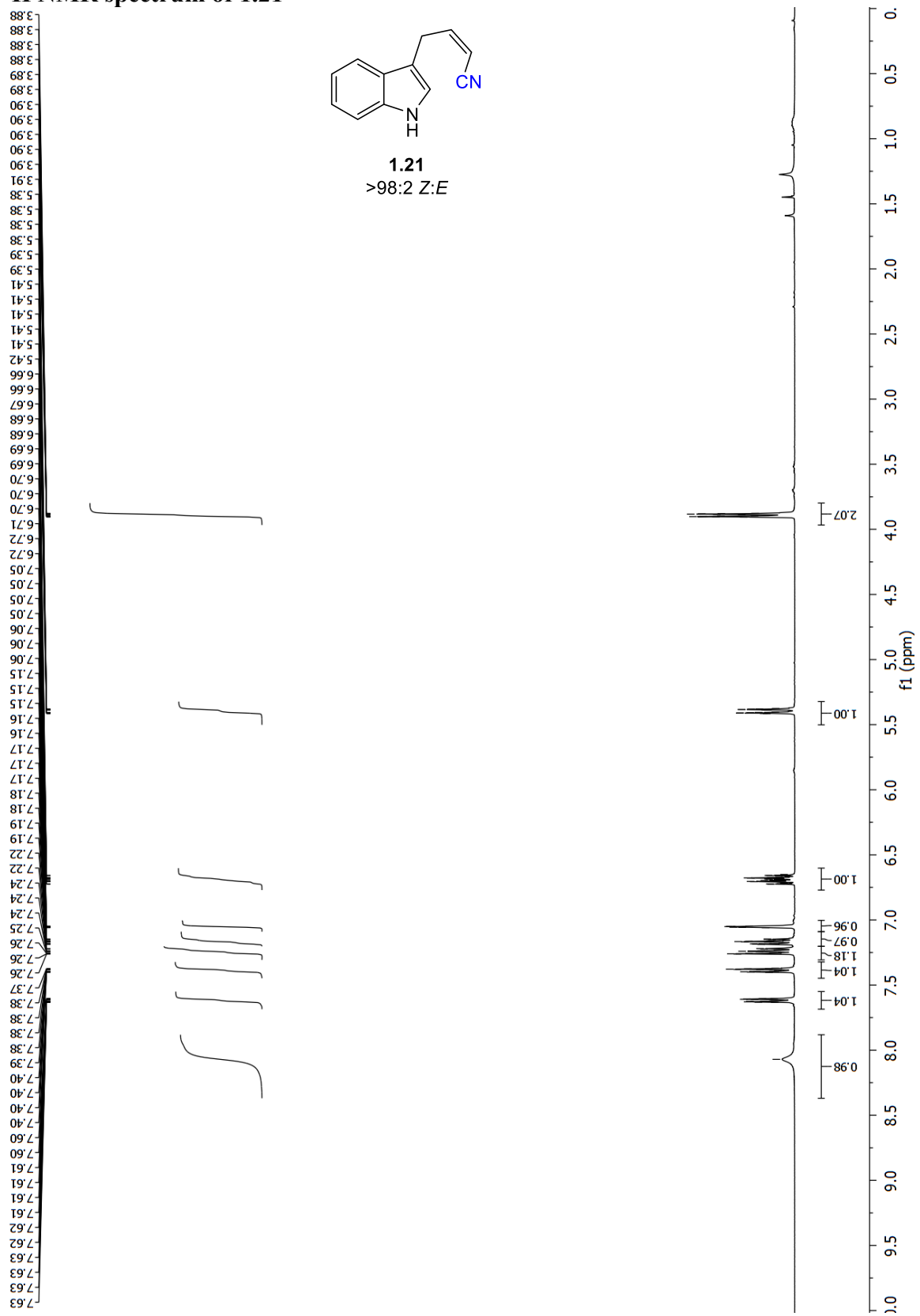
^{1}H NMR spectrum of 1.20



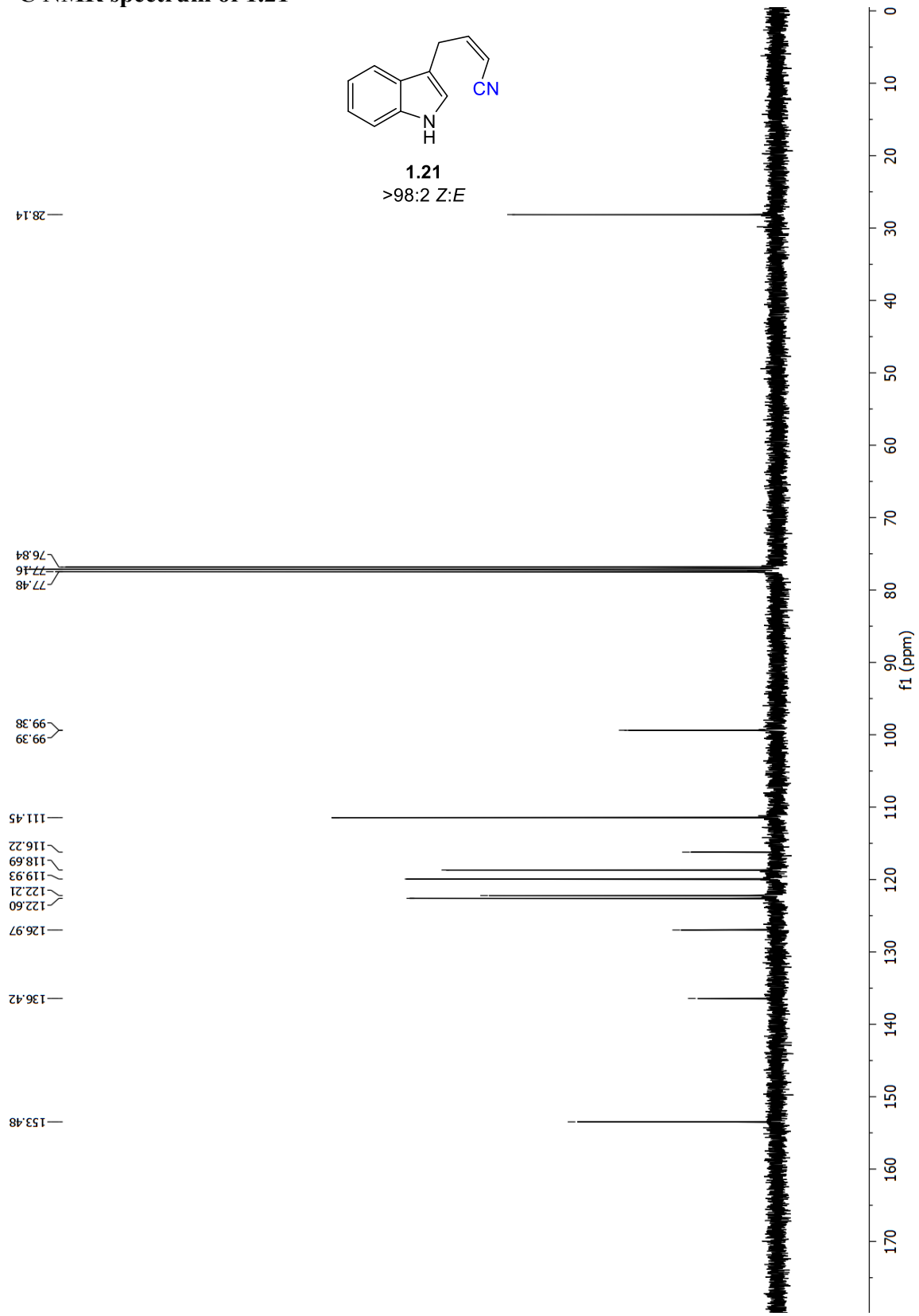
^{13}C NMR spectrum of 1.20



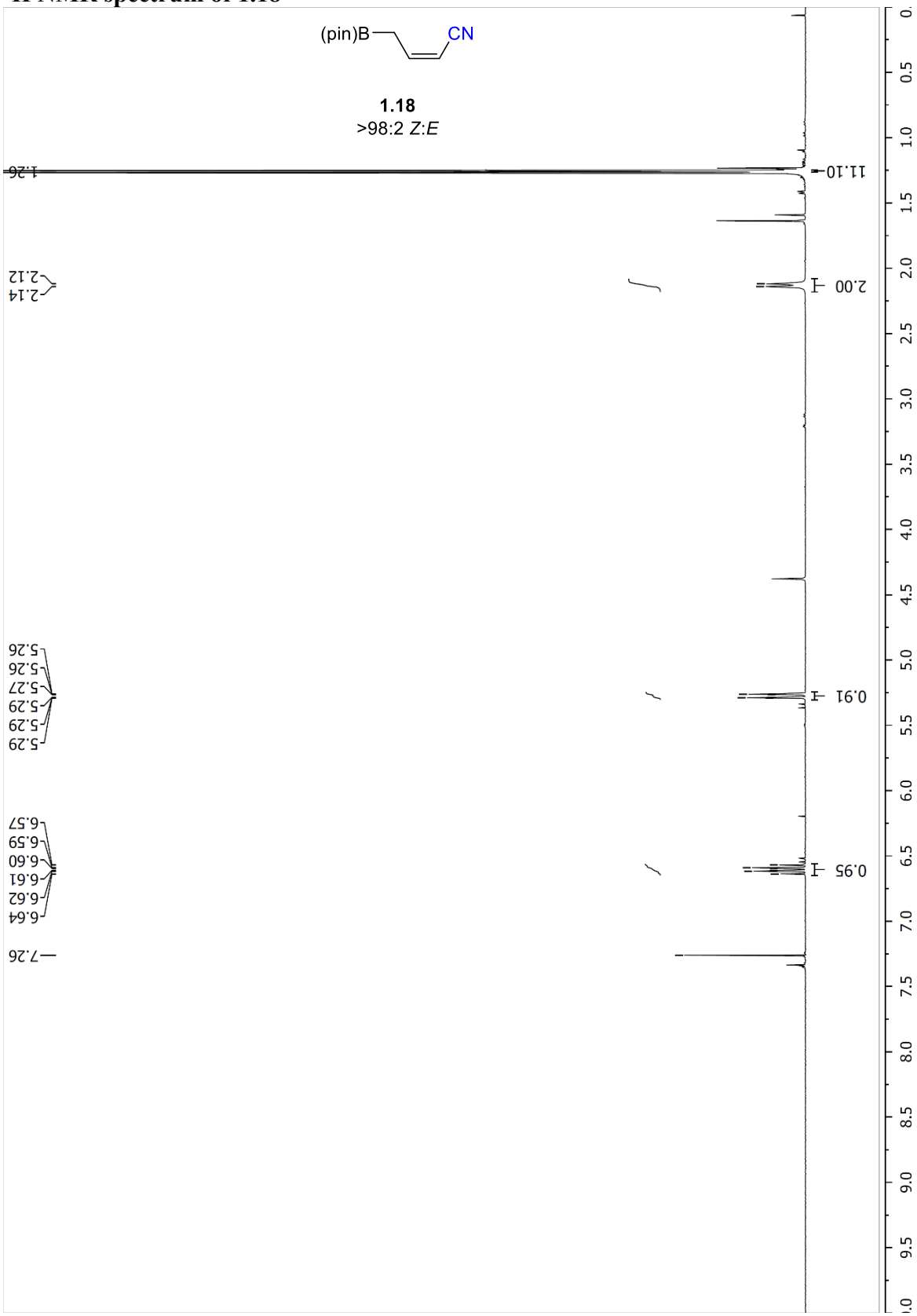
^{1}H NMR spectrum of 1.21



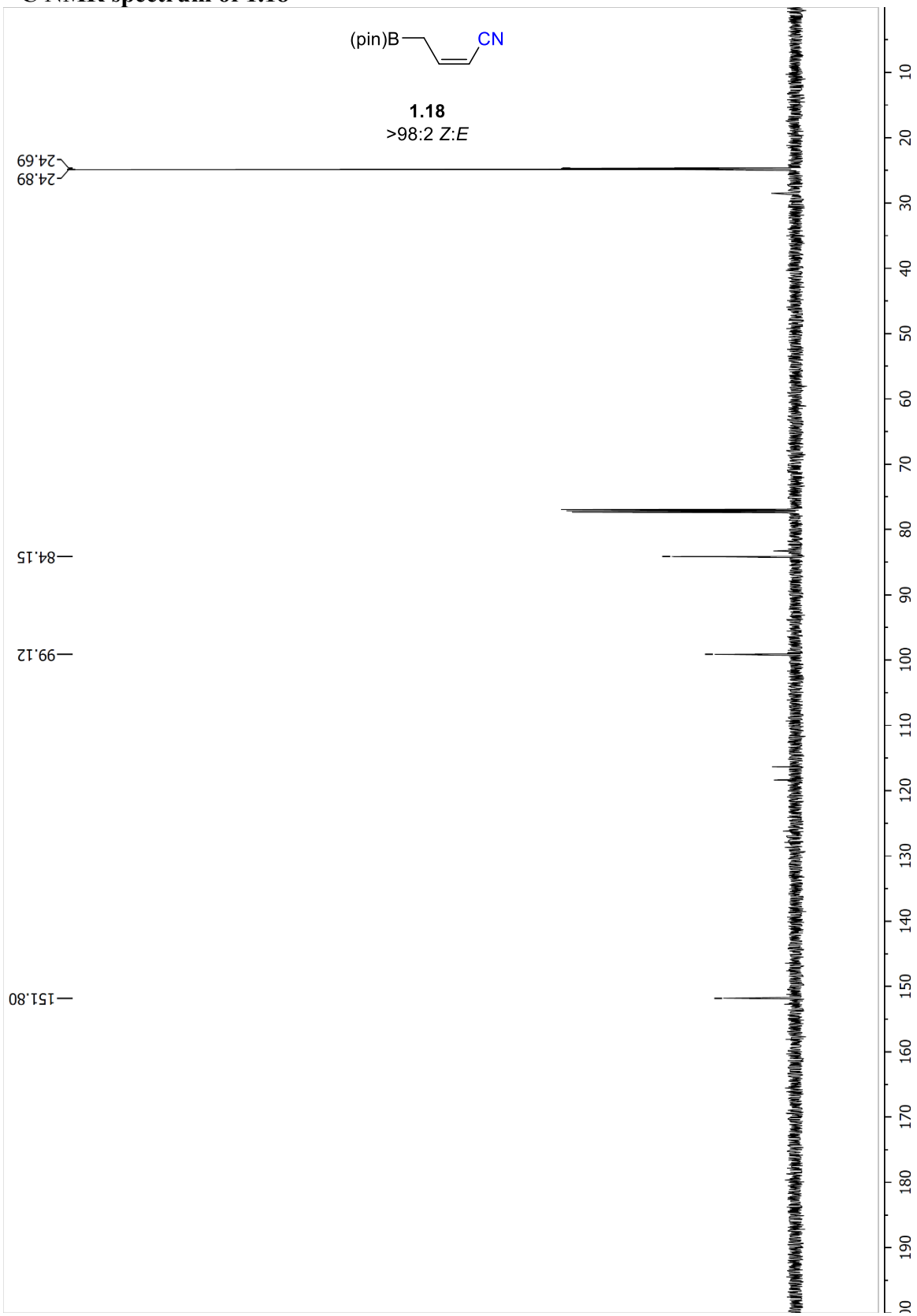
^{13}C NMR spectrum of 1.21



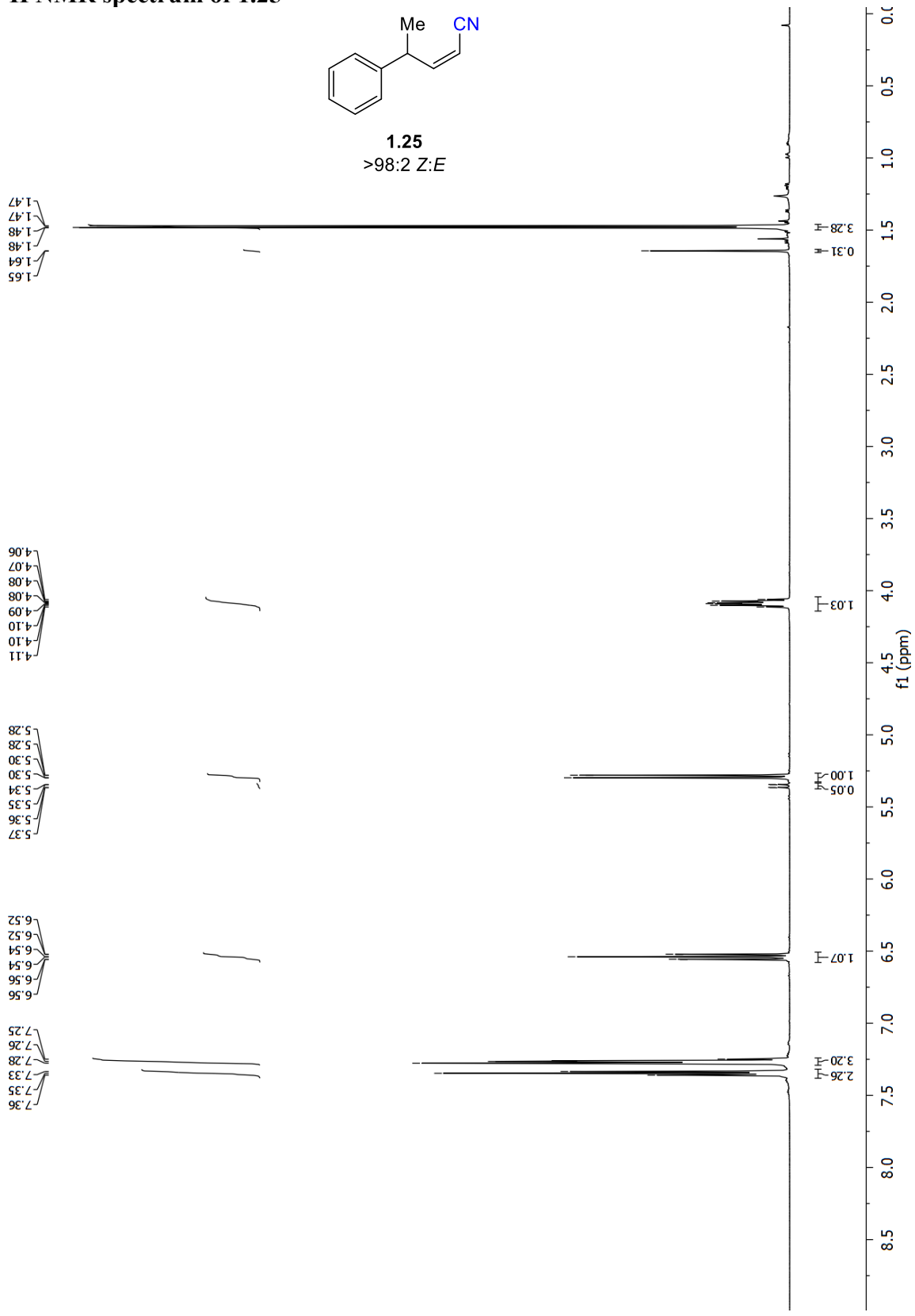
^{1}H NMR spectrum of 1.18



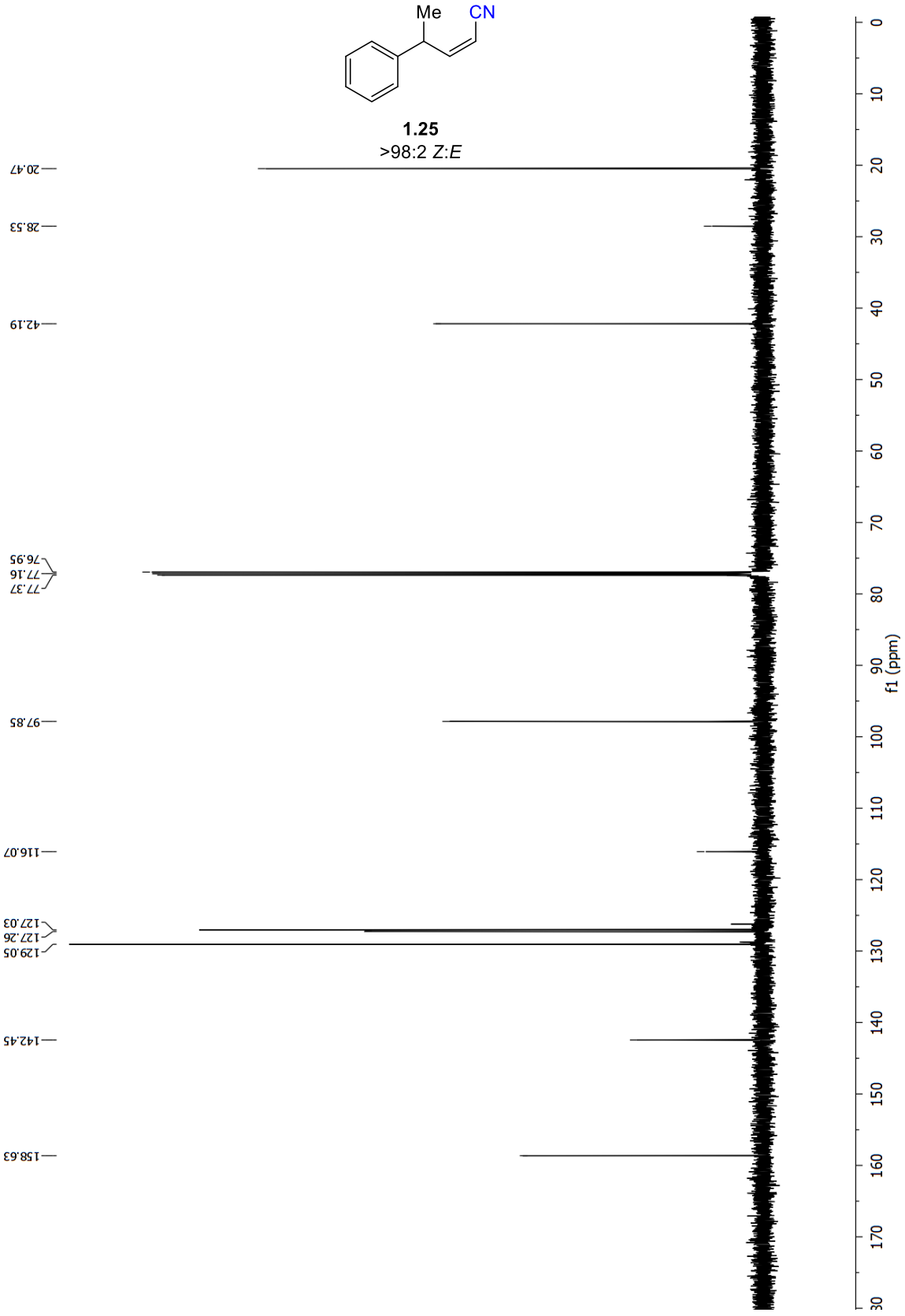
^{13}C NMR spectrum of 1.18



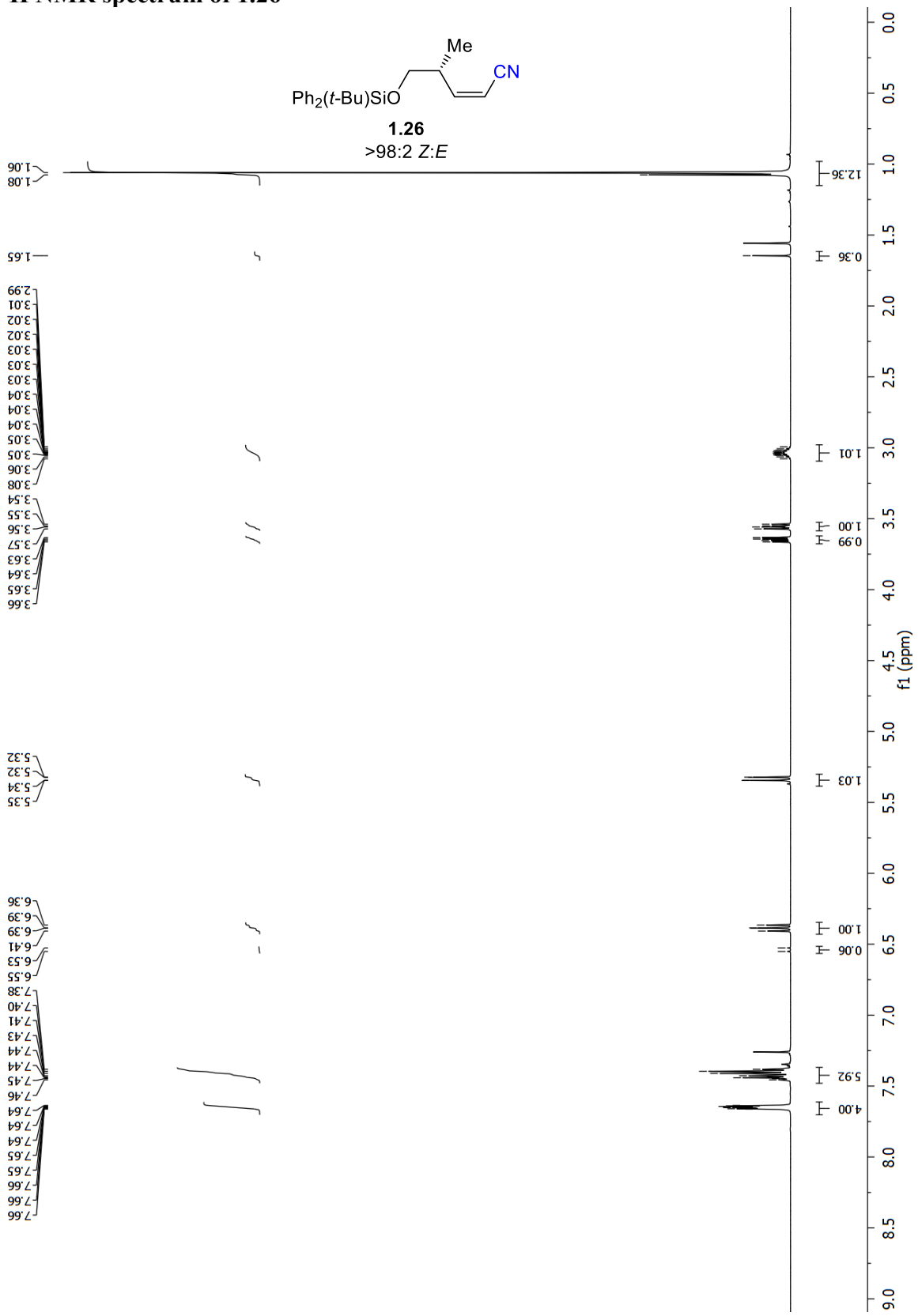
^{1}H NMR spectrum of 1.25



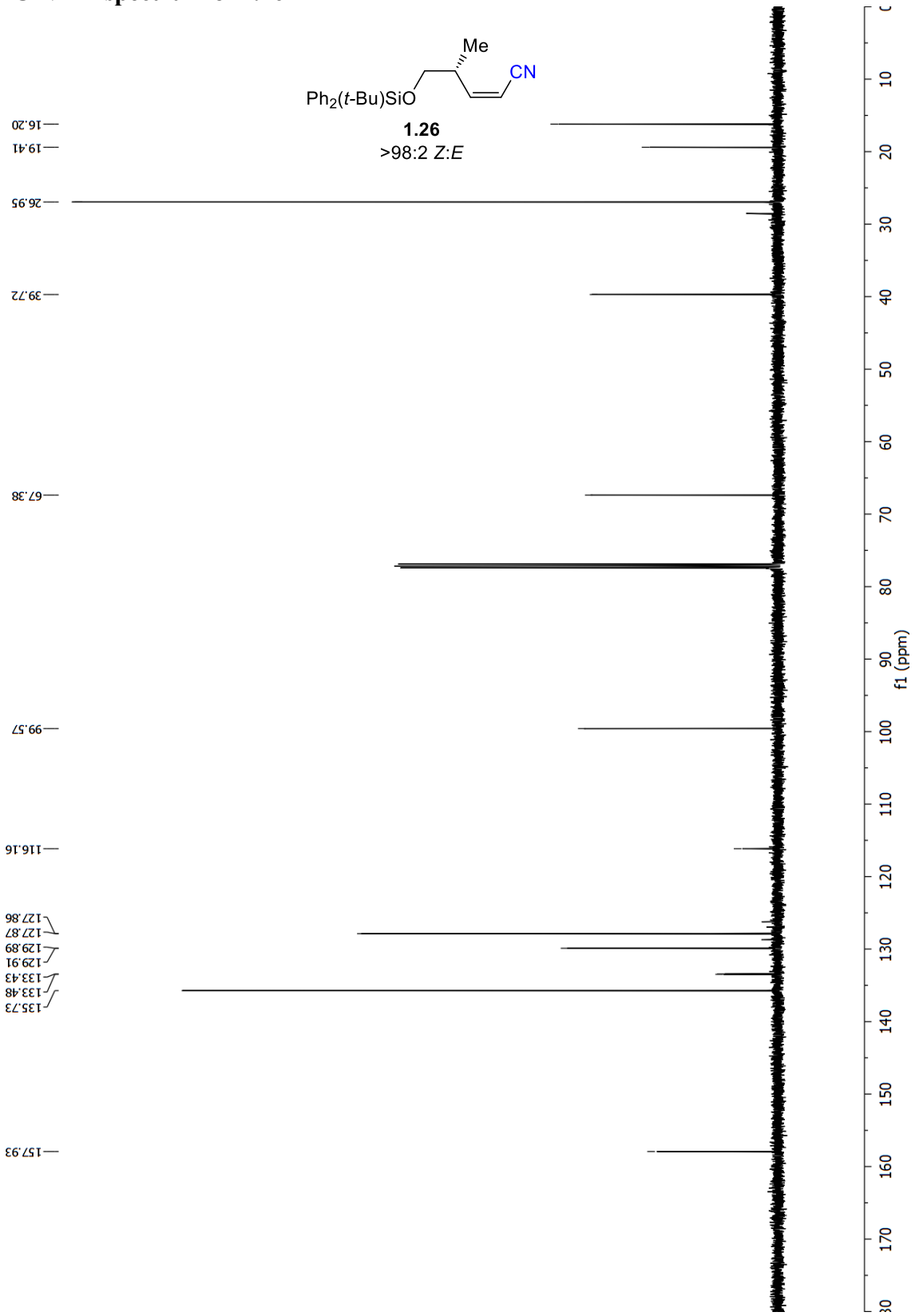
^{13}C NMR spectrum of 1.25



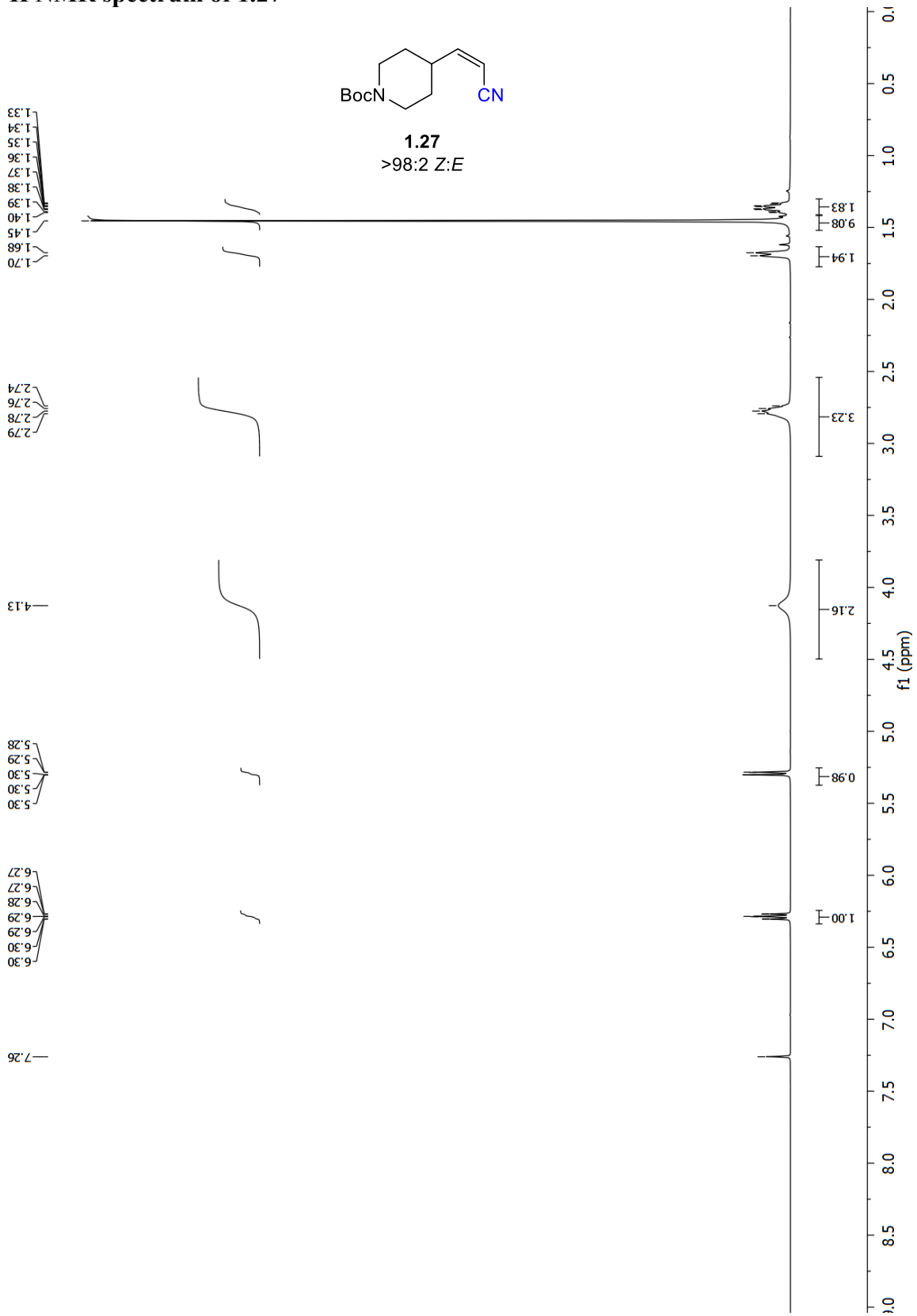
^{1}H NMR spectrum of 1.26



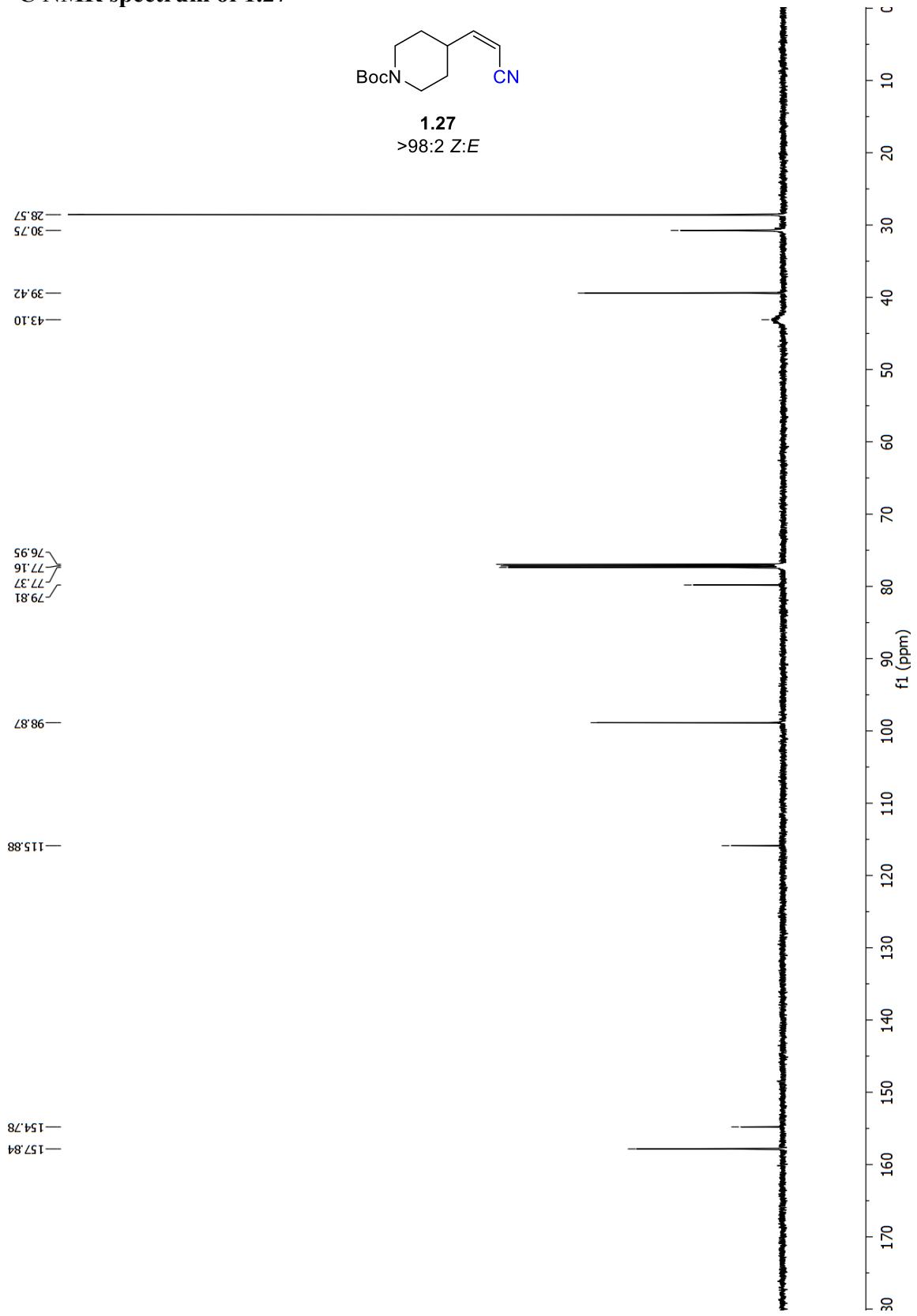
^{13}C NMR spectrum of 1.26



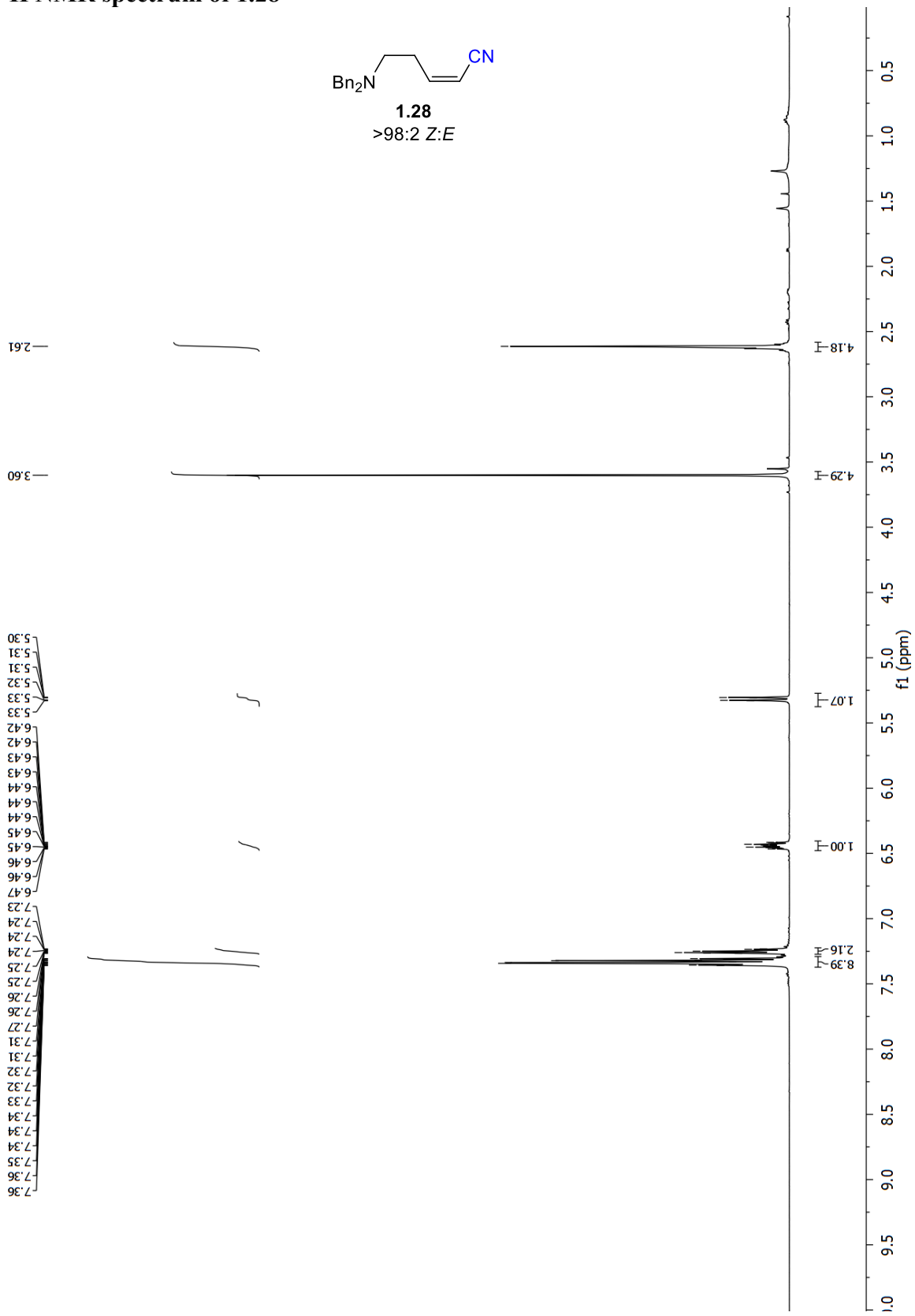
^{1}H NMR spectrum of 1.27



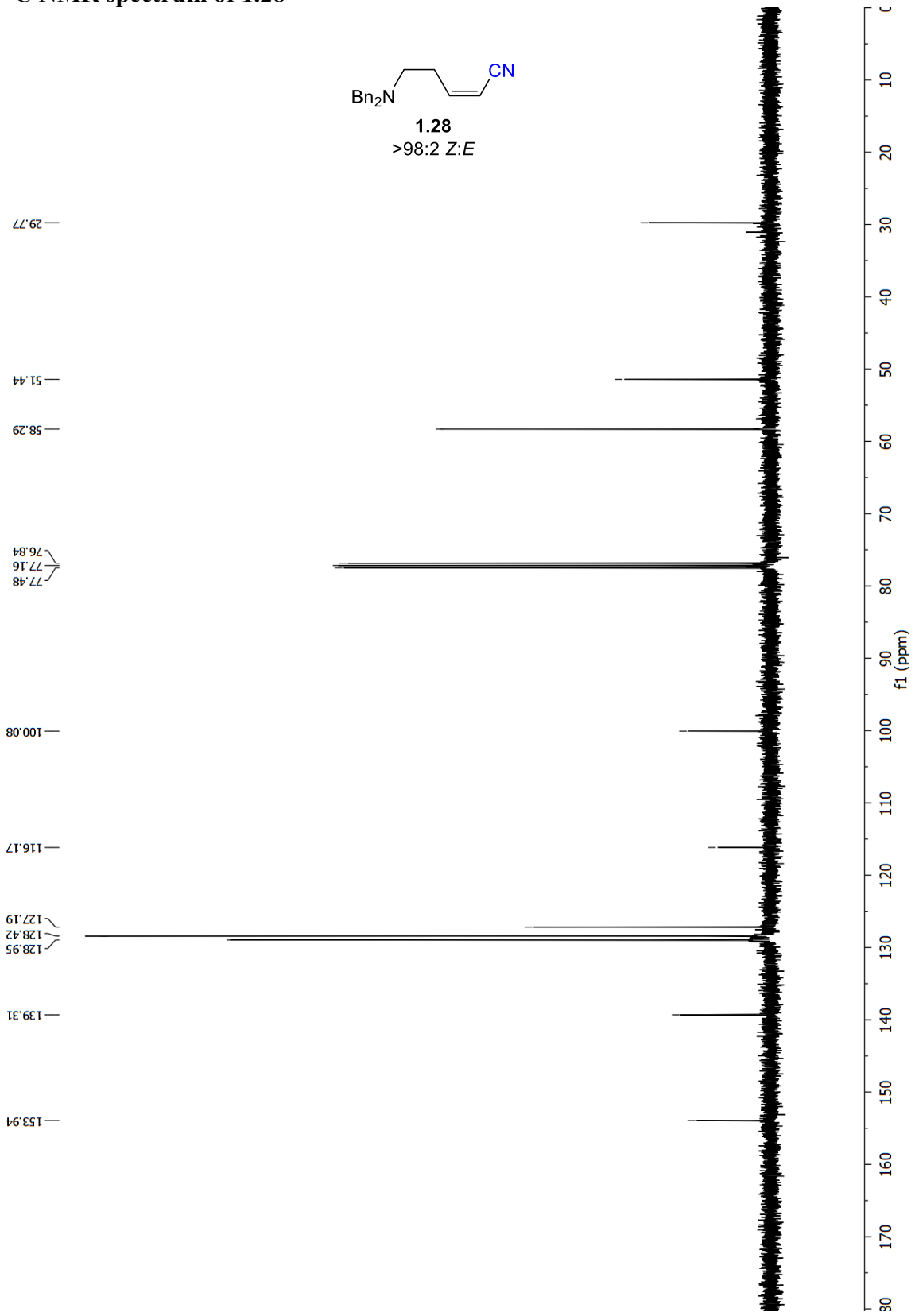
^{13}C NMR spectrum of 1.27



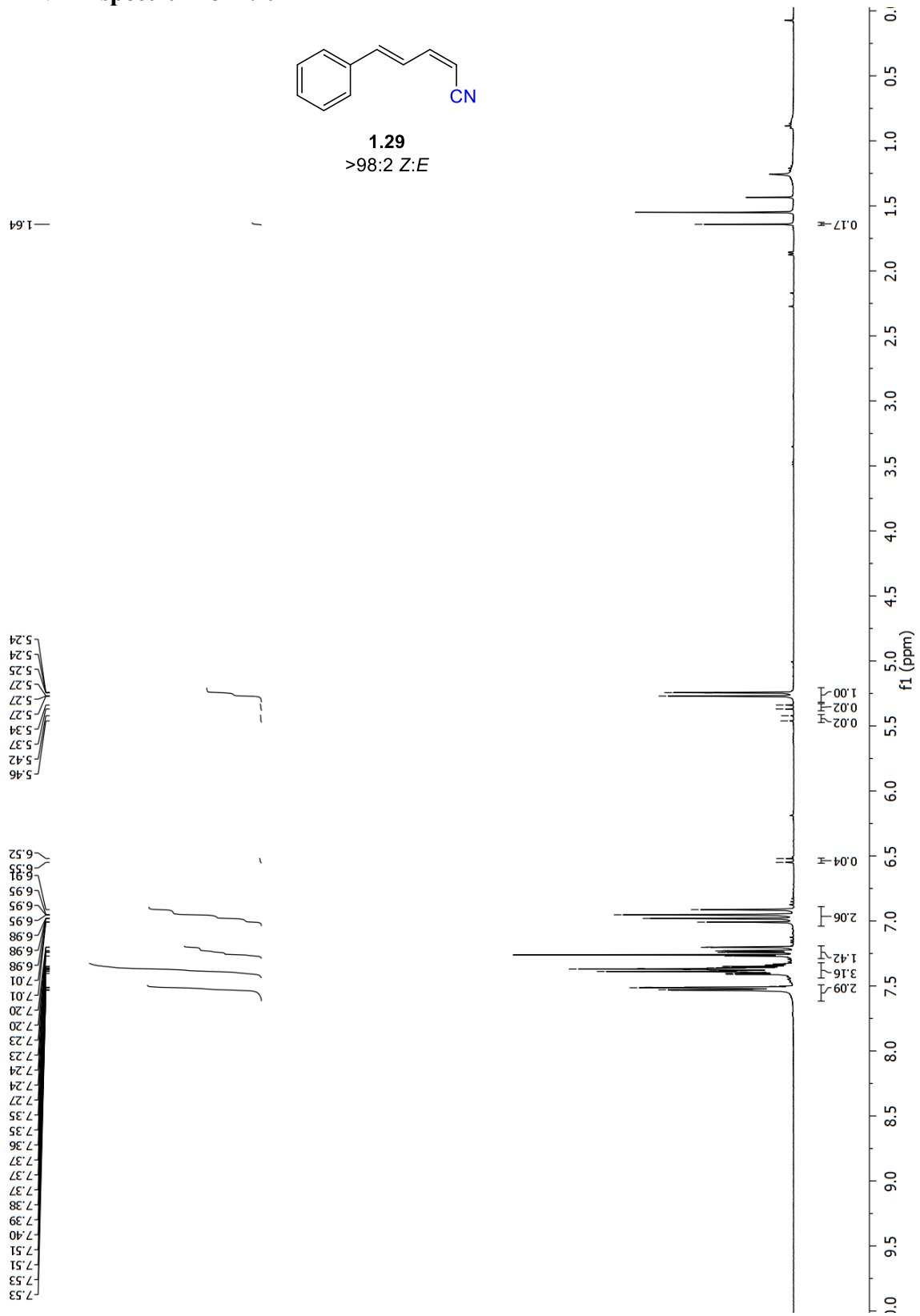
^{1}H NMR spectrum of 1.28



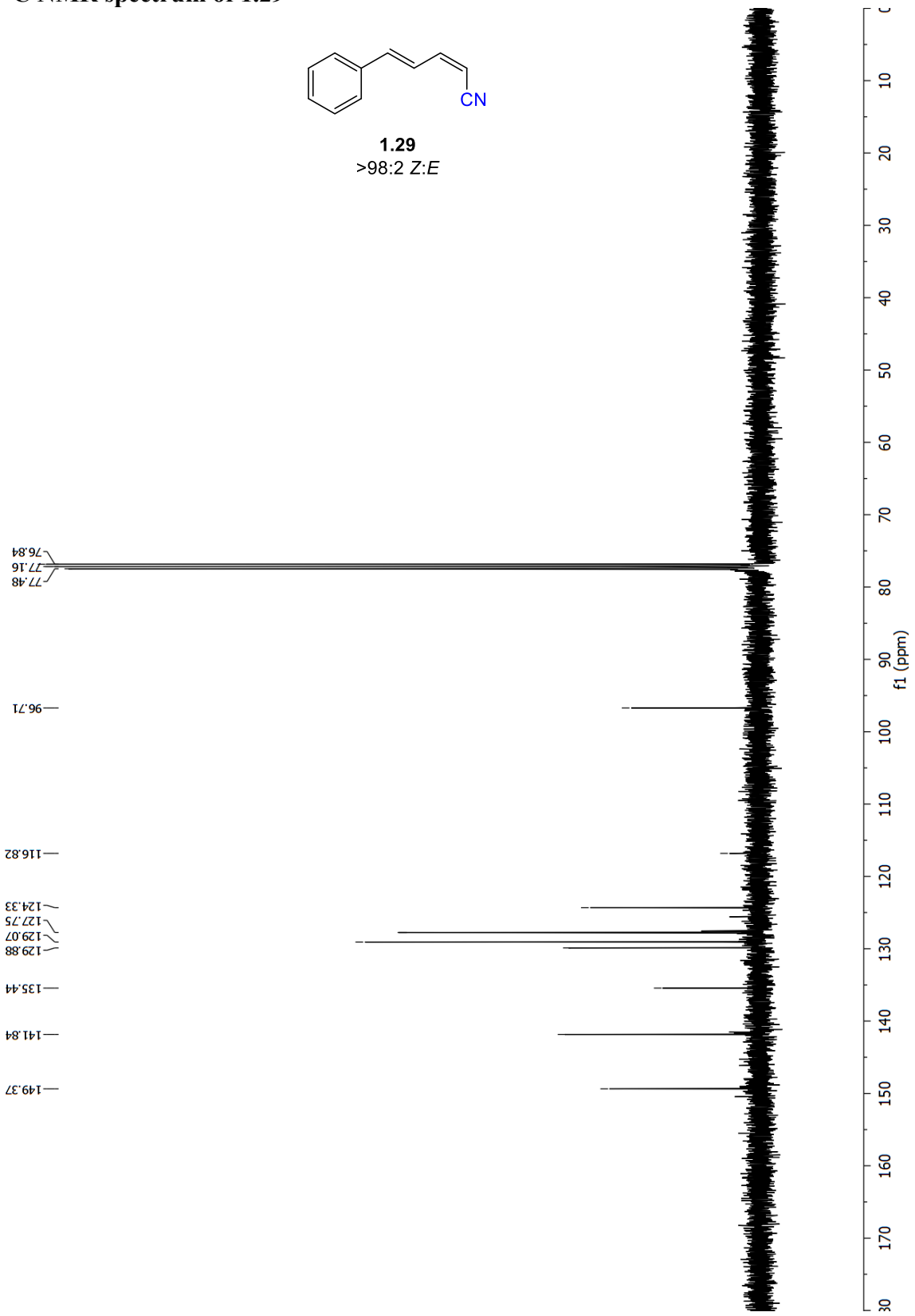
^{13}C NMR spectrum of 1.28



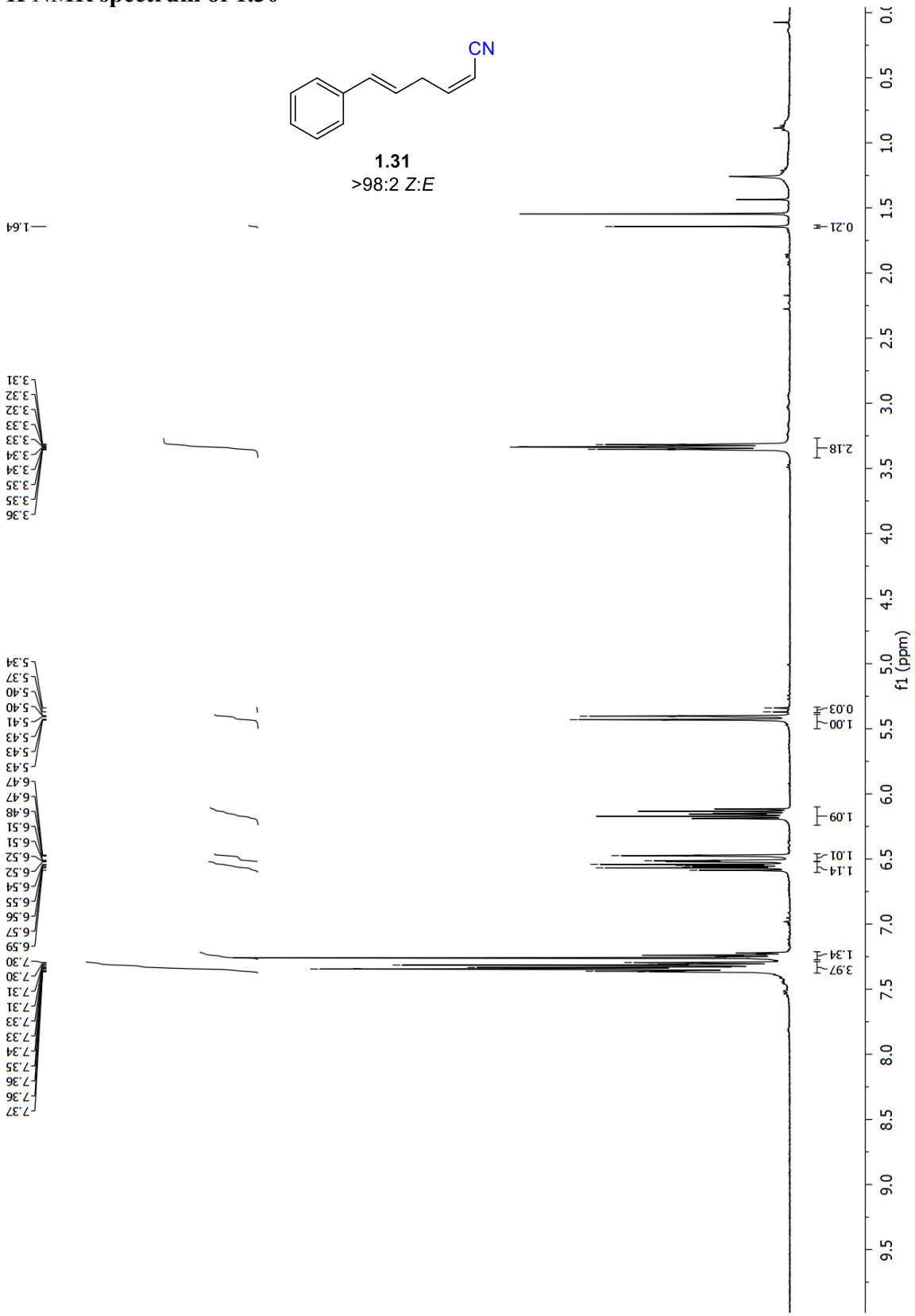
^{1}H NMR spectrum of 1.29



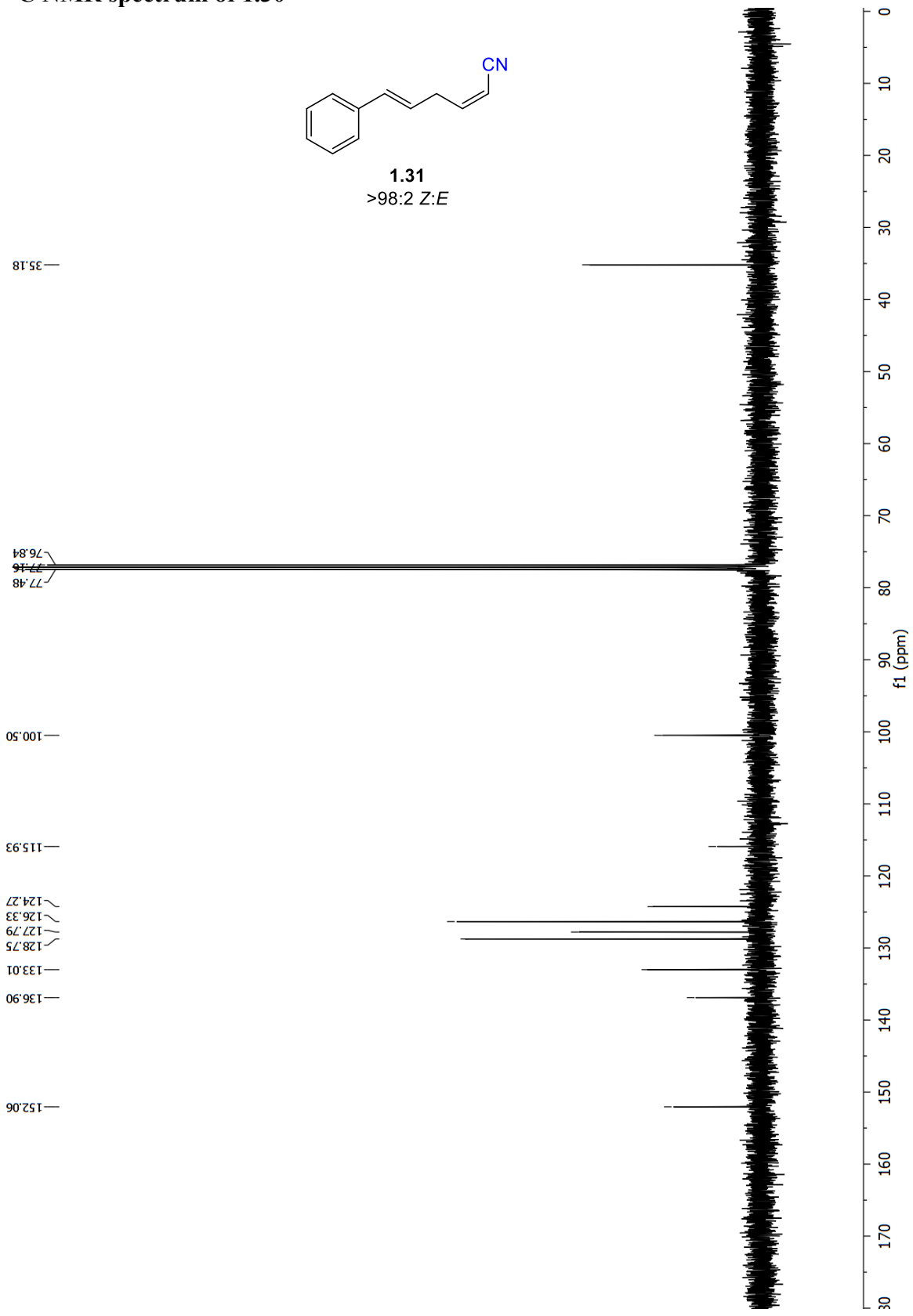
^{13}C NMR spectrum of 1.29



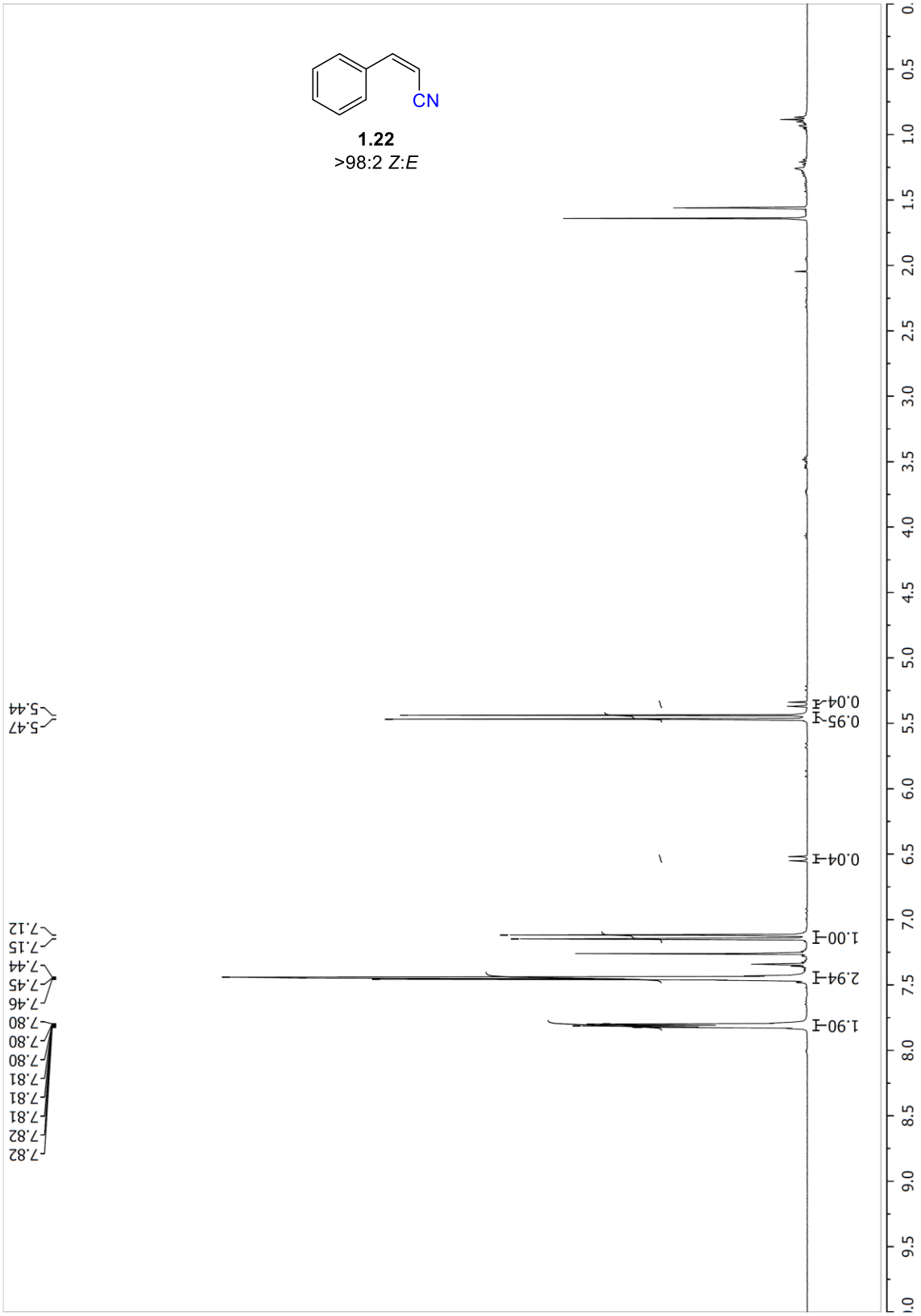
^{1}H NMR spectrum of 1.30



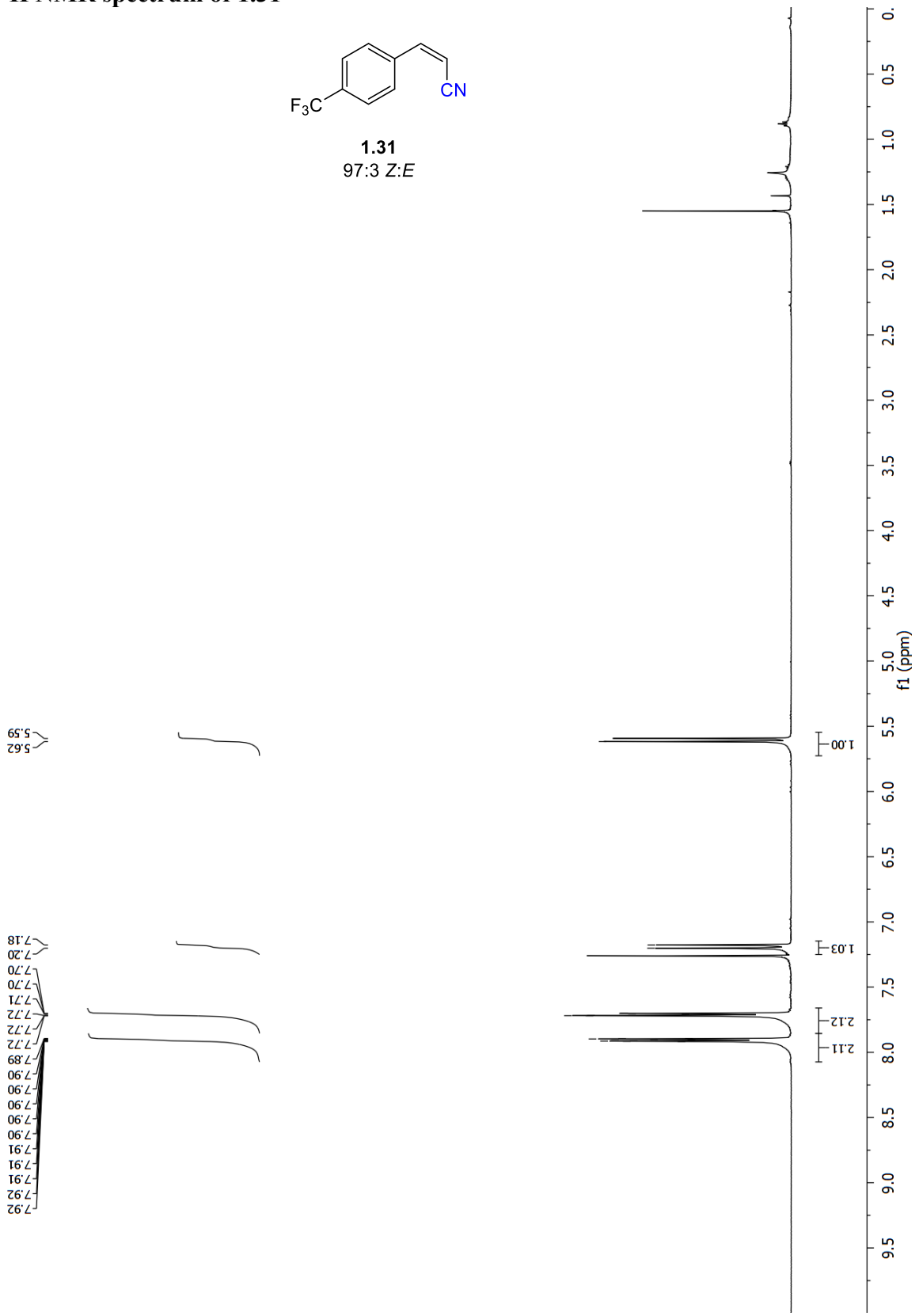
^{13}C NMR spectrum of 1.30



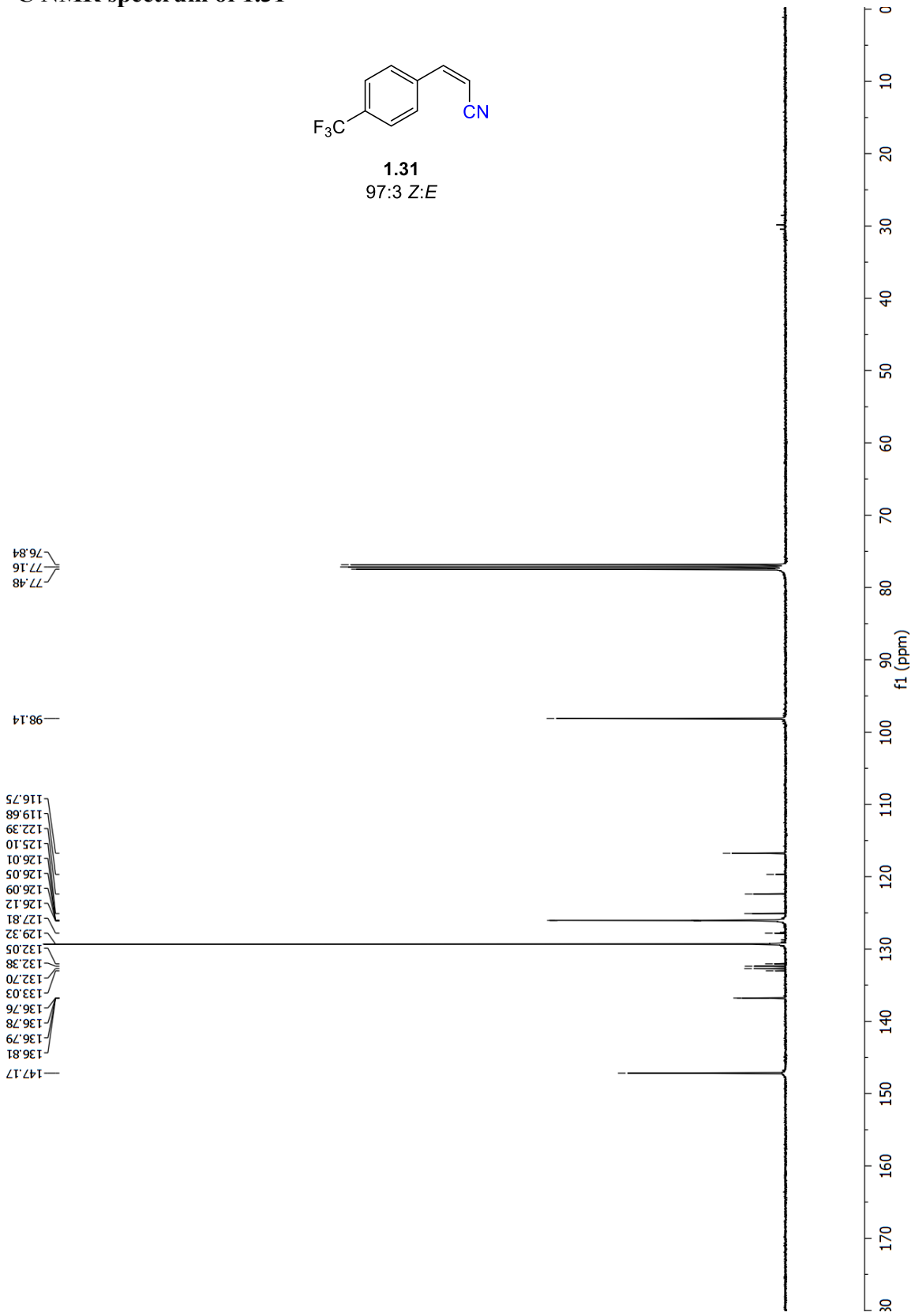
^{1}H NMR spectrum of 1.22



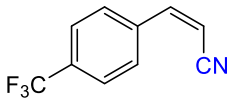
^{1}H NMR spectrum of 1.31



^{13}C NMR spectrum of 1.31

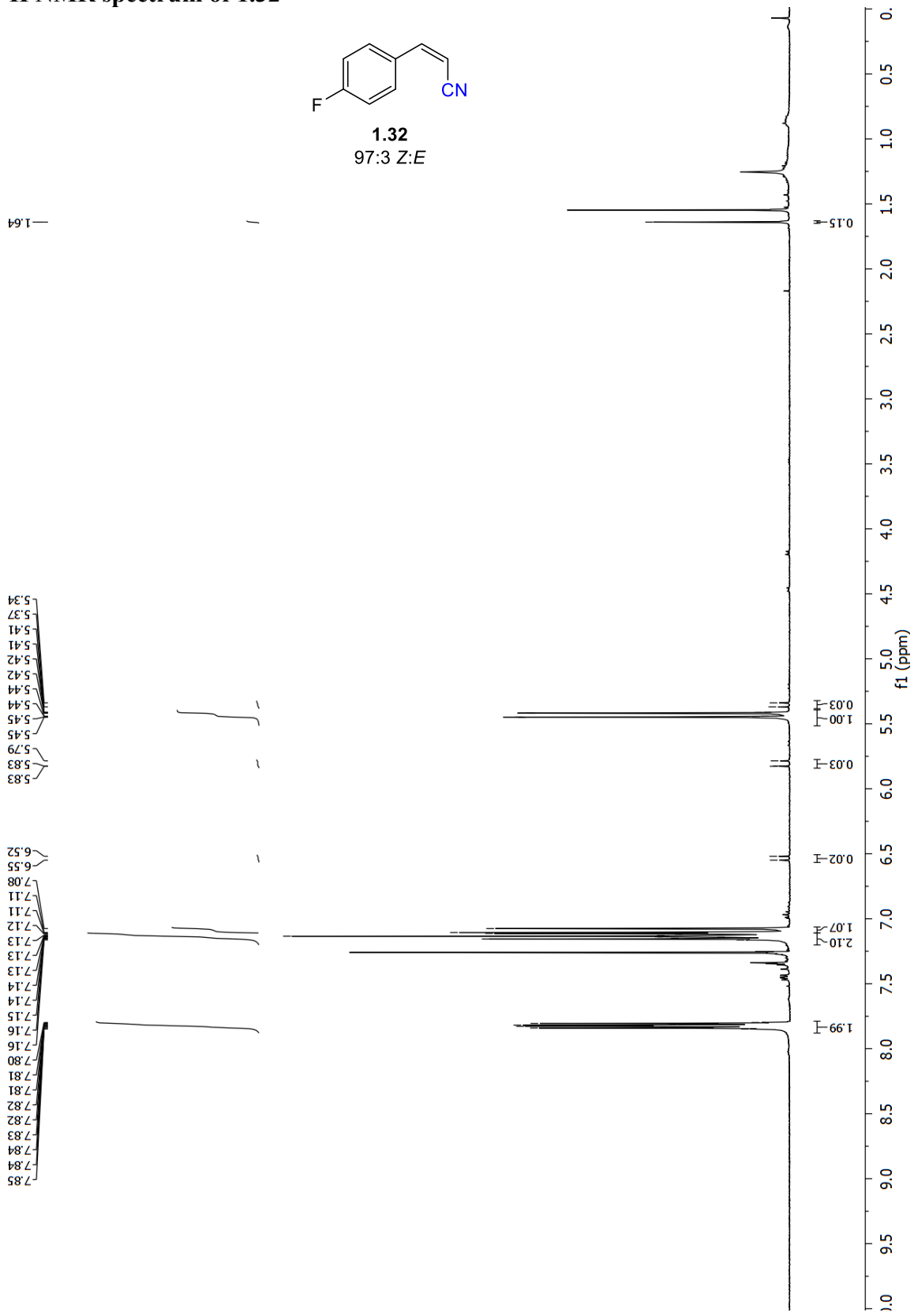


^{19}F NMR spectrum of 1.31

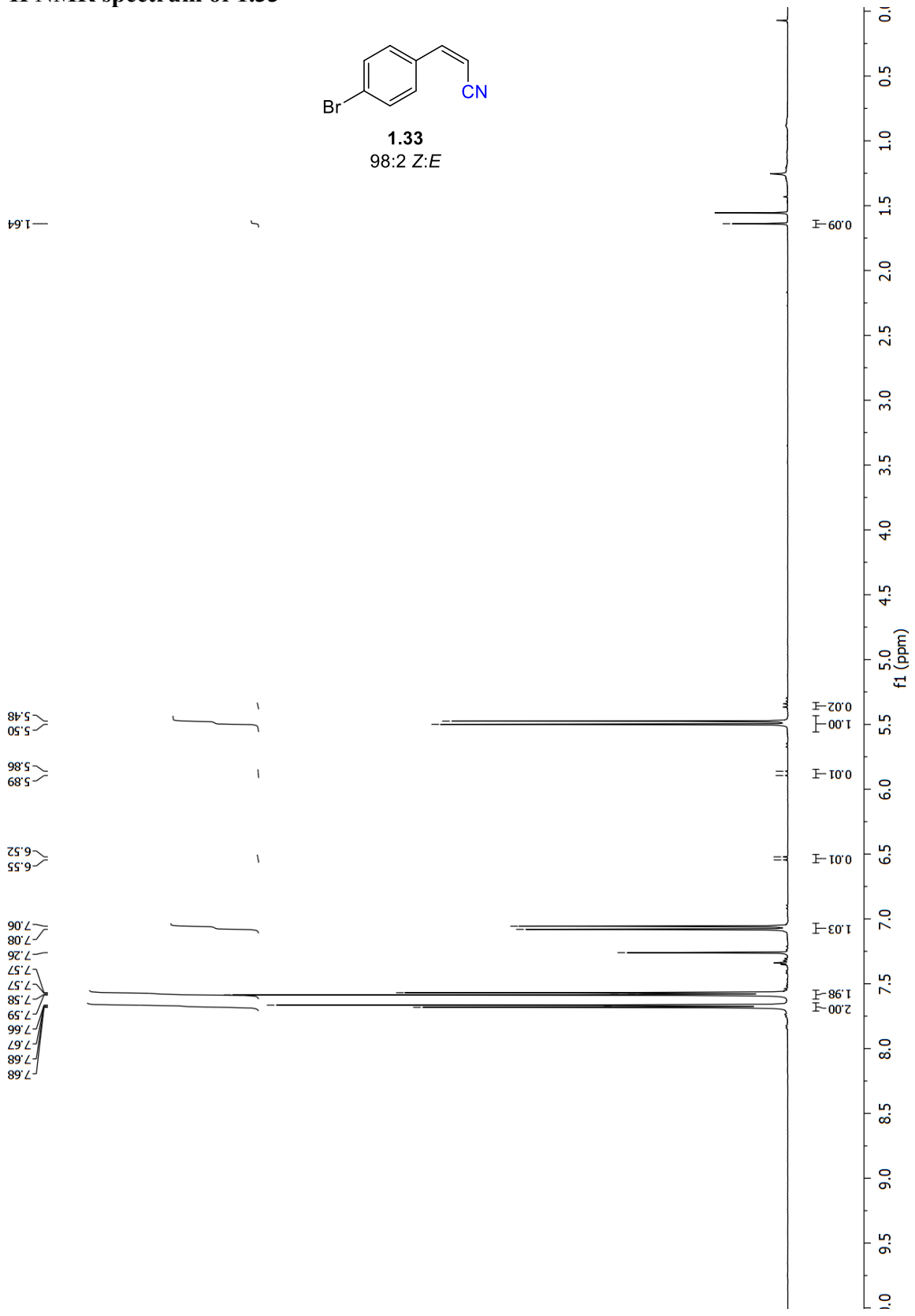


1.31
97:3 *Z*:*E*

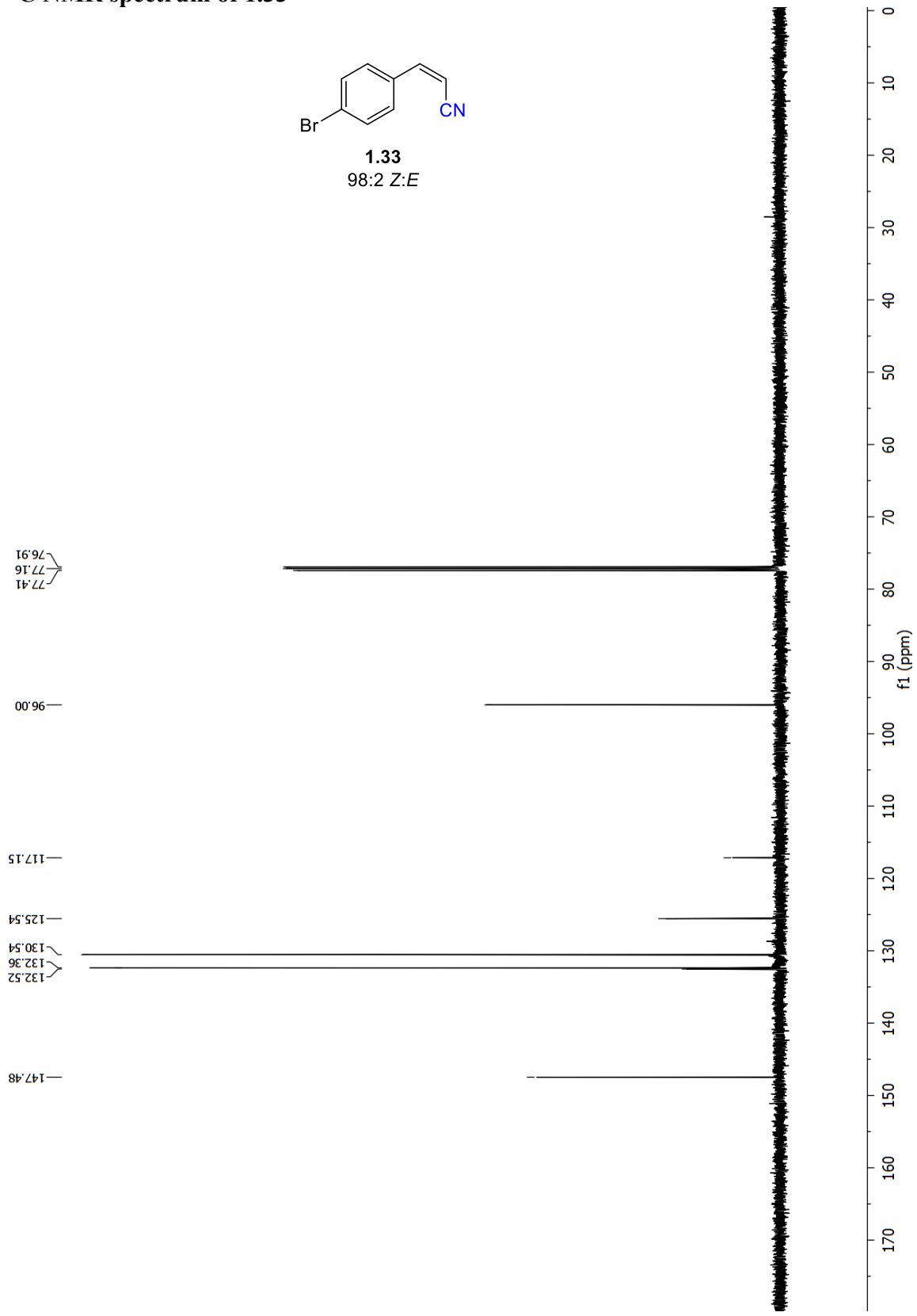
^{1}H NMR spectrum of 1.32



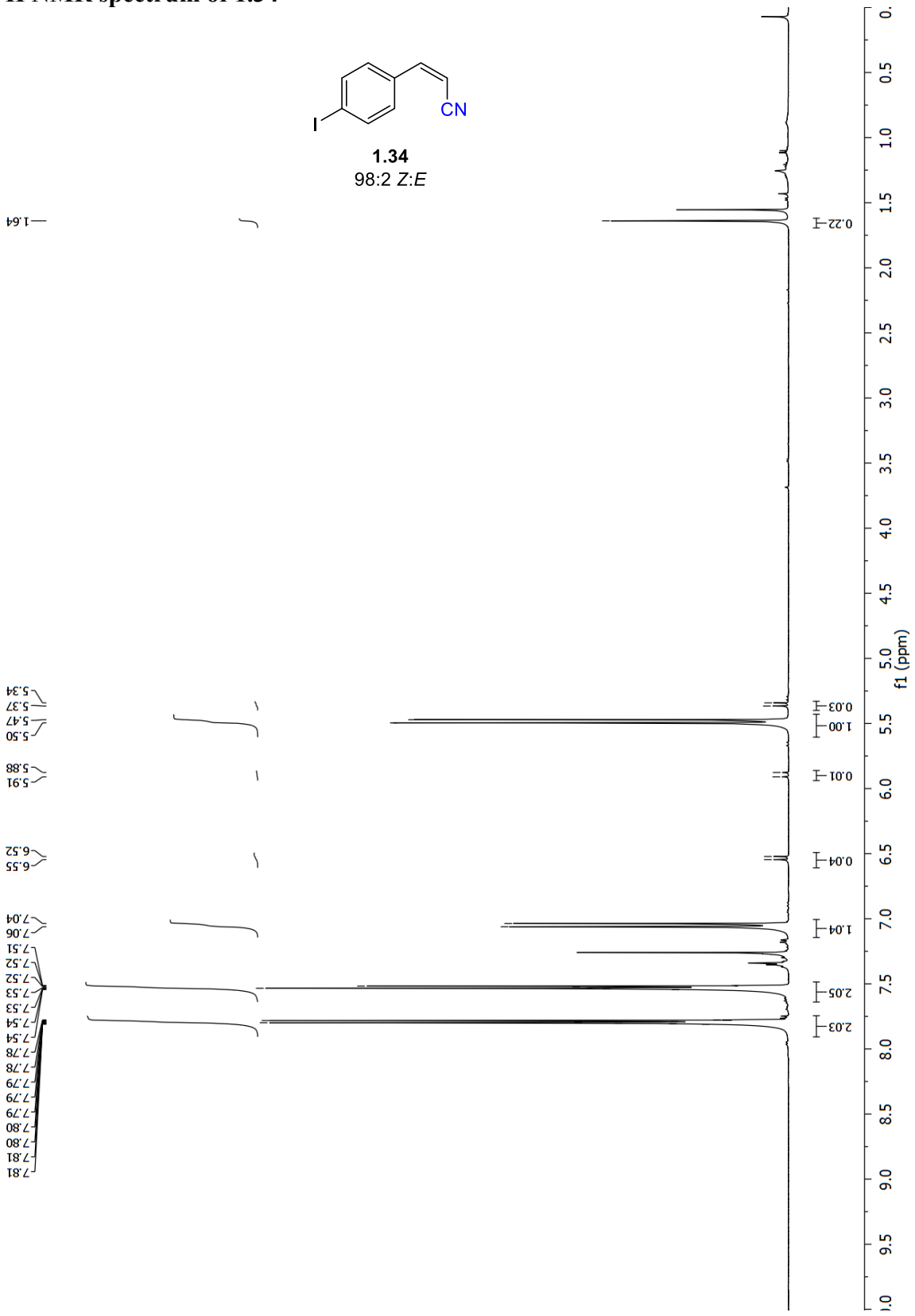
^{1}H NMR spectrum of 1.33



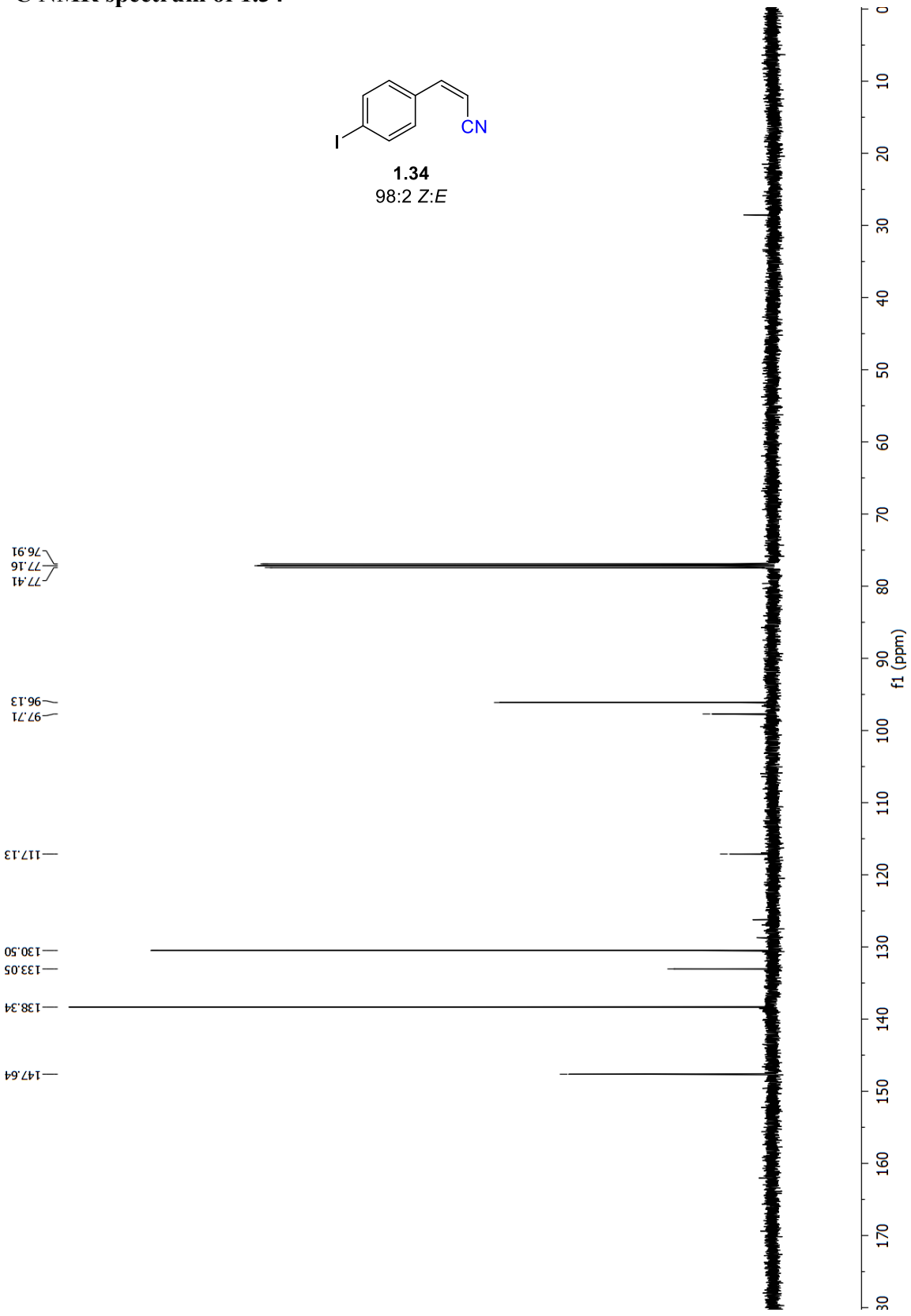
^{13}C NMR spectrum of 1.33



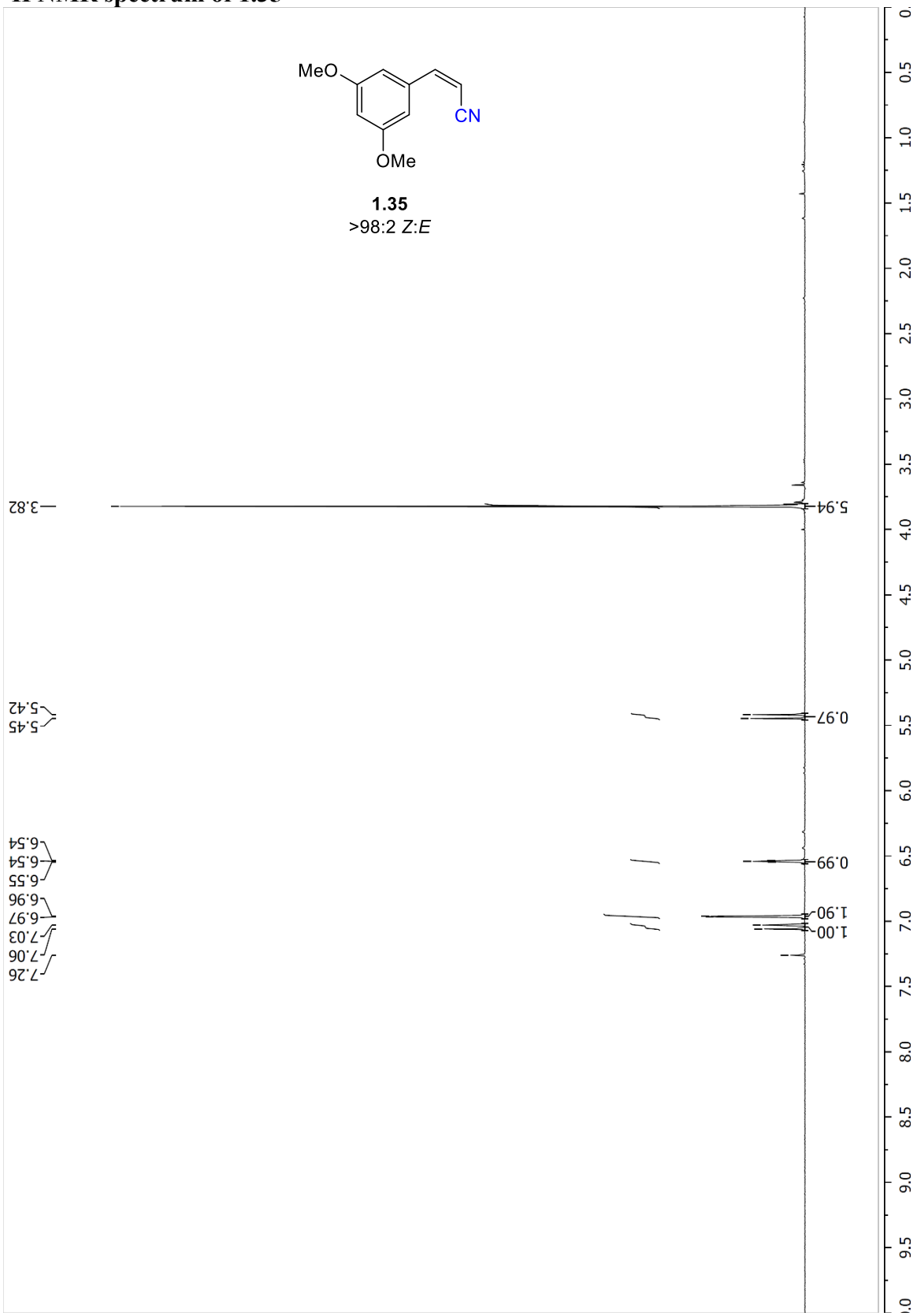
^{1}H NMR spectrum of 1.34



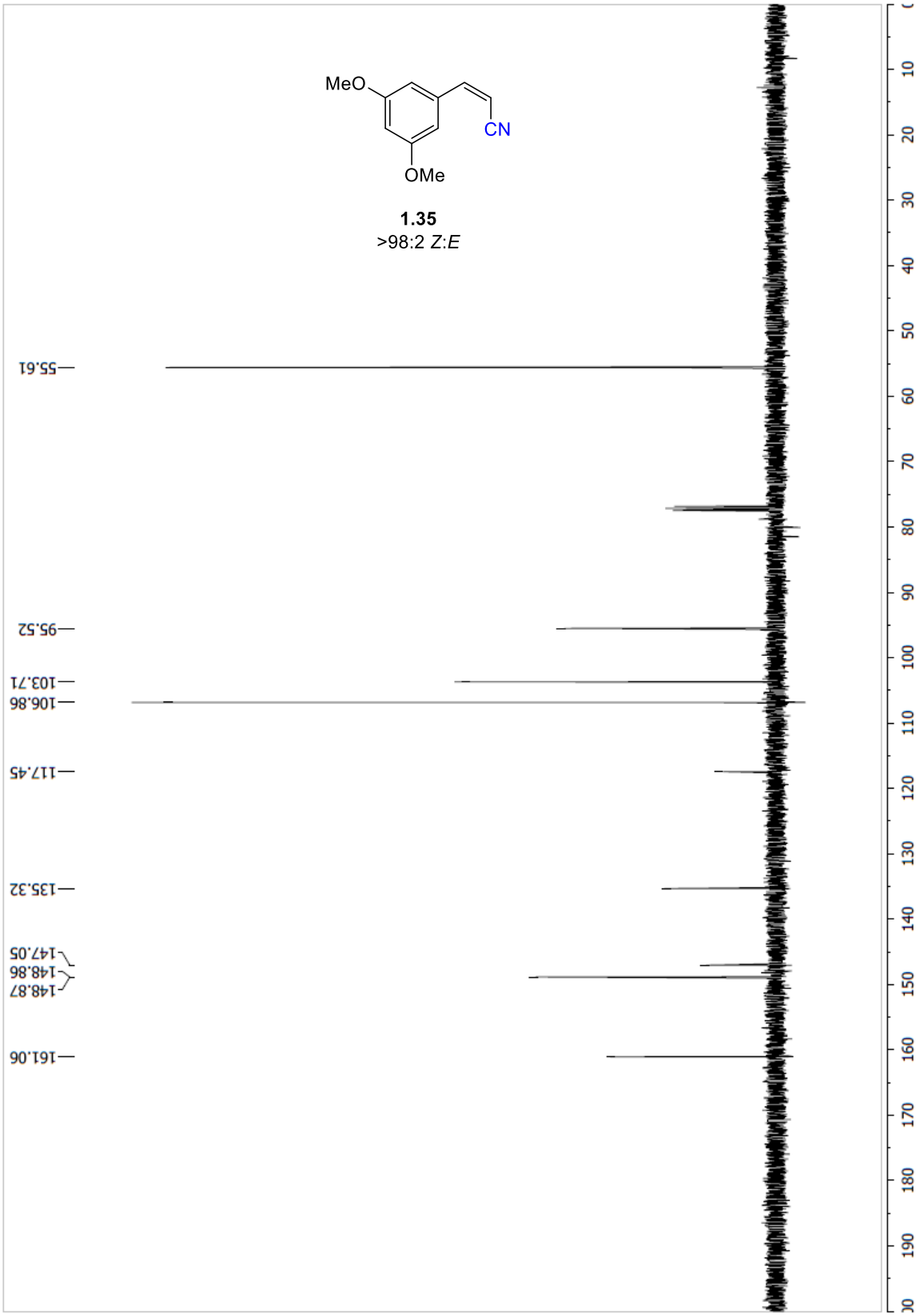
^{13}C NMR spectrum of 1.34



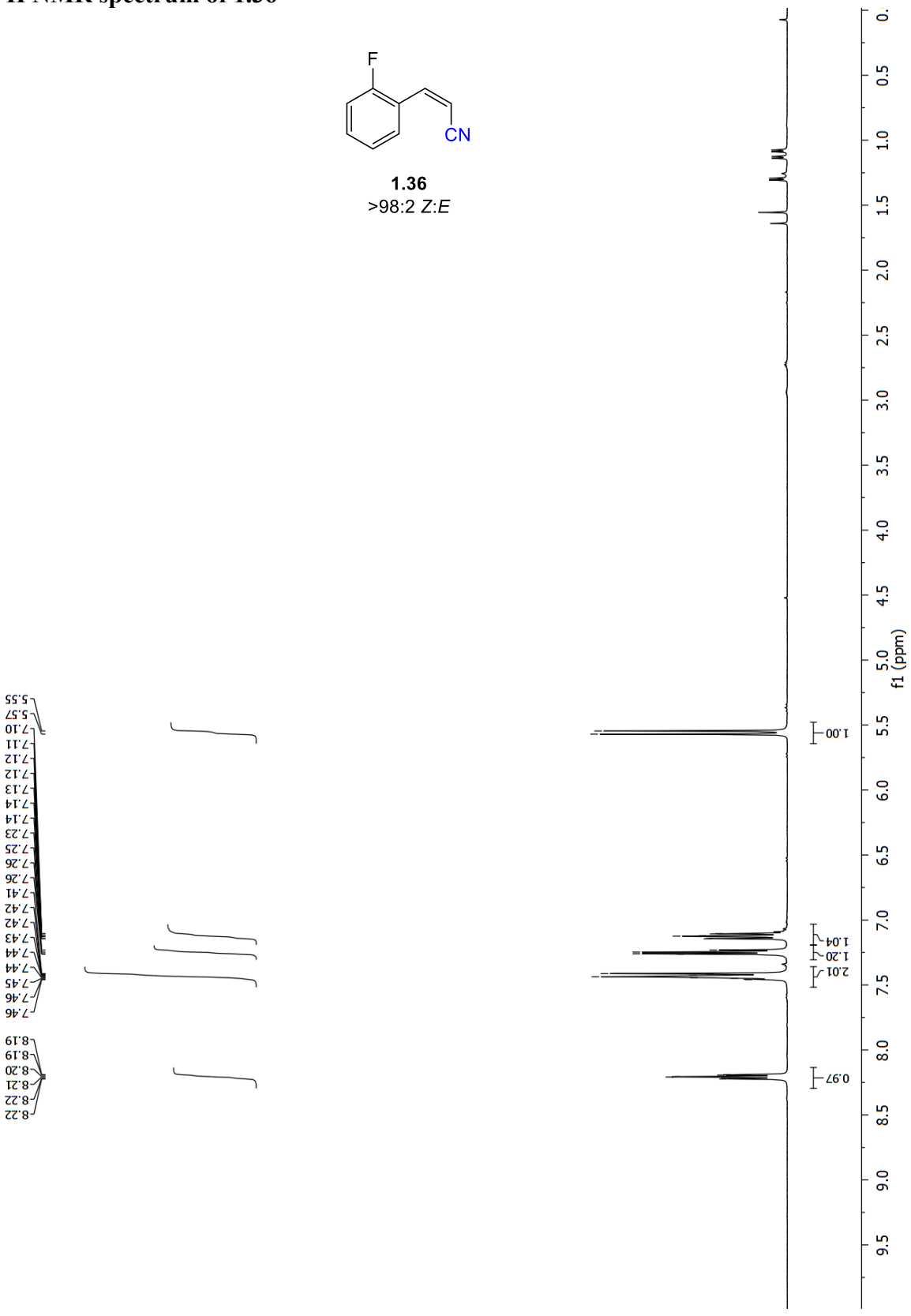
^{1}H NMR spectrum of 1.35



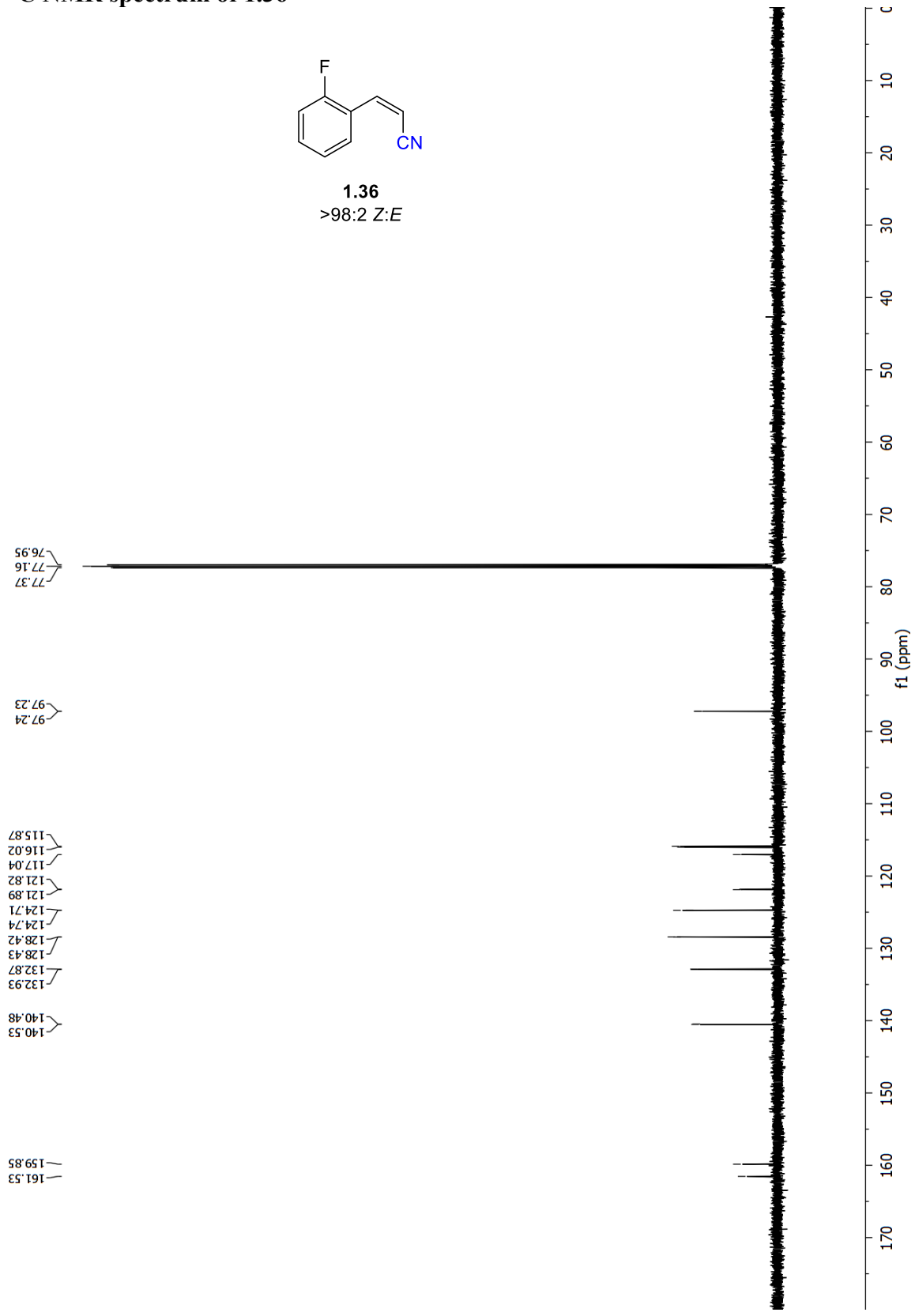
^{13}C NMR spectrum of 1.35



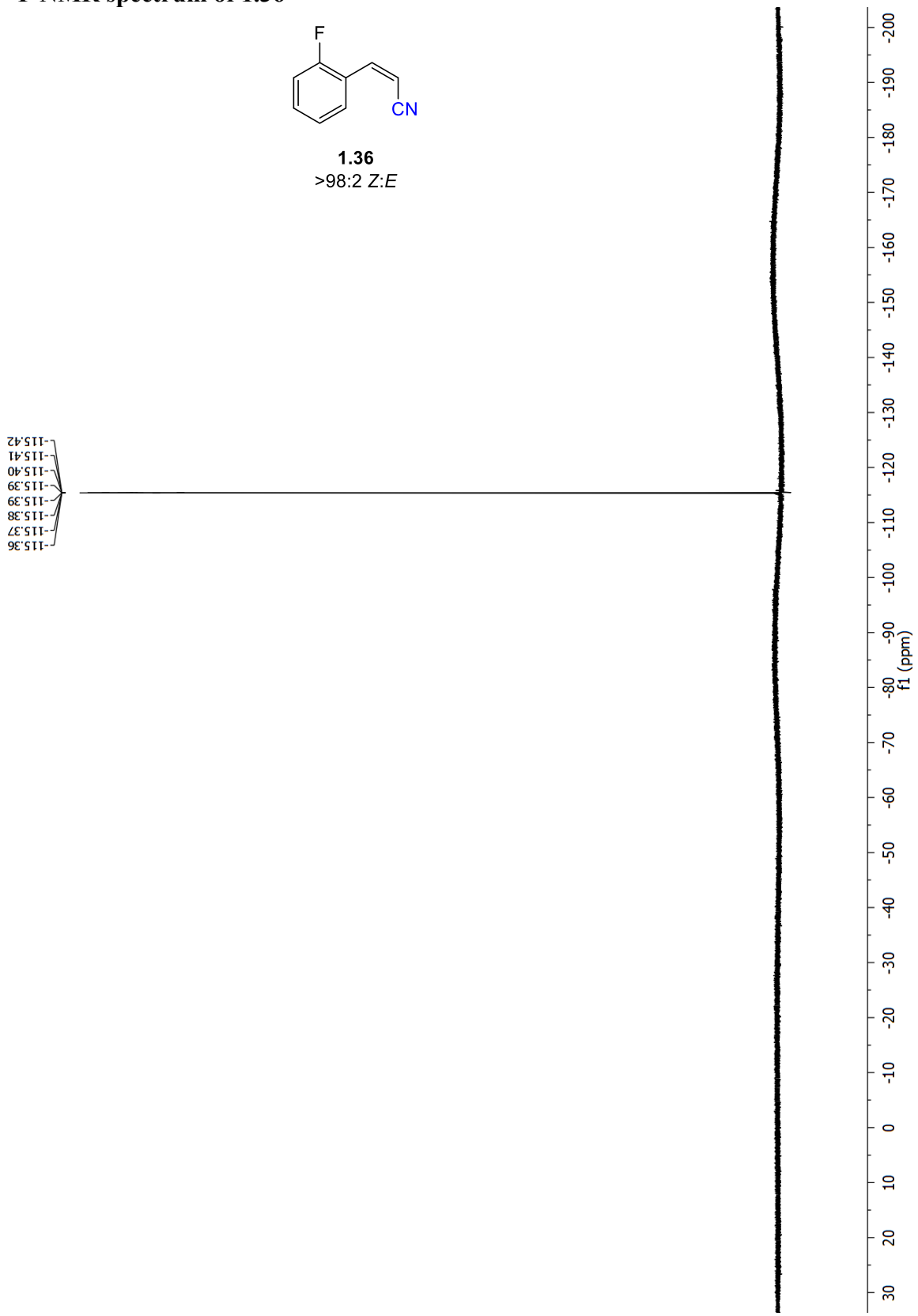
^{1}H NMR spectrum of 1.36



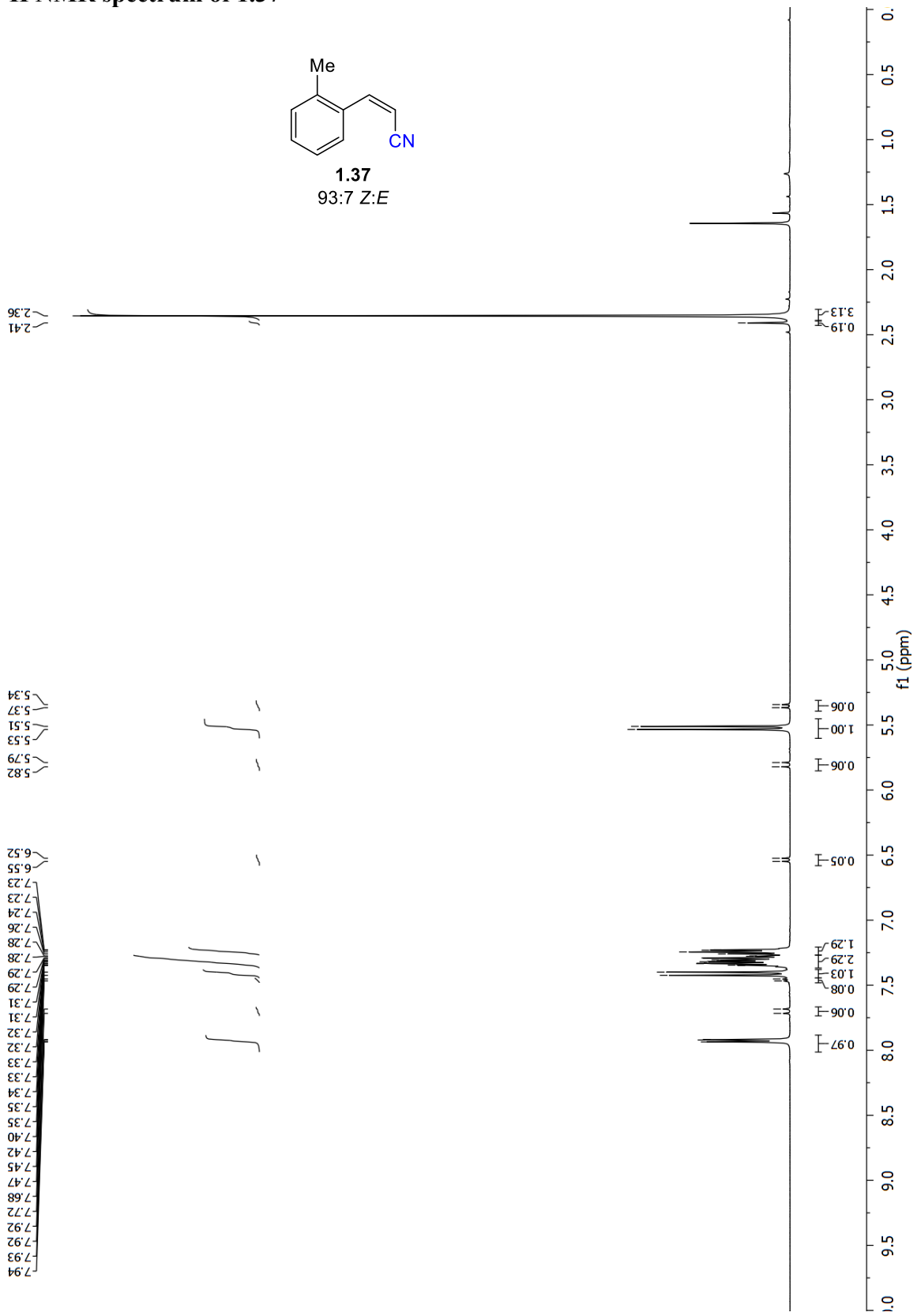
^{13}C NMR spectrum of 1.36



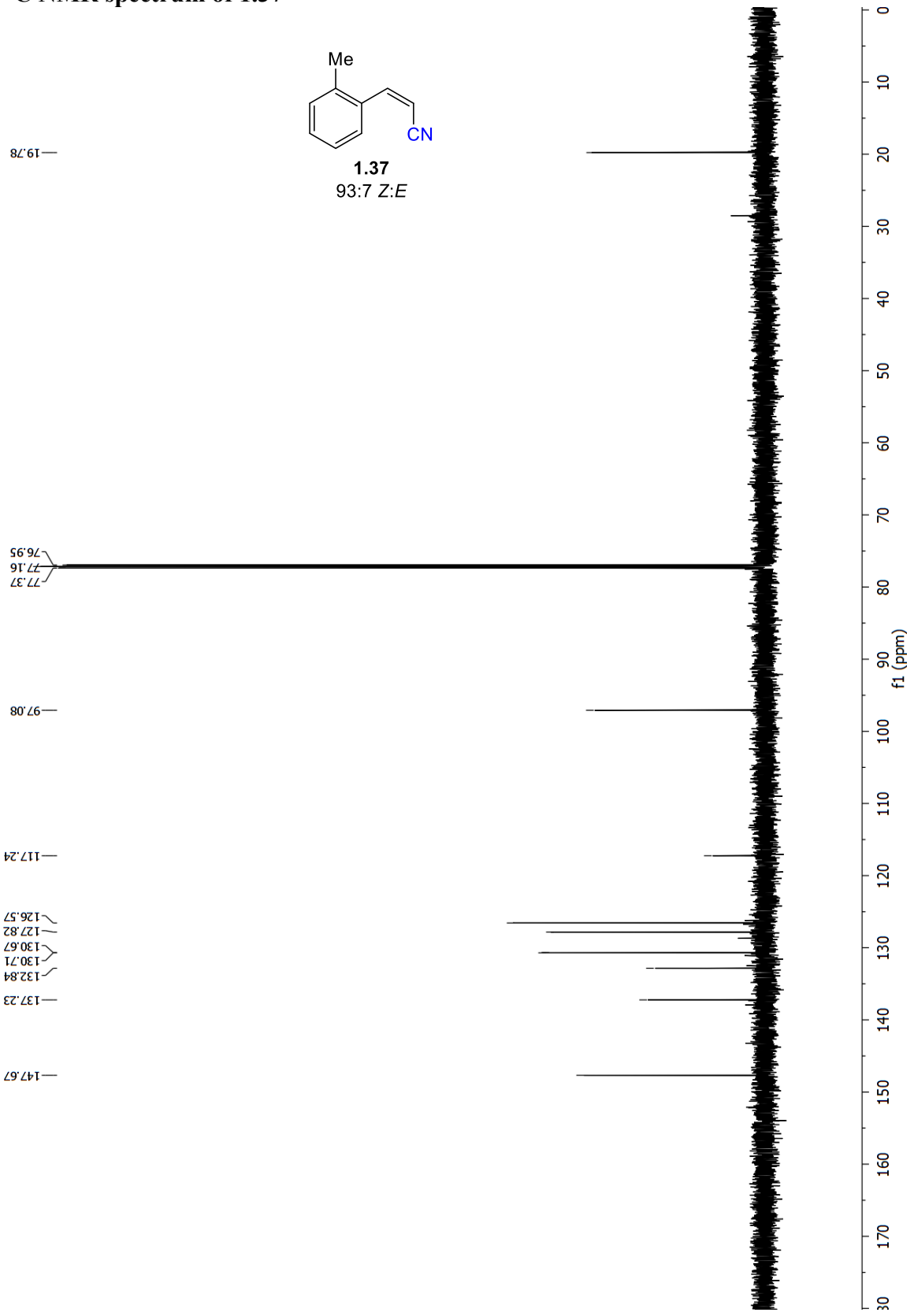
^{19}F NMR spectrum of 1.36



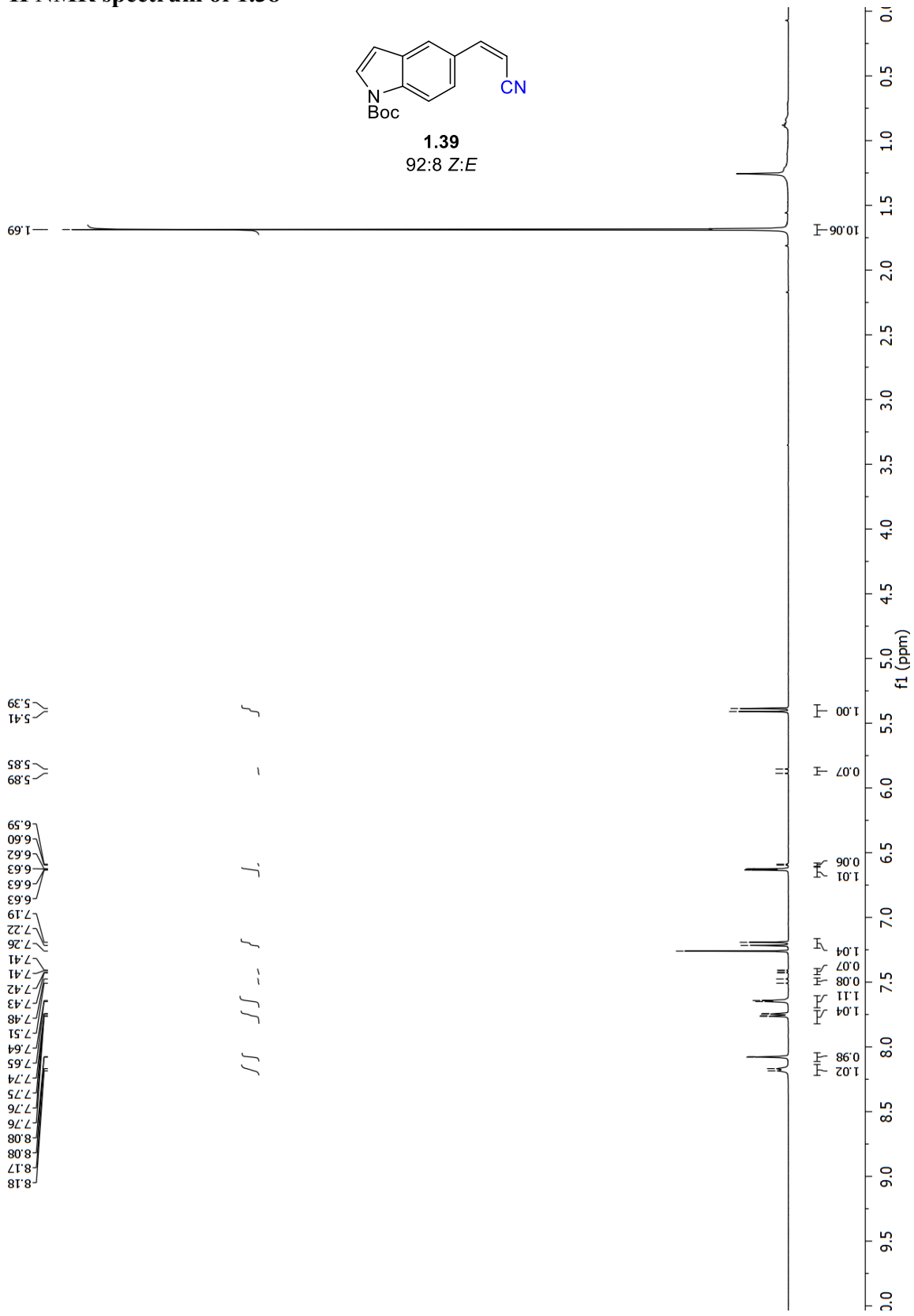
^{1}H NMR spectrum of 1.37



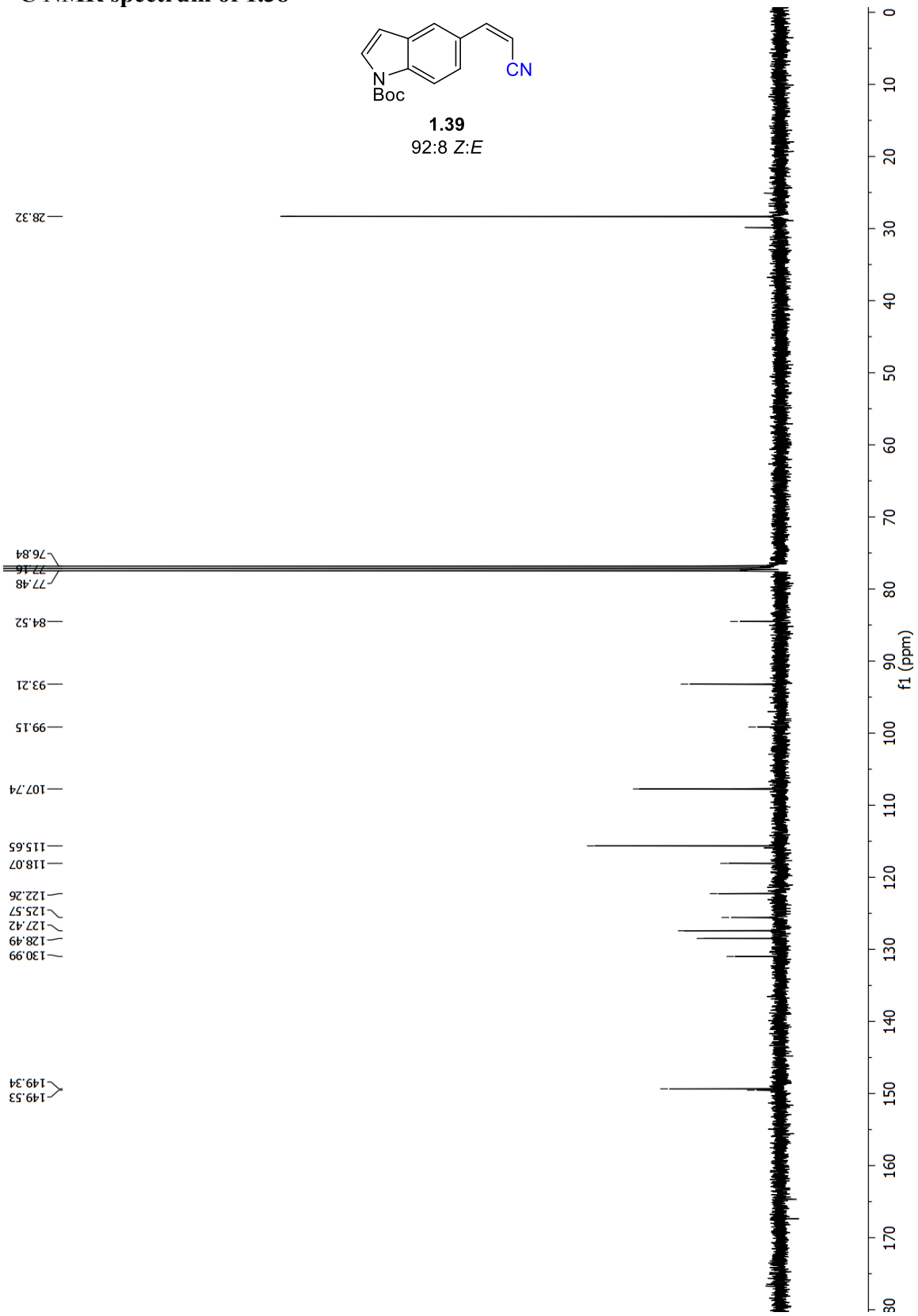
^{13}C NMR spectrum of 1.37



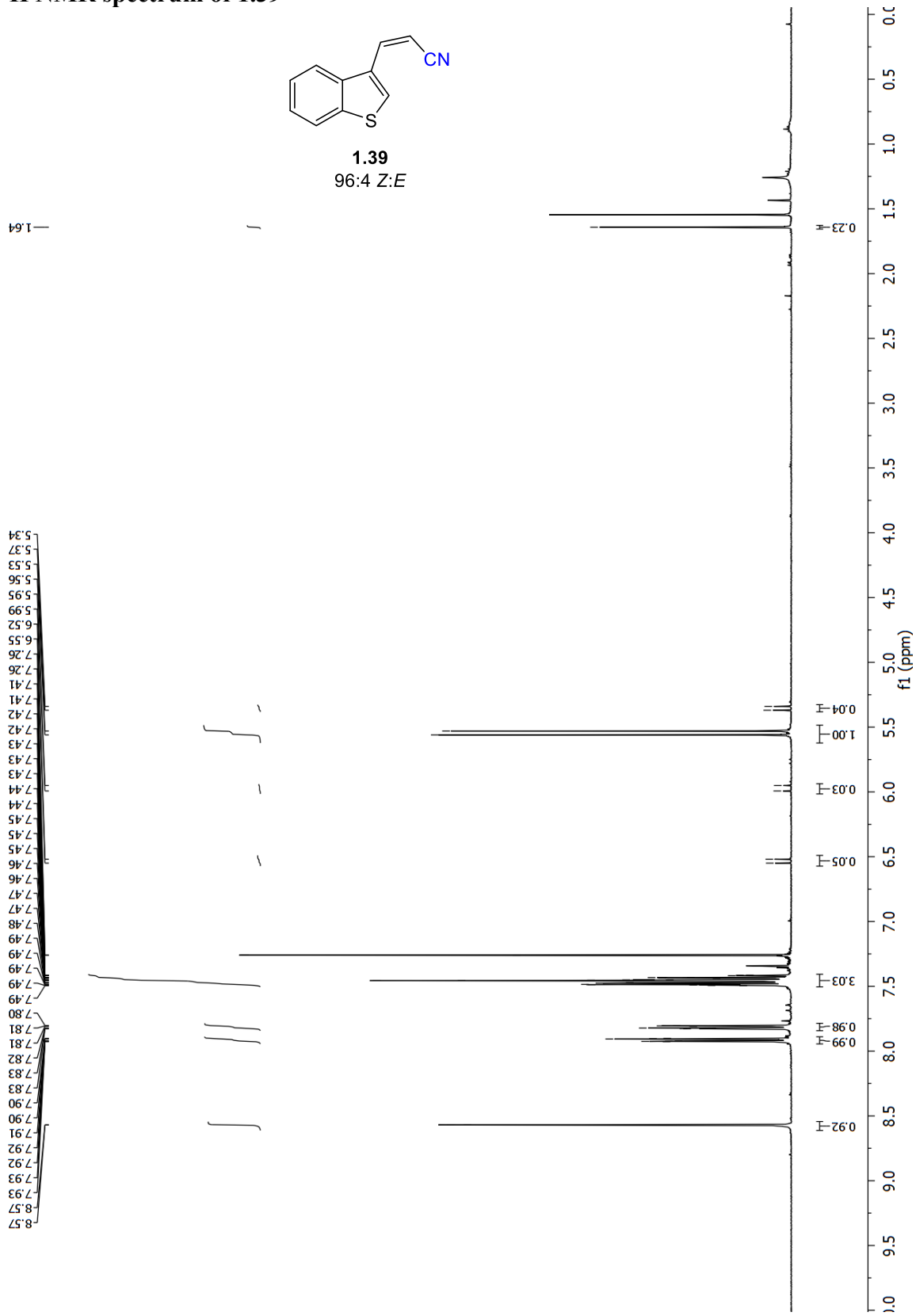
^{1}H NMR spectrum of 1.38



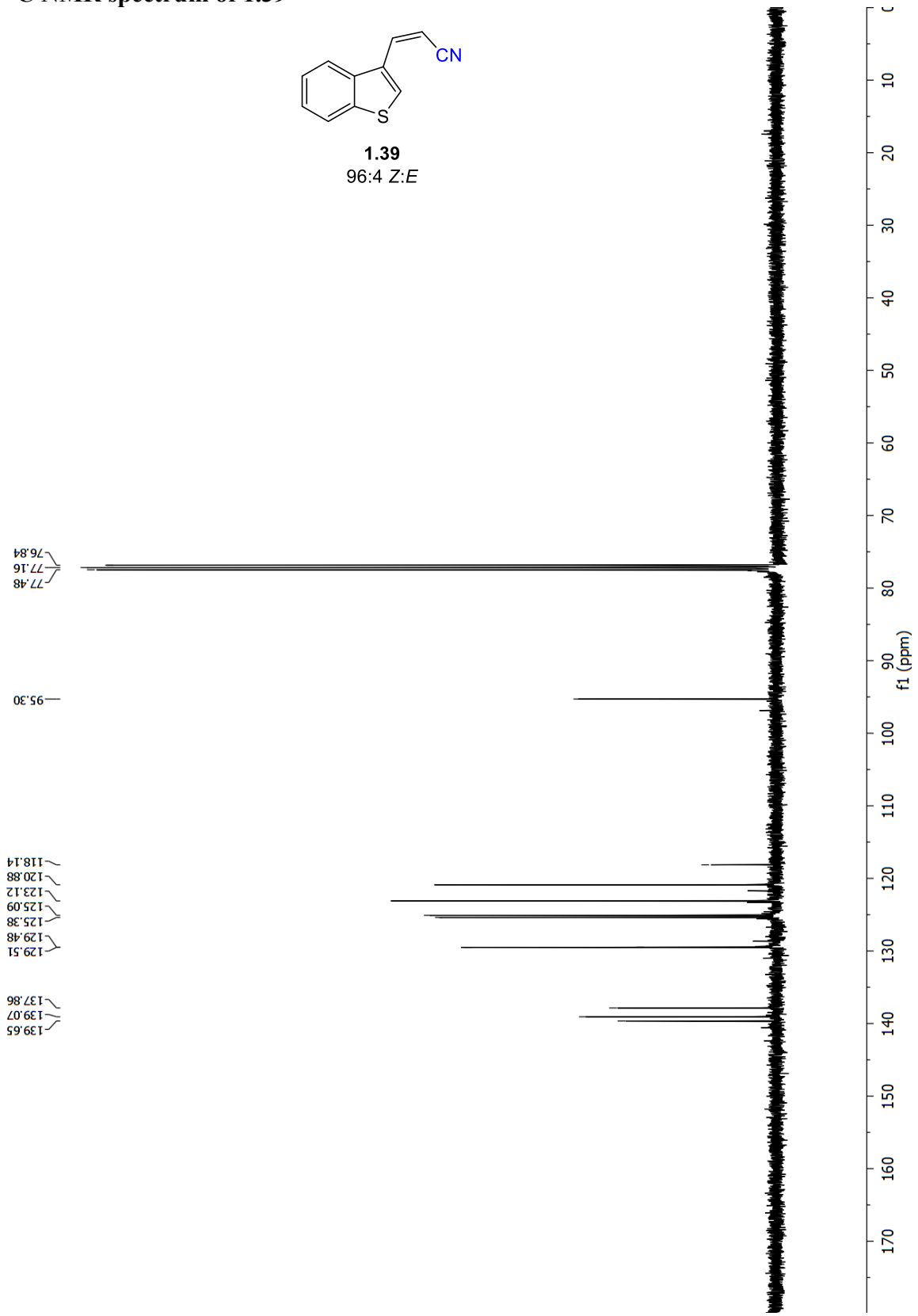
^{13}C NMR spectrum of 1.38



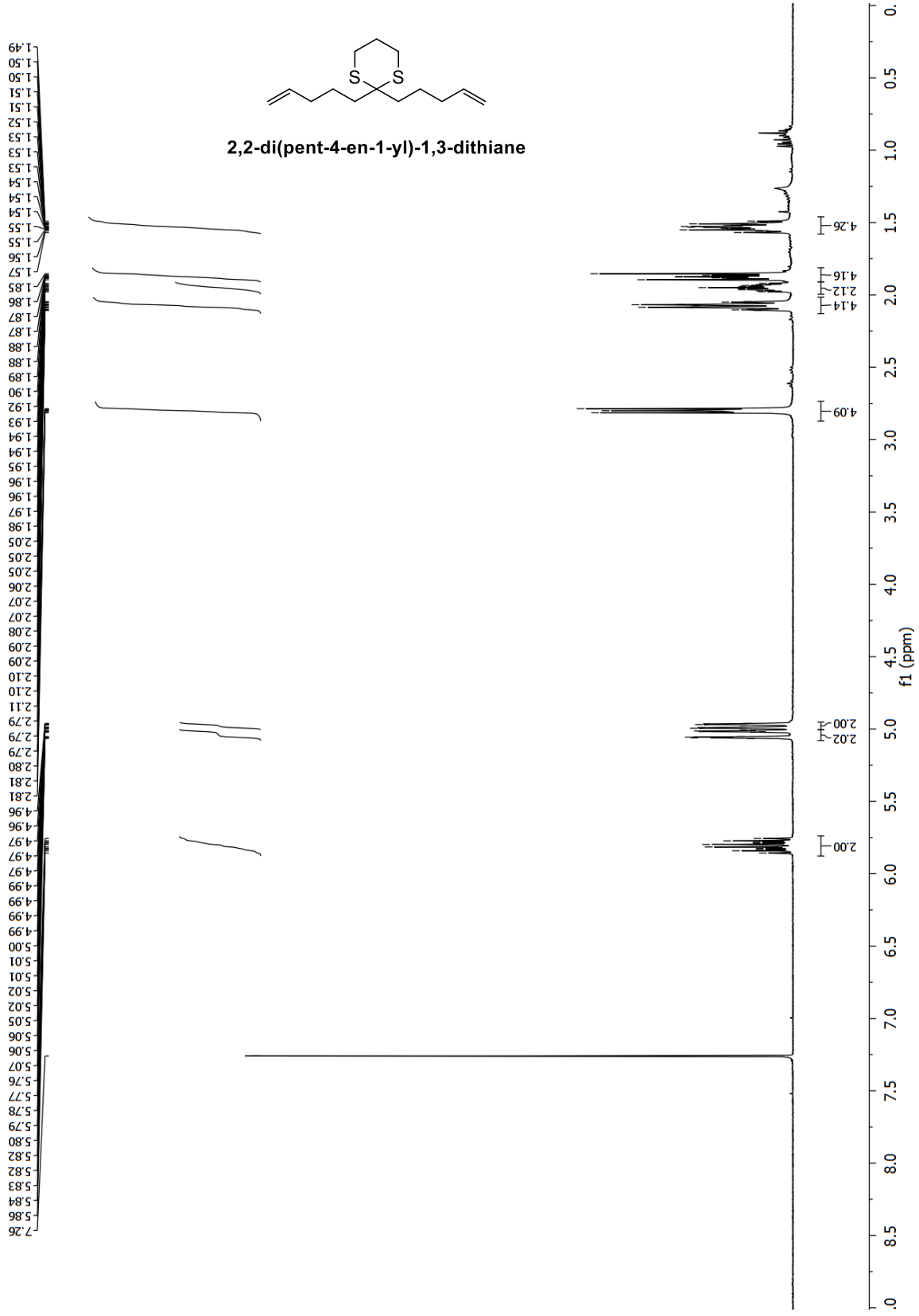
^{1}H NMR spectrum of 1.39



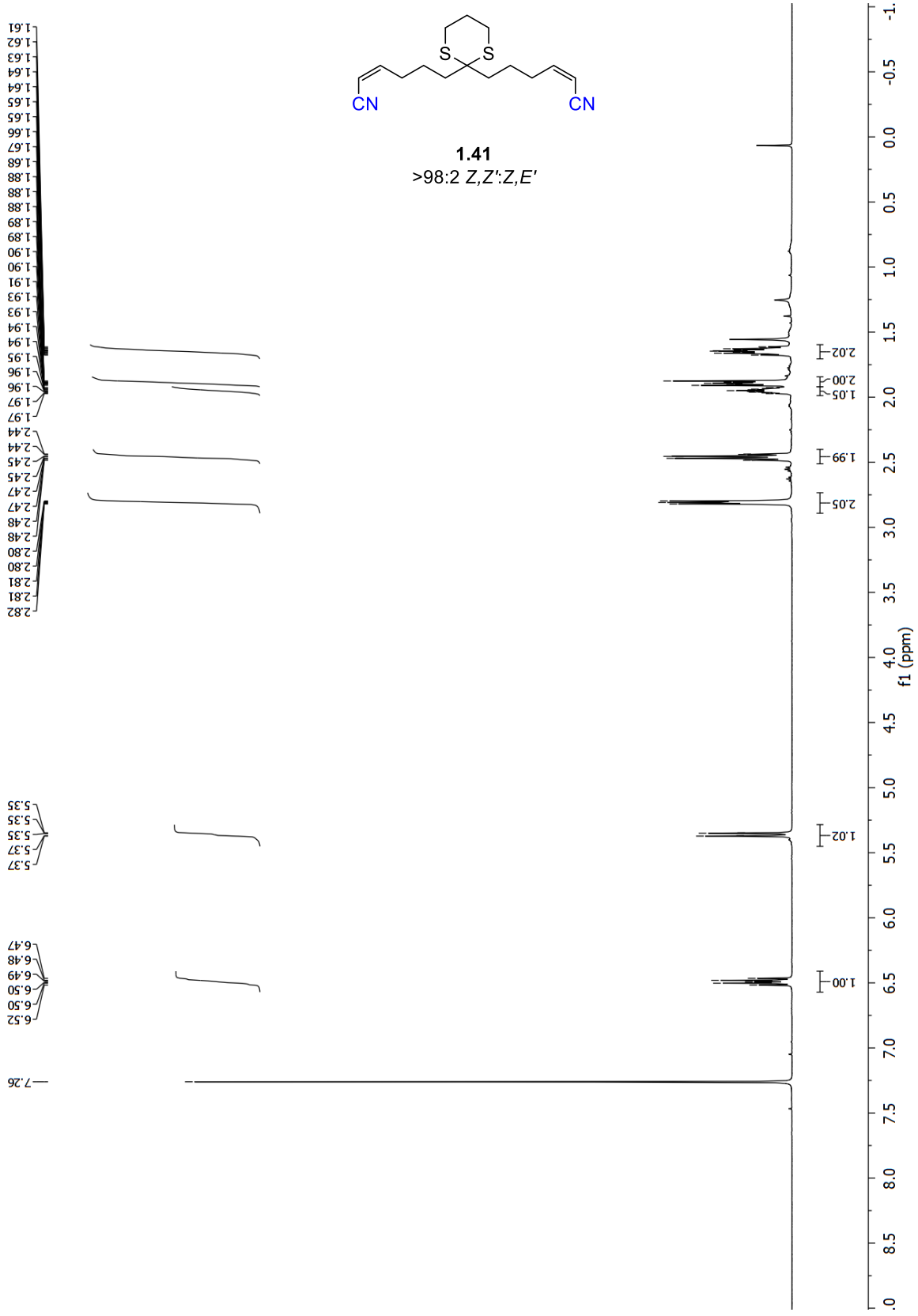
^{13}C NMR spectrum of 1.39



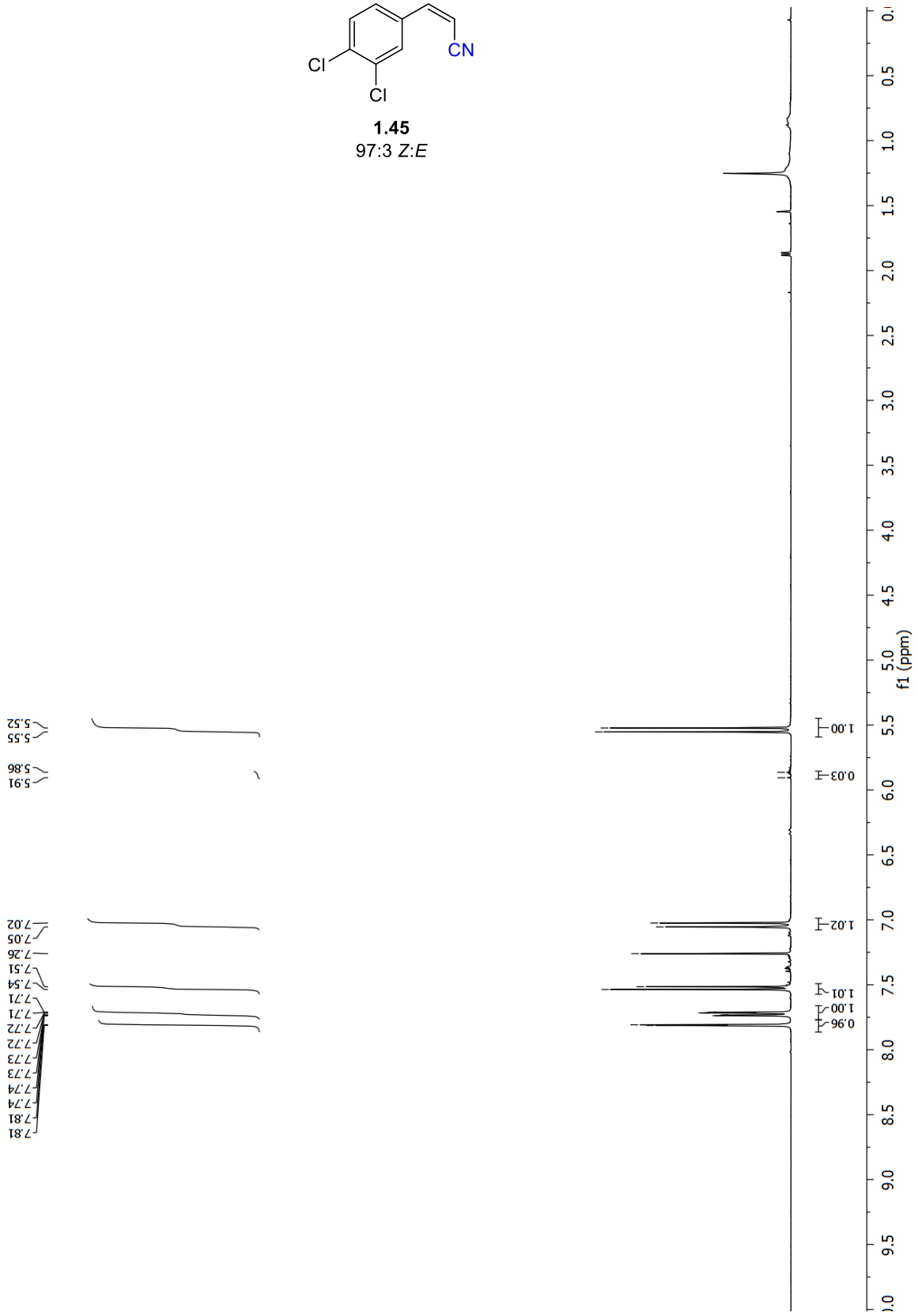
^{1}H NMR spectrum of 2,2-di(pent-4-en-1-yl)-1,3-dithiane



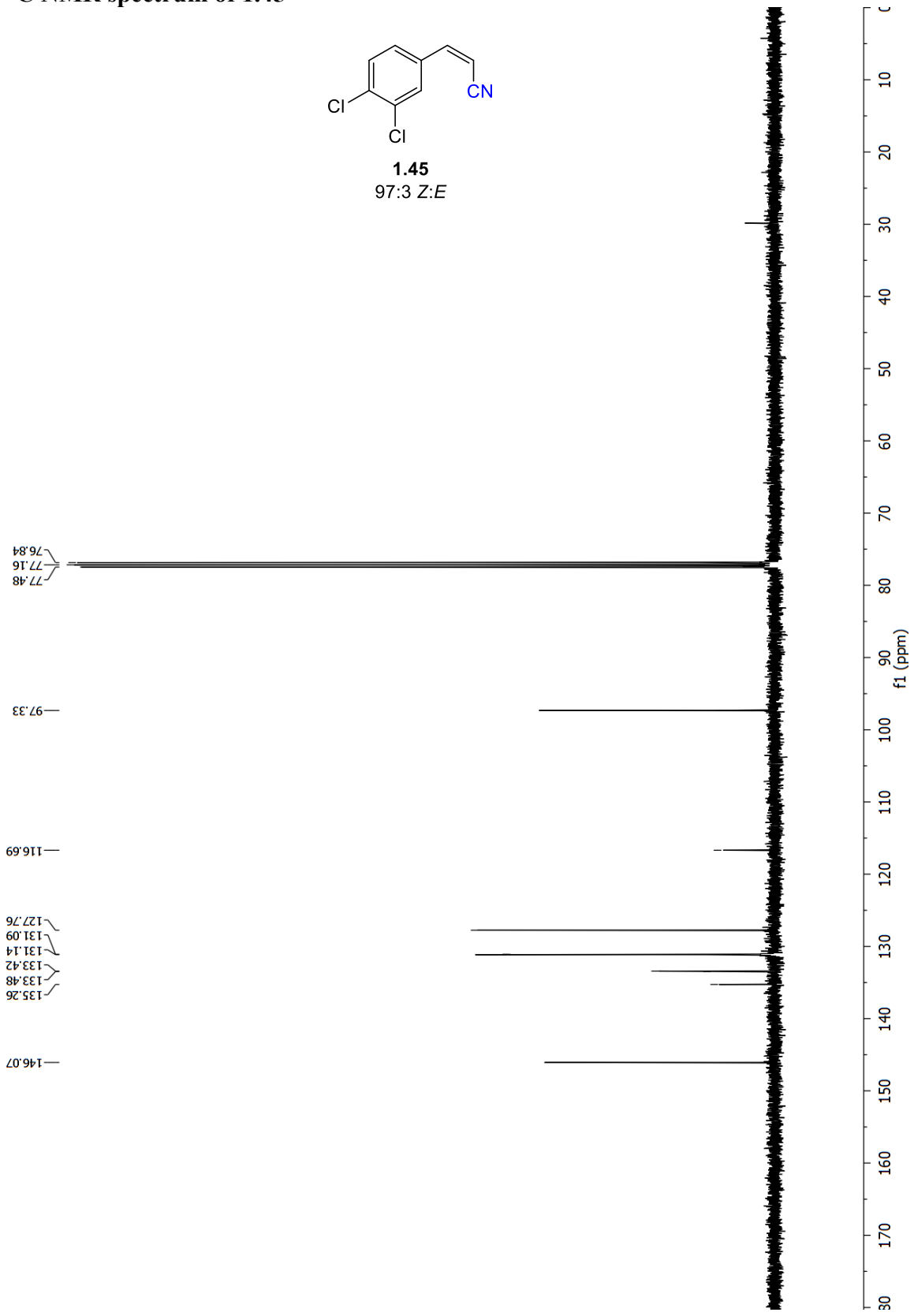
^{1}H NMR spectrum of 1.41



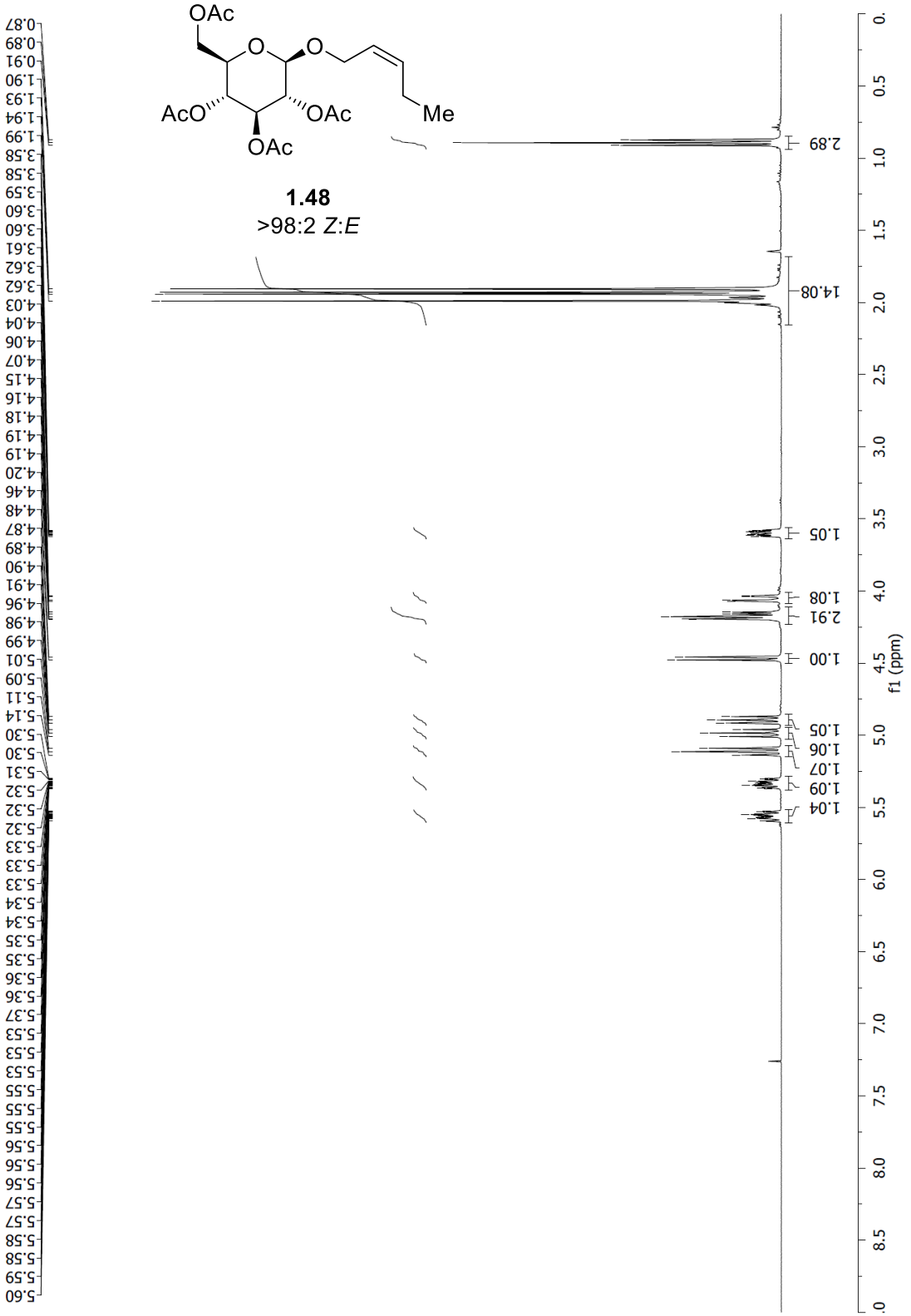
^{1}H NMR spectrum of 1.45



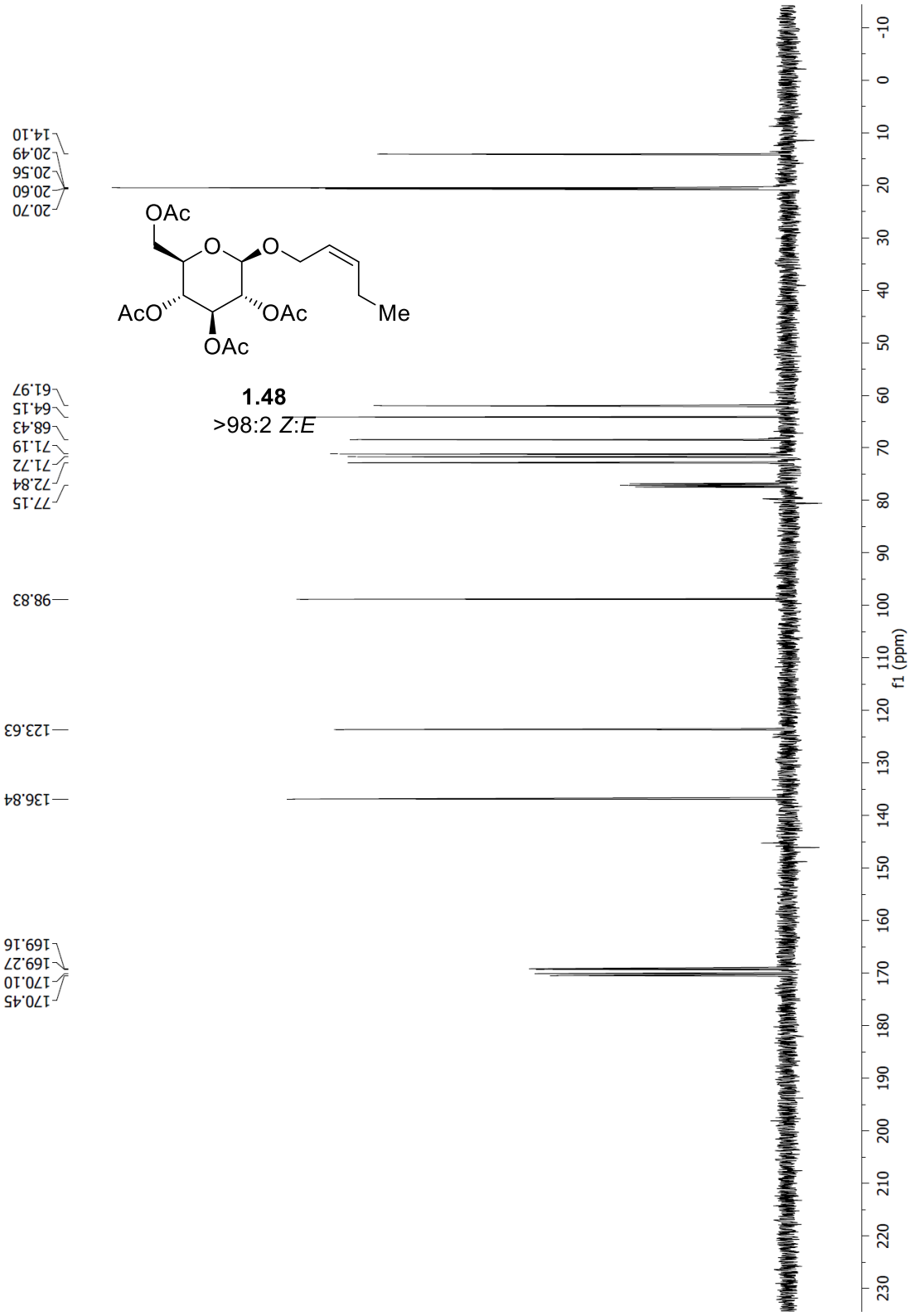
^{13}C NMR spectrum of 1.45



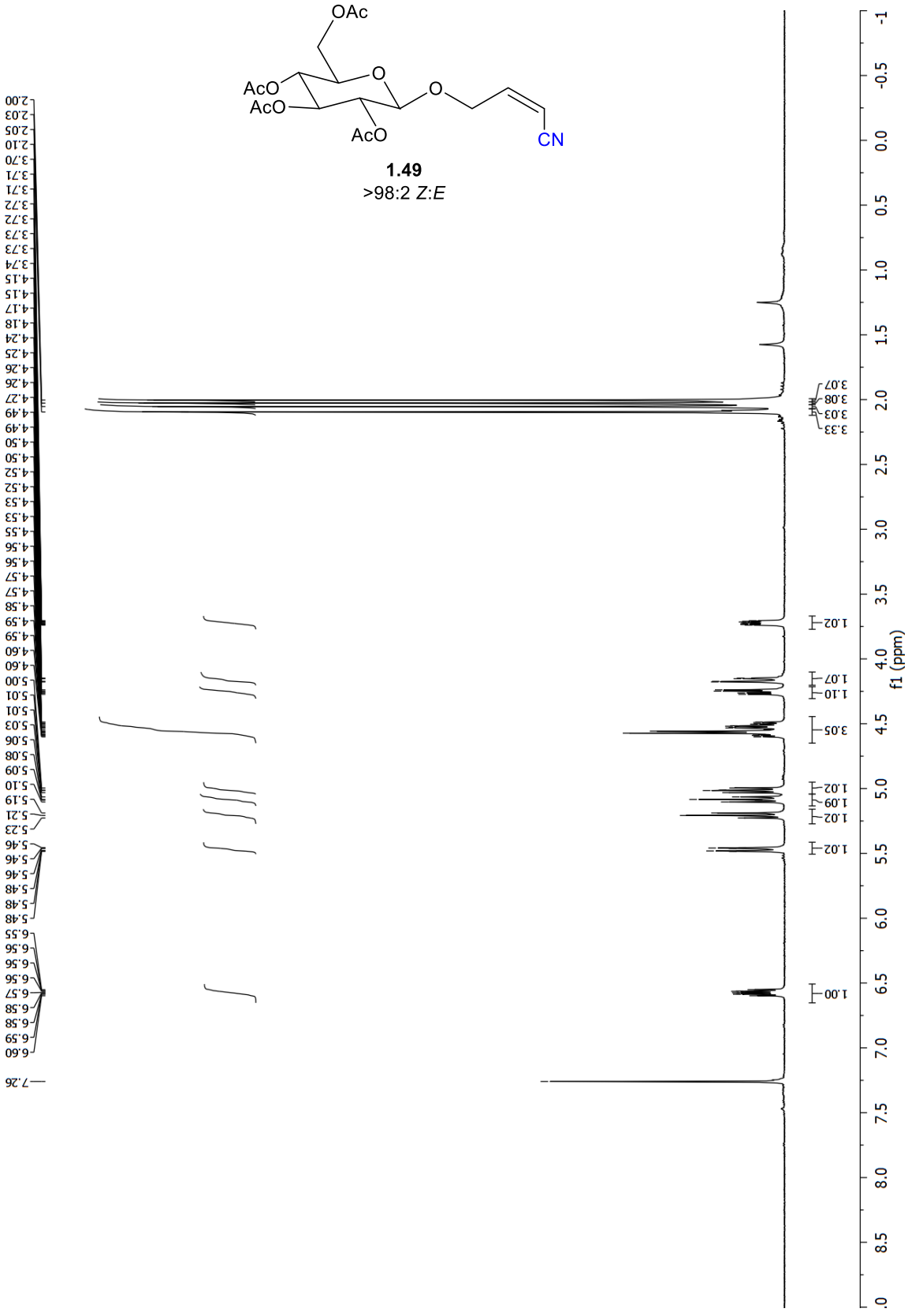
^{1}H NMR spectrum of 1.48



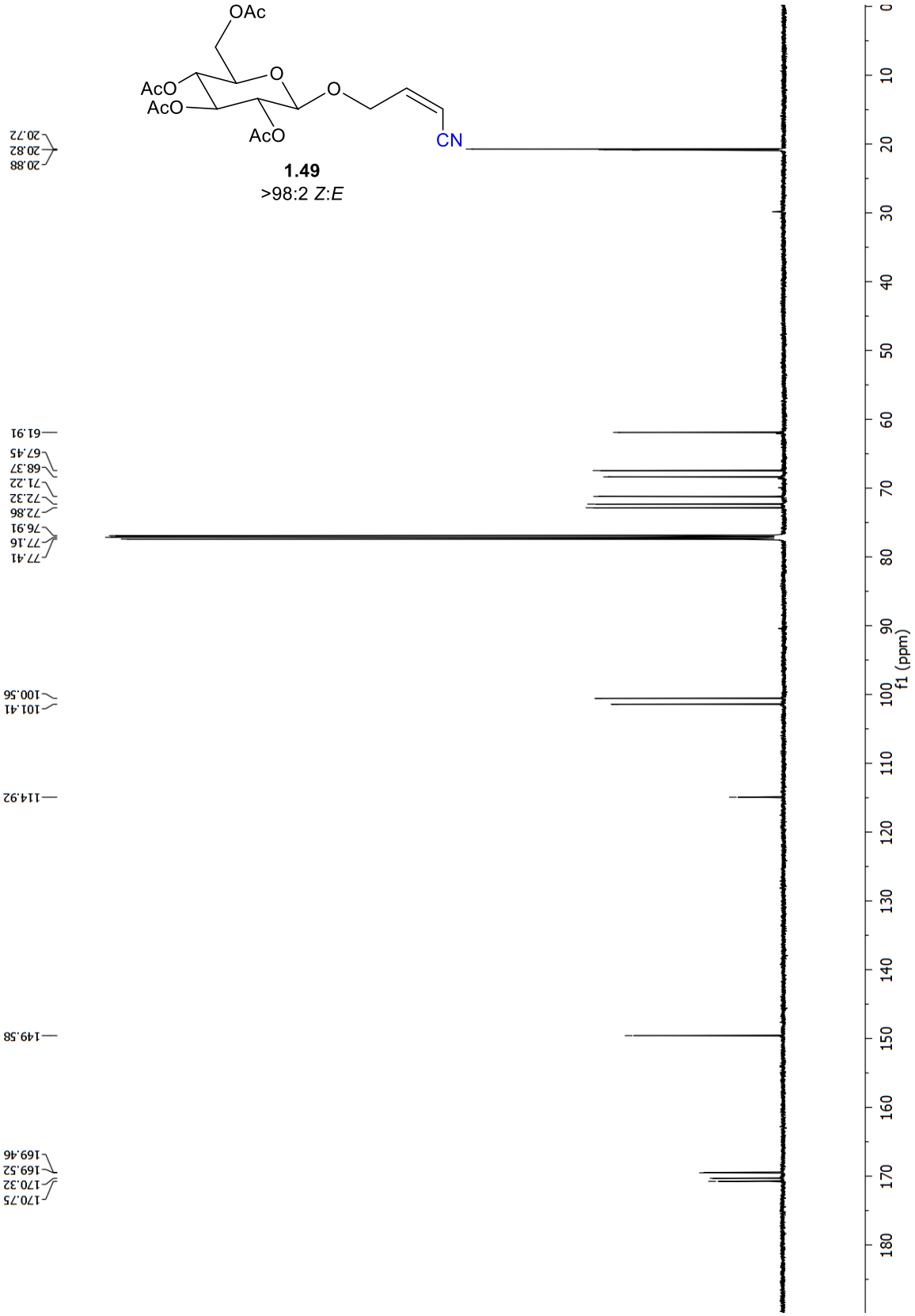
^{13}C NMR spectrum of 1.48



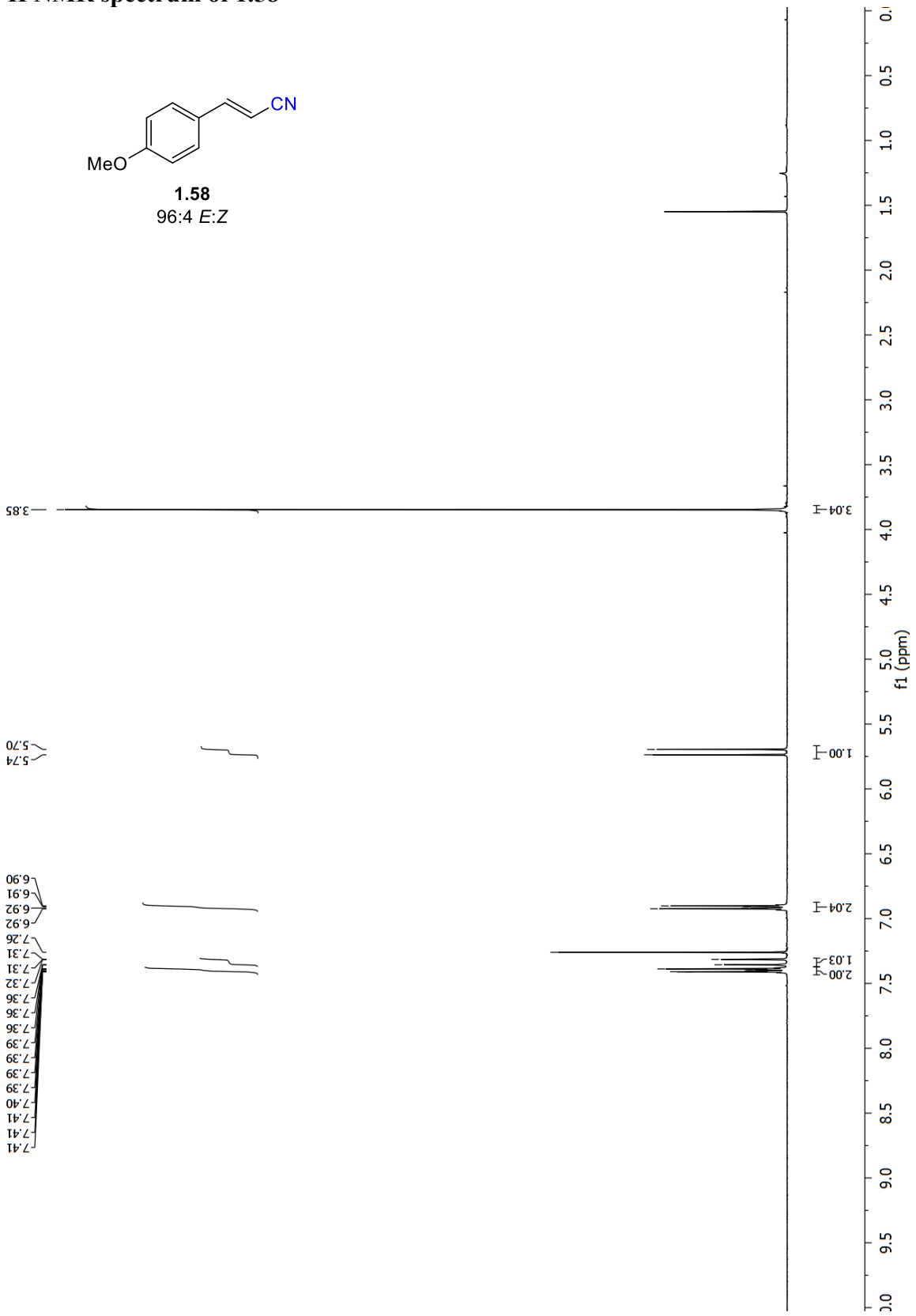
^{1}H NMR spectrum of 1.49



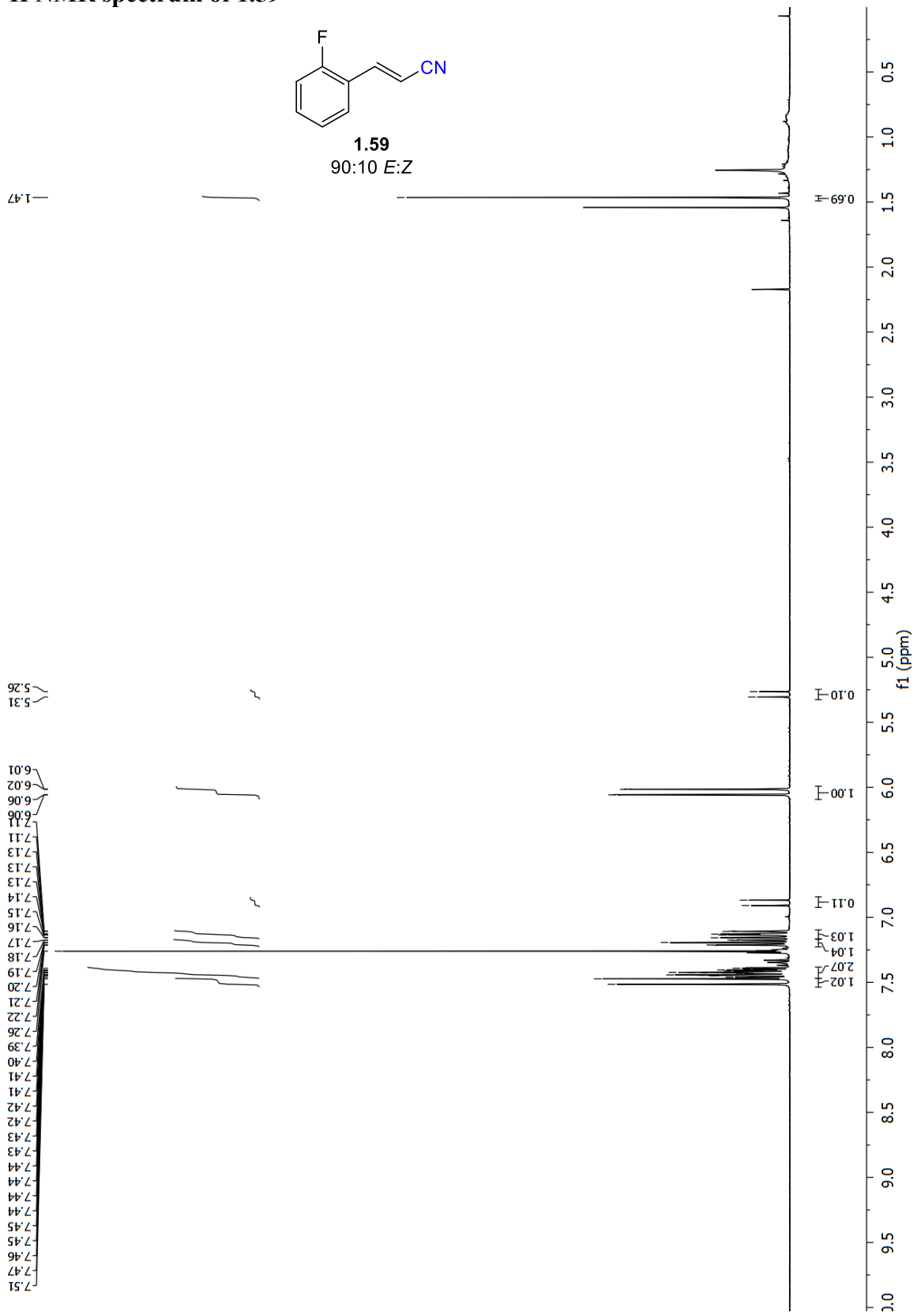
^{13}C NMR spectrum of 1.49



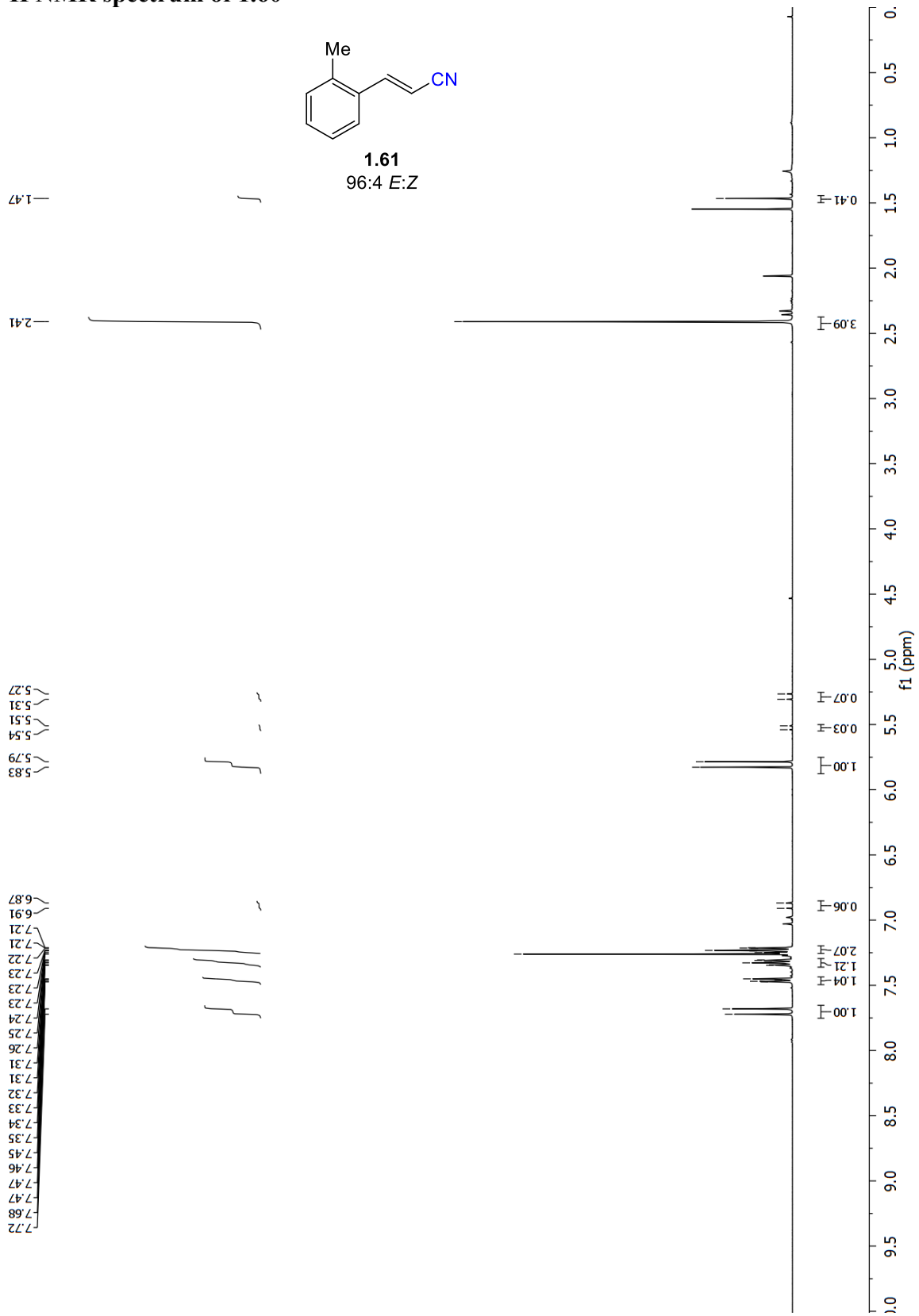
^{1}H NMR spectrum of 1.58



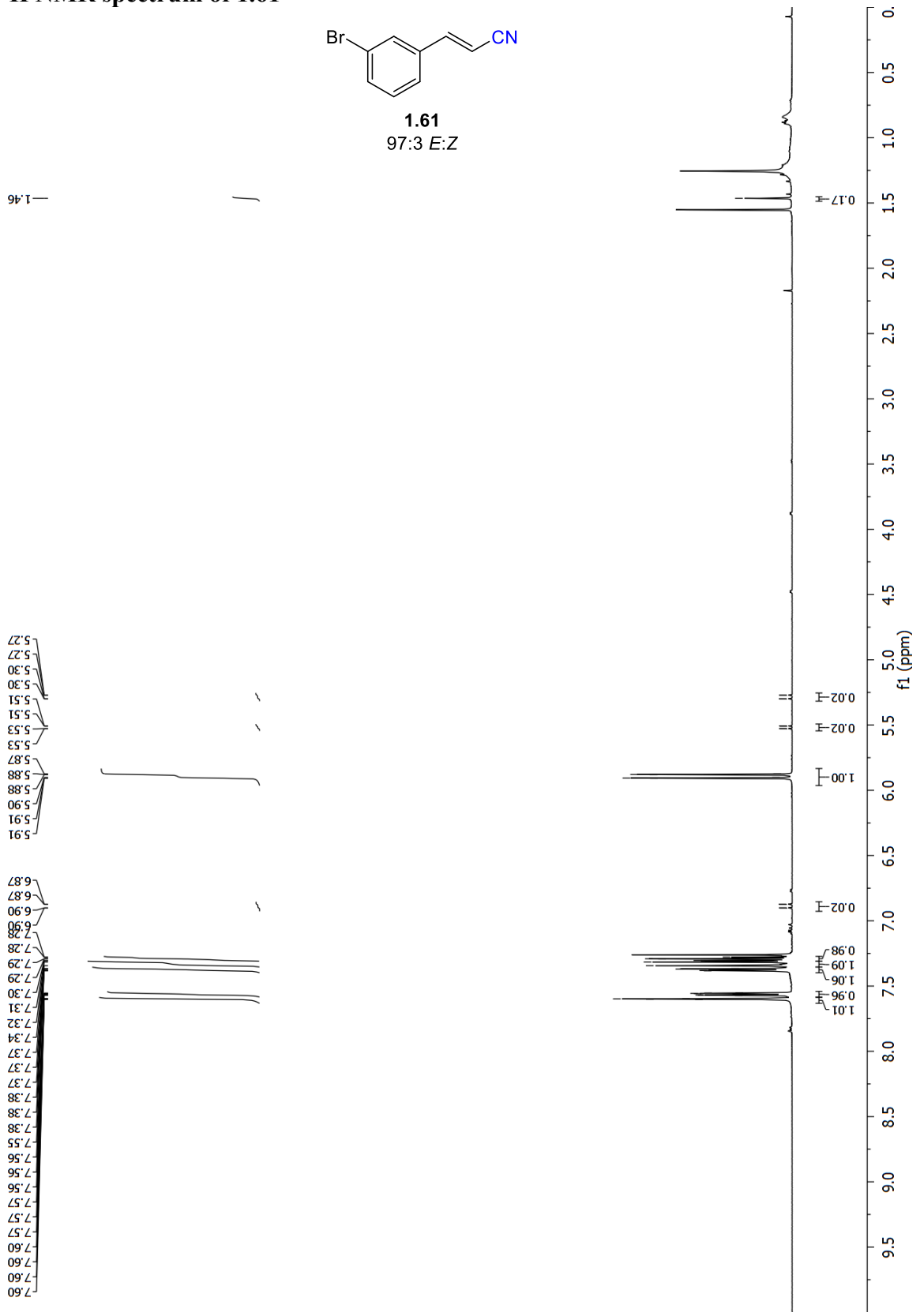
^{1}H NMR spectrum of 1.59



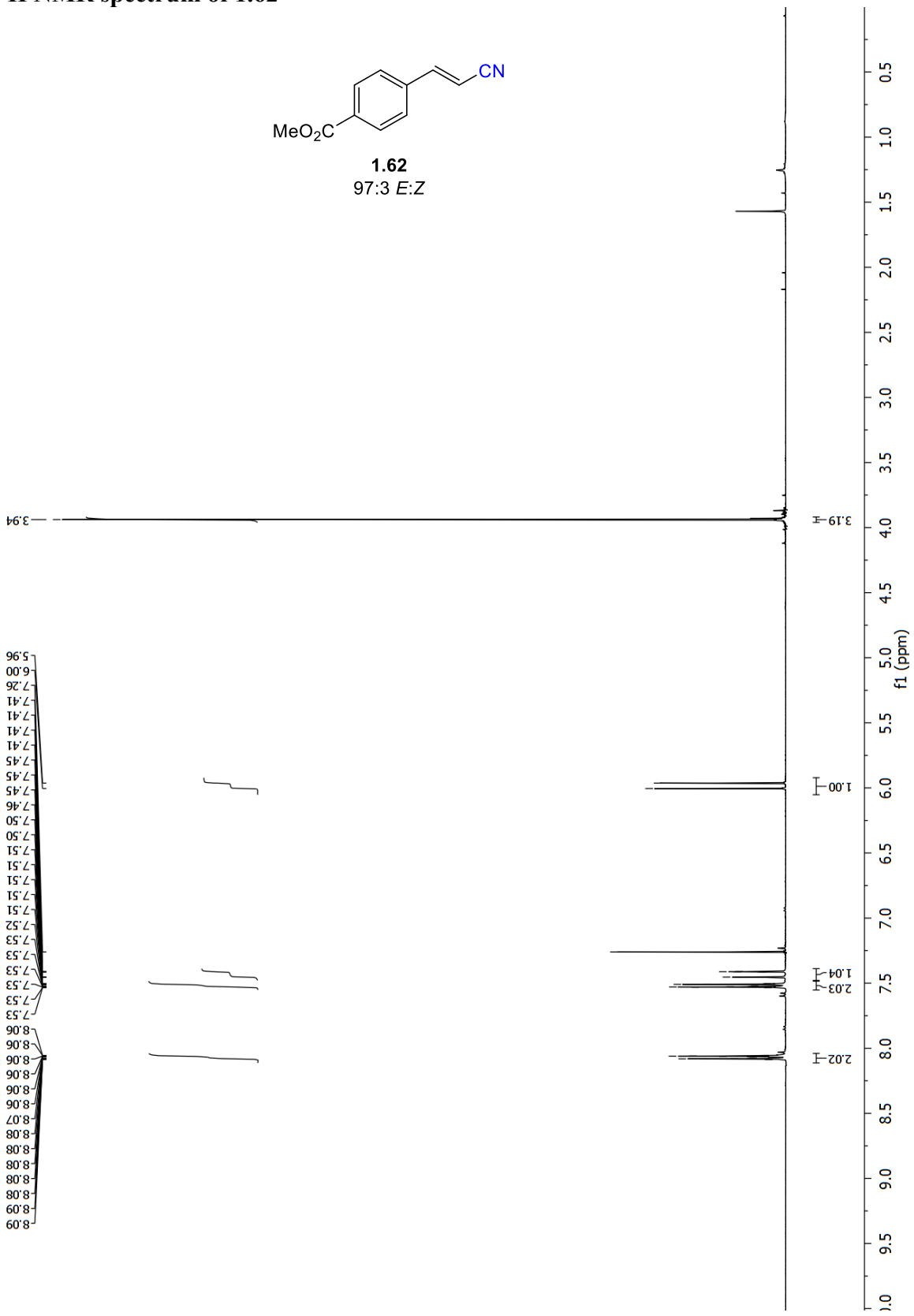
^{1}H NMR spectrum of 1.60



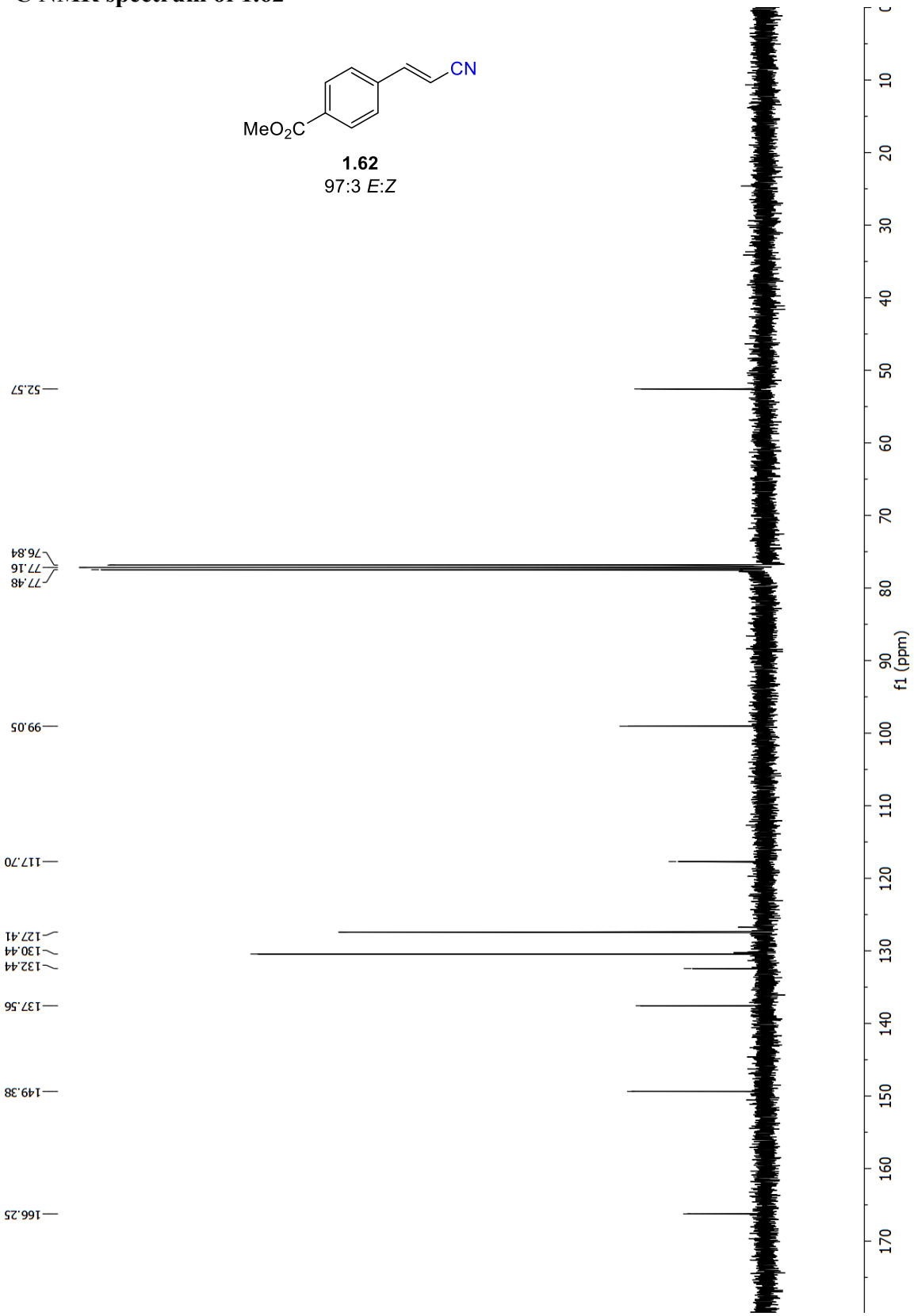
^{1}H NMR spectrum of 1.61



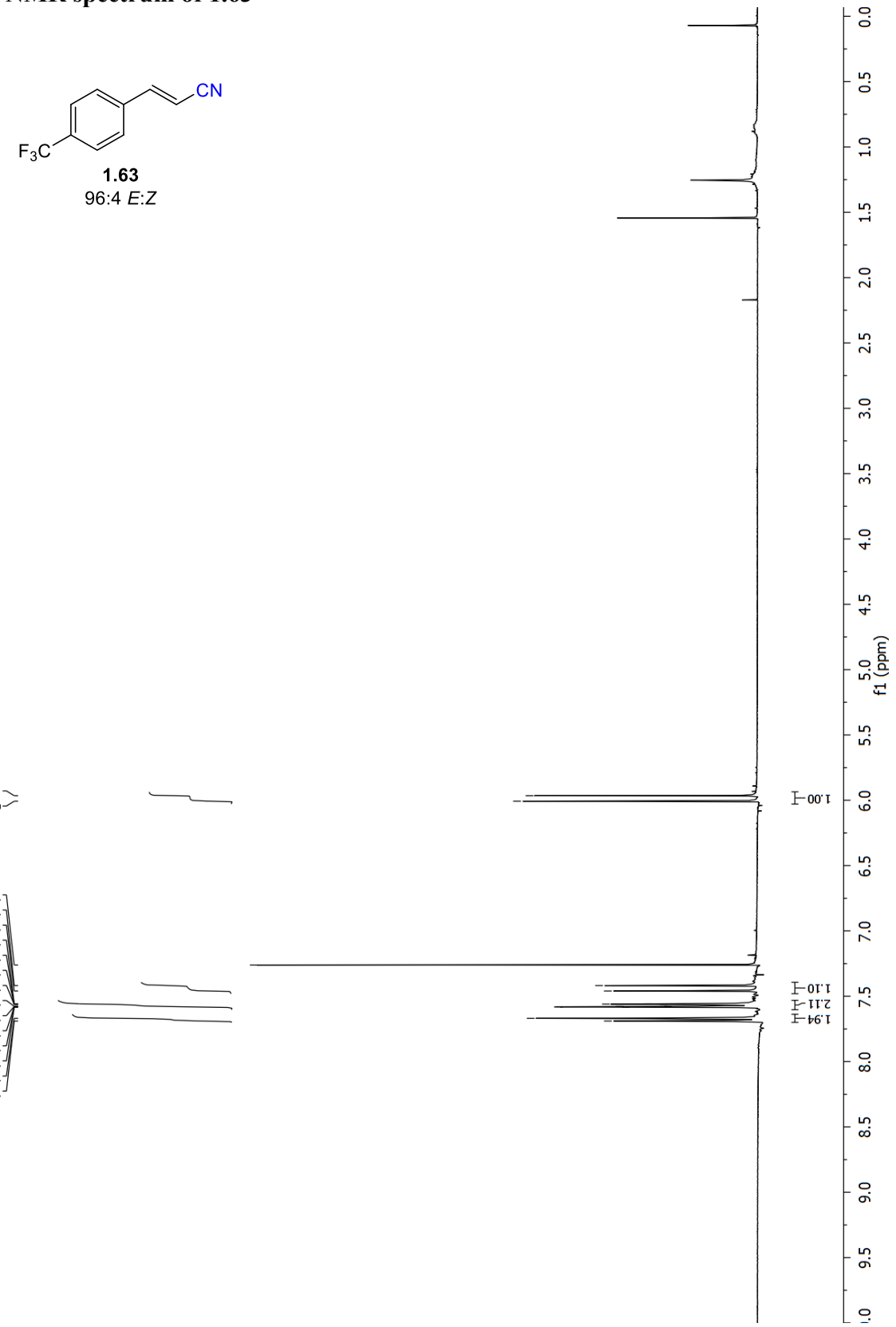
^{1}H NMR spectrum of 1.62



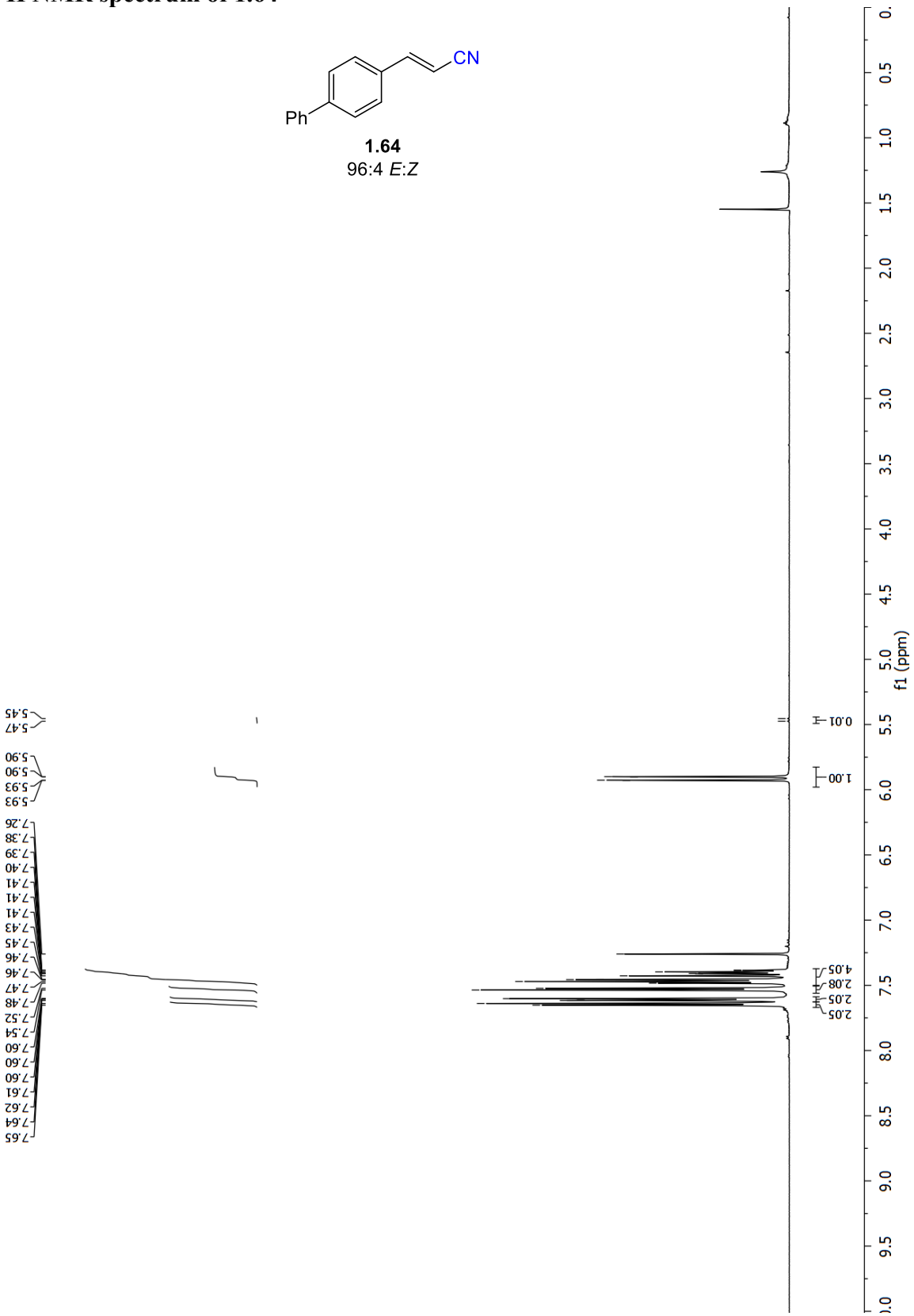
^{13}C NMR spectrum of 1.62



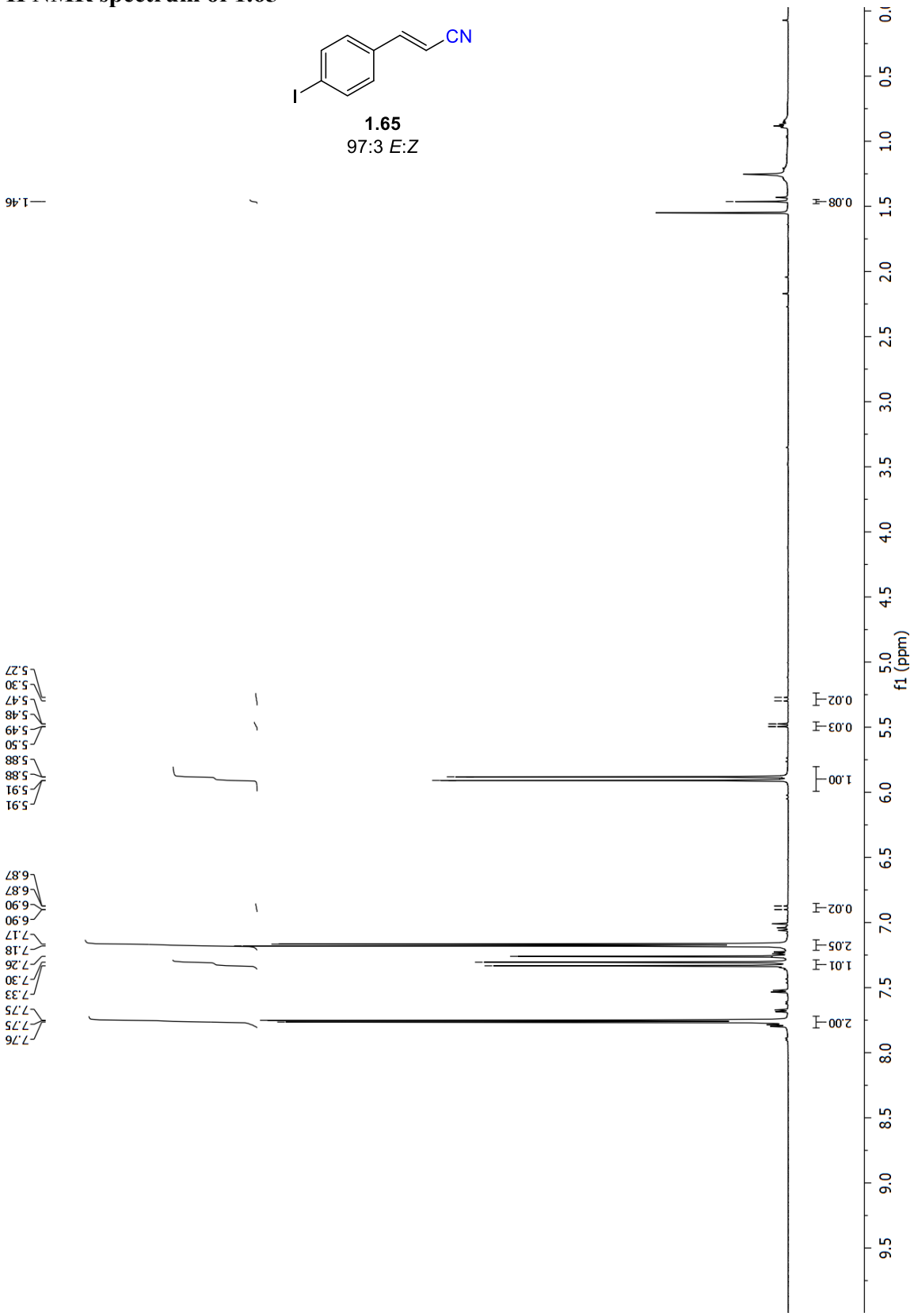
^{1}H NMR spectrum of 1.63



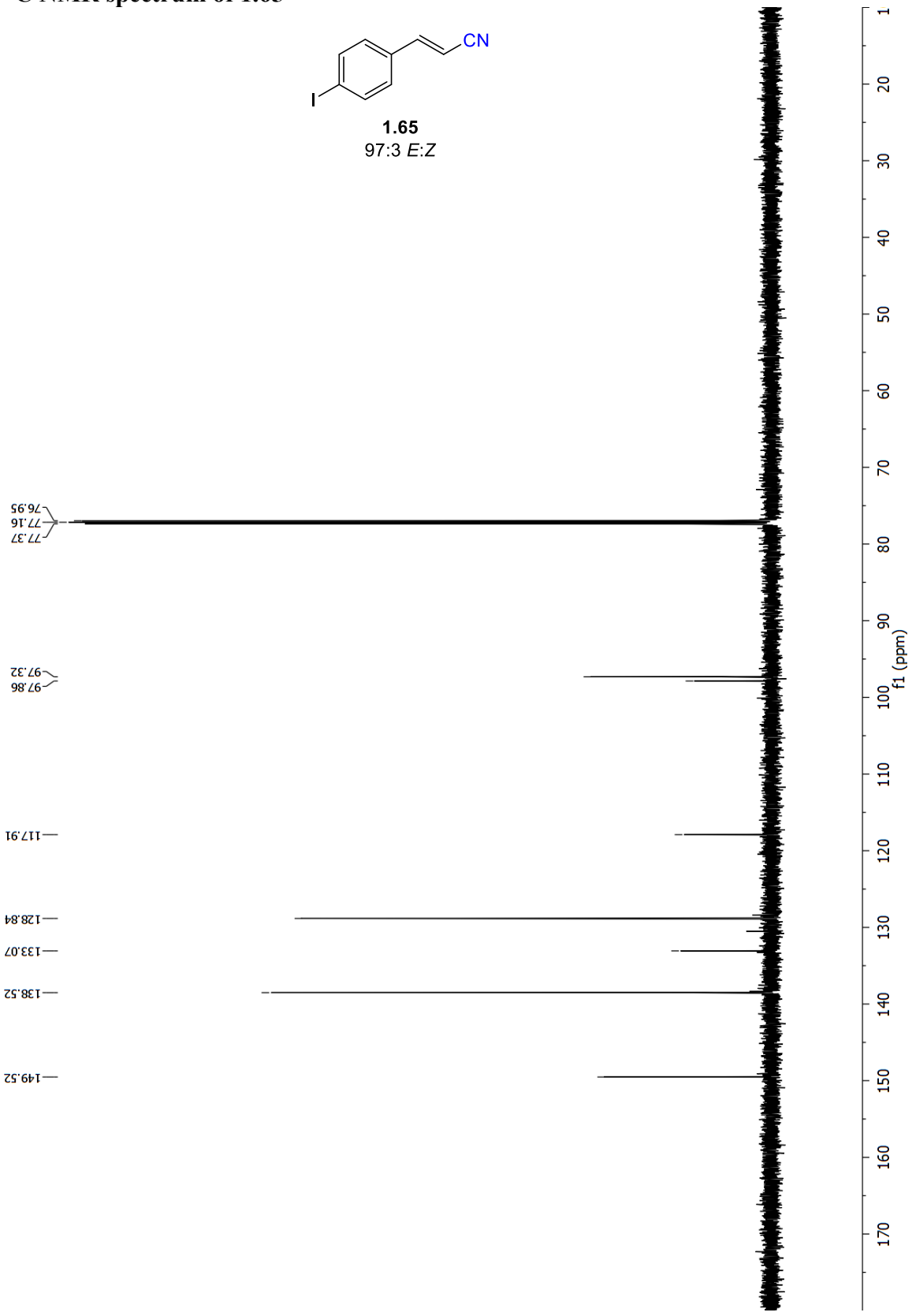
^{1}H NMR spectrum of 1.64



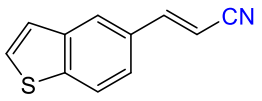
^{1}H NMR spectrum of 1.65



^{13}C NMR spectrum of 1.65

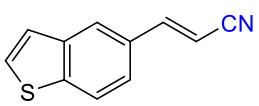


^{1}H NMR spectrum of 1.66



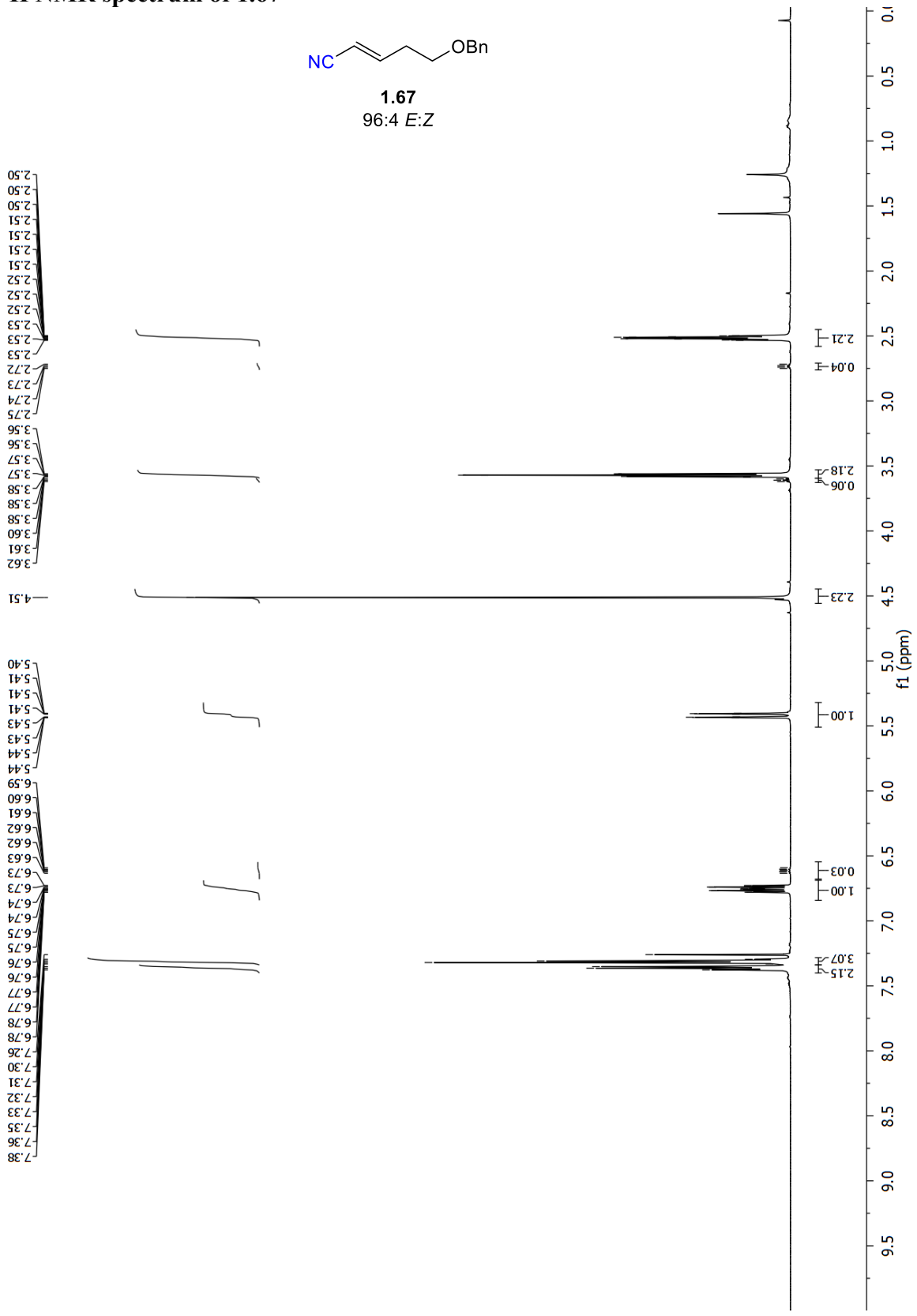
1.66
96:4 *E*:*Z*

^{13}C NMR spectrum of 1.66

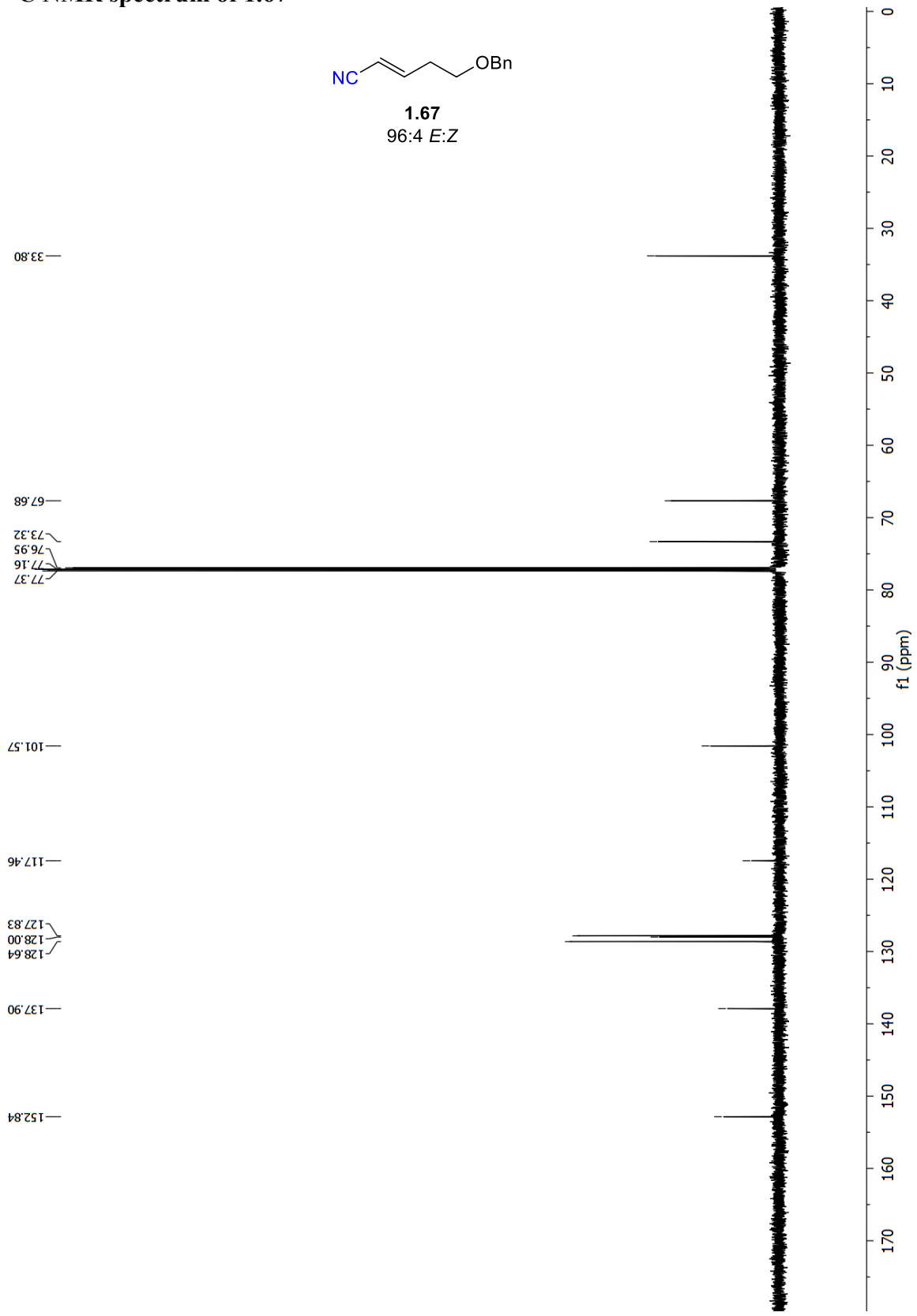


1.66
96:4 *E*:*Z*

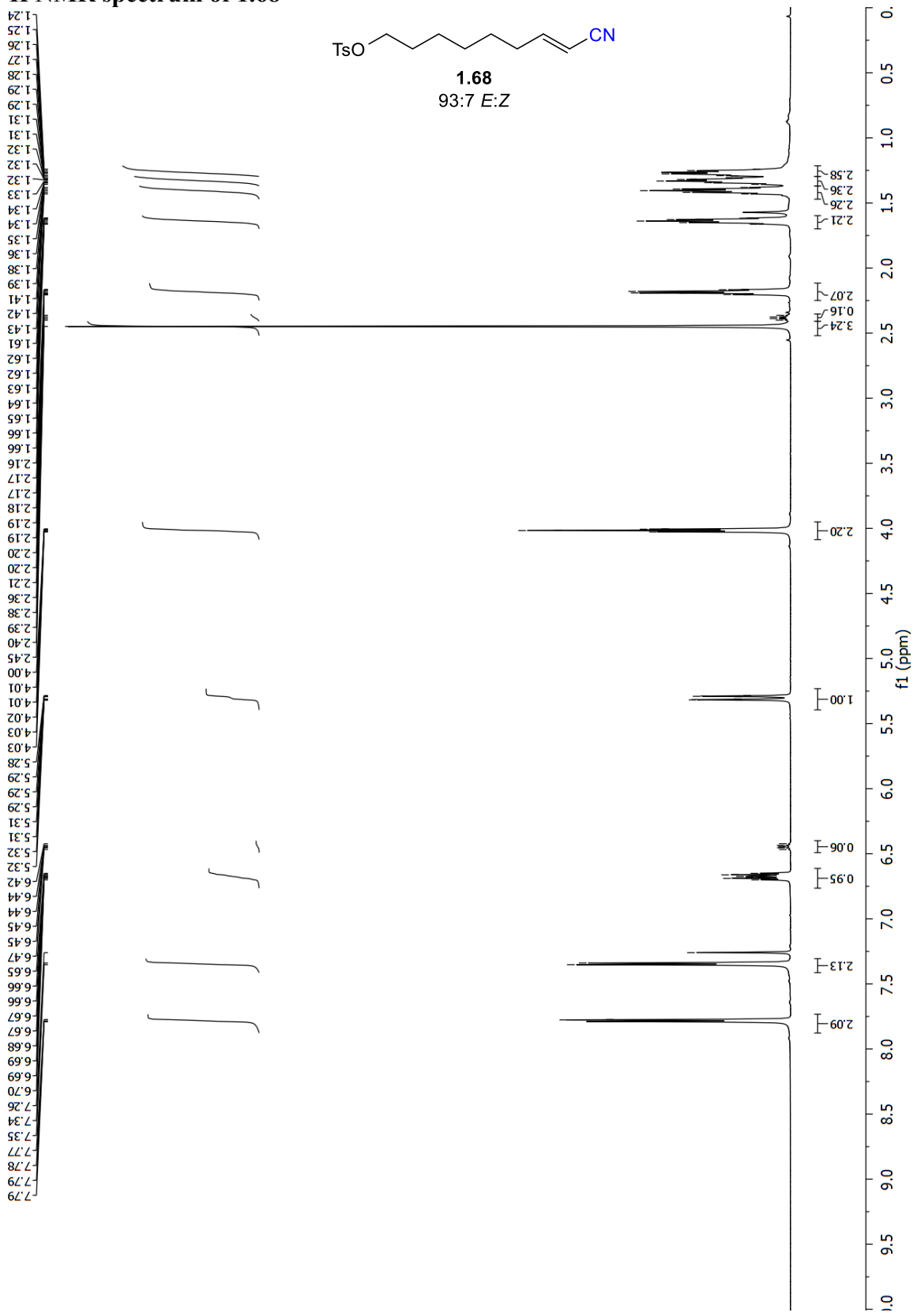
^{1}H NMR spectrum of 1.67



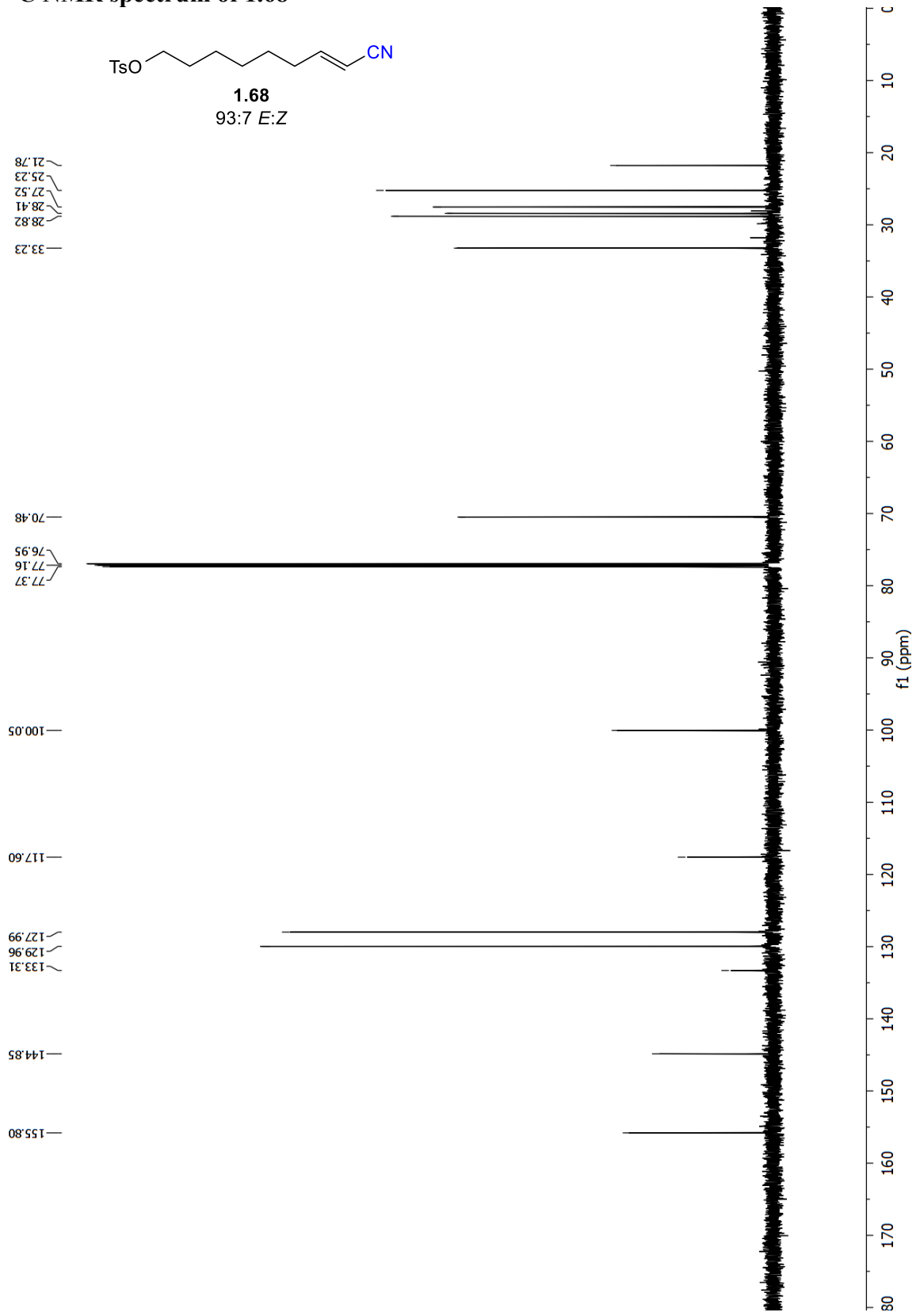
^{13}C NMR spectrum of 1.67



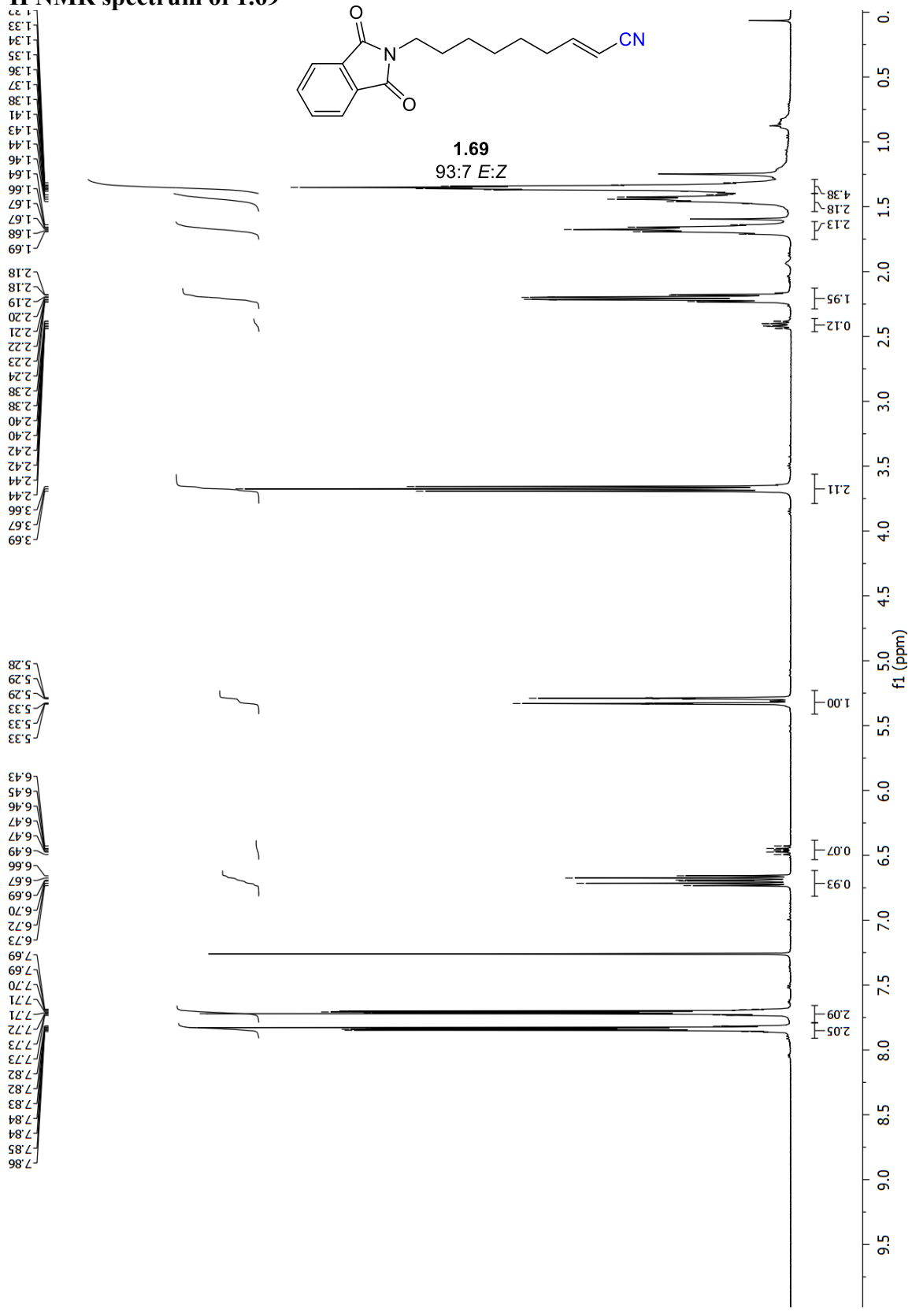
^{1}H NMR spectrum of 1.68



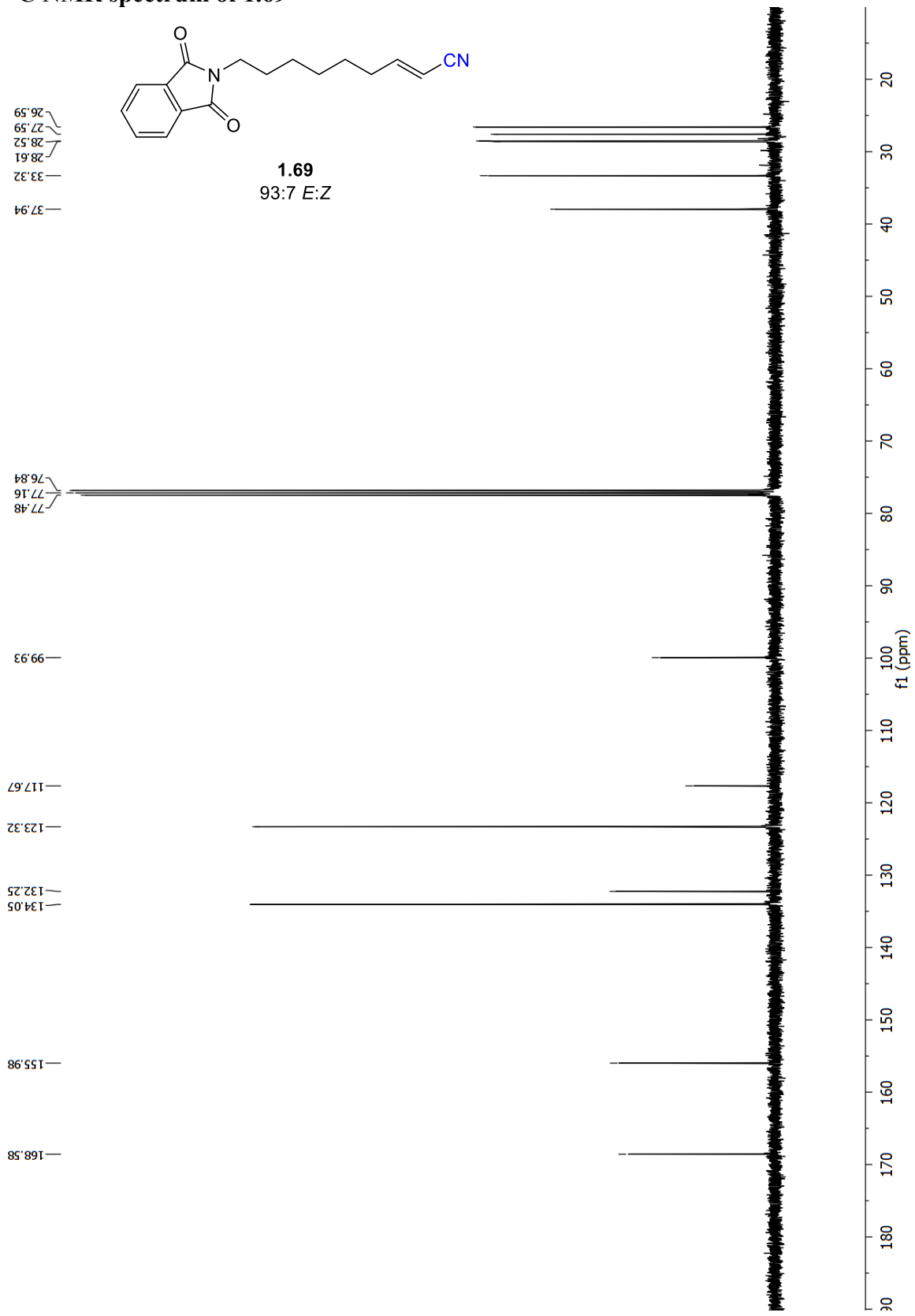
^{13}C NMR spectrum of 1.68



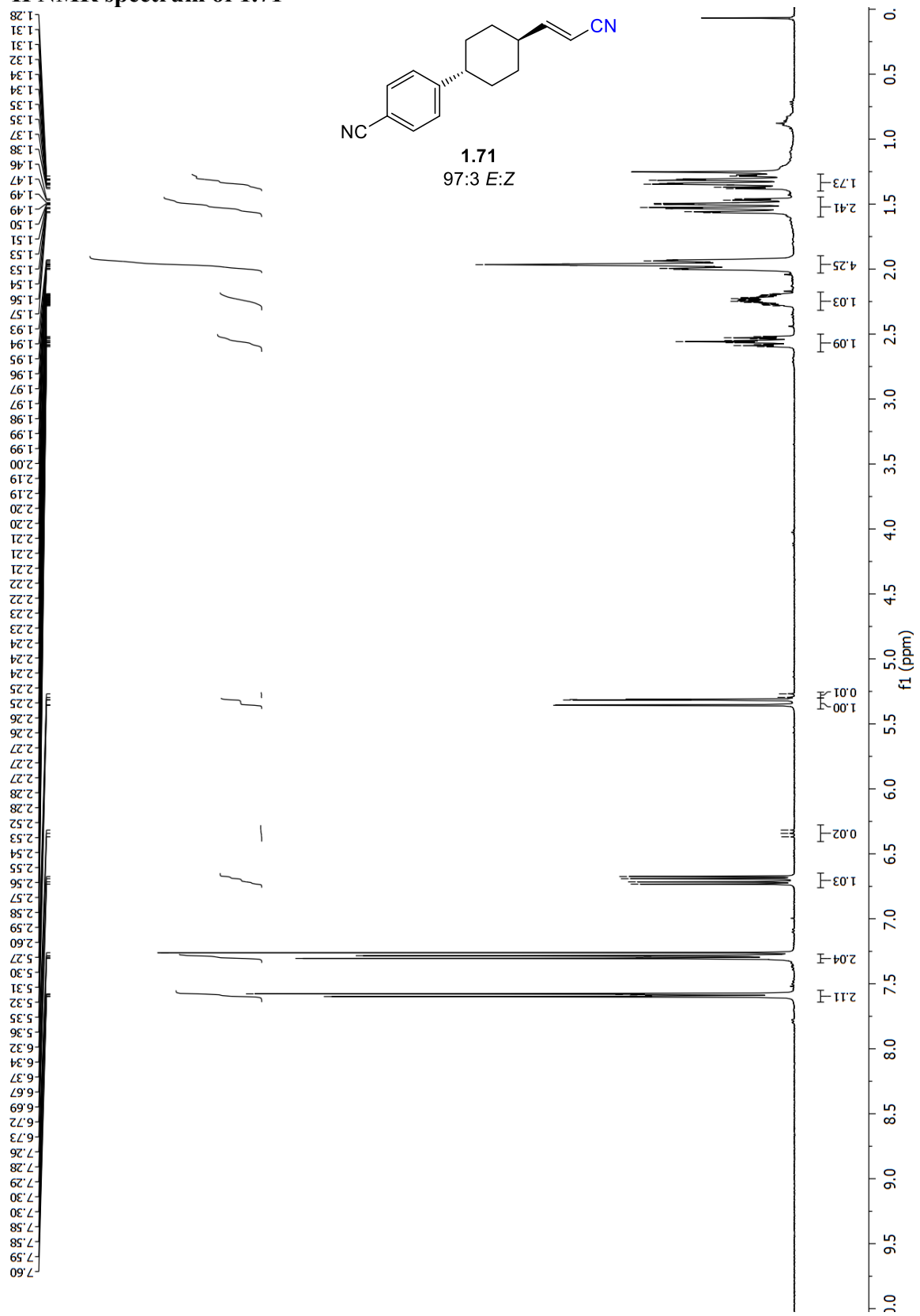
^{1}H NMR spectrum of 1.69



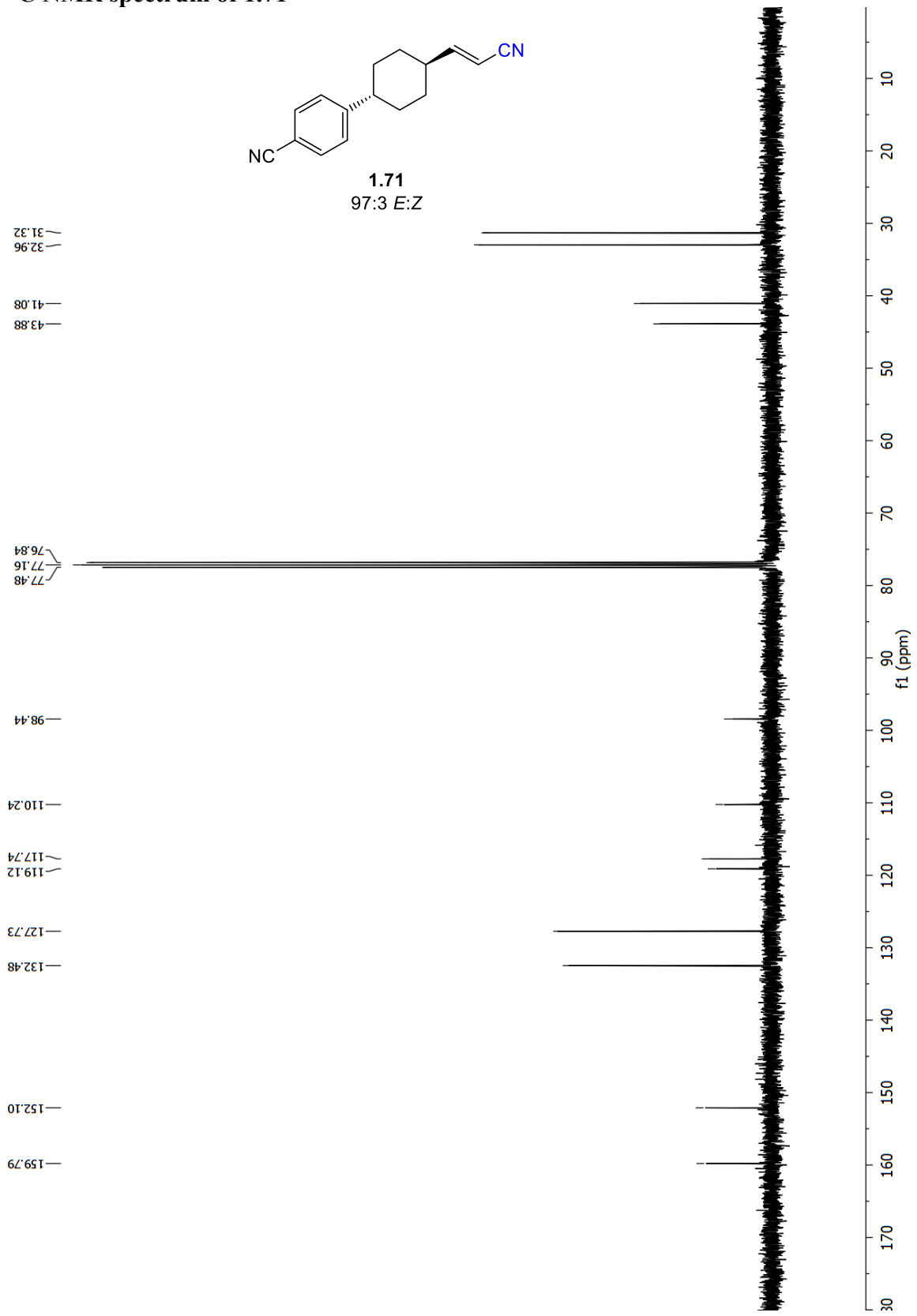
^{13}C NMR spectrum of 1.69



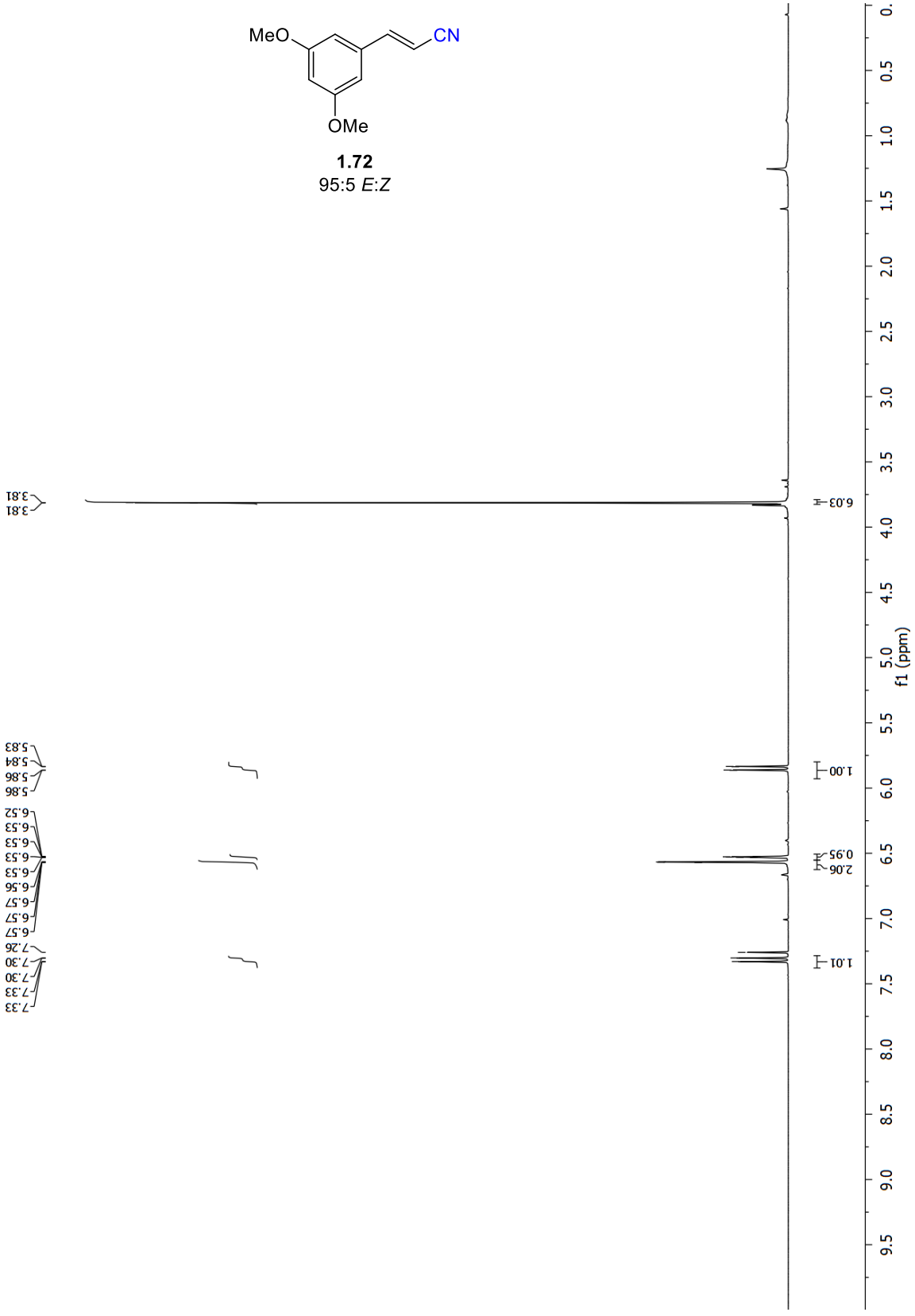
^{1}H NMR spectrum of 1.71



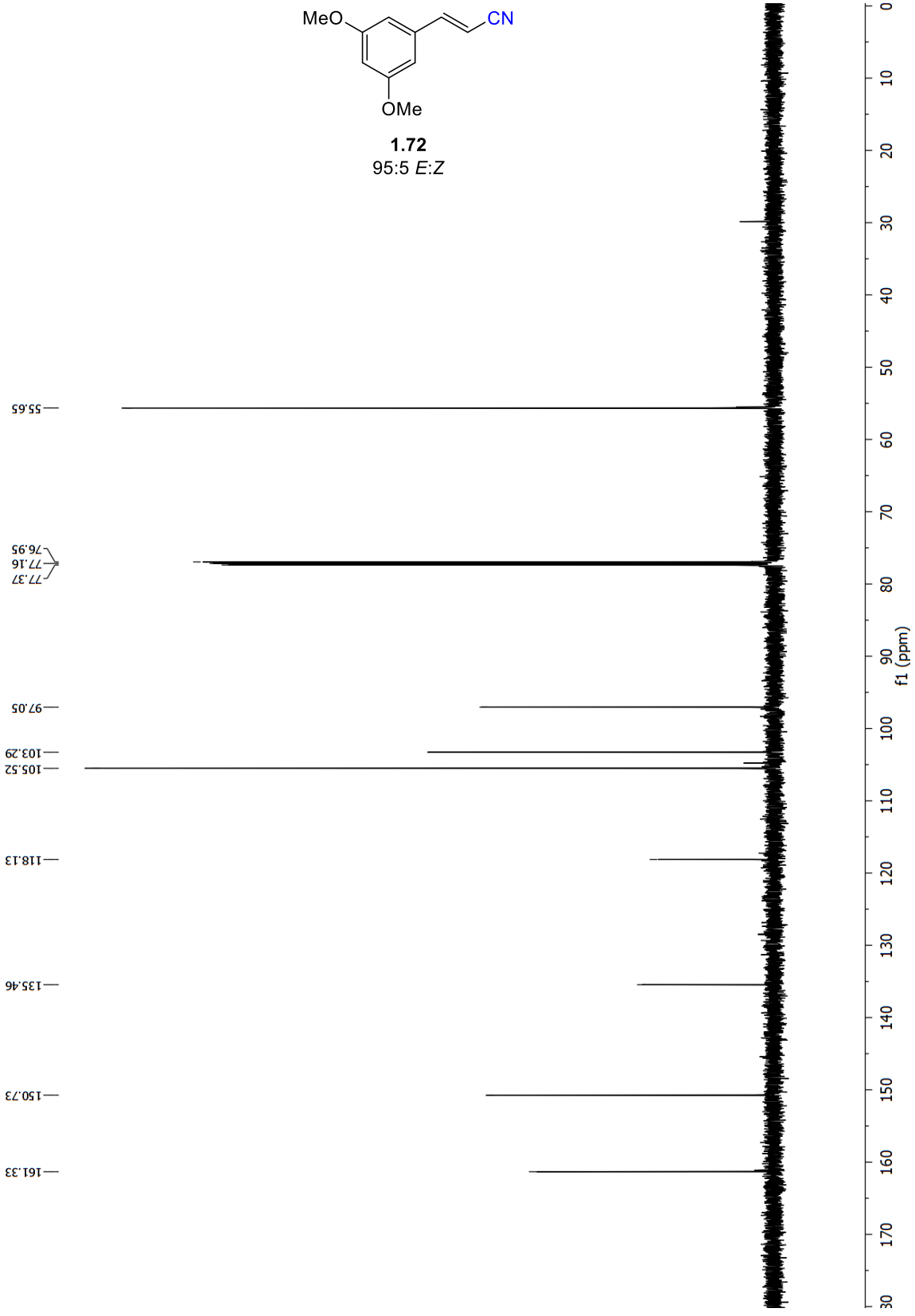
^{13}C NMR spectrum of 1.71



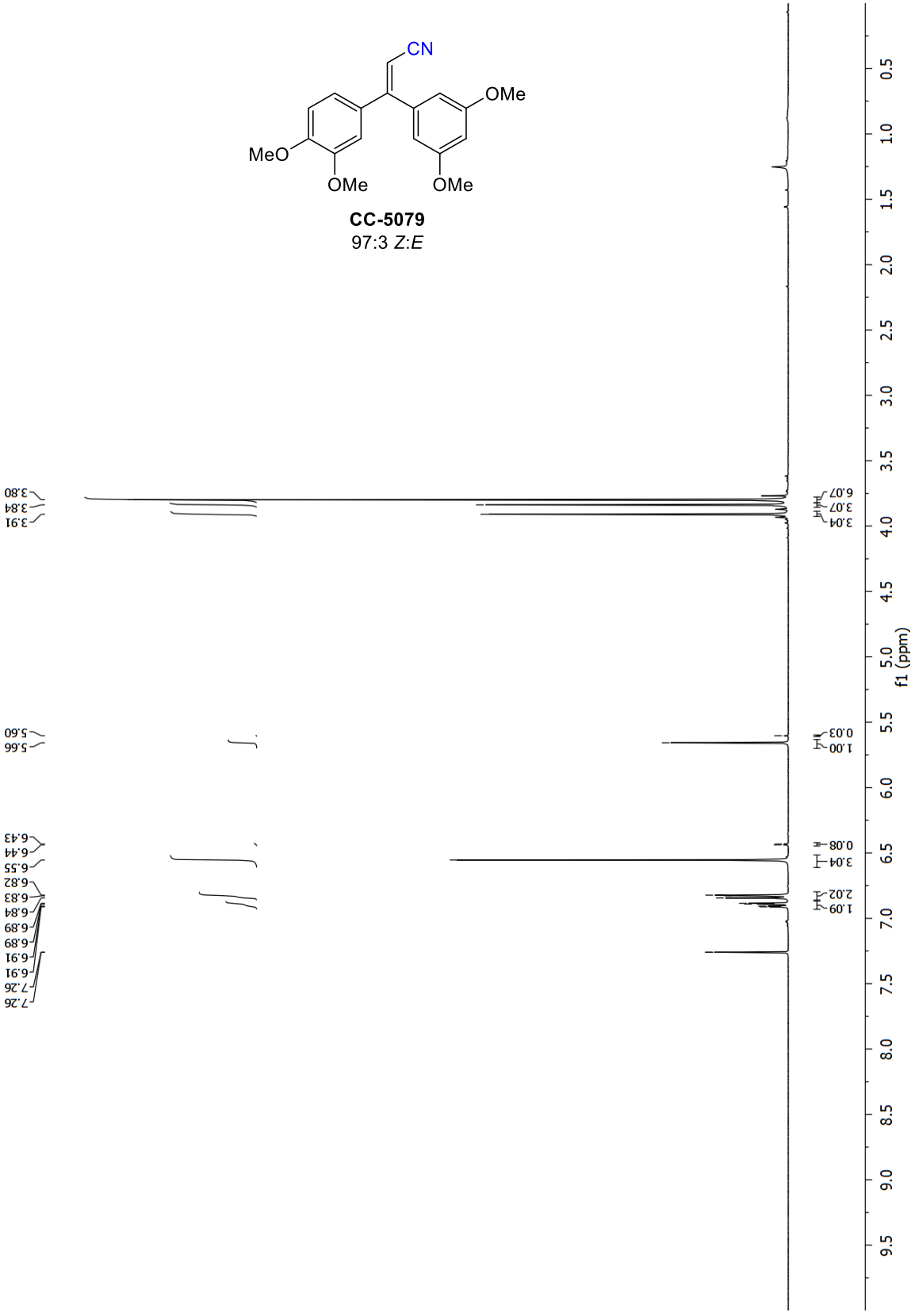
^{1}H NMR spectrum of 1.72



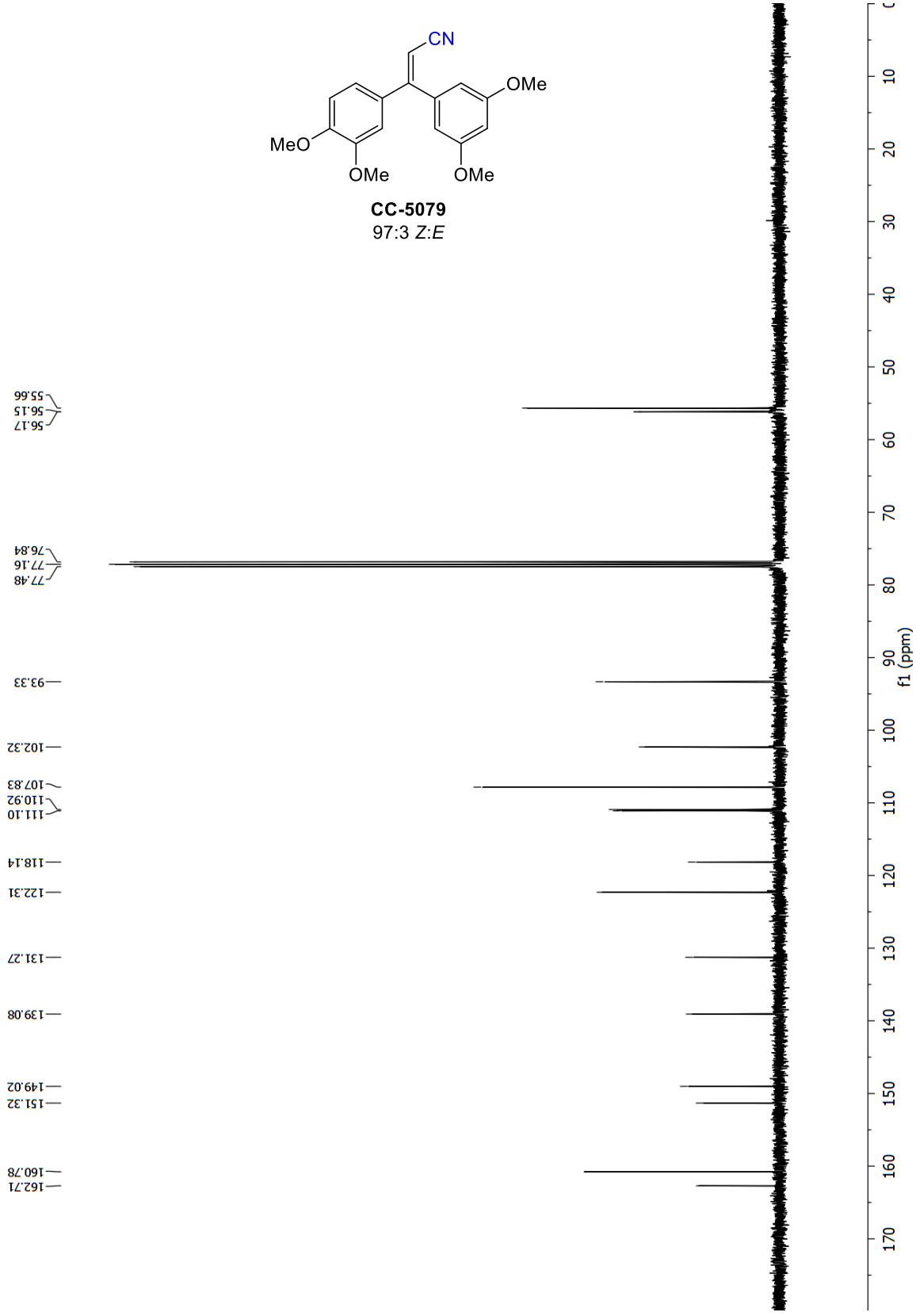
^{13}C NMR spectrum of 1.72



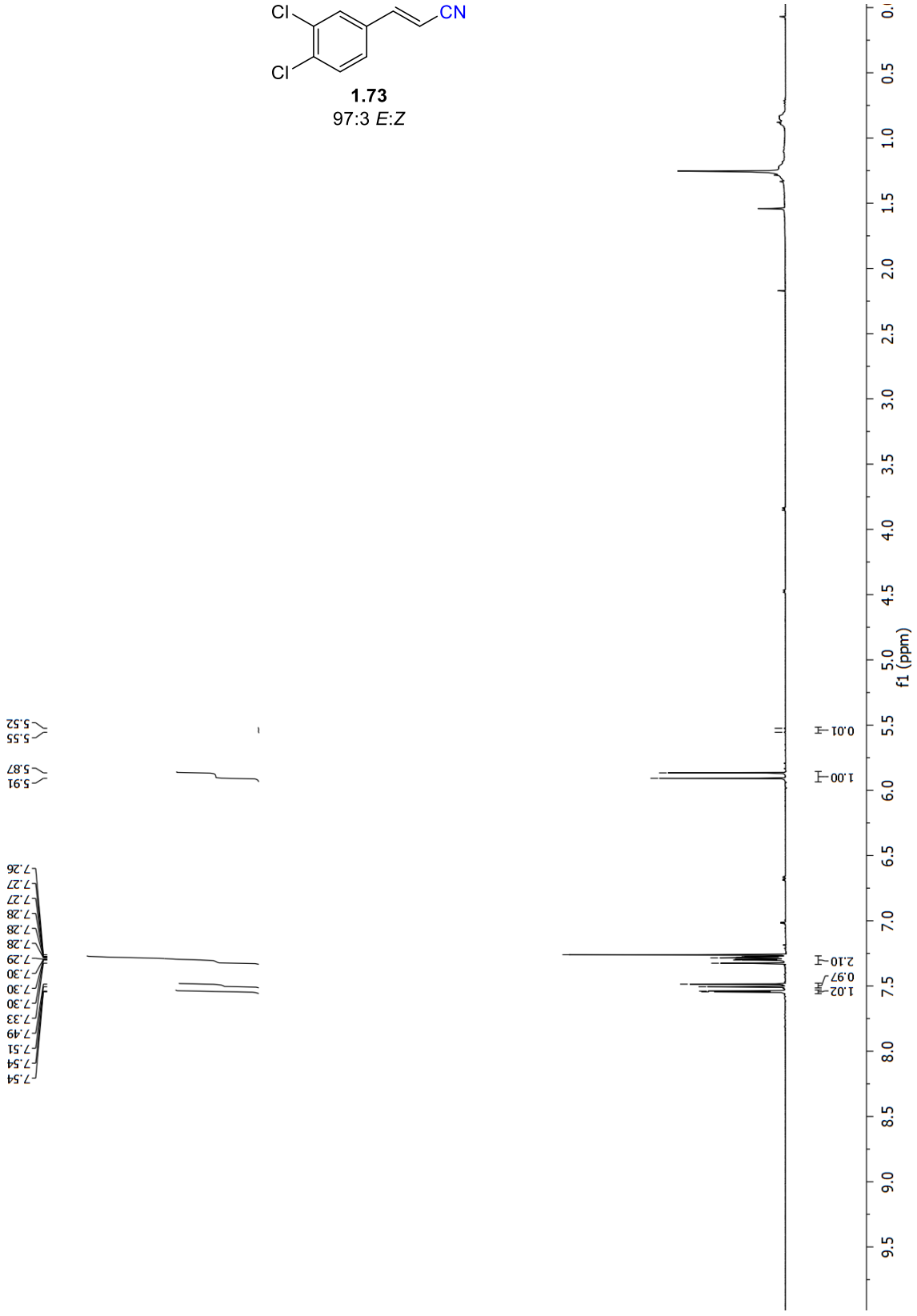
^{1}H NMR spectrum of CC-5079



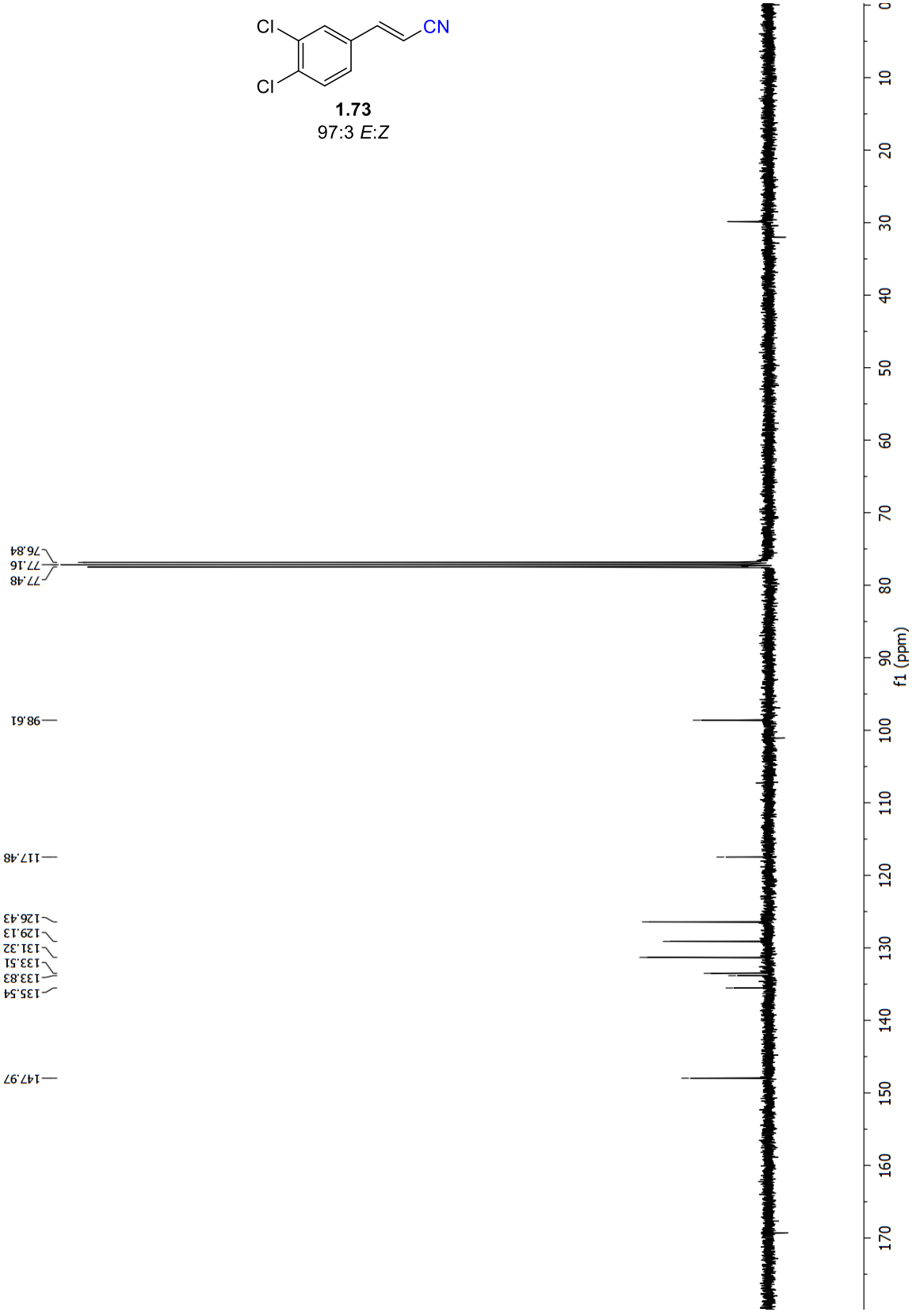
^{13}C NMR spectrum of CC-5079



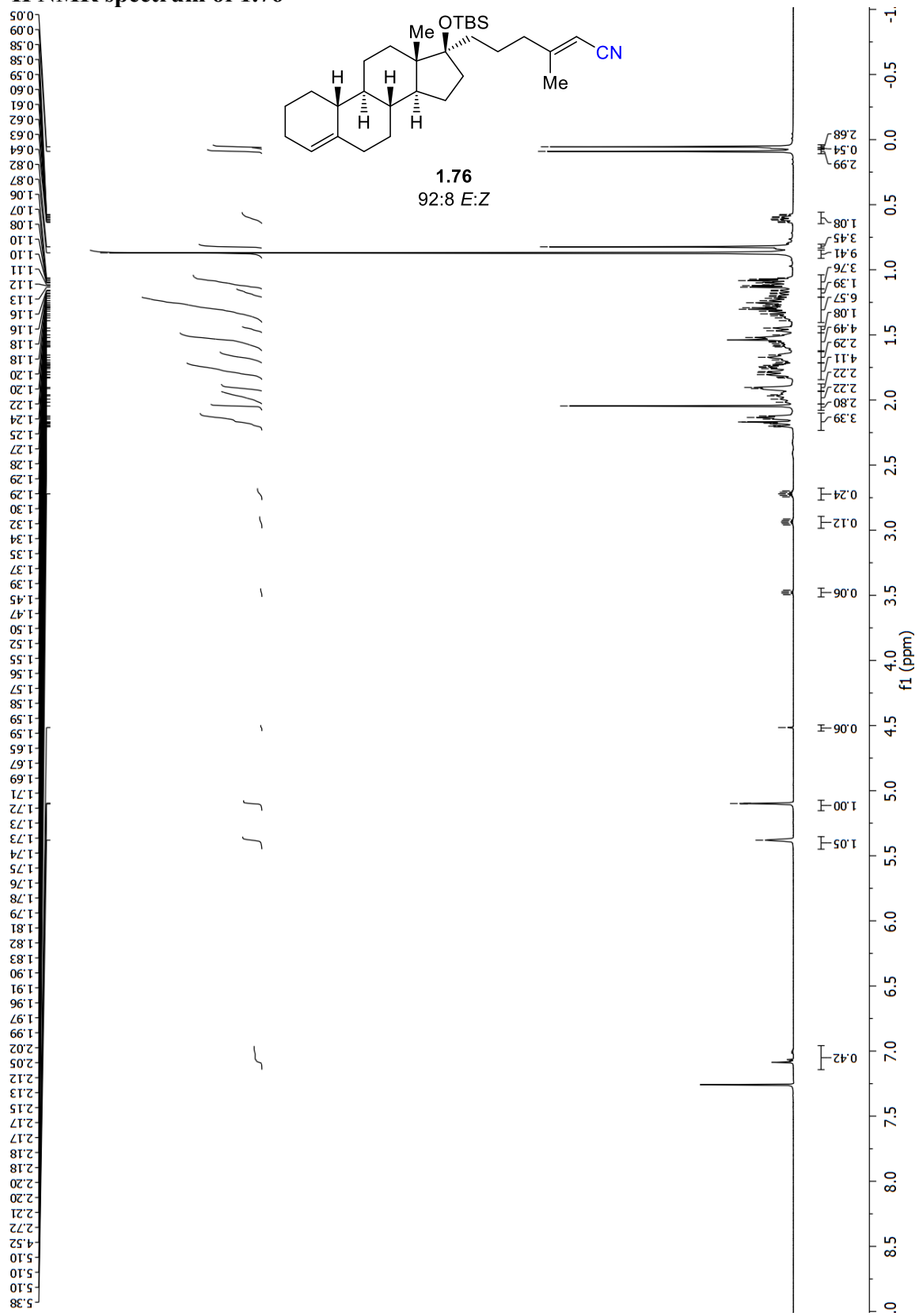
^{1}H NMR spectrum of 1.73



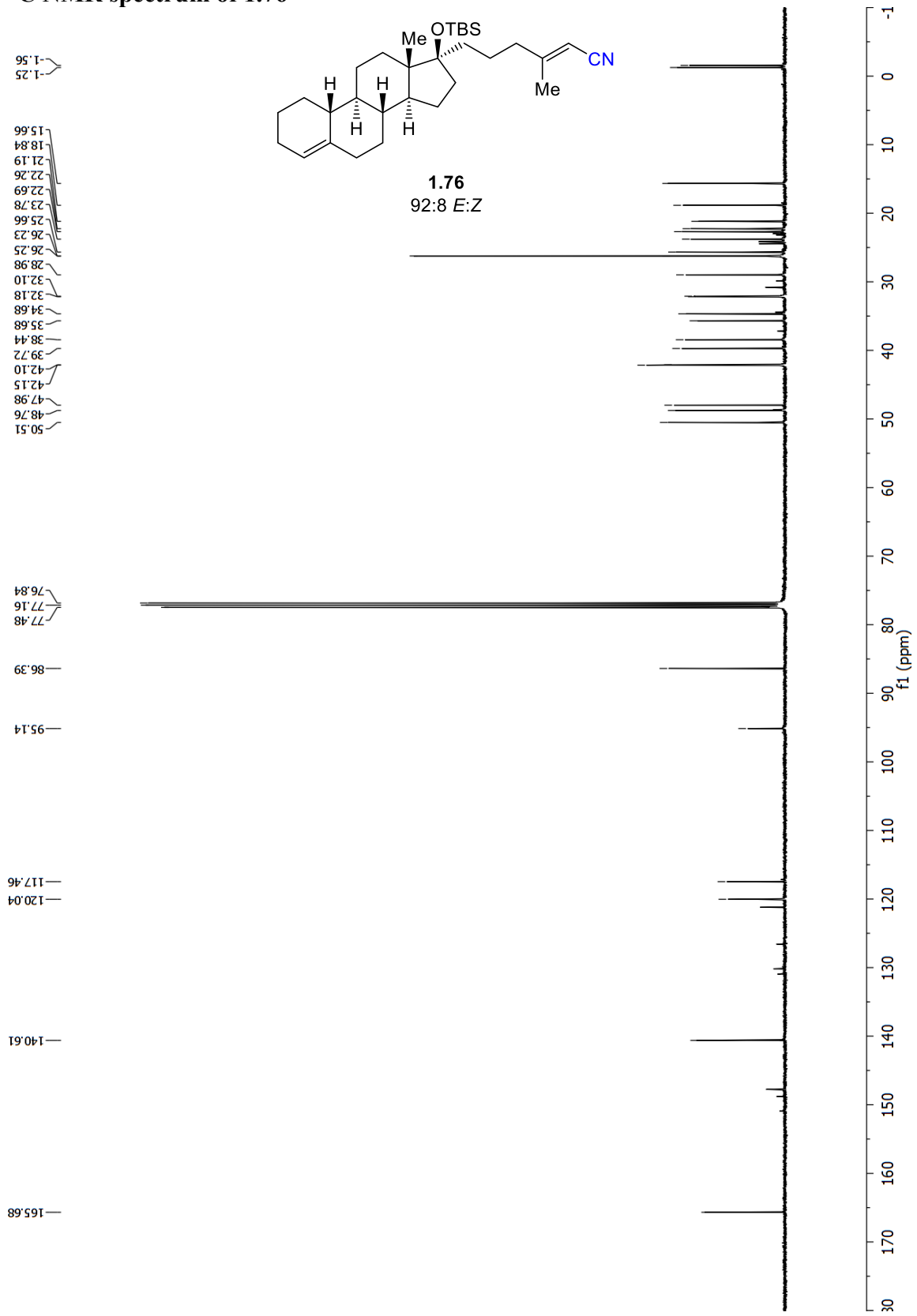
^{13}C NMR spectrum of 1.73



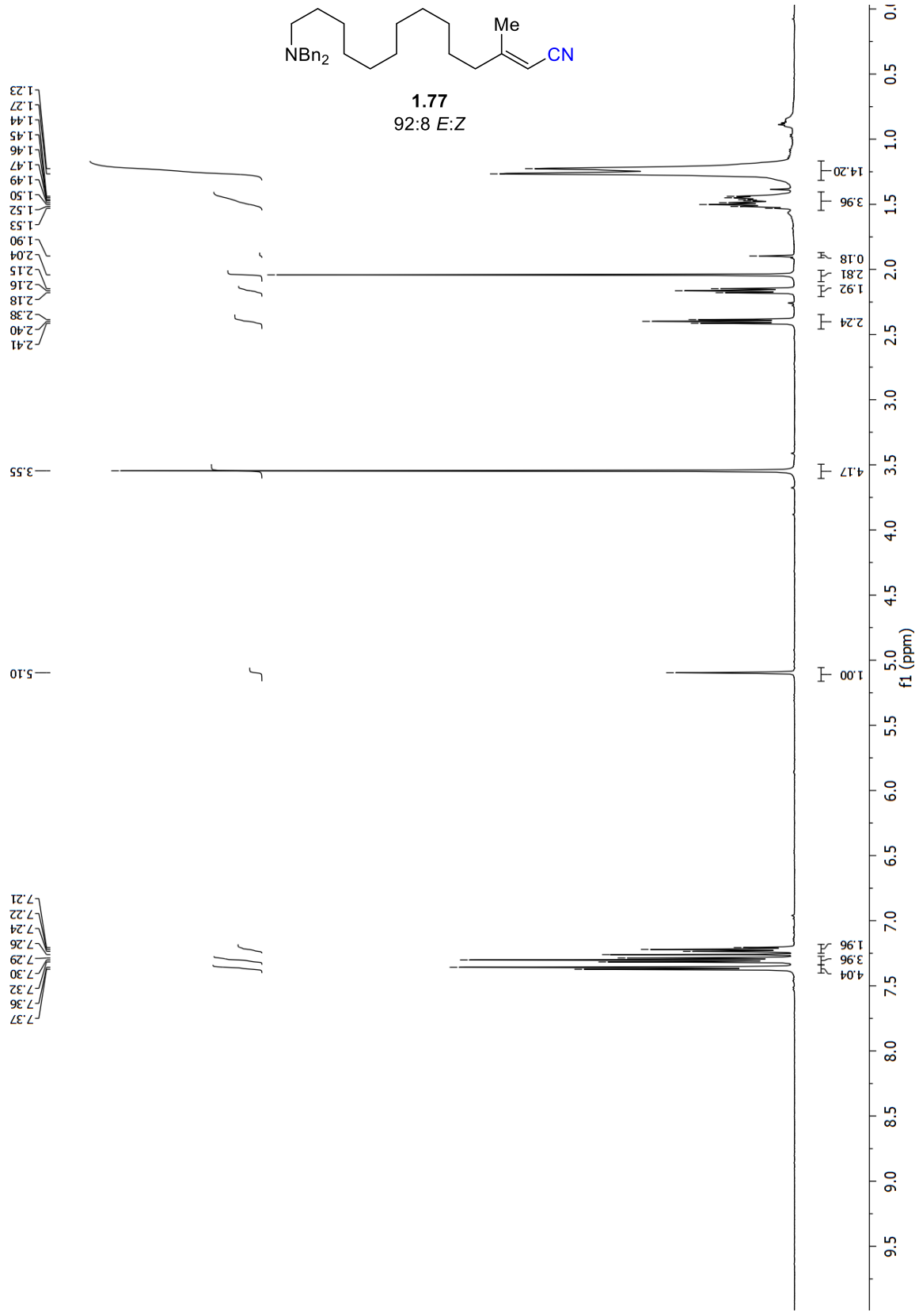
^{1}H NMR spectrum of 1.76



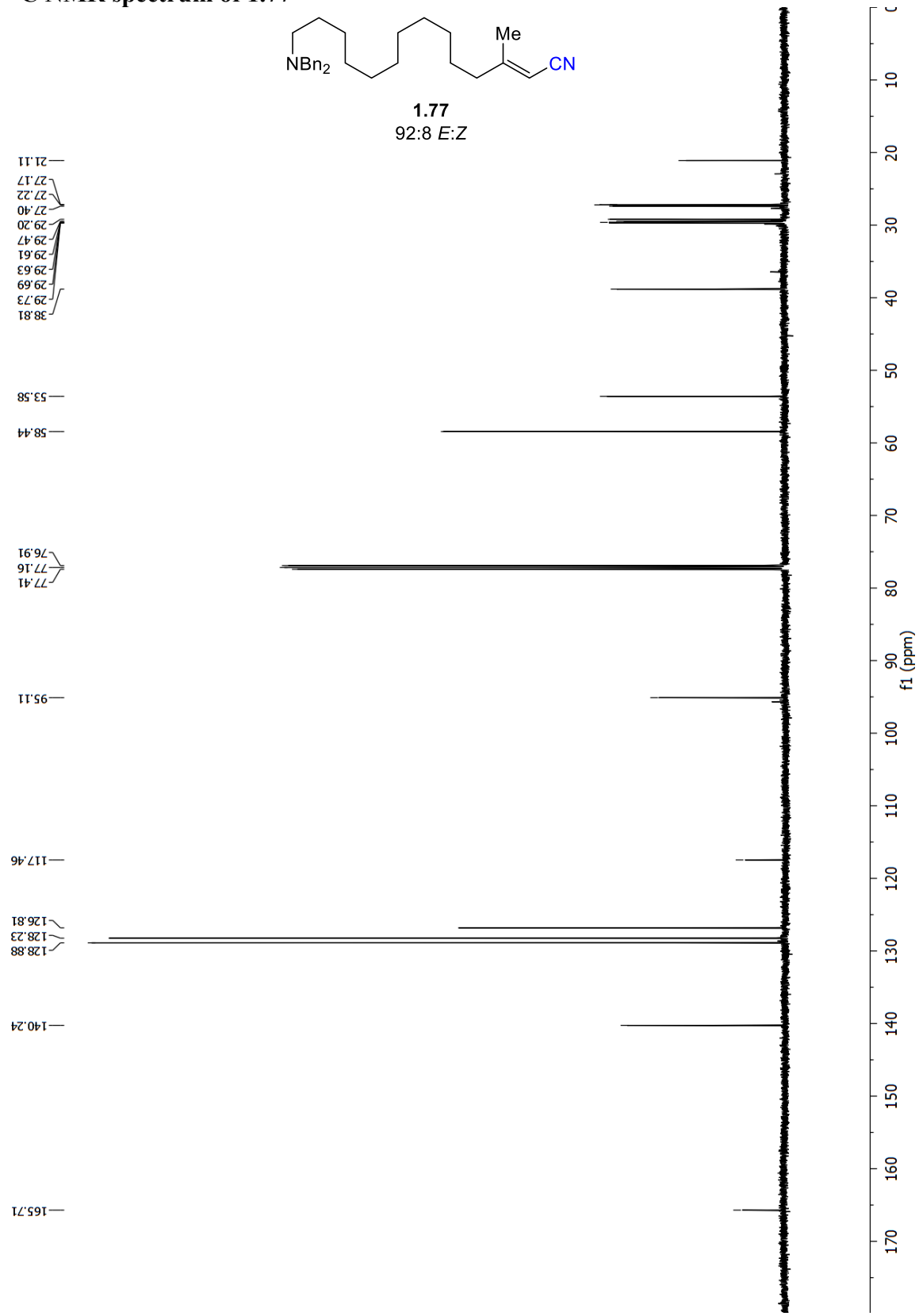
^{13}C NMR spectrum of 1.76



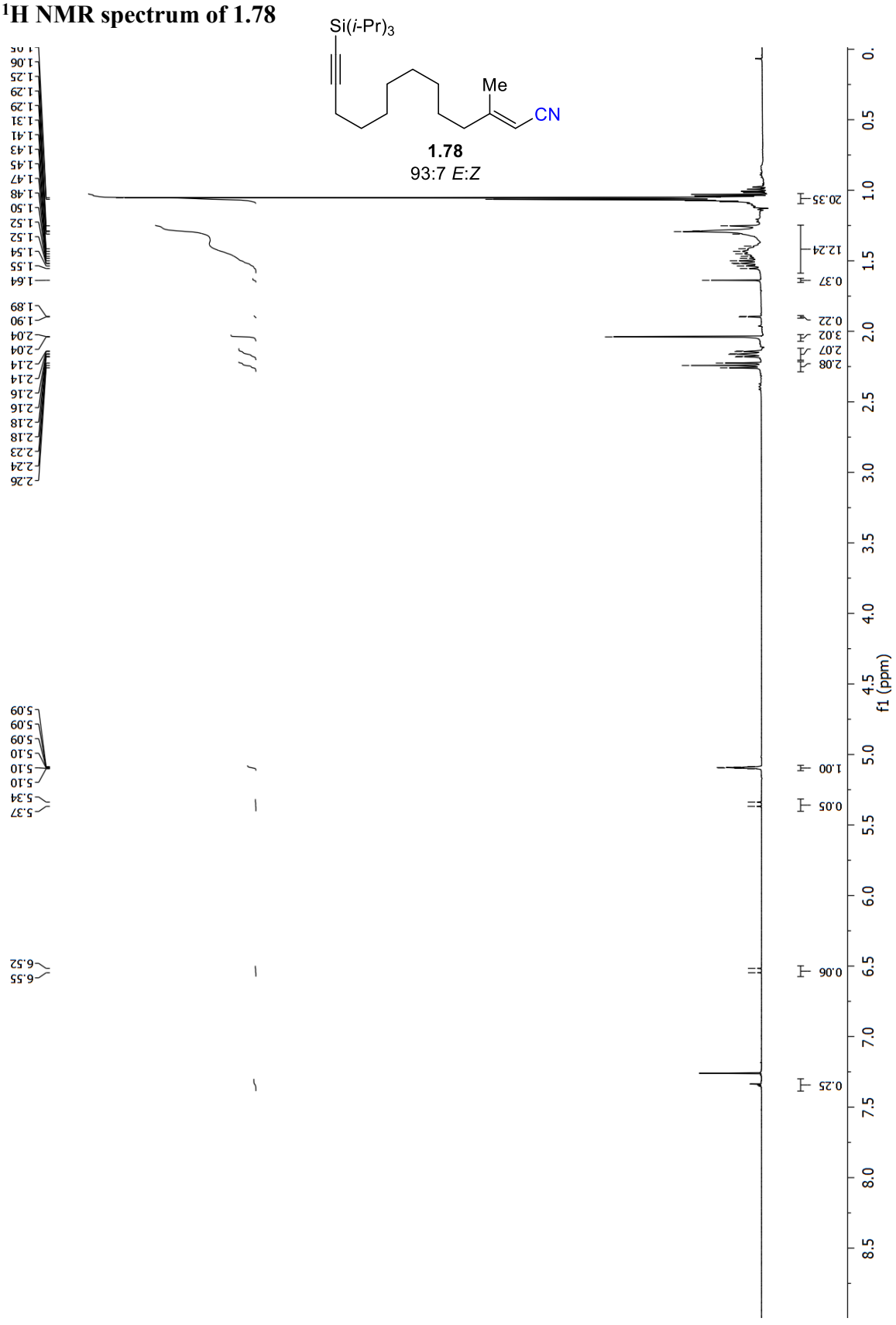
^{1}H NMR spectrum of 1.77



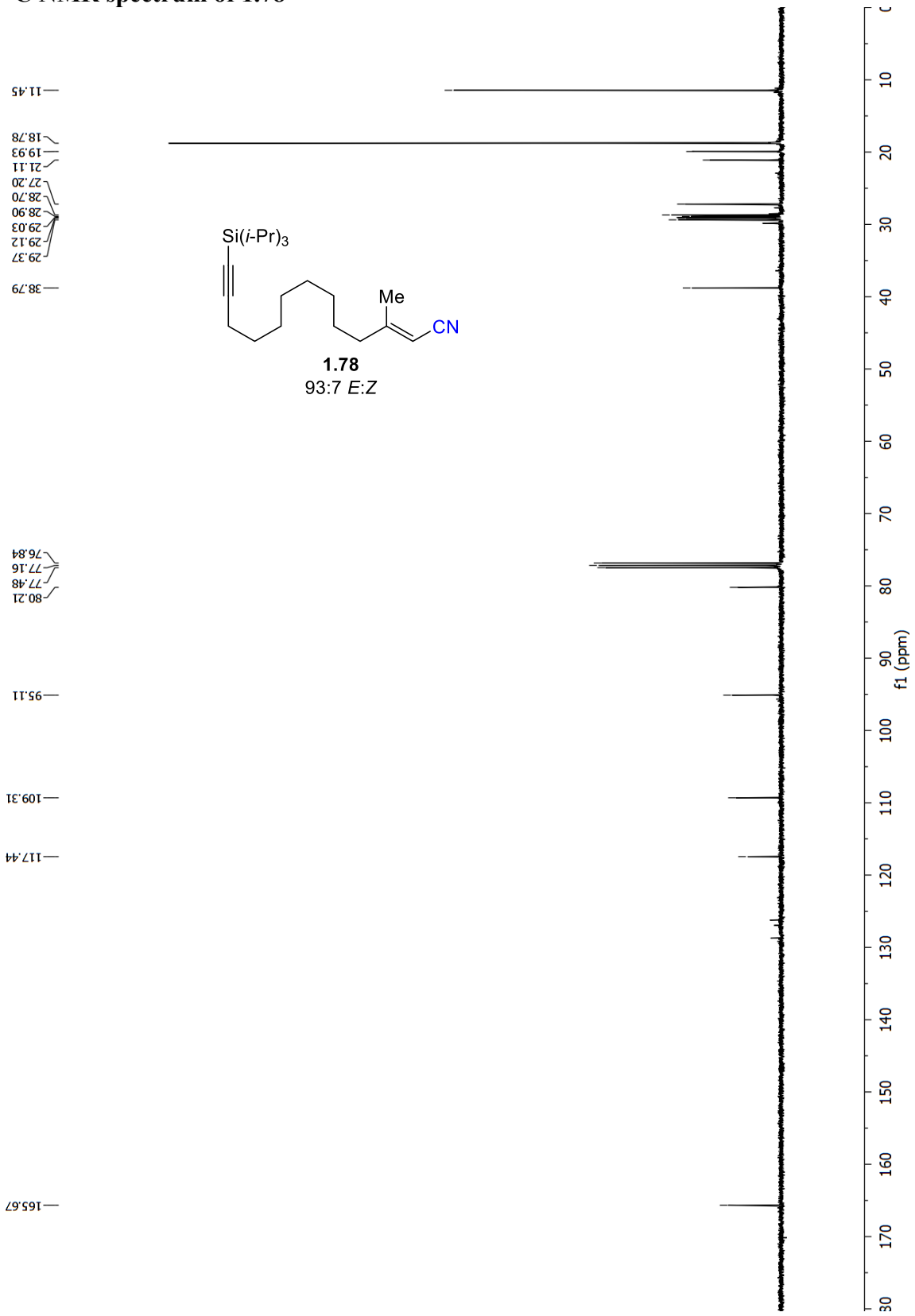
^{13}C NMR spectrum of 1.77



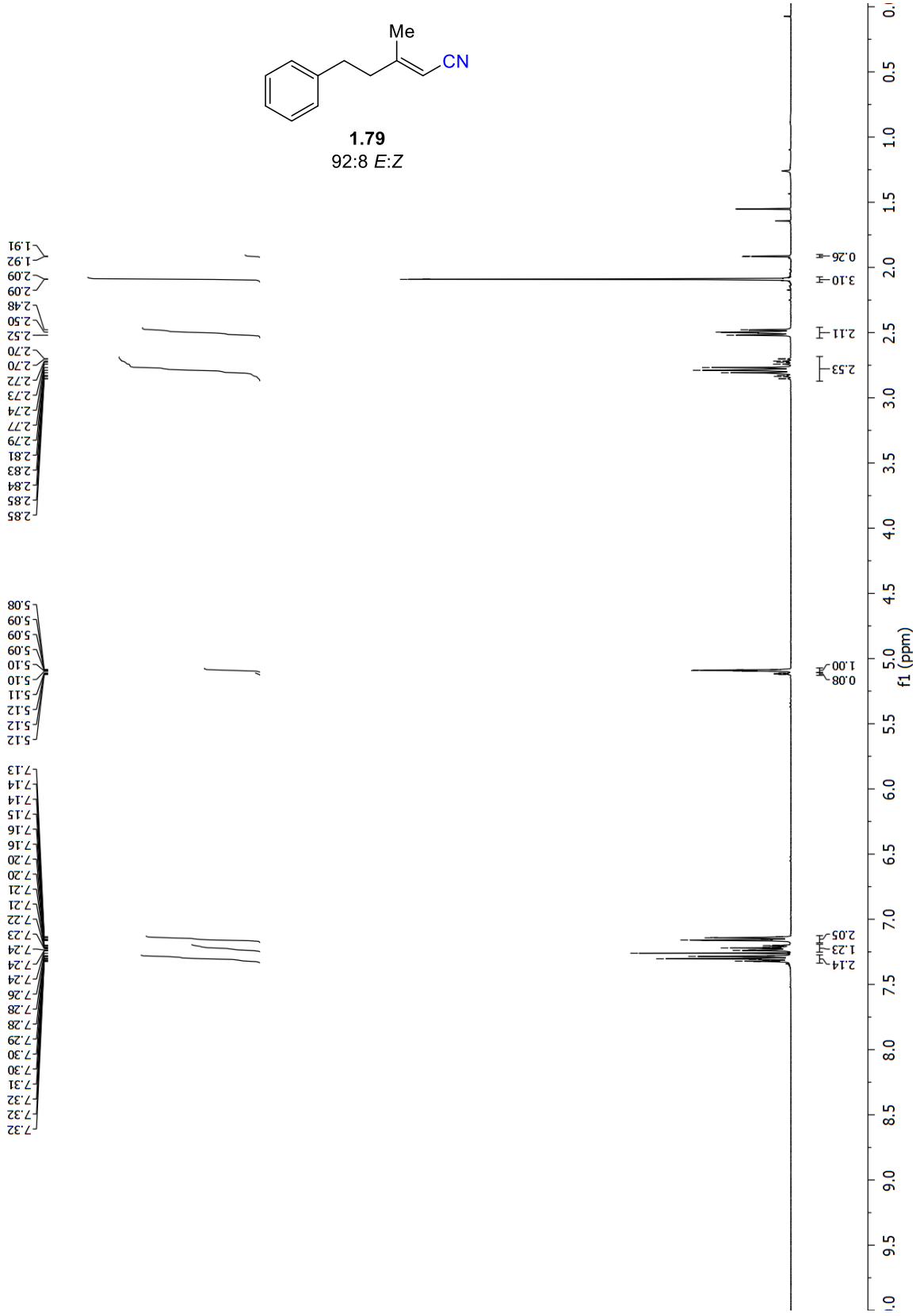
^{1}H NMR spectrum of 1.78



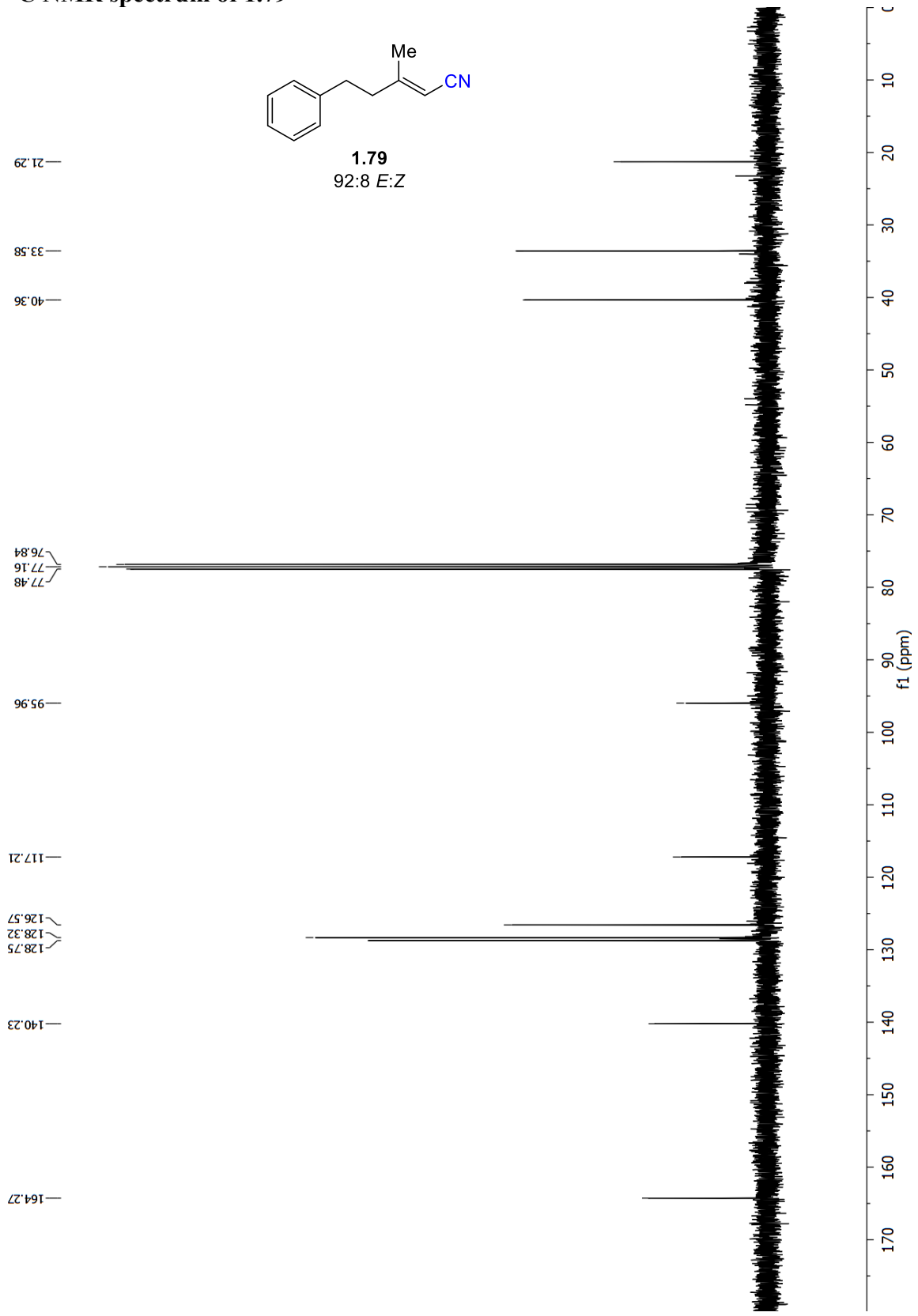
^{13}C NMR spectrum of 1.78



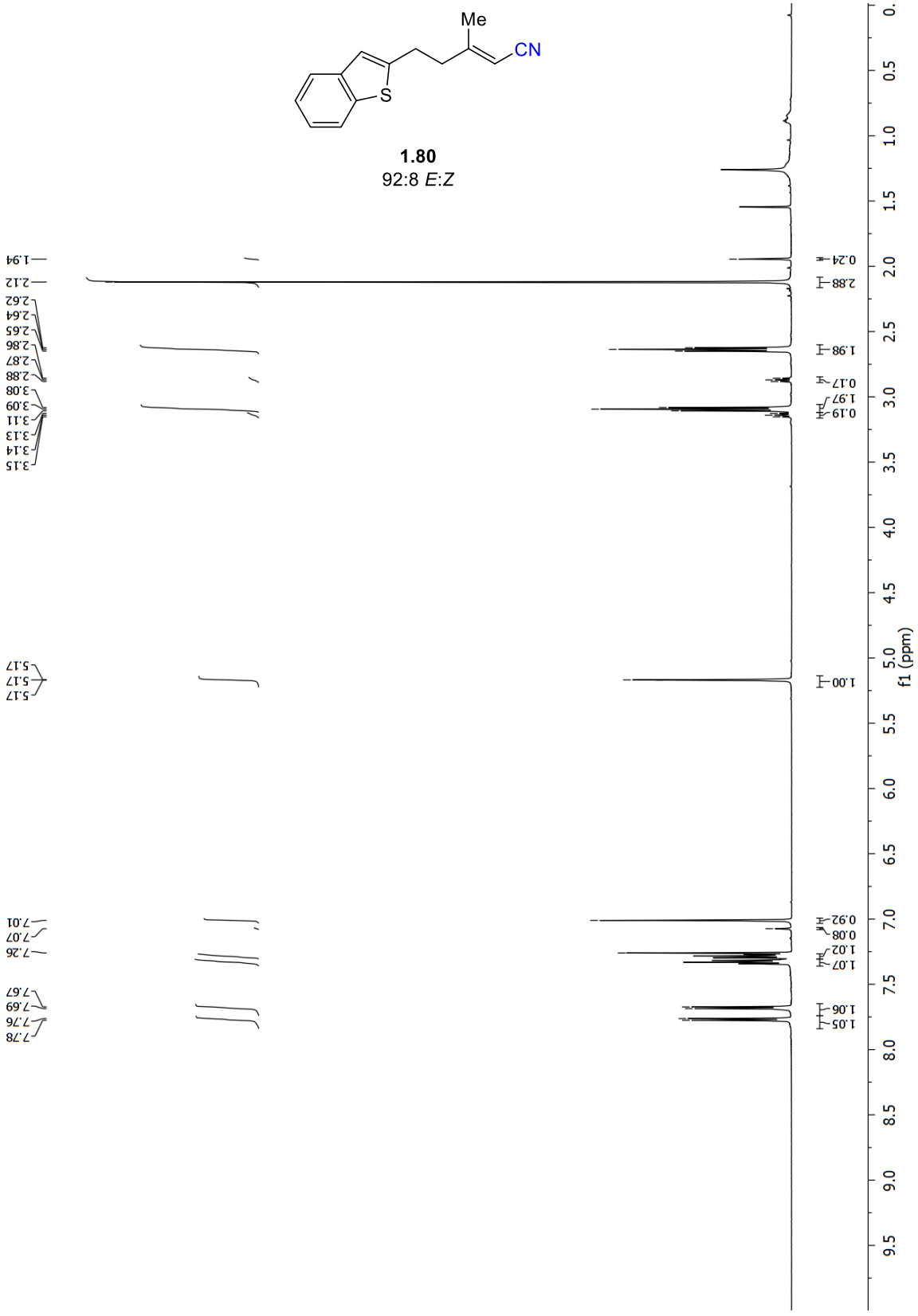
^{1}H NMR spectrum of 1.79



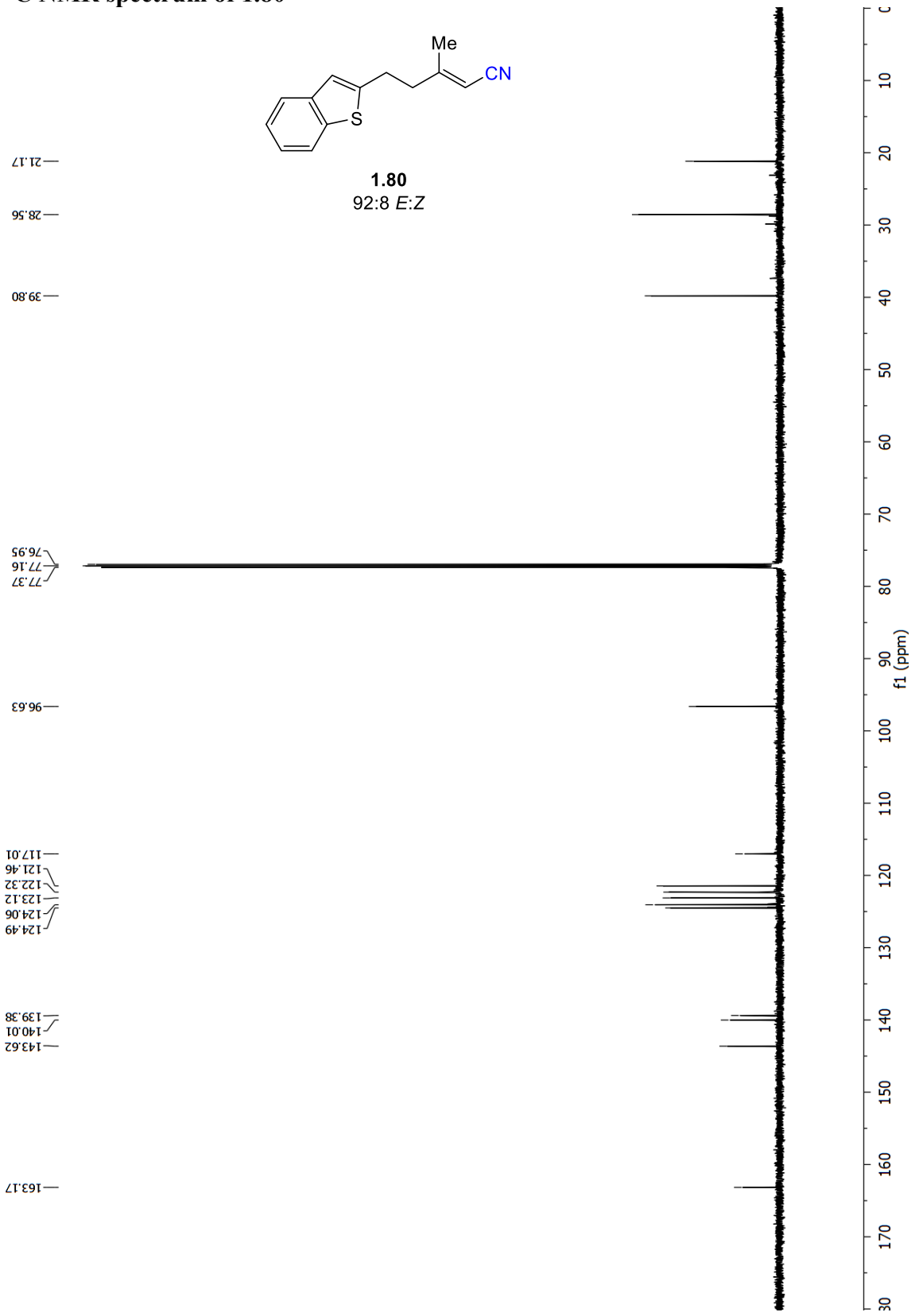
^{13}C NMR spectrum of 1.79



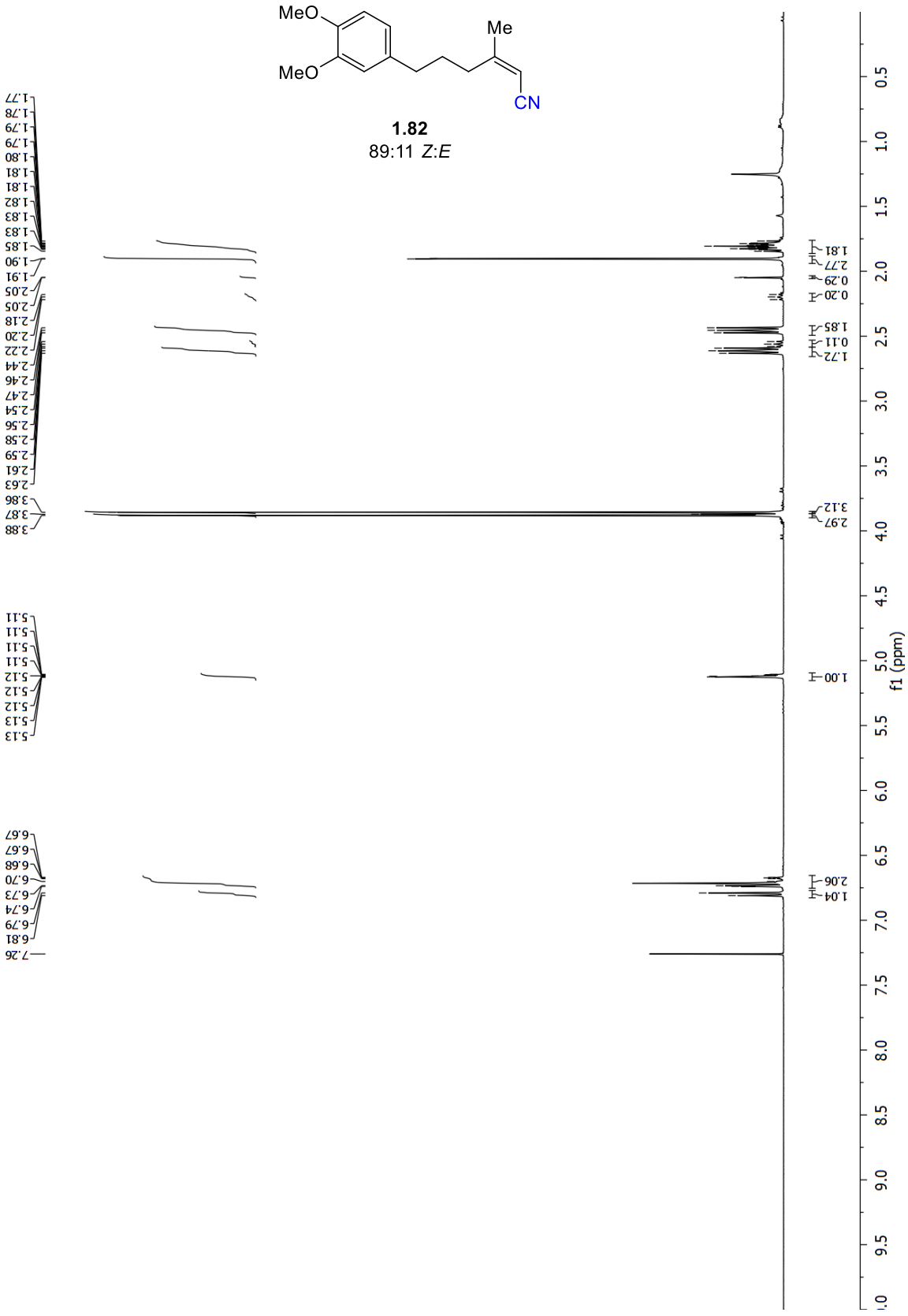
^{1}H NMR spectrum of 1.80



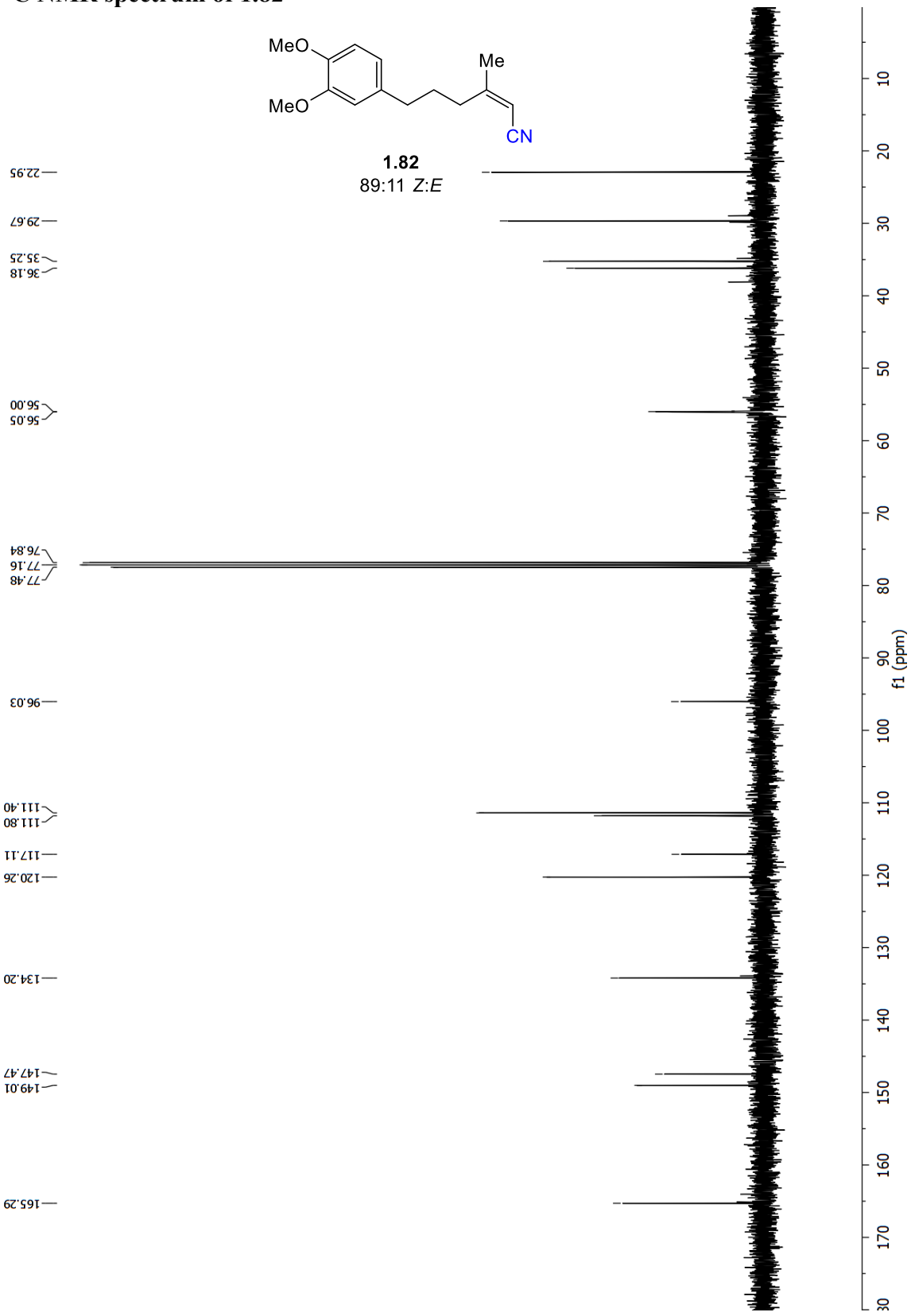
^{13}C NMR spectrum of 1.80



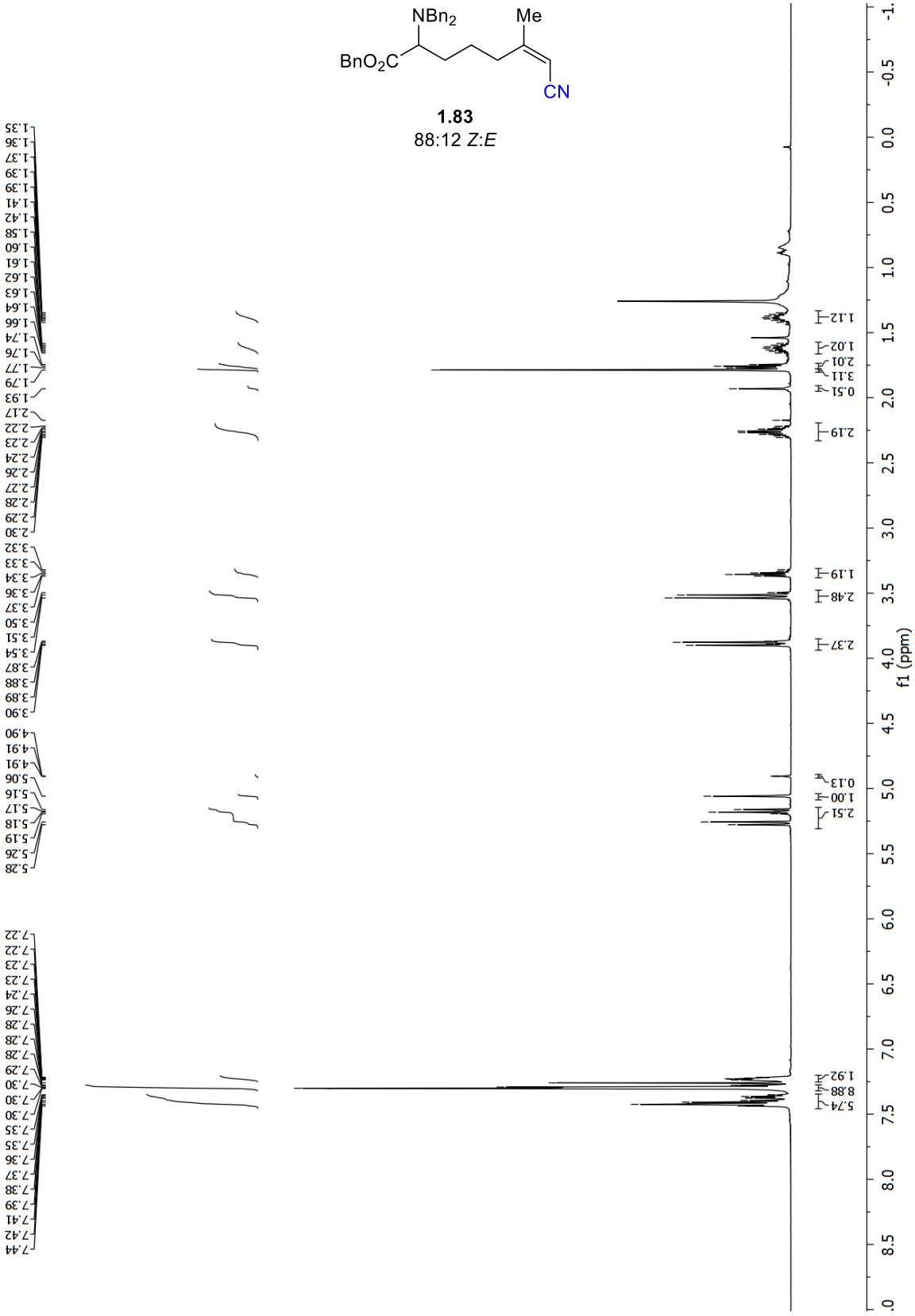
^{1}H NMR spectrum of 1.82



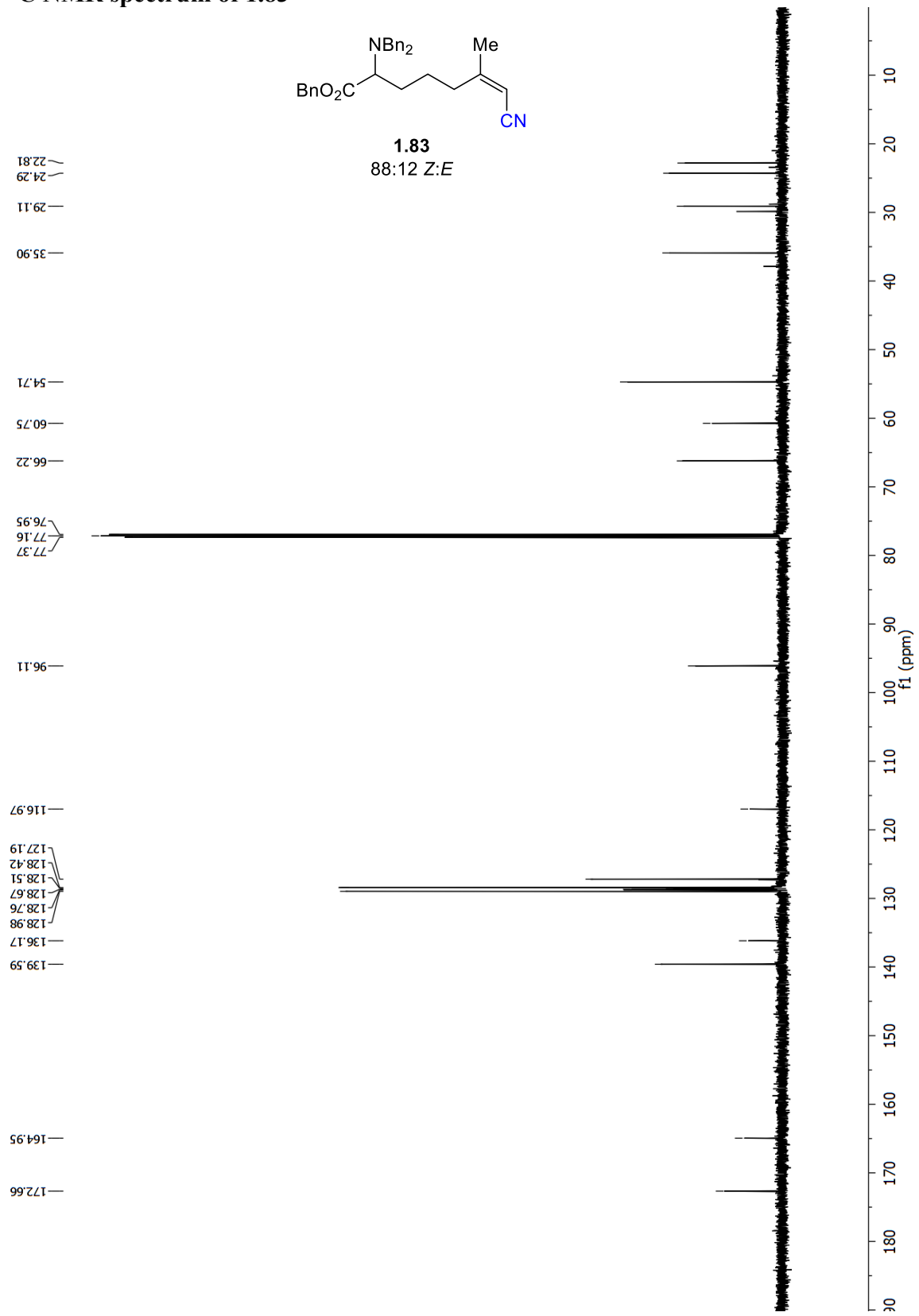
^{13}C NMR spectrum of 1.82



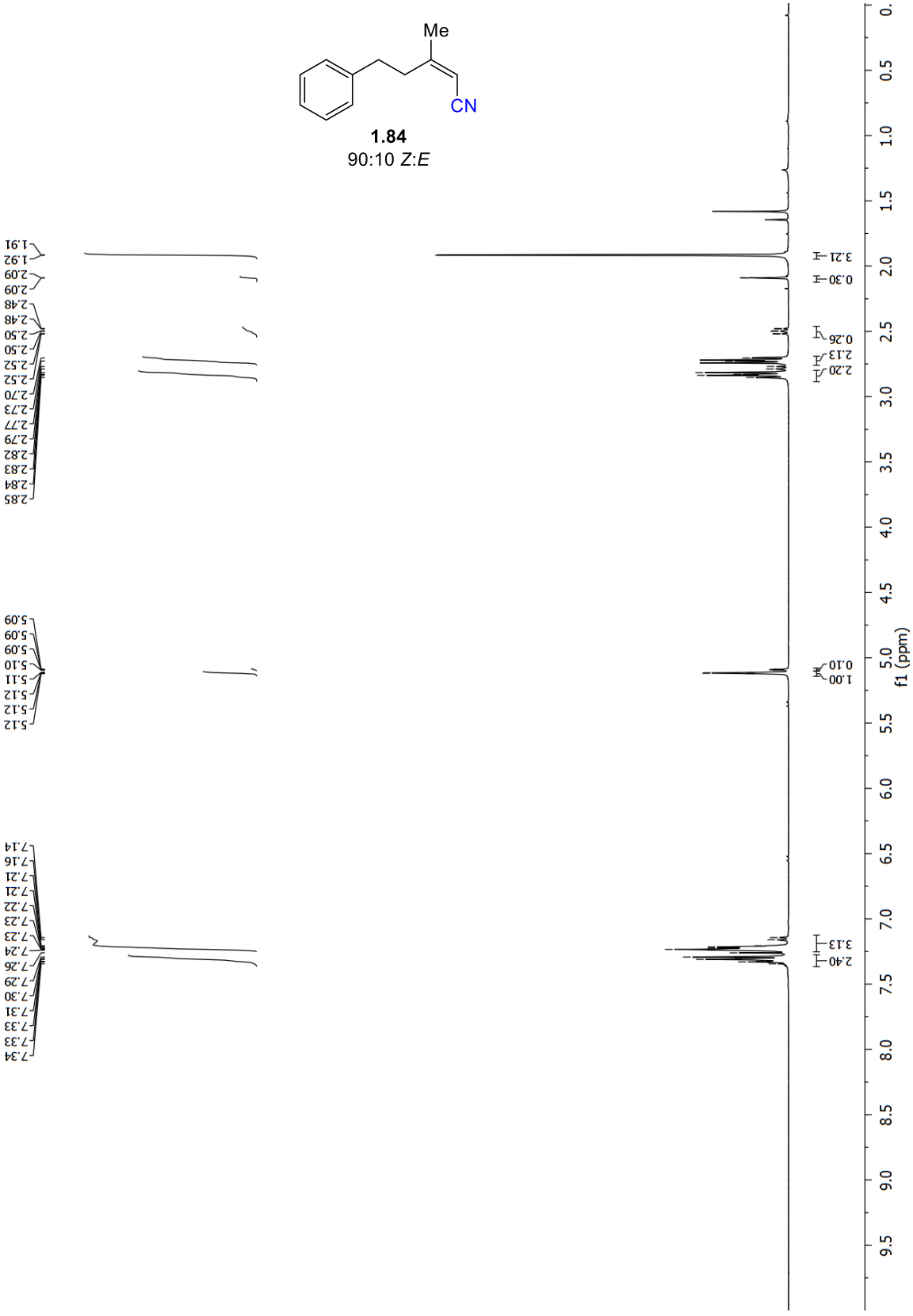
^{1}H NMR spectrum of 1.83



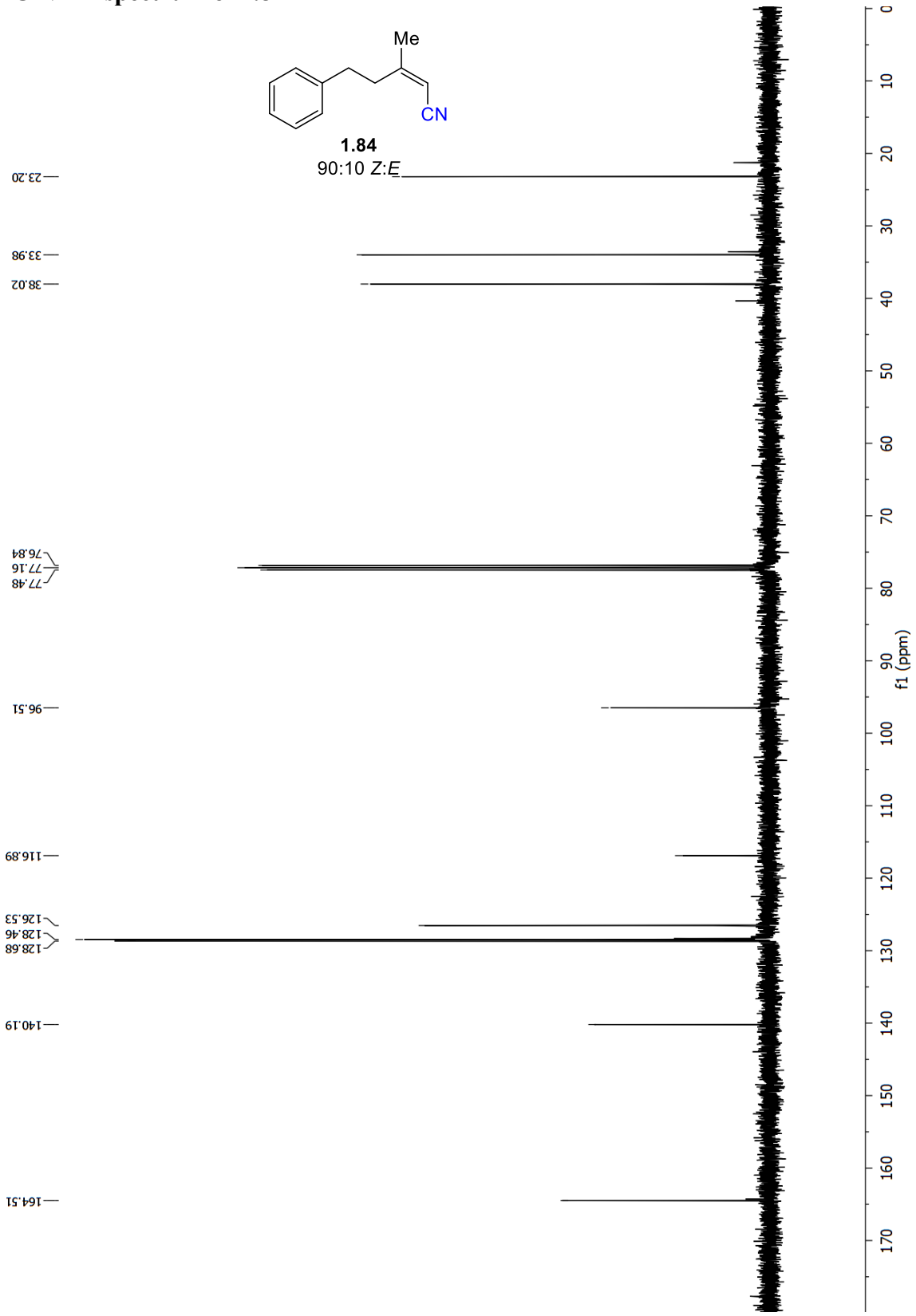
^{13}C NMR spectrum of 1.83



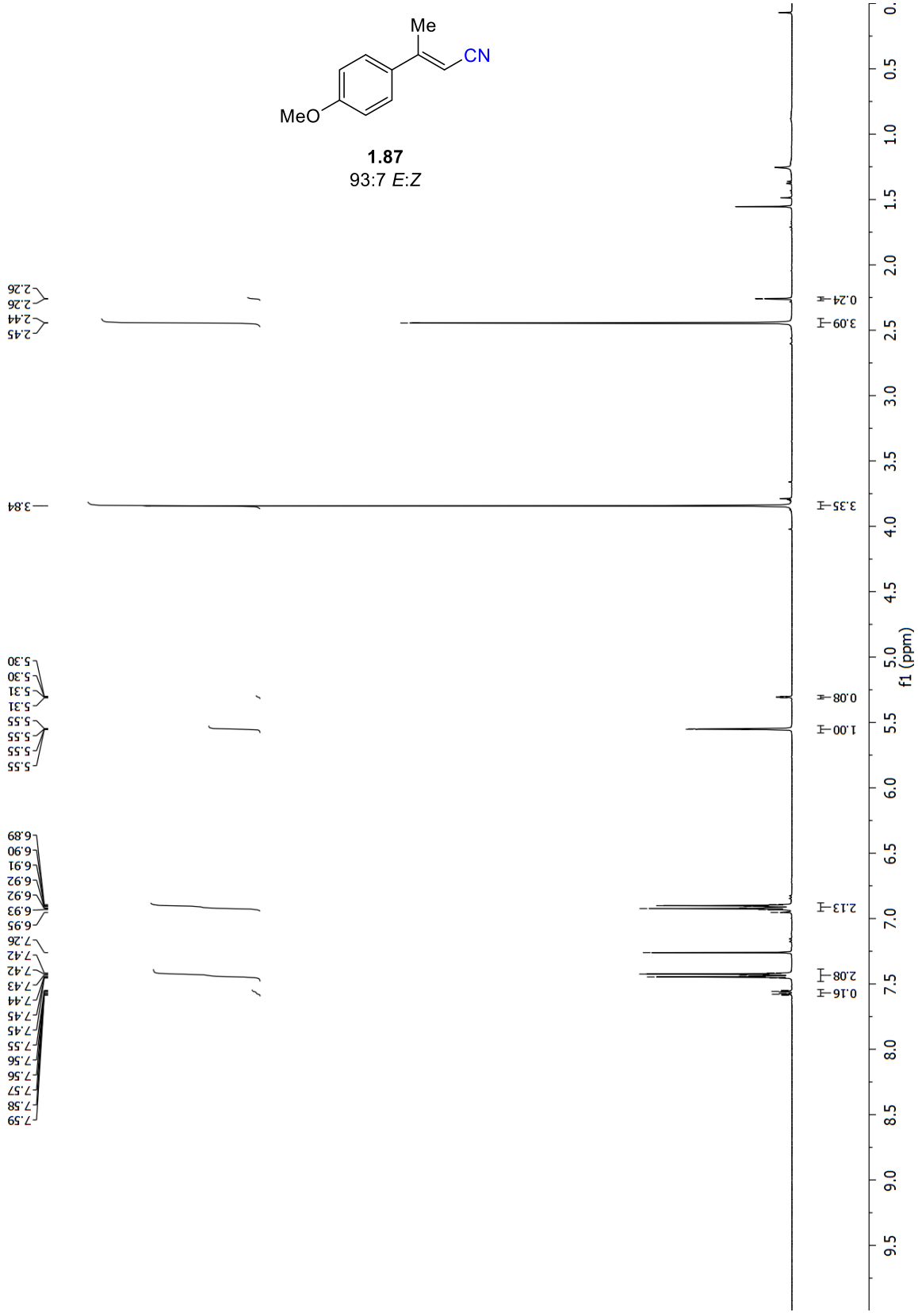
^{1}H NMR spectrum of 1.84



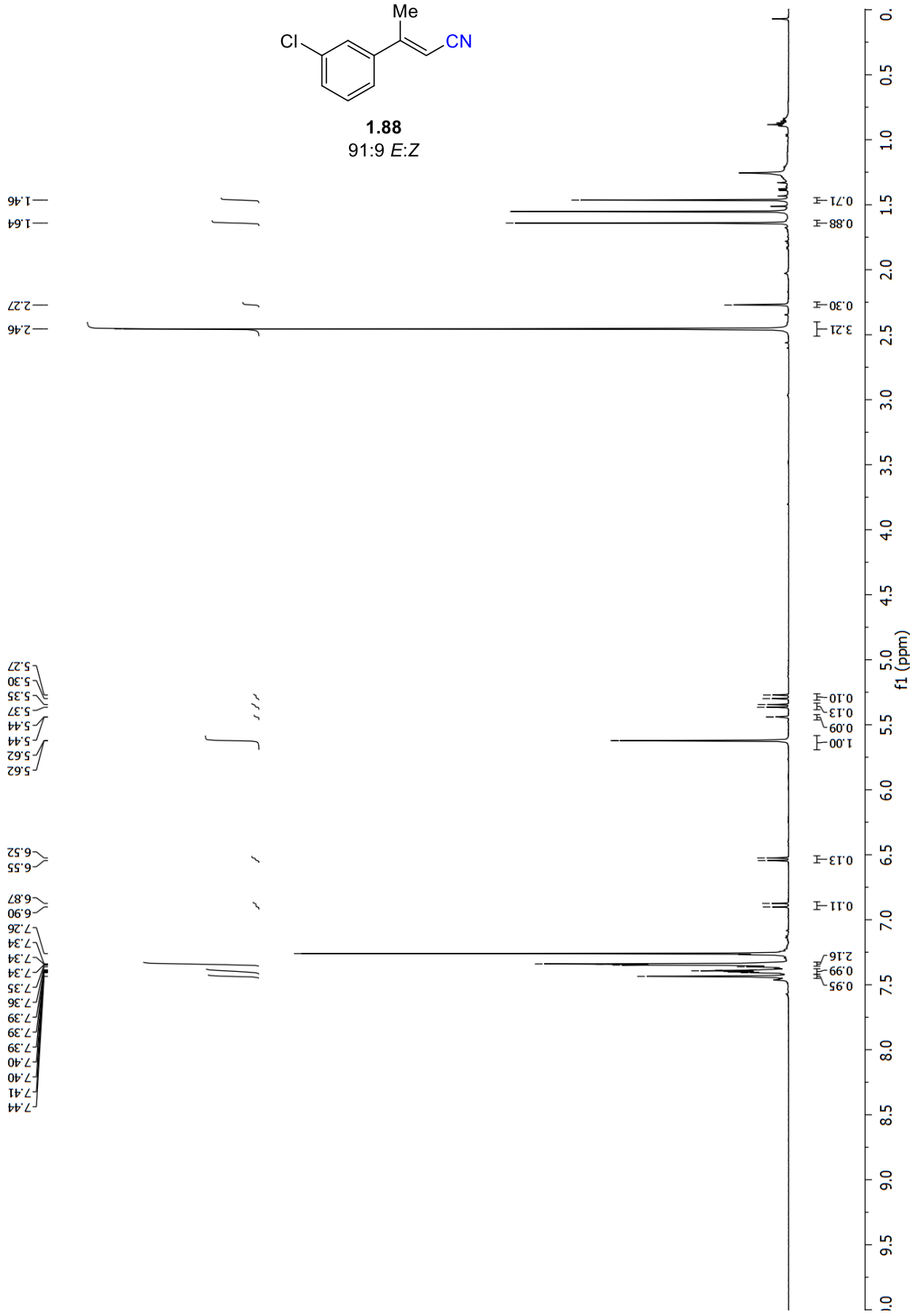
^{13}C NMR spectrum of 1.84



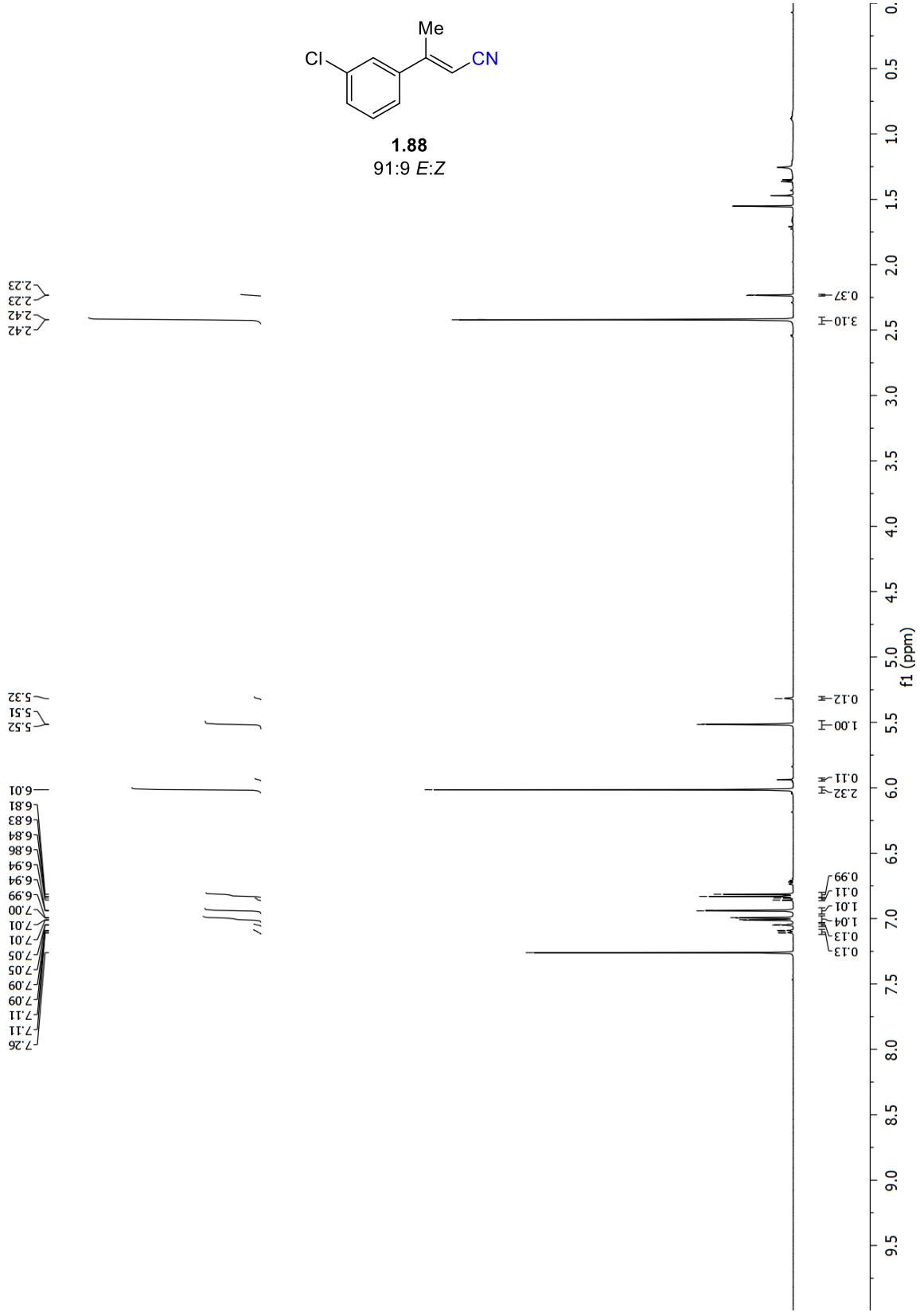
^{1}H NMR spectrum of 1.87



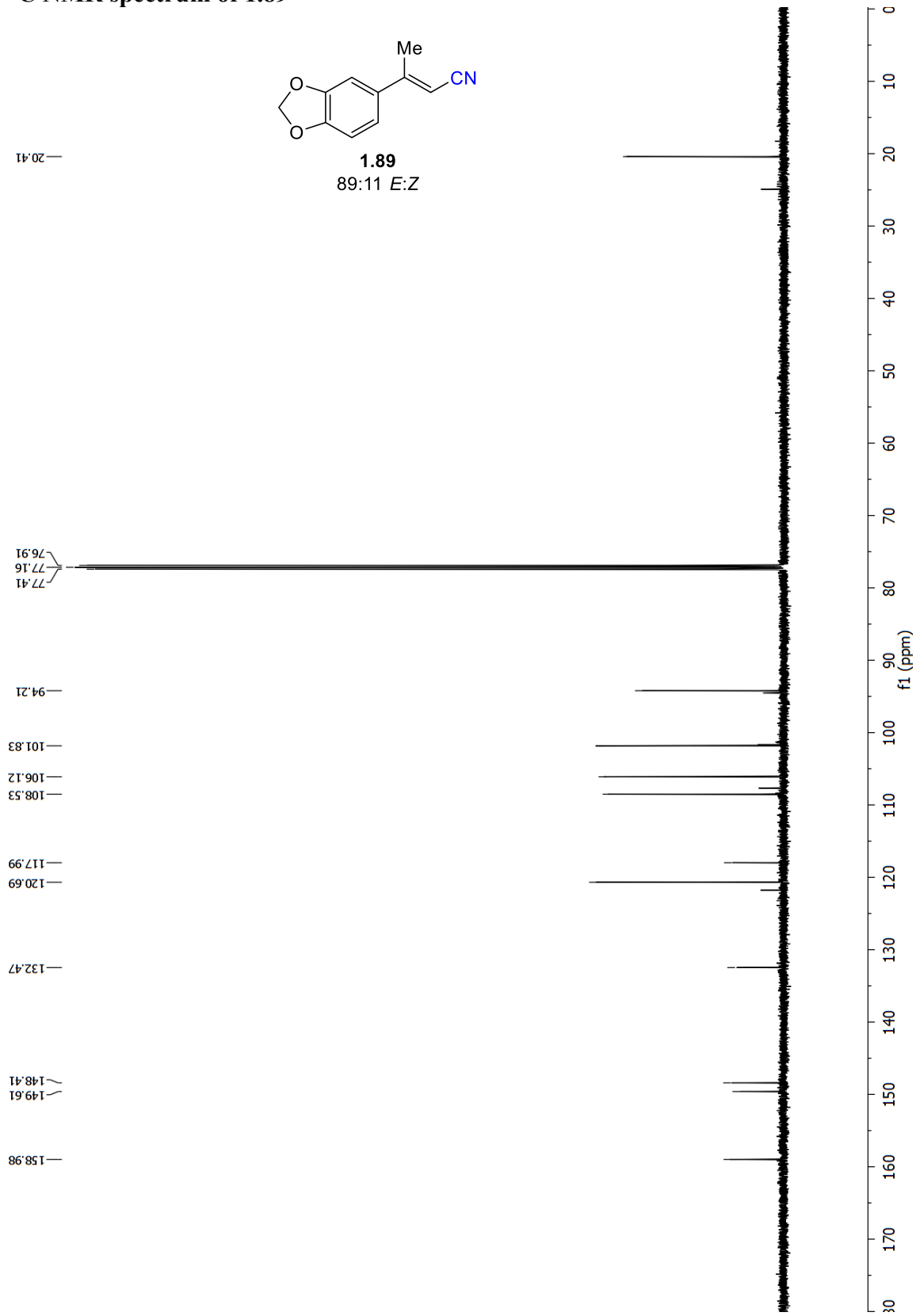
^{1}H NMR spectrum of 1.88



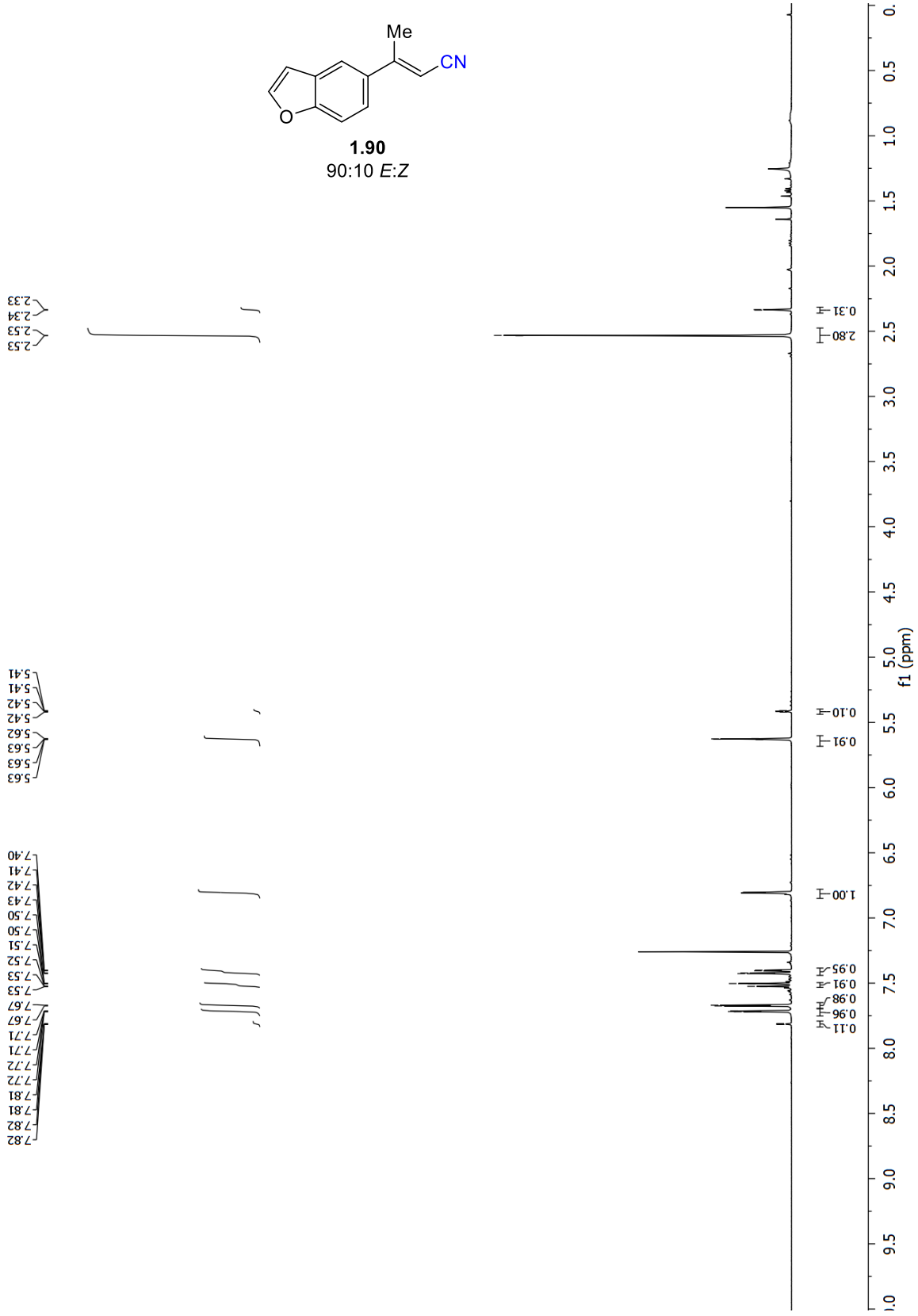
^{1}H NMR spectrum of 1.89



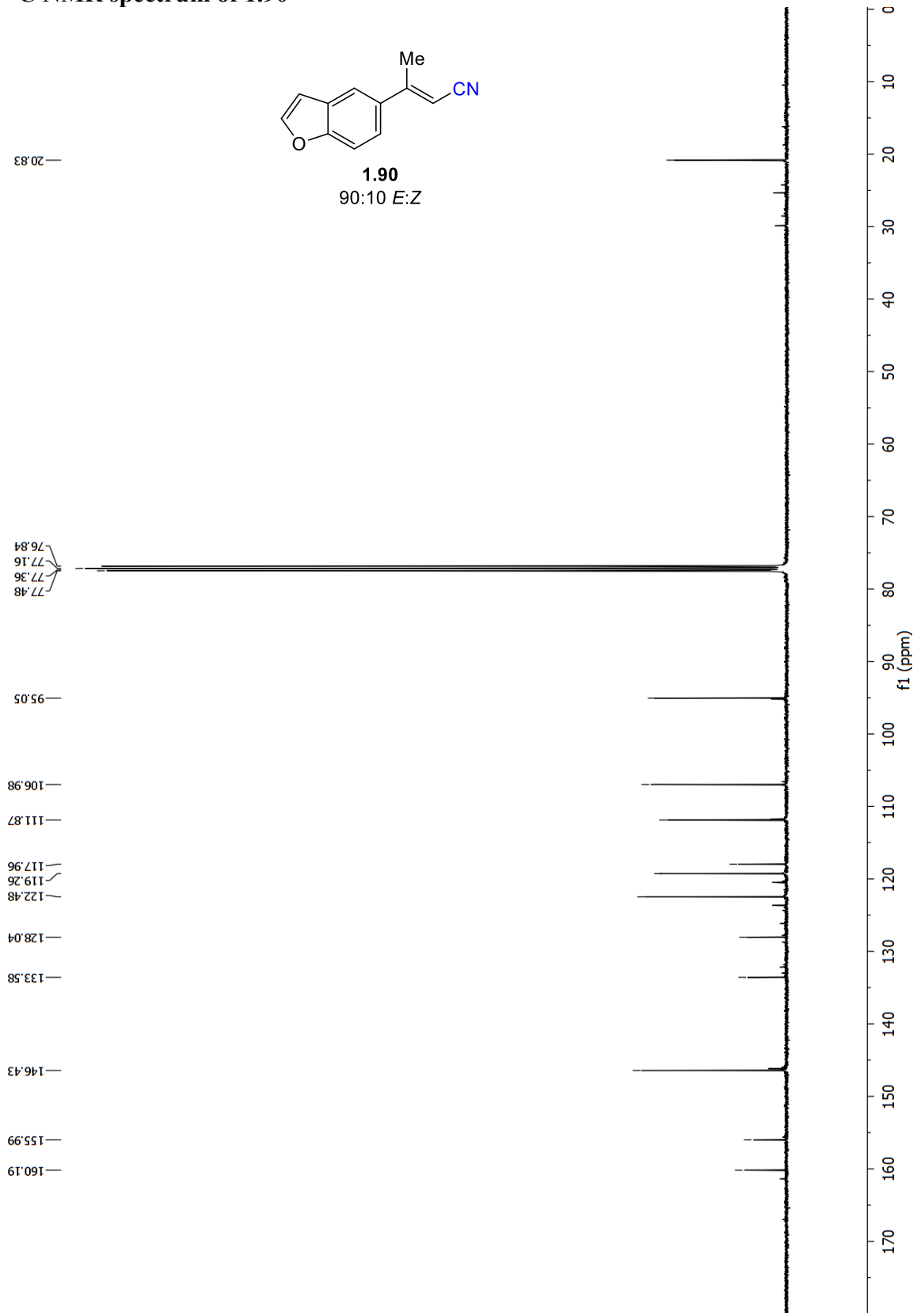
^{13}C NMR spectrum of 1.89



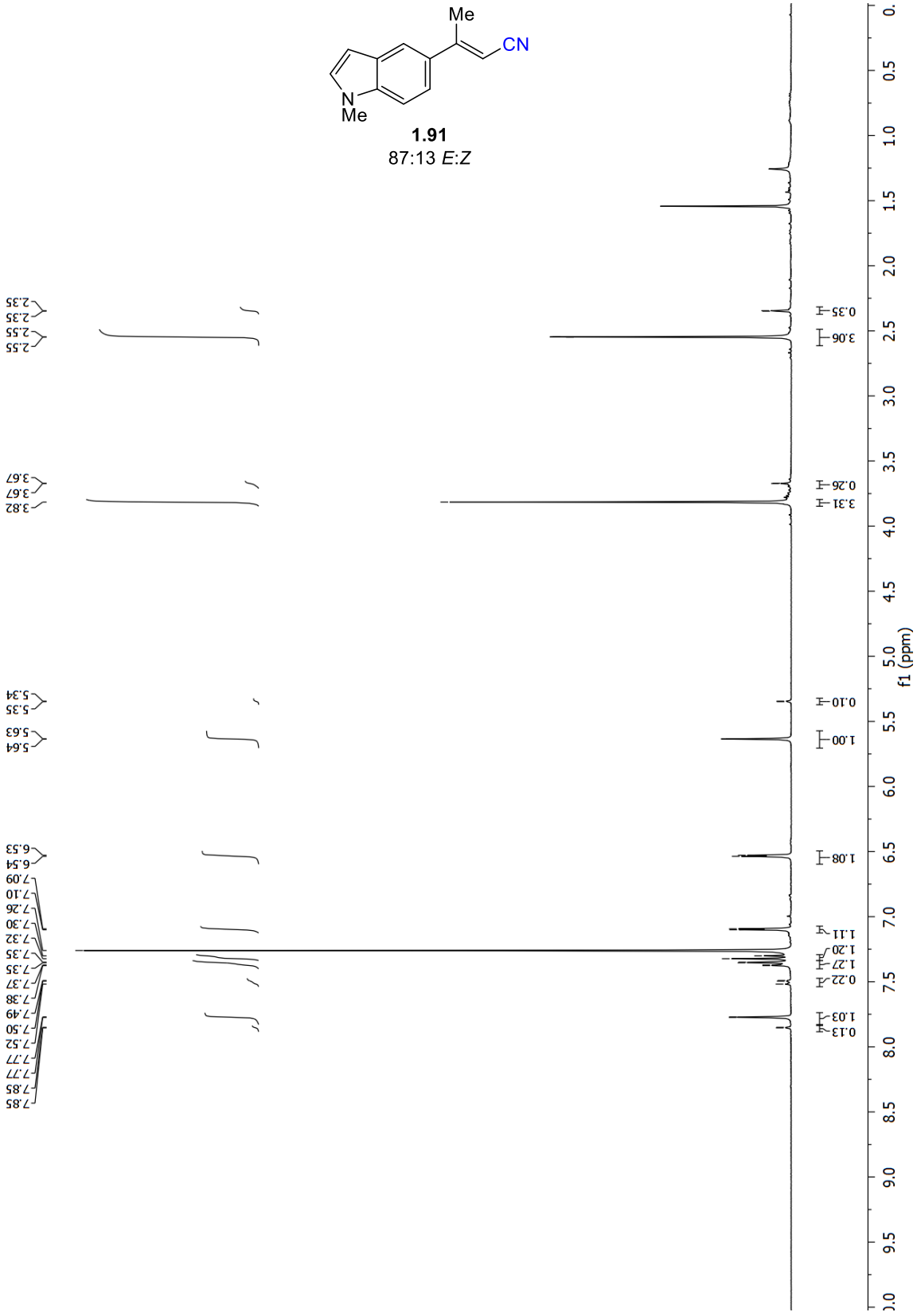
^{1}H NMR spectrum of 1.90



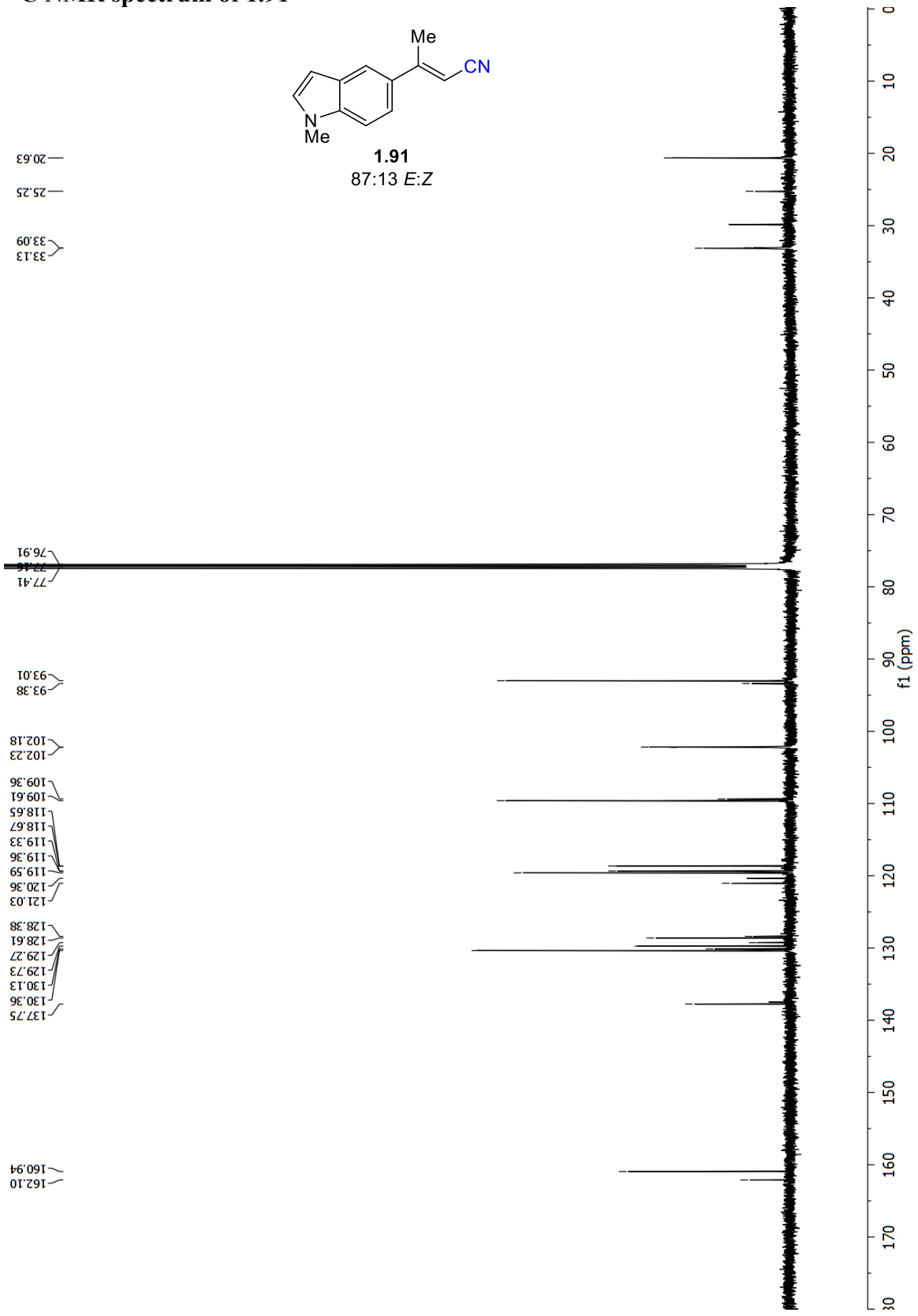
^{13}C NMR spectrum of 1.90



^{1}H NMR spectrum of 1.91



^{13}C NMR spectrum of 1.91



X-ray crystal structure for 1.76

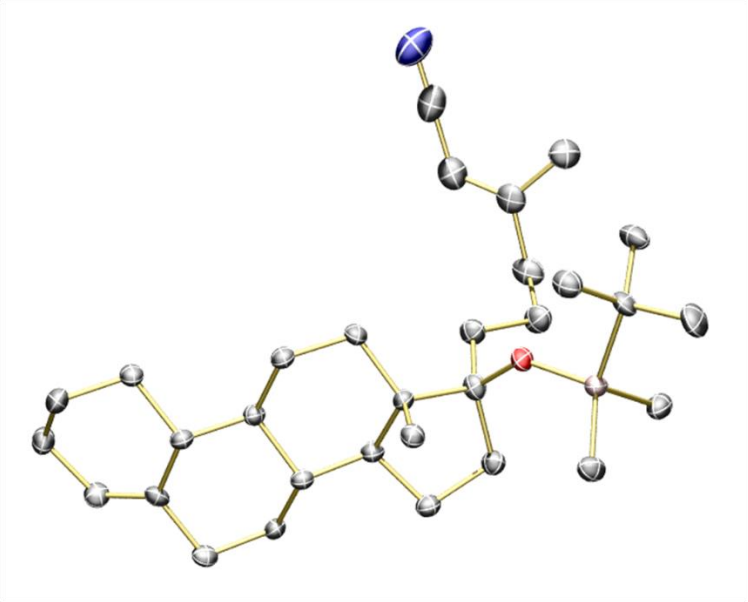


Table 1.1. Crystal data and structure refinement for **1.76**.

Identification code	$C_{31}H_{51}NOSi$	
Empirical formula	C_{31} H_{51} N O Si	
Formula weight	481.81	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.3883(3) Å	α= 90°.
	b = 10.3271(4) Å	β= 90°.
	c = 37.3224(12) Å	γ = 90°.
Volume	2847.69(18) $Å^3$	
Z	4	
Density (calculated)	1.124 Mg/m^3	
Absorption coefficient	0.880 mm^{-1}	
F(000)	1064	
Crystal size	0.240 x 0.140 x 0.080 mm^3	
Theta range for data collection	2.368 to 66.795°.	
Index ranges	-8<=h<=8, -12<=k<=11, -44<=l<=43	
Reflections collected	17845	
Independent reflections	4987 [R(int) = 0.1240]	
Completeness to theta = 66.795°	99.8 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7528 and 0.5740
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4987 / 0 / 314
Goodness-of-fit on F^2	0.991
Final R indices [I>2sigma(I)]	R1 = 0.0510, wR2 = 0.1064
R indices (all data)	R1 = 0.0786, wR2 = 0.1182
Absolute structure parameter	-0.01(4)
Extinction coefficient	n/a
Largest diff. peak and hole	0.199 and -0.247 e.Å^{-3}

Table 1.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **1.76**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si(1)	1732(2)	7718(1)	6467(1)	21(1)
O(1)	2164(4)	6191(3)	6387(1)	21(1)
N(1)	9031(8)	1713(5)	7025(1)	56(1)
C(1)	7556(9)	2012(5)	7074(1)	41(1)
C(2)	5706(7)	2348(5)	7142(1)	38(1)
C(3)	5132(7)	3489(5)	7262(1)	32(1)
C(4)	3168(7)	3739(5)	7329(1)	34(1)
C(5)	2308(7)	4715(5)	7062(1)	33(1)
C(6)	2198(6)	4157(4)	6684(1)	26(1)
C(7)	1182(6)	4992(4)	6407(1)	22(1)
C(8)	-855(6)	5169(4)	6509(1)	24(1)
C(9)	-1955(6)	4234(4)	6274(1)	23(1)
C(10)	-535(5)	3403(4)	6086(1)	19(1)
C(11)	-1081(5)	2661(4)	5749(1)	18(1)
C(12)	-2657(6)	1754(4)	5812(1)	20(1)
C(13)	-3169(6)	1044(4)	5466(1)	22(1)
C(14)	-1589(6)	353(4)	5303(1)	20(1)
C(15)	-1724(6)	-868(4)	5195(1)	24(1)

C(16)	-259(6)	-1591(4)	5001(1)	28(1)
C(17)	1133(6)	-656(4)	4848(1)	25(1)
C(18)	1713(6)	315(4)	5134(1)	21(1)
C(19)	124(6)	1154(4)	5263(1)	20(1)
C(20)	570(5)	1891(4)	5610(1)	19(1)
C(21)	2256(5)	2749(4)	5570(1)	20(1)
C(22)	2698(6)	3531(4)	5909(1)	20(1)
C(23)	1068(6)	4334(4)	6032(1)	18(1)
C(24)	6415(7)	4570(5)	7346(1)	36(1)
C(25)	821(6)	7997(4)	6928(1)	28(1)
C(26)	100(6)	8465(4)	6150(1)	27(1)
C(27)	4008(6)	8512(4)	6408(1)	23(1)
C(28)	4765(7)	8203(5)	6032(1)	31(1)
C(29)	5343(6)	7991(5)	6689(1)	31(1)
C(30)	3840(7)	9981(4)	6449(2)	38(1)
C(31)	651(6)	5379(4)	5751(1)	22(1)

Table 1.3. Bond lengths [Å] and angles [°] for **1.76**.

Si(1)-O(1)	1.637(3)
Si(1)-C(26)	1.857(4)
Si(1)-C(25)	1.869(4)
Si(1)-C(27)	1.884(4)
O(1)-C(7)	1.437(5)
N(1)-C(1)	1.147(7)
C(1)-C(2)	1.433(8)
C(2)-C(3)	1.330(7)
C(2)-H(2)	0.9500
C(3)-C(4)	1.495(7)
C(3)-C(24)	1.498(7)
C(4)-C(5)	1.553(6)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(6)	1.523(6)
C(5)-H(5A)	0.9900

C(5)-H(5B)	0.9900
C(6)-C(7)	1.542(6)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(23)	1.558(5)
C(7)-C(8)	1.562(6)
C(8)-C(9)	1.537(6)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.526(6)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.526(6)
C(10)-C(23)	1.539(6)
C(10)-H(10)	1.0000
C(11)-C(12)	1.512(6)
C(11)-C(20)	1.545(5)
C(11)-H(11)	1.0000
C(12)-C(13)	1.531(6)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-C(14)	1.498(6)
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(14)-C(15)	1.328(6)
C(14)-C(19)	1.519(6)
C(15)-C(16)	1.501(6)
C(15)-H(15)	0.9500
C(16)-C(17)	1.522(6)
C(16)-H(16A)	0.9900
C(16)-H(16B)	0.9900
C(17)-C(18)	1.525(6)
C(17)-H(17A)	0.9900
C(17)-H(17B)	0.9900
C(18)-C(19)	1.537(6)
C(18)-H(18A)	0.9900

C(18)-H(18B)	0.9900
C(19)-C(20)	1.539(6)
C(19)-H(19)	1.0000
C(20)-C(21)	1.536(6)
C(20)-H(20)	1.0000
C(21)-C(22)	1.534(6)
C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900
C(22)-C(23)	1.533(6)
C(22)-H(22A)	0.9900
C(22)-H(22B)	0.9900
C(23)-C(31)	1.536(6)
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800
C(25)-H(25A)	0.9800
C(25)-H(25B)	0.9800
C(25)-H(25C)	0.9800
C(26)-H(26A)	0.9800
C(26)-H(26B)	0.9800
C(26)-H(26C)	0.9800
C(27)-C(30)	1.530(6)
C(27)-C(29)	1.537(6)
C(27)-C(28)	1.542(6)
C(28)-H(28A)	0.9800
C(28)-H(28B)	0.9800
C(28)-H(28C)	0.9800
C(29)-H(29A)	0.9800
C(29)-H(29B)	0.9800
C(29)-H(29C)	0.9800
C(30)-H(30A)	0.9800
C(30)-H(30B)	0.9800
C(30)-H(30C)	0.9800
C(31)-H(31A)	0.9800
C(31)-H(31B)	0.9800
C(31)-H(31C)	0.9800

O(1)-Si(1)-C(26)	114.15(18)
O(1)-Si(1)-C(25)	112.84(18)
C(26)-Si(1)-C(25)	106.7(2)
O(1)-Si(1)-C(27)	102.91(17)
C(26)-Si(1)-C(27)	108.9(2)
C(25)-Si(1)-C(27)	111.3(2)
C(7)-O(1)-Si(1)	136.2(3)
N(1)-C(1)-C(2)	178.2(6)
C(3)-C(2)-C(1)	125.3(5)
C(3)-C(2)-H(2)	117.4
C(1)-C(2)-H(2)	117.4
C(2)-C(3)-C(4)	121.2(5)
C(2)-C(3)-C(24)	122.0(5)
C(4)-C(3)-C(24)	116.8(4)
C(3)-C(4)-C(5)	113.7(4)
C(3)-C(4)-H(4A)	108.8
C(5)-C(4)-H(4A)	108.8
C(3)-C(4)-H(4B)	108.8
C(5)-C(4)-H(4B)	108.8
H(4A)-C(4)-H(4B)	107.7
C(6)-C(5)-C(4)	111.6(4)
C(6)-C(5)-H(5A)	109.3
C(4)-C(5)-H(5A)	109.3
C(6)-C(5)-H(5B)	109.3
C(4)-C(5)-H(5B)	109.3
H(5A)-C(5)-H(5B)	108.0
C(5)-C(6)-C(7)	115.8(4)
C(5)-C(6)-H(6A)	108.3
C(7)-C(6)-H(6A)	108.3
C(5)-C(6)-H(6B)	108.3
C(7)-C(6)-H(6B)	108.3
H(6A)-C(6)-H(6B)	107.4
O(1)-C(7)-C(6)	105.8(3)
O(1)-C(7)-C(23)	110.8(3)
C(6)-C(7)-C(23)	112.6(3)

O(1)-C(7)-C(8)	113.5(3)
C(6)-C(7)-C(8)	111.8(3)
C(23)-C(7)-C(8)	102.6(3)
C(9)-C(8)-C(7)	107.3(3)
C(9)-C(8)-H(8A)	110.3
C(7)-C(8)-H(8A)	110.3
C(9)-C(8)-H(8B)	110.3
C(7)-C(8)-H(8B)	110.3
H(8A)-C(8)-H(8B)	108.5
C(10)-C(9)-C(8)	104.6(4)
C(10)-C(9)-H(9A)	110.8
C(8)-C(9)-H(9A)	110.8
C(10)-C(9)-H(9B)	110.8
C(8)-C(9)-H(9B)	110.8
H(9A)-C(9)-H(9B)	108.9
C(11)-C(10)-C(9)	118.6(3)
C(11)-C(10)-C(23)	114.2(3)
C(9)-C(10)-C(23)	103.7(3)
C(11)-C(10)-H(10)	106.5
C(9)-C(10)-H(10)	106.5
C(23)-C(10)-H(10)	106.5
C(12)-C(11)-C(10)	112.7(3)
C(12)-C(11)-C(20)	109.9(3)
C(10)-C(11)-C(20)	109.0(3)
C(12)-C(11)-H(11)	108.4
C(10)-C(11)-H(11)	108.4
C(20)-C(11)-H(11)	108.4
C(11)-C(12)-C(13)	110.8(3)
C(11)-C(12)-H(12A)	109.5
C(13)-C(12)-H(12A)	109.5
C(11)-C(12)-H(12B)	109.5
C(13)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	108.1
C(14)-C(13)-C(12)	112.2(4)
C(14)-C(13)-H(13A)	109.2
C(12)-C(13)-H(13A)	109.2

C(14)-C(13)-H(13B)	109.2
C(12)-C(13)-H(13B)	109.2
H(13A)-C(13)-H(13B)	107.9
C(15)-C(14)-C(13)	121.2(4)
C(15)-C(14)-C(19)	123.4(4)
C(13)-C(14)-C(19)	115.5(3)
C(14)-C(15)-C(16)	124.4(4)
C(14)-C(15)-H(15)	117.8
C(16)-C(15)-H(15)	117.8
C(15)-C(16)-C(17)	110.7(4)
C(15)-C(16)-H(16A)	109.5
C(17)-C(16)-H(16A)	109.5
C(15)-C(16)-H(16B)	109.5
C(17)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	108.1
C(16)-C(17)-C(18)	110.1(3)
C(16)-C(17)-H(17A)	109.6
C(18)-C(17)-H(17A)	109.6
C(16)-C(17)-H(17B)	109.6
C(18)-C(17)-H(17B)	109.6
H(17A)-C(17)-H(17B)	108.2
C(17)-C(18)-C(19)	112.1(4)
C(17)-C(18)-H(18A)	109.2
C(19)-C(18)-H(18A)	109.2
C(17)-C(18)-H(18B)	109.2
C(19)-C(18)-H(18B)	109.2
H(18A)-C(18)-H(18B)	107.9
C(14)-C(19)-C(20)	111.4(3)
C(14)-C(19)-C(18)	111.1(3)
C(20)-C(19)-C(18)	112.3(3)
C(14)-C(19)-H(19)	107.3
C(20)-C(19)-H(19)	107.3
C(18)-C(19)-H(19)	107.3
C(21)-C(20)-C(19)	112.1(3)
C(21)-C(20)-C(11)	112.1(3)
C(19)-C(20)-C(11)	111.6(3)

C(21)-C(20)-H(20)	106.9
C(19)-C(20)-H(20)	106.9
C(11)-C(20)-H(20)	106.9
C(20)-C(21)-C(22)	113.4(3)
C(20)-C(21)-H(21A)	108.9
C(22)-C(21)-H(21A)	108.9
C(20)-C(21)-H(21B)	108.9
C(22)-C(21)-H(21B)	108.9
H(21A)-C(21)-H(21B)	107.7
C(23)-C(22)-C(21)	111.4(3)
C(23)-C(22)-H(22A)	109.3
C(21)-C(22)-H(22A)	109.3
C(23)-C(22)-H(22B)	109.3
C(21)-C(22)-H(22B)	109.3
H(22A)-C(22)-H(22B)	108.0
C(22)-C(23)-C(31)	109.4(3)
C(22)-C(23)-C(10)	107.8(3)
C(31)-C(23)-C(10)	111.9(3)
C(22)-C(23)-C(7)	117.6(3)
C(31)-C(23)-C(7)	108.6(3)
C(10)-C(23)-C(7)	101.4(3)
C(3)-C(24)-H(24A)	109.5
C(3)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(3)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
Si(1)-C(25)-H(25A)	109.5
Si(1)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
Si(1)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5
Si(1)-C(26)-H(26A)	109.5
Si(1)-C(26)-H(26B)	109.5
H(26A)-C(26)-H(26B)	109.5

Si(1)-C(26)-H(26C)	109.5
H(26A)-C(26)-H(26C)	109.5
H(26B)-C(26)-H(26C)	109.5
C(30)-C(27)-C(29)	109.3(4)
C(30)-C(27)-C(28)	109.0(4)
C(29)-C(27)-C(28)	108.4(4)
C(30)-C(27)-Si(1)	110.3(3)
C(29)-C(27)-Si(1)	109.9(3)
C(28)-C(27)-Si(1)	110.0(3)
C(27)-C(28)-H(28A)	109.5
C(27)-C(28)-H(28B)	109.5
H(28A)-C(28)-H(28B)	109.5
C(27)-C(28)-H(28C)	109.5
H(28A)-C(28)-H(28C)	109.5
H(28B)-C(28)-H(28C)	109.5
C(27)-C(29)-H(29A)	109.5
C(27)-C(29)-H(29B)	109.5
H(29A)-C(29)-H(29B)	109.5
C(27)-C(29)-H(29C)	109.5
H(29A)-C(29)-H(29C)	109.5
H(29B)-C(29)-H(29C)	109.5
C(27)-C(30)-H(30A)	109.5
C(27)-C(30)-H(30B)	109.5
H(30A)-C(30)-H(30B)	109.5
C(27)-C(30)-H(30C)	109.5
H(30A)-C(30)-H(30C)	109.5
H(30B)-C(30)-H(30C)	109.5
C(23)-C(31)-H(31A)	109.5
C(23)-C(31)-H(31B)	109.5
H(31A)-C(31)-H(31B)	109.5
C(23)-C(31)-H(31C)	109.5
H(31A)-C(31)-H(31C)	109.5
H(31B)-C(31)-H(31C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 1.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **1.76**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1)	18(1)	22(1)	24(1)	-1(1)	-1(1)	1(1)
O(1)	20(2)	19(1)	25(2)	-1(1)	0(1)	-2(1)
N(1)	59(4)	47(3)	62(3)	8(2)	12(3)	16(3)
C(1)	57(4)	34(3)	31(3)	3(2)	4(3)	7(3)
C(2)	44(3)	36(3)	33(3)	3(2)	-1(2)	-4(3)
C(3)	38(3)	38(3)	19(2)	8(2)	-2(2)	0(2)
C(4)	32(3)	46(3)	24(2)	8(2)	-2(2)	-4(3)
C(5)	34(3)	40(3)	24(2)	-1(2)	-3(2)	6(2)
C(6)	26(2)	29(2)	22(2)	2(2)	-3(2)	2(2)
C(7)	26(2)	24(2)	16(2)	2(2)	0(2)	-2(2)
C(8)	23(2)	27(2)	22(2)	-1(2)	0(2)	2(2)
C(9)	18(2)	25(2)	27(2)	1(2)	2(2)	1(2)
C(10)	16(2)	22(2)	21(2)	1(2)	1(2)	1(2)
C(11)	15(2)	19(2)	21(2)	3(2)	1(2)	0(2)
C(12)	17(2)	22(2)	22(2)	-2(2)	1(2)	3(2)
C(13)	16(2)	22(2)	28(2)	3(2)	0(2)	-4(2)
C(14)	17(2)	23(2)	21(2)	4(2)	-5(2)	-2(2)
C(15)	22(2)	23(2)	26(2)	3(2)	3(2)	-4(2)
C(16)	28(3)	26(2)	28(2)	-5(2)	3(2)	0(2)
C(17)	24(2)	25(2)	27(2)	-5(2)	2(2)	4(2)
C(18)	16(2)	24(2)	23(2)	-1(2)	2(2)	-2(2)
C(19)	15(2)	21(2)	22(2)	1(2)	2(2)	1(2)
C(20)	17(2)	19(2)	22(2)	0(2)	0(2)	1(2)
C(21)	16(2)	23(2)	22(2)	0(2)	3(2)	1(2)
C(22)	15(2)	23(2)	23(2)	-2(2)	0(2)	-3(2)
C(23)	16(2)	19(2)	19(2)	-2(2)	1(2)	1(2)
C(24)	33(3)	34(3)	39(3)	8(2)	1(2)	-2(2)
C(25)	23(2)	26(2)	37(3)	-3(2)	4(2)	0(2)
C(26)	24(2)	24(2)	33(2)	4(2)	-5(2)	0(2)
C(27)	20(2)	26(2)	24(2)	-1(2)	-3(2)	-7(2)
C(28)	26(2)	38(3)	29(2)	0(2)	0(2)	-3(2)

C(29)	21(2)	45(3)	25(2)	-2(2)	-4(2)	-4(2)
C(30)	35(3)	31(2)	49(3)	-9(3)	0(3)	-12(2)
C(31)	20(2)	23(2)	22(2)	1(2)	0(2)	-2(2)

Table 1.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **1.76**.

	x	y	z	U(eq)
H(2)	4816	1704	7097	45
H(4A)	3019	4076	7575	40
H(4B)	2503	2908	7313	40
H(5A)	1076	4944	7145	39
H(5B)	3041	5517	7057	39
H(6A)	1597	3301	6698	31
H(6B)	3445	4011	6596	31
H(8A)	-1044	4969	6766	29
H(8B)	-1239	6074	6465	29
H(9A)	-2765	3692	6423	28
H(9B)	-2694	4715	6097	28
H(10)	-131	2740	6264	23
H(11)	-1440	3302	5561	22
H(12A)	-3711	2254	5900	24
H(12B)	-2327	1114	5999	24
H(13A)	-4137	410	5519	27
H(13B)	-3653	1677	5292	27
H(15)	-2821	-1314	5244	29
H(16A)	-799	-2105	4805	33
H(16B)	344	-2196	5169	33
H(17A)	606	-189	4641	30
H(17B)	2202	-1145	4763	30
H(18A)	2670	882	5035	25
H(18B)	2229	-159	5341	25

H(19)	-113	1816	5073	23
H(20)	859	1225	5796	23
H(21A)	2066	3355	5368	24
H(21B)	3306	2194	5510	24
H(22A)	3063	2932	6103	24
H(22B)	3730	4116	5859	24
H(24A)	7658	4287	7299	53
H(24B)	6295	4810	7599	53
H(24C)	6131	5320	7196	53
H(25A)	-302	7504	6959	43
H(25B)	573	8922	6961	43
H(25C)	1713	7712	7106	43
H(26A)	618	8466	5909	40
H(26B)	-152	9357	6225	40
H(26C)	-1028	7965	6150	40
H(28A)	3905	8495	5849	46
H(28B)	4949	7267	6009	46
H(28C)	5923	8650	5999	46
H(29A)	6517	8421	6660	46
H(29B)	5493	7056	6656	46
H(29C)	4872	8165	6929	46
H(30A)	3217	10182	6674	58
H(30B)	3144	10333	6247	58
H(30C)	5049	10371	6451	58
H(31A)	1723	5923	5715	33
H(31B)	-358	5916	5834	33
H(31C)	323	4964	5524	33

Table 1.6. Torsion angles [°] for **1.76**.

C(26)-Si(1)-O(1)-C(7)	-68.5(4)
C(25)-Si(1)-O(1)-C(7)	53.6(4)
C(27)-Si(1)-O(1)-C(7)	173.7(4)
C(1)-C(2)-C(3)-C(4)	-179.2(4)
C(1)-C(2)-C(3)-C(24)	-0.8(8)
C(2)-C(3)-C(4)-C(5)	-110.9(5)
C(24)-C(3)-C(4)-C(5)	70.6(5)
C(3)-C(4)-C(5)-C(6)	68.3(6)
C(4)-C(5)-C(6)-C(7)	173.8(4)
Si(1)-O(1)-C(7)-C(6)	-118.1(4)
Si(1)-O(1)-C(7)-C(23)	119.5(3)
Si(1)-O(1)-C(7)-C(8)	4.8(5)
C(5)-C(6)-C(7)-O(1)	60.9(5)
C(5)-C(6)-C(7)-C(23)	-178.0(4)
C(5)-C(6)-C(7)-C(8)	-63.1(5)
O(1)-C(7)-C(8)-C(9)	138.9(3)
C(6)-C(7)-C(8)-C(9)	-101.6(4)
C(23)-C(7)-C(8)-C(9)	19.3(4)
C(7)-C(8)-C(9)-C(10)	8.3(4)
C(8)-C(9)-C(10)-C(11)	-161.2(3)
C(8)-C(9)-C(10)-C(23)	-33.3(4)
C(9)-C(10)-C(11)-C(12)	-57.3(5)
C(23)-C(10)-C(11)-C(12)	179.9(3)
C(9)-C(10)-C(11)-C(20)	-179.6(3)
C(23)-C(10)-C(11)-C(20)	57.5(4)
C(10)-C(11)-C(12)-C(13)	179.4(3)
C(20)-C(11)-C(12)-C(13)	-58.9(4)
C(11)-C(12)-C(13)-C(14)	54.5(4)
C(12)-C(13)-C(14)-C(15)	132.3(4)
C(12)-C(13)-C(14)-C(19)	-49.2(5)
C(13)-C(14)-C(15)-C(16)	174.6(4)
C(19)-C(14)-C(15)-C(16)	-3.8(7)
C(14)-C(15)-C(16)-C(17)	-17.0(6)
C(15)-C(16)-C(17)-C(18)	48.4(5)

C(16)-C(17)-C(18)-C(19)	-62.2(5)
C(15)-C(14)-C(19)-C(20)	-134.1(4)
C(13)-C(14)-C(19)-C(20)	47.5(5)
C(15)-C(14)-C(19)-C(18)	-8.1(6)
C(13)-C(14)-C(19)-C(18)	173.5(3)
C(17)-C(18)-C(19)-C(14)	40.5(5)
C(17)-C(18)-C(19)-C(20)	165.9(3)
C(14)-C(19)-C(20)-C(21)	-177.7(3)
C(18)-C(19)-C(20)-C(21)	56.9(4)
C(14)-C(19)-C(20)-C(11)	-51.1(4)
C(18)-C(19)-C(20)-C(11)	-176.4(3)
C(12)-C(11)-C(20)-C(21)	-175.4(3)
C(10)-C(11)-C(20)-C(21)	-51.4(4)
C(12)-C(11)-C(20)-C(19)	57.9(4)
C(10)-C(11)-C(20)-C(19)	-178.1(3)
C(19)-C(20)-C(21)-C(22)	178.0(3)
C(11)-C(20)-C(21)-C(22)	51.7(5)
C(20)-C(21)-C(22)-C(23)	-54.3(5)
C(21)-C(22)-C(23)-C(31)	-66.1(4)
C(21)-C(22)-C(23)-C(10)	55.8(4)
C(21)-C(22)-C(23)-C(7)	169.5(3)
C(11)-C(10)-C(23)-C(22)	-59.8(4)
C(9)-C(10)-C(23)-C(22)	169.6(3)
C(11)-C(10)-C(23)-C(31)	60.5(4)
C(9)-C(10)-C(23)-C(31)	-70.1(4)
C(11)-C(10)-C(23)-C(7)	176.0(3)
C(9)-C(10)-C(23)-C(7)	45.4(4)
O(1)-C(7)-C(23)-C(22)	82.3(4)
C(6)-C(7)-C(23)-C(22)	-36.0(5)
C(8)-C(7)-C(23)-C(22)	-156.4(3)
O(1)-C(7)-C(23)-C(31)	-42.5(4)
C(6)-C(7)-C(23)-C(31)	-160.8(4)
C(8)-C(7)-C(23)-C(31)	78.8(4)
O(1)-C(7)-C(23)-C(10)	-160.5(3)
C(6)-C(7)-C(23)-C(10)	81.2(4)
C(8)-C(7)-C(23)-C(10)	-39.1(4)

O(1)-Si(1)-C(27)-C(30)	176.2(3)
C(26)-Si(1)-C(27)-C(30)	54.7(4)
C(25)-Si(1)-C(27)-C(30)	-62.7(4)
O(1)-Si(1)-C(27)-C(29)	-63.3(3)
C(26)-Si(1)-C(27)-C(29)	175.3(3)
C(25)-Si(1)-C(27)-C(29)	57.8(4)
O(1)-Si(1)-C(27)-C(28)	55.9(3)
C(26)-Si(1)-C(27)-C(28)	-65.6(3)
C(25)-Si(1)-C(27)-C(28)	177.0(3)

Symmetry transformations used to generate equivalent atoms:

Chapter Two

Traceless Protection for More Broadly Applicable Olefin Metathesis

2.1. Introduction

Olefin metathesis has made significant impacts on modern chemistry.[1] Various Mo-based alkylidenes and Ru-based carbenes have been introduced in recent years for stereoselective olefin metathesis transformations (Scheme 2.1.1).[2] These two types of complexes are complementary to each other in regard to substrate scope and functional group compatibility, and widely utilized in synthesis of valuable bioactive molecules. While Mo-based monoaryloxide pyrrolide (MAP) complexes **Mo-1a**–**1c** [3] and monoaryloxide chloride (MAC) complexes **Mo-2**[4] are both able to generate *Z*- and *E*-, di- and trisubstituted alkenyl halides, only MAC complexes can catalyze reactions to yield *Z*-F_3C-containing alkene products. Major shortcoming of these Mo-based complexes is their rapid decomposition against alcohol and carboxylic acid moieties. Therefore, these

(1) (a) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243–251. (b) Grubbs, R. H.; Wenzel, A. G.; O'Leary, D. J.; Khosravi, E. Eds., *Handbook of Metathesis,* Wiley-VCH, Weinheim, **2015**. (c) Hughes, D.; Wheeler, P.; Ene, D. *Org. Process Res. Dev.* **2017**, *21*, 1938–1962. (d) Dong, Y.; Matson, J. B.; Edgar, K. J. *Biomacromolecules* **2017**, *18*, 1661–1676. (e) Ogba, O. M.; Warner, N. C.; O'Leary, D. J.; Grubbs, R. H. *Chem. Soc. Rev.* **2018**, *47*, 4510–4544.
(2) (a) Hoveyda, A. H.; Malcolmson, S. J.; Meek, S. J.; Zhugralin, A. R. *Angew. Chem. Int. Ed.* **2010**, *49*, 34–44. (b) Fürstner, A. *Science* **2013**, *341*, 1357–1364. (c) Shahane, S.; Bruneau, C.; Fischmeister, C. *ChemCatChem* **2013**, *5*, 3436–3459. (d) Hoveyda, A. H. *J. Org. Chem.* **2014**, *79*, 4763–4792. (e) Hoveyda, A. H.; Khan, R. K. M.; Torker, S.; Malcolmson, S. J. in *Handbook of Metathesis, Vol. 2* (Eds.: R. H. Grubbs, D. J. O'Leary), Wiley-VCH, Weinheim, **2015**; pp. 503–562. (f) Montgomery, T. P.; Ahmed, T. S.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2017**, *56*, 11024–11036.
(3) (a) Koh, M. J.; Nguyen, T. T.; Zhang, H.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2016**, *531*, 459–465. (b) Nguyen, T. T.; Koh, M. J.; Shen, X.; Romiti, F.; Schrock, R. R.; Hoveyda, A. H. *Science* **2016**, *352*, 569–575. (c) Nguyen, T. T.; Koh, M. J.; Mann, T. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *552*, 347–354.
(4) Koh, M. J.; Nguyen, T. T.; Lam, J. K.; Torker, S.; Hyvl, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *542*, 80–85.

incompatible functional groups have to be protected first, followed by olefin metathesis transformations and necessary deprotection steps to afford the final desired product (Scheme 2.1.2). Reactions with **Ru-1**[5] can tolerate alcohol-containing substrates, but efficiency is lower with an allylic alcohol, and similar to Mo-based complexes, a carboxylic acid is not tolerated.[6] Alkenes bearing an alcohol and/or a carboxylic acid are suitable substrates for **Ru-2**[6,7]; however, unlike **Mo-1** and **Ru-1**, and similar to **Mo-2**, terminal alkenes cannot be used for Ru-dithiolate complexes **Ru-2**.[8] Although many advances have been achieved through these complexes, there are still important problems remaining to be solved, such as the efficient formation of hydroxy-containing alkenes with a versatile handle (e.g., Cl-, Br-, F_3C- and CN-groups).

Unsaturated hydrocarbons with a hydroxy or a carboxylic acid group are an important class of compounds in chemistry.[9] Many of them are renewable biomass materials (e.g., animal fats and vegetable oils), inexpensive and viable substitutes for dwindling petrochemicals[9], and biologically active organic molecules. The transformations to convert the aforementioned hydroxy-containing molecules to stereodefined alkenyl halide derivatives[3] by cross-metathesis without costly

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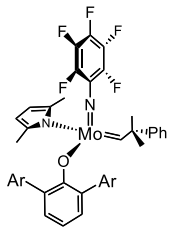
(5) (a) Keitz, B. K.; Endo, K.; Herbert, M. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 9686–9688. (b) Keitz, B. K.; Endo, K.; Patel, P. R.; Herbert, M. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **2012**, *134*, 693–699. (c) Herbert, M. B.; Marx, V. M.; Pederson, R. L.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 310–314.
(6) Koh, M. J.; Khan, R. K. M.; Torker, S.; Yu, M.; Mikus, M.; Hoveyda, A. H. *Nature* **2015**, *517*, 181–186.
(7) a) Khan, R. K. M.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2013**, *135*, 10258–10261. (b) Khan, R. K. M.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 14337–14340. (c) Koh, M. J.; Khan, R. K. M.; Torker, S.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2014**, *53*, 1968–1972. (d) Mikus, M. S.; Torker, S.; Xu, C.; Li, B.; Hoveyda, A. H. *Organometallics* **2016**, *35*, 3878–3892. (e) Mikus, M. S.; Torker, S.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 4997 –5002. (f) Ahmed, T. S.; Grubbs, R. H. *J. Am. Chem. Soc.* **2017**, *139*, 1532–1537. (g) Jung, K.; Kim, K.; Sung, J.-C.; Ahmed, T. S.; Hong, S. H.; Grubbs, R. H.; Choi, T.-L. *Macromolecules* **2018**, *51*, 4564–4571.
(8) (a) Xu, C.; Shen, X.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 10919–10928. (b) Xu, C.; Liu, Z.; Torker, S.; Shen, X.; Xu, D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 15640–15643.
(9) (a) Gunstone F. D. in *Oleochemical Manufacture and Applications, Vol. 1* (Ed. F. D. Gunstone, R. J. Hamilton), Academic Press, San Diego, **2001**. (b) Biermann, U.; Bornscheuer, U.; Meier, M. A. R.; Metzger, J. O.; Schäfer, H. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 3854–3871.

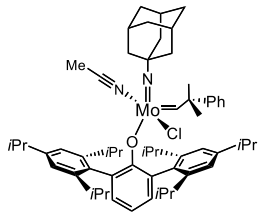
protection/deprotection sequences would be in high demand. Moreover, stereodefined alkenes with a F- or a F_3C-substituent would be especially attractive products as many studies[10] have shown such entities are vital to drug discoveries. The corresponding alkenyl Cl- or Br-moieties may be transformed into many valuable entities with stereospecific catalytic cross-coupling.[11] Therefore, as the only class of olefin metathesis catalysts being able to afford these high-value products, Mo-based complexes are needed for development of olefin metathesis of aforementioned unsaturated alcohols and carboxylic acids.

Scheme 2.1.1. Complexes Used in Kinectically Selective Olefin Metathesis



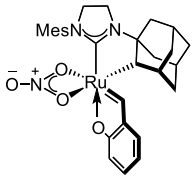
Mo-1a, Ar=Mes; **Mo-1b**, Ar=2,4,6-$Et_3C_6H_2$
Mo-1c, Ar=3,5-$(t\text{-Bu})_2C_6H_3$

Efficient with hindered and terminal alkenes,
Applicable to synthesis of *E*- and *Z*-, di- and trisubsituted alkenyl halides;
Intolerant of alcohols and carboxylic acids



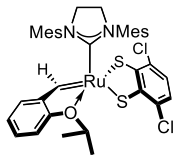
Mo-2

Efficient with hindered alkenes, but not terminal alkenes,
Applicable to synthesis of *Z*-alkenyl halides and *Z*-CF_3-substituted alkenes;
Intolerant of alcohols and carboxylic acids



Ru-1

Tolerant of alcohols, but less efficient with allylic alcohols,
Intolerant of carboxylic acids,
Inefficient with hindered alkenes,
Not applicable to synthesis of alkenyl halides or CF_3-containing alkenes



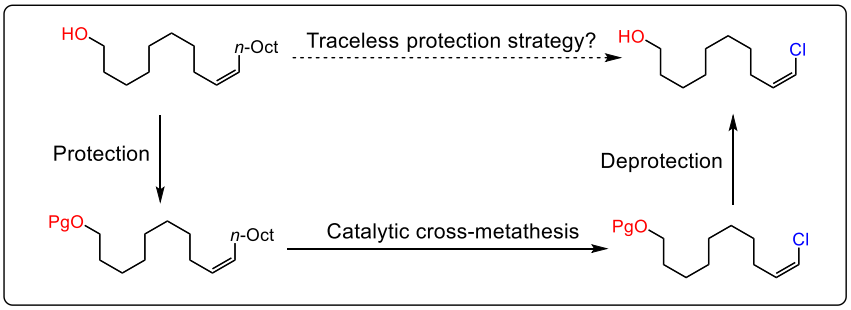
Ru-2

Tolerant of carboxylic acids,
Tolerant of allylic alcohols,
Efficient with hindered alkenes, but not terminal alkenes;
Not applicable to synthesis of alkenyl halides or CF_3-containing alkenes

(10) (a) Kolb, M.; Barth, J.; Heydt, J.-G.; Jung, M. J. *J. Med. Chem.* **1987**, *30*, 267–272. (b) Silverman, R. B.; Bichler, K. A.; Leon, A. J. *J. Am. Chem. Soc.* **1996**, *118*, 1253–1261. (c) Rosen, T. C.; Yoshida, S.; Kirk, K. L.; Haufe, G. *ChemBioChem* **2004**, *5*, 1033–1043. (d) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315–8359.
(11) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085.

Since we cannot bypass the protection/deprotection sequence for Mo-based complexes due to the rapid decomposition upon treatment with alcohols or carboxylic acids, we envisioned to develop a traceless-protection strategy to offer the following features (Scheme 2.1.2): (1) efficient and rapid protection of hydroxy-groups; (2) the *in-situ* protecting-agent is readily accessible and mild so that the olefin metathesis can still occur smoothly; (3) the transient protected substrate derivatives are not too basic nor nucleophilic (e.g., a metal alkoxide could decompose the Mo-based complexes); (4) the deprotection is simple, efficient and does not require further complicated procedures.

Scheme 2.1.2. Design of Olefin Metathesis with Hydroxy-Containing Alkenes

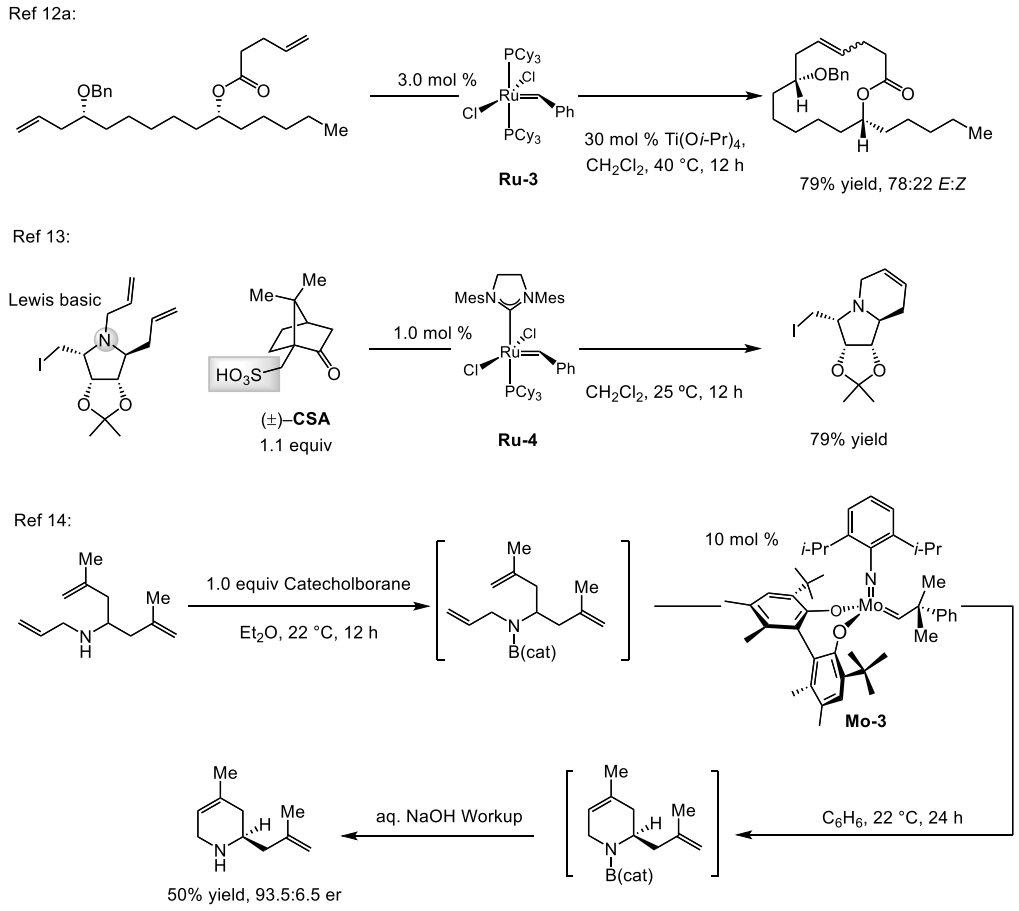


It is not completely unknown that a traceless protection can facilitate efficient olefin metathesis reactions with both Ru- and Mo-based complexes (Scheme 2.1.3). Lewis basic carbonyl-containing moieties or tertiary amines have shown negative impacts on the efficiency of olefin metathesis reactions with Ru-based catalysts. It has been formerly addressed by the addition of an appropriate additive (e.g., a Ti-based complex[12] or a Brønsted acid[13]) to bind to the Lewis basic site on the starting material. In 2005, we reported a case where the detrimental chelation of a Mo-alkylidene with an allylic and homoallylic secondary amine may be circumvented by pretreatment of the substrate with

(12) (a) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136. (b) Nevalainen, M.; Koskinen, A. M. P. *Angew. Chem. Int. Ed.* **2001**, *40*, 4060–4062.
(13) Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632–16633.

freshly distilled catecholborane with H_2 as the only side-product.[14] Subsequent treatment with aqueous NaOH release the free secondary amine product. We thus set out to identify a boron-hydride reagent that meets the criteria of being commercially available, inert to addition to alkenes (e.g., BH_3, 9-BBN or HB(cat) is not applicable), and able to react with hydroxy-group readily. These considerations led us to pinacolborane (HB(pin)), a reagent that meets our preliminary requirements and will be studied for cross-metathesis reactions.

Scheme 2.1.3. Previous Reports on Traceless Protection in Olefin Metahtesis Reactions



2.2. Traceless Protection for Alcohol-Containing Substrates with Pinacolborane

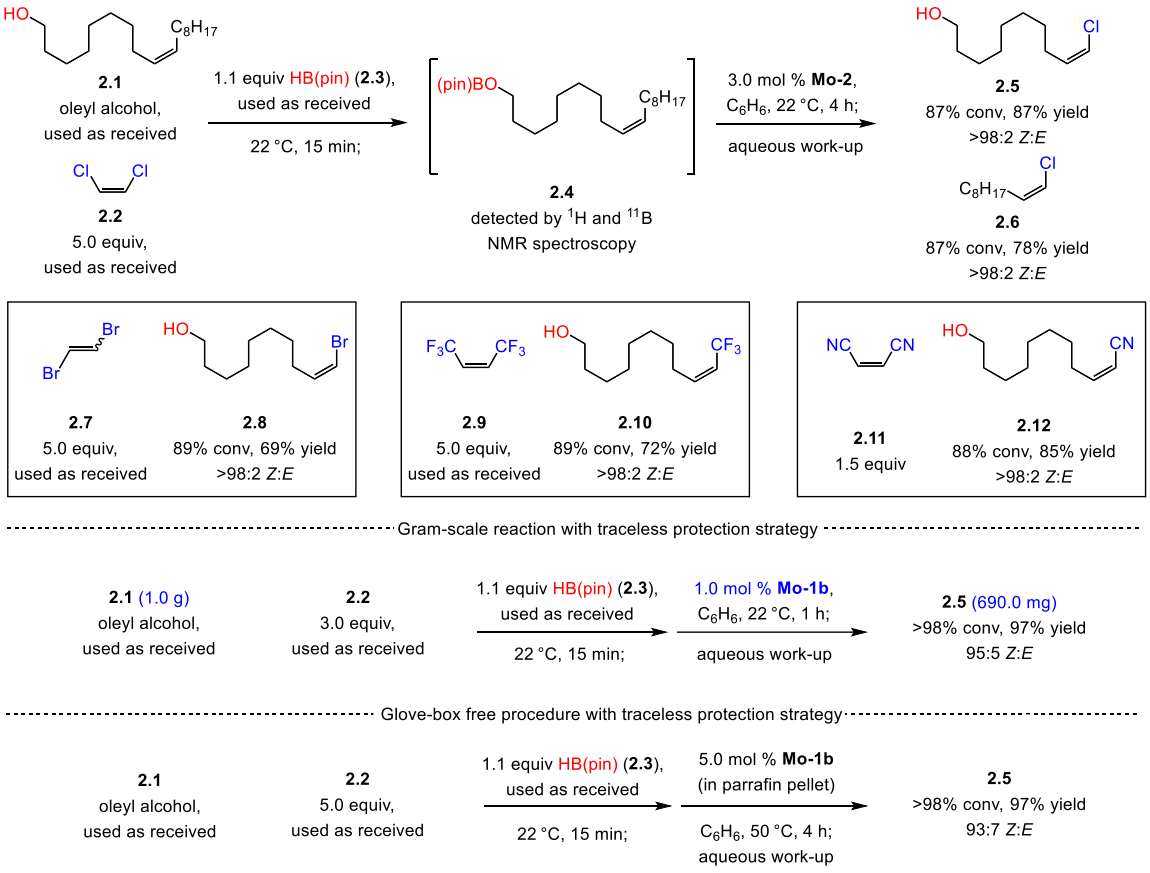
(14) Sattely, E. S.; Cortez, G. A.; Moebius, D. A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 8526–8533.

To probe the feasibility of pinacolborane reagent, we treated a mixture of oleyl alcohol **2.1** and *Z*-dichloroethene **2.2** with HB(pin) **2.3** for just 15 min to afford the corresponding borate ester **2.4** (observable by ^{1}H and ^{11}B NMR spectroscopy; Scheme 2.2.1), followed by the addition of 3.0 mol % of **Mo-2**. After the reaction, the hydrolysis happened during the routine silica gel chromatography, we isolated alcohol-containing *Z*-alkenyl chloride **2.5** and aliphatic *Z*-alkenyl chloride **2.6** in 87% and 78% yield, respectively, in stereoisomerically pure form. According to the same procedure, *Z*-alkenyl bromide **2.7** (69% yield, >98:2 *Z*:*E*), *Z*-F_3C-substituted alkene **2.10** (72% yield, >98:2 *Z*:*E*) and *Z*-alkenyl nitrile **2.12** (85% yield, >98:2 *Z*:*E*) can be synthesized efficiently.

The approach is amenable to gram-scale operations with **Mo-1b** complex in almost quantitative yield and 95:5 *Z*:*E* selectivity (Scheme 2.2.1). More importantly, the **Mo-1b** complex confined in a paraffin pellet[15] was able to catalyze the same reaction with similar efficiency and selectivity (97% yield, 93:7 *Z*:*E*), which can be performed without the requisite of a glove box (Scheme 2.2.1). As we mentioned in *2.1 Introduction*, oleyl alcohol is important renewable oil and maximizing the atom economy of the aforementioned transformation would be practical and valuable to the environment and sustainability. It is noteworthy that the oleyl alcohol, the halogen-containing reagents, and HB(pin), all commercially available, were used as received, highlighting the feasibility and practicality of the approach.

(15) Ondi, L.; Nagy, G. M.; Czirok, J. B.; Bucsai, A.; Frater, G. E. *Org. Process Res. Dev.* **2016**, *20*, 1709–1716.

Scheme 2.2.1. Traceless Protection of Oleyl Alcohol with HB(pin) with Mo-Based Complexes[a]

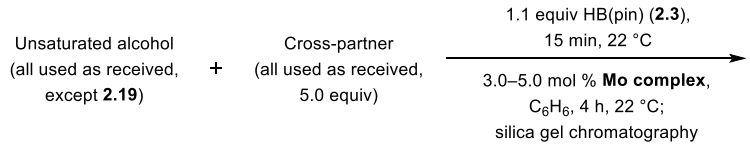


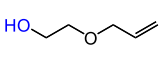
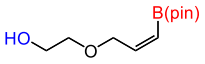
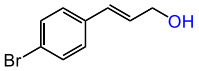
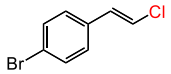
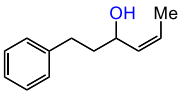
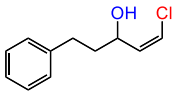
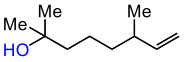
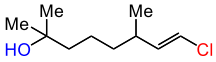
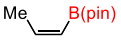
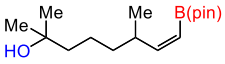
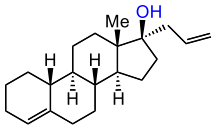
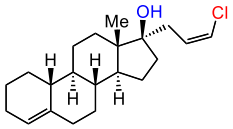
[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details.

Different unsaturated alcohols and cross-metathesis partners are suitable substrates with the assistance of the traceless protection (Scheme 2.2.2). Kinetically *Z*- or *E*-selective transformations with substrates bearing a primary aliphatic (**2.13**), a primary or secondary allylic (**2.16** and **2.19**, respectively), or a tertiary alcohol (**2.21** and **2.25**) were efficient, affording 1,2-disubstituted alkenyl boronates (**2.15** and **2.24**) or alkenyl halides (**2.18**, **2.20**, **2.22**, and **2.26**) in 59–93% yield and with high stereochemical purity (93 to >98% of one isomer). Among these representative examples, dihydromyrcenol **2.21** is another renewable biomass material and the allylestrenol **2.25** is a commercialized medicine to treat recurrent and threatened miscarriage. The ability to transform the

readily available alkenes to the corresponding versatile products with a chloro- or boron-substituent would offer the opportunity to convert the entities to a broad range of value-added derivatives through stereospecific functionalizations.

Scheme 2.2.2. Traceless Protection of Alcohol-Containing Substrates[a]



Entry	Substrates	Cross partner	Mo complex; mol %	Product	Conv%; Yield%	*Z*:*E*
1	 **2.13**	 **2.14**	**Mo-1b**; 3.0	 **2.15**	76; 64	>98:2
2	 **2.16**	 **2.17**	**Mo-1c**; 5.0	 **2.18**	>98; 59	<2:98
3	 **2.19**	 **2.2**	**Mo-2**; 5.0	 **2.20**	93; 91	>98:2
4	 **2.21** Dihydromyrcenol	 **2.17**	**Mo-1c**; 5.0	 **2.22**	97; 93	7:93
5		 **2.23**	**Mo-1b**; 5.0	 **2.24**	83; 65	>98:2
6	 **2.25** Allylestrenol	 **2.2**	**Mo-1b**; 5.0	 **2.26**	67; 61	>98:2

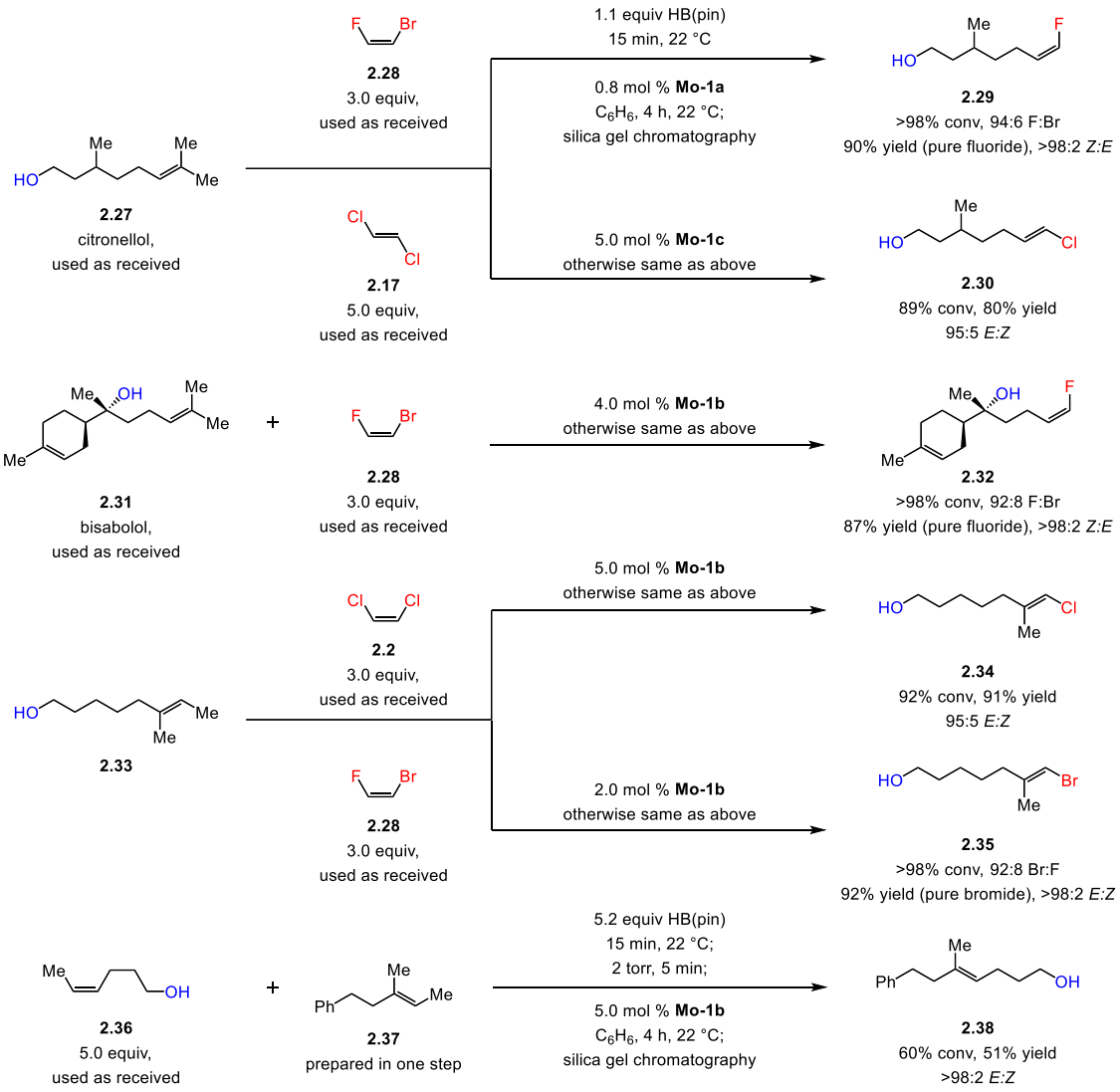
[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details.

In addition to the cross-metathesis reactions involving disubstituted alkenes, the strategy is applicable to that with more challenging trisubstituted alkenes (Scheme 2.2.3). Citronellol **2.27** was able to be converted into *Z*-alkenyl fluoride **2.29** with 94:6 fluoro:bromo selectivity, in 90% yield (pure fluoride) as pure *Z*-isomer. From the same substrate **2.27**, *E*-alkenyl chloride **2.30** was furnished in 80% yield and 95:5 *E*:*Z*

selectivity. *Z*-Alkenyl fluoride **2.32** was prepared from the natural product bisabolol **2.31** in 87% yield (pure fluoride) and with 98:2 *Z*:*E* selectivity. In light of the prevalence of compounds that contain an isoprenyl group along with a polar (e.g., hydroxy) group, the approach provides a cost-effective and stereoselective method for the synthesis of an assortment of valuable and readily functionalizable derivatives.

Traceless protection may be used in reactions that convert readily available trisubstituted alkenes into otherwise difficult-to-synthesize valuable alkenes (Scheme 2.2.3)[3c], including alkenyl chlorides (**2.30** and **2.34**), and bromide (**2.35**). More impressively, the trisubstituted olefin **2.38** bearing three different carbon-based substituents can be generated efficiently. The high yield (80–90%) and stereoisomeric purity (95 to >98% of one isomer) with which **2.29**[3c], **2.30**[3b] and **2.32**[3b] (Scheme 2.2.3) are formed is noteworthy because, generally, alkenyl halides bearing an unhindered alkyl substituent cannot be obtained efficiently from a terminal or a 1,2-disubstituted olefin. This is presumably due to the less likelihood of self-metathesis of the *gem*-dimethyl substituted substrates. Homocoupling of monosubstituted olefins and/or isomerization of the 1,2-disubstituted olefin is a complication with these less substituted alkenes, rendering fluoro:bromo selectivity for **2.29** and **2.32**, and *E*:*Z* selectivity for **2.30** lower (ca. 70:30). Details of the advantages of *gem*-dimethyl alkenes will be discussed in Chapter 4 about the stereoselective synthesis of trisubstituted F,Cl-substituted alkenes where *gem*-dimethyl alkenes are optimal substrates.

Scheme 2.2.3. Traceless Protection of Cross-Metathesis Reactions Involving Trisubstituted Alkenes[a]

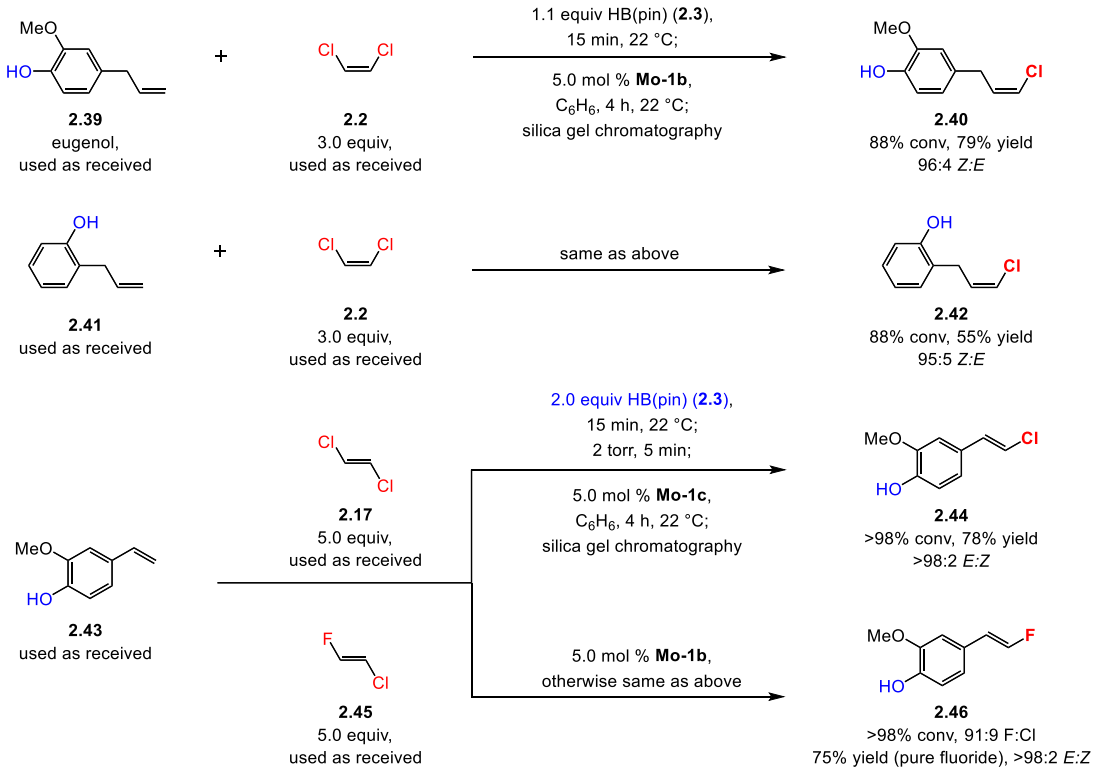


[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details.

Perhaps one of the most challenging and acidic hydroxy groups is the phenol group. We then tried to examine the *in-situ* protection method with such important moieties (Scheme 2.2.4). Commercially available eugenol **2.39** was successfully converted to the corresponding alkenyl chloride **2.40** in 79% yield with 96:4 *Z*:*E* selectivity. Although slightly less efficient due to the internal O→Mo chelation[14], *ortho*-substituted allylic phenol **2.42** was generated in 55% yield and 95:5 *Z*:*E* selectivity. When we tried to employ the same procedure for the synthesis of *E*-styrenyl halides **2.44**

and **2.46**, there was less than 5% consumption of the starting material. The low conversion might be due to reduced Lewis basicity of the phenol oxygen, leading to slower protection, a proposal that is supported by analysis of the relative rates of boronate formation between substrates **2.39** and **2.43** (see *Experimental Section* for details). We thus treated the substrate **2.43** with 2.0 equivalents of HB(pin) and observed complete protection of the phenol group after 15 min. The subsequent cross-metathesis reactions delivered **2.44** and **2.46** in 78% and 75% yield, respectively as a single isomer. With more borane present, it was necessary to subject the solution briefly to mild vacuum (5 min, 2 torr) to remove the excess HB(pin) to ensure maximum efficiency (e.g., with 2.0 equivalents of HB(pin) and without a vacuum: 40% conversion of eugenol **2.39** to **2.40**), which shows that excess HB(pin) and/or its long term exposure to a Mo-based complex can have an adverse impact (more on this in *Section 2.3*).

Scheme 2.2.4. Traceless Protection of Phenol-Containing Substrates[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details.

2.3. Traceless Protection for Carboxylic Acid-Containing Substrates with HB(trip)$_2$

After obtaining the desired products for alcohol- and phenol-containing cross-metathesis products, we thus turned to more challenging substrates containing carboxylic acids, which are also vital moieties in pharmaceuticals and natural products (Scheme 2.3.1). For oleic acid **2.47**, 2.0 equivalents of HB(pin) were needed, followed by brief mild vacuum, affording *Z*-alkenyl bromide **2.48** in 66% yield and with >98% *Z*:*E* selectivity. The need for excess borane was not surprising in light of the earlier results for more challenging phenol-containing aryl olefin substrates and the lower Lewis basicity of a carboxylic acid. What further complicated the matter for carboxylic acid substrates was the boron-containing by-products. For the control experiments, when we treated unsaturated acid **2.53** with 1.1 equivalents of HB(pin), the reaction generated multiple side-products, one

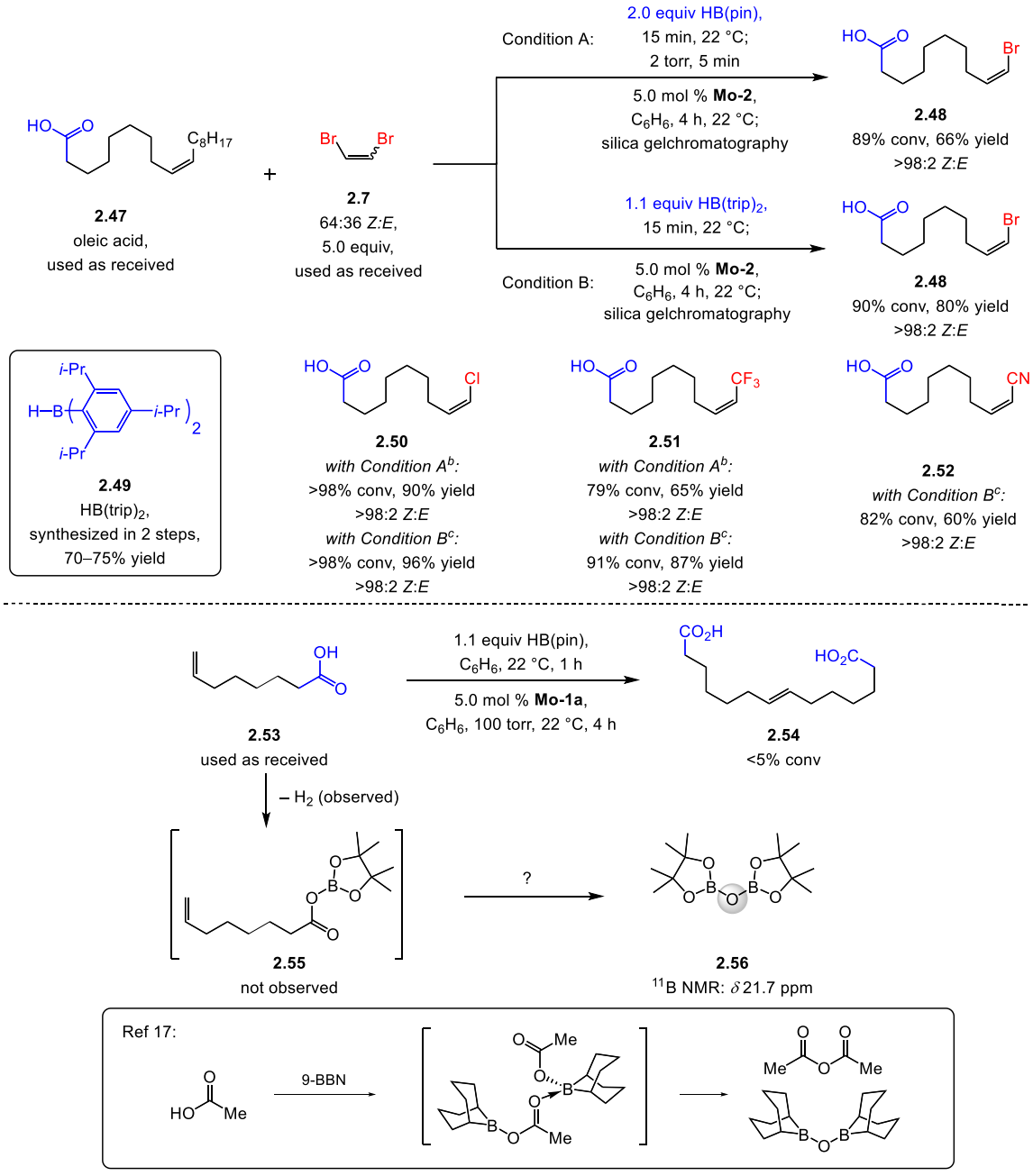
of which was confirmed to be (pin)BOB(pin) **2.56** (^{11}B NMR, δ = 21.7 ppm)[16], arising from bimolecular disproportionation of *in-situ* generated carboxyl boryl compounds **2.55** to give a carboxylic anhydride.[17] Similar observation was observed by the Brown group in 1977 when they treated the acetic acid with 9-BBN and also identified the BBN-O-BBN byproduct. The acid anhydride can chelate to the Mo-based complex and inhibit its reactivity (Scheme 2.3.1).

We thus envisioned that a new boron-hydride reagent is needed for the more challenging carboxylic acids and examined the effectiveness of $HB(trip)_2$ **2.49**, which contains two 2,4,6-triisopropyl phenyl ligands (Scheme 2.3.1). We surmised that this more sizeable alternative might be less susceptible to the aforementioned disproportionation; although, it was possible that protection step to release H_2 gas would be too slow. In the event, we prepared $HB(trip)_2$, a robust reagent that can be accessed in multi-gram quantities in two straightforward steps and 70–75% overall yield (Scheme 2.3.1). When treating the substrate and cross-metathesis partners with 1.1 equivalents of $HB(trip)_2$ under otherwise identical conditions, we were able to isolate **2.48** in 80% yield (vs. 66% with HB(pin)). There were no by-products and subjection to a mild vacuum was not necessary. The synthesis of *Z*-alkenyl chloride **2.50**, *Z*-F_3C-substituted alkene **2.51** and *Z*-alkenyl nitrile **2.52** further highlighted the scope of the transformation (Scheme 2.3.1). The smaller difference in yields for alkenyl chloride **2.50** might be attributed to the faster pace of this particular reaction, as compared to those involving less reactive (*Z*)-1,2-dibromoethene **2.7** (synthesis of **2.48**), (*Z*)-1,1,1,4,4,4-hexafluoro-2-butene **2.9** (synthesis of **2.51**) or maleonitrile **2.11** (synthesis of **2.52**), which in turn implies that as

(16) Ng, C. K.; Wu, J.; Hor, T. S. A.; Luo, H.-K. *Chem. Commun.* **2016**, *52*, 11842–11854.
(17) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1977**, *132*, 9–27.

the cross-metathesis rate is reduced, there is a stronger likelihood that the complex decomposition pathway would be competitive.

Scheme 2.3.1. Traceless Protection of Carboxylic Acids in Olefin Metathesis Reactions[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. [b]Condition A: 2.0 equiv HB(pin), 15 min, 22 °C; 2 torr, 5 min; 5.0 mol % **Mo-2**, C_6H_6, 4 h, 22 °C; silica gel chromatography. [c]Condition B: 1.1 equiv $HB(trip)_2$, 15 min, 22 °C; 5.0 mol % **Mo-2**, C_6H_6, 4 h, 22 °C; silica gel chromatography. See the experimental section for details.

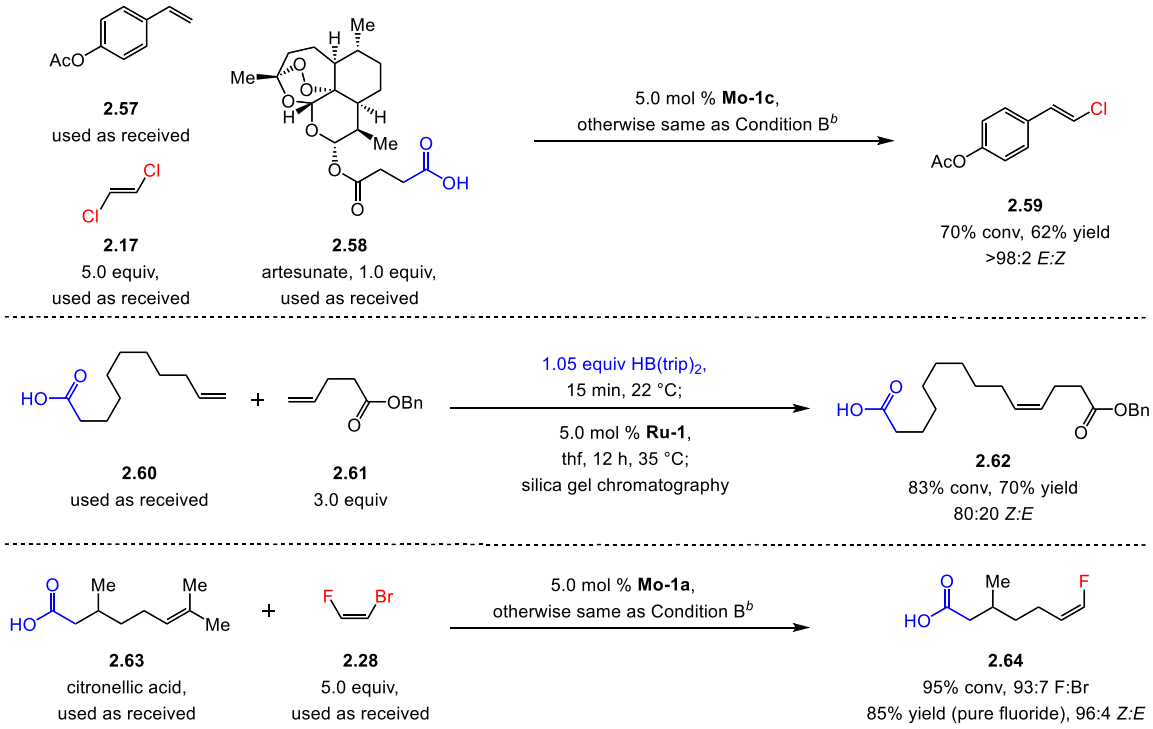
The conversion of aryl olefin **2.57** into *Z*-alkenyl chloride **2.59** in the presence of the antimalarial agent artesunate[18] **2.58** demonstrates tolerance of the approach with relatively sensitive functional groups (Scheme 2.3.2). *Z*-Selective cross-metathesis reaction with Ru-based complex **Ru-1** was also improved significantly. Without the traceless protection protocol, the carboxylic acid was not compatible with **Ru-1** complex. When treating the unsaturated carboxylic acid and ester with 1.05 equivalents of $HB(trip)_2$ and otherwise same conditions as before, we were able to secure the desired disubstituted alkene with two carbon based substituents in 70% yield and with 80:20 *Z*:*E* selectivity. Two important points merit note: (1) The intrinsic low *Z*:*E* selectivity with commercially available **Ru-1** can be addressed by the utilization of a more sterically demanding ligand as shown by Prof. Grubbs, where the same traceless protection protocol can be employed without affecting *Z*:*E* selectivity[19]; (2) this transformation is a representative case that demonstrates the utility of this traceless protection approach as if the acid needs to be protected before cross-metathesis, the siteselective deprotection of the diester could be very challenging.

Whereas citronellic acid **2.63** was converted into *Z*-alkenyl fluoride **2.64** in 85% yield and 96:4 *Z*:*E* selectivity in the presence of $HB(trip)_2$, there was <5% conversion when HB(pin) was used or when a combination of more sensitive **Mo-2** and $HB(trip)_2$ was employed. It suggests that the carboxylic acids are more challenging substrates than the corresponding alcohol derivatives, particularly when the more hindered trisubstituted alkenes were used as substrates. Productive cross-metathesis might be competing with the catalyst decomposition. It should be mentioned that after we published the report on this

(18) Luo, X.-D.; Shen, C.-C. *Med. Res. Rev.* **1987**, *7*, 29–52.
(19) Bronner, S. M.; Herbert, M. B.; Patel, P. R.; Marx, V. M.; Grubbs, R. H. *Chem. Sci.* **2014**, *5*, 4091–4098.

traceless protection method, the $HB(trip)_2$ has been commercially available and behaves in the similar manner as that was synthesized in our lab.

Scheme 2.3.2. Traceless Protection of Carboxylic Acids in More Challenging CM Reactions[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^1H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). [b]Condition B: 1.1 equiv $HB(trip)_2$, 15 min, 22 °C; 5.0 mol % **Mo-2**, C_6H_6, 4 h, 22 °C; silica gel chromatography. Experiments were run at least in triplicate. See the experimental section for details.

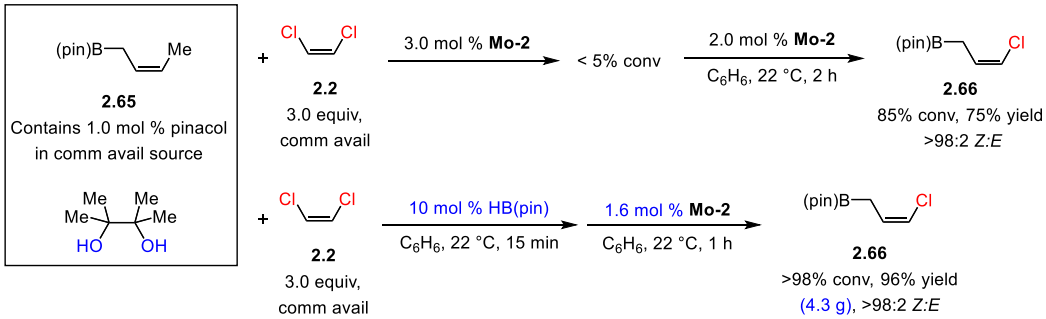
2.4. Traceless Protection for Removal of Impurities in Cross-Metathesis Reactions

We quickly realized that this traceless protection strategy may have broader application than protecting the hydroxy-containing substrates. In our group's efforts to yield *Z*-Cl-allylic B(pin)[20] reagent through cross-metathesis, the reaction required high catalyst loading (5.0 mol %). Later on, we found out that the first 3.0 mol % addition of the **Mo-2** complex was not catalyzing any metathesis reaction. Subsequent 2.0 mol % **Mo-2** complex was enough to catalyze the transformation to form the product **2.66** in 75% yield and as a single isomer. This clearly indicates that the first 3.0 mol % complex was

[20] Morrison, R. J.; van der Mei, F. W.; Romiti, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2020**, *142*, 436–447.

quenched by residual impurities, which was later found to be the trace amount of pinacol (~ 1 mol %) from the commercially available *Z*-crotyl-B(pin). Mindful of the efficient traceless protection of alcohols and carboxylic acids with boron-hydrides, we decided to employ the same strategy for the remaining pinacol impurities. When the same substrate was treated with 10 mol % HB(pin), only 1.6 mol % **Mo-2** complex was necessary to convert the *Z*-crotyl-B(pin) to the desired product **2.66** in 4.3 grams and 96% yield, as a single isomer.

Scheme 2.4.1. Traceless Protection for Removing Impurities in Cross-Metathesis Reactions[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details.

2.5. Conclusions

We have devised an efficient, practical and reliable traceless protection strategy to facilitate the cross-metathesis reactions with substrates bearing protic functional groups, including alcohols, phenols and carboxylic acids. Two boron-hydride reagents, HB(pin) and HB(trip)$_2$, have been identified to protect substrates effectively *in situ*. Many of the substrates used in the study for the traceless protection are biomass materials and the functionalization of such molecules offers the possibility of converting inexpensive chemicals to high-value compounds. Furthermore, the traceless protection strategy can also be applied to the removal of moisture and impurities, thus lowering the catalyst

loading for cross-metathesis reactions. The idea of *in-situ* protection is likely to have an immediate impact on many stereoselective chemical reactions.

2.6. Experimental Section

General

Unless otherwise noted, transformations were performed with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum line techniques. Infrared (IR) spectra were recorded on a Bruker FTIR Alpha (ATR Mode) spectrometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), or weak (w). ^1H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz), 500 (500 MHz), or 600 (600MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuterium incorporation as the internal standard ($CDCl_3$: δ 7.26 ppm, C_6D_6: δ 7.16 ppm, CD_2Cl_2: δ 5.32 ppm, CD_3OD: δ 3.31 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz), 500 (125 MHz), or 600 (150 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm, C_6D_6: δ 128.00 ppm, CD_2Cl_2: δ 5.32 ppm, CD_3OD: δ 3.31 ppm). ^{19}F NMR spectra were recorded on a Varian Unity INOVA 400 (376 MHz) spectrometer. High-resolution mass spectrometry was performed on a JEOL Accu TOF Dart (positive mode) at the Boston College Mass Spectrometry Facility. Melting points were determined using

a Thomas Hoover Uni-melt capillary melting point apparatus. Values for *E*:*Z* ratios of products were determined by ^{1}H NMR analysis of unpurified mixtures.

Solvents

Solvents (CH_2Cl_2, Et_2O, pentane, benzene and toluene) were purified under a positive pressure of dry argon gas by an Innovative Technologies purification system. Tetrahydrofuran was distilled from Na/benzophenone. Methanol was distilled over Mg. Acetone, *N*,*N*-dimethylformamide (anhydrous), 1,2-dimethoxyethane (anhydrous) and 1,4-dioxane (anhydrous) were used as received. Cross-metathesis products were purified with reagent grade solvents.

Reagents

Oleyl alcohol (Aldrich), *Z*-1,2-dichloroethene (Aldrich), HB(pin) (Oakwood), 1,2-dibromoethene (Aldrich), *Z*-1,1,1,4,4,4-hexafluoro-2-butene (Synquest), 2-allyloxyethanol (Aldrich), vinylboronic acid pinacol ester (TCI), 3-(4-bromophenyl)-2-propen-1-ol (Matrix), *E*-1,2-dichloroethene (TCI), dihydromyrcenol (Aldrich), *Z*-1-propenylboronic acid pinacol ester (Aldrich), allylestrenol (Combi-Blocks), citronellol (TCI), *Z*-1-bromo-2-fluoroethene (Synquest), bisabolol (AK Scientific, Inc.), *Z*-4-hexen-1-ol (TCI), eugenol (TCI), 2-allylphenol (Aldrich), 2-methoxy-4-vinylphenol (Combi-Blocks), *E*-1-chloro-2-fluoroethene (Synquest), oleic acid (Aldrich), citronellic acid (Aldrich), 10-undecenoic acid (Aldrich), Z-crotylboronic acid pinacol ester (Aldrich), Grubbs catalyst *Z*-selective (Aldrich), 2-bromo-1,3,5-triisopropylbenzene (Combi-Blocks), magnesium turning (Oakwood), methyl iodide (Oakwood), 4-vinylphenyl acetate (Aldrich), artesunate (TCI) were used as received.

(*E*)-6-Methyloct-6-en-1-ol (from 4-penten-1-ol (Alfa Aesar) and (*E*)-2-bromobut-2-ene (Aldrich)) and (*E*)-(3-methylpent-3-en-1-yl)benzene (from styrene (Aldrich) and (*E*)-2-bromobut-2-ene (Aldrich)) were prepared in analogy to a reported procedure[3c].

(*Z*)-1-Phenylhex-4-en-3-ol was prepared in analogy to a reported procedure[21].

Benzyl pent-4-enoate was prepared according to a reported procedure[8a].

Organometallic complexes

Mo-1a[22], **Mo-1b**[3a], **Mo-1c**[3b], and **Mo-2**[4] were prepared according to previously reported procedures. Mo complexes were manipulated under an atmosphere of N_2 in a glove box.

Bis(2,4,6-triisopropylphenyl)borane (HB(trip)$_2$, 2.49)[23]

A 150 mL two-necked round bottom flask equipped with a reflux condenser was charged with magnesium turnings (1.46 g, 60.00 mmol), iodine (10.0 mg, 0.0394 mmol) and 40 mL of anhydrous thf. The mixture was charged with 2-bromo-1,3,5-triisopropylbenzene (14.20 g, 50.00 mmol) in thf (10 mL) slowly, and the solution was heated to 70 °C for 2 h before being allowed to cool to 22 ℃. In a separate oven-dried 150 mL round bottom flask equipped with a reflux condenser was added freshly distilled BF_3•Et_2O (1.85 mL, 15.00 mmol) and Et_2O (10 mL). The mixture was allowed to cool to 0 °C, and a solution of freshly prepared 2,4,6-(*i*-Pr)$_3$phenylmagnesium bromide was slowly added with vigorous stirring. The mixture was allowed to warm to 22 ℃ and stir for 30 min, then it was heated to 70 ℃ for 3 h, after which it was allowed to cool to 22 ℃ and stir at the same temperature for 12 h. The volatiles were removed in vacuo and the residue yellow oil was extracted by pentane. Filtration of the resulting mixture and removal of the

(21) Joosten, A.; Persson, A. K. A.; Millet, R.; Johnson, M. T.; Bäckvall J.-E., *Chem. Eur. J.* **2012**, *18*, 15151–15157.
(22) Zhang, H.; Yu, E. C.; Torker, S.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 16493–16496.
(23) Pelter, A.; Smith, K.; Buss, D.; Norbury, A. *Tetrahedron Lett.* **1991**, *32*, 6239–6242.

volatiles in vacuo afforded $BF(trip)_2$ (4.91–5.24 g, 11.25–12.00 mmol, 75–80% yield) as light yellow solid.

Bis(2,4,6-triisopropylphenyl)borane ($HB(trip)_2$, 2.49): To an oven-dried 100 mL round bottom flask was added activated[23] KH (0.40 g, 10.00 mmol) and anhydrous thf (4 mL). The mixture was allowed to cool to 0 °C, after which it was charged with a solution of $BF(trip)_2$ (1.75 g, 4.00 mmol in 4 mL anhydrous thf). The mixture was allowed to warm to 22 °C and stir for 12 h. Iodomethane (0.50 mL, 8.00 mmol) was added slowly at 0 °C (vigorous methane gas release). The solution was then allowed to warm to 22 °C and stir at the same temperature for 2 h. The volatiles were removed in vacuo and the resulting yellow oil was extracted with pentane (3 x 20 mL). Filtration of the resulting mixture through a pad of celite and removal of the volatiles in vacuo afforded $HB(trip)_2$ as off-white solid (1.59 g, 3.80 mmol, 95% yield). **Melting point:** 86–88 °C. The spectral data for this compound were identical to those reported previously[23].

Cross-Metathesis Reactions

General Procedure: In a N_2-filled glove box, an oven-dried 8 mL vial equipped with a magnetic stir bar was charged with an alkene substrate and the corresponding cross partner. A borane, HB(pin) or $HB(trip)_2$, was added, resulting in H_2 evolution. Once the effervescence subsided, the solution was allowed to stir for 15 min to 1 h at 22 °C. A solution of **Mo-1a**, **Mo-1b**, **Mo-1c, Mo-2** or **Ru-1** in benzene or thf was then added and the mixture was allowed to stir for 1-12 h at 22-80 °C. The reaction was quenched by the addition of undistilled Et_2O and concentrated to dryness to afford dark or orange oil. Percent conversion was determined by ^1H NMR analysis of the unpurified mixture.

Purification was performed by silica gel chromatography or distillation under reduced pressure.

(*Z*)-10-Chlorodec-9-en-1-ol (2.5) and (*Z*)-1-chlorodec-1-ene (2.6): In a N_2-filled glove box, an oven-dried 8 mL vial equipped with a magnetic stir bar was charged with oleyl alcohol (26.8 mg, 0.100 mmol), *Z*-1,2-dichloroethene (48.5 mg, 0.500 mmol) and pinacolborane (16 μL, 0.110 mmol). Vigorous evolution of H_2 gas was observed. Once effervescence subsided, the solution was allowed to stir for 15 min at 22 °C. The resulting solution was treated with a solution of **Mo-2** (0.1 M in benzene, 30 μL, 3.0 μmol). The solution was allowed to stir for 4 h at 22 °C, after which the reaction was quenched by the addition of undistilled Et_2O. Analysis of the ^{1}H NMR spectrum of the unpurified mixture indicated 87% consumption of oleyl alcohol. The resulting red oil residue was purified by silica gel chromatography (5 → 20% EtOAc in hexanes) to afford **2.5** in >98:2 *Z:E* ratio as colorless oil (16.6 mg, 0.0870 mmol, 87% yield) and **2.6** in >98:2 *Z:E* ratio as colorless oil (13.6 mg, 0.0778 mmol, 78% yield). Spectral data for **2.5**: **IR (neat)**: 3320 (br), 2923 (s), 2852 (s), 1628 (w), 1462 (w), 1344 (w), 1306 (w), 1054 (m), 707 (m); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.01 (dd, J = 7.1, 1.8 Hz, 1H), 5.75 (qd, J = 7.1, 2.1 Hz, 1H), 3.64 (t, J = 6.4 Hz, 2H), 2.22 (q, J = 7.2 Hz, 2H), 1.56 (dd, J = 14.6, 7.6 Hz, 2H), 1.45 – 1.20 (m, 11H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 132.0, 118.0, 63.2, 32.9, 29.5, 29.5, 29.2, 28.5, 27.1, 25.9; **HRMS [M+H]$^+$** calcd for $C_{10}H_{20}OCl$: 191.1197, found: 191.1193. The spectral data of **2.6** were identical to those previously reported[24].

(24) Okuyama, T.; Takino, T.; Sato, K.; Oshima, K.; Imamura, S.; Yamataka, H.; Asano, T.; Ochiai, M. *Bull Chem. Soc. Jpn.* **1998**, *71*, 243–257.

Synthesis of 2.5 on gram-scale: In a N_2-filled glove box, an oven-dried 40 mL vial equipped with a magnetic stir bar was charged with oleyl alcohol (1.00 g, 3.72 mmol), *Z*-1,2-dichloroethene (1.08 g, 11.17 mmol) and pinacolborane (1.78 mL, 12.29 mmol). Vigorous evolution of H_2 gas was observed. Once effervescence subsided, the solution was allowed to stir for 15 min at 22 °C. The mixture was then treated with a solution of **Mo-1b** (0.1 M in benzene, 372 μL, 37.2 μmol). The mixture was allowed to stir for 1 h at 22 °C, after which the reaction was quenched by the addition of undistilled Et_2O and analysis of the ^{1}H NMR spectrum of the unpurified mixture indicated >98% consumption of oleyl alcohol. The resulting red oil was purified by silica gel chromatography (5 → 20% EtOAc in hexanes) to afford **2.5** in 95:5 *Z:E* ratio as colorless oil (690 mg, 3.62 mmol, 97% yield).

With a catalyst in a paraffin tablet: An oven-dried 5-mL Schlenk tube was charged with oleyl alcohol (26.8 mg, 0.100 mmol) and pinacolborane (16 μL, 0.110 mmol). Vigorous evolution of H_2 gas was observed. Once effervescence subsided, the solution was allowed to stir for 15 min at 22 °C. The paraffin tablet (5.0 wt% in **Mo-1b**, 92.0 mg, 0.005 mmol, 5.0 mol %) was introduced and the reaction vessel was sealed, evacuated and back-filled with N_2 three times. *Z*-1,2-Dichloroethene (37.8 μL, 0.500 mmol) and 0.2 mL toluene were added by syringe and the mixture was allowed to stir for 4 h at 50 °C. The mixture was then diluted with hexanes and the resulting yellow oil residue was purified by silica gel chromatography (100% hexanes → 10% EtOAc in hexanes) to afford **2.5** (18.5 mg, 0.097 mmol, 97% yield) in 93:7 *Z:E* ratio as colorless oil.

(*Z*)-10-Bromodec-9-en-1-ol (2.8): The same procedure as described above was used and the title compound was purified by silica gel chromatography (5% → 20% EtOAc in

hexanes) to afford **2b** in >98:2 *Z:E* ratio as colorless oil (16.3 mg, 0.693 mmol, 69% yield). **IR (neat)**: 3330 (br), 2922 (s), 2851 (m), 1620 (w), 1461 (w), 1337 (w), 1286 (w), 1054 (m), 696 (m), 662 (s); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.14 (dt, J = 7.0, 1.2 Hz, 1H), 6.08 (q, J = 7.0 Hz, 1H), 3.64 (t, J = 6.7 Hz, 2H), 2.18 (qd, J = 7.1, 1.3 Hz, 2H), 1.59 – 1.54 (m, 2H), 1.43 – 1.25 (m, 11H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 135.1, 107.7, 63.2, 32.9, 29.8, 29.5, 29.5, 29.2, 28.2, 25.9; **HRMS $[M+H]^+$** calcd for $C_{10}H_{20}OBr$: 235.0692, found: 235.0679.

(*Z*)-11,11,11-Trifluoroundec-9-en-1-ol (2.10): The same procedure as described above was used and the title compound was purified by silica gel chromatography (5% → 20% EtOAc in hexanes) to afford **2.10** in >98:2 *Z:E* ratio as colorless oil (16.2 mg, 0.722 mmol, 72% yield). **IR (neat)**: 3322 (br), 2925 (m), 2854 (m), 1668 (w), 1416 (w), 1274 (w), 1227 (w), 1117 (s), 702 (w); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 5.98 (dt, J = 11.6, 7.9 Hz, 1H), 5.57 (dqt, J = 12.0, 8.6, 1.7 Hz, 1H), 3.64 (t, J = 6.6 Hz, 2H), 2.29 (dtt, J = 9.9, 4.6, 2.2 Hz, 2H), 1.56 (p, J = 6.8 Hz, 2H), 1.47 – 1.38 (m, 1H), 1.37 – 1.25 (m, 10H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 143.3 (d, J = 5.4 Hz), 123.5 (q, J = 271.7 Hz), 118.4 (q, J = 33.2 Hz), 63.2, 32.9, 29.4, 29.4, 29.1, 29.0, 28.5, 25.8; **^{19}F NMR (376 MHz, $CDCl_3$)**: δ −58.1 (dt, J = 9.2, 2.7 Hz); **HRMS $[M+NH^4]^+$** calcd for $C_{11}H_{23}NOF_3$: 242.1726, found: 242.1727.

(*Z*)-11-Hydroxyundec-2-enenitrile (2.12): The same procedure as described above was used and the title compound was purified by silica gel chromatography (30% EtOAc in hexanes) to afford a 18.0 mg mixture of inseparable maleonitrile (2.5 mg, 0.0320 mmol, 32% yield) and **2.12** in >98:2 *Z:E* ratio (15.5 mg, 0.0854 mmol, 85% yield) as colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.5 (dt, J = 10.9, 7.7 Hz, 1H), 5.3 (dt, J = 10.9, 1.3

Hz. 1H), 3.6 (t, *J* = 6.6 Hz, 2H), 2.4 (qd, *J* = 7.6, 1.4 Hz, 2H), 1.6–1.5 (m, 2H), 1.4 – 1.3 (m, 2H), 1.4 –1.2 (m, 9H); maleonitrile: *δ* 6.2 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** *δ* 155.4, 116.2, 99.6, 63.1, 32.8, 32.0, 29.3, 29.3, 29.0, 28.3, 25.8; maleonitrile: *δ* 118.4; pinacol: *δ* 25.0; **HRMS [M+H]$^+$** $C_{11}H_{20}NO$ calcd 182.1539, found 182.1533.

(*Z*)-2-((3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)oxy)ethan-1-ol (2.15): The same procedure as described above was used and the title compound was purified by silica gel chromatography (10% → 25% EtOAc in hexanes) to afford **2.15** in >98:2 *Z:E* ratio as colorless oil (22.0 mg, 0.0964 mmol, 64% yield). **IR (neat)**: 3435 (br), 2878 (m), 2931 (w), 2874 (w), 1632 (m), 1421 (m), 1372 (m), 1322 (m), 1259 (s), 1143 (s), 1111 (s), 967 (m), 845 (s), 741 (m); **^{1}H NMR (400 MHz, CD_3OD)**: δ 6.64 – 6.37 (m, 1H), 5.46 (dt, *J* = 13.9, 1.6 Hz, 1H), 4.33 (dd, *J* = 6.2, 1.6 Hz, 2H), 3.74 – 3.60 (m, 2H), 3.60 – 3.48 (m, 2H), 1.27 (s, 12H); **^{13}C NMR (100 MHz, CD_3OD)**: δ 151.4, 84.6, 75.8, 72.6, 71.3, 62.1, 25.2; **HRMS [M+H]$^+$** calcd for $C_{11}H_{22}BO_4$: 229.1613, found: 229.1614.

(*E*)-1-Bromo-4-(2-chlorovinyl)benzene (2.18): The same procedure as described above was used and the title compound was purified by silica gel chromatography (100% hexanes) to afford **2.18** in >98:2 *E:Z* ratio as an off-white solid (12.8 mg, 0.0589 mmol, 59% yield). The spectral data of **2.18** were identical to those previously reported[25].

(*Z*)-1-Chloro-5-phenylpent-1-en-3-ol (2.20): The same procedure as described above was used and the title compound was purified by silica gel chromatography (2% →10% EtOAc in hexanes) to afford **2.20** in >98:2 *Z:E* ratio as colorless oil (93% weight of chloroalkene accounting for the mass of starting material, 19.2 mg, 0.0908 mmol, 91% yield). **IR (neat)**: 3326 (br), 3014 (w), 2921 (w), 1627 (w), 1494 (w), 1452 (w), 1298 (w), 1048 (m), 1029 (m), 920 (w), 720 (m), 697 (s), 616 (w); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ

(25) Bull, J. A.; Mousseau, J. J.; Charette, A. B. *Org. Lett.* **2008**, *10*, 5485–5488.

7.29 (t, *J* = 7.6 Hz, 2H), 7.25 – 7.16 (m, 3H), 6.13 (dd, *J* = 7.3, 1.2 Hz, 1H), 5.87 (dd, *J* = 8.1, 7.2 Hz, 1H), 4.73 (td, *J* = 7.7, 7.2, 5.5 Hz, 1H), 2.78 (ddd, *J* = 13.8, 10.1, 5.8 Hz, 1H), 2.70 (ddd, *J* = 14.0, 9.9, 6.4 Hz, 1H), 1.97 (dddd, *J* = 13.4, 9.9, 7.5, 5.8 Hz, 1H), 1.87 (ddt, *J* = 13.6, 10.0, 6.0 Hz, 1H), 1.76 (d, *J* = 3.3 Hz, 1H); **^{13}C NMR (125 MHz, CDCl$_3$)**: δ 141.7, 134.5, 128.6, 128.6, 126.1, 119.5, 67.4, 38.0, 31.6; **HRMS [M+H-H$_2$O]$^+$** calcd for $C_{11}H_{12}Cl$: 179.0622, found: 179.0620.

(*E*)-8-Chloro-2,6-dimethyloct-7-en-2-ol (2.22): The same procedure as described above was used and the title compound was purified by silica gel chromatography (2% → 10% EtOAc in hexanes) to afford **2.22** in 93:7 *E:Z* ratio as colorless oil (17.8 mg, 0.0933 mmol, 93% yield). **IR (neat)**: 3372 (br), 2963 (m), 2931 (m), 2874 (w), 1632 (w), 1460 (w), 1375 (m), 1149 (w), 935 (s), 908 (w), 763 (m); **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 5.92 (d, *J* = 13.2 Hz, 1H), 5.78 (dd, *J* = 13.3, 8.5 Hz, 1H), 2.20 (m, *J* = 6.7 Hz, 2H), 1.47 – 1.39 (m, 2H), 1.38 – 1.27 (m, 4H), 1.21 (s, 6H), 1.01 (d, *J* = 6.8 Hz, 3H), alcohol *OH* proton for **2.22** is not observed; **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 139.6, 116.0, 71.1, 44.0, 37.2, 36.1, 29.5, 22.1, 20.4; **HRMS [M+H-H$_2$O]$^+$** calcd for $C_{10}H_{18}Cl$: 173.1092, found: 173.1084.

(*Z*)-2,6-Dimethyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-7-en-2-ol (2.24): The same procedure as described above was used and the title compound was purified by silica gel chromatography (5% → 25% EtOAc in hexanes) to afford **2.24** in >98:2 *Z:E* ratio as colorless oil (18.4 mg, 0.0652 mmol, 65% yield). **IR (neat)**: 3383 (br), 2974 (m), 2934 (m), 1626 (m), 1420 (m), 1370 (m), 1258 (s), 1143 (s), 968 (m), 778 (m); **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 6.13 (dd, *J* = 13.5, 9.9 Hz, 1H), 5.26 (dd, *J* = 13.5, 0.5 Hz, 1H), 2.97 – 2.84 (m, 1H), 1.54 − 1.21 (m, 18H), 1.18 (d, *J* = 2.7 Hz, 6H), 0.95 (d, *J* = 6.6 Hz,

3H), alcohol *OH* proton for **2.24** is not observed; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 160.9, 82.9, 71.1, 44.0, 37.6, 36.1, 29.5, 29.2, 25.0, 25.0, 22.1, 21.4; **HRMS [M+H]$^+$** calcd for $C_{16}H_{32}BO_3$: 282.2448, found: 282.2435.

(8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-((*Z*)-3-Chloroallyl)-13-methyl-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-ol (2.26): The same procedure as described above was used and the title compound was purified by silica gel chromatography (2% → 20% EtOAc in hexanes) to afford **2.26** in >98:2 *Z:E* ratio as colorless oil (20.4 mg, 0.0609 mmol, 61% yield). **IR (neat)**: 3436 (br), 2919 (s), 2850 (m), 1625 (w), 1434 (w), 1378 (w), 1335 (w), 1298 (w), 1175 (w), 1107 (w), 992 (m), 896 (w), 806 (w), 695 (m), 675 (w), 594 (w); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.18 (dt, *J* = 7.1, 1.6 Hz, 1H), 6.02 (td, *J* = 7.6, 5.8 Hz, 1H), 5.39 (s, 1H), 2.48 (ddd, *J* = 15.0, 8.0, 1.4 Hz, 1H), 2.35 (dd, *J* = 15.0, 5.6 Hz, 1H), 2.21 (dt, *J* = 13.5, 3.1 Hz, 1H), 2.06 – 1.82 (m, 6H), 1.81 – 1.65 (m, 2H), 1.62 – 1.50 (m, 2H), 1.44 – 1.05 (m, 10H), 0.92 (s, 3H), 0.90 – 0.82 (m, 1H), 0.67 (qd, *J* = 13.6, 11.9, 4.2 Hz, 1H); **^{13}C NMR (125 MHz, C_6D_6)**: δ 140.3, 129.4, 120.2, 119.7, 82.8, 50.1, 50.0, 46.8, 42.2, 42.2, 35.9, 35.7, 35.6, 32.1, 31.9, 29.1, 26.2, 25.9, 23.8, 22.5, 14.4; **HRMS [M+H-H_2O]$^+$** calcd for $C_{21}H_{30}OCl$: 317.2031, found: 317.2030.

(*Z*)-7-Fluoro-3-methylhept-6-en-1-ol (2.29): The same procedure as described above was used and the title compound was purified by silica gel chromatography (5% → 20% EtOAc in hexanes) to afford **2.29** in >98:2 *Z:E* ratio as colorless oil (94% weight of fluoroalkene accounting for the mass of bromoalkene, 27.9 mg, 0.179 mmol, 90% yield). **IR (neat)**: 3330 (br), 2955 (m), 2922 (s), 2872 (w), 1671 (s), 1457 (m), 1378 (s), 1048 (s), 960 (s), 751 (s); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.42 (ddt, *J* = 86.0, 4.7, 1.5 Hz, 1H),

4.69 (dtd, *J* = 43.4, 7.6, 4.7 Hz, 1H), 3.75 – 3.59 (m, 2H), 2.22 – 2.02 (m, 2H), 1.68 – 1.53 (m, 2H), 1.44 – 1.32 (m, 2H), 1.22 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 147.7 (d, *J* = 255.8 Hz), 111.1 (d, *J* = 5.4 Hz), 61.1, 39.8, 36.6 (d, *J* = 1.9 Hz), 29.1, 20.3 (d, *J* = 5.0 Hz), 19.4; **^{19}F NMR (376 MHz, CDCl$_3$)**: *δ* −131.3 (ddt, *J* = 85.9, 43.4, 1.7 Hz); **HRMS [M+H]$^+$** calcd for $C_8H_{16}FO$: 147.1185, found: 147.1190.

(*E*)-7-Chloro-3-methylhept-6-en-1-ol (2.30): The same procedure as described above was used and the title compound was purified by silica gel chromatography (2% → 10% EtOAc in hexanes) to afford **2.30** in 95:5 *E:Z* ratio as colorless oil (13.0 mg, 0.0799 mmol, 80% yield). **IR (neat)**: 3332 (br), 2953 (m), 2923 (s), 2870 (m), 1636 (w), 1457 (w), 1378 (w), 1057 (s), 1009 (w), 929 (s), 809 (m), 744 (w); **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 5.98 – 5.83 (m, 2H), 3.68 (d, *J* = 7.1 Hz, 2H), 2.17 – 1.98 (m, 2H), 1.65 – 1.55 (m, 2H), 1.48 – 1.34 (m, 2H), 1.30 – 1.18 (m, 2H), 0.90 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 134.1, 116.9, 61.1, 39.8, 36.3, 29.1, 28.6, 19.4; **HRMS [M+H-H$_2$O]$^+$** calcd for $C_8H_{14}Cl$: 145.0779, found: 145.0780.

(*Z*)-6-Fluoro-2-((*R*)-4-methylcyclohex-3-en-1-yl)hex-5-en-2-ol (2.32): The same procedure as described above was used and the title compound was purified by silica gel chromatography (2% → 5% EtOAc in hexanes) to afford **2.32** in 98:2 *Z:E* ratio as colorless oil (90% weight of fluoroalkene accounting for the mass of bromoalkene, 20.6 mg, 0.0873 mmol, 87% yield). **IR (neat)**: 3435 (br), 3007 (m), 2959 (s), 1670 (s), 1637 (m), 1376 (s), 1240 (w), 1103 (s), 1018 (w), 962 (s), 916 (s), 800 (w), 750 (s), 431(w); **^{1}H NMR (500 MHz, CDCl$_3$)**: δ 6.58 – 6.33 (m, 1H), 5.46 – 5.34 (m, 1H), 4.89 – 4.65 (m, 1H), 2.25 – 2.16 (m, 2H), 2.08 – 1.94 (m, 3H), 1.93 – 1.85 (m, 1H), 1.81 (q, *J* = 14.7, 12.8 Hz, 1H), 1.65 (s, 3H), 1.56 (ddq, *J* = 17.6, 8.2, 5.5, 4.0 Hz, 3H), 1.34 – 1.21 (m, 1H),

1.14 (dd, *J* = 14.8, 1.2 Hz, 3H), alcohol *OH* proton for **2.32** is not observed; **^{13}C NMR (125 MHz, $CDCl_3$)**: Fluroalkene: δ 147.8 (dd, *J* = 256.2, 2.4 Hz), 134.2 (d, *J* = 32.3 Hz), 120.7 (d, *J* = 22.9 Hz), 111.3 (dd, *J* = 5.2, 2.6 Hz), 74.3, 43.4 (d, *J* = 49.7 Hz), 39.4 (dd, *J* = 98.2, 1.8 Hz), 31.2 (d, *J* = 4.2 Hz), 26.6 (d, *J* = 101.4 Hz), 24.0 (d, *J* = 4.7 Hz), 23.5 (d, *J* = 2.7 Hz), 23.3, 17.2 (dd, *J* = 29.1, 5.3 Hz). Bromoalkene (resolved peaks only): δ 135.1, 108.0; **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −130.9 (ddd, *J* = 85.6, 43.5, 8.0 Hz); **HRMS $[M+H-H_2O]^+$** calcd for $C_{13}H_{20}F$: 195.1544, found: 195.1550.

(*E*)-7-Chloro-6-methylhept-6-en-1-ol (2.34): The same procedure as described above was used and the title compound was purified by silica gel chromatography (5% → 20% EtOAc in hexanes) to afford **2.34** in 95:5 *E:Z* ratio as colorless oil (14.8 mg, 0.0909 mmol, 91% yield). **IR (neat)**: 3326 (br), 2929 (s), 2856 (m), 1637 (w), 1459 (w), 1377 (w), 1308 (w), 1180 (w), 1071 (w), 1051 (m), 1010 (w), 773 (m), 730 (w); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 5.79 (d, *J* = 1.4 Hz, 1H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.07 (td, *J* = 7.4, 1.2 Hz, 2H), 1.76 (d, *J* = 1.4 Hz, 3H), 1.64 – 1.53 (m, 2H), 1.52 – 1.40 (m, 2H), 1.40 – 1.29 (m, 2H), alcohol *OH* proton for **2.34** is not observed; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 138.8, 112.0, 63.0, 37.2, 32.7, 27.4, 25.4, 16.5; **HRMS $[M+H]^+$** calcd for $C_8H_{16}OCl$: 163.0884, found: 163.0880.

(*E*)-7-Bromo-6-methylhept-6-en-1-ol (2.35): The same procedure as described above was used and the title compound was purified by silica gel chromatography (5% → 20% EtOAc in hexanes) to afford **2.35** in >98:2 *E:Z* ratio as colorless oil (19.0 mg, 0.0917 mmol, 92% yield). **IR (neat)**: 3325 (br), 2928 (s), 2855 (m), 1630 (w), 1458 (w), 1376 (w), 1282 (w), 1160 (w), 1071 (m), 1050 (s), 1010 (w), 770 (m), 710 (s), 558 (w); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 5.89 (q, *J* = 1.3 Hz, 1H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.17 –

2.08 (m, 2H), 1.78 (d, *J* = 1.2 Hz, 3H), 1.57 (dq, *J* = 8.0, 6.7 Hz, 2H), 1.51 – 1.41 (m, 2H), 1.38 – 1.29 (m, 2H) , alcohol *OH* proton for **15b** is not observed; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 141.8, 101.2, 63.0, 38.4, 32.7, 27.4, 25.4, 19.1; **HRMS $[M+H]^+$** calcd for $C_8H_{16}OBr$: 207.0379, found: 207.0373.

(*E*)-5-Methyl-7-phenylhept-4-en-1-ol (2.38): The same procedure as described above was used and the title compound was purified by silica gel chromatography (2% → 10% EtOAc in hexanes) to afford **2.38** in >98:2 *E:Z* ratio as colorless oil (10.4 mg, 0.0509 mmol, 51% yield). **IR (neat)**: 3320 (br), 2927 (m), 2854 (w), 1601 (w), 1493 (w), 1452 (m), 1381 (w), 1054 (m), 1030 (w), 743 (w), 697 (s), 517 (w); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.31 – 7.25 (m, 2H), 7.18 (dd, *J* = 7.6, 5.8 Hz, 3H), 5.14 (t, *J* = 7.3 Hz, 1H), 3.58 (t, *J* = 6.5 Hz, 2H), 2.71 (dd, *J* = 9.3, 6.8 Hz, 2H), 2.29 (t, *J* = 8.1 Hz, 2H), 2.07 (q, *J* = 7.3 Hz, 2H), 1.67 (s, 3H), 1.58 (p, *J* = 6.6 Hz, 2H), alcohol *OH* proton for **2.38** is not observed; **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 142.5, 135.3, 128.5, 128.4, 125.8, 124.5, 62.8, 41.7, 34.8, 32.8, 24.4, 16.2; **HRMS $[M+H]^+$** calcd for $C_{14}H_{21}O$: 205.1587, found: 205.1580.

(*Z*)-4-(3-Chloroallyl)-2-methoxyphenol (2.40): The same procedure as described above was used and the title compound was purified by silica gel chromatography (2% → 10% EtOAc in hexanes) to afford **2.40** in 96:4 *Z:E* ratio as colorless oil (15.6 mg, 0.0785 mmol, 79% yield). **IR (neat)**: 3516 (br), 2934 (w), 2842 (w), 1606 (w), 1510 (s), 1450 (w), 1430 (m), 1366 (w), 1264 (s), 1231 (s), 1203 (m), 1147 (m), 1119 (m), 1031 (m), 850 (w), 816 (m), 754 (s), 690 (m), 556 (w); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.85 (d, *J* = 8.5 Hz, 1H), 6.71 (dt, *J* = 4.0, 2.0 Hz, 2H), 6.13 (dt, *J* = 7.0, 1.6 Hz, 1H), 5.93 (q, *J* = 7.2 Hz, 1H), 5.49 (s, 1H), 3.88 (s, 3H), 3.51 (dd, *J* = 7.3, 1.5 Hz, 2H); **^{13}C NMR (100 MHz,**

$CDCl_3$): δ 146.5, 144.1, 130.9, 130.7, 121.0, 118.5, 114.3, 110.9, 55.9, 32.9; **HRMS [M+H]$^+$** calcd for $C_{10}H_{12}O_2Cl$: 199.0520, found: 199.0512.

(*Z*)-2-(3-Chloroallyl)phenol (2.42): The same procedure as described above was used and the title compound was purified by silica gel chromatography (2% → 10% EtOAc in hexanes) to afford **2.42** in 95:5 *Z:E* ratio as colorless oil (9.2 mg, 0.0546 mmol, 55% yield). **IR (neat)**: 3530 (br), 2921 (w), 1627 (w), 1590 (w), 1500 (w), 1454 (m), 1334 (w), 1257 (w), 1204 (w), 1231 (s), 1167 (w), 1092 (w), 1041 (m), 843 (m), 749 (s), 701 (m); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.14 (qd, *J* = 7.7, 1.7 Hz, 2H), 6.89 (td, *J* = 7.5, 1.2 Hz, 1H), 6.79 (dd, *J* = 7.9, 1.2 Hz, 1H), 6.16 (dt, *J* = 7.0, 1.6 Hz, 1H), 5.96 (q, *J* = 7.2 Hz, 1H), 4.77 (s, 1H), 3.58 (dd, *J* = 7.3, 1.6 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 153.8, 130.4, 129.6, 128.1, 124.9, 121.2, 119.0, 115.6, 28.3; **HRMS [M+H]$^+$** calcd for $C_9H_{10}OCl$: 169.0415, found: 169.0406.

(*E*)-4-(2-Chlorovinyl)-2-methoxyphenol (2.44): The same procedure as described above was used and the title compound was purified by silica gel chromatography (2% → 10% EtOAc in hexanes) to afford **2.44** in >98:2 *E:Z* ratio as colorless oil (14.4 mg, 0.0779 mmol, 78% yield). **IR (neat)**: 3503 (br), 3071 (w), 2921 (w), 2848 (w), 1588 (w), 1510 (s), 1462 (w), 1425 (w), 1369 (w), 1271 (s), 1213 (m), 1154 (m), 1121 (w), 1031 (m), 928 (w), 836 (w), 783 (m), 738 (w), 572 (w); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 6.87 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.84 – 6.80 (d, *J* = 1.8 Hz, 1H), 6.79 (d, *J* = 1.8 Hz, 1H), 6.75 (dd, *J* = 13.6, 1.6 Hz, 1H), 6.49 (dd, *J* = 13.5, 1.7 Hz, 1H), 5.64 (d, *J* = 1.6 Hz, 1H), 3.90 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 146.8, 146.1, 133.2, 127.6, 120.1, 116.5, 114.8, 108.3, 56.1; **HRMS [M+H]$^+$** calcd for $C_9H_{10}O_2Cl$: 185.0364, found: 185.0357.

(*E*)-4-(2-Fluorovinyl)-2-methoxyphenol (2.46): The same procedure as described above was used and the title compound was purified by silica gel chromatography (2% → 10% EtOAc in hexanes) to afford **2.46** in >98:2 *E:Z* ratio as colorless oil (90% weight of fluoroalkene accounting for the mass of chloroalkene, 14.0 mg, 0.0749 mmol, 75% yield). **IR (neat)**: 3514 (br), 2937 (w), 2845 (w), 1659 (w), 1595 (w), 1513 (s), 1463 (w), 1424 (w), 1369 (w), 1257 (s), 1213 (m), 1206 (w), 1185 (w), 1158 (m), 1122 (m), 1082 (s), 1030 (m), 910 (m), 803 (w), 767 (w), 594 (w); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.09 (ddd, J = 83.7, 11.3, 1.2 Hz, 1H), 6.89 – 6.84 (m, 1H), 6.77 (dd, J = 8.0, 1.9 Hz, 1H), 6.73 (d, J = 2.0 Hz, 1H), 6.34 (dd, J = 19.5, 11.3 Hz, 1H), 5.59 (d, J = 1.2 Hz, 1H), 3.90 (d, J = 1.3 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)**: Fluroalkene: δ 149.1 (d, J = 256.8 Hz), 146.8, 145.4 (d, J = 1.9 Hz), 124.9 (d, J = 11.6 Hz), 119.7 (d, J = 3.3 Hz), 114.9, 113.9 (d, J = 16.2 Hz), 108.6 (d, J = 2.6 Hz), 56.1. Chloroalkene (resolved peaks only): δ 133.2, 120.1, 116.5, 114.8, 108.3; **HRMS [M+H]$^+$** calcd for $C_9H_{10}FO_2$: 169.0659, found: 169.0655.

(*Z*)-10-Bromodec-9-enoic acid (2.48) with HB(pin): The same procedure as described above was used and the title compound was purified by silica gel chromatography (5% → 10% EtOAc in hexanes) to afford **2.48** in >98:2 *Z:E* ratio as colorless oil (16.4 mg, 0.0658 mmol, 66% yield). **IR (neat)**: 2924 (m), 2853 (w), 1705 (s), 1620 (w), 1410 (w), 934 (w), 698 (w), 668 (w); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.14 (d, J = 7.1 Hz, 1H), 6.08 (q, J = 6.9 Hz, 1H), 2.35 (t, J = 7.5 Hz, 2H), 2.19 (q, J = 7.1 Hz, 2H), 1.64 (t, J = 7.2 Hz, 2H), 1.41 (q, J = 6.7 Hz, 2H), 1.33 (d, J = 3.9 Hz, 6H), carboxylic acid *OH* proton for **2.48** was not observed; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 179.4, 135.1, 107.8, 34.0, 29.8,

29.1, 29.1, 29.0, 28.2, 24.8; **HRMS [M+H]$^+$** calcd for $C_{10}H_{18}O_2Br$: 249.0485, found: 249.0484.

(*Z*)-10-Bromodec-9-enoic acid (2.48) with HB(trip)$_2$: The same procedure as described above was used and the title compound was purified by silica gel chromatography (5% → 20% EtOAc in hexanes) to afford **2.48** in >98:2 *Z:E* ratio as colorless oil (19.9 mg, 0.0799 mmol, 80% yield).

(*Z*)-10-Chlorodec-9-enoic acid (2.50) with HB(pin): The same procedure as described above was used and the title compound was purified by silica gel chromatography (5% → 20% EtOAc in hexanes) to afford **2.50** in >98:2 *Z:E* ratio as colorless oil (18.4 mg, 0.0899 mmol, 90% yield). **IR (neat)**: 2922 (m), 2850 (w), 1707 (s), 1622 (w), 1415 (w), 937 (w), 695 (w), 671 (w); **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 11.55 (br, 1H), 6.05 (dt, *J* = 7.0, 1.6 Hz, 1H), 5.74 (q, *J* = 7.0 Hz, 1H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.21 (qd, *J* = 7.2, 1.6 Hz, 2H), 1.63 (p, *J* = 7.3 Hz, 2H), 1.5 – 1.2 (m, 8H); **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 179.4, 135.1, 107.8, 34.0, 29.8, 29.1, 29.1, 29.0, 28.2, 24.8; **HRMS [M+H]$^+$** calcd for $C_{10}H_{18}O_2Cl$: 205.0990, found: 205.0979.

(*Z*)-10-Chlorodec-9-enoic acid (2.50) with HB(trip)$_2$: The same procedure as described above was used and the title compound was purified by silica gel chromatography (5% → 20% EtOAc in hexanes) to afford **2.50** in >98:2 *Z:E* ratio as colorless oil (19.6 mg, 0.0958 mmol, 96% yield).

(*Z*)-11,11,11-Trifluoroundec-9-enoic acid (2.51) with HB(pin): The same procedure as described above was used and the title compound was purified by silica gel chromatography (5% → 20% EtOAc in hexanes) to afford **2.51** in >98:2 *Z:E* ratio as colorless oil (15.6 mg, 0.0655 mmol, 66% yield). **IR (neat)**: 2925 (m), 2855 (w), 1707

(m), 1668 (w), 1415 (w), 1275(w), 1235 (w), 1117 (s), 1091 (m), 936 (w), 703 (w); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 11.02 (s, 1H), 5.97 (dt, *J* = 11.6, 7.9 Hz, 1H), 5.58 (dq, *J* = 10.7, 8.6 Hz, 1H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.29 (qt, *J* = 7.6, 2.1 Hz, 2H), 1.64 (p, *J* = 7.3 Hz, 2H), 1.42 (p, *J* = 7.0 Hz, 2H), 1.37 – 1.21 (m, 8H); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 179.7, 143.2 (d, *J* = 5.3 Hz), 123.5 (q, *J* = 271.6 Hz), 118.5 (q, *J* = 33.4 Hz), 34.1, 29.1, 29.1, 29.0, 28.9, 28.4, 24.8; **^{19}F NMR (376 MHz, $CDCl_3$)**: δ −58.1 (dt, J = 9.0, 2.2 Hz); **HRMS [M+H]$^+$** calcd for $C_{11}H_{18}O_2F_3$: 239.1253, found: 239.1250.

(*Z*)-11,11,11-Trifluoroundec-9-enoic acid (2.51) with HB(trip)$_2$: The same procedure as described above was used and the title compound was purified by silica gel chromatography (5% → 20% EtOAc in hexanes) to afford **2.51** in >98:2 *Z:E* ratio as colorless oil (20.8 mg, 0.0873 mmol, 87% yield).

(*Z*)-10-Cyanodec-9-enoic acid (2.52) with HB(trip)$_2$: The same procedure as described above was used and the title compound was purified by silica gel chromatography (20% → 40% EtOAc in hexanes) to afford a 12.1 mg mixture of inseparable **2.52** in >98:2 *Z*:*E* ratio (11.7 mg, 0.0599 mmol, 60% yield) and maleonitrile (0.4 mg, 0.00509 mmol, 0.5% yield) as colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$)**: *δ* 6.5 (dt, *J* = 10.9, 7.7 Hz, 1H), 5.3 (dt, *J* = 10.9, 1.4 Hz, 1H), 2.4 (qd, *J* = 7.5, 1.3 Hz 2H), 2.4 (t, *J* = 7.5 Hz, 2H), 1.7 – 1.6 (m, 2H), 1.5 – 1.4 (m, 2H), 1.4 – 1.3 (m, 6H); maleonitrile: *δ* 6.2 (s, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** *δ* 179.5, 155.2, 116.2, 99.7, 34.0, 31.9, 29.0, 29.0, 28.9, 28.3, 24.7; **HRMS [M+H]$^+$** $C_{11}H_{18}NO_2$ calcd 196.1332, found 196.1341.

(*E*)-4-(2-Chlorovinyl)phenyl acetate (2.59): The same procedure as described above was used and the title compound was purified by silica gel chromatography (100% hexanes → 2% Et_2O in hexanes) to afford **2.59** in >98:2 *E:Z* ratio as an off-white solid

(12.2 mg, 0.0620 mmol, 62% yield) and artesunate was recovered in 85% yield (32.6 mg, 0.0849 mmol, 85% yield). The spectral data for **2.59** were identical to those previously reported[25].

(*Z*)-14-(Benzyloxy)-14-oxotetradec-10-enoic acid (2.62): The same procedure as described above was used and the title compound was purified by silica gel chromatography (2% → 10% EtOAc in hexanes) to afford **2.62** in 80:20 *Z:E* ratio as colorless oil (24.4 mg, 0.0704 mmol, 70% yield). **IR (neat)**: 2921 (m), 2851 (w), 1734 (m), 1704 (s), 1497 (w), 1454 (w), 1380 (w), 1285 (w), 1154 (m), 965 (w), 734 (w), 696 (m); **^{1}H NMR (500 MHz, $CDCl_3$)**: *Z* isomer: δ 10.95 (s, 1H), 7.42 – 7.27 (m, 5H), 5.50 – 5.27 (m, 2H), 5.12 (d, *J* = 2.2 Hz, 2H), 2.45 – 2.32 (m, 4H), 2.07 – 1.99 (m, 2H), 1.63 (p, J = 7.4 Hz, 2H), 1.42 – 1.06 (m, 12H); *E* isomer (resolved peaks only): δ 1.95 (q, *J* = 6.7 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$)**: *Z* isomer : δ 179.5, 173.3, 136.2, 131.7, 128.7, 128.3, 128.3, 127.4, 66.4, 34.6, 34.1, 29.7, 29.4, 29.3, 29.3, 29.2, 27.3, 24.8, 23.0; *E* isomer (resolved peaks only): δ 136.2, 132.0, 128.0, 66.3, 32.6, 29.5, 29.4, 29.2, 28.1; **HRMS [M+H]$^+$** calcd for $C_{21}H_{31}O_4$: 347.2217, found: 347.2204.

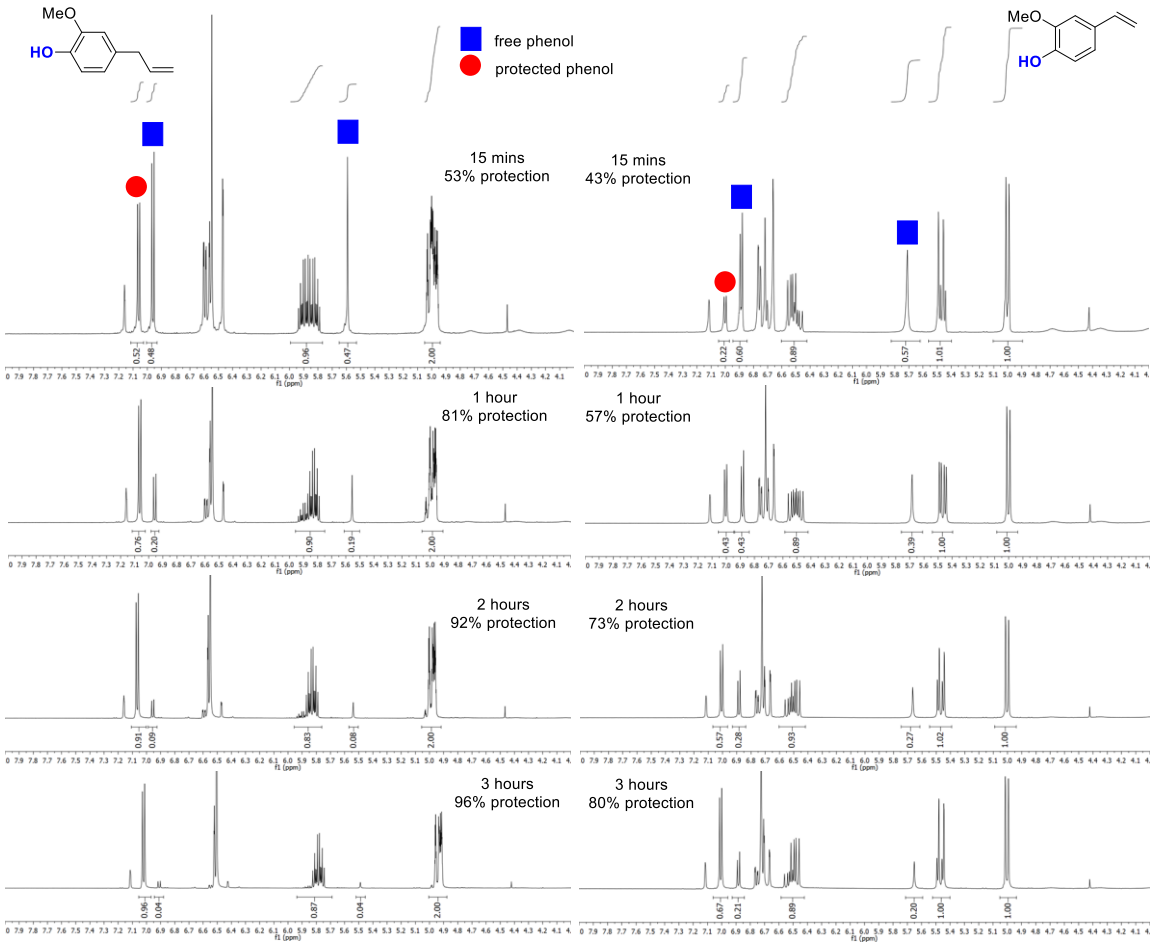
(*Z*)-7-Fluoro-3-methylhept-6-enoic acid (2.64): The same procedure as described above was used and the title compound was purified by silica gel chromatography (5% → 20% EtOAc in hexanes) to afford **2.64** in 96:4 *Z:E* ratio as colorless oil (91% weight of fluoroalkene accounting for the mass of bromoalkene, 14.9 mg, 0.0849 mmol, 85% yield). **IR (neat)**: 2922 (w), 1703 (s), 1671 (m), 1410 (w), 1381 (w), 1296 (w), 1235 (w), 1172 (w), 1043 (w), 953 (w), 754 (w); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 10.97 (s, 1H), 6.56 – 6.33 (m, 1H), 4.71 (dtd, *J* = 43.1, 7.5, 4.7 Hz, 1H), 2.37 (dd, *J* = 15.2, 6.0 Hz, 1H), 2.16 (ddd, *J* = 20.5, 15.6, 8.2 Hz, 3H), 2.00 (h, *J* = 6.8 Hz, 1H), 1.50 – 1.41 (m, 1H), 1.35 –

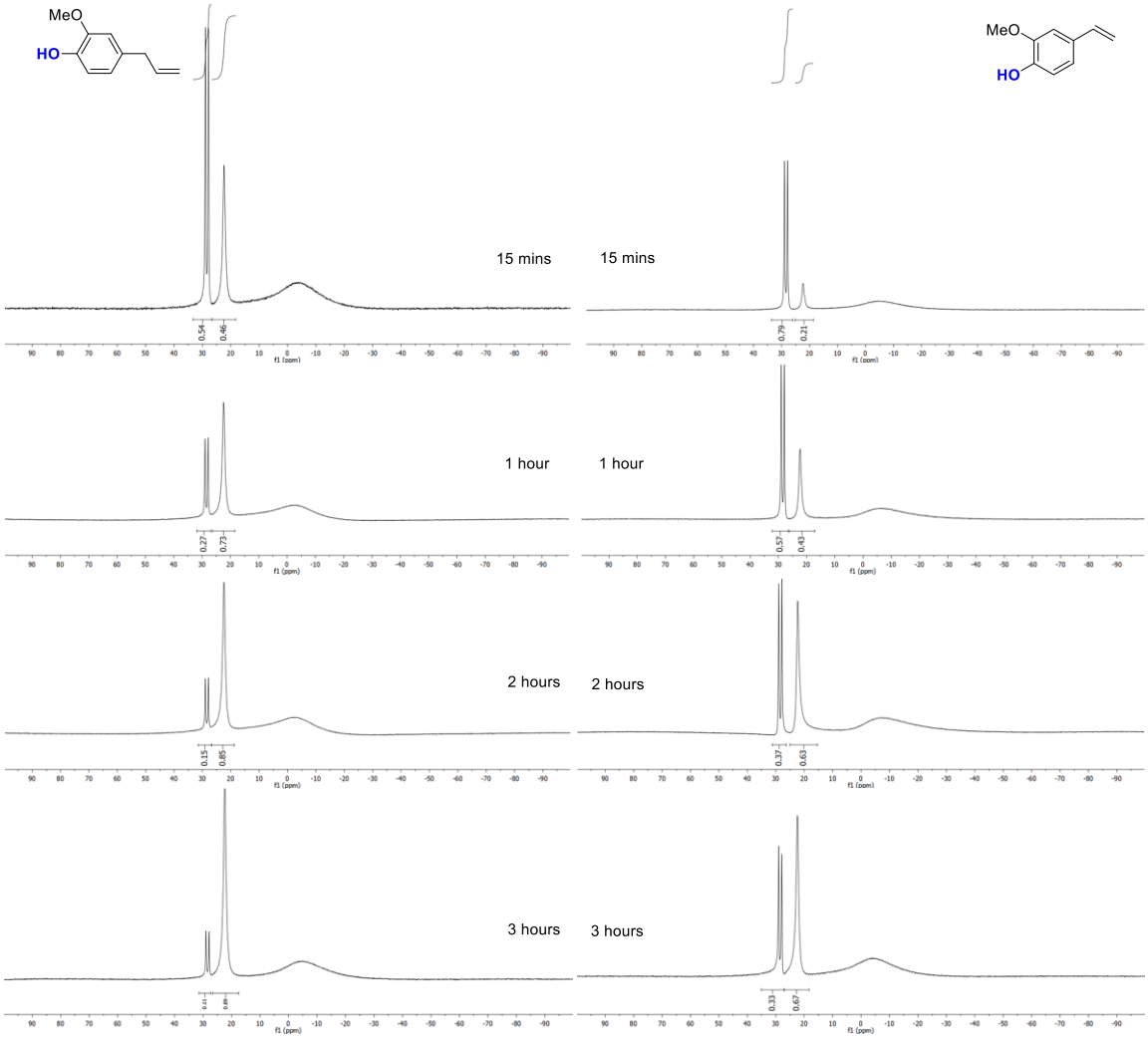
1.27 (m, 1H), 1.00 (d, J = 6.7 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 179.3, 148.0 (d, J = 256.4 Hz), 110.6 (d, J = 5.2 Hz), 41.4, 36.0 (d, J = 1.9 Hz), 29.7, 20.3 (d, J = 5.2 Hz), 19.5; **^{19}F NMR (564 MHz, $CDCl_3$)**: δ − 130.7 (dd, J = 85.8, 43.2 Hz); **HRMS $[M+H]^+$** calcd for $C_8H_{14}O_2F$: 161.0972, found: 161.0963.

(*Z*)-2-(3-Chloroallyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.66): The same procedure as described above was used and the title compound was purified by distillation under reduced pressure to afford **2.66** (4.3 g, 98% purity by weight, 20.8 mmol, 96% yield) in >98:2 *Z*:*E* ratio as clear colorless oil. The spectral data for this compound is consistent with those previously reported[3a].

Relative Rates of Boronate Formation with Allyl and Styrenyl phenols

In a N_2-filled glove box, an oven-dried NMR tube was charged with eugenol (49.2 mg, 0.300 mmol), pinacolborane (48.0 μL, 0.330 mmol) and C_6D_6 (500 μL); evolution of H_2 gas was observed. The NMR tube was removed from the glove box and reaction progress was monitored by ^{1}H and ^{11}B NMR analysis. Another NMR tube was charged with 2-methoxy-4-vinylphenol (45.0 mg, 0.300 mmol), pinacolborane (48.0 μL, 0.330 mmol) and C_6D_6 (500 μL); evolution of H_2 gas was observed. The NMR tube was removed from the glove box and reaction progress was monitored by analysis of ^{1}H and ^{11}B NMR spectra. The relevant ^{1}H and ^{11}B NMR spectra illustrated below:

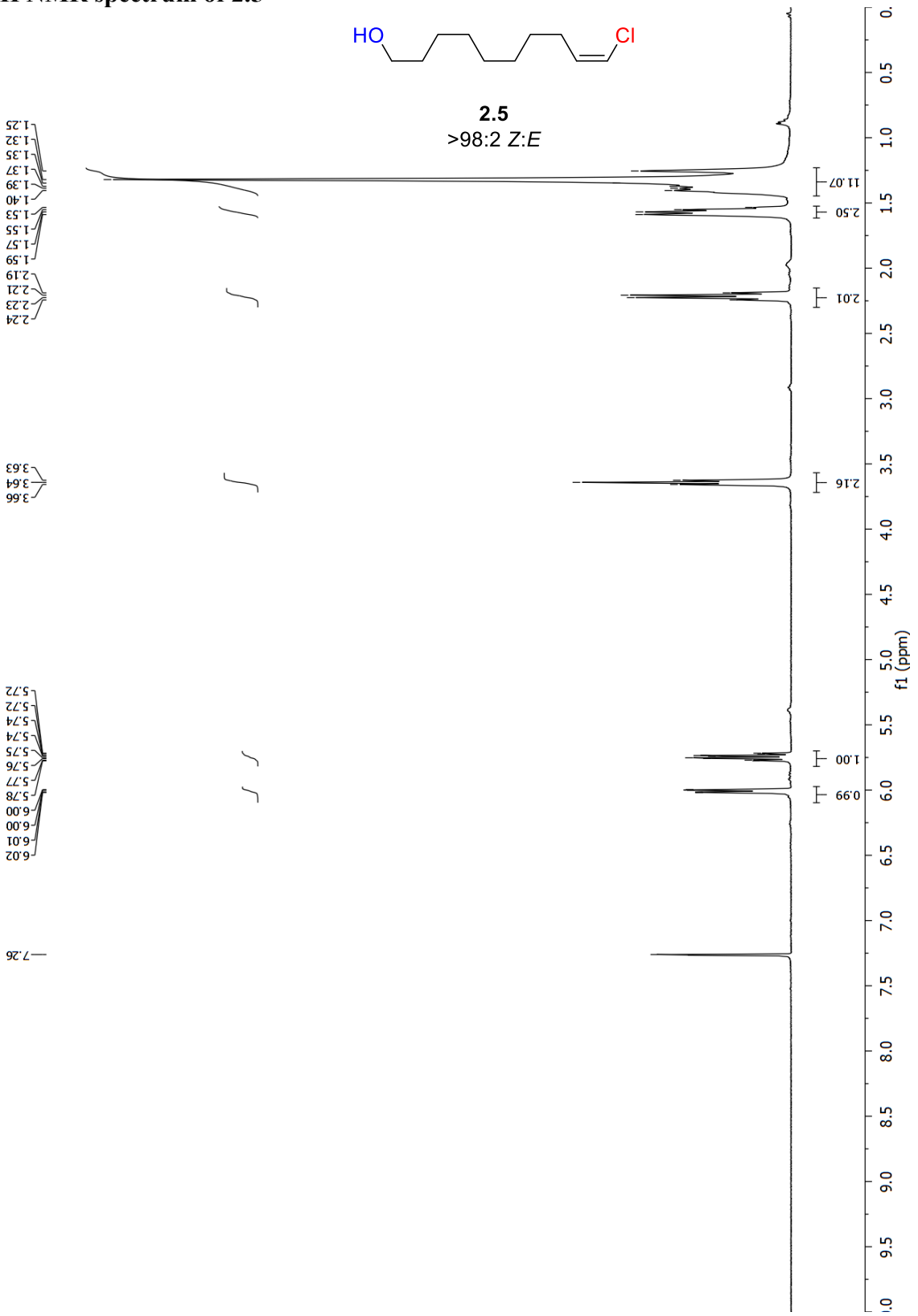

MeO
HO
free phenol
protected phenol
MeO
HO
15 mins
53% protection
15 mins
43% protection
1 hour
81% protection
1 hour
57% protection
2 hours
92% protection
2 hours
73% protection
3 hours
96% protection
3 hours
80% protection



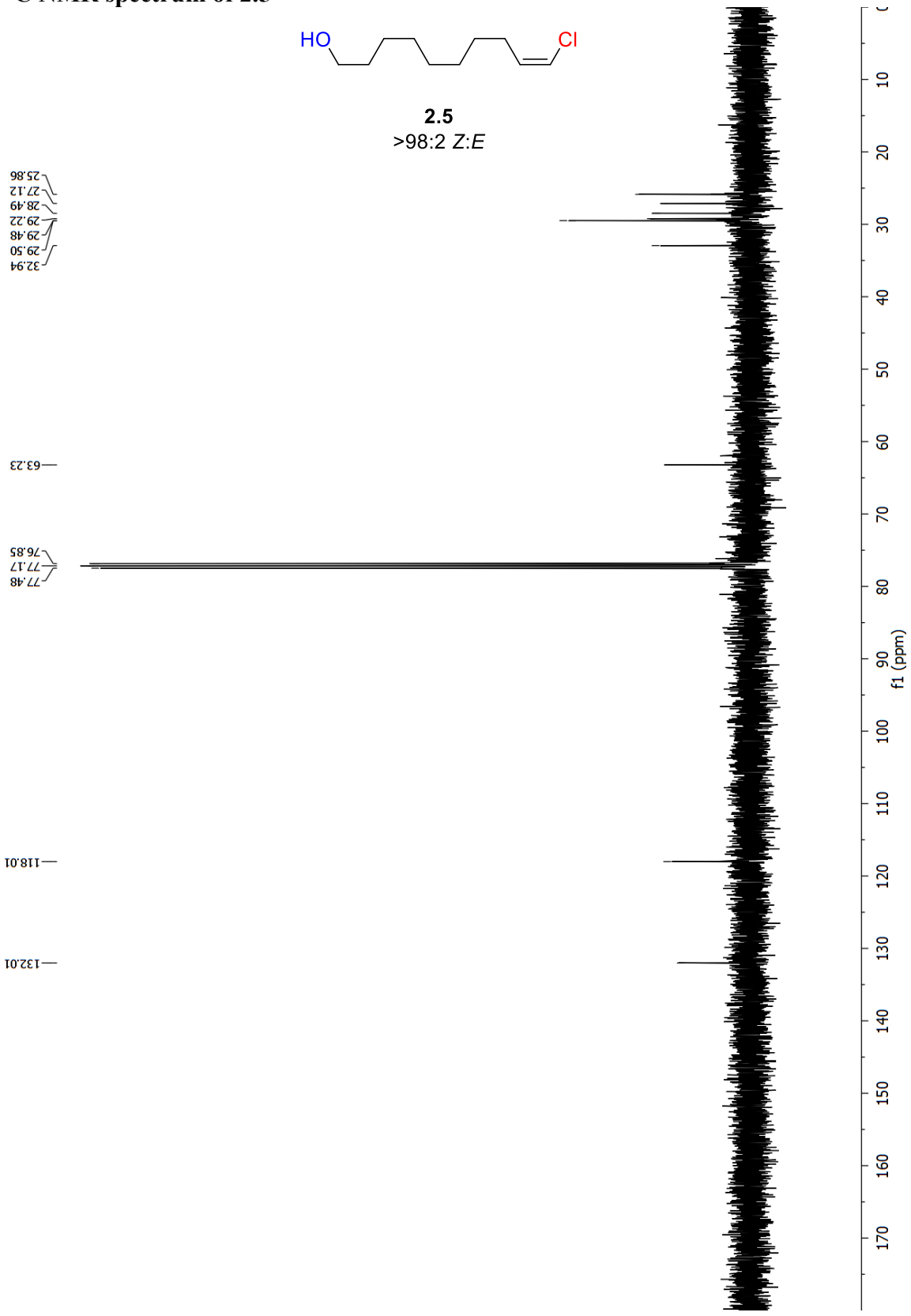
Conclusion: Formation of the boronate derived from eugenol is faster than 2-methoxy-4-vinylphenol (with HB(pin)). These observations offer a plausible rationale for why with allylphenol, 1.1 equiv HB(pin) is sufficient for efficient boronate formation whereas with 2-methoxy-4-vinylphenol, larger amounts of the same borane are needed (2.0 equiv HB(pin)).

NMR Spectra

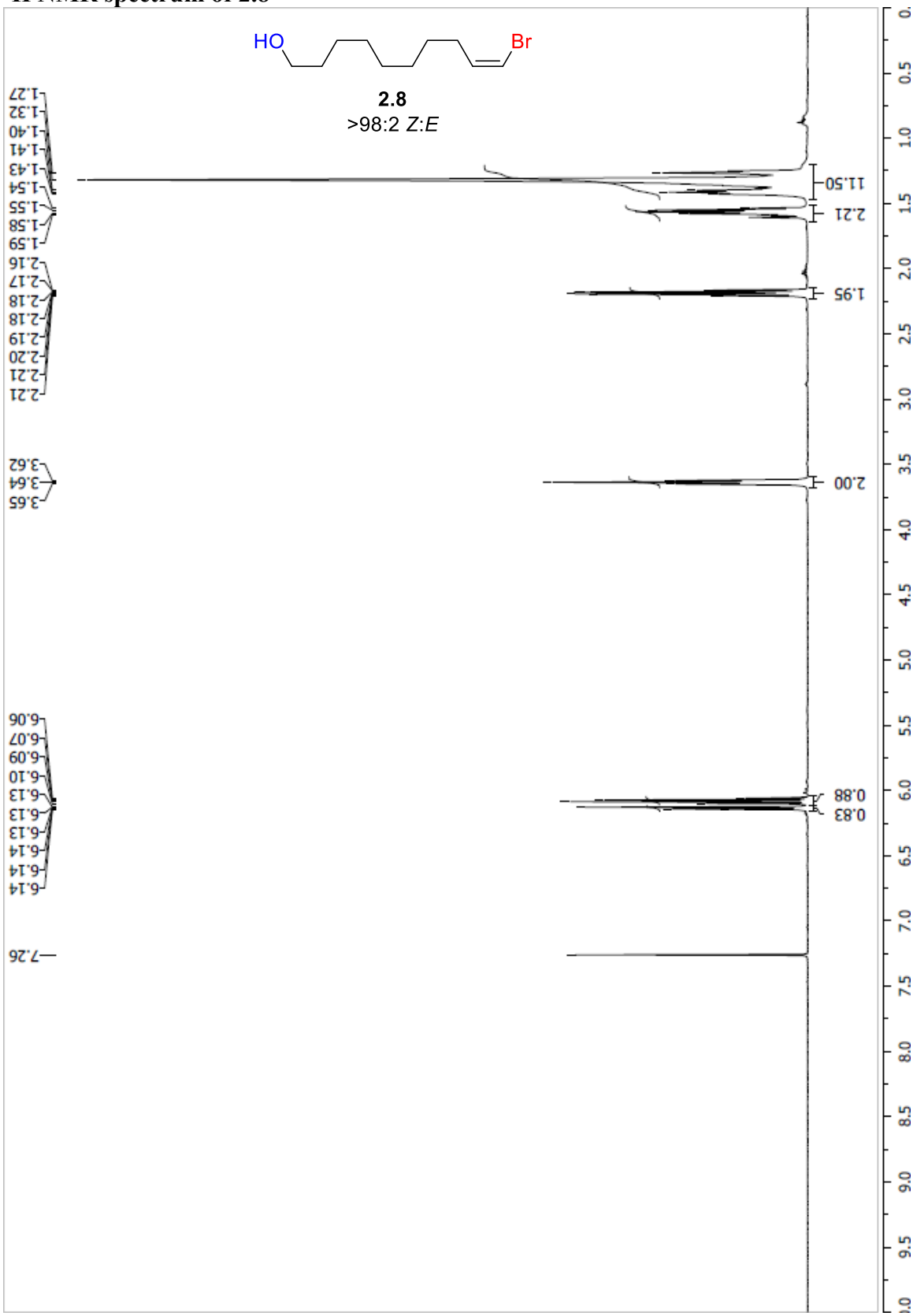
^{1}H NMR spectrum of 2.5



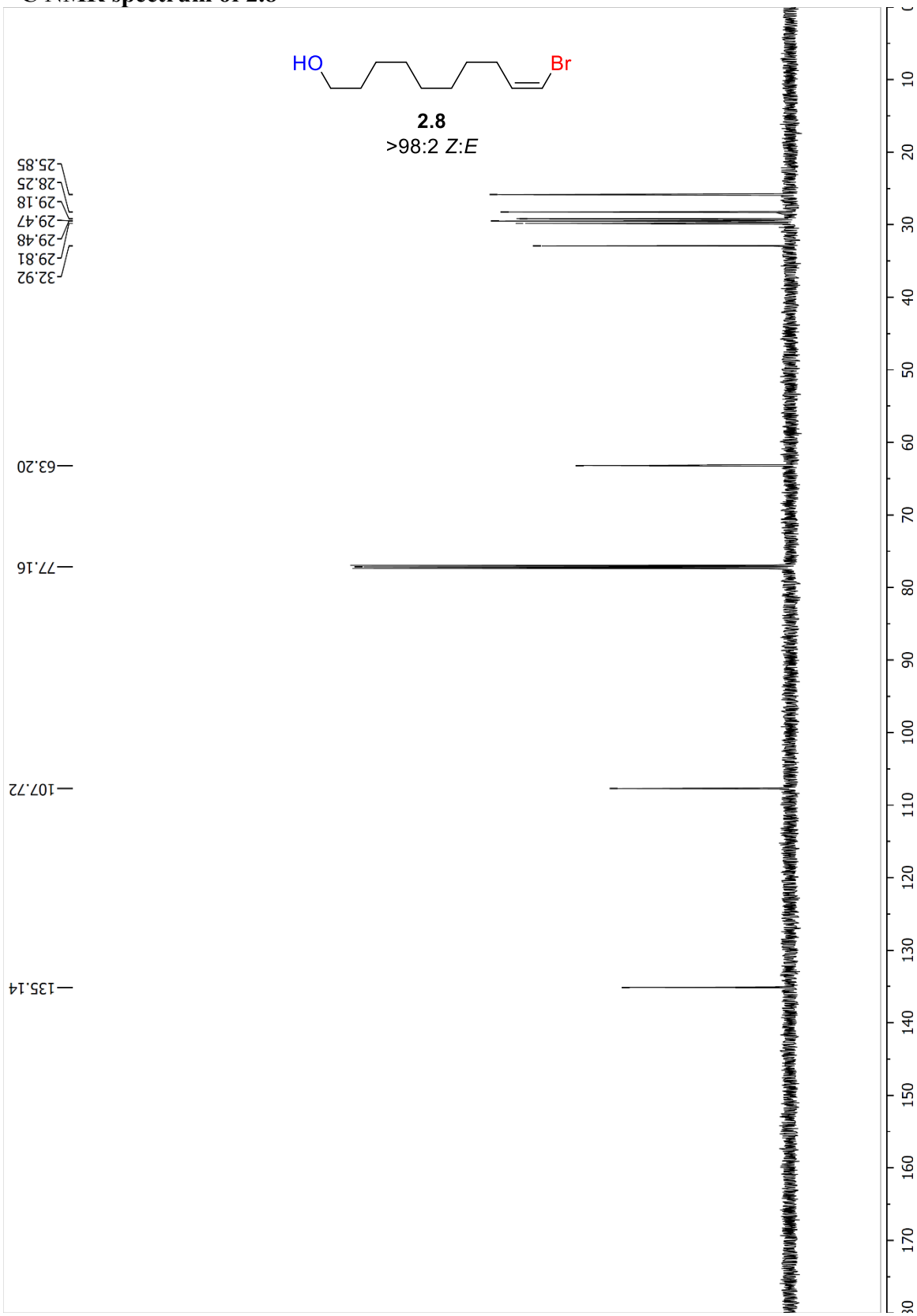
^{13}C NMR spectrum of 2.5



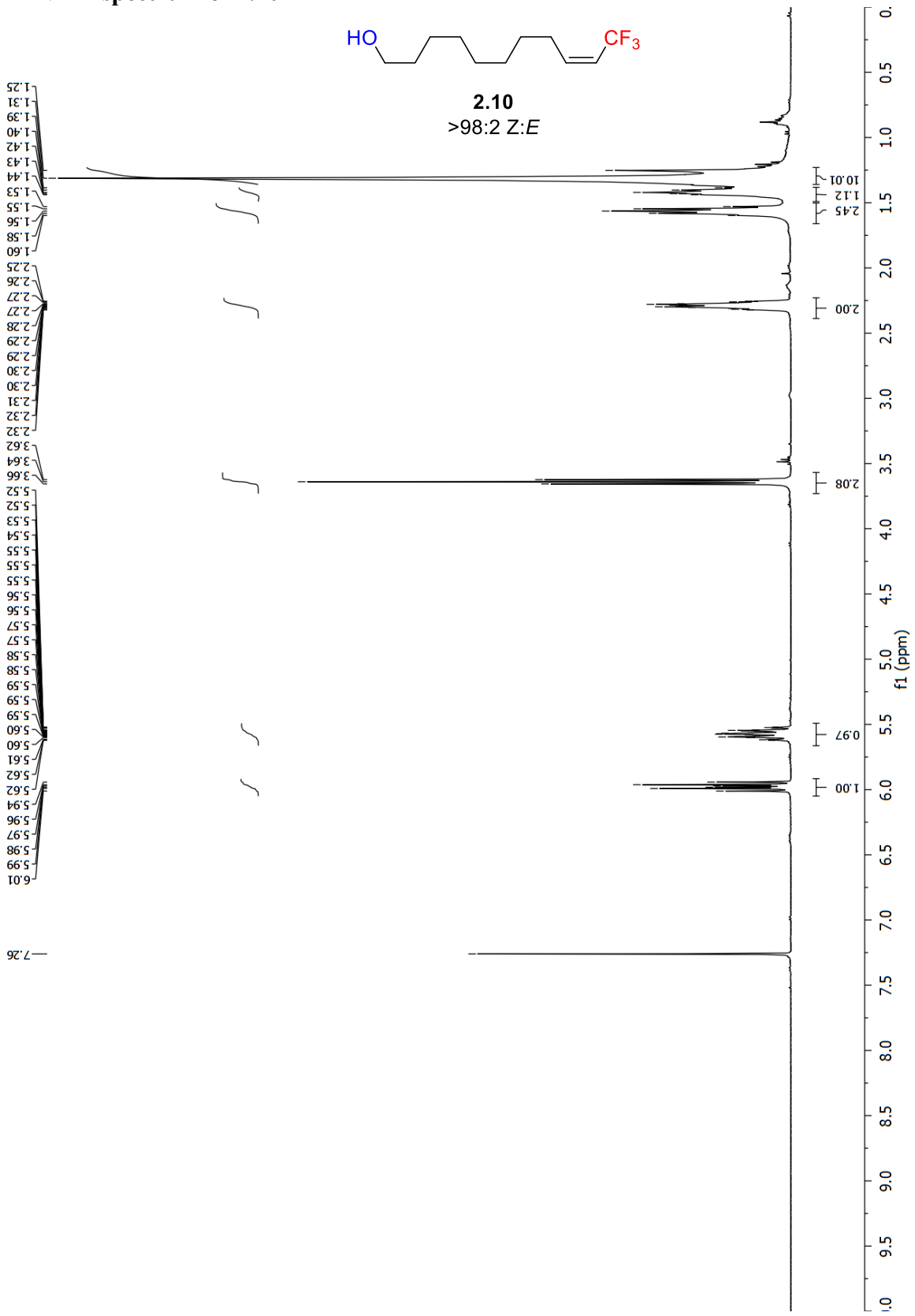
^{1}H NMR spectrum of 2.8



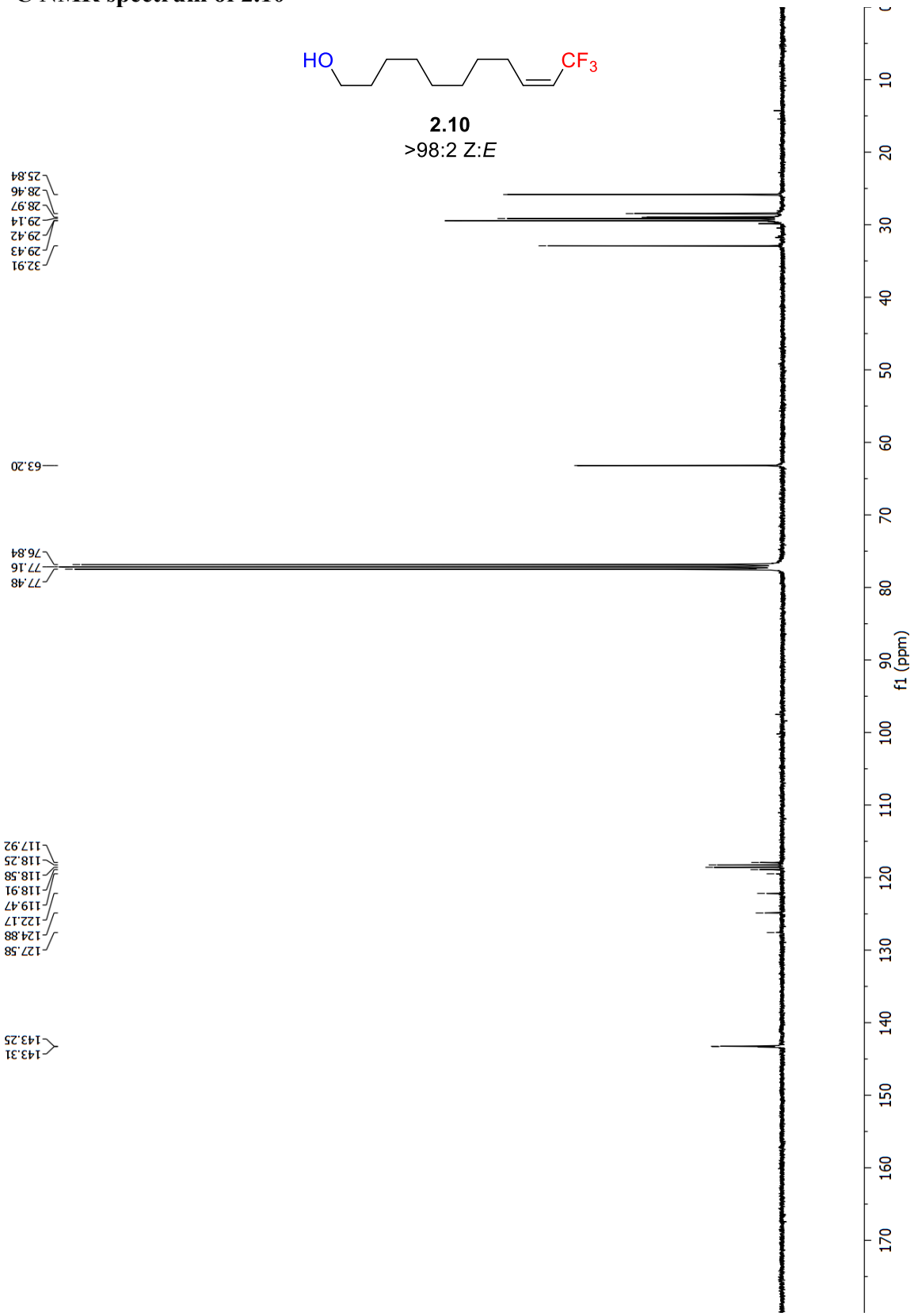
^{13}C NMR spectrum of 2.8



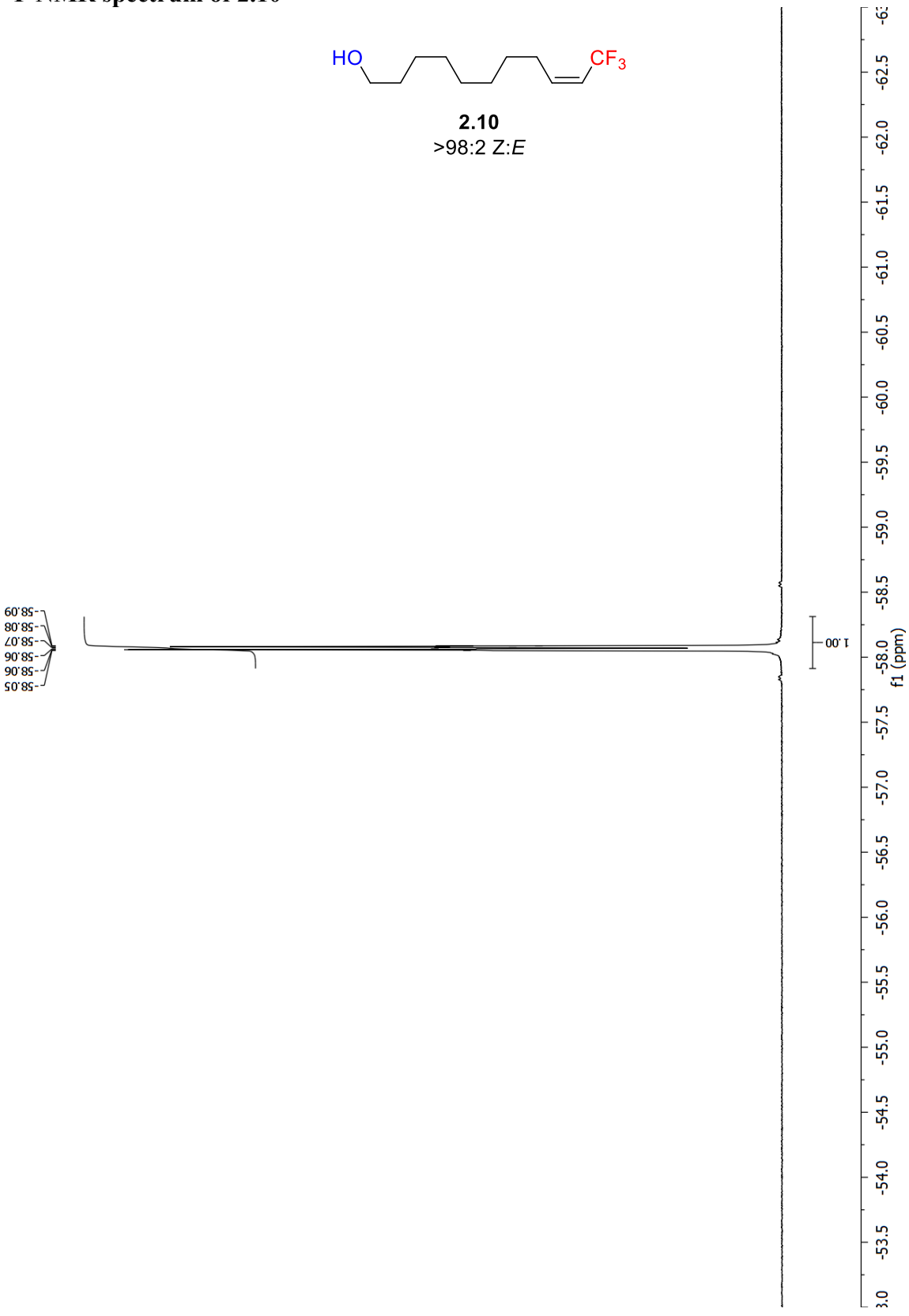
^{1}H NMR spectrum of 2.10



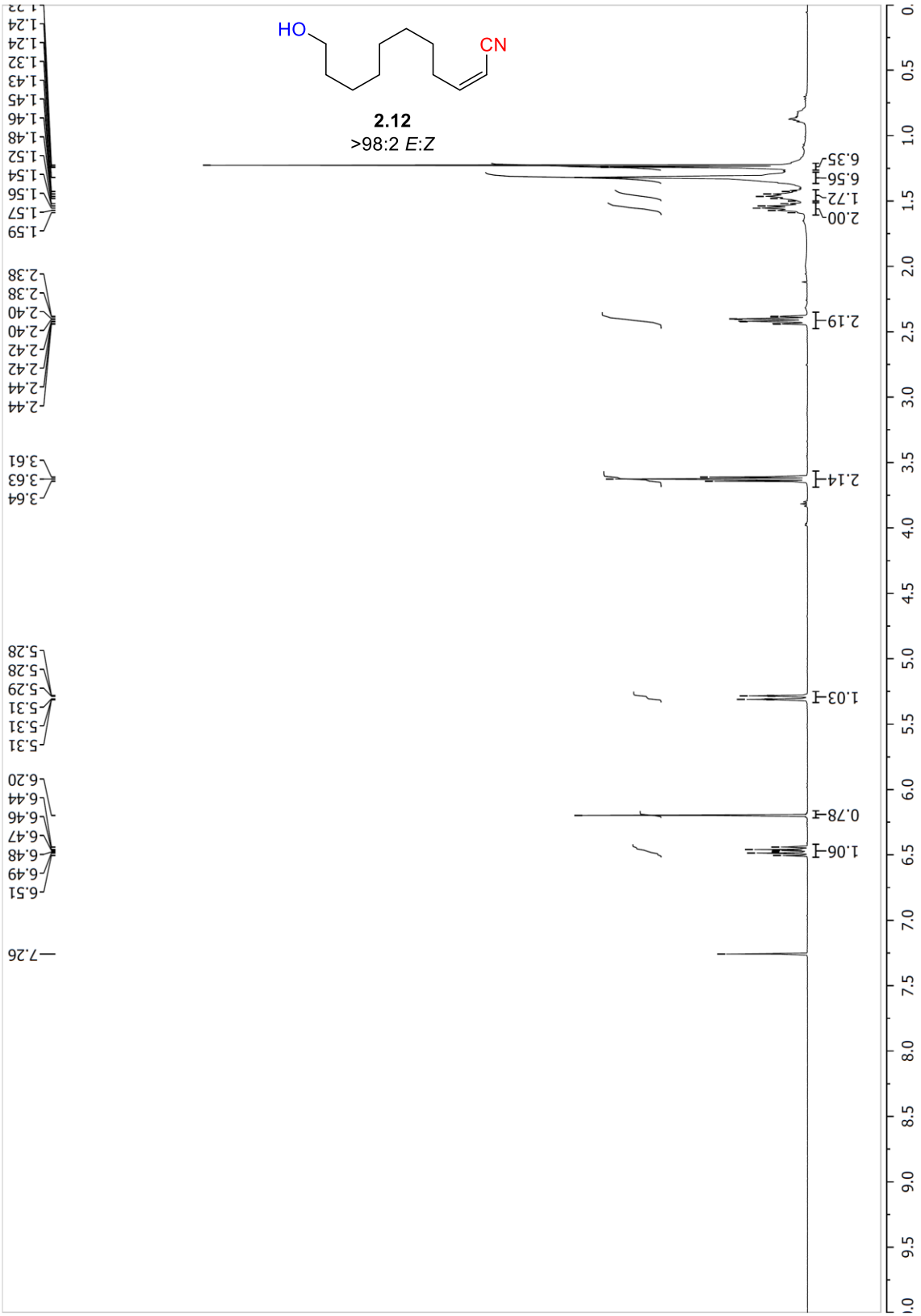
^{13}C NMR spectrum of 2.10



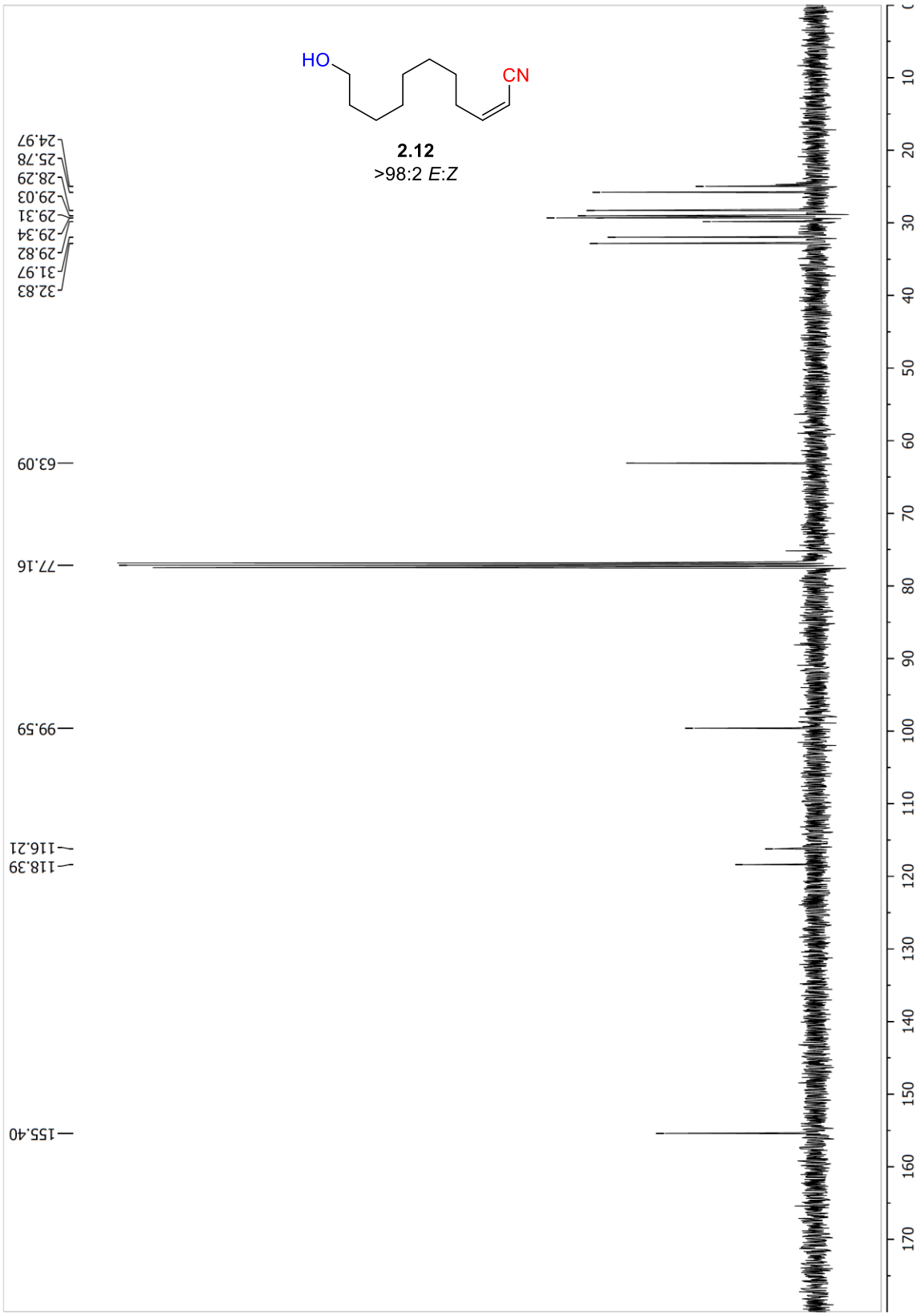
^{19}F NMR spectrum of 2.10



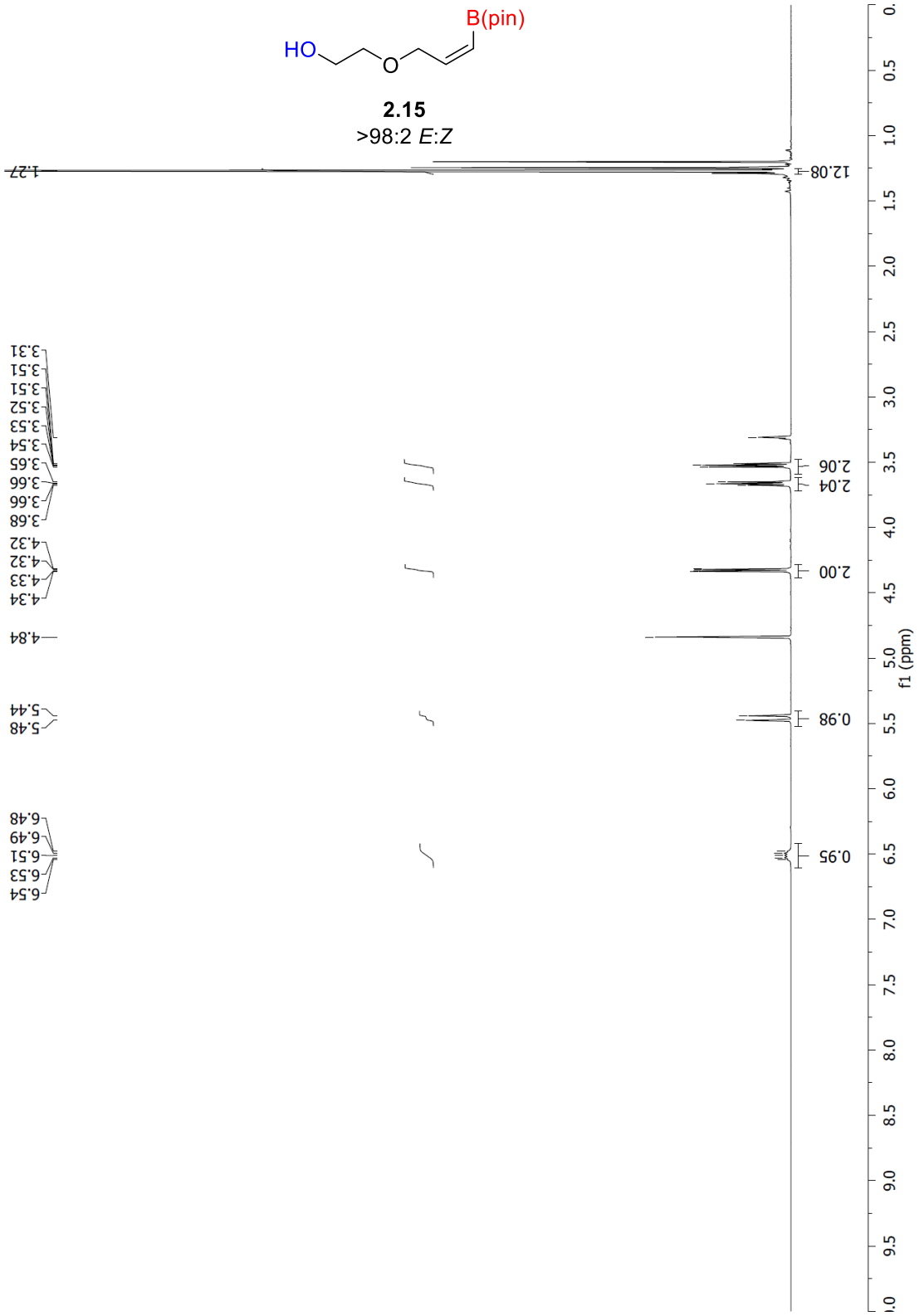
^{1}H NMR spectrum of 2.12



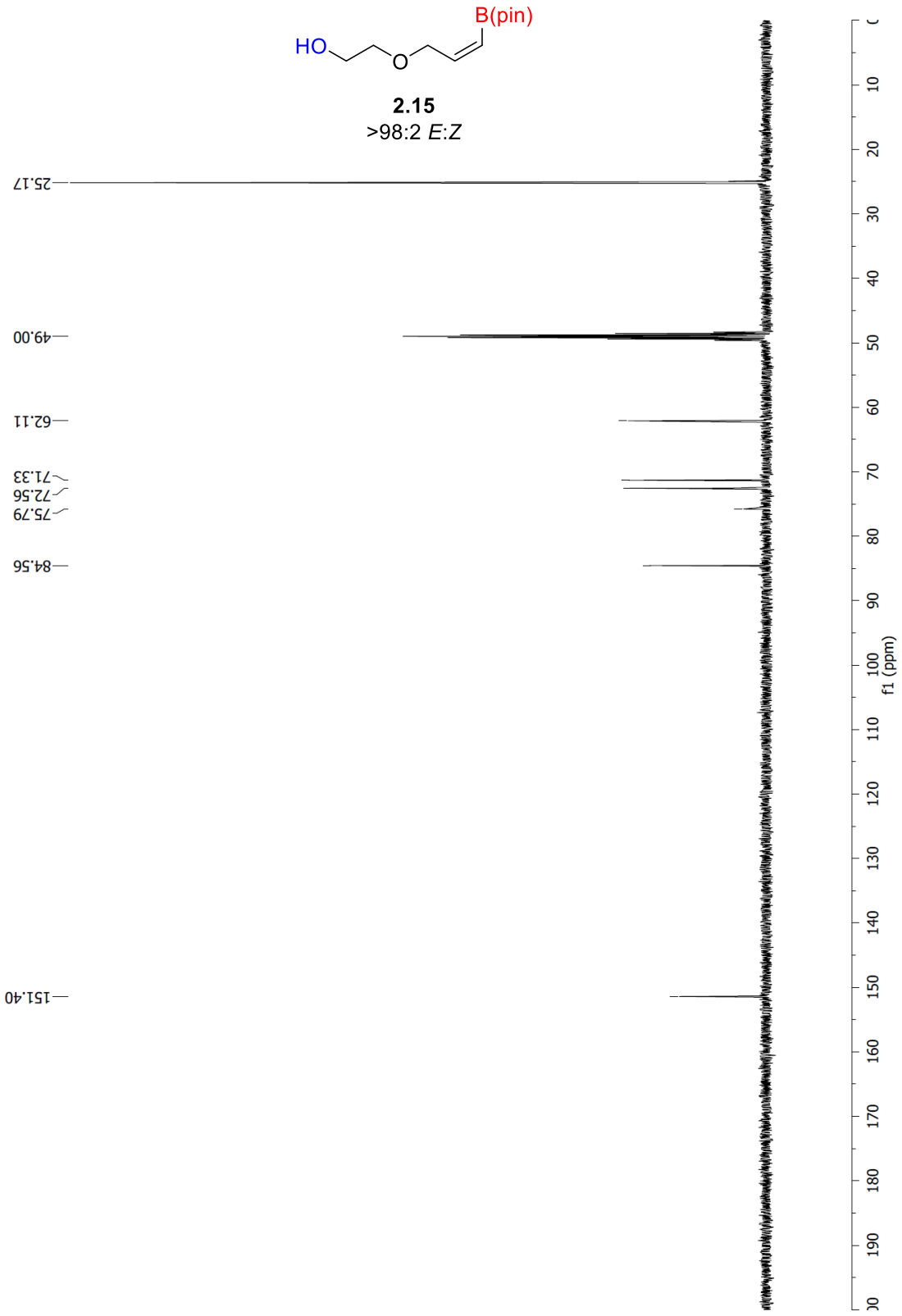
^{13}C NMR spectrum of 2.12



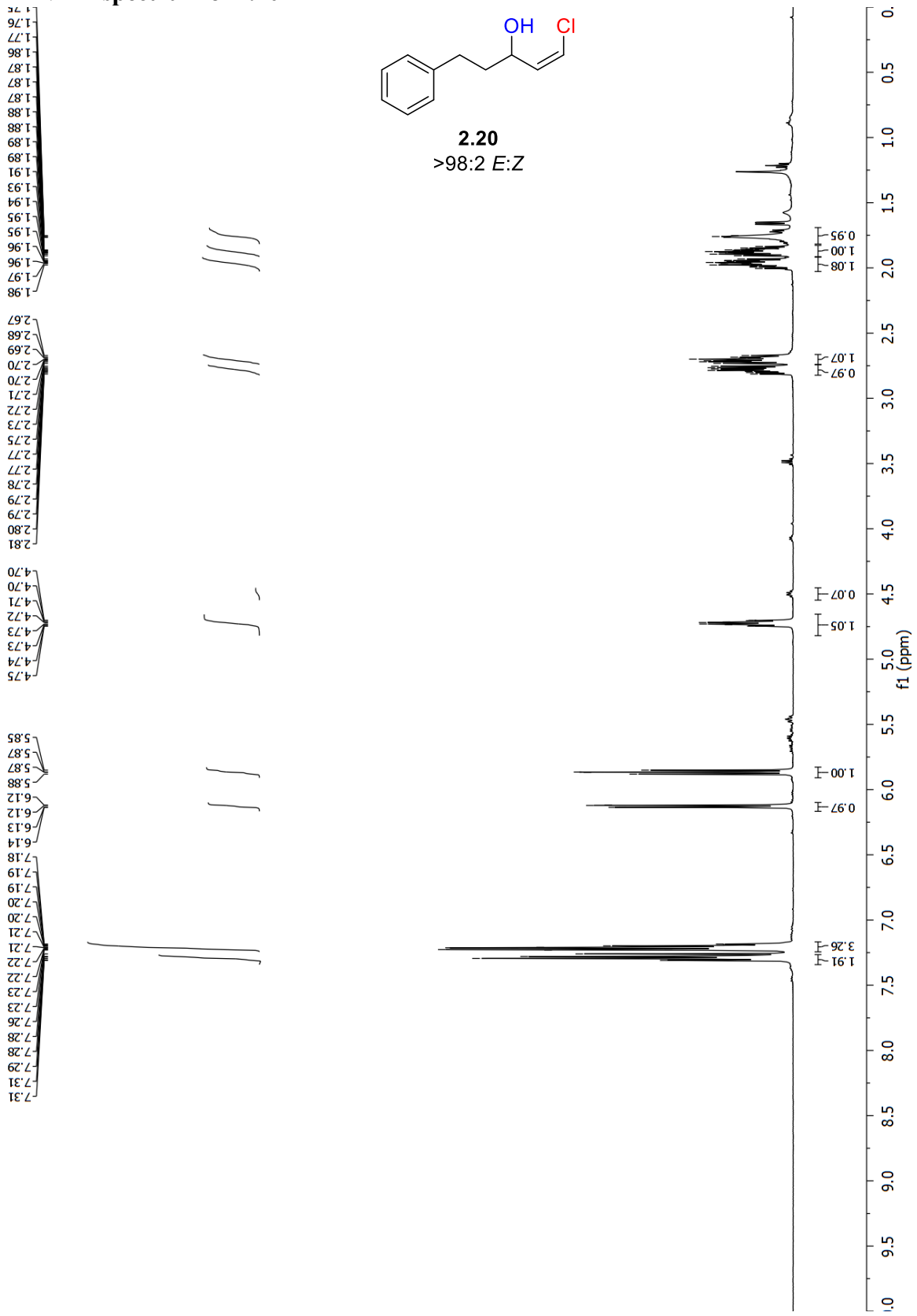
^{1}H NMR spectrum of 2.15



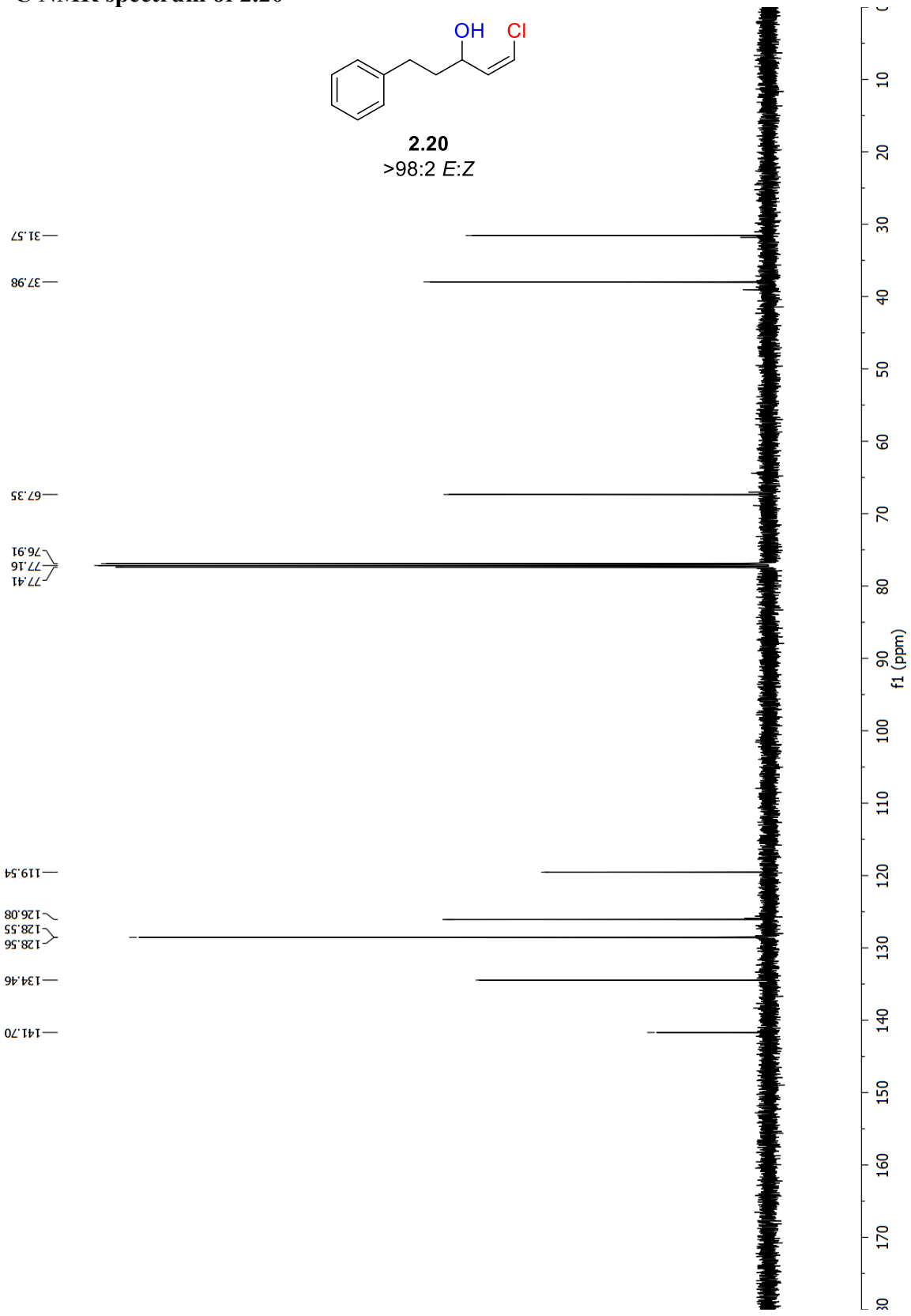
^{13}C NMR spectrum of 2.15



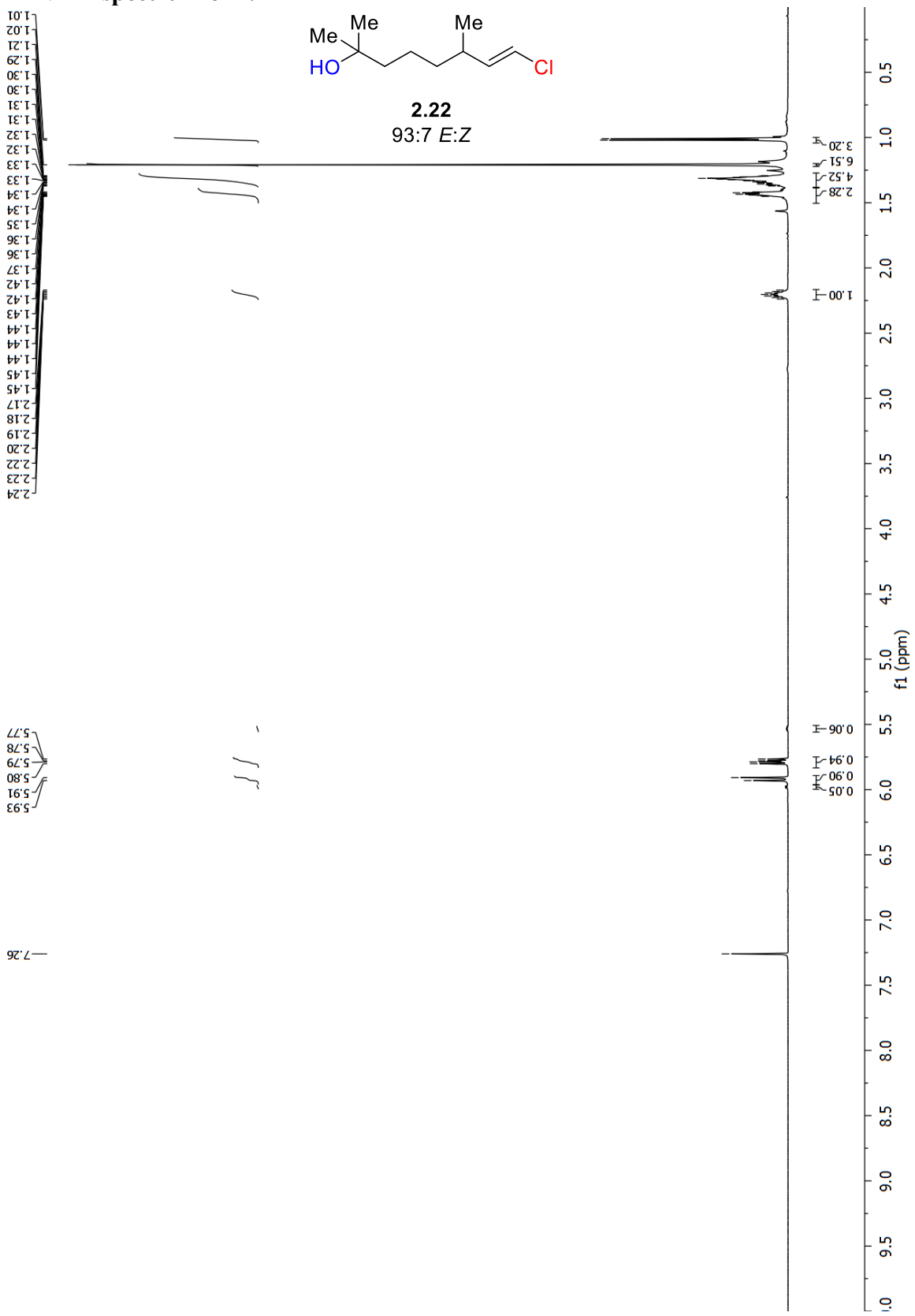
^{1}H NMR spectrum of 2.20



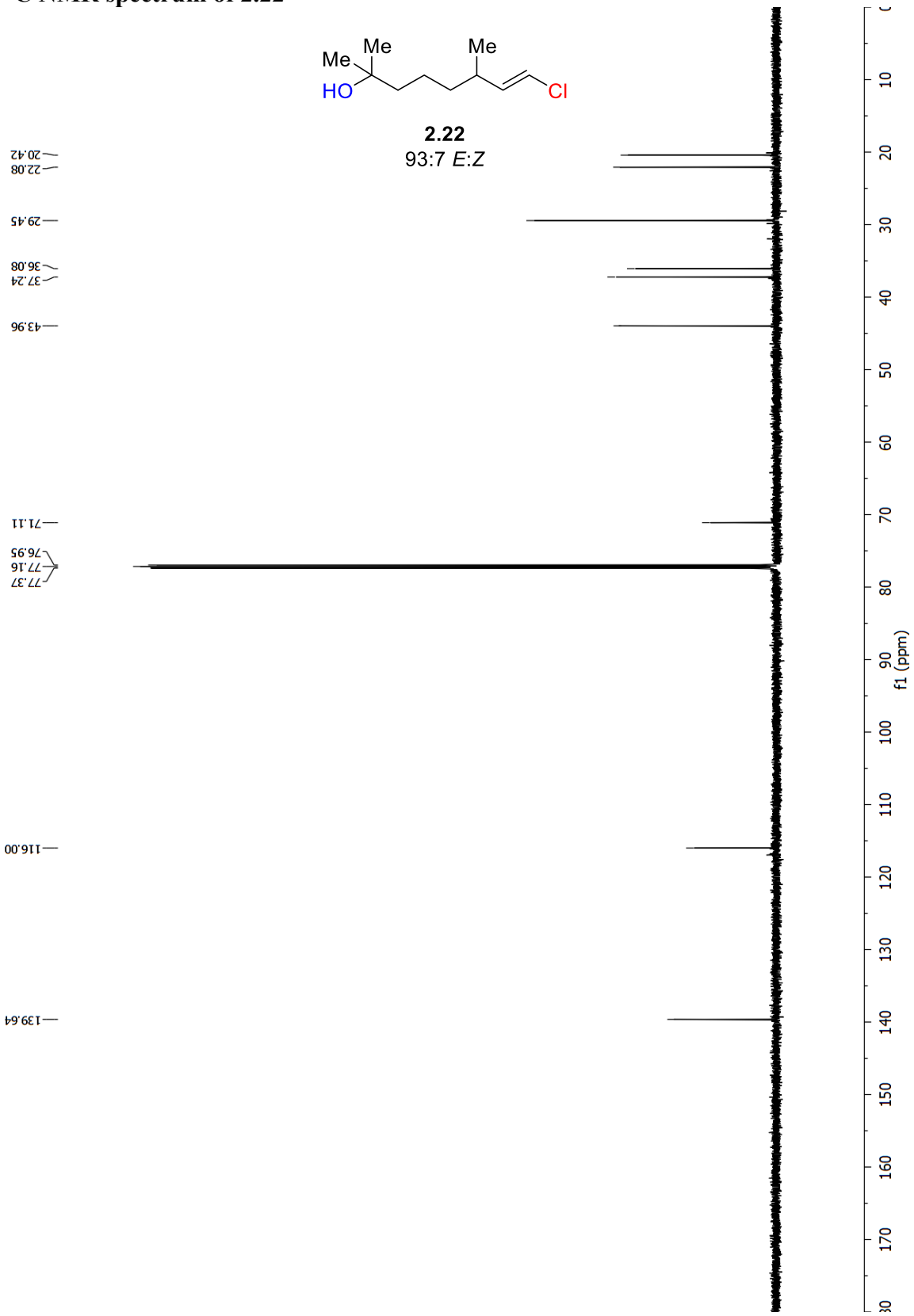
^{13}C NMR spectrum of 2.20



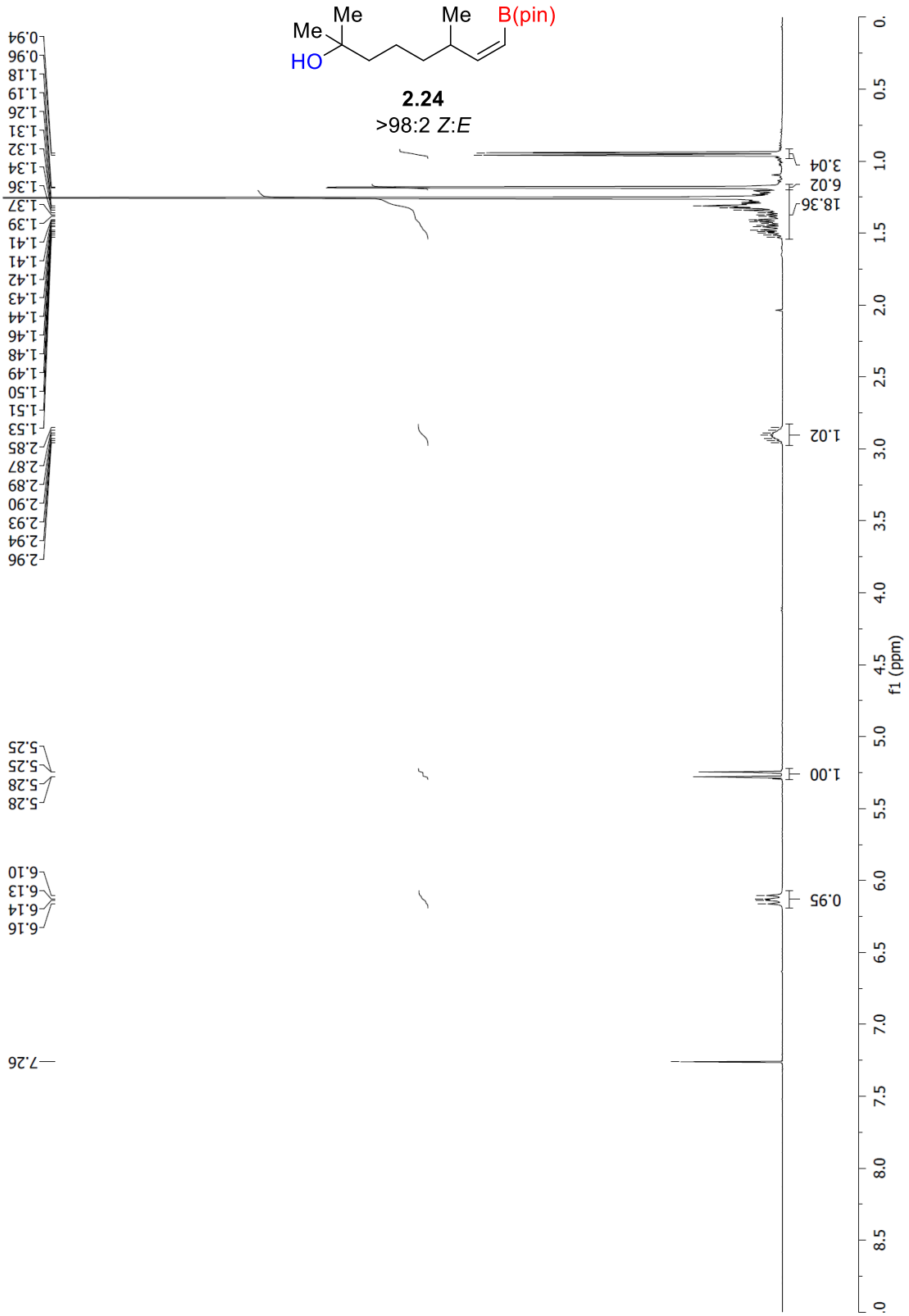
^{1}H NMR spectrum of 2.22



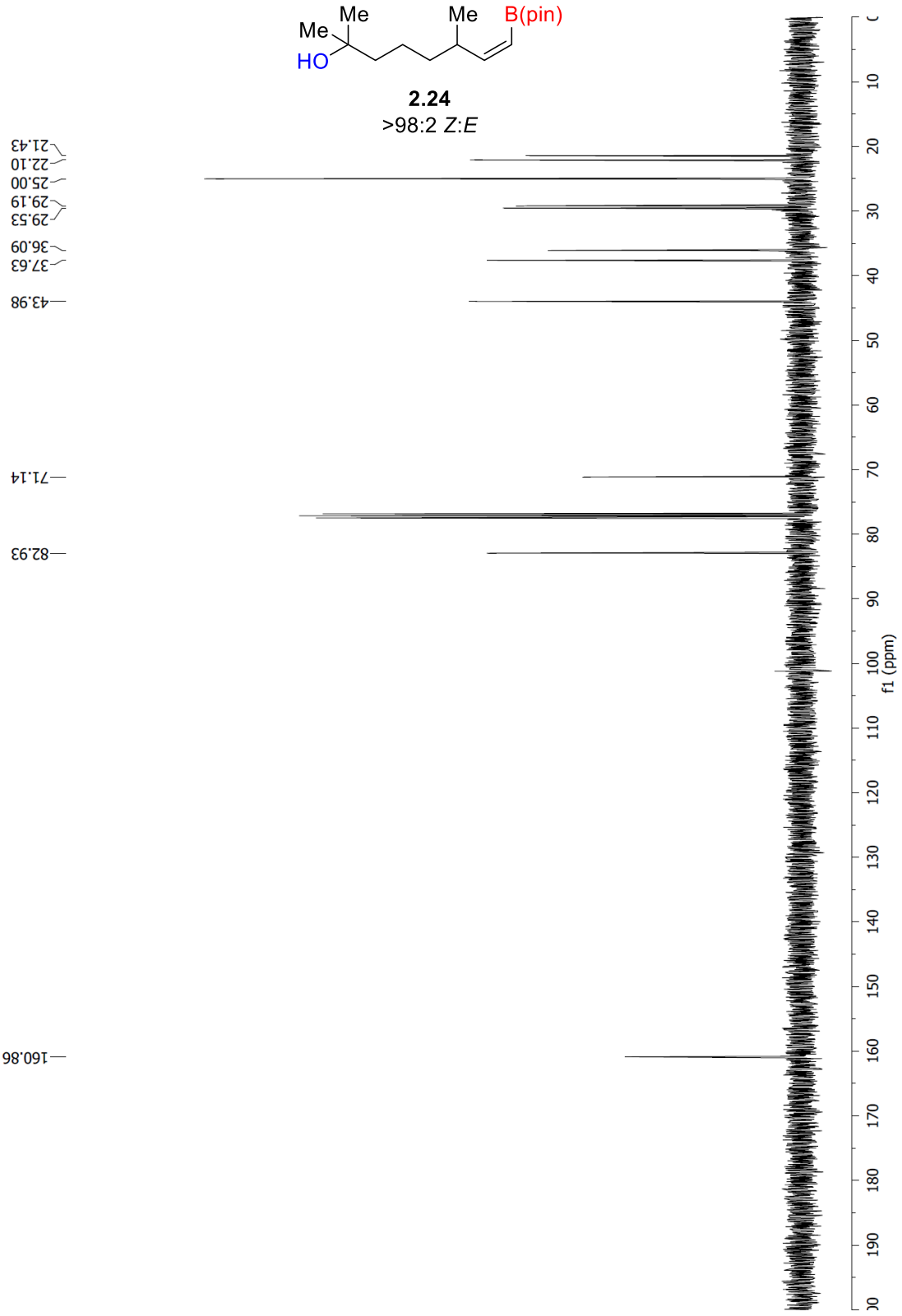
^{13}C NMR spectrum of 2.22



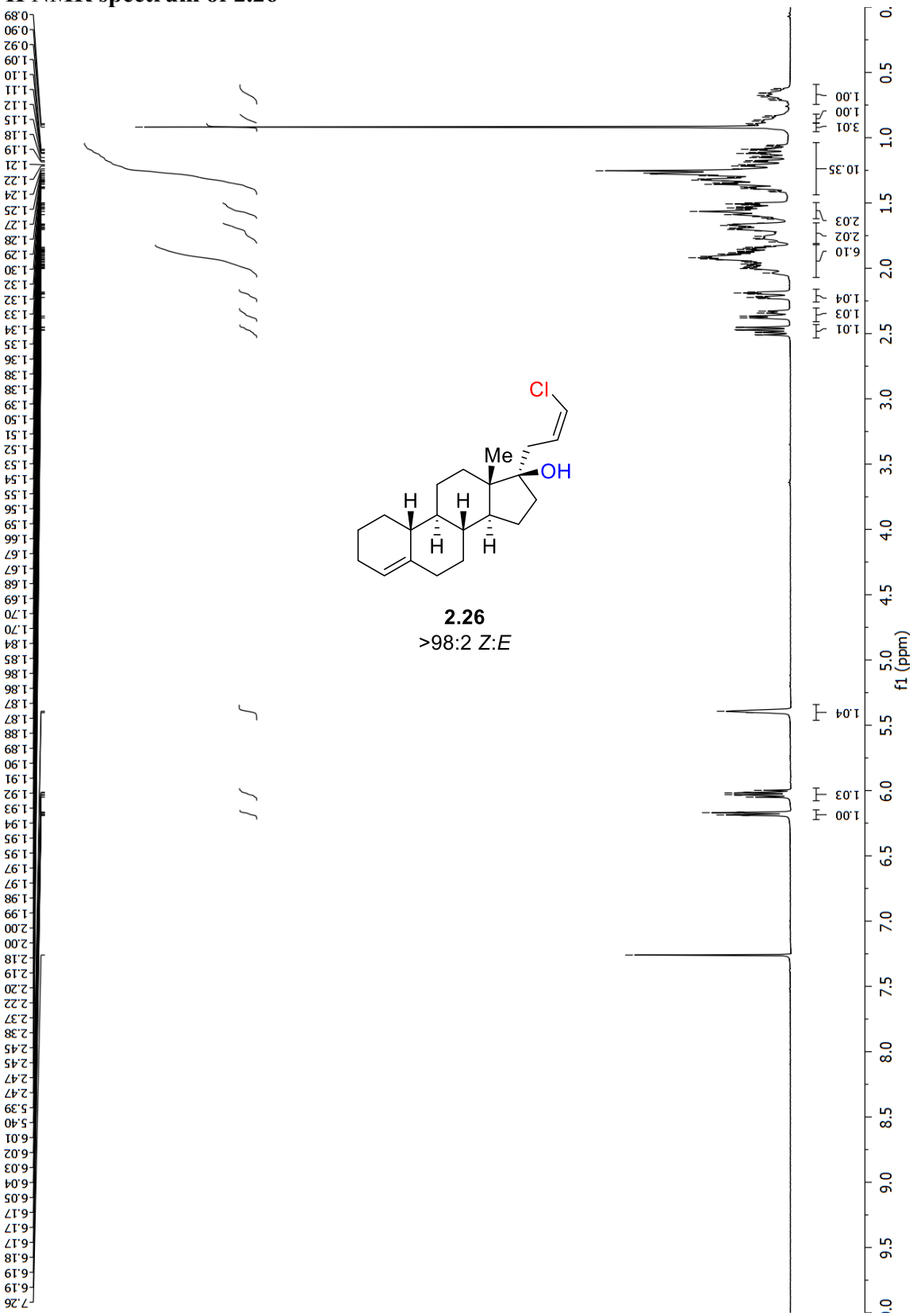
^{1}H NMR spectrum of 2.24



^{13}C NMR spectrum of 2.24

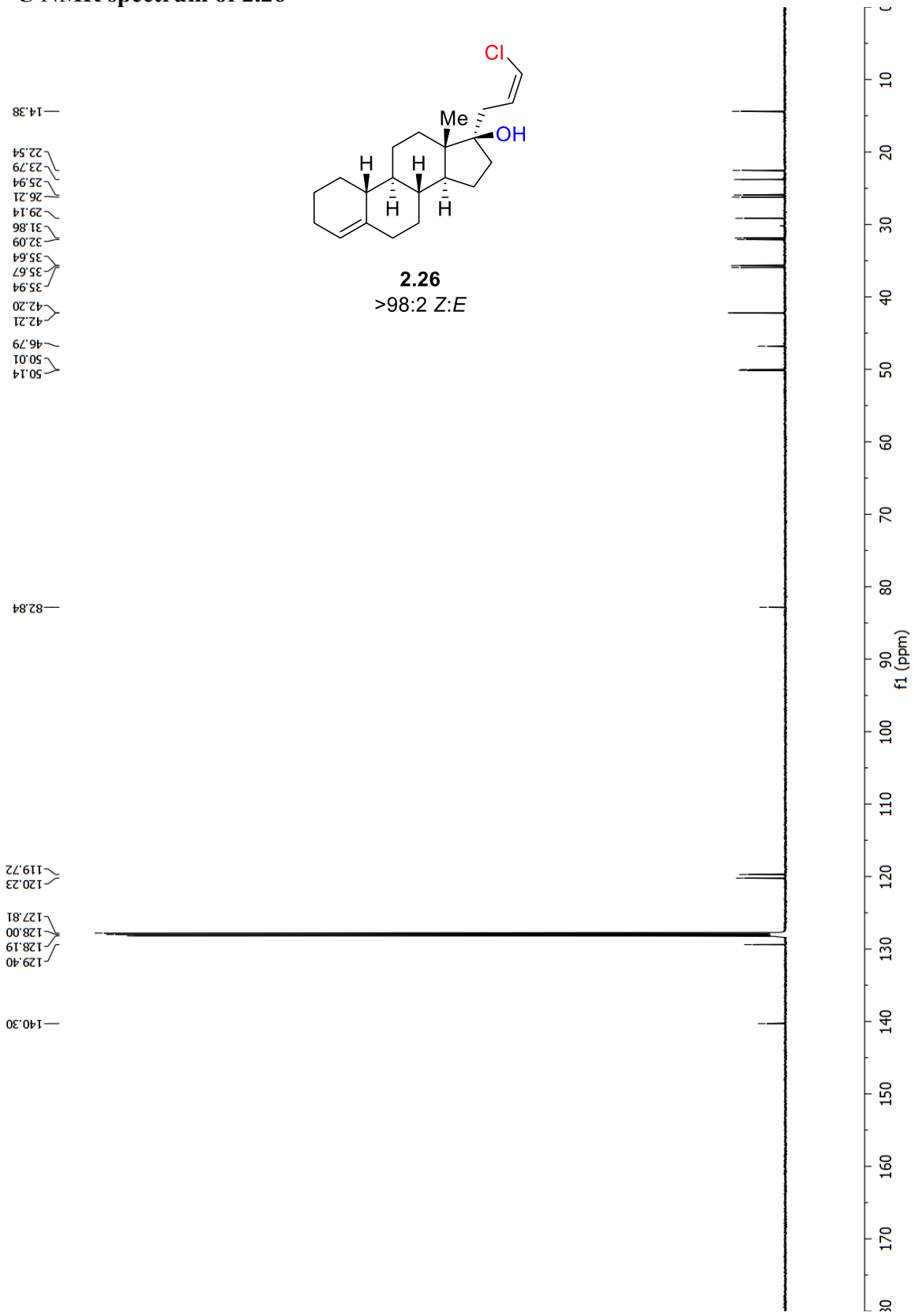


^{1}H NMR spectrum of 2.26



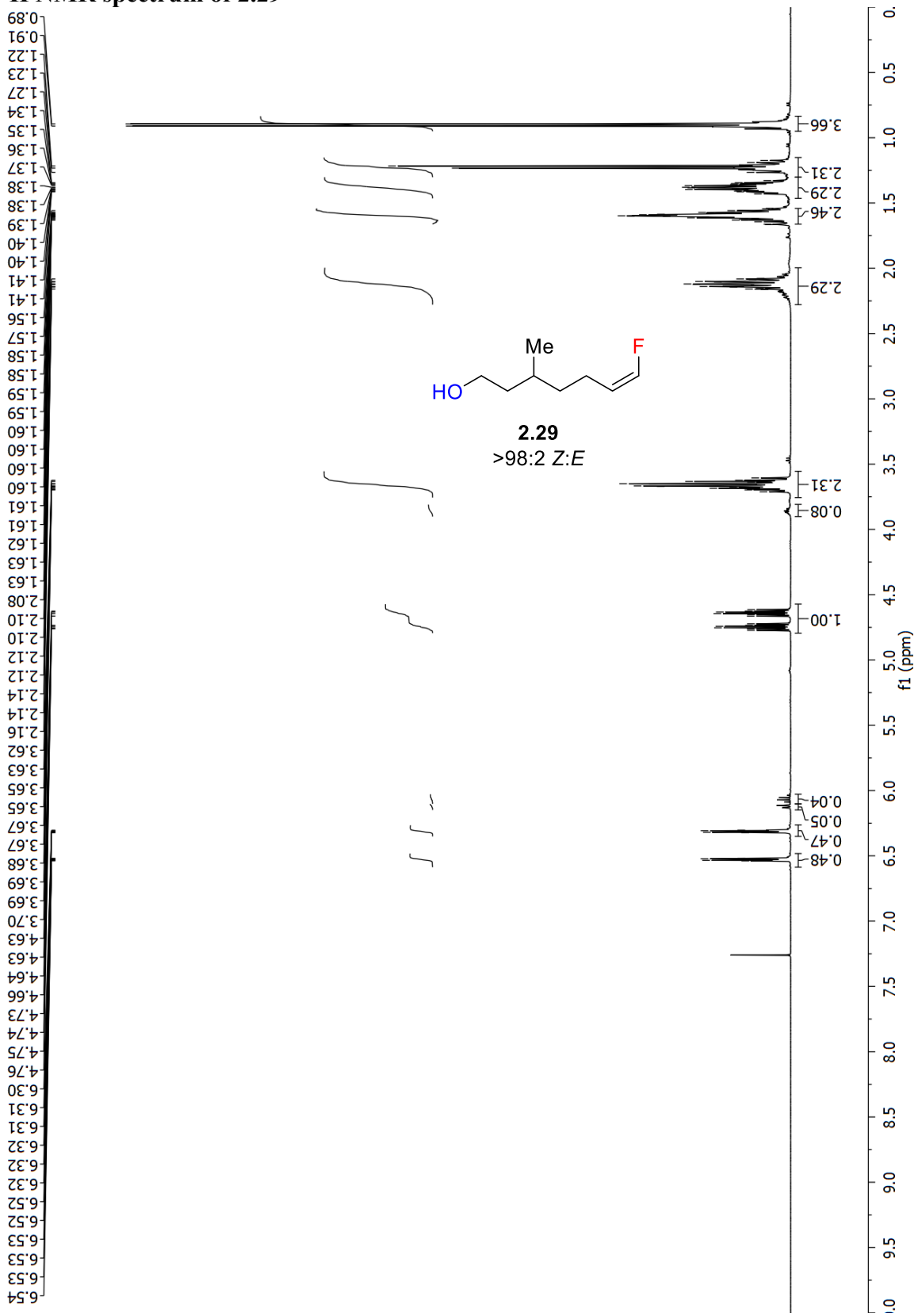
2.26
>98:2 *Z*:*E*

^{13}C NMR spectrum of 2.26

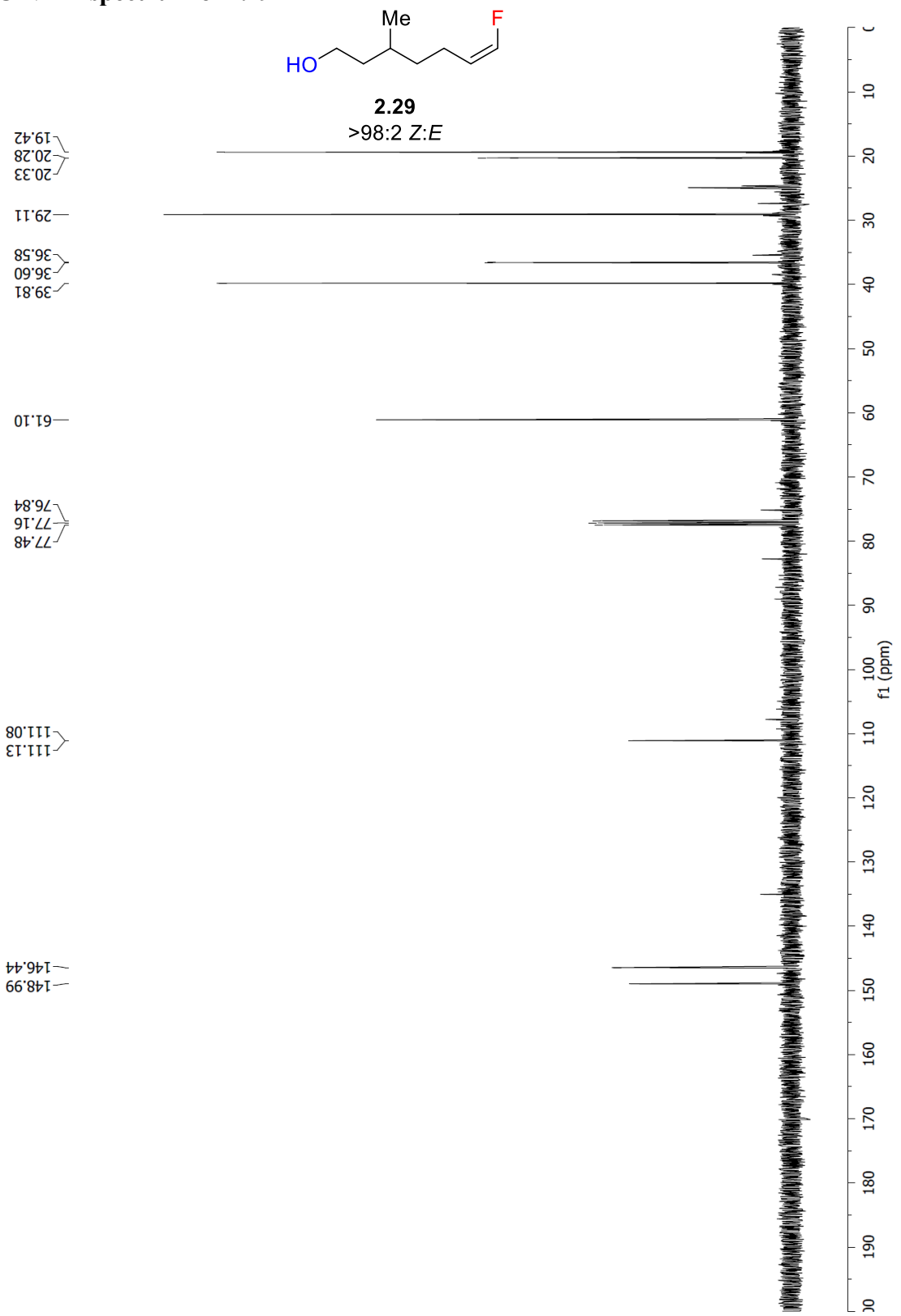


2.26
>98:2 *Z*:*E*

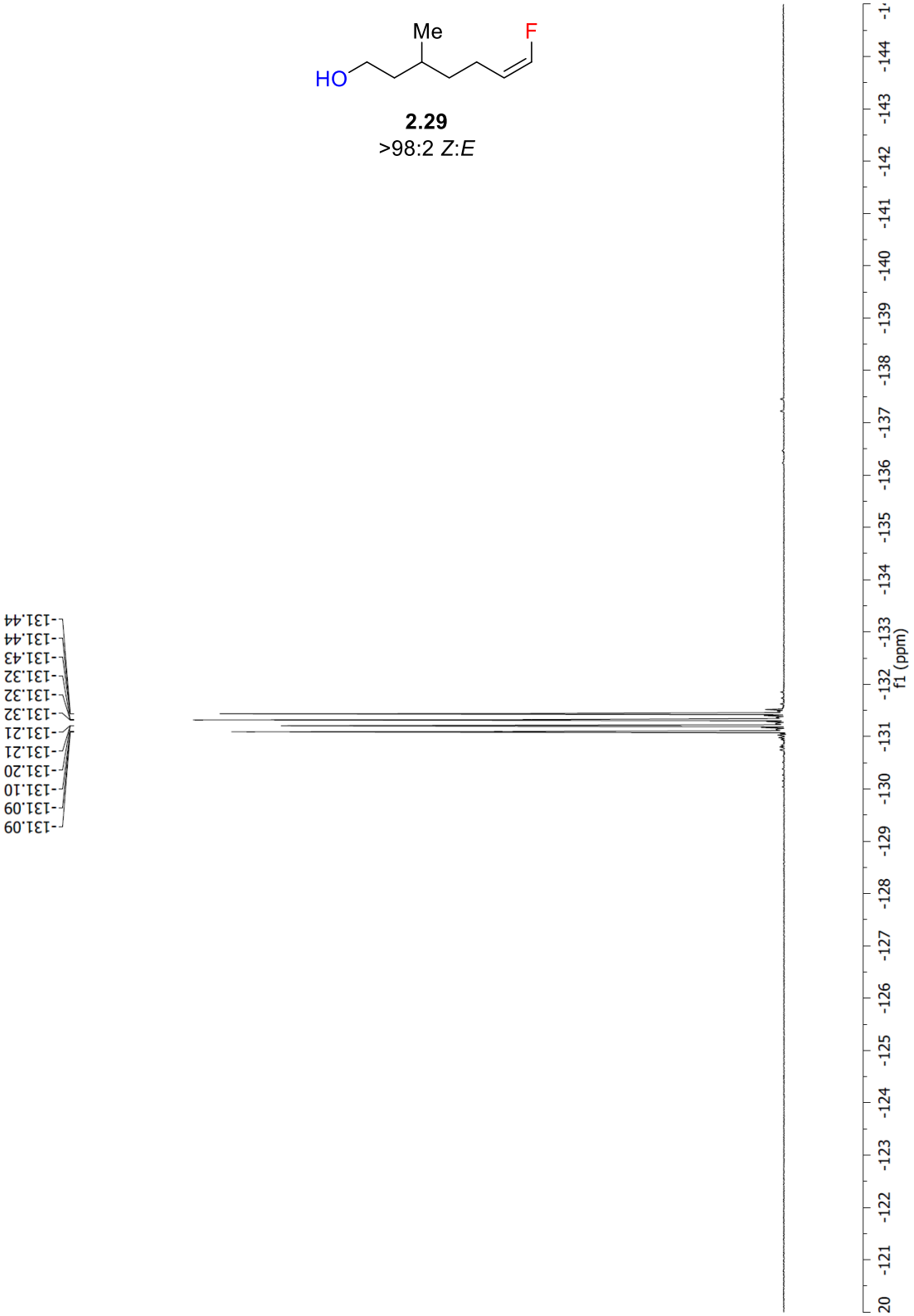
^{1}H NMR spectrum of 2.29



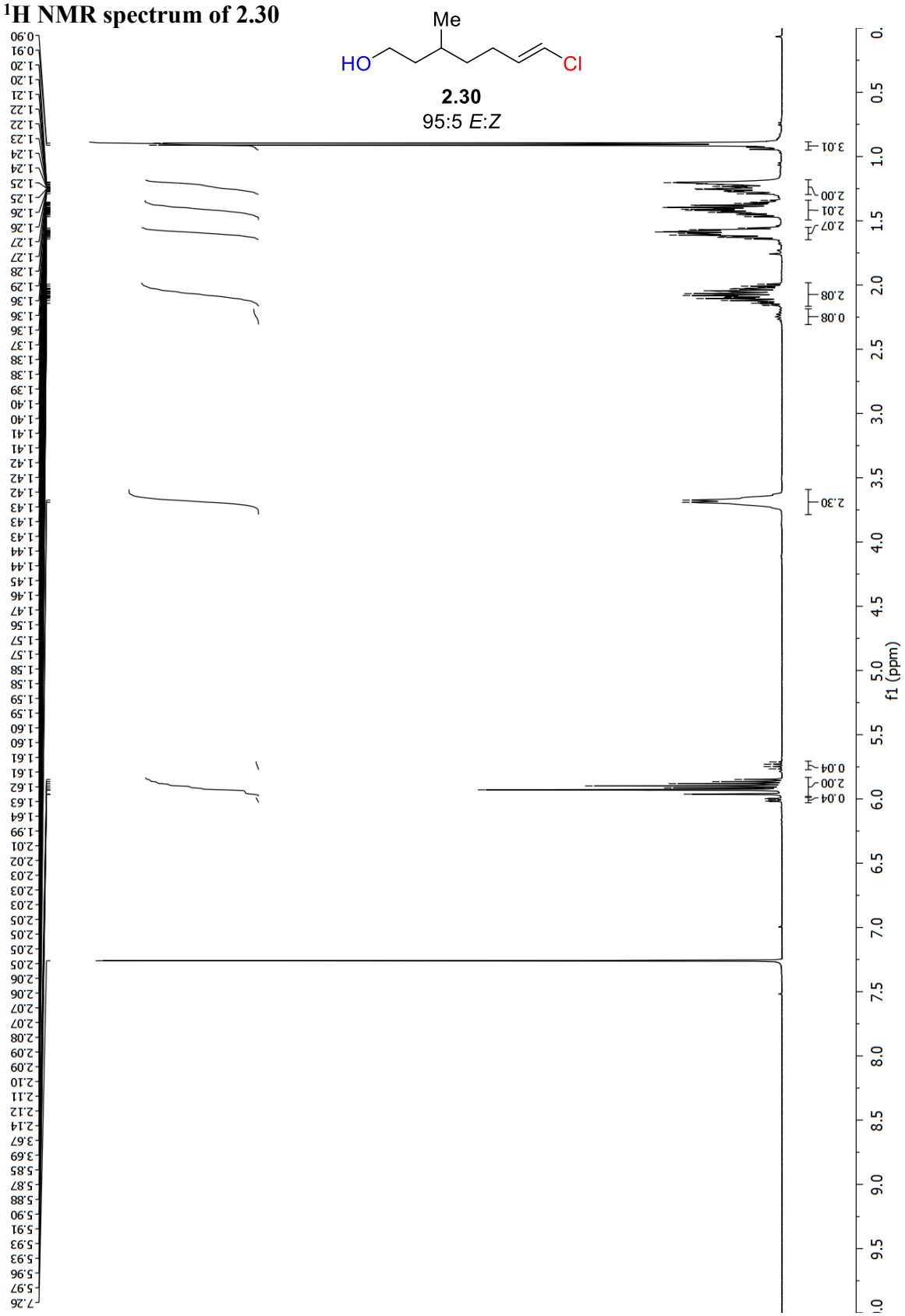
^{13}C NMR spectrum of 2.29



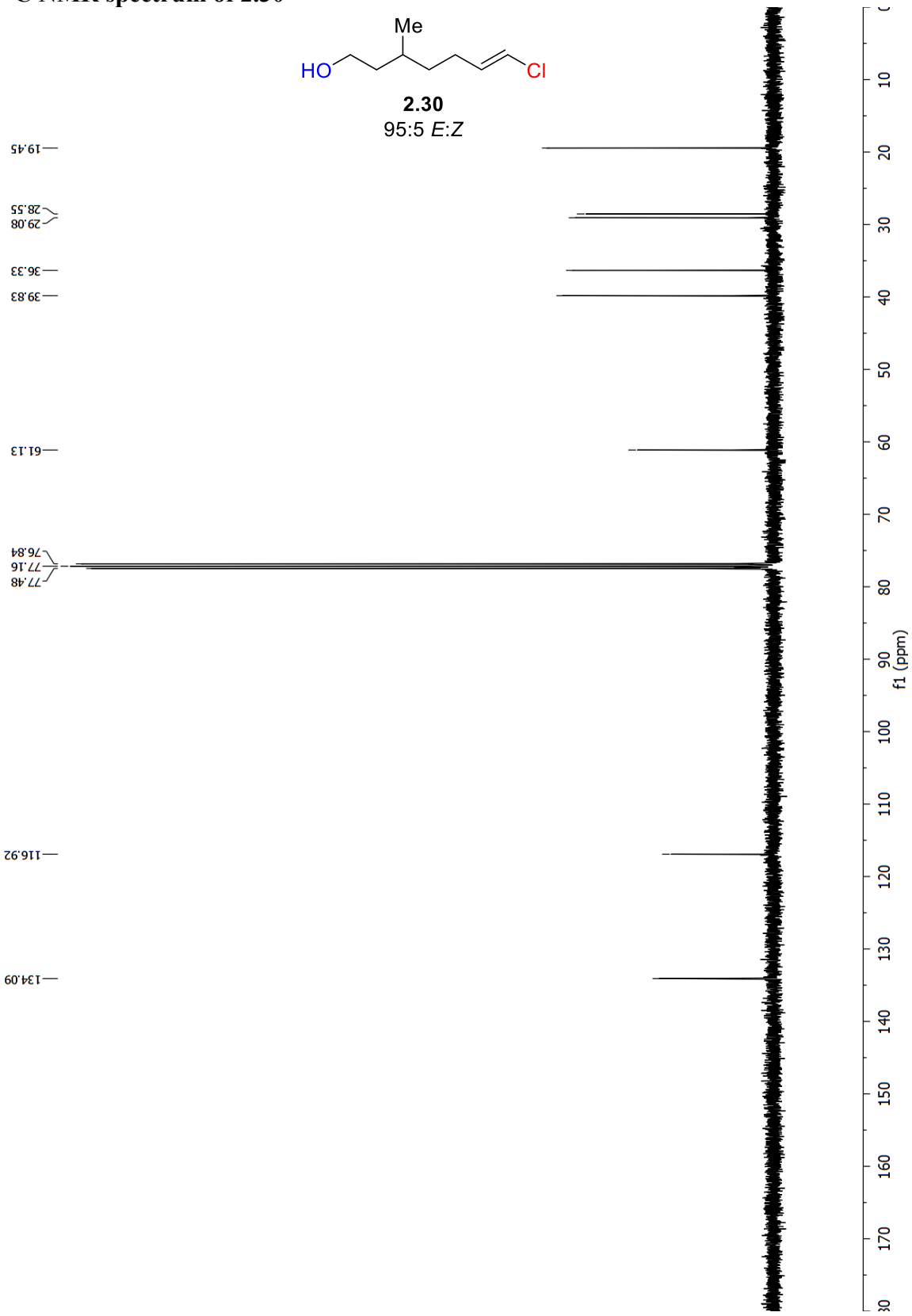
^{19}F NMR spectrum of 2.29



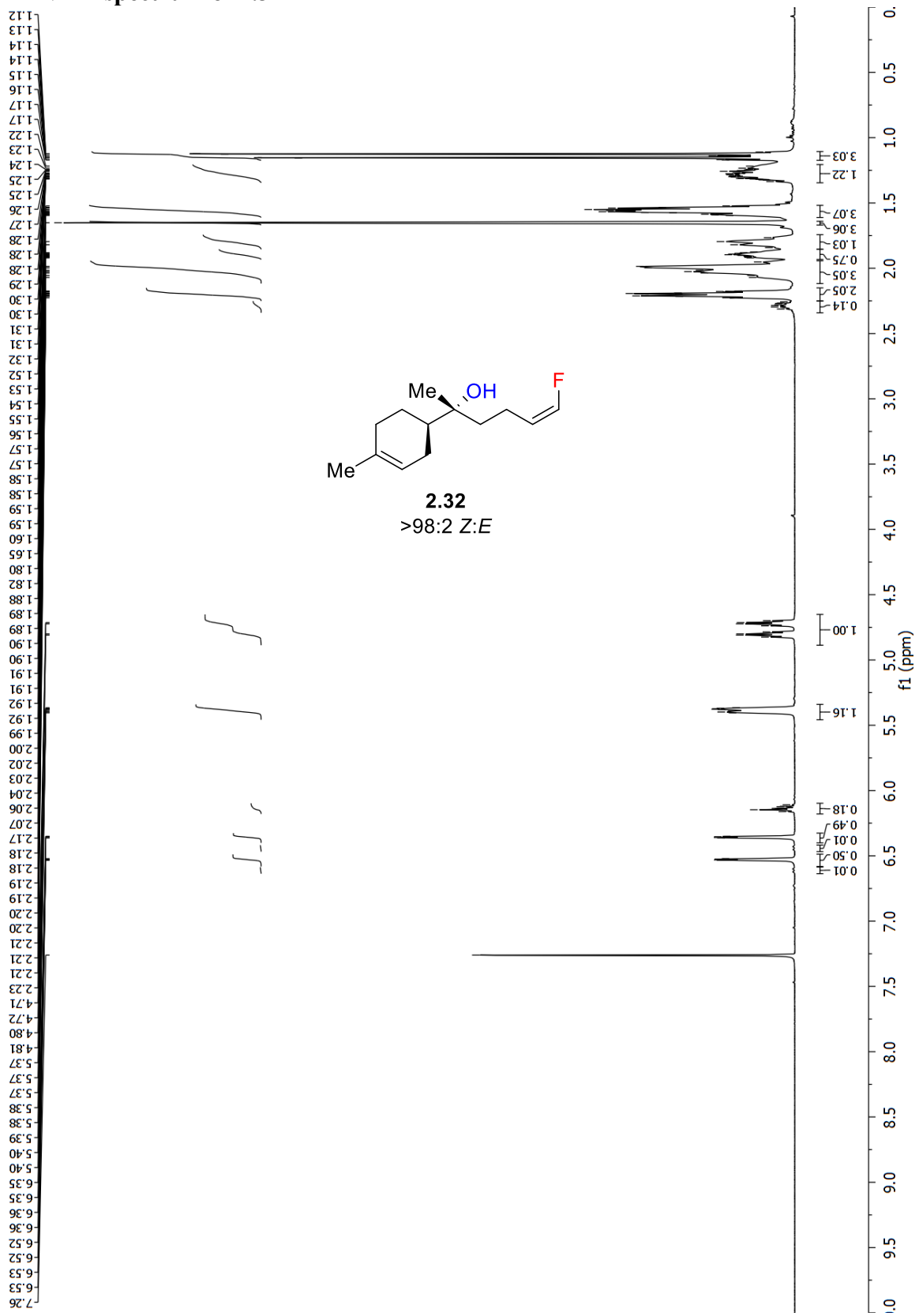
^{1}H NMR spectrum of 2.30



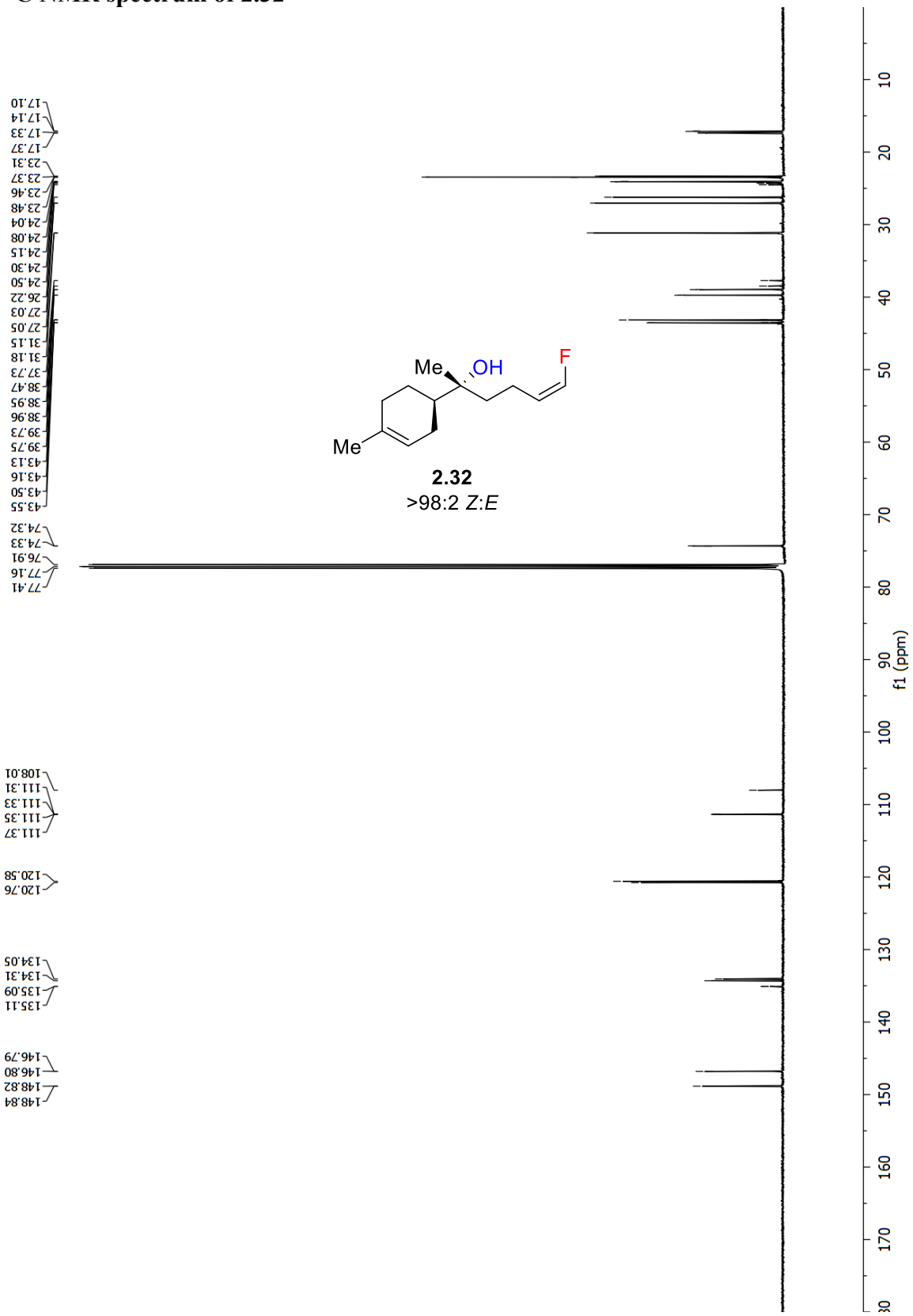
^{13}C NMR spectrum of 2.30



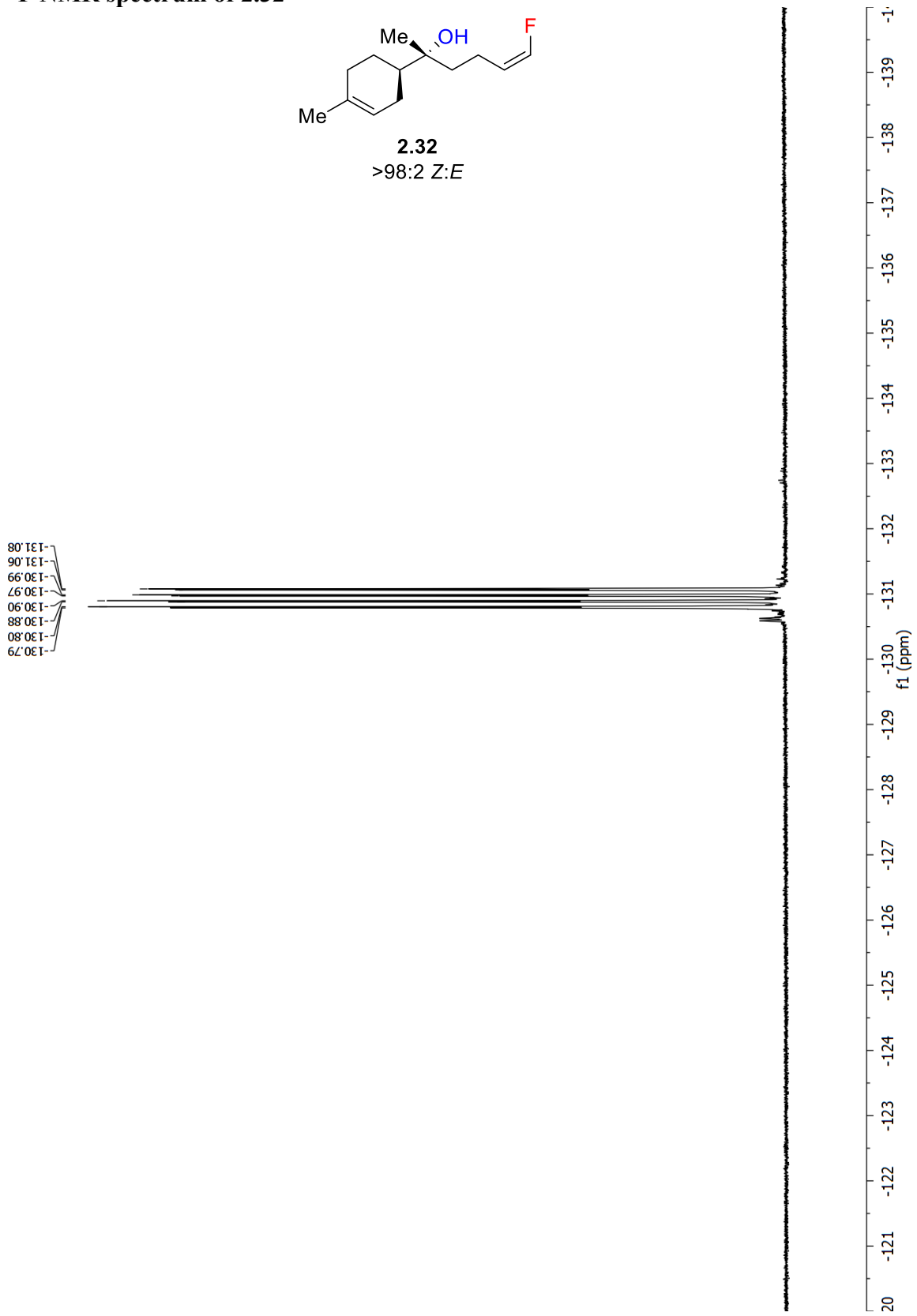
^{1}H NMR spectrum of 2.32



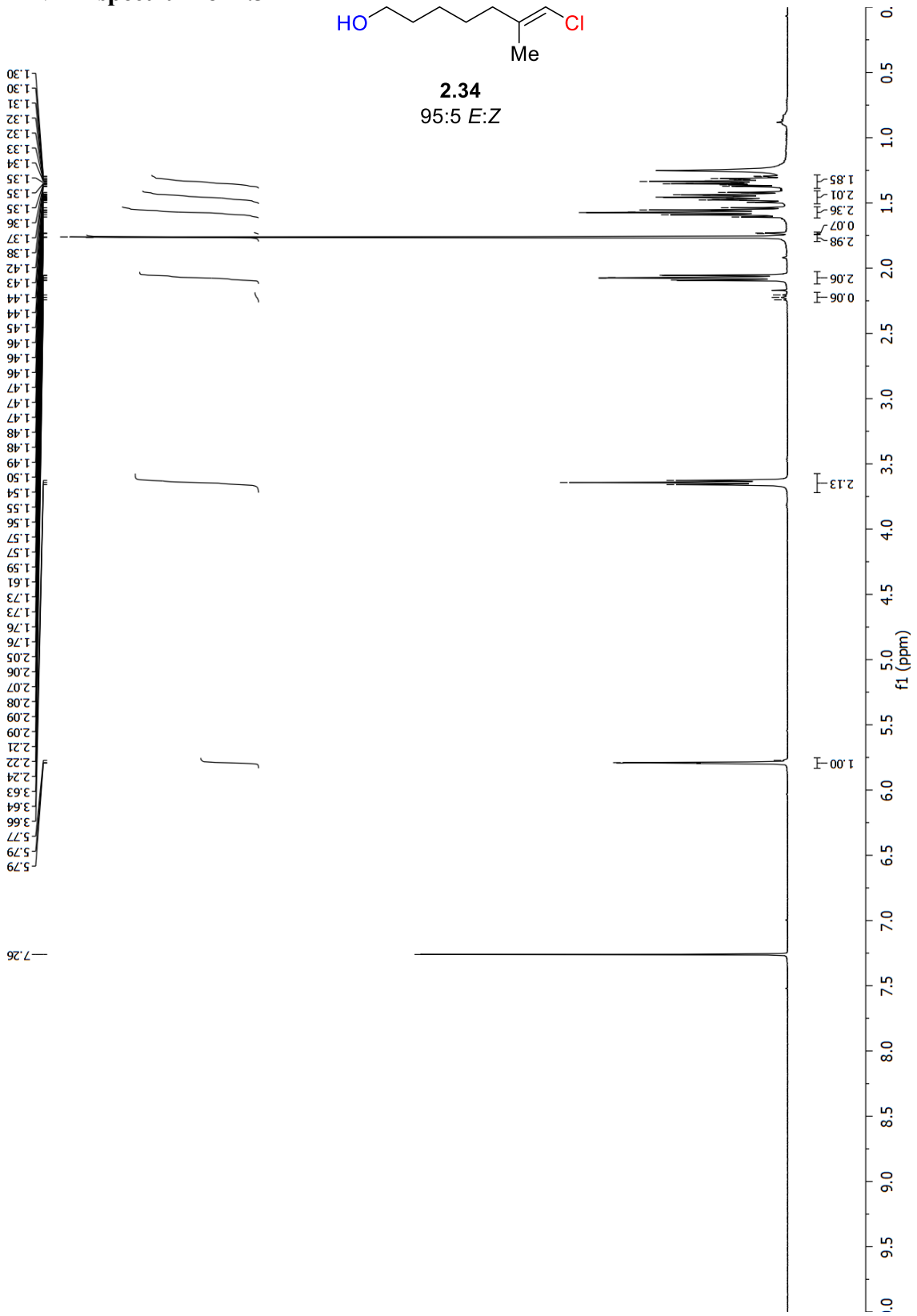
^{13}C NMR spectrum of 2.32



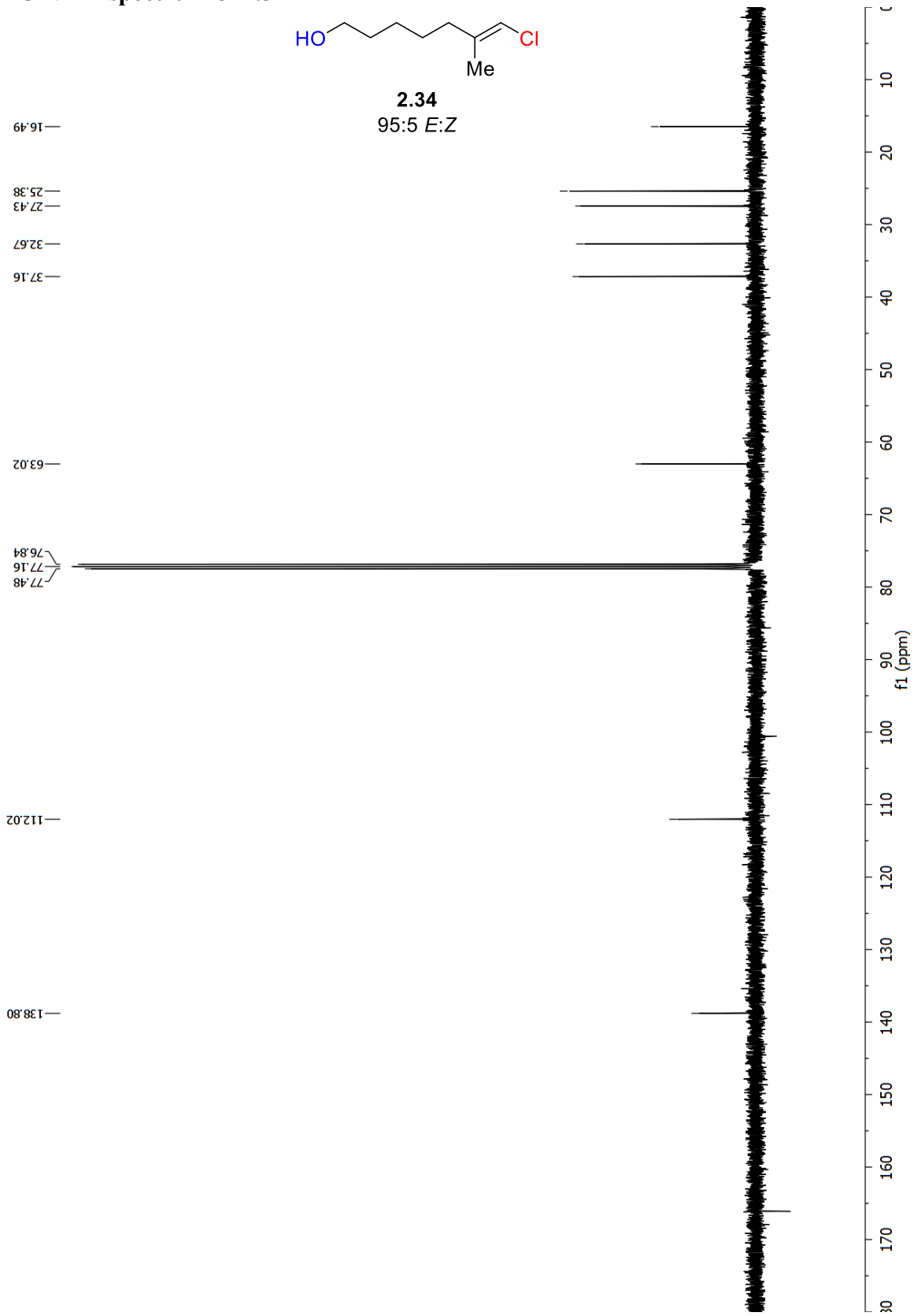
^{19}F NMR spectrum of 2.32



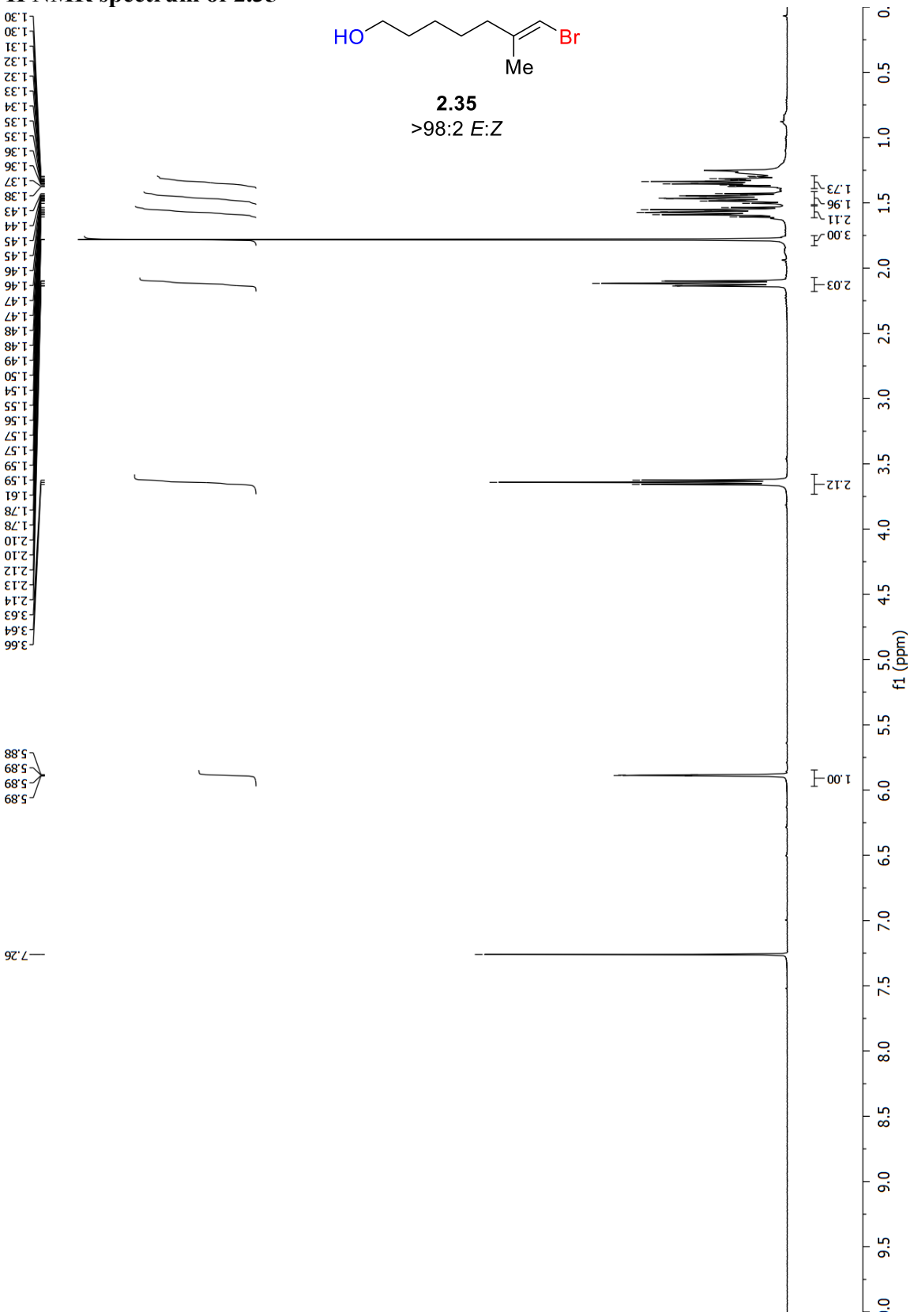
^{1}H NMR spectrum of 2.34



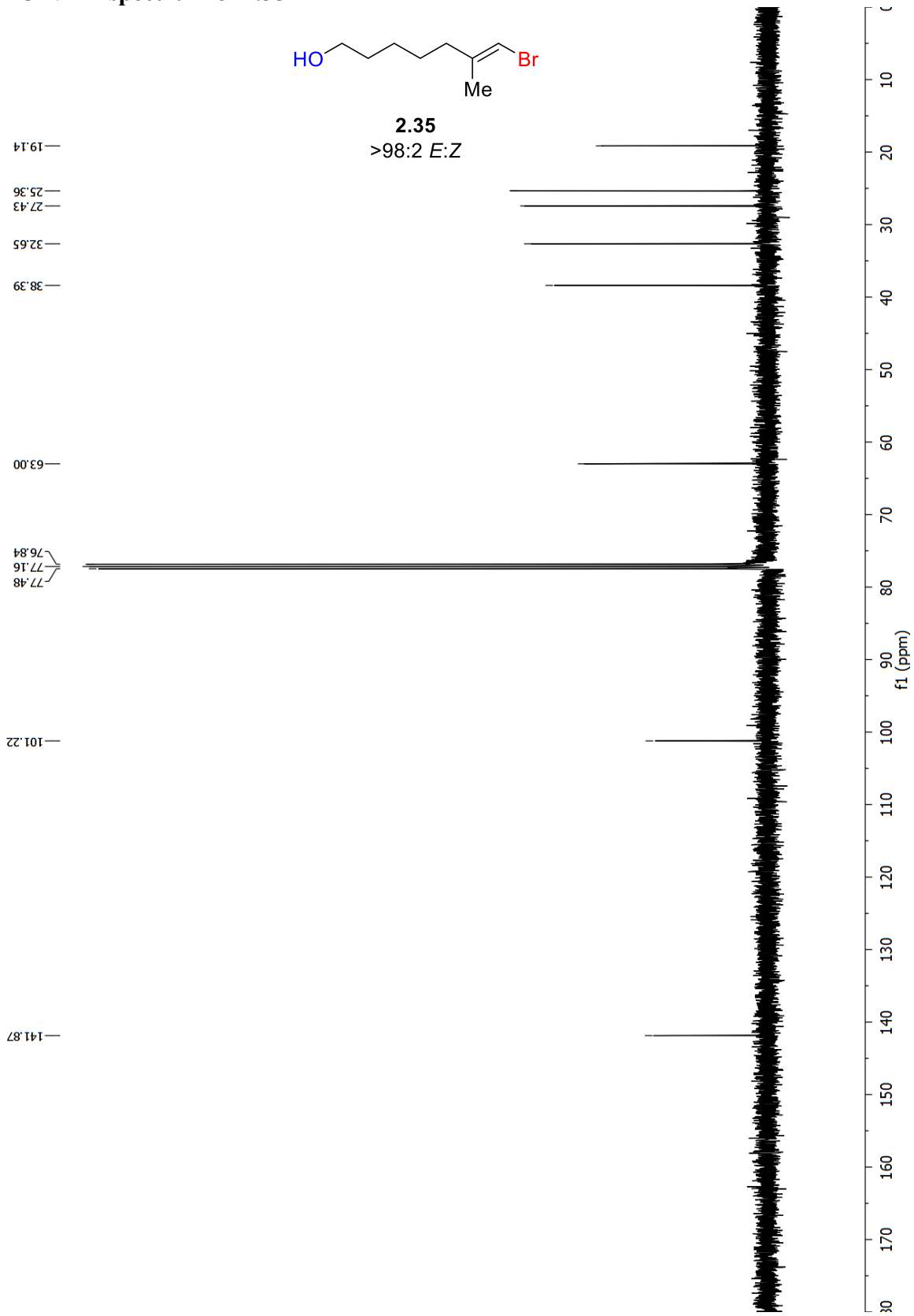
^{13}C NMR spectrum of 2.34



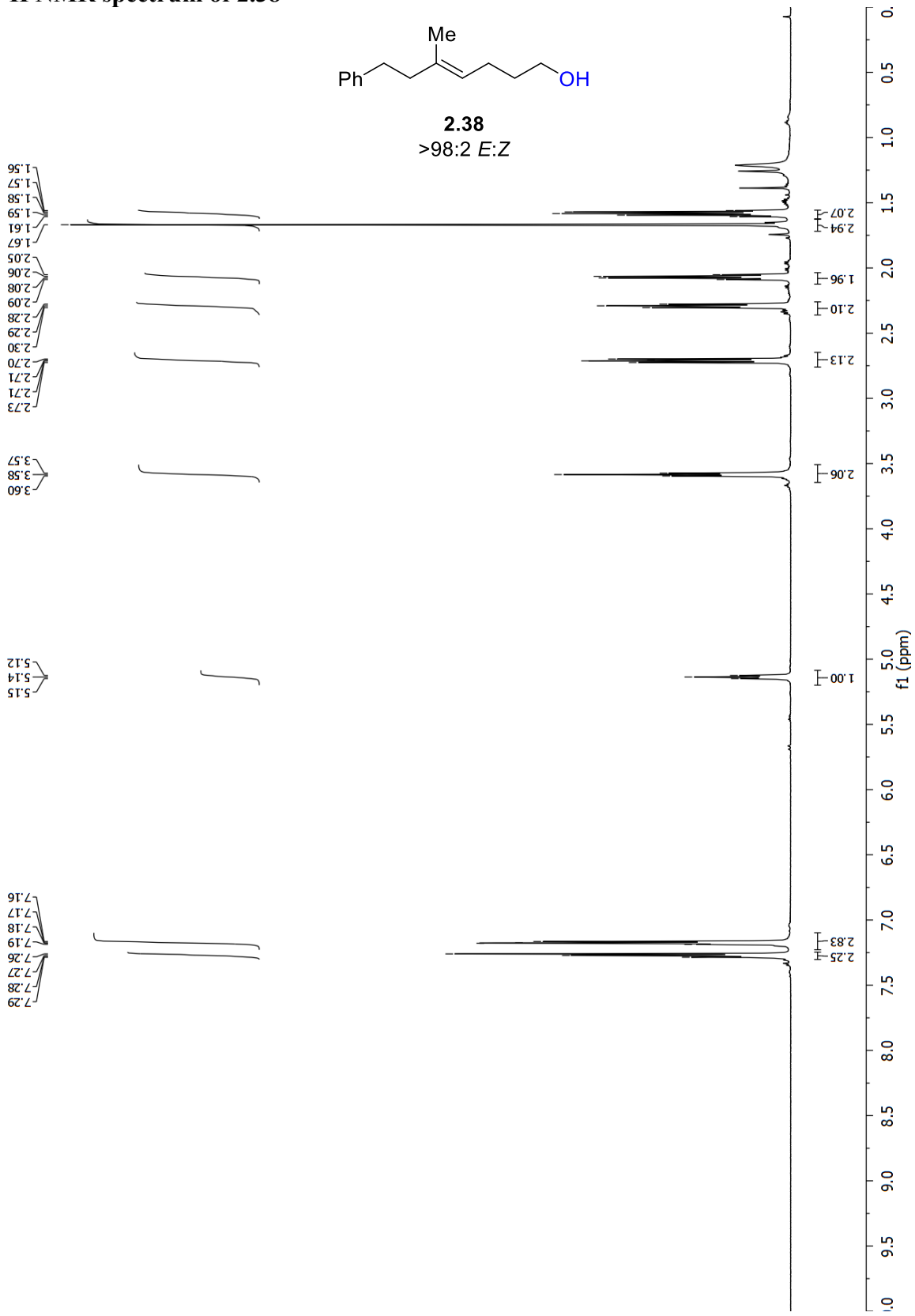
^{1}H NMR spectrum of 2.35



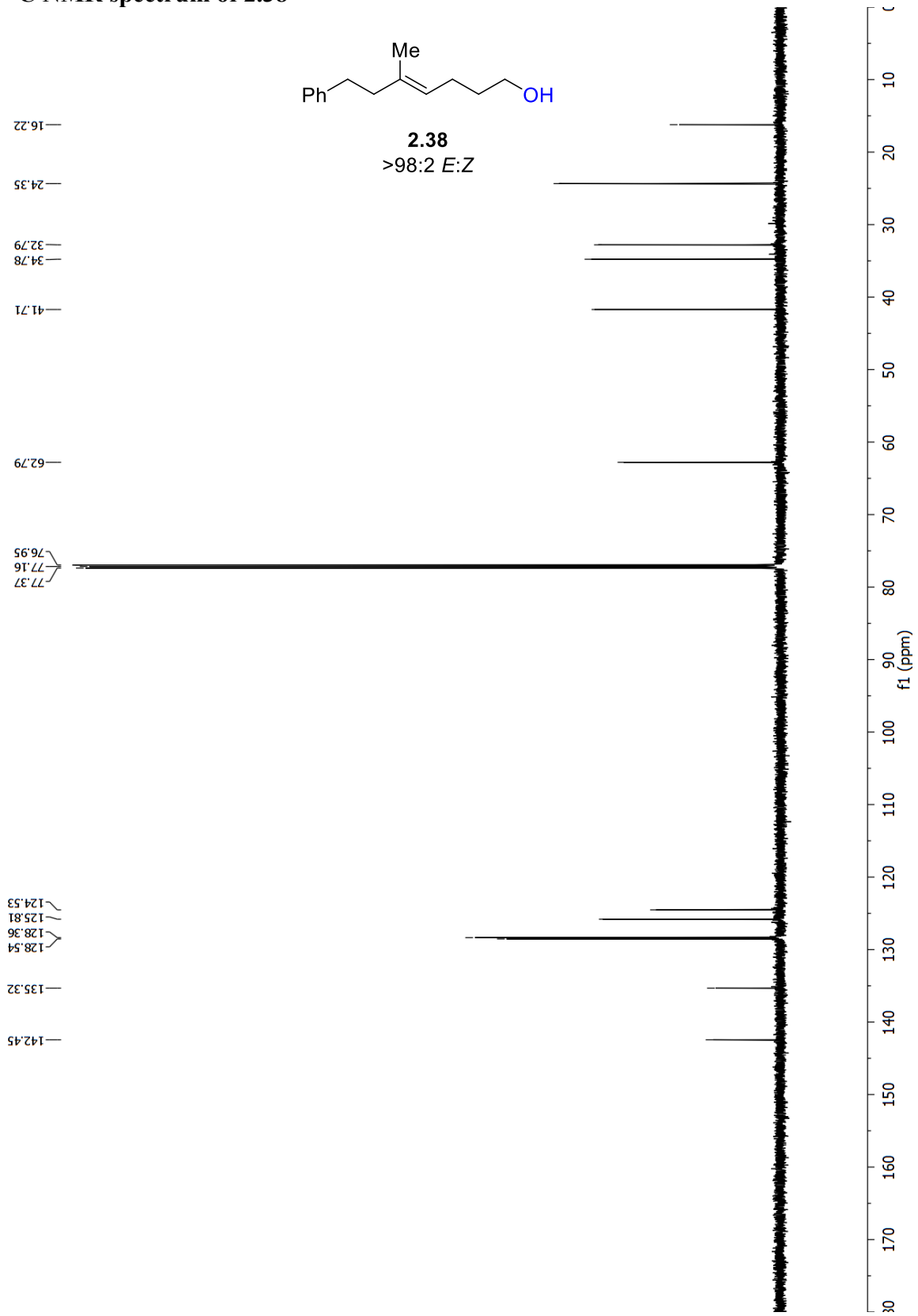
^{13}C NMR spectrum of 2.35



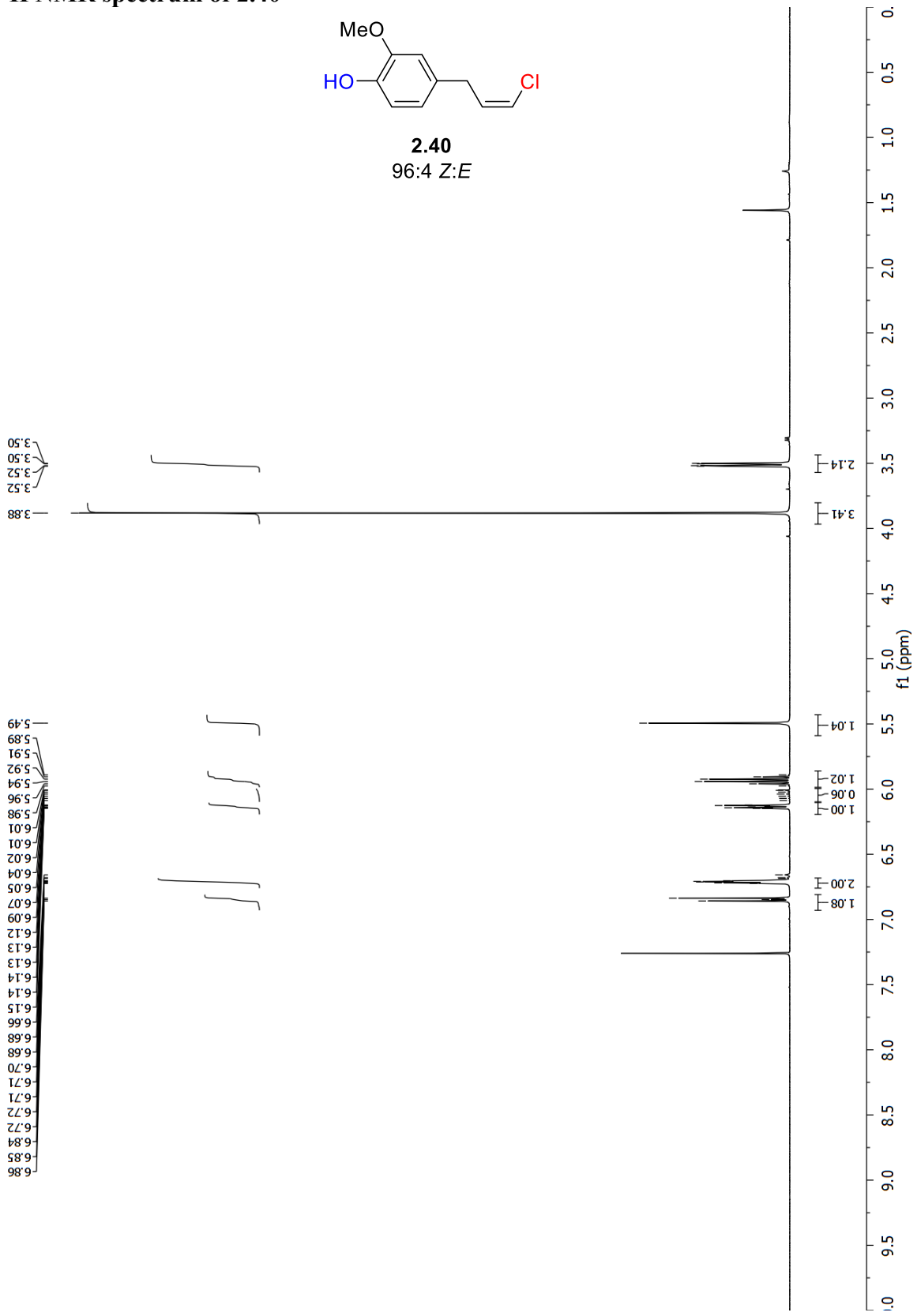
^{1}H NMR spectrum of 2.38



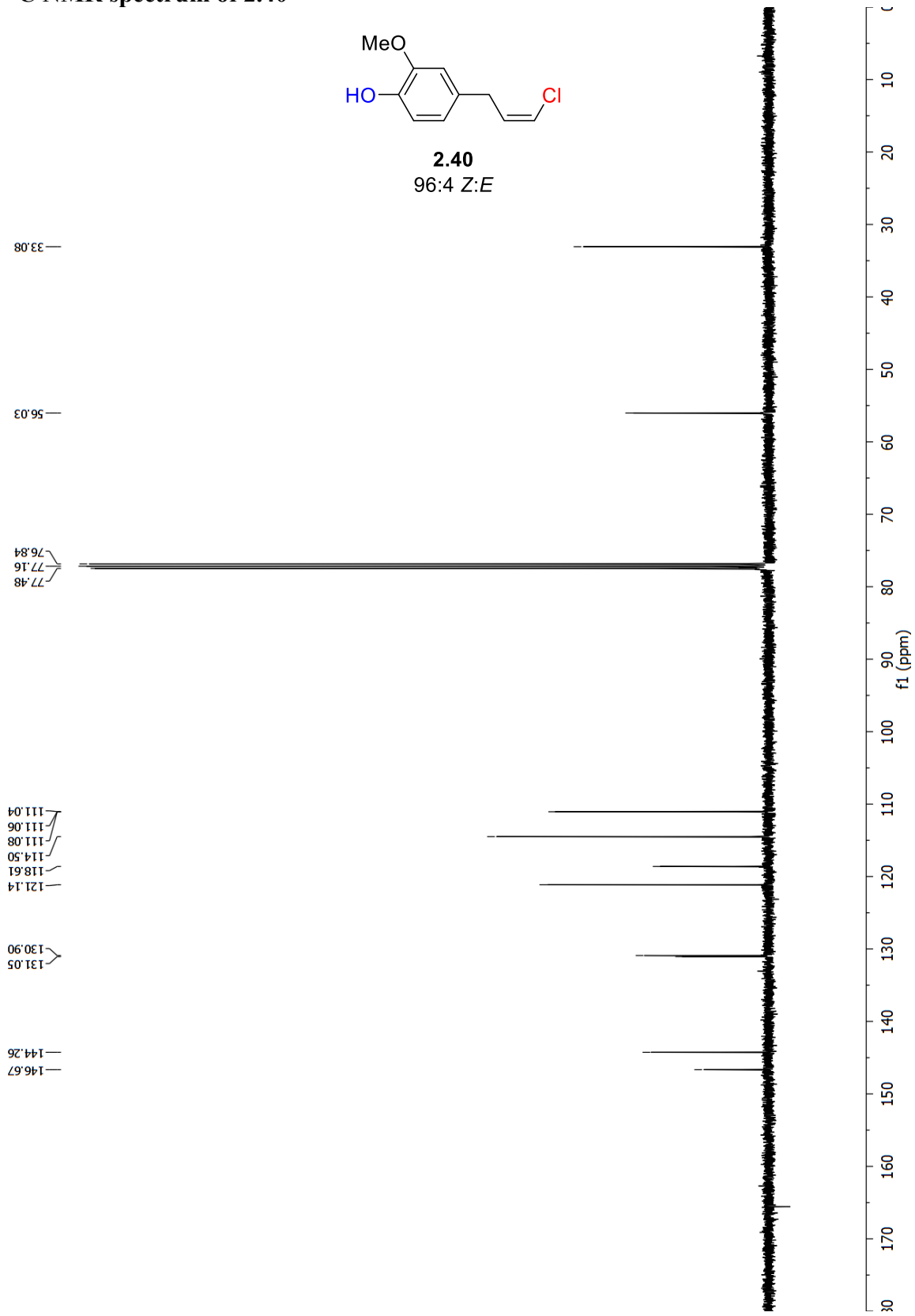
^{13}C NMR spectrum of 2.38



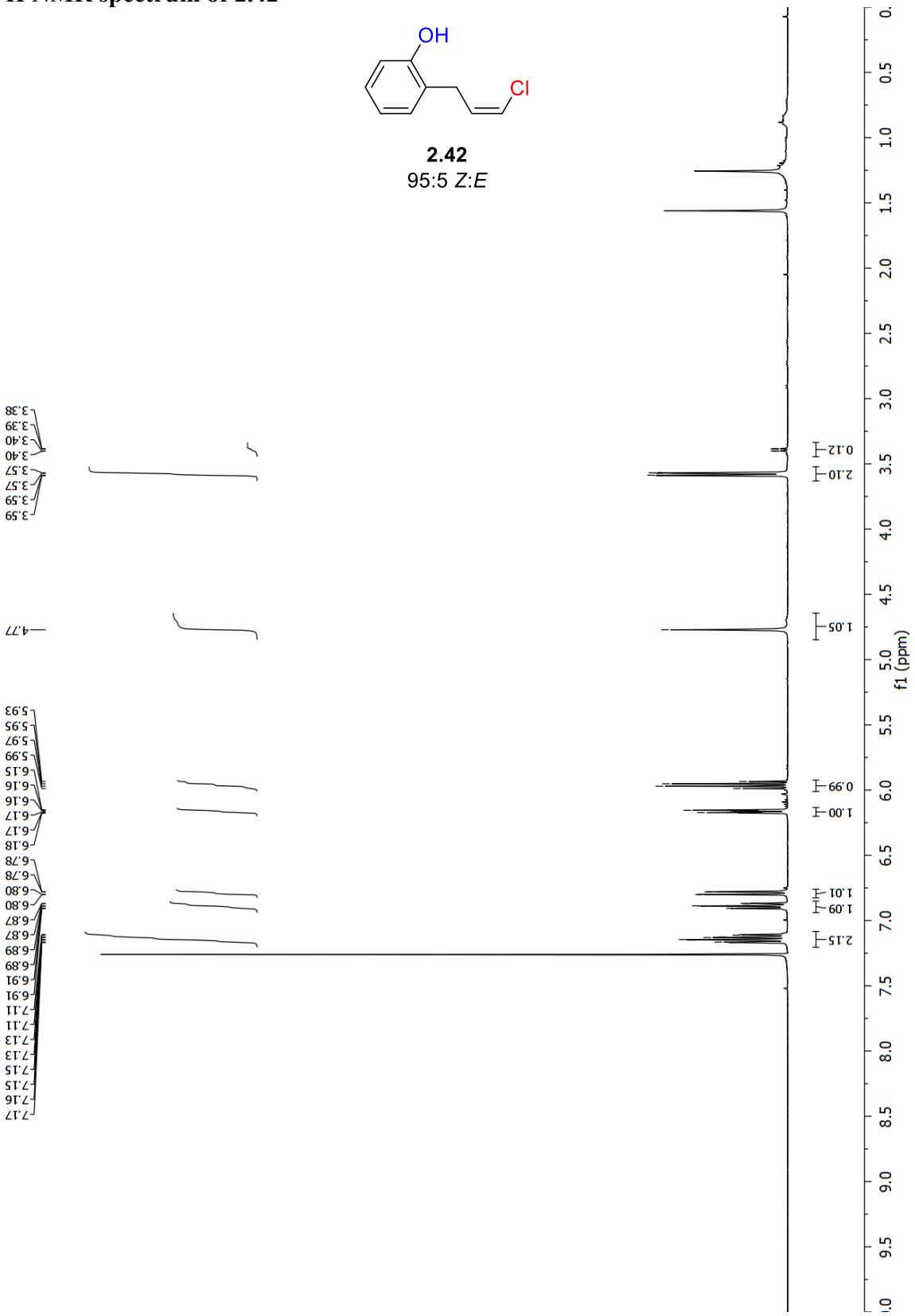
^{1}H NMR spectrum of 2.40



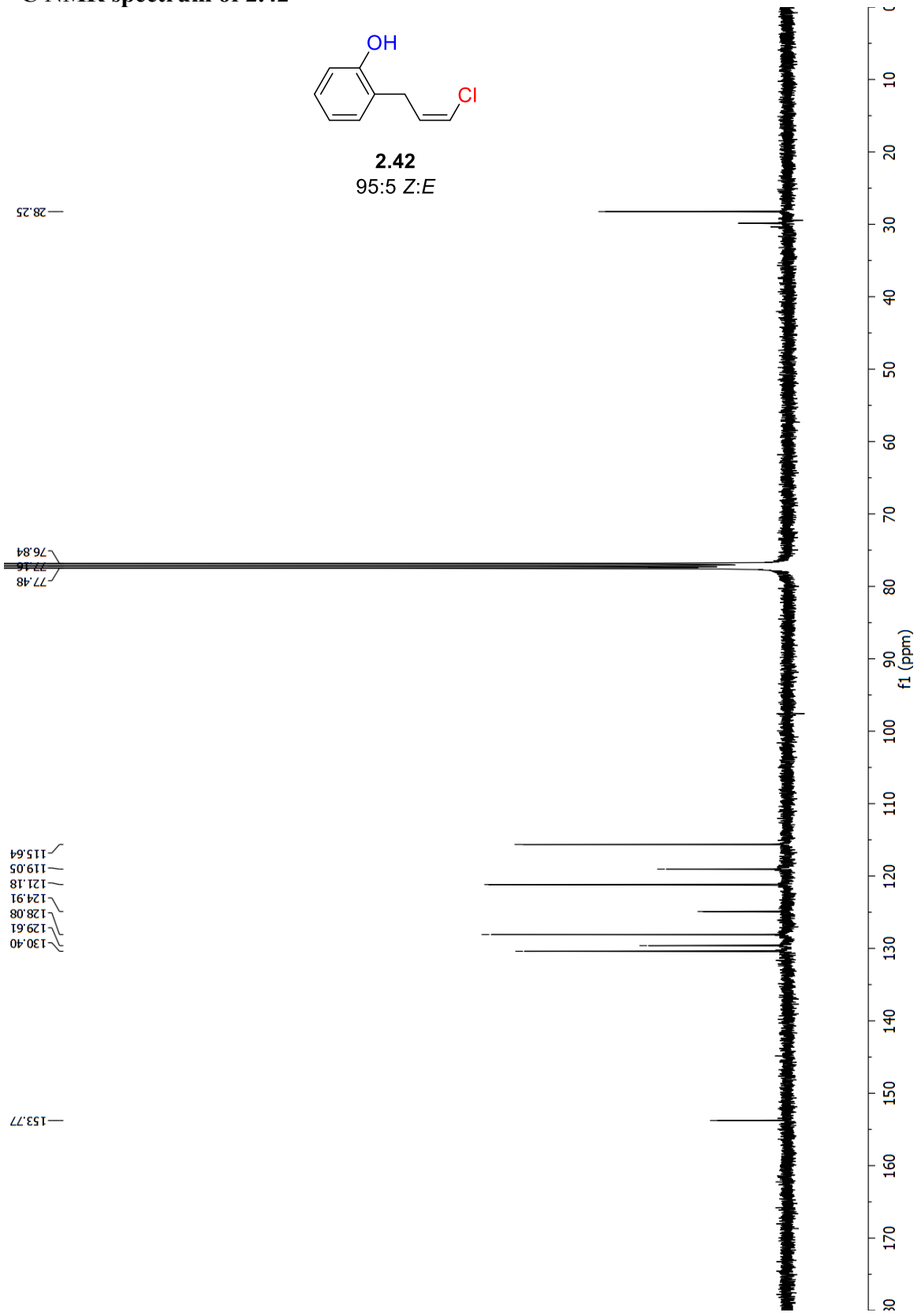
^{13}C NMR spectrum of 2.40



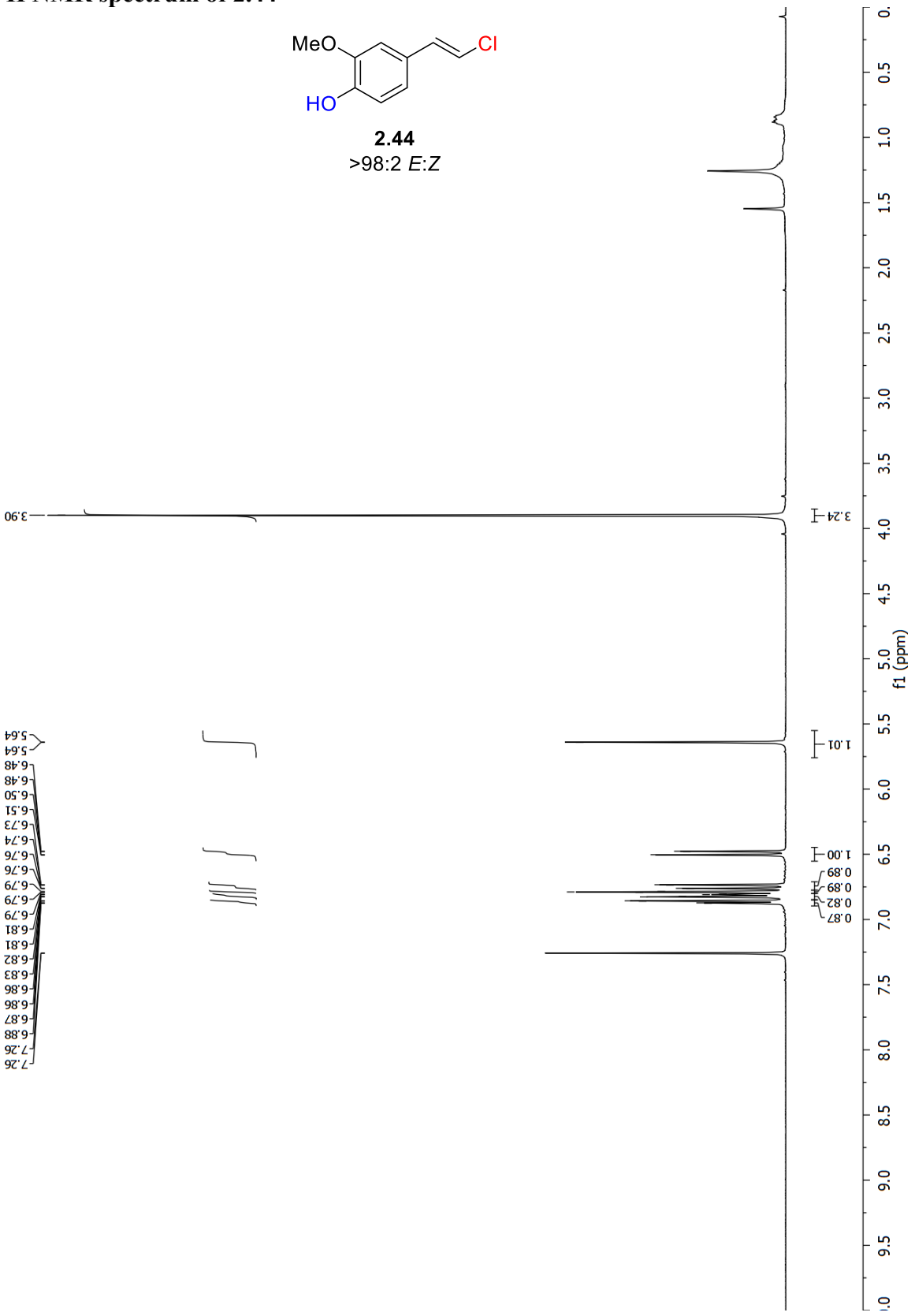
^{1}H NMR spectrum of 2.42



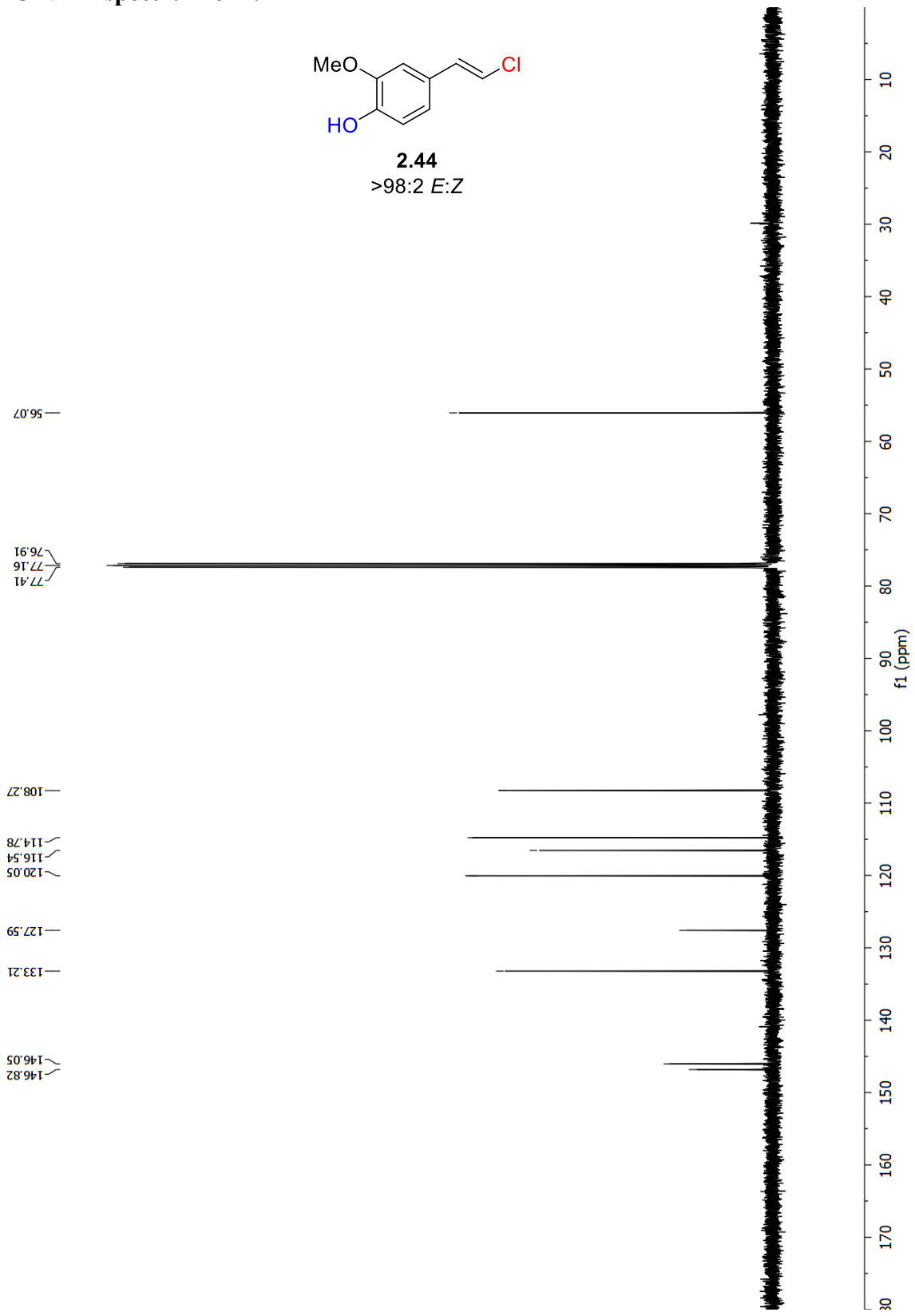
^{13}C NMR spectrum of 2.42



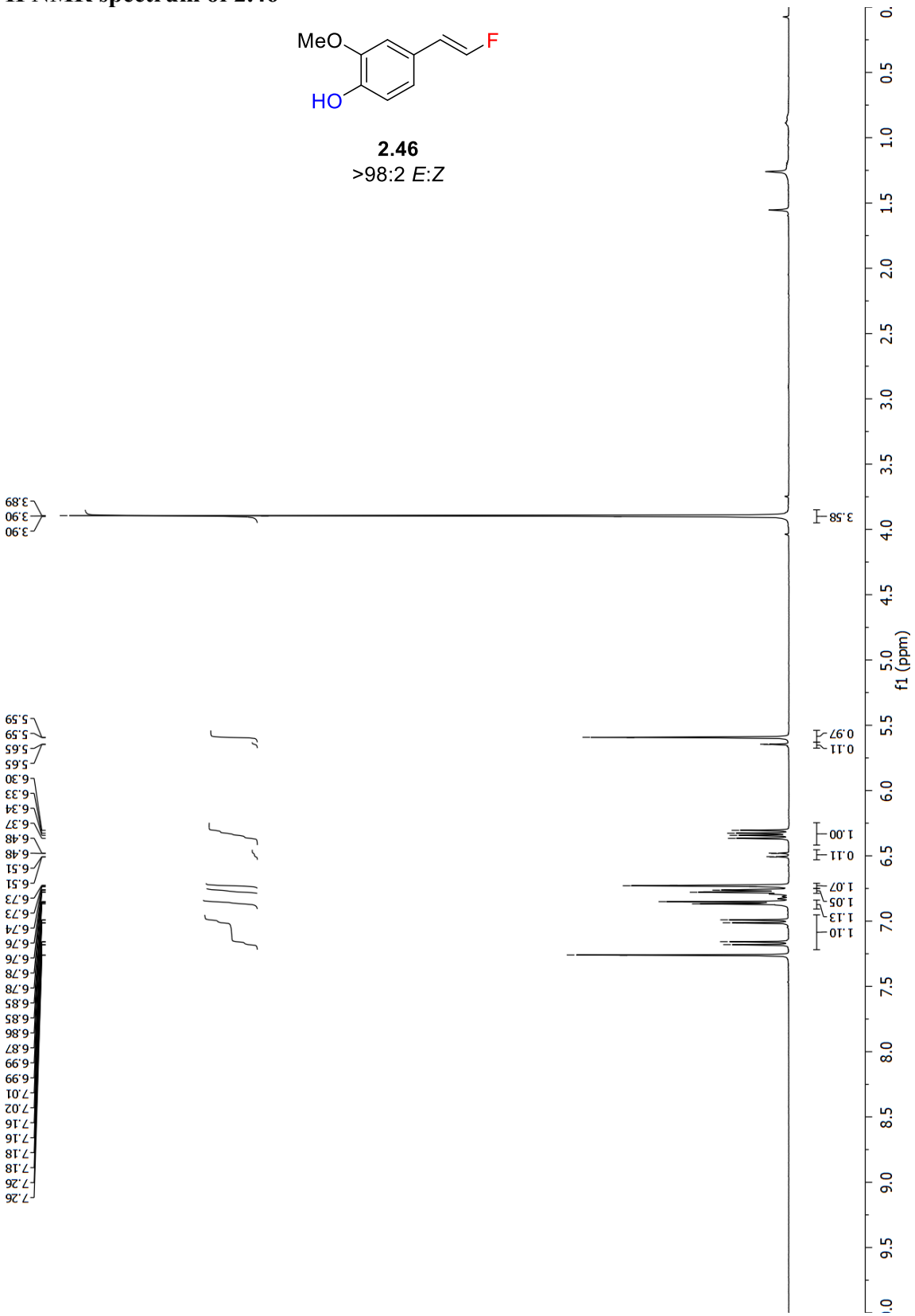
^{1}H NMR spectrum of 2.44



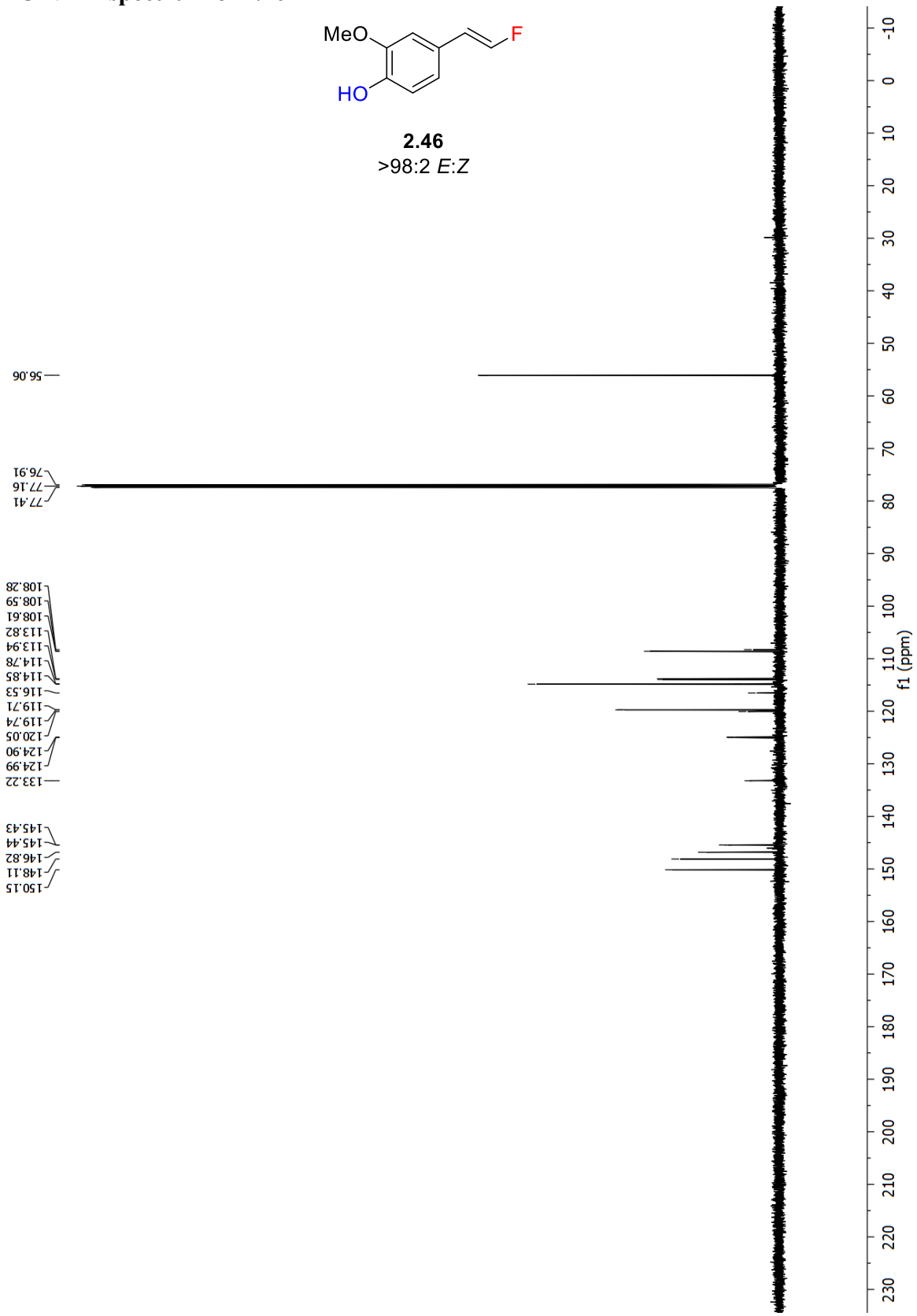
^{13}C NMR spectrum of 2.44



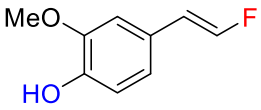
^{1}H NMR spectrum of 2.46



^{13}C NMR spectrum of 2.46

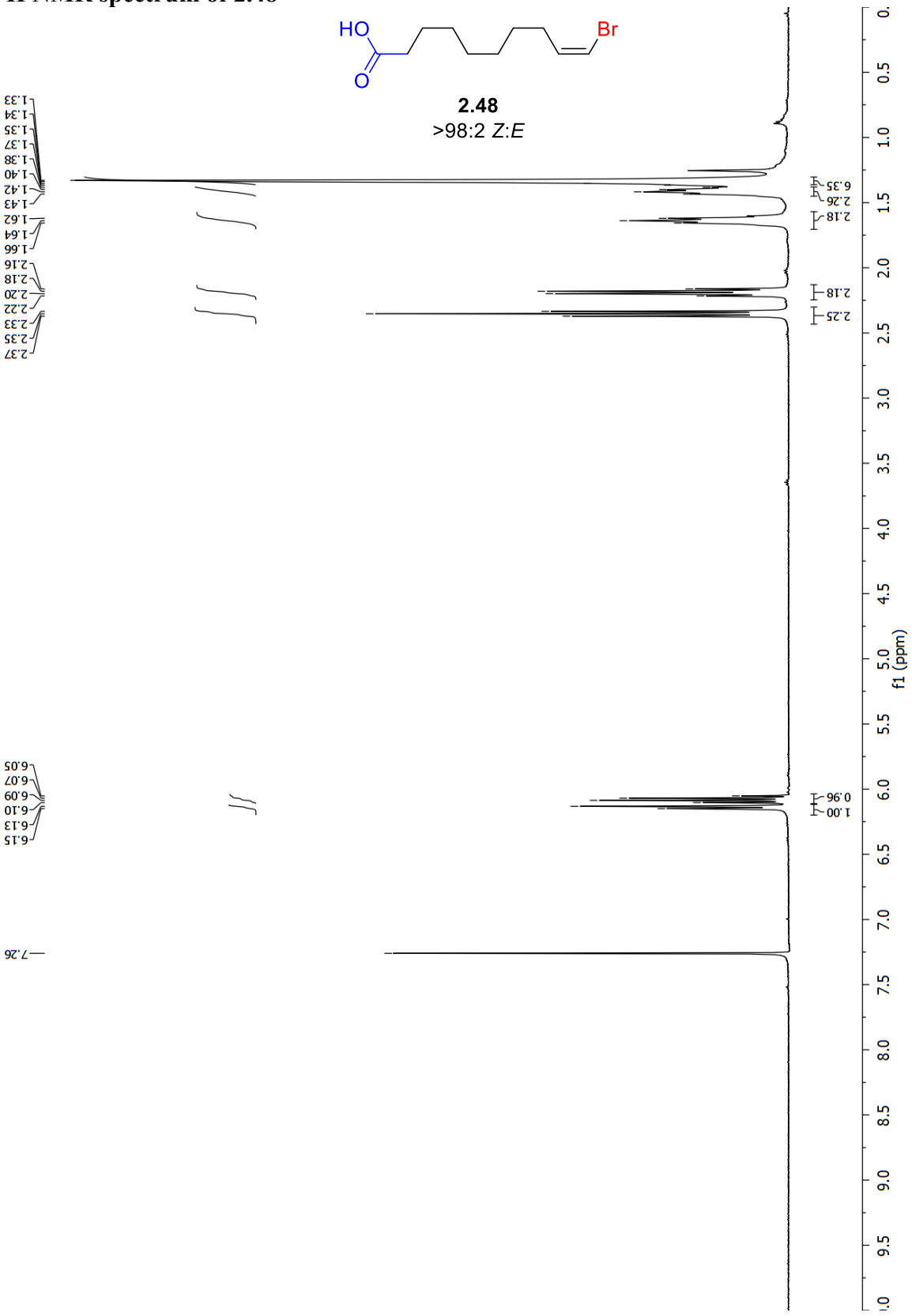


^{19}F NMR spectrum of 2.46

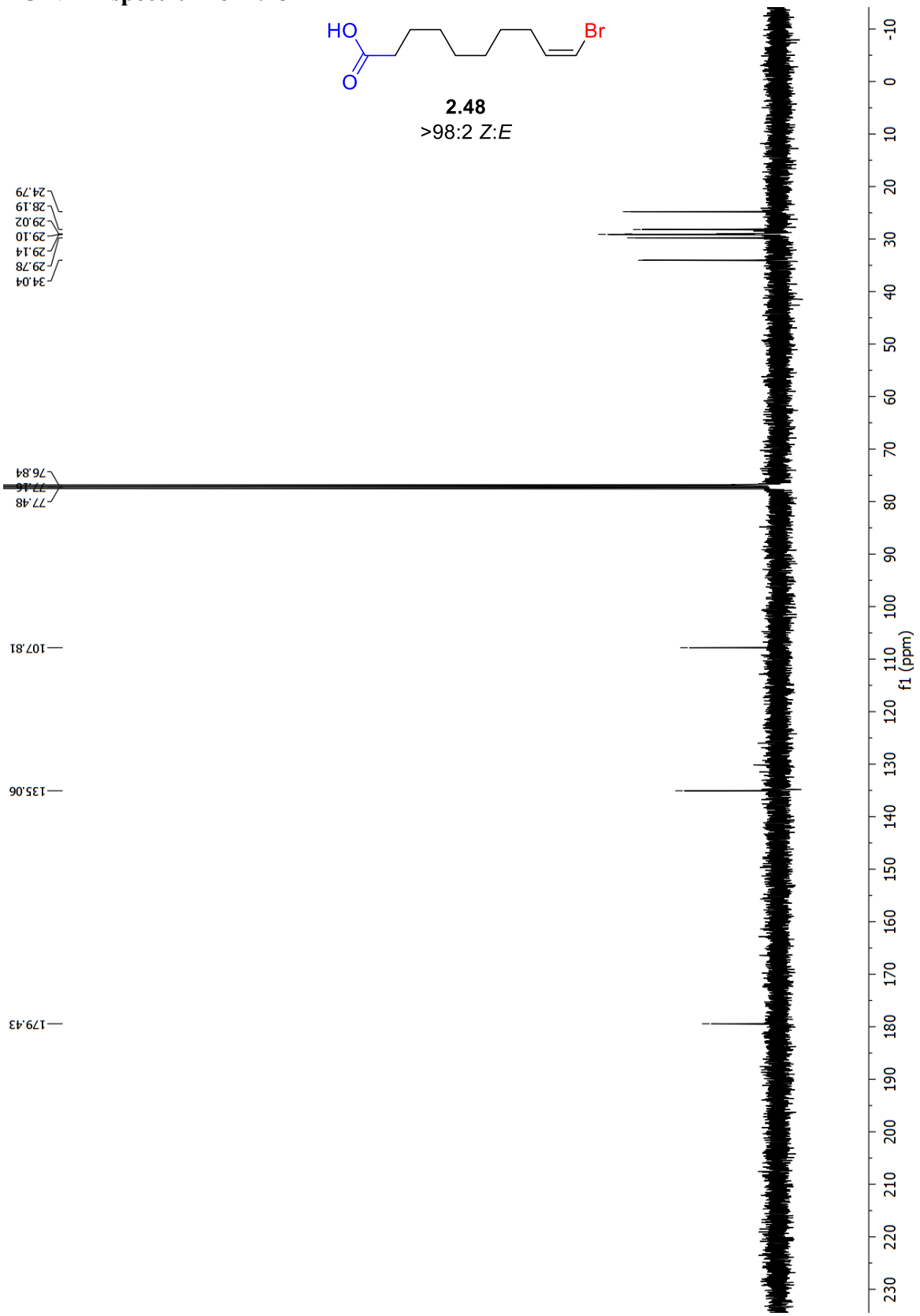


2.46
>98:2 *E*:*Z*

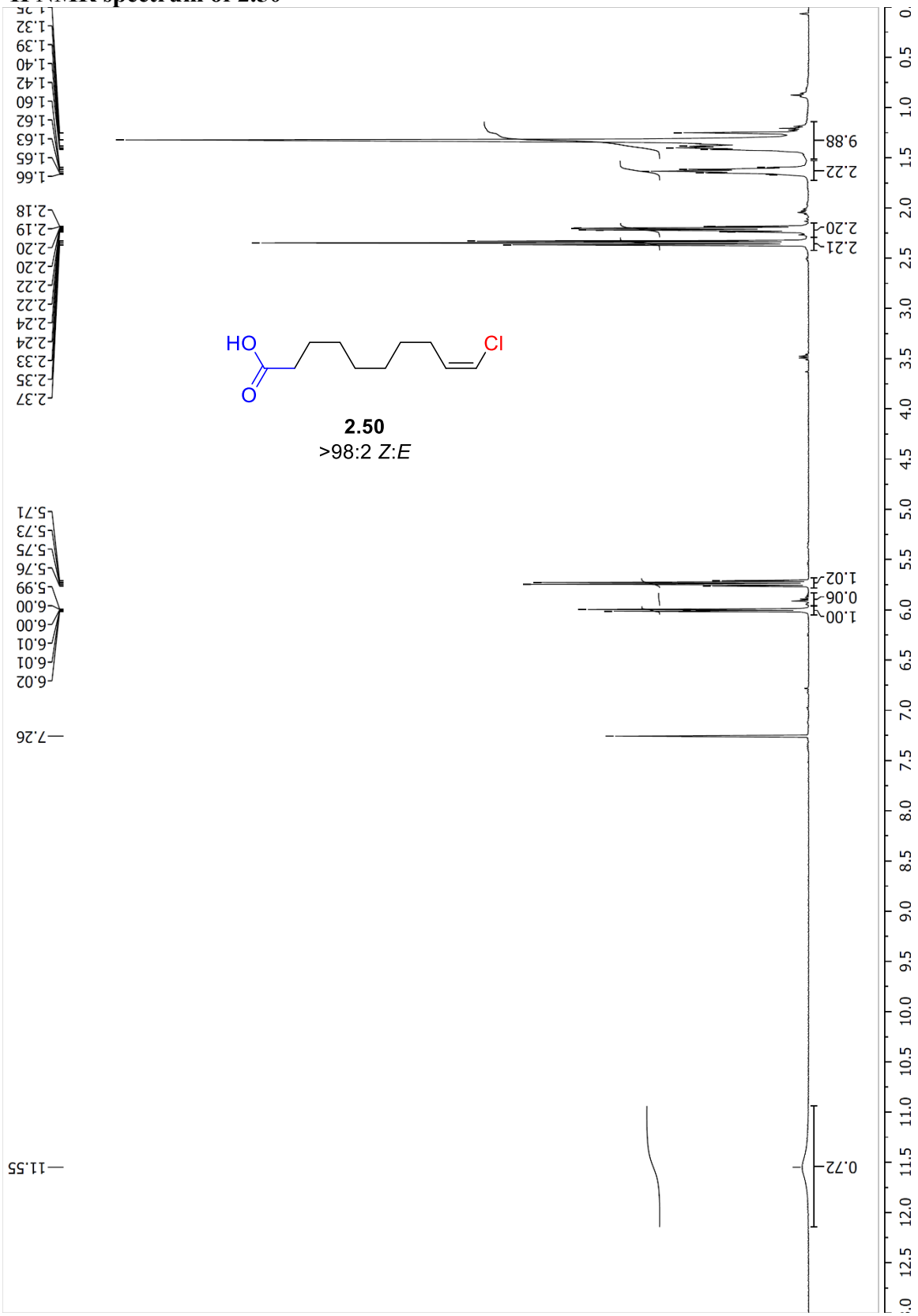
^{1}H NMR spectrum of 2.48



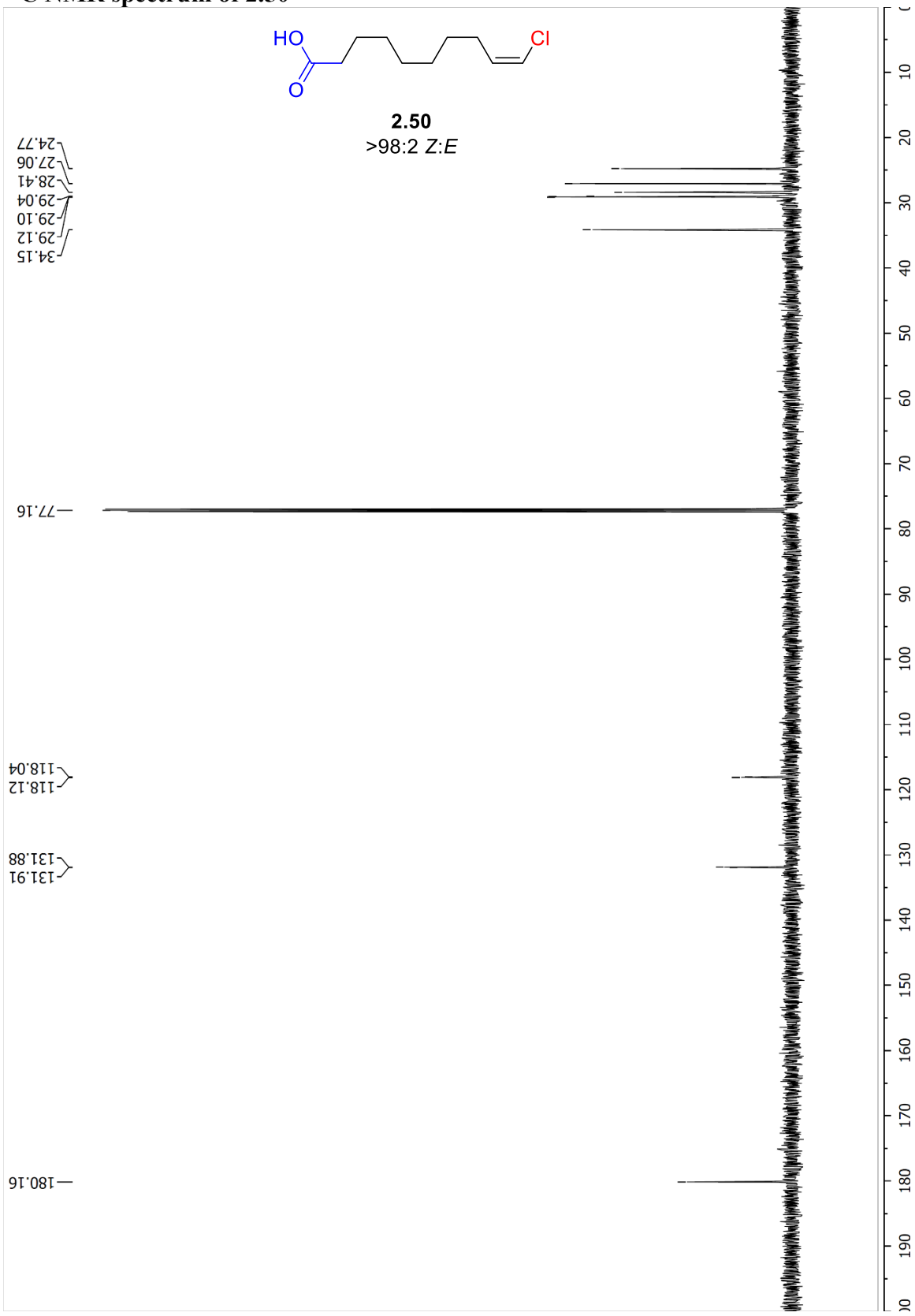
^{13}C NMR spectrum of 2.48



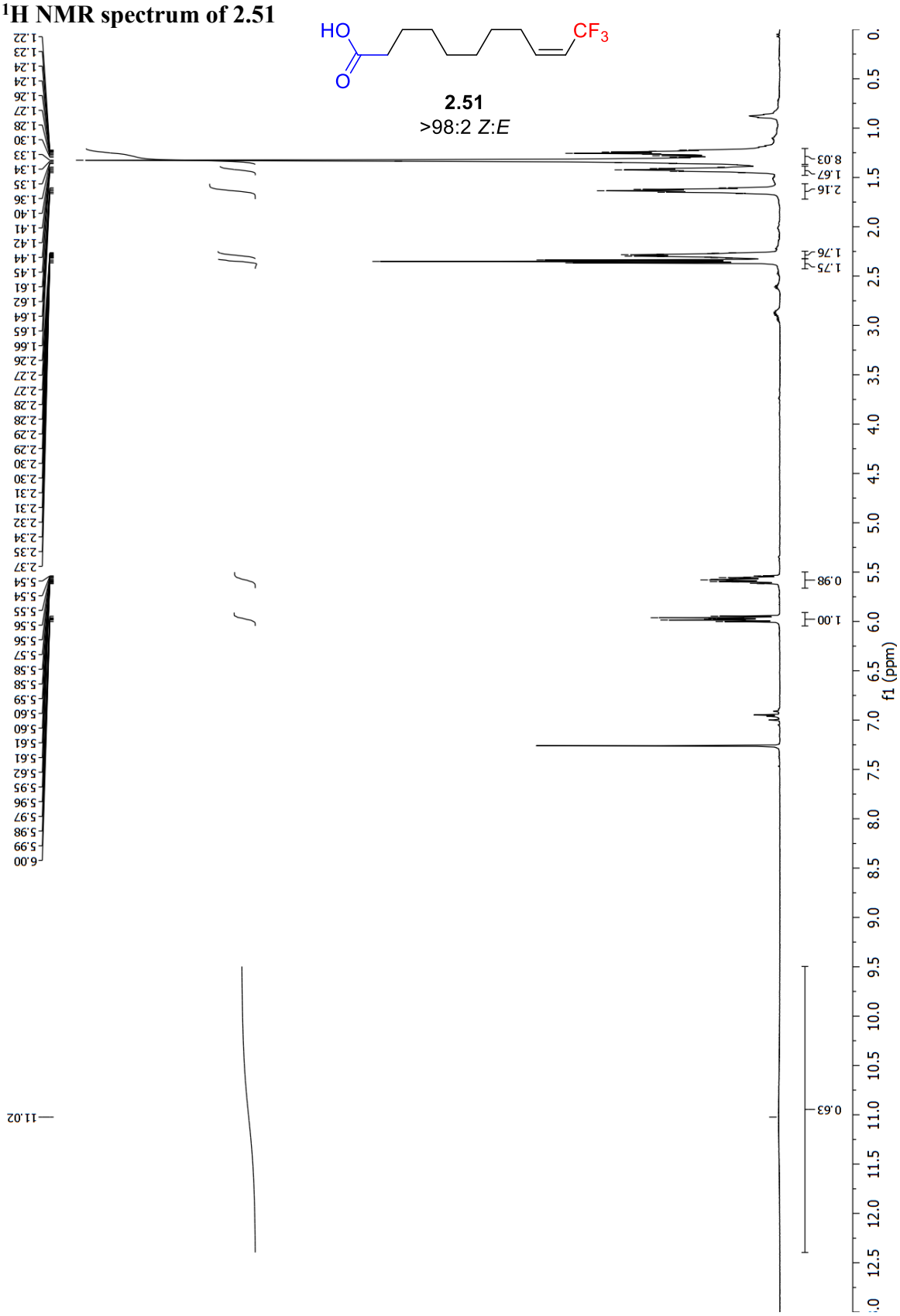
^{1}H NMR spectrum of 2.50



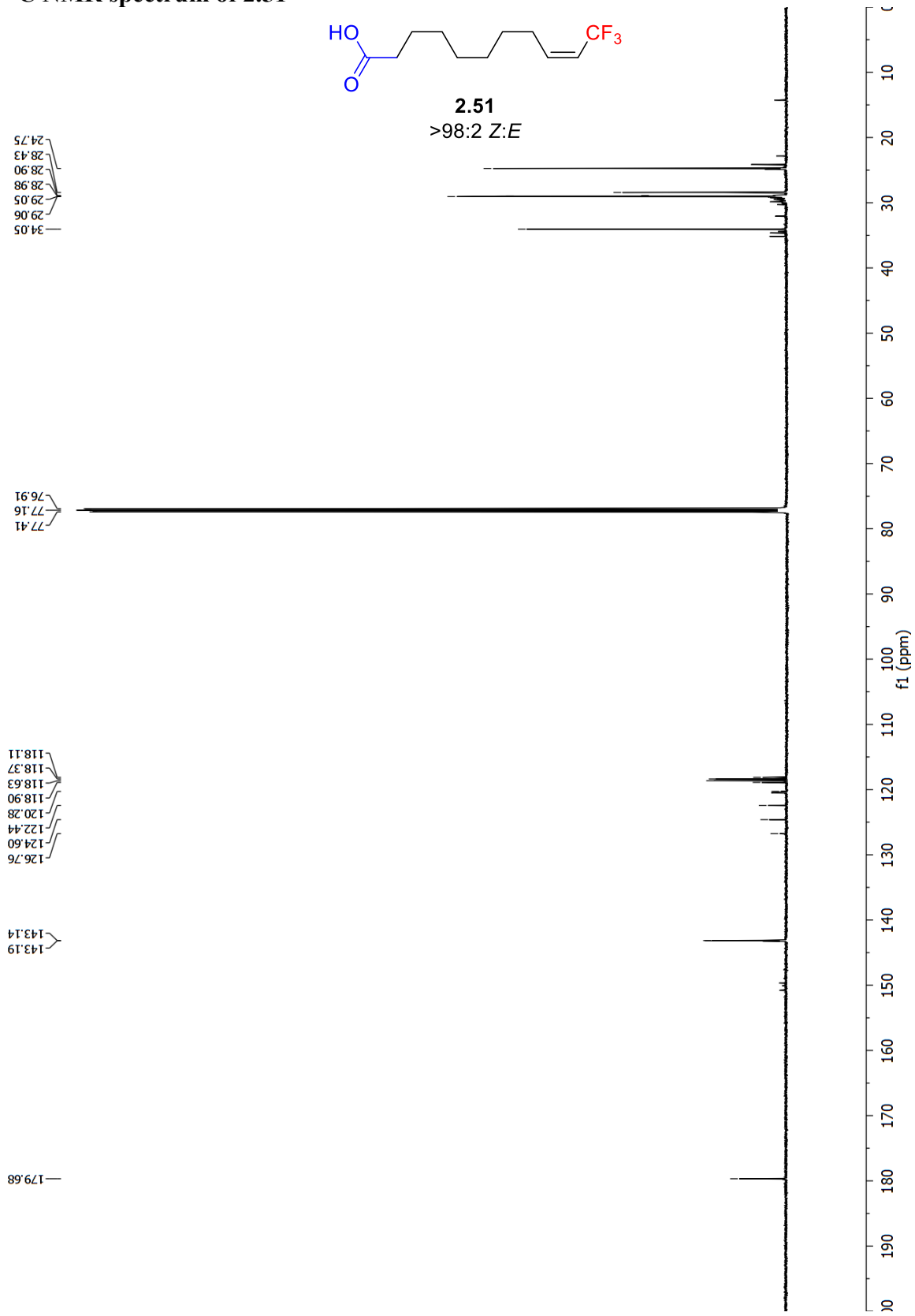
^{13}C NMR spectrum of 2.50



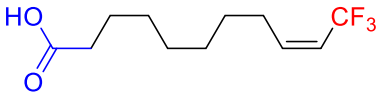
^{1}H NMR spectrum of 2.51



^{13}C NMR spectrum of 2.51

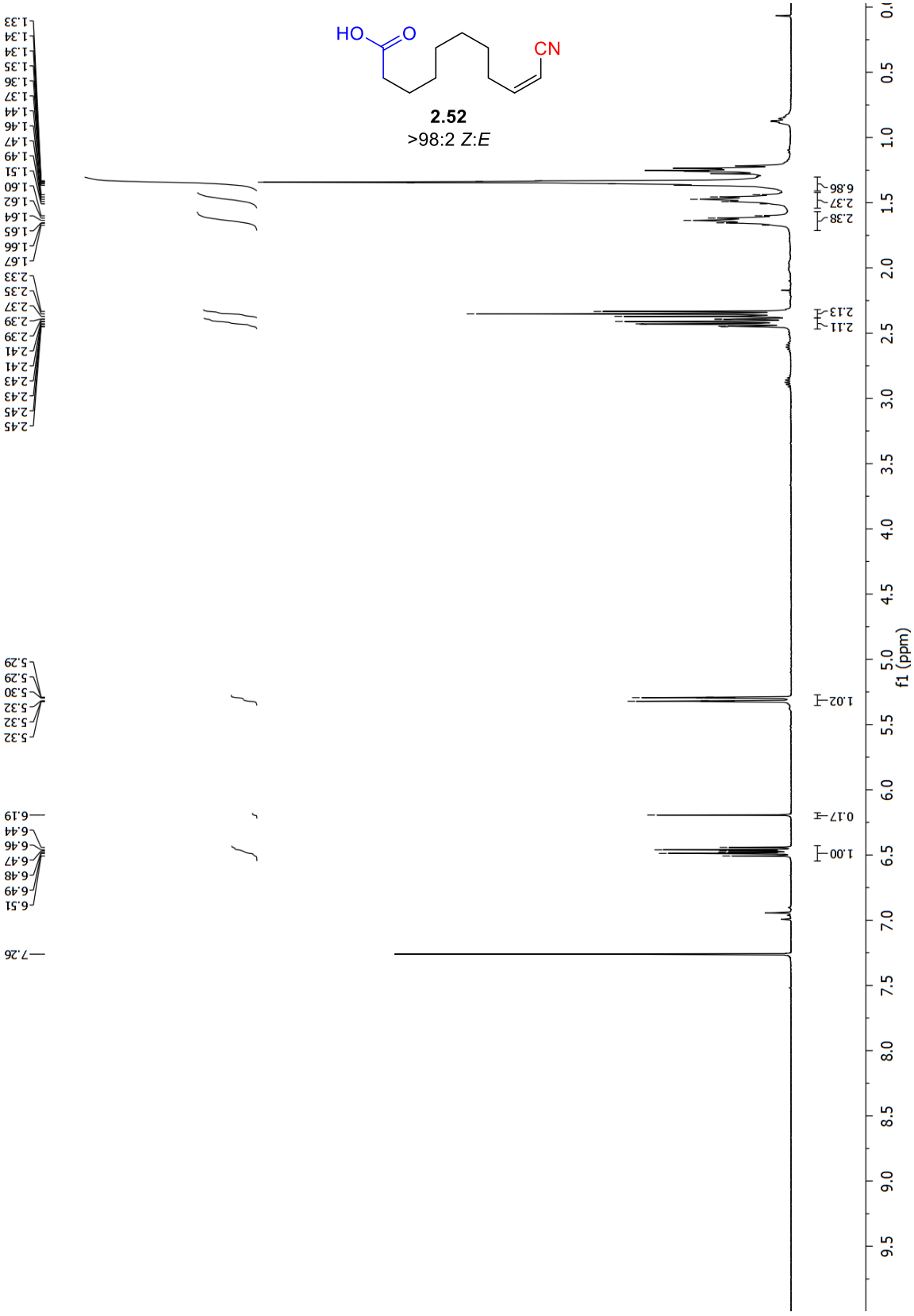


^{19}F NMR spectrum of 2.51

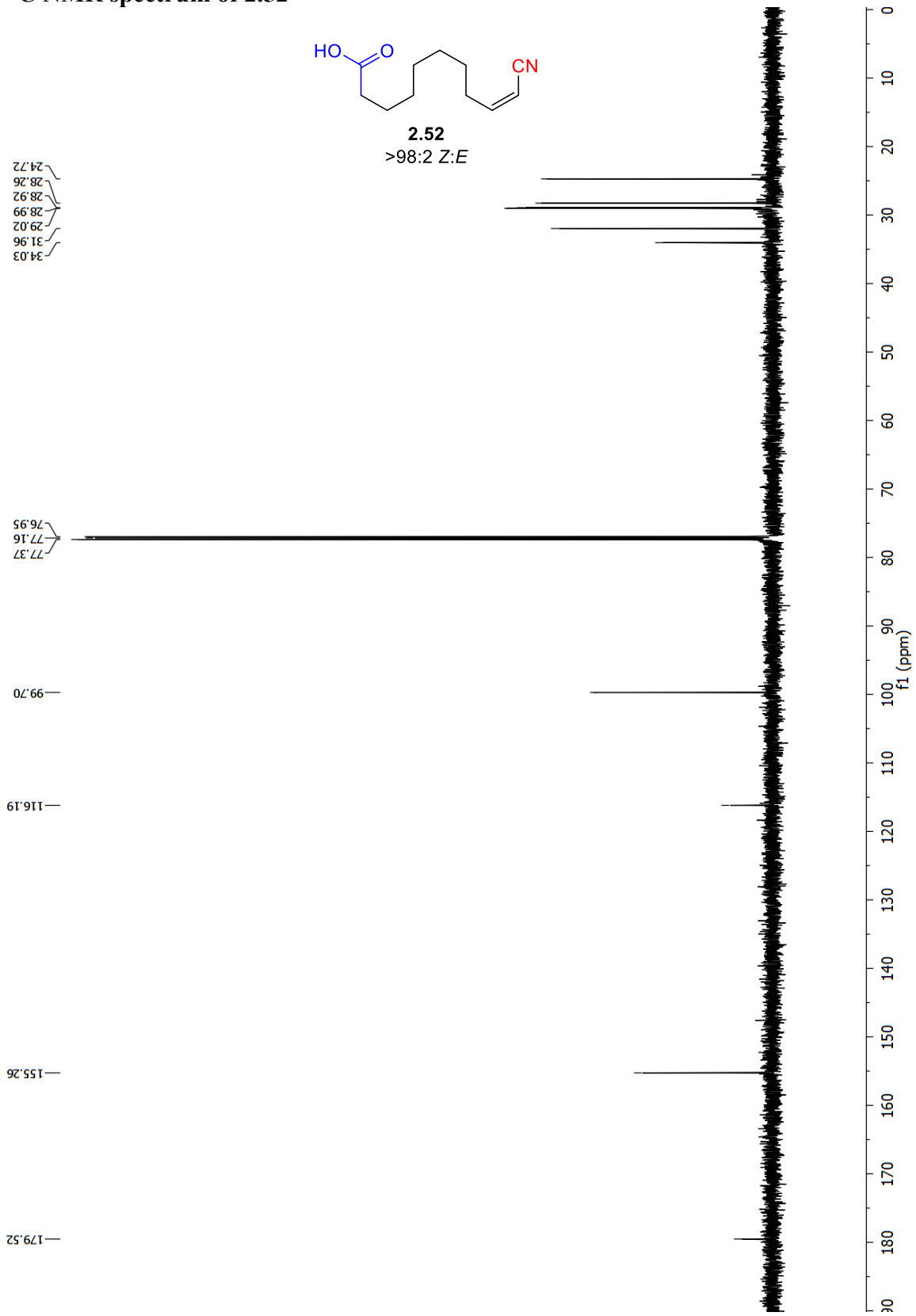


2.51
>98:2 *Z*:*E*

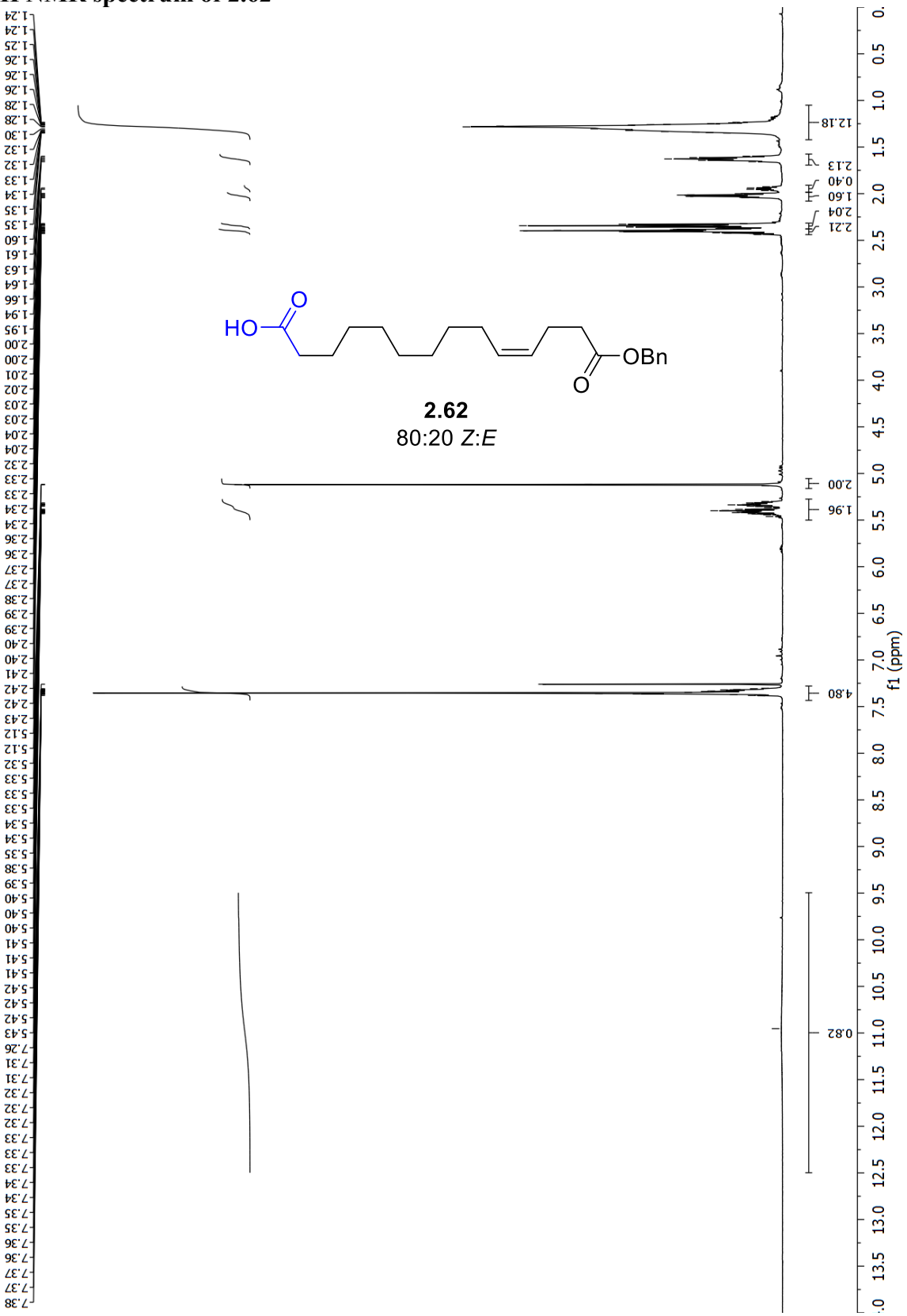
^{1}H NMR spectrum of 2.52



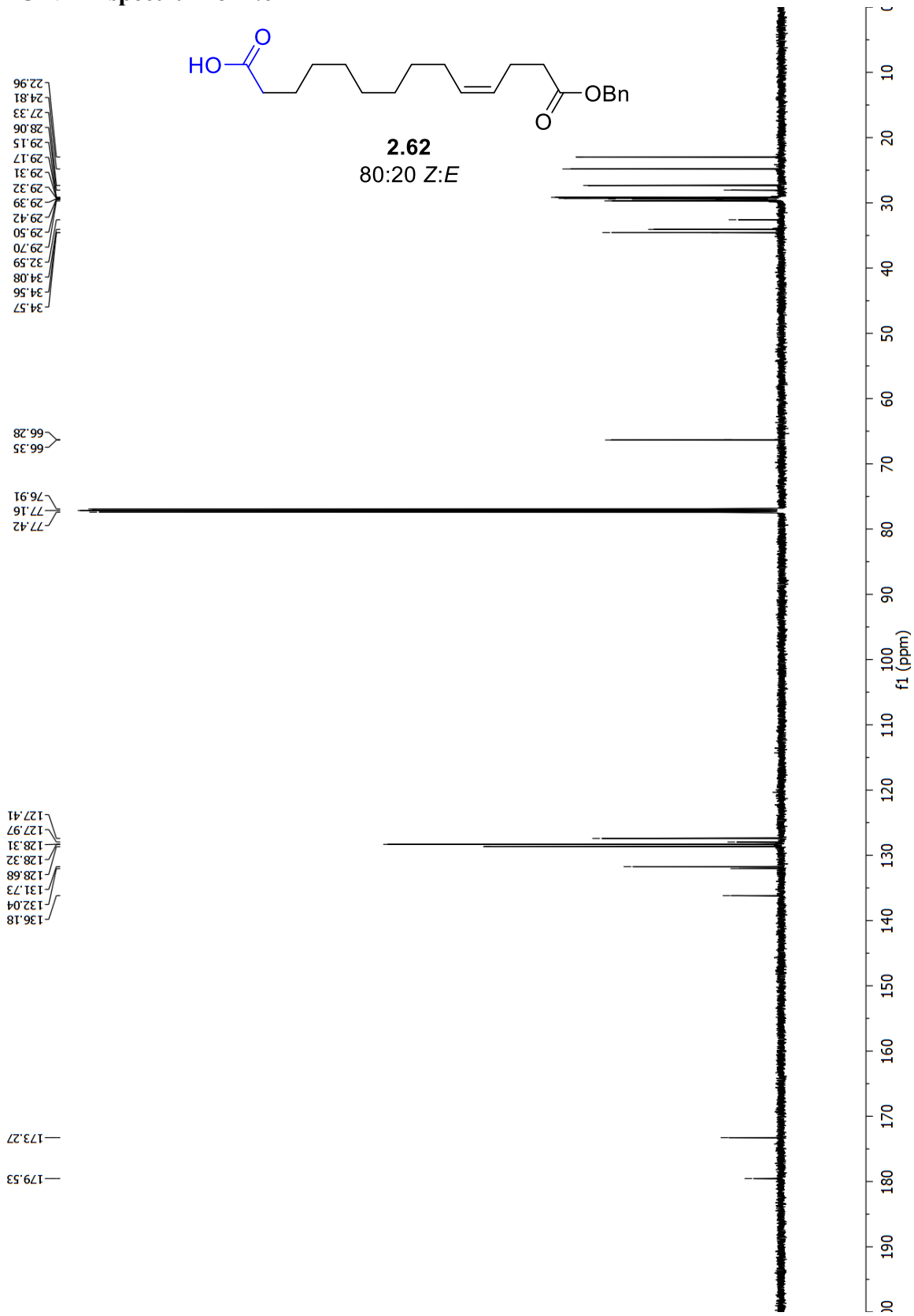
^{13}C NMR spectrum of 2.52



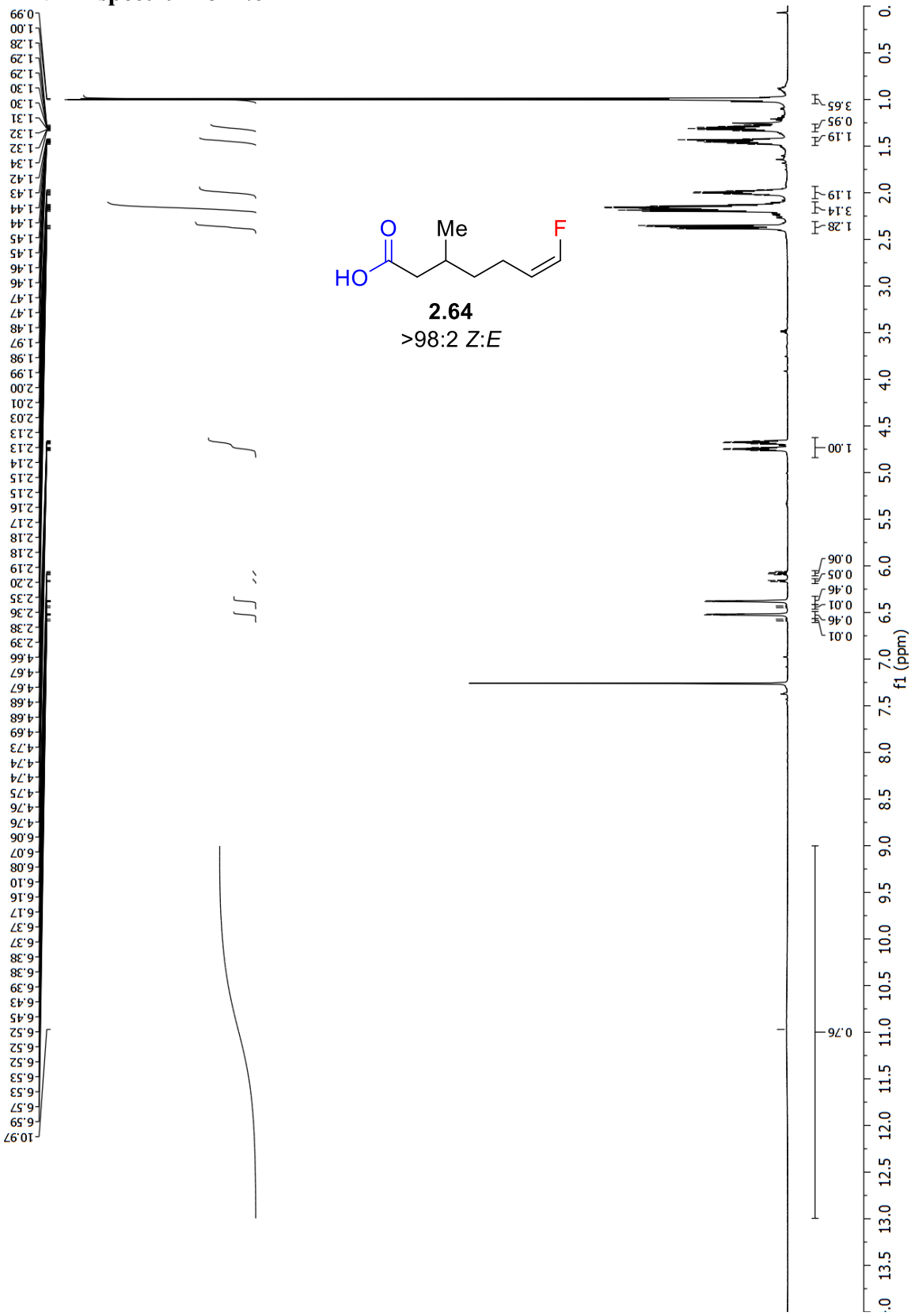
^{1}H NMR spectrum of 2.62



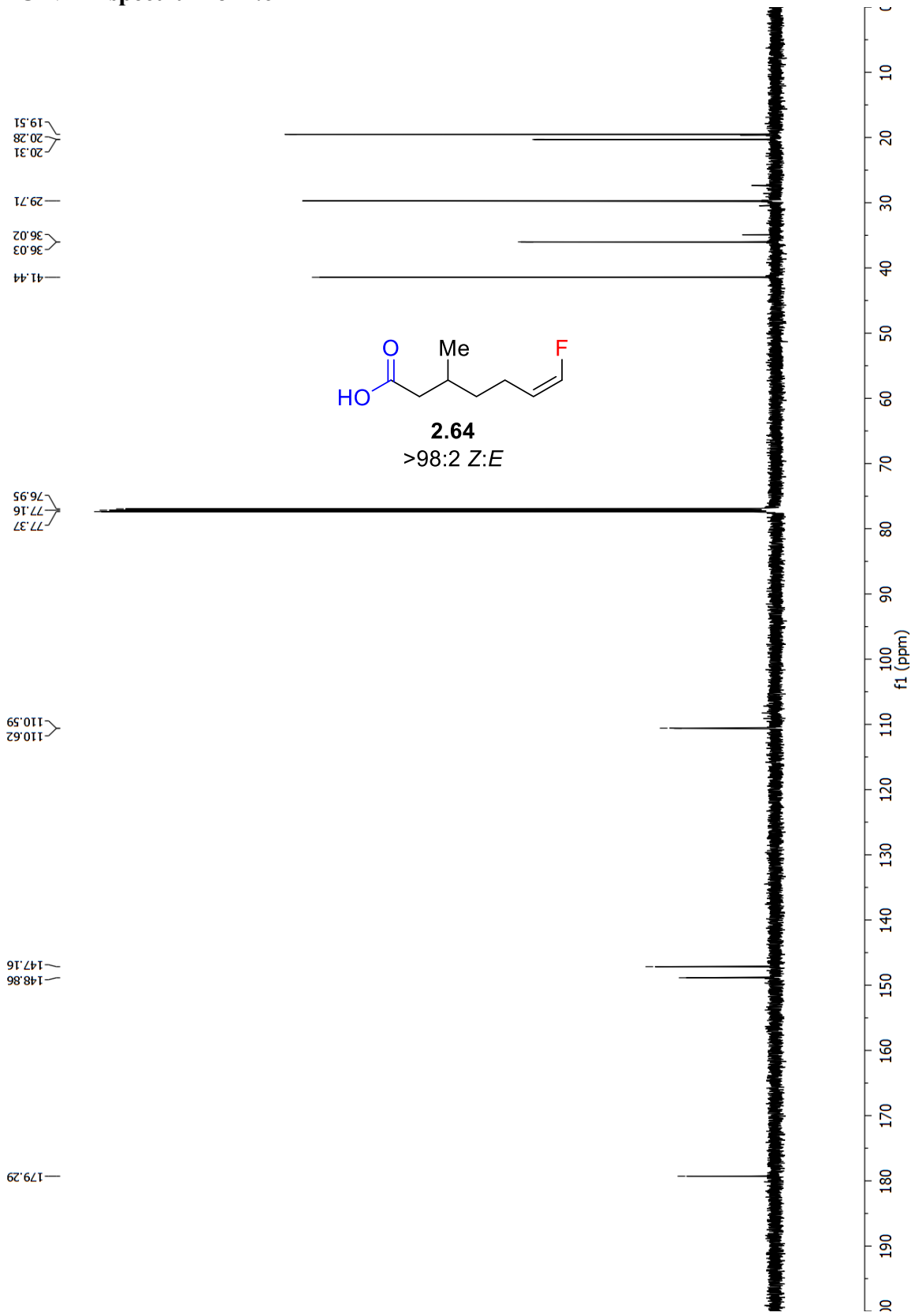
^{13}C NMR spectrum of 2.62



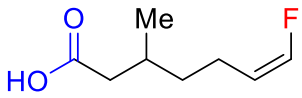
^{1}H NMR spectrum of 2.64



^{13}C NMR spectrum of 2.64



^{19}F NMR spectrum of 2.64



2.64
>98:2 *Z*:*E*

Chapter Three

E- and Z-Trisubstituted Macrocyclic Alkenes for Natural Product Synthesis and Skeletal Editing

3.1. Introduction

Macrocycles are a unique class of compounds in chemical space with important bioactivities and great potential as therapeutic candidates[1]. Among many macrocycles containing different scaffolds and functional groups, macrocyclic alkenes are particularly attractive because of not only their widespread existence in natural products, but also their versatility to be converted to other valuable motifs through stereospecific transformations (e.g., hydrogenation[2] and epoxidation[3]). To access such entities, macrocyclic ring-closing metathesis (MRCM) reactions have emerged as an important disconnection strategy[4]. The major challenge with MRCM reactions, as other macrocyclization methods, is the energy barrier to fuse two ends of an acyclic precursor[5]. A variety of stereoselective olefin metathesis complexes and strategies have been developed to furnish *Z*-[6] and *E*-macrocyclic[7] disubstituted alkenes, which proved to be

(1) Marsault, E.; Peterson, M. K. *J. Med. Chem.* **2011**, *54*, 1961–2004.
(2) Houri, A. F.; Xu, Z.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943–2944.
(3) Wang, C.; Haeffner, F.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 1939 –1943.
(4) (a) Hanson, P. R.; Maitram, S.; Chegondi, R.; Markley, J. L. in *Handbook of Metathesis Vol. 2* (eds Grubbs, R. H. & O'Leary, D. J.) 1–170 (Wiley–VCH, **2014**). (b) Mallinson, J.; Collins, I. *Future Med. Chem.* **2012**, *4*, 1409–1438. (c) Gradillas, A.; Perez-Castells, J. in *Metathesis in Natural Product Synthesis* (eds Cossy, J., Arseniyades, S. & Meyer, C.) 149–182 (Wiley–VCH, **2010**).
(5) Martí-Centelles, V.; Pandey, M. D.; Burguete, M. I.; Luis, S. V. *Chem. Rev.* **2015**, *115*, 8736–8834.
(6) (a) Hoveyda, A. H. *J. Org. Chem.* **2014**, *79*, 4763–4792. (b) Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88–93. (c) Wang, C.; Yu, M.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Chem. Eur. J.* **2013**, *19*, 2726–2740. (d) Marx, V. M.; Herbert, M. B.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2013**, *135*, 94–97. (e) Xu, C.; Shen, X.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 31, 10919–10928. (f) Ahmed, T. S.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2017**, *56*, 11213–11216.

efficient in the synthesis of natural products and medicine candidates. It is vital to synthesize the macrocyclic alkenes in high stereoselectivity because the geometry of the double bond could critically influence a compound's bioactivity and the stereochemical outcome of any subsequent reactions.

Macrocyclic trisubstituted alkenes, compared to their disubstituted variant, are also widely found in many natural products, as shown in Scheme 3.1.1, with 12–24 membered cycles and in both *Z*- and *E*-isomers. Many research groups have attempted to synthesize them efficiently and selectively, while many limitations still remain. Apart from the MRCM methods that will be discussed below, several other strategies have been examined to afford these precious bioactive compounds (Scheme 3.1.2). For example, the Hoye group utilized the Pd–Cl addition to a terminal alkyne and the ensuing allylic substitution to generate the trisubstituted alkenyl chloride in the synthesis of (–)-Haterumalide NA/(–)-Oocydin A.[8] While the reaction is considerably high-yielding, it only led to 42:58 *Z*:*E* selectivity with the *Z*-isomer being the desired product. Later on, in the total synthesis of 5,6-hydrocineromycin and rhizoxin D, the Fürstner group applied a hydroxy-directed hydrostannation to the macrocyclic alkyne that was made through macrocyclic alkyne metathesis.[9] The reaction is highly efficient and stereoselective, but the involvement of highly toxic tin-hydride and precious ruthenium complexes, the necessity of a propargylic alcohol as the directing group and the fact that only *Z*-alkenyl stannane can be synthesized have severely limited the application of this method.

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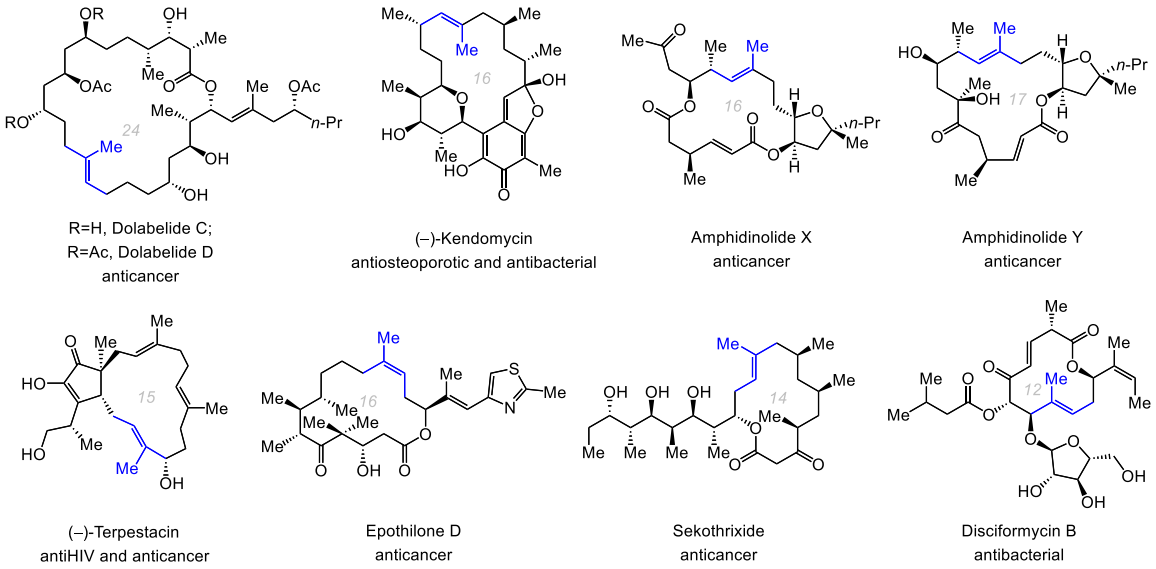
(7) Shen, X.; Nguyen, T. T.; Koh, M. J.; Xu, D.; Speed, A. W. H.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *541*, 380–385.
(8) Hoye, T. R.; Wang, J. *J. Am. Chem. Soc.* **2005**, *127*, 6950–6951.
(9) (a) Rummelt, S. M.; Preindl, J.; Sommer, H.; Fürstner, A. *Angew. Chem. Int. Ed.* **2015**, *54*, 6241–6245. (b) Karier, P.; Ungeheuer, F.; Ahlers, A.; Anderl, F.; Wille, C.; Fürstner, A. *Angew. Chem. Int. Ed.* **2019**, *58*, 248–253.

Moreover, both of the aforementioned methods necessitated the use of acetylenes, which are less stable and more difficult-to-synthesize compared to alkenes. Therefore, these strategies are less ideal in complex natural product synthesis than MRCM methods.

Scheme 3.1.1. Natural Products Containing Macrocyclic Trisubstituted Olefins

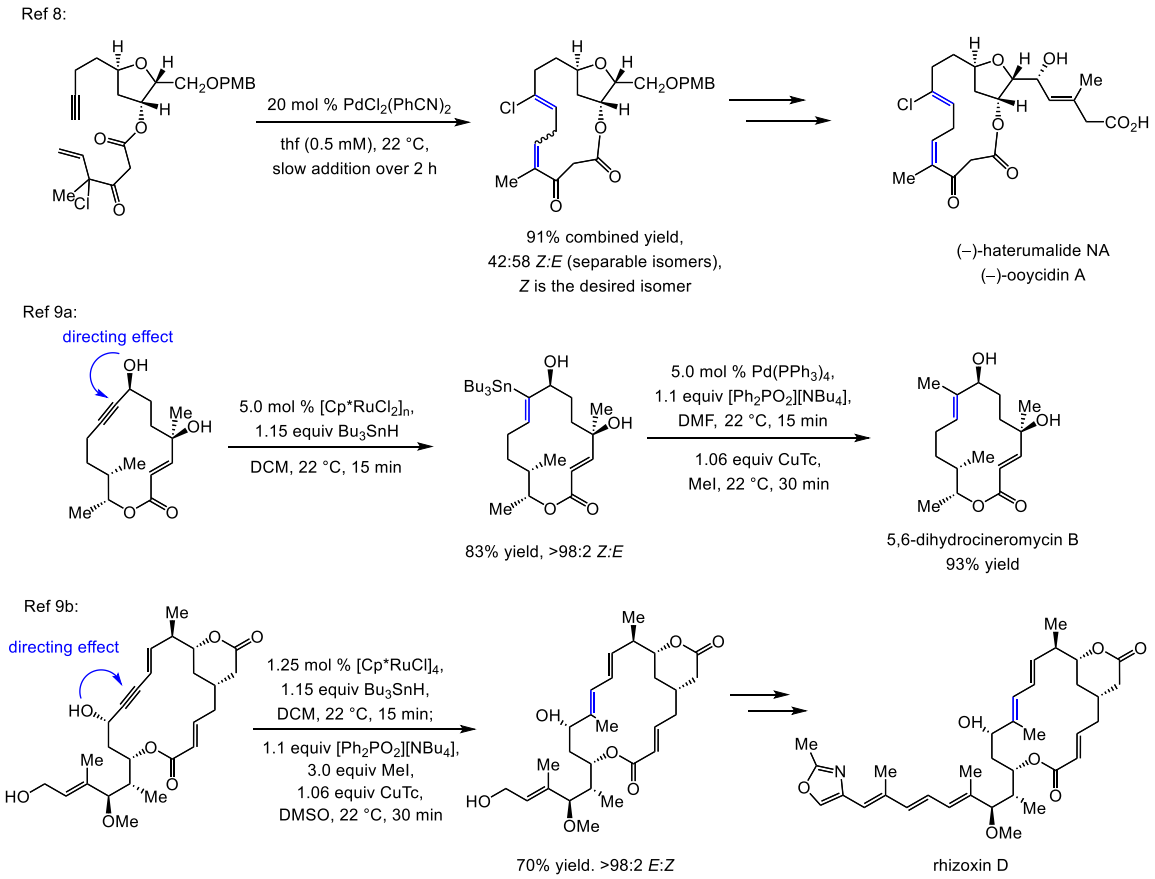


Although many advances have been achieved in macrocyclic disubstituted MRCM reactions, examples of stereoselective trisubstituted MRCM reactions are scarce, which is likely because the more hindered alkenes are less reactive and there is a smaller energy difference between the *Z*- and *E*-isomers of the trisubstituted alkenes[10] (Scheme 3.1.3). For example, in 1995, our group successfully synthesized the 14-membered *Z*-macrocyclic trisubstituted alkene *en route* to the total synthesis Fluvirucin B_1[2]. However, the >98:2 *Z*:*E* selectivity is possibly an outcome of substrate control. When the Amat group generated a similar macrocycle containing the C–C double bond at a different position, there was a complete loss of the alkene selectivity in the MRCM reaction.[11] Similarly, the Vilarassa group also reported that if the methyl substituent on the alkene

(10) Cuvigny, T.; du Penhoat, H.; Julia, M. *Tetrahedron Lett.* **1980**, *21*, 1331–1334.
(11) Guignard, G.; Llor, N.; Molins, E.; Bosch, J.; Amat, M. *Org. Lett.* **2016**, *18*, 1788−1791.

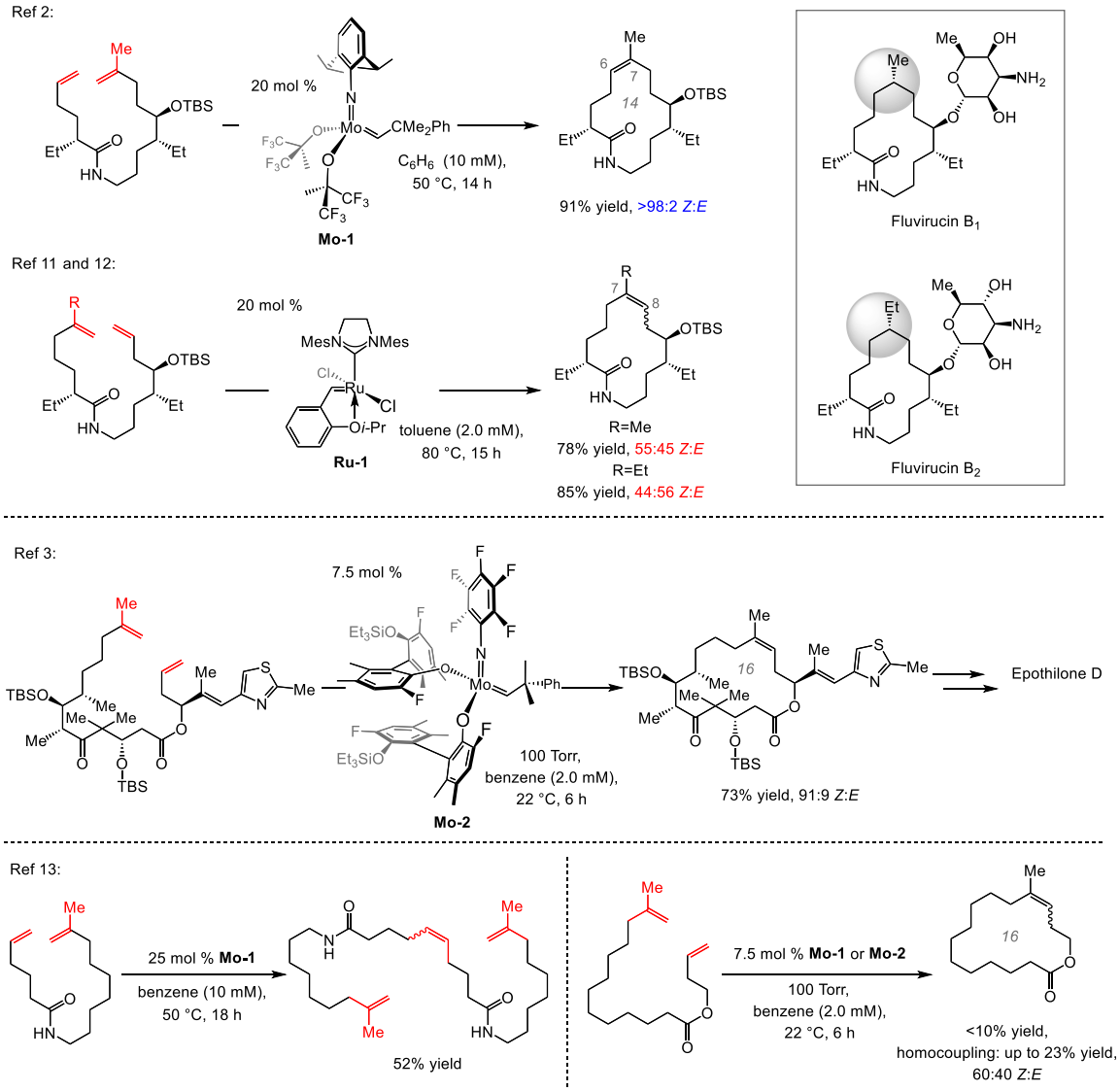
was altered to an ethyl group, the MRCM reaction also became non-selective[12]. Similar substrate control was also observed in the synthesis of Epothilone D, where a fluorinated bisaryloxide complex **Mo-2** was used to afford the desired product in 73% yield and 91:9 *Z*:*E* selectivity.[3] In both stereoselective instances, we found that if all the substituents on the macrocycles were removed, there was little macrocyclic product formation with minimal selectivity (Scheme 3.1.2) [13], suggesting that the substrate pre-organization is essential to assist the desired macrocyclization.

Scheme 3.1.2. Non-MRCM Methods towards Macrocyclic Trisubstituted Alkenes in Total Synthesis



(12) Llàcer, E.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2009**, *11*, 3198−3201.
(13) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302–10316.

Scheme 3.1.3. Substrate-Controlled Trisubstituted MRCM in Natural Product Synthesis



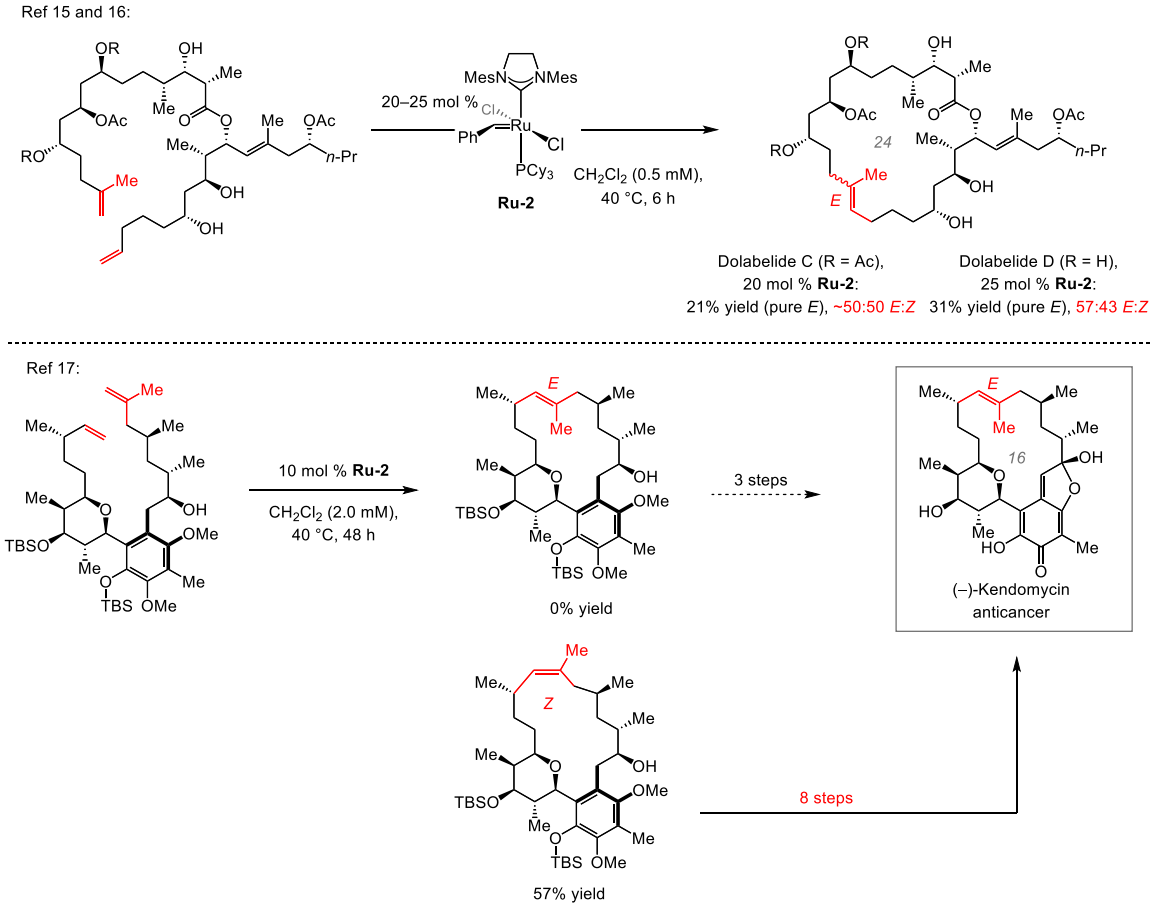
While the aforementioned cases can indeed give access to the products in high yield, a more frequently encountered scenario is that the macrocyclic trisubstituted RCM reactions suffer from low efficiency (Scheme 3.1.4). In the two reported syntheses of Dolabelide, an important class of anti-cancer agents in nature[14], the lack of reliability in MRCM reactions is particularly costly, which is at the final stage of multi-step synthesis of a complex molecule. In both cases, 20–25 mol % **Ru-2** was necessary to deliver the

(14) (a) Ojika, M.; Nagoya, T.; Yamada, K. *Tetrahedron Lett.* **1995**, *36*, 7491–7494. (b) Suenaga, K.; Nagoya, T.; Shibata, T.; Kigoshi, H.; Yamada, K. *J. Nat. Prod.* **1997**, *60*, 2, 155–157.

product in 21% and 31% yield respectively for Dolabelide C[15] and D.[16] The issues with the state-of-the-art in the synthesis include not only high catalyst loadings and low product yields, but also minimal stereocontrol (about 1:1 *Z*:*E* for both cases), alkene isomerization and tedious purifications. Considering the lengthy synthesis to generate such metathesis diene substrates (49 steps and 32 steps for Dolabelide C and D respectively), the current MRCM methods are not ideal. What makes the situation worse is that sometimes the substrate control gave completely the opposite isomer of the desired product. In the case of Kendomycin[17], 5 additional steps were required to convert the undesired *Z*-isomer to the natural product bearing the corresponding *E*-trisubstituted alkene. The reliability of the state-of-the-art in macrocyclic trisubstituted alkene synthesis was further questioned that regardless of the efficiency, stereoselectivity or conditions, there are reports that the macrocycles cannot be formed at all, forcing the synthetic chemists to reroute their synthesis.[18]

(15) Hanson, P. R.; Chegondi, R.; Nguyen, J.; Thomas, C. D.; Waetzig, J. D.; Whitehead, A. *J. Org. Chem.* **2011**, *76*, 4358–4370.
(16) Park, P. K.; O'Malley, S. J.; Schmidt, D. R.; Leighton, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 2796–2797.
(17) Smith, III, A. B.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2005**, *127*, 6948–6949.
(18) (a) Rodríguez-Escrich, C.; Urpí, F.; Vilarrasa, F. *Org. Lett.* **2008**, *10*, 5191–5194. (b) Helmboldt, H.; Hiersemann, M. *J. Org. Chem.* **2009**, *74*, 1698–1708. (c) Hoye, T. R.; Danielson, M. E.; May, A. E.; Zhao, H. *J. Org. Chem.* **2010**, *75*, 7052–7060.

Scheme 3.1.4. Low Selectivity and Low Efficiency Often Observed in Trisubstituted MRCM Reactions



Despite the fact that current macrocyclic RCM reactions for trisubstituted alkenes have many limitations, it still remains as the first choice when chemists are trying to synthesize macrocyclic trisubstituted olefins in natural product synthesis (see Section 3.7 for the bibliography of macrocyclic trisubstitued alkene synthesis in natural products). In these endeavors, while some syntheses are betting on the substrate control to afford the desired product, others are just trying to generate any amount of the desired product, followed by separation of various isomers, regardless of efficiency and selectivity. Therefore, a practical and reliable stereoselective synthesis of macrocyclic trisubstituted alkenes is needed to address these shortcomings. Two methods have been reported to solve this important problem and offered a reliable solution, while the transformations are

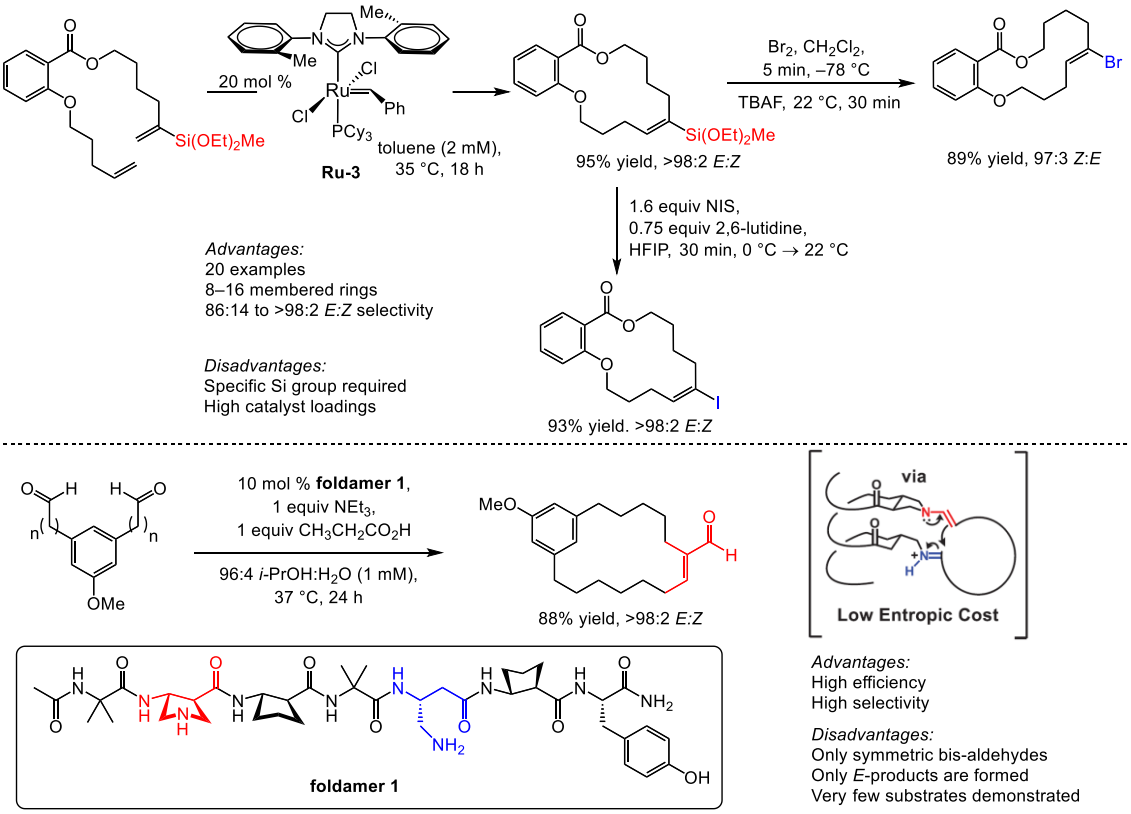
hardly general (Scheme 3.1.5). Firstly, the Young group discovered that a NHC−Ru-based complex **Ru-3** can catalyze the MRCM reaction of a diene substrate bearing an alkenyl silane to deliver a macrocyclic *E*-trisubstituted alkene with high yield and high selectivity[19]. Limitations still remain because the reaction requires a unique silane unit to improve reactivity, which could be hard to be installed in a complex molecule synthesis and the high catalyst loading (20 mol %) could be costly. It is noteworthy that the silane-containing macrocycles are relatively versatile, and can be easily converted to *E*- or *Z*-alkenyl halides[20] through stereospecific reactions to offer opportunities for diversity-oriented synthesis, an important branch of drug discovery and synthetic chemistry (Scheme 3.1.5). Secondly, the Gellman group developed a strategy wherein a peptide foldamer was utilized as the catalyst for the macrocyclization of a bis-aldehyde substrate, delivering *E*-trisubstituted α,β-unsaturated aldehyde (Scheme 3.1.5).[21] While the method is highly efficient and stereoselective, a key limitation of the method is the requirement of a symmetrical bis-aldehyde, to avoid issues with the poor regio-selectivity. The authors demonstrated a natural product synthesis of Robustol by hydrogenating the alkene and removing the aldehyde unit, but many other natural products with trisubstituted alkenes are not possible to be synthesized in this way. Furthermore, only *E*-products can be afforded with this method, limiting the diversity of the macrocycles.

It is notable that, these less substituted macrocycles, other than serving as the model reaction products for potential natural product synthesis, are highly sought-after

(19) Wang, Y.; Jimenez, M.; Hansen, A. S.; Raiber, E.-A.; Schreiber, S. L.; Young, D. W. *J. Am. Chem. Soc.* **2011**, *133*, 9196–9199.
(20) Wang, Y.; Jimenez, M.; Sheehan, P.; Zhong, C.; Hung, A. W.; Tam, C. P.; Young, D. W. *Org. Lett.* **2013**, *15*, 1218–1221.
(21) Girvin, Z. C.; Andrews, M. K.; Liu, X.; Gellman, S. H. *Science* **2019**, *366*, 1528–1531.

musks[22], which are valuable molecules for perfume industry. The ability to synthesize unsaturated macrocycles, regardless of their ring-size, substitution pattern, stereochemical identity or ring-strain, is in high demand in drug development[23] and framework editing.[24] Therefore, we aim to develop a general and reliable macrocyclic trisubstituted RCM reaction to offer a potential solution in cyclizing complex molecules efficiently and selectively.

Scheme 3.1.5. State-of-the-Art Methods to Generate Macrocyclic Trisubstituted Alkenes



3.2. Reaction Development and Mechanistic Findings

(22) (a) Sytniczuk, A.; Forcher, G.; Grotjahn, D. B.; Grela, K. *Chem. Eur. J.* **2018**, *24*, 10403–10408. (b) Sytniczuk, A.; Milewski, M.; Kajetanowicz, A.; Grela, K. *Russ. Chem. Rev.* **2020**, *89*, 469–490.
(23) (a) Mallinson, J.; Collins, I. *Future Med. Chem.* **2012**, *4*, 1409–1438. (b) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845–5859.
(24) (a) Peng, L. F.; Stanton, B. Z.; Maloof, N.; Wang, X.; Schreiber, S. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6319–6325. (b) Yi, S.; Varun, B. V.; Choi, Y.; Park, S. B. DOI:10.3389/fchem.2018.00507.

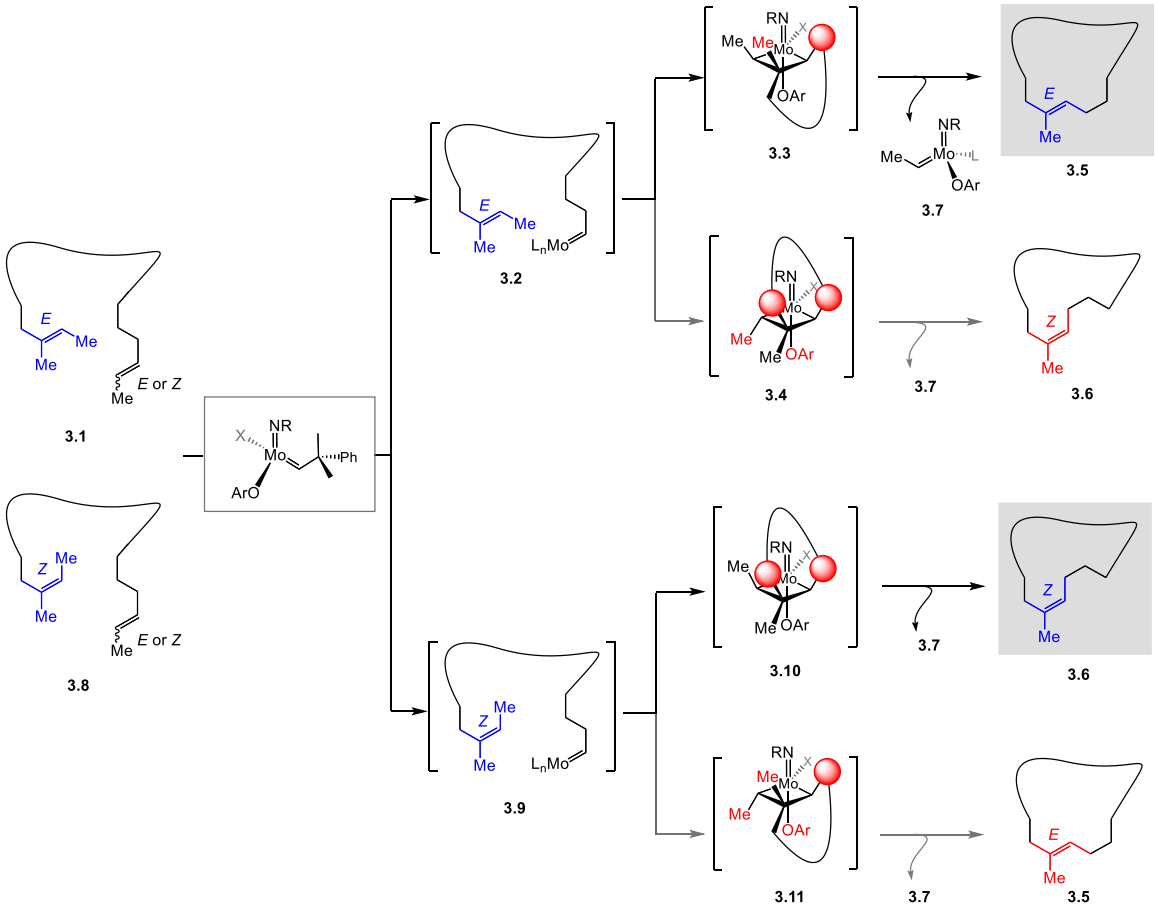
Compared to olefin metathesis of disubstituted alkenes, that of trisubstituted olefins is far less developed. Among the few cross-metathesis reactions reported for trisubstituted alkenes, a halide (chloride or bromide)[25], a pseudo-halide (nitrile, see Chapter 1, Section 1.4 for details), or an allylic alcohol or ether[26] is often required. That is presumably due to their smaller size to accommodate the hindered metallacyclobutane (MCB) intermediate and the related cross-partner that is readily available and can be used in excess amounts. With no precedents in MRCM methods to afford a broad scope of trisubstituted alkenes, we tried to adapt what we learnt in CM reactions to MRCM reactions, mindful that these two transformations are different in many aspects.

We first entertained the possibility that a stereo-retentive process would be ideal to deliver *E*- or *Z*-macrocyclic trisubstituted alkenes (Scheme 3.2.1). We envisioned that a stereodefined diene substrate (**3.1**) can be converted to the corresponding Mo-alkylidene **3.2**, which can deliver the *E*-macrocycle **3.5** or *Z*-macrocycle **3.6** through two potential MCBs **3.3** and **3.4** respectively. As discussed in Chapter 1, Section 1.3, the C-α position of the MCB is more prone to be influenced by the steric repulsion from the large aryloxide ligand than the C-β position. Therefore, MCB **3.3** is more favored with the substituent at C-α pointing towards the small imido group. In the meantime, the Mo-ethylidene **3.7** is released and reacts with the substrate **3.1** to regenerate **3.2**, turning over the catalytic cycle. Similarly, the diene substrate **3.8** with a *Z*-trisubstituted alkene should form the *Z*-macrocycle **3.6** preferably through MCB **3.10**. According to this proposal, the stereoretentive process should be more selective than the stereoselective process, namely with a substrate bearing a 1,1-disubstituted and a mono-substituted olefin. This is because

(25) Nguyen, T. T.; Koh, M. J.; Mann, T. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *552*, 347–354.
(26) Xu, C.; Liu, Z.; Torker, S.; Shen, X.; Xu D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 15640–15643.

the stereodefined trisubstituted alkene has an extra handle at the C-α position to help control the selectivity. More importantly, as mentioned in Chapter 1, Section 1.4 and previous publications[27], a stereoretentive reaction will not involve the short-living methylidene (e.g., compared to ethylidene **3.7**), with more trisubstituted olefin formation when the metathesis reaction takes longer.

Scheme 3.2.1. Proposal of Stereoretentive MRCM to Afford Macrocyclic Trisubstituted Alkenes

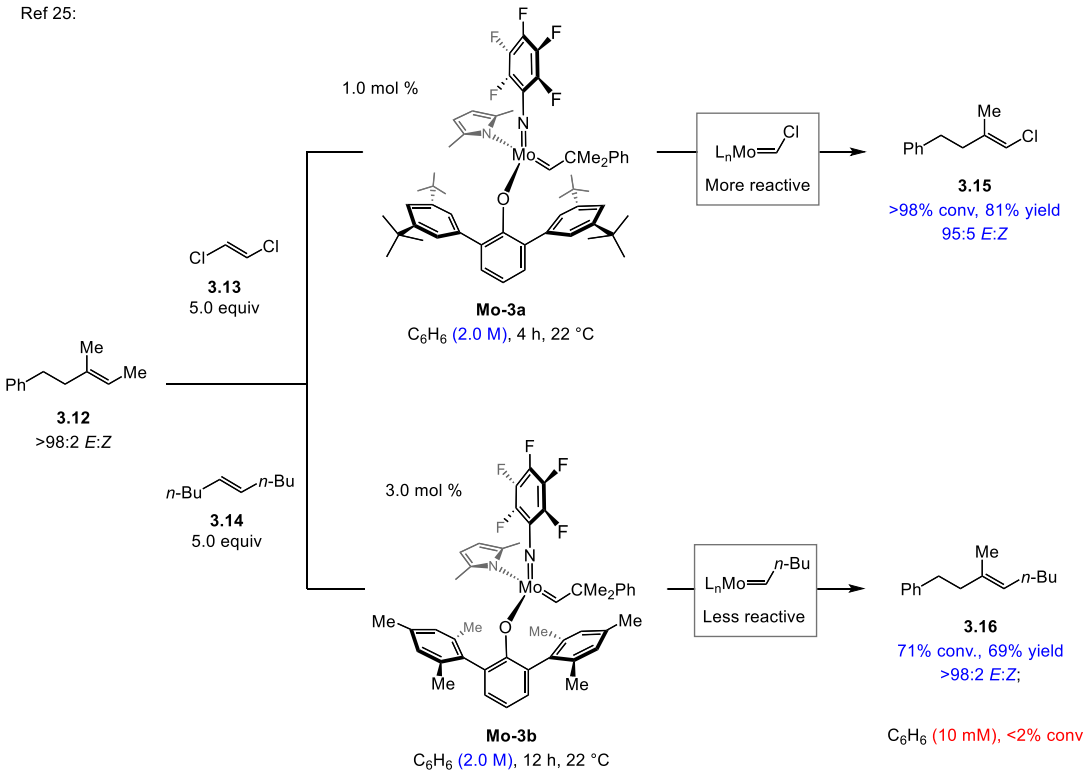


The above plan with stereoretentive process seemed promising, at least on account of our previous findings on the cross-metathesis of trisubstituted alkenes[25] (Scheme 3.2.2), where the stereodefined trisubstituted alkenyl chlorides and alkenes with an alkyl substituent were prepared. However, this initial proposal was quickly challenged

(27) Hoveyda, A. H.; Liu, Z.; Qin, C.; Koengeter, T.; Mu, Y. *Angew. Chem. Int. Ed.* **2020**, *59*, 22324–22348.

by several discouraging factors. Firstly, for cross-metathesis reactions, the reactions were mostly run at very high concentration (2.0 M), where solvents were used solely for transferring the Mo-complexes[2.5] As we learnt from previous MRCM reactions for both di- and trisubstituted alkenes[6,7,10–13,15–17,19,21] and many other macrocylization reactions[8,21], a dilute reaction solution is needed (e.g., 0.5–2.0 mM). It was thus frustrating to see that when we ran the previous cross-metathesis reaction at 10 mM (Scheme 3.2.2), which is actually a high concentration for most of the RCM reactions, no product **3.16** was observed. Secondly, in a cross-metathesis reaction, typically excess amounts of the reaction partner (e.g., **3.13** and **3.14**) are required to maximize the reaction efficiency. The advantage is not applicable to RCM reactions due to the nature of intramolecular reactions where the ratio is fixed at 1:1. Thirdly, whereas the known olefin metathesis reactions always involve a Mo alkylidene with a small substitutent (e.g., a halide or a nitrile, see Chapter 1, Section 1.4 for details), transformations with alkyl-substituted alkylidenes are less common. It is notable that compared with transformations involving chlorides (e.g., towards **3.15**), reactions with alkyl substituent (e.g., towards **3.16**) are slower due to the more hindered alkyl-substituted alkylidene and therefore, 3.0 mol % **Mo-3b** and 12 h are required.

Scheme 3.2.2. Previous Studies of Cross-Metathesis with Trisubstituted Alkenes



We thus had to pin our hope on the intramolecular nature of ring-closing, where the effective concentration could be higher, namely the two alkenes of a diene are closer to each other compared to those in cross-metathesis. We then set out to examine our proposal and selected the MRCM of a stereodefined diene substrate **3.17** to afford the 20-membered macrocylic lactone **3.18** as the model process. After testing the Mo-based complexes **Mo-2** and **Mo-3a**−**3b** that were found to be optimal for trisubstituted cross-metathesis reactions, we were glad to see that there was appreciable conversion to the desired product **3.18** (18−58%) and the desired product can be isolated in 46% yield, in contrary to the control experiments on cross-metathesis at the same concentration (10 mM, Scheme 3.2.2). However, it was surprising for us to find out that the selectivity for macrocyclic trisubstituted alkenes are lost almost completely. This is highly unusual because for cross-metathesis reactions, although the efficiency could be problematic

sometimes, the selectivity is generally very high (Scheme 3.2.2). We then decided to investigate the catalytic cycle more thoroughly to understand the cause of low selectivity.

From the diene substrate **3.17**, the MRCM proceeds through the alkylidene **3.19** and the MCB **3.20**, which can further collapse to afford the desired macrocycle **3.18** and release the *syn*-ethylidene **3.21**. The ethylidene can further react with the substrate **3.17** again to regenerate the alkylidene **3.19** and more importantly the *Z*-butene **3.22**. We proposed that the often ignored byproduct *Z*-butene could account for the erosion of selectivity due to their small size and higher reactivity. The *Z*-butene can recombine with the alkylidene **3.21** in a different manner through MCB **3.23** to form the *anti*-ethylidene **3.24** and the *E*-butene **3.25**. Generally, *anti*-alkylidenes are shorter-living but much more reactive than *syn*-alkylidenes. Therefore, after reaction with the *anti*-ethylidene, substrate **3.17** can be isomerized to the derivative **3.27** with a *Z*-trisubstituted alkene through MCB **3.26**. As we mentioned in Scheme 3.2.1, starting from a *Z*-trisubstituted olefin, we would preferably obtain a *Z*-macrocycle **3.28** due to the stereoretentive process. What makes the isomerization worse is that the *E*-butene can also react with the *syn*-ehylidene **3.21** to form the problematic *anti*-ethylidene **3.24** through MCB **3.29**.

We then set out to find experimental evidence and identify the solutions to the pre-metathesis isomerization issues. Firstly, if our rationale stands, there should be a relation between the selectivity and the aryloxide ligand size because the smaller aryloxide would leave more space for the formation of an *anti*-ethylidene. Indeed, we found that **Mo-3a** afforded the macrocycle in lower selectivity than **Mo-3b** (52:48 vs. 66:34 *E*:*Z*) as MCB **3.30** is less crowded at the C-α postion and allows the methyl group to point towards the large aryloxide ligand, compared to MCB **3.31** derived from the

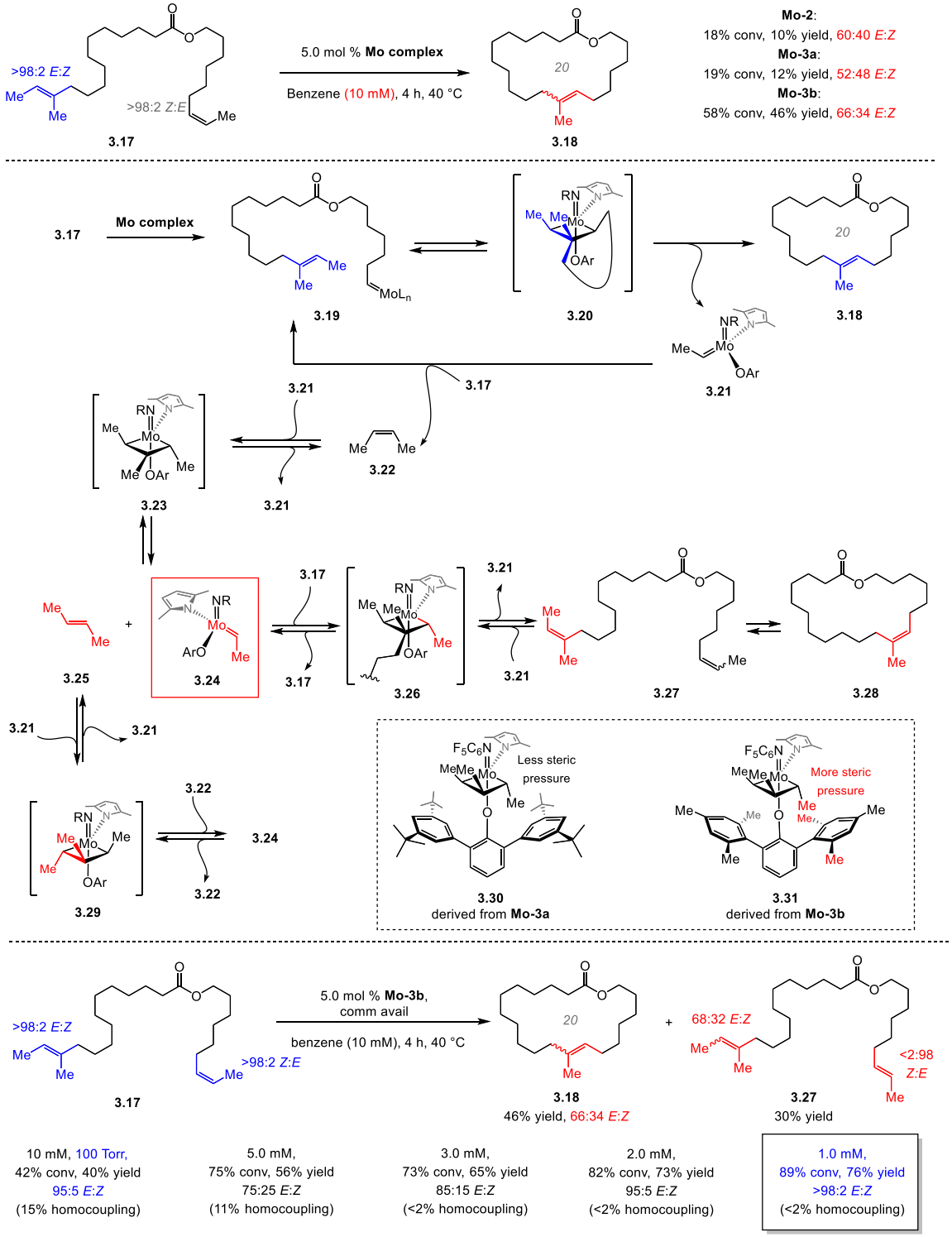
complex **Mo-3b**. Secondly, as shown in Scheme 3.2.3, we attributed the low stereoselectivity to pre-metathesis isomerization. Therefore, we envisoned that determination of stereopurity of recovered diene substrates could provide further experimental evidence. We discovered that the trisubstituted olefin of the starting material has been isomerized to 68:32 *E*:*Z* ratio and the disubstituted olefin has been fully isomerized to the thermally more stable *E*-alkene. Later control experiment showed that the *Z*:*E* ratio of disubstituted olefins is inconsequential for the stereoselectivity of macrocyclic trisubstituted alkenes. These two observations together proved our rationale that the stereopurity of the trisubstituted starting alkene would be translated to the macrocycle selectivity, which was 66:34 *E*:*Z* ratio. Thirdly, we hypothesized that the removal of the volatile *Z*-butene, which could cause the starting olefin isomerization, would improve the *E*:*Z* selectivity. Indeed, when we ran the MRCM reaction at 10 mM under mild vacuum (100 torr), we can isolate the macrocyclic product in 95:5 *E*:*Z* ratio but only in 40% yield.

The moderate yield is presumably due to the bimolecular catalyst decomposition, which would be more severe at higher concentration, and the competitive self-metathesis product formation[27]. A second way to minimize the effects of *Z*-butene is through dilution, in which occasion the shorter-living *anti*-alkylidene should be very quickly converted to the *syn*-alkylidene before having chance to isomerize the substrate, according to an early study on Mo-alkylidene interconversions. [28] Based on aforementioned hypothesis, when the macrocyclization was performed at increasing dilutions, without the request of reduced pressure, not only the efficiency, but also, more uniquely, the stereochemical control was improved significantly. At 1.0 mM

[28] Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed*. **2003**, *42*, 4592–4633.

concentration and ambient pressure, in the presence of 5.0 mol % of commercial available Mo-complex **Mo-3b**, the MRCM reaction of diene substrate **3.17** delivered desired *E*-macrocycle **3.18** in 76% yield and >98:2 *E*:*Z* selectivity. It is noteworthy that, as in the cross-metathesis reactions[25], the stereoisomeric purity of the disubstituted alkene has minimal influence on the reaction outcome. Macrocyclization of the substrate with a *E*-1,2-disubstituted alkene afforded the same product in 72% yield and 95:5 *E*:*Z* selectivity. Equally notable is that compared to a traditional stereoselective process from a diene substrate containing a monosubstituted and a 1,1-disubstituted alkene, this method can still generate the macrocycle in moderate yield and afford less self-metathesis product at higher concentration (10 mM), which is likely due to the absence of the short-living methylidene complex[27].

Scheme 3.2.3. Stereoretentive MRCM Reaction Development and Solution of Unexpected Isomerization[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details.

3.3. Scope of Various E- and Z-Macrocyclic Trisubstituted Alkenes

Under the optimal condition, a variety of *E*-macrocyclic trisubstituted alkenes can be synthesized efficiently and stereoselectively ranging from 12−22 membered rings (**3.33**−**3.42**, **3.44**). Meta-cyclophanes (**3.33**), macrocyclic lactones (**3.34**−**3.39**), carbocycles (**3.40**−**3.41**) and lactams (**3.42**, **3.44**) are all compatible with trisubstituted MRCM conditions. Efficient formation of 12- (**3.39**) and 13-membered (**3.38**) rings required slightly higher catalyst loadings and longer reaction period, due to their larger ring strain. The lower *E*:*Z* ratio for the 13-membered ring may be attributed to the slower rate of cyclization, allowing higher possibility for the aforementioned isomerization of the diene substrate prior to ring formation (Scheme 3.2.3). Synthesis of the macrocycles **3.40** and **3.41** shows that the method is applicable to carbocycles, which are seldom reported for MRCM reactions and confirmed claims[21] that such macrocycles cannot be synthesized efficiently are inherently incorrect.

The MRCM reactions involving macrocyclic lactams are more complicated than the corresponding lactones, presumably because of stronger Lewis basicity of the amide moiety and their ability to chelate to the Lewis acidic Mo-complex. When we subjected the secondary amide-containing substrate to the same conditions, no conversion to the desired product **3.42** was observed. A similar *in-situ* protection strategy, which was effective in Chapter 2 for hydroxy/carboxylic acid-containing substrates, was considered here again. When tris(pentafluorophenyl)borane $B(C_6F_5)_3$, an *in-situ* protecting agent for the secondary amides through the Lewis acid and base binding, was added, the MRCM reaction afforded the macrocycle **3.42** in 75% yield and 95:5 *E*:*Z* selectivity.[7] However, this early discovery was found to lack generality. When we tried to apply it to the generation of the 14-membered lactam **3.43**, the MRCM transformation in the presence

of $B(C_6F_5)_3$ only gave 16% conversion to the product (see the analysis below for details). After the Boc-protection of the secondary amide of the diene substrate, the Boc-amide macrocycle **3.44** was successfully formed in 80% yield. It merits note that the optimal complex for **3.44** is **Mo-3c**, where a less sterically demanding tetraphenylaryloxide ligand is utilized.

The same RCM conditions proved to be efficient for *Z*-macrocyclic trisubstituted alkenes as well. A similar set of macrocyclic alkenes ranging from 12−22 membered rings (**3.46**−**3.54**, **3.56** and **3.57**) were accessed efficiently, despite slight erosion of selectivity compared to *E*-trisubstituted alkenes. Similar trends in selectivity between *E*- and *Z*- products were also observed in trisubstituted cross-metathesis reactions[25], owing to the smaller energy gap between the two competing MCBs **3.58** and **3.59** (Scheme 3.3.2). While **3.58** has the major steric repulsion between the substitutent at C-α and the large aryloxide ligand, the eclipsing effect between two large substituents also exists in MCB **3.59**. For the all-carbon ring structure **3.54**, the typical complex **Mo-3b** only gave the desired product in 10% yield although as a single isomer. The use of the electronically activated complex **Mo-3d**[29] bearing a *para*-bromo-aryloxide ligand led to 65% yield of the desired macrocycle in slightly diminished 90:10 *Z*:*E* selectivity.

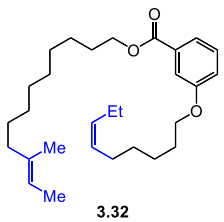
Similar with the *E*-macrocyclic trisubstituted alkenes, macrocyclic lactams were found to be problematic again. While the aforementioned 19-membered ring **3.42** was synthesized successfully in the presence of $B(C_6F_5)_3$, the corresponding *Z*-macrocycle **3.55** was highly efficient but with near complete loss of selectivity. Analogous to *E*-lactam **3.43**, the Boc-protected amide derivative **3.56** was isolated in 70% yield and in

(29) Ferreira, M. A. B.; De Jesus Silva, J.; Grosslight, S.; Fedorov, A.; Sigman, M. S.; Copéret, C. *J. Am. Chem. Soc.* **2019**, *141*, 10788–10800.

94:6 *Z*:*E* selectivity. Similarly, the 14-membered *Z*-lactam **3.57** can be generated in 40% yield and in >98:2 *Z*:*E* selectivity, while requiring 10 mol % **Mo-3a** due to the higher strain for a smaller 14-membered ring.

Although the MRCM reactions of secondary amide substrates with the addition of $B(C_6F_5)_3$ proved success for certain substrates, it is less effective for the more challenging substrates. The above findings are still being investigated in our lab while we have some proposals: (1) there might be an unfavorable interaction between the $B(C_6F_5)_3$ and the Mo-based catalyst (Scheme 3.3.2). When the transformations towards **3.48**, **3.49** and **3.51** were carried out in the presence of $B(C_6F_5)_3$, the corresponding macrocyclic alkenes were formed in much lower selectivity (66:34, 58:42 and 67:33 respectively); (2) upon the binding of the carbonyl group of the secondary amide to the Lewis acid, the conformation of the substrate has changed significantly owing to the large size of $B(C_6F_5)_3$. Whereas it has less effect on the larger 19-membered macrocycle **3.42**, the smaller 14-membered macrocycle **3.43** could be severely influenced. It should also be noted that secondary amide substrates are challenging not only for the macrocyclic trisubstituted RCM, but also in other types of olefin metathesis reactions. There are only two reported cases[2,6c] that a secondary amide was compatible with W- or Mo-based complexes, none of which contains an electron-withdrawing pentafluorophenylimido ($=NC_6F_5$) group that was used in trisubstituted MRCM reactions here. Nevertheless, the additive effects gave us better understanding of the catalytic system and as we will demonstrate below that this could be useful in reversing the natural selectivity of MRCM reaction in the preparation of Fluvirucin B_1.[2]

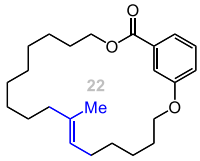
Scheme 3.3.1. Scope of Various *E*- and *Z*-Macrocyclic Trisubstituted Alkenes[a]



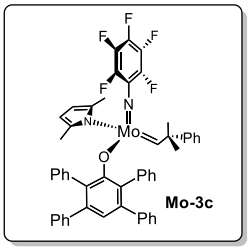
3.32

5.0 mol % **Mo-3b**, comm avail

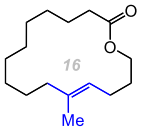
C_6H_6 (1.0 mM), 40 °C, 4 h



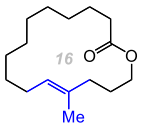
3.33
93% conv, 93% conv to pdt
93% yield, >98:2 *E*:*Z*



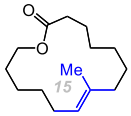
Mo-3c



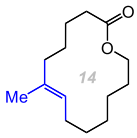
3.34
95% conv, 85% conv to pdt
82% yield, >98:2 *E*:*Z*



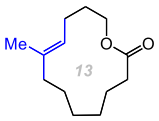
3.35
86% conv, 83% conv to pdt
82% yield, >98:2 *E*:*Z*



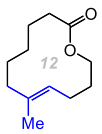
3.36
94% conv, 92% conv to pdt
91% yield, >98:2 *E*:*Z*



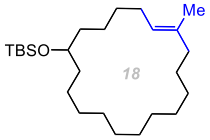
3.37
88% conv, 78% conv to pdt
75% yield, >98:2 *E*:*Z*



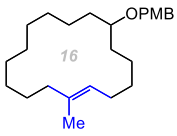
3.38*
64% conv, 48% conv to pdt
48% yield, 90:10 *E*:*Z*



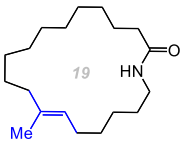
3.39*
79% conv, 62% conv to pdt
56% yield, >98:2 *E*:*Z*



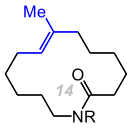
3.40
80% conv, 77% conv to pdt
71% yield (after deprotection)
95:5 *E*:*Z*



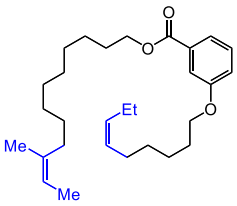
3.41
66% conv, 64% conv to pdt
59% yield, >98:2 *E*:*Z*



3.42, <2% conv;
with 1.0 equiv $B(C_6F_5)_3$
93% conv, 93% conv to pdt
80% yield, 95:5 *E*:*Z*



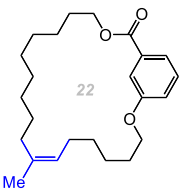
R=H, **3.43**,
with 1.0 equiv $B(C_6F_5)_3$
16% conv to pdt, *E*:*Z* ND
R=Boc, **3.44**,**
96% conv, 94% conv. to pdt
82% yield, 91:9 *E*:*Z*



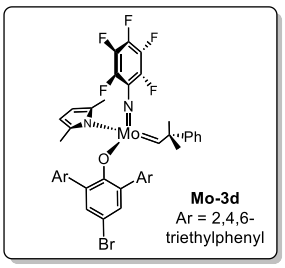
3.45

5.0 mol % **Mo-3b**, comm avail

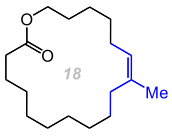
C_6H_6 (1.0 mM), 40 °C, 4 h



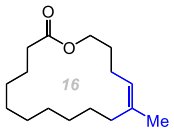
3.46
92% conv, 92% conv to pdt
87% yield, 90:10 *Z*:*E*



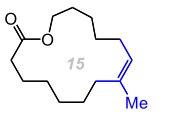
Mo-3d
Ar = 2,4,6-triethylphenyl



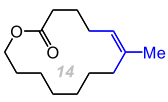
3.47
86% conv, 82% conv to pdt
80% yield, >98:2 *Z*:*E*



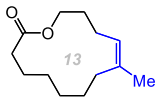
3.48
88% conv, 85% conv to pdt
83% yield, 90:10 *Z*:*E*



3.49
91% conv, 90% conv to pdt
82% yield, 88:12 *Z*:*E*

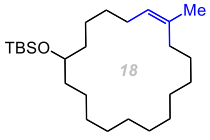


3.50
75% conv, 73% conv to pdt
70% yield, 96:4 *Z*:*E*

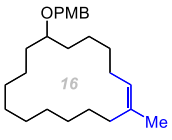


3.51*
80% conv, 70% conv to pdt
63% yield, 92:8 *Z*:*E*

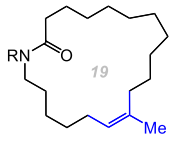
3.52*
83% conv, 82% conv to pdt
58% yield, 93:7 *Z*:*E*



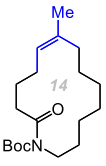
3.53
75% conv, 75% conv. to pdt
71% yield (after deprotection)
90:10 *Z*:*E*



3.54†
69% conv, 65% conv to pdt
64% yield, 90:10 *Z*:*E*



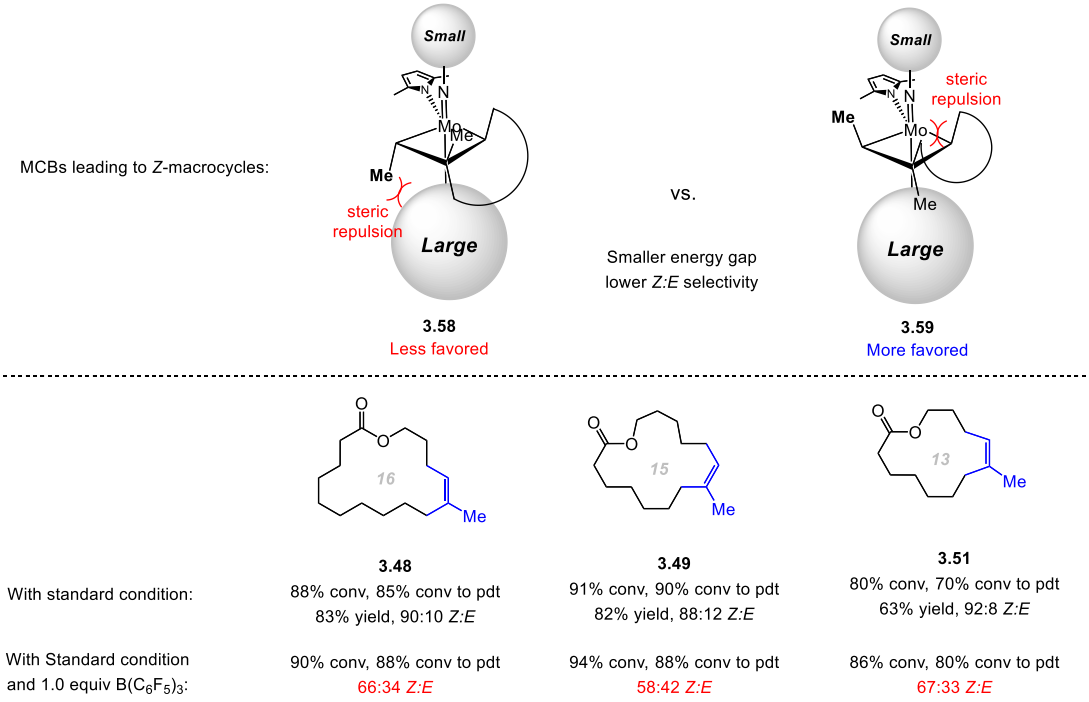
R=H, **3.55**,with 1.0 equiv $B(C_6F_5)_3$
94% conv, 88% yield, 55:45 *Z*:*E*;
R=Boc, **3.56**
75% conv, 72% conv to pdt
70% yield, 94:6 *Z*:*E*



3.57††
62% conv, 42% conv to pdt
40% yield, >98:2 *Z*:*E*

[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. *With 10 mol % **Mo-3b**, 12 h. **with 5.0 mol% **Mo-3c**, 12 h. †With 10 mol % **Mo-3d**, 12 h. ††With 10 mol % **Mo-3a**, 12 h. See the experimental section for details.

Scheme 3.3.2. MCBs Comparison for *Z*-Macrocycles and Control Experiments with $B(C_6F_5)_3$

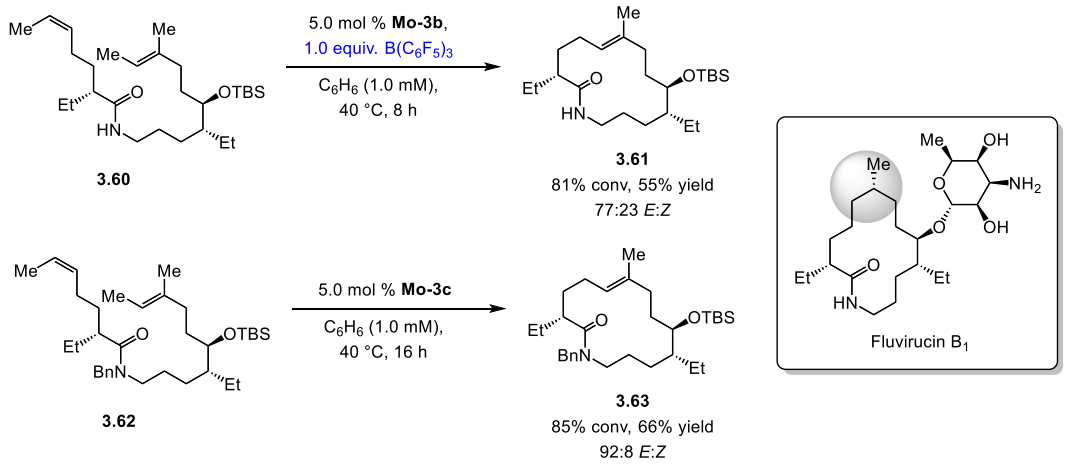


3.4. Reversing Substrate-Controlled Selectivity

The goal of this study is to provide a reliable strategy to overcome substrate control through stereoretentive trisubstituted MRCM reactions. Therefore, one of the most challenging transformations would be reversing the intrinsic selectivity, namely, furnishing a MRCM product as a single isomer that was previously synthesized as the other isomer by stereoselective MRCM. We then chose to investigate the synthesis of macrocycle **3.61**, that was previously yielded only as a *Z*-isomer *en route* to the synthesis of anti-fungal reagent Fluvirucin B_1 (Scheme 3.1.3). Accordingly, we prepared the secondary amide substrate **3.60** (see the *Experimental Section* for detailed procedures), and not surprisingly, with the optimal complex **Mo-3b** for the model substrate, there was no consumption of the secondary amide-containing diene **3.60** (Scheme 3.4.1), an observation mentioned in Section 3.3 regarding secondary amide substrates. In the presence of stoichiometric amount of $B(C_6F_5)_3$, we were able to isolate the desired

product **3.61** in 55% yield and 77:23 *E*:*Z* selectivity, representing a notable reversion on the selectivity (Schemem 3.1.3, >98:2 *Z*:*E* ratio). To further increase the selectivity in the stereoretentive MRCM process, we envisioned that a more flexible tertiary amide might be more suitable substrate for enabling more flexible conformations and reversing the stereoselectivity, as opposed to the rigid secondary amide substrates. To probe this proposal, we prepared the benzyl protected tertiary amide **3.62** and indeed, the *E*-macrocyclic trisubstitued alkene **3.63** was generated in 66% yield and in 92:8 *E*:*Z* selectivity. Considering the significance of the olefin geometry in a bioactive compound, this approach offers a great opportunity for stereodivergent framework editing of many other different macrocyclic drug candidates (e.g., Epothilone D) as well.[23]

Scheme 3.4.1. Reversing Substrate-Controlled Selectivity in the Synthesis of Fluvirucin B_1[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details.

3.5. Stereoselective Total Synthesis of Dolabelide C

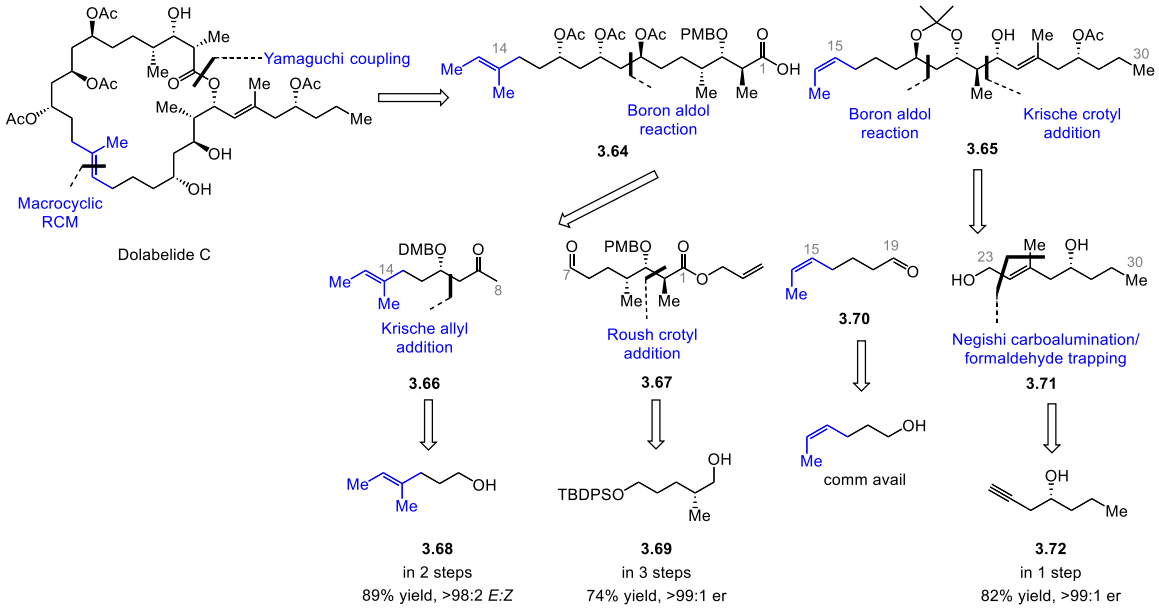
Another key aspect to be considered for a stereospecific catalytic reaction is whether it is reliable in the late stage of total synthesis of a complex molecule, where many sensitive functional groups exist. With such questions in mind, we set out to examine our trisubstituted MRCM approach in the total synthesis of Dolabelide C, a member of a

potent anticancer Dolabelide family. Dolabelide C features 11 stereogenic centers, a 24-membered macrocyclic trisubstituted alkene and an acyclic trisubstituted alkene in the side chain, which would be an appropriate test for the efficiency, chemo-, regio- as well as stereoselectivity of our protocol.

The retrosynthetic analysis commenced with the MRCM reaction of an acyclic precursor that can be assembled through Yamaguchi esterification of two fragments **3.64** and **3.65**, which could be synthesized in the convergent manner (Scheme 3.5.1). For the fragment **3.64**, we envisioned that the boron-aldol reaction can be utilized to form the C–C bond in a 1,3,5-triol motif, which was further traced to the fragments **3.66** and **3.67**. For compound **3.66**, the β-hydroxy ketone could be afforded by an allyl addition/Wacker oxidation sequence and therefore, the unsaturated trisubstituted alcohol, **3.68**, can serve as the starting point for fragment **3.66** synthesis. Another β-hydroxy carbonyl-containing compound **3.67** could be synthesized by the crotyl addition/oxidation sequence and correspondingly, the previously reported compound **3.69** can be identified as the suitable intermediate. For fragment **3.65**, which also contains a similar polyketide moiety as fragment **3.64**, we envisaged that a similar boron-aldol reaction and crotyl addition sequence would be applicable, which led us to compounds **3.70** and **3.71**. The unsaturated aldehyde **3.70** was synthesized in a previous report from the commercially available alcohol, while the unsaturated diol fragment **3.71** could potentially be formed with a carboalumination method reported by Negishi *et al.* [30], followed by paraformaldehyde trapping, from the alcohol-containing acetylene **3.72**.

(30) Negishi, E., van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639–6647.

Scheme 3.5.1. Retrosynthetic Analysis of Dolabelide C

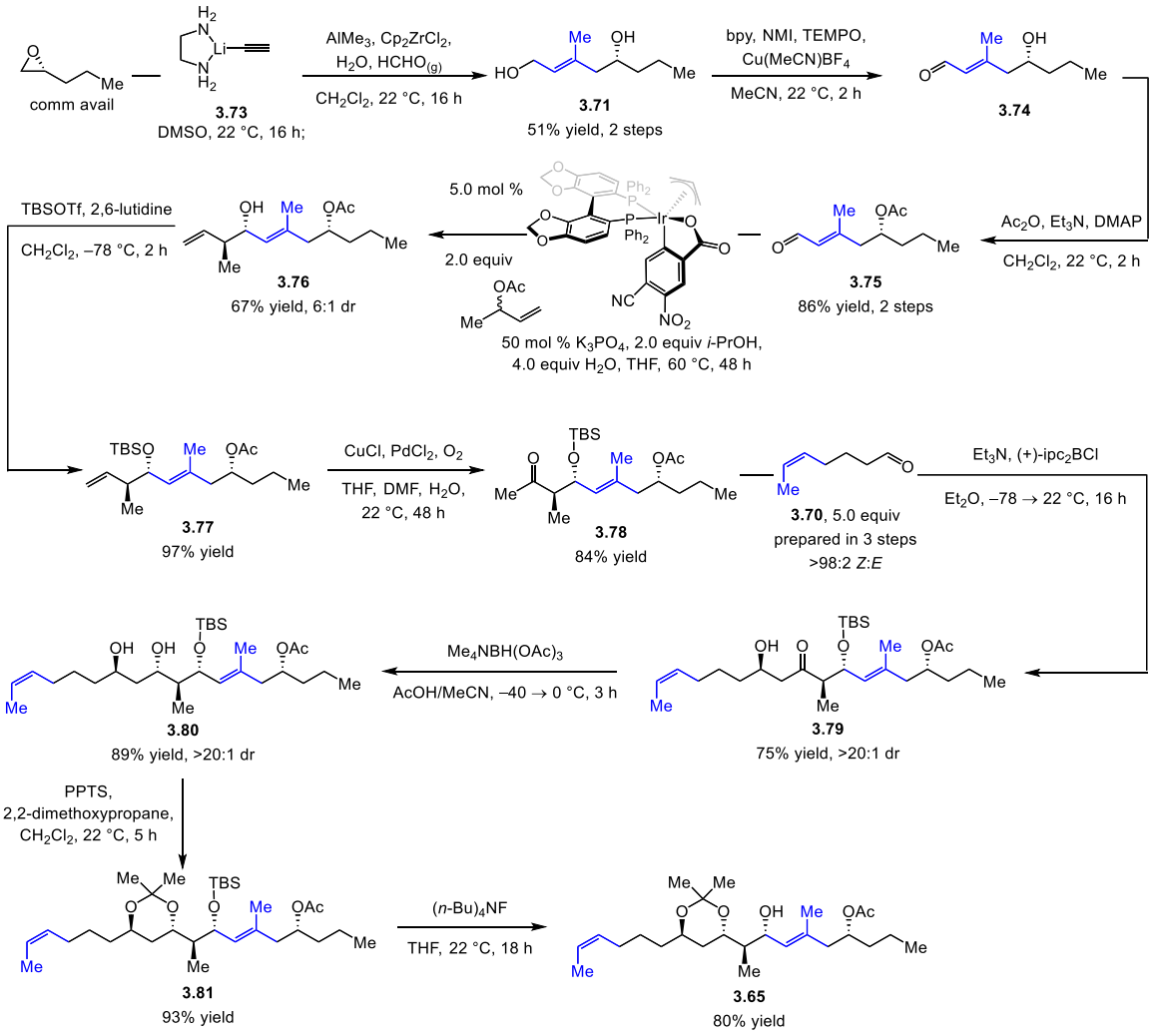


We began our synthesis by preparing the *E*-trisubstituted diol fragment **3.71** in 51% yield over 2 steps (Scheme 3.5.2), through the addition of lithium acetylene to a commercially available and enantioenriched epoxide, followed by the directed Negishi carboalumination reaction with $AlMe_3$ and the *in-situ* trapping of the alkenyl aluminum species with paraformaldehyde. The oxidation procedure adopted from Stahl's method[31] delivered the conjugated aldehyde **3.74**, which was immediately protected as **3.75** before purification. The subsequent crotyl addition reaction was most efficient under Krische's conditions[32], which required 5.0 mol % of iridium complex and 48 hours to form the desired product **3.76** in 67% yield and 6:1 dr. The secondary allylic alcohol was protected with a TBS group before the Wacker oxidation that afforded the ketone **3.78** in 84% yield. Boron aldol reaction of the resulting intermediate with the unsaturated aldehyde, prepared

(31) Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 16901–16910.
(32) Gao, X.; Townsend, I. A.; Krische, M. J. *J. Org. Chem.* **2011**, *76*, 2350–2354.

from known procedures[33], delivered the desired β-hydroxy ketone **3.79** in 75% yield as a single diastereomer. The subsequent diastereoselective Evans-Saksena reduction of the ketone effectively generated the *anti*-diol **3.80** in 89% yield, which was protected as the acetonide **3.81** in 93% yield. Removal of the silyl ether gave the desired fragment **3.65**.

Scheme 3.5.2. Fragment **3.65** Synthesis in Total Syntheis of Dolabelide C[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details.

In order to accomplish the synthesis of fragment **3.67**, oxidation of a mono-protected enantioenriched diol **3.69**, synthesized in multi-gram scale according to

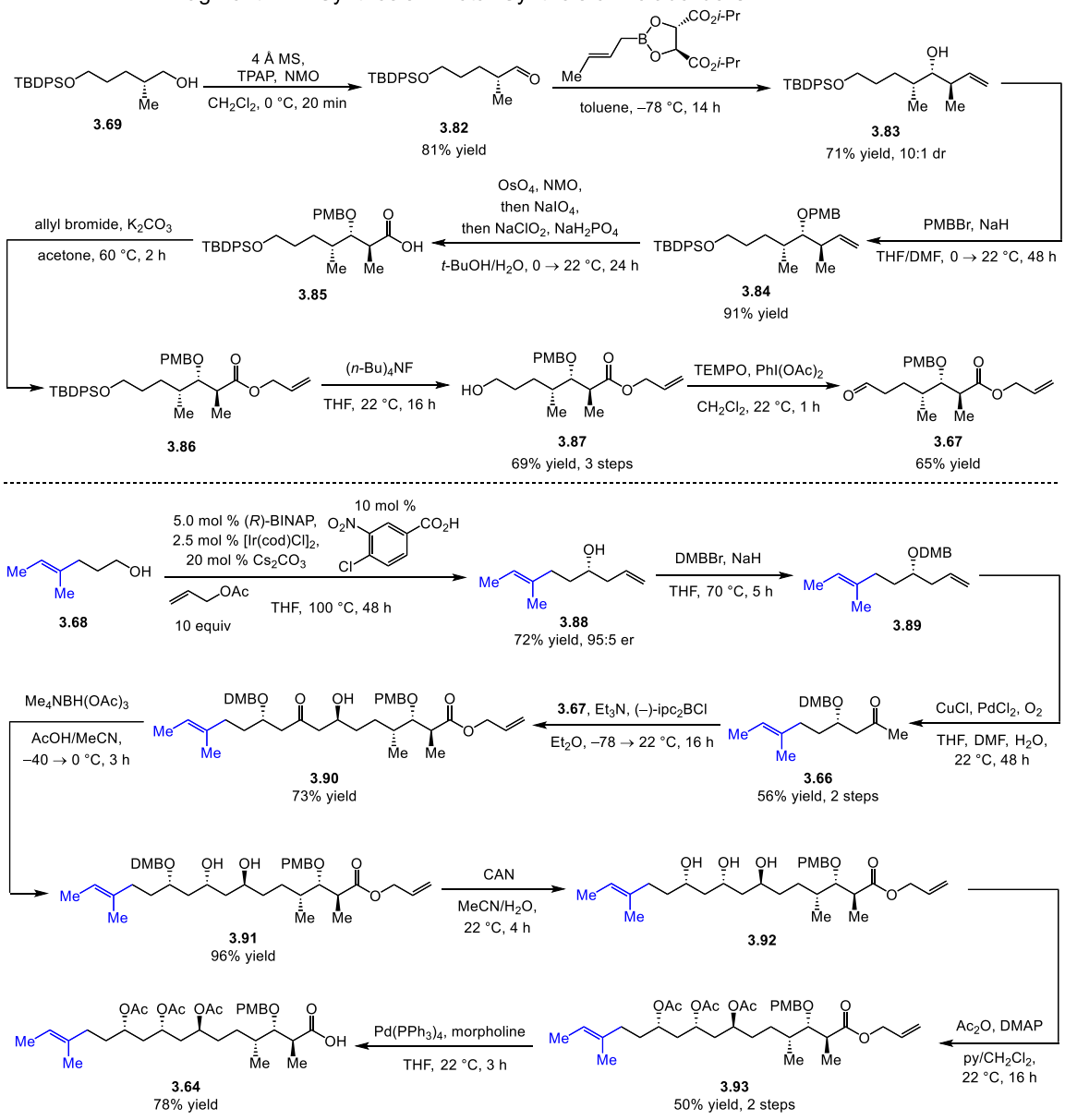
(33) Denmark, S. E.; Cramer, C. J.; Dappen, M. S. *J. Org. Chem.* **1987**, *52*, 877–887.

reported procedures[34], followed by the Roush crotyl addition delivered the secondary alcohol **3.83** in 58% yield over 2 steps and 10:1 dr. The subsequent PMB protection and the one-pot oxidative cleavage of the monosubstituted alkene afforded carboxylic acid **3.85**, which without any purification, was subjected to esterification and TBS deprotection conditions to furnish the primary alcohol **3.87** in 63% yield after 4 steps. Oxidation of the alcohol **3.87** gave the desired product **3.67**, ready for use in the boron-aldol reaction for preparation of the fragment **3.64**.

For the synthesis of fragment **3.64**, shown in Scheme 3.5.3, we began with the Krische allyl addition of the primary alcohol **3.68**, synthesized in 3 steps according to reported protocols[35], followed by the 3,4-dimethoxyl benzyl (DMB) protection of the secondary alcohol to afford the diene **3.89**, which without any purification, was treated with Wacker oxidation conditions to generate the corresponding methyl ketone **3.66**. In combination with the freshly prepared aldehyde **3.67**, ketone **3.66** was converted to the β-hydroxy ketone **3.90** in 73% yield as a single diastereomer. Subsequent Evans-Saksena reduction, DMB deprotection and acetylation of triol gave the desired tri-acetate **3.93** in 48% yield over 3 steps. The carboxylic acid intermediate **3.64** was thus furnished by the Tsuji-Trost reaction of allyl ester **3.93**. It should be noted that **3.64** was isolated in 91:9 diastereoselectivity, a selectivity that can be traced back to the Roush crotyl addition step, but the diastereomers are separated at the last step of the total synthesis.

(34) Schultz, E. E.; Sarpong, R. *J. Am. Chem. Soc.* **2013**, *135*, 4696–4699.
(35) Ho, N.-H.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 2018–2021.

Scheme 3.5.3. Fragment **3.64** Synthesis in Total Syntheis of Dolabelide C[a]

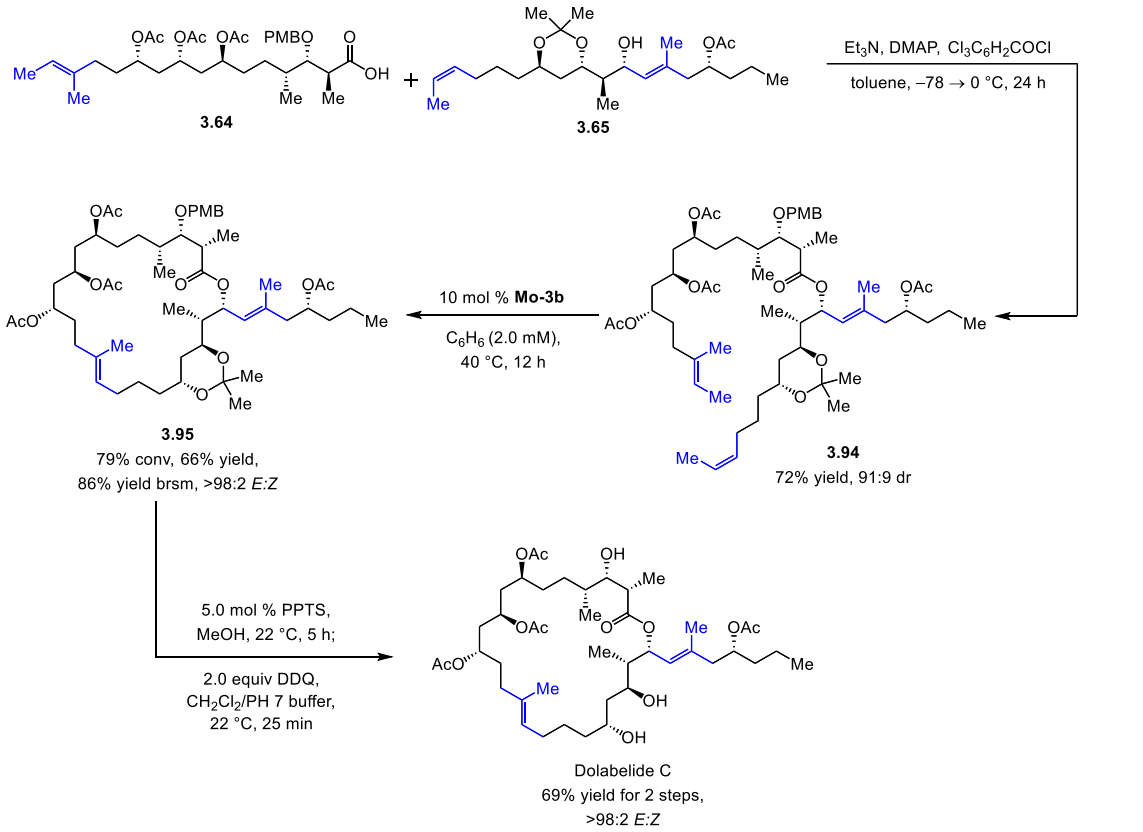


[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details.

With both key intermediates **3.64** and **3.65** in hand, the Yamaguchi esterification was performed and the triene **3.94** was yielded successfully in 72% yield (Scheme 3.5.4). When we subjected the substrate **3.94** to 10 mol % of **Mo-3b** in C_6H_6 (2.0 mM) at 40 °C for 12 h, we were able to isolate the desired macrocycle **3.95** in 66% yield as a single *E*-isomer and recover 20% of the starting material. It is notable that there is no competitive

reaction at the acyclic trisubstituted alkene on the side chain, presumably because of the steric hindrance at the alkene and the electronic deficiency of the allylic ether motif. After two additional deprotection steps, the natural product Dolabelide C was isolated in 69% yield as a single *E*-isomer and a single diastereomer. The current synthesis represents the first stereoselective total synthesis of a member of this important class of bioactive compounds. We concluded the synthesis with 19 longest linear sequences (LLS) in 2.0% yield and 39 total steps, a significant advance from the previously reported synthesis with 27 LLS in 0.7% yield and 50 total steps.[15] More importantly, we proved the reliability of the current trisubstituted MRCM method in the 37th step of the complex molecule synthesis, demonstrating the robustness and feasibility of the approach.

Scheme 3.5.4. End Game for Total Syntheis of Dolabelide C[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. See the experimental section for details. brsm: based on recovered starting material.

3.6. Conclusions

We demonstrated a practical and broadly applicable solution to a critical drawback in one of the most widely used transformations in synthetic chemistry. For the first time, a general strategy to synthesize a wide range of macrocyclic trisubstituted alkenes in either stereoisomeric form is accessible with the commercially available Mo-complex under mild conditions. In contrast to the cross-metathesis reactions that necessitated the involvement of a small substituent (chloride, bromide or nitrile) and presence of superstoichiometric amounts of reaction partners, this method is particularly attractive to deliver trisubstituted alkenes bearing three carbon-based substitutents with high efficiency and selectivity. The ability to deliver a single isomer (in Dolabelide C synthesis) through a kinetically controlled stereoretentive process compared to 1:1 *E*:*Z* selectivity in state-of-the-art synthesis, or that to reverse the stereoselectivity originating from the natural preference to access the other isomer (in Fluvirucin B_1 fragment synthesis), offers chemists a robust solution to make whichever isomer needed instead of counting on what the substrate control leads to. Given that many of the bioactive compounds and drug candidates contain macrocyclic trisubstituted alkenes, this current strategy can generate products with various ring sizes in either stereoisomer, providing a valuable tool for the synthesis of framework edited analogues to navigate the uncultivated chemical and biology diversity space.

The study also provided two important mechanistic insights: (1) not only the efficiency, but also the stereoselectivity can be significantly affected by the substrate and catalyst concentration in a kinetically controlled process; (2) the *anti*-alkylidene could severely diminish the stereoisomeric purity of the starting material. This was not very

common in cross-metathesis reactions because the halide-substituted alkenes are electronically less reactive and therefore, more difficult to be isomerized. Moreover, even if a small portion of cross-metathesis partners were isomerized, the remaining excess amounts of unisomerized disubstituted substrates would still deliver the products with desired stereochemical outcome.

The stereoretentive transformations, compared to the stereoselective reactions requiring a monosubstituted and a 1,1-disusbtituted alkene, is much more efficient and stereoselective, a finding in line with our previous discoveries. A possible alternativep strategy with the macrocylization after the trisubstituted cross-metathesis reaction is possible but would be much less attractive because cross-metathesis would require excess amounts of highly valuable late stage intermediate as reaction partners. These attributes make the current strategy the indispensable way to generate macrocyclic trisubstituted alkenes.

3.7. Experimental Section

3.7.1. Bibliography for Synthesis of Macrocyclic Trisubstituted Alkenes in Natural Product Synthesis

3.7.1.1. MRCM reactions that are not stereoselective:

a) Content, S.; Dutton, C. J.; Roberts, L. *Bioorg. & Med. Chem. Lett.* **2003**, *13*, 321–325.

b) Park, P. K.; O'Malley, S. J.; Schmidt, D. R.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *128*, 2796–2797.

c) Nicolaou, K. C.; Xu, H. *Chem. Comm.* **2006**, 600–602.

d) Dai, W.-M.; Chen, Y.; Jin, J.; Wu, J.; Lou, J.; He, Q. *Synlett* **2008**, *11*, 1737–1741.

e) Tannert, R.; Hu, T.-S.; Arndt, H. D.; Waldmann, H. *Chem. Comm.* **2009**, 1493–1495.

f) Llácer, E.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2009**, *11*, 3198–3201.

g) Hanson, P. R.; Chegondi, R.; Nguyen, J.; Thomas, C. D.; Waetzig, J. D.; Whitehead. A. *J. Org. Chem.* **2011**, *76*, 4358–4370.

h) Arndt, H. D.; Rizzo, S.; Nöcker, C.; Wakchaure, V. N.; Milroy, L.-G.; Bieker, V.; Calderon, A.; Tran, T. T. N.; Brand, S.; Dehmelt, L.; Waldmann, H. *Chem. Eur. J.*, **2015**, *21*, 5311–5316.

i) Guignard, G.; Llor, N.; Molins, E.; Bosch, J.; Amat, M. *Org. Lett.* **2016**, *18*, 1788−1791.

3.7.1.2. MRCM reactions that afford only the undesired stereoisomer:

a) Smith, III, A. B.; Mesaros, E. F.; Meyer E. A. *J. Am. Chem. Soc.* **2015**, *127*, 6948−6949.

b) McGrath, N. A.; Lee, C. A.; Araki, H.; Brichacek, M.; Njardarson, J. T. *Angew. Chem. Int. Ed.* **2008**, *47*, 9450–9453.

c) Toelle, N.; Weinstabl, H.; Gaich, T.; Mulzer, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3859–3862.

3.7.1.3. MRCM reactions that afford the desired stereoisomer (under substrate-control):

a) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302–10316.

b) Nicolaou, K. C.; Montagnon, T.; Vassilikogiannakis, G.; Mathison, C. J. N. *J. Am. Chem. Soc.* **2005**, *127*, 8872–8888.

c) Jin, J.; Chen, Y.; Li, Y.; Wu, J.; Dai, W.-M. *Org. Lett.* **2007**, *9*, 2585–2588.

d) Trost, B. M.; Dong, G.; Vance, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 4540–4541.

e) Fuwa, H.; Saito, A.; Sasaki, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3041–3044.

f) Yun, S. Y.; Hansen, E. C.; Volchkov, I.; Cho, E. J.; Lo, W. Y.; Lee, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 4261–4263.

g) Wang, C.; Haeffner, F.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 1939–1943.

h) Terayama, N., Yasui, E., Mizukami, M., Miyashita, M. and Nagumo, S. *Org. Lett.* **2014**, *16*, 2794−2797.

i) Yu, M.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2015**, *54*, 215–220.

j) Matsuzawa, A.; Shiraiwa, J.; Kasamatsu, A.; Sugita, K. *Org. Lett.* **2018**, *20*, 1031−1033.

k) Waser, P.; Altmann, K.-H. *Angew. Chem. Int. Ed.* **2020**, *59*, 17393–17397.

l) Anketell, M. J.; Sharrock, T. M.; Paterson, I. *Angew. Chem. Int. Ed.* **2020**, *59*, 1572–1576.

***3.7.1.4. Unsuccessful MRCM reactions**:*

a) Rodríguez-Escrich, C.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2008**, *10*, 5191–5194.

b) Helmboldt, H.; Hiersemann, M. *J. Org. Chem.* **2008**, *74*, 1698–1708.

c) Hoye, T. R.; Danielson, M. E.; May, A. E.; Zhao, H. *J. Org. Chem.* **2010**, *75*, 7052–7060.

***3.7.1.5. Non-RCM methods**:*

a) Hoye, T. R.; Wang, J. *J. Am. Chem. Soc.* 2005, **127**, 6950–6951.

b) Rummelt, S. M.; Preindl, J.; Sommer, H.; Fürstner, A. *Angew. Chem. Int. Ed.* **2015**, *54*, 6241–6245.

c) Trost, B. M.; Bai, W.-J.; Stivala, C. E.; Hohn, C.; Poock, C.; Heinrich, M.; Xu, S.; Rey, J. *J. Am. Chem. Soc.* **2018**, *140*, 17316−17326.

d) Karier, P.; Ungeheuer, F.; Ahlers, A.; Anderl, F.; Wille, C.; Fürstner, A. *Angew. Chem. Int. Ed.* **2019**, *58*, 248–253.

3.7.2. General

Unless otherwise noted, transformations were performed with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum line techniques. Infrared (IR) spectra were recorded on a Bruker FTIR Alpha (ATR Mode) or a Jasco FTIR 4600 (ATR mode) spectrometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), or weak (w). ^1H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz), 500 (500 MHz), or 600 (600MHz) spectrometer or a Bruker Avance III HD 400 (400MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuterium incorporation as the internal standard ($CDCl_3$: δ 7.26 ppm, C_6D_6: δ 7.16 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz), 500 (125 MHz), or 600 (150 MHz) spectrometer or a Bruker Avance III HD III 400 (100 MHZ) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm, C_6D_6: δ 128.00 ppm). High-resolution mass spectrometry was performed on a JEOL Accu TOF Dart (positive mode) at the Boston College Mass Spectrometry Facility or on a Thermo Scientific Exactive Plus EMR Orbitrap (positive mode) at the Supramolecular Science and Engineering Institute Mass Spectrometry Facility. Values for *E*:*Z* ratios of products were determined by ^1H NMR analysis of unpurified mixtures.

Solvents:

Solvents (CH_2Cl_2, Et_2O, pentane, benzene and toluene) were purified under a positive pressure of dry argon gas by an Innovative Technologies purification system. Tetrahydrofuran was distilled from Na/benzophenone. Methanol was distilled over Mg. Acetone, *N*,*N*-dimethylformamide (anhydrous), dimethyl sulfoxide (anhydrous), acetonitrile (anhydrous), isopropanol (anhydrous), 1,2-dimethoxyethane (anhydrous) and 1,4-dioxane (anhydrous) were used as received. All purification procedures of macrocyclic RCM products were carried out with reagent grade solvents (purchased from Fisher) under bench-top conditions.

Please Note: The purity of the solvent used is key to the efficiency of the RCM reactions. Solvents must be subjected to ketyl radical test prior to use.

Reagents:

(*Z*)-Non-7-en-1-yl (*E*)-12-methyltetradec-12-enoate (**3.17**), (*Z*)-hex-4-en-1-yl (*E*)-11-methyltridec-11-enoate (precursor to **3.34**), (*Z*)-non-6-en-1-yl (*E*)-8-methyldec-8-enoate (precursor to **3.36**), (*Z*)-non-7-en-1-yl (*E*)-6-methyloct-6-enoate (precursor to **3.37**), (*Z*)-hex-4-en-1-yl (*E*)-8-methyldec-8-enoate (precursor to **3.38**), (*Z*)-hex-4-en-1-yl (*E*)-7-methylnon-7-enoate (precursor to **3.39**) were prepared by esterification[6e] of carboxylic acids bearing terminal alkenes (all commercially available, used as received) and alcohols bearing *Z*-disubstituted alkenes (all commercially available, used as received), followed by 9-BBN hydroboration/Suzuki-Miyaura cross-coupling with *E*-2-bromo-butene (Aldrich) in analogy to reported procedures[25].

(*E*)-10-Methyldodec-10-en-1-yl 3-(((*Z*)-non-6-en-1-yl)oxy)benzoate (**3.32**) was prepared by Mitsunobu reaction[36] of ethyl 3-hydroxybenzoate (Aldrich) and (*Z*)-non-6-en-1-ol (Aldrich), followed by hydrolysis of ester[37], esterification[6e] with non-8-en-1-ol (TCI America) and 9-BBN hydroboration/Suzuki-Miyaura cross-coupling with *E*-2-bromo-butene (Aldrich) in analogy to reported procedures[25].

(*E*)-4-Methylhex-4-en-1-yl (*Z*)-tridec-11-enoate (precursor to **3.35**) was prepared by esterification[6e] of dec-9-enoic acid (Oakwood) and (*E*)-4-methylhex-4-en-1-ol (as shown later in the total synthesis of dolabelide C), followed by 9-BBN hydroboration/Suzuki-Miyaura cross-coupling with (*Z*)-1-bromo-propene (Aldrich) in analogy to reported procedures[25].

tert-Butyldimethyl(((3*Z*,21*E*)-21-methyltricosa-3,21-dien-9-yl)oxy)silane (precursor to **3.40**) was prepared by Grignard reagent (from 11-bromoundec-1-ene (Oakwood)) addition to aldehyde (from (*Z*)-non-6-en-1-ol (Aldrich))[38], followed by TBS protection[39] and 9-BBN hydroboration/Suzuki-Miyaura cross-coupling with *E*-2-bromo-butene (Aldrich) in analogy to reported procedures[25].

1-Methoxy-4-((((3*Z*,19*E*)-19-methylhenicosa-3,19-dien-9-yl)oxy)methyl)benzene (precursor to **3.41**) was prepared by Grignard reagent (from 9-bromonon-1-ene (Combi-blocks)) addition to aldehyde (from (*Z*)-non-6-en-1-ol (Aldrich))[38], followed by PMB protection[40] and 9-BBN hydroboration/Suzuki-Miyaura cross-coupling with *E*-2-bromo-butene (Aldrich) in analogy to reported procedures[25].

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(36) Shigehisa, H.; Ano, T.; Honma, H.; Ebisawa, K.; Hiroya, K. *Org. Lett.* **2016**, *18*, 3622–3625.
(37) Legrand, F. X. Six, N.; Slomianny, C.; Bricout, H.; Tilloy, S.; Monflier, E., *Adv. Synth. Catal.* **2011**, *353*, 1325–1334.
(38) Joosten, A.; Persson, A. K. Å.; Millet, R.; Johnson, M. T.; Bäckvall, J.-E. *Chem. Eur. J.* **2012**, *18*, 15151–15157.
(39) Aponick, A.; Li, C.-Y.; Palmes, J. A. *Org. Lett.* **2009**, *11*, 121–124.
(40) Tseng, H.-R.; Luh, T.-Y. *J. Org. Chem.* **1997**, *62*, 4568–4569.

(*E*)-12-Methyl-*N*-((*Z*)-non-6-en-1-yl)tetradec-12-enamide (precursor to **3.42**) was prepared by 9-BBN hydroboration/Suzuki-Miyaura cross-coupling with methyl undec-10-enoate (from undec-10-enoic acid (Alfa Aesar)) and *E*-2-bromo-butene (Aldrich)[25], followed by ester hydrolysis[37] and amide coupling[7] with (*Z*)-non-6-en-1-amine (from (*Z*)-non-6-en-1-ol (Aldrich)) in analogy to reported procedures.

(*E*)-7-Methyl-*N*-((*Z*)-non-6-en-1-yl)non-7-enamide (precursor to **3.43**) was prepared by 9-BBN hydroboration/Suzuki-Miyaura cross-coupling[25] with methyl hex-5-enoate (from hex-5-enoic acid (TCI America)) and *E*-2-bromo-butene (Aldrich), followed by ester hydrolysis[37] and amide coupling[7] with (*Z*)-non-6-en-1-amine (from (*Z*)-non-6-en-1-ol (Aldrich)) in analogy to reported procedures.

tert-Butyl ((*E*)-7-methylnon-7-enoyl)((*Z*)-non-6-en-1-yl)carbamate (precursor to **3.44**) was prepared by the Boc protection[7] of (*E*)-7-Methyl-*N*-((*Z*)-non-6-en-1-yl)non-7-enamide (precursor to **3.43**) in analogy to reported procedures.

(*Z*)-Non-6-en-1-yl (*Z*)-11-methyltridec-11-enoate (precursor to **3.47**), (*Z*)-hex-4-en-1-yl (Z)-11-methyltridec-11-enoate (precursor to **3.48**), (*Z*)-non-6-en-1-yl (*Z*)-8-methyldec-8-enoate (precursor to **3.49**), (*Z*)-8-methyldec-8-en-1-yl (*Z*)-oct-5-enoate (precursor to **3.50**), (*Z*)-hex-4-en-1-yl (*Z*)-8-methyldec-8-enoate (precursor to **3.51**), (*Z*)-hex-4-en-1-yl (*Z*)-7-methylnon-7-enoate (precursor to **3.52**) were prepared by esterification[6e] of carboxylic acids bearing terminal alkenes (all commercially available, used as received) and alcohols bearing *Z*-disubstituted alkenes (all commercially available, used as received), followed by 9-BBN hydroboration/Suzuki-Miyaura cross-coupling with *Z*-2-bromo-butene (Aldrich) or Z-2-chloro-butene (TCI America) in analogy to reported procedures[25].

(*Z*)-10-Methyldodec-10-en-1-yl 3-(((*Z*)-non-6-en-1-yl)oxy)benzoate (**3.45**) was prepared by Mitsunobu reaction[36] of ethyl 3-hydroxybenzoate (Aldrich) and (*Z*)-non-6-en-1-ol (Aldrich), followed by hydrolysis of ester[37], esterification[6e] with non-8-en-1-ol (TCI America) and 9-BBN hydroboration/Suzuki-Miyaura cross-coupling with *Z*-2-bromo-butene (Aldrich) in analogy to reported procedures[25].

tert-Butyldimethyl(((3*Z*,21*Z*)-21-methyltricosa-3,21-dien-9-yl)oxy)silane (precursor to **3.53**) was prepared by Grignard reagent (from 11-bromoundec-1-ene (Oakwood)) addition to aldehyde (from (*Z*)-non-6-en-1-ol (Aldrich))[38], followed by TBS protection[39] and 9-BBN hydroboration/Suzuki-Miyaura cross-coupling with *Z*-2-bromo-butene (Aldrich) in analogy to reported procedures[25].

1-Methoxy-4-((((3*Z*,19*E*)-19-methylhenicosa-3,19-dien-9-yl)oxy)methyl)benzene (precursor to **3.54**) was prepared by Grignard reagent (from 9-bromonon-1-ene (Combi-blocks)) addition to aldehyde (from (*Z*)-non-6-en-1-ol (Aldrich))[38], followed by PMB protection[40] and 9-BBN hydroboration/Suzuki-Miyaura cross-coupling with *E*-2-bromo-butene (Aldrich) in analogy to reported procedures[25].

(*Z*)-12-Methyl-*N*-((*Z*)-non-6-en-1-yl)tetradec-12-enamide (precursor to **3.55**) was prepared by 9-BBN hydroboration/Suzuki-Miyaura cross-coupling[25] with methyl undec-10-enoate (from undec-10-enoic acid (Alfa Aesar)) and *Z*-2-bromo-butene (Aldrich), followed by ester hydrolysis[37] and amide coupling[7] with (*Z*)-non-6-en-1-amine (from (*Z*)-non-6-en-1-ol (Aldrich)) in analogy to reported procedures[25].

tert-Butyl ((*Z*)-12-methyltetradec-12-enoyl)((*Z*)-non-6-en-1-yl)carbamate (precursor to **3.56**) was prepared by the Boc protection[7] of (*Z*)-12-Methyl-*N*-((*Z*)-non-6-en-1-yl)tetradec-12-enamide (precursor to **3.55**) in analogy to reported procedures.

tert-Butyl ((Z)-8-methyldec-8-en-1-yl)((Z)-oct-5-enoyl)carbamate (precursor to **3.57**) was prepared by 9-BBN hydroboration/Suzuki-Miyaura cross-coupling[25] with hept-6-en-1-ol (Combi-blocks) and *Z*-2-bromo-butene (Aldrich), followed by a modified Gabriel amine synthesis[41], amide coupling[7] with (*Z*)-oct-5-enoic acid (from (*Z*)-oct-5-en-1-ol (Aldrich)) and Boc protection[7] in analogy to reported procedures.

(*R*)-2-Propyloxirane (A2B Chem), lithium acetylide ethylenediamine complex (Aldrich), trimethylaluminum (Aldrich), bis(cyclopentadienyl)zirconium(IV) dichloride (Strem), paraformaldehyde (Aldrich), 2,2'-bipyridine (Aldrich), 1-methylimidazole (Aldrich), TEMPO (Oakwood), tetrakis(acetonitrile)copper(I) tetrafluoroborate (TCI America), acetic anhydride (Oakwood), 4-dimethylaminopyridine (Oakwood), triethyl amine (Aldrich), potassium phosphate tribasic (Aldrich), 3-buten-2-yl acetate (TCI America), 2,6-lutidine (ACROS), *tert*-butyldimethylsilyl trifluoromethanesulfonate (Oakwood), copper(I) chloride (Strem), palladium chloride (Strem), (−)-DIP-chloride (Aldrich), *cis*-4-hexen-1-ol (Alfa Aesar), methanesulfonyl chloride (Alfa Aesar), potassium cyanide (Fisher Scientific), diisobutylaluminum hydride (Aldrich), tetramethylammonium triacetoxyborohydride (Santa Cruz), 2,2-dimethoxypropane (Oakwood), pyridinium *p*-toluenesulfonate (Aldrich), tetrabutylammonium fluoride (Oakwood), tetrapropylammonium perruthenate (Oakwood), *N*-methylmorpholine *N*-oxide (Aldrich), *E*-2-butene (Aldrich), diethanolamine (Oakwood), *n*-butyl lithium (Aldrich), (−)-diisopropyl D-tartrate (Oakwood), sodium hydride (Strem), osmium tetraoxide (Alfa Aesar), sodium periodate (Aldrich), sodium chlorite (Alfa Aesar), sodium dihydrogen phosphate monohydrate (Alfa Aesar), allyl bromide (Aldrich), potassium carbonate (Fisher Scientific), (diacetoxyiodo)benzene (ACROS), methacrolein (Aldrich),

(41) Sen, S. E.; Roach, S. L. *Synthesis* **1995**, 756–758.

methylmagnesium bromide (Aldrich), propionic acid (ACROS), triethyl orthopropionate (Alfa Aesar), lithium aluminumhydride (Aldrich), allyl acetate (Oakwood), bis(1,5-cyclooctadiene)diiridium(I) dichloride (TCI America), (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (Oakwood), 4-chloro-3-nitrobenzoic acid (TCI America), 3,4-dimethoxybenzyl alcohol (Alfa Aesar), ammonium cerium(IV) nitrate (Aldrich), tetrakis(triphenylphosphine)palladium(0) (TCI America), morpholine (Alfa Aesar), 2,4,6-trichlorobenzoic chloride (Alfa Aesar), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (Aldrich), Ph=7 buffer (Fisher Scientific), 9-borabicyclo[3.3.1]nonane solution (0.5 M, Aldrich), *E*-2-bromo-butene (Aldrich), *Z*-2-bromo-butene (Aldrich), *Z*-2-chloro-butene (TCI America), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (Strem), *tert*-butyldimethylsilyl chloride (Oakwood), di-*tert*-butyl dicarbonate (Oakwood), 4-methoxybenzyl chloride (TCI America), tris(pentafluorophenyl)borane (TCI America) were used as received.

Mo-2[12], **Mo-3a**[42], **Mo-3b**[43], and **Mo-3c**[25] were prepared according to previously reported procedures. Mo complexes were manipulated under an atmosphere of N_2 in a glove box.

General procedure for *in situ* preparation of Mo-3d for spectroscopic analysis: In a N_2-filled glove box, an oven-dried 4 mL vial equipped with a magnetic stir bar was charged with pentafluorophenylimido Mo bispyrrolide complex[44] (59.7 mg, 0.10 mmol), (1'r,3's)-5'-bromo-2,2",4,4",6,6"-hexaethyl-[1,1':3',1"-terphenyl]-2'-ol [45] (49.4 mg, 0.10 mmol) and C_6H_6 (1.0 mL). This resulted in a dark-red solution. The vial was capped and

(42) Nguyen, T. T.; Koh, M. J.; Shen, X.; Romiti, F.; Schrock, R. R.; Hoveyda, A. H. *Science* **2016**, *352*, 569–575.
(43) Koh, M. J.; Thach, T. T.; Zhang, H.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2016**, *531*, 459–465.
(44) Yuan, J.; Schrock, R. R.; Müller, P.; Axtell, J. C.; Dobereiner, G. E. *Organometallics* **2012**, *31*, 4650–4653.
(45) Schowner, R.; Elser, I.; Toth, F.; Robe, E.; Frey, W., Buchmeiser, M. R. *Chem. Eur. J.* **2018**, *24*, 13336–13347.

the mixture was allowed to stir for 2 h at 22 °C, after which it was transferred to a screw cap NMR tube through a pipette. The tube was capped and sealed with Teflon tape.

For *in situ* generated complexes, only the diagnostic alkylidene α-proton signal of the *syn*-alkylidene of **Mo-3d** is reported: **^{1}H NMR (600 MHz, C_6D_6)**: δ 11.35 (1H, s).

3.7.3. Macrocyclic Ring-Closing Metathesis (MRCM) Reactions

General Procedure: In a N_2-filled glove box, an oven-dried 100 mL round-bottom flask equipped with a magnetic stir bar was charged with a linear diene substrate and benzene (1.0 mM). A solution of **Mo-3b** in benzene was subsequently added, and the mixture was allowed to stir for 4–12 h at 40 °C. At this time, the reaction was quenched by the addition of wet (undistilled) Et_2O and concentrated in vacuo to dryness (percent conversion and *Z*:*E* selectivity ratio was determined by ^{1}H NMR analysis of the unpurified mixture). Purification was performed through silica gel chromatography.

(*E*)-13-Methyloxacycloicos-13-en-2-one (3.18): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried round-bottom flask containing (*Z*)-non-7-en-1-yl (*E*)-12-methyltetradec-12-enoate (18.2 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The mixture was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^{1}H NMR analysis of the unpurified mixture revealed 89% consumption of (*Z*)-non-7-en-1-yl (*E*)-12-methyltetradec-12-enoate. The resulting red oil was purified by silica gel chromatography (2% EtOAc in hexanes) to afford **3.18** as colorless oil (11.7 mg, 0.0379 mmol, 76% yield, >98:2 *E*:*Z*). **IR (neat)**: 2922 (s), 2851 (s), 1734 (s), 1459 (m), 1347 (m), 1243 (m), 1170 (m); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 5.10 (t, J = 7.0 Hz, 1H), 4.11 (t, J = 6.4 Hz, 2H), 2.34–2.29 (m, 2H), 2.02–1.99 (m, 4H), 1.67–1.56 (m, 4H), 1.55 (s, 3H),

1.42–1.24 (m, 18H), 1.26–1.14 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 174.1, 134.4, 125.8, 64.3, 39.1, 34.9, 29.9, 29.5, 29.3, 29.3, 29.2, 9.0, 28.6, 28.5, 27.7, 27.6, 26.4, 26.3, 25.5, 15.4; **HRMS [M+H]$^+$** calcd for $C_{20}H_{37}O_2$: 309.2788, found: 309.2784.

3.18 *Formation through E-disubstituted alkene substrate*. Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried round-bottom flask containing (*E*)-non-7-en-1-yl (*E*)-12-methyltetradec-12-enoate (18.2 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^{1}H NMR analysis of the unpurified mixture revealed 85% consumption of (*E*)-non-7-en-1-yl (*E*)-12-methyltetradec-12-enoate. The resulting red oil was purified by silica gel chromatography (2% EtOAc in hexanes) to afford **3.18** in 95:5 *E*:*Z* ratio as colorless oil (11.1 mg, 0.0359 mmol, 72% yield).

(*E*)-9-Methyl-2,19-dioxa-1(1,3)-benzenacycloicosaphan-8-en-20-one (3.33): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried round-bottom flask containing (*E*)-10-methyldodec-10-en-1-yl 3-(((*Z*)-non-6-en-1-yl)oxy)benzoate (22.1 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^{1}H NMR analysis of the unpurified mixture revealed 93% consumption of (*E*)-10-methyldodec-10-en-1-yl 3-(((*Z*)-non-6-en-1-yl)oxy)benzoate. The resulting red oil was purified by silica gel chromatography (2% $\rightarrow$ 5% EtOAc in hexanes) to afford **3.33** in >98:2 *E*:*Z* ratio as colorless oil (17.4 mg, 0.0467 mmol, 93% yield). **IR (neat)**: 2923 (s), 2852 (m), 1718 (s), 1584 (m), 1487 (w), 1463 (w), 1442 (w), 1384 (w), 1280 (s), 1220 (s), 1102 (m), 1072

(w), 1022 (w), 755 (m); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.65 (dt, J = 7.8, 1.3 Hz, 1H), 7.51 (dd, J = 2.7, 1.6 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.07 (ddd, J = 8.2, 2.6, 1.0 Hz, 1H), 5.11 (t, J = 7.6 Hz, 1H), 4.35–4.28 (m, 2H), 3.96 (t, J = 6.5 Hz, 2H), 2.08 (q, J = 6.1 Hz, 2H), 1.98 (t, J = 7.2 Hz, 2H), 1.82–1.76 (m, 2H), 1.74 (dt, J = 8.1, 5.3 Hz, 2H), 1.58 (s, 3H), 1.56–1.50 (m, 2H), 1.48–1.24 (m, 14H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 166.6, 159.1, 135.6, 132.0, 129.6, 124.5, 122.1, 119.1, 114.9, 68.3, 65.0, 39.2, 29.5, 29.4, 29.1, 28.6, 28.6, 28.4, 28.3, 27.4, 27.0, 26.3, 25.3, 16.1; **HRMS [M+H]$^+$** calcd for $C_{24}H_{37}O_3$: 373.2737, found: 373.2728.

(*E*)-12-Methyloxacyclohexadec-12-en-2-one (3.34): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried round-bottom flask containing (*Z*)-hex-4-en-1-yl (*E*)-11-methyltridec-11-enoate (15.4 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^{1}H NMR analysis of the unpurified mixture revealed 95% consumption of (*Z*)-hex-4-en-1-yl (*E*)-11-methyltridec-11-enoate. The resulting red oil was purified by silica gel chromatography (2% EtOAc in hexanes) to afford **3.34** as colorless oil (10.4 mg, 0.0412 mmol, 82% yield, >98:2 *E*:*Z*). **IR (neat)**: 2922 (s), 2851 (m), 1734 (s), 1459 (m), 1378 (w), 1345 (w), 1248 (m), 1207 (w), 1173 (m), 1129 (w), 1093 (w), 1039 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.16 (t, J = 7.6 Hz, 1H), 4.08 (t, J = 6.5 Hz, 2H), 2.36–2.26 (m, 2H), 2.16 (q, J = 6.5 Hz, 2H), 2.07–2.00 (m, 2H), 1.75 (dt, J = 12.7, 6.5 Hz, 2H), 1.68 (q, J = 6.7 Hz, 2H), 1.58 (s, 3H), 1.40 (dt, J = 13.3, 7.2 Hz, 2H), 1.35–1.14 (m, 10H); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 174.7, 135.6, 123.9, 63.5, 38.8, 34.6, 28.2, 27.8, 27.8, 27.0,

26.8, 25.9, 25.7, 25.0, 23.8, 15.6; **HRMS [M+H]$^+$** calcd for $C_{16}H_{29}O_2$: 253.2162, found: 253.2157.

(*E*)-12-Methyloxacyclohexadec-12-en-2-one (3.35): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried round-bottom flask containing (*E*)-4-methylhex-4-en-1-yl (*Z*)-tridec-11-enoate (15.4 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^{1}H NMR analysis of the unpurified mixture revealed 86% consumption of (*E*)-4-methylhex-4-en-1-yl (*Z*)-tridec-11-enoate. The resulting red oil was purified by silica gel chromatography (2% EtOAc in hexanes) to afford **3.35** as colorless oil (10.4 mg, 0.0412 mmol, 82% yield, >98:2 *E*:*Z*). **IR (neat)**: 2922 (s), 2852 (m), 1734 (s), 1459 (m), 1359 (w), 1249 (w), 1207 (m), 1172 (m), 1111 (w), 1092 (w), 1045 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 5.19 (t, J = 7.1 Hz, 1H), 4.07–4.00 (m, 2H), 2.35–2.30 (m, 2H), 2.16 (t, J = 6.4 Hz, 2H), 2.05 (q, J = 6.3 Hz, 2H), 1.79–1.73 (m, 2H), 1.69 (dt, J = 12.8, 6.6 Hz, 2H), 1.58 (s, 3H), 1.38–1.23 (m, 12H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 174.5, 132.6, 127.1, 62.5, 35.4, 33.7, 28.1, 27.5, 27.1, 27.1, 26.7, 26.4, 26.0, 25.5, 24.9, 15.5; **HRMS [M+H]$^+$** calcd for $C_{16}H_{29}O_2$: 253.2162, found: 253.2157.

(*E*)-9-Methyloxacyclopentadec-9-en-2-one (3.36): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried round-bottom flask containing (*Z*)-non-6-en-1-yl (*E*)-8-methyldec-8-enoate (15.4 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The mixture was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^{1}H NMR analysis of the unpurified mixture revealed 94% consumption of (*Z*)-non-6-en-1-yl (*E*)-8-

methyldec-8-enoate. The resulting red oil was purified by silica gel chromatography (2% EtOAc in hexanes) to afford **3.36** as colorless oil (10.8 mg, 0.0453 mmol, 91% yield, >98:2 *E*:*Z*). **IR (neat)**: 2924 (s), 2853 (m), 1734 (s), 1457 (w), 1383 (w), 1235 (m), 1179 (m), 1135 (w); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 5.04 (t, J = 7.0 Hz, 1H), 4.14–4.10 (m, 2H), 2.34–2.30 (m, 2H), 2.06–2.01 (m, 4H), 1.66 (dt, J = 13.2, 7.2 Hz, 2H), 1.64–1.59 (m, 2H), 1.55 (s, 3H), 1.45 (dt, J = 12.7, 6.7 Hz, 2H), 1.39 (dq, J = 10.8, 6.5, 5.5 Hz, 2H), 1.34–1.28 (m, 4H), 1.18 (dq, J = 14.2, 7.0 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 174.1, 134.7, 126.1, 63.1, 38.6, 34.2, 28.7, 28.6, 28.4, 27.2, 27.1, 26.2, 25.2, 23.9, 15.4; **HRMS [M+H]$^+$** calcd for $C_{15}H_{27}O_2$: 239.2006, found: 239.2009.

(*E*)-7-Methyloxacyclotetradec-7-en-2-one (3.37): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried round-bottom flask containing (*Z*)-non-7-en-1-yl (*E*)-6-methyloct-6-enoate (14.0 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^{1}H NMR analysis of the unpurified mixture revealed 88% consumption of (*Z*)-non-7-en-1-yl (*E*)-6-methyloct-6-enoate. The resulting red oil was purified by silica gel chromatography (2% EtOAc in hexanes) to afford **3.37** as colorless oil (8.4 mg, 0.0374 mmol, 75% yield, >98:2 *E*:*Z*). **IR (neat)**: 2922 (s), 2852 (m), 1730 (s), 1459 (m), 1378 (w), 1260 (m), 1207 (w), 1081 (w), 1021 (w), 972 (w); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 5.12 (t, J = 7.5 Hz, 1H), 4.10–4.06 (m, 2H), 2.27 (t, J = 7.6 Hz, 2H), 2.10–2.01 (m, 4H), 1.69–1.61 (m, 4H), 1.58 (s, 3H), 1.49–1.43 (m, 4H), 1.43–1.38 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 174.2, 143.0, 127.1, 65.8, 37.9, 34.7, 28.9, 27.8, 27.7, 27.3, 26.9, 25.9, 23.8, 16.2; **HRMS [M+H]$^+$** calcd for $C_{14}H_{25}O_2$: 223.1693, found: 223.1682.

(*E*)-9-Methyloxacyclotridec-9-en-2-one (3.38): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 60 μL, 6.0 μmol) was transferred by syringe to an oven-dried round-bottom flask containing (*Z*)-hex-4-en-1-yl (*E*)-8-methyldec-8-enoate (16.0 mg, 0.060 mmol) and benzene (60.0 mL, 1.0 mM). The solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^1H NMR analysis of the unpurified mixture revealed 64% consumption of (*Z*)-hex-4-en-1-yl (*E*)-8-methyldec-8-enoate. The resulting red oil was purified by silica gel chromatography (2% EtOAc in hexanes) to afford **3.38** as colorless oil (6.0 mg, 0.0285 mmol, 48% yield, 90:10 *E*:*Z*). **IR (neat)**: 2922 (s), 2853 (m), 1731 (s), 1447 (w), 1353 (w), 1230 (m), 1190 (w), 1176 (w), 1141 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *E* isomer: δ 5.24 (t, J = 7.8 Hz, 1H), 4.17–4.12 (m, 2H), 2.32–2.27 (m, 2H), 2.19 (q, J = 6.8 Hz, 2H), 2.06–2.00 (m, 2H), 1.87–1.81 (m, 2H), 1.69–1.64 (m, 2H), 1.57 (s, 3H), 1.52–1.44 (m, 2H), 1.37–1.25 (m, 4H); *Z* isomer (resolved signals only): δ 5.06 (t, J = 7.4 Hz, 1H), 4.12–4.09 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)**: *E*-isomer: δ 174.8, 133.8, 125.7, 66.1, 38.3, 33.6, 28.1, 27.2, 26.8, 25.9, 25.3, 24.8, 15.2; *Z*-isomer (resolved signals only): δ 124.4, 63.2, 34.8, 30.2, 28.3, 27.7, 27.1, 25.9, 25.4, 23.9, 23.2; **HRMS [M+H]$^+$** calcd for $C_{13}H_{23}O_2$: 211.1693, found: 211.1693.

(*E*)-8-Methyloxacyclododec-8-en-2-one (3.39): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 60 μL, 6.0 μmol) was transferred by syringe to an oven-dried round-bottom flask containing (*Z*)-hex-4-en-1-yl (*E*)-7-methylnon-7-enoate (15.2 mg, 0.060 mmol) and benzene (60.0 mL, 1.0 mM). The mixture was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^1H NMR analysis of the unpurified mixture revealed 79% consumption of (*Z*)-hex-4-en-1-yl (*E*)-7-

methylnon-7-enoate. The resulting red oil was purified by silica gel chromatography (2% EtOAc in hexanes) to afford **3.39** as colorless oil (6.6 mg, 0.0336 mmol, 56% yield, >98:2 *E*:*Z*). **IR (neat)**: 2924 (m), 2852 (w), 1291 (s), 1449 (w), 1327 (w), 1293 (w), 1246 (s), 1201 (w), 1143 (m), 1073 (m), 1036 (w), 1015 (w), 970 (w), 795 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.33 (t, J = 7.2 Hz, 1H), 4.15–4.09 (m, 2H), 2.34–2.26 (m, 2H), 2.21 (q, J = 6.7 Hz, 2H), 2.11 (t, J = 6.5 Hz, 2H), 1.84–1.76 (m, 2H), 1.63–1.56 (m, 2H), 1.53 (s, 3H), 1.51–1.45 (m, 2H), 1.20–1.10 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 173.8, 131.3, 127.8, 66.6, 36.4, 35.5, 28.4, 27.7, 24.9, 23.4, 21.9, 14.6; **HRMS $[M+H]^+$** calcd for $C_{12}H_{21}O_2$: 197.1536, found: 197.1532.

(*E*)-7-Methylcyclooctadec-6-en-1-ol (3.40): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried round-bottom flask containing *tert*-butyldimethyl(((3*Z*,21*E*)-21-methyltricosa-3,21-dien-9-yl)oxy)silane (23.2 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^{1}H NMR analysis of the unpurified mixture revealed 80% consumption of *tert*-butyldimethyl(((3*Z*,21*E*)-21-methyltricosa-3,21-dien-9-yl)oxy)silane. The resulting red oil was dissolved into THF (100 μL) and tetrabutylammonium fluoride (1.0 M, 100 μL, 0.100 mmol) was added to the resulting solution at 22 °C. The reaction mixture was allowed to warm up to 50 °C and stir at the same temperature for 12 h, after which the mixture was concentrated in vacuo and the resulting dark oil was purified by silica gel chromatography (5% → 10% EtOAc in hexanes) to afford **3.40** as colorless oil (10.0 mg, 0.0357 mmol, 71% yield, 95:5 *E*:*Z*). **IR (neat)**: 3335 (br), 2921 (s), 2851 (m), 1458 (w), 1363 (w), 1070 (w), 720 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.11 (t, J = 7.3

Hz, 1H), 3.68 (t, *J* = 5.8 Hz, 1H), 2.02 (dt, *J* = 23.2, 6.6 Hz, 4H), 1.58 (s, 3H), 1.48 (q, *J* = 6.5 Hz, 2H), 1.42–1.22 (m, 24H), alcohol *OH* proton for **3.40** is not observed; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 135.1, 125.0, 70.9, 39.3, 37.0, 35.2, 29.7, 28.2, 27.7, 27.7, 27.5, 27.5, 27.1, 27.0, 26.9, 26.9, 24.3, 24.2; **HRMS [M+H]$^+$** calcd for $C_{19}H_{37}O$: 281.2839, found: 281.2845.

(*E*)-7-((4-Methoxybenzyl)oxy)-1-methylcyclohexadec-1-ene (3.41): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried round-bottom flask containing 1-methoxy-4-((((3*Z*,19*E*)-19-methylhenicosa-3,19-dien-9-yl)oxy)methyl)benzene (22.1 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^{1}H NMR analysis of the unpurified mixture revealed 66% consumption of 1-methoxy-4-((((3*Z*,19*E*)-19-methylhenicosa-3,19-dien-9-yl)oxy)methyl)benzene. The resulting red oil was purified by silica gel chromatography (5% EtOAc in hexanes) to afford **3.41** as colorless oil (11.0 mg, 0.0295 mmol, 59% yield, >98:2 *E*:*Z*). **IR (neat)**: 2924 (s), 2852 (m), 1612 (w), 1511 (m), 1459 (m), 1350 (w), 1300 (w), 1245 (s), 1170 (w), 1080 (m), 1038 (m), 885 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.26 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.10 (t, *J* = 7.3 Hz, 1H), 4.44 (dd, *J* = 36.9, 11.3 Hz, 2H), 3.80 (s, 3H), 3.40–3.28 (m, 1H), 2.14–1.96 (m, 4H), 1.70–1.58 (m, 2H), 1.55 (s, 3H), 1.46–1.15 (m, 20H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 159.1, 134.8, 131.5, 129.3, 125.8, 113.9, 78.1, 70.2, 55.4, 39.1, 32.8, 30.7, 29.9, 28.0, 27.6, 27.5, 27.3, 26.7, 26.4, 25.2, 24.1, 22.2, 15.3; **HRMS [M+H]$^+$** calcd for $C_{25}H_{41}O_2$: 373.3101, found: 373.3102.

(*E*)-13-Methylazacyclononadec-13-en-2-one (3.42): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried round-bottom flask containing (*E*)-12-methyl-*N*-((*Z*)-non-6-en-1-yl)tetradec-12-enamide (18.2 mg, 0.050 mmol), tris(pentafluorophenyl)borane (25.6 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^1H NMR analysis of the unpurified mixture revealed 93% consumption of (*E*)-12-methyl-*N*-((*Z*)-non-6-en-1-yl)tetradec-12-enamide. The resulting red oil was purified by silica gel chromatography (10% → 15% → 20 % EtOAc in hexanes) to afford **3.42** as colorless oil (11.7 mg, 0.0398 mmol, 80% yield, 95:5 *E*:*Z*). **IR (neat)**: 3287 (br),2923(s), 2852 (m), 1642 (m), 1553 (w), 1511 (w), 1460 (m), 1369 (w), 1274 (w), 1081 (w), 962 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.43 (br, 1H), 5.09 (t, J = 6.5 Hz, 1H), 3.26 (q, J = 5.7 Hz, 2H), 2.15 (t, J = 7.2 Hz, 2H), 2.04 (q, J = 6.2 Hz, 2H), 1.97 (t, J = 6.8 Hz, 2H), 1.63–1.58 (m, 2H), 1.57 (s, 3H), 1.55–1.46 (m, 2H), 1.46–1.16 (m, 18H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 173.5, 135.4, 124.5, 39.7, 39.1, 37.2, 29.6, 29.5, 28.3, 28.3, 28.2, 28.1, 27.9, 27.6, 27.4, 26.6, 26.4, 25.4, 16.1; **HRMS [M+H]$^+$** calcd for $C_{19}H_{36}NO$: 294.2791, found: 294.2787.

***tert*-Butyl (*E*)-8-methyl-2-oxoazacyclotetradec-8-ene-1-carboxylate (3.44)**: Following the general procedure, a solution of **Mo-3c** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried round-bottom flask containing *tert*-butyl ((*E*)-7-methylnon-7-enoyl)((*Z*)-non-6-en-1-yl)carbamate (19.7 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The mixture was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^1H NMR analysis of the unpurified mixture revealed 96% consumption of *tert*-butyl ((*E*)-7-methylnon-7-enoyl)((*Z*)-non-6-en-1-

yl)carbamate. The resulting red oil was purified by silica gel chromatography (2% → 5% EtOAc in hexanes) to afford **3.44** as colorless oil (13.2 mg, 0.0408 mmol, 82% yield, 91:9 *E*:*Z*). **IR (neat)**: 292 (s), 2852 (m), 1612 (w), 1511 (m), 1459 (m), 1350 (w), 1300 (w), 1245 (s), 1170 (w), 1080 (m), 1038 (m), 885 (w); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 4.99 (t, J = 7.4 Hz, 1H), 3.79 (br, 2H), 2.82 (br, 2H), 2.06–1.98 (m, 4H), 1.71–1.63 (m, 2H), 1.53 (s, 3H), 1.52 (s, 9H), 1.52–1.49 (m, 2H), 1.42–1.34 (m, 4H), 1.20–1.10 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 176.8, 154.2, 134.7, 126.5, 82.7, 43.8, 39.0, 38.1, 29.0, 29.0, 28.2, 27.1, 27.0, 26.0, 25.4, 25.2, 15.7; **HRMS [M+H]$^+$** calcd for $C_{19}H_{34}NO_3$: 324.2533, found: 324.2531.

(*Z*)-9-Methyl-2,19-dioxa-1(1,3)-benzenacycloicosaphan-8-en-20-one (3.46): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried round-bottom flask containing (*Z*)-10-methyldodec-10-en-1-yl 3-(((*Z*)-non-6-en-1-yl)oxy)benzoate (22.1 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^{1}H NMR analysis of the unpurified mixture revealed 92% consumption of (*Z*)-10-Methyldodec-10-en-1-yl 3-(((*Z*)-non-6-en-1-yl)oxy)benzoate. The resulting red oil was purified by silica gel chromatography (2% → 5% EtOAc in hexanes) to afford **3.46** as colorless oil (16.3 mg, 0.0438 mmol, 87% yield, 90:10 *Z*:*E*). **IR (neat)**: 2923 (s), 2851 (m), 1720 (s), 1585 (m), 1488 (w), 1464 (w), 1435 (w), 1382 (w), 1273 (s), 1221 (s), 1103 (w), 1071 (m), 1029 (w), 755 (s), 682 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *Z* isomer: δ 7.66 (dt, J = 7.6, 1.3 Hz, 1H), 7.50 (dd, J = 2.6, 1.5 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.08 (ddd, J = 8.2, 2.6, 1.0 Hz, 1H), 5.08 (t, J = 7.4 Hz, 1H), 4.35–4.31 (m, 2H), 4.00 (t, J = 6.8 Hz, 2H), 2.10–1.96

(m, 4H), 1.82–1.73 (m, 4H), 1.67 (s, 3H), 1.57–1.50 (m, 2H), 1.46–1.25 (m, 14H); *E*-isomer (resolved signals only): δ 5.11 (t, J = 7.6 Hz, 1H), 3.96 (t, J = 6.6 Hz, 2H), 1.58 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$)**: *Z* isomer: δ 166.6, 159.0, 135.9, 131.9, 129.6, 125.2, 122.2, 120.1, 114.2, 68.0, 65.4, 31.7, 29.8, 29.6, 29.5, 29.2, 29.1, 29.1, 28.6, 28.1, 28.0, 26.7, 25.6, 23.7; *E*-isomer (resolved signals only): δ 124.5, 122.1, 119.1, 114.9, 68.3, 65.0, 39.2, 29.4, 29.1, 28.6, 28.6, 28.4, 28.3, 27.4, 27.1, 26.3, 25.3, 16.1; **HRMS [M+H]$^+$** calcd for $C_{24}H_{37}O_3$: 373.2737, found:373.2728.

(*Z*)-12-Methyloxacyclooctadec-12-en-2-one (3.47): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried round-bottom flask containing (*Z*)-non-6-en-1-yl (*Z*)-11-methyltridec-11-enoate (17.5 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^{1}H NMR analysis of the unpurified mixture revealed 86% consumption of (*Z*)-non-6-en-1-yl (*Z*)-11-methyltridec-11-enoate. The resulting red oil was purified by silica gel chromatography (2% EtOAc in hexanes) to afford **3.47** as colorless oil (11.2 mg, 0.0399 mmol, 80% yield, >98:2 *Z*:*E*). **IR (neat)**: 2923 (s), 2852 (m), 1734 (s), 1460 (w), 1375 (w), 1346 (w), 1232 (w), 1172 (w), 1152 (w), 1099 (w), 866 (w), 725 (w); **^{1}H NMR (500 MHz, CDCl$_3$):** δ 5.10 (t, J = 7.6 Hz, 1H), 4.11 (t, J = 6.1 Hz, 2H), 2.37–2.30 (m, 2H), 2.03–1.95 (m, 4H), 1.67 (s, 3H), 1.66–1.57 (m, 4H), 1.42–1.25 (m, 16H); **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 174.0, 136.0, 125.1, 64.2, 34.5, 30.9, 30.0, 29.1, 28.6, 28.5, 28.3, 28.2, 28.1, 27.9, 27.3, 26.2, 25.4, 23.6; **HRMS [M+H]$^+$** calcd for $C_{18}H_{33}O_2$: 281.2475, found:281.2479.

(*Z*)-12-Methyloxacyclohexadec-12-en-2-one (3.48): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried round-bottom flask containing (*Z*)-hex-4-en-1-yl (Z)-11-methyltridec-11-enoate (15.4 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^1H NMR analysis of the unpurified mixture revealed 88% consumption of (*Z*)-hex-4-en-1-yl (Z)-11-methyltridec-11-enoate. The resulting red oil was purified by silica gel chromatography (2% EtOAc in hexanes) to afford **3.48** as colorless oil (10.5 mg, 0.0416 mmol, 83% yield, 90:10 *Z*:*E*). **IR (neat)**: 2924 (s), 2853 (m), 1734 (s), 1448 (m), 1376 (w), 1343 (w), 1250 (m), 1173 (m), 1131 (w), 1093 (w), 1068 (w), 1036 (w), 973 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** *Z* isomer: δ 5.09 (t, J = 7.2 Hz, 1H), 4.15–4.10 (m, 2H), 2.38–2.33 (m, 2H), 2.12 (q, J = 7.9 Hz, 2H), 2.04–1.98 (m, 2H), 1.68 (s, 3H), 1.67–1.61 (m, 4H), 1.42–1.24 (m, 12H); *E* isomer (resolved signals only): δ 5.16 (t, J = 7.1 Hz, 1H), 4.08 (t, J = 6.5 Hz, 2H), 2.35–2.27 (m, 2H), 1.80–1.72 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)**: *Z*-isomer: δ 174.3, 136.3, 124.0, 64.1, 34.3, 30.9, 29.5, 27.8, 27.3, 27.1, 27.0, 26.7, 26.2, 25.3, 24.1, 23.4; *E*–isomer (resolved signals only): δ 135.6, 63.4, 38.8, 34.6, 31.8, 28.2, 26.9, 26.8, 25.9, 25.6, 25.0, 23.7, 15.6; **HRMS $[M+H]^+$** calcd for $C_{16}H_{29}O_2$: 253.2162, found: 253.2167.

(*Z*)-9-Methyloxacyclopentadec-9-en-2-one (3.49): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried round-bottom flask containing (*Z*)-non-6-en-1-yl (*Z*)-8-methyldec-8-enoate (15.4 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^1H NMR

analysis of the unpurified mixture revealed 91% consumption of (*Z*)-non-6-en-1-yl (*Z*)-8-methyldec-8-enoate. The resulting red oil was purified by silica gel chromatography (2% EtOAc in hexanes) to afford **3.49** as colorless oil (9.8 mg, 0.0412 mmol, 82% yield, 88:12 *Z*:*E*). **IR (neat)**: 2926 (s), 2853 (m), 1733 (s), 1448 (w), 1376 (w), 1338 (w), 1248 (m), 1183 (w), 1157 (m), 1083 (w), 1052 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *Z* isomer: δ 5.14 (t, J = 7.7 Hz, 1H), 4.18–4.14 (m, 2H), 2.36–2.31 (m, 2H), 2.06 (t, J = 7.0 Hz, 2H), 2.01–1.95 (m, 2H), 1.71–1.60 (m, 4H), 1.65 (s, 3H), 1.49–1.43 (m, 2H), 1.43–1.30 (m, 6H), 1.27–1.21 (m, 2H); *E*-isomer (resolved signals only): δ 5.05 (t, J = 7.4 Hz, 1H), 4.14–4.10 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)**: *Z* isomer: δ 174.3, 135.3, 126.2, 64.7, 34.5, 29.8, 29.3, 28.7, 28.3, 27.9, 27.0, 27.0, 26.4, 25.0, 23.2; *E* isomer (resolved signals only): δ 134.7, 126.1, 63.1, 38.6, 34.2, 28.7, 28.6, 28.4, 27.2, 27.1, 26.2, 25.2, 23.9, 15.4; **HRMS $[M+H]^+$** calcd for $C_{15}H_{27}O_2$: 239.2006, found: 239.2019.

(*Z*)-7-Methyloxacyclotetradec-6-en-2-one (3.50): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried round-bottom flask containing (*Z*)-8-methyldec-8-en-1-yl (*Z*)-oct-5-enoate (14.8 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^{1}H NMR analysis of the unpurified mixture revealed 75% consumption of (*Z*)-8-methyldec-8-en-1-yl (*Z*)-oct-5-enoate. The resulting red oil was purified by silica gel chromatography (2% EtOAc in hexanes) to afford **3.50** as colorless oil (7.8 mg, 0.0348 mmol, 70% yield, 94:6 *Z*:*E*). **IR (neat)**: 2926 (s), 2857 (m), 1732 (s), 1459 (m), 1376 (w), 1348 (w), 1244 (m), 1190 (w), 1157 (m), 1132 (m), 1066 (w), 1045 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** *Z* isomer: δ 5.09 (t, J = 7.6 Hz, 1H), 4.19–4.13 (m, 2H), 2.39–2.33 (m, 2H), 2.05–1.92 (m,

4H), 1.73–1.60 (m, 4H), 1.67 (s, 3H), 1.50–1.31 (m, 8H); *E* isomer (resolved signals only): δ 5.21–5.16 (m, 1H), 4.13–4.09 (m, 2H); **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 173.9, 136.8, 124.1, 63.0, 34.9, 29.7, 27.7, 27.2, 26.8, 26.2, 25.6, 24.8, 23.5, 23.2; **HRMS [M+H]$^+$** calcd for $C_{14}H_{25}O_2$: 225.1849, found: 225.1860.

(*Z*)-9-Methyloxacyclotridec-9-en-2-one (3.51): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 60 μL, 6.0 μmol) was transferred by syringe to an oven-dried round-bottom flask containing (*Z*)-hex-4-en-1-yl (*Z*)-8-methyldec-8-enoate (16.0 mg, 0.060 mmol) and benzene (60.0 mL, 1.0 mM). The solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^{1}H NMR analysis of the unpurified mixture revealed 80% consumption of (*Z*)-hex-4-en-1-yl (*Z*)-8-methyldec-8-enoate. The resulting red oil was purified by silica gel chromatography (2% EtOAc in hexanes) to afford **3.51** in 92:8 *Z*:*E* ratio as colorless oil (8.0 mg, 0.0380 mmol, 63% yield). **IR (neat)**: 2924 (s), 2854 (m), 1733 (s), 1447 (w), 1375 (w), 1331 (w), 1224 (m), 1193 (w), 1162 (w), 1133 (w), 1100 (w), 1034 (w); **^{1}H NMR (500 MHz, CDCl$_3$):** *Z* isomer: δ 5.06 (t, J = 6.7 Hz, 1H), 4.13–4.08 (m, 2H), 2.34–2.28 (m, 2H), 2.18 (qd, J = 7.1, 1.5 Hz, 2H), 2.06 (t, J = 6.9 Hz, 2H), 1.77–1.66 (m, 4H), 1.65 (s, 3H), 1.49–1.39 (m, 4H), 1.26–1.21 (m, 2H); *E* isomer (resolved signals only): δ 5.24 (t, J = 7.6 Hz, 1H), 4.17–4.13 (m, 2H), 1.57 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 174.8, 136.3, 124.4, 63.2, 34.8, 30.2, 28.3, 27.7, 27.1, 25.9, 25.4, 23.9, 23.2; **HRMS [M+H]$^+$** calcd for $C_{13}H_{23}O_2$: 211.1693, found: 211.1690.

(*Z*)-8-Methyloxacyclododec-8-en-2-one (3.52): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 60 μL, 6.0 μmol) was transferred by syringe to an oven-dried round-bottom flask containing (*Z*)-hex-4-en-1-yl (*Z*)-8-methyldec-8-enoate

(15.2 mg, 0.060 mmol) and benzene (60.0 mL, 1.0 mM). The solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^1H NMR analysis of the unpurified mixture revealed 80% consumption of (*Z*)-hex-4-en-1-yl (*Z*)-8-methyldec-8-enoate. The resulting red oil was purified by silica gel chromatography (2% EtOAc in hexanes) to afford **3.52** as colorless oil (6.8 mg, 0.0346 mmol, 58% yield, 93:7 *Z*:*E*). **IR (neat)**: 2960 (m), 2923 (s), 2853 (m), 1734 (s), 1455 (w), 1328 (w), 1249 (s), 1141 (m), 1073 (w), 978 (w), 891 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** *Z* isomer: δ 5.05 (t, J = 7.4 Hz, 1H), 4.02–3.94 (m, 2H), 2.35 (dd, J = 7.3, 5.0 Hz, 2H), 2.27 (q, J = 6.5 Hz, 2H), 2.19–2.09 (m, 2H), 1.76 (dt, J = 12.2, 6.1 Hz, 2H), 1.71 (dt, J = 12.5, 6.3 Hz, 2H), 1.63 (s, 3H), 1.44 (qd, J = 6.8, 4.1 Hz, 2H), 1.24–1.17 (m, 2H); *E* isomer (resolved signals only): δ 4.21–4.18 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 174.3, 136.4, 124.3, 62.4, 35.8, 28.2, 26.8, 25.5, 24.8, 23.4, 23.1, 22.9; **HRMS [M+H]$^+$** calcd for $C_{12}H_{21}O_2$: 197.1536, found: 197.1531.

(*Z*)-7-Methylcyclooctadec-6-en-1-ol (3.53): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried round-bottom flask containing *tert*-butyldimethyl(((3*Z*,21*Z*)-21-methyltricosa-3,21-dien-9-yl)oxy)silane (23.2 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^1H NMR analysis of the unpurified mixture revealed 75% consumption of *tert*-butyldimethyl(((3*Z*,21*Z*)-21-methyltricosa-3,21-dien-9-yl)oxy)silane. The resulting red oil was dissolved into THF (100 μL) and tetrabutylammonium fluoride (1.0 M, 100 μL, 0.100 mmol) was added to the resulting solution at 22 °C. The resulting mixture was allowed to warm up to 50 °C and stir at the same temperature for 12 h, after

which the mixture was concentrated in vacuo and the resulting dark oil was purified by silica gel chromatography (5% → 10% EtOAc in hexanes) to afford **3.53** as colorless oil (10.0 mg, 0.0357 mmol, 71% yield, 90:10 *Z*:*E*). **IR (neat)**: 3329 (br), 2921 (s), 2851 (m), 1458 (w), 1374 (w), 1070 (w), 1000 (w), 720 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.12 (t, J = 8.3 Hz, 1H), 3.73 – 3.63 (m, 1H), 2.07–1.92 (m, 4H), 1.67 (s, 3H), 1.58–1.24 (m, 26H), alcohol *OH* proton for **3.53** is not observed; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 135.9, 125.2, 71.3, 36.0, 35.6, 31.4, 30.1, 28.7, 28.3, 28.3, 28.0, 27.9, 27.6, 27.0, 26.8, 26.6, 25.0, 23.6, 22.8; **HRMS [M+H]$^+$** calcd for $C_{19}H_{37}O$: 281.2839, found: 281.2838.

(*Z*)-7-((4-Methoxybenzyl)oxy)-1-methylcyclohexadec-1-ene (3.54): Following the general procedure, a solution of **Mo-3d** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried round-bottom flask containing 1-methoxy-4-((((3*Z*,19*Z*)-19-methylhenicosa-3,19-dien-9-yl)oxy)methyl)benzene (23.2 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The solution was allowed to stir for 12 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^{1}H NMR analysis of the unpurified mixture revealed 69% consumption of 1-methoxy-4-((((3*Z*,19*Z*)-19-methylhenicosa-3,19-dien-9-yl)oxy)methyl)benzene. The resulting red oil was purified by silica gel chromatography (5% EtOAc in hexanes) to afford **3.54** as colorless oil (12.1 mg, 0.0325 mmol, 64% yield, 90:10 *Z*:*E*). **IR (neat)**: 2924 (s), 2852 (S), 1612 (w), 1511 (s), 1460 (m), 1353 (w), 1300 (m), 1245 (s), 1170 (w), 1075 (m), 1038 (s), 819 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.26 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.14 (t, J = 7.6 Hz, 1H), 4.52–4.35 (m, 2H), 3.80 (s, 3H), 3.43–3.32 (m, 1H), 2.16–1.88 (m, 4H), 1.67 (s, 3H), 1.66–1.55 (m, 2H), 1.52–1.21 (m, 20H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 159.1, 134.8, 131.5, 129.3, 125.8, 113.9, 78.1, 70.2, 55.4, 39.1, 32.8, 30.7, 29.9, 28.0,

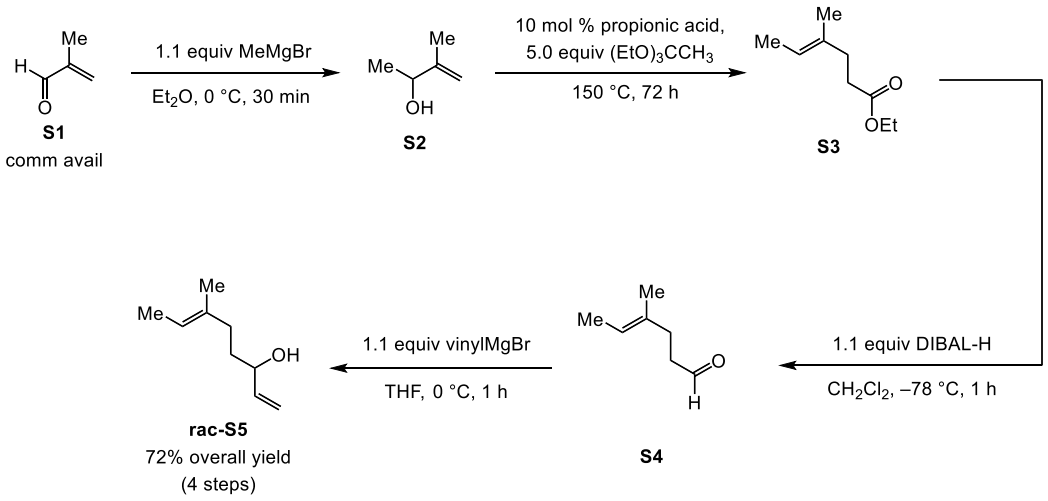
27.6, 27.5, 27.3, 26.7, 26.4, 25.2, 24.1, 22.2, 15.3; **HRMS [M+H]$^+$** calcd for $C_{25}H_{41}O_2$: 373.3101, found: 373.3093.

***tert*-Butyl (Z)-13-methyl-2-oxoazacyclononadec-13-ene-1-carboxylate (3.56)**: Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried round-bottom flask containing *tert*-butyl ((*Z*)-12-methyltetradec-12-enoyl)((*Z*)-non-6-en-1-yl)carbamate (16.0 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The solution was allowed to stir for 4 h at 40 °C. The reaction was quenched by the addition of wet Et_2O and ^{1}H NMR analysis of the unpurified mixture revealed 84% consumption of *tert*-butyl ((*Z*)-12-methyltetradec-12-enoyl)((*Z*)-non-6-en-1-yl)carbamate. The resulting red oil was purified by silica gel chromatography (2% → 5% EtOAc in hexanes) to afford **3.56** as colorless oil (13.8 mg, 0.0351 mmol, 70% yield, 94:6 *Z*:*E*). **IR (neat)**: 2923 (m), 2852 (m), 1729 (s), 1693 (m), 1456 (w), 1367 (m), 1286 (w), 1247 (w), 1142 (s), 1075 (w), 854 (w), 776 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.08 (t, J = 6.8 Hz, 1H), 3.72 (t, J = 6.9 Hz, 2H), 2.86 (dd, J = 7.0, 5.8 Hz, 2H), 2.04–1.90 (m, 4H), 1.70–1.60 (m, 2H), 1.66 (s, 3H), 1.53 (s, 9H), 1.57–1.47 (m, 2H), 1.39–1.22 (m, 18H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 176.4, 153.8, 135.9, 125.2, 76.8, 44.4, 38.0, 31.7, 30.0, 28.8, 28.7, 28.7, 28.7, 28.4, 28.3, 28.2, 28.2, 27.8, 27.1, 26.6, 25.3, 23.7; **HRMS [M+H]$^+$** calcd for $C_{24}H_{44}NO_3$: 394.3316, found: 394.3321.

***tert*-Butyl (*Z*)-7-methyl-2-oxoazacyclotetradec-6-ene-1-carboxylate (3.57)**: Following the general procedure, a solution of **Mo-3a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried round-bottom flask containing *tert*-butyl ((*Z*)-8-methyldec-8-en-1-yl)((*Z*)-oct-5-enoyl)carbamate (19.7 mg, 0.050 mmol) and benzene (50.0 mL, 1.0 mM). The mixture was allowed to stir for 12 h at 40 °C. The reaction was

quenched by the addition of wet Et_2O and ^1H NMR analysis of the unpurified mixture revealed 84% consumption of *tert*-butyl ((*Z*)-8-methyldec-8-en-1-yl)((*Z*)-oct-5-enoyl)carbamate. The resulting red oil was purified by silica gel chromatography (2% → 5% EtOAc in hexanes) to afford **3.57** as colorless oil (6.4 mg, 0.0198 mmol, 40% yield, >98:2 *Z*:*E*). **IR (neat)**: 2927 (m), 2858 (w), 1729 (s), 1692 (m), 1455 (w), 1366 (s), 1350 (m), 1290 (w), 1232 (w), 1204 (w), 1143 (s), 1094 (w), 1014 (w), 853 (w), 775 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.02 (t, J = 8.2 Hz, 1H), 4.00–3.80 (br, 2H), 2.98–2.78 (br, 2H), 2.02 (q, J = 7.2 Hz, 2H), 1.93–1.83 (m, 2H), 1.77–1.69 (m, 2H), 1.67 (s, 3H), 1.60–1.54 (m, 2H), 1.51 (s, 9H), 1.38–1.33 (m, 4H), 1.27–1.20 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 176.2, 153.9, 137.3, 124.4, 82.7, 43.6, 37.4, 30.9, 28.2, 27.1, 26.5, 26.2, 25.8, 25.7, 25.7, 24.0, 22.9; **HRMS [M+H]$^+$** calcd for $C_{19}H_{34}NO_3$: 324.2533, found: 324.2536.

3.7.4. Stereoselective Synthesis of E-Fluvirucin B$_1$



(*E*)-6-Methylocta-1,6-dien-3-ol (*rac*-S5): To a flame-dried round-bottom flask containing a solution of methacrolein **S1**(4.97 mL, 60.0 mmol) in Et_2O (75 mL) at 0 °C, was added MeMgBr (3.0 M in Et_2O, 22.0 mL, 66.0 mmol). The mixture was allowed to

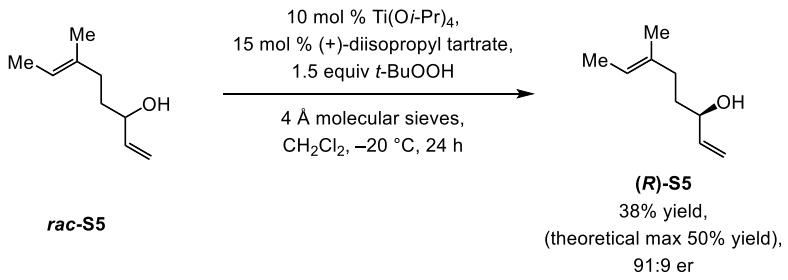
stir at 0 °C for 30 min, after which the reaction was quenched by the addition of an aqueous solution of 1.0 M HCl (150 mL). The solution was diluted by the addition of Et_2O (50 mL). The layers were separated, and the aqueous layer was washed with Et_2O (3 × 40 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (100 mL), dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo to afford alcohol **S2** as colorless oil. This material was used in the subsequent step without purification.

A mixture of **S2**, triethyl orthoacetate (55.0 mL, 300 mmol) and propionic acid (449 μL, 6.00 mmol) was heated at 150 ℃ in a sealed tube. The mixture was allowed to stir at 150 ℃ for 72 h, after which it was allowed to cool to 22 ℃. It was then poured into an aqueous solution of 1.0 M HCl (200 mL) and diluted with EtOAc (150 mL). The layers were separated, and the aqueous layer was washed with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the volatiles were removed in vacuo to afford ester **S3** as pale-yellow oil. This material was used in the next step without purification.

In a flame-dried round-bottom flask, **S3** was dissolved in CH_2Cl_2 (180 mL) at 22 ℃ and the solution was allowed to cool to −78 ℃. Diisobutylaluminium hydride (dibal–H, 1.0 M solution in hexanes, 66.0 mL, 66.0 mmol) was added slowly with the temperature of the reaction being maintained at below −65 ℃. The mixture was then allowed to stir for 1 h at −78 ℃, the flask was removed from the cooling bath and the reaction was quenched by addition of a saturated aqueous solution of potassium sodium tartrate (500 mL). The mixture was allowed to stir vigorously for 3 h at 22 ℃, after which it was washed with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and

the volatiles were removed in vacuo to deliver aldehyde **S4** as colorless oil. This material was used in the next step without purification.

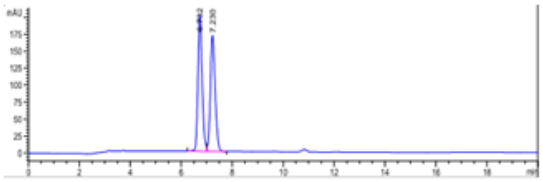
To a flame-dried round-bottom flask containing a solution of **S4** in THF (100 mL) maintained at 0 °C was added vinylMgBr (0.7 M in THF, 94.3 mL, 66.0 mmol). The solution was allowed to stir at 0 °C for 1 h, after which the reaction was quenched by the addition of an aqueous solution of 1.0 M HCl (200 mL). The mixture was washed with Et_2O (3 × 80 mL), and the combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (100 mL), dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo to afford yellow oil. Purification by silica gel chromatography (5% → 10% EtOAc in petroleum ether) furnished racemic alcohol ***rac*-S5** as colorless oil (6.06 g, 43.2 mmol, 72% yield for 4 steps). **IR (neat):** 3340 (m), 2980 (m), 2918 (s), 2860 (m), 1444 (m), 1381 (w), 1059 (m), 991 (s), 921 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.85 (ddd, J = 16.9, 10.4, 6.1 Hz, 1H), 5.28–5.17 (m, 1H), 5.20 (dt, J = 17.3, 1.4 Hz, 1H), 5.08 (dt, J = 10.5, 1.4 Hz, 1H), 4.06 (q, J = 6.3 Hz, 1H), 2.14–1.96 (m, 2H), 1.88 (s, 1H), 1.65–1.57 (m, 2H), 1.59 (s, 3H), 1.55 (dt, J = 6.7, 1.1 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 141.3, 135.5, 118.9, 114.6, 73.0, 35.5, 35.3, 15.7, 13.4; **HRMS $[M+H]^+$** calcd for $C_9H_{17}O$: 141.1274, found: 141.1271.



(*R*,*E*)-6-methylocta-1,6-dien-3-o ((*R*)-S5): ***r*ac-S5** was resolved according to the method outlined by Sharpless[46]. Accordingly, ***rac*-S5** (4.11 g, 29.3 mmol) was dissolved in CH_2Cl_2 (120 mL) in a flame-dried 250 mL round-bottom flask. To this solution, (+)-*L*-diisopropyl tartarate (924 μL, 4.40 mmol) was added followed by 4Å molecular sieves (1.30 g). The reaction solution was allowed to cool to –20 °C and titanium tetraisopropoxide (889 μL, 2.93 mmol) was added. The mixture was then allowed to stir at –20 °C for 30 min before *tert*-butyl hydroperoxide was added (5.5 M in decane, 7.99 mL, 44.0 mmol). The resulting mixture was allowed to stir at –20 °C for 24 h, after which the reaction was quenched by the addition of an aqueous solution of iron sulfate and tartaric acid (4.5 g of $FeSO_4$ and 1.50 g of tartaric acid in 50 mL of H_2O). The mixture was washed with CH_2Cl_2 (3 × 200 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo to afford yellow oil. Purification by silica gel chromatography (5% → 10% EtOAc in petroleum ether) gave **(*R*)-S5** as colorless oil (1.56 g, 11.1 mmol, 38% yield out of a theoretical maximum of 50%). Spectroscopic analysis indicated that a single isomer was generated (>98:2 dr). **IR (neat):** 3340 (m), 2980 (m), 2918 (s), 2860 (m), 1444 (m), 1381 (w), 1059 (m), 991 (s), 921 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.85 (ddd, J = 16.9, 10.4, 6.1 Hz, 1H), 5.28–5.17 (m, 1H), 5.20 (dt, J = 17.3, 1.4 Hz, 1H), 5.08 (dt, J = 10.5, 1.4 Hz, 1H), 4.06 (q, J = 6.3 Hz, 1H), 2.14–1.96 (m, 2H), 1.88 (s, 1H), 1.65–1.57 (m, 2H), 1.59 (s, 3H), 1.55 (dt, J = 6.7, 1.1 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 141.3, 135.5, 118.9, 114.6, 73.0, 35.5, 35.3, 15.7, 13.0; **HRMS [M+H]$^+$** calcd for $C_9H_{17}O$: 141.1274, found: 141.1271; **$[\alpha]_D^{20}$** = –12.2 (*c* 1.0, $CHCl_3$) for an enantiomerically enriched sample of 91:9 er

(46) Schultz, E. E.; Sarpong, R. *J. Am. Chem. Soc.* **2013**, *135*, 4696–4699.

Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material of the derived benzoyl ester; Chiralcel OD-H column, 99.9:0.1 hexanes/*i*-PrOH, 0.5 mL/min, 254 nm.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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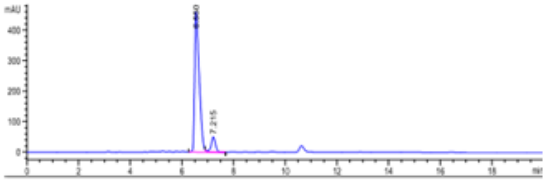
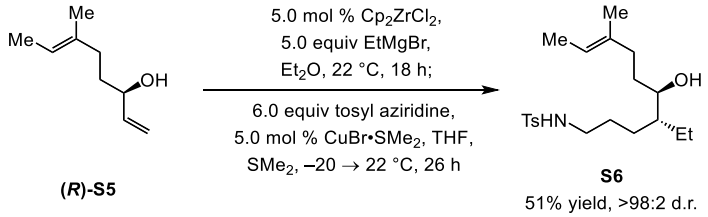
2	7.230	VB	0.1975	2211.89844	170.29729	49.0315



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.550	BV R	0.1819	5683.45996	460.83801	90.7832
2	7.215	VB E	0.1722	577.01721	50.17455	9.2168

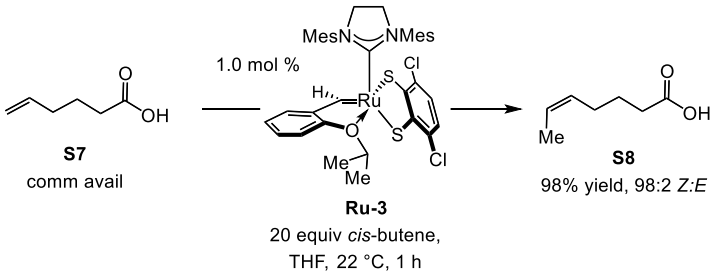
Retention Time	Area	Area%	Retention Time	Area	Area%
6.732	2299.27563	50.9685	6.550	5683.45996	90.7832
7.230	2211.89844	49.0315	7.215	577.01721	9.2168



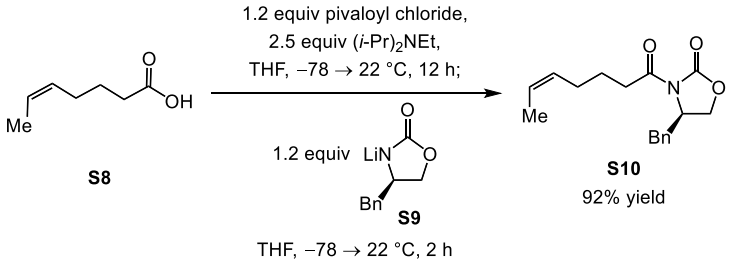
***N*-((4*R*,5*R*,*E*)-4-Ethyl-5-hydroxy-8-methyldec-8-en-1-yl)-4-methylbenzenesulfonamide (S6):** To a solution of allylic alcohol **(*R*)-S5** (380 mg, 2.71 mmol) in Et_2O (7 mL) at 0 °C was added EthylMgBr (3.0 M in Et_2O, 4.50 mL, 13.6 mmol). The mixture was allowed to stir at 0 °C for 5 min, after which the cooling bath was removed and zirconocene dichloride (40 mg, 0.14 mmol) was added. The solution was allowed to stir for 18 h at 22 °C, as thin layer chromatography (10% EtOAc in petroleum ether) indicated complete conversion after this amount of time. In a separate

flame-dried round-bottom flask, *N*-tosyl aziridine (3.20 g, 16.3 mmol, synthesized in one step according to a reported procedure[9]) was dissolved in THF (15 mL) at 22 °C. The latter solution was quickly added to the original flask through a cannula and the mixture was allowed to cool to –20 °C.

A flame-dried 10 mL round-bottom flask was charged with CuBr•SMe_2 (28 mg, 0.14 mmol), THF (1.5 mL) and SMe_2 (1.5 mL). The mixture was transferred to the aforementioned reaction flask cooled at –20 °C, after which the reaction mixture was allowed to warm to 22 °C over 2 h. The resulting mixture was allowed to stir for 24 h at 22 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (50 mL) and the resulting mixture was washed with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the volatiles were removed in vacuo to give dark brown oil. Purification by silica gel chromatography (10% → 30% EtOAc in petroleum ether) afforded *N*-tosyl amine **S6** as colorless oil (508 mg, 1.38 mmol, 51% yield, with 10% of an unidentified byproduct). **IR (neat):** 3507 (w), 3277 (w), 2929 (m), 2871 (m), 2360 (w), 2341 (w), 1148 (w), 1322 (m), 1156 (s), 1093 (m), 814 (m), 662 (s), 551 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.74 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 5.25 (qd, J = 6.7, 1.4 Hz, 1H), 4.72 (t, J = 6.5 Hz, 1H), 3.55 (dq, J = 8.0, 3.8 Hz, 1H), 2.93 (q, J = 6.5 Hz, 2H), 2.42 (s, 3H), 2.12 (dt, J = 14.5, 7.7 Hz, 1H), 2.00 (dt, J = 14.5, 7.5, 1H), 1.60 (s, 3H), 1.57 (d, J = 6.7 Hz, 3H), 1.58–1.50 (m, 1H), 1.51–1.11 (m, 9H), 0.84 (t, J = 7.1 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 143.4, 137.2, 135.9, 129.8, 127.3, 119.2, 73.3, 44.8, 43.6, 36.8, 31.4, 27.7, 26.6, 22.2, 21.6, 15.7, 13.5, 12.1; **HRMS [M+H]$^+$** calcd for $C_{20}H_{34}NO_3S$: 368.2254, found: 368.2247; **$[\alpha]_D^{20}$** = +7.8 (*c* 1.0, $CHCl_3$).

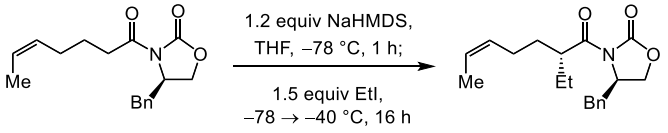


(*Z*)-Hept-5-enoic acid (S8): (*Z*)-Hept-5-enoic acid was prepared in accordance with a reported procedure[6e]. A flame-dried round-bottom flask equipped with a magnetic stir bar was charged with 5-hexenoic acid (**S7**, 1.19 mL, 10.0 mmol), *Z*-butene (17.5 mL, 200 mmol), THF (10 mL), and NHC–Ru-based complex **Ru-3** (76.7 mg, 0.10 mmol). The mixture was allowed to stir for 1 h at 22 °C, after which the volatiles were removed in vacuo. The resulting black oil residue was purified by silica gel chromatography (10% EtOAc in petroleum ether) and filtered through a small plug of activated charcoal to afford **S8** in 98:2 *Z:E* ratio as colorless oil (1.10 g, 9.80 mmol, 98% yield). **IR (neat):** 3015 (w), 2936 (m), 1708 (s), 1412 (m), 1240 (m), 939 (w), 700 (w); **^{1}H NMR (400 MHz, CDCl$_3$):** δ 11.56 (s, 1H), 5.50 (dqt, J = 10.8, 7.3, 1.5 Hz, 1H), 5.35 (dtq, J = 10.8, 7.3, 1.8 Hz, 1H), 2.37 (t, J = 7.3 Hz, 2H), 2.11 (q, J = 7.3 Hz, 2H), 1.71 (p, J = 7.3 Hz, 2H), 1.63–1.56 (m, 3H); **^{13}C NMR (100 MHz, CDCl$_3$):** δ 180.2, 129.3, 125.3, 33.5, 26.2, 24.6, 12.9; **HRMS [M+H]$^+$** Calcd for $C_7H_{13}O_2$: 129.0910, Found: 129.0909.



(*R*,*Z*)-4-Benzyl-3-(hept-5-enoyl)oxazolidin-2-one (S10): A flame-dried round-bottom flask containing a solution of acid **S8** (1.00 g, 7.80 mmol) in THF (21 mL) at –78 °C was

charged with *i*-Pr_2NEt (3.40 mL, 19.5 mmol) and pivaloyl chloride (1.15 mL, 9.36 mmol). The mixture was allowed to stir at –78 °C for 15 min, after which the flask was removed from the cooling bath and allowed to stir for 12 h at 22 °C. The resulting suspension was added by cannula to a solution of **S9** in THF at –78 °C (prepared freshly by adding *n*-BuLi (1.6 M solution in hexanes, 5.85 mL, 9.36 mmol) to (*R*)-(–)-4-benzyl-2-oxazolidinone (1.66 g, 9.36 mmol) in THF (21 mL) at –78 °C). After 30 min at –78 °C, the solution was removed from the cooling bath and allowed to stir for 90 min at 22 °C. At this time, the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (80 mL) and washed with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo to furnish pale-yellow oil. Purification by silica gel chromatography (10% EtOAc in petroleum ether) afforded oxazolidinone **S10** as colorless oil (2.06 g, 7.17 mmol, 92% yield). **IR (neat):** 3012 (w), 2921 (w), 1777 (s), 1698 (s), 1454 (w), 1384 (m), 1351 (m), 1291 (w), 1209 (m), 1098 (w), 1012 (w), 761 (w), 743 (w), 701 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.30–7.10 (m, 5H), 5.43 (ddtd, J = 10.7, 7.3, 6.7, 5.2 Hz, 1H), 5.33 (dtd, J = 10.7, 7.3, 1.7 Hz, 1H), 4.60 (ddt, J = 10.7, 6.9, 3.5 Hz, 1H), 4.16–4.04 (m, 2H), 3.22 (dd, J = 13.4, 3.5 Hz, 1H), 2.96–2.79 (m, 2H), 2.69 (dd, J = 13.4, 9.6 Hz, 1H), 2.08 (q, J = 7.3 Hz, 2H), 1.69 (dtt, J = 11.5, 7.3, 3.5 Hz, 2H), 1.55 (d, J = 6.7 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 173.4, 153.6, 135.4, 129.6, 129.5, 129.1, 127.4, 125.1, 66.3, 55.3, 38.0, 35.1, 26.3, 24.1, 12.9; **HRMS [M+Na]$^+$** calcd for $C_{17}H_{21}NO_3Na$: 310.1425, Found: 310.1404; **$[\alpha]_D^{20}$** = –166.4 (*c* 1.0, $CHCl_3$).

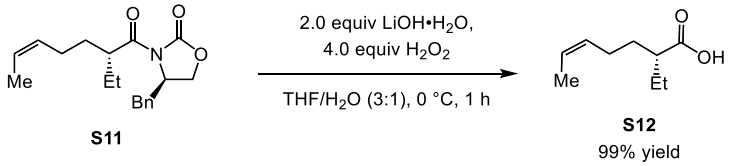


S10

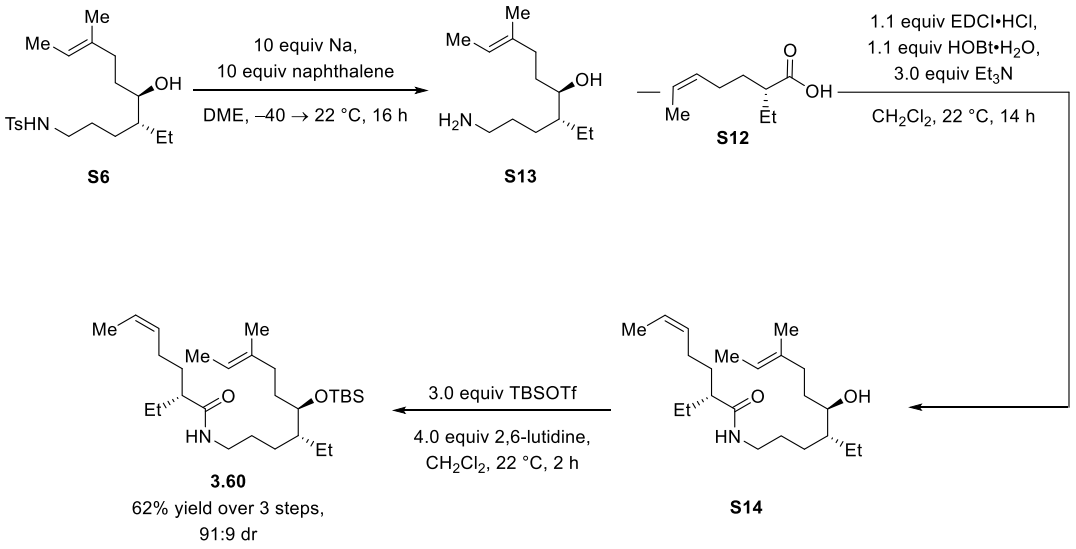
S11
79% yield, >98:2 dr

(*R*)-4-Benzyl-3-((*R*,*Z*)-2-ethylhept-5-enoyl)oxazolidin-2-one (S11): To a solution of **S10** (1.50 g, 5.22 mmol) in THF (20 mL) at –78 °C was added dropwise sodium bis(trimethylsilyl)amide (2.0 M in THF, 3.13 mL, 6.26 mmol). The solution was allowed to stir at –78 °C for 1 h, after which ethyl iodide (630 μL, 7.83 mmol) was added in a dropwise manner and the mixture was allowed to warm to –40 °C. The reaction was allowed to stir for 16 h at –40 °C. At this time, the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (80 mL) at –30 °C, and the resulting mixture was allowed to warm to 22 °C, after which it was washed with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo to furnish pale-yellow oil. Purification by silica gel chromatography (5% EtOAc in petroleum ether) delivered oxazolidinone **S11** in >98:2 dr ratio as colorless oil (1.30 g, 4.12 mmol, 79% yield). **IR (neat):** 2965 (w), 2929 (w), 1775 (s), 1693 (s), 1454 (w), 1384 (m), 1348 (m), 1208 (s), 1183 (m), 1097 (m), 1050 (w), 1017 (w), 760 (w), 740 (m), 701 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35 (tt, J = 6.7, 1.2 Hz, 2H), 7.34–7.22 (m, 3H), 5.46 (dddd, J = 10.7, 7.4, 4.5, 3.4 Hz, 1H), 5.37 (dtd, J = 10.7, 7.4, 1.7 Hz, 1H), 4.78–4.65 (m, 1H), 4.17 (d, J = 4.6 Hz, 2H), 3.78 (tt, J = 7.4, 5.5 Hz, 1H), 3.35 (dd, J = 13.3, 3.4 Hz, 1H), 2.73 (dd, J = 13.3, 10.0 Hz, 1H), 2.16–1.99 (m, 2H), 1.88–1.73 (m, 2H), 1.71–1.49 (m, 5H), 0.99 (t, J = 7.4 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 176.7, 153.3, 135.6, 129.9, 129.5, 129.1, 127.4, 124.6, 66.0, 55.6, 43.8, 38.3, 31.1, 25.7, 24.9,

12.8, 11.5; **HRMS [M+Na]$^+$** calcd for $C_{19}H_{25}NO_3Na$: 338.1727, found: 338.1719; **$[\alpha]_D^{20}$** = –105.5 (*c* 1.0, $CHCl_3$).



(*R*,*Z*)-2-Ethylhept-5-enoic acid (S12): To a solution of **S11** (255 mg, 0.81 mmol) in THF (3 mL) and H_2O (1 mL) at 0 °C were added hydrogen peroxide (30 wt % aqueous, 367 μL, 3.24 mmol) and LiOH•H_2O (886 mg, 21.6 mmol). The solution was allowed to stir at 0 °C for 1 h after which the starting material was determined to be completely consumed by thin layer chromatography (10% EtOAc in petroleum ether). The mixture was diluted with H_2O (3 mL) and the pH of the mixture was adjusted to 12 by addition of an aqueous solution of 1.0 M NaOH. The resulting mixture was washed with CH_2Cl_2 (2 × 4 mL) to recover the chiral auxiliary. The aqueous layer was acidified to pH = ~1 by addition of an aqueous solution of 2.0 M HCl and washed with CH_2Cl_2 (4 × 4 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the volatiles were removed in vacuo to afford carboxylic acid **S12** as colorless oil (126 mg, 0.8 mmol, 99% yield). This material was used in the next step without purification.



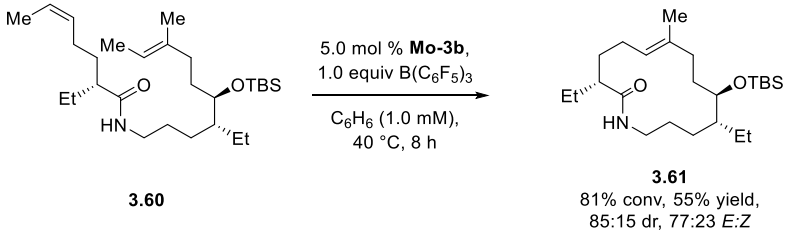
(*R*,*Z*)-*N*-((4*R*,5*R*,*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-ethyl-8-methyldec-8-en-1-yl)-2-ethylhept-5-enamide (3.60): To a suspension of sodium (184 mg, 8.00 mmol) in 1,2-dimethoxyethane (8 mL) at 22 °C was added naphthalene (1.03 g, 8.00 mmol), and the mixture was allowed to stir for 1 h at 22 °C, leading the solution to turn dark-green. The mixture was cooled to –40 °C, after which it was charged with a solution of *N*-tosyl amine **S6** (294 mg, 0.80 mmol) in 1,2-dimethoxyethane (8 mL) in a dropwise fashion. The dark-green mixture was allowed to stir for 30 min at –40 °C, after which the cooling bath was removed and the solution was allowed to stir for 1 h at 22 °C. At this time, EtOH was added until the solution turned colorless (ca. 1 mL of EtOH). The volatiles were removed in vacuo to afford pale-yellow oil. Purification by filtration through a short plug (8 cm) of silica gel (100% CH_2Cl_2 → 25% MeOH in CH_2Cl_2 → 100% MeOH) delivered amine **S13** as pale yellow oil (contaminated with 10–15% unidentified impurities). This material was used in the next step without further purification.

To a solution of amine **S13**, triethylamine (334 μL, 2.40 mmol) and carboxylic acid **S12** (126 mg, 0.8 mmol) in CH_2Cl_2 (5 mL) at 22 °C were added 1-Hydroxybenzotriazole

hydrate (135 mg, 0.88 mmol) and *N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide hydrochloride (169 mg, 0.88 mmol). The mixture was allowed to stir for 14 h at 22 °C, after which it was treated with an aqueous solution of 1.0 M HCl (10 mL) and subsequently washed with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered and the volatiles were removed in vacuo to give amide **S14** as yellow oil. This material was used in the next step without purification.

To a solution of amide **S14** in CH_2Cl_2 (8 mL) were added freshly distilled 2,6-lutidine (373 μL, 3.20 mmol) and TBSOTf (551 μL, 2.40 mmol) sequentially at 22 °C. The solution was allowed to stir for 2 h at 22 °C, after which a saturated aqueous solution of $CuSO_4$ (20 mL) was added and the resulting mixture was washed with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo to deliver yellow oil. Purification by silica gel chromatography (5% EtOAc in petroleum ether) afforded diene **3.60** as colorless oil (231 mg, 496 μmol, 62% yield over 3 steps). Diastereomeric purity was established by analysis of the ^{1}H NMR spectrum (91:9 dr). **IR (neat):** 3294 (w), 2929 (s), 2858 (m), 1642 (s), 1550 (w), 1461 (w), 1254 (m), 1061 (m), 835 (m), 773 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.51–5.27 (m, 3H), 5.19 (dddd, J = 8.1, 6.7, 5.4, 1.5 Hz, 1H), 3.63 (dt, J = 7.5, 3.4 Hz, 1H), 3.33–3.14 (m, 2H), 2.12–1.93 (m, 3H), 1.96–1.81 (m, 2H), 1.58 (s, 3H), 1.55 (d, J = 7.3 Hz, 3H), 1.76–1.36 (m, 12H), 1.37–1.21 (m, 3H), 1.12 (ddd, J = 12.4, 9.1, 6.0 Hz, 1H), 0.91–0.85 (m, 6H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 175.5, 136.1, 130.1, 124.5, 118.3, 73.7, 49.3, 45.4, 40.0, 36.5, 32.6, 31.0, 28.5, 26.8, 26.2,

26.1, 24.9, 23.0, 18.2, 15.9, 13.4, 12.9, 12.5, 12.3, –4.1, –4.2; **HRMS [M+Na]$^+$** calcd for $C_{28}H_{55}NO_2SiNa$: 488.3894, Found: 488.3884; **[α]$_D^{20}$** = –4.8 (*c* 1.0, $CHCl_3$).

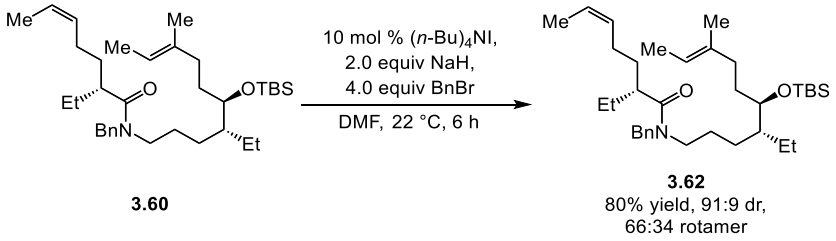


3.60

3.61
81% conv, 55% yield,
85:15 dr, 77:23 *E:Z*

(3*R*,10*R*,11*R*,*E*)-10-((*tert*-butyldimethylsilyl)oxy)-3,11-diethyl-7-methylazacyclotetradec-6-en-2-one (3.61): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 12.5 μL, 1.25 μmol) was transferred by syringe to an oven-dried round bottom flask that contained **3.60** (11.6 mg, 0.025 mmol), tris(pentafluorophenyl)borane (12.8 mg, 0.025 mmol), and benzene (25.0 mL, 1.0 mM). The solution was allowed to stir for 8 h at 40 °C, after which the reaction was quenched by the addition of wet Et_2O and ^{1}H NMR analysis of the unpurified mixture revealed 81% consumption of **3.60**. The resulting red oil was purified by silica gel chromatography (5% → 10% EtOAc in hexanes) to afford **3.61** in 77:23 *E*:*Z* and 85:15 dr ratio as colorless oil (5.6 mg, 0.0146 mmol, 55% yield). **IR (neat)**: 3294 (m), 2926 (s), 2854 (s), 1639 (s), 1551 (m), 1460 (w), 1379 (w), 1249 (m), 1068 (s), 1003 (w), 833 (s), 771 (s), 704 (w); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 5.35 (s, 1H), 5.18 (t, *J* = 6.2 Hz, 1H), 3.65 (dddd, *J* = 16.0, 12.3, 7.9, 4.3 Hz, 1H), 3.53 (dt, *J* = 8.0, 4.3 Hz, 1H), 3.00–2.92 (m, 1H), 2.26–2.19 (m, 1H), 2.20–2.02 (m, 1H), 2.01 (t, *J* = 7.3 Hz, 2H), 1.93 (tdd, *J* = 9.0, 6.1, 2.9 Hz, 1H), 1.82–1.71 (m, 1H), 1.72–1.58 (m, 4H), 1.57 (s, 3H), 1.52 (ddd, *J* = 10.3, 8.0, 4.4 Hz, 2H), 1.48–1.36 (m, 4H), 1.34–1.22 (m, 2H), 0.94–0.88 (m, 6H), 0.87 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 176.12, 135.7, 123.9, 73.5, 50.0, 41.6, 39.7, 34.4, 32.2, 31.9, 27.9, 27.3, 26.8, 26.1, 26.0, 21.1, 18.3, 15.8, 12.4, 11.7, –3.9, –4.6;

HRMS [M+H]$^+$ calcd for $C_{24}H_{48}NO_2Si$: 410.3449, found: 410.3440; **$[\alpha]_D^{20}$** = –99.8 (*c* 0.40, $CHCl_3$).

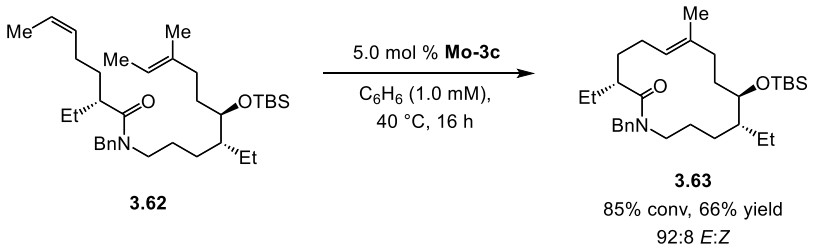


3.60

3.62
80% yield, 91:9 dr,
66:34 rotamer

(*R*,*Z*)-*N*-benzyl-*N*-((4*R*,5*R*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-4-ethyl-8-methyldec-8-en-1-yl)-2-ethylhept-5-enamide (3.62): To sodium hydride (2.4 mg, 0.10 mmol) and tetrabutylammonium iodide (1.8 mg, 0.005 mmol) in DMF (0.5 mL) was added **3.60** (23.3 mg, 0.05 mmol). After 25 min, the mixture was charged with benzyl bromide (34.3 mg, 0.20 mmol) in a dropwise fashion. The solution was allowed to stir for 6 h at 22 °C, at which point the mixture was decanted into a saturated aqueous solution of NH_4Cl (1.0 mL). The aqueous phase was washed with Et_2O (3 x 1.5 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting yellow oil was purified by silica gel chromatography (1% → 2% EtOAc in hexanes) to afford **3.62** (22.2 mg, 0.40 mmol, 80% yield) as colorless oil. **IR (neat):** 2926 (s), 2854 (m), 1642 (s), 1459 (m), 1377 (w), 1252 (m), 1159 (w), 1076 (m), 967 (w), 835 (s), 773 (m), 727 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37–7.15 (m, 5H), 5.49–5.25 (m, 2H), 5.22–5.15 (m, 1H), 4.73–4.49 (m, 2H), 3.65–3.56 (m, 1H), 3.45–3.06 (m, 2H), 2.60–2.43 (m, 1H), 2.11–1.80 (m, 4H), 1.79–1.65 (m, 2H), 1.64–1.51 (m, 12H), 1.50–1.32 (m, 4H), 1.31–1.07 (m, 4H), 0.94–0.79 (m, 15H), 0.02 (dd, J = 11.3, 5.6 Hz, 6H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 176.1, 138.5, 136.0, 130.2, 128.6, 128.3, 127.3, 124.6, 118.4, 73.5, 48.6, 47.5, 45.7, 42.5, 36.6, 32.7, 30.8, 27.9, 26.7, 26.1,

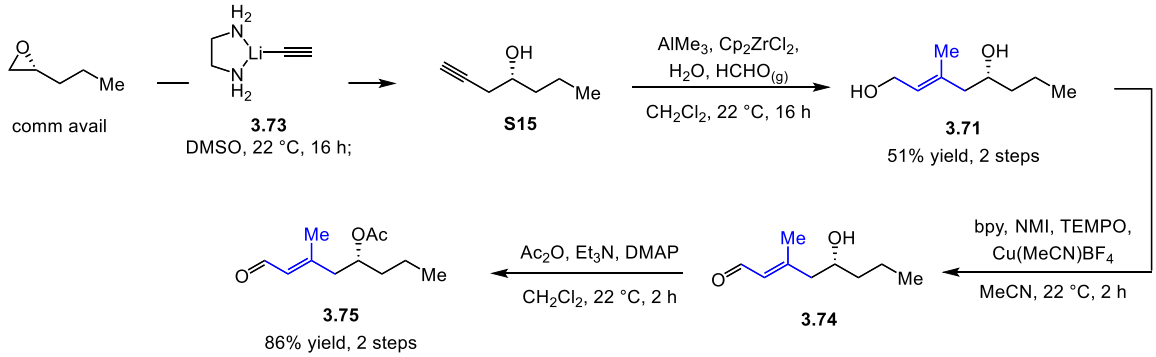
25.0, 23.2, 18.2, 15.9, 13.5, 13.0, 12.6, 12.4, 12.2, –4.1; **HRMS [M+H]$^+$** calcd for $C_{35}H_{62}NO_2Si$: 556.4544; found: 556.4540; **[α]$_D^{20}$** +3.8 (*c* 0.37, $CHCl_3$).



(3*R*,10*R*,11*R*,*E*)-1-benzyl-10-((*tert*-butyldimethylsilyl)oxy)-3,11-diethyl-7-methylazacyclotetradec-6-en-2-one (3.63): Following the general procedure, a solution of **Mo-3c** in benzene (0.1 M, 25.0 μL, 2.5 μmol) was transferred by syringe to an oven-dried round bottom flask that contained **3.62** (13.9 mg, 0.025 mmol) and benzene (25.0 mL, 1.0 mM). The solution was allowed to stir for 12 h at 40 °C, after which the reaction was quenched by the addition of wet Et_2O and ^{1}H NMR analysis of the unpurified mixture revealed 85% consumption of **3.62**. The resulting red oil was purified by silica gel chromatography (2% → 5% EtOAc in hexanes) to afford **3.63** in 92:8 *E*:*Z* and 91:9 dr ratio as colorless oil (8.3 mg, 0.0166 mmol, 66% yield). **IR (neat)**: 2926 (s), 2854 (m), 1640 (s), 1460 (m), 1358 (w), 1250 (m), 1135 (w), 1101 (m), 1054 (s), 898 (w), 834 (s), 772 (s), 737 (w), 698 (m); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.39–7.18 (m, 5H), 5.19 (t, *J* = 7.0 Hz, 1H), 5.00 (d, *J* = 14.8 Hz, 1H), 4.25 (d, *J* = 14.8 Hz, 1H), 3.58 (ddd, *J* = 9.2, 4.9, 1.8 Hz, 1H), 3.35 (td, *J* = 13.7, 4.5 Hz, 1H), 2.94 (ddd, *J* = 14.5, 12.5, 5.2 Hz, 1H), 2.66 (tt, *J* = 9.2, 4.8 Hz, 1H), 2.11 (q, *J* = 6.1 Hz, 3H), 2.00 (ddd, *J* = 14.7, 11.6, 3.9 Hz, 1H), 1.76–1.61 (m, 6H), 1.60 (s, 3H), 1.48 (dtd, *J* = 15.0, 7.5, 2.9 Hz, 1H), 1.43–1.36 (m, 1H), 1.31 (ddt, *J* = 11.6, 8.6, 4.1 Hz, 2H), 1.18–1.13 (m, 1H), 1.10–1.03 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.89 – 0.85 (m, 3H), 0.85 (s, 9H), 0.02 (s, 3H), –0.06 (s, 3H); **^{13}C NMR**

(100 MHz, $CDCl_3$): δ 176.4, 138.6, 135.2, 128.6, 128.2, 127.3, 125.2, 71.0, 48.4, 47.4, 41.9, 39.9, 36.0, 32.9, 31.2, 26.2, 26.0, 25.7, 25.1, 24.2, 20.5, 18.3, 15.2, 12.6, 12.3, –3.6, –4.5; **HRMS [M+H]$^+$** calcd for $C_{31}H_{54}NO_2Si$: 500.3918, found: 500.3914; **$[\alpha]_D^{20}$** = –4.3 (*c* 0.22, $CHCl_3$).

3.7.5. Stereoselective Total Synthesis of Dolabelide C



(*R*)-6-Methyl-8-oxooct-6-en-4-yl acetate (3.75): To a stirring solution of Cp_2ZrCl_2 (2.25 g, 7.7 mmol) in CH_2Cl_2 (150 mL) in a flame-dried two-neck flask was charged with $AlMe_3$ (2.0 M in Ptoluene, 46.2 mL, 92.4 mmol) over a period of 10 min at –20 °C, resulting in a light-yellow solution. After 15 min at −20 °C, H_2O (0.55 mL, 30.8 mmol) was added in a dropwise manner over a period of 25 min (**CAUTION**: highly exothermic, copious amounts of gas released). The mixture was allowed to stir at for 30 min −20 °C, after which **S15** (3.45 g, 30.8 mmol, synthesized in one step in analogy to a reported procedure[47]) was added over a period of 5 min. The cooling bath was removed and the mixture was allowed to stir for 5 h at 22 °C. The resulting orange solution was then allowed to cool to 0 °C.

A flame-dried two-necked flask containing paraformaldehyde (5.56 g, 185 mmol) was connected to the aforementioned reaction flask with a 5/16” tube (see the reported

(47) Bates, R. W.; Lu, Y. *J. Org. Chem.* **2009**, *74*, 9460–9465.

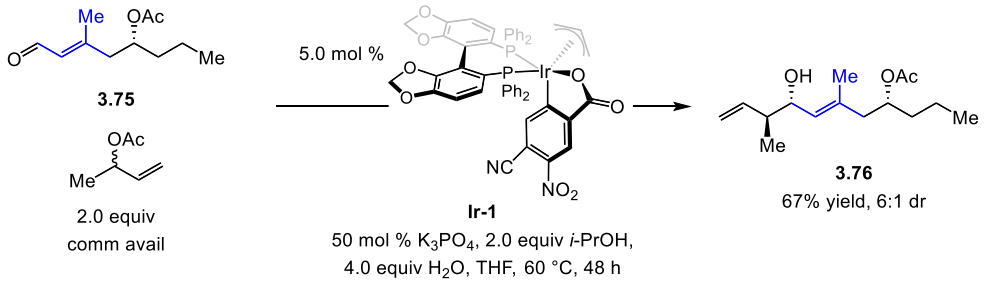
procedure[48] for a detailed description of the setup). Paraformaldehyde was thermally cracked at 150 °C and transferred by cannula to the aforementioned mixture under a strong nitrogen stream over a period of 45 min. After 15 min, the reaction was quenched by the addition of a saturated aqueous solution of K_2CO_3 (15 mL). The resulting mixture was allowed to warm to 22 °C and stir at this temperature for 12 h. The layers were separated and the aqueous layer was washed with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the volatiles were removed in vacuo to afford red oil, which was passed through a plug of silica gel (washed with 33% EtOAc in hexanes) to afford **3.71** as red oil. This material was used immediately in the subsequent step (^{1}H NMR analysis indicated ~60% yield of desired diol).

To the unpurified alcohol (2.93 g, 18.1 mmol) in MeCN (100 mL) was added *N*-methylimidazole (0.16 mL, 1.98 mmol), 2,2'-bipyridine (156 mg, 0.99 mmol), TEMPO (155 mg, 0.99 mmol), and $Cu(MeCN)_4BF_4$ (310 mg, 0.99 mmol). The resulting dark-red reaction mixture was purged with O_2 for 5 min, after which it was allowed to stir for 2.5 h at 22 °C under O_2 atmosphere, leading to a bright green solution. The mixture was diluted with EtOAc (20 mL) and H_2O (15 mL), the layers were separated, and the aqueous layer was washed with EtOAc (2 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford aldehyde **3.74** as orange oil, which was used directly in the subsequent step.

The aforementioned unpurified aldehyde **3.74** was dissolved in CH_2Cl_2 (100 mL) and the solution was allowed to cool to 4 °C (water bath), after which it was charged with DMAP

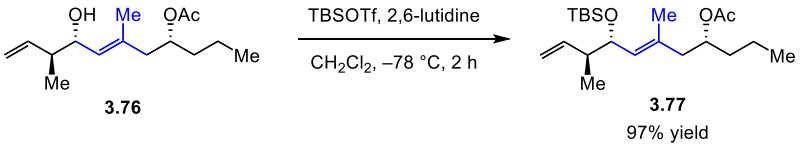
(48) Wan, K. K.; Iwasaki, K.; Umotoy, J. C.; Wolan, D. W.; Shenvi, R. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 2410–2415.

(232 mg, 1.90 mmol) and acetic anhydride (9.0 mL, 95 mmol), followed by Et_3N (18.4 mL, 133 mmol). The water bath was removed and the mixture was allowed to stir for 1 h at 22 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (25 mL). The layers were separated and the aqueous layer was washed with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the volatiles were removed in vacuo. The resulting brown oil was purified by silica gel chromatography (15% → 33% Et_2O in hexanes) to afford **3.75** (2.63 g, 13.3 mmol, 70% overall yield for 2 steps) as colorless oil. **IR (neat):** 2960 (m), 2935 (m), 2874 (m), 1736 (s) , 1675 (s), 1633 (w), 1440 (w), 1374 (w), 1236 (m), 1196 (s), 1126 (m), 1113 (w), 1069 (w), 1046 (m), 1022 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.94 (d, J = 8.0 Hz, 1H), 5.83 (dq, J = 8.0, 1.2 Hz, 1H), 5.09 (tt, J = 8.1, 4.8 Hz, 1H), 2.43 (ddd, J = 13.6, 8.3, 0.9 Hz, 1H), 2.34 (ddd, J = 13.6, 4.8, 1.0 Hz, 1H), 2.18 (d, J = 1.4 Hz, 3H), 1.98 (s, 3H), 1.64–1.43 (m, 2H), 1.43–1.23 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 191.0, 170.7, 159.3, 129.8, 71.1, 45.9, 36.6, 21.1, 18.7, 17.7, 13.9; **HRMS [M+H]$^+$** calcd for $C_{11}H_{19}O_3$: 199.1334, found: 199.1334; **$[\alpha]_D^{20}$** +45 (*c* 0.2, CH_2Cl_2).



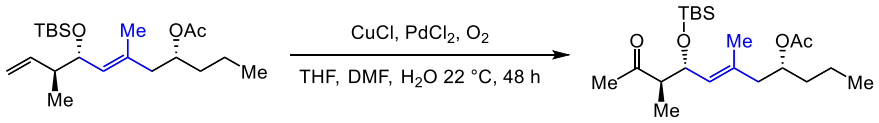
(4*R*,8*S*,9*S*,*E*)-8-Hydroxy-6,9-dimethylundeca-6,10-dien-4-yl acetate (3.76): A pressure vial was charged with Ir-based complex **Ir-1** (688 mg, 0.67 mmol) and K_3PO_4 (1.41 g, 6.65 mmol). It was then capped with a rubber septum and purged with Ar for

5 min. The mixture was charged with a solution of **3.75** (2.60 g, 13.3 mmol) in THF (9 mL), followed by anhydrous *i*-PrOH (2.0 mL, 26.6 mmol), H_2O (1.2 mL, 66.5 mmol) and but-3-en-2-yl acetate (3.33 mL, 26.6 mmol). The septum was quickly replaced by a teflon-lined screw-cap and the mixture was allowed to stir for 30 min at 22 °C, then for 48 h at 60 °C. The volatiles were removed in vacuo to afford red oil, which was purified by silica gel chromatography (10% → 15% → 25% Et_2O in hexanes) to afford **3.76** (1.75 g, 6.90 mmol, 52% yield) in 6:1 dr as colorless oil. **IR (neat):** 3330 (w), 2921 (s), 2923 (s), 2862 (s), 1760 (s), 1460 (m), 1399 (m), 1300 (m), 1260 (s), 831 (s); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 5.80–5.71 (m, 1H), 5.19 (dt, J = 8.9, 1.3 Hz, 1H), 5.16–5.09 (m, 2H), 5.03 (ddd, J = 13.0, 7.6, 5.4 Hz, 1H), 4.08 (dd, J = 8.9, 7.5 Hz, 1H), 2.29–2.22 (m, 1H), 2.24–2.16 (m, 2H), 2.02 (s, 3H), 1.72 (s, 3H), 1.62 (s, 1H), 1.54–1.47 (m, 2H), 1.38 (dddd, J = 13.6, 9.2, 7.6, 6.3 Hz, 1H), 1.31 (dq, J = 7.8, 5.8, 5.0 Hz, 1H), 0.96 (dd, J = 6.9, 1.0 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 171.1, 140.9, 136.0, 128.9, 116.5, 72.1, 71.4, 45.2, 45.0, 36.3, 21.4, 18.7, 17.3, 16.1, 14.1; **HRMS** $[M+NH_4]^+$ calcd for $C_{15}H_{30}NO_3$: 272.2220, found: 272.2203; **$[\alpha]_D^{20}$** +32 (*c* 0.3, CH_2Cl_2).



(4*R*,8*S*,9*S*,*E*)-8-((*tert*-Butyldimethylsilyl)oxy)-6,9-dimethylundeca-6,10-dien-4-yl acetate (3.77): To a stirring solution of alcohol **3.76** (1.76 g, 6.80 mmol) in CH_2Cl_2 (50 mL) at −78 °C, was added 2,6-lutidine (2.90 mL, 24.9 mmol) and TBSOTf (2.80 mL, 12.4 mmol). The mixture was allowed to stir for 3 h at 22 °C, then diluted with Et_2O (3 x20 mL). At this point, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (15 mL). The layers were separated and the aqueous phase was washed with

Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give yellow oil, which was purified by silica gel chromatography (0% → 5% Et_2O in hexanes) to afford **3.77** (2.35 g, 6.40 mmol, 96% yield) as colorless oil. **IR (neat):** 3230 (w), 2955 (s), 2923 (s), 2852 (s), 1771 (s), 1460 (m), 1390 (m), 1302 (m), 1256 (s), 1151 (m), 1109 (m), 1094 (s), 836 (s); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 5.78 (ddd, J = 17.0, 10.7, 7.8 Hz, 1H), 5.18 (dq, J = 8.9, 1.2 Hz, 1H), 5.03–4.93 (m, 3H), 4.17 (dd, J = 9.0, 5.6 Hz, 1H), 2.27 (ddd, J = 13.8, 6.6, 1.0 Hz, 1H), 2.22–2.16 (m, 2H), 2.01 (s, 3H), 1.64 (d, J = 1.4 Hz, 3H), 1.54–1.44 (m, 2H), 1.40–1.22 (m, 2H), 0.95 (d, J = 6.9 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H), 0.86 (s, 9H), 0.01 (s, 3H), –0.03 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 170.9, 141.3, 131.6, 130.9, 114.3, 73.0, 72.6, 45.4, 44.5, 36.0, 26.0, 21.5, 18.6, 18.3, 17.2, 15.6, 14.1, –4.1, –4.8; **HRMS $[M+NH_4]^+$** calcd for $C_{21}H_{44}NO_3Si$: 386.3085, found: 386.3073; **$[\alpha]_D^{20}$** +9 (*c* 0.014, CH_2Cl_2).

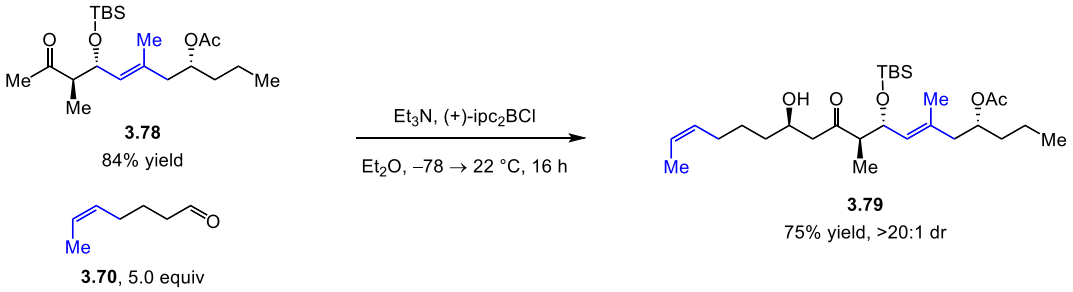


3.77
97% yield

3.78
84% yield

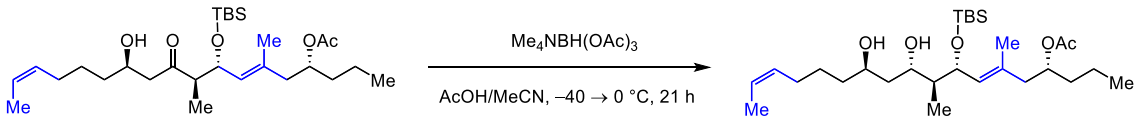
(4*R*,8*R*,9*R*,*E*)-8-((*tert*-Butyldimethylsilyl)oxy)-6,9-dimethyl-10-oxoundec-6-en-4-yl acetate (3.78): To a solution of **3.77** (1.84 g, 5.00 mmol) in THF (10 mL), DMF (40 mL) and H_2O (10 mL) was added CuCl (743 mg, 7.5 mmol) and then $PdCl_2$ (221 mg, 1.25 mmol). The mixture was purged with O_2 for 15 min, after which it was allowed to stir for 72 h at 22 °C under O_2 atmosphere. The mixture was treated with Et_2O (20 mL) and filtered through celite. The filtrate was concentrated partially under reduced pressure, then charged with Et_2O (20 mL) and an aqueous solution of 1 M HCl (20 mL). The layers

were separated and the aqueous phase was washed with Et_2O (3 x 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to leave behind yellow oil, which was purified by silica gel chromatography (6% → 10% → 12% EtOAc in hexanes), affording **3.78** (1.62 g, 4.20 mmol, 84% yield) as colorless oil. The characterization data were fully consistent with that reported in the literature[16].



(4*R*,6*E*,8*R*,9*R*,12*R*,16*Z*)-8-((*tert*-Butyldimethylsilyl)oxy)-12-hydroxy-6,9-dimethyl-10-oxooctadeca-6,16-dien-4-yl acetate (3.79): To a stirring solution of (+)-ipc$_2$BCl (620 mg, 1.95 mmol) in Et_2O (6 mL) at 0 °C, was added triethylamine (0.42 mL, 3.00 mmol), resulting in the formation of a white precipitate. After 30 min, the mixture was charged with a solution of **3.78** (310 mg, 0.75 mmol) in Et_2O (4 mL) through cannula. The heterogeneous mixture was allowed to stir for 90 min at 0 °C, after which it was allowed to cool to −78 °C and charged with a solution of **3.70** (420.6 mg, 3.75 mmol, prepared in 66% yield in 3 steps, according to reported procedures[33]) in Et_2O (4 mL). The mixture was allowed to stir for 3.5 h at −78 °C and then warmed to 22 °C and stir at this temperature for 15 h. At this time, the solution was allowed to cool to 0 °C, and the reaction was quenched by the addition of MeOH (5 mL) and pH 7 buffer (1.5 mL), yielding a yellow solution. To this mixture was added H_2O_2 (30 wt % aqueous, 1 mL) in a dropwise manner during a period of 5 min and the resulting cloudy mixture was

allowed to stir for 1 h at 22 °C. The mixture was diluted with CH_2Cl_2 (15 mL) and H_2O (15 mL). The layers were separated, and the aqueous phase was washed with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine, dried, filtered, and concentrated in vacuo. The resulting yellow solid was purified by silica gel chromatography (20% → 25% Et_2O in hexanes) to afford an inseparable mixture of **3.79** (0.563 mmol) and (+)-isopinocampheol. This material was used immediately in the subsequent step.

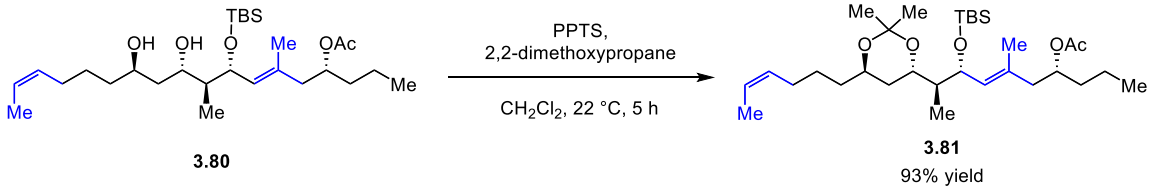


3.79

3.80
89% yield, >98:2 dr

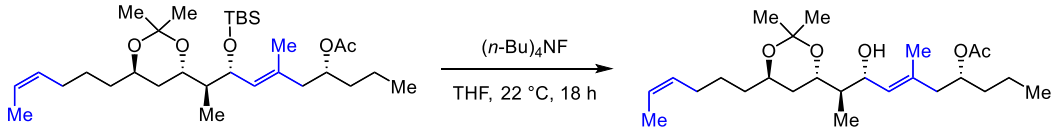
(4*R*,6*E*,8*R*,9*S*,10*S*,12*R*,16*Z*)-8-((*tert*-Butyldimethylsilyl)oxy)-10,12-dihydroxy-6,9-dimethyloctadeca-6,16-dien-4-yl acetate (3.80): A solution containing $Me_4NBH(OAc)_3$ (747 mg, 2.80 mmol), AcOH (4 mL), and CH_3CN (4 mL) was allowed to stir for 30 min at 22 °C. The mixture was then allowed to cool to –40 °C and charged with a solution of **3.79** in THF (1.5 mL) and CH_3CN (2 mL). The resulting solution was allowed to stir for 1 h at –40 °C, after which it was stored for 20 h at −20 °C in the freezer. The reaction was quenched at −20 °C by the addition of a saturated aqueous solution of potassium sodium tartrate (20 mL), and the mixture was allowed to stir for 30 min at 22 °C. The heterogeneous mixture was washed with CH_2Cl_2 (4 x 10 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo to give yellow oil, which was purified by silica gel chromatography (20% → 25% Et_2O in hexanes) to afford **3.80** (249.5 mg, 0.50 mmol, 89% yield). **IR (neat):** 3432 (br), 2958 (m), 2933 (m), 2858 (m),

1740 (m), 1472 (w), 1464 (w), 1375, 910 (s), 836 (w), 775 (w), 666 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.49–5.32 (m, 2H), 5.19 (dd, J = 9.3, 1.6 Hz, 1H), 5.03 (dd, J = 6.9, 5.5 Hz, 1H), 4.61 (dd, J = 9.1, 4.7 Hz, 1H), 4.32 (br, 1H), 3.97–3.83 (m, 2H), 3.51 (br, 1H), 2.33–2.16 (m, 2H), 2.06 (q, J = 6.9 Hz, 2H), 2.02 (s, 3H), 1.77–1.68 (m, 1H), 1.68 (d, J = 1.3 Hz, 3H), 1.64 (dt, J = 6.4, 3.8 Hz, 2H), 1.60 (dd, J = 6.1, 1.1 Hz, 3H), 1.55–1.44 (m, 4H), 1.44–1.28 (m, 4H), 0.90 (d, J = 7.3 Hz, 3H), 0.88 (s, 9H), 0.69 (d, J = 6.9 Hz, 3H), 0.07 (s, 3H), 0.02 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 170.9, 133.5, 130.8, 130.7, 124.1, 76.1, 74.0, 72.6, 68.9, 44.4, 44.4, 39.6, 37.3, 36.3, 27.0, 26.0, 25.9, 21.5, 18.6, 18.1, 17.5, 14.1, 12.9, 12.8, –3.6, –4.9; **HRMS [M]$^+$** calcd for $C_{28}H_{54}O_5Si$: 498.3741; found: 498.3750; **$[\alpha]_D^{20}$** +50 (c 1.4, $CHCl_3$).



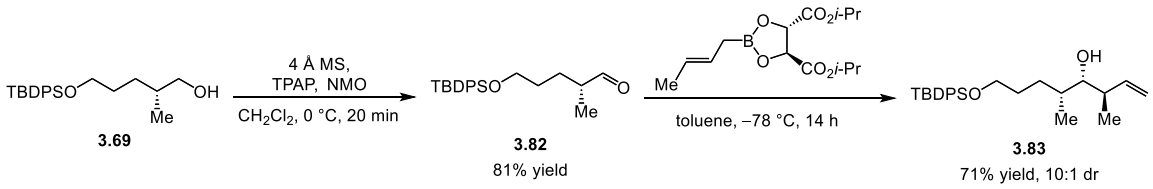
(4*R*,8*R*,9*S*,*E*)-8-((*tert*-Butyldimethylsilyl)oxy)-9-((4*S*,6*R*)-6-((*Z*)-hex-4-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-6-methyldec-6-en-4-yl acetate (3.81): To a solution of **3.80** (49.8 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL) and 2,2-dimethoxypropane (0.7 mL) was added PPTS (2.5 mg, 10 µmol). The mixture was allowed to stir for 5 h at 22 °C, after which the volatiles were removed in vacuo to give colorless solid, which was purified by silica gel chromatography (5% Et_2O in hexanes) to afford **3.81** (50.0 mg, 0.093 mmol, 93% yield) as colorless oil. **IR (neat)**: 2931 (br), 2854 (m), 1725 (m), 1377 (w), 1263 (s), 1023 (s), 906 (s), 729 (s); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 5.52–5.30 (m, 2H), 5.24–5.17 (m, 1H), 5.02 (p, J = 6.5 Hz, 1H), 4.38 (dd, J = 9.3, 5.6 Hz, 1H), 3.78 (dt, J = 9.3, 6.7 Hz, 1H), 3.70 (dq, J = 7.3, 5.2 Hz, 1H), 2.27 (dd, J = 13.8, 6.8 Hz, 1H), 2.17 (dd, J = 13.8,

6.3 Hz, 1H), 2.09–2.01 (m, 2H), 2.01 (s, 3H), 1.77 (td, J = 7.2, 5.6 Hz, 1H), 1.74–1.60 (m, 4H), 1.59 (dd, J = 6.3, 1.4 Hz, 3H), 1.55–1.30 (m, 9H), 1.31 (s, 3H), 1.28 (s, 3H), 0.89 (t, J = 7.6 Hz, 3H), 0.86 (s, 9H), 0.80 (d, J = 7.0 Hz, 3H), 0.01 (s, 3H), –0.03 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.8, 132.4, 130.6, 129.6, 124.1, 100.1, 72.3, 69.7, 67.1, 66.8, 45.1, 44.7, 36.1, 35.7, 35.4, 26.8, 26.0, 25.6, 25.2, 24.9, 21.5, 18.7, 18.2, 17.3, 14.1, 12.9, 9.8, –3.8, –4.8; **HRMS [M-H]$^+$** calcd for $C_{31}H_{57}O_5Si$: 537.3970; found: 537.3982; **$[\alpha]_D^{20}$** +68 (c 2.5, $CHCl_3$).



(4*R*,8*R*,9*R*,*E*)-9-((4*S*,6*R*)-6-((*Z*)-Hex-4-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-8-hydroxy-6-methyldec-6-en-4-yl acetate (3.65): To a solution of **3.81** (396.6 mg, 0.74 mmol) in THF (4.0 mL) at 0 °C was added a solution of tetrabutylammonium fluoride (1 M in THF, 2.38 mL, 2.38 mmol). The mixture was allowed to warm to 22 °C and stir for 18 h, after which the reaction was quenched by the addition of H_2O (5 mL) and then Et_2O (10 mL). The layers were separated and the aqueous phase was washed with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give yellow oil, which was purified by silica gel chromatography (10% → 15% EtOAc in hexanes) to furnish **3.65** (250.0 mg, 0.588 mmol, 80% yield) as colorless oil. **IR (neat)**: 3476 (br), 2980 (w), 2931 (m), 2871 (w), 1734 (s), 1455 (w), 1374 (s), 1224 (s), 1019 (m), 988 (s), 731 (m); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 5.48–5.40 (m, 1H), 5.40–5.32 (m, 1H), 5.19–5.13 (m, 1H), 5.03 (tt, J = 7.2, 5.5 Hz, 1H), 4.26 (t, J = 8.7 Hz, 1H), 3.81 (s, 1H), 3.80–3.68 (m, 2H), 2.28–2.16 (m, 2H), 2.07–2.03

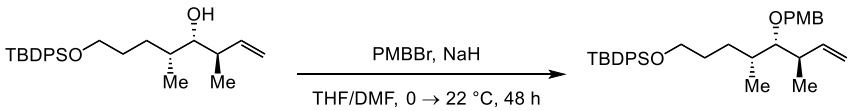
(m, 2H), 2.02 (s, 3H), 1.71 (d, J = 1.4 Hz, 3H), 1.64 (dt, J = 8.9, 6.6 Hz, 3H), 1.61–1.57 (m, 3H), 1.54–1.41 (m, 5H), 1.38 (s, 3H), 1.34 (s, 3H), 1.39–1.23 (m, 3H), 0.89 (t, J = 7.3 Hz, 3H), 0.70 (d, J = 6.9 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 171.0, 135.1, 130.5, 129.4, 124.2, 100.7, 72.7, 72.4, 72.2, 66.7, 44.9, 44.2, 38.1, 36.3, 35.5, 26.8, 25.4, 24.7, 24.7, 21.3, 18.7, 17.3, 14.0, 12.9, 11.5; **HRMS [M+H]$^+$** calcd for $C_{25}H_{45}O_5$: 425.3262; found: 425.3239; **$[\alpha]_D^{20}$** −184 (*c* 3.3, $CHCl_3$).



(*R*)-5-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpentanal (3.82): To a stirring solution of **3.69** (5.24 g, 14.70 mmol, prepared in accordance with a reported procedure[34] in 74% yield) and powdered 4 Å molecular sieves (3.58 g) in CH_2Cl_2 (140.0 mL) was added *N*-methylmorpholine *N*-oxide (2.58 g, 22.05 mmol) and tetrapropylammonium perruthenate (258.3 mg, 0.735 mmol). After 20 min, the mixture was diluted with 10% EtOAc in hexanes (150 mL), filtered through a small plug of silica gel and concentrated in vacuo to give **3.82** (4.22 g, 11.91 mmol, 81% yield) as colorless oil, which was used without purification in the next step.

(3*R*,4*S*,5*R*)-8-((*tert*-Butyldiphenylsilyl)oxy)-3,5-dimethyloct-1-en-4-ol (3.83): To a solution of freshly prepared diisopropyl (4*S*,5*S*)-2-((*E*)-but-2-en-1-yl)-1,3,2-dioxaborolane-4,5-dicarboxylate[15] (4.62 g, 15.5 mmol) in toluene (60 mL) stirring at −78 °C was added 4 Å molecular sieve (582 mg). After 30 min, a solution of freshly prepared **3.82** (3.43 g, 9.7 mmol) in toluene (8 mL) was added dropwise over 5 min. The mixture was allowed to stir for 14 h at –78 °C, at which time the reaction was quenched

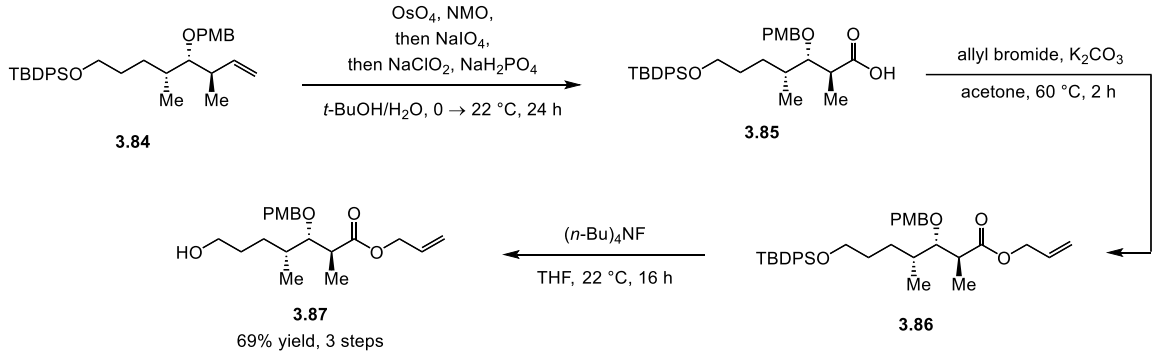
by the addition of an aqueous solution of 2 M NaOH (10 mL). The solution was allowed to warm to 0 °C and stir for 30 min, after which it was filtered through celite (EtOAc wash). The filtrate was diluted with EtOAc (20 mL) and H_2O (15 mL) and the layers were separated. The aqueous phase was washed with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford yellow oil, which was purified by silica gel chromatography (15% Et_2O in hexanes) to afford **3.83** (2.83 g, 6.89 mmol, 71% yield) as colorless oil. **IR (neat):** 2956 (m), 2927 (m), 2854 (s), 1459 (m), 1426 (m), 1337 (m), 1106 (s), 1090 (s), 975 (m), 799 (m); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.72–7.66 (m, 4H), 7.47–7.35 (m, 6H), 5.80–5.70 (m, 1H), 5.16–5.13 (m, 1H), 5.11 (s, 1H), 3.68 (t, J = 6.5 Hz, 2H), 3.19 (dd, J = 7.8, 3.8 Hz, 1H), 2.30 (h, J = 7.2 Hz, 1H), 1.61 (ddq, J = 12.5, 9.9, 6.4 Hz, 3H), 1.55–1.44 (m, 2H), 1.39–1.29 (m, 1H), 1.07 (s, 9H), 0.97 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 141.5, 135.7, 134.3, 129.7, 127.7, 116.4, 77.1, 64.2, 42.1, 34.5, 30.4, 30.4, 27.0, 19.4, 16.8, 13.0; **HRMS [M+H]$^+$** calcd for $C_{26}H_{39}O_2Si$: 411.2714; found: 411.2709; **$[\alpha]_D^{20}$** +8 (*c* 0.1, CH_2Cl_2).



3.83 **3.84** 91% yield

***tert*-Butyl(((4*R*,5*S*,6*R*)-5-((4-methoxybenzyl)oxy)-4,6-dimethyloct-7-en-1-yl)oxy)diphenylsilane (3.84):** To a suspension of sodium hydride (60% in paraffin, 600 mg, 15.0 mmol) in 1:1 THF:DMF (10 mL) cooled to 0 °C, was added **3.83** (2.05 g, 5.0 mmol) over 5 min. The mixture was allowed to stir for 25 min, after which freshly prepared *para*-methoxybenzyl bromide (2.61 g, 13.0 mmol) was added in a dropwise manner. The mixture was allowed to stir at 0 °C for 15 min, and was subsequently

allowed to warm to 22 °C. After 48 h, the mixture was decanted into an aqueous solution of pH 7 buffer (15 mL). The aqueous phase was washed with Et_2O (3 x 15 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting orange oil was purified by silica gel chromatography (5% → 10% Et_2O in hexanes) to afford **3.84** (2.42 g, 4.55 mmol, 91% yield) as colorless oil. **IR (neat):** 2927 (m), 2854 (s), 1540 (w), 1511 (m), 1459 (m), 1426 (m), 1244 (s), 1106 (s), 1085 (s), 700 (m); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.72–7.67 (m, 4H), 7.46–7.35 (m, 6H), 7.31–7.25 (m, 2H), 6.86 (dq, J = 8.6, 2.2, 1.5 Hz, 2H), 5.94 (ddd, J = 17.3, 10.3, 7.9 Hz, 1H), 5.05 (ddd, J = 17.3, 2.0, 1.1 Hz, 1H), 5.01 (ddd, J = 10.3, 2.0, 0.8 Hz, 1H), 4.53 (d, J = 10.6 Hz, 1H), 4.45 (d, J = 10.6 Hz, 1H), 3.80 (s, 3H), 3.67 (t, J = 6.3 Hz, 2H), 3.06 (dd, J = 6.0, 4.8 Hz, 1H), 2.55–2.43 (m, 1H), 1.73–1.59 (m, 2H), 1.59–1.46 (m, 2H), 1.36–1.28 (m, 1H), 1.08 (s, 9H), 1.04 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 159.2, 142.0, 135.7, 134.3, 131.5, 129.7, 129.3, 127.7, 114.2, 113.8, 87.0, 74.5, 64.4, 55.4, 41.1, 35.7, 30.5, 30.4, 26.9, 19.2, 17.6, 14.6; **HRMS [M+H]$^+$** calcd for $C_{34}H_{47}O_3Si$: 531.3289; found: 531.3289; **$[\alpha]_D^{20}$** +45 (*c* 3.5, CH_2Cl_2).



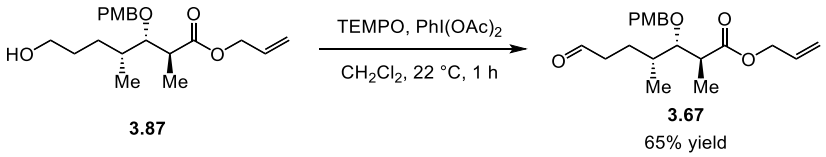
Allyl (2*S*,3*S*,4*R*)-7-hydroxy-3-((4-methoxybenzyl)oxy)-2,4-dimethylheptanoate (3.87): To a solution of **3.84** (2.43 g, 4.58 mmol) in *t*-BuOH (42 mL) was added a solution of *N*-methylmorpholine *N*-oxide (698 mg, 5.95 mmol) in H_2O (4.4 mL), followed by OsO_4 (4

wt % aqueous, 1.16 mL). The mixture was allowed to stir for 15 h at 22 ℃, at which time $NaIO_4$ (1.37 g, 6.4 mmol) was added. The resulting cloudy mixture was allowed to stir for 5 h at 22 °C before it was allowed to cool to 0 °C and charged with 2-methyl-2-butene (3.67 mL, 36.64 mmol), $NaH_2PO_4 \bullet H_2O$ (3.16 g, 22.9 mmol), and $NaClO_2$ (80 wt %, 2.59 g, 22.9 mmol) in a sequential manner. The mixture was allowed to warm to 22 ℃ over a period of 3 h after which it was allowed to cool to 0 °C. The acidity of the solution was adjusted to pH = 2 by the addition of an aqueous solution of 1 M HCl. Then the mixture was diluted by the addition of EtOAc (30 mL) and the layers were separated. The aqueous phase was washed with EtOAc (3 x 25 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford **3.85** as dark oil. This material was used immediately in the subsequent step.

To a solution of the aforementioned unpurified acid in acetone (50 mL) was added K_2CO_3 (1.27 g, 9.16 mmol) and then allyl bromide (1.98 mL, 22.9 mmol). The resulting heterogeneous mixture was allowed to stir for 2 h at 60 ℃, after which the volatiles were removed in vacuo to afford brown oil. The oil was dissolved in Et_2O (20 mL) and an aqueous solution of 0.5 M HCl (15 mL) and the phases were separated. The aqueous phase was washed with Et_2O (3 x 25 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford **3.86** as dark oil, which was immediately used in the next step.

To a solution of the aforementioned unpurified ester in THF (30 mL), which was allowed to cool to 0 ℃, was added AcOH (167 μL, 2.29 mmol), followed by tetrabutylammonium fluoride solution (1 M in THF, 13.74 mL, 13.74 mmol). The mixture was allowed to warm to 22 °C and stir for 16 h, after which the reaction was quenched by the addition of

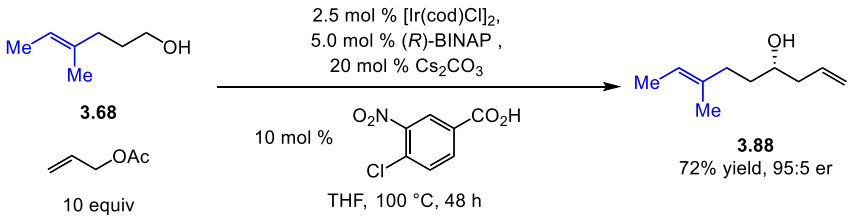
H_2O (5 mL). The solution was subsequently diluted with Et_2O (10 mL) and the layers were separated. The aqueous phase was washed with Et_2O (3 x 20 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo. The resulting yellow oil was purified by silica gel chromatography (20% → 40% EtOAc in hexanes) to afford **3.87** (1.11 g, 3.17 mmol, 69% overall yield for three steps) as colorless oil. **IR (neat):** 3428 (br), 2934 (w), 2876 (w), 1730 (m), 1611 (w), 1513 (m), 1457 (2), 1378 (w), 1341 (w), 1301 (w), 1247 (s), 1174 (m), 1109 (m), 1059 (m), 981 (w), 933 (w), 822 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.21 (d, J = 8.2 Hz, 2H), 6.88–6.82 (m, 2H), 5.89 (ddt, J = 16.5, 11.0, 5.7 Hz, 1H), 5.30 (dd, J = 17.1, 1.9 Hz, 1H), 5.24–5.16 (m, 1H), 4.62–4.50 (m, 2H), 4.49 (d, J = 3.9 Hz, 2H), 3.79 (s, 3H), 3.63 (dt, J = 12.7, 4.6 Hz, 3H), 2.79 (dt, J = 9.4, 7.1 Hz, 1H), 1.73–1.59 (m, 2H), 1.59–1.45 (m, 2H), 1.40–1.30 (m, 1H), 1.29–1.24 (m, 1H), 1.13 (d, J = 7.1 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 175.7, 159.2, 132.3, 131.3, 129.2, 118.4, 113.7, 84.4, 74.3, 65.3, 63.1, 55.4, 43.5, 34.9, 31.0, 30.7, 14.4, 13.6; **HRMS $[M+H]^+$** calcd for $C_{20}H_{31}O_5$: 351.2166; found: 351.2169; **$[\alpha]_D^{20}$** +5.0 (*c* 0.52, $CHCl_3$).



3.87 **3.67**
65% yield

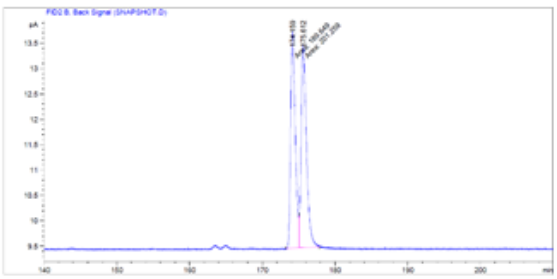
Allyl (2*S*,3*S*,4*R*)-3-((4-methoxybenzyl)oxy)-2,4-dimethyl-7-oxoheptanoate (3.67): To a solution of **3.87** (1.00 g, 2.80 mmol) in CH_2Cl_2 (30 mL) was added $PhI(OAc)_2$ (1.26 g, 3.92 mmol), followed by TEMPO (44.0 mg, 0.28 mmol). The mixture was allowed to stir at 22 °C for 1 h, after which the reaction was quenched by the addition of a saturated solution of aqueous $Na_2S_2O_3$ (25 mL). The solution was diluted by the addition of Et_2O (25 mL) and the layers were separated. The aqueous phase was washed with Et_2O (3 x 20

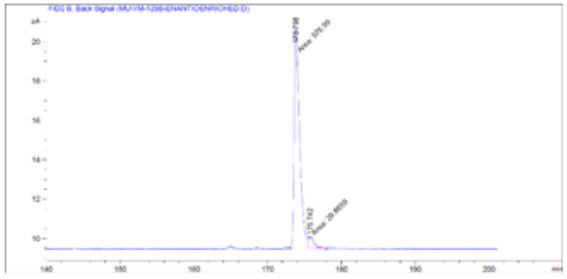
mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo. The resulting red oil was passed through a pad of silica gel (10% → 20% EtOAc in hexanes) to afford **3.67** (634.0 mg, 1.82 mmol, 65% yield) as colorless oil, which was immediately used in the next step without purification.



(*S*,*E*)-7-Methylnona-1,7-dien-4-ol (3.88): A pressure vessel was charged with Cs_2CO_3 (651 mg, 2.0 mmol), 4-chloro-3-nitrobenzoic acid (201 mg, 1.0 mmol), $[Ir(cod)Cl]_2$ (168 mg, 0.25 mmol) and (*R*)-BINAP (312 mg, 0.5 mmol). This mixture was subsequently dissolved in THF (50 mL), and **3.68** (1.14 g, 10 mmol, synthesized in 3 steps according to reported procedures[35]), and allyl acetate (5.4 mL) were added. The resulting heterogeneous red mixture was allowed to stir for 20 min at 22 °C, after which it was allowed to heat to 100 °C and stir at this temperature for 48 h. The mixture was then allowed to cool to 22 °C and the volatiles were removed in vacuo. The resulting orange oil was purified by silica gel chromatography (12% → 15% Et_2O in hexanes) to afford **3.88** (1.09 g, 7.1 mmol, 71% yield) as colorless oil. **IR (neat):** 3343 (br), 2974 (m), 2854 (m), 1669 (s), 1438 (m), 1341 (m), 1064 (s), 991 (s), 816 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.92–5.71 (m, 1H), 5.33–5.19 (m, 1H), 5.16–5.13 (m, 1H), 5.11 (d, J = 1.1 Hz, 1H), 3.63 (tt, J = 7.9, 4.6 Hz, 1H), 2.36–2.24 (m, 1H), 2.22–2.09 (m, 2H), 2.09–2.00 (m, 1H), 1.67 (s, 1H), 1.63–1.60 (m, 3H), 1.61–1.52 (m, 5H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 135.8, 135.0, 118.9, 118.1, 70.8, 42.1, 36.1, 35.0, 15.7, 13.5.; **HRMS [M]$^+$** calcd for $C_{10}H_{19}O$: 155.1430; found: 155.1427; **$[\alpha]_D^{20}$** −29 (*c* 1.5, $CHCl_3$) for a 95:5 er sample.

Enantiomeric purity of **3.88** was determined by GC analysis in comparison with authentic racemic material; alpha–dex column, 50–150 °C, 10 psi, carrier gas: helium.





Retention time	Area	Area%	Retention time	Area	Area%
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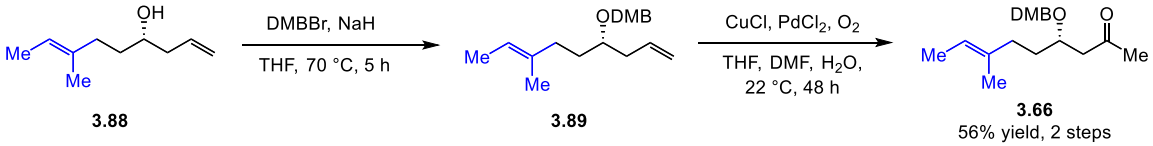
175.612	201.26	51.484	175.742	29.86	4.921

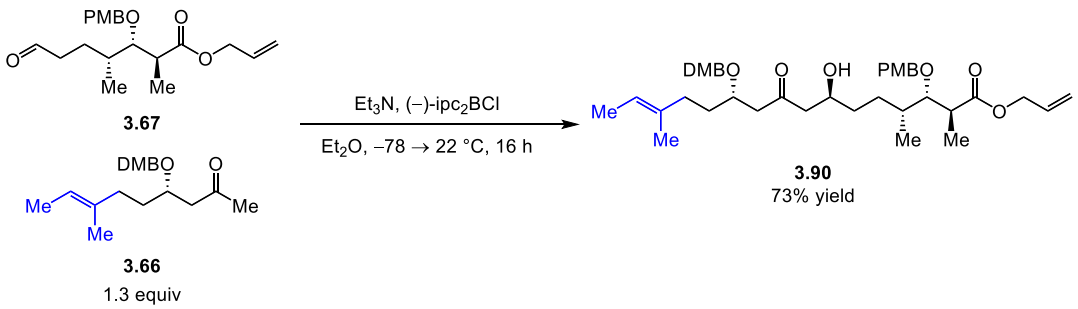


3.88 **3.89** **3.66**
56% yield, 2 steps

(*S*,*E*)-4-((3,4-Dimethylbenzyl)oxy)-7-methylnon-7-en-2-one (3.66): To a solution of NaH (60 % in parrafin, 312 mg, 7.80 mmol) in THF (7.5 mL), which was cooled to at 0 °C, was added **3.88** (802.1 mg, 5.20 mmol). The mixture was allowed to stir for 10 min, after which DMBBr (1.80 g, 7.80 mmol) was added and the solution was allowed to warm to 70 °C and stir at this temperature for 5 h. The reaction was then quenched by the addition of H_2O (10 mL) and diluted with Et_2O (10 mL). The layers were separated and the aqueous layer was washed with Et_2O (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo to afford **3.89** as colorless oil. This material was used immediately without purification.

To a 150 mL round-bottom flask containing the aforementioned unpurified diene, was added DMF (28.0 mL) and CuCl (623.0 mg, 6.30 mmol), followed by H_2O (4.2 mL) and

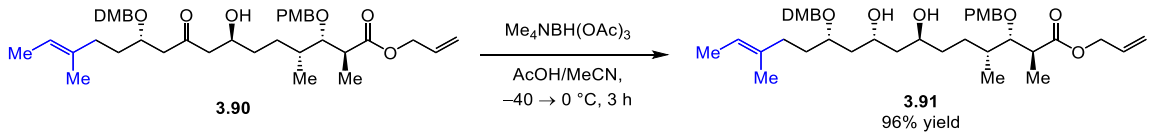
$PdCl_2$ (186.2 mg, 1.05 mmol). The solution was purged with O_2 (balloon) for 5 min and allowed to stir at 22 °C under O_2 atmosphere for 48 h. The solution was then passed through a plug of celite and diluted with hexanes (10 mL) and brine (10 mL). The layers were separated and the aqueous layer was washed with hexanes (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo. The resulting dark oil was purified by silica gel chromatography (10% → 20% EtOAc in hexanes) to afford **3.66** (950.6 mg, 2.97 mmol, 56% overall yield for two steps) as colorless oil. **IR (neat):** 2930 (m), 2857 (s), 1710 (s), 1590 (m), 1513 (s), 1351 (m), 1260 (s), 1154 (m), 1026 (s), 763 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.86 (t, J = 2.3 Hz, 1H), 6.84–6.79 (m, 2H), 5.20 (dddd, J = 7.9, 6.6, 5.3, 1.3 Hz, 1H), 4.48–4.39 (m, 2H), 3.92–3.89 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.74 (dd, J = 15.8, 7.5 Hz, 1H), 2.51 (dd, J = 15.9, 4.9 Hz, 1H), 2.15 (s, 3H), 2.04 (dtd, J = 7.5, 4.4, 3.8, 1.8 Hz, 2H), 1.74–1.60 (m, 2H), 1.59 (s, 3H), 1.56 (dt, J = 6.6, 1.1 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 207.7, 149.1, 148.7, 135.2, 131.2, 120.4, 118.8, 111.4, 111.0, 75.2, 71.6, 56.0, 55.9, 48.7, 35.3, 32.8, 31.3, 15.8, 13.5; **HRMS [M]$^+$** calcd for $C_{19}H_{28}O_4$: 320.1982; found: 320.1977; **$[\alpha]_D^{20}$** −190 (*c* 1.8, CH_2Cl_2).



Allyl (2*S*,3*S*,4*R*,7*S*,11*S*,*E*)-11-((3,4-dimethylbenzyl)oxy)-7-hydroxy-3-((4-methoxybenzyl)oxy)-2,4,14-trimethyl-9-oxohexadec-14-enoate (3.90): To a stirring solution of **(**–)-ipc$_2$BCl (907.0 mg, 3.17 mmol) in Et_2O (10 mL) cooled to −78 °C, freshly

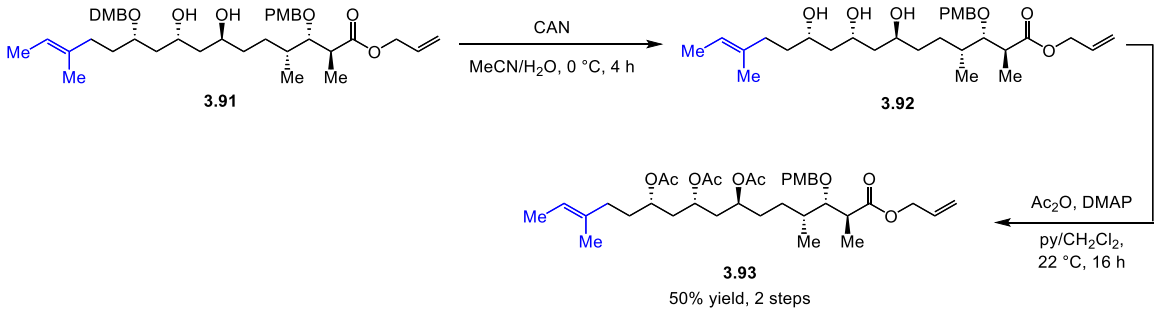
distilled Et_3N (505.5 μL, 3.64 mmol)was added, affording a colorless suspension. After 10 min, a solution of **3.66** (785.0 mg, 2.45 mmol) in Et_2O (6 mL) was added in a dropwise manner. The resulting mixture was allowed to stir for 1 h at 0 ℃, then was then allowed to cool to –78 ℃, after which it was charged, in a dropwise manner, with a solution of **3.67** (650.0 mg, 1.87 mmol) in Et_2O (4 mL). The mixture was allowed to stir for 30 min at –78 ℃ and then stand for 16 h at –20 ℃ in the freezer. At this time, the reaction was quenched by the addition of a solution of pH 7 buffer/MeOH (20 mL, 1:1 v/v). The mixture was allowed to warm to 0 ℃ and H_2O_2 (3.5 mL, 30 wt % aqueous) was added. The mixture was then allowed to warm to 22 ℃ and stir for 1 h, after which it was diluted by the addition of CH_2Cl_2 (10 mL) and H_2O (10 mL), and the layers were separated. The aqueous phase was washed with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford colorless oil, which was purified by silica gel chromatography (15% → 25% EtOAc in hexanes) to afford **3.90** (913.60 mg, 1.37 mmol, 73% yield) as colorless oil. **IR (neat):** 2931 (m), 2912 (m), 2862 (m), 1712 (s), 1612 (m), 1512 (s), 1357 (s), 1245 (s), 1173 (s), 1078 (s), 1034 (s), 820 (s), 513 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.19 (d, J = 8.6 Hz, 2H), 6.86–6.81 (m, 5H), 5.88 (ddt, J = 17.3, 10.4, 5.8 Hz, 1H), 5.29 (dt, J = 17.2, 1.5 Hz, 1H), 5.25–5.15 (m, 2H), 4.55 (tt, J = 5.6, 1.4 Hz, 2H), 4.47 (d, J = 1.7 Hz, 2H), 4.46–4.37 (m, 2H), 3.96 (dd, J = 13.4, 5.2 Hz, 1H), 3.93–3.88 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.77 (s, 3H), 3.62 (dd, J = 9.2, 2.2 Hz, 1H), 3.02 (d, J = 3.2 Hz, 1H), 2.81–2.70 (m, 2H), 2.63–2.55 (m, 1H), 2.54–2.44 (m, 2H), 2.07–1.99 (m, 2H), 1.76–1.60 (m, 4H), 1.60–1.58 (m, 3H), 1.58–1.54 (m, 3H), 1.51–1.39 (m, 2H), 1.34–1.20 (m, 1H), 1.10 (d, J = 7.1 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 211.0,

175.7, 159.1, 149.1, 148.8, 135.1, 132.3, 131.3, 131.0, 129.2, 120.5, 119.0, 118.4, 113.7, 111.4, 111.0, 84.3, 75.1, 74.4, 71.6, 67.9, 65.3, 56.0, 55.9, 55.4, 50.6, 48.4, 43.5, 35.2, 35.1, 34.7, 32.6, 30.5, 15.8, 14.5, 13.5, 13.5. **HRMS [M+H]$^+$** calcd for $C_{39}H_{57}O_9$: 669.3997; found: 669.3994; **[α]$_D^{20}$** +13 (*c* 1.5, CH_2Cl_2).



Allyl (2*S*,3*S*,4*R*,7*S*,9*R*,11*S*,*E*)-11-((3,4-dimethylbenzyl)oxy)-7,9-dihydroxy-3-((4-methoxybenzyl)oxy)-2,4,14-trimethylhexadec-14-enoate (3.91): A 150 mL round-bottom flask was charged with a solution of $Me_4NBH(OAc)_3$ (2.85 g, 9.79 mmol, 90%) in AcOH (15 mL) and CH_3CN (7.5 mL), which was allowed to stir for 20 min at 22 °C. This mixture was allowed to cool to –40 °C and charged with a solution of **3.90** (980.0 mg, 1.40 mmol) in CH_3CN (7.5 mL). The solution was allowed to stir for 2 h at –40 °C, after which it was allowed to warm to 0 °C and stir for an additional 1 h. The reaction was quenched by the addition of a saturated aqueous solution of potassium sodium tartrate (5 mL). The solution was then allowed to stir vigorously for 10 min, after which it was filtered through celite and washed with EtOAc (5 mL). The filtrate was diluted with EtOAc (10 mL) and H_2O (10 mL), the layers were separated, and the aqueous layer was washed with EtOAc (3 x 15 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (2 x 10 mL) and brine, dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo. The resulting yellow oil was purified by silica gel chromatography (50% → 66% EtOAc in hexanes) to afford **3.91** as colorless oil (1.0 g, 1.46 mmol, 96% yield, >98:2 dr). **IR (neat):** 3423 (br), 2932 (m), 2859 (m), 1729 (s), 1610 (w), 1512 (s), 1452 (m), 1241 (s), 1173 (s), 1028 (s), 807 (s); **^{1}H NMR (400 MHz,**

$CDCl_3$): δ 7.22–7.17 (m, 2H), 6.89–6.78 (m, 5H), 5.87 (ddt, J = 17.3, 10.3, 5.8 Hz, 1H), 5.29 (dq, J = 17.2, 1.6 Hz, 1H), 5.25–5.20 (m, 1H), 5.18 (dt, J = 10.4, 1.3 Hz, 1H), 4.60 (d, J = 11.0 Hz, 1H), 4.54 (tt, J = 5.7, 1.3 Hz, 2H), 4.48 (d, J = 1.9 Hz, 2H), 4.36 (d, J = 11.0 Hz, 1H), 4.18–4.07 (m, 2H), 3.91–3.81 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.77 (s, 3H), 3.70 (dp, J = 10.3, 3.1 Hz, 1H), 3.64 (dd, J = 9.2, 2.1 Hz, 1H), 3.20 (br, 1H), 2.77 (dd, J = 9.2, 7.1 Hz, 1H), 2.12–1.93 (m, 2H), 1.89–1.72 (m, 2H), 1.72–1.63 (m, 6H), 1.61 (d, J = 1.3 Hz, 3H), 1.57 (d, J = 6.5 Hz, 3H), 1.53–1.45 (m, 2H), 1.36–1.24 (m, 1H), 1.10 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 175.8, 159.1, 149.2, 148.9, 135.2, 132.3, 131.3, 130.4, 129.2, 120.6, 118.8, 118.4, 113.7, 111.3, 111.1, 84.4, 79.9, 74.4, 70.6, 70.2, 69.2, 65.2, 56.0, 56.0, 55.3, 43.5, 42.8, 40.5, 35.8, 35.2, 34.6, 31.7, 30.8, 15.9, 14.5, 13.5, 13.5; **HRMS $[M+H]^+$** calcd for $C_{39}H_{59}O_9$: 671.4154; found: 671.4157; **$[\alpha]_D^{20}$** +49 (*c* 4.5, $CHCl_3$).

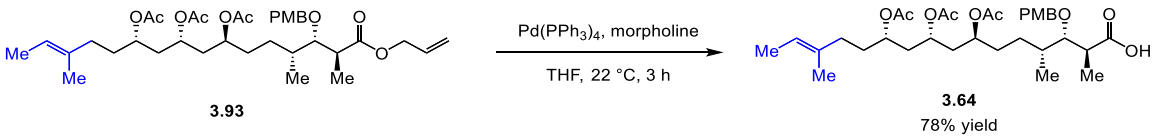


(6*S*,8*R*,10*S*,13*R*,14*S*,15*S*,*E*)-16-(Allyloxy)-14-((4-methoxybenzyl)oxy)-3,13,15-trimethyl-16-oxohexadec-2-ene-6,8,10-triyl triacetate (3.93): To a solution of **3.91** (469.6 mg, 0.70 mmol) in MeCN (10 mL) and H_2O (6 mL) at at 0 °C, was added CAN (652.3 mg, 1.19 mmol) and the mixture was allowed to stir at 0 °C until thin layer chromatography indicated complete consumption of **3.91**. The reaction was then quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (10 mL) and the mixture was diluted by the addition of EtOAc (15 mL). The layers were separated and the

aqueous layer was washed with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo to afford **3.92** as orange oil. This material was used immediately in the next step without purification.

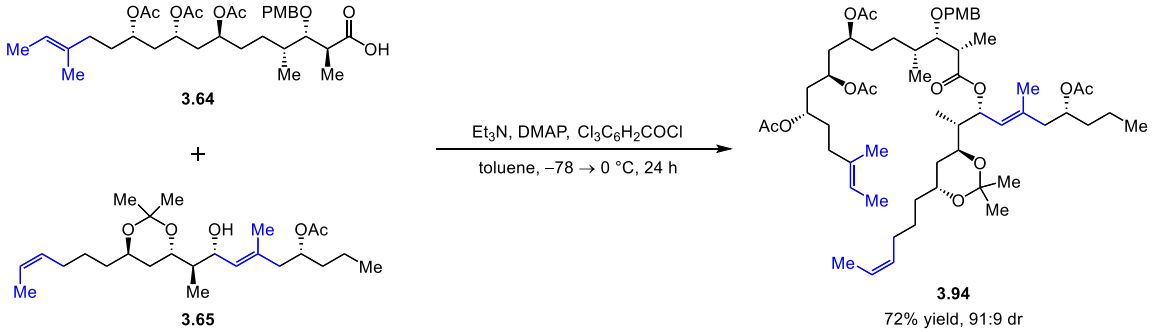
To a stirring solution of **3.92** in CH_2Cl_2 (1 mL) in freshly distilled pyridine (1 mL) at 0 °C, was added DMAP (85.5 mg, 0.70 mmol) and freshly distilled Ac_2O (1.9 mL, 20.1 mmol). After 10 min, the solution was allowed to warm to 22 °C and stir for 16 h at 22 °C. At this time, the solution was diluted with CH_2Cl_2 (5 mL) and the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (5 mL). The layers were separated and the aqueous phase was washed with Et_2O (2x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo to afford red oil, which was purified by silica gel chromatography (15% → 25% EtOAc in hexanes) to afford **3.93** (226.3 mg, 0.35 mmol, 50% overall yield for 2 steps) as colorless oil. **IR (neat):** 2933 (w), 1733 (s), 1612 (w), 1513 (m), 1455 (w), 1371 (m), 1240 (s), 1174 (m), 1029 (s), 940 (w), 821 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.20 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.88 (ddt, J = 17.2, 10.4, 5.8 Hz, 1H), 5.29 (dq, J = 17.2, 1.6 Hz, 1H), 5.24–5.14 (m, 2H), 5.00–4.80 (m, 3H), 4.55 (tt, J = 5.5, 1.4 Hz, 2H), 4.52–4.40 (m, 2H), 3.79 (s, 3H), 3.60 (dd, J = 9.0, 2.7 Hz, 1H), 2.76 (dq, J = 9.0, 7.1 Hz, 1H), 2.03 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.99–1.92 (m, 2H), 1.89 (ddd, J = 14.2, 7.7, 6.4 Hz, 1H), 1.86–1.52 (m, 8H), 1.58 (s, 3H), 1.54 (d, J = 6.5 Hz, 3H), 1.43 (td, J = 12.9, 6.2 Hz, 1H), 1.31–1.21 (m, 1H), 1.10 (d, J = 7.1 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 175.7, 170.8, 170.7, 170.6, 159.1, 134.7, 132.3, 131.2, 129.2, 119.1, 118.5, 113.8, 84.1, 74.4, 70.9, 70.1, 67.4, 65.3, 55.4, 43.4, 39.2, 38.7, 35.3,

35.0, 33.1, 32.6, 30.0, 21.3, 21.2, 21.2, 15.7, 14.4, 13.6, 13.5; **HRMS [M+Na]$^+$** calcd for $C_{36}H_{54}NaO_{10}$: 669.3609; found: 669.3612; **[α]$_D^{20}$** +8 (*c* 0.70 , $CHCl_3$).



(2*S*,3*S*,4*R*,7*S*,9*R*,11*S*,*E*)-7,9,11-Triacetoxy-3-((4-methoxybenzyl)oxy)-2,4,14-trimethylhexadec-14-enoic acid (3.64): To a solution of **3.93** (65.2 mg, 0.10 mmol) in THF (1 mL) was added $Pd(PPh_3)_4$ (11.7 mg, 0.01 mmol) and freshly distilled morpholine (87.8 µL, 1.00 mmol). The resulting yellow solution was allowed to stir for 3 h at 22 °C after which the volatiles were removed in vacuo, leaving behind red oil. This residue was dissolved in EtOAc (5 mL) and the resulting solution was charged with an aqueous solution of 1 M HCl (2 mL). The layers were separated and the aqueous layer was washed with EtOAc (3 x 2 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo, affording yellow oil, which was purified by silica gel chromatography (25% EtOAc in hexanes) to afford **3.64** (47.3 mg, 0.078 mmol, 78% yield) as pale yellow oil. **IR (neat):** 2918 (w), 1735 (s), 1612 (w), 1513 (m), 1457 (w), 1372 (m), 1244 (s), 1174 (w), 1119 (w), 1029 (m), 951 (w), 821 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.89 (br, 1H), 7.20 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.18 (dddd, J = 8.0, 6.6, 5.2, 1.5 Hz, 1H), 4.95 (dp, J = 9.6, 3.2 Hz, 1H), 4.91–4.83 (m, 2H), 4.56–4.42 (m, 2H), 3.75 (s, 3H), 3.55 (dd, J = 7.8, 3.4 Hz, 1H), 2.75 (p, J = 7.1 Hz, 1H), 2.03 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.98–1.93 (m, 2H), 1.89 (ddd, J = 14.2, 7.7, 6.3 Hz, 1H), 1.83–1.50 (m, 8H), 1.57 (s, 3H), 1.54 (d, J = 5.9 Hz, 3H), 1.43 (ddt, J = 14.9, 9.3, 6.1 Hz, 1H), 1.27–1.22 (m, 1H), 1.15 (d, J = 7.1 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 180.3, 170.8, 170.8, 170.6, 159.3, 134.7,

130.6, 129.4, 119.1, 113.9, 113.8, 84.0, 74.4, 71.0, 70.1, 67.4, 55.3, 43.0, 39.1, 38.5, 35.3, 32.8, 32.6, 29.6, 21.3, 21.2, 21.1, 15.6, 14.4, 14.0, 13.5; **HRMS [M+H]$^+$** calcd for $C_{33}H_{51}O_{10}$: 607.3477; found: 607.3474; **[α]$_D^{20}$** +9 (*c* 0.83, $CHCl_3$).



(6*S*,8*R*,10*S*,13*R*,14*S*,15*S*,*E*)-16-(((2*S*,3*R*,7*R*,*E*)-7-Acetoxy-2-((4*S*,6*R*)-6-((*Z*)-hex-4-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-5-methyldec-4-en-3-yl)oxy)-14-((4-methoxybenzyl)oxy)-3,13,15-trimethyl-16-oxohexadec-2-ene-6,8,10-triyl triacetate (3.94): To A solution containing carboxylic acid **3.64** (55.3 mg, 0.091 mmol), secondary alcohol **3.65** (58.2 mg, 0.137 mmol), and DMAP (445.3 mg, 3.644 mmol) in dry toluene (18mL) at –78 °C, was added triethylamine (269.0 µL, 1.914 mmol) and 2,4,6-trichlorobenzoyl chloride (284.9 µL, 1.822 mmol). The mixture was allowed to stir for 22 h at –78 °C. The mixture was then allowed to warm to –40 °C during a period of 1 h and then to 0 °C over a period of 1.5 h. The mixture was diluted with Et_2O (15 mL), after which the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was washed with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo to afford light yellow oil, which was purified by silica gel chromatography (10% → 12% → 15% EtOAc in hexanes) to afford **3.94** (66.4 mg, 0.066 mmol, 72% yield) as colorless oil. **IR (neat)**: 2934 (m), 1734 (s), 1613 (w), 1455

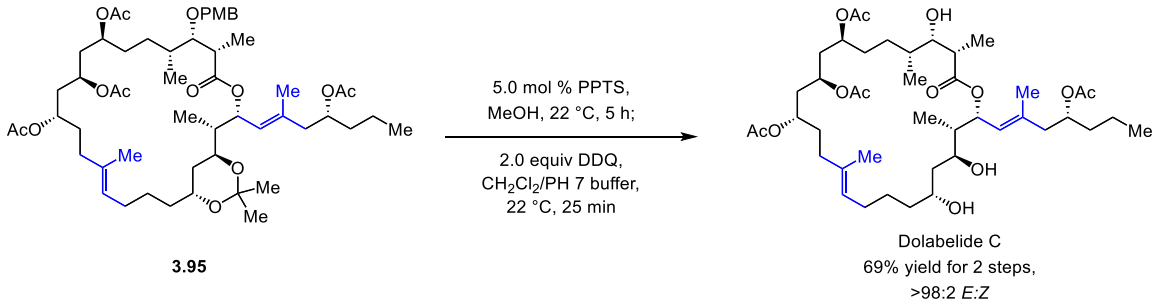
(w), 1373 (m), 1241 (s), 1177 (m), 1023 (m), 938 (w), 821 (w); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.17 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.65 (dd, J = 9.8, 5.5 Hz, 1H), 5.50–5.29 (m, 2H), 5.22–5.08 (m, 2H), 5.00–4.79 (m, 4H), 4.49 (d, J = 10.9 Hz, 1H), 4.33 (d, J = 11.0 Hz, 1H), 3.77 (s, 3H), 3.76–3.65 (m, 1H), 3.62–3.48 (m, 2H), 2.73–2.60 (m, 1H), 2.11 (dd, J = 13.9, 6.6 Hz, 1H), 2.02 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 2.05–1.93 (m, 5H), 1.92–1.81 (m, 1H), 1.75 (s, 3H), 1.79–1.69 (m, 2H), 1.70–1.58 (m, 4H), 1.58 (dd, J = 6.6, 1.4 Hz, 3H), 1.57 (s, 3H), 1.54 (d, J = 6.5 Hz, 3H), 1.60–1.49 (m, 3H), 1.50–1.31 (m, 8H), 1.31 (s, 3H), 1.25 (s, 3H), 1.30–1. 16 (m, 4H),1.05 (d, J = 7.1 Hz, 3H), 0.89–0.82 (m, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 175.2, 170.7, 170.7, 170.7, 170.6, 159.0, 138.7, 134.7, 131.4, 130.5, 128.9, 124.1, 122.6, 119.1, 113.7, 100.3, 83.4, 73.9, 72.3, 71.4, 71.0, 70.1, 67.4, 67.3, 66.6, 55.3, 44.4, 43.6, 42.1, 39.2, 38.6, 36.1, 36.0, 35.7, 35.3, 34.9, 33.0, 32.6, 30.0, 26.8, 25.5, 25.0, 24.9, 21.4, 21.3, 21.2, 21.2, 18.5, 17.9, 15.7, 14.8, 14.1, 13.5, 13.4, 12.9, 9.8; **HRMS [M+NH$_4$+MeCN]$^+$** calcd for $C_{60}H_{99}N_2O_{14}$: 1071.7091; found: 1071.7072; **[α]$_D^{20}$** +3.7 (*c* 0.91, $CHCl_3$).

3.94
72% yield, 91:9 dr

3.95
79% conv, 66% yield,
86% yield brsm, >98:2 *E:Z*

(1*S*,2*S*,3*R*,6*S*,7*S*,8*R*,11*S*,13*R*,15*S*,23*R*,*E*)-3-((*R*,*E*)-4-Acetoxy-2-methylhept-1-en-1-yl)-7-((4-methoxybenzyl)oxy)-2,6,8,18,25,25-hexamethyl-5-oxo-4,24,26-trioxabicyclo[21.3.1]heptacos-18-ene-11,13,15-triyl triacetate (3.95): Following the general procedure, a solution of **Mo-3b** in benzene (0.1 M, 17 μL, 1.7 μmol) was

transferred by syringe to an oven-dried round-bottom flask that contained **3.94** (16.6 mg, 0.017 mmol) dissolved in benzene (8.5 mL, 2.0 mM). The mixture was allowed to stir for 12 h at 40 °C, after which the reaction was quenched by the addition of wet (undistilled) Et_2O. ^1H NMR analysis of the unpurified mixture indicated 79% consumption of **3.94**. Removal of the volatiles left behind red oil, which was purified by silica gel chromatography (10% → 13% → 16% EtOAc in hexanes), affording macrocyclic alkene **3.95** as colorless oil (10.4 mg, 0.0109 mmol, 66% yield, >98:2 *E*:*Z*) and recovered **3.94** as colorless oil (3.3 mg, 0.032 mmol, 20% yield). **IR (neat)**: 2923 (m), 2856 (w), 1734 (s), 1513 (w), 1457 (w), 1373 (m), 1240 (s), 1175 (w), 1022 (m), 946 (w), 819 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.19 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 5.46 (dd, J = 9.4, 7.9 Hz, 1H), 5.165.08 (m, 2H), 5.02–4.81 (m, 4H), 4.53 (d, J = 10.9 Hz, 1H), 4.38 (d, J = 10.8 Hz, 1H), 3.89 (dt, J = 10.6, 5.6 Hz, 1H), 3.79 (s, 3H), 3.77–3.70 (m, 1H), 3.61 (dd, J = 7.6, 3.1 Hz, 1H), 2.76 (p, J = 6.9 Hz, 1H), 2.19 (dd, J = 13.9, 6.7 Hz, 1H), 2.10 (dd, J = 13.8, 6.6 Hz, 1H), 2.04 (s, 3H), 2.01 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 2.06–1.96 (m, 4H), 1.77 (d, J = 1.3 Hz, 3H), 1.59 (d, J = 1.3 Hz, 3H), 1.91–1.53 (m, 10H), 1.51–1.34 (m, 9H), 1.32 (s, 3H), 1.29 (s, 3H), 1.28–1.19 (m, 3H), 1.15 (d, J = 7.2 Hz, 3H), 0.95–0.83 (m, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 174.2, 170.7, 170.7, 170.6, 170.4, 159.1, 137.5, 134.1, 131.2, 129.1, 125.3, 125.0, 113.8, 100.3, 82.8, 73.2, 72.2, 72.0, 70.6, 69.5, 68.0, 66.9, 66.4, 55.4, 55.4, 44.5, 43.4, 41.3, 38.5, 37.9, 36.0, 35.33, 35.1, 34.3, 33.2, 32.3, 32.0, 29.8, 27.8, 25.0, 25.0, 24.9, 21.4, 21.3, 21.2, 18.6, 17.6, 16.2, 14.6, 14.1, 13.8, 10.5; **HRMS $[M+NH_4]^+$** calcd for $C_{54}H_{88}NO_{14}$: 974.6199, found: 974.6207; **$[\alpha]_D^{20}$** +1.8 (*c* 0.46, $CHCl_3$).



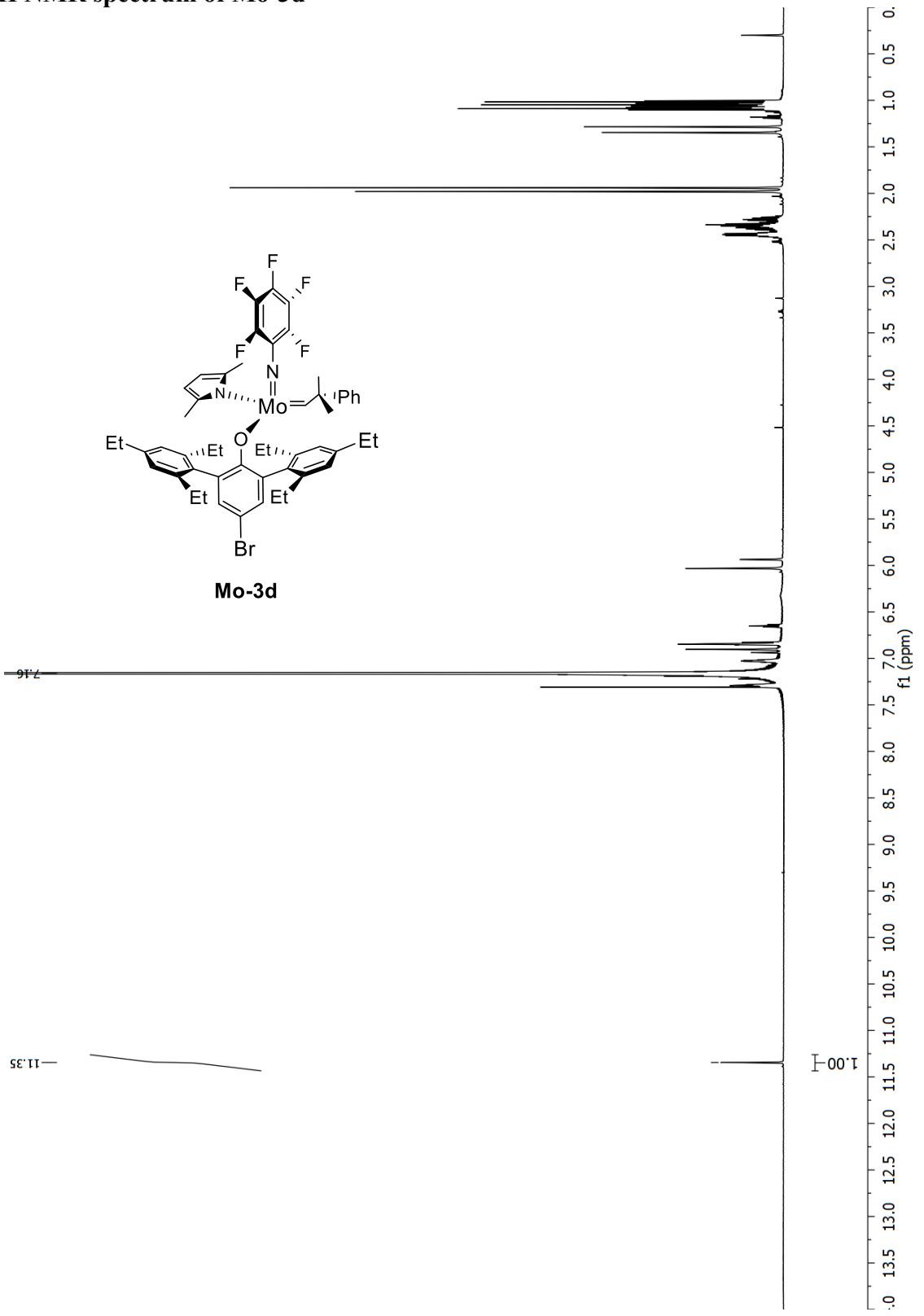
(3*S*,4*S*,5*R*,8*S*,10*R*,12*S*,20*R*,22*S*,23*S*,24*R*,*E*)-24-((*R*,*E*)-4-Acetoxy-2-methylhept-1-en-1-yl)-4,20,22-trihydroxy-3,5,15,23-tetramethyl-2-oxooxacyclotetracos-15-ene-8,10,12-triyl triacetate (Dolabelide C): To a solution of **3.95** (10.5 mg, 0.011 mmol) in MeOH (1.1 mL) was added a solution of PPTS in MeOH (0.1 M, 5.5 µL, 0.55 µmol), and the mixture was allowed to stir for 5 h at 22 °C. At this point, TLC analysis indicated complete disappearance of **3.95**. The solution was diluted with EtOAc (2 mL) and the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (2 mL). The layers were separated and the aqueous phase was washed with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and the volatiles were removed to give colorless oil, which was used immediately without purification.

To a solution of the aforementioned colorless oil in CH_2Cl_2 (0.7 mL) at 22 °C was added pH 7 buffer (0.7 mL) and DDQ (5.0 mg, 0.022 mmol) and the mixture was allowed to stir for 25 min at 22 °C. The solution was diluted with CH_2Cl_2 (1.5 mL), after which the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (0.3 mL). The layers were separated and the aqueous layer was washed with CH_2Cl_2 (3 x 2 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo to give orange oil, which was purified by silica gel chromatography (30% → 40% → 50% EtOAc in hexanes) to afford **Dolabelide C** as

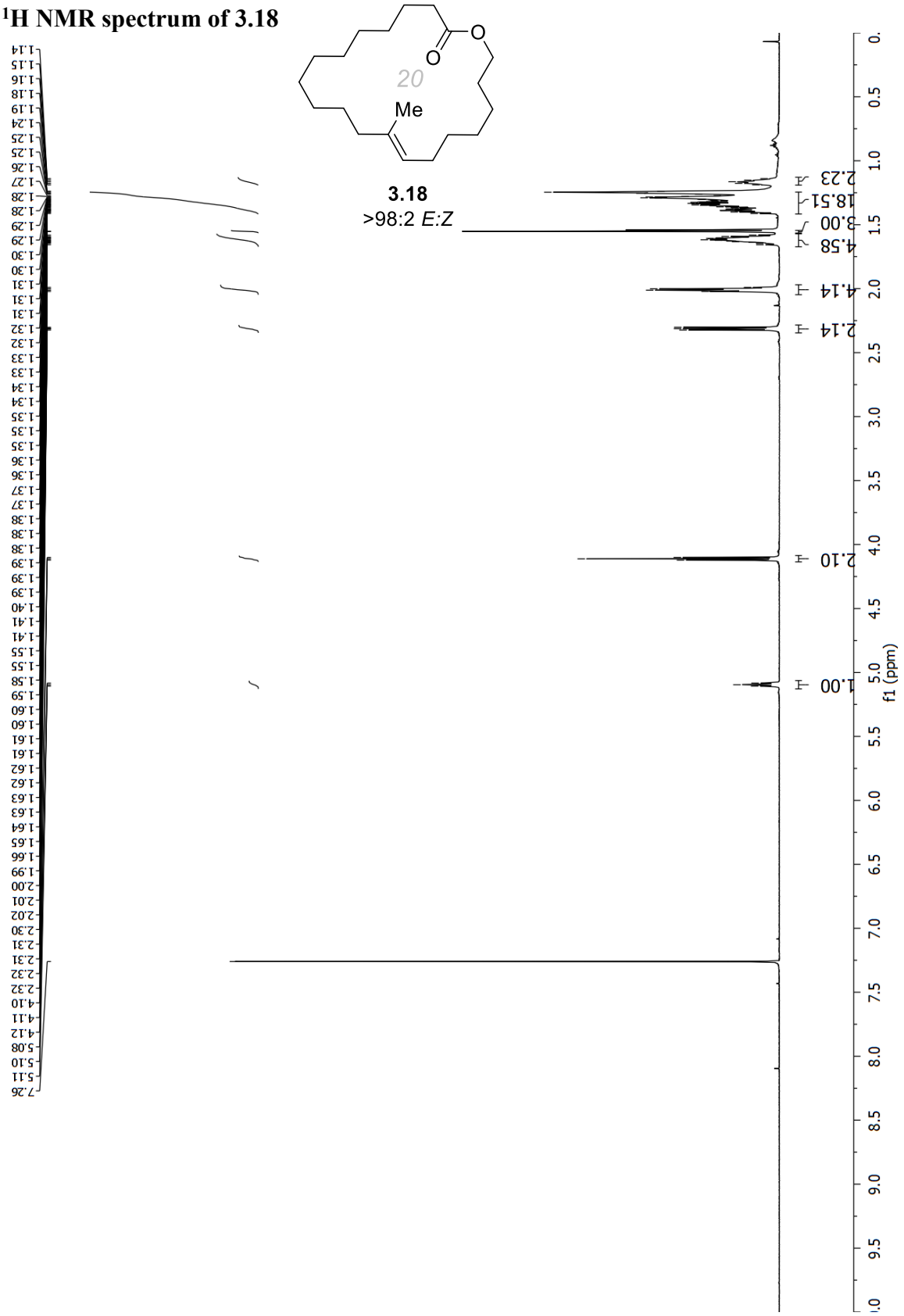
colorless oil (6.1 mg, 0.0076 mmol, 69% yield). **IR (neat)**: 3412 (br), 2926 (m), 2853 (w), 1734 (s), 1455 (w), 1373 (m), 1239 (s), 1097 (w), 1022 (m), 947 (w), 805 (w), 605 (w); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 5.35 (t, J = 9.1 Hz, 1H), 5.10–5.06 (m, 2H), 5.03 (tt, J = 7.2, 5.4 Hz, 1H), 4.94 (td, J = 8.7, 5.3 Hz, 1H), 4.85 (ddq, J = 12.5, 8.6, 4.9, 4.4 Hz, 2H), 4.08 (s, 1H), 3.94 (s, 1H), 3.60–3.52 (m, 2H), 3.19 (s, 1H), 2.60–2.54 (m, 1H), 2.49 (s, 1H), 2.26 (dd, J = 14.0, 7.2 Hz, 1H), 2.21 (dd, J = 14.0, 5.6 Hz, 1H), 2.07 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 2.11–1.95 (m, 4H), 1.90–1.82 (m, 2H), 1.80 (d, J = 1.3 Hz, 3H), 1.79–1.69 (m, 3H), 1.63 (dt, J = 9.3, 5.2 Hz, 2H), 1.59 (s, 3H), 1.58–1.44 (m, 10H), 1.43–1.26 (m, 4H), 1.21 (ddd, J = 13.3, 11.9, 6.6 Hz, 1H), 1.07 (d, J = 7.1 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H), 0.84 (dd, J = 6.9, 2.2 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 173.9, 171.3, 171.1, 170.8, 170.5, 138.1, 133.2, 126.8, 125.2, 74.7, 73.3, 72.4, 60.0, 69.4, 68.8, 68.3, 67.8, 45.2, 44.5, 42.9, 39.3, 37.1, 36.4, 36.2, 35.2, 34.8, 32.0, 31.9, 29.9, 28.5, 26.9, 25.2, 21.4, 21.3, 21.3, 21.2, 18.7, 17.8, 15.4, 14.1, 13.8, 12.8, 10.7; **HRMS $[M+Na]^+$** calcd for $C_{43}H_{72}NaO_{13}$: 819.4865, found: 819.4862; **$[\alpha]_D^{20}$** +8.3 (*c* 0.36, $CHCl_3$). The data were fully consistent with those reported previously[15].

NMR Spectra

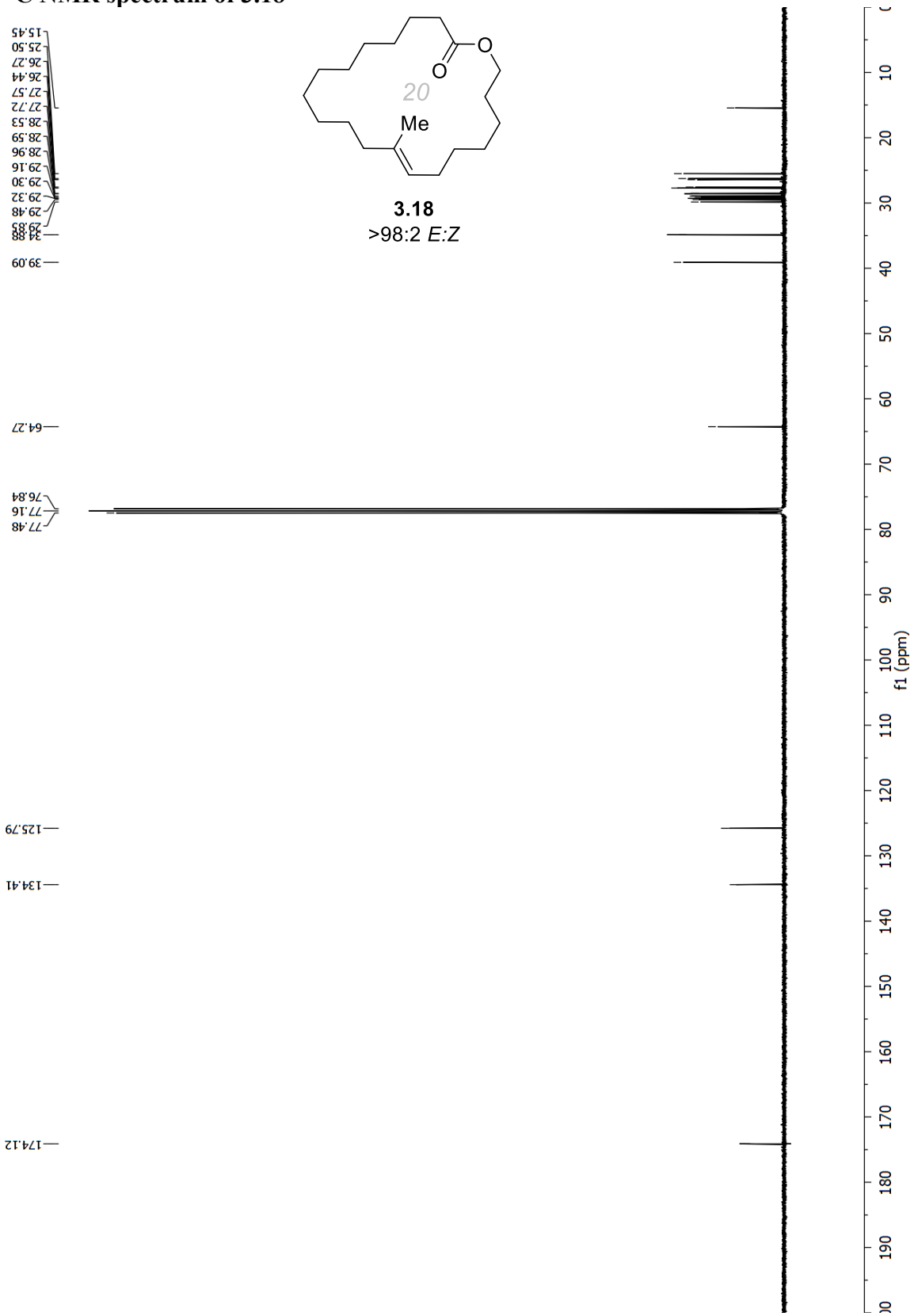
^{1}H NMR spectrum of Mo-3d



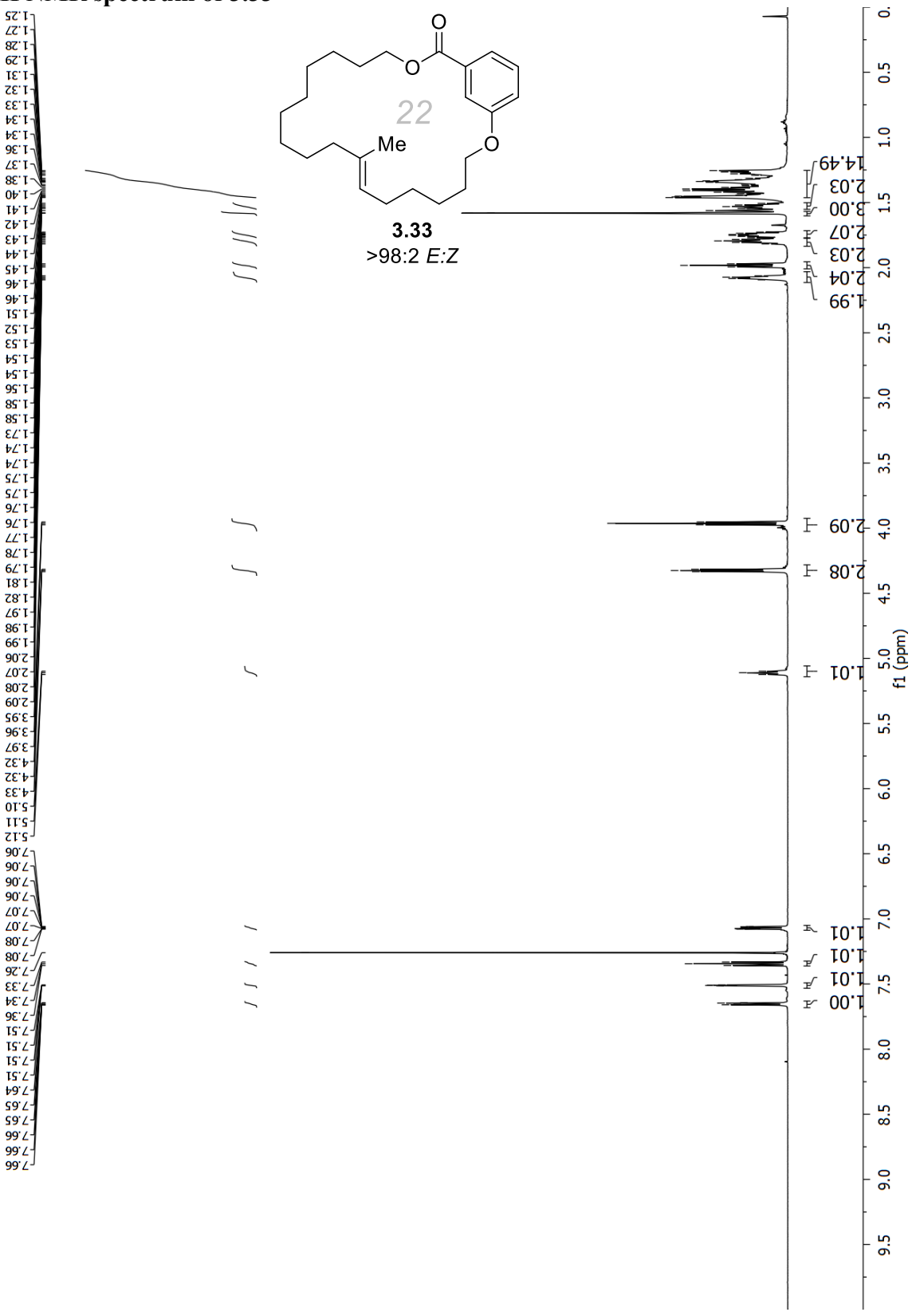
^{1}H NMR spectrum of 3.18



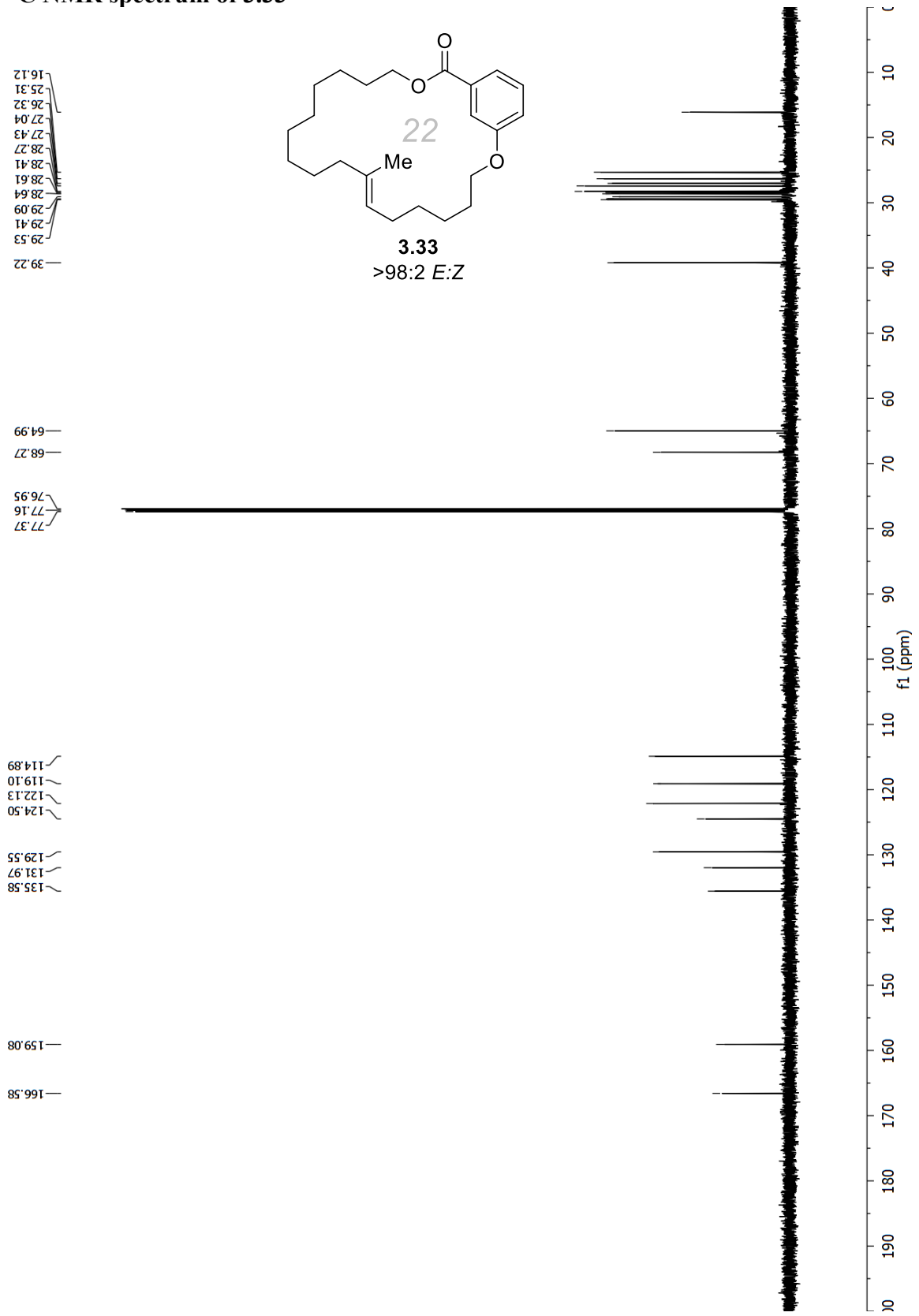
^{13}C NMR spectrum of 3.18



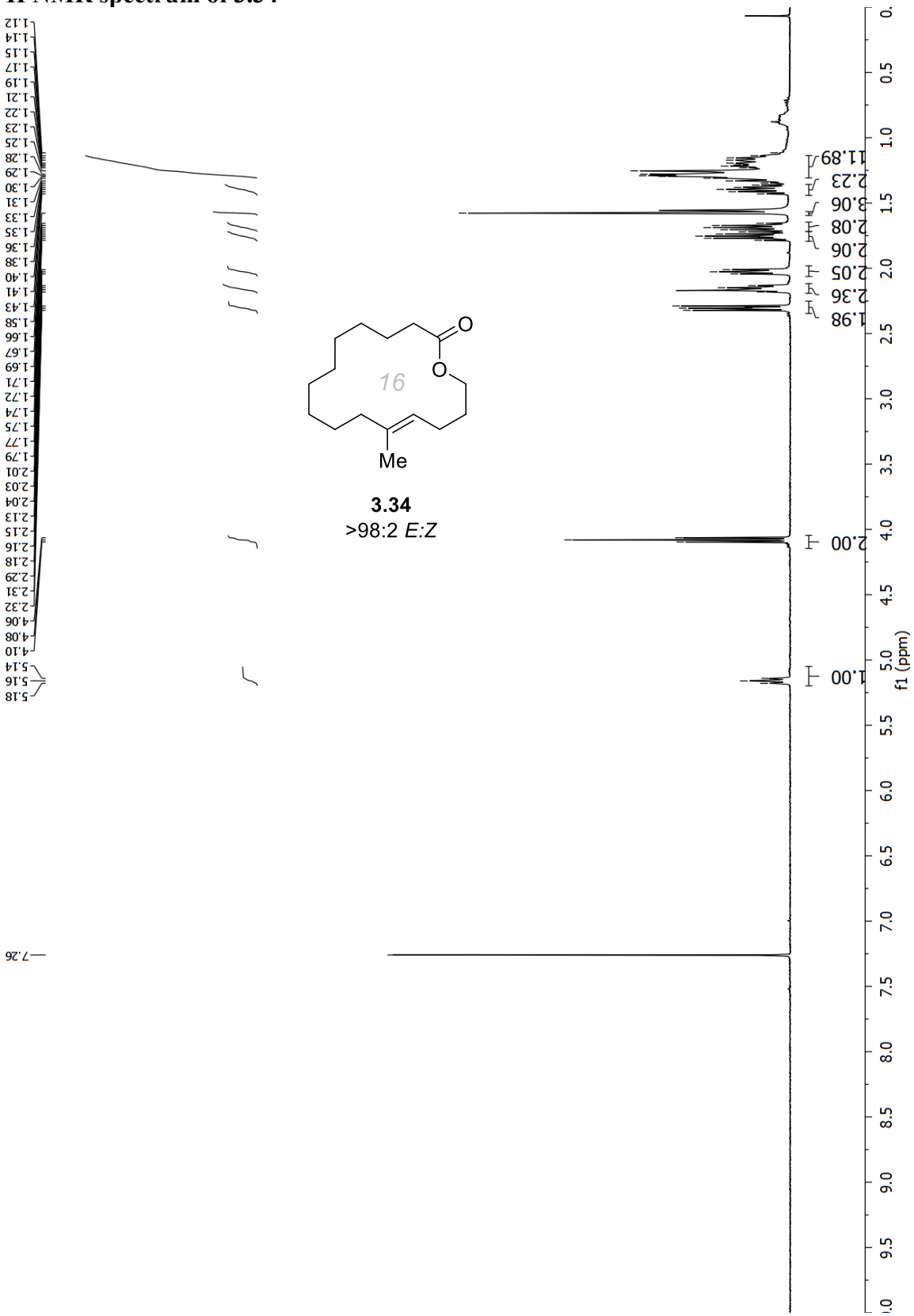
^{1}H NMR spectrum of 3.33



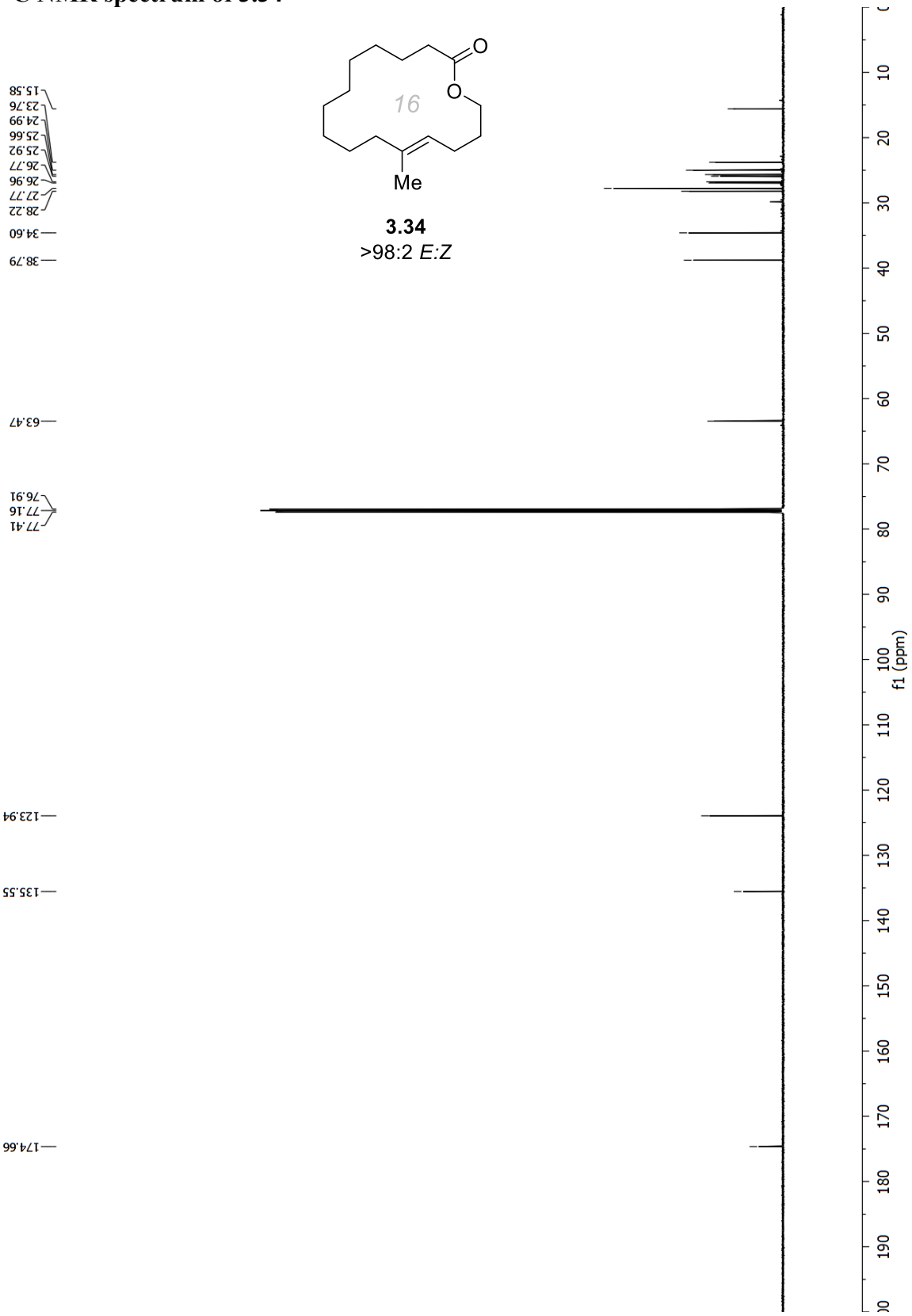
^{13}C NMR spectrum of 3.33



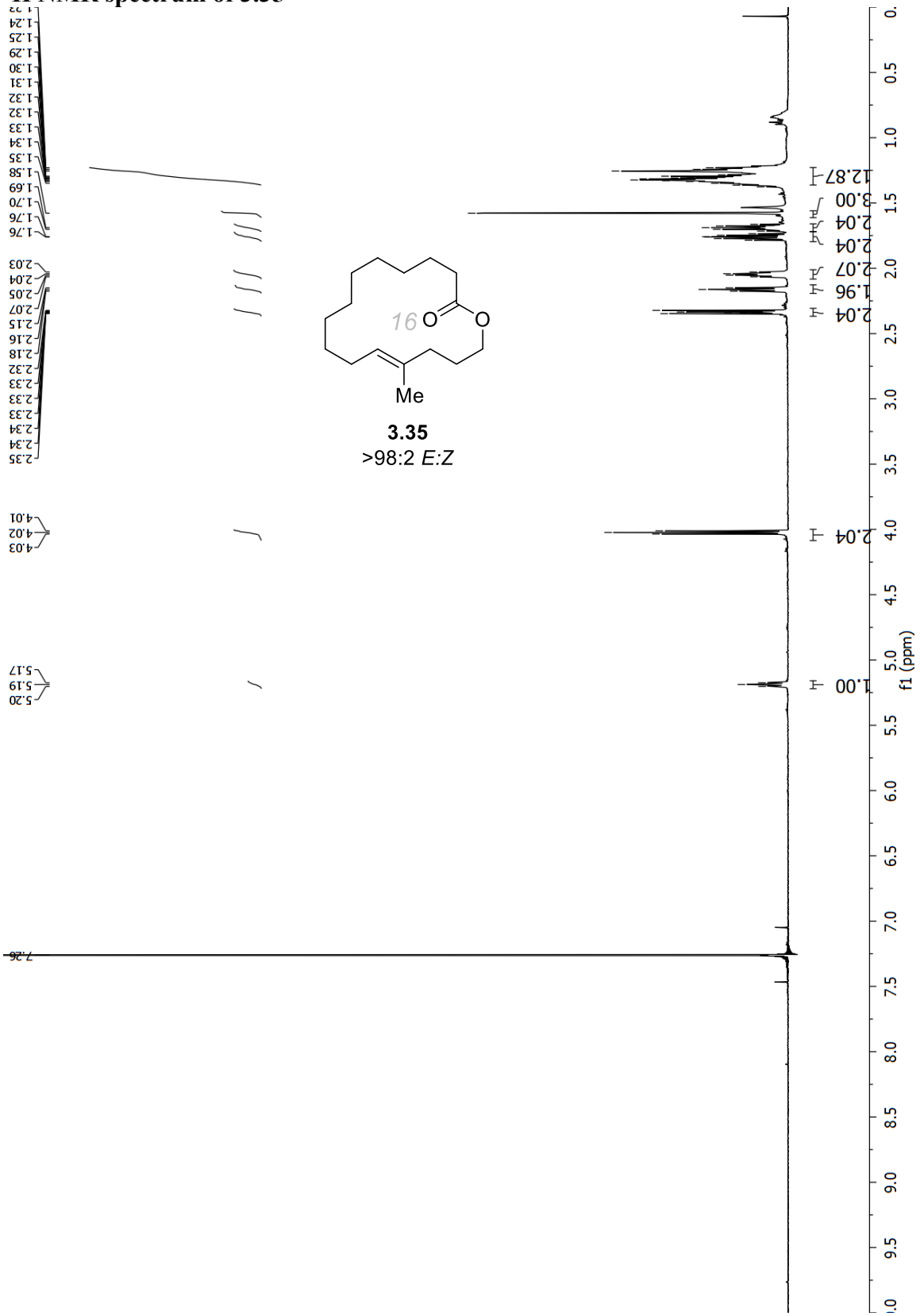
^{1}H NMR spectrum of 3.34



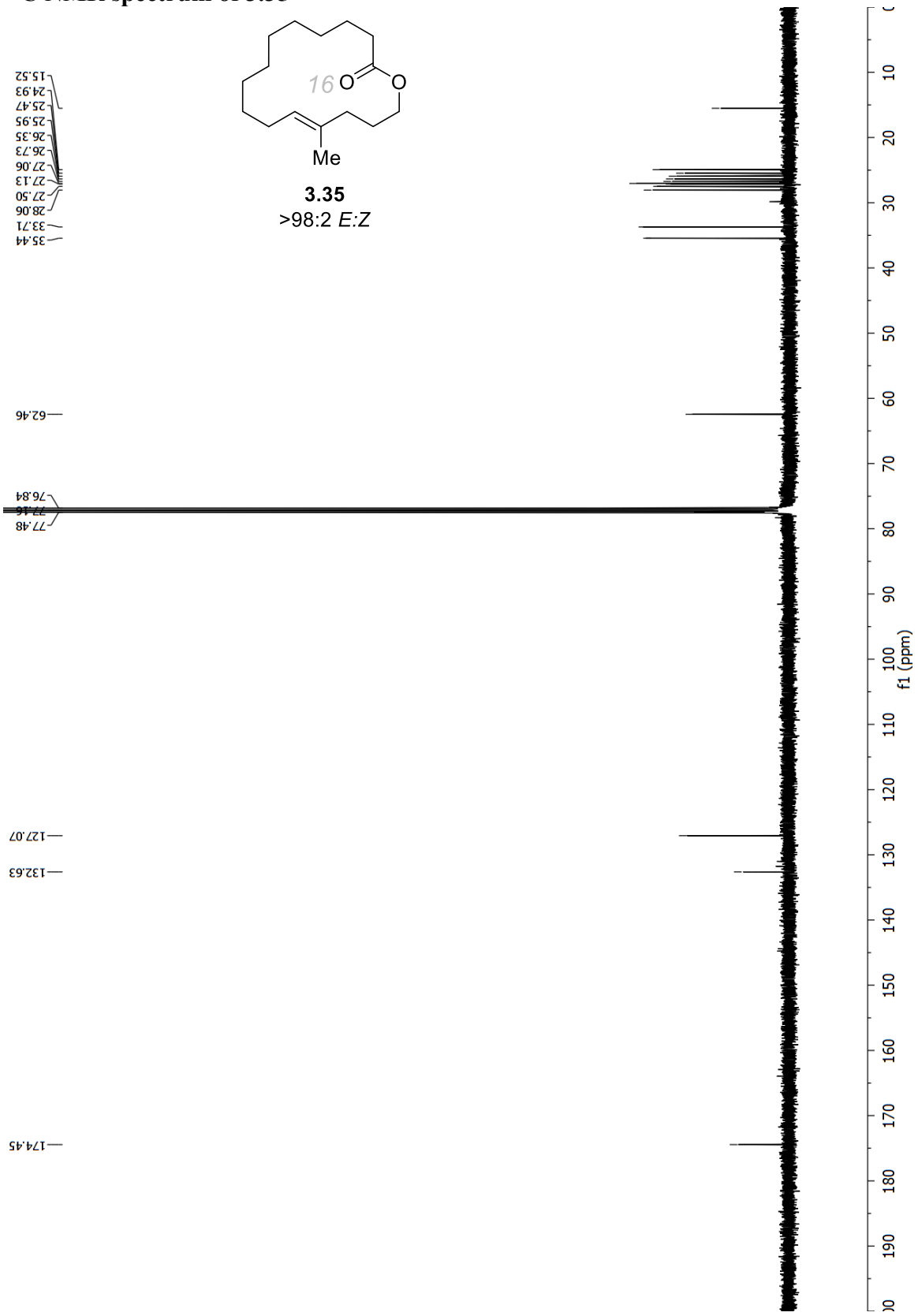
^{13}C NMR spectrum of 3.34



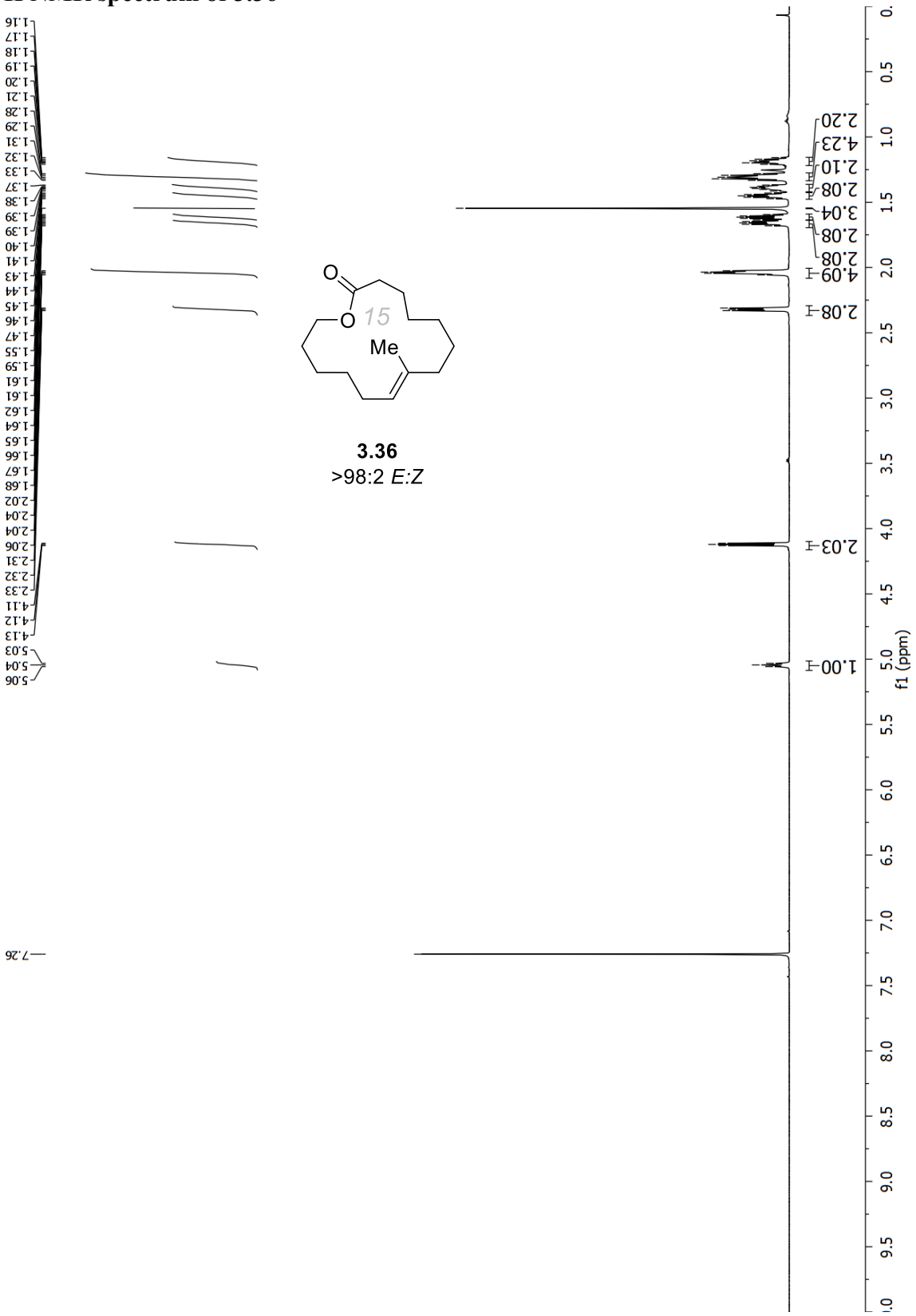
^{1}H NMR spectrum of 3.35



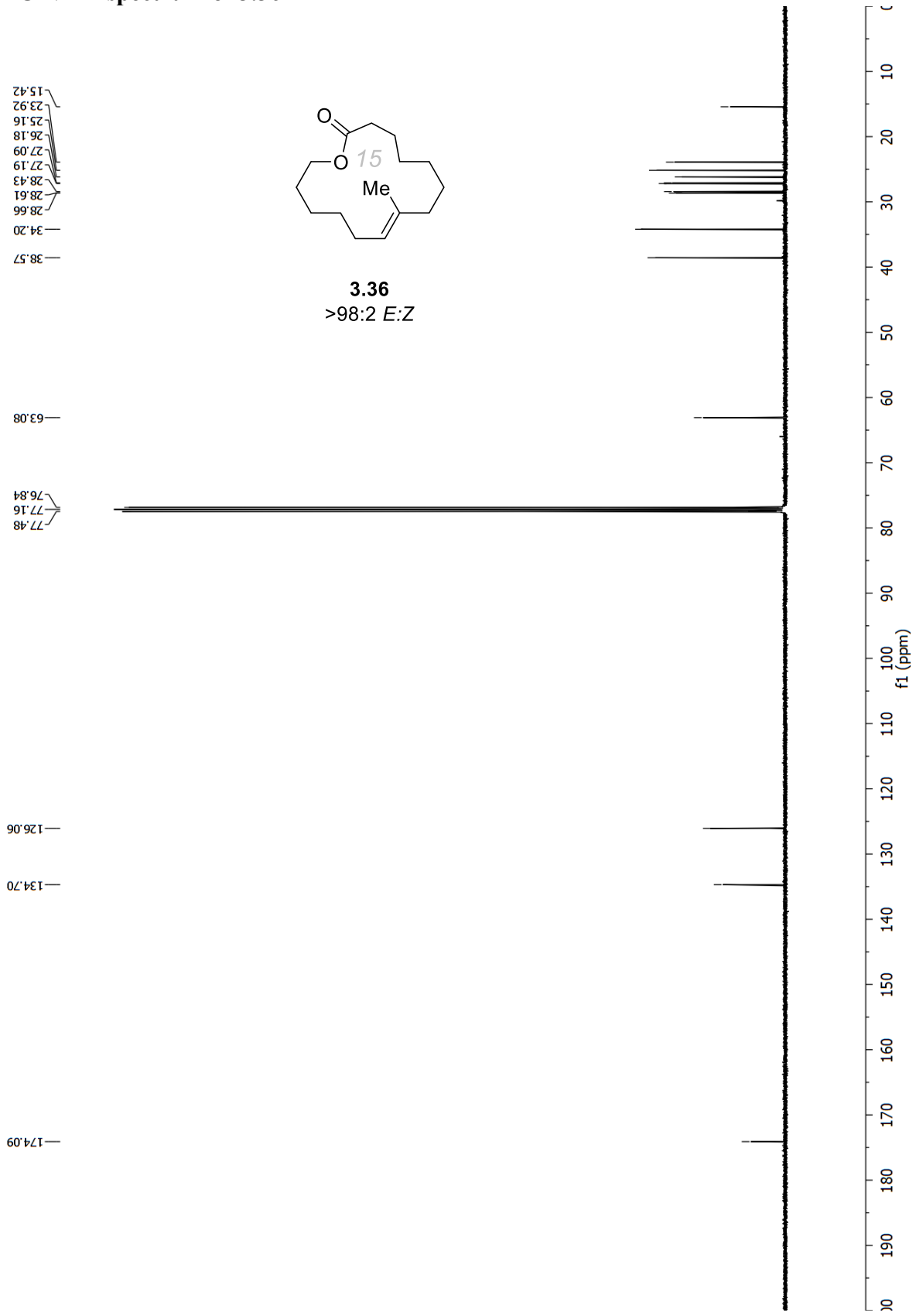
^{13}C NMR spectrum of 3.35



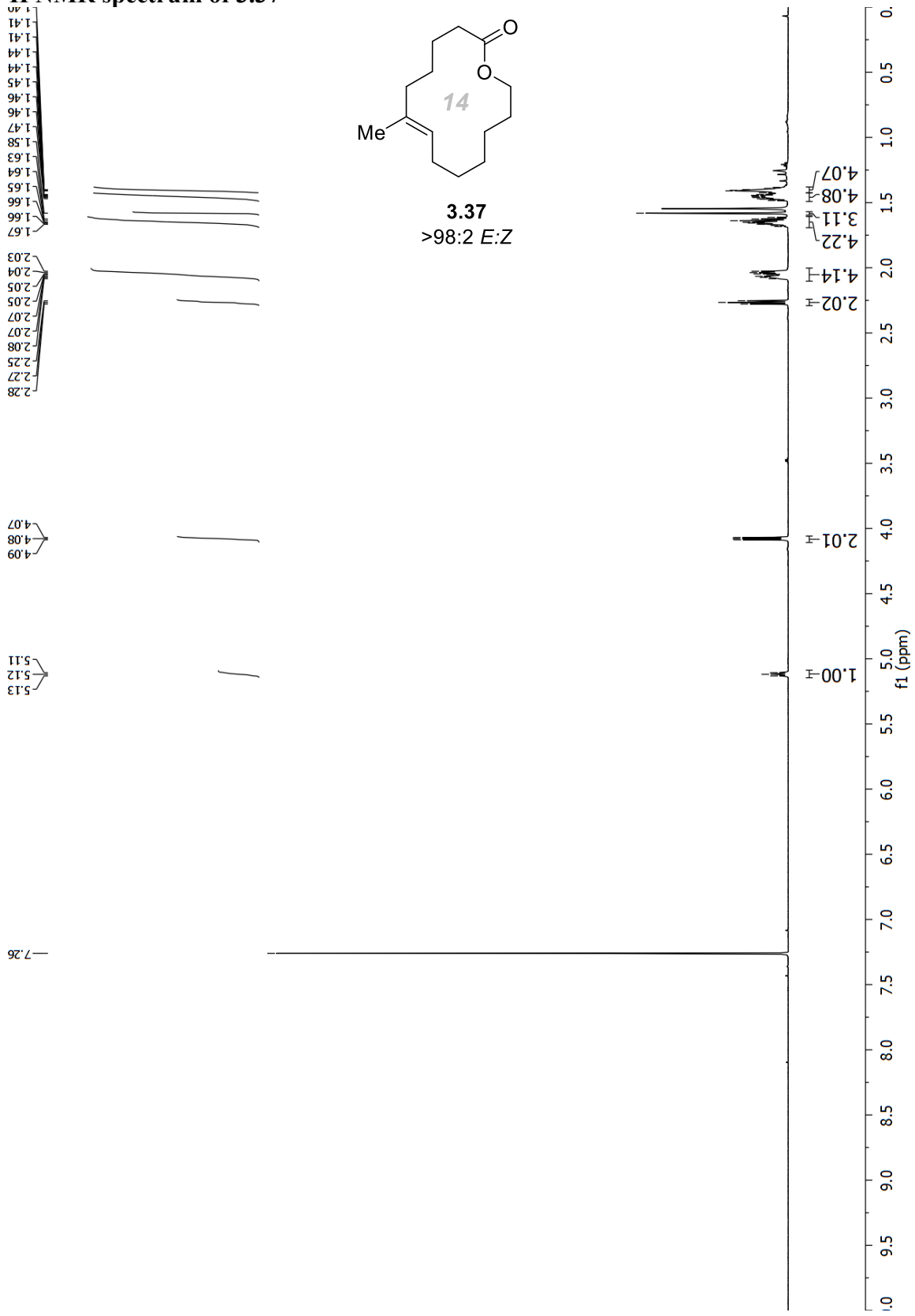
^{1}H NMR spectrum of 3.36



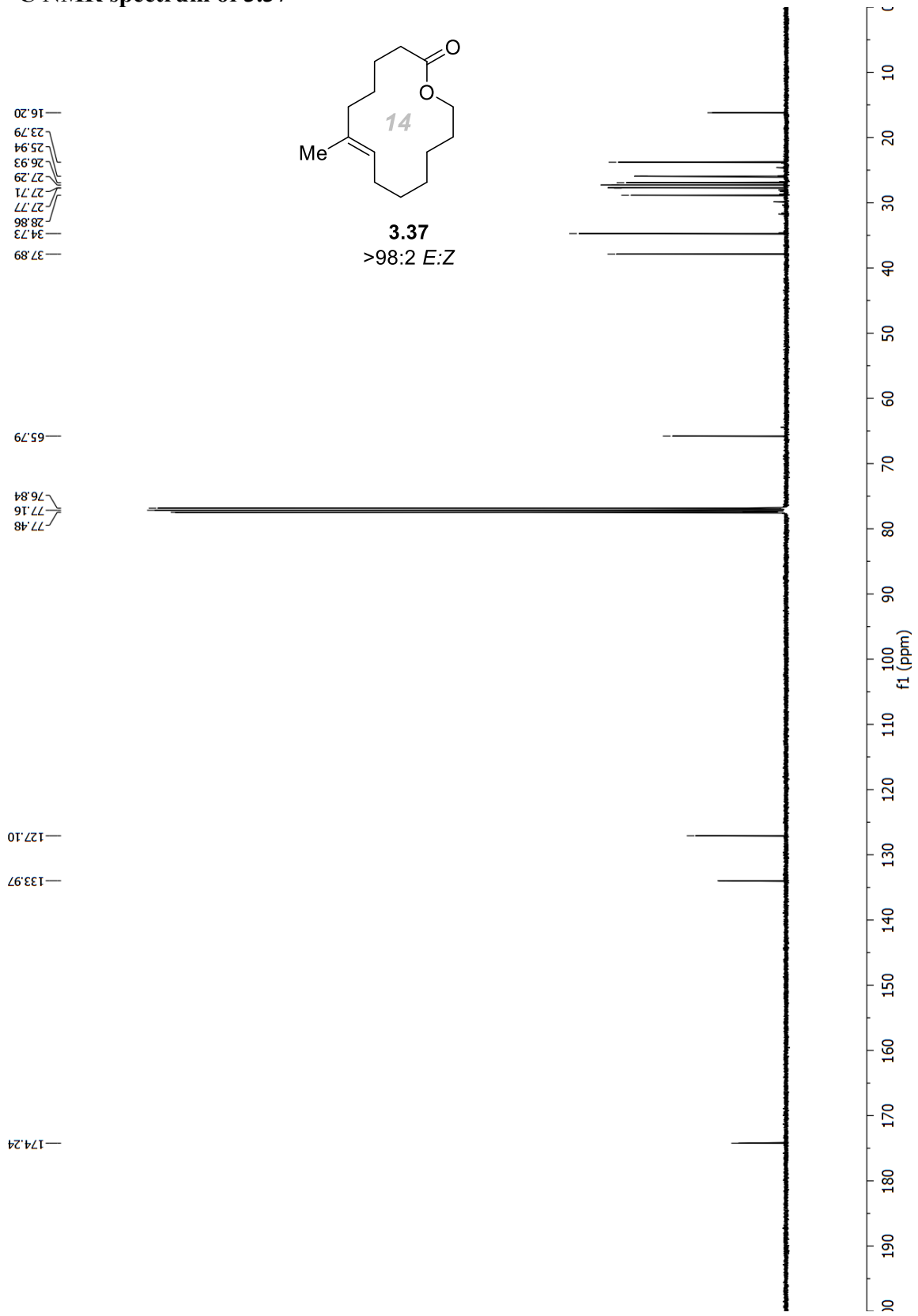
^{13}C NMR spectrum of 3.36



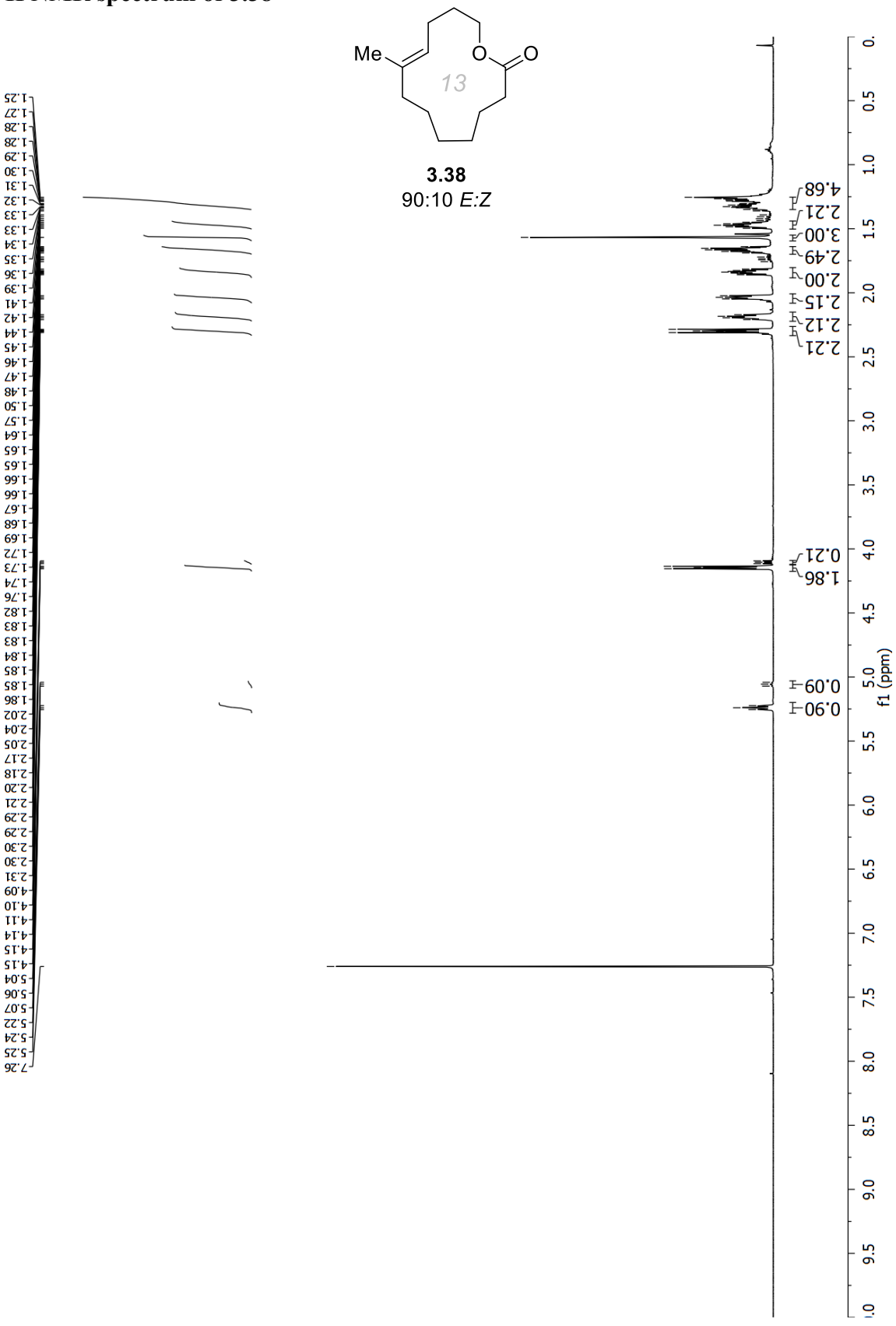
^{1}H NMR spectrum of 3.37



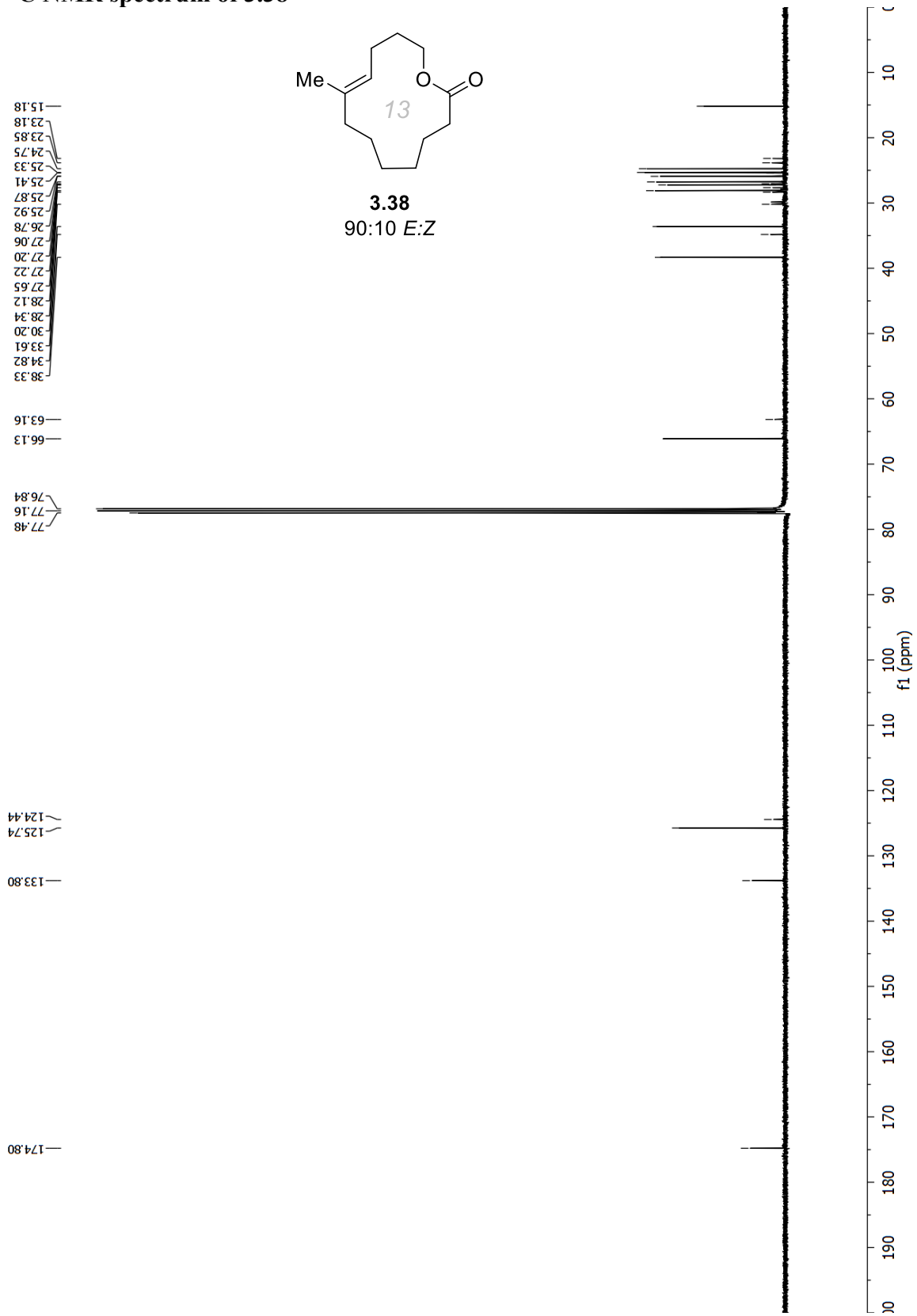
^{13}C NMR spectrum of 3.37



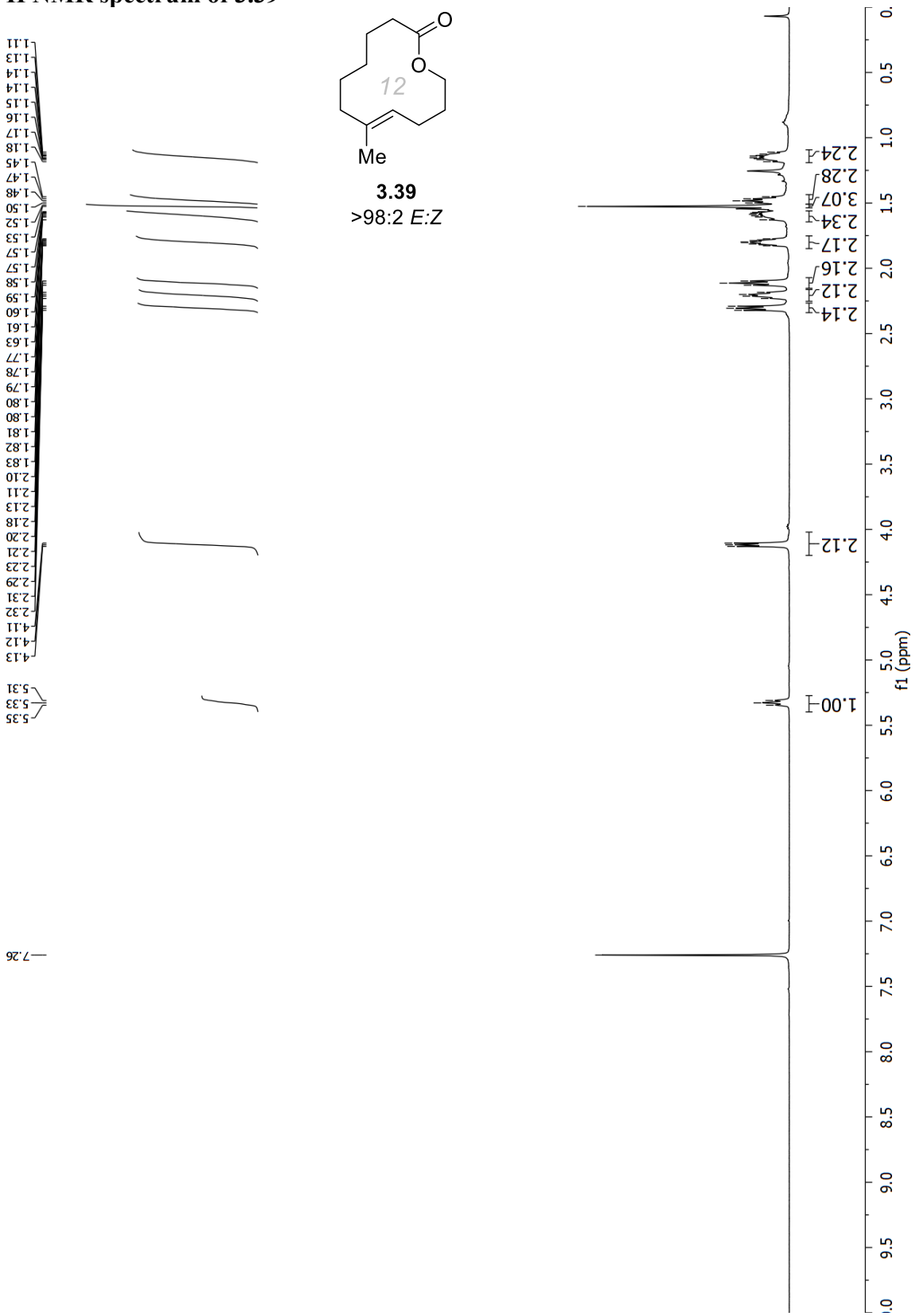
^{1}H NMR spectrum of 3.38



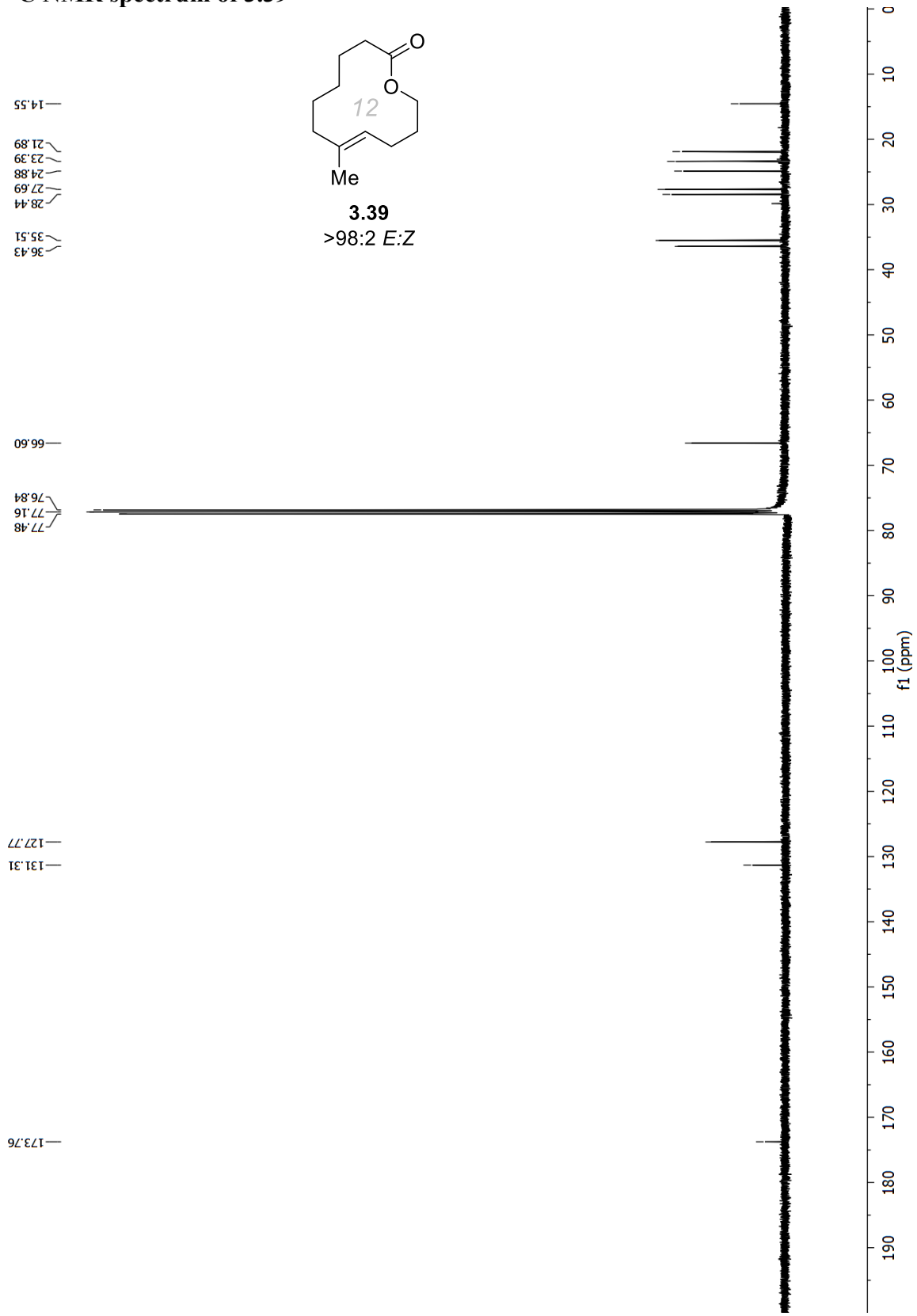
^{13}C NMR spectrum of 3.38



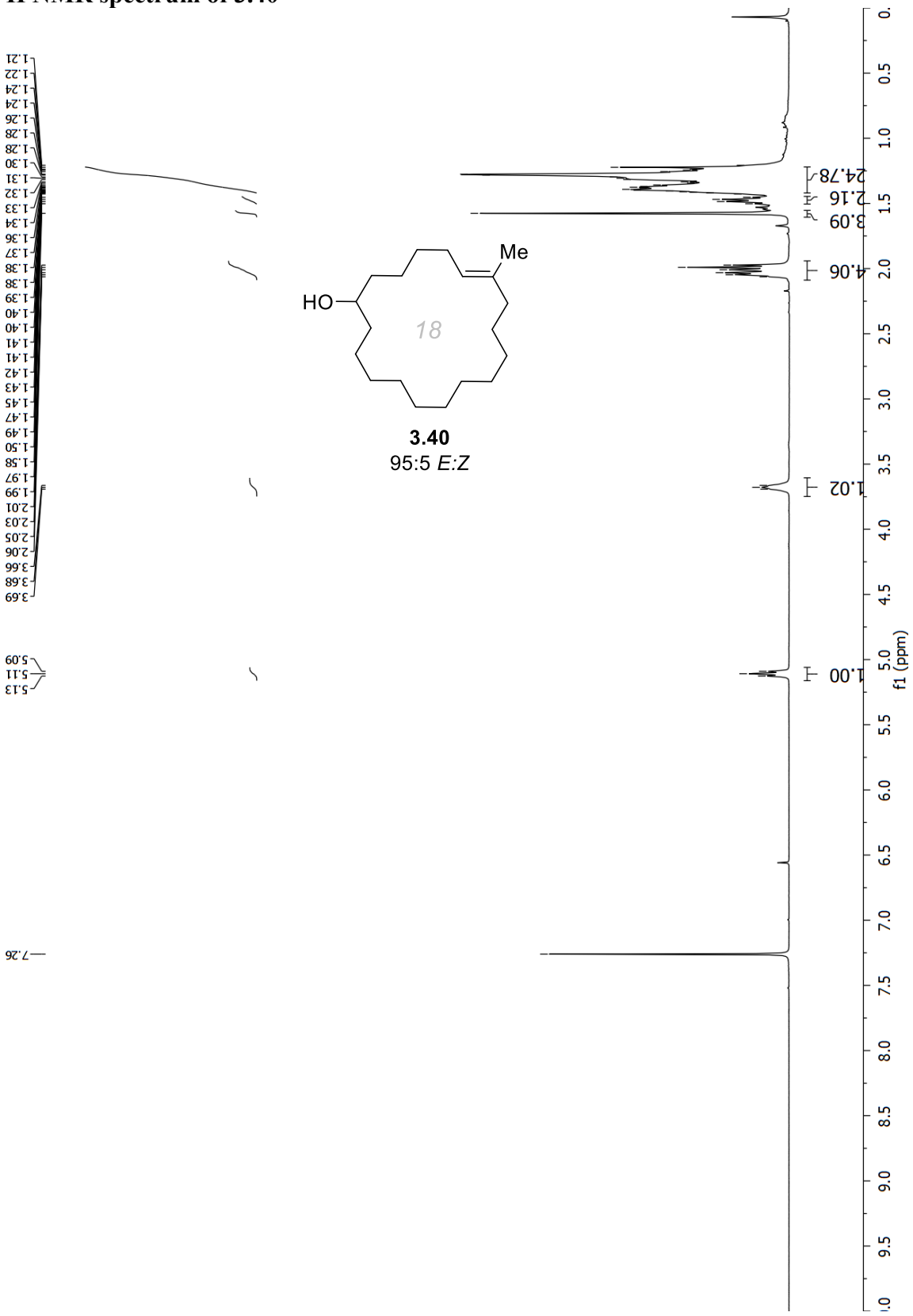
^{1}H NMR spectrum of 3.39



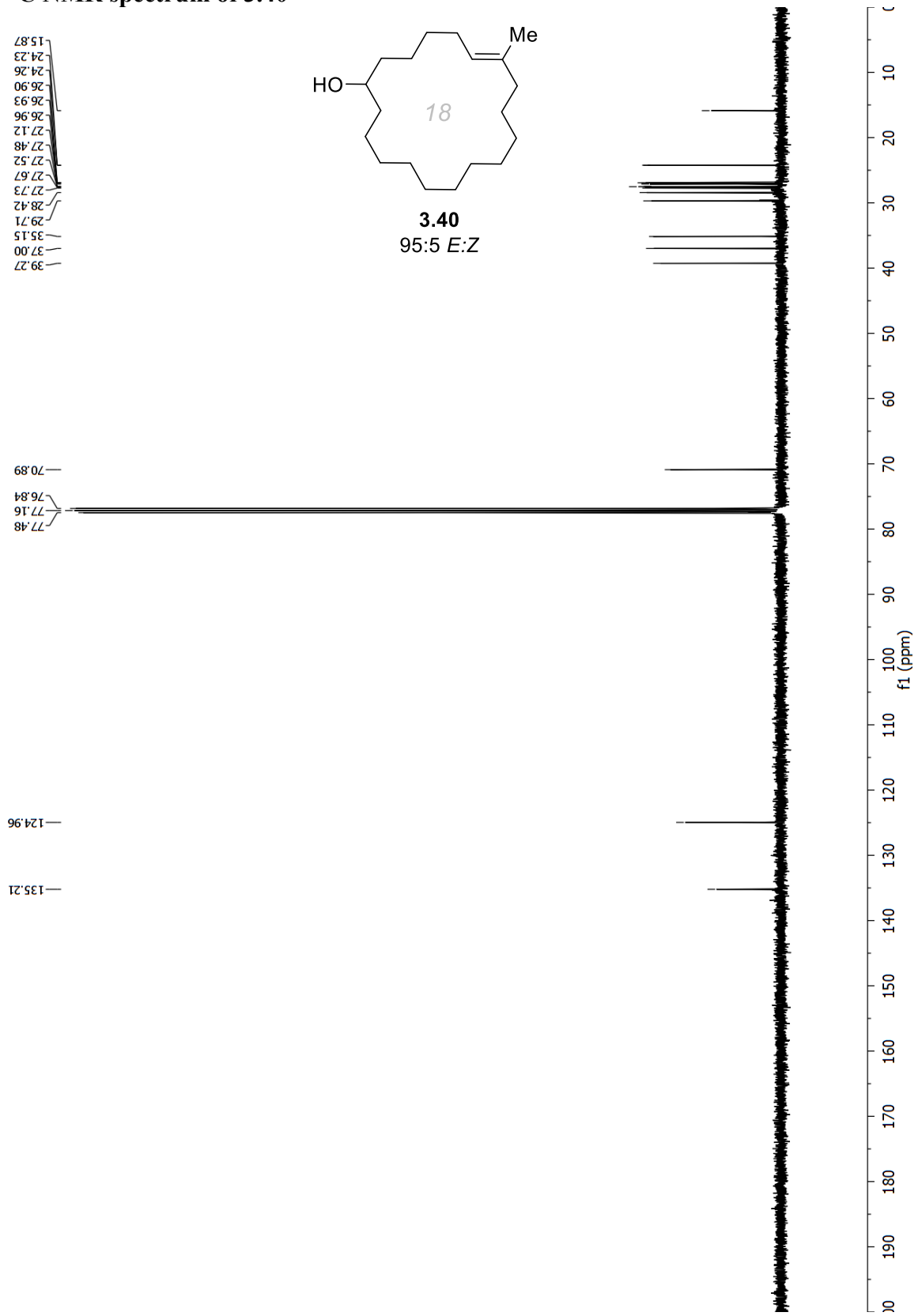
^{13}C NMR spectrum of 3.39



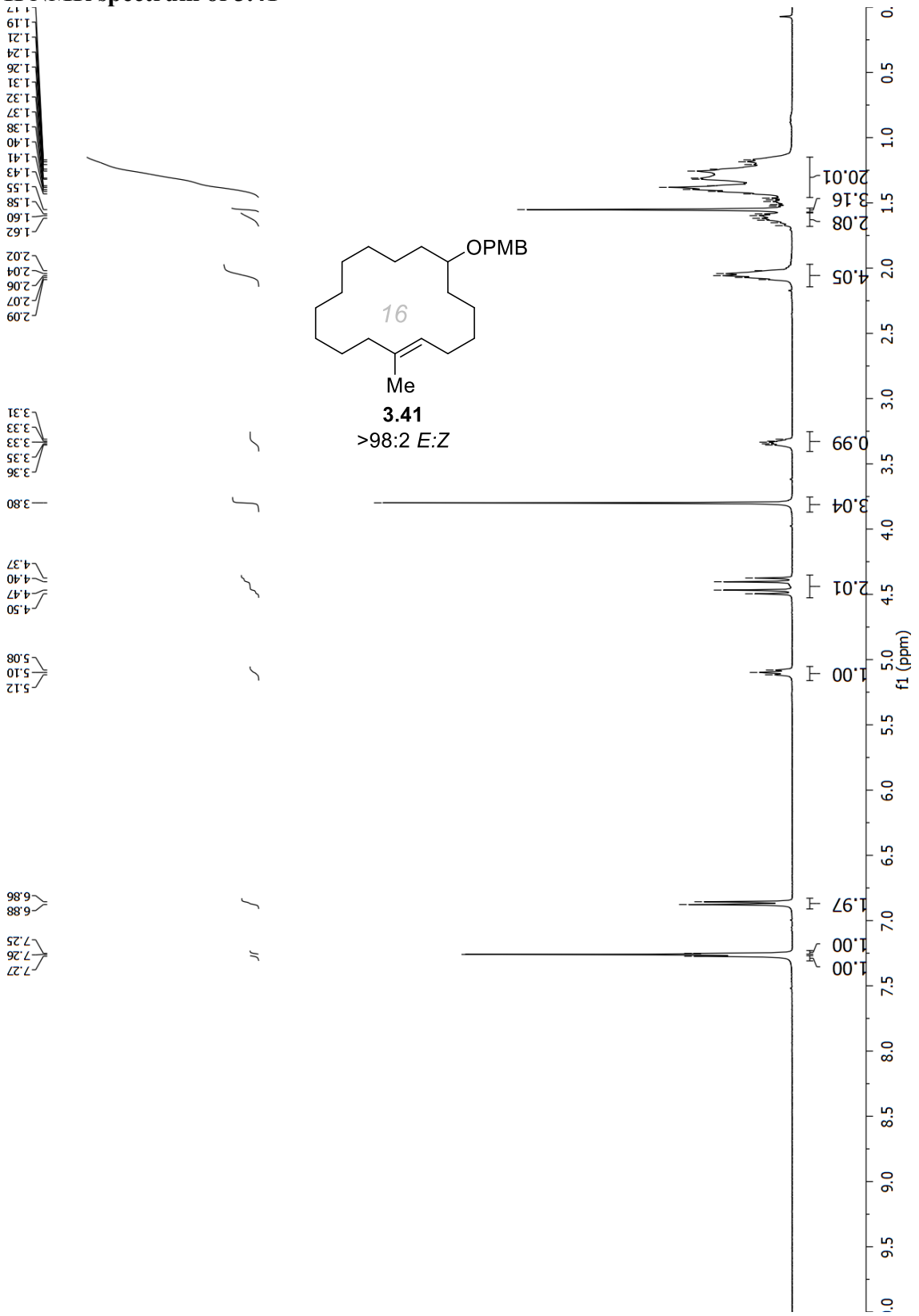
^{1}H NMR spectrum of 3.40



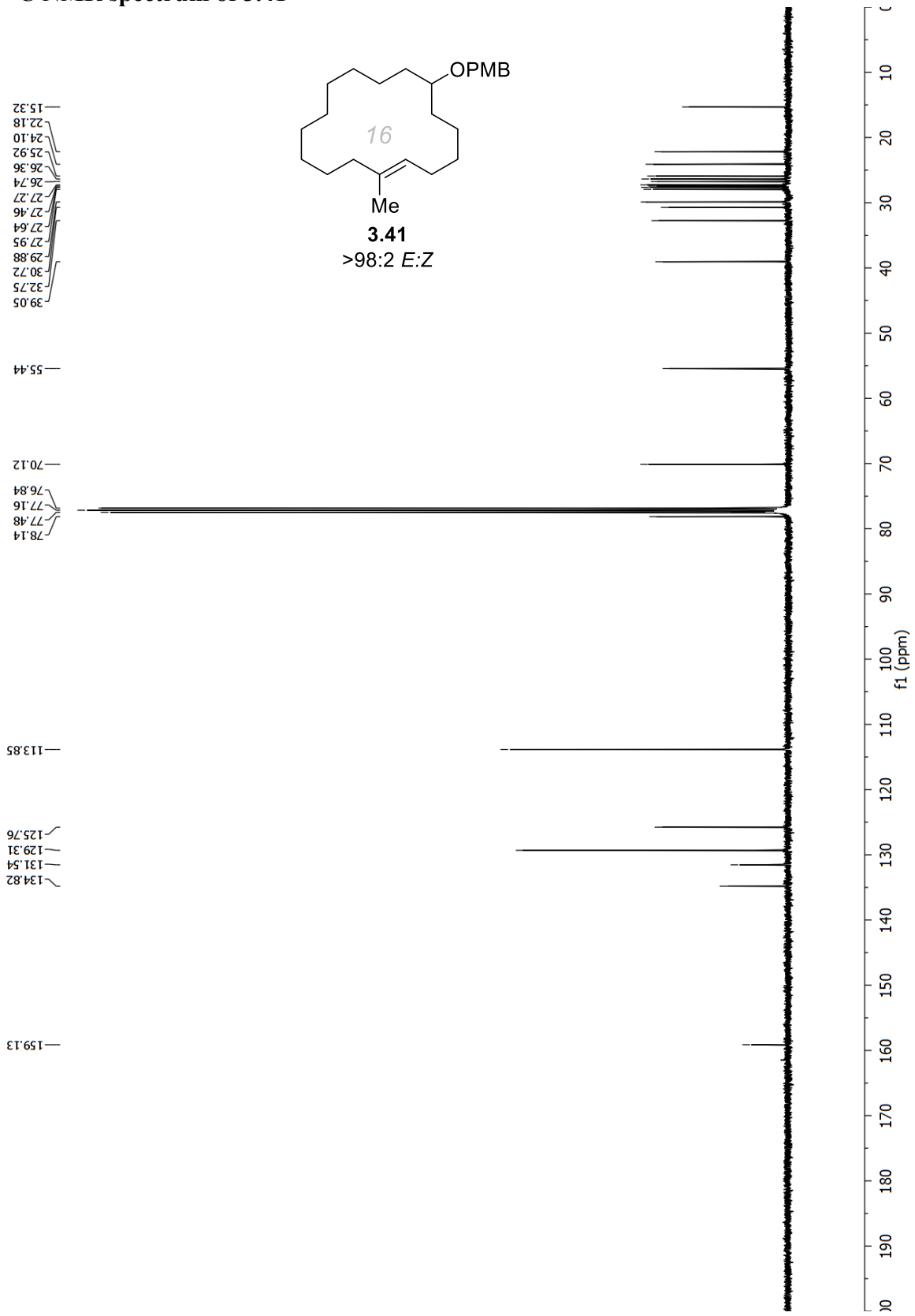
^{13}C NMR spectrum of 3.40



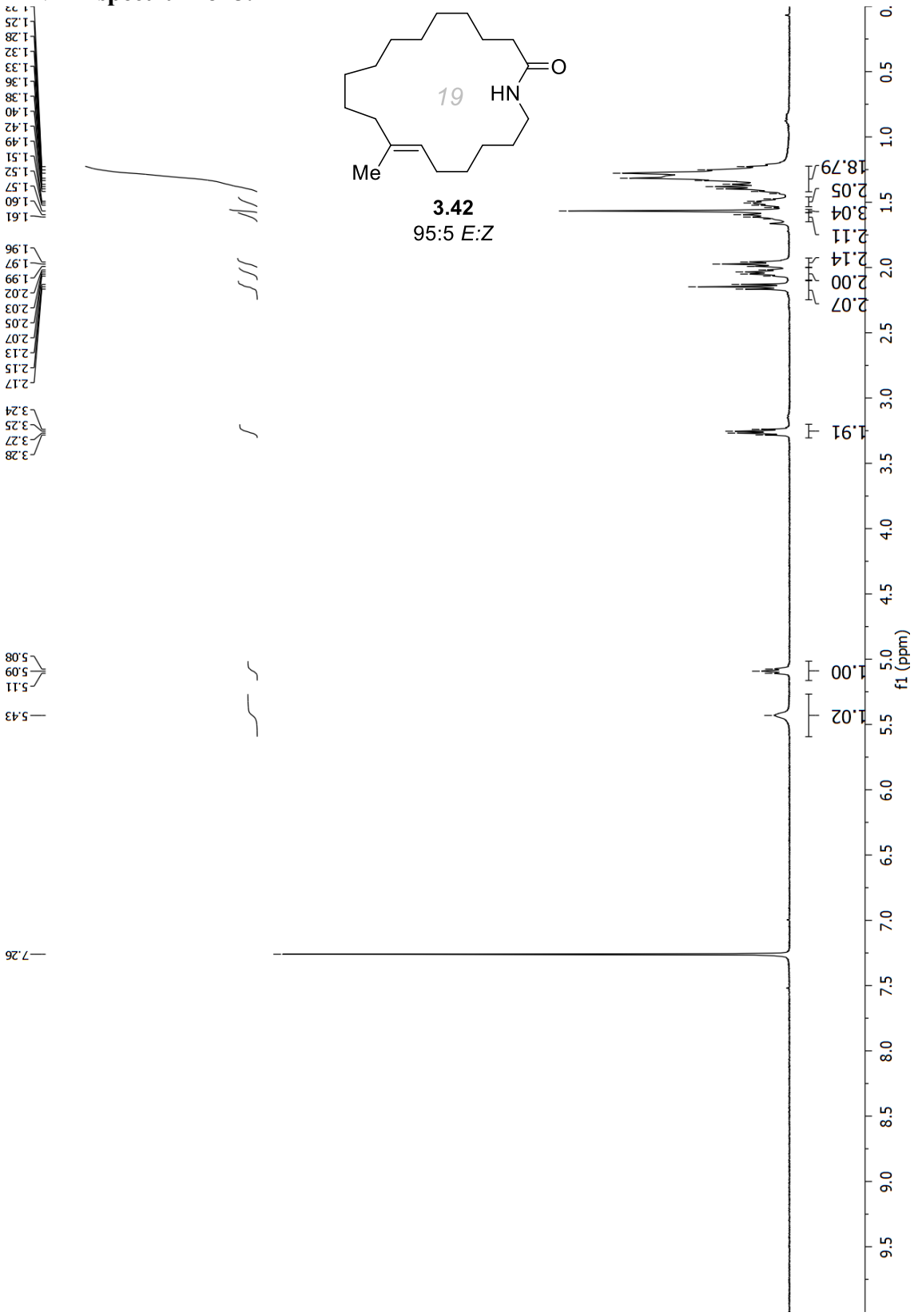
^{1}H NMR spectrum of 3.41



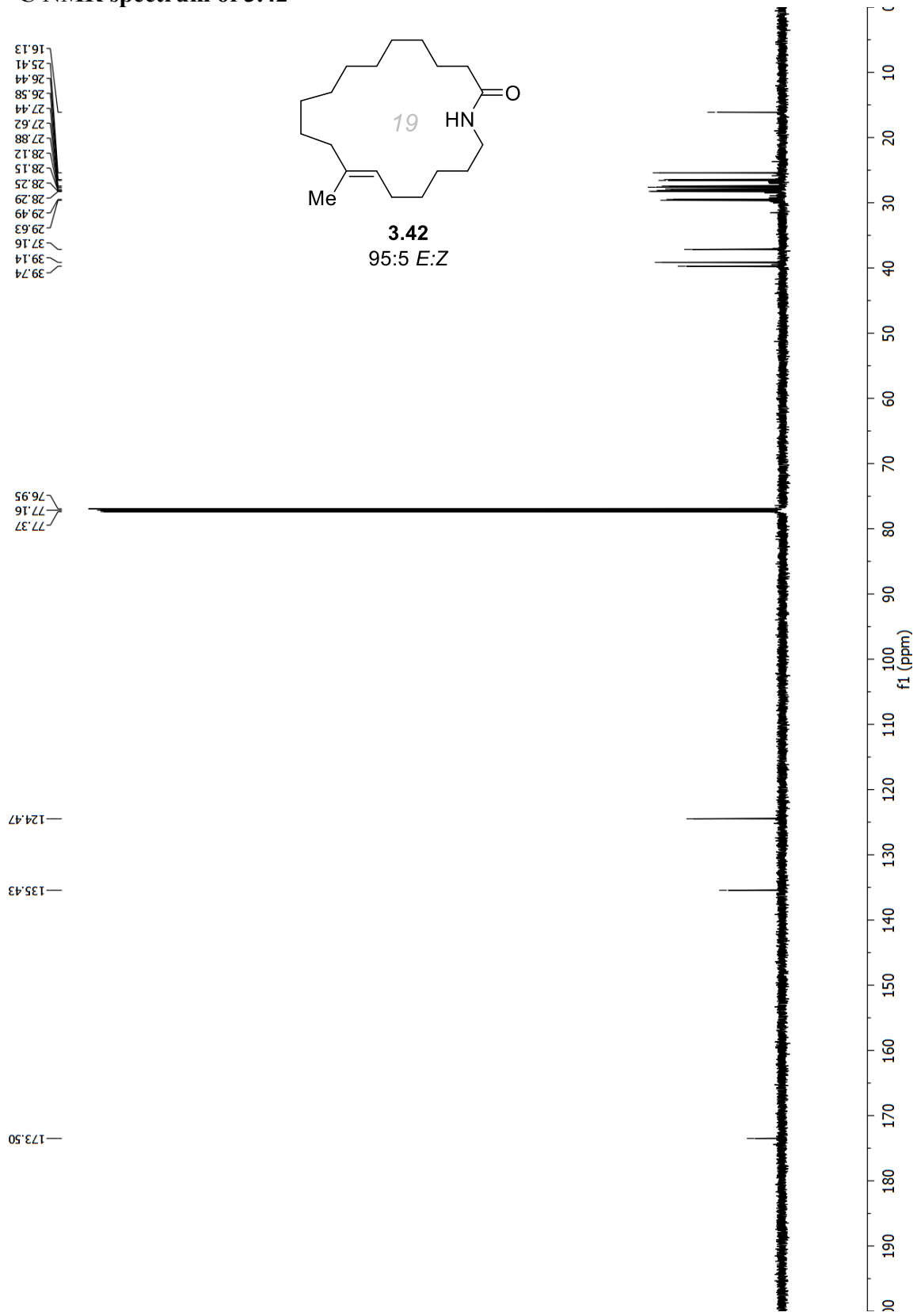
^{13}C NMR spectrum of 3.41



^{1}H NMR spectrum of 3.42

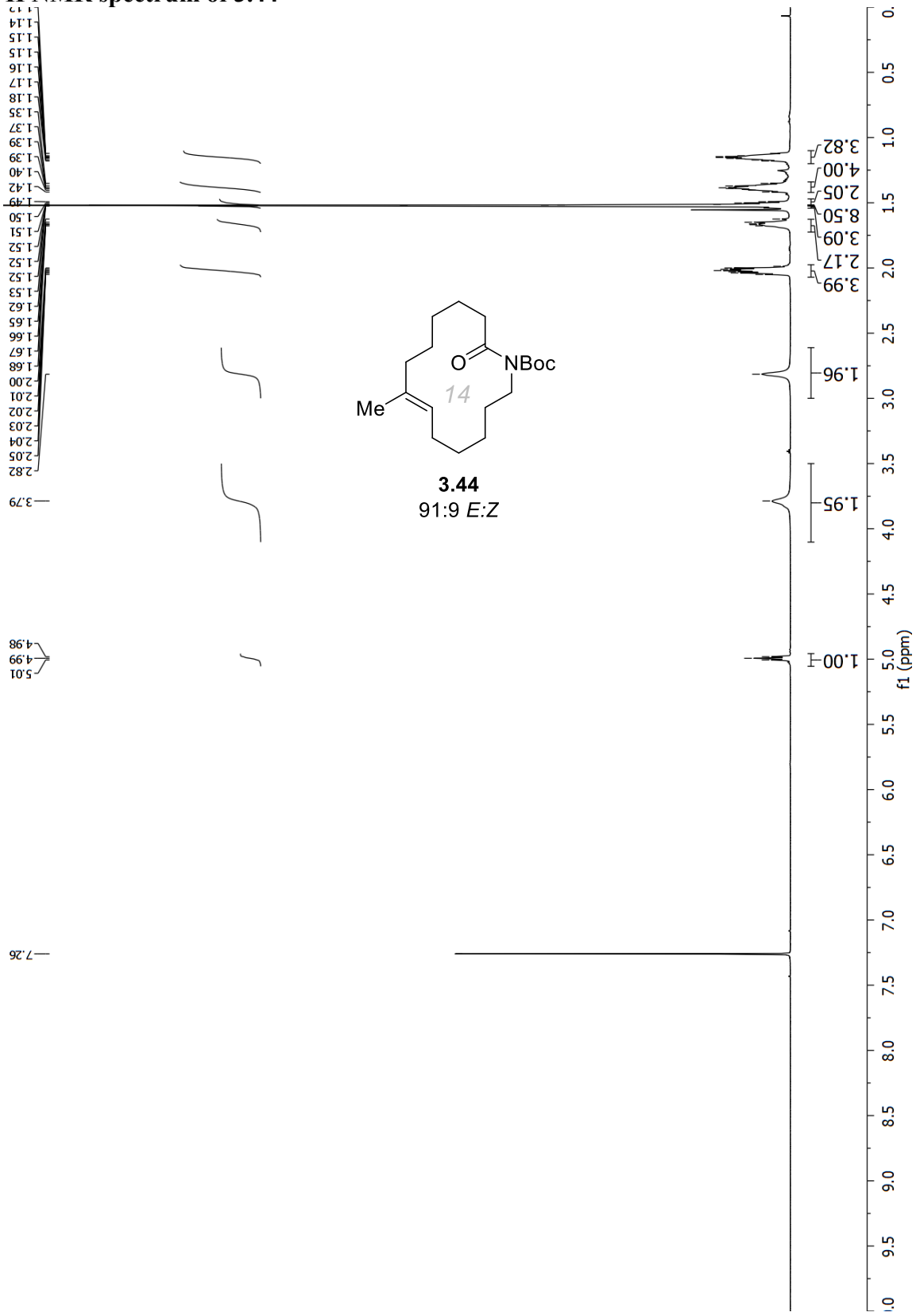


^{13}C NMR spectrum of 3.42

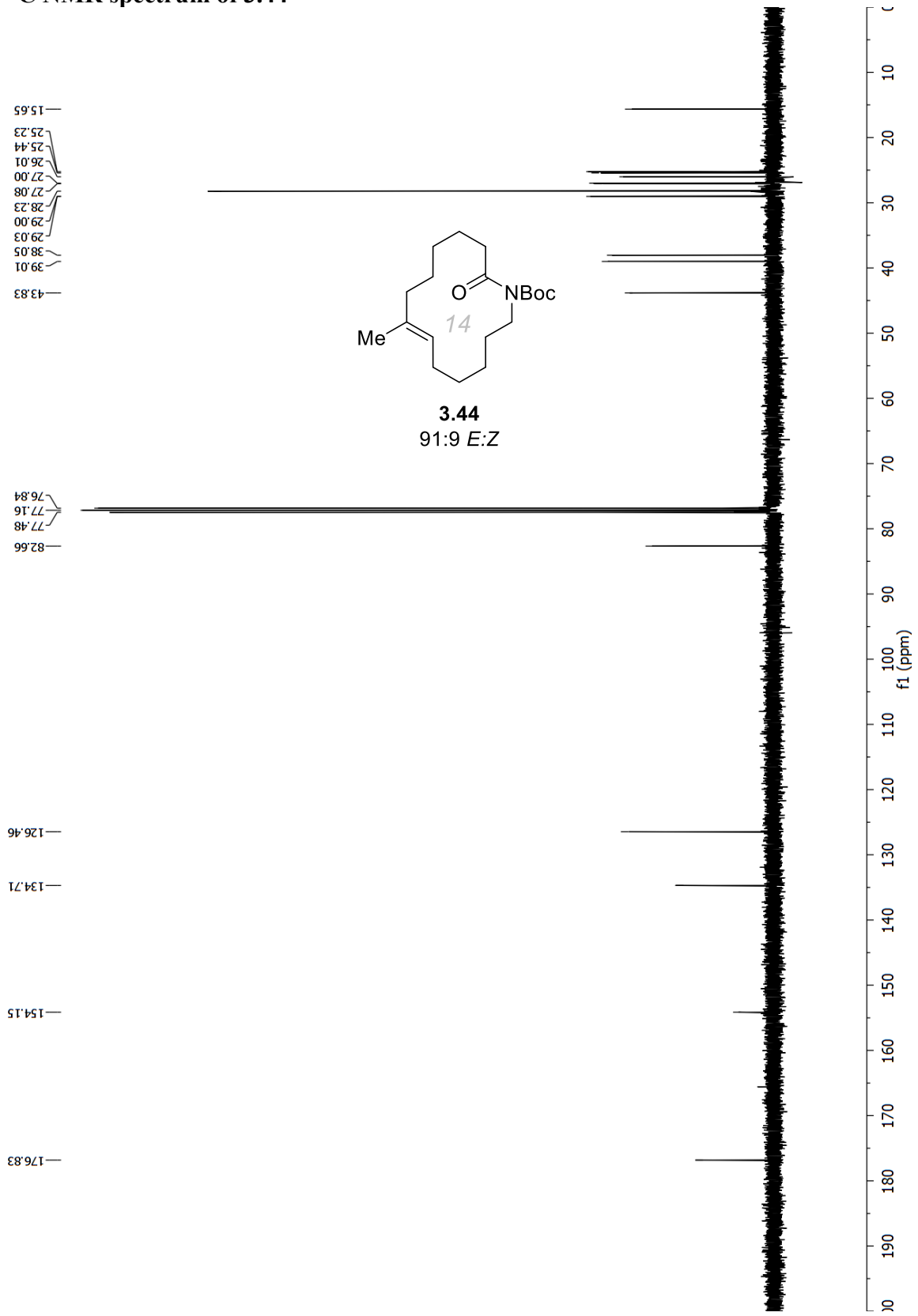


3.42
95:5 *E:Z*

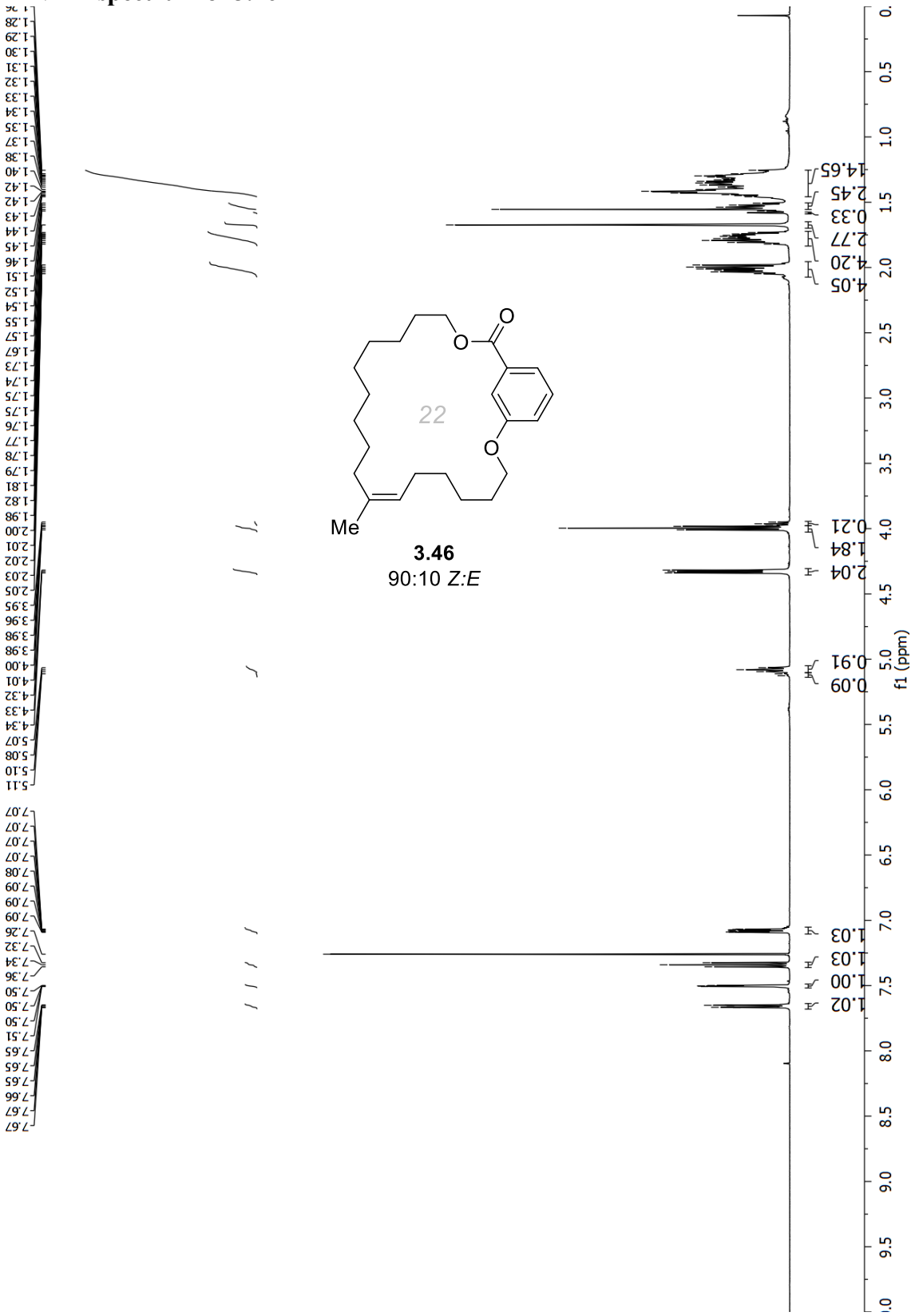
^{1}H NMR spectrum of 3.44



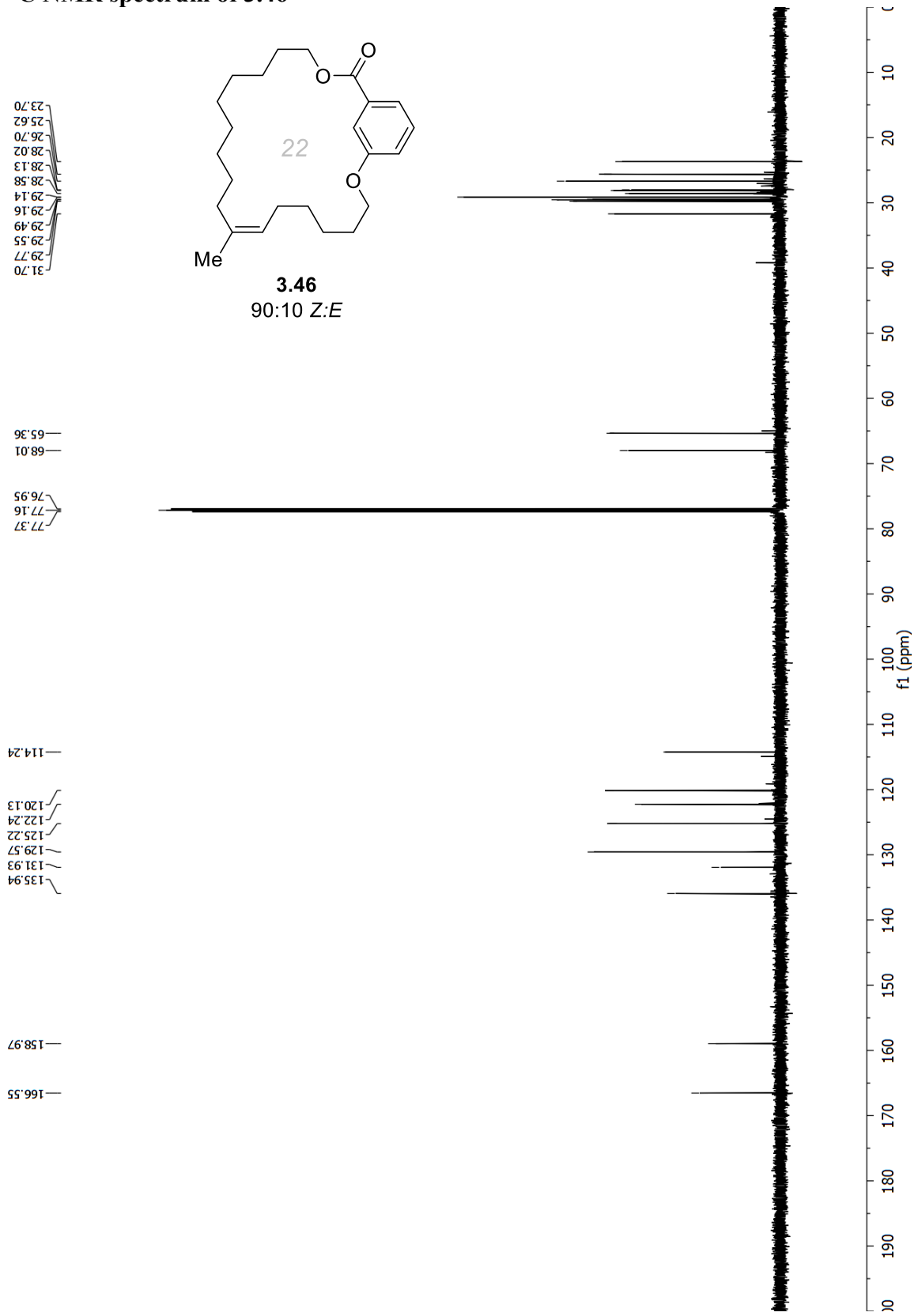
^{13}C NMR spectrum of 3.44



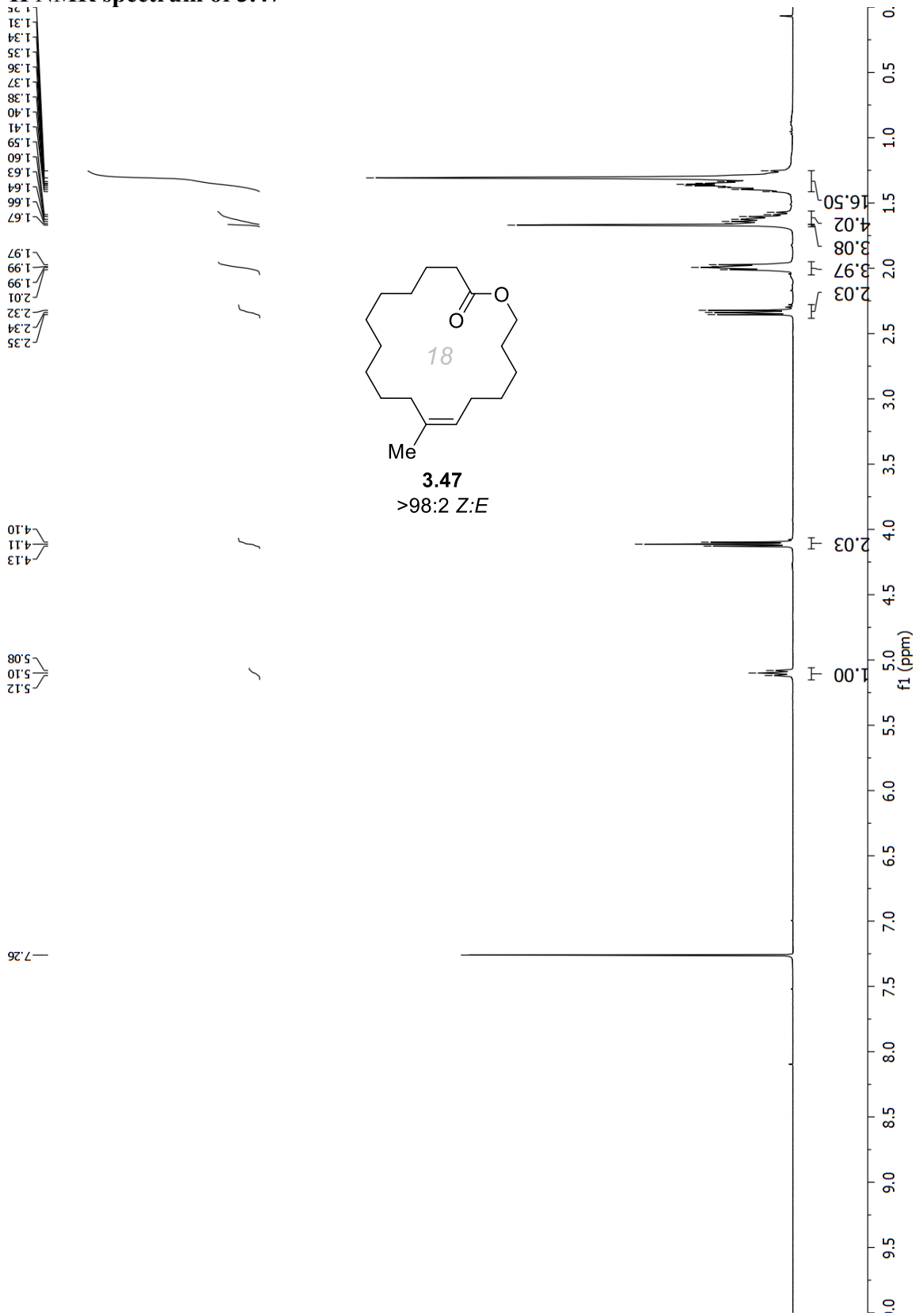
^{1}H NMR spectrum of 3.46



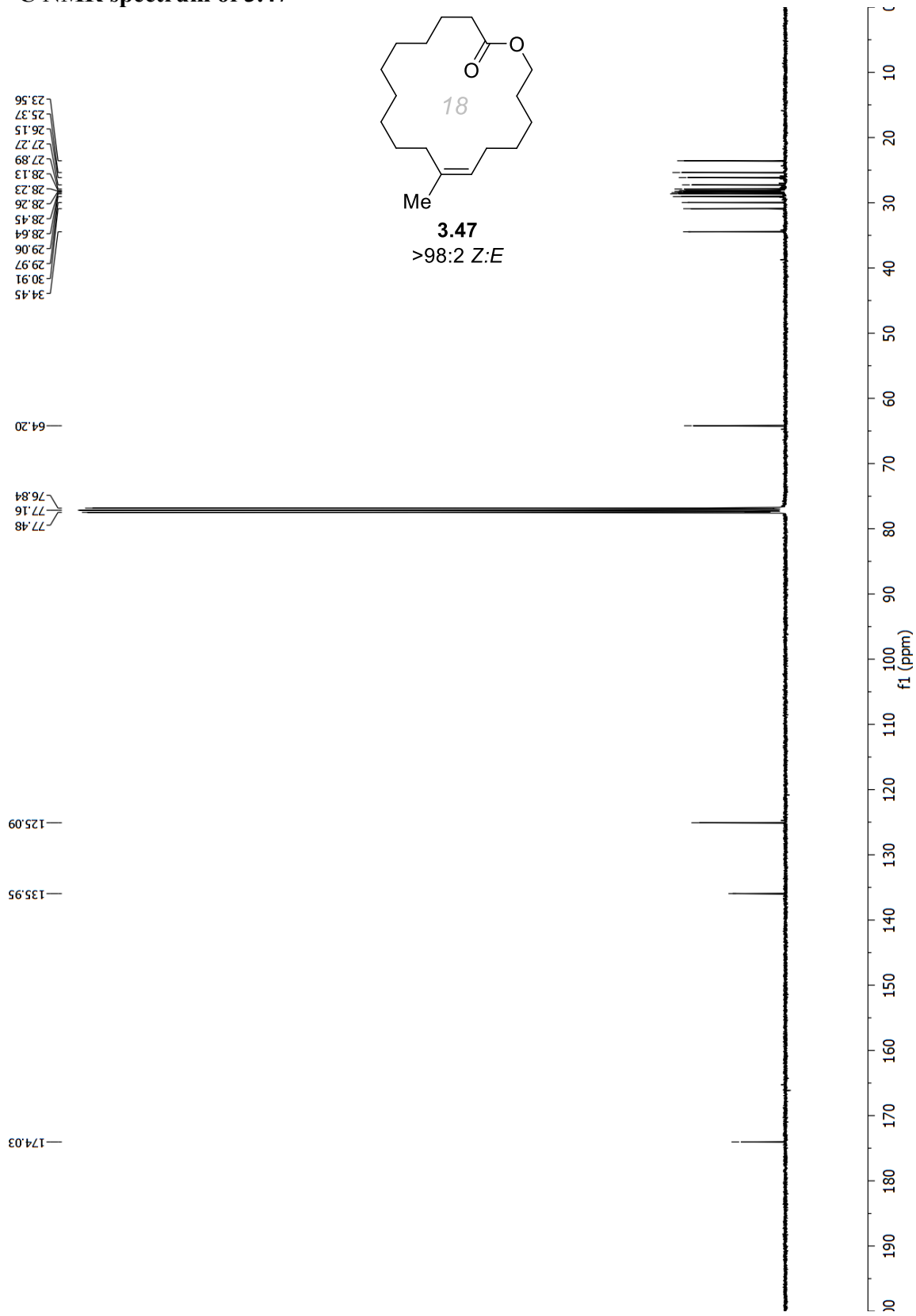
^{13}C NMR spectrum of 3.46



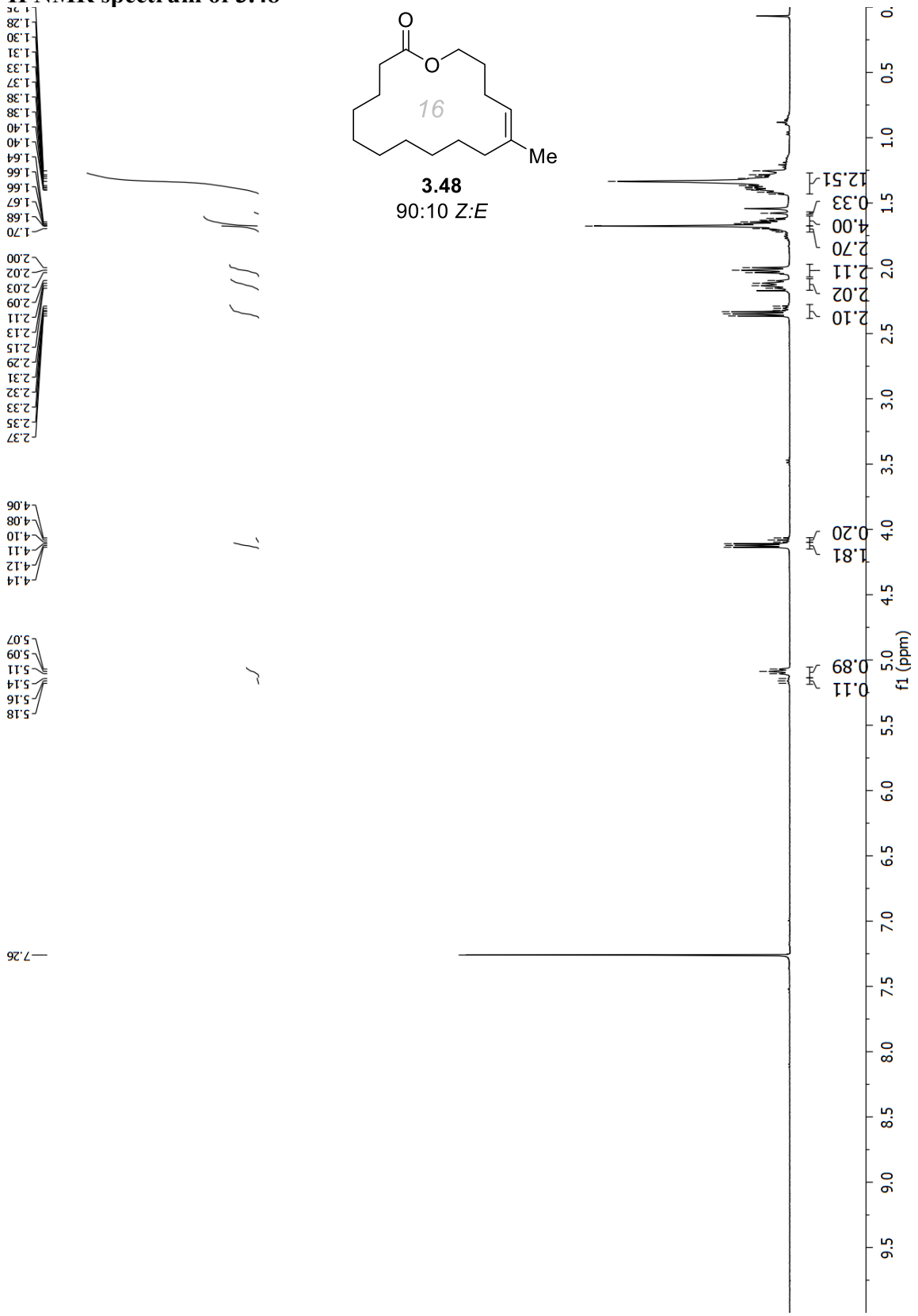
^{1}H NMR spectrum of 3.47



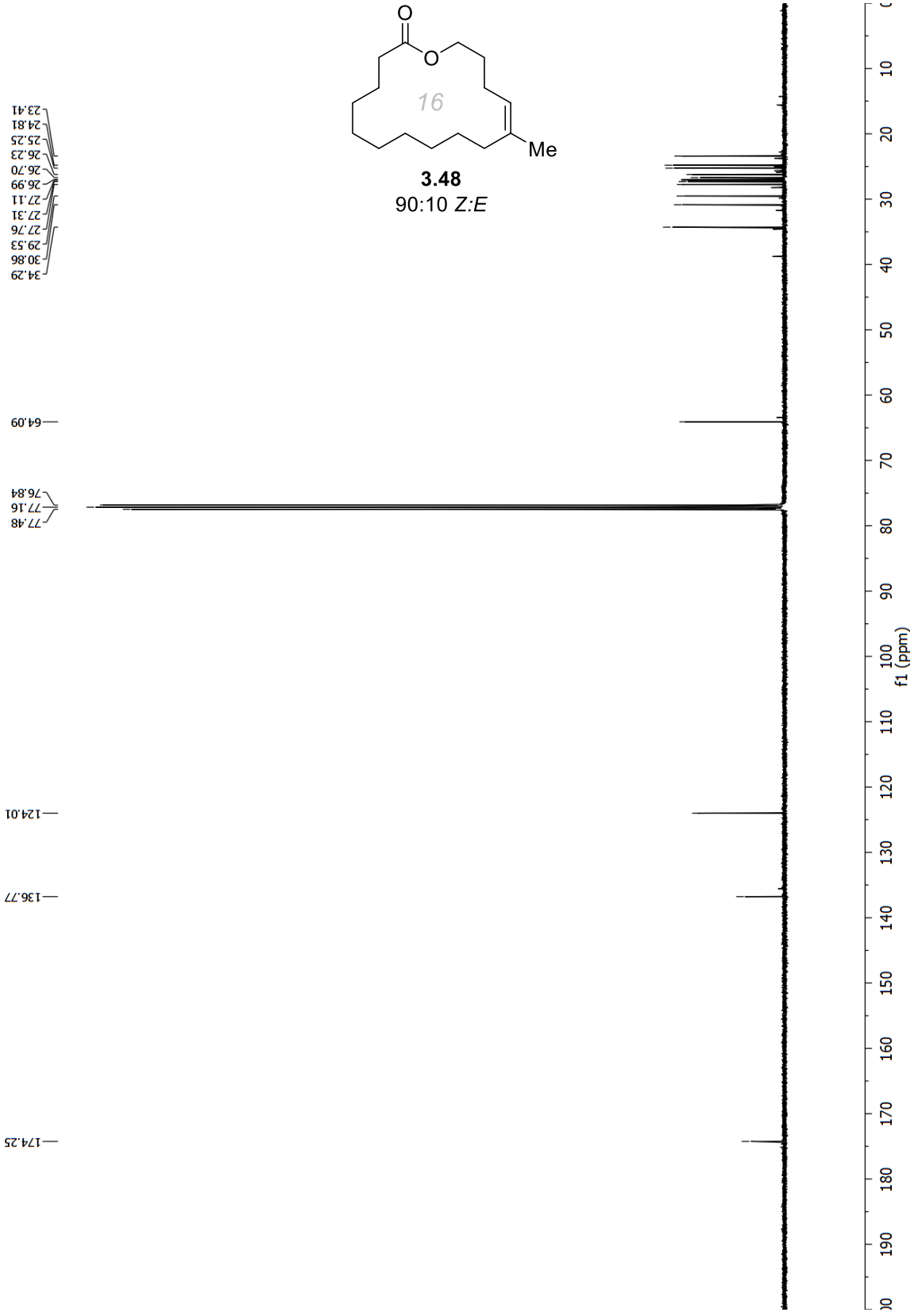
^{13}C NMR spectrum of 3.47



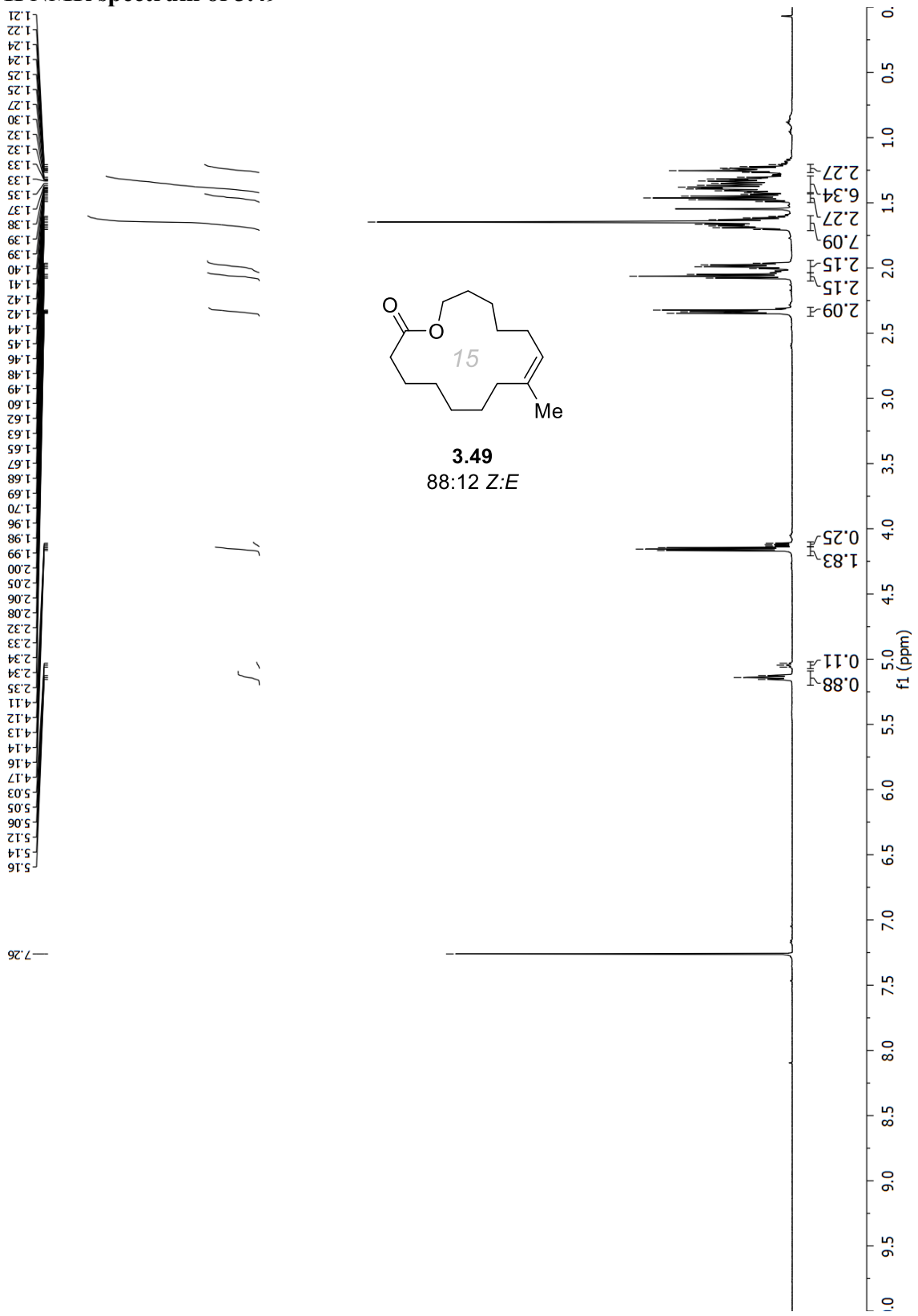
^{1}H NMR spectrum of 3.48



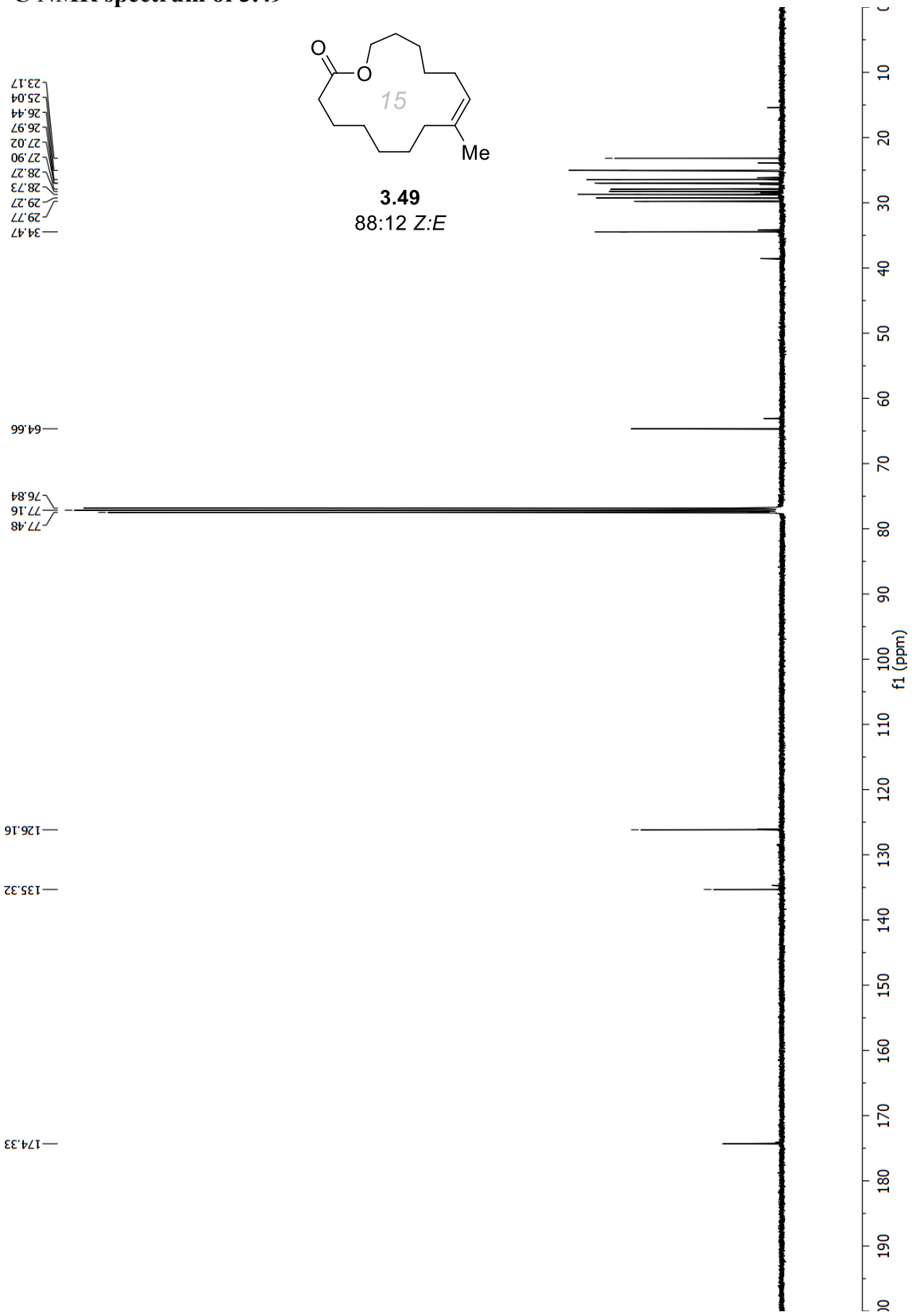
^{13}C NMR spectrum of 3.48



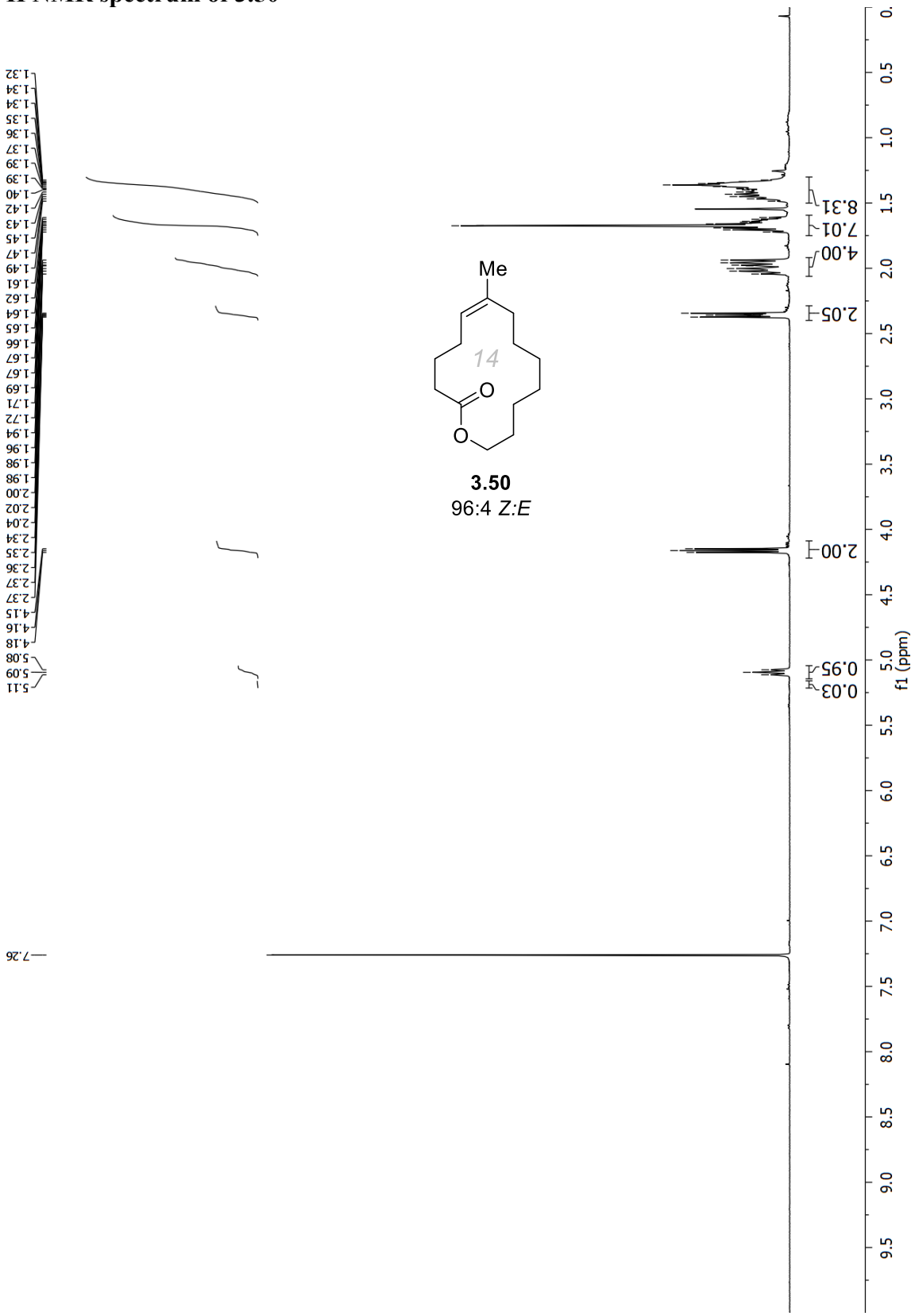
^{1}H NMR spectrum of 3.49



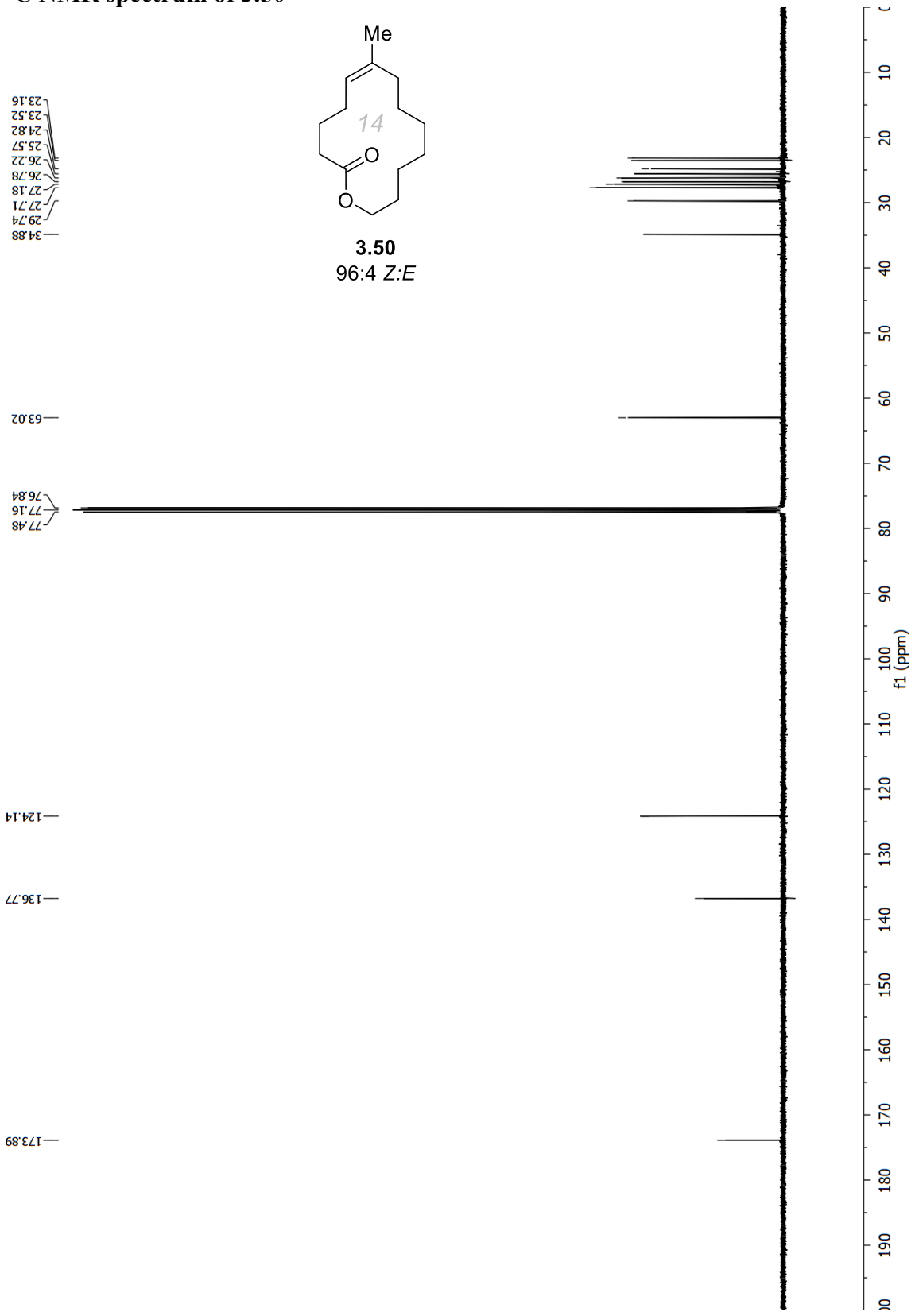
^{13}C NMR spectrum of 3.49



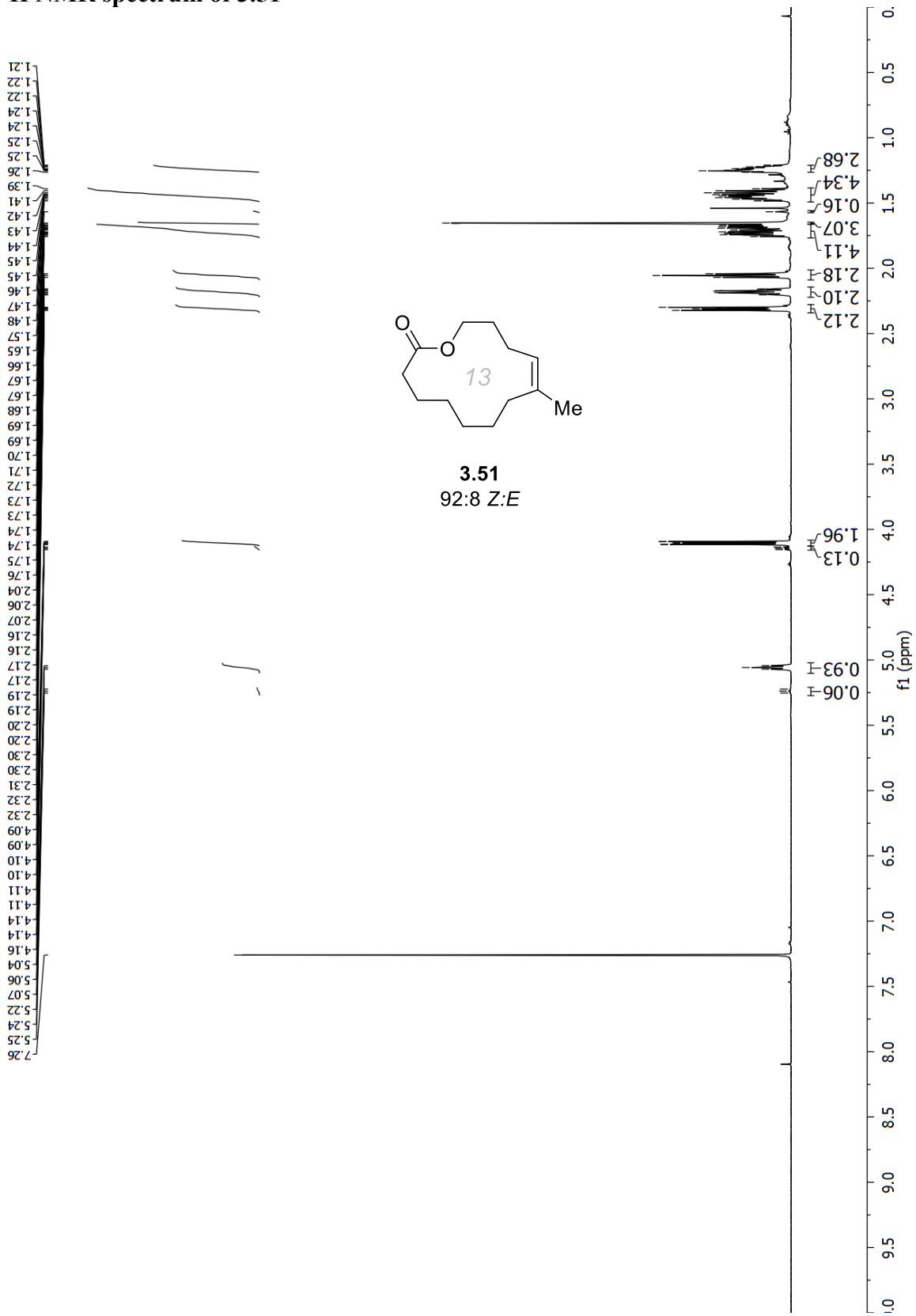
^{1}H NMR spectrum of 3.50



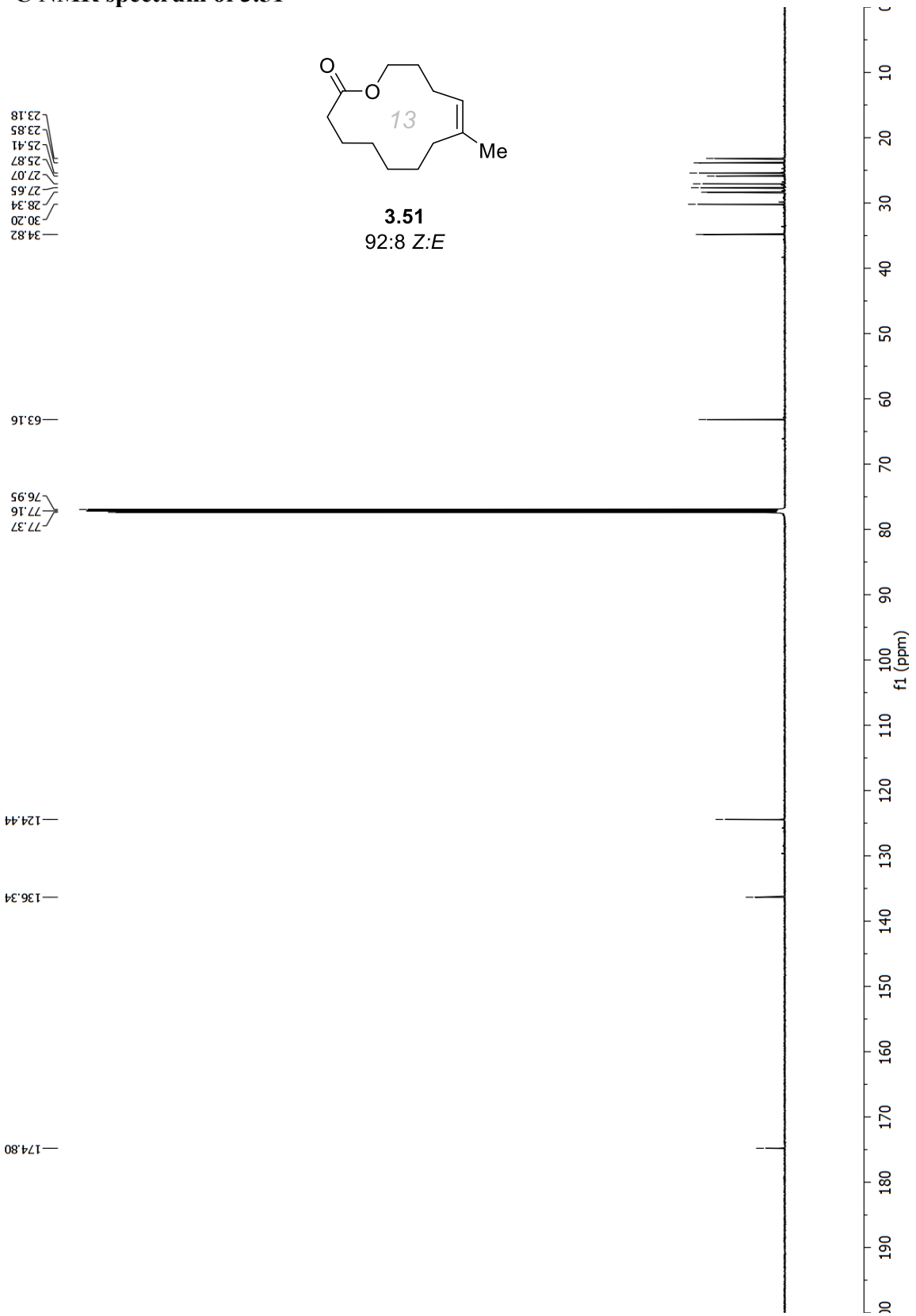
^{13}C NMR spectrum of 3.50



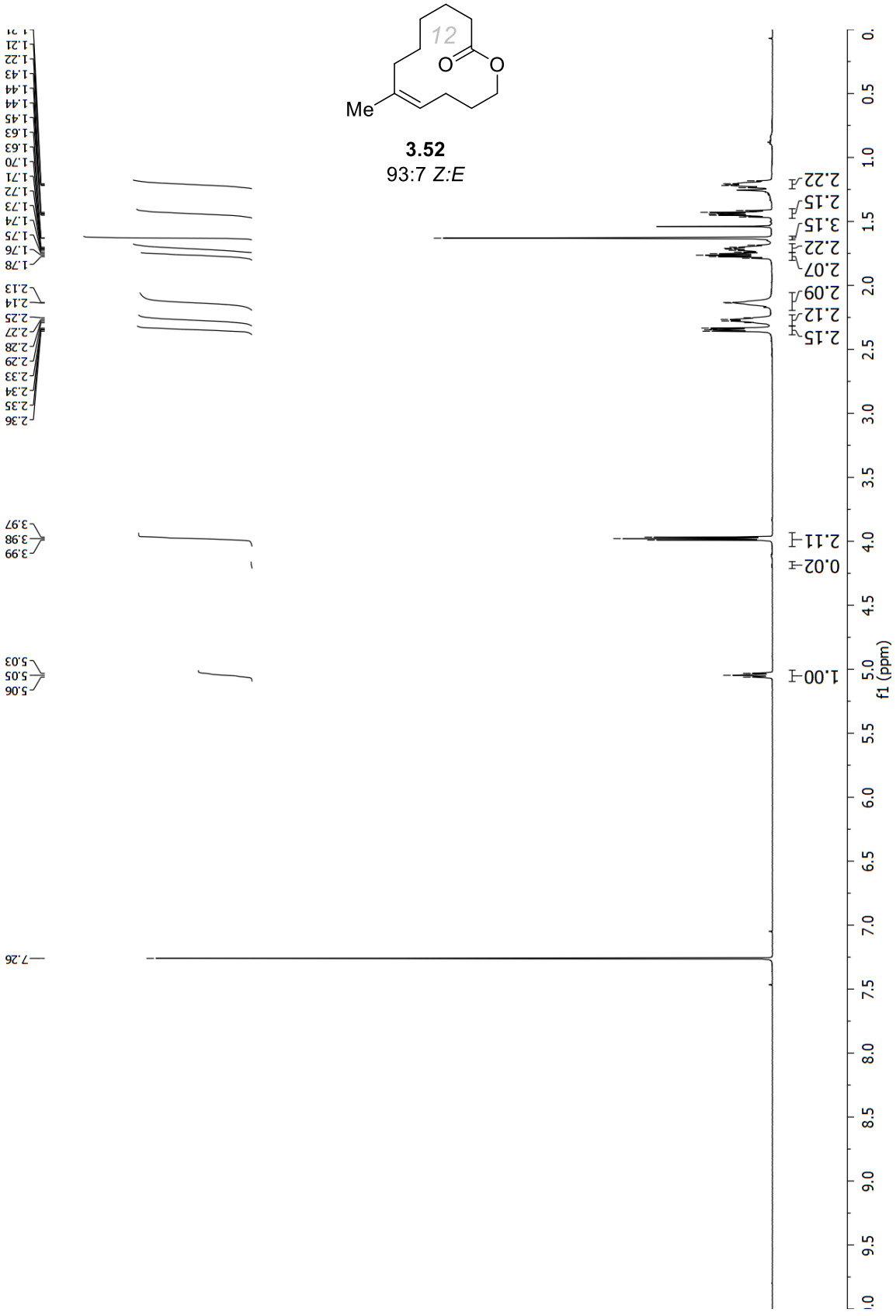
^{1}H NMR spectrum of 3.51



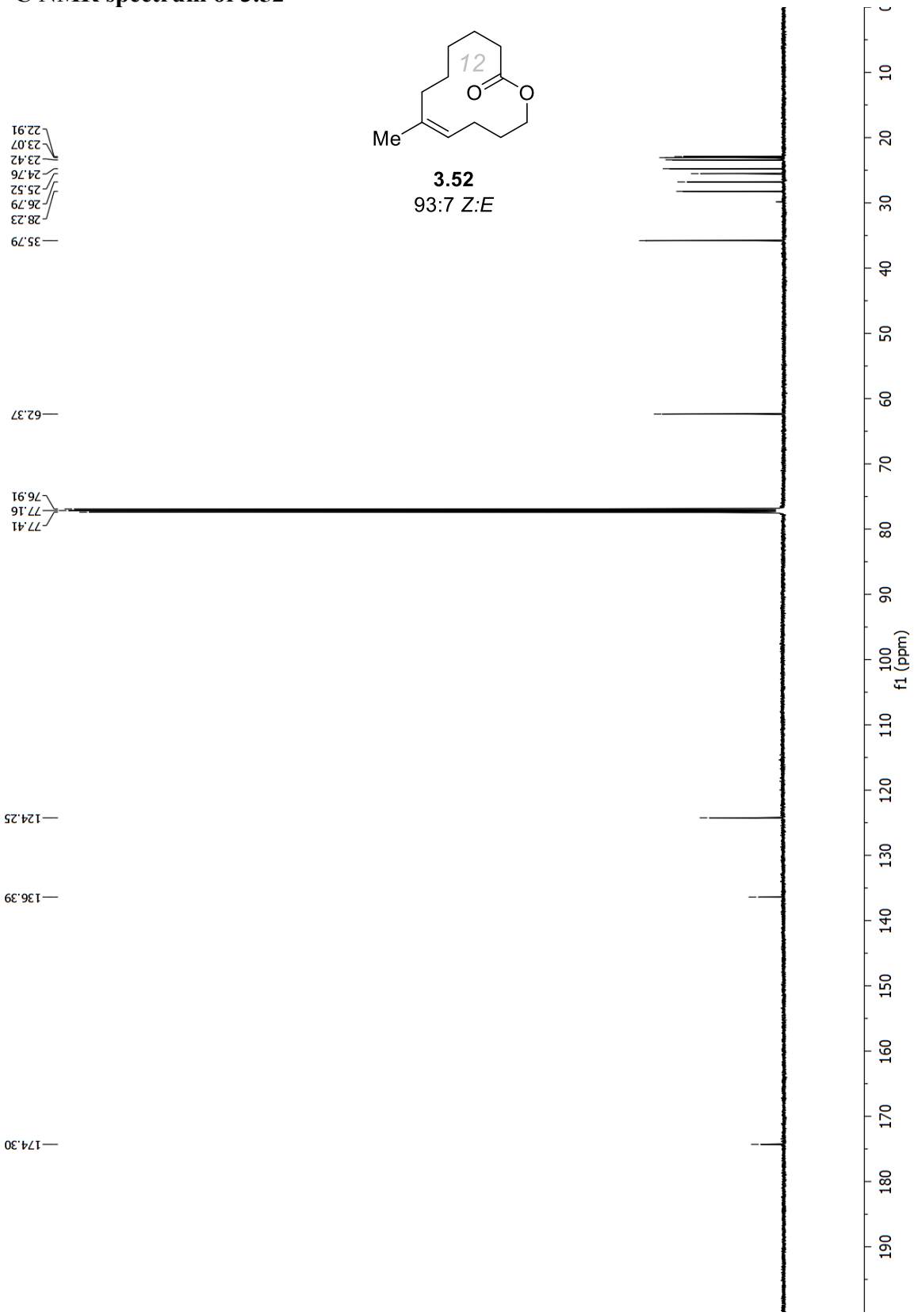
^{13}C NMR spectrum of 3.51



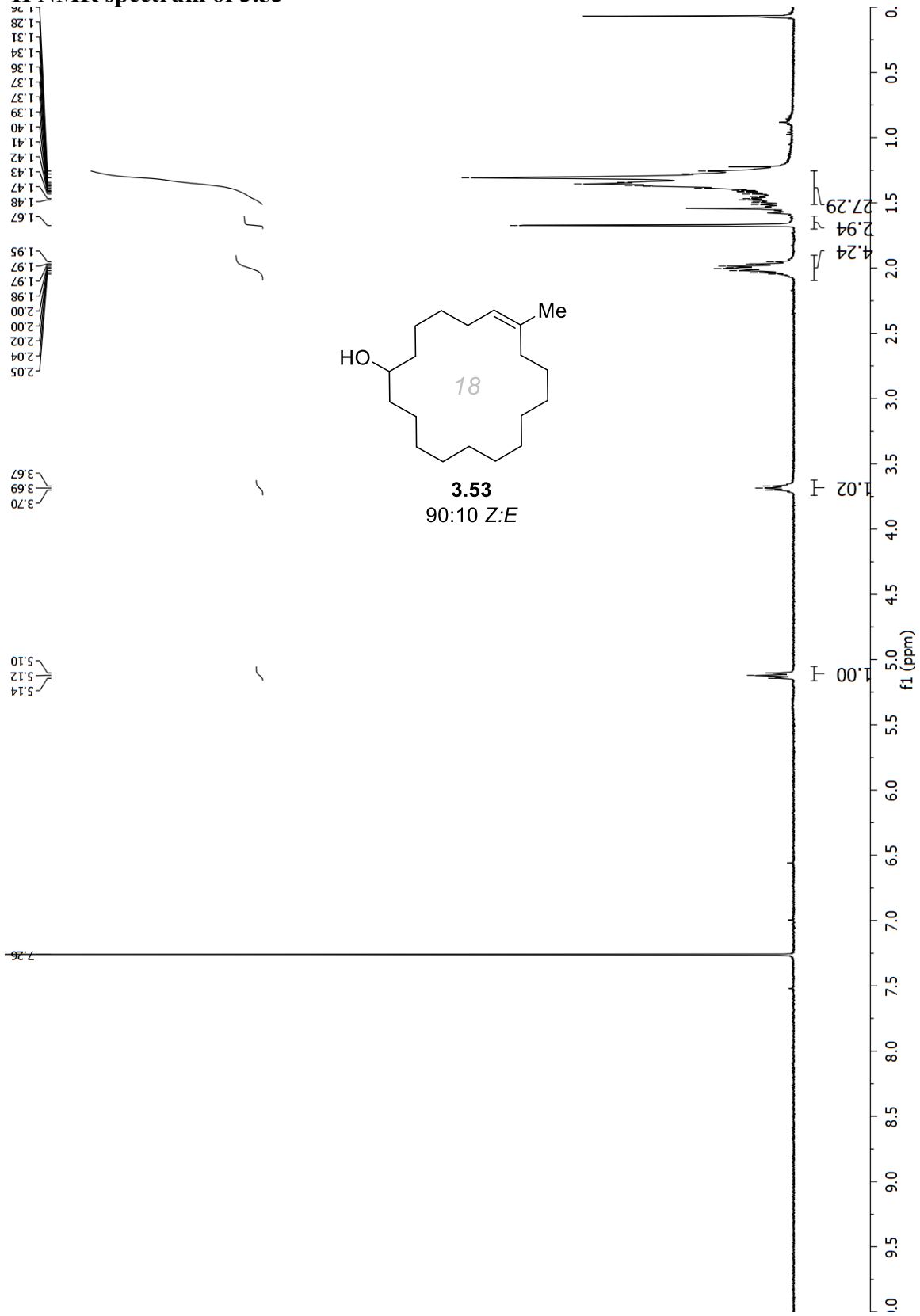
^{1}H NMR spectrum of 3.52



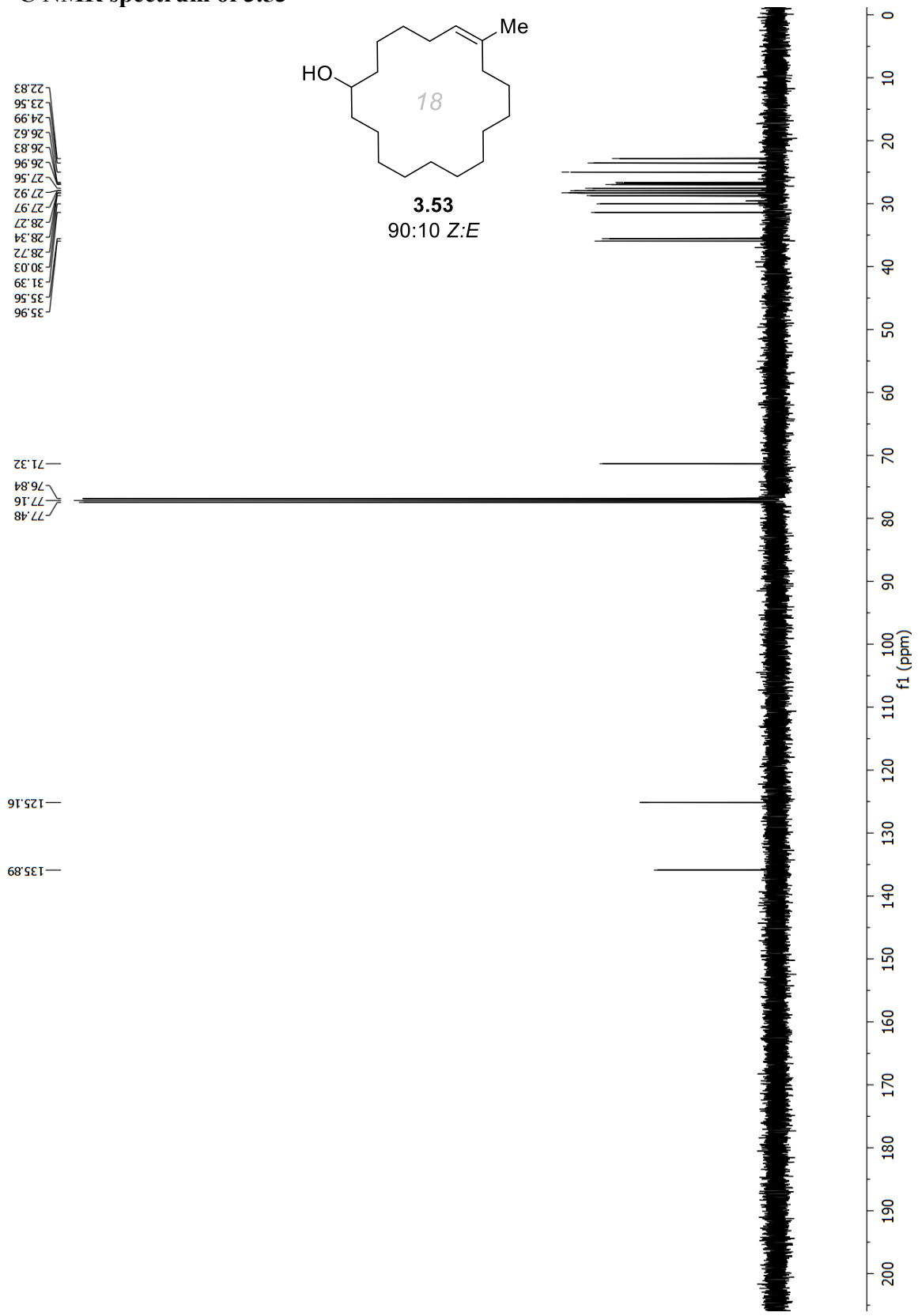
^{13}C NMR spectrum of 3.52



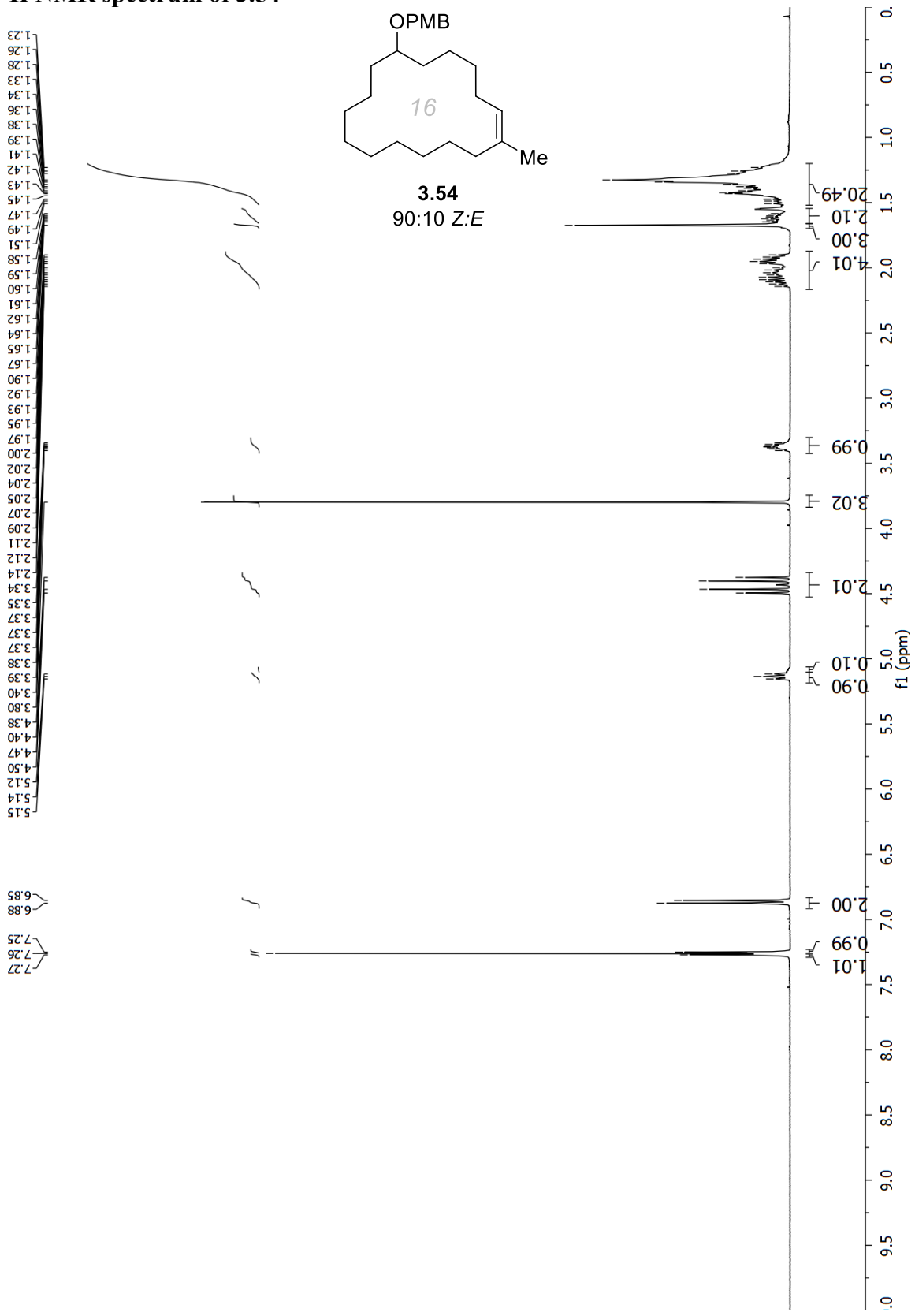
^{1}H NMR spectrum of 3.53



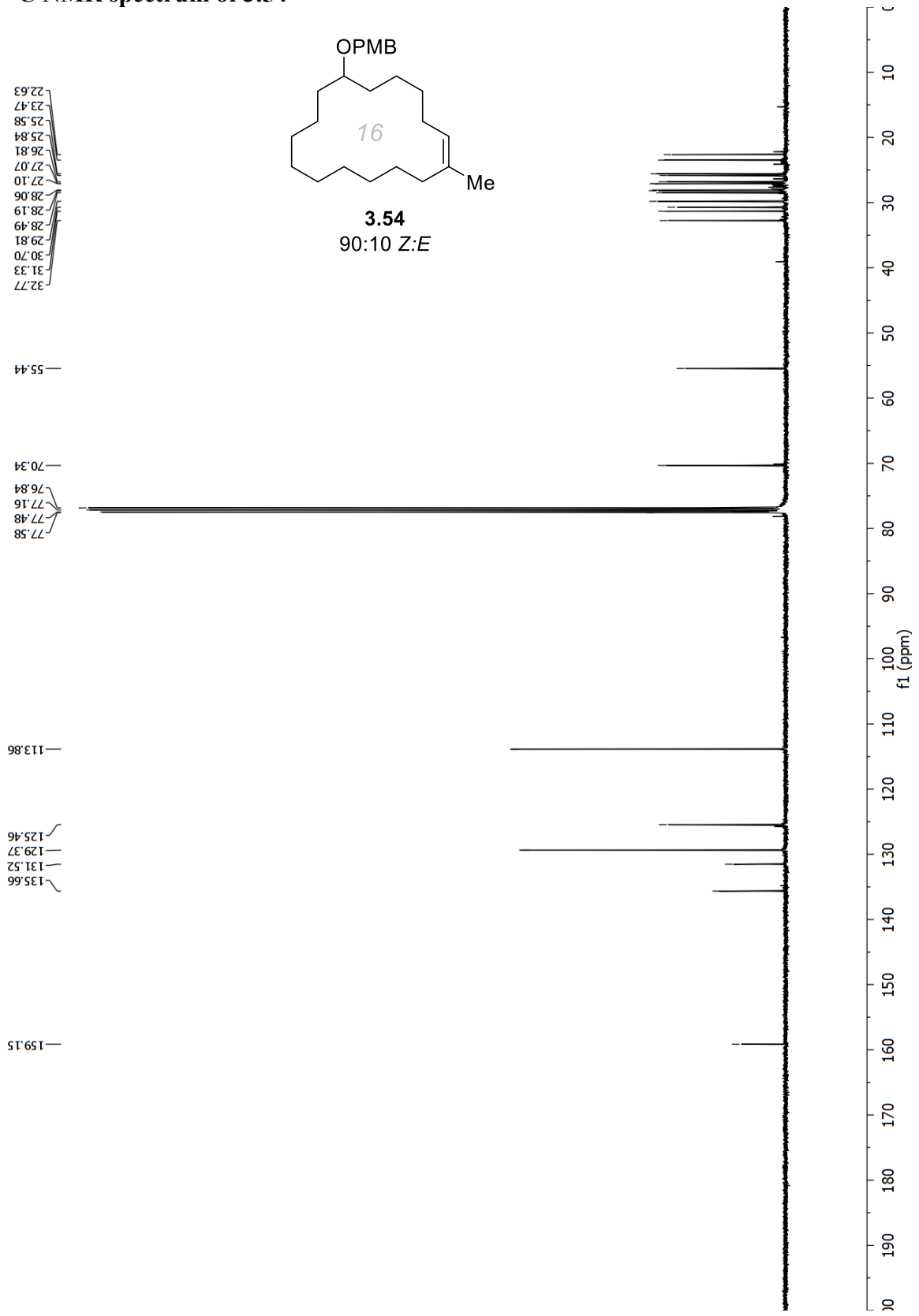
^{13}C NMR spectrum of 3.53



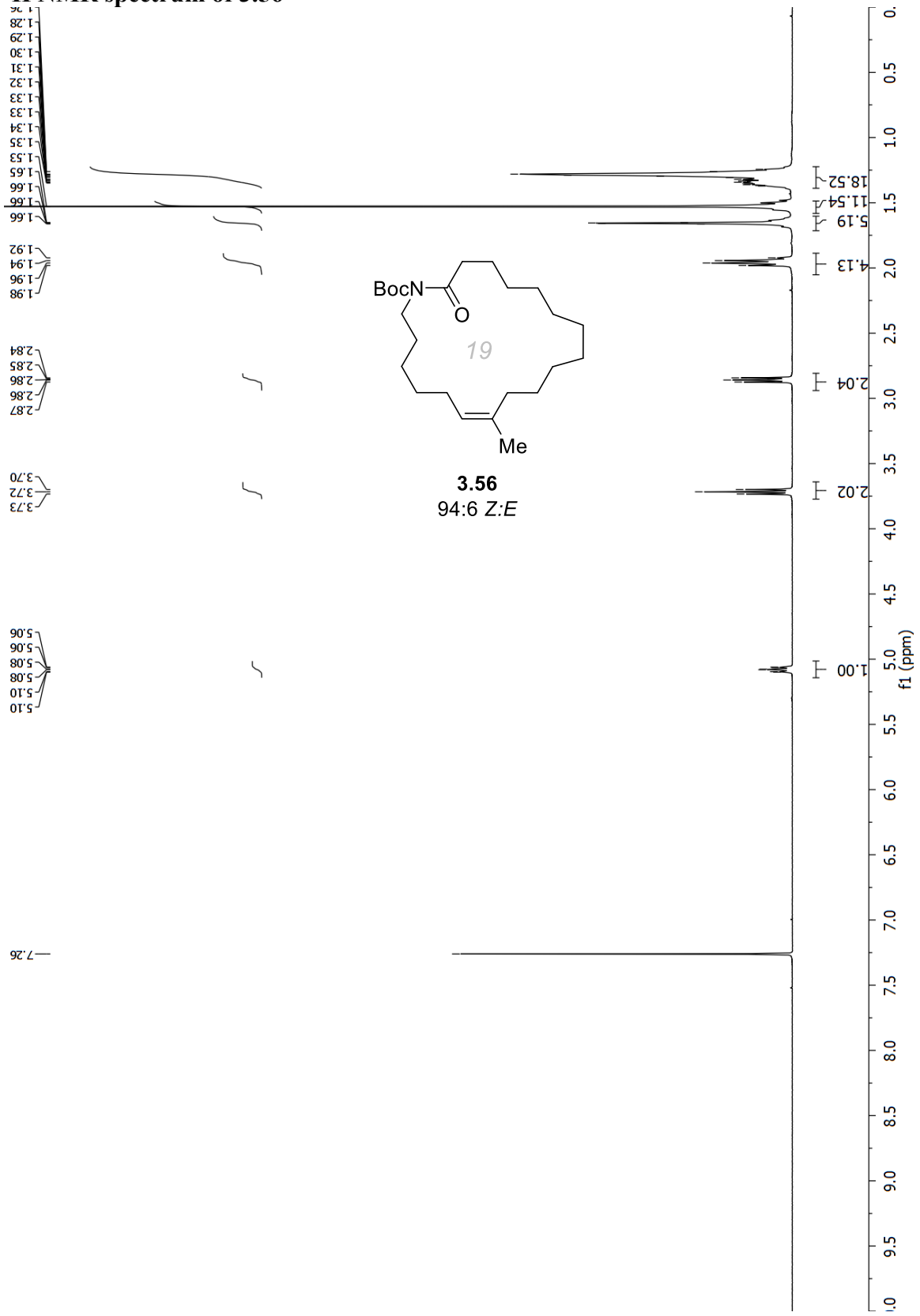
^{1}H NMR spectrum of 3.54



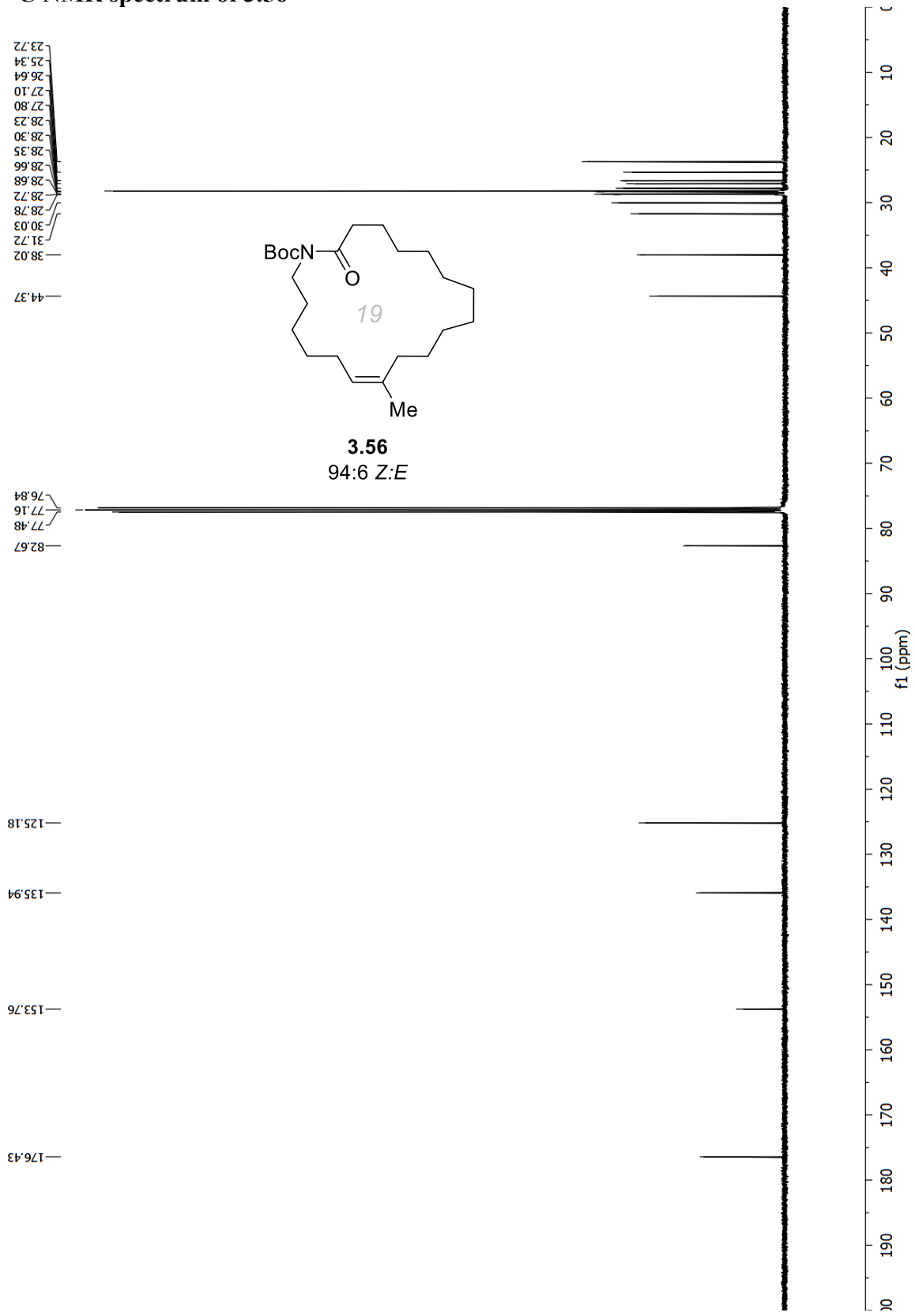
^{13}C NMR spectrum of 3.54



^{1}H NMR spectrum of 3.56

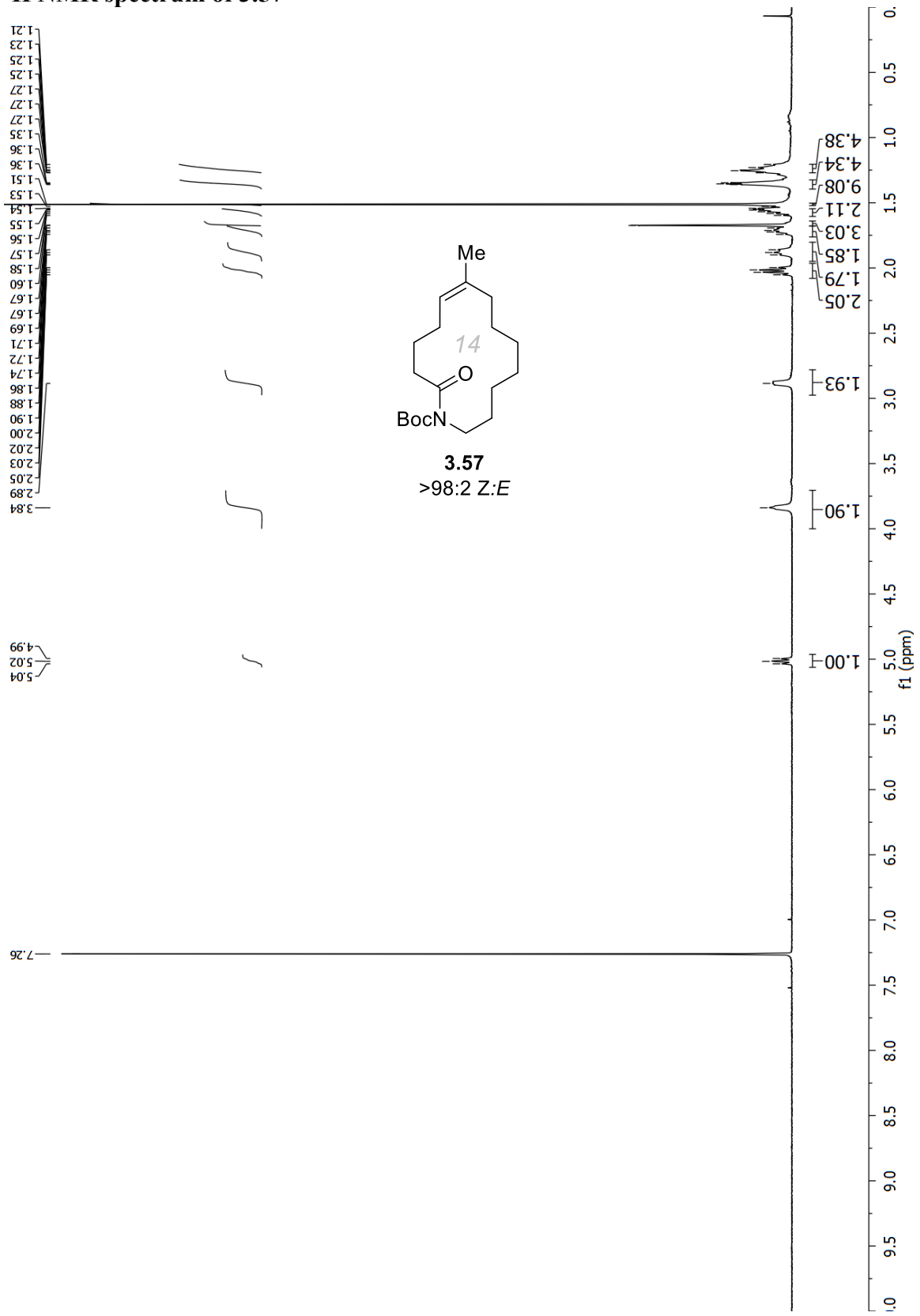


^{13}C NMR spectrum of 3.56

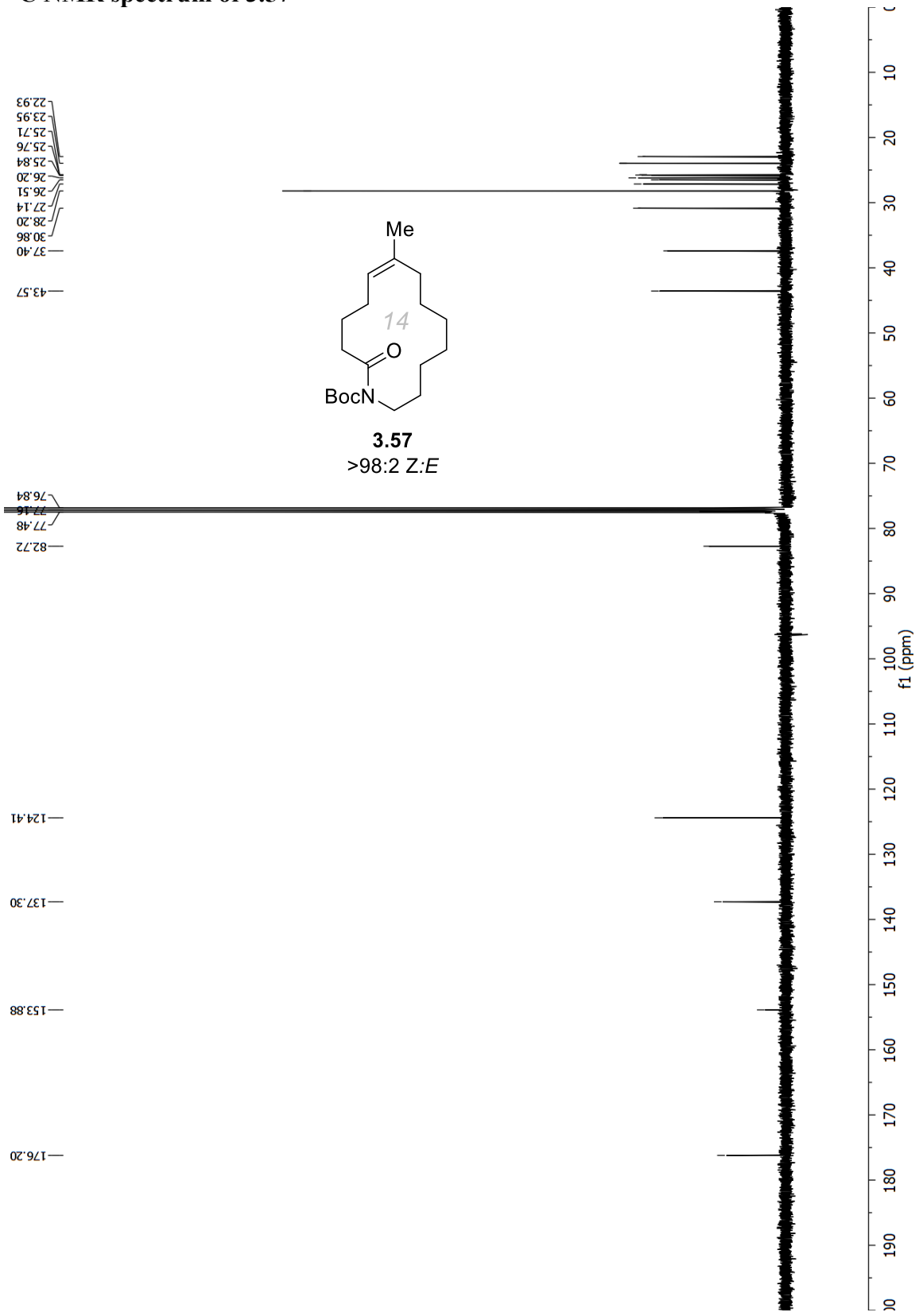


3.56
94:6 *Z:E*

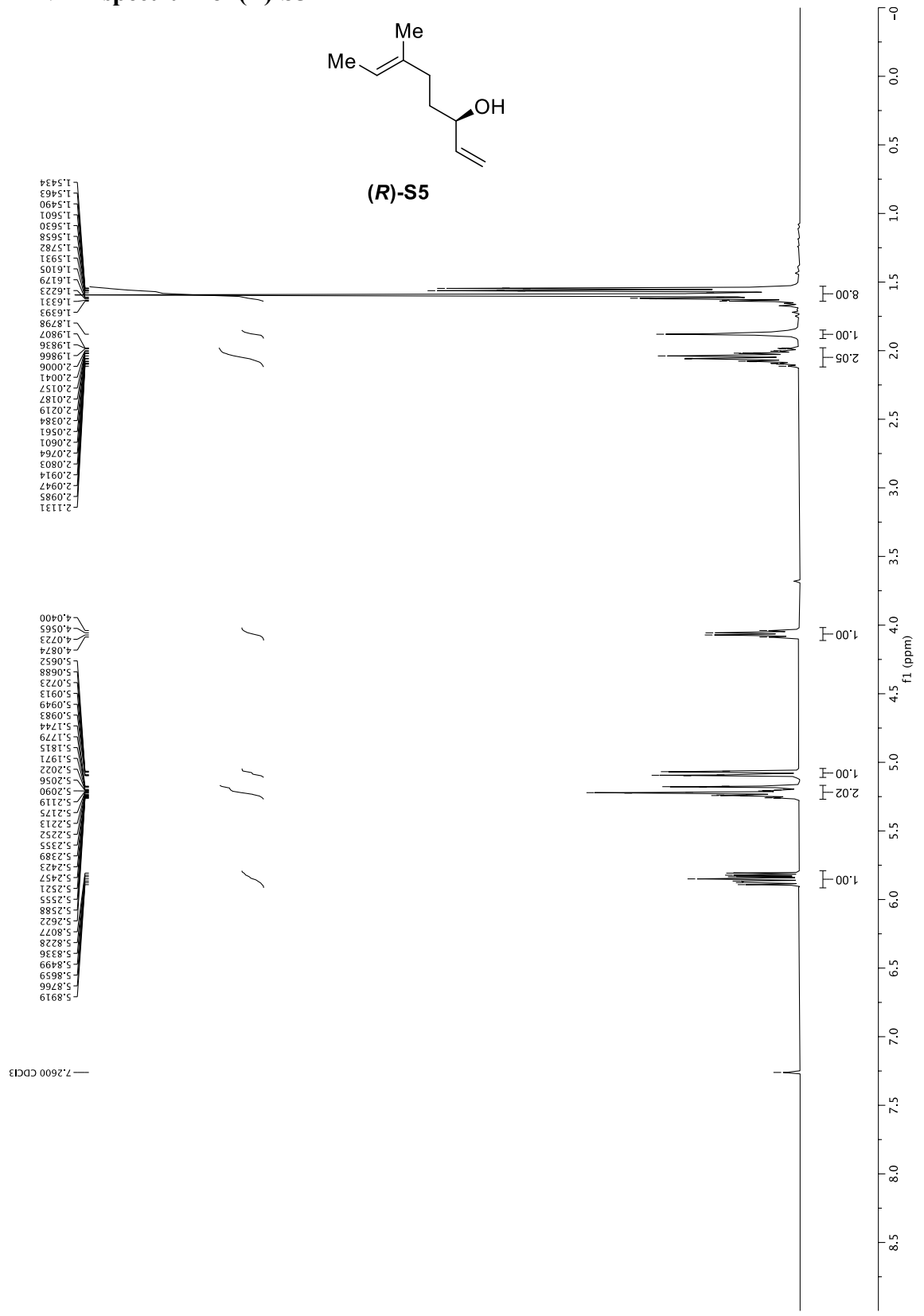
^{1}H NMR spectrum of 3.57



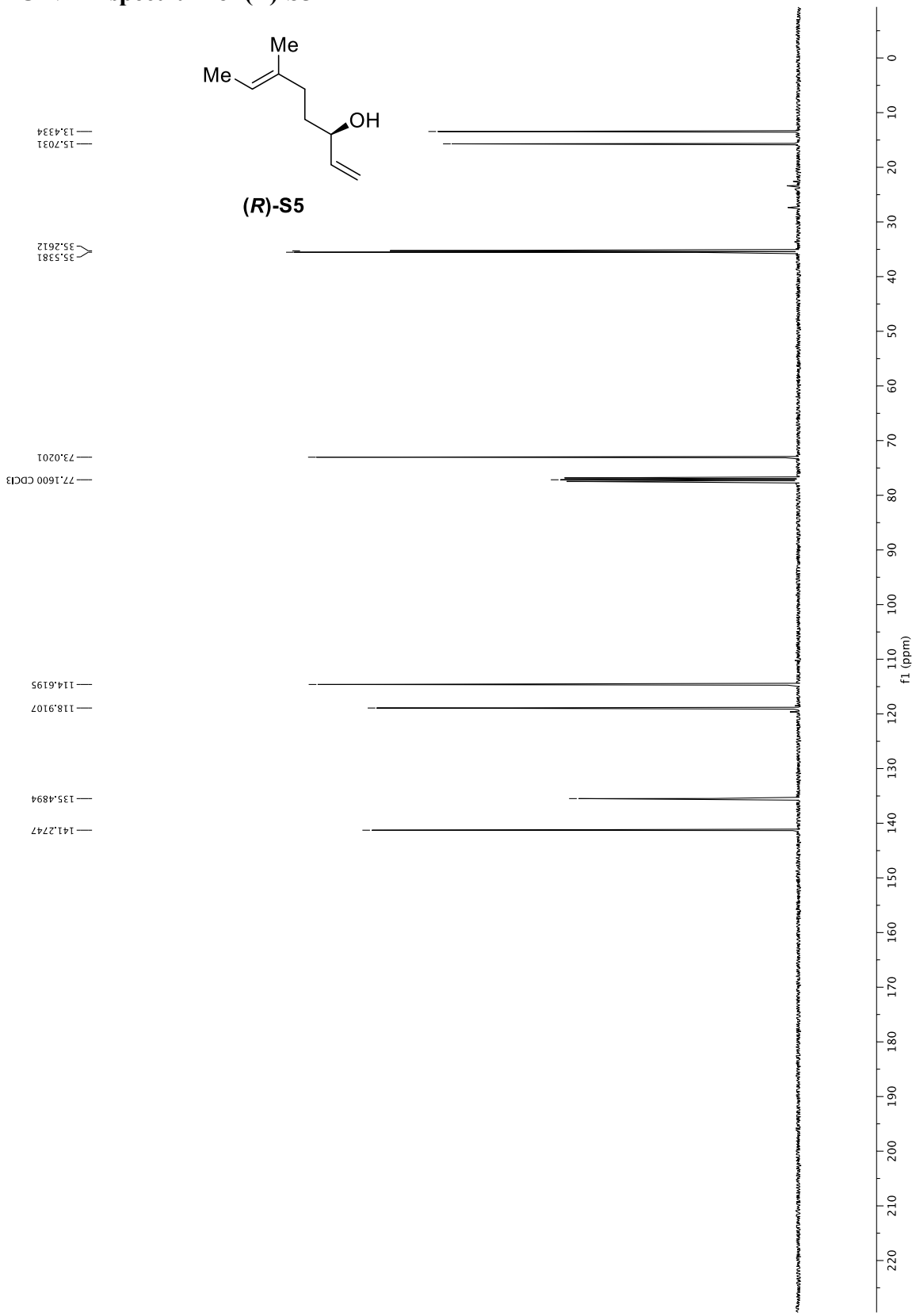
^{13}C NMR spectrum of 3.57



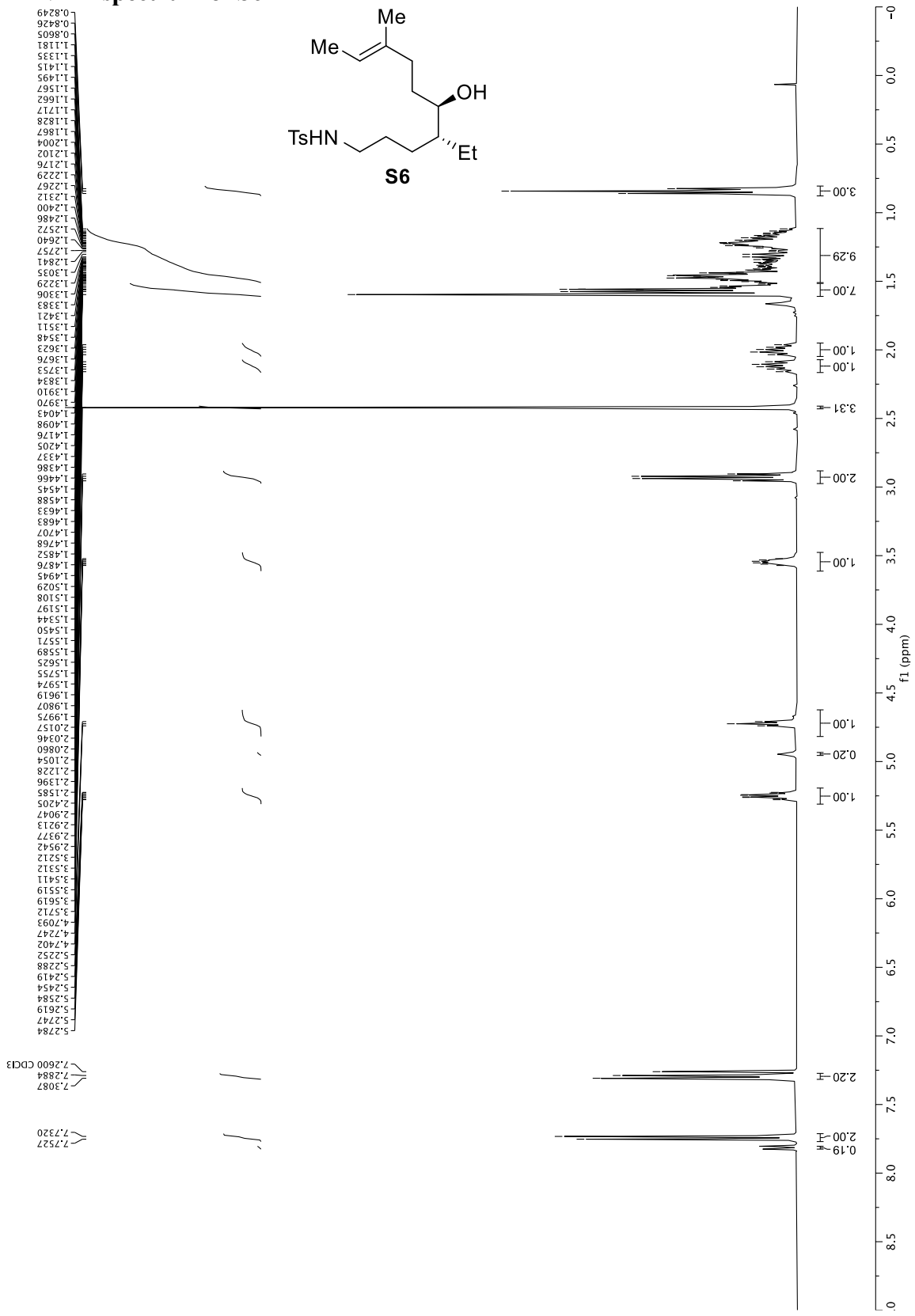
^{1}H NMR spectrum of (*R*)-S5



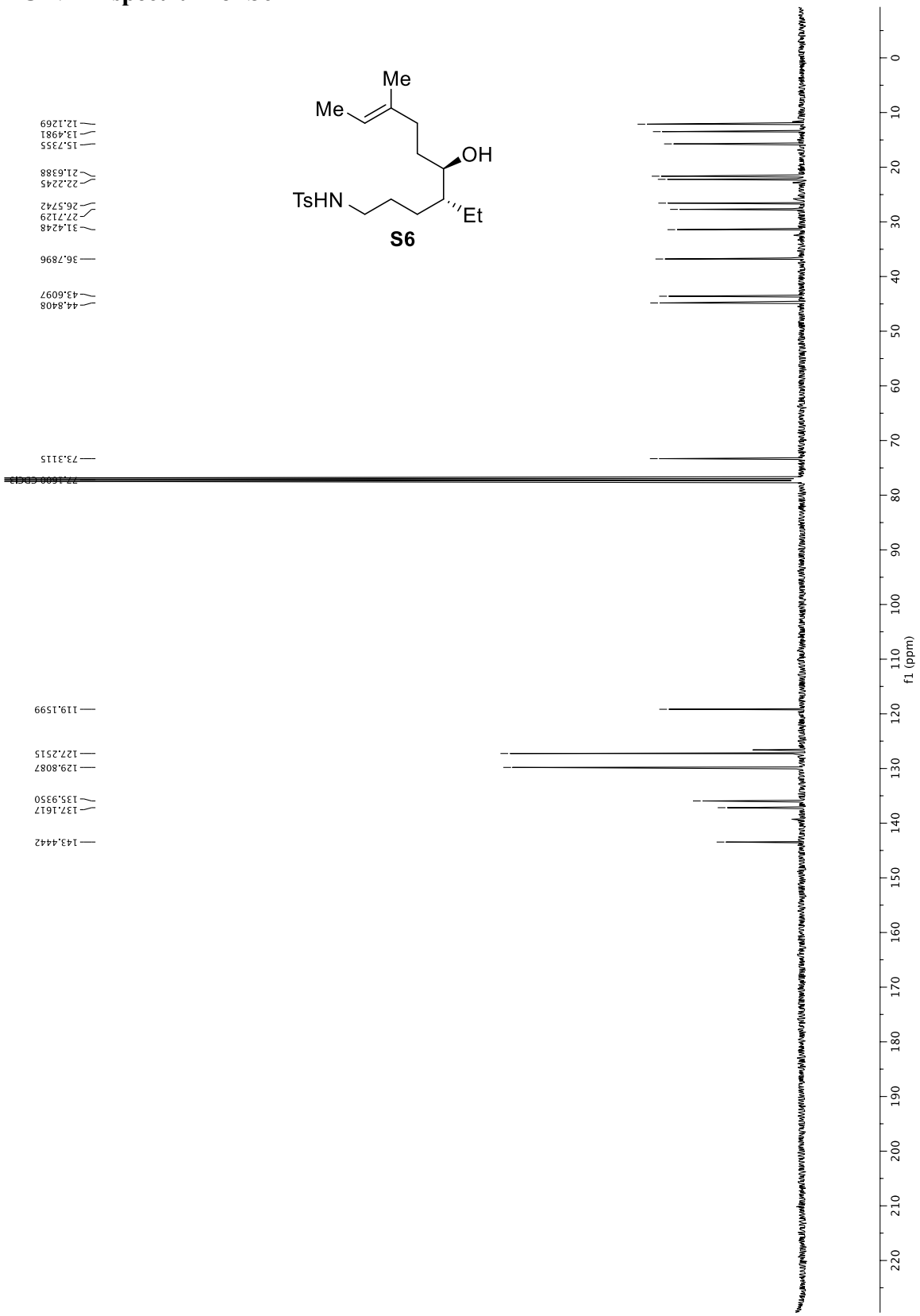
^{13}C NMR spectrum of (*R*)-S5



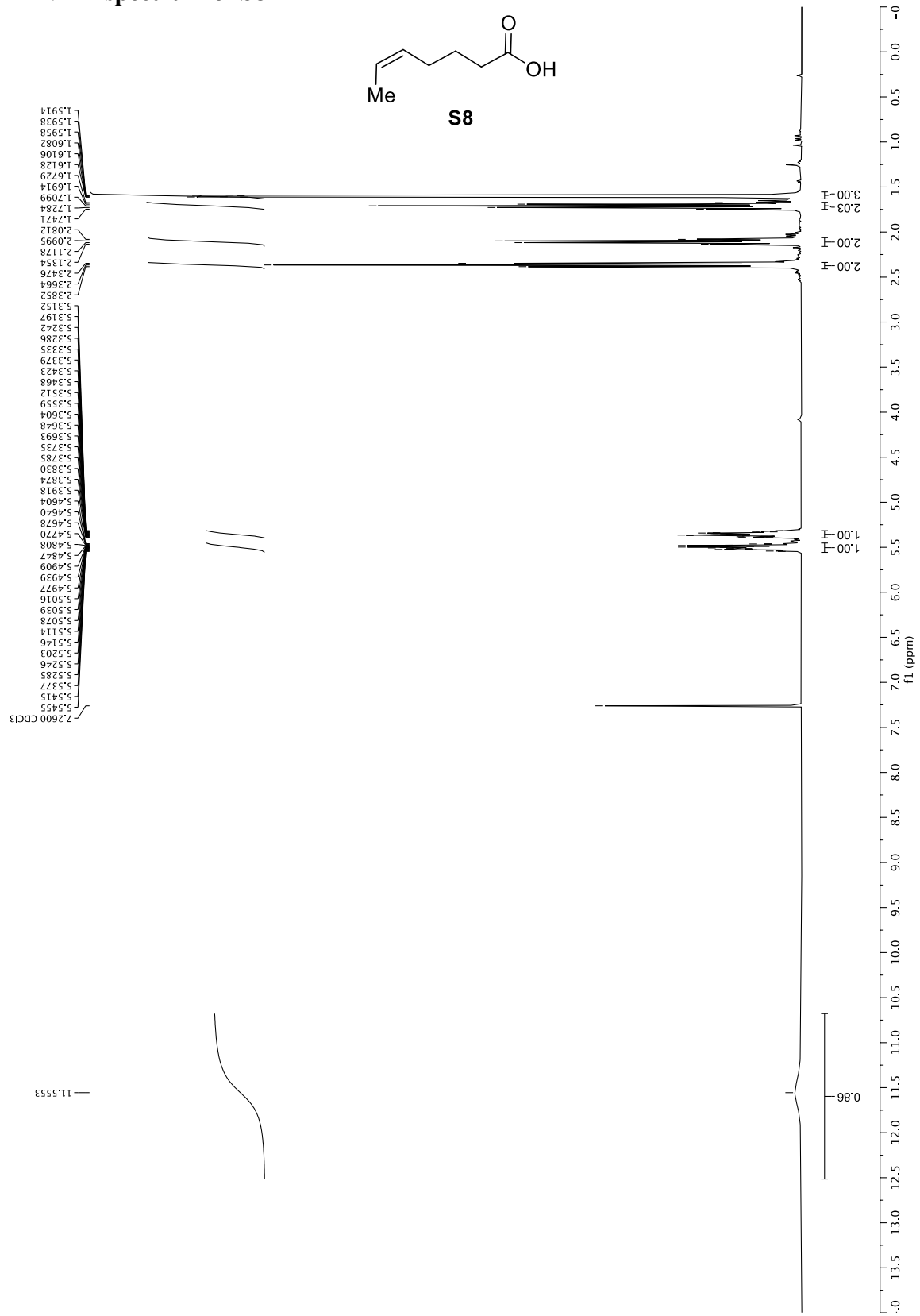
^{1}H NMR spectrum of S6



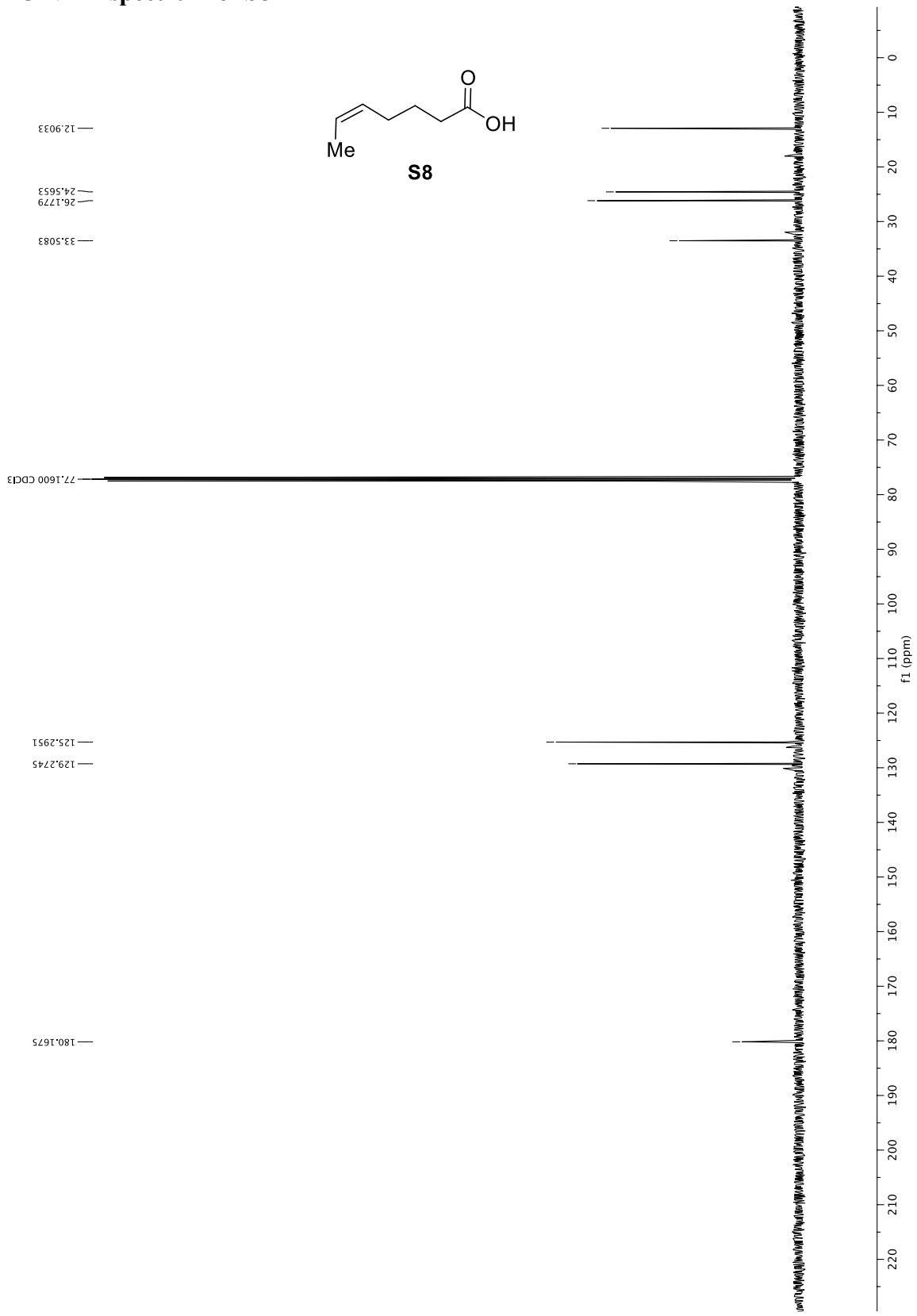
^{13}C NMR spectrum of S6



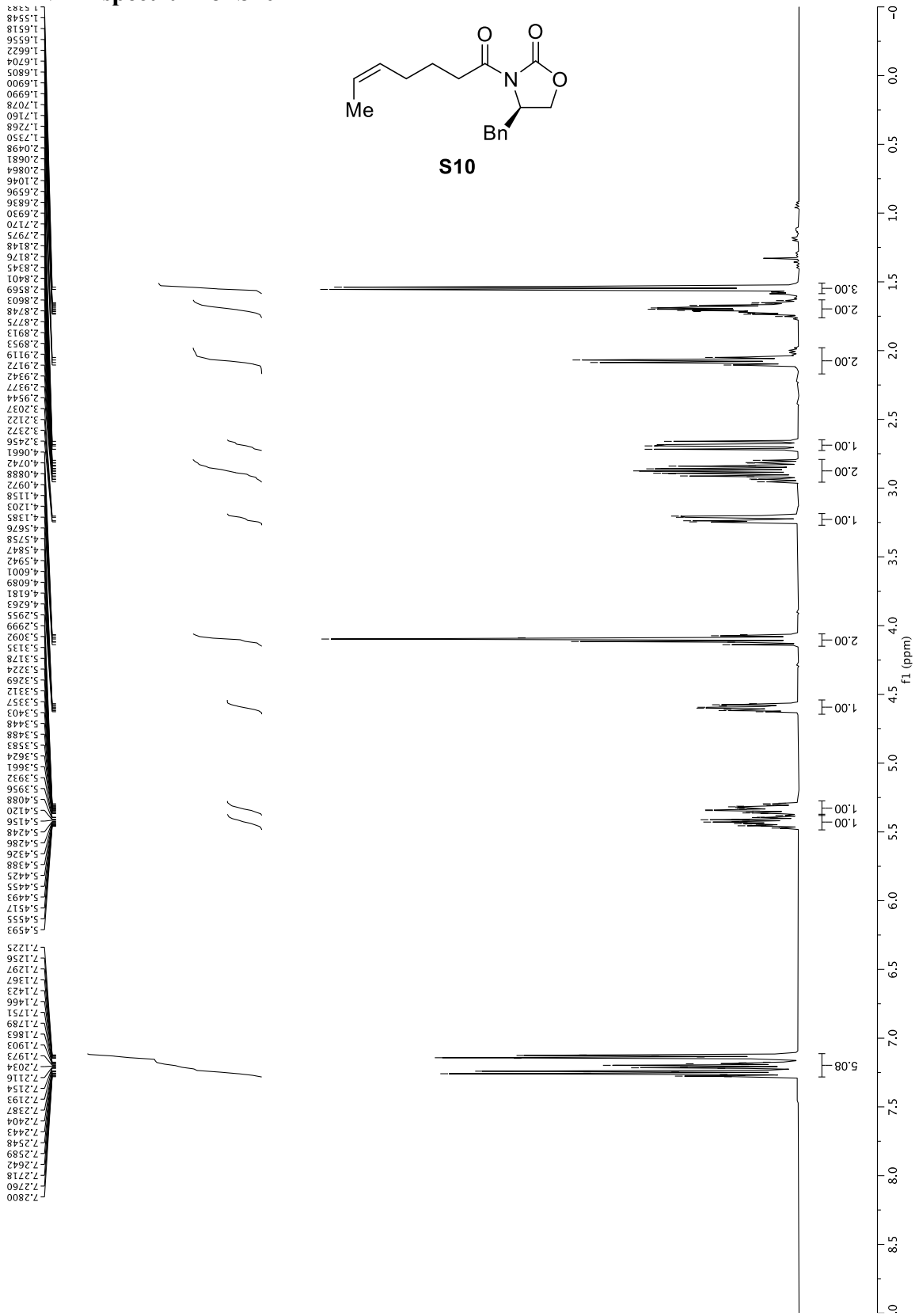
^{1}H NMR spectrum of S8



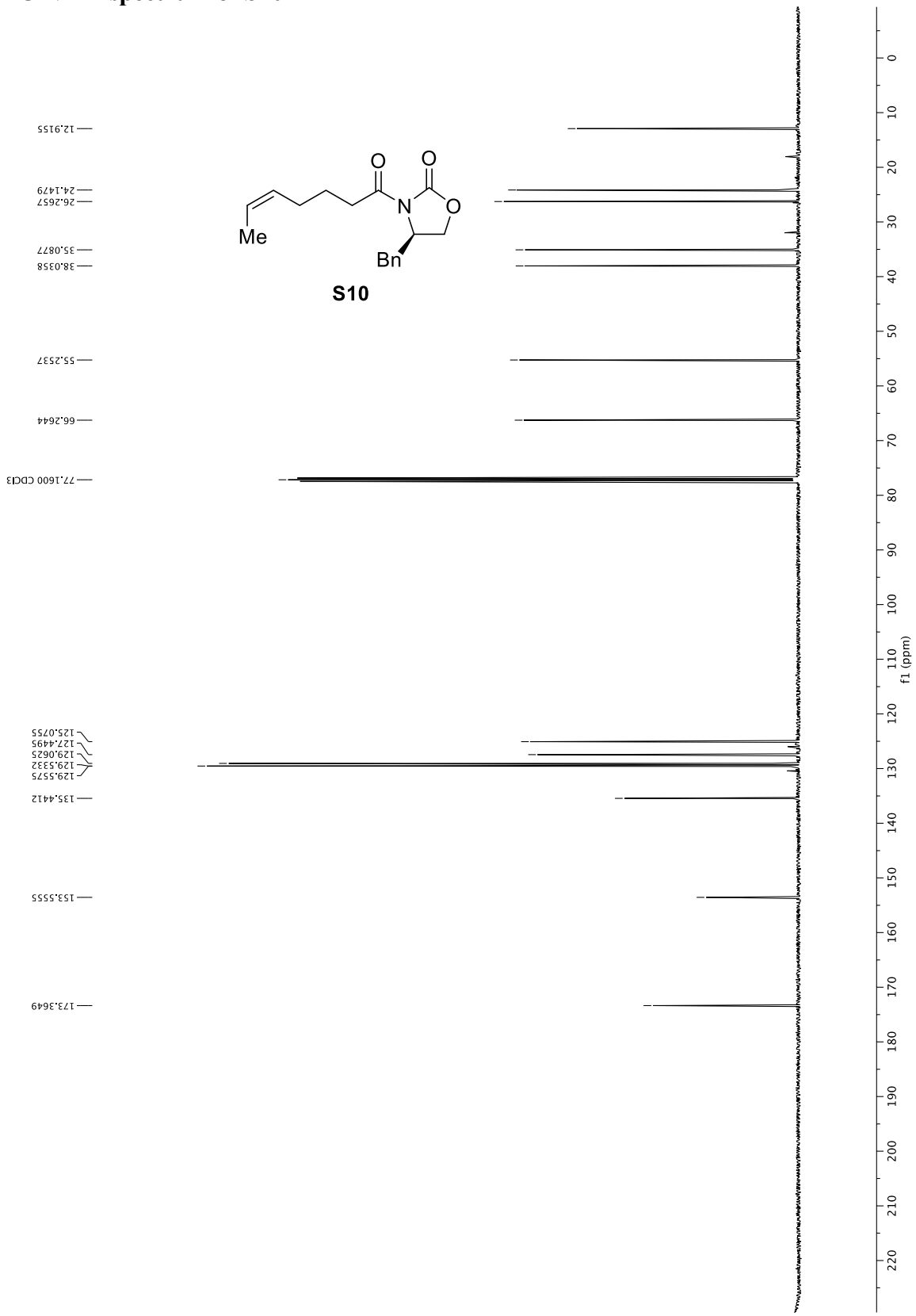
^{13}C NMR spectrum of S8



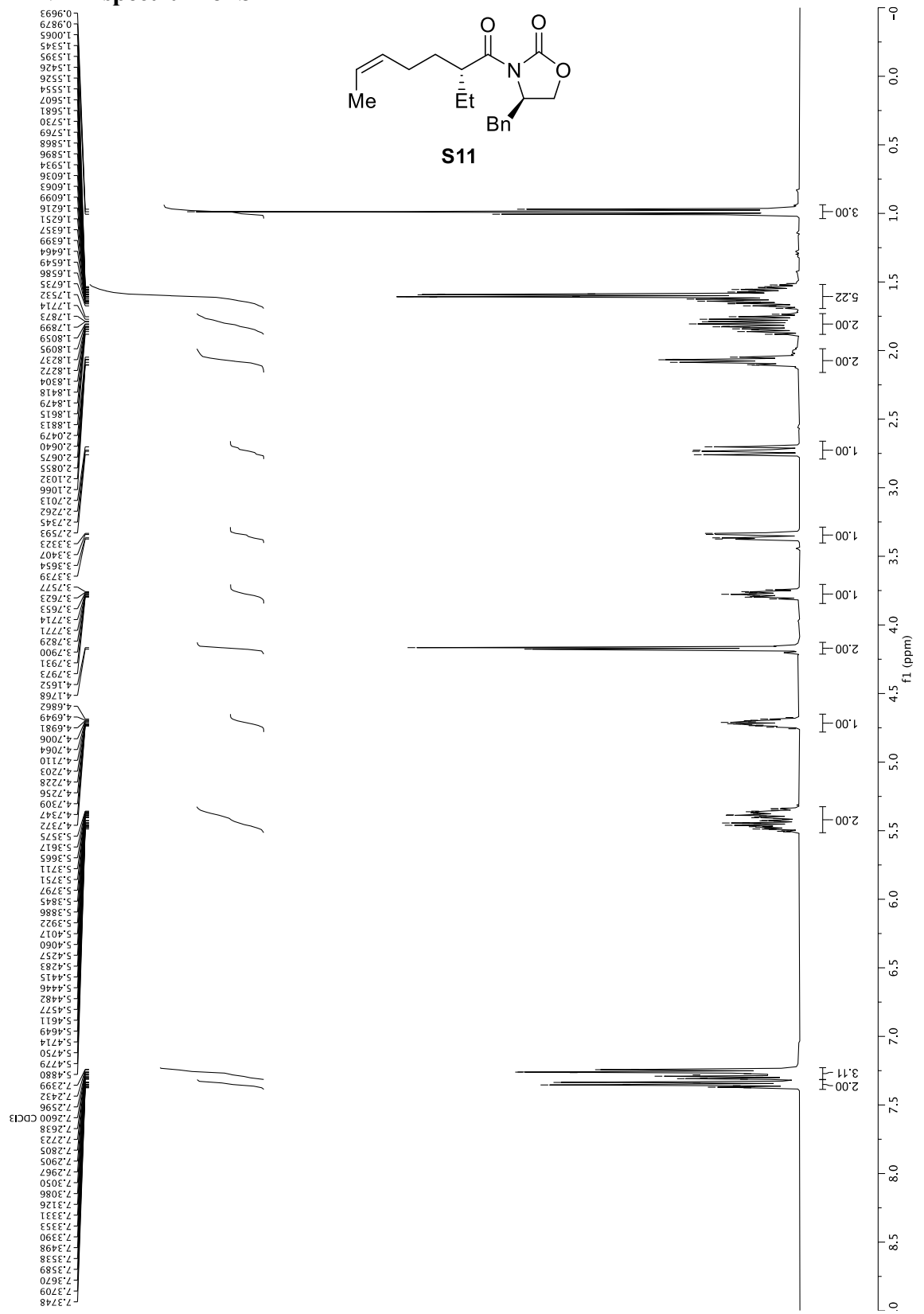
^{1}H NMR spectrum of S10



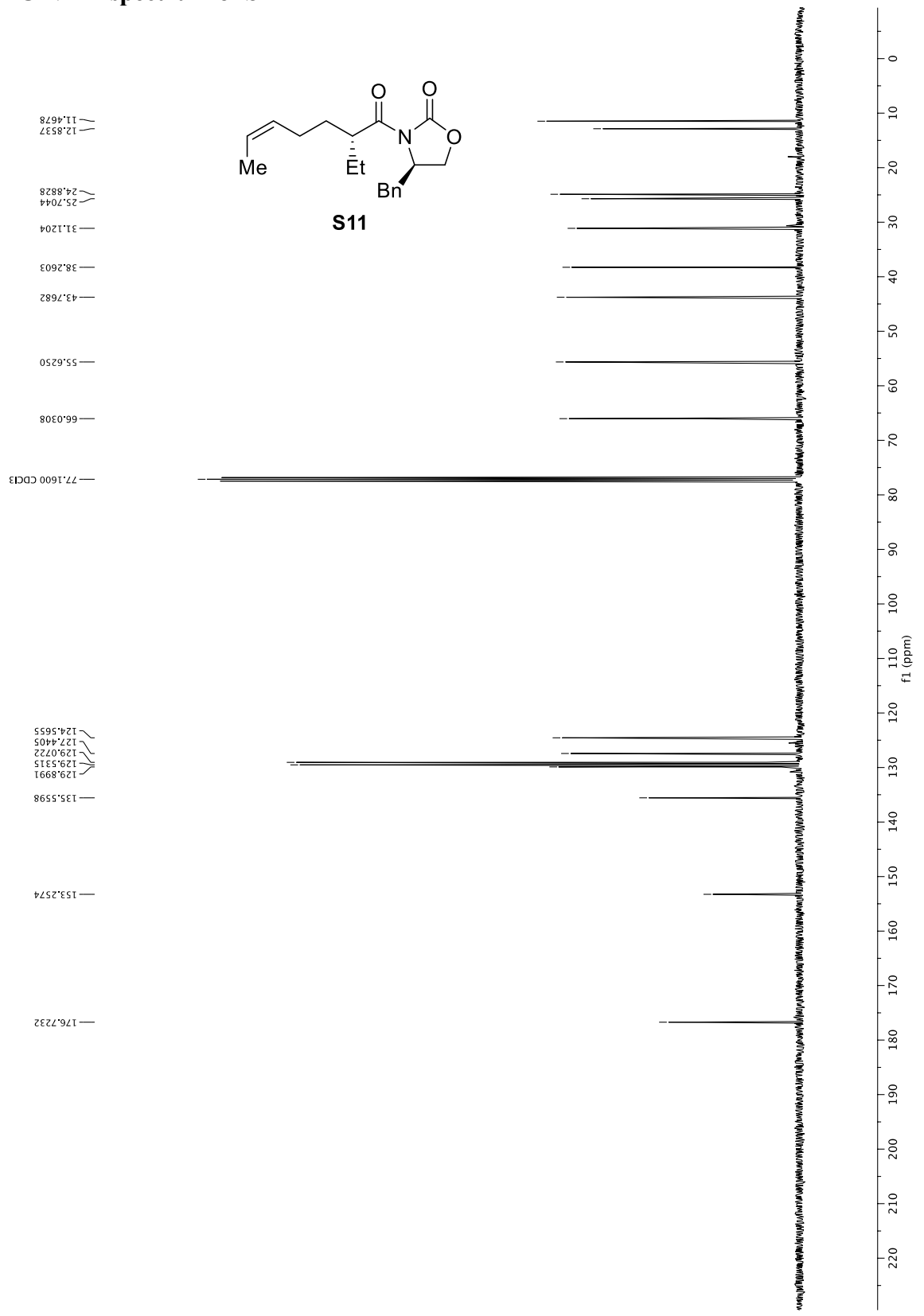
^{13}C NMR spectrum of S10



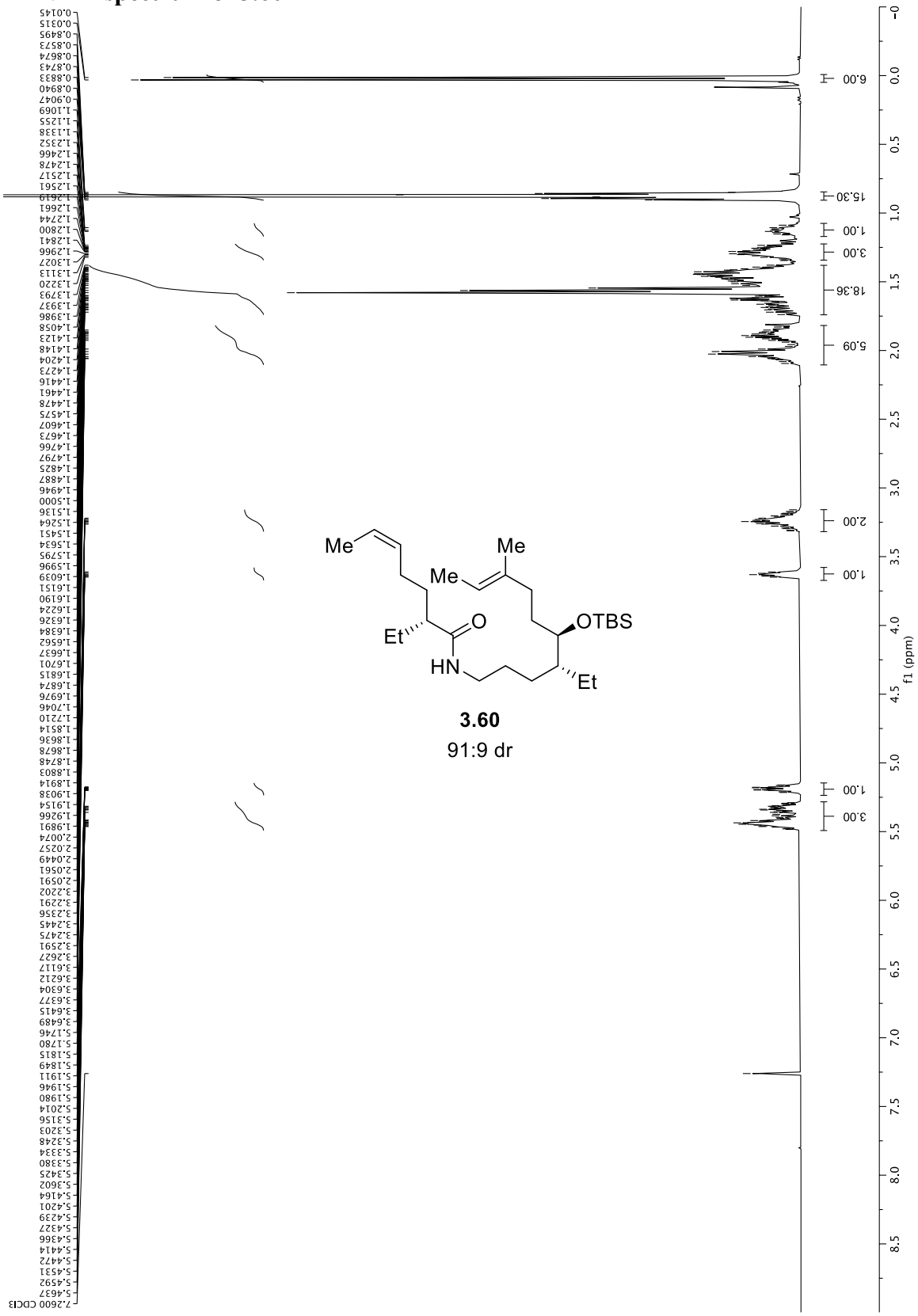
^{1}H NMR spectrum of S11



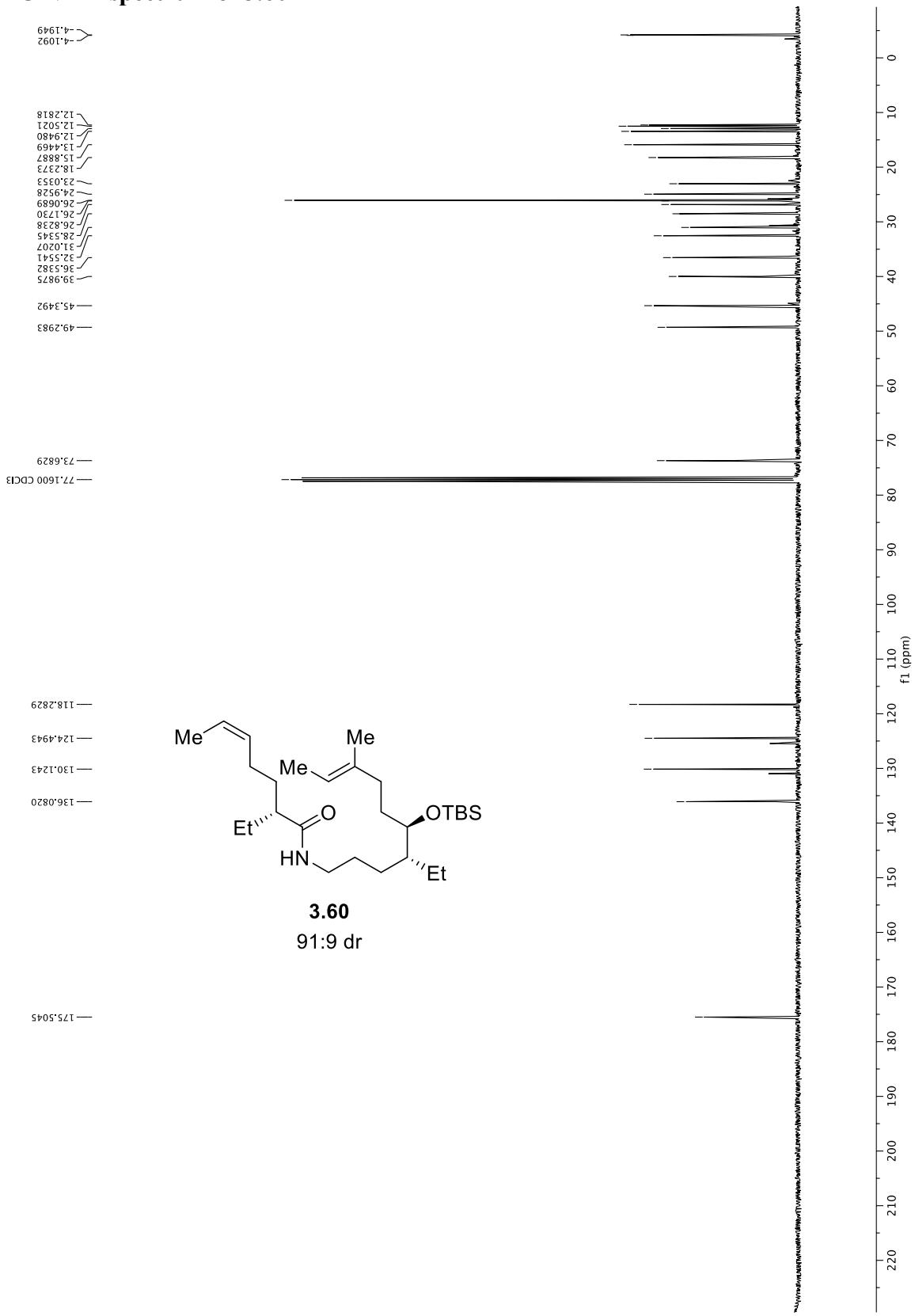
^{13}C NMR spectrum of S11



^{1}H NMR spectrum of 3.60



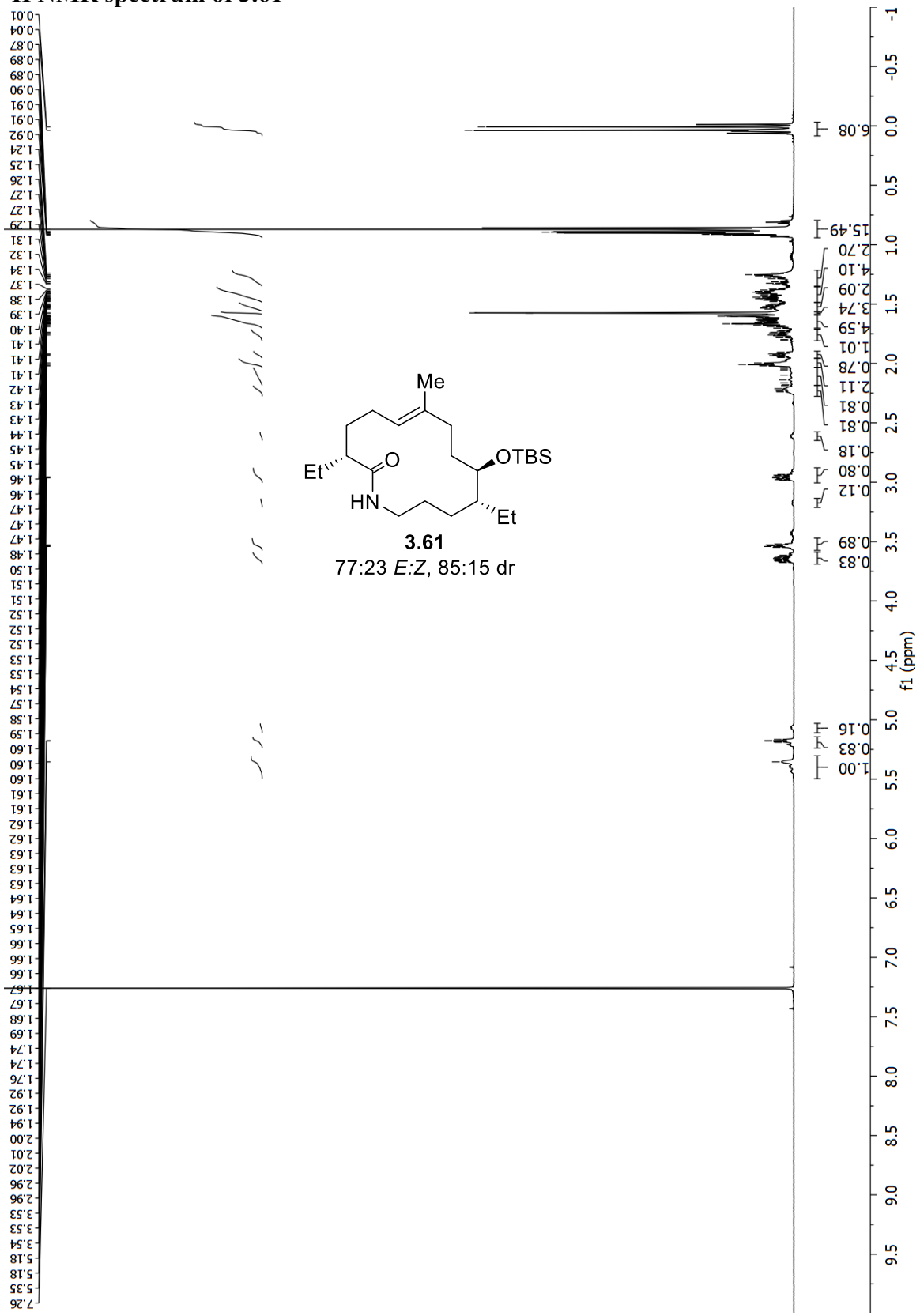
^{13}C NMR spectrum of 3.60



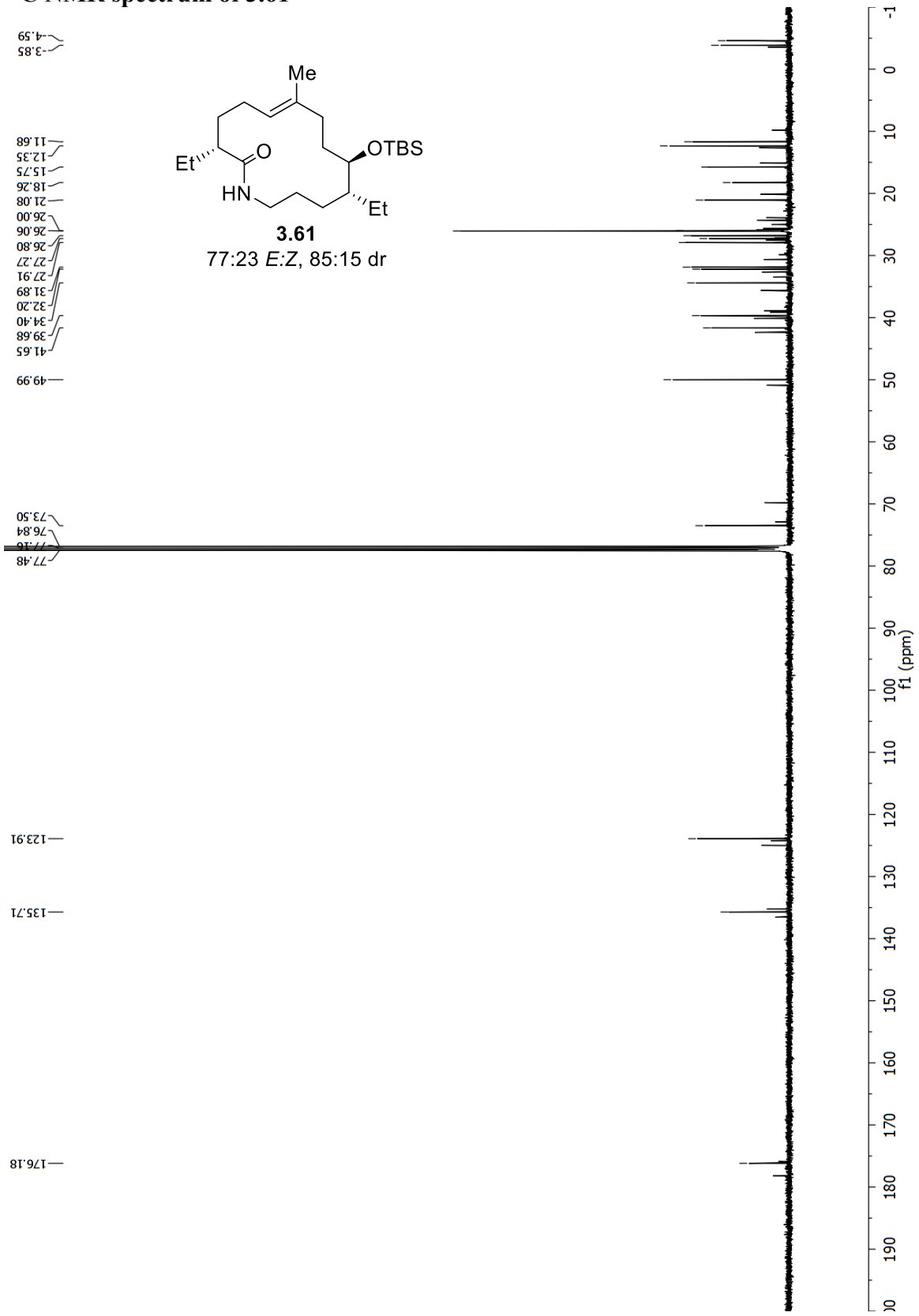
3.60

91:9 dr

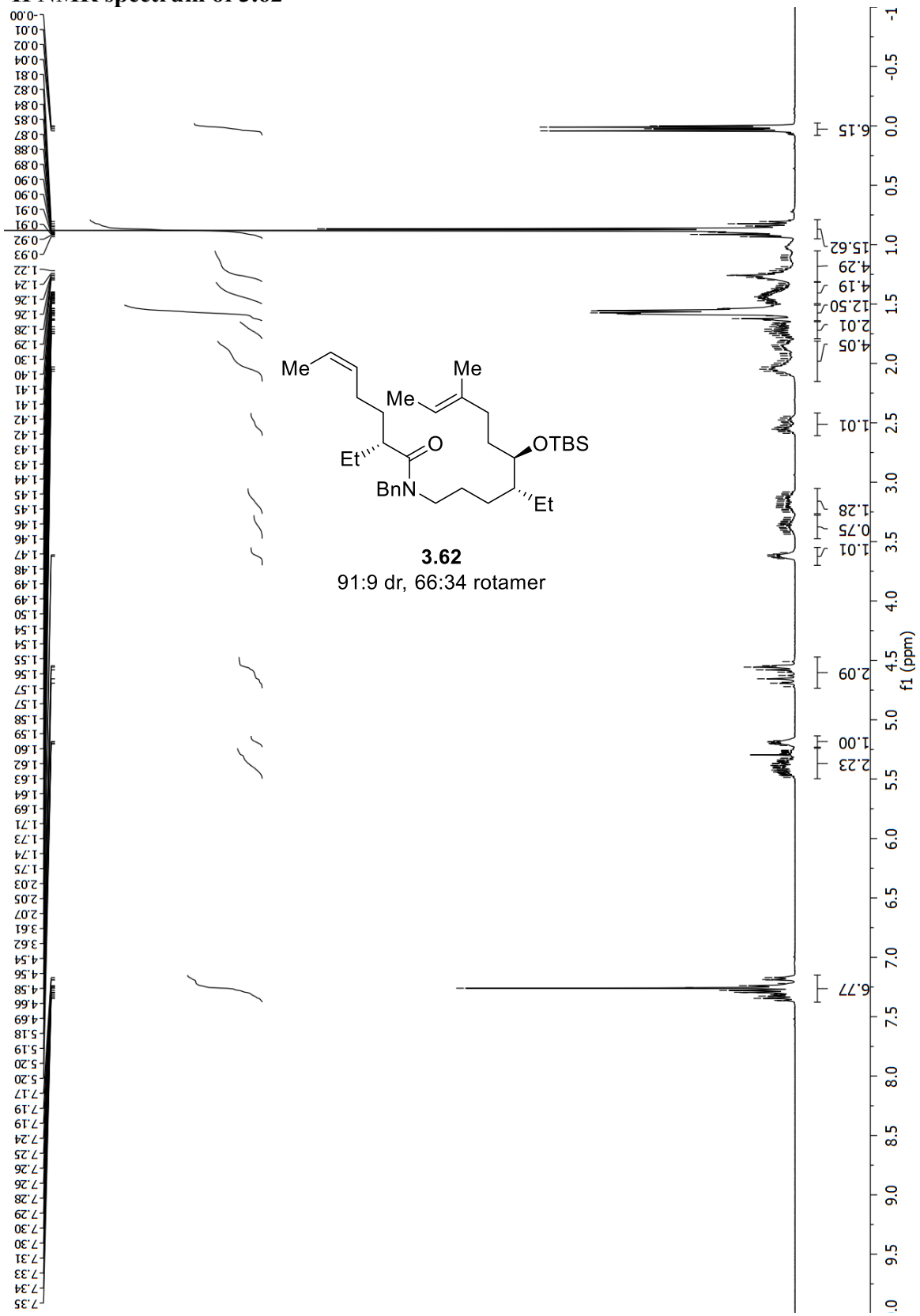
^{1}H NMR spectrum of 3.61



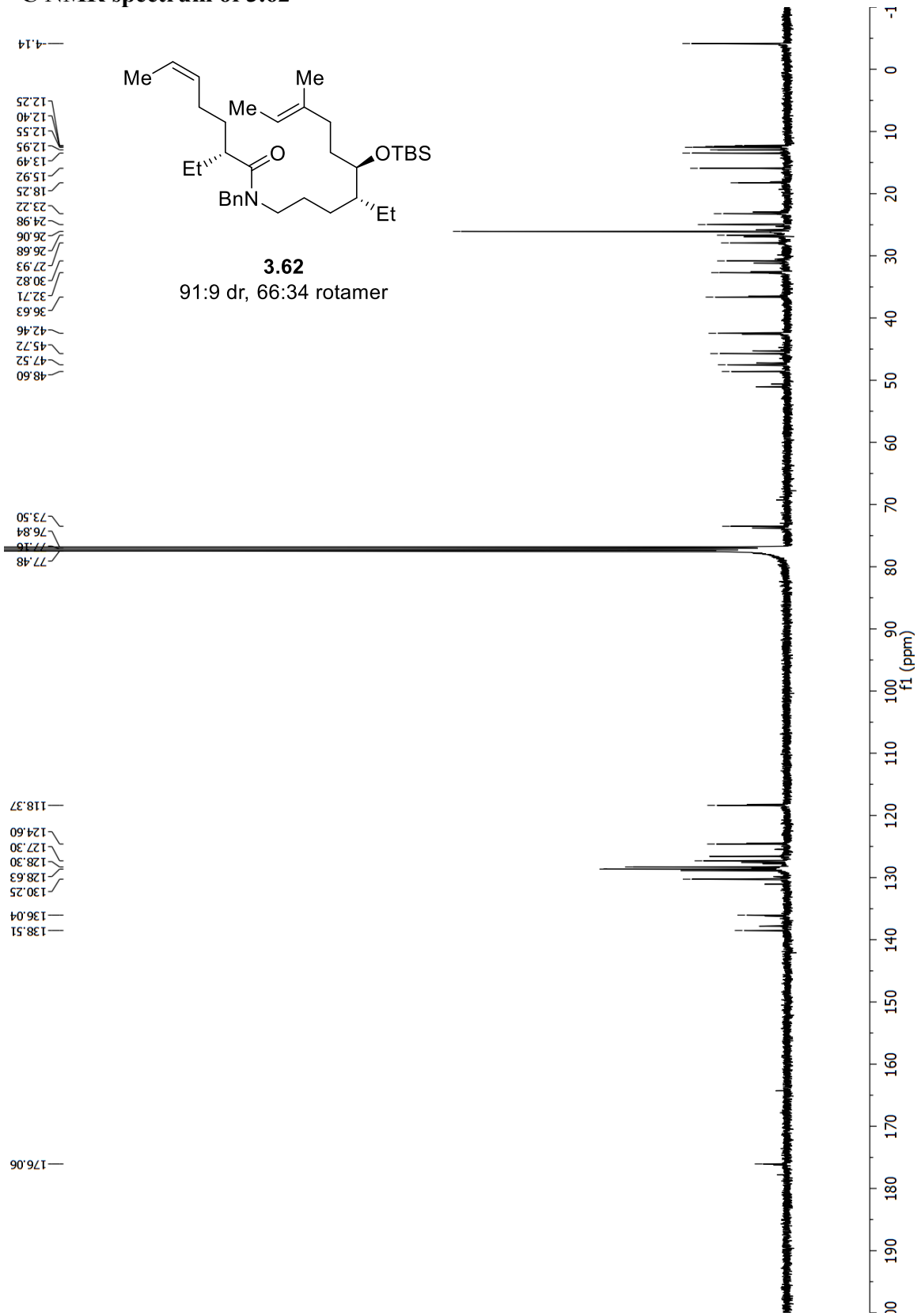
^{13}C NMR spectrum of 3.61



^{1}H NMR spectrum of 3.62



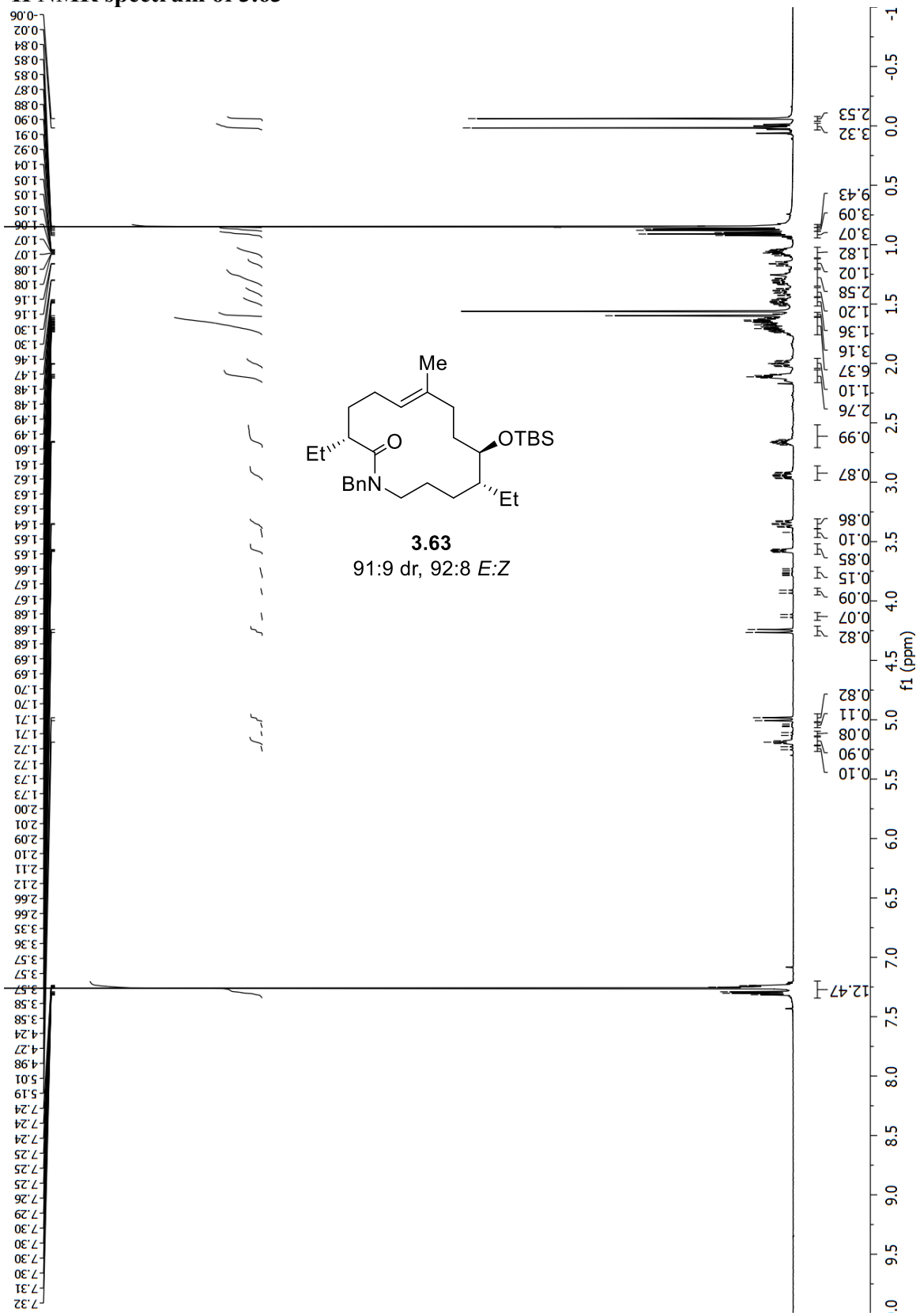
^{13}C NMR spectrum of 3.62



3.62

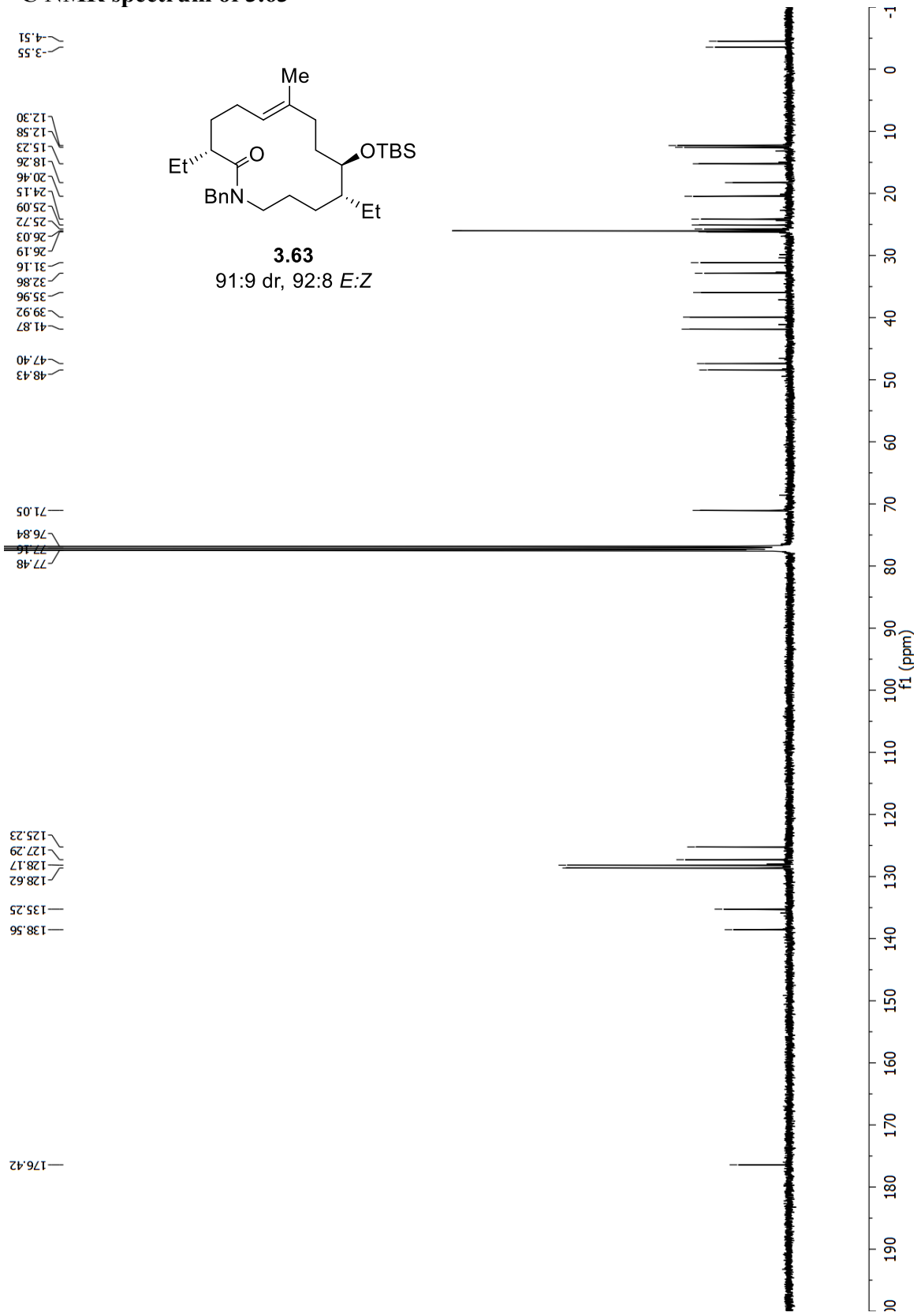
91:9 dr, 66:34 rotamer

^{1}H NMR spectrum of 3.63

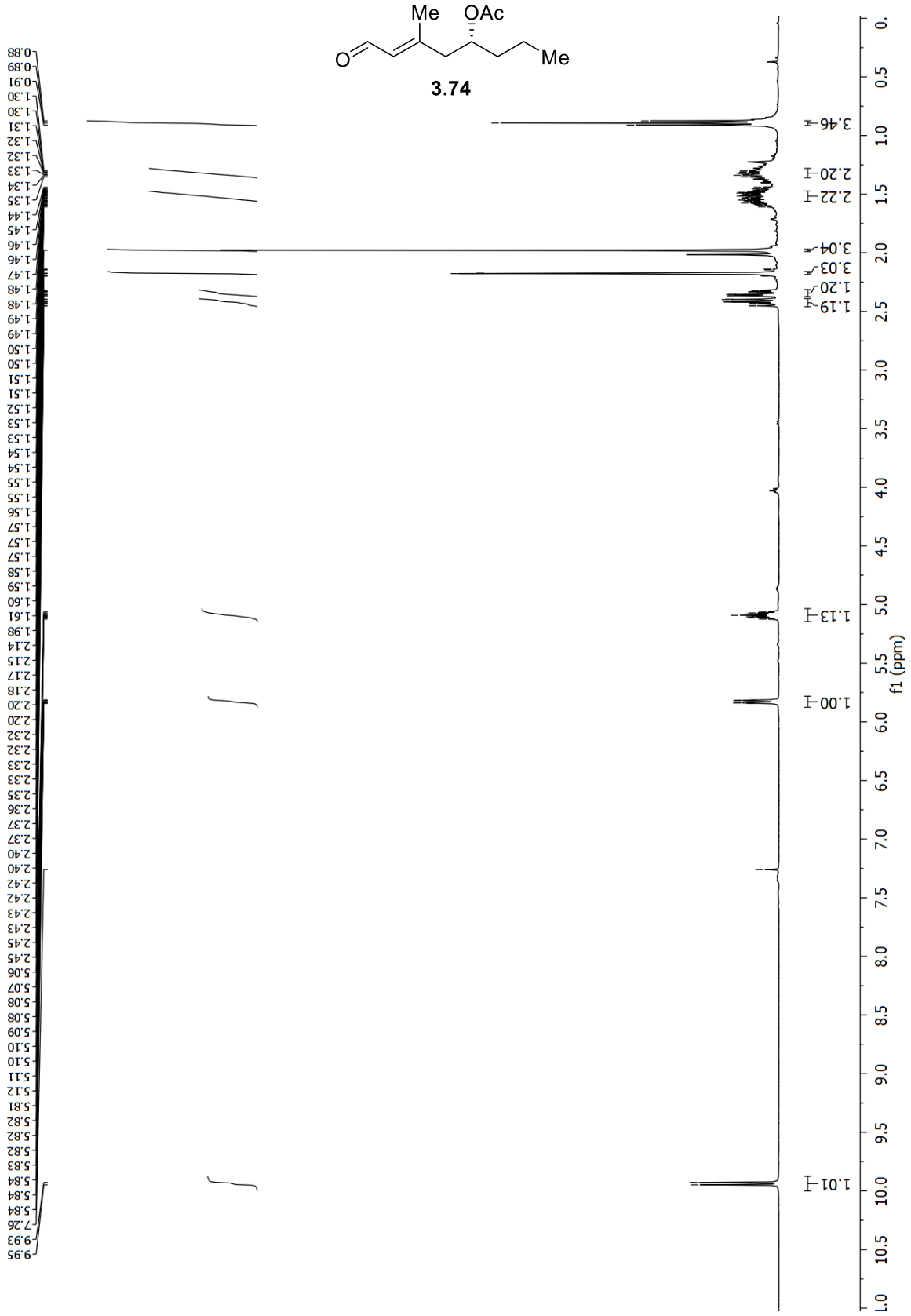


3.63
91:9 dr, 92:8 *E:Z*

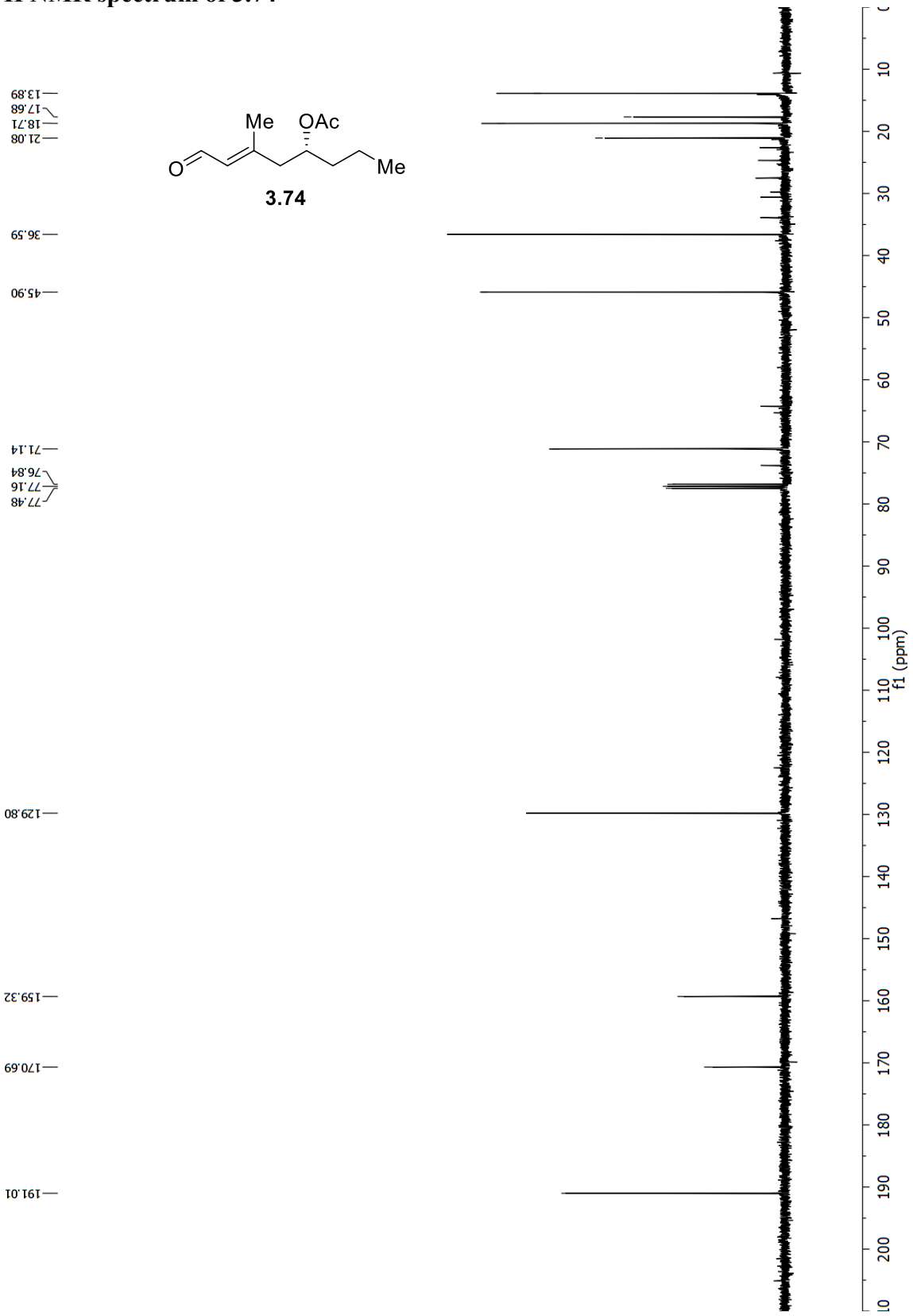
^{13}C NMR spectrum of 3.63



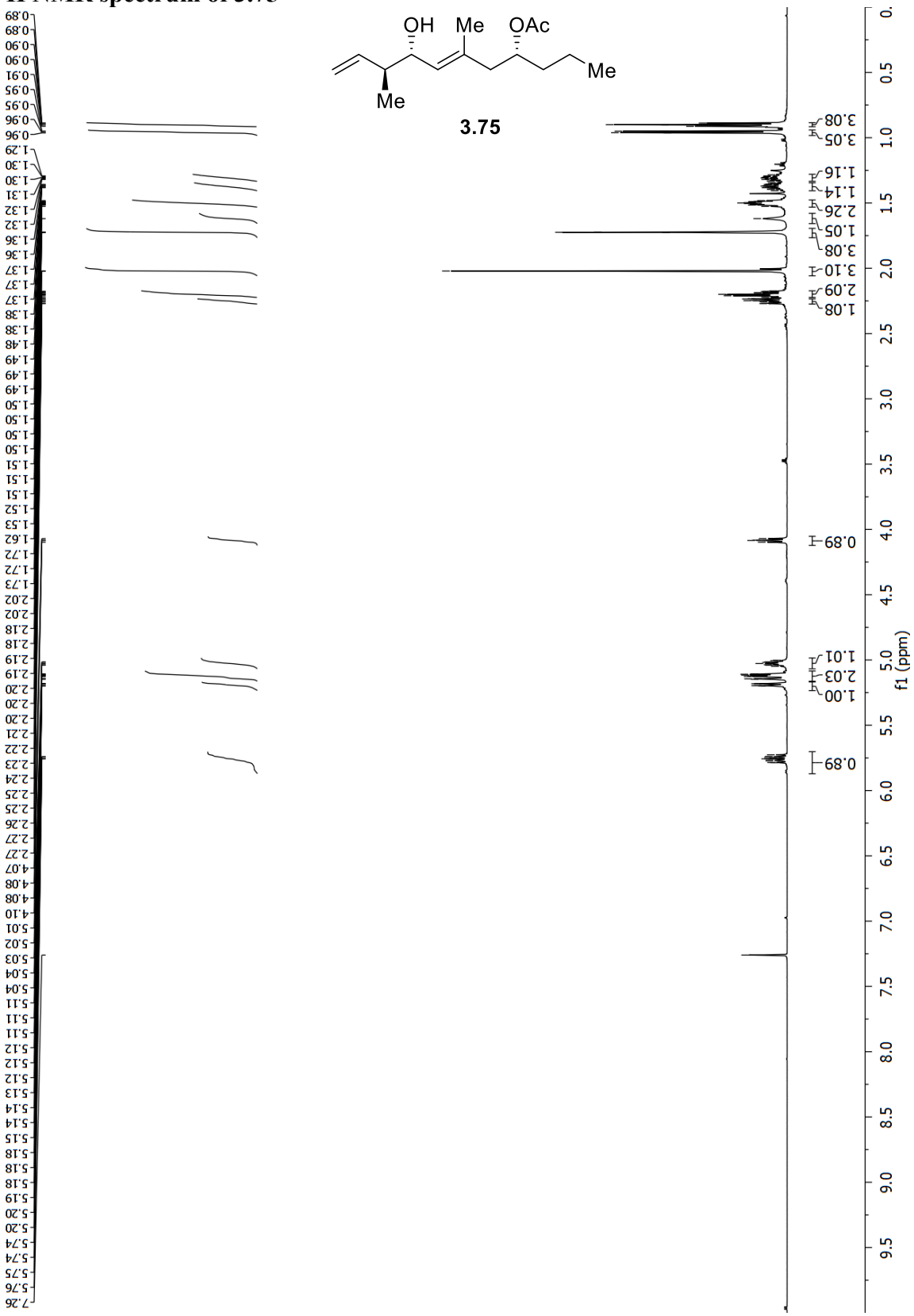
^{1}H NMR spectrum of 3.74



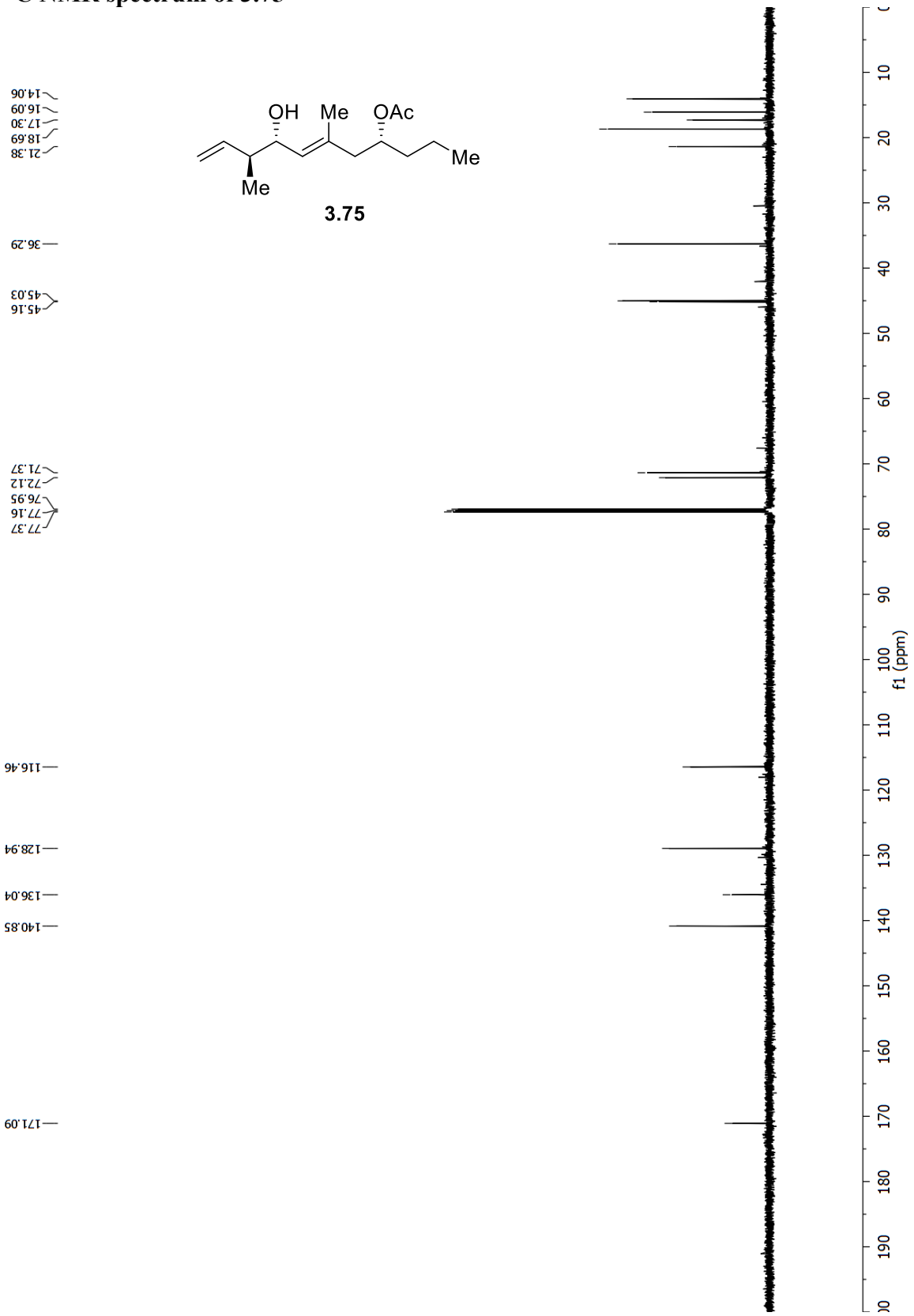
^{1}H NMR spectrum of 3.74



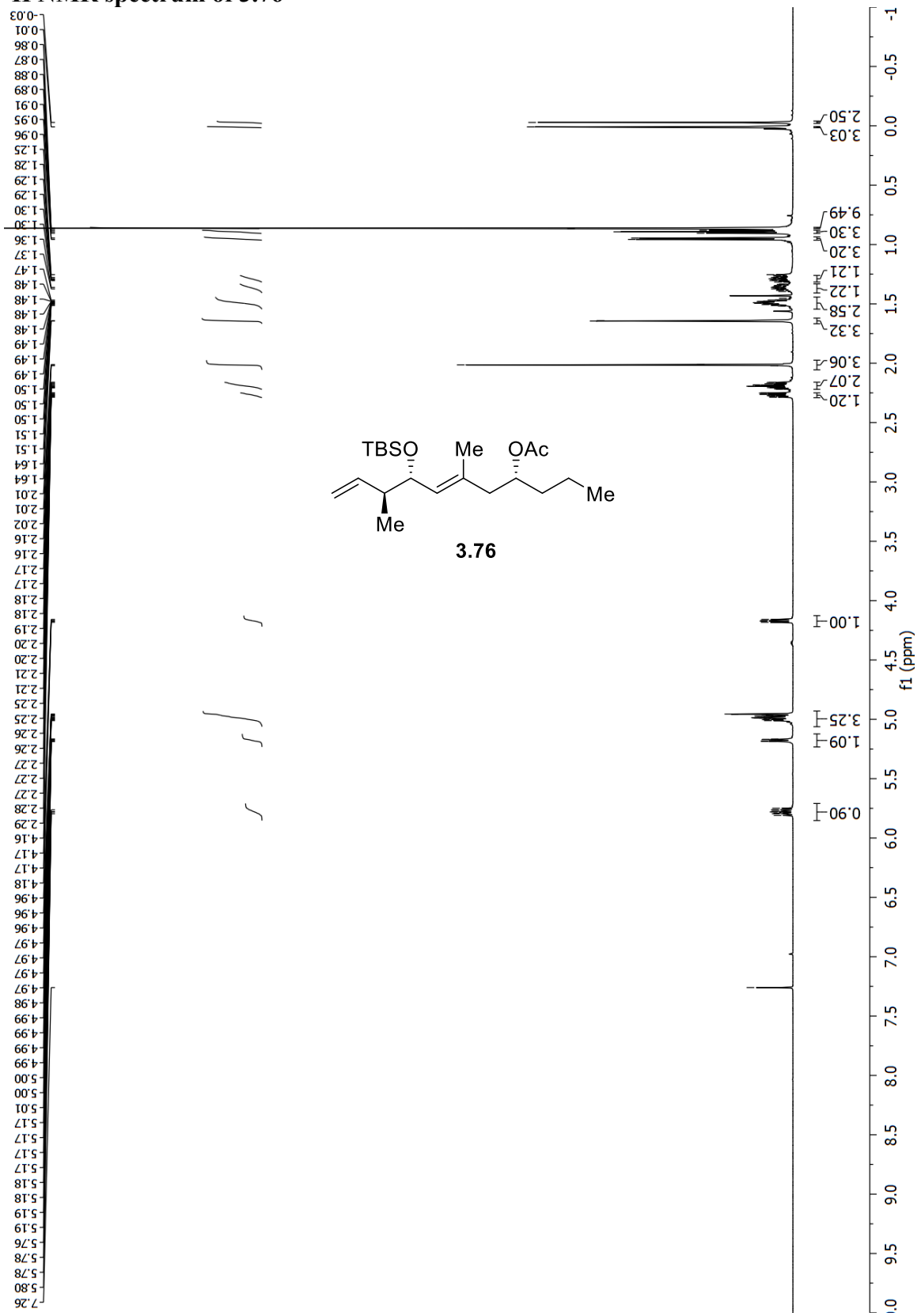
^{1}H NMR spectrum of 3.75



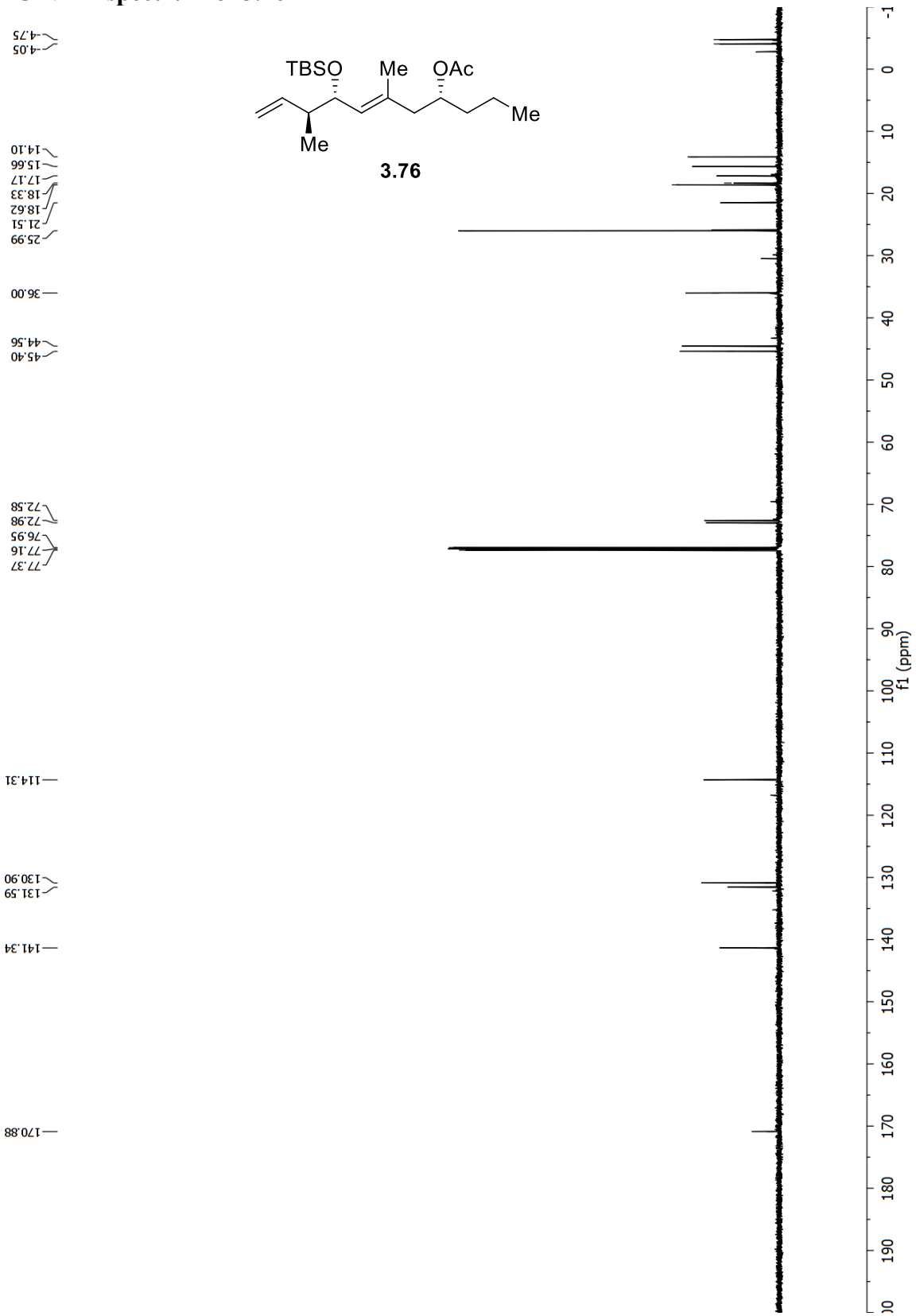
^{13}C NMR spectrum of 3.75



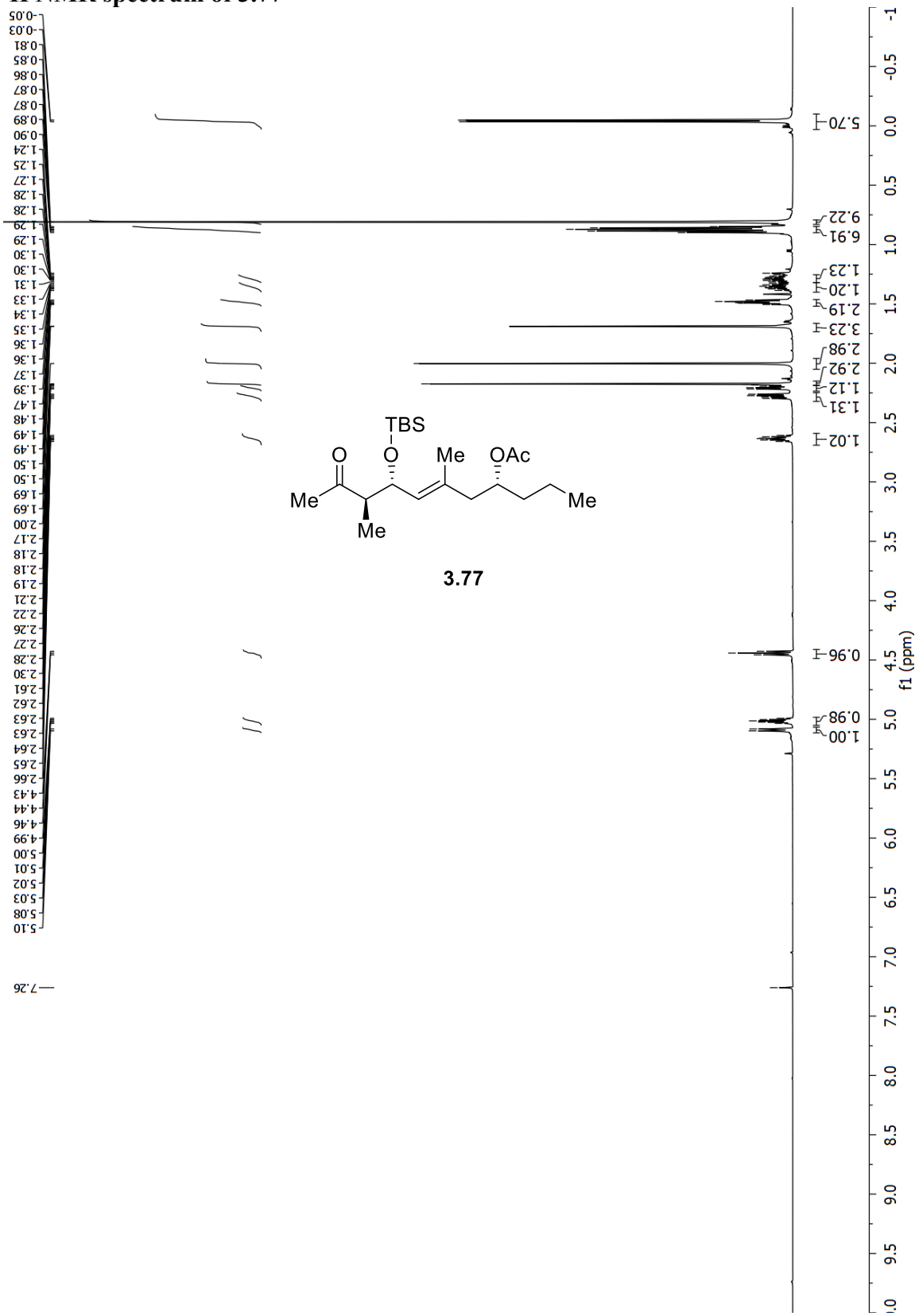
^{1}H NMR spectrum of 3.76



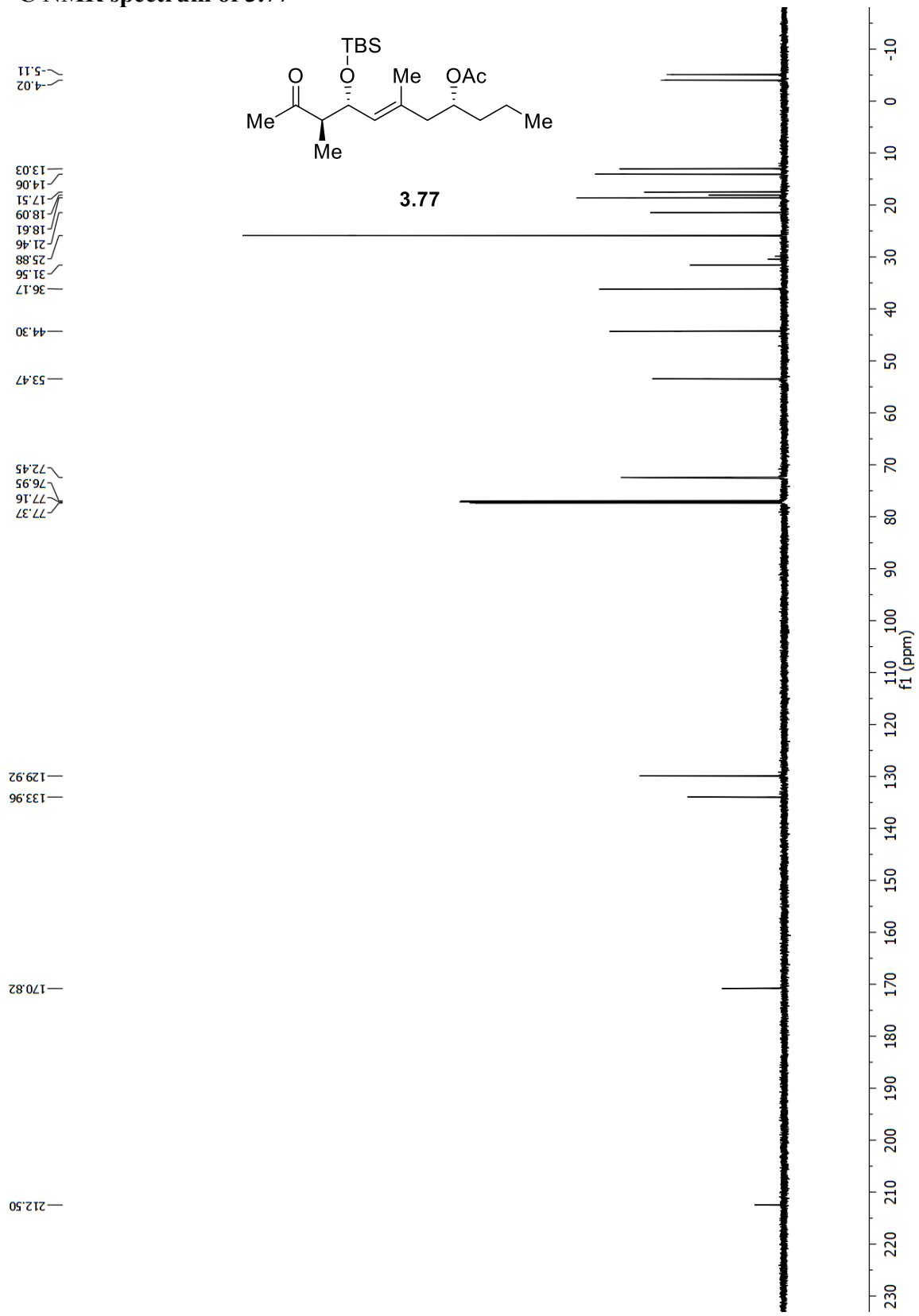
^{13}C NMR spectrum of 3.76



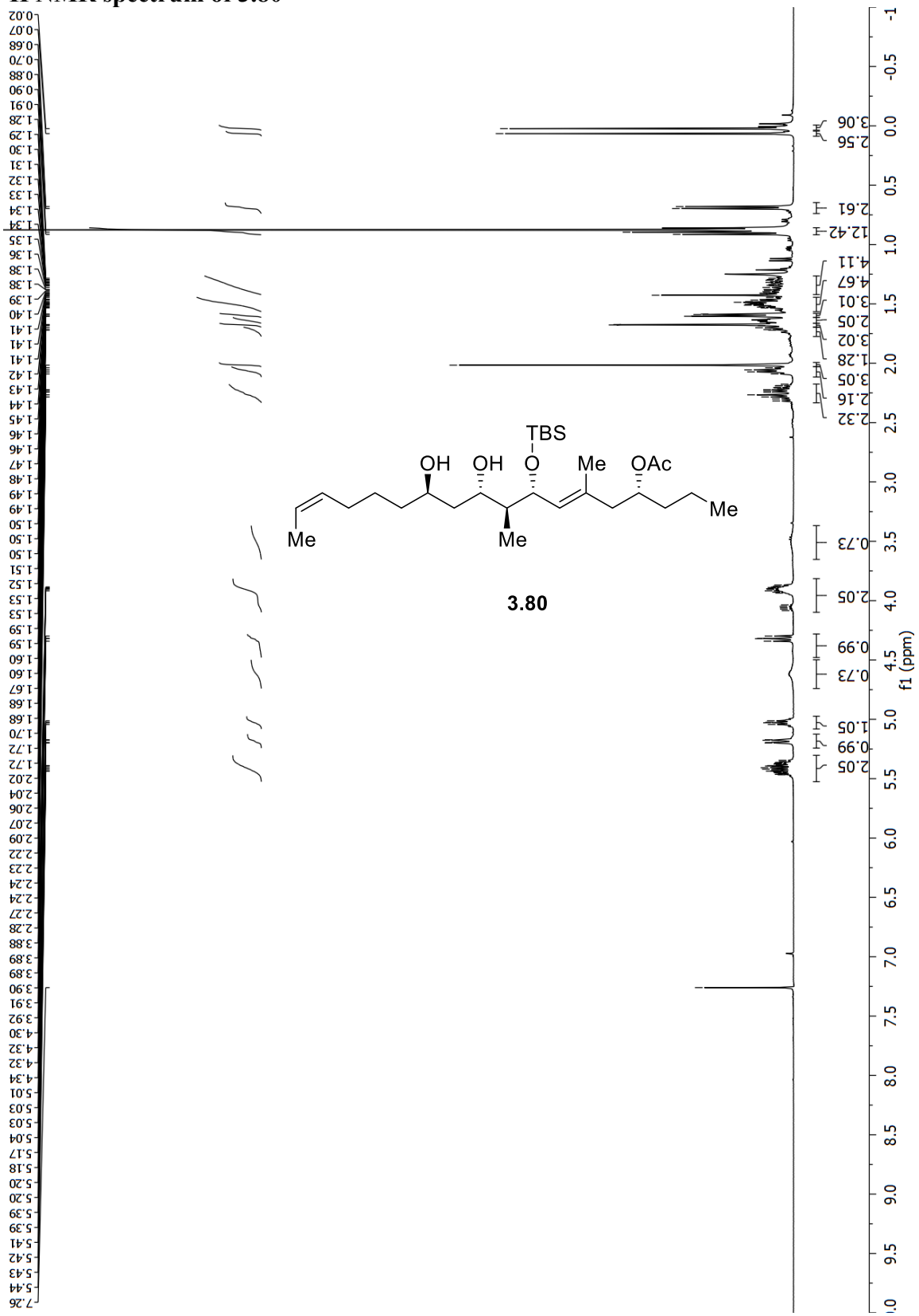
^{1}H NMR spectrum of 3.77



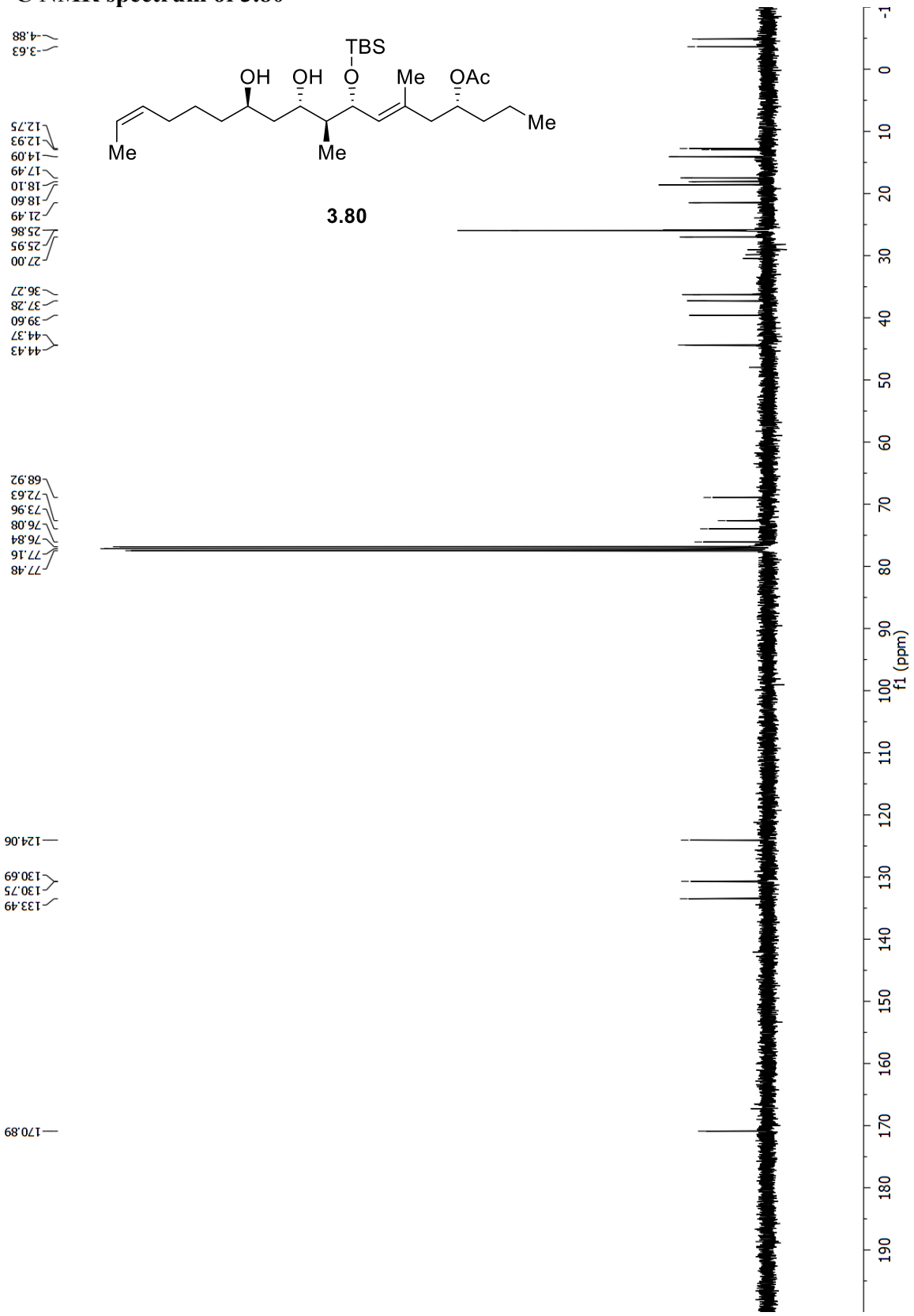
^{13}C NMR spectrum of 3.77



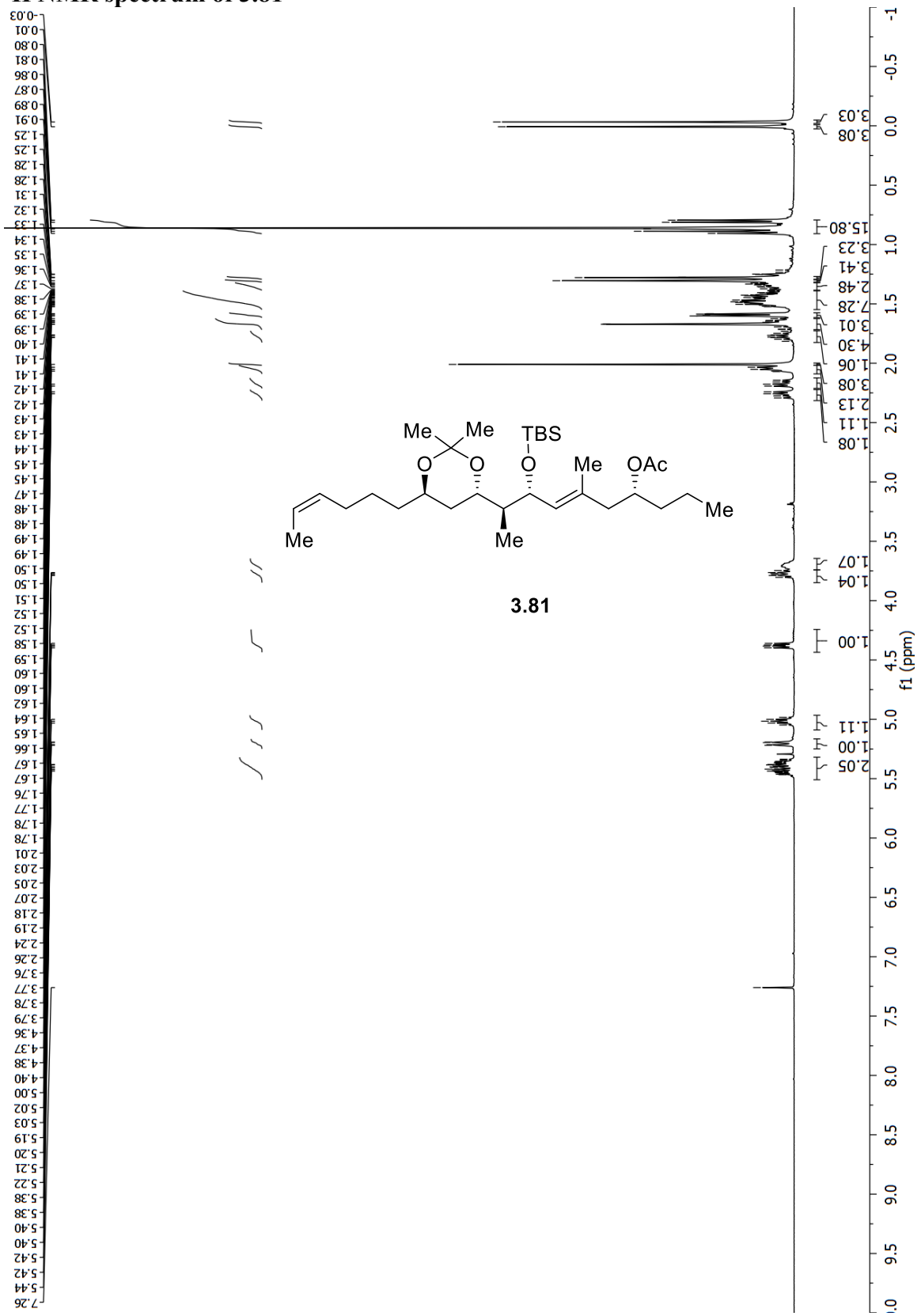
^{1}H NMR spectrum of 3.80



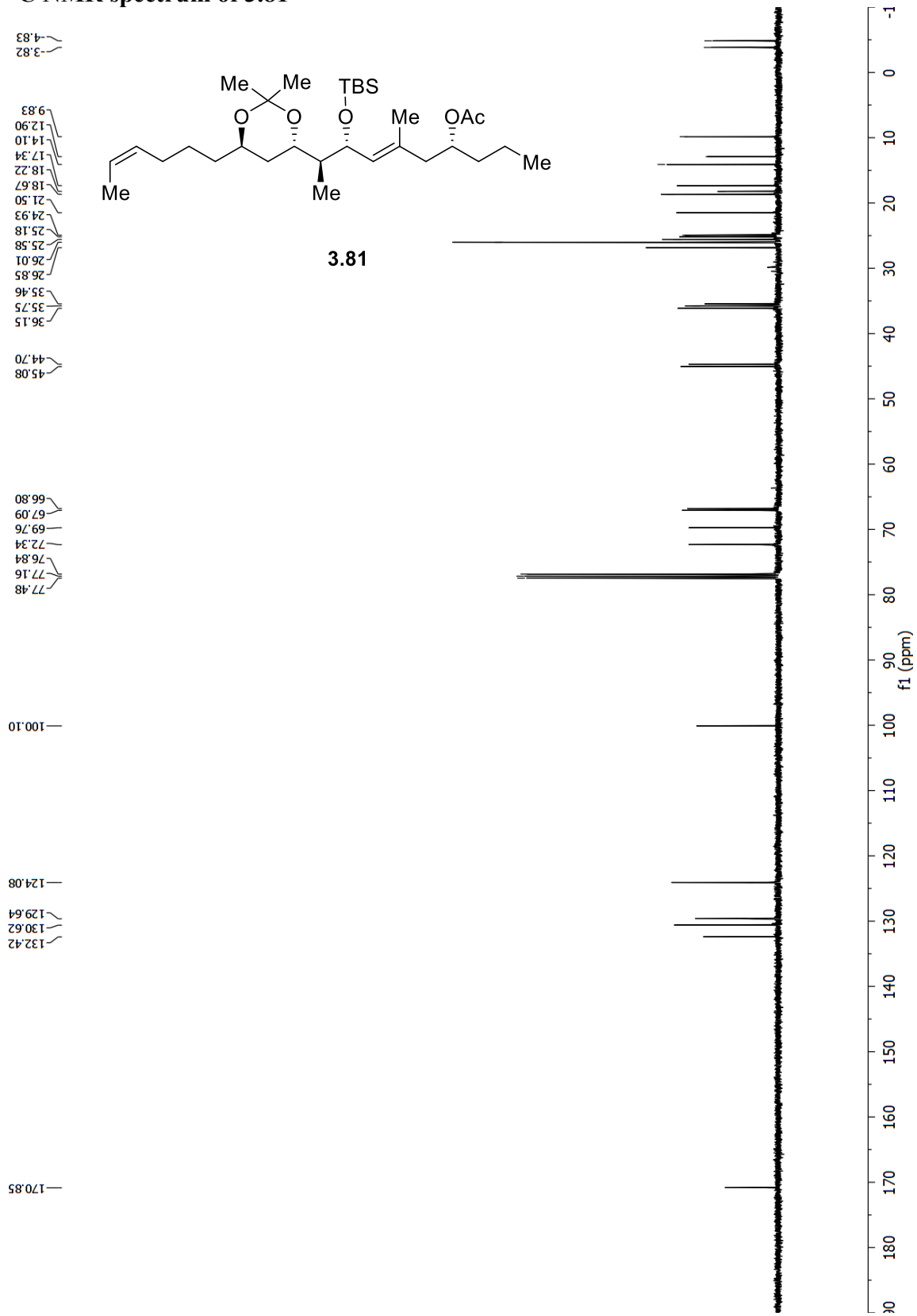
^{13}C NMR spectrum of 3.80



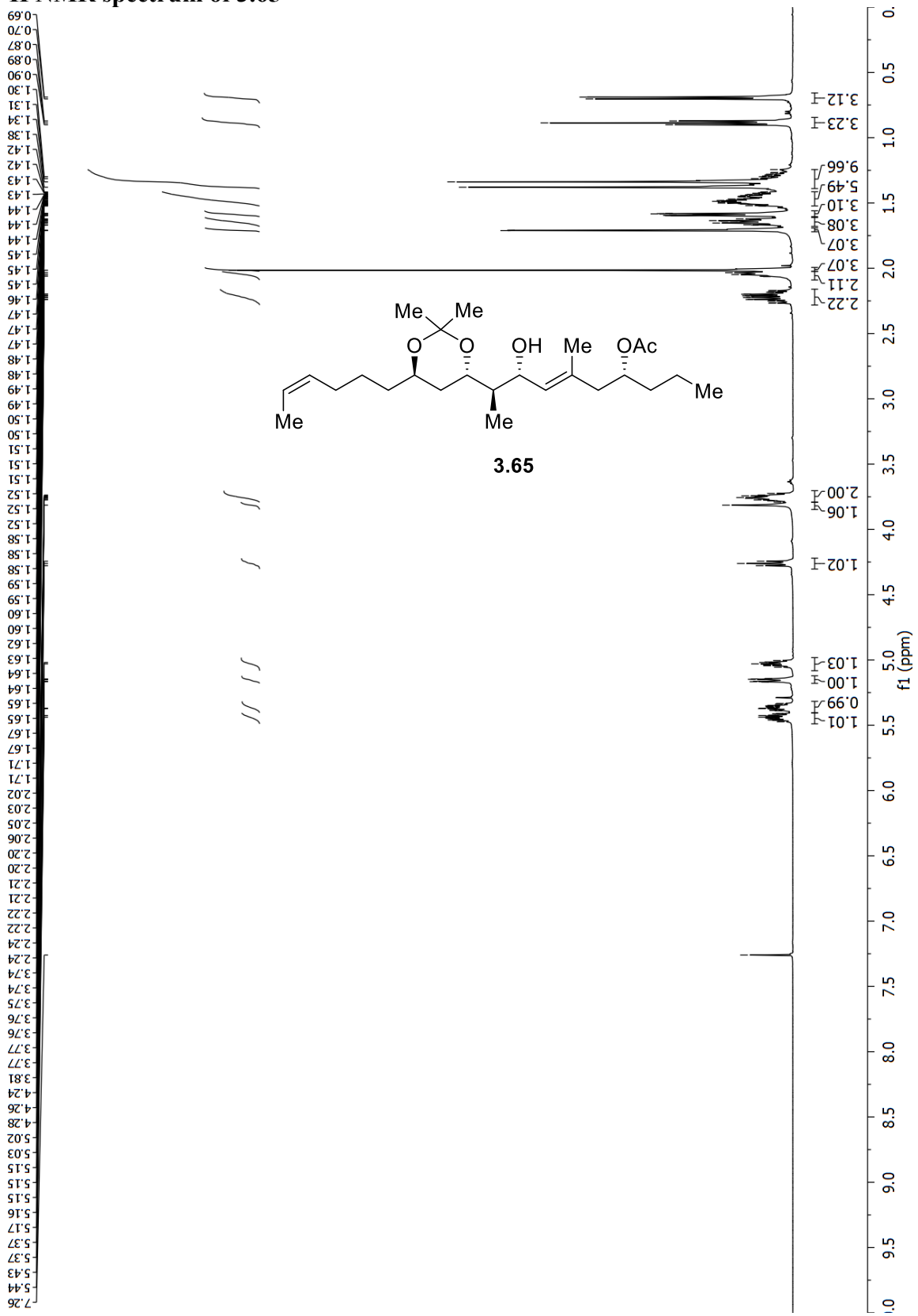
^{1}H NMR spectrum of 3.81



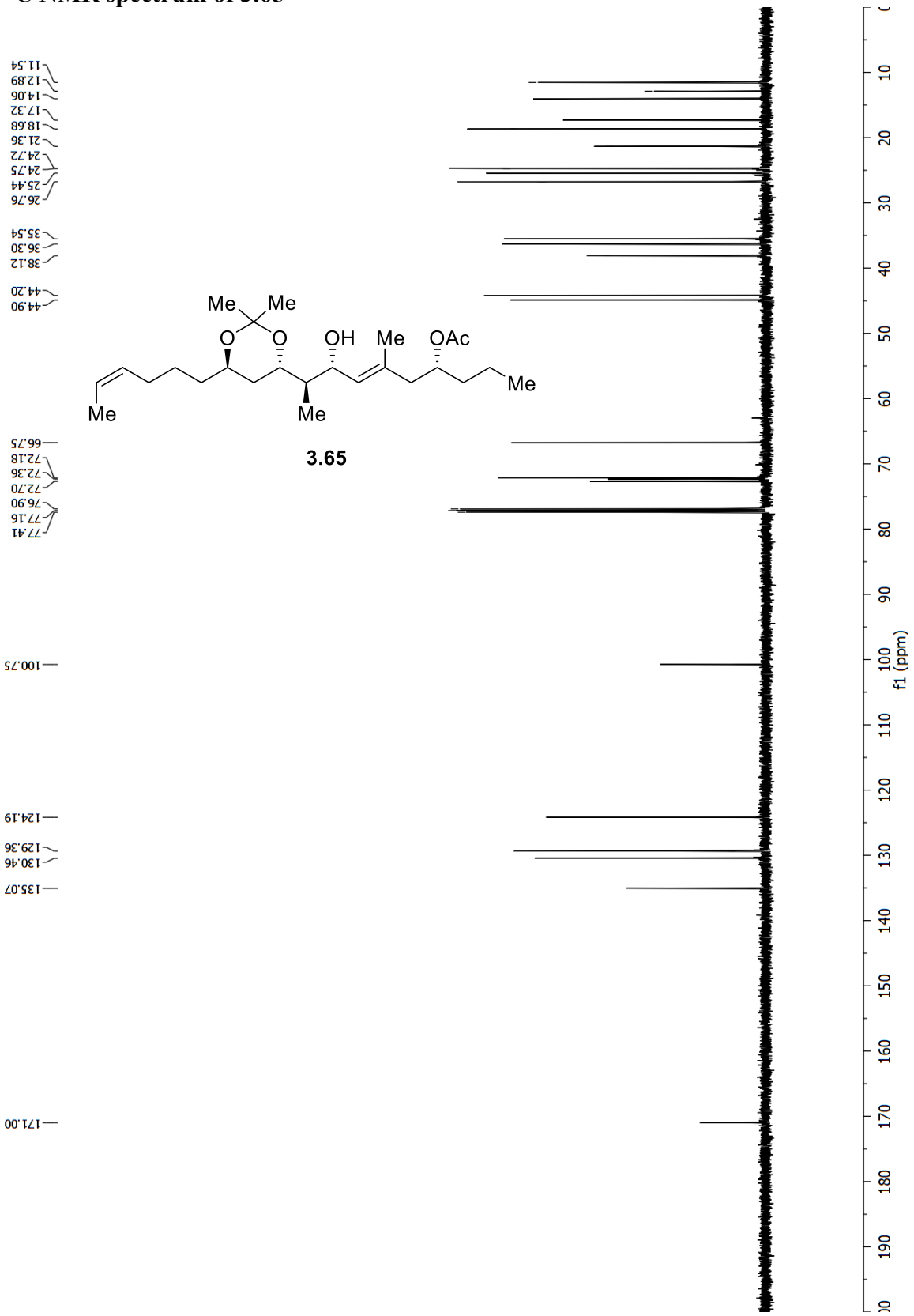
^{13}C NMR spectrum of 3.81



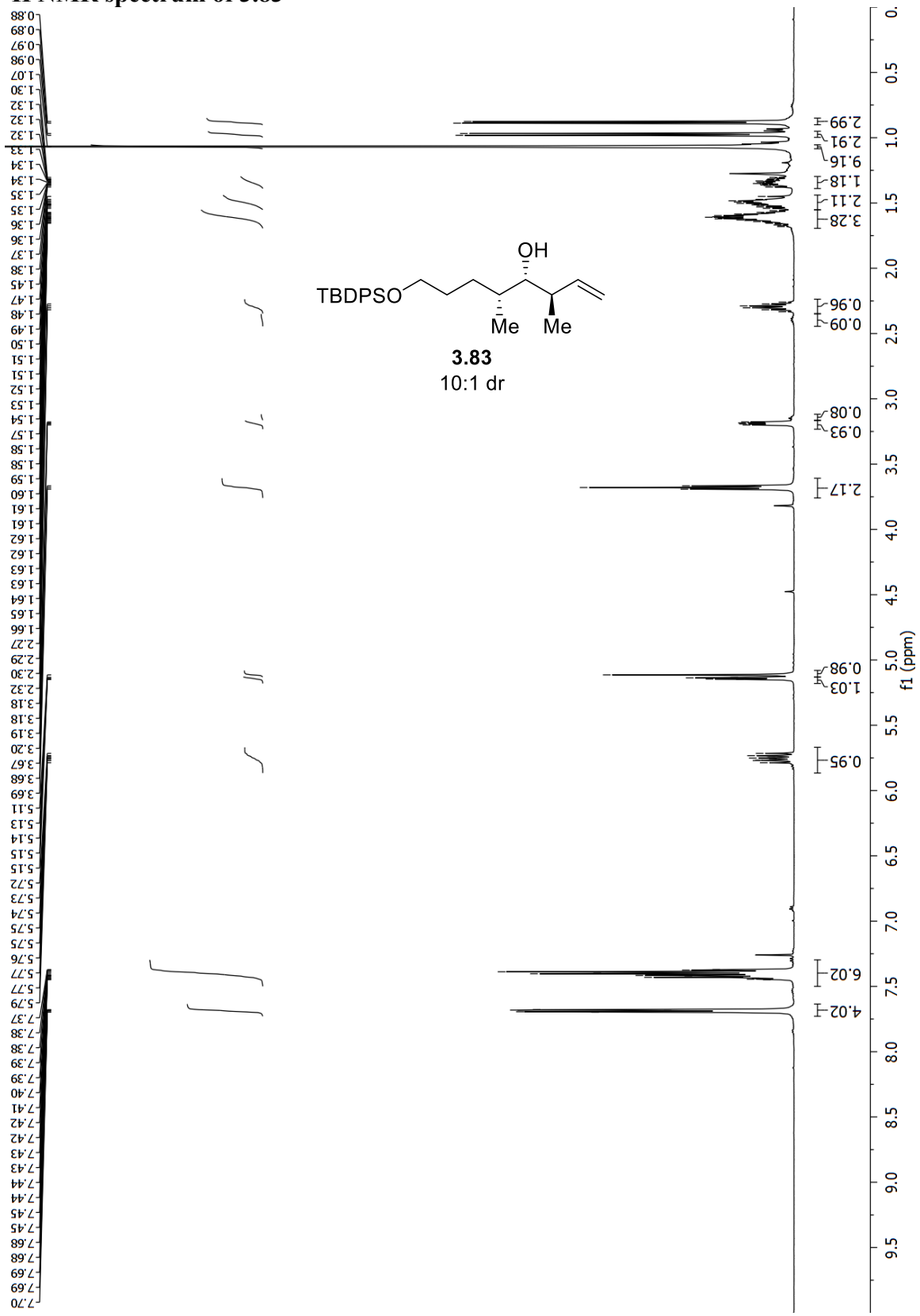
^{1}H NMR spectrum of 3.65



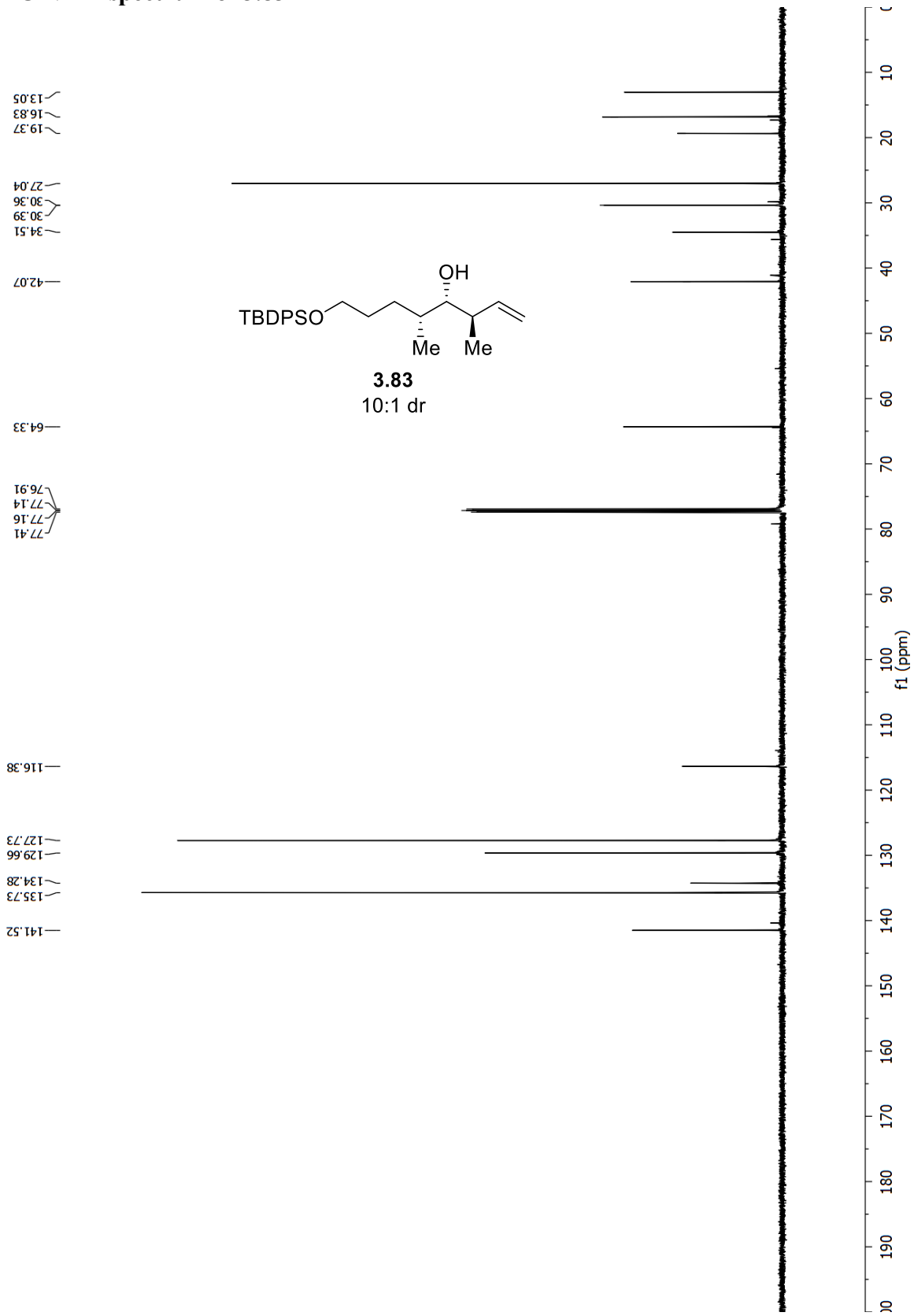
^{13}C NMR spectrum of 3.65



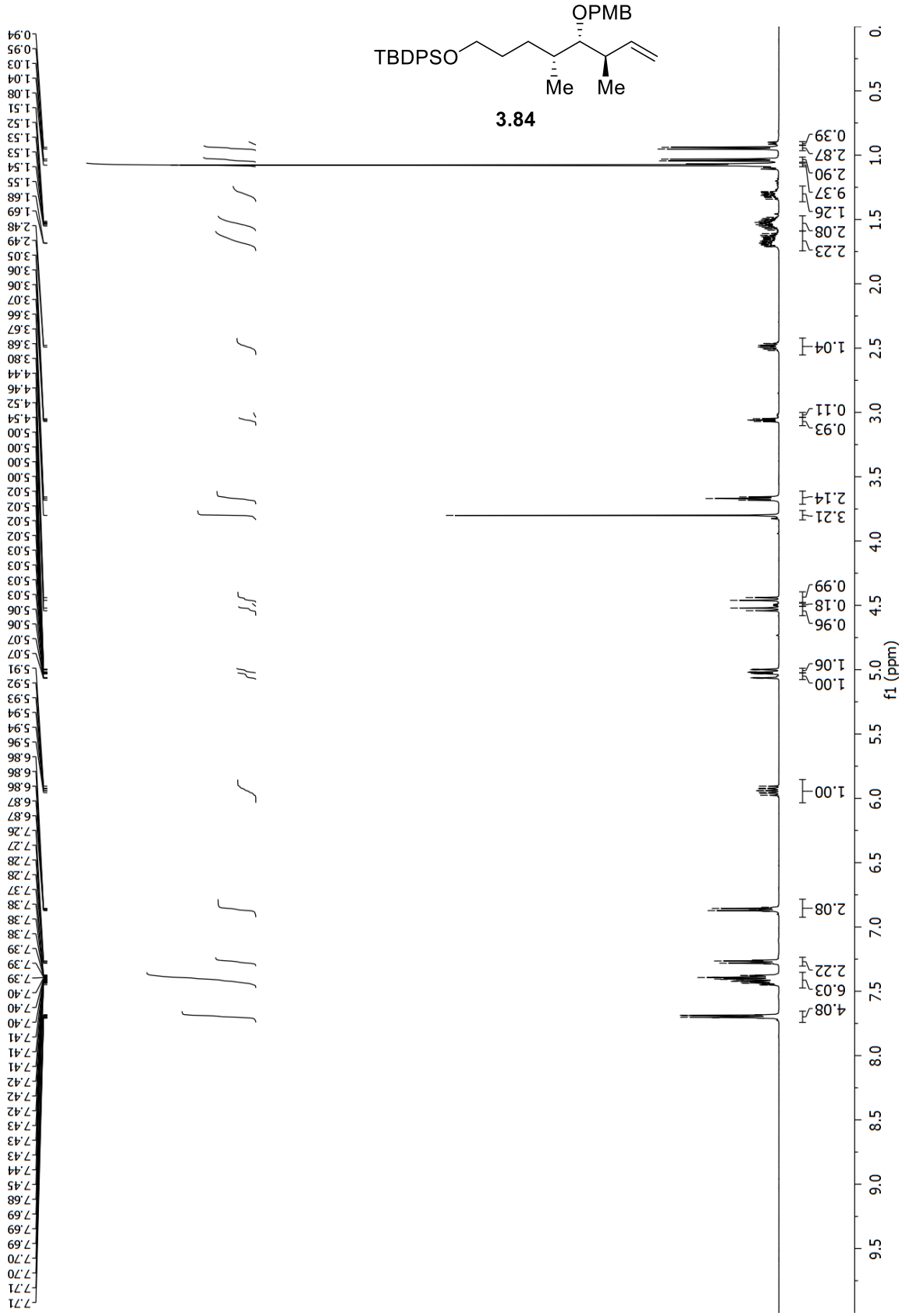
^{1}H NMR spectrum of 3.83



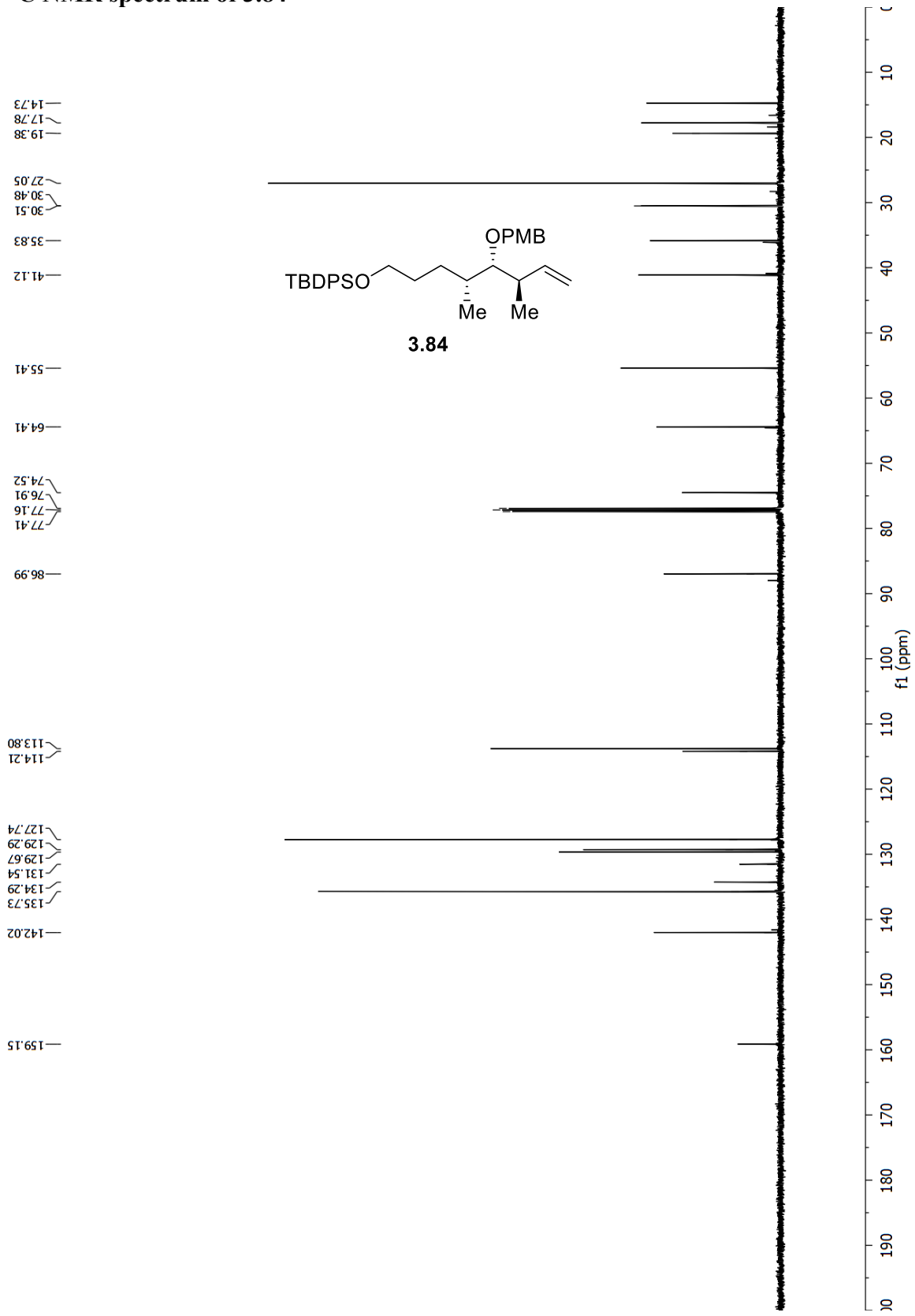
^{13}C NMR spectrum of 3.83



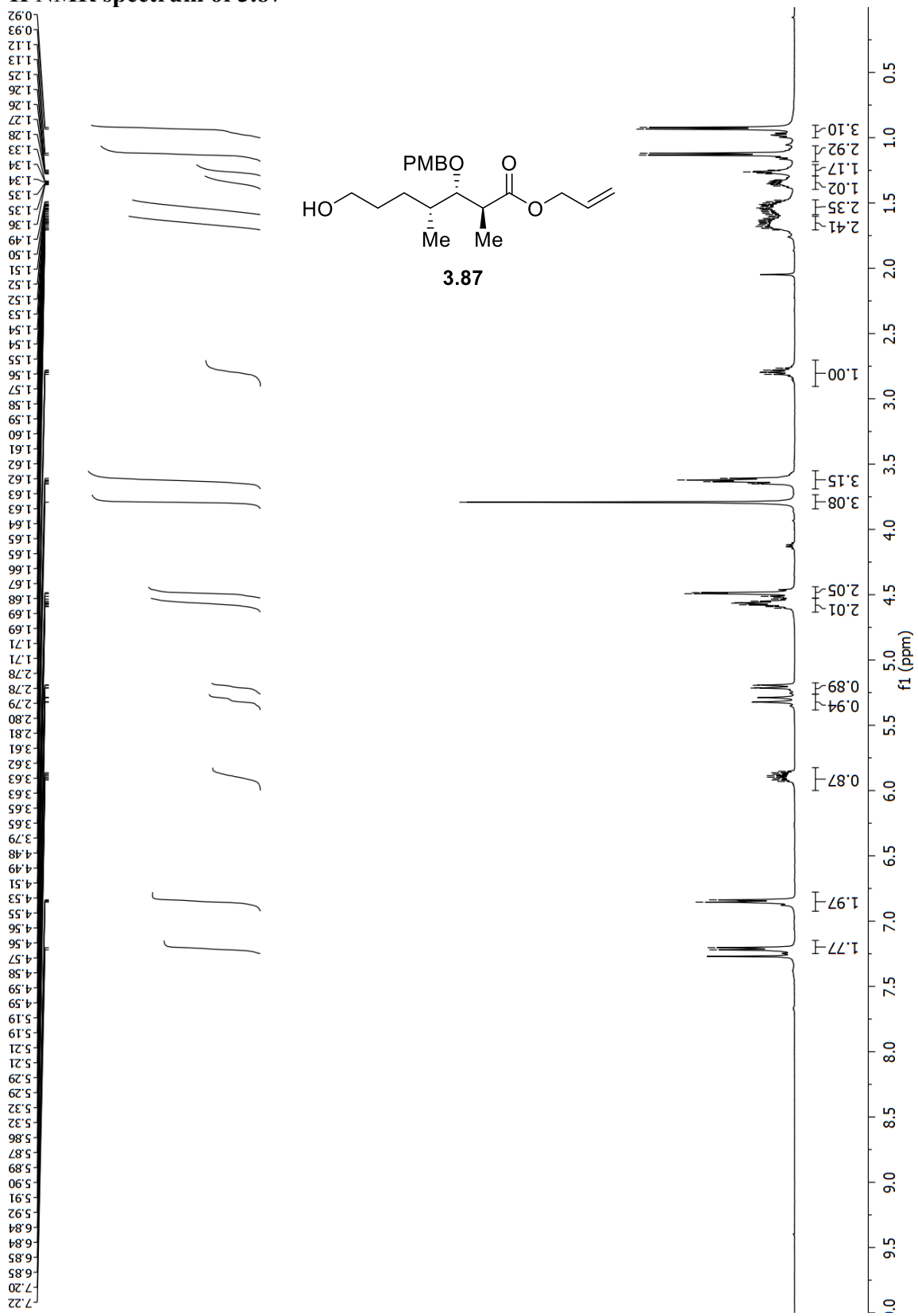
^{1}H NMR spectrum of 3.84



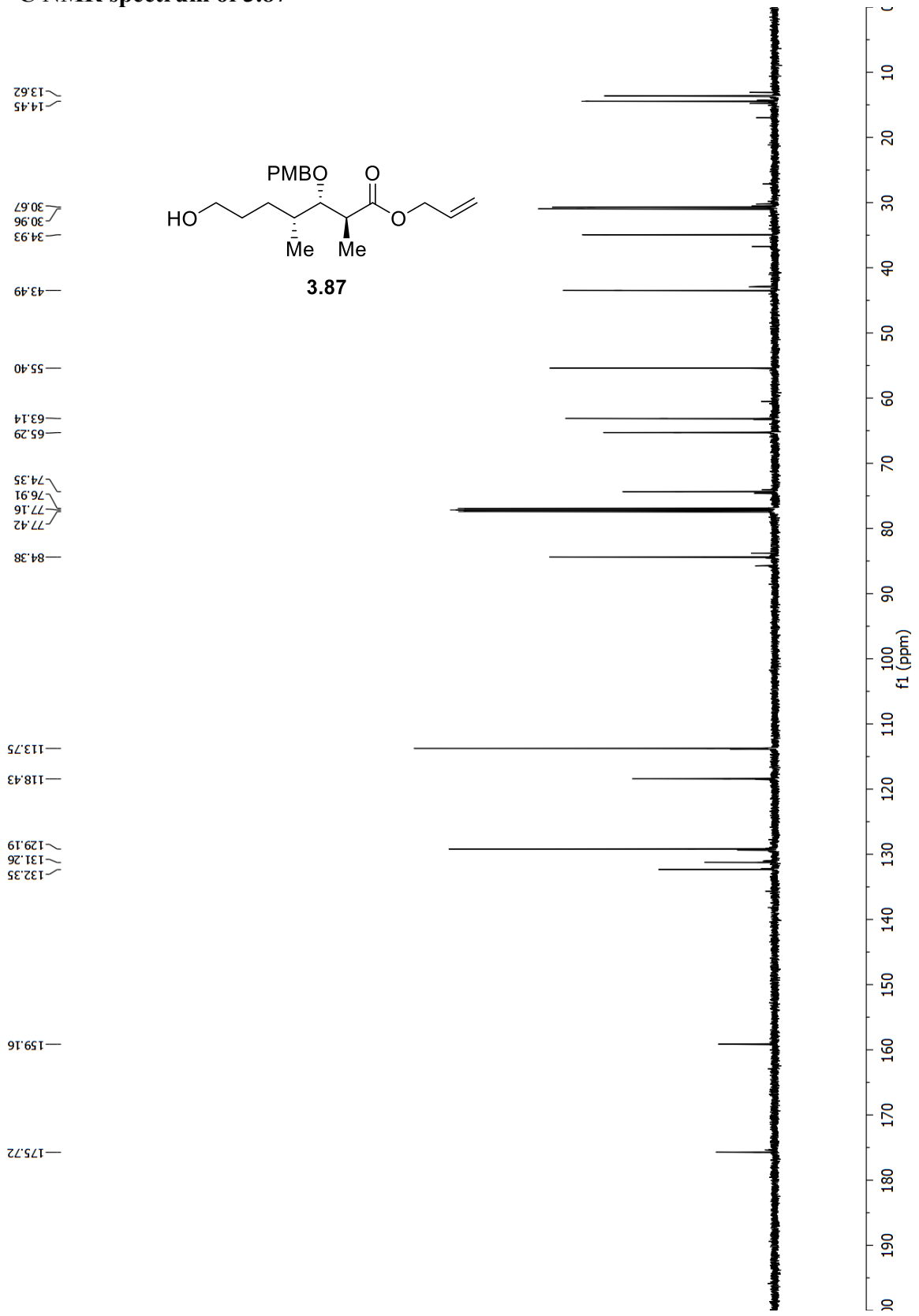
^{13}C NMR spectrum of 3.84



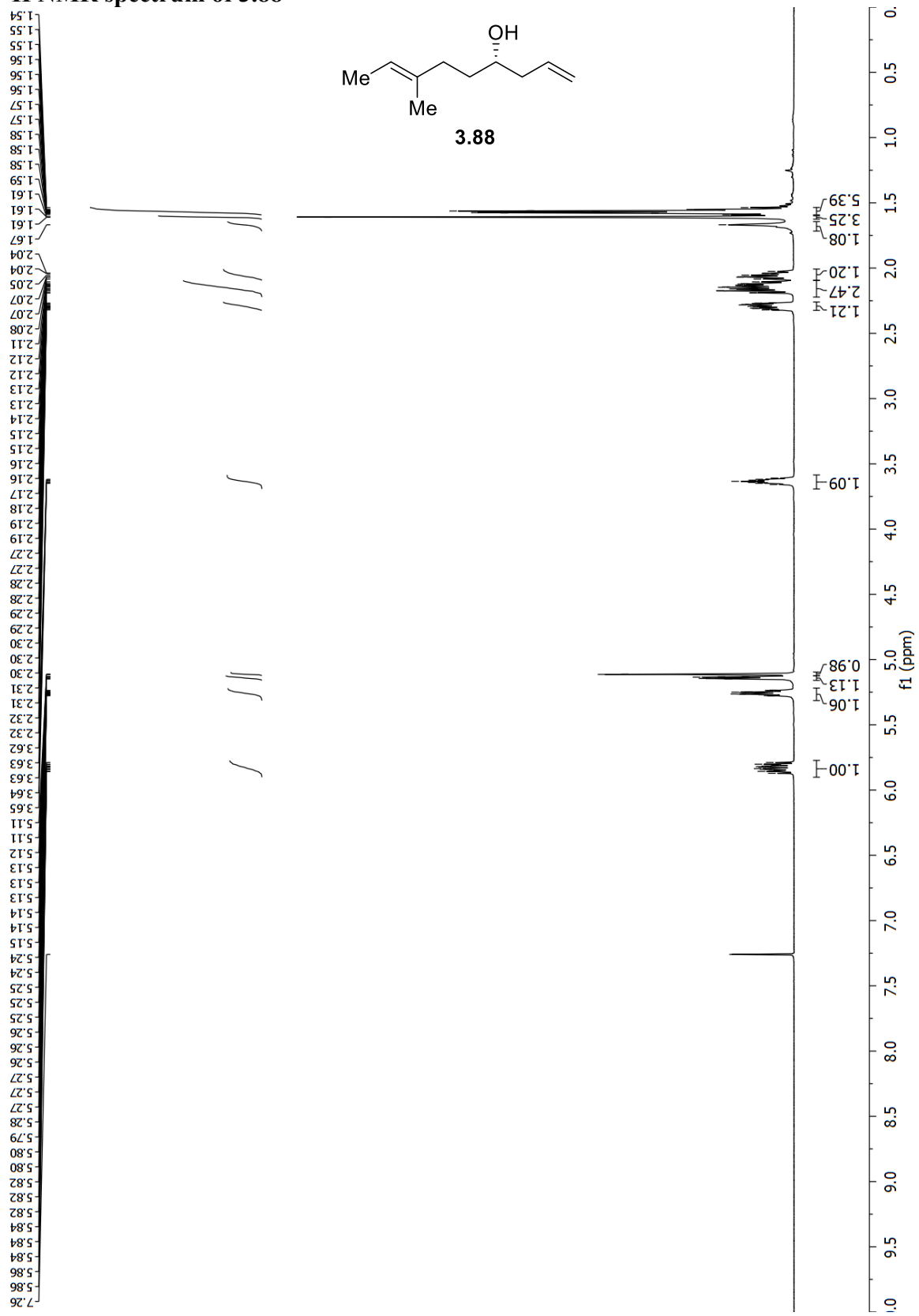
^{1}H NMR spectrum of 3.87



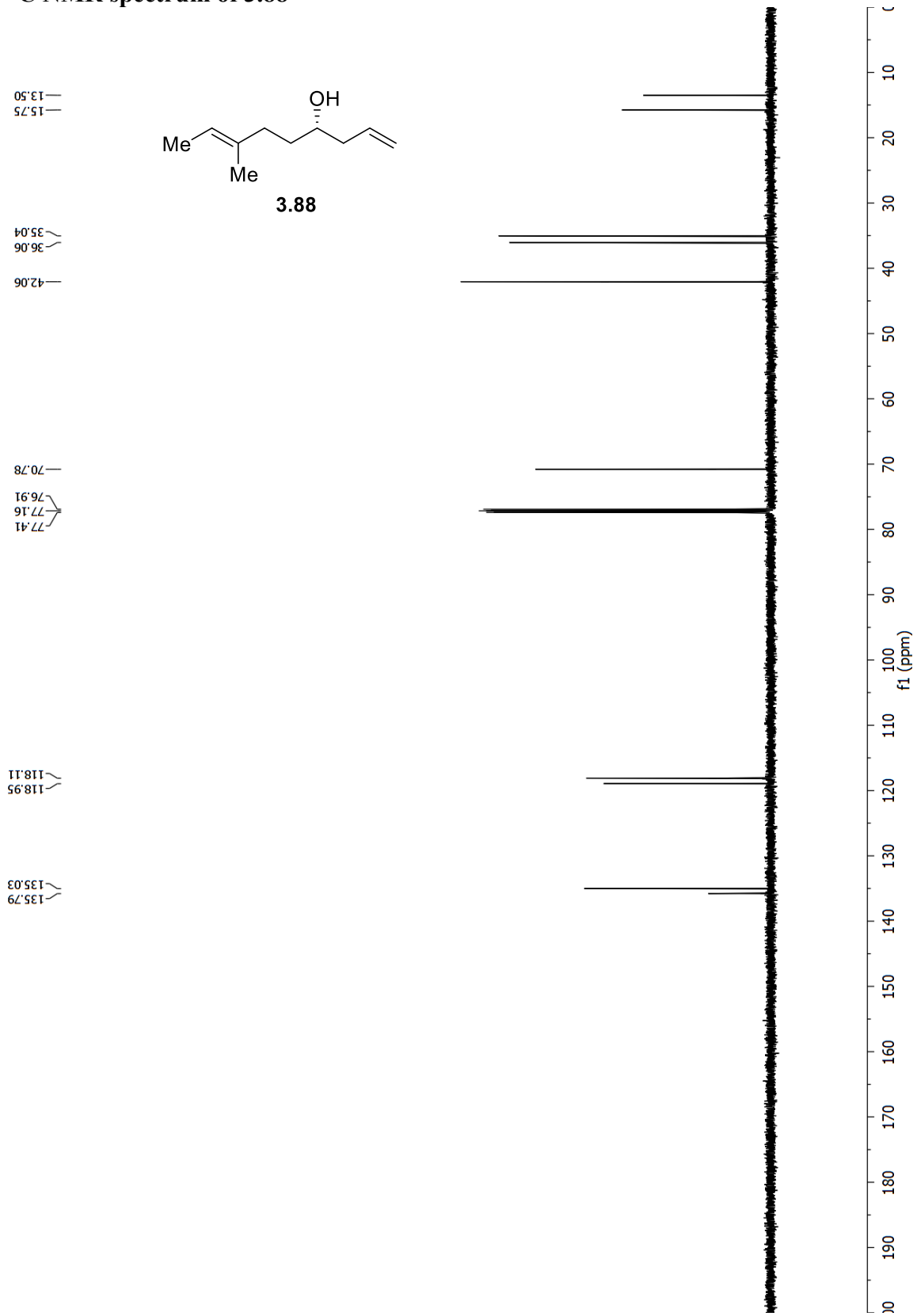
^{13}C NMR spectrum of 3.87



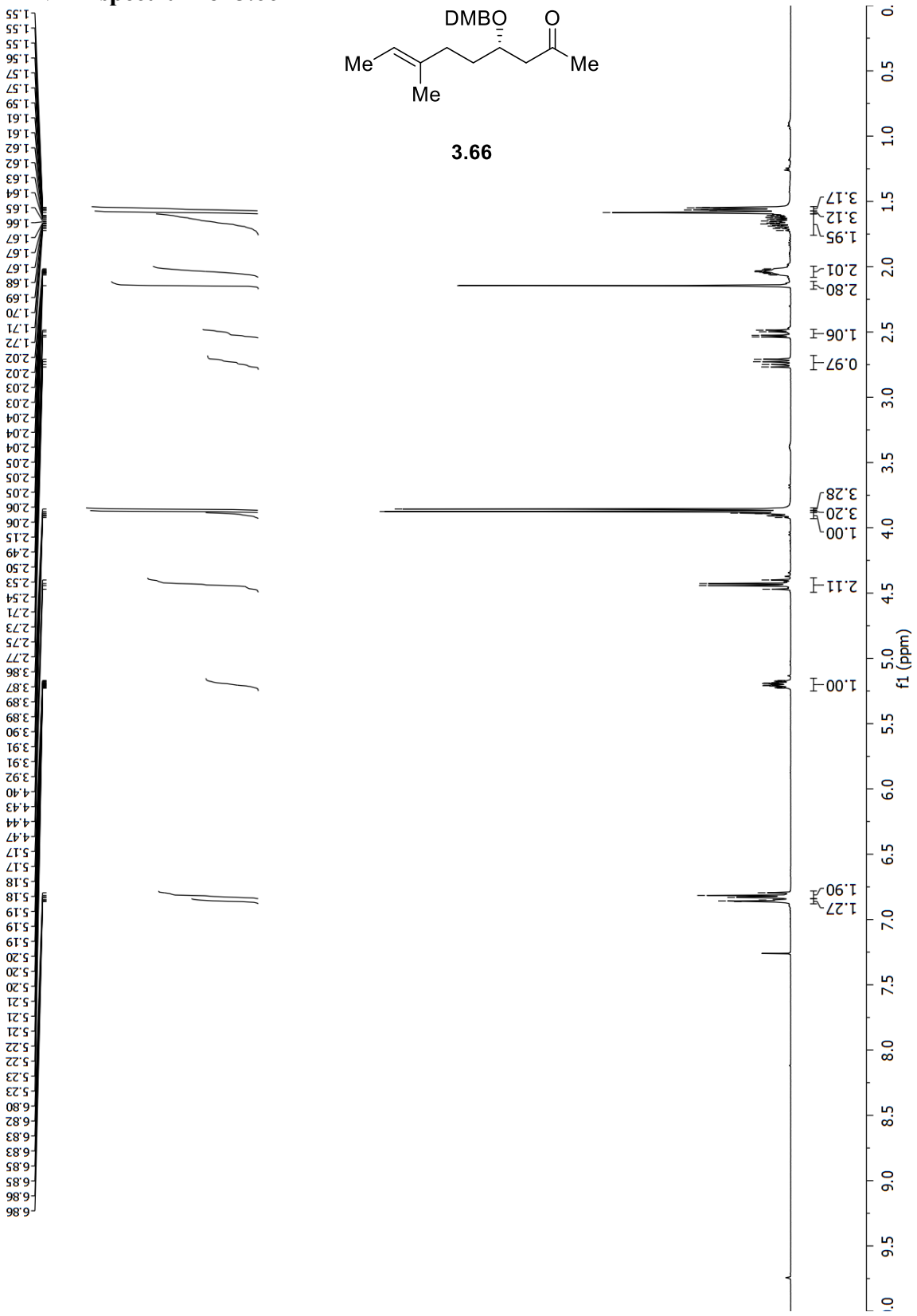
^{1}H NMR spectrum of 3.88



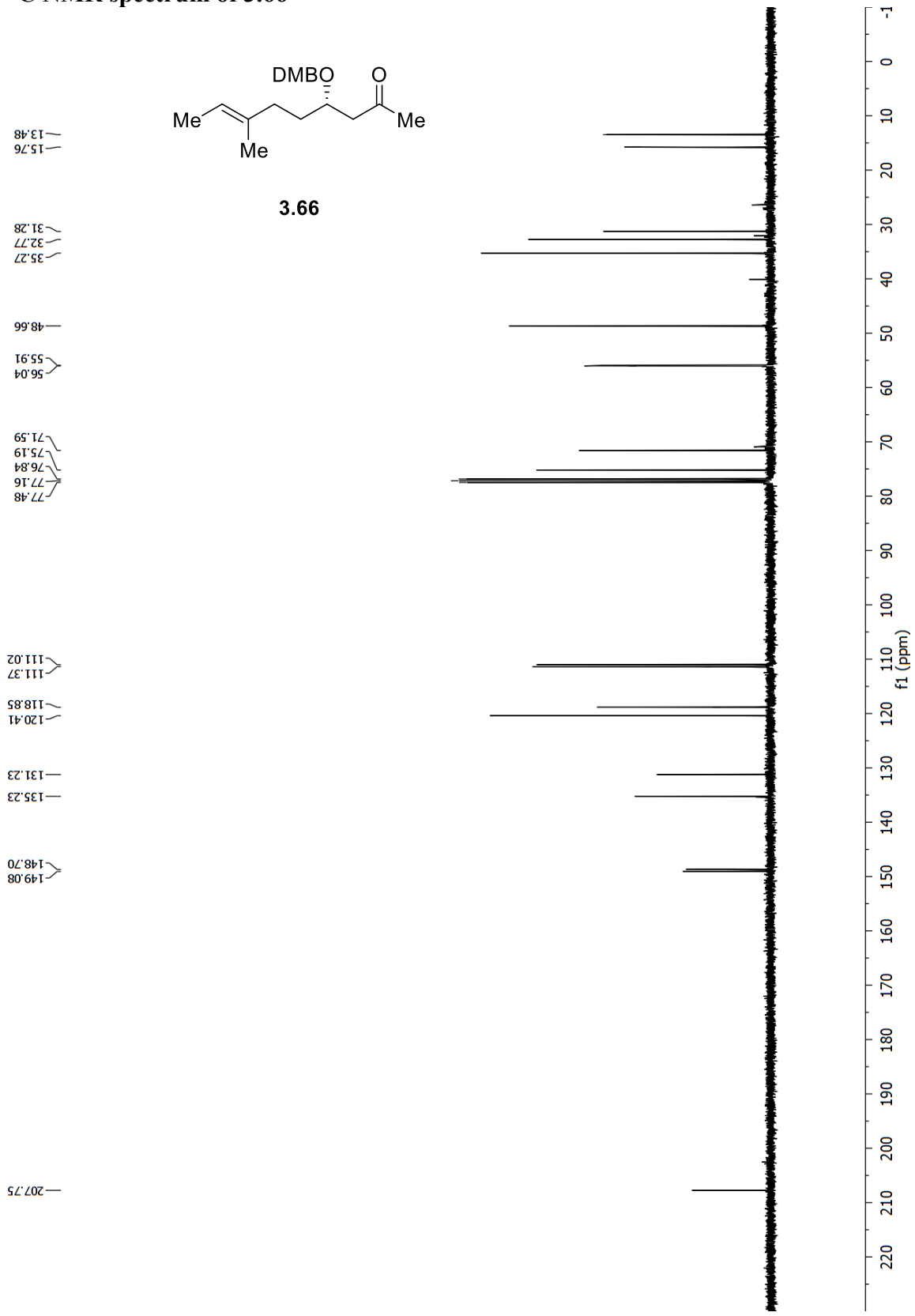
^{13}C NMR spectrum of 3.88



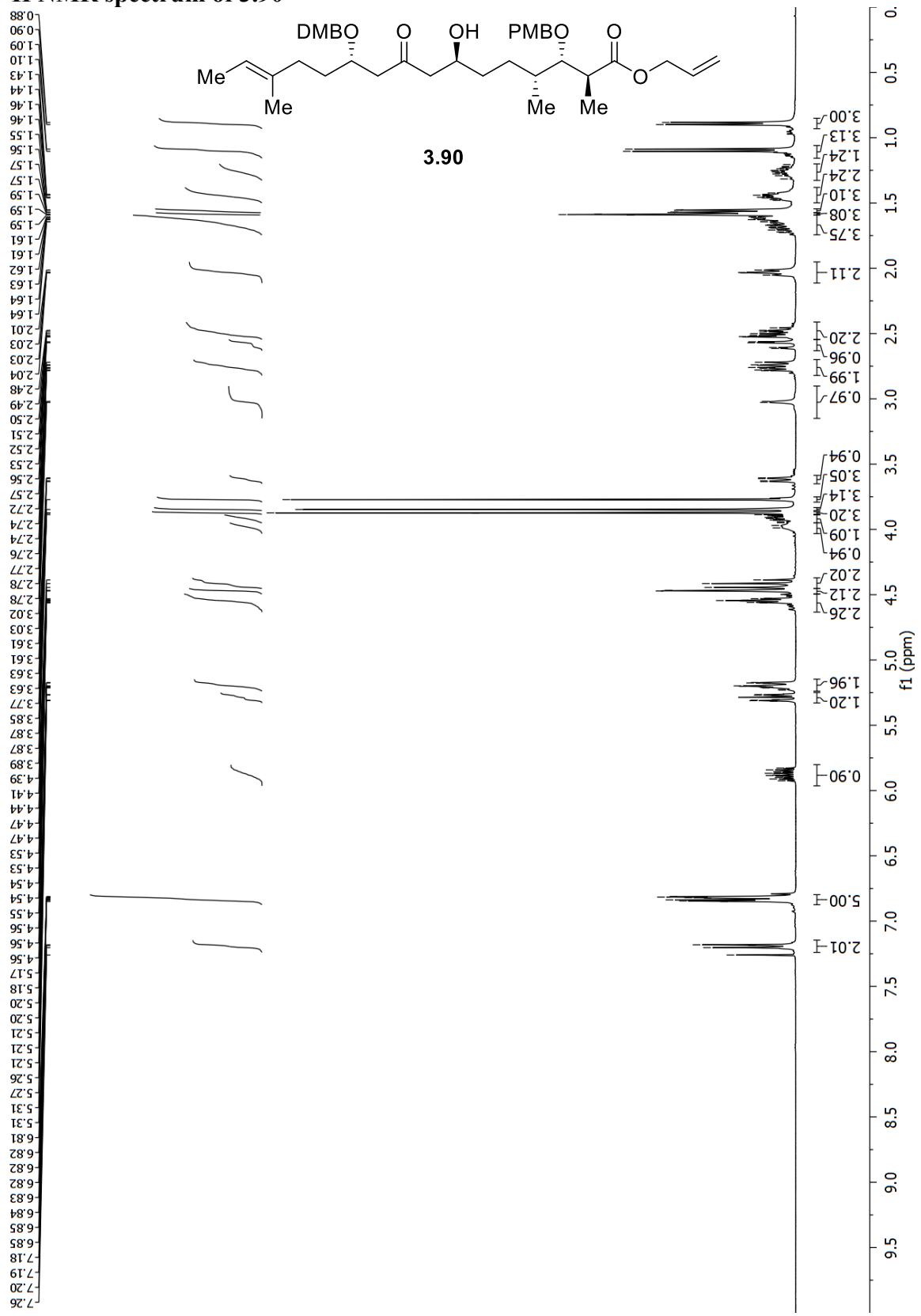
^{1}H NMR spectrum of 3.66



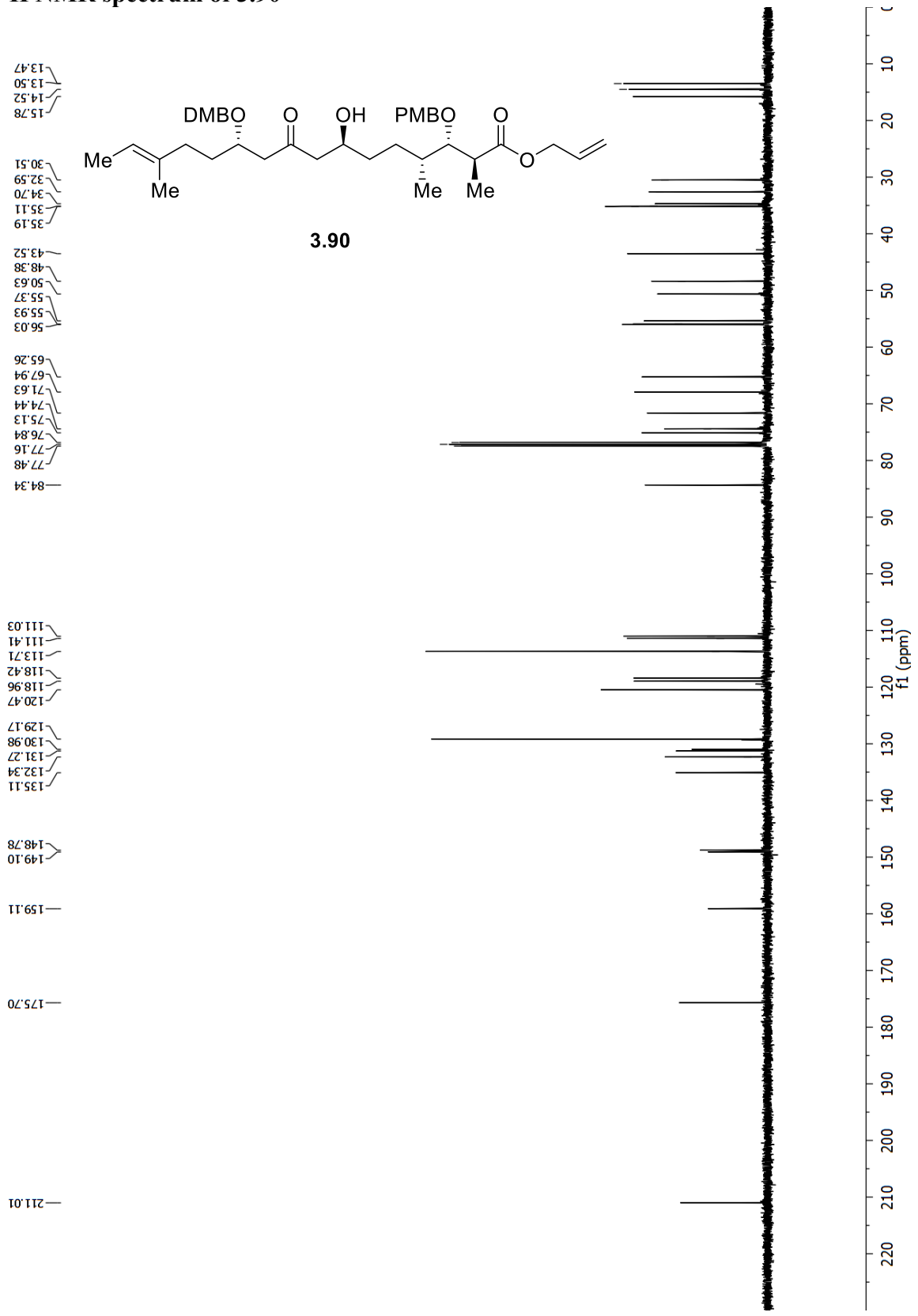
^{13}C NMR spectrum of 3.66



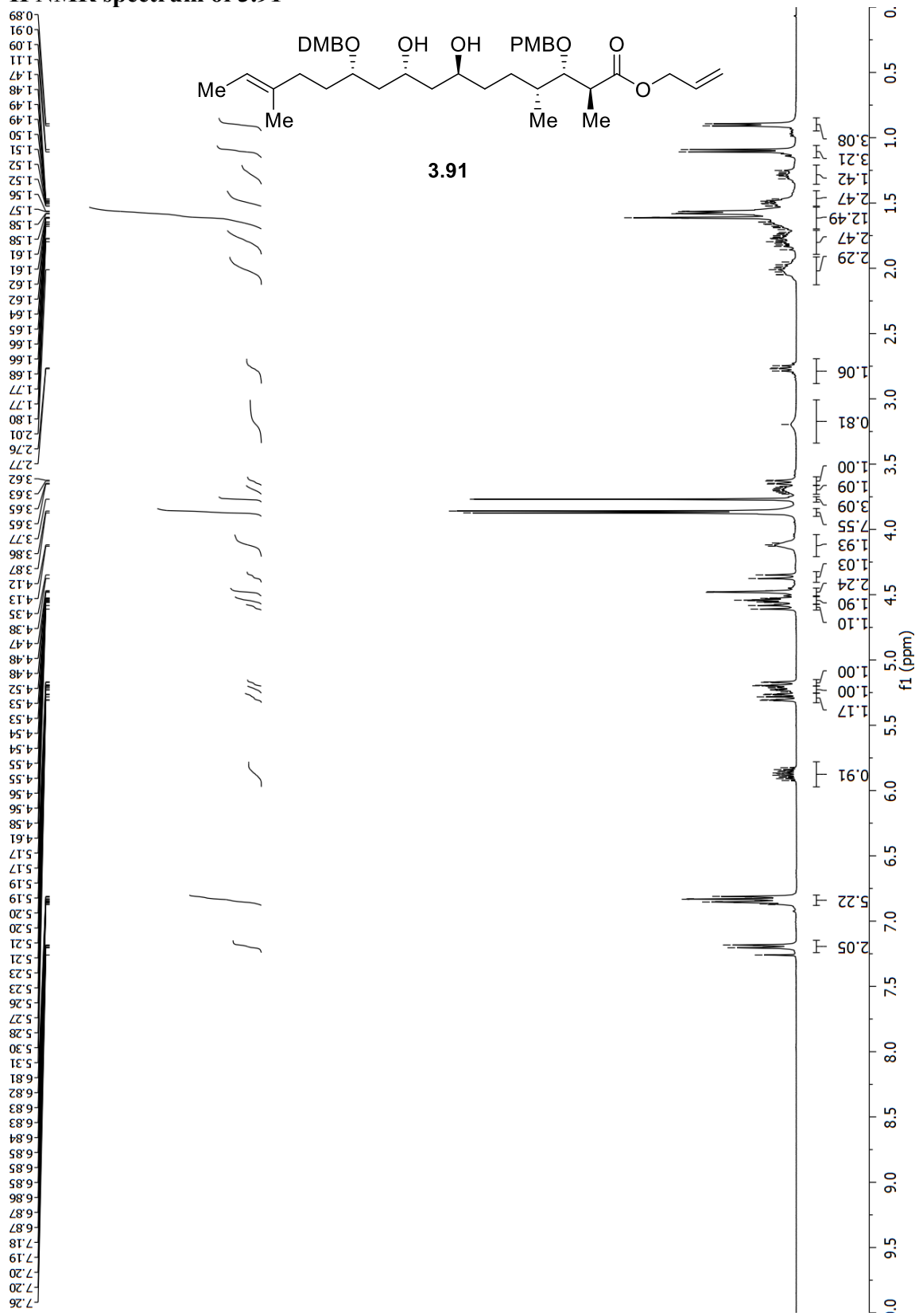
^{1}H NMR spectrum of 3.90



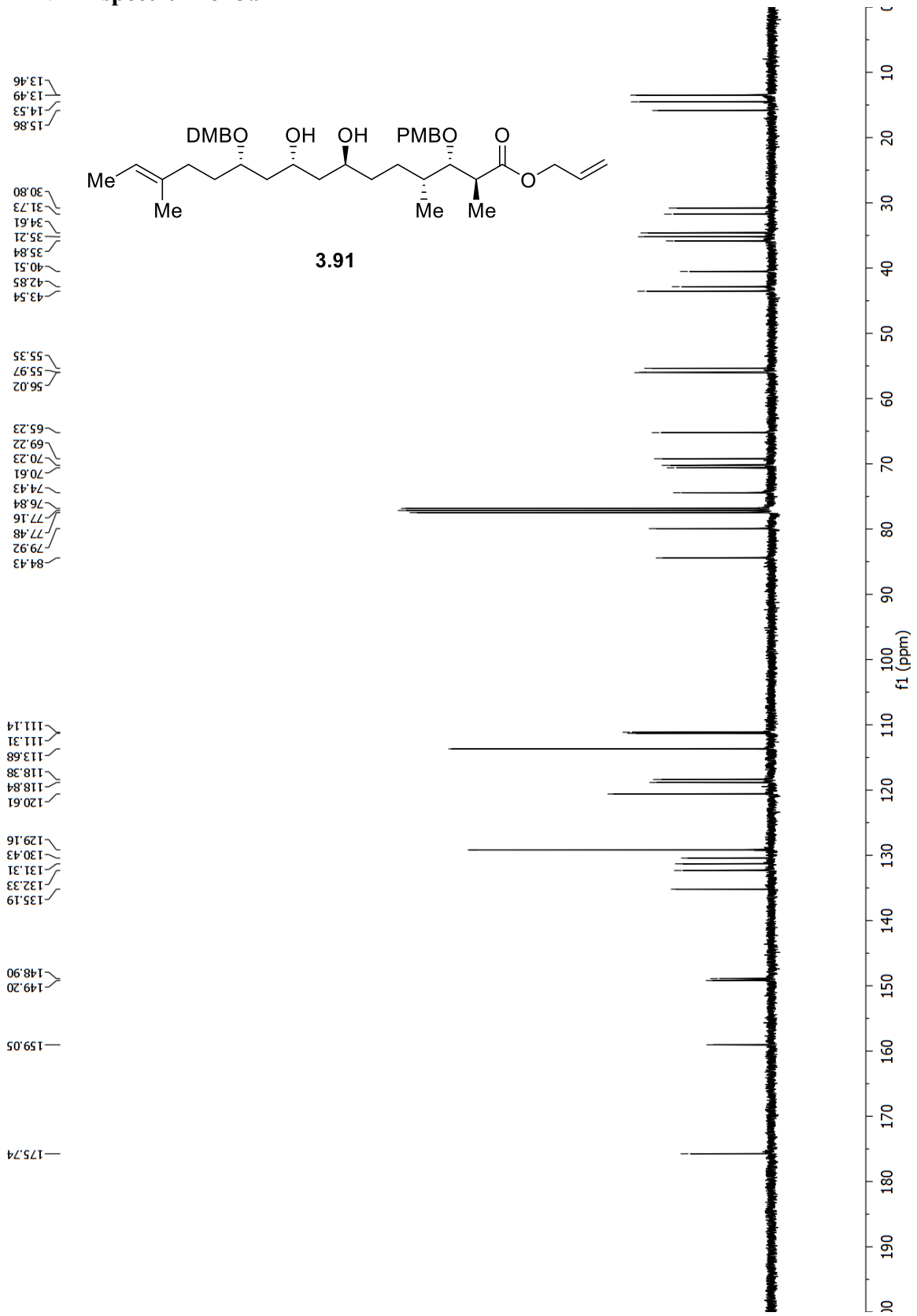
^{1}H NMR spectrum of 3.90



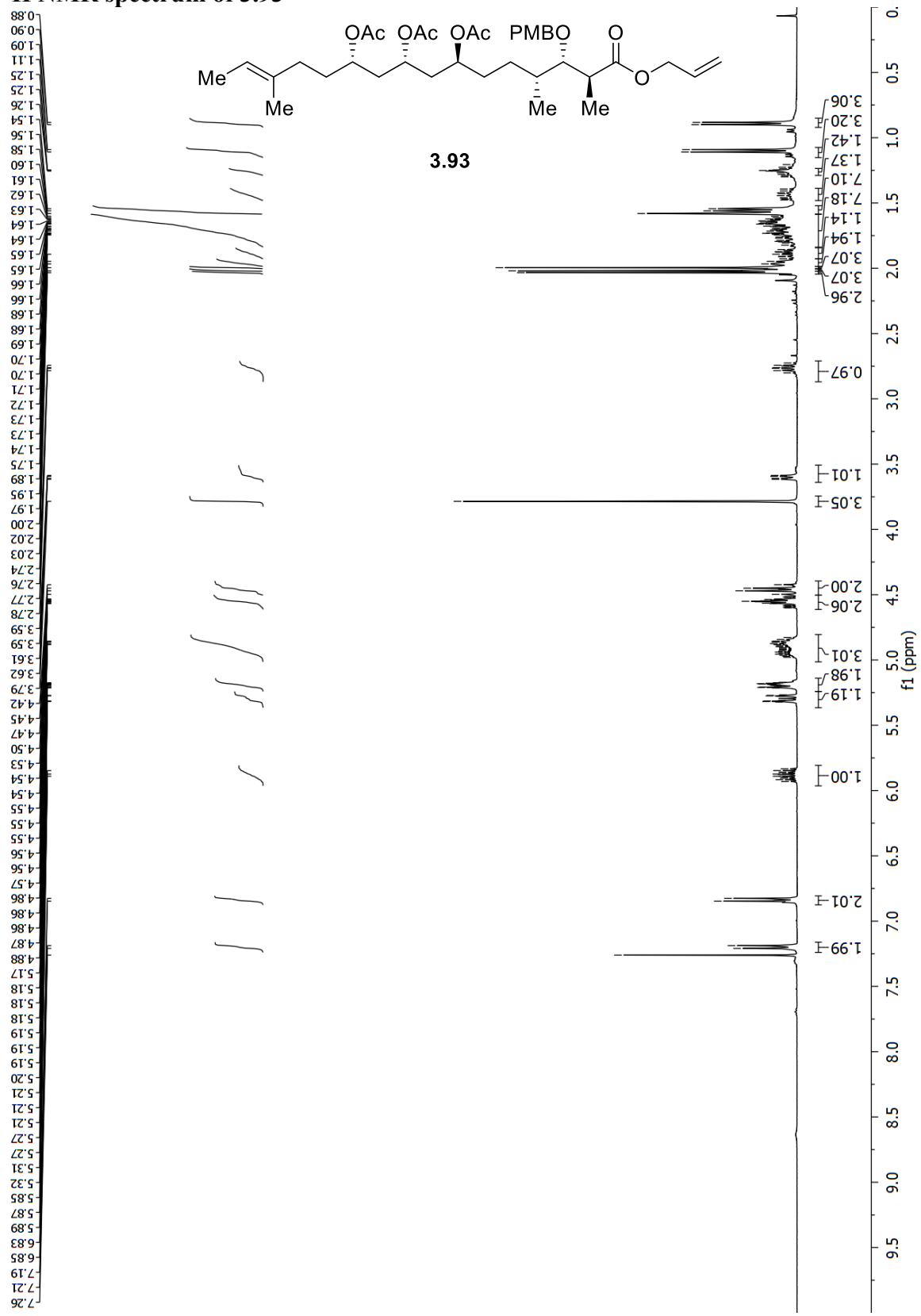
^{1}H NMR spectrum of 3.91



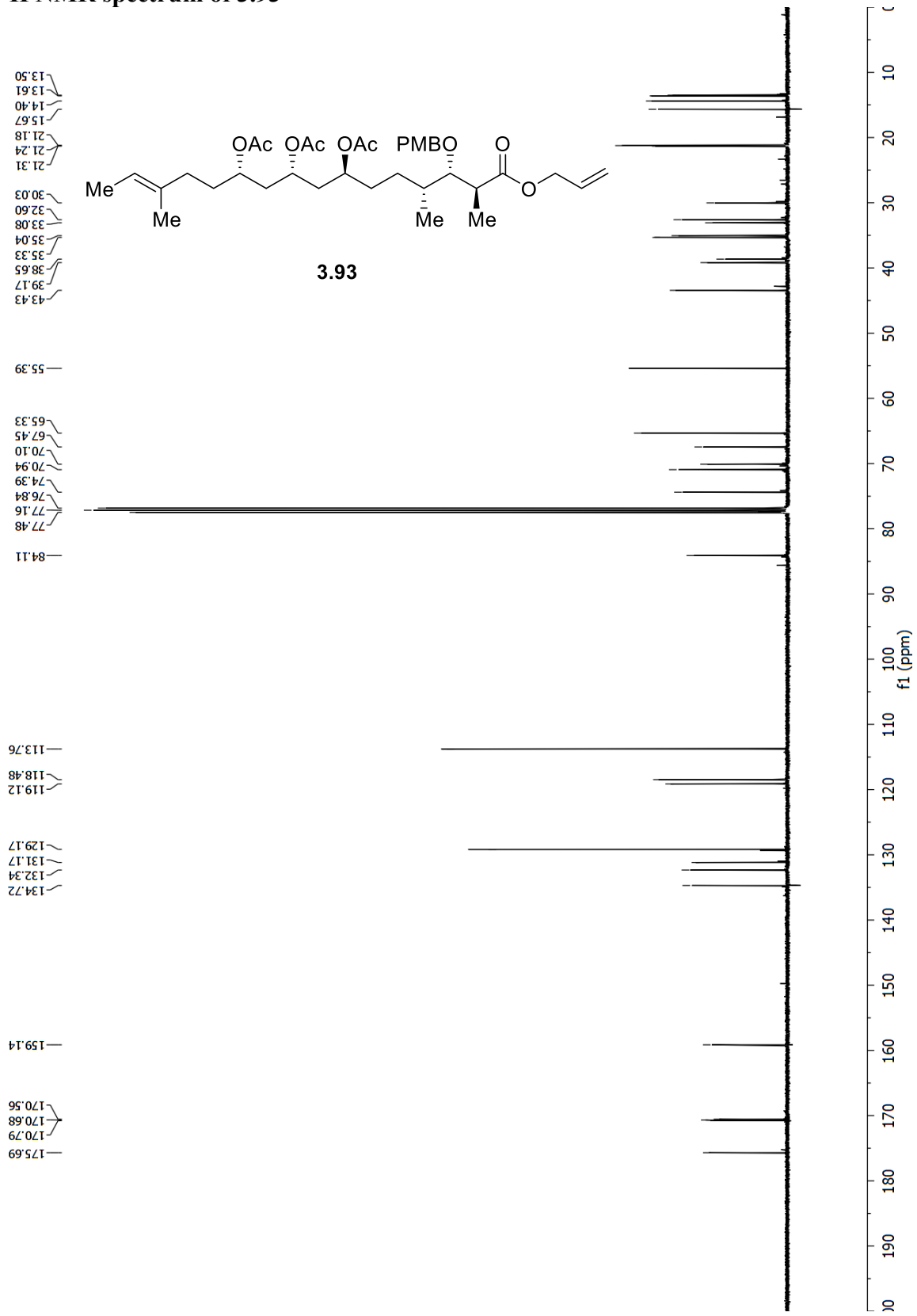
^{1}H NMR spectrum of 3.91



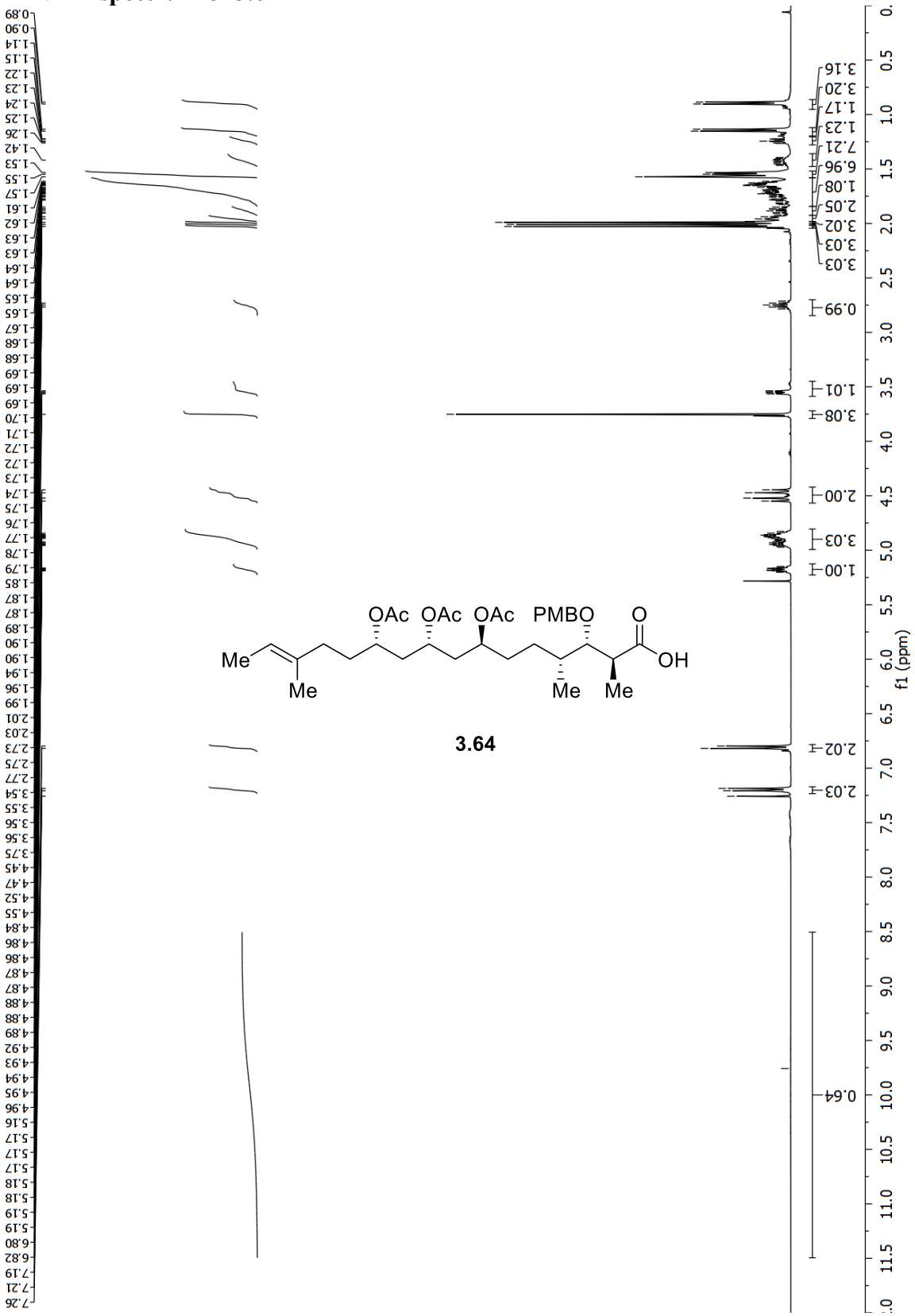
^{1}H NMR spectrum of 3.93



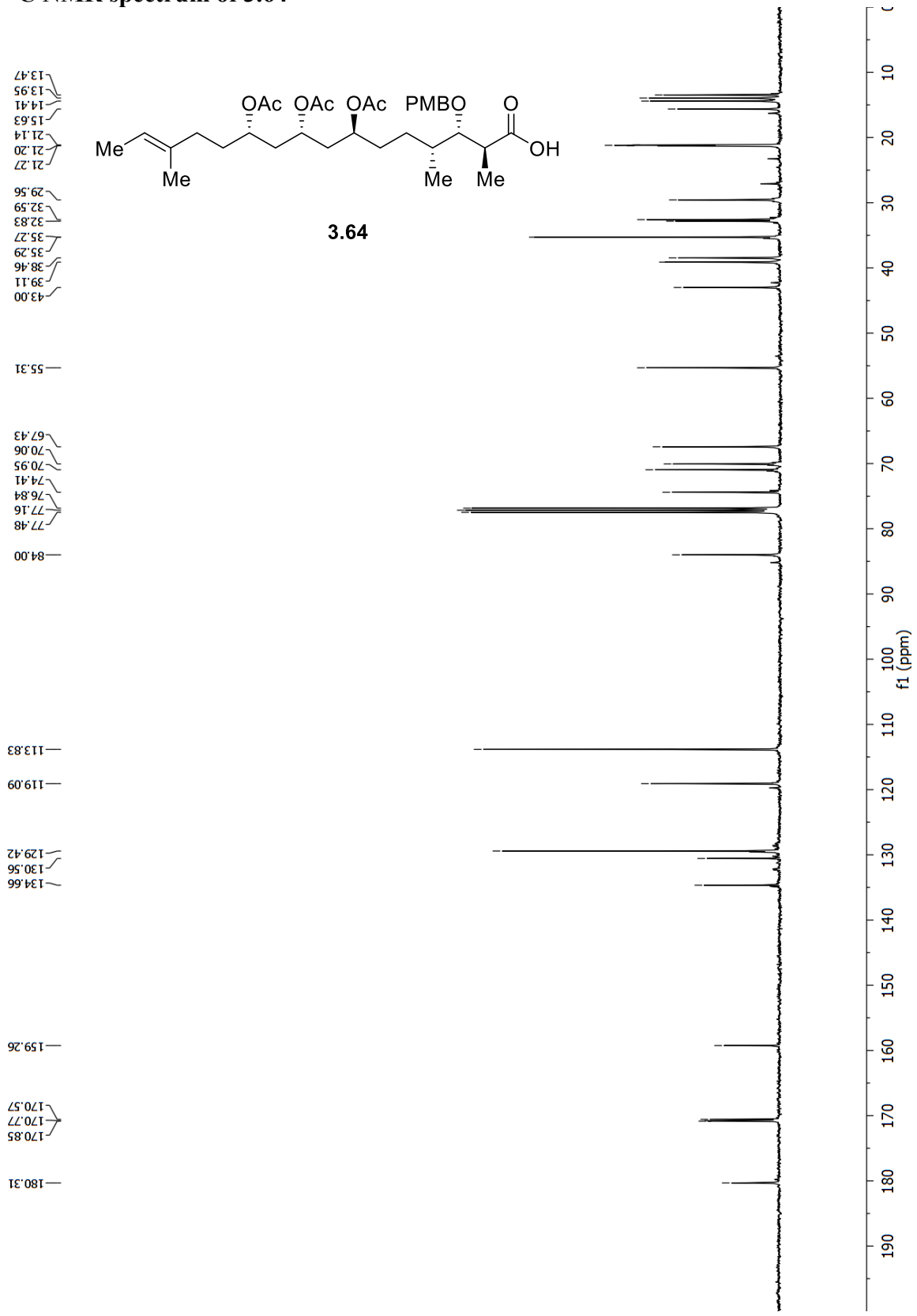
^{1}H NMR spectrum of 3.93



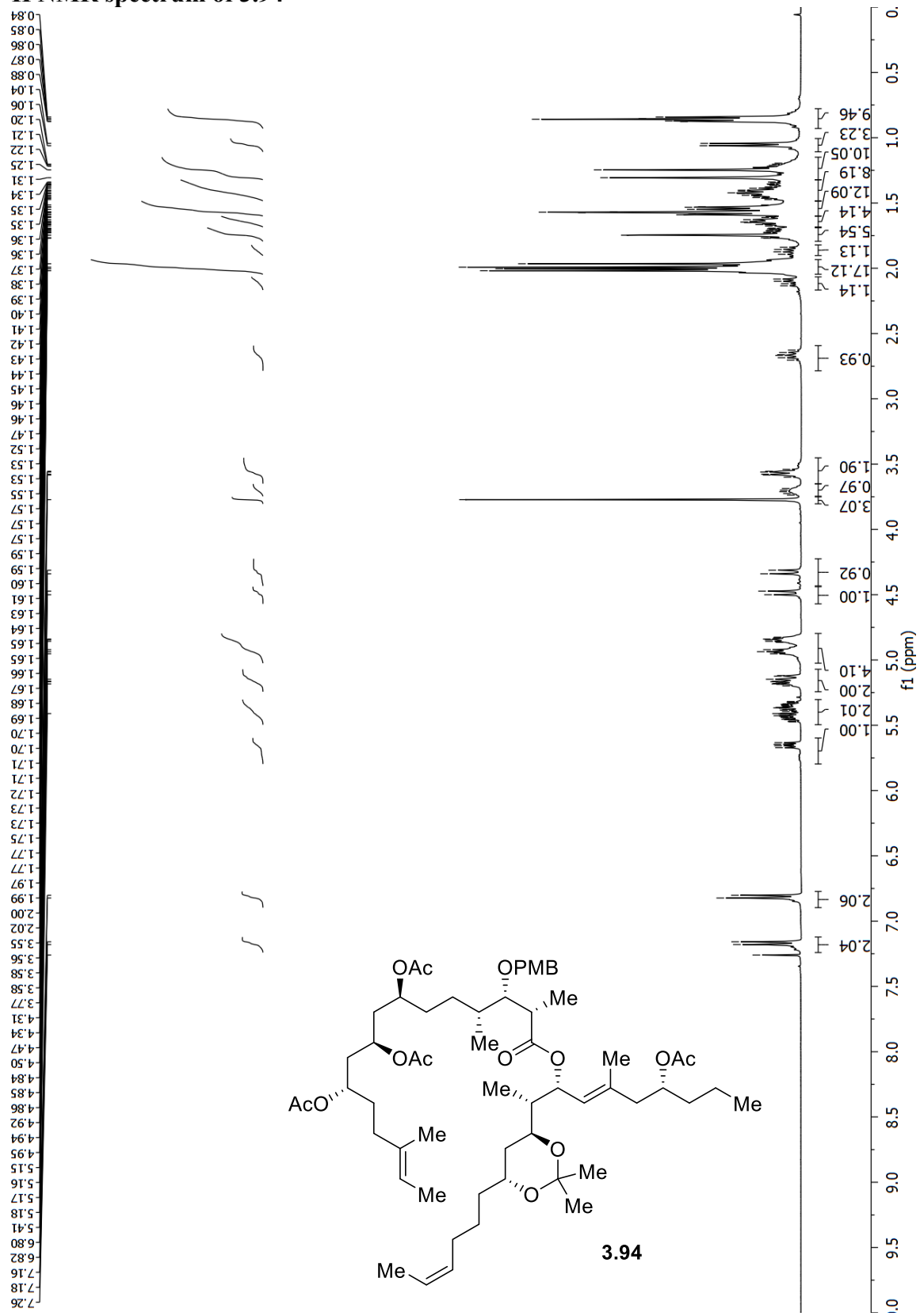
^{1}H NMR spectrum of 3.64



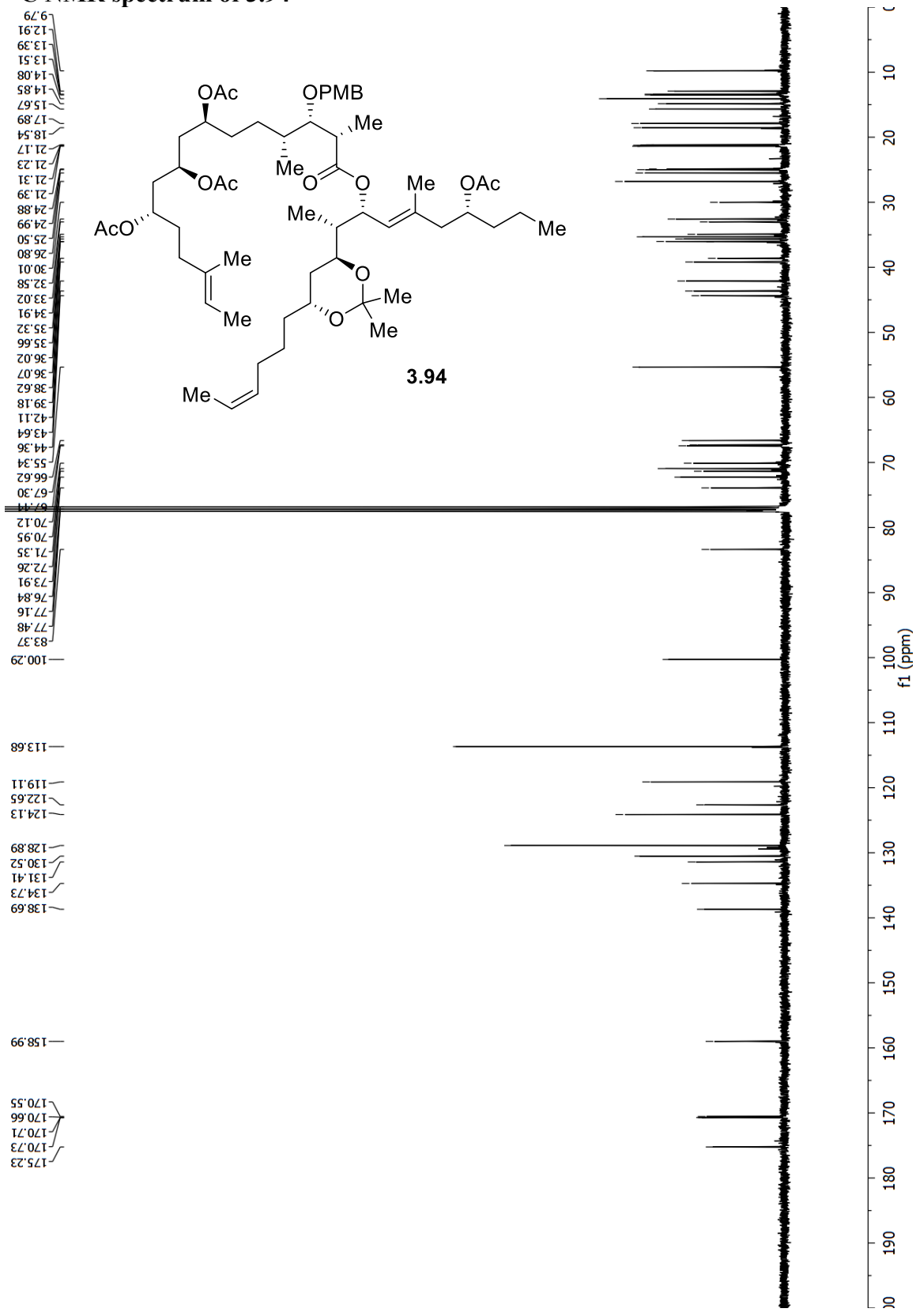
^{13}C NMR spectrum of 3.64



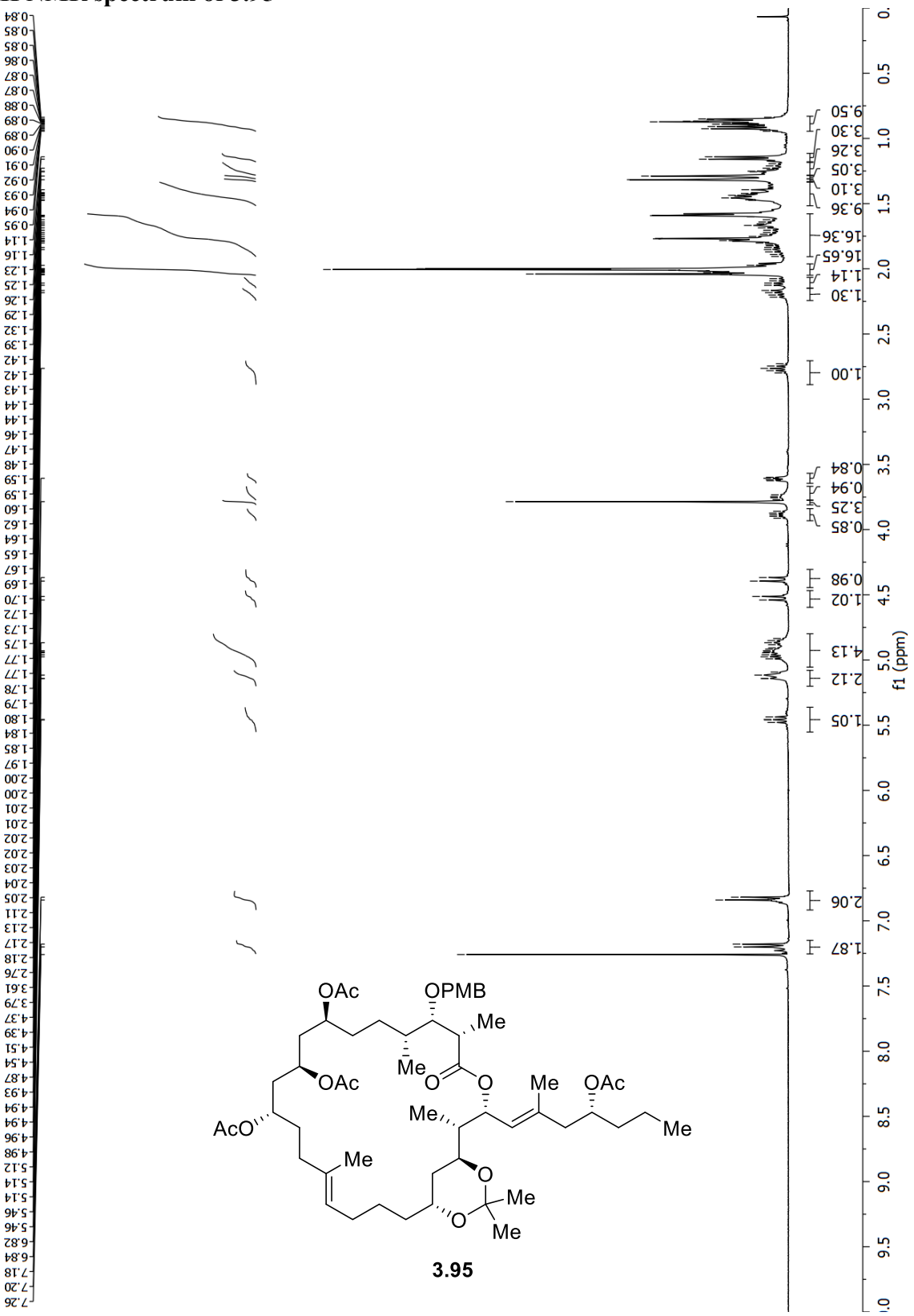
^{1}H NMR spectrum of 3.94



^{13}C NMR spectrum of 3.94

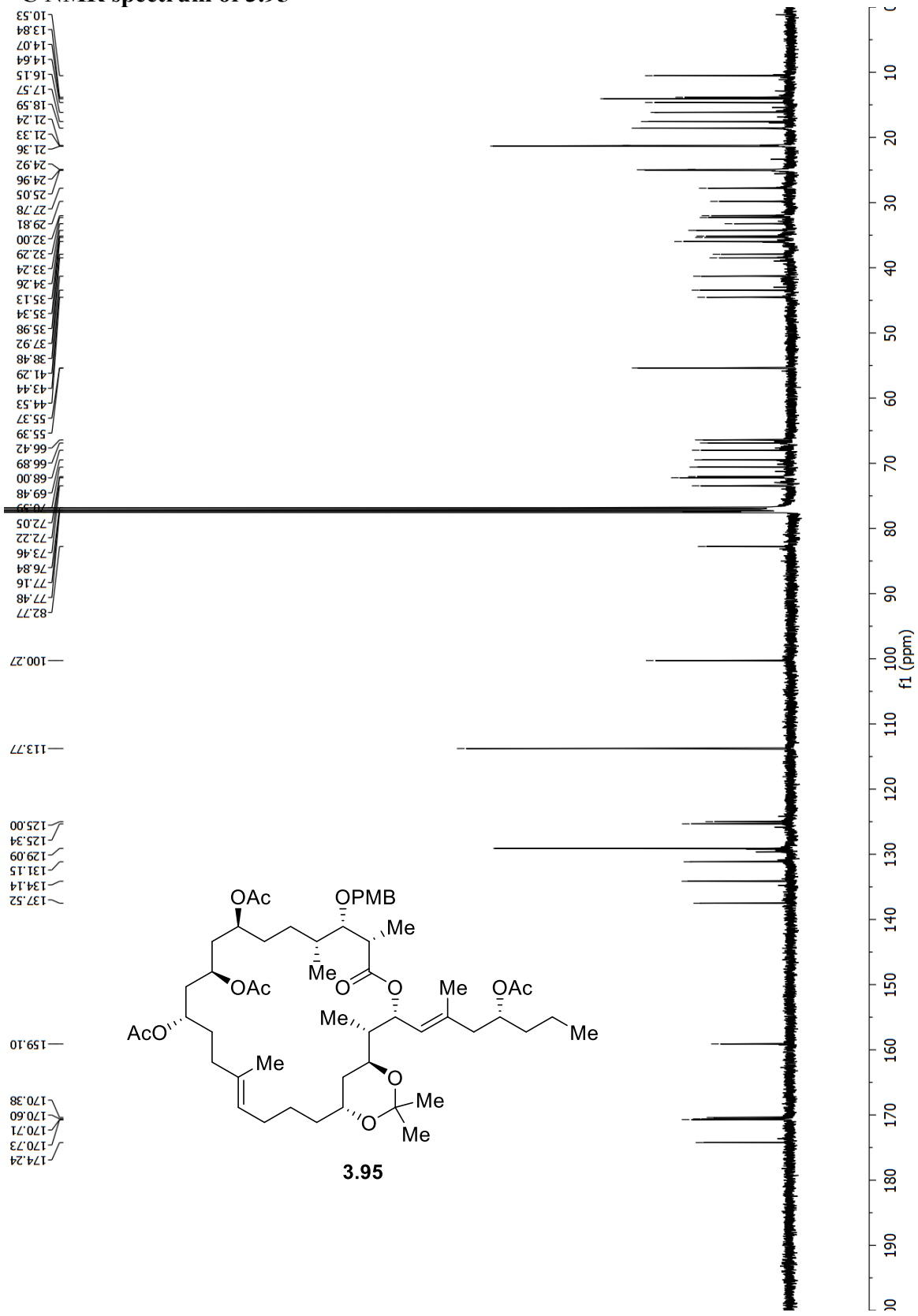


^{1}H NMR spectrum of 3.95



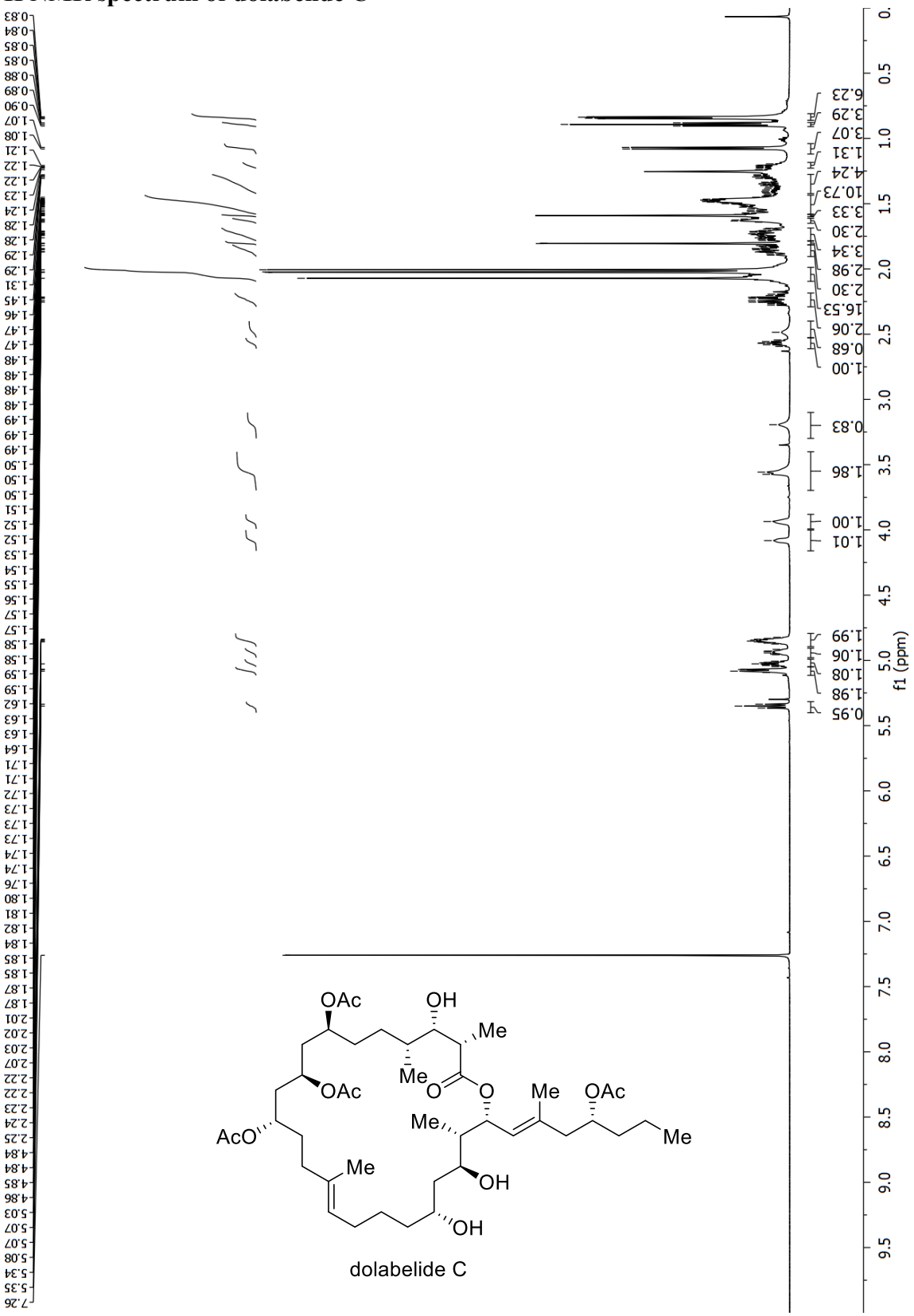
3.95

^{13}C NMR spectrum of 3.95



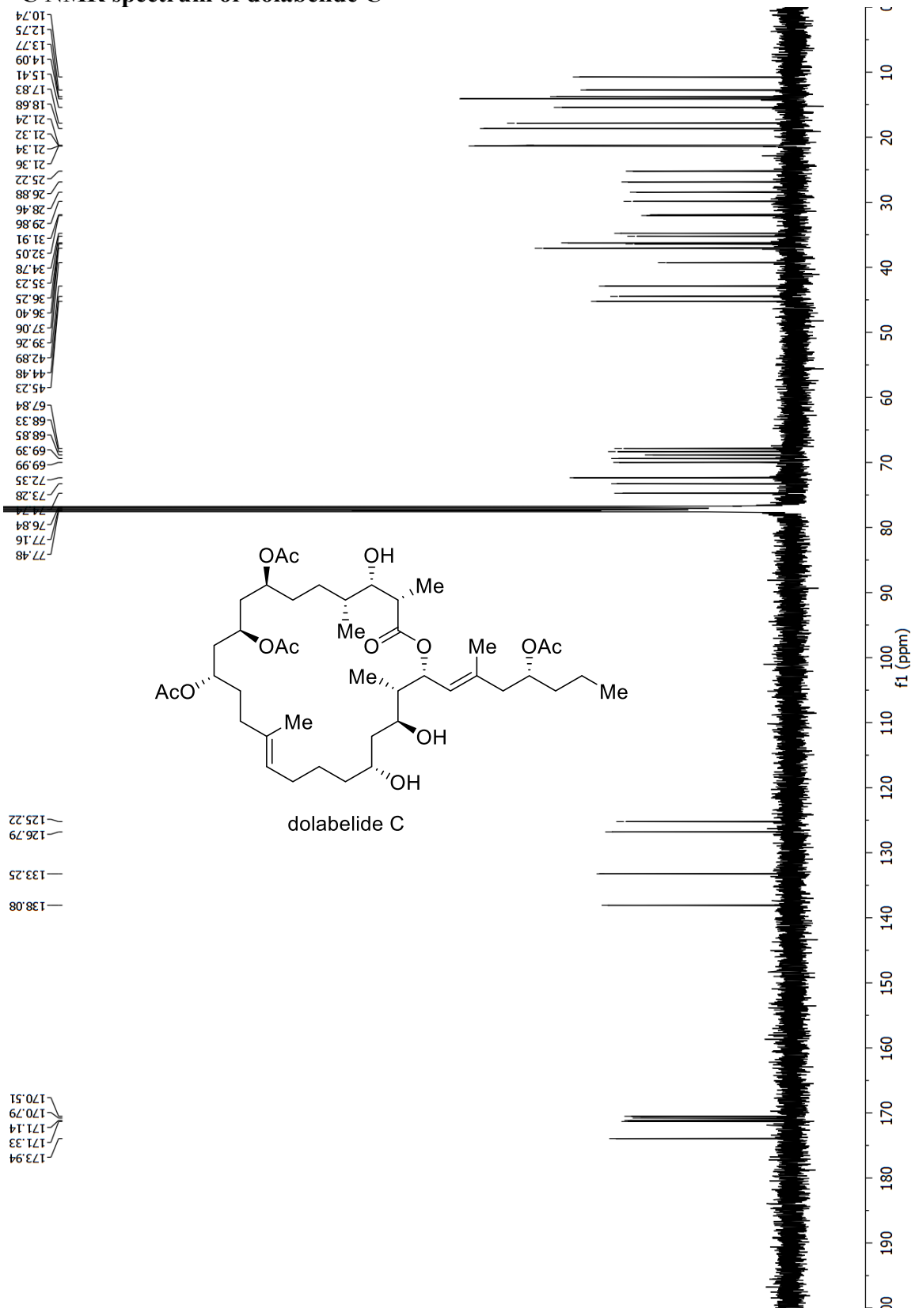
3.95

^{1}H NMR spectrum of dolabelide C



dolabelide C

^{13}C NMR spectrum of dolabelide C



Chapter Four

Stereodefined Alkenes with a Fluoro-Chloro Terminus as an Enabling Compound Class

4.1. Introduction

Fluorine-containing organic molecules are among the most important compounds in drug discovery, agrochemical development, and materials science.[1] Among such valuable chemicals, trisubstituted alkenyl fluorides are a notable subset of organofluorine compounds. They are encountered in many bioactive molecules and play an important role in finding new medicines. In the case of *Z*-trisubstituted alkenyl fluorides, they oftentimes serve as a mimic for secondary amide bonds[2], the vital linkage between amino acids in a peptide chain, impacting a peptide's stability, folding tendencies, and many other significant functions. It has been demonstrated that the replacement of the amide bond in Leu-enkephalin [3] with a trisubstituted alkenyl fluoride improved its physiochemical properties and metabolic stability significantly, enabling better bioavailability and superior distribution in the central nervous system (Scheme 4.1.1). Equally important are *E*-trisubstituted fluorine-containing alkenes as they are peptide turn

(1) (a) Jeschke, P. *ChemBioChem* **2004**, *5*, 570–589. (b) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. *J. Chem. Soc. Rev.* **2011**, *40*, 3496–3508. (c) Berger, A. A.; Völler, J.-S.; Budisa, N.; Koksch, B. *Acc. Chem. Res.* **2017**, *50*, 2093–2103. (d) Meanwell, N. A. *J. Med. Chem.* **2018**, *61*, 5822–5880. (e) Mei, H.; Remete, A, M.; Zou, Y.; Moriwaki, H.; Fustero, S.; Kiss, L.; Soloshonok, V. A.; Han, J. *Chinese Chem. Lett.* **2020**, *31*, 2401–2413.
(2) (a) Oishi, S.; Kamitani, H.; Kodera, Y.; Watanabe, K.; Kobayashi, K.; Narumi, T.; Tomita, K.; Ohno, H.; Naito, T.; Kodama, E.; Matsuoka, M.; Fujii, N. *Org. Biomol. Chem.* **2009**, *7*, 2872–2877. (b) Yanai, H.; Taguchi, T. *Eur. J. Org. Chem.* **2011**, 5939–5954. (c) Landelle, G.; Bergeron, M.; Turcotte-Savard, M.-O.; Paquin, J.-F. *Chem. Soc. Rev.* **2011**, *40*, 2867–2908. (d) Drouin, M.; Hamel, J.-D.; Paquin, J.-F. *Synthesis* **2018**, *50*, 881–995.
(3) Altman, R. A.; Sharma, K. K.; Rajewski, L. G.; Toren, P. C.; Baltezor, M. J.; Pal, M.; Karad, S. N. *ACS Chem. Neurosci.* **2018**, *9*, 1735–1742.

inducers[4], which are metabolically stable surrogates for the higher energy secondary amide bond, offering a great opportunity for studying their biological activities.[5] Furthermore, substitution of one or more C-H bonds with C-F bonds was found to increase the metabolic stability, binding affinity, and bioavailability of a drug candidate.[6] A representative example is 5-fluoro-resorcynolide[7], originating from a member of an important kinase-inhibitor family and involving a *E*-trisubstituted alkenyl fluoride moiety. The introduction of a fluorine atom to this bioactive molecule slowed down the conjugate addition of the α,β-unsaturated ketone by the cysteine residue of the kinase and therefore enhanced its inhibiting activity (Scheme 4.1.1).

Due to the rare presence of fluorine in natural products, chemical synthesis emerged as the only way to introduce fluorine into organic molecules. Although research into fluorine chemistry has drawn significant attention in synthetic chemistry[8], the methods to afford stereoselective trisubstituted alkenyl fluorides remain scarce[2b]. The lack of available methods has not only limited drug discoveries with valuable fluorinated compounds, but also thwarted studies in many other branches of scientific research, such as materials science, with fluoro-nematic acid[9] being an illustrative case (Scheme 4.1.1). Previously, it could only be synthesized and studied as a stereoisomeric mixture of *Z*- and

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(4) (a) Dumy, P.; Keller, M.; Ryan, D. E.; Rohwedder, B.; Wöhr, T.; Mutter, M. *J. Am. Chem. Soc.* **1997**, *119*, 918–925. (b) Niida, A.; Tomita, K.; Mizumoto, M.; Tanigaki, H.; Terada, T.; Oishi, S.; Otaka, A.; Inui, K.-I.; Fujii, N. *Org. Lett.* **2006**, *8*, 613–616.

(5) Marraud, M.; Dupont, V.; Grand, V.; Zerkout, S.; Lecoq, A.; Boussard, G.; Vidal, J.; Collet, A.; Aubry, A. *Biopolymers* **1993**, *33*, 1135–1148.

(6) (a) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637–643. (b) O'Hagan, D. *J. Fluor. Chem.* **2010**, *131*, 1071–1081.

(7) Jogireddy, R.; Barluenga, S.; Wissinger, N. *ChemMedChem* **2010**, *5*, 670–673.

(8) (a) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470–477. (b) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. Chem. Rev. 2011, 111, 455–529. (c) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264. (d) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826–870 (2015). (e) Zhu, Y.; Han, J.; Wang, J.; Shibata, N.; Sodeoka, M.; Soloshonok, V. A.; Coelho, J. A. S.; Toste, F. D. *Chem. Rev.* **2018**, *118*, 3887−3964.

(9) Hirschmann, H.; Schüpfer, S.; Reiffenrath, V.; Schoen, S. European Patent EP 1 215 270 B1, Sept 1, 2004.

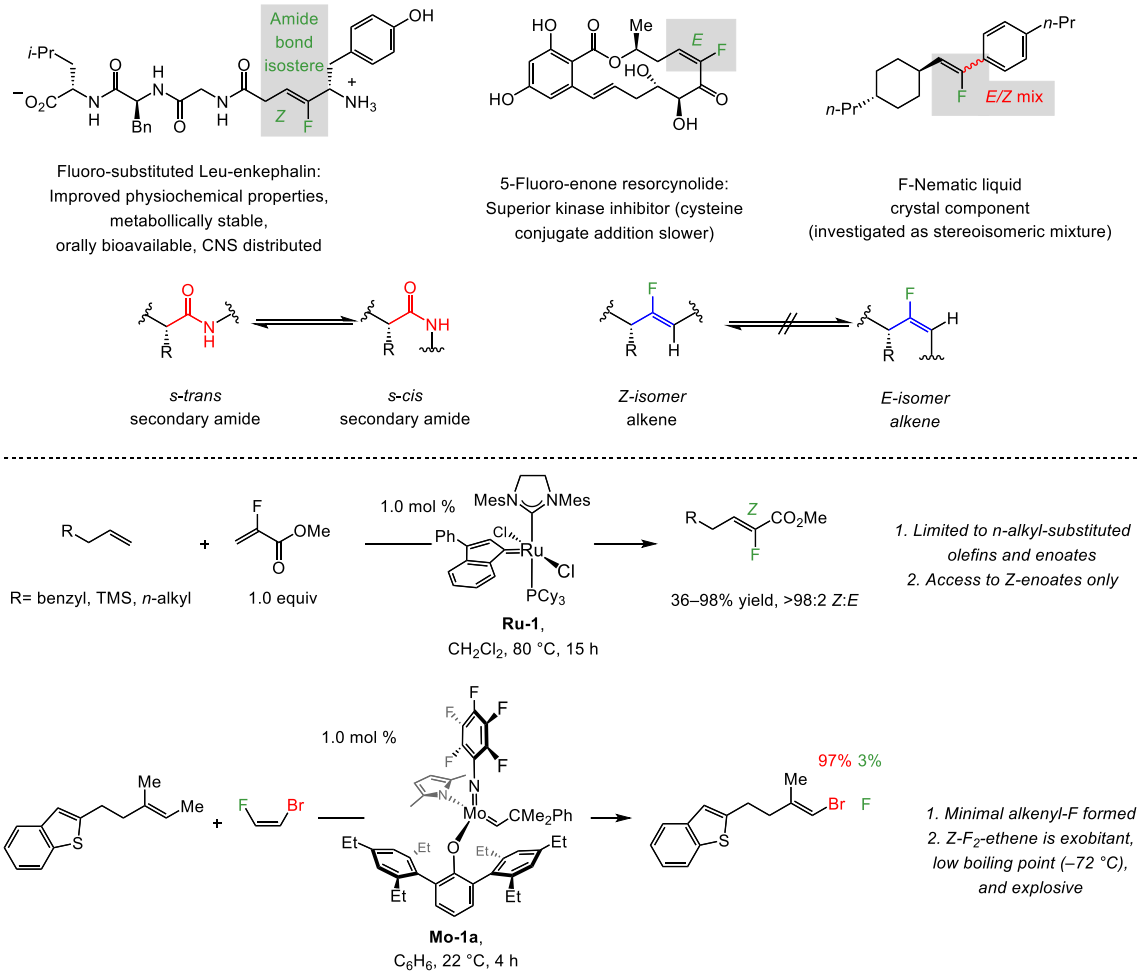
E-isomers, and the function and property of each isomer was not able to be investigated. Several studies have attempted to solve this issue but limitations remain.[2,10] In most cases, only aryl-substituted fluorine-containing olefins can be accessed. Stereoselectivity is another issue as either there is low *E*:*Z* selectivity or only the *Z*-isomer can be obtained, which is actually the low energy secondary amide bond analogue, rendering the exploration of the other isomer impossible. A compendium of previous reports on synthesis of trisubstituted alkenyl fluorides can be found in the *Experimental Section*.

Olefin metathesis, one of the most attractive strategies to generate alkenes, has certainly been examined as a potential strategy to afford these valuable fluorinated olefins. There is a report that a *gem*-difluoro trisubstituted alkene can be formed through a catalytic cross-metathesis reaction, where the stereoselectivity is not an issue. However, functionalization of such products is limited.[11] In 2020, Couve-Bonnaire *et al.*[12] disclosed that the use of a Ru-based complex, methyl-2-fluoroacrylate, and aliphatic terminal alkenes can deliver *Z*-trisubstituted alkenyl fluorides. The transformation is efficient and stereoselective affording a variety of fluoride-containing products. Nonetheless, the method is limited to generating only α,β-unsaturated esters in one stereoisomer and only unhindered aliphatic olefins are tolerated, limiting the method's applicability to complex molecule synthesis severely. In our previous studies towards trisubstituted alkenyl halides, corresponding bromides and chlorides could be efficiently and stereoselectively generated, but the respective fluorides could not be accessed. This is due to the *Z*-F,Br-ethene starting material and the predominant formation of the Br-alkylidene (see Ref 13

(10) Burton, D. J.; Yang, Z.-Y.; Qiu, W. *Chem. Rev.* **1996**, *96*, 1641–1715.
(11) Takahira, Y.; Morizawa, Y. *J. Am. Chem. Soc.* **2015**, *137*, 7031–7034.
(12) Nouaille, A.; Pannecoucke, X.; Poisson, T.; Couve-Bonnaire, S. *Adv. Synth. Catal.* **2011**, *363*, 2140–2147.

for more details).[13] A potential alternative approach employing *Z*-F_2-ethene is not ideal as the reagent is expensive, explosive, and has a low boiling point (−72 °C). Therefore, development of an efficient and practical cross-metathesis reaction to afford trisubstituted alkenyl fluorides is in demand.

Scheme 4.1.1. Impacts of Trisubstituted Alkenyl Fluorides and the State-of-the-Art Cross-Metathesis



We thus envisioned that a good way to synthesize a large variety of trisubstituted alkenyl fluorides could be through the synthesis of an olefin containing both fluorine and a versatile functional handle so that the product can be easily functionalized to form a large number of valuable fluorine-containing compounds. Indeed, it has been explored

(13) Nguyen, T. T.; Koh, M. J.; Mann, T. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *552*, 347–354.

before that a trisubstituted alkenyl fluorides were afforded with a boryl-[14] or an iodo-unit[15]. Although the products can undergo stereospecific transformations readily, the requirement of the multistep substrate synthesis and the limitation of generating only aryl olefins in one isomer demand a better catalytic stereoselective method.

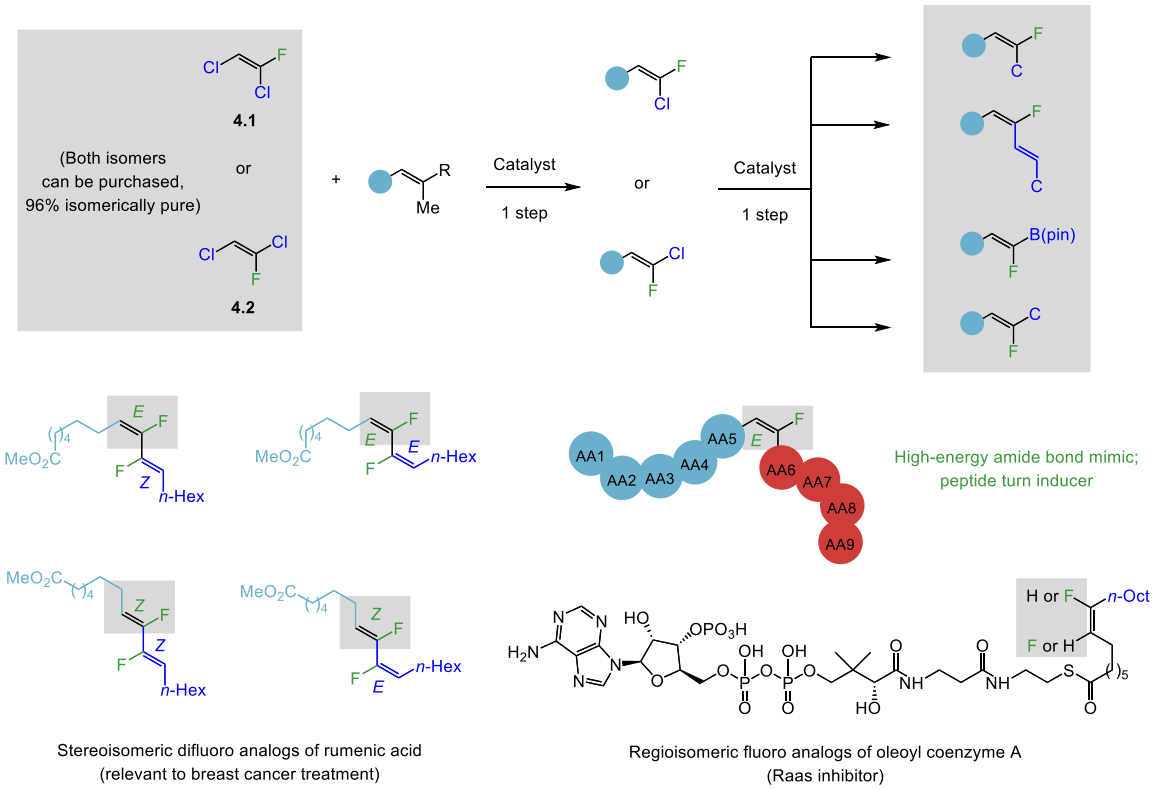
4.2. Proposed Solution and Reaction Development

We aimed to utilize a cross-metathesis strategy to synthesize these valuable moieties. Only three studies have been disclosed for trisubstituted alkene synthesis[13,16] (also see Chapter 1, Section 1.4) and all of them involve stereoretentive processes[17] to facilitate stereochemical control as well as to improve catalyst longevity.[13] With the state-of-the-art in mind, we were led to examine the feasibility of stereoretentive cross-metathesis to generate trisubstituted olefins with a fluoro,chloro-terminus (Scheme 4.2.1). The commercially available but rarely utilized trihalo-agents **4.1** and **4.2** could serve as suitable cross-partners with appropriate physical properties (e.g., boiling point at 32 and 38 °C, respectively). We envisaged that if we can successfully obtain the cross-metathesis products stereoselectively, they can be readily converted to sundry other valuable and otherwise hard-to-access trisubstituted alkenyl fluorides.[15a,18] Once we can access these valuable entities with a functional handle, such as C-B and C-C bonds, an assortment of fluoro-substituted analogs of bioactive molecules, including fluoro-rumenic acid [19]

(14) (a) Sakaguchi, H.; Uetake, Y.; Ohashi, M.; Niwa, T.; Ogoshi, S.; Hosoya, T. *J. Am. Chem. Soc.* **2017**, *139*, 12855–12862. (b) Zhang, J.; Dai, W.; Liu, Q.; Cao, S. *Org. Lett.* **2017**, *19*, 3283–3286.
(15) (a) Andrei, D.; Wnuk, S. F. *J. Org. Chem.* **2006**, *71*, 405–408. (b) Isoda, M.; Uetake, Y.; Takimoto, T.; Tsuda, J.; Hosoya, T.; Niwa, T. *J. Org. Chem.* **2021**, *86*, 1622–1632.
(16) Xu, C.; Liu, Z.; Torker, S.; Shen, X.; Xu, D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 15640–15643.
(17) Montgomery, T. P.; Ahmed, T. S.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2017**, *56*, 11024–11036.
(18) Chen, C.; Wilcoxen, K.; Strack, N.; McCarthy, J. R. *Tetrahedron Lett.* **1999**, *40*, 827–830.
(19) Bougnoux, P.; Hajjaji, N.; Maheo, K.; Couet, C.; Chevalier, S. *Prog. Lipid Res.* **2010**, *49*, 76–86.

(slowing metastatic regrowth in breast cancer) and oleoyl coenzyme A[20] (regulator of renin-angiotensin system (Raas) interaction with DNA in mycobacteria) as well as the aforementioned peptide amide bond mimics, could be potentially synthesized (Scheme 4.2.1).

Scheme 4.2.1. Potential Cross-Metathesis Method and Its Representative Applications



We set out to test the model process with 1,2-disubstituted alkene **4.3** and trihalo-agent **4.1**. In this way, the unstable methylidene should be avoided.[21] We chose the *Z*-isomer as it is faster-initiating compared to the corresponding *E*-isomer. After some conditions screening, we identified Mo-complex **Mo-1a** as the suitable complex, which was able to promote the transformation to generate the desired alkene **4.4** in 41%

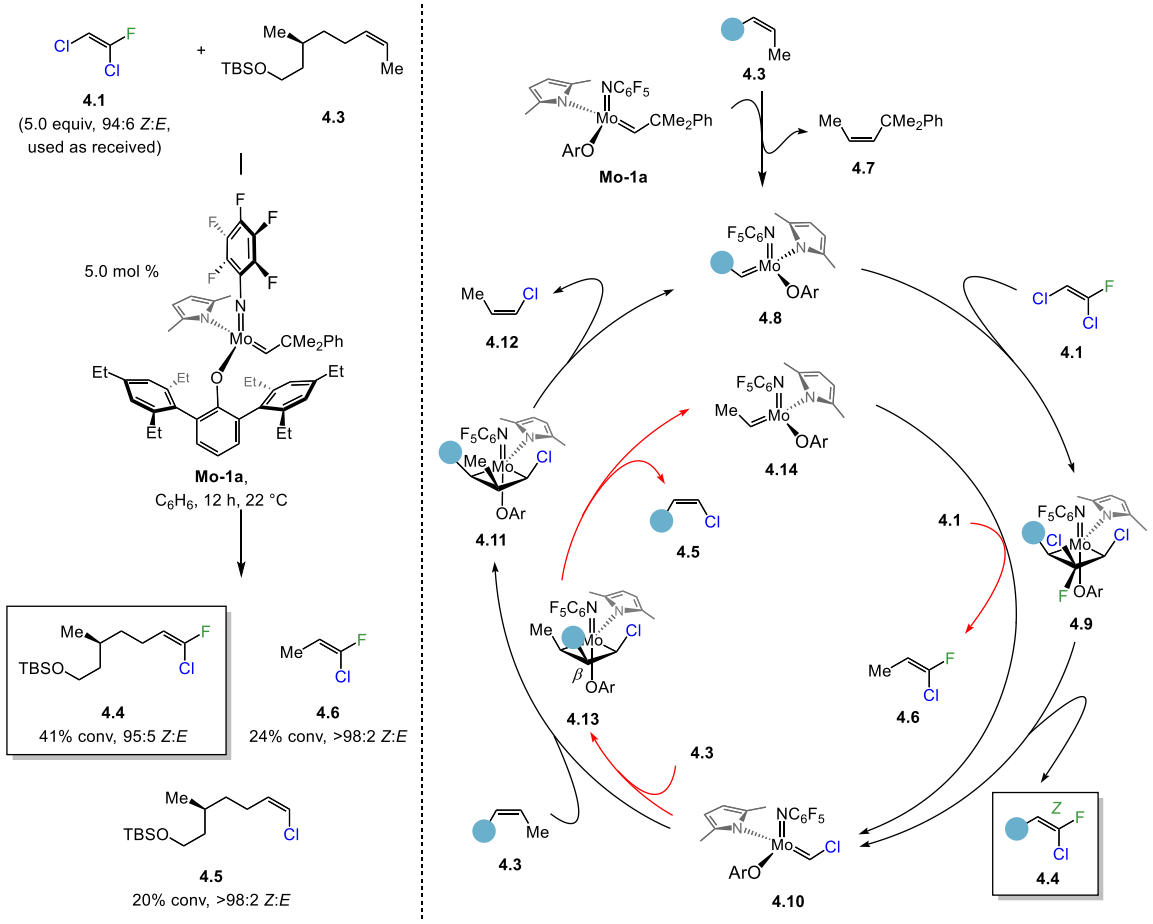
(20) Turapov, O.; Wadde, S. J.; Burke, B.; Glenn, S.; Sarybaeva, A. A.; Tudo, G.; Labesse, G.; Young, D. I.; Young, M.; Andrew, P. W.; Butcher, P. D.; Cohen-Gonsaud, M.; Mukamolova, G. V. *J. Biol. Chem.* **2014**, *289*, 25241–25249.
(21) Hoveyda, A. H.; Liu, Z.; Qin, C.; Koengeter, T.; Mu, Y. *Angew. Chem. Int. Ed.* **2020**, *59*, 22324–22348.

conversion. Although it has been a great improvement that cross-metathesis reactions can involve an electron-deficient and sterically hindered trihalo-alkene, it remained unclear why there was also 20% conversion to disubstituted alkenyl chloride **4.5**. We thus turned to investigate the catalytic cycle more deeply (Scheme 4.2.2), hoping to find potential solution to suppress the byproduct formation. For the productive catalytic cycle, we reasonned that substrate **4.3** will first react with Mo-complex **Mo-1a** due to less steric repulsion of a 1,2-disubstituted alkene, followed by the reaction between alkylidene **4.8** and F,Cl-substituted olefin reagent **4.1** to afford metallacyclobutane **4.9**, exhibiting the fully substituted carbon sitting at the C-β position.[22] The desired product would thus be delivered after the collapse of metallacyclobutane **4.9**, releasing Cl-substituted alkylidene **4.10**, which would react with substrate **4.3** to turn over the catalytic cycle through metallacyclobutane **4.11**.

Regarding the byproduct formation, we proposed that there could likely be a regioselectivity issue when Cl-substituted alkylidene **4.10** reacted with disubstituted starting material **4.3**. The methyl-substituent would be at the C-α to generate the alternative metallacyclobutane **4.13**, the cyclo-reversion of which would give byproduct **4.5**, turning over the catalytic cycle through the formation of alkylidene **4.10**. The generation of methyl-substituted alkene **4.6** supported our hypothesis. Therefore, such byproduct pathway should be avoided to enhance the reaction efficiency.

(22) Nguyen. T. T.; Koh, M. J.; Shen, X.; Romiti, F.; Schrock, R. R.; Hoveyda, A. H. *Science* **2016**, *352*, 569−575.

Scheme 4.2.2. Cross-Metathesis with 1,2-Disubstituted Alkenes and Limitation Analysis[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate.

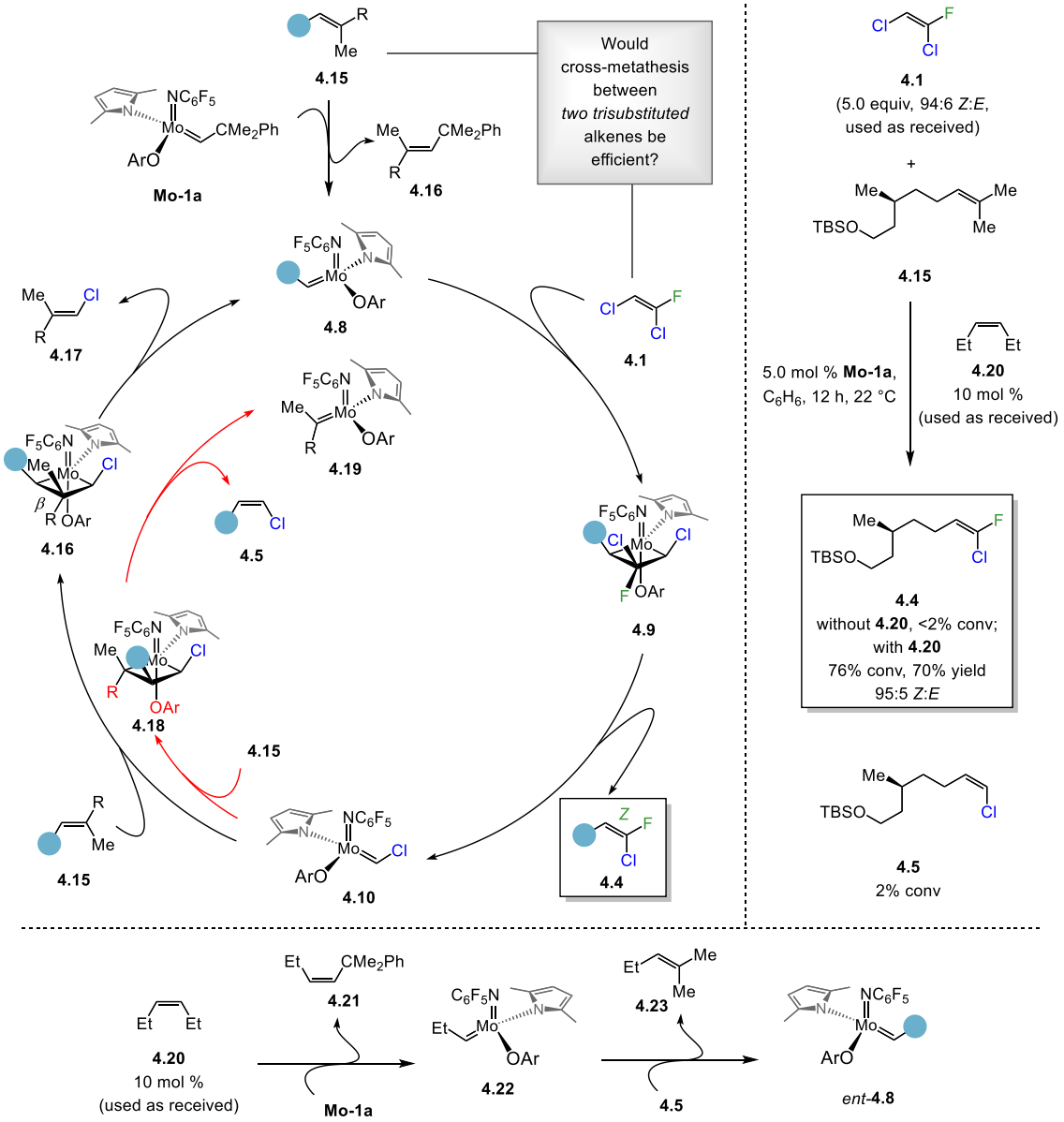
Possible solution could be the addition of an extra substituent on the substrate (e.g., alkene **4.15**) to discourage the formation of metallacyclobutane **4.18** and less reactive 1,1-disubstituted alkylidene **4.19** (Scheme 4.2.2). Compared to the favored metallacyclobutane **4.16**, where the fully substituted carbon resides at C-β, the less favored metallacyclobutane **4.18** exhibits a much bulkier C-α, which results in more steric pressure due to the larger aryloxide ligand (see Chapter 1, Section 1.3 for details). This proposal sounded reasonable initially, but soon we realized that some challenges of this plan were unprecedented: (1) There are only a few cases of stereodefined synthesis of trisubstituted alkenes and they always utilize a stereodefined trisusbtituted olefin and a

disusbstituted alkene as substrates. Reactions between two trisubstituted alkenes have never been reported, particularly with trihalo-substituted olefins; (2) The Mo-based complexes for this process need to be sufficiently reactive for two sterically hindered substrate, while at the same time being long-lived enough to promote the relatively slow trisubstituted alkene cross-metathesis, with minimal erosion of the kinetic selectivity.

Nevertheless, we set out to perform the reaction with a *gem*-dimethyl alkene **4.15** under otherwise same conditions (Scheme 4.2.2). The results confirmed our previous worries about this transformation as no substrate conversion nor product formation was observed after 12 h. Upon close inspection, it was surprising that we did not find any initiation product **4.16**, which suggests that complex **Mo-1a** was not converted to **4.8** to enter the catalytic cycle at all. We thus added a catalytic amount of a *Z*-1,2-disubstituted olefin, *Z*-hex-3-ene **4.20**, to facilitate the initiation process and afford *ent*-**4.8** through alkylidene **4.22** (Scheme 4.2.2). Under otherwise identical conditions, we were able to isolate the desired product **4.5** in 70% yield and 95:5 *Z*:*E* selectivity. A similar observation[23] with regard to a promoter has been discovered before, employing ethylene gas, which may not be ideal in this case due to the generation of a methylidene complex[21] that shortens the catalyst life-time and lowers the stereoisomeric purity of the trisubstituted product.[13] Upon further screening, we found the commercially available **4.20** to be the optimal small alkene for the complex initiation because other 1,2-disubstituted alkenes are either expensive chemicals, difficult to handle (e.g., *Z*-1,2-butene) and/or contain hetereoatoms to complicate the productive reaction (e.g., *Z*-1,2-dichloroethene[24]).

(23) Schrock, R. R.; Hoveyda, A. H. *Angew. Chemie. Int. Ed.* **2003**, *38*, 4592−4633.
(24) Koh, M. J.; Nguyen, T. T.; Zhang, H.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2016**, *531*, 459–465.

Scheme 4.2.2. Cross-Metathesis with Trisubstituted Alkenes and the Initiation Pathway[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate.

4.3. Scope and Stereodivergency of the Approach

With the optimized conditions for efficient and stereoretentive catalytic reaction between two trisubstituted olefins, an assortment of trisubstituted F,Cl-substituted alkenes can be synthesized (Scheme 4.3.1). Fluorinated trisubstituted olefins bearing a bromide **4.24**, a tertiary amine **4.25**, a B(pin) **4.26**, and an acetal unit **4.27** can all be

generated in up to 86% yield and 95:5 *Z*:*E* ratio. Hetereocycles are compatible with the catalytic system as products containing a C-2 substituted indole **4.28**, a benzofuran **4.29**, a benzothiophene **4.30** and a lactone **4.31** from the natural product auraptene were synthesized efficiently and in high *Z*:*E* selectivity. The reaction is also highly chemoselective for diene substrates and the products can be afforded with another alkene present in the same molecule, such as the diene with an electron-deficient dichloro-alkene **4.32**, a cyclic trisusbtituted alkene **4.33** and an unsaturated ester **4.34**. It is worth mentioning that **4.33** was directly synthesized from the natural product bisabolol, with the HB(pin) *in-situ* protection method we discovered in Chapter 2.

As one of the most challenging substrates in olefin metathesis, α-branched olefins were found to be problematic under the previous conditions. Monosubstituted alkenes were identified to be suitable for α-branched substrates, possibly due to the slow homocoupling and less likelihood of a short-living methylidene being formed. With the slightly bulkier **Mo-1b** and the aryloxide ligand bearing 2,4,6-triisopropyl groups, we can successfully isolate the desired product **4.36** in 70% yield and >98:2 *Z*:*E* ratio. Similarly, the Boc-piperidine substituted alkene **4.37** was afforded in 52% yield and 94:6 *Z*:*E* selectivity. The β-branched case **4.38** was better synthesized from a *Z*-1,2-disubstituted alkene, a balance of steric hindrance between a *gem*-dimethyl alkene and a monosubstituted alkene.

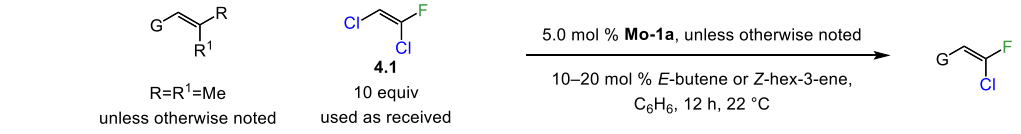
Another important class of products are aryl-substituted olefins, which are oftentimes difficult to access, partly due to the competitive homo-coupling. While the monoaryl pyrrolide (MAP) complexes were examined to be less effective, monoaryl chloride (MAC) complex **Mo-2**, firstly developed for the generation of *Z*-F_3C-substituted

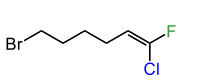
alkenes[25], was able to catalyze the cross-metathesis to form aryl-substituted product **4.41** in 56% yield. In the case of volatile products, a subsequent cross-coupling reaction was employed to convert the C-Cl bonds to the C-C bonds in enone products **4.42** and **4.43**. It is noteworthy that Horner-Wardsworth-Emmons reactions can only preferentially generate the *E*-enones, leaving the *Z*-enones inaccessible.

The *E*-trisubstituted fluorine-containing alkenes were similarly accessed with the *E*-F,Cl-reagent **4.2** under similar reaction conditions (Scheme 4.3.2). The substrate scope is equally broad and different *n*-alkyl-substituted products **4.44**–**4.49**, α-branched product **4.50**, β-branched product **4.51** as well as the aryl-substituted product **4.52**−**4.53** can all be obtained in 40–73% yield and 93:7 to >98:2 *E*:*Z* selectivity. For the sterically hindered allylic ether **4.54**, a Sonogashira coupling reaction, concomitant with silyl group removal, following cross-metathesis reaction would deliver the enyne product **4.55** in 41% yield over 2 steps. The allylic silane product **4.56** can be synthesized in analogous manner.

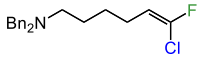
(25) Koh, M. J.; Nguyen, T. T.; Lam, J. K.; Torker, S.; Hyvl, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *542*, 80–85.

Scheme 4.3.1. Scope of *Z*-F,Cl-substituted Olefins[a]

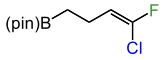




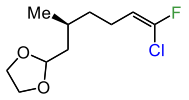
4.24
96% conv, 86% yield
95:5 *Z*:*E*



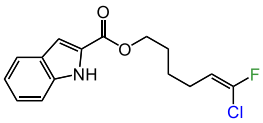
4.25
90% conv, 77% yield
95:5 *Z*:*E*



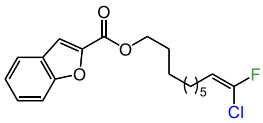
4.26
85% conv, 81% yield
95:5 *Z*:*E*



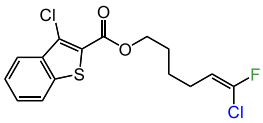
4.27
76% conv, 63% yield
95:5 *Z*:*E*



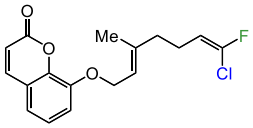
4.28
65% conv, 52% yield
95:5 *Z*:*E*



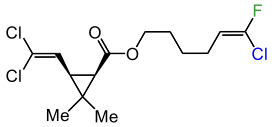
4.29
88% conv, 82% yield
95:5 *Z*:*E*



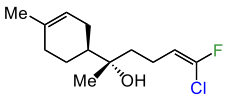
4.30
62% conv, 60% yield
94:6 *Z*:*E*



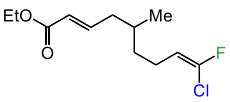
4.31
61% conv, 52% yield
95:5 *Z*:*E*



4.32
88% conv, 84% yield
94:6 *Z*:*E*

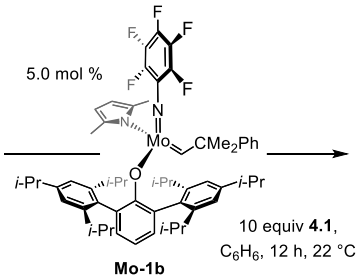


4.33*
68% conv, 56% yield
97:3 *Z*:*E*

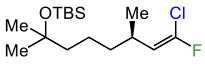


4.34
61% conv, 50% yield
>98:2 *Z*:*E*

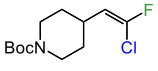
4.35



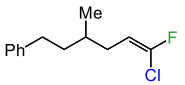
Mo-1b



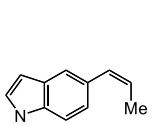
4.36
91% conv, 70% yield
>98:2 *Z*:*E*



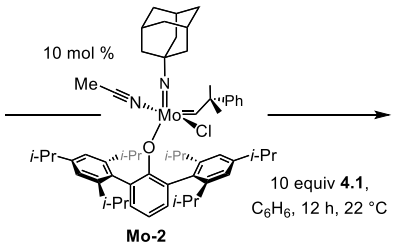
4.37
R=H, R[1]=Me
91% conv, 70% yield
>98:2 *Z*:*E*



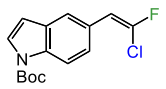
4.38
R=H, R[1]=Me
91% conv, 70% yield
>98:2 *Z*:*E*



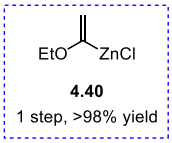
4.39



Mo-2

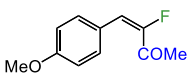


4.41
81% conv, 56% yield
92:8 *Z*:*E*

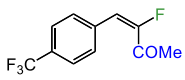


4.40
1 step, >98% yield

After cross-metathesis reaction:
2.5 mol % Pd(*t*-Bu$_3$P)$_2$, 2.0 equiv **4.40**,
THF/NMP (1.8/1), 2 h, 80°C; HCl



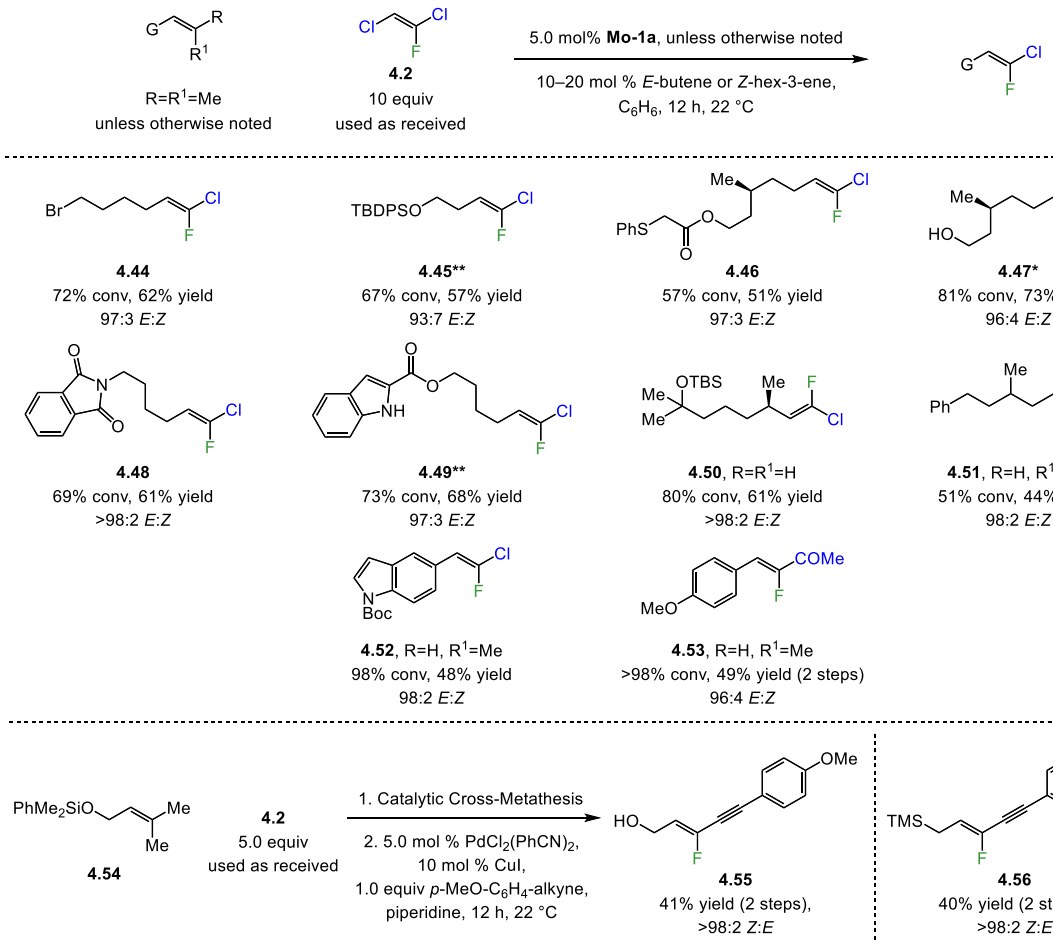
4.42
57% yield (2 steps)
91:9 *Z*:*E*



4.43
45% yield (2 steps)
93:7 *Z*:*E*

[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. *HB(pin) was used for traceless protection. Bn, benzyl; pin, pinacolato; Boc, *t*-butylcarbonate.

Scheme 4.3.2. Scope of *E*-F,Cl-substituted Olefins[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. *HB(pin) was used for traceless protection. **10 mol % of complex **Mo-1a** was used. Bn, benzyl; pin, pinacolato; Boc, *t*-butylcarbonate.

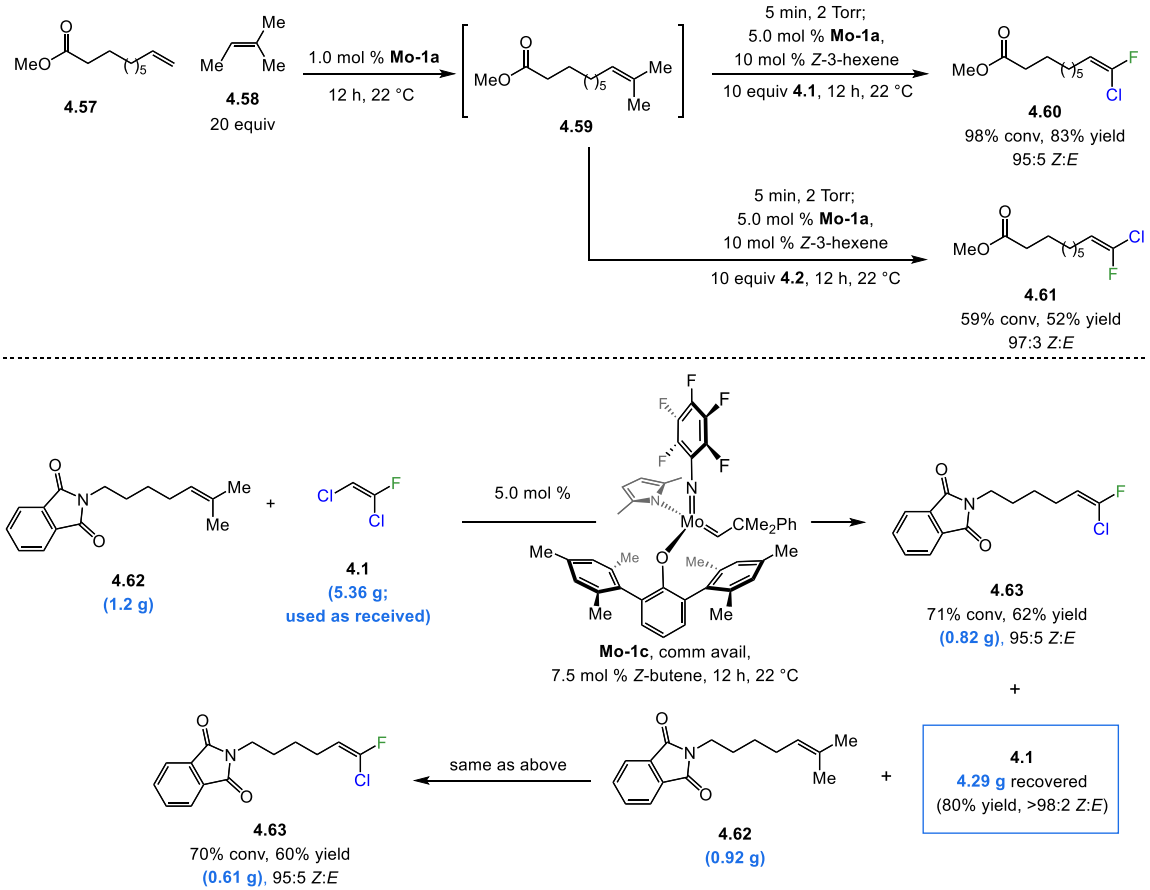
As discussed in Section 4.2, a trisubstituted alkene is not only the possible but also the optimal substrate. Many of the *gem*-dimethyl alkenes are naturally occurring bioactive molecules (e.g., indomethacin (anti-inflammatory[26]), auraptene (anti-cancer[27]) and imperatonin (anti-convulsant[28])), others are inexpensive renewable chemicals (e.g., geraniol, farnesol and linalool). However, terminal alkenes can serve as the starting material as well. We found that treatment of terminal alkene **4.57** with 20 equivalents of

(26) Hart, F. D.; Boardman, P. L. *Br. Med. J.* **1963**, 965–970.
(27) Bibak, B.; Shakeri, F.; Barreto, G. E.; Keshavarzi, Z.; Sathyapalan, T.; Sahebkar, T. *BioFactors* **2019**, *45*, 867–879.
(28) Luszczki, J. J.; Wojda, E.; Andres-Mach, M.; Cisowski, W.; Glensk, M.; Glowniak, K.; Czuczwar, S. J. *Epilepsy Res.* **2009**, *85*, 293–299.

2-methyl-2-butene **4.58** and 1.0 mol % **Mo-1a** generated the *gem*-dimethyl alkene **4.59** *in situ*. Following treatment under mild vacuum to remove excess **4.58**, trisubstituted olefin **4.59** was directly subjected to the cross-metathesis conditions, affording the F,Cl-substituted alkene **4.60** in 83% yield and in 95:5 *Z*:*E* selectivity. Similarly, the *E*-trisubstituted alkenyl fluoride **4.61** was formed in 52% yield and in 97:3 *E*:*Z* selectivity.

The cross-metathesis transformation is practical and scalable, as demonstrated by reaction of 1.2 grams of **4.62** to desired product **4.63** in 0.82 gram (62% yield, 95:5 *Z*:*E* ratio) with commercially available complex **Mo-1c**. Excess amounts of cross-partner **4.1** were recovered in 80% yield and re-subjected to the reaction condition to give the same product **4.63** in 60% yield and 95:5 *Z*:*E* selectivity.

Scheme 4.3.3. Cross-Metathesis Reaction with Terminal Alkenes and Scalability of the Aporoach[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. *HB(pin) was used for traceless protection.

4.4. Readily modifiable Z- and E-F,Cl-substituted products

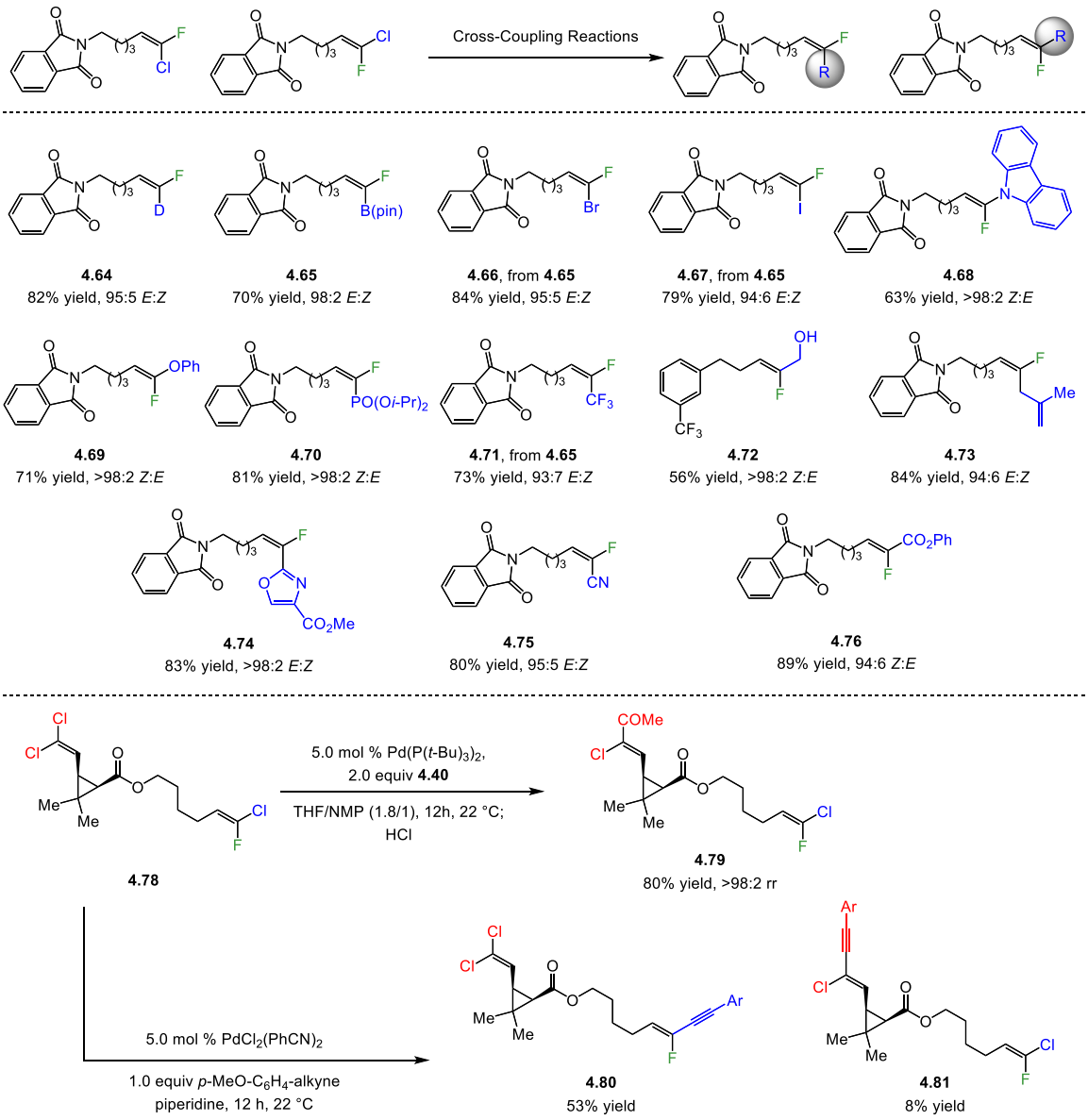
The aforementioned *Z*- and *E*-F,Cl-substituted alkenes are versatile and modifications of these entities delivered a wide range of trisusbtituted alkenyl fluorides (Scheme 4.4.1). The regio- and stereoselective synthesis of F,D-substituted alkene product **4.64** is noteworthy as both fluorine and deuterium are important labeling groups in drug discovery.[29] The corresponding alkenyl borate **4.65**, alkenyl bromide **4.66**, and alkenyl iodide **4.67** are all suitable substrates for stereospecific cross-coupling reactions. As shown later in Section 4.5, they can be effectively utilized in palladium-catalyzed cross-coupling reactions to form otherwise difficult-to-access C-C bonds. Moreover, the C-Cl bond can be directly converted to various other valuable entities, such as enamine **4.68**, enol ether **4.69**, alkenyl phosphonate **4.70**, CF_3-substituted alkene **4.71**, allylic alcohol **4.72**, 1,4-diene **4.73**, alkenyl oxazole **4.74**, alkenyl nitrile **4.75** and α,β-unsaturated carboxylic ester **4.76**.

The ability to synthesize the diene substrate as shown in Scheme 4.3.1 offered us a chance to examine whether the cross-coupling reactions are chemoselective to different alkenyl chlorides. We selected the diene product **4.78** that bears a *gem*-diCl-substituted alkene and also a F,Cl-substituted alkene as a cross-coupling substrate. The Negishi cross-coupling reaction occurred exclusively on the chlorine atom on the *E*-position of the *gem*-diCl-substituted alkene to generate the enone product **4.79** in 80% yield. Unexpectedly, under the Sonogashira coupling conditions, the C-Cl bond geminal to the C-F bond was selectively transformed to give **4.80** in 53% yield with a minor product **4.81** due to reaction at the diCl-substituted alkene in 8% yield. It merits note that when

(29) Pirali, T.; Serafini, M.; Cargnin, S.; Genazzani, A. A. *J. Med. Chem.* **2019**, *62*, 5276–5297.

we attempted to run cross-coupling reactions directly on the trihalo-agents **4.1** and **4.2**, the products were formed in low regioselectivity and low conversion in most cases.

Scheme 4.4.1. Access towards Various *E*- and *Z*-Trisubstituted Alkenyl Fluorides[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate.

4.5. Site-, Regio- and Stereospecific Fluoro-Labelling of Bioactive Compounds

With the method to synthesize a wide range of trisubstituted alkenyl fluorides in hand, we set out to incorporate the fluorine atom site-specifically into bioactive compounds

(Scheme 4.5.1). With the *in-situ* protection/cross-metathesis sequence described in Chapter 2, the primary alcohol **4.82** was converted to the F,Cl-containing product, followed by the Sonogashira cross-coupling to afford enyne product **4.84** in 81% yield and with complete stereoretention. The subsequent two steps transformed the primary alcohol to the hydroxy amine moiety, generating the fluoro-labeled Hachijodine G, a naturally occurring anti-leukemic alkaloid[30], in 64% overall yield.

Moreover, starting from trisubstituted alkene **4.86**, with the identical cross-metathesis reaction and the Suzuki cross-coupling conditions, 1,3-diene **4.88** was synthesized in 85% yield over 2 stepss. The following ester hydrolysis and the macrocyclic lactone formation yielded the fluoro-substituted coriolide **4.89** [31], a macrocyclic pheromone, sitespecifically in 77% yield over 2 steps.

The approach also gives the chance to regiospecifically introduce a fluorine atom into a bioactive molecule (Scheme 4.5.1). For example, catalytic cross-metathesis of substrate **4.86**, followed by Negishi cross-coupling delivered alkenyl fluoride **4.90** in 81% yield over 2 steps as a single isomer. Similarly, the trisubstituted alkenyl fluoride **4.93** can be synthesized in 77% yield over 2 steps as a single isomer. Both **4.90** and **4.93** can potentially serve as the key intermediates in the synthesis of the Oleyl coenzyme A[32] to regioselectively label the bioactive compound at either side of the disubstituted alkene.

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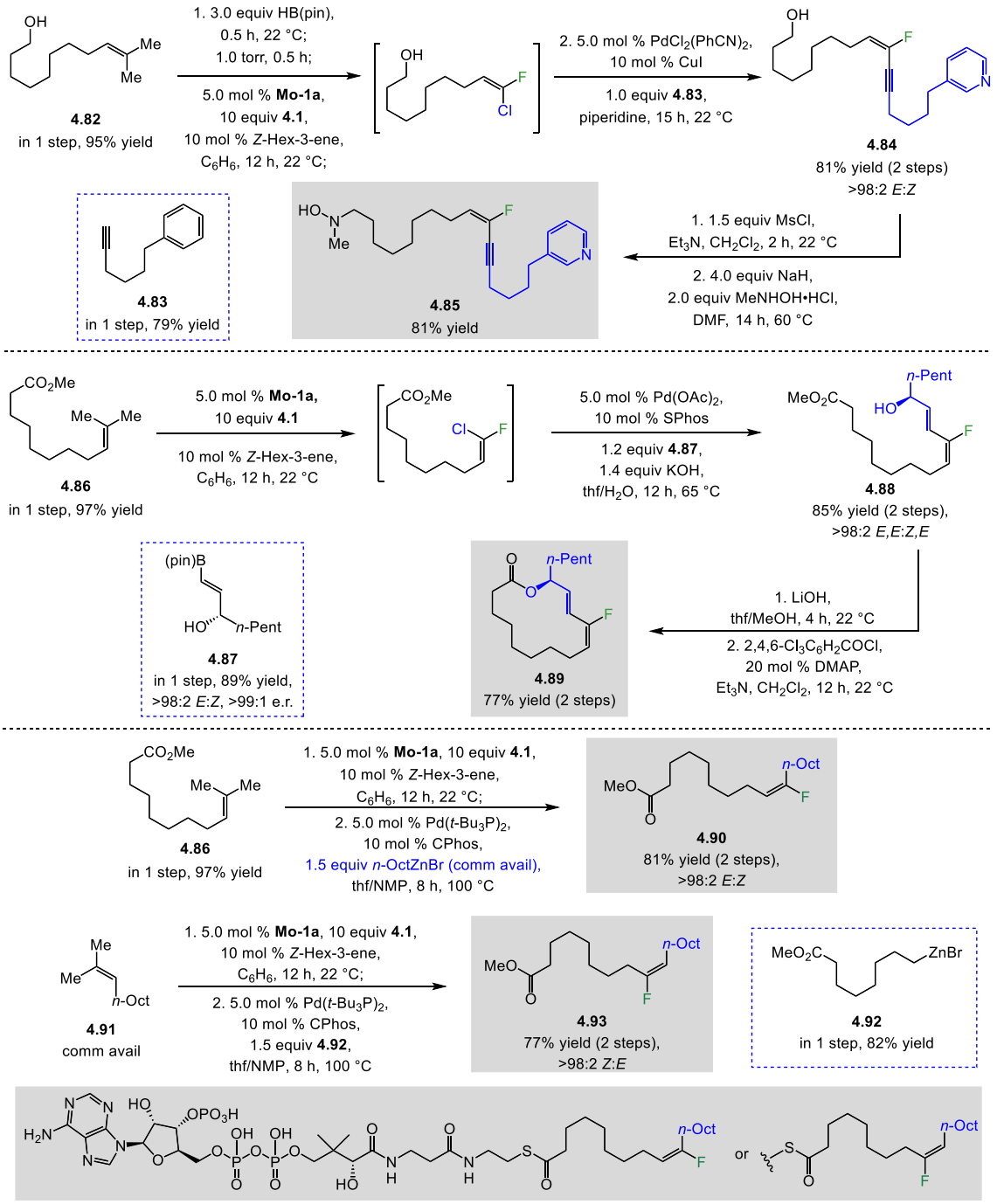
(30) Tsukamoto, S.; Takahashi, M.; Matsunaga, S.; Fusetani, N.; van Soest, R. W. M. *J. Nat. Prod.* **2000**, *63*, 682–684.
(31) Schulz, S.; Yildizhan, S.; Stritzke, K.; Estrada, C.; Gilbert, L. E. *Org. Biomol. Chem.* **2007**, *5*, 3434-3441.
(32) Nie, L.; Ren, Y.; Janakiraman, A.; Smith, S.; Schulz, H. *Biochemistry* **2008**, *47*, 9618–9626.

Scheme 4.5.1. Site-, Regio- and Stereoselective Fluorination of Bioactive Compounds[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. SPhos, 2-dicyclohexylphosphino-2',6'-dimethoxy biphenyl; DMF, dimethylformamide; THF, tetrahydrofuran; DMAP, dimethylaminopyridine; C-Phos, 2'(dicyclohexylphosphanyl)-*N2*,*N2*,*N6*,*N6*-tetra methyl[1,1'-biphenyl]-2,6-diamine.

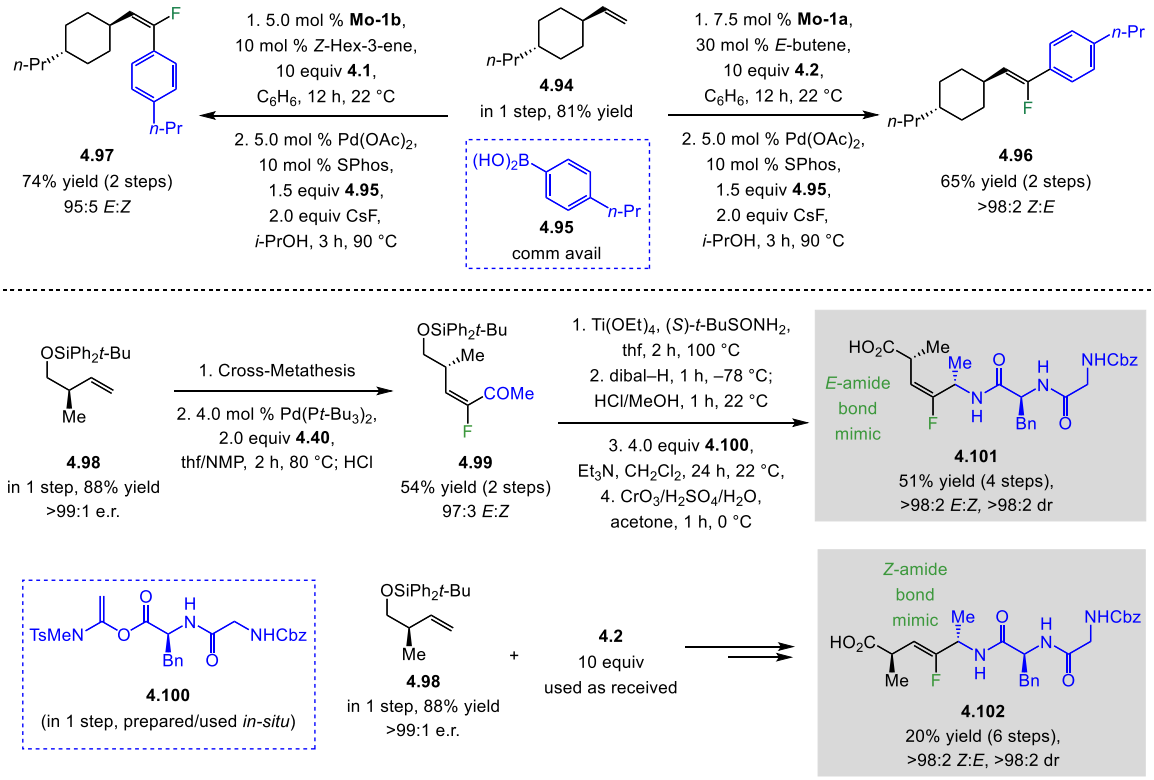
The access to both isomers of trihalo-alkenes **4.1** and **4.2** enables the potential diastereodivergent synthesis of bioactive molecules with trisubstituted alkenyl fluorides

(Scheme 4.5.2). For instance, cross-metathesis of sterically hindered α-branched monosubstituted substrate **4.94** with **4.1** and **4.2**, followed by the cross-coupling reaction with commercially available boronic acid **4.95**, afforded the *Z*- and *E*-isomers of the fluoro-Nematic liquid component **4.96** and **4.97** in 65% and 74% yield and >98:2 *Z*:*E* and 95:5 *E*:*Z* ratio, respectively.

As mentioned in Section 4.1, trisubstituted alkenyl fluorides are suitable analogs of amide bonds in a peptide structure. Therefore, we set out to prepare the *E*- and *Z*-amide bond mimics through the cross-metathesis transformation (Scheme 4.5.2). Cross-metathesis and cross-coupling sequence of the homoallylic silyl ether **4.98**, produced in 1 step in an enantioenriched fashion and containing a challenging α-branched olefin and a sizable silyl ether group, afforded the desired enone **4.99** in 54% yield over 2 steps. The synthesis of compound **4.99** represents an improvement over the previous synthesis, which required 5 steps and led to 24% overall yield.[33] The subsequent imine formation, reduction, combination with the enol amide[34] and oxidation of the alcohol delivered the *E*-amide bond mimic **4.101** in 51% yield over 4 steps and in a diastereomerically pure manner (>98:2 *E*:*Z* and >98:2 dr). With **4.2** as the cross-partner under otherwise same conditions, the corresponding *Z*-amide bond analog **4.102** was isolated in 20% overall yield after 6 steps and as a single diastereomer (>98:2 *E*:*Z* and >98:2 dr).

(33) Dutheuil, G.; Paturel, C.; Lei, X.; Couve-Bonnaire, S.; Pannecoucke, X. *J. Org. Chem.* **2006**, *71*, 4316–4319.
(34) Dutheuil, G.; Couve-Bonnaire, S.; Pannecoucke, X. *Angew. Chem. Int. Ed.* **2007**, *46*, 1290–1292.

Scheme 4.5.2. Diastereodivergent Synthesis of Monofluoro-labeled Bioactive Compounds[a]

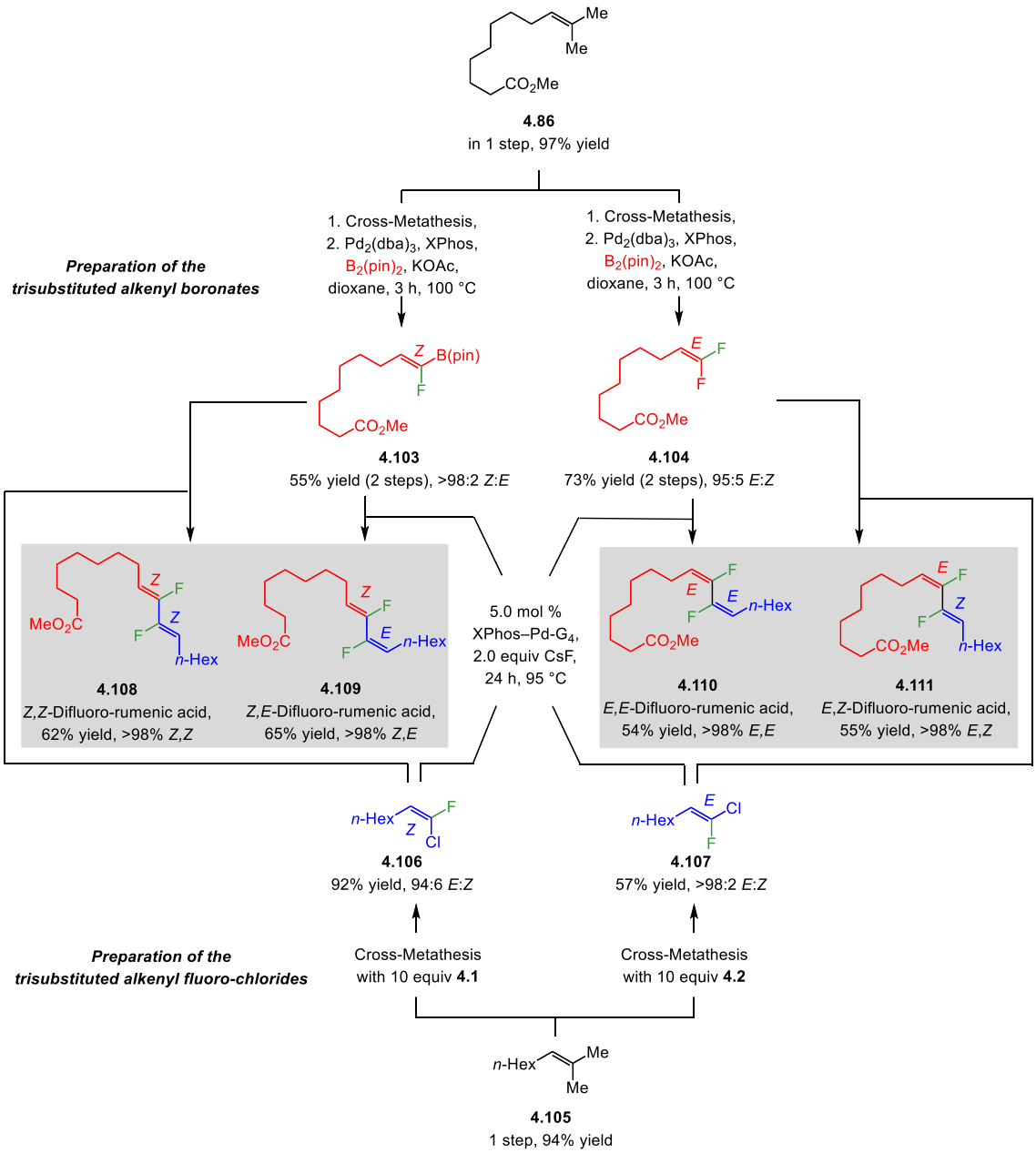


[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. SPhos, 2-dicyclohexylphosphino-2',6'-dimethoxy biphenyl; DIBAL–H, diisobutylaluminum hydride; Cbz, carboxylbenzyl; THF, tetrahydrofuran.

After obtaining a broad scope of monofluoro-substituted alkenes, we tried to use the synergy of cross-metathesis and cross-coupling to synthesize the difluoro-labeled analogues of a diene-containing bioactive compound. The compounds in Scheme 4.5.3 are cases in point. The preparation of the *E*- and *Z*-trisubstituted alkenyl boronates **4.103** and **4.104** can be achieved efficiently through a sequence of cross-coupling and cross-metathesis from readily accessible alkene **4.86**. The direct cross-metathesis furnished the F,Cl-substituted alkene products **4.106** and **4.107** in 92% and 57% yield, 94:6 *Z*:*E* and >98:2 *E*:*Z* ratio. With these four fragments, we were able to utilize the Suzuki cross-coupling reaction to access all four potential stereoisomers of the difluoro analogs of Rumenic acid methyl ester **4.108**–**4.111** in 54–65% yield and with full stereoretention. It is important to note that monofluoro-Rumenic methyl esters can also be effectively

synthesized when a non-fluoro-substituted alkenyl boronate or chloride is used for the Suzuki reaction, offering options when different fluoro-substituted alkenes are required.

Scheme 4.5.3. Diastereodivergent Synthesis of Difluoro-labeled Bioactive Compounds[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields correspond to purified products (±5%). Experiments were run at least in triplicate. pin, pinacolato; dba, dibenzylideneacetone; XPhos, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl; G4, fourth-generation.

4.6. Conclusions

Trisubstituted alkenyl fluorides, one of the most valuable classes of fluorine-containing organic compounds, were synthesized efficiently and selectively through a cross-metathesis reaction. The method yielded a large variety of fluorine-tagged bioactive compounds site-, regio- and diastereoselectively. It is noteworthy that with MAP complexes, two trisubstituted alkenes can be the suitable substrates for cross-metathesis reactions. The *gem*-dimethyl alkenes are readily available with many of them being inexpensive feedstock reagents. The trihalo-reagents are commercially available and excess thereof can be recovered after a multi-gram scale reaction. There is, however, room for improvement as it would be desirable if the turnover number was higher (up to 17 for the reaction so far).

Considering the prevalence and importance of organofluorine compounds in many branches of scientific research, the present approach is poised to have a significant impact on several fronts. The *E*- and *Z*-trisubstituted alkenyl fluorides are mimics of amide bonds in peptides, and the method can provide a wide range of analogs to be tested in biological studies. In combination with catalytic cross-coupling transformations, the cross-metathesis protocol can introduce one or two fluorine atoms to bioactive molecules at different sites, with excellent stereoisomeric purity for both isomers. It is notable that state-of-the-art methods are mostly limited to aryl cases and/or only one isomer can be synthesized. This study offers a relatively general strategy to obtain trisubsituted alkenyl fluorides with various functional groups, regardless of steric factors and electronic attributes.

This discovery also debunks the previously hold belief that cross-metathesis of two trisubstituted alkenes is not likely to be efficient. We found that with suitable Mo-

based complexes, two sterically hindered substrates, one of which being an electron-deficient trihalo-alkene can be optimal for a cross-metathesis reaction. A small alkene promotor is necessary to help the initiation of the Mo-complex. The current advance will likely help us improve other challenging trisubstituted alkenes syntheses and, potentially, allow us to synthesize the tetrasubstituted alkene efficiently in the future.

4.7. Experimental Section

4.7.1. Alternative Methods for Synthesis of Trisubstituted Alkenyl Fluorides

(a) Akiyama, S.; Kubota, K.; Mikus, M. S.; Paioti, P. H. S.; Romiti, F.; Liu, Q.; Zhou, Y.; Hoveyda, A. H.; Ito, H. *Angew. Chem. Int. Ed.* **2019**, *58*, 11998–12003.

(b) Bartlett, P. A.; Otake, A. *J. Org. Chem.* **1995**, *60*, 3107–3111.

(c) Jogireddy, R.; Barluenga, S.; Wissinger, N. *ChemMedChem* **2010**, *5*, 670-673.

(d) Sano, S.; Kuroda, Y.; Saito. K.; Ose, Y.; Nagao, Y. *Tetrahedron* **2006**, *62*, 11881-11890.

(e) Zygalski, L.; Middel, C.; Harms, K.; Koert, U. *Org. Lett.* **2018**, *20*, 5071–5074.

(f) Prakash, G. K. S.; Chacko, S.; Vaghoo, H.; Shao, N.; Gurung, L.; Mathew, T.; Olah, G. A. *Org. Lett.* **2009**, *11*, 1127–1130.

(g) Pacheco, M. C.; Gouverneur, V. *Org. Lett.* **2005**, *7*, 1267–1270.

(h) Gauthier, R., Manone, M.; Paquin, J.-F. *Org. Lett.* **2019**, *21*, 9024–9037.

(i) Guo, R.; Qi, X.; Xiang, H.; Geaneotes, P.; Wang, R.; Liu, P.; Wang, Y.-M. *Angew. Chem. Int. Ed.* **2020**, *59*, 16651–16660.

(j) Kondoh, A., Koda, K.; Terada, M. *Org. Lett.* **2019**, *21*, 2277–2280.

(k) Andrei, D.; Wnuk, S. F. *J. Org. Chem.* **2006**, *71*, 405–408.

(l) Lu, X.; Wang, Y.; Zhang, B.; Pi, J.-J.; Wang, X.-X.; Gong, T.-J.; Xiao, X.; Fu, Y. *J. Am. Chem. Soc.* **2017**, *139*, 12632–12637.

(m) Sakaguchi, H.; Uetake, Y.; Ohashi, M.; Niwa, T.; Ogoshi, S.; Hosoya. T. *J. Am. Chem. Soc.* **2017**, *139*, 12855–12862.

(n) Zhang, J., Dai, W., Liu, Q.; Cao, S. *Org. Lett.* **2017**, *19*, 3283–3286.

(o) Isoda, M.; Isoda, M.; Uetake, Y.; Takimoto, T.; Tsuda, J.; Hosoya, T.; Niwa, T. *J. Org. Chem.* **2021**, *86*, 1622–1632.

4.7.2. General

Unless otherwise noted, transformations were performed with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum line techniques. Infrared (IR) spectra were recorded on a Bruker FTIR Alpha (ATR Mode) spectrometer, υ_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), or weak (w). ^1H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz), 500 (500 MHz) or 600 (600 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuterium incorporation as the internal standard ($CDCl_3$: δ 7.26 ppm, CD_3OD: δ 3.31 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz), 500 (125 MHz), or 600 (150 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm, CD_3OD: δ 49.00 ppm). ^{19}F NMR spectra were recorded on a Varian Unity INOVA 400 (376 MHz), 500 (470 MHz),

or 600 (564 MHz) spectrometer without proton decoupling. High-resolution mass spectrometry was performed on a Micromass LCT ESI-MS and JEOL Accu TOF Dart (positive mode) at the Boston College Mass Spectrometry Facility. Melting points were determined using a Thomas Hoover Uni-melt capillary melting point apparatus. Values for *Z:E* ratios were determined by analysis of the ^{1}H NMR spectra of unpurified product mixtures. Conversion and stereoisomeric ratios were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields correspond to isolated and purified products (±5%).

Solvents

CH_2Cl_2, Et_2O, pentane, benzene, and toluene were purified under a positive pressure of dry Ar by a modified Innovative Technologies purification system. Tetrahydrofuran (THF) was distilled from Na/benzophenone. Methanol was distilled over Mg. Acetone, *N*,*N*-dimethylformamide (anhydrous), 1,2-dimethoxyethane (anhydrous), 1-methyl-2-pyrrolidinone (anhydrous), and 1,4-dioxane (anhydrous) were used as received. Purification of cross-metathesis (CM) products were carried out under standard conditions with reagent grade solvents (purchased from Fisher) in a fume hood.

Reagents

Bisabolol (Aldrich), auraptene (Aldrich), citronellol (Aldrich), 2-methylbut-2-ene (Aldrich), 7-bromo-2-methyl-2-heptene (Aldrich), 4,4,5,5-tetramethyl-2-(4-methylpent-3-en-1-yl)-1,3,2-dioxaborolane (Aldrich), methyl dec-9-enoate (Aldrich), (*E*)-1-Methoxy-4-(prop-1-en-1-yl)benzene (Aldrich), 2-methyl-2-undecene (Aldrich), ethyl vinyl ether (Aldrich), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Aldrich), 4-ethenylpiperidine-1-carboxylic acid *tert*-butyl ester (Combi-blocks), methyl 9-decenoate (Aldrich), 2-methyl-

2-undecene (Aldrich) were either distilled (from CaH_2 or $CaCl_2$) under vacuum or dried by azeotropic distillation (with anhydrous benzene) prior to use.

(*E*)-1,2-dichloro-1-fluoroethene (Synquest) and (*Z*)-1,2-dichloro-1-fluoroethene (Synquest) were used as received. (*Z*)-Hex-3-ene (Aldrich), and (*E*)-but-2-ene (Aldrich) were used as received.

6-Methylhept-5-en-1-ol was prepared according to a previously reported procedure[35]. 10-Methylundec-9-en-1-ol (**4.82**, from 9-decen-1-ol (Aldrich)), methyl 10-methylundec-9-enoate (**4.86**, from methyl 9-decenoate (Aldrich)), 2-methylnon-2-ene (**4.105**, from oct-1-ene (Aldrich)), 10-methylundec-9-en-1-ol (from 9-decen-1-ol (Combi-blocks)), were prepared according to a previously reported procedure[36]. *N,N*-Dibenzyl-6-methylhept-5-en-1-amine (substrate of compound **4.25**, from 7-bromo-2-methyl-2-heptene (Aldrich)) was prepared in analogy to a reported procedure [37] . 2-(6-Methylhept-5-en-1-yl)isoindoline-1,3-dione (**4.62**, from 7-bromo-2-methyl-2-heptene (Aldrich)) was prepared according to a previously reported procedure[38].

(*S*)-*tert*-Butyl((3,7-dimethyloct-6-en-1-yl)oxy)dimethylsilane (substrate of compound **4.4**, from (*S*)-citronellol (Aldrich)), dimethyl((4-methylpent-3-en-1-yl)oxy)(phenyl)silane (substrate of compound **4.45**, from 4-methyl-3-penten-1-ol (Santa cruz)), (*R*)-*tert*-butyl((2-methylbut-3-en-1-yl)oxy)diphenylsilane (**4.98**, from (2*R*)-2-methylbut-3-en-1-ol (Chemspace), (*R*)-*tert*-butyl((2,6-dimethyloct-7-en-2-yl)oxy)dimethylsilane (**4.35**, from (*R*)-2,6-dimethyloct-7-en-2-ol (Aldrich)), dimethyl((3-methylbut-2-en-1-yl)oxy)(phenyl)silane (**4.54,** from 3-methyl-2-buten-1-ol (Aldrich)) were prepared

(35) An, X.; Zha, Q.; Wu, Y. *Org. Lett.* **2019**, *21*, 1542–1546.
(36) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939–1942.
(37) Banik, S. M.; Medley, J. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2016**, *138*, 5000–5003.
(38) Wang, Y.; Wang, J.; Li, G.-X.; He, G.; Chen, G. *Org. Lett.* **2017**, *19*, 1442–1445.

according to a previously reported procedure[39]. (*S*)-2-(2,6-Dimethylhept-5-en-1-yl)-1,3-dioxolane (substrate of compound **4.27**, from (*S*)-citronellal (Aldrich)) were prepared according to a previously reported procedure[40]. 6-Methylhept-5-en-1-yl 1H-indole-2-carboxylate (substrate of compound **4.28**, from indole-2-carboxylic acid (AK Scientific)), (*S*)-*O*-(3,7-dimethyloct-6-en-1-yl) S-phenyl carbonothioate (substrate of compound **4.46**, from thiophenoxyacetic acid (Combi-blocks) and (*S*)-citronellol (Aldrich)), were was prepared according to a previously reported procedure[41].

10-Methylundec-9-en-1-yl benzofuran-2-carboxylate (substrate of compound **4.29**, from benzofuran-2-carbonyl chloride (Combi-blocks)), 6-methylhept-5-en-1-yl 3-chlorobenzo[*b*]thiophene-2-carboxylate (substrate of compound **4.30**, from 3-chlorobenzo[*b*]thiophene-2-carbonyl chloride (Oakwood)), 6-methylhept-5-en-1-yl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate (substrate of compound **4.32**, from cypermethric acid chloride (AK Scientific)), were prepared according to a previously reported procedure[42]. Ethyl (*E*)-5,9-dimethyldeca-2,8-dienoate (substrate of compound **4.34**, from citronellal (Aldrich)) was prepared according to a previously reported procedure[43]. (*Z*)-(3-Methylhept-5-en-1-yl)benzene (substrate of compound **4.38**, from (3-methylbut-3-en-1-yl)benzene [44] and (*Z*)-1-bromo-1-propene (Aldrich)) was prepared according to a previously reported procedure[45]. (*Z*)-But-2-en-1-yltrimethylsilane

(39) Aponick, A.; Li, C.-Y.; Palmes, J. A. *Org. Lett.* **2009**, *11*, 121–124.
(40) Heinrich, M.; Murphy, J.J.; Ilg, M. K.; Letort, A.; Flasz, J.; Philipps, P.; Fürstner, A. *Angew. Chem. Int. Ed*. **2018**, *57*, 13575–13581.
(41) Cai, Y.; Zhao, W.; Wang, S.; Liang, Y.; Yao, Z.-J. *Org. Lett.* **2019**, *21*, 9836–9840.
(42) Xie, Y.; Sun, P.-W.; Li, Y.; Wang, S.; Ye, M.; Li, Z. *Angew. Chem. Int. Ed.* **2019**, *58*, 7097–7101.
(43) Yoshida, M.; Otaka, H.; Doi, T. Eur. *J. Org. Chem.* **2014**, 6010–6016.
(44) Lebel, H.; Guay, D.; Paquet, V.; Huard, K. *Org. Lett.* **2004**, *6*, 3047–3050.
(45) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Sato, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321.

was prepared according to a previously reported procedure[46]. (*Z*)-1-(Prop-1-en-1-yl)-3-(trifluoromethyl)benzene (from 4-trifluoromethylphenyl boronic acid, pinacol ester (Combi-blocks) and (*Z*)-1-bromo-1-propene (Aldrich)), *tert*-butyl (*Z*)-5-(prop-1-en-1-yl)-1H-indole-1-carboxylate (**4.39**, from *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-1-carboxylate (Oakwood) and (*Z*)-1-bromo-1-propene (Aldrich)) were synthesized by cross-coupling according to a reported procedure[47]. 3-(5-Hexyn-1-yl)pyridine (**4.83**, from 5-(pyridin-3-yl)pentanal (Chemspace)) was prepared according to a previously reported procedure [48] . (*S,E*)-1-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)oct-1-en-3-ol (**4.87**, from (*S*)-1-octyn-3-ol (Aldrich)) was prepared according to a previously reported procedure [49] . 1-((*N*,4-Dimethylphenyl)sulfonamido)vinyl ((benzyloxy)carbonyl)glycyl-*L*-phenylalaninate (**4.100**, from *N*-ethynyl-*N*,4-dimethylbenzenesulfonamide (Aldrich) and ((benzyloxy)carbonyl)glycyl-*L*-phenylalanine (Aldrich)) was prepared according to a previously reported procedure[50].

Cesium fluoride (Aldrich), copper(II) bromide (Strem), copper(I) iodide (Strem), trifluoromethyl(1,10-phenanthroline)copper(I) (Strem), copper(I) cyanide (Strem), palladium(II) acetate (Strem), tris(dibenzylideneacetone)dipalladium (Strem), bis(tri-*tert*-butylphosphine)palladium(0) (Aldrich), tetrakis(triphenylphosphine)palladium(0) (Aldrich), di(1-adamantyl)-*n*-butylphosphine (Aldrich), XPhos (Strem), SPhos (Strem), *t*BuXPhos (Aldrich), CyJohnPhos (Strem), CPhos (Aldrich), lithium methoxide (Strem),

(46) Tietze, L. F.; Völkel, L.; Wulff, C.; Weigand, B.; Bittner, C.; McGrath, P.; Johnson, K.; Schäfer, M. *Chem. Eur. J.* **2001**, *7*, 1304–1308.
(47) Fristrup, P.; Tanner, D.; Norrby, P.-O. *Chirality* **2003**, *15*, 360–368.
(48) Goundry, W. R. F.; Baldwin, J. E.; Lee, V. *Tetrahedron* **2003**, *59*, 1719–1729.
(49) Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 7859–7871.
(50) Hu, L.; Xu, S.; Zhao, Z.; Yang, Y.; Peng, Z.; Yang, M.; Wang, C.; Zhao, J. *J. Am. Chem. Soc.* **2016**, *138*, 13135–13138.

2,4,6-trichlorobenzoyl chloride (Oakwood), potassim acetate (Aldrich), ethyl oxazole-4-carboxylate (Aldrich), phenyl formate (Aldrich), 1-(vinyloxy)butane (Aldrich), *n*-octylzinc bromide (Aldrich), 4-popylphenylboronic acid (Combi-blocks), bis(tri-*tert*-butylphosphine)palladium (Aldrich), bis(benzonitrile)palladium chloride (Strem), 4-ethynylanisole (Oakwood), tributyl(2-methylallyl)stannane (Oakwood), titanium(IV) ethoxide (Aldrich), diisobutylaluminium hydride (Aldrich) were used as received. (8-Methoxy-8-oxooctyl)zinc bromide (**4.92**, from methyl 8-bromooctanoate (Aldrich)) was prepared according to a previously reported procedure[51]. (1-Ethoxyvinyl)zinc(II) chloride (**4.40**) was prepared according to a previously reported procedure [52]. Bis(pinacolato)diboron (Frontier Scientific) was recrystallized from pentane prior to use.

Organometallic complexes

Mo monoaryloxide pyrrolide (MAP) complexes **Mo-1a**, and **Mo-1b** were synthesized *in situ* according to the previously reported procedures[53]. Complex **Mo-2** was also prepared according to a previously reported method[25]. Mo monoaryloxide pyrrolide (MAP) complex **Mo-1c** was purchased from Strem and used as received without purification. Mo complexes were manipulated under an atmosphere of N_2.

4.7.3. Synthesis of Trisubstituted Fluoro-Chloro Alkenes

General procedure A. In a N_2-filled glovebox, an oven-dried vial equipped with a magnetic stir bar was charged with the alkene substrate and the corresponding organohalogen reagent ((*E*)-1,2-dichloro-1-fluoroethene or (*Z*)-1,2-dichloro-1-fluoroethene). A solution of **Mo-1a**, **Mo-1b, Mo-1c** or **Mo-2** in benzene was

(51) An, L..; Xu, C.; Zhang, X. *Nat. Commun.* **2017**, *8*, 1460–1468.
(52) Edwards, J. T.; Merchant, R. R.; McClymont, K. S.; Knouse, K. W.; Qin, T.; Malins, L. R.; Vokits, B.; Shaw, S. A.; Bao, D.-H.; Wei, F.-L.; Zhou, T.; Eastgate, M. D.; Baran, P. S. *Nature* **2017**, *545*, 213–218.
(53) Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3844–3845.

subsequently added, followed by a solution of (*E*)-but-2-ene or (*Z*)-hex-3-ene in benzene. The vial was capped and the resulting mixture was allowed to stir for 4–12 h at 22 °C. At this time, the reaction was quenched by the addition of wet (undistilled) $CHCl_3$ (or $CHCl_3$ for ^1H NMR analysis; percent conversion was determined by ^1H NMR analysis of the unpurified mixture). Purification was performed through silica gel chromatography or preparative thin layer chromatography.

General procedure B. In a N_2-filled glovebox, an oven-dried vial equipped with a magnetic stir bar was charged with the alkene substrate. 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane was added, resulting in H_2 gas evolution. Once the effervescence subsided, the solution was allowed to stir for 30 min at 22 °C, after which the volatiles were removed *in vacuo* (1 torr, 0.5 h). The corresponding organohalogen reagent ((*E*)-1,2-dichloro-1-fluoroethene or (*Z*)-1,2-dichloro-1-fluoroethene) and a solution of **Mo-1a**, **Mo-1b** or **Mo-1c** in benzene were added, followed by the addition of a solution of (*E*)-but-2-ene or (*Z*)-hex-3-ene in benzene. The vial was capped and the resulting mixture was allowed to stir for 4–12 h at 22 °C. The reaction was then quenched by the addition of wet (undistilled) $CHCl_3$ (or $CDCl_3$ for ^1H NMR analysis; percent conversion was determined by ^1H NMR analysis of the unpurified mixture). Purification was performed through silica gel chromatography or preparative thin layer chromatography.

(*S,Z*)-*tert*-Butyl((7-chloro-7-fluoro-3-methylhept-6-en-1-yl)oxy)dimethylsilane (4.4): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 20 μL, 2.0 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (23.0 mg, 0.2000 mmol) and (*S*)-*tert*-butyl((3,7-dimethyloct-6-en-1-yl)oxy)dimethylsilane (10.8 mg, 0.0399 mmol). This was followed by the addition of a

solution of (*Z*)-hex-3-ene in benzene (1.0 M, 4 μL, 4.0 μmol). The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Spectroscopic analysis of the unpurified mixture indicated 76% consumption of (*S*)-*tert*-butyl((3,7-dimethyloct-6-en-1-yl)oxy)dimethylsilane. Removal of the volatiles in vacuo afforded brown oil, which was purified by silica gel chromatography (pentane → 3% Et_2O in pentane) to afford **4.4** (8.2 mg, 0.0279 mmol, 70% yield) in 95:5 *Z:E* ratio as colorless oil. **IR (neat)**: 2952 (m), 2922 (s), 2852 (m), 1678 (w), 1461 (w), 1253 (m), 1096 (m), 834 (s), 774 (m); **^{19}F NMR (376 MHz, $CDCl_3$)**: *Z* isomer (major): δ −78.4 (d, J = 10.9 Hz); *E* isomer (minor): δ −82.1 (d, J = 29.0 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: *Z* isomer (major): δ 5.24 (dt, J = 10.9, 7.6 Hz, 1H), 3.71–3.53 (m, 2H), 2.19–1.89 (m, 2H), 1.66–1.50 (m, 2H), 1.49–1.30 (m, 2H), 1.40–1.17 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H); *E* isomer (resolved signals only): δ 4.88–4.76 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 144.3 (d, J = 295.9 Hz), 105.4 (d, J = 18.7 Hz), 61.3, 39.8, 36.0 (d, J = 2.5 Hz), 29.8, 29.0, 26.1, 23.8, 19.5, −5.1; **HRMS[M+H]$^+$**: Calcd for $C_{14}H_{29}OFSiCl$: 295.1654, found: 295.1667.

(*Z*)-6-Bromo-1-chloro-1-fluorohex-1-ene (4.24): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 100 μL, 10.0 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (230.0 mg, 2.0000 mmol) and 7-bromo-2-methylhept-2-ene (19.0 mg, 0.0994 mmol). A solution of (*Z*)-hex-3-ene in benzene (1.0 M, 20 μL, 20.0 μmol) was then added. The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Spectroscopic analysis of the unpurified mixture showed 96% consumption of 7-bromo-2-methylhept-2-ene. Removal of the volatiles in vacuo afforded brown oil, which was

purified by silica gel chromatography (pentane) to give **4.24** (18.4 mg, 0.0855 mmol, 86% yield) in 95:5 *Z:E* ratio as colorless oil. **IR (neat)**: 2935 (m), 2857 (w), 1677 (m), 1453 (w), 1248 (w), 1116(s), 828 (w), 667 (w); **^{19}F NMR (470 MHz, $CDCl_3$)**: *Z* isomer (major): δ −77.3 (d, J = 11.0 Hz); *E* isomer (minor): δ −81.2 (d, J = 28.8 Hz); **^{1}H NMR (600 MHz, $CDCl_3$)**: *Z* isomer (major): δ 5.26 (dt, J = 10.7, 7.6 Hz, 1H), 3.41 (t, J = 6.8 Hz, 2H), 2.08 (qd, J = 7.5, 1.4 Hz, 2H), 1.88 (m, 2H), 1.57 (q, J = 7.6 Hz, 2H); *E* isomer (resolved signals only): δ 4.84 (dt, J = 29.1, 7.9 Hz, 1H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 145.0 (d, J = 296.7 Hz), 104.6 (d, J = 19.6 Hz), 33.4, 32.0, 27.3 (d, J = 2.7 Hz), 25.4 (d, J = 3.5 Hz); **HRMS[M+H]$^+$**: Calcd for $C_6H_{10}BrFCl$: 214.9633, found: 214.9643.

(*Z*)-*N,N*-Dibenzyl-6-chloro-6-fluorohex-5-en-1-amine (4.25): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 20 μL, 2.0 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (46.0 mg, 0.4000 mmol) and *N,N*-dibenzyl-6-methylhept-5-en-1-amine (12.4 mg, 0.0403 mmol). A solution of (*Z*)-hex-3-ene in benzene (1.0 M, 4 μL, 4.0 μmol) was added, and the mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture revealed 80% consumption of *N,N*-dibenzyl-6-methylhept-5-en-1-amine. Removal of the volatiles in vacuo left behind brown oil, which was purified by silica gel chromatography (pentane → 9% Et_2O in pentane) to afford **4.25** (10.3 mg, 0.0310 mmol, 77% yield) in 95:5 *Z:E* ratio as colorless oil. **IR (neat)**: 3024 (w), 2924 (m), 2854 (m), 1676 (m), 1451 (m), 1115(s), 742 (s), 696 (s); **^{19}F NMR (470 MHz, $CDCl_3$)**: *Z* isomer (major): δ −78.2 (d, J = 11.2 Hz); *E* isomer (minor): δ −82.0 (d, J = 29.4 Hz); **^{1}H NMR (500 MHz, $CDCl_3$)**: *Z* isomer (major): δ 7.36 (d, J = 7.3 Hz, 4H), 7.31 (t, J = 7.5 Hz, 4H), 7.23 (t, J = 7.1 Hz, 2H), 5.19 (dt, J = 10.8,

7.6 Hz, 1H), 3.54 (s, 4H), 2.41 (t, J = 7.0 Hz, 2H), 1.94 (q, J = 7.4 Hz, 2H), 1.51 (dd, J = 13.3, 5.9 Hz, 2H), 1.38 (dd, J = 14.8, 7.3 Hz, 2H); *E* isomer (resolved signals only): δ 4.77 (dt, J = 29.2, 7.8 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 144.5 (d, J = 295.9 Hz), 140.0, 128.9, 128.3, 126.9, 105.2 (d, J = 18.6 Hz), 58.5, 53.1, 30.5, 26.4 (d, J = 2.6 Hz), 26.0 (d, J = 3.4 Hz); **HRMS[M+H]$^+$**: Calcd for $C_{20}H_{24}NFCl$: 332.1576, found: 332.1577.

(*Z*)-2-(4-Chloro-4-fluorobut-3-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.26): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 100 μL, 10.0 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (230.0 mg, 2.0000 mmol) and 4,4,5,5-tetramethyl-2-(4-methylpent-3-en-1-yl)-1,3,2-dioxaborolane (21.0 mg, 0.1000 mmol). A solution of (*Z*)-hex-3-ene in benzene (1.0 M, 20 μL, 20.0 μmol) was then added. The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture revealed 85% consumption of 4,4,5,5-tetramethyl-2-(4-methylpent-3-en-1-yl)-1,3,2-dioxaborolane. Removal of the volatiles left behind brown oil, which was purified by silica gel chromatography (pentane $\rightarrow$ 3% Et_2O in pentane) to afford **4.26** (19.0 mg, 0.0810 mmol, 81% yield) in 95:5 *Z:E* ratio as colorless oil. **IR (neat)**: 2976 (m), 2928 (w), 1676 (m), 1372 (s), 1302 (s), 1143(s), 966 (w), 846 (w); **^{19}F NMR (470 MHz, $CDCl_3$)**: *Z* isomer (major): δ −79.3 (d, J = 11.6 Hz); *E* isomer (minor): δ −82.1 (d, J = 29.0 Hz). **^{1}H NMR (500 MHz, $CDCl_3$)**: *Z* isomer (major): δ 5.31 (dt, J = 10.9, 7.6 Hz, 1H), 2.16 (td, J = 7.7, 1.5 Hz, 2H), 1.26 (s, 12H), 0.90 (t, J = 7.7 Hz, 2H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 127.2 (d, J = 267.7 Hz), 107.1 (d, J = 18.4 Hz), 83.4, 29.1, 25.0, 20.9 (d, J = 3.6 Hz); **^{11}B NMR (160 MHz, $CDCl_3$)**: δ 33.62 (s). **HRMS[M+H]$^+$**: Calcd for $C_{10}H_{18}O_2BFCl$: 235.1067, found: 235.1072.

(*S*,*Z*)-2-(6-Chloro-6-fluoro-2-methylhex-5-en-1-yl)-1,3-dioxolane (4.27): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 40 μL, 4.0 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (92.0 mg, 0.8000 mmol) and (*S*)-2-(2,6-dimethylhept-5-en-1-yl)-1,3-dioxolane (15.8 mg, 0.0797 mmol). This was followed by the addition of a solution of (*Z*)-hex-3-ene in benzene (1.0 M, 8 μL, 8.0 μmol). The mixture was allowed to stir for 12 h at 22 °C, at which time the reaction was quenched by the addition of wet $CHDCl_3$. Analysis of the unpurified mixture revealed 76% consumption of (*S*)-2-(2,6-dimethylhept-5-en-1-yl)-1,3-dioxolane. Removal of the volatiles in vacuo yielded brown oil, which was purified by silica gel chromatography (pentane → 9% acetone in pentane) to afford **4.27** (11.2 mg, 0.0503 mmol, 63% yield) in 95:5 *Z:E* ratio as colorless oil. **IR (neat)**: 2952 (m), 2916 (m), 2874 (m), 1677 (m), 1408 (w), 1116(s), 1037 (m), 824 (m), 672 (w); **^{19}F NMR (470 MHz, $CDCl_3$)**: *Z* isomer (major): δ −78.2 (d, J = 10.8 Hz); *E* isomer (minor): δ −82.0 (d, J = 29.1 Hz). **^{1}H NMR (500 MHz, $CDCl_3$)**: *Z* isomer (major): δ 5.25 (dt, J = 10.8, 7.6 Hz, 1H), 4.90 (t, J = 5.0 Hz, 1H), 3.96 (d, J = 3.2 Hz, 2H), 3.84 (d, J = 2.5 Hz, 2H), 2.21–1.87 (m, 2H), 1.76–1.58 (m, 2H), 1.57–1.43 (m, 2H), 1.27 (ddt, J = 13.7, 9.0, 4.4 Hz, 1H), 0.97 (d, J = 6.5 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 144.4 (d, J = 295.9 Hz), 105.2 (d, J = 19.0 Hz), 103.7, 64.8 (d, J = 12.6 Hz), 40.9, 36.2, 29.0, 23.7 (d, J = 3.5 Hz), 19.8; **HRMS[M+H]$^+$**: Calcd for $C_{10}H_{17}O_2FCl$: 223.0896, found: 223.0891.

(*Z*)-6-Chloro-6-fluorohex-5-en-1-yl 1*H*-indole-2-carboxylate (4.28): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 20 μL, 2.0 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (46.0 mg, 0.4000 mmol) and 6-methylhept-5-en-1-yl 1H-indole-2-carboxylate (10.8 mg, 0.0398

mmol). A solution of (*Z*)-hex-3-ene in benzene (1.0 M, 4 μL, 4.0 μmol) was added and the resulting solution was allowed to stir for 12 h at 22 °C. At this time, the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture revealed 65% consumption of 6-methylhept-5-en-1-yl 1H-indole-2-carboxylate. Removal of the volatiles in vacuo gave brown oil, which was purified by silica gel chromatography (pentane → 20% Et_2O in pentane) to afford **4.28** (6.1 mg, 0.0206 mmol, 52% yield) in 95:5 *Z:E* ratio as colorless oil. **IR (neat)**: 3286 (m), 2924 (m), 2860 (w), 1675 (s), 1531 (m), 1432(m), 1170 (m), 1122 (m), 776 (w), 750 (m); **^{19}F NMR (470 MHz, $CDCl_3$)**: *Z* isomer (major): δ −77.6 (d, J = 11.0 Hz); *E* isomer (minor): δ −82.1 (d, J = 29.0 Hz). **^{1}H NMR (500 MHz, $CDCl_3$)**: *Z* isomer (major): δ 8.51 (s, 1H), 8.26–8.06 (m, 1H), 7.93 (d, J = 2.9 Hz, 1H), 7.57–7.40 (m, 1H), 7.35–7.26 (m, 2H), 5.30 (dt, J = 10.9, 7.7 Hz, 1H), 4.36 (t, J = 6.5 Hz, 2H), 2.14 (q, J = 7.4 Hz, 2H), 1.83 (dt, J = 14.4, 6.5 Hz, 2H), 1.67–1.56 (m, 2H); *E* isomer (resolved signals only): δ 4.87 (dt, J = 29.4, 7.8 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 165.3, 144.9 (d, J = 296.0 Hz), 136.2, 131.05, 125.9, 123.4, 122.2, 121.7, 111.6, 109.3, 104.9 (d, J = 19.1 Hz), 63.6, 28.5, 25.9 (d, J = 3.4 Hz), 25.5 (d, J = 2.8 Hz); **HRMS[M+H]$^+$**: Calcd for $C_{15}H_{16}NO_2FCl$: 296.0848, found: 296.0852.

(*Z*)-10-Chloro-10-fluorodec-9-en-1-yl benzofuran-2-carboxylate (4.29): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 20 μL, 2.0 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (46.0 mg, 0.4000 mmol) and 10-methylundec-9-en-1-yl benzofuran-2-carboxylate (13.2 mg, 0.0402 mmol), followed by the addition of a solution of (*Z*)-hex-3-ene in benzene (1.0 M, 4 μL, 4.0 μmol). The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified

mixture indicated 88% consumption of 10-methylundec-9-en-1-yl benzofuran-2-carboxylate. Removal of the volatiles in vacuo left behind brown oil, which was purified by silica gel chromatography (pentane → 9% Et_2O in pentane) to afford **4.29** (10.8 mg, 0.0329 mmol, 82% yield) in 95:5 *Z:E* ratio as colorless oil. **IR (neat)**: 2925 (m), 2853 (m), 1729 (s), 1676 (m), 1562 (m), 1327 (s), 1176(s), 1095 (m), 749 (m); **^{19}F NMR (376 MHz, $CDCl_3$)**: *Z* isomer (major): δ −78.3 (d, J = 10.9 Hz); *E* isomer (minor): δ −82.1 (d, J = 29.9 Hz). **^{1}H NMR (400 MHz, $CDCl_3$)**: *Z* isomer (major): δ 7.68 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.52 (s, 1H), 7.45 (ddd, J = 8.4, 7.1, 1.3 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 5.25 (dt, J = 11.0, 7.7 Hz, 1H), 4.38 (t, J = 6.8 Hz, 2H), 2.02 (q, J = 7.6, 7.1 Hz, 2H), 1.83–1.70 (m, 2H), 1.48–1.30 (m, 10H); *E* isomer (resolved signal only): δ 4.83 (dt, J = 29.2, 7.7 Hz, 1H); (*Z*)-10-chlorodec-9-en-1-yl benzofuran-2-carboxylate (resolved signals only): δ 6.00 (dt, J = 6.8, 1.5 Hz, 1H), 5.74 (q, J = 7.1 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 159.8, 155.8, 145.8, 144.5 (d, J = 295.7 Hz), 127.7, 127.1, 123.9, 122.9, 113.8, 112.5, 105.3 (d, J = 18.7 Hz), 65.7, 29.3, 29.3, 29.0, 28.8, 28.7, 26.15 (d, J = 3.2 Hz), 26.0; **HRMS[M+H]$^+$**: Calcd for $C_{19}H_{23}O_3FCl$: 353.1314, found: 353.1323.

(*Z*)-6-Chloro-6-fluorohex-5-en-1-yl 3-chlorobenzo[*b*]thiophene-2-carboxylate (4.30): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 20 µL, 2.0 µmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (46.0 mg, 0.4000 mmol) and 6-methylhept-5-en-1-yl 3-chlorobenzo[*b*]thiophene-2-carboxylate (12.8 mg, 0.0398 mmol). This was followed by the addition of a solution of (*Z*)-hex-3-ene in benzene (1.0 M, 4 µL, 4.0 µmol). The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture revealed 62% consumption

of 6-methylhept-5-en-1-yl 3-chlorobenzo[*b*]thiophene-2-carboxylate. Removal of the volatiles in vacuo yielded brown oil, which was purified by silica gel chromatography (pentane → 9% Et_2O in pentane) to afford **4.30** (6.1 mg, 0.0239 mmol, 60% yield) in 94:6 *Z:E* ratio as colorless oil. **IR (neat)**: 2949 (m), 2937 (m), 2849 (w), 1722 (s), 1700 (m), 1676 (m), 1512 (m), 1284 (m), 1228 (s), 1059 (m), 752 (m); **^{19}F NMR (376 MHz, $CDCl_3$)**: *Z* isomer (major): δ −77.4 (d, J = 10.8 Hz); *E* isomer (minor): δ −81.3 (d, J = 27.5 Hz). **^{1}H NMR (400 MHz, $CDCl_3$)**: *Z* isomer (major): δ 7.98 (dt, J = 7.0, 1.2 Hz, 1H), 7.88–7.77 (m, 1H), 7.62–7.44 (m, 2H), 5.30 (dt, J = 10.7, 7.7 Hz, 1H), 4.39 (t, J = 6.4 Hz, 2H), 2.26–2.04 (m, 2H), 1.83 (dt, J = 13.9, 6.5 Hz, 2H), 1.60 (p, J = 7.4 Hz, 2H); *E* isomer (resolved signals only): δ 4.88 (dt, J = 29.3, 7.9 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 161.5, 145.0 (d, J = 296.6 Hz), 138.7, 137.2, 128.3, 127.4, 126.1, 125.6, 124.0, 122.91, 104.7 (d, J = 19.5 Hz), 65.4, 28.1, 25.8 (d, J = 3.7 Hz), 25.3 (d, J = 2.7 Hz); **HRMS[M+H]$^+$**: Calcd for $C_{15}H_{14}O_2FSCl_2$: 347.0070, found: 347.0077.

8-(((2*E*,6*Z*)-7-Chloro-7-fluoro-3-methylhepta-2,6-dien-1-yl)oxy)-2H-chromen-2-one (4.31): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 20 µL, 2.0 µmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (46.0 mg, 0.4000 mmol) and (*E*)-8-((3,7-dimethylocta-2,6-dien-1-yl)oxy)-2H-chromen-2-one (12.0 mg, 0.0402 mmol). A solution of (*Z*)-hex-3-ene in benzene (1.0 M, 4 µL, 4.0 µmol) was added, and the mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture indicated 61% consumption of (*E*)-8-((3,7-dimethylocta-2,6-dien-1-yl)oxy)-2H-chromen-2-one. Removal of the volatiles in vacuo gave brown oil, which was purified by silica gel chromatography (pentane → 9% acetone in pentane) to afford **4.31**

(6.8 mg, 0.0210 mmol, 52% yield) in 95:5 *Z:E* ratio as colorless oil. **IR (neat)**: 2934 (w), 2899 (m), 2849 (w), 1732 (s), 1611 (s), 1276 (m), 1120 (m), 999 (m), 833 (m), 614 (w) cm^{-1}; **^{19}F NMR (376 MHz, $CDCl_3$)**: *Z* isomer (major): δ −77.4 (d, J = 10.7 Hz); *E* isomer (minor): δ −81.0 (d, J = 29.2 Hz). **^{1}H NMR (400 MHz, $CDCl_3$)**: *Z* isomer (major): δ 7.62 (d, J = 9.5 Hz, 1H), 7.35 (d, J = 8.5 Hz, 1H), 6.92–6.73 (m, 2H), 6.24 (d, J = 9.4 Hz, 1H), 5.47 (t, J = 6.7 Hz, 1H), 5.22 (dt, J = 9.9, 6.9 Hz, 1H), 4.60 (d, J = 6.5 Hz, 2H), 2.29–2.10 (m, 4H), 1.76 (s, 3H); 8-(((2*E*,6*Z*)-7-chloro-3-methylhepta-2,6-dien-1-yl)oxy)-2H-chromen-2-one (resolved signals only): δ 6.02 (d, J = 7.8 Hz, 1H), 5.76–5.68 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 162.1, 161.4, 156.0, 144.8 (d, J = 297.0 Hz), 143.5, 140.7, 128.8, 119.8, 113.4, 113.3, 112.6, 104.4 (d, J = 19.8 Hz), 101.7, 65.4, 38.3 (d, J = 2.7 Hz), 24.4 (d, J = 3.5 Hz), 16.7; **HRMS[M+H]$^{+}$**: Calcd for $C_{17}H_{17}O_3FCl$: 323.0837, found: 323.0844.

(*Z*)-6-Chloro-6-fluorohex-5-en-1-yl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate (4.32): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 20 μL, 2.0 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (46.0 mg, 0.4000 mmol) and 6-methylhept-5-en-1-yl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate (12.6 mg, 0.0395 mmol). The mixture was charged with a solution of (*Z*)-hex-3-ene in benzene (1.0 M, 4 μL, 4.0 μmol) and allowed to stir for 12 h at 22 °C, after which the reaction was quenched by addition of wet $CDCl_3$. Analysis of the unpurified mixture indicated 88% consumption of 6-methylhept-5-en-1-yl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate. Removal of the volatiles in vacuo gave brown oil, which was purified by silica gel chromatography (pentane → 5% Et_2O in pentane) to afford **4.32** (11.4 mg, 0.0332 mmol,

84% yield) in 94:6 *Z:E* ratio as colorless oil. **IR (neat)**: 2957 (m), 2925 (m), 2870 (w), 1731 (s), 1273 (m), 1132(m), 739 (m), 689 (m); **^{19}F NMR (376 MHz, $CDCl_3$)**: *Z* isomer (major): δ −77.5 (d, J = 10.8 Hz); *E* isomer (minor): δ −81.4 (d, J = 28.9 Hz). **^{1}H NMR (400 MHz, $CDCl_3$)**: *Z* isomer (major): δ 6.26 (d, J = 9.0 Hz, 1H), 5.27 (dt, J = 10.3, 7.7 Hz, 1H), 4.07 (t, J = 6.6 Hz, 2H), 2.15–1.97 (m, 3H), 1.83 (d, J = 8.5 Hz, 1H), 1.66 (m, 2H), 1.48 (m, 2H), 1.25 (d, J = 3.3 Hz, 6H); *E* isomer (resolved signals only): δ 4.85 (dt, J = 29.0, 7.8 Hz, 1H); (*Z*)-6-chlorohex-5-en-1-yl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate: δ 6.05 (d, J = 7.5 Hz, 1H), 5.75 (q, J = 7.2 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 170.7, 144.9 (d, J = 296.5 Hz), 125.1, 120.7, 104.8 (d, J = 19.1 Hz), 64.1, 32.6, 32.0, 28.5, 28.1, 25.8 (d, J = 3.5 Hz), 25.3 (d, J = 2.7 Hz), 15.1; **HRMS[M+H]$^+$**: Calcd for $C_{14}H_{19}O_2FCl_3$: 343.0429, found: 343.0433.

(*S*,*Z*)-6-Chloro-6-fluoro-2-((*S*)-4-methylcyclohex-3-en-1-yl)hex-5-en-2-ol (4.33): Based on general procedure B, an oven-dried vial equipped with a magnetic stir bar was charged with (*S*)-6-methyl-2-((*S*)-4-methylcyclohex-3-en-1-yl)hept-5-en-2-ol (8.8 mg, 0.0396 mmol). 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (15.3 mg, 0.1190 mmol) was added, resulting in H_2 evolution. After effervescence subsided, the solution was allowed to stir for 30 min at 22 °C, after which the volatiles were removed in vacuo (1 Torr, 30 min). (*Z*)-1,2-dichloro-1-fluoroethene (46.0 mg, 0.4000 mmol), a solution of **Mo-1a** in benzene (0.1 M, 20 µL, 2.0 µmol), and a solution of (*Z*)-hex-3-ene in benzene (1.0 M, 4 µL, 4.0 µmol) were added. The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by addition of wet $CHCl_3$. Analysis of the unpurified mixture showed 66% consumption of (*S*)-6-methyl-2-((*S*)-4-methylcyclohex-3-en-1-yl)hept-5-en-2-ol. Removal of the volatiles in vacuo produced brown oil, which was purified by silica

gel chromatography (pentane → 9% acetone in pentane) to afford **4.33** (5.5 mg, 0.0222 mmol, 56% yield) in 97:3 *Z:E* ratio as colorless oil. **IR (neat)**: 3423 (m), 2960 (m), 2922 (s), 1677 (w), 1450 (m), 1375 (m), 1295 (w), 1116 (s), 930 (w), 825 (w); **^{19}F NMR (470 MHz, $CDCl_3$)**: *Z* isomer (major): δ −78.4 (d, J = 10.5 Hz); *E* isomer (minor): δ −82.1 (d, J = 29.7 Hz). **^{1}H NMR (600 MHz, $CDCl_3$)**: *Z* isomer (major): δ 5.39 (d, J = 15.6 Hz, 1H), 5.29 (dt, J = 10.2, 7.7 Hz, 1H), 2.13 (q, J = 8.3 Hz, 2H), 2.00 (s, 2H), 1.93–1.77 (m, 2H), 1.65 (s, 3H), 1.57 (d, J = 6.1 Hz, 2H), 1.31 (td, J = 12.0, 5.7 Hz, 2H), 1.14 (d, J = 15.7 Hz, 4H), the alcoholic proton was not observed; *E* isomer (resolved signals only): δ 4.87 (dt, J = 29.6, 7.5 Hz, 1H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 144.5 (d, J = 296.2 Hz), 134.4, 120.4, 105.4 (d, J = 19.1 Hz), 74.1, 43.1, 39.0 (d, J = 2.8 Hz), 31.1, 27.0, 26.2, 24.1 (d, J = 13.8 Hz), 23.5 (d, J = 4.0 Hz), 20.5 (d, J = 3.6 Hz); **HRMS[M+H]$^+$**: Calcd for $C_{13}H_{21}OFCl$: 247.1259, found: 247.1256.

Ethyl (2*E*,8*Z*)-9-chloro-9-fluoro-5-methylnona-2,8-dienoate (4.34): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (115.0 mg, 1.0000 mmol) and ethyl (*E*)-5,9-dimethyldeca-2,8-dienoate (22.4 mg, 0.0999 mmol). This was followed by the addition of a solution of (*Z*)-hex-3-ene in benzene (1.0 M, 10 μL, 8.0 μmol). The mixture was allowed to stir for 12 h at 22 °C, after which a solution of **Mo-1a** in benzene (0.1 M, 50 μL, 5.0 μmol) was added by syringe. The mixture was allowed to stir for another 12 h at 22 °C. At this time, the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture indicated 57% consumption of ethyl (*E*)-5,9-dimethyldeca-2,8-dienoate. Removal of the volatiles in vacuo yielded brown oil, which was purified by preparative thin layer chromatography (5% Et_2O in

pentane) to afford **4.34** (12.5 mg, 0.0502 mmol, 50% yield) in >98:2 *Z:E* ratio as colorless oil. **IR (neat)**: 2960 (m), 2926 (m), 2853 (w), 1719 (s), 1678 (m), 1461 (m), 1308 (m), 1264 (m), 1043 (m), 982 (w); **^{19}F NMR (376 MHz, $CDCl_3$)**: δ −77.9 (d, J = 10.8 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.92 (dt, J = 15.3, 7.5 Hz, 1H), 5.82 (d, J = 15.5 Hz, 1H), 5.24 (dt, J = 10.8, 7.6 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 2.22 (dt, J = 13.4, 6.4 Hz, 1H), 2.06 (m, 3H), 1.72–1.60 (m, 1H), 1.47–1.37 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H); ethyl (*E*)-3-chloroacrylate: δ 7.13 (d, J = 15.9 Hz, 1H), 5.81 (d, J = 15.9 Hz, 1H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 166.67, 147.60, 144.62 (d, J = 299.2 Hz), 122.90, 105.06 (d, J = 18.9 Hz), 60.35, 39.54, 35.49, 32.03, 23.82, 19.47, 14.42; **HRMS[M+H]$^{+}$**: Calcd for $C_{12}H_{19}ClFO_2$: 249.1052, found: 249.1058.

(*R,Z*)-*tert*-Butyl((8-chloro-8-fluoro-2,6-dimethyloct-7-en-2-yl)oxy)dimethylsilane (4.36): Based on general procedure A, a solution of **Mo-1b** in benzene (0.1 M, 20 µL, 2.0 µmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (46.0 mg, 0.4000 mmol) and (*R*)-*tert*-butyl((2,6-dimethyloct-7-en-2-yl)oxy)dimethylsilane (10.8 mg, 0.0399 mmol). This was followed by the addition of a solution of (*Z*)-hex-3-ene in benzene (1.0 M, 4 µL, 4.0 µmol). The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture indicated 91% consumption of (*R*)-*tert*-butyl((2,6-dimethyloct-7-en-2-yl)oxy)dimethylsilane. Removal of the volatiles in vacuo gave brown oil, which was purified by silica gel chromatography (pentane → 1% Et_2O in pentane) to afford **4.36** (9.0 mg, 0.0279 mmol, 70% yield) in >98:2 *Z:E* ratio as colorless oil. **IR (neat)**: 2952 (m), 2920 (s), 2850 (m), 1459 (m), 1377 (m), 1250 (m), 1039 (m), 833 (s), 770 (s; **^{19}F NMR (376 MHz, $CDCl_3$)**: *Z* isomer (major): δ −79.2 (d, J = 11.4 Hz);

E isomer (minor): δ −82.1 (d, J = 30.0 Hz); **^{1}H NMR (400 MHz, CDCl$_3$)**: *Z* isomer (major): δ 5.05 (dd, J = 11.2, 10.0 Hz, 1H), 2.42–2.21 (m, 1H), 1.44–1.23 (m, 6H), 1.17 (s, 6H), 1.00 (d, J = 6.7 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 6H); **^{13}C NMR (126 MHz, CDCl$_3$)**: δ 143.9 (d, J = 295.8 Hz), 111.1 (d, J = 15.9 Hz), 73.5, 45.1, 37.6 (d, J = 2.2 Hz), 32.9 (d, J = 3.4 Hz), 30.1, 29.8, 25.9, 22.0, 20.6 (d, J = 3.0 Hz), –1.9; **HRMS[M+H]$^+$**: Calcd for $C_{16}H_{33}OFSiCl$: 323.1968, found: 323.1960.

***tert*-Butyl (*Z*)-4-(2-chloro-2-fluorovinyl)piperidine-1-carboxylate (4.37):** Based on general procedure A, a solution of **Mo-1b** in benzene (0.1 M, 40 µL, 4.0 µmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (92.0 mg, 0.8000 mmol) and *tert*-butyl 4-vinylpiperidine-1-carboxylate (16.8 mg, 0.0795 mmol). A solution of (*Z*)-hex-3-ene in benzene (1.0 M, 8 µL, 8.0 µmol) was added and the mixture was allowed to stir for 12 h at 22 °C. At this time, the reaction was quenched by the addition of wet $CHCl_3$, after which analysis of the unpurified mixture showed 56% consumption of *tert*-butyl 4-vinylpiperidine-1-carboxylate. Removal of the volatiles in vacuo afforded brown oil, which was purified by silica gel chromatography (pentane → 45% CH_2Cl_2 in pentane) to afford **4.37** (10.9 mg, 0.0413 mmol, 52% yield) in 94:6 *Z:E* ratio as colorless oil. **IR (neat)**: 2967 (w), 2926 (m), 2850 (w), 1695 (s), 1420 (m), 1364 (w), 1171 (m), 1146 (m), 973 (w); **^{19}F NMR (470 MHz, CDCl$_3$)**: *Z* isomer (major): δ −78.1 (d, J = 10.6 Hz); *E* isomer (minor): δ −80.1 (d, J = 29.0 Hz); **^{1}H NMR (500 MHz, CDCl$_3$)**: *Z* isomer (major): δ 5.26–5.05 (m, 1H), 4.05 (s, 2H), 2.89–2.69 (m, 2H), 2.29 (q, J = 10.1, 8.8 Hz, 1H), 1.68 (d, J = 11.1 Hz, 2H), 1.46 (s, 9H), 1.36–1.27 (m, 2H); *E* isomer (resolved signal only): δ 4.74 (dd, J = 29.3, 9.3 Hz, 1H); **^{13}C NMR (151 MHz, CDCl$_3$)**: δ 154.9, 144.4 (d, J = 298.5 Hz), 109.0 (d, J = 17.9 Hz), 79.7, 34.4 (d, J = 3.6

Hz), 31.3, 29.9, 28.6; **HRMS[M+H]$^+$**: Calcd for $C_{12}H_{20}O_2FNCl$: 264.1161, found: 264.1155.

(*Z*)-(6-Chloro-6-fluoro-3-methylhex-5-en-1-yl)benzene (4.38): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 40 μL, 4.0 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (92.0 mg, 0.8000 mmol) and (*Z*)-(3-methylhept-5-en-1-yl)benzene (15.0 mg, 0.0797 mmol). This was followed by the addition of a solution of (*Z*)-hex-3-ene in benzene (1.0 M, 8 μL, 8.0 μmol). The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$ and analysis of the unpurified mixture showed 61% consumption of (*Z*)-(3-methylhept-5-en-1-yl)benzene. Removal of the volatiles in vacuo afforded brown oil, which was purified by preparative thin layer chromatography (45% CH_2Cl_2 in pentane) to afford **4.38** (9.9 mg, 0.0438 mmol, 55% yield) in 92:8 *Z:E* ratio as colorless oil. **IR (neat)**: 2955 (m), 2923 (s), 2853 (m), 1674 (m), 1494 (m), 1453 (m), 1101 (w), 1030 (s), 745 (m), 697 (s); **^{19}F NMR (470 MHz, $CDCl_3$)**: *Z* isomer (major): δ −76.8 (d, J = 11.1 Hz); *E* isomer (minor): δ −81.4 (d, J = 29.1 Hz). **^{1}H NMR (400 MHz, $CDCl_3$)**: *Z* isomer (major): δ 7.35–7.26 (m, 2H), 7.25–7.12 (m, 3H), 5.27 (dt, J = 11.2, 7.8 Hz, 1H), 2.79–2.46 (m, 2H), 2.18–2.02 (m, 1H), 2.01–1.92 (m, 1H), 1.72–1.56 (m, 2H), 1.55–1.43 (m, 1H), 0.96 (d, J = 6.5 Hz, 3H); *E* isomer (resolved signals only): δ 4.84 (dt, J = 29.2, 8.0 Hz, 1H); (*Z*)-(6-chloro-3-methylhex-5-en-1-yl)benzene: δ 6.07 (d, J = 7.1 Hz, 1H), 5.76 (q, J = 7.2 Hz, 1H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 145.0 (d, J = 295.9 Hz), 142.6, 128.5, 128.4, 125.8, 103.8 (d, J = 19.1 Hz), 38.3, 33.5, 33.3 (d, J = 2.8 Hz), 32.6 (d, J = 2.7 Hz), 19.4; **HRMS[M+H]$^+$**: Calcd for $C_{13}H_{17}FCl$: 227.7269, found: 227.7277.

***tert*-Butyl (*Z*)-5-(2-chloro-2-fluorovinyl)-1*H*-indole-1-carboxylate (4.41):** Based on the general procedure A, a solution of **Mo-2** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (57.5 mg, 0.5000 mmol) and *tert*-butyl (*Z*)-5-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate (12.7 mg, 0.0493 mmol). The mixture was allowed to stir for 4 h at 22 °C, after which a solution of **Mo-2** in benzene (0.1 M, 25 μL, 2.5 μmol) was added by syringe. The solution was allowed to stir for another 4 h at 22 °C, at which time the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture indicated 81% consumption of *tert*-butyl (*Z*)-5-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate. Removal of the volatiles in vacuo afforded brown oil, which was purified by preparative thin layer chromatography (3% Et_2O in pentane) to afford **4.41** (8.2 mg, 0.0277 mmol, 56% yield) in 92:8 *Z:E* ratio as colorless oil. **IR (neat)**: 2977 (m), 2926 (m), 2849 (m), 1734 (s), 1600 (m), 1468 (m), 1369 (s), 1334 (m), 1161 (m), 1099 (m), 1022 (w), 765 (w); **^{19}F NMR (376 MHz, $CDCl_3$)**: *Z* isomer (major): δ −73.0 (d, J = 12.9 Hz); *E* isomer (minor): δ −75.8 (d, J = 31.5 Hz); **^{1}H NMR (500 MHz, $CDCl_3$)**: *Z* isomer (major): δ 8.11 (d, J = 8.5 Hz, 1H), 7.69 (s, 1H), 7.60 (d, J = 3.7 Hz, 1H), 7.38 (dd, J = 8.7, 1.8 Hz, 1H), 6.56 (d, J = 3.7 Hz, 1H), 6.49 (d, J = 13.0 Hz, 1H), 1.68 (s, 9H); *E* isomer (resolved signals only): δ 5.90 (d, J = 30.7 Hz, 1H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 149.7, 143.9 (d, J = 296.4 Hz), 134.7, 130.8, 128.5, 126.8, 125.6 (d, J = 7.6 Hz), 124.9 (d, J = 3.1 Hz), 120.8 (d, J = 3.2 Hz), 107.5 (d, J = 28.0 Hz), 107.4, 84.1, 28.3; **HRMS[M+H]$^+$**: Calcd for $C_{15}H_{16}CFlNO_2$: 296.0848, found: 296.0849.

(*E*)-3-Fluoro-4-(4-methoxyphenyl)but-3-en-2-one (4.42): Based on general procedure A, a solution of **Mo-2** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to

an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (57.5 mg, 0.5000 mmol) and (*Z*)-1-methoxy-4-(prop-1-en-1-yl)benzene (7.4 mg, 0.0499 mmol). The mixture was allowed to stir for 4 h at 22 °C, after which a solution of **Mo-2** in benzene (0.1 M, 25 μL, 2.5 μmol) was added by syringe and the solution was allowed to stir for 4 h at 22 °C. At this time, the mixture was exposed to air and the volatiles were carefully removed in vacuo. The resulting orange oil was placed under N_2 atm (glove box) and charged with $Pd(P(t\text{-}Bu)_3)_2$ (1.3 mg, 0.0025 mmol), (1-ethoxyvinyl)zinc chloride (0.39 M, 256 μL, 0.1000 mmol), and THF/NMP (0.9 mL/0.5 mL). The mixture was then allowed to stir for 2 h at 80 °C, after which the solution was cooled to 22 °C and charged with a 3M solution of aqueous HCl (1mL). The mixture was allowed to stir for 1 h, after which the aqueous layer was washed with Et_2O (3 x 10 mL). The combined organic layers were washed successively with a saturated solution of NaCl solution (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$ and the volatiles were removed in vacuo to afford yellow oil, which was purified by silica gel chromatography (hexanes → 9% Et_2O in hexanes) to afford **4.42** (5.5 mg, 0.0283 mmol, 57% yield) in >98:2 *E:Z* ratio as yellow solid, and (*Z*)-3-fluoro-4-(4-methoxyphenyl)but-3-en-2-one (0.6 mg, 0.0030 mmol). **M.p.**: 41–43 °C; **IR (neat)**: 2953 (m), 2924 (s), 2850 (m), 1700 (m), 1600 (m), 1510 (s), 1256 (m), 1176 (s), 1031 (w), 828 (w); **^{19}F NMR (376 MHz, $CDCl_3$)**: δ −114.8 (dq, J = 26.2, 5.3 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.68 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.65 (d, J = 26.1 Hz, 1H), 3.83 (s, 3H), 2.34 (d, J = 5.2 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 193.03 (d, J = 39.7 Hz), 160.79 (d, J = 1.7 Hz), 152.30 (d, J = 252.6 Hz), 132.3 (d, J = 3.0 Hz), 123.3 (d, J = 10.3 Hz), 120.7 (d, J = 29.0 Hz), 113.8, 55.5, 28.4 (d, J = 1.9 Hz); **HRMS[M+H]$^+$**: Calcd for $C_{11}H_{12}FO_2$: 195.0816, found: 195.0811.

(*E*)-3-Fluoro-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one (4.43): Based on general procedure A, a solution of **Mo-2** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (57.5 mg, 0.5000 mmol) and (*Z*)- 1-(2-chloro-2-fluorovinyl)-4-(trifluoromethyl)benzene (9.3 mg, 0.0499 mmol). The mixture was allowed to stir for 4 h at 22 °C, at which time a solution of **Mo-2** in benzene (0.1 M, 25 μL, 2.5 μmol) was added by syringe. The mixture was allowed to stir for 4 h at 22 °C, after which it was exposed to air the volatiles were carefully removed in vacuo. The resulting orange oil was placed under N_2 atm (glove box) and charged with $Pd(P(t\text{-}Bu)_3)_2$ (1.3 mg, 0.0025 mmol), and (1-ethoxyvinyl)zinc chloride (0.39 M, 256 μL, 0.1000 mmol) followed by THF/NMP (0.9 mL/0.5 mL). The mixture was allowed to stir for 2 h at 80 °C. The solution was then allowed to cool to 22 °C and was charged with a 3M solution of aqueous HCl (1mL). The mixture was allowed to stir for another hour, after which the aqueous layer was washed with Et_2O (3 x 10 mL). The combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$ and concentrated in vacuo to afford yellow oil, which was purified by silica gel chromatography (hexanes → 9% Et_2O in hexanes) to afford **4.43** (5.2 mg, 0.0224 mmol, 45% yield) in >98:2 *E:Z* ratio as yellow solid, and (*Z*)-3-fluoro-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one (0.4 mg, 0.0017 mmol). **M.p.**: 48–50 °C; **IR (neat)**: 2957 (m), 2924 (m), 2853 (m), 1700 (m), 1618 (m), 1311 (s), 1164 (s), 1119 (s), 890 (w), 837 (m); **^{19}F NMR (376 MHz, $CDCl_3$)**: δ −62.9, −110.6 (dq, J = 23.7, 5.1 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.67 (d, J = 8.2 Hz, 2H), 7.61 (d, J = 8.2 Hz, 2H), 6.68 (d, J = 23.6 Hz, 1H), 2.36 (d, J = 4.9 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 192.8 (d, J = 39.5 Hz), 153.8 (d, J = 262.4 Hz), 134.6 (d, J

= 11.2 Hz), 131.0, 130.3 (d, *J* = 3.0 Hz), 125.2 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.2 Hz), 118.2 (d, *J* = 28.2 Hz), 28.2 (d, *J* = 2.2 Hz); **HRMS[M+H]$^+$**: Calcd for $C_{11}H_9F_4O$: 233.0584, found: 233.0591.

(*E*)-6-Bromo-1-chloro-1-fluorohex-1-ene (4.44): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 50 µL, 5.0 µmol) was transferred by syringe to an oven-dried vial containing (*E*)-1,2-dichloro-1-fluoroethene (115.0 mg, 1.0000 mmol) and 7-bromo-2-methylhept-2-ene (19.0 mg, 0.0994 mmol). This was followed by the addition of a solution of (*E*)-but-2-ene in hexanes (6.6 M, 3.0 µL, 20.0 µmol). The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture indicated 72% consumption of 7-bromo-2-methylhept-2-ene. Removal of the volatiles in vacuo afforded brown oil, which was purified by silica gel chromatography (pentane) to afford **4.44** (13.2 mg, 0.0614 mmol, 62% yield) in 3:97 *Z:E* ratio as colorless oil. **IR (neat)**: 2920 (m), 2910 (m), 1447 (w), 1236 (w), 1059 (m), 907 (s), 730 (s), 651 (m); **^{19}F NMR (470 MHz, $CDCl_3$)**: *E* isomer (major): δ −81.3 (d, *J* = 28.9 Hz); *Z* isomer (minor): δ −77.3 (d, *J* = 10.9 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 4.84 (dt, *J* = 29.0, 7.8 Hz, 1H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.14 (qd, *J* = 7.5, 2.3 Hz, 2H), 1.87 (dt, *J* = 14.6, 6.9 Hz, 2H), 1.54 (p, *J* = 7.5 Hz, 2H); (*Z*)-6-bromo-1-chlorohex-1-ene (resolved signals only): δ 6.05 (d, *J* = 7.1 Hz, 1H), 5.74 (q, *J* = 7.1 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 127.2 (d, *J* = 291.7 Hz), 106.2 (d, *J* = 17.2 Hz), 33.4, 32.0, 27.5 (d, *J* = 2.2 Hz), 24.2 (d, *J* = 1.4 Hz); **HRMS[M+H]$^+$**: Calcd for $C_6H_{10}FBrCl$: 214.9633, found: 214.9628.

(*E*)-*tert*-Butyl((4-chloro-4-fluorobut-3-en-1-yl)oxy)diphenylsilane (4.45): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 40 µL, 4.0 µmol) was

transferred by syringe to an oven-dried vial containing (*E*)-1,2-dichloro-1-fluoroethene (46.0 mg, 0.4000 mmol) and *tert*-butyl((4-methylpent-3-en-1-yl)oxy)diphenylsilane (13.5 mg, 0.0399 mmol). A solution of (*E*)-but-2-ene in hexanes (6.6 M, 2.4 µL, 16.0 µmol) was added, and the resulting mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture showed 67% consumption of *tert*-butyl((4-methylpent-3-en-1-yl)oxy)diphenylsilane. Removal of the volatiles in vacuo afforded brown oil, which was purified by silica gel chromatography (pentane → 1% Et_2O in pentane) to afford **4.45** (7.5 mg, 0.0208 mmol, 52% yield) in 7:93 *Z:E* ratio as colorless oil. **IR (neat)**: 2955 (m), 2927 (m), 2855 (m), 1678 (m), 1426 (m), 1109 (s), 1039 (m), 739 (m), 700 (m), 504 (m); **^{19}F NMR (470 MHz, $CDCl_3$)**: *E* isomer (major): δ −80.6 (d, J = 29.4 Hz); *Z* isomer (minor): δ −76.5 (d, J = 10.2 Hz); **^{1}H NMR (600 MHz, $CDCl_3$)**: *E* isomer (major): δ 7.65 (d, J = 6.7 Hz, 4H), 7.43 (t, J = 7.3 Hz, 2H), 7.39 (t, J = 7.2 Hz, 4H), 4.93 (dt, J = 29.3, 7.7 Hz, 1H), 3.66 (t, J = 6.4 Hz, 2H), 2.34 (dtd, J = 8.6, 6.5, 2.3 Hz, 2H), 1.05 (s, 9H); *Z* isomer (resolved signals only): δ 5.34 (dt, J = 10.8, 7.6 Hz, 1H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 143.9 (d, J = 301.1 Hz), 135.7, 133.8, 129.8, 127.8, 103.9 (d, J = 16.8 Hz), 62.6 (d, J = 2.3 Hz), 28.6, 26.9, 19.3; **HRMS[M+H]$^+$**: Calcd for $C_{20}H_{25}OFClSi$: 363.1342, found: 363.1349.

(*S*,*E*)-7-Chloro-7-fluoro-3-methylhept-6-en-1-yl 2-(phenylthio)acetate (4.46): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 40 µL, 4.0 µmol) was transferred by syringe to an oven-dried vial containing (*E*)-1,2-dichloro-1-fluoroethene (46.0 mg, 0.4000 mmol) and (*S*)-3,7-dimethyloct-6-en-1-yl 2-(phenylthio)acetate (12.2 mg, 0.0398 mmol). This was followed by the addition of a solution of (*E*)-but-2-ene in hexanes (6.6 M, 1.2 µL, 8.0 µmol). The mixture was allowed to stir for 12 h at 22 °C,

after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture showed 57% consumption of (*S*)-3,7-dimethyloct-6-en-1-yl 2-(phenylthio)acetate. Removal of the volatiles in vacuo afforded brown oil, which was purified by silica gel chromatography (pentane → 9% Et_2O in pentane) to afford **4.46** (6.7 mg, 0.0203 mmol, 51% yield) in 3:97 *Z:E* ratio as colorless oil. **IR (neat)**: 2954 (m), 2924 (m), 2853 (w), 1731 (s), 1676 (m), 1457 (m), 1274 (s), 1130(m), 739 (m), 689 (m); **^{19}F NMR (470 MHz, $CDCl_3$)**: *E* isomer (major): δ −81.8 (d, J = 29.2 Hz); *Z* isomer (minor): δ −78.0 (d, J = 10.6 Hz); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.43–7.39 (m, 2H), 7.30 (t, J = 7.5 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H), 4.80 (dt, J = 29.2, 7.8 Hz, 1H), 4.20–4.06 (m, 2H), 3.64 (s, 2H), 2.22–1.96 (m, 2H), 1.67–1.58 (m, 1H), 1.48 (q, J = 6.6 Hz, 1H), 1.43–1.32 (m, 2H), 1.25–1.17 (m, 1H), 0.87 (d, J = 6.6 Hz, 3H); (*S,Z*)-7-chloro-3-methylhept-6-en-1-yl 2-(phenylthio)acetate (resolved signals only): δ 6.00 (d, J = 7.0 Hz, 1H), 5.71 (q, J = 7.1 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 169.9, 143.1 (d, J = 300.5 Hz), 135.1, 130.0, 129.2, 127.1, 106.8 (d, J = 17.4 Hz), 63.9, 36.9, 36.0, 35.2, 29.2, 22.6, 19.2; **HRMS[M+H]$^+$**: Calcd for $C_{16}H_{21}O_2FSCl$: 331.0929, found: 331.0922.

(*S,E*)-7-Chloro-7-fluoro-3-methylhept-6-en-1-ol (4.47): Based on general procedure B, an oven-dried vial equipped with a magnetic stir bar was charged with (*S*)-3,7-dimethyloct-6-en-1-ol (12.4 mg, 0.0795 mmol). 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (30.6 mg, 0.2390 mmol) was added, resulting in H_2 evolution. Once effervescence subsided, the solution was allowed to stir for 30 min at 22 °C, after which the volatiles were removed in vacuo (1 Torr, 30 min). (*E*)-1,2-Dichloro-1-fluoroethene (92.0 mg, 0.8000 mmol) and a solution of **Mo-1a** in benzene (0.1 M, 40 µL, 4.0 µmol) were added, followed by the addition of a solution of (*E*)-but-2-ene in hexanes (6.6 M, 2.4 µL, 16.0

μmol). The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture indicated 81% consumption of (*S*)-3,7-dimethyloct-6-en-1-ol. Removal of the volatiles in vacuo afforded brown oil, which was purified by silica gel chromatography (pentane → 9% acetone in pentane) to afford **4.47** (10.5 mg, 0.0581 mmol, 73% yield) in 4:96 *Z:E* ratio as colorless oil. **IR (neat)**: 3334 (s), 2953 (m), 2923 (s), 2870 (m), 1676 (m), 1456 (w), 1046 (s), 1009 (m), 802 (w), 732 (w; **^{19}F NMR (470 MHz, $CDCl_3$)**: *E* isomer (major): δ −82.0 (d, J = 29.7 Hz); *Z* isomer (minor): δ −78.2 (d, J = 11.0 Hz); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 4.83 (dt, J = 29.3, 7.7 Hz, 1H), 3.69 (tt, J = 10.5, 4.4 Hz, 2H), 2.19–2.05 (m, 2H), 1.66–1.57 (m, 2H), 1.40 (ddd, J = 15.5, 8.8, 4.4 Hz, 2H), 1.28–1.11 (m, 1H), 0.91 (d, J = 6.3 Hz, 3H) (hydroxy proton was undetected); (*S*,*Z*)-7-chloro-3-methylhept-6-en-1-ol (resolved signals only): δ 6.01 (d, J = 7.1 Hz, 1H), 5.74 (q, J = 7.1 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 143.1 (d, J = 300.2 Hz), 107.0 (d, J = 17.2 Hz), 61.1, 39.8, 36.3, 29.1, 22.7 (d, J = 1.5 Hz), 19.4; **HRMS[M+H]$^+$**: Calcd for $C_8H_{15}OFCl$: 181.0790, found: 181.0801.

(*E*)-2-(6-Chloro-6-fluorohex-5-en-1-yl)isoindoline-1,3-dione (4.48): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing (*E*)-1,2-dichloro-1-fluoroethene (115.0 mg, 1.0000 mmol) and 2-(6-methylhept-5-en-1-yl)isoindoline-1,3-dione (25.7 mg, 0.1000 mmol), followed by the addition of a solution of (*E*)-but-2-ene in hexanes (6.6 M, 3.0 μL, 20.0 μmol). The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture showed 69% consumption of 2-(6-methylhept-5-en-1-yl)isoindoline-1,3-dione. Removal of the

volatiles in vacuo afforded brown oil, which was purified by silica gel chromatography (pentane → 10% Et_2O in pentane) to afford **4.48** (17.2 mg, 0.0610 mmol, 61% yield) in <2:98 *Z:E* ratio as colorless oil. **IR (neat)**: 2946 (m), 2922 (m), 2858 (w), 1710 (s), 1676 (w), 1395 (m), 1372 (w), 1040 (w), 719 (m); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −81.4 (d, J = 29.1 Hz); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.85 (dd, J = 5.4, 3.1 Hz, 2H), 7.71 (dd, J = 5.4, 3.0 Hz, 2H), 4.83 (dt, J = 29.0, 7.8 Hz, 1H), 3.69 (t, J = 7.2 Hz, 2H), 2.15 (qd, J = 7.5, 2.3 Hz, 2H), 1.83–1.63 (m, 2H), 1.44 (p, J = 7.5 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 168.5, 143.4 (d, J = 300.7 Hz), 134.0, 132.2, 123.3, 106.3 (d, J = 16.4 Hz), 37.7, 28.1, 26.3, 24.6; **HRMS[M+H]$^+$**: Calcd for $C_{14}H_{14}O_2FNCl$: 282.0692, found: 282.0699.

(*E*)-6-Chloro-6-fluorohex-5-en-1-yl 1*H*-indole-2-carboxylate (4.49): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 40 µL, 4.0 µmol) was transferred by syringe to an oven-dried vial containing (*E*)-1,2-dichloro-1-fluoroethene (46.0 mg, 0.4000 mmol) and 6-methylhept-5-en-1-yl 1*H*-indole-2-carboxylate (10.8 mg, 0.0398 mmol). This was followed by the addition of a solution of (*E*)-but-2-ene in hexanes (6.6 M, 2.4 µL, 16.0 µmol). The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture indicated 73% consumption of 6-methylhept-5-en-1-yl 1*H*-indole-2-carboxylate. Removal of the volatiles in vacuo afforded brown oil, which was purified by silica gel chromatography (pentane → 20% Et_2O in pentane) to afford **4.49** (8.0 mg, 0.0271 mmol, 68% yield) in 3:97 *Z:E* ratio as colorless oil. **IR (neat)**: 3325 (m), 3282 (m), 2923 (w), 1675 (s), 1531 (m), 1434 (m), 1175 (m), 1043 (m), 751 (m); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −81.4 (d, J = 29.3 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 8.52 (br, 1H), 8.17 (dd, J = 6.3, 3.0 Hz, 1H), 7.93 (d, J = 3.0 Hz, 1H), 7.46–7.40 (m, 1H), 7.32–7.27 (m, 2H),

4.88 (dt, *J* = 29.1, 7.8 Hz, 1H), 4.35 (t, *J* = 6.5 Hz, 2H), 2.21 (qd, *J* = 7.6, 2.4 Hz, 2H), 1.83 (dt, *J* = 14.4, 6.7 Hz, 2H), 1.60 (q, *J* = 7.6 Hz, 2H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 165.3, 143.4 (d, *J* = 300.3 Hz), 136.2, 131.0, 125.9, 123.4, 122.2, 121.7, 111.6, 109.3, 106.4, 63.5, 28.5, 25.7, 24.8; **HRMS[M+H]$^+$**: Calcd for $C_{15}H_{16}O_2FNCl$: 296.0848, found: 296.0856.

(*R*,*E*)-*tert*-Butyl((8-chloro-8-fluoro-2,6-dimethyloct-7-en-2-yl)oxy)dimethylsilane (4.50): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 20 µL, 2.0 µmol) was transferred by syringe to an oven-dried vial containing (*E*)-1,2-dichloro-1-fluoroethene (46.0 mg, 0.4000 mmol) and (*R*)-*tert*-butyl((2,6-dimethyloct-7-en-2-yl)oxy)dimethylsilane (10.8 mg, 0.0400 mmol). A solution of (*E*)-but-2-ene in hexanes (6.6 M, 1.2 µL, 8.0 µmol) was subsequently added. The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture indicated 80% consumption of (*R*)-*tert*-butyl((2,6-dimethyloct-7-en-2-yl)oxy)dimethylsilane. Removal of the volatiles in vacuo afforded brown oil, which was purified by silica gel chromatography (pentane) to afford **4.50** (7.9 mg, 0.0244 mmol, 61% yield) in <2:98 *Z:E* ratio as colorless oil. **IR (neat)**: 2953 (m), 2927 (s), 2853 (m), 1674 (w), 1459 (w), 1250 (m), 1038 (s), 833 (m), 770 (m); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −82.1 (d, *J* = 29.5 Hz); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 4.65 (dd, *J* = 29.6, 10.0 Hz, 1H), 2.69–2.45 (m, 1H), 1.42–1.26 (m, 6H), 1.17 (d, *J* = 3.2 Hz, 6H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 6H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 142.5 (d, *J* = 299.8 Hz), 112.9 (d, *J* = 16.9 Hz), 73.5, 45.0, 37.7, 30.9, 30.1, 29.8, 26.0, 22.1, 20.8, –1.9; **HRMS[M+H]$^+$**: Calcd for $C_{16}H_{33}OFSiCl$: 323.1968, found: 323.1961.

(*E*)-(6-Chloro-6-fluoro-3-methylhex-5-en-1-yl)benzene (4.51): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 20 μL, 2.0 μmol) was transferred by syringe to an oven-dried vial containing (*E*)-1,2-dichloro-1-fluoroethene (46.0 mg, 0.4000 mmol) and (*Z*)-(3-methylhept-5-en-1-yl)benzene (7.5 mg, 0.0399 mmol). This was followed by the addition of a solution of (*E*)-but-2-ene in hexanes (6.6 M, 1.2 μL, 8.0 μmol). The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$ and analysis of the unpurified mixture revealed 51% consumption of (*Z*)-(3-methylhept-5-en-1-yl)benzene. Removal of the volatiles in vacuo afforded brown oil, which was purified by silica gel chromatography (pentane) to afford **4.51** (4.0 mg, 0.0176 mmol, 44% yield) in <2:98 *Z:E* ratio as colorless oil. **IR (neat)**: 2955 (m), 2923 (s), 2853 (m), 1674 (w), 1494 (w), 1453 (m), 1101 (m), 1030 (m), 745 (m), 697 (s); **^{19}F NMR (564 MHz, $CDCl_3$)**: δ −81.4 (d, J = 29.1 Hz); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.31–7.24 (m, 2H), 7.18 (t, J = 7.2 Hz, 3H), 4.84 (dt, J = 29.1, 8.0 Hz, 1H), 2.73–2.48 (m, 2H), 2.18–1.96 (m, 2H), 1.69–1.53 (m, 2H), 1.52–1.44 (m, 1H), 0.96 (d, J = 6.6 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 143.4 (d, J = 300.6 Hz), 142.6, 138.5, 128.5, 125.8, 105.3 (d, J = 17.1 Hz), 38.3, 33.5, 32.6, 32.1, 19.4; **HRMS[M+H]$^+$**: Calcd for $C_{13}H_{17}FCl$: 227.0997, found: 227.1005.

***tert*-Butyl (*E*)-5-(2-chloro-2-fluorovinyl)-1*H*-indole-1-carboxylate (4.52):** Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 25 μL, 2.5 μmol) was transferred by syringe to an oven-dried vial containing (*E*)-1,2-dichloro-1-fluoroethene (57.5 mg, 0.5000 mmol) and *tert*-butyl (*Z*)-5-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate (12.7 mg, 0.0493 mmol). The resulting solution was allowed to stir for 12 h at 22 °C. At this time, a solution of **Mo-1a** in benzene (0.1 M, 25 μL, 2.5 μmol) was added by syringe,

and the mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture showed >98% consumption of *tert*-butyl (*E*)-5-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate. Removal of the volatiles in vacuo afforded brown oil, which was purified by preparative thin layer chromatography (3% Et_2O in pentane) to afford **4.52** (7.0 mg, 0.0237 mmol, 48% yield) in 2:98 *Z:E* ratio as colorless oil. **IR (neat)**: 2972 (m), 2925 (m), 2853 (w), 1735 (s), 1660 (m), 1469 (m), 1369 (s), 1335 (m), 1255 (m), 1022 (m), 764 (m); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −75.8 (d, J = 30.7 Hz); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.09 (s, 1H), 7.61 (d, J = 15.0 Hz, 2H), 7.33 (d, J = 8.7 Hz, 1H), 6.55 (d, J = 3.8 Hz, 1H), 5.90 (d, J = 30.7 Hz, 1H), 1.67 (s, 9H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 149.7, 143.8 (d, J = 310.9 Hz), 131.0, 126.8, 126.7, 126.7, 124.6, 120.7, 115.4, 110.5 (d, J = 10.4 Hz), 107.5, 84.1, 28.3; **HRMS[M+H]$^+$**: Calcd for $C_{15}H_{16}FClNO_2$: 296.0848, found: 296.0853.

(*Z*)-3-Fluoro-4-(4-methoxyphenyl)but-3-en-2-one (4.53): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 25 µL, 2.5 µmol) was transferred by syringe to an oven-dried vial containing (*E*)-1,2-dichloro-1-fluoroethene (57.5 mg, 0.5000 mmol) and (*Z*)-1-methoxy-4-(prop-1-en-1-yl)benzene (7.4 mg, 0.0499 mmol). The mixture was allowed to stir for 12 h at 22 °C, after which a solution of **Mo-1a** in benzene (0.1 M, 25 µL, 2.5 µmol) was added by syringe. The mixture was allowed to stir for 12 h at 22 °C, and then the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture indicated >98% consumption of (*Z*)-1-methoxy-4-(prop-1-en-1-yl)benzene. The volatiles were carefully removed in vacuo, affording orange oil, which was placed under N_2 atm (glove box) and charged with $Pd(P(t\text{-}Bu)_3)_2$ (1.3 mg, 0.0025 mmol), and (1-ethoxyvinyl)zinc chloride (0.39 M, 256 µL, 0.1000 mmol) and finally

THF/NMP (0.9 mL/0.5 mL). The mixture was allowed to stir for 2 h at 80 °C, after which the solution was allowed to cool to 22 °C. The solution was charged with 1 mL of a 3M aqueous solution of HCl, and the mixture was allowed to stir for 1 h at 22 °C. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. The volatiles were removed in vacuo to afford yellow oil, which was purified by silica gel chromatography (hexanes → 9% Et_2O in hexanes) to afford **4.53** (4.6 mg, 0.0237 mmol, 49% yield) in >98:2 *Z:E* ratio as yellow solid, and (*E*)-3-fluoro-4-(4-methoxyphenyl)but-3-en-2-one (0.3 mg, 0.0015 mmol). **M.p.**: 71–73 °C; **IR (neat)**: 3004 (m), 2932 (m), 2839 (m), 1673 (m), 1629 (m), 1599 (s), 1257 (s), 1177 (m), 1020 (m), 893 (m), 828 (s); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −126.7 (dt, J = 37.1, 3.3 Hz); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.63 (d, J = 8.3 Hz, 2H), 6.93 (d, J = 8.3 Hz, 2H), 6.79 (d, J = 36.7 Hz, 1H), 3.85 (s, 3H), 2.40 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 192.3 (d, J = 32.5 Hz), 161.0 (d, J = 3.5 Hz), 153.3 (d, J = 267.8 Hz), 132.6 (d, J = 8.6 Hz), 123.8 (d, J = 4.2 Hz), 115.9 (d, J = 6.1 Hz), 114.5, 55.5, 25.7; **HRMS[M+H]$^+$**: Calcd for $C_{11}H_{12}FO_2$: 195.0816, found: 195.0825.

(*E*)-3-Fluoro-4-(4-methoxyphenyl)but-3-en-2-one (4.55): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 50 µL, 5.0 µmol) was transferred by syringe to an oven-dried vial containing (*E*)-1,2-dichloro-1-fluoroethene (115.0 mg, 1.0000 mmol) and dimethyl((3-methylbut-2-en-1-yl)oxy)(phenyl)silane (22.0 mg, 0.1000 mmol), followed by the addition of a solution of (*E*)-but-2-ene in hexanes (6.6 M, 3.0 µL, 20.0 µmol). The resulting solution was allowed to stir for 12 h at 22 °C, after which a solution of **Mo-1a** in benzene (0.1 M, 50 µL, 5.0 µmol) and of *E*-but-2-ene in toluene (6.6 M, 3.0

μL, 20.0 μmol) were added by syringe. The mixture was allowed to stir for 12 h at 22 °C, after which was exposed to air. Careful removal of the volatiles in vacuo afforded orange oil, which was charged with $PdCl_2(PhCN)_2$ (2.0 mg, 0.0050 mmol), CuI (2.0 mg, 0.0100 mmol), and 1-ethynyl-4-methoxybenzene (26.4 mg, 0.2000 mmol) in piperidine (1.0 mL). The mixture was allowed to stir for 15 h at 22 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded brown oil, which was purified by preparative thin layer chromatography (10% EtOAc in hexanes) to afford **4.55** (8.5 mg, 0.0412 mmol, 41% yield) in >98:2 *E:Z* ratio as light yellow oil. **IR (neat)**: 2950 (m), 2921 (s), 2851 (m), 1602 (m), 1507 (s), 1461 (w), 1288 (m), 1251 (s), 1173 (m), 831 (w); **^{19}F NMR (564 MHz, $CDCl_3$)**: δ −105.4 (d, J = 32.4 Hz); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.43 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.49 (dt, J = 32.4, 7.1 Hz, 1H), 4.35 (t, J = 6.2 Hz, 2H), 3.83 (s, 3H), hydroxy proton not observed; **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 160.6, 154.0 (d, J = 239.9 Hz), 133.5 (d, J = 2.2 Hz), 115.1 (d, J = 18.4 Hz), 114.3, 109.1, 92.4, 91.8, 56.1, 55.5; **HRMS[M+H]$^+$**: Calcd for $C_{12}H_{12}FO_2$: 207.0816, found: 207.0810.

(*E*)-3-Fluoro-4-(4-methoxyphenyl)but-3-en-2-one (4.56): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 50 μL, 5.0 μmol) was transferred by syringe to an oven-dried vial containing (*E*)-1,2-dichloro-1-fluoroethene (115.0 mg, 1.0000 mmol) and dimethyl((3-methylbut-2-en-1-yl)oxy)(phenyl)silane (22.0 mg, 0.1000 mmol). The mixture was allowed to stir for 12 h at 22 °C, after which a solution of **Mo-1a** in benzene

(0.1 M, 50 μL, 5.0 μmol) was added by syringe and the mixture was allowed to stir for 12 h at 22 °C. At this time, the mixture was exposed to air and the volatiles carefully removed in vacuo, affording orange oil, which was treated with $PdCl_2(PhCN)_2$ (2.0 mg, 0.0050 mmol), CuI (2.0 mg, 0.0100 mmol), and 1-ethynyl-4-methoxybenzene (26.4 mg, 0.2000 mmol) in piperidine (1 mL). The mixture was allowed to stir for 15 h at 22 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL). The combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. The volatiles were removed in vacuo to afford brown oil, which was purified by preparative thin layer chromatography (2% EtOAc in hexanes) to afford **4.56** (10.5 mg, 0.0400 mmol, 40% yield) in >98:2 *E:Z* ratio as light yellow oil. **IR (neat)**: 2951 (m), 2921 (s), 2851 (m), 1603 (m), 1507 (s), 1287 (m), 1248 (s), 1168 (m), 1034 (w), 831 (s), 541 (w); **^{19}F NMR (376 MHz, $CDCl_3$)**: δ −113.9 (d, J = 32.8 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.41 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.31 (dt, J = 33.0, 9.1 Hz, 1H), 3.82 (s, 3H), 1.62 (dd, J = 9.2, 1.6 Hz, 2H), 0.07 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 160.2, 156.1 (d, J = 174.0 Hz), 133.3 (d, J = 1.9 Hz), 132.8, 114.2, 106.5 (d, J = 0.6 Hz), 81.0, 80.6, 55.5, 16.0, −1.6 ; **HRMS[M+H]$^+$**: Calcd for $C_{15}H_{20}FOSi$: 263.1262, found: 263.1267.

Methyl (*Z*)-10-chloro-10-fluorodec-9-enoate (4.60): In a N_2-filled glovebox, an oven-dried vial equipped with a magnetic stir bar was charged with methyl dec-9-enoate (18.4 mg, 0.1000 mmol) and 2-methylbut-2-ene (1.1 mL, 2.0000 mmol). A solution of **Mo-1a** in benzene (0.1 M, 10 μL, 1.0 μmol) was added and the mixture was allowed to stir for 12 h at 22 °C. The volatiles were then removed in vacuo (2 Torr, 5 min). (*Z*)-1,2-

Dichloro-1-fluoroethene (115.0 mg, 1.0000 mmol), a benzene solution of **Mo-1a** (0.1 M, 50 μL, 5.0 μmol), and a benzene solution of (*Z*)-hex-3-ene (1.0 M, 10 μL, 10.0 μmol) were added. The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture revealed 98% consumption of methyl 10-methylundec-9-enoate. Removal of the volatiles in vacuo afforded brown oil, which was purified by silica gel chromatography (pentane) to afford **4.60** (19.6 mg, 0.0830 mmol, 83% yield) in 95:5 *Z:E* ratio as colorless oil. **IR (neat)**: 2927 (m), 2855 (m), 1739 (s), 1677 (m), 1460 (w), 1196 (m), 1170 (m), 1117 (m); **^{19}F NMR (376 MHz, $CDCl_3$)**: *Z* isomer (major): δ −78.3 (d, J = 11.0 Hz); *E* isomer (minor): δ −82.2 (d, J = 28.9 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 5.24 (dt, J = 10.7, 7.7 Hz, 1H), 3.66 (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 2.02 (q, J = 7.2 Hz, 2H), 1.61 (q, J = 7.2 Hz, 2H), 1.34 (m, 8H); **^{13}C NMR (126 MHz, $CDCl_3$)**: δ 174.4, 144.5 (d, J = 295.9 Hz), 105.3 (d, J = 18.7 Hz), 51.6, 34.2, 29.2, 29.1, 28.9, 28.7 (d, J = 2.4 Hz), 26.1 (d, J = 3.3 Hz), 25.0; **HRMS[M+H]$^+$**: Calcd for $C_{11}H_{19}O_2FCl$: 237.1052, found: 237.1056.

Methyl (*E*)-10-chloro-10-fluorodec-9-enoate (4.61): In a N_2-filled glovebox, an oven-dried vial equipped with a magnetic stir bar was charged with methyl dec-9-enoate (18.4 mg, 0.1000 mmol) and 2-methylbut-2-ene (1.1 mL, 2.0000 mmol). A solution of **Mo-1a** in benzene (0.1 M, 10 μL, 1.0 μmol) was added and the mixture was allowed to stir for 12 h at 22 °C. The volatiles were removed in vacuo (2 Torr, 5 min) and (*E*)-1,2-dichloro-1-fluoroethene (115.0 mg, 1.0000 mmol) a solution of **Mo-1a** in benzene (0.1 M, 50 μL, 5.0 μmol) and then a solution of (*E*)-but-2-ene in hexane (6.6 M, 3.0 μL, 20.0 μmol) were added. The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture indicated 59%

consumption of methyl 10-methylundec-9-enoate. Removal of the volatiles in vacuo afforded brown oil, which was purified by silica gel chromatography (pentane) to afford **4.61** (12.3 mg, 0.0520 mmol, 52% yield) in 3:97 *Z:E* ratio as colorless oil. **IR (neat)**: 2924 (m), 2854 (m), 1739 (s), 1677 (w), 1273 (m), 1460 (m), 1196 (m), 1118 (m), 699 (w); **^{19}F NMR (376 MHz, $CDCl_3$)**: *E* isomer (major): δ −82.2 (d, J = 29.1 Hz); *Z* isomer (minor): δ −78.3 (d, J = 9.9 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 4.82 (dt, J = 29.2, 7.8 Hz, 1H), 3.66 (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 2.11–1.99 (m, 2H), 1.67–1.55 (m, 2H), 1.30 (m, 8H); **^{13}C NMR (126 MHz, $CDCl_3$)**: δ 174.3, 143.0 (d, J = 300.3 Hz), 106.9 (d, J = 17.2 Hz), 51.6, 34.2, 29.2, 29.0, 28.9, 28.9, 27.0, 25.0; **HRMS[M+H]$^+$**: Calcd for $C_{11}H_{19}O_2FCl$: 237.1052, found: 237.1050.

(*Z*)-2-(6-Chloro-6-fluorohex-5-en-1-yl)isoindoline-1,3-dione (4.63): Based on general procedure A, a solution of **Mo-1c** in benzene (0.1 M, 2350 μL, 235 μmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (5.4050 g, 47.0 mmol) and 2-(6-methylhept-5-en-1-yl)isoindoline-1,3-dione (1200 mg, 4.7 mmol). This was followed by the addition of a solution of (*Z*)-hex-3-ene in benzene (1.0 M, 352 μL, 352 μmol). The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture indicated 71% consumption of 2-(6-methylhept-5-en-1-yl)isoindoline-1,3-dione. *Z*-1,2-Dichloro-1-fluoroethene solution was recovered through Kugelrohr distillation (ambient pressure; 4.2890 g of *Z*-1,2-dichloro-1-fluoroethene in 0.6730 g benzene). The remaining brown oil residue was then purified by silica gel chromatography (pentane → 10% EtOAc in pentane) to afford **4.63** (820.8 mg, 2.9 mmol, 62% yield) in 95:5 *Z:E* ratio as colorless oil.

The solution of recovered *Z*-1,2-dichloro-1-fluoroethene was re-used directly. A solution of **Mo-1c** in benzene (0.1 M, 1800 μL, 180 μmol) was transferred by syringe to an oven-dried vial containing *Z*-1,2-dichloro-1-fluoroethene solution (4.7910 g, 86.4% wt, 36 mmol) and 2-(6-methylhept-5-en-1-yl)isoindoline-1,3-dione (919.8 mg, 3.6 mmol). This was followed by the addition of a solution of *Z*-hex-3-ene in benzene (1.0 M, 270 μL, 270 μmol). The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture showed 70% consumption of 2-(6-methylhept-5-en-1-yl)isoindoline-1,3-dione. The volatiles were removed in vacuo to afford brown oil, which was purified by silica gel chromatography (pentane → 10% EtOAc in pentane) to afford **4.63** (608.4 mg, 2.1600 mmol, 60% yield) in 95:5 *Z:E* ratio as colorless oil. **IR (neat)**: 2854 (w), 1770 (m), 1710 (s), 1677 (m), 1395 (m), 1371 (m), 1038 (m), 718 (m); **^{19}F NMR (470 MHz, $CDCl_3$)**: *Z* isomer (major): δ −77.5 (d, J = 10.9 Hz); *E* isomer (minor): δ −81.4 (d, J = 28.2 Hz); **^{1}H NMR (500 MHz, $CDCl_3$)**: *Z* isomer (major): δ 7.83 (dd, J = 5.4, 3.0 Hz, 2H), 7.70 (dd, J = 5.5, 3.0 Hz, 2H), 5.23 (dt, J = 10.3, 7.7 Hz, 1H), 3.68 (t, J = 7.2 Hz, 2H), 2.08 (q, J = 7.5 Hz, 2H), 1.69 (p, J = 7.4 Hz, 2H), 1.44 (p, J = 7.4 Hz, 2H); *E* isomer (resolved signal only): δ 4.81 (dt, J = 28.9, 7.9 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 168.4, 144.7 (d, J = 296.5 Hz), 133.9, 132.1, 123.2, 104.5 (d, J = 19.5 Hz), 37.6, 27.9, 25.9, 25.6; **HRMS[M+H]$^+$**: Calcd for $C_{14}H_{14}O_2FNCl$: 282.0692, found: 282.0695.

4.7.4. Diversification of Trisubstituted Alkenyl Fluorides

(*E*)-2-(6-Fluorohex-5-en-1-yl-6-d)isoindoline-1,3-dione (4.64): Prepared based on a previously disclosed protocol[54]. An oven-dried vial was charged with $Pd(OAc)_2$ (0.9 mg,

(54) Janni, M.; Peruncheralathan, S. *Org. Biomol. Chem.* **2016**, *14*, 3091–3097.

0.0040 mmol), $(Ad)_2P(n\text{-Bu})$ (2.9 mg, 0.0081 mmol), and K_3PO_4 (25.4 mg, 0.1200 mmol), followed by (*Z*)-2-(6-chloro-6-fluorohex-5-en-1-yl)isoindoline-1,3-dione (22.4 mg, 0.0794 mmol) in CD_3OD (0.05 mL) and toluene (0.4 mL). The mixture was allowed to stir for 2 h at 70 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated solution of aqueous NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. The volatiles were removed in vacuo to afford yellow oil, which was purified by silica gel chromatography (5% → 15% Et_2O in hexanes) to afford **4.64** (16.2 mg, 0.0654 mmol, 82% yield) in 95:5 *E:Z* ratio as light yellow oil. **IR (neat)**: 2927 (m), 2859 (m), 1770 (m), 1708 (s), 1650 (m), 1395 (s), 1370 (m), 1039 (m), 718 (m); **^{19}F NMR (470 MHz, $CDCl_3$)**: *Z* isomer (major): δ −126.0 – −136.1 (m); *E* isomer (minor): δ −131.2 (dt, J = 42.7, 12.5 Hz); **^{1}H NMR (500 MHz, $CDCl_3$)**: *Z* isomer (major): δ 7.84 (dd, J = 5.5, 3.1 Hz, 2H), 7.71 (dd, J = 5.5, 3.0 Hz, 2H), 5.49–5.21 (m, 1H), 3.69 (t, J = 7.2 Hz, 2H), 1.96 (qd, J = 7.6, 2.1 Hz, 2H), 1.69 (p, J = 7.4 Hz, 2H), 1.42 (p, J = 7.5 Hz, 2H); *E* isomer (resolved signal only): δ 4.70 (dt, J = 42.9, 7.6 Hz, 1H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 168.5, 148.8 (d, J = 281.6 Hz), 134.0, 132.3, 123.3, 110.9 (d, J = 8.3 Hz), 37.8, 28.0, 26.9 (d, J = 3.0 Hz), 24.6 (d, J = 9.8 Hz); **HRMS[M+H]$^+$**: Calcd for $C_{14}H_{14}O_2FDN$: 249.1144, found: 249.1140.

(*E*)-2-(6-Fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-en-1-yl)isoindoline-1,3-dione (4.65): Prepared based on a previously reported procedure[55]. In a N_2-filled glove box, an oven-dried vial was charged with $Pd_2(dba)_3$ (1.8 mg, 0.0020

(55) Billingsley, K. L.; Barder, T. E.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5359–5363.

mmol), XPhos (3.8 mg, 0.0080 mmol), $B_2(pin)_2$ (40.6 mg, 0.1600 mmol), and KOAc (15.7 mg, 0.1600 mmol), followed by (*Z*)-2-(6-chloro-6-fluorohex-5-en-1-yl)isoindoline-1,3-dione (22.4 mg, 0.0794 mmol) in 1,4-dioxane (0.8 mL). The mixture was allowed to stir for 3 h at 100 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with EtOAc (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (10% → 20% Et_2O in hexanes) to give **4.65** (20.7 mg, 0.0556 mmol, 70% yield) in 98:2 *E:Z* ratio as light yellow oil. **IR (neat)**: 2976 (m), 2930 (m), 2859 (w), 1770 (w), 1709 (s), 1394 (m), 1370 (m), 1141 (m), 1077 (m); **^{19}F NMR (470 MHz, $CDCl_3$)**: *Z* isomer (major): δ −124.1 (d, J = 25.6 Hz); *E* isomer (minor): δ −130.2 (d, J = 49.4 Hz); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.85 (ddd, J = 5.4, 3.1, 1.0 Hz, 2H), 7.72 (ddd, J = 5.4, 3.0, 1.0 Hz, 2H), 6.00 (dt, J = 29.9, 8.5 Hz, 1H), 3.70 (td, J = 7.2, 1.0 Hz, 2H), 2.33 (tdd, J = 8.3, 6.8, 1.0 Hz, 2H), 1.76–1.65 (m, 2H), 1.45 (q, J = 7.7 Hz, 2H), 1.30 (s, 12H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 168.5, 134.0, 132.3, 128.9 (d, J = 13.3 Hz), 123.3, 84.4, 37.9, 28.0, 27.2 (d, J = 2.7 Hz), 24.9, 24.5 (d, J = 10.4 Hz). The C adjacent to the B could not be detected. **HRMS[M+H]$^+$**: Calcd for $C_{20}H_{26}O_4FBN$: 374.1933, found: 374.1939.

(*Z*)-2-(6-Bromo-6-fluorohex-5-en-1-yl)isoindoline-1,3-dione (4.66): Prepared based on a previously reported method[56]. In a N_2-filled glove box, an oven-dried vial was charged with $Pd_2(dba)_3$ (1.8 mg, 0.0020 mmol), XPhos (3.8 mg, 0.0080 mmol), $B_2(pin)_2$ (40.6 mg, 0.1600 mmol), and KOAc (15.7 mg, 0.1600 mmol). (*Z*)-2-(6-Chloro-6-fluorohex-5-en-1-

(56) Thompson, A. L. S.; Kabalka, G. W.; Akula, M. R.; Huffman, J. W. *Synthesis* **2005**, 547–550.

yl)isoindoline-1,3-dione (22.4 mg, 0.0794 mmol) in 1,4-dioxane (0.8 mL) was added. The mixture was allowed to stir for 3 h at 100 °C, after which the mixture was filtered through short plug of celite and washed with EtOAc (3 x 5 mL). The filtrate was concentrated in vacuo to furnish orange oil, which was subjected to $CuBr_2$ (54.0 mg, 0.2400 mmol), MeOH (0.8 mL), and H_2O (0.8 mL). The mixture was allowed to stir for 6 h at 80 °C under air. At this time, the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL). The combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. The volatiles were removed in vacuo to give yellow oil, which was purified by silica gel chromatography (5% → 15% Et_2O in hexanes) to afford **4.66** (21.8 mg, 0.0669 mmol, 84% yield for two steps) in 95:5 *Z:E* ratio as light yellow oil. **IR (neat)**: 2925 (m), 2858 (w), 1770 (m), 1709 (s), 1395 (m), 1371 (m), 1108 (m), 718 (m), 529 (w); **^{19}F NMR (470 MHz, $CDCl_3$)**: *Z* isomer (major): δ −71.5 (d, J = 13.2 Hz); *E* isomer (minor): δ −75.7 (d, J = 31.4 Hz). **^{1}H NMR (400 MHz, $CDCl_3$)**: *Z* isomer (major): δ 7.85 (dd, J = 5.5, 3.0 Hz, 2H), 7.72 (dd, J = 5.4, 3.1 Hz, 2H), 5.46 (dt, J = 12.8, 7.5 Hz, 1H), 3.70 (t, J = 7.2 Hz, 2H), 2.20–2.00 (m, 2H), 1.71 (dt, J = 15.0, 7.4 Hz, 2H), 1.50–1.35 (m, 2H); *E* isomer (resolved signals only): δ 4.99 (dt, J = 30.8, 7.7 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 168.5, 137.2, 134.0, 132.2, 123.3, 109.4 (d, J = 15.0 Hz), 37.7, 28.0, 27.1, 25.9; **HRMS[M+H]$^+$**: Calcd for $C_{14}H_{14}O_2NFBr$: 326.0186, found: 326.0177.

(*Z*)-2-(6-Fluoro-6-iodohex-5-en-1-yl)isoindoline-1,3-dione (4.67): Prepared based on a reported procedure[57]. In a N_2-filled glove box, an oven-dried reaction vial was charged

(57) Partridge, B. M.; Hartwig, J. F. *Org. Lett.* **2013**, *15*, 140–143.

with $Pd_2(dba)_3$ (1.8 mg, 0.0020 mmol), XPhos (3.8 mg, 0.0080 mmol), $B_2(pin)_2$ (40.6 mg, 0.1600 mmol), and KOAc (15.7 mg, 0.1600 mmol). This was followed by the addition of (*Z*)-2-(6-chloro-6-fluorohex-5-en-1-yl)isoindoline-1,3-dione (22.4 mg, 0.0794 mmol) in 1,4-dioxane (0.8 mL). The mixture was allowed to stir for 3 h at 100 °C, after which it was filtered through a short plug of celite and washed by EtOAc (3 x 5 mL). The filtrate was concentrated in vacuo to afford orange oil, which was treated with CuI (1.5 mg, 0.0079 mmol), 1,10-phenanthraline (2.9 mg, 0.0161 mmol), KI (19.9 mg, 0.1200 mmol), MeOH (0.8 mL), and H_2O (0.8 mL). The mixture was allowed to stir for 3 h at 70 °C in air. At this time, the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with an aqueous saturated solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$ and the volatiles were removed in vacuo. The resulting yellow oil residue was purified by silica gel chromatography (5% → 15% Et_2O in hexanes) to afford **4.67** (23.4 mg, 0.0627 mmol, 79% yield for two steps) in 95:5 *Z:E* ratio as light yellow oil. **IR (neat)**: 2935 (m), 2857 (w), 1769 (w), 1707 (s), 1395 (m), 1370 (m), 1094 (w), 718 (m); **^{19}F NMR (376 MHz, $CDCl_3$)**: *Z* isomer (major): δ −65.9 (d, J = 17.1 Hz); *E* isomer (minor): δ −70.4 (d, J = 34.9 Hz). **^{1}H NMR (400 MHz, $CDCl_3$)**: *Z* isomer (major): δ 7.85 (dd, J = 5.5, 2.9 Hz, 2H), 7.72 (dd, J = 5.5, 2.9 Hz, 2H), 5.70–5.38 (m, 1H), 3.90–3.63 (m, 2H), 2.01 (t, J = 7.5 Hz, 2H), 1.70 (q, J = 7.6 Hz, 2H), 1.45 (q, J = 7.6 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 168.6, 134.1, 132.3, 123.4, 117.7 (d, J = 11.9 Hz), 110.5 (d, J = 325.3 Hz), 37.8, 29.8 (d, J = 3.5 Hz), 28.1, 26.0 (d, J = 2.9 Hz); **HRMS[M+H]$^+$**: Calcd for $C_{14}H_{14}O_2FIN$: 374.0028, found: 374.0033.

(*Z*)-2-(6-(9*H*-Carbazol-9-yl)-6-fluorohex-5-en-1-yl)isoindoline-1,3-dione (4.68): Synthesized in accordance with a reported procedure[58]. In a N_2-filled glove box, an oven-dried vial was charged with $Pd(O(t\text{-}Bu)_3)_2$ (2.0 mg, 0.0039 mmol), and NaOH (4.5 mg, 0.1120 mmol), and 9*H*-carbazole (14.7 mg, 0.0880 mmol). This was followed by (*E*)-2-(6-chloro-6-fluorohex-5-en-1-yl)isoindoline-1,3-dione (22.4 mg, 0.0794 mmol) in toluene (0.8 mL). The mixture was allowed to stir for 3 h at 100 °C, after which it was filtered through a short plug of celite and washed with EtOAc (3 x 5 mL). The filtrate was concentrated in vacuo to give yellow oil, which was purified by silica gel chromatography (5% → 15% EtOAc in hexanes) to afford **4.68** (21.3 mg, 0.0517 mmol, 65% yield) in >98:2 *Z:E* ratio as light yellow oil. **IR (neat)**: 2919 (m), 2849 (m), 1770 (w), 1708 (s), 1443 (m), 1394 (m), 1157 (s), 755 (m), 719 (m); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −95.2 (d, J = 28.6 Hz); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 8.09–7.99 (m, 2H), 7.87 (dd, J = 5.4, 3.0 Hz, 2H), 7.73 (dd, J = 5.5, 3.0 Hz, 2H), 7.53 (dd, J = 8.1, 1.1 Hz, 2H), 7.47 (ddd, J = 8.3, 7.1, 1.2 Hz, 2H), 7.34–7.29 (m, 2H), 5.11 (dt, J = 28.5, 7.7 Hz, 1H), 3.81 (t, J = 7.2 Hz, 2H), 2.50 (qd, J = 7.5, 2.4 Hz, 2H), 1.90 (p, J = 7.3 Hz, 2H), 1.65 (tt, J = 15.2, 7.6 Hz, 2H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 168.6, 145.9 (d, J = 266.3 Hz), 139.9, 134.1, 132.3, 126.6, 126.5, 123.9, 123.4, 121.2, 120.4, 110.8, 37.9, 29.9, 28.4, 24.0; **HRMS[M+H]$^+$**: Calcd for $C_{26}H_{22}O_2FN_2$: 413.1660, found: 413.1666.

(*Z*)-2-(6-Fluoro-6-phenoxyhex-5-en-1-yl)isoindoline-1,3-dione (4.69): Synthesized according to a reported protocol[59]. In a N_2-filled glove box, an oven-dried vial was charged with RockPhos-Pd-G3 (3.4 mg, 0.0040 mmol), and Cs_2CO_3 (78.2 mg, 0.2399 mmol), phenol (11.3 mg, 0.1202 mmol), followed by (*E*)-2-(6-chloro-6-fluorohex-5-en-1-

(58) Kim, G. H.; Lampande, R.; Par, M. J.; Bae, H. W.; Kong, J. H.; Kwon, J. H.; Park, J. H.; Park, Y. W.; Song, C. E. *J. Phys. Chem. C* **2014**, *118*, 28757–28763.
(59) Zhang, Y. Ni, G.; Li, C.; Xu, S.; Zhang, Z; Xie, X. *Tetrahedron* **2015**, *71*, 4927–4932.

yl)isoindoline-1,3-dione (22.4 mg, 0.0794 mmol) in toluene (0.8 mL). The mixture was allowed to stir for 12 h at 100 °C, after which it was filtered through a short plug of celite and washed by EtOAc (3 x 5 mL). The volatiles were removed in vacuo to afford yellow oil, which was purified by silica gel chromatography (5% → 15% Et_2O in hexanes) to afford **4.69** (19.1 mg, 0.0564 mmol, 71% yield) in >98:2 *Z:E* ratio as light yellow oil. **IR (neat)**: 2936 (m), 2857 (w), 1770 (w), 1710 (s), 1590 (m), 1395(m), 1206 (m), 755 (w), 719 (m); **^{19}F NMR (376 MHz, $CDCl_3$)**: δ −91.6 (d, J = 27.1 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.84 (dd, J = 5.5, 3.1 Hz, 2H), 7.70 (dd, J = 5.5, 3.1 Hz, 2H), 7.31 (q, J = 7.9 Hz, 2H), 7.07 (dd, J = 24.7, 7.7 Hz, 3H), 4.29 (dt, J = 27.2, 7.7 Hz, 1H), 3.87–3.46 (m, 2H), 2.14 (q, J = 7.6 Hz, 2H), 1.73 (p, J = 7.4 Hz, 2H), 1.46 (p, J = 7.6 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 168.5, 154.6 (d, J = 299.6 Hz), 134.0, 132.2, 129.7, 123.9, 123.3, 116.7, 110.1, 88.1 (d, J = 27.4 Hz), 37.8, 28.1, 26.9 (d, J = 2.0 Hz), 22.9; **HRMS[M+H]$^+$**: Calcd for $C_{20}H_{19}O_3FN$: 340.1343, found: 340.1343.

Diisopropyl (*Z*)-(6-(1,3-dioxoisoindolin-2-yl)-1-fluorohex-1-en-1-yl)phosphonate (4.70): Obtained by the use of a reported method[60]. In a N_2-filled glove box, an oven-dried vial was charged with $Pd(OAc)_2$ (0.9 mg, 0.0040 mmol), dppf (3.3 mg, 0.0060 mmol), DIPEA (15.5 mg, 0.1200 mmol), and diisopropyl phosphonate (15.9 mg, 0.0960 mmol). This was followed by (*Z*)-2-(6-chloro-6-fluorohex-5-en-1-yl)isoindoline-1,3-dione (22.4 mg, 0.0794 mmol) in DMF (0.72 mL) and DME (0.08 mL). The mixture was allowed to stir for 12 h at 115 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated

(60) Berger, O.; Petit, C.; Deal, E. L.; Montchamp, J.-L. *Adv. Synth. Catal.* **2013**, *355*, 1361–1373.

solution of aqueous NaCl (10 mL), then water (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the volatiles were removed in vacuo to afford yellow oil, which was purified by silica gel chromatography (10% → 30% EtOAc in hexanes) to afford **4.70** (26.4 mg, 0.0642 mmol, 81% yield) in >98:2 *Z:E* ratio as light yellow oil. **IR (neat)**: 2979 (m), 2931 (m), 2864 (w), 1712 (s), 1395 (m), 1258 (m), 987 (m), 720 (m); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −120.7 (dd, J = 105.2, 29.7 Hz); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.84 (dd, J = 5.3, 3.1 Hz, 2H), 7.71 (dd, J = 5.5, 3.0 Hz, 2H), 6.01 (ddt, J = 31.4, 28.5, 8.4 Hz, 1H), 4.69 (dq, J = 12.6, 6.3 Hz, 2H), 3.70 (t, J = 7.1 Hz, 2H), 2.54 (q, J = 8.2 Hz, 2H), 1.73 (p, J = 7.4 Hz, 2H), 1.48 (m, 2H), 1.35 (d, J = 6.2 Hz, 6H), 1.32 (d, J = 6.2 Hz, 6H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 168.5 , 153.3–150.6 (m), 134.0, 132.3, 126.5 (dd, J = 31.1, 12.5 Hz), 123.4, 72.1 (d, J = 5.5 Hz), 37.9, 28.3, 27.0, 24.5 (d, J = 6.5 Hz), 24.0 (dd, J = 32.3, 4.4 Hz); **^{31}P NMR (243 MHz, $CDCl_3$)**: δ −1.25 (d, J = 105.3 Hz); **HRMS[M+H]$^+$**: Calcd for $C_{20}H_{28}O_5FNP$: 412.1684, found: 412.1680.

(*E*)-2-(6,7,7,7-Tetrafluorohept-5-en-1-yl)isoindoline-1,3-dione (4.71): Prepared based on a known protocol[61]. In a N_2-filled glove box, an oven-dried vial was charged with $Pd_2(dba)_3$ (1.8 mg, 0.0020 mmol), XPhos (3.8 mg, 0.0080 mmol), $B_2(pin)_2$ (40.6 mg, 0.1600 mmol), and KOAc (15.7 mg, 0.1600 mmol). (*Z*)-2-(6-Chloro-6-fluorohex-5-en-1-yl)isoindoline-1,3-dione (22.4 mg, 0.0794 mmol) in 1,4-dioxane (0.8 mL) was added. The mixture was allowed to stir for 3 h at 100 °C, after which it was filtered through a short celite plug and washed with EtOAc (3 x 5 mL). The volatiles were removed in vacuo, leaving behind orange oil, which was treated with (phen)$CuCF_3$ (37.6 mg, 0.0960 mmol), KF (6.0 mg, 0.0800 mmol), and DMF (0.8 mL). The mixture was removed from

(61) Litvinas, N. D.; Fier, P. S.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 536–539.

the glovebox and attached to air-filled balloon, allowing air to be introduced into the DMF solution; this continued for 10 min. At this time, the balloon was removed and the mixture was allowed to stir for 18 h at 50 °C, at which time the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. The volatiles were removed in vacuo to afford yellow oil, which was purified by silica gel chromatography (5% → 15% Et_2O in hexanes) to afford **4.71** (18.3 mg, 0.0580 mmol, 73% yield for two steps) in 93:7 *E:Z* ratio as light yellow oil. **IR (neat)**: 2939 (m), 2858 (w), 1710 (s), 1437 (w), 1395 (m), 1192(m), 1140 (m), 718 (m), 529 (w); **^{19}F NMR (470 MHz, $CDCl_3$)**: *Z* isomer (major): δ −67.2 (d, J = 7.8 Hz), −125.9 – −131.0 (m); *E* isomer (minor): δ −72.5 (d, J = 9.8 Hz).; **^{1}H NMR (400 MHz, $CDCl_3$)**: *Z* isomer (major): δ 7.84 (dd, J = 5.4, 2.9 Hz, 2H), 7.71 (dd, J = 5.5, 3.0 Hz, 2H), 5.64 (dt, J = 21.5, 8.4 Hz, 1H), 3.69 (t, J = 7.0 Hz, 2H), 2.26 (d, J = 8.2 Hz, 2H), 1.70 (p, J = 7.3 Hz, 2H), 1.48 (q, J = 7.8 Hz, 2H); *E* isomer (resolved signal only): δ 5.31 (dt, J = 18.5, 8.8 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 168.5, 145.7 (d, J = 288.7 Hz), 134.1, 132.2, 123.4, 127.6 (q, J = 242.3 Hz), 115.3 (d, J = 13.2 Hz), 37.6, 28.1, 26.6, 23.3; **HRMS[M+H]$^+$**: Calcd for $C_{15}H_{14}O_2F_4N$: 316.0955, found: 316.0969.

(*E*)-1-(4-Chloro-4-fluorobut-3-en-1-yl)-3-(trifluoromethyl)benzene (S1): Based on general procedure A, a solution of **Mo-1b** in benzene (0.1 M, 20 μL, 2.0 μmol) was transferred by syringe to an oven-dried vial containing *Z*-1,2-dichloro-1-fluoroethene (46.0 mg, 0.4000 mmol) and 1-(4-methylpent-3-en-1-yl)-3-(trifluoromethyl)benzene (9.2 mg, 0.0403 mmol). This was followed by the addition of a solution of *E*-but-2-ene in

toluene (6.6 M, 1.2 μL, 8.0 μmol). The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture indicated 63% consumption of 1-(4-methylpent-3-en-1-yl)-3-(trifluoromethyl)benzene. Removal of the volatiles gave brown oil, which was purified by silica gel chromatography (pentane) to afford **S1** (5.1 mg, 0.0202 mmol, 50% yield) in 4:96 *Z:E* ratio as colorless oil. **IR (neat)**: 2956 (m), 2919 (m), 1677 (w), 1449 (w), 1326 (s), 1163 (m), 1126 (s), 1073 (m), 801 (m), 701 (w) cm^{-1}; **^{19}F NMR (376 MHz, $CDCl_3$)**: δ −62.7 (s), −80.3 (d, J = 28.7 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.42 (dq, J = 25.7, 7.8 Hz, 4H), 4.86 (dt, J = 28.9, 7.8 Hz, 1H), 2.76 (t, J = 7.7 Hz, 2H), 2.45 (q, J = 7.9 Hz, 2H); (*Z*)-(2-methylhex-3-en-2-yl)benzene: δ 5.65 (d, J = 15.5 Hz, 1H), 5.27 (q, J = 8.0 Hz, 1H); (*Z*)-1-(4-chlorobut-3-en-1-yl)-3-(trifluoromethyl)benzene: δ 6.07 (d, J = 7.2 Hz, 1H), 5.76 (q, J = 7.1 Hz, 1H); 1-(4-methylpent-3-en-1-yl)-3-(trifluoromethyl)benzene: δ 5.14 (m, 1H) **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 143.9 (d, J = 301.7 Hz), 141.7, 131.9, 130.8, 129.0, 127.2 (q, J = 280.2 Hz), 125.2 (q, J = 3.7 Hz), 123.2 (q, J = 3.9 Hz), 105.4 (d, J = 17.3 Hz), 35.0 (d, J = 2.2 Hz), 26.6; **HRMS[M+H]$^+$**: Calcd for $C_{11}H_{10}F_4Cl$: 253.0402, found: 253.0411.

(*E*)-2-Fluoro-5-(3-(trifluoromethyl)phenyl)pent-2-en-1-ol (4.72): Prepared according to a reported procedure[62]. In a N_2-filled glove box, an oven-dried vial was charged with $Pd_2(dba)_3$ (1.8 mg, 0.0020 mmol), XPhos (3.8 mg, 0.0080 mmol), $B_2(pin)_2$ (40.6 mg, 0.1600 mmol), and KOAc (15.7 mg, 0.1600 mmol). This was followed by the addition of (*Z*)-1-(4-chloro-4-fluorobut-3-en-1-yl)-3-(trifluoromethyl)benzene (20.2 mg, 0.0800 mmol) in 1,4-dioxane (0.8 mL). The mixture was allowed to stir for 3 h at 100 °C, after

(62) Sun, Y.; Zhou, Y.; Shi, Y.; del Pozo, J.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2019**, *141*, 12087−12099.

which it was filtered through a short plug of celite and washed with EtOAc (3 x 5 mL). The volatiles were removed in vacuo to afford orange oil, which was treated with $ClCH_2I$ (56.3 mg, 0.3200 mmol) and Et_2O (0.8 mL). To this mixture, at −78 °C, was added 2.5 M *n*-BuLi (96 µL, 0.2400 mmol) dropwise, and the mixture was allowed to warm to 0 °C in 1 h. At this time, the reaction was quenched, at 0 °C, by the addition of 2 M aqueous solution of NaOH (0.2 mL) and H_2O_2 (0.1 mL, 30% wt in H_2O). The mixture was allowed to warm to 22 °C and stir for 1 h, after which a saturated aqueous solution of $Na_2S_2O_3$ (0.4 mL) was added. The mixture was allowed to stir for 30 min at 22 °C. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (5% → 15% Et_2O in hexanes) to furnish **4.72** (11.1 mg, 0.0448 mmol, 56% yield for two steps) in <2:98 *E:Z* ratio as light yellow oil. **IR (neat)**: 2922 (s), 2850 (m), 1731 (s), 1450 (m), 1328 (s), 1163 (m), 1125 (s), 1072 (m), 800 (w), 702 (m); **^{19}F NMR (376 MHz, $CDCl_3$)**: δ −63.0 (s), −119.3 (dt, J = 36.6, 14.2 Hz); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.51–7.34 (m, 4H), 4.85 (dt, J = 36.2, 7.6 Hz, 1H), 4.09 (d, J = 15.4 Hz, 2H), 2.76 (t, J = 7.7 Hz, 2H), 2.45 (q, J = 7.7 Hz, 2H); the hydroxy proton was undetectable; **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 159.7 (d, J = 253.6 Hz), 142.0, 132.0, 131.9, 129.8 (d, J = 284.3 Hz), 128.5, 125.2 (q, J = 3.9 Hz), 123.4–123.2 (m), 115.8 (d, J = 15.0 Hz), 61.8, 32.1, 22.8; **HRMS[M+H]$^+$**: Calcd for $C_{12}H_{13}F_4O$: 249.0897, found: 249.0888.

(*E*)-2-(6-Fluoro-8-methylnona-5,8-dien-1-yl)isoindoline-1,3-dione (4.73): Prepared according to a reported procedure[63]. In a N_2-filled glove box, an oven-dried vial was charged with Pd(P*t*-Bu)$_3$ (2.0 mg, 0.0039 mmol), CsF (24.3 mg, 0.1600 mmol), and tributyl(2-methylallyl)stannane (30.5 mg, 0.0881 mmol). (*Z*)-2-(6-Chloro-6-fluorohex-5-en-1-yl)isoindoline-1,3-dione (22.4 mg, 0.0794 mmol) in 1,4-dioxane (0.8 mL) was added, and the mixture was allowed to stir for 3 h at 90 °C. At this time, the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated solution of NaCl (10 mL) and water (2 x 10 mL) and dried over $MgSO_4$. The volatiles were removed in vacuo to afford yellow oil, which was purified by silica gel chromatography (5% → 15% Et_2O in hexanes) to afford **4.73** (20.2 mg, 0.0672 mmol, 84% yield) in 94:6 *E:Z* ratio as light yellow oil. **IR (neat)**: 2931 (m), 2855 (w), 1708 (s), 1394 (w), 1370 (m), 1336 (m), 1036 (m), 718 (m), 529 (w); **^{19}F NMR (470 MHz, CDCl$_3$)**: *E* isomer (major): δ −101.5 (q, J = 22.7 Hz); *Z* isomer (minor): δ −106.9 – −107.3 (m); **^{1}H NMR (400 MHz, CDCl$_3$)**: *E* isomer (major): δ 7.84 (dd, J = 5.4, 3.1 Hz, 2H), 7.71 (dd, J = 5.5, 3.0 Hz, 2H), 5.10 (dt, J = 21.3, 7.9 Hz, 1H), 4.86–4.69 (m, 2H), 3.69 (t, J = 7.2 Hz, 2H), 2.92 (d, J = 23.4 Hz, 2H), 2.00 (q, J = 7.7 Hz, 2H), 1.77–1.64 (m, 5H), 1.43–1.35 (m, 2H); *Z* isomer (resolved signal only): δ 5.39–5.26 (m, 1H); **^{13}C NMR (101 MHz, CDCl$_3$)**: δ 168.6, 157.9 (d, J = 247.5 Hz), 140.7, 134.1, 132.3, 123.4, 112.7, 106.8 (d, J = 21.4 Hz), 37.9, 36.8 (d, J = 29.4 Hz), 28.2, 27.2, 25.2 (d, J = 9.0 Hz), 22.3; **HRMS[M+H]$^+$**: Calcd for $C_{18}H_{21}O_2FN$: 302.1551, found: 302.1562.

(63) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343–6348.

Ethyl (*E*)-2-(6-(1,3-dioxoisoindolin-2-yl)-1-fluorohex-1-en-1-yl)oxazole-4-carboxylate (4.74): Prepared in analogy to a reported procedure[64]. In a N_2-filled glove box, an oven-dried vial was charged with $Pd(OAc)_2$ (0.9 mg, 0.0040 mmol), CyJohnPhos (2.8 mg, 0.0080 mmol), $CsCO_3$ (52.2 mg, 0.1601 mmol), and ethyl oxazole-4-carboxylate (11.3 mg, 0.0801 mmol). This was followed by the addition of (*Z*)-2-(6-chloro-6-fluorohex-5-en-1-yl)isoindoline-1,3-dione (44.9 mg, 0.1600 mmol) in 1,4-dioxane (0.8 mL). The mixture was allowed to stir for 18 h at 110 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated solution of aqueous NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. The volatiles were removed in vacuo to give yellow oil, which was purified by silica gel chromatography (5% → 15% Et_2O in hexanes) to afford **4.74** (25.7 mg, 0.0665 mmol, 83% yield) in >98:2 *E:Z* ratio as light yellow oil. **IR (neat)**: 2934 (m), 2860 (w), 1741 (m), 1709 (s), 1395 (m), 1370 (m), 1107 (m), 1022 (m), 720 (m); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −122.5 (d, J = 20.8 Hz); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.23 (s, 1H), 7.84 (dd, J = 5.4, 3.2 Hz, 2H), 7.71 (dd, J = 5.5, 3.1 Hz, 2H), 5.83 (dt, J = 21.2, 8.3 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 3.72 (t, J = 7.2 Hz, 2H), 2.65 (q, J = 7.8 Hz, 2H), 1.75 (p, J = 7.3 Hz, 2H), 1.58–1.54 (m, 2H), 1.38 (t, J = 7.1 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 168.4, 160.7, 146.3, 143.9, 143.4, 134.5, 133.9, 132.1, 123.2, 117.3 (d, J = 17.7 Hz), 61.4, 37.6, 28.0, 26.5 (d, J = 2.3 Hz), 24.6 (d, J = 5.8 Hz), 14.2; **HRMS[M+H]$^+$**: Calcd for $C_{20}H_{20}O_5FN_2$: 387.1351, found: 387.1351.

(64) Verrier, C.; Hoarau, C.; Marsais, F. *Org. Biomol. Chem.* **2009**, *7*, 647–650.

(*E*)-7-(1,3-Dioxoisoindolin-2-yl)-2-fluorohept-2-enenitrile (4.75): Synthesized according to a reported protocol[65]. In a N_2-filled glove box, an oven-dried vial was charged with $Pd(PPh_3)_4$ (1.8 mg, 0.0016 mmol), CuCN (14.4 mg, 0.1600 mmol), followed by (*Z*)-2-(6-chloro-6-fluorohex-5-en-1-yl)isoindoline-1,3-dione (22.4 mg, 0.0794 mmol) in NMP (0.8 mL). The mixture was allowed to stir for 12 h at 135 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated solution of aqueous NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (10% → 20% EtOAc in hexanes) to afford **4.75** (17.3 mg, 0.0636 mmol, 80% yield) in 5:95 *Z:E* ratio as light yellow oil. **IR (neat)**: 2941 (m), 2861 (w), 1706 (s), 1665 (w), 1435 (m), 1395 (m), 1362 (m), 1036 (m), 718 (m), 529 (w); **^{19}F NMR (470 MHz, $CDCl_3$)**: *E* isomer (major): δ −122.3 (d, J = 13.9 Hz); *Z* isomer (minor): δ −124.2 (d, J = 32.3 Hz); **^{1}H NMR (500 MHz, $CDCl_3$)**: *E* isomer (major): δ 7.85 (dd, J = 5.5, 3.1 Hz, 2H), 7.72 (dd, J = 5.5, 3.1 Hz, 2H), 6.10 (dt, J = 13.9, 8.4 Hz, 1H), 3.72 (t, J = 7.1 Hz, 2H), 2.36–2.20 (m, 2H), 1.74 (dt, J = 15.3, 7.2 Hz, 2H), 1.53 (dt, J = 15.0, 7.4 Hz, 2H); *Z* isomer (resolved signal only): δ 5.74 (dt, J = 32.4, 7.9 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 168.3, 134.0, 132.9 (d, J = 240.9 Hz), 132.0, 125.9 (d, J = 15.5 Hz), 123.2, 110.9 (d, J = 47.7 Hz), 37.3, 28.0, 27.9, 25.8; **HRMS[M+H]$^+$**: Calcd for $C_{15}H_{14}O_2FN_2$: 273.1034, found: 273.1048.

(65) Lal, B.; Gangopadhyay, A. K.; Jagtap, P. G.; Tanpure, R.; Rao, V. S. V. V.; Gupte, R. D.; Subbarayan, P.; Asudani, Gope. *Indian J. Chem.* **2007**, *46B*, 1815-1832.

Phenyl (*Z*)-7-(1,3-dioxoisoindolin-2-yl)-2-fluorohept-2-enoate (4.76): Prepared based on a reported procedure[66]. In a N_2-filled glove box, an oven-dried vial was charged with $Pd(OAc)_2$ (0.3 mg, 0.0015 mmol), P(*t*-Bu)$_3$•HBF_4 (1.8 mg, 0.0060 mmol), and Et_3N (10.1 mg, 0.1000 mmol). This was followed by the addition of (*E*)-2-(6-chloro-6-fluorohex-5-en-1-yl)isoindoline-1,3-dione (14.1 mg, 0.0500 mmol) and phenyl formate (12.3 mg, 0.1000 mmol) in MeCN (0.1 mL). The mixture was allowed to stir for 15 h at 100 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (5% $\rightarrow$ 15% Et_2O in hexanes) to afford **4.76** (16.3 mg, 0.0444 mmol, 89% yield) in 94:6 *E:Z* ratio as light yellow oil. **IR (neat)**: 2949 (m), 2922 (m), 2851 (m), 1747 (m), 1711 (s), 1395 (w), 1371 (w), 1193 (m), 1070 (w), 719 (m); **^{19}F NMR (376 MHz, $CDCl_3$)**: *Z* isomer (major): δ −129.8 (d, J = 32.4 Hz); *E* isomer (minor): δ −122.01 (d, J = 20.1 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: *Z* isomer (major): δ 7.85 (dd, J = 5.5, 3.1 Hz, 2H), 7.72 (dd, J = 5.5, 3.1 Hz, 2H), 7.40 (t, J = 7.9 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 6.33 (dt, J = 32.6, 8.1 Hz, 1H), 3.73 (t, J = 7.1 Hz, 2H), 2.40 (t, J = 7.9 Hz, 2H), 1.78 (m, 2H), 1.58 (m, 2H); *E* isomer (resolved signal only): δ 6.08 (dt, J = 20.9, 8.4 Hz, 1H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 168.58, 160.36, 147.93 (d, J = 290.2 Hz), 134.11, 134.04, 132.24, 129.67, 126.36, 123.40, 122.07 (d, J = 11.6 Hz), 121.53, 37.69, 28.41, 25.72, 24.22; **HRMS[M+H]$^+$**: Calcd for $C_{21}H_{19}FNO_4$: 368.1293, found: 368.1294.

(66) Ueda, T.; Konishi, H.; Manabe, K. *Org. Lett.* **2012**, *14*, 3100–3103.

4.7.5. Chemoselective Cross-Coupling

(*E*)-6-Chloro-6-fluorohex-5-en-1-yl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate (4.78): Based on general procedure A, a solution of **Mo-1a** in benzene (0.1 M, 40 μL, 4.0 μmol) was transferred by syringe to an oven-dried vial containing (*E*)-1,2-dichloro-1-fluoroethene (46.0 mg, 0.4000 mmol) and 6-methylhept-5-en-1-yl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate (12.6 mg, 0.0395 mmol). A solution of (*E*)-but-2-ene in hexane (6.6 M, 2.4 μL, 16.0 μmol) was added and the mixture was allowed to stir for 12 h at 22 °C. At this time, the reaction was quenched by addition of wet $CHCl_3$. Analysis of the unpurified mixture showed 75% consumption of 6-methylhept-5-en-1-yl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate. Removal of the volatiles in vacuo afforded brown oil, which was purified by silica gel chromatography (pentane $\rightarrow$ 5% Et_2O in pentane) to afford **4.78** (8.8 mg, 0.0257 mmol, 65% yield) in 3:97 *Z:E* ratio as colorless oil. **IR (neat)**: 2954 (m), 2928 (m), 2853 (w), 1722 (s), 1677 (w), 1413 (m), 1183 (m), 1139 (m), 922 (m), 814 (w); **^{19}F NMR (470 MHz, $CDCl_3$)**: *E* isomer (minor): δ −81.4 (d, J = 29.0 Hz); *Z* isomer (minor): δ −77.5 (d, J = 10.6 Hz); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 6.26 (d, J = 9.0 Hz, 1H), 4.85 (dt, J = 29.1, 7.8 Hz, 1H), 4.06 (t, J = 6.6 Hz, 2H), 2.15 (qd, J = 7.6, 2.4 Hz, 2H), 2.02 (t, J = 8.7 Hz, 1H), 1.82 (d, J = 8.5 Hz, 1H), 1.69–1.61 (m, 2H), 1.50–1.41 (m, 2H), 1.25 (d, J = 4.7 Hz, 6H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 170.7, 143.5 (d, J = 300.8 Hz), 125.1, 120.7, 106.4 (d, J = 17.4 Hz), 64.1, 32.6, 32.0, 29.5, 28.2, 27.5, 25.5 (d, J = 2.3 Hz), 24.7, 15.1; **HRMS[M+H]$^+$**: Calcd for $C_{14}H_{19}O_2FCl_3$: 343.0429, found: 343.0433.

(*E*)-6-Chloro-6-fluorohex-5-en-1-yl 3-((*Z*)-2-chloro-3-oxobut-1-en-1-yl)-2,2-dimethyl-cyclopropane-1-carboxylate (4.79): In a N_2-filled glove box, an oven-dried

vial was charged with $Pd(P(t\text{-}Bu_3))_2$ (2.6 mg, 0.0050 mmol), and (*E*)-6-chloro-6-fluorohex-5-en-1-yl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate (41.2 mg, 0.1200 mmol) in THF/NMP (0.9 mL/0.5 mL). This was followed by the addition of (1-ethoxyvinyl)zinc chloride (0.39 M, 256 μL, 0.1000 mmol). The mixture was allowed to stir for 12 h at 22 °C, after which it was charged with a 3M aqueous solution of HCl (1 mL) and allowed to stir for 1 h. At this time, the aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (hexanes → 10% Et_2O in hexanes) to furnish **4.79** (28.0 mg, 0.0797 mmol, 80% yield) as colorless oil. **IR (neat)**: 2952 (m), 2923 (m), 2852 (w), 1721 (s), 1688 (w), 1412 (m), 1356 (w), 1189 (m), 1143 (m), 1043 (w), 814 (w); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −81.4 (d, J = 28.9 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.44 (d, J = 9.5 Hz, 1H), 4.85 (dt, J = 29.1, 7.8 Hz, 1H), 4.08 (t, J = 6.5 Hz, 2H), 2.42 (s, 3H), 2.38–2.29 (m, 2H), 2.15 (qd, J = 7.6, 2.5 Hz, 1H), 2.10–2.03 (m, 1H), 1.66 (dt, J = 14.5, 6.9 Hz, 2H), 1.51–1.42 (m, 2H), 1.34 (d, J = 5.8 Hz, 6H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 204.6, 162.2, 150.2 (d, J = 290.0 Hz), 138.5, 132.2, 106.4 (d, J = 17.7 Hz), 64.5, 34.5, 33.1, 28.7, 28.1, 26.2, 25.5, 24.7, 15.3; **HRMS[M+H]$^+$**: Calcd for $C_{16}H_{22}O_3FCl_2$: 351.0925, found: 351.0935.

(*Z*)-6-Fluoro-8-(4-methoxyphenyl)oct-5-en-7-yn-1-yl 3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylate (4.80): In a N_2-filled glove box, an oven-dried vial was charged with $PdCl_2(PhCN)_2$ (2.0 mg, 0.0050 mmol), CuI (2.0 mg, 0.0100 mmol), 1-ethynyl-4-methoxybenzene (13.2 mg, 0.1000 mmol) and (*E*)-6-chloro-6-fluorohex-5-

en-1-yl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate (41.2 mg, 0.1200 mmol) in piperdine (1.0 mL). The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. and Removal of the volatiles in vacuo afforded brown oil, which was purified by silica gel chromatography (hexanes → 10% Et_2O in hexanes) to afford **4.80** (23.2 mg, 0.0528 mmol, 53% yield) as colorless oil. Spectroscopic analysis (^{1}H NMR) indicated the presence of 8% **4.81**. **IR (neat)**: 2952 (m), 2923 (m), 2853 (w), 1722 (s), 1603 (m), 1507 (s), 1458 (w), 1288 (m), 1251 (s), 1181 (m), 1139 (m), 1031 (m), 831 (w); **^{19}F NMR (564 MHz, $CDCl_3$)**: δ −109.5 (d, J = 32.9 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.41 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 6.27 (d, J = 9.0 Hz, 1H), 5.26 (dt, J = 33.0, 7.8 Hz, 1H), 4.08 (t, J = 6.5 Hz, 2H), 3.82 (s, 3H), 2.26 (d, J = 8.1 Hz, 2H), 2.01 (t, J = 8.8 Hz, 1H), 1.83 (d, J = 8.5 Hz, 1H), 1.68 (q, J = 7.1, 6.7 Hz, 2H), 1.57–1.45 (m, 2H), 1.25 (d, J = 3.2 Hz, 6H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 170.7, 160.4, 141.8 (d, J = 236.1 Hz), 133.4, 125.7, 125.1, 116.5 (d, J = 20.7 Hz), 114.3, 114.2, 90.6, 90.6, 64.3, 55.5, 32.6, 32.0, 30.5, 28.6, 25.5, 24.4, 15.1; **HRMS[M+H]$^+$**: Calcd for $C_{23}H_{26}O_3FCl_2$: 439.1238, found: 439.1237.

4.7.6. Synthesis of Fluoro-Hachijodine G

(*Z*)-10-Chloro-10-fluorodec-9-en-1-ol (S2): Based on general procedure B, an oven-dried vial equipped with a magnetic stir bar was charged with 10-methylundec-9-en-1-ol (18.4 mg, 0.0998 mmol). 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (38.4 mg, 0.2999 mmol) was added, causing H_2 evolution. Once effervescence subsided, the solution was

allowed to stir for 30 min at 22 °C, after which the volatiles were removed in vacuo (1 Torr, 30 min). (*Z*)-1,2-Dichloro-1-fluoroethene (115.0 mg, 1.0000 mmol) and a solution of **Mo-1a** in benzene (0.1 M, 50 μL, 5.0 μmol) were added, followed by a solution of (*Z*)-hex-3-ene in benzene (1.0 M, 10 μL, 10.0 μmol). The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture indicated 98% consumption of 10-methylundec-9-en-1-ol. Removal of the volatiles in vacuo afforded brown oil, which was purified by silica gel chromatography (pentane → 9% EtOAc in pentane) to furnish **S2** (18.7 mg, 0.0896 mmol, 90% yield) in 95:5 *Z:E* ratio as colorless oil. **IR (neat)**: 3322 (m), 2924 (s), 2853 (m), 1677 (m), 1462 (w), 1116 (m), 1055 (w), 822 (w), 670 (w); **^{19}F NMR (564 MHz, $CDCl_3$)**: *Z* isomer (major): δ −78.4 (d, J = 11.0 Hz); *E* isomer (minor): δ −82.2 (d, J = 28.9 Hz); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 5.34–5.20 (m, 1H), 3.64 (t, J = 6.7 Hz, 2H), 2.02 (q, J = 7.5 Hz, 2H), 1.56 (q, J = 7.0 Hz, 2H), 1.38–1.26 (m, 10H); hydroxy proton was unobservable; **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 127.3 (d, J = 298.3 Hz), 105.3 (d, J = 18.8 Hz), 63.2, 32.9, 29.5, 29.4, 29.0, 28.8, 26.2 (d, J = 3.5 Hz), 25.8; **HRMS[M+H]$^+$**: Calcd for $C_{10}H_{19}ClFO$: 209.1103, found: 209.1109.

(*E*)-10-Fluoro-16-(pyridin-3-yl)hexadec-9-en-11-yn-1-ol (4.84): In a N_2-filled glove box, an oven-dried vial was charged with $PdCl_2(PhCN)_2$ (1.2 mg, 0.0030 mmol), CuI (1.2 mg, 0.0060 mmol), and 3-(hex-5-yn-1-yl)pyridine (9.6 mg, 0.0600 mmol), followed by (*Z*)-10-chloro-10-fluorodec-9-en-1-ol (15.0 mg, 0.0720 mmol) in piperdine (0.2 mL). The mixture was allowed to stir for 15 h at 22 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a

saturated aqueous solution of NaCl (10 mL), water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (hexanes → 15% EtOAc in hexanes), delivering **4.84** (17.9 mg, 0.0540 mmol, 90% yield) in >98:2 *E:Z* ratio as light yellow oil. **IR (neat)**: 3359 (m), 2925 (S), 2852 (m), 2230 (w), 1657 (w), 1423 (m), 1057 (m), 795 (w), 713 (m); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −106.9 (dt, J = 14.8, 4.7 Hz); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 8.46 (d, J = 6.3 Hz, 2H), 7.52 (dd, J = 7.9, 1.9 Hz, 1H), 7.23 (dd, J = 7.8, 4.8 Hz, 1H), 5.52 (dt, J = 15.6, 8.1 Hz, 1H), 3.62 (t, J = 6.5 Hz, 2H), 2.76 (t, J = 7.7 Hz, 2H), 2.43 (td, J = 6.8, 4.6 Hz, 2H), 2.11 (q, J = 7.6 Hz, 2H), 1.90 (m, 3H), 1.55 (p, J = 6.7 Hz, 2H), 1.45–1.30 (m, 11H), hydroxy proton was not observed; **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 150.0, 147.7, 141.9 (d, J = 230.0 Hz), 136.7, 136.1 123.6, 116.0 (d, J = 23.7 Hz), 95.9 (d, J = 7.5 Hz), 72.4 (d, J = 43.9 Hz), 63.0, 33.0, 31.9, 29.6 (d, J = 1.2 Hz), 29.5, 29.4, 29.3, 29.3, 29.1, 26.6 (d, J = 4.4 Hz), 25.9, 18.8 (d, J = 2.1 Hz); **HRMS[M+H]$^+$**: Calcd for $C_{21}H_{31}FNO$: 332.2384, found: 332.2389.

Fluoro-hachijodine G (4.85): Prepared based a reported procedure[67]. An oven-dried vial was charged with (*E*)-10-fluoro-16-(pyridin-3-yl)hexadec-9-en-11-yn-1-ol (14.6 mg, 0.0440 mmol,), and triethylamine (9.2 µL, 0.0660 mmol) in CH_2Cl_2 (0.1 mL). The mixture was allowed to cool to 0 °C and MsCl (5.2 µL, 0.0660 mmol) was added dropwise, after which the mixture was allowed to warm to 22 °C and stir for 2 h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with EtOAc (3 x 5 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x

(67) Kushwaha, K.; Kaushik, N. K.; Kaushik, N.; Chand, M.; Kaushik, R.; Choi, E. H.; Jain, S. C. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2237–2244.

10 mL), and dried over $MgSO_4$. The volatiles were removed in vacuo to afford yellow oil containing (*E*)-10-fluoro-16-(pyridin-3-yl)hexadec-9-en-11-yn-1-ol (>98% conv. based on ^1H NMR spectrum analysis). In a N_2-filled glove box, an oven-dried vial was charged with NaH (4.2 mg, 0.1760 mmol) and DMF (0.1 mL), followed by the addition of *N*-methylhydroxylamine hydrochloride (7.3 mg, 0.0880 mmol). The vessel was removed from the glove box, and the mixture was allowed to stir for 10 min at 22 °C, after which a freshly prepared sample of the aforementioned yellow oil in DMF (0.1 mL) was added in a dropwise manner. The mixture was allowed to heat to 60 °C and stir at that temperature for 14 h. The mixture was allowed to cool to 22 °C and the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with EtOAc (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded orange oil, which was purified by silica gel chromatography (10% $\rightarrow$ 40% EtOAc in hexanes) to afford **4.85** (10.2 mg, 0.0282 mmol, 64% yield) in >98:2 *E:Z* ratio as colorless oil. **IR (neat)**: 2956 (s), 2852 (m), 1725 (w), 1690 (w), 1455 (m), 1422 (m), 1284 (w), 1024 (w), 713 (m); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −106.8 (dt, J = 15.0, 4.9 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 8.47 (d, J = 5.0 Hz, 2H), 7.52 (dt, J = 7.8, 2.0 Hz, 1H), 7.23 (dd, J = 7.8, 4.8 Hz, 1H), 5.51 (dt, J = 14.9, 8.1 Hz, 1H), 3.51 (t, J = 6.7 Hz, 2H), 3.36 (s, 3H), 2.82–2.70 (m, 2H), 2.43 (td, J = 6.9, 4.7 Hz, 2H), 2.11 (q, J = 7.1 Hz, 2H), 1.97–1.87 (m, 2H), 1.75 (dt, J = 14.4, 6.8 Hz, 2H), 1.43–1.25 (m, 12H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 149.9, 149.3, 147.6, 141.7 (d, J = 230.0 Hz), 136.4, 135.8, 123.3, 115.7 (d, J = 24.5 Hz), 95.8 (d, J = 7.4 Hz),

72.2 (d, J = 43.7 Hz), 45.1, 32.6, 31.8, 29.4 (d, J = 2.1 Hz), 29.4, 29.2, 29.1, 28.9, 28.8, 26.8, 26.5, 18.6; **HRMS[M+H]$^+$**: Calcd for $C_{22}H_{34}FN_2O$: 361.2650, found: 361.2644.

4.7.7. Synthesis of Fluoro-(S)-Coriolide

Methyl (*Z*)-10-chloro-10-fluorodec-9-enoate (S3): Based on general procedure A, a solution of **Mo-1b** in benzene (0.1 M, 100 µL, 10.0 µmol) was transferred by syringe to an oven-dried vial containing (*Z*)-1,2-dichloro-1-fluoroethene (230.0 mg, 2.00 mmol) and methyl 10-methylundec-9-enoate (42.4 mg, 0.1997 mmol). A solution of (*Z*)-hex-3-ene in benzene (1.0 M, 20 µL, 20.0 µmol) was added. The mixture was allowed to stir for 12 h at 22 °C, after which the reaction was quenched by the addition of wet $CHCl_3$. Analysis of the unpurified mixture indicated 88% consumption of methyl 10-methylundec-9-enoate. Removal of the volatiles in vacuo afforded brown oil, which was purified by silica gel chromatography (pentane → 3% EtOAc in pentane) to afford **S3** (38.8 mg, 0.1640 mmol, 82% yield) in 95:5 *Z:E* ratio as colorless oil. **IR (neat)**: 2927 (m), 2855 (m), 1739 (s), 1677 (m), 1435 (w), 1244(m), 1196 (m), 1170 (m), 1117 (m); **^{19}F NMR (376 MHz, $CDCl_3$)**: δ −78.3 (d, J = 11.0 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 5.24 (dt, J = 10.7, 7.7 Hz, 1H), 3.66 (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 2.02 (q, J = 7.2 Hz, 2H), 1.61 (q, J = 7.2 Hz, 2H), 1.41–1.27 (m, 8H); **^{13}C NMR (126 MHz, $CDCl_3$)**: δ 174.4, 144.5 (d, J = 295.9 Hz), 105.3 (d, J = 18.7 Hz), 51.6, 34.2, 29.2, 29.1, 28.9, 28.7 (d, J = 2.4 Hz), 26.1 (d, J = 3.3 Hz), 25.0; **HRMS[M+H]$^+$**: Calcd for $C_{11}H_{19}ClFO_2$: 237.1052, found: 237.1056.

Methyl (*S*,9*E*,11*E*)-10-fluoro-13-hydroxyoctadeca-9,11-dienoate (4.88): In a N_2-filled glove box, an oven-dried vial was charged with $Pd(OAc)_2$ (1.1 mg, 0.0050 mmol), Sphos (4.1 mg, 0.0100 mmol), KOH (7.8 mg, 0.1400 mmol), and methyl (*Z*)-10-chloro-10-

fluorodec-9-enoate (23.7 mg, 0.1001 mmol). This was followed by the addition of (*S*,*E*)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-1-en-3-ol (30.5 mg, 0.1200 mmol). A 10:1 THF/H_2O mixture (1 mL) was added, and the mixture was allowed to stir for 12 h at 65 °C. At this time, the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (10% → 30% CH_2Cl_2 in hexanes) to afford **4.88** (29.1 mg, 0.0886 mmol, 89% yield) in >98:2 *E:Z* ratio as light yellow oil. **IR (neat)**: 3516 (w), 2928 (s), 2854 (m), 1737 (s), 1459 (m), 1247(m), 1170 (m), 962 (m), 577 (w); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −118.4 (dd, J = 27.8, 21.1 Hz); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 6.30 (dd, J = 27.8, 15.5 Hz, 1H), 6.04 (dd, J = 15.5, 5.9 Hz, 1H), 5.14 (dt, J = 21.1, 8.2 Hz, 1H), 4.24 (p, J = 5.9 Hz, 1H), 3.67 (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 2.06 (q, J = 7.5 Hz, 2H), 1.71–1.54 (m, 4H), 1.45–1.21 (m, 14H), 0.89 (t, J = 6.6 Hz, 3H) (The alcoholic proton was not observed); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 174.4, 155.6 (d, J = 239.9 Hz), 133.8, 117.5 (d, J = 24.9 Hz), 109.6 (d, J = 21.9 Hz), 72.2, 51.6, 37.5, 34.2, 31.9, 29.8, 29.1, 29.1, 28.9, 25.2, 25.1, 25.0, 22.7, 14.2; **HRMS[M+H]$^+$**: Calcd for $C_{19}H_{34}FO_3$: 329.2486, found: 329.2476.

Fluoro-(*S*)-coriolide (4.89): Prepared in analogy to a reported protocol[68]. An oven-dried vial was charged with methyl (*S*,9*E*,11*E*)-10-fluoro-13-hydroxyoctadeca-9,11-dienoate (14.9 mg, 0.046 mmol) in a mixture of 1:1 THF/MeOH (0.5 mL), after which a 1.8 N aqueous solution of LiOH (125 μL, 0.2300 mmol) was added. The mixture was allowed

(68) Basabe, P.; Bodero, O.; Marcos, I. S.; Díez, D.; Blanco, A.; de Román, M.; Urones, J. G. *J. Org. Chem.* **2009**, *74*, 7750–7754.

to stir for 4 h at 22 °C. At this time, the pH was adjusted to ~2 by the addition of sufficient amounts of a 1N aqueous solution of HCl, after which the mixturte was washed with EtOAc (3 x 10 mL). The combined organic layers were washed successively with a saturated aqueous solution of NaCl (5 mL), then water (2 x 5 mL), and dried over $MgSO_4$. Removal of the volatiles afforded yellow oil, which was dissolved in toluene (1.5 mL) and the mixture was allowed to cool to 0 °C. A solution of Et_3N in toluene (171.6 μL in 15 mL, 0.0598 mmol) and 2,4,6-trichlorobenzoyl chloride in toluene (171.6 μL in 15 mL, 0.0552 mmol) were added, and the mixture was allowed to stir for 12 h at 22 °C. The mixture was then charged with DMAP (11.2 mg in 1.5 mL toluene, 0.0919 mmol) and allowed to stir for 2 h at 22 °C and for 1 h at 110 °C. After the mixture was allowed to cool to 22 °C, removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (hexanes → 8% EtOAc in hexane) to give **4.89** (10.5 mg, 0.0354 mmol, 77% yield) in >98:2 *E:Z* ratio as colorless oil. **IR (neat)**: 2957 (m), 2925 (m), 2870 (w), 1731 (s), 1273 (m), 1132(m), 739 (m), 689 (m); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −119.8 (dd, J = 28.7, 19.5 Hz); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 6.27 (dd, J = 29.6, 16.0 Hz, 1H), 6.05 (dd, J = 15.5, 3.5 Hz, 1H), 5.61–5.46 (m, 1H), 5.18 (ddd, J = 18.5, 10.6, 7.4 Hz, 1H), 2.58 (ddd, J = 14.9, 11.5, 3.7 Hz, 1H), 2.40 (ddd, J = 15.2, 6.3, 4.1 Hz, 1H), 2.28–2.10 (m, 1H), 2.00–1.86 (m, 2H), 1.71–1.57 (m, 3H), 1.28 (d, J = 22.6 Hz, 14H), 0.89 (t, J = 6.7 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 172.8, 156.8 (d, J = 242.4 Hz), 129.7, 116.4 (d, J = 24.8 Hz), 108.9 (d, J = 19.7 Hz), 72.1, 34.9, 32.9, 31.7, 27.5 (d, J = 3.1 Hz), 26.8, 26.2, 25.4, 25.1, 24.9, 22.6, 22.4 (d, J = 8.6 Hz), 14.1; **HRMS[M+H]$^+$**: Calcd for $C_{18}H_{30}FO_2$: 297.2224, found: 297.2229.

4.7.8. Regiodivergent Synthesis of Fluoro-Oleyl-Coenzyme A Fragments

Methyl (*E*)-10-fluorooctadec-9-enoate (4.90): Based on general procedure A, an oven-dried vial equipped with a magnetic stir bar was charged with methyl 10-methylundec-9-enoate (21.0 mg, 0.1000 mmol), (*Z*)-1,2-dichloro-1-fluoroethene (115.0 mg, 1.0000 mmol) and a solution of **Mo-1a** in benzene (0.1 M, 50 µL, 5.0 µmol). This was followed by the addition of a solution of (*Z*)-hex-3-ene in benzene (1.0 M, 10 µL, 10.0 µmol). The mixture was allowed to stir for 12 h at 22 °C, after which the volatiles were removed in vacuo and the resulting residue was passed through a short plug of celite and silica gel. After Et_2O wash (15 mL), the filtrate was carefully concentrated in vacuo to leave behind orange oil, which was charged with $Pd(OAc)_2$ (1.2 mg, 0.0053 mmol), CPhos (4.4 mg, 0.0101 mmol), octylzinc bromide (375 µL, 0.4 M in thf, 0.1500 mmol) and toluene (250 µL). The mixture was allowed to stir for 14 h at 65 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (hexanes → 3% Et_2O in hexanes), delivering **4.90** (25.4 mg, 0.0809 mmol, 81% yield) in >98:2 *E:Z* ratio as light yellow oil. **IR (neat)**: 2924 (s), 2853 (m), 1740 (m), 1699 (w), 1460 (w), 1435 (w), 1191 (m), 1171 (m), 847 (w); **^{19}F NMR (564 MHz, $CDCl_3$)**: δ −105.2 (d, J = 23.0 Hz); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 4.97 (dt, J = 22.4, 7.9 Hz, 1H), 3.67 (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 2.19 (dt, J = 23.4, 7.5 Hz, 2H), 1.89 (t, J = 7.4 Hz, 2H), 1.65–1.58 (m, 2H), 1.49 (t, J = 7.3 Hz, 2H), 1.33–1.25 (m, 18H), 0.88 (t, J = 6.8 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 174.4, 160.3 (d, J = 245.8 Hz), 105.5 (d, J = 21.4 Hz), 77.4, 77.2, 76.9, 51.6, 34.2, 32.0, 30.2,

29.5, 29.4, 29.2, 29.2, 29.0, 28.1, 27.9, 26.6, 25.6 (d, J = 9.6 Hz), 25.1, 22.8, 14.3; **HRMS[M+H]$^+$**: Calcd for $C_{19}H_{36}FO_2$: 315.2694, found: 315.2702.

Methyl (*E*)-9-fluorooctadec-9-enoate (4.93): Based on general procedure A, an oven-dried vial equipped with a magnetic stir bar was charged with methyl 2-methylundec-2-ene (16.8 mg, 0.1000 mmol), (*Z*)-1,2-dichloro-1-fluoroethene (115.0 mg, 1.0000 mmol), a solution of **Mo-1a** in benzene (0.1 M, 50 µL, 5.0 µmol), and a solution of (*Z*)-hex-3-ene in benzene (1.0 M, 10 µL, 10.0 µmol). The mixture was allowed to stir for 12 h at 22 °C, after which the volatiles were removed in vacuo the residue was passed through a short plug of celite and silica gel, followed by Et_2O wash (15 mL). The volatiles were carefully removed in vacuo to afford orange oil, which was charged with $Pd(OAc)_2$ (1.2 mg, 0.0053 mmol), CPhos (4.4 mg, 0.0101 mmol), (8-methoxy-8-oxooctyl)zinc bromide (250 µL, 0.6 M in thf, 0.1500 mmol) and toluene (166 µL). The mixture was allowed to stir for 14 h at 65 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the solvents in vacuo afforded yellow oil, which was purified by silica gel chromatography (hexanes → 3% Et_2O in hexanes) to afford **4.93** (24.2 mg, 0.0771 mmol, 77% yield) in >98:2 *E:Z* ratio as light yellow oil. **IR (neat)**: 2923 (s), 2852 (m), 1740 (s), 1698 (w), 1462 (m), 1434 (m), 1195 (w), 1170 (m), 848 (w); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −105.3 (q, J = 23.1 Hz); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 4.98 (dt, J = 22.5, 7.9 Hz, 1H), 3.67 (s, 3H), 2.30 (t, J = 7.6 Hz, 2H), 2.19 (dt, J = 23.2, 7.4 Hz, 2H), 1.90 (q, J = 7.4 Hz, 2H), 1.66–1.60 (m, 2H), 1.52–1.45 (m, 2H), 1.32–1.23 (m, 18H), 0.88 (t, J = 7.0 Hz, 3H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.4, 160.1 (d, J = 245.4 Hz), 105.7 (d, J = 21.4 Hz), 51.6, 34.2, 32.0, 30.2, 29.6, 29.4, 29.3, 29.2, 28.9, 28.1, 27.9, 26.5, 25.6 (d, J = 9.4 Hz), 25.1, 22.8, 14.3; **HRMS[M+H]$^+$**: Calcd for $C_{19}H_{36}FO_2$: 315.2694, found: 315.2698.

4.7.9. Diastereodivergent Synthesis of F-Nematic Liquid Crystal Components

(*Z*)-F-Nematic liquid (4.96): Based on general procedure A, an oven-dried vial equipped with a magnetic stir bar was charged with (1*R*,4*S*)-1-propyl-4-vinylcyclohexane (30.4 mg, 0.2000 mmol), (*E*)-1,2-dichloro-1-fluoroethene (230.0 mg, 2.0000 mmol), a solution of **Mo-1a** in benzene (0.1 M, 150 µL, 15.0 µmol), and a solution of (*E*)-but-2-ene in hexane (6.6 M, 9.0 µL, 60.0 µmol). The mixture was allowed to stir for 12 h at 22 °C, after which it was exposed to air. Careful removal of the volatiles in vacuo afforded orange oil, which was charged with $Pd(OAc)_2$ (2.0 mg, 0.0100 mmol), SPhos (8.0 mg, 0.0200 mmol), CsF (60.5 mg, 0.4000 mmol), (4-propylphenyl)boronic acid (49.0 mg, 0.3000 mmol), and *i*-PrOH (0.5 mL). The mixture was allowed to stir for 3 h at 90 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (pentane → hexanes), furnishing **4.96** (37.5 mg, 0.1300 mmol, 65% yield) in >98:2 *Z:E* ratio as light yellow oil. **IR (neat)**: 2954 (m), 2925 (m), 2848 (w), 1677 (w), 1510 (m), 1447 (m), 1071 (m), 739 (m), 846 (m), 814 (w); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −121.6 (d, J = 38.3 Hz); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.39 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 5.18 (dd, J = 38.4, 9.2 Hz, 1H), 2.71–2.51 (m, 3H), 1.78 (t, J = 13.1 Hz, 4H), 1.63 (h, J = 7.3 Hz, 2H), 1.33 (dt,

J = 14.8, 7.5 Hz, 2H), 1.22–1.10 (m, 5H), 1.05–0.86 (m, 8H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 155.8 (d, *J* = 244.6 Hz), 143.1, 130.6 (d, *J* = 29.6 Hz), 128.6, 123.9, 111.3 (d, *J* = 18.3 Hz), 39.9, 37.9, 37.0, 33.4, 33.0, 29.8, 24.6, 20.1, 14.6, 13.9; **HRMS[M+H]$^+$**: Calcd for $C_{20}H_{30}F$: 289.2326, found: 289.2334.

(*E*)-F-Nematic liquid (4.97): Based on general procedure A, an oven-dried vial equipped with a magnetic stir bar was charged with (1*R*,4*S*)-1-propyl-4-vinylcyclohexane (15.2 mg, 0.1000 mmol), (*Z*)-1,2-dichloro-1-fluoroethene (115.0 mg, 1.0000 mmol), a solution of **Mo-1b** in benzene (0.1 M, 50 µL, 5.0 µmol), and a solution of (*Z*)-hex-3-ene in benzene (1.0 M, 10 µL, 10.0 µmol). The mixture was allowed to stir for 12 h at 22 °C, after which it was exposed to air and the volatiles were carefully removed in vacuo to afford orange oil, which was charged with Sphos-Pd-G4 (4.0 mg, 0.0050 mmol), CsF (30.2 mg, 0.2000 mmol), (4-propylphenyl)boronic acid (24.5 mg, 0.1500 mmol), and dioxane (0.4 mL). The mixture was allowed to stir for 3 h at 90 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuous afforded yellow oil, which was purified by silica gel chromatography (pentane → hexanes) to give **4.97** (21.3 mg, 0.0739 mmol, 74% yield) in 95:5 *E:Z* ratio as light yellow oil. **IR (neat)**: 2954 (m), 2920 (s), 2848 (m), 1677 (w), 1509 (w), 1446 (w), 1073 (m), 1043 (w), 846 (w), 814 (w); **^{19}F NMR (564 MHz, $CDCl_3$)**: *Z* isomer (major): δ −103.2 (d, *J* = 23.1 Hz); *E* isomer (minor): δ −121.6 (d, *J* = 38.3 Hz); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.35 (d, *J* = 7.9 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 5.17 (dd, *J* = 23.1, 10.6 Hz, 1H), 2.61 (t, *J* = 7.7 Hz, 2H), 2.20 (ddd, *J* = 14.7, 9.3,

5.4 Hz, 1H), 1.80–1.71 (m, 4H), 1.65 (p, *J* = 7.4 Hz, 2H), 1.31 (dd, *J* = 14.9, 7.5 Hz, 2H), 1.16 (ddd, *J* = 20.4, 11.0, 5.4 Hz, 4H), 0.99–0.85 (m, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)**: *δ* 156.1 (d, *J* = 239.7 Hz), 143.7, 128.5, 127.5, 127.5, 114.1 (d, *J* = 22.2 Hz), 39.9, 38.0, 36.9, 34.0 (d, *J* = 2.3 Hz), 32.8, 30.5, 24.5, 20.1, 14.5, 14.0; **HRMS[M+H]$^+$**: Calcd for $C_{20}H_{30}F$: 289.2326, found: 289.2321.

4.7.10. Diastereodivergent Synthesis of Peptides with E- and Z-Amide Bond Mimics

(*R*,*E*)-6-((*tert*-Butyldiphenylsilyl)oxy)-3-fluoro-5-methylhex-3-en-2-one (4.99): Based on general procedure A, an oven-dried vial equipped with a magnetic stir bar was charged with (*R*)-*tert*-butyl((2-methylbut-3-en-1-yl)oxy)diphenylsilane (32.4 mg, 0.1000 mmol), (*Z*)-1,2-dichloro-1-fluoroethene (115.0 mg, 1.0000 mmol), a solution of **Mo-1b** in benzene (0.1 M, 100 μL, 10.0 μmol), and a solution of (*Z*)-hex-3-ene in benzene (1.0 M, 10 μL, 10.0 μmol). The mixture was allowed to stir for 12 h at 22 °C, after which it was exposed to air. Careful removal of the volatiles in vacuo afforded orange oil, which was charged with $Pd(P\textit{t}\text{-}Bu_3)_2$ (2.6 mg, 0.0050 mmol), (1-ethoxyvinyl)zinc chloride (0.39 M, 512 μL, 0.2000 mmol), and THF/NMP (1.8 mL/1.0 mL). The mixture was allowed to stir for 2 h at 80 °C, and then cool to 22 °C, after which a 3M aqueous solution of HCl (2 mL) was added. The resulting mixture was allowed to stir for an addition hour, after which the aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (hexanes → 9% Et_2O in hexanes) to afford **4.99** (20.7 mg, 0.0539 mmol, 54% yield) in 97:3 *Z:E* ratio as colorless oil. **IR (neat)**: 3068 (m), 2957 (m), 2928 (m), 2855 (m), 1694 (m), 1654 (m), 1426 (m), 1359

(m), 1284 (m), 1106 (s), 1058 (m), 822 (m), 739 (m), 700 (s), 613 (m), 503 (s); **^{19}F NMR (376 MHz, $CDCl_3$)**: *Z* isomer (major): δ −118.6 (dq, *J* = 20.6, 4.4, 3.8 Hz); *E* isomer (minor): δ −127.5 (dq, *J* = 34.4, 2.9 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.68–7.59 (m, 4H), 7.49–7.33 (m, 6H), 5.65 (dd, *J* = 22.6, 9.6 Hz, 1H), 3.80–3.38 (m, 3H), 2.28 (d, *J* = 4.9 Hz, 3H), 1.05–1.06 (m, 12H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 194.5 (d, *J* = 40.1 Hz), 153.4 (d, *J* = 255.7 Hz), 135.7 (d, *J* = 2.6 Hz), 133.7 (d, *J* = 2.4 Hz), 129.8, 127.8, 124.3 (d, *J* = 17.2 Hz), 68.2 (d, *J* = 2.3 Hz), 32.8 (d, *J* = 5.5 Hz), 27.9 (d, *J* = 2.7 Hz), 26.9, 19.4, 17.0 (d, *J* = 2.6 Hz); **HRMS[M+H]$^+$**: Calcd for $C_{23}H_{30}FO_2Si$: 385.1994, found: 385.1999.

Benzyl (2-(((*S*)-1-(((2*S*,5*R*,*E*)-3-fluoro-6-hydroxy-5-methylhex-3-en-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)carbamate (S4): Prepared in analogy to a reported method[34,50]. An oven-dried vial was charged with (*R,E*)-6-((*tert*-butyldiphenylsilyl)oxy)-3-fluoro-5-methylhex-3-en-2-one (115.0 mg, 0.3000 mmol), (*S*)-*tert*-butylsulfinylamine (52.2 mg, 0.1601 mmol), $Ti(OEt)_4$ (11.3 mg, 0.0801 mmol, 2.5 equiv.), and THF (2.5 mL). The mixture was heated to reflux for 2 h, after which it was allowed to cool to 22 °C and then –78 °C. At this time, the mixture was charged with DIBAL (213 µL, 1.2 mmol) in a dropwise manner, after which it was allowed to stir for 1 h at −78 °C. The solution was allowed to warm to 22 °C, and the resulting suspension was passed through a plug of celite. The filter cake was washed with EtOAc (3 x 10 mL), and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded yellow oil, which was dissolved in MeOH (0.6 mL), and then a 4N aqueous solution of HCl in dioxane (0.3 mL, 1.2 mmol) was added. The mixture was allowed to stir for 1 h at 22 °C. Removal of the volatiles in vacuo afforded

yellow solid, which was dissolved in an in situ prepared solution of 1-((*N*,4-dimethylphenyl)sulfonamido)vinyl ((benzyloxy)carbonyl)glycyl-*L*-phenylalaninate solution*. After the addition of Et_3N (174.0 μL, 1.2 mmol), the mixture was allowed to stir for 24 h at 22 °C. Removal of the volatiles in vacuo afforded brown oil, which was purified by silica gel chromatography (25% EtOAc in hexanes → 10% MeOH in CH_2Cl_2) to afford **S4** (94.6 mg, 0.1950 mmol, 65% yield) in >98:2 *E:Z* ratio as light yellow oil. (*Preparation: *N*-ethynyl-*N*,4-dimethylbenzenesulfonamide (275.9 mg, 1.32 mmol) was added to ((benzyloxy)carbonyl)glycyl-L-phenylalanine (427.2 mg, 1.20 mmol) in CH_2Cl_2 (1.2 mL) and the mixture was allowed to stir for 1 h at 22 °C). **IR (neat)**: 3375 (m), 3303 (m), 2928 (m), 2871 (m), 2477 (m), 2411 (m), 1702 (m), 1642 (s), 1449 (s), 1359 (m), 1261 (m), 1170 (m), 1036 (m), 742 (m), 698 (m); **^{19}F NMR (376 MHz, $CDCl_3$)**: δ −120.2 (dd, J = 28.6, 21.5 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.40–7.28 (m, 5H), 7.28–7.07 (m, 6H), 6.65–6.43 (m, 1H), 5.66 (s, 1H), 5.08 (s, 2H), 4.91 (dt, J = 28.8, 7.4 Hz, 1H), 4.80 (dd, J = 21.3, 10.5 Hz, 1H), 4.68 (q, J = 7.2 Hz, 1H), 3.94–3.78 (m, 2H), 3.48 (dd, J = 10.9, 5.6 Hz, 1H), 3.28 (dd, J = 10.7, 8.3 Hz, 1H), 3.05–2.95 (m, 2H), 2.60 (d, J = 8.7 Hz, 1H), 2.32 (s, 1H), 1.24 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H).; **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 169.8, 169.0, 158.9 (d, J = 252.1 Hz), 156.8, 136.2, 136.2, 129.4, 128.7, 128.7, 128.4, 128.2, 127.2, 109.8 (d, J = 18.8 Hz), 67.7 (d, J = 2.9 Hz), 67.4, 54.6, 44.5, 43.0 (d, J = 27.7 Hz), 38.9, 33.9 (d, J = 8.3 Hz), 18.3, 17.6 (d, J = 1.9 Hz); **HRMS[M+H]$^+$**: Calcd for $C_{26}H_{33}FN_3O_5$: 486.2399, found: 486.2304.

(8*S*,11*S*,14*R*,*E*)-8-Benzyl-12-fluoro-11,14-dimethyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazapentadec-12-en-15-oic acid (4.101): Prepared based on reported

procedure[69]. At 0 °C, an oven-dried reaction vial was charged with benzyl (2-(((*S*)-1-(((2*S,5R,Z*)-3-fluoro-6-hydroxy-5-methylhex-3-en-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)carbamate (38.7 mg, 0.0800 mmol) in acetone (0.8 mL). This was followed by the addition of a 3N aqueous solution of Jones reagent (80 μL, 0.24 mmol). The mixture was allowed to stir for 1 h at 0 °C, after which it was treated with *i*-PrOH (48 mg, 0.8 mmol) and water (10.4 mL). The resulting solution was washed with EtOAc (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$. Removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (10% → 35% EtOAc in hexanes) to afford **4.101** (30.7 mg, 0.0616 mmol, 77% yield) in >98:2 *E:Z* ratio as viscous liquid. **IR (neat)**: 3032 (m), 2928 (m), 2420 (m), 2207 (m), 2044 (m), 1701 (m), 1644 (s), 1452 (s), 1361 (m), 1258 (m), 1176 (m), 699 (m), 571 (m); **^{19}F NMR (376 MHz, CD_3OD)**: δ −122.8 (dd, J = 29.1, 20.0 Hz); **^{1}H NMR (400 MHz, CD_3OD)**: δ 7.56–7.00 (m, 10H), 5.09 (s, 2H), 5.02–4.86 (m, 2H), 4.60 (t, J = 6.9 Hz, 1H), 3.85–3.63 (m, 2H), 3.48–3.33 (m, 1H), 3.07 (dd, J = 13.8, 6.2 Hz, 1H), 2.90 (dd, J = 14.0, 7.5 Hz, 1H), 1.36–1.27 (m, 3H), 1.22 (d, J = 6.8 Hz, 3H), the acidic proton was not observed; **^{13}C NMR (101 MHz, CD_3OD)**: δ 186.9, 170.6, 170.4, 158.7 (d, J = 253.4 Hz), 157.6, 136.6, 136.4, 128.9, 128.0, 128.0, 127.6, 127.5, 126.4, 107.5 (d, J = 22.3 Hz), 66.5, 54.0, 43.5, 42.2 (d, J = 27.0 Hz), 37.67, 29.3, 17.7, 15.8 (d, J = 1.4 Hz); **HRMS[M+H]$^+$**: Calcd for $C_{26}H_{31}FN_3O_6$: 500.2191, found: 500.2195.

(*R*,*Z*)-6-((*tert*-Butyldiphenylsilyl)oxy)-3-fluoro-5-methylhex-3-en-2-one (S5): Based on general procedure A, an oven-dried vial equipped with a magnetic stir bar was charged with (*R*)-*tert*-butyl((2-methylbut-3-en-1-yl)oxy)diphenylsilane (32.4 mg, 0.1000

(69) Jiang, Z.-X.; Qing, F.-L. *J. Org. Chem.* **2004**, *69*, 5486–5489.

mmol), (*E*)-1,2-dichloro-1-fluoroethene (115.0 mg, 1.0000 mmol), a solution of **Mo-1a** in benzene (0.1 M, 120 μL, 12.0 μmol), and a solution of (*E*)-but-2-ene in hexane (6.6 M, 2.3 μL, 15.1 μmol). The mixture was allowed to stir for 12 h at 22 °C, after which it was exposed to air and the volatiles were carefully removed in vacuo to afford orange oil, which was treated with $Pd(P\textit{t}\text{-}Bu_3)_2$ (2.6 mg, 0.0050 mmol), (1-ethoxyvinyl)zinc chloride (0.39 M, 512 μL, 0.2000 mmol) and THF/NMP (1.8 mL/1.0 mL). The mixture was allowed to stir for 2 h at 80 °C, after which it was allowed to cool to 22 °C. A 3M aqueous solution of HCl (2 mL) was added and the mixture was allowed to stir for 1 h. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (hexanes → 9% Et_2O in hexanes) to afford **S5** (16.5 mg, 0.0430 mmol, 43% yield) in >98:2 *E:Z* ratio as colorless oil. **IR (neat)**: 3047 (m), 2957 (m), 2855 (w), 1707 (m), 1640 (m), 1426 (m), 1362 (m), 1109 (s), 1077 (m), 822 (m), 700 (s), 504 (m); **^{19}F NMR (376 MHz, $CDCl_3$)**: δ −127.5 (dq, J = 34.4, 2.9 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.70–7.59 (m, 4H), 7.50–7.33 (m, 6H), 5.96 (dd, J = 34.5, 9.7 Hz, 1H), 3.67–3.50 (m, 2H), 2.96 (dh, J = 9.5, 6.6 Hz, 1H), 2.28 (d, J = 2.7 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H), 1.05 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 191.7 (d, J = 31.7 Hz), 155.0 (d, J = 260.8 Hz), 135.7, 133.6 (d, J = 1.5 Hz), 129.7, 127.8, 122.5 (d, J = 12.3 Hz), 67.5 (d, J = 2.0 Hz), 32.9 (d, J = 1.9 Hz), 26.9, 25.7, 19.4, 16.4 (d, J = 1.9 Hz); **HRMS[M+H]$^+$**: Calcd for $C_{23}H_{30}FO_2Si$: 385.1994, found: 385.1986.

Benzyl (2-(((*S*)-1-(((2*S,5R,Z*)-3-fluoro-6-hydroxy-5-methylhex-3-en-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)carbamate (S6): An oven-dried vial was

charged with (*R,Z*)-6-((tert-butyldiphenylsilyl)oxy)-3-fluoro-5-methylhex-3-en-2-one (115.0 mg, 0.3000 mmol), (*S*)-*tert*-butylsulfinylamine (52.2 mg, 0.1601 mmol), $Ti(OEt)_4$ (11.3 mg, 0.0801 mmol), and THF (2.5 mL). The mixture was allowed to reflux for 2 h and was the allowed to cool sequentially to 22 and then –78 °C. At this time, DIBAL (213 µL, 1.2 mmol) was added dropwise, and the mixture was allowed to stir for 1 h at –78 °C. After the mixture was allowed to warm to 22 °C, the suspension was filtered through a plug of celite and the filter cake was washed with EtOAc (3 x 10 mL). The combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL) and water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded yellow oil, which was dissolved in MeOH (0.6 mL), and treated with a 4N aqueous solution of HCl in dioxane (0.3 mL, 1.2 mmol). The mixture was allowed to stir for 1 h at 22 °C and the volatiles were removed in vacuo to afford yellow solid, which was dissolved in in-situ prepared* solution of 1-((*N*,4-dimethylphenyl)sulfonamido)vinyl ((benzyloxy)carbonyl)glycyl-L-phenylalaninate[52] and then Et_3N (174.0 µL, 1.2 mmol). The mixture was allowed to stir for 24 h at 22 °C, after which the volatiles were removed in vacuo to afford brown oil, which was purified by silica gel chromatography (25% EtOAc in hexanes → 10% MeOH in CH_2Cl_2) to afford **S6** (90.2 mg, 0.1860 mmol, 62% yield) in >98:2 *Z:E* ratio as light yellow oil. (*Preparation: *N*-ethynyl-N,4-dimethylbenzenesulfonamide (275.9 mg, 1.32 mmol, 4.4 equiv.) and ((benzyloxy)carbonyl)glycyl-L-phenylalanine (427.2 mg, 1.20 mmol, 4 equiv.) were dissolved in CH_2Cl_2 (1.2 mL) and allowed to stir for 1 h at 22 °C). **IR (neat)**: 3375 (m), 3306 (m), 2928 (m), 2871 (m), 2477 (m), 2411 (m), 1702 (m), 1642 (s), 1449 (s), 1359 (m), 1261 (m), 1370 (m), 1036 (m), 742 (w), 698 (m); **^{19}F NMR (376 MHz, $CDCl_3$)**: *δ*

−121.2 (dd, *J* = 37.6, 13.1 Hz); **^{1}H NMR (400 MHz, CDCl$_3$)**: *δ* 7.40–7.30 (m, 7H), 7.17 (d, *J* = 7.3 Hz, 3H), 6.82 (s, 1H), 6.36 (s, 1H), 5.63 (s, 1H), 5.07 (d, *J* = 6.9 Hz, 3H), 4.68–4.48 (m, 3H), 3.79 (s, 2H), 3.57–3.47 (m, 1H), 3.34 (t, *J* = 8.3 Hz, 1H), 3.05 (s, 2H), 2.73 (dd, *J* = 15.9, 8.3 Hz, 1H), 1.23 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR (101 MHz, CDCl$_3$)**: *δ* 170.3, 169.5, 158.6 (d, *J* = 258.5 Hz), 157.1, 136.2, 136.0, 129.4, 128.9, 128.7, 128.5, 128.2, 127.3, 109.0 (d, *J* = 13.6 Hz), 67.6, 67.5, 55.0, 46.8 (d, *J* = 29.6 Hz), 44.9, 38.1, 32.2 (d, *J* = 2.7 Hz), 18.0, 16.8; **HRMS[M+H]$^{+}$**: Calcd for $C_{26}H_{33}FN_3O_5$: 486.2399, found: 486.2305.

(8*S*,11*S*,14*R*,*Z*)-8-Benzyl-12-fluoro-11,14-dimethyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazapentadec-12-en-15-oic acid (4.102): An oven-dried reaction vial was charged with benzyl (2-(((*S*)-1-(((2*S,5R,Z*)-3-fluoro-6-hydroxy-5-methylhex-3-en-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)carbamate (24.2 mg, 0.0500 mmol) in acetone (0.5 mL), and a 3N aqueous solution of Jones' reagent (50 μL, 0.15 mmol) at 0 °C. The mixture was allowed to stir for 1 h at 0 °C, after which it was charged with *i*-PrOH (30 mg, 0.5 mmol) and water (6.5 mL). The mixture was washed with EtOAc (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$. Removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (10% → 35% EtOAc in hexanes) to afford **4.102** (18.2 mg, 0.0365 mmol, 73% yield) in >98:2 *Z:E* ratio as viscous liquid. **IR (neat)**: 3374 (m), 3289 (m), 2928 (m), 2472 (m), 2419 (m), 1701 (m), 1642 (s), 1451 (s), 1359 (m), 1172 (m), 1118 (m), 971 (m), 698 (m); **^{19}F NMR (376 MHz, CDCl$_3$)**: *δ* −78.0 (d, *J* = 10.8 Hz); **^{1}H NMR (400 MHz, CD$_3$OD)**: *δ* 7.37–7.17 (m, 10H), 5.16–4.89 (m, 3H), 4.56 (dd, *J* = 25.7, 6.7 Hz, 2H), 3.72 (d, *J* = 6.5 Hz, 2H), 3.39 (t, *J* = 8.1 Hz, 1H), 3.09 (dd, *J* = 13.8, 6.4 Hz, 1H),

2.91 (dd, *J* = 13.7, 7.9 Hz, 1H), 1.27 (d, *J* = 7.6 Hz, 3H), 1.20 (d, *J* = 7.1 Hz, 3H), carboxylic acid proton was not observed; **^{13}C NMR (101 MHz, CD_3OD)**: δ 188.2, 172.4, 171.9, 160.7, 160.4 (d, *J* = 268.2 Hz), 138.1, 138.9, 130.4, 129.5, 129.5, 129.1, 128.9, 127.9, 107.6 (d, *J* = 21.2 Hz), 67.9, 55.9, 47.0, 46.7 (d, *J* = 1.0 Hz), 44.9, 39.0, 18.9, 18.0 (d, *J* = 1.5 Hz); **HRMS[M+H]$^+$**: Calcd for $C_{26}H_{31}FN_3O_6$: 500.2191, found: 500.2190.

4.7.11. Diastereodivergent Synthesis of Difluoro-Rumenic Acids

Methyl (*Z*)-10-fluoro-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dec-9-enoate (4.103): Based on general procedure A, an oven-dried vial equipped with a magnetic stir bar was charged with methyl 10-methylundec-9-enoate (21.2 mg, 0.1000 mmol), (*E*)-1,2-dichloro-1-fluoroethene (115.0 mg, 1.0000 mmol), a solution of **Mo-1a** in benzene (0.1 M, 75 µL, 7.5 µmol), and a solution of (*E*)-but-2-ene in hexanes (6.6 M, 4.5 µL, 29.7 µmol). The mixture was allowed to stir for 12 h at 22 °C, after which it was exposed to air and the volatiles were carefully removed in vacuo. The resulting orange oil was treated with $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol), XPhos (4.8 mg, 0.0100 mmol), $B_2(pin)_2$ (50.8 mg, 0.2000 mmol), KOAc (19.6 mg, 0.2000 mmol), and 1,4-dioxane (1.0 mL). The mixture was allowed to stir for 3 h at 100 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. and Removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (hexanes → 10% Et_2O in hexanes) to furnish **4.103** (18.0 mg, 0.0550 mmol, 55% yield) in >98:2 *E:Z* ratio as light yellow oil. **IR (neat)**: 2977 (m), 2925 (m), 2855 (m), 1736 (s), 1432 (m), 1400 (m), 1376 (m), 1167 (m), 1074 (m), 858

(w); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −131.0 (d, J = 41.8 Hz); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 5.61 (dt, J = 44.8, 7.5 Hz, 1H), 3.67 (s, 3H), 2.24 (dt, J = 56.0, 7.5 Hz, 4H), 1.72–1.57 (m, 2H), 1.21–1.30 (m, 20H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 174.4, 128.7 (d, J = 15.4 Hz), 84.6, 51.6, 34.2, 32.1, 29.8, 29.2, 29.1, 25.1, 24.8, 22.8, the carbon next to boron was not observed; **^{11}B NMR (160 MHz, $CDCl_3$)**: δ 22.45 (s). **HRMS[M+H]$^+$**: Calcd for $C_{17}H_{31}O_4BF$: 329.2294, found: 329.2302.

Methyl (*E*)-10-fluoro-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dec-9-enoate (4.104): Based on general procedure A, an oven-dried vial equipped with a magnetic stir bar was charged with methyl 10-methylundec-9-enoate (21.2 mg, 0.1000 mmol), (*Z*)-1,2-dichloro-1-fluoroethene (115.0 mg, 1.0000 mmol), a solution of **Mo-1a** in benzene (0.1 M, 50 µL, 5.0 µmol), and a solution of (*Z*)-hex-3-ene in benzene (1.0 M, 10 µL, 10.0 µmol). The mixture was allowed to stir for 12 h at 22 °C, after which it was exposed to air and the volatiles were carefully removed in vacuo to afford orange oil, which was charged with $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol), XPhos (4.8 mg, 0.0100 mmol), $B_2(pin)_2$ (50.8 mg, 0.2000 mmol), KOAc (19.6 mg, 0.2000 mmol), and 1,4-dioxane (1.0 mL). The mixture was allowed to stir for 3 h at 100 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. and Removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (hexanes → 10% Et_2O in hexanes) to afford **4.104** (23.9 mg, 0.0730 mmol, 73% yield) in 95:5 *E:Z* ratio as light yellow oil. **IR (neat)**: 2976 (m), 2924 (m), 2853 (m), 1737 (s), 1433 (m), 1400 (m), 1371 (m), 1329 (m), 1167 (m), 1077 (m),

857 (w); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −125.0 (d, J = 29.9 Hz); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.01 (dt, J = 30.2, 8.5 Hz, 1H), 3.66 (s, 3H), 2.30 (t, J = 7.5 Hz, 4H), 1.68–1.57 (m, 2H), 1.23–1.31 (m, 20H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 174.4, 129.7 (d, J = 12.6 Hz), 84.3, 51.5, 34.2, 29.8, 29.8, 29.2, 29.1, 28.7, 25.1, 24.9, the carbon next to boron was not observed; **^{11}B NMR (160 MHz, $CDCl_3$)**: δ 27.77 (s). **HRMS[M+H]$^+$**: Calcd for $C_{17}H_{31}O_4BF$: 329.2294, found: 329.2299.

(*Z,Z*)-Difluoro-rumenic ester (4.108): Based on general procedure A, an oven-dried vial equipped with a magnetic stir bar was charged with 2-methylnon-2-ene (140.0 mg, 1.0000 mmol), (*E*)-1,2-dichloro-1-fluoroethene (1150.0 mg, 10.0000 mmol), a solution of **Mo-1a** in benzene (0.1 M, 750 µL, 75 µmol), and a solution of (*E*)-but-2-ene in hexane (6.6 M, 45 µL, 297 µmol). The mixture was allowed to stir for 12 h at 22 °C, after which it was exposed to air and the volatiles were carefully removed to afford brown oil, which was purified by silica gel chromatography (pentane) to give a mixture of (*E*)-1-chloro-1-fluorooct-1-ene in pentane (80% by weight accounting for pentane mass; 117.0 mg, 0.5686 mmol, 57% yield) in >98:2 *E:Z* ratio. In a N_2-filled glove box, an oven-dried vial was charged with Xphos-Pd-G2 (4.2 mg, 0.0050 mmol), CsF (30.2 mg, 0.2000 mmol), (*E*)-1-chloro-1-fluorooct-1-ene (80% by weight accounting for pentane mass; 20.5 mg, 0.1 mmol), methyl (*Z*)-10-fluoro-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dec-9-enoate (45.9 mg, 0.1400 mmol), and dioxane (1.0 mL). The mixture was allowed to stir for 24 h at 90 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the

volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (hexanes → 9% CH_2Cl_2 in hexanes) to deliver **4.108** (20.5 mg, 0.0621 mmol, 62% yield) in >98% *Z,Z* ratio as colorless oil. **IR (neat)**: 2923 (s), 2852 (m), 1740 (s), 1435 (m), 1361 (w), 1273 (m), 1245 (m), 1169 (m), 966 (w); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −122.3 (t, J = 26.3 Hz), −127.3 (dd, J = 36.3, 28.2 Hz); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 5.54–5.34 (m, 1H), 5.12 (ddt, J = 8.6, 5.5, 1.5 Hz, 1H), 3.68 (s, 3H), 2.30 (q, J = 7.2 Hz, 2H), 2.17 (q, J = 8.3, 7.2 Hz, 1H), 2.10–1.99 (m, 1H), 1.96 (q, J = 6.6 Hz, 2H), 1.78–1.56 (m, 7H), 1.47–1.22 (m, 14H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 174.5, 146.8 (d, J = 239.2 Hz), 146.6 (d, J = 227.8 Hz), 106.7 (d, J = 13.7 Hz), 106.5 (d, J = 12.9 Hz), 51.6, 34.3, 32.7, 30.5, 29.9, 29.4, 29.3, 29.2, 29.1, 28.1, 25.8, 25.1, 17.8, 14.2; **HRMS[M+NH_4]$^+$**: Calcd for $C_{19}H_{36}F_2O_2N$: 348.2708, found: 348.2709.

(*Z,E*)-Difluoro-rumenic ester (4.109): Based on general procedure A, an oven-dried vial equipped with a magnetic stir bar was charged with 2-methylnon-2-ene (140.0 mg, 1.0000 mmol), (*Z*)-1,2-dichloro-1-fluoroethene (1150.0 mg, 10.0000 mmol), a solution of **Mo-1a** in benzene (0.1 M, 500 µL, 50.0 µmol), and a solution of (*Z*)-hex-3-ene in benzene (1.0 M, 100 µL, 100.0 µmol). The mixture was allowed to stir for 12 h at 22 °C, after which it was exposed to air and the volatiles were carefully removed in vacuo to afford brown oil, which was purified by silica gel chromatography (pentane) to afford a mixture of (*Z*)-1-chloro-1-fluorooct-1-ene in pentane (76% by weight accounting for pentane mass; 199.2 mg, 0.9197 mmol, 92% yield) in 94:6 *Z:E* ratio. In a N_2-filled glove box, an oven-dried vial was charged with Xphos-Pd-G2 (4.2 mg, 0.0050 mmol), CsF (30.2 mg, 0.2000 mmol), (*Z*)-1-chloro-1-fluorooct-1-ene (76% by weight accounting for pentane mass; 21.6 mg, 0.1000 mmol), methyl (*Z*)-10-fluoro-10-(4,4,5,5-tetramethyl-

1,3,2-dioxaborolan-2-yl)dec-9-enoate (45.9 mg, 0.1400 mmol), and dioxane (1.0 mL). The mixture was allowed to stir for 24 at 90 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (hexanes → 9% CH_2Cl_2 in hexanes), affording **4.109** (21.5 mg, 0.0651 mmol, 65% yield) in >98% *Z,E* ratio as colorless oil. **IR (neat)**: 2922 (s), 2852 (m), 1739 (s), 1454 (m), 1434 (m), 1195 (m), 1169 (m), 1018 (m), 725 (w); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −122.3 (t, J = 26.3 Hz), −127.3 (dd, J = 36.3, 28.2 Hz); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 5.55–5.02 (m, 2H), 3.67 (s, 3H), 2.30 (td, J = 7.5, 1.7 Hz, 2H), 2.19 (dq, J = 14.6, 7.3 Hz, 2H), 1.95 (q, J = 6.6 Hz, 2H), 1.67–1.57 (m, 4H), 1.45–1.20 (m, 14H), 0.88 (t, J = 6.6 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 174.5, 149.5 (d, J = 242.8 Hz), 149.1 (d, J = 246.0 Hz), 110.6 (d, J = 15.2 Hz), 110.6 (d, J = 13.8 Hz), 51.6, 34.3, 32.7, 31.7, 30.5, 29.9, 29.3, 29.1, 28.1, 25.9, 25.1, 22.8, 17.8, 14.2; **HRMS[M+NH_4]$^+$**: Calcd for $C_{19}H_{36}F_2O_2N$: 348.2708, found: 348.2706.

(*E,E*)-Difluoro-rumenic ester (4.110): Based on general procedure A, an oven-dried vial equipped with a magnetic stir bar was charged with 2-methylnon-2-ene (140.0 mg, 1.0000 mmol), (*Z*)-1,2-dichloro-1-fluoroethene (1150.0 mg, 10.0000 mmol), a solution of **Mo-1a** in benzene (0.1 M, 500 µL, 50.0 µmol), and a solution of (*Z*)-hex-3-ene in benzene (1.0 M, 100 µL, 100.0 µmol). The mixture was allowed to stir for 12 h at 22 °C, after which it was exposed to air and the volatiles were carefully removed in vacuo to afford brown oil, which was purified by silica gel chromatography (pentane) to furnish

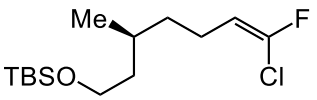
(*Z*)-1-chloro-1-fluorooct-1-ene in pentane (76% by weight accounting for pentane mass; 199.2 mg, 0.9197 mmol, 92% yield) in 94:6 *Z:E* ratio. In a N_2-filled glove box, an oven-dried reaction vial was charged with Xphos-Pd-G2 (4.2 mg, 0.0050 mmol), CsF (30.2 mg, 0.2000 mmol), (*Z*)-1-chloro-1-fluorooct-1-ene (76% by weight accounting for the mass of pentane, 21.7 mg, 0.1000 mmol) and methyl (*E*)-10-fluoro-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dec-9-enoate (45.9 mg, 0.1400 mmol) followed by dioxane (1.0 mL). The mixture was allowed to stir for 24 h at 95 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded yellow oil, which was purified by preparative thin layer chromatography (9% CH_2Cl_2 in hexanes) to afford **4.110** (17.8 mg, 0.0540 mmol, 54% yield) in >98% *E,E* ratio as colorless oil. **IR (neat)**: 2923 (s), 2853 (m), 1740 (s), 1455 (m), 1435 (m), 1196 (m), 1169 (m), 1107 (w), 859 (w); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −113.3 – −113.9 (m); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 5.55–5.38 (m, 1H), 5.23–4.92 (m, 1H), 3.67 (s, 3H), 2.31 (t, J = 7.6 Hz, 3H), 2.08–1.90 (m, 3H), 1.67–1.58 (m, 4H), 1.43–1.27 (m, 14H), 0.89 (t, J = 6.9 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 174.5, 147.6 (d, J = 236.0 Hz), 147.5 (d, J = 226.8 Hz), 114.5 (d, J = 16.7 Hz), 114.3 (d, J = 11.1 Hz), 51.6, 34.3, 31.7, 30.5, 29.9, 29.5, 29.3, 29.1, 28.1, 25.7, 25.1, 22.7, 17.8, 14.2; **HRMS[M+NH_4]$^+$**: Calcd for $C_{19}H_{36}F_2O_2N$: 348.2708, found: 348.2699.

(*E*,*Z*)-Difluoro-rumenic ester (4.111): Based on general procedure A, an oven-dried vial equipped with a magnetic stir bar was charged with 2-methylnon-2-ene (140.0 mg, 1.0000 mmol), (*E*)-1,2-dichloro-1-fluoroethene (1150.0 mg, 10.0000 mmol), a solution of

Mo-1a in benzene (0.1 M, 750 µL, 75 µmol), and a solution of (*E*)-but-2-ene in hexane (6.6 M, 45 µL, 297 µmol). The mixture was allowed to stir for 12 h at 22 °C, after which it was exposed to air and the volatiles were carefully removed in vacuo to afford brown oil, which was purified by silica gel chromatography (pentane) to give a mixture of pentane and (*E*)-1-chloro-1-fluorooct-1-ene (80% by weight, accounting for the mass of pentane, 117.0 mg, 0.5686 mmol, 57% yield) in >98:2 *E:Z* ratio. In a N_2-filled glove box, an oven-dried vial was charged with Xphos-Pd-G2 (4.2 mg, 0.0050 mmol), CsF (30.2 mg, 0.2000 mmol), (*E*)-1-chloro-1-fluorooct-1-ene (80% by weight accounting for pentane mass; 20.5 mg, 0.1 mmol), methyl (*E*)-10-fluoro-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dec-9-enoate (45.9 mg, 0.1400 mmol), and dioxane (1.0 mL). The reaction mixture was allowed to stir for 24 h at 95 °C, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was washed with Et_2O (3 x 10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaCl (10 mL), then water (2 x 10 mL), and dried over $MgSO_4$. Removal of the volatiles in vacuo afforded yellow oil, which was purified by silica gel chromatography (hexanes → 9% CH_2Cl_2 in hexanes) to afford **4.111** (18.2 mg, 0.0551 mmol, 55% yield) in >98% *E,Z* ratio as colorless oil. **IR (neat)**: 2924 (s), 2854 (m), 1740 (w), 1643 (s), 1463 (m), 1435 (w), 1261 (w), 1196 (w), 1089 (m), 802 (w); **^{19}F NMR (470 MHz, $CDCl_3$)**: δ −122.2 (t, J = 26.3 Hz), −127.45 (dd, J = 36.6, 28.1 Hz); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 5.37–5.07 (m, 2H), 3.66 (s, 3H), 2.30 (t, J = 7.6 Hz, 2H), 2.19 (dq, J = 15.2, 7.8 Hz, 4H), 1.66–1.59 (m, 4H), 1.43–1.29 (m, 14H), 0.89 (t, J = 6.7 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 174.4, 149.3 (d, J = 233.5 Hz), 149.1 (d, J = 235.8 Hz), 110.8 (d, J = 13.7 Hz), 110.4 (d, J = 21.5 Hz), 51.6, 34.2, 31.7, 30.1, 29.8,

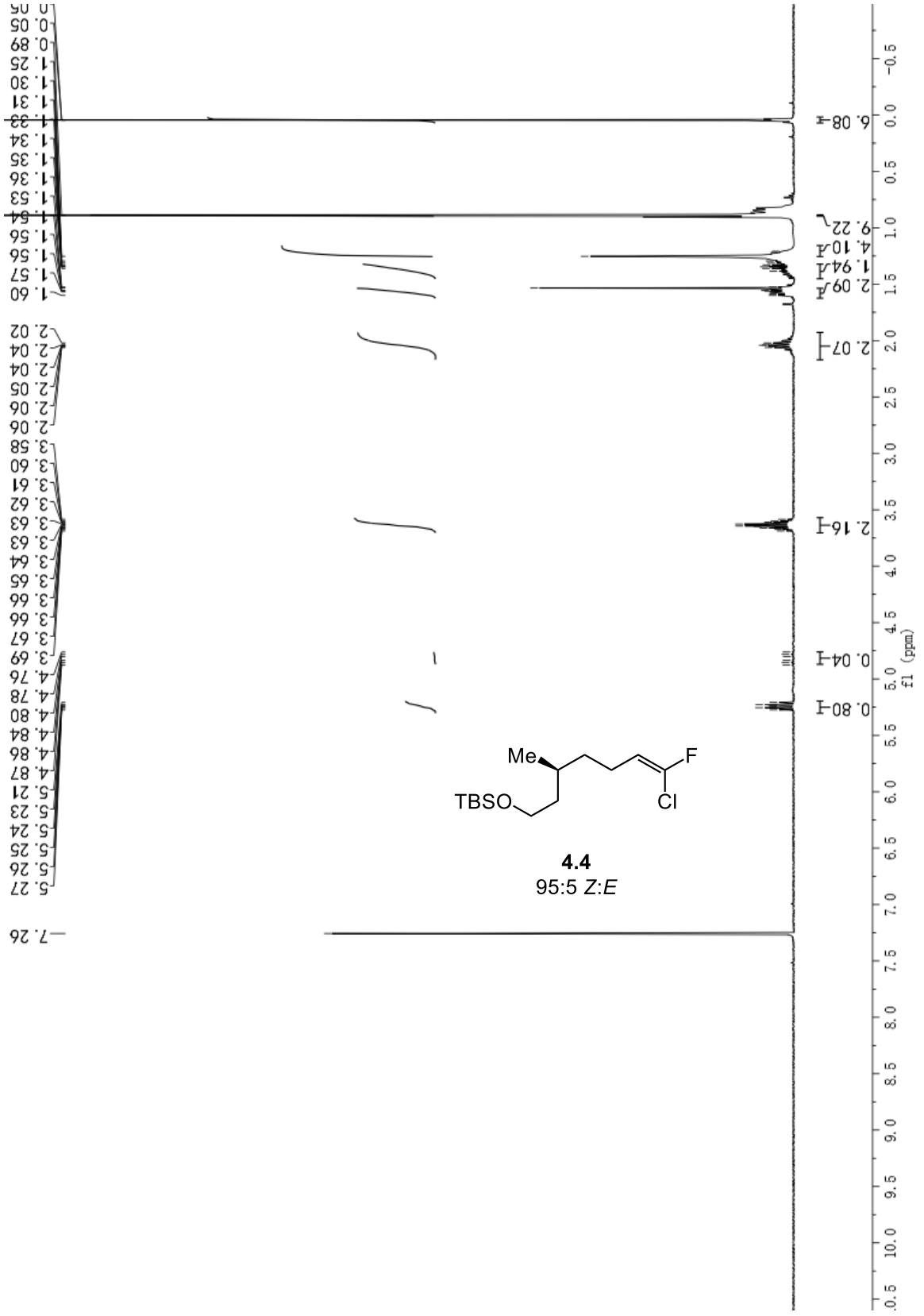
29.2, 29.2, 29.1, 29.0, 25.0, 24.5, 23.7, 22.7, 14.2; **HRMS[M+NH$_4$]$^+$**: Calcd for $C_{19}H_{36}F_2O_2N$: 348.2708, found: 348.2710.

^{19}F NMR Spectrum of 4.4

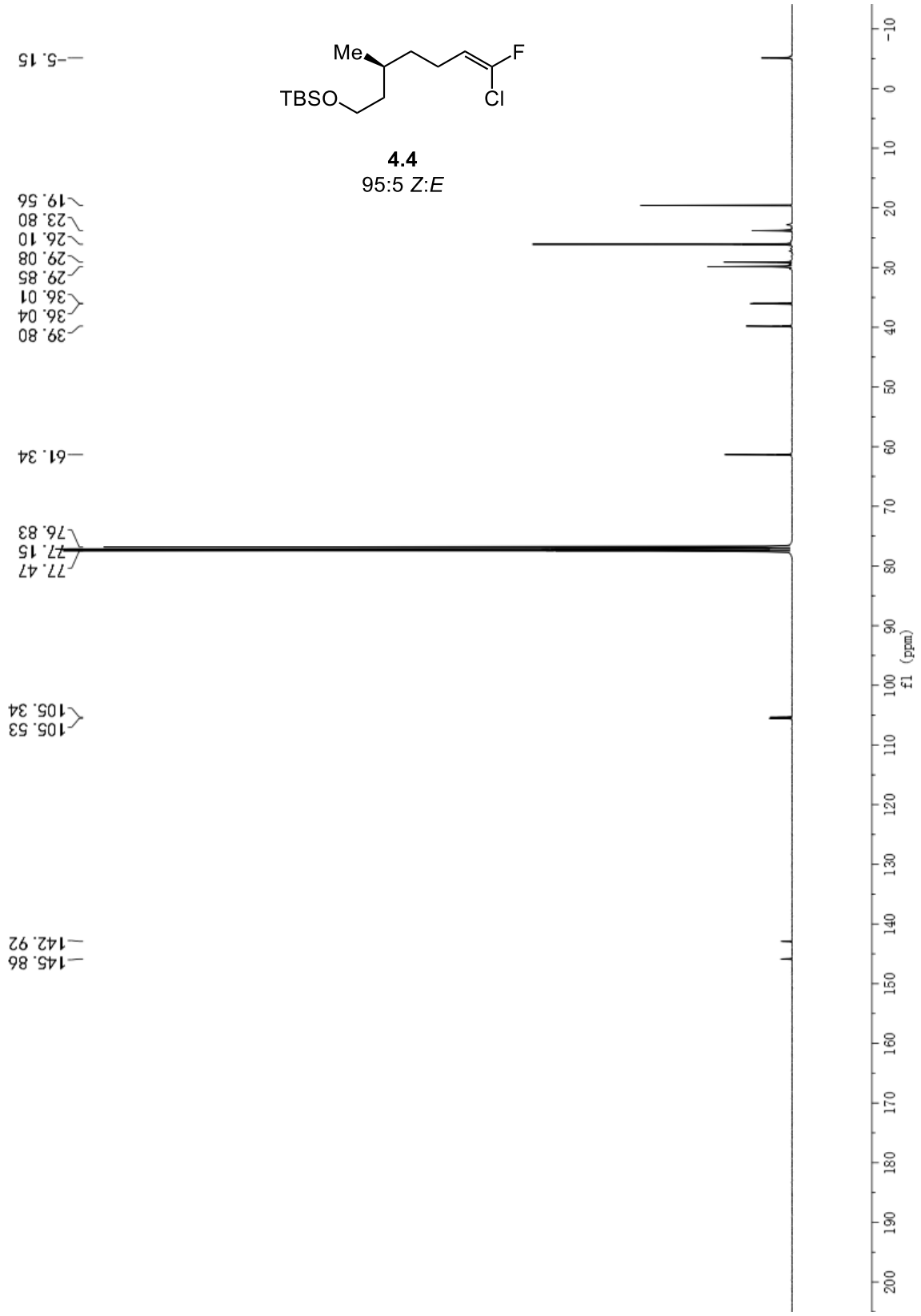


4.4
95:5 *Z*:*E*

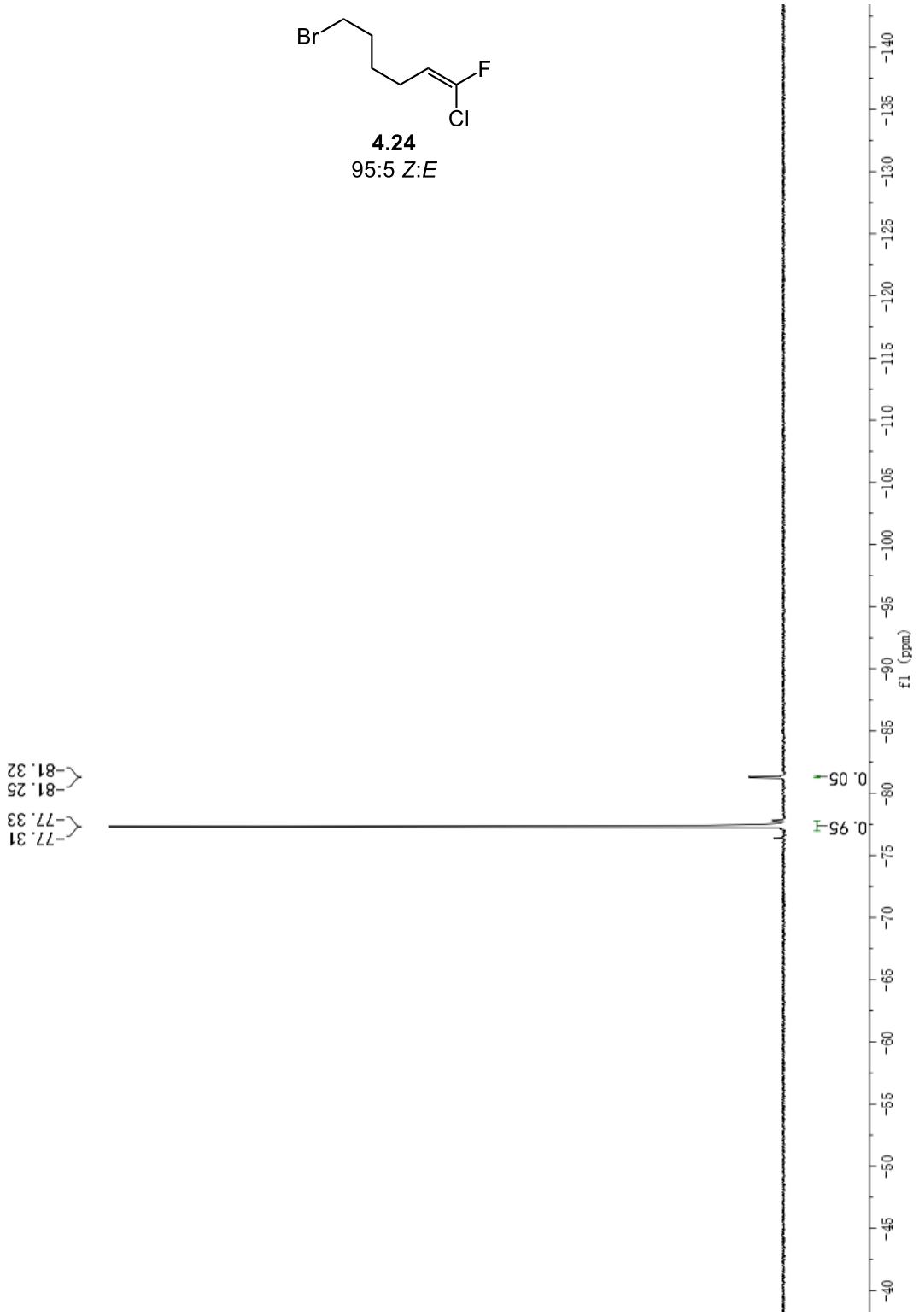
^{1}H NMR Spectrum of 4.4



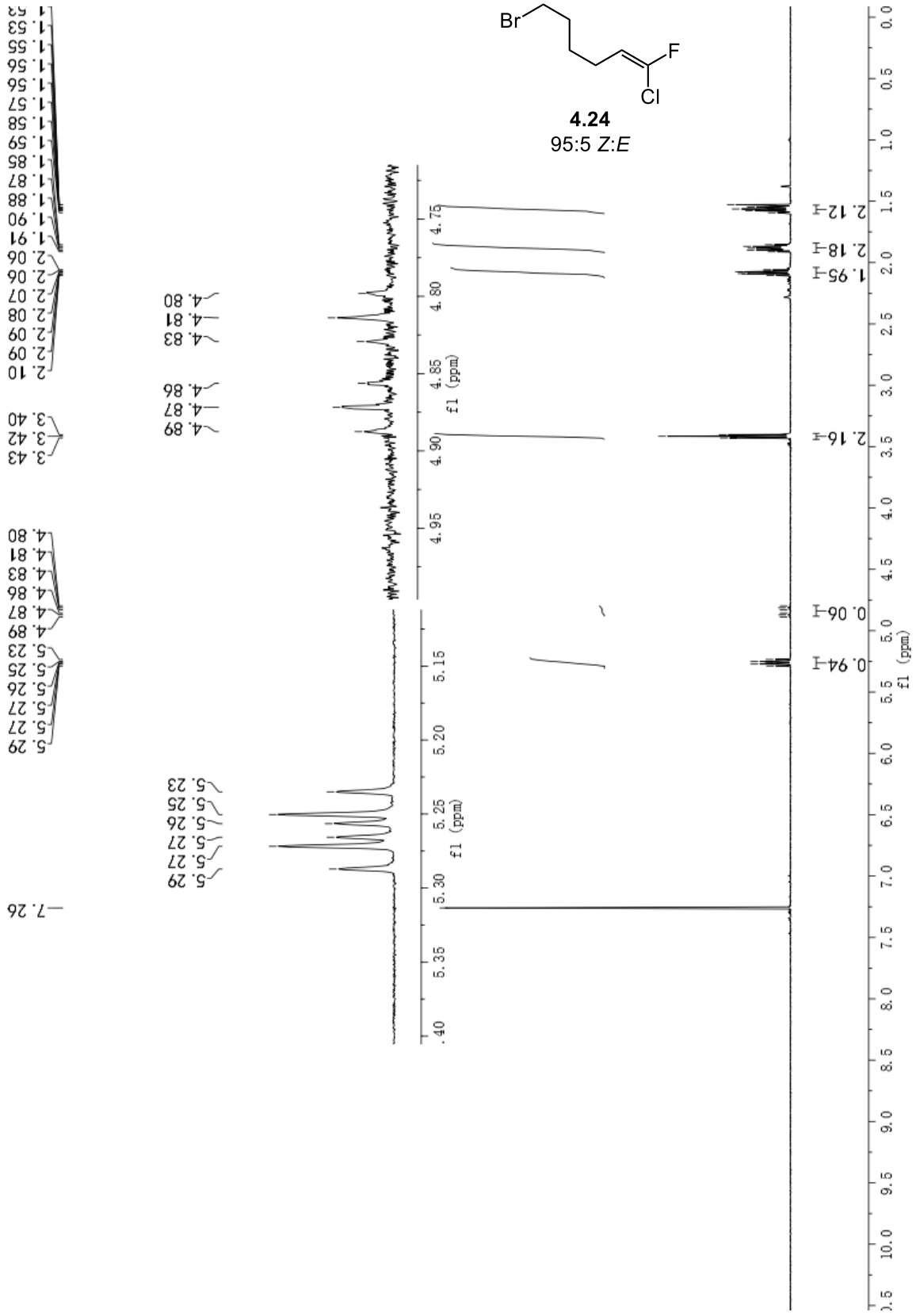
^{13}C NMR Spectrum of 4.4



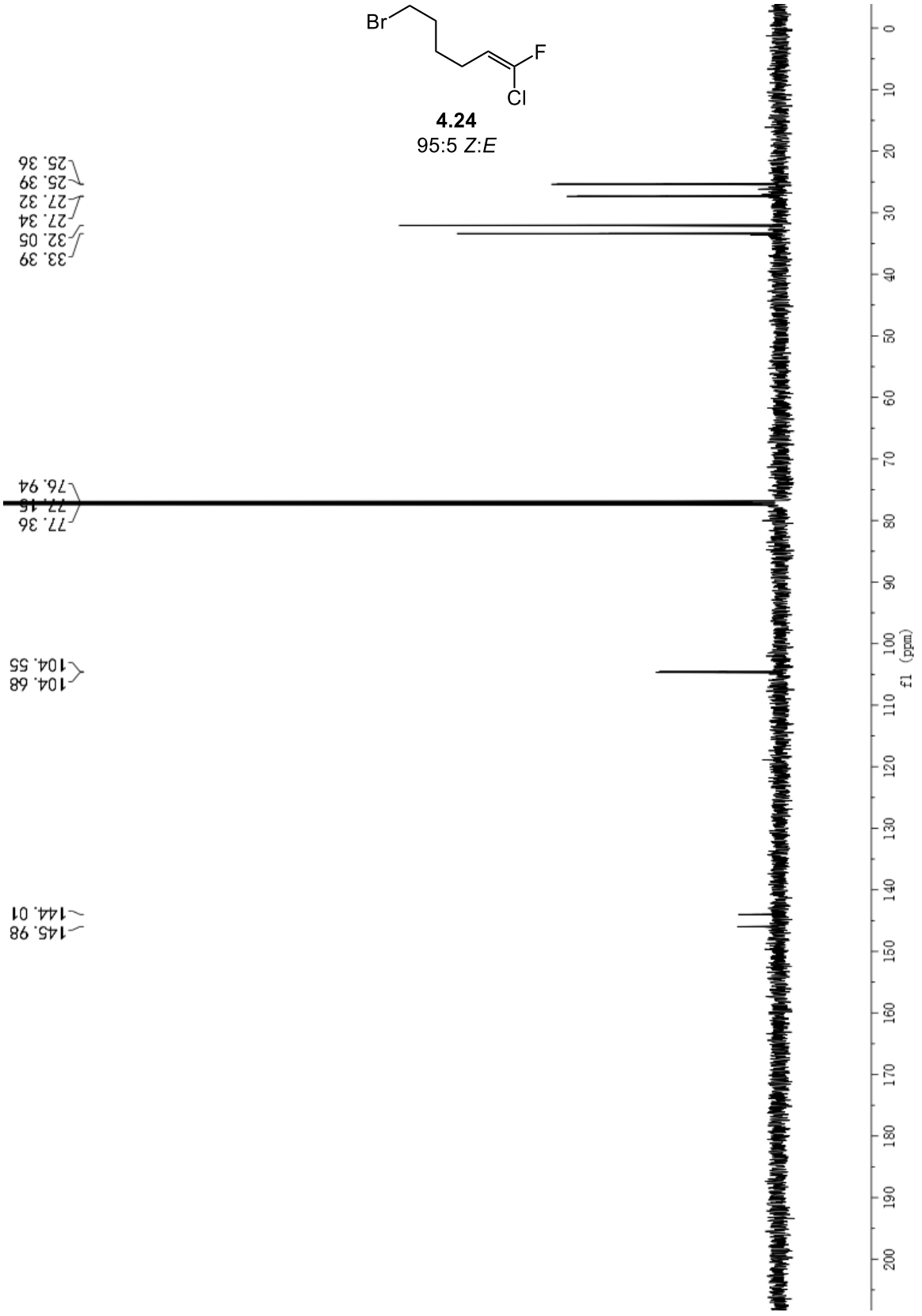
^{19}F NMR Spectrum of 4.24



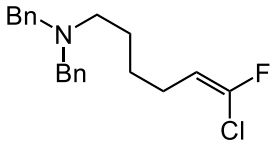
^{1}H NMR Spectrum of 4.24



^{13}C NMR Spectrum of 4.24

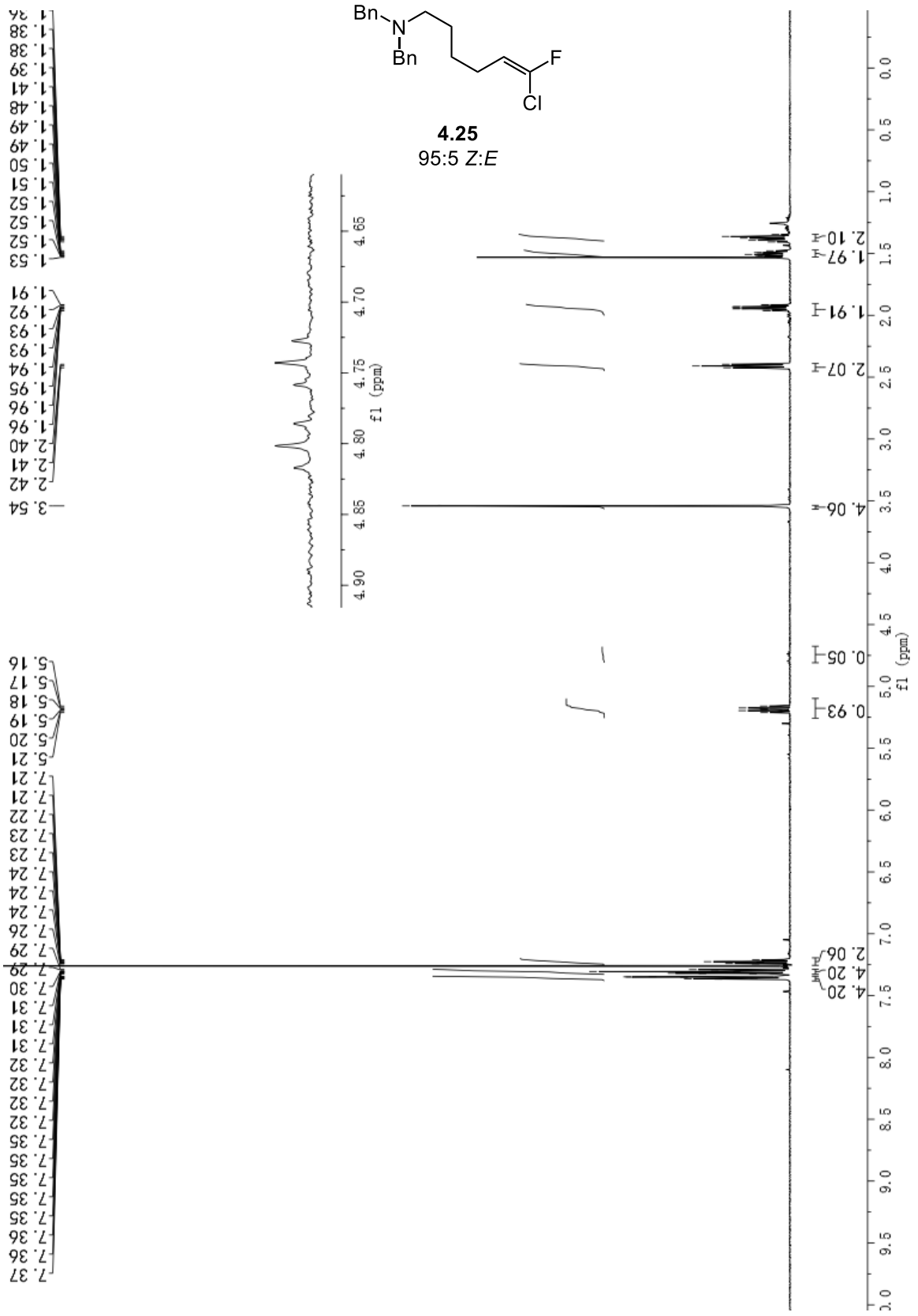


^{19}F NMR Spectrum of 4.25

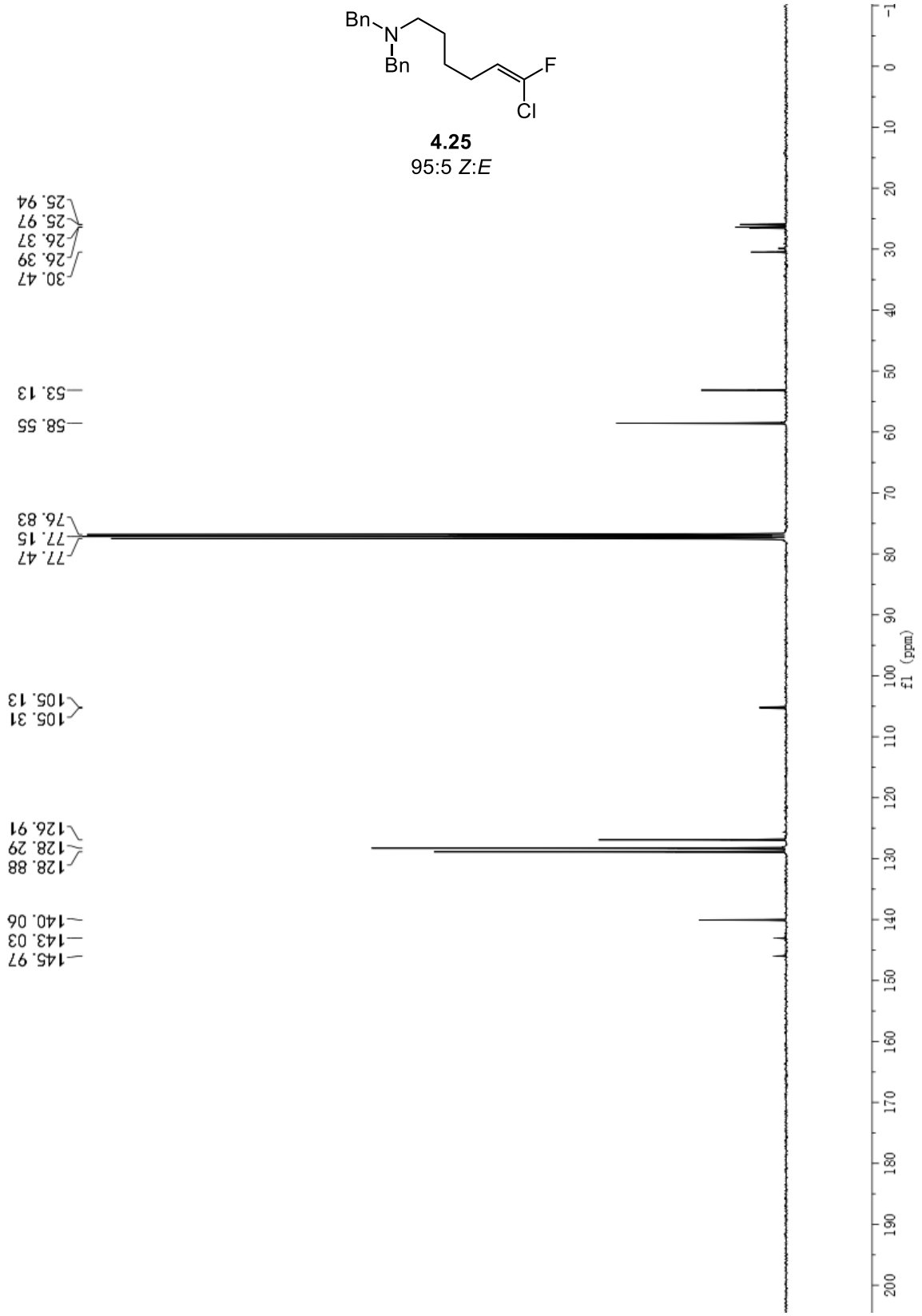


4.25
95:5 *Z*:*E*

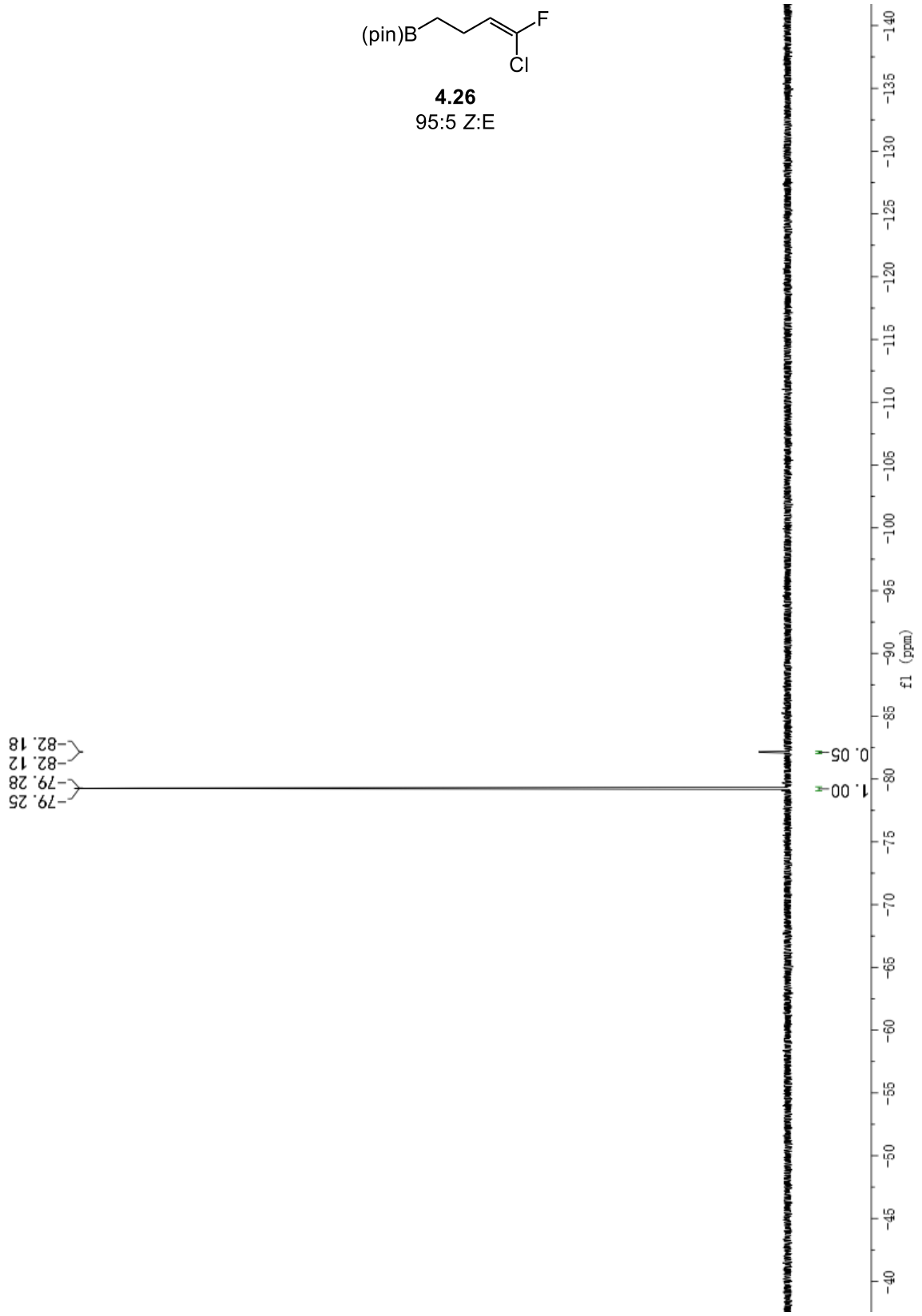
^{1}H NMR Spectrum of 4.25



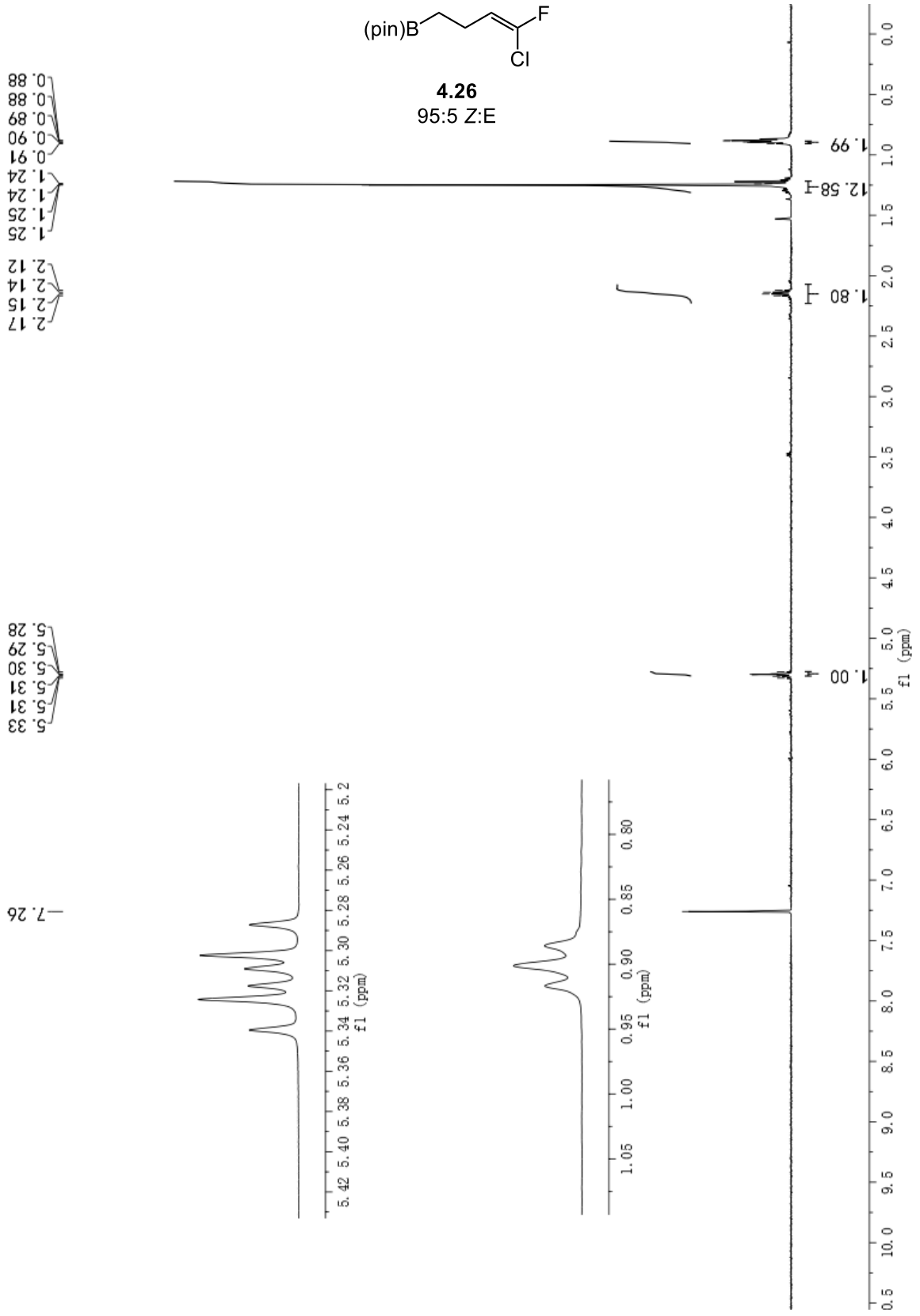
^{13}C NMR Spectrum of 4.25



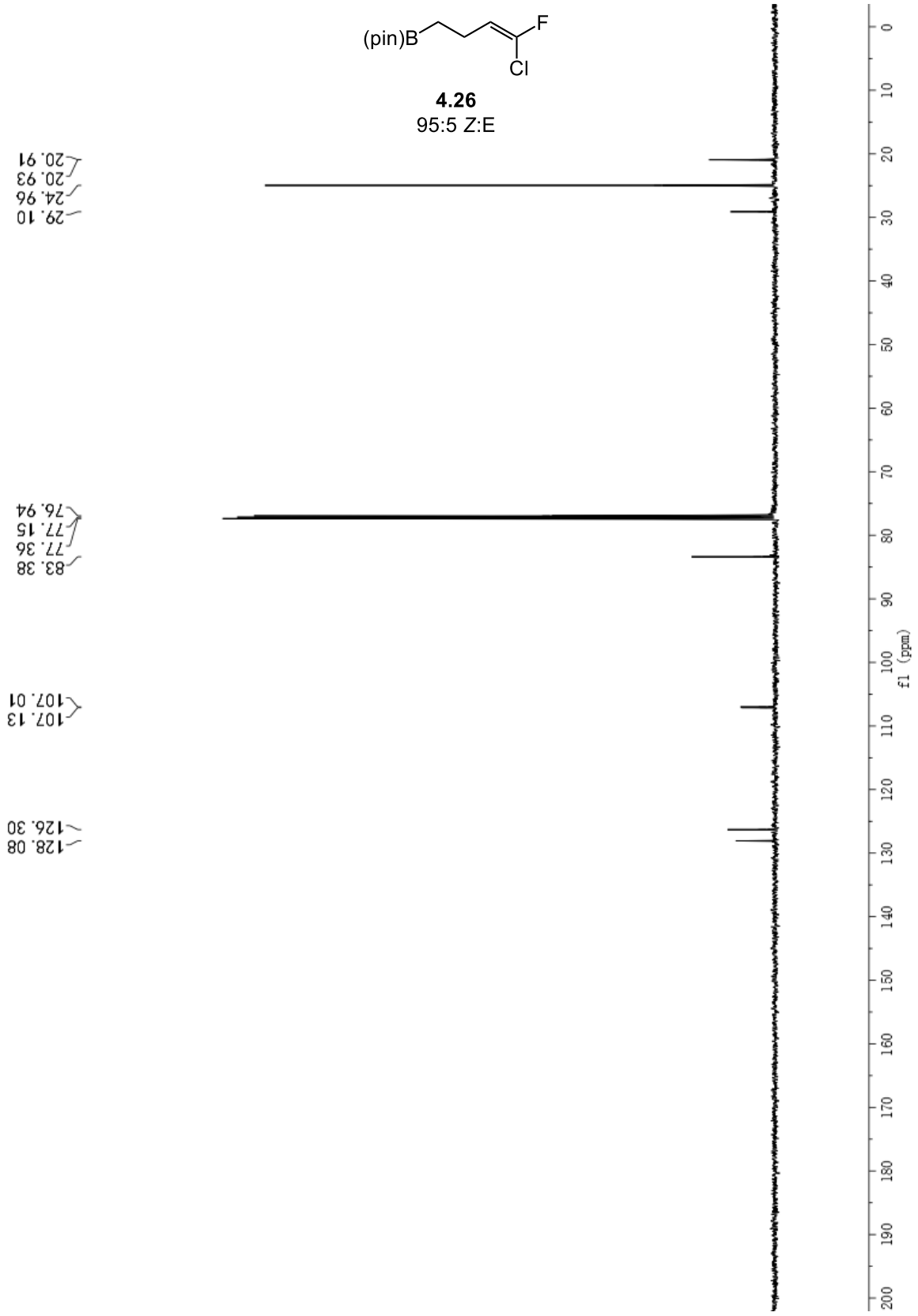
^{19}F NMR Spectrum of 4.26



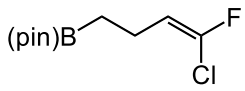
^{1}H NMR Spectrum of 4.26



^{13}C NMR Spectrum of 4.26

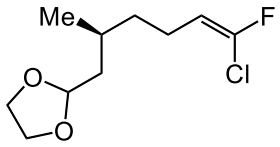


^{11}B NMR Spectrum of 4.26



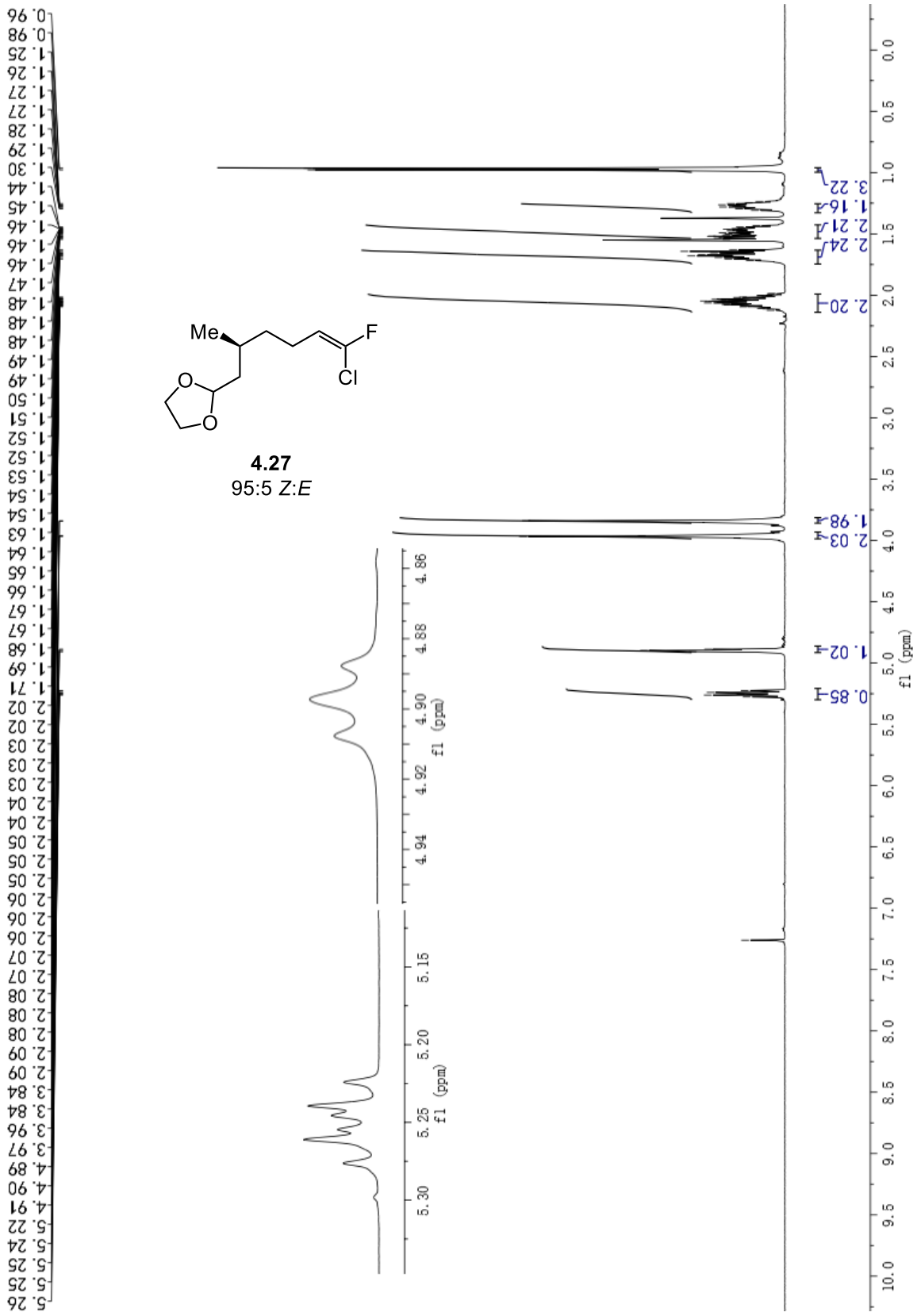
4.26
95:5 Z:E

^{19}F NMR Spectrum of 4.27

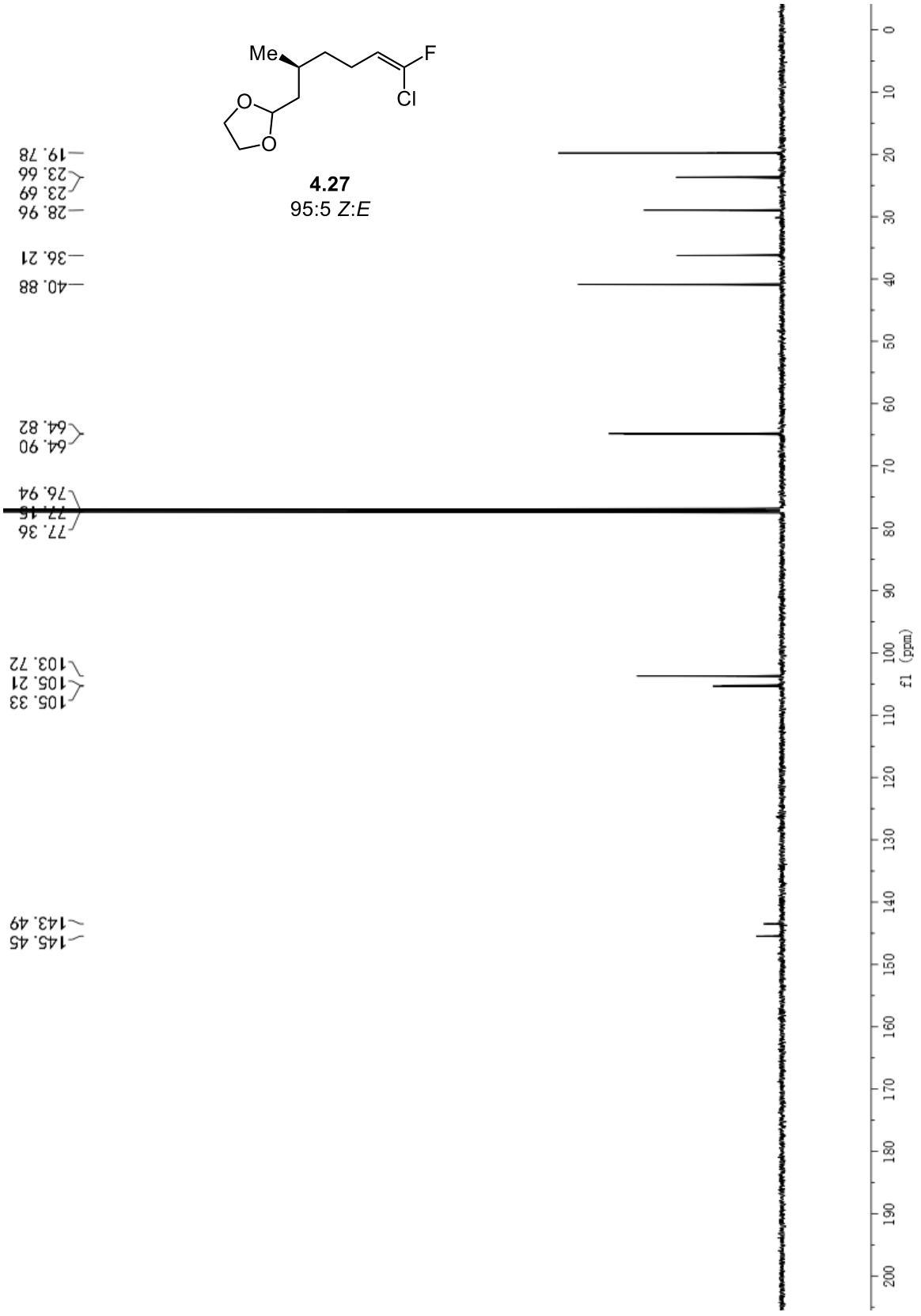


4.27
95:5 *Z*:*E*

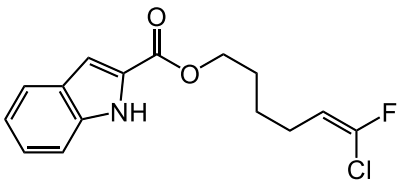
^{1}H NMR Spectrum of 4.27



^{13}C NMR Spectrum of 4.27

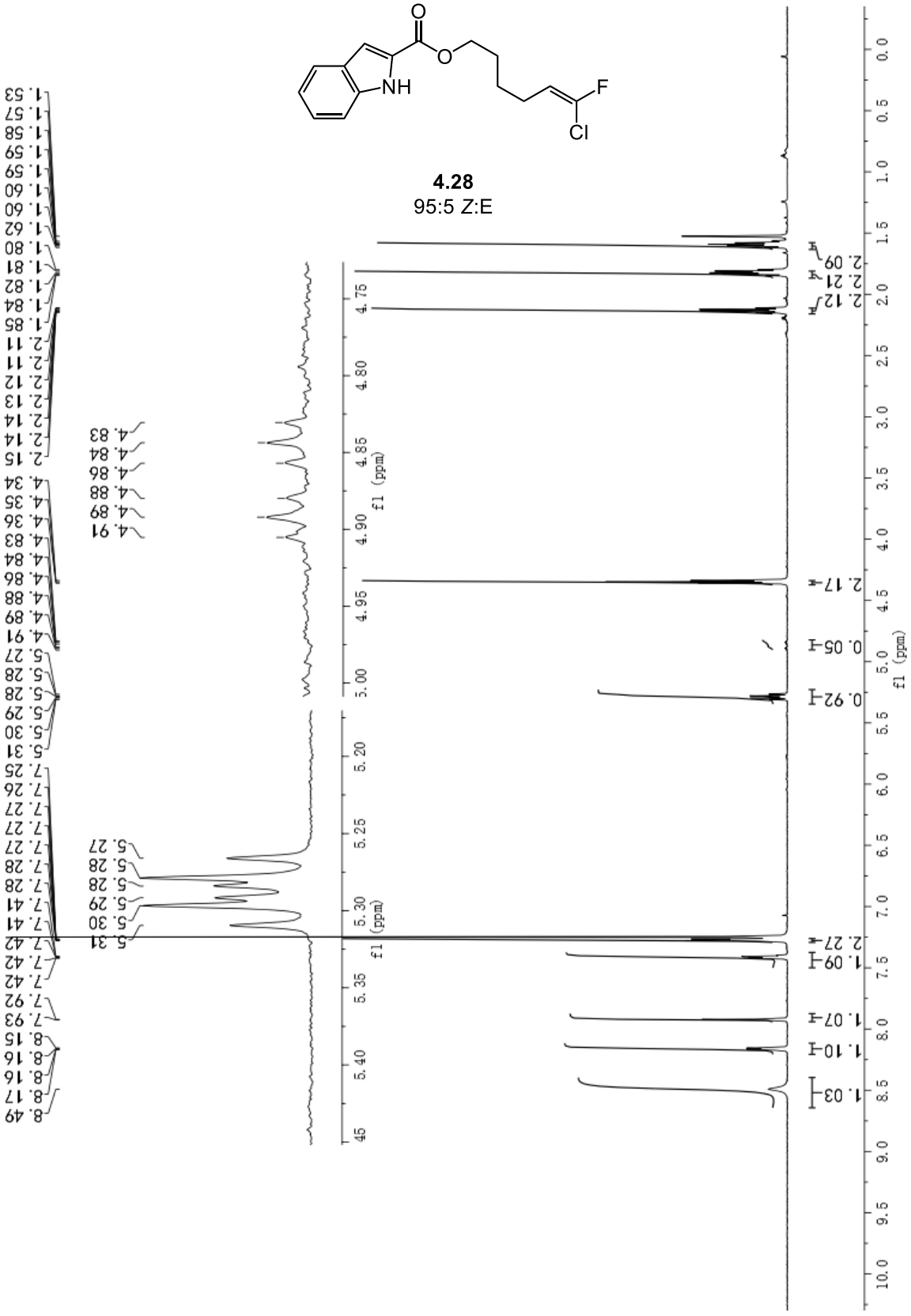


^{19}F NMR Spectrum of 4.28

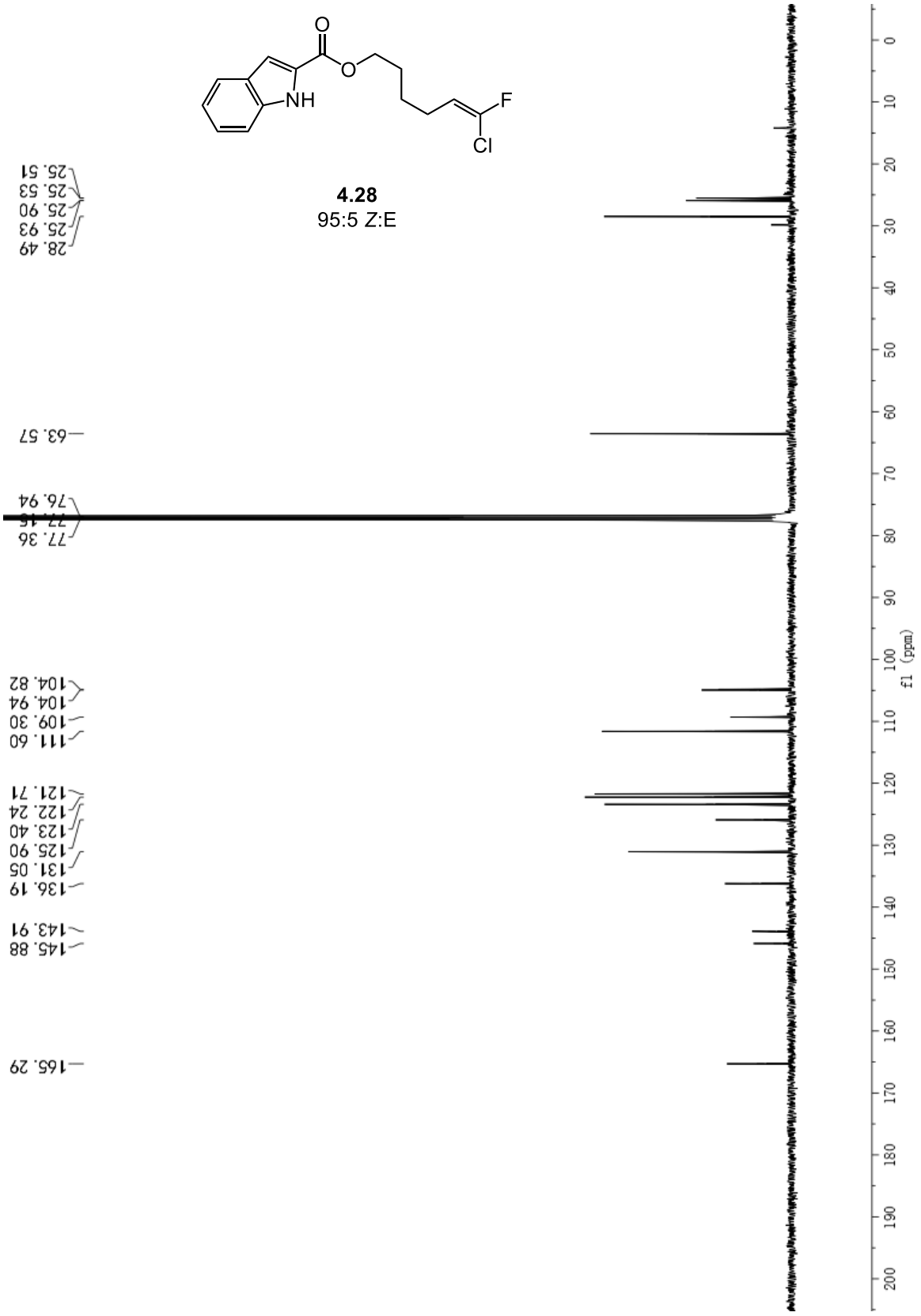


4.28
95:5 Z:E

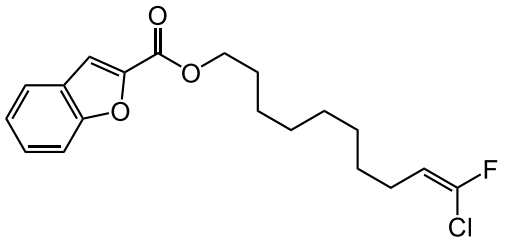
^{1}H NMR Spectrum of 4.28



^{13}C NMR Spectrum of 4.28

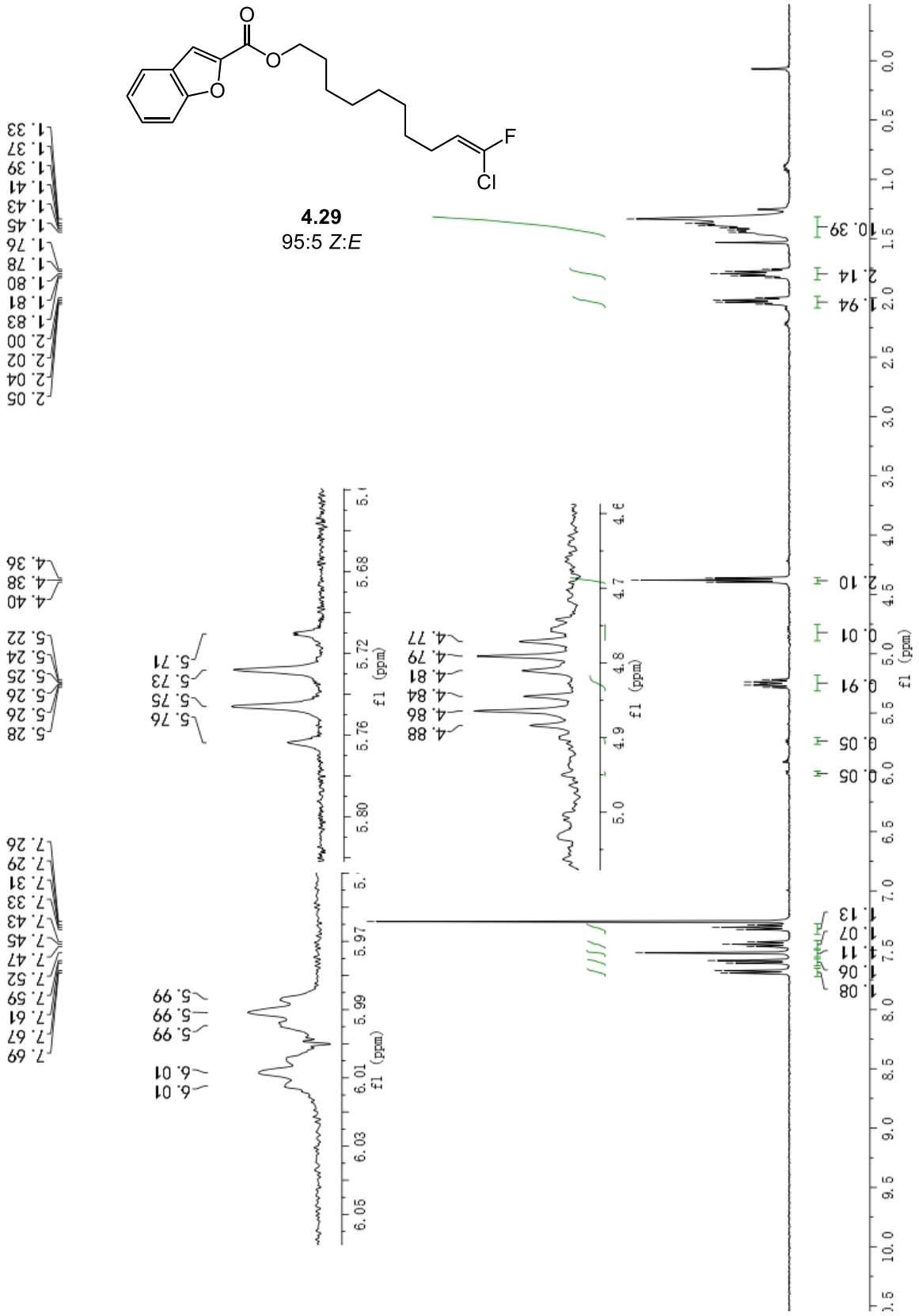


^{19}F NMR Spectrum of 4.29

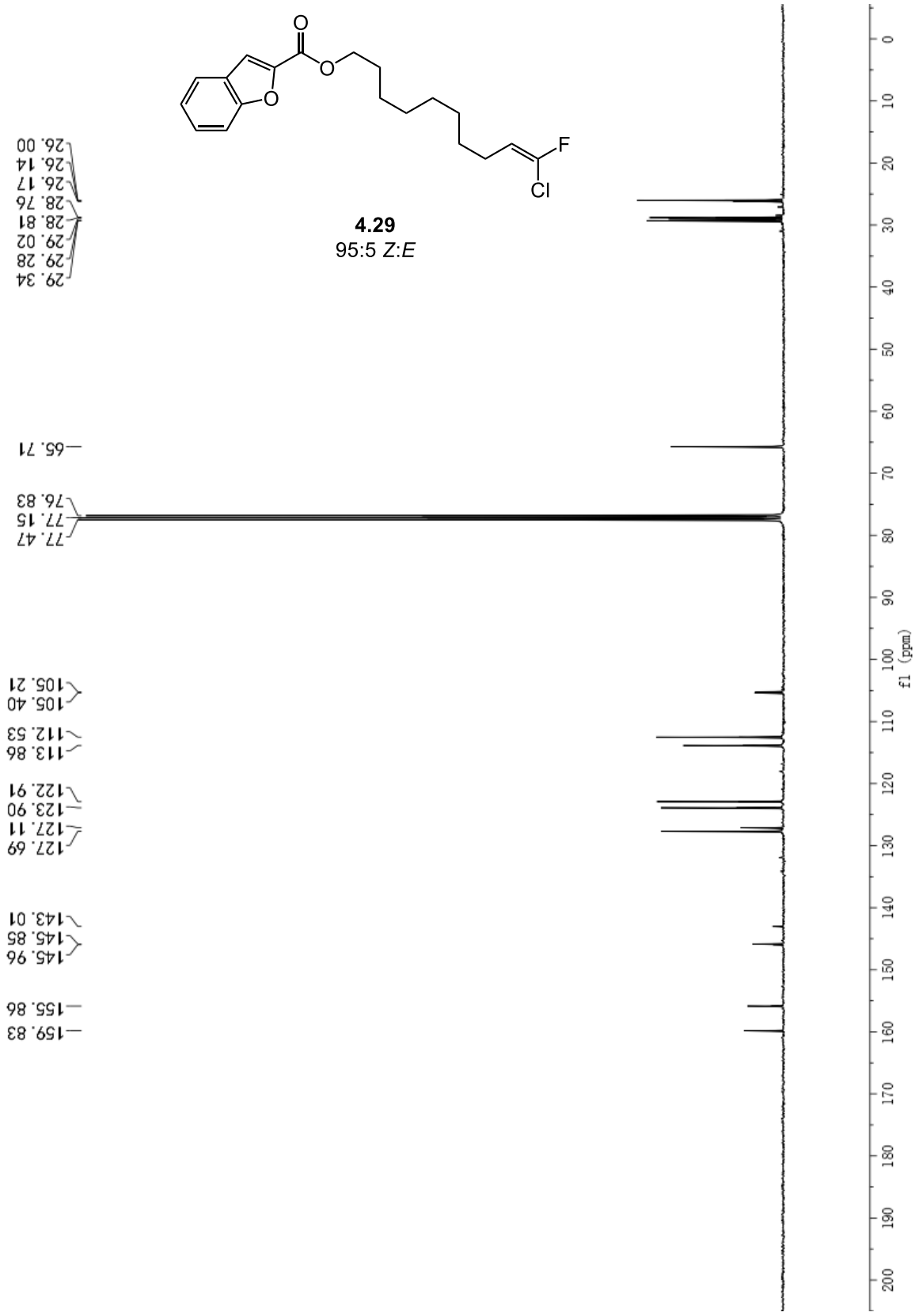


4.29
95:5 *Z*:*E*

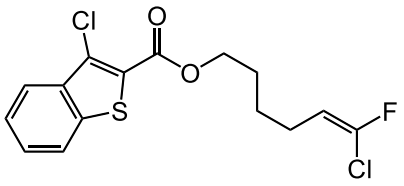
^{1}H NMR Spectrum of 4.29



^{13}C NMR Spectrum of 4.29

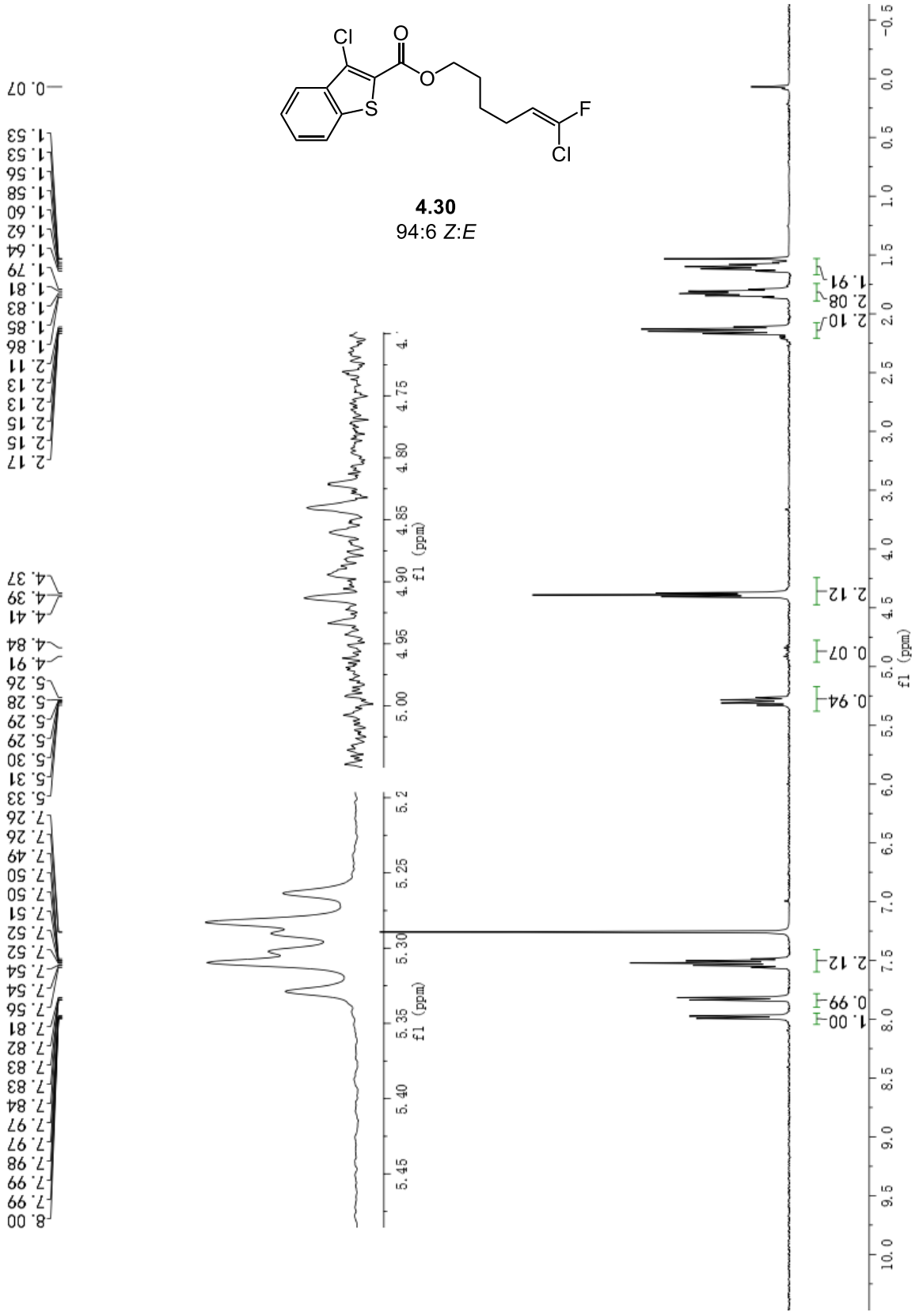


^{19}F NMR Spectrum of 4.30

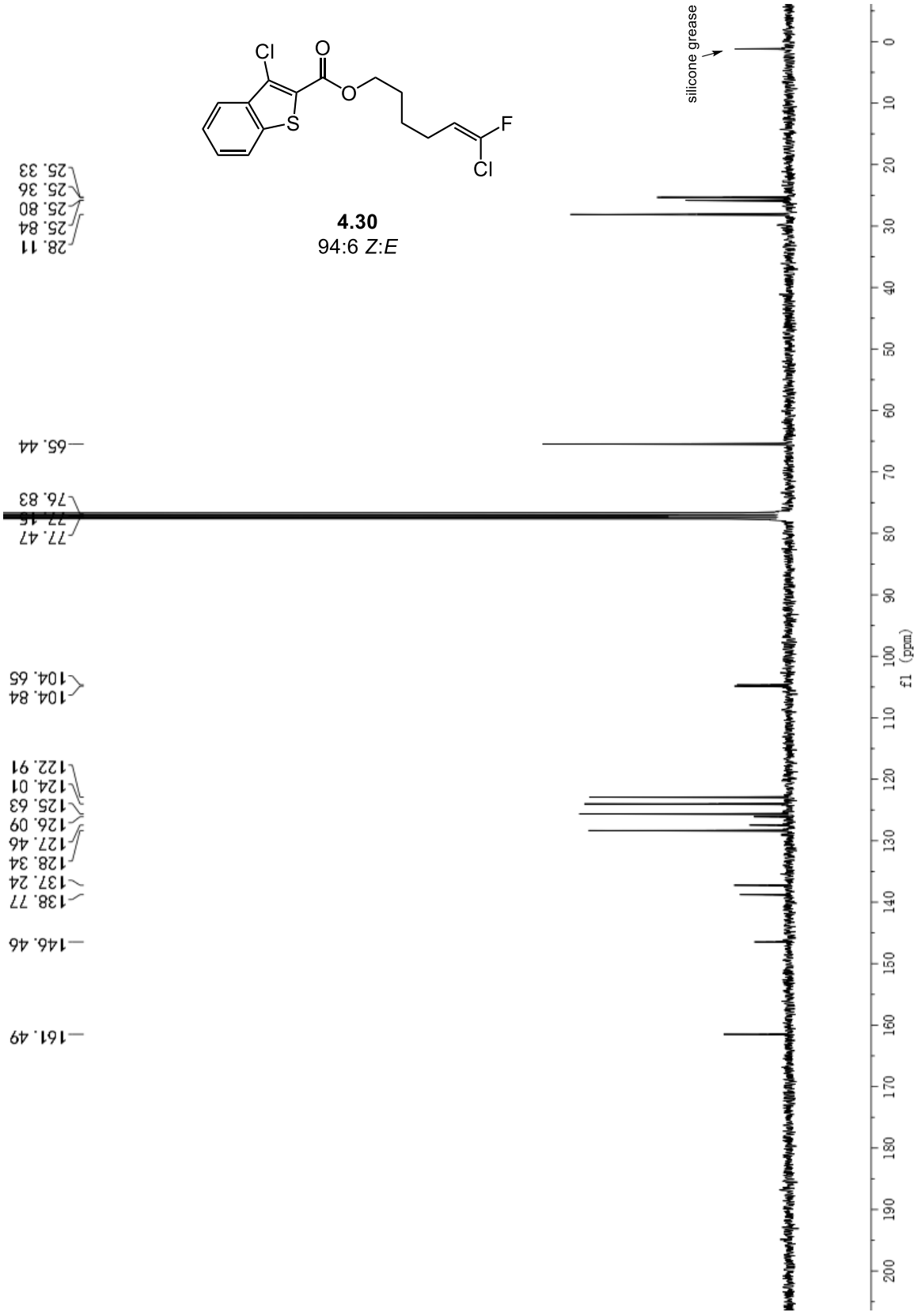


4.30
94:6 *Z*:*E*

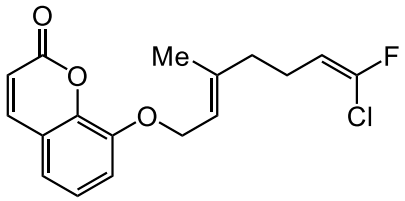
^{1}H NMR Spectrum of 4.30



^{13}C NMR Spectrum of 4.30

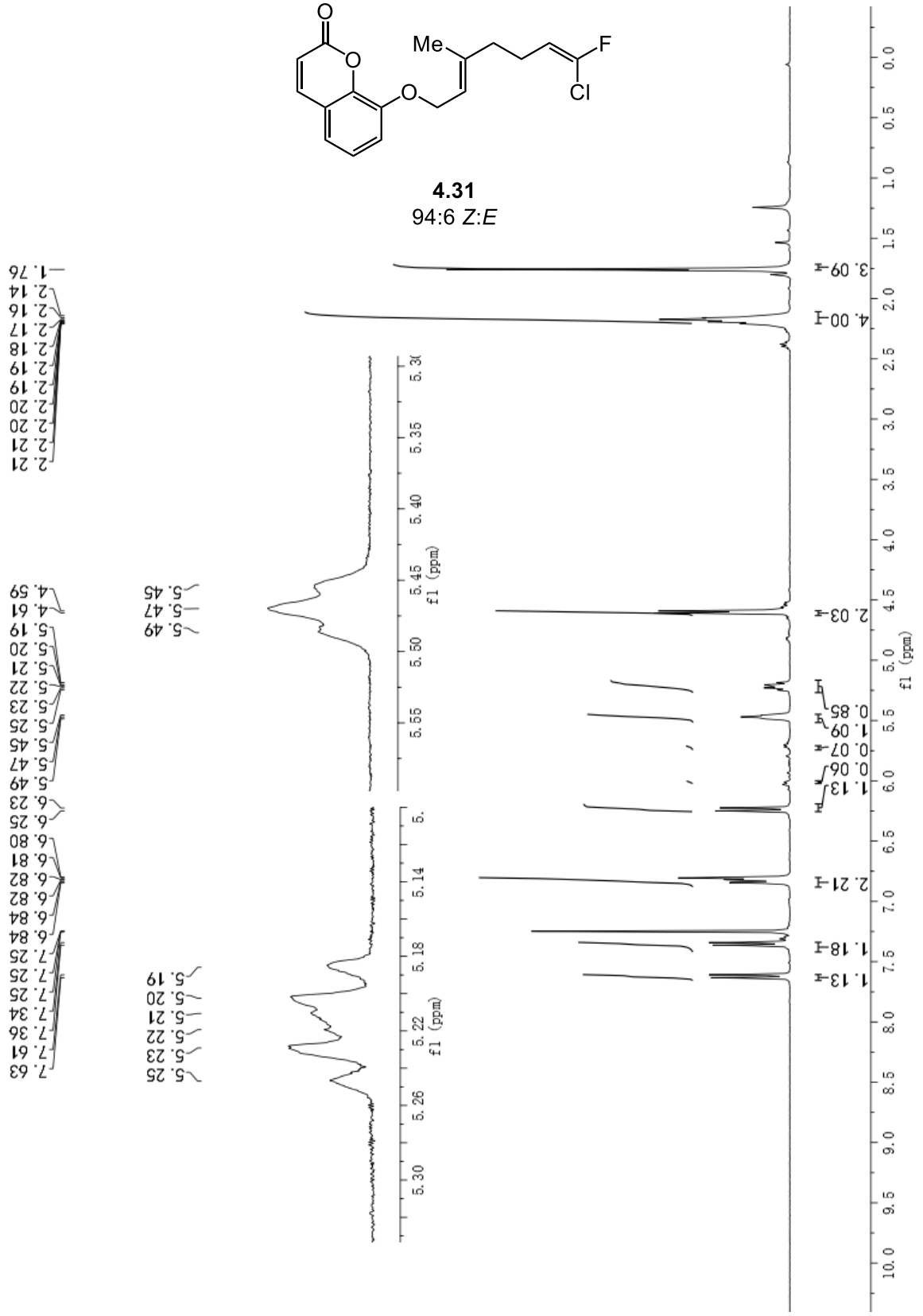


^{19}F NMR Spectrum of 4.31

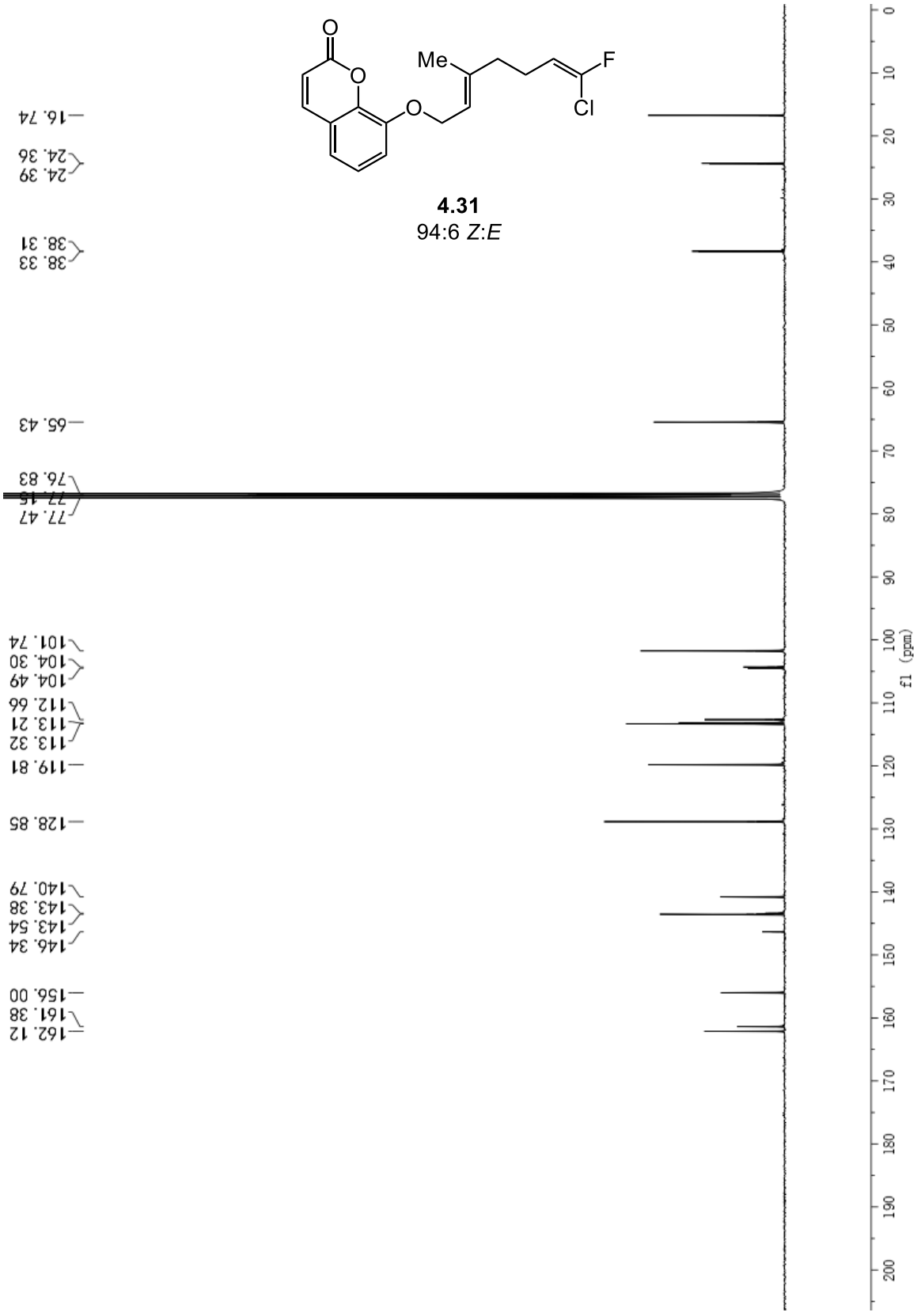


4.31
94:6 *Z*:*E*

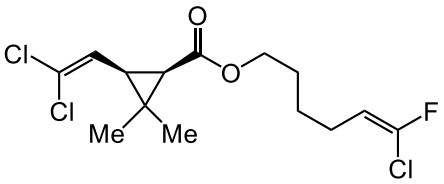
^{1}H NMR Spectrum of 4.31



^{13}C NMR Spectrum of 4.31

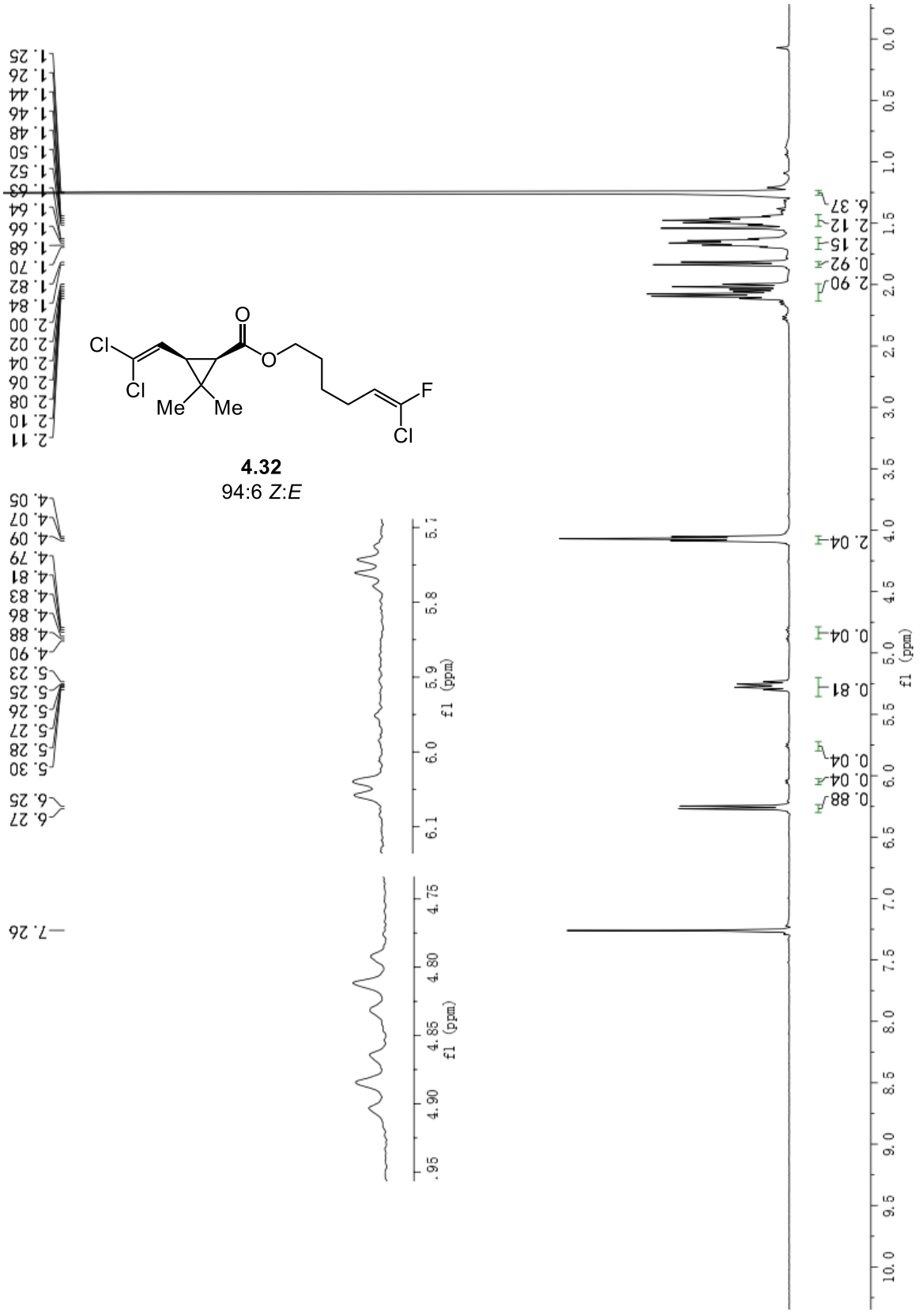


^{19}F NMR Spectrum of 4.32



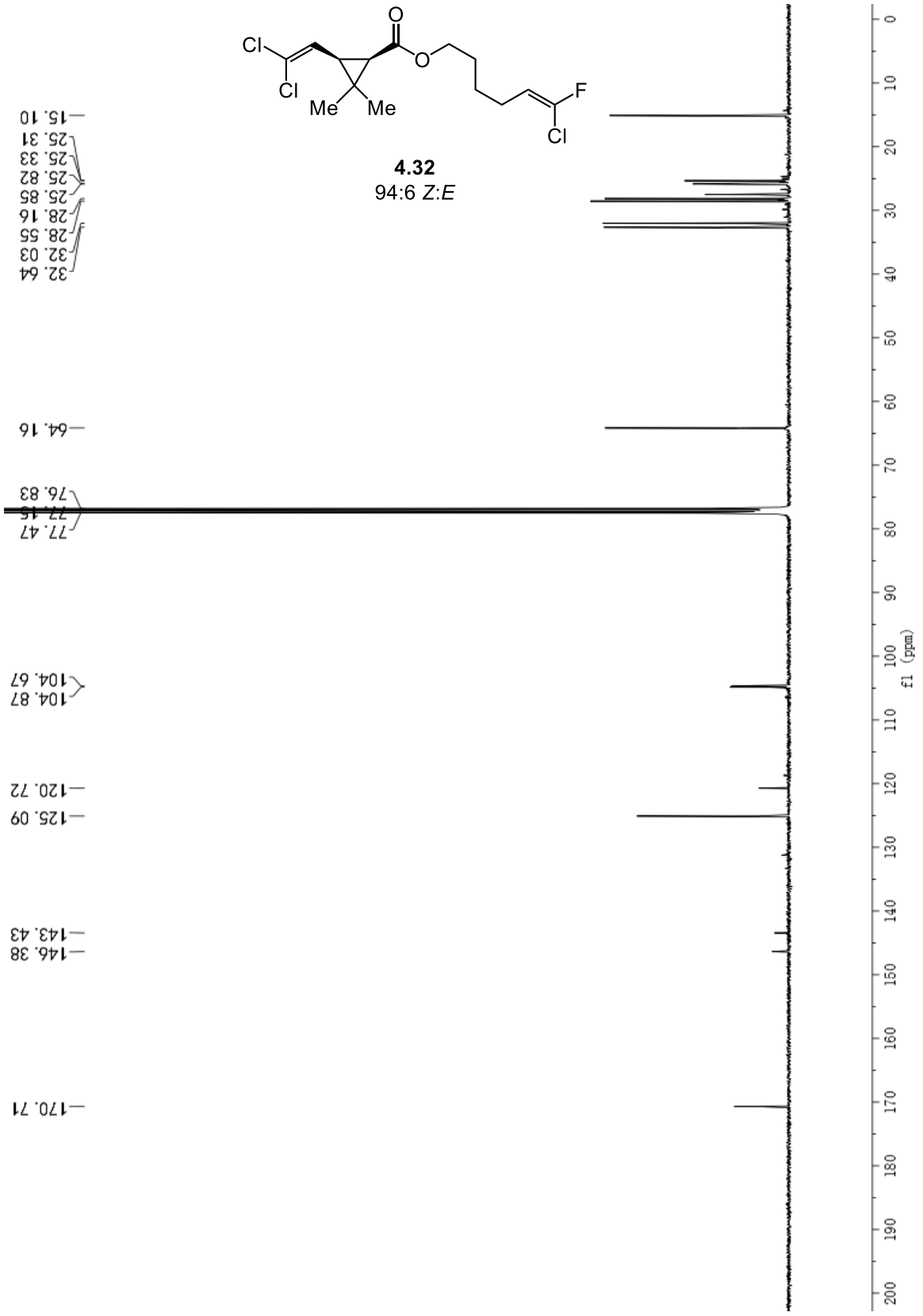
4.32
94:6 *Z*:*E*

^{1}H NMR Spectrum of 4.32

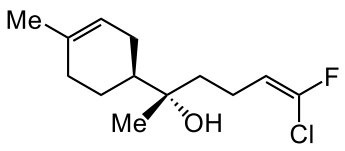


4.32
94:6 *Z*:*E*

^{13}C NMR Spectrum of 4.32

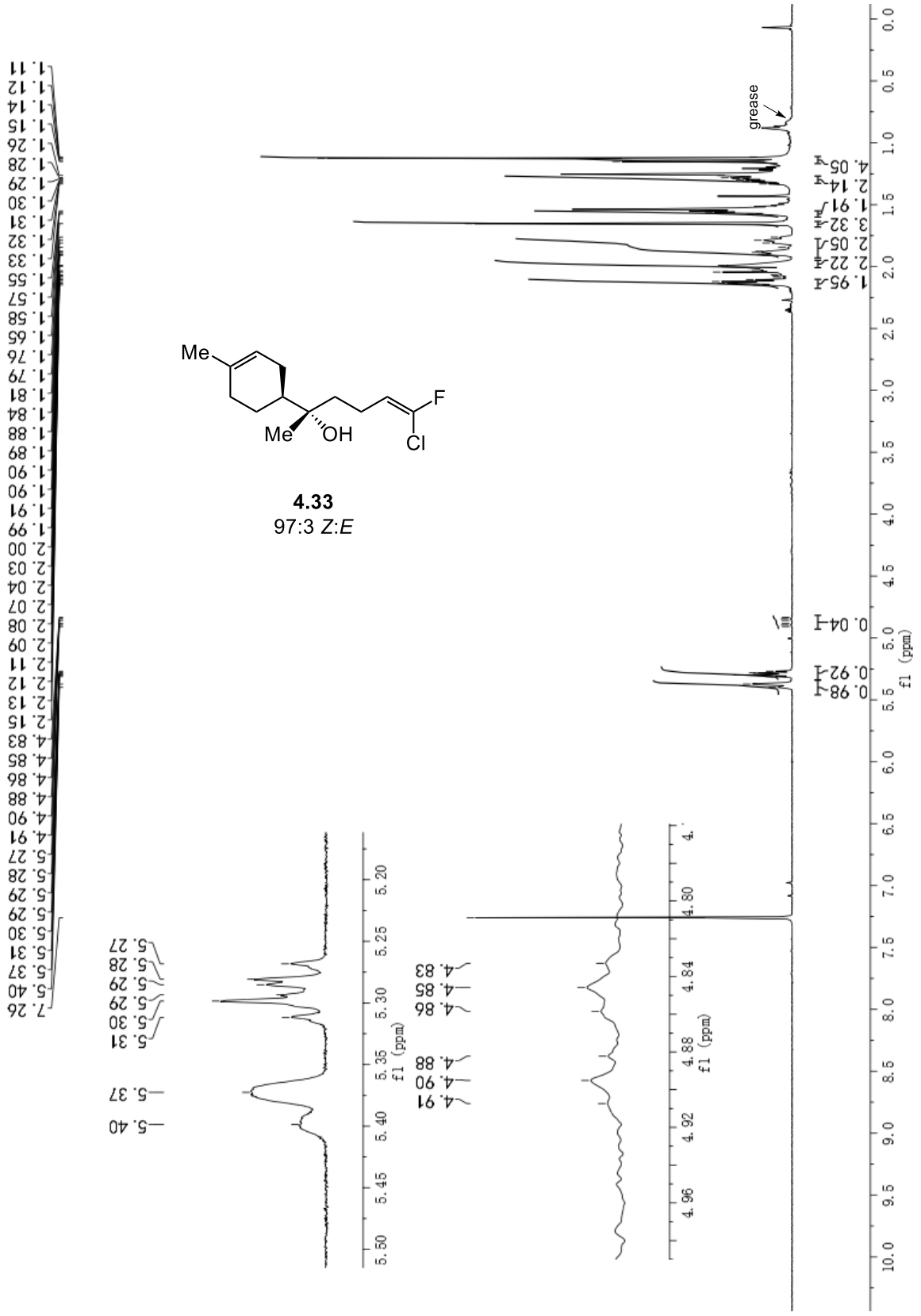


^{19}F NMR Spectrum of 4.33



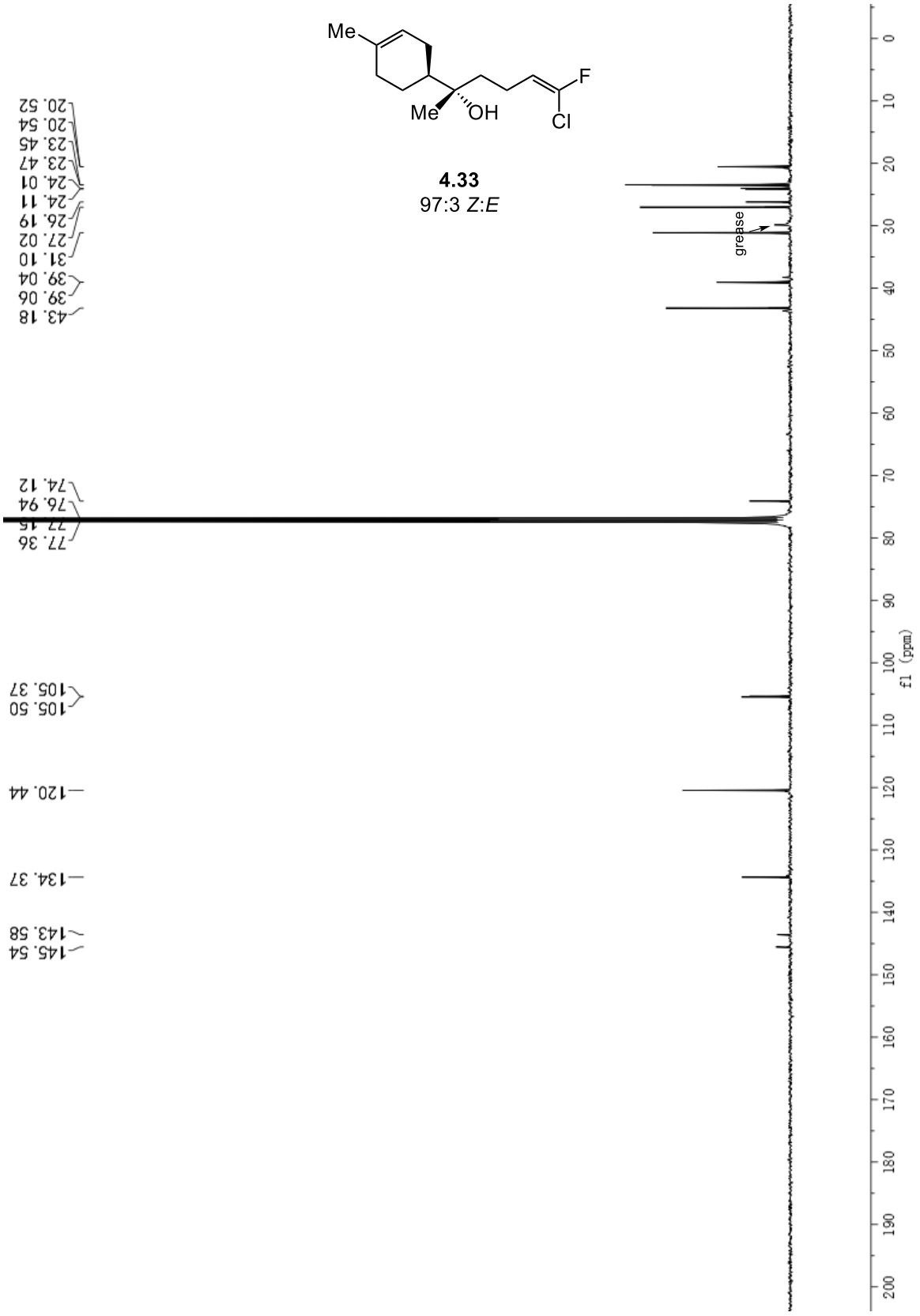
4.33
97:3 *Z*:*E*

^{1}H NMR Spectrum of 4.33

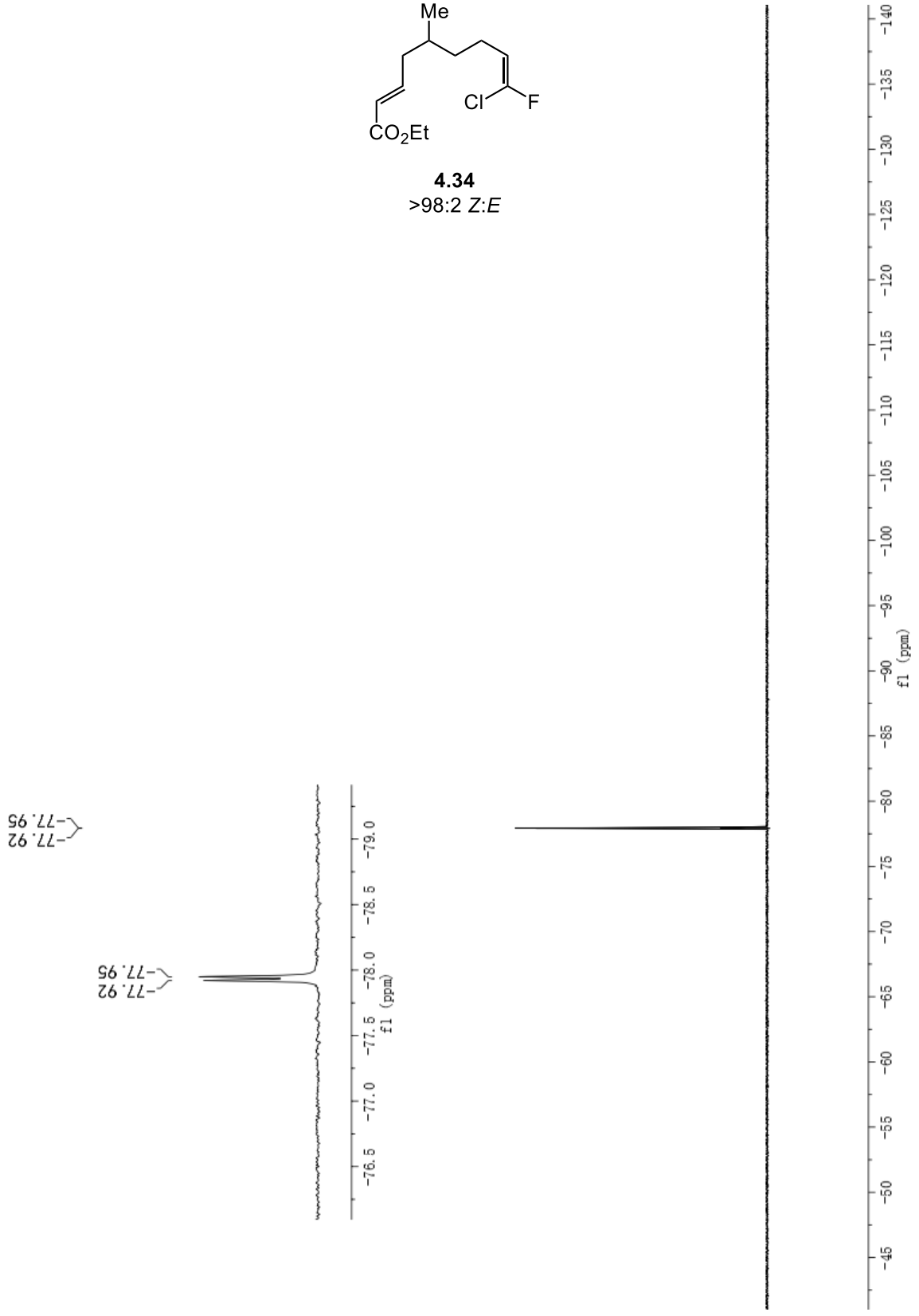


4.33
97:3 *Z*:*E*

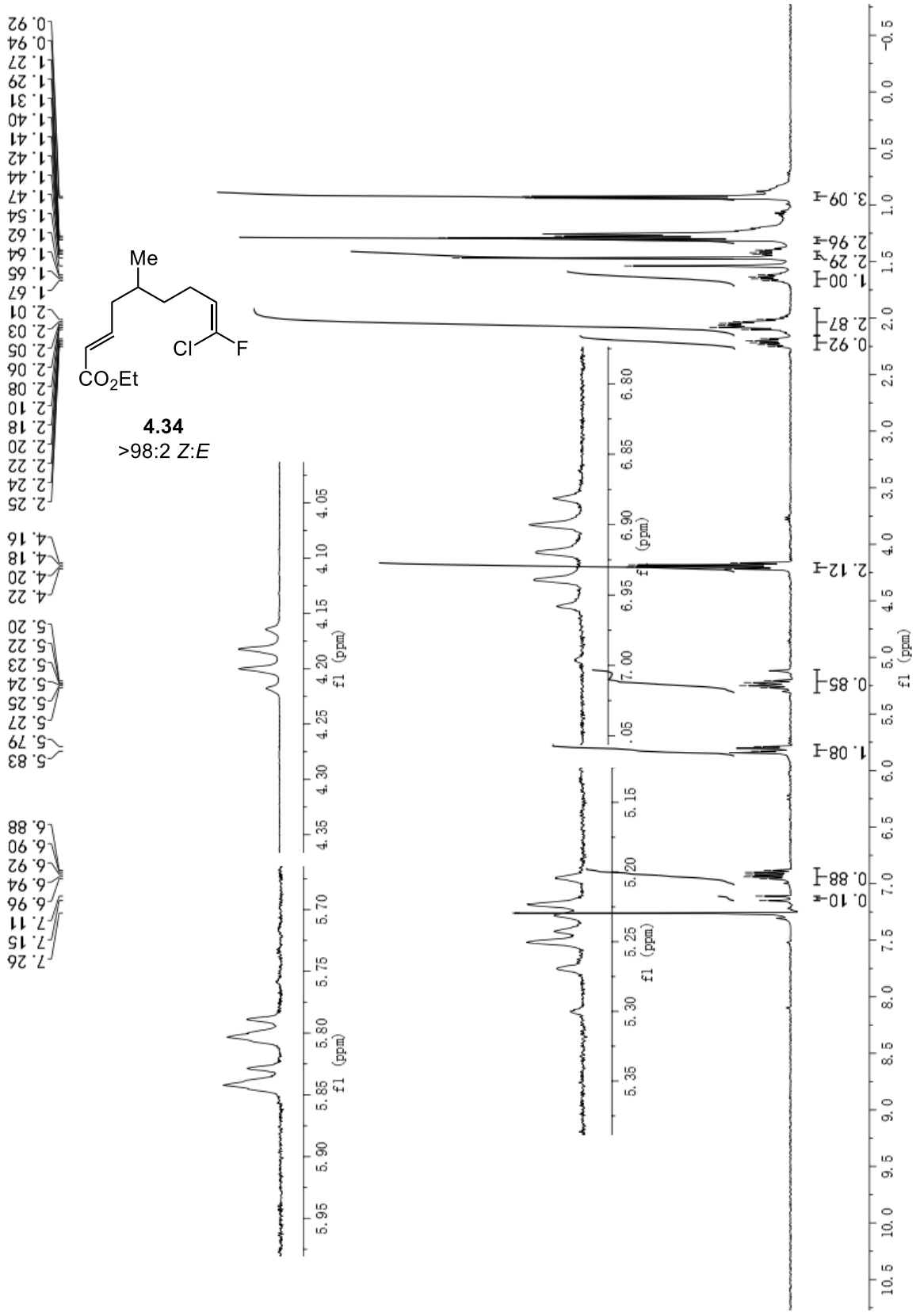
^{13}C NMR Spectrum of 4.33



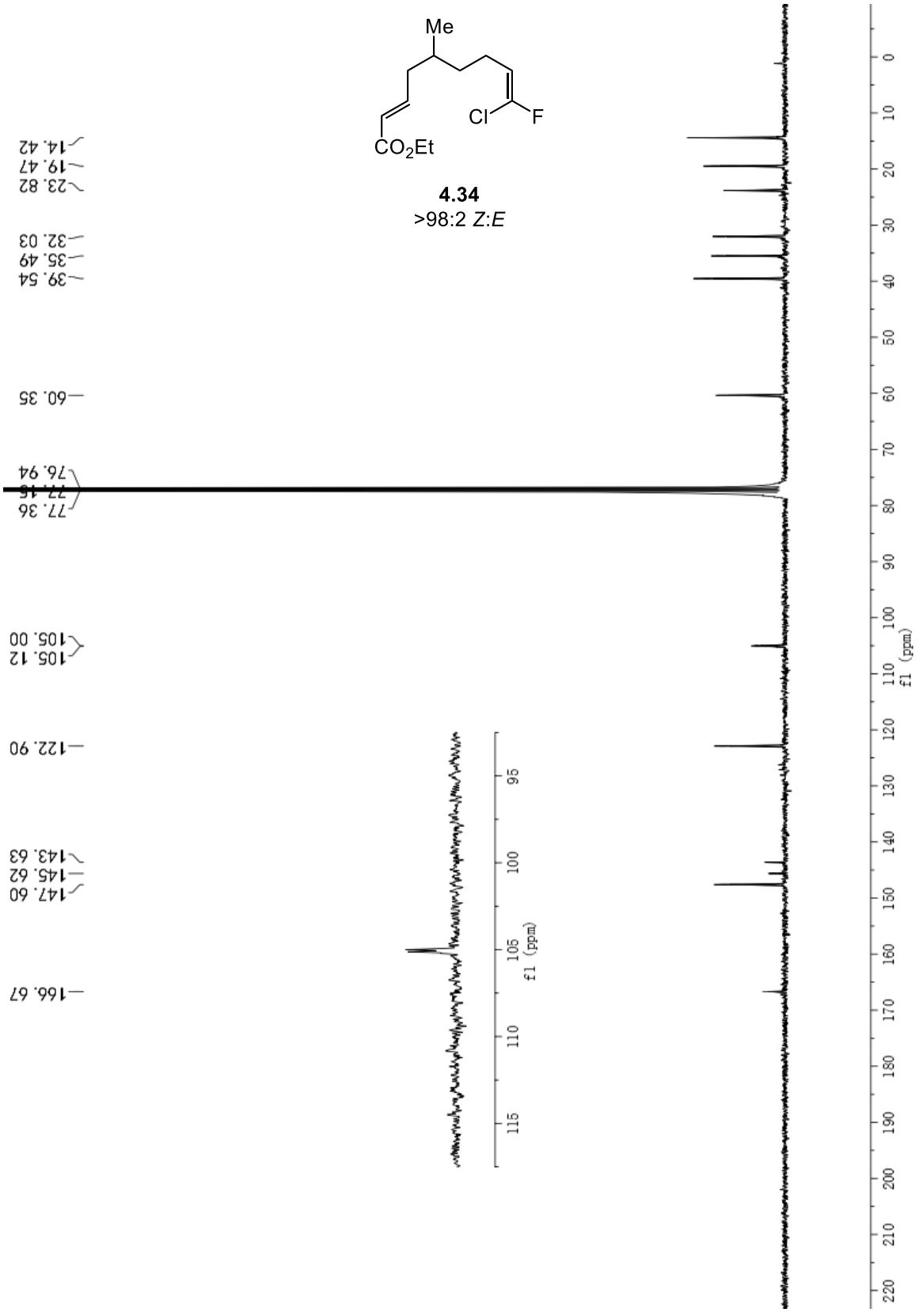
^{19}F NMR Spectrum of 4.34



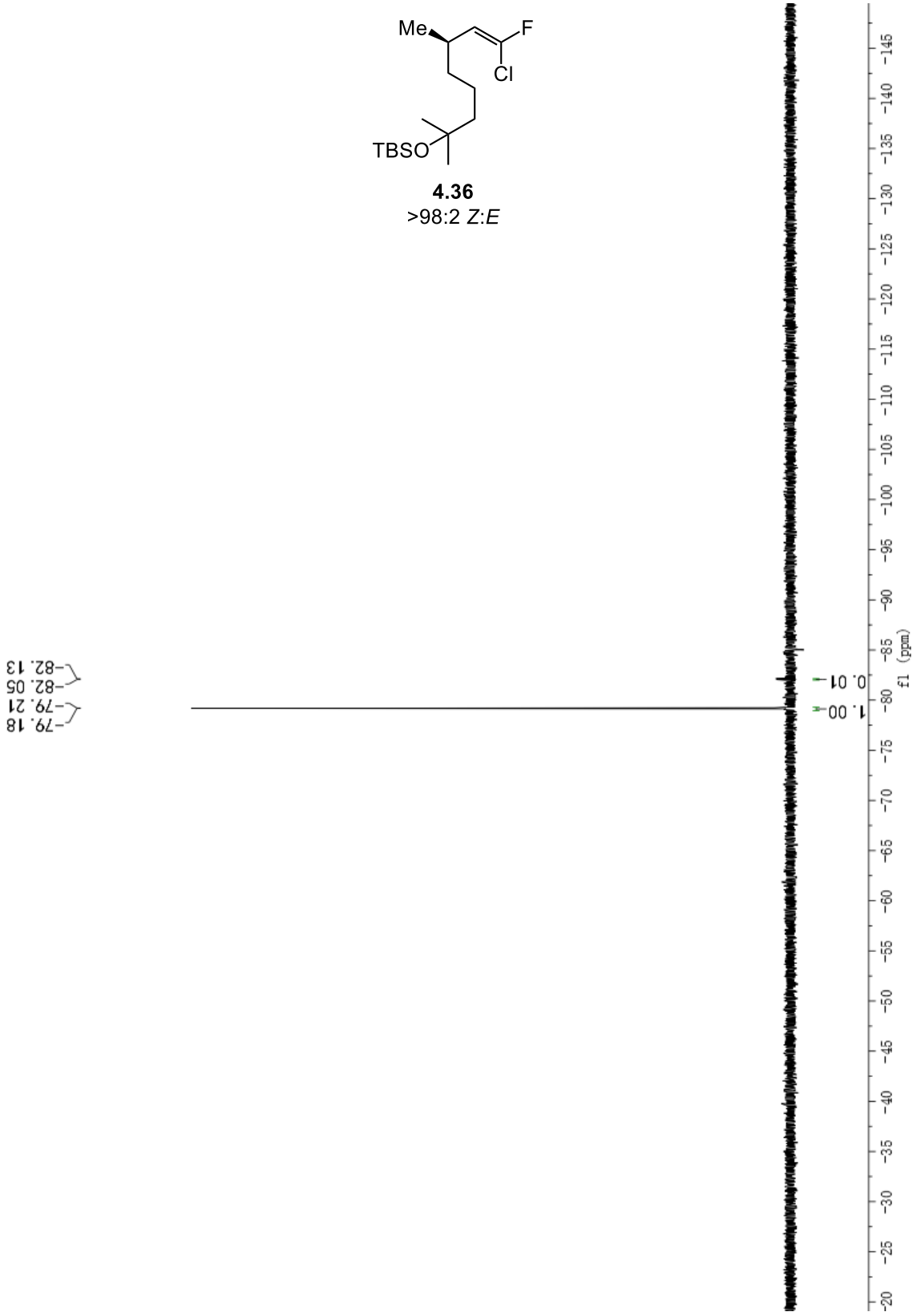
^{1}H NMR Spectrum of 4.34



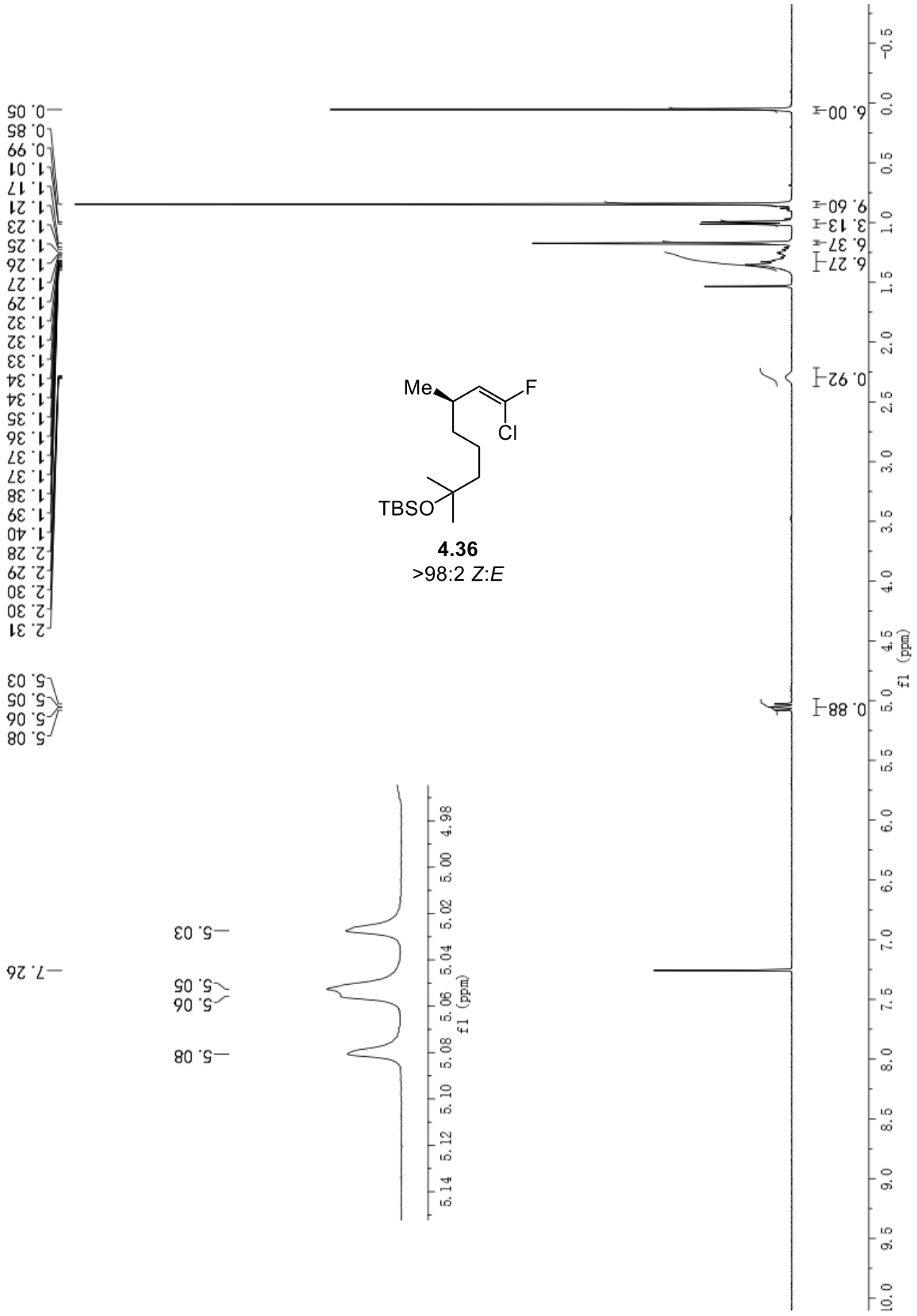
^{13}C NMR Spectrum of 4.34



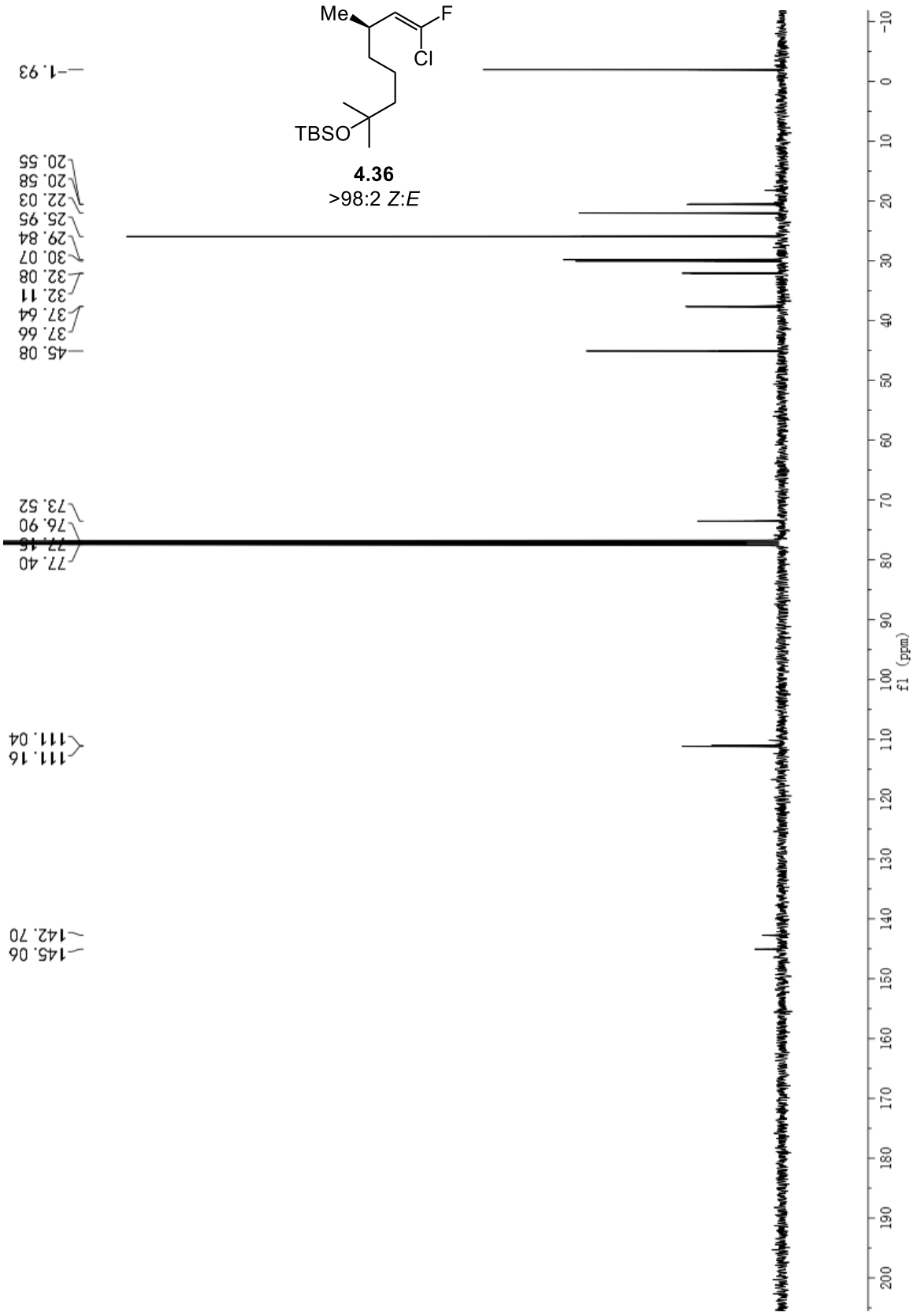
^{19}F NMR Spectrum of 4.36



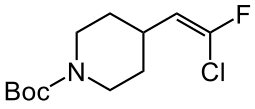
^{1}H NMR Spectrum of 4.36



^{13}C NMR Spectrum of 4.36

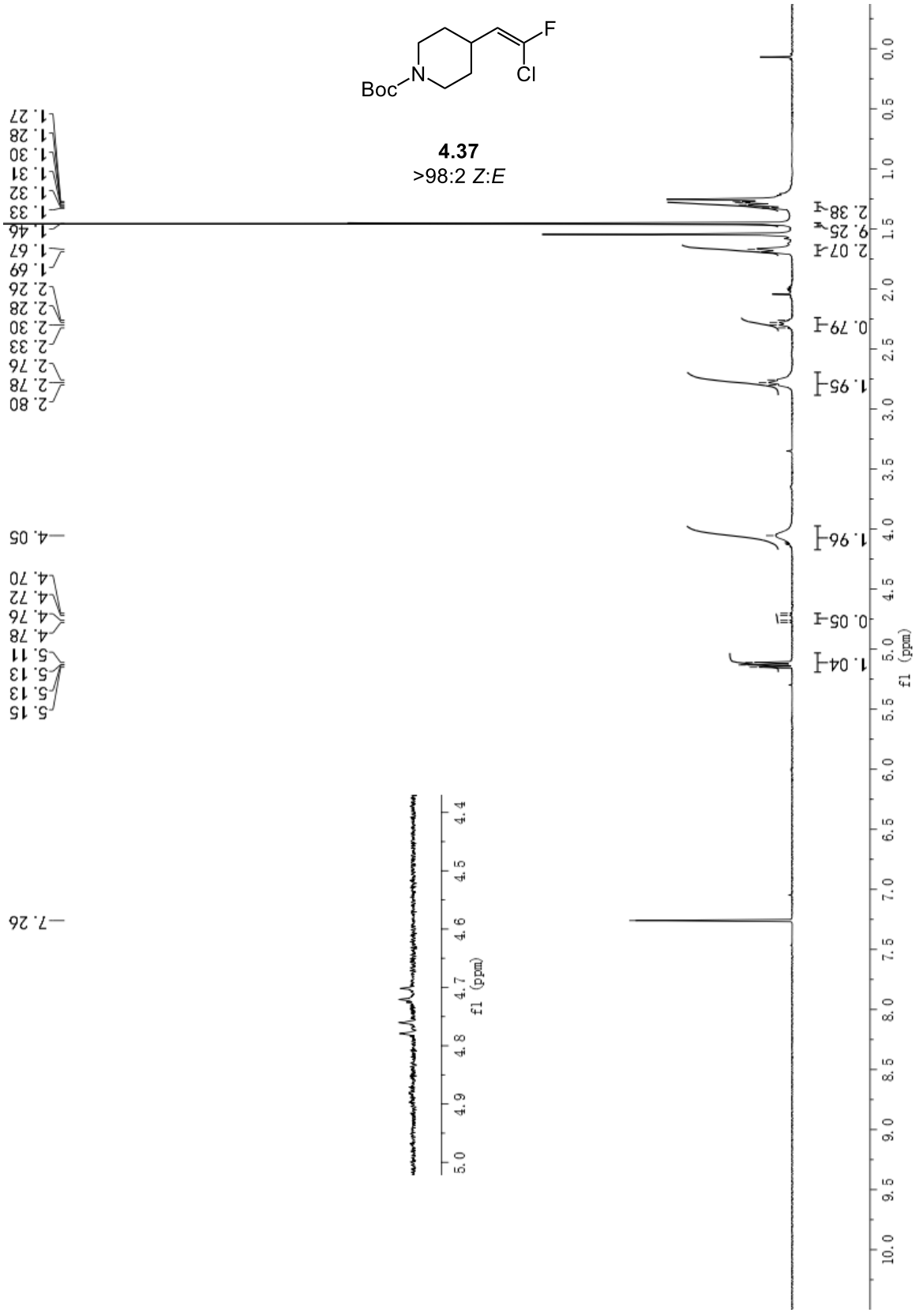


^{19}F NMR Spectrum of 4.37

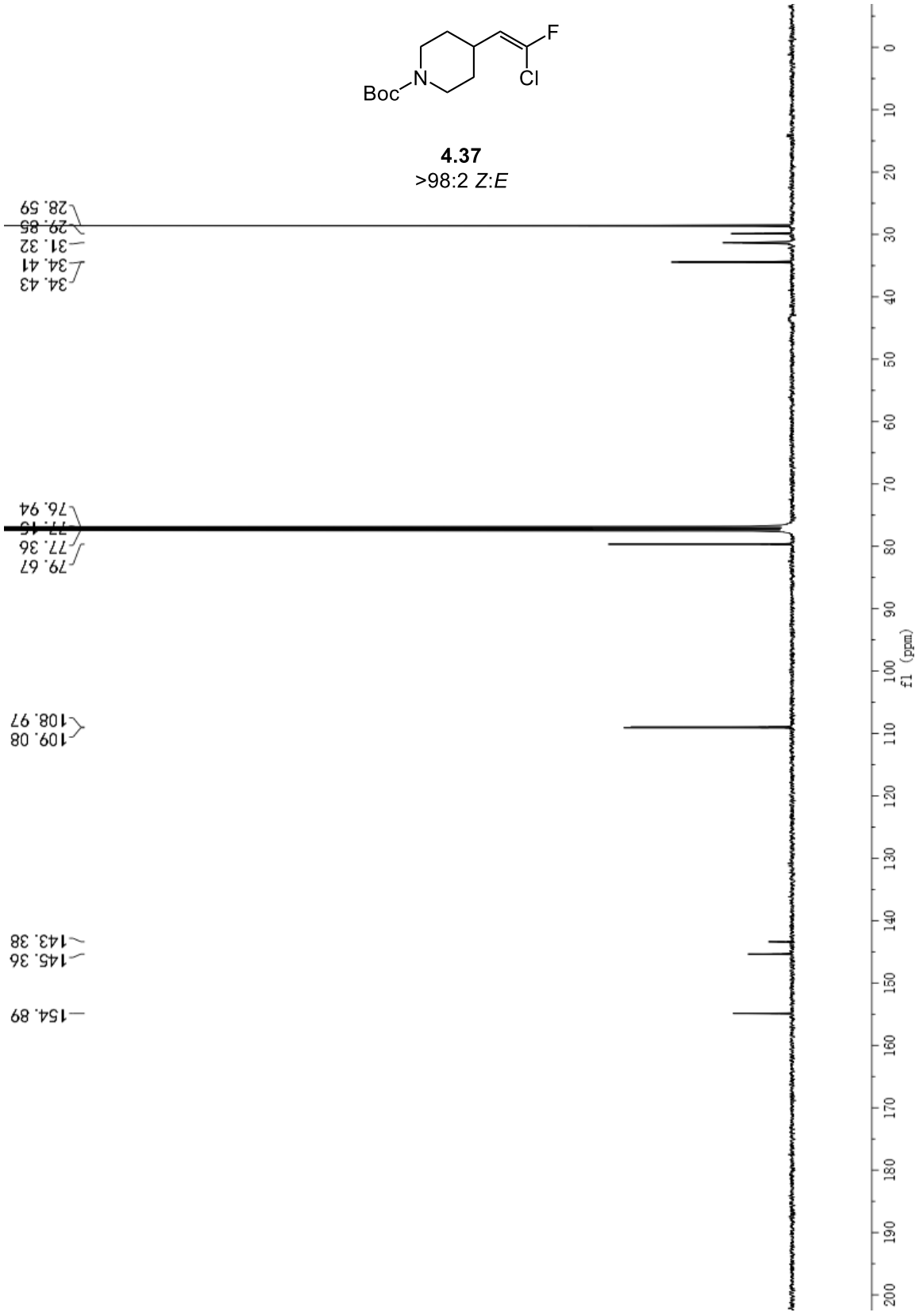


4.37
>98:2 *Z*:*E*

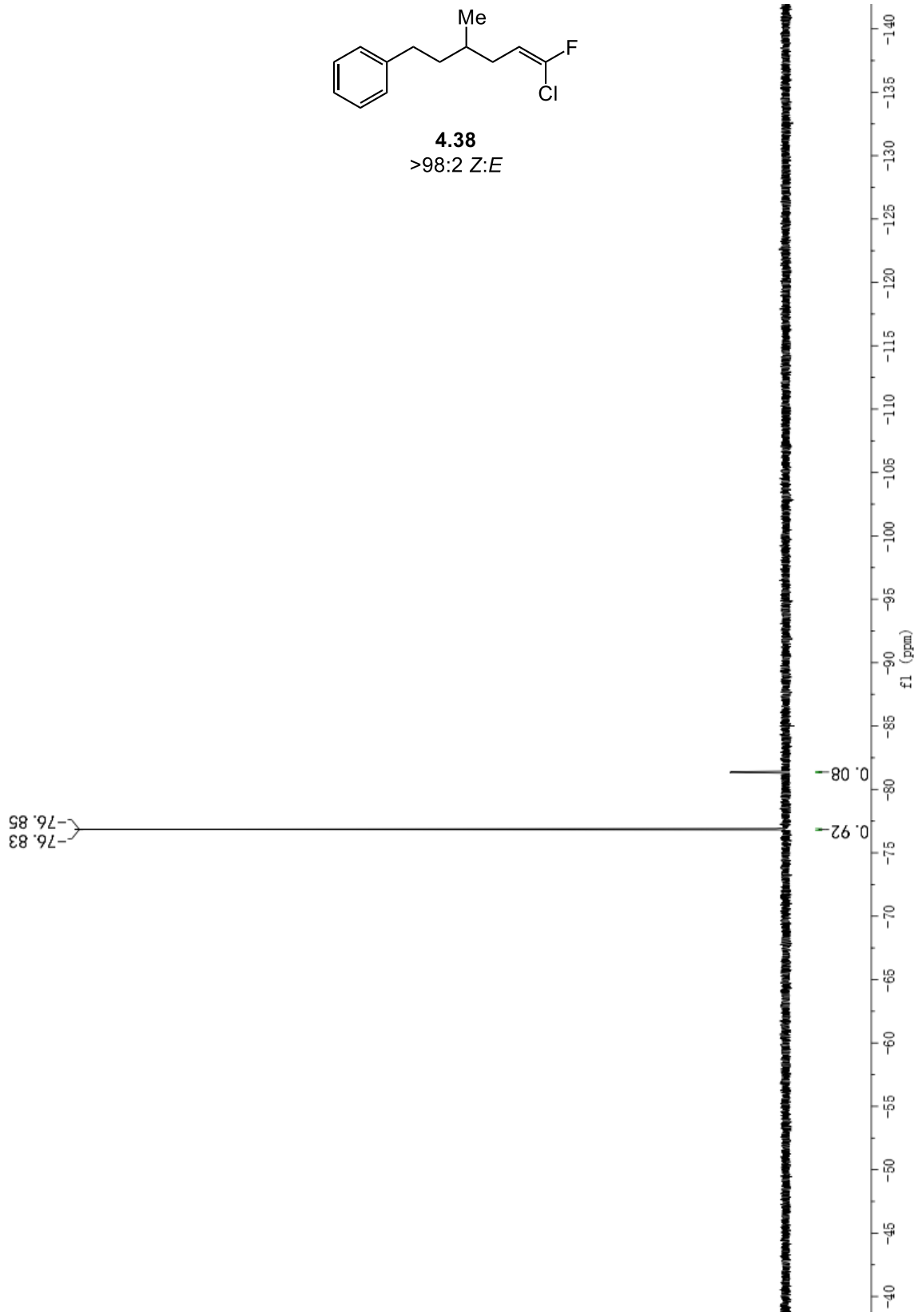
^{1}H NMR Spectrum of 4.37



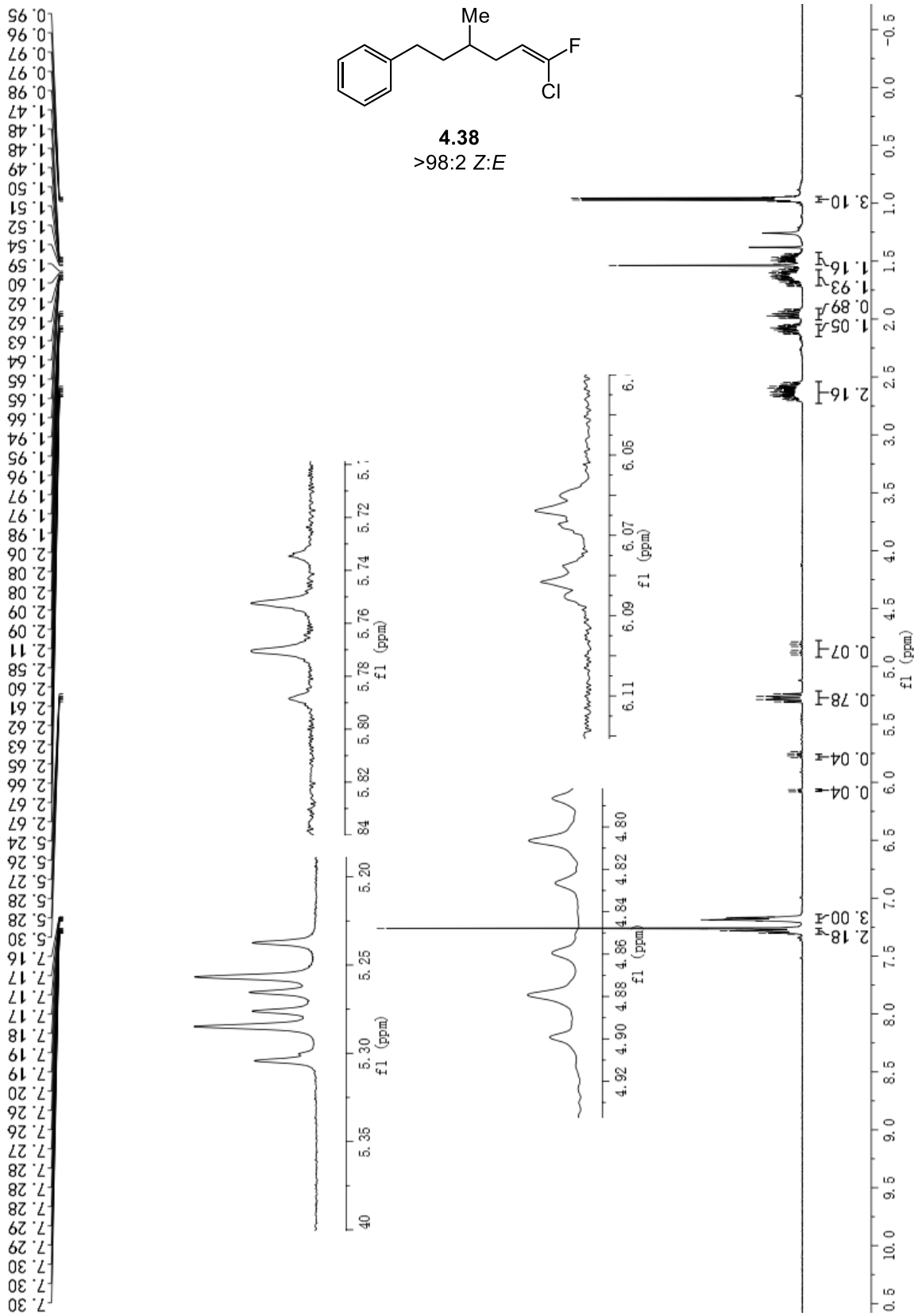
^{13}C NMR Spectrum of 4.37



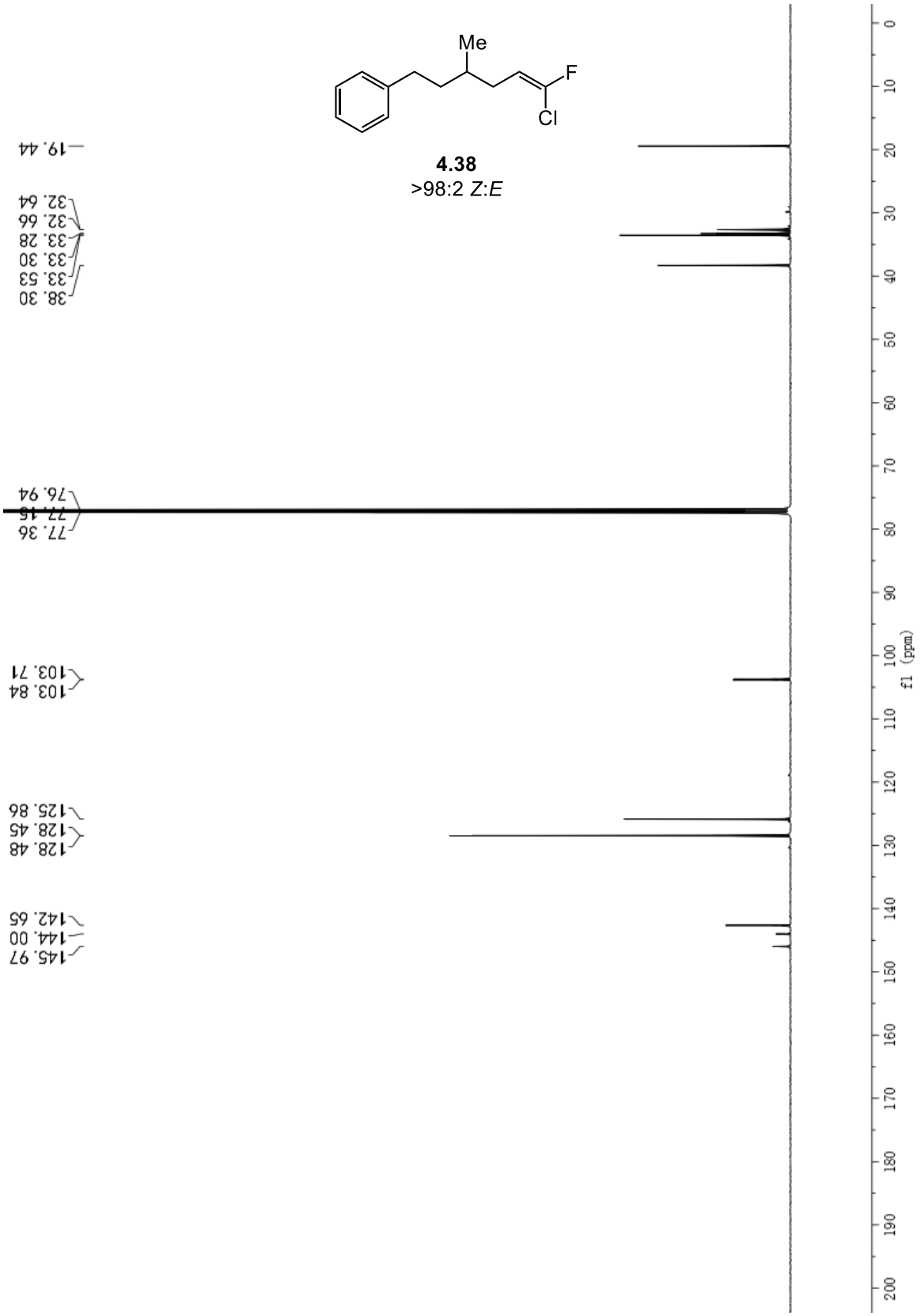
^{19}F NMR Spectrum of 4.38



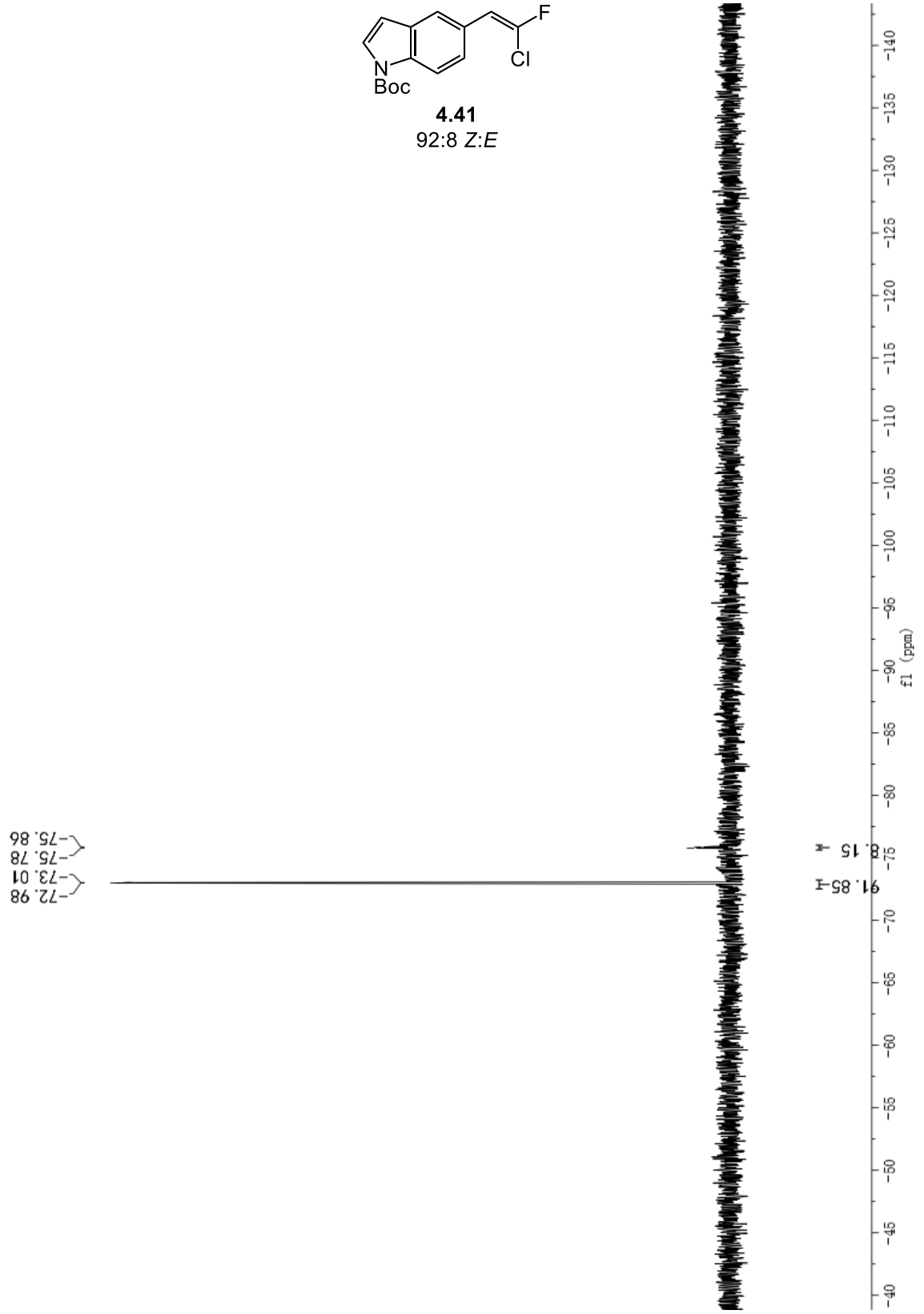
^{1}H NMR Spectrum of 4.38



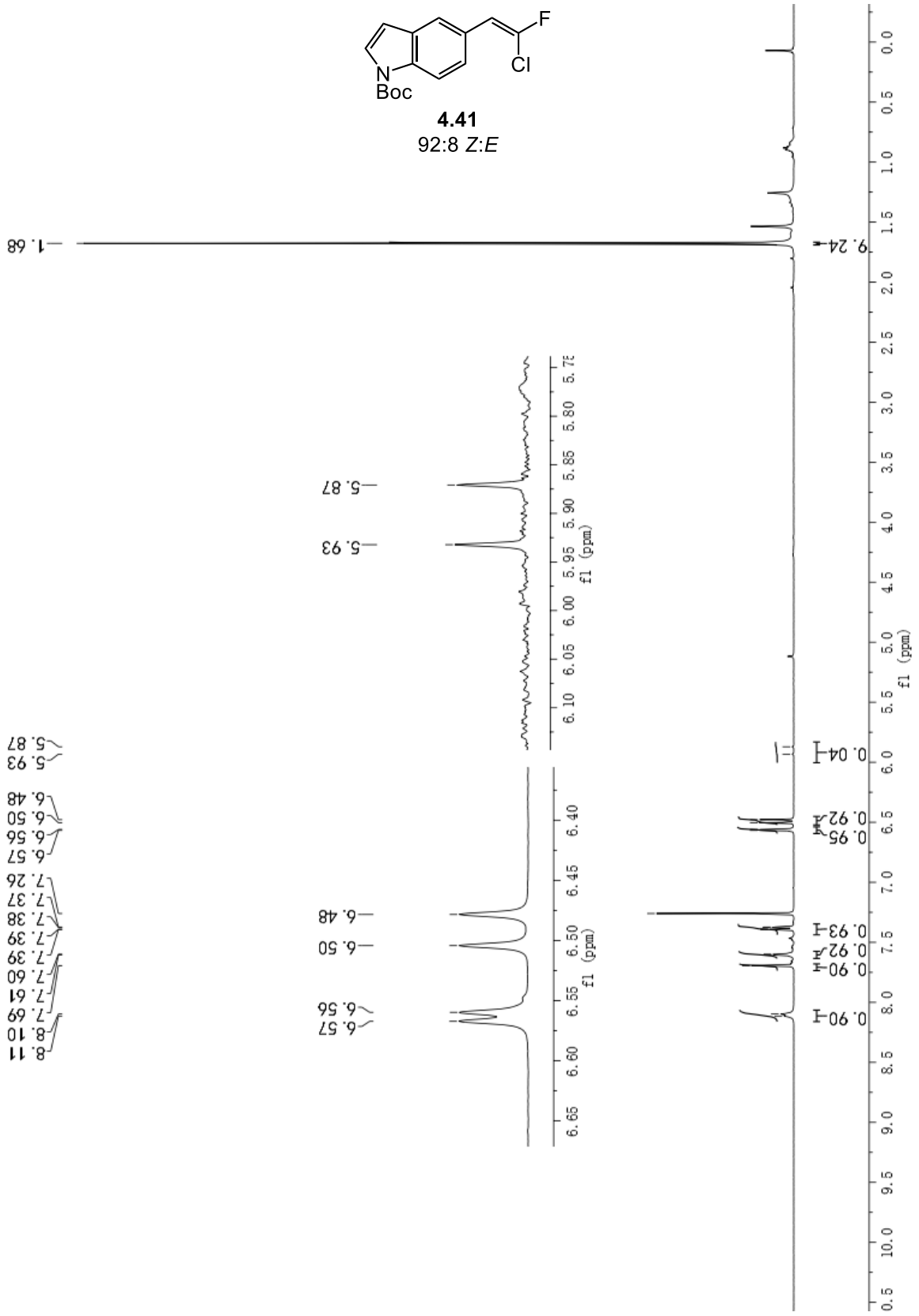
^{13}C NMR Spectrum of 4.38



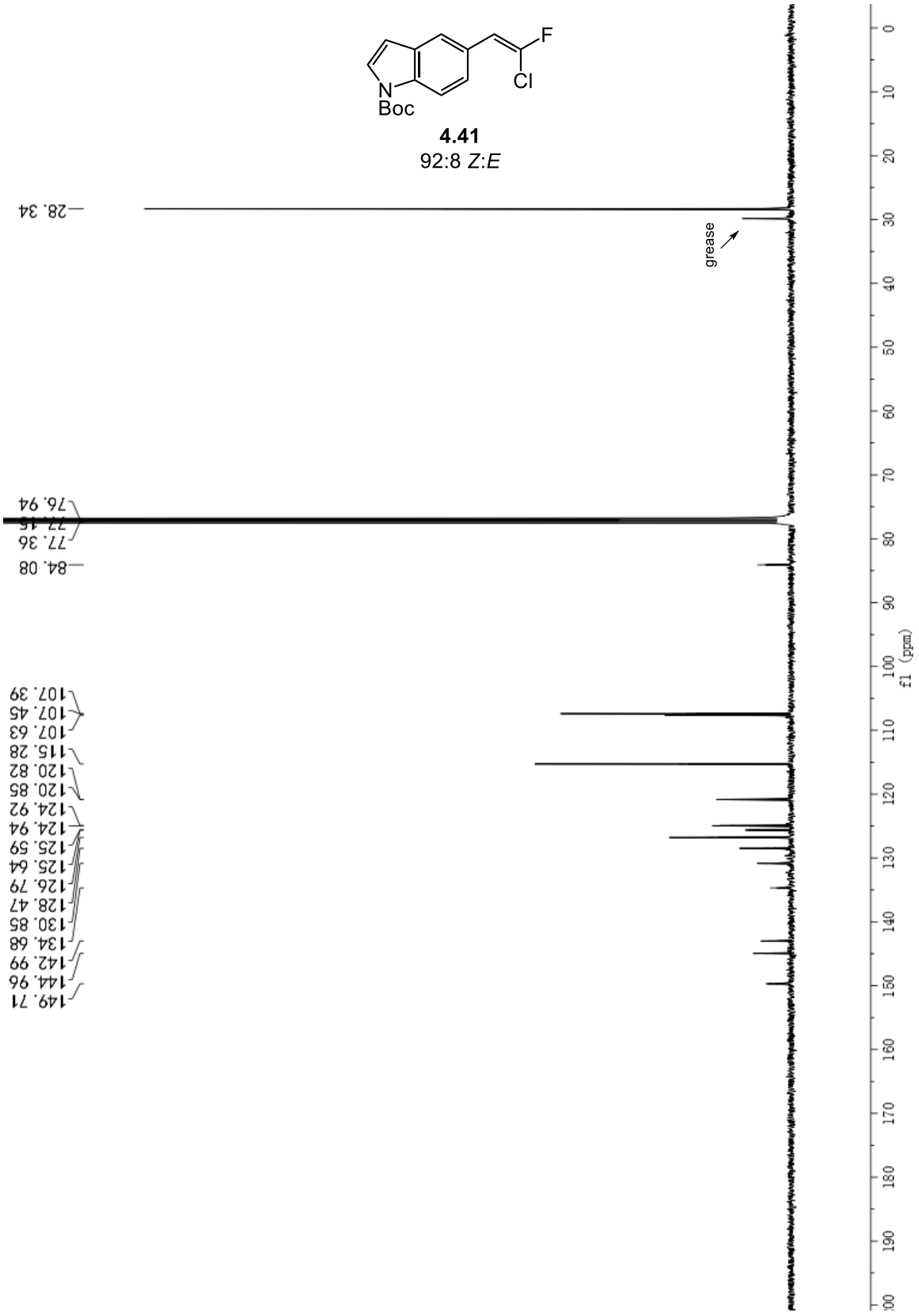
^{19}F NMR Spectrum of 4.41



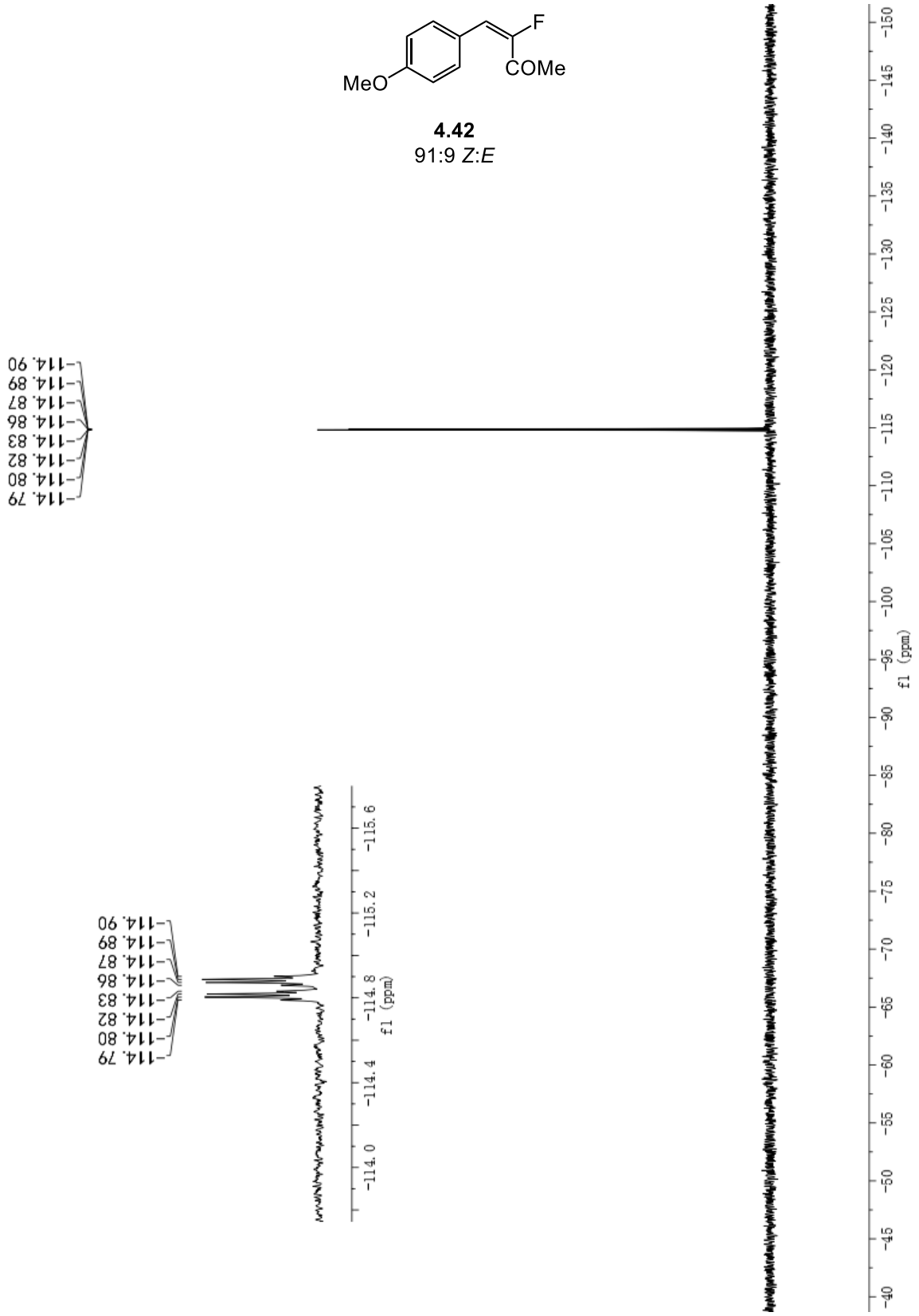
^{1}H NMR Spectrum of 4.41



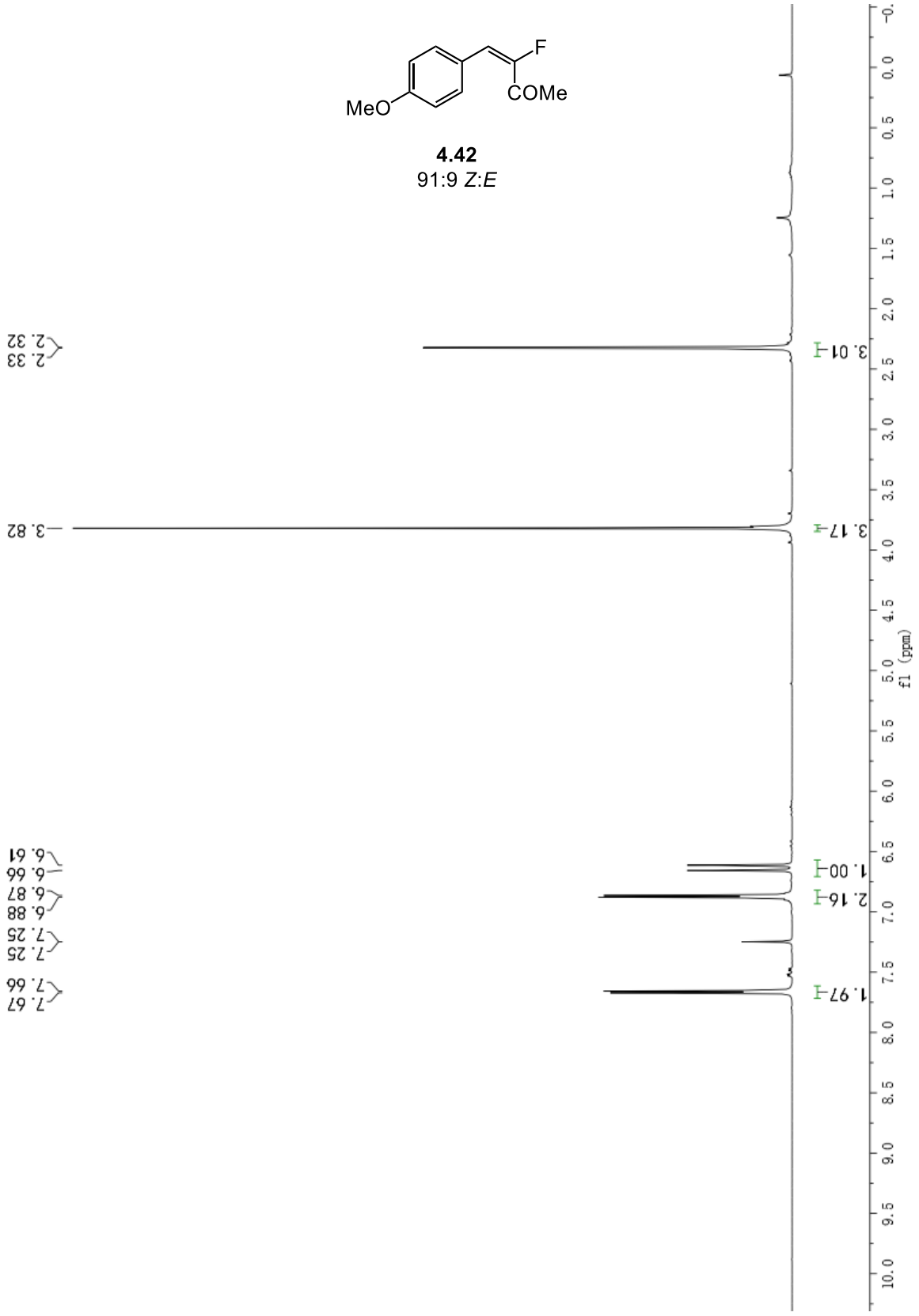
^{13}C NMR Spectrum of 4.41



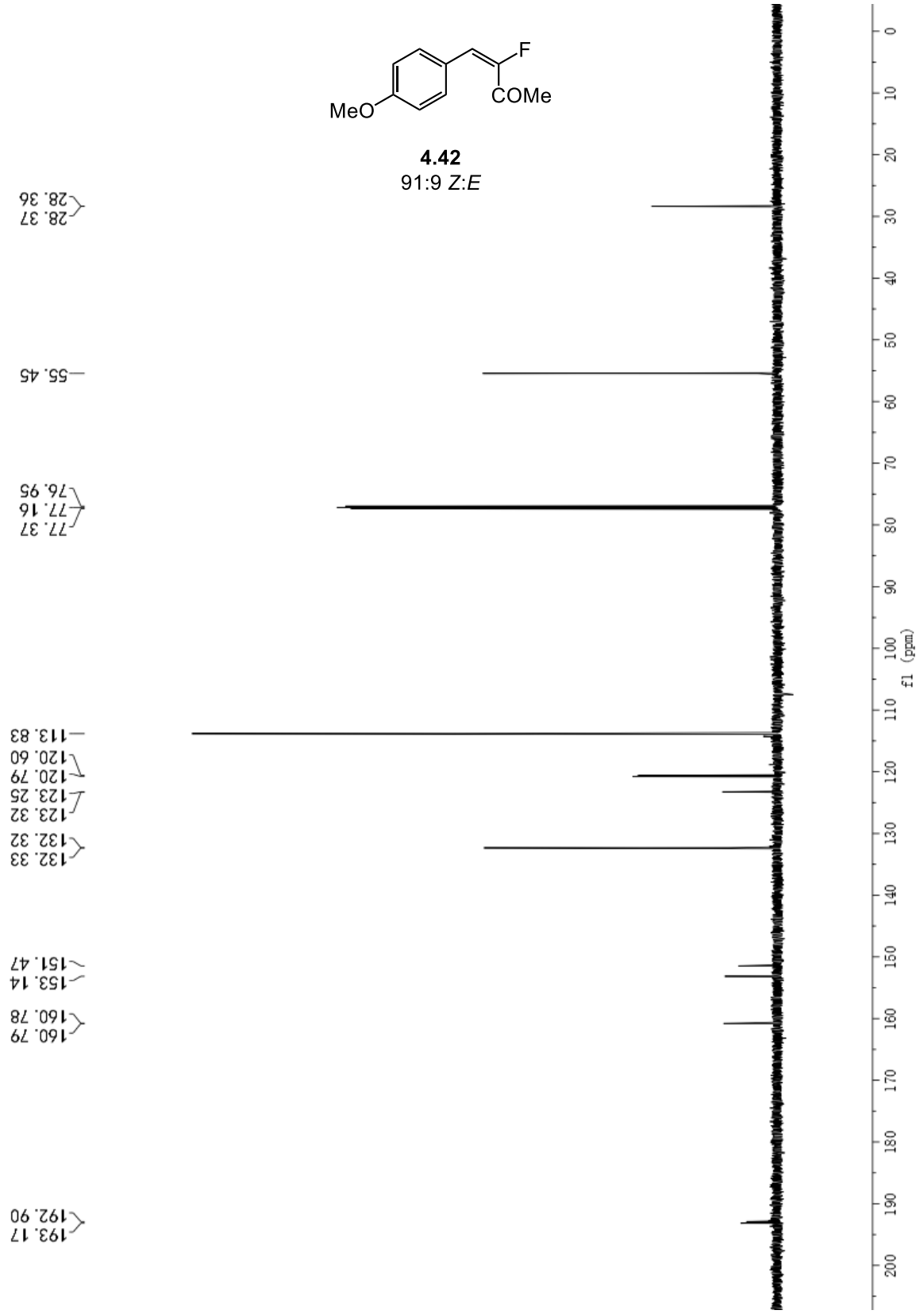
^{19}F NMR Spectrum of 4.42



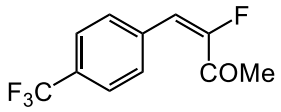
^{1}H NMR Spectrum of 4.42



^{13}C NMR Spectrum of 4.42

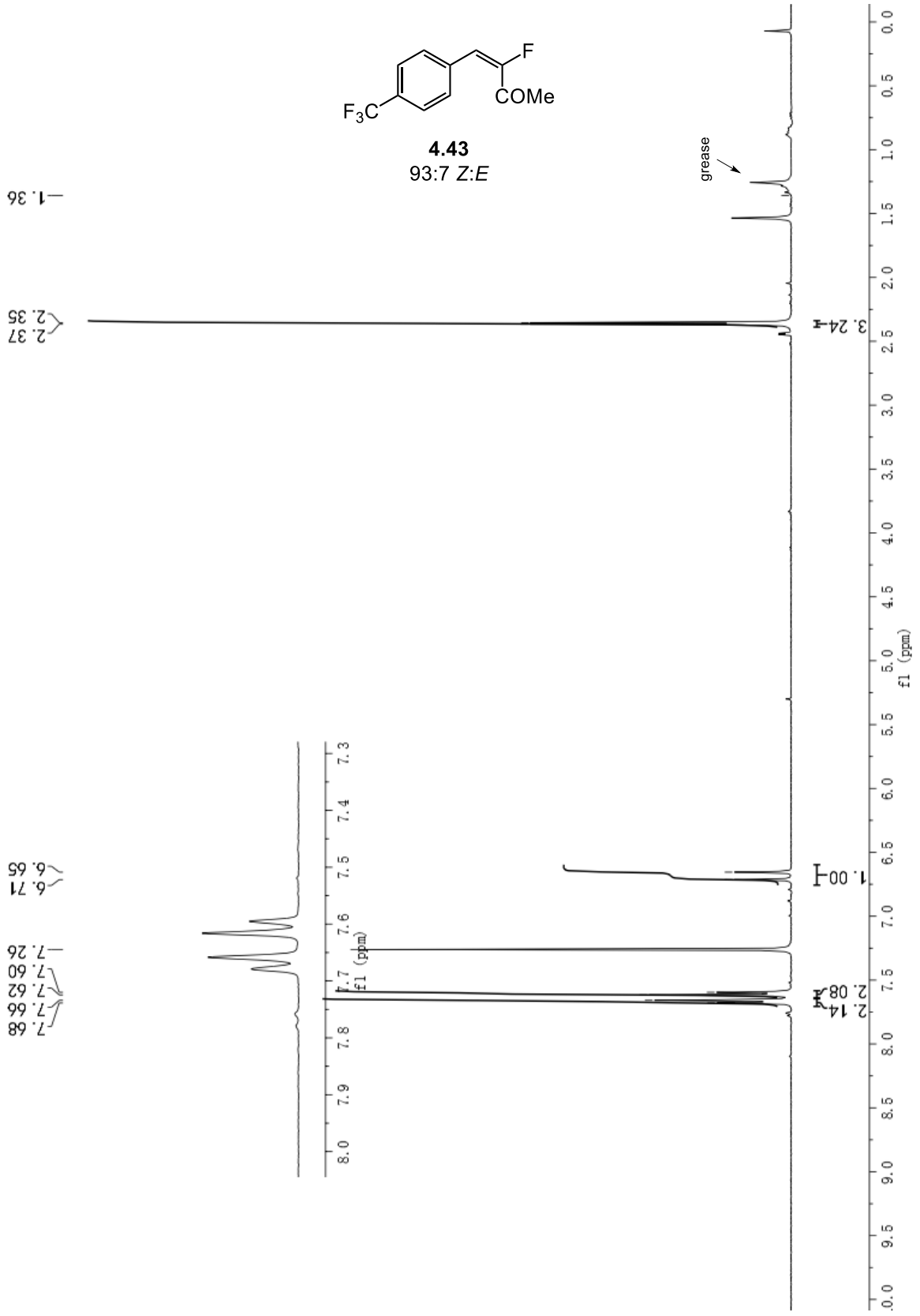


^{19}F NMR Spectrum of 4.43

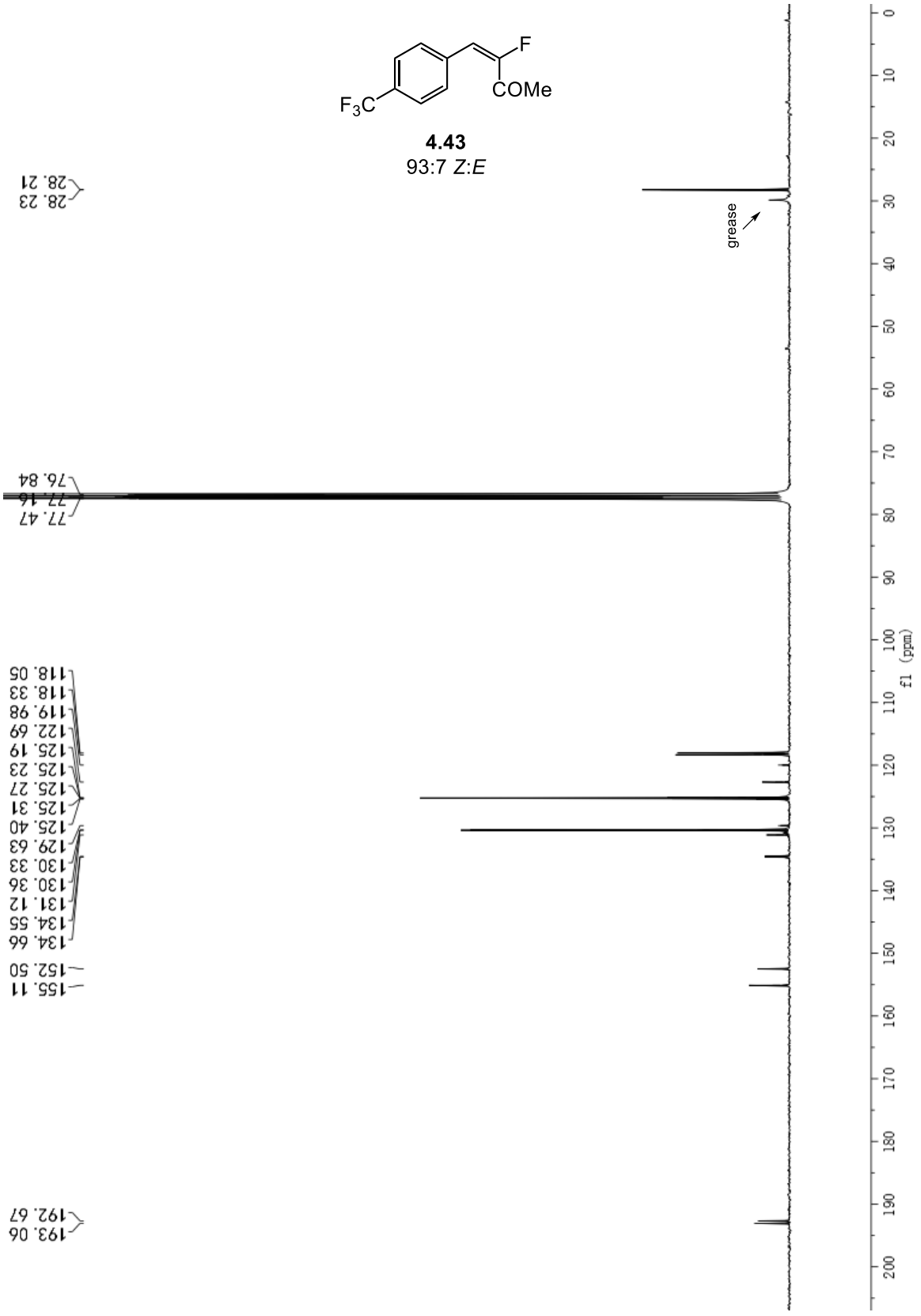


4.43
93:7 *Z*:*E*

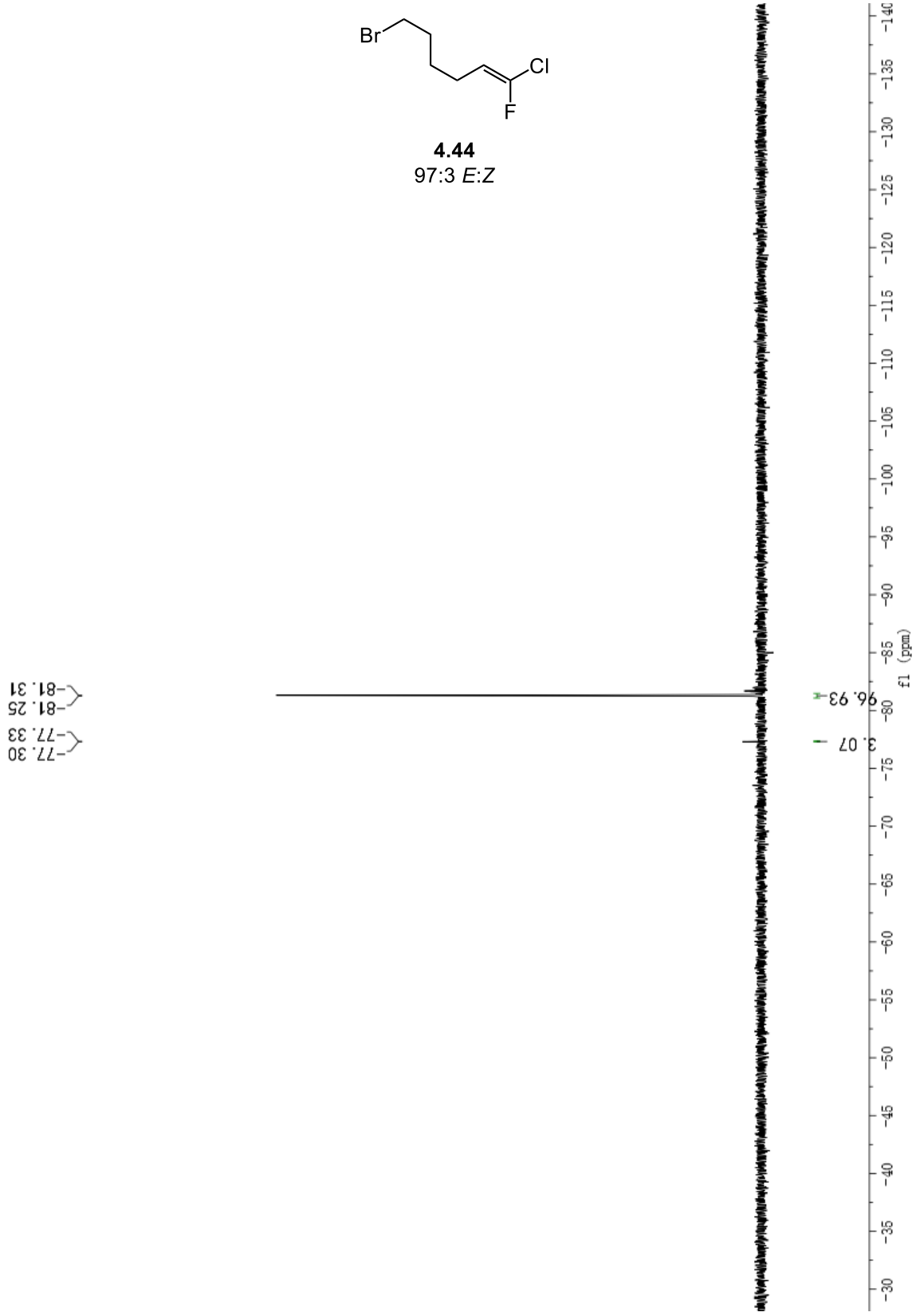
^{1}H NMR Spectrum of 4.43



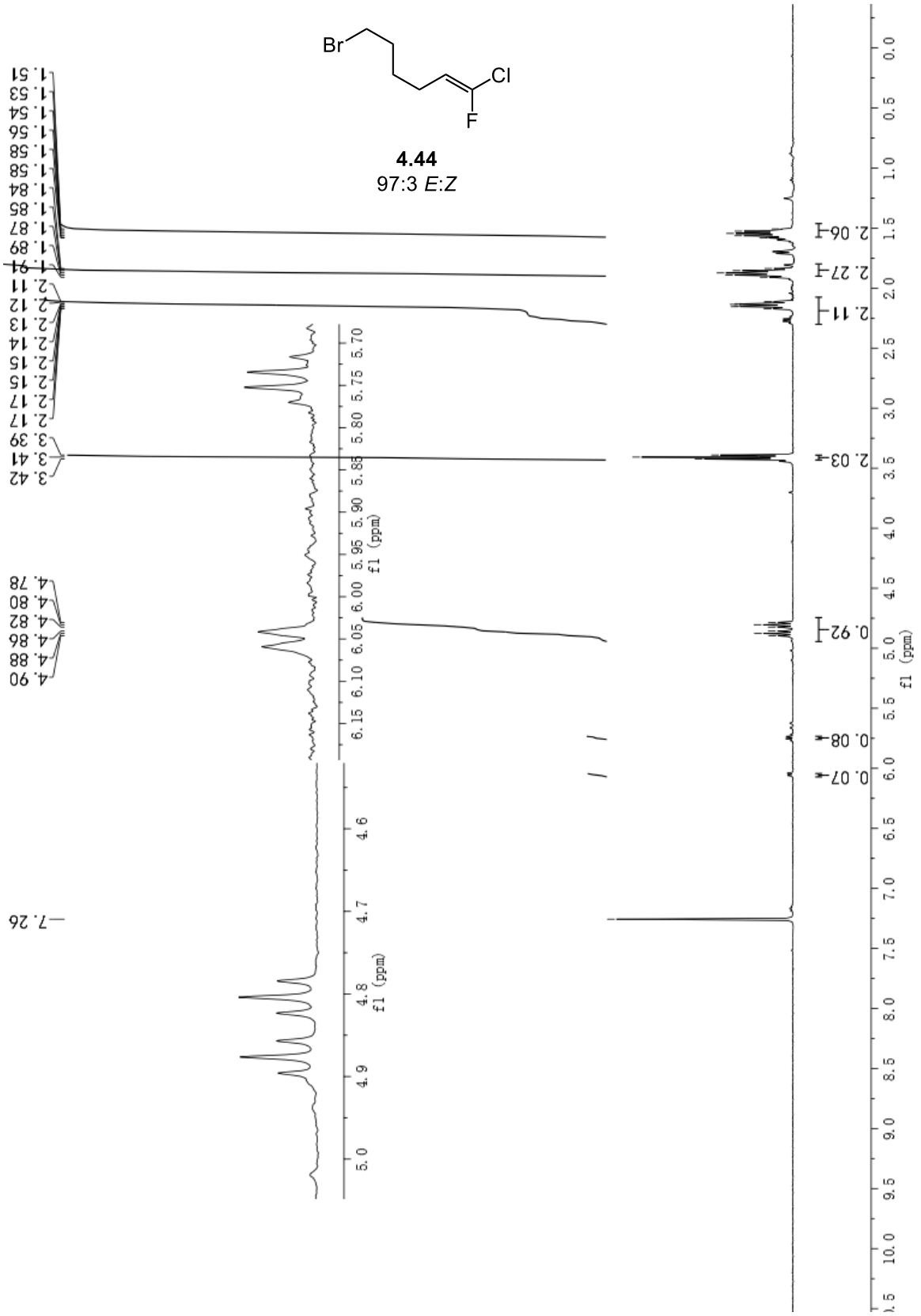
^{13}C NMR Spectrum of 4.43



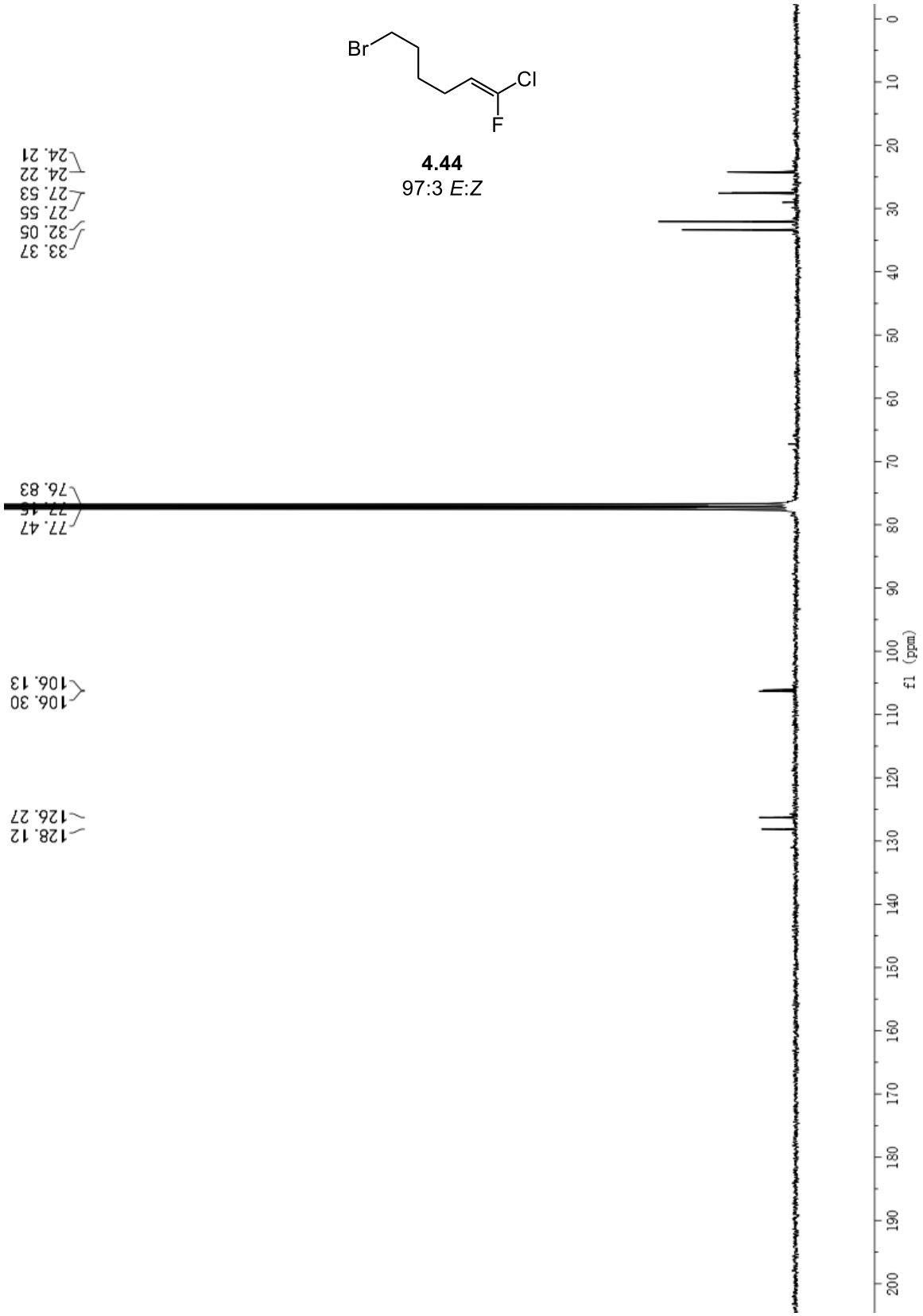
^{19}F NMR Spectrum of 4.44



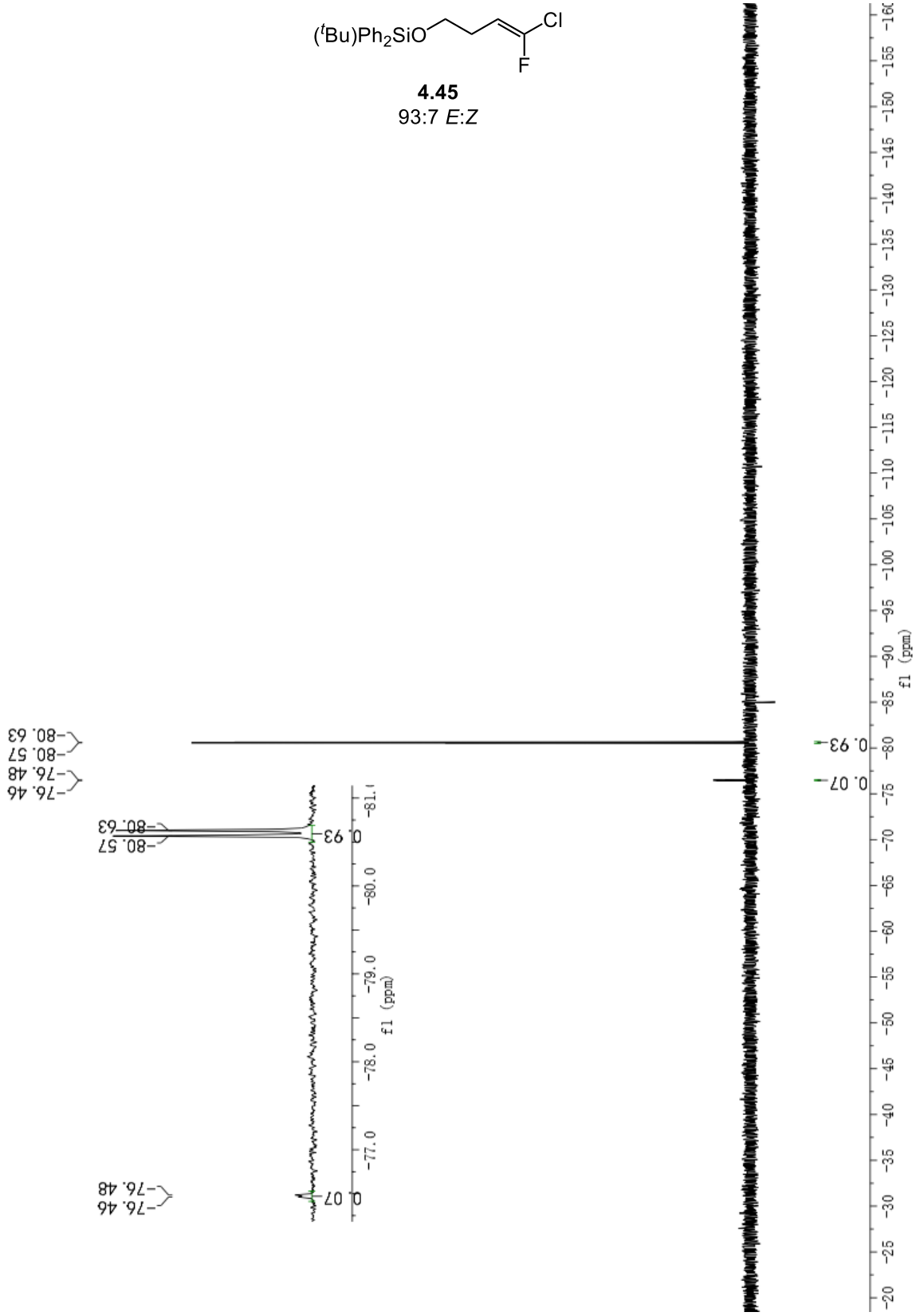
^{1}H NMR Spectrum of 4.44



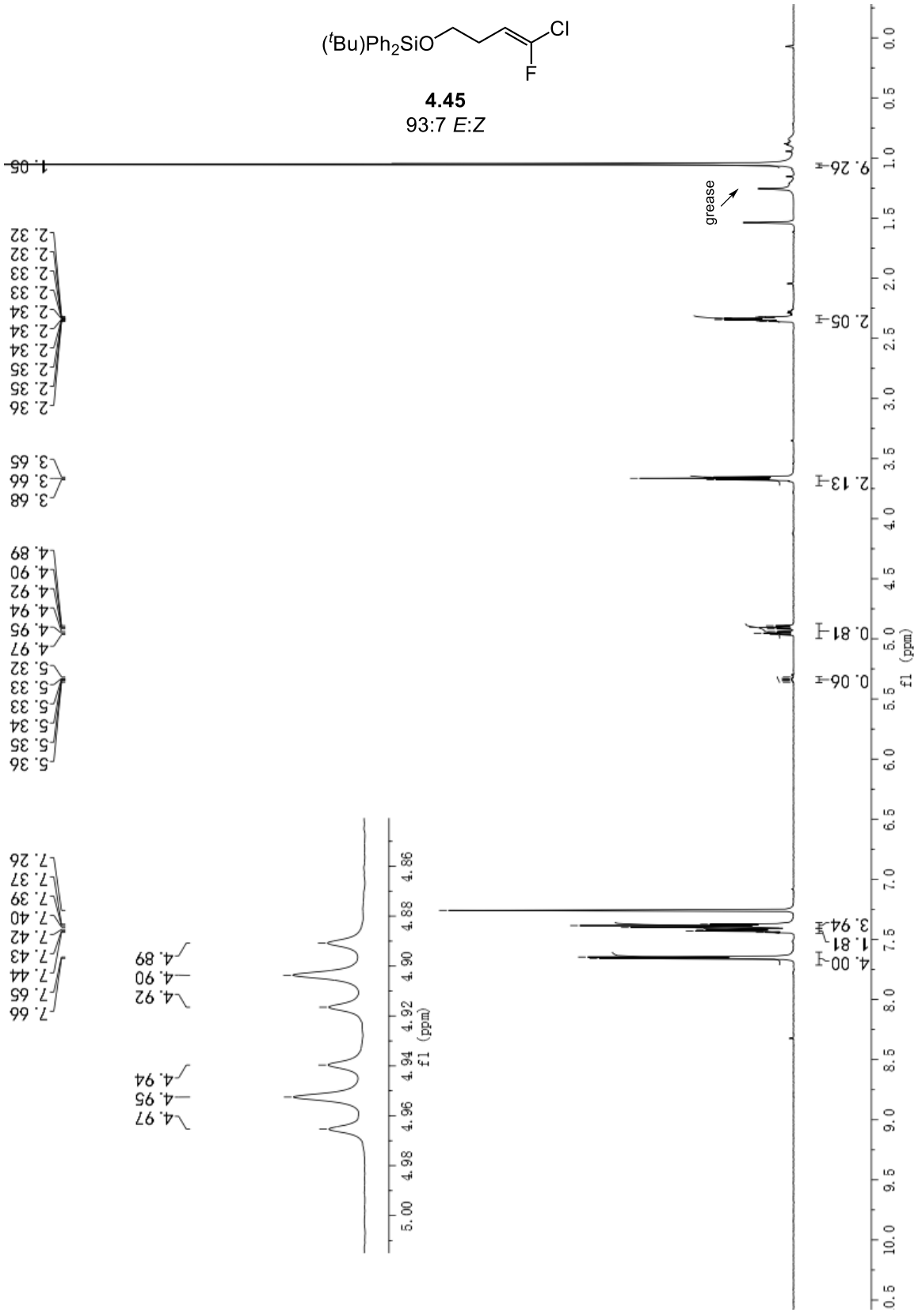
^{13}C NMR Spectrum of 4.44



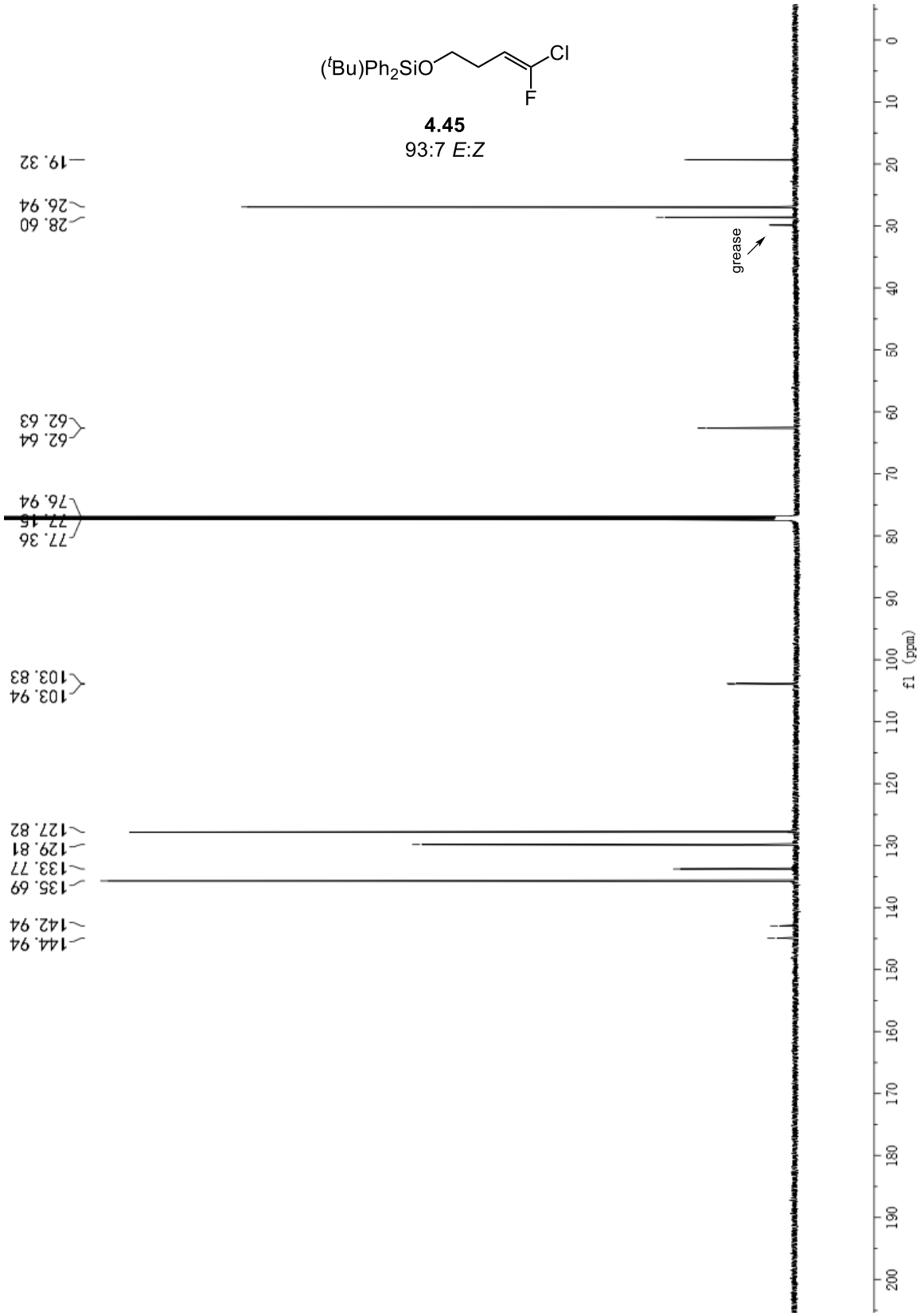
^{19}F NMR Spectrum of 4.45



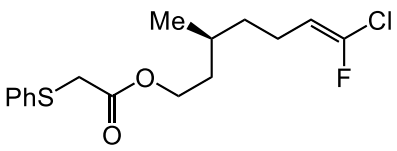
^{1}H NMR Spectrum of 4.45



^{13}C NMR Spectrum of 4.45

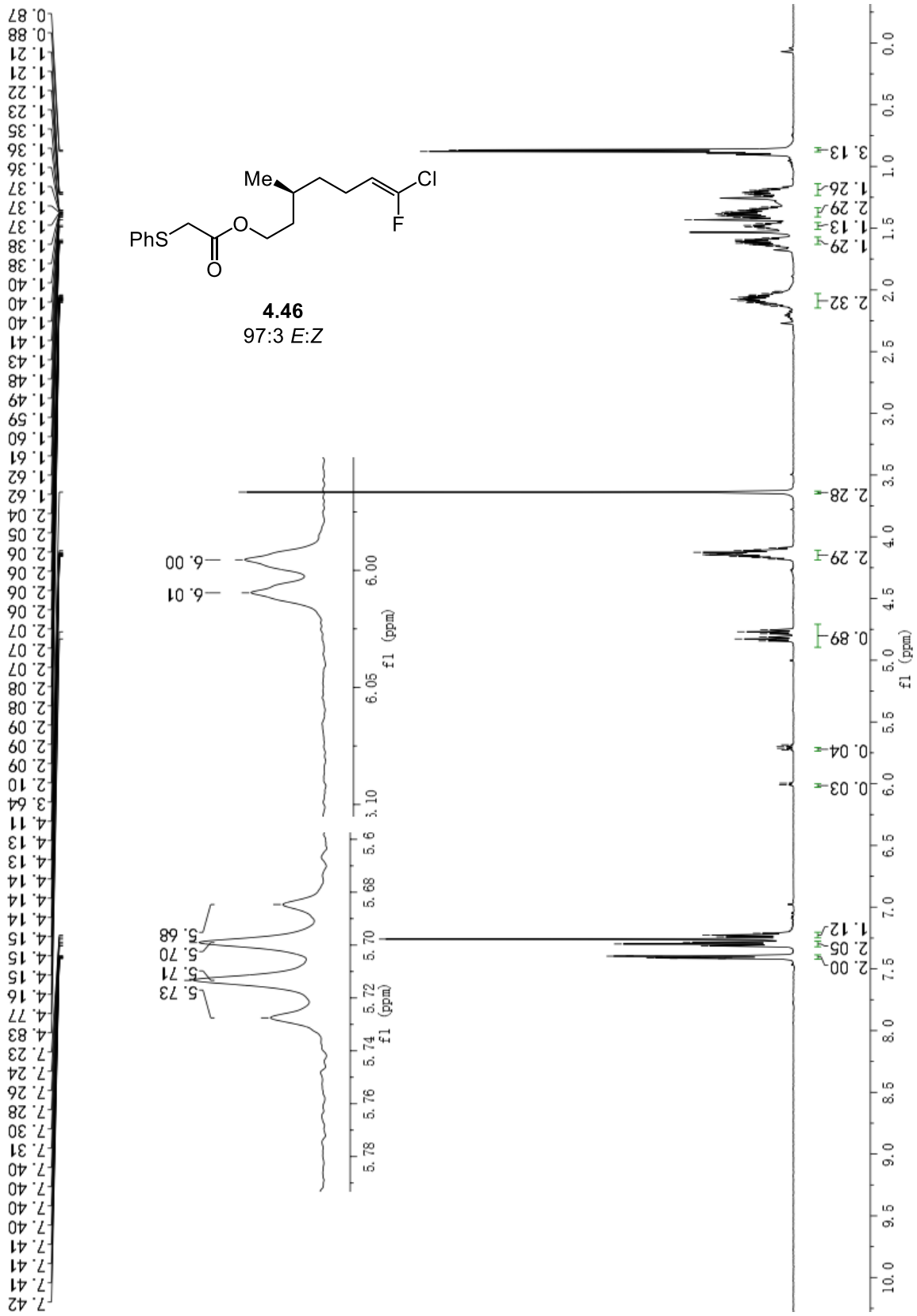


^{19}F NMR Spectrum of 4.46

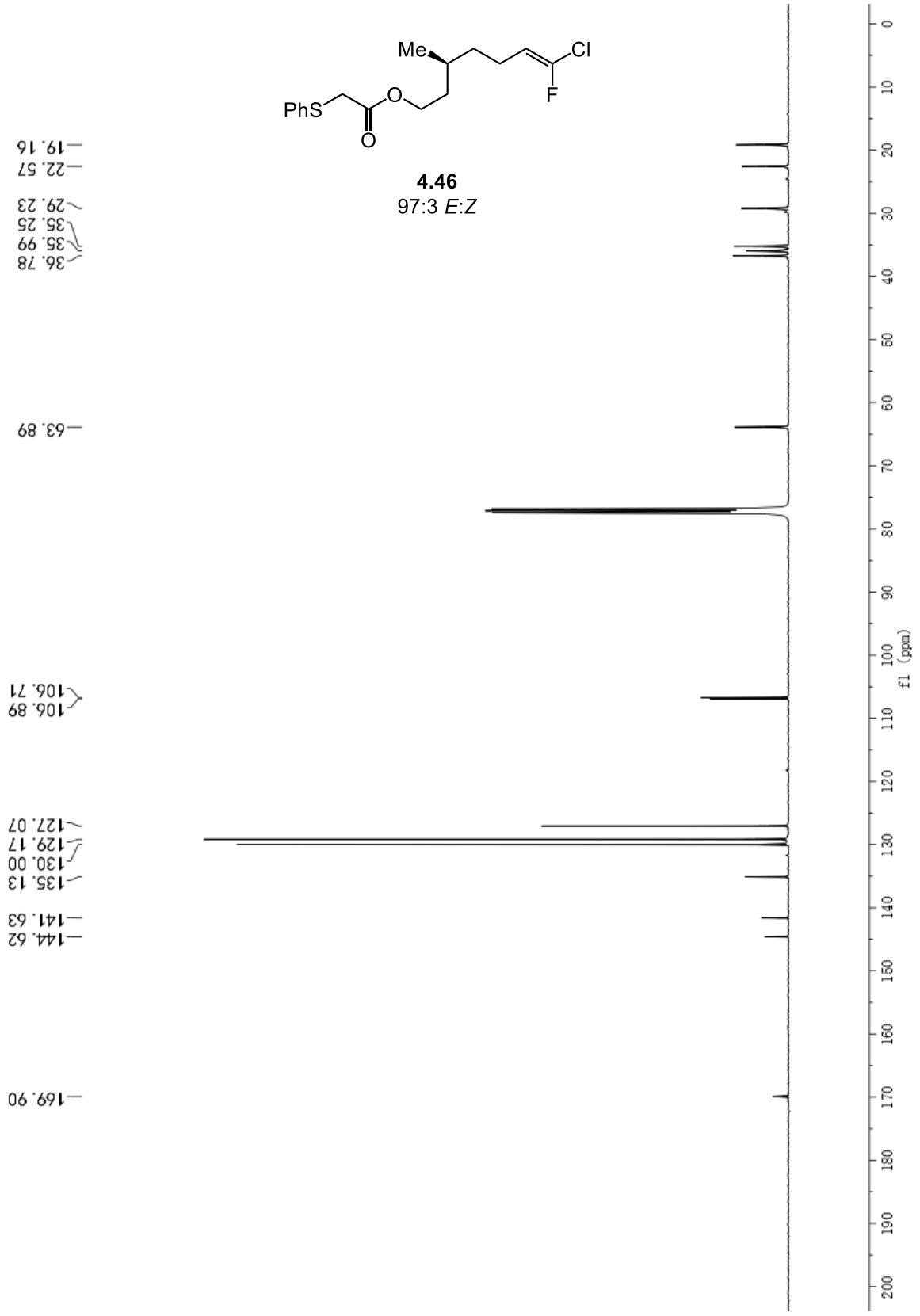


4.46
97:3 *E*:*Z*

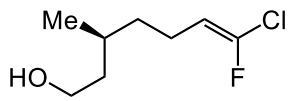
^{1}H NMR Spectrum of 4.45



^{13}C NMR Spectrum of 4.46

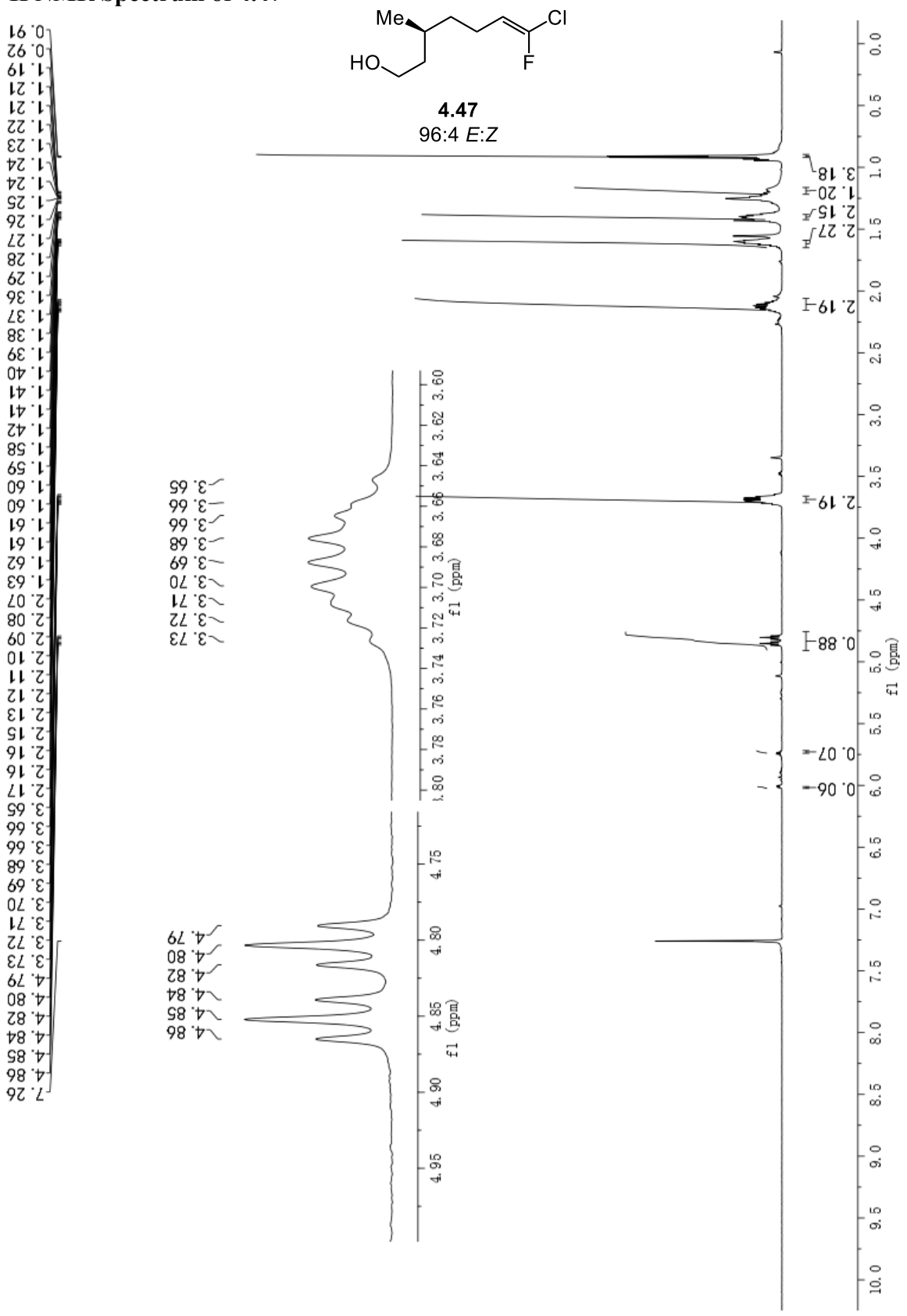


^{19}F NMR Spectrum of 4.47

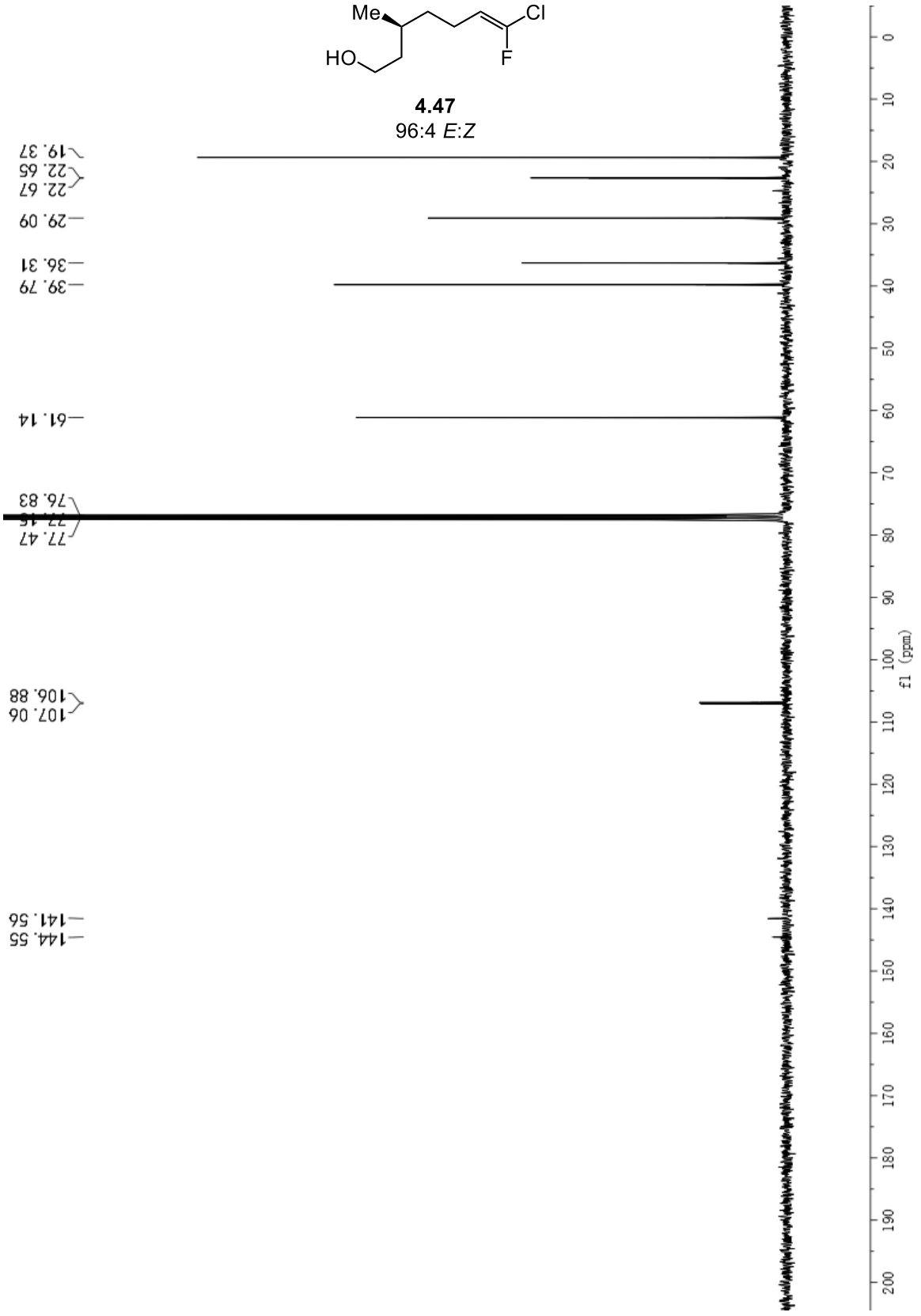


4.47
96:4 *E*:*Z*

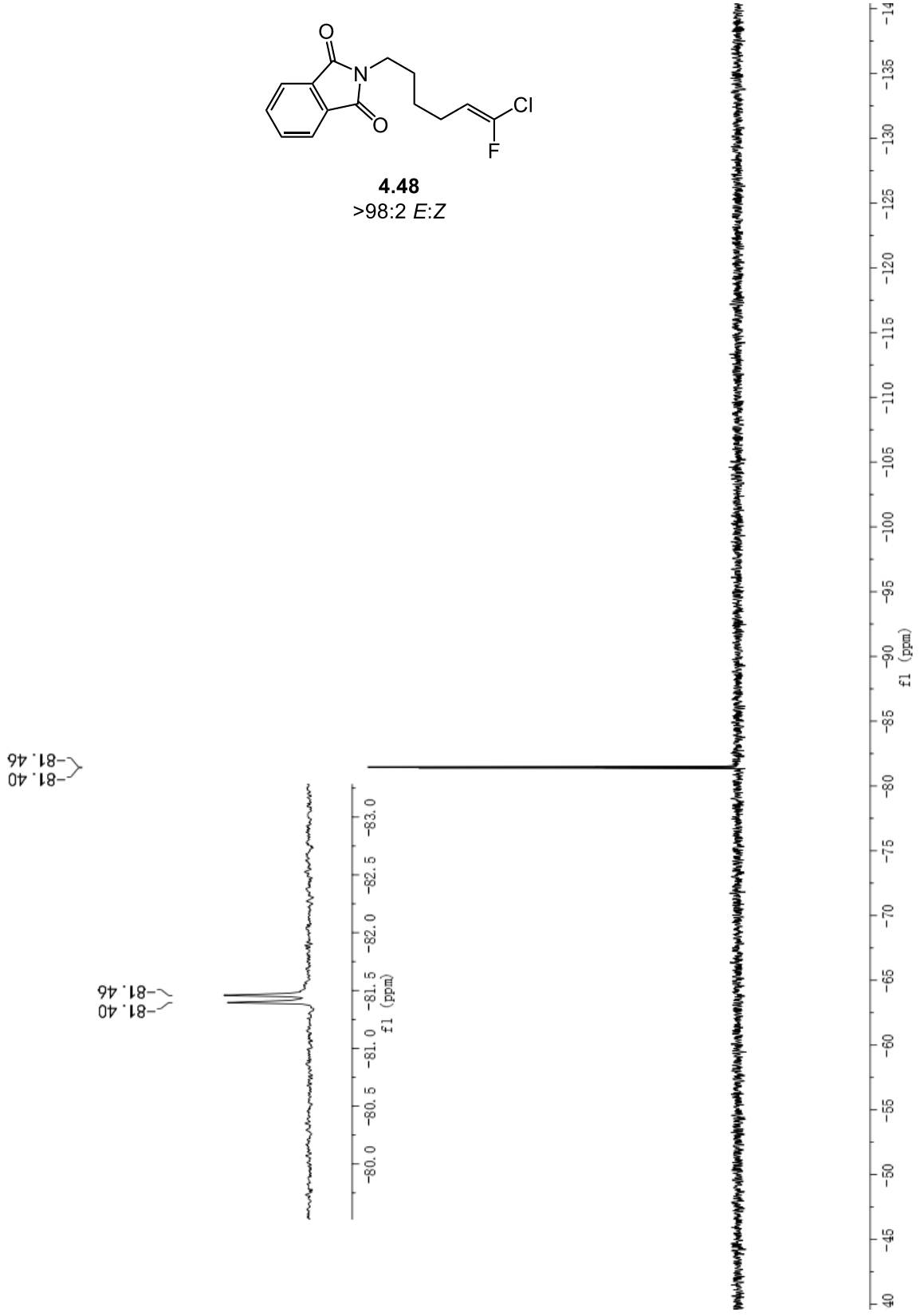
^{1}H NMR Spectrum of 4.47



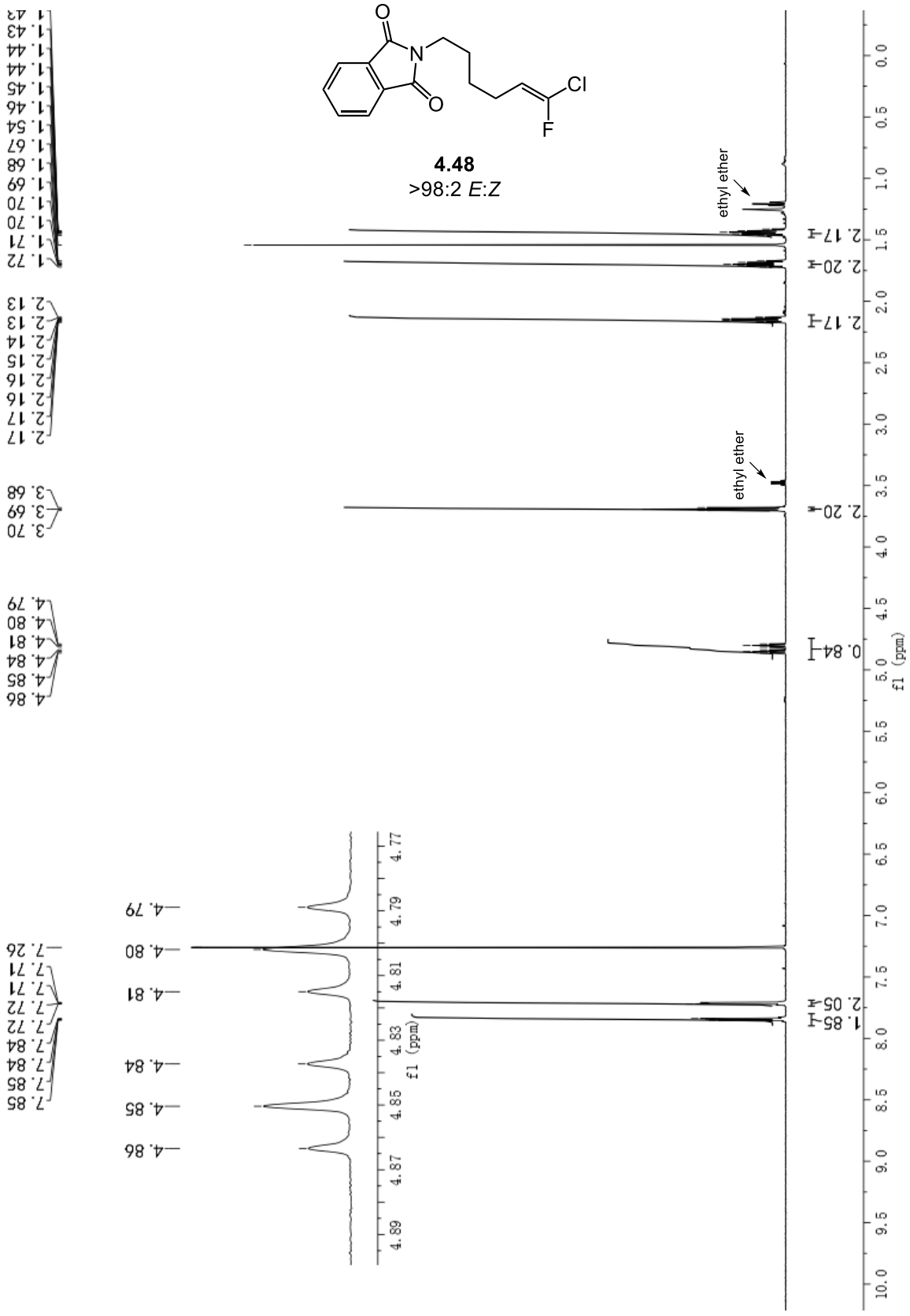
^{13}C NMR Spectrum of 4.47



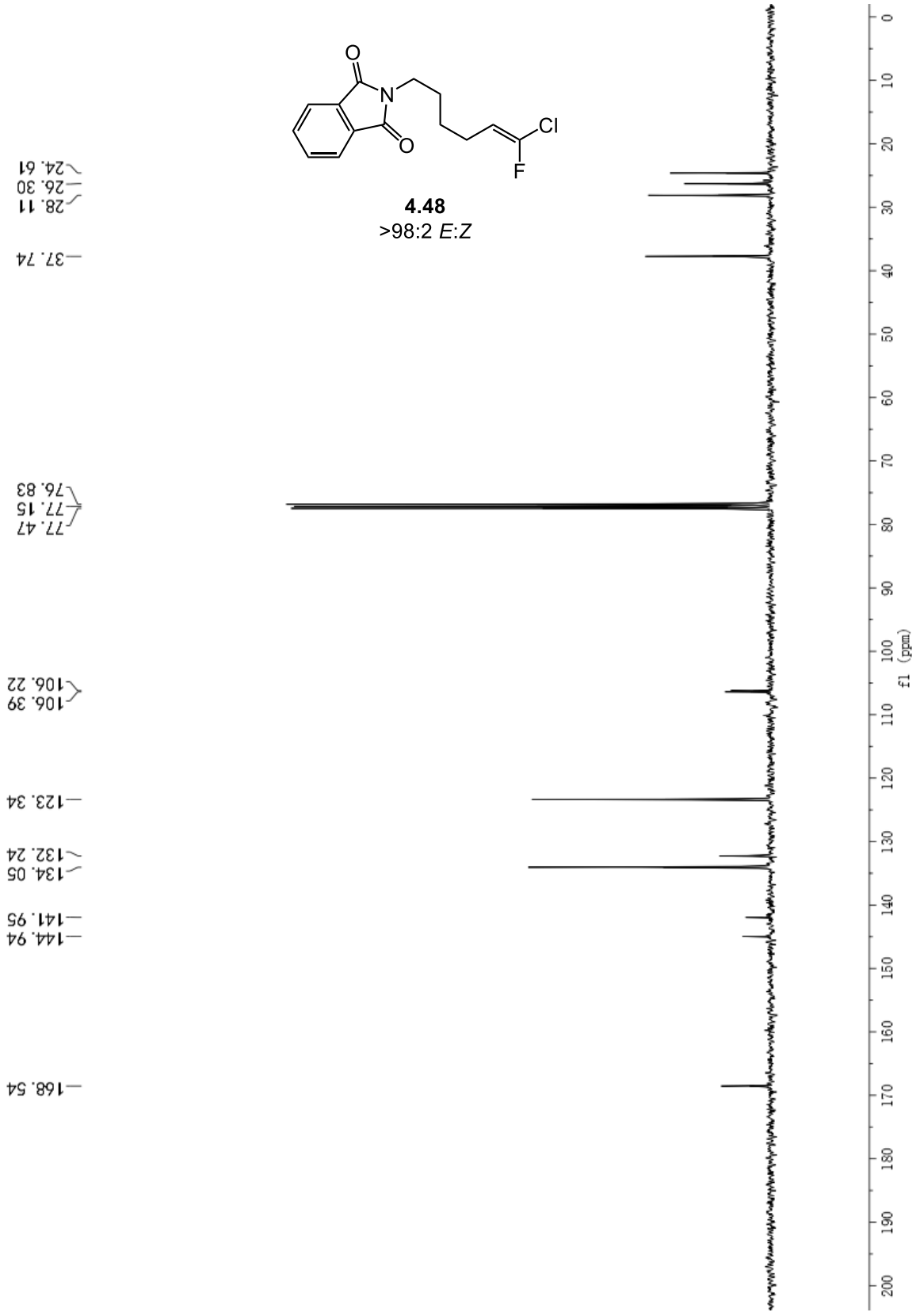
^{19}F NMR Spectrum of 4.48



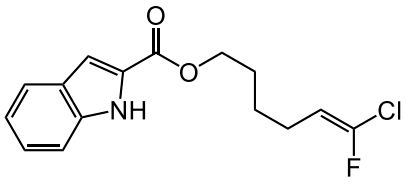
^{1}H NMR Spectrum of 4.48



^{13}C NMR Spectrum of 4.48

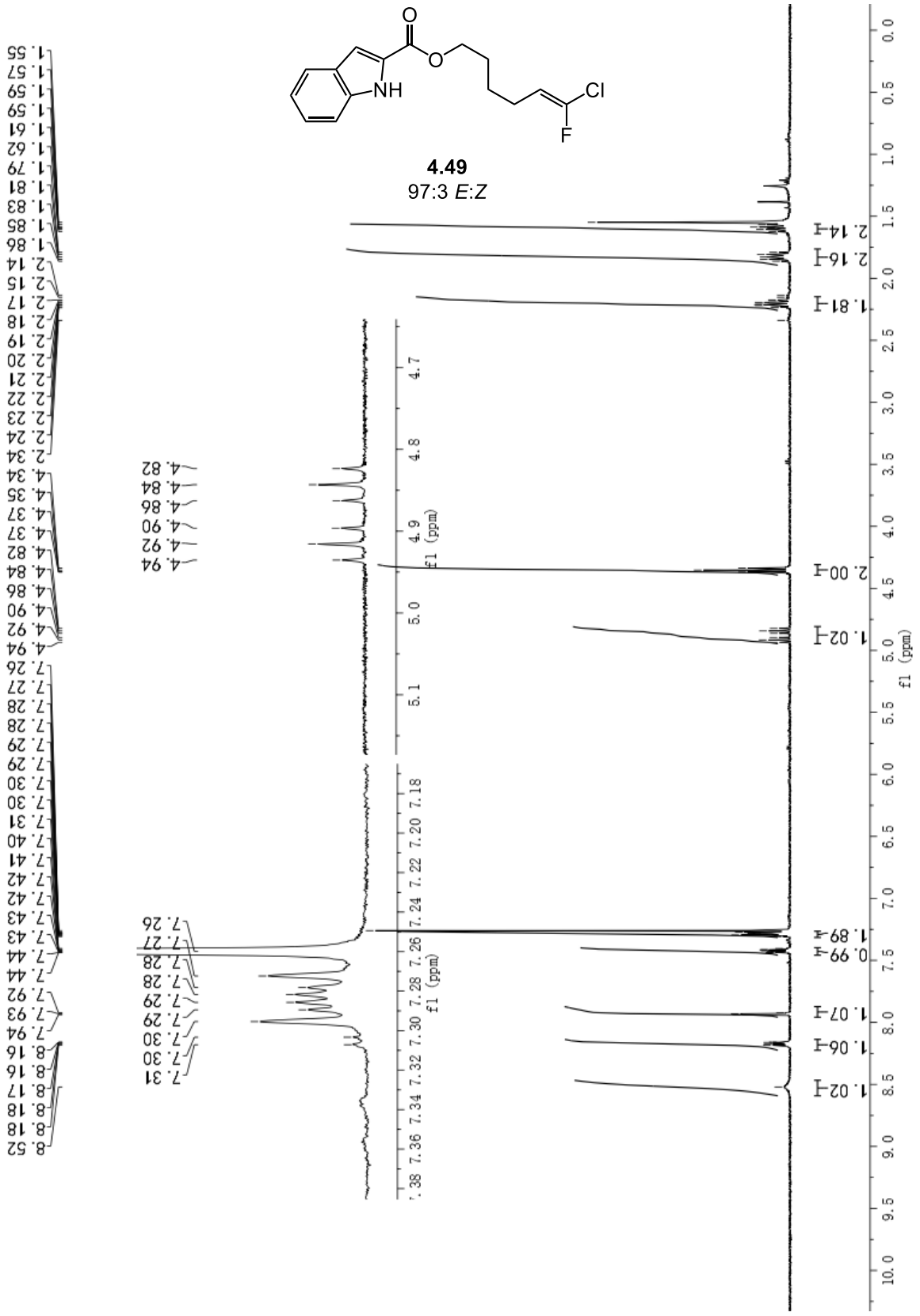


^{19}F NMR Spectrum of 4.49

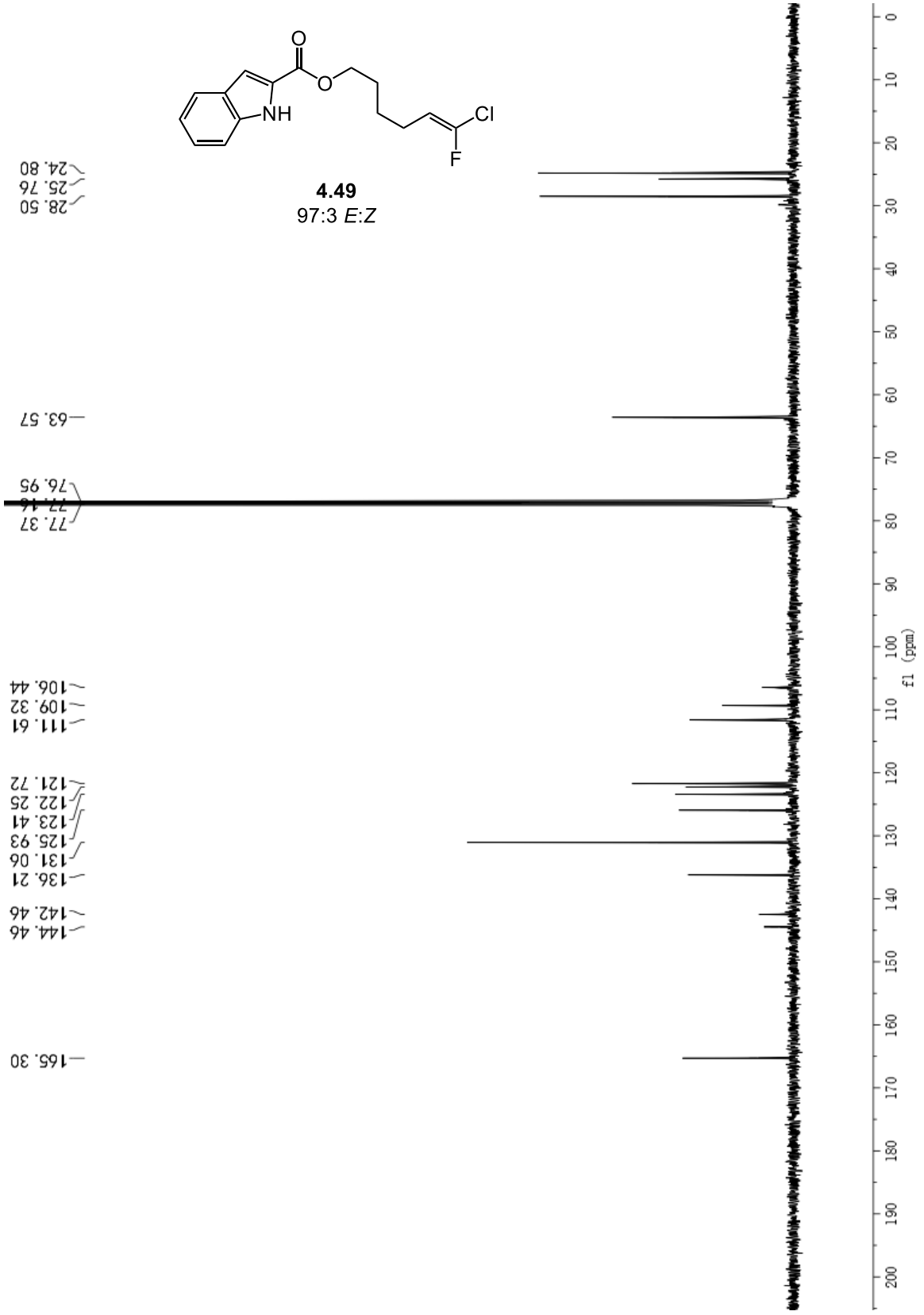


4.49
97:3 *E*:*Z*

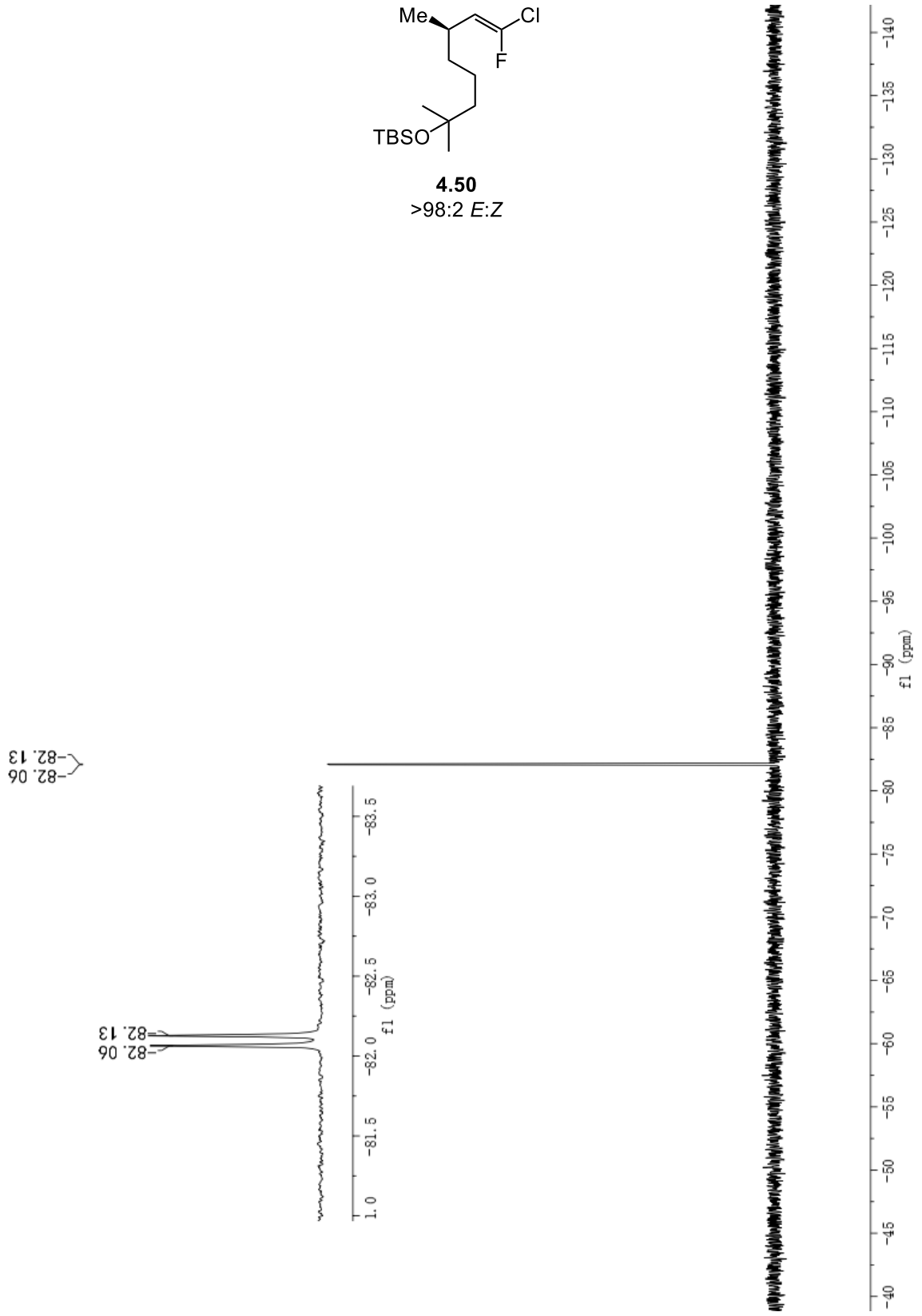
^{1}H NMR Spectrum of 4.49



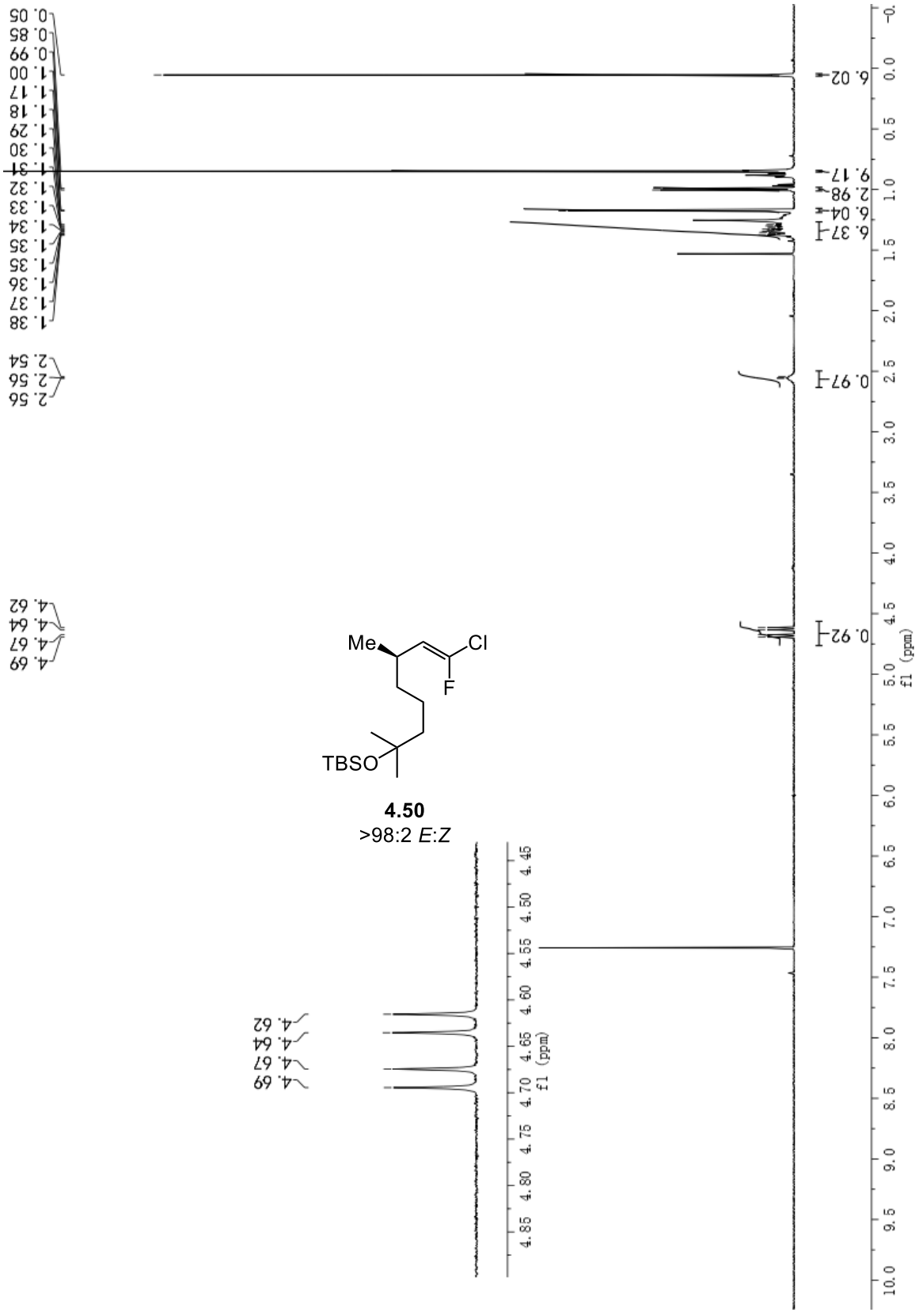
^{13}C NMR Spectrum of 4.49



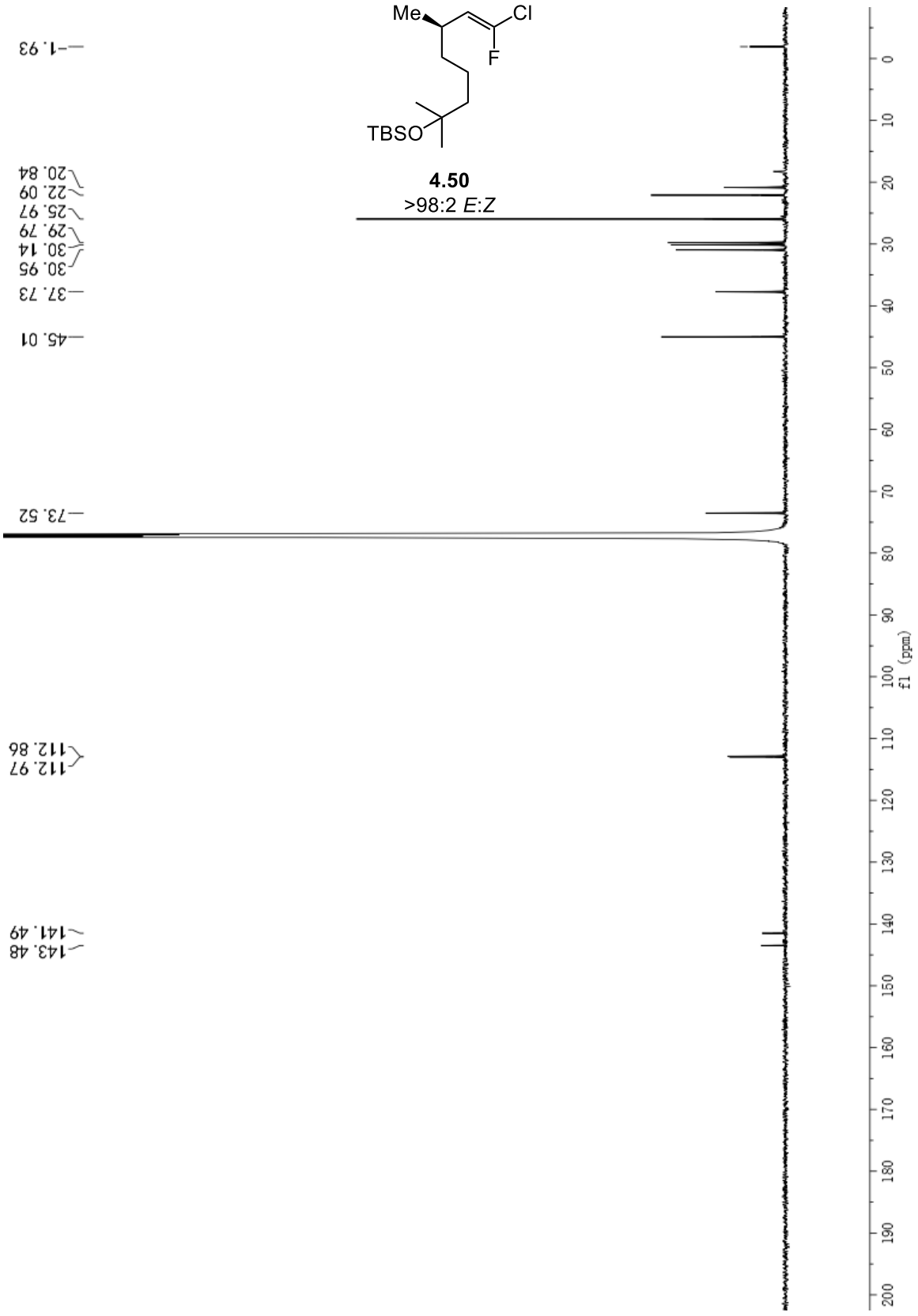
^{19}F NMR Spectrum of 4.50



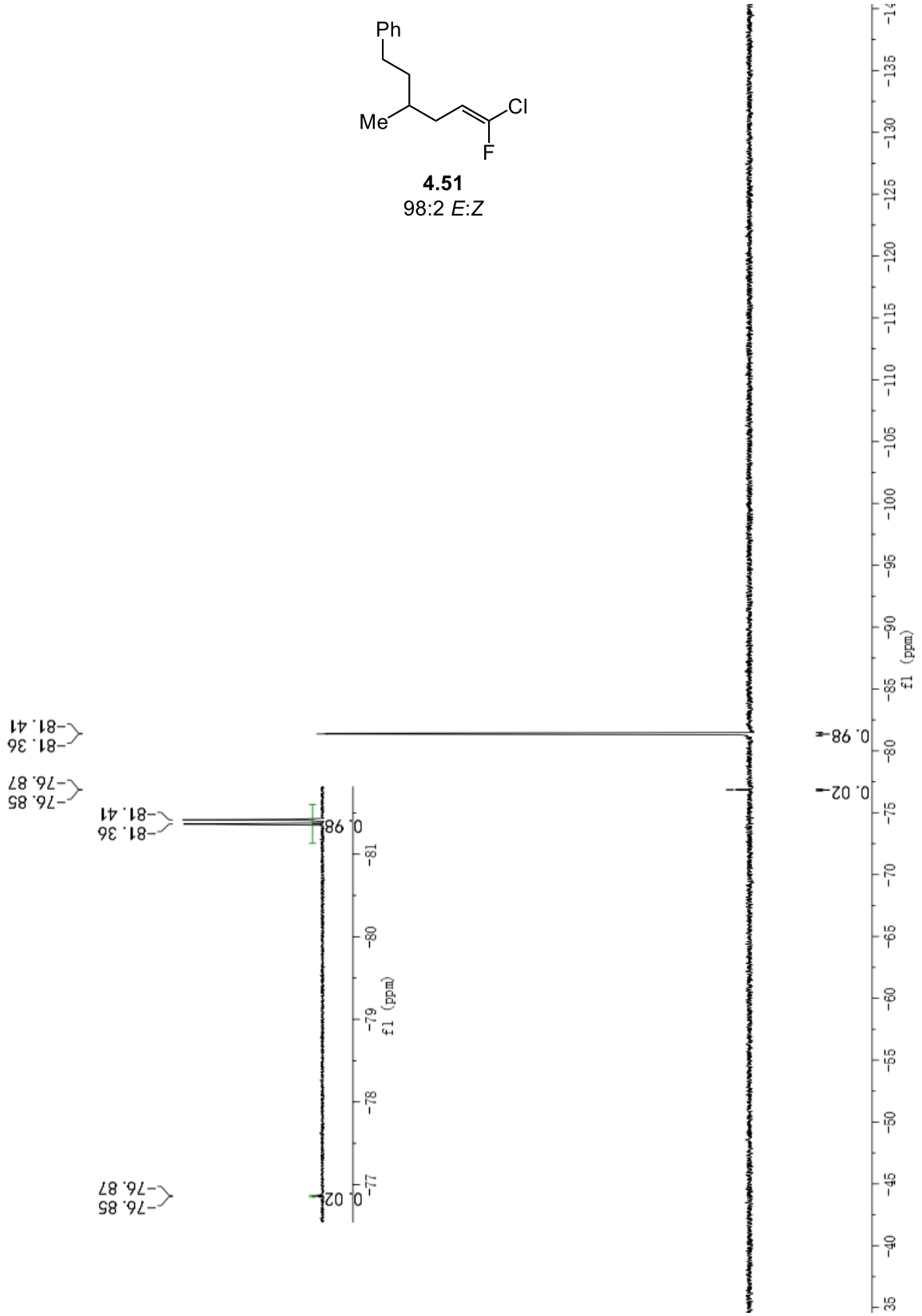
^{1}H NMR Spectrum of 4.50



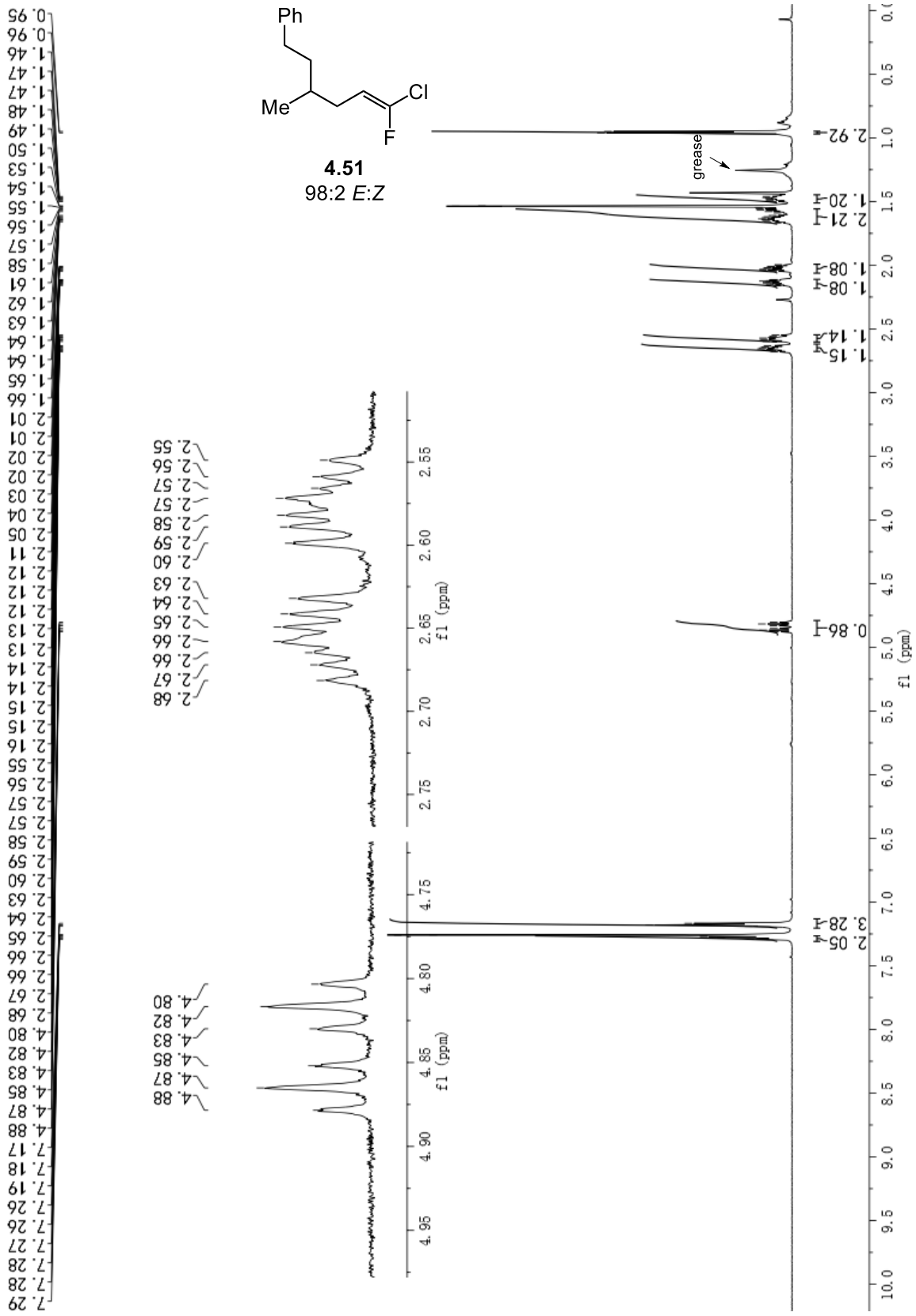
^{13}C NMR Spectrum of 4.50



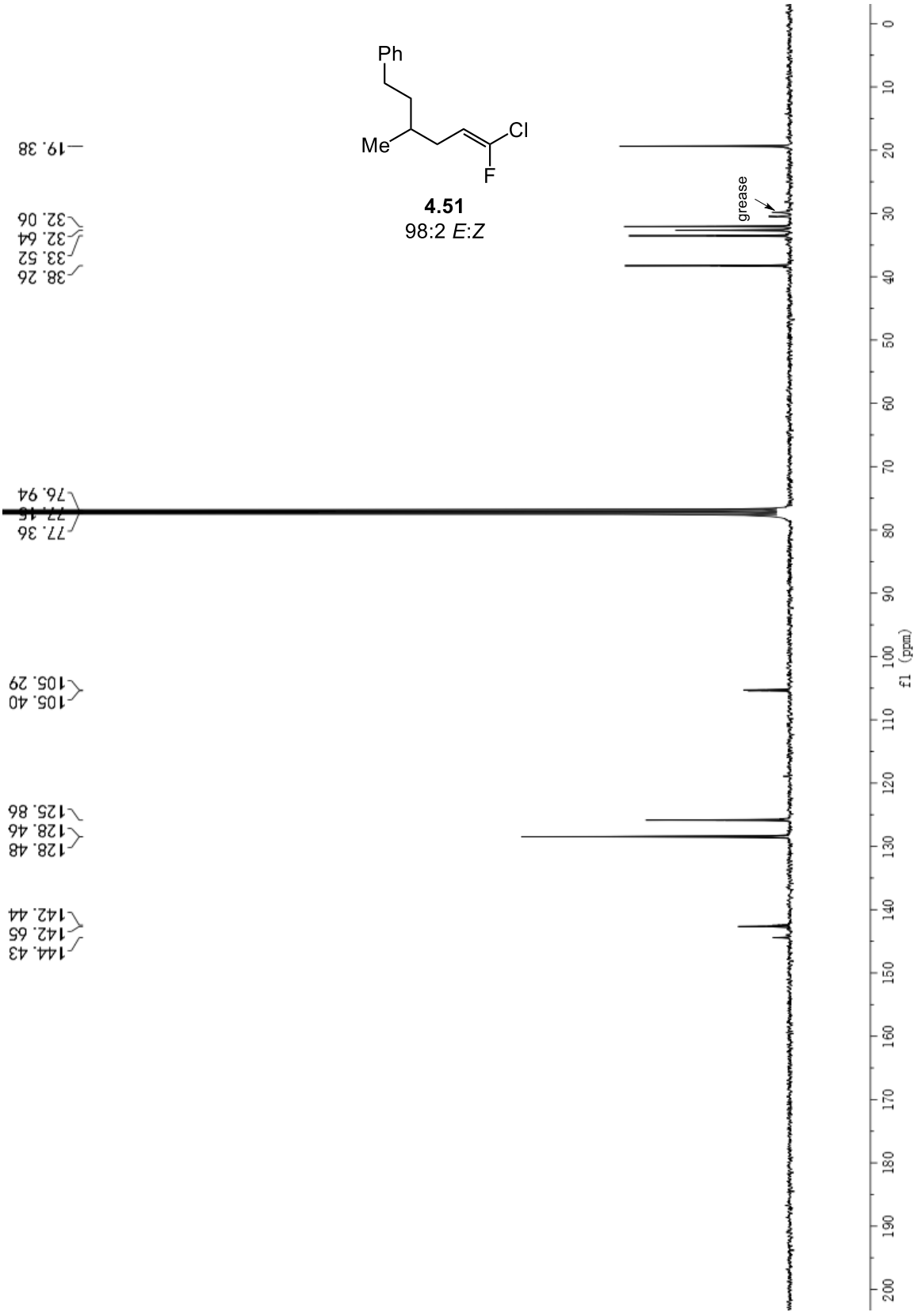
^{19}F NMR Spectrum of 4.51



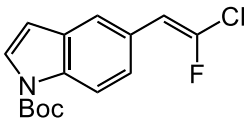
^{1}H NMR Spectrum of 10h



^{13}C NMR Spectrum of 4.51

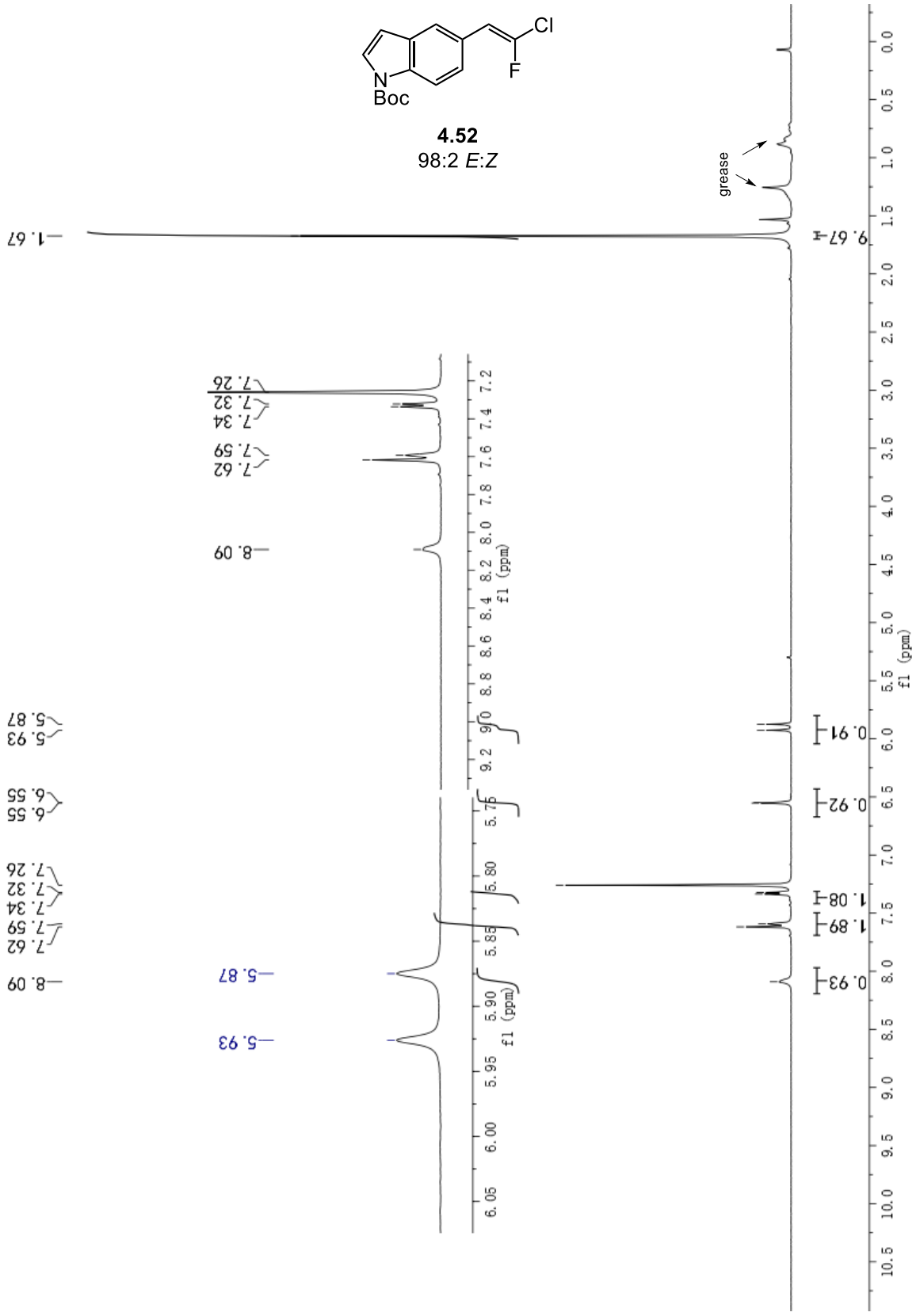


^{19}F NMR Spectrum of 4.52

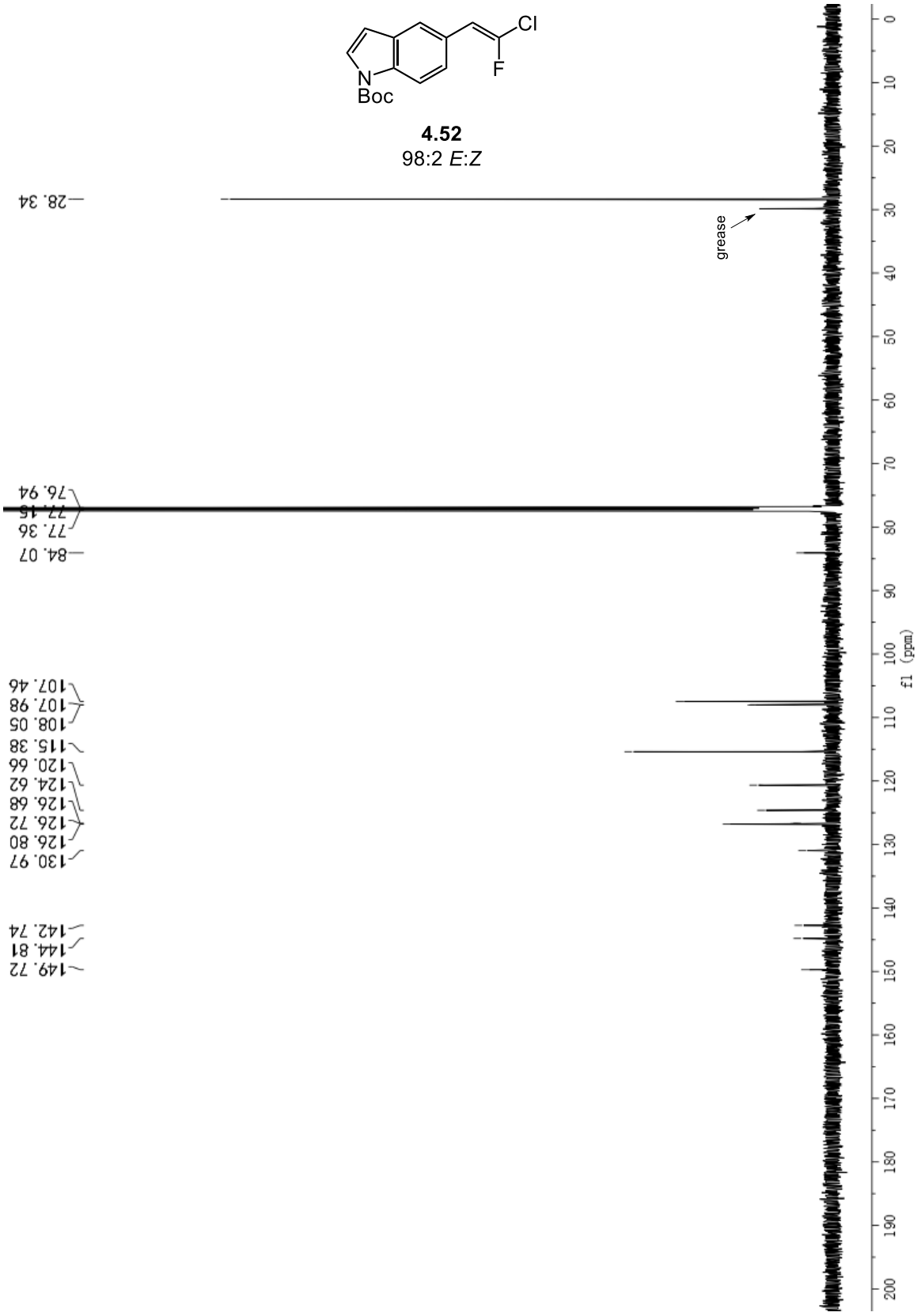


4.52
98:2 *E*:*Z*

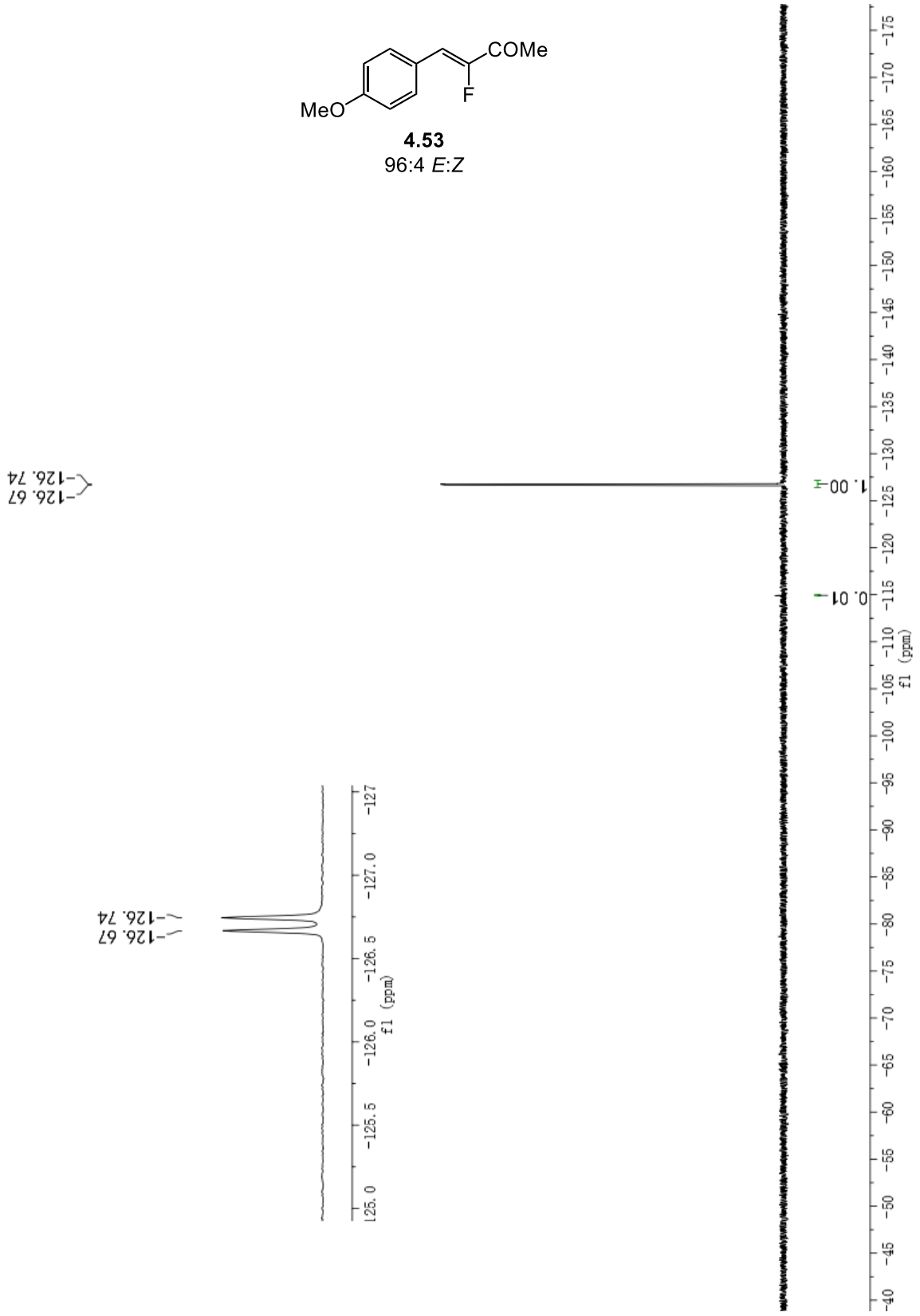
^{1}H NMR Spectrum of 4.52



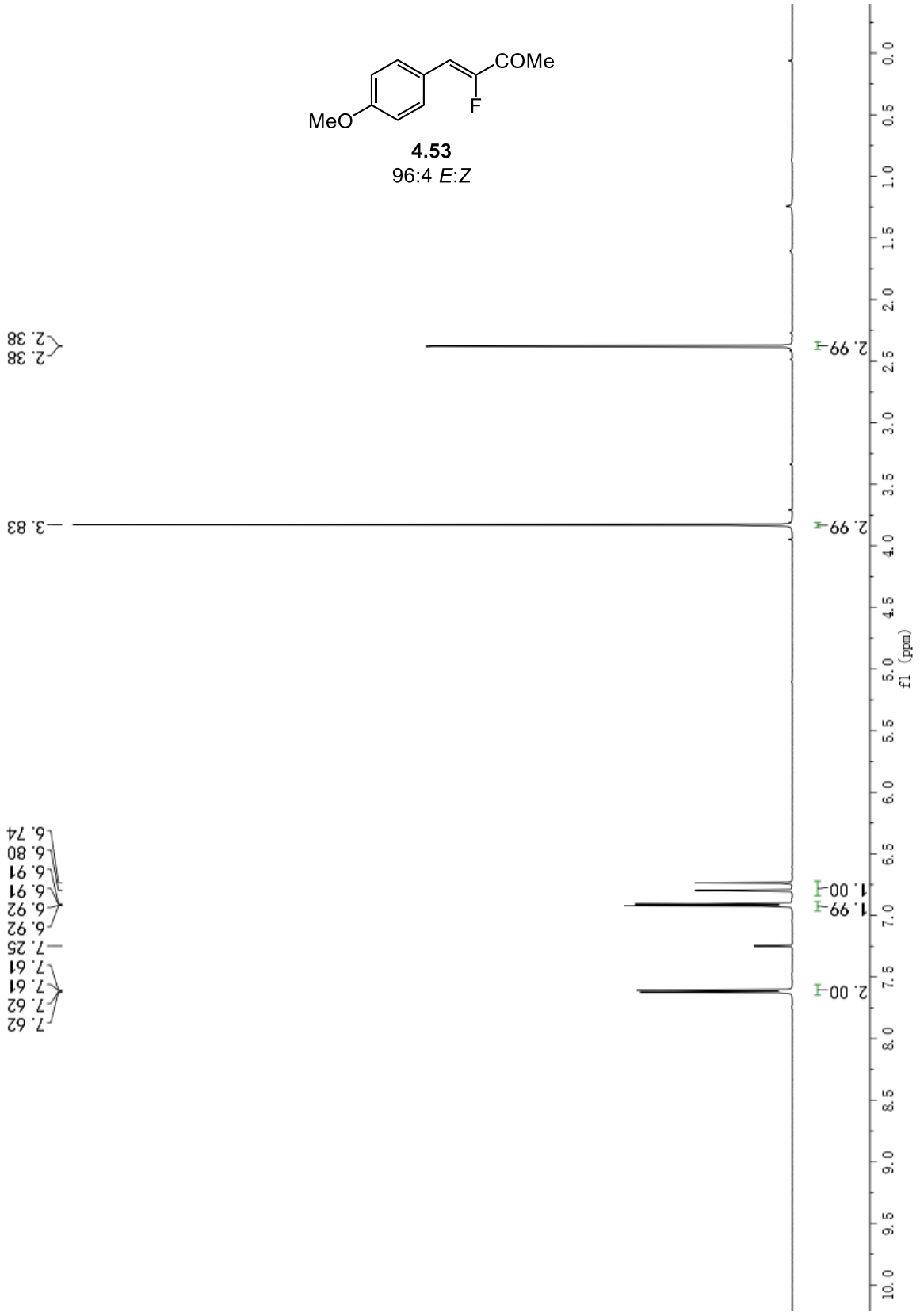
^{13}C NMR Spectrum of 4.52



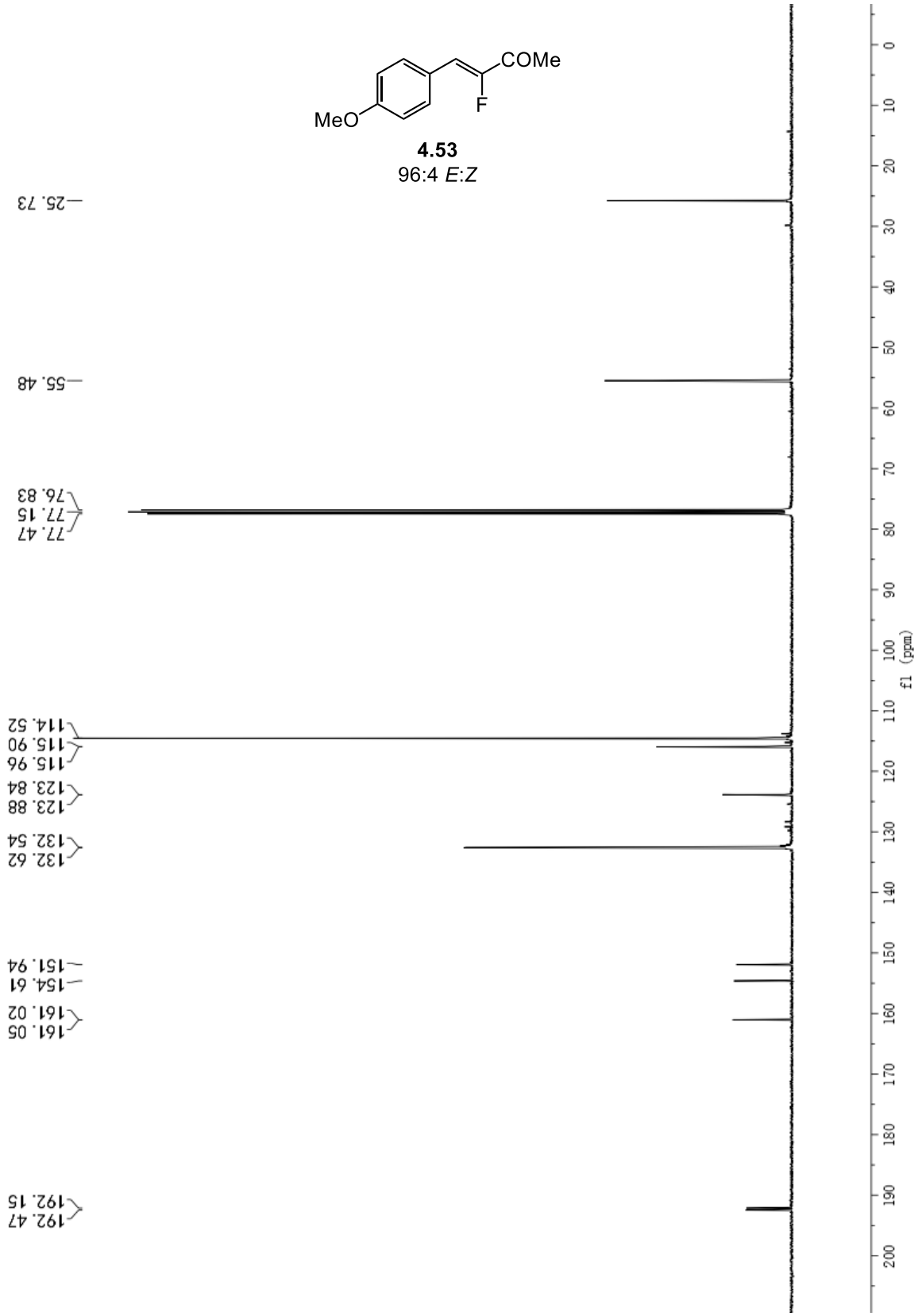
^{19}F NMR Spectrum of 4.53



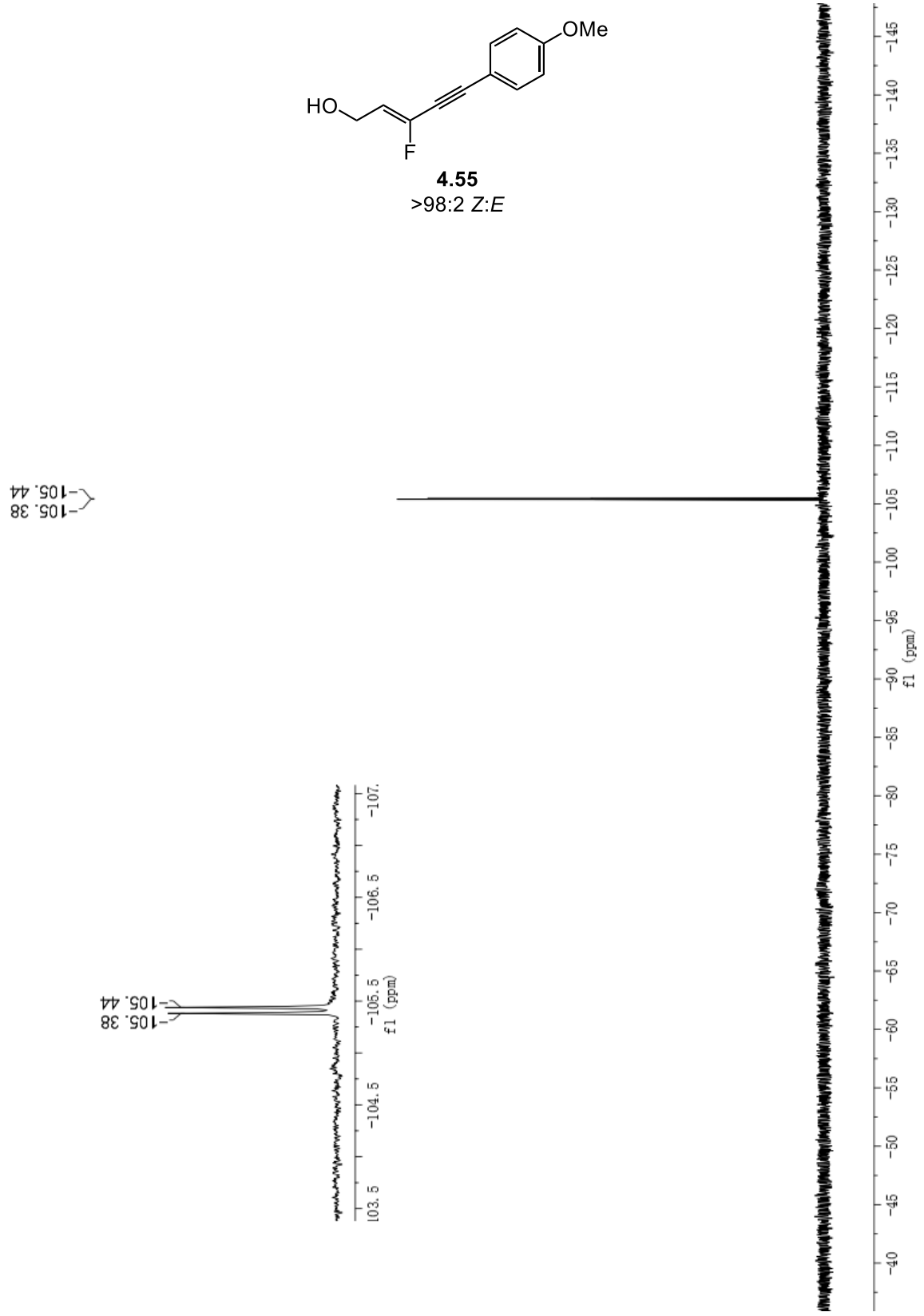
^{1}H NMR Spectrum of 4.53



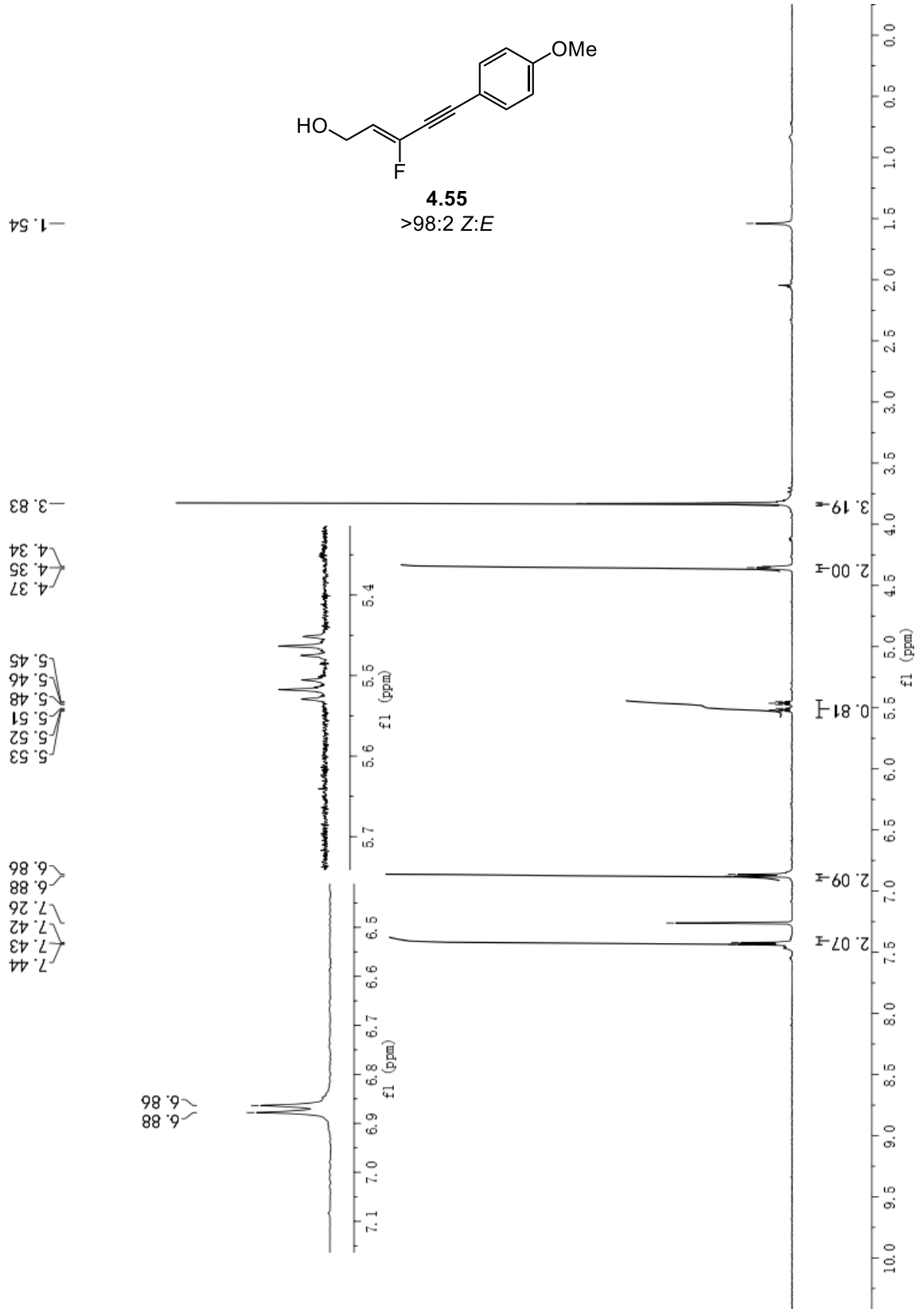
^{13}C NMR Spectrum of 4.53



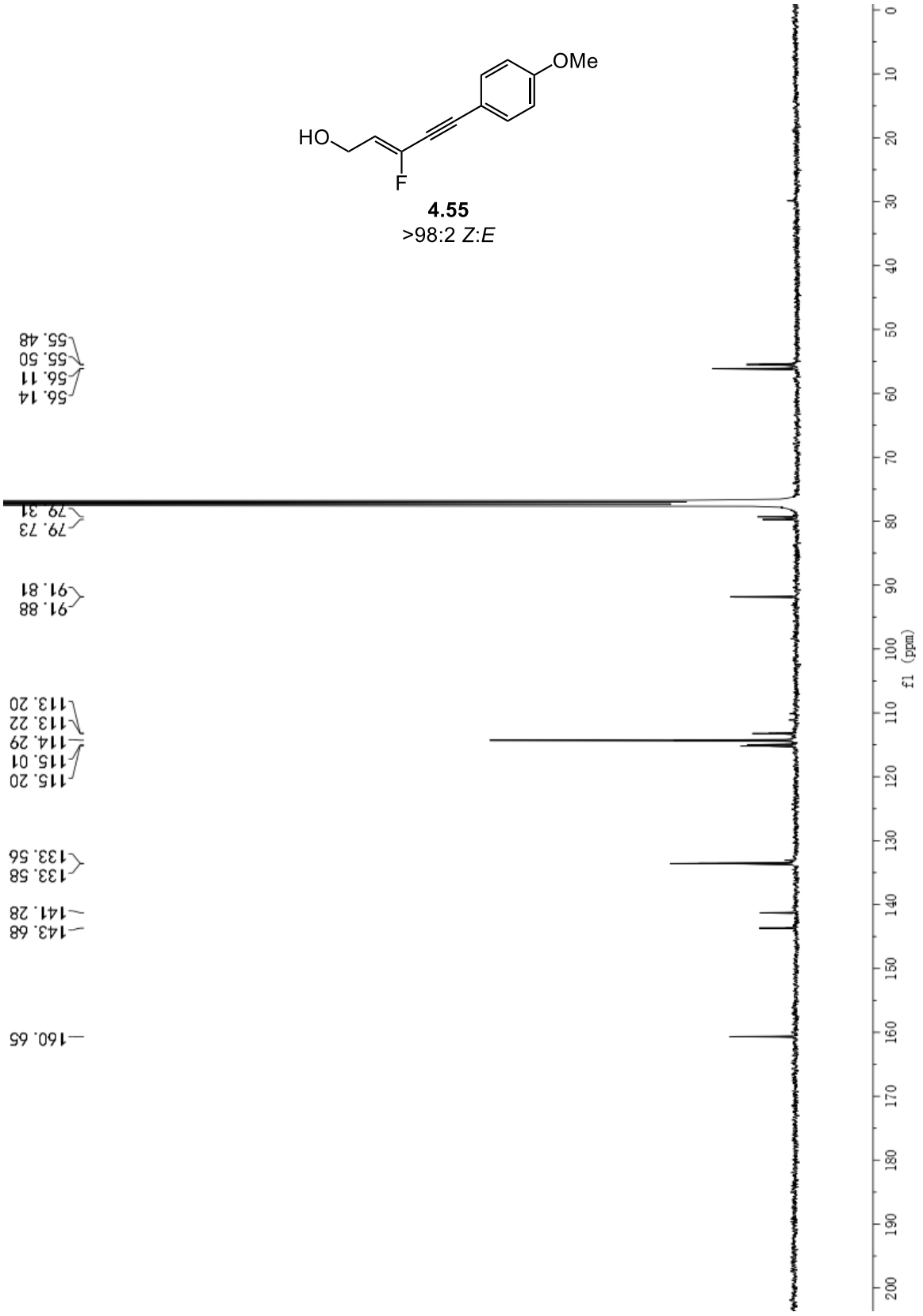
^{19}F NMR Spectrum of 4.55



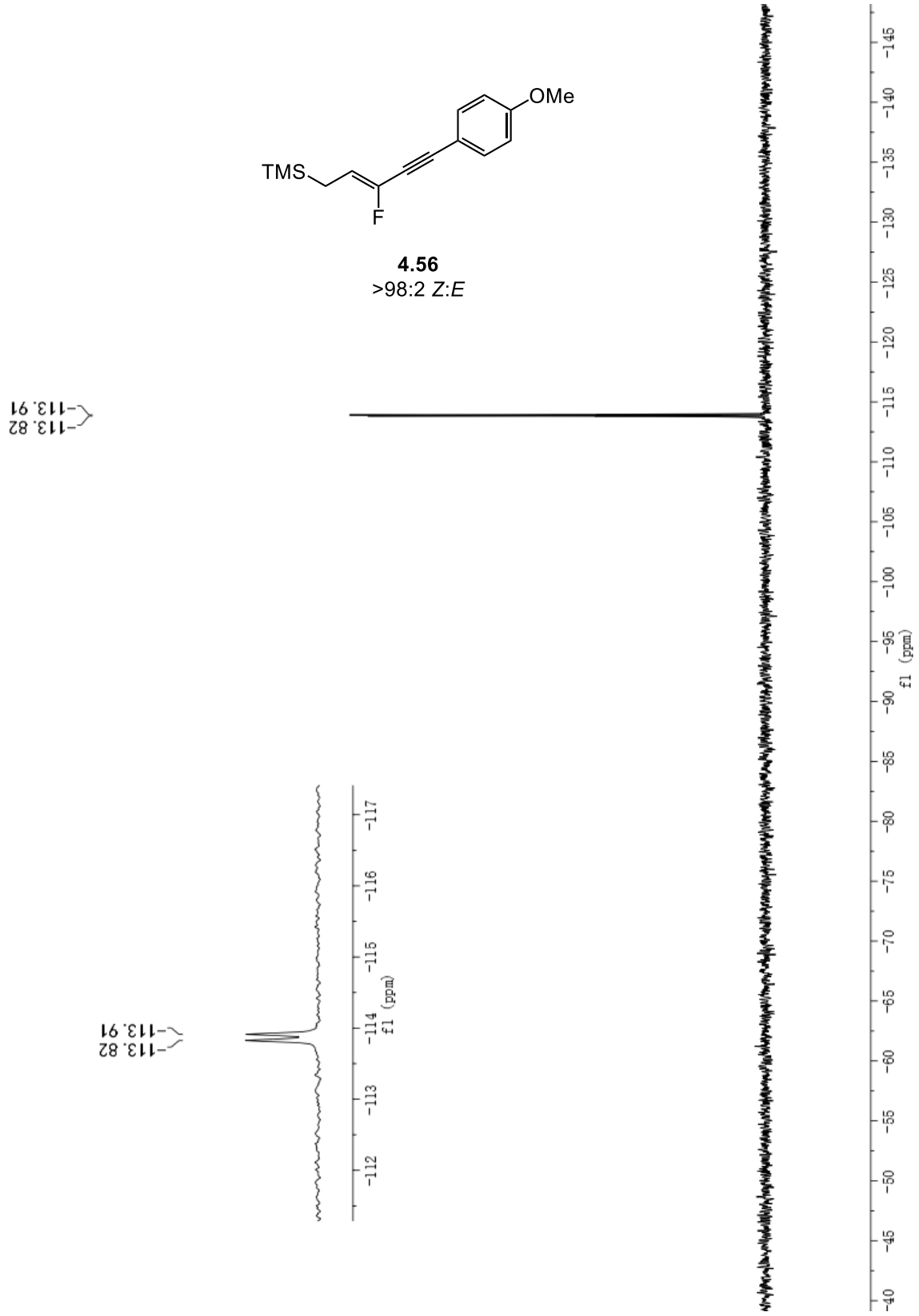
^{1}H NMR Spectrum of 4.55



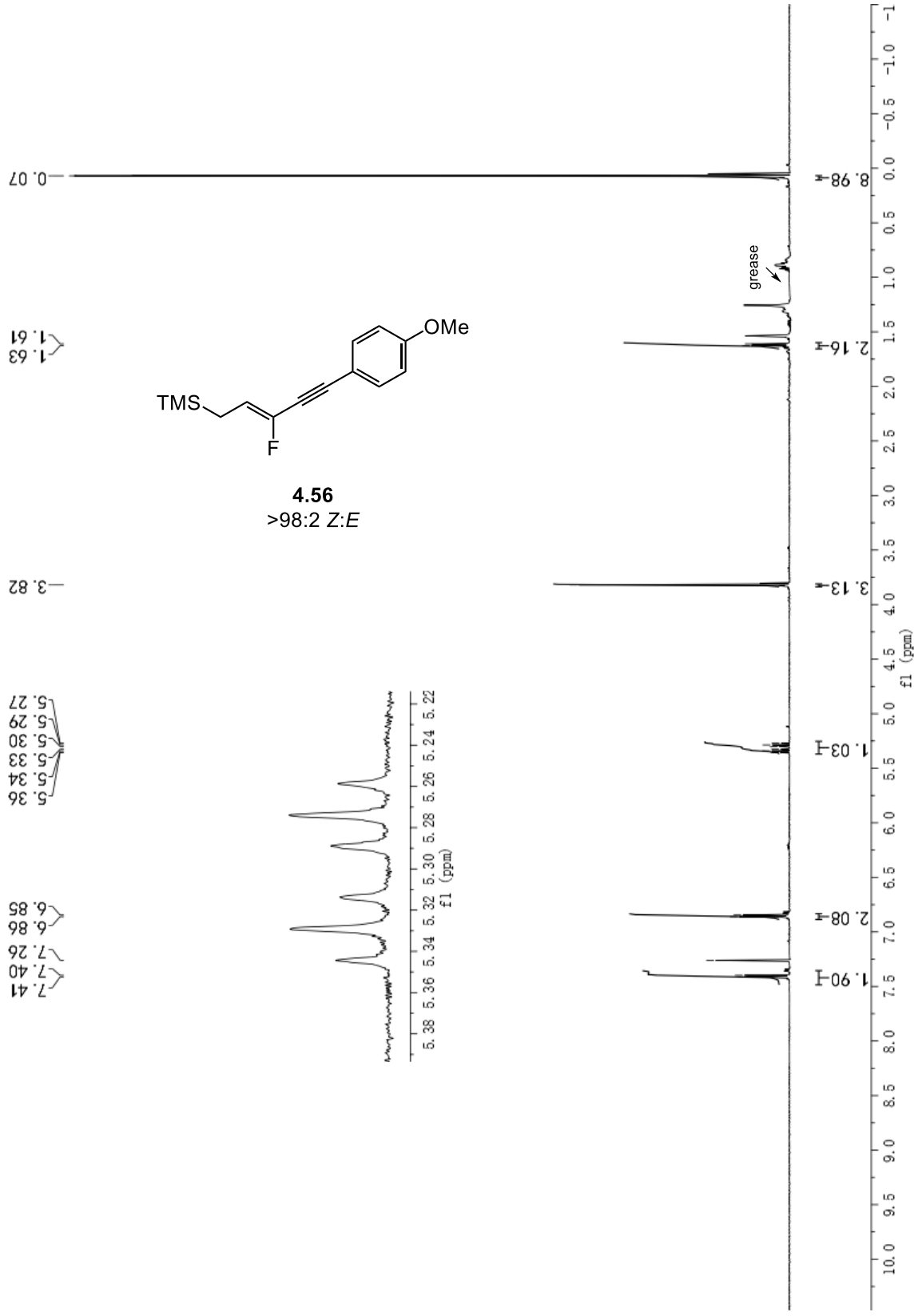
^{13}C NMR Spectrum of 4.55



^{19}F NMR Spectrum of 4.56

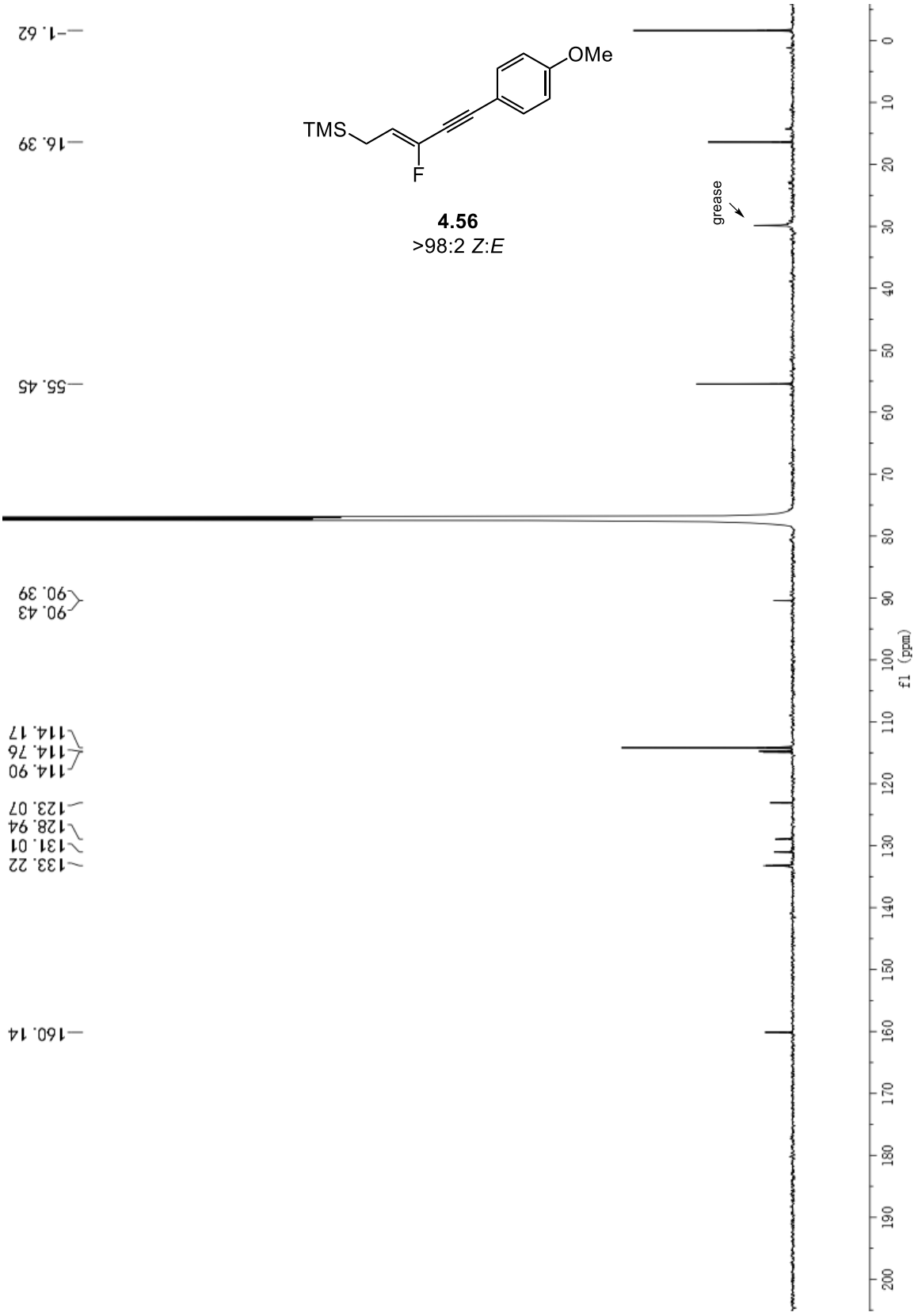


^{1}H NMR Spectrum of 4.56

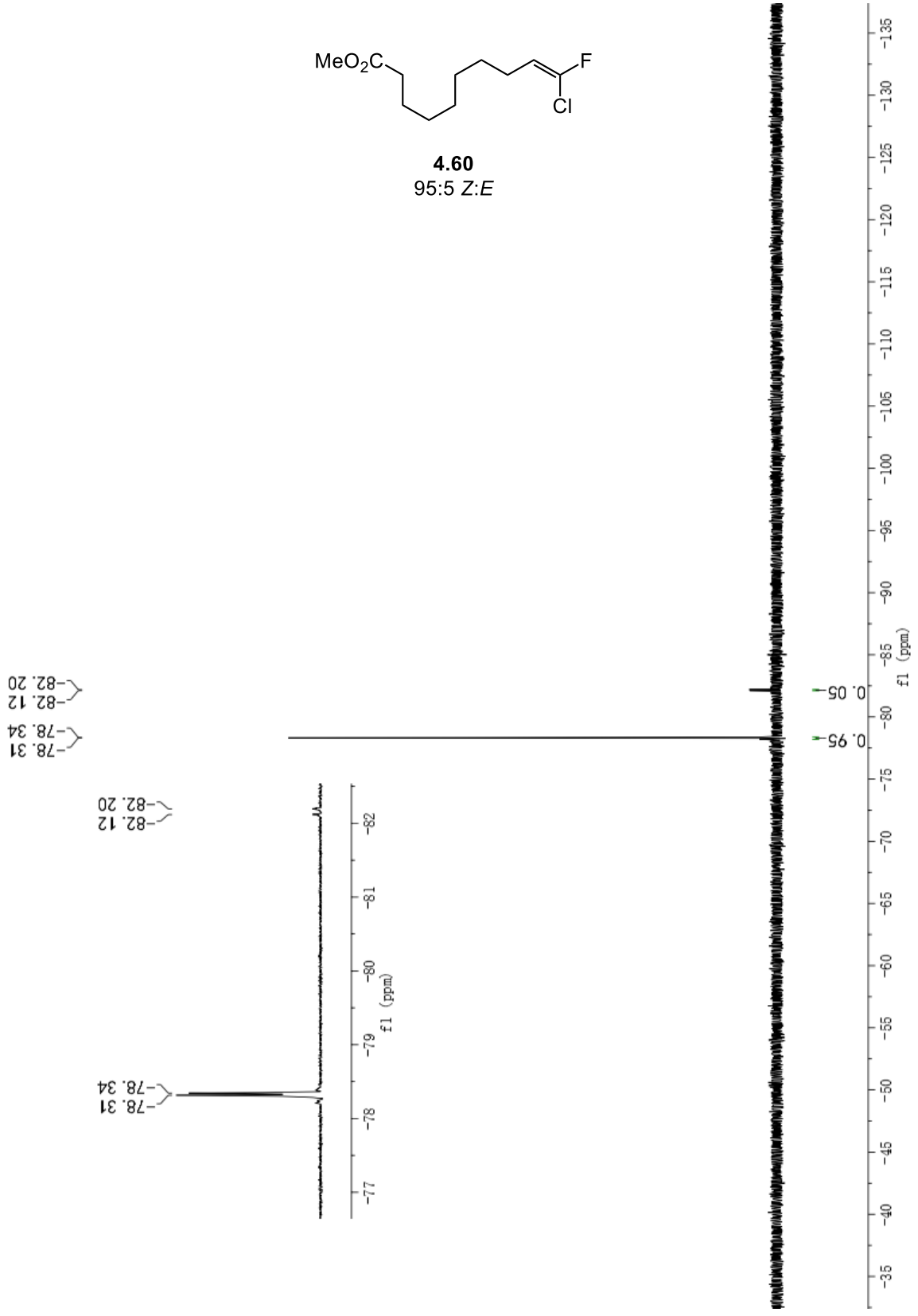


4.56
>98:2 *Z*:*E*

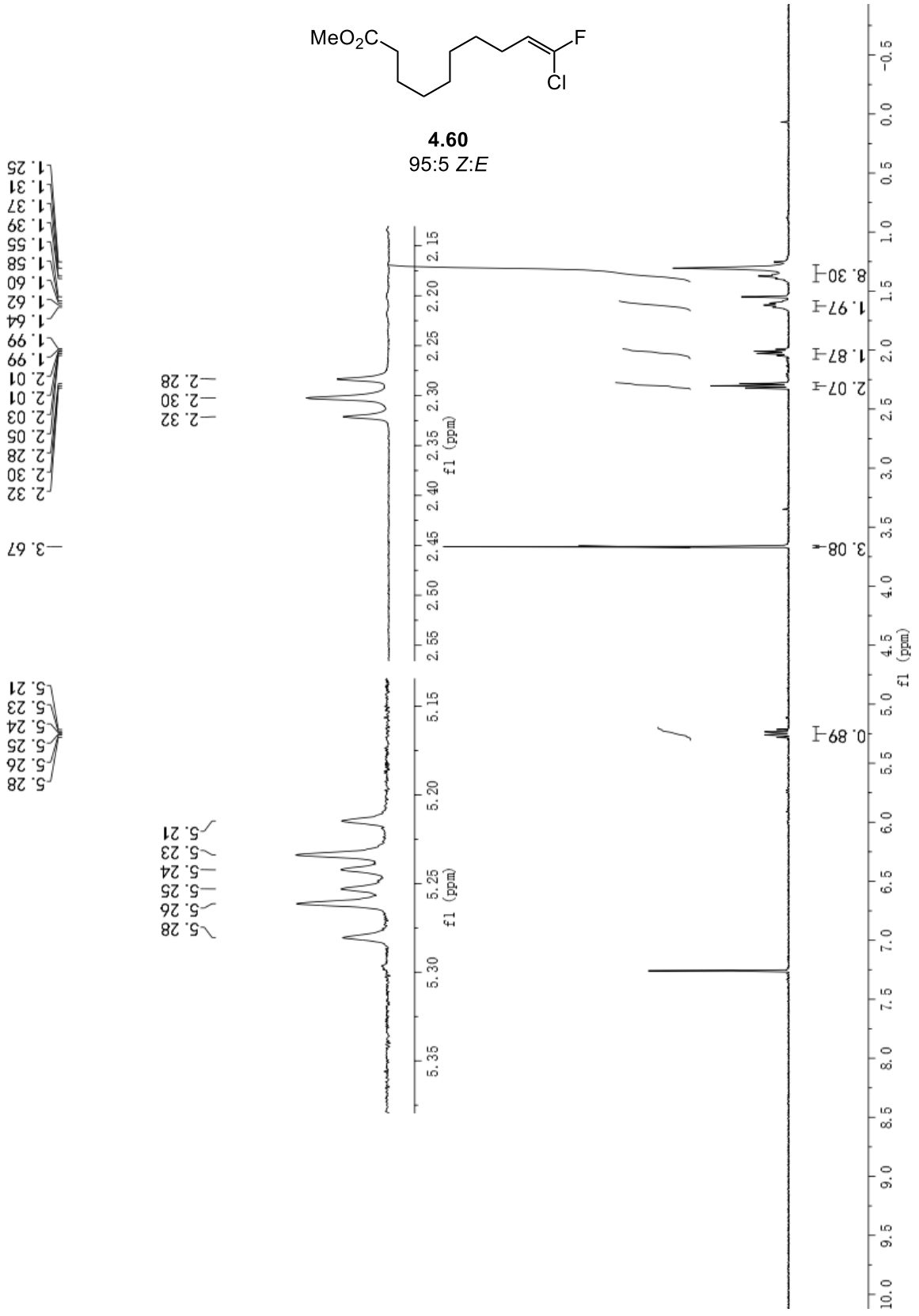
^{13}C NMR Spectrum of 4.56



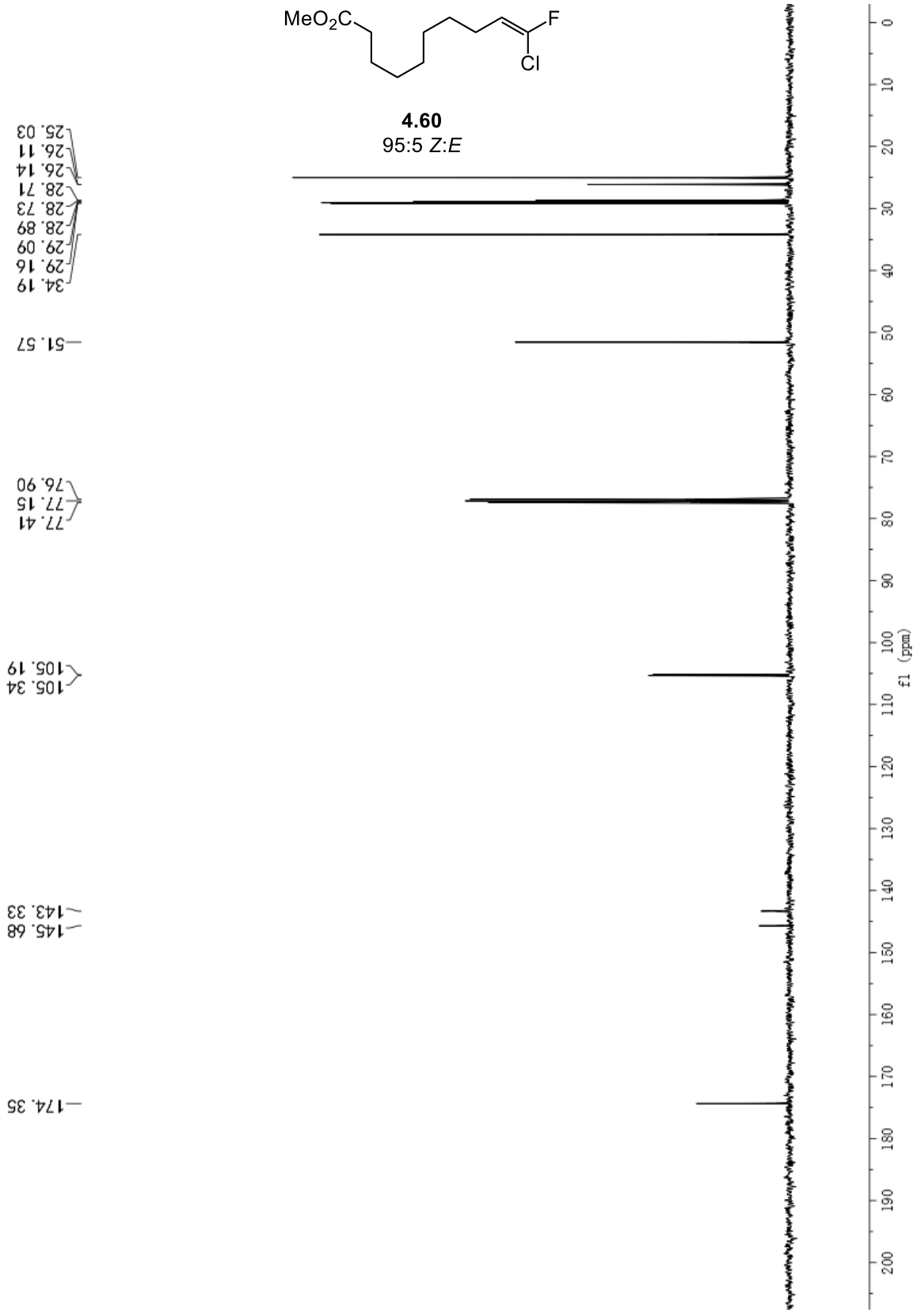
^{19}F NMR Spectrum of 4.60



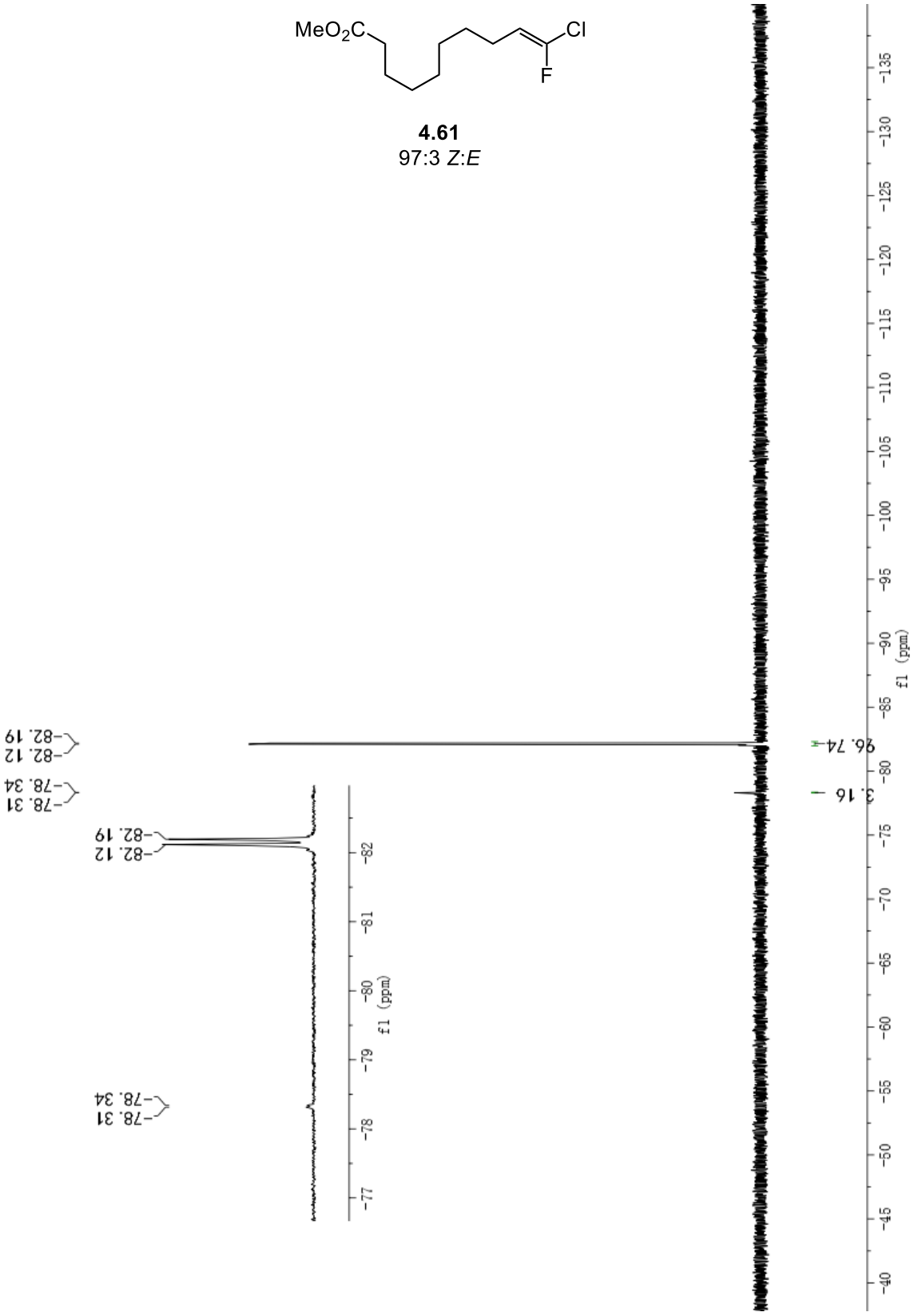
^{1}H NMR Spectrum of 4.60



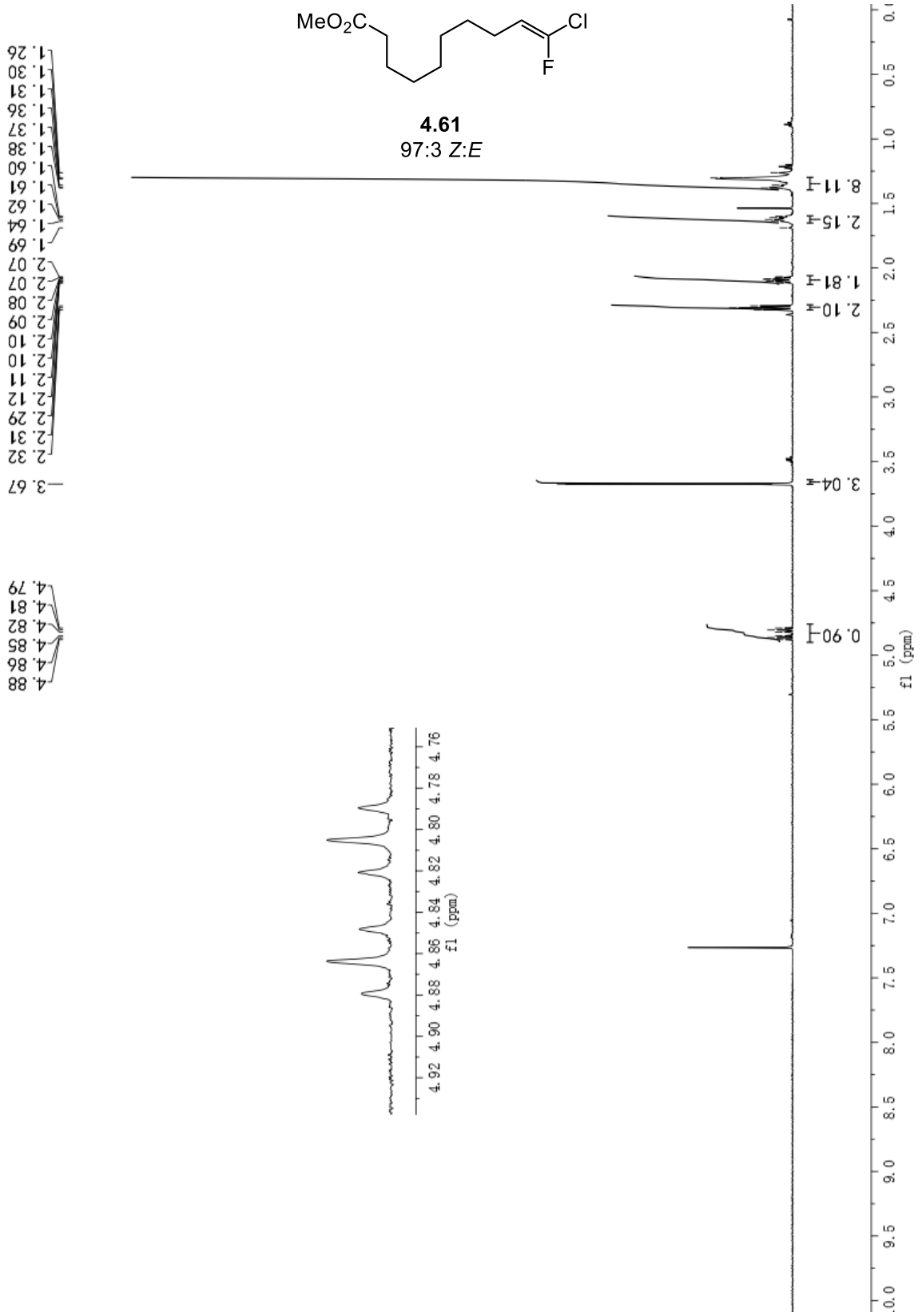
^{13}C NMR Spectrum of 4.60



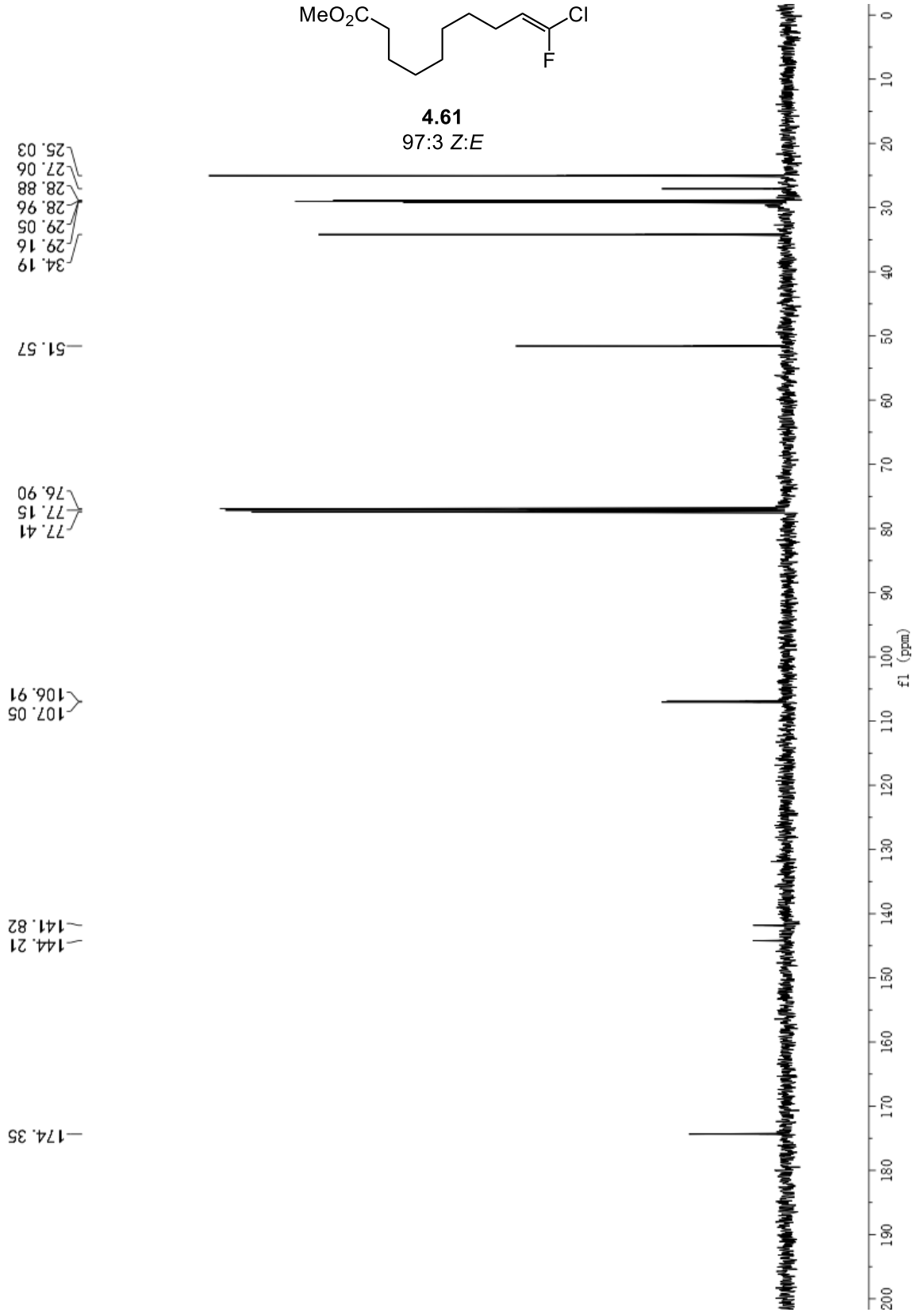
^{19}F NMR Spectrum of 4.61



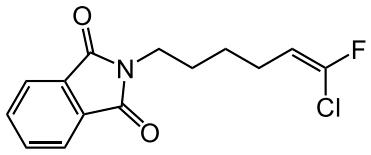
^{1}H NMR Spectrum of 4.61



^{13}C NMR Spectrum of 4.61

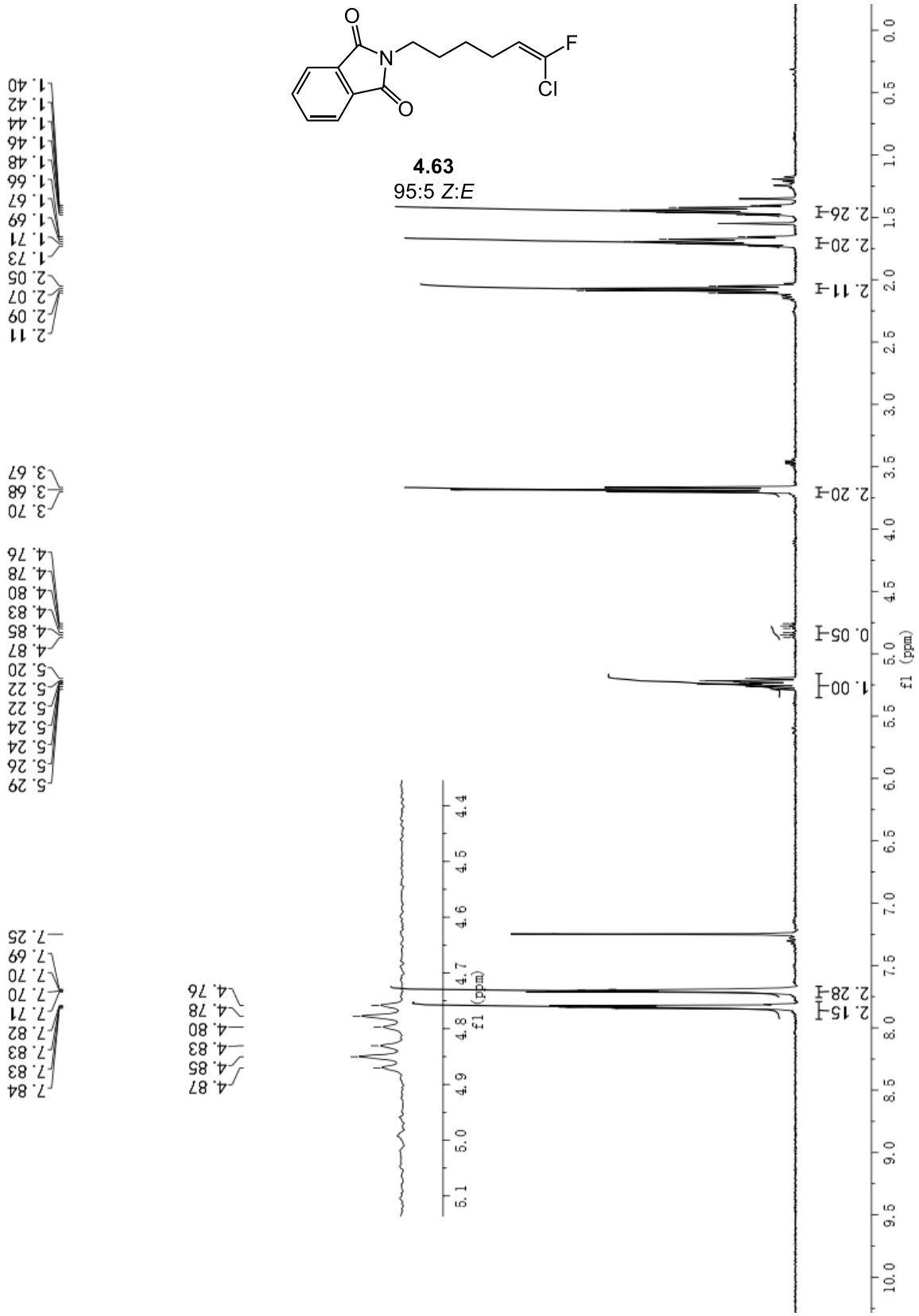


^{19}F NMR Spectrum of 4.63

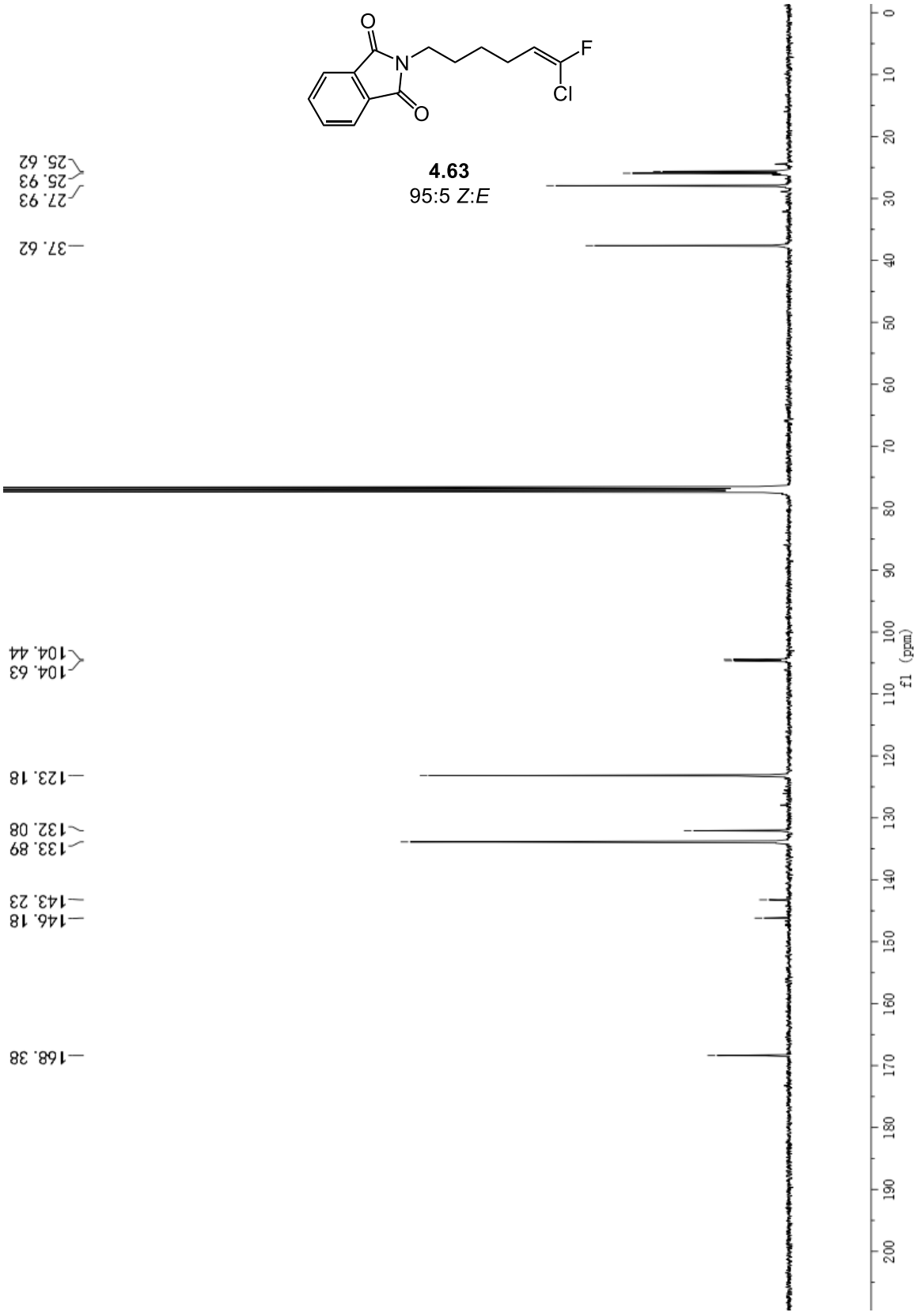


4.63
95:5 *Z*:*E*

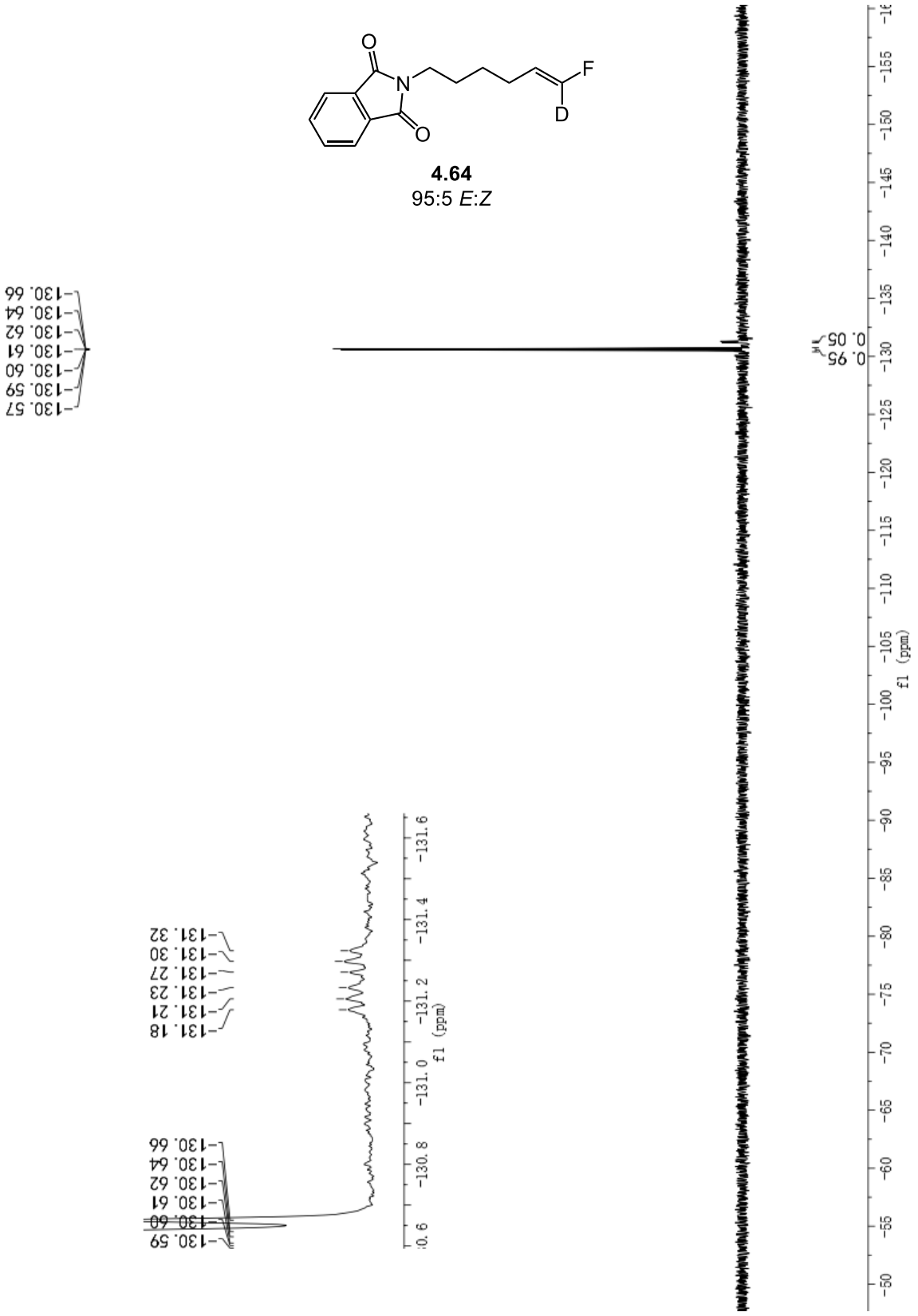
^{1}H NMR Spectrum of 4.63



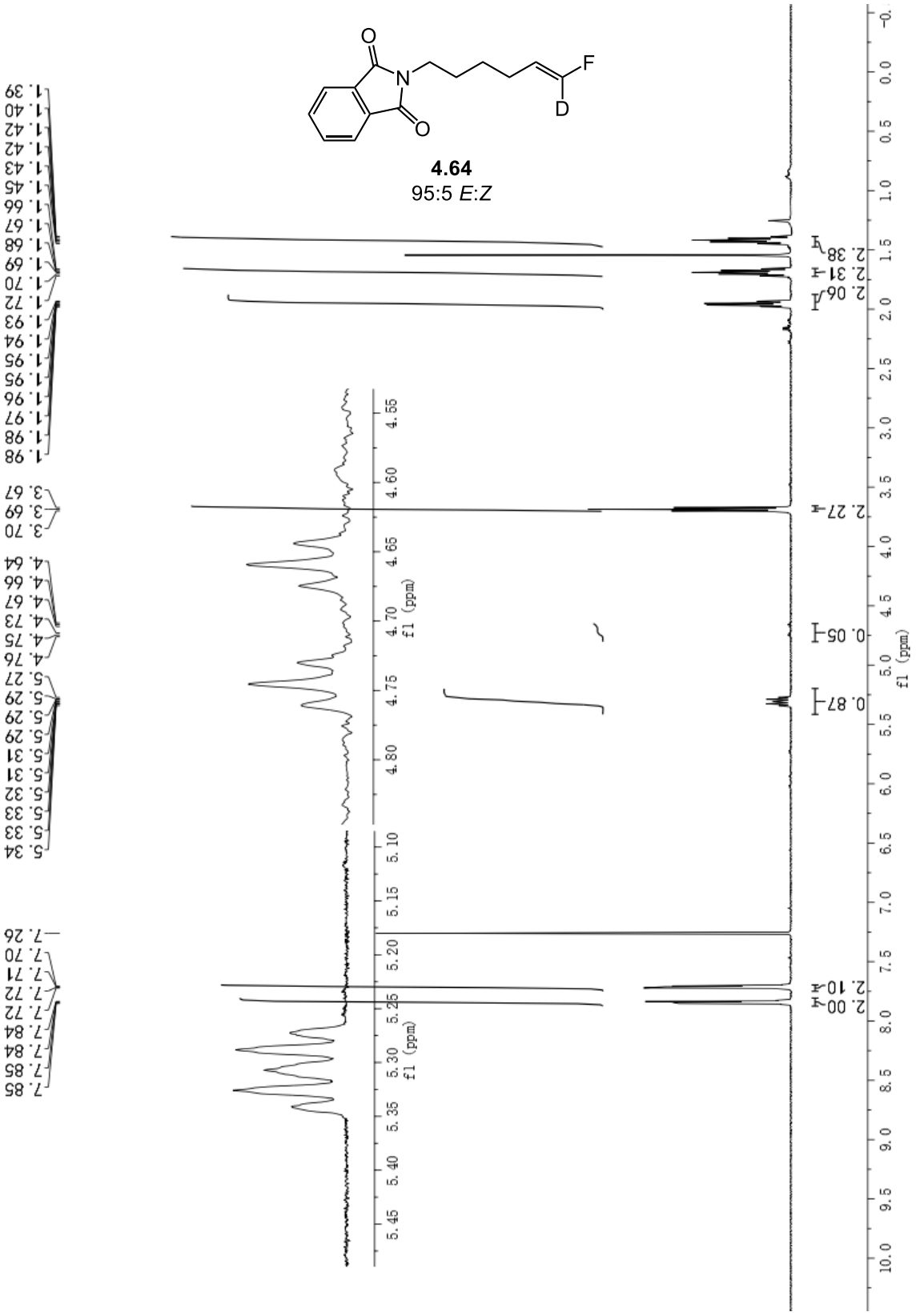
^{13}C NMR Spectrum of 4.63



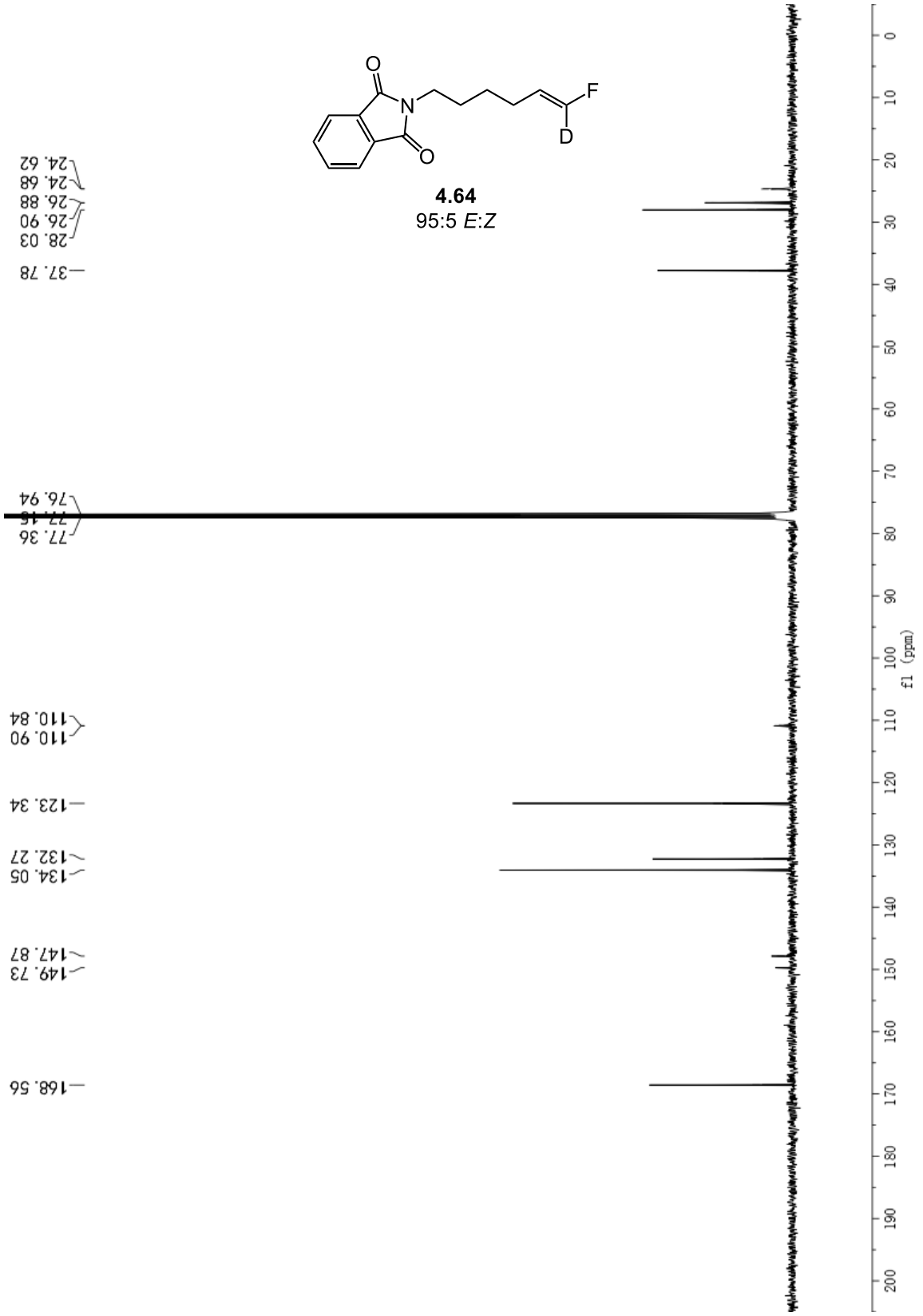
^{19}F NMR Spectrum of 4.64



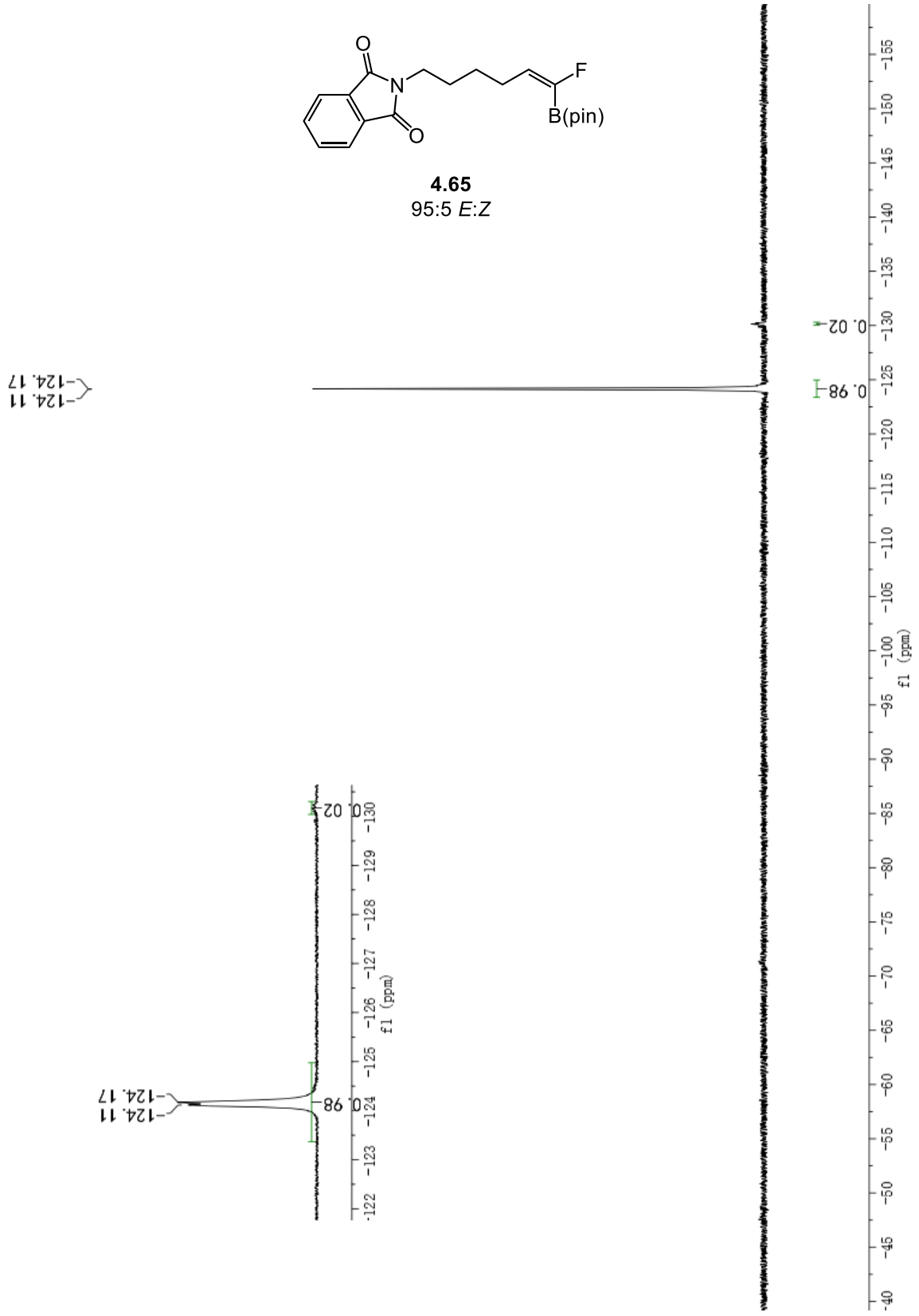
^{1}H NMR Spectrum of 4.64



^{13}C NMR Spectrum of 4.64

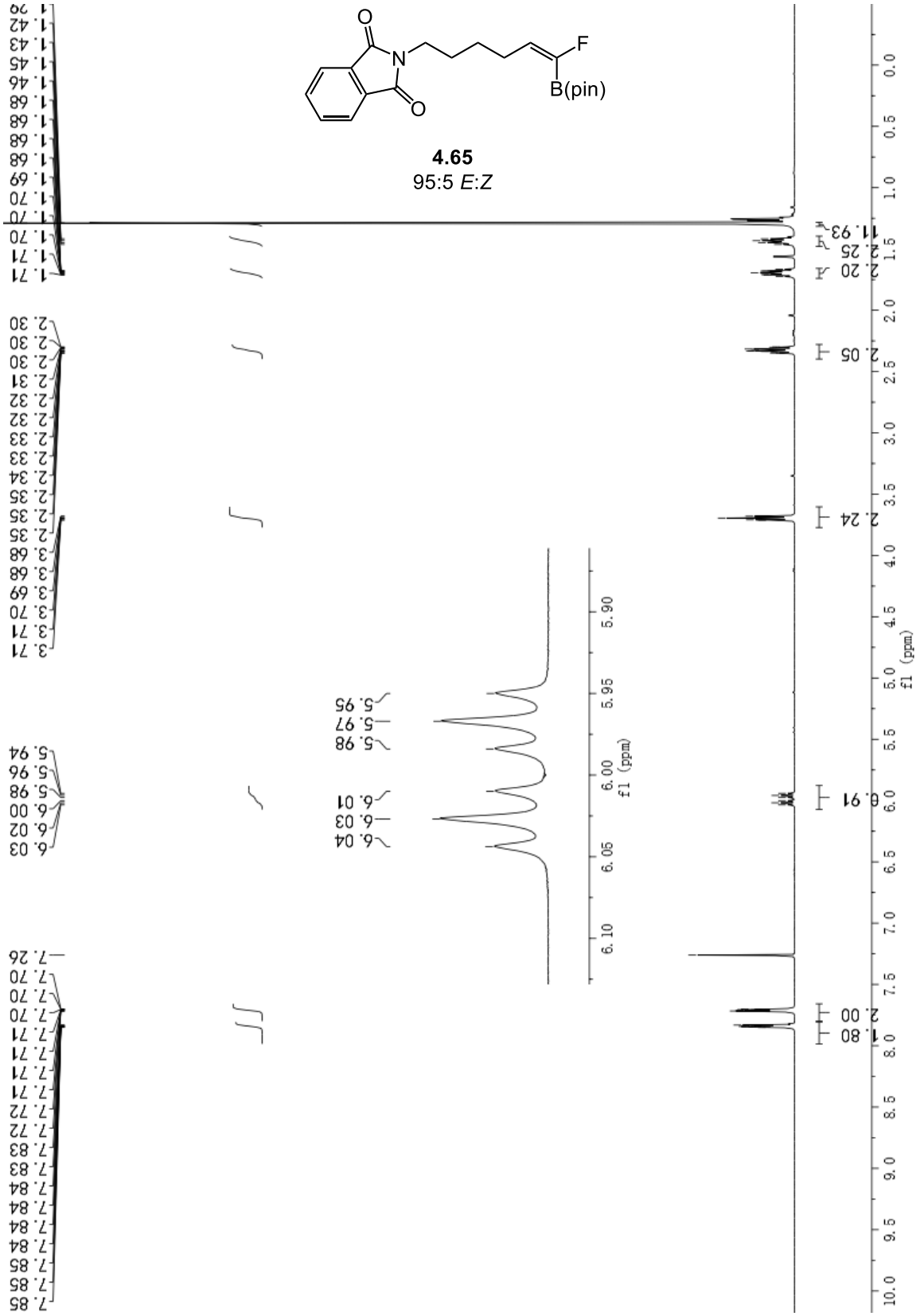


^{19}F NMR Spectrum of 4.65

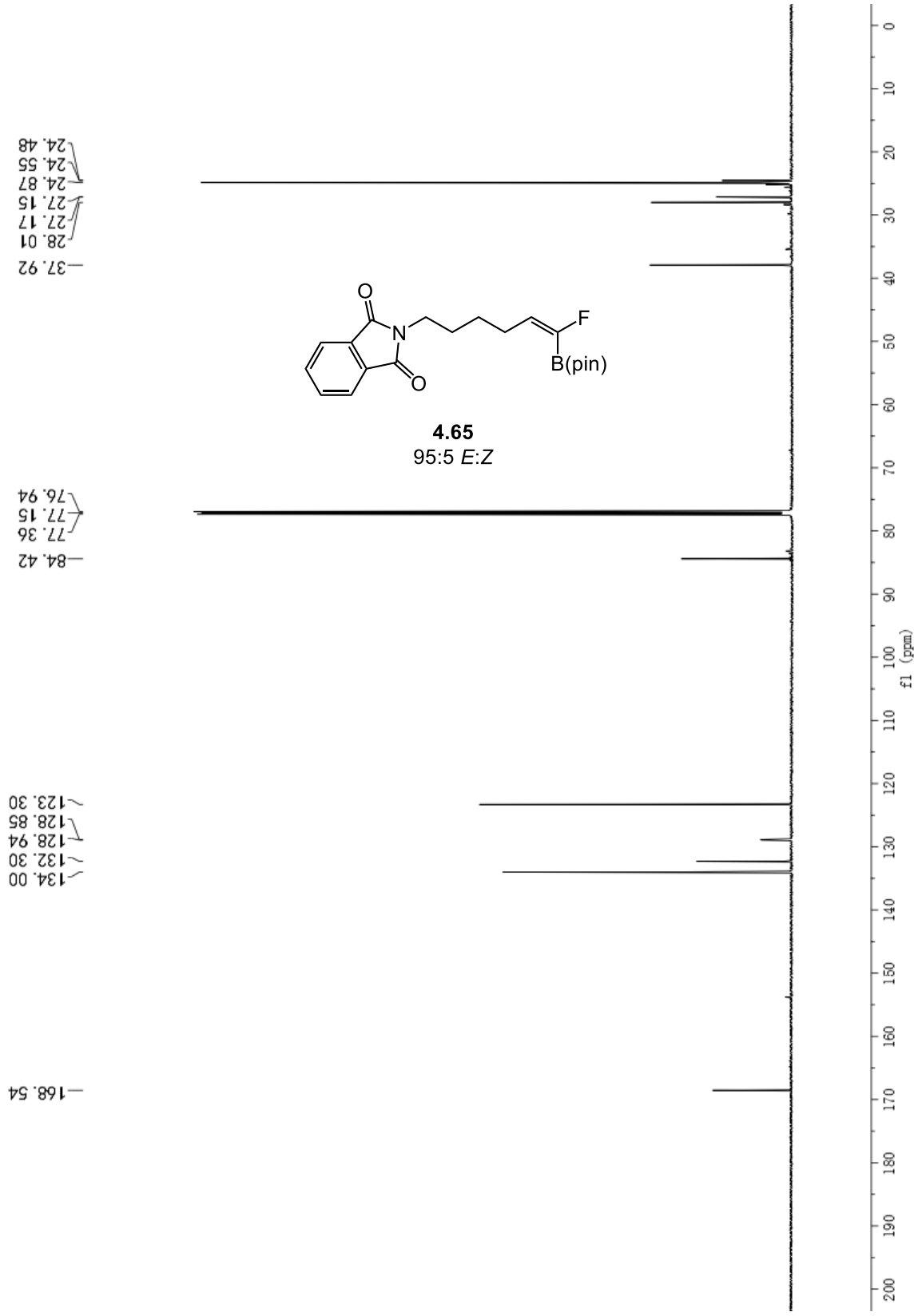


4.65
95:5 *E*:*Z*

^{1}H NMR Spectrum of 4.65

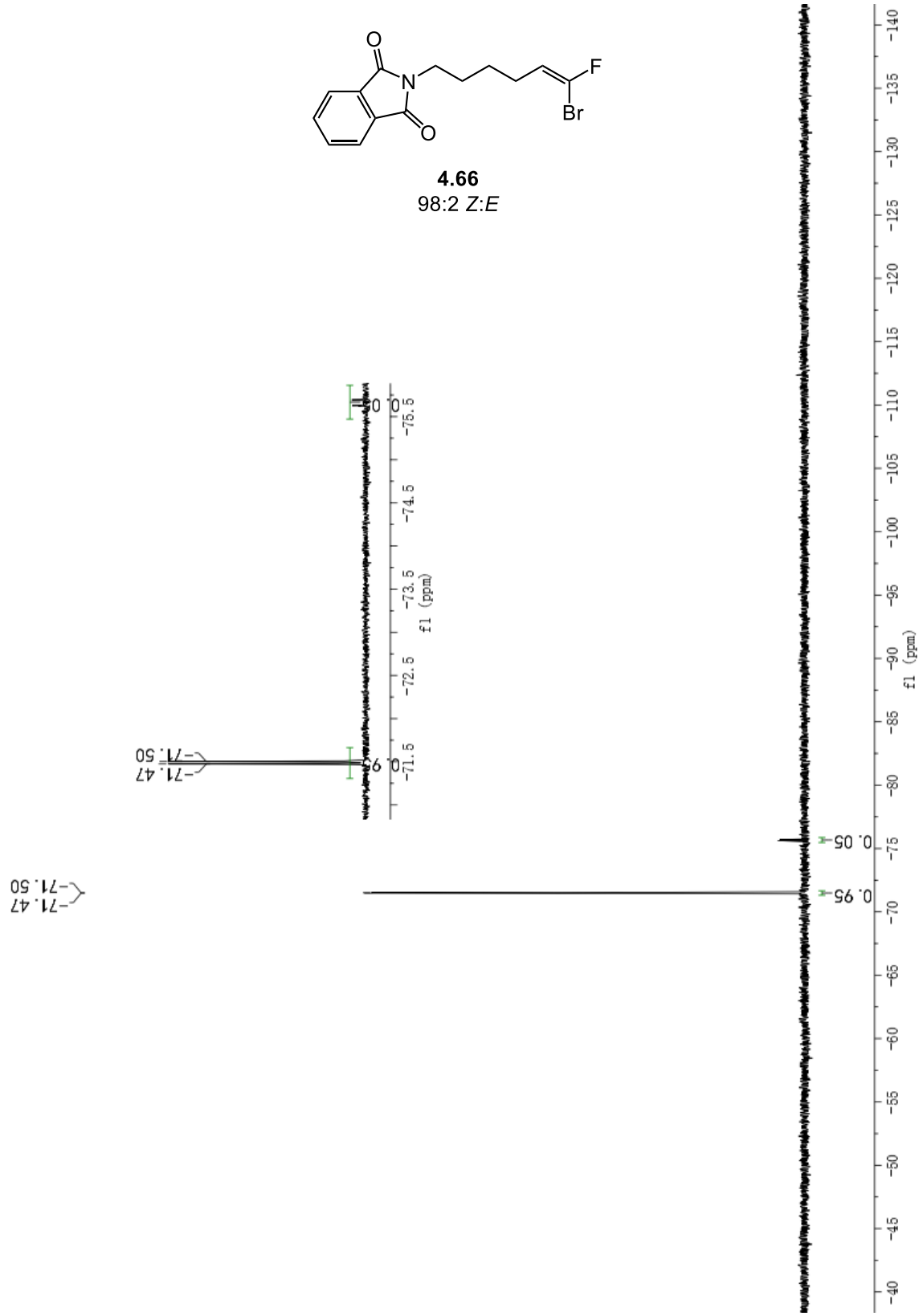


^{13}C NMR Spectrum of 4.65

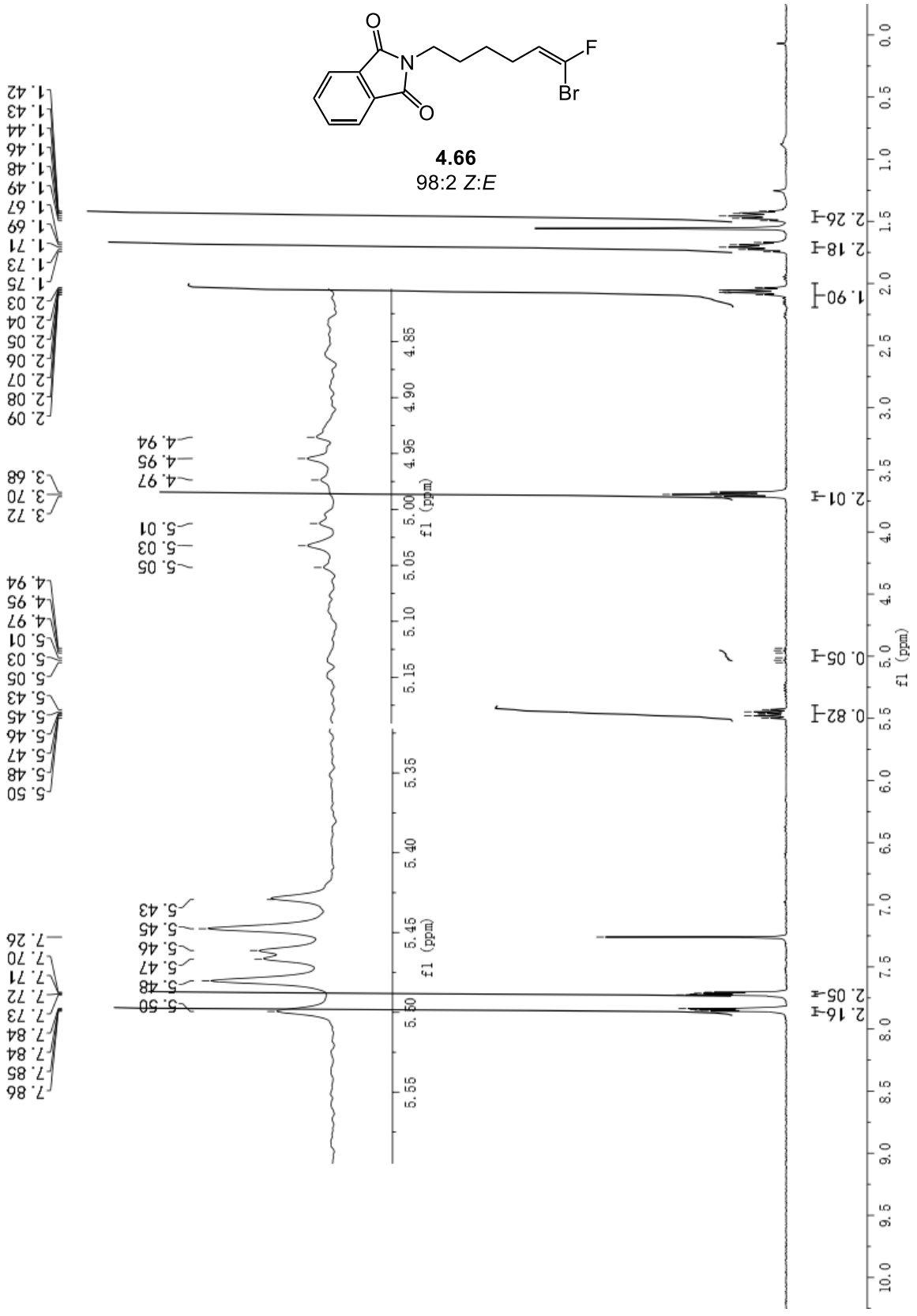


4.65
95:5 *E*:*Z*

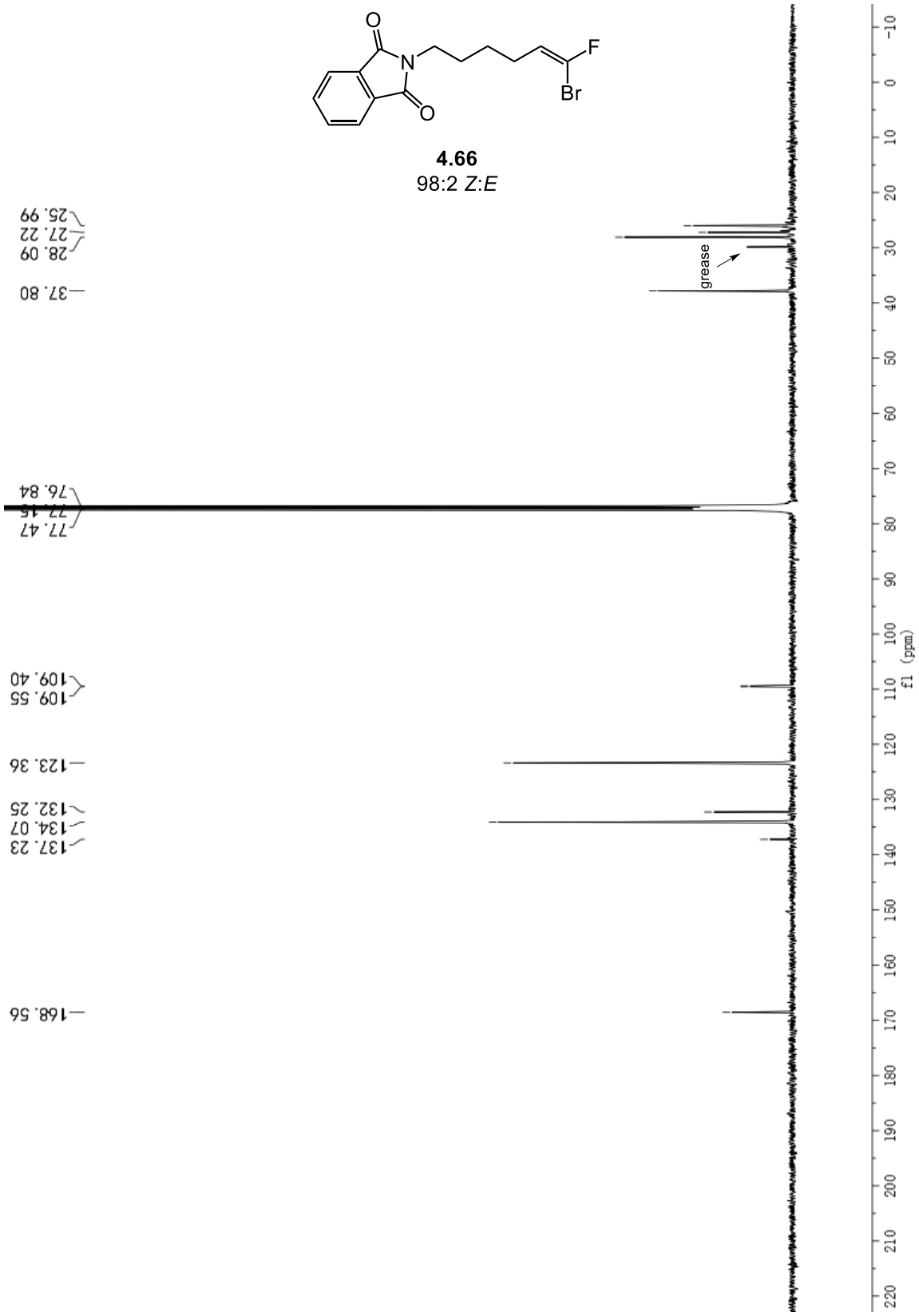
^{19}F NMR Spectrum of 4.66



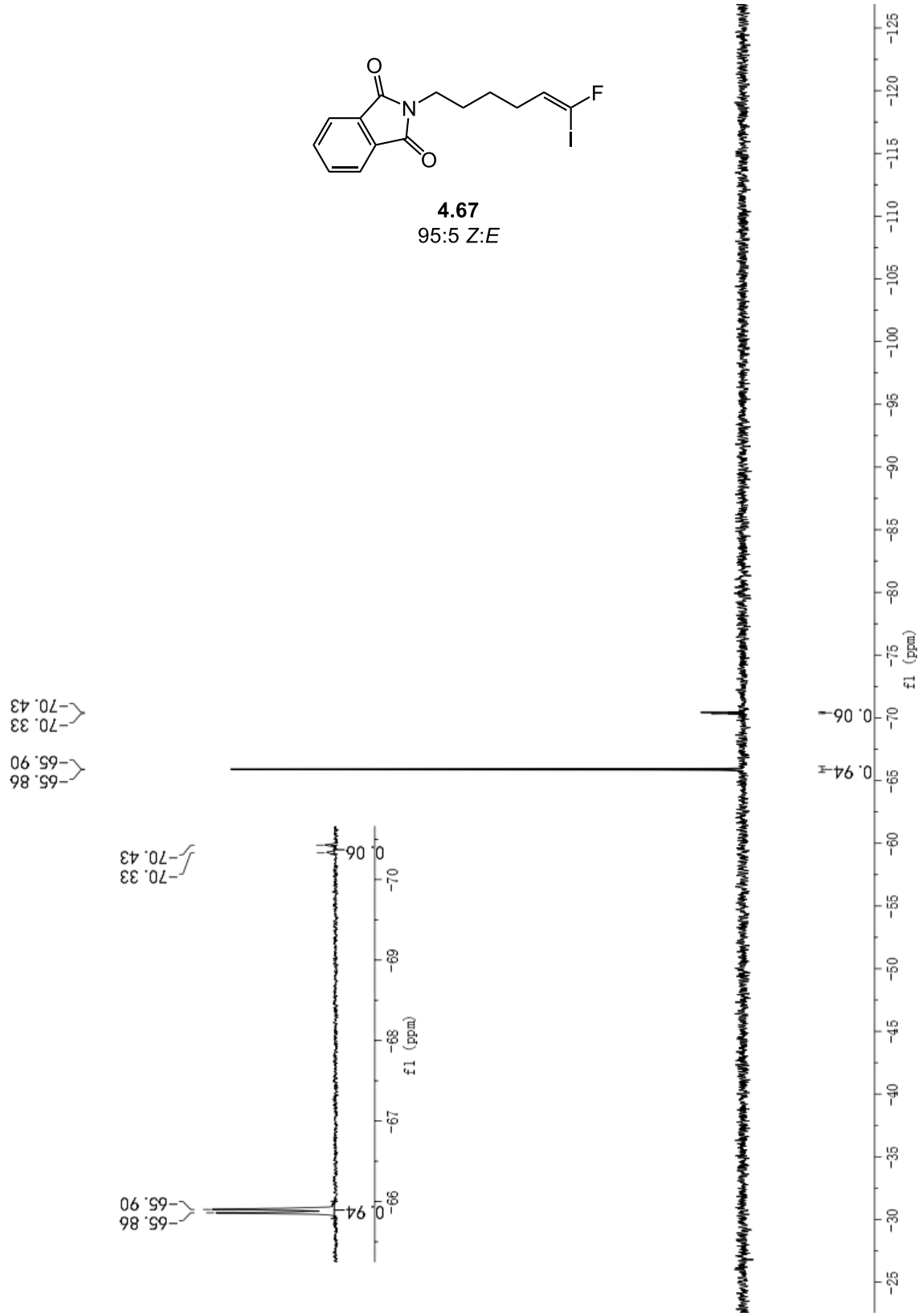
^{1}H NMR Spectrum of 4.66



^{13}C NMR Spectrum of 4.66

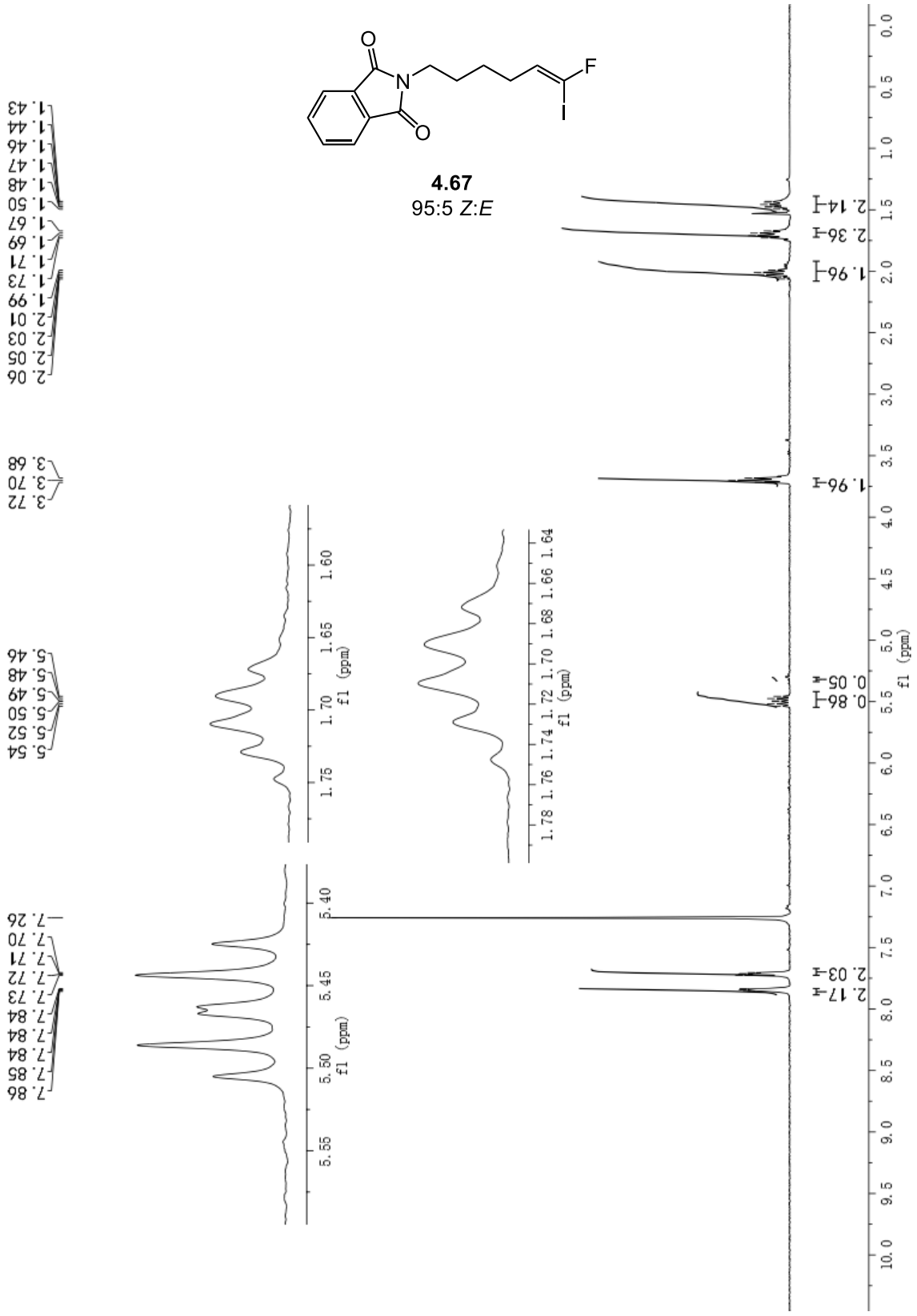


^{19}F NMR Spectrum of 4.67

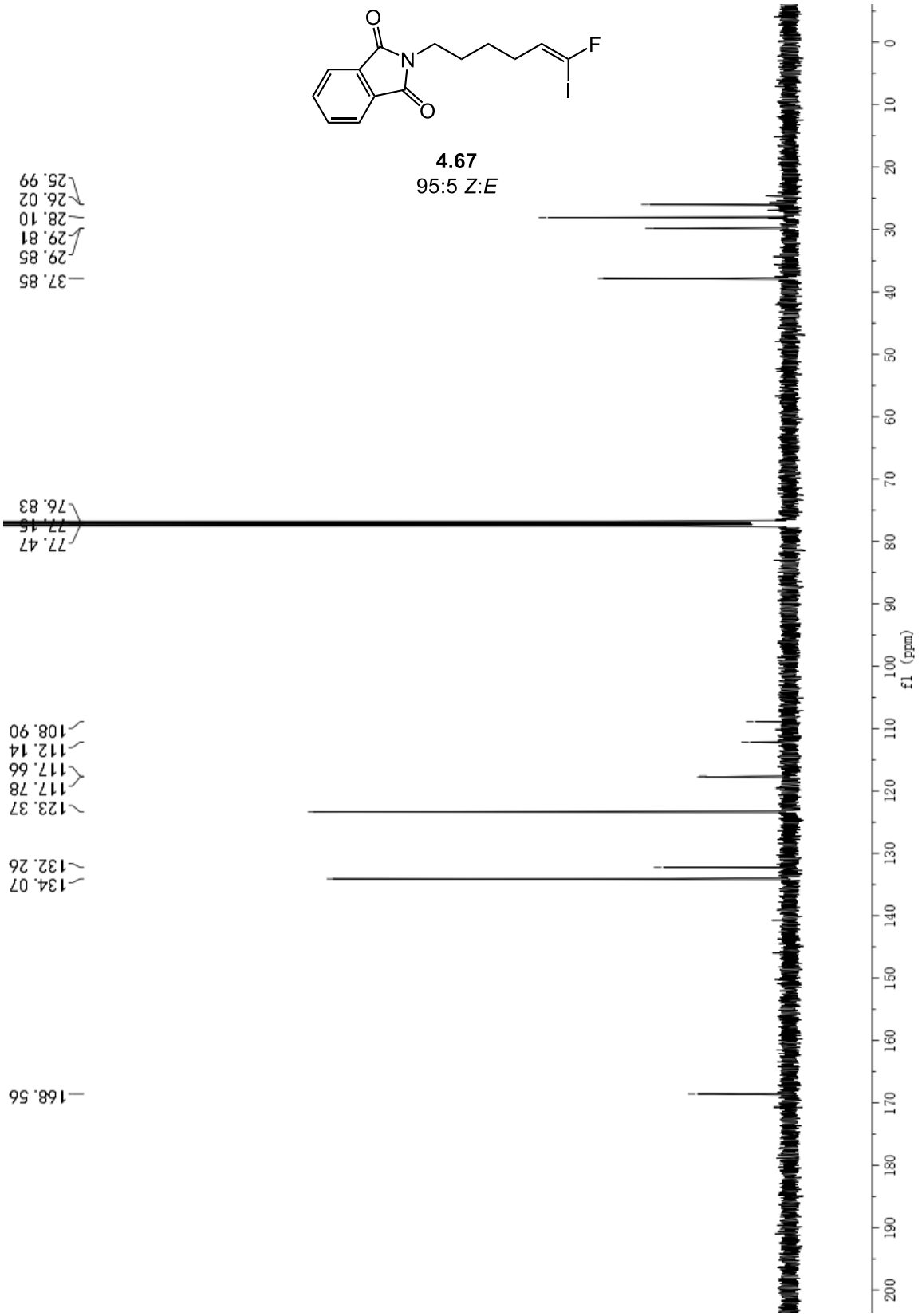


4.67
95:5 *Z*:*E*

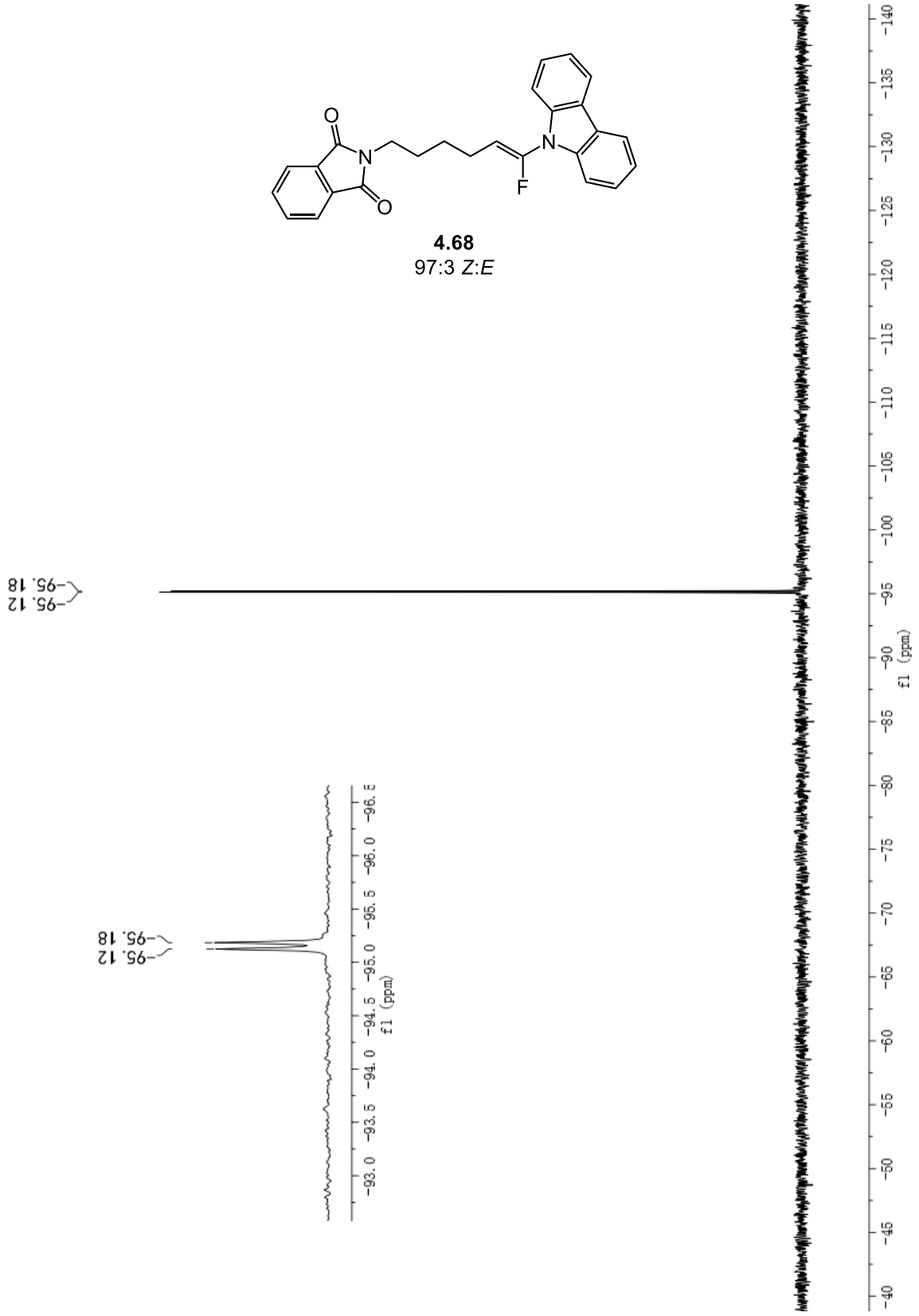
^{1}H NMR Spectrum of 4.67



^{13}C NMR Spectrum of 4.67

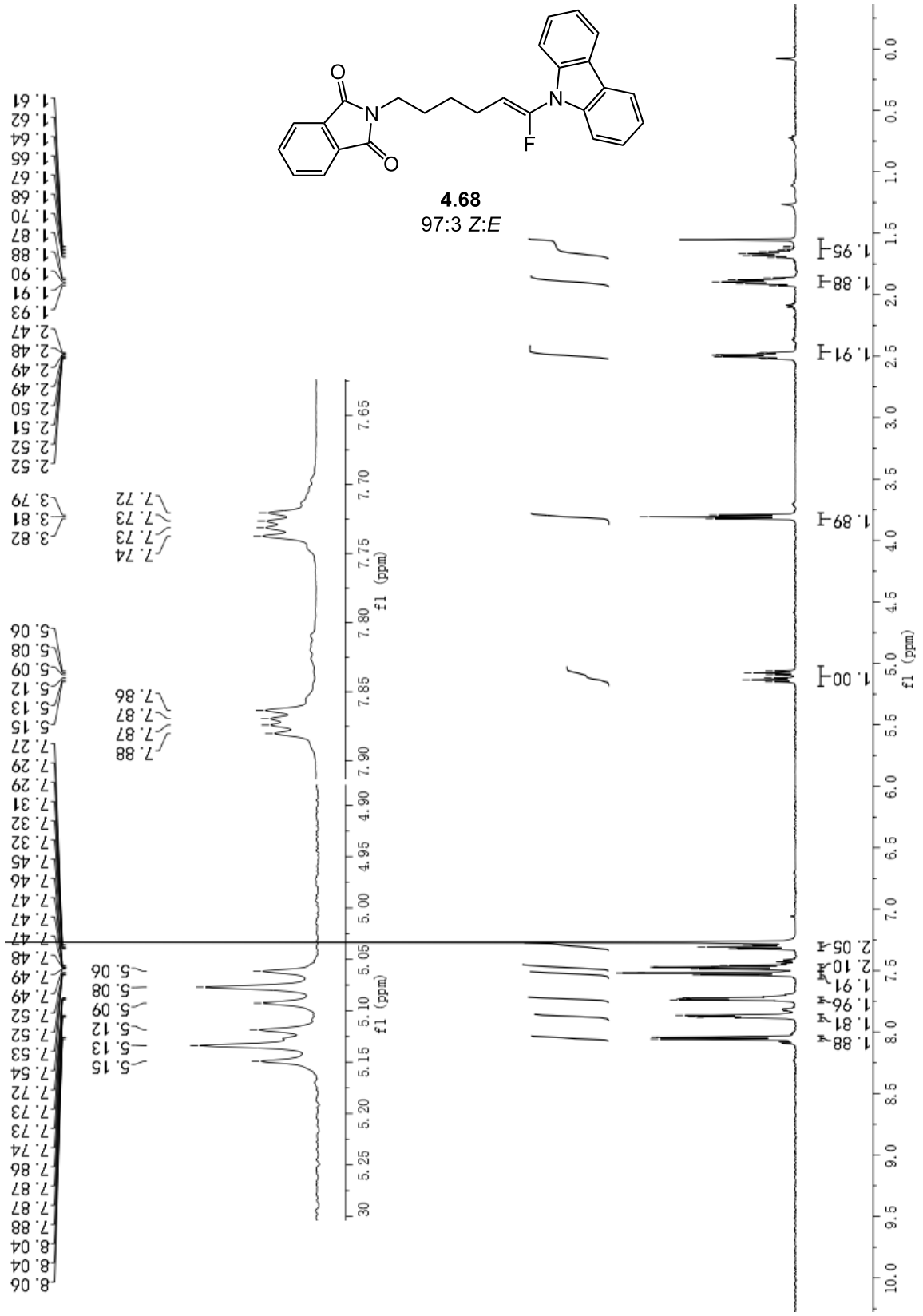


^{19}F NMR Spectrum of 4.68

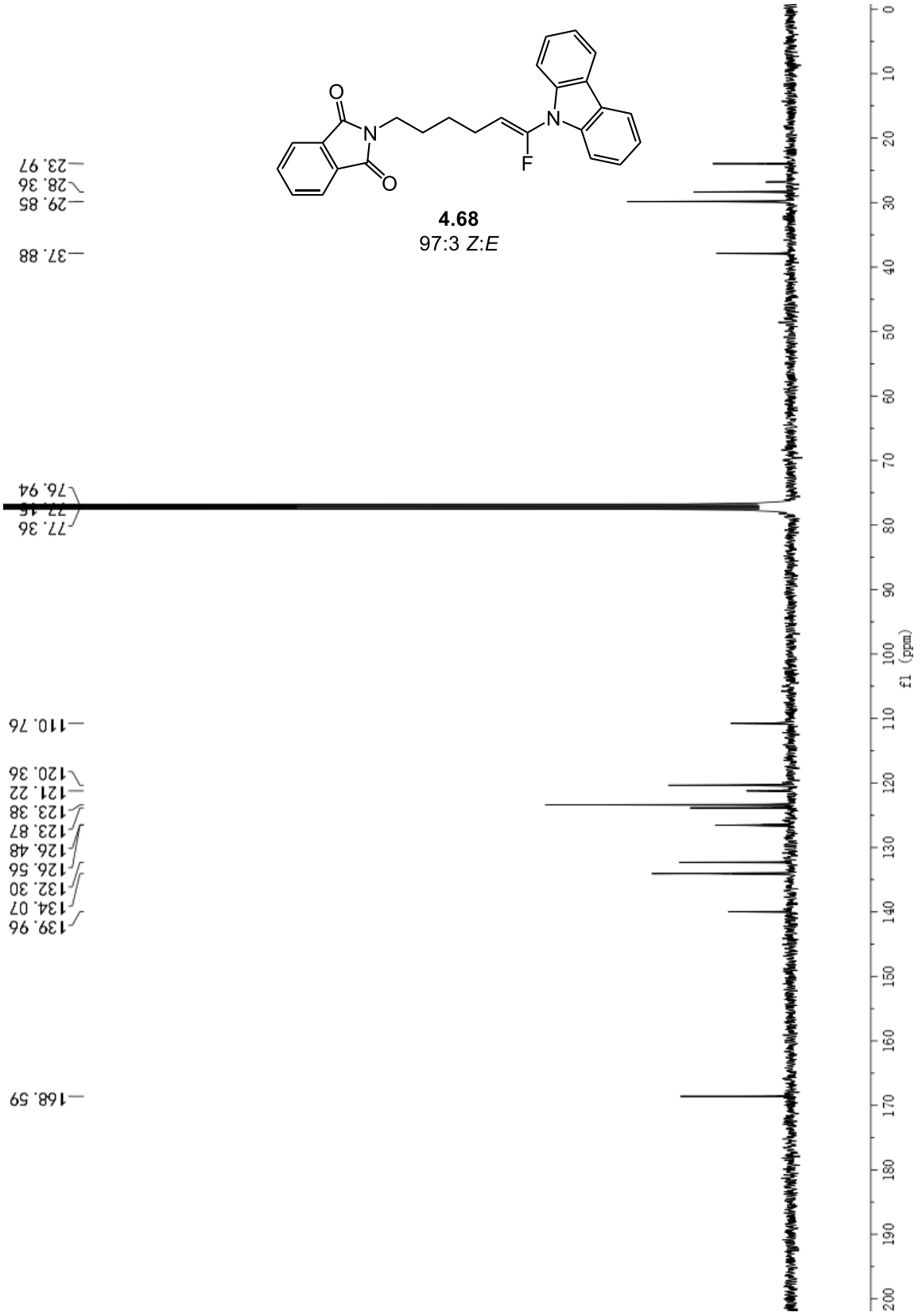


4.68
97:3 *Z*:*E*

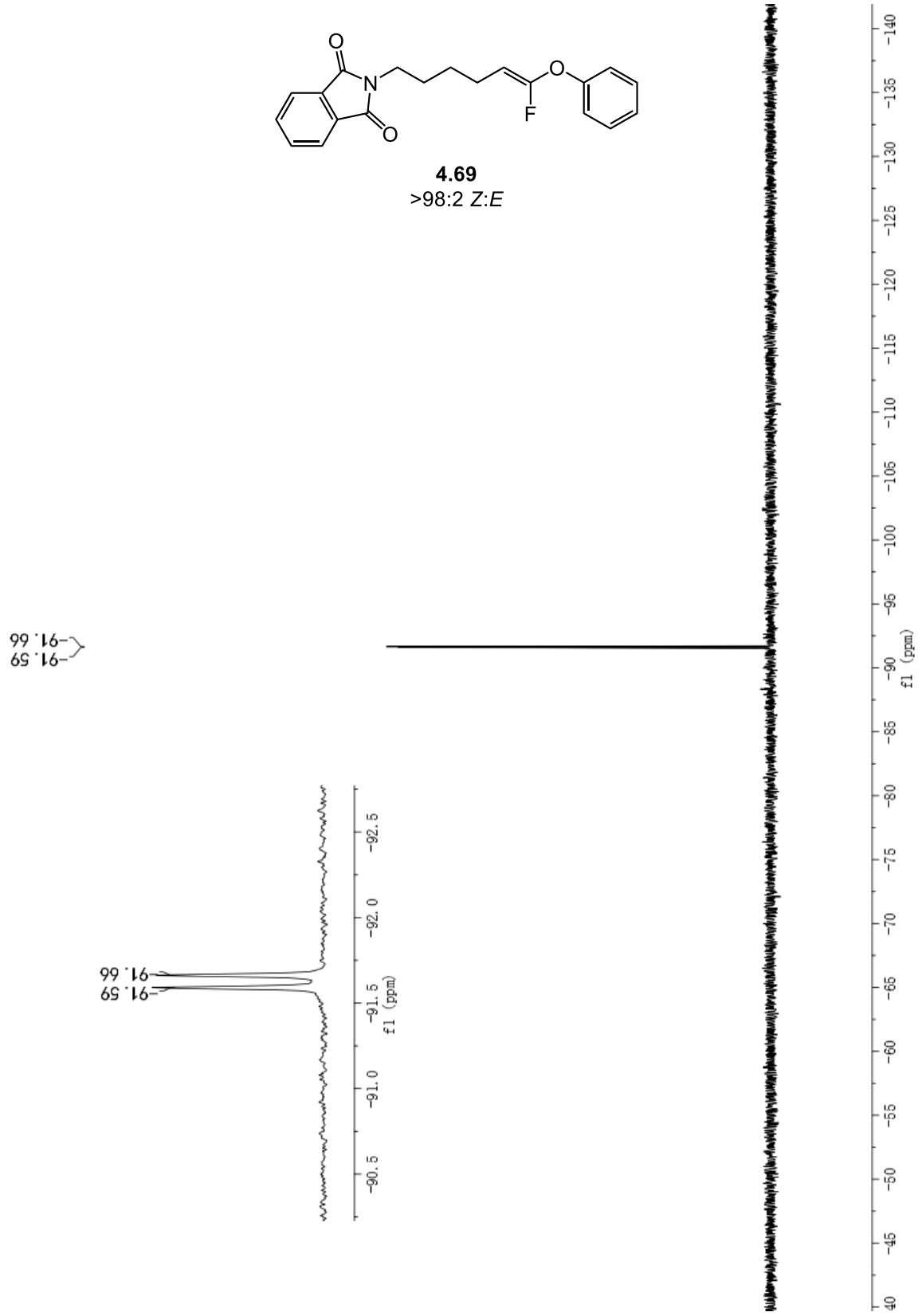
^{1}H NMR Spectrum of 4.68



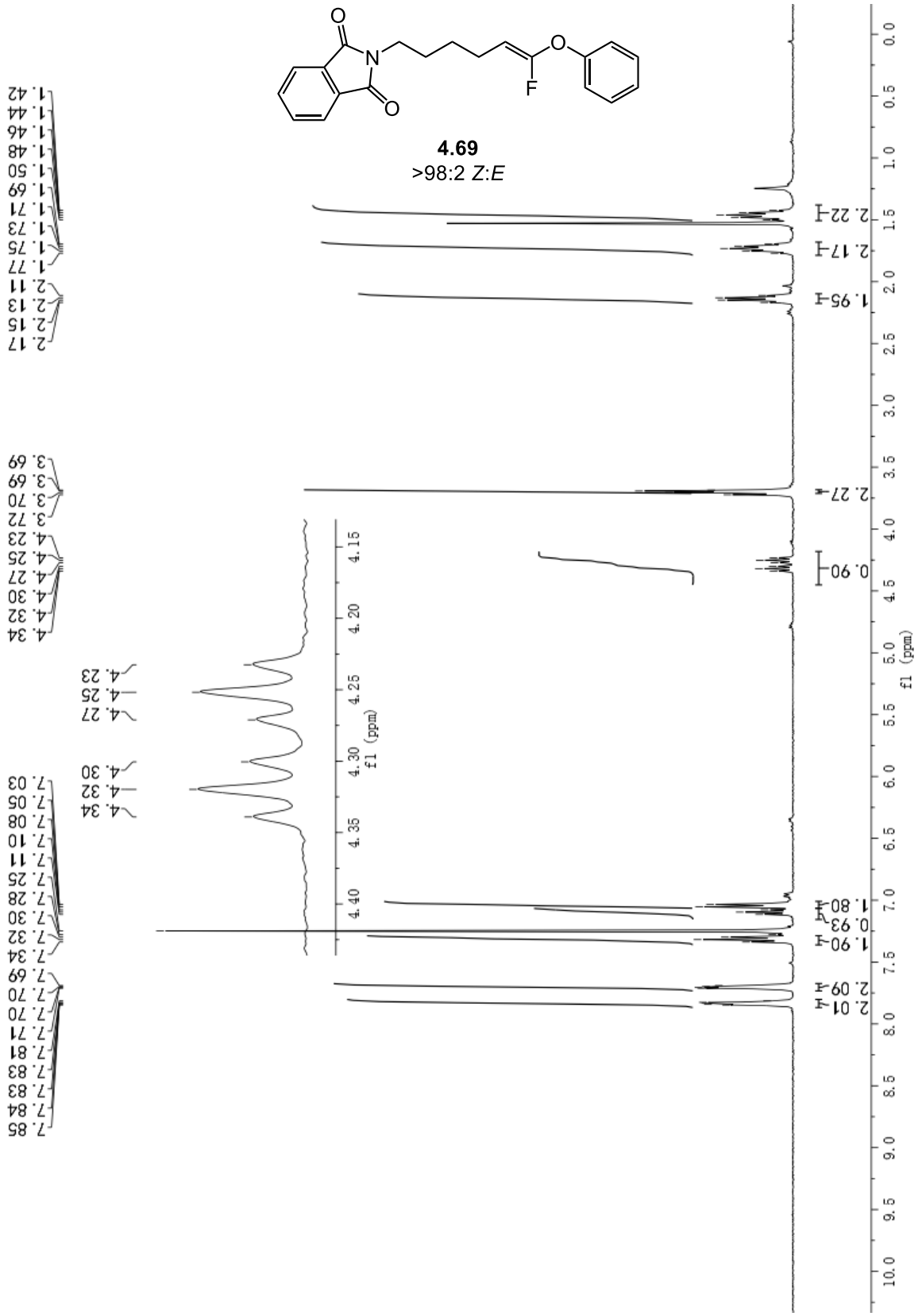
^{13}C NMR Spectrum of 4.68



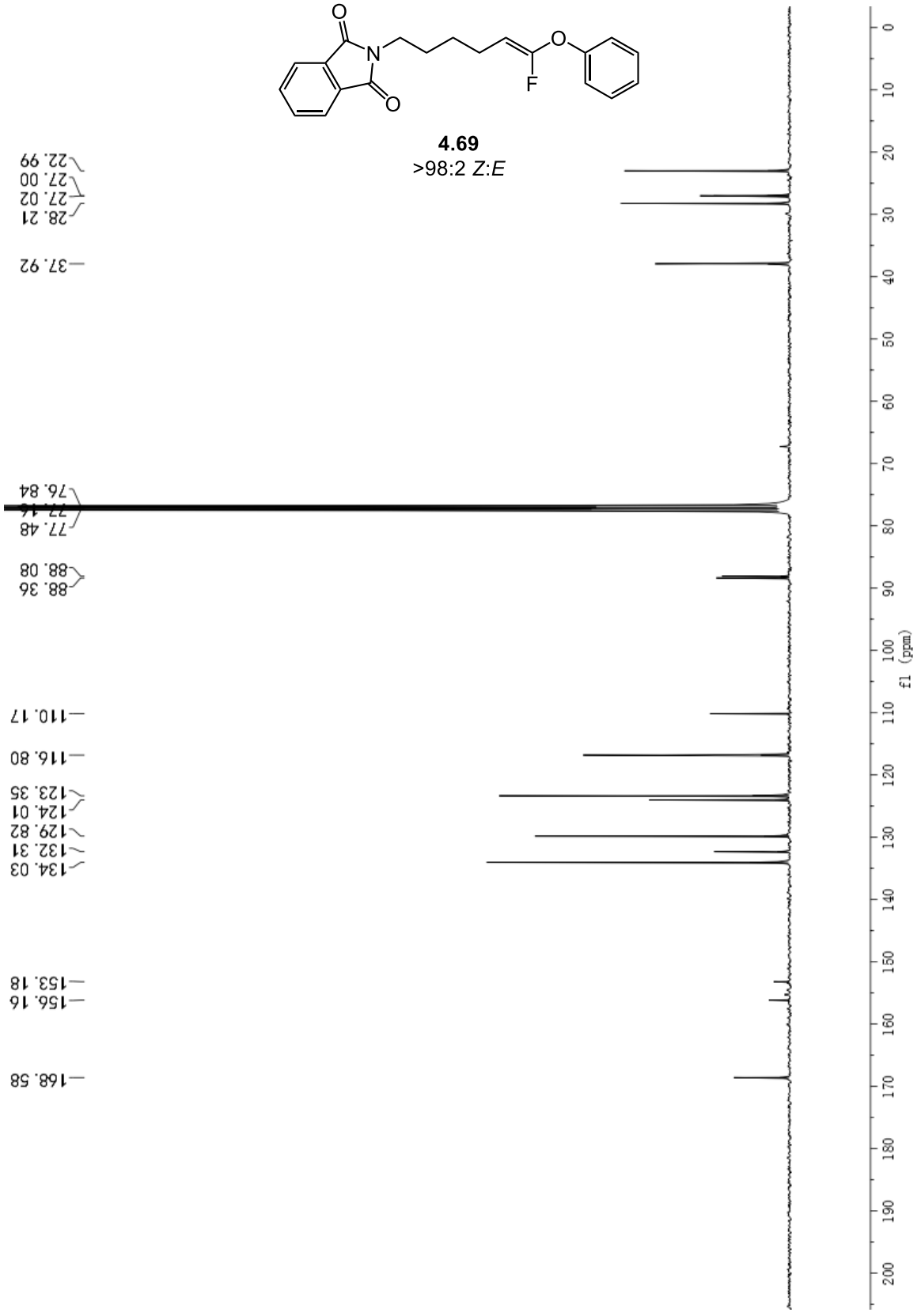
^{19}F NMR Spectrum of 4.69



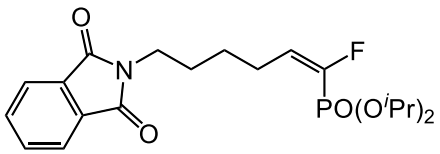
^{1}H NMR Spectrum of 4.69



^{13}C NMR Spectrum of 4.69

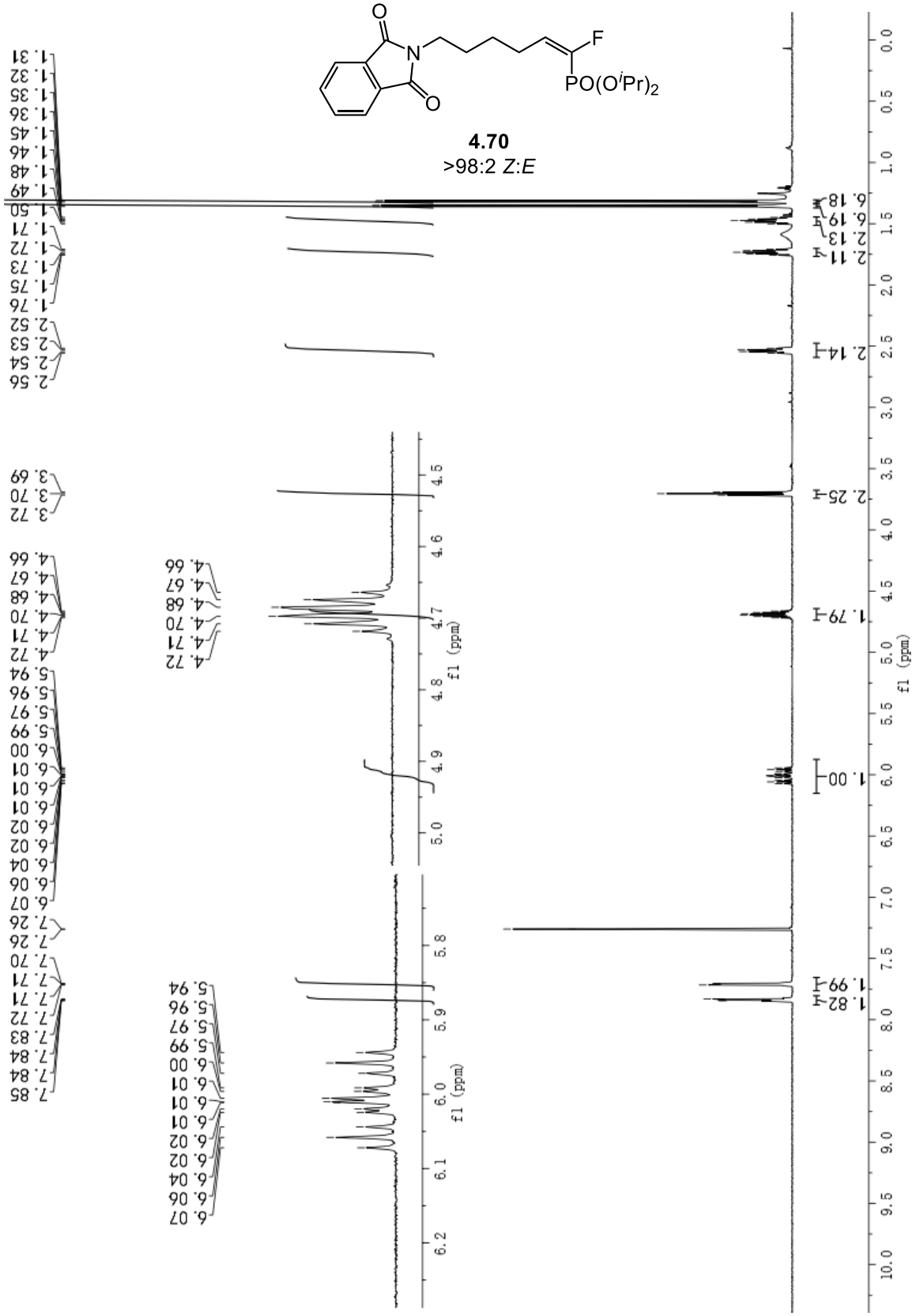


^{19}F NMR Spectrum of 4.70

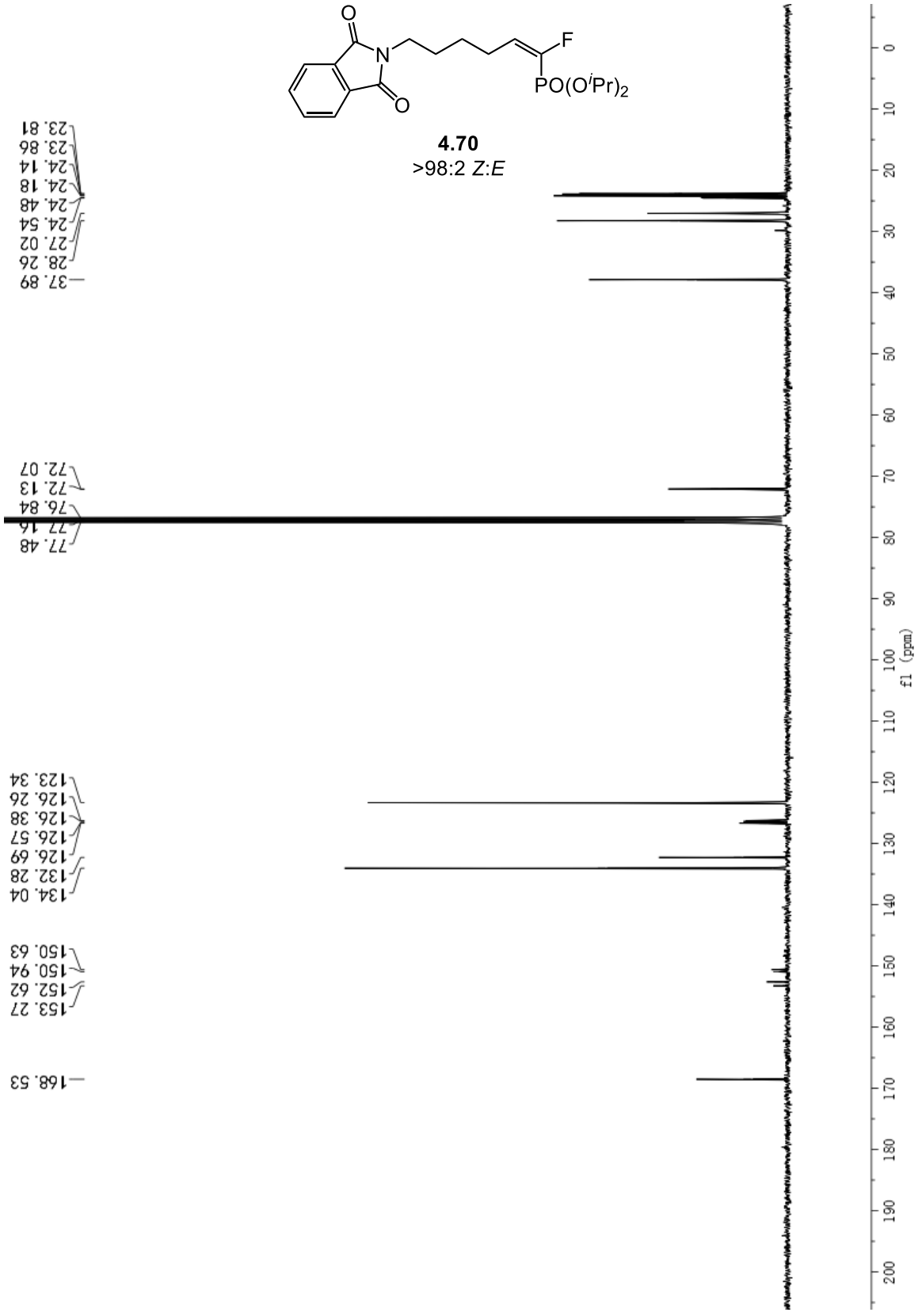


4.70
>98:2 *Z*:*E*

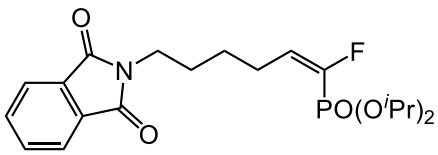
^{1}H NMR Spectrum of 4.70



^{13}C NMR Spectrum of 4.70

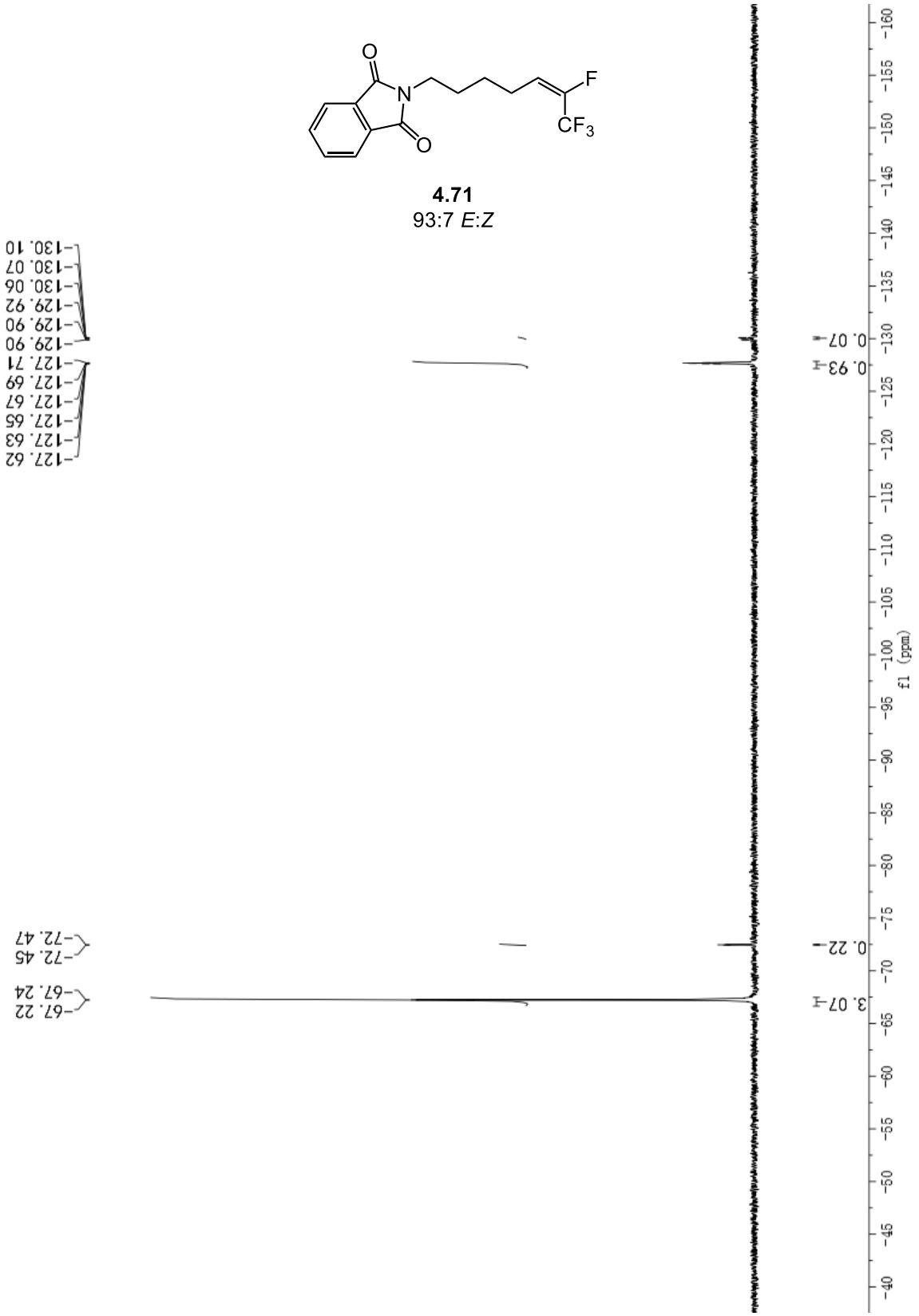


^{31}P NMR Spectrum of 4.70

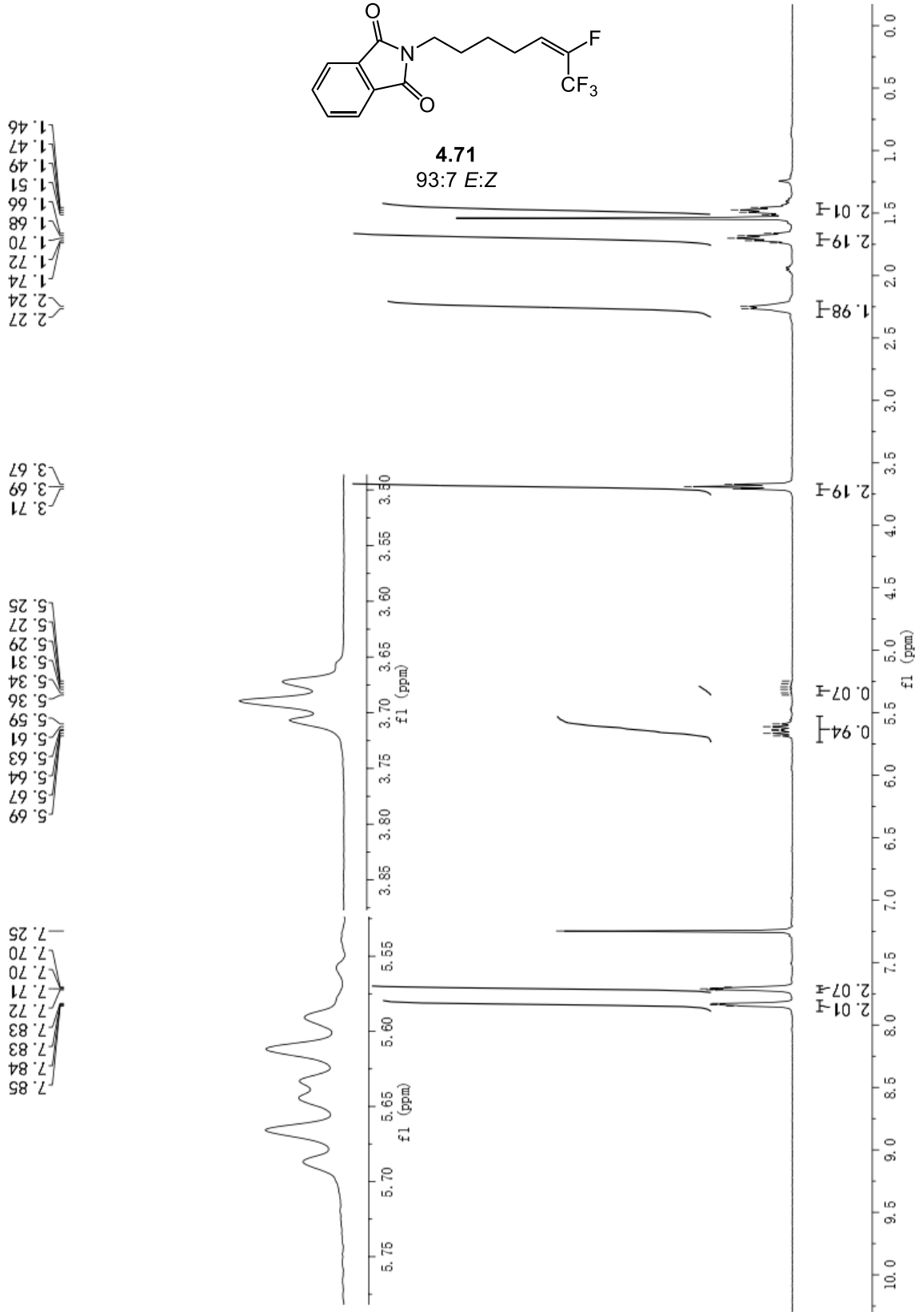


4.70
>98:2 *Z*:*E*

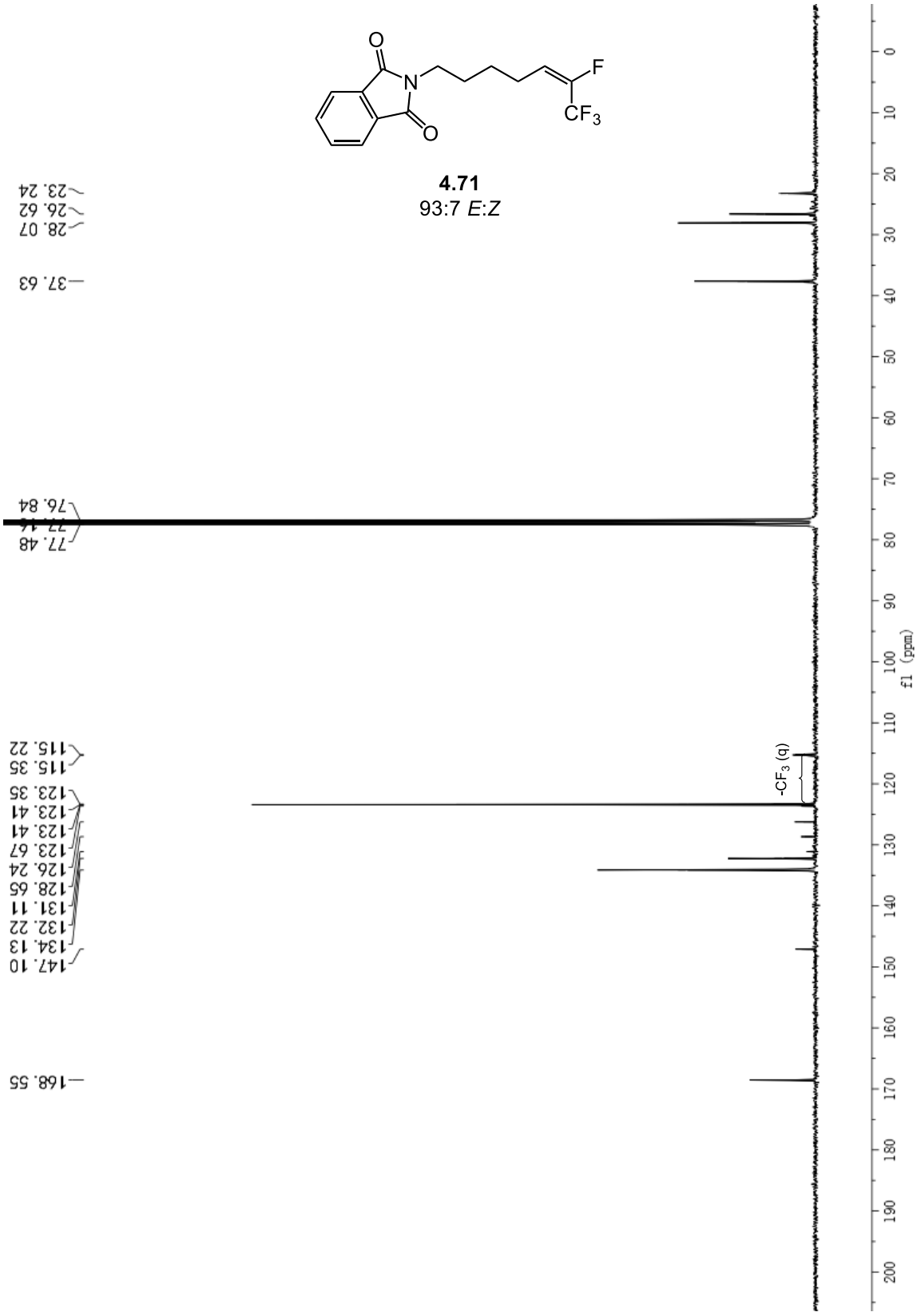
^{19}F NMR Spectrum of 4.71



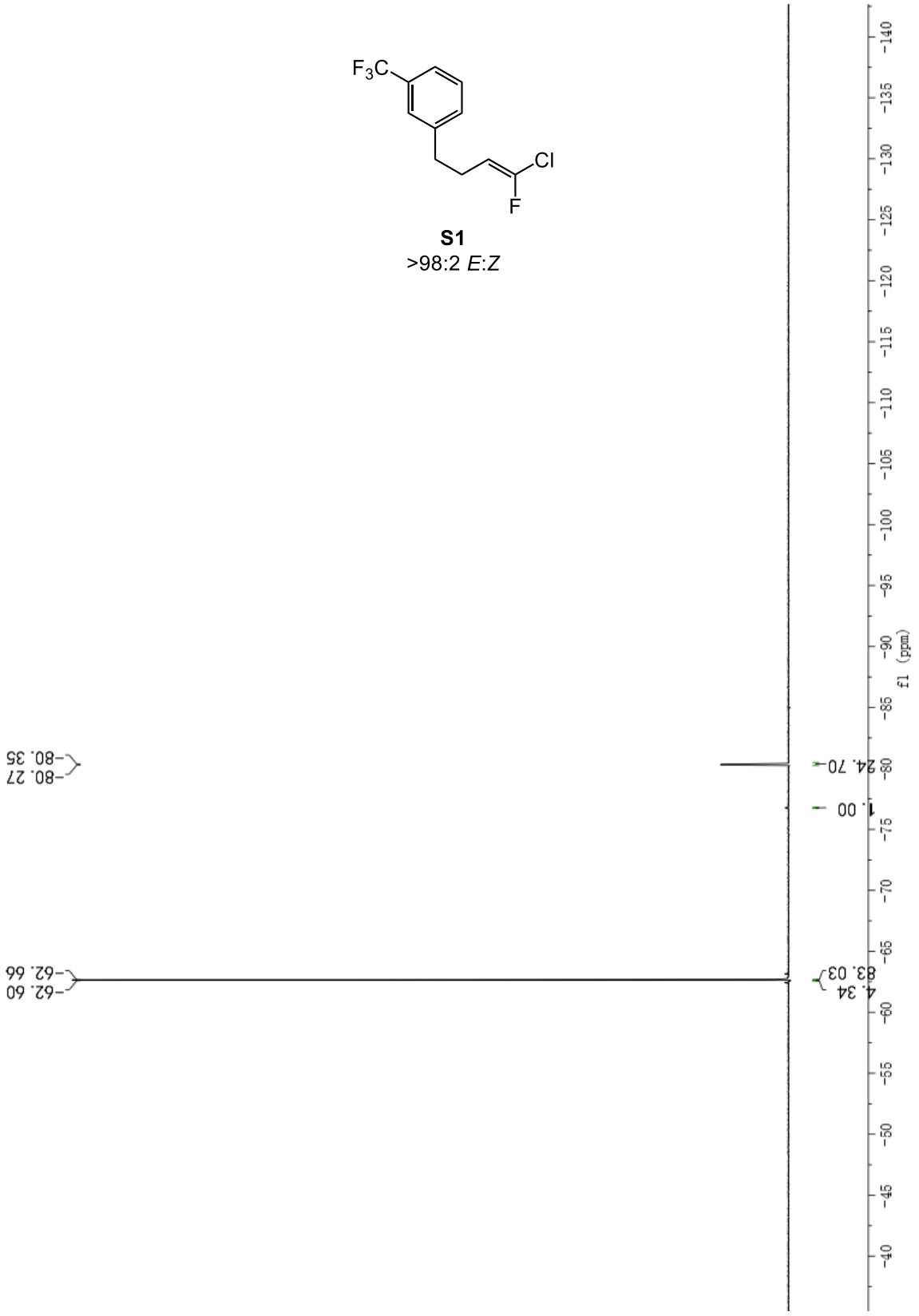
^{1}H NMR Spectrum of 4.71



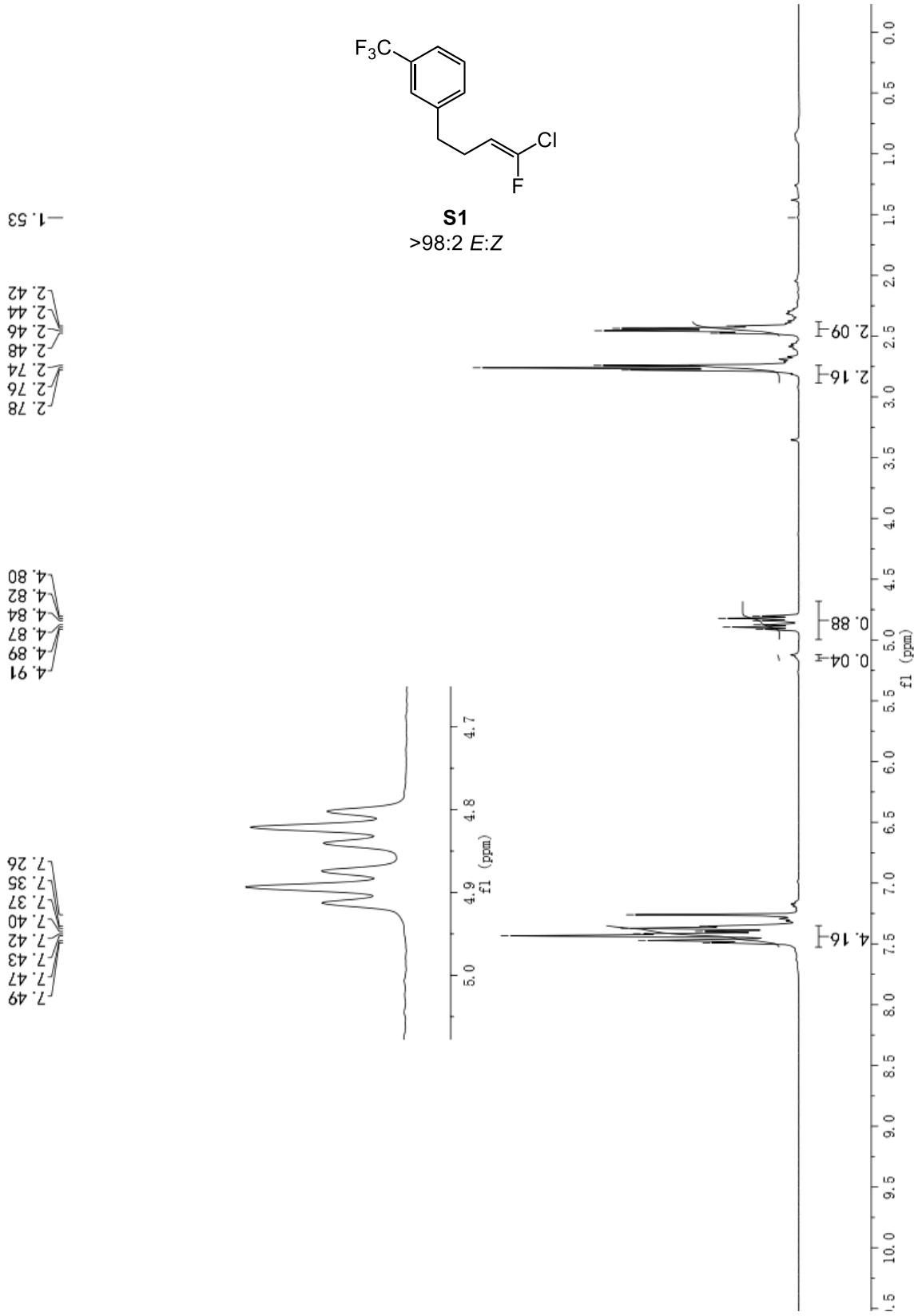
^{13}C NMR Spectrum of 4.71



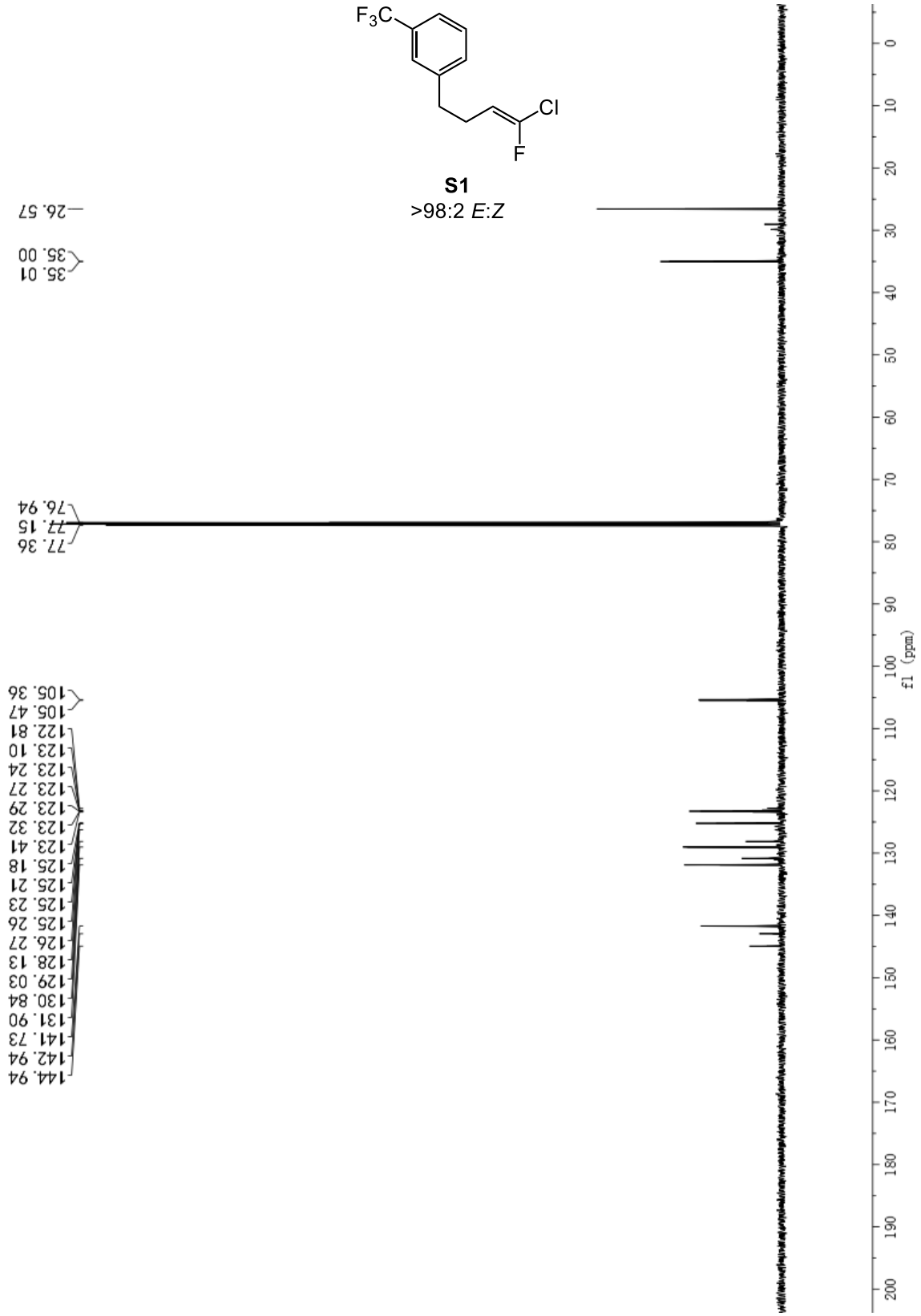
^{19}F NMR Spectrum of S1



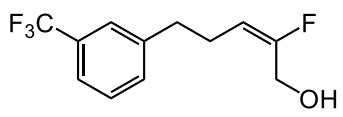
^{1}H NMR Spectrum of S1



^{13}C NMR Spectrum of S1

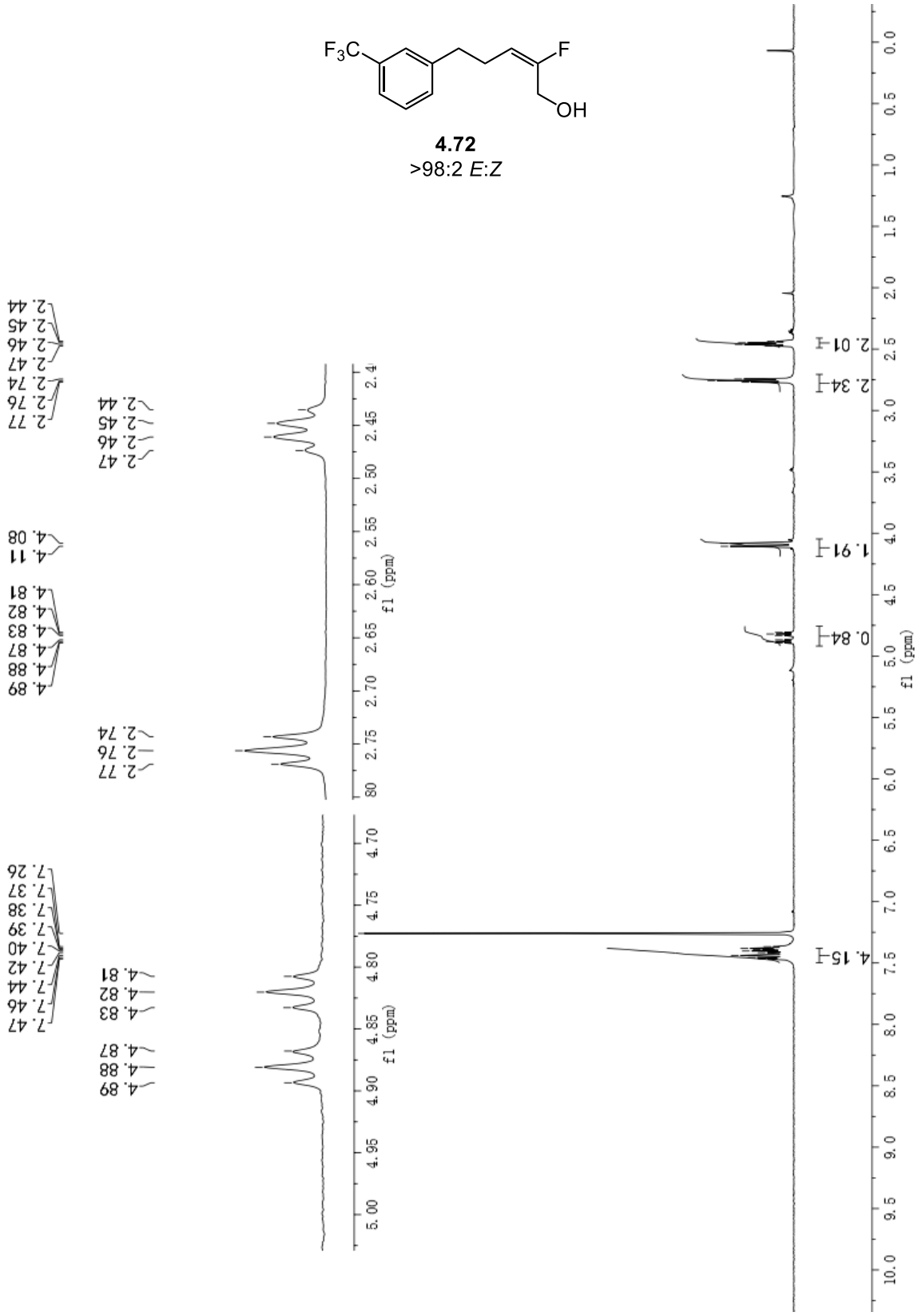


^{19}F NMR Spectrum of 4.72

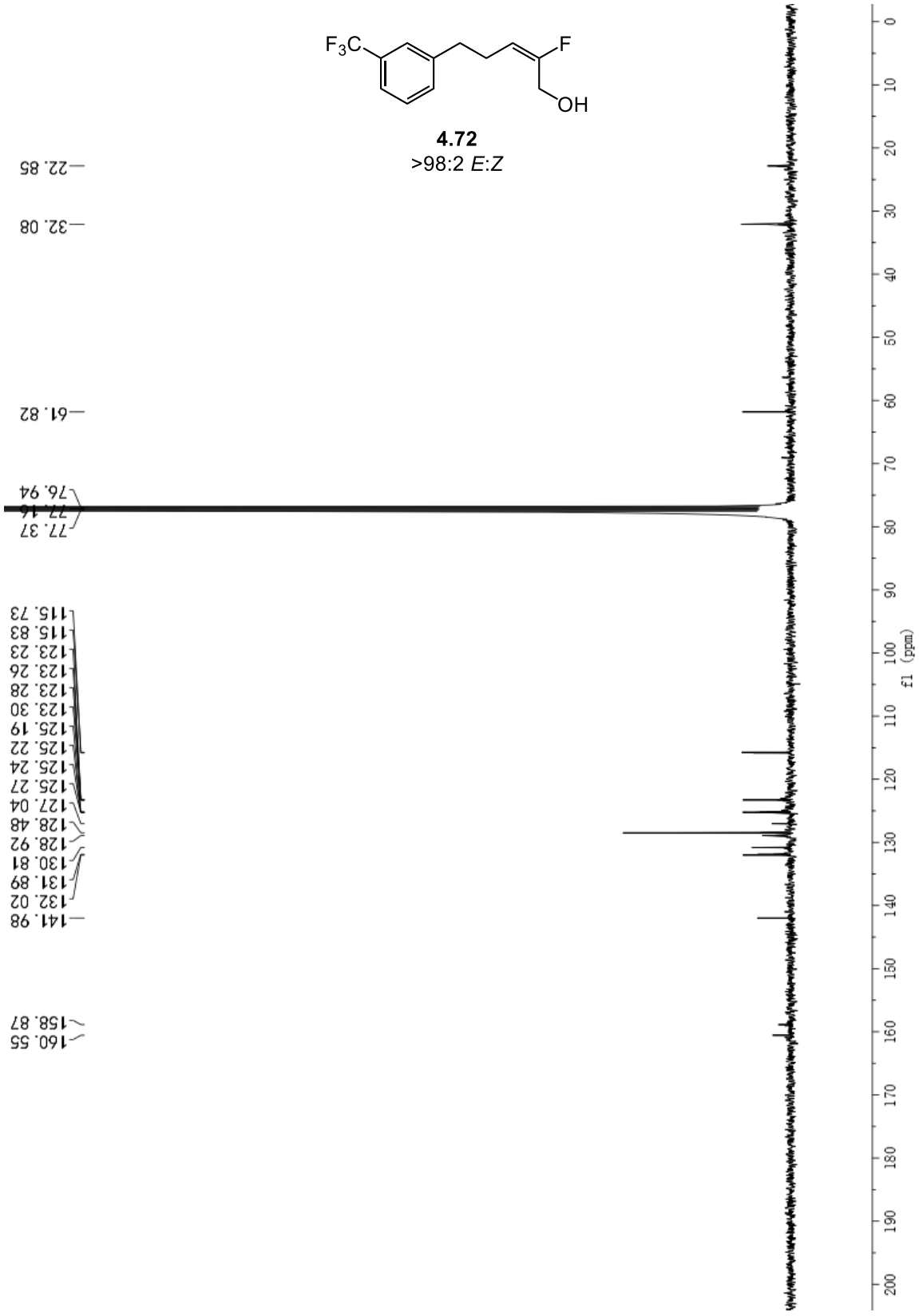


4.72
>98:2 *E*:*Z*

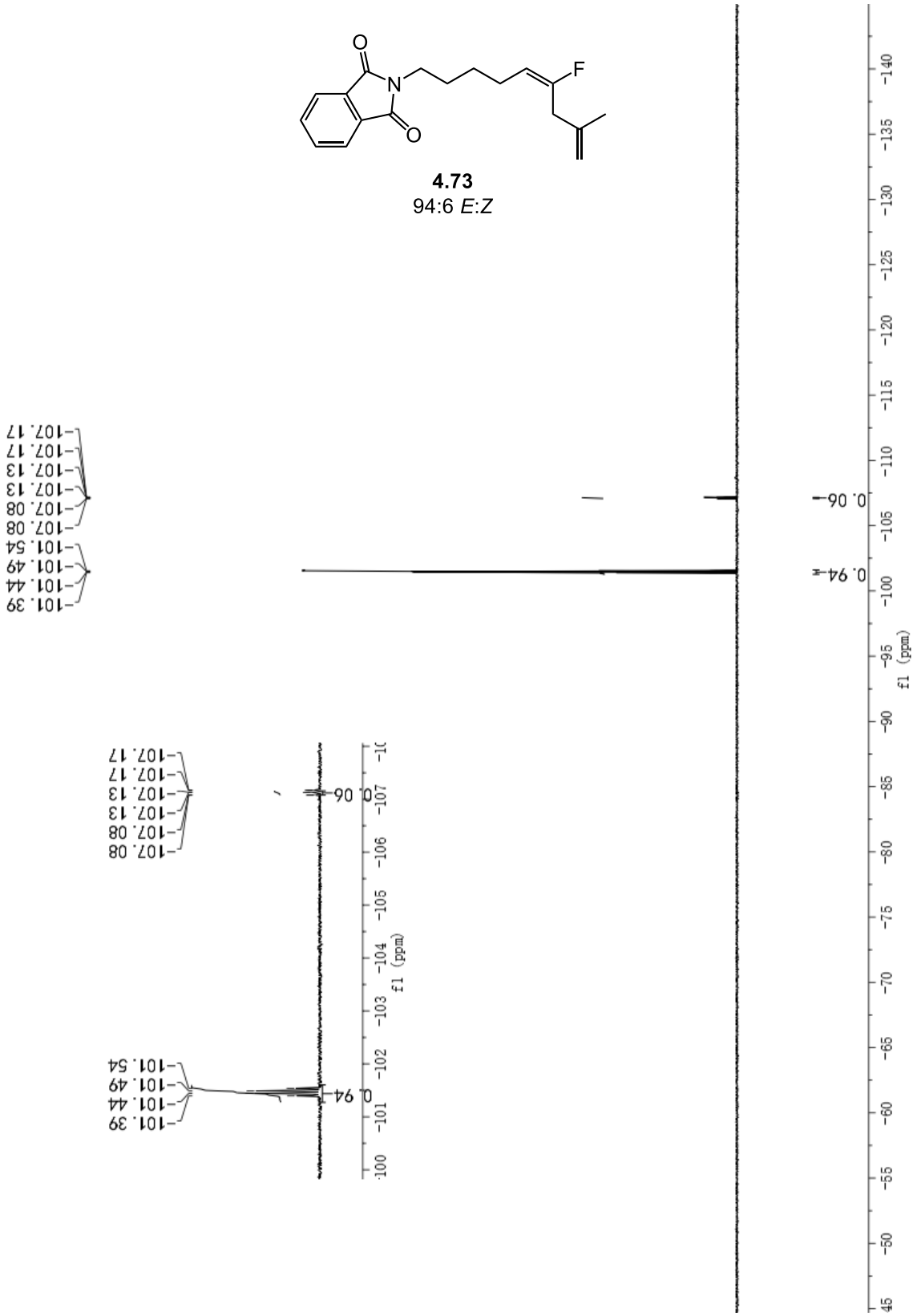
^{1}H NMR Spectrum of 4.72



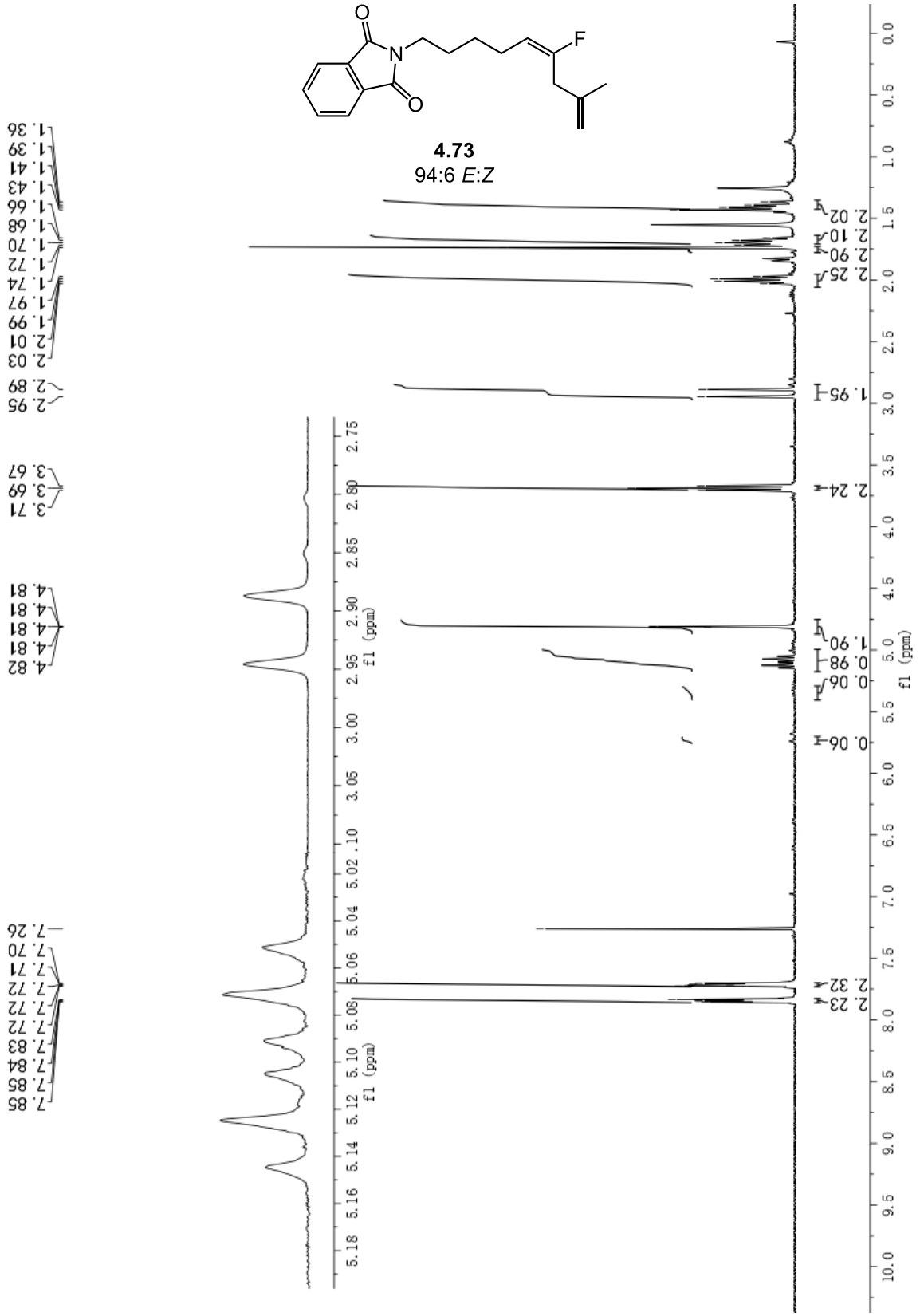
^{13}C NMR Spectrum of 4.72



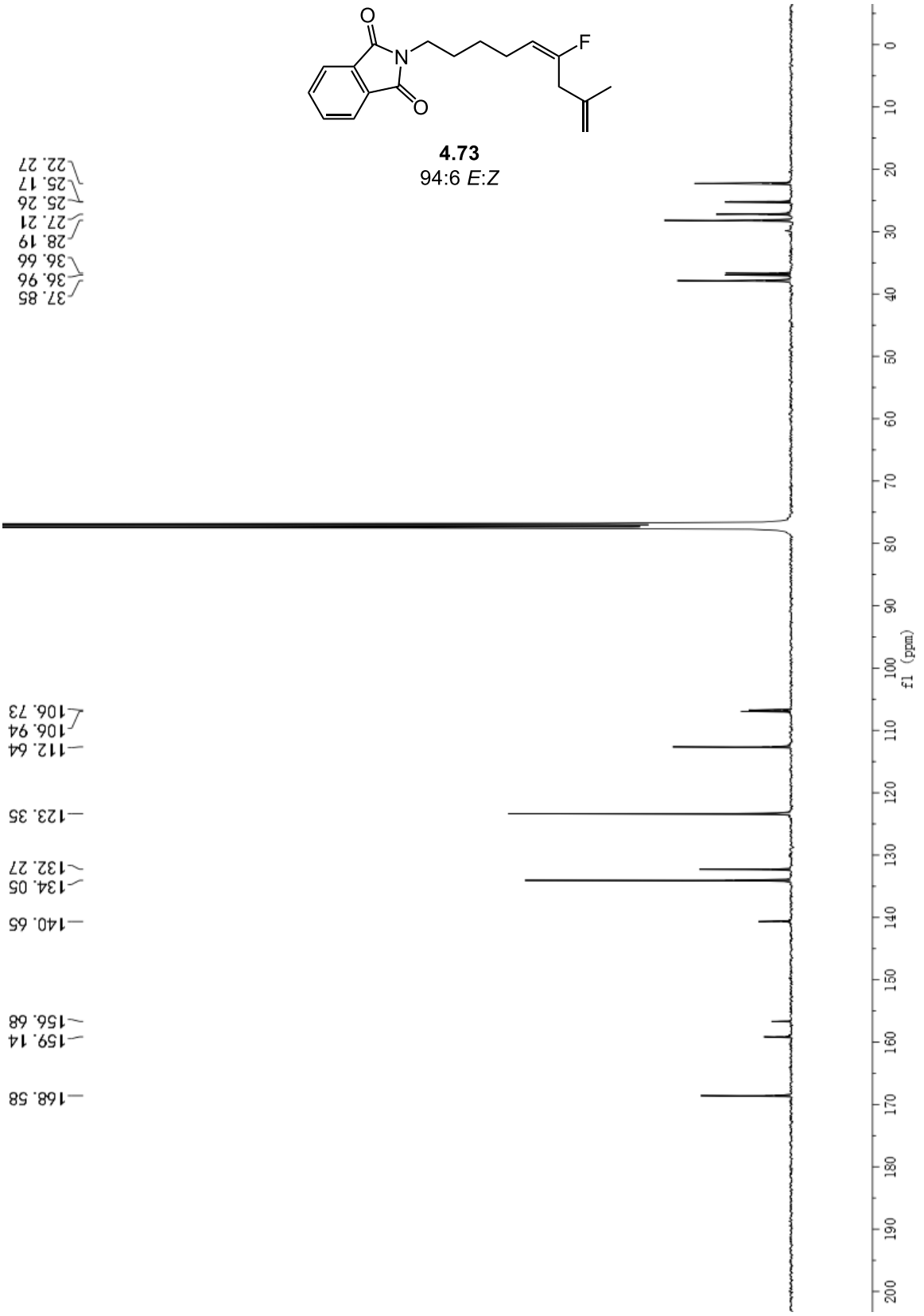
^{19}F NMR Spectrum of 4.73



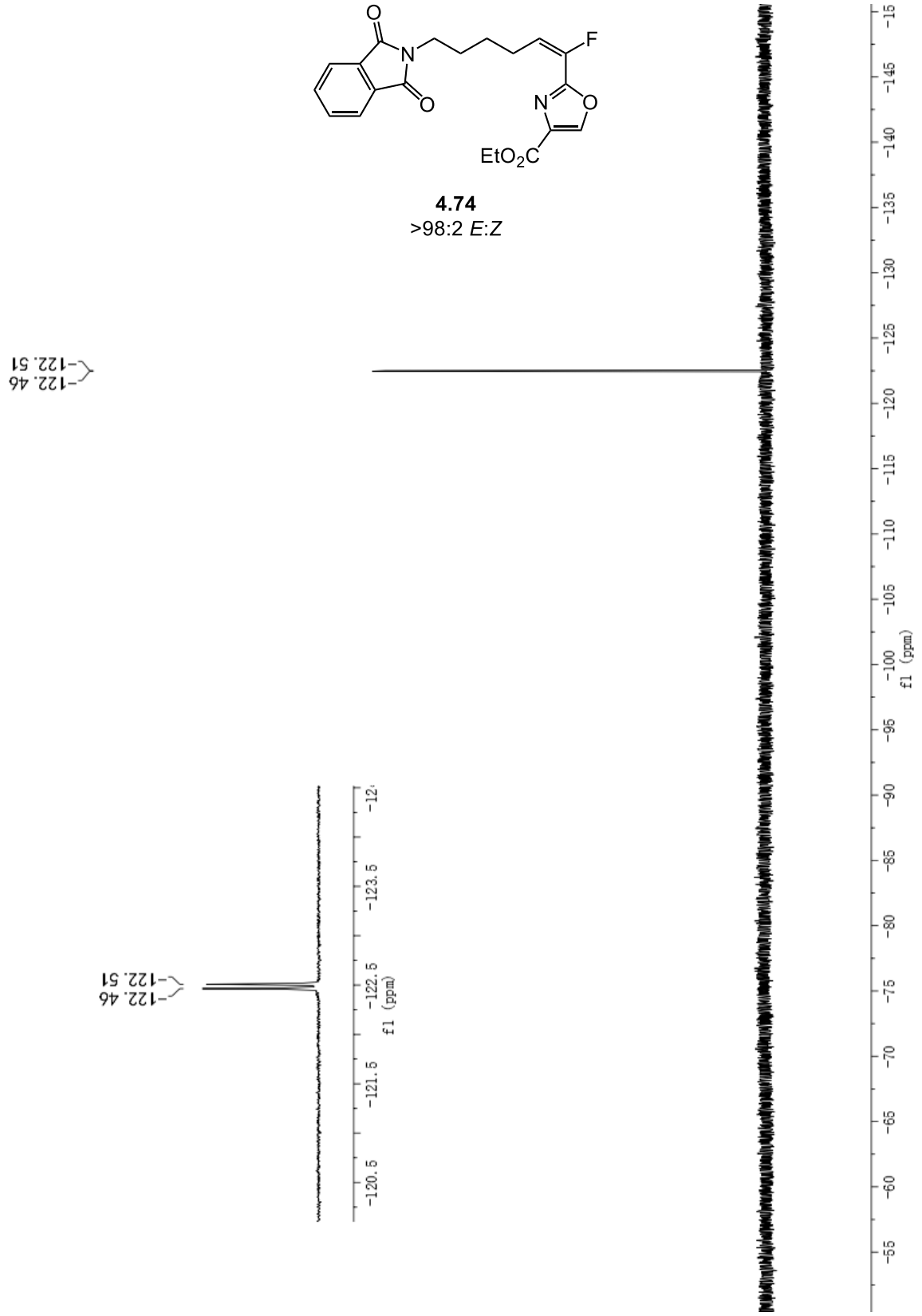
^{1}H NMR Spectrum of 4.73



^{13}C NMR Spectrum of 4.73

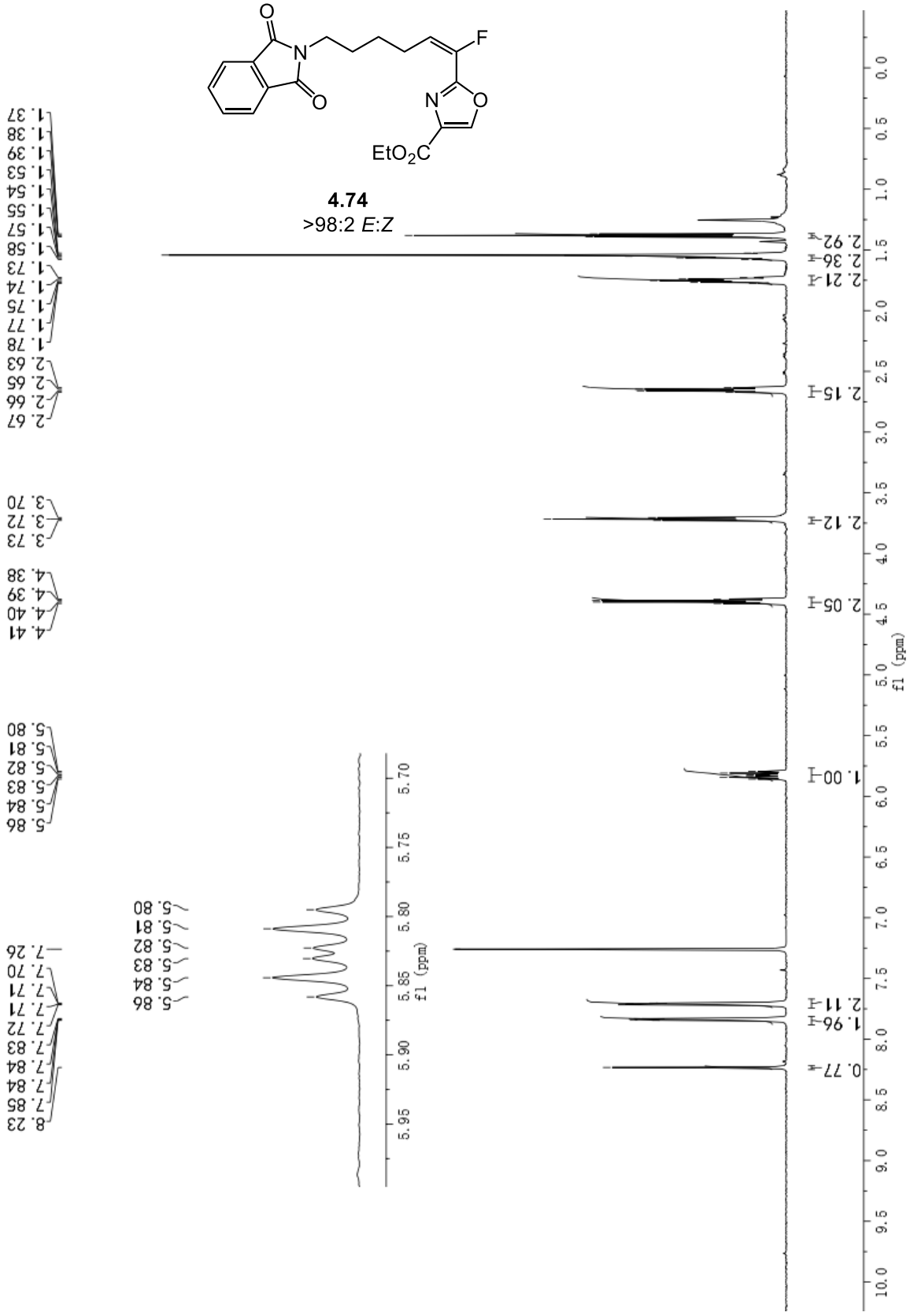


^{19}F NMR Spectrum of 4.74

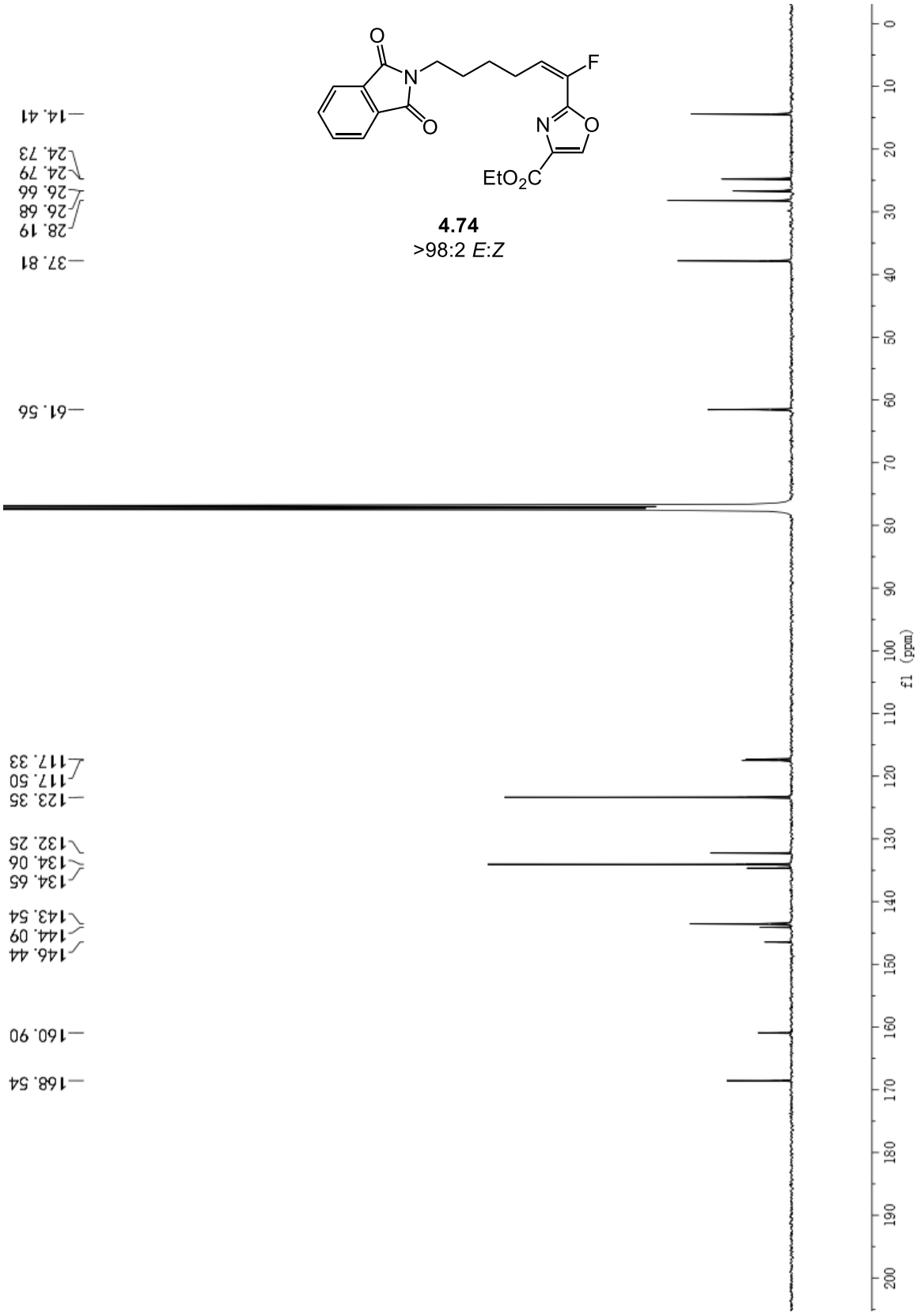


4.74
>98:2 *E*:*Z*

^{1}H NMR Spectrum of 4.74

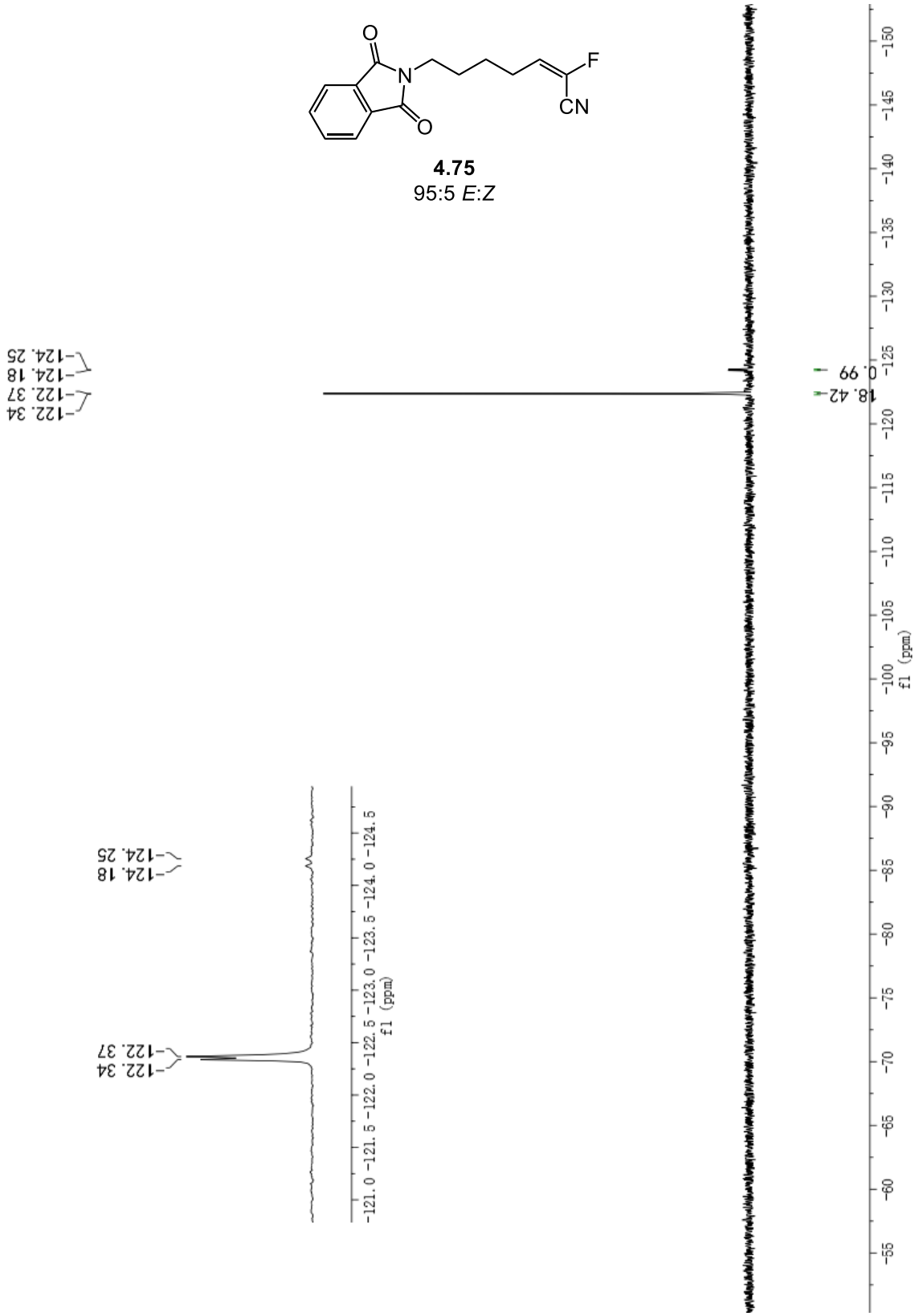


^{13}C NMR Spectrum of 4.74

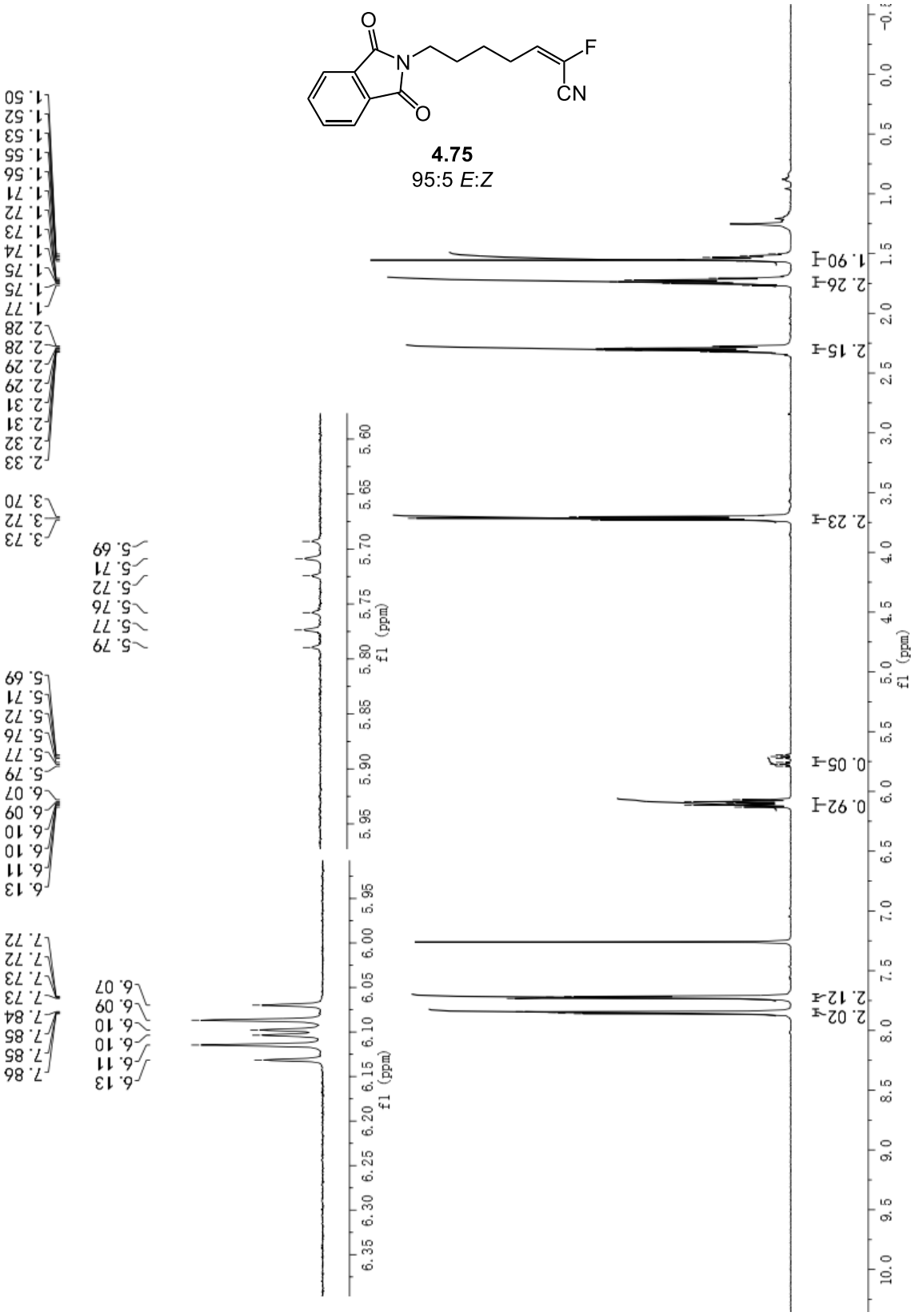


4.74
>98:2 *E*:*Z*

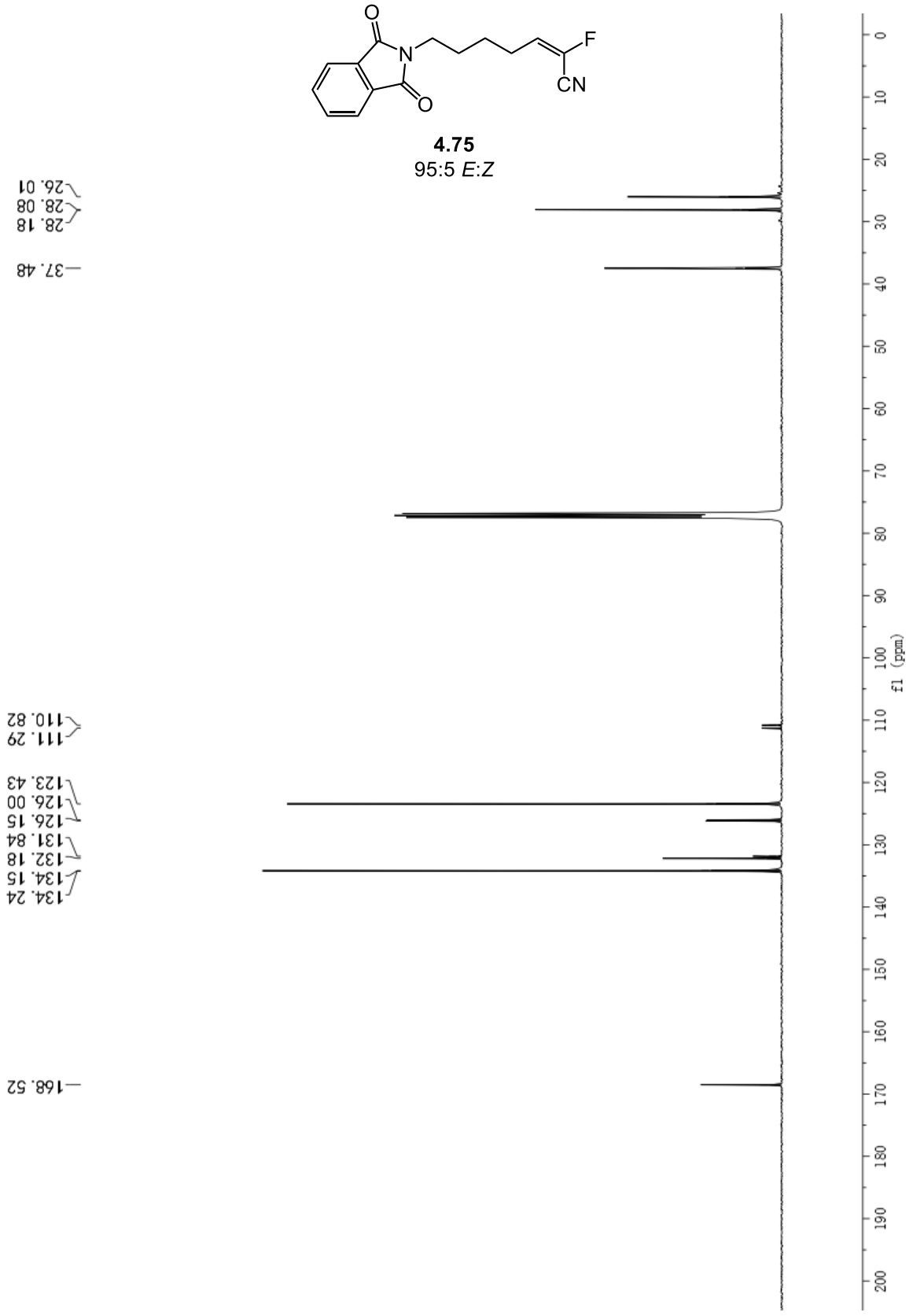
^{19}F NMR Spectrum of 4.75



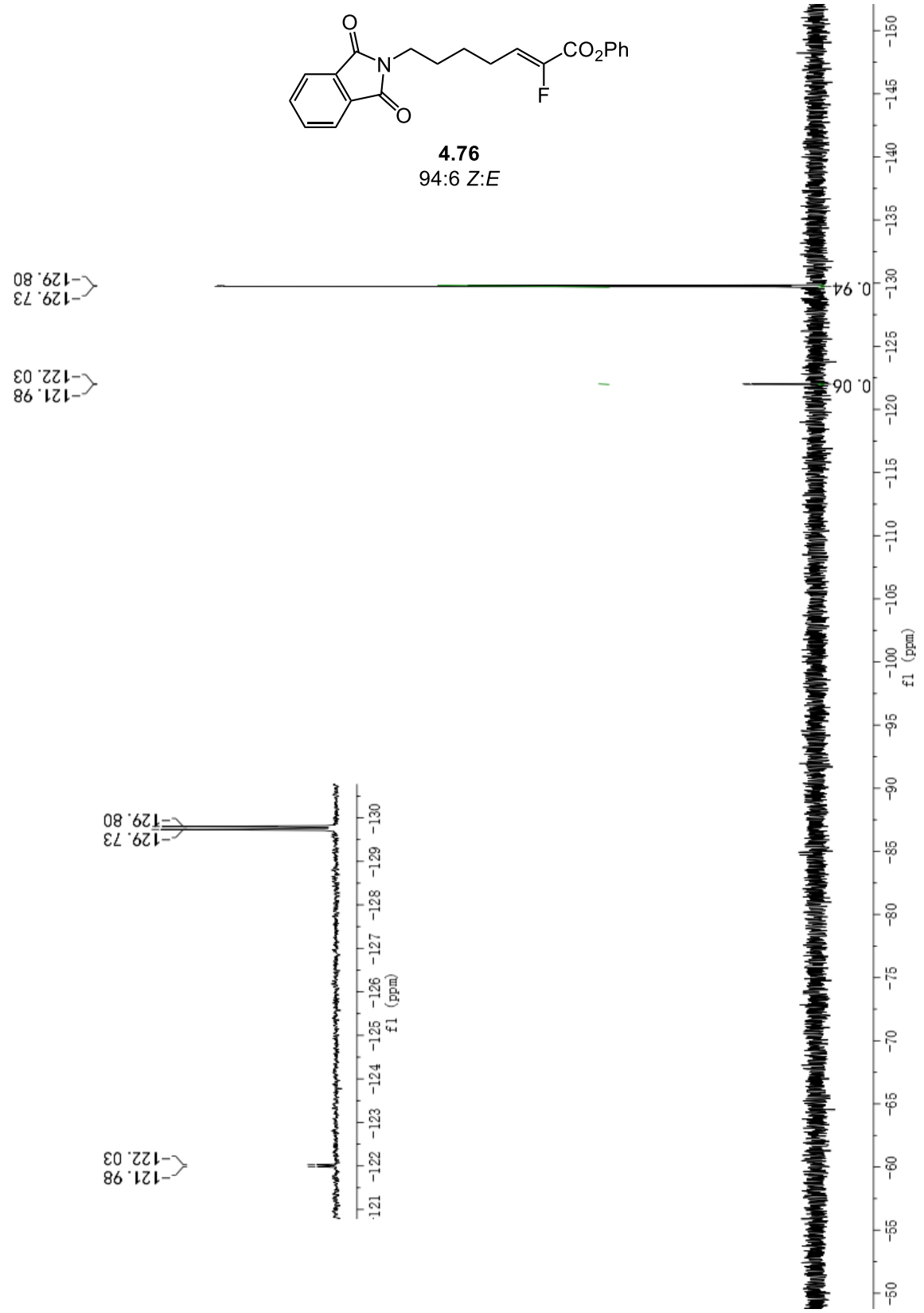
^{1}H NMR Spectrum of 4.75



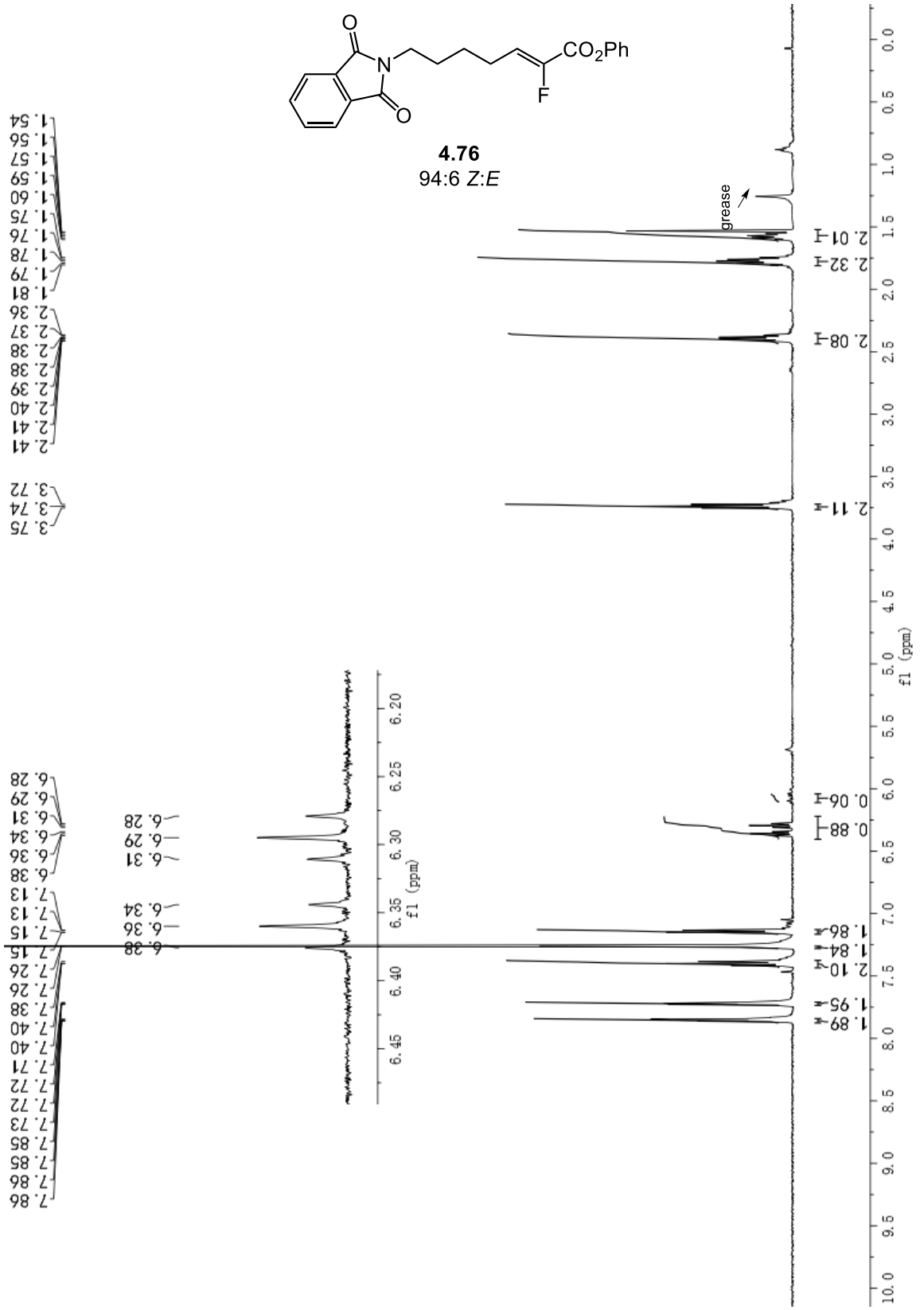
^{13}C NMR Spectrum of 4.75



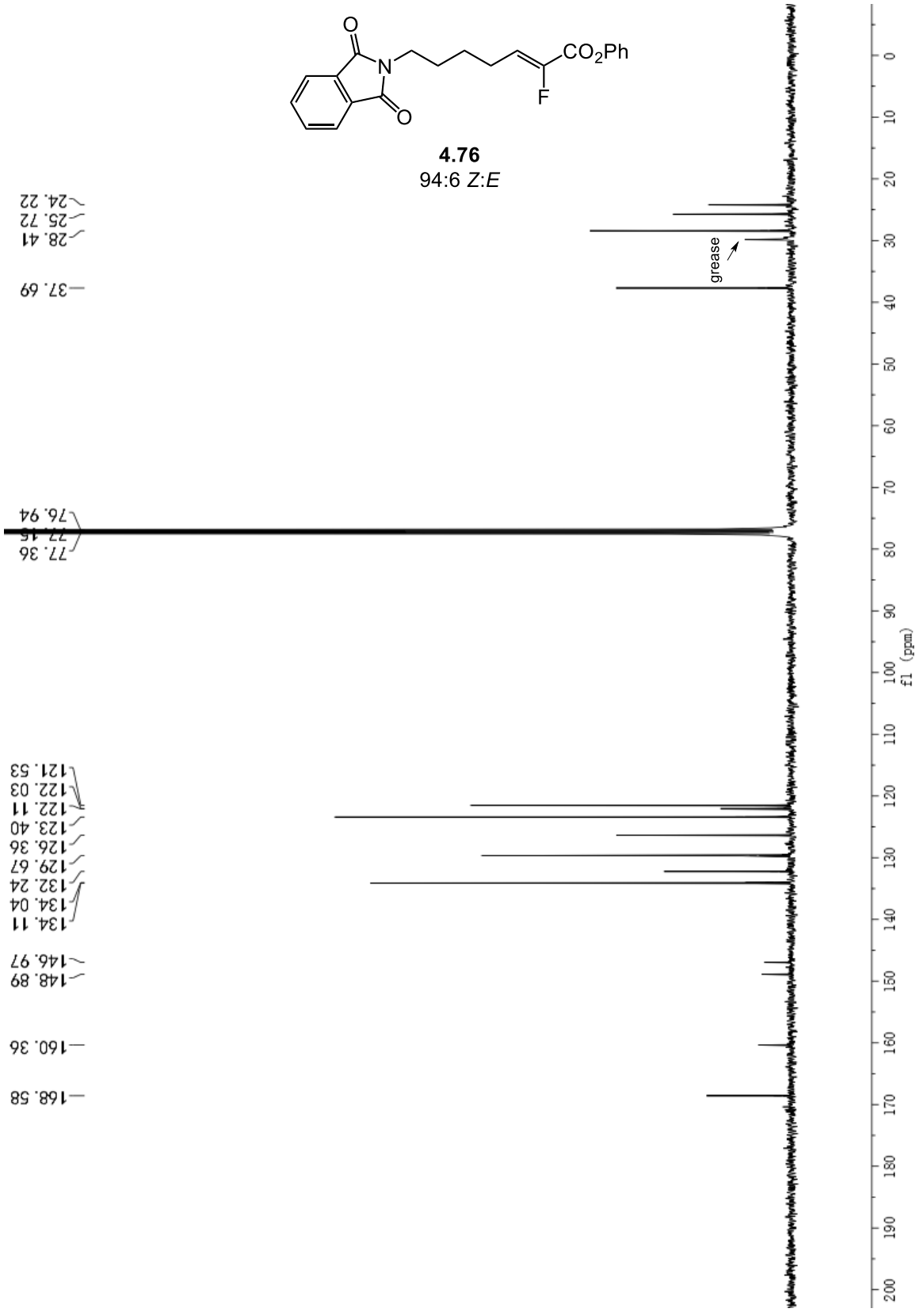
^{19}F NMR Spectrum of 4.76



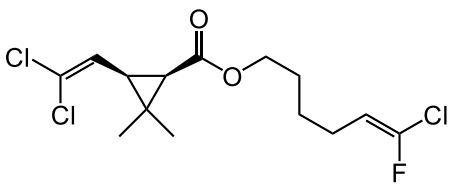
^{1}H NMR Spectrum of 4.76



^{13}C NMR Spectrum of 4.76

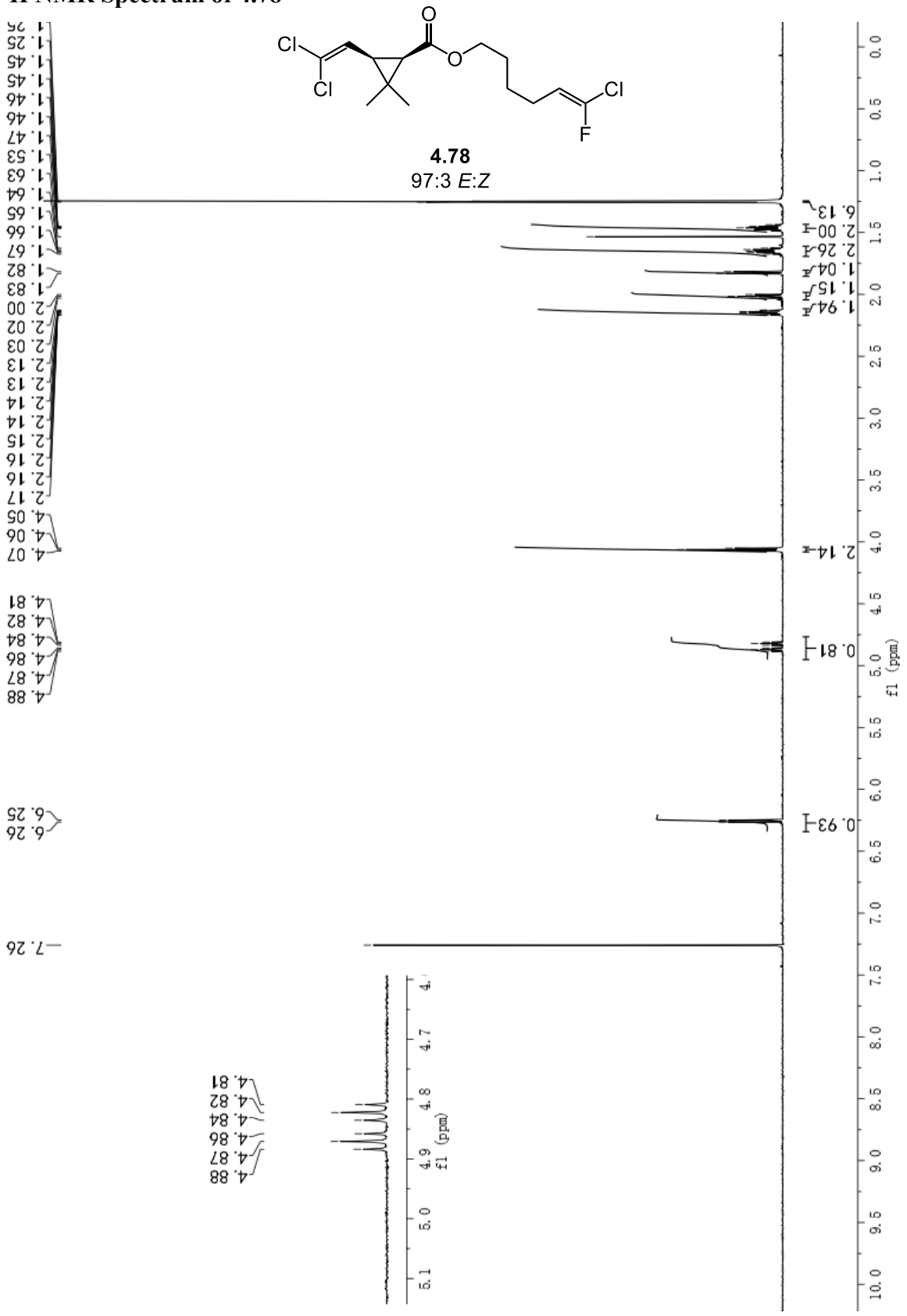


^{19}F NMR Spectrum of 4.78

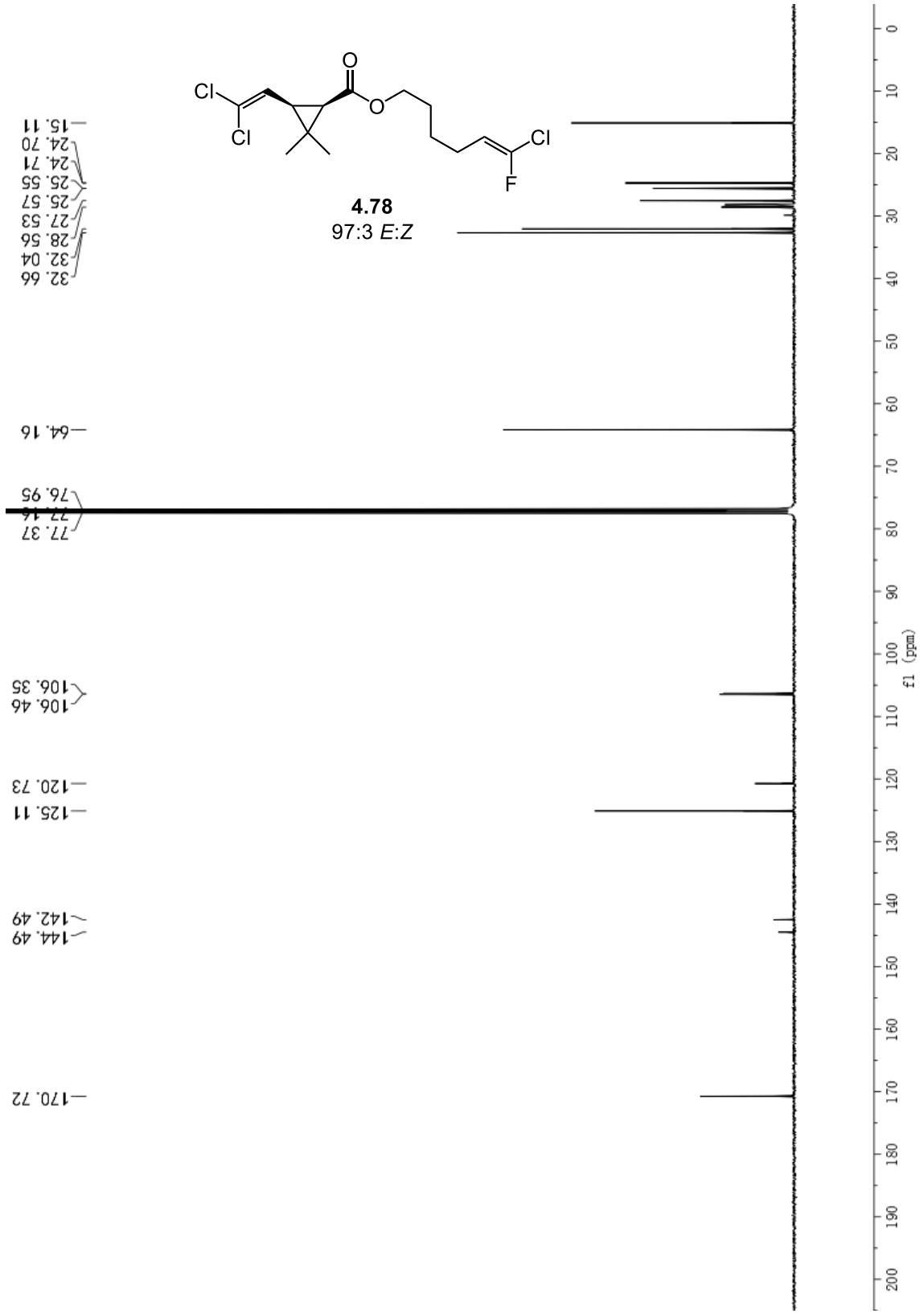


4.78
97:3 *E*:*Z*

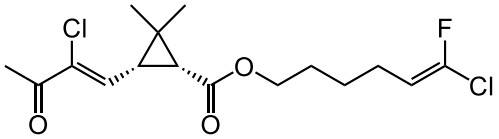
^{1}H NMR Spectrum of 4.78



^{13}C NMR Spectrum of 4.78

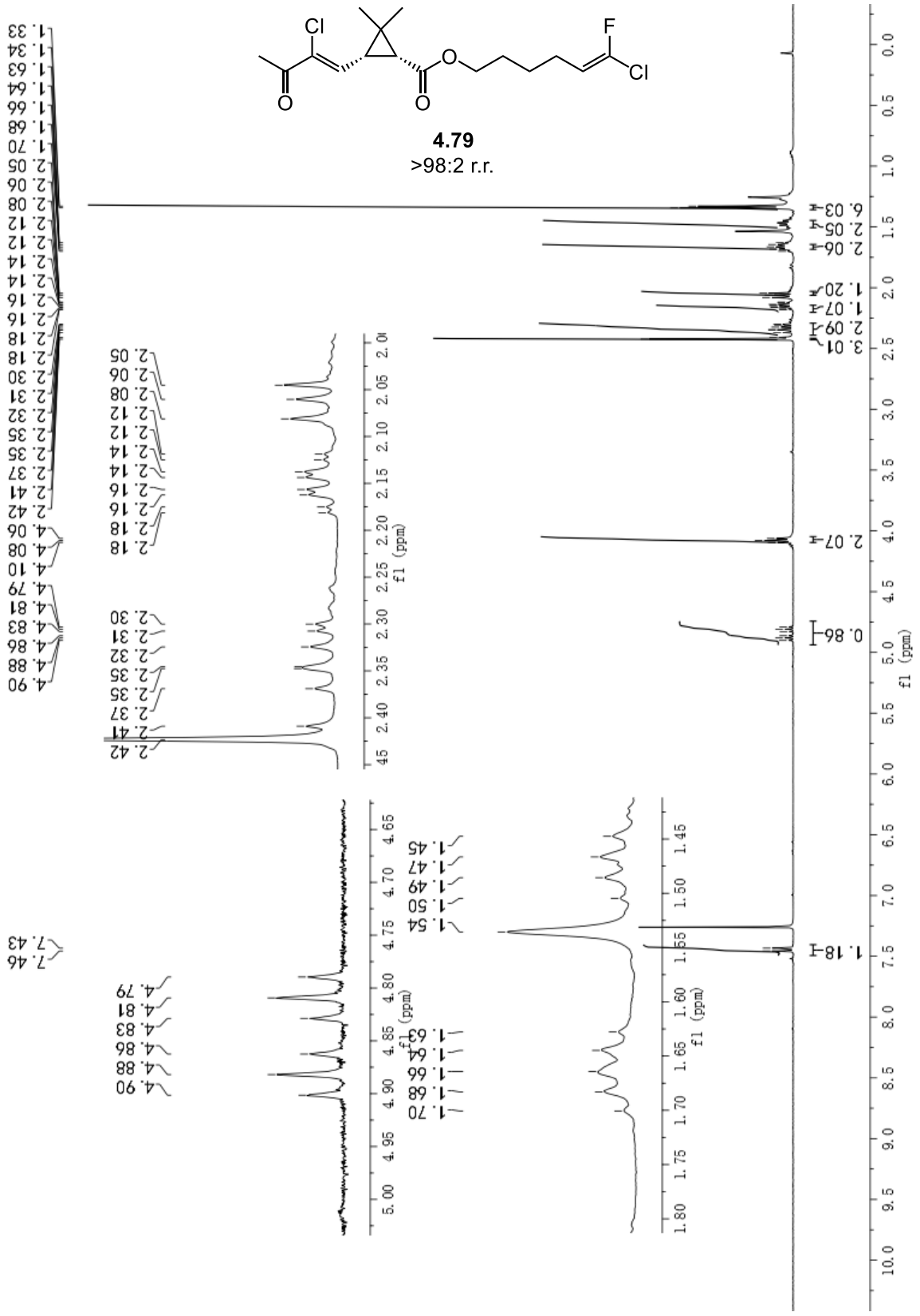


^{19}F NMR Spectrum of 4.79

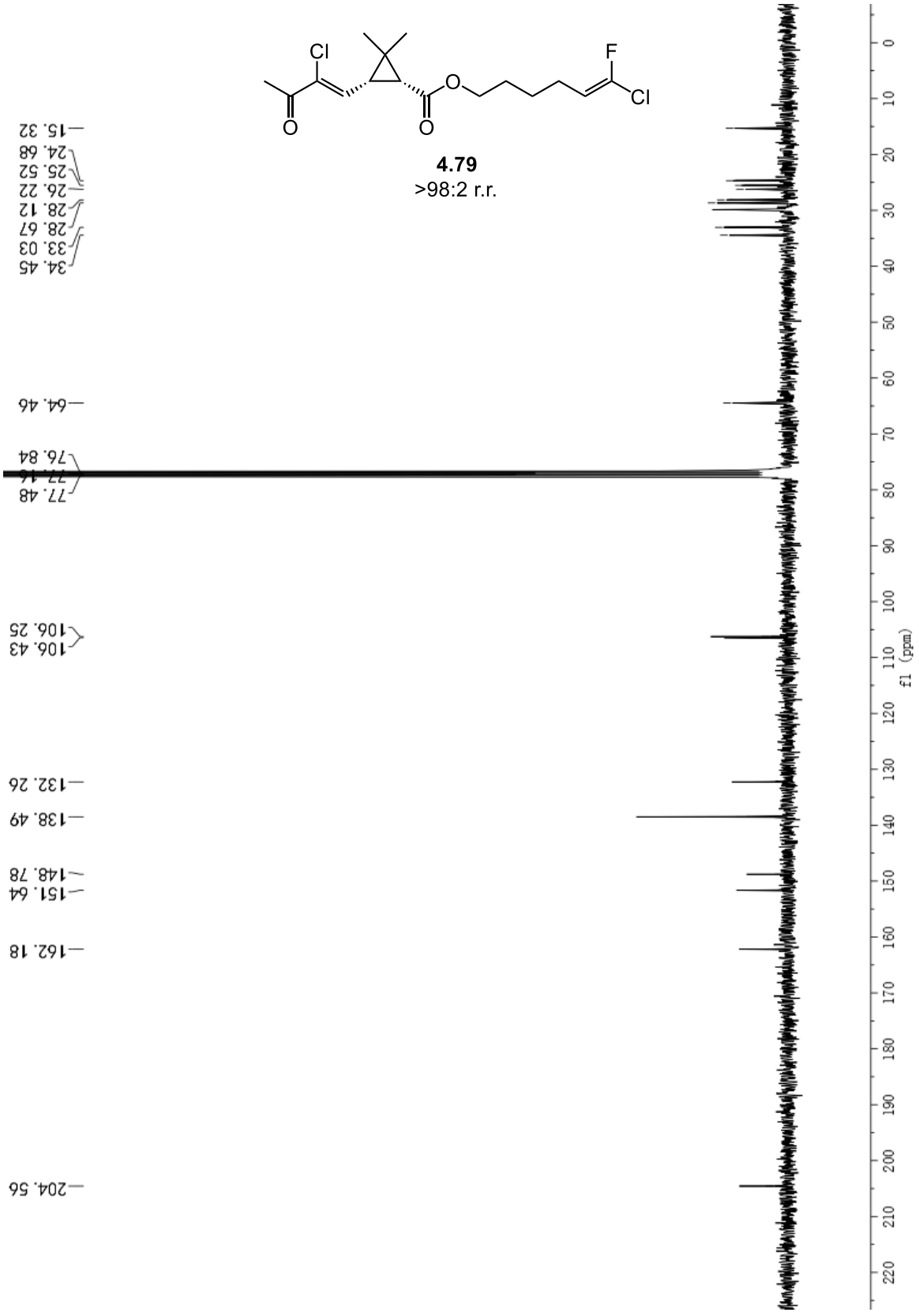


4.79
>98:2 r.r.

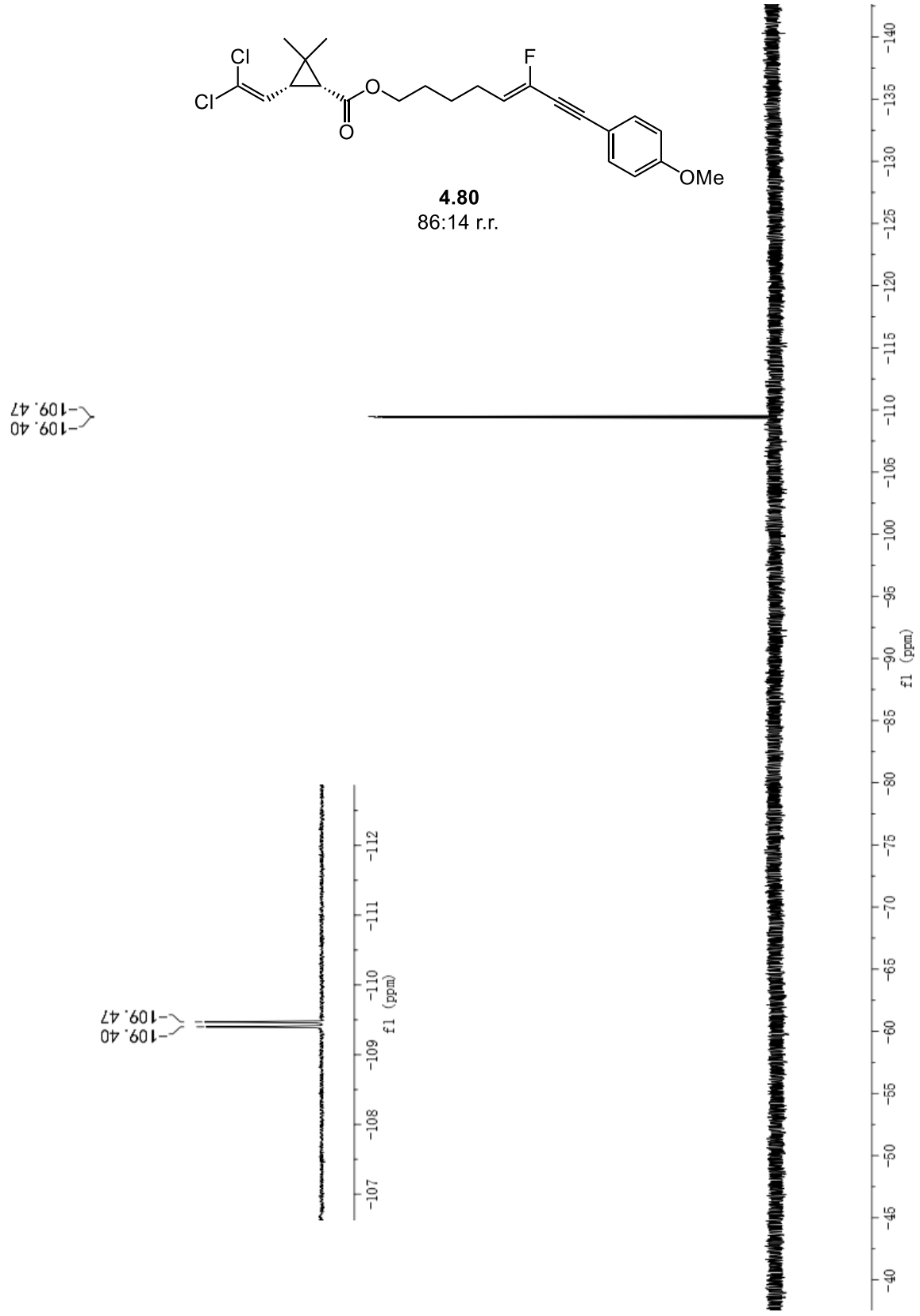
^{1}H NMR Spectrum of 4.79



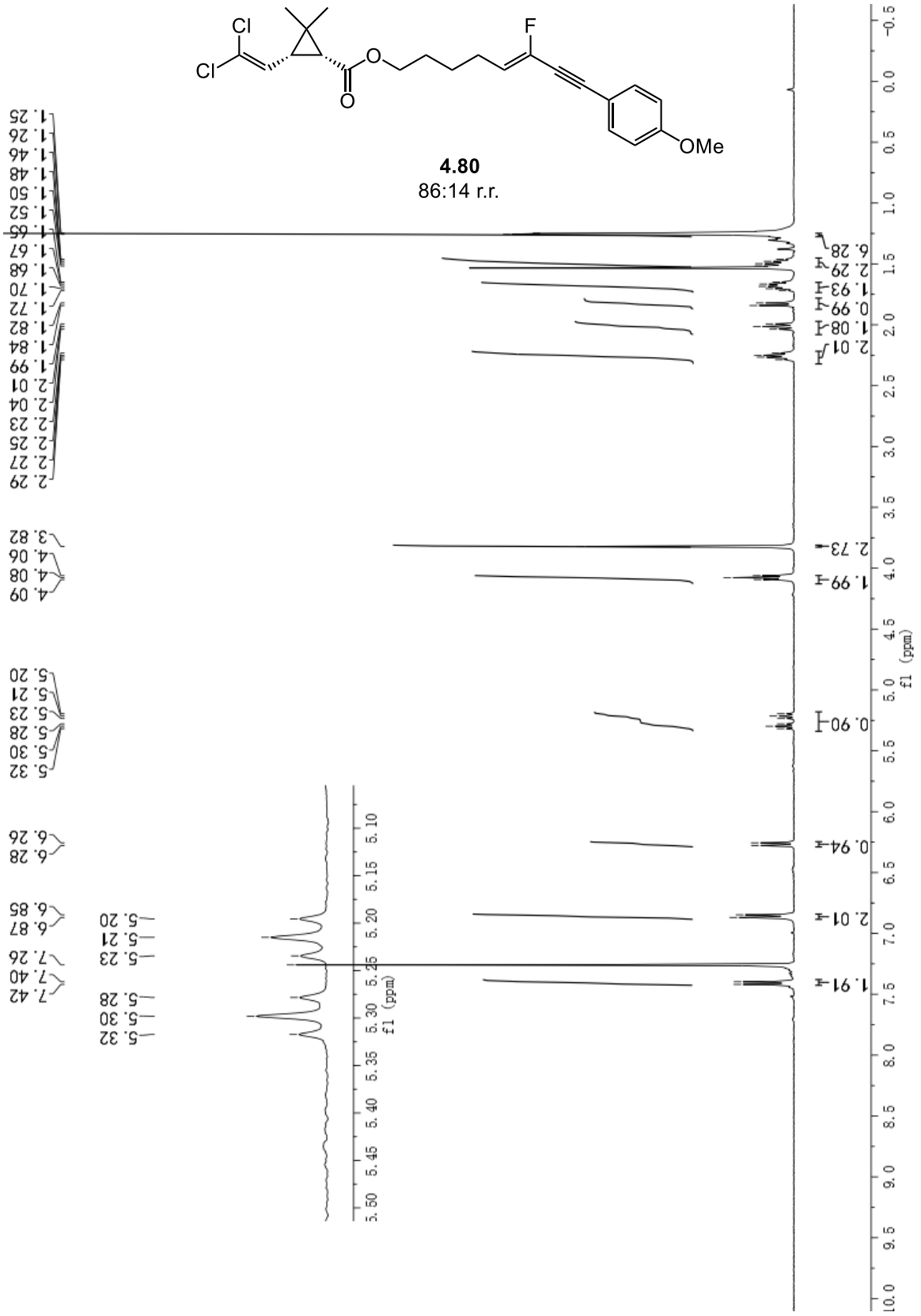
^{13}C NMR Spectrum of 4.79



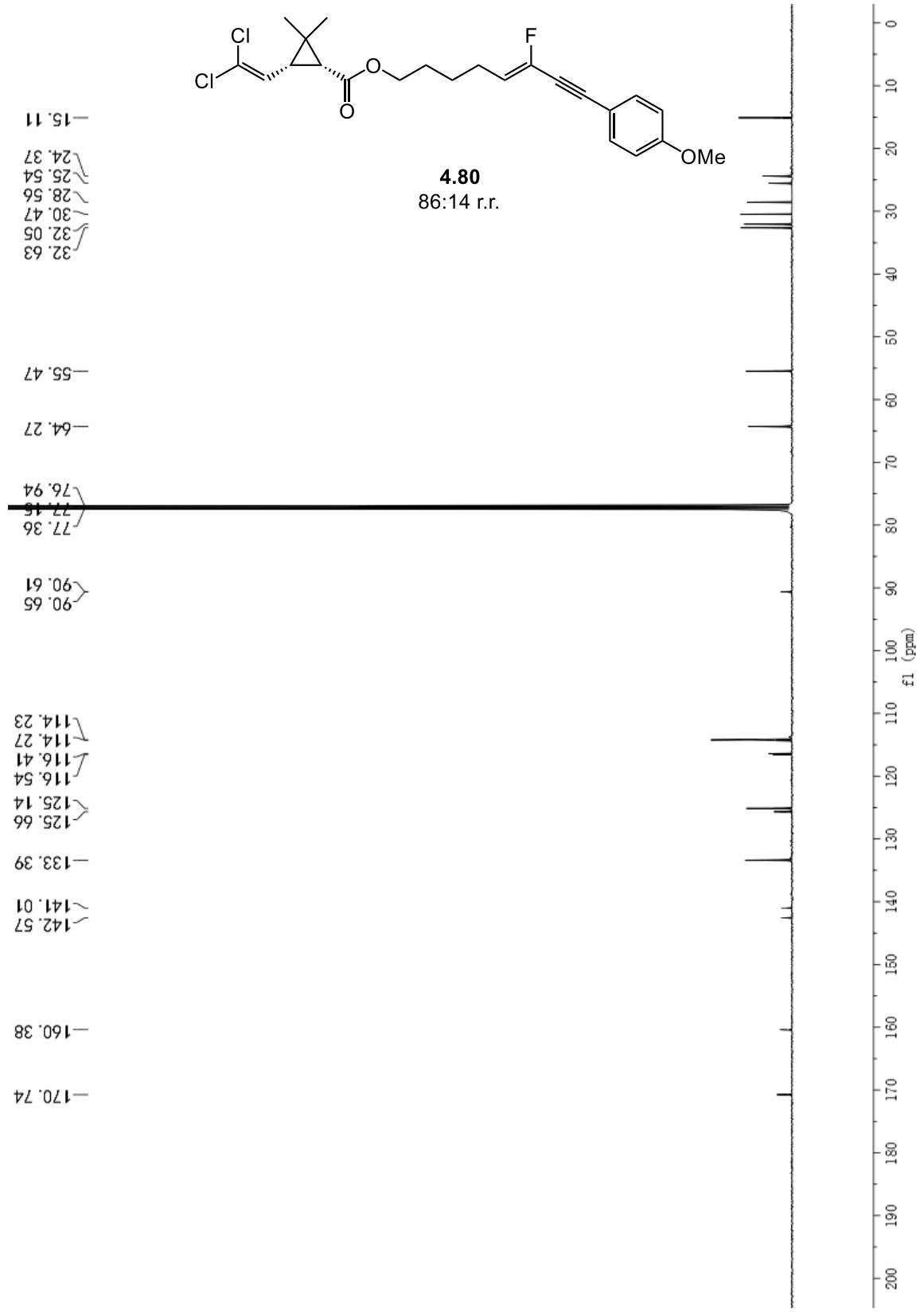
^{19}F NMR Spectrum of 4.80



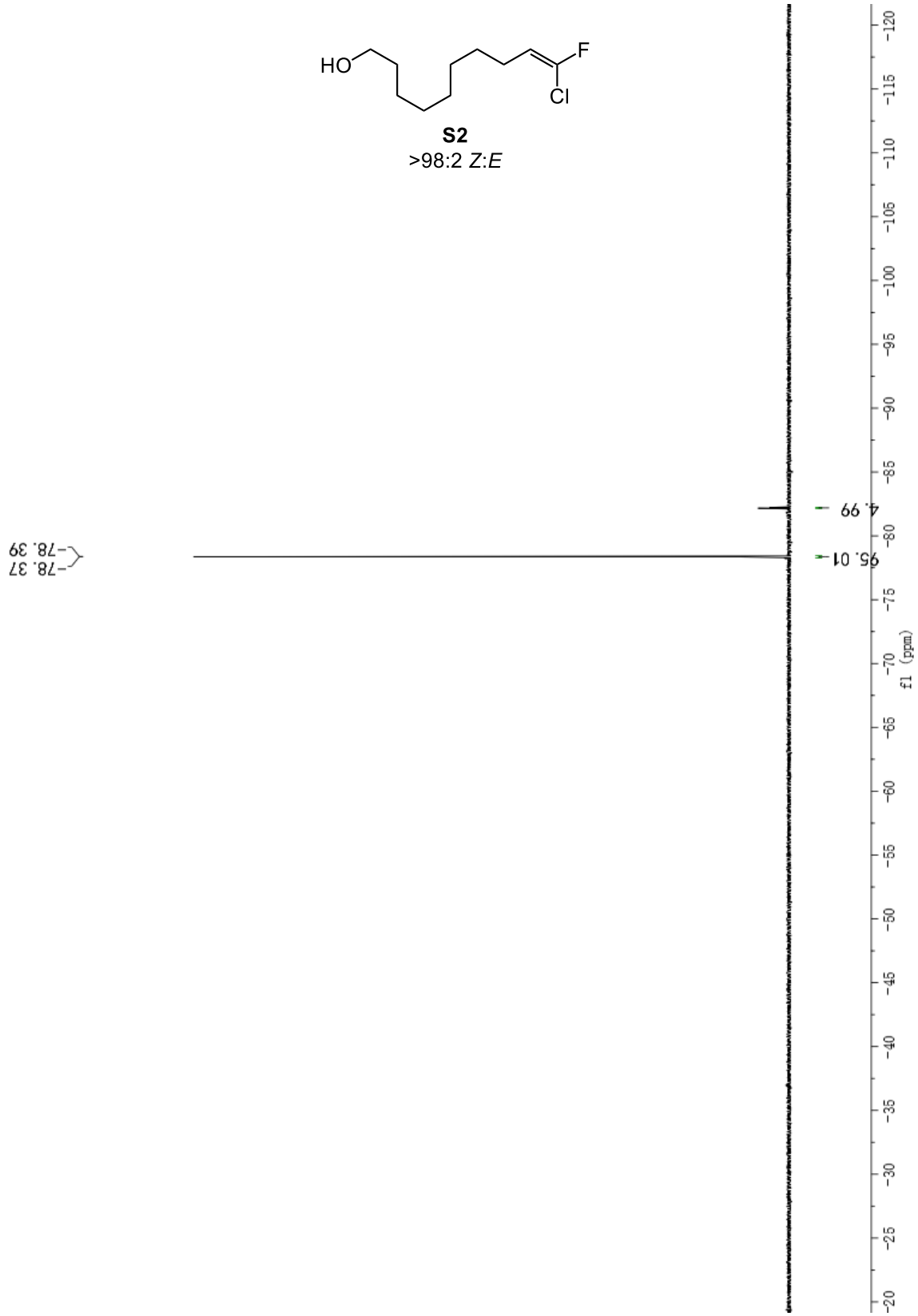
^{1}H NMR Spectrum of 4.80



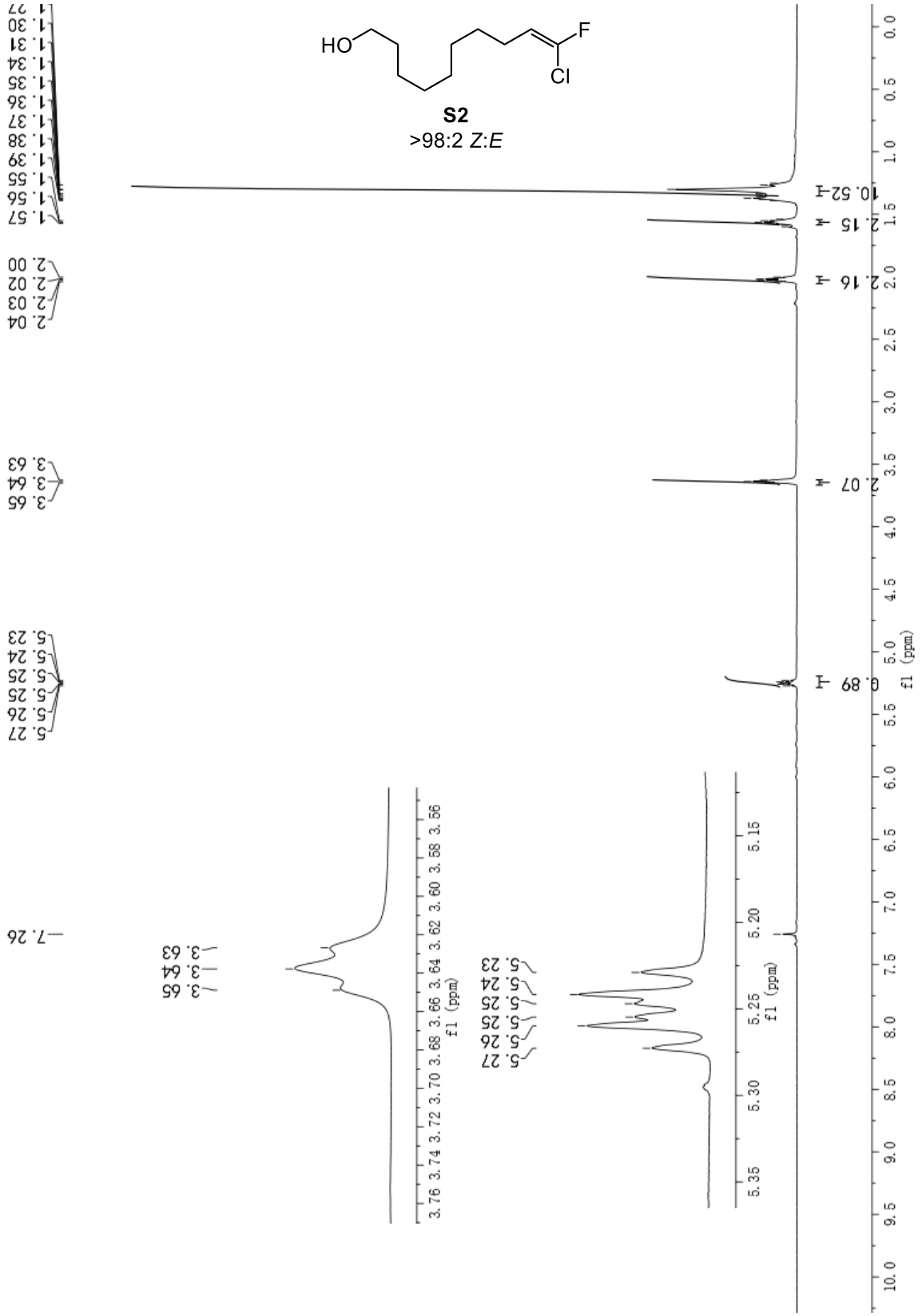
^{13}C NMR Spectrum of 4.80



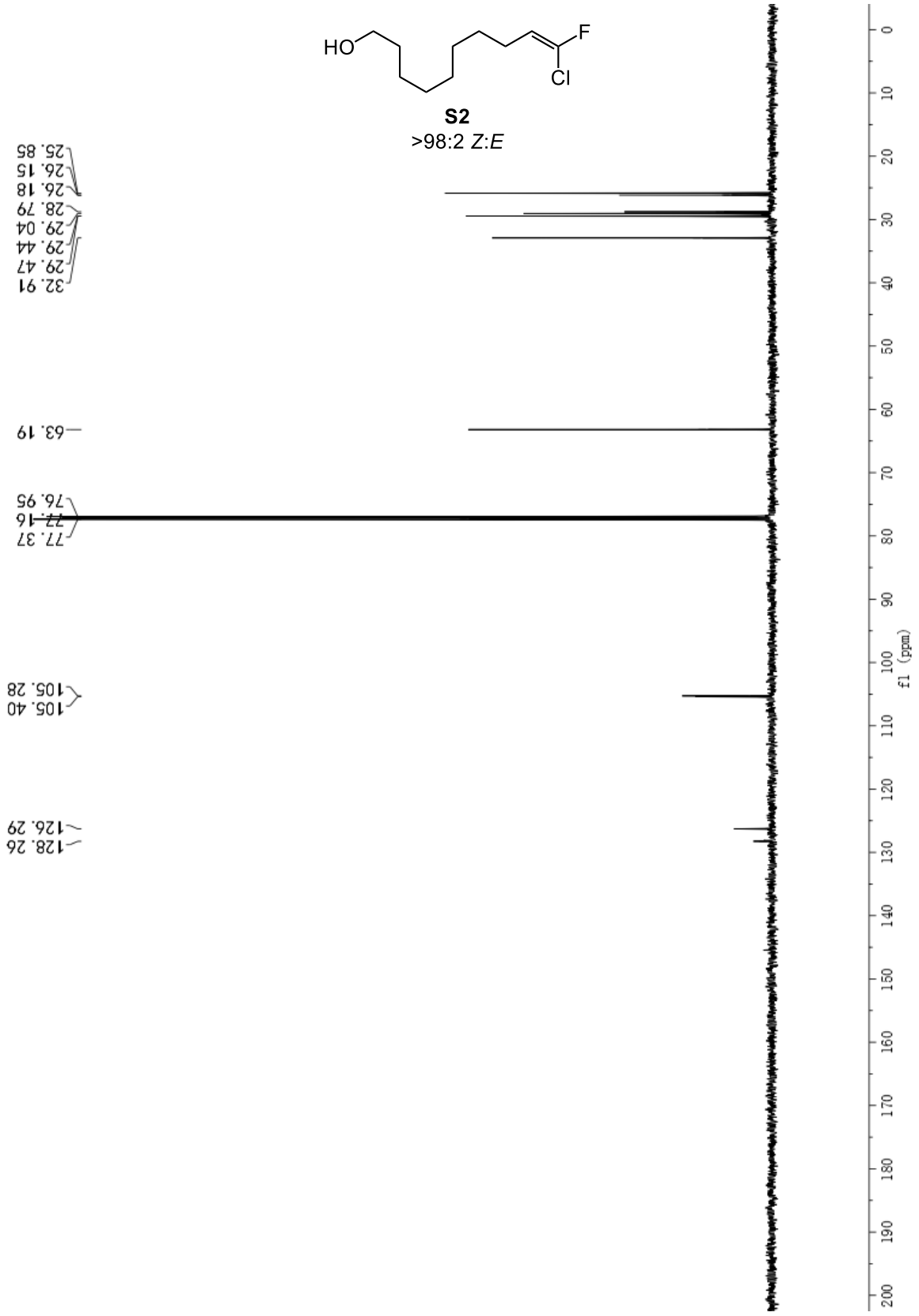
^{19}F NMR Spectrum of S2



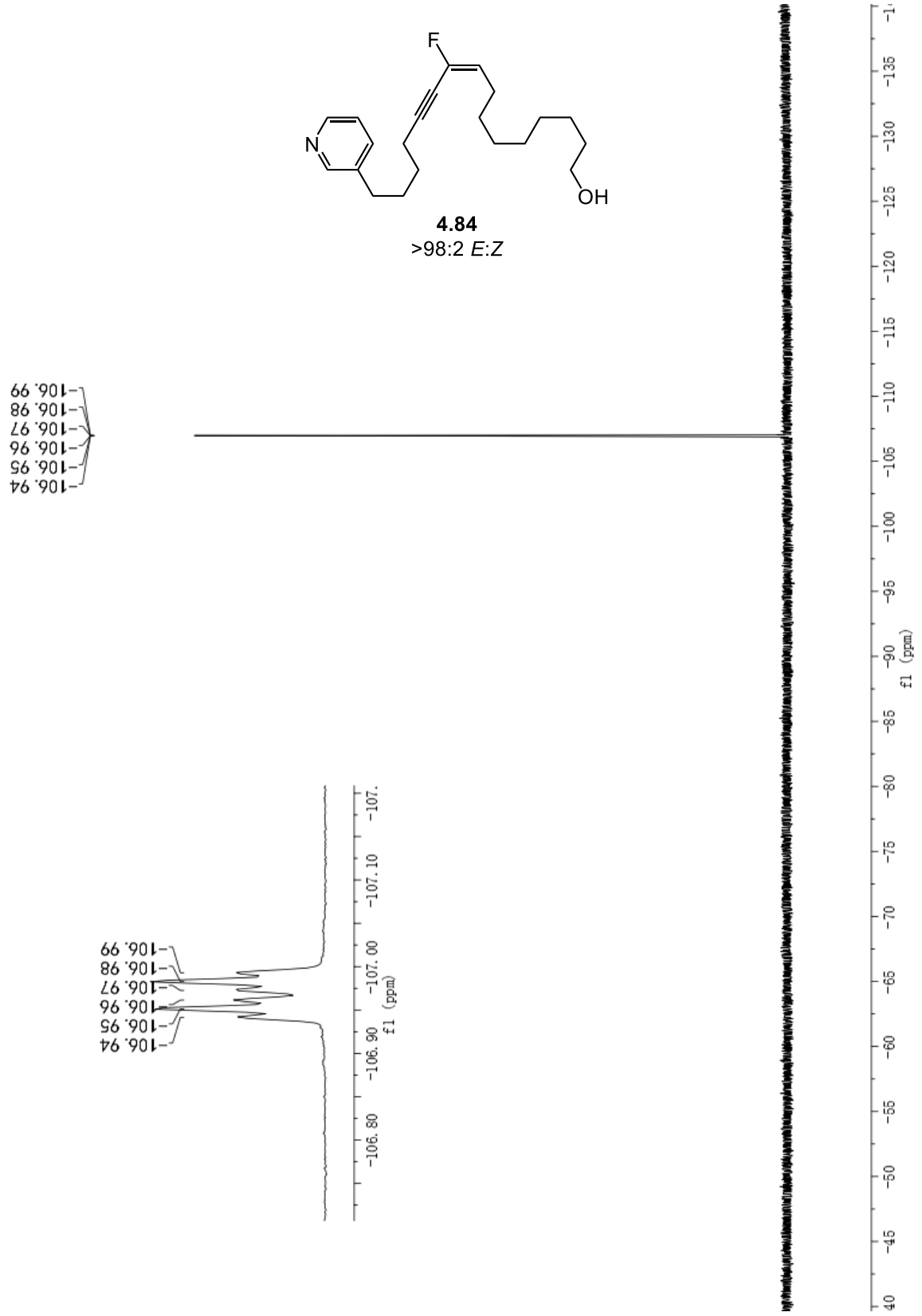
^{1}H NMR Spectrum of S2



^{13}C NMR Spectrum of S2

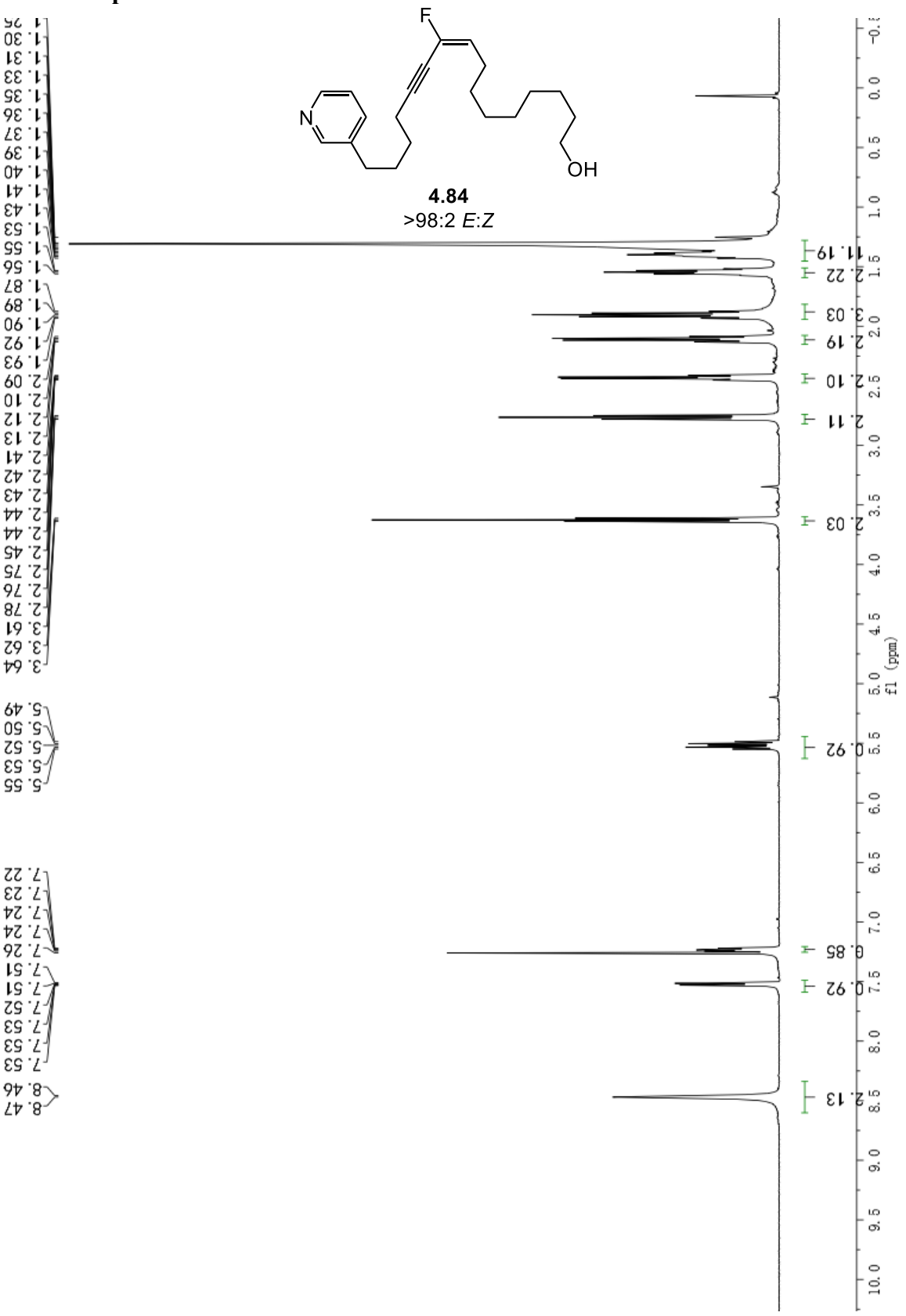


^{19}F NMR Spectrum of 4.84

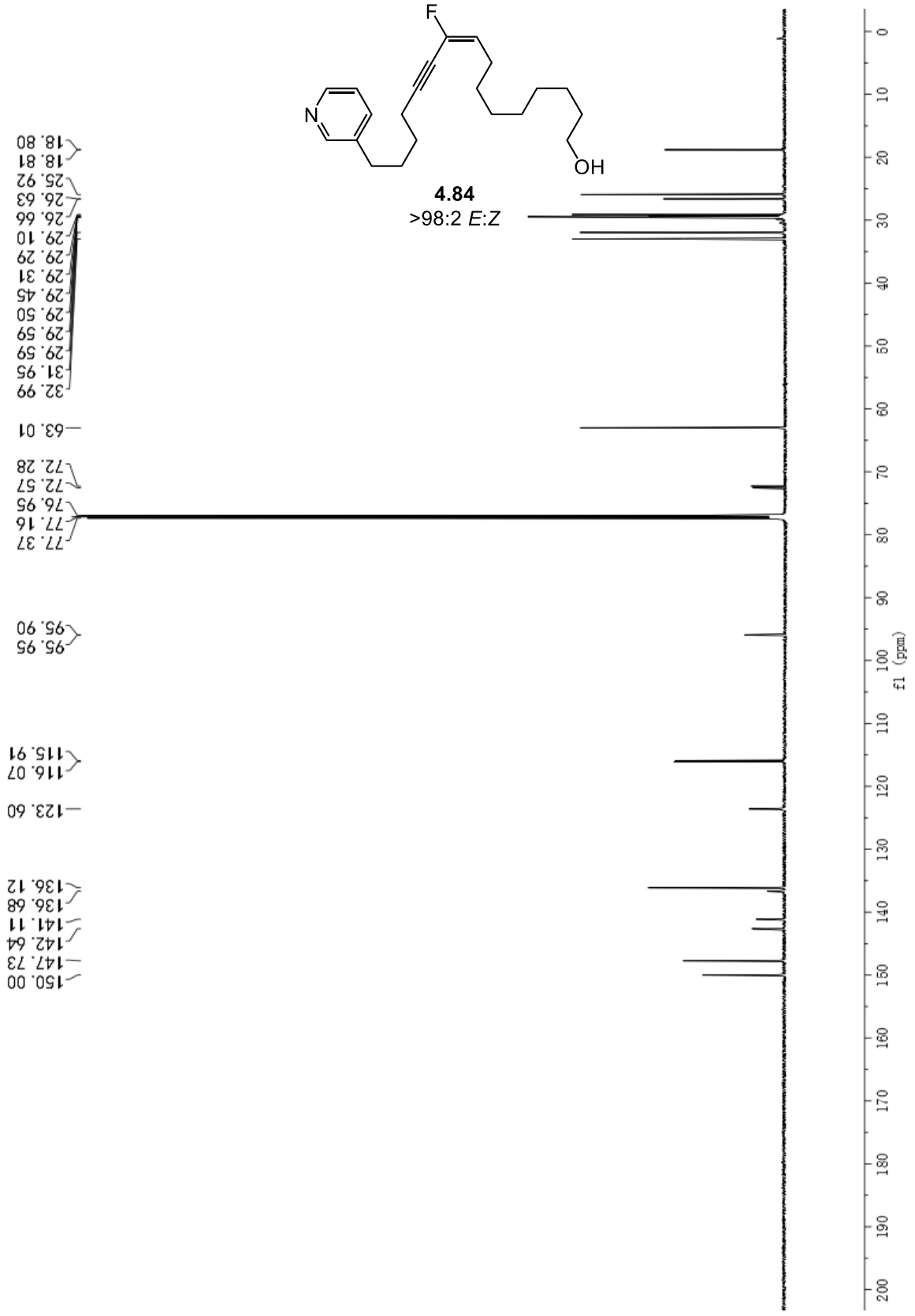


4.84
>98:2 *E*:*Z*

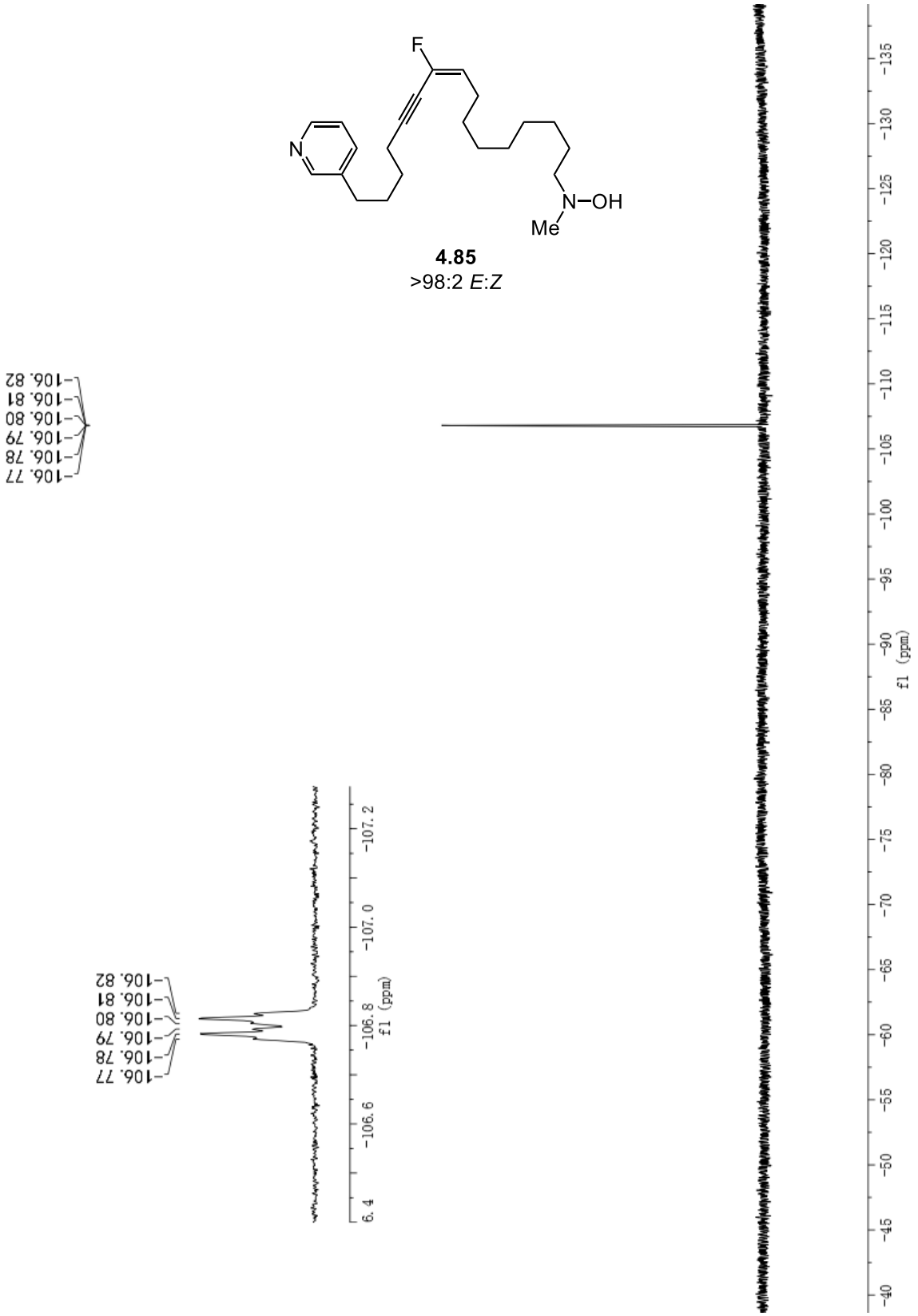
^{1}H NMR Spectrum of 4.82



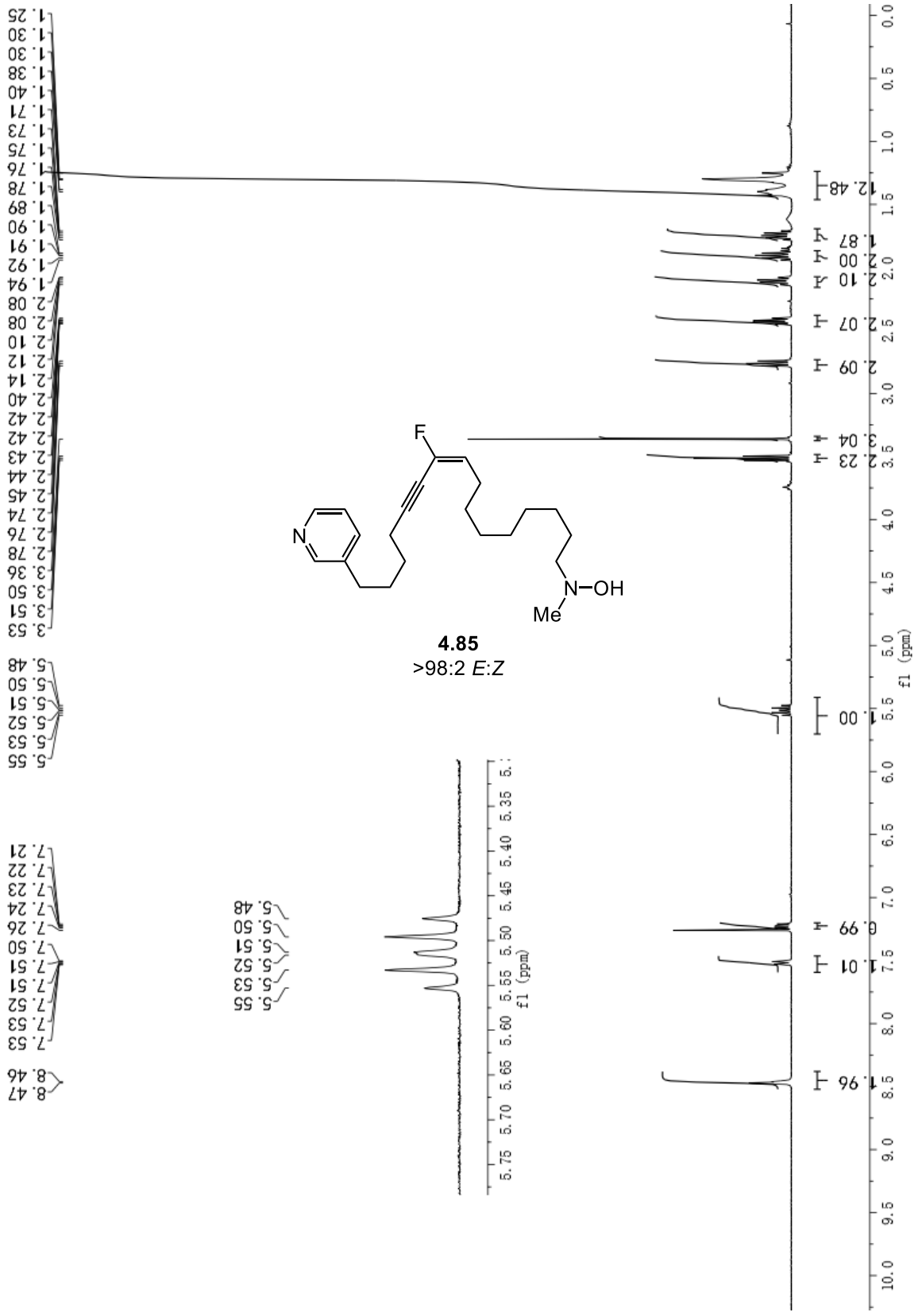
^{13}C NMR Spectrum of 4.82



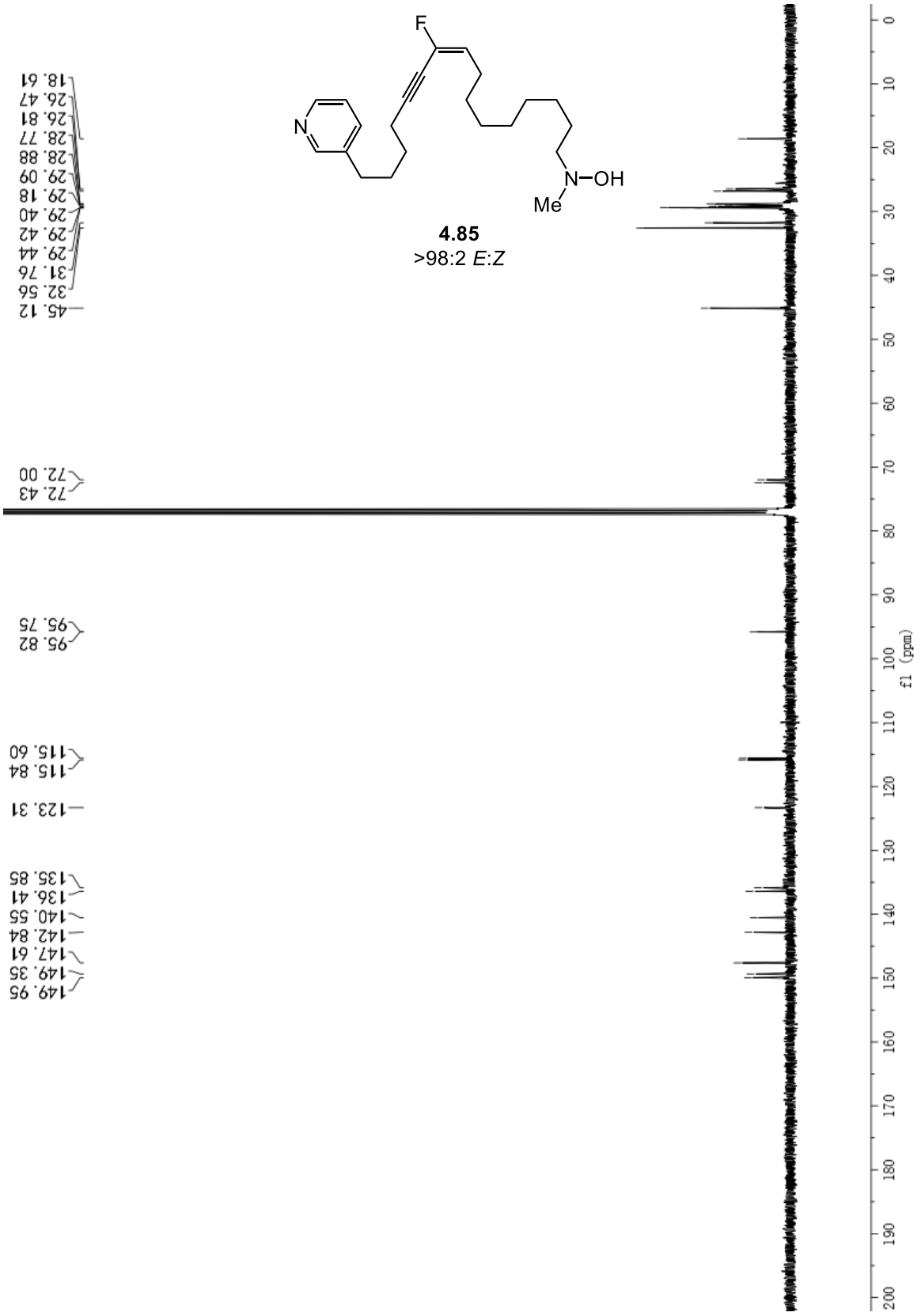
^{19}F NMR Spectrum of Fluoro-hachijodine G (4.85)



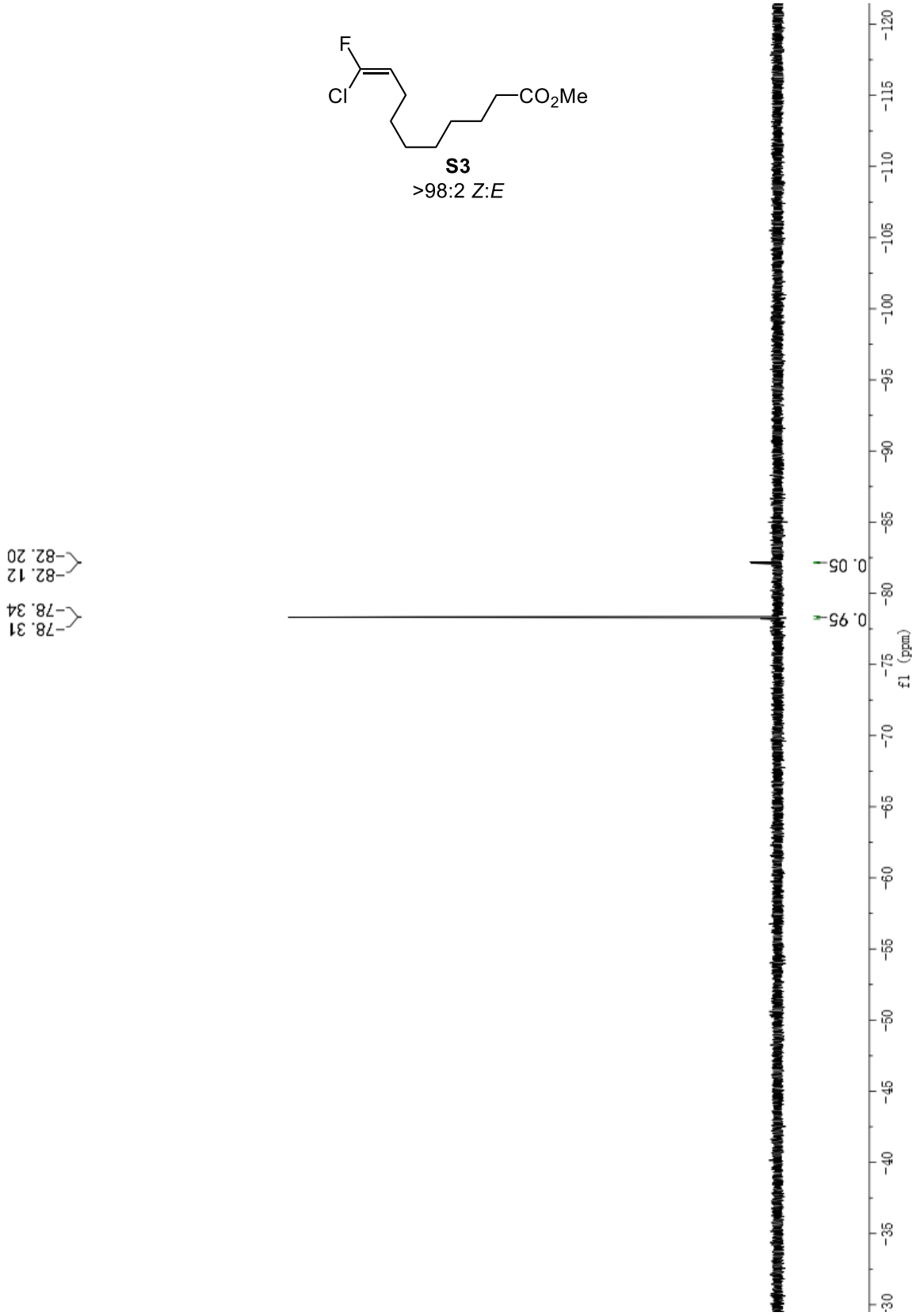
^{1}H NMR Spectrum of Fluoro-hachijodine G (4.85)



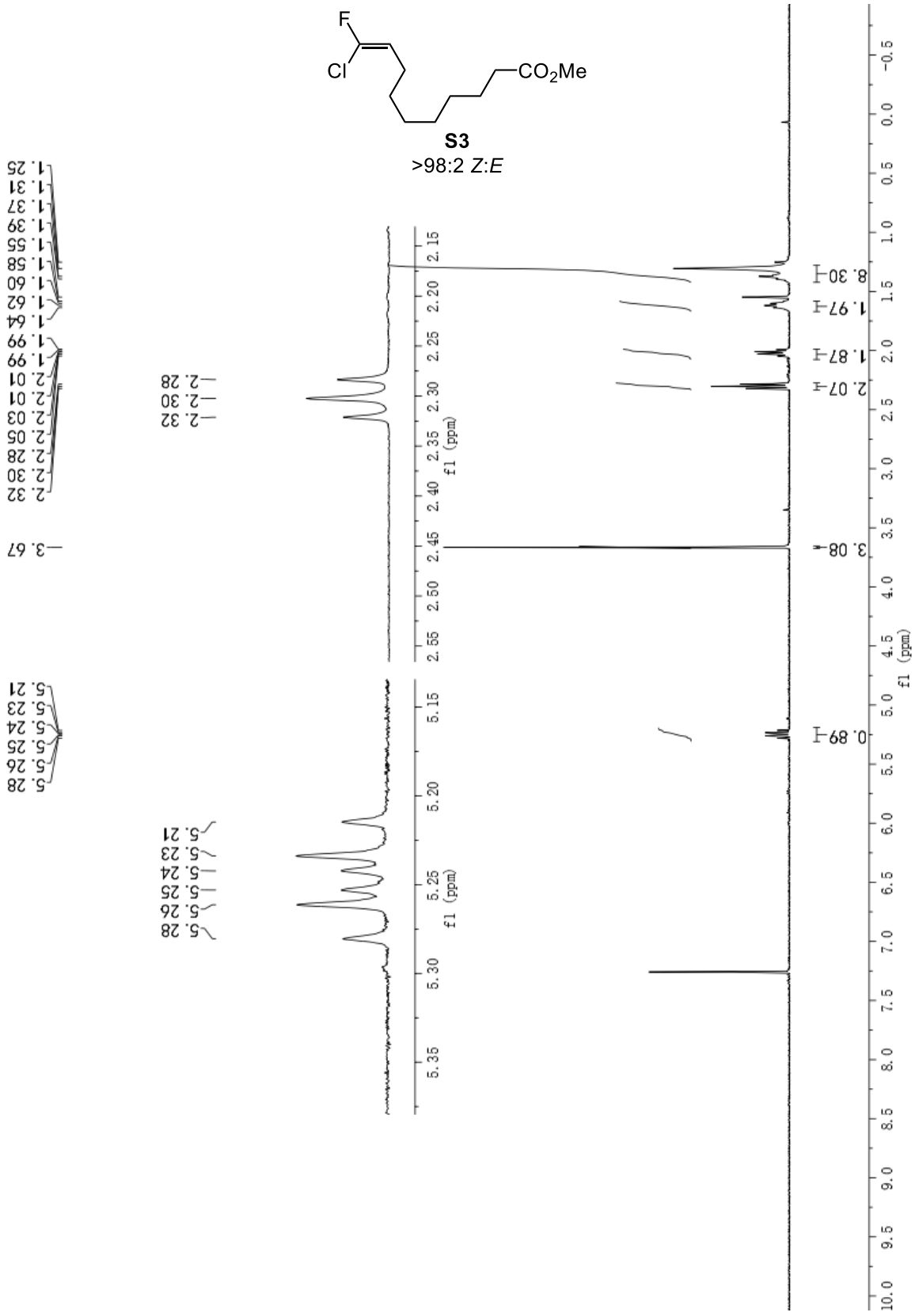
^{13}C NMR Spectrum of Fluoro-hachijodine G (4.85)



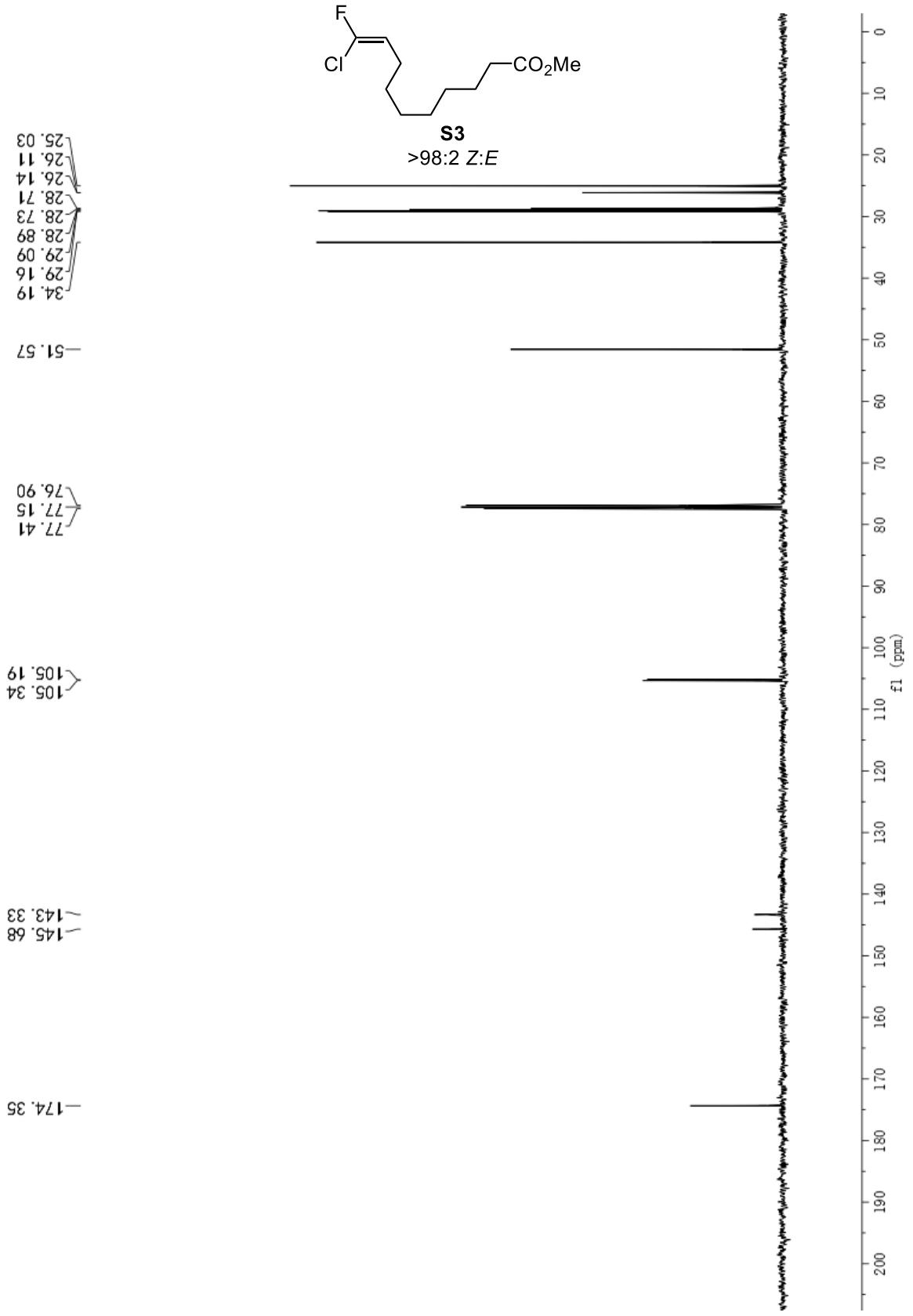
^{19}F NMR Spectrum of S3



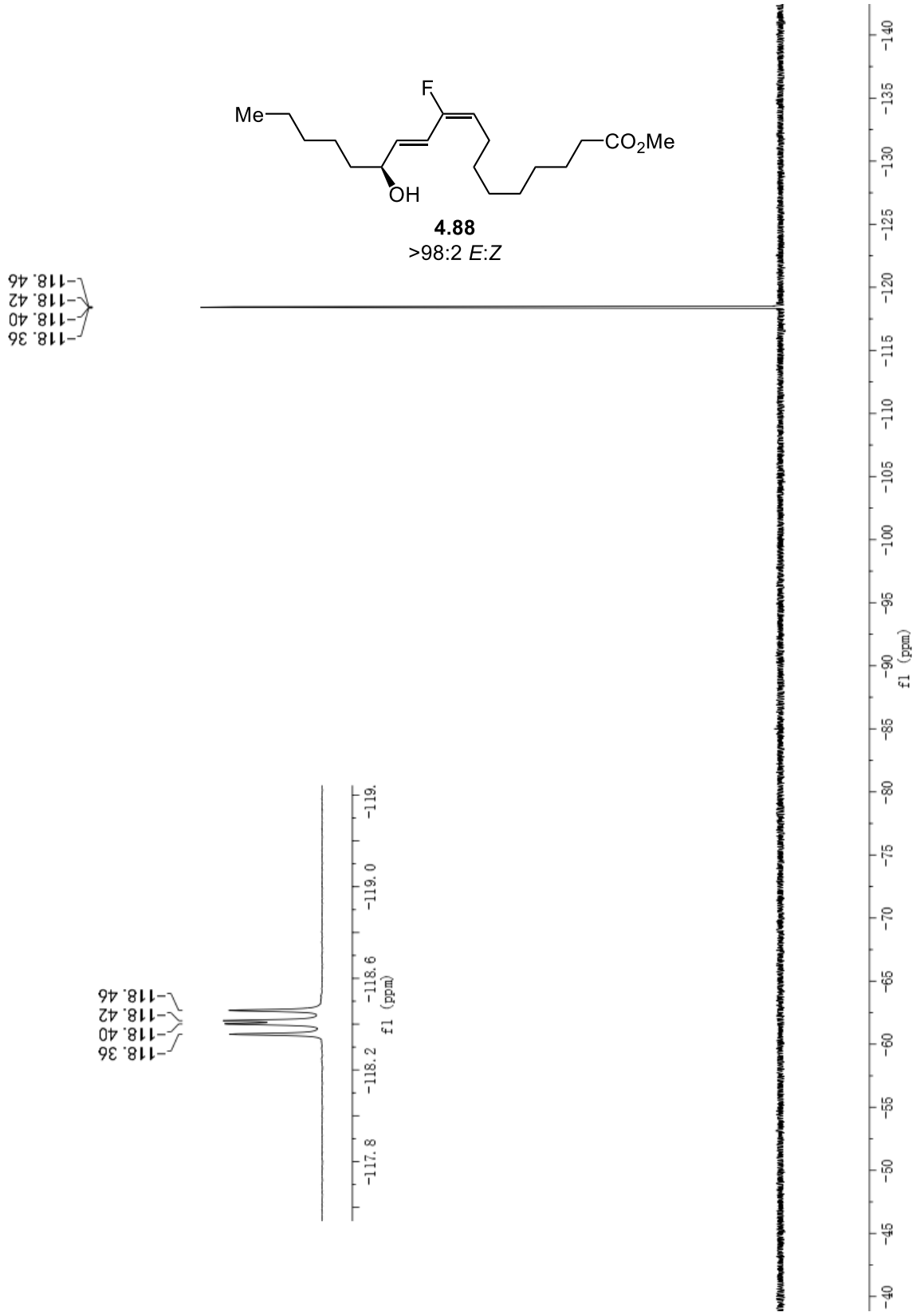
^{1}H NMR Spectrum of S3



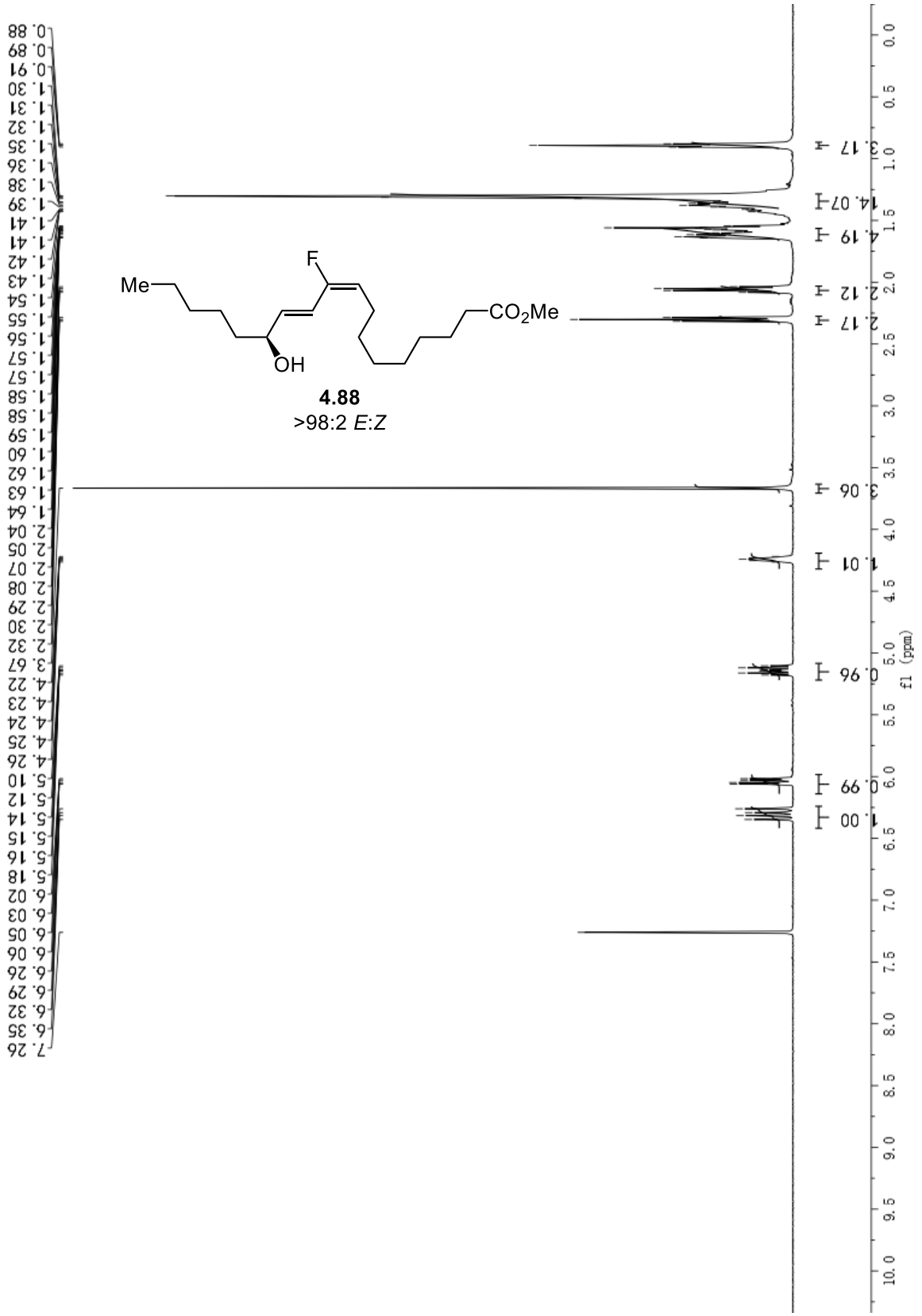
^{13}C NMR Spectrum of S3



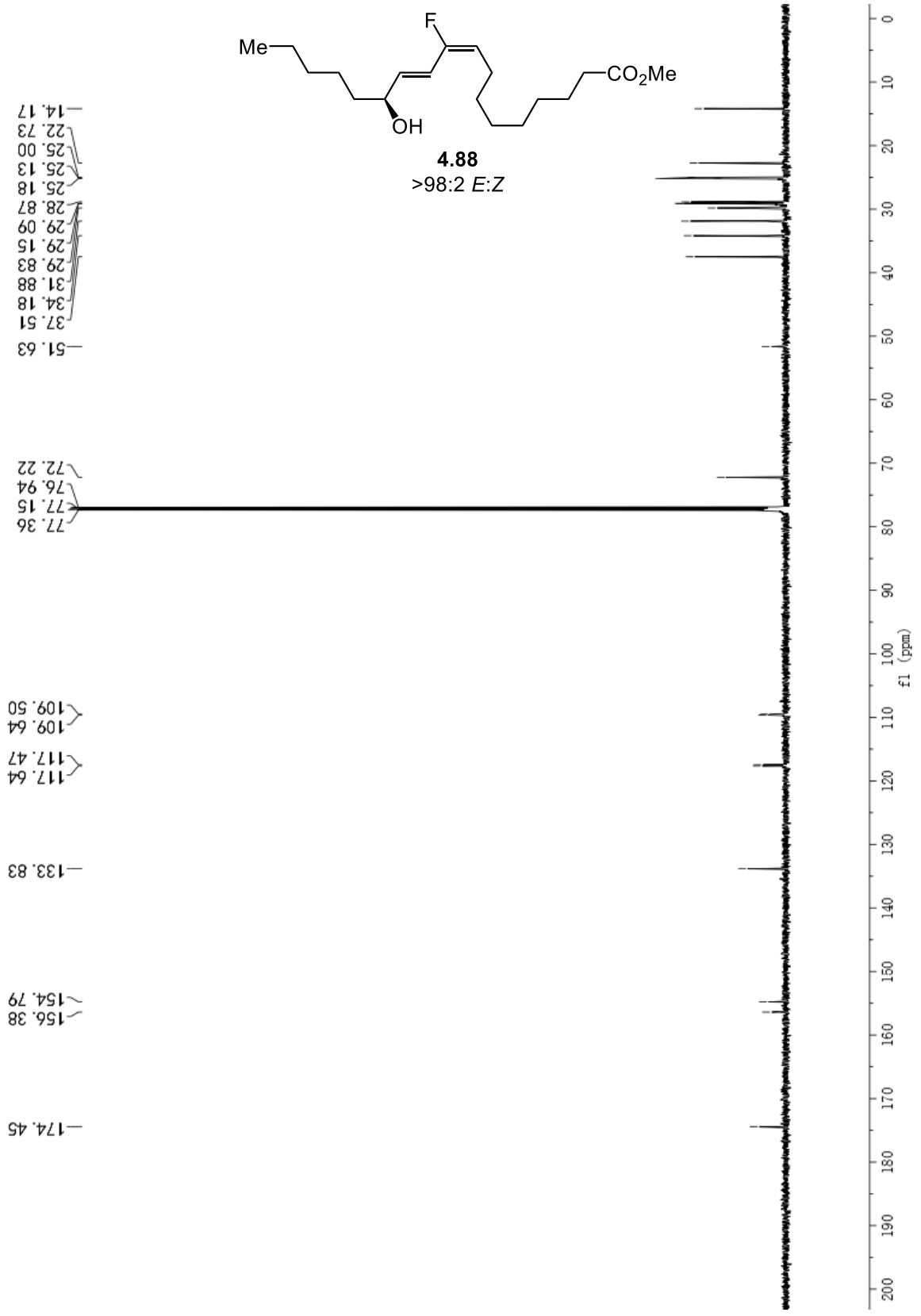
^{19}F NMR Spectrum of 4.88



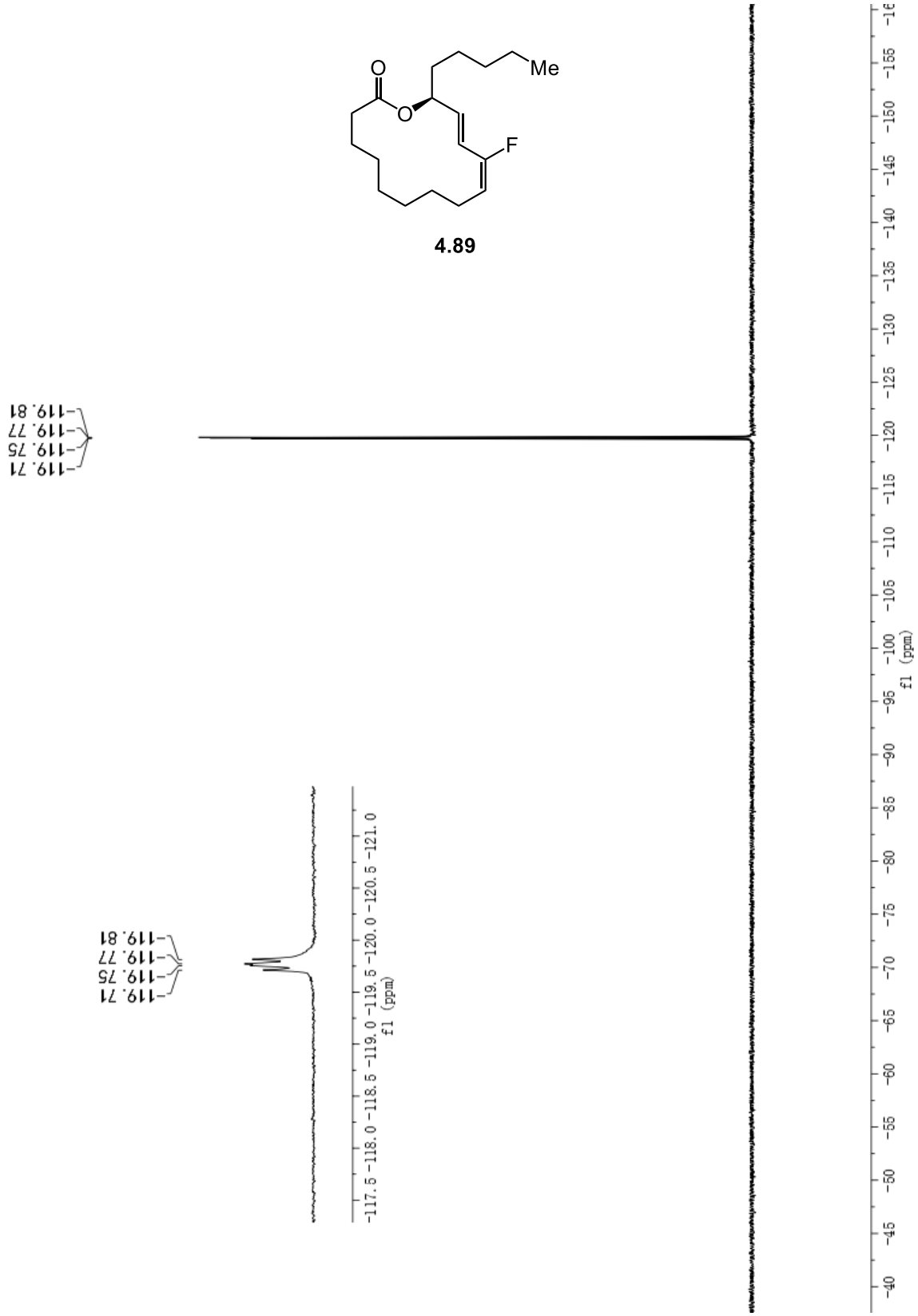
^{1}H NMR Spectrum of 4.88



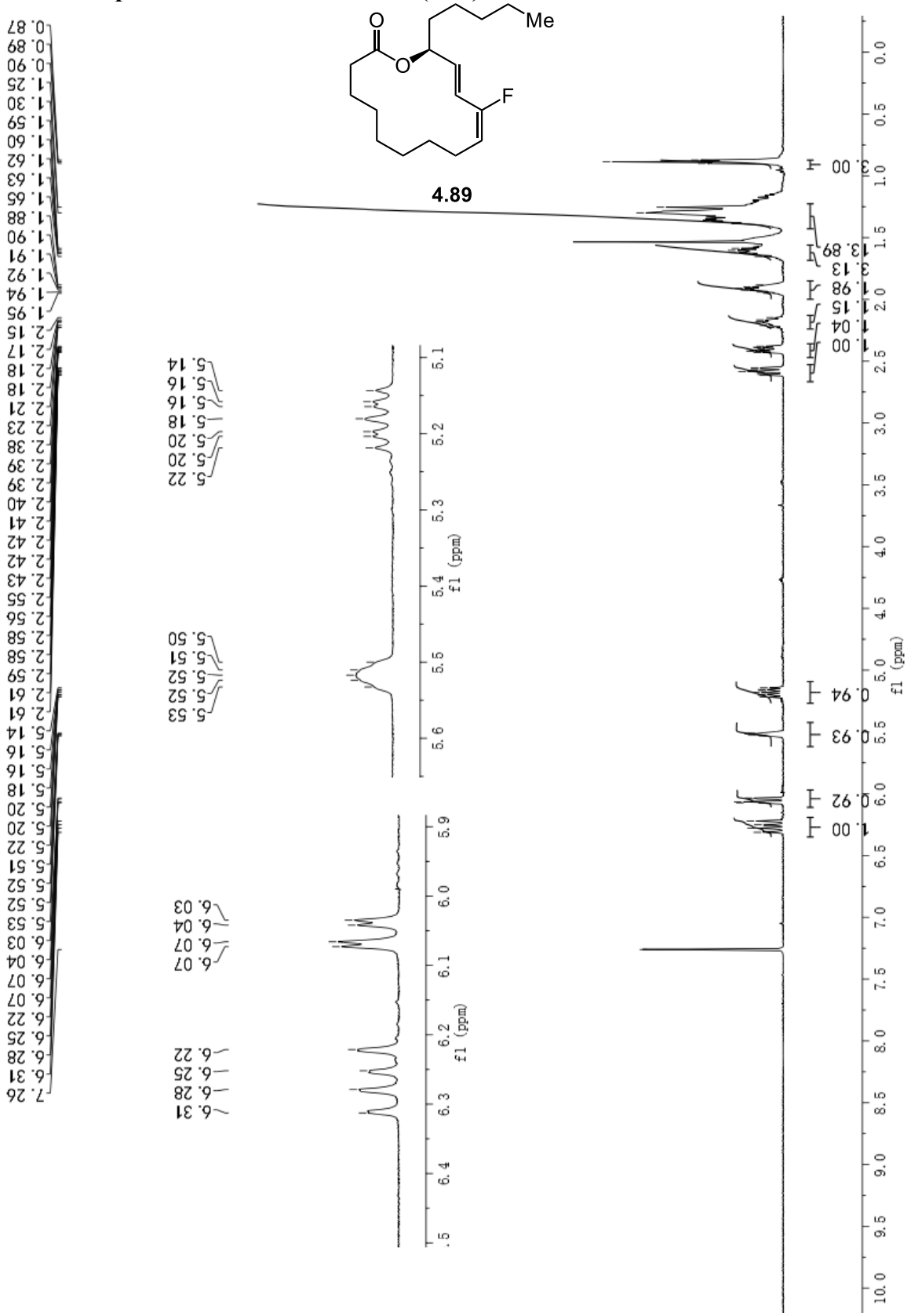
^{13}C NMR Spectrum of 4.88



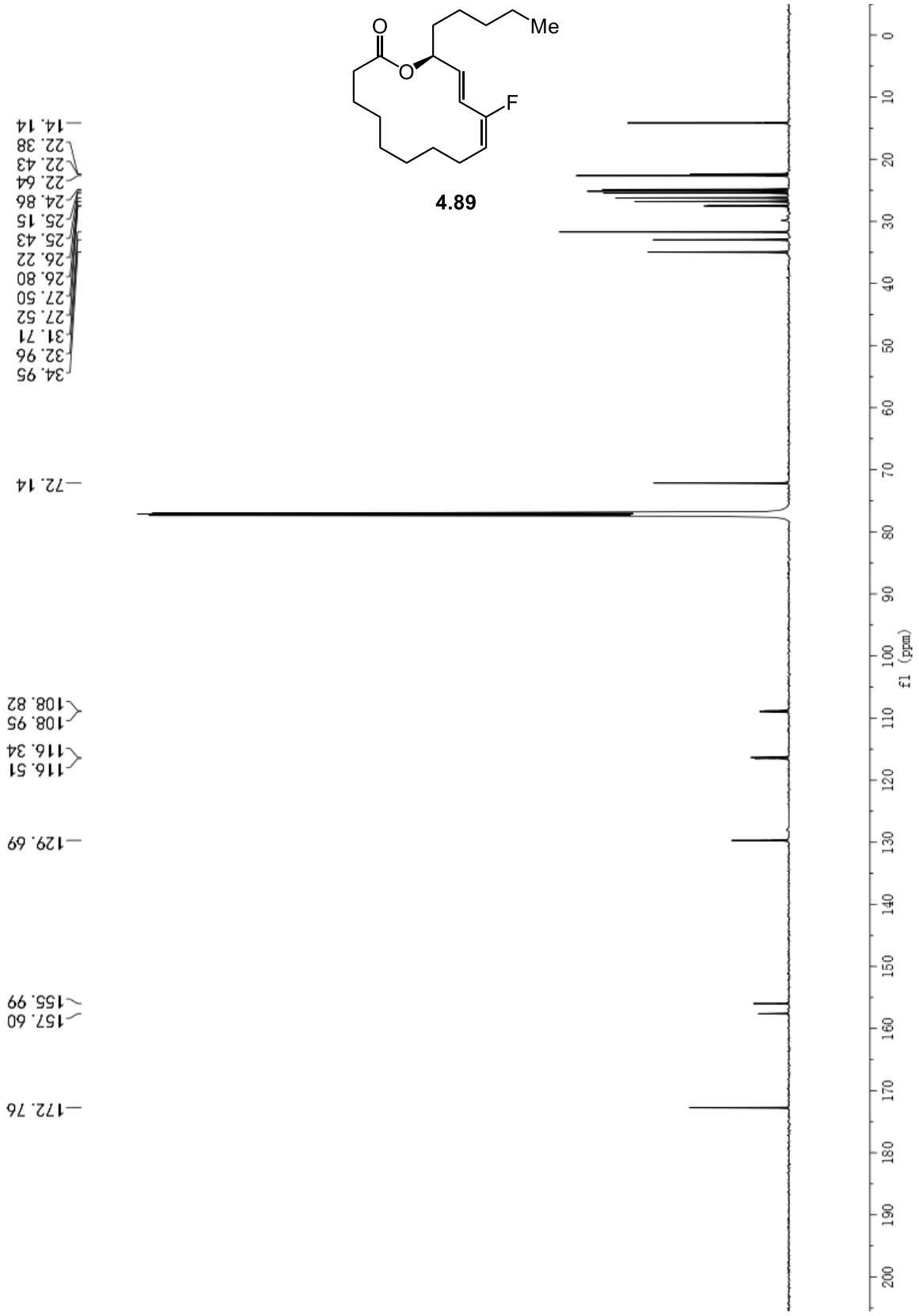
^{19}F NMR Spectrum of fluoro-coriolide (4.89)



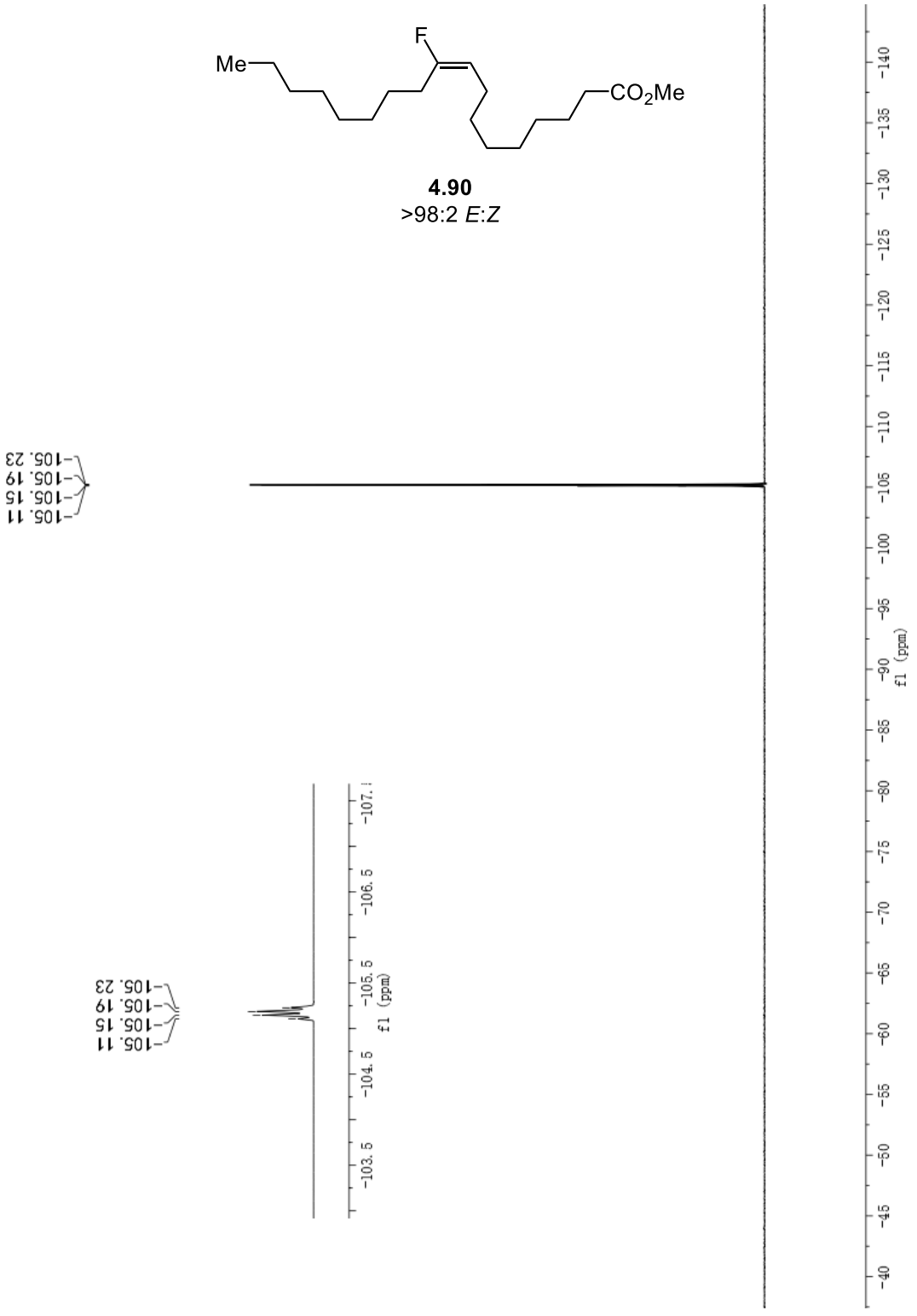
^{1}H NMR Spectrum of Fluoro-coriolide (4.89)



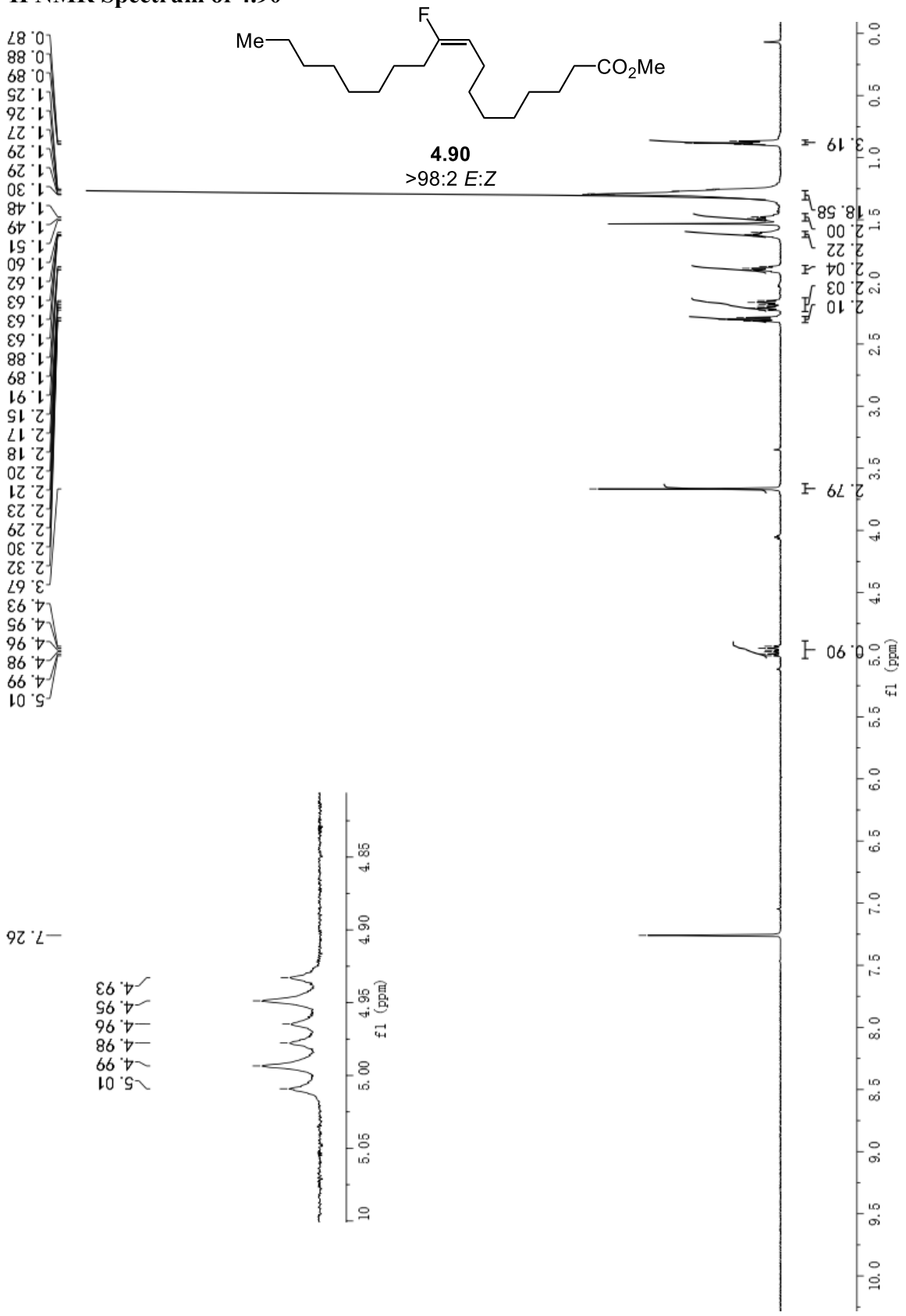
^{13}C NMR Spectrum of Fluoro-coriolide (4.89)



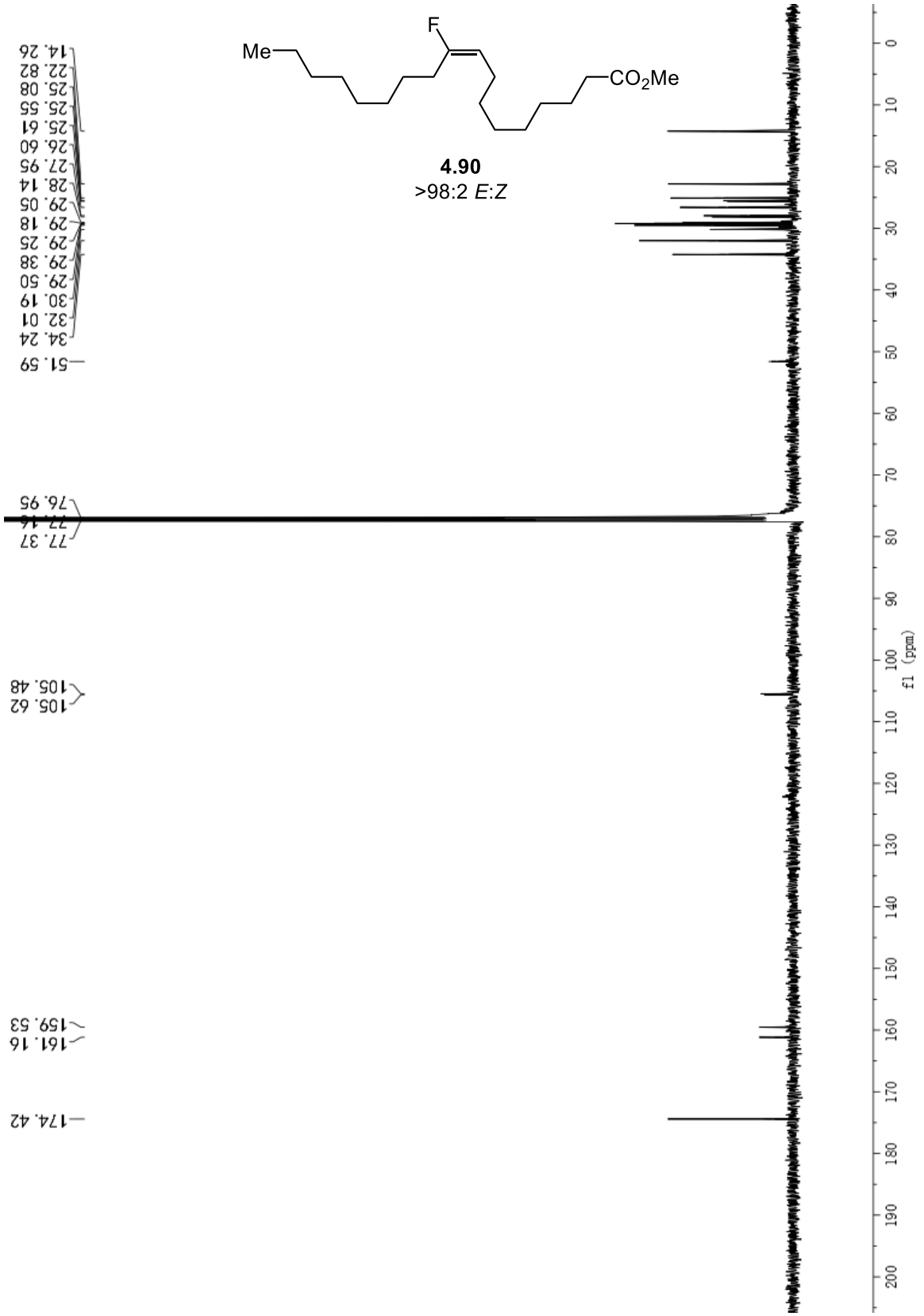
^{19}F NMR Spectrum of 4.90



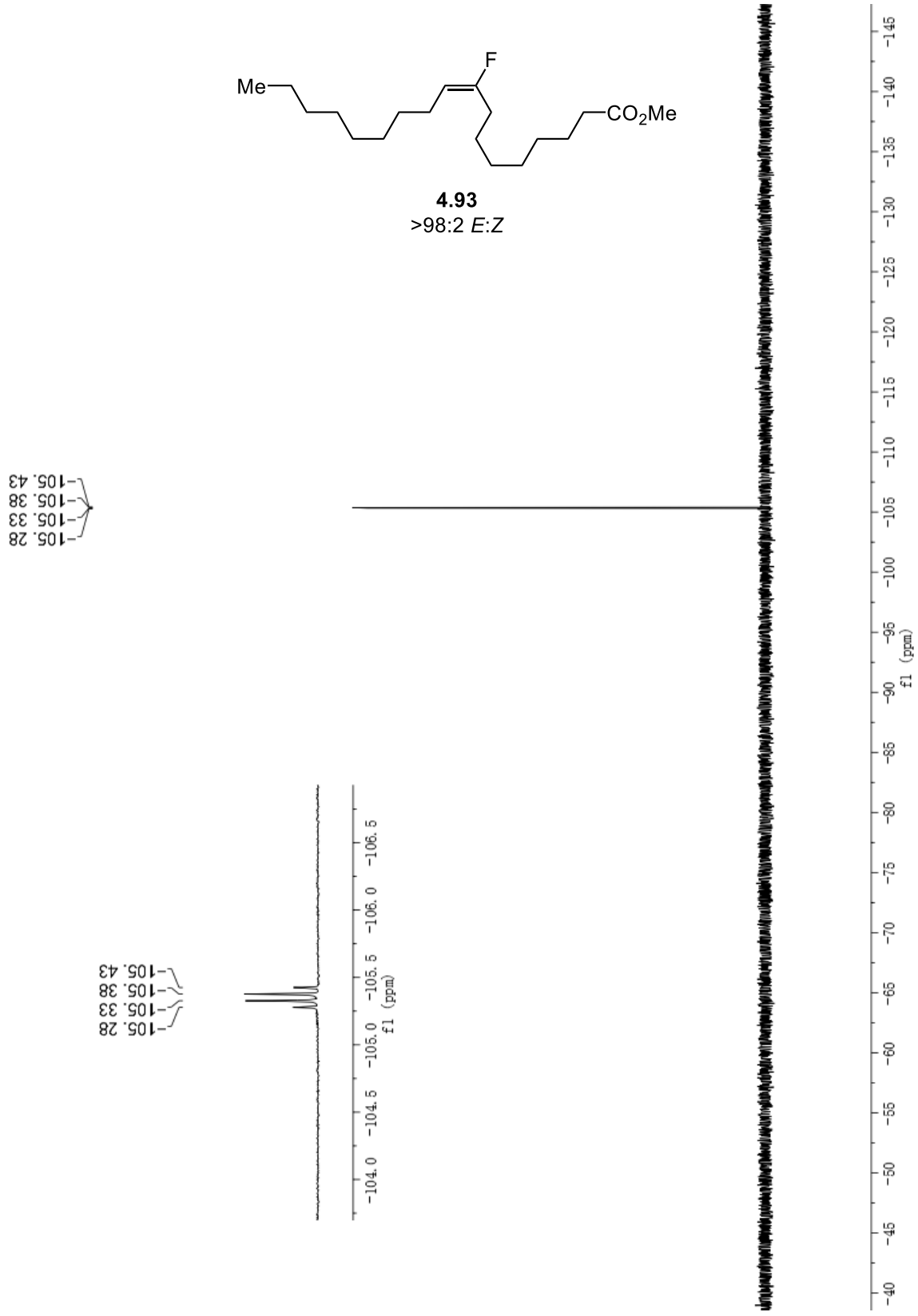
^{1}H NMR Spectrum of 4.90



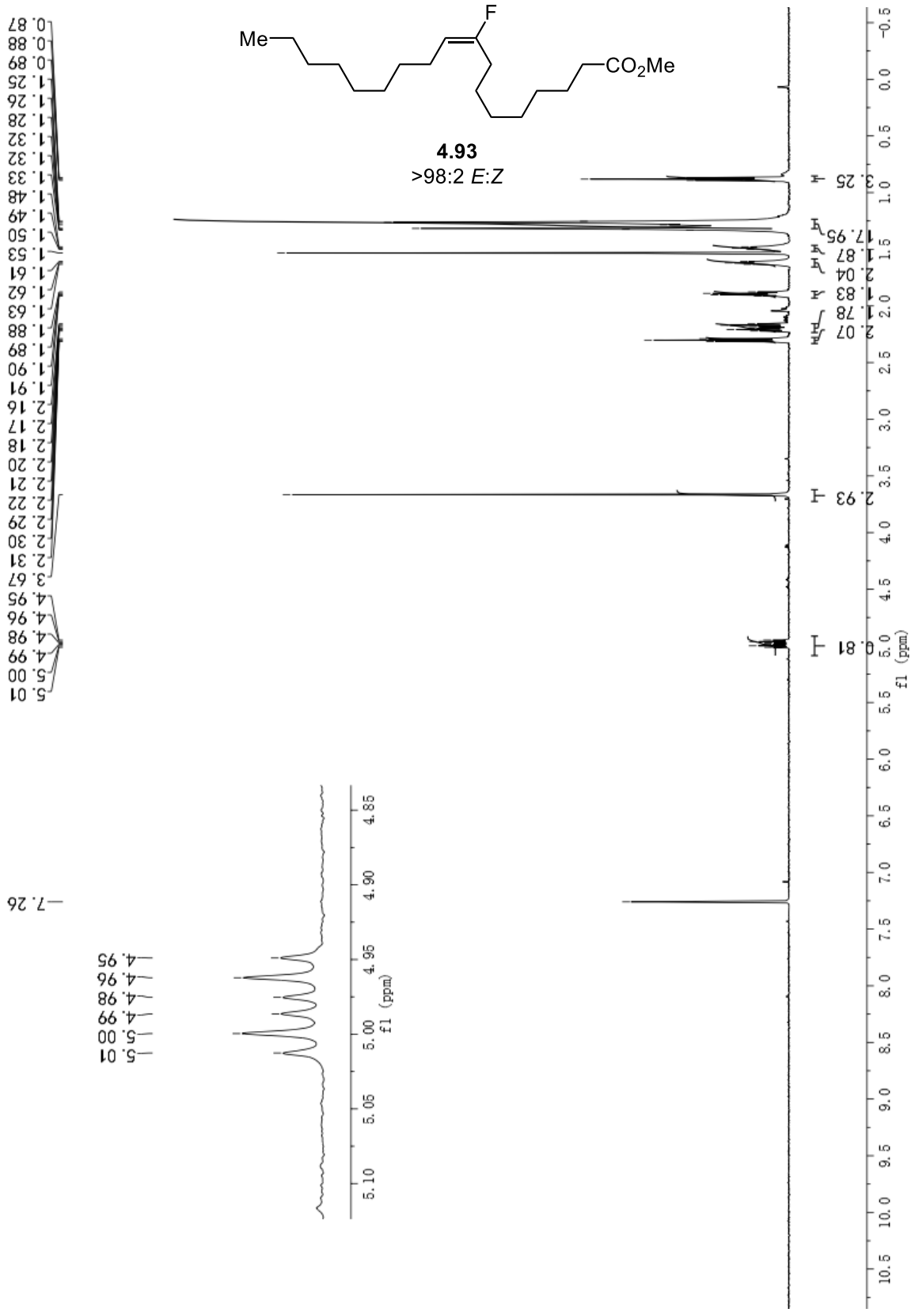
^{13}C NMR Spectrum of 4.90



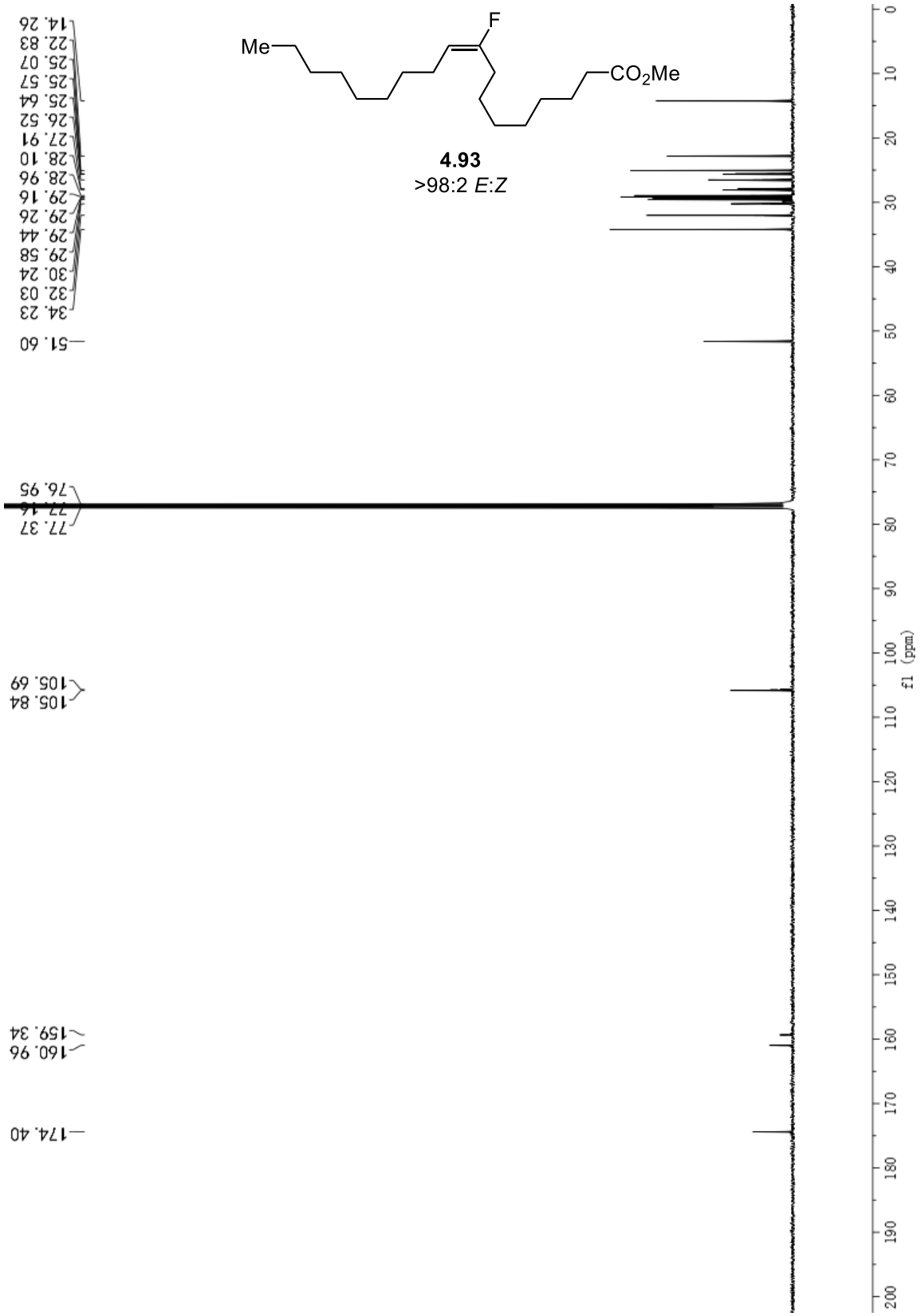
^{19}F NMR Spectrum of 4.93



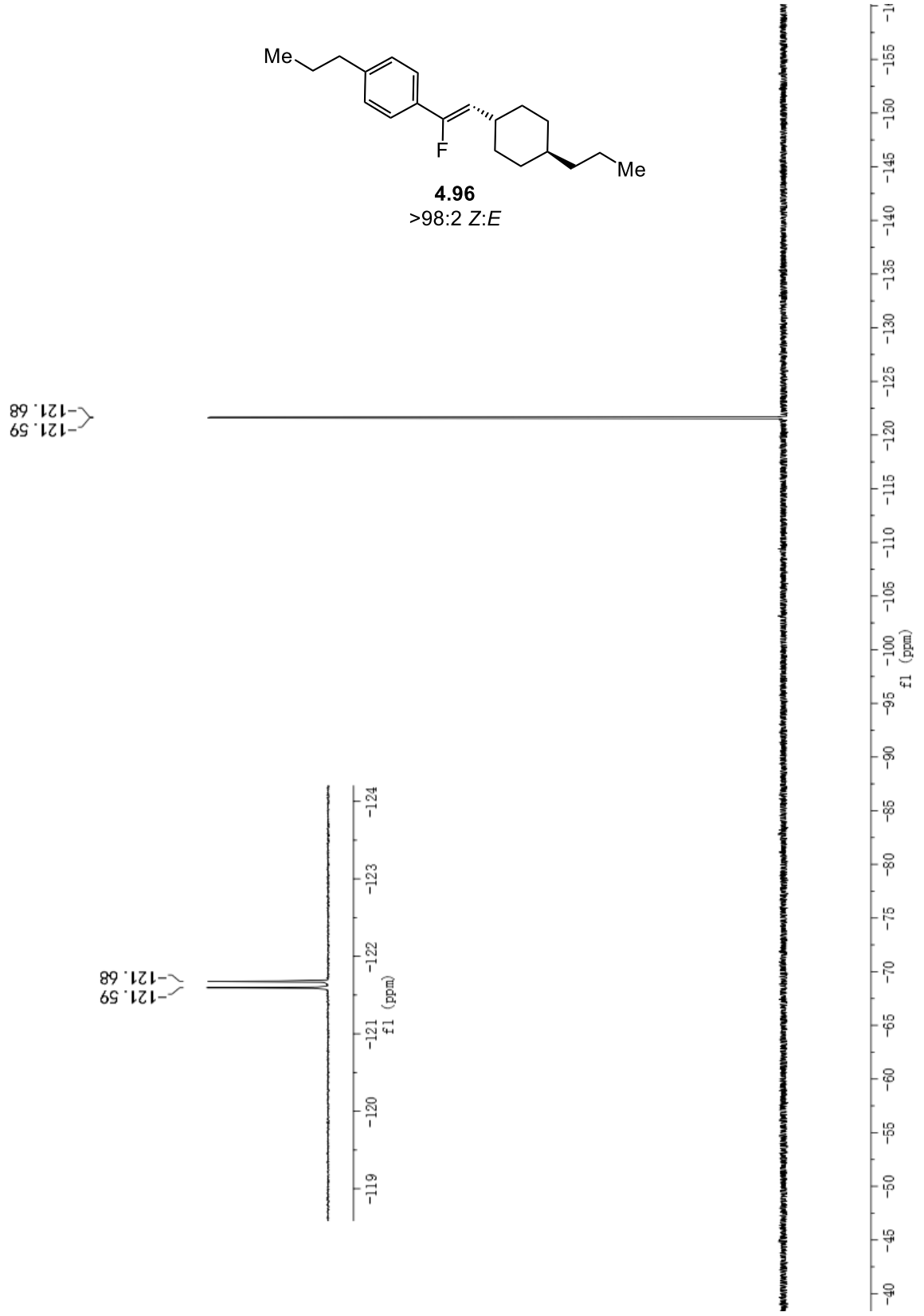
^{1}H NMR Spectrum of 4.93



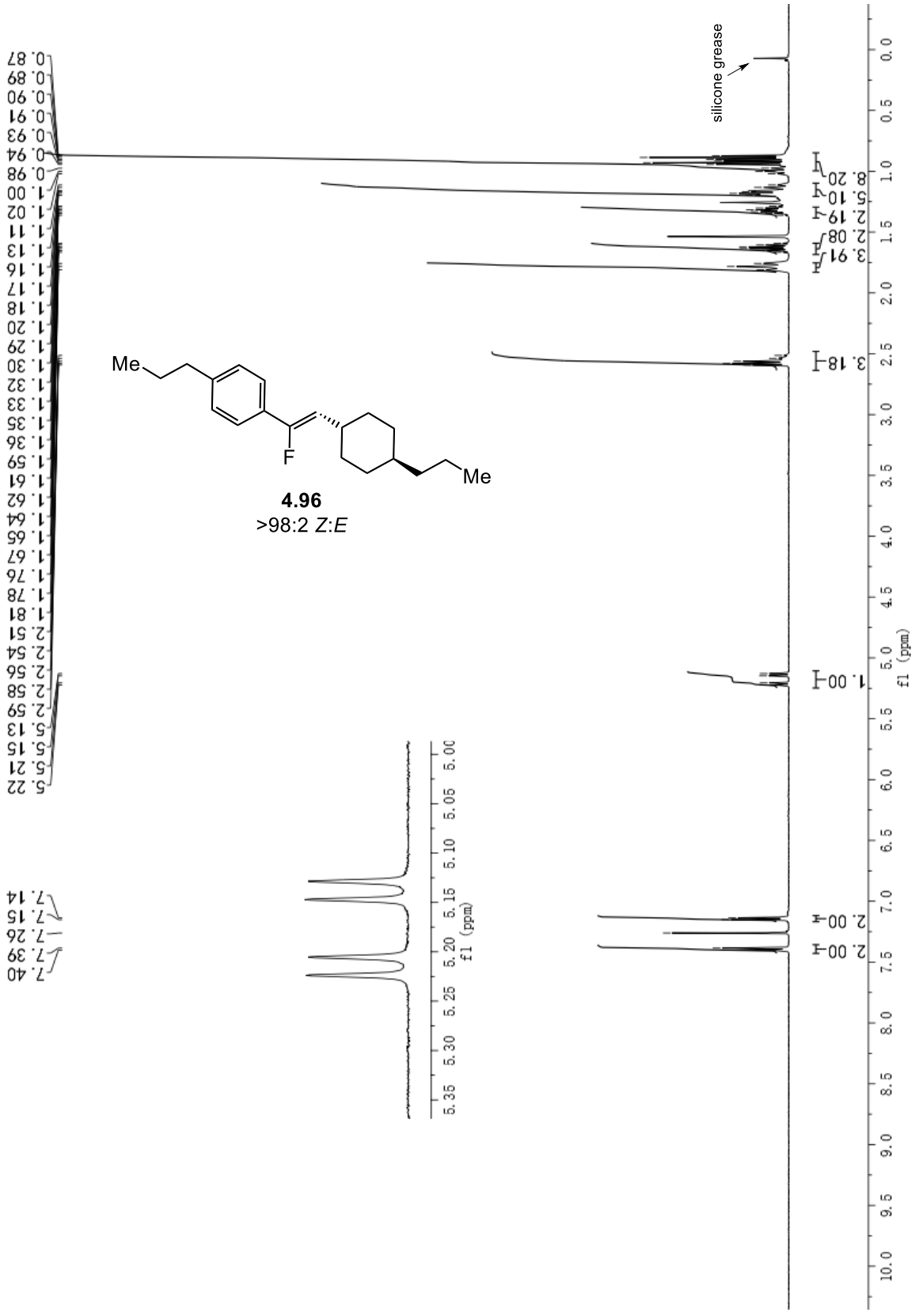
^{13}C NMR Spectrum of 4.93



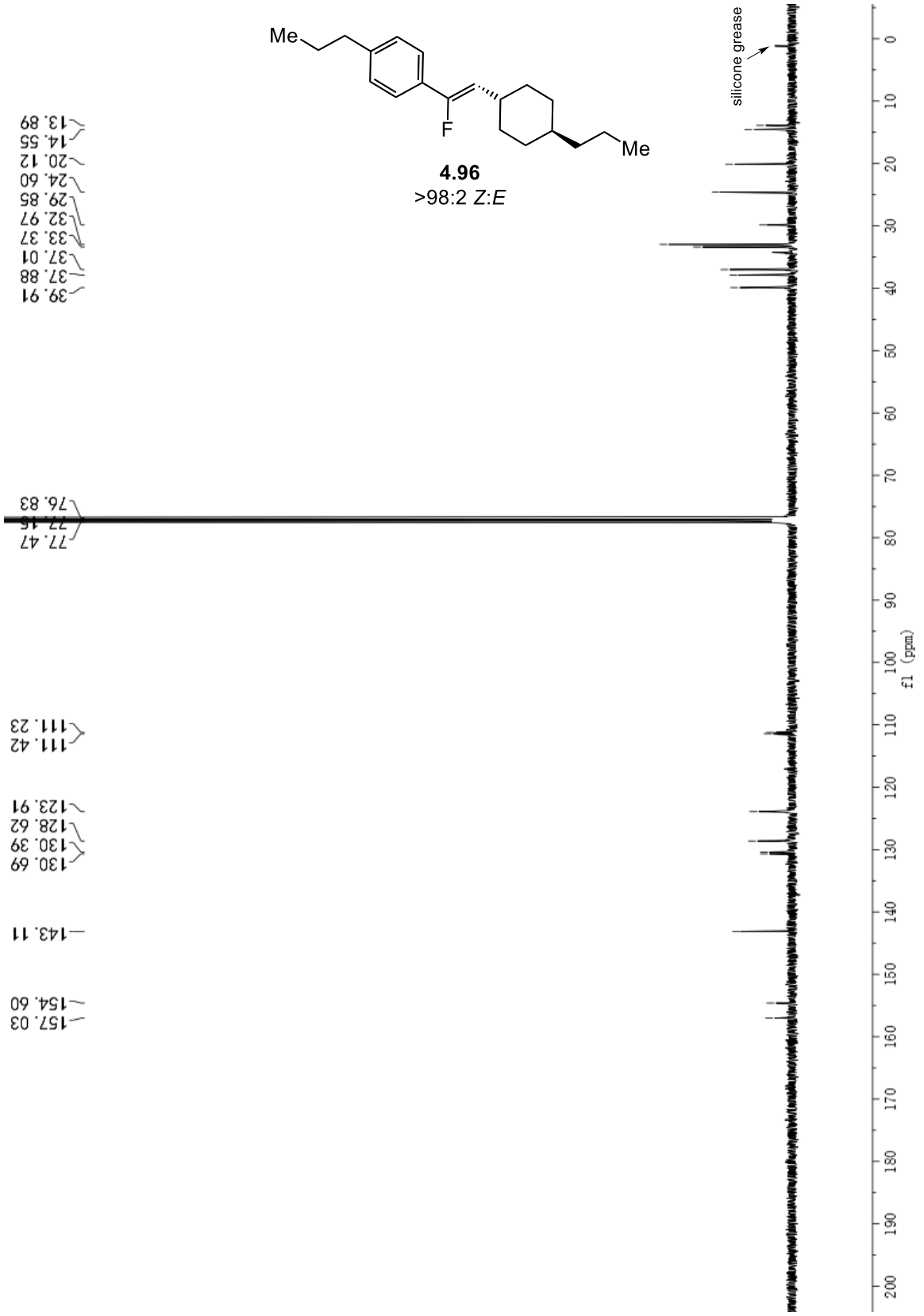
^{19}F NMR Spectrum of (*Z*)-F-Nematic liquid (4.96)



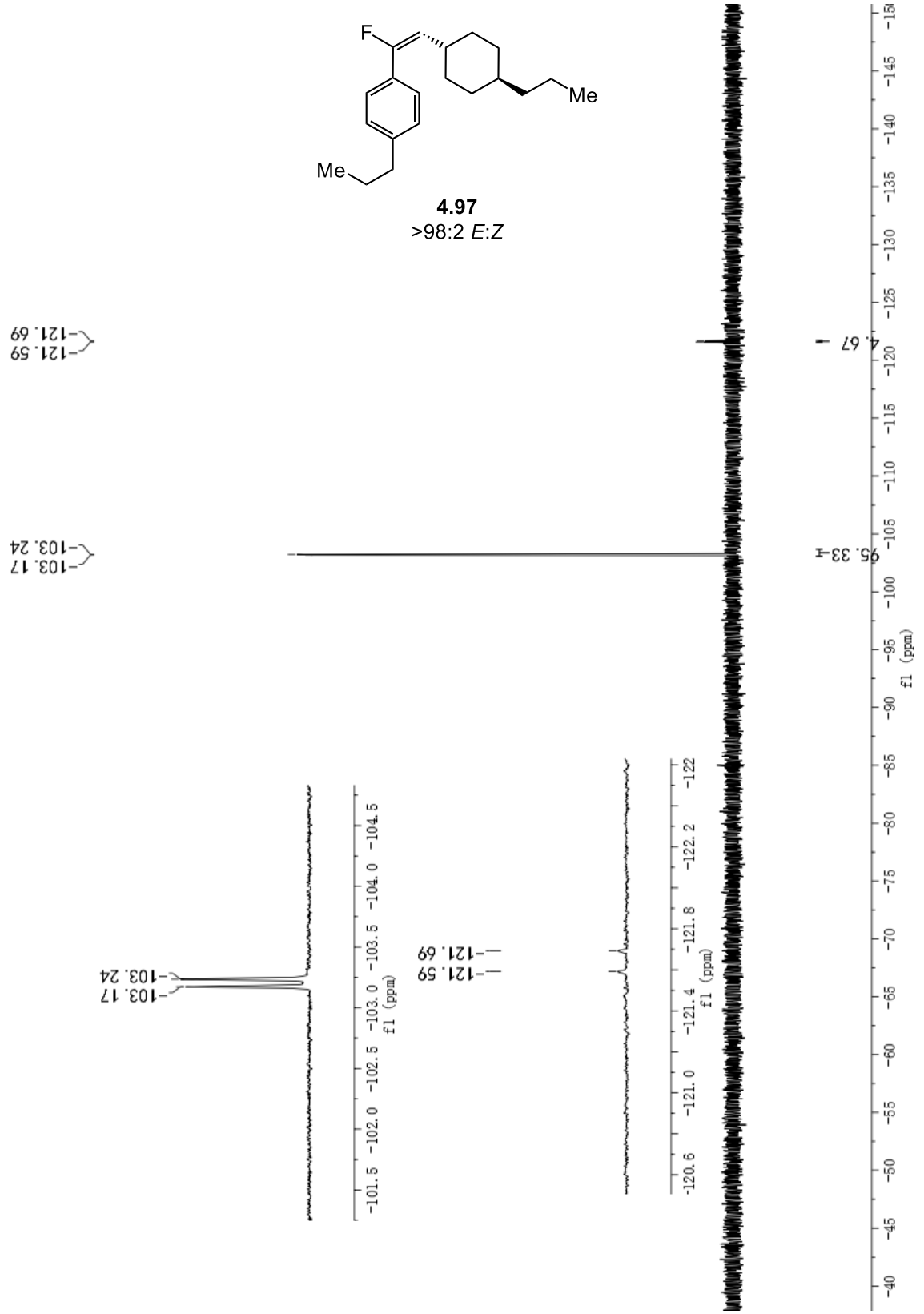
^{1}H NMR Spectrum of (*Z*)-F-Nematic liquid (4.96)



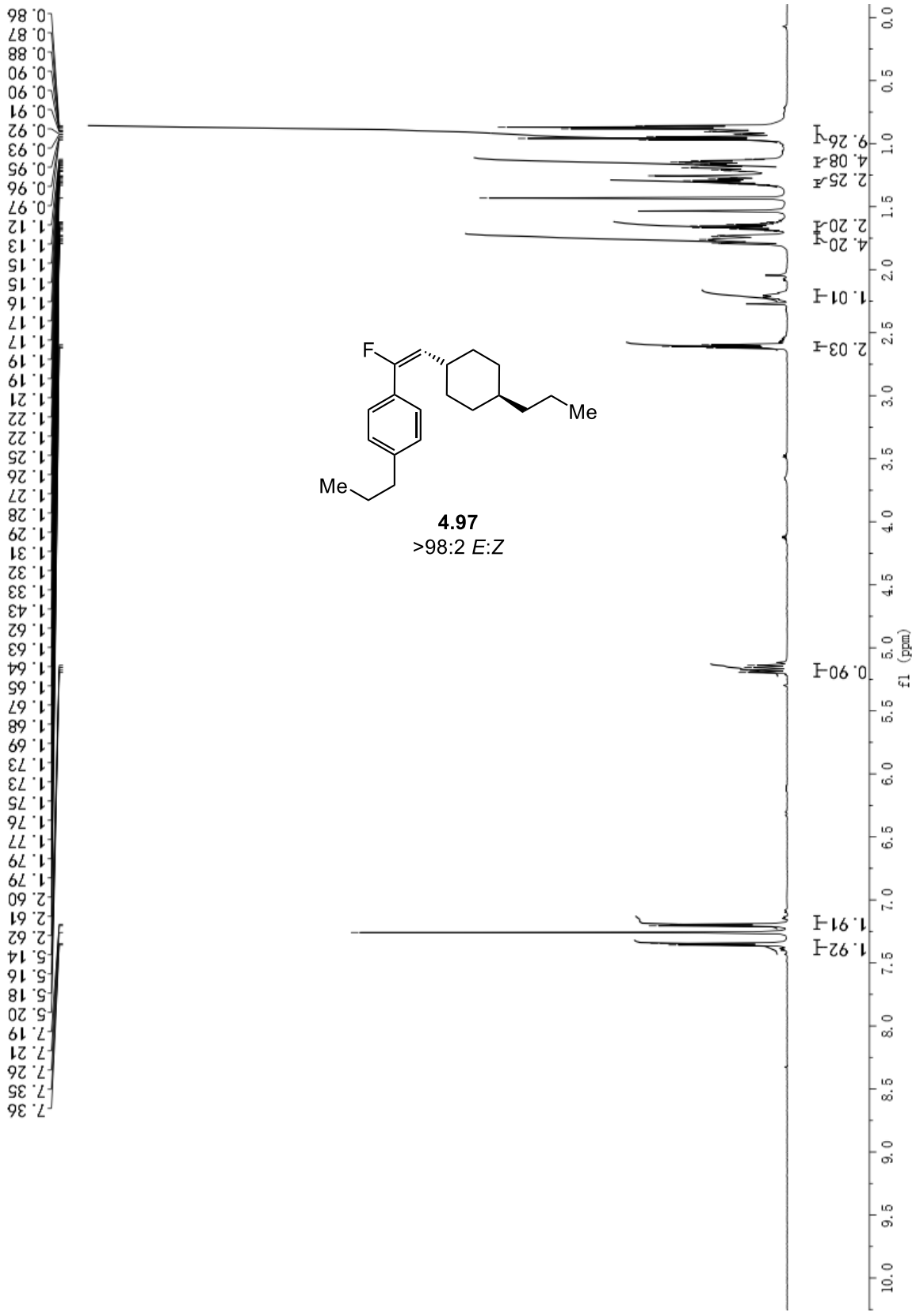
^{13}C NMR Spectrum of (*Z*)-F-Nematic liquid (4.96)



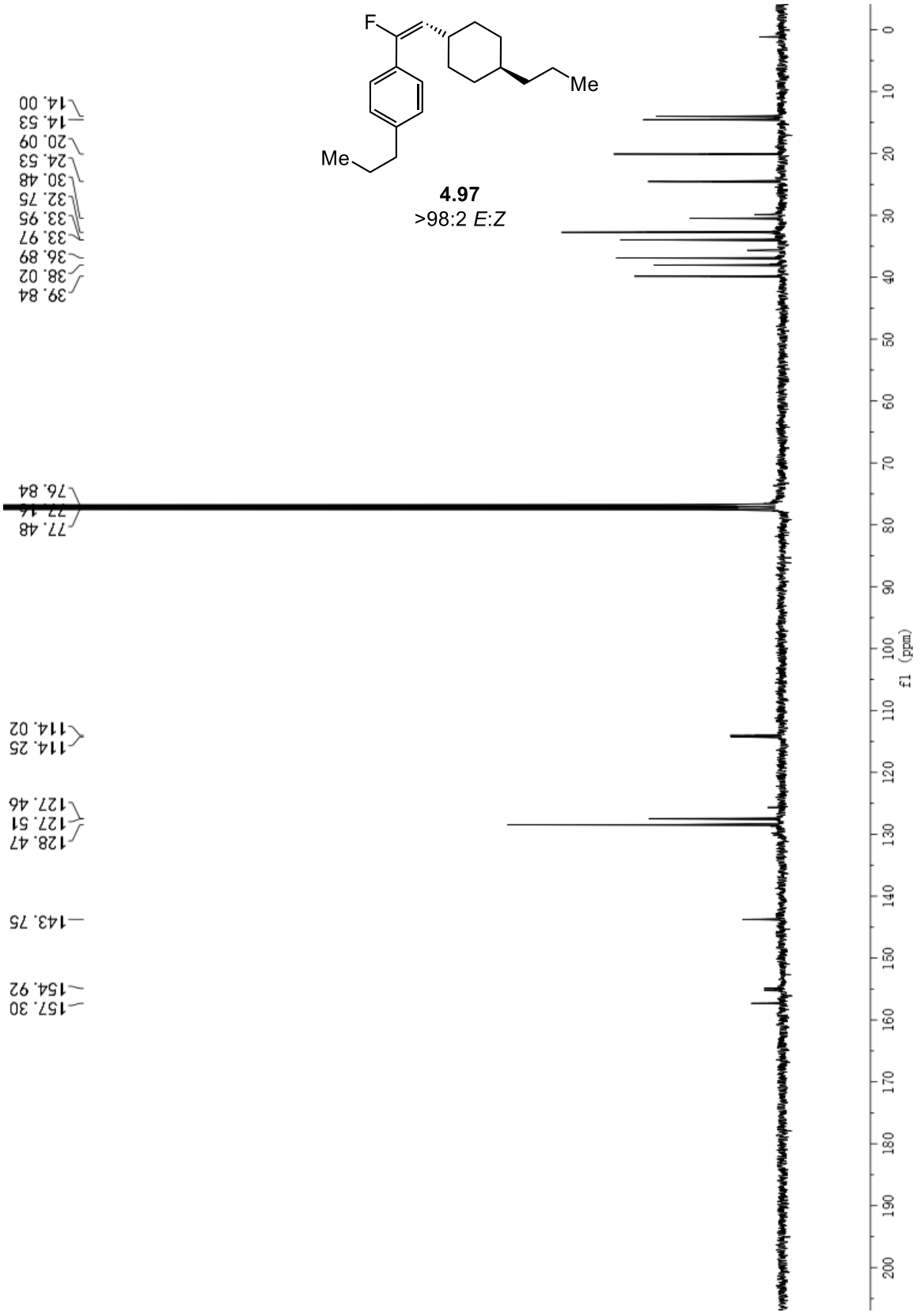
^{19}F NMR Spectrum of (*E*)-F-Nematic liquid (4.97)



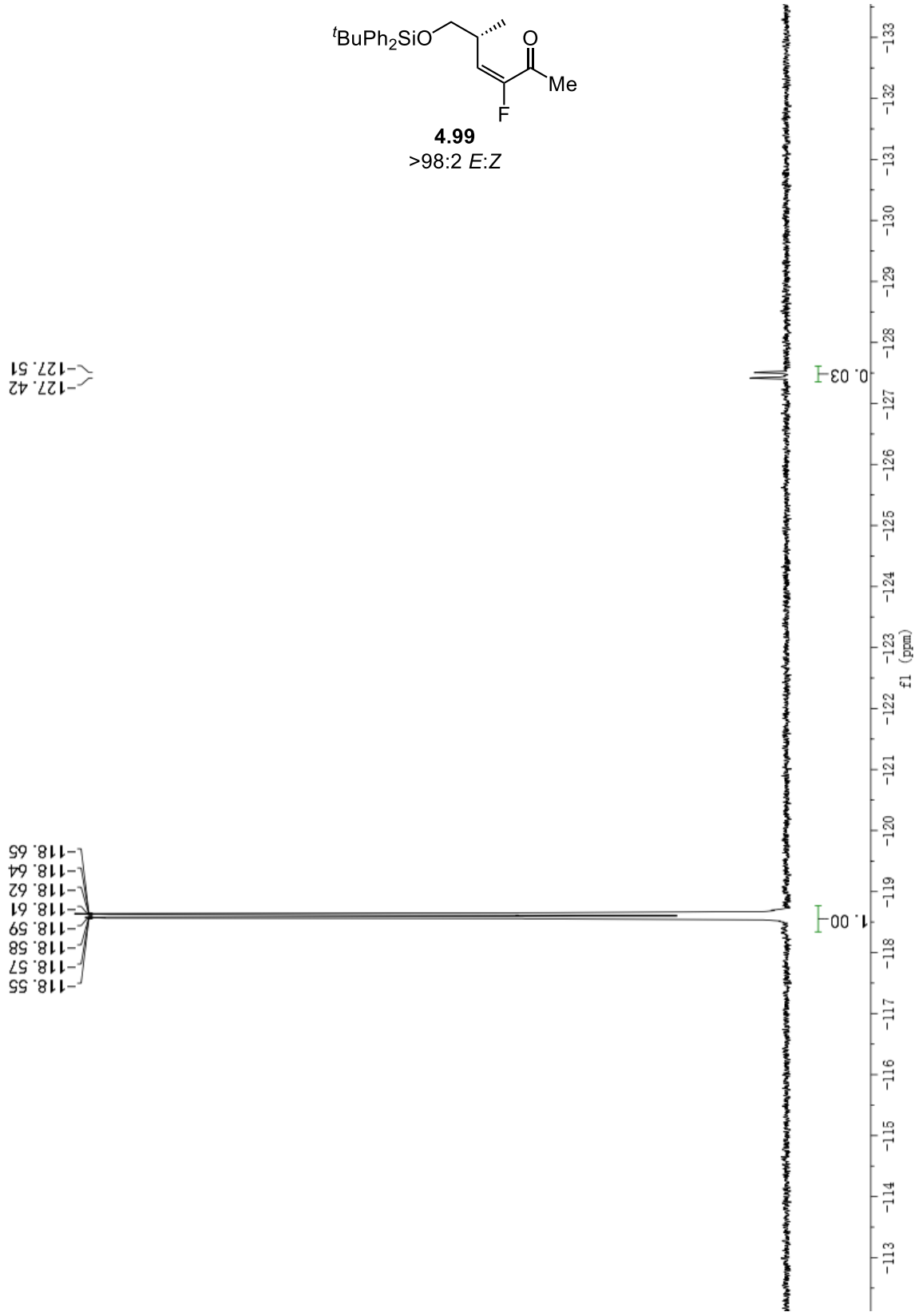
^{1}H NMR Spectrum of (*E*)-F-Nematic liquid (4.97)



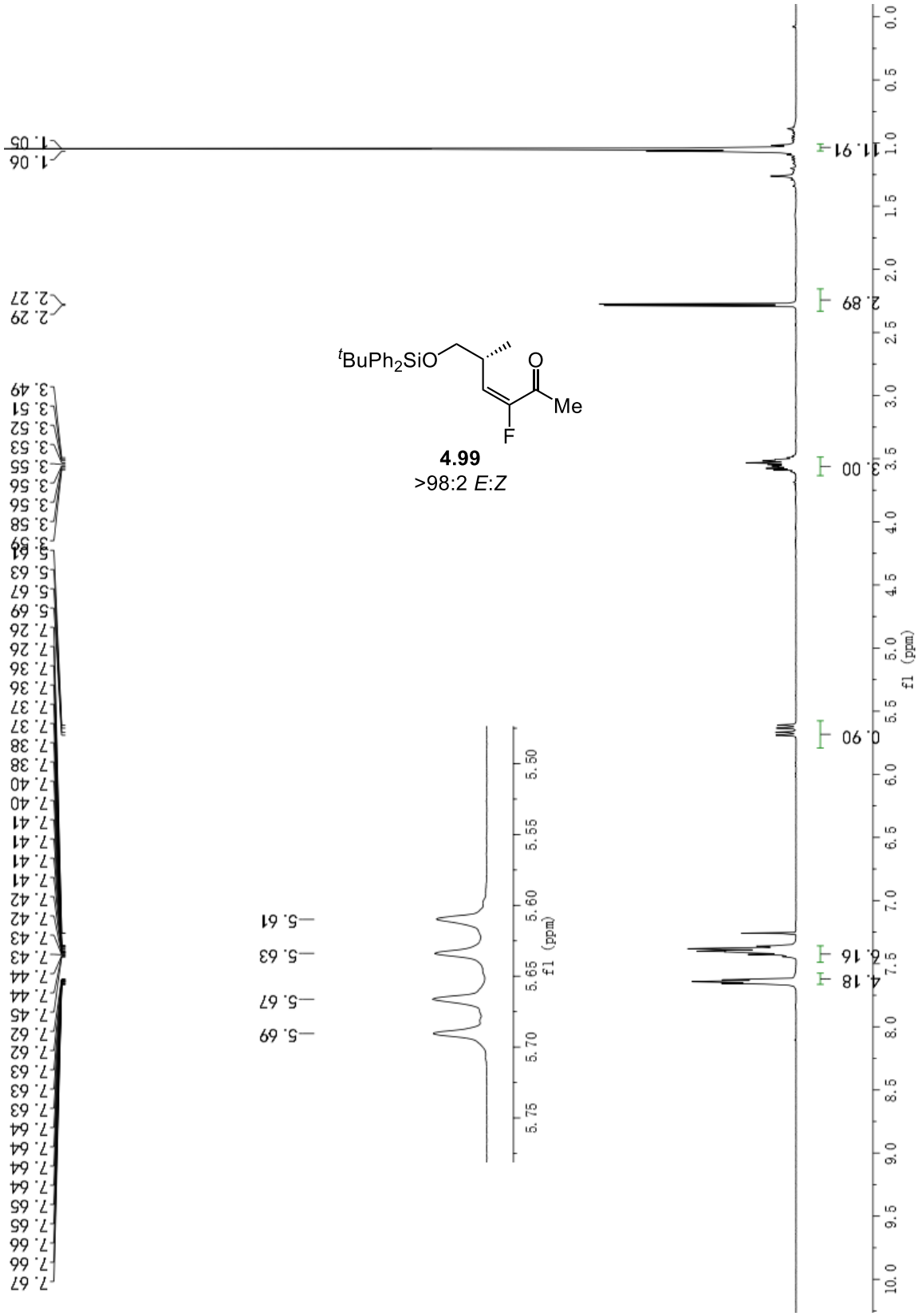
^{13}C NMR Spectrum of (*E*)-F-Nematic liquid (4.97)



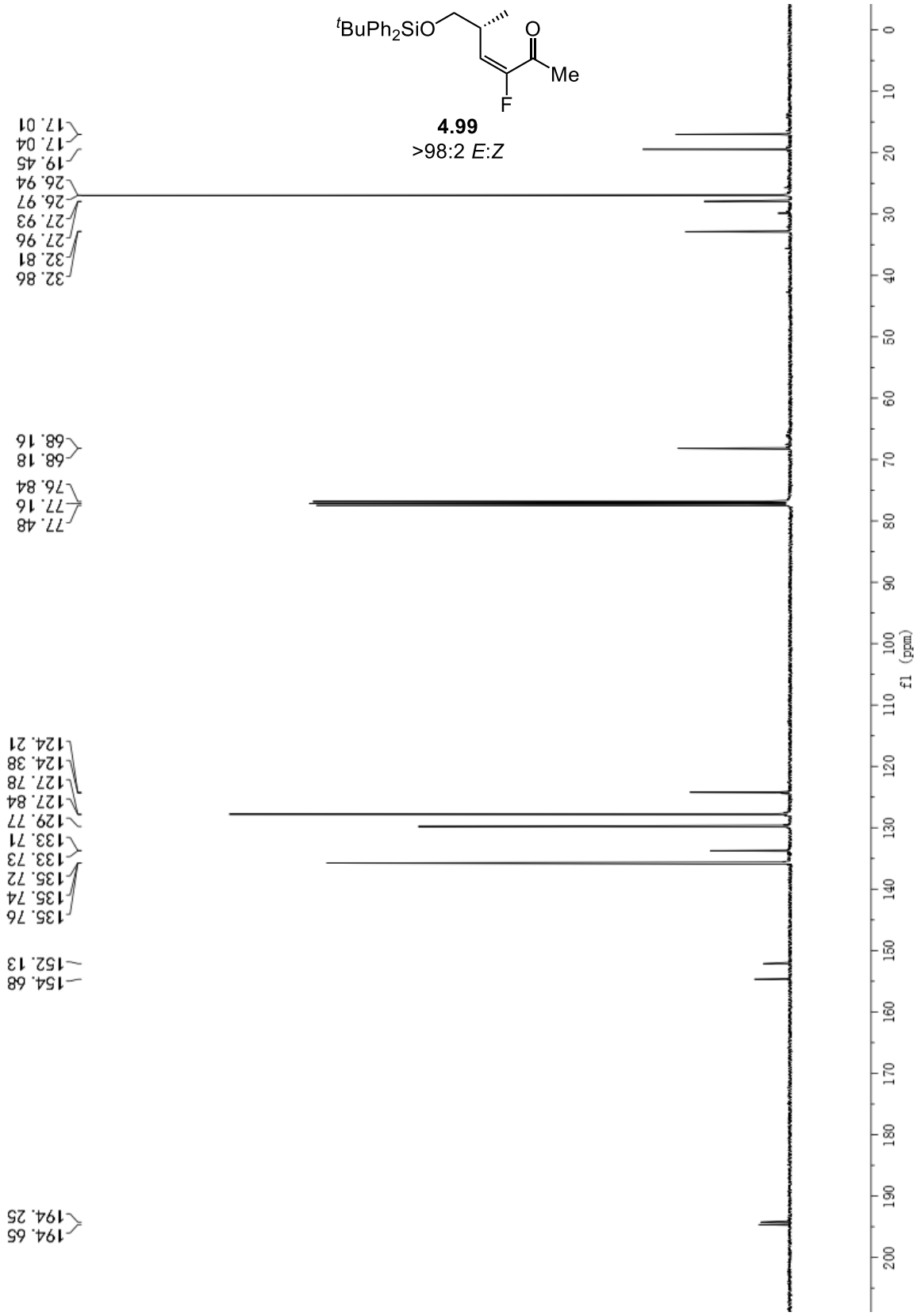
^{19}F NMR Spectrum of 4.99



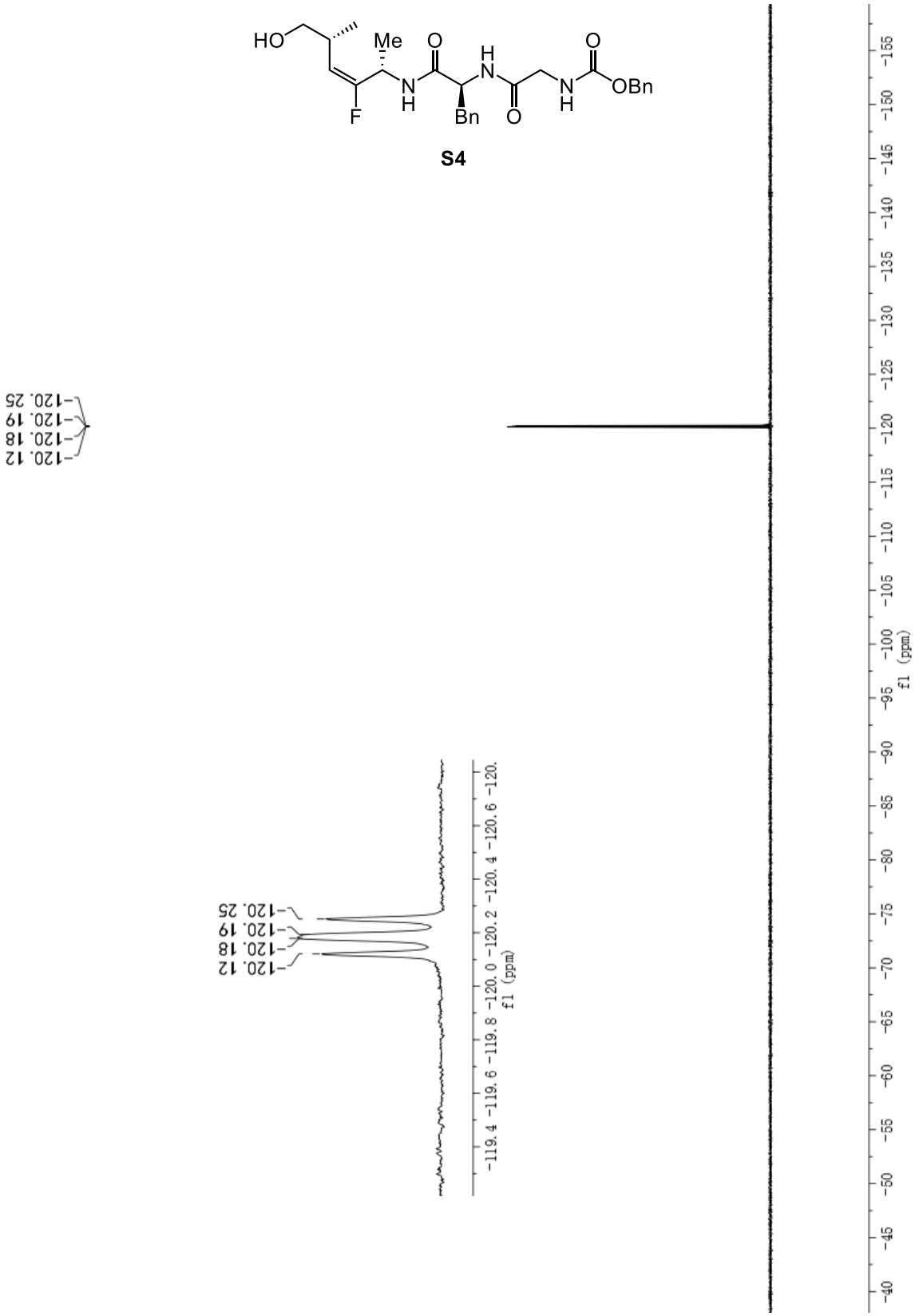
^{1}H NMR Spectrum of 4.99



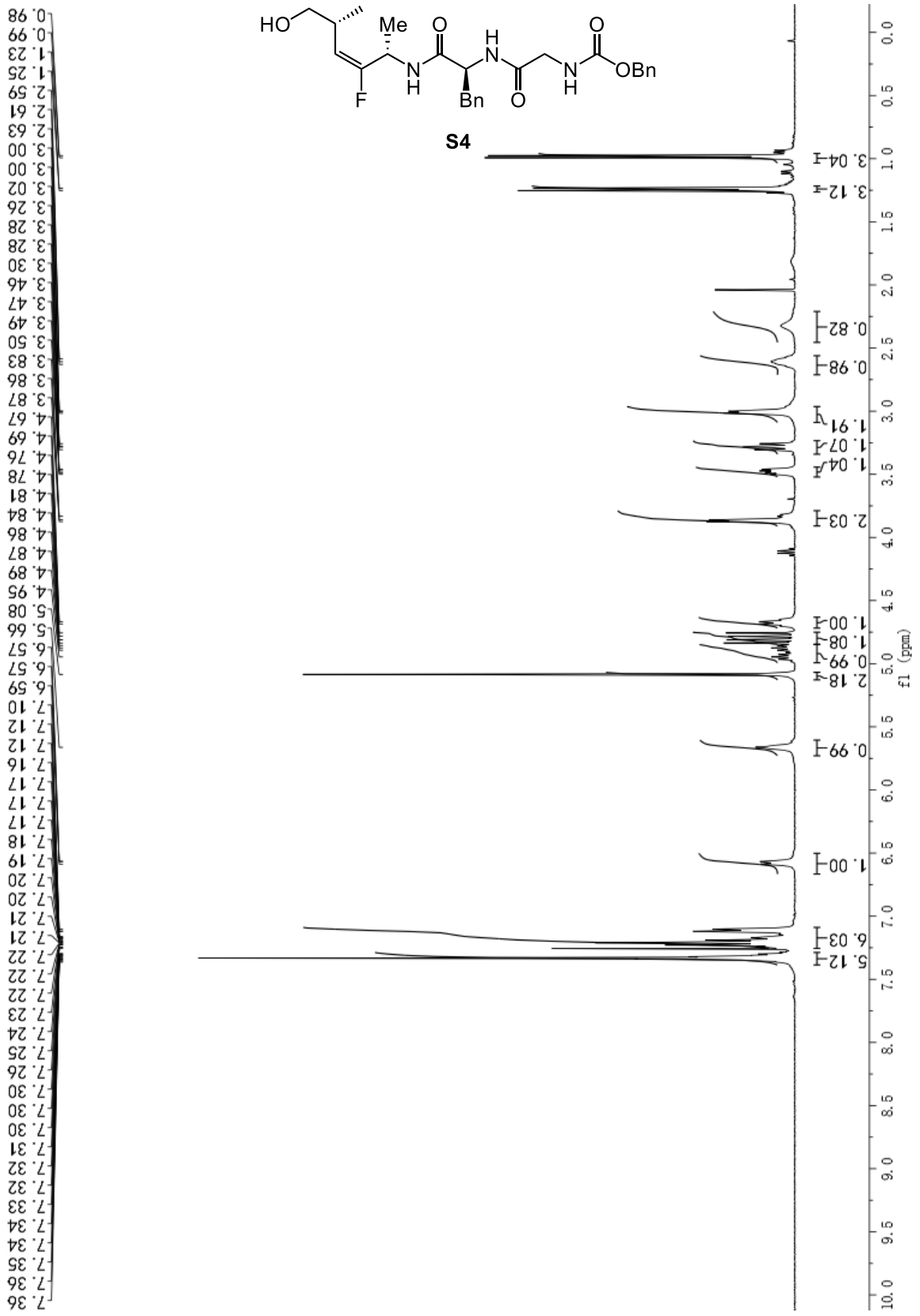
^{13}C NMR Spectrum of 4.99



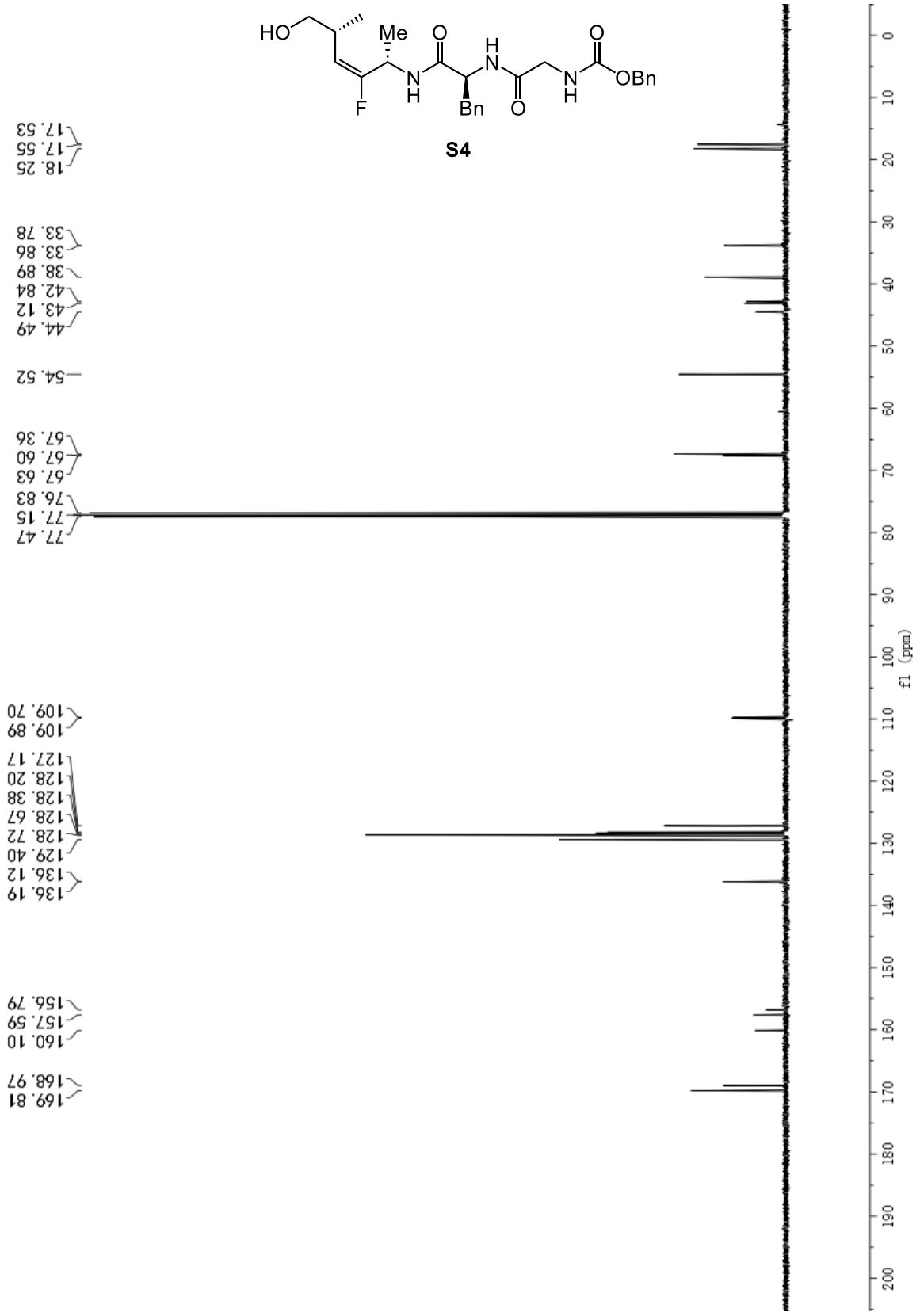
^{19}F NMR Spectrum of S4



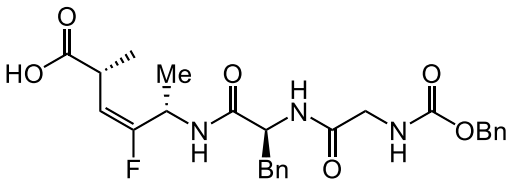
^{1}H NMR Spectrum of S4



^{13}C NMR Spectrum of S4

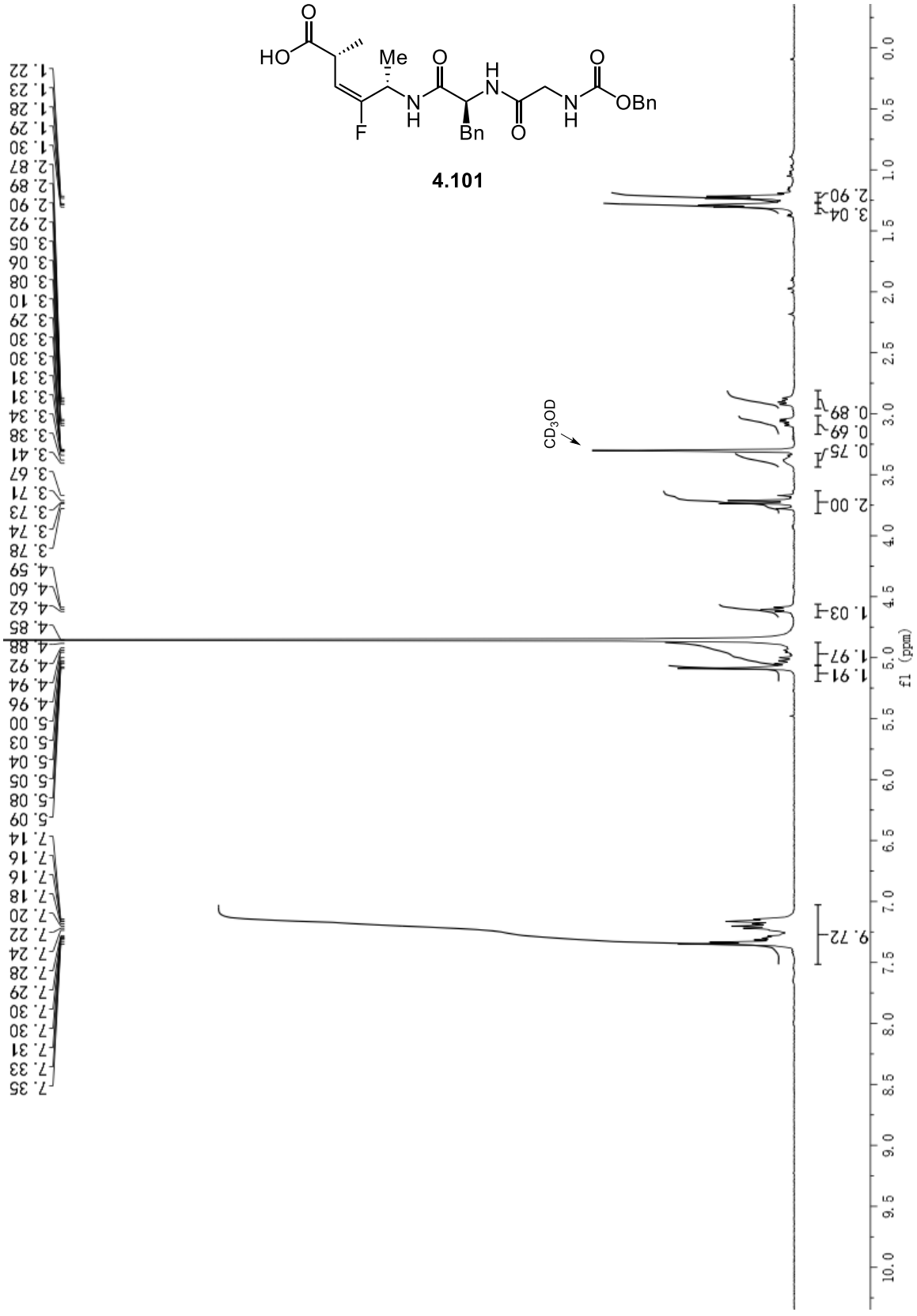


^{19}F NMR Spectrum of 4.101

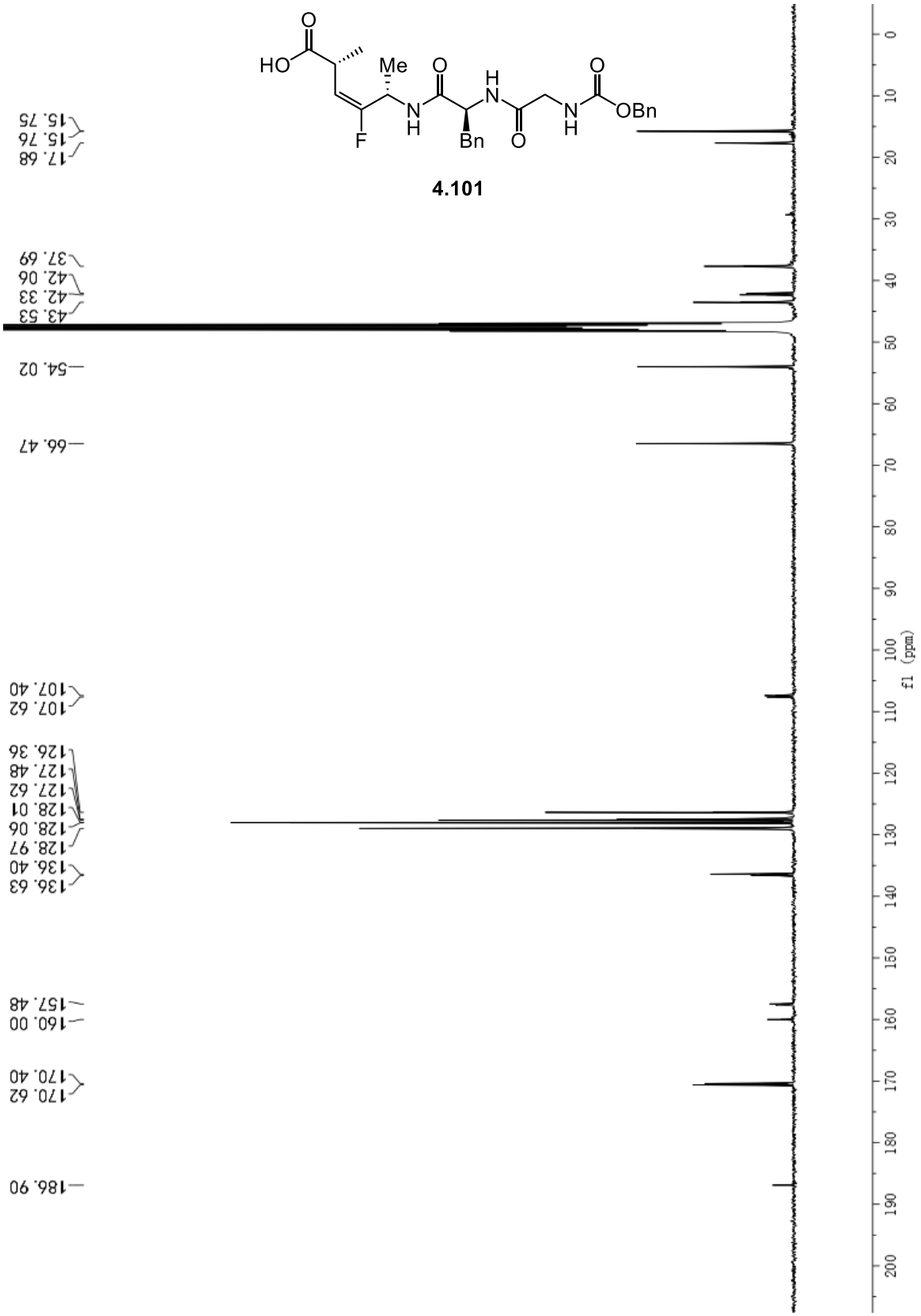


4.101

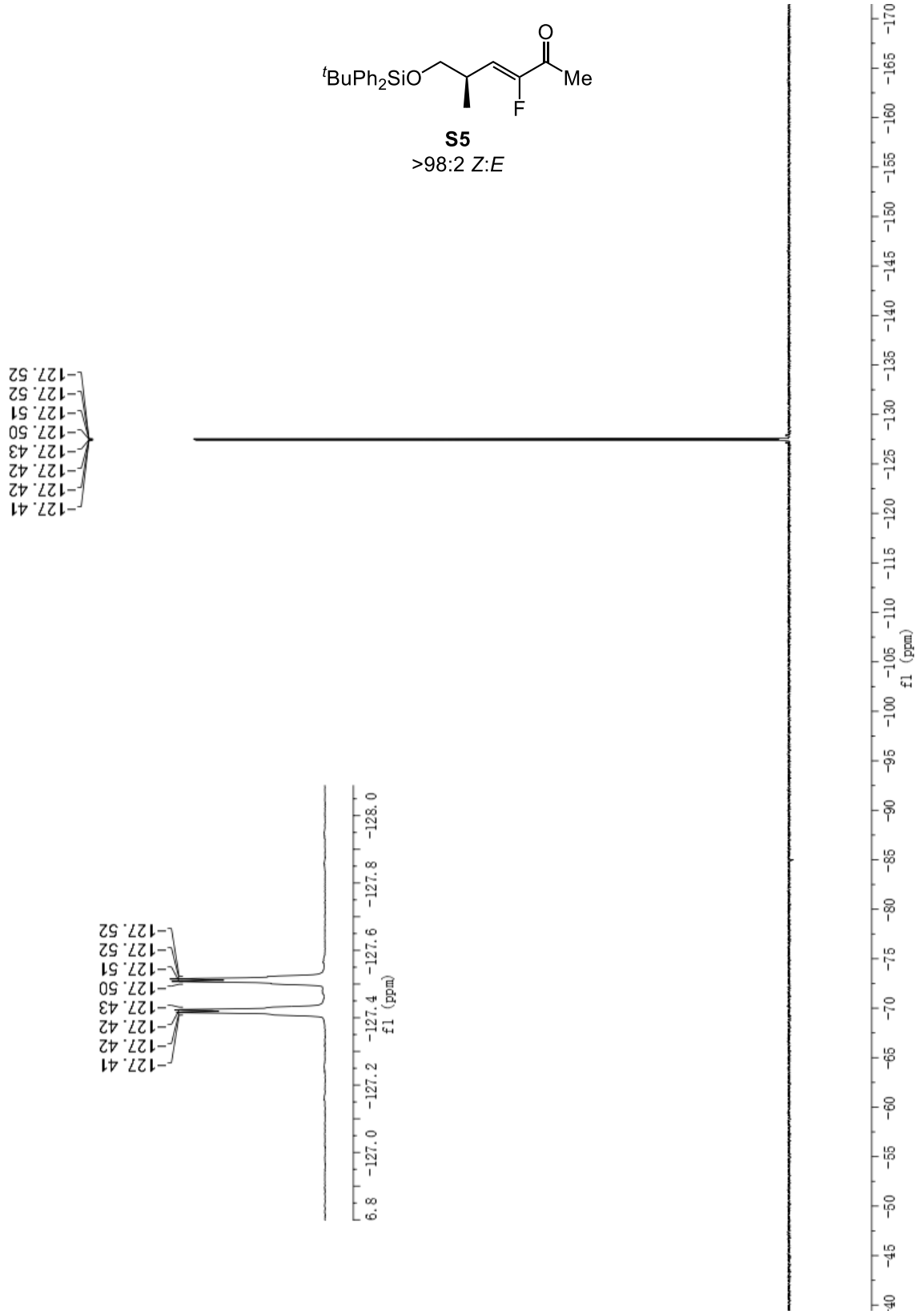
^{1}H NMR Spectrum of 4.101



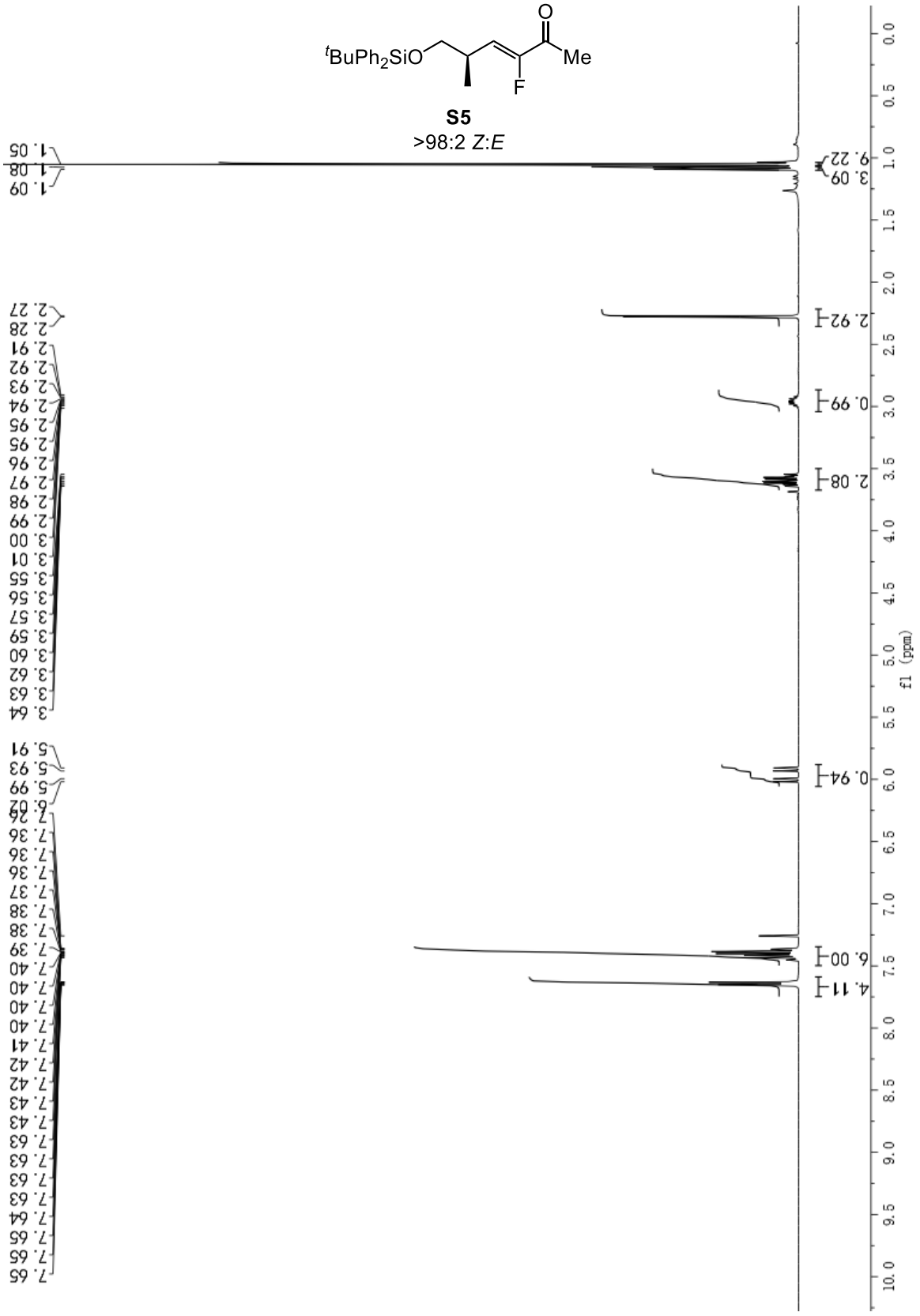
^{13}C NMR Spectrum of 4.101



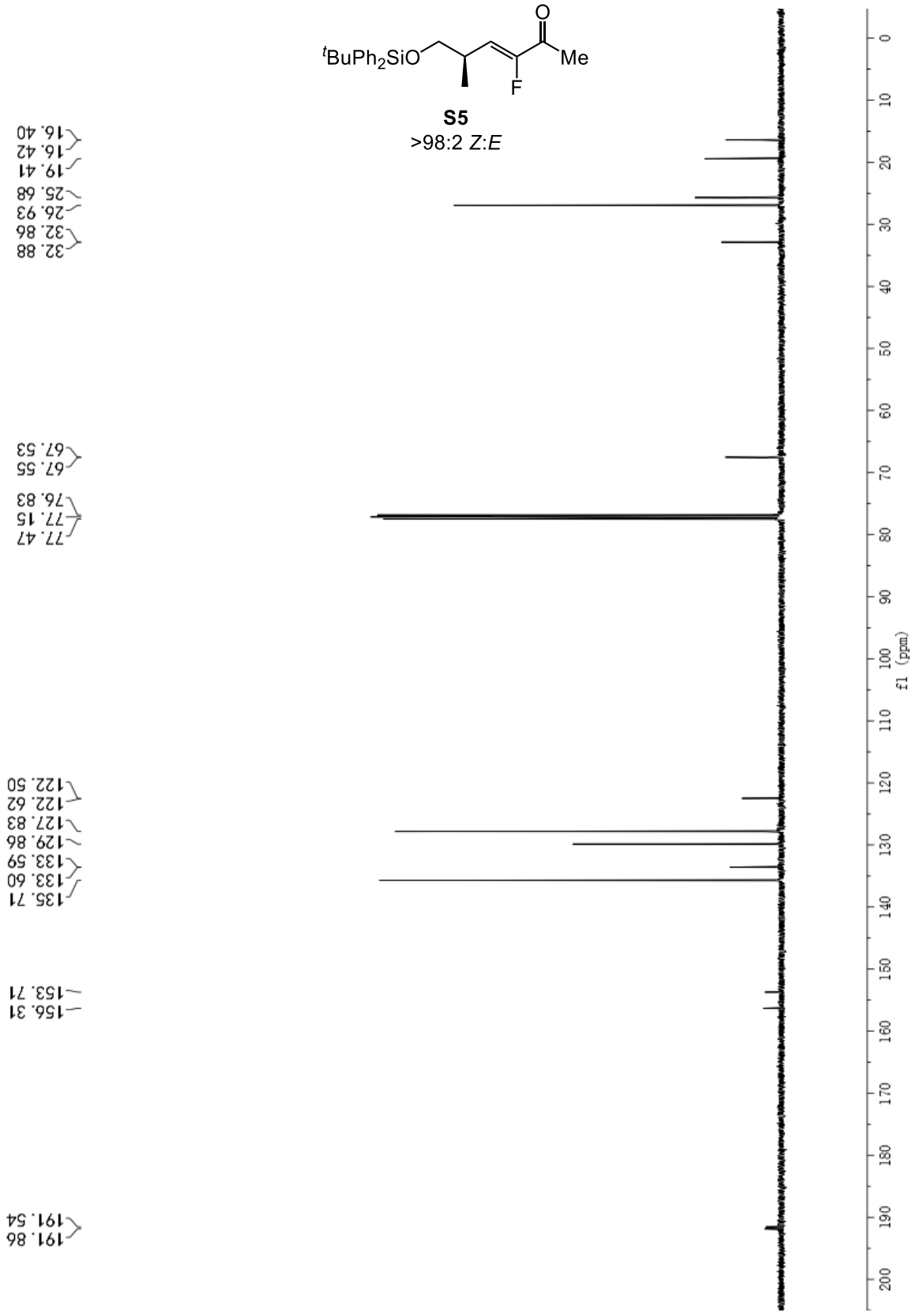
^{19}F NMR Spectrum of S5



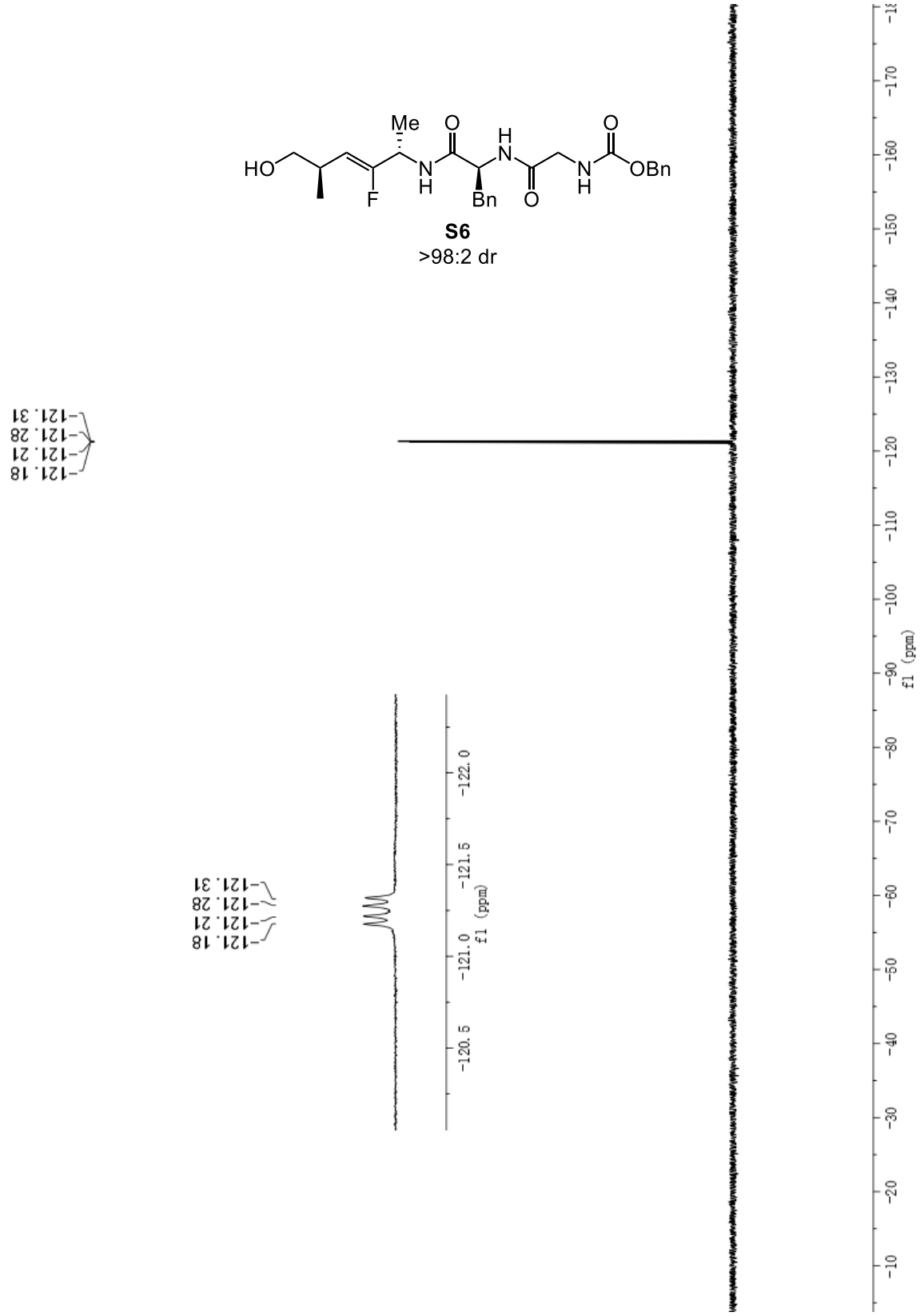
^{1}H NMR Spectrum of S5



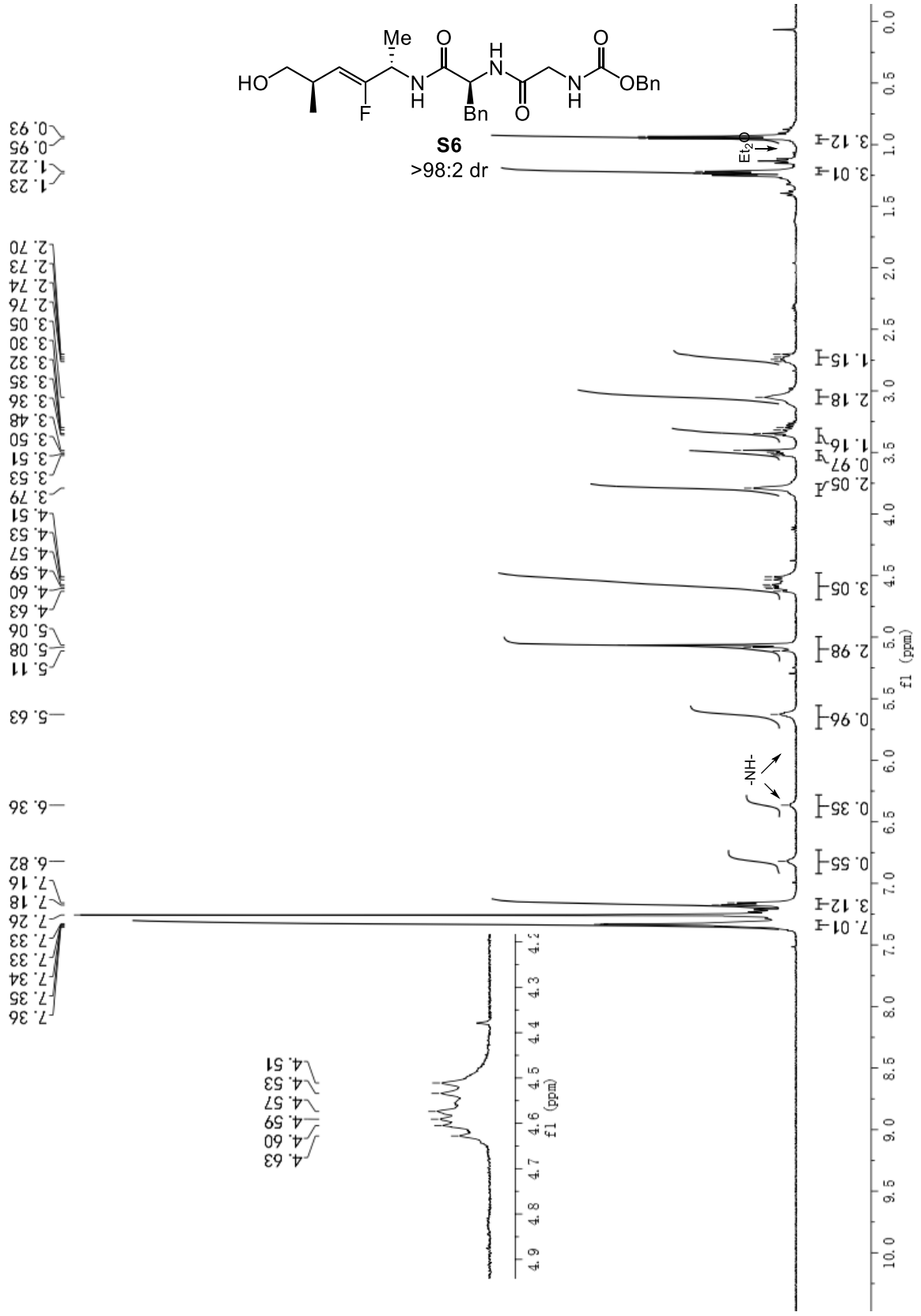
^{13}C NMR Spectrum of S5



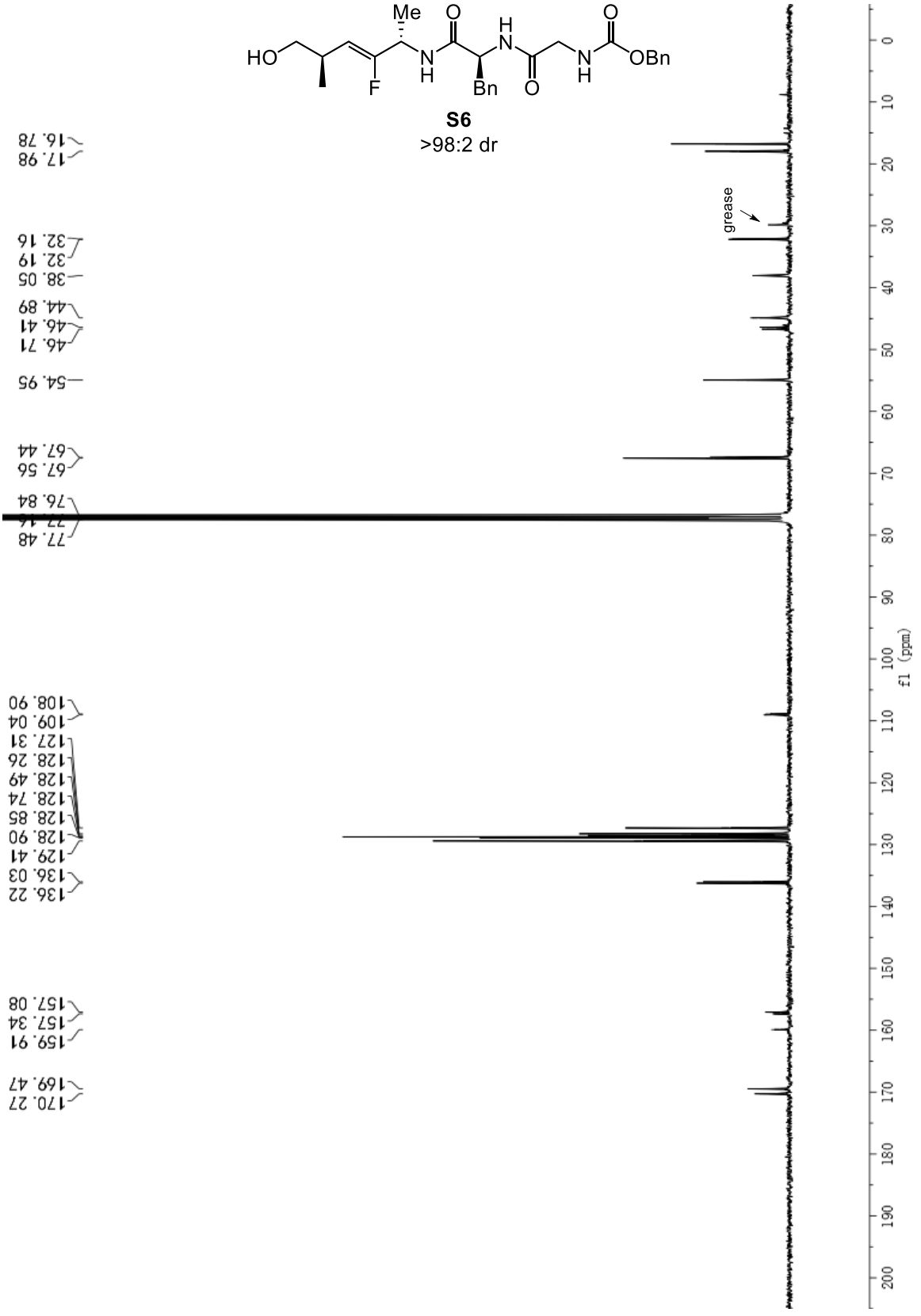
^{19}F NMR Spectrum of S6



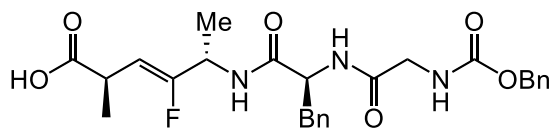
^{1}H NMR Spectrum of S6



^{13}C NMR Spectrum of S6

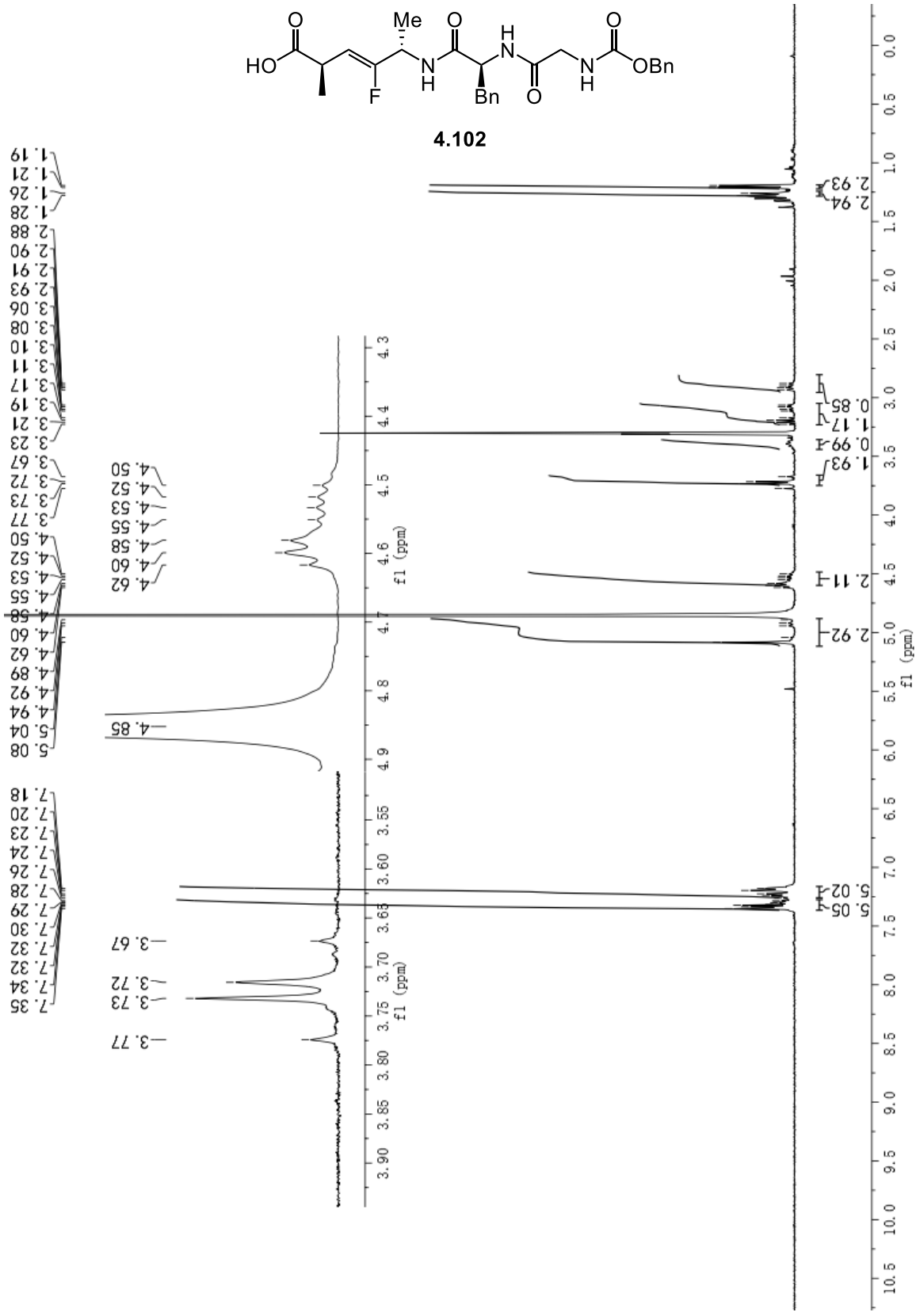


^{19}F NMR Spectrum of 4.102

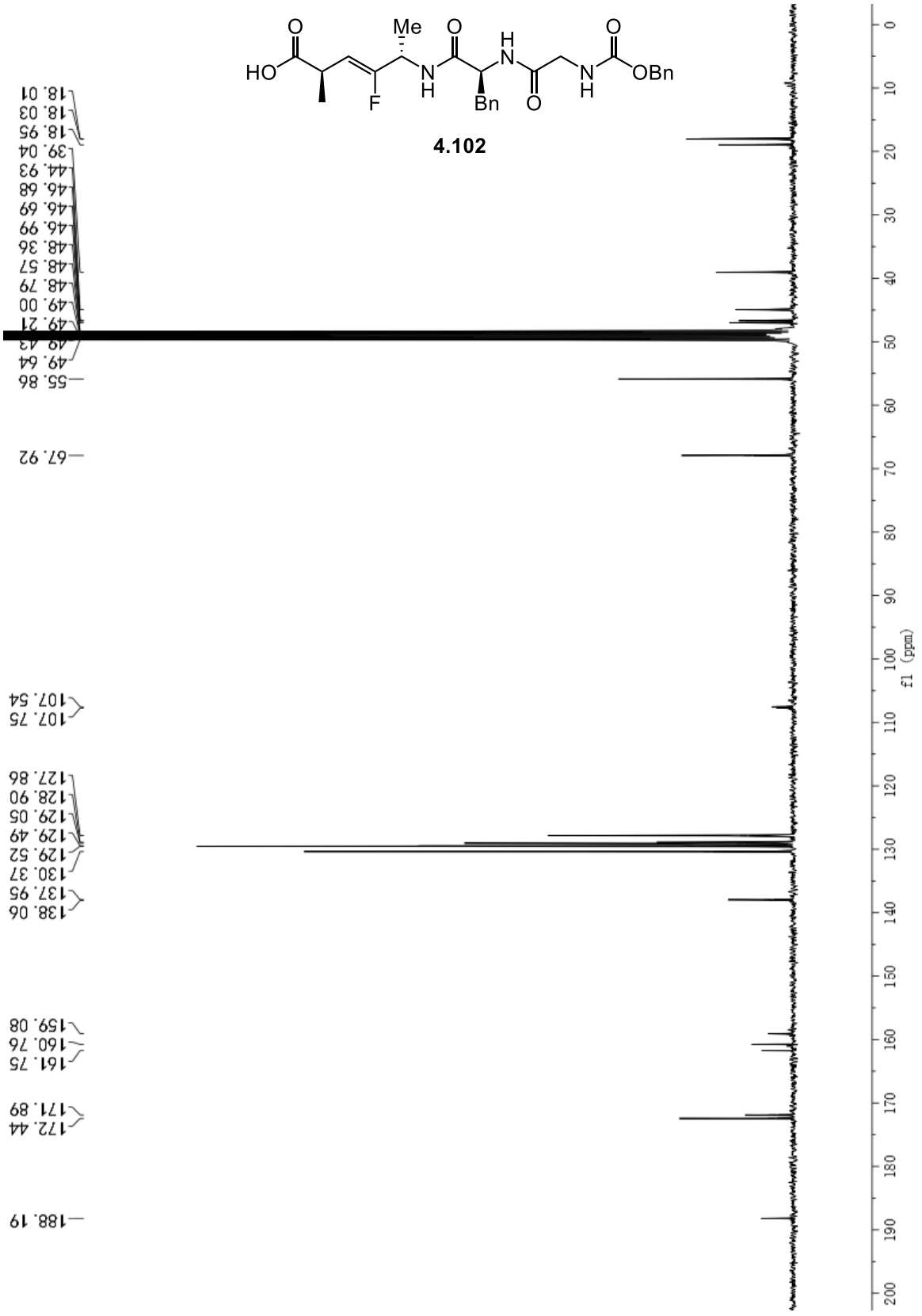


4.102

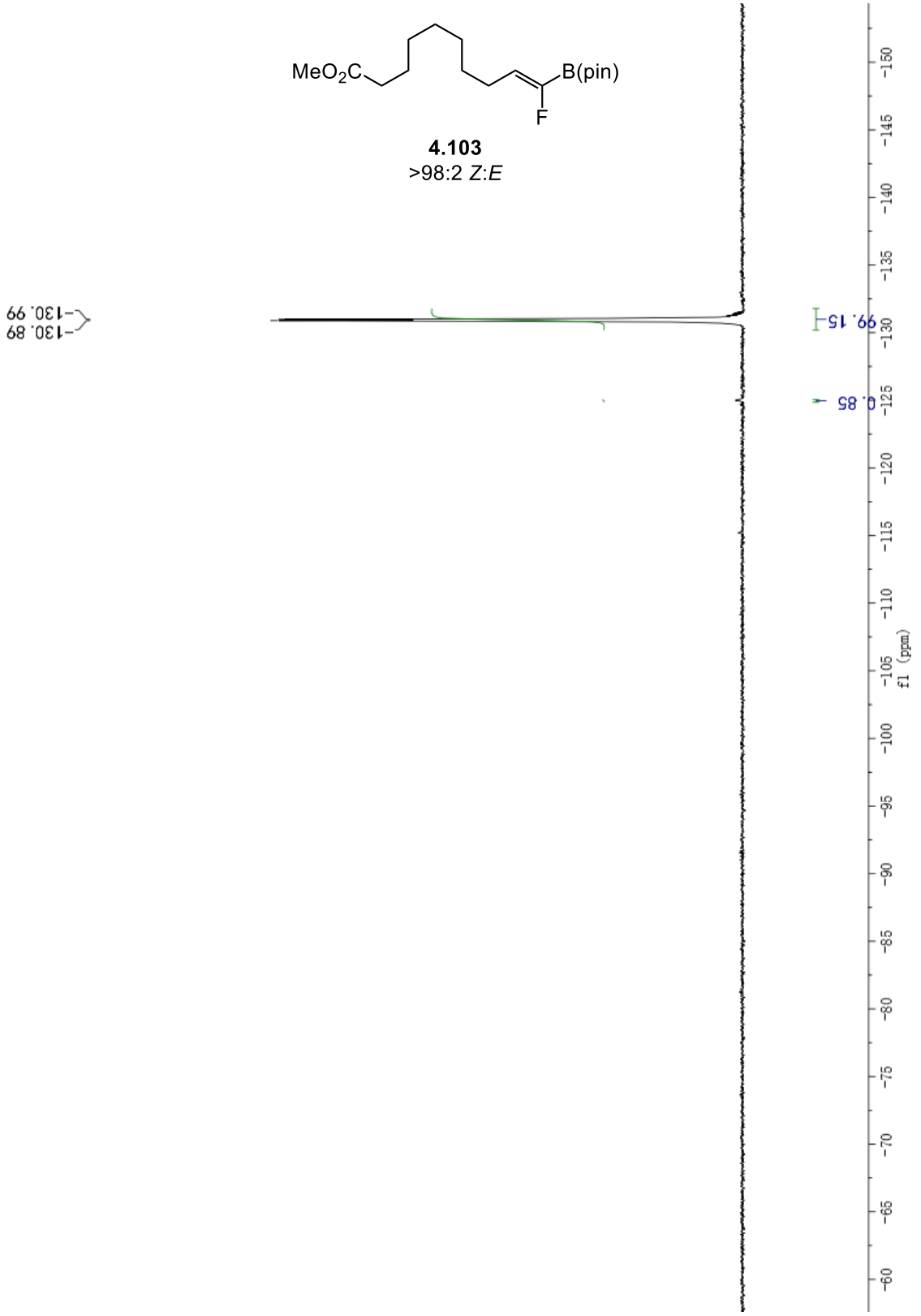
^{1}H NMR Spectrum of 4.102



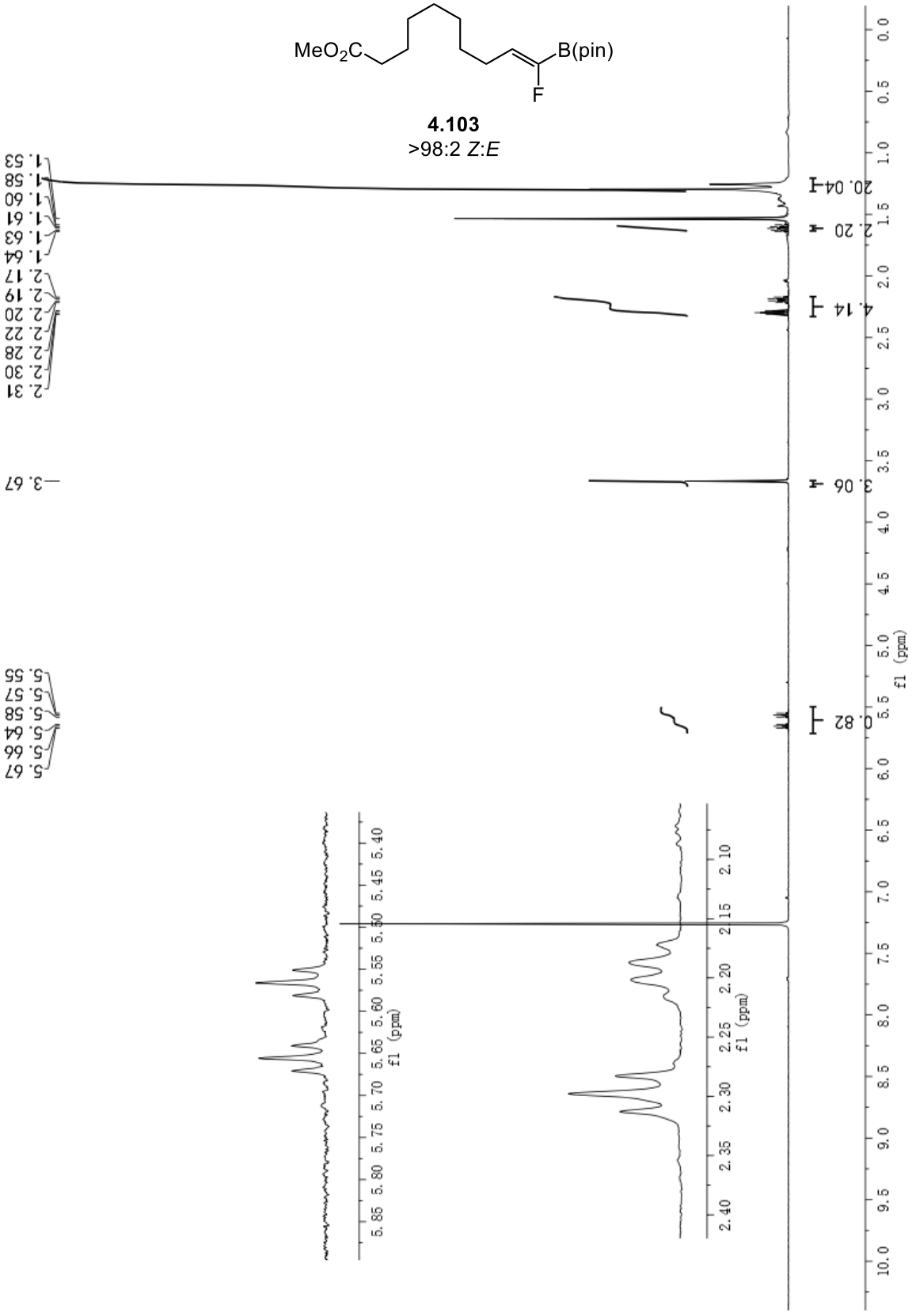
^{13}C NMR Spectrum of 4.102



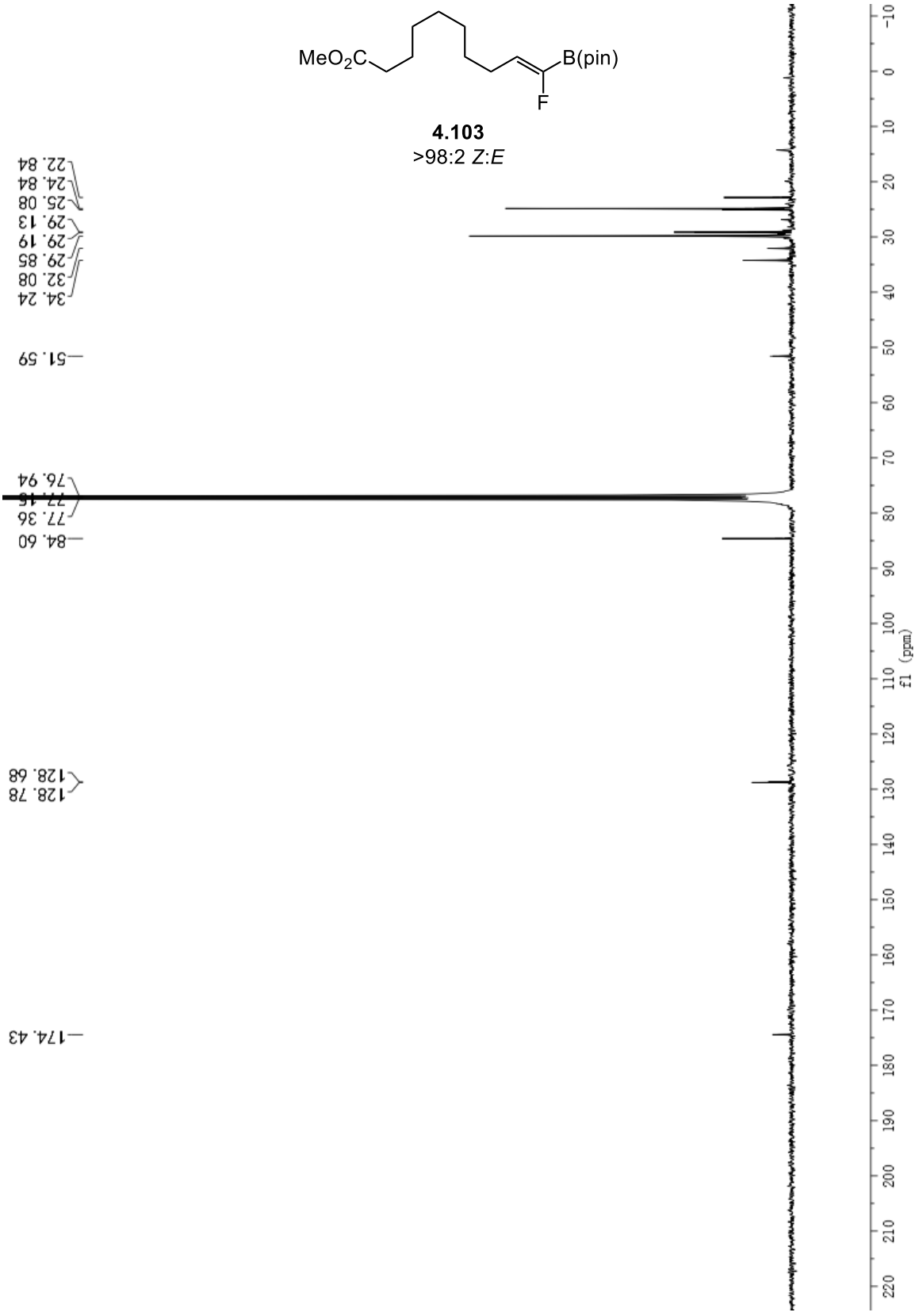
^{19}F NMR Spectrum of 4.103



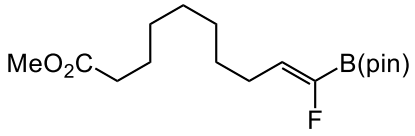
^{1}H NMR Spectrum of 4.103



^{13}C NMR Spectrum of 4.103

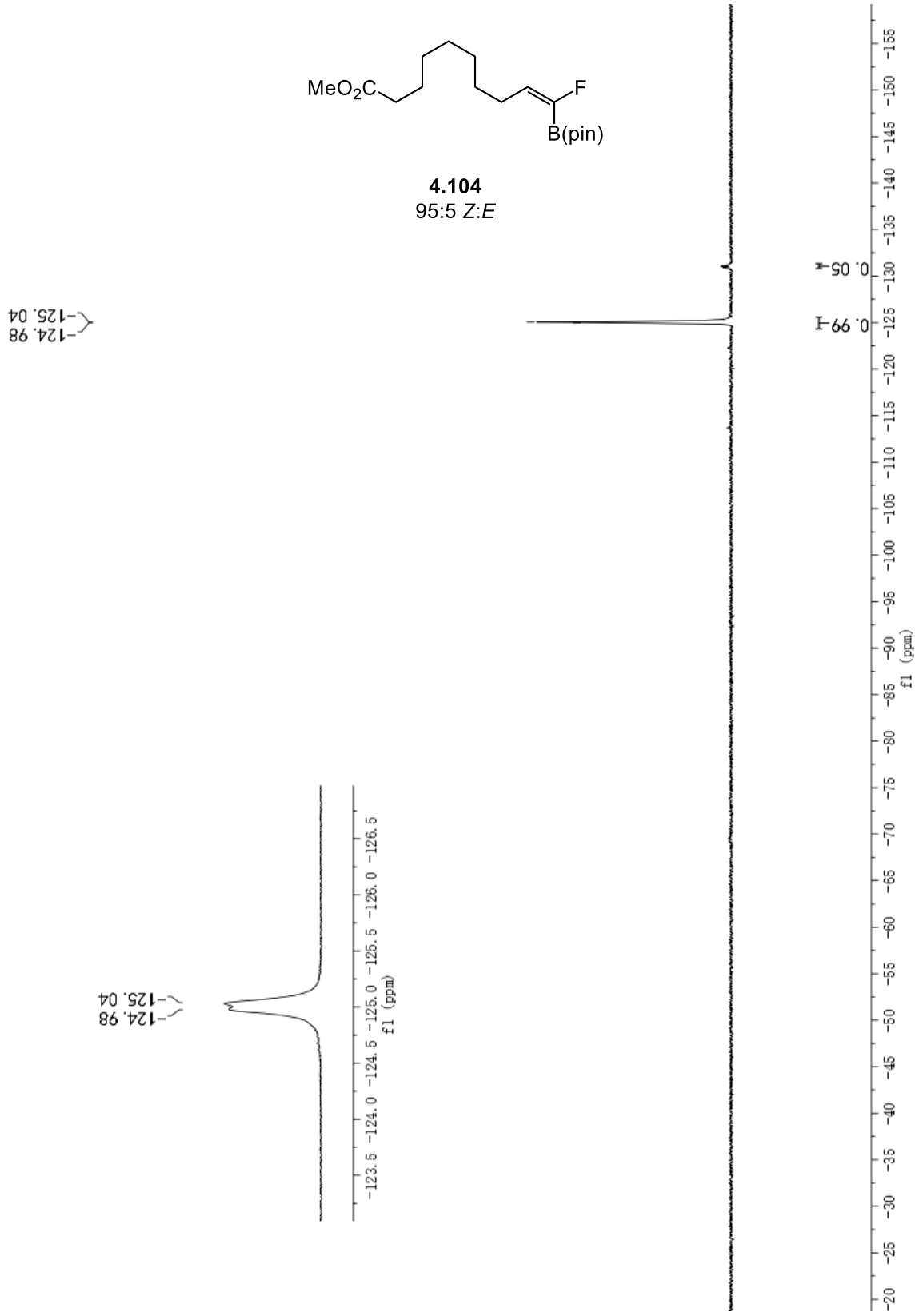


^{11}B NMR Spectrum of 4.103

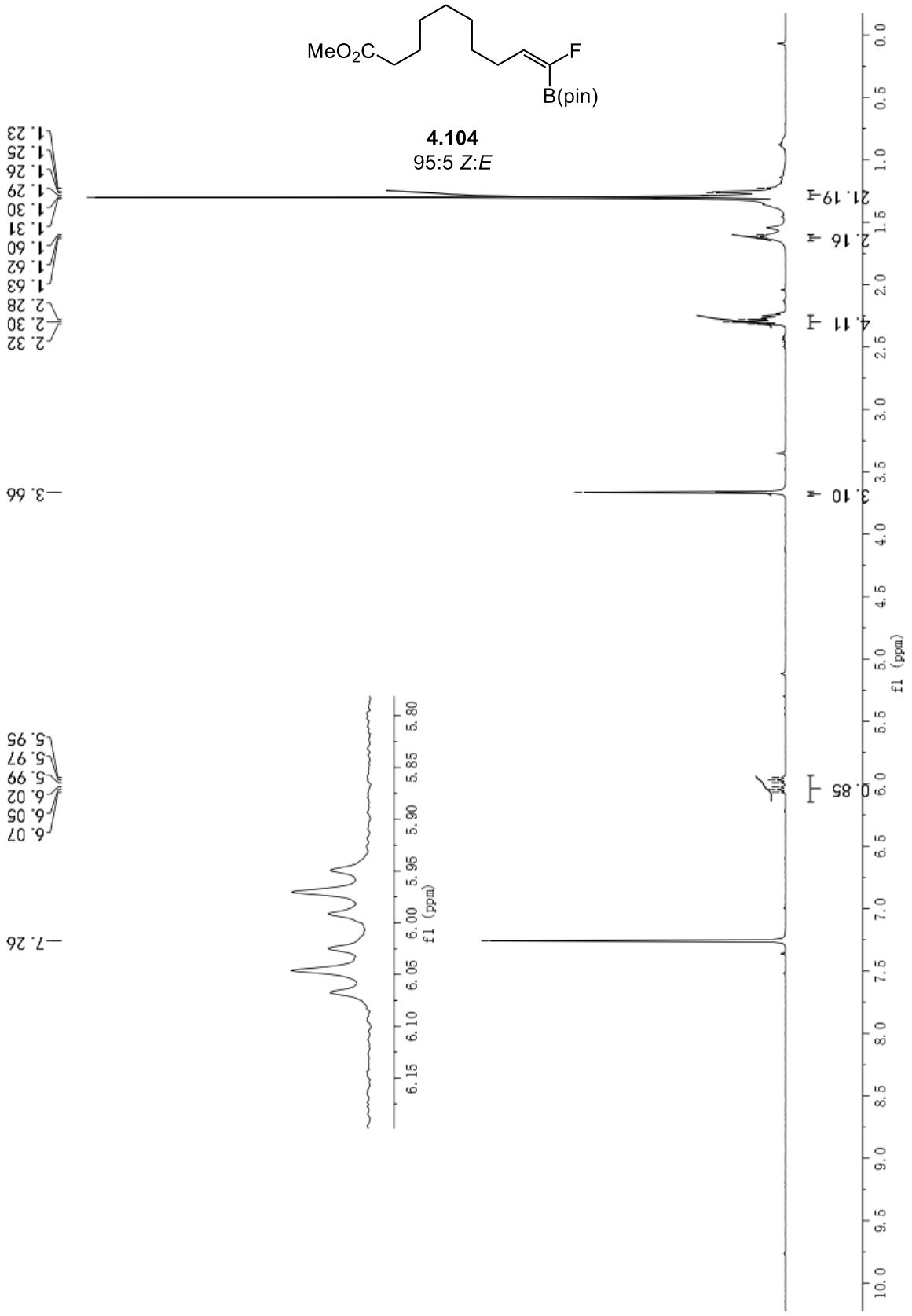


4.103
>98:2 *Z*:*E*

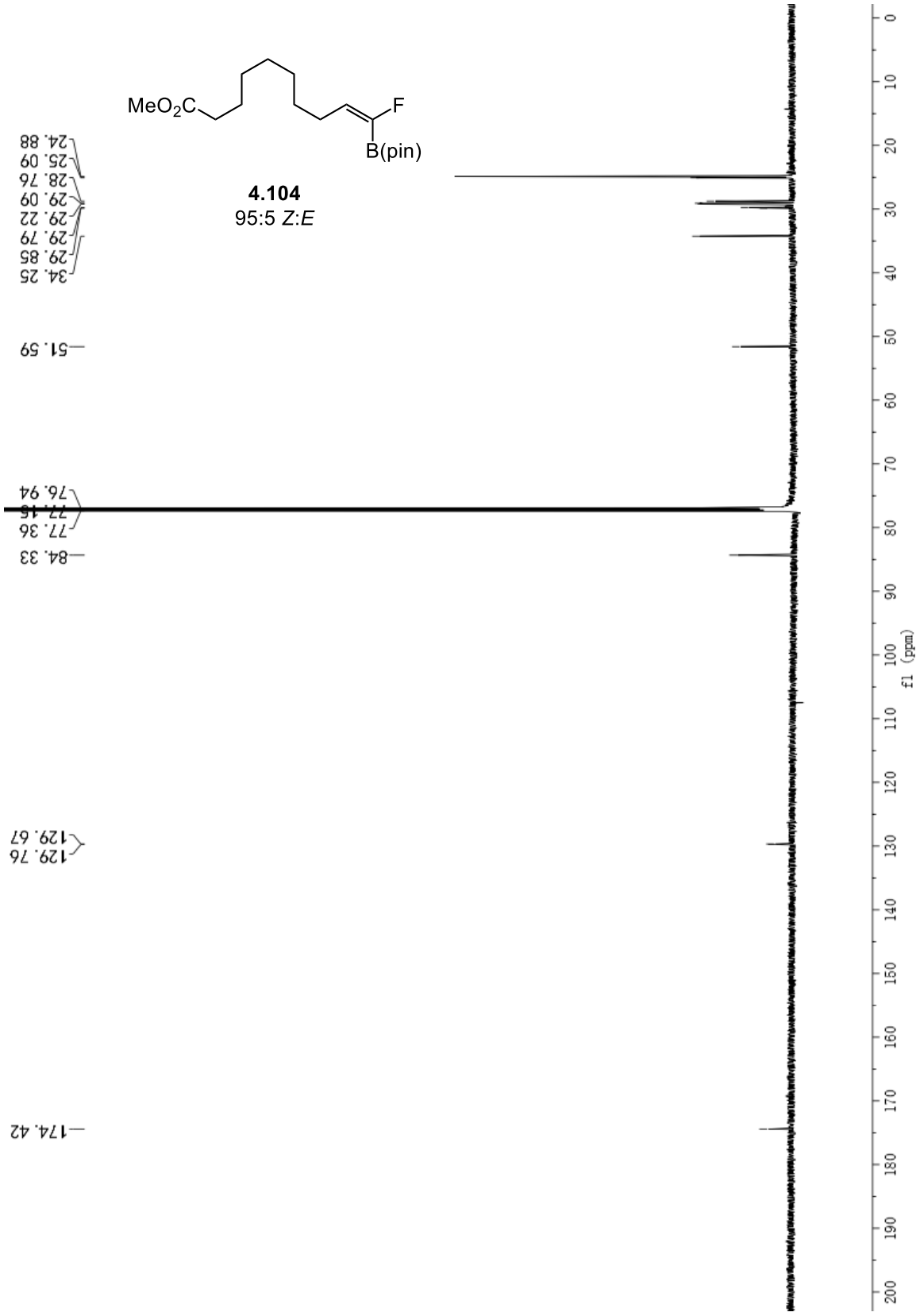
^{19}F NMR Spectrum of 4.104



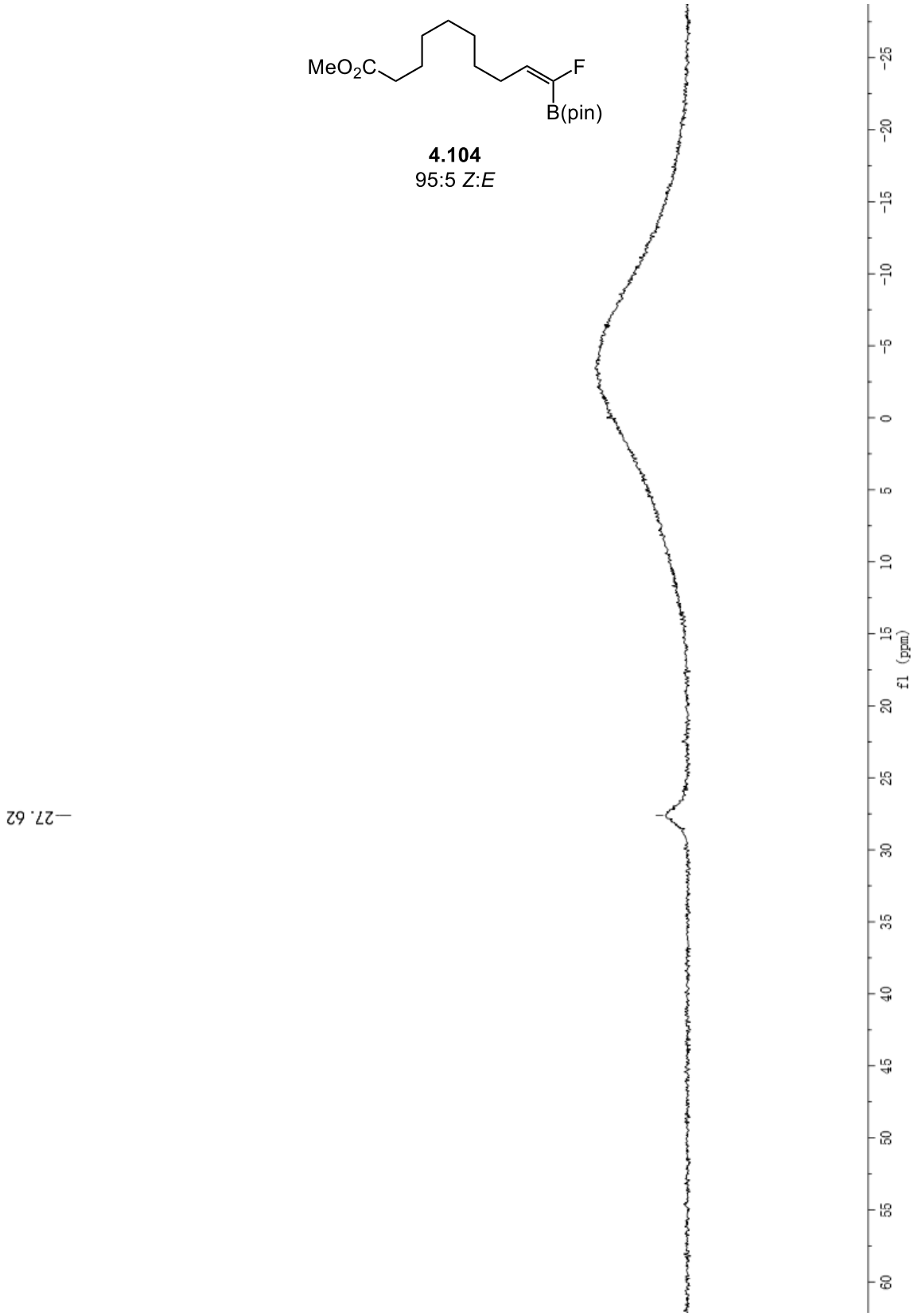
^{1}H NMR Spectrum of 4.104



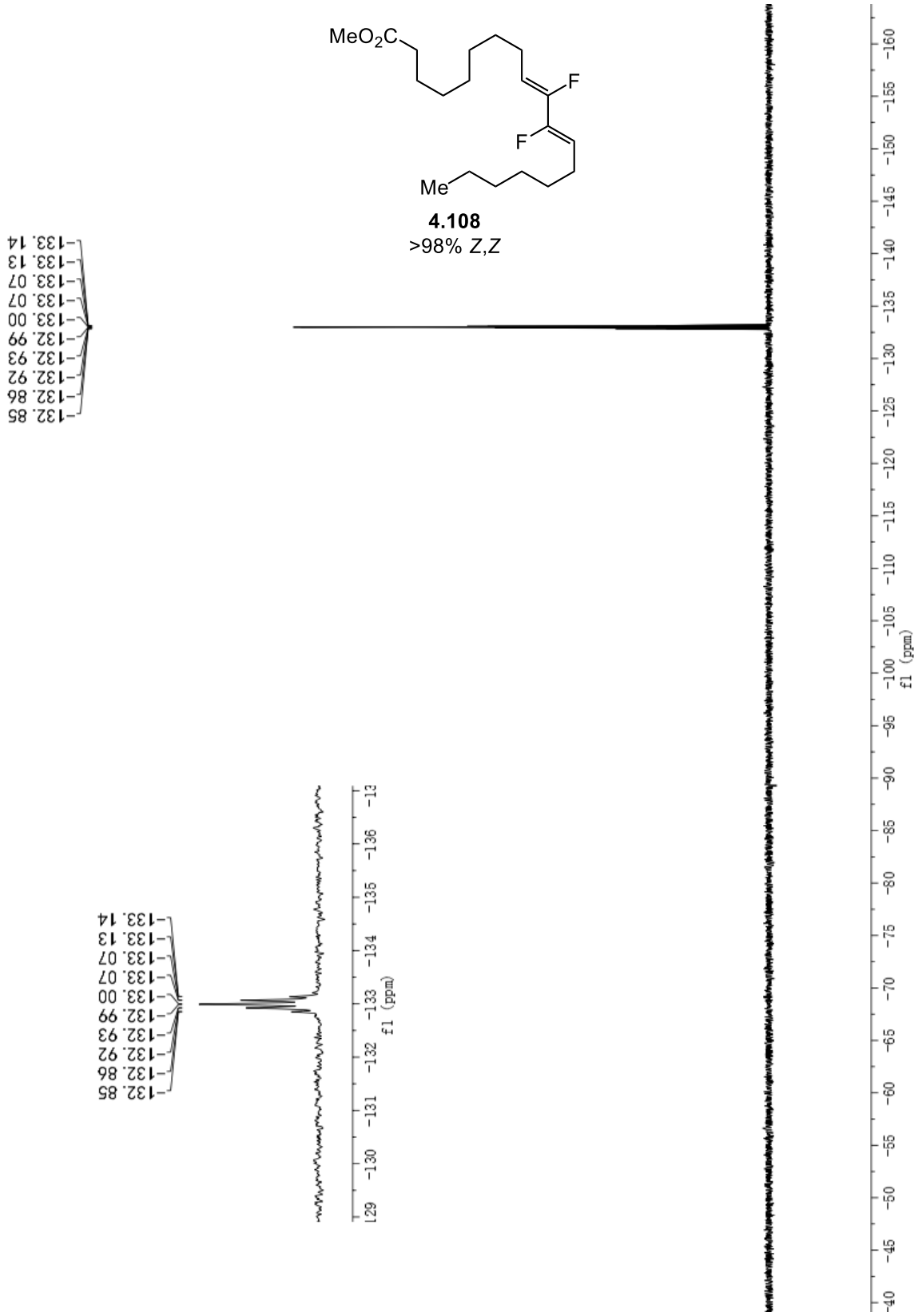
^{13}C NMR Spectrum of 4.104



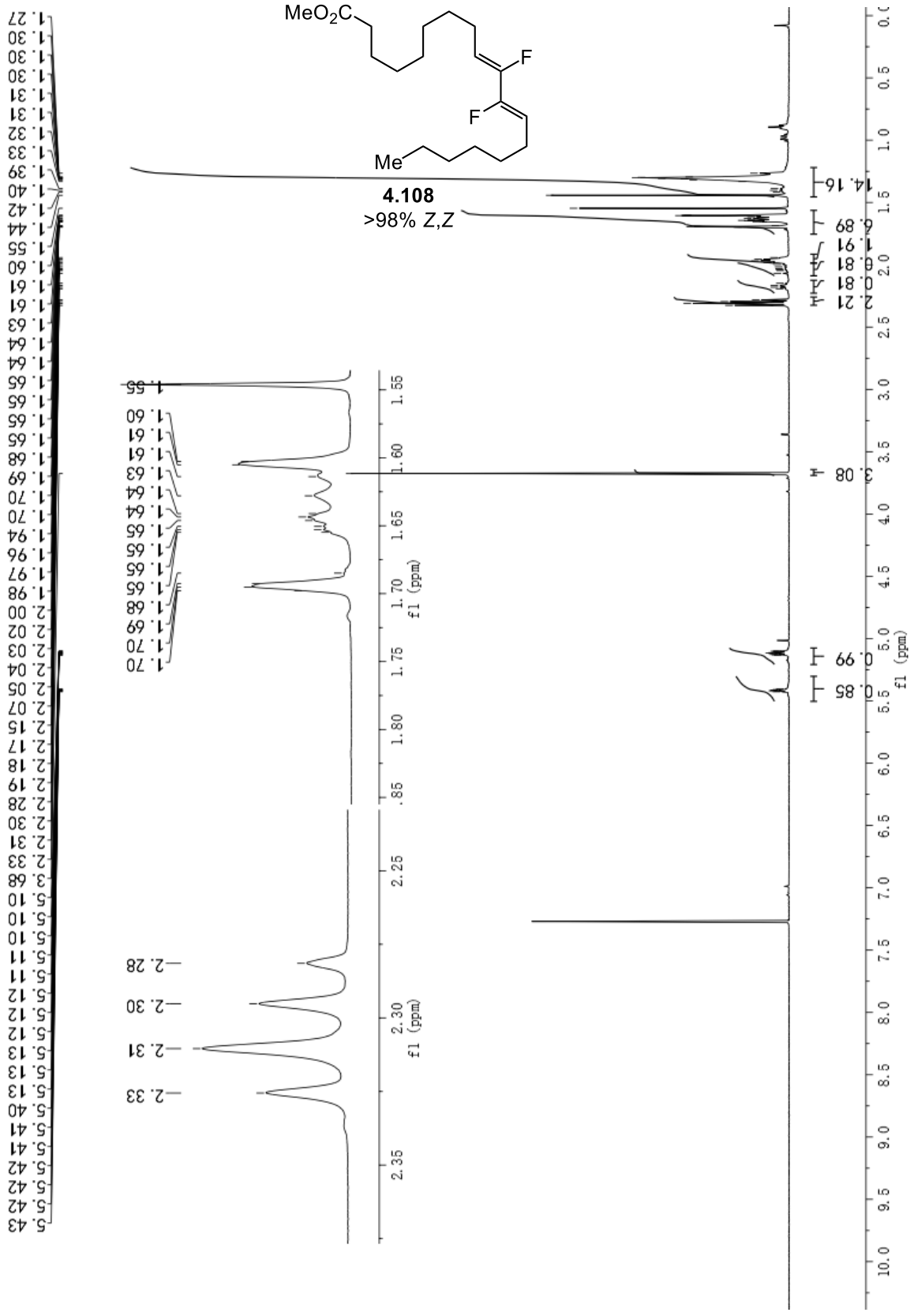
^{11}B NMR Spectrum of 4.104



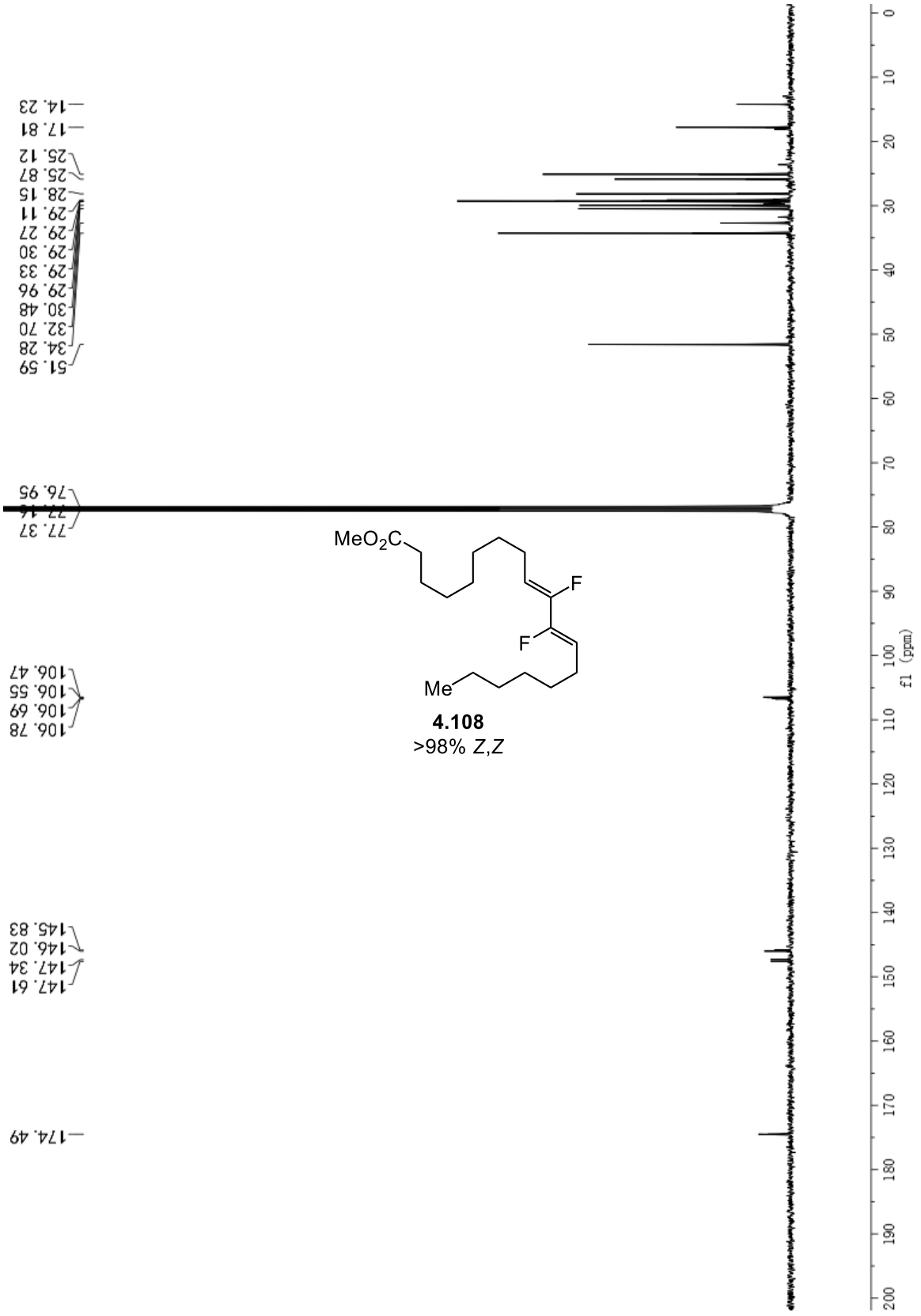
^{19}F NMR Spectrum of *Z,Z*-Difuoro-rumenic ester (4.108)



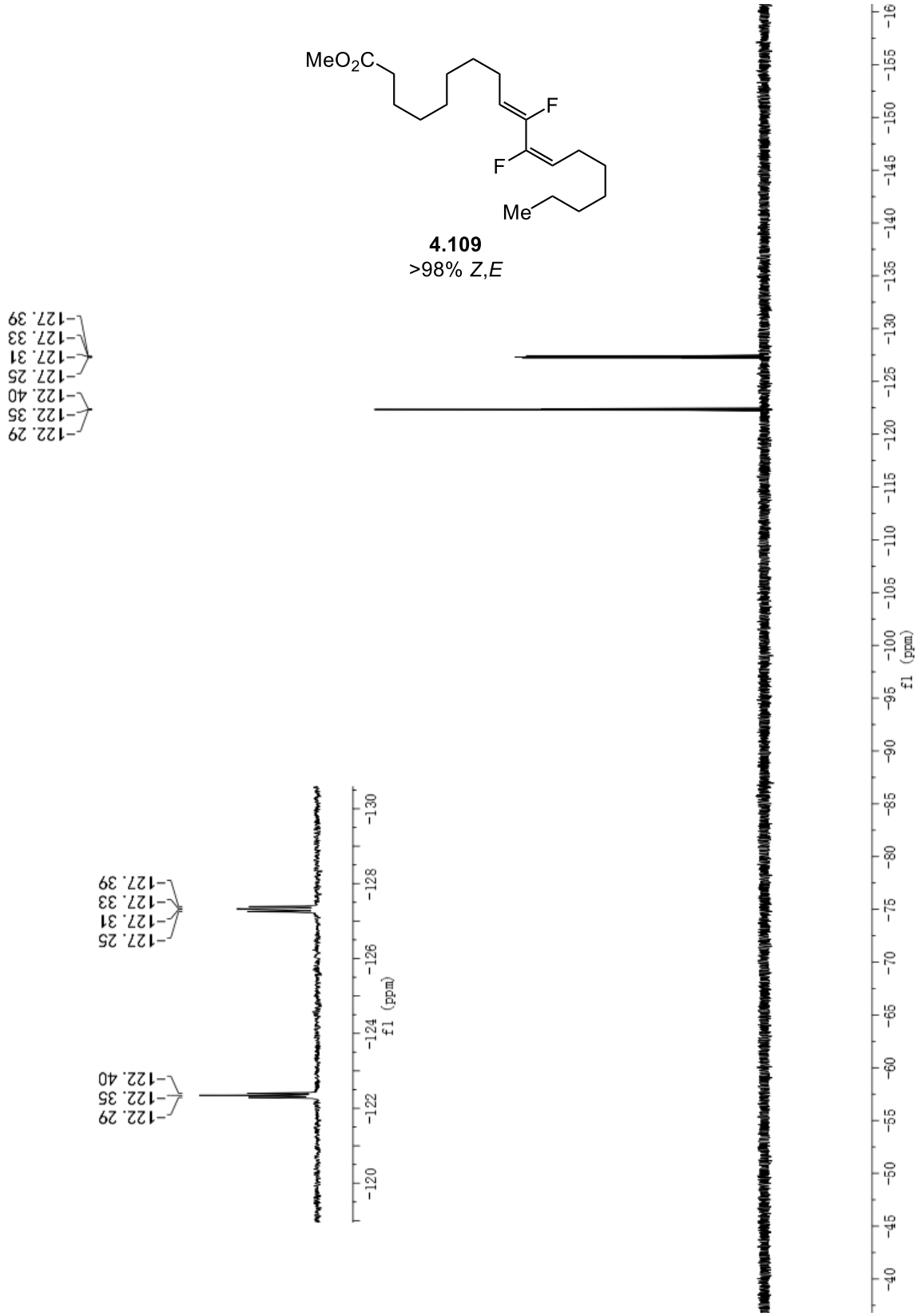
^{1}H NMR Spectrum of *Z,Z*-Difuoro-rumenic ester (4.108)



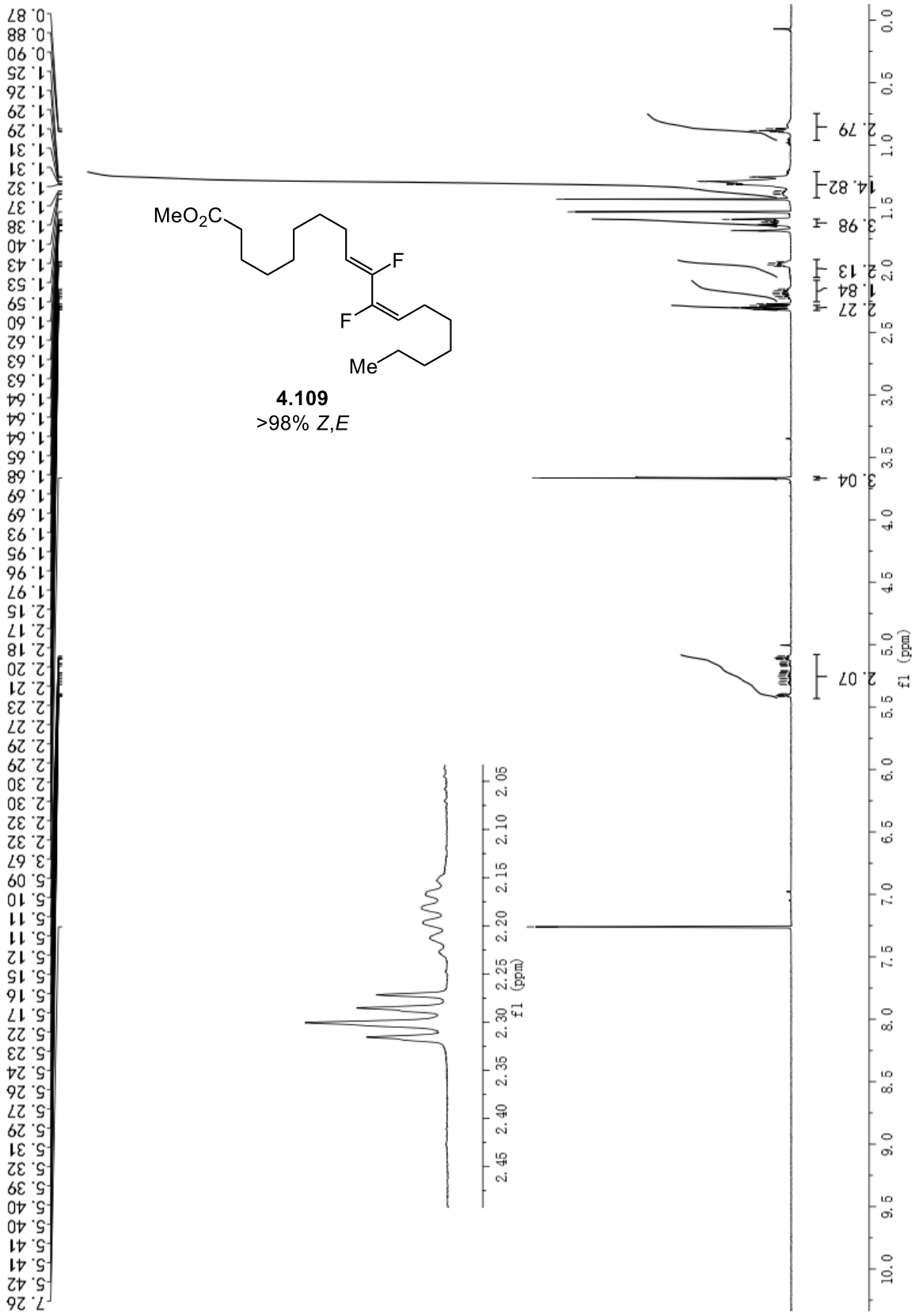
^{13}C NMR Spectrum of *Z,Z*-Difuoro-rumenic ester (4.108)



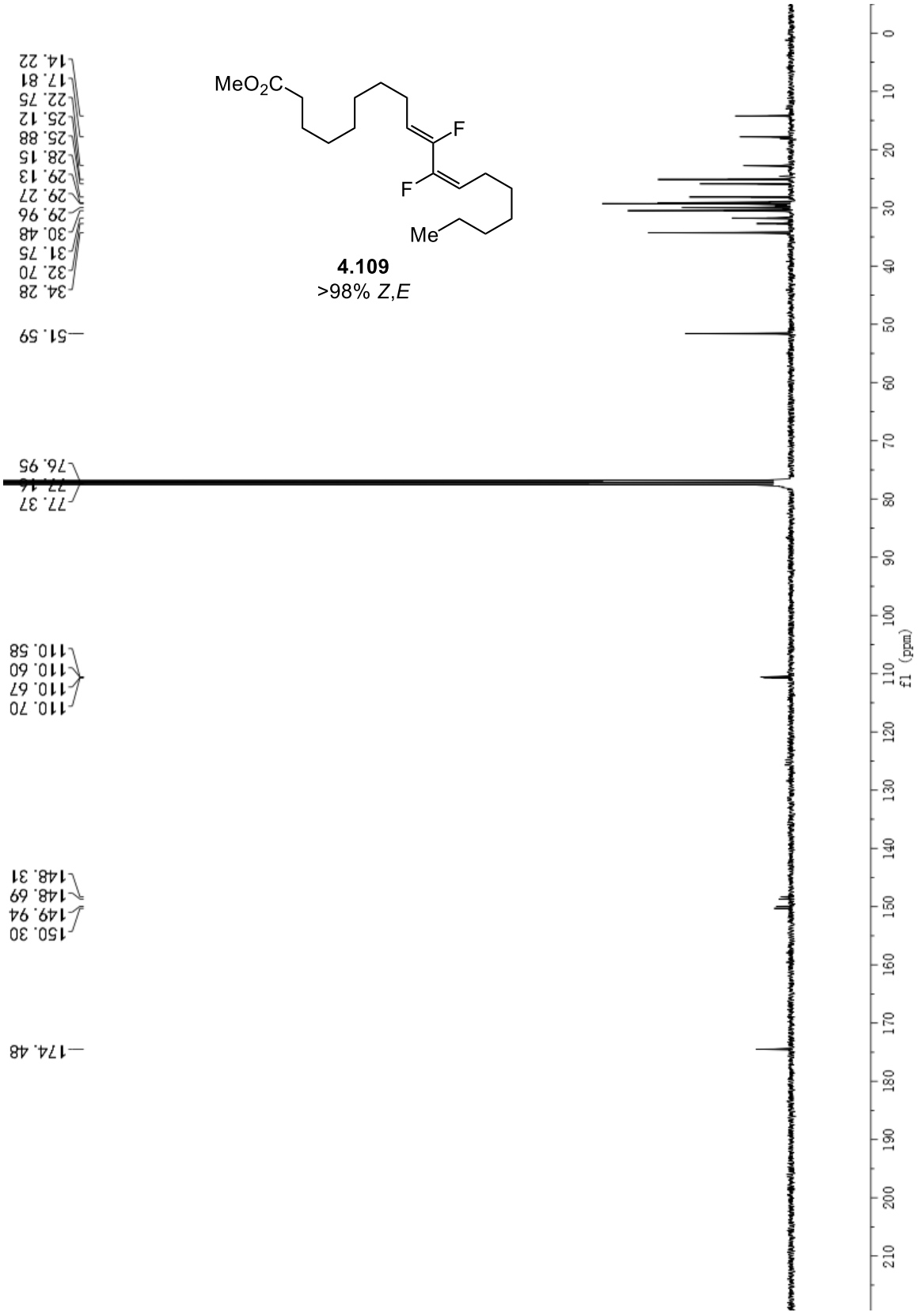
^{19}F NMR Spectrum of *Z,E*-Difluoro-rumenic ester (4.109)



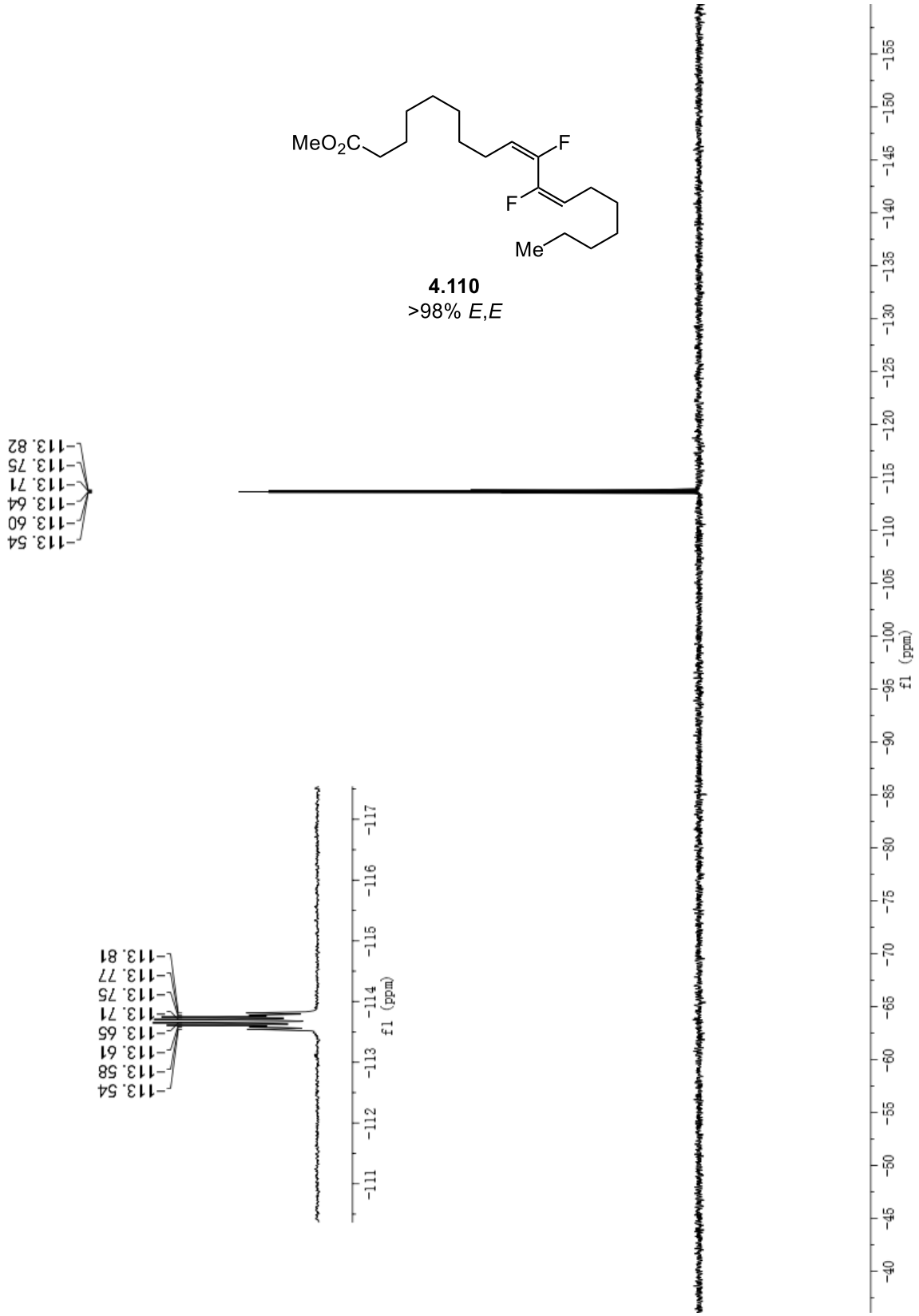
^{1}H NMR Spectrum of *Z,E*-Difluoro-rumenic ester (4.109)



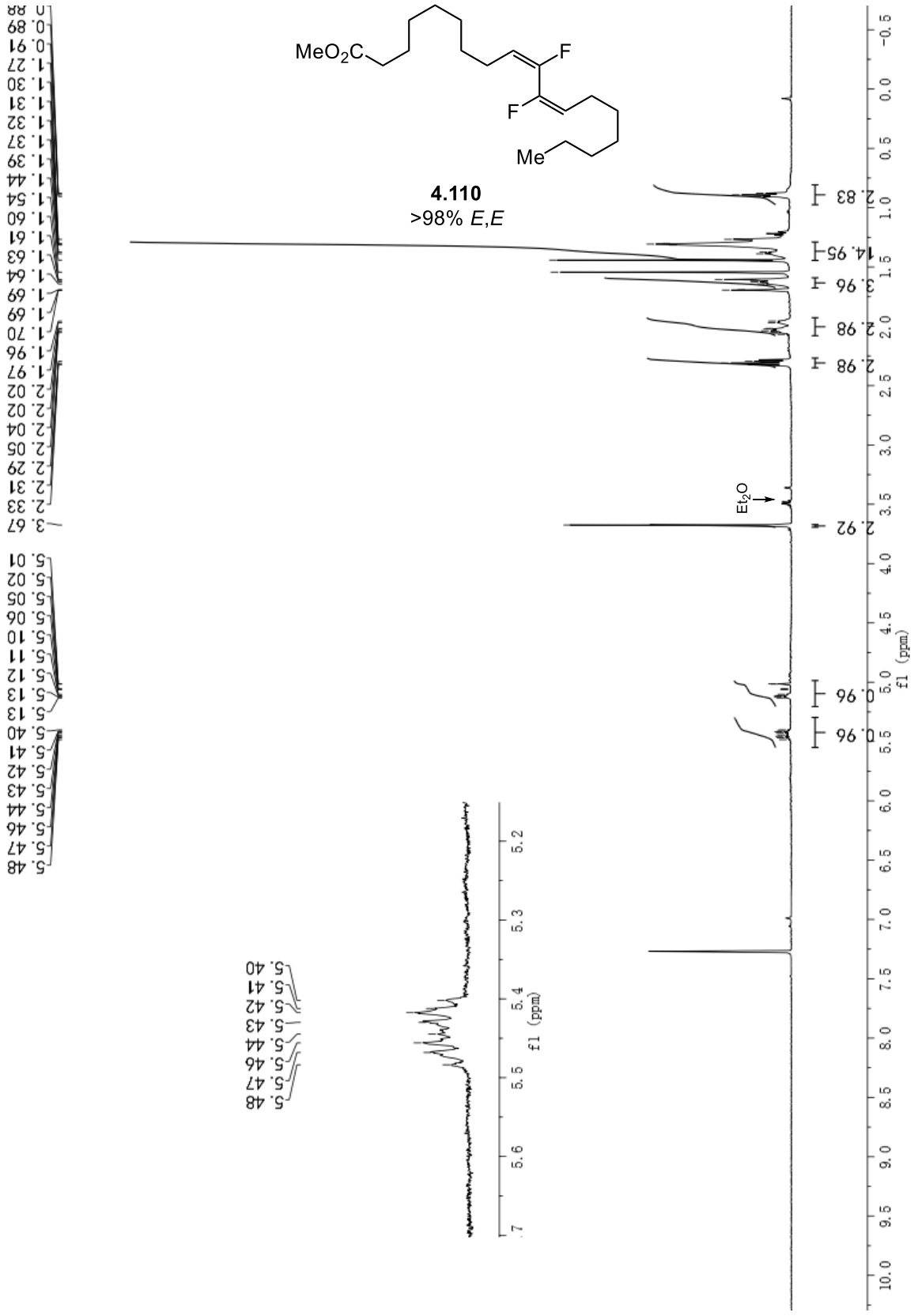
^{13}C NMR Spectrum of *Z,E*-Difluoro-rumenic ester (4.109)



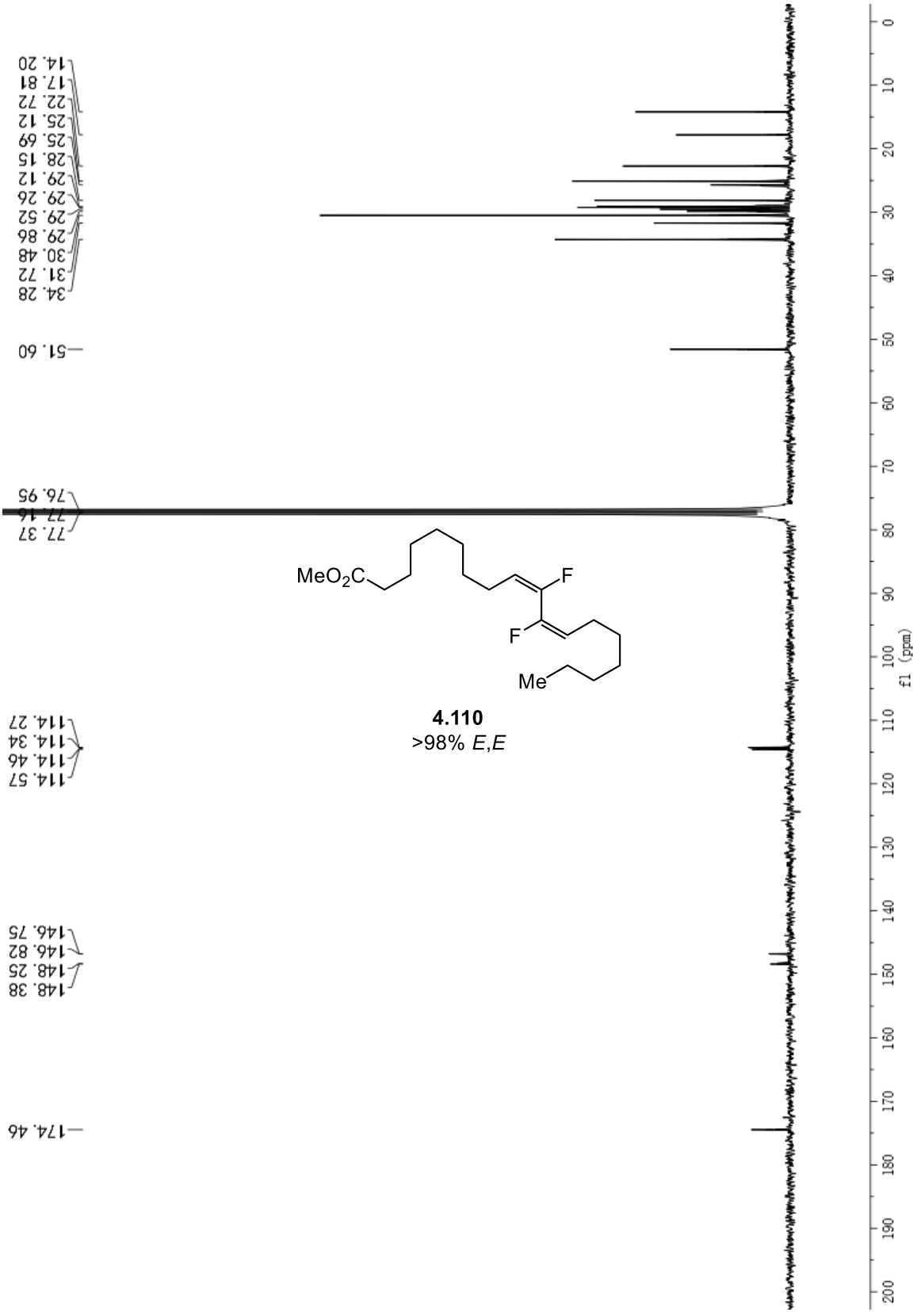
^{19}F NMR Spectrum of *E,E*-Difluoro-rumenic ester (4.110)



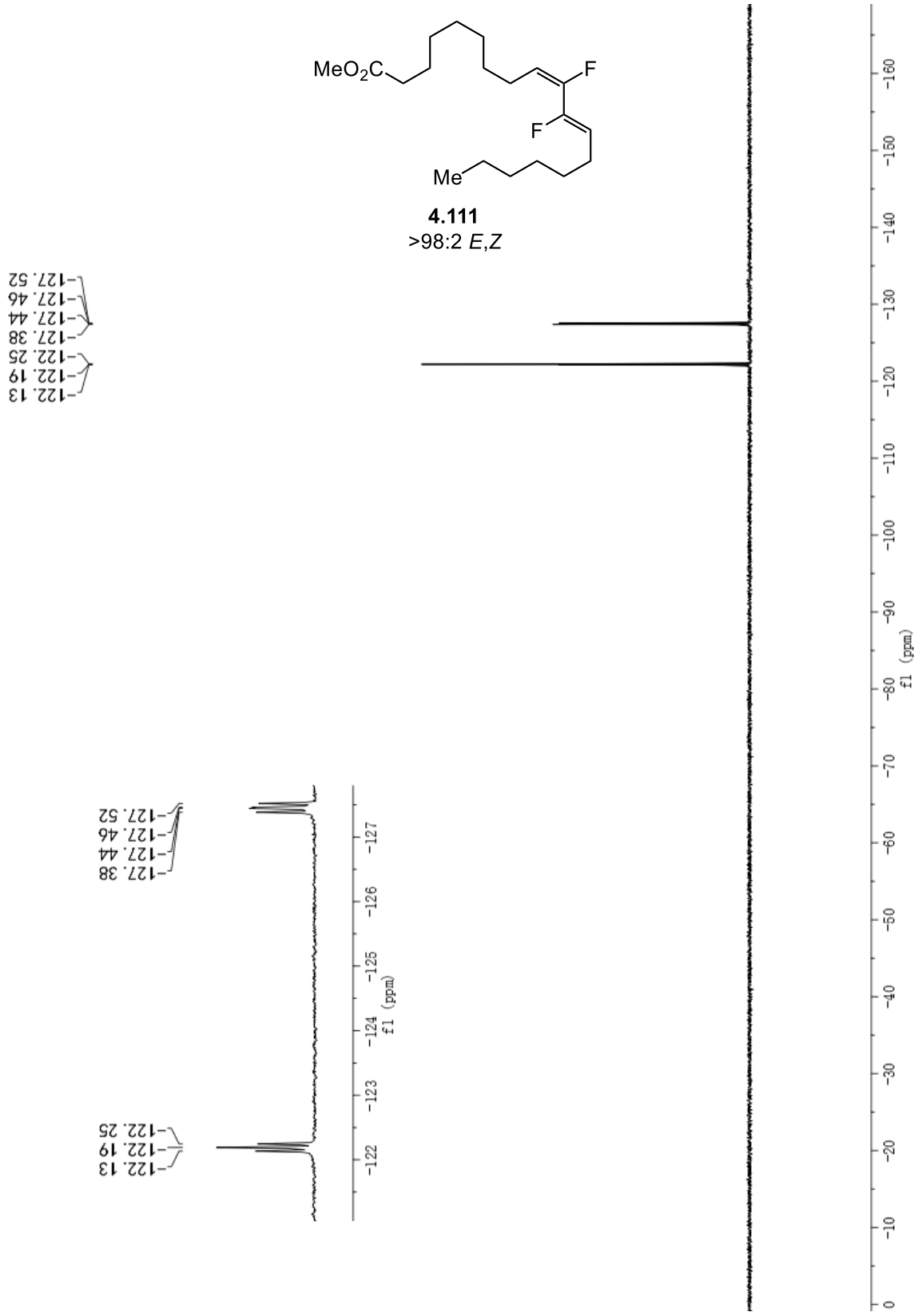
^{1}H NMR Spectrum of *E,E*-Difluoro-rumenic ester (4.110)



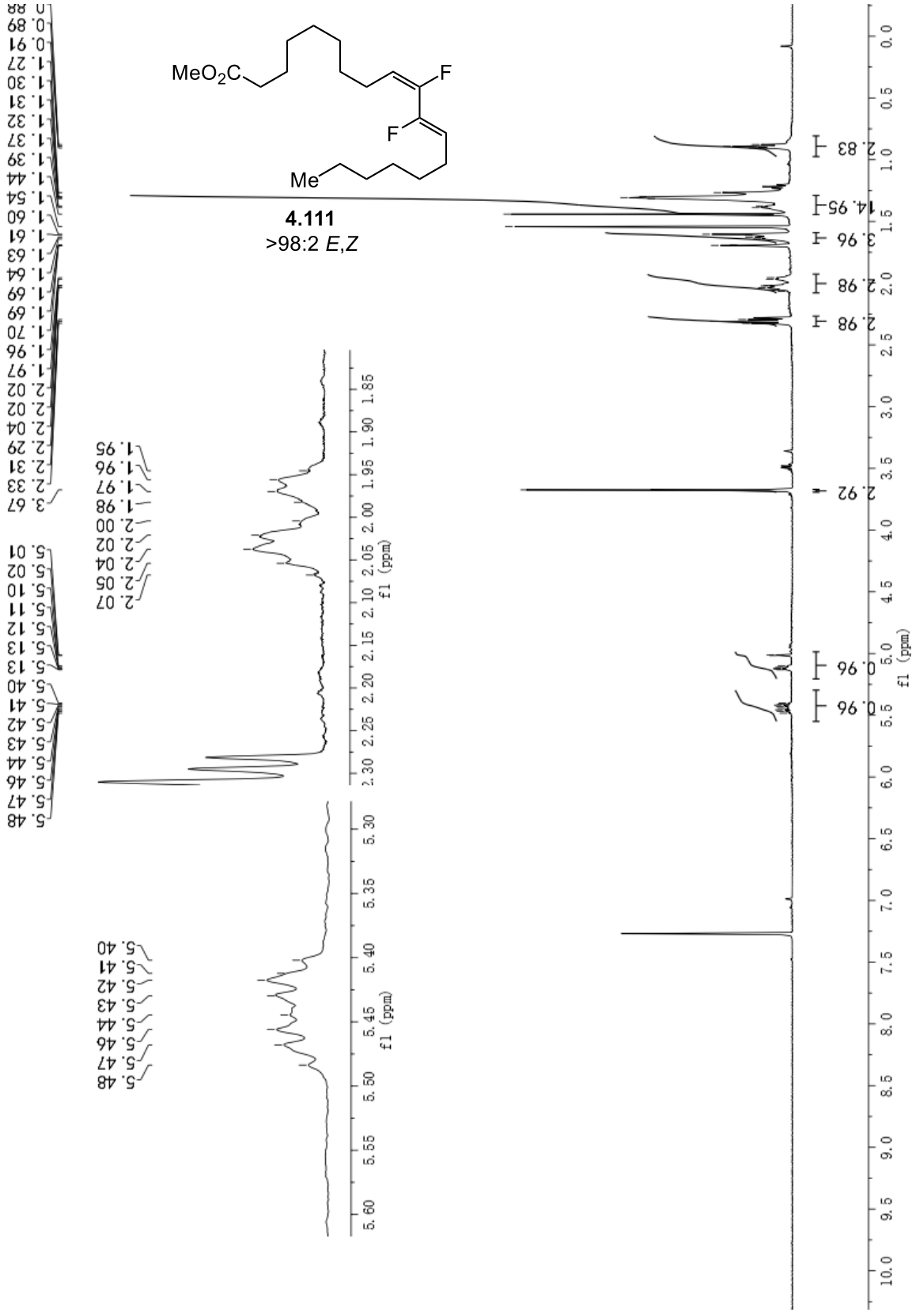
^{13}C NMR Spectrum of *E,E*-Difluoro-rumenic ester (4.110)



^{19}F NMR Spectrum of *E,Z*-Difluoro-rumenic ester (4.111)



^{1}H NMR Spectrum of *E,Z*-Difluoro-rumenic ester (4.111)



^{13}C NMR Spectrum of *E*,*Z*-Difluoro-rumenic ester