Boston College

The Graduate School of Arts and Sciences

Department of Chemistry

STEREOSELECTIVE OLEFIN METATHESIS REACTIONS CATALYZED BY MOLYBDENUM MONOARYLOXIDE MONOPYRROLIDE COMPLEXES

a dissertation

By

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Doctor of Philosophy

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Stereoselective Olefin Metathesis Reactions Catalyzed by Molybdenum Monoaryloxide Monopyrrolide Complexes

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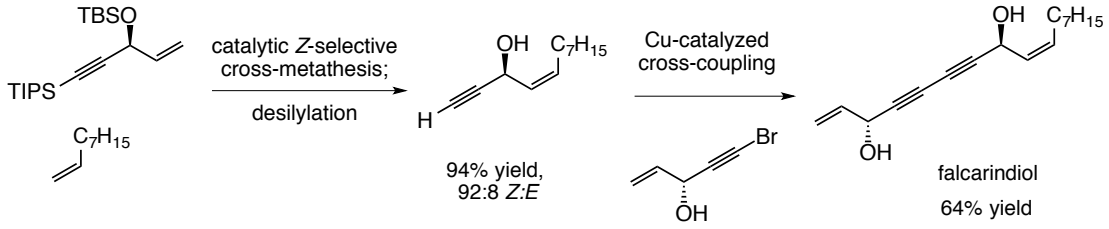
Abstract

Chapter 1: Efficient *Z*-Selective Cross-Metathesis of Secondary Allylic Ethers

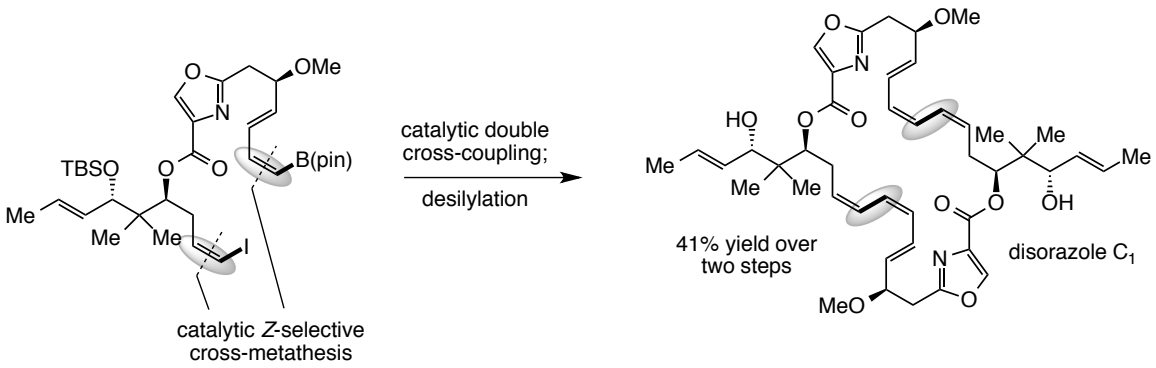


Efficient *Z*-selective cross-metathesis of secondary allylic ethers were catalyzed by monoaryloxide monopyrrolide molybdenum complexes. Reactions involving both silyl and benzyl protected ethers were demonstrated, as well as ethers containing alkyl, aryl and alkynyl substituents. Mechanistic studies were performed, and the reactions were applied to the total synthesis of several ene-diyne natural products.

Chapter 2. Stereoselective Total Synthesis of Disorazole C_1

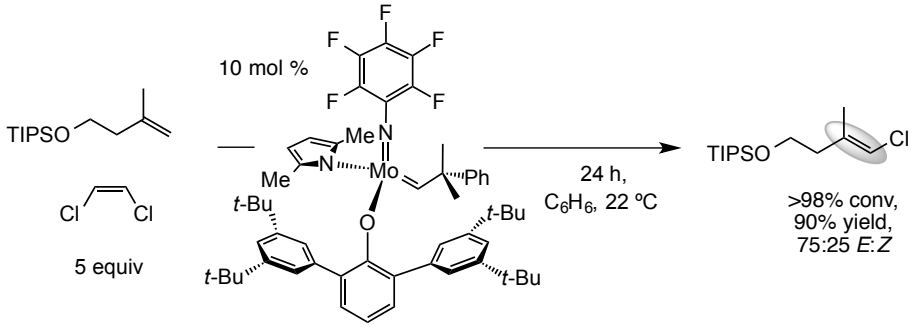
The stereoselective total synthesis of disorazole C_1 is reported. The synthesis was completed in 12 longest linear steps. Our synthesis demonstrates the utility of *Z*-selective cross-metathesis to form both alkenyl borons and alkenyl halides. Another key

transformation was a one-pot Suzuki-dimerization reaction to form a symmetric 30 membered ring in relatively high yield.



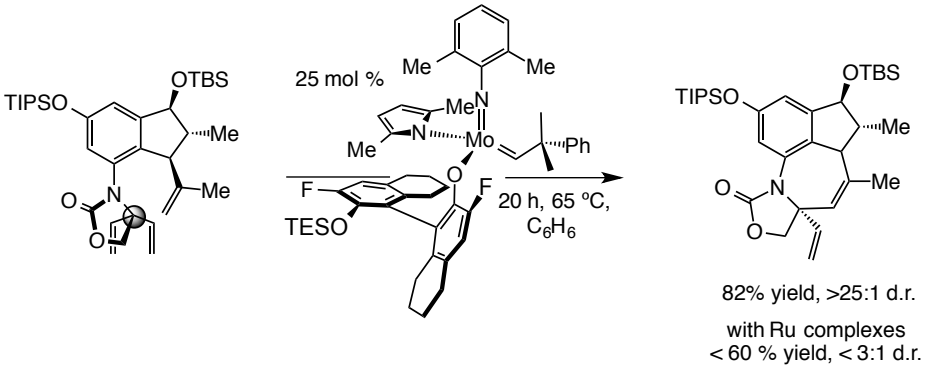
Chapter 3. Stereoselective Cross-Metathesis to Form Trisubstituted Alkenes

Initial studies into the stereoselective formation of trisubstituted olefins through molybdenum catalyzed cross-metathesis have been performed. Our mechanistic understanding of the reaction lead us to focus on the synthesis of alkenyl halides, which can be obtained in up 90% yield and 75:25 *E*:*Z* selectivity.



Chapter 4: Ring-Closing Metathesis in the Synthesis of Natural Products

Development of highly efficient and selective ring-closing metathesis reactions have enabled collaborators to successfully implement routes in total synthesis endeavors. A diastereoselective seven-membered ring-closing metathesis enabled the successful synthesis of (±)-tetrapetalone A methyl-aglycon. An enantioselective ring-closing metathesis to form a six membered ring has provided access to enantioenriched aspidosperma alkaloids.



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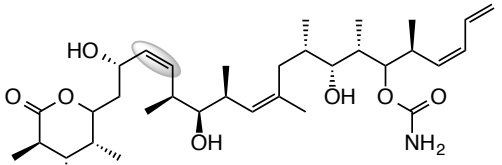
Chapter 4. Ring-Closing Metathesis in the Synthesis of Natural Products

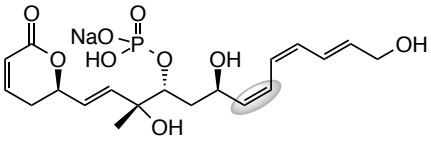
Chapter 1. Efficient *Z*-Selective Cross-Metathesis of Secondary Allylic Ethers

1.1 Introduction

Scheme 1.1. Representative *Z*-Allylic Alcohol Containing Natural Products



1.1 Discodermolide



1.2 Fostriecin

Allylic alcohols are pervasive in organic chemistry; they can be used in substrate directed reactions,[1] as precursors to phosphates,[2] carbonates[3] and chlorides[4] for allylic substitutions, and are also found in natural products such as discodermolide[5] **1.1** and fostriecin [6] **1.2** (scheme 1.1). In any of the aforementioned applications, the stereochemical identity of the double bond is crucial, performing an operation on a mixture of double bond isomers will necessarily lead to a mixture of products, and often the *E* and *Z* isomers have disparate reactivity,[7] or biological activity. The existing

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1. Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.

2. a) Shi, Y.; Jung, B.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2015**, *137*, 8948–8964. b) Nagao, K.; Yokoburi, U.; Makida, Y.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012**, *134*, 8982–8987.

3. a) Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634–10637.

4 Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2426–2428.

5. a) Smith, A. B., III; Freeze, B. S. *Tetrahedron* **2008**, 64, 261–298 and references therein. b) Yu, Z.; Ely, R. J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2014**, *53*, 9632–9636. c) Smith, A. B. III; Sugasawa, K.; Onur, A.; Yang, C.-P. H.; Horwitz, S. B. *J. Med. Chem.* **2011**, *54*, 6319–6327. d) Lemos, E. d.; Poree, F.-H.; Bourin, A.; Barbion, J.; Agouridas, E.; Lannou, M.-I.; Commercon, A.; Betzer, J.-F.; Pancrazi, A.; Ardisson, J. *Chem. Eur. J.* **2008**, *14*, 11092–11112.

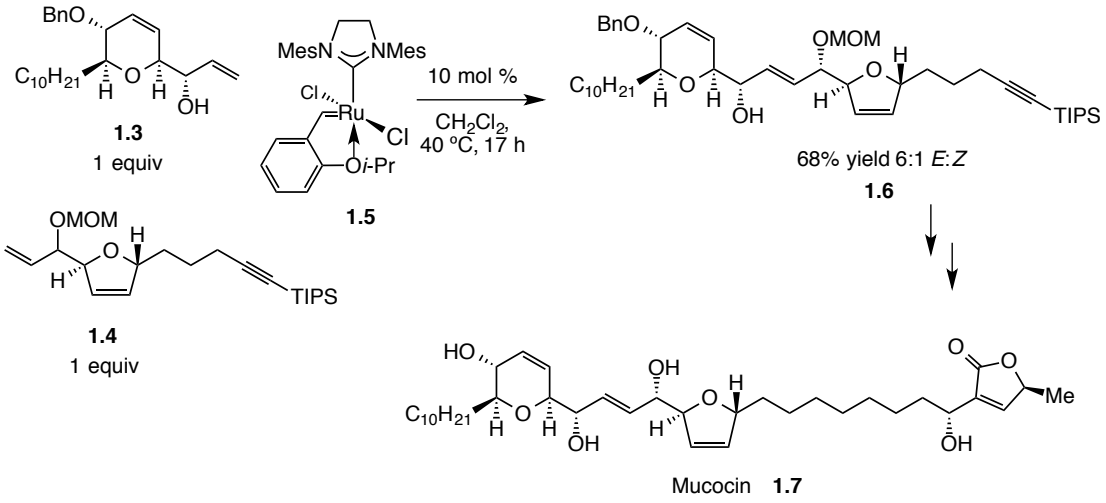
6. a) Boger, D. L.; Ichikawa, S.; Zhong, W. *J. Am. Chem. Soc.* **2001**, *123*, 4161–4167. b) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3667–3670. c) Gao, D.; O'Doherty, G. A. *Org. Lett.* **2010**, *12*, 3752–3755.

7. a) Cannon, J. S.; Kirsch, S. F.; Overman, L. E.; Sneddon, H. F. *J. Am. Chem. Soc.* **2010**, *132*, 15192–15203. b) Cannon, J. S.; Kirsch, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **2010**, *132*, 15185–15191.

methods for synthesis of allylic alcohols require a single isomer of alkenyl halide or metal for addition to an aldehyde, or on the very toxic[8] and unreliable[9] Lindlar hydrogenation. Wittig reactions to form the olefin from an α-siloxyaldehyde result in unpredictable selectivities, as well as generating a stoichiometric amount of triphenylphosphine oxide waste.[10]

1.2 Background

Scheme 1.2. Cross-Metathesis in the Synthesis of Mucocin



As an alternative to these methods, the cross-metathesis[11] (CM) and ring-opening cross-metathesis[12] (ROCM) of allylic alcohols using ruthenium catalysts is well described. These reactions additionally benefit from a directing and activating H bonding

8. Lindlar, H.; Dubuis, R. *Org. Synth.* **1966**, *46*, 89.

9. Ralston, K. J.; Ramstadius, H. C.; Brewster, R. C.; Niblock, H. S.; Hulme, A. N. *Angew. Chem. Int. Ed.* **2015**, *54*, 7086–7090. (In the supporting information of this total synthesis, they are unable to successfully reproduce a reported partial hydrogenation)

10. a) Wittman, M. D.; Kallmerten, J. *J. Org. Chem.* **1987**, *52*, 4303–4307. b) Kadirvel, M.; Stimpson, W. T.; Moumene-Afifi, S.; Arsic, B.; Glynn, N.; Halliday, N.; Williams, P.; Gilbert, P.; McBain, A. J.; Freeman, S.; Gardiner, J. M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2625–2628.

11. a) Fuwa, H.; Yamaguchi, H.; Sasaki, M. *Org. Lett.* **2010**, *12*, 1848–1851. b) Lin. Y. A.; Chalker, J. M.; Floyd, N.; Bernardes, G. J. L.; Davis, B. G. *J. Am. Chem. Soc.* **2008**, *130*, 9642–9643.

12. Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378–8379.

interaction between the alcohol proton and the chloride of the ruthenium complex.[13] A particular CM worth noting was performed with **1.3** and **1.4** where only a single equivalent of each partner was required using the styrene ether containing Ru catalyst **1.5** to obtain **1.6** in good yield and moderate selectivity for the desired *E* olefin.[14] This material was further elaborated into mucocin. The CM catalyzed by typical Ru based catalysts, with a few predictable exceptions,[15] delivers mostly the *E* olefin. Newly discovered *Z*-selective Ru catalysts from the Grubbs[16] and Hoveyda[17] groups, while apparently tolerant of unprotected primary alchohols[18] have only been demonstrated to be effective with molecules containing very small allylic branches[19] and have not been shown to react with secondary alcohols.

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13. Forman, G. S.; McConnell, A. E.; Tooze, R. P.; Rensburg, W. J.; Meyer, W. H.; Kirk, M. M.; Dwyer, C. L.; Serfontein, D. W. *Organometallics* **2005**, 24, 4528–4542.

14. Crimmins, M. T.; Zhang, Y.; Diaz, F. A. *Org. Lett.* **2008**, *8*, 2369–2372.

15. a) Randl, S.; Gessler, S.; Wakamatsu, H. Blechert, S. *Synlett*, **2001**, 430–432 b) Love, J. A.; Morgan, J. P.; Trnka, T. M. Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 4035–4037.

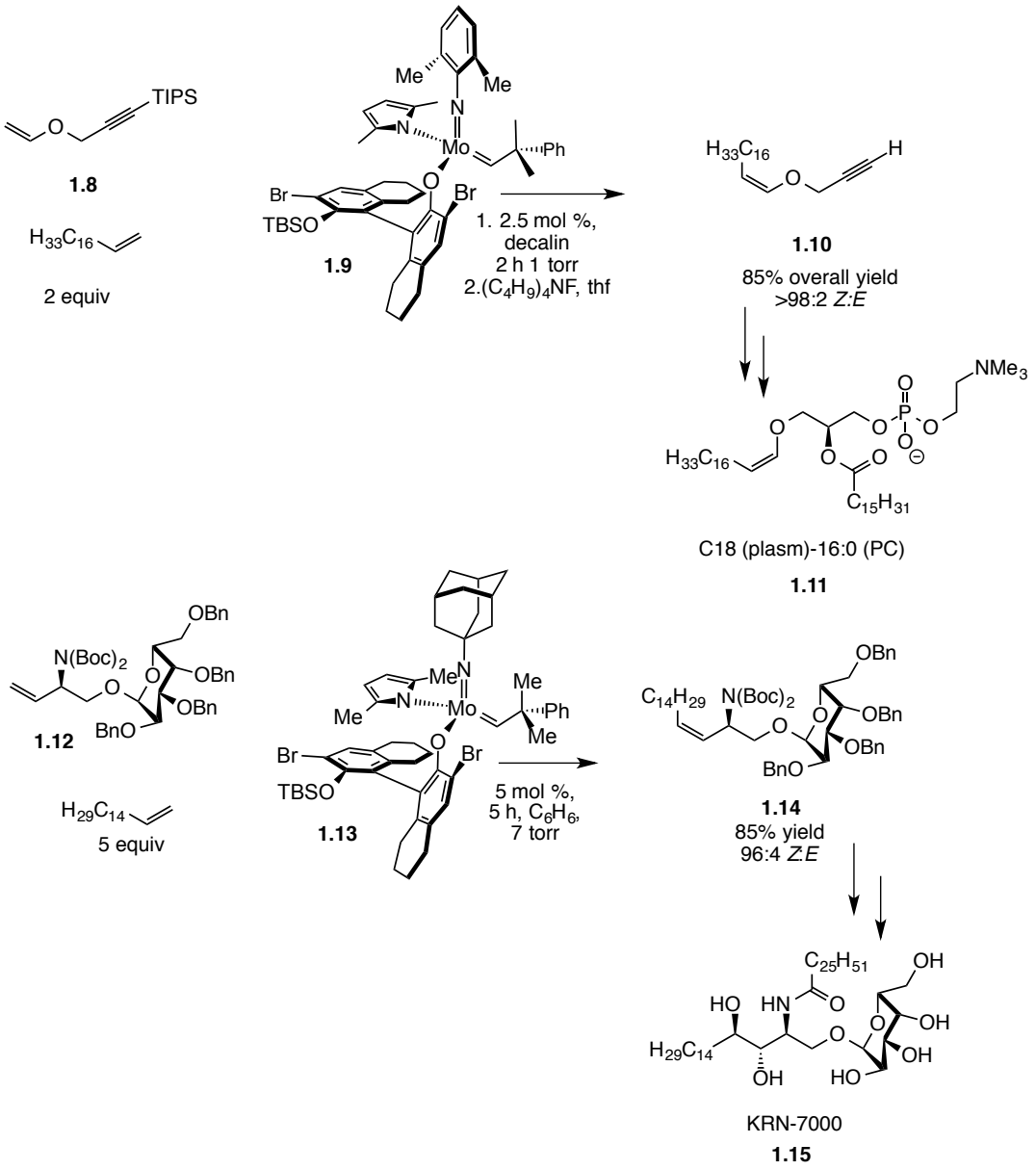
16. a) Keitz, B. K.; Endo, K.; Herbert, M. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 9686–9688. b) Keitz, B. K.; Endo, K.; Patel, P. R.; Herbert, M. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **2012**, *134*, 693–699. c) Rosebrugh, L. E.; Herbert, M. B.; Marx, V. M.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2013**, *135*, 1276–1279.

17. a) Koh, M. J.; Khan, R. K. M.; Torker, S.; Yu, M.; Mikus, M. S.; Hoveyda, A. H. *Nature* **2014**, *517*, 181–186. b) Khan, R. K. M.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 14337–14340. c) Mikus, M. S.; Torker, S. *unpublished data*.

18. Herbert, M. B.; Marx, V. M.; Pederson, R. L.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 310–314.

19. Quigley, B. L.; Grubbs, R. H. *Chem. Sci.* **2014**, *5*, 501–506.

Scheme 1.3. Molybdenum Catalyzed *Z*-Selective Cross-Metathesis



A CM method to deliver the *Z* isomer of allylic alcohols and ethers, particularly in complex settings, would fill an important gap in chemical synthesis; we hypothesized that our group's monoaryloxide-monopyrrolide (MAP) catalyst [20] could effect this transformation. We had previously discovered these catalysts were effective in

20. a) Singh, R.; Schrock, R. R.; Muller, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2007**, *129*, 12654–12655. b) Malcolmson, S. J.; Meek, S. J; Sattley, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *456*, 933–937. c) Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 943–953.

producing *Z* enol ethers and allylic amides.[21] Subjection of enol ether **1.8** to octadecene and MAP catalyst **1.9** afforded, after desilylation, a single isomer of **1.10** which was carried on in a formal synthesis of plasmalogen **1.11**.[22] Plasmalogens are cell membrane components that are particularly abundant in muscle and nerve tissues[23] and may be anti-oxidants in the body; the *E* enol ether has greatly reduced anti-oxidant activity.[24] We had also applied MAP catalysts in the Z-selective CM of enantioenriched allylic amides including **1.12** and related compounds. Adamantyl-imido containing catalyst **1.13**[25] was able to catalyze the reaction between **1.12** and hexadecane affording **1.14** in 86% yield and 96:4 *Z*:*E* selectivity. This material was utilized in a formal synthesis of potent immunostimulant[26] KRN7000 **1.15**. The *Z*-olefin of **1.14** was dihydroxylated resulting in the diol present in the final product. The relationship between the alcohols, and hence the double bond geometry in the cross-metathesis, is crucial for biological activity.[27] The CM method towards **1.15** has important biological implications, while the molecule shows promise as an immunological adjuvant; its extreme hydrophobicity renders it insoluble in water and only suitable for injections. Shorter alkyl chains, which could be easily installed by a *Z*-selective CM, do not significantly decrease the biological activity,[28] and may confer some water solubility.

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21. Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature*, **2011**, *471*, 461–466.

22. Qin, D.; Byun, H.-S.; Bittman, R. *J. Am. Chem. Soc.* **1999**, *121*, 662–668.

23. Horrocks, L. A.; Sharma, M. In *Phospholipids;* Hawthorne, J. N., Ansell, G. B. Eds,; Elsevier: Amsterdam, **1982**; pp 51.

24. Lankalapalli, R. S.; Eckelkamp, J. T.; Sircar, D.; Ford, D. A.; Subbaiah, P. V.; Bittman, R. *Org. Lett.* **2009**, *11*, 2784–2787.

25. Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3844–3845.

26. Borg, N. A.; Wun, K. S.; Kjer-Nielsen, L.; Wilce, M. C. J.; Pellicci, D. G.; Koh, R.; Besra, G. S.; Bharadwaj, M.; Godfrey, D. I.; McCluskey, J.; Rossjoh, J. *Nature,* **2007**, *448*, 44–49.

27. a) Llaveria, J.; Diaz, Y.; Matheu, M. I.; Castillon, S. *Org. Lett.* **2008**, *11*, 205–208. b) Trappeniers, M.; Goormans, S.; Beneden, K. V.; Decruy, T.; Linclau, B.; Al-Shamkhani, A.; Elliott, T.; Ottensmeier, C.; Werner, J. M.; Elewaut, D.; Calenbergh, S. V. *ChemMedChem*, **2008**, *3*, 1061–1070.

28. Michieletti, M.; Bracci, A. Compostella, F.; Libero, G. D.; Mori, L.; Fallarini, S.; Lombardi, G.; Panza, L. *J. Org. Chem.* **2008**, *73*, 9192–9195.

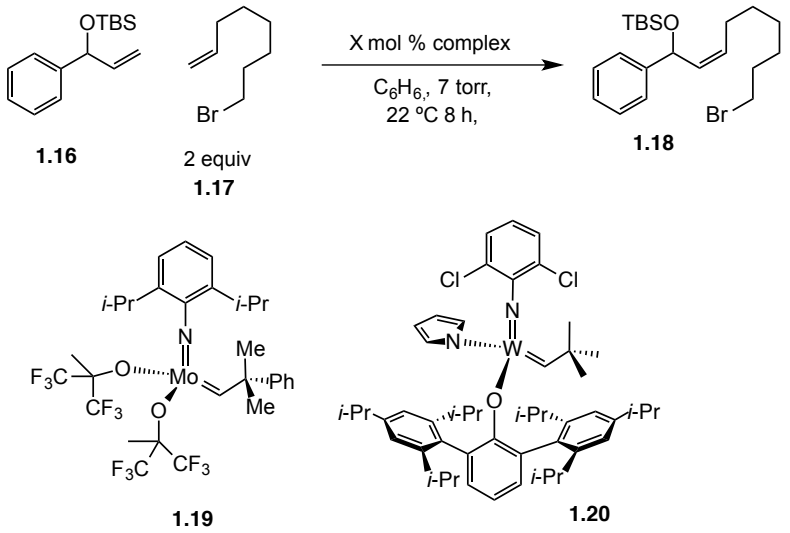
The application of vacuum in both of these cases bears discussion, while it serves to remove ethylene, this has different consequences depending on the catalyst employed. In the enol ether CM catalyzed by **1.9**, vacuum helps to maintain high *Z*-selectivity, without vacuum the catalyst can react with ethylene, to form a Mo methylidene, which then reacts with the product, reverting it to the starting materials establishing a thermodynamic equilibrium and eroding kinetic *Z* selectivity. In the allylic amide reaction catalyzed by **1.13**, vacuum is necessary to achieve high conversion. Without vacuum, the methylidene derived from **1.13** can react with ethylene, forming an unsubstituted metallacyclobutane, which can decompose in well precedented pathways to a catalytically inactive Mo-(IV) olefin species.[29] Based on this, and other data, adamantyl imido catalysts seem to be particularly prone to this decomposition. In the synthesis of **1.14** aryl-imido catalyst **1.9** was much less efficient than **1.13** presumably due to the greater steric pressure imposed by an allylic amide versus enol ether.

1.3 Formation of Secondary *Z*-Allylic Ethers by Cross-Metathesis

1.3.a Synthesis of TBS Allylic Ethers

29. a) Tsang, W. C. P.; Jamieson, J. Y.; Aeilts, S. L.; Hultzsch, K. C.; Schrock, R. R.; Hoveyda, A. H. *Organometallics,* **2004**, *23*, 1997–2007. b) For a computational study, see: Solans-Monfort, X.; Coperet, C.; Eisenstein, O. *J. Am. Chem. Soc.* **2010**, *132*, 7750–7757.

Table 1.1. Catalyst Screening for Secondary TBS Allylic Ether Cross-Metathesis[a]



entry	complex; mol%	conv (%)[b,c]	yield (%)[d]	*Z*:*E*[c]
1	**1.5;** 5	95	80	5:95
2	**1.19**; 5	98	76	5:95
3	**1.9**; 5	64	62	81:19
4	**1.13**; 3	79	69	95:5
5	**1.20**; 5	25	20	>95:5

a) Reactions performed under N_2 atmosphere with a vacuum of 7 torr (930 Pascal). b) Conversion refers to consumption of the limiting starting material. c) Determined by ^{1}H NMR analysis of unpurified mixtures. d) Yield of isolated and purified products.

With the precedent shown in scheme 1.3, and a synthetic need, we set about developing the first *Z*-selective cross-metathesis of allylic ethers[30] (table 1.1). We found that the CM between TBS ether **1.16** and 8-bromo-1-octene **1.17** proceeded readily with Ru catalyst **1.5**[31] and bis-hexafluoro-*tert*-butanol Mo catalyst **1.19**[32] affording the CM product **1.18** in acceptable yield, and with the predicted high *E* selectivity. When we

30. Mann, T. J.; Speed, A. W. H.; Shrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 8395–8400.

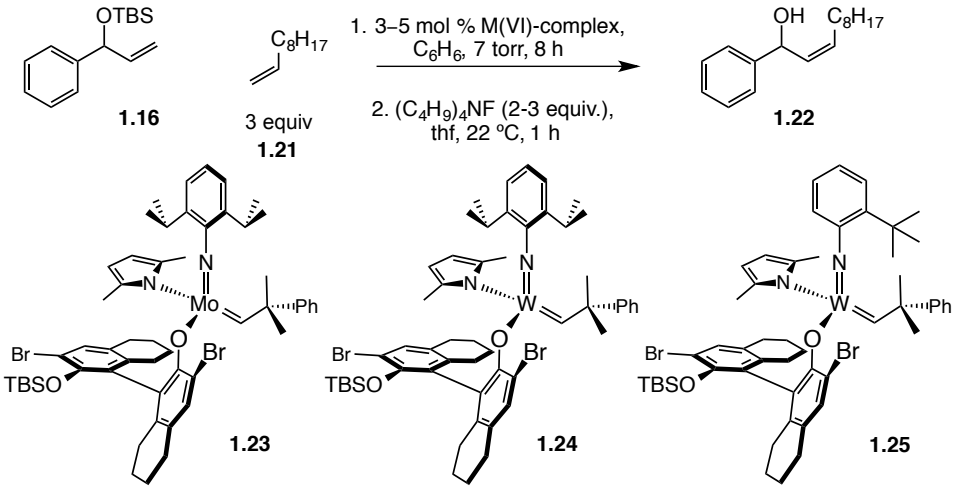
31. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

32. a) Murdzek, J. S.; Schrock, R. R. *Organometallics,* **1987**, *6*, 1373–1374. b) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886.

switched to MAP catalyst **1.9** we obtained 62% yield of **1.18** with 81% *Z*-selectivity. This moderate yield and selectivity is unsurprising based on the previously mentioned allylic amide study, the methyl substituents on **1.9** render it too large to react effectively with substrates containing an allylic branch. The situation improved dramatically when we employed **1.13**, and were able to obtain **1.18** in 69% yield and 95:5 *Z*:*E* selectivity. Tungsten based catalysts have been shown to be more *Z* selective than their Mo-based analogues[33] so we employed **1.20**, which was one of the only tungsten catalysts available at the time, and observed a single olefin isomer of the product, albeit with only 20% yield.

33. Jiang, A. J.; Zhao, Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 16630–16631.

Table 1.2. Catalyst Screening for Secondary TBS Allylic Ether Cross-Metathesis with 1-Decene[a]



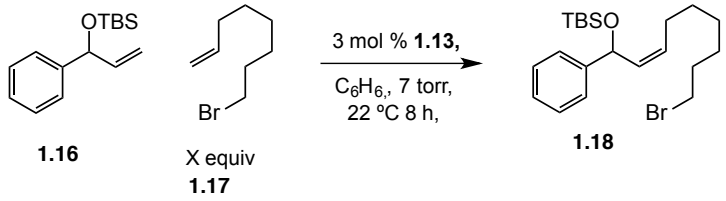
entry	complex; mol%	conv (%)[b,c]	yield (%)[d]	*Z:E*[c]
1	**1.5;** 5	95	83	5:95
2	**1.19**; 5	98	80	5:95
3	**1.9**; 5	55	47	55:45
4	**1.13**; 3	89	86	92:8
5	**1.20**; 5	17	14	47:53
6	**1.23**; 5	21	nd	53:47
7	**1.24**; 5	<2	na	na
8	**1.25**; 5	32	nd	92:8

a) Reactions performed under N_2 atmosphere with a vacuum of 7 torr (930 Pascal). b) Conversion refers to consumption of the limiting starting material. c) Determined by ^{1}H NMR analysis of unpurified mixtures. d) Yield of isolated and purified products, after exposure to $(C_4H_9)_4NF$. nd = not determined; na = not applicable.

We investigated these catalysts, and others, in the reaction between **1.16** and 1-decene **1.21** to afford **1.22** (table 1.2). Similar results as before were obtained with **1.5**, and with **1.19**, product was obtained in high yield and *E* selectivity (entries 1 and 2). Complexes **1.9** and **1.20** inexplicably fare worse when **1.21** was used as the excess cross partner, **1.22** was only obtained in 47 and 14% yield respectively, and as a nearly equal mixture of olefins in both cases (Table 1.1. vs Table 1.2 entries 3 and 5). Again, adamantyl imido Mo catalyst **1.13** proved to be the optimal catalyst, and **1.22** was

obtained in 86% yield and 92:8 *Z*:*E* selectivity. We also examined diisopropylphenyl imido catalyst **1.23**, which was structurally related to the optimal catalyst in allylic amide enantioselective ring-closing reactions,[20b] but only 21% conversion to a 53:47 mixture of olefins was obtained. The direct tungsten analogue **1.24**[34] failed to provide any product, and 2-*tert*-butylphenyl-imido catalyst **1.25**[35] gave only 32% conversion and 92% *Z* selectivity.

Table 1.3. Screening of Equivalents of 8-Bromo-1-Octene[a]



1.16 X equiv **1.17** **1.18**

entry	equiv. **1.17**	conv (%)[b,c]	yield (%)[d]	*Z*:*E*[c]
1	10	<2	na	na
2	3	72	65	95:5
3	2	79	69	95:5
4	1.5	67	65	90:10
5	1.0	56	45	91:9

a) Reactions performed under N_2 atmosphere with a vacuum of 7 torr (930 Pascal). b) Conversion refers to consumption of the limiting starting material. c) Determined by ^{1}H NMR analysis of unpurified mixtures. d) Yield of isolated and purified products. na = not applicable.

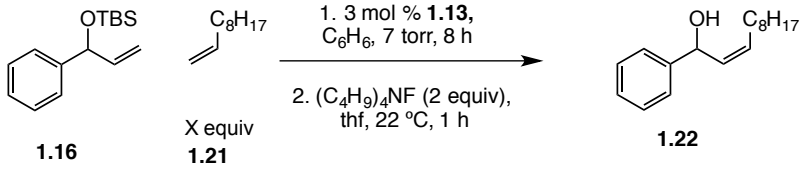
Having identified **1.13** as the optimal catalyst, we investigated the effect of cross-partner equivalents on the CM. In the case of **1.17** a large excess (10 equiv, table 1.3 entry 1) produced no reaction. This was surprising since based on our previous cross-metathesis report,[21] we thought larger excesses of the cross-partner would lead to a more

34. Jiang, A. J.; Simpson, J. H.; Muller, P.; Schrock, R. R. *J. Am. Chem. Soc.* **2009**, *131*, 7770–7780.

35. Schrock, R. R.; Jiang, A. J.; Marinescu, S. C.; Simpson, J. H.; Muller, P. *Organometallics,* **2010**, *29,* 5241–5251.

efficient reaction. Recalling previous studies in the group[36] we hypothesized that a gross excess of one olefin might lead to the catalyst engaging in degenerate processes with the excess olefin at the expense of productive reaction. Indeed, lowering the cross partner loading to 3 equiv lead to **1.18** in 65% yield and 95:5 *Z*:*E* selectivity, further reduction to 2 equiv lead to a slightly improved yield. Olefin selectivity and yield were slightly reduced at 1.5 and 1.0 equiv (entries 4 and 5).

Table 1.4. Screening of Equivalents of 1-Decene[a]



entry	equiv **1.21**	conv (%)[b,c]	yield (%)[d]	*Z*:*E*[c]
1	10	85	80	94:6
2	3	89	86	92:8
3	2	84	82	88:12
4	1.5	69	65	88:12

a) Reactions performed under N_2 atmosphere with a vacuum of 7 torr (930 Pascal). b) Conversion refers to consumption of the limiting starting material. c) Determined by ^{1}H NMR analysis of unpurified mixtures. d) Yield of isolated and purified products, after exposure to $(C_4H_9)_4NF$.

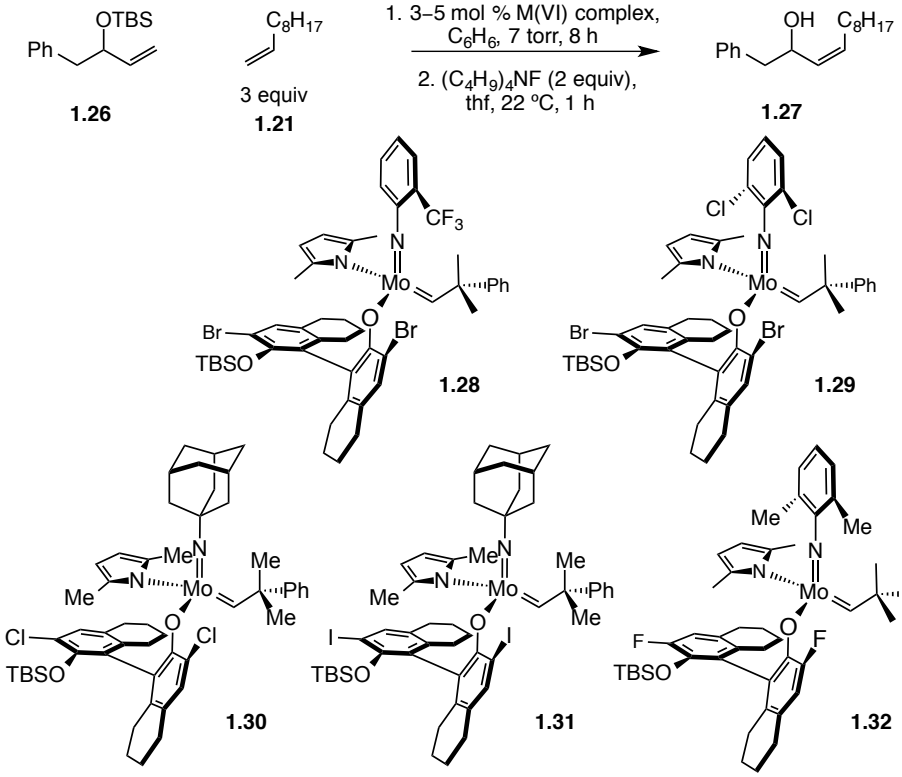
Equivalency screening with **1.21** lead to slightly different findings (table 1.4), in this case high conversion to **1.22** was observed even at 10 equiv. Optimal results were obtained at 3 equiv rather than 2 and a 1.0 equiv. reaction was not attempted. The most plausible explanation for these discrepancies is that under the 7 torr vacuum of the reaction **1.21** is appreciably volatile, whereas **1.17** is not, therefore a reaction which began with 10 equiv of **1.21** would over time have a lower loading of this olefin. While reactions at 100 torr are now frequently employed in our group when dealing with

36. a) La, D. S.; Ford, J. G.; Sattely, E. S.; Bonitatebus, P. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 11603–11604. b) La, D. S.; Sattely, E. S.; Ford, J. G.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 7767–7778.

slightly volatile olefins,[37] we did not have this same equipment at the time these allylic ether studies were conducted; the only options for pressure were 1 torr, 7 torr or sealed vials.

37. Kiesewetter, E. T.; O'Brien, R. V; Yu, M.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2013**, *135*, 6026–6029.

Table 1.5. Catalyst Screening for Benzyl Substituted TBS ether[a]



entry	complex; mol%	conv (%)[b,c]	yield (%)[d]	*Z:E*[c]
1	**1.9;** 5	43	35	54:46
2	**1.13**; 3	43	37	86:14
3	**1.28;** 5	95	91	64:36
4	**1.29**; 5	76	60	49:51
5	**1.30**; 2.5	67	nd	79:21
6	**1.31**; 3.5	20	nd	85:15
7	**1.32**; 5	>98	90	24:76
8	**1.20**; 5	38	25	95:5
9	**1.24**; 5	4	nd	nd
10	**1.25**; 5	30	nd	42:58

a) Reactions performed under N_2 atmosphere with a vacuum of 7 torr (930 Pascal). b) Conversion refers to consumption of the limiting starting material. c) Determined by ^{1}H NMR analysis of unpurified mixtures. d) Yield of isolated and purified products, after exposure to $(C_4H_9)_4NF$. nd = not determined.

As we moved on to additional substrates such as benzyl substituted TBS allylic ether **1.26** our standard catalyst **1.13** performed poorly (table 1.5, entry 2) and further catalyst screening was conducted. We applied a systematic strategy of investigating available imido groups, with our established brominated aryloxide ligand, as well as different aryloxides with our existing adamantyl-imido scaffold. Catalysts bearing electron-withdrawing imidos **1.28**[37] and **1.29** (entries 3 and 4) delivered higher conversion, although lower olefin selectivity. Closer inspection reveals that these low selectivities may arise from post-metathesis olefin isomerization, and that employing such catalysts at a lower reaction time may yield an improved reaction. The groups on the aryl oxide show a similar trend, a smaller and more electron withdrawing Cl unit (vs. Br in **1.13**), gives higher conversion and lower selectivity. The less electron withdrawing and more sizable iodine provided lower conversion and no improvement in selectivity. The catalyst containing a fluorinated aryloxide and an adamantyl imido was not screened, as this MAP catalyst is formed in only 7% conversion from its precursors.[38] Instead, we tested the fluorinated ligand along with a dimethylphenyl imido **1.32**[39] (entry 7), and we saw quantitative conversion, although low selectivity. Again, the prospect of using this catalyst along with a shortened reaction time can only be described as a missed opportunity. Tungsten based catalysts (entries 8–10) provided only low conversion.

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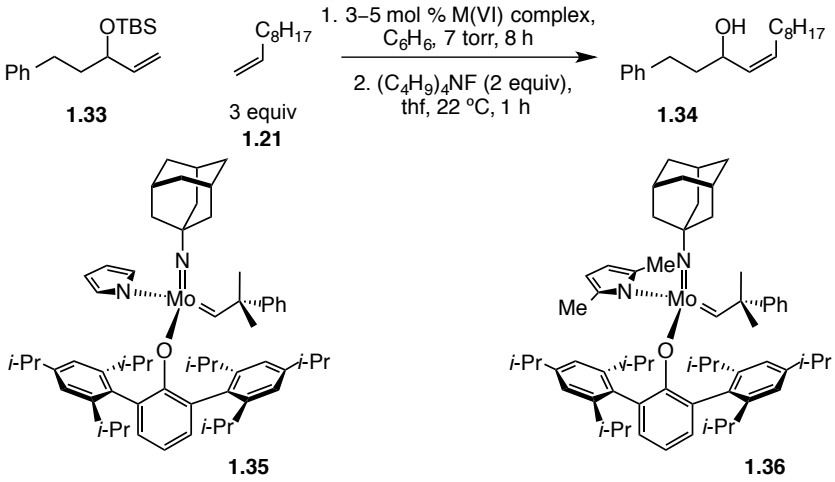
38. Yu. M; Ibrahem, I.; Hasegawa, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 2788–2799.

39. Carlsen, P. N.; Mann, T. J.; Hoveyda, A. H.; Frontier, A. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 9334–9338.

Table 1.6. Catalyst Screening for Phenyl Ethyl Substituted TBS ether[a]



entry	complex; mol%	conv. (%)[b,c]	yield (%)[d]	*Z:E*[c]
1	**1.9;** 5	52	48	54:46
2	**1.13**; 3	60	54	82:18
3	**1.28;** 5	95	91	52:48
4	**1.29**; 5	80	71	49:51
5	**1.30**; 2.5	79	nd	73:27
6	**1.31**; 3.5	28	nd	85:15
7	**1.32**; 5	96	90	18:82
8	**1.35**; 5	20	nd	88:12
9	**1.36**; 5	9	nd	55:45
10	**1.20**; 5	40	28	96:4
11	**1.24**; 5	6	nd	nd
12	**1.25**; 5	38	nd	42:58

a) Reactions performed under N_2 atmosphere with a vacuum of 7 torr (930 Pascal). b) Conversion refers to consumption of the limiting starting material. c) Determined by ^{1}H NMR analysis of unpurified mixtures. d) Yield of isolated and purified products, after exposure to $(C_4H_9)_4NF$. nd = not determined.

We conducted a similar catalyst screen using substrate **1.33** (table 1.6). The results were largely the same as in table 1.5; catalysts **1.28, 1.29** and **1.32** gave high yield, low selectivity and were not tried at lowered reaction times (entries 3,4 and 7). Tungsten catalysts performed poorly (entries 10–12). In an attempt to improve selectivity we also

inspected the hexaisopropylterphenyl ligand in combination with the adamantyl-imido to form catalysts **1.35** and **1.36**[40] (entries 8 and 9), but selectivity was not dramatically improved and conversions were very low.

Concurrent with these catalyst screening and reaction optimization endeavors, we also worked on expanding the substrate scope of the TBS allylic ether CM utilizing complex **1.13** (table 1.7). A polar phenyl ester derived from 4-pentenoic acid was well tolerated with substrate **1.16** and lead to **1.37** in 72% yield with 95% *Z* selectivity. We also explored the reaction with vinylcyclohexane to afford **1.38**, unfortunately, vinylcyclohexane was too volatile to be used under vacuum, and so we heated the reaction instead. While some product was formed, we were only able to isolate **1.38** in 19% yield. Consistent with our stereochemical model for *Z*-selectivity, this very bulky substituent provided perfect *Z*-selectivity. We also studied the TBS ether of commercially available 1-decen-3-ol to afford **1.39** (entry 3); the results were similar to those obtained in the transformation of **1.33** to **1.34** (61% yield 78% *Z* vs. 58% yield 82% *Z*, table 1.6 entry 2). These data established that the poor reactivity and selectivities in tables 1.5 and 1.6 was not due to any effects of the phenyl group in those substrates. We also investigated the CM of heteroaryl substituted allylic ethers, such as **1.40**, which was formed smoothly under our standard conditions. Neither 2, nor 3-pyrridyl containing substrates afforded any trace of products **1.41** and **1.42** respectively. Based on intermediates in the synthesis of some alkylidene catalysts that contain pyridine coordinated to the metal, and an isolated Mo-dipyridine structure[41] the failure to obtain **1.41** and **1.42** was unsurprising.

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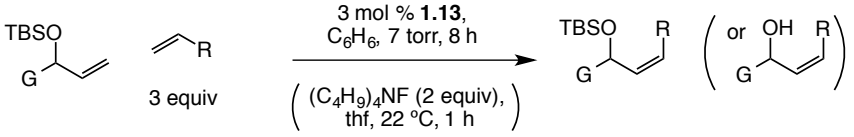
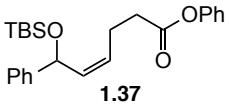
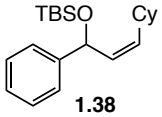
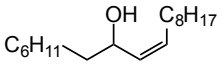
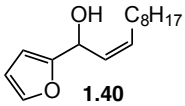
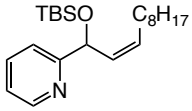
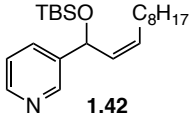
40. Flook, M. M.; Jiang, A. J.; Schrock, R. R.; Muller, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7962–7963.

41. a) Kiesewetter, E. T. *unpublished data* b) for a related study involving coordination of nitrogenous ligands to MAP complexes, see: Lichtsheidl, A. G.; Ng, V. W. L.; Muller, P.; Takase, M. K.; Schrock, R. R.; Malcolmson, S. J.; Meek, S. J.; Li, B.; Kiesewetter, E. T.; Hoveyda, A. H. *Organometallics*, **2012**, *31*, 4558–4564.

Table 1.7. Substrate Scope for Secondary TBS Allylic Ethers[a]



entry	Z-Alkene Product	conv. (%)[b,c]	yield (%)	*Z*:*E*[c]
1	 **1.37**	83	72[d]	95:5
2[d]	 **1.38**	25	19[e]	>98:2
3	 **1.39**	68	61[f]	78:22
4	 **1.40**	82	80[f]	95:5
5	 **1.41**	<2	na	na
6	 **1.42**	<2	na	na

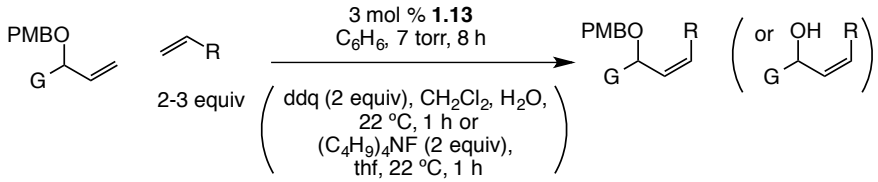
a) Reactions performed under N_2 atmosphere with a vacuum of 7 torr (930 Pascal). b) Conversion refers to consumption of the limiting starting material. c) Determined by ^{1}H NMR analysis of unpurified mixtures. d) reaction conducted in a sealed vial at 50 °C e) Yield of isolated and purifed products. f) Yield of isolated and purified products, after exposure to $(C_4H_9)_4NF$. na = not applicable.

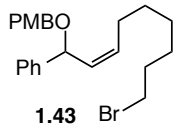
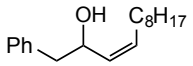
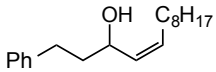
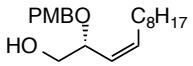
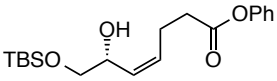
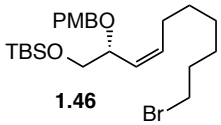
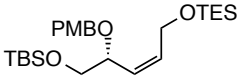
1.3.b Synthesis of PMB Allylic Ethers

In an effort to improve the reactivity and selectivity in the CM to form alkyl ethers **1.27**, **1.34** and **1.39** we expanded our efforts to include *para*-methoxybenzyl (PMB) ethers (table 1.8). The PMB analogue of our original substrate **1.16** reacted

smoothly with **1.17** to form **1.43** in high yield and selectivity. The formation of **1.27** and **1.34** proceeded with similar yield and conversion with a PMB containing substrate as with a TBS ether, but this time only a single isomer of the product was observed. The reasons for this difference will be discussed later. We next examined the differentially protected (*S*)–diol that would afford products **1.44** – **1.47**. We found this substrate, which was initially intended as an analogue of our allylic amide **1.12**, highly reactive and selective with a variety of cross partners with yields ranging from 70 to 87% and selectivities between 90:10 and >98:2. Of particular synthetic note was the differentially protected, enantiomericly enriched triol **1.47**, which after oxidation of the olefin could be elaborated into deoxy sugars.

Table 1.8. Substrate Scope for Secondary PMB Allylic Ethers[a]



entry	*Z*-alkene product	conv (%)[b,c]	yield (%)	*Z*:*E*[c]
1	 **1.43**	90	85[d]	>98:2
2	 **1.27**	43	39[f]	>98:2
3	 **1.34**	66	60[f]	>98:2
4	 **1.44**	93	87[e]	>98:2
5	 **1.45**	89	87[f]	90:10
6	 **1.46**	82	70[d]	92:8
7	 **1.47**	91	72[d]	92:8

a) Reactions performed under N_2 atmosphere with a vacuum of 7 torr (930 Pascal). b) Conversion refers to consumption of the limiting starting material. c) Determined by ^1H NMR analysis of unpurified mixtures. d) Yield of isolated and purifed products. e) Yield of isolated and purified products, after exposure to $(C_4H_9)_4NF$. f) Yield of isolated and purified products, after exposure to ddq.

1.3.c Synthesis of Alkyne Containing Allylic Ethers, and Mechanistic Implications

Encouraged by the formation of unhindered secondary ethers **1.44–1.47**, we turned our attention to alkyne containing TBS ethers (table 1.9). The product bearing a TIPS alkyne unit **1.48** was obtained readily in high stereochemical purity (entry 1). Phenyl alkyne containing TBS ethers were obtained in 60-68% yield as single olefin isomers (**1.49–1.51** entries 2-4). The electronics of the phenyl unit seemed to play no role in this transformation, phenyl, 4-methoxyphenyl and 4-(trifluoromethyl)phenyl units seemed to be equally well tolerated. Alkyl substituents, on the other hand, behaved very differently. Compound **1.52** bearing a *tert*-butyl group on the alkyne was obtained in 76% yield and 90:10 *Z*:*E*, but only after dropping the catalyst loading to 1.5 mol% and decreasing the reaction time to 1 h. Attempts to run this reaction under our standard conditions gave poor olefin selectivity. A substrate bearing an *n*-hexyl group (corresponding to **1.53**) gave no product at all. Furthermore, adding a stoichiometric amount of this substrate to otherwise productive reactions (those to form **1.48** and **1.49**) completely inhibited formation of the expected product. We propose that the alkyne data in aggregate can be explained due to coordination of the molybdenum catalyst to exposed Lewis basic alkynes.[42] The highly exposed *n*-hexyl alkyne sequestered the catalystcompletely, shutting down reactivity. Phenyl alkynes participated in a reversible coordination, which attenuated catalyst reactivity, inhibiting post metathesis isomerization and leading to high selectivity. While the sterically encumbered *tert*-butyl alkyne had very little catalyst coordination and behaved as if the ether contained only a very small substituent, leading to high reactivity and relatively lower selectivity.

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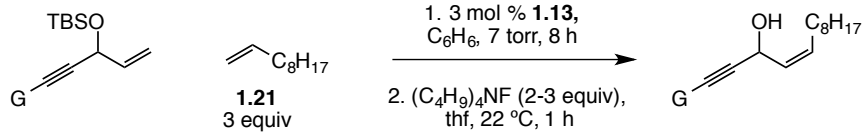
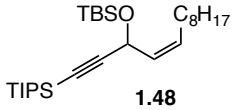
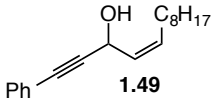
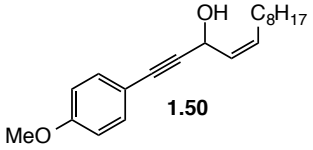
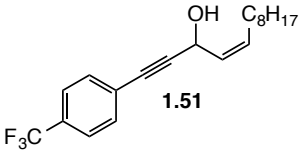
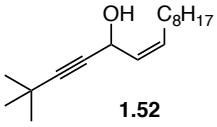
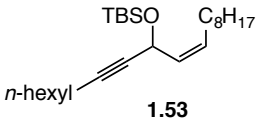
42. Kim, K. H.; Ok, T.; Lee, K.; Lee, H.-S.; Chang, K. T.; Ihee, H.; Sohn, J.H. *J. Am. Chem. Soc.* **2010**, *132*, 12027–12033.

Table 1.9. Substrate Scope for Alkyne Substituted TBS Allylic Ethers[a]



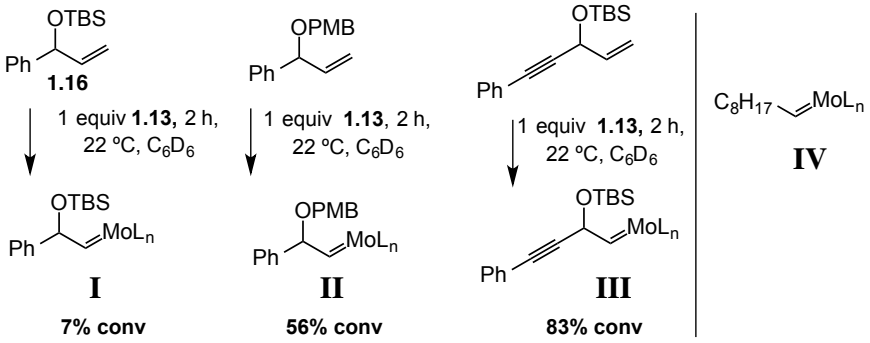
entry	*Z*-Alkene Product	conv (%)[b, c]	yield (%)[d]	*Z*:*E*[c]
1	 **1.48** (isolated after desilylation)	87	84	92:8
2	 **1.49**	72	68	>98:2
3	 **1.50**	66	60	>98:2
4	 **1.51**	73	64	>98:2
5	 **1.52**	84	76	90:10
6	 **1.53**	<2	na	na

a) Reactions performed under N_2 atmosphere with a vacuum of 7 torr (930 Pascal). b) Conversion refers to consumption of the limiting starting material. c) Determined by ^1H NMR analysis of unpurified mixtures. d) Yield of isolated and purified products, after exposure to $(C_4H_9)_4NF$. na = not applicable

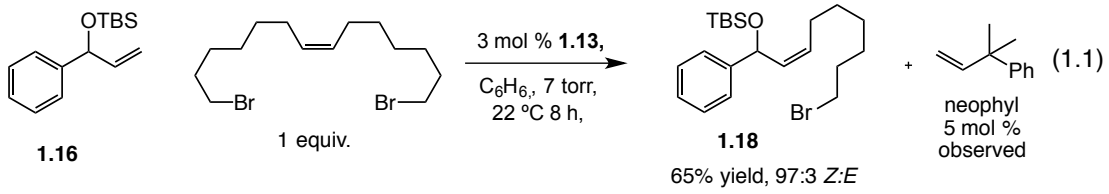
In an attempt to explain the differences between TBS, PMB and TBS-alkyne containing ethers, we treated a substrate of each class with a stoichiometric amount of catalyst **1.13**, in the absence of any cross-partner (scheme 1.4). After two hours, in benzene, only 7% conversion to a new alkylidene was observed with the TBS ether **1.16**. In the same amount of time, 56% of the PMB ether and 83% of the alkyne containing ether were consumed. These data show that the alkylidene derived from the TBS ether

(**I**) formed slower than its PMB analogue (**II**), which was slower yet than the alkyne containing ether (**III**). This trend also relates to their selectivity, alkyne ethers were more selective than PMB ethers, which are more selective than TBS ethers.

Scheme 1.4. Differing Rates of Alkylidene Formation[a]



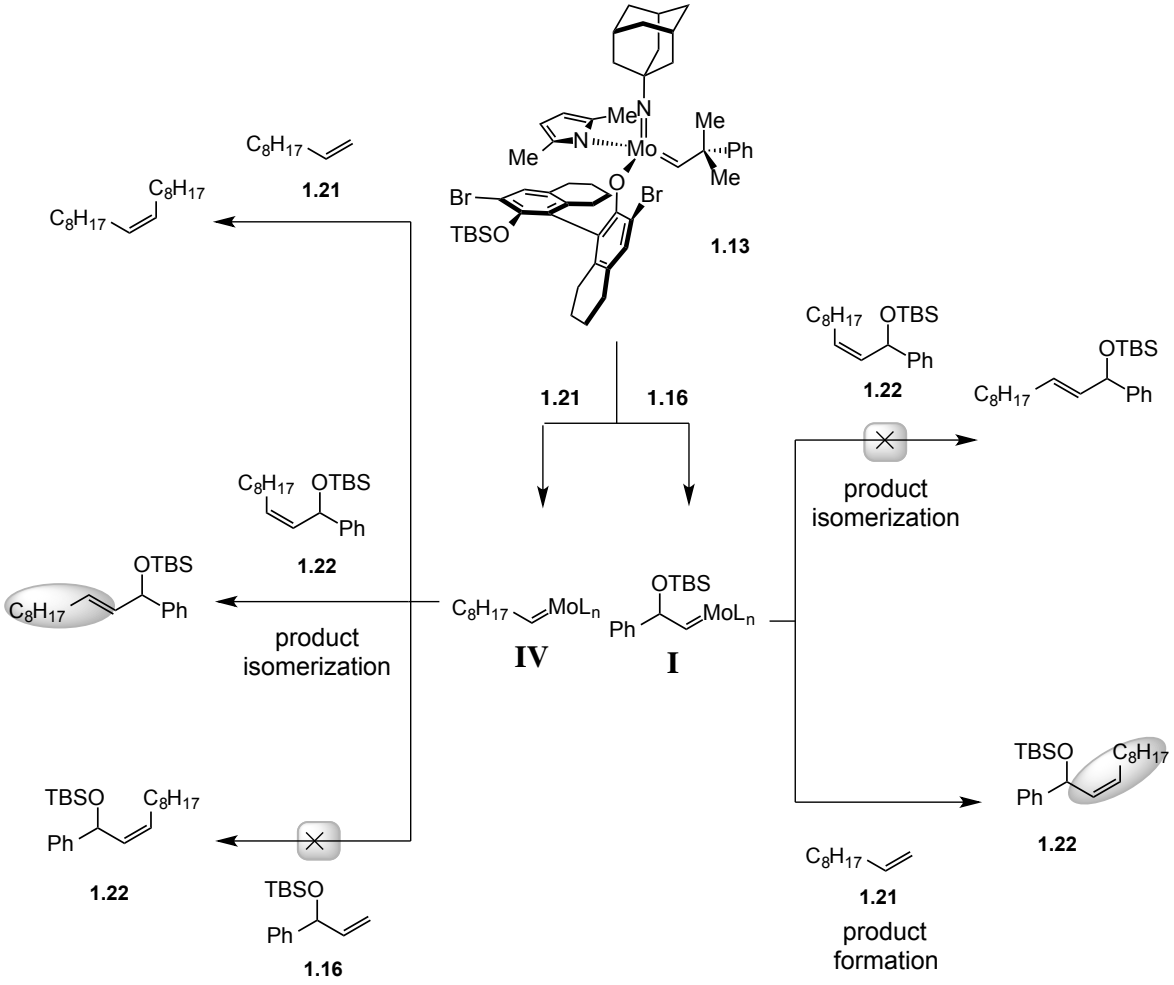
While we had demonstrated the formation of allylic ether substituted alkylidenes **I**-**III** we were not yet sure that these were viable intermediates in the catalytic cycle. We then exposed allylic ether **1.1** to the *Z*-homodimer of **1.17** and found that even in a sealed vial, product could be obtained with similar yields and selectivities as under the standard conditions (eq. 1.1). Additionally, the neophyll unit derived from the starting alkylidene is clearly evident in the ^{1}H NMR of the crude reaction mixture. This demonstrates that the first catalytic cycle occurs from the allylic ether substituted alkylidene, otherwise the catalyst would have performed a productive CM between the neophyl initiator and the internal olefin, and neophyl would not be observed.



Together we believe these data support the kinetic hypothesis presented in scheme 1.5, the CM between **1.16** and **1.21** to form **1.22** is presented as a typical reaction. Under the reaction conditions, the metathesis catalyst has a choice of two alkylidenes to form, the one derived from the allylic ether **I**, or the one derived from the unhindered cross-

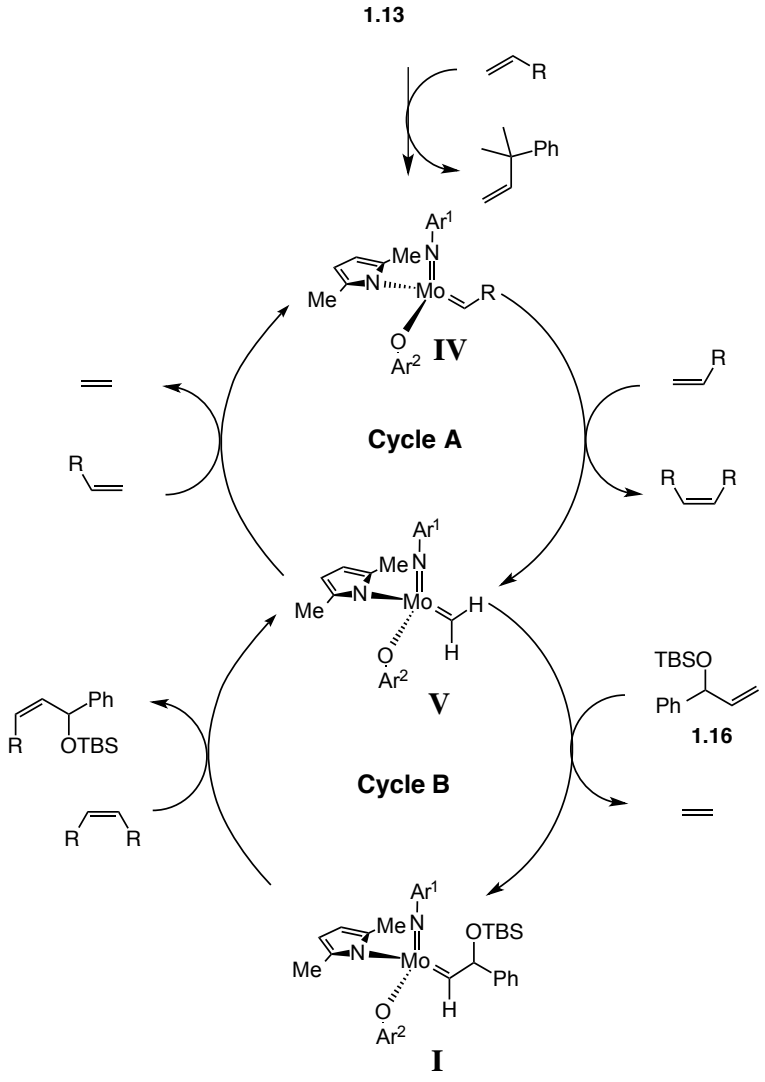
partner (**IV**). We propose that **I** is more likely to react with cross-partner **1.21** to form product, than **IV** is to form product through reaction with **1.16**. This can be rationalized through an enthalpic and a statistical argument. With **I**, the enthalpic penalty for reaction with a sterically demanding olefin has already been paid, whereas with **IV** this penalty is assessed in the formation of putative metallacyclobutane. Statistically, the reaction is usually performed with a two to three fold excess of the unhindered cross-partner, so the odds of alkylidene **IV** encountering substrate **1.16** are lower than the probability of **I** encountering the cross partner. This is particularly true later in the reaction when the amount of substrate **1.16** is substantially diminished. We additionally propose that alkylidene **IV** is primarily responsible for post-metathesis isomerization through formation of a trisubstituted metallacycle. Under vacuum, and in a concentrated excess of olefins, methylidenes, which would take the product back to one of the starting materials and a new alkylidene, are unlikely to be present. Therefore, our observed post-metathesis isomerization must be from reaction by either **I** or **IV**. The trisubstituted metallacycle that would form from **1.22** and **I** is very sterically hindered and unlikely to form, whereas that from **IV** and **1.22** is much easier to imagine. We then suggest, that both the reactivity, and the selectivity of sterically hindered cross-metatheses conducted with group (VI) initiators are controlled by the rate at which the substrate (vs. unhindered cross partner) derived alkylidene **I** (or **II** or **III**) are formed. The substrates that form this alkylidene faster should be more reactive and more selective.

Scheme 1.5. An Explaination of Allylic Ether Selectivity[a]



We propose the two productive catalytic cycles indicated in scheme 1.6. The catalyst first initiates with the α–olefin to form alkylidene **IV** which mainly engages with additional equivalents of α–olefin, forming its homodimer, and methylidene **V**. Methylidene **V** can then form alkylidene **I** (cycle A), or **IV**. Both of these situations release ethylene. Once **IV**, is generated it can react with the homodimer of the α–olefin to produce product and reform methylidene **V**. The identity of the allylic ether is critical for determining how much of its lifetime the catalyst spends in product forming cycle B. The amount of time in cycle B, determines both the extent of productive reaction, and for reasons discussed in scheme 1.5, the *Z*-selectivity.

Scheme 1.6. Productive Catalytic Cycles in Allylic Ether CM



1.4 Synthesis of *Z*-Allylic Alcohol Containing Ene-Diyne Natural Products

Having established a method, its scope and elucidated some mechanistic points, we applied our CM method to the synthesis of some small allylic alcohol containing natural products (scheme 1.6). We initially targeted falcarindiol **1.58**.[43] Our CM reaction

43. a) For the isolation, see: Bohlmann, F.; Niedballa, U.; Rode, K. M. *Chem. Ber.* **1966,** *99*, 3552–3558. b) For the first total synthesis, see: Zheng, G.; Lu, W.; Cai, J. *J. Nat. Prod.* **1999**, *62*, 626–628. c) For a synthesis closely related to ours, see: Ratnayaka, A. S.; Hemscheidt, T. *Org. Lett.* **2002**, *4*, 4667–4669.

between TIPS protected enantiomerically enriched **1.54** and 1-nonene **1.55** provided the product in 94% yield and 92% *Z* selectivity. Unfortunately, we had to increase the cross-partner loading to 10 equiv due to the increased volatility of 1-nonene versus 1-decene. Due to the increased cross-partner loading we also had to increase the catalyst loading to 4.5 mol% from our usual 3 mol%. The free alkyne was then subjected to a well precedented[43] Cu-catalyzed Cadiot-Chodkiewicz [44] cross-coupling that afforded the desired natural product in 64% yield. We were then intrigued by our ability to efficiently produce ethnopharmacological compound **1.61**, and its C16 epimer, due to some discrepancies in the literature over the configuration of this stereocenter.[45] The initial CM proceeded well under our standard conditions, and the cross-couplings both afforded their respective products in 64% yield. Unfortunately, the distal relationship between C11 and C16 results in **1.61** and ***epi*-1.61** having identical proton and carbon NMR spectra. Optical rotations were obtained over several wavelengths, but did not exhibit differences that would enable identification of the natural product. Never the less, we feel these syntheses illustrate the synthetic utility of combining CM with traditional cross-coupling methods, both are bond-forming reactions that can be applied in the late stage of a synthesis to enable rapid diversification of starting materials.

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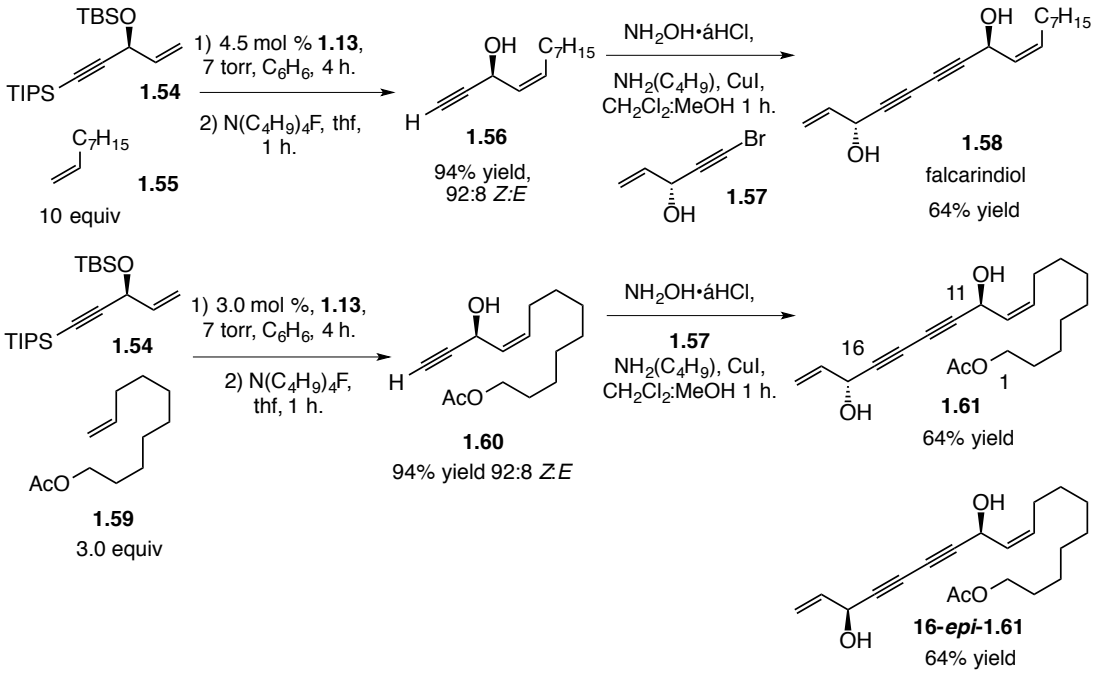
44. a) Chodkiewicz, W. *Ann. Chim. Paris* **1957**, *2*, 819. b) Cadiot, P.; Chodkiewicz, W. in *Chemistry of Acetylenes* Viehe, H. G. Ed; Marcel Dekker: New York, **1969**, pp. 597.

45. a) Liu, J.-H.; Zschocke, S.; Bauer, R. *Phytochemistry* **1998**, *49*, 211–213 b) Kobaisy, M.; Abramowski, Z.; Lermer, L.; Saxena, G.; Hancock, R. E. W.; Towers, G. H. N.; Doxsee, D.; Stokes, R. W. *J. Nat. Prod.* **1997**, *60*, 1210–1213. c) Meng, L.-Z.; Huang, W. H.; Wang, C.-Z.; Yuan, C.-S.; Li, S.-P. *Molecules* **2014**, *19*, 6142–6162.

Scheme 1.6. Synthesis of Diyne Containing *Z*-Allylic Alcohol Natural Prodcuts



As a final demonstration of this method, we turned to the more complicated trocheliophorolide C.[46] We had to substantially alter our CM protocol to achieve acceptable yields. The typical allylic ether CM had been performed with an allylic ether that had to be prepared in at least two steps, with unhindered partners that were either commercial materials, or prepared in one step. In the case of CM between **1.62** and **1.63**[47] both of the CM partners took four steps to prepare, and were of equal value. Through our previous reactions we had also established that allylic ethers do not self-metathesize to form 1,4-bisallylic ethers, whereas the unhindered partner typically does. In the case of **1.63**, unlike all previous olefins used, the self-metathesis product is a solid, which causes the reaction to turn heterogeneous as it forms. In the case of allylic ethers, unlike with allylic amides, the reaction halts if the mixture becomes a solid. So, in order to limit formation of the self-metathesis product of **1.63**, we reversed our normal stoichiometry and used **1.63** as the limiting reagent. The excess of valuable **1.62** that was

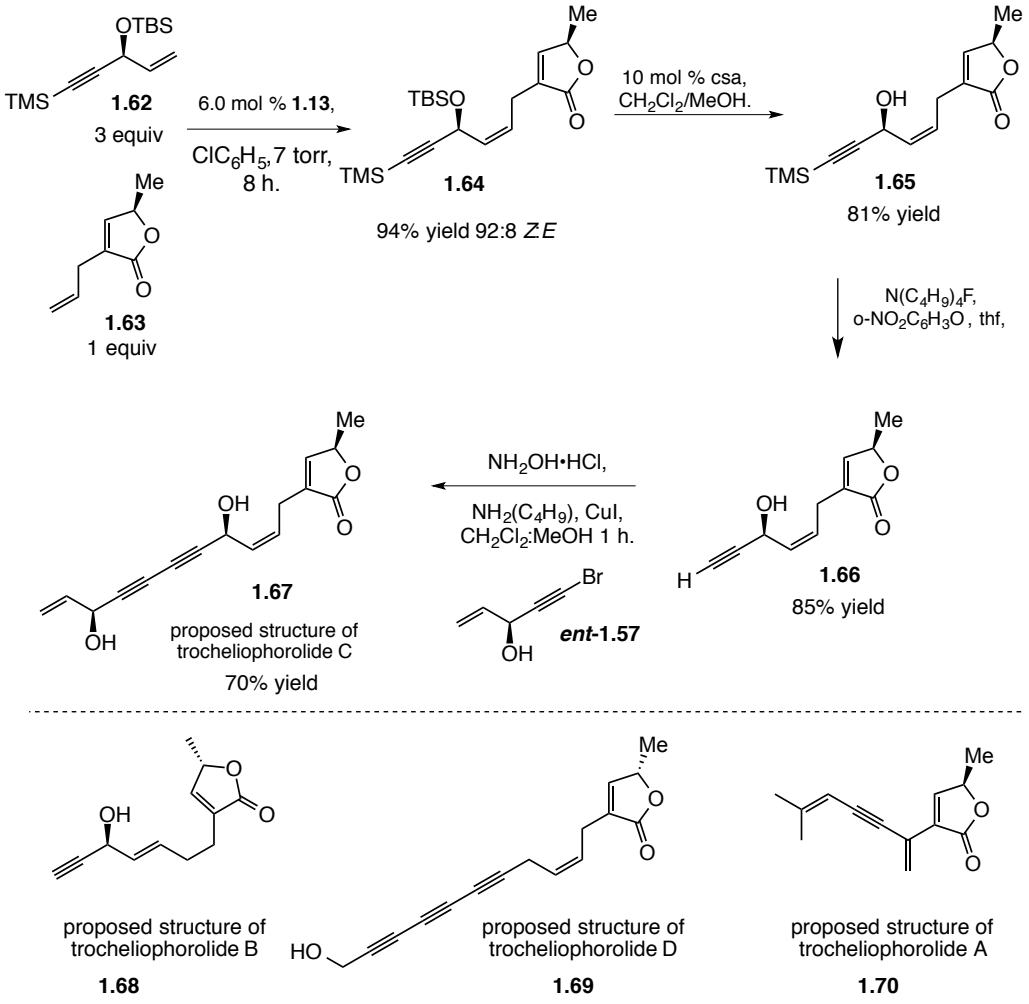
46. Rezanka, T.; Dembitsky, V. M. *Tetrahedron* **2001**, *57*, 8743–8749.

47. Jiang, S.; Liu, Z.-H.; Sheng, G.; Zeng, B.-B.; Cheng, X.-G.; Wu, Y.-L.; Yao, Z.-H. *J. Org. Chem.* **2002**, *67*, 3404–3408.

not consumed in the reaction could be recovered and reused, increasing the synthetic efficiency of our protocol. We additionally employed chlorobenzene as the reaction solvent as this is substantially less volatile than benzene, in order to prevent a solidification of the reaction medium. Having made these changes, after a doubling of our catalyst loading we were able to obtain **1.64** in 56% yield with a 92:8 *Z*:*E* ratio. This material had to be desilylated in a stepwise manner, first with 10 mol% camphorsulfonic acid, then with tetrabutyl-ammonium fluoride buffered with nitrophenol.[48] Exposure of the material to unbuffered tetrabutyl-ammonium fluoride lead to decomposition, and the buffered solution was not capable of removing the TBS ether. With **1.66** in hand we applied copper cross-coupling to obtain our desired product **1.67** in 70% yield. Unfortunately, the spectra of **1.67** did not match those from the isolation paper. The isolation NMR was only presented as tabulated data, the spectrum was not included, nor was the solvent of the NMR indicated. Therefore we took our NMR spectra in a variety of solvents, none of which matched the isolation report. The allylic protons of the allyl furanone are significantly downfield from the isolation data, and do not change substantially along the synthetic route from **1.63** to **1.67**.

48. Myers, A. G.; Goldberg, S. D. *Angew. Chem. Int. Ed.* **2000**, *39*, 2732–2735.

Scheme 1.7. Synthesis of the Reported Structure of Trocheliophorlide C



Based on previous reports, our discrepancies with the isolation report were not surprising. The Trost group has synthesized the reported structure of trocheliophorolide B **1.68**,[49] and the Kim group has made proposed trocheliophorolide D **1.69**.[50] These two compounds also did not match with the spectra reported in the same isolation paper that proposed **1.67**. Neither of these two groups proposes what the isolated structure might be. Even after DFT aided NMR simulations we were also unable to suggest a structure for the trocheliophorolides, and believe there must be some error in the reported data.

49. Trost, B. M.; Quintard, A. *Org. Lett.* **2012**, *14*, 4698–4700.

50. Hwang, S.; Kim, J. H.; Kim, H. S.; Kim, S. *Eur. J. Org. Chem.* **2011**, 7414–7418.

Additionally, the presumably unstable **1.70** has been the subject of several masters theses, but not completed.[51] It is unlikely that **1.70** corresponds to any natural product.

1.5 Conclusions

We have established the first, and still only, method for *Z*-selective cross-metathesis to form secondary allylic ethers and their alcohols. We have explored the scope of ethers that can be employed in this transformation, including aryl, alkyl and alkynyl groups. We have also investigated the beneficial effect of employing a PMB protecting group rather than a *tert*-butyldimethylsilyl protecting group. Additionally we have applied this method to the synthesis of three natural products, and disproved the reported structure of a fourth.

1.6 Experimental

General**.** All reactions were carried out in oven-dried (135 °C) or flame-dried glassware under an inert atmosphere of dry N_2 unless otherwise stated. All substrates were either dried by azeotropic distillation with C_6H_6 or distilled from CaH_2 prior to use in reactions with Mo- and W-based complexes. Infrared (IR) spectra were recorded on a Bruker FT-IR Alpha (ATR Mode) spectrometer. Bands are characterized as strong (s), medium (m), weak (w) or broad (br). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz) or Varian VNMRS 400 (400 MHz), Varian VNMRS 500 (500 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuteration as the internal reference ($CDCl_3$: 7.26 ppm, C_6D_6: 7.16 ppm). ^{19}F chemical shifts are reported in ppm from BF_3•Et_2O as an external reference. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, br = broad, m = multiplet, ap = apparent), and coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Unity INOVA 400 (100 MHz) or Varian VNMRS 500 (125 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal reference ($CDCl_3$: 77.16 ppm). *Z*:*E* ratios were determined by

51. a) Spencer, W. T. *Masters Thesis* Rochester Institute of Technology, Rochester, NY, **2008.** b) Dorn, S. *Masters Thesis* Rochester Institute of Technology, Rochester, NY, **2010**. c) Swartzenberg, J. *Masters Thesis* Rochester Institute of Technology, Rochester, NY **2012**.

analysis of the crude reaction mixture by ^{1}H NMR spectra. High–resolution mass spectrometry was performed on a Micromass LCT ESI-MS (positive mode) and JEOL Accu TOF Dart (positive mode) at the Boston College and the University of Illinois Mass Spectrometry Facilities. Optical rotation values were recorded on a Rudolph Research Analytical Autopol IV polarimeter, or an Atago AT-300 polarimeter

Vacuum Pumps: Edwards RV8 two stage rotary vane pump or a KNF Laboport Diaphragm pump connected to a Welch Labaid vacuum controller generates a vacuum of 7 or 100 torr at point of connection to the reaction vessel.

Solvents: Solvents were purged with Ar and purified under a positive pressure of dry Ar by a modified Innovative Technologies purification system. Toluene (Fisher), dichloromethane (Fisher), benzene (Alfa Aesar) and pentane (Fisher, purification: *n*-pentane was allowed to stir over concentrated H_2SO_4 for three days, washed with water, followed by a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, and filtered before use in a solvent purification system) were passed successively through activated copper and alumina columns. Tetrahydrofuran was purchased from Aldrich and purified by distillation from sodium benzophenone ketyl immediately prior to use. Acetone was purchased from Pharmco-AAPER and used as received. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Fisher) under typical bench-top conditions.

Metal-based Complexes: Mo bis-alkoxide complex **1.19** was prepared according to a previously reported procedure.[32] Ruthenium-based complex **1.5** was purchased from Aldrich and recrystallized from pentane/dichloromethane prior to use. Mo mono-aryloxide pyrrolide MAP complexes **1.9**,[21] **1.13**,[25] **1.28**,[37] **1.30**,[38] **1.31**,[38] **1.32**,[39] **1.35**[40] and **1.36**[40] were prepared *in situ* as 0.1 M solutions in benzene. Tungsten MAP complexes **1.20**,[33] **1.24**,[34] and **1.25**[35] were prepared and isolated according to published procedures.

Reagents:

Allyl alcohol was purchased from Aldrich and used as received.

α-Vinyl benzyl alcohol was purchased from Aldrich and used as received.

Acrolein was purchased from Aldrich, and distilled from flame dried $CaSO_4$ prior to use.

***d_6*-Benzene** was purchased from Cambridge Isotope Laboratories and distilled from Na onto activated 4 Å molecular sieves prior to use.

***tert*-Butyldimethylsilyl chloride** was purchased from Strem and used as received.

***n*-Butylamine** was purchased from Aldrich and used as received.

***n*-Butyllithium** in hexanes was purchased from Strem and titrated before use.

***N*-Bromosuccinimide** was purchased from Aldrich and recrystallized from boiling water prior to use.

Borane•Me_2S was purchased from Aldrich and used as received.

8-Bromo-1-octene was purchased from Aldrich and vacuum distilled from CaH_2 before use.

Camphorsulfonic acid was purchased from Aldrich and used as received.

Chlorobenzene was purchased from Aldrich and distilled from CaH_2 under vacuum prior to use.

***d*–Chloroform** was purchased from Cambridge Isotope Laboratories and stored over activated 4 Å molecular sieves prior to use.

Cu salts were purchased from Strem and used as received.

1-Decene was purchased from Aldrich and vacuum distilled from CaH_2 before use.

1-Decene-3-ol was purchased from Aldrich and used as received.

9-Decenyl-1-acetate was purchased from TCI and vacuum distilled from CaH_2 before use.

2,3-Dichloro-5,6-dicyano-*p*-benzoquinone was purchased from Aldrich and used as received.

Imidazole was purchased from Lancaster and recrystallized from acetone/hexanes prior to use.

Lipase PS was obtained from Amano, stored at 4 ºC and used as received.

γ–MnO_2 was prepared according to a literature procedure.[52]

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52. For preparation of γ-MnO_2, see: *Encyclopedia of Organic Reagents*; L. A. Paquette, Ed.; John Wiley & Sons; West Sussex, England, 1995.

Methanol was purchased from Aldrich and dried over 4 Å activated molecular sieves and sparged with N_2 prior to use.

4-Methoxybenzyl alcohol was purchased from Aldrich and used as received.

4-Methoxybenzyl-2,2,2-trichloroacetimidate was purchased from Aldrich and used as received or prepared according to a literature procedure.[53]

4 Å Molecular sieves were purchased as beads from Aldrich, ground into a powder, activated in an oven at 135 ºC and cooled under N_2 before use.

***o*-Nitrophenol** was purchased from Aldrich and used as received.

1-Nonene was purchased from Aldrich and vacuum distilled from CaH_2 before use.

Potassium carbonate was purchased from Fisher Scientific and used as received.

Pyridinium *para*-toluenesulfonate was purchased from Aldrich and used as received.

Silver nitrate was purchased from Strem and used as received.

Sodium hydride (60 % in mineral oil) was purchased from Aldrich and used as received.

Tetra-*n*-butyl ammonium fluoride trihydrate was purchased from Acros and used as a 1 M solution in tetrahydrofuran.

Trichloroacetonitrile was purchased from Aldrich and used as received.

Triisopropylsilyl acetylene was purchased from Aldrich and used as received.

Trimethylsilyl acetylene was purchased from Aldrich and used as received.

Vinylbenzyl alcohol was purchased from Aldrich and used as received.

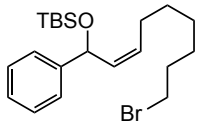
Vinyl acetate was purchased from Aldrich and used as received.

Vinyl magnesium bromide was purchased from Aldrich and used as received.

General Procedure for Mo-catalyzed Cross-Metathesis. In an N_2-filled glove box, an oven-dried 8 mL vial equipped with a stir bar was charged with allylic alcohol **1.16** (19.5 mg, 0.0785 mmol), 8-bromo-1-octene **1.17** (26 μL, 0.16 mmol, 2 equiv); then a solution of **1.13** in benzene (39 μL, 0.0024 mmol, 3 mol %). The vial was capped with a septum vented by an 18-gauge needle; the vessel was immediately placed under a vacuum of 7

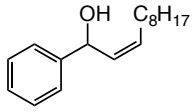
53. R. Chegondi, M. M. L. Tan, P. R. Hanson, *J. Org. Chem.* **2011**, *76*, 3909–3916.

torr and the mixture was allowed to stir for 8 h.[54] The reaction was quenched by removal from the glove box and by addition of $CDCl_3$ (% conversion and *Z:E* selectivity determined by ^{1}H NMR of the unpurified mixture). Purification by silica gel chromatography (50:1 hexanes:CH_2Cl_2) afforded **1.18** as yellow oil (21.7 mg, 0.0527 mmol, 67% yield, 95% *Z*).



1.18

(*Z*)-((9-Bromo-1-phenylnon-2-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (1.18): Following the general procedure, to a vial containing **1.16** (19.5 mg, 0.0785 mmol), 8-bromo-1-octene **1.17** (26 μL, 0.16 mmol, 2 equiv) was added, followed by a solution of **1.13** (39 μL, 0.0024 mmol, 3 mol %). The solution was allowed to stir under a vacuum of 7 torr for 8 h; purification of the resulting residue by silica gel chromatography (50:1 hexanes:CH_2Cl_2) afforded **1.18** as yellow oil (21.7 mg, 0.0527 mmol, 67% yield, 95% *Z*). **IR (neat):** 2928 (w), 2855 (w), 1461 (w), 1252 (w), 1063 (m), 834 (m), 775 (m), 738 (w), 697 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.32 (m, 4H), 7.21 (m, 1H), 5.67–5.61 (m, diagnostic signal for *E* isomer, 1H) 5.55–5.48 (m, 2H), 5.44–5.35 (m, 1H), 3.41 (t, *J* = 6.4 Hz, 2H), 2.28–2.17 (m, 2H), 1.90–1.82 (m, 2H), 1.54–1.26 (m, 6H) 0.92 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 144.9, 134.1, 129.1, 128.4, 127.0, 125.9, 70.5, 34.1, 32.9, 28.8, 28.3, 28.1, 26.1, 18.5, –4.2, –4.5; **HRMS (ESI+):** Calcd for $C_{21}H_{34}{}^{79}BrOSi$ $[M–H]^+$: 409.1562; found: 409.1572.

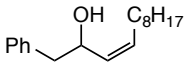


1.22

(*Z*)–1-Phenylundec-2-en-1-ol (1.22): Following the general procedure, to a vial containing **1.16** (18.2 mg, 0.0733 mmol), 1-decene **1.21** was added (41 μL, 0.22 mmol, 3

54. It should be noted that under these conditions much of the benzene is removed *in vacuo*, and the reaction runs essentially neat. Residual benzene is typically observed in the crude ^{1}H NMR.

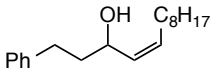
equiv) followed by a solution of **1.13** (37 μL, 0.0022 mmol, 3 mol %). The solution was allowed to stir under a vacuum of 7 torr for 8 h; subsequent desilylation was effected by exposure to a solution of 1.0 M tetra-*n*-butyl ammonium fluoride in thf for 1 h (146 μL, 0.146 mmol, 2 equiv). The solution was diluted by addition of Et_2O to precipitate tetra-*n*-butyl ammonium fluoride. The resulting suspension was filtered through a short plug of silica gel, was further washed with Et_2O, and the filtrate was concentrated *in vacuo* and purified by silica gel chromatography (30:1 hexanes:Et_2O) to afford **1.22** as yellow oil (15.5 mg, 0.0632 mmol, 86% yield, 95% *Z*). **IR (neat):** 3342 (br), 2955 (m), 2922 (s), 2853 (m), 1493 (w), 1452 (m), 1378 (w), 1261 (w), 1192 (w), 1029 (m), 910 (w), 844 (w), 804 (m), 739 (m), 697 (s), 650 (w), 512 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.51–7.31 (m, 4H), 7.31–7.19 (m, 1H), 5.77 (diagnostic signal for *E* isomer dt, *J* = 15.3, 6.4 Hz, 1H). 5.75–5.40 (m, 3H), 2.37–2.06 (m, 2H), 1.79 (s, 1H), 1.40 (m, 3H), 1.35–1.11 (m, 12H), 1.00–0.79 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 143.9, 132.7, 132.0, 128.6, 127.6, 126.0, 69.9, 32.0, 29.7, 29.6, 29.50, 29.4, 27.9, 22.8, 14.3; **HRMS (ESI+):** Calcd for $C_{17}H_{25}$ $[M+H-H_2O]^+$: 229.19563; found: 229.19578.



1.27

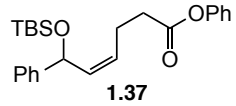
(*Z*)-1-Phenyldodec-3-en-2-ol (1.27): Following the general procedure, to a vial containing the requisite allyl silyl ether **1.26** (18.8 mg, 0.0716 mmol), was added 1-decene **1.21** (41 μL, 0.22 mmol, 3 equiv) followed by a solution of **1.13** (72 μL, 0.00430 mmol, 3 mol %). The solution was allowed to stir under a vacuum of 7 torr for 8 h; desilylation was effected by exposure to a 1.0 M solution of tetra-*n*-butyl ammonium fluoride in thf for 1 h (142 μL, 0.142 mmol, 2 equiv). The resulting mixture was diluted with Et_2O to precipitate tetra-*n*-butyl ammonium fluoride, the suspension was filtered through a short plug of silica gel, which was washed with Et_2O, then the filtrate was concentrated *in vacuo* and purified by silica gel chromatography (20:1 hexanes:Et_2O) to afford **1.27** as yellow oil (7.2 mg, 0.028 mmol, 38% yield, 76% *Z*). **IR (neat):** 3348 (br), 3086 (w), 3063 (w), 3028 (w), 3005 (m), 2923 (s), 2853 (m), 1496 (w), 1457 (m), 1378 (w), 1315 (w), 1270 (w), 1078 (m), 1028 (m), 743 (m), 699 (s), 595 (w); **^{1}H NMR (400**

MHz, $CDCl_3$): δ 7.32–7.26 (m, 2H), 7.23–7.18 (m, 3H), 5.65 (diagnostic signal for *E* isomer dt, *J* = 15.5, 6.4 Hz, 1H). 5.58–5.33 (m, 2H), 4.64 (ddd, *J* = 7.1, 7.1, 7.1 Hz, 1H), 2.79 (dddd, *J* = 13.4, 13.4, 13.4, 6.6 Hz, 2H), 2.05–1.84 (m, 2H), 1.53 (s, 1H), 1.41–1.05 (m, 12H), 0.86 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 138.0, 132.9, 131.5, 129.7, 128.6, 126.6, 69.0, 44.3, 32.0, 29.6, 29.6, 29.4, 27.9, 27.9, 22.8, 14.3; **HRMS (ESI+):** Calcd for $C_{18}H_{27}$ $[M+H–H_2O]^+$: 243.21128; found: 243.21214.



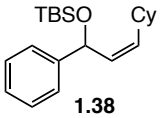
1.34

(*Z*)-1-Phenyltridec-4-en-3-ol (1.34): Following the general procedure, to a vial containing the requisite allyl silyl ether **1.33** (17.9 mg, 0.0648 mmol), was added 1-decene **1.21** (37 μL, 0.19 mmol, 3 equiv) followed by a solution of **1.13** (32 μL, 0.0019 mmol, 3 mol %). The solution was allowed to stir under a vacuum of 7 torr for 8 h; desilylation was effected by exposure to a 1.0 M solution of tetra-*n*-butyl ammonium fluoride in thf for 1 h (130 μL, 0.130 mmol, 2 equiv). The resulting mixture was diluted with Et_2O to precipitate tetra-*n*-butyl ammonium fluoride, the suspension was filtered through a short plug of silica gel, which was washed with Et_2O, then the filtrate was concentrated *in vacuo* and purified by silica gel chromatography (20:1 hexanes:Et_2O) to afford **1.34** as yellow oil (9.3 mg, 0.035 mmol, 55% yield, 80% *Z*).). **IR (neat):** 3342 (br), 3026 (w), 3005 (m), 2922 (m), 2853 (m), 1603 (w), 1496 (w), 1455 (m), 1378 (w), 1301 (w), 1176 (w), 1044 (m), 1031 (m), 1008 (w), 970 (w), 914 (w), 816 (w), 745 (m), 722 (s), 698 (w), 622 (w), 575 (w), 514 (w), 465 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.38–7.21 (m, 2H), 7.22–7.10 (m, 2H), 6.99–6.81 (m, 1H), δ 5.66 (diagnostic signal for *E* signal ddt, *J* = 15.4, 6.7, 0.9 Hz, 1H), 5.60–5.15 (m, 2H), 4.46 (dt, *J* = 8.6, 6.5 Hz, 1H), 2.78–2.59 (m, 2H), 2.13–1.98 (m, 2H), 1.99–1.67 (m, 2H), 1.48–1.12 (m, 10H), 0.91 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 142.1, 133.0, 132.4, 128.5, 128.5, 125.9, 67.3, 39.2, 32.0, 31.9, 29.8, 29.6, 29.4, 29.4, 27.9, 22.8, 14.3; **HRMS (ESI+):** Calcd for $C_{19}H_{29}$ $[M+H–H_2O]^+$ 257.22693; found: 257.22683.



1.37

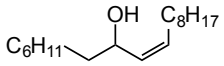
(*Z*)–Phenyl-6-((*tert*-butyldimethylsilyl)oxy)-6-phenylhex-4-enoate (1.37): Following the general procedure, in a vial containing **1.16** (17.9 mg, 0.0721 mmol), was weighed phenyl pent-4-enoate (25.4 mg, 0.140 mmol, 2 equiv) followed by the addition of a solution of **1.13** (36 μL, 0.0022 mmol, 3 mol %). The solution was allowed to stir under a vacuum of 7 torr for 8 h. Purification of the resulting residue by silica gel chromatography (100:1 hexanes:Et_2O) afforded **1.37** as a yellow oil (19.0 mg, 0.0499 mmol, 69 % yield, 95% *Z*). **IR (neat):** 3063 (w), 3027 (w), 2954 (m), 2928 (m), 2886 (w), 2856 (m), 1760 (s), 1593 (m), 1492 (m), 1472 (w), 1462 (w), 1416 (w), 1389 (w), 1361 (w),1251 (w), 1194 (s), 1162 (m), 1134 (s), 1084 (s), 1062 (s), 1026 (s), 1004 (m), 967 (m), 914 (w), 866 (m), 834 (s), 775 (s), 749 (s), 689 (s), 671 (s), 614 (m), 527 (w), 497 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.43–7.28 (m, 6H), 7.27–7.17 (m, 2H), 7.12–7.02 (m, 2H), 5.68–5.59 (m, 1H), 5.55 (d, *J* = 8.8 Hz, 1H), 5.46 (m, 1H), 5.17 (diagnostic signal for *E* isomer, d, *J* = 6.0 Hz, 1H), 2.72–2.62 (m, 4H), 0.92 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 171.5, 150.8, 144.5, 135.6, 129.6, 128.4, 127.1, 126.3, 126.0, 125.8, 121.7, 70.5, 34.3, 26.0, 23.5, 18.4, –4.3, –4.6; **HRMS (ESI+):** Calcd for $C_{24}H_{31}O_3Si$ $[M–H]^+$: 395.20425; found: 395.20605.



1.38

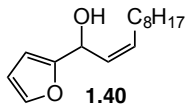
(*Z*)-*tert*-butyl((3-cyclohexyl-1-phenylallyl)oxy)dimethylsilane) (1.38): Following the general procedure, to a vial containing the allyl silyl ether **1.16** (19.9 mg, 0.0801mmol), was added vinyl cyclohexane (22 μL, 0.16 mmol, 3 equiv) followed by a solution of **1.13** (40 μL, 0.0024 mmol, 3 mol %). The mixture was allowed to heat with stirring to 50 ºC for 8 h then concentrated *in vacuo* and purified by silica gel chromatography (100% hexanes) to afford **1.38** as yellow oil (5.1 mg, 0.015 mmol, 19% yield, >98% *Z*). **IR (neat):** 2925 (m), 2852 (m), 1448 (w), 1250 (m), 1063 (s), 887 (m), 834 (s), 774 (s), 737 (s), 696 (s), 671 (s). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39–7.27 (m, 3H), 7.24–7.18 (m, 1H), 5.54 (d, *J* = 8.9 Hz, 1H), 5.38 (ddd, *J* = 10.9, 8.9, 0.8 Hz, 1H), 5.24 (ddd, *J* = 10.9,

10.1, 0.9 Hz, 1H), 2.54–2.36 (m, 1H), 1.84–1.58 (m, 5H), 1.38–1.01 (m, 6H), 0.92 (s, 8H), 0.08 (s, 3H), 0.05 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 144.8, 134.9, 131.4, 128.0, 126.6, 125.6, 70.4, 37.0, 33.1, 33.0, 25.9, 25.8, 25.8, 25.7, 18.2, -4.4, -4.8.



1.39

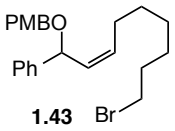
(*Z*)-Octadec-9-en-8-ol (1.39): Following the general procedure, to a vial containing the requisite allyl silyl ether (18.4 mg, 0.0680 mmol), was added 1-decene **1.21** (38 μL, 0.20 mmol, 3 equiv) followed by a solution of **1.13** (34 μL, 0.0020 mmol, 3 mol %). The mixture was allowed to stir under a vacuum of 7 torr for 8 h; desilylation was effected by exposure to a solution of tetra-*n*-butyl ammonium fluoride for 1 h (136 μL, 0.136 mmol, 2 equiv). The solution was diluted with Et_2O to precipitate tetra-*n*-butyl ammonium fluoride, the suspension was filtered through a short plug of silica gel, which was washed with Et_2O, the filtrate was then concentrated *in vacuo* and purified by silica gel chromatography (50:1 hexanes:Et_2O) to afford **1.39** as yellow oil (11.1 mg, 0.0415 mmol, 61% yield, 78% *Z*). **IR (neat):** 3351 (br), 3005 (m), 2923 (s), 2854 (m), 1464 (m), 1378 (m), 1307 (w), 1252 (w), 1122 (w), 1042 (w), 1013 (w), 723 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.77 (diagnostic signal for *E* isomer dt, *J* = 15.3, 6.4 Hz, 1H), 5.58–5.42 (m, 1H), 5.42–5.29 (ddd, *J* = 17.4, 10.4, 7.0 Hz, 1H), 4.42 (ddt, *J* = 8.8, 6.5, 0.9 Hz, 1H), 2.08 (dddd, *J* = 12.3, 7.3, 5.1, 1.5 Hz, 2H), 1.69–1.49 (m, 2H), 1.49–1.17 (m, 22H), 0.89 (t, *J* = 6.7 Hz, 6H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 132.7, 132.6, 67.9, 37.7, 32.0, 32.0, 29.8, 29.7, 29.6, 29.5, 29.4, 29.4, 27.9, 25.6, 22.8, 22.8, 14.2; **HRMS (ESI+):** Calcd for $C_{18}H_{35}$ $[M+H–H_2O]^+$: 251.27384; found: 251.27384.



1.40

(*Z*)-1-(Furan-2-yl)undec-2-en-1-ol (1.40): Following the general procedure, to a vial containing the requisite allyl silyl ether (41.9 mg, 0.169 mmol), 1-decene was added **1.21** (92 μL, 0.51 mmol, 3 equiv) followed by a solution of **1.13** (85 μL, 0.0051 mmol, 3 mol %). The solution was allowed to stir under a vacuum of 7 torr for 8 h. Subsequent

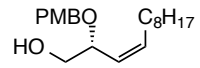
desilylation was effected by exposure to a solution of tetra-*n*-butyl ammonium fluoride for 1 h (338 μL, 0.338 mmol, 2 equiv). The resulting solution was diluted with Et_2O to precipitate tetra-*n*-butyl ammonium fluoride, the suspension was filtered through a short plug of silica gel, which was washed with Et_2O, concentrated *in vacuo* and purified by silica gel chromatography (10:1 hexanes:Et_2O) to afford **1.40** as yellow oil (31.9 mg, 0.135 mmol, 80% yield, 95% *Z*). **IR (neat):** 3356 (br), 3018 (w), 2956 (m), 2923 (s), 2854 (m), 1503 (m), 1464 (m), 1378 (m), 1309 (m), 1263 (m), 1223 (m), 1183 (m), 1147 (m), 1008 (m), 931 (m), 918 (m), 884 (w), 798 (w), 732 (w), 598 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39 (dd, *J* = 2.0, 0.8 Hz, 1H); 6.32 (dd, *J* = 3.2, 1.6 Hz, 1H); 6.28 (dt, *J* = 3.2, 0.8 Hz, 1H); 5.75–5.61 (m, 2H) 5.86–5.78 (diagnostic signal for *E* isomer, m, 1H). 5.52 (d, *J* = 8 Hz, 1H); 2.20–2.04 (m, 2H); 1.27 (m, 12H); 0.88 (t, *J* = 7 Hz, 3H); **^{13}C NMR (100 MHz $CDCl_3$):** δ 155.9, 142.5, 134.4, 128.4 110.4, 106.4 64.0, 32.1, 29.6, 29.6, 29.5, 29.4, 27.9, 22.9 14.3; **HRMS (ESI+):** Calcd for $C_{15}H_{23}O$ $[M+H-H_2O]^+$: 219.17489; found: 219.17536.



1.43

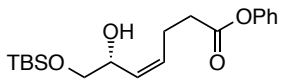
(*Z*)-1-(((9-Bromo-1-phenylnon-2-en-1-yl)oxy)methyl)-4-methoxybenzene (1.43): Following the general procedure, to a vial containing the requisite allyl *p*-methoxybenzyl ether (38.6 mg, 0.152 mmol), 8-bromo-1-octene was added **1.17** (51 μL, 0.30 mmol, 2 equiv) followed by a solution of **1.13** (76 μL, 0.0046 mmol, 3 mol %). The solution was allowed to stir under a vacuum of 7 torr for 8 h, then purified by silica gel chromatography (100:1 hexanes:Et_2O) to afford **1.43** as yellow oil (53.8 mg, 0.129 mmol, 85% yield, >98% *Z*). **IR (neat):** 3007 (w), 2925 (m), 2854 (m), 1612 (m), 1586 (w), 1512 (w), 1492 (m), 1453 (m), 1301 (m), 1246 (s), 1172 (m), 1064 (m), 1036 (m), 820 (m), 742 (m), 699 (m), 644 (m), 561 (w), 514 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.41–7.31 (m, 4H), 7.30–7.22 (m, 3H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.66–5.54 (m, 2H), 5.14 (d, *J* = 7.6 Hz, 1H), 4.49–4.38 (m, 2H), 3.81 (s, 3H), 3.39 (t, *J* = 6.8 Hz, 2H), 2.20–2.02 (m, 2H), 1.83 (ddd, *J* = 7.0, 7.0, 7.0 Hz, 2H), 1.46–1.20 (m, 6H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 159.2, 142.2, 132.7, 130.9, 130.7, 129.5, 128.6, 127.6, 126.9, 113.9, 75.9, 69.6, 55.4,

34.0, 32.8, 29.4, 28.5, 28.1, 27.9; **HRMS (ESI+):** Calcd for $C_{15}H_{20}{}^{79}Br$ $[M+H–C_8H_{10}O_2]^+$: 279.07484; found: 279.07355.



1.44

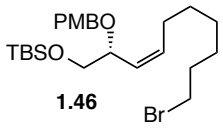
(*R,Z*)-2-((4-Methoxybenzyl)oxy)dodec-3-en-1-ol (1.44): Following the general procedure, to a vial containing the requisite allyl *p*-methoxybenzyl ether (44.4 mg, 0.138 mmol),[55] 1-decene **1.21** was added (75 μL, 0.41 mmol, 3 equiv) followed by a solution of **1.13** (69 μL, 0.0041 mmol, 3 mol %). The solution was allowed to stir under a vacuum of 7 torr for 8 h; subsequent removal of the silyl group was effected by exposure of the mixture to a solution of tetra-*n*-butyl ammonium fluoride for 1 h (276 μL, 0.276 mmol, 2 equiv). The resulting solution was diluted with Et_2O to precipitate tetra-*n*-butyl ammonium fluoride, the suspension was filtered through a short plug of silica gel, which was washed with Et_2O, the filtrate was concentrated *in vacuo* and purified by silica gel chromatography (5:1 hexanes:EtOAc) to afford **1.44** as yellow oil (36.8 mg, 0.120 mmol, 87% yield, >98% *Z*). **IR (neat):** 3433 (br), 3005 (m), 2924 (s), 2854 (m), 1613 (m), 1586 (w), 1513 (s), 1464 (m), 1302 (m), 1248 (s), 1173 (m), 1038 (s), 822 (m), 758 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.72 (dtd, *J* = 11.2, 7.5, 1.1 Hz, 1H), 5.29 (dddd, *J* = 11.0, 9.2 Hz, 1.5, 1.5, 1H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.35–4.25 (m, 2H), 3.93–3.84 (diagnostic for *E* isomer, m, 1H). 3.80 (s, 3H), 3.65–3.43(m, 2H), 2.16 (br, s, 1H), 2.07 (ttd, *J* = 14.5, 7.1, 1.6 Hz, 1H), 1.42–1.11 (m, 7H), 0.88 (t, *J* = 7.0 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 159.4, 136.4, 130.5, 129.6, 126.7, 114.0, 75.3, 70.0, 65.4, 55.4, 32.0, 29.8, 29.6, 29.4, 29.4, 28.1, 22.8, 14.2; **HRMS (ESI+):** Calcd for $C_{20}H_{36}NO_3$ $[M+NH_4]^+$: 338.26952 found, 338.26816; **$[\alpha]^{23.4}_D$** = –29.94 (*c* = 1.00 $CHCl_3$).



1.45

55. B. M. Trost, E. J. McEachern, F. D. Toste, *J. Am. Chem. Soc.* **1998**, 120, 12702–12703.

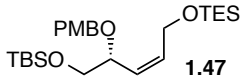
(*R*,*Z*)-Phenyl-7-((*tert*-butyldimethylsilyl)oxy)-6-hydroxyhept-4-enoate (1.45): Following the general procedure, to a vial containing the requisite allyl *p*-methoxybenzyl ether (27.0 mg, 0.0837 mmol), was added phenyl-4-pentenoate (44.3 mg, 0.251 mmol, 3 equiv) followed by a solution of **1.13** (42 μL, 0.0025 mmol, 3 mol %). The mixture was allowed to stir under a vacuum of 7 torr for 8 h. Subsequent removal of the *p*-methoxybenzyl group was effected by exposure of the mixture to DDQ (28.5 mg, 0.125 mmol, 1.5 equiv) in 1 mL CH_2Cl_2 and 100 μL H_2O at 0 ºC for 1 h. The resulting mixture was diluted with water, and the aqueous layer was washed with CH_2Cl_2 (3 x 10 mL); the organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford red oil, which was purified by silica gel chromatography (5:1 hexanes:Et_2O) to afford **1.45** as yellow oil (25.2 mg, 0.0736 mmol, 88% yield, 90% *Z* **IR (neat):** 3456 (br), 2954 (m), 2928 (m), 2856 (m), 1759 (s), 1593 (w), 1493 (m), 1472 (w), 1462 (w), 1361 (m), 1253 (s), 1194 (m), 1162 (s), 1109 (s), 1069 (s), 1006 (m), 915 (w), 888 (s), 834 (m), 814 (m), 777 (m), 752(s), 669 (m), 668 (m), 498 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.43–7.31 (dd, *J* = 7.6, 6.8 Hz, 2H), 7.25–7.19 (dd, *J* = 7.6, 6.8 Hz, 1H), 7.08 (d, *J* = 7.9 Hz, 2H), 5.85 (diagnostic signal for *E* isomer, dd, *J* = 14.9, 7.1 Hz, 1H), 5.73–5.55 (m, 1H), 5.47 (ddd, *J* = 11.1, 8.0, 1.7 Hz, 1H), 4.54 (s, 1H), 3.60 (dd, *J* = 10.0, 3.7, Hz, 1H), 3.46 (dd, *J* = 10.0, 8.0, Hz, 1H), 2.72–2.57 (m, 2H), 2.52 (dddd, *J* = 14.4, 7.6 Hz, 2H), 0.91 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 171.6, 150.8, 131.4, 130.1, 129.6, 126.0, 121.7, 68.4, 66.9, 34.3, 26.0, 23.6, 18.5, –5.2, –5.2; **HRMS (ESI+):** Calcd for $C_{19}H_{31}O_4Si$ $[M+H]^+$: 351.19916; found: 351.20038 **$[\alpha]^{23.4}_D$** = –9.99 (*c* = 1.00 $CHCl_3$).



1.46

(*R*,*Z*)-((10-Bromo-2-((4-methoxybenzyl)oxy)dec-3-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (1.46): Following the general procedure, to a vial containing the requisite allyl *p*-methoxybenzyl ether (43.0 mg, 0.133 mmol), was added 8-bromo-1-octene **1.17** (45 μL, 0.27 mmol, 2 equiv) followed by a solution of **1.13** (67 μL, 0.0040 mmol, 3 mol %). The solution was allowed to stir under a vacuum of 7 torr for 8 h. The resulting residue was purified by silica gel chromatography (200:1 hexanes:Et_2O) to

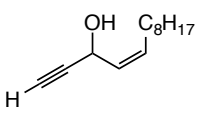
afford **1.46** as yellow oil (45.2 mg, 0.0931 mmol, 70% yield, 92% *Z*). **IR (neat):** 3003 (w), 2938 (m), 2855 (m), 1612 (w), 1513 (m), 1463 (m), 1301 (w), 1247 (s), 1172 (w), 1082 (m), 1038 (s) 1007 (m), 835 (s), 776 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.65 (ddt, *J* = 11.1, 7.4, 1.1 Hz, 1H), 5.38–5.33 (diagnostic signal for *E* isomer m, 1H), 5.29 (dddd, *J* = 11.0, 9.2 Hz, 1.5, 1.5, 1H), 4.56 (d, *J* = 11.8, Hz, 1H), 4.37 (d, *J* = 11.7 Hz, 1H), 4.20 (dddd, *J* = 9.0, 6.5, 5.2, 1.1 Hz, 1H), 3.80 (s, 3H), 3.72 (dd, *J* = 10.6, 6.6 Hz, 1H), 3.54 (dd, *J* = 10.5, 5.1 Hz, 1H), 3.40 (t, *J* = 6.8 Hz, 2H), 2.04 (dtd, *J* = 14.9, 7.1, 1.7 Hz, 2H), 1.85 (tt, *J* = 7.6, 7.2 Hz, 2H), 1.51–1.19 (m, 6H), 0.89 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 159.1, 134.9, 131.1, 129.3, 128.3, 113.8, 75.2, 70.0, 66.5, 55.4, 34.0, 32.9, 29.7, 28.6, 28.2, 28.0, 26.0, 18.6, –5.0, –5.1; **HRMS (ESI+):** Calcd for $C_{24}H_{42}BrO_3Si$ $[M+H]^+$: 485.20866; found: 485.20997; $[\alpha]^{23.4}_D$ = –14.91 (*c* = 0.67 $CHCl_3$).



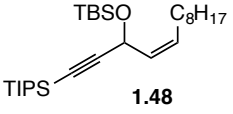
1.47

(*R,Z*)-3,3-diethyl-8-((4-methoxybenzyl)oxy)-11,11,12,12-tetramethyl-4,10-dioxa-3,11-disilatridec-6-ene (1.47): Following the general procedure, to a vial containing the requisite allyl *p*-methoxybenzyl ether (49.4 mg, 0.154 mmol), (allyloxy)triethylsilane was added (82.3 mg, 0.479 mmol, 3 equiv) followed by a solution of **1.13** (80 μL, 0.0048 mmol, 3 mol %). The mixture was allowed to stir under a vacuum of 7 torr for 8 h, then purified by silica gel chromatography (50:1 hexanes:Et_2O) to afford **1.47** as yellow oil (49.0 mg, 0.105 mmol, 68% yield, 92% *Z*). **IR (neat):** 2954 (m), 2930 (m), 2876 (m), 2857 (m), 1613 (w), 1586 (w), 1513 (m), 1463 (m), 1412 (w), 1388 (w), 1361 (w), 1301 (w), 1248 (s), 1172 (w), 1081 (s), 1039 (m), 1007 (m), 961 (w), 939 (w), 836 (s), 777 (m), 744 (m), 729 (m), 668 (m), 404 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.27 (d, *J* = 8.6 Hz, 1H), 6.86 (d, 2H), 5.80 (dddd, *J* = 11.3, 7.2, 4.9, 1.1 Hz, 1H), 5.69–5.56 (diagnostic signal for *E* isomer m, 1H), 5.37 (ddd, *J* = 11.1, 8.0, 1.7 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.37 (d, *J* = 11.6 Hz, 1H), 4.26 (ddd, *J* = 13.5, 7.2, 1.7 Hz, 1H), 4.21–4.06 (m, 2H), 3.80 (s, 1H), 3.72 (dd, *J* = 10.4, 6.3 Hz, 1H), 3.52 (dd, *J* = 10.4, 5.6 Hz, 1H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.88 (s, 9H), 0.60 (q, *J* = 8.0 Hz, 6H), 0.04 (s, 3H), 0.03 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 159.2, 134.6, 130.8, 129.4, 128.9, 113.8, 75.4, 70.3, 66.2, 59.5,

55.4, 26.1, 18.5, 6.9, 4.6, –5.1, –5.2; **HRMS (ESI+):** Calcd for $C_{25}H_{46}O_4Si_2$ $[M+H]^+$: 467.30129; found: 467.30315; $[\alpha]^{23.8}_D = -39.39$ (c = 1.00 $CHCl_3$).

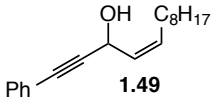


obtained from



1.48

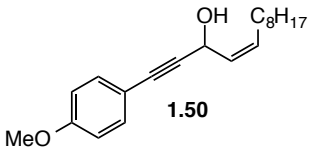
(*Z*)-tridec-4-en-1-yn-3-ol: Following the general procedure, to a vial containing the requisite allyl silyl ether (25.5 mg, 0.0718 mmol), 1-decene **1.21** was added (40 μL, 0.22 mmol, 3 equiv) followed by a solution of **1.13** (36 μL, 0.0022 mmol, 3 mol %). The mixture was allowed to stir under a vacuum of 7 torr for 8 h, then purified by silica gel chromatography (20:1 hexanes:Et_2O) to afford **(*Z*)-tridec-4-en-1-yn-3-ol** as yellow oil (11.7 mg, 0.0602 mmol, 84% yield, 92% *Z*). **IR (neat):** 3311 (br), 2956 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.92 ((diagnostic signal for *E* isomer, dtd, J = 15.0, 6.8, 1.2 Hz, 1H), 5.70–5.51 (m, 2H), 5.15 (ddd, J = 7.4, 4.8, 2.2 Hz, 1H), 2.50 (d, J = 2.2 Hz, 1H), 2.18–2.08 (m, 2H), 1.79 (d, J = 5.0 Hz, 1H), 1.48–1.17 (m, 12H), 0.97–0.80 (m, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 134.6, 128.9, 84.4, 73.2, 58.4, 32.2, 29.7, 29.6, 29.6, 29.6, 27.9, 23.0, 14.4. **HRMS (ESI+):** Calcd for $C_{13}H_{21}$ $[M+H-H_2O]^+$: 177.16439; found: 177.16433.



1.49

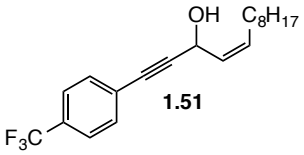
(*Z*)–1-phenyltridec-4-en-1-yn-3-ol (1.49): Following the general procedure, to a vial containing the requisite allyl silyl ether (47.1 mg, 0.173 mmol), was added 1-decene **1.21** (94 μL, 0.52 mmol, 3 equiv) followed by catalyst solution of **1.13** (87 μL, 0.0052 mmol, 3 mol %). The solution was allowed to stir under a vacuum of 7 torr for 8 h. Subsequent removal of the silyl group was effected by exposure of the mixture to a 1.0 M THF solution of tetra-*n*-butyl ammonium fluoride for 1 h (346 μL, 0.346 mmol, 2 equiv). The solution was diluted with ether, to precipitate tetra-*n*-butyl ammonium fluoride, the suspension was filtered through a short plug of silica gel, which was washed with Et_2O; then the filtrate was concentrated *in vacuo* and purified by silica gel chromatography (20:1 hexanes:Et_2O) to afford **1.49** as yellow oil (31.1 mg, 0.116 mmol, 67% yield, >98%

Z). **IR (neat):** 3362 (br), 3062 (w), 3020 (w), 2955 (m), 2923 (s), 2854 (m), 1727 (w), 1708 (w), 1654 (w), 1598 (w), 1490 (m), 1464 (m), 1442 (m), 1404 (w), 1378 (w), 1306 (w), 1259 (w), 1070 (s), 1029 (s), 1014 (m), 996 (w), 916 (w), 832 (w), 816 (w), 755 (s), 735 (w), 691 (s), 614 (w), 525 (w); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.48–7.41 (m, 2H), 7.33–7.27 (m, 3H), 5.69–5.56 (m, 2H), 5.38 (d, *J* = 7.6 Hz, 1H), 2.18 (dt, *J*= 7.2, 6.1 Hz, 2H), 1.93 (s, br, 1H), 1.46–1.37 (m, 2H), 1.37–1.20 (m, 9H), 0.87 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 133.9, 131.8, 129.1, 128.6, 128.4, 122.7, 89.3, 85.0, 58.9, 32.0, 29.6, 29.5, 29.4, 29.4, 27.8, 22.8, 14.2; **HRMS (ESI+):** Calcd for $C_{19}H_{25}$ [M+H–H_2O]$^+$: 253.19563; found: 253.19642.



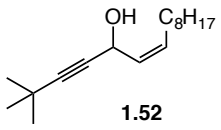
1.50

(*Z*)-1-(4-Methoxyphenyl)tridec-4-en-1-yn-3-ol (1.50): Following the general procedure, to a vial containing the requisite allyl silyl ether (48.0 mg, 0.159 mmol) was added 1-decene **1.21** (87 μL, 0.48 mmol, 3 equiv) followed by a solution of **1.13** (80 μL, 0.0048 mmol, 3 mol %). The solution was allowed to stir under a vacuum of 7 torr for 8 h. Removal of the silyl group was effected by exposure of the mixture to a 1.0 M THF solution of tetra-*n*-butyl ammonium fluoride for 1 h (318 μL, 0.318 mmol, 2.0 equiv). The solution was diluted with Et_2O to precipitate tetra-*n*-butyl ammonium fluoride, the suspension was filtered through a short plug of silica gel, which was washed with Et_2O; then filtrate was concentrated *in vacuo* and purified by silica gel chromatography (25:1 hexanes:Et_2O) to afford **1.50** as a yellow oil (29.3 mg, 0.0977 mmol, 61% yield, >98% *Z*). **IR (neat):** 3414 (br), 2954 (w), 2924 (m), 2854 (m), 2204 (m), 1722 (w), 1643 (w), 1603 (s), 1570 (w), 1509 (s), 1464 (w), 1441 (w), 1290 (m), 1249 (s), 1169 (m), 1106 (w), 1032 (m), 832 (m), 807 (w), 538 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.42–7.32 (m, 2H), 6.87–6.78 (m, 2H), 5.70–5.54 (m, 2H), 5.36 (d, *J* = 7.5 Hz, 1H), 3.81 (s, 3H), 2.17 (td, *J* = 7.1, 5.8 Hz, 2H), 1.90 (s, 1H) 1.47–1.20 (m, 11H), 0.92–0.83 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 159.8, 133.7, 133.3, 129.3, 114.8, 114.0, 88.0, 84.9, 58.9, 55.4, 32.0, 29.6, 29.6, 29.4, 29.4, 27.8, 22.8, 14.2; **HRMS (ESI+):** Calcd for $C_{20}H_{27}O_1$ [M+H–H_2O]$^+$: 283.20619; found: 283.20541.



1.51

(*Z*)-1-(4-(Trifluoromethyl)phenyl)tridec-4-en-1-yn-3-ol (1.51): Following the general procedure, to a vial containing the requisite allyl silyl ether (42.5 mg, 0.125 mmol), was added 1-decene **1.21** (68 μL, 0.38 mmol, 3 equiv) followed by a solution of **1.13** (63 μL, 0.0038 mmol, 3 mol %). The resulting mixture was allowed to stir under a vacuum of 7 torr for 8 h. Removal of the silyl group was effected by exposure of the mixture to a solution of tetra-*n*-butyl ammonium fluoride for 1 h (250 μL, 0.250 mmol, 2 equiv). The mixture was diluted with Et_2O, to precipitate tetra-*n*-butyl ammonium fluoride, the suspension was filtered through a short plug of silica gel, which was washed with Et_2O; then the filtrate was concentrated *in vacuo* and purified by silica gel chromatography (30:1 hexanes:Et_2O) to afford **1.51** as yellow oil (29.2 mg, 0.0863 mmol, 69% yield, >98% *Z*). **IR (neat):** 3370 (br), 2956 (w), 2925 (m), 2855 (w), 2216 (w), 1714 (w), 1648 (w), 1615 (w), 1465 (w), 1406 (w), 1321 (s), 1168 (s), 1129 (s), 1106 (w), 1017 (m), 842 (w), 598 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.60–7.49 (m, 4H), 5.70–5.59 (m, 2H), 5.39 (d, *J* = 7.0 Hz, 1H), 2.23–2.11 (m, 2H), 1.96 (br s, 1H), 1.41 (dd, *J* = 7.3, 7.3 Hz, 2H), 1.37–1.15 (m, 8H), 0.87 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 137.4, 132.0, 130.2 (q, *J* = 35 Hz), 128.7, 126.6, 125.4 (q, *J* = 273.7 Hz), 125.3 (q, *J* = 4.0 Hz), 91.8, 83.6, 58.8, 32.0, 29.9, 29.6, 29.5, 29.4, 29.4, 29.4, 27.9, 22.8, 14.2; **^{19}F NMR (399 MHz, $CDCl_3$)** –63.5; **HRMS (ESI+):** Calcd for $C_{20}H_{24}F_3$ $[M+H–H_2O]^+$: 321.18301; found: 321.18227.

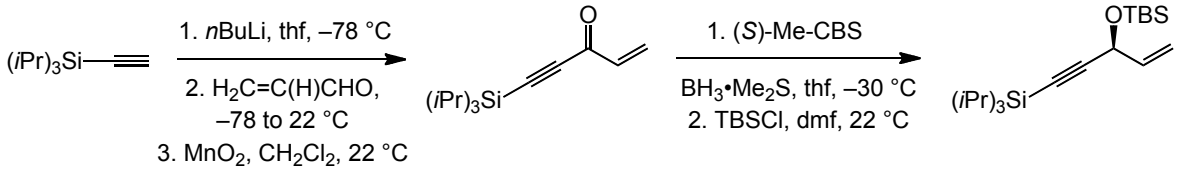


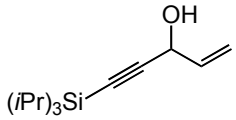
1.52

(*Z*)–2,2-Dimethylpentadec-6-en-3-yn-5-ol (1.52): Following the general procedure, to a vial containing the requisite allyl silyl ether (30.8 mg, 0.122 mmol), was added 1-decene **1.21** (74 μL, 0.37 mmol, 3 equiv) followed by a solution of **1.13** (30 μL, 0.0018 mmol, 1.5 mol %). The reaction was allowed to stir under a vacuum of 7 torr for 8 h. Removal

of the silyl group was accomplished by exposure of the mixture to a solution of tetra-*n*-butyl ammonium fluoride for 1 h (244 μL, 0.244 mmol, 2 equiv). The resulting mixture was diluted with Et_2O to precipitate tetra-*n*-butyl ammonium fluoride, the suspension was filtered through a short plug of silica gel, which was washed with Et_2O, the filtrate was then concentrated *in vacuo* and purified by silica gel chromatography (40:1 hexanes:EtOAc) to afford **1.52** as yellow oil (23.4 mg, 0.0934 mmol, 76% yield, 90% *Z*). **IR (neat):** 3333 (br), 2965 (m), 2924 (s), 2859 (m) 1458 (m) 1378 (m), 1362 (m) 1263 (m) 1204 (m) 1032 (m) 968 (m), 847 (w) 749 (w) 722 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.60–5.48, (m, 2H), 5.13 (br, 1H), 2.14–2.09 (m, 2H), 1.27 (m, 12H), 1.23 (diagnostic signal for *E* isomer, s, 9H), 1.21 (s, 9H), 0.88 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 133.1, 130.1, 93.9, 79.0, 58.5, 31.1, 31.1, 29.6, 29.6, 29.4, 29.4, 27.7, 27.5, 22.8, 14.3; **HRMS (ESI+):** Calcd $[M+H-H_2O]^+$: 233.22693; found, 233.22750.

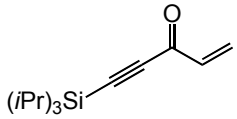
Synthesis of Enyne-Containing Natural Products



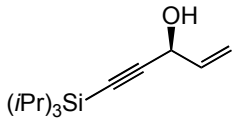


(±)-5-(Tri-*iso*-propylsilyl)pent-1-en-4-yn-3-ol: A flame-dried 500 mL flask equipped with a stir bar was charged with tri-*iso*-propylsilyl acetylene (6.5 mL, 29 mmol, 1.0 equiv) and tetrahydrofuran (145 mL) was added. The mixture was allowed to cool to –78 ºC; then *n*-butyllithium was added (20.4 mL, 1.42 M in hexanes, 29.0 mmol, 1.0 equiv). The solution was allowed to stir for 30 minutes at which point acrolein was added (2.3 mL, 35 mmol, 1.2 equiv) and the mixture was allowed to warm to 4 ºC over 1.5 h. The reaction was quenched by the addition of a saturated solution of aqueous NH_4Cl. The aqueous layer was washed with Et_2O (3 x 75 mL); the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to afford yellow oil,

which was purified by silica gel chromatography (10:1 hexanes:Et_2O) to afford the desired alcohol as clear colorless oil (6.21 g, 26.0 mmol, 90 % yield).

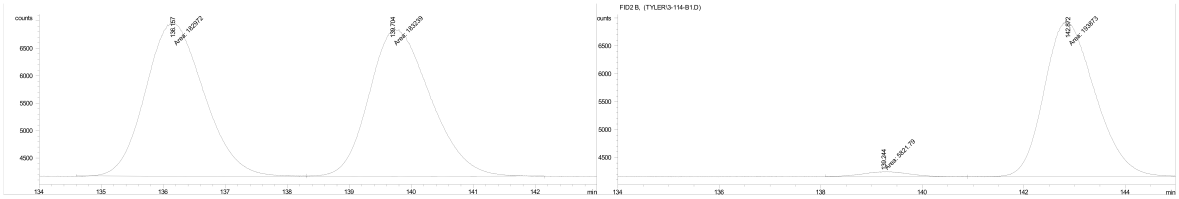


5-(Tri-*iso*-propylsilyl)pent-1-en-4-yn-3-one: A 100 mL Erlenmeyer flask equipped with stir bar was charged with the aforementioned alcohol (500 mg, 2.1 mmol), dissolved in 20 mL CH_2Cl_2, followed by addition of MnO_2 (1.00 g, 11.5 mmol, 5.5 equiv). The mixture was allowed to stir for 24 h, at which point it was filtered through Celite and concentrated *in vacuo* to afford the desired enone as yellow oil (492.3 mg, 2.08 mmol, >98% yield). This material was carried forward without purification. **IR (neat):** 2944 (m), 2893 (w), 2866 (m), 2150 (w), 1654 (s), 1610 (w), 1462 (m), 1399 (m), 1368 (m), 1274 (m), 1240 (s), 1227 (s), 1127 (m), 1072 (m), 1016 (m), 988 (s), 919 (m), 882 (w), 815 (s), 794 (s), 677 (s), 661 (s), 617 (s), 547 (m), 505 (w), 468 (m), 448 (m), 412 (m). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.62 (dd, *J* = 17.4, 1.0 Hz, 1H), 6.41 (dd, *J* = 17.4, 10.3 Hz, 1H), 6.20 (dd, *J* = 10.2, 1.0 Hz, 1H), 1.29–0.95 (m, 21H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 178.7, 138.3, 133.8, 102.0, 97.0, 18.7, 11.2; **HRMS (ESI+):** Calcd for $C_{14}H_{25}OSi$ $[M+H]^+$: 237.16747; found: 237.16786.



(*S*)–5-(Tri-*iso*-propylsilyl)pent-1-en-4-yn-3-ol: In an N_2-filled glove box an oven-dried 500 mL round bottom flask equipped with a stir bar was charged with (*S*)–Me-CBS reagent (3.5 g, 13 mmol, 2 equiv), the flask was sealed with a rubber septum and electrical tape. The vessel was removed from the glove box and tetrahydrofuran (63 mL) was added along with the requisite ketone (1.5 g, 6.3 mmol, 1 equiv). The flask was allowed to cool to –30 ºC and BH_3•Me_2S was added (657 μL, 6.90 mmol, 1.1 equiv). The mixture was allowed to stir for 10 minutes, after which it was quenched at –30 ºC by the addition of MeOH (CAUTION: temperature must be controlled carefully until hydrogen evolution has ceased). The mixture was diluted by addition of Et_2O, and washed with a

saturated aqueous solution of 2:1 NaOH:$NaHCO_3$ (3 x 20 mL) then with brine, and concentrated *in vacuo* to afford yellow oil, which was purified by SiO_2 chromatography (25:1 hexanes:Et_2O) to afford the desired alcohol as colorless oil (1.22 g, 5.1 mmol, 81% yield). Enantiomeric purity (97:3 er) was determined by GC analysis (β–dex column, 110 ºC, 15 psi) in comparison to authentic racemic material. **IR (neat):** 3313 (br), 2943 (m), 2891 (m), 2865 (m), 2170 (w), 1643 (w), 1463 (m), 1403 (m), 1384 (m), 1367 (m), 1244 (m), 1114 (m), 1016 (s), 984 (s), 926 (m), 881 (s), 728 (m), 674 (s), 659 (s), 513 (m), 476 (m), 452 (m), 412 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.99 (ddd, *J* = 17.0, 10.1, 5.1 Hz, 1H), 5.52 (ddd, *J* = 16.9, 1.5, 1.5 Hz, 1H), 5.23 (dd, *J* = 10.1, 1.3 Hz, 1H), 4.98–4.84 (m, 1H), 1.89 (s, 1H), 1.08 (d, *J* = 1.7 Hz, 21H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 137.1, 116.6, 106.1, 87.6, 63.8, 18.7, 11.3**; HRMS (ESI+):** Calcd for $C_{14}H_{27}OSi$ $[M+H]^+$: 239.18312; found: 239.18199; **$[\alpha]^{23.8}_D$** = +23.80 (*c*= 1.00 $CHCl_3$).



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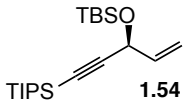
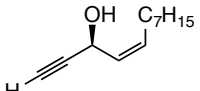
1	136.157	182972.5	49.964	1	139.244	5316.5	2.680
2	139.704	183238.8	50.036	2	142.872	193097.7	97.320



1.54

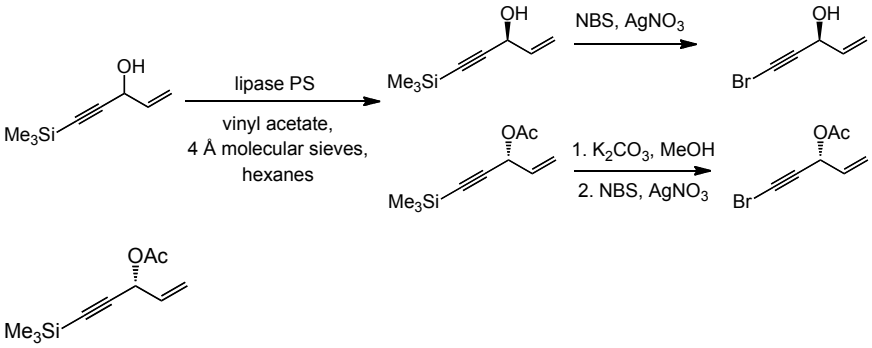
(*S*)-*tert*-Butyldimethyl((5-(tri-*iso*-propylsilyl)pent-1-en-4-yn-3-yl)oxy)silane (1.54): A 50 mL round bottom flask equipped with stir bar was charged sequentially with the aforementioned enantiomerically enriched alcohol (1.12 g, 4.70 mmol), imidazole (353 mg, 5.20 mmol 1.1 equiv), dimethylformamide (3 mL) and *tert*-butyldimethylsilyl chloride (778 mg, 5.20 mmol, 1.1 equiv). The solution was allowed to stir for 1 h, and then the reaction was quenched by the addition of water. The aqueous layer was washed twice with hexanes, the combined organic layers were washed with brine (4 x 5 mL), dried over $MgSO_4$, filtered and concentrated to afford yellow oil which was further

purified by SiO_2 chromatography (100 % hexanes) and distilled in a kugelrohr apparatus (130 ºC, 3 h, 0.2 torr) to afford **1.54** as clear colorless oil (1.42 g, 4.03 mmol, 86% yield). **IR (neat):** 2943 (s), 2892 (s), 2865 (s), 1463 (m), 1388 (w), 1362 (w), 1252 (m), 1132 (m), 1070 (s), 1030 (m), 883 (m), 837 (s), 778 (s), 674 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.91 (ddd, *J* = 17.0, 10.1, 4.6 Hz, 1H), 5.53–5.37 (m, 1H), 5.14 (d, *J* = 10.1 Hz, 1H), 4.94 (d, *J* = 4.6 Hz, 1H), 1.07 (s, 21H), 0.92 (s, 9H), 0.151 (s, 3H), 0.149 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 138.0, 115.0, 107.0, 86.4, 76.7, 64.3, 25.9, 18.7, 11.4, –4.4, –4.7; **HRMS (ESI+):** Calcd for $C_{20}H_{41}OSi_2$ $[M+H]^+$: 353.26959; found: 353.27028. **$[\alpha]^{25.0}_D$** = –40.78 (*c* = 1.00 $CHCl_3$).

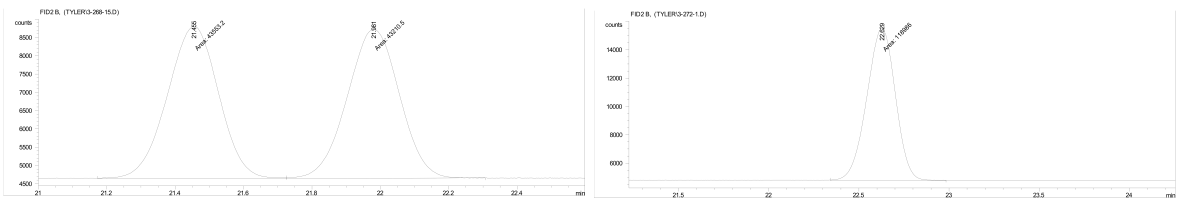


1.56

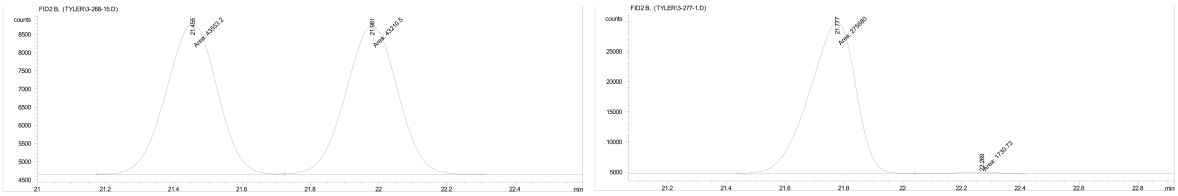
(*S,Z*)-Dodec-4-en-1-yn-3-ol (1.56): Following the general procedure, to a vial containing **1.54** (25.8 mg, 0.0730 mmol) was added 1-nonene **1.55** (93 μL, 0.73 mmol, 10 equiv) followed by a solution of **1.13** (55 μL, 0.0033 mmol, 4.5 mol %). The resulting mixture was allowed to stir under a vacuum of 7 torr for 8 h. Removal of the silyl group was effected by exposure of the mixture to a 1.0 M THF solution of tetra-*n*-butyl ammonium fluoride for 1 h (219 μL, 0.219 mmol, 3 equiv). The solution was diluted with Et_2O to precipitate tetra-*n*-butyl ammonium fluoride, the suspension was filtered through a short plug of silica gel, which was washed with Et_2O. The filtrate was concentrated *in vacuo* and the resulting residue was purified by silica gel chromatography (20:1 hexanes:EtOAc) to afford **1.56** as a yellow oil (12.5 mg, 0.0693 mmol, 94% yield, 92% *Z*). **IR (neat):** 3377 (br), 3311 (br), 2923 (s), 2854 (m), 2349 (w), 1464 (m), 1420 (m), 1249 (m), 1212 (s), 1186 (m), 1141 (m), 1016 (m), 933 (m), 840 (m), 652 (m), 607 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.77–5.40 (m, 2H), 5.15 (ddd, *J* = 7.5, 5.1, 2.2 Hz, 1H), 4.84 (diagnostic signal for *E* signal, m, 1H), 2.50 (d, *J* = 2.2 Hz, 1H), 2.13 (q, *J* = 7.0 Hz, 2H), 1.77 (d, *J* = 5.1 Hz, 1H), 1.39 (m, 2H), 1.28 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 134.3, 128.7, 84.2, 73.0, 58.2, 31.9, 29.5, 29.3, 29.3, 27.8, 22.8, 14.2; **HRMS (ESI+):** Calcd for $C_{12}H_{19}$ $[M+H–H_2O]^+$: 163.14868; found: 163.14812; **$[\alpha]^{25.0}_D$** = +64.97 (*c* = 1.00 $CHCl_3$).



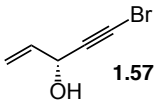
(*R*)–5-(Trimethylsilyl)pent-1-en-4-yn-3-yl acetate: This material was prepared by a modified version of a previously reported procedure.[43C] A flame-dried 250 mL round bottom flask with stir bar was charged with lipase (*Pseudomonas fluorescens*) (545 mg, 42 mg/mmol), molecular sieves (2.0 g 154 mg/mmol), dry hexanes (100 mL), the allylic alcohol (2.0 g, 13 mmol) and vinyl acetate (6.0 mL, 65 mmol, 5 equiv). The suspension was allowed to stir at 22 ºC for 48 h, at which point the reaction was determined to be complete by ^{1}H NMR analysis. The mixture was thus filtered through Celite and the filtrate was concentrated *in vacuo* to afford yellow oil, which was purified by silica gel chromatography (50:1 hexanes:Et_2O to 5:1 hexanes:Et_2O) to afford the (*S*)-acetate (1.1 g, 5.6 mmol, 43% yield) and the resolved alcohol (890 mg, 5.8 mmol, 44% yield) as colorless oils. The enantiomeric purity of the alcohol (>99:1 e.r.) was determined by acetylation and subsequent GC analysis (*β*–dex column, 100 ºC, 10 psi) in comparison to authentic racemic acetate. The enantiomeric purity of the acetate (99:1 e.r.) was established by GC analysis (*β*–dex column, 100 ºC, 10 psi) in comparison to the authentic racemic acetate. Spectra matched those reported in the literature.[43c]



#	Time	Area	Area%	#	Time	Area	Area%
1	21.455	43553.2	50.197	1	–	–	–
2	21.981	43210.5	49.803	2	22.629	118986.5	100.000

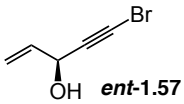


#	Time	Area	Area%	#	Time	Area	Area%
1	21.455	43553.2	50.197	1	21.777	275679.5	99.376
2	21.981	43210.5	49.803	2	22.269	1730.7 84	0.624



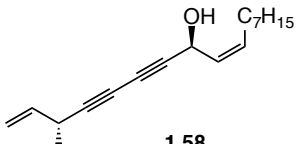
1.57

(*R*)-5-Bromopent-1-en-4-yn-3-ol (1.57): A 100 mL round bottom flask with stir bar was charged with the abovementioned enantiomerically enriched acetate (1.00 g, 5.10 mmol), MeOH (5 ml) and K_2CO_3 (1.50 g, 10.2 mmol, 2 equiv). The resulting suspension was allowed to stir for 2.5 h, after which the reaction was quenched by the addition of water. The aqueous layer was washed with Et_2O (3 x 5 mL), the organic layers were dried over Na_2SO_4 and filtered. The organic solvent was removed by distillation under N_2. The distillation flask was wrapped in foil and acetone (3 mL) was added to the oil residue then $AgNO_3$ (259 mg, 1.50 mmol, 0.3 equiv), and *N*–bromosuccinimide (1.30 g, 7.60 mmol, 1.5 equiv) were added. The resulting solution was allowed to stir in the dark for 1 h and the mixture was diluted with water. The aqueous layer was washed with Et_2O (3 x 10 mL), the combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The organic solvent was distilled off under N_2 to deliver yellow oil which was purified by SiO_2 chromatography (5:1 pentane:Et_2O) to afford **1.57** as yellow oil (454 mg, 2.35 mmol, 46% yield over 2 steps). Spectral data matched those reported in the literature.[43c]



***ent*-1.57**

(*S*)-5-Bromopent-1-en-4-yn-3-ol (*ent*-1.57): A 25 mL round bottom flask equipped with a stir bar was wrapped in aluminum foil then charged sequentially with the aforementioned enantiomerically enriched alcohol (156 mg, 1.01 mmol), acetone (1 mL), $AgNO_3$ (51.4 mg, 0.303 mmol, 0.3 equiv) and *N*–bromosuccinimide (269 mg, 1.52 mmol, 1.5 equiv). The solution was allowed to stir in the dark for 3 h, after which it was diluted with water. The aqueous layer was washed with Et_2O (3 x 5 mL), the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford yellow oil, which was purified by SiO_2 chromatography (5:1 pentane:Et_2O) to afford (***ent*-1.57**) as a yellow oil (140 mg, 0.87 mmol, 86 % yield). Spectral data matched those reported in the literature.

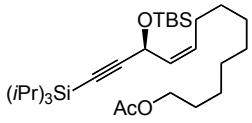


1.58
falcarindiol

Falcarindiol (1.58): The following reaction was conducted with oven-dried glassware based on a reported procedure.[56] Please note that all operations (including purification) were performed in the absence of light. An oven-dried 8 mL vial equipped with stir bar was charged with propargyl alcohol **1.56** (11.1 mg, 0.0616 mmol, 1 equiv); CuCl was then added (1.2 mg 0.012 mmol, 0.20 equiv) followed by MeOH (1 mL), NH_2OH•HCl (4.2 mg, 0.62 mmol, 1.0 equiv) and *n*-butylamine (60 μL, 0.62 mmol, 10 equiv). The mixture was allowed to cool to 0 ºC and a solution of alkynyl bromide **1.57** (14.9 mg, 0.0924 mmol, 1.5 equiv) was introduced into the mixture as a CH_2Cl_2 solution (1 mL) over a period of 1 h by syringe pump. The mixture turned immediately green upon addition of **1.57**, after the addition was complete, the mixture was allowed to stir for an additional 2 h. The reaction was quenched by the addition of water, the aqueous layer

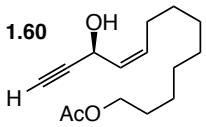
56. H. Yun, S. J. Danishefsky, *J. Org. Chem.* **2003**, *68*, 4519–4522.

was washed with EtOAc (3 x 10 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford yellow oil which was subsequently purified by SiO_2 chromatography (3:1 hexanes:EtOAc) to afford **1.58** as colorless oil (10.2 mg, 0.0392 mmol, 64% yield). **IR (neat):** 3330 (br), 2956 (m), 2926 (s), 2855 (m), 1464 (w), 1407 (w), 1379 (w), 1303 (w), 1264 (w), 1118 (w), 1015 (s), 986 (s), 933 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.94 (ddd, *J* = 17.2, 10.2, 5.3 Hz, 1H), 5.61 (ddd, *J* = 10.7, 7.3 Hz, 7.3 1H), 5.55–5.43 (m, 2H), 5.26 (ddd, *J* = 10.1, 1.1, 1.1 Hz, 1H), 5.21 (br d, *J* = 8.3 Hz, 1H), 4.94 (br s, 1H), 2.11 (dddd, *J* = 7.4, 7.4, 7.4, 1.5 Hz, 2H), 1.92 (br s, 1H), 1.86 (br s, 1H), 1.46–1.34 (m, 2H), 1.27 (m, 10H), 0.88 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 135.9, 134.9, 127.8, 117.5, 80.0, 78.4, 70.5, 68.8, 63.7, 58.8, 31.9, 29.4, 29.3, 29.2, 27.8, 22.8, 14.2; **HRMS (ESI+):** Calcd for $C_{17}H_{23}O$ $[M+H-H_2O]^+$: 243.17489 found: 243.17478; **$[\alpha]^{22}_D$** = +150.48 (*c* = 1.02 $CHCl_3$), **$[\alpha]_{365}$** = +763.1 (*c* = 0.031 CH_3CN), **$[\alpha]_{405}$** = +588.0 (*c* = 0.031 CH_3CN), **$[\alpha]_{436}$** =+527.0 (*c*=0.031 CH_3CN), **$[\alpha]_{546}$** = +588.0 (*c* = 0.031 CH_3CN), **$[\alpha]_{589}$** = +199.3 (*c* = 0.031 CH_3CN), **$[\alpha]_{633}$** = +167.6 (*c* = 0.031 CH_3CN).

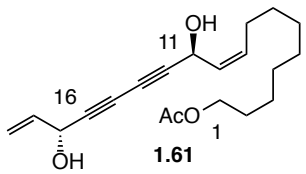


(*S*,*Z*)–11-((*tert*-Butyldimethylsilyl)oxy)-13-(triisopropylsilyl)tridec-9-en-12-yn-1-yl acetate: According to the general procedure for cross–metathesis, a vial containing silyl ether **1.54** (32.6 mg, 0.0921 mmol) was charged with terminal alkene **1.59** (54.8 mg, 0.276 mmol, 3 equiv) and then a solution of **1.13** (46 μL, 0.0028 mmol, 3 mol %). The mixture was allowed to stir under a vacuum of 7 torr for 8 h. The resulting residue was purified by silica gel chromatography (Gradient from 200:1 hexanes:Et_2O to 50:1 hexanes:Et_2O) to deliver the *Z* disubstituted alkene as yellow oil (45.3 mg, 0.0866 mmol, 94% yield, 92% *Z*). **IR (neat):** 2928 (s), 2859 (s), 1743 (s), 1463 (m), 1387 (w), 1364 (w), 1236 (s), 1061 (br), 882 (w), 859 (w), 836 (s), 777 (s), 676 (s), 662 (s); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.53 (ddd, *J* = 10.8, 7.8, 0.8 Hz, 1H), 5.43 (m, 1H), 5.15 (d, *J* = 8.0 Hz, 1H), 4.90 (diagnostic signal for *E* isomer, d, *J* = 5.2 Hz, 1H), 4.05 (t, *J* = 6.8 Hz, 2H), 2.08 (m, 2H), 2.04 (s, 3H), 1.61 (t, *J* = 7.2, 2H), 1.43–1.25 (m, 12H), 1.05 (s, 21H),

0.99 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); **^{13}C NMR (100 MHz $CDCl_3$):** δ 171.4, 131.0, 130.9, 108.6, 84.7, 64.8, 59.8, 29.5, 29.5, 29.3, 28.8, 27.8, 26.0, 25.9, 21.2, 18.7, 18.4, 11.4, –4.2, –4.5; **HRMS (ESI+):** Calcd for $C_{30}H_{59}O_3Si_2$ $[M+H]^+$: 523.40027; found: 523.40013; **$[\alpha]^{25.0}_D$** = +412.2 (*c* = 1.00 $CHCl_3$).

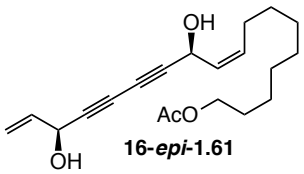


(*S*,*Z*)–11-Hydroxytridec-9-en-12-yn-1-yl acetate (1.60): To a vial containing the aforementioned silyl ether (35.0 mg, 0.0670 mmol) was added a solution of tetra-*n*-butyl ammonium fluoride (1 M in THF; 340 μL, 0.340 mmol, 3.0 equiv), and the mixture was allowed to stir for 1 h. The solution was diluted with Et_2O to precipitate tetra-*n*-butyl ammonium fluoride. The resulting suspension was filtered through a short plug of silica gel, which was washed with Et_2O; the filtrate was concentrated *in vacuo* and purified by silica gel chromatography (2:1 hexanes:EtOAc) to afford **1.60** as yellow oil (12.5 mg, 0.0693 mmol, 94% yield, 92% *Z*): **IR (neat):** 3429 (br), 3298 (s), 3020 (w), 2926 (m), 2855 (m), 1736 (s), 1657 (w), 1366 (m), 1242 (s), 1028 (s), 649 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.80–5.40 (m, 2H), 5.13 (br, *J* = 4.9, 2.3 Hz, 1H), 4.03 (t, *J* = 6.8 Hz, 2H), 2.49 (d, *J* = 2.2 Hz, 1H), 2.18–2.05 (m, 2H), 2.03 (s, 3H), 1.82 (d, *J* = 5.0 Hz, 1H), 1.66–1.49 (m, 3H), 1.45–1.20 (m, 12H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 171.4, 134.2, 128.8, 84.2, 73.0, 64.8, 58.2, 29.4, 29.4, 29.3, 29.2, 28.7, 27.7, 26.0, 21.2; **HRMS (ESI+):** Calcd for $C_{15}H_{25}O_3$ $[M+H–H_2O]^+$: 253.18089; found: 253.18037; **$[\alpha]^{25.0}_D$** = +20.12 (*c* = 1.00 $CHCl_3$).



(11-*S*,16-*R*,*Z*)–11,16-Dihydroxyoctadeca-9,17-dien-12,14-diyn-1-yl acetate (1.61): The following reaction was conducted under nitrogen in oven-dried glassware according to a previously reported procedure.[56] All operations were performed in the absence of light. An oven-dried 8 mL vial equipped with stir bar was charged with alkyne substrate **1.60**

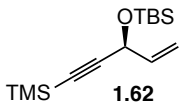
(10.2 mg, 0.040 mg, 1 equiv); CuI was subsequently added (0.8 mg 0.008 mmol, 0.2 equiv), followed by MeOH (1 mL) and NH_2OH•HCl (2.8 mg, 0.040 mmol, 1.0 equiv) and *n*-butylamine (40 μL, 0.404 mmol, 10 equiv). The mixture was allowed to cool to 0 ºC and bromoalkyne **1.57** (9.7 mg, 0.061 mmol, 1.5 equiv) was introduced as a CH_2Cl_2 solution (1 mL) over a period of 1 h by syringe pump. The mixture turned green immediately upon addition of bromide **1.57**. After addition was complete the mixture was allowed to stir an additional 2 h, after which the reaction was quenched by the addition of water. 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 concentrated *in vacuo* to afford yellow oil, which was purified by silica gel chromatography (gradient from 3:1 hexanes:EtOAc to 1:1 hexanes:EtOAc) to afford **1.61** as a colorless oil (8.6 mg, 0.026 mmol, 64 % yield). **IR (neat):** 3396 (br), 3021 (w), 2925 (s), 2854 (m), 1736 (m), 1716 (s), 1655 (w), 1553 (w), 1460 (m), 1390 (m), 1366 (m), 1258 (s), 1118 (w), 1024 (s), 932 (m); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 5.94 (ddd, *J* = 17.0, 10.2, 5.3 Hz, 1H), 5.60 (dtd, *J* = 10.6, 7.4, 1.0 Hz, 1H), 5.55–5.44 (m, 2H), 5.26 (ddd, *J* = 10.2, 1.4, 0.9 Hz, 1H), 5.20 (ddt, *J* = 8.4, 5.2, 0.9 Hz, 1H), 5.01–4.90 (m, 1H), 4.06 (t, *J* = 6.8 Hz, 2H), 2.18–2.08 (m, 2H), 2.05 (s, 3H), 1.88 (d, *J* = 5.2 Hz, 1H), 1.66–1.58 (m, 2H), 1.41–1.35 (m, *J* = 6.8, 3.8 Hz, 2H), 1.36–1.25 (m, 10H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 171.6, 136.0, 134.6, 128.0, 117.4, 79.9, 78.5, 70.3, 68.9, 64.8, 63.6, 58.8, 30.5, 29.4, 29.2, 29.1, 28.7, 27.7, 25.9, 21.2; **HRMS (ESI+):** Calcd for $C_{20}H_{27}O_3$ $[M+H-H_2O]^+$: 315.19602; found, 315.19743; $[\alpha]^{22}_D$ = +123.7 (*c* = 1.00 $CHCl_3$), $[\alpha]_{365}$ = +551.20 (*c* = 0.028 MeCN), $[\alpha]_{405}$ = +405.43 (*c* = 0.028 MeCN), $[\alpha]_{436}$ = +345.1 (*c* = 0.028 MeCN), $[\alpha]_{546}$ = +180.11 (*c* = 0.028 MeCN), $[\alpha]_{589}$ = +123.5 (*c* = 0.028 MeCN), $[\alpha]_{633}$ = +145.64 (*c* = 0.028 MeCN).



16-*epi*-1.61

(11-*S*,16-*S*,*Z*)-11,16-Dihydroxyoctadeca-9,17-dien-12,14-diyn-1-yl acetate (16-*epi*-1.61): The following reaction was conducted under nitrogen in oven-dried glassware according to a previously reported procedure.[56] All operations were performed in the

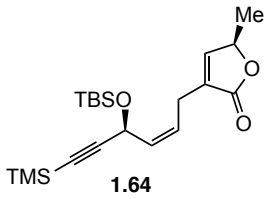
absence of light. An oven-dried 8 mL vial equipped with stir bar was charged with alkyne substrate **1.60** (10.2 mg, 0.0404 mg, 1 equiv), CuI was added (0.8 mg 0.008 mmol, 0.2 equiv) followed by MeOH (1 mL) and NH_2OH•HCl (2.8 mg, 0.04 mmol, 1 equiv) and *n*-butylamine (40 μL, 0.40 mmol, 10 equiv). The mixture was allowed to cool to 0 ºC and ***ent*-1.57** was introduced (9.7 mg, 0.061 mmol, 1.5 equiv) as a CH_2Cl_2 solution (1 mL) over a period of 1 h by syringe pump. The mixture turned green immediately upon addition of bromide **1.57**. After addition was complete the mixture was allowed to stir an additional 2 h, after which the reaction was quenched by the addition of water. The reaction was then quenched by the addition of water, 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 concentrated to afford yellow oil, which was subsequently purified by silica gel chromatography (gradient from 3:1 hexanes:EtOAc to 1:1 hexanes:EtOAc) to afford **16-*epi*–1.61** as colorless oil (8.6 mg, 0.026 mmol, 64% yield). **IR (neat):** 3389 (br), 3021 (w), 2926 (s), 2854 (m), 1736 (m), 1716 (s), 1655 (w), 1554 (w), 1461 (m), 1390 (m), 1367 (m), 1255 (s), 1118 (w), 1026 (s), 933 (m); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 5.94 (ddd, *J* = 17.0, 10.2, 5.3 Hz, 1H), 5.60 (ddt, *J* = 10.6, 7.4, 1.0 Hz, 1H), 5.55–5.44 (m, 2H), 5.26 (ddd, *J* = 10.2, 1.4, 0.9 Hz, 1H), 5.20 (ddt, *J* = 8.4, 5.2, 0.9 Hz, 1H), 5.01–4.90 (m, 1H), 4.06 (t, *J* = 6.8 Hz, 2H), 2.18–2.08 (m, 2H), 2.05 (s, 3H), 1.88 (d, *J* = 5.2 Hz, 1H), 1.66–1.58 (m, 2H), 1.41–1.35 (m, 2H), 1.36–1.25 (m, 10H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 171.6, 136.0, 134.6, 128.0, 117.4, 79.9, 78.5, 77.5, 77.4, 76.8, 70.3, 68.9, 64.8, 63.6, 58.7, 30.5, 29.3, 29.2, 29.1, 28.7, 27.7, 25.9, 21.2; **HRMS (ESI+):** Calcd for $C_{20}H_{27}O_3$ $[M+H–H_20]^+$: 315.19602 found, 315.19661; **$[\alpha]^{22}_D$** = +165.0 (*c* = 1.00 $CHCl_3$); **$[\alpha]_{365}$** = >999 (*c* = 0.028 MeCN), **$[\alpha]_{405}$** = +956.2 (*c* = 0.028 MeCN), **$[\alpha]_{436}$** = +777.6 (*c* = 0.028 MeCN), **$[\alpha]_{546}$ =** +402.0 (*c*= 0.028 MeCN), **$[\alpha]_{589}$ = +302.4** (*c* = 0.028 MeCN), **$[\alpha]_{633}$ = +248.5** (*c* = 0.028 MeCN).



1.62

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-(trimethylsilyl)pent-1-en-4-yne (1.62) IR (neat): 2958 (w), 2930 (w), 2898 (w), 2858 (w), 2174 (w), 1472 (w), 1464 (w), 1407 (w), 1362

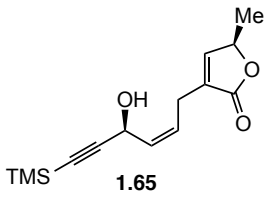
(w), 1327 (w), 1250 (m), 1134 (w), 1071 (m), 1031 (m), 1006 (m), 982 (w), 926 (w), 911 (w), 833 (s), 776 (m), 699 (m), 629 (w), 580 (w), 511 (w), 492 (w), 403 (w), 379 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.89 (ddd, *J* = 17.1, 10.1, 4.7 Hz, 1H), 5.40 (ddd, *J* = 16.9, 1.5, 1.5 Hz, 1H), 5.13 (ddd, *J* = 10.2, 1.6, 1.6 Hz), 4.89 (ddd, *J* = 4.8, 1.7, 1.7 Hz, 1H), 0.93 (s, 9H), 0.17 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 137.7, 115.0, 105.3, 90.2, 64.2, 26.0, 18.5, –0.1, –4.3, –4.6; **HRMS (ESI+):** Calcd for $C_{14}H_{29}O_1Si_2^+$ $[M+H]^+$: 269.17494 found, 269.17569; **$[\alpha]^{24.5}_D$** = –39.96 (*c* = 1.00 $CHCl_3$).



1.64

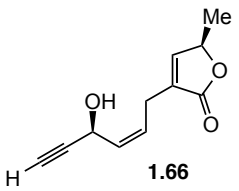
(*R*)-3-((*S*,*Z*)–4-(*tert*-Butyldimethylsilyloxy)-6-(trimethylsilyl)hex-2-en-5-ynyl)-5-methylfuran-2(5*H*)-one (1.64): The following transformation was carried out according to the above-mentioned cross-metathesis procedure. Silyl ether **1.62** (168 mg, 0.627 mmol, 3 equiv) and allyl furanone **1.63** (28.9 mg, 0.209 mmol, 1 equiv) were mixed in an oven dried 4 mL vial equipped with a stir bar and chlorobenzene (0.21 mL) was added. To the resulting solution was added Mo complex **1.13** (0.21 mL, 0.013 mmol, 0.06 equiv). The vessel was equipped with a vacuum adapter and placed under 100 torr vacuum. The solution rapidly turned from light orange to blood red. The mixture was allowed to stir under vacuum for 5.5 hours, after which time it was removed from the glove box, exposed to ambient atmosphere and a ^{1}H NMR was recorded to assess conversion; complete consumption (>98%) of furanone **1.63** was observed. The resulting residue was purified by silica gel chromatography (5% EtOAc/hexanes) to afford **1.64** as clear colorless oil. (44.1 mg, 0.116 mmol, 56% yield, 91% *Z*). **IR (neat):** 2957 (w), 2930 (w) 2857 (w), 2171 (w), 1755 (s), 1250 (m), 1069 (m), 838 (s), 778 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.03 (ap. q, *J* = 1.9 Hz, 1H), 5.73–5.69 (m, 1H), 5.56 (dtd, *J* = 10.8, 7.4, 1.2 Hz, 1H), 5.10 (dd, *J* = 7.8, 1.4 Hz, 1H), 5.04–4.95 (m, 1H), 3.09 (ap. dd, *J* = 7.4, 1.8 Hz, 2H), 1.40 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.14 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 173.4, 150.0, 133.5, 132.4, 125.1, 105.9, 89.6, 77.9,

59.6, 25.9, 23.8, 19.2, 18.4, –0.1, –4.2, –4.5; **HRMS (ESI+):** Calcd for $C_{20}H_{38}NO_3Si_2^+$ $[M+NH_4]^+$: 396.2385; found: 396.2381; $[\alpha]^{24.8}_D$ = + 39.9 (*c* = 1.00 $CHCl_3$).



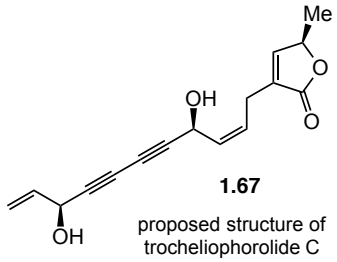
1.65

(*R*)–3-((*S*,*Z*)-4-Hydroxy-6-(trimethylsilyl)hex-2-en-5-ynyl)-5-methylfuran-2(5*H*)-one (1.65): Silyl ether **1.64** (40.0 mg, 0.105 mmol, 1 equiv) was dissolved in 3 mL of a 1:1 mixture of CH_2Cl_2:MeOH. To this mixture mixture was added (±)-camphorsulfonic acid (3 mg, 0.01 mmol, 0.1 equiv). TLC analysis (50% EtOAc/hexanes) showed complete consumption (>98%) of the furanone after 7 hours. The solution was then diluted with 50 mL 50% EtOAc/hexanes and washed with 15 mL of a half-saturated aqueous solution of $NaHCO_3$ and 15 mL brine, respectively. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Analysis of the ^{1}H NMR spectrum of the resulting residue indicated no erosion of the *Z*:*E* ratio. The residue was purified by silica gel chromatography (gradient of 20% to 30% EtOAc/hexanes), affording **1.65** as clear colorless oil (22.7 mg, 0.0858 mmol, 81% yield). Some, but not complete, separation of the olefin isomers occurred under the stated chromatography conditions, and the characterized material is now 96:4 *Z*:*E*. The earlier eluting fractions were enriched in the *Z* isomer. **IR (neat):** 3416 (br.) 2960 (w), 2900 (w) 2172 (w) 1750 (s), 1321 (w), 1250 (w), 1027 (w), 844 (s), 760 (w). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.10 (ap. q, *J* = 1.6 Hz, 1H), 5.77 (dd, *J* = 9.5, 9.0 Hz, 1H), 5.57 (ap. qd, *J*= 8.8, 1.6 Hz, 1H), 5.21 (dd, *J* = 8.4, 3.7 Hz, 1H), 5.04–4.99 (m, 1H), 3.20 (AB ddd, 16.2, 8.8, 1.4 Hz, 1H), 3.09 (AB ddd, 16.7, 7.1, 1.4 Hz, 1H), 2.77 (br. s, 1H), 1.42 (d, *J* = 6.8 Hz, 3H), 0.16 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 173.7, 150.6, 132.5, 131.8, 126.9, 105.1, 90.1, 78.0, 58.4, 24.0, 19.1, 0.0; **HRMS (ESI+):** Calcd for $C_{14}H_{21}O_3Si^+$ $[M+H]^+$: 265.1254; found: 265.1267; $[\alpha]^{22.6}_D$ = + 169.7 (*c* = 1.00 $CHCl_3$).



1.66

(*R*)-3-((*S*,*Z*)-4-Hydroxyhex-2-en-5-ynyl)-5-methylfuran-2(5*H*)-one (1.66): Allylic alcohol **1.66** (27.5 mg, 0.104 mmol, 1 equiv) was dissolved in 3 mL tetrahydrofuran. To this solution was added *o*-nitrophenol (43 mg, 0.31 mmol, 3 equiv), causing the solution to turn pale yellow. To this mixture tetrabutylammonium fluoride tri-hydrate (66 mg, 0.21 mmol, 2 equiv) was added, upon which the solution became dark yellow/orange. After 1 hour, TLC analysis (50% EtOAc/hexanes) showed complete consumption of the starting material. The reaction was quenched with 5 mL of a saturated solution of NH_4Cl and washed with 25 mL 50 % mixture of EtOAc/hexanes. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography with a gradient of 20 % EtOAc/hexanes (to remove the *o*-nitrophenol), followed by 40% EtOAc/hexanes, affording the desired terminal alkyne **1.66** (16.9 mg, 0.0879 mmol, 85% yield) as clear colorless oil. **IR (neat):** 3407 (br), 3291 (br), 2983 (w), 2934 (w), 1744 (s), 1322 (w), 1084 (w), 1026 (m), 657 (br); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.11 (ap. dd, *J* = 1.6, 1.4 Hz, 1H), 5.81–5.76 (m, 1H), 5.62–5.54 (m, 1H), 5.26–5.22 (m, 1H), 5.07–4.99 (m, 1H), 3.26–3.16 (m, 1H), 3.14–3.05 (m, 1H), 2.96 (br. S, 1H), 2.50 (d, *J* = 2.1 Hz, 1H), 1.42 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 173.8, 150.8, 132.3, 131.6, 127.2, 83.6, 78.0, 73.3, 57.8, 24.0, 19.1; **HRMS (ESI+):** Calcd for $C_{11}H_{15}O_3^+$ [M+H]$^+$: 193.0859; found: 193.0869; $[\alpha]^{22.3}_D$ = +149.7 (*c* = 1.00 $CHCl_3$).



1.67

proposed structure of trocheliophorolide C

(*R*)-3-((4-*S*,9-*S*,*Z*)-4,9-Dihydroxyundeca-2,10-dien-5,7-diynyl)-5-methylfuran-2(5*H*)-one (Proposed structure for trocheliophorolide C; 1.67): The following reaction was conducted under nitrogen in oven-dried glassware according to a previously reported

procedure[56]. The above-mentioned terminal alkyne **1.66** (18.4 mg, 0.0957 mmol, 1 equiv) was dissolved in 2 mL MeOH (deoxygenated by sparging with N_2 for 20 minutes). The vessel was wrapped in aluminum foil to exclude light and cooled to 0 °C. *n*-Butylamine (0.094 mL, 0.96 mmol, 10 eq) was added to the solution, followed by CuI (1.8 mg, 0.00096 mmol, 0.1 equiv) and hydroxylamine hydrochloride (7 mg, 0.1 mmol, 1 equiv). Over the following hour, a solution of alkynyl bromide ***ent*-1.57** (30.7 mg, 0.191 mmol, 2 equiv) in 2 mL CH_2Cl_2 was added in a drop-wise manner. The resulting solution turned from light yellow to dark orange over time. The mixture was allowed to stir for an additional 2 h, after which, TLC analysis (50% EtOAc/hexanes) showed that alkynyl bromide remained, but the *Z* alkene-containing terminal alkyne was fully consumed. The reaction was then quenched by the addition of 2 mL of a saturated aqueous solution of NH_4Cl. The mixture was then diluted with 20 mL 50% EtOAc/hexanes, washed with a saturated aqueous solution of NH_4Cl and brine. The organic layer was dried over Na_2SO_4, filtered, then concentrated *in vacuo*. The resulting brown residue was purified by silica gel chromatography (40% EtOAc/hexanes) to yield trocheliophorolide C (as proposed), **1.67** (18.2 mg, 0.067 mmol, 70% yield) as a semi-stable yellow oil.[57] **IR (neat):** 3375 (br), 3087 (w), 3028 (w), 2983 (w), 2932 (w), 2871 (w), 1730 (s), 1650 (w), 1480 (w), 1321 (m), 1084 (m), 1022 (s), 958 (m), 933 (w), 865 (w), 589 (w), 502 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.11 (ap. q, *J* = 1.6 Hz, 1H), 5.97–5.88 (m, 1H), 5.78–5.72 (m, 1H), 5.64–5.57 (m, 1H), 5.49–5.43 (m, 1H), 5.30 (d, *J* = 8.2 Hz, 1H), 5.28–5.23 (m, 1H), 5.07–5.00 (m, 1H), 4.95–4.92 (m, 1H), 3.23–3.14 (m, 1H), 3.13–3.04 (m, 1H), 1.43 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.0, 151.0, 135.9, 131.4, 127.6, 117.43, 79.5, 78.6, 78.3, 70.2, 69.1, 63.5, 58.4, 24.1, 19.1; **HRMS (ESI+):** Calcd for $C_{16}H_{20}NO_4$ $[M+NH_4^+]^+$: 290.1386; found, 290.1404; $[\alpha]^{23.4}_D$ = +299.7 (*c* = 0.10 $CHCl_3$); **$[\alpha]^{23.4}_D$** = +811.7 (*c* = 0.11 EtOH).

^{1}H NMR spectra for 1.67 recorded in four other solvents:

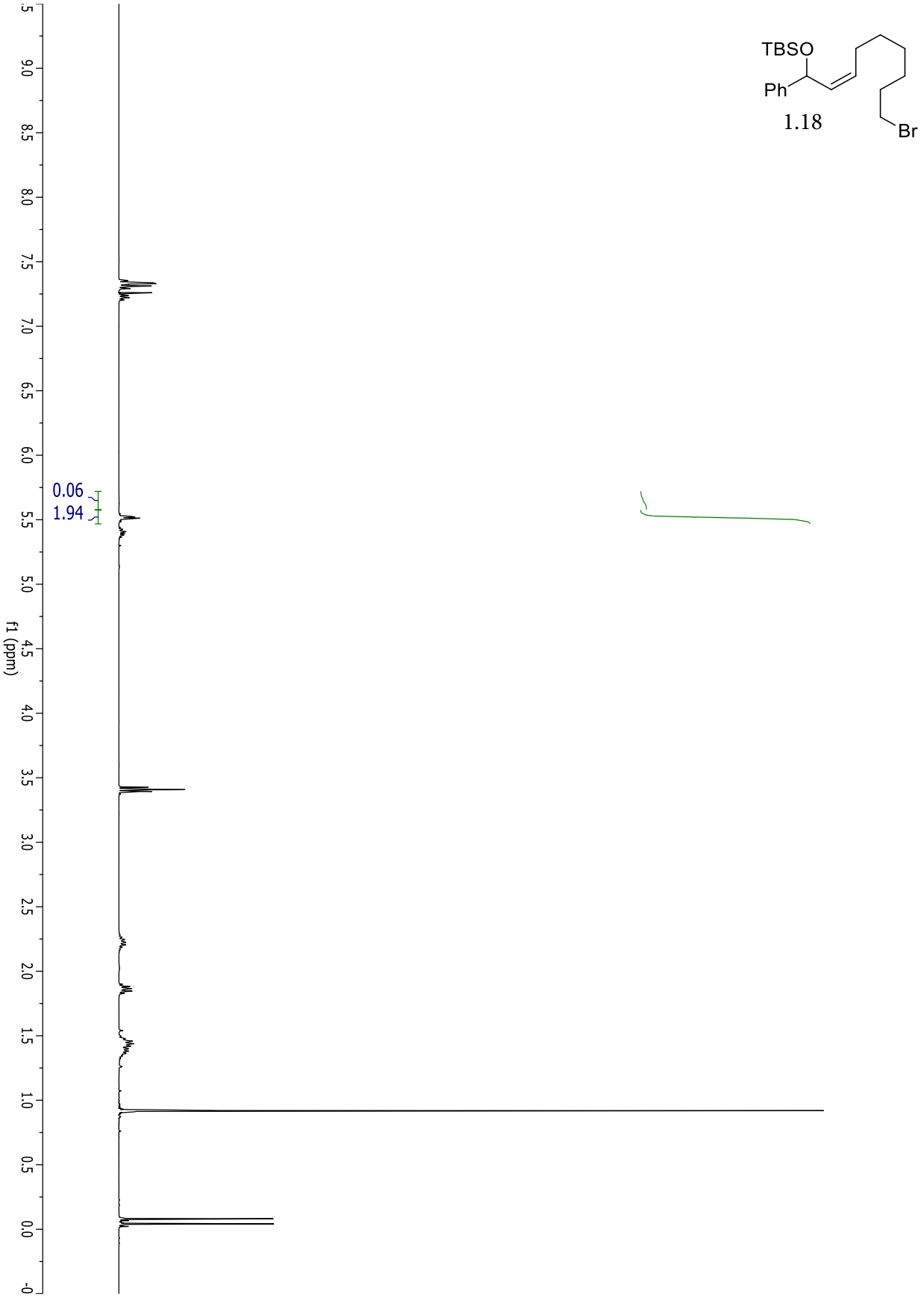
57. Compound **1.67** slowly turns red and solidifies upon storage in the oil form. Compound **1.67** was stored in frozen benzene, under N_2 protected from light. Special precautions were not taken to exclude air from the preparation of the NMR samples.

^{1}H NMR (400 MHz, **C_6D_6**): δ 6.01 (ap. q, *J* = 1.6 Hz, 1H), 5.80–5.58 (m, 2H), 5.26 (dt, *J* = 17.1, 1.4 Hz, 1H), 5.19 (m, 1H), 5.10 (d, *J* = 8.2 Hz, 1H), 4.91 (dt, *J* = 10.2, 1.3 Hz, 1H), 4.57 (dd, *J* = 5.2, 0.9 Hz, 1H), 4.16 (m, 1H), 2.84 (m, 1H), 2.79–2.63 (m, 1H), 0.78 (d, *J* = 6.8 Hz, 3H).

^{1}H NMR (400 MHz, **CD_3OD**): δ 7.28 (d, *J* = 1.6 Hz, 1H), 5.91 (ddd, *J* = 17.1, 10.2, 5.5 Hz, 1H), 5.77–5.57 (m, 2H), 5.39 (dt, *J* = 17.1, 1.4 Hz, 1H), 5.24 (dd, *J* = 6.8, 0.8 Hz, 1H), 5.19 (dt, *J* = 10.2, 1.3 Hz, 1H), 5.09 (m, 1H), 4.88 (dt, *J* = 5.6, 0.7 Hz, 1H), 3.14–3.03 (m, 2H), 1.39 (d, *J* = 6.8 Hz, 3H).

^{1}H NMR (400 MHz, **CD_3CN**): δ 6.95–6.91 (m, 1H), 5.65 (dddd, *J* = 16.7, 10.2, 5.5, 0.9 Hz, 1H), 5.49–5.33 (m, 2H), 5.18–5.07 (m, 1H), 4.98 (d, *J* = 5.3 Hz, 1H), 4.96–4.91 (m, 1H), 4.77 (dd, *J* = 6.9, 1.9 Hz, 1H), 4.70–4.57 (m, 1H), 3.6)3–3.40 (br m, 2H 2.79 (dt, *J* = 3.6, 1.9 Hz, 2H), 1.10 (d, *J* = 6.8, 3H).

^{1}H NMR (400 MHz, **C_5D_5N**): δ 7.09 (dd, *J* = 1.6, 0.9 Hz, 1H), 6.23 (ddd, *J* = 17.0, 10.1, 5.2 Hz, 1H), 6.14–5.99 (m, 1H), 5.92–5.70 (m, 2H), 5.65 (dt, *J* = 17.0, 1.5 Hz, 1H), 5.36 (dt, *J* = 5.3, 1.4 Hz, 1H), 5.25 (dd, *J* = 10.1, 0.6 Hz, 1H), 5.03–4.81 (m, 1H), 3.39–3.19 (m, 2H), 1.23 (d, *J* = 6.8 Hz, 3H). Decomposition to an insoluble red solid was observed after removal of d_5-pyridine.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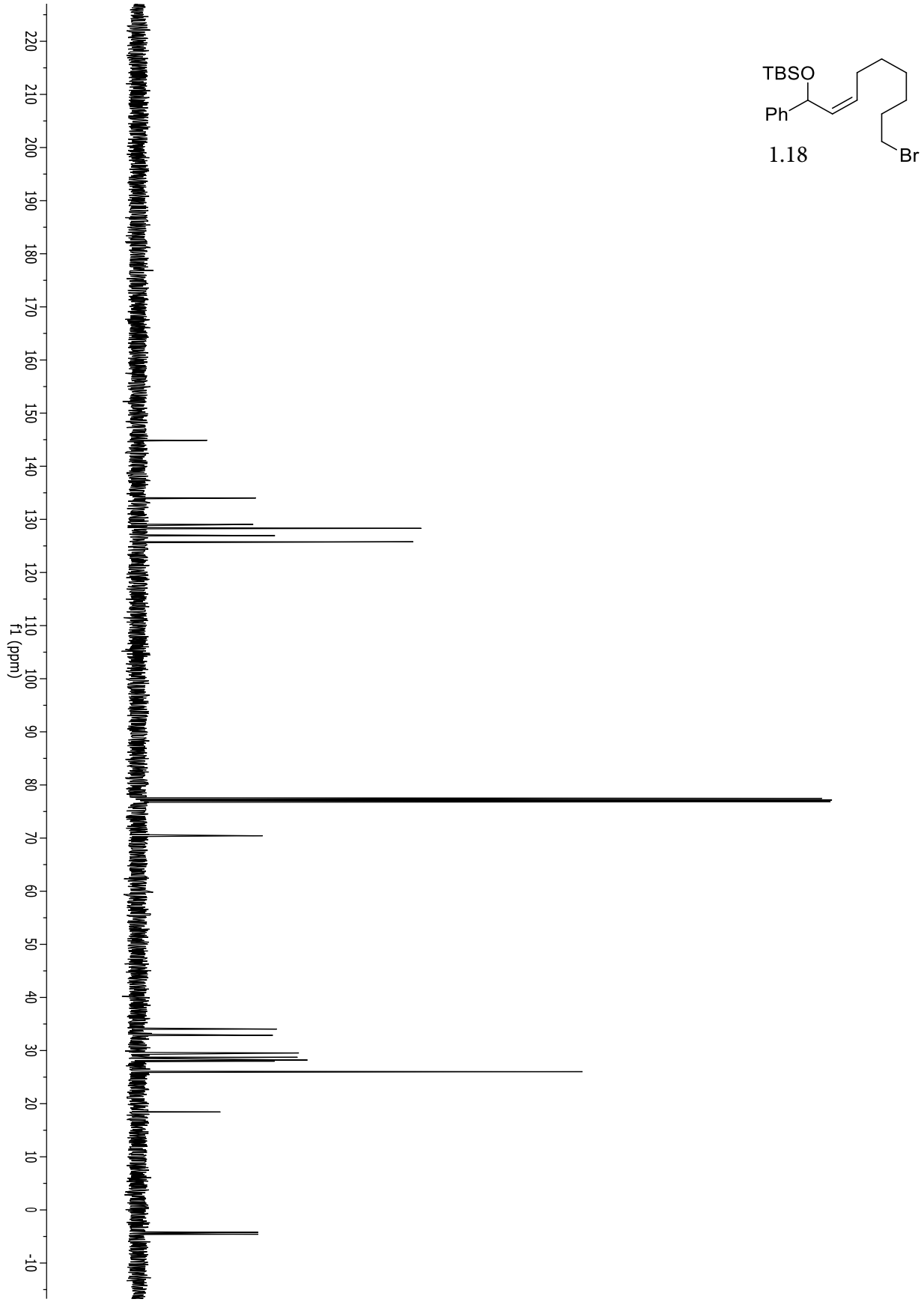
Br
0.06
1.94
f1 (ppm)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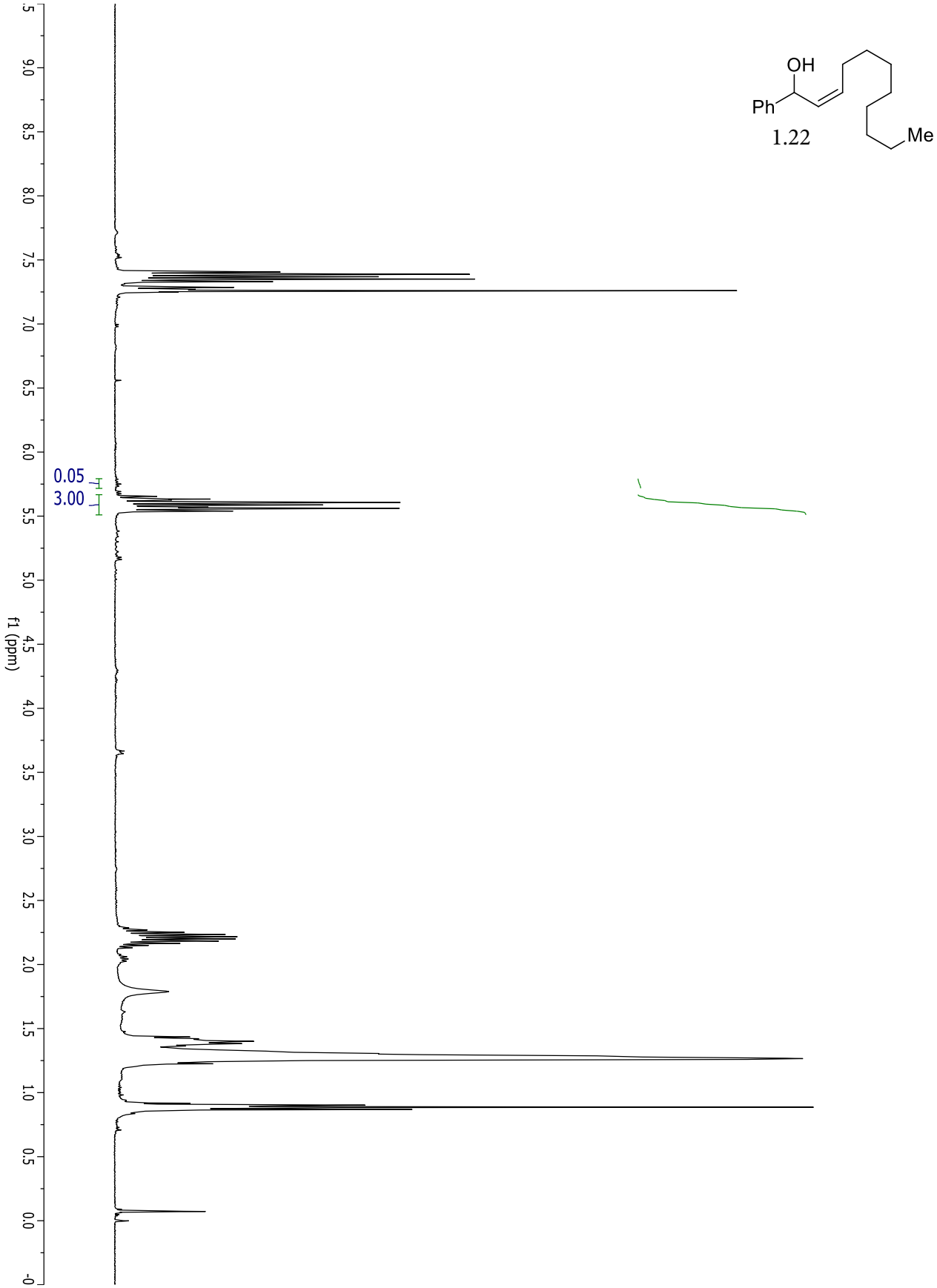
0
-10

TBSO
Ph
Br

1.18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Me
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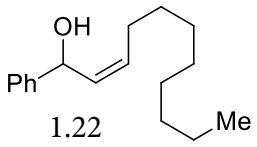
3.00
f1 (ppm)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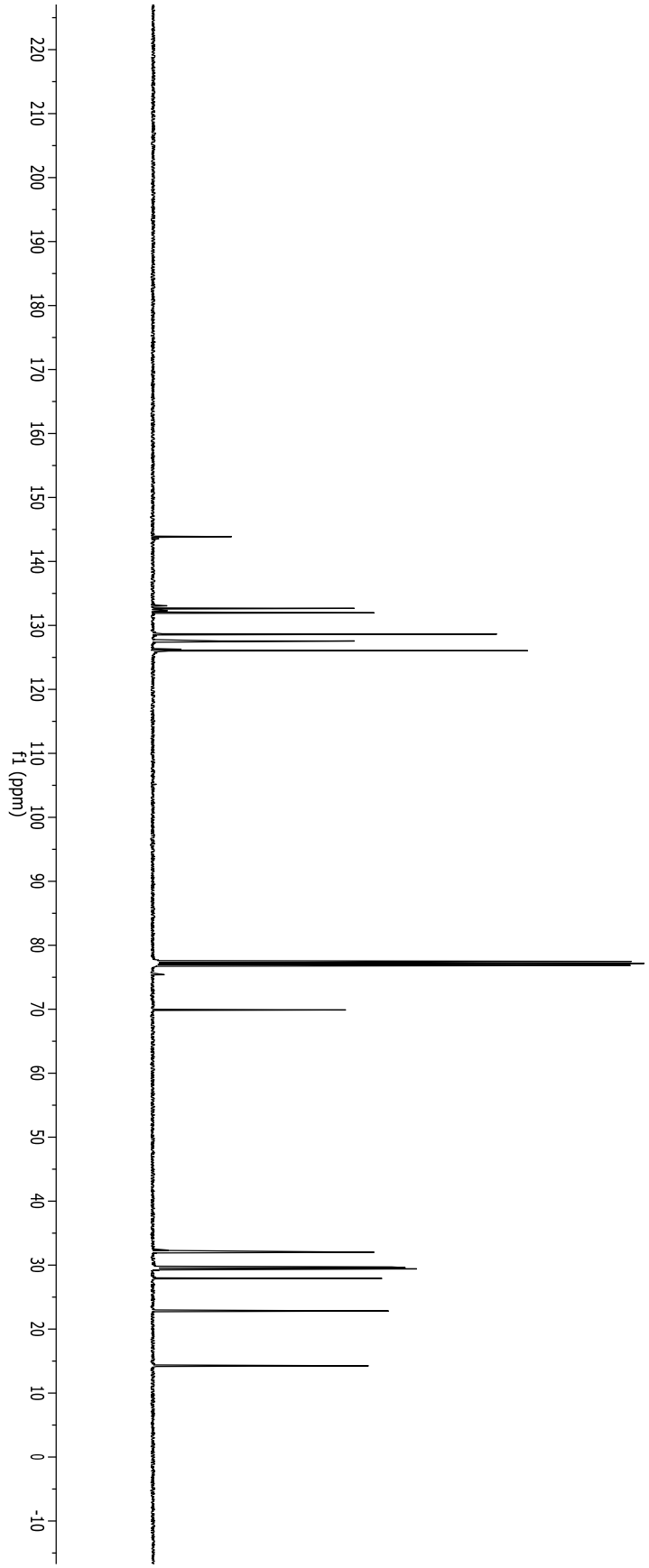
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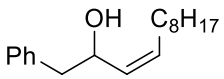
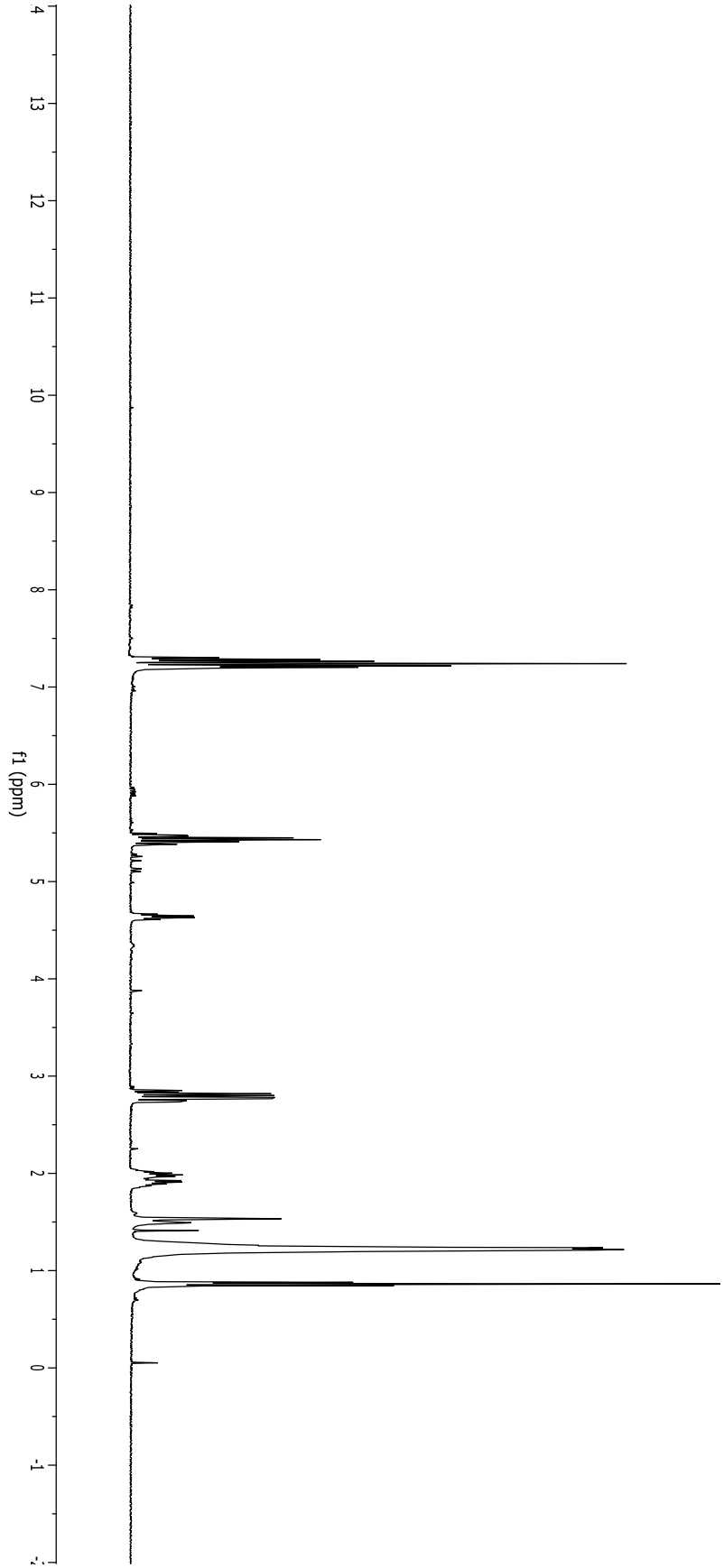
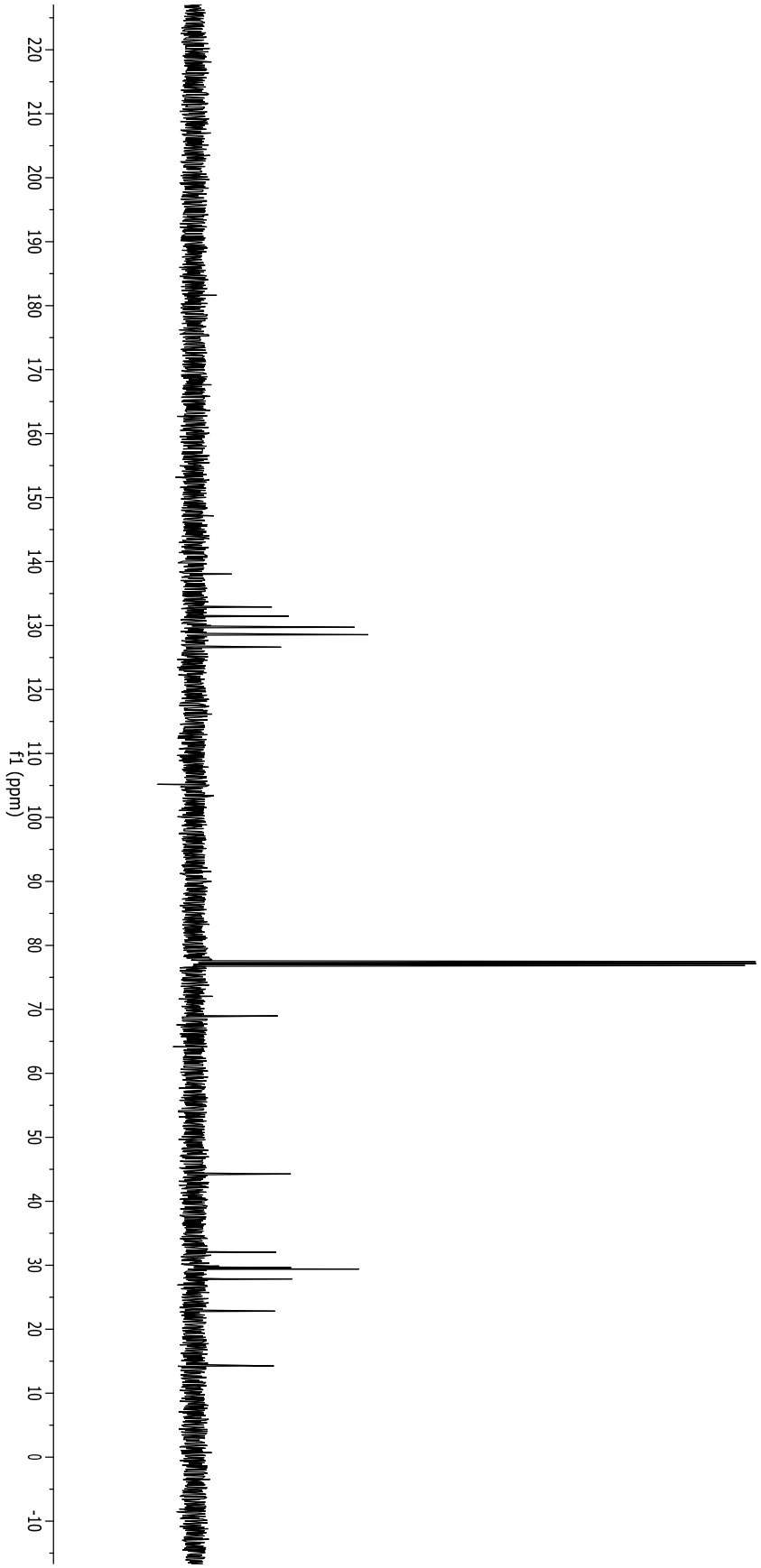


1.27

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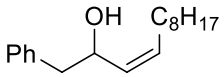
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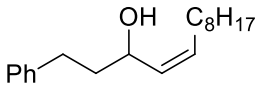
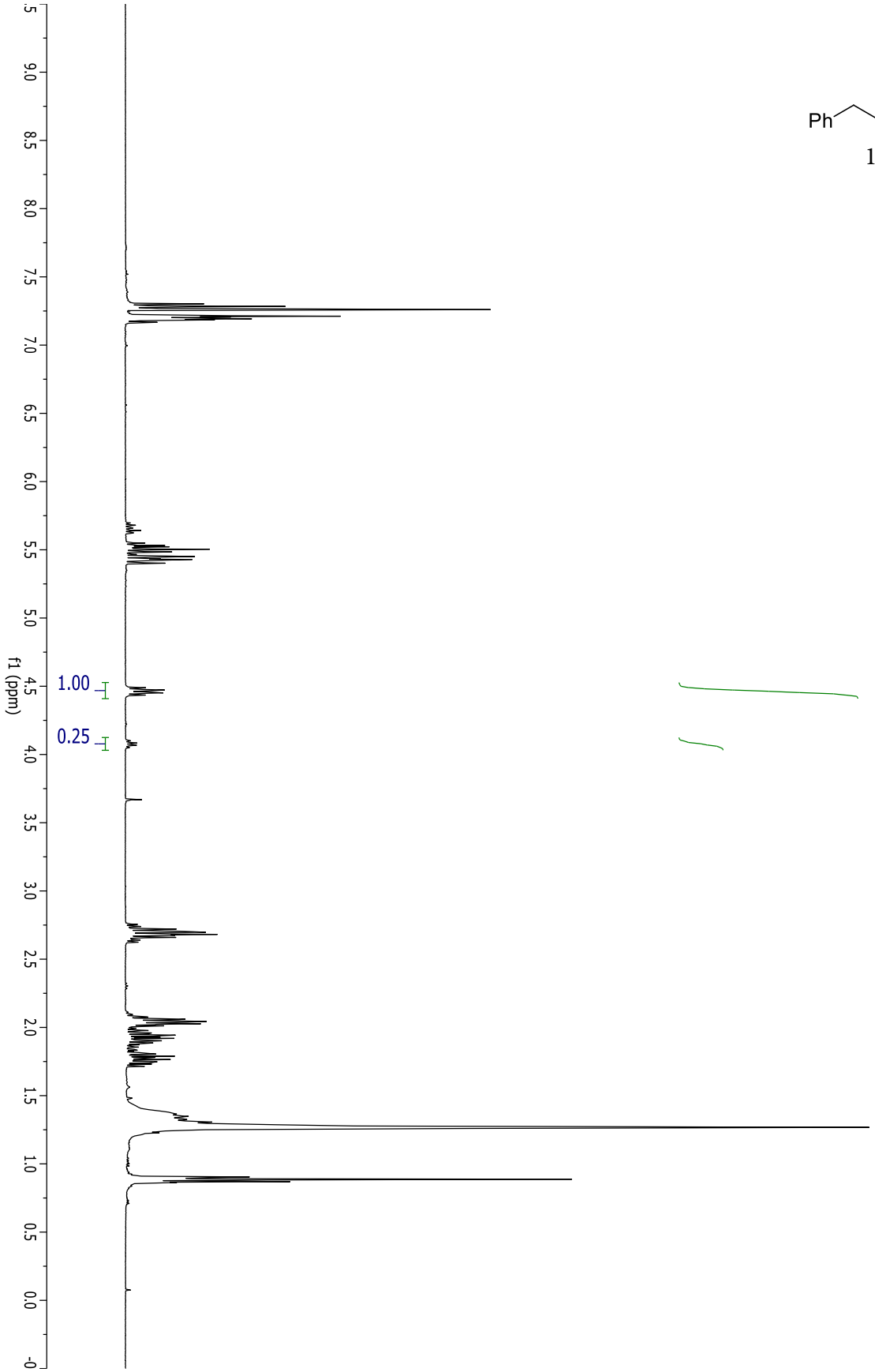
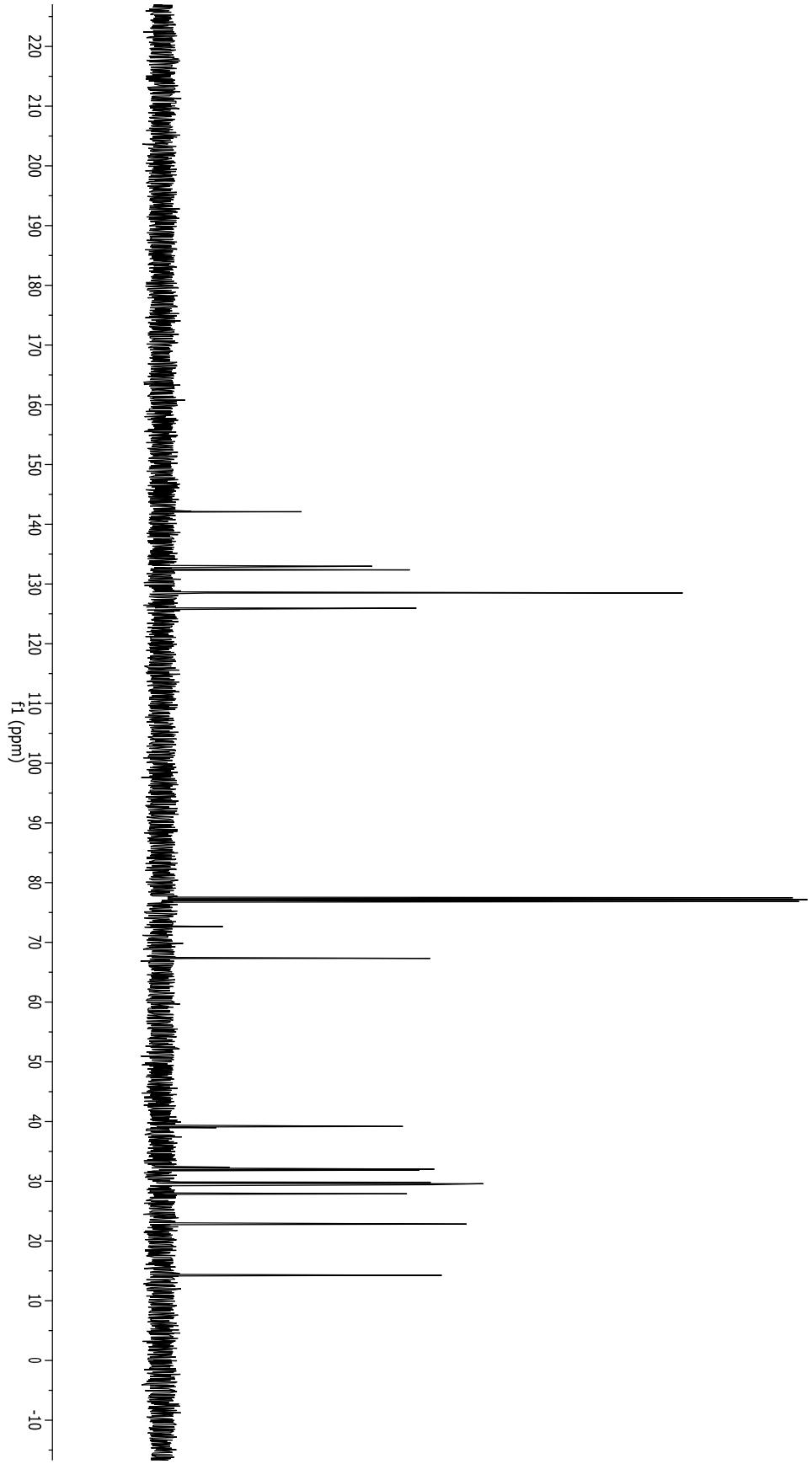
C8H17
Ph

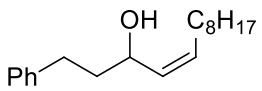
1.27



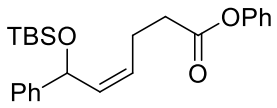
1.34



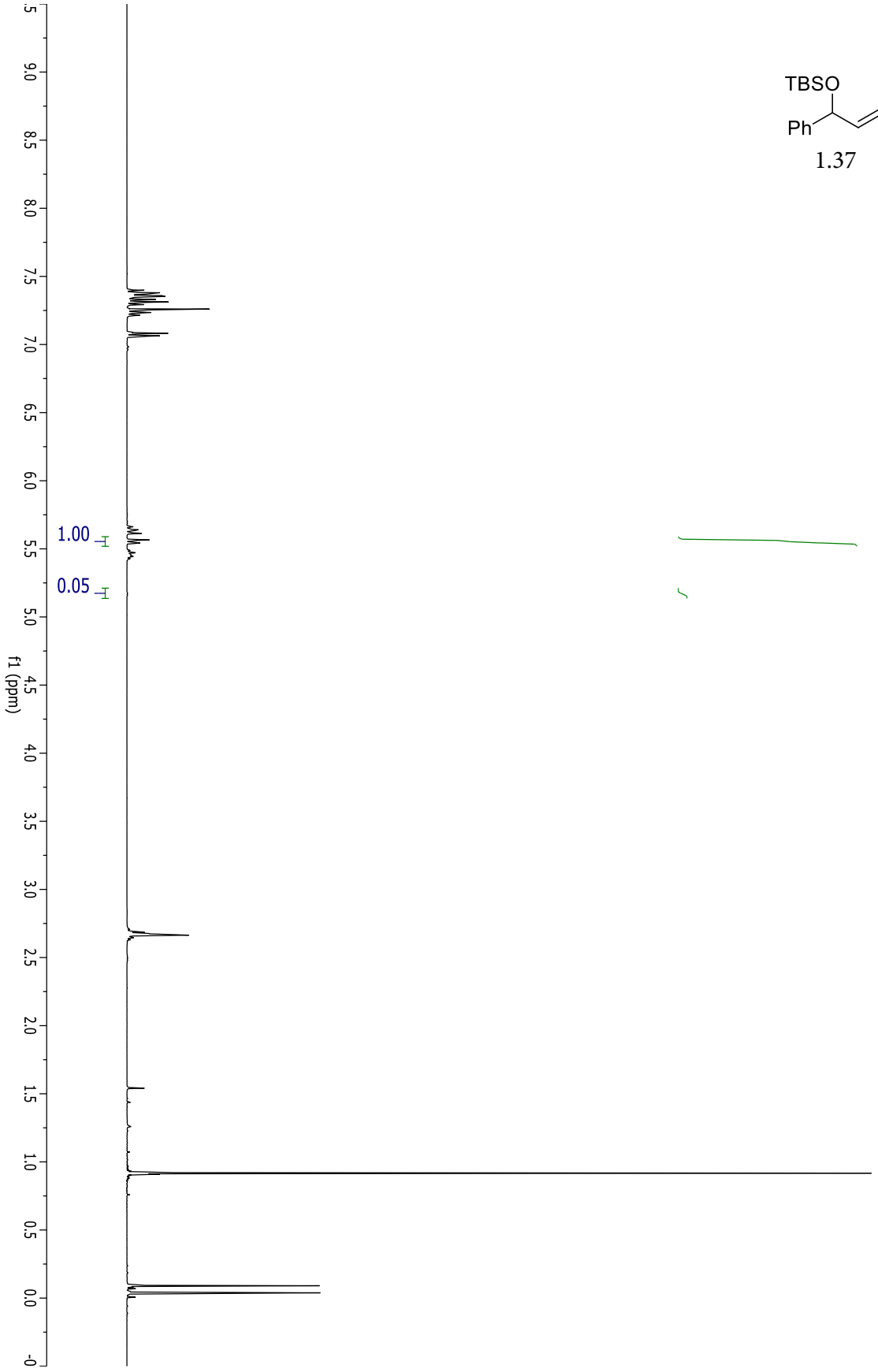

f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

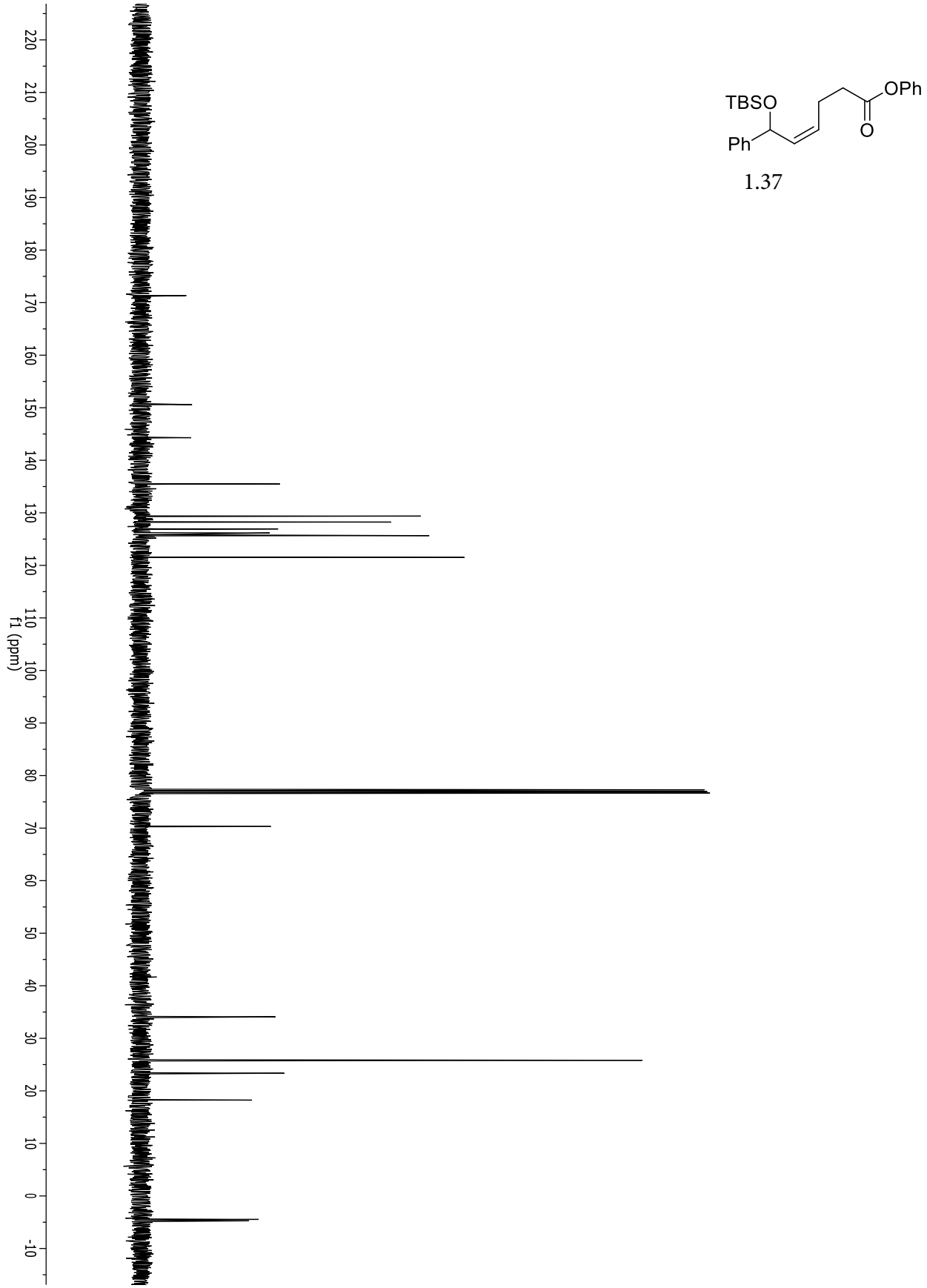

OH
C_8H_{17}
Ph

1.34


TBSO
Ph
OPh
O

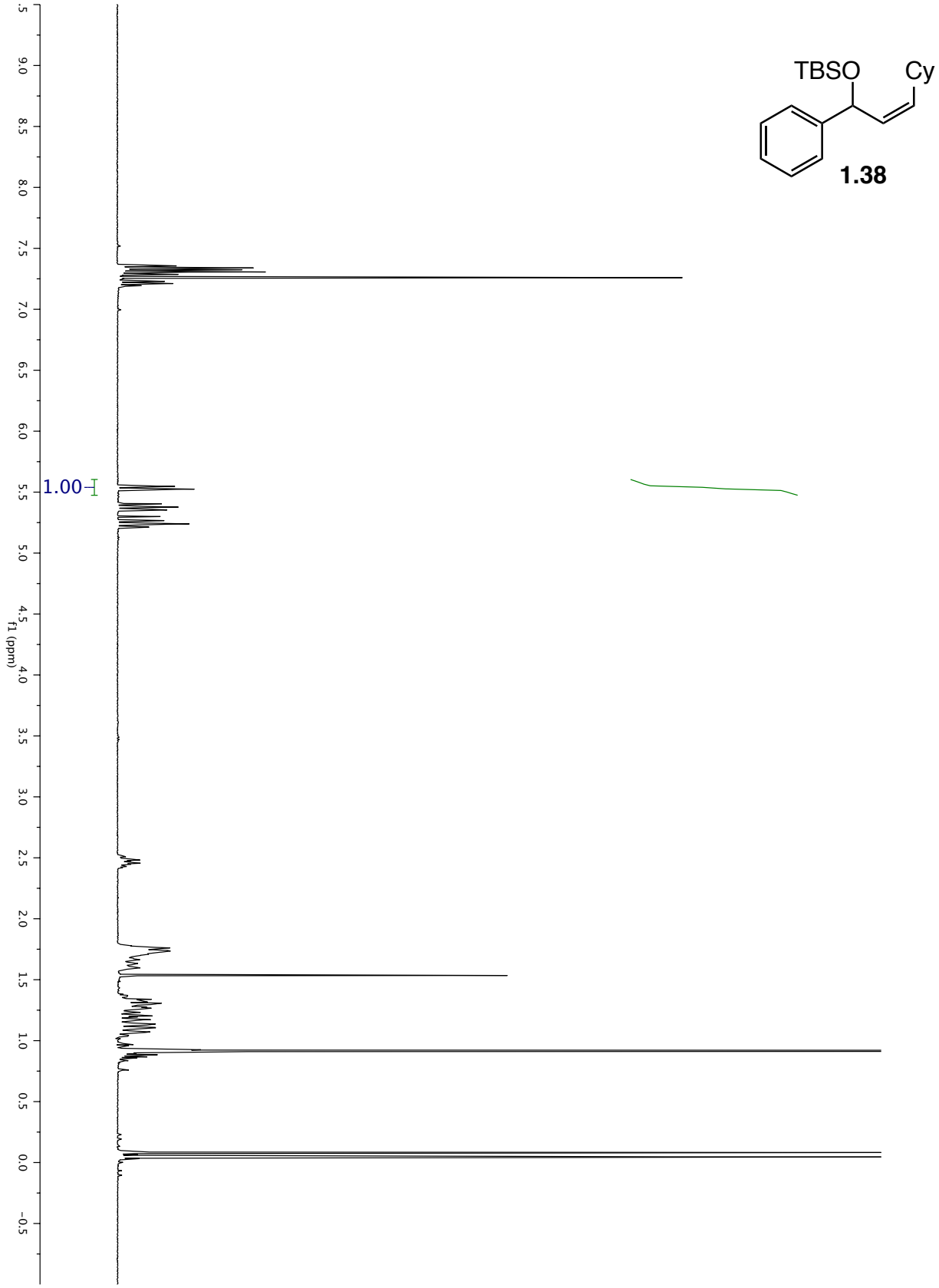
1.37

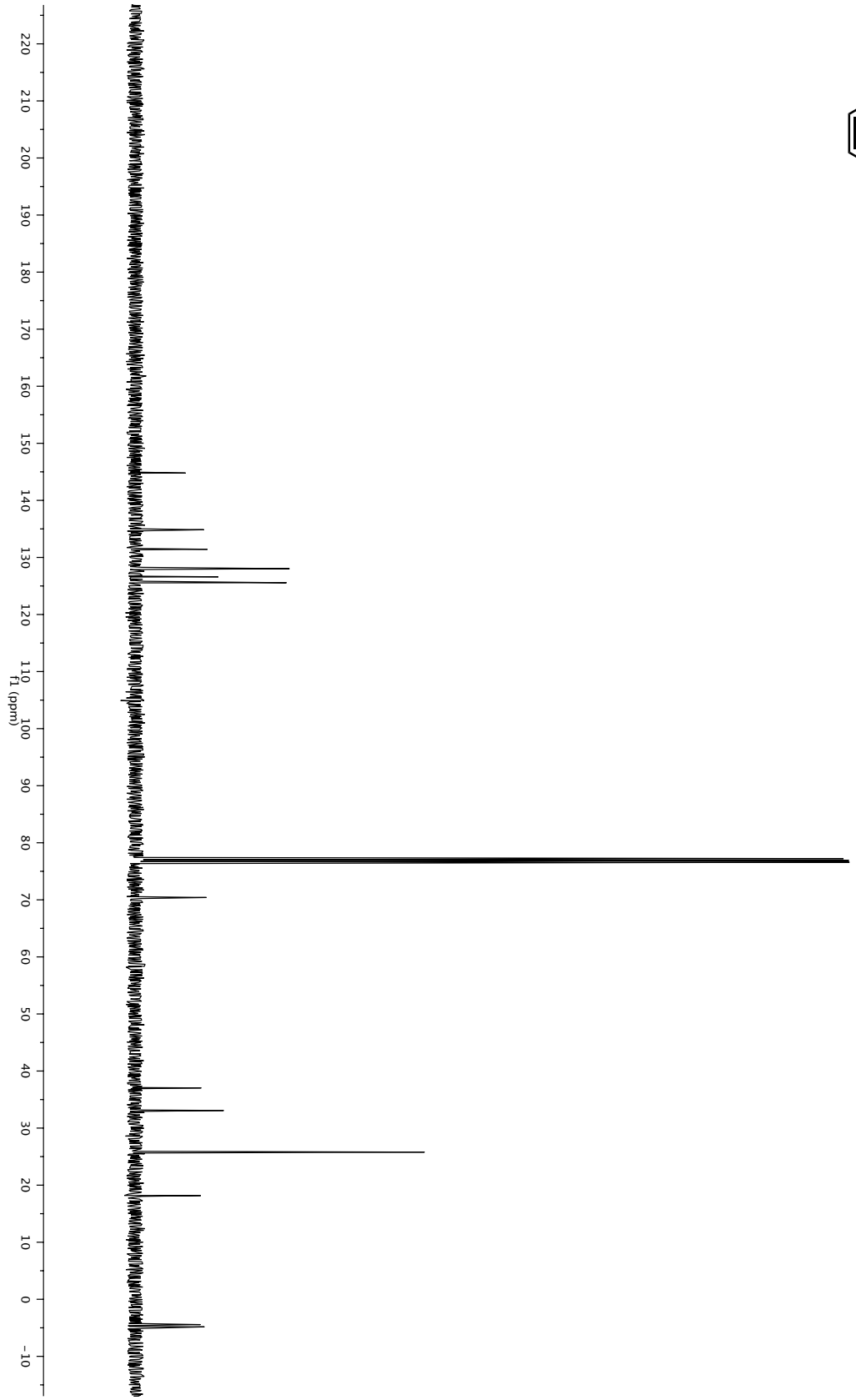

1.00
0.05
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

TBSO
Ph
OPh
O

1.37


TBSO
Cy
1.38
1.00
f1 (ppm)


f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
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60
50
40
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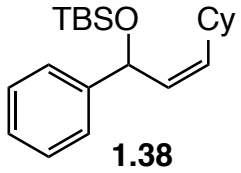
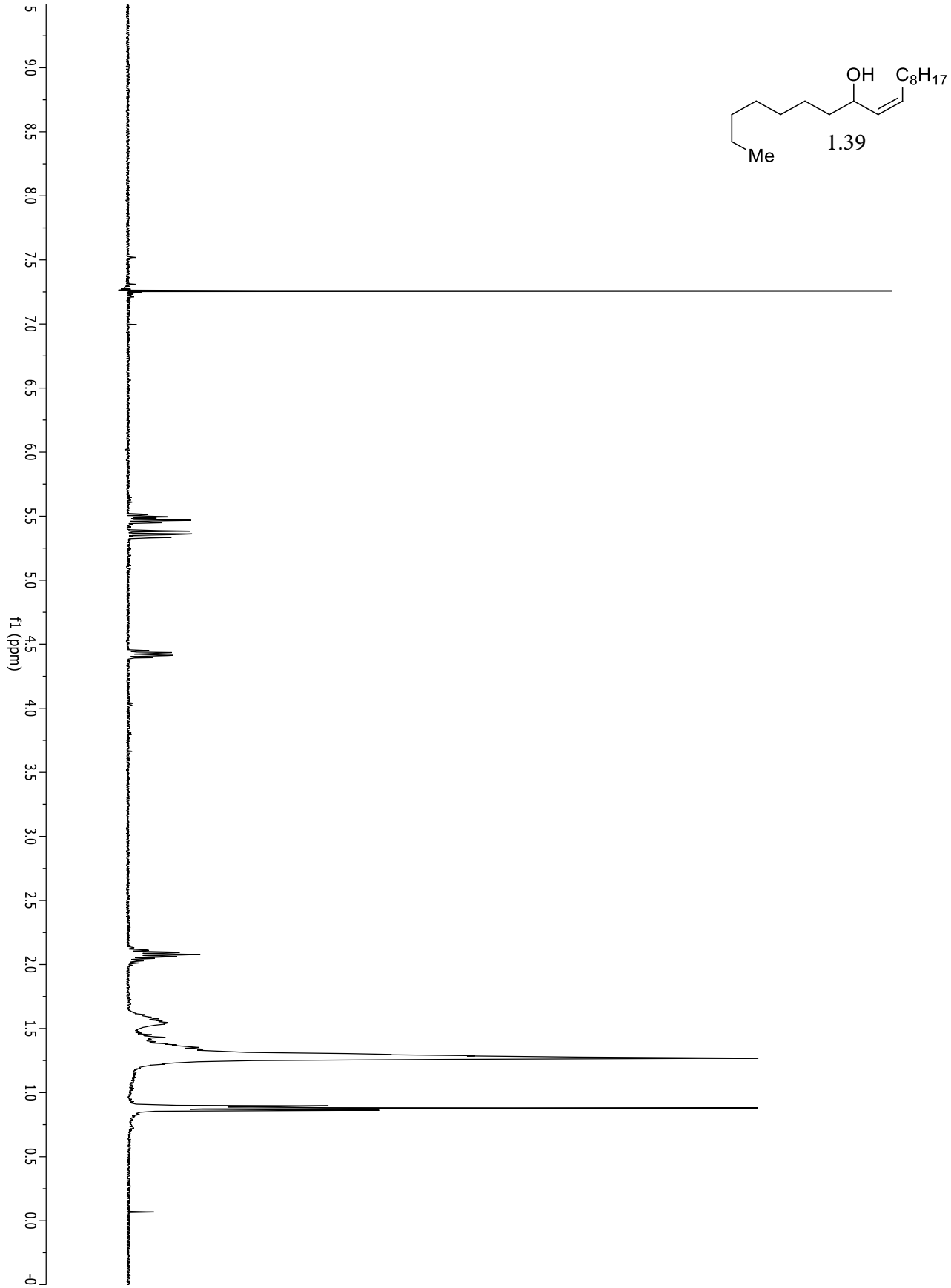
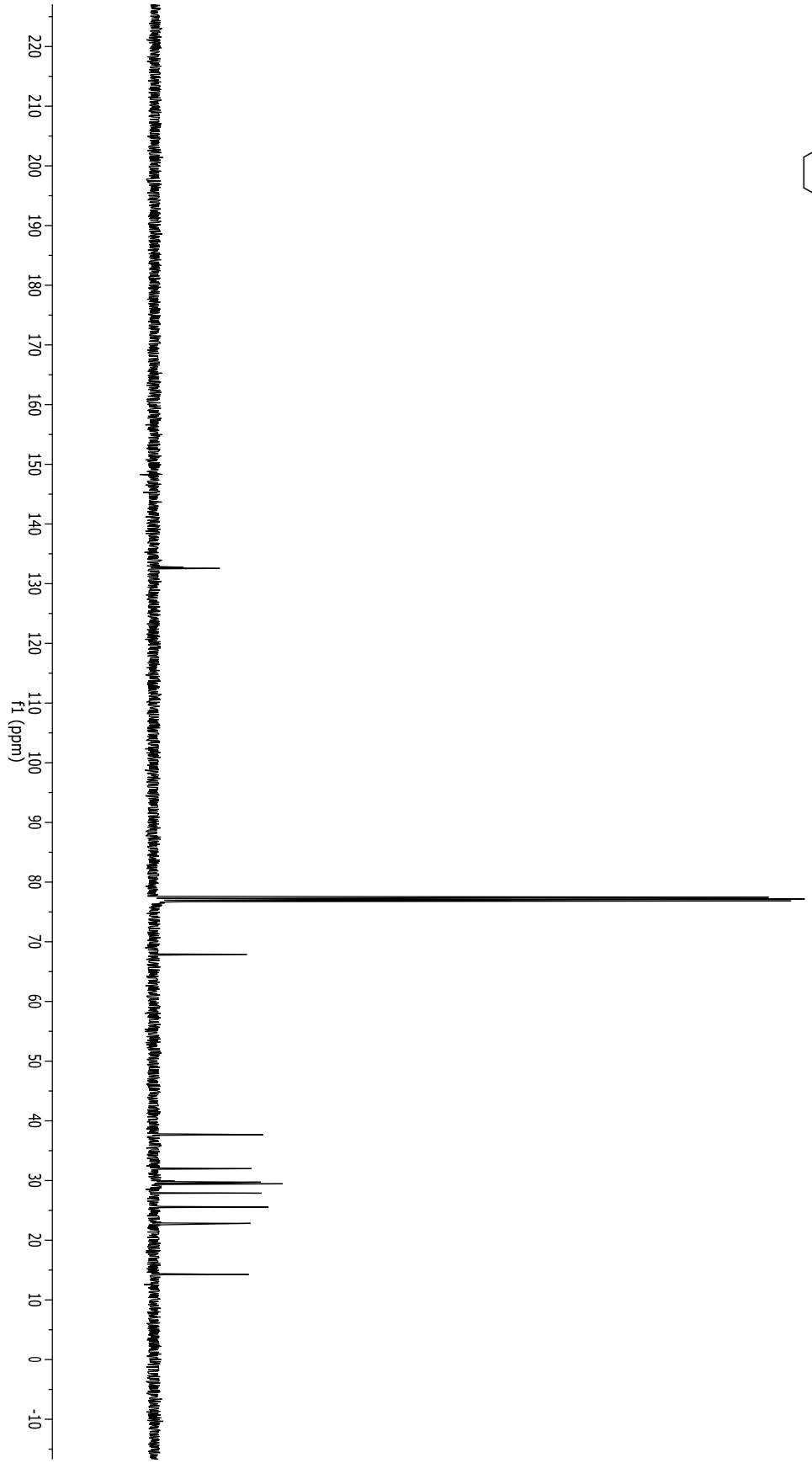
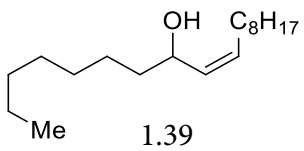
20
10
0
-10


TBSO
Cy

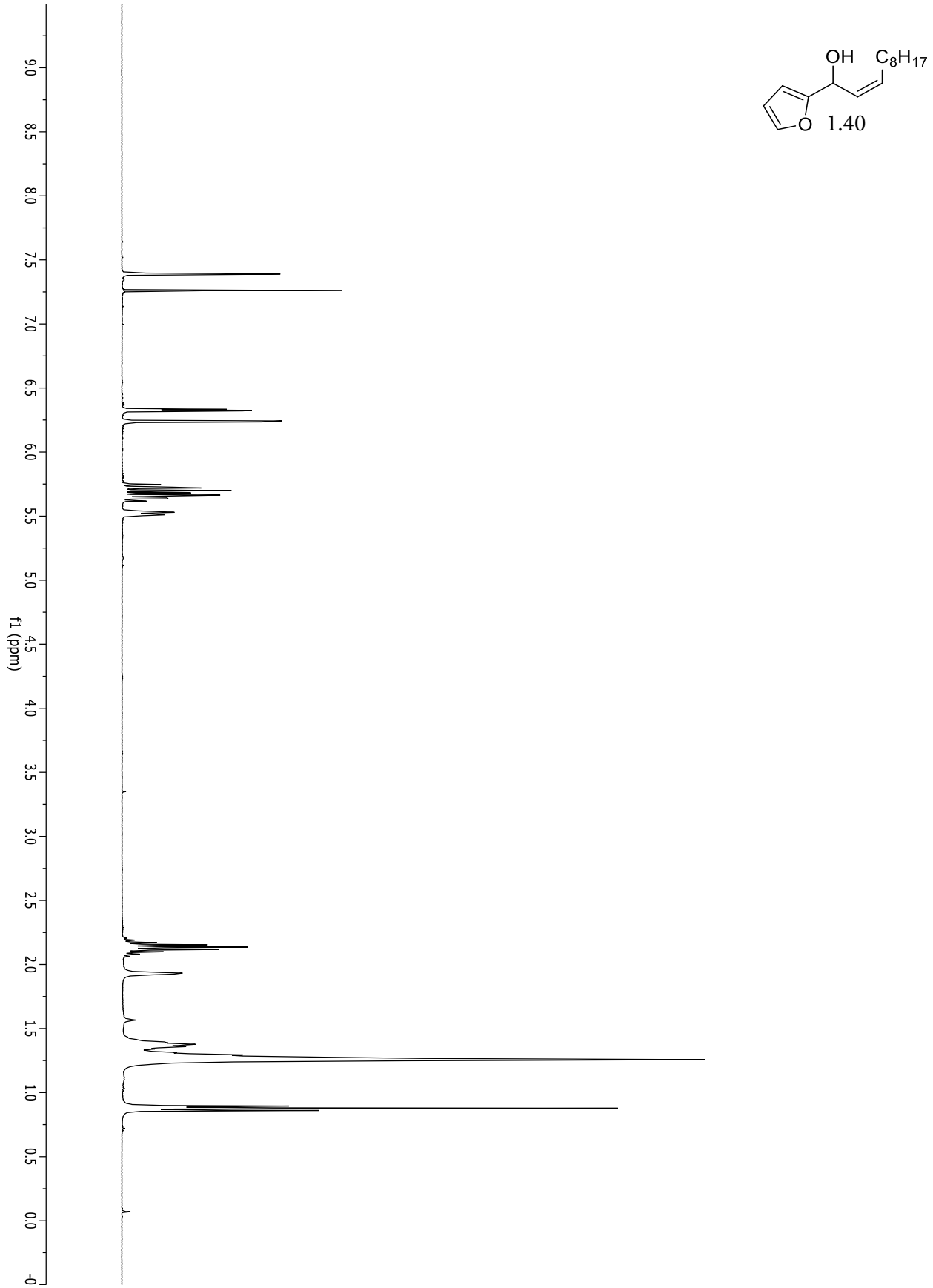
1.38

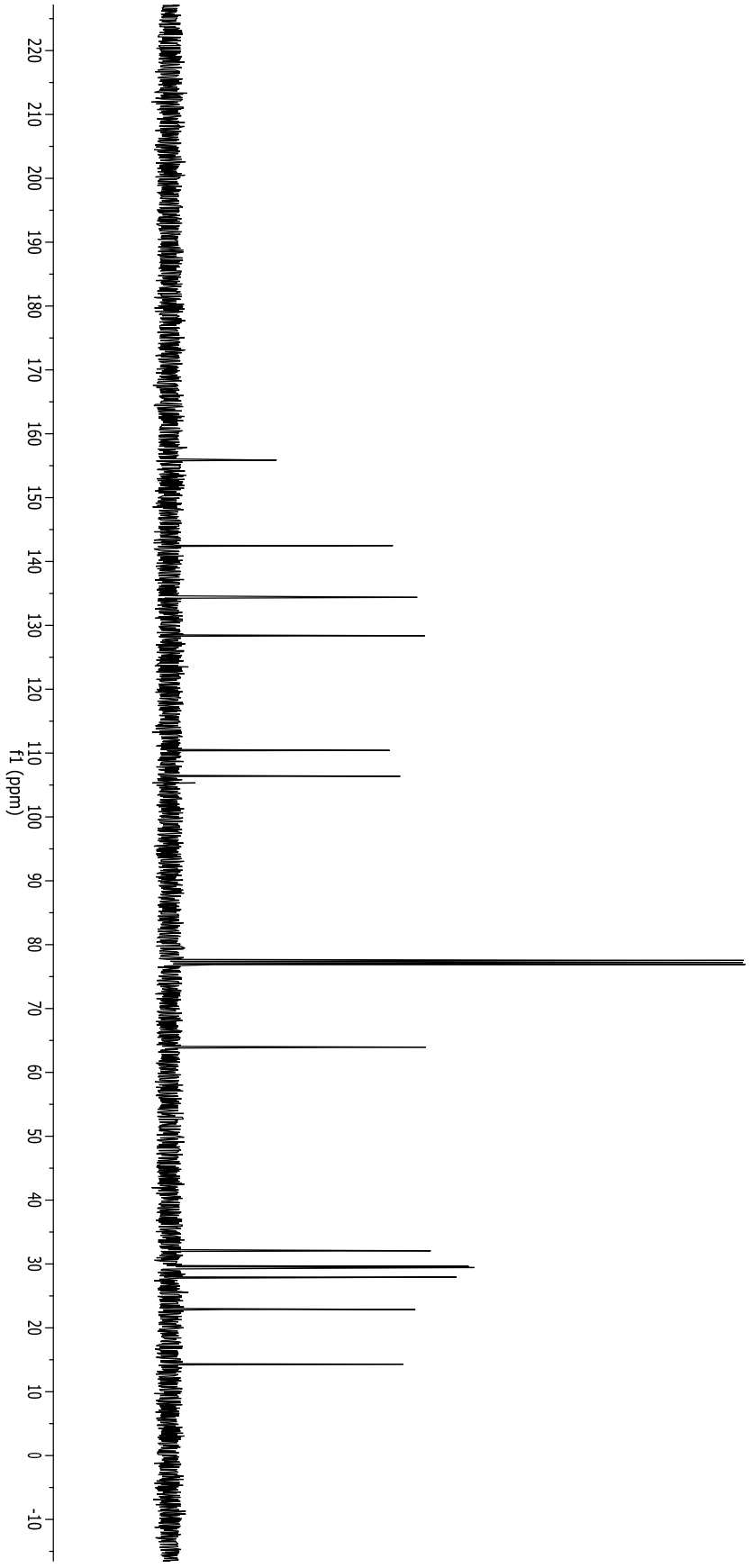

OH
C_8H_{17}
Me
1.39
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

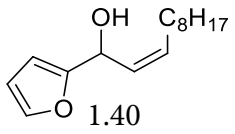

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
C_8H_{17}
Me

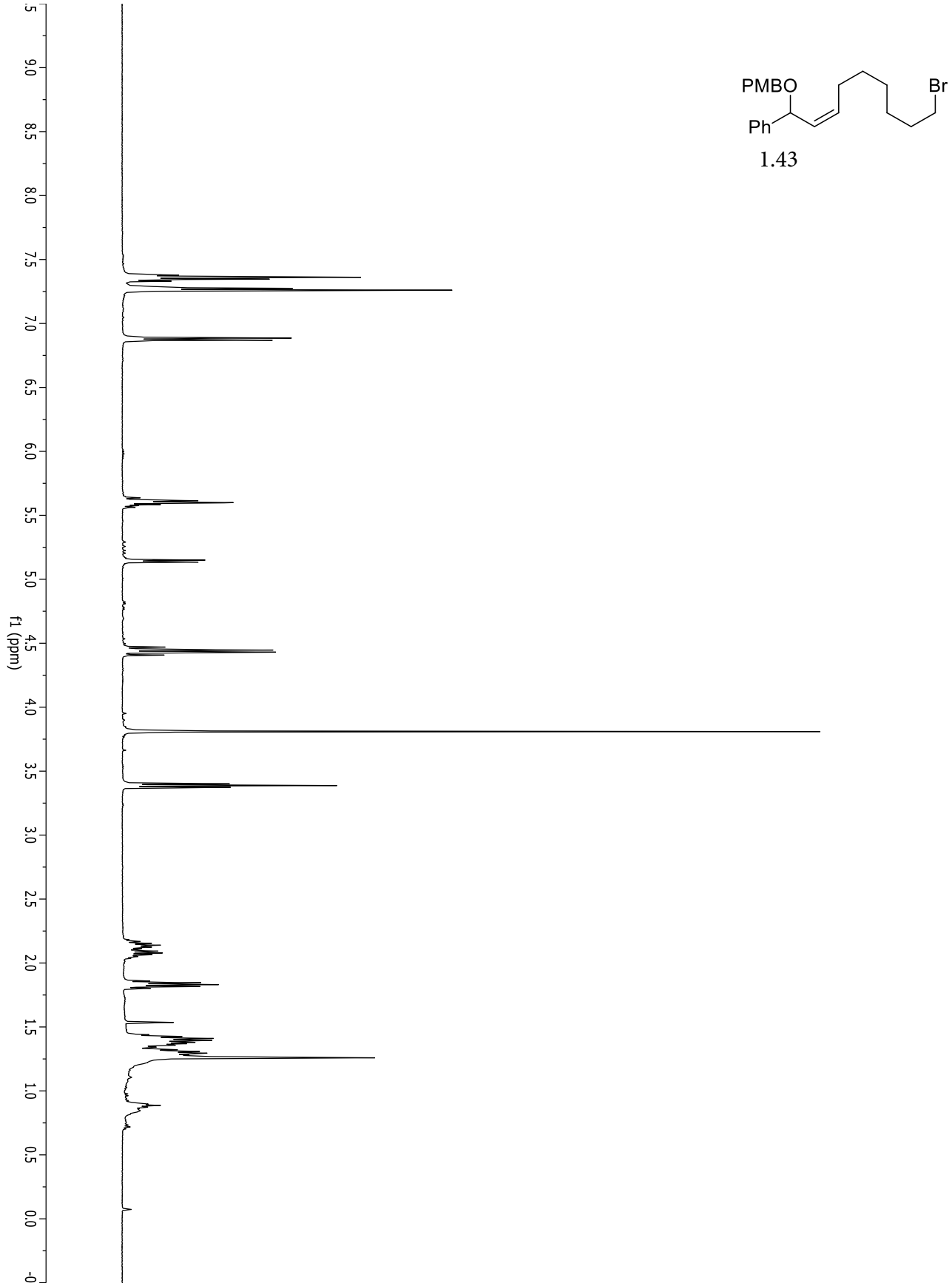
1.39

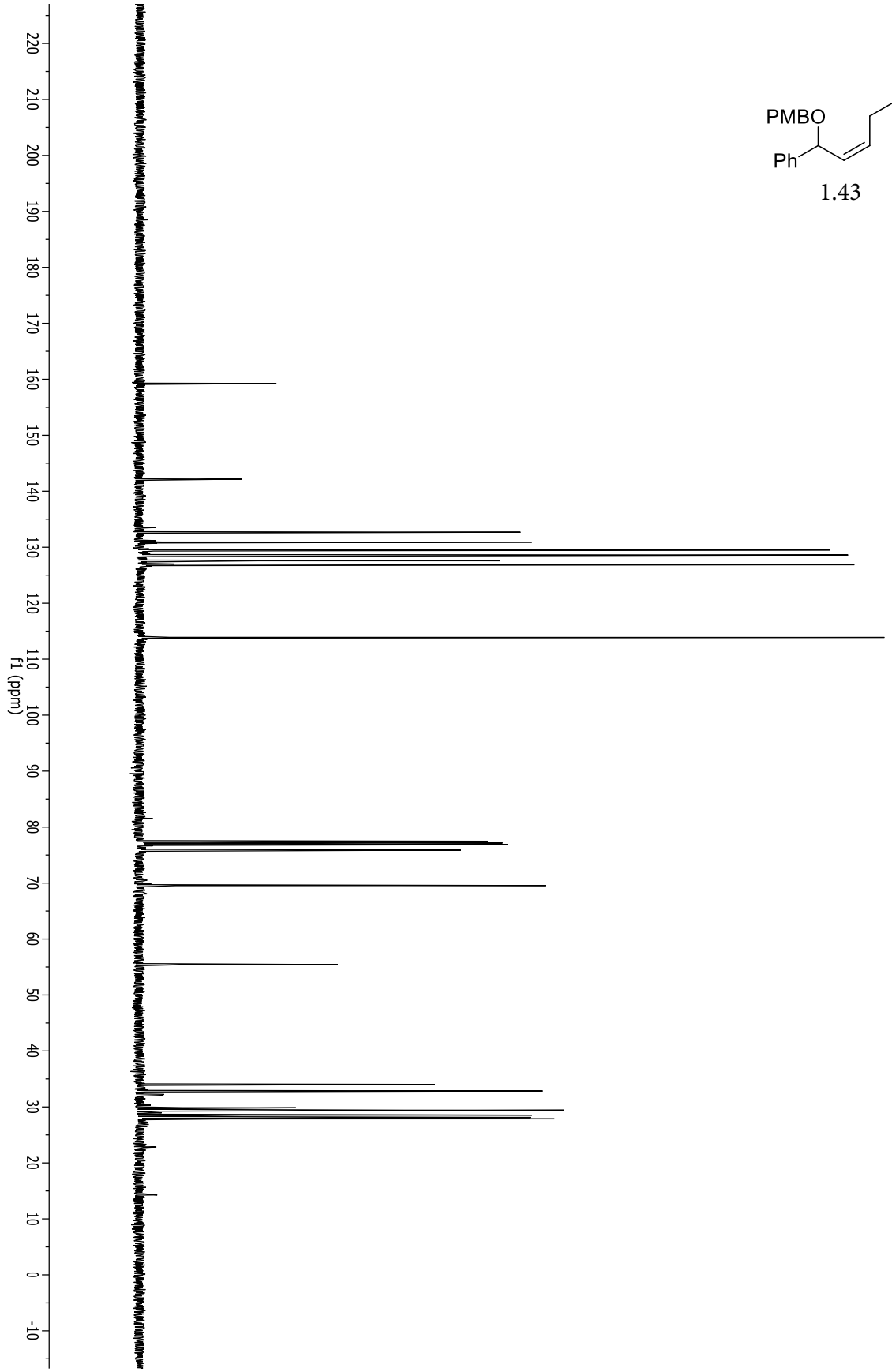

OH
C_8H_{17}
O
1.40
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0


f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


OH
C8H17
O

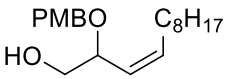
1.40


PMBO
Br
Ph
1.43
f1 (ppm)

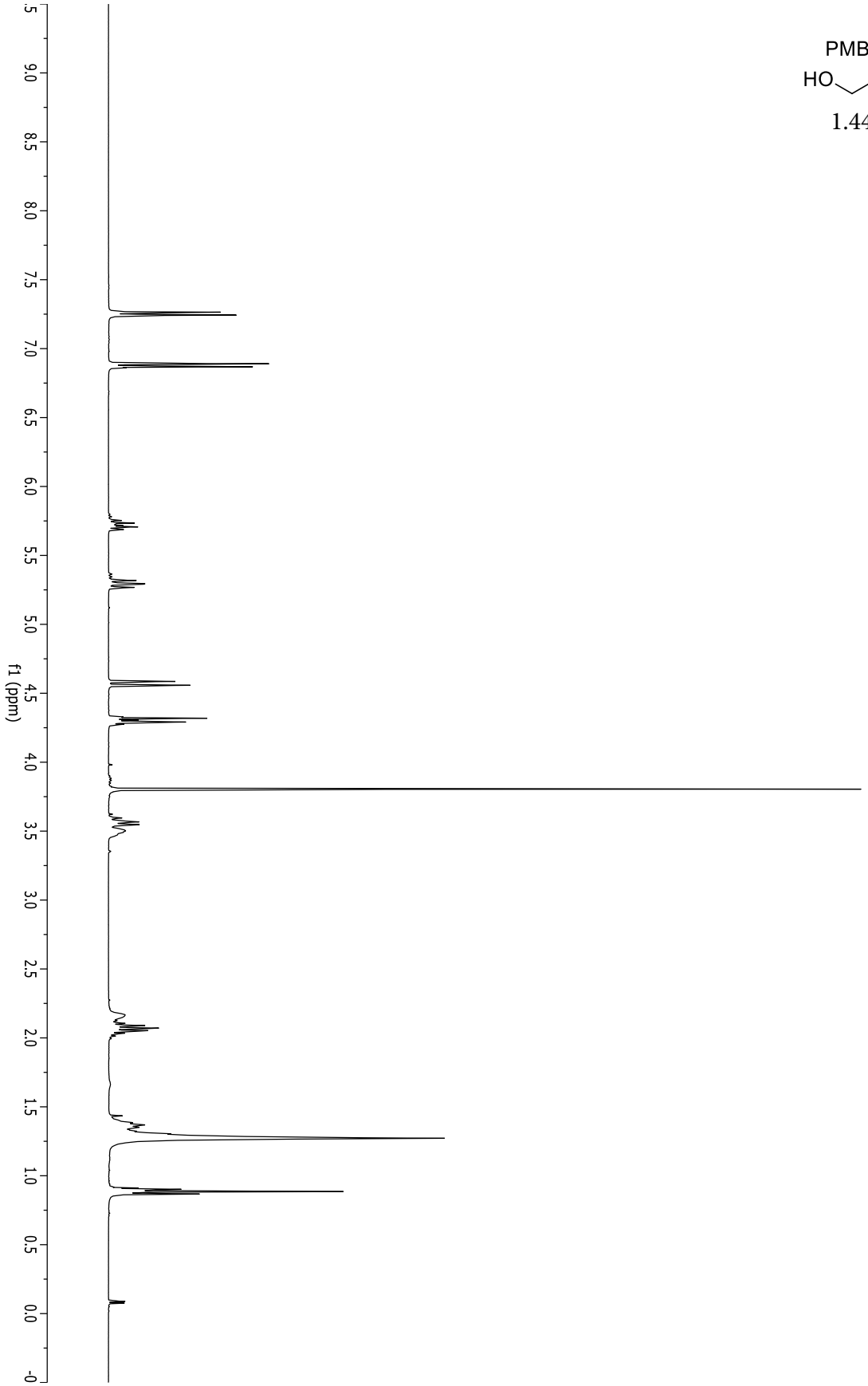

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

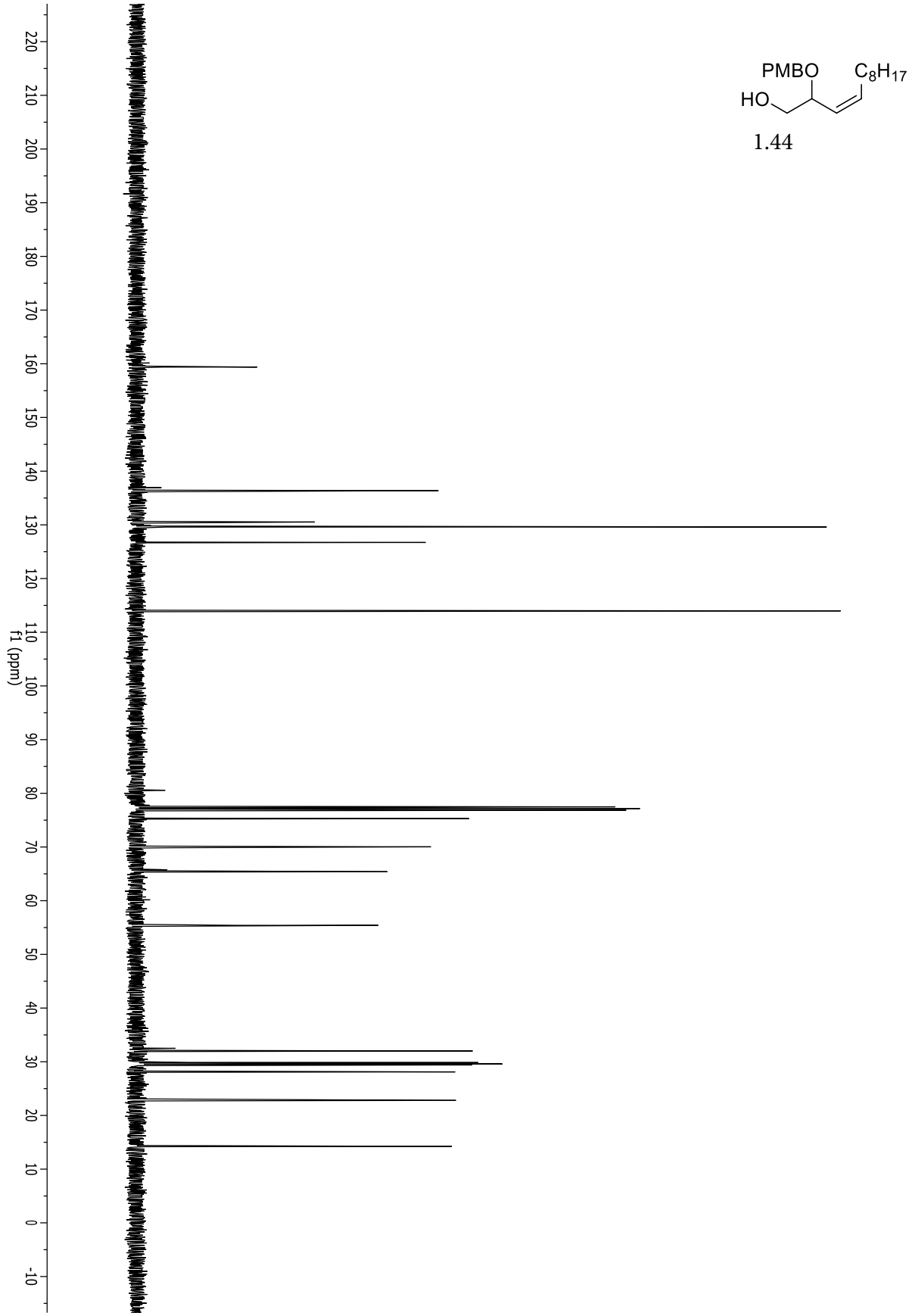
PMBO
Br
Ph

1.43

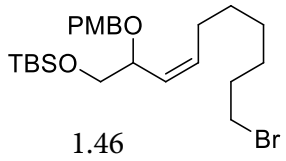

PMBO
C_8H_{17}
HO

1.44

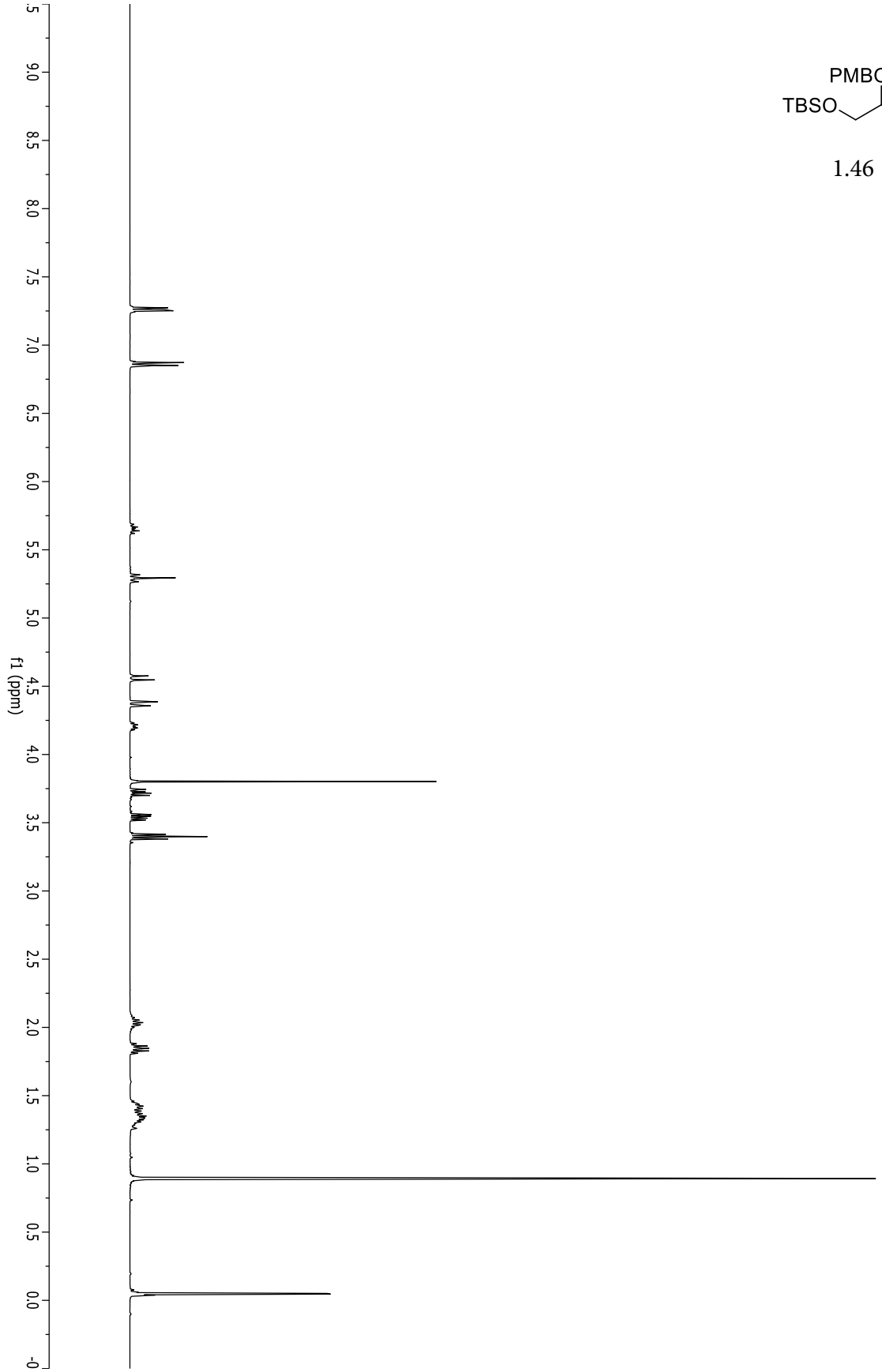

f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

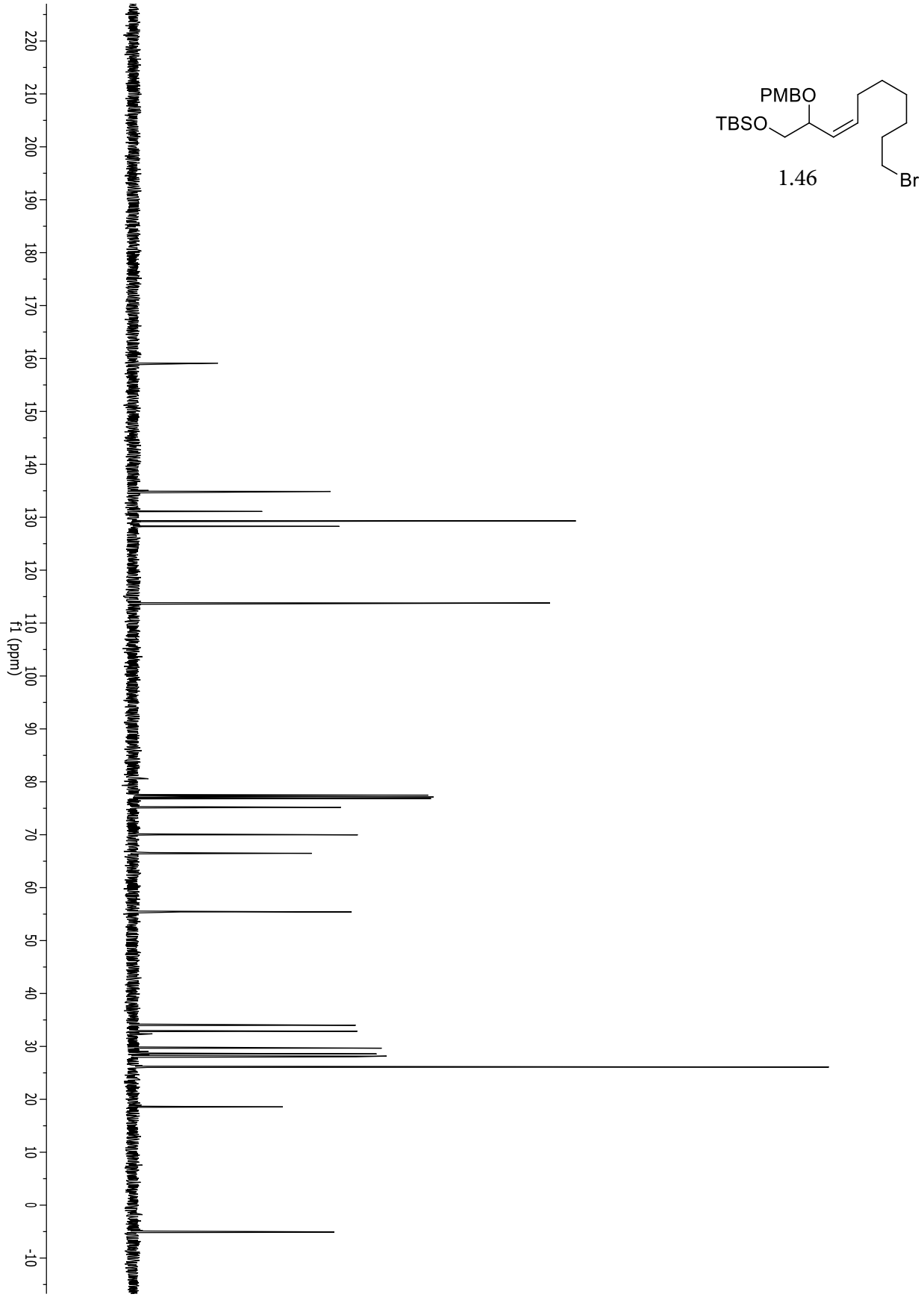

PMBO
C_8H_{17}
HO
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

1.44


PMBO
TBSO
Br

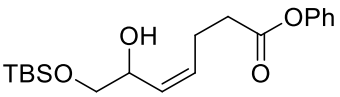
1.46


f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

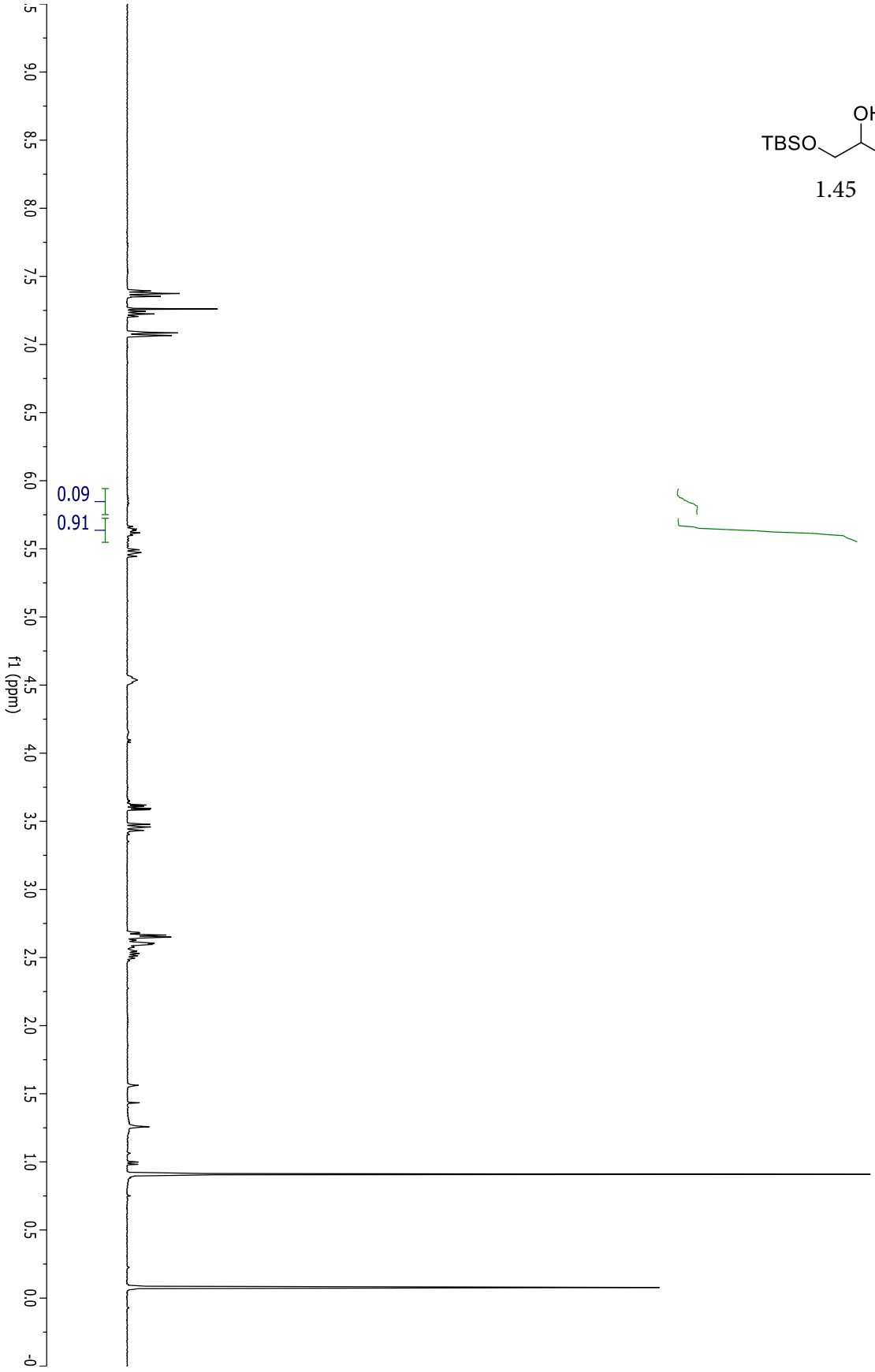

f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

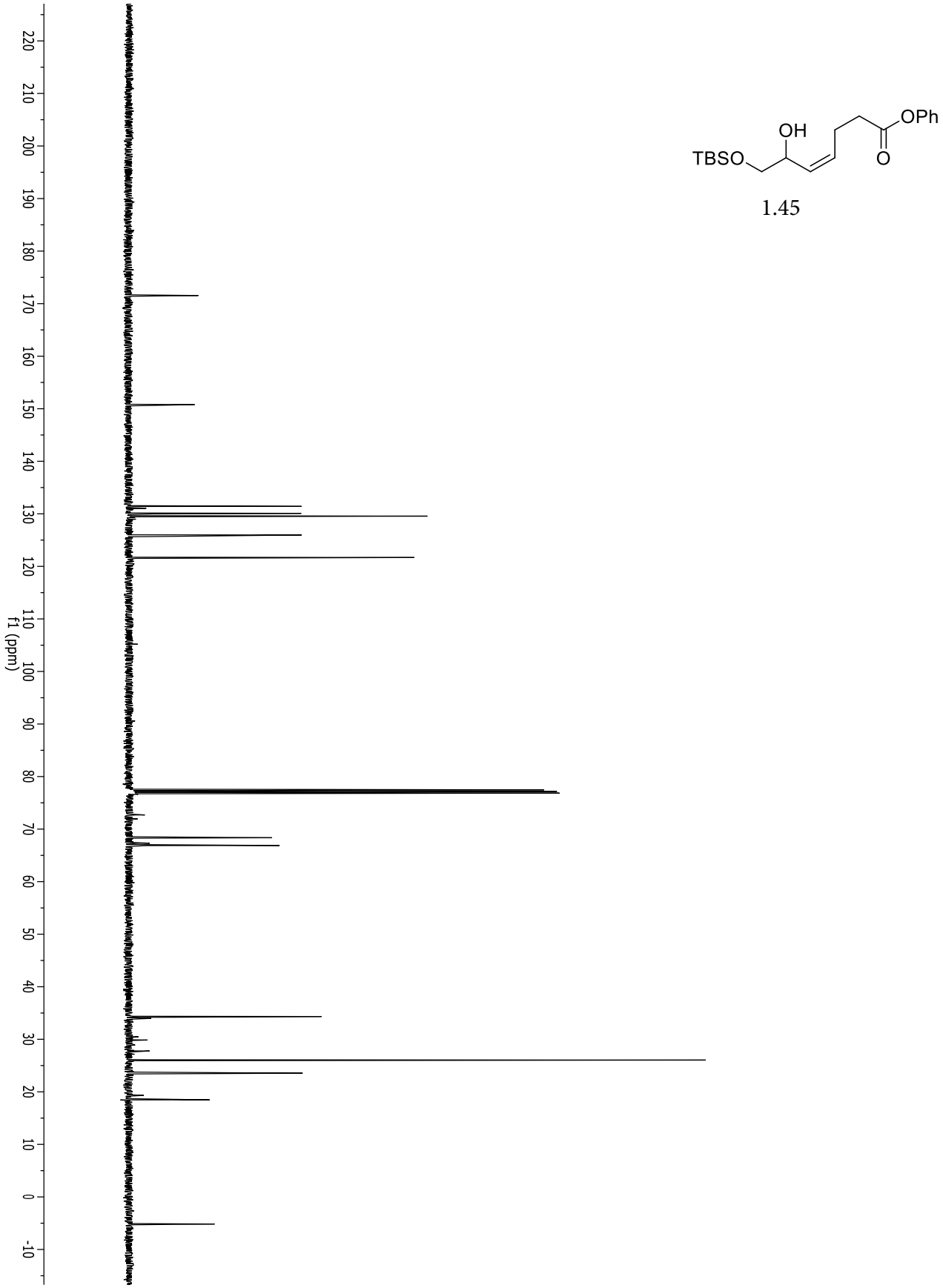
PMBO
TBSO
Br

1.46



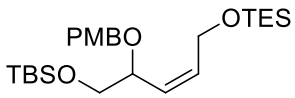
1.45



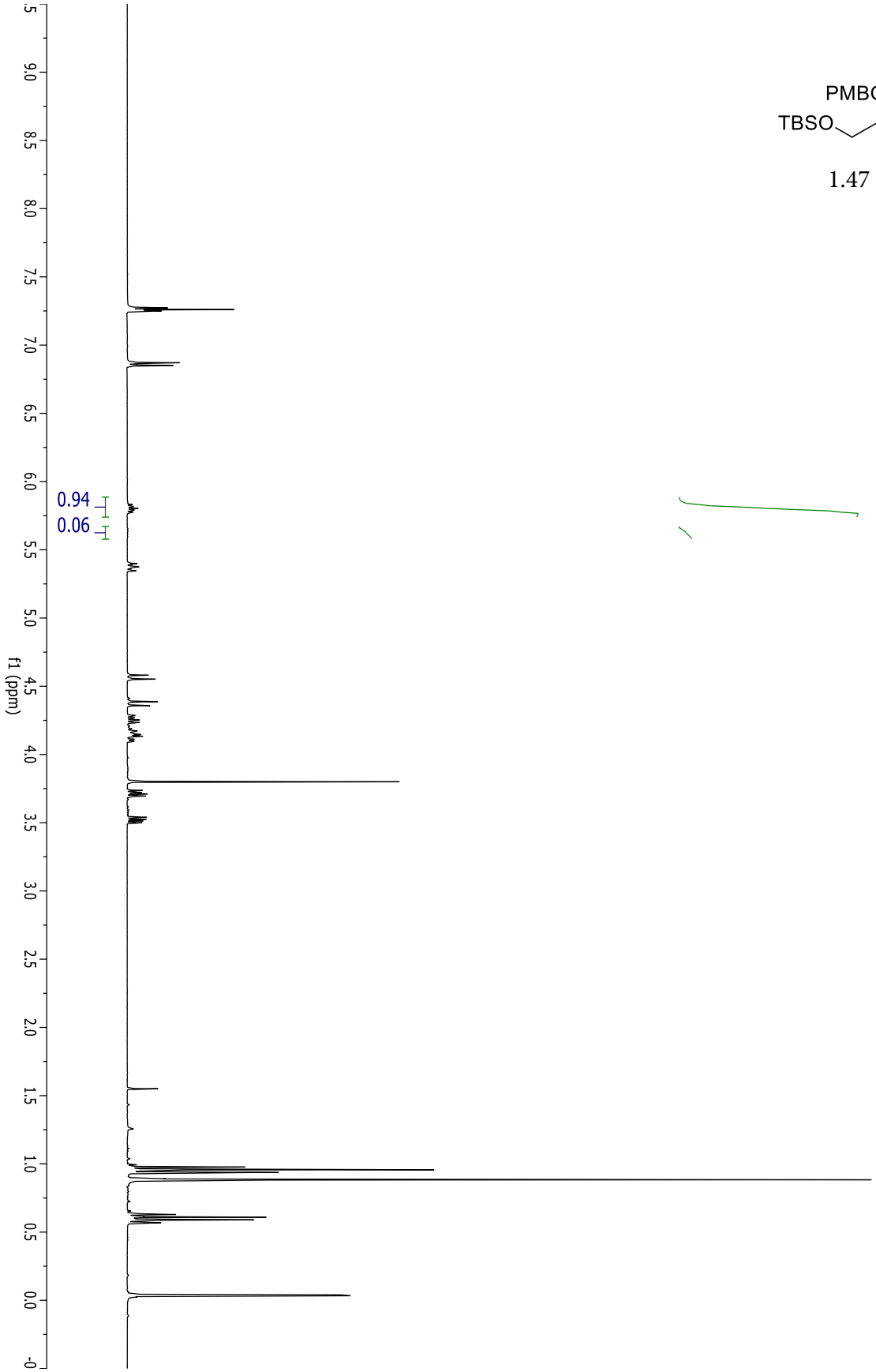

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

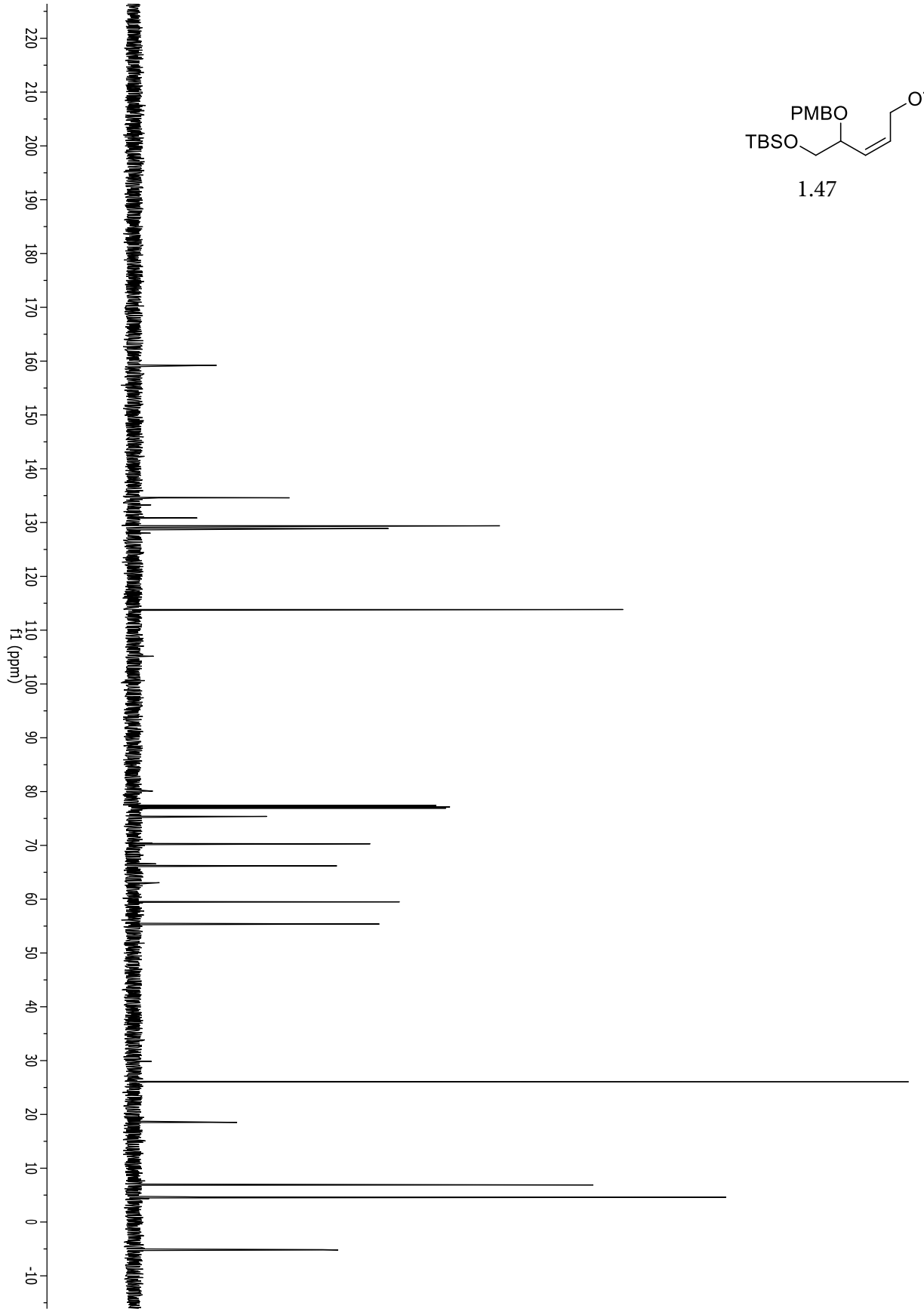
OH
OPh
TBSO
O

1.45



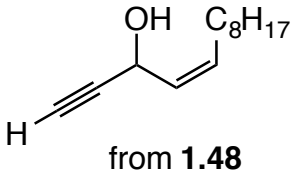
1.47



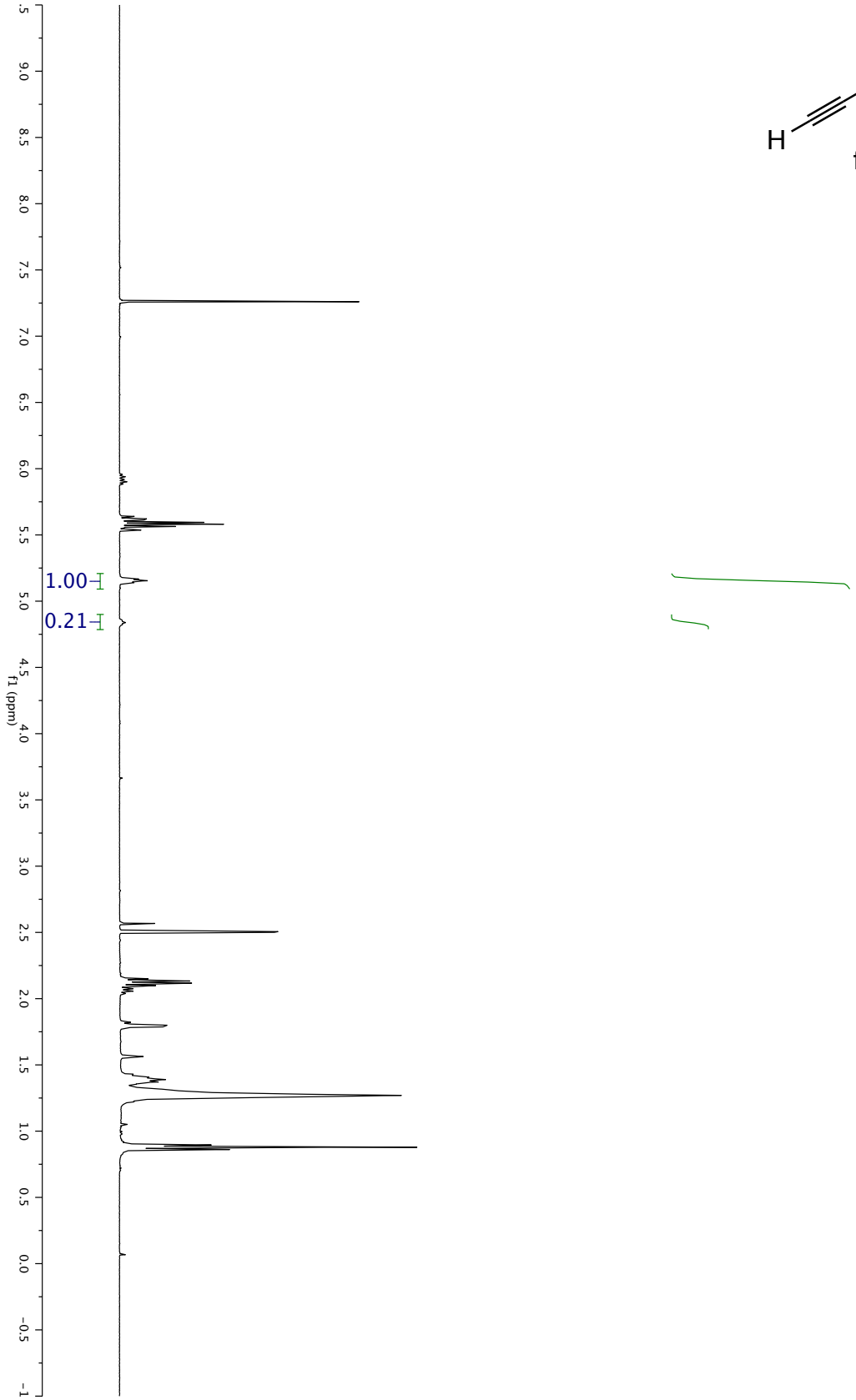

f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

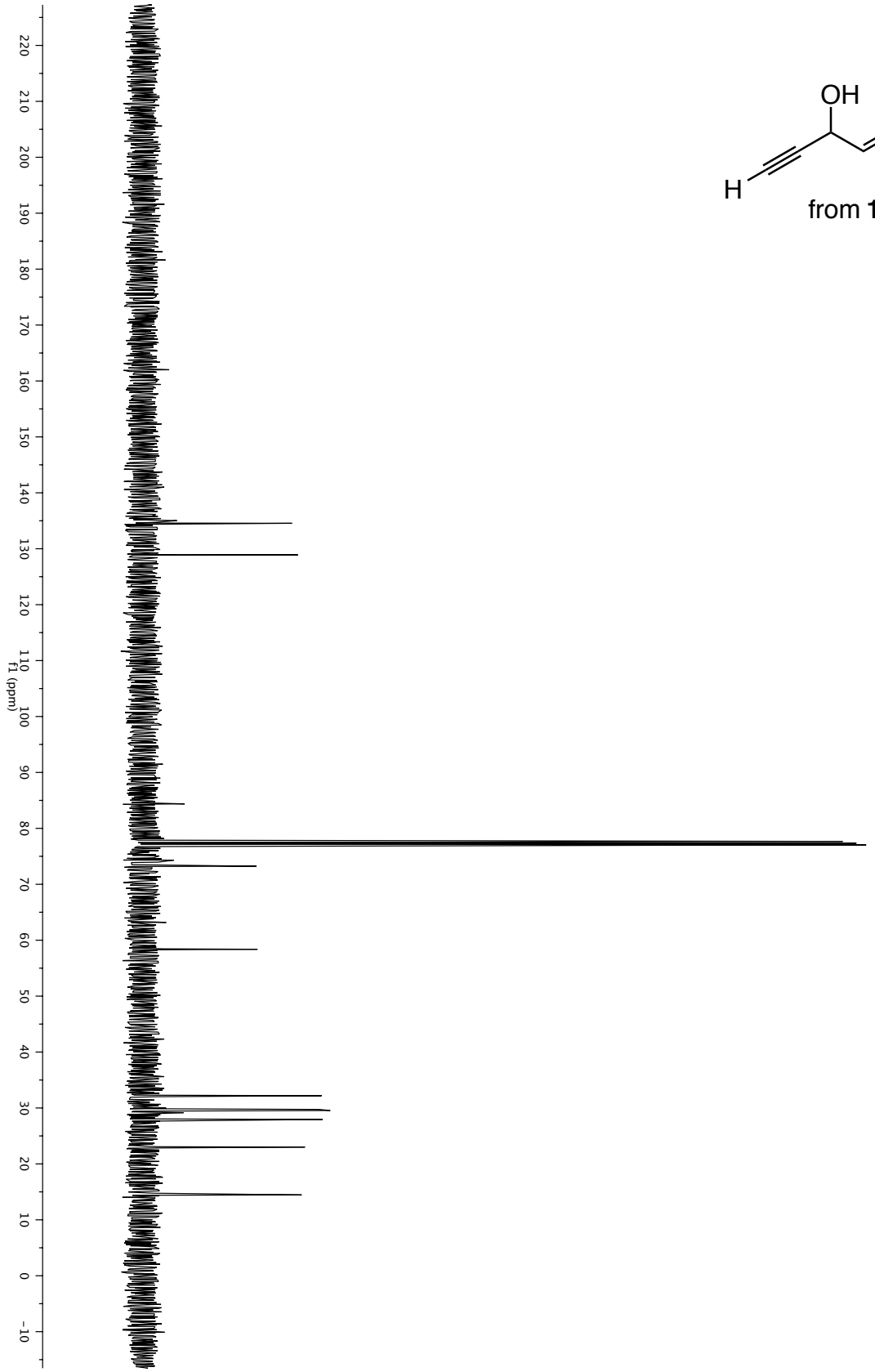
OTES
PMBO
TBSO

1.47



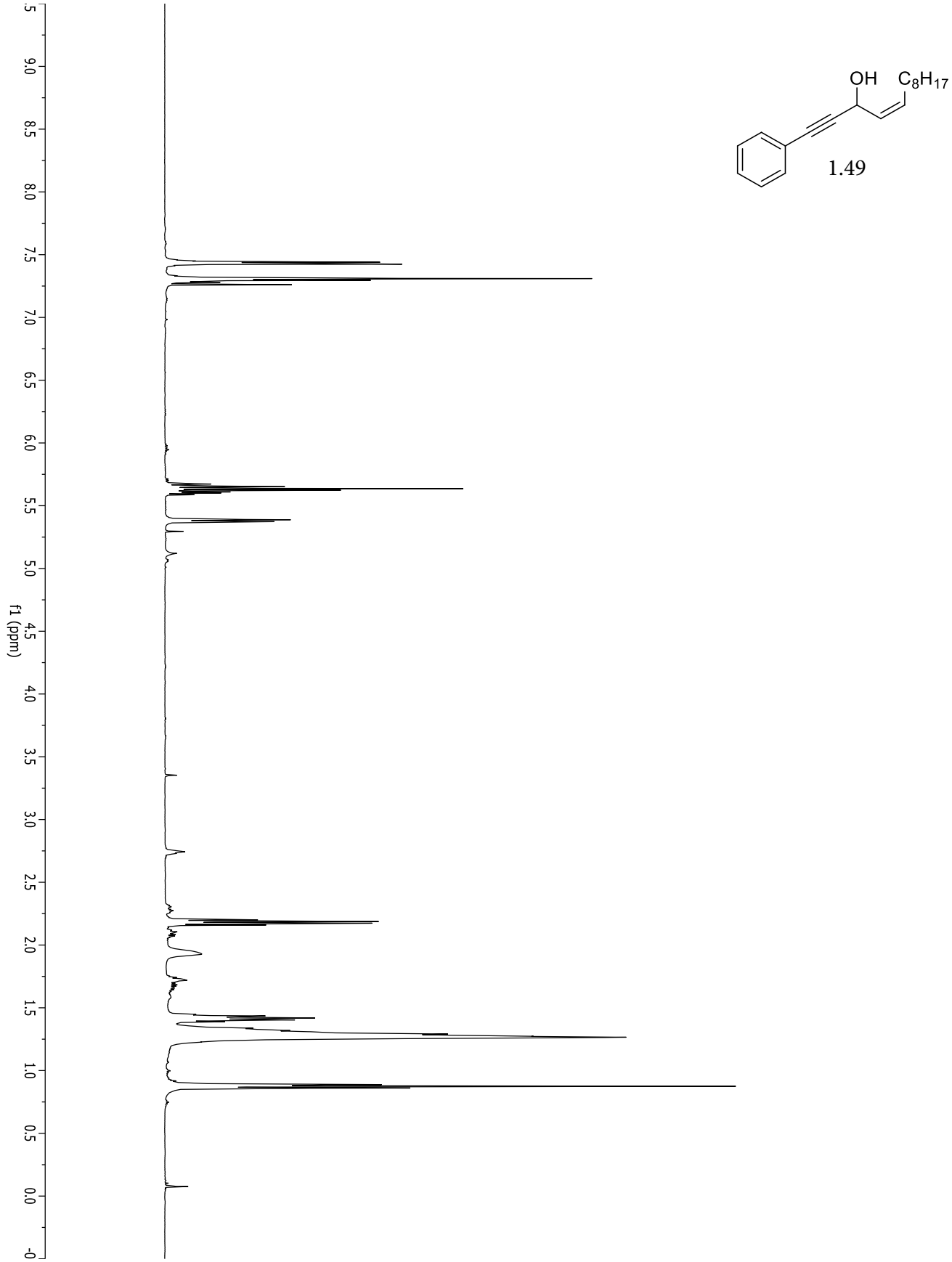
from **1.48**

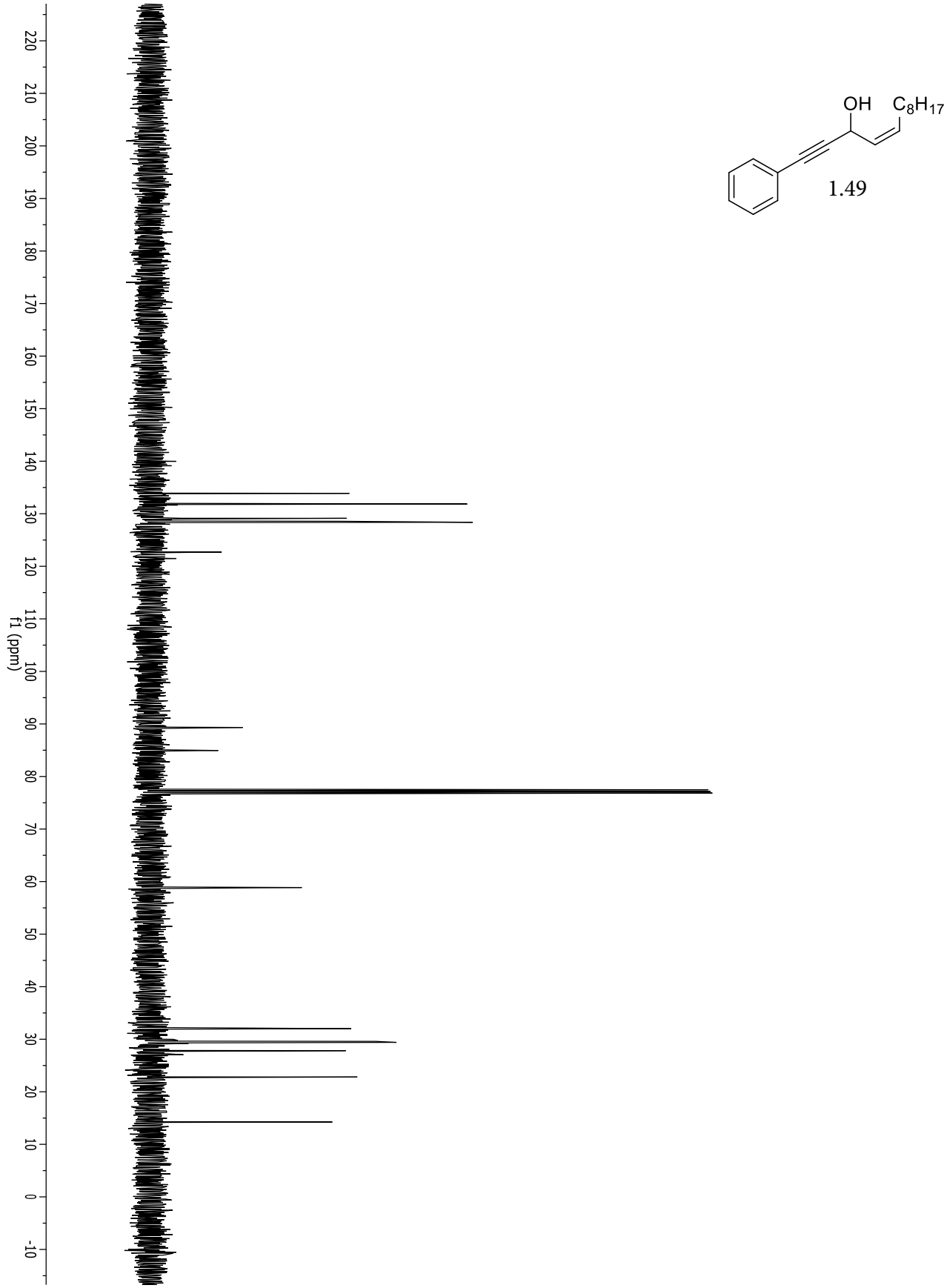


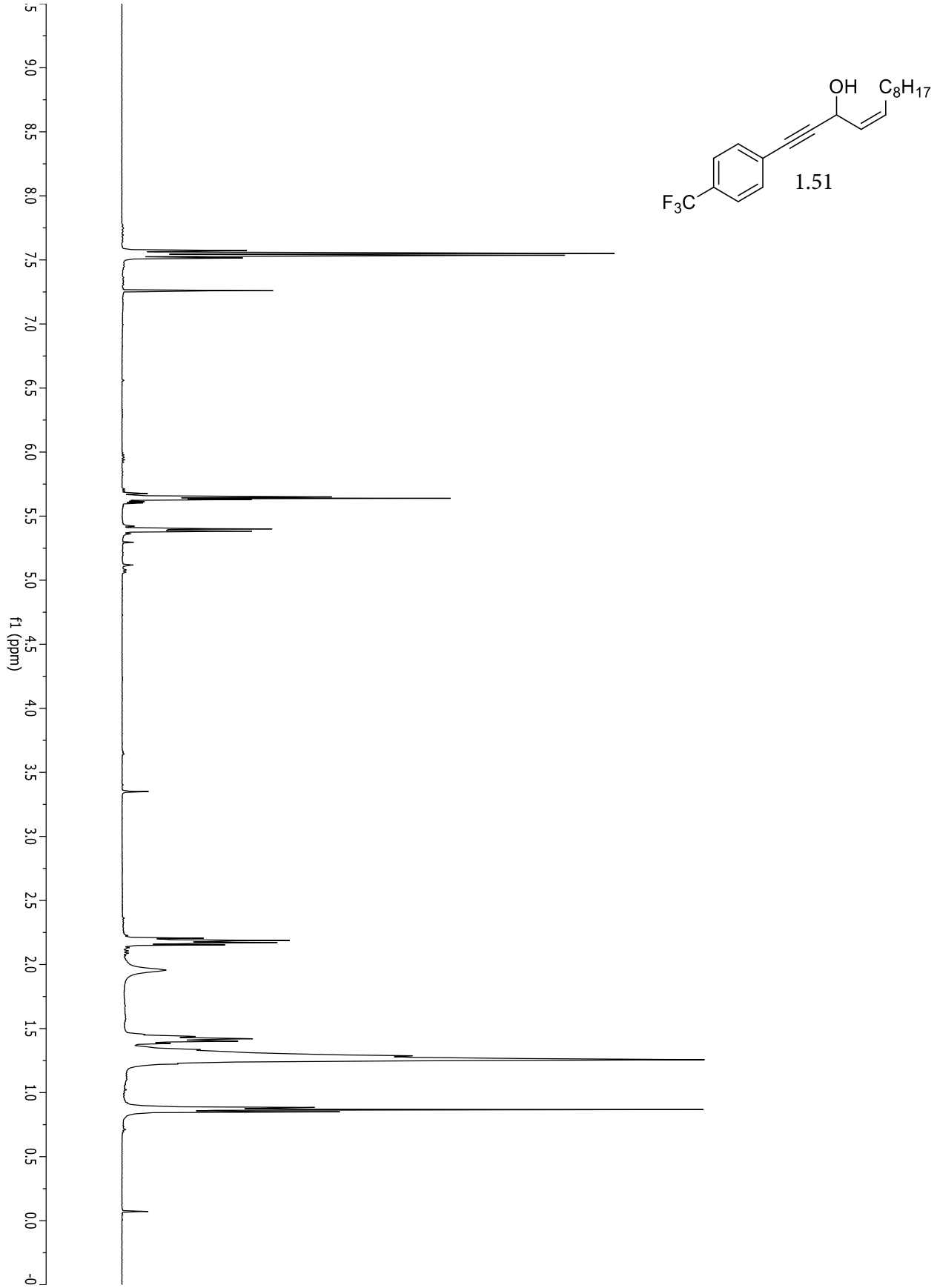

f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

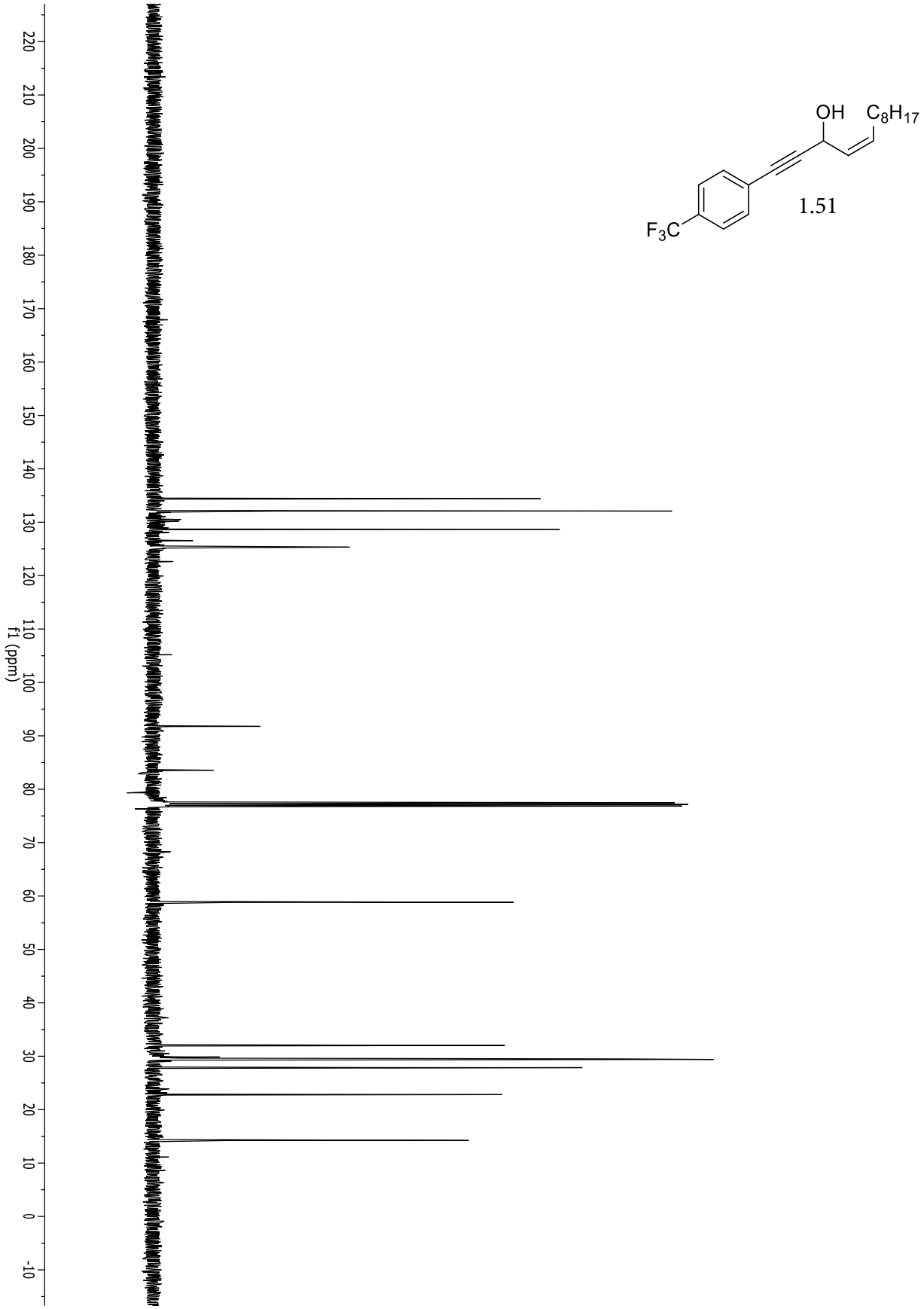
OH
C_8H_{17}
H

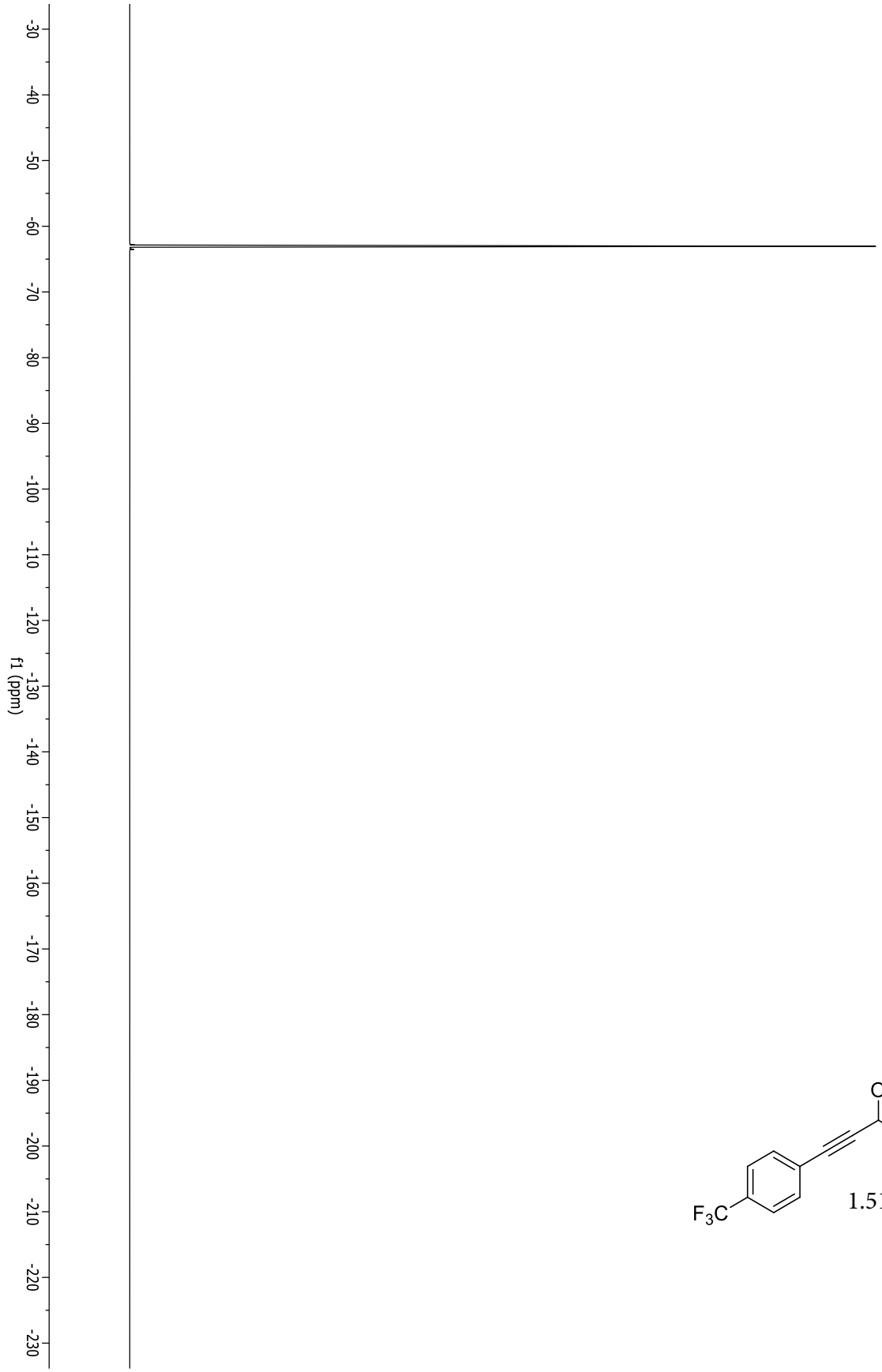
from **1.48**


OH
C_8H_{17}
1.49
f1 (ppm)


OH
C_8H_{17}
1.49
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

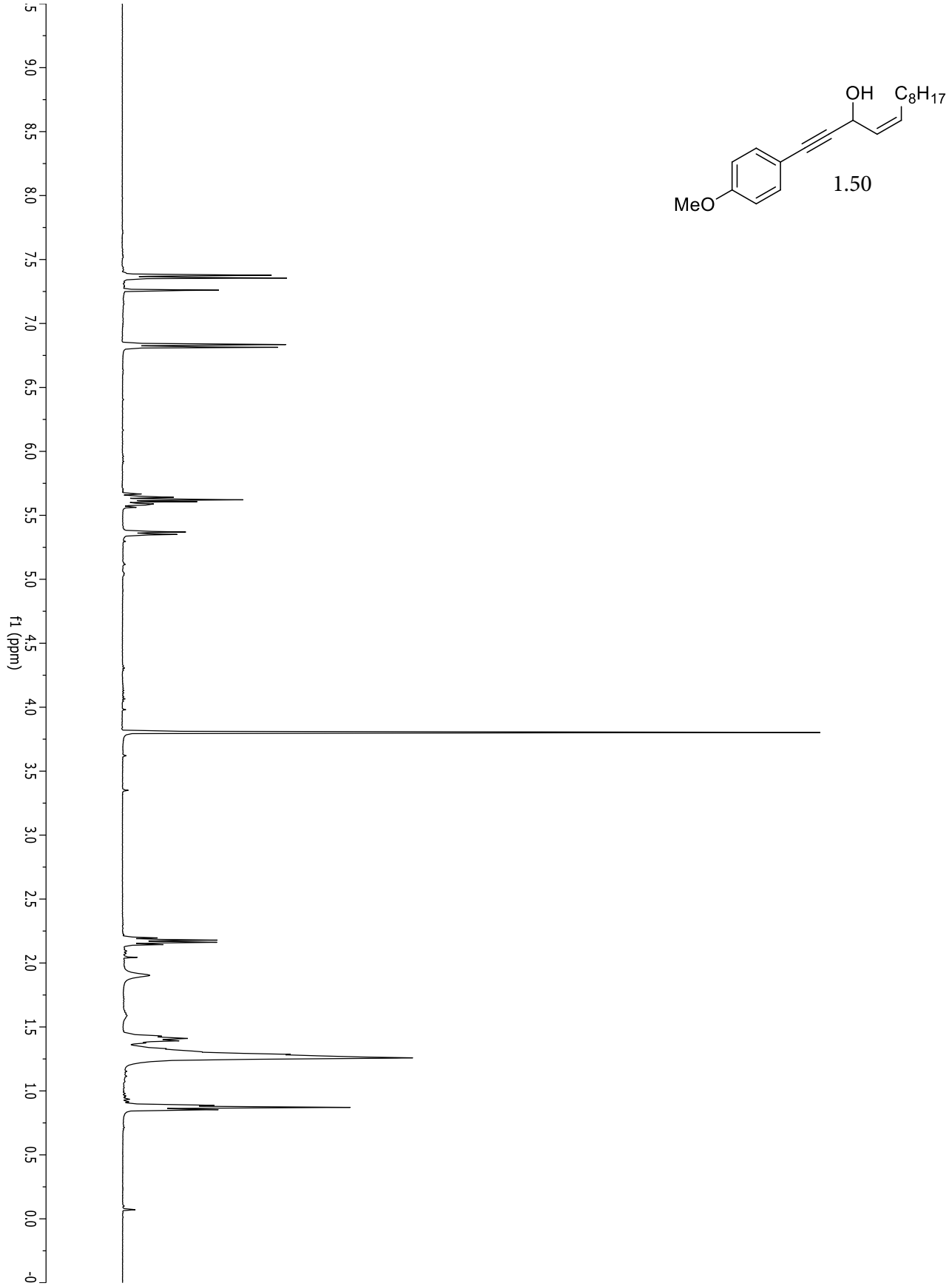

OH
C_8H_{17}
F_3C
1.51
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

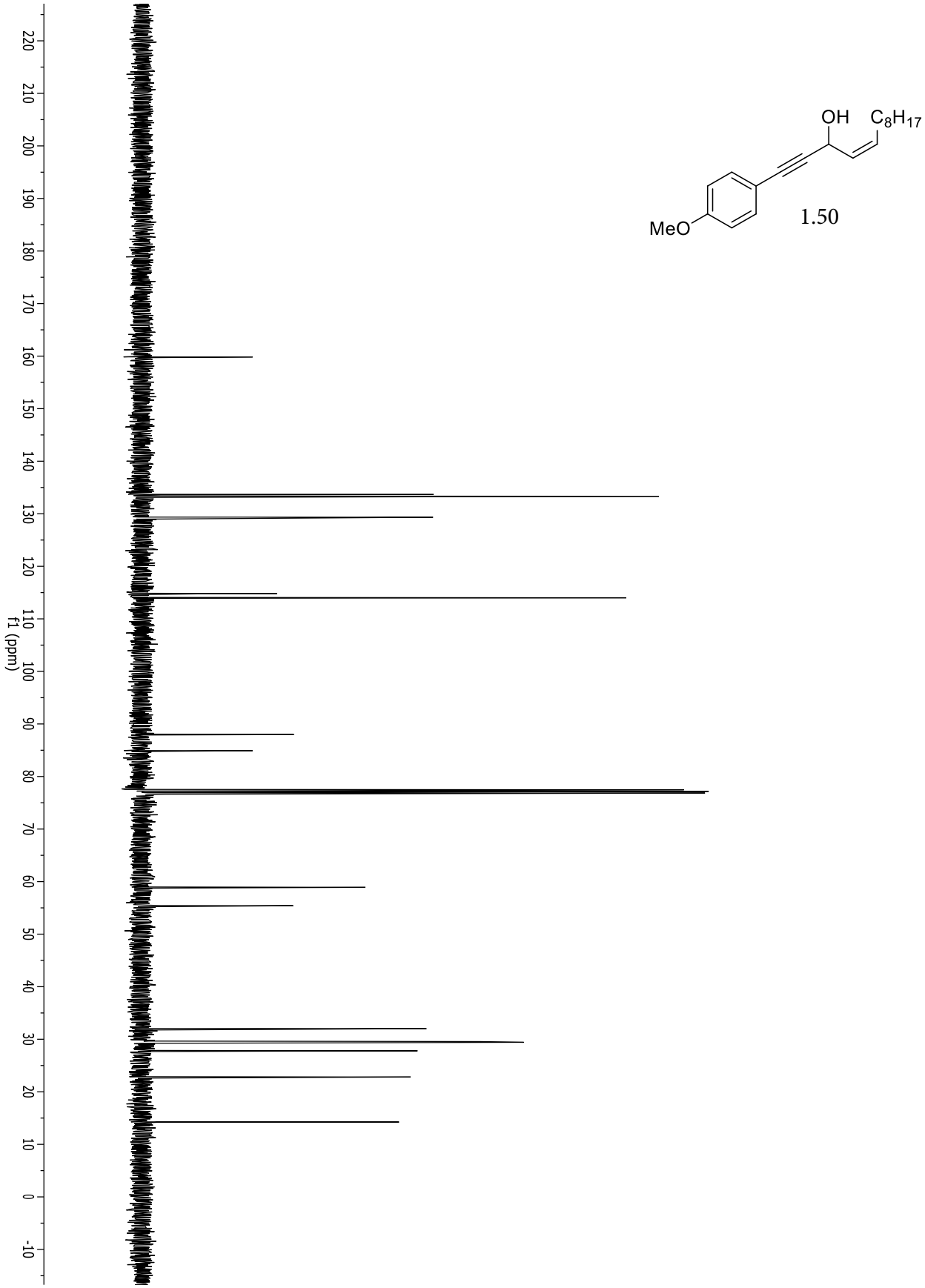

OH
C_8H_{17}
F_3C
1.51
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

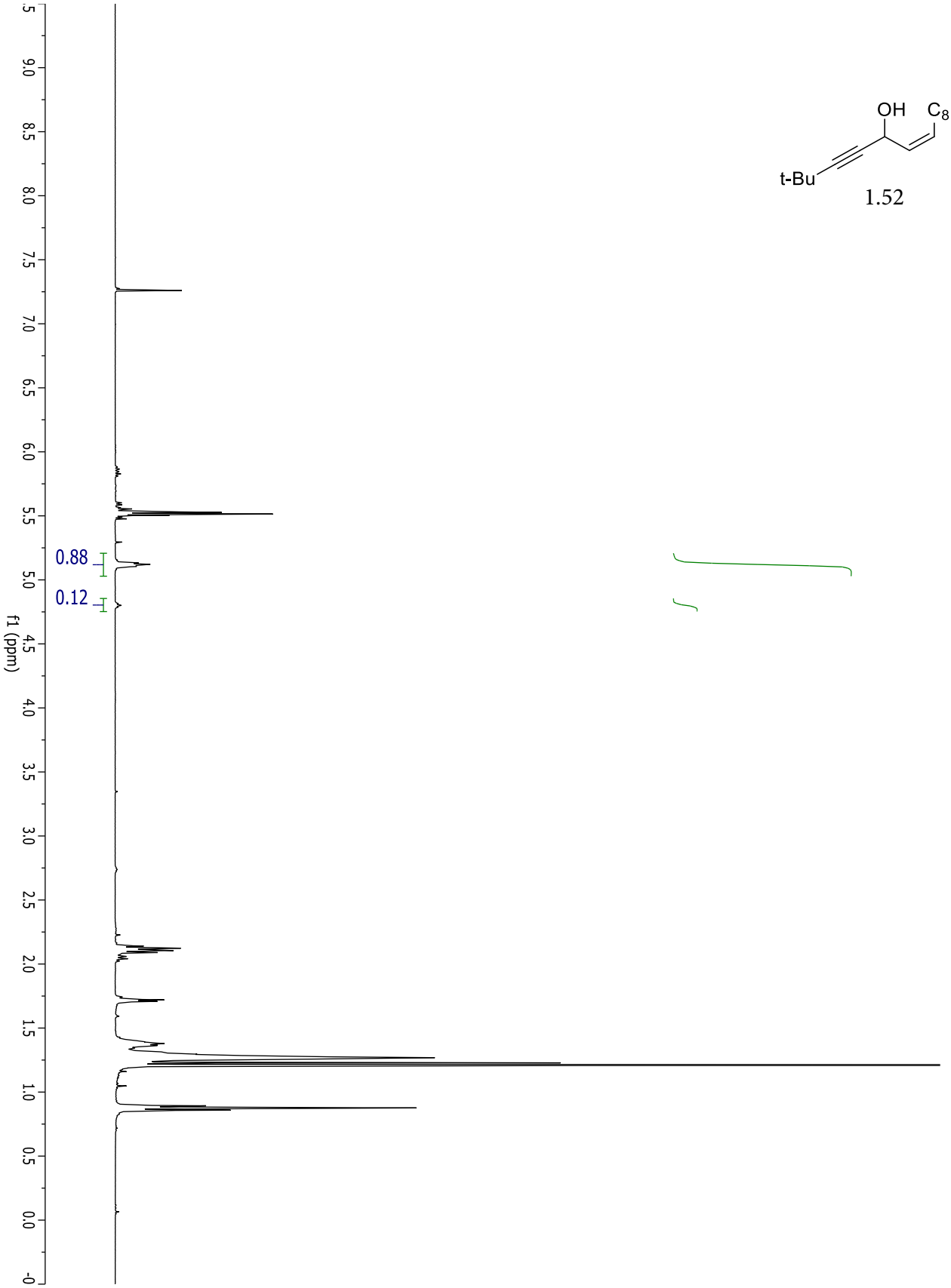

-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
f1 (ppm)

OH
C_8H_{17}
F_3C

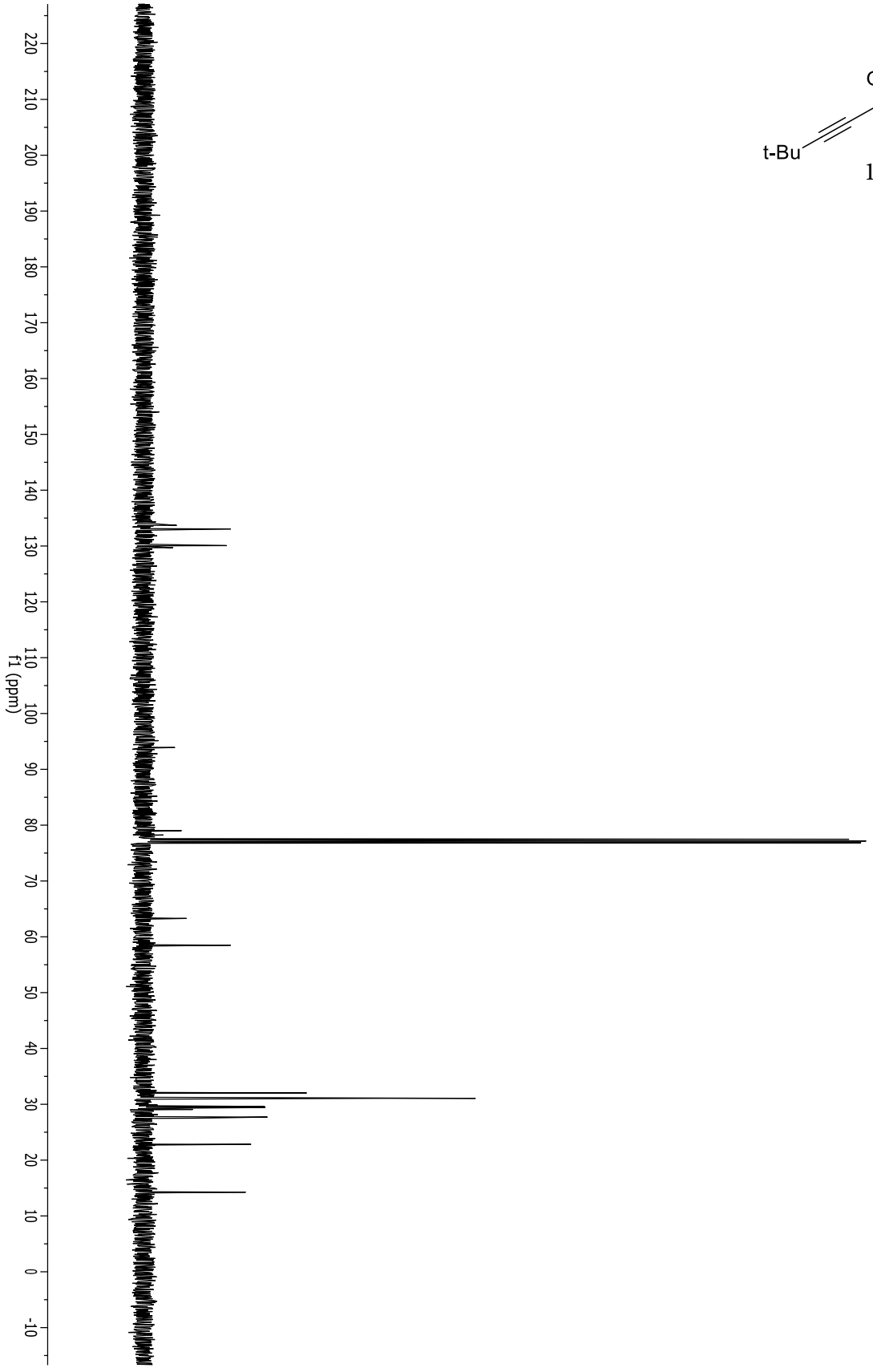
1.51


OH
C_8H_{17}
MeO
1.50
f1 (ppm)
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0


OH
C_8H_{17}
MeO
1.50
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

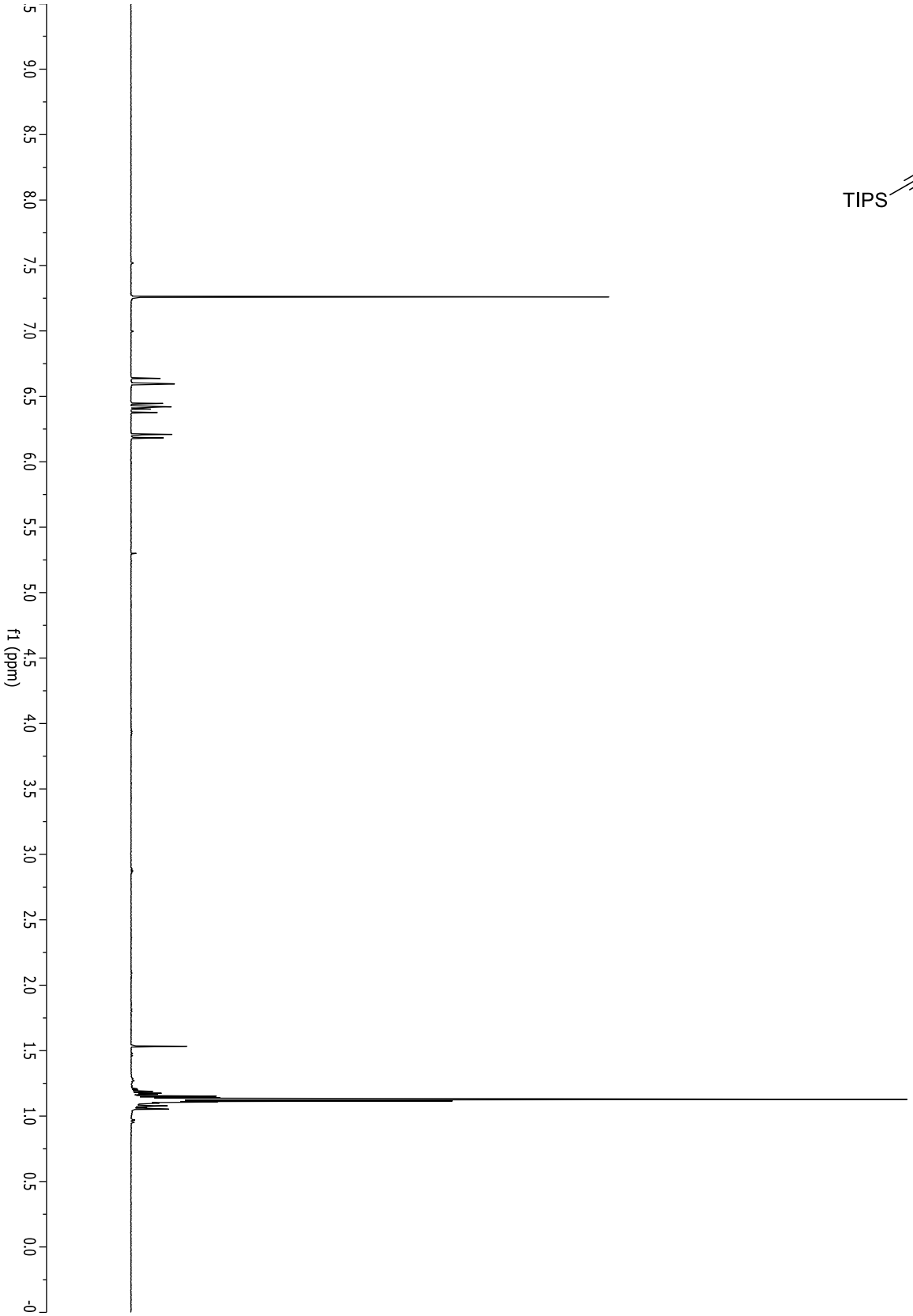


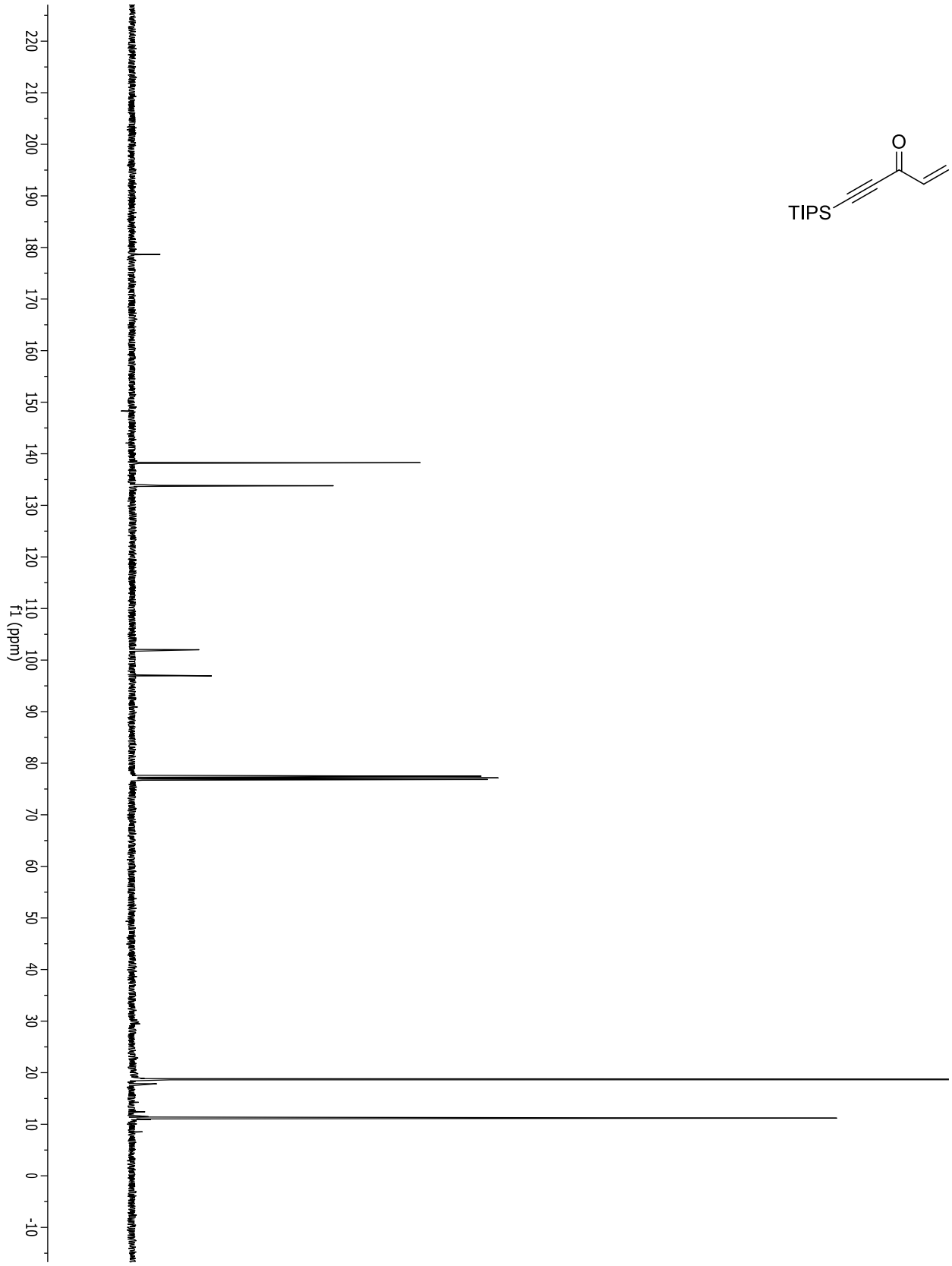
1.52

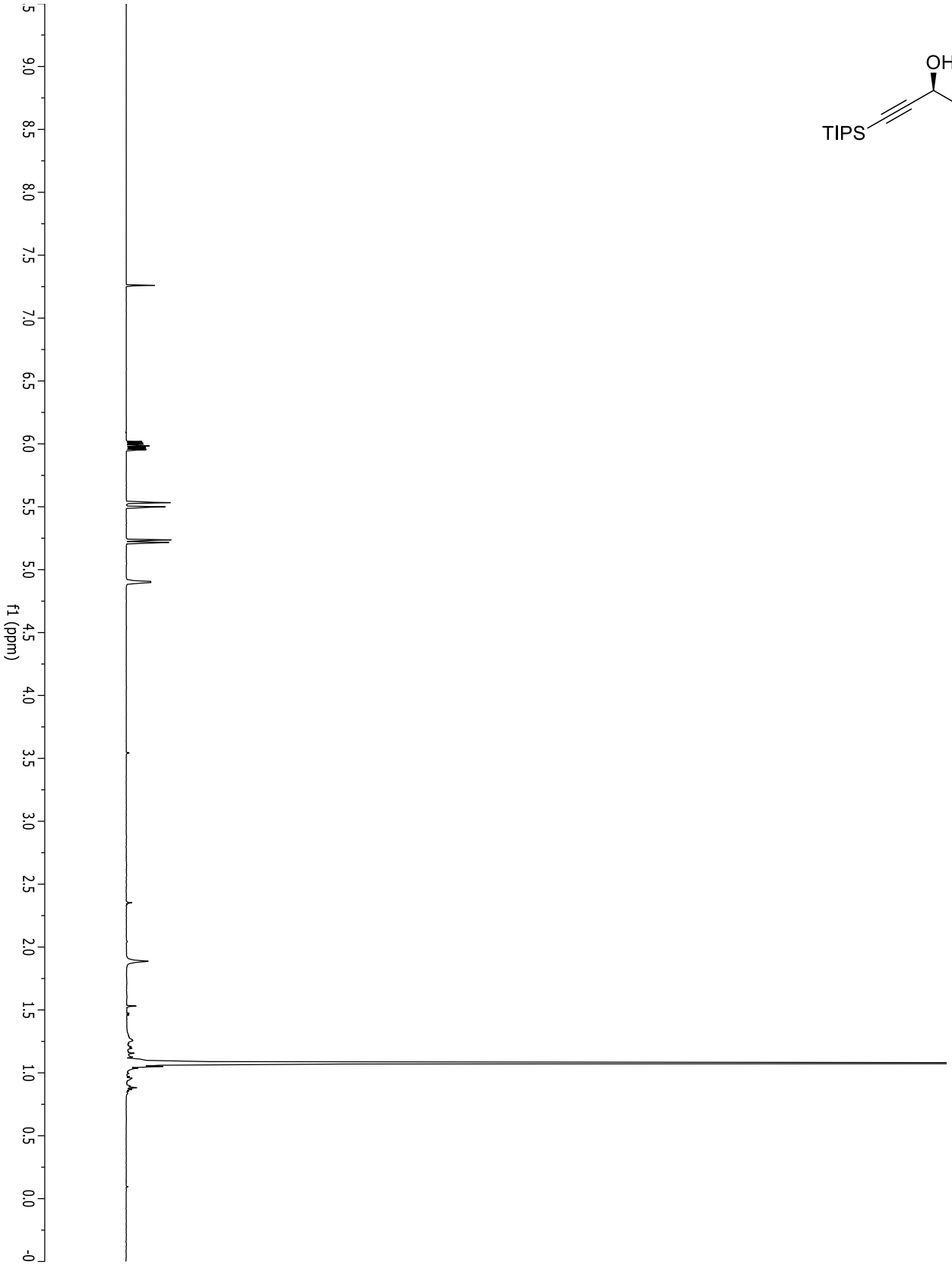

f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

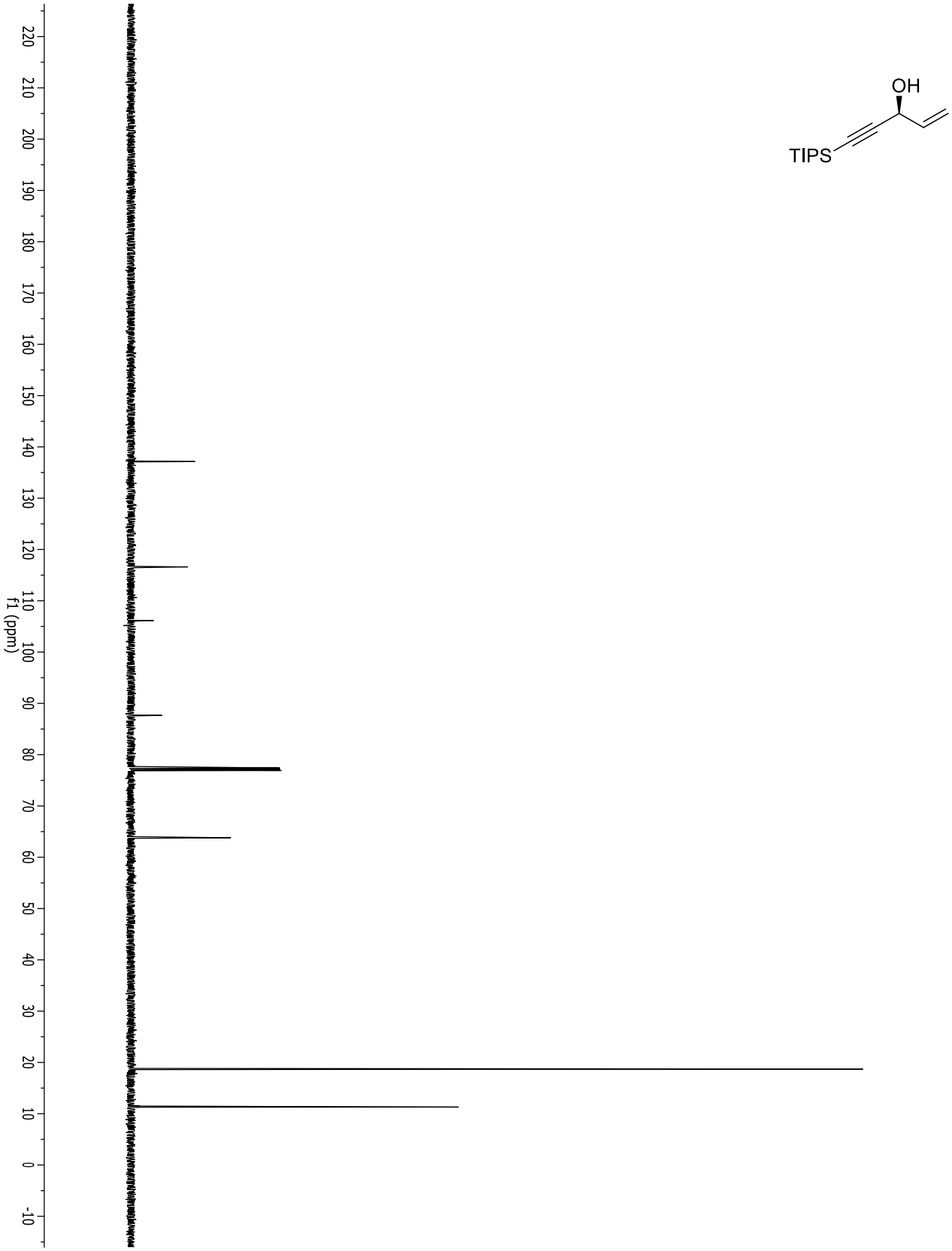
OH
C_8H_{17}
t-Bu

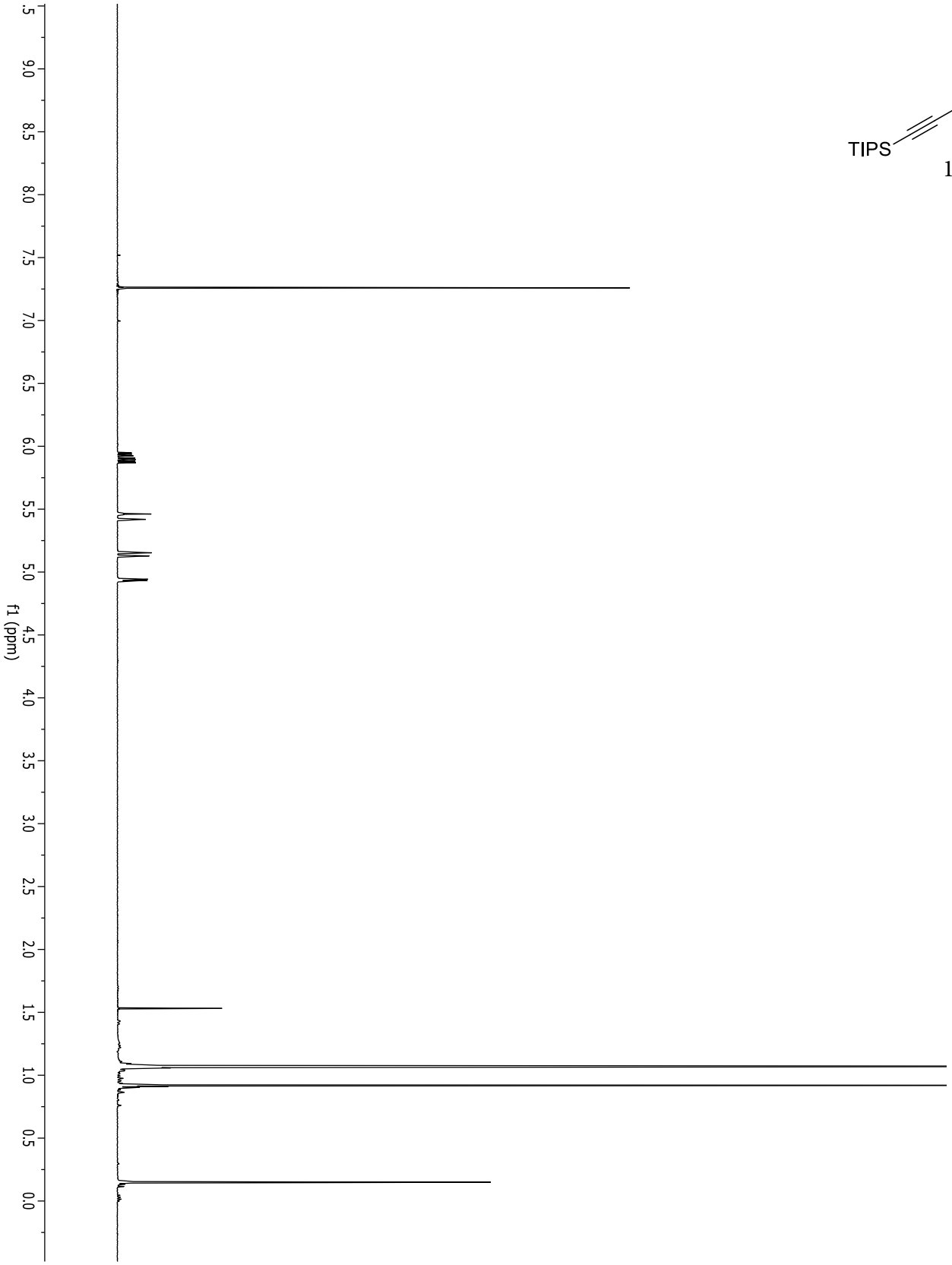
1.52

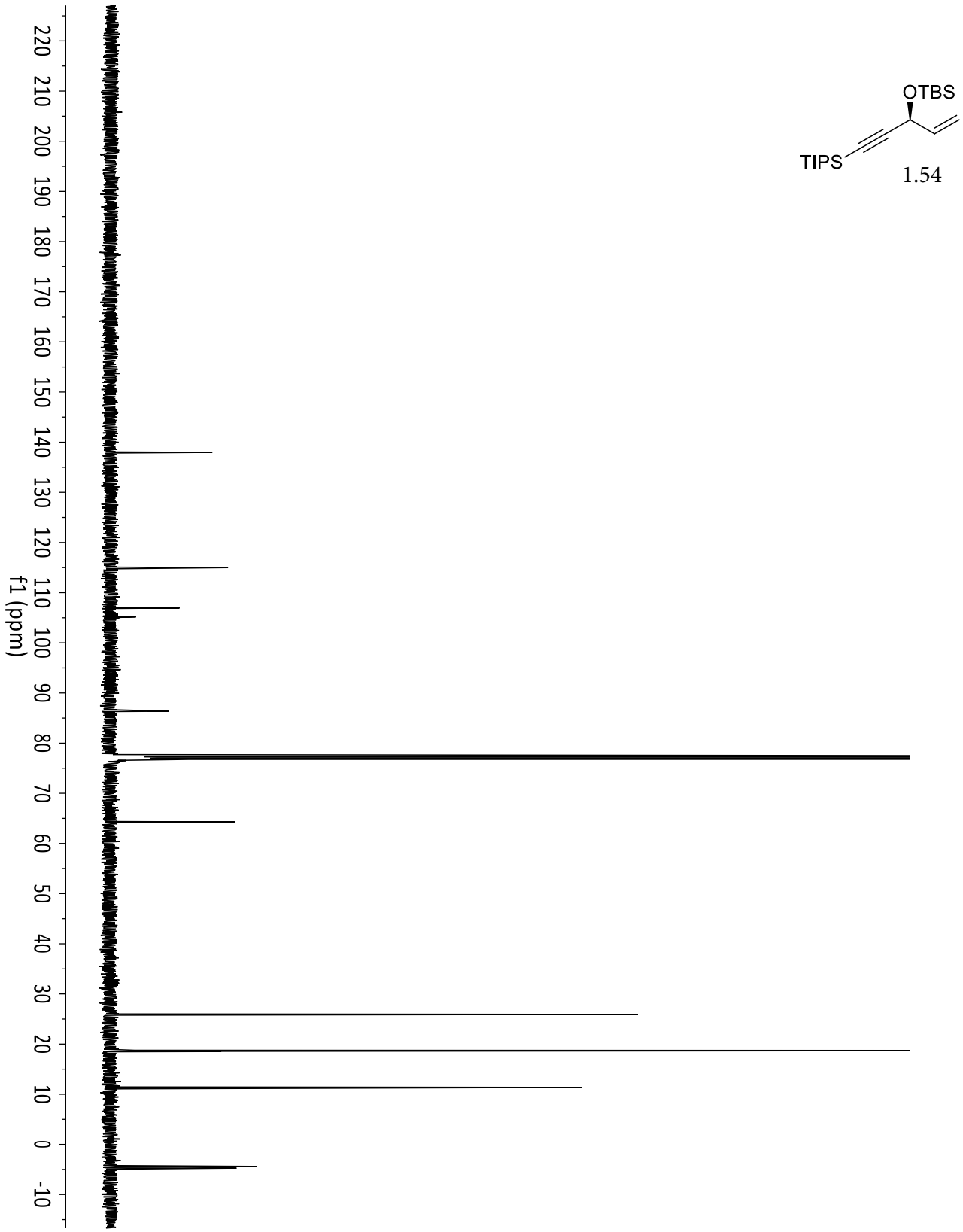

O
TIPS
f1 (ppm)
.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0

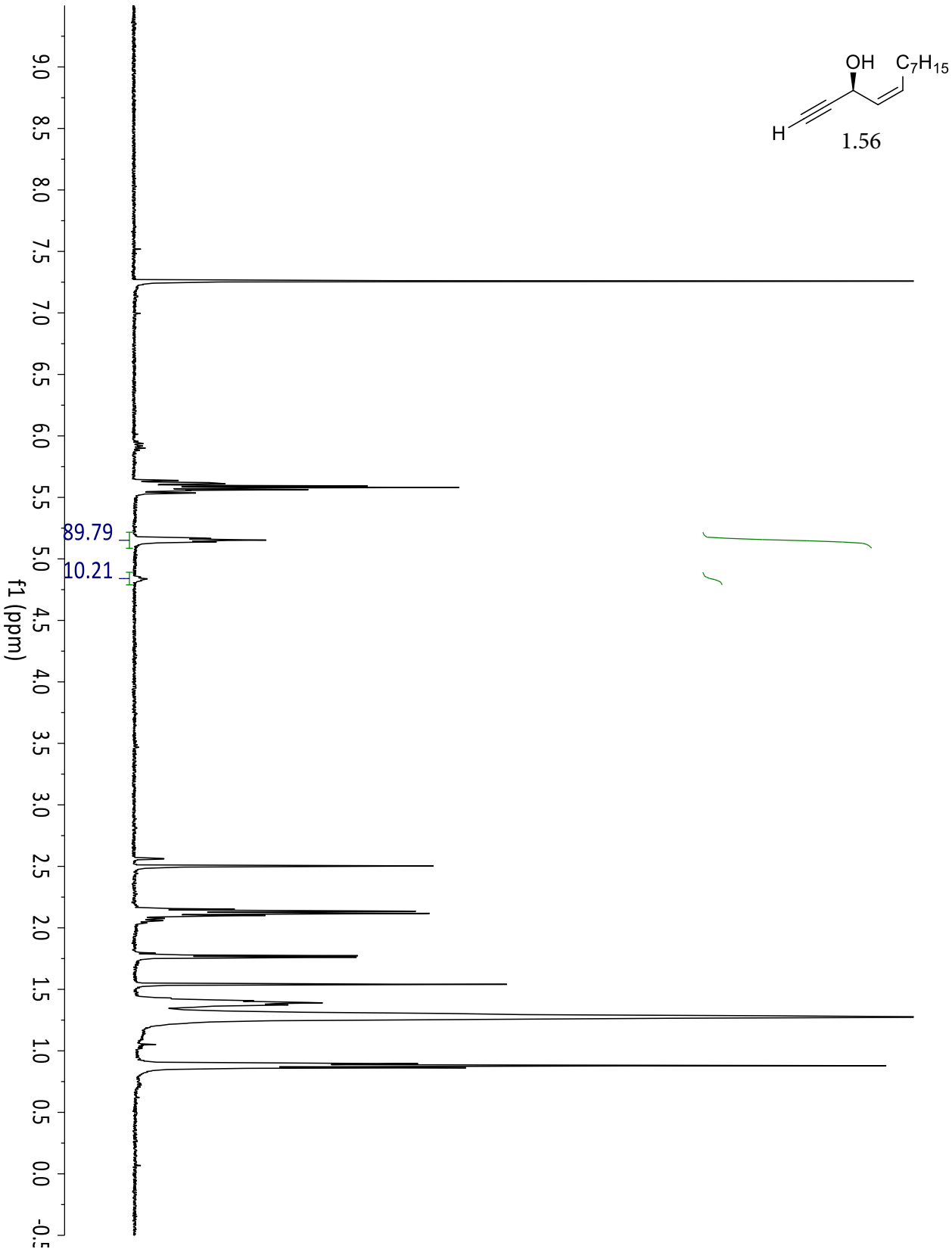

O
TIPS
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

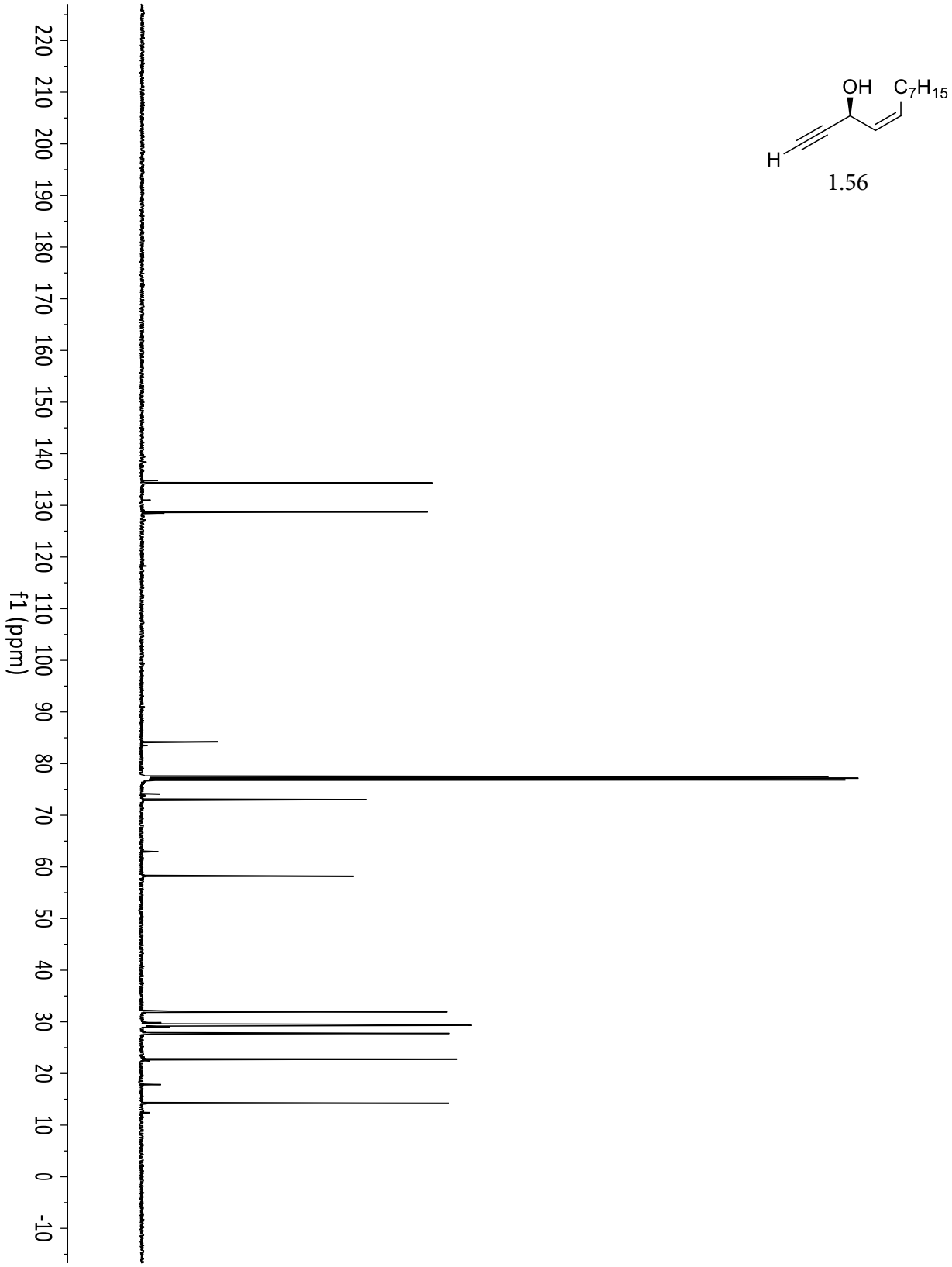

OH
TIPS
f1 (ppm)
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0


OH
TIPS
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


OTBS
TIPS
1.54
f1 (ppm)

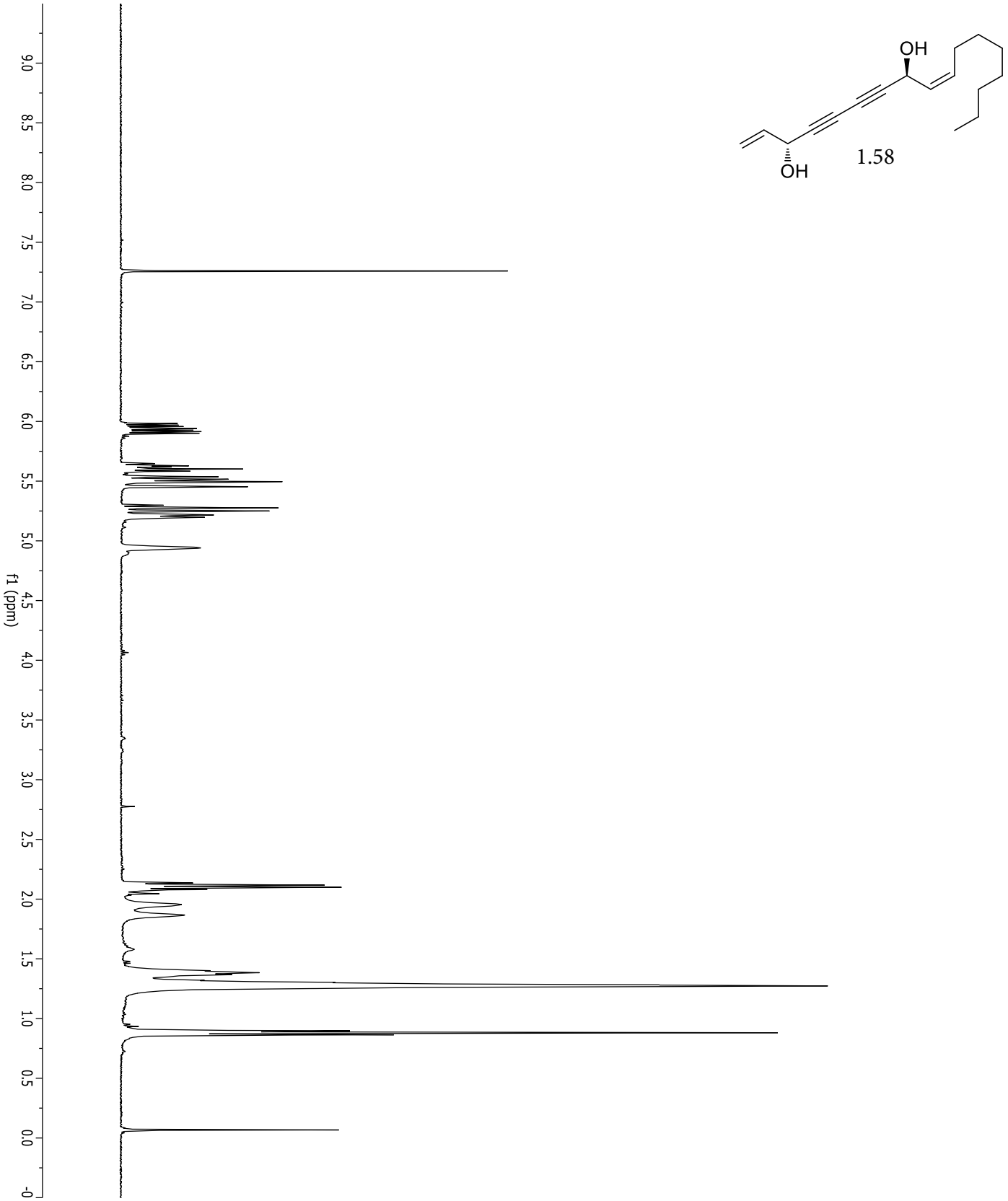

OTBS
TIPS
1.54
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


OH
C7H15
H
1.56
89.79
10.21
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

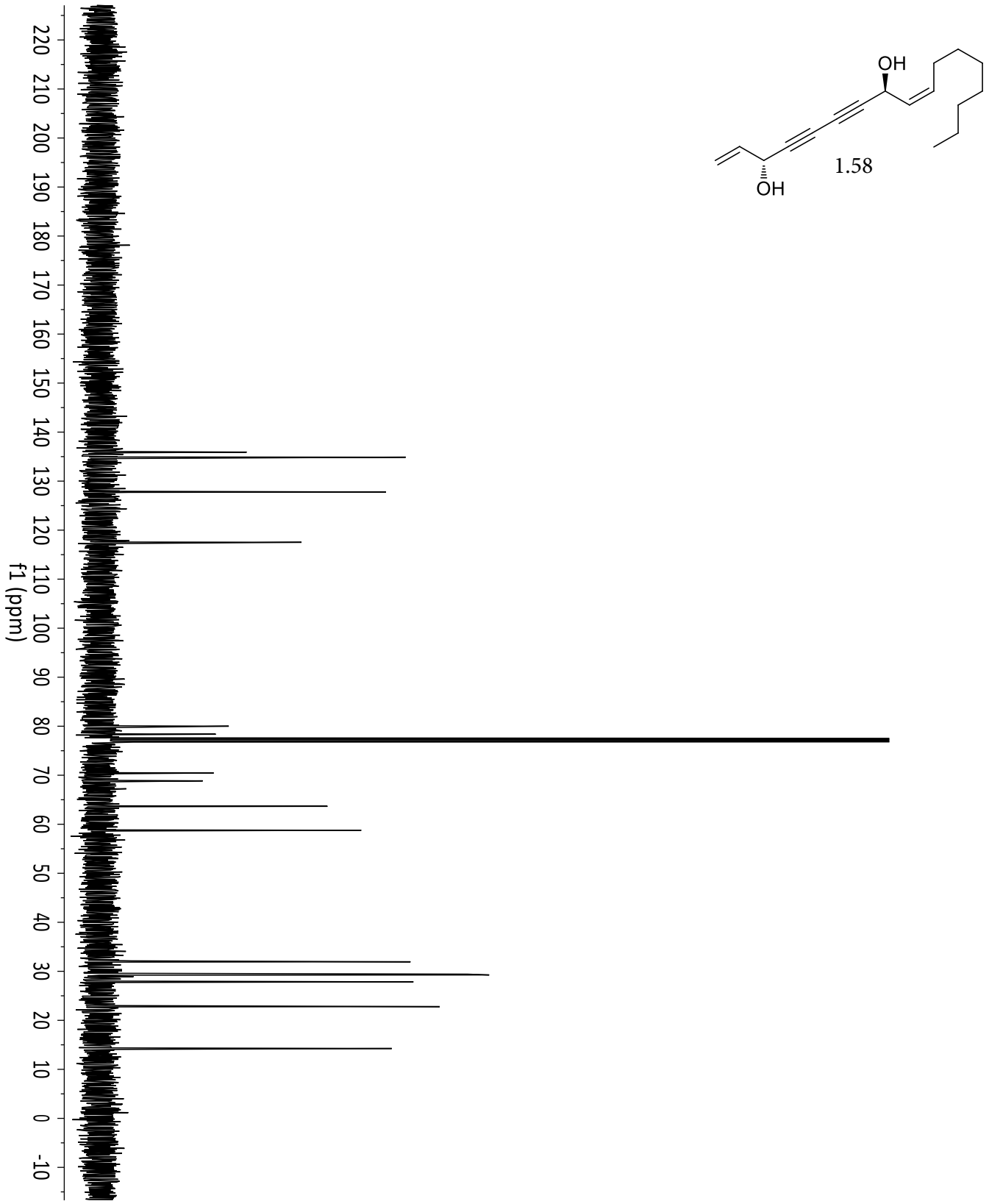

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

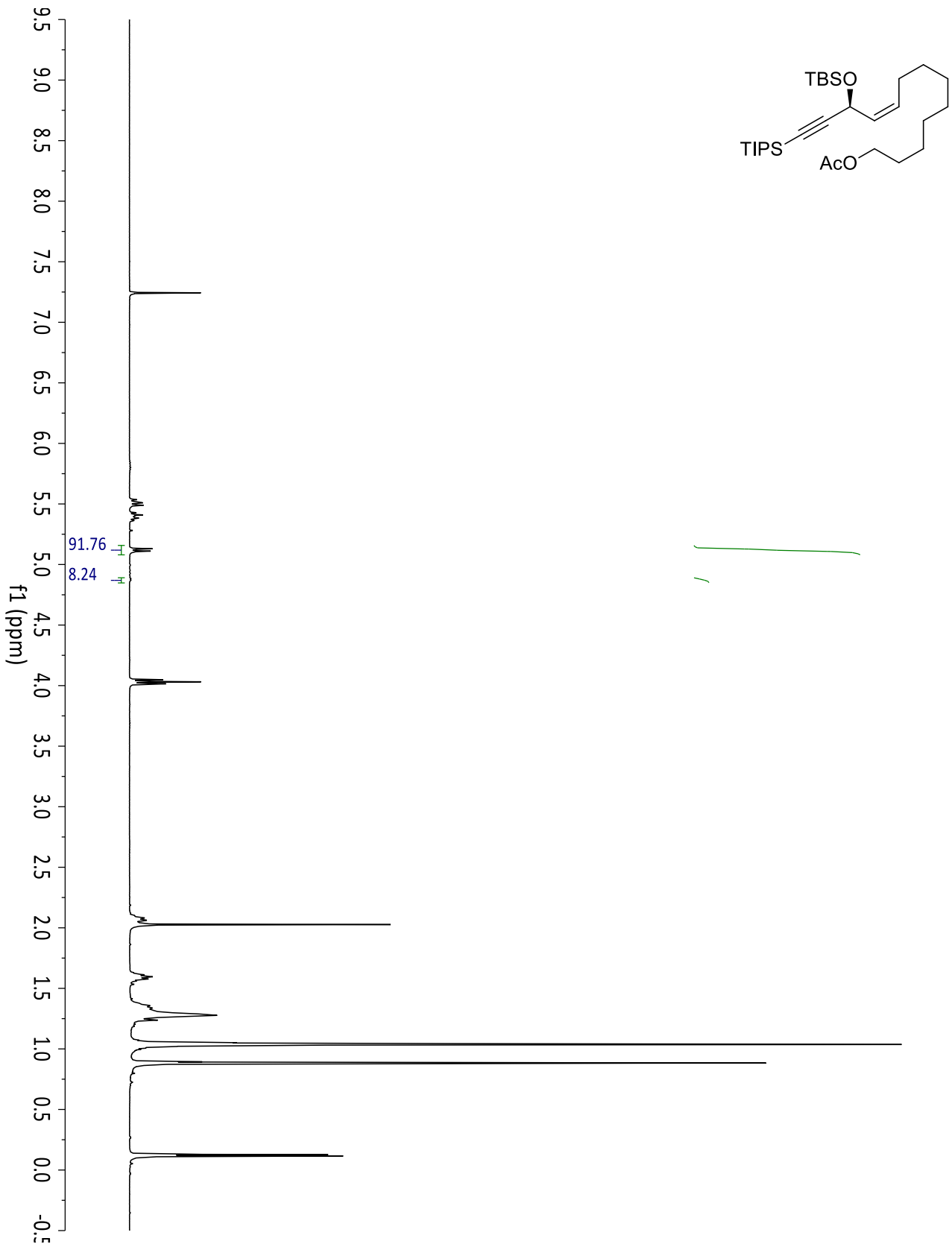
OH
C7H15
H

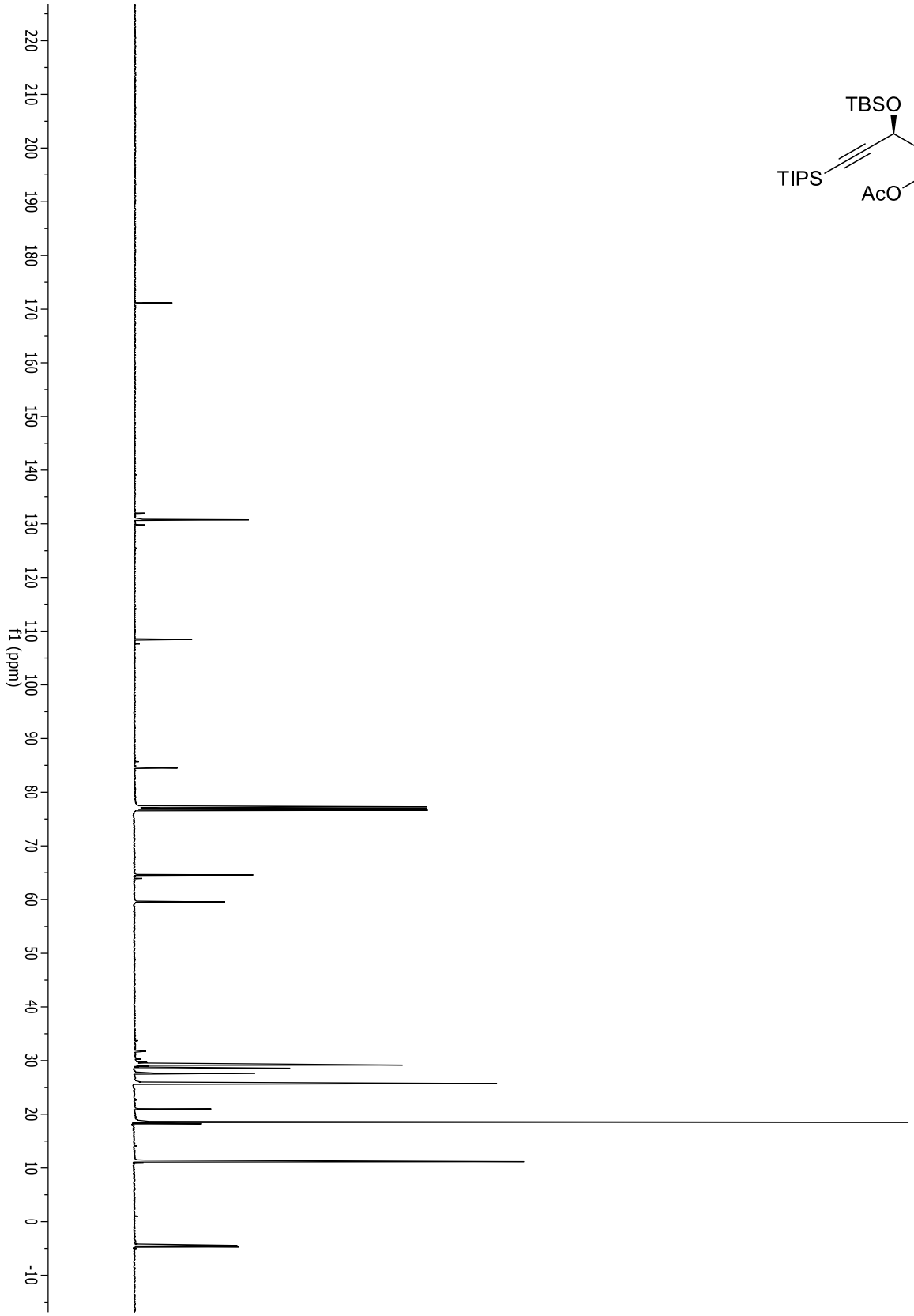
1.56

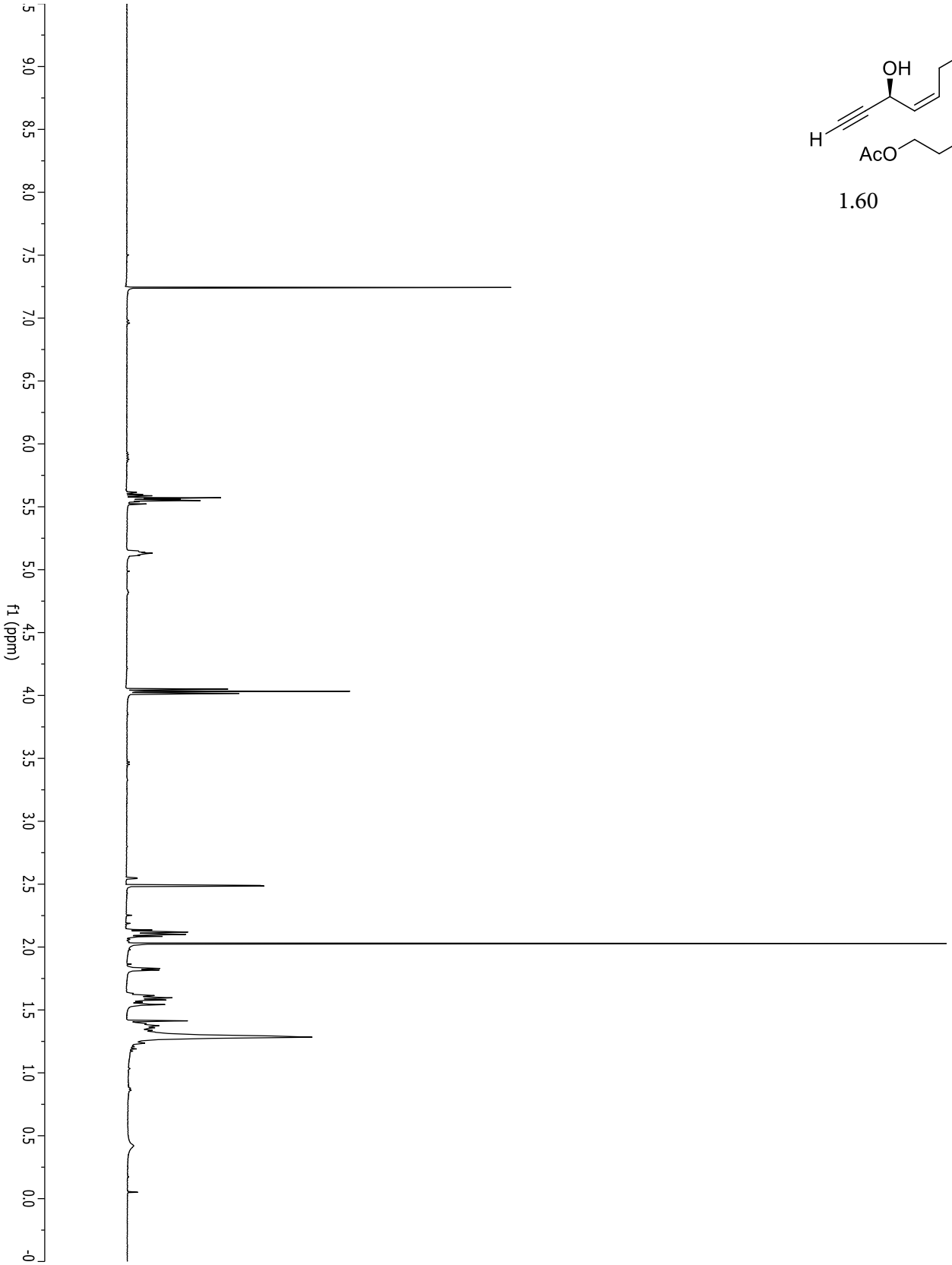


1.58

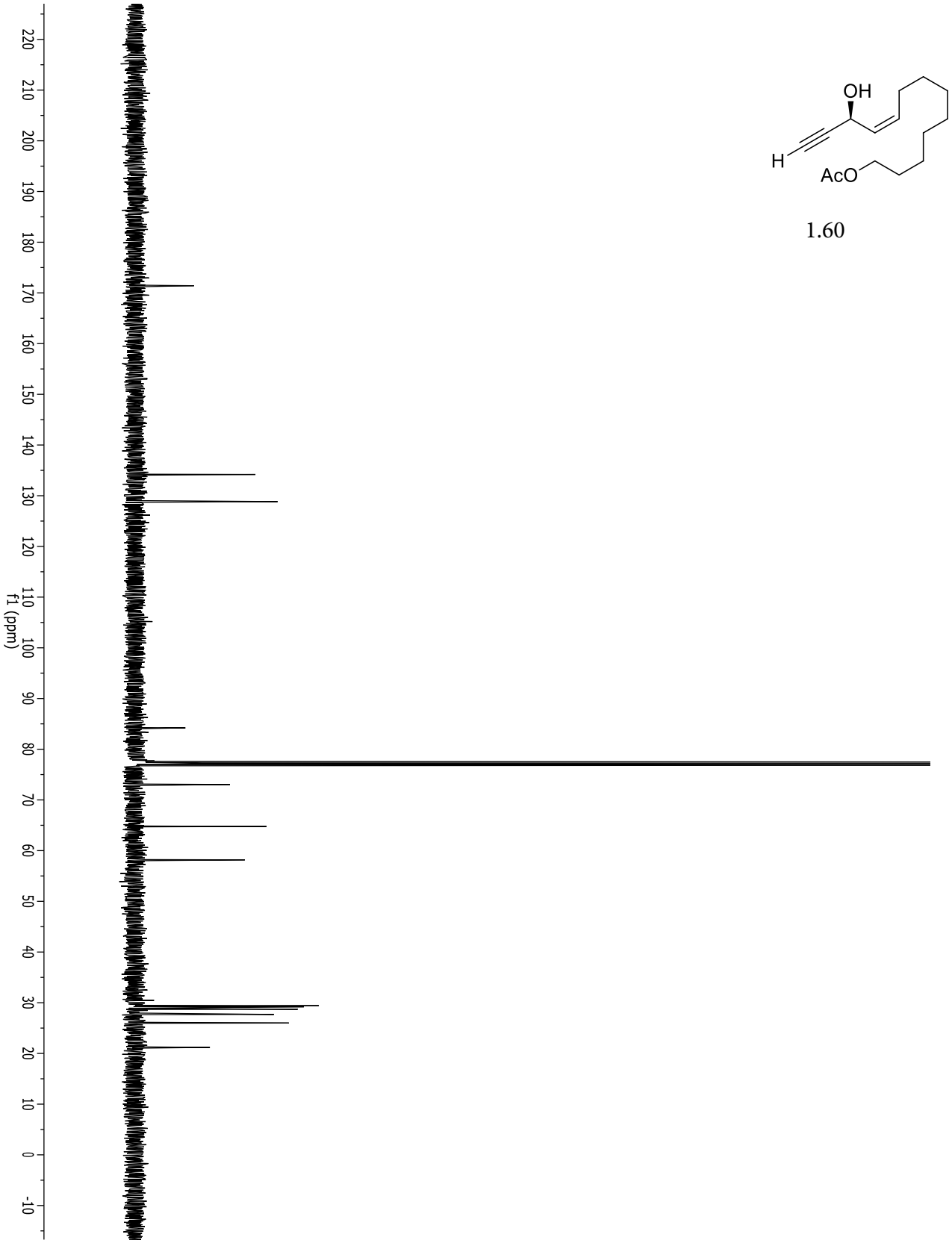

OH
OH
1.58
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


TBSO
TIPS
AcO
91.76
8.24
f1 (ppm)
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


TBSO
TIPS
AcO
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

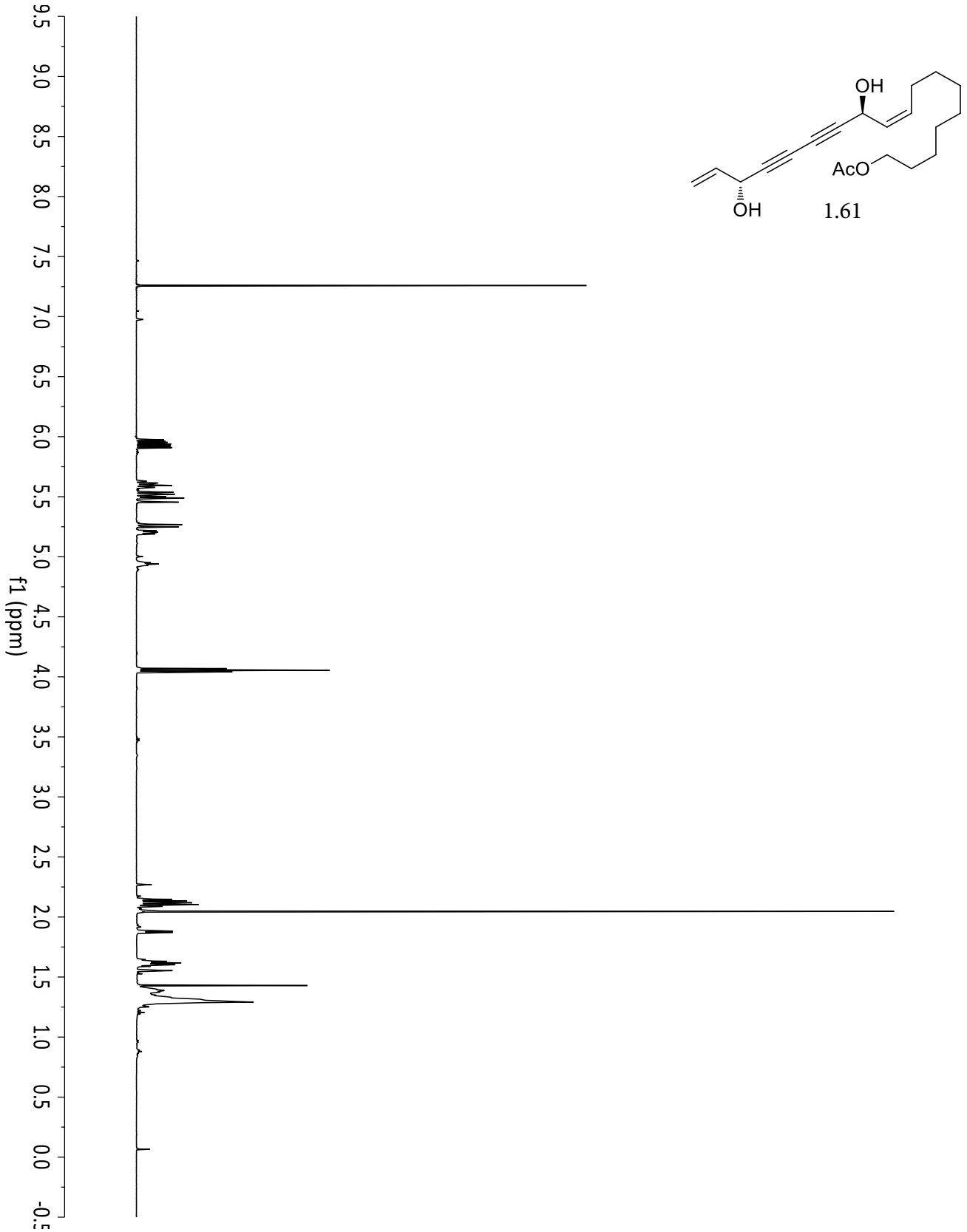


1.60


f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

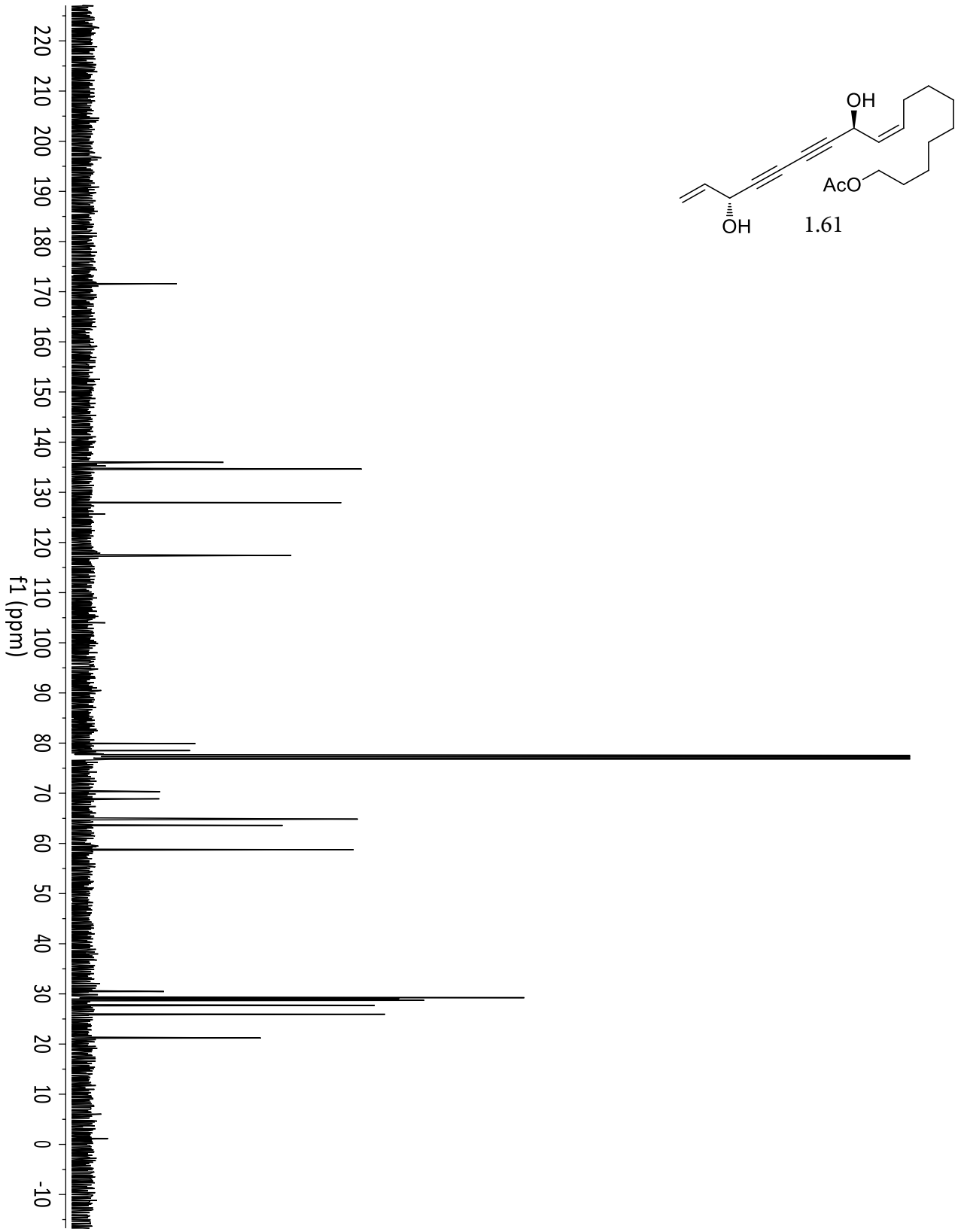
OH
H
AcO

1.60


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

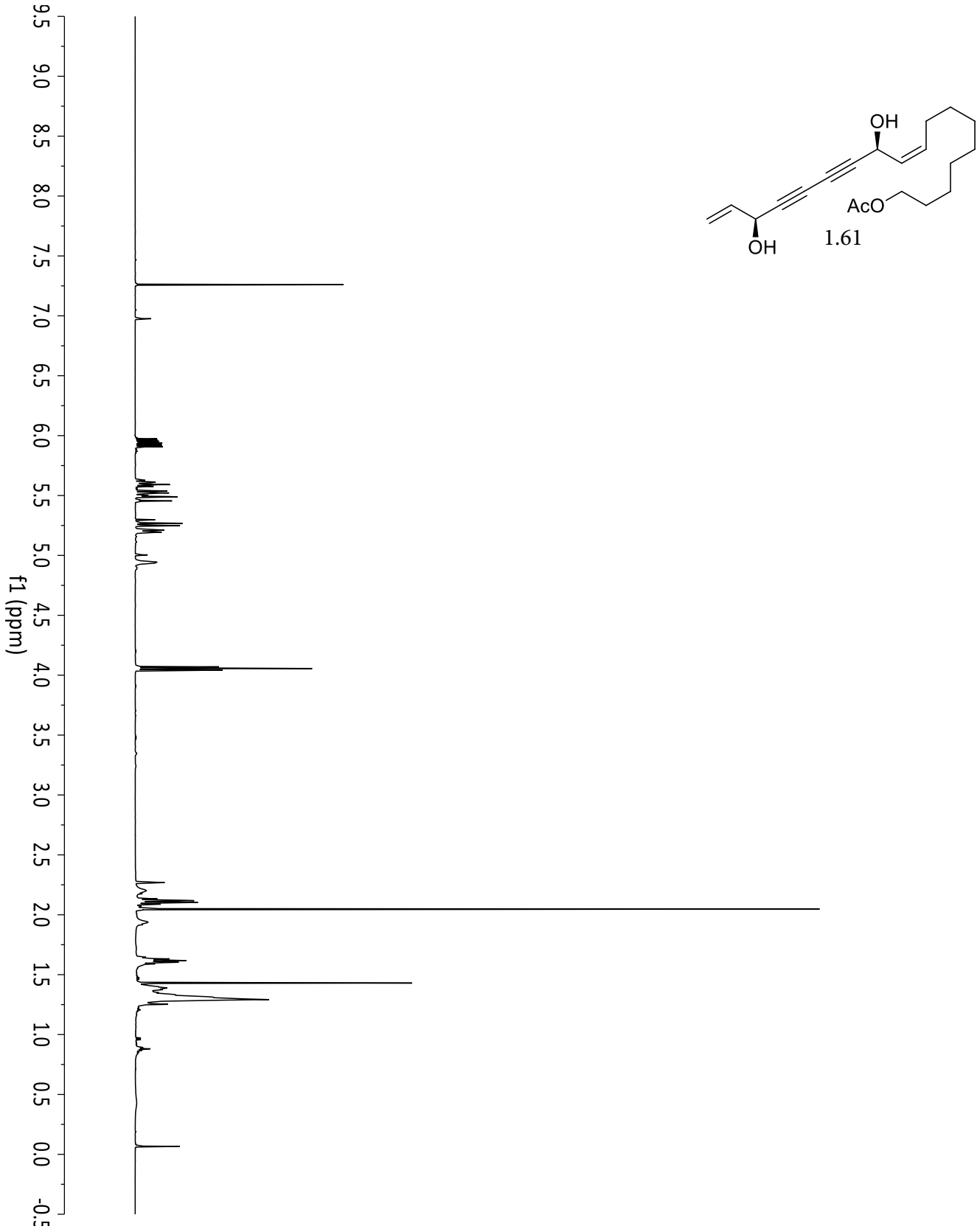
OH
AcO
OH

1.61


f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

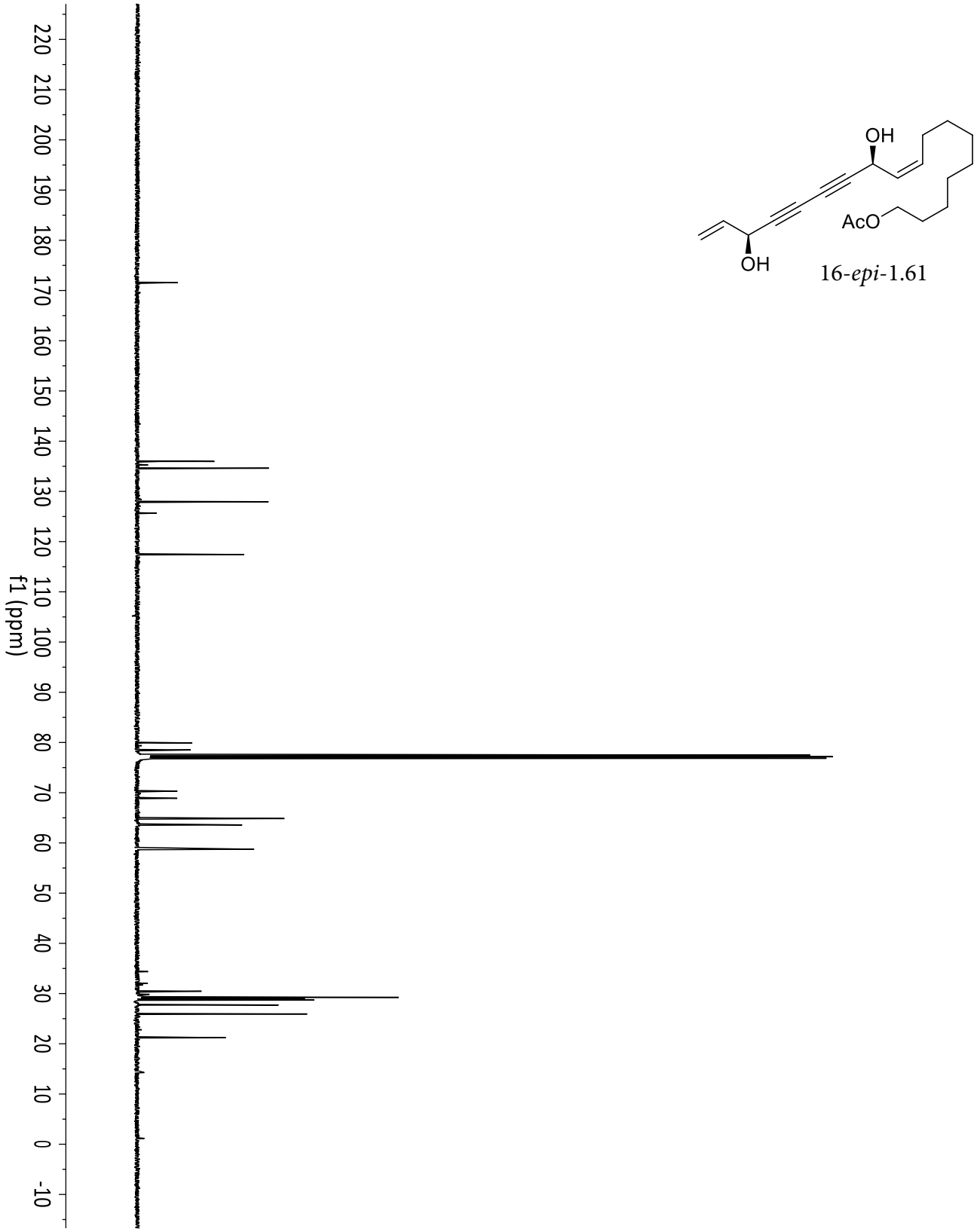
OH
AcO
OH

1.61

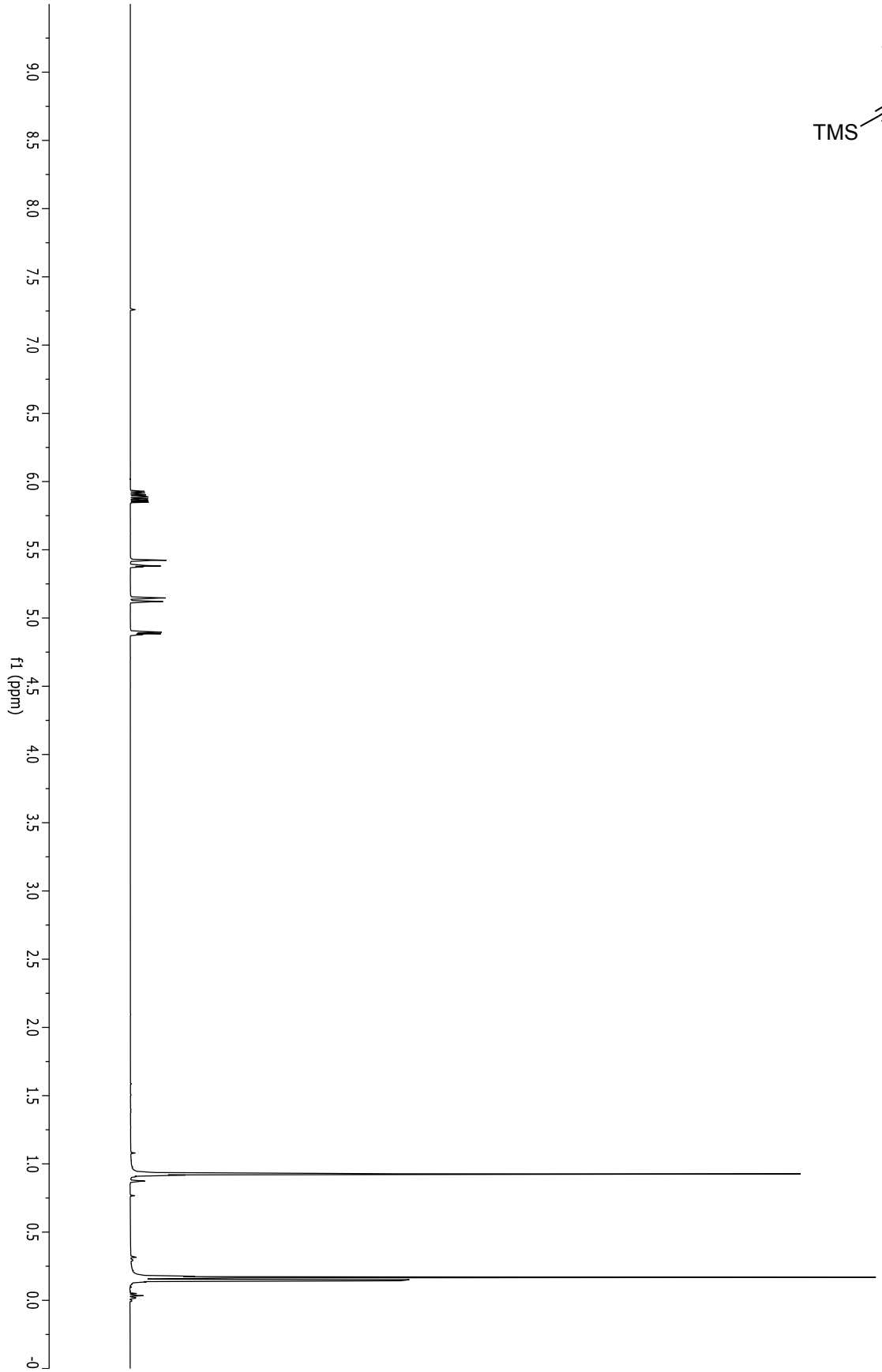

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

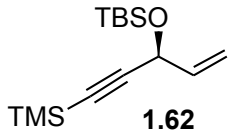
OH
AcO
OH

1.61

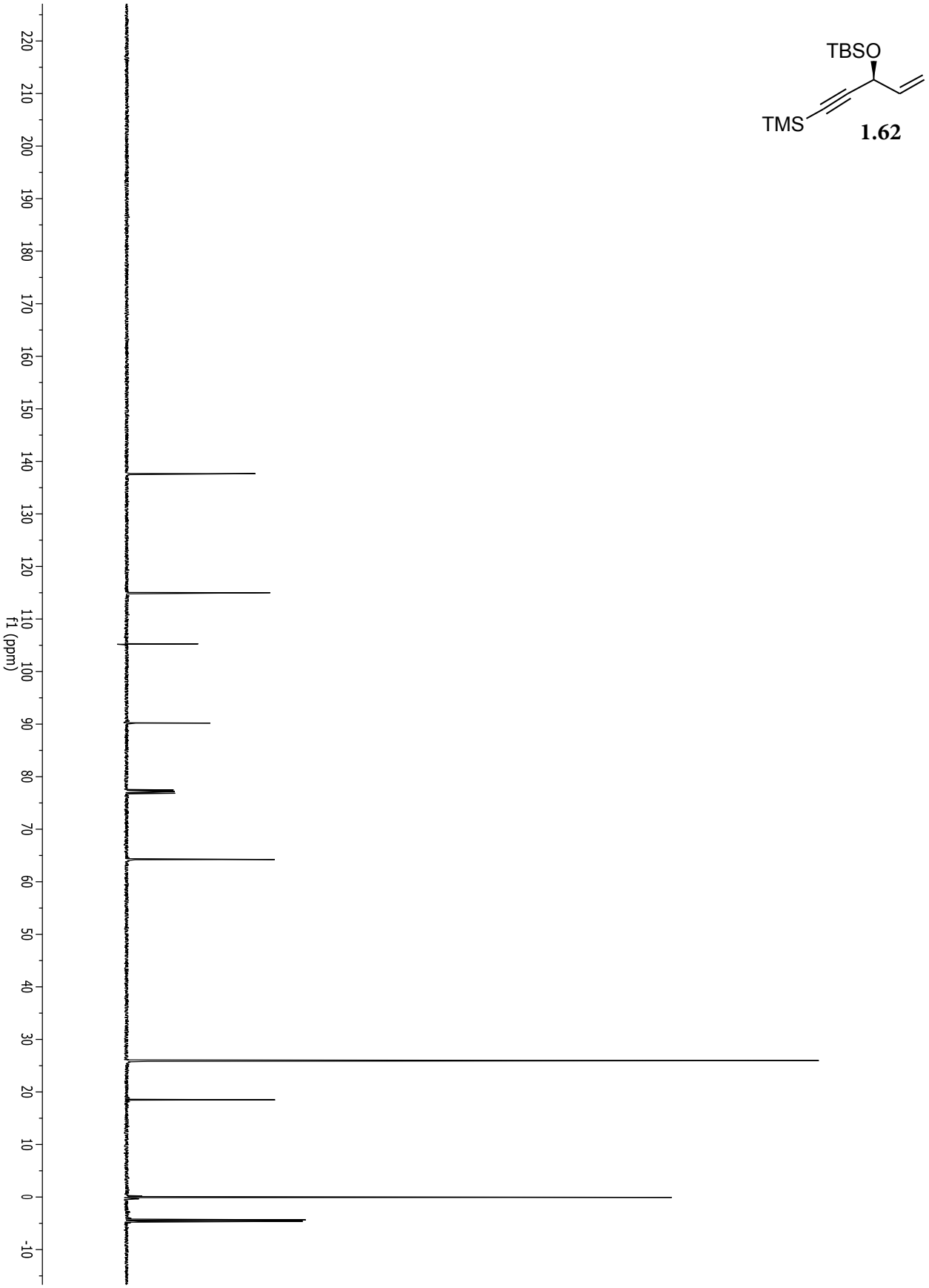

OH
AcO
OH
f1 (ppm)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

16-*epi*-1.61


9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

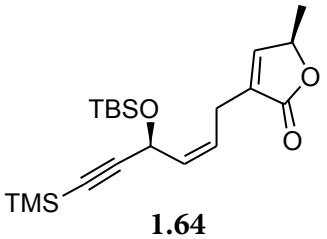

TBSO
TMS

1.62

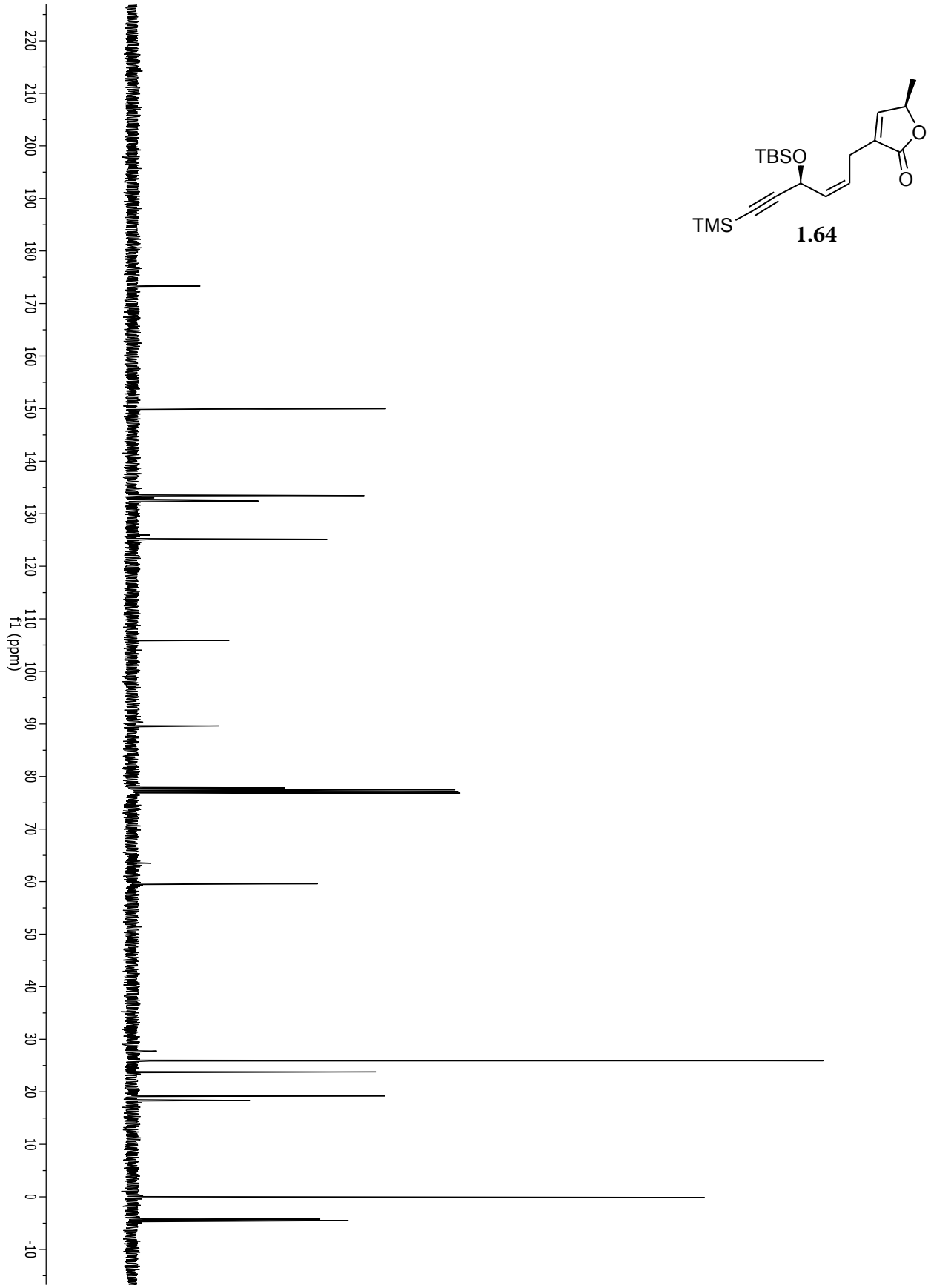

f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

TBSO
TMS

1.62

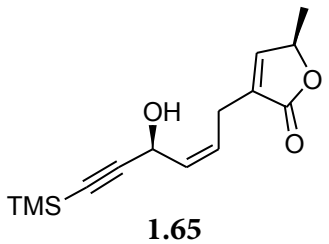


1.64

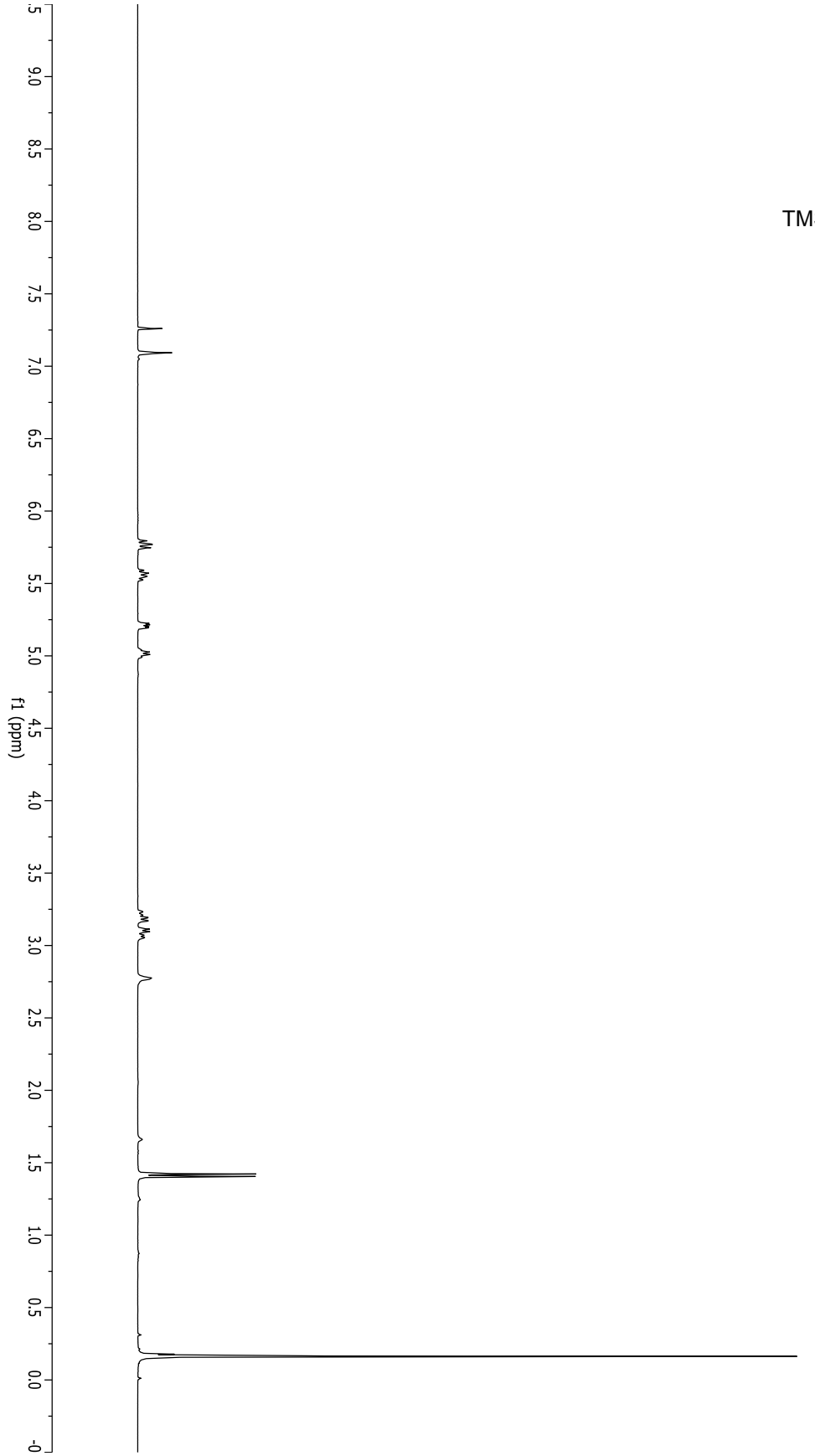

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

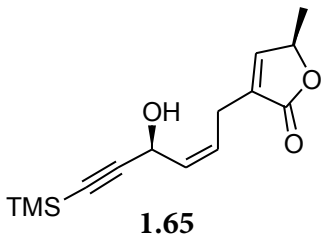
TBSO
O
O
TMS

1.64

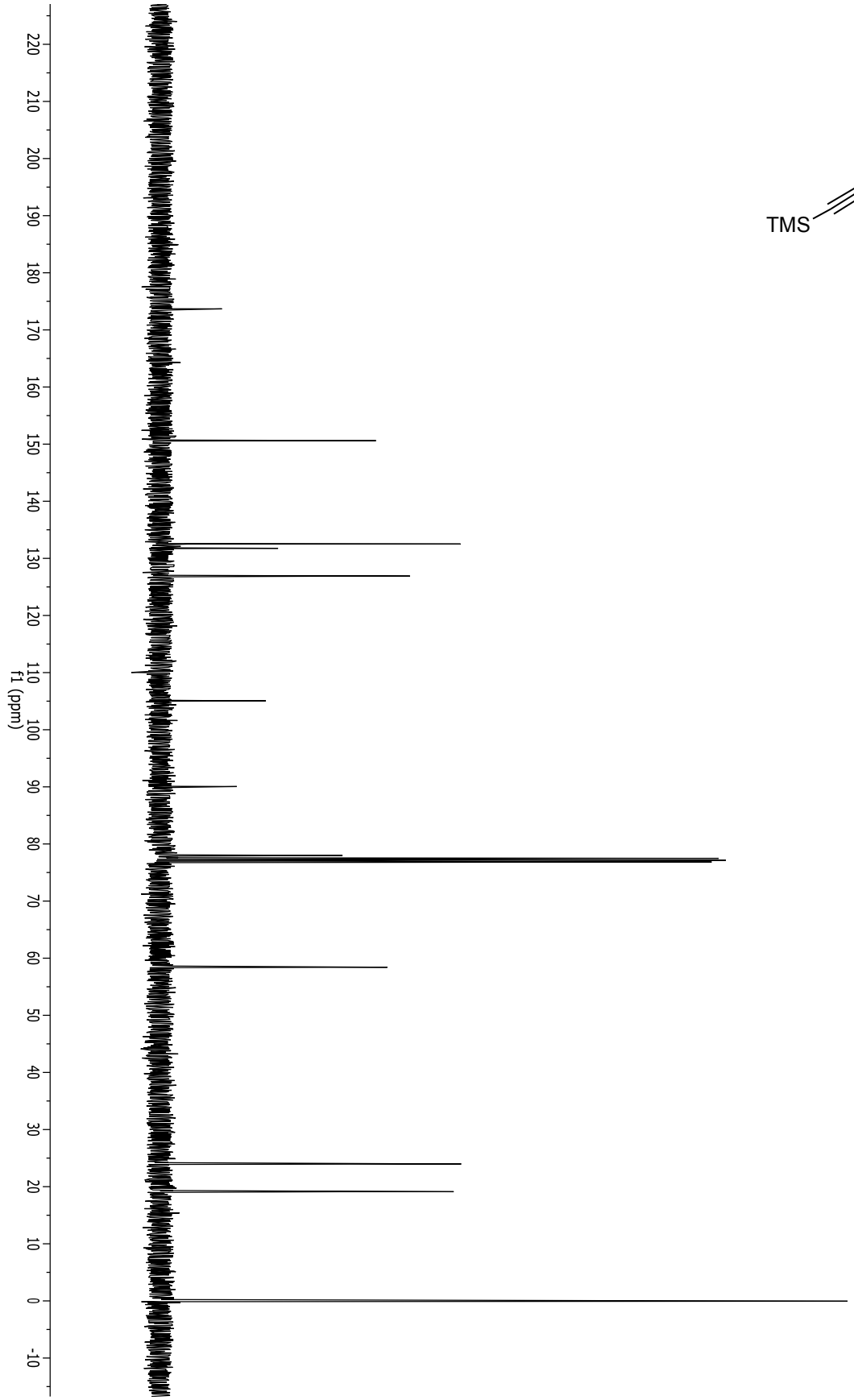

OH
O
O
TMS

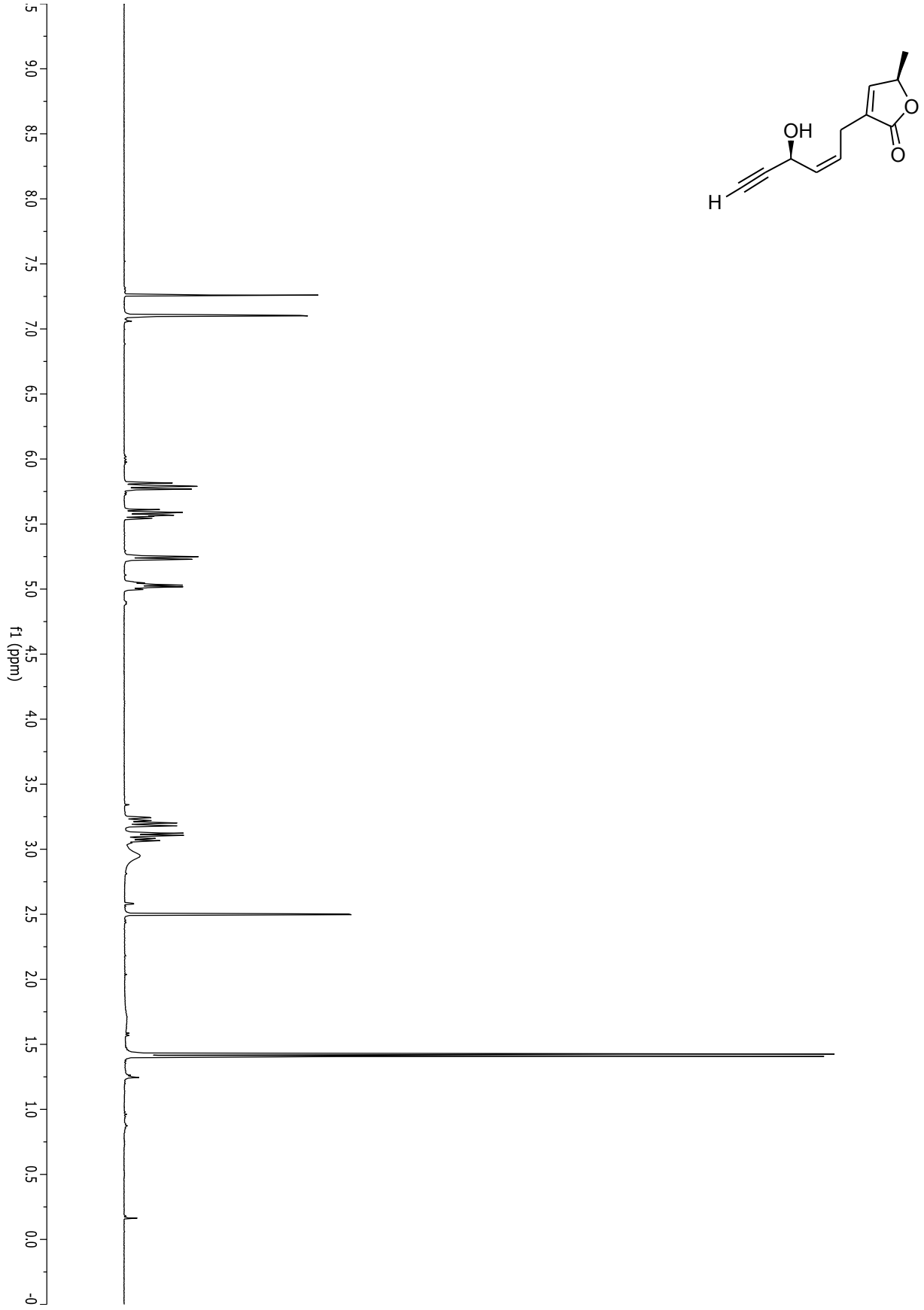
1.65

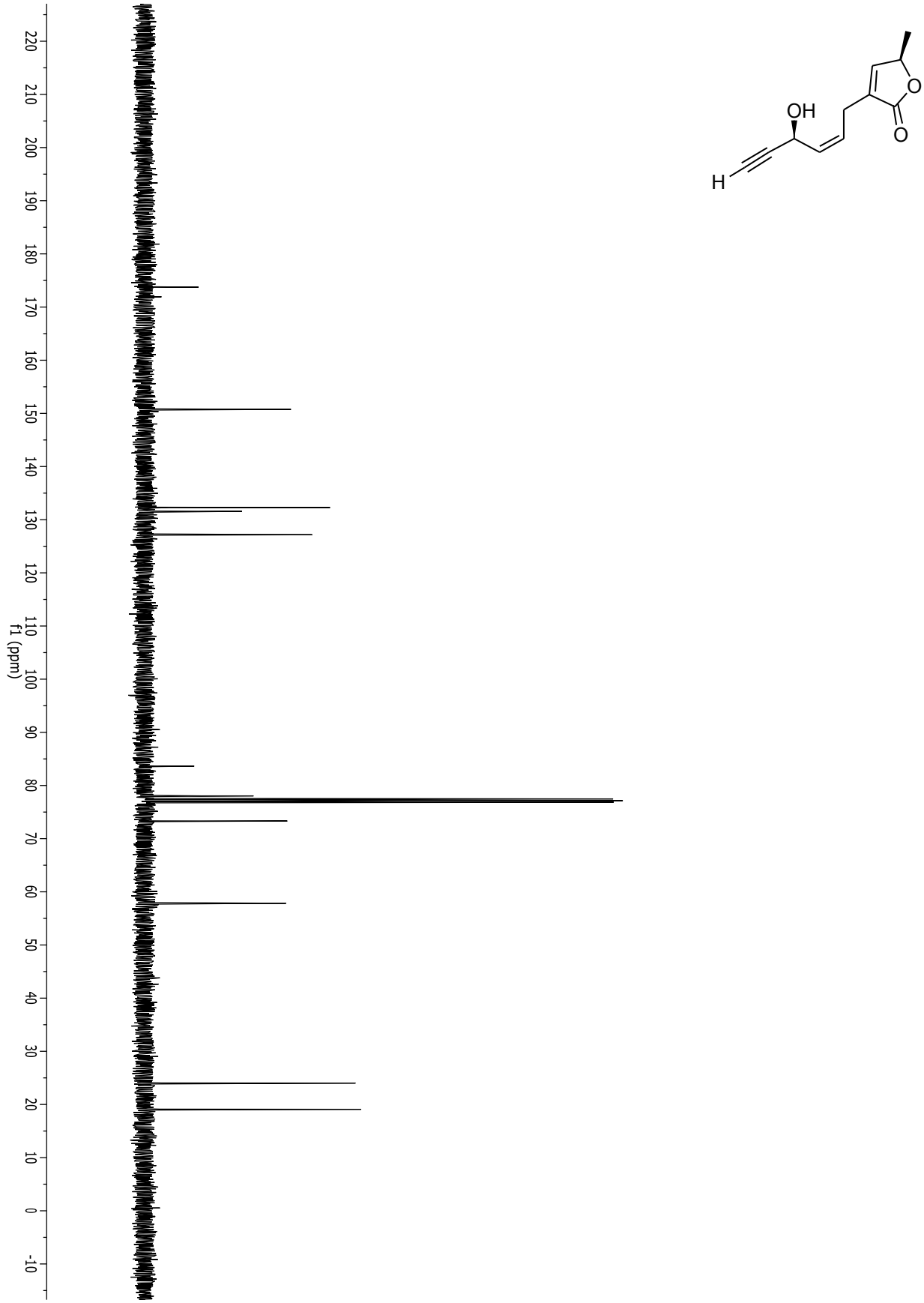

f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

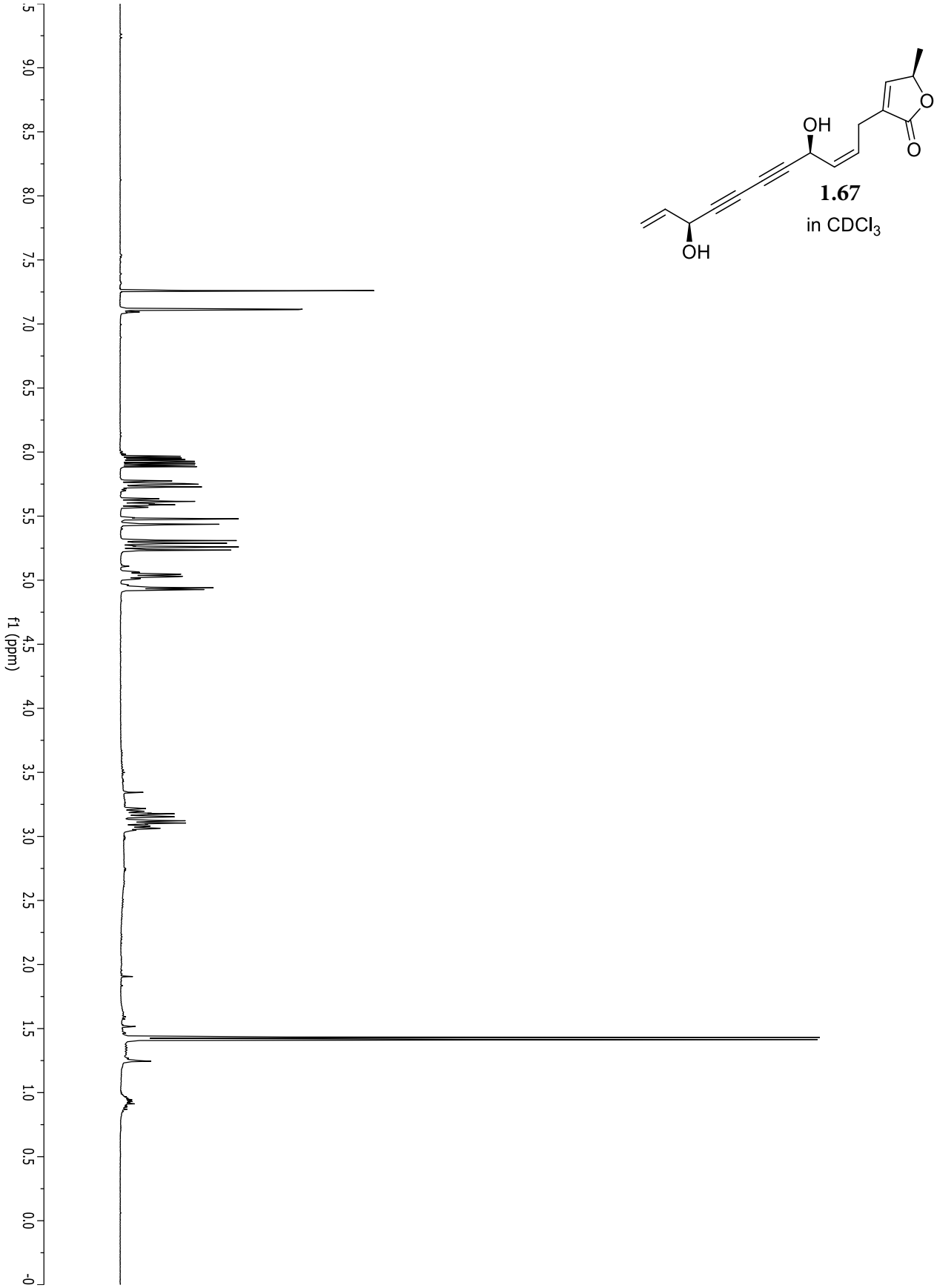

OH
O
O
TMS

1.65


f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

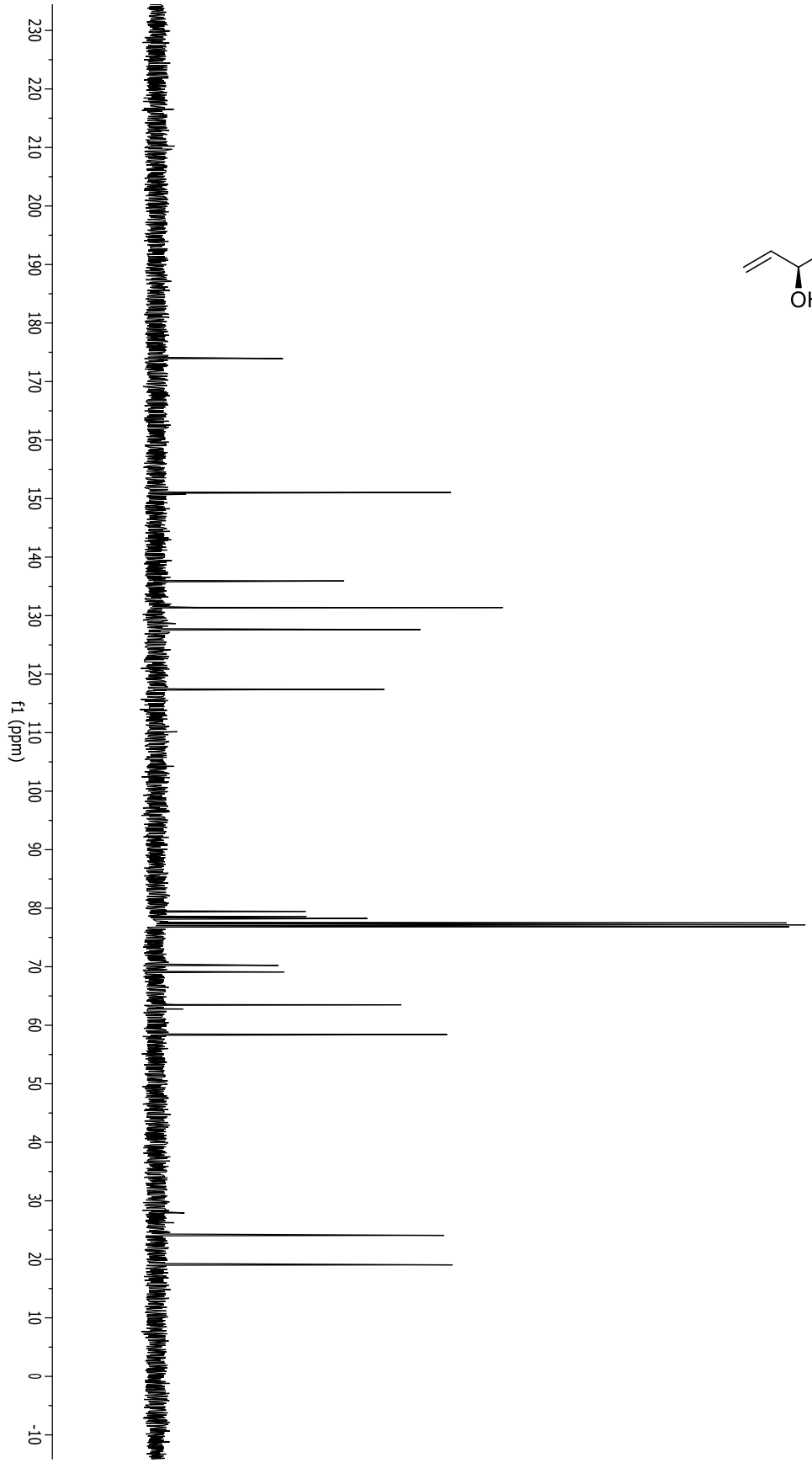

OH
O
O
H
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

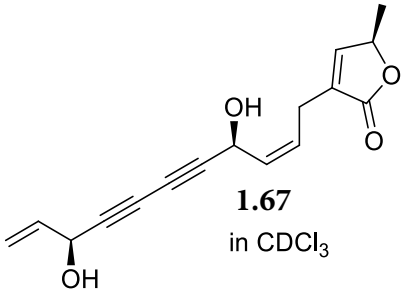

f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
OH
O
O
H



1.67

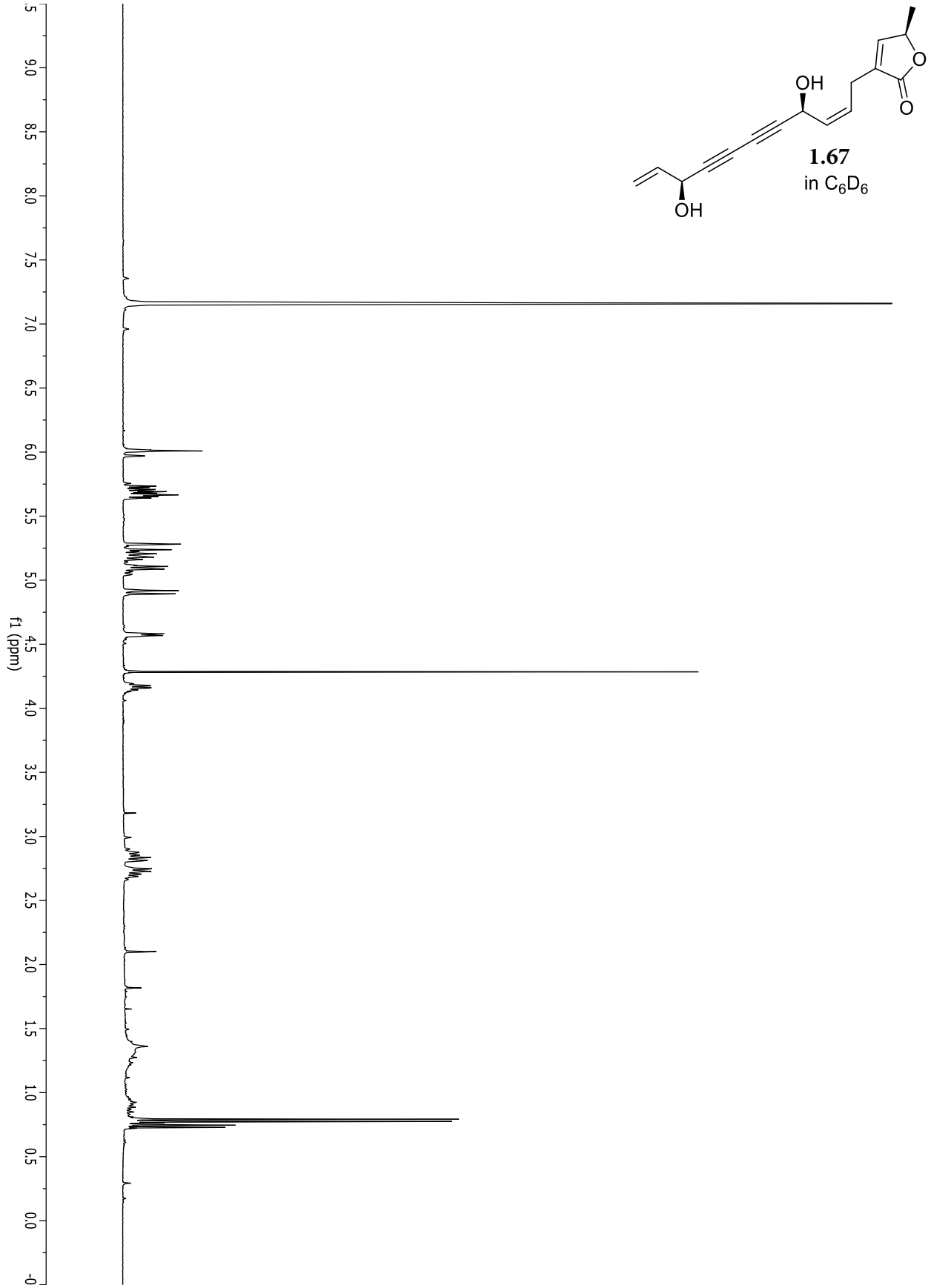
in $CDCl_3$


f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

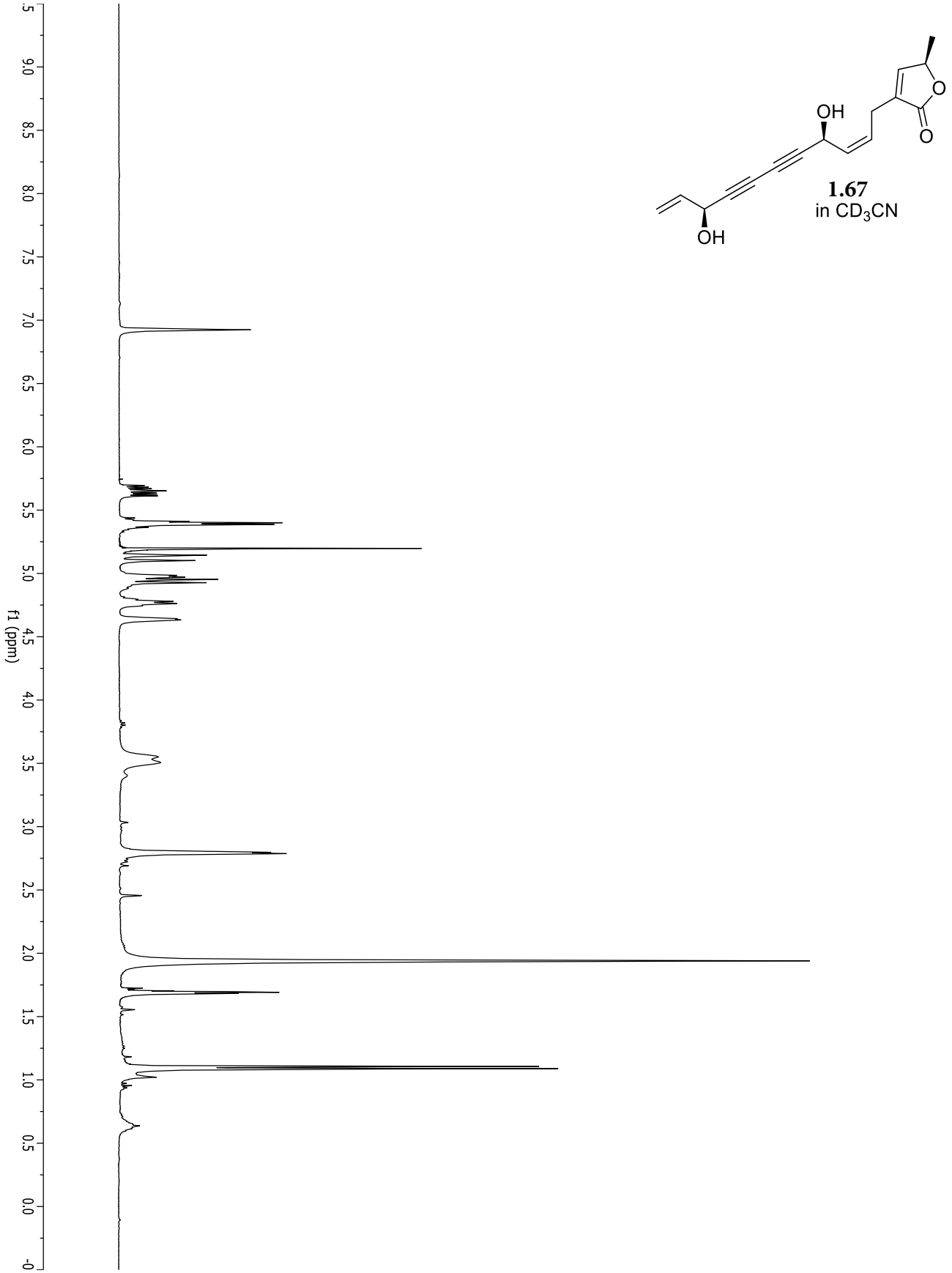

OH
O
O
OH

1.67

in $CDCl_3$



1.67
in C_6D_6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OH
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in CD3CN
f1 (ppm)
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8.0
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7.0
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4.5
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2.5
2.0
1.5
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0.5
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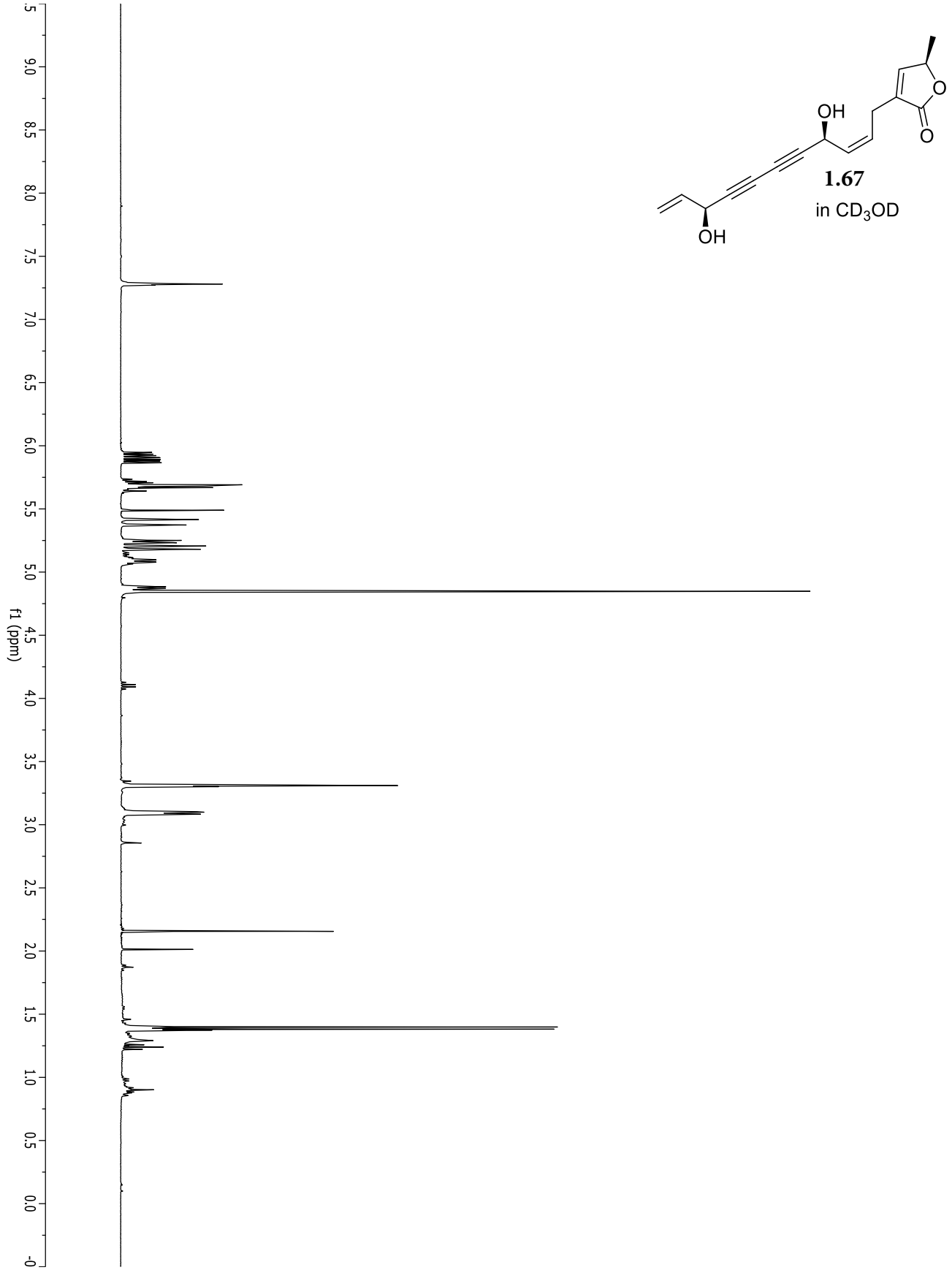
OH
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in CD3OD
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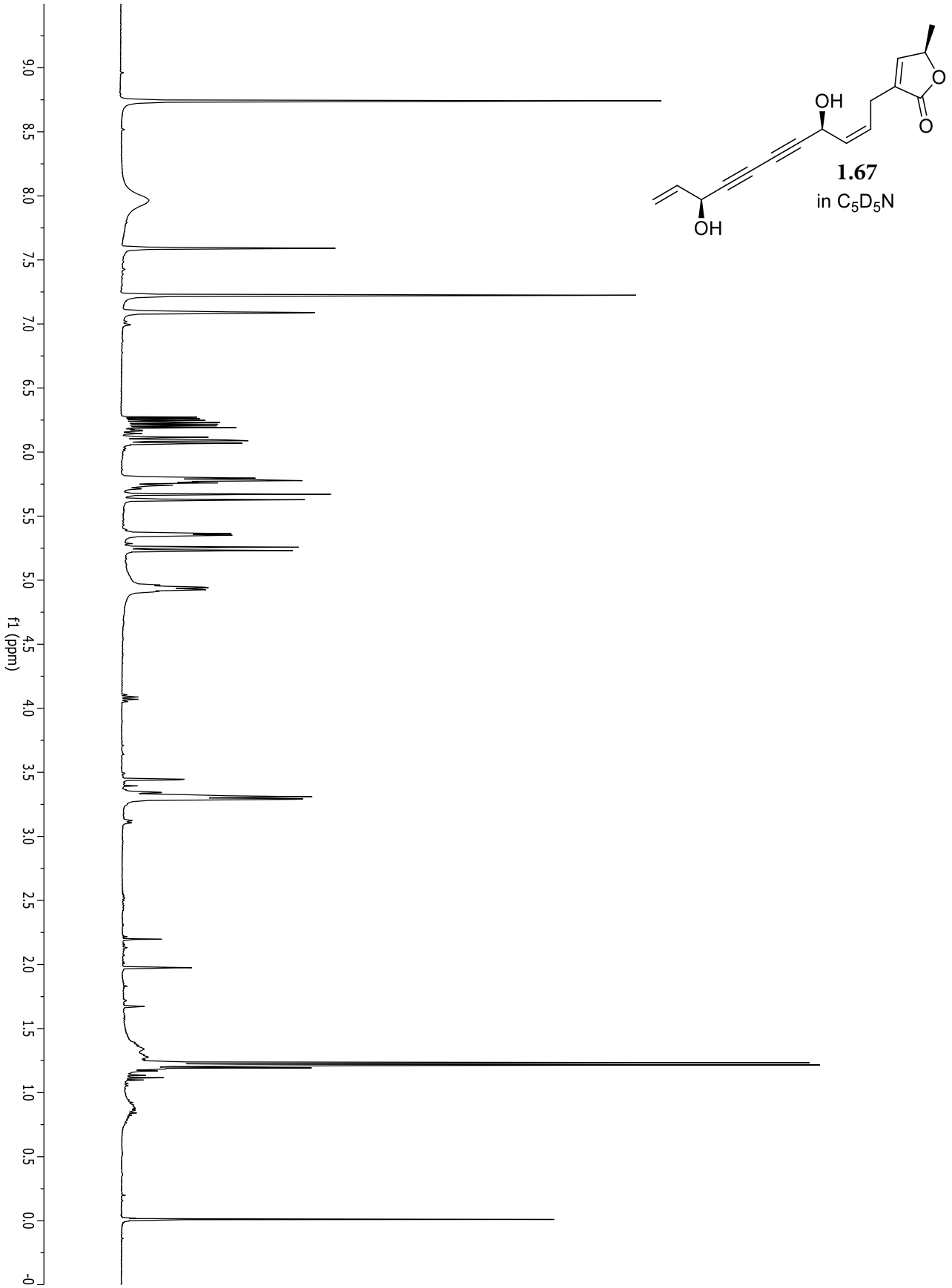
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f1 (ppm)
9.0
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7.0
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3.5
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2.5
2.0
1.5
1.0
0.5
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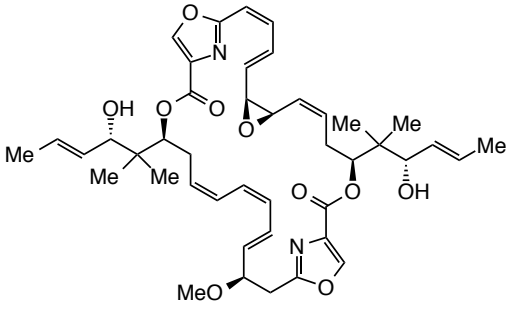
-0

1.67
in C_5D_5N

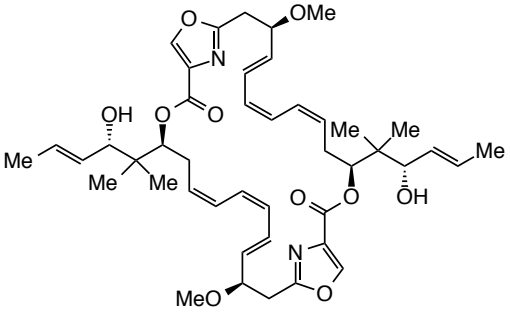
Chapter 2. Stereoselective Total Synthesis of Disorazole C_1

2.1 Introduction

Figure 2.1. Disorazole Natural Products



2.1 Disorazole A_1



2.2 Disorazole C_1

The disorazole family of natural products is a group of 29 structural realated compounds (figure 2.1) isolated in 1994[1] from the fermentation broth of sorangium cellulosum, a myxobacteria that also produces epothiolones, sorangicins, sorangiolides and chivosazoles. Disorazole A_1 **2.1**, the most prevalent disorazole shows potent cytotoxic activity against human cancer cells (IC_{50}s as low as 3 pm).[2] Extensive biological testing has determined that disorazole A_1 serves as a microtubule polymerization inhibitor, and binds to the same domain as *vinca* alkaloids. The disorazoles also show anti-fungal, but not antibacterial or antiviral activities. Due to its intriguing structure, C_2 symmetry, its promising biological activity and its low natural abundance, most synthetic efforts have been devoted to disorazole C_1 **2.2**, which has resulted in three successful syntheses[3] including one from our group.[3b] These syntheses, as well as failed efforts, will be discussed. We were attracted to the *Z,Z,E*-triene moiety

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1. Jansen, R.; Irschik, H.; Reichenbach, H.; Wray, V.; Hofle, G.; *Leibigs Ann. Chem.* **1994**, 759–773.

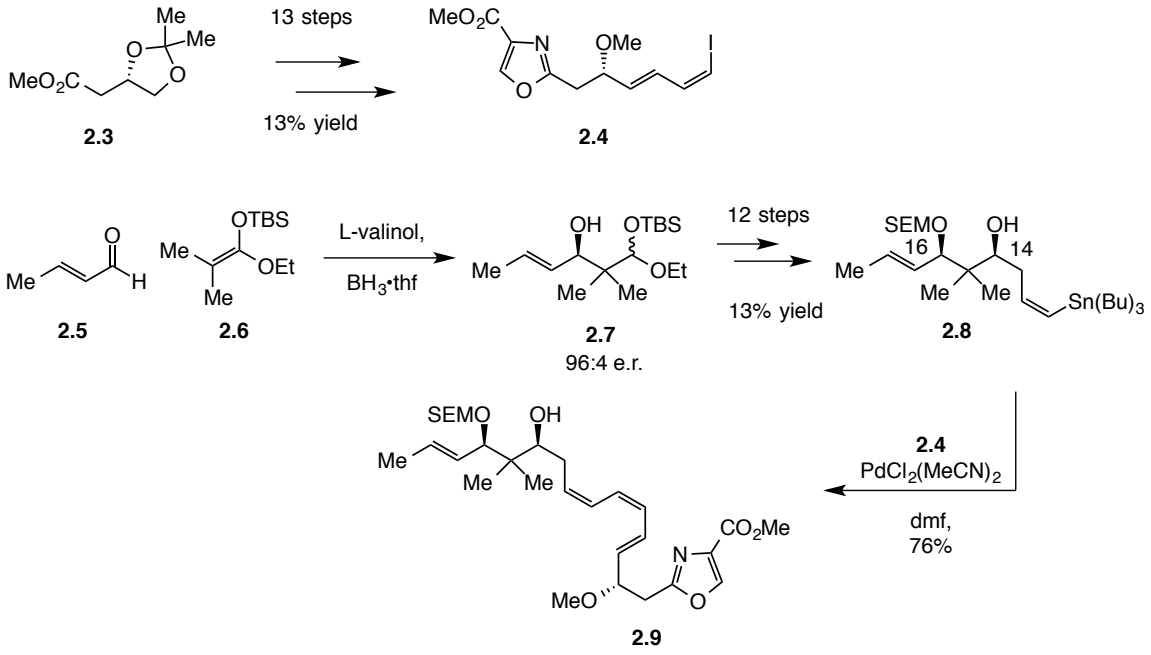
2. For a review containing biological data see: Hopkins, C. D.; Wipf, P. *Nat. Prod. Rep.* **2009**, *26*, 585–601.

3. a) Wipf, P.; Graham, T. H. *J. Am. Chem. Soc.* **2004,** *126*, 15346–15347. b) Speed, A. W. H.; Mann, T. J.; O'Brien, R. V.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 16136–16139. c) Ralston, K. J.; Ramstadius, H. C.; Brewster, R. C.; Niblock, H. S.; Hulme, A. N. *Angew. Chem. Int. Ed.* **2015**, *54*, 7086–7090.

of the disorazoles, and hoped that application of our *Z*-selective cross-metathesis (CM) of alkenyl boron compounds could substantially improve on the existing synthesis.

2.2 Background

Scheme 2.1. Meyers' First Generation Route Towards Disorazole C_1



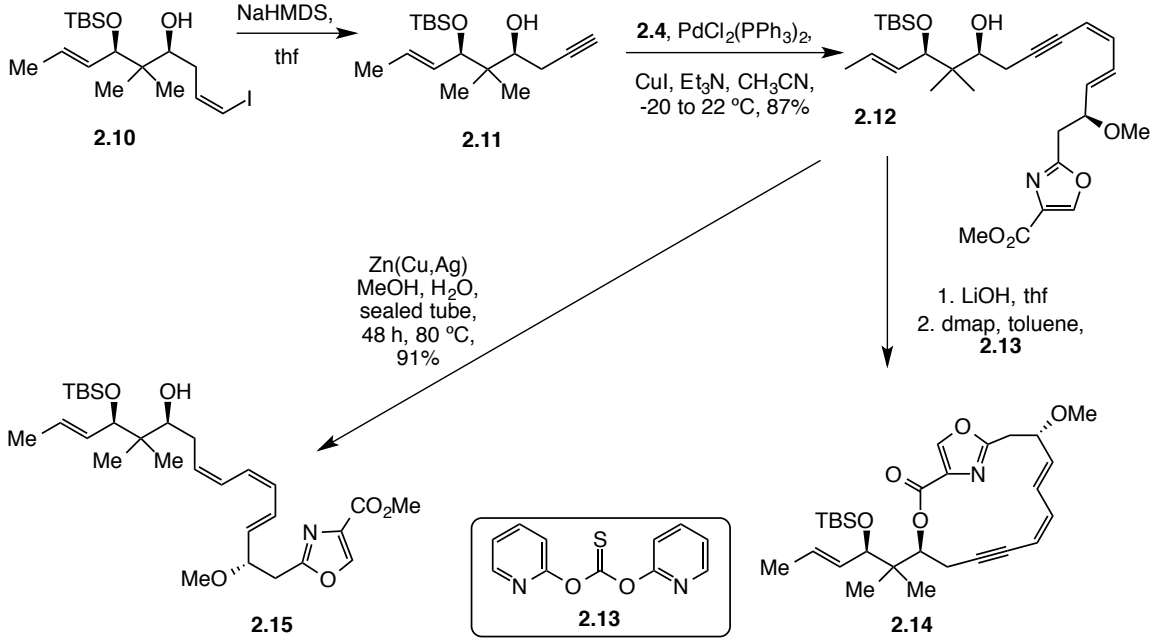
Meyers reported the first efforts towards disorazole C1 (scheme 2.1).[4] Alkenyl iodide **2.4**, was prepared in 13 steps from known L-malic acid derivative **2.3**. The synthesis of Meyers' organometallic coupling partner commences with a D-valinol promoted aldol reaction between *E*-crotanal **2.5** and silyl-ketene acetal **2.6**.[5] The Meyers group elaborated **2.7** into organostannane **2.8** over 12 steps. It is worth noting that **2.8** will not afford a natural disorazole since it has the incorrect stereochemistry at the C-16 stereogenic center. Both the relative and absolute stereochemistry of the disorazoles were unknown until Wipf's successful synthesis, the isolation group only reported the gross structure. This first approach from the Meyer's group concludes with a Stille coupling

4. Hillier, M. C.; Park, D. H.; Price, A. T.; Ng, R.; Meyers, A. I. *Tetrahedron Lett.* **2000**, *41*, 2821–2824.

5. Kiyooka, S; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276–2278.

between **2.4** and **2.8** resulting in the formation of *Z,Z,E*-triene **2.9**. They mention that hydrolysis and esterification-lactonization protocols failed to elaborate **2.9** into the desired macrocycle. They attributed this failure to the sensitivity of the triene moiety, and embarked upon a second-generation route where one of the olefins of the triene moiety was masked as an alkyne (scheme 2.2).[6]

Scheme 2.2. Meyers' Second Generation Route Towards Disorazole C_1



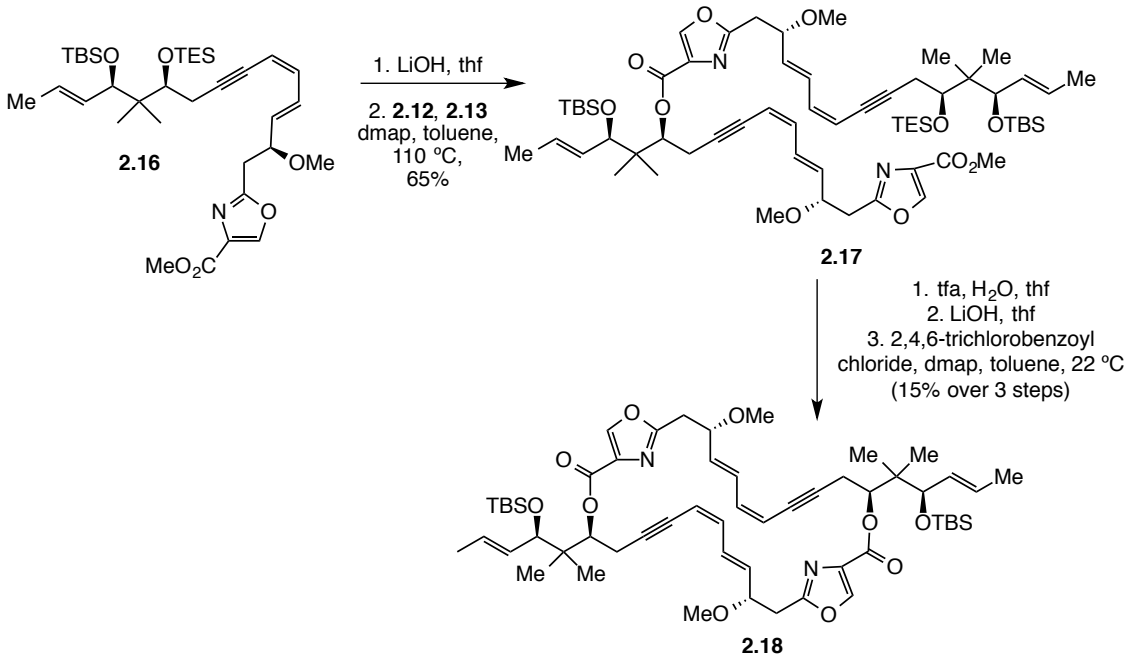
Meyers obtained **2.10** by a similar sequence as **2.8**, but with a revised protecting group scheme. Deprotonation with NaHMDS afforded alkyne **2.11**, which readily underwent Sonogashira coupling with **2.4** to furnish dienyne **2.12**. A one-pot procedure of hydrolysis and esterification-lactonaization using Shiina conditions[7] failed to provide the desired macrocycle, and only cyclic monomer **2.14** was obtained. While they were unable to reduce the alkyne after macrocyclization, exposure of **2.12** to Zn and Cu-Ag couple at 80 ºC for 2 d gave **2.15**, although some olefin isomerization occurred. To circumvent the formation of **2.14**, they implemented a two-step procedure (scheme 2.3), in which a portion of **2.12** was TES protected then hydrolyzed and esterified with free

6. Hillier, M. C.; Price, A. T.; Meyers, A. I. *J. Org. Chem.* **2001**, *66*, 6037–6045.

7. Saitoh, K.; Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1998**, *27*, 679–680.

alcohol **2.12** resulting in linear compound **2.17**. After TES deprotection, ester hydrolysis and macrolactonization under Yamaguchi conditions[8] they obtained macrocycle **2.18** (15% over three steps). In the cyclization reaction they still observed a significant quantity of **2.14**. They were unable to reduce the alkyne, nor desilylate **2.18**, so they did not succeed in completing the synthesis of disorazole C_1.

Scheme 2.3. Meyers' Endgame Towards Disorazole C_1

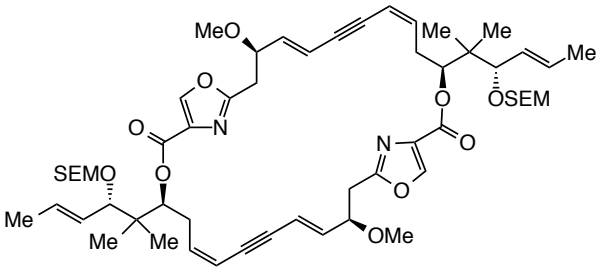


Hoffmann has prepared advanced intermediate **2.19**,[9] which contains a different protecting groups than **2.18**, the alkyne in a different position, and the appropriate stereochemistry. However, the SEM deportection, and alkyne partial hydrogenation were not demonstrated.

8. Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446–11459.

9. Niess, B.; Hartung, I. V.; Haustedt, L. O.; Hoffmann, H. M. R *Eur. J. Org. Chem* **2006**, 1132–1143.

Figure 2.2. Hoffmann's Disorazole Intermediate



2.19

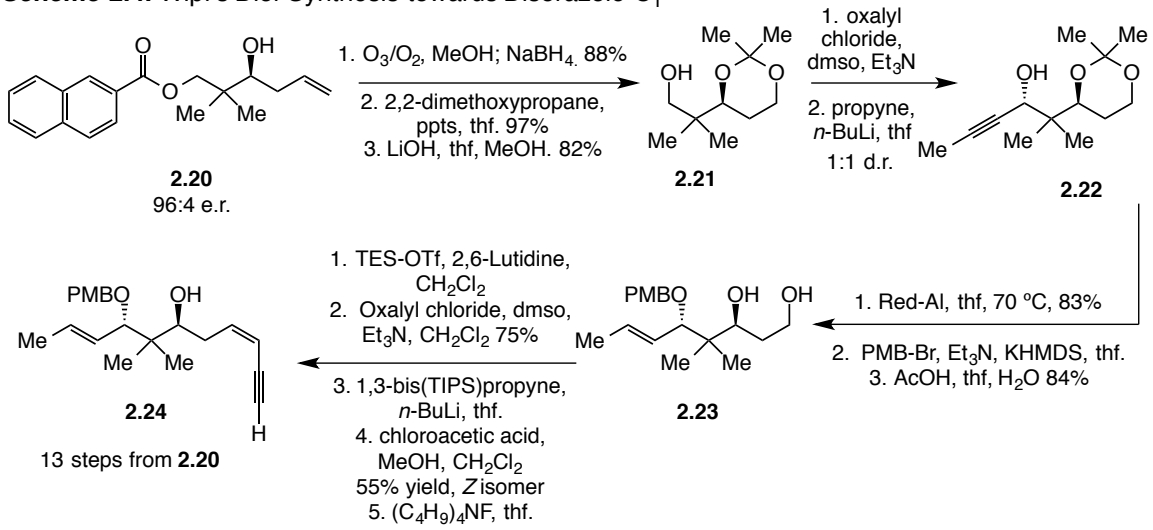
As Wipf has successfully synthesized disorazole C_1, his synthesis will be described in detail, in order to draw comparisons with our work. His strategy relies on the same key steps as the revised Meyers synthesis, assembling a macrocyclic diene-yne through Sonogashira coupling and macrolactonization, but the Wipf group successfully removed the protecting groups and performed Lindlar hydrogentation.[10] The Wipf synthesis commenced with homoallyl alcohol **2.20** prepared by a Ti-binol promoted allylation as described by Carreria[11] (96:4 e.r.). The olefin was ozonized with a reductive workup, the resulting diol was acetal protected, and the ester hydrolyzed to afford **2.21**. The primary alcohol was oxidized under Swern conditions, and addition of propynyllithium to the resulting aldehyde gave **2.22**, as an equal mixture of diastereomers (41 and 44% yield). As neither the absolute nor relative stereochemistry of disorazole C_1 had not been determined at the time, it is likely the synthetic planning included this non-selective step to allow preparation of both isomers of the final product. A directed *E*-selective reduction of the alkyne using Red-Al, followed by PMB protection, and acetal deprotection resulted in diol **2.23**. The diol was bis-TES protected, followed by a Swern oxidation, the acidic conditions of which deprotected the primary TES group then oxidized the free alcohol to the desired aldehyde. The aldehyde was then exposed to lithiated 1,3-bis(TIPS) propyne, resulting in an 8:1 mixture of *Z* and *E* enynes, which were separated after cleavage of the TES group with chloroacetic acid (55% yield *Z* isomer). The alkynyl TIPS group was then removed with *n*-Bu_4NF, to afford alkyne **2.24**.

---

10. Lindlar, H.; Dubuis, R. *Org. Synth.* **1966**, *46*, 89.

11. Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106–8125.

Scheme 2.4. Wipf's Diol Synthesis towards Disorazole C_1



Wipf began the synthesis of his oxazole containing fragment with β-hydroxynitrile **2.25**, which was silyl protected, and then converted to aldehyde **2.26** with diisobutyl aluminum hydride. The aldehyde was reacted with TMS-acetylene and diethyl zinc in the presence of a substoichiometric quantity of Ti(O-*i*Pr)$_4$ and (*S*)-Binol (0.5 equiv and 0.2 equiv respectively)[12] to give the free alcohol in 96:4 e.r.. The alcohol was subsequently methylated, with concomitant loss of the alkynyl TMS group, under phase transfer conditions with dimethyl sulfate to deliver alkyne **2.27**. Oxidation to the carboxylic acid **2.28** was achieved by a one-pot two-step procedure involving first treatment with HF in acetonitrile, to remove the TIPS group, then neutralization and a one-step TEMPO/Pinnick oxidation.[13] The oxazole was formed by a procedure developed by Wipf.[14] First, the acid was coupled with serine methyl ester, the resulting hydroxyamide was cyclized by sequential exposure to DAST and then potassium carbonate at -78 ºC. The oxazoline was then oxidized with $BrCCl_3$ in the presence of dbu. For Wipf, in the presence of his free alkyne, the oxidation procedure resulted in a mixture of the expected alkyne **2.29** (31% yield), and the brominated alkyne **2.30** (37%

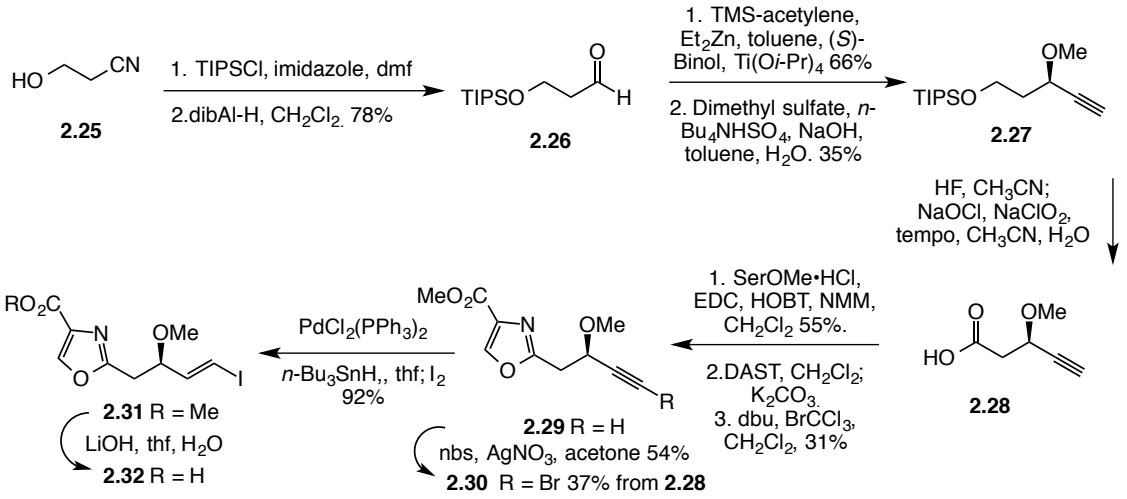
12. Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143–4146.

13. Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564–2566.

14. Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165–1168.

yield). The free alkyne **2.29** was subsequently transformed into **2.30** with *N*-bromosuccinamide and silver nitrate in acetone. Palladium catalyzed hydrostannylation followed by quenching with molecular iodine afforded **2.31**,[15] which can be readily hydrolyzed to the free acid **2.32**.

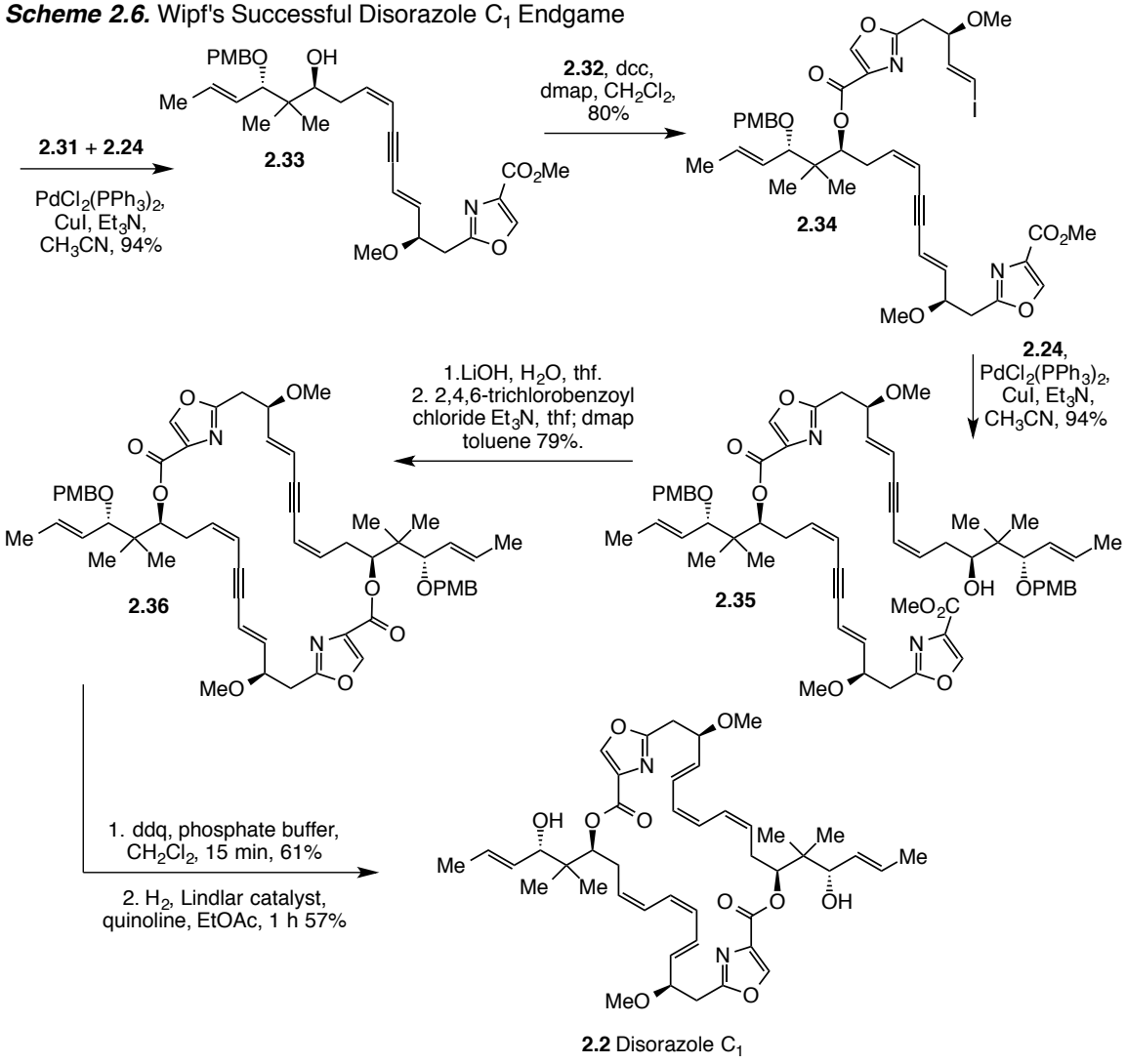
Scheme 2.5. Wipf's Oxazole Synthesis towards Disorazole C_1



Wipf's endgame commenced with a Sonogashira reaction between, ester **2.31**, and alcohol **2.24**, to afford the linear diene-yne **2.33** which was then acylated with oxazole containing acid **2.32**, resulting in **2.34**. This alkynyl iodide was subjected to another Sonogashira reaction with **2.24** to give the linear compound **2.35**, which underwent facile macrolactonization under the Yamaguchi conditions. While this four-step procedure from linear monomer **2.33** to macrocycle **2.36** seems lengthy, it is a step shorter than the strategy used by Meyers (scheme 2.2 and 2.3). Wipf next subjected his macrocycle **2.36** to oxidative removal of the PMB protecting group, by using ddq with a phosphate buffer. The use of an alkyne to mask the triene moiety was crucial at this step, as ddq would certainly destroy any conjugated triene. Our own experience revealed ddq to be incompatable with even dienes. Finally, partial hydrogenation afforded disorazole C_1 in 57% yield.

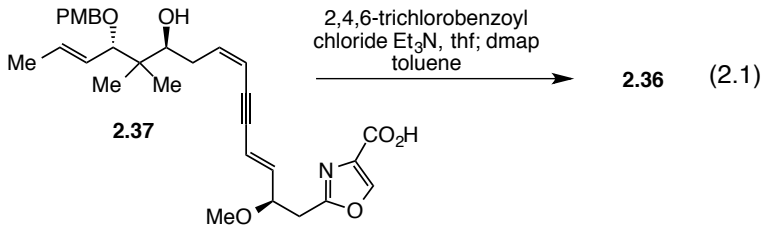
15. Zhang, H. X.; Guibe, F.; Balavonine, G. *J. Org. Chem.* **1990**, *55*, 1857–1867.

Scheme 2.6. Wipf's Successful Disorazole C_1 Endgame



While this was the first successful synthesis, several points bear mentioning. While beautifully utilized in this case, partial hydrogenation is a notoriously unreliable method,[4c] and as a heterogenous protocol, reactivity can vary widely between different batches of the catalyst. Additionally, the catalyst contains toxic palladium, and highly toxic lead, to use such elements in the last stage of a synthesis of a biologically active molecule would be problematic. A strategy that could circumvent this hydrogenation would be quite valuable. The formation of the macrocycle from the linear monomer is somewhat lengthy. Later, Wipf described a direct one-pot formation of macrocycle **2.36**

by exposing seco acid **2.37** to the Yamaguchi protocol (equation 2.1). Unfortunately, no experimental details were provided.[16]



Three additional endeavors bear some mention. Firstly, Wipf has also synthesized a disorazole C_1 derivative **2.38**[17] where the central *Z*-alkene of the triene has been cyclopropanated. The authors hoped that their derivitized disorazole would be more stable than the parent compound, and similarly biologically active. While **2.38** maintains IC_{50}s between 25 and 50 [nM] against a variety of human colon cancer cell lines, it was about 4 times less potent than **2.2**. Kalesse has prepared two truncated disorazoles **2.40** and **2.41**,[18] which are related to disorazole Z.[19] Kalesse successfully enacted a double esterification on triene containing seco acid **2.39** (and its all *E* analogue) to afford macrocyclic compounds. While Kalesse's final two steps were low yielding, 26% for the cyclization, 22% for the deprotection, his success in this area encouraged us to attempt such a strategy. The *Z,E,E* triene **2.40** showed low nanomolar IC_{50}s against a variety of mammalian cancer cell lines, while *E,E,E* triene **2.41** was 10-50 times less potent.

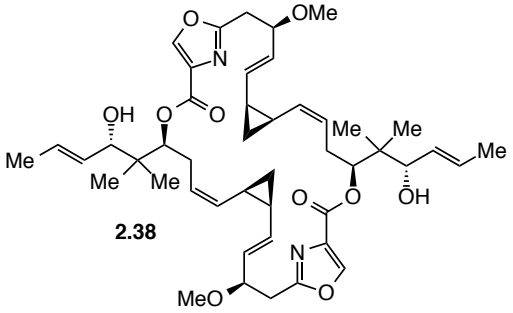
16. Wipf, P.; Graham, T. H. Xiao, J. *Pure Appl. Chem.* **2007**, *79*, 753–762.

17. Hopkins, C. D.; Schmitz, J. C.; Chu, E.; Wipf, P. *Org. Lett.* **2011**, *13*, 4088–4091.

18. Schackel, R.; Hinkelmann, B.; Sasse, F.; Kalesse, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1619–1622.

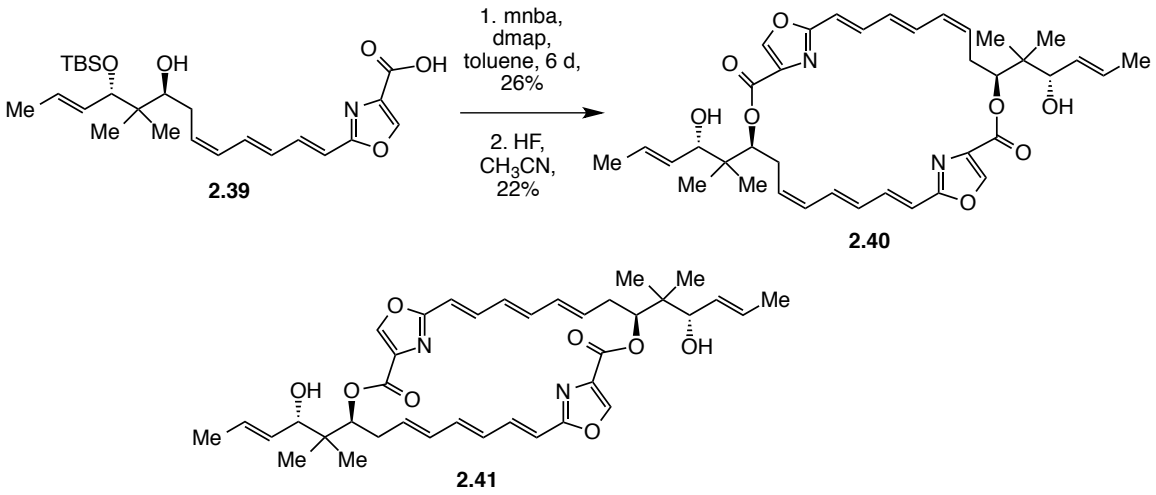
19. Irschik, H.; Jansen, R.; Sasse, F. European Patent Application EP 1743897A1, **2007**.

Figure 2.3. Wipf's Cyclopropanated Disorazole C_1



2.38

Scheme 2.7. Kalesse's Truncated Disorazoles



2.39

2.40

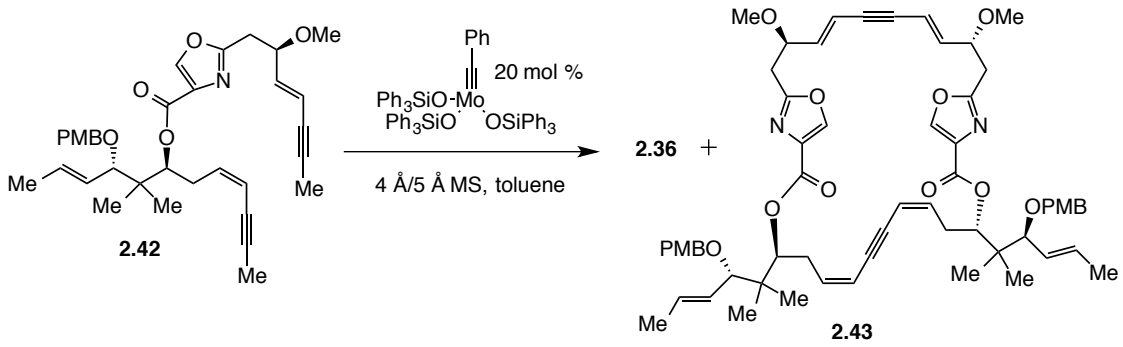
2.41

Subsequent to our synthesis, Hulme has intercepted Wipf's macrocyclic intermediate **2.36**, through the utilization of an alkyne cross-metathesis/ring-closing metathesis catalyzed by Furstner's tris-triphenylsiloxy containing Mo catalyst.[20] Hulme's CM/RCM event afforded a 5:1 mixture of **2.36** and head-to-head macrocycle **2.43**, they explain this favorable selectivity by hypothesized that the sequence was under thermodynamic control, and that the isomer more closely resembling the natural product was favored. In Hulme's supporting information, they are unable to reproduce Wipf's Lindlar hydrogenation, and obtain disorazole C_1 in only 10% yield for the final step. While the Hulme synthesis contained an interesting strategy, their longest linear sequence was 18 steps, which is only a slight improvement over Wipf's 20 steps 11 years prior.

20. Heppekausen, J.; Stade, R.; Kondoh, A.; Seidel, G.; Goddard, R.; Furstner, A. *Chem. Eur. J.* **2012**, *18*, 10281–10299.

Ultimately, Hulme's failure to reproduce Wipf's high yielding Lindlar hydrogenation highlights the synthetic importance of alternative methods of *Z*-alkene formation.

Scheme 2.8. Hulme's Alkyne Metathesis Route to Disorazole C_1



62% yield of the mixture, **2.36:2.43** 5:1

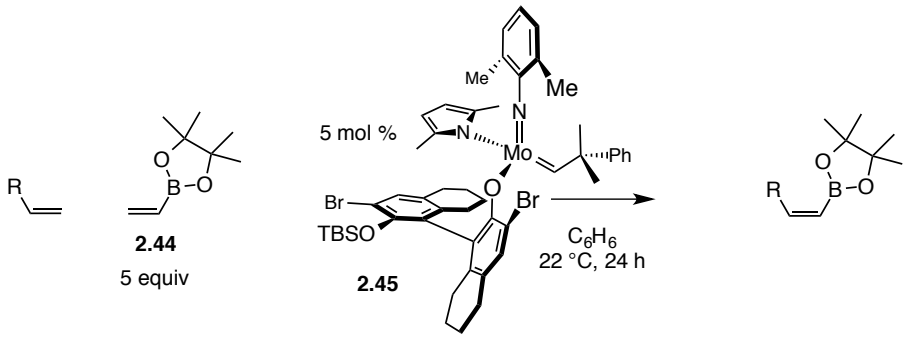
Our interest in disorazole C_1 began during our studies in alkenyl boron cross-metathesis.[21] In the presence of vinyl B(pin) **2.44** and 5 mol % of complex **2.45**, terminal olefins can be efficiently transformed into *Z*-alkenyl boron containing compounds. Some representative cases are shown in scheme 5, enol ethers **2.46**, protected amines **2.47**, substrates with beta-branching **2.48** all give yields >70% and *Z*:*E* ratios ≥90:10. Most importantly for our disorazole studies, a 1,3-diene **2.49** provides acceptable yields and selectivities, furthermore 1,3-dienes are not compatible with the Grubbs *Z*-selective catalysts.[22] We also demonstrated this reaction in the formation of β-*Z*-alkenyl boron containing styrenes (scheme 2.10 **2.50 -> 2.52**). Efficient and selective reaction with a styrene requires substantial changes to the reaction conditions, including a 100 torr vacuum, and use of complex **2.51**. We also reported the application of *Z*-styrenyl B(pin) **2.52** in a Suzuki cross-coupling with **2.53** to form combretastatin A_4 **2.54**. The *Z*-isomer of **2.54** is a potent anti-proliferative compound, and the *E*-isomer is approximately 10,000

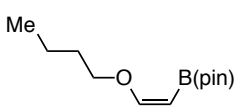
21. Kiesewetter, E. T.; O'Brien, R. V; Yu, M.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2013**, *135*, 6026–6029.

22. 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) Rosebrugh, L. E.; Herbert, M. B.; Marx, V. M.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2013**, *135*, 1276–1279.

times less potent. This dependence on olefin stereochemistry in the final product demonstates the synthetic utility of combining catalytic cross-coupling (CC) with substrate preparation through CM.

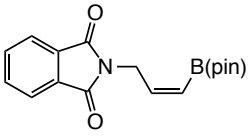
Scheme 2.9. *Z*-Selective Metathesis to Form Alkenyl Boron Compounds





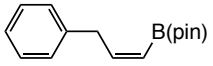
2.46

80% yield *Z,* 93:7 *Z:E*



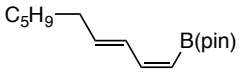
2.47

70% yield, 93:7 *Z:E*



2.48

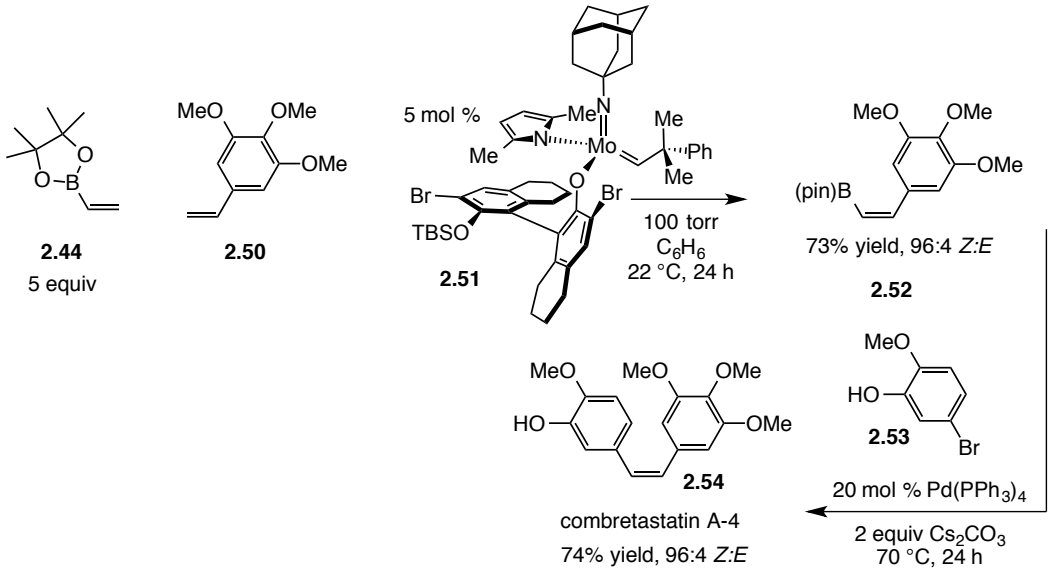
69% yield, 93:7 *Z:E*



2.49

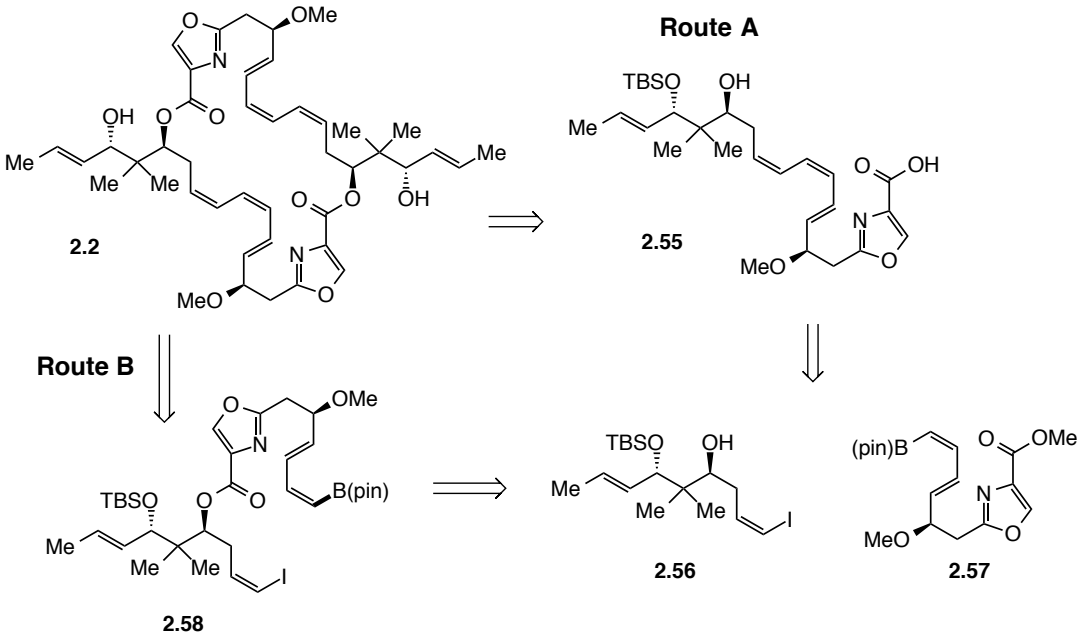
72% yield, 93:7 *Z:E*

Scheme 2.10. *Z*-Selective Cross-Metathesis in the Synthesis of Combretastatin A-4



2.3 Total Synthesis of Disorazole C_1

Scheme 2.11. Retrosynthetic Analysis of Disorazole C_1

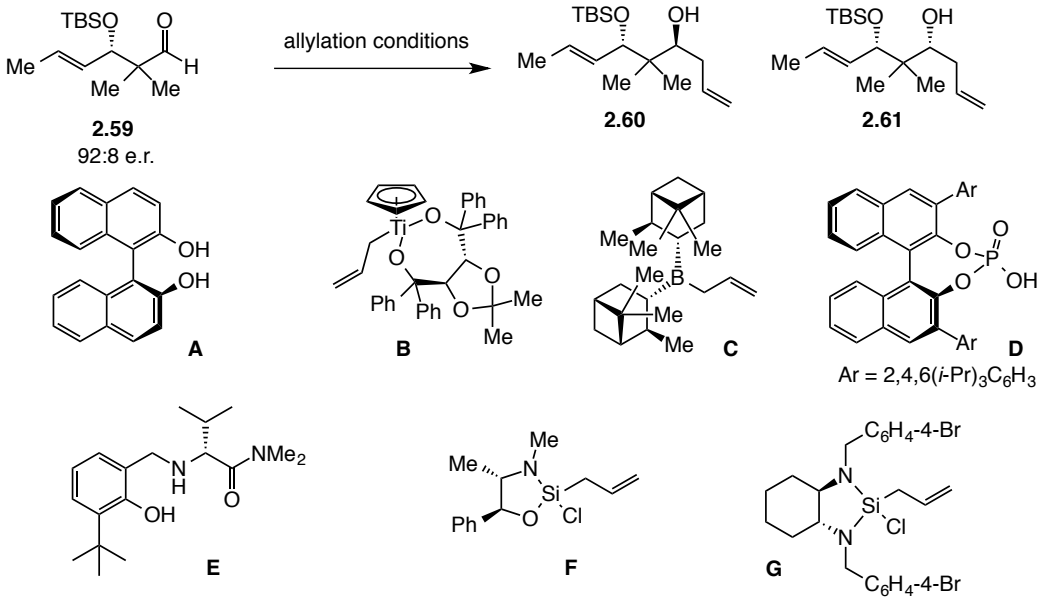


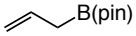
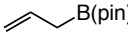
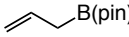
Having successfully developed our CM method for installing an alkenyl boron unit, we devised the retrosynthetic strategy outlined in scheme 2.11. Encouraged by the reports of Kalesse and Wipf, we hoped that **2.2** could be derived from a one-pot

esterification-macrolactonization of **2.55** (route A). We speculated that the failure of Meyers to enact a similar procedure was due to adventitious tin left over in his triene from the previous Stille coupling. Organotin has been implicated in other low yielding and non-selective processes involving conjugated olefins.[23] We further disconnected **2.55** into cross-coupling partners **2.56** and **2.57**. The *Z*-alkenyl boron in **2.57** could be prepared by our CM protocol on the corresponding terminal diene, and the *Z*-alkenyl iodide in **2.56** could result from boron-iodine exchange on a *Z*-alkenyl boron, also installed through CM. An alternative procedure for macrocycle assembly would be an inter- then intramolecular Suzuki-coupling of two molecules of **2.58** (route B). Fortunately **2.58** can be derived from the same units **2.56** and **2.57**, so our plan was easily rerouted in the event of a failure to transform **2.55** into the desired macrocycle.

23. a) Congreve, M. S.; Holmes, A. B.; Hughes, A. B.; Looney, M. G. *J. Am. Chem. Soc.* **1993**, *115*, 5815–5816. b) Nenaff, N.; Whiting, A. *Org. Lett.* **1999**, *1*, 1137–1139.

Table 2.1. Optimization of the Allyl Addition Reaction to Obtain **2.60**



entry	allylation reagents	conditions	conv (%)[a]	**2.60:2.61**[a]	yield (%)[b]
1	1 equilv. **A** 1 equiv. $Ti(O\textit{i}\text{-}Pr)_4$ 1.1 equiv	4 Å MS (4 g/mol) CH_2Cl_2, -78 to -20 ºC, 48 h	<2	na	na
2	1.2 equiv **B**	toluene -78 ºC, 4 h	<2	na	na
3	5 equiv **C**	Et_2O -100 to 22 ºC	<2	na	na
4	1.1 equiv. 	Et_2O, 22 ºC, 18 h	52	32:68	43
5	5 mol% **D** 1.5 equiv. 	toluene, 22 ºC, 20 h	>98	25:75	nd
6	10 mol % **E** 10 mol % NaO*t*-Bu 1.5 equiv 	toluene, 22 ºC, 20 h	30	50:50	nd
7	1.0 equiv **F**	toluene, 17 h, -15 ºC	<2	na	na
8	1.0 equiv **F** 5 mol % $Sc(OTf)_3$	toluene, 17 h, -15 ºC	>98	50:50	na
9	1.1 equiv **G**	CH_2Cl_2 -10 ºC, 4 h	<2	na	na
10	1.1 equiv **G** 5 mol % $Sc(OTf)_3$	CH_2Cl_2 -10 ºC, 4 h	>98	91:9	>98

a) Conversion is determined by ^1H NMR analysis of unpurified mixtures. b) Yield of isolated and purified products. na = not applicable; nd = not determined.

Our synthesis of **2.56** began with the allylation of aldehyde **2.59** (table 2.1), which had been previously synthesized by Kalesse, using a similar aldol protocol as Meyers (see scheme 1, **2.5** + **2.6** -> **2.7**). After reduction with $NaBH_4$ and analysis with Mosher's esters[24] we found the enantioselectivity of this transformation to be 92:8. We found **2.59** very difficult to allylate, the conditions developed by Keck,[25] Duthaler-Hafner[26] and Brown[27] all failed to provide any conversion to **2.60** or its undesired diastereomer **2.61** (entries 1-3). Wipf had used **B** to allylate a similar compound in his synthesis of **2.38**, however his alcohol was 3,4-DMBM protected, which has a much smaller steric presence. While the Brown reagent **C** provided no product, treatment with allyl-pinacolatoboron (allyl-B(pin), at room temperature, provided 43% yield of an inseperable 1:2 mixture of **2.60** and **2.61**. Based on this result we attribute the failure of the previous conditions to steric hindrance around the aldehyde, as alkyl boron complex **C** should be more electronically activated than allyl-B(pin) but is more sterically hindered. Having seen productive reaction with allyl-B(pin), we attempted catalysis of the allyl-B(pin) addition using chiral additives. Unfortunately, while high reactivity was seen using chiral phosphoric acid **D**,[28] no improvement in the diastereoselectivity was observed (entry 5). When we used amino-phenol **E**, which has been established to promote the reaction between allyl-B(pin) and imines,[29] a small improvement to a 1:1 ratio of **2.60**:**2.61** was seen (entry 6). We next resorted to Leighton's first- and second-generation allylating reagents **F**[30] and **G**.[31] In both cases no reaction was observed until 5 mol % $Sc(OTf)_3$[32]

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24. For the initial report, see: a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519. For a detailed procedure, see: b) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nature Protocols* **2007**, *2*, 2451–2458.

25. Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827–7828.

26. Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321–2336. b) ref 20.

27. Brown, H. C.; Desai, M. C.; Jadhav, P. K. *J. Org. Chem.* **1982**, *47*, 5065–5069.

28. Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884–11886.

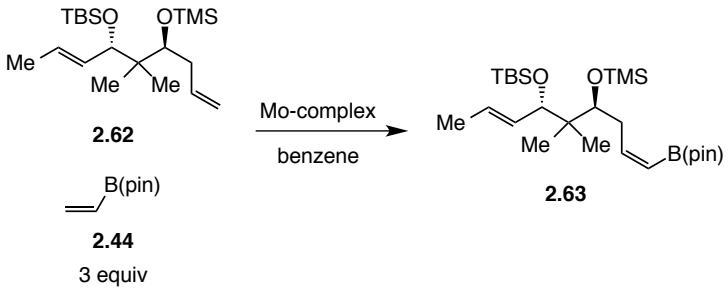
29. Silverio, D.; Torker, S.; Pilyugina, T.; Vieira, E. M.; Snapper, M. L.; Haeffner, F.; Hoveyda, A. H. *Nature*, **2013**, *494*, 216–221.

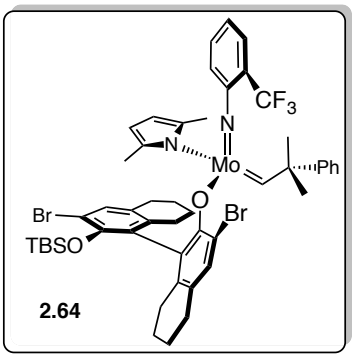
30. Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920–7921.

31. Kubota, K.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2003**, *42*, 946–948.

was added (entries 7 and 9). The catalyzed reaction with **F**, provided an equal mixture of diasteromers, but **G** provided 91:9 selectivity of the desired diastereomer **2.60** and quantitiative yield (entry 10). As **2.59** had only a 92:8 enantiomeric ratio, 91:9 corresponds to near-perfect selectivity in the allylation step, as most of the minor diasteromer must be ***ent*-2.61**, derived from ***ent*-2.59**.

Table 2.2. *Z*-Selective Cross-Metathesis of Protected Diol **2.62**





entry	Mo-complex (mol %)	pressure	conv (%)	yield (%)	*Z*:*E*
1	**2.45** (7.5)	100 torr	30	nd	90:10
2	**2.51** (7.5)	100 torr	60	nd	90:10
3	**2.64** (10)	ambient	>98	74	64:36
4	**2.64** (3)	100 torr	>98	72	>98:2

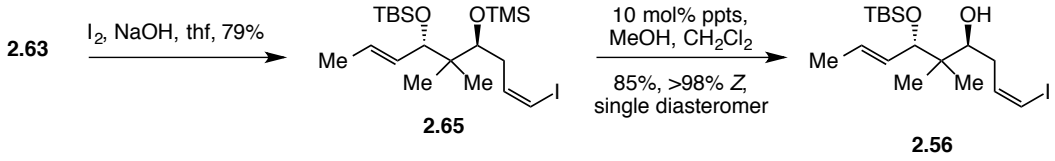
a) Determined by ^{1}H NMR analysis of unpurified mixtures. b) Yield of isolated and purified products. nd = not determined.

Metathesis substrate **2.62** was readily obtained from **2.60**, with TMSCl (92% yield). We initially exposed this molecule to our standard vinyl-B(pin) CM conditions with dimethylphenyl imido Mo-complex **2.45** (table 2.2, entry 1) but the results were quite disappointing, **2.63** was obtained in only 30% conv, albeit 90:10 *Z*:*E* selectivity. The use of complex **2.51**, which was effective for styrenes, slightly improves the conversion to 60%. The more Lewis acidic, trifluoromethyl containing **2.64** afforded **2.63** with quantitative conversion and 74% yield, but *Z*-selectivity eroded to only 64%.

32. Kim, H.; Ho, S.; Leighton, J. L. *J. Am. Chem. Soc.* **2011**, *133*, 6517–6520.

When reaction was attempted with **2.64** under a slight vacuum of 100 torr, **2.63** was obtained without forming a detectible quantity of the *E*-isomer. The difference between conversion and yield can be explained by the tendancy of alkenyl-B(pin) compounds to decompose upon purification by silica gel chromatography. The reactivity and selectivity of this reaction was easily explained by the hindered steric environment near the olefin, which inhibited the metathesis reaction with a sizable B(pin) moiety. Because of this inhibition, the electronically unactivated catalysts **2.45** and **2.51** were reluctant to provide product. The highly active **2.64**, is not only reactive enough to provide **2.63**, but in the presence of ethylene, breakdown **2.63** into it's starting materials, establishing thermodynamic equilibrium, and eroding *Z*-selectivity. Without ethylene, this isomerization cannot occur, and the *Z*-selectivity is preserved. If vinyl-B(pin) is omitted from this reaction an RCM to form a six membered ring occurs.[33] Additionally, the CM of **2.62** *Z*-1,2-dichloroethylene, which would provide an alkenyl halide directly, was attempted, but RCM occurred preferentially to CM. This implies that the catalyst has a strong preference to form the B(pin) substituted alkylidene.

Scheme 2.11. Completion of *Z*-Alkenyl Iodide



Metathesis product **2.63** was readily transformed into the cross-coupling partner **2.56** (scheme 2.11). First, a stereoretentive boron-iodine exchange[34] produced *Z*-vinyl iodide **2.65**, and then acidic deprotection of the TMS group gave **2.56**. After deprotection, **2.56** was separable from its diastereomer derived from **2.61**. It is important to note that we had previously attempted this route with a TES analogue, however the deprotection was less selective, and resulted in a mixture of alcohol and diol.

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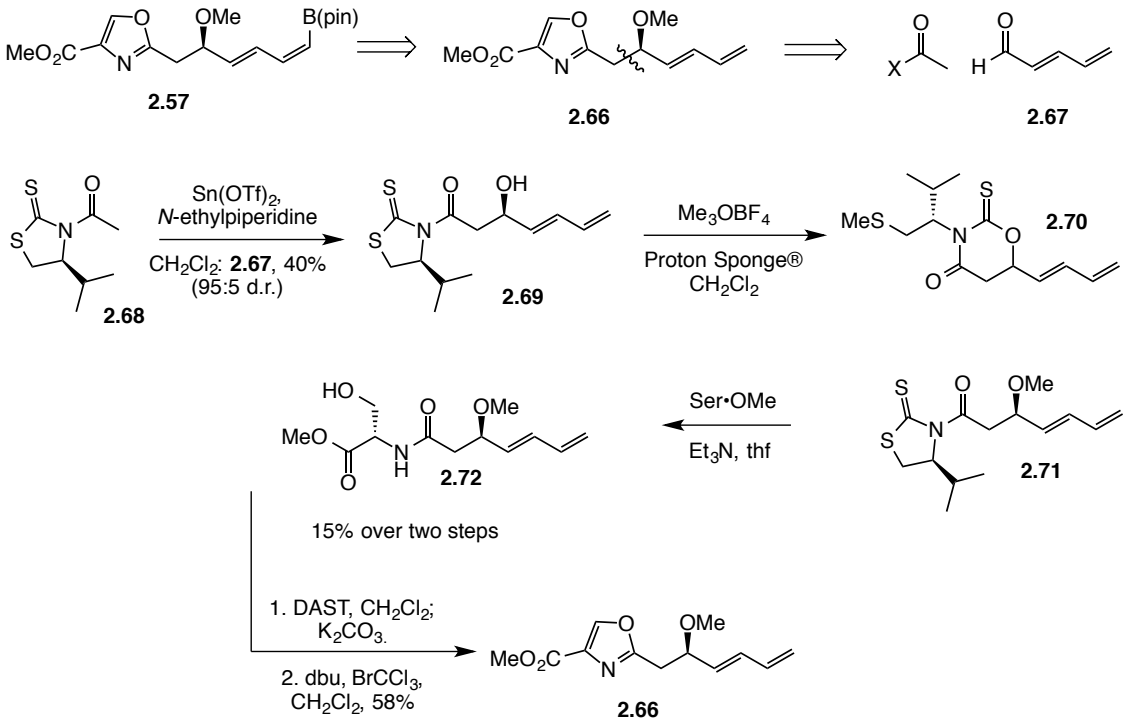
33. See the experimental section for details.

33. Morrill, C.; Grubbs, R. H, *J. Org. Chem.* **2003**, *68*, 6031–6034.

Scheme 2.12. Inital Strategy Towards Oxazole Fragment



Having secured iodine fragment **2.56**, we began studies aimed at securing dienyl-B(pin) **2.57**. Our initial strategy is outlined described in scheme 2.12. We envisioned ultimately preparing **2.66** from an aldol reaction involving pentadienal **2.67**[35] and an acetate loaded chiral auxiliary. Our initial studies involved the conditions developed by Nagao, where **2.68** was enolized with $Sn(OTf)_2$ and *N*-ethylpiperidine, then reacted with **2.67**. This reaction provided **2.69** as a 95:5 mixture of separable diastereomers but only 40% yield was obtained. Other auxiliaries and conditions were even less efficient, including oxazolidine thiones. Methylation of **2.69** was problematic and gave an inseperable mixture of **2.70** (major isomer) and desired **2.71**. The rearrangement to afford compounds such as **2.70** has been previously reported[36] and begins with methylation of the thiazole sulfur instead of the hydroxyl group. The free hydroxyl group then attacked the activated sulfonium compound at the thiazole carbon to form the six membered ring **2.70**. Nevertheless, we were able to react this mixture with serine-methyl

34. Woods, G. F.; Sanders, H. *J. Am. Chem. Soc.* **1946**, *68*, 2483–2485.

35. Adamczyk, M.; Mattingly, P. G.; Pan, Y. *Tetrahedron Lett.* **1995**, *36*, 5303–5306.

ester, to afford **2.72**, which was now separable from **2.70**. Even though **2.72** was obtained in only 15% yield over these two steps, we were able to carry it forward to **2.66** through the previously mentioned DAST cyclization and $BrCCl_3$ oxidation. This sequence gave **2.66** in only 4% overall yield for five steps which is extremely poor for the first stage of a total synthesis. Furthermore, the aldol reaction to afford **2.69** demanded the use of freshly prepared $Sn(OTf)_2$ as commercial samples were found to be heavily contaminated with other tin compounds which were detrimental to conversion and selectivity. Additionally, **2.67** was not commercially available, and the procedure for its formation worked poorly in our hands. Once obtained **2.67** was difficult to separate from Et_2O, which was critical as the aldol reaction demands dichloromethane as the solvent. With these considerations in hand, we began to devise alternative routes to **2.66**.

Figure 2.4. Failed Strategies Towards Oxazole Fragment

Two failed routes towards **2.66** are shown in figure 2.4. We obtained β-keto ester **2.73** derived from a crossed-Claisen condensation of *tert*-butyl acetate and pentadienoate, but exposure of this compound to CBS or Noyori[37] conditions resulted in only destruction of the diene moiety. We hoped to enact an enzymatic kinetic resolution on alcohol **2.74**, but it was not accepted by any of the enzymes we tried.

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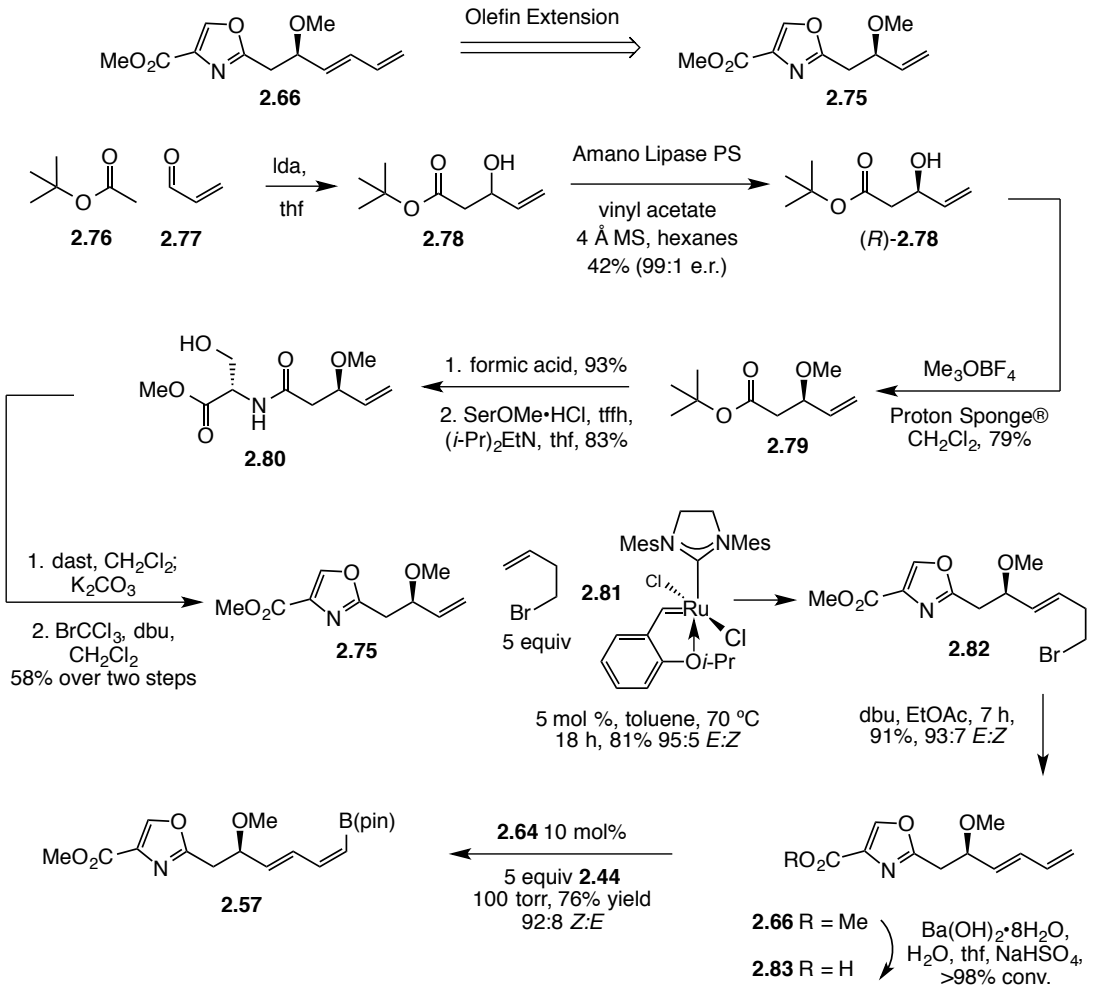
36. Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629–631.

Scheme 2.13. Revised Oxazole Synthesis

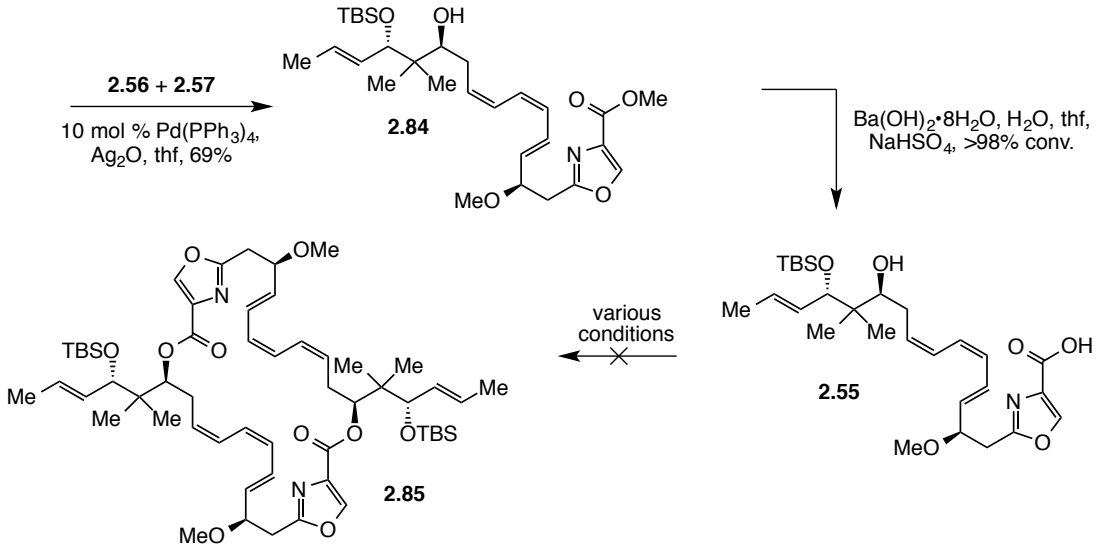


We next embarked upon a completely revised procedure (scheme 2.13), wherein diene-containing **2.66** could be derived from alkene **2.75** by an cross-metathesis based extension process (scheme 2.13). We began with aldol reaction between *tert*-butyl acetate **2.76** and acrolien **2.77**, to afford beta-hydroxy ester **2.78**. This was a known substrate for enzymatic kinetic resolution,[38] which provided us with multi-gram quantities of (*R*)-**2.78** in 99:1 e.r. Methylation with Meerwein salt and Proton Sponge® resulted in the formation of **2.79** in 79% yield. Protonolysis with neat formic acid (93%) and amide formation promoted by tffh resulted in serinate **2.80** (83%), which after subjection to the previously mentioned oxazole formation procedure (DAST, K_2CO_3; $BrCCl_3$) delivered

37. Seiser, T.; Kamena, F.; Cramer, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 6483–6485.

oxazole-ene **2.75** (58% over 2 steps). This set the stage for us to develop an olefin extension procedure to obtain **2.66**. There is a single literature report[39] of such a process, although the substrate scope was limited to formation of dienoates and did not include unactivated olefins. We found that exposure of **2.75** to 5 equiv of 1-bromo-3-butene and 5 mol % of styrene ether containing Ru initiator **2.81**, resulted in 81% yield of homo-allylbromide **2.82** as a separable 95:5 *E* to *Z* mixture. Elimination of the bromide to form **2.66** was readily enacted by diazobicycloundecene in ethyl acetate (91% yield 93:7 *E*:*Z*). We had also attempted CM with 3-buten-2-ol, but only ~20% yield was obtained in the metathesis, and both Martin's sulfurane[40] and Burgess's reagent[41] failed to dehydrate the product. Molybdenum based catalysts[42] failed to provide quantitative conversion of **2.75**. Ester **2.66** is readily hydrolyzed with $Ba(OH)_2 \bullet 8H_2O$ to afford acid **2.83**. Having obtained substantial quantities of **2.66**, we were able to effect the *Z*-selective CM to form **2.57** with the same conditions developed in table 2.2 (complex **2.64**, 100 torr, 76% yield 92:8 *Z*:*E*).

Scheme 2.14. Unsuccessful Macrolactonization-Dimerization



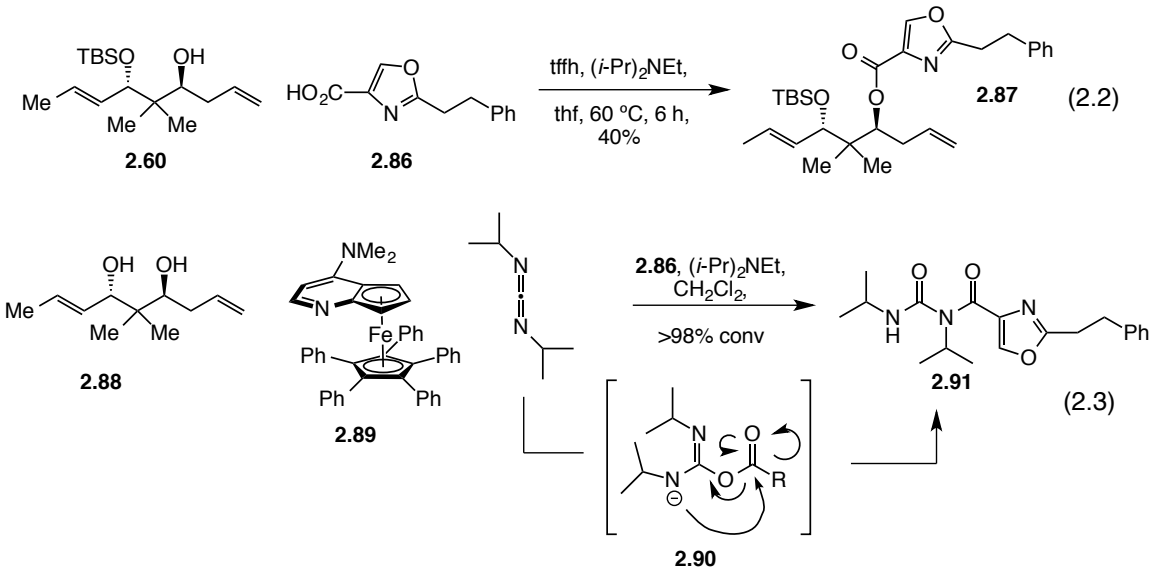
38. Lipshutz, B. H.; Ghorai, S.; Boskovic, Z. V. *Tetrahedron* **2008**, *64*, 6949–6954.

39. Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327–4329.

40. Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744–4745.

41. a) Murdzek, J. S.; Schrock, R. R. *Organometallics,* **1987**, *6*, 1373–1374. b) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3875

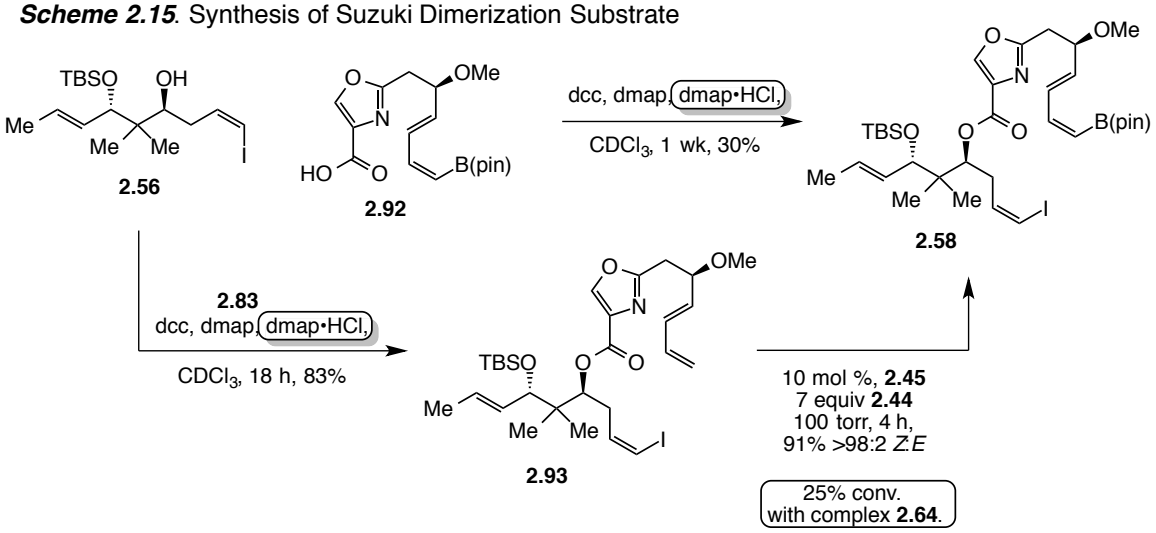
With our cross-coupling partners in hand, we endeavored complete the synthesis of disorazole C_1 by triene formation then esterification-lactonization (route A, scheme 2.11). Initial triene formation was highly efficient, affording cross-coupling product **2.84** in 69% yield from **2.68** and **2.67**, with the first conditions we tried $Pd(PPh_3)_4$ and Ag_2O under anhydrous conditions in thf. Unfortunately, after hydrolysis of the methyl ester with $Ba(OH)_2 \bullet 8H_2O$, we found seco acid **2.66** to be unstable to purification or storage. Therefore, we subjected **2.66** directly to Yamaguchi and Shiina macrolactonization conditions as well as dcc and dmap. None of these conditions produced any detectible quantity of macrocyclic **2.85**, no triene was recoverable from these reactions, and the oxazole also appears to decompose. We were forced to reevaluate our approach and explore route B.



Since the esterification of **2.85** was the problematic step in route A, we began to investigate the esterification (equation 2.2). Ample quantities of **2.60** were available, but the enzymatic kinetic resolution (scheme 2.13) represented a material bottleneck so we used model oxazole **2.86**. After extensive screening of reagents used in peptide coupling, we found that tffh in thf at 60 °C could provide 40% yield of **2.87**, and this was the highest yield obtained. We attribute this failure of acylation to the hindered steric

environment near the reacting alcohol. We hoped that Fu's[43] chiral dmap catalysts (**2.89** and its enantiomer) could differentiate the unhindered alcohols in **2.88**, but when we attempted this reaction, only acyl urea **2.91** was observed (eq. 2.3). The key step in this urea formation is a rearrangement of **2.90**, if the acylation is slow; this rearrangement becomes competitive, destroying the acid starting material.

Scheme 2.15. Synthesis of Suzuki Dimerization Substrate



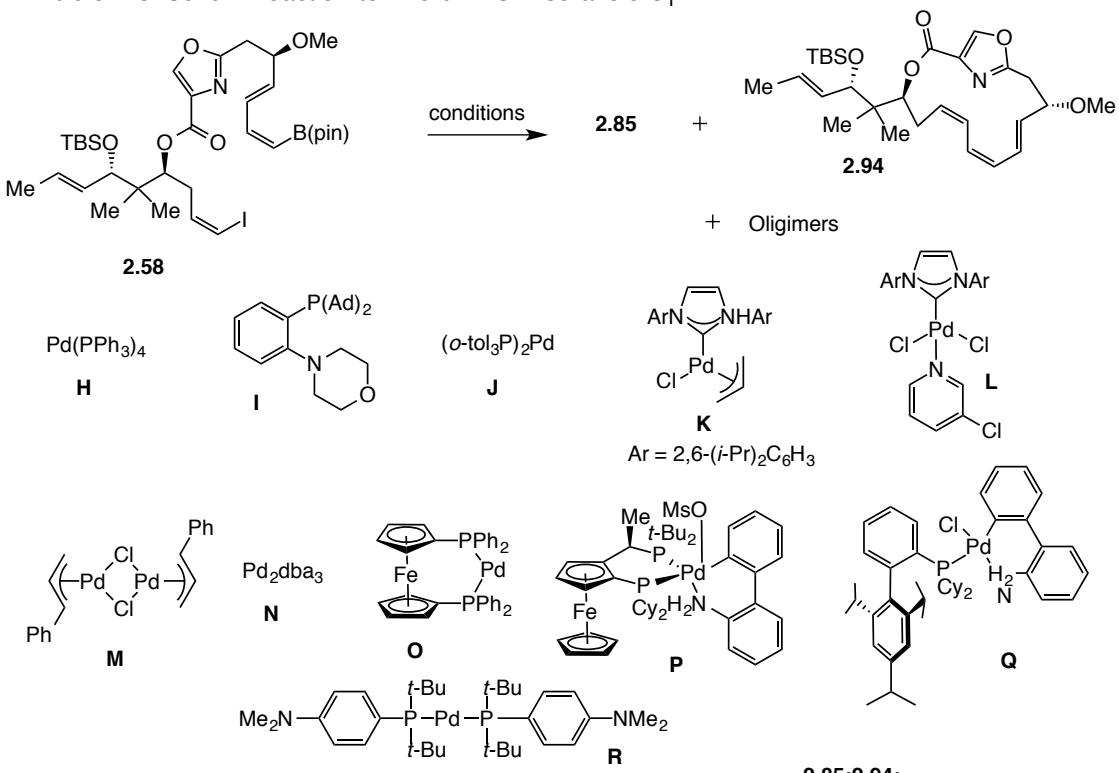
Fortunately, suppression of this acyl urea formation can be enacted by addition of dmap•HCl,[44] but as shown in scheme 2.15, application of these conditions to esterification of **2.56** with **2.92** (derived from hydrolysis of **2.57**) results in only 30% yield of **2.58** after 1 week of reaction. When the B(pin) moiety was removed, and the acylation was attempted with oxazole-diene **2.83**, 83% yield of **2.93** was obtained after only 18 h. We surmise that the B(pin) unit must coordinate with the carboxylate moiety and lower its nucleophilicity. As esterification reactions are not typically inhibited by B(pin) moieties we propose this must be an intramolecular chelation and particular to this molecule. Arriving at **2.93** gave us the opportunity to demonstrate our *Z*-selective alkenyl B(pin) CM at this late stage. Complex **2.64** only gave 25% conv to the desired product **2.58**. We hypothesize that **2.64** is capable of reacting with the *Z*-alkenyl iodide portion of **2.93**, this generates a Mo-complex bearing iodine on the alkylidene, which

42. Ruble, J.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230–7231.

43. Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394–2395.

then decomposes leading to low conversion. Fortunately, 10 mol % of complex **2.45** was capable of reacting with the unhindered diene and generated **2.58** in 91% yield as a single olefin isomer. This catalyst is less likely to react with disubstituted olefins and hence with the alkenyl iodide, and so avoids this decomposition pathway.

Table 2.3. Suzuki Reaction to Afford TBS-Disorazole C_1



Entry	solvent; base	complex (mol %), concentration	conv (%)	**2.85:2.94:** oligomers	yield (%)
1	thf; Ag_2O	**H** (20); 0.014	>95	complex mixture	na
2	thf; Ag_2O	**H**+**I** (20); 0.014	>95	14:10:76	9
3	thf; KO*t*-Bu	**H**+**I** (20); 0.014	>95	complex mixture	na
4	thf; Ag_2O	**J** (20); 0.009	10	nd	nd
5	thf; KO*t*-Bu	**J** (20); 0.009	>95	13:7:80	nd
6	thf; KO*t*-Bu	**J** (100); 0.001	>95	11:42:47	nd
7	thf; KO*t*-Bu	**K** (20); 0.009	<2	na	na
8	thf; KO*t*-Bu	**L** (20); 0.009	<2	na	na
9	thf; KO*t*-Bu	**M**+**I** (20); 0.009	<10	nd	nd
10	thf; KO*t*-Bu	**N**+**I** (20); 0.009	<10	nd	nd
11	CD_3OD; KO*t*-Bu	**J** (20); 0.007	>95	27:0:73	nd
12	CD_3OD; Cs_2CO_3	**J** (5); 0.007	>95	31:0:69	nd
13	CD_3OD; KO*t*-Bu	**O** (5); 0.007	>95	50:0:50	31
14	CD_3OD; Cs_2CO_3	**O** (5); 0.007	>95	complex mixture	na
15	CD_3OD; KO*t*-Bu	**O** (5); 0.002	30	nd	nd
16	CD_3OD; KO*t*-Bu	**J** (5); 0.002	>95	75:0:25	43
17	CH_3OH; Cs_2CO_3	**J** (5); 0.002	>95	80:0:20	54
18	CH_3OH; Cs_2CO_3	**J** (5); 0.004	>95	66:0:34	60
19	CD_3OD; Cs_2CO_3	**P** (5); 0.007	>95	complex mixture	na
20	CD_3OD; Cs_2CO_3	**Q** (5); 0.007	>95	20% alkene isomerization	nd
21	CD_3OD; Cs_2CO_3	**R** (5); 0.008	>95	20% alkene isomerization	nd

a) Determined by ^1H NMR analysis of unpurified mixtures. b) Yield of isolated and purified products. na = not applicable; nd = not determined.

Having obtained our Suzuki-dimerization substrate **2.58**, it was now upon us to identify the appropriate cross-coupling conditions to afford macrocycle **2.85** (table 2.3). Some features of this reaction should be mentioned. Firstly, as Meyers' study would suggest, our system could easily form a monomeric 15-membered ring **2.94**. Suzuki substrate **2.58** was also capable of undergoing sequential intermolecular reactions and forming oligimeric materials of varying lengths. A successful reaction would therefore need to have a finely balanced concentration, not so concentrated as to favor more than one intermolecular reaction (leading to oligomers) and not so dilute as to allow substantial formation of monomer **2.94**. Given the advanced state of cross-coupling reactions[45] we were confident this was a problem with a solution. Paterson has also employed a cross-coupling-dimerization reaction in the synthesis of elalolide, but his system is incapable of monomer formation.[46] We began with the same conditions for formation of linear triene **2.84** (although more dilute), and unsurprisingly observed only a complex mixture (entry 1). We next attempted addition of Mor-DalPhos **I**, and observed 14% conversion to desired macrocycle **2.85**, accompanied by 10% **2.94** and 76% oligimerization. From this mixture we were able to isolate 9% **2.85**. Using potassium *tert*-butoxide as the base under otherwise identical conditions only leads to a complex mixture. We next employed **J** as our palladium source (entries 4-6). Silver oxide was an inappropriate base for these conditions and leads to only 10% consumption of starting material. Potassium *tert*-butoxide did much better, but the ratio of product to byproducts was the same as entry 2. A stoichiometric amount of **J** under highly dilute conditions suppressed formation of oligomers, but encouraged formation of **2.94**, and conversion to **2.85** was not improved. Catalysts **K**, **L**, **M** and **N** (last two with added **I**) failed to convert starting materials (entries 7-10). A breakthrough occurred when *deuterio*-methanol was employed as the solvent (entires 11-21), now the reaction catalyzed by **J** afforded 27% **2.85** with no concomitant formation of **2.94**, the balance of the material was oligimeric. We attribute this selectivity to a conformational change within **2.58** that

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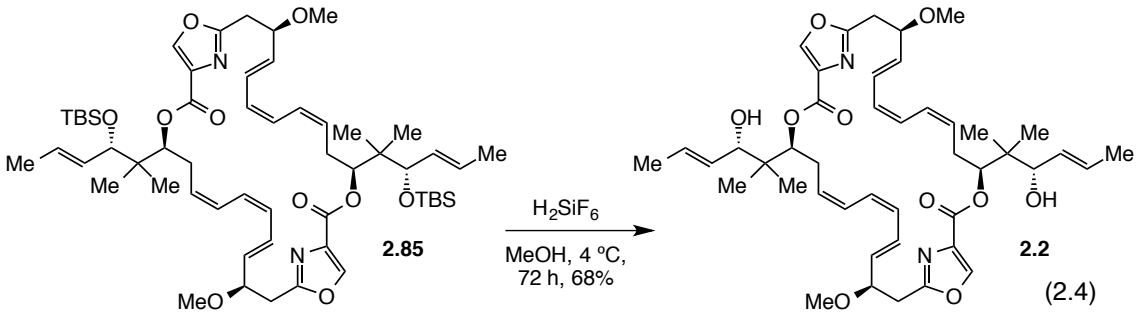
44. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489.

45. Paterson, I.; Lombart, H.-G.; Allerton, C. *Org. Lett.* **1999**, *1*, 19–22.

disfavors the intramolecular reaction. Employing **O** as the catalyst results in a 1:1 mixture of **2.85** and oligomers when potassium *tert*-butoxide is used as the base (31% yield of **2.85**), but a complex mixture with cesium carbonate (a more common base under protic conditions), and low conversion at lower concentrations. Returning to catalyst **J** at dilute conditions of 2 mM gave favorable ratios of **2.85**: oligomers (entries 16 and 17), but with formation of a previously unobserved byproduct which we suspected to be an atropisomer of **2.85**. This byproduct was unstable to purification and was neither isolated nor characterized. Our highest yield of 60% was obtained at 4 mM with 5 mol % **J** and Cs_2CO_3 as the base in methanol. Highly active cross-coupling catalysts **P, Q** and **R**, lead to complex mixtures and alkene isomerization (entries 19-21). Our dimerization-cyclization reaction compares favorably to analogous reactions in disorazole synthesis; it is much more efficient than Kalesse's (26% yield after 6 days of reaction time) and slightly higher than Hulme's (62% for a 5:1 mixture of isomers).



(2.4)

Having obtained macrocycle **2.85**, all that was left was to desilylate. Desilylation, to afford disorazole C_1 **2.2**, was accomplished in 68% yield with hexafluorosilicic acid at 4 ºC.

2.4 Conclusions

We have demonstrated the stereoselective total synthesis of disorazole C_1 in 12 longest linear steps and 8% overall yield. In terms of synthetic efficiency this is a dramatic improvement over Wipf, 20 steps and 1.5% overall yield. More importantly, our synthesis demonstrates the utility of combining *Z*-selective CM, with catalytic cross-coupling in order to efficiently access complex molecules that would be difficult to access by other methods, including direct CM. Furthermore, our route demonstrates the

reliability of our CM method, by installing the final alkenyl boron unit late stage (step 10 out of 12). We also show the versatility of the MAP catalyst scaffold, as different complexes were optimal at different stages of the synthesis. We hope this synthesis will serve as inspiration for other efforts to utilize CM and cross-coupling in a synergistic fashion.

2.5 Experimental

Genral: All reactions were carried out in oven-dried (135 °C) or flame-dried glassware under an inert atmosphere of dry N_2 unless otherwise stated. All reactions and products containing conjugated alkenes were protected from light by wrapping reaction vessels in aluminum foil. Thin layer chromatography (TLC) analysis was accomplished on 250 μm SiliCycle plates, with visualization provided by ceric ammonium molybdate, potassium permanganate or anisaldehyde stains, or UV fluorescence quenching. Compounds were purified by silica gel chromatography on SiliCycle SilaFlash 230-400 mesh silica gel. All substrates were dried by azeotropic distillation with C_6H_6 prior to use in reactions with Mo- based complexes. Infrared (IR) spectra were recorded on a Bruker FTIR Alpha (ATR Mode) spectrometer. Bands are characterized as strong (s), medium (m), weak (w) or broad (br). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 500 (500 MHz), Varian VNMRS 400 (400 MHz), Varian VNMRS 500 (500 MHz) or Varian VNMRS 600 (600 MHz). Chemical shifts (*d*) are reported in ppm from tetramethylsilane, referenced to the solvent resonance resulting from incomplete deuteration ($CDCl_3$: *d* 7.26, CD_3OD: *d* 3.32). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, br = broad, m = multiplet, app = apparent), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Unity INOVA 400 (100 MHz), Varian VNMRS 500 (125 MHz) or VNMRS 600 (150 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal reference ($CDCl_3$: *d* 77.0, CD_3OD: *d* 49.0). Values for the *Z:E* ratios were determined by analysis of the crude reaction mixture by ^{1}H NMR spectra. High-resolution mass spectrometry was performed on a Micromass LCT ESI-MS (positive mode) and JEOL Accu TOF Dart (positive mode) at the Boston

College Mass Spectrometry Facility. Optical rotation values were recorded on an Atago AT-300 polarimeter.

Vacuum Pump: A KNF Laboport Diaphragm pump connected to a Welch Labaid vacuum controller generates a vacuum of 100 torr at point of connection to the reaction vessel inside a glovebox.

Solvents: Solvents were purged with Ar and purified under a positive pressure of dry Ar by a modified Innovative Technologies purification system. Toluene (Fisher), dichloromethane (Fisher), benzene (Alfa Aesar) and pentane (Fisher, purification: *n*-pentane was allowed to stir over concentrated H_2SO_4 for three days, washed with water, followed by a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, and filtered before use in a solvent purification system.) were passed successively through activated copper and alumina columns. Tetrahydrofuran (thf) was purchased from Aldrich and purified by distillation from sodium benzophenone ketyl immediately prior to use. Acetone was purchased from Pharmco-AAPER and used as received. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Fisher) under bench-top conditions.

Organometallic Complexes: Mo monoaryloxide pyrrolide (MAP) complexes **2.45**,[47] **2.51**[48] and **2.64**[21] were prepared *in situ* according to previously reported procedures. Ru-based complex **2.81** was prepared according to a previously reported procedure, purified by silica gel chromatography and re-crystallized from pentane/dichloromethane prior to use.[49]

Reagents

Barium hydroxide octahydrate was purchased from Aldrich and used as received.

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46. Meek, S.; O'Brien, R.V.; Llaveria, J.; Schrock, R.R.; Hoveyda, A.H. *Nature*. **2011**, *471*, 461–466.

47. Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2009**, *131*, 3844–3845.

48. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2000**, *122*, 8168–8179.

(*R*,*R*)-1,3-Bis[(4-bromophenyl)methyl]-2-chlorooctahydro-2-allyl-1*H*-1,3,2-benzodiazasilole was prepared according to a published procedure and recrystallized from pentane prior to use.[31]

Bis(tri-*o*-tolylphosphine)palladium(0) was purchased from Strem and used as received.

4-Bromo-1-butene was purchased from Aldrich and passed through basic alumina before use.

Bromotrichloromethane was purchased from Aldrich and used as received

***tert*-Butyldimethylsilyl chloride (TBSCl)** was purchased from Strem and used as received.

***n*-Butyllithium** in hexanes was purchased from Strem and titrated before use.

Celite® was purchased from Fisher and used as received.

Cesium carbonate was purchased from Strem and used as received.

***d*-Chloroform** was purchased from Cambridge Isotope Laboratories and stored over activated 4 Å molecular sieves prior to use.

Chlorotrimethylsilane (TMSCl) was purchased from Acros Organics and used as received.

Crotonaldehyde was purchased from Aldrich and vacuum distilled prior to use.

1,8-Diazabicycloundec-7-ene (dbu) was purchased from Aldrich and used as received.

***N,N'*-Dicyclohexylcarbodiimide** was purchased from Advanced Chemtech and used as received.

Diethylamino sulfur trifluoride (dast) was purchased from Matrix Scientific and used as received.

Diisopropylethylamine (dipea) was purchased from Oakwood and used as received.

Dimethylamino pyridine (dmap) was purchased from Advanced Chemtech and used as received.

Dimethylamino pyridinium hydrochloride (dmap•HCl) was prepared from dmap and acetyl chloride in methanol and recrystallized from methanol then stored under vacuum prior to use.

Fluoro-*N,N,N'N'*-tetramethylformamidinium hexafluorophosphate (tffh) was purchased from Aldrich and used as received.

Fluorosilicic acid was purchased from Aldrich as a 35% aqueous solution and used as received.

Formic acid was purchased from Eastman Kodak and used as received.

Iodine was purchased from Alfa Aesar and used as received.

***d_4*-Methanol** was purchased from Cambridge Isotope labs and used as received.

Methanol was purchased from Aldrich and dried over 4 Å activated molecular sieves prior to use.

Methyl isobutyrate was purchased from Aldrich and used as received

4 Å Molecular sieves were purchased as beads from Aldrich, activated in an oven at 135 ºC and allowed to cool under N_2 before use.

Potassium carbonate was purchased from Fisher Scientific and used as received.

Potassium *tert*-butoxide was purchased from Strem and used as received.

Proton sponge® was purchased from Alfa Aesar and used as received.

Pyridinium *para*-toluenesulfonate (ppts) was purchased from Aldrich and used as received.

Scandium triflate was purchased from Strem and used as received.

L-Serine methyl ester hydrochloride was purchased from Combi-Blocks and used as received.

Silver(I) oxide was purchased from Alfa Aesar and used as received

Sodium borohydride was purchased from Aldrich and used as received.

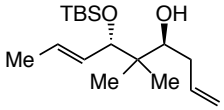
Sodium hydroxide was purchased as pellets from Fisher, and used as received.

Tetrakis(triphenylphosphine)palladium(0) was purchased from Strem and used as received.

Trimethyloxonium tetrafluoroborate was purchased from Aldrich, and used as received.

Vinylboronic acid pinacol ester (Vinyl–B(pin)) was purchased from Aldrich, purified by silica gel chromatography on silica using 20% ether in pentane (unpurified) as eluent to remove isopropanol present as an impurity, and distilled from CaH_2 before use.

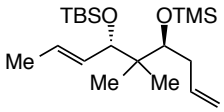
Experimental Procedures & Analytical Data



2.60

(4*S*,6*S*,*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-5,5-dimethylnona-1,7-dien-4-ol (2.60): Aldehyde **2.59**[18] (10.3 g, 40.1 mmol, 1 equiv) was added to an oven-dried 500 mL oven dried round bottom flask equipped with a stir bar and placed under N_2 atm. Dichloromethane (100 mL) was added, and the resulting solution was allowed to cool to an internal temperature of –15 °C (ice/acetone), and a temperature of under –10 °C was maintained over the course of the entire process. (*R*,*R*)-1,3-Bis[(4-bromophenyl)methyl]-2-chlorooctahydro-2-allyl-1*H*-1,3,2-benzodiazasilole, (**G**, 25.4 g, 45.8 mmol, 1.14 equiv) was then added, followed by scandium triflate (0.986 g, 2.00 mmol, 0.05 equiv). The resulting cloudy yellow solution was allowed to stir for 3 h, after which time TLC analysis (10% acetone/hexanes, $KMnO_4$ stain) showed complete consumption of aldehyde **2.59**. The volatiles were removed *in vacuo* to afford a foamy yellow residue. This was suspended in 250 mL Et_2O and a 100 mL solution of 1N HCl was added at 22 °C, resulting in the formation of a thick white precipitate. The mixture was allowed to stir vigorously for 30 min, after which time it was filtered and the filter cake was washed with 100 mL Et_2O. The filter cake consisted of pure diamine HCl salt that could be used to regenerate the reagent **G**.[Error! Bookmark not defined.55] The resulting layers were separated, and the aqueous layer was washed with three 100 mL portions of Et_2O. The combined organic phases were washed with 1 N solution of HCl, a saturated solution of aqueous $NaHCO_3$, then brine, dried over anhydrous Na_2SO_4, filtered and concentrated

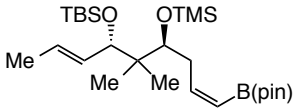
in vacuo to afford yellow oil. This was passed through a short plug of silica gel with 50% EtOAc/ hexanes to afford homoallylic alcohol **2.60** as pale yellow liquid (12.0 g, 40.2 mmol, >98% yield). Analysis by ^{1}H NMR spectroscopy showed a 91:9 mixture of inseparable *anti* and *syn* diastereomers. **TLC R_f:** 0.35 (5% EtOAc/ hexanes); **IR (neat):** 3494 (br), 2957 (m), 2930 (m), 2857 (m), 1669 (w), 1471 (m), 1253 (m), 1050 (s), 835 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.01–5.90 (m, 1H), 5.57–5.54 (m, 2H), 5.14–5.05 (m, 2H), 4.23 (s, 1H), 3.85 (d, J = 5.9 Hz, 1H), 3.75 (ddd, J = 9.8, 3.1, 1.6 Hz, 1H), 2.19–2.06 (m, 2H), 1.72 (d, J = 4.7 Hz, 3H), 0.98 (s, 3H), 0.89 (s, 9H), 0.73 (s, 3H), 0.07 (s, 3H), 0.01 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 137.0, 130.2, 128.6, 116.1, 84.5, 75.7, 40.8, 36.5, 25.9, 22.7, 19.6, 18.0, 17.7, –4.0, –5.1; **HRMS (DART):** Calcd for $C_{17}H_{34}SiO_2$ [M+H$^+$]: 299.2401; Found: 299.2406; **Specific Rotation:** $[\alpha]_D^{20}$ –16.0 (*c* 1.00 $CHCl_3$).



2.62

(4*S*,6*S*,*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-5,5-dimethyl-4-((trimethylsilyl)oxy)nona-1,7-diene (2.62): Alcohol **2.60** (12.0 g, 40.2 mmol, 1 equiv) was placed in a 500 mL oven dried round bottom flask equipped with a stir bar under N_2 atm. Dichloromethane (60 mL) was added, and the mixture was allowed to cool to 0 °C. To the mixture was added dmap (491 mg, 4.02 mmol, 0.1 equiv), followed by dipea (14.0 mL, 80.4 mmol, 2 equiv) and $(Me)_3SiCl$ (7.65 mL, 60.3 mmol, 1.5 equiv). The resulting mixture was allowed to stir for 3 h as the ice bath (allowed to melt to ambient temperature). The reaction was then quenched by the addition of 100 mL of a saturated aqueous solution of $NaHCO_3$. The mixture was diluted with 150 mL hexanes. The layers were separated and the organic layer was washed with a solution of brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford an opaque white oil. This residue was passed through a short plug of silica gel with hexanes to afford **S1** as clear colorless liquid (13.7 g, 37.0 mmol, 92% yield). **TLC R_f:** 0.85 (hexanes); **IR (neat):** 2957 (w), 2930 (w), 2885 (w), 2857 (w), 1448 (w), 1249 (m), 1081 (m), 1050 (m), 972 (m), 910 (m), 832 (s), 773 (m), 670 (m), 484 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.84–5.73

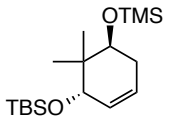
(m, 1H), 5.54–5.45 (m, 1H), 5.45–5.37(m, 1H), 5.04 (dt, *J* = 5.5, 1.5 Hz, 1H), 5.01–5.00 (m, 1H), 3.88 (d, *J* = 8.2 Hz, 1H), 3.55 (dd, *J* = 9.4, 2.7 Hz, 1H), 2.30–2.25 (m, 1H), 2.10–2.01 (m, 1H), 1.69 (dd, *J* = 5.9, 1.2 Hz, 3H), 0.88 (s, 9H), 0.83 (s, 3H), 0.79 (s, 3H), 0.08 (s, 9H), 0.02 (s, 3H), –0.03 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 137.8, 131.7, 127.5, 116.1, 78.7, 77.5, 43.6, 37.2, 25.9, 19.8, 19.2, 18.2, 17.7, 1.1, –3.3, –4.7; **HRMS (DART):** Calcd for $C_{20}H_{42}O_2Si_2$ [M+H$^+$]: 371.2796. Found: 371.2817; **Specific Rotation:** $[\alpha]_D^{20.1}$ –22.0 (*c* 10.0 $CHCl_3$).



2.63

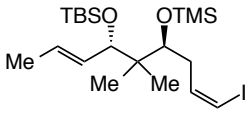
(1*Z*,4*S*,6*S*,7*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-5,5-dimethyl-4-((trimethylsilyl)oxy)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nona-1,7-diene (2.63): In an N_2-filled glovebox, alkene **2.62** (1.05 g, 2.83 mmol, 1 equiv) and vinyl–B(pin) (1.44 mL, 8.49 mmol, 3 equiv) were placed in an oven dried 8 mL vial equipped with a stir bar. To this mixture was added a 0.1 M solution of Mo complex **2.64** in benzene (0.81 mL, 0.081 mmol, 0.029 equiv). The vial was immediately fitted with a vacuum adaptor and evacuated to 100 torr. The resulting dark orange mixture was allow to stir under these conditions at 22 °C for 20 h. The vial was then removed from the glove box, and analysis of the unpurified reaction mixture by ^{1}H NMR analysis indicated 75% conversion to the desired alkenyl–B(pin). The dark brown oil was purified by silica gel chromatography (2% EtOAc/hexanes) to afford *Z*-alkenyl–B(pin) **2.63** as clear colorless oil (1.02g, 2.04 mmol, corrected yield: 72%). The product was isolated as a single stereoisomer (>98% *Z*) and in 91:9 diastereomeric ratio (dr) ratio. **TLC R_f:** 0.70 (5% EtOAc/ hexanes); **IR (neat):** 2957 (w), 2930 (w), 2885 (w), 2857 (w), 1628 (w), 1471 (w), 1422 (w), 1249 (m), 1145 (m), 1048 (m), 970 (w), 833 (s), 772 (m), 679 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.50 (dt, *J* = 13.3, 7.4 Hz, 1H), 5.58–5.48 (m, 1H), 5.47–5.36 (m, 2H), 3.93 (d, *J* = 7.3 Hz, 1H), 3.57 (dd, *J* = 8.6, 3.1 Hz, 1H), 2.66 (dddd, *J* = 14.5, 7.4, 3.1, 1.5 Hz, 1H), 2.51–2.42 (m, 1H), 1.68 (dd, *J* = 6.3, 1.6 Hz, 3H), 1.27 (s, 12H), 0.88 (s, 9H), 0.83 (s, 3H), 0.77 (s, 3H), 0.08 (s, 9H), 0.02 (s, 3H), –0.03 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 153.8, 131.8, 127.1, 118.6 (br), 82.8, 77.1, 78.1, 43.9,

35.7, 26.0, 25.0, 24.7, 19.5, 19.3, 18.2, 17.7, 1.0, –3.3, –4.6; **HRMS (ESI+):** Calcd for $C_{26}H_{53}BO_4Si_2$ [M+Na^+]: 519.3468; Found: 519.3485; **Specific Rotation:** $[\alpha]_D^{20}$ –29.90 (*c* 1.00 $CHCl_3$).



***tert*-Butyl(((1*S*,5*S*)-6,6-dimethyl-5-((trimethylsilyl)oxy)cyclohex-2-en-1-yl)oxy)dimethylsilane:** In an N_2-filled glovebox, alkene **2.62** (57.1 mg, 0.154 mmol, 1 equiv) was placed in an oven dried 8 mL vial equipped with a stir bar. To this mixture was added a 0.1 M solution of Mo complex **2.64** in benzene (47.1 μL, 4.63 μmol, 0.03 equiv). The vial was immediately fitted with a vacuum adaptor and evacuated to 100 torr. The resulting dark orange mixture was allow to stir under these conditions at 22 °C for 24 h. The vial was then removed from the glove box, and analysis of the unpurified reaction mixture by ^{1}H NMR analysis indicated 95% conversion to the desired alkenyl–B(pin). The dark brown oil was purified by silica gel chromatography (2% EtOAc/hexanes) to afford carbocycle as clear colorless oil (50.2 mg, 0.147 mmol, 95% yield).

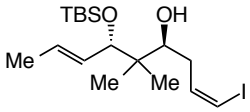
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.73–5.43 (m, 2H), 3.94–3.79 (m, 1H), 3.73 (dd, *J* = 6.4, 5.0 Hz, 1H), 2.23 (ddd, *J* = 17.0, 5.1, 2.3 Hz, 1H), 2.02–1.82 (m, 1H), 0.88 (s, 9H), 0.85 (s, 3H), 0.83 (s, 3H), 0.08 (d, *J* = 0.4 Hz, 9H), 0.04 (s, 6H).



2.65

(1*Z*,4*S*,6*S*,7*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-iodo-5,5-dimethyl-4-((trimethylsilyl)oxy)nona-1,7-diene (2.65): *Z*-Alkenyl–B(pin) **2.63** containing ~3 mol % of the aryloxide ligand generated from Mo complex **2.64** (430 mg, corrected mass, 0.866 mmol, 1 equiv) was placed in a foil wrapped 50 mL round bottomed flask that was equipped with a stir bar under N_2 atm; thf (8.6 mL) was added. To the clear colorless solution was added 1.73 mL of 3 M aqueous solution of NaOH, and the resulting turbid yellow mixture was allowed to stir for 5 min. Iodine (439 mg, 1.73 mmol, 2 equiv) was added, and the dark brown solution was allowed to stir for 10 h. At this point, the pale yellow solution was diluted with 50 mL of hexanes, and washed with

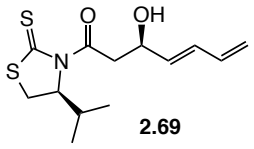
20 mL of a solution of brine. The organic layer was separated and dried over Na_2SO_4, filtered and concentrated *in vacuo* to furnish yellow oil, which was purified by silica gel chromatography (100 % hexanes) to afford *Z*-alkenyl iodide **2.65** (340 mg, 0.684 mmol, 79% yield) as clear colorless liquid (>98% *Z*, 91:9 dr). **TLC R_f:** 0.85 (hexanes); **IR (neat):** 2956 (w), 2930 (w), 2883 (w), 2857 (w), 1447 (w), 1251 (m), 1083 (m), 1051 (m), 836 (s), 774 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.48–6.40 (m, 1H, diagnostic for *E* isomer), 6.30–6.21 (m, 2H), 5.62–5.53 (m, 1H), 5.48–5.40 (m, 1H), 3.90 (d, J = 8.6 Hz, 1H), 3.65 (dd, J = 7.4, 4.0 Hz, 1H), 2.36–2.24 (m, 2H), 1.70 (dd, J = 6.3, 1.6 Hz, 3H), 0.88 (s, 9H), 0.85 (s, 3H), 0.80 (s, 3H), 0.09 (s, 9H), 0.03 (s, 3H), –0.02 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 140.4, 131.5, 127.9, 82.7, 78.6, 76.0, 43.7, 38.2, 26.0, 19.9, 19.5, 18.2, 18.7, 0.91, –3.3, –4.6; **Specific Rotation:** $[\alpha]_D^{20}$ –49.98 (*c* 1.00 $CHCl_3$).



2.56

(1*Z*,4*S*,6*S*,7*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-iodo-5,5-dimethylnona-1,7-dien-4-ol (2.56): *Z*-Alkenyl iodide **2.65** (340 mg, 0.684 mmol, 1 equiv) was placed in a 25 mL round bottom flask under air, and 10 mL of a 1:1 mixture of dichloromethane and MeOH was added. Pyridine *p*-toluenesulfonate (ppts; 17 mg, 0.0684 mmol, 0.1 equiv) was added and the resulting mixture was allowed to stir at 22 °C under air without special protection from ambient light. After 10 min, TLC analysis (10% EtOAc/hexanes, $KMnO_4$) indicated complete consumption of the starting material. The reaction was quenched through addition of 10 mL of a saturated aqueous solution of $NaHCO_3$ and the resulting mixture was diluted by addition of 50 mL 10% EtOAc/hexanes. The layers were separated and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford pale yellow oil, which was purified by silica gel chromatography (2% EtOAc/hexanes) to afford alcohol **2.56** (246 mg, 0.580 mmol, 85% yield) as clear colorless oil. This procedure allowed for complete separation of the *syn* and *anti* isomers, yield of alkenyl iodide represents only the *anti* isomer (>98% *Z*). **TLC R_f:** 0.70 (10% EtOAc/hexanes); **IR (neat):** 3480 (br), 2957 (m), 2931 (m), 2883 (w), 2857 (m), 1470 (w), 1254 (m), 1032 (m), 929 (w), 836 (s),

776 (m), 686 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.50–6.40 (m, 1H), 6.26 (t, J = 7.4, 1.2 Hz, 1H), 5.58–5.53 (m, 2H), 4.43 (ap. t, J = 1.6 Hz, 1H), 3.87 (d, J = 7.0 Hz, 1H), 3.75 (dt, J = 9.8, 2.0 Hz, 1H), 2.31–2.23 (m, 1H), 2.21–2.10 (m, 1H), 1.72 (d, J = 5.1 Hz, 3H), 1.00 (s, 3H), 0.89 (s, 9H), 0.79 (s, 3H), 0.07 (s, 3H), 0.02 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 139.7, 129.9, 128.9, 84.5, 83.1, 75.4, 40.7, 37.6, 25.8, 22.7, 19.8, 18.0, 17.7, –4.0, –5.1; **HRMS (ESI+):** Calcd for $C_{17}H_{33}IO_2Si$ [M+Na^+]: 447.1187; Found: 447.1333; **Specific Rotation:** $[\alpha]_D^{23.3}$ –68.2 (*c* 3.85 $CHCl_3$).

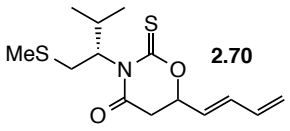


2.69

(*R*,*E*)-3-Hydroxy-1-((*S*)-4-isopropyl-2-thioxothiazolidin-3-yl)hepta-4,6-dien-1-one (2.69): Freshly prepared $Sn(OTf)_2$ (1.65 g, 3.96 mmol, 1.3 equiv) was placed in a flame dried 25 mL round bottom flask that was equipped with a stir bar under N_2; CH_2Cl_2 (2 mL) was introduced, followed by *N*-ethylpiperidine (544 μL, 3.96 mmol, 1.3 equiv). The mixture was allowed to cool to —30 ºC and a CH_2Cl_2 (1 mL) solution of thiazolidinethione **2.68**[50] (744 mg, 3.66 mmol, 1.2 equiv) was added. The mixture was allowed to stir for 1 h, at this point the mixture was allowed to cool to —78 ºC and a CH_2Cl_2 (1 mL) solution of pentadieneal **2.67** (250 mg, 3.05 mmol, 1 equiv) was added. The mixture was allowed to stir for 1 h, at which point water was added, and the mixture allowed to warm to 23 ºC. The resulting suspension was filtered through Celite ®, the layers were separated, and the aqueous later washed with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with a saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered and concentrated to afford a yellow oil. ^{1}H NMR analysis of this residue indicated a 95:5 ratio of diastereomers. The mixture was purified by silica gel chromatography (20% Et_2O/hexanes) to afford a single diastereomer of aldol aduct **2.69** (318 mg, 1.23 mmol, 40% yield) as a yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.43–6.24 (m, 2H), 5.77 (m 1H), 5.24 (d, J = 14.7 Hz, 1H), 5.20–5.06 (m, 1H), 4.73 (m, 1H), 3.73–3.61 (m, 1H), 3.61–3.43 (m, 1H), 3.34 (dd, J = 17.5, 8.8 Hz, 1H), 3.04 (dd, J = 11.5,

49. Nagao, Y.; Min, D. W.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Org. Chem.* **1990**, *55*, 1148–1157.

1.2 Hz, 1H), 2.85 (d, *J* = 4.3 Hz, 1H), 2.37 (d, *J* = 6.8 Hz, 1H), 1.07 (dd, *J* = 7.0, 2.2 Hz, 3H), 1.03–0.93 (m, 3H).

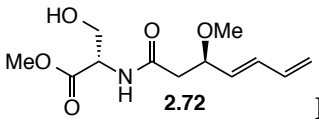


6-((*E*)-Buta-1,3-dien-1-yl)-3-((*S*)-3-methyl-1-(methylthio)butan-2-yl)-2-thioxo-1,3-oxazinan-4-one (2.70): Aldol aduct **2.69** *R*-**2.78**[38] (800 mg, 2.80 mmol, 1 equiv) was placed in a 250 mL oven-dried round bottom flask, equipped with a stir bar under N_2 atm. CH_2Cl_2 (10 mL) then Proton Sponge® (3.00 g, 14.0 mmol, 5 equiv) was added, followed by trimethyloxonium tetrafluoroborate (1.24 g, 8.40 mmol, 3 equiv). The resulting suspension was allowed to stir for 3 h, after which time it was filtered through a pad of Celite®. The filtrate was washed exhaustively with saturated aqueous solution of $NaHSO_4$ until TLC analysis (20% EtOAc/hexanes, CAM) indicated complete removal of Proton Sponge®. The organic layer was then washed with a solution of brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow oil, which was purified by silica gel chromatography. The resulting yellow oil is an inseparable mixture of rearrangement product **2.70** and desired methyl ether **2.71**.

This mixture of compounds was subsequently added to a 25 mL round bottom flask, equipped with stir bar under N_2 atm and thf (5 mL) was added. Serine methyl ester HCl salt (415 mg, 2.67 mmol) was introduced followed by triethylamine (563 μL, 4.02 mmol). The resulting suspension was allowed to stir for 3 h, at which time the mixture was diluted with EtOAc, washed with water, then washed with a saturated aqueous solution of NaCl, and the organic layer concentrated to afford a yellow oil. The mixture was purified by silica gel chromatography (gradient of 50% EtOAc/hexanes to 100% EtOAc) to afford rearrangement product **2.70** (no yield recorded) as yellow crystals as well as **2.72** (105 mg, 0.408 mmol, 10% yield over two steps) as a white solid.

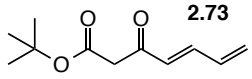
2.70: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.41–6.20 (m, 2H), 5.71 (dd, *J* = 14.1, 6.6 Hz, 1H), 5.29 (d, *J* = 16.1 Hz, 1H), 5.18 (d, *J* = 9.8 Hz, 1H), 4.75–4.55 (m, 1H), 4.50 (ddd, *J* = 10.3, 8.1, 5.0 Hz, 1H), 3.24 (dd, *J* = 11.1, 8.1 Hz, 1H), 3.04 (dd, *J* = 11.1, 5.1 Hz, 1H),

2.71 (dd, *J* = 16.0, 11.9 Hz, 1H), 2.52 (dd, *J* = 16.0, 2.9 Hz, 1H), 2.43 – 2.26 (m, 1H), 2.19 (s, 3H), 0.98 (dd, *J* = 7.5, 6.7 Hz, 6H).



2.72

Methyl ((*R*,*E*)-3-methoxyhepta-4,6-dienoyl)-*L*-serinate (2.72) **^{1}H NMR (400 MHz, $CDCl_3$):** 6.46–6.11 (m, 2H), 5.55 (dd, *J* = 14.9, 7.8 Hz, 1H), 5.29–5.20 (m, 1H), 5.20–5.02 (m, 1H), 4.65 (ddd, *J* = 7.3, 7.3, 3.7 Hz, 1H), 4.01 (dddd, *J* = 8.1, 8.1, 4.1, 0.9 Hz, 1H), 3.91 (m, 2H), 3.78 (s, 3H), 3.32 (s, 3H), 2.64 – 2.49 (m, 2H), 2.44 (dd, *J* = 15.0, 4.1 Hz, 1H).



2.73

***tert*-butyl (*E*)-3-oxohepta-4,6-dienoate (2.73):** Lithium diisopropyl amide (23.8 mmol, 3 equiv, in 100 mL thf) was prepared in a 250 mL round bottom flask equipped with stirbar under N_2 atm; the solution was allowed to cool to –78 ºC and *tert*-butyl acetate (3.20 mL, 23.8 mmol, 3.0 equiv) was introduced. The mixture was allowed to stir for 30 min, then ethyl (*E*)-penta-2,4-dienoate[51] (1.00 g, 7.90 mmol, 1 equiv) was added, and the mixture allowed to stir for 3 h. The reaction was then quenched by the addition of a saturated aqueous solution of NH_4Cl, and diluted with EtOAc. The layers were separated, and the aqueous layer was washed with EtOAc. The combined organic layers were washed with a saturated aqueous solution of NaCl, dried over Na_2SO_4 filtered and concentrated to afford yellow oil. The mixture was purified by silica gel chromatography (5% Et_2O/hexanes) to afford β-keto-ester **2.73** (718 mg, 3.61 mmol, 46% yield) as a yellow oil and a 2:1 mixture of enol:keto tautomers. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 12.13–11.77 (s, 1H, enol), 7.14 (ddt, *J* = 15.6, 10.8, 0.7 Hz, 1H, keto), 7.07–6.91 (m, 1H, enol), 6.42 (m, 1 H overlapping enol and keto), 6.22 (dd, *J* = 15.6, 0.7 Hz, 1H, keto), 5.90–5.81 (m, 1H, enol), 5.72–5.62 (m, 1H, keto), 5.60–5.50 (m, 1H, keto), 5.53–5.40 (m, 1H, enol), 5.39–5.27 (m, 1H, enol), 4.96 (s, 1H, enol), 3.48 (s, 2H, keto), 1.47 (s, 9H, enol), 1.43 (s, 9H, keto).

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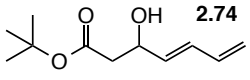
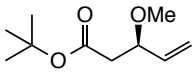
50. Rodriguez, J. Waegell, B. *Synthesis* **1988**, 534–535.



2.74

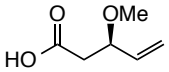
***tert*-butyl (*E*)-3-hydroxyhepta-4,6-dienoate (2.74):** β-keto-ester 2.73 (617 mg, 3.12 mmol, 1 equiv) was placed in a 100 mL round bottom flask, equipped with stir bar under air; MeOH (50 mL) was added. $CeCl_3 \bullet 7H_2O$ (1.16 g, 3.12 mmol, 1.0 equiv) was introduced, and the mixture stirred at 22 ºC until it was homogenous. The mixture was then allowed to cool to 0 ºC and $NaBH_4$ (117 mg, 3.12 mmol, 1.0 equiv) was added slowly as a solid in portions. A copious amount of gas was generated. The mixture was allowed to stir for 30 min after addition of $NaBH_4$ was complete, then the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ and diluted with EtOAc. The layers were separated, and the aqueous layer washed with EtOAc, the combined organic layers were dried over Na_2SO_4 filtered and concentrated to afford yellow oil. The mixture was purified by silica gel chromatography (20% Et_2O/hexanes) to afford **2.74** (268 mg, 1.35 mmol, 43% yield) as a clear colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.44–6.13 (m, 2H), 5.70 (dd, *J* = 14.4, 5.8 Hz, 1H), 5.27–5.16 (m, 1H), 5.10 (dd, *J* = 9.5, 1.8 Hz, 1H), 4.60–4.46 (m, 1H), 3.13 (d, *J* = 4.4 Hz, 1H), 2.59–2.33 (m, 2H), 1.45 (d, *J* = 2.5 Hz, 9H). **^{13}C NMR (100 MHz, $CDCl_3$):** *δ* 171.8, 136.3, 134.2, 131.4, 118.0, 81.6, 68.6, 42.4.



2.79

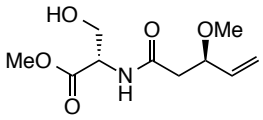
***tert*-Butyl (*R*)-3-Methoxypent-4-enoate (2.79):** Allylic alcohol *R*-**2.78**[38] (4.00 g, 23.3 mmol, 1 equiv) was placed in a 250 mL oven-dried round bottom flask, equipped with a stir bar under N_2 atm. CH_2Cl_2 (116 mL) then Proton Sponge® (15.0 g, 69.9 mmol, 3 equiv) were added, followed by trimethyloxonium tetrafluoroborate (8.81 g, 46.5 mmol, 2 equiv). The resulting suspension was allowed to stir for 3 h, after which time it was filtered through a pad of Celite®. The filtrate was washed exhaustively with saturated aqueous solution of $NaHSO_4$ until TLC analysis (20% EtOAc/hexanes, CAM) indicated complete removal of Proton Sponge®. The organic layer was then washed with a solution of brine, dried over Na_2SO_4 and concentrated *in vacuo* to give yellow oil, which was purified by silica gel chromatography (3% Et_2O/ pentane, then switching to

20% EtOAc/hexanes) to afford methyl ether **2.79** (3.43 g, 18.4 mmol, 79% yield) as clear colorless oil. Additionally, unreacted alcohol *R*-**2.78** (477 mg, 2.77 mmol, 12% yield) was recovered as the more polar eluent. **TLC R_f:** 0.43 (20% Et_2O/ hexanes); **IR (neat):** 2980 (m), 2932 (m), 2823 (w), 2363 (w), 2341 (w), 1730 (s), 1455 (m), 1421 (m), 1392 (m), 1367 (s), 1279 (m), 1254 (m), 1210 (m), 1154 (s), 1123 (w), 1101 (s), 1018 (w), 991 (m), 928 (s), 845 (m), 765 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.92–5.42 (m, 1H), 5.24 (ddd, *J* = 17.2, 1.6, 1.0 Hz, 1H), 5.19 (ddd, *J* = 10.3, 1.6, 0.8 Hz, 1H), 3.98–3.90 (m, 1H), 3.26 (s, 3H), 2.48 (dd, *J* = 14.9, 8.0 Hz, 1H), 2.33 (dd, *J* = 14.9, 5.7 Hz, 1H), 1.42 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.9, 137.0, 117.4, 80.3, 79.2, 56.2, 42.0, 27.9; **HRMS (DART):** Calcd for $C_{10}H_{19}O_3$ [M+H^+]: 187.13342; Found: 187.13300; **Specific Rotation:** $[\alpha]_D^{22.5}$ –17.95 (*c* 0.90 $CHCl_3$).



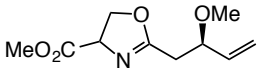
S1

(*R*)-3-Methoxypent-4-enoic acid (S1): Ester **2.79** (513 mg, 2.75 mmol, 1 equiv) was placed in a 25 mL round bottom flask, equipped with a stir bar and neat formic acid (4 mL) was added. The mixture was allowed to stir for 2.5 h, after which time TLC analysis indicated complete consumption of the starting material. Formic acid was removed *in vacuo* and the resulting residue was dissolved in toluene and subjected to vacuum (azeotrope) until ^{1}H NMR analysis showed complete removal of formic acid. Acid **S1** (330 mg, 2.56 mmol, 93% yield) was obtained as clear yellow liquid, which was used directly in the following transformation. **TLC R_f:** 0.40 (EtOAc); **IR (neat):** 3085 (br) 2935 (m), 2836 (m), 1712 (s), 1424 (m), 1295 (m), 1212 (m), 1173 (m), 1124 (m), 1101 (m), 1066 (m), 1016 (m), 991 (m), 933 (m), 837 (m), 693 (w) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 11.10 (s, 1H), 5.71 (ddd, *J* = 17.6, 10.3, 7.8 Hz, 1H), 5.38–5.28 (m, 2H), 4.13 (ddd, *J* = 8.1, 8.1, 4.9 Hz, 1H), 3.36 (s, 3H), 2.72 (dd, *J* = 15.8, 8.5 Hz, 1H), 2.60 (dd, *J* = 15.9, 4.9 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 175.9, 135.9, 119.1, 78.9, 56.5, 40.4; **HRMS (DART):** Calcd for $C_6H_{11}O_3$ [M+H^+]: 131.07082; Found: 131.07068; **Specific Rotation:** $[\alpha]_D^{21.7}$ –9.08 (*c* 11.0 $CHCl_3$).



2.80

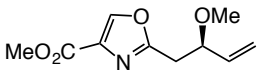
Methyl ((*R*)-3-methoxypent-4-enoyl)-L-serinate (2.80): Carboxylic acid **S1** (82 mg, 0.63 mmol, 1 equiv) was placed in a 25 mL round bottom flask, and thf (2 mL) was added. Diisopropylethylamine (0.252 mL, 1.45 mmol, 2.3 equiv) was introduced, followed by tffh (183 mg, 0.693 mmol, 1.1 equiv). The mixture was allowed to stir for 2 h and serine methyl ester•HCl salt (117 mg, 0.756 mmol, 1.2 equiv) was added. The resulting clear light yellow solution was allowed to stir for an additional 3 h, then diluted with EtOAc, washed with a 1N solution of HCl, and a solution of brine, and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the resulting yellow greasy solid residue was purified by silica gel chromatography (EtOAc) to deliver amide **2.80** (121 mg, 0.523 mmol, 83% yield) as light yellow oil. **TLC R_f:** 0.25 (EtOAc); **IR (neat):** 3338 (br), 3079 (w), 2952 (m), 2886 (w), 2826 (w), 1742 (s), 1649 (s), 1534 (s), 1438 (m), 1356 (w), 1210 (s), 1145 (w), 1089 (s), 993 (m), 933 (m), 837 (w), 576 (br) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.33–7.27 (br, 1H), 5.72 (ddd, J = 17.2, 10.3, 7.4 Hz, 1H), 5.34–5.23 (m, 2H), 4.68 (ddd, J = 7.4, 3.8, 3.8 Hz, 1H), 4.00–3.96 (m, 1H), 3.95–3.93 (m, 2H), 3.80 (s, 3H), 3.36 (s, 3H), 2.54 (dd, J = 15.1, 8.2 Hz, 1H), 2.47 (dd, J = 15.1, 3.9 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 170.8, 136.6, 118.1, 79.3, 63.6, 56.5, 54.9, 52.7, 42.4; **HRMS (DART):** Calcd for $C_{10}H_{11}NO_5$ [M+H$^+$]: 232.11850; Found: 232.11833; **Specific Rotation:** $[\alpha]_D^{22.5}$ +35.0 (*c* 10.0 $CHCl_3$).



S2

Methyl (*S*)-2-((*R*)-2-methoxybut-3-en-1-yl)-4,5-dihydrooxazole-4-carboxylate (S2): Serinate **2.80** (411 mg, 1.78 mmol, 1 equiv) was placed in an oven-dried 25 mL round bottom flask equipped with a stir bar and dichloromethane (4 mL) was added. The mixture was allowed to cool to –78 °C under N_2 atm. DAST (0.235 mL, 1.78 mmol, 1.0 equiv) was added and the mixture was allowed to stir for 3 h. At this time, K_2CO_3 (490 mg, 3.55 mmol, 2 equiv) was introduced into the mixture and the cooling bath was removed. After being allowed to stir for one additional h, the reaction was quenched by the addition of 15 mL of a saturated aqueous solution of NH_4Cl and the

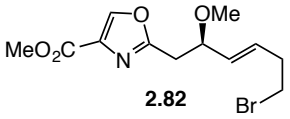
layers were separated. The aqueous layer was washed with two 20 ml portions of dichloromethane. The combined organic phases were washed with a solution of brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product as yellow oil. Optimal yields were realized by carrying the material to the next step without further analysis or purification. **TLC R_f:** 0.21 (50% EtOAc/ hexanes); **IR (neat):** 2981 (w), 2954 (m), 2926 (m), 2853 (w), 2824 (w), 1740 (s), 1661 (s), 1437 (m), 1363 (m), 1203 (s), 1175 (s), 1097 (s), 983 (s), 931 (m), 832 (w), 785 (w), 750 (w), 687 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.72–5.50 (m, 1H), 5.27–5.06 (m, 2H), 4.71–4.60 (m, 1H), 4.42 (ddd, J = 8.8, 7.7, 2.6 Hz, 1H), 4.32 (ddd, J = 10.6, 8.7, 2.6 Hz, 1H), 3.96–3.83 (m, 1H), 3.70 (s, 3H), 3.21 (s, 3H), 2.67–2.53 (m, 1H), 2.49–2.36 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 171.6, 167.7, 136.9, 118.1, 79.5, 69.3, 68.0, 56.4, 52.6, 34.5; **HRMS (DART):** Calcd for $C_{10}H_{16}NO_4$ $[M+H^+]$: 214.10793; Found: 214.10757; **Specific Rotation:** $[\alpha]_D^{23.1}$ +109.89 (*c* 1.00 $CHCl_3$).



2.75

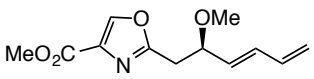
Methyl (*R*)-2-(2-methoxybut-3-en-1-yl)oxazole-4-carboxylate (2.75): Unpurified **S2** (1.78 mmol theoretical, 1 equiv) was placed in a 25 mL oven-dried round bottom flask equipped with a stir bar; dichloromethane (5 mL) was added. The mixture was allowed to cool to 0 °C under N_2 atm. To this faint yellow solution was added dbu (0.489 mL, 3.56 mmol, 2 equiv) and $BrCCl_3$ (0.350 mL, 3.56 mmol, 2 equiv). The resulting light brown solution was allowed to stir in the dark for 16 h at 4 °C. At this time, the reaction was diluted with 30 mL dichloromethane and washed with two 10 mL portions of a saturated aqueous solution of NH_4Cl and then a solution of brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford brick-red oil, which was purified by silica gel chromatography (20% EtOAc/ hexanes) to afford oxazole **2.75** (219 mg, 1.03 mmol, 58% yield from **2.80**) as light yellow oil. **TLC R_f:** 0.47 (50% EtOAc/hexanes); **IR (neat):** 3158 (w), 3104 (w), 2985 (w), 2952 (w), 2825 (w), 1743 (s), 1585 (m), 1438 (w), 1323 (m), 1203 (w), 1107 (s), 1000 (m), 936 (m), 805 (m), 764 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.13 (s, 1H), 5.68 (ddd, J = 17.2, 10.3, 7.7 Hz, 1H), 5.27–5.15 (m, 2H), 4.10–3.98 (m, 1H), 3.86 (s, 3H), 3.23 (s, 3H), 3.07

(dd, *J* = 14.9, 7.6 Hz, 1H), 2.96 (dd, *J* = 14.9, 5.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 162.7, 161.6, 143.8, 136.6, 133.2, 118.6, 80.1, 56.4, 52.0, 34.5; **HRMS (DART):** Calcd for $C_{10}H_{14}NO_4$ [M+H$^+$]: 212.09228. Found: 212.09266; **Specific Rotation:** $[\alpha]_D^{22.1}$ –5.8 (*c* 12.0 $CHCl_3$).



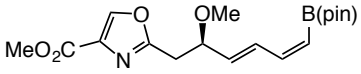
2.82

Methyl (*R*,*E*)-2-(6-bromo-2-methoxyhex-3-en-1-yl)oxazole-4-carboxylate (2.82): Oxazole **2.75** (350 mg, 1.66 mmol, 1 equiv) was placed in a 25 mL flame-dried round-bottom flask equipped with a stir bar under N_2 atm; toluene (1 mL) was added. To the solution was added 4-bromo-1-butene (0.84 mL, 8.3 mmol, 5 equiv) followed by Ru complex **2.81** (52 mg, 0.083 mmol, 0.05 equiv). The resulting green solution was allowed to stir at 70 °C for 18 h, until TLC analysis indicated complete consumption of the starting material. The mixture was then concentrated *in vacuo* and the resulting opaque red oil residue was purified by silica gel chromatography (40% EtOAc/hexanes) to afford homoallyl bromide **2.82** as light yellow oil (426 mg, 1.34 mmol, 81% yield, > 98% *E*). **TLC R_f:** 0.23 (40% EtOAc/hexanes); **IR (neat):** 3159 (br) 2992 (w), 2950 (m), 2824 (w), 1742 (s), 1585 (s), 1439 (m), 1323 (m), 1267 (m), 1203 (m), 1145 (m), 1105 (s), 1003 (m), 973 (m), 805 (m), 766 (m), 559 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.07 (s, 1H), 5.56 (dtd, *J* = 15.4, 6.7, 0.7 Hz, 1H), 5.43–5.25 (m, 1H), 3.98 (dddd, *J* = 8.1, 7.1, 6.2, 0.8 Hz, 1H), 3.79 (s, 4H), 3.26 (td, *J* = 6.8, 3.7 Hz, 2H), 3.16 (s, 4H), 3.01 (dd, *J* = 14.8, 7.3 Hz, 1H), 2.89 (dd, *J* = 14.8, 6.2 Hz, 1H), 2.49 (qd, *J* = 6.7, 1.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 162.4, 161.3, 143.6, 133.0, 131.4, 79.2, 56.0, 51.8, 34.9, 34.4, 31.7; **HRMS (DART):** Calcd for $C_{12}H_{17}BrNO_4$ [M+H$^+$]: 318.03410; Found: 318.03453; **Specific Rotation:** $[\alpha]_D^{22.5}$ –9.99 (*c* 1.00 $CHCl_3$).



Methyl (*R*,*E*)-2-(2-methoxyhexa-3,5-dien-1-yl)oxazole-4-carboxylate (2.66): Homoallyl bromide **2.82** (1.01 g, 3.16 mmol, 1 equiv) was placed in a foil-wrapped 25 mL round bottom flask and EtOAc (6 mL) was added. To the resulting

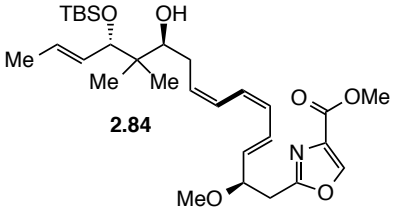
mixture was added dbu (1.43 ml, 9.48 mmol, 3 equiv) at 22 °C, causing a thick precipitate to form immediately. The mixture was allowed to stir for 7 h, after which time TLC analysis indicated complete consumption of alkyl bromide **2.82**. At this time, the mixture was diluted with 30 mL EtOAc and washed with two 15 mL portions of a saturated aqueous solution of NH_4Cl followed by a solution of brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting brown oil was purified by silica gel chromatography (30% EtOAc/hexanes) to afford diene **2.66** as light yellow oil (680 mg, 2.89 mmol, 91% yield). **TLC R_f:** 0.25 (25% EtOAc/hexanes); **IR (neat):** 3153 (br) 3089 (w), 2951 (m), 2925 (m), 2852 (w), 2825 (w), 1743 (s), 1584 (s), 1438 (m), 1322 (s), 1226 (w), 1201 (m), 1151 (m), 1135 (m), 1102 (s), 1004 (s), 943 (m), 911 (m), 805 (m), 764 (m), 675 (m), 556 (w), 504 (w) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.13 (s, 1H), 6.29 (dt, J = 16.7, 10.2 Hz, 1H), 6.23–6.15 (m, 1H), 5.55 (dd, J = 15.1, 7.9 Hz, 1H), 5.20 (dd, J = 16.6, 1.5 Hz, 1H), 5.10 (dd, J = 10.1, 1.6 Hz, 1H), 3.87 (s, 4H), 3.23 (s, 4H), 3.09 (dd, J = 14.9, 7.7 Hz, 1H), 2.97 (dd, J = 14.9, 5.8 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 162.7, 161.6, 143.9, 135.7, 134.3, 133.3, 131.7, 118.6, 79.3, 56.4, 52.0, 34.8; **HRMS (DART):** Calcd for $C_{12}H_{16}NO_4$ $[M+H^+]$: 238.10793; Found: 238.10775; **Specific Rotation:** $[\alpha]_D^{22.5}$ –20.0 (*c* 1.00 $CHCl_3$).



2.57

Methyl 2-((*R*,3*E*,5*Z*)-2-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-3,5-dien-1-yl)oxazole-4-carboxylate (2.57): Diene **2.66** was first placed in a 30 mL vial and subjected to azeotropic removal of water (with three 5 mL portions of benzene). In a glovebox, a sample of diene **2.66** (75 mg, 0.32 mmol, 1 equiv) was placed in an 8 mL oven-dried vial equipped with a stir bar. Vinyl–B(pin) **2.44** (270 μL, 1.6 mmol, 5 equiv) was added, followed by a 0.1 M solution of Mo complex **2.64** in benzene (320 μL, 0.032 mmol, 0.1 equiv). The vial was fitted with a vacuum adaptor and the resulting orange solution was placed under 100 torr vacuum and allowed to stir for 18 h. At this time, the vessel was removed from the glovebox and the viscous dark brown oil was purified by silica gel chromatography (20% EtOAc/hexanes) to afford dienylboronic ester **2.57** as light brown oil (92:8 *Z*:*E*; 93 mg, 0.26 mmol, 80% yield).

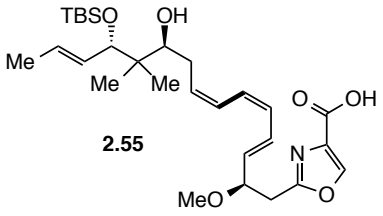
TLC R_f: 0.26 (25% EtOAc/ hexanes). **IR (neat):** 3153 (br) 3089 (w), 2951 (m), 2925 (m), 2852 (w), 2825 (w), 1743 (s), 1584 (s), 1438 (m), 1322 (s), 1226 (w), 1201 (m), 1151 (m), 1135 (m), 1102 (s), 1004 (s), 943 (m), 911 (m), 805 (m), 764 (m), 675 (m), 556 (w), 504 (w) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.24–7.98 (m, 1H), 7.13–6.94 (m, 1H), 6.80 (ddd, J = 13.9, 10.8, 3.1 Hz, 1H), 5.72–5.60 (m, 1H), 5.49–5.31 (m, 1H), 4.35–4.12 (m, 1H), 3.88 (s, 3H), 3.24 (s, 3H), 3.13–3.02 (m, 1H), 3.02–2.91 (m, 1H), 1.26 (s, 12H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 162.9, 161.6, 148.7, 143.8, 135.6, 133.8, 133.3, 83.2, 79.3, 56.5, 52.0, 34.7, 24.8; **HRMS (DART):** Calcd for $C_{12}H_{16}NO_4$ [M+H$^+$]: 238.10793. Found: 238.10775; **Specific Rotation:** $[\alpha]_D^{23.0}$ –19.98 (*c* 1.00 $CHCl_3$).



2.84

Methyl 2-((2*R*,3*E*,5*Z*,7*Z*,10*S*,12*S*,13*E*)-12-((*tert*-butyldimethylsilyl)oxy)-10-hydroxy-2-methoxy-11,11-dimethylpentadeca-3,5,7,13-tetraen-1-yl)oxazole-4-carboxylate (2.84): *Z*-Dienyl–B(pin) **2.57** (56 mg, 0.16 mmol, 1.1 equiv) and *Z*-alkenyl iodide **2.56** (60.0 mg, 0.14 mmol, 1 equiv) were placed in a 5 mL oven-dried flask equipped with a stir bar and thf (1 mL) was added. The flask was wrapped in aluminum foil, and silver oxide (36 mg, 0.16 mmol, 1.1 equiv) and $Pd(PPh_3)_4$ (16 mg, 0.014 mmol, 0.1 equiv) were added to the mixture. The resulting black suspension/yellow solution was allowed to stir for 12 h at 22 °C, aftter which he following protocol was conducted swiftly in a darkened hood, or in foil-wrapped glassware to minimize exposure to light. The brown suspension was diluted with 5 mL 50% EtOAc/hexanes, and filtered through Celite® to remove the brown solid; this afforded a dark yellow-brown solution that was filtered through a short plug of silica gel affording a nearly colorless solution. At this time, the volatiles were removed *in vacuo* to afford dark yellow oil, which was purified by silica gel chromatography (20% EtOAc/hexanes) to afford *Z,Z,E*-triene **2.84** as pale yellow oil (52 mg, 0.97 mmol, 69% yield). It should be noted that, although triene **2.84** can be isolated and purified at the ambient laboratory conditions, exposure of this material to air over several hours results

in extensive decomposition to intractable products. **TLC R_f:** 0.26 (25% EtOAc/hexanes); **IR (neat):** 3478 (br), 2955 (m), 2930 (m), 2856 (m), 1746 (s), 1584 (m), 1470 (m), 1387 (m), 1322 (m), 1142 (s), 1106 (m), 835 (s), 774 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.14 (s, 1H), 6.86 (dd, *J* = 18.3, 11.4 Hz, 1H), 6.49 (ap. t, *J* = 11.4 Hz, 1H), 6.27 (ap. t, *J* = 11.3 Hz, 1H), 5.96 (ap. t, *J* = 11.0 Hz, 1H), 5.76 (dd, *J* = 18.3, 7.4 Hz, 1H), 5.60–5.49 (m, 3H), 4.35 (br. s, 1H), 4.16 (q, *J* = 6.2 Hz, 1H), 3.90 (s, 3H), 3.85 (d, *J* = 6.65, 1H), 3.69 (dd, *J* = 9.0, 3.5 Hz, 1H), 3.23 (s, 3H), 3.10 (dd, *J* = 14.9, 7.4 Hz, 1H), 3.29 (dd, *J* = 14.9, 5.9 Hz), 2.34–2.20 (m, 2H), 1.70 (d, *J* = 5.9 Hz, 3H), 0.98 (s, 3H), 0.87 (s, 9H), 0.73 (s, 3H), 0.05 (s, 3H), 0.00 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 162.7, 161.6, 143.9, 133.2, 132.2, 132.0, 130.0, 129.0, 128.7, 127.5, 125.8, 124.2, 84.5, 79.6, 76.0, 56.5, 52.0, 40.8, 34.8, 30.0, 25.8, 22.7, 19.6, 17.9, 17.7, –4.0, –5.1; **HRMS (ESI+):** Calcd for $C_{29}H_{47}NO_6Si$ [M+Na^+]: 556.3065; Found: 556.3088; **Specific Rotation:** $[\alpha]_D^{23.1}$ – 15.7 (*c* 1.00 $CHCl_3$)

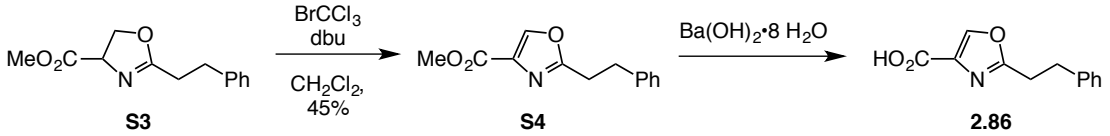


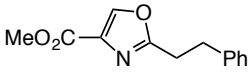
2.55

2-((2*R*,3*E*,5*Z*,7*Z*,10*S*,12*S*,13*E*)-12-((*tert*-Butyldimethylsilyl)oxy)-10-hydroxy-2-methoxy-11,11-dimethylpentadeca-3,5,7,13-tetraen-1-yl)oxazole-4-carboxylic acid (2.55): *Z,Z,E*-Triene **2.84** (20 mg, 0.037 mmol, 1 equiv) was placed in a 25 mL round bottom flask equipped with a stir bar under N_2 atm and thf (1.5 mL) was added. To this solution was added $Ba(OH)_2$•$8H_2O$ (12 mg, 0.037 mmol, 1 equiv) as a solution in 1.5 mL water, causing the mixture to turn turbid. The yellow mixture was allowed to stir for 90 min, until TLC analysis (30% EtOAc/hexanes) indicated complete consumption of the starting material. The reaction was then quenched through addition of 2 mL of a saturated solution of aqueous $NaHSO_4$, resulting in precipitation of $BaSO_4$. The mixture was washed with EtOAc, and the combined clear organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Analysis by ^{1}H NMR spectroscopy indicated that the resulting yellow oil (**2.55**; 20 mg, > 98% yield) contained impurities; however, repeated attempts at purification by silica gel

chromatography led to further decomposition. Complete decomposition of the neat oil was observed after storage after 12–16 h at –15 °C. **TLC R_f:** 0.05 (50% EtOAc/ hexanes); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.21 (s, 1H), 6.69 (dd, J = 15.3, 11.7 Hz, 1H), 6.51 (app t, J = 11.4 Hz, 1H), 6.29 (app t, J = 11.4 Hz, 1H), 5.99 (app t, J = 11.4 Hz, 1H), 5.76 (app t, J = 19.7 Hz, 1H), 5.64–5.49 (m, 3H), 4.22–4.14 (m, 1H), 3.85 (d, J = 6.8 Hz, 1H), 3.72 (dd, J = 15.0, 5.9 Hz, 1H), 3.26 (s, 3H), 3.17–3.09 (m, 1H), 3.02 (dd, J = 15.0, 5.9 Hz, 1H), 1.71 (d, J = 4.7 Hz, 3H), 1.00 (s, 3H), 0.88 (s, 9H), 0.75 (s, 3H), 0.07 (s, 3H), 0.01 (s, 3H).

Scheme 2.16. Preparation of Model Oxazole **2.86**

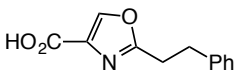




S4

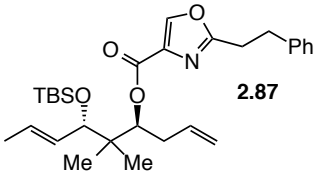
Methyl 2-phenethyloxazole-4-carboxylate (S4): Oxazoline **S3**[52] (760 mg, 3.26 mmol 1 equiv) was placed in a 100 mL oven-dried round bottom flask equipped with a stir bar; dichloromethane (15 mL) was added. The mixture was allowed to cool to 0 °C under N_2 atm. To this faint yellow solution was added dbu (0.877 mL, 5.87 mmol, 1.8 equiv) and $BrCCl_3$ (0.675 mL, 6.84 mmol, 2.1 equiv). The resulting light brown solution was allowed to stir in the dark for 16 h at 4 °C. At this time, the reaction was diluted with 30 mL dichloromethane and washed with two 10 mL portions of a saturated aqueous solution of NH_4Cl and then a solution of brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford brick-red oil, which was purified by silica gel chromatography (20% EtOAc/ hexanes) to afford oxazole **S4** (360 mg, 1.56 mmol, 45% yield) as an off white solid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.15 (s, 1H), 7.46 – 7.01 (m, 5H), 3.92 (s, 3H), 3.12 (s, 4H).

51. Sakaura, A.; Kondo, R.; Ishihara, K. *Org. Lett.* **2005**, *7*, 1971–1974.



2.86

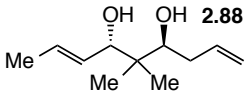
2-phenethyloxazole-4-carboxylic acid (2.86): Ester **S4** (230 mg, 0.994 mmol, 1 equiv) was placed in a 25 mL round bottom flask under air, and thf (6 mL) was added. To this solution was added $Ba(OH)_2 \bullet 8H_2O$ (314 mg, 0.994 mmol, 1 equiv) as a solution in water (6 mL), causing the mixture to turn turbid. The resulting mixture was allowed to stir for 1 h at which time TLC analysis (30% EtOAc/hexanes) indicated complete consumption of the starting material. The reaction was then quenched by the addition of a 2 mL solution of saturated aqueous $NaHSO_4$, which caused precipitation of $BaSO_4$. The mixture was then was washed with EtOAc. The combined clear organic layers were dried over Na_2SO_4, filtered and the volatiles were removed *in vacuo*. The resulting beige solid proved to be unstable to silica gel chromatography and was therefore used without purification. **TLC R_f:** 0.05 (50% EtOAc/hexanes); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.05 (broad s, 1H), 8.23 (s, 1H), 7.59–6.84 (m, 5H), 3.54–2.75 (m, 4H).



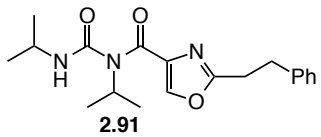
2.87

(4*S*,6*S*,*E*)-6-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethylnona-1,7-dien-4-yl 2-phenethyloxazole-4-carboxylate (2.87): Unpurified acid **2.86** (32 mg, 0.15 mmol, 1 equiv) was placed in a 5 mL round bottom flask, and CH_2Cl_2 (1 mL) was added. Diisopropylethylamine (26 μL, 0.15 mmol, 1.0 equiv) was introduced, followed by tffh (46 mg, 0.15 mmol, 1.0 equiv). The resulting mixture was allowed to stir for 2 h at which time TLC analysis (30% EtOAc/hexanes) indicated complete consumption of the starting material. The mixture was concentrated under a stream of N_2, then Et_2O was added. The resulting suspension was filtered through Celite®. The filtrate was concentrated to afford the acyl fluoride as a tan solid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.27 (s, 1H), 7.47–6.94 (m, 5H), 3.54–3.23 (urea signal m, 4H), 3.13 (m, 4H), 1.87–1.74 (urea signal m, 7H). Alcohol **2.60** (44 mg, 0.15 mmol, 1 equiv) was placed in a 25 mL round bottom flask, and thf (1 mL) was added. Khmds (29 mg, 0.15 mmol, 1.0 equiv) was introduced, and the resulting mixture was allowed to stir for 5 min, at which time the

previousy prepared acyl fluoride (0.15 mmol, 1 equiv in 1 mL thf) was introduced. The resulting mixture was allowed to stir for 3.5 h. The reaction was then quenched through addition of 2 mL of a saturated solution of aqueous NH_4Cl, The mixture was washed with EtOAc, and the combined clear organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting brown oil was purified by silica gel chromatography (5% EtOAc/hexanes) to afford ester **2.87**, contaminated with numerous byproducts, as a brown oil (29 mg, 0.060 mmol, ~40% yield). As this material could not be fully separated from byproducts, it was not fully characterized. The NMR of the mixture is included.

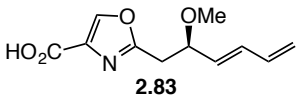


(4*S*,6*S*,*E*)-5,5-dimethylnona-1,7-diene-4,6-diol (2.88): Silyl ether **2.60** (250 mg, 0.837 mmol, 1 equiv) was placed in a 50 ml round bottom flask under air, and CH_2Cl_2 (6 mL) and MeOH (6 mL) were added. Camphorsulfonic acid (19.4 mg, 0.0837 mmol, 0.1 equiv) was introduced and the mixture allowed to stir for 20 h. Volatiles were removed and the resulting residue was purified by silica gel chromatography (30% EtOAc/hexanes) to give **2.88** (127 mg, 0.686 mmol, 82% yield) **TLC R_f:** 0.5 (50% EtOAc/hexanes); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.01–5.78 (m, 1H), 5.75–5.64 (m, 1H), 5.64–5.53 (m, 1H), 5.22–5.10 (m, 2H), 3.96 (dd, *J* = 7.2, 4.6 Hz, 1H), 3.65–3.55 (m, 1H), 2.98 (d, *J* = 4.6 Hz, 1H), 2.65 (d, *J* = 3.2 Hz, 1H), 2.44–2.27 (m, 1H), 2.24–2.06 (m, 1H), 1.73 (ddd, *J* = 6.3, 1.3, 0.6 Hz, 3H), 0.92 (s, 3H), 0.90 (s, 3H).



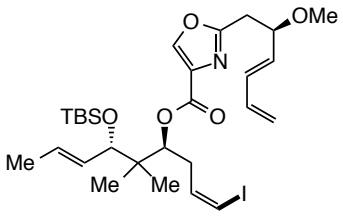
***N*-isopropyl-*N*-(isopropylcarbamoyl)-2-phenethyloxazole-4-carboxamide (2.91):** In a glovebox, a sample of diol **2.88** (30 mg, 0.16 mmol, 1 equiv) was placed in an 8 mL oven-dried vial equipped with a stir bar. Diisopropylcarbodiimide (28 mg, 0.18 mmol 1.1 equiv), diisopropylethyamine (62 mg, 0.36 mmol, 2.2 equiv), and acid **2.86** were added, followed by CH_2Cl_2 (1 mL) Fu's chiral dmap **2.89** was added and the mixture allowed to stir for three days. The volatiles were removed to afford a violet

solid. Urea **2.91** was not isolated, but the ^{1}H NMR spectrum of the crude reaction mixture is included.



2.83

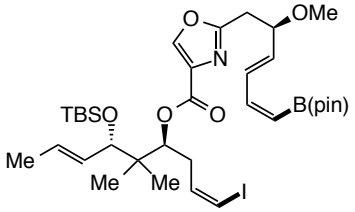
(*R*,*E*)-2-(2-Methoxyhexa-3,5-dien-1-yl)oxazole-4-carboxylic acid (2.83): Ester **2.66** (412 mg, 1.74 mmol, 1 equiv) was placed in a 25 mL round bottom flask under air and thf (8 mL) was added. To this solution was added $Ba(OH)_2 \bullet 8H_2O$ (548 mg, 1.74 mmol, 1 equiv) as a solution in water (8 mL), causing the mixture to turn turbid. The resulting mixture was allowed to stir for 1 h at which time TLC analysis (30% EtOAc/hexanes) indicated complete consumption of the starting material. The reaction was then quenched by the addition of a 2 mL solution of saturated aqueous $NaHSO_4$, which caused precipitation of $BaSO_4$. The mixture was then was washed with EtOAc. The combined clear organic layers were dried over Na_2SO_4, filtered and the volatiles were removed *in vacuo*. The resulting beige solid proved to be unstable to silica gel chromatography and was therefore used without purification. **TLC R_f:** 0.05 (50% EtOAc/hexanes); **IR (neat):** 3400 (br), 2932 (m), 2827 (m), 2681 (w), 2546 (w), 1719 (s), 1587 (m), 1279 (w), 1229 (w), 1162 (m), 1105 (s), 1005 (m), 911 (m), 770 (m), 734 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 11.95 (br. s, 1H), 8.24 (s, 1H), 6.40–6.20 (m, 2H), 5.60 (dd, J = 15.3, 8.2 Hz, 1H), 5.24 (d, J = 15.6 Hz, 1H), 5.14 (d, J = 9.5 Hz, 1H), 4.16 (ap. q, J = 5.9 Hz, 1H), 3.26 (s, 3H), 3.16 (dd, J = 14.9, 7.8 Hz, 1H), 3.06 (dd, 14.9, 5.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 164.6, 163.2, 144.7, 135.6, 134.4, 132.8, 131.4, 118.6, 79.2, 56.4, 34.4; **HRMS (DART):** Calcd for $C_{11}H_{13}NO_4$ [M+H$^+$]: 224.0917; Found: 224.0923; **Specific Rotation:** $[\alpha]_D^{20.2}$ –15.1 (*c* 8.5 $CHCl_3$).



2.93

(1*Z*,4*S*,6*S*,7*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-iodo-5,5-dimethylnona-1,7-dien-4-yl 2-((*R*,*E*)-2-methoxyhexa-3,5-dien-1-yl)oxazole-4-

carboxylate (2.93): Unpurified acid **2.83**(1.74 mmol, theoretical), alcohol **14** (740 mg, 1.74 mmol, 1 equiv) and dmap (425 mg, 3.48 mmol, 2 equiv) were placed in a 25 mL oven-dried round bottom flask containing a stir bar and wrapped in foil under N_2 atm; $CDCl_3$ (6 mL) was added followed by dmap•HCl (551 mg, 3.48 mmol, 2 equiv). To this mixture was added dcc (1.07 g, 5.22 mmol, 3 equiv), and the resulting turbid dark brown solution was allowed to stir for 18 h in the dark until analysis of an aliquot by ^{1}H NMR spectroscopy showed complete consumption of the acid. Volatiles were removed and the resulting tacky yellow solid residue was purified by silica gel chromatography (10% EtOAc/hexanes) to give **2.93** as viscous clear colorless oil (910 mg, 1.45 mmol, 83% yield). **TLC R_f:** 0.55 (20% EtOAc/hexanes). **IR (neat):** 2954 (m), 2930 (m), 2883 (w), 2823 (m), 2119 (w), 1743 (s), 1719 (m), 1583 (m), 1310 (m), 1201 (m), 1101 (s), 1055 (m), 835 (s), 760 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.08 (s, 1H), 6.85–6.16 (m, 2H), 6.19 (ap s, 2H), 5.62 (m, 2H), 5.26 (dd, J = 7.0, 3.6 Hz, 1H), 5.25–5.20 (m, 1H), 5.13 (dd, J = 10.2, 0.9 Hz, 1H), 4.15 (ap. q, J = 7.8 Hz, 1H), 3.83 (d, J = 7.8 Hz, 1H), 3.26 (s, 3H), 3.11 (dd, J = 14.9, 7.8 Hz, 1H), 2.99 (dd, J = 14.9, 5.9 Hz, 1H), 2.61–2.46 (m, 2H), 1.68 (d, J = 5.1 Hz, 3H), 0.97 (s, 3H), 0.94 (s, 3H), 0.87 (s, 9H), –0.02 (s, 3H), –0.05 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 162.7, 160.6, 143.5, 138.0, 135.8, 134.2, 133.4, 131.9, 131.1, 128.4, 118.6, 84.5, 79.3, 79.0, 76.5, 56.5, 42.7, 36.2, 34.8, 26.0, 20.2, 19.3, 18.2, 17.8, –3.5, –5.0; **HRMS (DART):** Calcd for $C_{28}H_{44}INO_5Si$ [M+H$^+$]: 630.2106; Found: 630.2116; **Specific Rotation:** $[\alpha]_D^{21.8}$ +10.0 (*c* 10.0 $CHCl_3$).



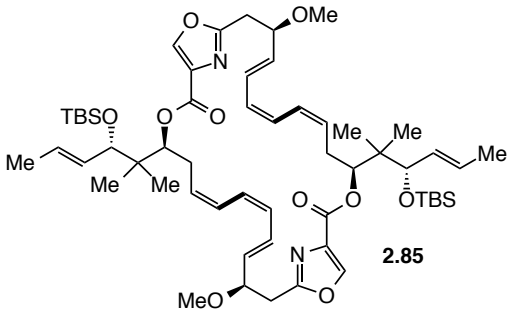
2.58

(1*Z*,4*S*,6*S*,7*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-iodo-5,5-dimethylnona-1,7-dien-4-yl 2-((*R*,3*E*,5*Z*)-2-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-3,5-dien-1-yl)oxazole-4-carboxylate (2.58): ***Ester bond formation procedure:*** Ester **2.57** (19 mg, 0.052 mmol, 1 equiv) was placed in a 10 mL round bottom flask equipped containing a magnetic stir bar, and thf (1 mL) was added.

To this solution was added $Ba(OH)_2 \bullet 8H_2O$ (16 mg, 0.052 mmol, 1 equiv) as a solution in 1 mL water. The resulting turbid dark yellow solution was allowed to stir for 4 h, at which time TLC analysis (30% EtOAc/hexanes) indicated complete substrate consumption. The reaction was then quenched by the addition of 2 mL of a saturated solution of aqueous $NaHSO_4$; this resulted in precipitation of $BaSO_4$. The mixture was washed with EtOAc, and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford **2.92** as pale yellow oil (14 mg, 0.0400 mmol, 76% yield). Partial characterization data: **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.94–8.92 (br. proton, 1H), 8.24 (s, 1H), 7.06 (dd, *J* = 15.3, 11.0 Hz, 1H), 6.83 (dd, *J* = 13.3, 11.0 Hz, 1H), 5.71 (dd, *J* = 15.3, 8.1 Hz, 1H), 5.46 (d, *J* = 13.1 Hz, 1H), 4.30–4.24 (m, 1H), 3.28 (s, 3H), 3.13 (dd, *J* = 15.2, 9.6 Hz, 1H), 3.03 (dd, *J* = 15.2, 5.1 Hz, 1H), 1.29 (s, 12H). Acid **2.92** (0.040 mmol) and alcohol **2.56** (18.7 mg, 0.0441 mmol, 1 equiv), dmap (24 mg, 0.200 mmol, 5 equiv) were combined in a 25 mL oven-dried round bottom flask containing a stir bar and wrapped in foil under N_2 atm; $CDCl_3$ (0.6 mL) was then added followed by dmap•HCl (25 mg, 0.160 mmol, 4 equiv). To this mixture was added dcc (41 mg, 0.200 mmol, 5 equiv). Analysis by ^{1}H NMR spectroscopy showed incomplete consumption of starting materials at 24, 48 and 168 h. After 168 h, no decomposition was noted by ^{1}H NMR spectroscopy. Accordingly, the mixture was filtered through Celite®, the volatiles were removed and the resulting brown oil was purified by silica gel chromatography (10% EtOAc/hexanes) to give **17** as clear colorless oil (12 mg, 0.016 mmol, 40% yield, >98% *Z*). Characterization data is in agreement with material prepared by the olefin metathesis route described below.

Olefin metathesis procedure: Tetraene **2.93** (196 mg, 0.311 mmol, 1 equiv) was placed in an oven-dried 25 ml round bottom flask containing a stir bar. The vessel was then placed in a N_2-filled glovebox and subjected to azeotriopic removal of moisture with three 5 mL portions of anhydrous benzene. At this time, vinyl–B(pin) (240 μL, 1.42 mmol, 4.5 equiv) and a 0.1 M solution of Mo complex **2.45** in benzene (283 μL, 0.0283 mmol, 0.091 equiv) were added. A vacuum adapter was fitted to the flask, and the resulting orange solution was placed under a 100 torr vacuum and allowed to stir for 2 h. At this time, the mixture became sufficiently viscous as to impede proper stirring.

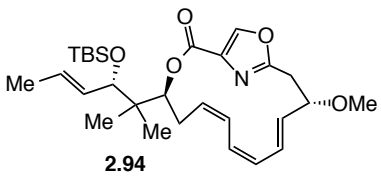
Analysis of a 1 mg aliquot sample by ^{1}H NMR spectroscopy indicated ~70% conversion to the desired product. Vinyl–B(pin) (150 μL, 0.811 mmol, 2.8 equiv) was added and the mixture was re-subjected to 100 torr vacuum. After 2 h, analysis by ^{1}H NMR spectroscopy showed >95% conversion and formation of the desired product with 95:5 *Z*:*E* selectivity. The resulting brown oil was purified by silica gel chromatography (10% EtOAc/hexanes) to afford **17** as clear colorless oil (214 mg, 0.283 mmol, 91% yield, >98% *Z*). **NOTE**: Care must be taken in chromatography to ensure removal of the byproduct produced from homocoupling of vinyl–B(pin), as this byproduct can participate in the cross-coupling process described below. **TLC R_f:** 0.50 (20% EtOAc/ hexanes); **IR (neat):** 2976 (m), 2930 (m), 2883 (m), 2856 (m), 2823 (m), 1743 (m), 1718 (m), 1587 (m), 1470 (m), 1331 (m), 1301 (s), 1213 (w), 1142 (s), 1104 (s), 1054 (m), 969 (m), 834 (s), 774 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.07 (s, 1H), 7.06 (dd, *J* = 15.3, 11.0 Hz, 1H), 6.82 (dd, *J* = 13.3, 11.4 Hz, 1H), 6.20–6.15 (m, 2H), 5.68 (dd, *J* = 15.2, 8.2 Hz, 1H), 5.59–5.41 (m, 3H), 5.25 (dd, *J* = 9.8, 3.5 Hz, 1H), 4.25–4.22 (m, 1H), 3.82 (d, *J* = 7.8 Hz), 3.25 (s, 3H), 3.08 (dd, *J* = 14.9, 8.6 Hz, 1H), 2.99 (dd, *J* = 10.2, 4.8 Hz, 1H), 2.60–2.45 (m, 2H), 1.66 (d, *J* = 5.1 Hz, 3H), 1.28–1.23 (m, 12 H), 0.96 (s, 3H), 0.93 (s, 3H), 0.86 (s, 9H), –0.03 (s, 3H), –0.06 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 162.9, 160.6, 148.9, 143.4, 138.0, 135.7, 133.7, 133.4, 131.1, 128.4, 84.5, 83.2, 79.3, 79.0, 76.5, 56.6, 42.7, 36.2, 34.8, 25.9, 24.8, 20.2, 19.3, 18.2, 17.8, –3.5, –5.0; **HRMS (DART):** Calcd for $C_{34}H_{55}BINO_7Si$ [M+H$^+$]: 756.2958; Found: 756.2964; **Specific Rotation:** $[\alpha]_D^{22.6}$ +9.0 (*c* 10.0 $CHCl_3$).



2.85

(1^2*Z*,14^2*Z*,4*S*,6*Z*,8*Z*,10*E*,12*R*,17*S*,19*Z*,21*Z*,23*E*,25*R*)-4,17-bis((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylhex-4-en-2-yl)-12,25-dimethoxy-3,16-dioxa-1(4,2),14(2,4)-dioxazolacyclohexacosaphane-6,8,10,19,21,23-hexaene-2,15-dione

(2.85): The reaction was performed in a N_2-filled glovebox. A solution of Cs_2CO_3 (5.6 mg, 0.0172 mmol, 1 equiv) in dry/deoxygenated methanol (4.3 mL) was used to dissolve dienyl–B(pin)/alkenyl–iodide **2.58** (13.0 mg, 0.0172 mmol, 1 equiv) in a 25 mL round bottom flask. To the resulting pale yellow solution was added $Pd[(o\text{-tol})_3P]_2$ (0.6 mg, 0.000875 mmol, 0.05 equiv), which did not completely dissolve. The resulting mixture was allowed to stir at 22 °C in the dark for 24 h, at which time TLC analysis indicated complete consumption of **17**. The mixture was filtered through Celite®, and the volatiles were removed *in vacuo* to afford a yellow residue. Analysis of the 400 MHz ^{1}H NMR spectrum of the unpurified mixture (CD_3OD) indicated the presence of an approximately 9:1 ratio of **2.85**:oligomeric **S3**; the 15-membered byproduct **2.94** was not detected (<2%). Purification was accomplished by silica gel chromatography (50% EtOAc/ hexanes) to afford **2.85** (5.2 mg, 0.0052 mmol, 60% yield) as white film. **TLC R_f:** 0.15 (20% EtOAc/ hexanes); **IR (neat):** 2955 (m), 2929 (m), 2856 (m), 1742 (s), 1584 (m), 1471 (m), 1361 (m), 1310 (w), 1170 (m), 1101 (s), 1056 (m), 972 (w), 835 (m) cm^{-1}; **^{1}H NMR (400 MHz, CD_3OD):** δ 8.24 (s, 2H), 6.52 (dd, J = 14.9, 8.6 Hz, 2H), 6.41 (ap. t, J = 11.3 Hz, 2H), 6.30 (ap. q, J = 11.0 Hz, 2H), 5.93 (ap q., J = 11.3 Hz, 2H), 5.68–5.43 (m, 8H), 5.24 (dd, J = 11.0, 2.0 Hz), 4.16 (ap. q, J = 5.9 Hz, 2H), 3.93 (ap. q, J = 8.6 Hz, 2H), 3.24 (s, 6H), 3.02 (dd, J = 15.3, 7.0 Hz, 2H), 2.79 (dd, J = 15.7, 5.5 Hz, 2H), 2.72 (ap. q, J = 14.1 Hz, 2H), 2.40 (dd, J = 13.7, 5.9 Hz, 2H), 1.72 (d, J = 5.9 Hz, 6H), 1.03 (s, 6H), 0.97 (s, 6H), 0.90 (s, 18H), 0.03 (s, 6H), 0.00 (s, 6H); **^{13}C NMR** (100 MHz, CD_3OD): δ 164.1, 162.1, 145.7, 134.2, 132.5, 130.9, 129.9, 129.8, 129.3, 127.3, 127.4, 126.8, 80.5, 80.4, 78.4, 56.8, 43.6, 36.0, 30.8, 29.5, 27.3, 26.5, 25.0, 20.4, 19.5, 19.1, 17.9, –3.2, –4.7; **HRMS (ESI+):** Calcd for $C_{56}H_{86}N_2O_{10}Si_2$ [M+H$^+$]: 1003.5894; Found: 1003.5890; **Specific Rotation:** $[\alpha]_D^{20}$ –108 (*c* 0.73 $CHCl_3$).

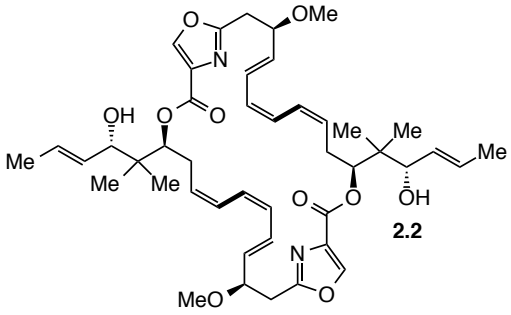


2.94

(1^2*Z*,4*S*,6*Z*,8*Z*,10*E*,12*R*)-4-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylhex-4-en-2-yl)-12-methoxy-3-oxa-1(4,2)-oxazolacyclotridecaphane-6,8,10-trien-2-one (2.94): TLC R_f: 0.20 (20%

EtOAc/hexanes); **IR (neat):** 2954 (m), 2930 (m), 2855 (m), 1745 (m), 1579 (w), 1470 (w), 1310 (w), 1252 (w), 1104 (s), 1056 (m), 981 (m), 835 (m), 774 (m) cm^{-1}; **^{1}H NMR (400 MHz, CD_3OD):** δ 8.19 (s, 1H), 6.21 (t, J = 9.4 Hz, 1H), 6.05 (t, J = 9.8 Hz, 1H), 5.94–5.75 (m, 2H), 5.56–5.47 (m, 2H), 5.40–5.27 (m, 2H), 5.24 (dd, J = 11.4, 2.0 Hz, 1H), 4.05–3.97 (m, 1H), 3.92 (d, J = 8.2 Hz, 1H), 3.38 (dd, J = 13.3, 5.9 Hz, 1H), 3.34 (s, 3H), 2.79 (dd, J = 13.3, 10.2 Hz, 1H), 2.54 (q, J = 12.5 Hz, 1H), 2.26–2.20 (m, 1H), 1.71 (dd, J = 6.3, 1.2 Hz, 3H), 1.00 (s, 3H), 0.95 (s, 3H), 0.91 (s, 9H), 0.02 (s, 3H), –0.01 (s, 3H); **^{13}C NMR (100 MHz, CD_3OD):** δ 163.7, 162.6, 145.5, 135.0, 132.6, 132.0, 131.7, 131.3, 130.2, 129.8, 128.1, 126.8, 83.3, 80.1, 78.7, 57.2, 43.1, 35.6, 30.9, 26.5, 20.2, 19.4, 19.1, 17.9, –3.1, –4.7; **LRMS (ESI+):** Calcd for $C_{28}H_{43}NO_5Si$ [M+Na^+]: 524.2803; Found: 524.72; **Specific Rotation:** $[\alpha]_D^{21.2}$ –158 (*c* 0.57 CH_3OH).

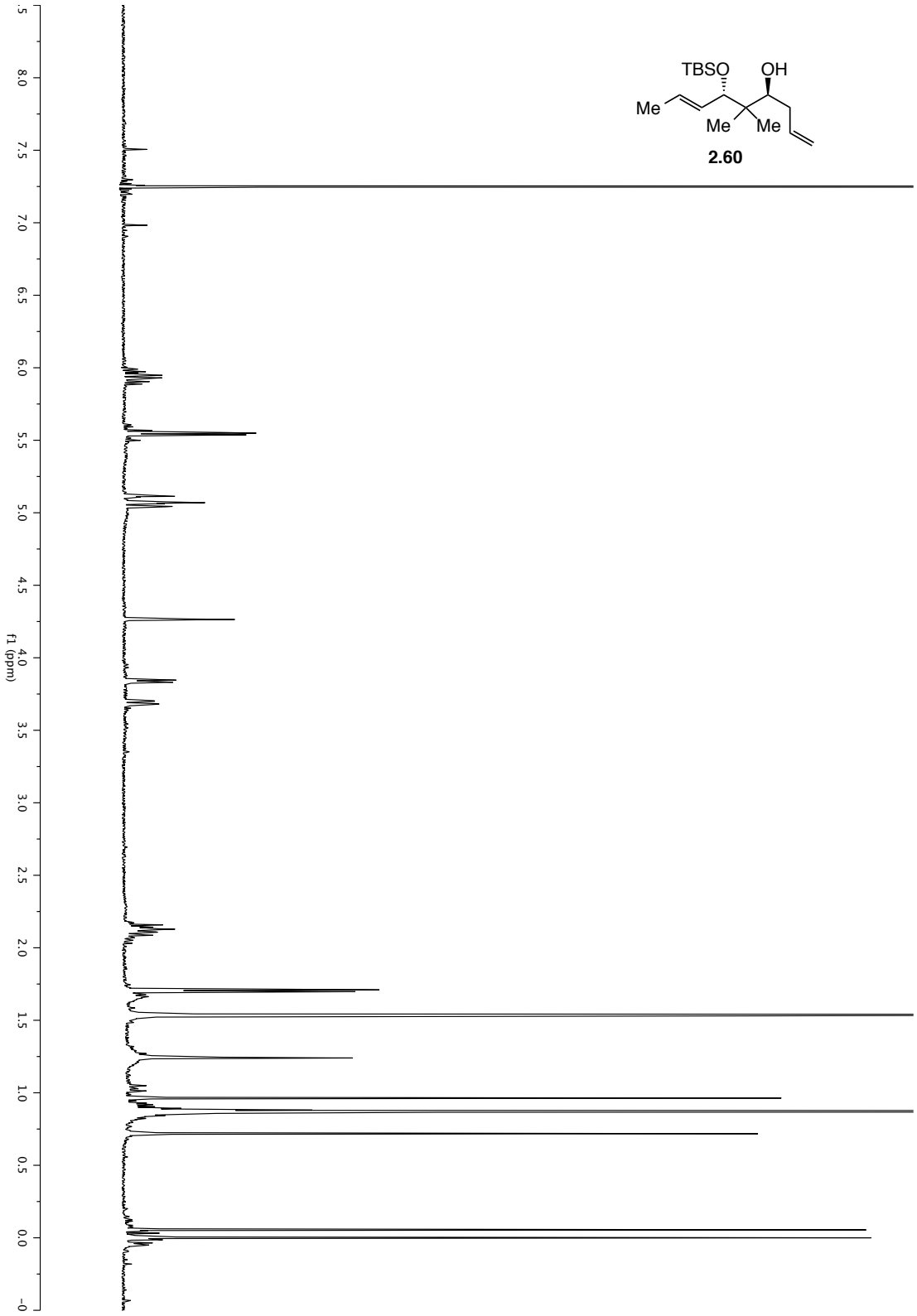
Oligomeric byproduct TLC R_f: 0.05 (20% EtOAc/ hexanes); The peaks on the ^{1}H NMR spectrum are broad, and are given as ranges: **^{1}H NMR (400 MHz, CD_3OD):** δ 8.38–8.28 (1H), 6.73–6.61 (1H), 6.49–6.39 (1H), 6.34–6.24 (1H), 6.00–6.59 (1H), 5.64–5.45 (3H), 5.26–5.18 (1H), 4.19–4.11 (1H), 3.91 (d, J = 8.2 Hz, 1H), 3.24–3.17 (3H), 3.12–2.91 (m, 2H), 2.74–2.40 (2H), 1.74–1.65 (m, 3H), 1.01–0.97 (3H), 0.89–0.86 (9H), 0.02–0.05 (6H).



2.2

Disorazole C_1 (2.2): Bis-silyl ether **2.85** (9.7 mg, 0.0097 mmol, 1 equiv) was placed in a 25 mL recovery flask, and 2 mL methanol was added. The solution was allowed to cool to 0 °C and 0.25 mL of an aqueous solution of H_2SiF_6 (30% in water) was added. The mixture was allowed to stir in the dark at 4 °C for 72 h, after which time TLC analysis (60% EtOAc/hexanes, CAM visualization) showed no spots less polar than the desired product. At this time, 50 mL EtOAc was added followed by two 10 mL portions of a saturated aqueous solution of $NaHCO_3$ and then a

solution of brine; the organic layer was subsequently dried over Na_2SO_4, solids and the voaltiles were removed by filtration and *in vacuo*, respectively. Purification of the resulting yellow oily residue by silica gel chromatography afforded disoarzole C_1 (5.1 mg, 0.0066 mmol, 68% yield) as white film. Characterization data were in agreement with that obtained by Wipf and Graham[3a]. **TLC R_f:** 0.25 (60% EtOAc/hexanes); **IR (neat):** 3433 (br), 2926 (m), 1736 (m), 1671 (m), 1583 (m), 1466 (w), 1448 (w), 1370 (w), 1311 (w), 1220 (w), 1173 (m), 1106 (s), 987 (m) cm^{-1}; **^{1}H NMR (600 MHz, CD_3OD):** δ 8.23 (s, 2H), 6.48 (dd, *J* = 15.3, 11.4 Hz, 2H), 6.38 (app t, *J* = 11.3 Hz, 2H), 6.27 (dd, *J* = 11.4, 11.1 Hz, 2H), 5.90 (dd, *J* = 11.2, 10.9 Hz, 2H), 5.66 (dq, *J* = 15.3, 6.3 Hz, 2H), 5.57 (ddd, *J* = 15.2, 7.8, 1.4 Hz, 2H), 5.54 (dd, *J* = 15.0, 8.3 Hz, 2H), 5.48 (app dt, *J* =10.0, 6.7 Hz, 2H), 5.24 (dd, *J* = 11.3, 2.0 Hz, 2H), 4.11 (ddd, *J* = 7.8, 7.2, 5.5 Hz, 2H), 3.82 (d, *J* = 7.8 Hz, 2H), 3.20 (s, 6H), 2.98 (dd, *J* = 15.3, 7.0 Hz, 2H), 2.76 (dd, *J* = 15.5, 5.4 Hz, 2H), 2.67 (dd, *J* = 13.7, 10.7 Hz, 2H), 2.37 (dd, *J* = 14.1, 6.3 Hz, 2H), 1.68 (dd, *J* = 6.4, 1.3 Hz, 6H), 0.99 (s, 6H), 0.93 (s, 6H); **^{13}C NMR (150 MHz, CD_3OD):** δ 164.13, 162.26, 145.84, 134.15, 134.08, 131.67, 130.89, 129.98, 129.64, 129.30, 127.37, 126.80, 80.56, 78.75, 77.84, 56.83, 42.70, 35.98, 29.24, 23.75, 19.24, 19.35, 18.04; **HRMS (ESI+):** Calcd for $C_{44}H_{58}N_2O_{10}$ [M+Na^+]: 797.3984 Found: 797.3980; **Specific Rotation:** $[\alpha]_D^{22.0}$ –148 (*c* 0.27 $CHCl_3$).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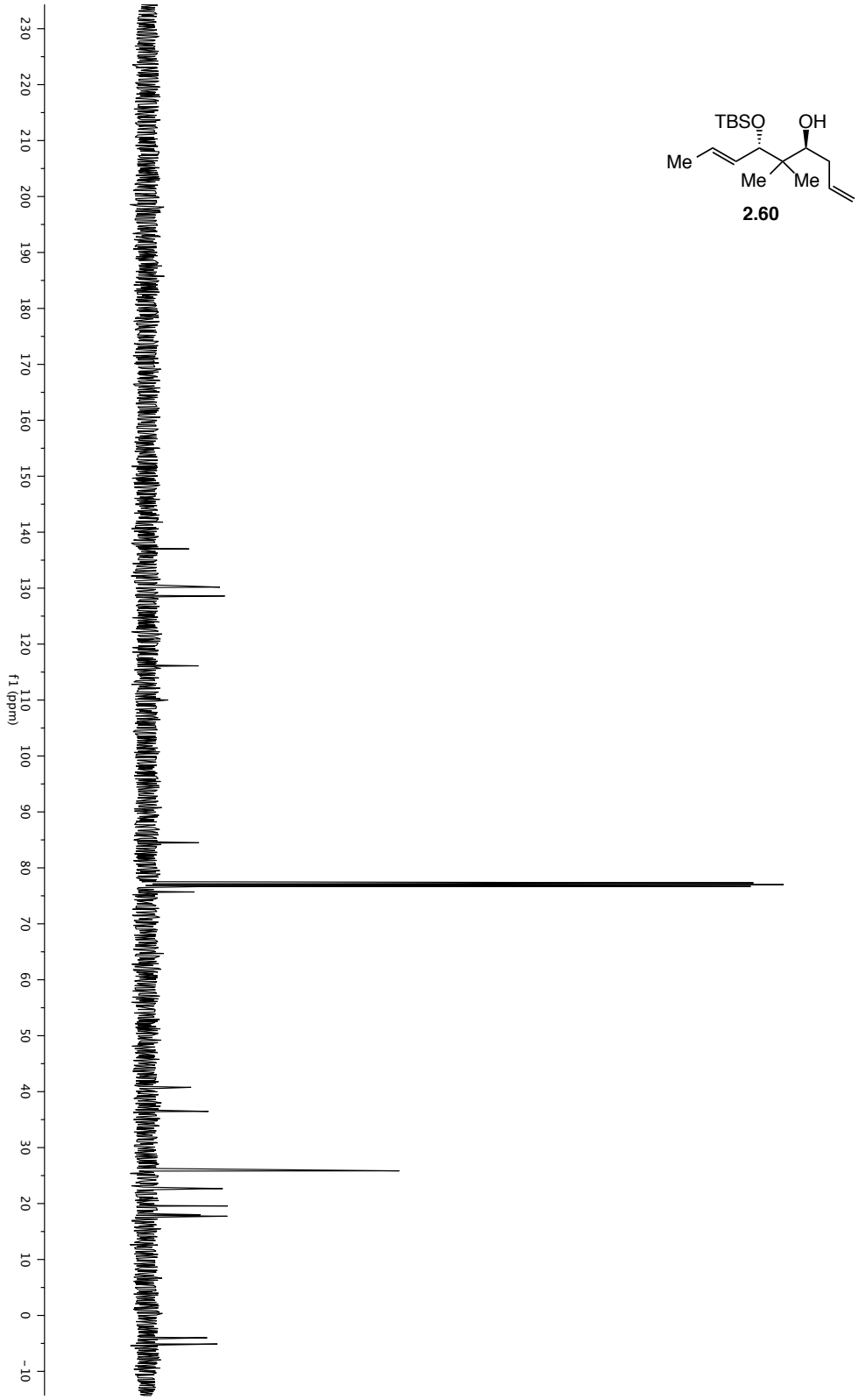
Me
Me
Me
2.60
f1 (ppm)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OH
Me
Me
Me
2.60
f1 (ppm)
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220
210
200
190
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0
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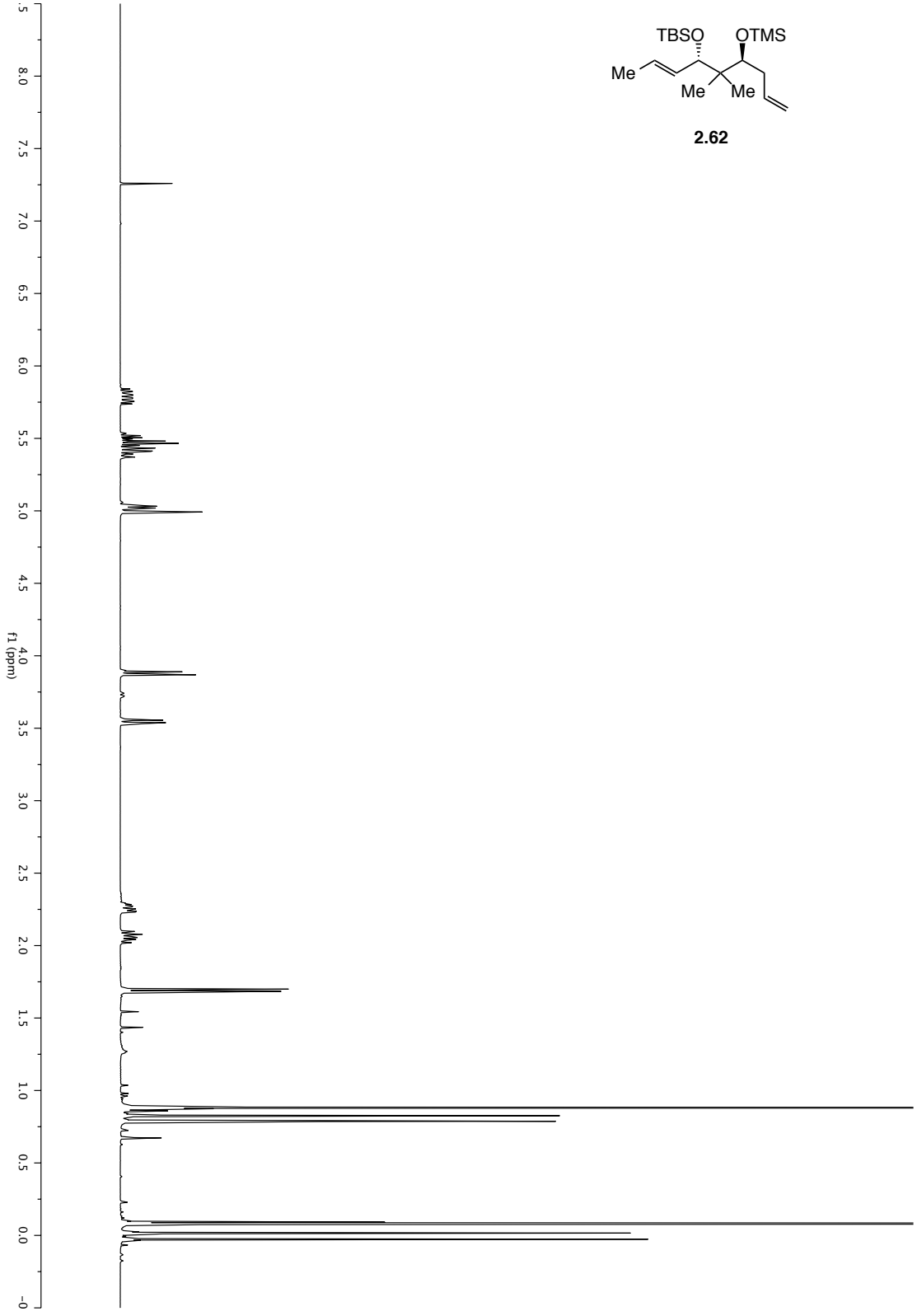
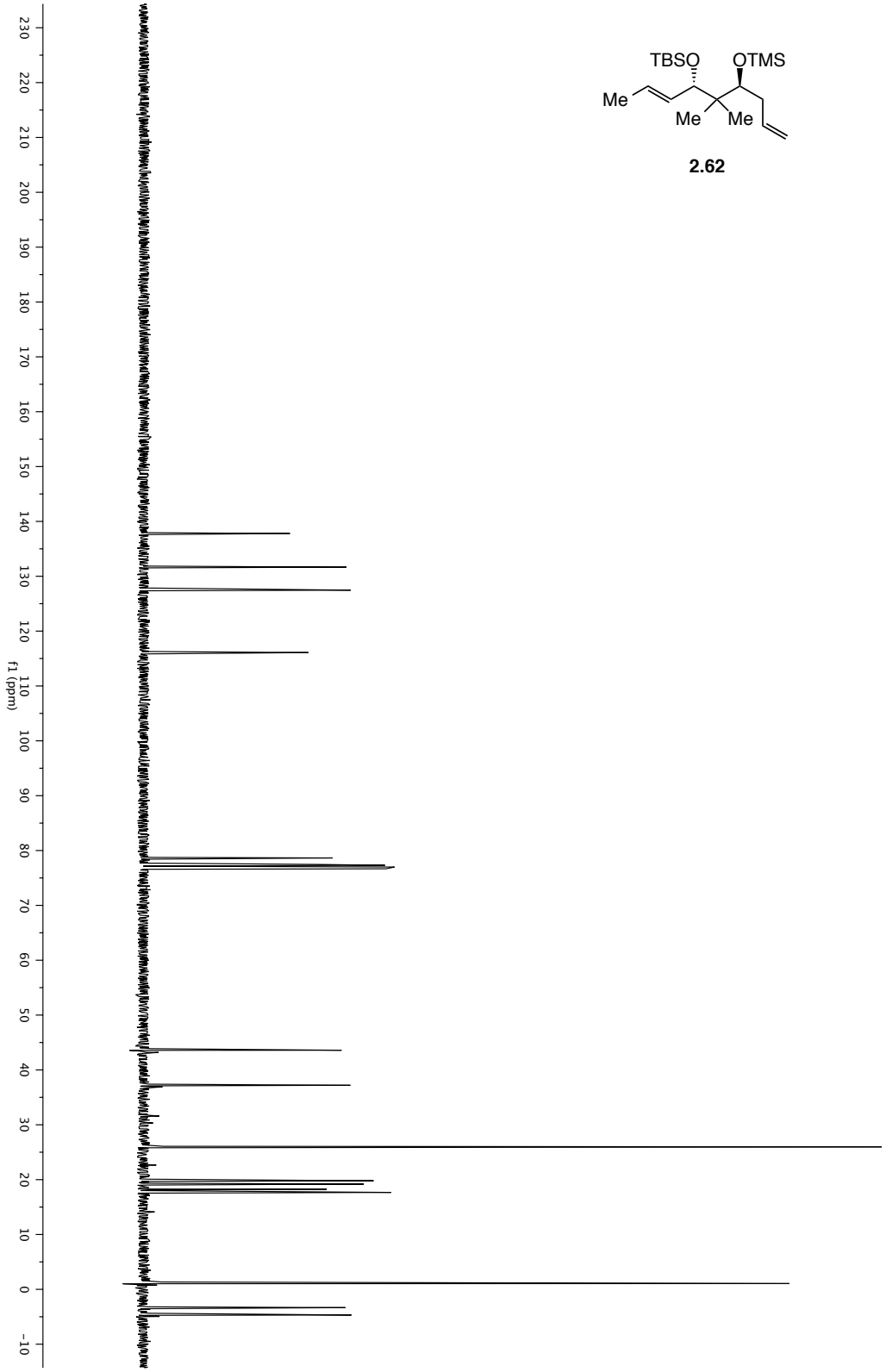
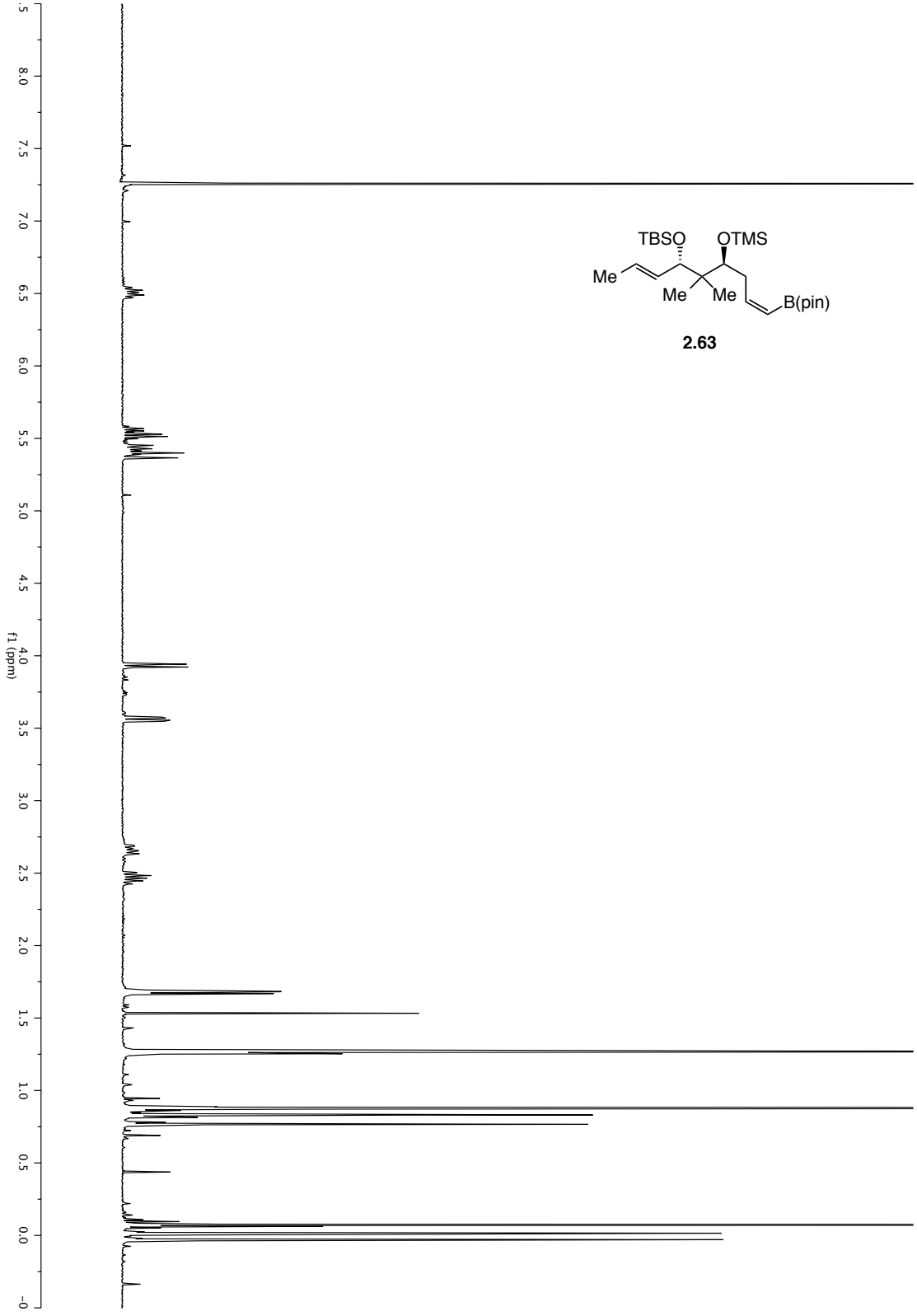


2.62



2.62



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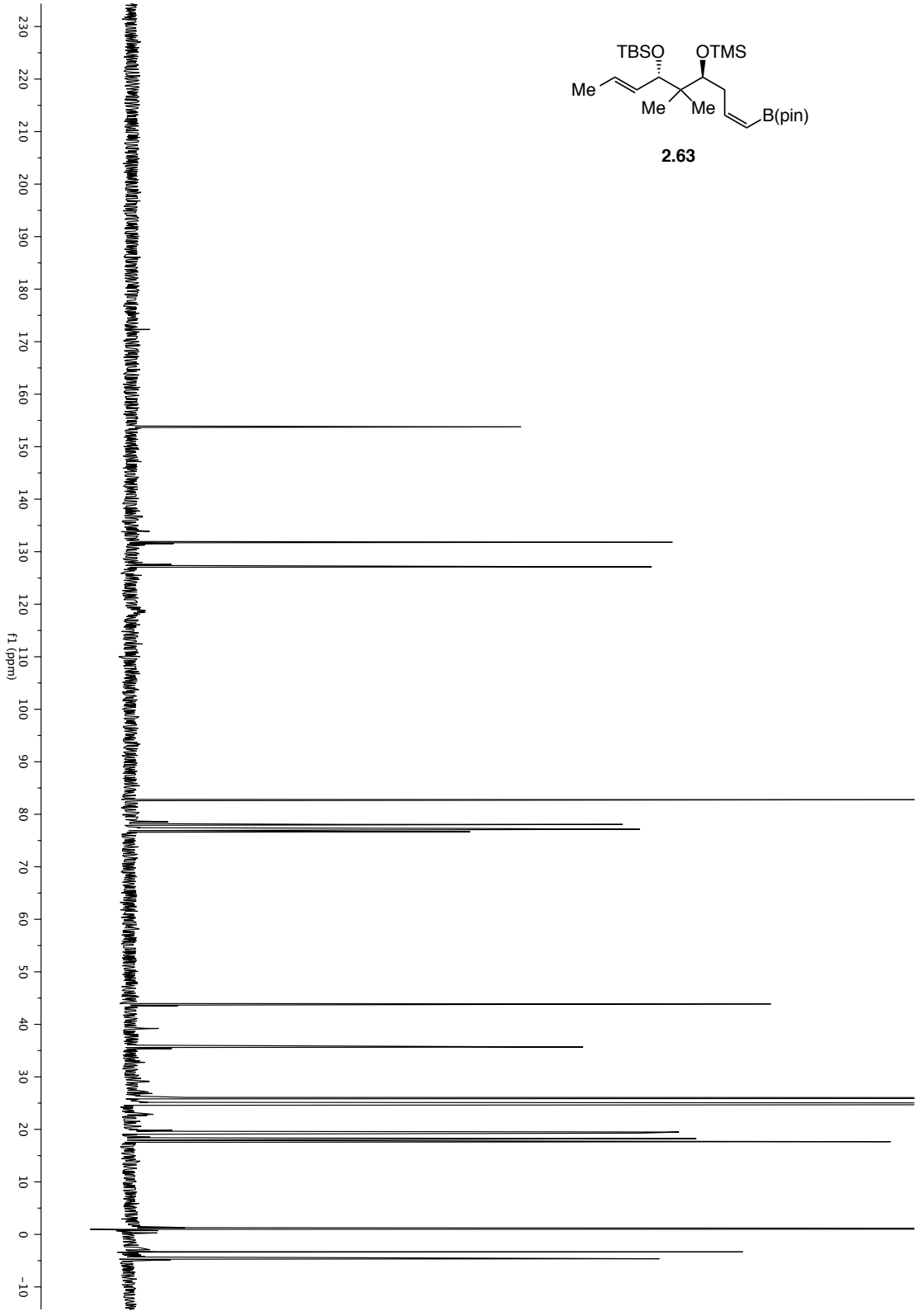

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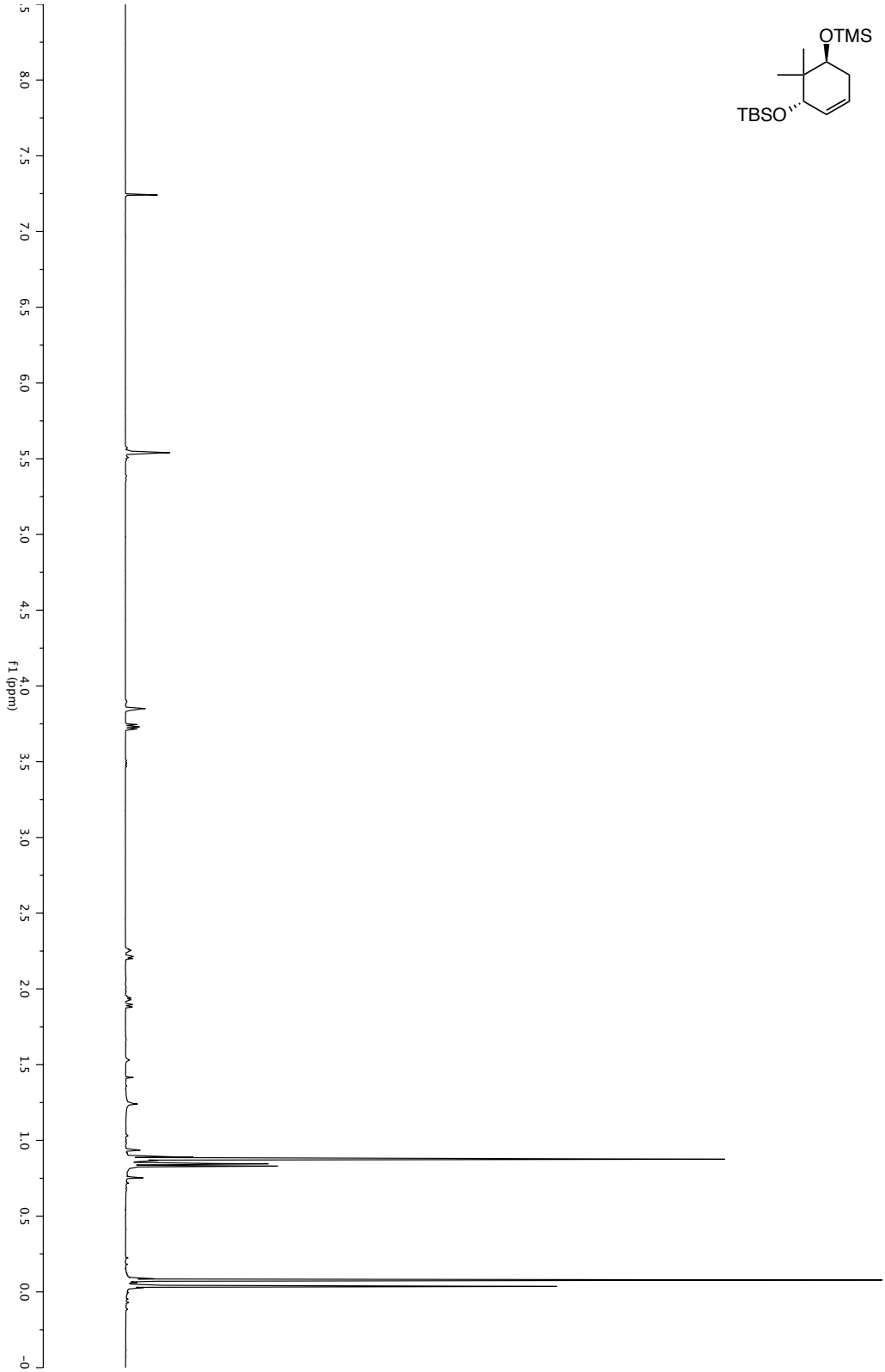
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7.0
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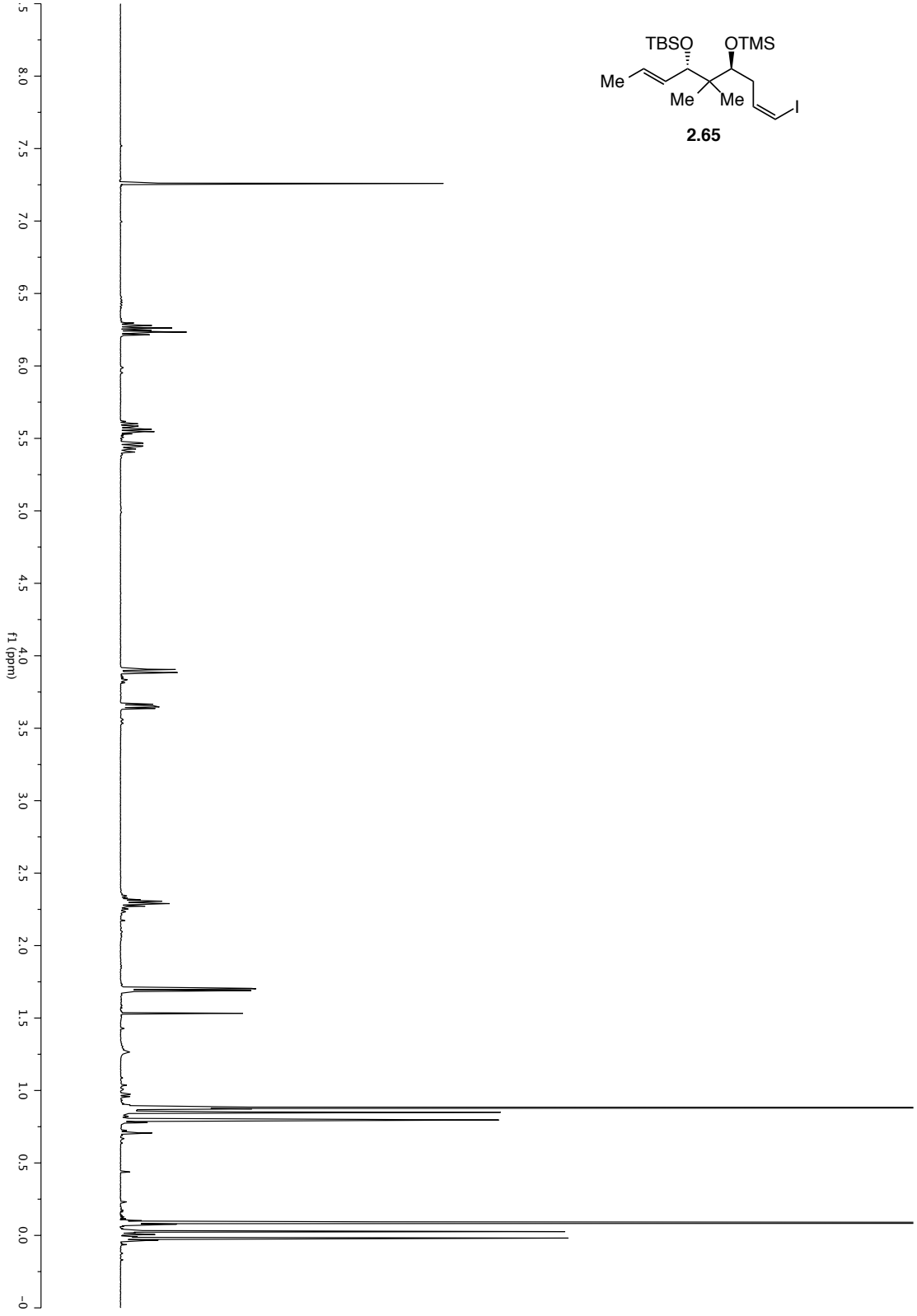
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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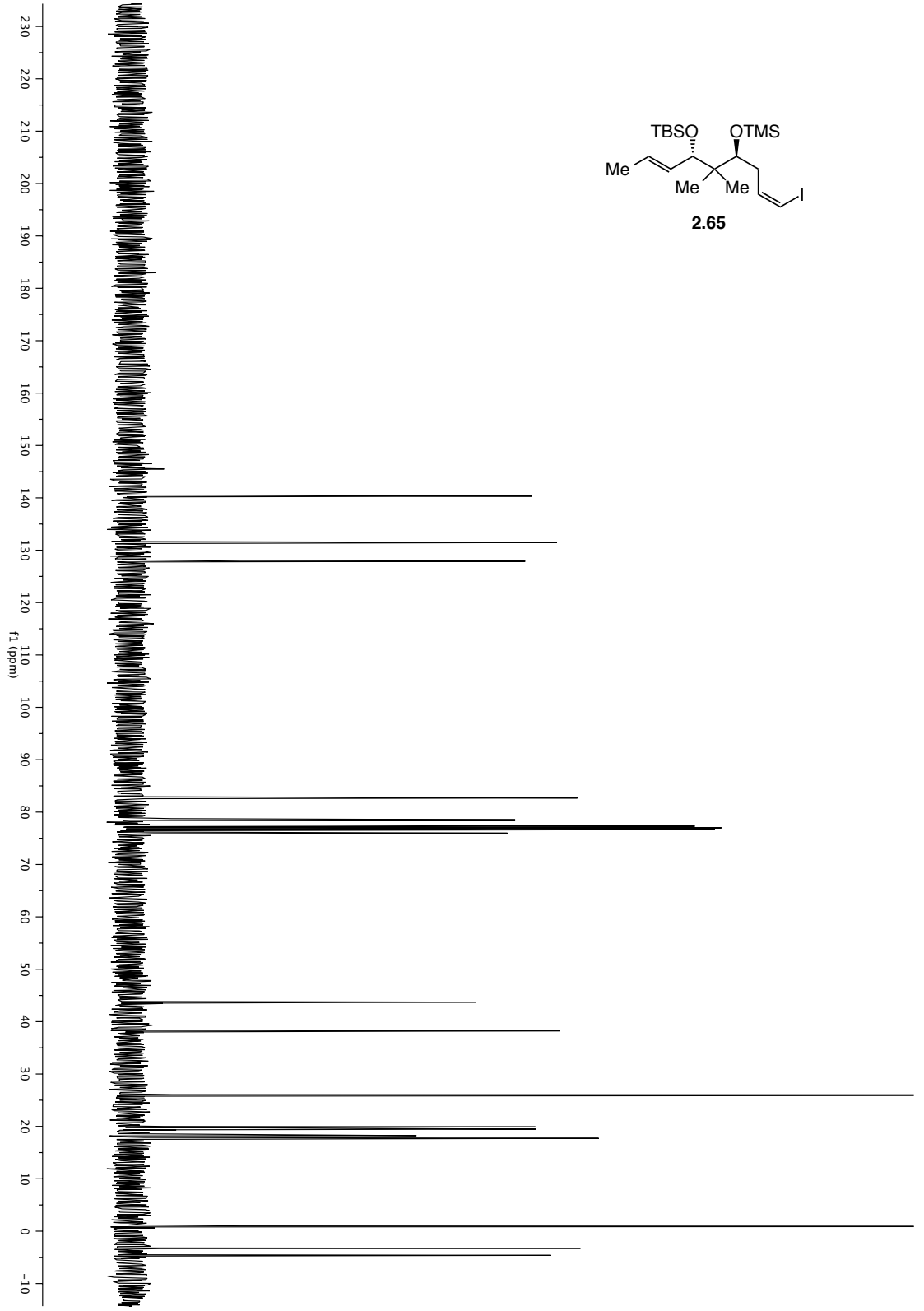
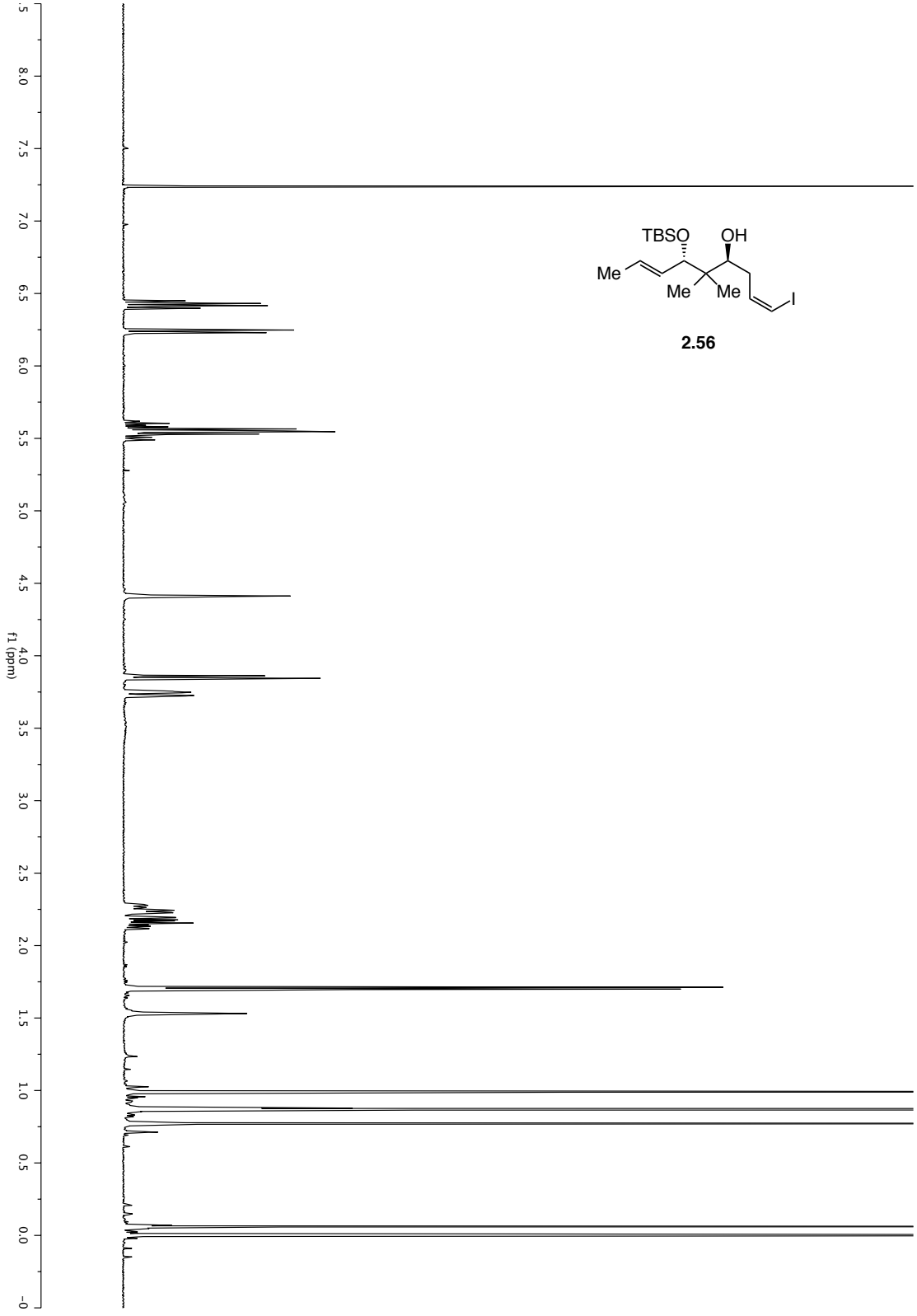
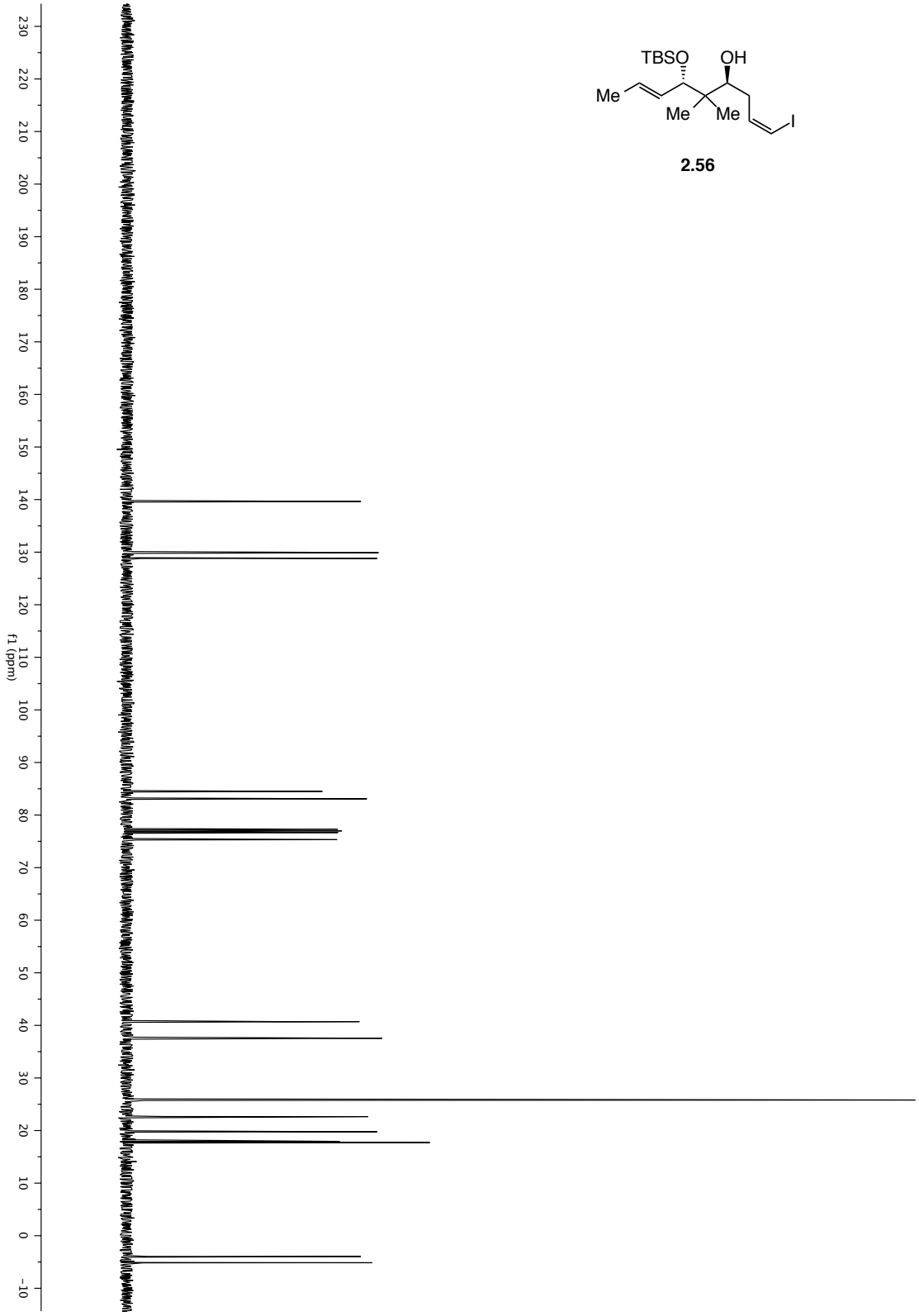
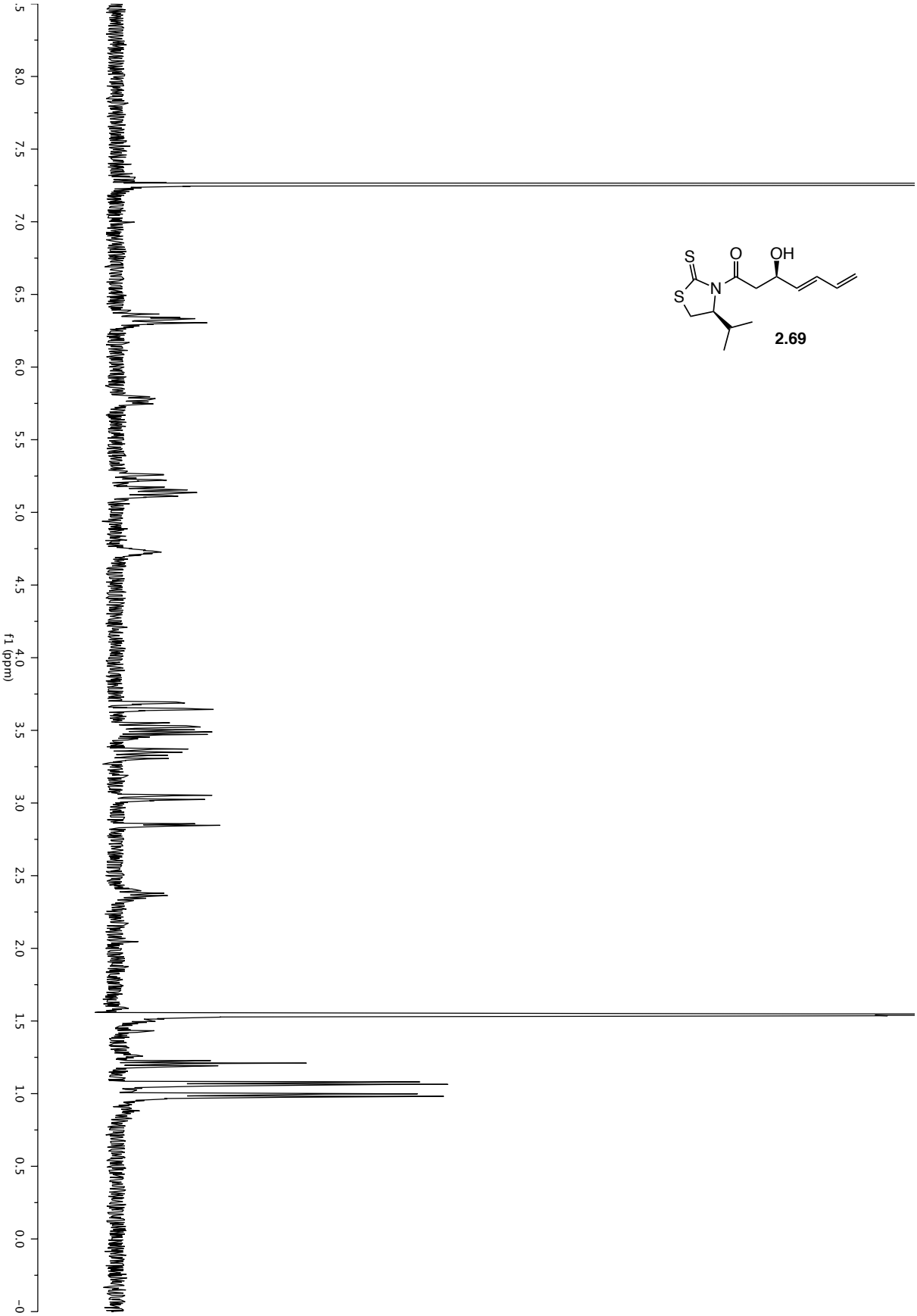
OTMS
Me
Me
Me
I
2.65
f1 (ppm)


TBSO
OTMS
Me
Me
Me
I
2.65
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10



2.56


TBSO
OH
Me
Me
Me
I
2.56
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10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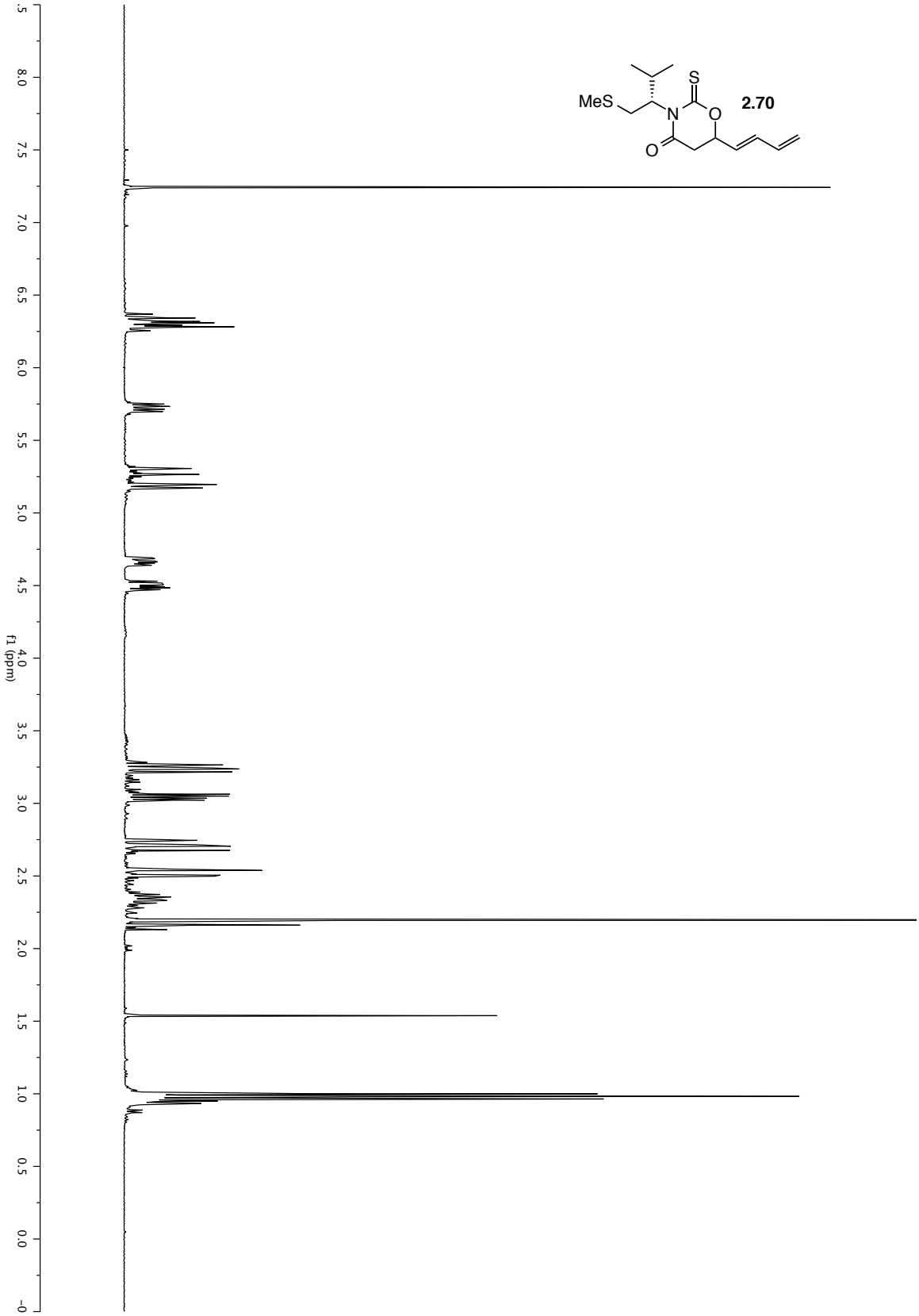
O
OH
N
S
2.69
f1 (ppm)


MeS
S
N
O
O
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f1 (ppm)
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7.5
7.0
6.5
6.0
5.5
5.0
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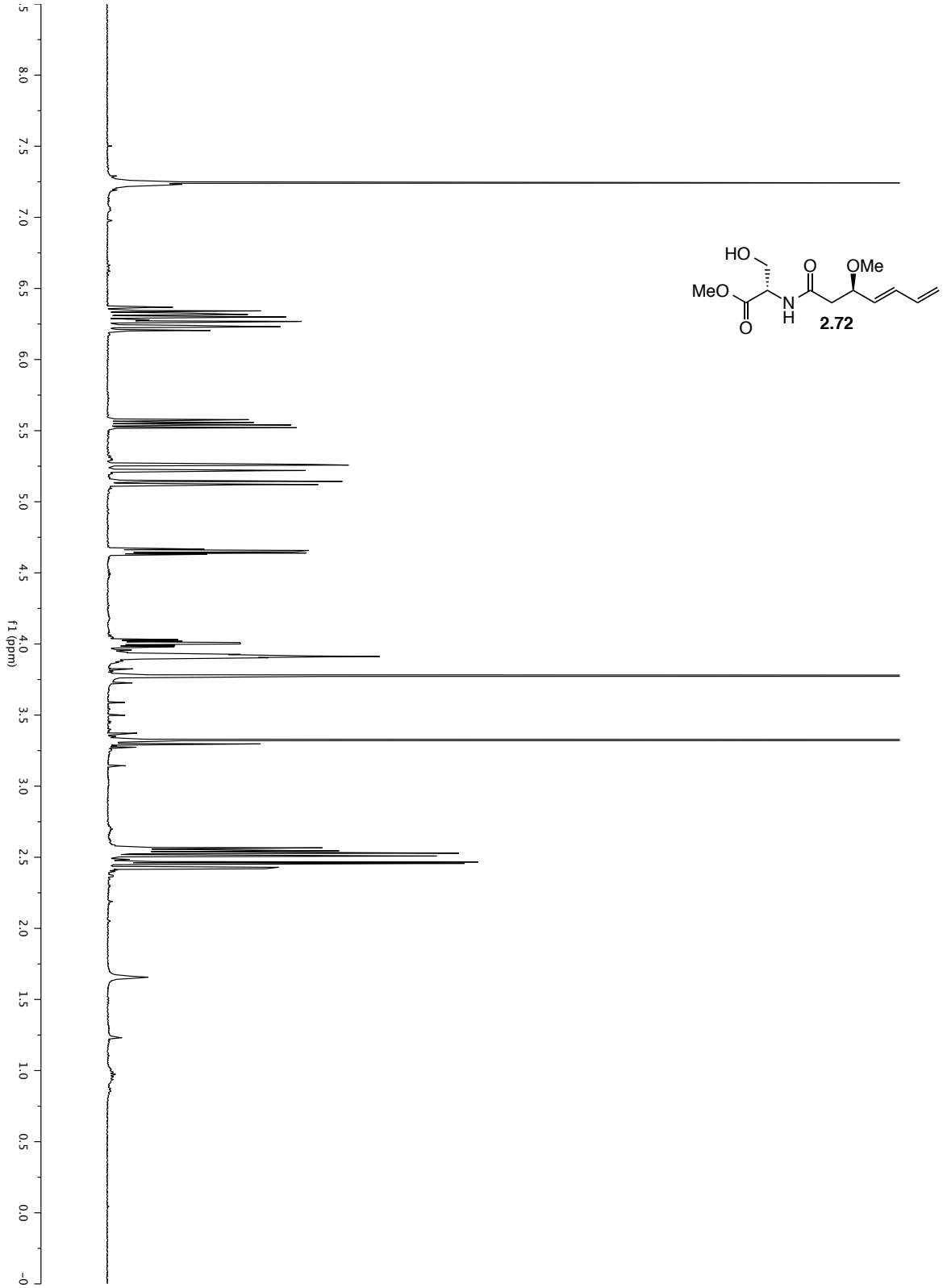
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0


HO
O
OMe
MeO
N
H
O
2.72
f1 (ppm)
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7.5
7.0
6.5
6.0
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5.0
4.5
4.0
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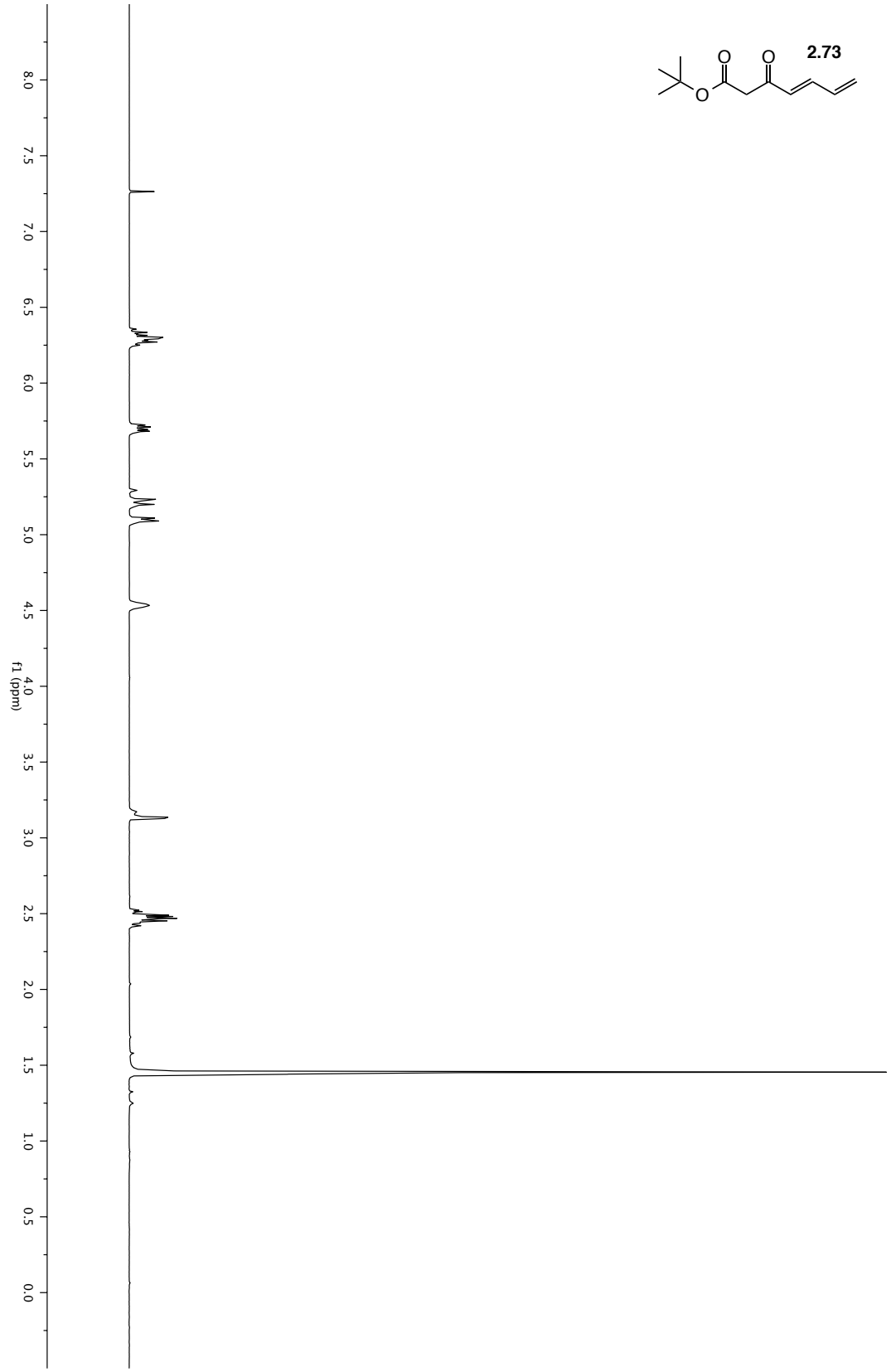
2.0
1.5
1.0
0.5
0.0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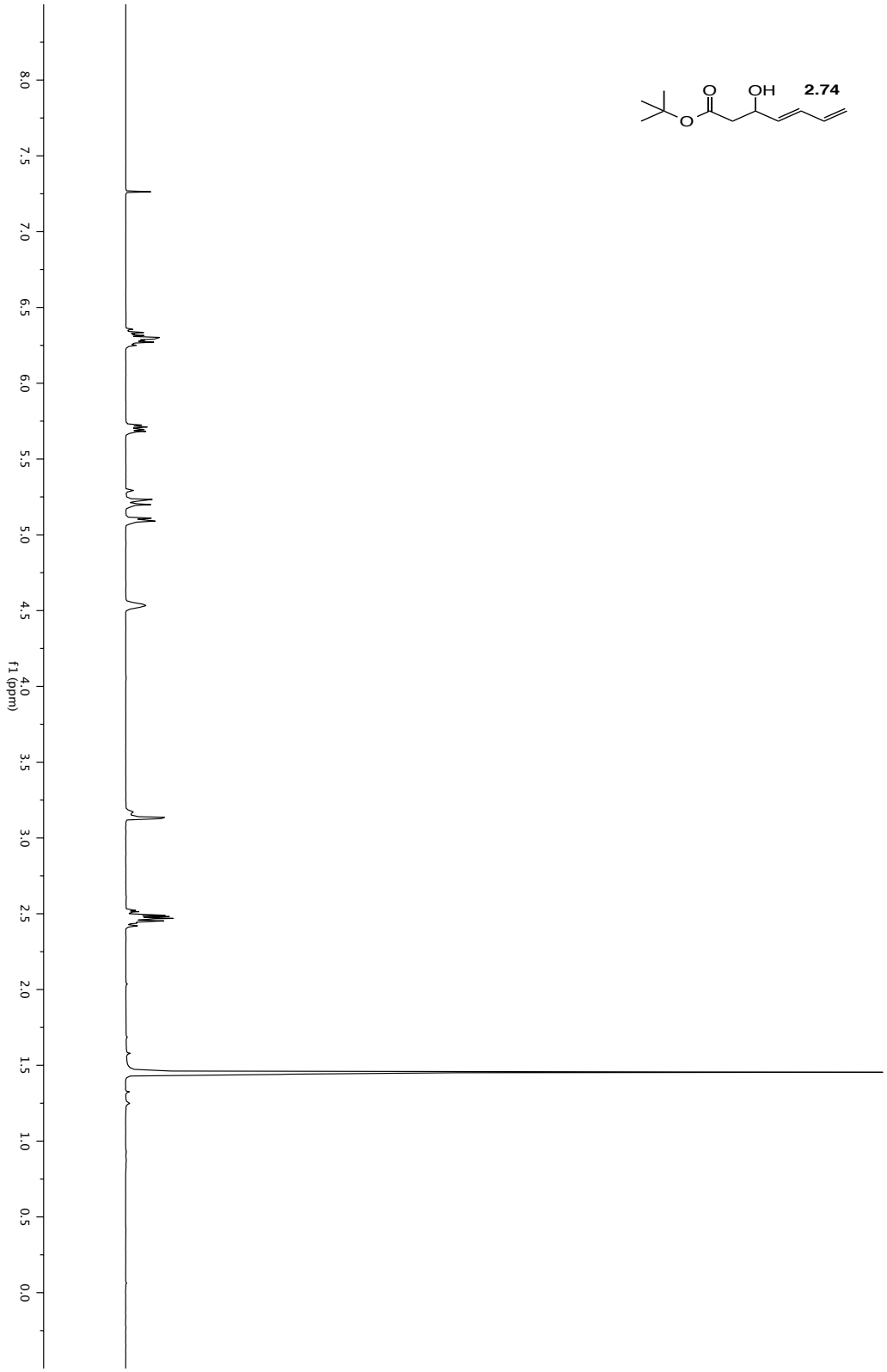
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
OH
2.74
O
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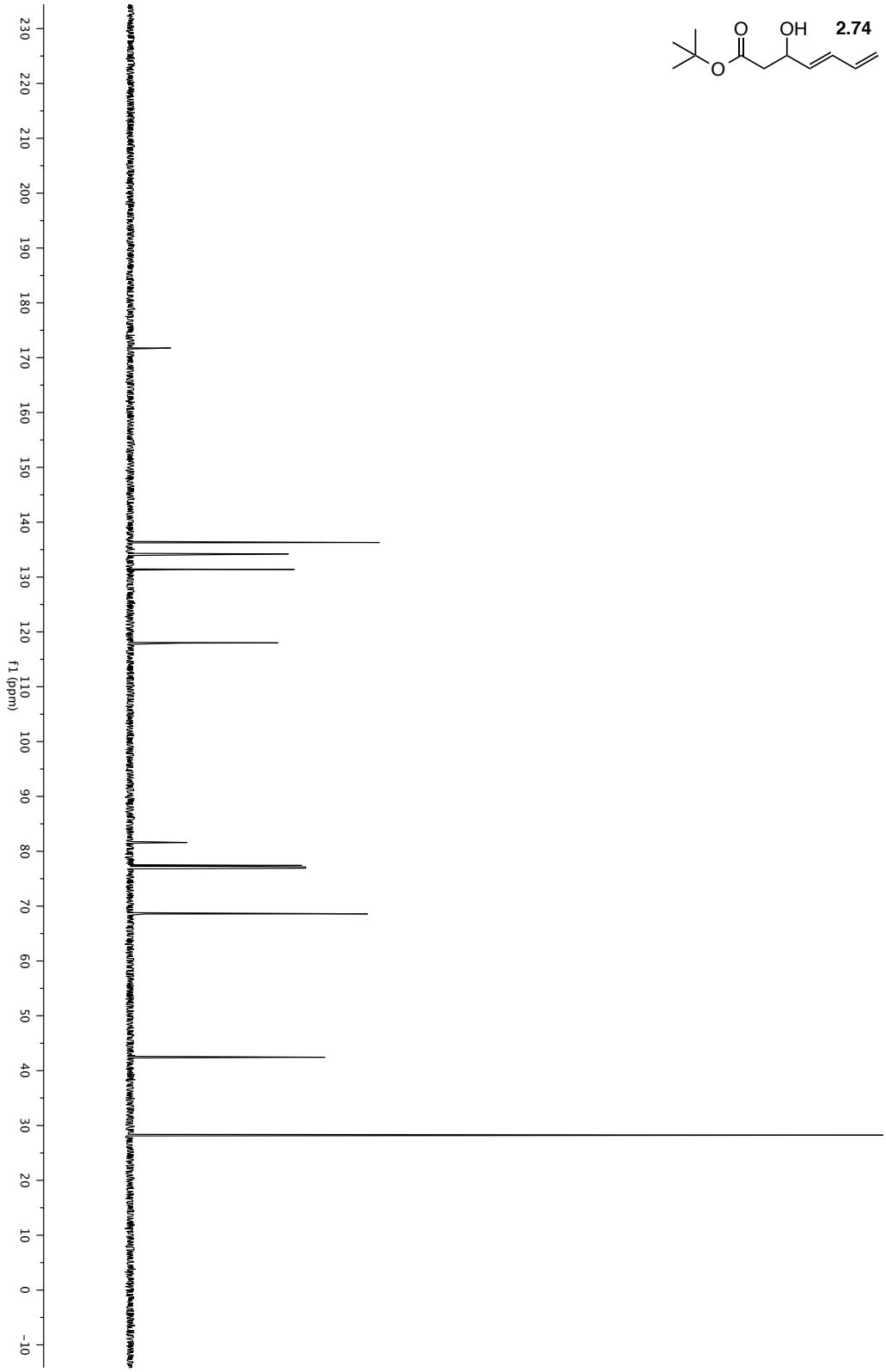
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
OH
2.74
O
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
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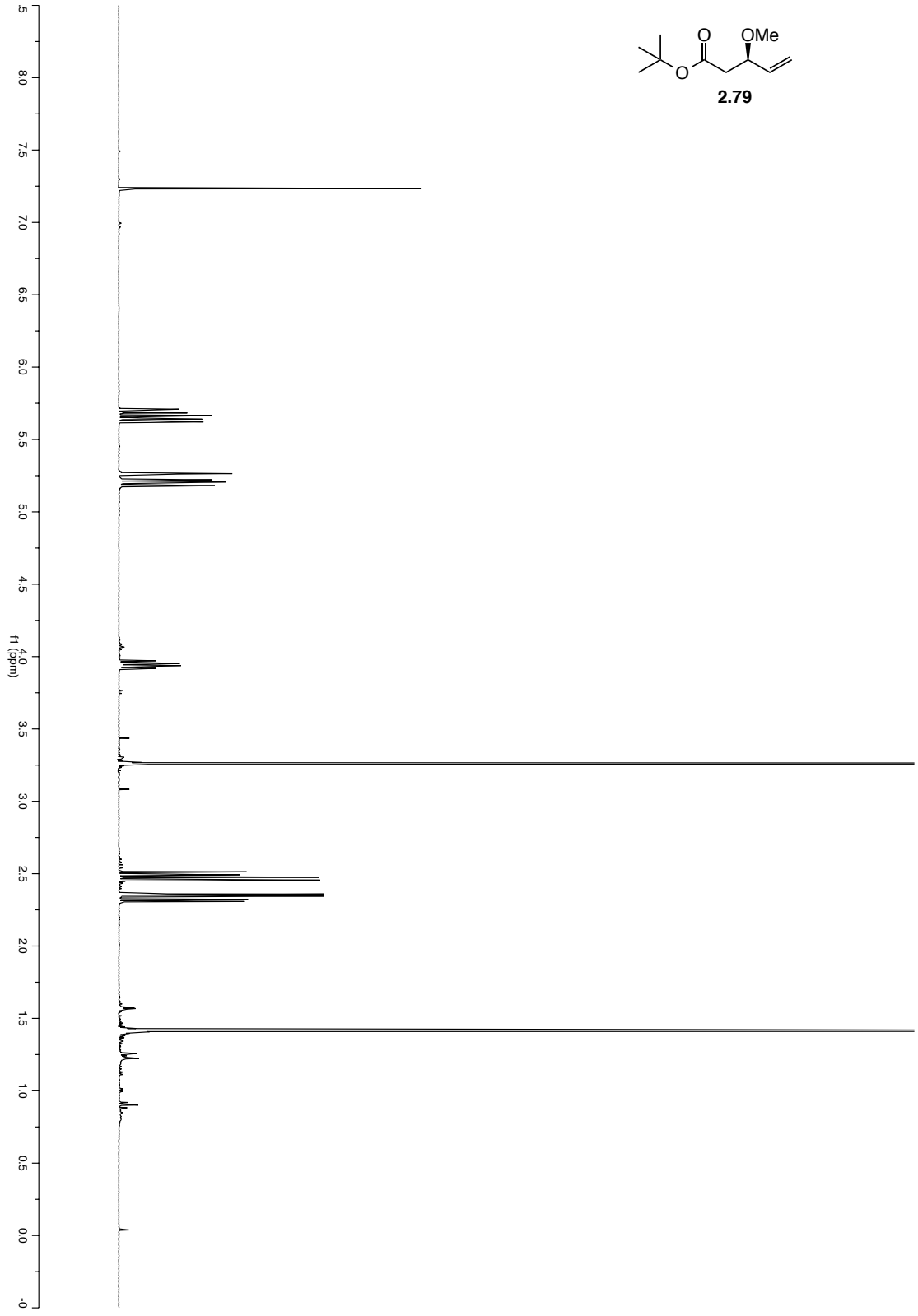
O
OMe
O
2.79
f1 (ppm)
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8.0
7.5
7.0
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6.0
5.5
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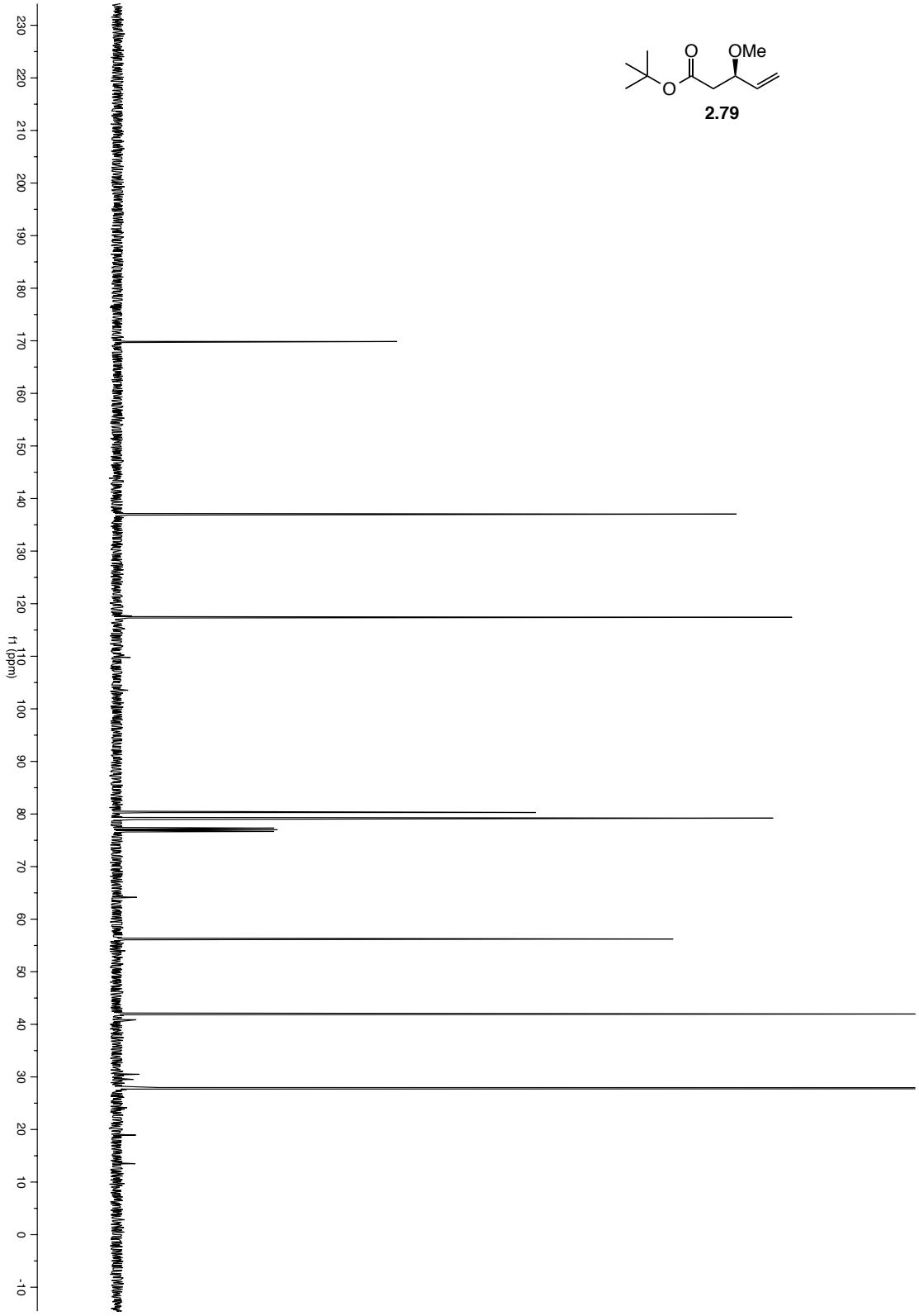
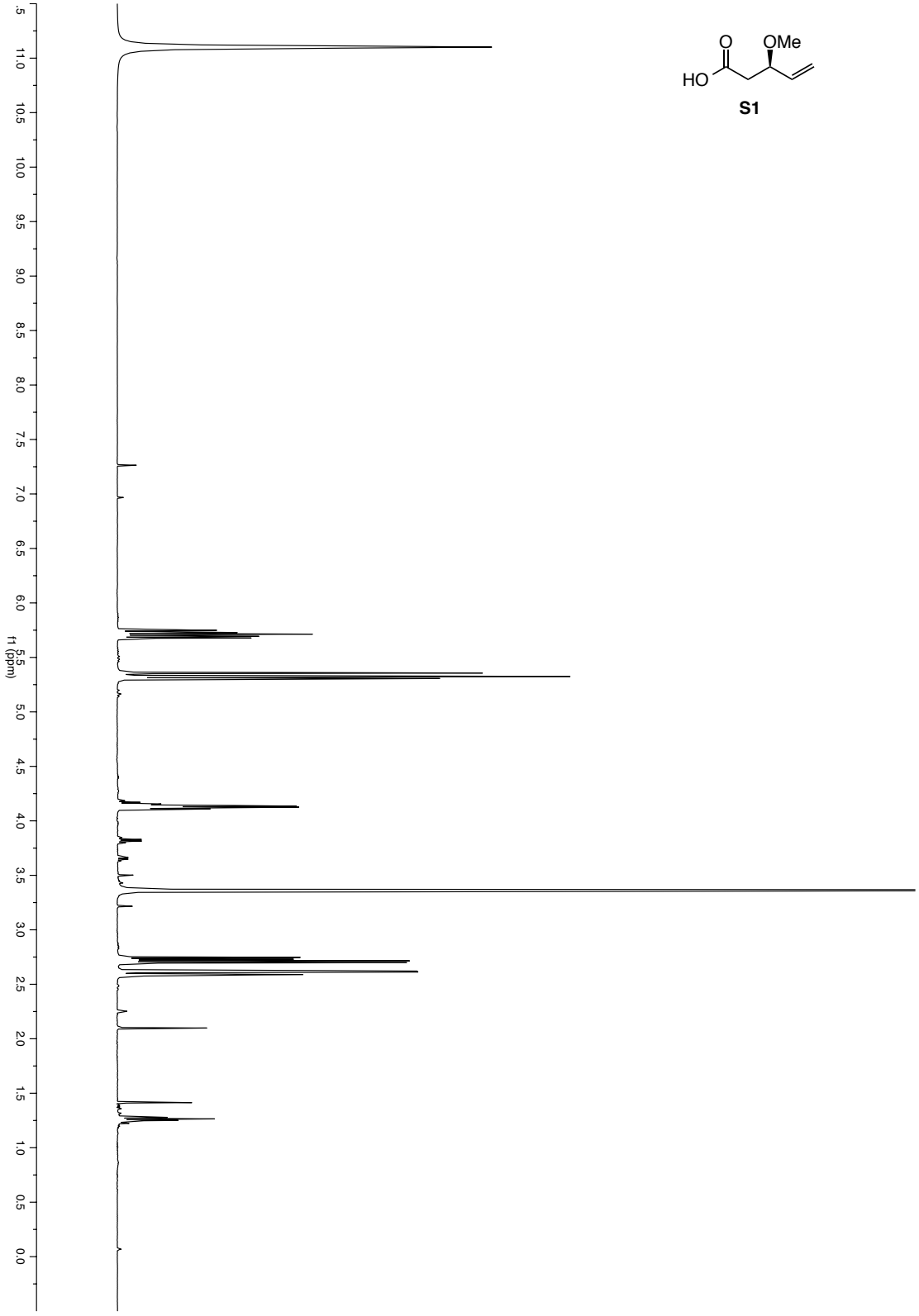
2.0
1.5
1.0
0.5
0.0
-0


O
OMe
O
2.79
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


O
OMe
HO
S1
f1 (ppm)
11.0
10.5
10.0
9.5
9.0
8.5
8.0
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7.0
6.5
6.0
5.5
5.0
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4.0
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3.0
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2.0
1.5
1.0
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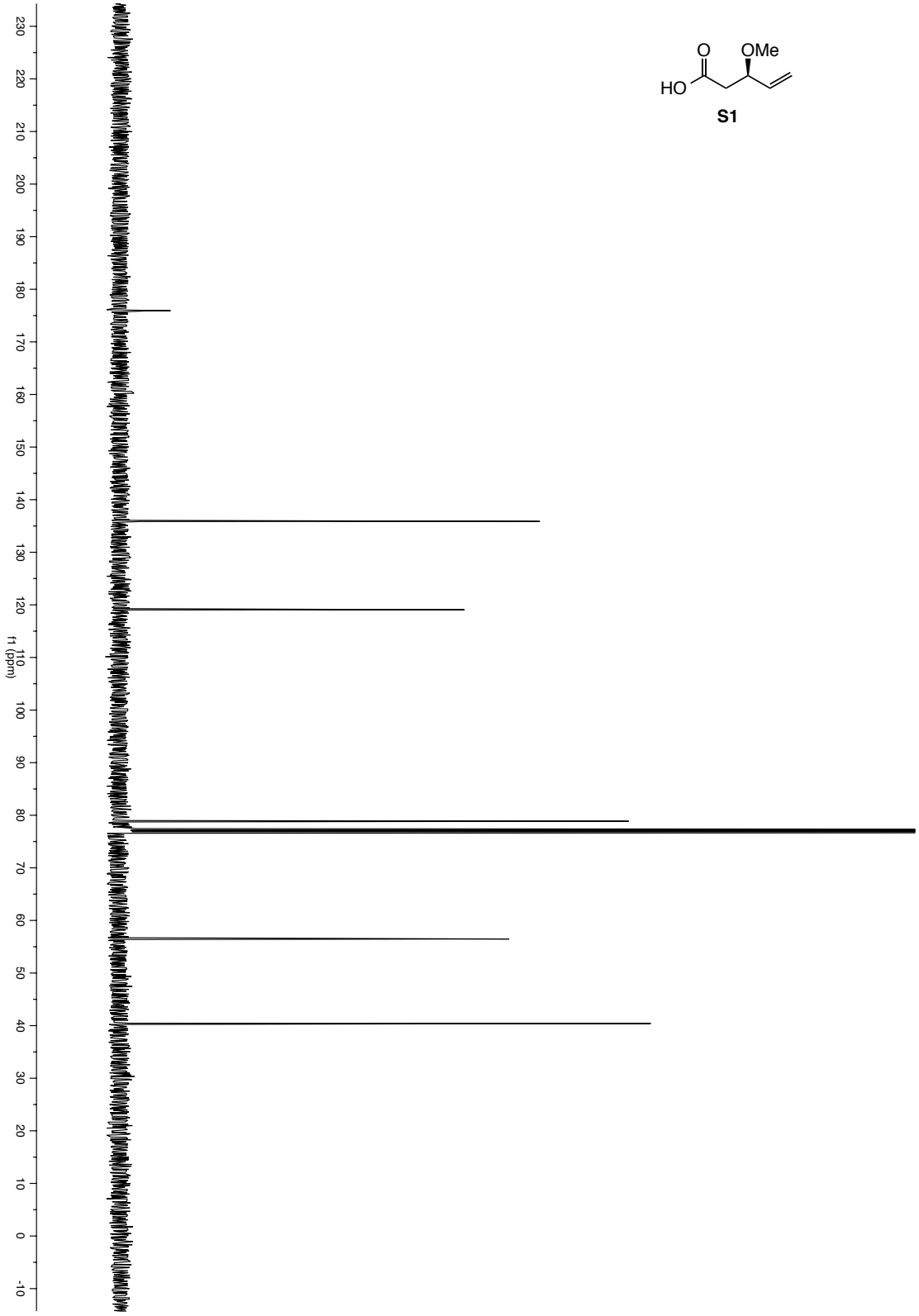
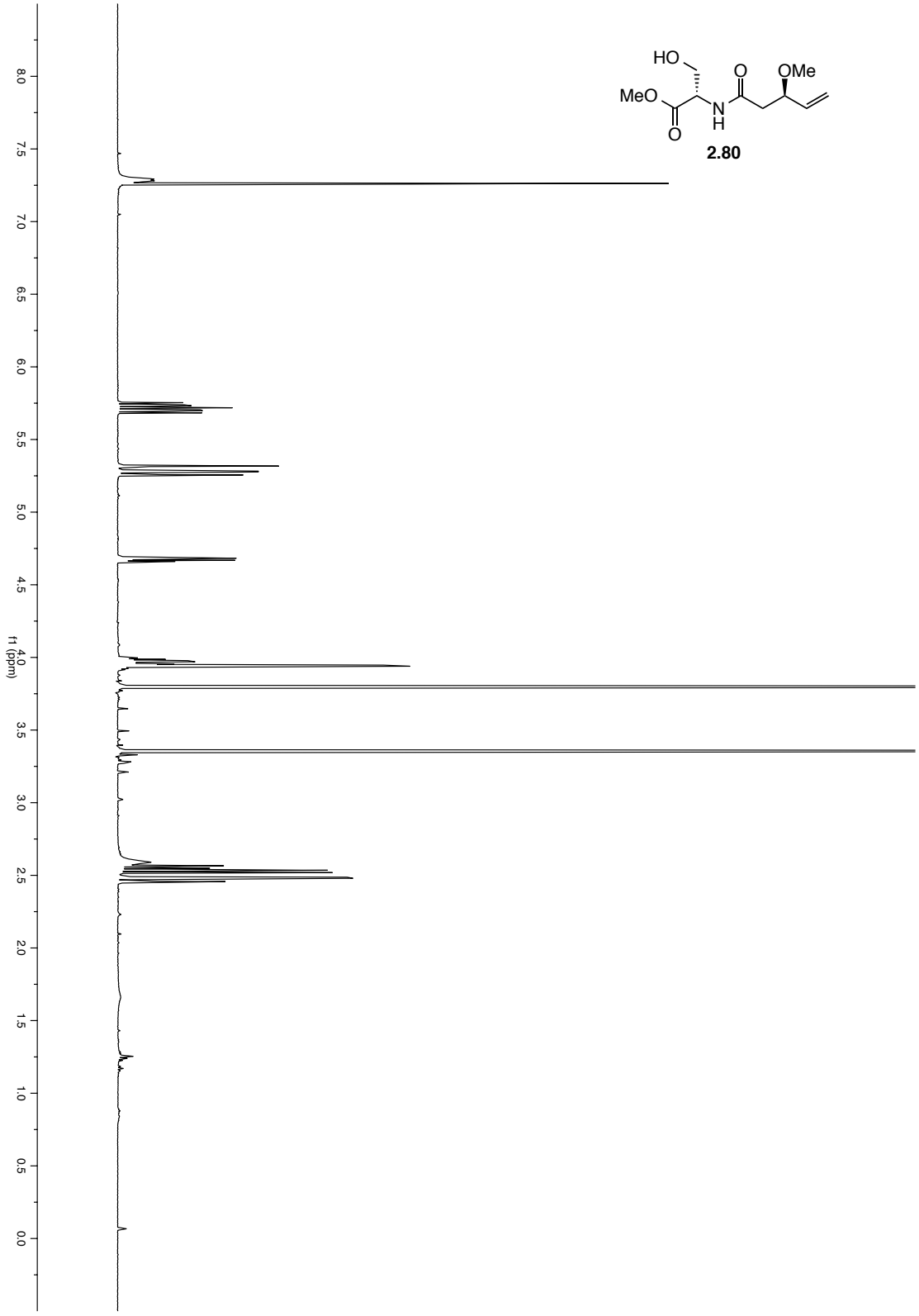

O
OMe
HO
S1
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


HO
O
OMe
MeO
N
H
O
2.80
f1 (ppm)
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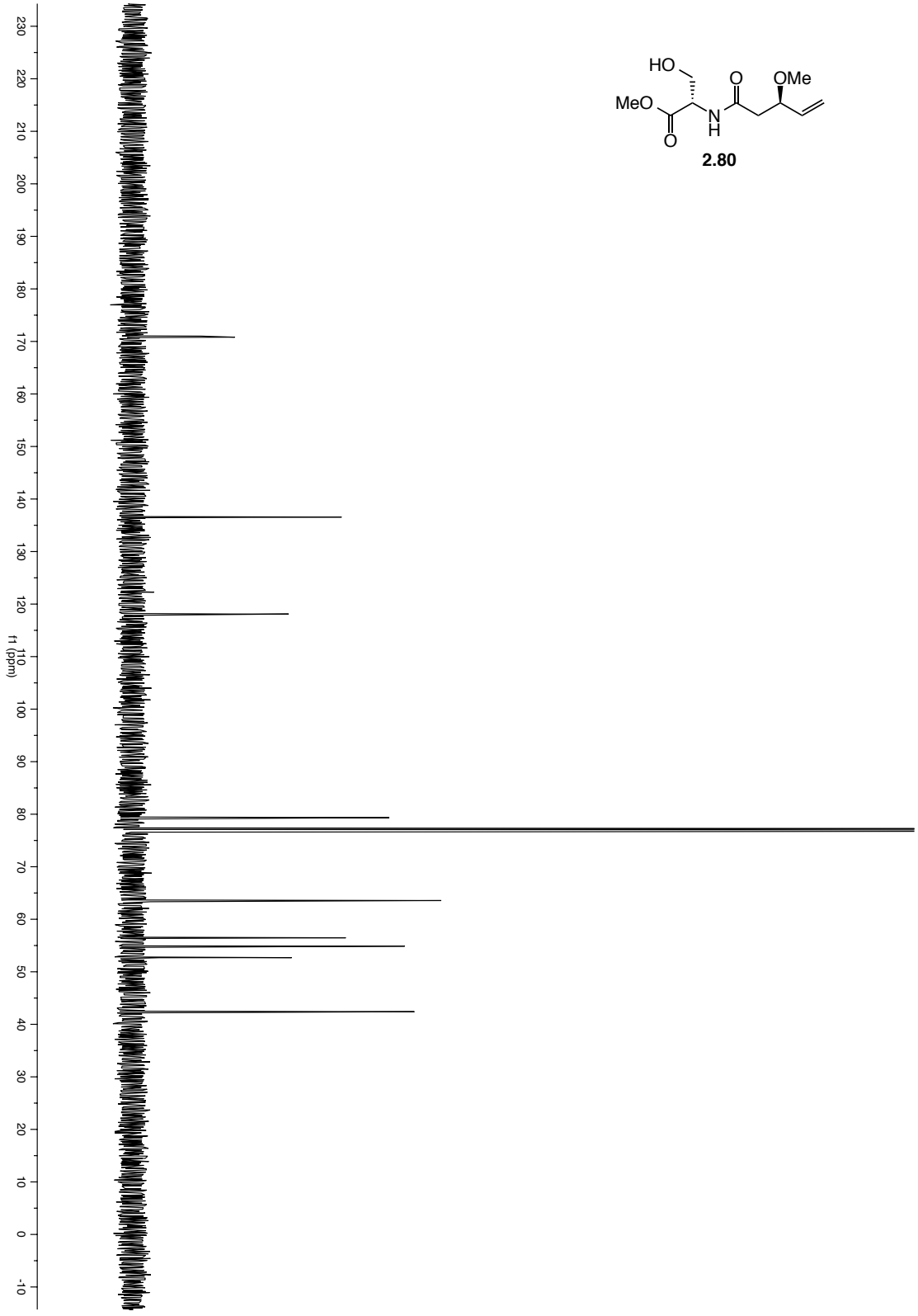
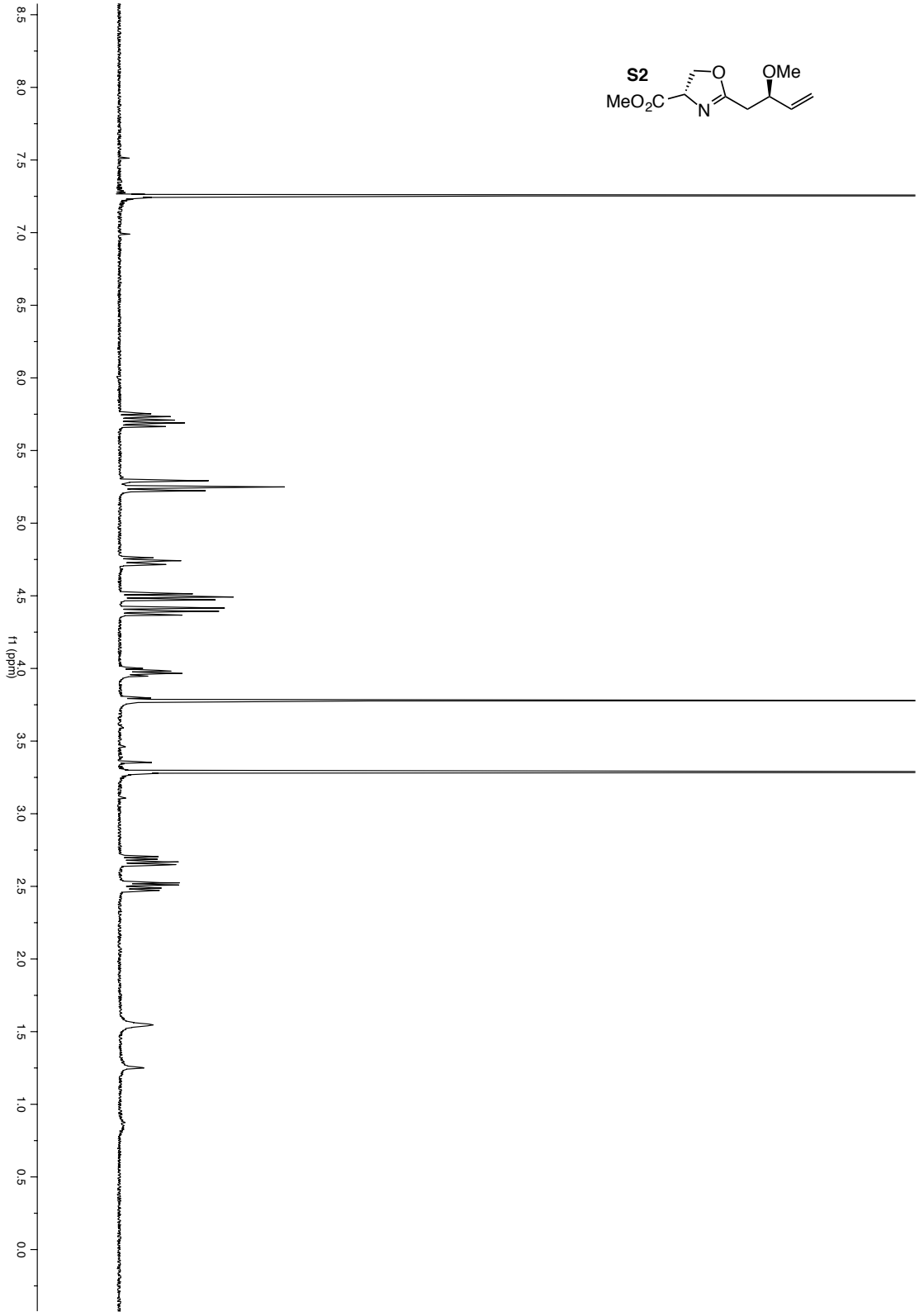
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


HO
O
OMe
MeO
N
H
O
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

2.80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MeO2C
N
O
OMe
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6.5
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4.0
3.5
3.0
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2.0
1.5
1.0
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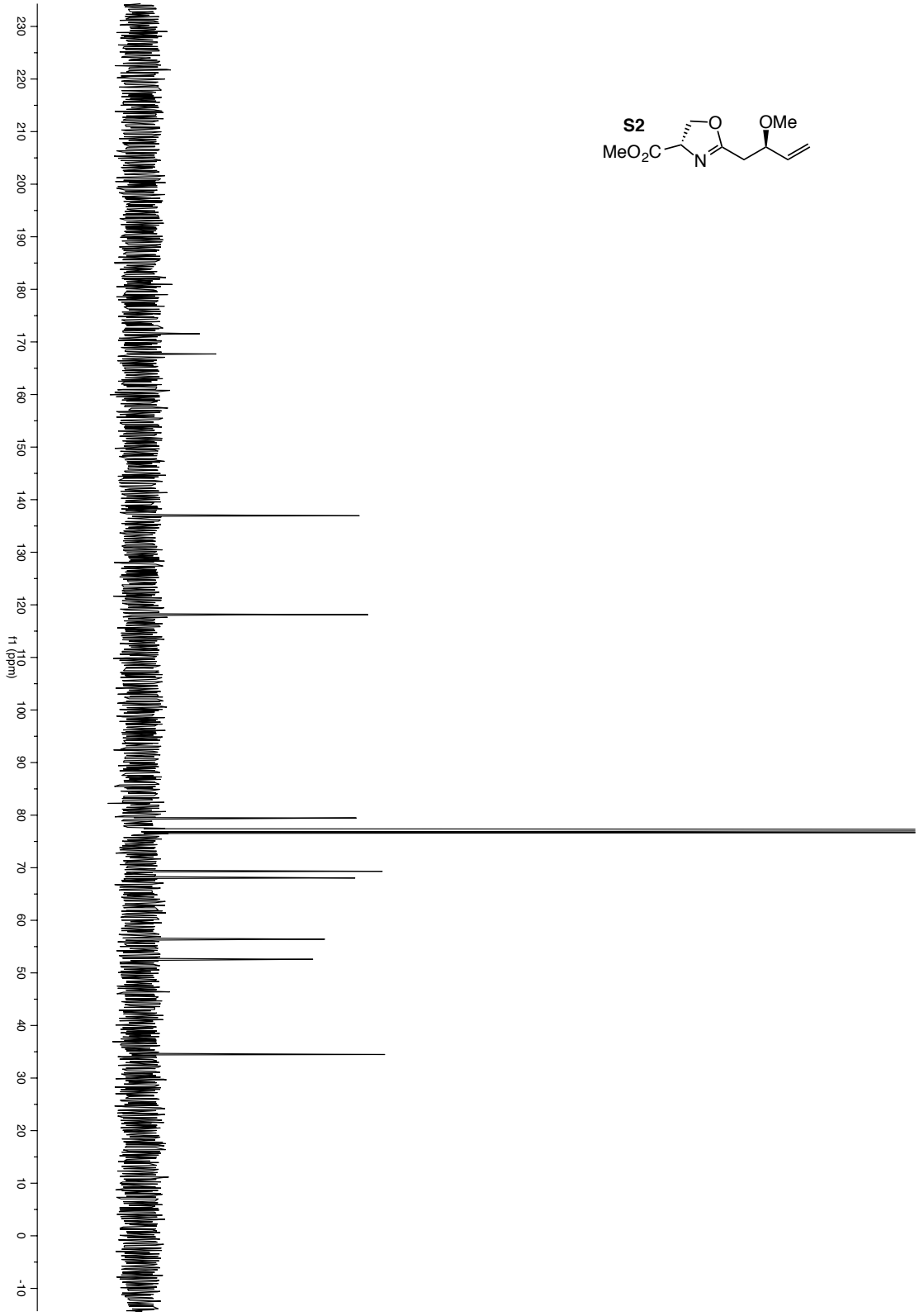
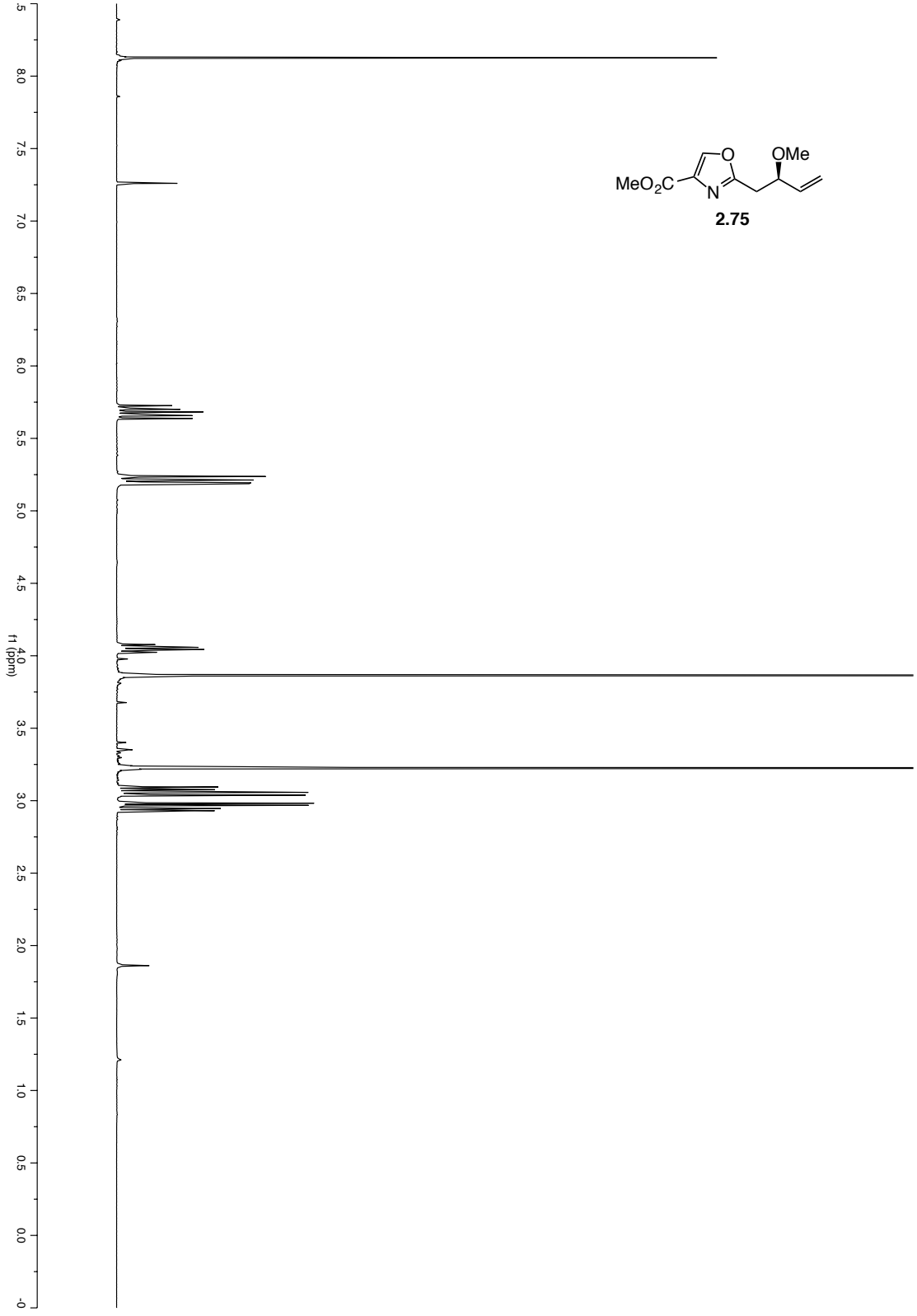
0.0


S2
MeO2C
N
O
OMe
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10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O
OMe
N
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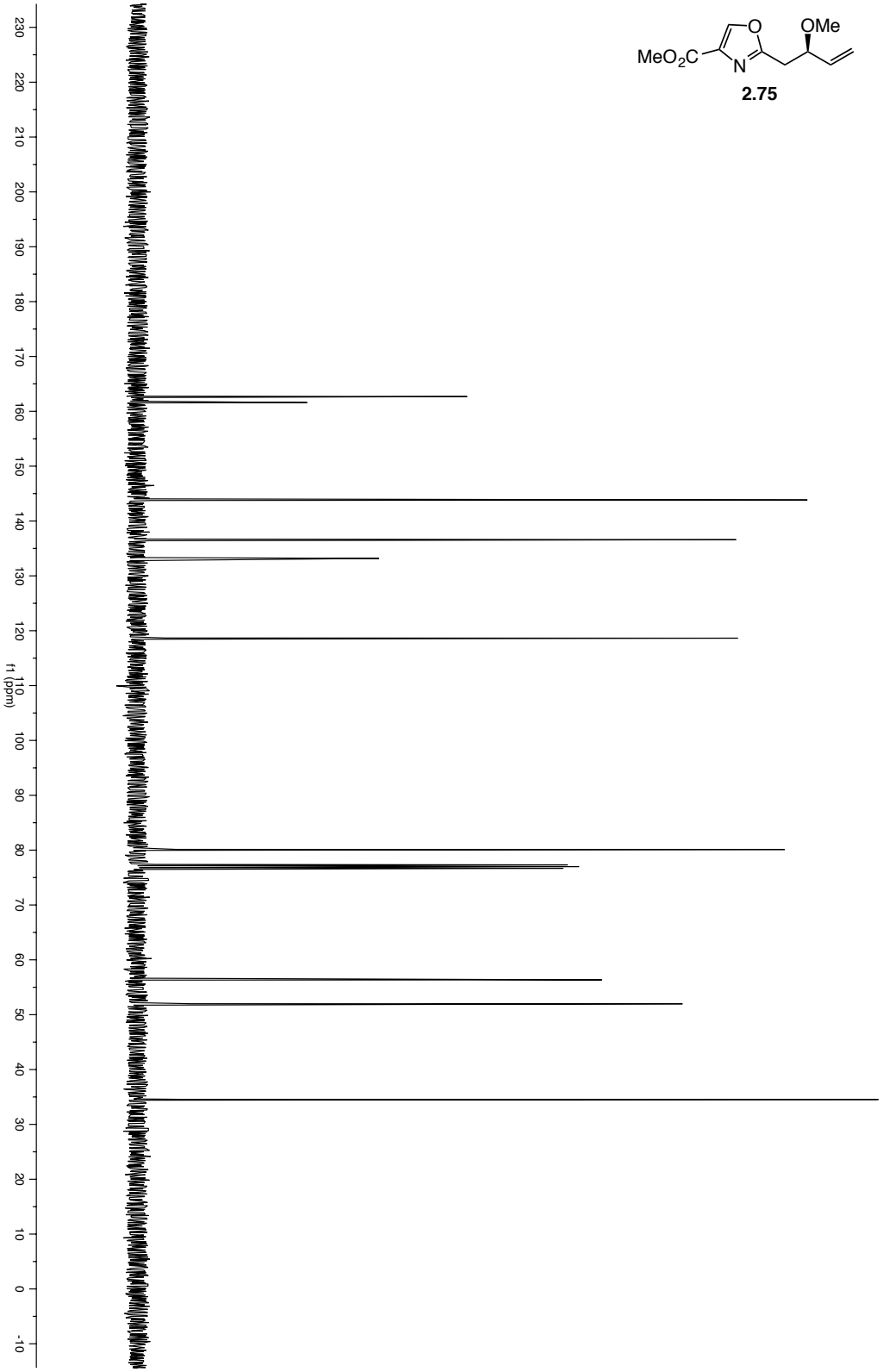
MeO2C
O
N
OMe
2.75
f1 (ppm)
230
220
210
200
190
180
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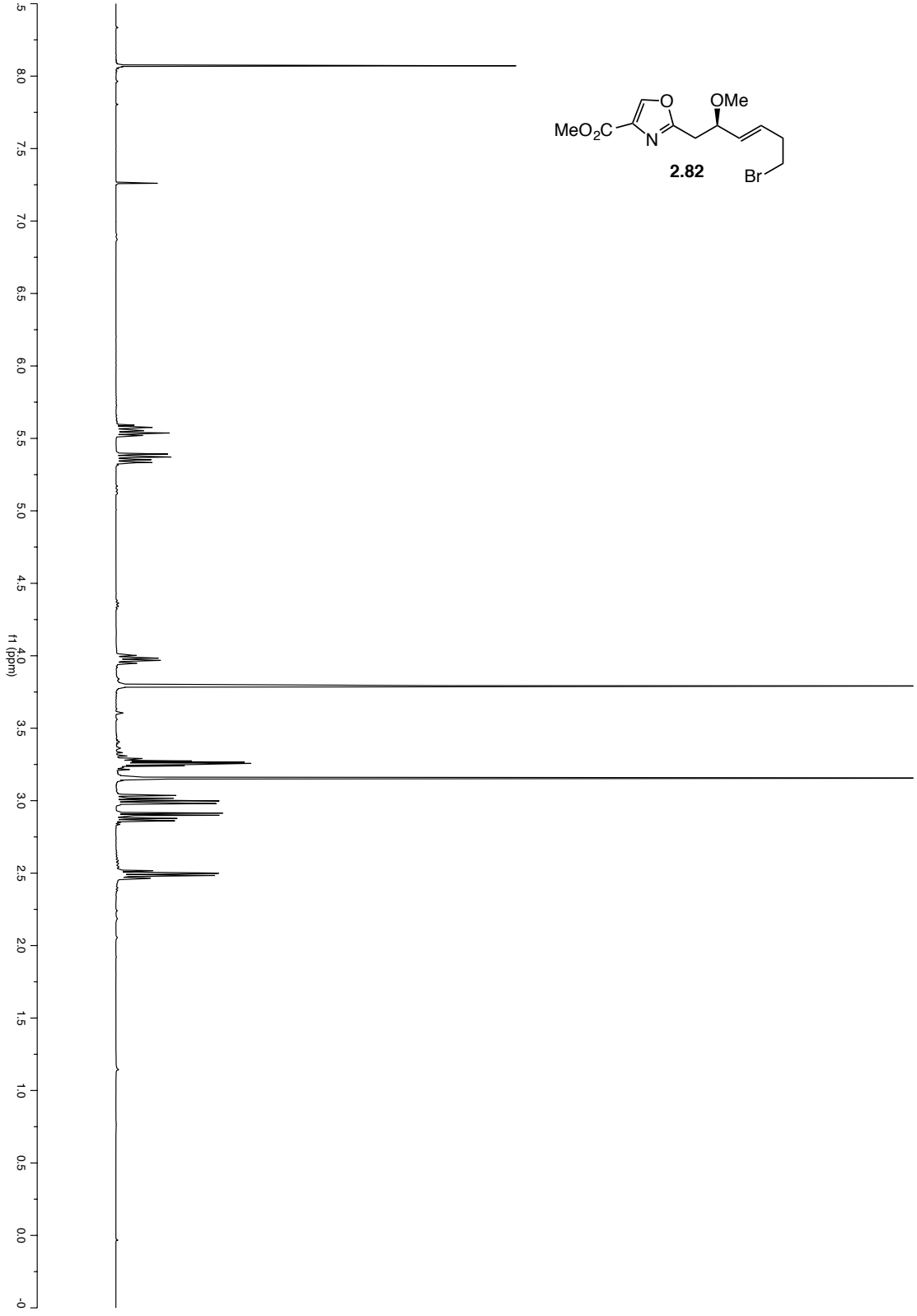
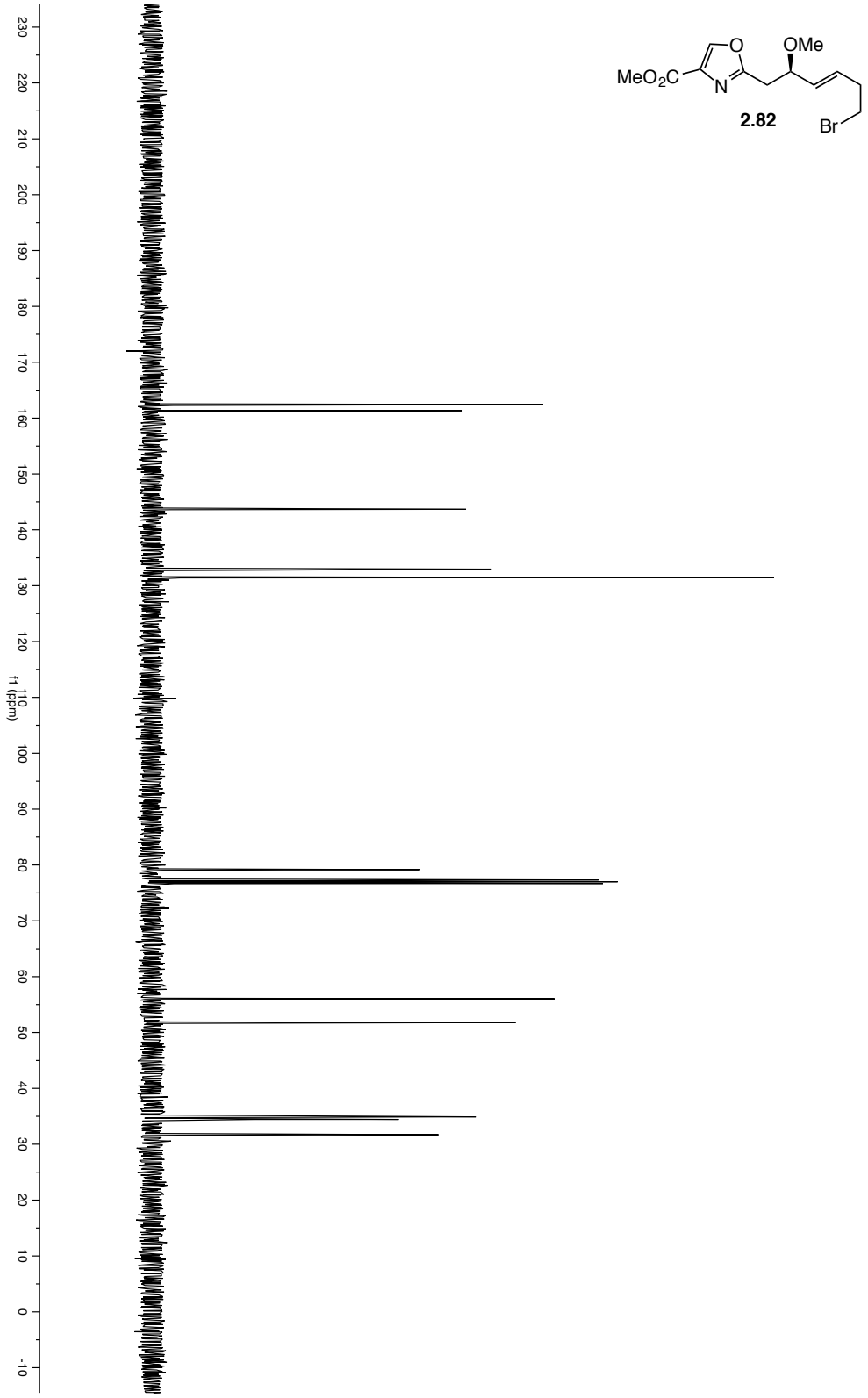

MeO2C
O
N
OMe
Br
2.82
f1 (ppm)


MeO2C
O
N
OMe
Br
2.82
f1 (ppm)
230
220
210
200
190
180
170
160
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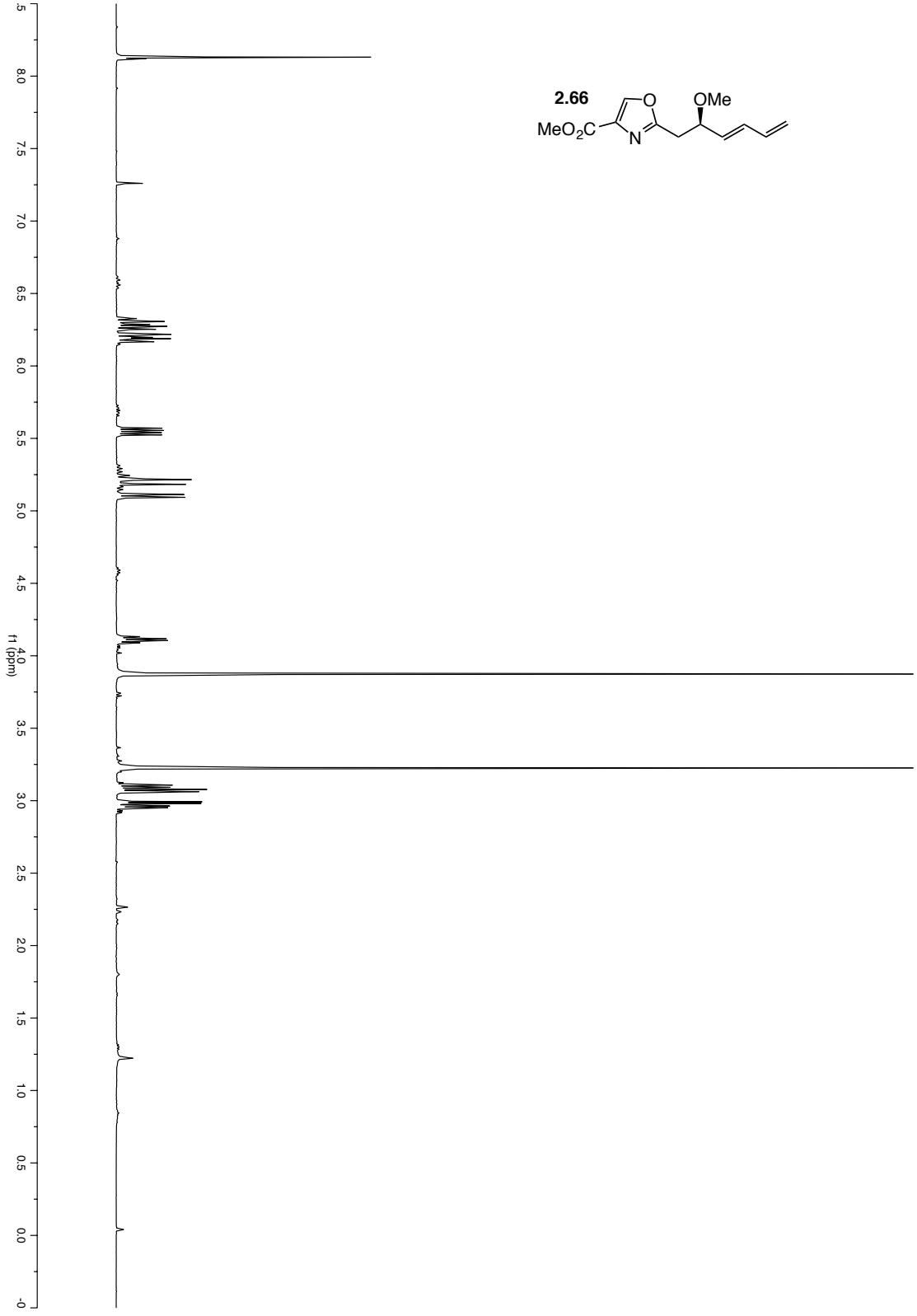
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10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MeO2C
N
O
OMe
f1 (ppm)
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6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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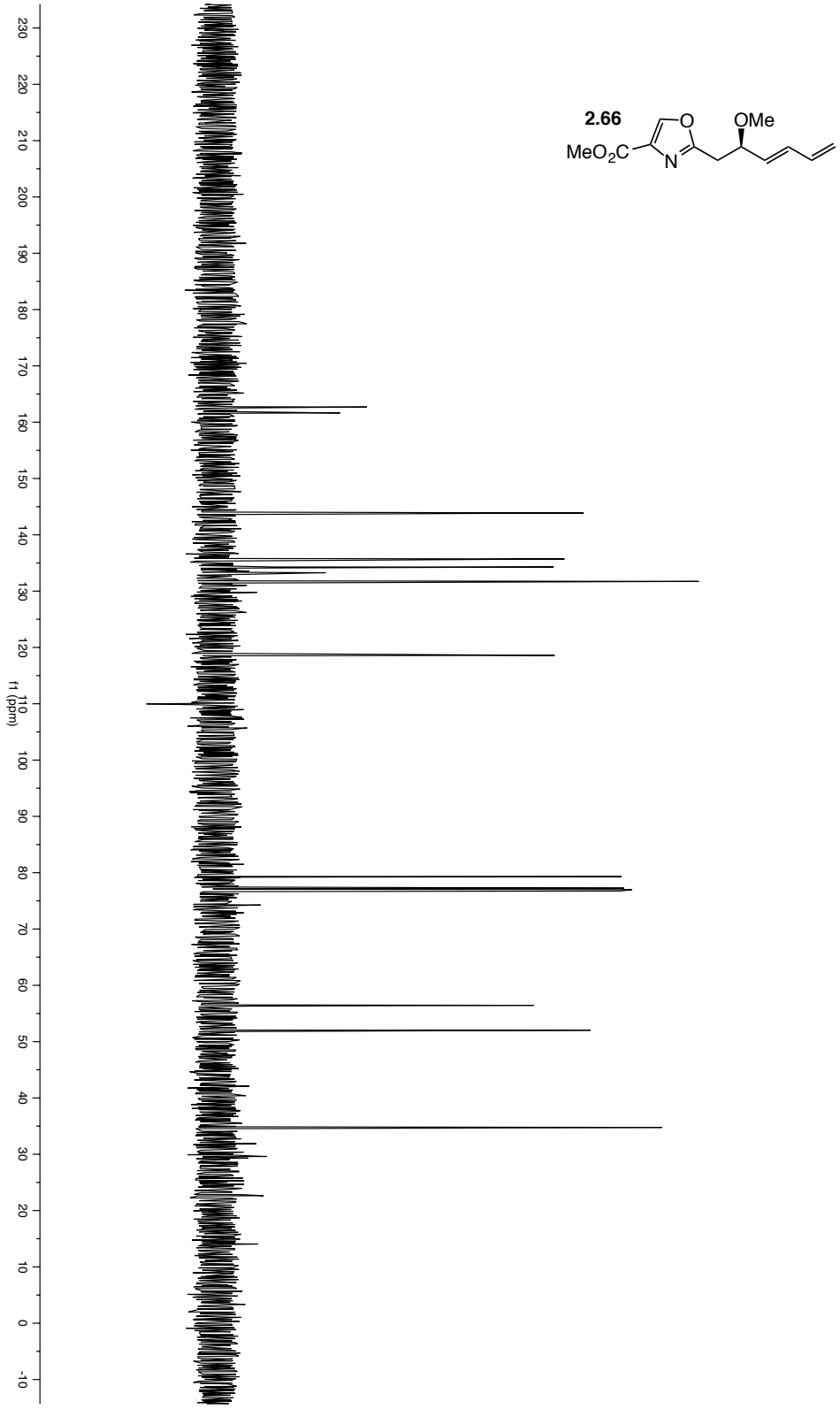
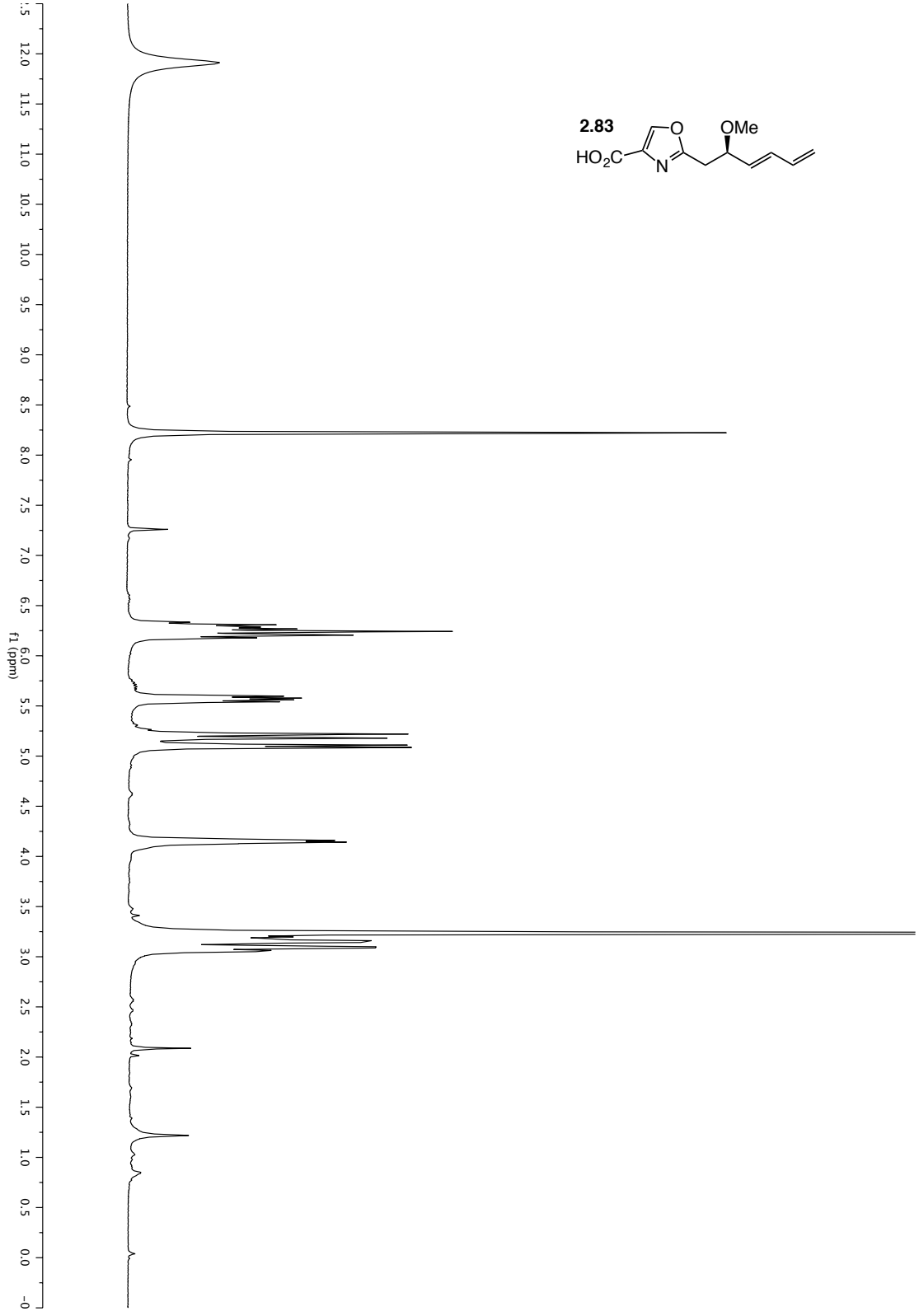
2.0
1.5
1.0
0.5
0.0


2.66
MeO2C
N
O
OMe
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10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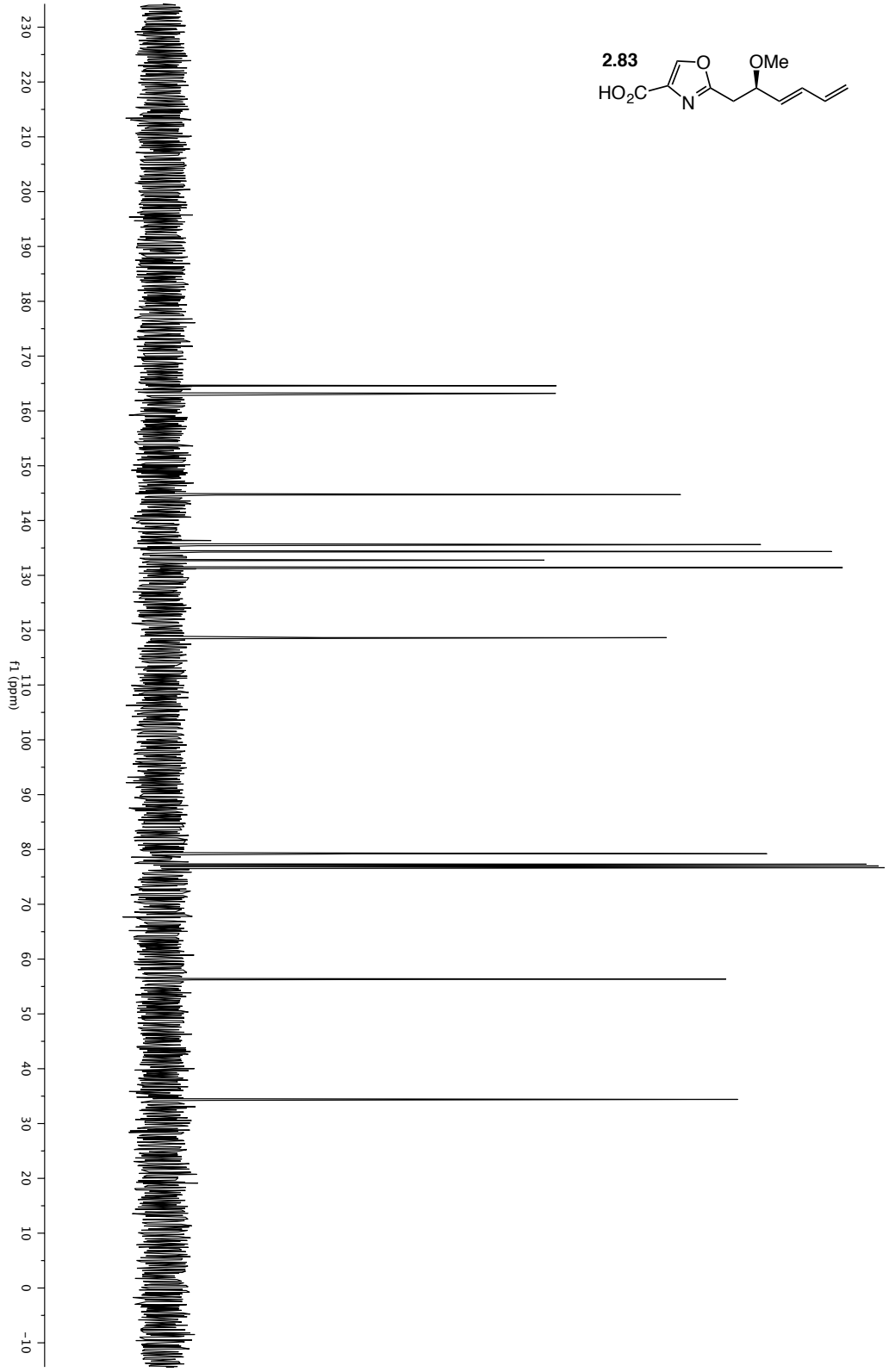
HO2C
N
O
OMe
f1 (ppm)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HO2C
N
O
OMe
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50
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30
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10
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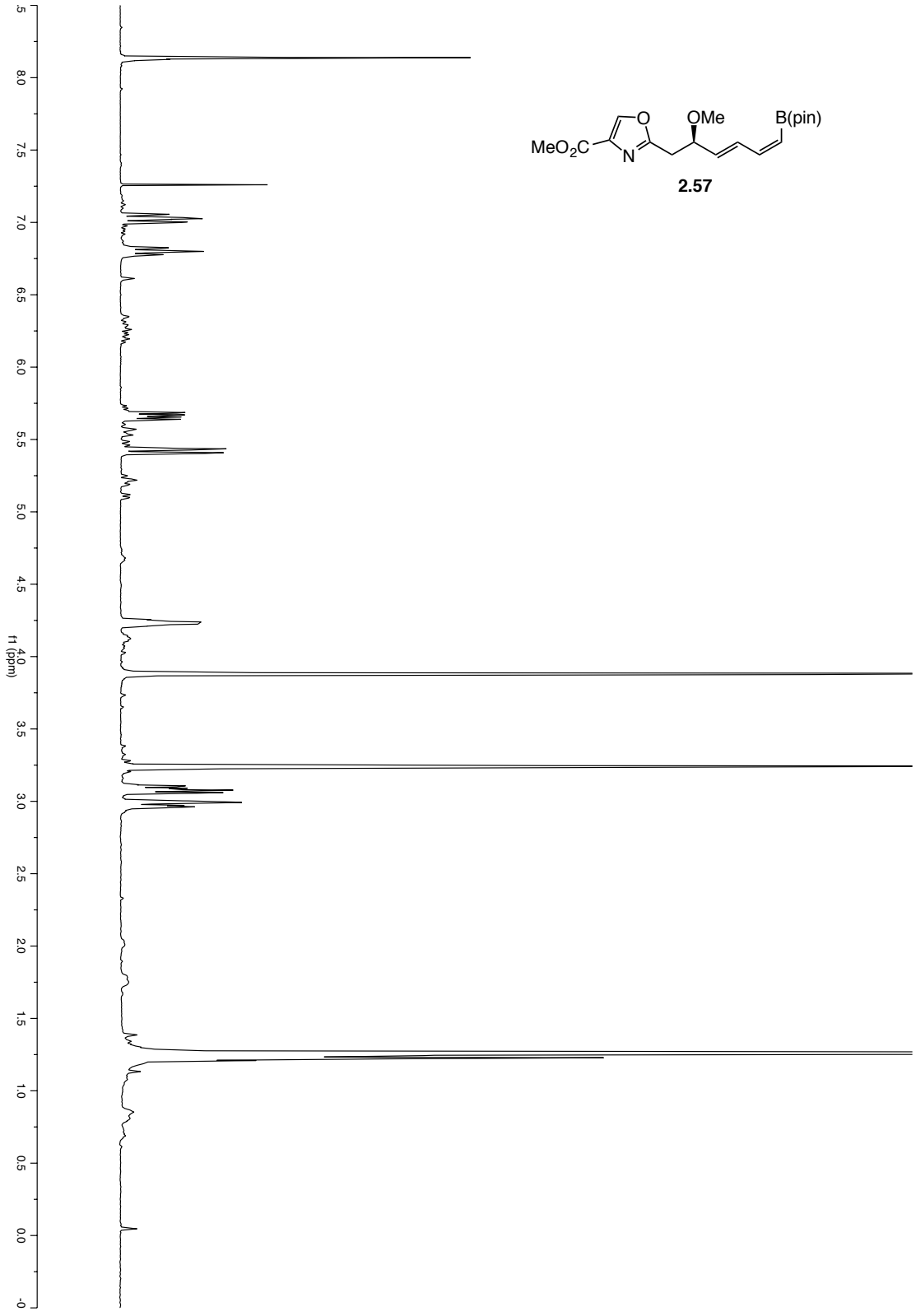
-10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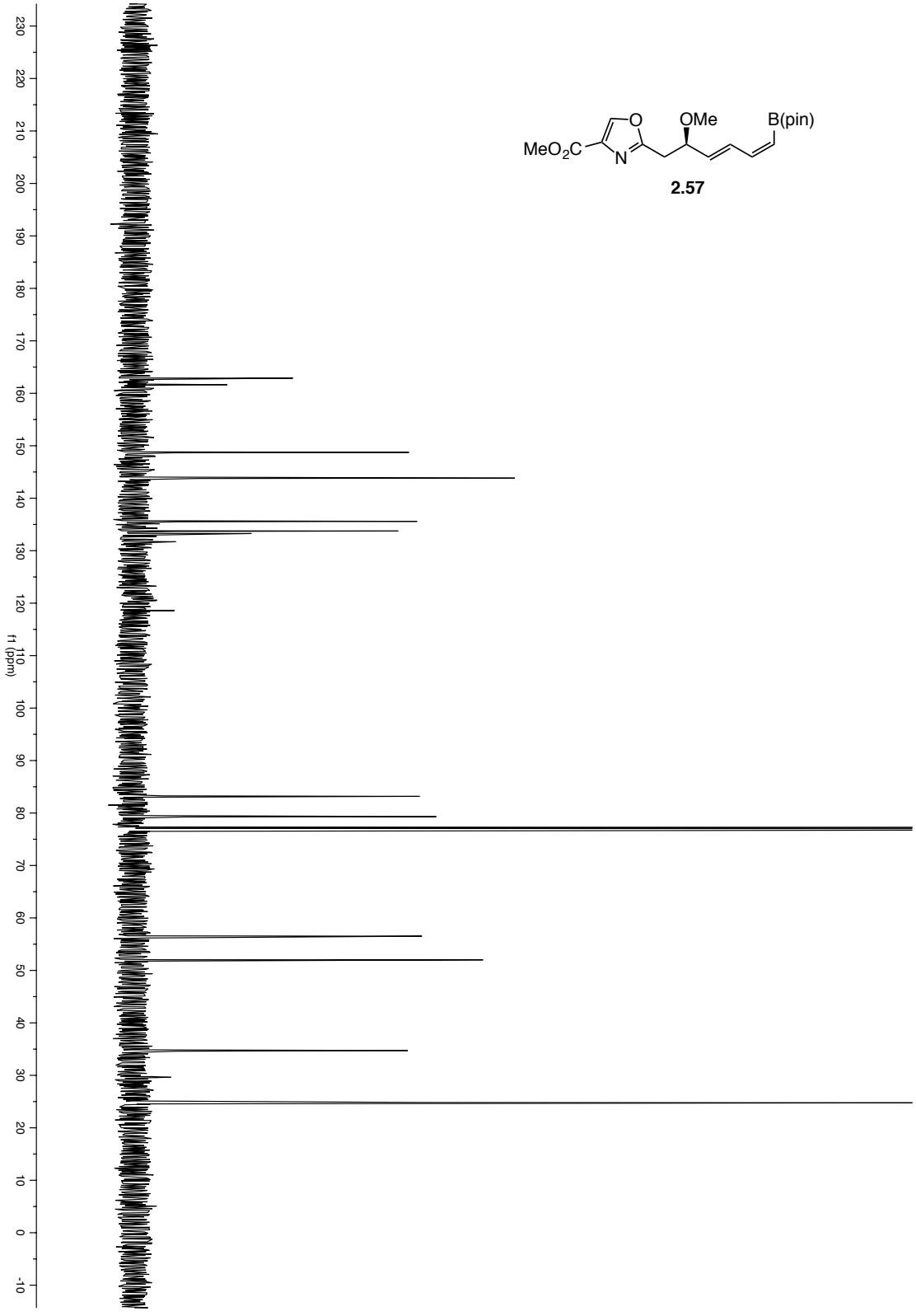
1.0
0.5
0.0
MeO2C
O
N
OMe
B(pin)

2.57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100
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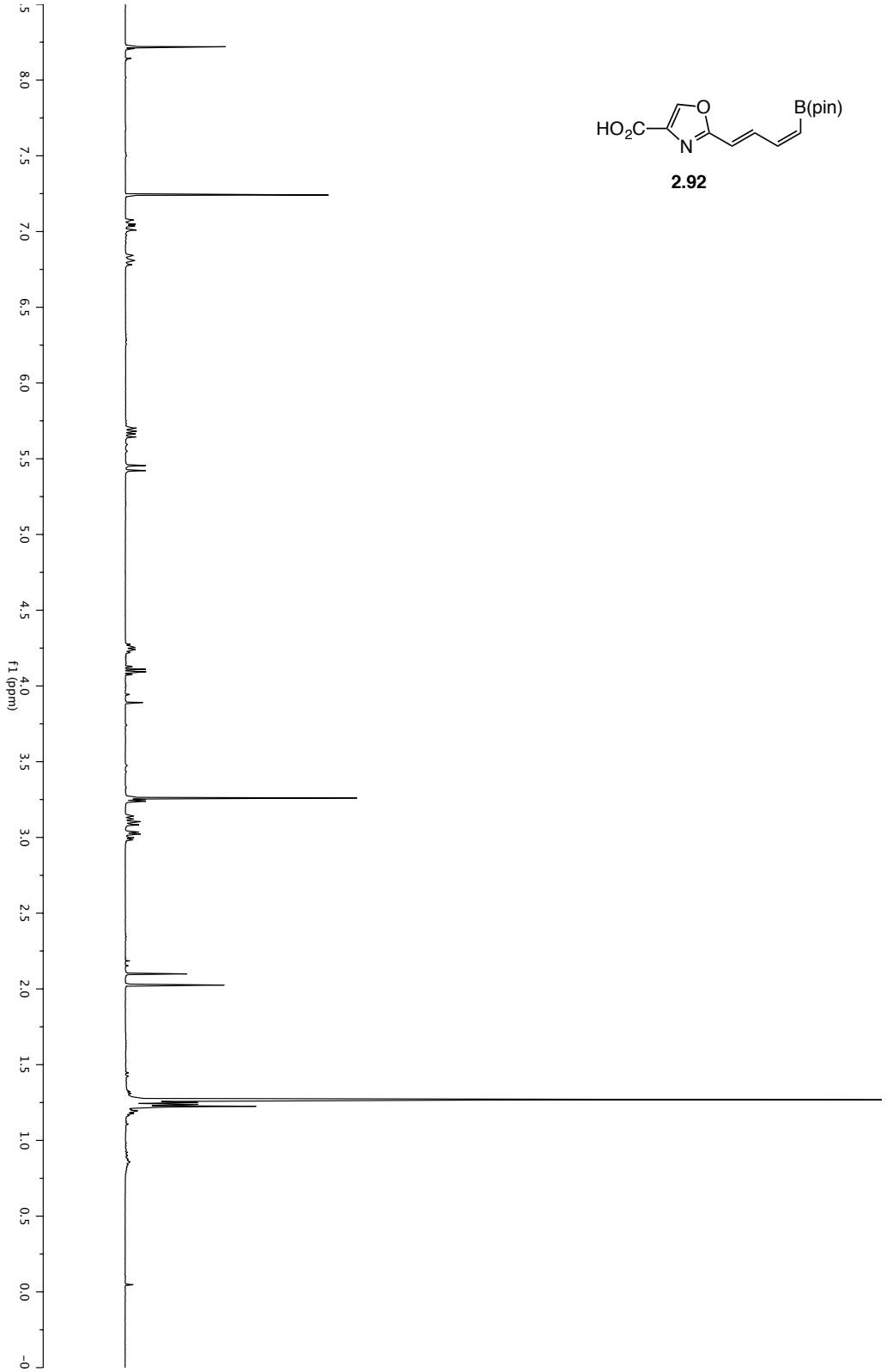
50
40
30
20
10
0
-10

MeO2C
N
O
OMe
B(pin)

2.57



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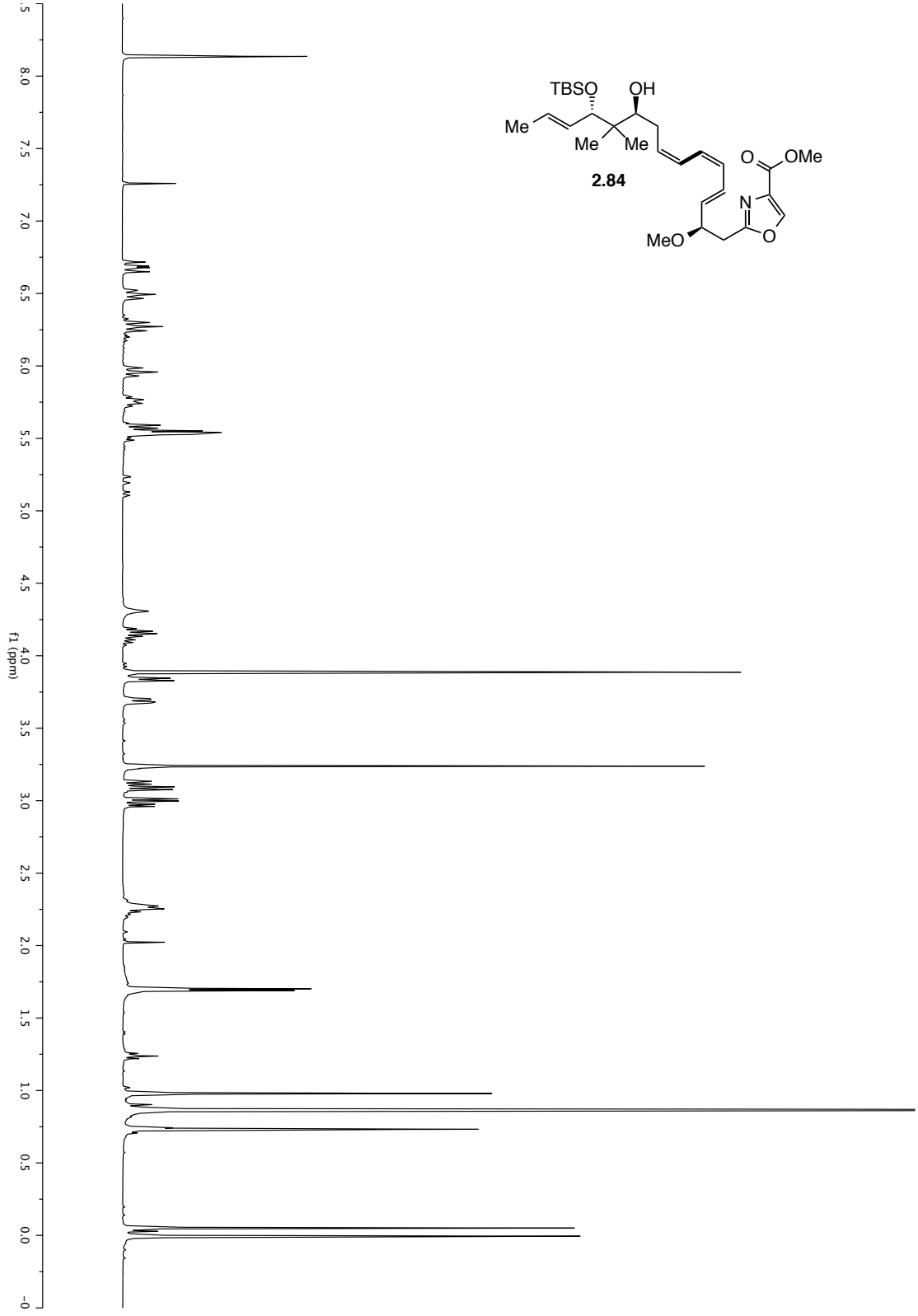
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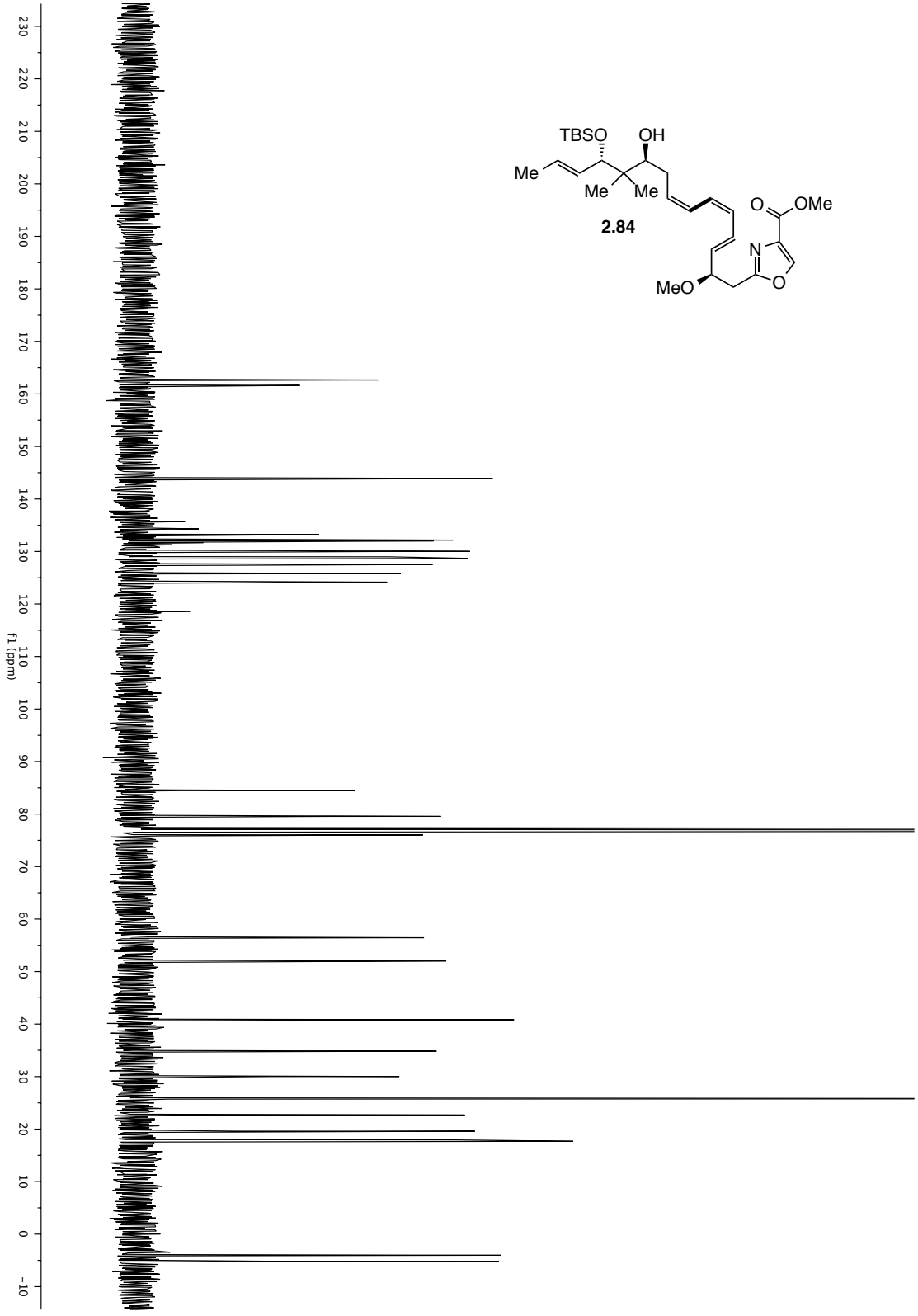
Me
Me
Me
O
OMe
N
O
MeO
2.84
f1 (ppm)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OH
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Me
Me
O
OMe
N
O
MeO
2.84
f1 (ppm)
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200
190
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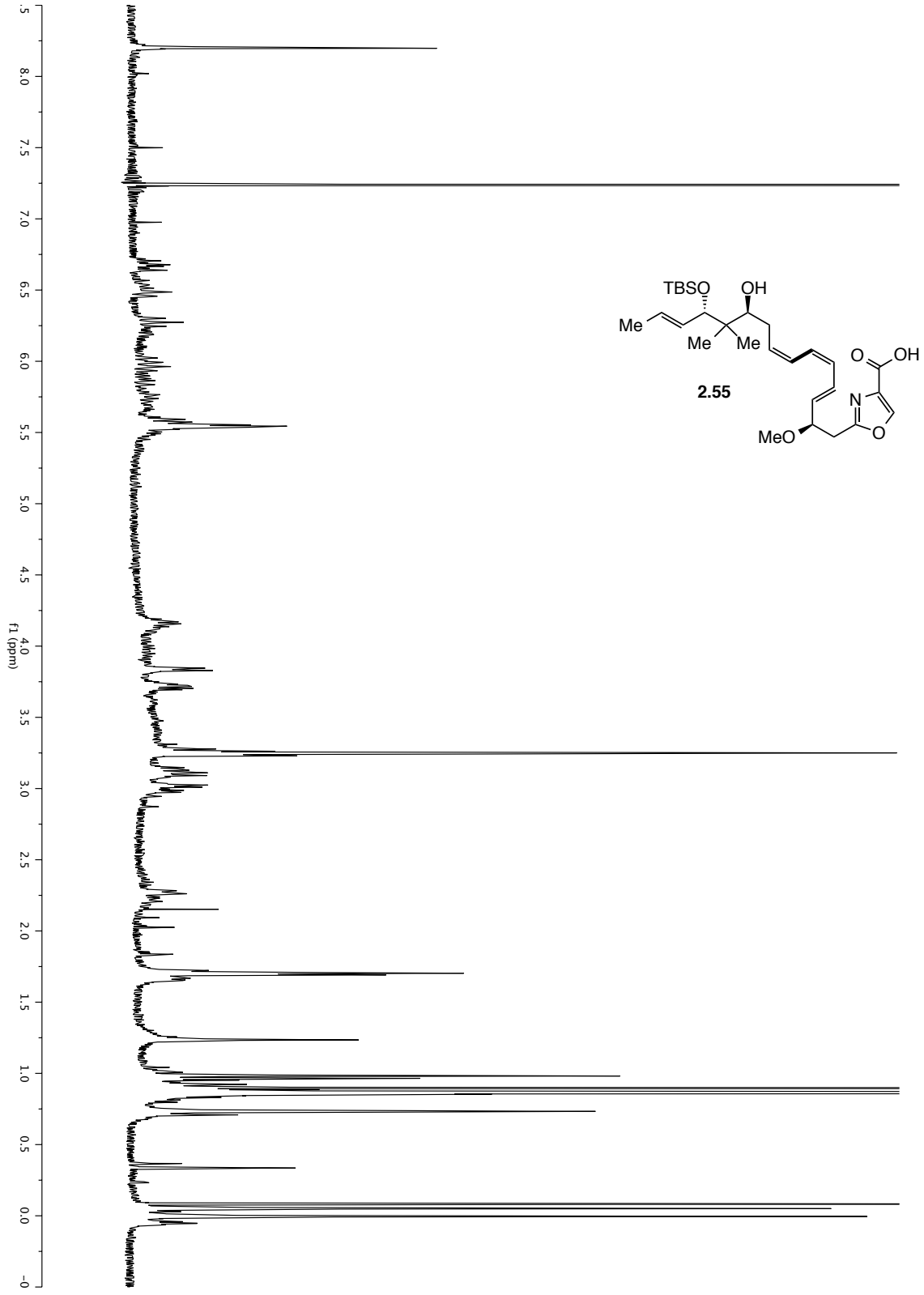
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OH
N
O
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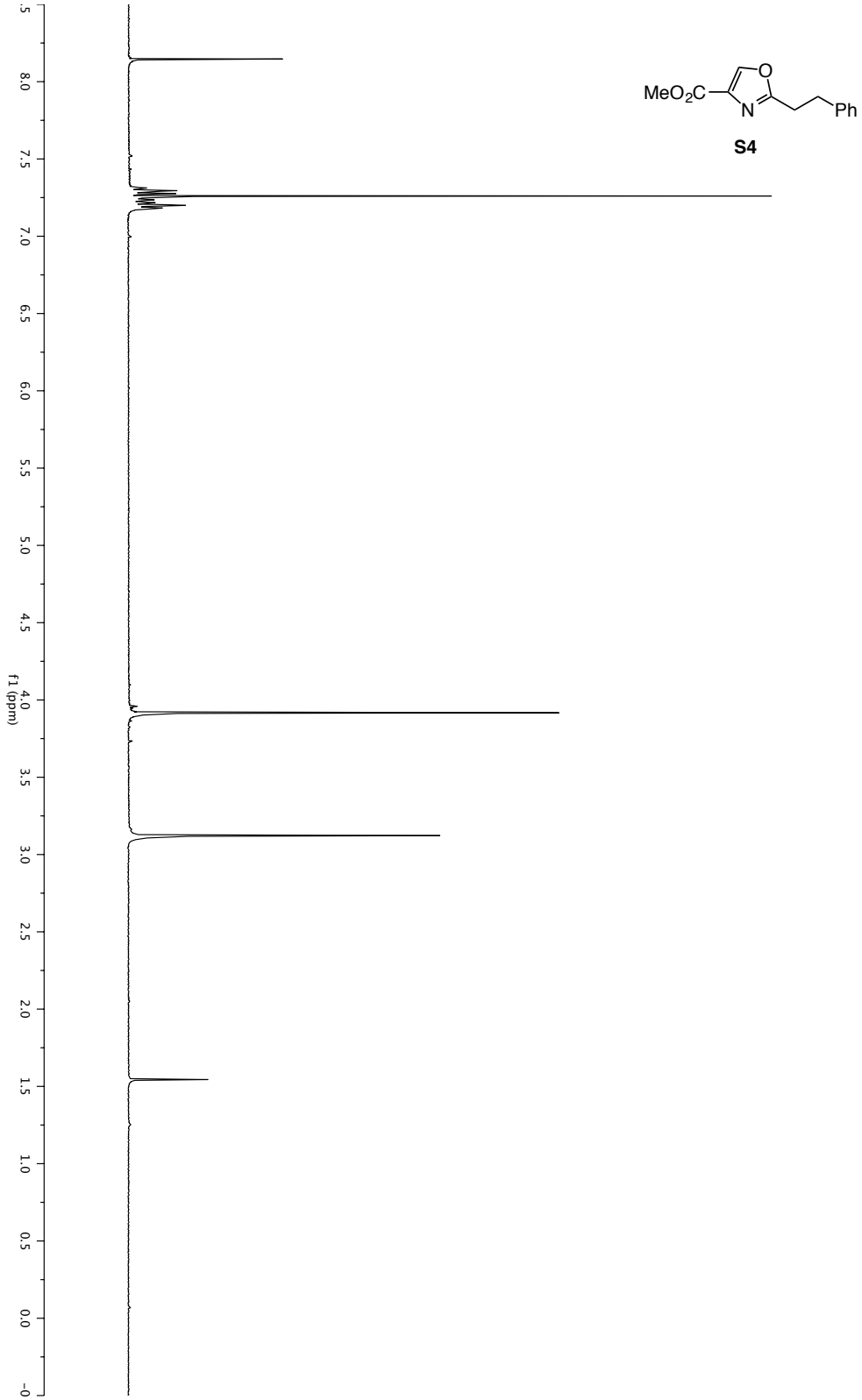
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O
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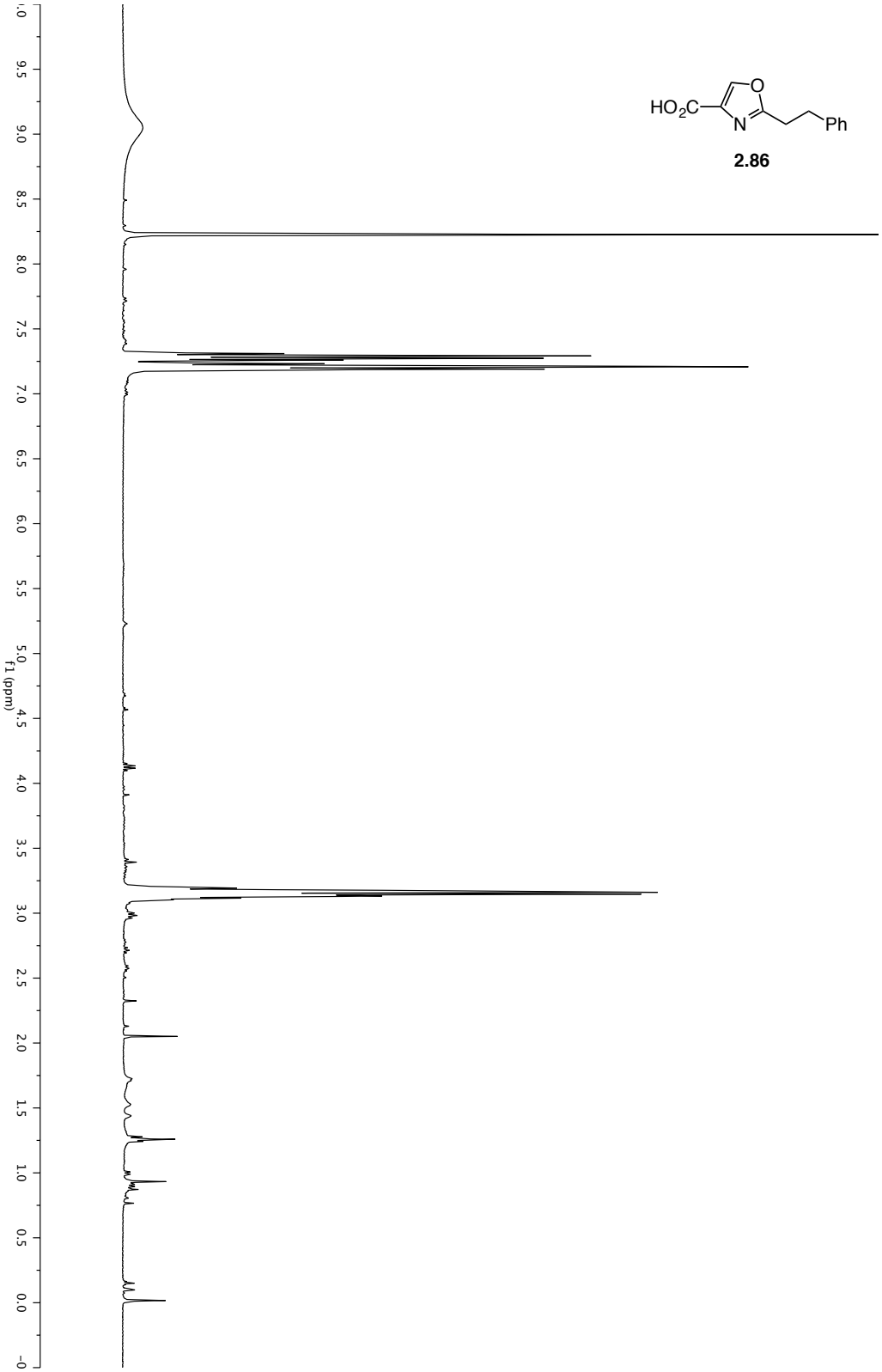
Ph
S4
f1 (ppm)


HO2C
O
N
Ph
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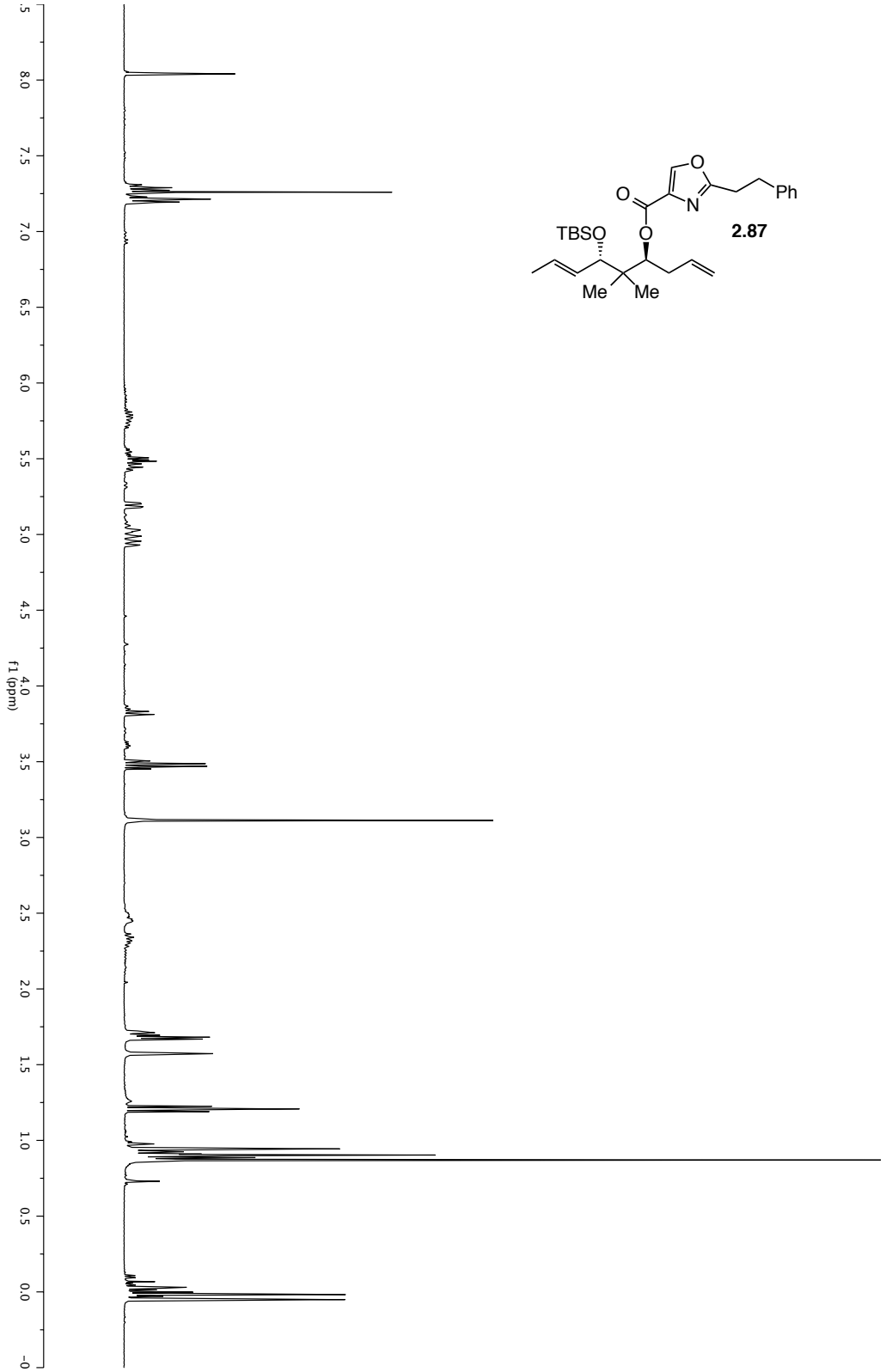
f1 (ppm)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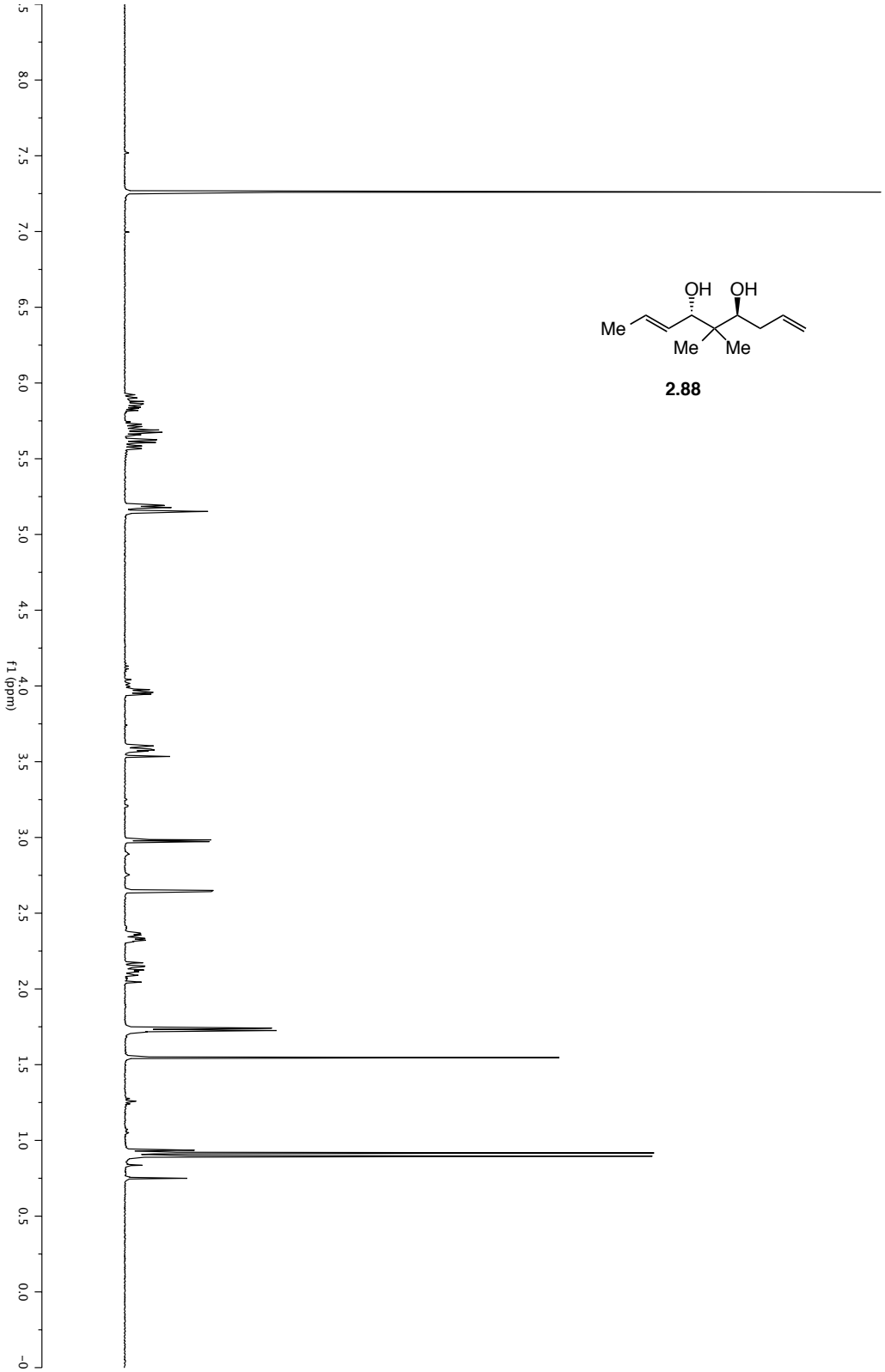
0.5
0.0
O
O
N
Ph
TBSO
O
Me
Me

2.87



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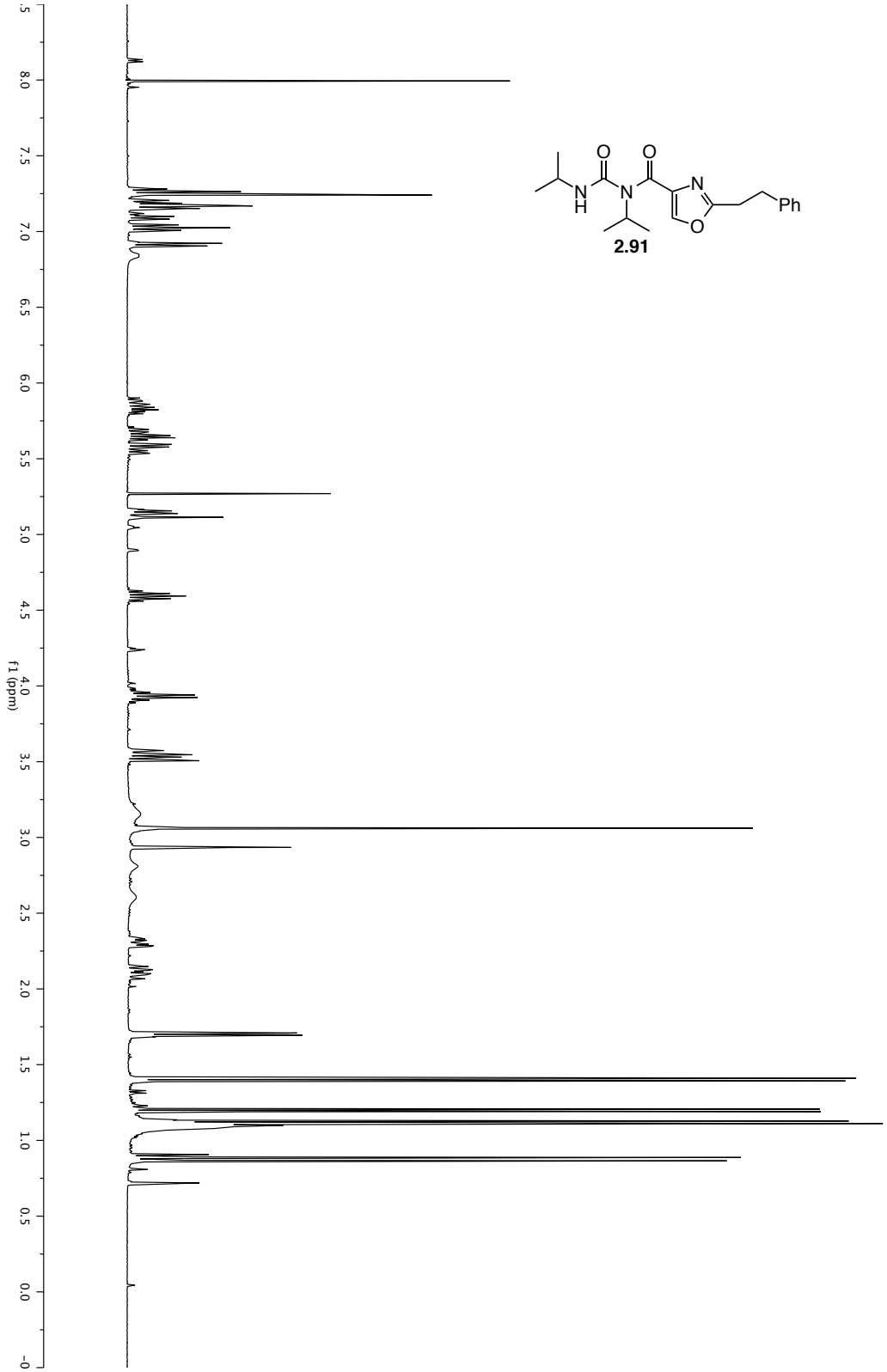

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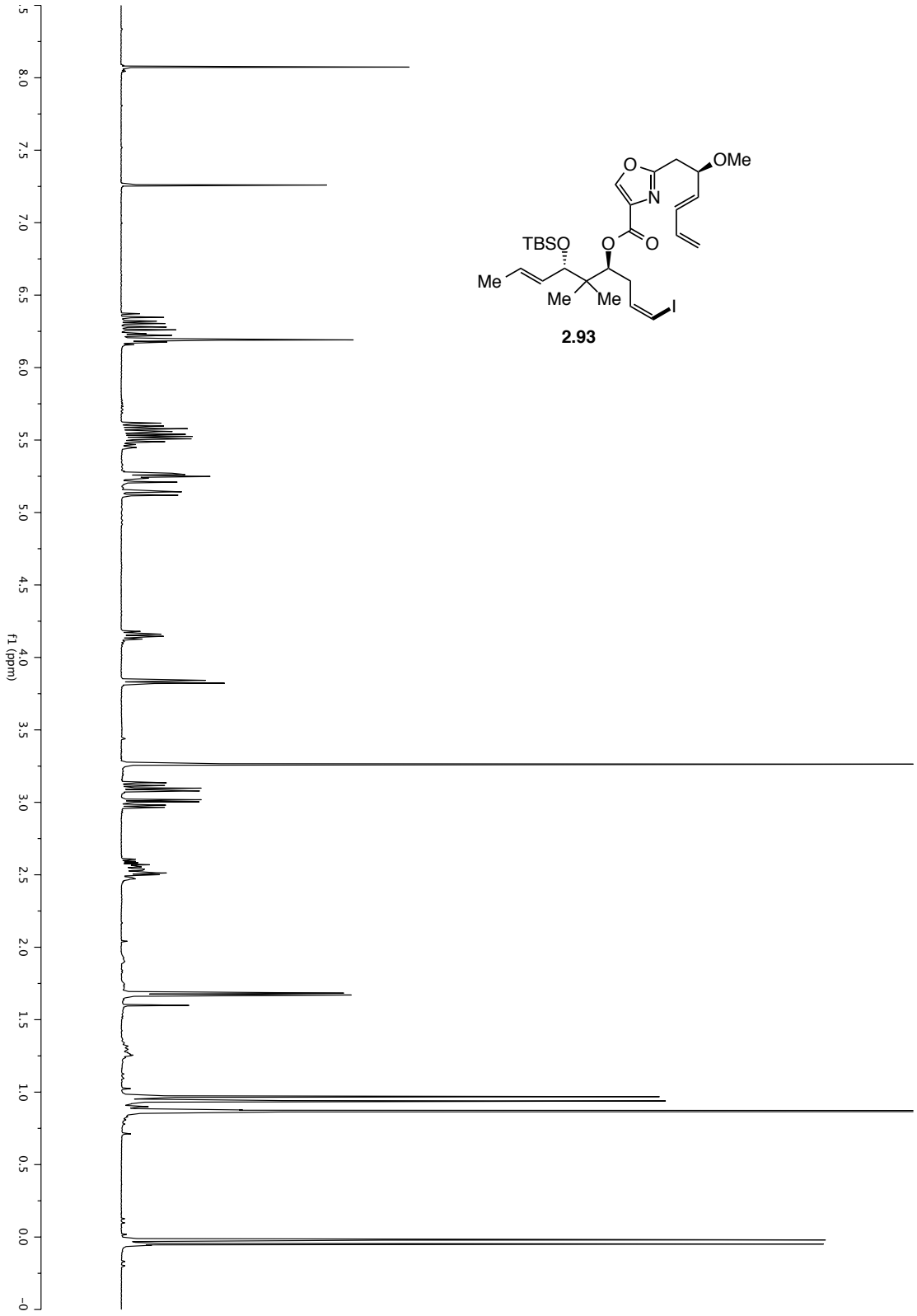
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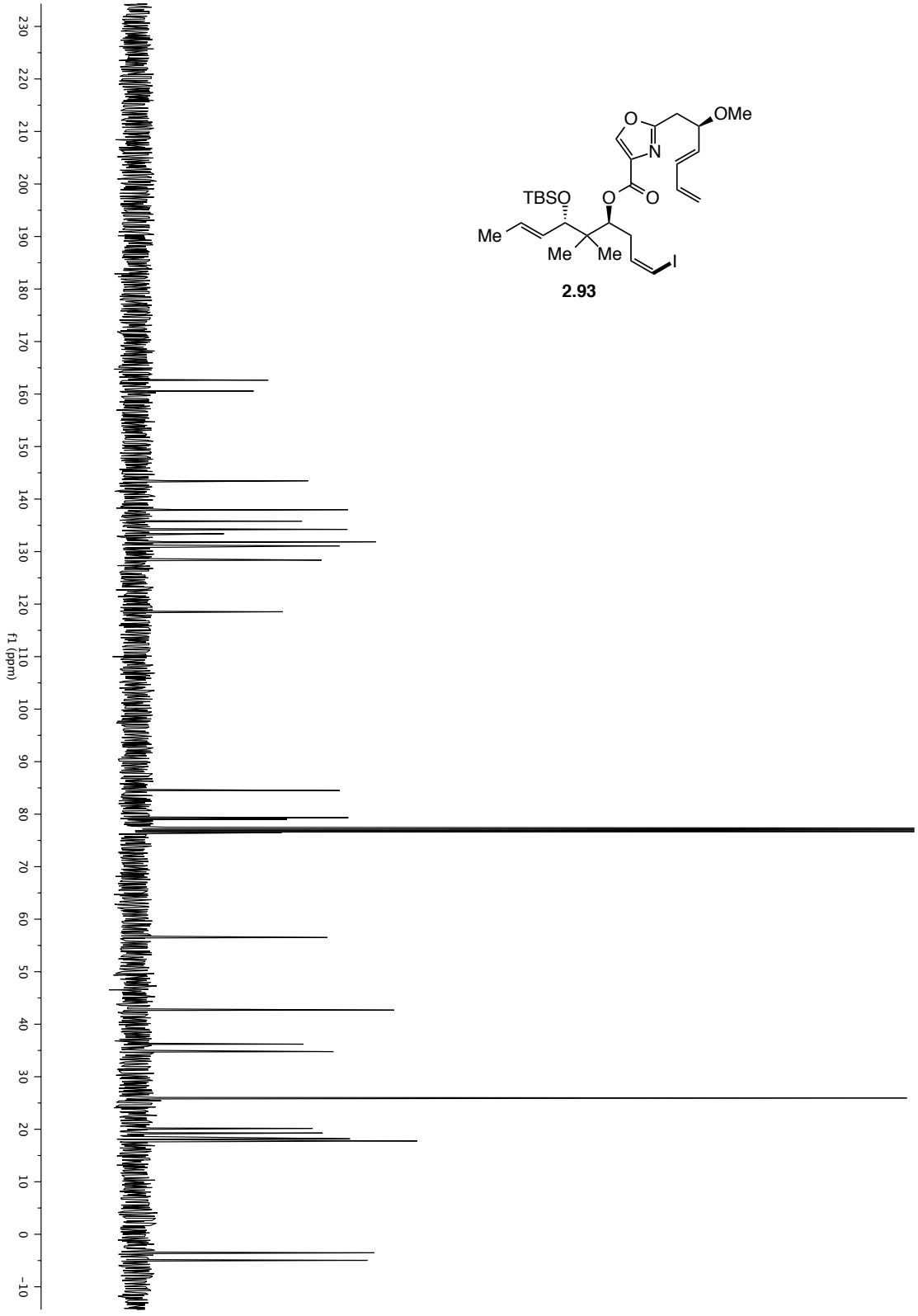
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.0
O
N
OMe
TBSO
O
O
Me
Me
Me
I

2.93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200
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160
150
140
130
120
110
100
90
80
70
60
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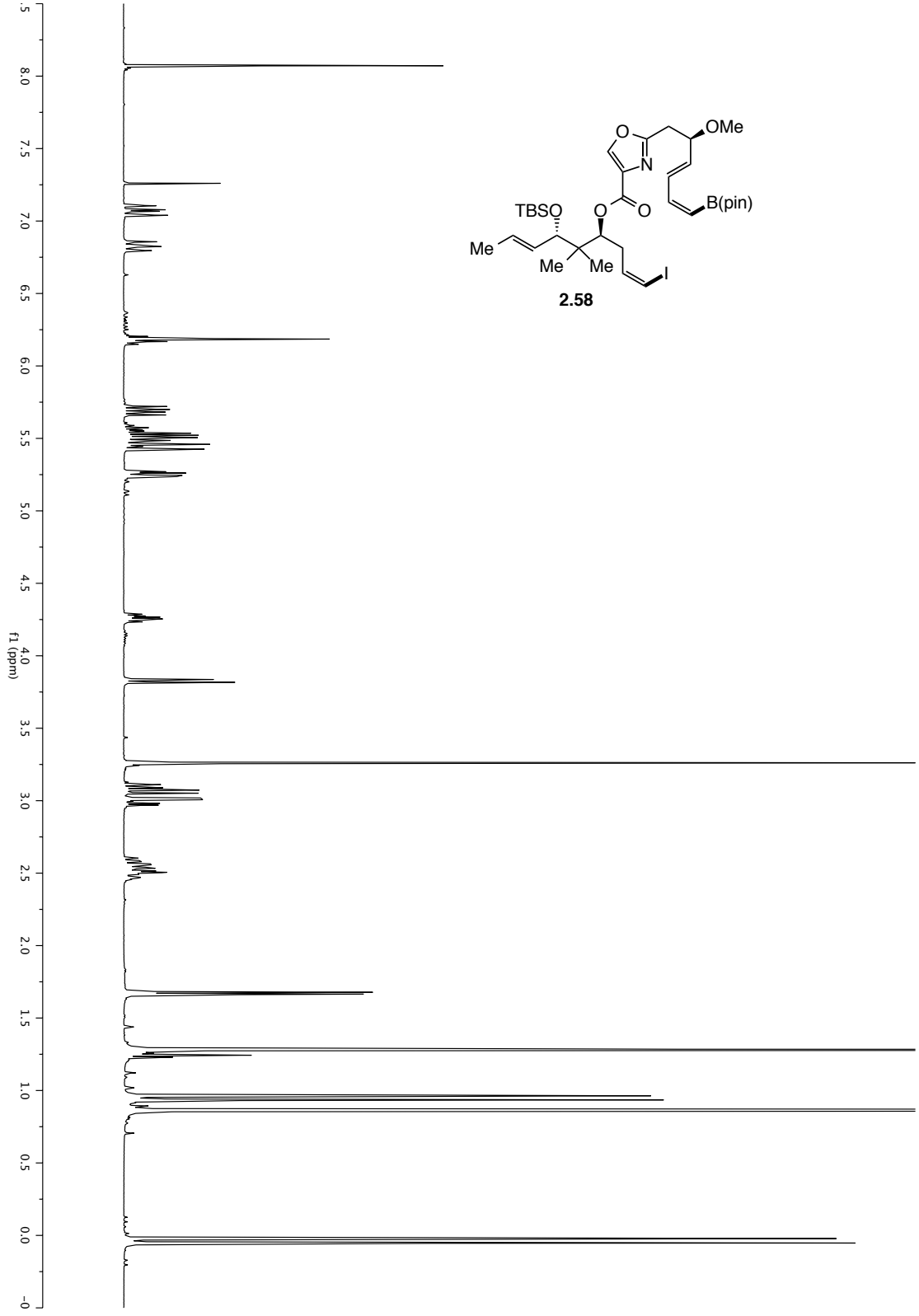
20
10
0
-10
O
N
OMe
TBSO
O
O
Me
Me
Me
I

2.93



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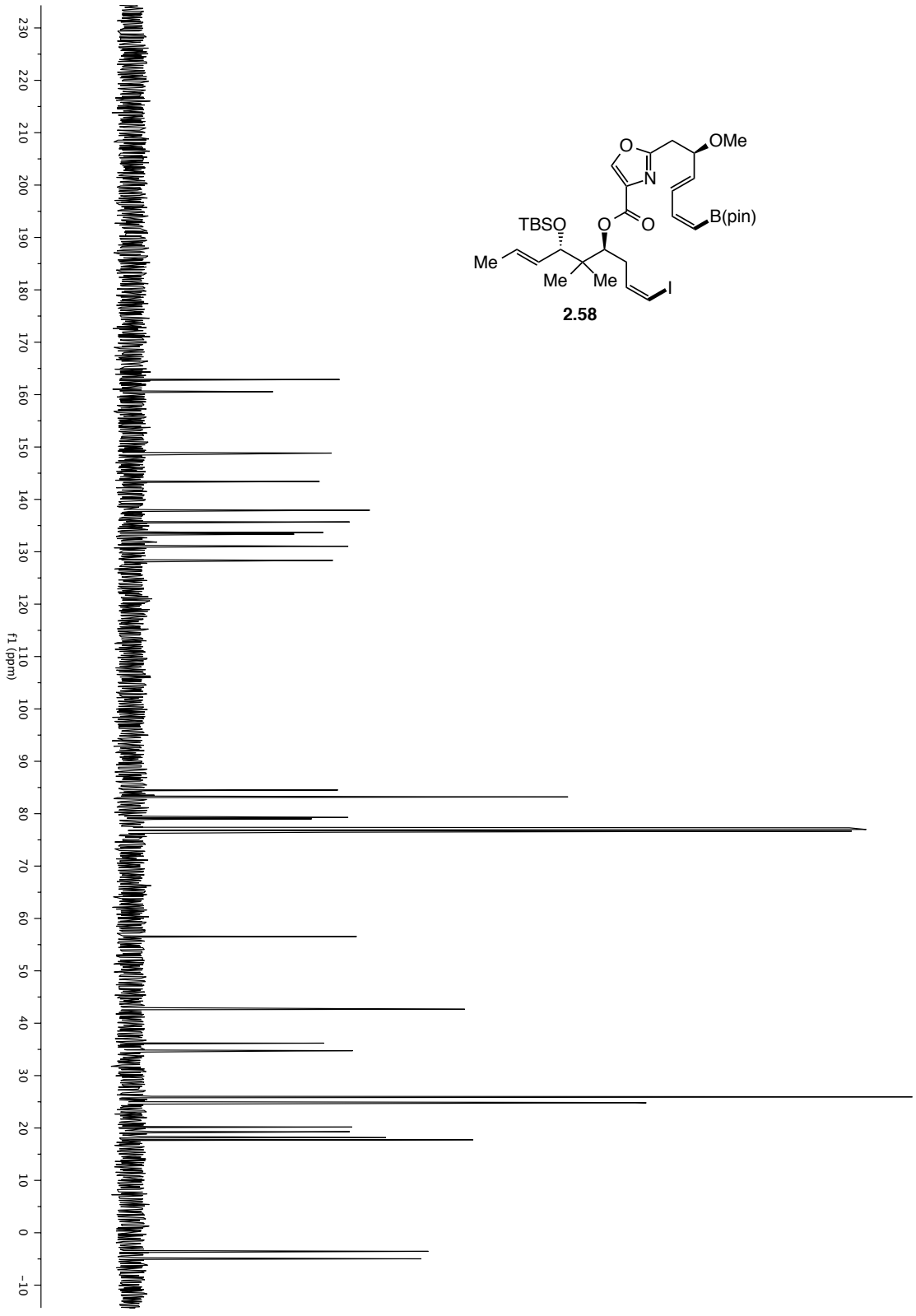
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200
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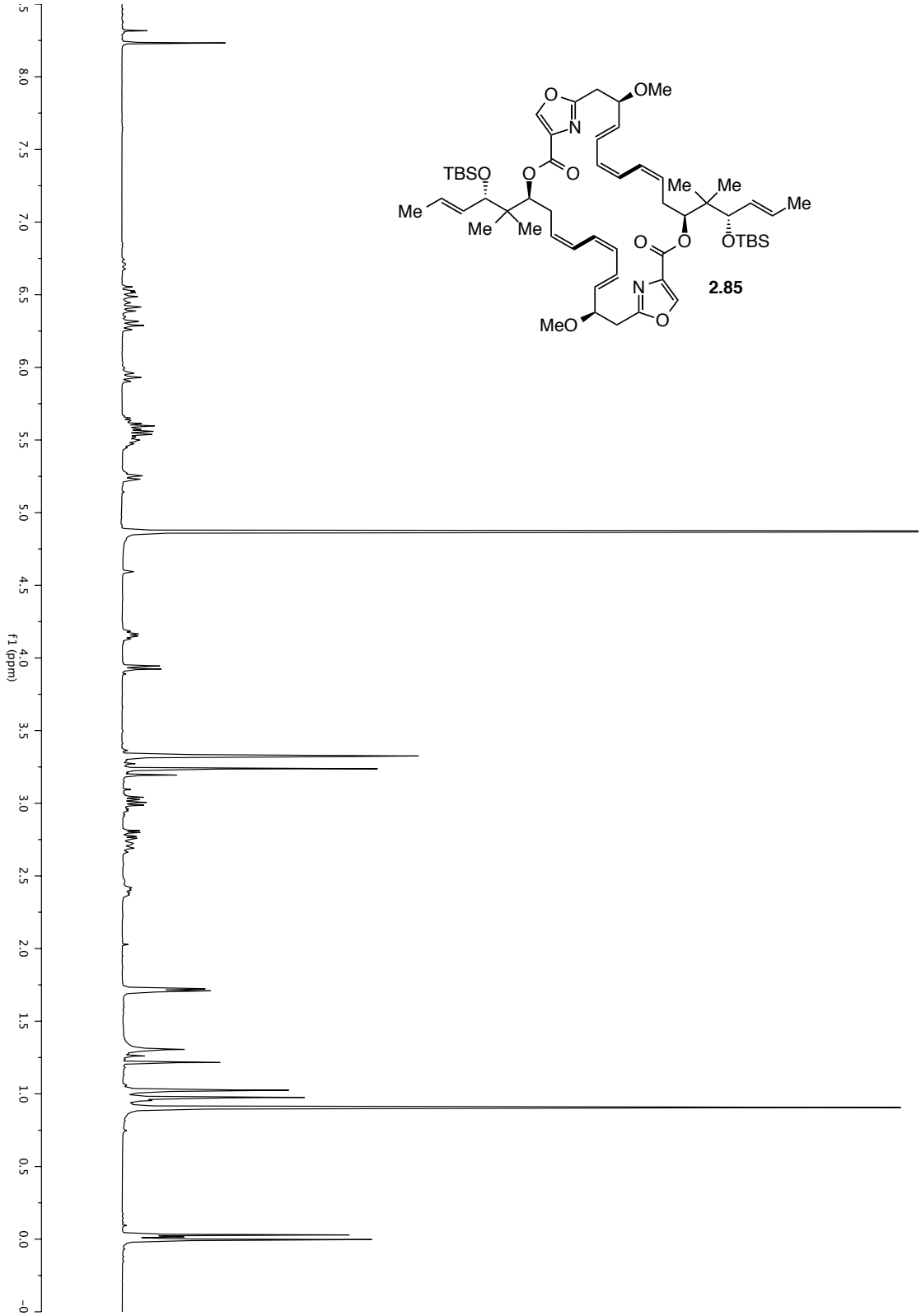
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
O
N
OMe
B(pin)
TBSO
O
O
Me
Me
Me
I

2.58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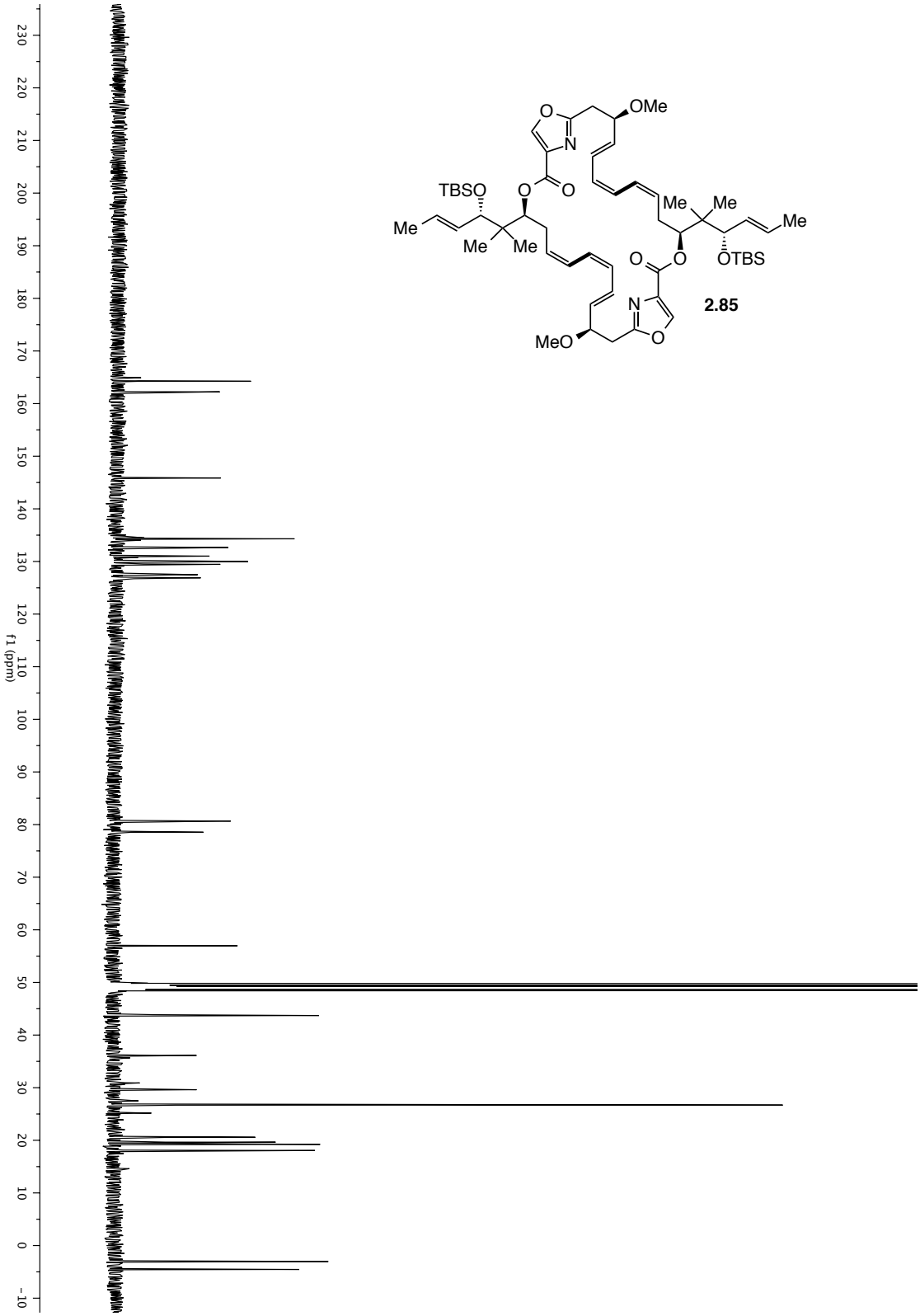
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
OMe
TBSO
Me
Me
Me
Me
Me
Me
OTBS
MeO
2.85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200
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140
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100
90
80
70
60
50
40
30
20
10
0
-10
OMe
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TBSO
O
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Me
Me
Me
Me
Me
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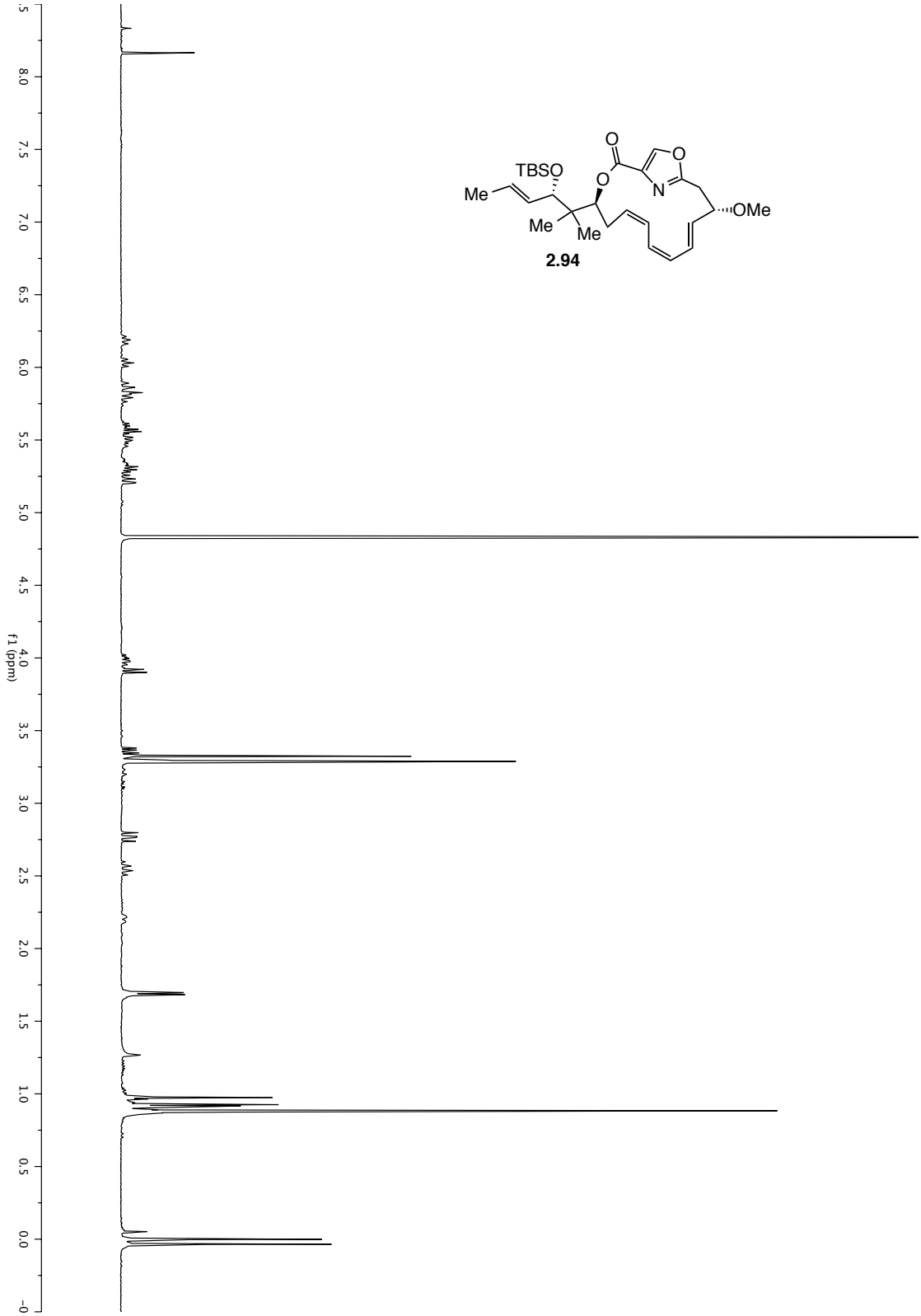
O
O
OTBS
N
MeO
O

2.85



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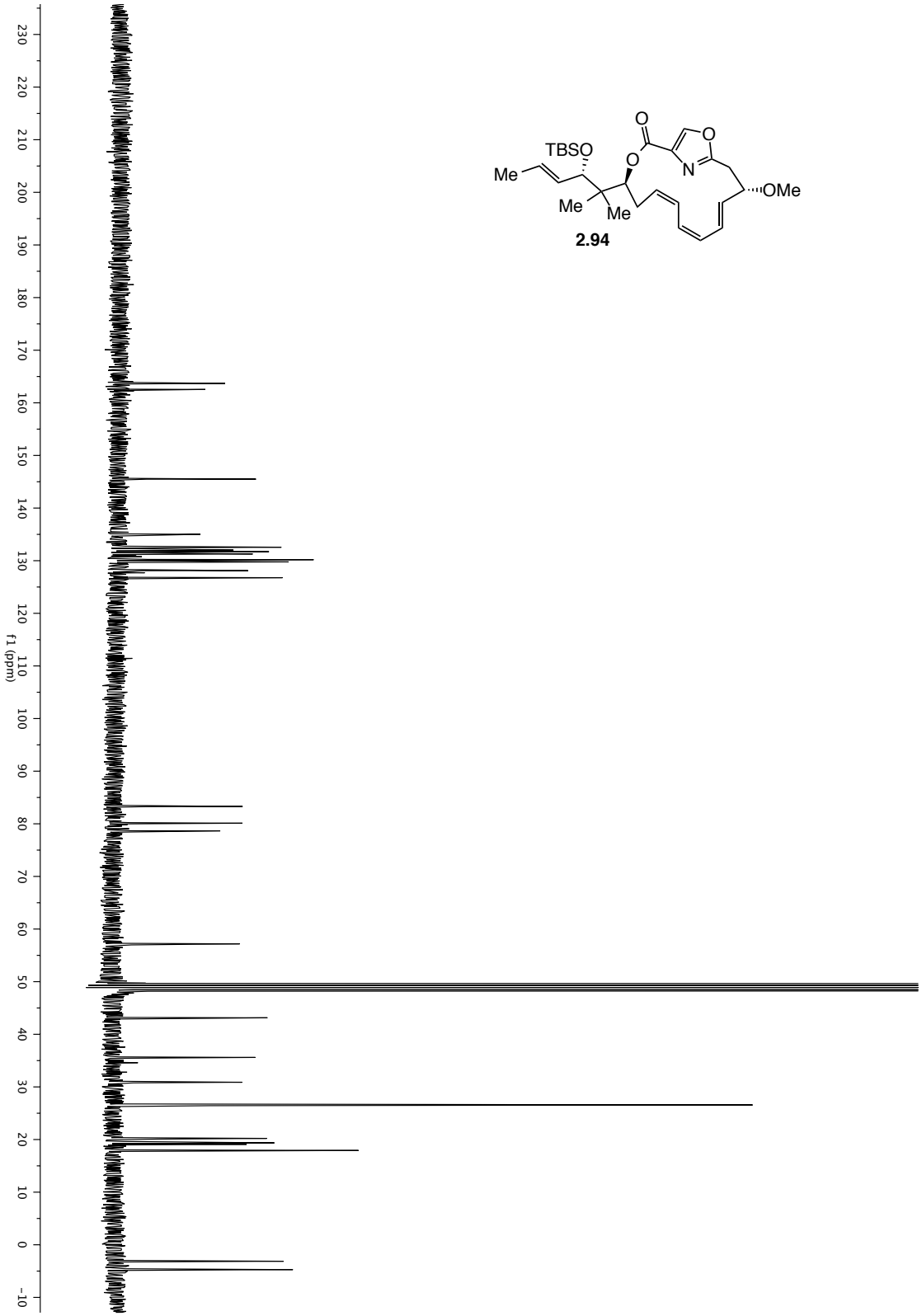
f1 (ppm)
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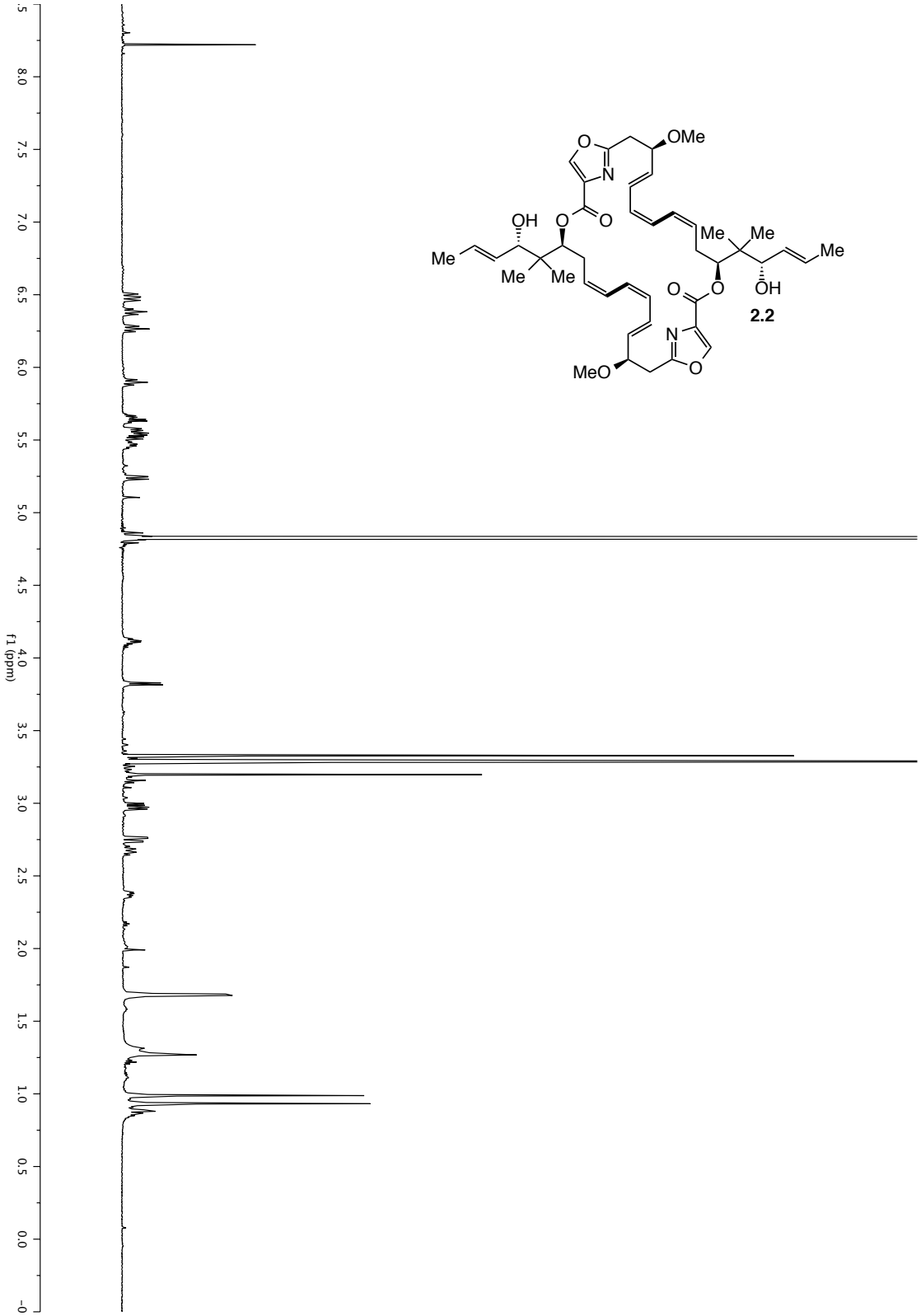
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

TBSO
Me
Me
Me
O
O
O
N
OMe

2.94


f1 (ppm)
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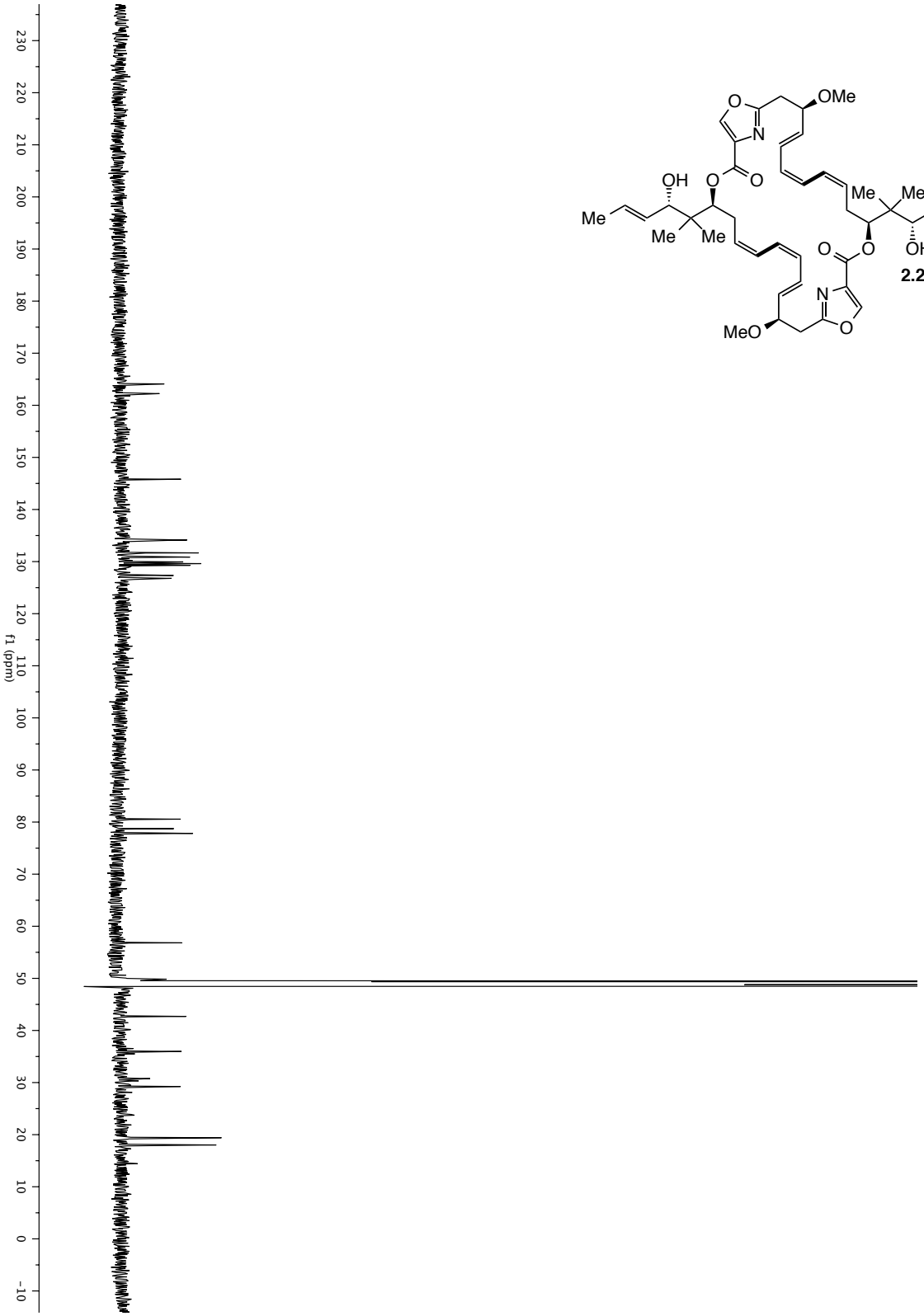
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
OMe
OH
Me
Me
Me
Me
Me
Me
OH
MeO
2.2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100
90
80
70
60
50
40
30
20
10
0
-10

OMe
O
N
OH
O
O
Me
Me
Me
Me
Me
Me
O
O
OH
N
MeO
O

2.2

Chapter 3. Stereoselective Cross-Metathesis to Form Trisubstituted Alkenes

3.1 Introduction

Stereoselective formation of trisubstituted olefins is often problematic. Carbometalation of an alkyne, followed by trapping of the carbon-metal bond, requires harsh conditions that are incompatable with many functional groups. Wittig type reactions suffer from low reactivity and unpredictable selectivities. While significant efforts have been devoted to, and large strides made in ring-closing metathesis (RCM) to form trisubstituted olefins, only a small number of studies have used cross-metathesis (CM) to form trisubstituted olefins. This area of metathesis remains underdeveloped, this chapter details our group's recent studies in this area.

3.2 Background

Shortly after the disclosure of *N*-heterocyclic carbene supported Ru complex **3.1**,[1] the Grubbs group disclosed the first examples of CM to form trisubstituted olefins.[2] The complete results of this disclosure are presented in table 3.1. Using 5 mol % of **3.1**, 2-methylundecene was metathesized with a variety of α-olefins to afford products such as alkenyl dioxolane **3.2**, allyl sulfonylbenzene **3.3**, allylacetate **3.4** and acetate containing alkyl olefins **3.5**, with yields from 53–87% and *E*:*Z* selectivities between 70:30 to 77:23 (table 3.1). Other disubstituted olefins were used as represented by **3.6** and **3.7**, with similar yields and selectivities as before.

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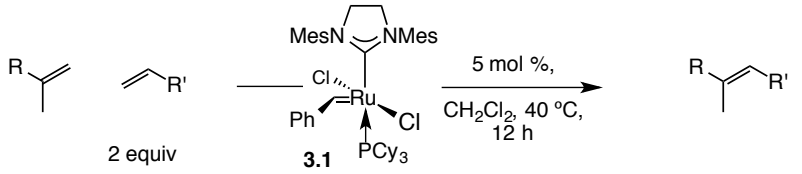
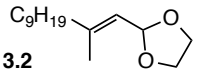
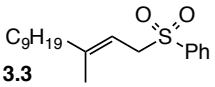
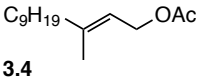
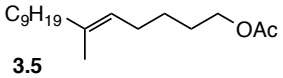
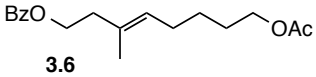
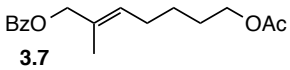
1. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

2. Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751–1753.

Table 3.1. Grubbs' Initial Trisubstituted Cross-Metathesis



entry	product	yield (%)[c]	*E*:*Z*
1[a]	 **3.2**	67	75:25
2	 **3.3**	87	77:23
3[b]	 **3.4**	53	71:29
4	 **3.5**	60	70:30
5	 **3.6**	80	73:27
6	 **3.7**	81	80:20

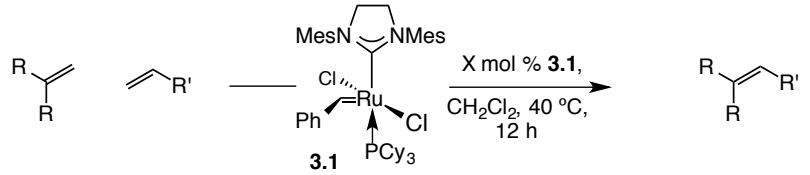
a) Reaction performed with 3 equiv of alpha olefin, added in 0.5 equiv portions every 1.5 h. b) Reaction performed with the dimer of the alpha olefin . c) Yield of isolated and purified products.

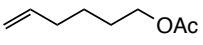
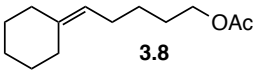
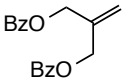
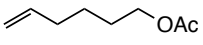
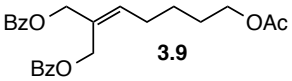
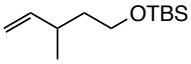
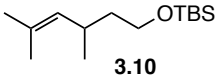
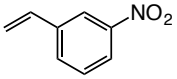
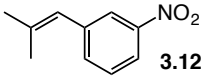
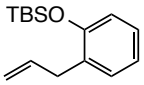
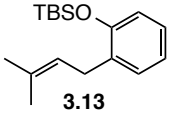
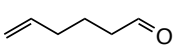
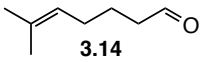
To address the seemingly insurmountable problem of selectivity, the Grubbs group conducted a study using symmetrically substituted olefins[3] (table 3.2). Olefins such as methylene cyclohexane and protected methylene propane diol reacted efficiently with terminal olefins to afford products **3.8** and **3.9** in 65 and 48% yield respectively. More importantly, they found that a metathesis reaction using condensed isobutylene can convert terminal olefins to a prenyl group such as in **3.10**. As using condensed gases is inconvenient on laboratory scale, they extended this method to use 2-methyl-2-butene **3.11**, which is a low boiling liquid. The prenyl group can then be installed on a variety of

3. Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939–1942.

olefins, including styrenes **3.12**, allyl benzenes **3.13** and alkyl olefins with a free aldehyde **3.14** (among others), with yields >90%.

Table 3.2. Grubbs' Trisubstituted CM with Symmetric Olefins



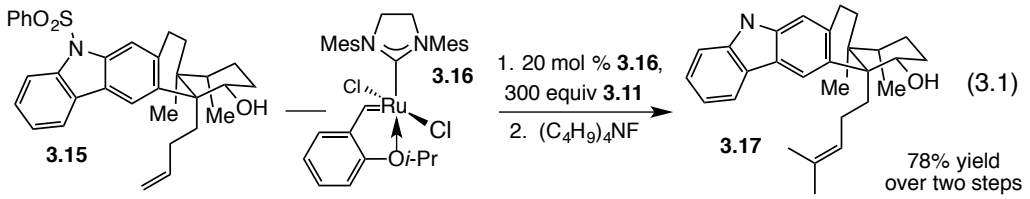
entry	disubstituted olefin	alpha olefin	**3.1** (mol %)	temp (°C)	product	yield (%)[a]
1	 1 equiv	 2 equiv	3	40	 **3.8**	65
2	 1 equiv	 2 equiv	3	40	 **3.9**	48
3	 condensed	 1 equiv	1	23	 **3.10**	72
4	 **3.11** "neat"	 1 equiv	1	23	 **3.12**	96
5	**3.11** "neat"	 1 equiv	1	23	 **3.13**	99
6	**3.11** "neat"	 1 equiv	1	23	 **3.14**	91

a) Yield of isolated and purified products.

This prenylation with **3.11** has been applied in a number of total synthesis[4] a representative case reported by Li is shown in eq. 3.1.[5] Exposure of terminal olefin **3.15**

4. a) Lindermayer, K.; Plietker, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 12183-12186. b) Suetsugu, S.; Nishiguchi, H.; Tsukano, C.; Takemoto, Y. *Org. Lett.* **2014**, *16*, 996-999. c) Wang, H.; Reisman, S. E. *Angew. Chem. Int. Ed.* **2014**, *53*, 6206-6210. d) Boyce, J. H.; Porco, J. A. *Angew. Chem. Int. Ed.* **2014**, *53*, 7832-7837.

to 20 mol % styrene ether containing complex **3.16**[6] and 300 equiv of **3.11** resulted in tubingensin **3.17** after indole deprotection with tetrabutylammonium fluoride, in 78% yield over two steps.



The CM involving disubstituted olefins containing an α-branch such as **3.18** is much more difficult due to the increased sterics near the reaction site (scheme 3.1). The Grubbs group developed Ru complex **3.20** in order to inhibit non-productive olefin metathesis with sterically bulky olefins,[7] but only 7% yield of **3.21** was obtained (vs. 17% when complex **3.16** was employed) (scheme 3.1A). As a solution to this problem, the Robinson group utilized trisubstituted olefin **3.22** with 30 equiv of **3.18** and 5 mol % **3.16** at high temperature and prolonged reaction times to obtain 90% yield of **3.21** (scheme 3.1B). When terminal olefin **3.19** was substituted for **3.21**, they obtained only 17% yield. In the presence of an α-olefin it is less likely that the disubstituted Ru carbene derived from **3.18** will form. The presence of terminal olefins can also lead to unstable Ru methylidenes. In the presence of a large excess of **3.18**, the propagating Ru carbene will be derived from **3.18** rather than **3.22**. As a result of this, there are only two possible metallacycles in the Robinson system, whereas systems with terminal α-olefins have more modes of reaction. Metallacycle **I** would to the desired product **3.21**, and a dimethyl substituted Ru carbene. Metallacycle **II** would lead to product **3.23**, which was not observed. Metallacycle **II** suffers from severe eclipsing interactions between the *gem*-dimethyl unit derived from the substrate, and the *gem*-dialkyl moiety derived from the Ru

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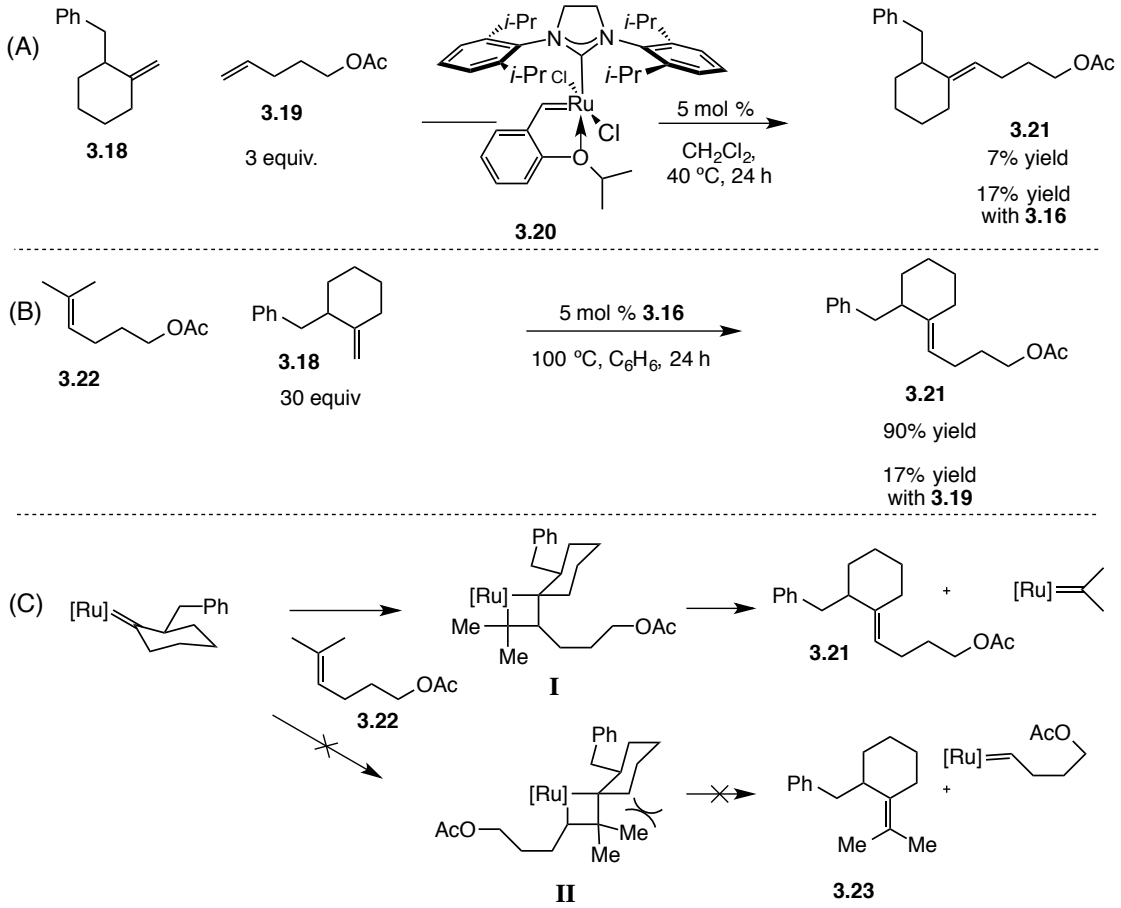
5. Bian, M.; Wang, Z.; Xiong, X.; Matera, C.; Nicolaou, K. C.; Li, A. *J. Am. Chem. Soc.* **2012**, *134*, 8078–8081.

6. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

7. Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441–444.

carbene. As metallacycle **I** only contains one of these eclipsing interactions, it, and **3.21**, were formed exclusively.

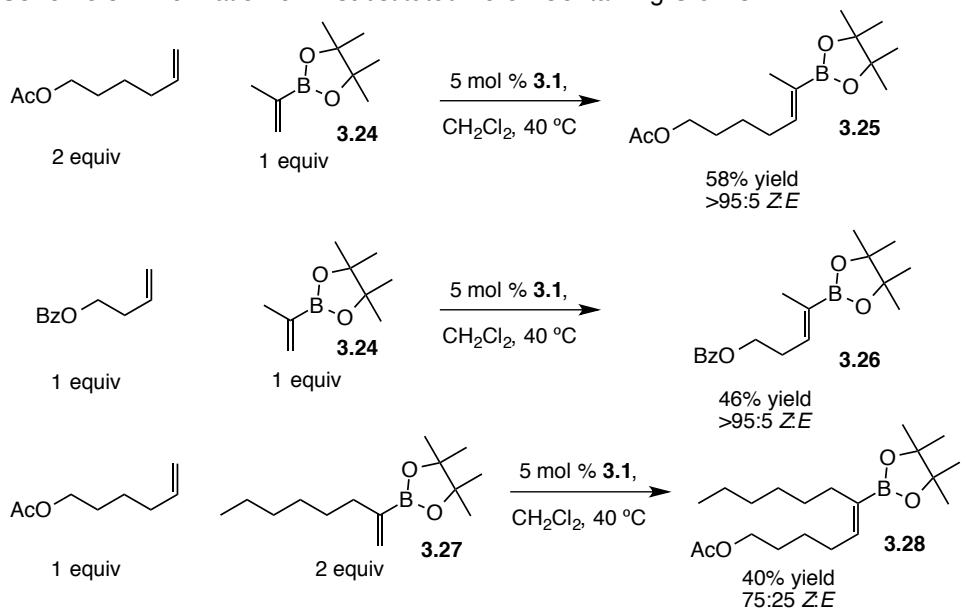
Scheme 3.1. Formation of Hindered Trisubstituted Olefins



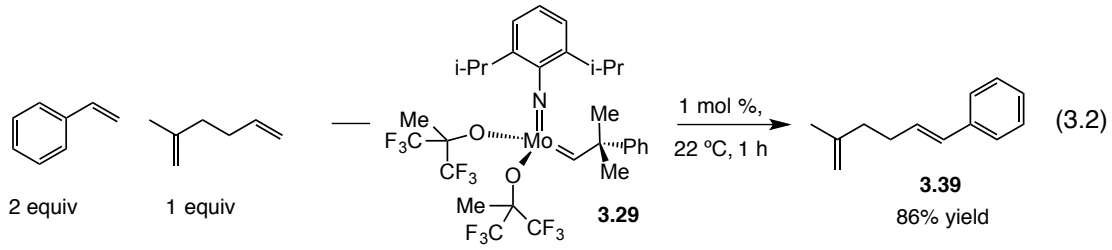
The Grubbs group has also disclosed formation of trisubstituted alkenyl borons through CM[8] (scheme 3.2). Complex **3.1** catalyzed the reaction between isopropenyl boronic acid pinacol ester B(pin) and a variety of terminal olefins affording products such as **3.25** and **3.26** with perfect *Z* selectivity, but yields of 58 and 46%, respectively. More substituted alkenyl B(pin) compounds such as **3.27** resulted in products of similarly low yield (40%) but also decreased selectivity (3:1 *Z*:*E*).

8. Morrill, C.; Funk, T. W.; Grubbs, R. H. *Tetrahedron Lett.* **2004**, *45*, 7733–7736.

Scheme 3.2. Formation of Trisubstituted Boron Containing Olefins



In the first example of CM,[9] Crowe demonstrated that terminal disubstituted olefins did not react with styrene in one hour in the presence of Mo complex **3.29**,[10] instead he observed exclusive formation of **3.39** in 86% yield (eq 3.2). Based on our studies (*vide infra*) this datum is a result of the short reaction time. Given a longer reaction time formation of a trisubstituted olefin could have been observed.



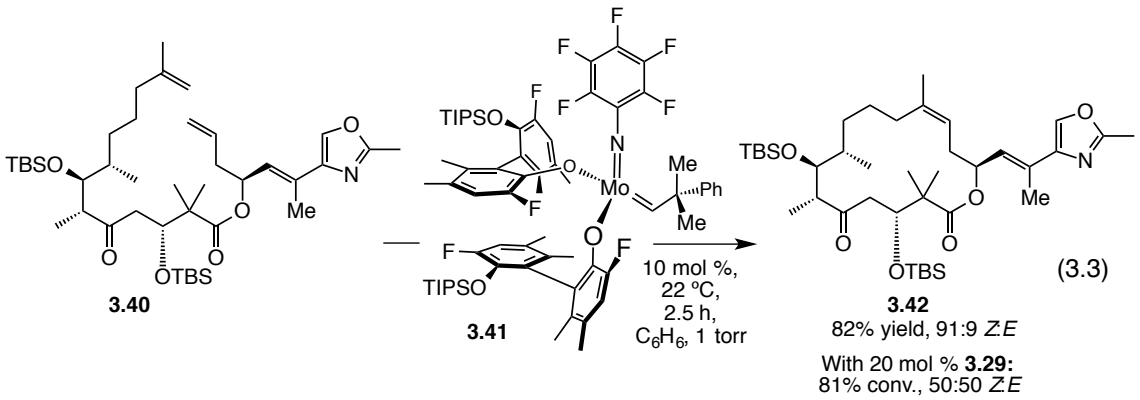
(3.2)

Our group has been active in the development of RCM to form trisubstituted macrocycles (eq 3.3). In the RCM of **3.40** we found that Mo–bisaryloxide complex **3.41** delivered *tert*-butyldimethylsilyl protected epothilone D **3.42**, in 82% yield with 91% *Z*

9. Crowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115*, 10998–10999.

10. a) Murdzek, J. S.; Schrock, R. R. *Organometallics,* **1987**, *6*, 1373–1374. b) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886.

selectivity.[11] When Mo complex **3.29** was used, **3.42** was obtained with only 50% *Z* selectivity. Encouraged by the reactivity and selectivity of bisaryloxide Mo catalysts such as **3.41** we had hoped to demonstrate the RCM of a variety of simpler marcocycles containing a trisubstituted olefin. Unfortunately, these efforts failed and products were obtained with only 50:50 *Z*:*E* olefin selectivity and yields from 40–60%.[12]



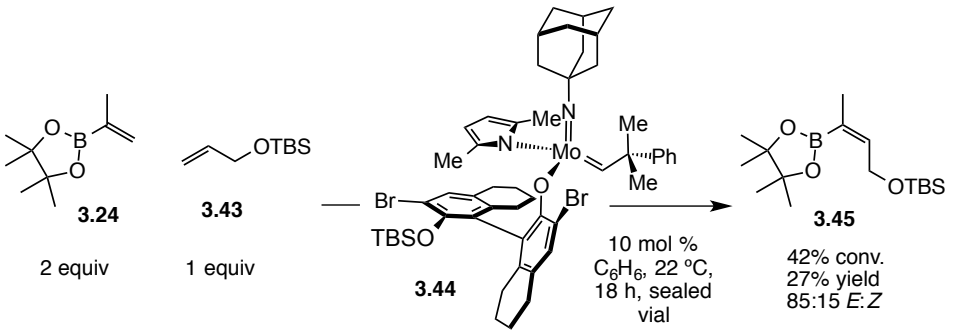
As an extension of our studies into vinyl-B(pin) CM,[13] we found that Mo containing monoaryloxide-monopyrrolide (MAP) complexes such as **3.44** can promote the metathesis of **3.24** with TBS protected allyl alcohol **3.43**[14] although in only 27% yield (eq 3.4). Unfortunately, reproducibility issues lead to difficulties in improving this reaction.

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

12. Miao Yu, *unpublished data*.

13. 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.

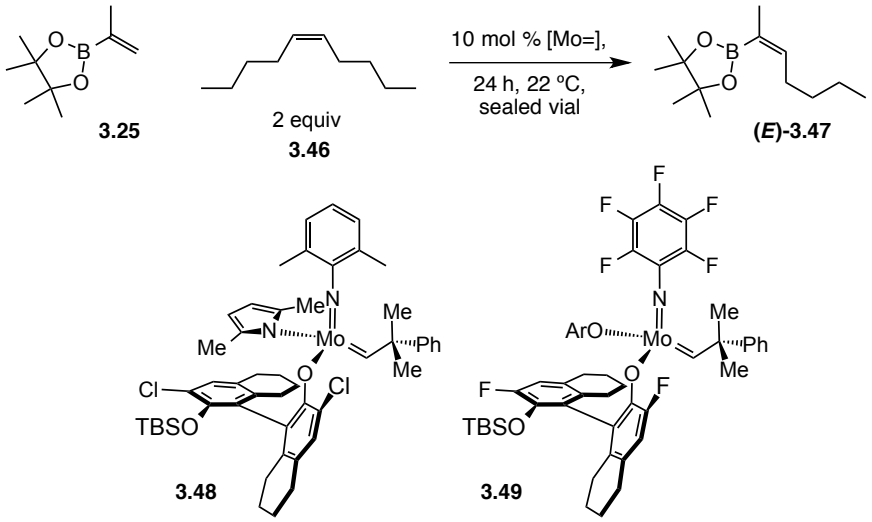
14. O'Brien R. V. *Ph.D. Thesis* Boston College, Chestnut Hill, MA, **2011**.



(3.4)

3.3 CM to form Trisubstituted Olefins

Table 3.2. CM to Afford Trisubstituted Alkenyl Boron Compounds[a]



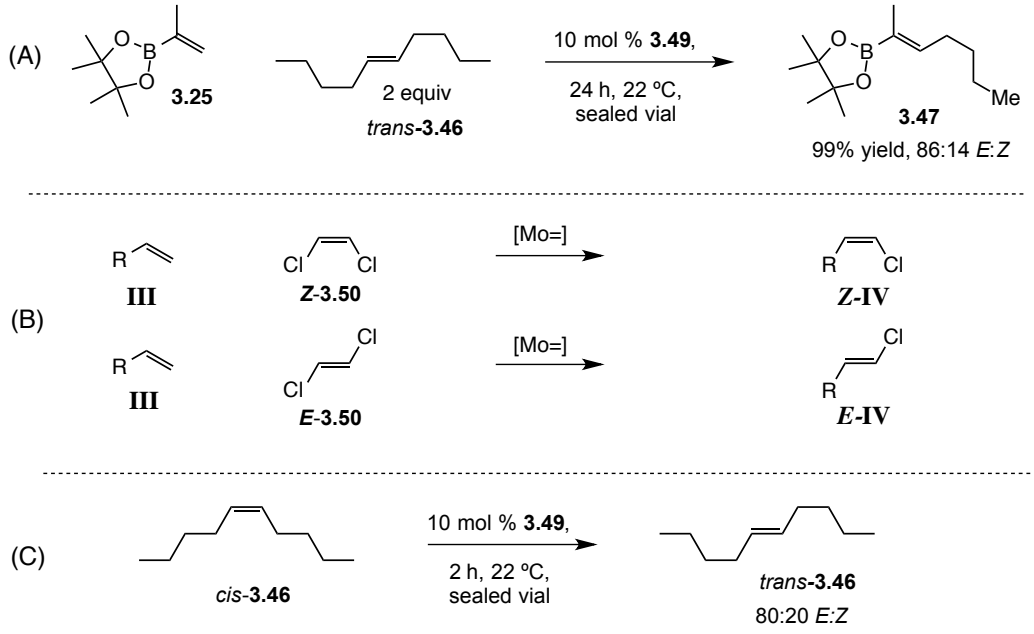
entry[a]	complex	yield (%)[b]	*E*:*Z*[c]
1	**3.48**	31	76:24
2	**3.49**	99	14:86
3	**3.29**	62	10:90
4	**3.16**	59	12:88

a) Reactions performed under N_2 atmosphere. b) Yield of isolated and purified product. c) Determined by analysis of ^{1}H NMR spectra of unpurified mixtures.

While trying to improve the reaction shown in eq 3.4, we moved to internal olefins such as *cis*-5-decene **3.46**, in order to minimize the generation of ethylene and

unstable Mo methylidenes. After testing several complexes in the metathesis of **3.25** and **3.46** to afford **3.47**, we noticed a puzzling trend in the selectivity. While MAP complex **3.48** afforded predominantly the *E*-isomer.[15] Bisaryloxide complex **3.49** afforded **3.47** with 86% *Z*-selectivity, which is the same stereoisomer as with **3.29** and **3.1**. Based on our results in the RCM towards epothilone B (eq 3.2) we had expected **3.49** to give the same *E*-selectivity afforded with the MAP complex.

Scheme 3.3. Selectivity Experiments for Trisubstituted Olefins



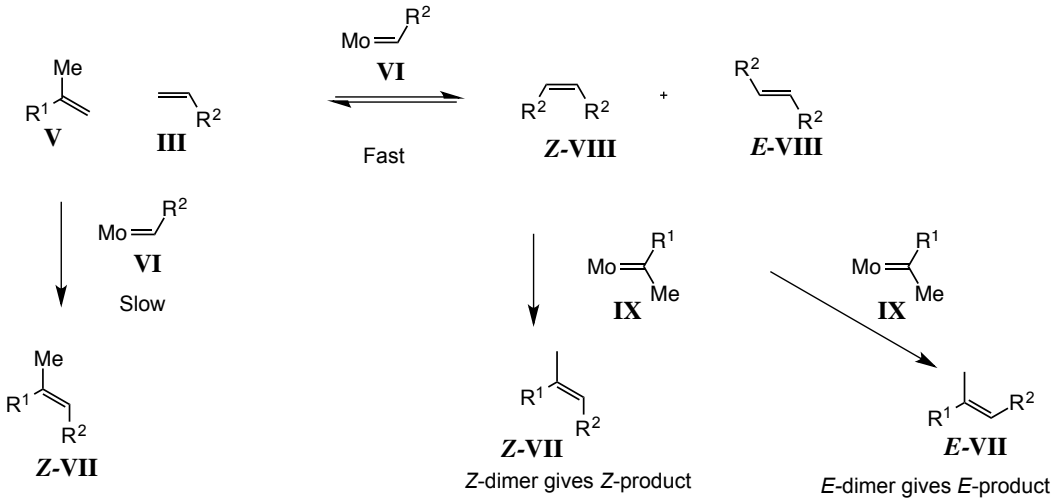
To investigate the cause of this selectivity we conducted the experiments shown in scheme 3.3. When **3.25** was mixed with *trans*-**3.46** in the presence of 10 mol % bisaryloxide **3.49**, we observed **3.47** formed with the same selectivity and yield as when *cis*-**3.46** was used (cf. table 3.2) (scheme 3.3A). Observations within our group[16] have shown that CM employing an α-olefin (**III**) and *Z*-dichloroethylene (***Z*-3.50**), which does not isomerize to ***E*-3.50** under metathesis conditions, affords *Z*-alkenyl halide products ***Z*-IV**. Utilizing *E*-dichloroethylene ***E*-3.50** affords *E*-products (scheme 3.3B). The

16. IUPAC nomenclature gives boron lower priority than carbon, hence the isomer with the bulky B(pin) group *syn* to the new alkyl group is the *E* isomer.

16. Thach T. Nguyen; Ming Joo Koh, Xiao Shen, Filippo Romiti *unpublished data*.

selectivity observed in the trisubsituted olefin products could also be a reflection of internal olefin geometry during the reaction. Exposure of *cis*-**3.46** to complex **3.49** for 2 h, lead to an 80:20 *E*:*Z* mixture now favoring *trans*-**3.46** (scheme 3.3C). In light of this data, we hypothesized that the CM to form trisubstituted olefins occurs along the pathways outlined in scheme 3.4. We propose that the initial reaction between a 2,2-disubstituted olefin **V** and Mo complex **VI** to afford product **VII** is slow. Instead alkylidene **VI** reacts rapidly with the α-olefin **III** to generate mainly ***Z*-** and ***E*-VIII**. Complexes that are highly selective for the formation of **VIII** from **III**, are often not very active, and will not produce substantial amounts of trisubstituted product **VII**. Even if a highly active catalyst was initially selective in this step, it could easily revert homodimer **VIII** back into terminal **III**, establishing a thermodynamic equilibrium, which would ultimately erode any kinetic selectivity imparted by the catalyst. Later in the reaction, the mixture consists of mainly internal olefins ***Z***- and ***E*-VIII**, which can react with the Mo alkylidene **IX**, (generated from 2,2-disubstituted olefin **V**), to afford trisubstituted product **VII**. In this scenario, the olefin geometry of **VII** is reflective of the geometry of homodimer **VIII**.

Scheme 3.4. Selectivity in Trisubstituted Cross-Metathesis



With this scenario in mind we needed a cross-metathesis partner that would not participate in homodimerization (c.f. **III** to **VIII** scheme 3.4), or if the starting material was an internal olefin, not participate in metathesis-based isomerization. This

understanding then limited the reaction scope to enol ethers, acrylates and dichloroethylene **3.50**. Based on previous success in our group,[16] we choose to develop the CM shown in table 3.3, wherein disubstituted olefin **3.60** was mixed with **3.50** in the presence of a variety of Mo containing complexes (figure 3.1) to afford trisubstituted *E*-alkenyl chloride **3.61**. Complex **3.44** which was marginally effective in the formation of trisubstituted B(pin)-containing olefins gave <2% conversion to product in this case (entry 1). We next explored pentafluorophenyl imido supported complexes **3.51**–**3.59**, as these have been effective in the CM of **3.50** with α-olefins (scheme 3.3B). We found that 10 mol % of **3.51** could afford 55% conv with 80:20 *E*:*Z* selectivity. The closely related **3.52** gives only slightly higher conversion (60%). Tetraphenylphenol containing complexes **3.53** and **3.54** do not improve conversion, nor do diphenylphenol based complexes **3.55**–**3.58**. However, when complex **3.59** was employed, quantitative conversion to product was observed, although with 75:25 *E*:*Z* selectivity. We propose that the tetra-*tert*-butylterphenyl ligand is uniquely effective for two reasons; Firstly, it lacks *ortho*-substituents, which allows enough space for one group of the metallacyclobutane to point towards the aryloxide ligand. Secondly, the 3,5-*tert*-butyl groups provide steric protection for the complex, and inhibit bimolecular catalyst decomposition,[17] which results in a longer living catalyst that is able to achieve higher conversion than others.

17. Tsang, W. C. P.; Hultzsch, K. C.; Alexander, J. B.; Bonitatebus, P. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 2652–2666.

Figure 3.1. Complexes Used to Obtain Trisubstituted Alkenyl Chlorides

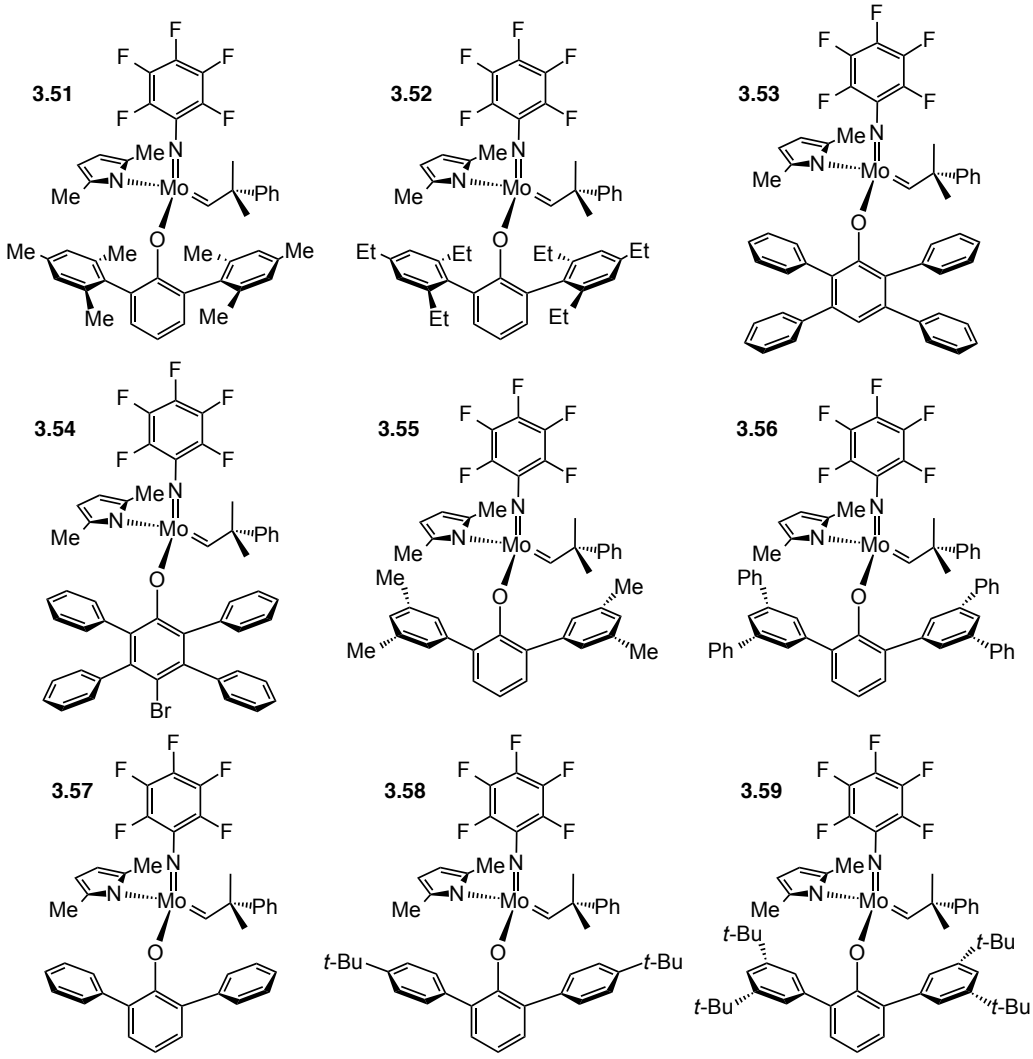
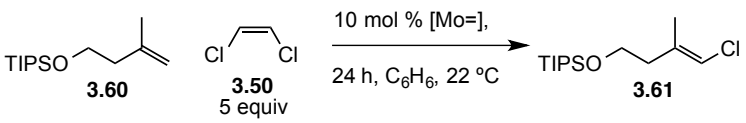


Table 3.3. Catalyst Screening for Trisubsituted Alkenyl Chlorides[a]

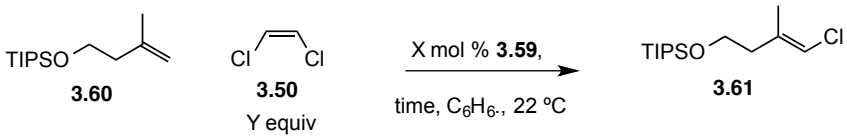


entry	complex	conv (%)[b]	*E*:*Z*[b]
1	**3.44**	<5	na
2	**3.51**	55	80:20
3	**3.52**	60	75:25
4	**3.53**	50	75:25
5	**3.54**	48	81:19
6	**3.55**	40	75:25
7	**3.56**	39	78:22
8	**3.57**	31	83:17
9	**3.58**	35	81:19
10	**3.59**	>98	75:25

a) Reactions performed under N_2 atmosphere in a sealed vial. b) Determined by analysis of ^{1}H NMR spectra of unpurified mixtures. na = not applicable

In an attempt to improve the selectivity, we attempted an optimization of the reaction conditions as shown in table 3.4. Employing 20 equiv of **3.50** does not improve the selectivity (entry 2 vs. entry 1), but lowering the amount of **3.50** to 2 equiv is detrimental, only 76% conv was obtained with 68:32 *E*:*Z* selectivity (entry 3). Lower catalyst loading provides only a slight decrease in conversion to 89% (entry 4), although purification of alkenyl chloride **3.61** from the starting material **3.60** was difficult, we opted to continue our studies at 10 mol %. The reaction was complete in as few as twelve hours (entry 5).

Table 3.4. Optimization of CM to Afford Trisubstituted Alkenyl Chlorides[a]



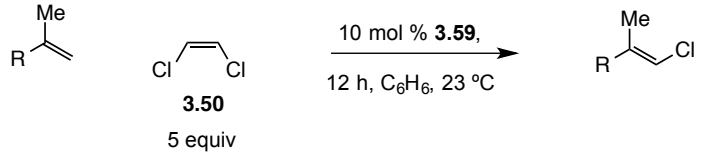
entry	mol % **3.59**	equiv **3.50**	time (h)	conv (%)[b]	*E*:*Z*[b]
1	10	5	24	>98	75:25
2	10	20	24	>98	74:26
3	10	2	24	76	68:32
4	5	5	24	89	75:25
5	10	5	12	>98	75:25

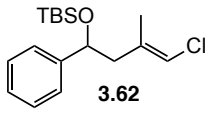
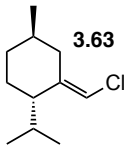
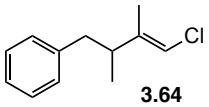
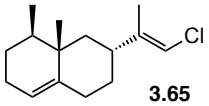
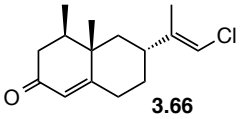
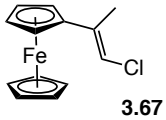
a) Reactions performed under N_2 atmosphere in a sealed vial.
b) Determined by analysis of ^{1}H NMR spectra of unpurified mixtures.

Our inability to identify a more selective catalyst or reaction conditions led us to explore the reaction with other substrates (table 3.5). We hypothesized that the low selectivity in the formation of **3.61** was due to an inability of our complex to effectively differentiate between the CH_3 group, and the slightly larger CH_2 group. We investigated the formation of **3.62** which contains a β-branch, and although high conversion and yield were obtained, the selectivity was similarly low (71:29 *E*:*Z*, entry 1). More hindered **3.63**, derived from menthol, was generated with perfect selectivity, but only 10% conv was obtained (entry 2). The formation of slightly less bulky **3.64**, which contains an α-methyl group (vs. α-isopropyl in **3.63**) was more efficient, affording product in 58% yield, and 93:7 *E*:*Z* olefin selectivity (entry 3). The CM of **3.50** and valencene gave **3.65** in low yield (35%) and low selectivity (75:25 *E*:*Z*, entry 4). The selectivity was much lower than we anticipated, but this was likely a result of the low purity of valencene. Commercial samples begin at ~65% purity, and after purification by distillation still contain a mixture of olefins. As **3.40** *en route* to epothilone D, contains an unprotected ketone, we subjected nootkatone to our CM conditions without protecting the ketone to afford **3.65**, but no reaction was observed (entry 5). We also produced ferrocenyl chloride **3.67** in 45% conversion, as a single olefin isomer, but the material was not separable from the terminal olefin. Alkenyl chlrodies **3.62–3.64** were purified with

$AgNO_3$-impregnated silica gel, but $AgNO_3$ oxidation of ferrocene to ferrocenium nitrate is well known.

Table 3.5. CM to form Trisubstituted Alkenyl Chlorides[a]



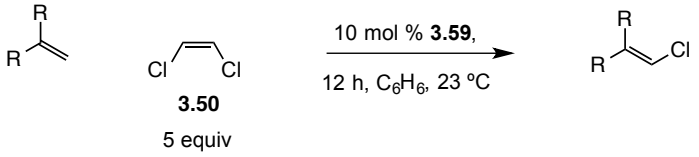
entry	product	conv (%)[b]	yield (%)[c]	*E:Z*[b]
1	 **3.62**	>98	77	71:29
2	 **3.63**	10	nd	>98:2
3	 **3.64**	65	58	93:7
4	 **3.65**	43	35	75:25
5	 **3.66**	<2	na	na
6	 **3.67**	45%	nd	>98:2

a) Reactions performed under N_2 atmosphere in a sealed vial. b) Determined by analysis of ^1H NMR spectra of unpurified mixtures. c) Yield of isolated and purified product. na = not applicable; nd = not determined

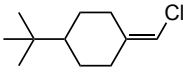
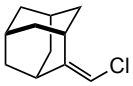
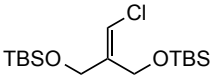
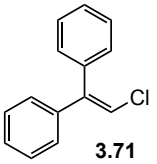
As we were still having difficulty obtaining high selectivity, we decided to perform CM on a symmetrically disubstituted olefins (table 3.6). When 4-*tert*-butylmethylenecyclohexane was subjected to our CM conditions **3.68** was obtained

readily in 90% yield. The adamantyl containing alkenyl chloride **3.69** was obtained in higher yield when 20 equivalents of **3.50** were used, although this was still lower yield than with **3.68**. Inspired by Grubbs report of CM with symmetric olefins, we explored the reaction with TBS-protected methylenepropanediol, and obtained **3.70** in 46% yield. The reaction with 1,1-diphenylethylene is reluctant to proceed, only 5% conv to **3.71** was observed.

Table 3.6. CM to form Symmetrically Substituted Trisubstituted Alkenyl Chlorides[a]



3.50
5 equiv

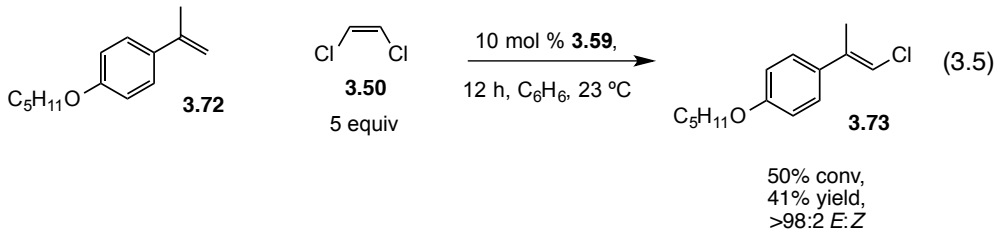
entry	product	conv (%)[b]	yield (%)[c]
1	 **3.68**	95	90
2[d]	 **3.69**	70	62
3	 **3.70**	50	46
4	 **3.71**	5	nd

a) Reactions performed under N_2 atmosphere in a sealed vial. b) Determined by analysis of ^{1}H NMR spectra of unpurified mixtures. c) Yield of isolated and purified product. d) Reaction performed with 20 equiv. of **3.50.** nd = not determined

Because of the importance of aryl units in drug-like molecules, and other studies in our group that show high CM reactivity with styrenes[18,13] we demonstrated the alkenyl chloride CM with styrene **3.72** (eq 3.5). We choose this particular substrate due to its

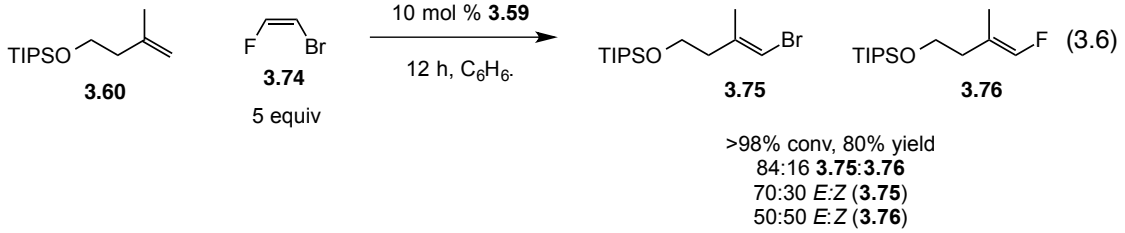
18. a) Elsie Yu *unpublished data*. b) Brett Johnson *unpublished data*.

low volatility, and that electron rich styrenes have been shown to be more active in other CM systems. Alkenyl chloride **3.73** was obtained in 41% yield and as a single olefin isomer.



(3.5)

As fluorinated compounds often have unique physical and biochemical properties,[19] but their syntheses can be lengthy,[20] we attempted CM involving commercially available 1-bromo-2-fluoroethylene **3.74**. Unfortunately, we obtained an 85:15 mixture of alkenyl bromide **3.77** to alkenyl fluoride **3.78** (eq. 3.6).



(3.6)

Based on this result, we propose the mechanism shown in scheme 3.5. Due to spectroscopic evidence of neophylene **3.77** in the unpurified reaction mixture, the starting complex must initiate with **3.60** to form disubstituted alkylidene **IX**. Alkylidene **IX** then reacts with **3.74** to generate fluorinated product, and bromo-alkylidene **X.** Computational studies indicate formation of a fluoro-alkylidene is energetically prohibitive[21]. This explains formation of ~10% fluorinated product. Alkylidene **X** can then react with

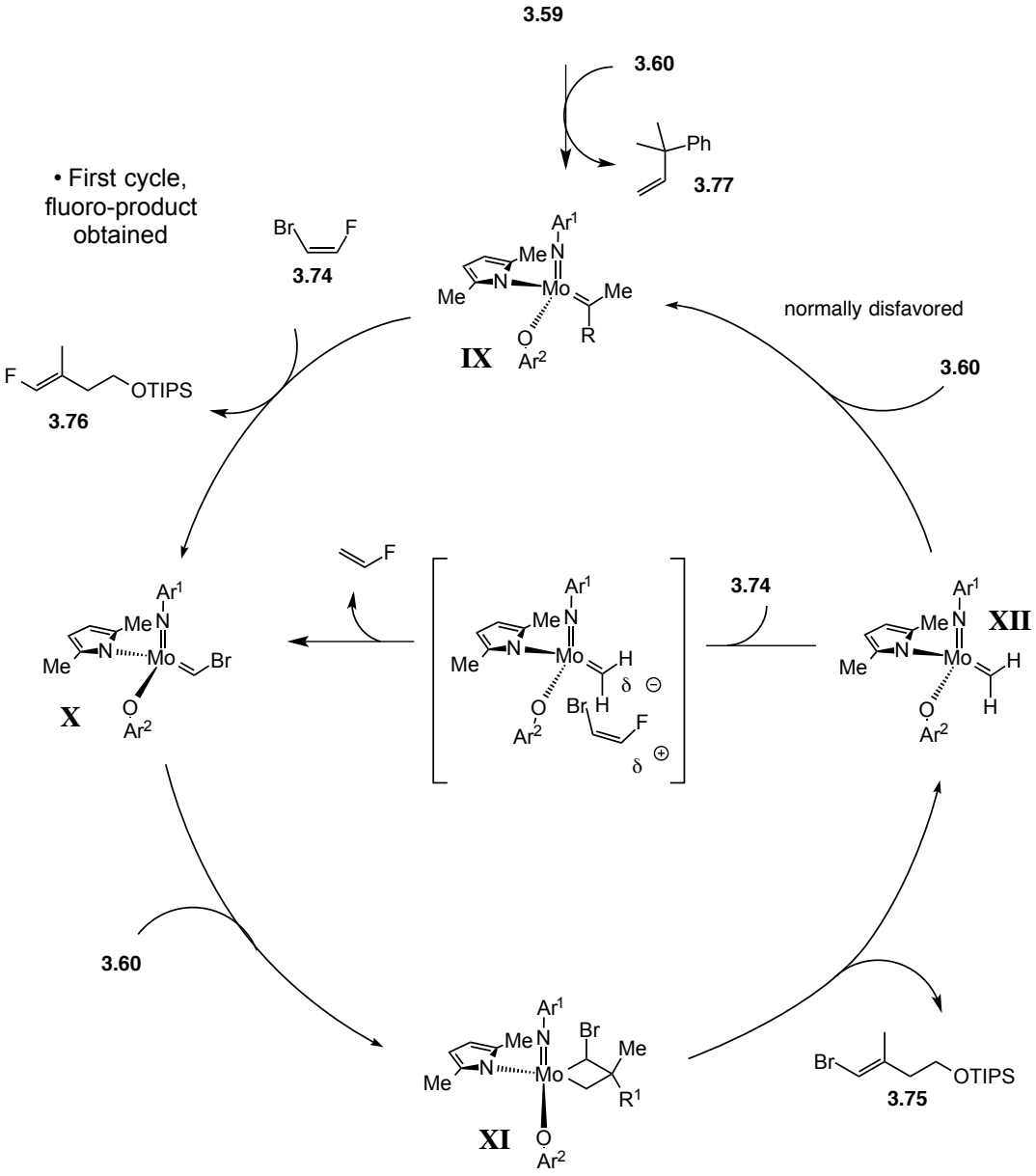
19. Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; Pozo, C. d.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432–2506.

20. McDonald, I, A.; Palfreyman, M. G.; Jung, M.; Bey, P. *Tetrahedron Lett.* **1985**, *26*, 4091–4092.

21. Sebastian Torker, unpublished data.

disubstituted olefin **3.60** through the intermediacy of metallacycle **XI**, to form **3.75** and Mo methylidene **XII**. We then propose that methylidene **XII** reacts with **3.74**, regenerating bromoalkylidene **X** and releasing vinyl fluoride. Methylidene **XII** prefers to react with **3.74** to form **X** (vs. reacting with **3.60** to generate **IX)** due to the greater steric hindrance of **IX** and is highly polarized with a partial positive charge on the carbon adjacent to the fluorine, and the molybdenum complex polarized with a partial negative charge on the alkylidene carbon. Thus **XII** and **3.74** are electronically matched to react, whereas **3.60** is relatively non-polarized.

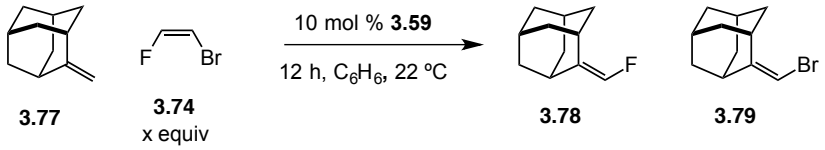
Scheme 3.5. Explaination of Halogen Chemoselectivity



In an attempt to obtain fluorinated products, we considered the possibility that a more hindered alkyl olefin would slow down the reaction from bromoalkylidene **X** to form brominated products, and that the greater sterics on the olefin would favor reaction through **IX** forming fluorinated products. As shown in table 3.6, this hypothesis was at least partially true. When adamantaone derived **3.77** is subjected to CM with **3.74** under our standard conditions, we observed 74:26 ratio of alkenyl fluoride **3.78** to alkenyl bromide **3.79** (entry 1). Both reduced and much larger amounts of **3.74** seem to favor the

formation of **3.79** over that of (entries 2 and 3). Unfortunately, **3.78** was too volatile to be isolated.

Table 3.7. Reversing Halogen Chemoselectivty with Sterically Hindered **3.77**[a]



3.77 **3.74** x equiv **3.78** **3.79**

entry	equiv **3.76**	conv (%)[b]	**3.78**[b]	**3.79**[b]
1	5	80	74	26
2	1.1	73	10	90
3	20	62	50	50

a) Reactions performed under N_2 atmosphere in a sealed vial.
b) Determined by analysis of ^{1}H NMR spectra of unpurified mixtures.

3.4 Conclusions

We have demonstrated the first steps towards a useful stereoselective CM to form trisusbstituted olefins. Through mechanistically driven experiments we have elucidated some of the factors that govern the selectivity of this class of CM. These studies are also relevant towards future applications with B(pin), enol ether and acrylate mono-substituted cross-partners.

3.5 Experimental

General: All reactions were carried out in oven-dried (135 °C) or flame-dried glassware under an inert atmosphere of dry N_2 unless otherwise stated. Thin layer chromatography (TLC) analysis was accomplished on 250 μm SiliCycle plates, with visualization provided by potassium permanganate or UV fluorescence quenching. Compounds were purified by silica gel chromatography on SiliCycle SilaFlash 230-400 mesh silica gel. All substrates were dried by azeotropic distillation with C_6H_6 prior to use in reactions with Mo- based complexes, or distilled under vacuum from CaH_2. Infrared (IR) spectra were recorded on a Bruker FTIR Alpha (ATR Mode) spectrometer. Bands are characterized as

strong (s), medium (m), weak (w) or broad (br). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 500 (500 MHz), Varian VNMRS 400 (400 MHz), Varian VNMRS 500 (500 MHz) or Varian VNMRS 600 (600 MHz). Chemical shifts (*d*) are reported in ppm from tetramethylsilane, referenced to the solvent resonance resulting from incomplete deuteration ($CDCl_3$: *d* 7.26) Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, br = broad, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Unity INOVA 400 (100 MHz), Varian VNMRS 500 (125 MHz) or VNMRS 600 (150 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal reference ($CDCl_3$: *d* 77.16). Values for the *Z:E* ratios were determined by analysis of the crude reaction mixture by ^{1}H NMR spectra. High-resolution mass spectrometry was performed on a JEOL Accu TOF Dart (positive mode) at the Boston College Mass Spectrometry Facility.

Solvents: Benzene (Alfa Aesar) was purged with Ar and purified under a positive pressure of dry Ar by a modified Innovative Technologies purification system.

Organometallic Complexes: Mo monoaryloxide pyrrolide (MAP) complexes **3.44**[22] and **3.49**[11] were prepared *in situ* according to previously reported procedures. Complexes **3.29**, **3.48**, and **3.51**–**3.59** were prepared *in situ* by procedures analogous to those for **3.44**. Ru-based complex **3.16** was prepared according to a previously reported procedure, purified by silica gel chromatography and re-crystallized from pentane/dichloromethane prior to use[23].

Reagents

***Z*-1-Bromo-2-fluoroethylene dichloroethylene (3.74)** was purchased from Synquest and used as received.

***Z*-Dichloroethylene (3.50)** was purchased from Synquest and used as received.

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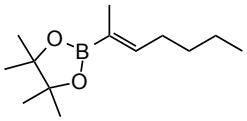
22. Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3844–3845.

23. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

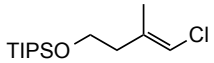
Isopropenyl B(pin) (3.25) was purchased from Frontier, purified by silica gel chromatography on silica using 20% ether in pentane as eluent to remove isopropanol present as an impurity, and distilled from CaH_2 before use.

General Procedure for Mo-catalyzed Cross-Metathesis. In an N_2-filled glove box, an oven-dried 4 mL vial equipped with a stir bar was charged with disubstituted olefin **3.60** (10.8 mg, 0.0446 mmol, 1 equiv), *Z*-dichloroethylene **3.50** (16.9 μL, 0.223 mmol, 5.0 equiv); then a 0.1 M solution **3.59** (44.6 μL, 0.00446 mmol, 10 mol %). The vial was tightly capped and the mixture was allowed to stir for 12 h. The reaction was quenched by removal from the glove box and by addition of $CDCl_3$ (% conversion and *Z:E* selectivity determined by ^{1}H NMR of the unpurified mixture). Then the mixture was purified by chromatography on $AgNO_3$-impregnated silica gel (10 wt %) (100% pentane) to afford **3.61** (11.1 mg, 0.0401 mmol, 90% yield, 75:25 *E*:*Z*) as colorless oil.



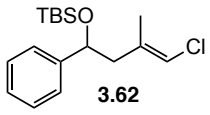
(*Z*)-3.47

(*Z*)-2-(hept-2-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.47): Following the general procedure, to a vial containing isopropenyl B(pin) **3.25** (19.0 mg, 0.113 mmol, 1 equiv), *cis*-5-decene **3.50** (31.6 mg, 0.226 mmol, 2.0 equiv) was added, followed by a solution of **3.49** (113 μL, 0.00113 mmol, 10 mol %). The vial was tightly capped and the solution allowed to stir for 12 h, then purified by silica gel chromatography (2% Et_2O/hexanes) to afford **3.47** (25.1 mg, 0.112 mmol, 99% yield, 86:14 *Z*:*E*) as colorless oil. **TLC R_f:** 0.2 (5% Et_2O/hexanes); **IR (neat):** 2978 (m), 2959 (m), 2928 (m), 2860 (w), 1632 (m), 1459 (w), 1411 (m), 1370 (s), 1338 (m), 1301 (m), 1271 (w), 1214 (s), 1141 (m), 1084 (w), 972 (m), 861 (w), 669 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.30 (br t, *J* = 6.9, Hz, 1H), 6.04 (*E* isomer, br s, 1H), 2.29 (*E* isomer, d, *J* = 7.3 Hz, 1H), 2.25–1.95 (m, 2H), 1.66 (dd, *J* = 1.8, 0.9 Hz, 3H), 1.44–1.26 (m, 4H), 1.28–1.15 (s, 12H), 1.03–0.70 (t, *J* = 5.5 Hz 3H).; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 146.8, 83.2, 31.2, 28.5, 25.0, 22.7, 14.1; **HRMS (DART+):** Calcd for $C_{13}H_{26}B_1O_2$ $[M+H]^+$: 225.20258; found: 225.20206.



3.61

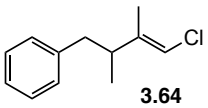
(*E*)-((4-chloro-3-methylbut-3-en-1-yl)oxy)triisopropylsilane (3.61): Following the general procedure, to a vial containing disubstituted olefin **3.60** (10.8 mg, 0.0446 mmol, 1 equiv), *Z*-dichloroethylene **3.50** (16.9 μL, 0.223 mmol, 5.0 equiv) was added, followed by a solution of **3.59** (44.6 μL, 0.00446 mmol, 10 mol %). The vial was tightly capped and the solution allowed to stir for 12 h, then purified by chromatography on $AgNO_3$-impregnated silica gel (10 wt %) (100% hexanes) to afford **3.61** (11.1 mg, 0.0401 mmol, 90% yield, 75:25 *E*:*Z*) as colorless oil. **TLC R_f:** 0.7 (100% pentane); **IR (neat):** 2943 (m), 2893 (m), 2866 (m), 1463 (w), 1382 (w), 1107, (w), 1069 (m), 1013 (w), 996 (w), 917 (w), 882 (w), 788 (w), 736 (w), 681 (w), 659 (w); **^{1}H NMR (400 MHz, $CDCl_3$)):** δ 5.85 (*E* isomer, s, 1H), 5.83 (*Z* isomer, s, 1H), 3.79 (*Z* isomer, t, *J* = 6.9 Hz, 2H), 3.76 (*E* isomer, t, *J* = 6.6 Hz, 2H), 2.47 (*Z* isomer, t, *J* = 6.9 Hz, 2H), 2.30 (*E* isomer, t, *J* = 6.6 Hz, 2H), 1.19–0.95 (m, 21H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 136.7 (*Z* isomer), 136.2 (*E* isomer), 113.5 (*E* isomer), 112.8 (*Z* isomer), 61.9 (*E* isomer), 61.2 (*Z* isomer), 40.6 (*E* isomer), 35.8 (*Z* isomer), 22.0 (stereochemistry unclear), 18.1 (*E*/*Z* overlapping), 17.0 (stereochemistry unclear), 12.1 (*E*/*Z* overlapping). **HRMS (DART+):** Calcd for $C_{14}H_{30}ClOSi$ $[M+H]^+$: 277.17544; found: 277.17585.



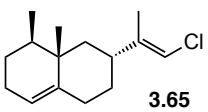
3.62

(*E*)-*tert*-butyl((4-chloro-3-methyl-1-phenylbut-3-en-1-yl)oxy)dimethylsilane (3.62): ^{1}H NMR (600 MHz, $CDCl_3$): Following the general procedure, to a vial containing the requisite disubstituted olefin (8.0 mg, 0.029 mmol, 1 equiv), *Z*-dichloroethylene **3.50** (11 μL, 0.15 mmol, 5.0 equiv) was added, followed by a solution of **3.59** (29 μL, 0.0029 mmol, 10 mol %). The vial was tightly capped and the solution allowed to stir for 12 h, then purified by chromatography on $AgNO_3$-impregnated silica gel (10 wt %) (100% pentane) to afford **3.62** (6.9 mg, 0.022 mmol, 77% yield, 71:29 *E*:*Z*) as colorless oil. **TLC R_f:** 0.8 (100% hexanes); **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.73–6.90 (m, 5H), 5.84 (*Z* isomer, dd, *J* = 1.6, 0.7 Hz, 1H), 5.83–5.69 (*E* isomer, m, 1H), 4.90 (*Z* isomer, dd, *J* = 8.3, 5.3 Hz, 1H), 4.71 (*E* isomer, dd, *J* = 8.4, 4.1 Hz, 1H), 2.62 (*Z* isomer, dd, *J* = 13.1, 8.3 Hz, 1H), 2.42 (*E* and *Z*

overlapping, m, 1H), 2.28 (*E* isomer ddd, *J* = 13.6, 4.2, 1.1 Hz, 1H), 1.80 (*E* isomer, d, *J* = 1.4 Hz, 3H), 1.69 (*Z* isomer, d, *J* = 1.6 Hz, 3 H), 0.87 (d, *J* = 4.1 Hz, 9H), 0.00 (s, 3H), –0.18 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** (*E* isomer only): δ 145.1, 135.2, 128.3, 127.3, 125.9, 114.9, 73.4, 48.8, 25.9, 18.3, 17.4, –4.6, –5.0. **IR (neat):** 3066 (w), 3029 (w), 2954 (m), 2929 (m), 2887 (w), 2857 (m), 1479 (m), (1454 (m), 1362 (m), 1306 (w), 1254 (w), 1179 (w), 1090 (m), 1069 (m), 938 (m), 835 (s), 776 (s), 699 (s), 668 (m), 548 (w); **HRMS (DART+):** Calcd for $C_{11}H_{12}Cl$ $[M+H–HOSiC_6H_{15}]^+$: 179.06275; found: 179.06266.

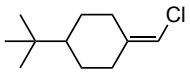


3.64 **(*E*)-(4-chloro-2,3-dimethylbut-3-en-1-yl)benzene (3.64):** Following the general procedure, to a vial containing the requisite disubstituted olefin (14.0 mg, 0.0873 mmol, 1 equiv), *Z*-dichloroethylene **3.50** (33.1 μL, 0.437 mmol, 5.0 equiv) was added, followed by a solution of **3.59** (87.3 μL, 0.00873 mmol, 10 mol %). The vial was tightly capped and the solution allowed to stir for 12 h, then purified by chromatography on $AgNO_3$-impregnated silica gel (10 wt %) (100% pentane) to afford **3.64** (9.9 mg, 0.0506 mmol, 58% yield, 93:7 *E*:*Z*) as colorless oil: **TLC R_f:** 0.95 (100% hexanes); **IR (neat):** 2982 (w), 2935 (w), 2906 (w), 2873 (w), 1749 (m), 1729 (m), 1464 (w), 1444 (w), 1369 (m), 1302 (m), 1246 (m), 1173 (m), 1154 (m), 1095 (m), 1022 (m), 972 (m), 858 (m), 820 (m), 749 (m), 479 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.32 –7.24 (m, 4H), 7.22 –7.15 (m, 1H), 7.14–7.07 (m, 2H), 5.76 (d, *J* = 1.3, Hz, 1H), 5.72 (diagnostic signal *Z* isomer d, *J* = 1.6 Hz, 1H), 2.84–2.65 (m, 1H), 2.64–2.44 (m, 2H), 1.78 (d, *J* = 1.4, 3H), 1.03 (d, *J* = 6.6, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 142.3, 140.5, 129.1, 128.4, 126.2, 112.6, 43.0, 41.6, 18.8, 13.7; **HRMS (DART+):** Calcd for $C_{12}H_{16}Cl$ $[M+H]^+$: 195.09405; found: 195.09496.



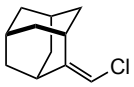
3.65 **(3*R*,4a*S*,5*R*)-3-((*E*)-1-chloroprop-1-en-2-yl)-4a,5-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalene (3.65):** Following the general procedure, to a

vial containing the requisite disubstituted olefin (9.7 mg, 0.048 mmol, 1 equiv), *Z*-dichloroethylene **3.50** (18 μL, 0.24 mmol, 5.0 equiv) was added, followed by a solution of **3.59** (48 μL, 0.0048 mmol, 10 mol %). The vial was tightly capped and the solution allowed to stir for 12 h, then purified by chromatography on $AgNO_3$-impregnated silica gel (10 wt %) (100% pentane) to afford **3.65** (3.9 mg, 0.016 mmol, 35% yield, 75:25 *E*:*Z*) as colorless oil: **TLC R_f:** 0.95 (100% hexanes); **IR (neat):** 2965 (m), 2922 (m), 2856 (m), 1633 (w), 1455 (w), 1437 (w), 1380 (w), 1310 (w), 1060 (w), 1048 (w), 1018 (w), 983 (w), 907 (w), 882 (w), 869 (w), 844 (w), 811 (w), 784 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.85–5.81 (m, 1H), 5.71 (diagnostic signal for the *Z* isomer, dd, *J* = 1.6, 0.6 Hz, 1H), 5.32 (dt, *J* = 4.8, 2.3 Hz, 1H), 2.43–2.19 (m, 3H), 2.12–1.85 (m, 5H), 1.86–1.76 (m, 1H), 1.75–1.63 (m, 5H), 1.61 (d, *J* = 1.6 Hz, 1H), 1.39 (ddd, *J* = 4.7, 2.7, 1.1 Hz, 4H), 1.34–1.15 (m, 3H), 1.00 (d, *J* = 0.7 Hz, 1H), 0.92 (d, *J* = 0.6 Hz, 3H), 0.89–0.79 (m, 5H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 143.4, 142.5, 120.7, 112.0, 110.6, 44.5, 42.9, 41.1, 38.0, 35.0, 32.7, 31.1, 27.2, 26.0, 22.5, 18.5, 17.4, 15.8, 14.9, 14.2, 9.0. **HRMS (DART+):** Calcd for $C_{15}H_{24}Cl$ $[M+H]^+$: 239.15665; found: 239.15696.

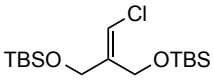


3.68

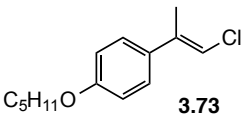
1-(*tert*-butyl)-4-(chloromethylene)cyclohexane (3.68): Following the general procedure, to a vial containing the requisite disubstituted olefin (9.8 mg, 0.064 mmol, 1 equiv), *Z*-dichloroethylene **3.50** (24 μL, 0.32 mmol, 5.0 equiv) was added, followed by a solution of **3.59** (64 μL, 0.0064 mmol, 10 mol %). The vial was tightly capped and the solution allowed to stir for 12 h, then purified by chromatography on $AgNO_3$-impregnated silica gel (10 wt %) (100% pentane) to afford **3.68** (10.8 mg, 0.0580 mmol, 90% yield) as colorless oil. **TLC R_f:** 0.95 (100% hexanes); **IR (neat):** 2951 (m), 2927 (m), 2865 (m), 1469 (w), 1444 (w), 1394 (w), 1365 (m), 1297 (w), 987 (w), 848 (m), 814 (m), 792 (m), 747 (m); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 5.75 (t, *J* = 2.0 Hz, 1H), 3.10–2.80 (m, 1H), 2.46–2.25 (m, 1H), 2.08–1.93 (m, 1H), 1.88 (m, 2H), 1.79–1.66 (m, 1H), 1.17 (dd, *J* = 12.0, 3.0 Hz, 1H), 1.05 (m, 2H), 0.86 (s, 9H). **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 142.1, 108.0, 48.0, 34.0, 32.4, 28.6, 28.4, 27.6, 27.4.



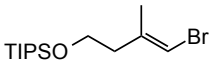
3.69 **2-(chloromethylene)adamantine (3.69):** Following the general procedure, to a vial containing the requisite disubstituted olefin (3.0 mg, 0.020 mmol, 1 equiv), *Z*-dichloroethylene **3.50** (7.7 μL, 0.010 mmol, 5.0 equiv) was added followed by a solution of **3.59** (20 μL, 0.0020 mmol, 10 mol %). The vial was tightly capped and the solution allowed to stir for 12 h, then purified by chromatography on $AgNO_3$-impregnated silica gel (10 wt %) (100% pentane) to afford **3.69** (2.3 mg, 0.0126 mmol, 62 % yield) as colorless oil. **TLC R_f:** 0.95 (100% hexanes); **TLC R_f:** 0.95 (100% hexanes); **IR (neat):** 2922 (m), 2852(m), 1463 (w), 1449 (w), 1259 (w), 1098 (m), 1029 (w), 837 (w), 798 (w), 768 (w). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.73 (s, 1H), 3.11 (d, J = 4.0 Hz, 1H), 2.47 (s, 1H), 1.95 (s, 2H), 1.85 (dd, J = 15.8, 11.9 Hz, 4H), 1.73 (d, J = 12.3 Hz, 4H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 149.8, 104.1, 39.4, 38.1, 37.0, 32.0, 28.3. **HRMS (DART+):** Calcd for $C_{11}H_{15}Cl$ $[M+H]^+$: 182.08623; found: 182.08566.

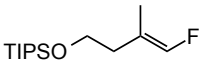


3.70 **6-(chloromethylene)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (3.70):** Following the general procedure, to a vial containing the requisite disubstituted olefin (6.1 mg, 0.019 mmol, 1 equiv), *Z*-dichloroethylene **3.50** (7.3 μL, 0.0.096 mmol, 5.0 equiv) was added followed by a solution of **3.59** (19 μL, 0.0019 mmol, 10 mol %). The vial was tightly capped and the solution allowed to stir for 12 h, then purified by chromatography on $AgNO_3$-impregnated silica gel (10 wt %) (100% pentane) to afford **3.70** (3.1 mg, 0.0089 mmol, 46% yield) as colorless oil. **TLC R_f:** 0.8 (100% hexanes); **IR (neat):** 2955 (m), 2929 (m), 2887 (w), 2857 (m), 1638 (w), 1472 (w), 1389 (w), 1379 (w), 1361 (m), 1257 (w), 1163 (br), 1074 (m), 1028 (m), 834 (m), 801 (m), 775 (m), 669 (m); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.08 (s, 1H), 4.37 (s, 2H), 4.26 (s, 2H), 0.91 (s, 9H), 0.90 (s, 9H), 0.08 (s, 6H), 0.07 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 140.8, 113.7, 63.0, 59.3, 26.0, 18.5, –5.3. **HRMS (DART+):** Calcd for $C_{16}H_{36}ClO_2Si_2$ $[M+H]^+$: 351.19423; found: 351.19336.



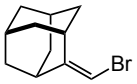
3.73 **(*E*)-1-(1-chloroprop-1-en-2-yl)-4-(pentyloxy)benzene (3.73):** Following the general procedure, to a vial containing the requisite disubstituted olefin (6.5 mg, 0.0.32 mmol, 1 equiv), *Z*-dichloroethylene **3.50** (12 μL, 0.16 mmol, 5.0 equiv) was added followed by a solution of **3.59** (32 μL, 0.0032 mmol, 10 mol %). The vial was tightly capped and the solution allowed to stir for 12 h, then purified by chromatography on $AgNO_3$-impregnated silica gel (10 wt %) (100% pentane) to afford **3.73** (3.1 mg, 0.013 mmol, 41% yield, >98:2 *E*:*Z*) as colorless oil. **TLC R_f:** 0.8 (100% hexanes); **IR (neat):** 2954 (w), 2924 (w), 2871 (w), 1608 (w), 1511 (w), 1285 (w), 1252 (w), 1239 (w), 1024 (w), 989 (w), 835 (w), 796 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.28–7.18 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.22 (d, J = 1.4 Hz, 1H), 3.94 (t, J = 6.6 Hz, 2H), 2.15 (d, J = 1.4 Hz, 3H), 1.83–1.70 (m, 2H), 1.40 (m, 4H), 0.91 (t, J = 7.1 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 159.1, 138.1, 132.7, 127.1, 114.6, 110.2, 68.2, 29.1, 28.4, 22.6, 17.0, 14.2. **HRMS (DART+):** Calcd for $C_{14}H_{20}ClO_1$ $[M+H]^+$: 239.12027; found: 239.11989.



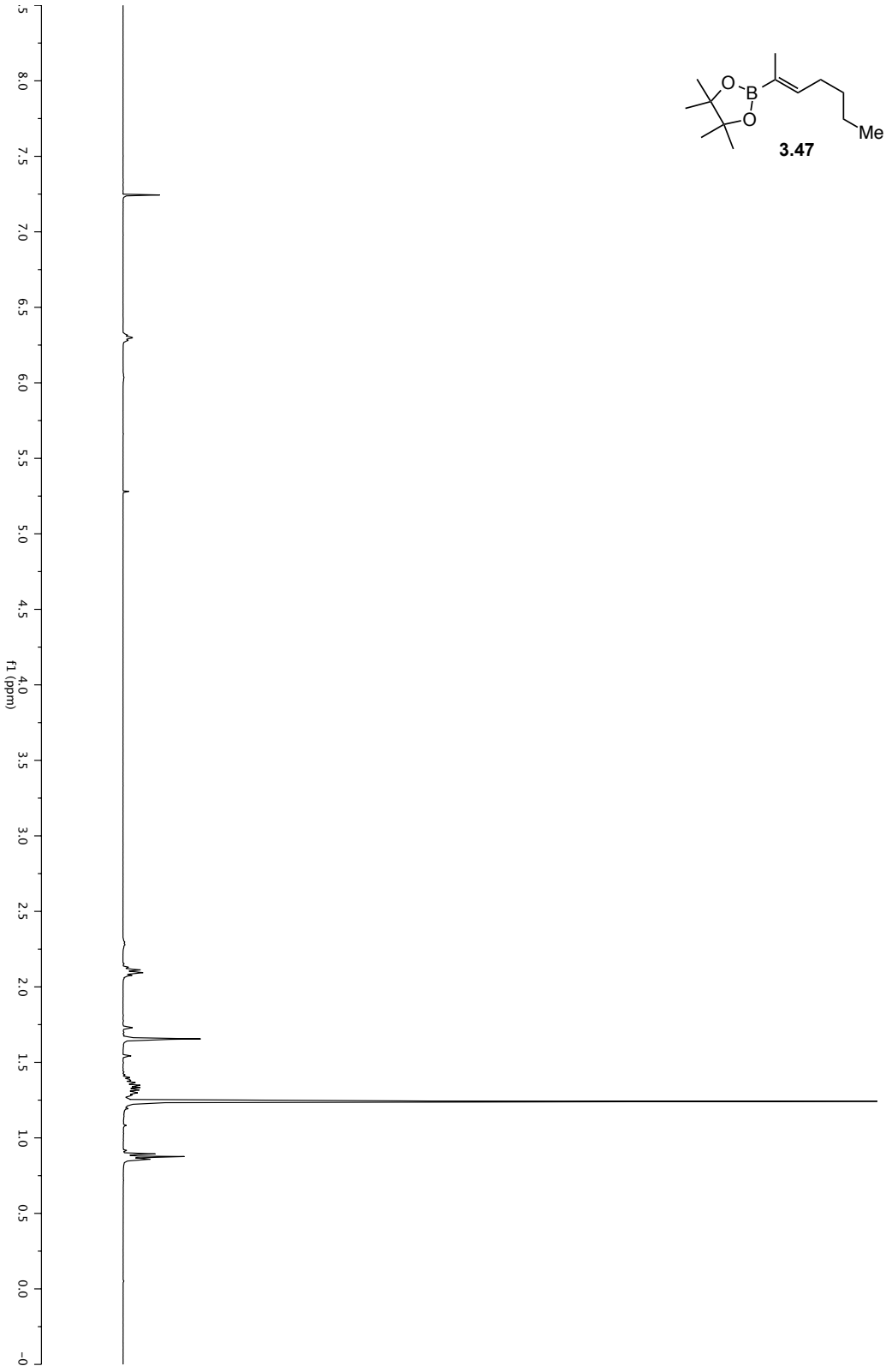
3.75 and 

3.76 **(*E*)-((4-bromo-3-methylbut-3-en-1-yl)oxy)triisopropylsilane (3.75)** and **(*E*)-((4-fluoro-3-methylbut-3-en-1-yl)oxy)triisopropylsilane (3.76):** Following the general procedure, to a vial containing disubstituted olefin **3.60** (10.8 mg, 0.0446 mmol, 1 equiv), *Z*-1-bromo-2-fluoroethylene dichloroethylene **3.74** (16.7 μL, 0.224 mmol, 5.0 equiv) was added followed by a solution of **3.59** (44.6 μL, 0.00446 mmol, 10 mol %). The vial was tightly capped and the solution allowed to stir for 12 h, then purified by chromatography on $AgNO_3$-impregnated silica gel (10 wt %) (100% pentane) to afford **3.75** and **3.76** as an inseparable 85:15 mixture (11.1 mg, 0.0357 mmol, 80% yield, **3.75** 70:30 *E*:*Z*, **3.76** 50:50 *E*:*Z*) as colorless oil. **TLC R_f:** 0.7 (100% hexanes); **IR (neat):** 2942 (s), 2893 (w), 2866 (s), 1463 (m), 1382 (w), 1288 (w), 1248 (w), 1159 (w), 1159 (s), 1069 (m), 1013 (m), 996 (m), 916 (m), 882 (m), 773 (m), 742 (m), 714 (m), 681 (m), 658 (m); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.49 (**3.76**, dd, J = 16.7, 1.8 Hz, 1H), 6.35 (**3.76** d, J = 15.5 Hz, 1H),

5.95 (*E* isomer **3.75**, d, *J* = 1.3 Hz, 1H), 5.92 (*Z* isomer **3.75** d, *J* = 1.5 Hz,1H), 3.92–3.57 (m, 2H), 2.48 (*Z* isomer **3.75**, t, *J* = 6.9 Hz, 2H), 2.35 (*E* isomer **3.75**, t, *J* = 6.9 Hz, 1H), 1.85 (*Z* isomer **3.75**, d, *J* = 1.5 Hz, 1H), 1.83 (*E* isomer **3.75**, d, *J* = 1.3 Hz, 2H), 1.24–0.95 (m, 21H); **^{13}C NMR (101 MHz, $CDCl_3$)** (only **3.75** is visible): δ 140.0 (*Z* isomer), 139.2 (*E* isomer), 102.8 (*E* isomer), 101.9 (*Z* isomer), 61.8 (*E* isomer), 61.2 (*Z* isomer), 41.7 (*E* isomer), 38.1 (*Z* isomer), 23.4 (stereochemical identity is unclear), 19.7 (stereochemical identity is unclear), 18.1, 12.1; **HRMS (DART+): 3.75** Calcd for $C_{14}H_{30}BrOSi$ $[M+H]^+$: 321.12493; found: 321.12630 . **3.76** Calcd for $C_{14}H_{30}FOSi$ $[M+H]^+$: 261.20499; found: 261.20457.



3.79 **2-(bromomethylene)adamantine (3.79):** Following the general procedure, to a vial containing the requisite disubstituted olefin (3.0 mg, 0.020 mmol, 1 equiv), *Z*-1-bromo-2-fluoroethylene dichloroethylene **3.74** (7.5 μL, 0.10 mmol, 5.0 equiv) was added, followed by a solution of **3.59** (20 μL, 0.0020 mmol, 10 mol %). The vial was tightly capped and the solution allowed to stir for 12 h, then purified by chromatography on $AgNO_3$-impregnated silica gel (10 wt %) (100% hexanes) to afford **3.79** (1.0 mg, 0.0044 mmol, 21% yield) as colorless oil. Fluoroalkene **3.78** could not be isolated due to volatility. **TLC R_f:** 0.65 (100% pentane); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 5.80 (s, 1H), 3.09 (s, 2H), 2.57 (s, 2H), 1.95 (s, 2H), 1.93–1.81 (m, 4H), 1.75 (m, 4H); **HRMS (DART+):** Calcd for $C_{11}H_{16}Br$ $[M+H]^+$: 227.04354; found: 227.4465.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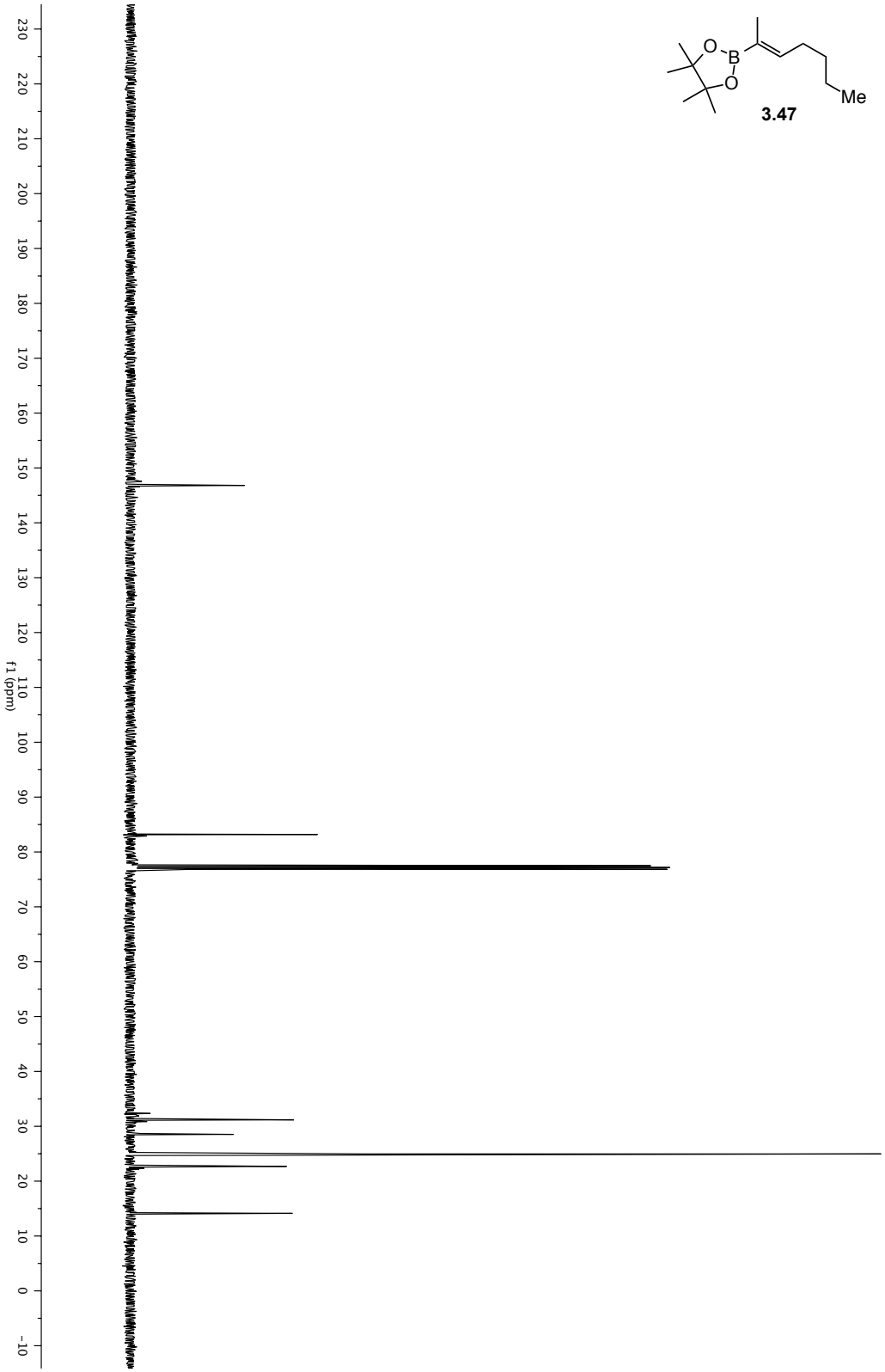
B
O
Me
3.47
f1 (ppm)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Me
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f1 (ppm)
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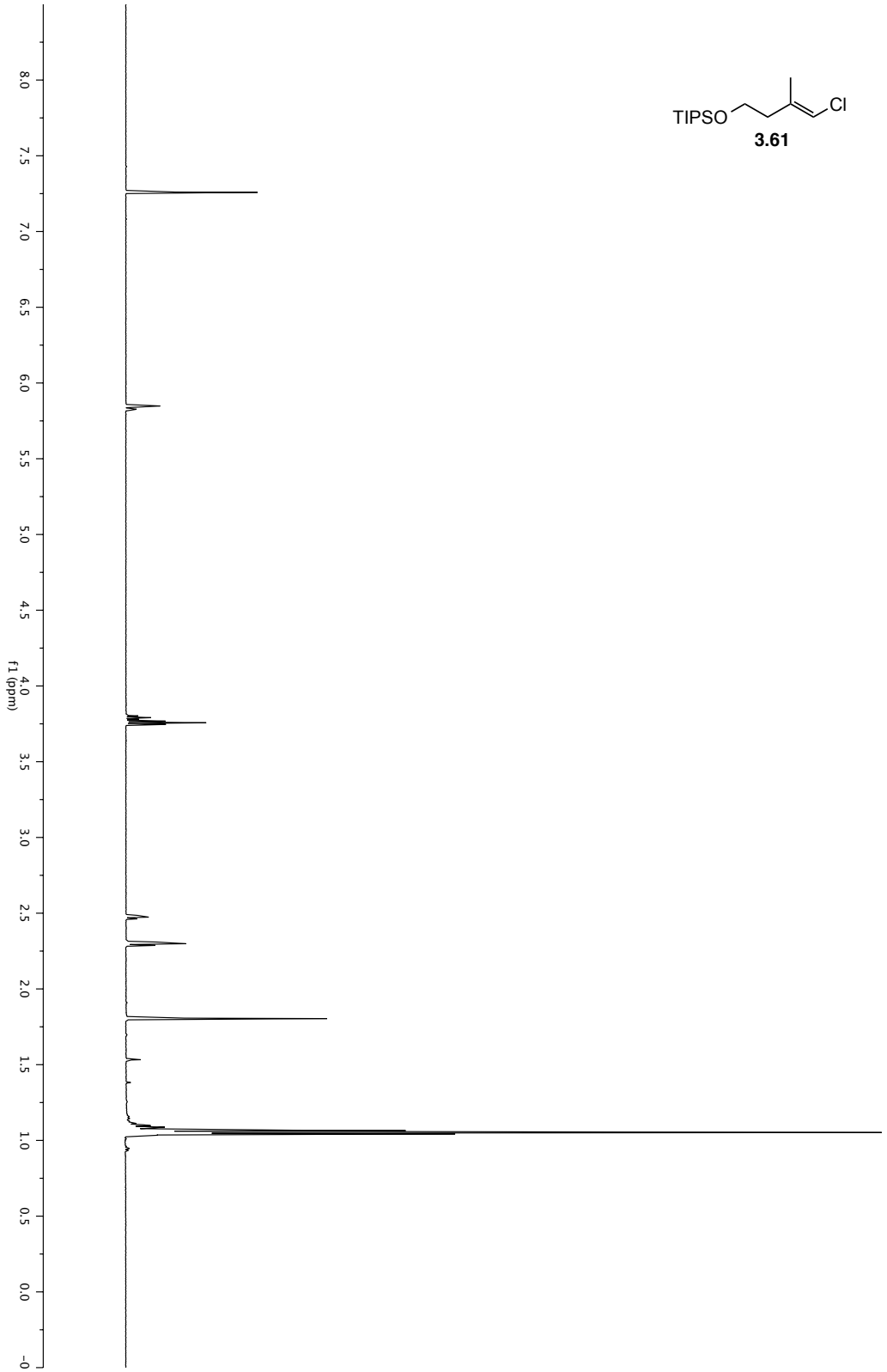
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4.0
3.5
3.0
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2.0
1.5
1.0
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0.0
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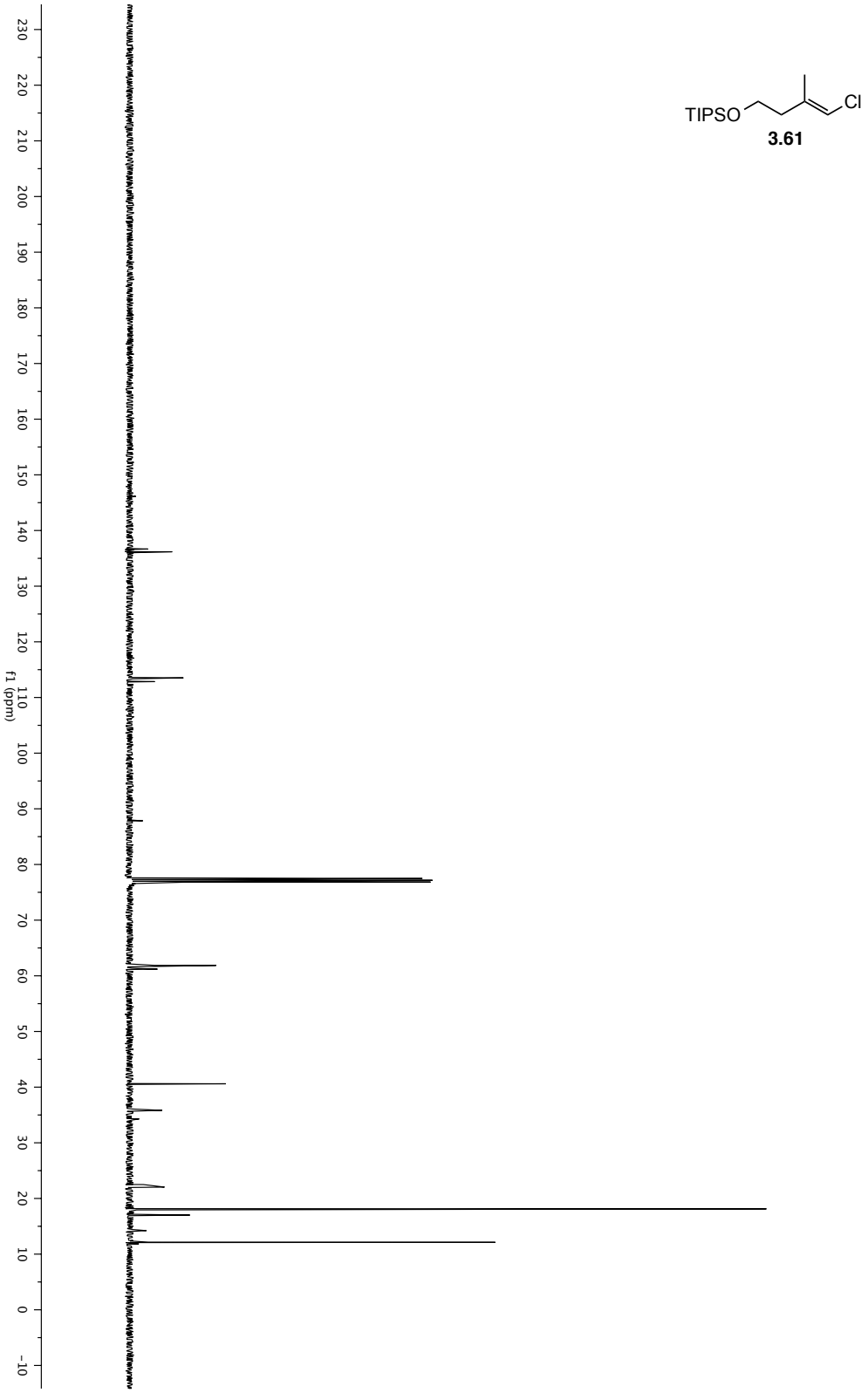
TIPSO
Cl
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f1 (ppm)
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60
50
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10
0
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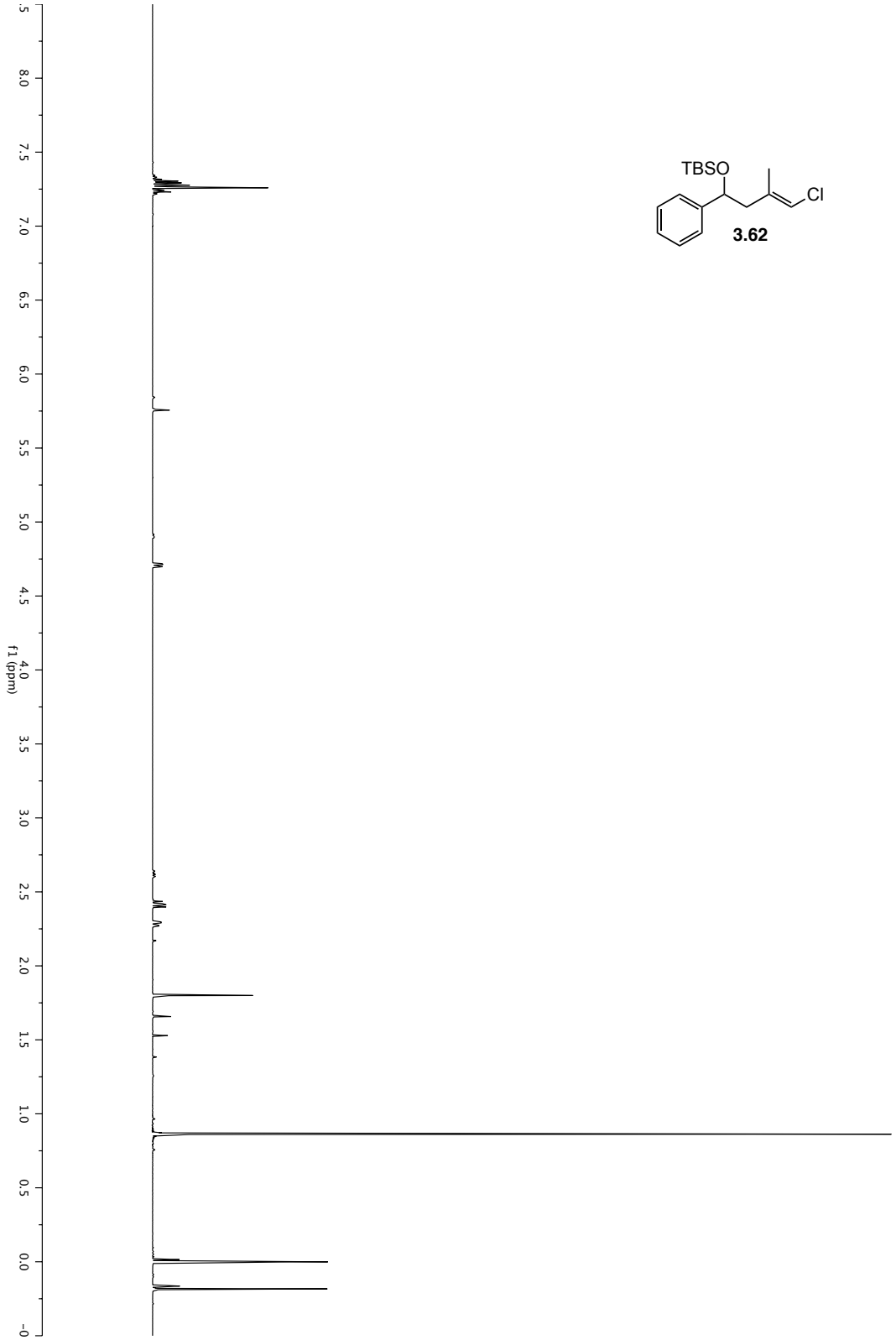
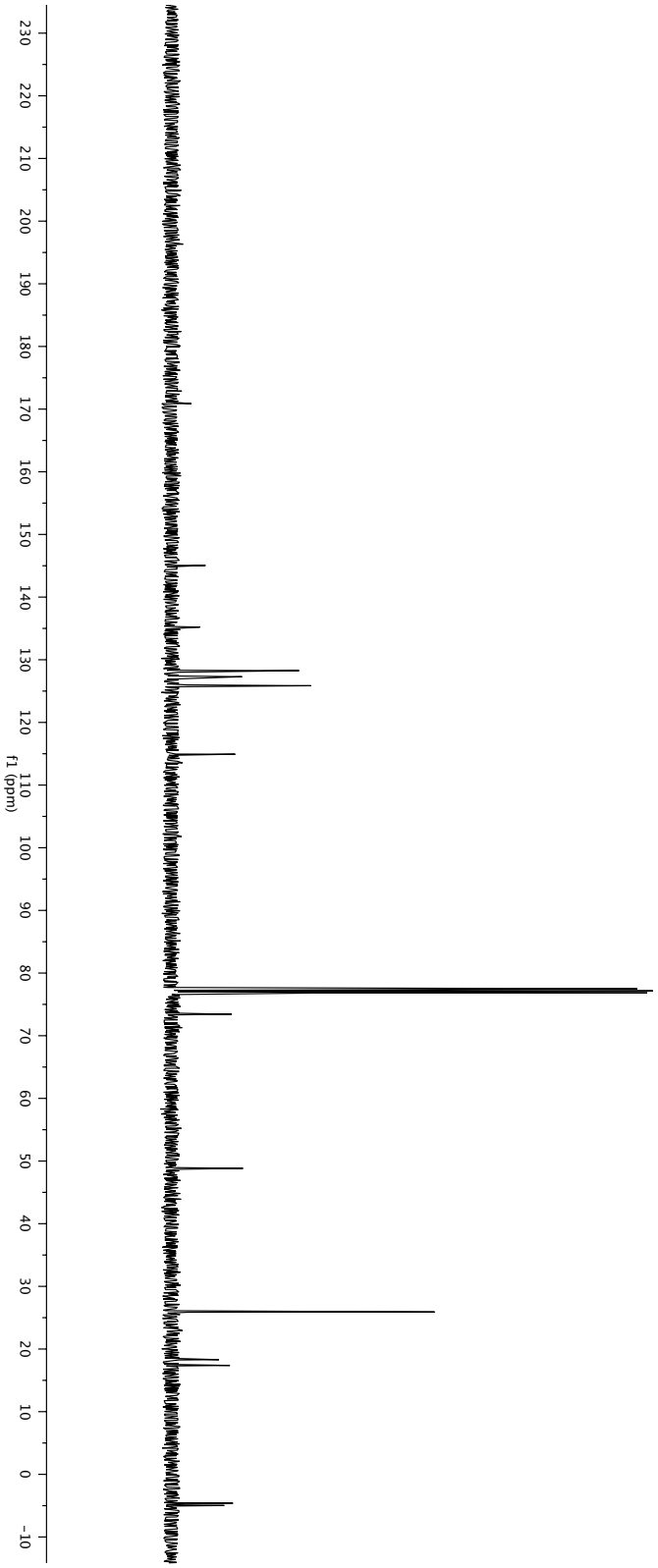

TBSO
Cl
3.62
f1 (ppm)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30
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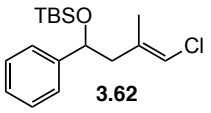
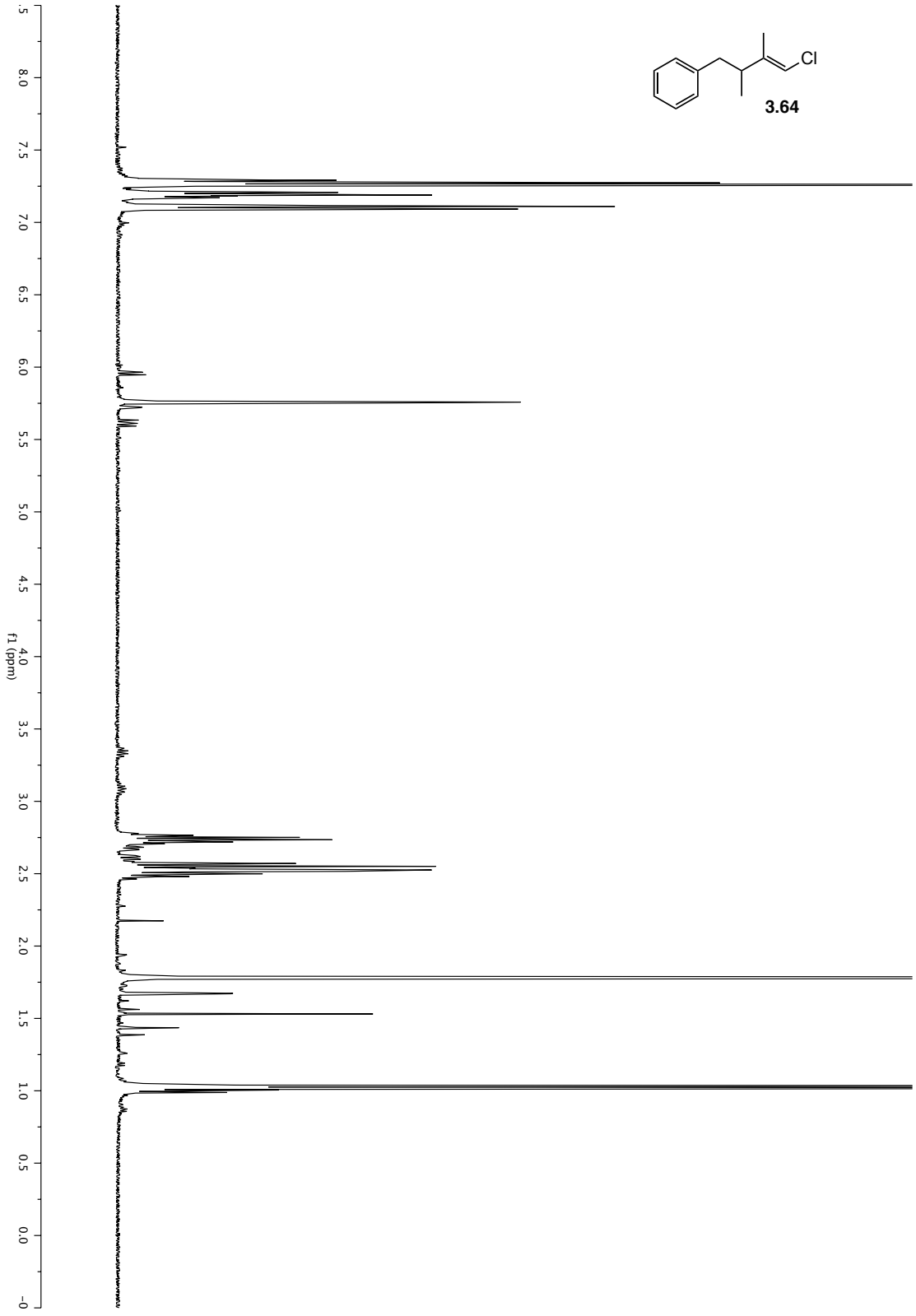
10
0
-10
f1 (ppm)


TBSO
Cl

3.62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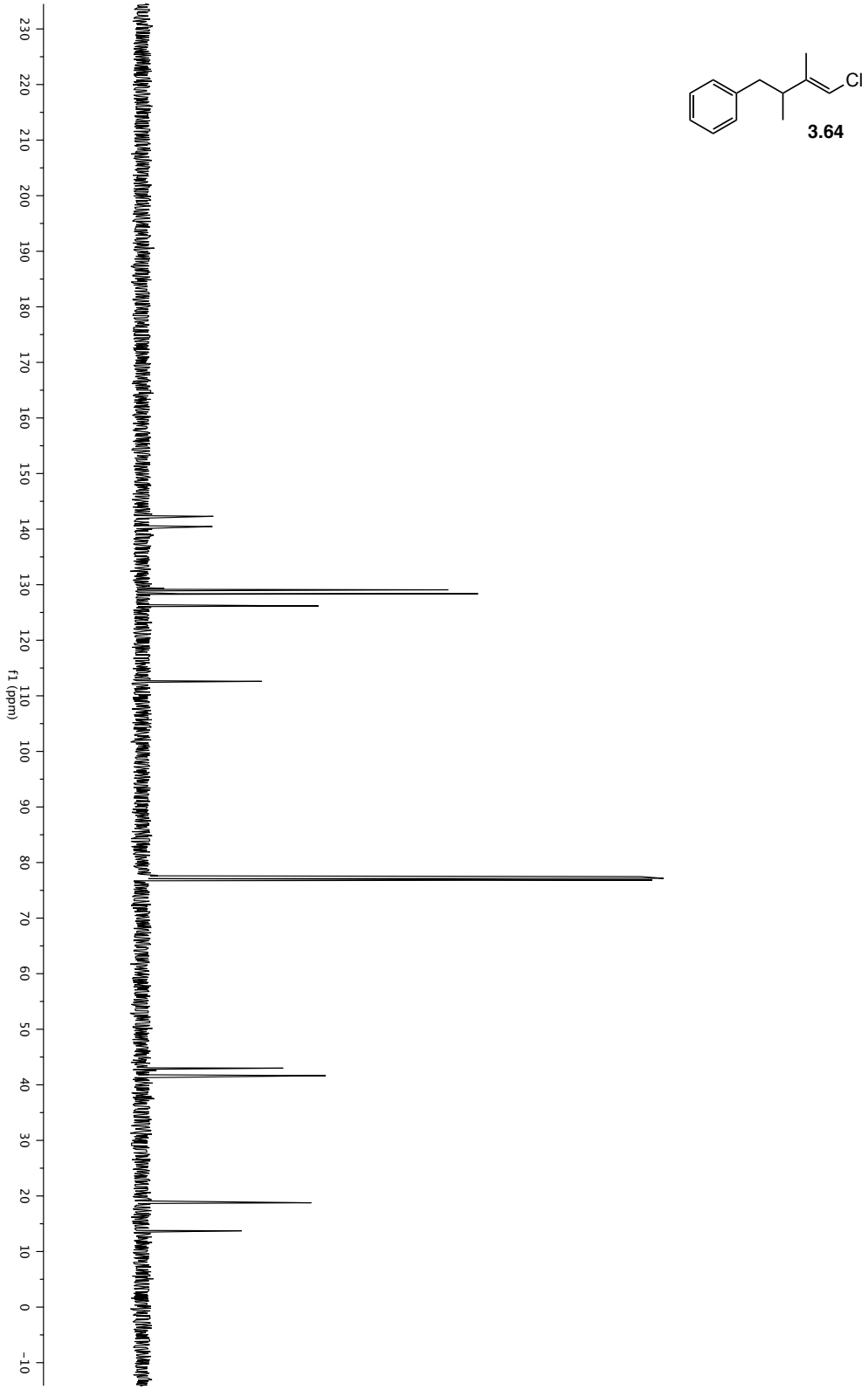
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200
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80
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40
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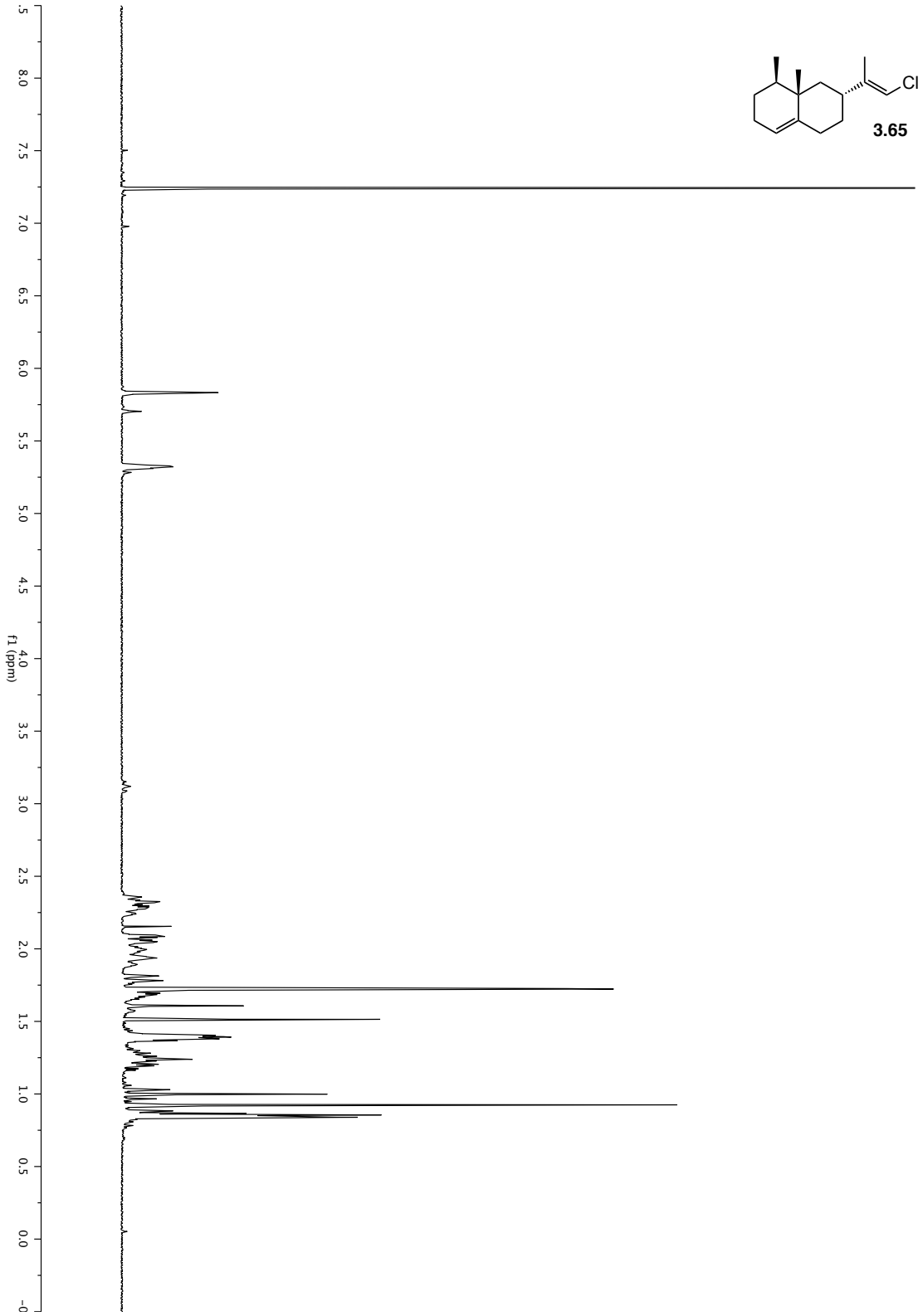
-10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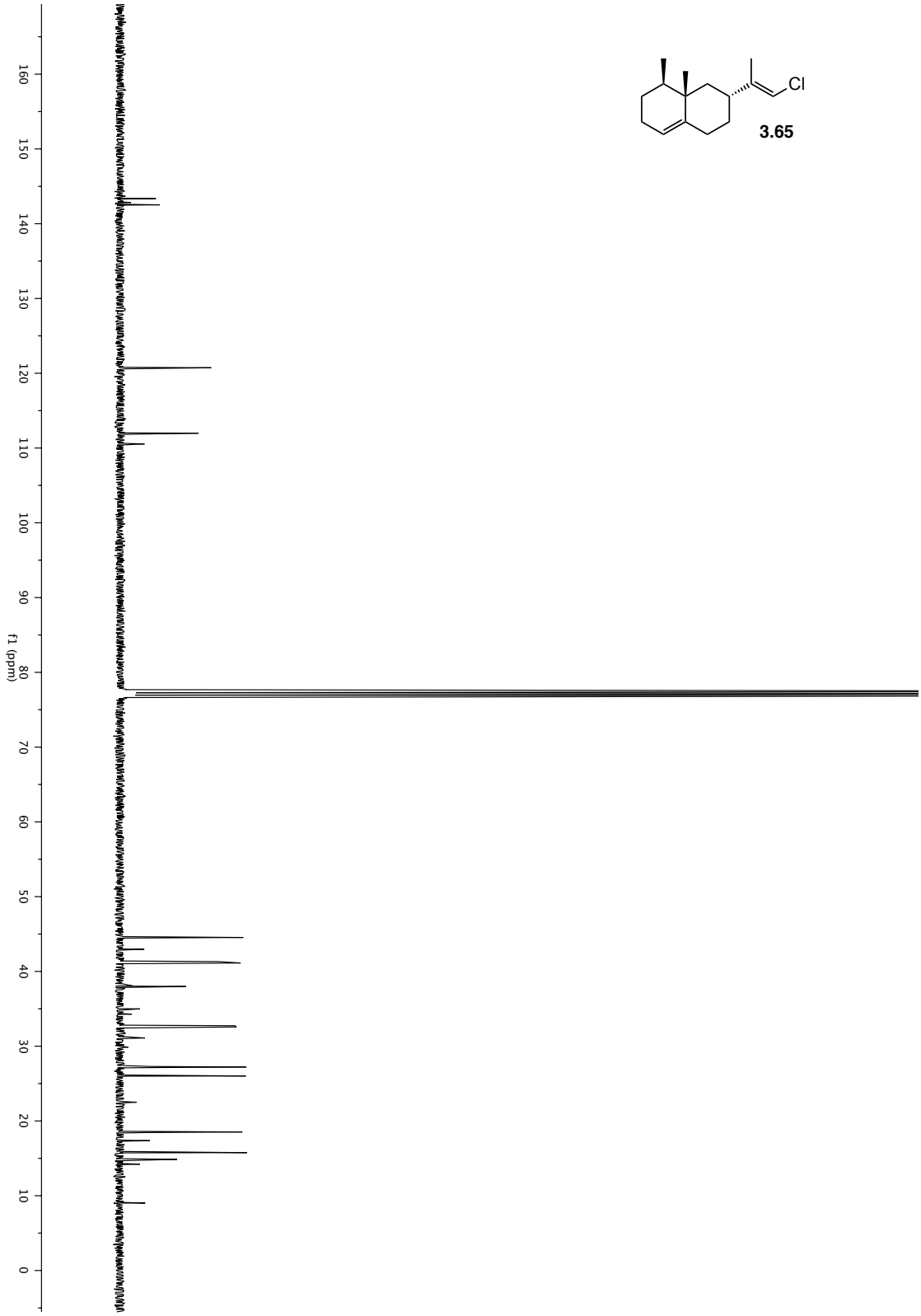
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10
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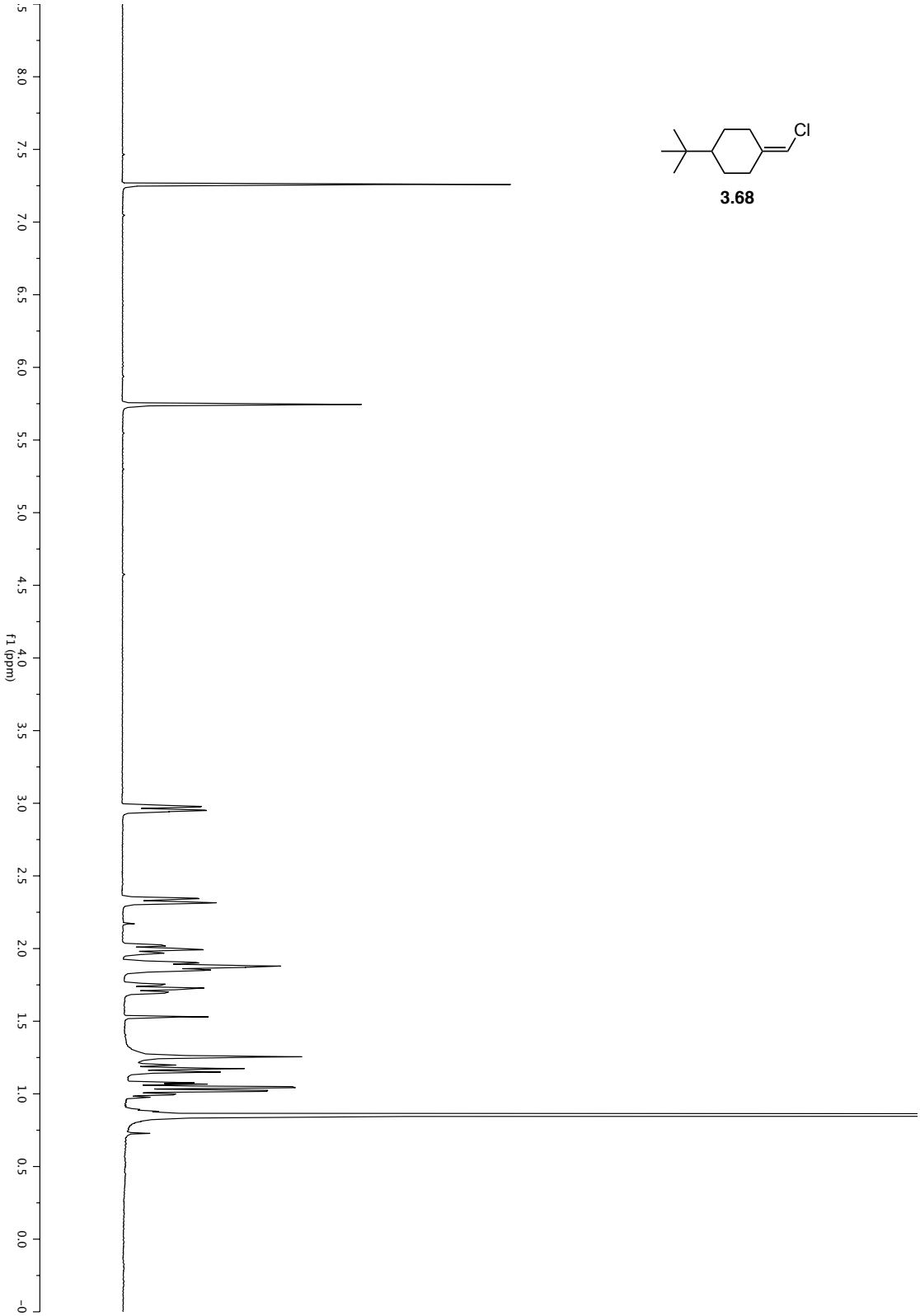
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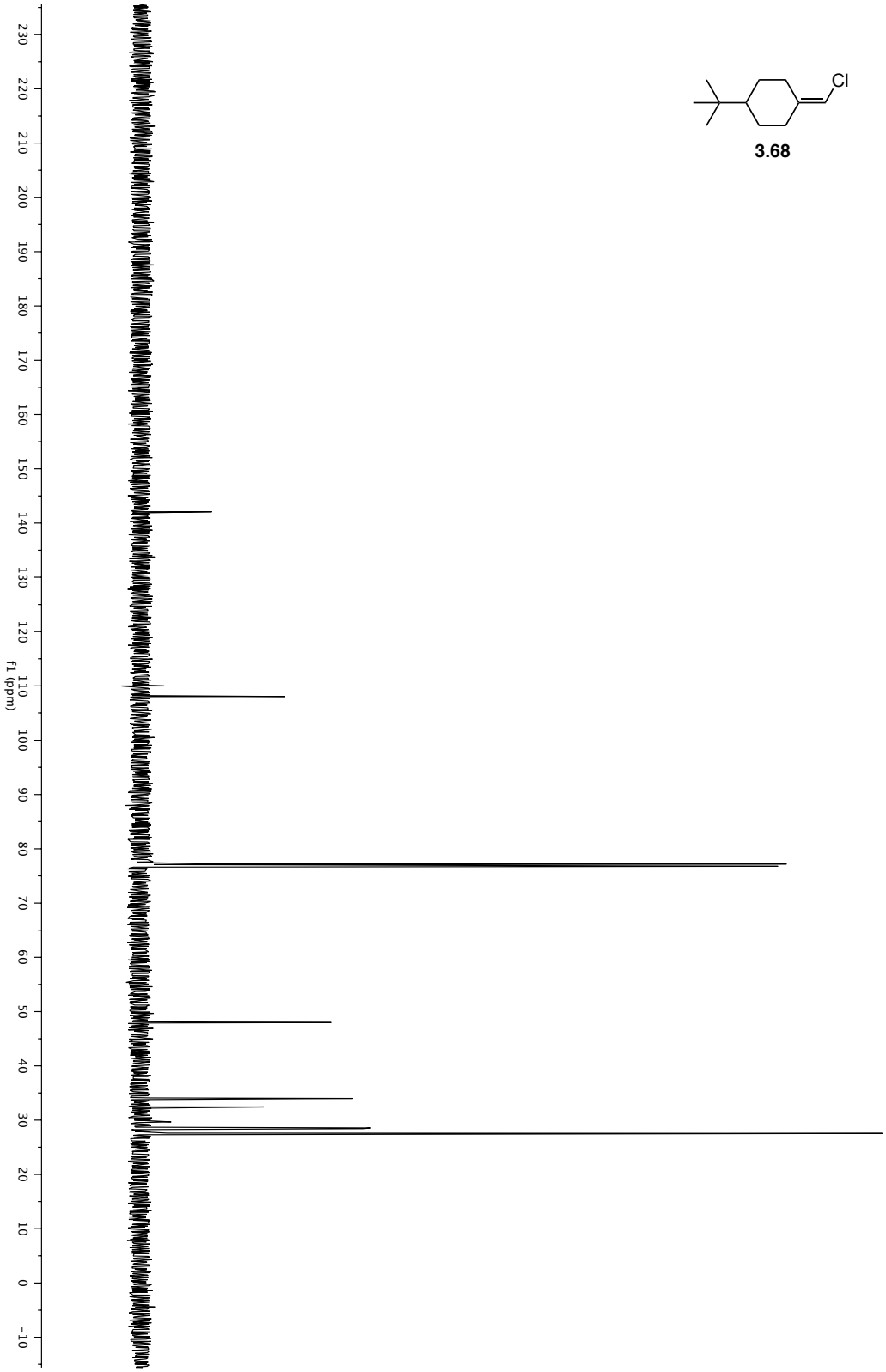
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f1 (ppm)
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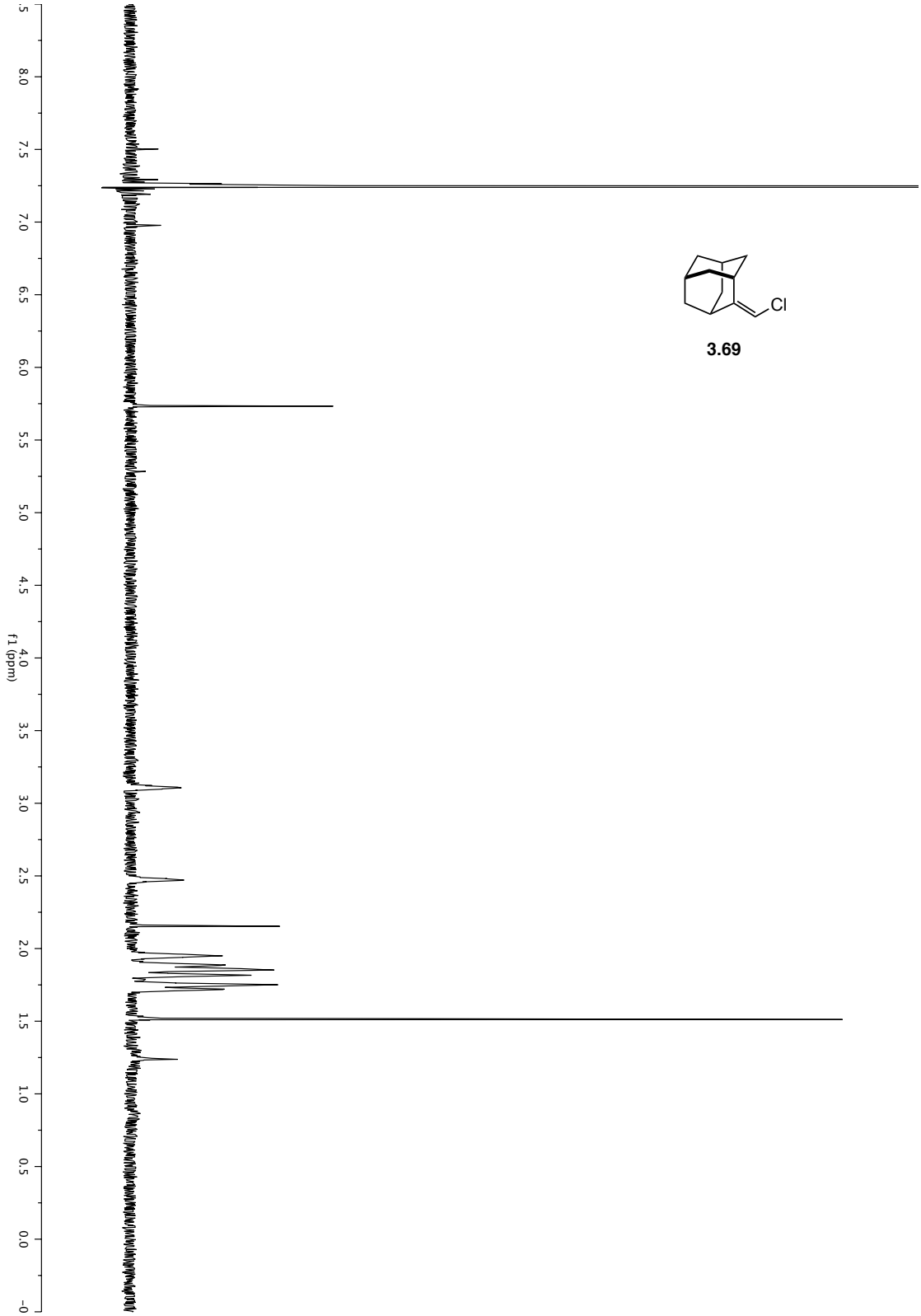
-10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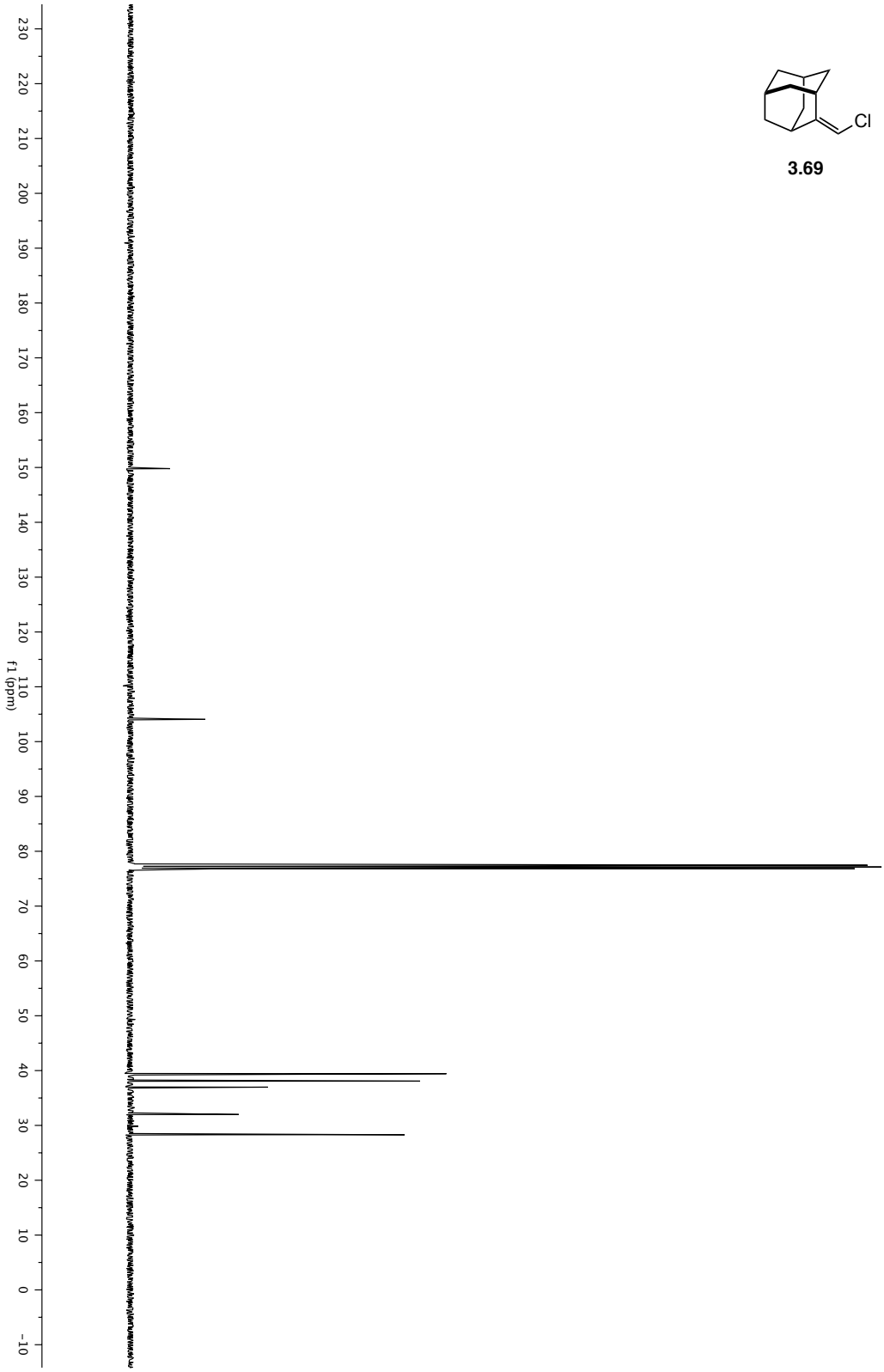
f1 (ppm)


Cl
3.69
f1 (ppm)
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220
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200
190
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160
150
140
130
120
110
100
90
80
70
60
50
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30
20
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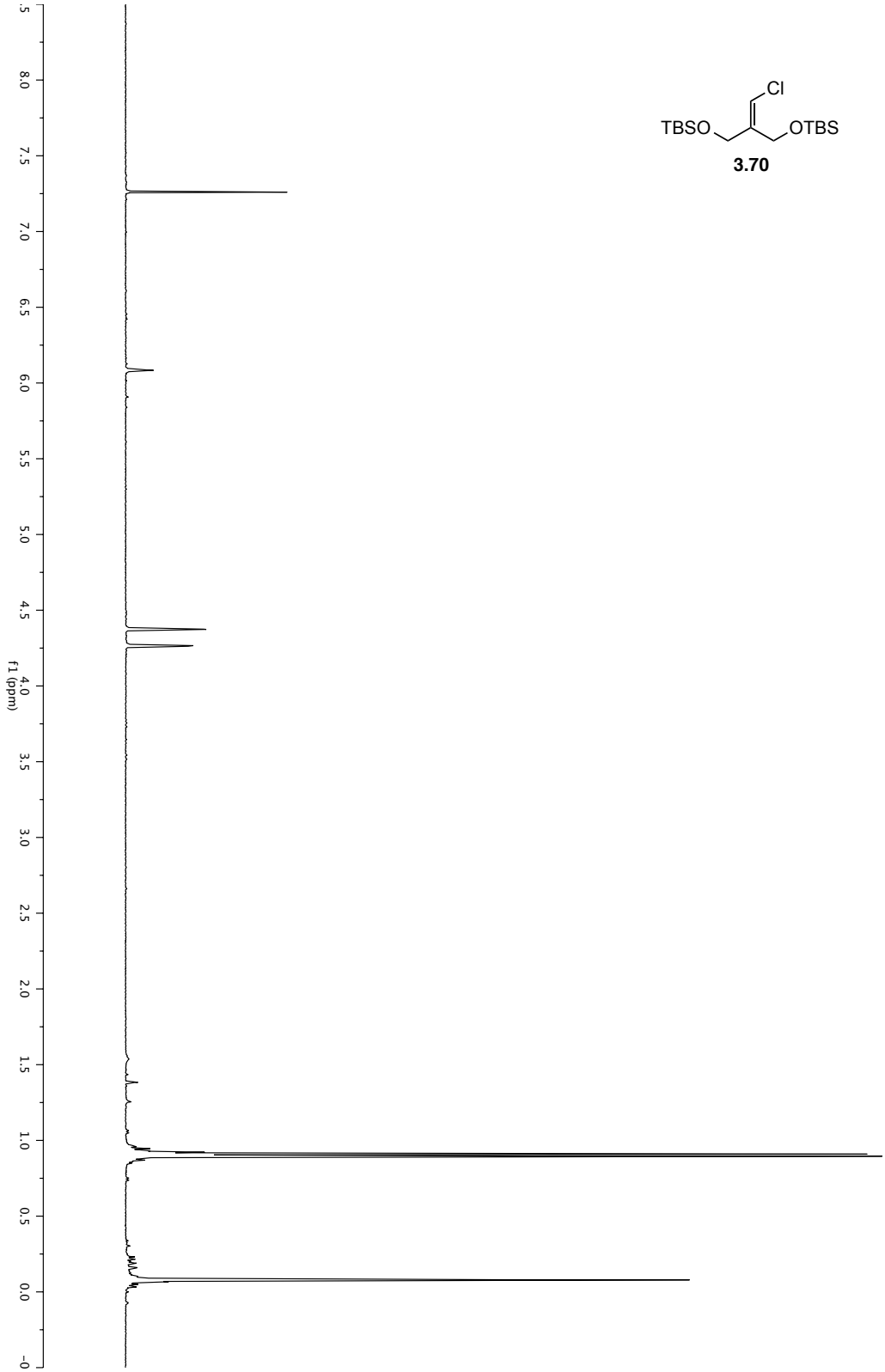
0
-10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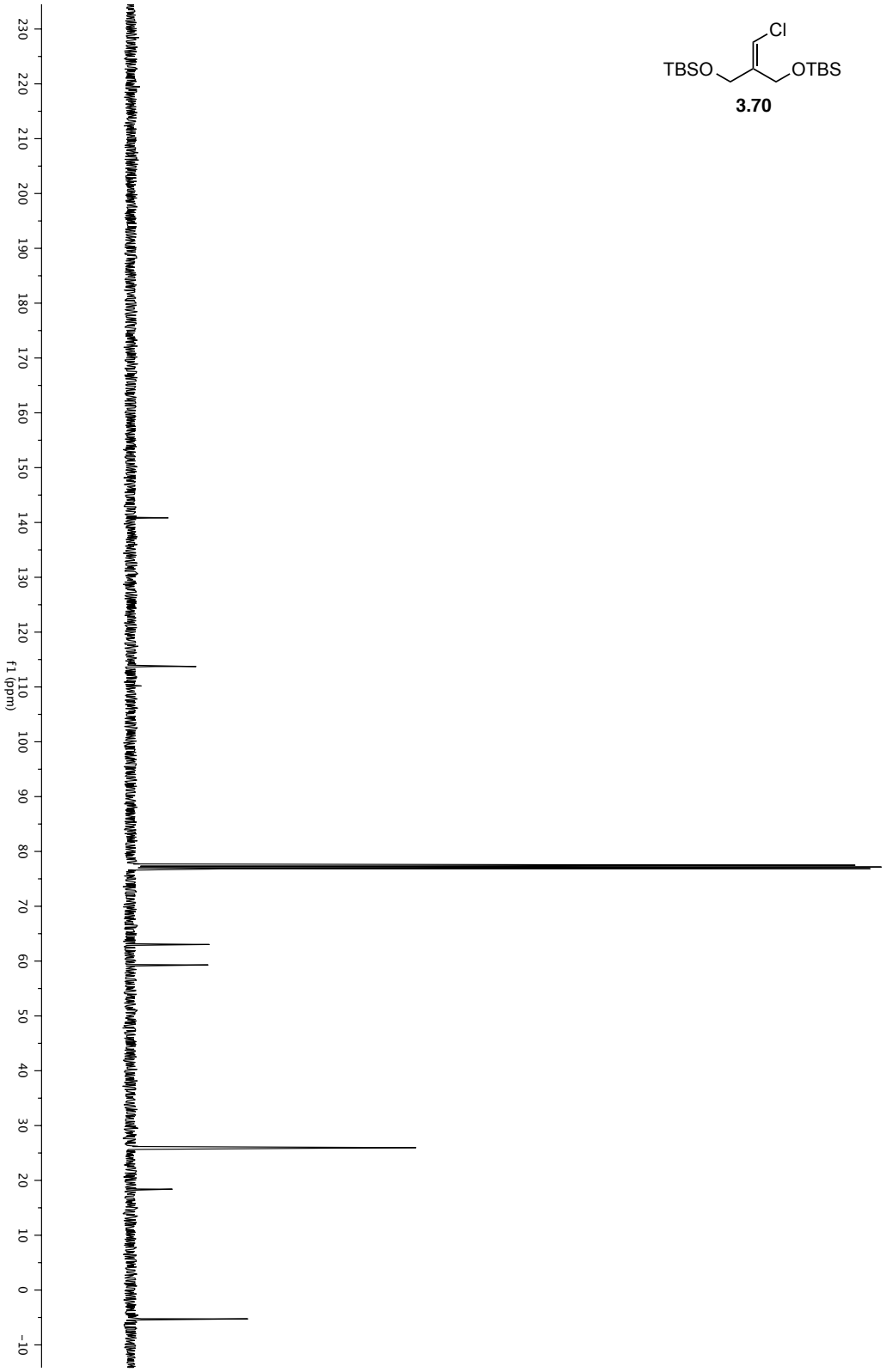
TBSO
OTBS
3.70
f1 (ppm)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40
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20
10
0
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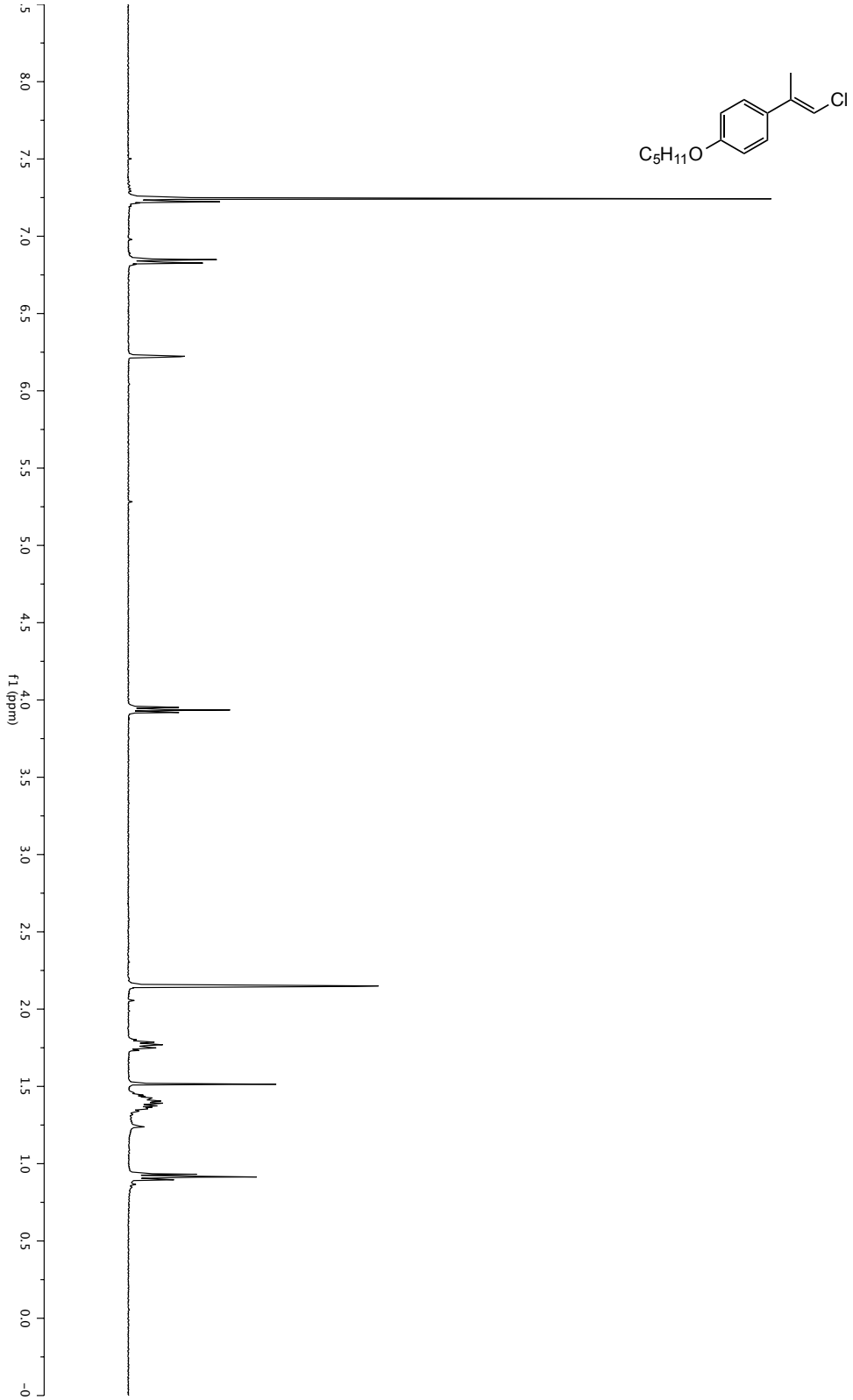
Cl
TBSO
OTBS

3.70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$C_5H_{11}O$
f1 (ppm)
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6.5
6.0
5.5
5.0
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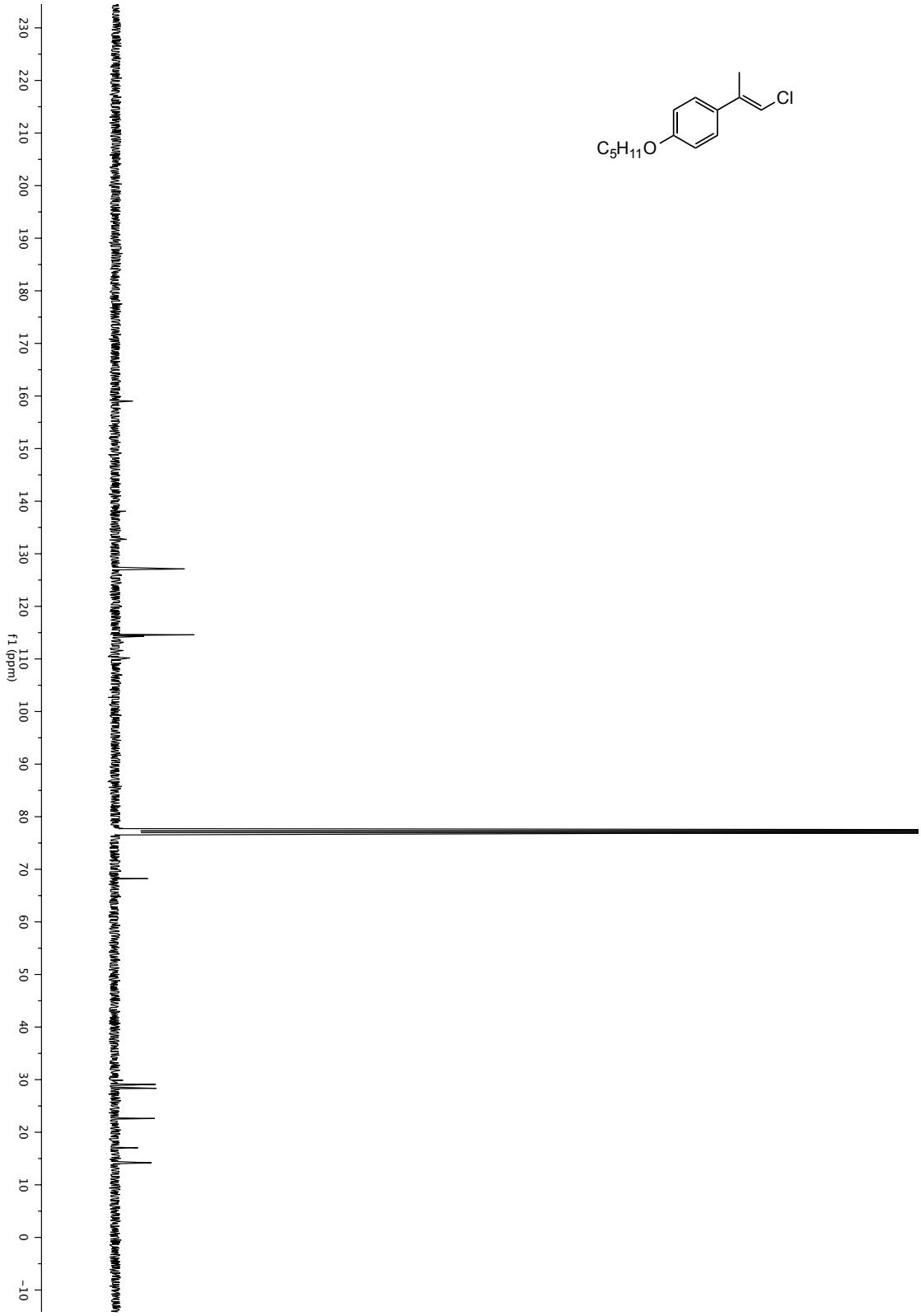
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Cl
$C_5H_{11}O$
f1 (ppm)
230
220
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200
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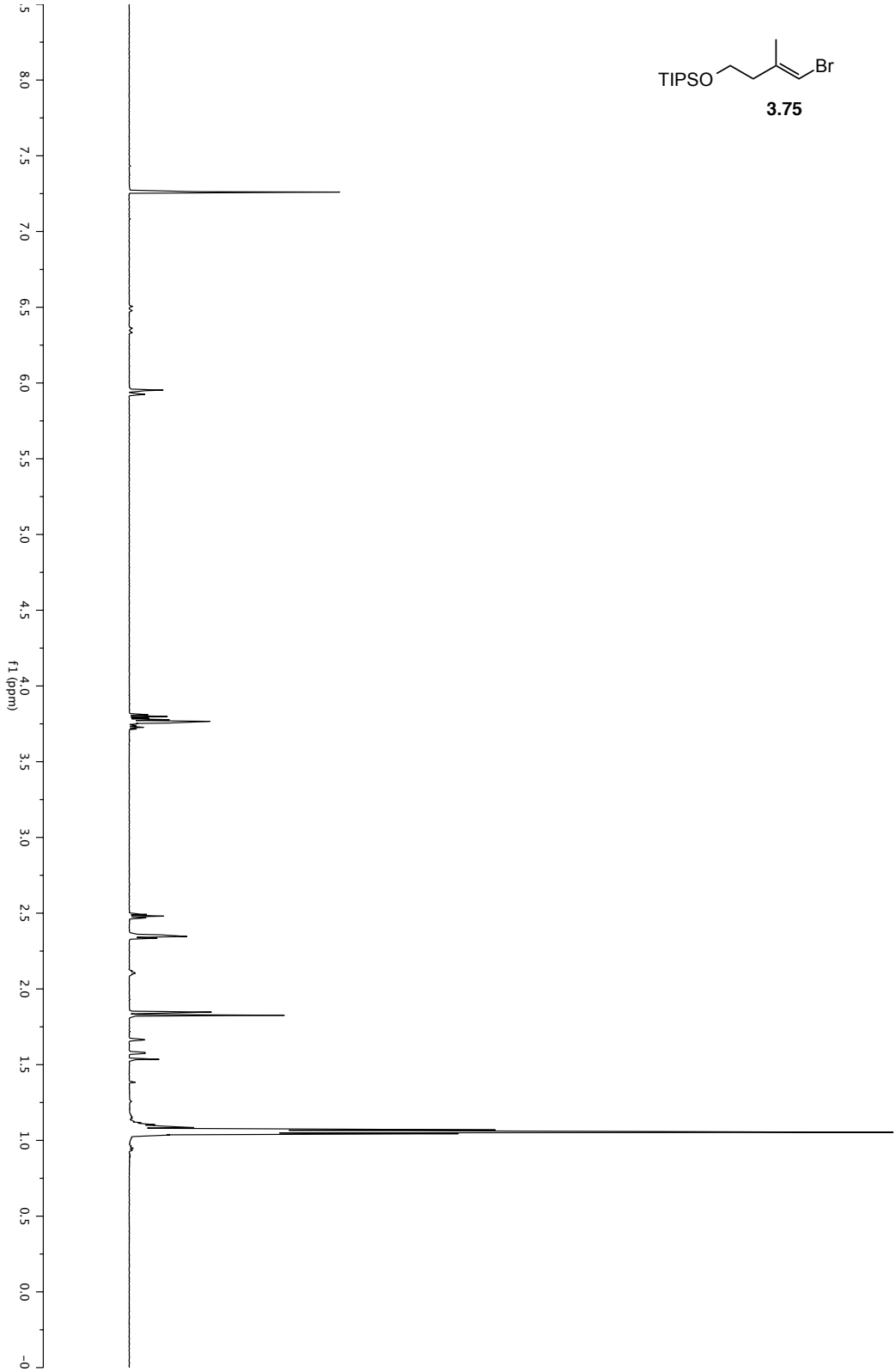
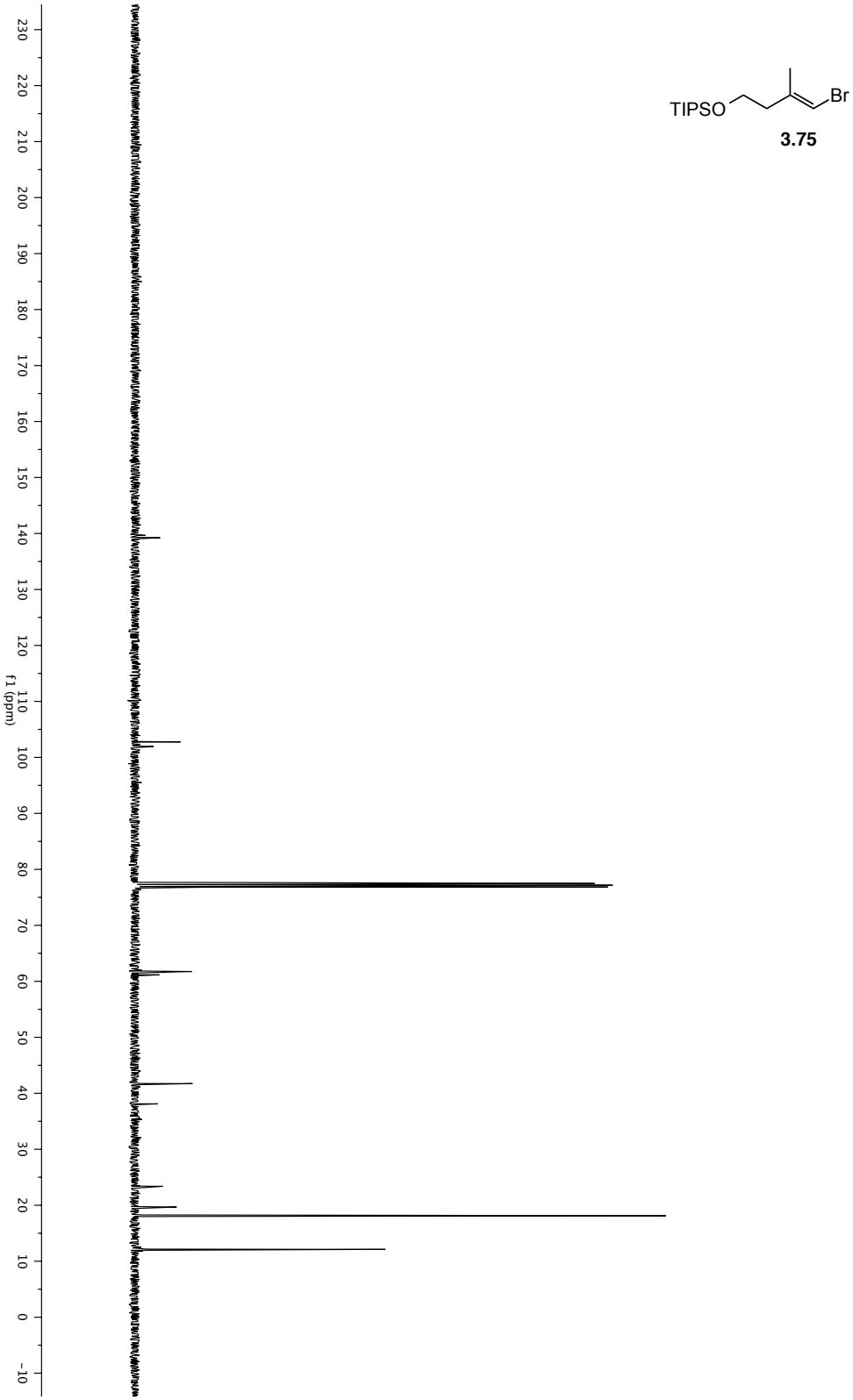

TIPSO
Br
3.75
f1 (ppm)


230
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30
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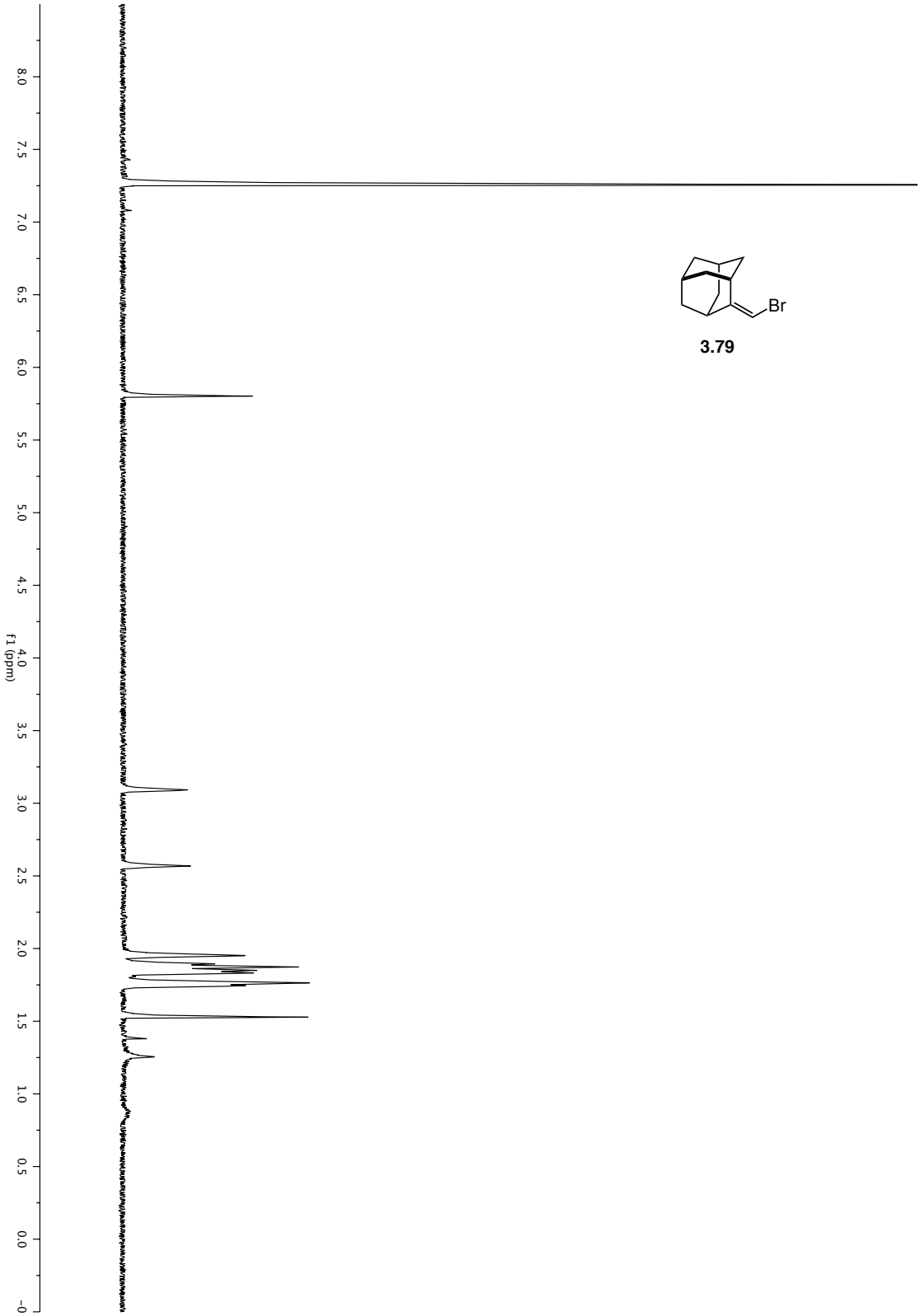
0
-10
f1 (ppm)

TIPSO
Br

3.75



3.79

Chapter 4. Ring-Closing Metathesis in the Synthesis of Natural Products

4.1 Introduction

Since its introduction by Villemin[1] and Tsuji[2] for the formation of macrocyclic ketones and lactone natural products, and initial reports by Grubbs[3] using well defined catalysts[4] to form small oxygen containing heterocycles, ring-closing metathesis (RCM) has become a method of choice in the synthesis of cyclic products, both in methodological studies and in total synthesis.[5] Ring-closing metathesis is particularly well studied in the context of the formation of 5 to 8 membered rings.[6] Our group has been involved with enantioselective RCM since 1998;[7] as such we had been approached for collaborative efforts in a diastereoselective RCM in the synthesis of tetrapetalone A, and an enantioselective RCM towards aspidosperma alkaloids. This chapter details these successful collaborations.

---

1. Villemin, D. *Tetrahedron* **1980**, *21*, 1715–1718.

2. Tsuji, J.; Hashiguchi, S. *Tetrahedron Lett*. **1980**, *21*, 2955–2958.

3. Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc*. **1992**, *114*, 5426–5426.

4. Murdzek, J. S.; Schrock, R. R. *Organometallics* **1987**, *6*, 1373–1374.

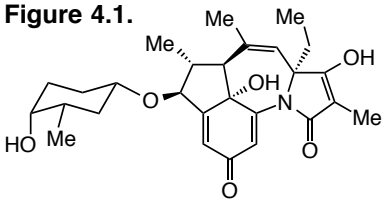
5. For some pertinent reviews, see: a) Hoveyda, A. H.; Malcolmson, S. J.; Meek, S. J.; Zhugralin, A. *Angew. Chem. Int. Ed*. **2010**, *49*, 34–44. b) Hoveyda, A. H.; Zhugralin, A. *Nature,* **2007**, *450*, 243–251. c) Deiters, A.; Martin, S. F. *Chem. Rev*. **2004**, *104*, 2199–2238.

6. For small carbocycles, see: a) Blanchard, N.; Eustache, J. in *Metathesis in Natural Product Synthesis* Cossy, J.; Arseniyadis, S; Meyer, C. Eds.; **2010** Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, pp 1–45. For small nitrogen containing cycles, see: b) van den Broek, S. A. M. W.; Meeuwissen, S. A.; van Pelft, F.L.; Rutjes, F. P. J. T. in *Metathesis in Natural Product Synthesis* Cossy, J.; Arseniyadis, S; Meyer, C. Eds.; **2010** Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, pp 45–83. For small oxygen containing cycles, see: c) Rainier, J. D. in *Metathesis in Natural Product Synthesis* Cossy, J.; Arseniyadis, S; Meyer, C. Eds.; **2010** Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, pp 84–124.

7. Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc*. **1998**, *120*, 4041–4041.

4.2 Synthesis of Tetrapetalone A-Me Aglycon: Background

Figure 4.1.



4.1 Tetrapetalone A

Tetrapetalone A (**4.1**) has attracted significant attention from the synthetic community since its isolation[8] and structural reassignment,[8b] predominately due to it's novel tetracyclic structure. Biologically, it inhibits soybean lipooxygenase, which is closely related to arachidonate 5-lipooxygenase in humans. This enzyme produces leukotrienes from arachidonic acid.[9] Overproduction of leukotrienes often causes inflammatory diseases such as asthma,[10] so an efficient modular route to **4.1** could be of clinical importance. The Frontier group contacted us in order to assist in a ring-closing metathesis (RCM) that was crucial to their ultimately successful synthesis.[11] Our group developed the ring-closing metathesis reaction, but their entire synthesis, as well as background is presented for context. There are also two methodological studies, which include applications towards tetrapetalone A.[12,13] The final molecules generated in these reports are far from **4.1** and it is hard to imagine them being elaborated into the natural product, these reports will not be discussed.

---

8. a) Komoda, T.; Sugiyama, Y.; Abe, N.; Imachi, M.; Hirota, H.; Hirota, A. *Tetrahedron Lett*. **2003**, 44, 1659–1661. b) Komoda, T.; Sugiyama, Y. Abe, N.; Imachi, M.; Hirota, H.; Koshino, H,; Hirota, A. *Tetrahedron Lett*. **2003**, *44,* 7417–7419.

9. Nelson, D. L.; Cox, M. M. in *Lehninger Principles of Biochemistry, Fifth Edition* W. H. Freeman and Co: United States, **2008** pp. 359.

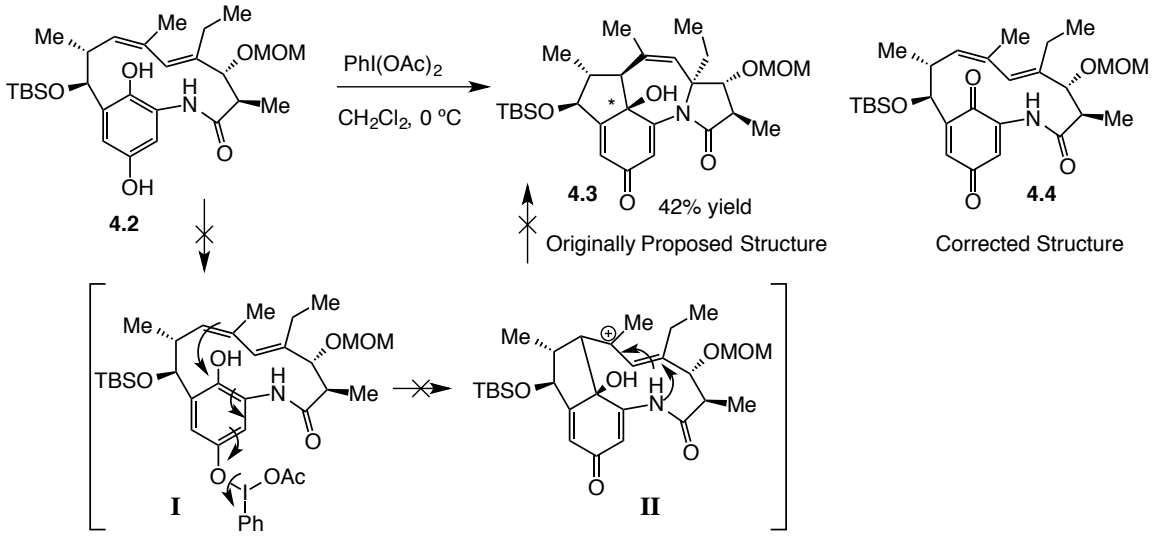
10. O'Byrne, P. M; Israel, E.; Drazen, J. M. *Ann. Intern. Med*. **1997**, *127*, 472.

11. Carlsen, P. N.; Mann, T. J.; Hoveyda, A. H.; Frontier, A. J. *Angew. Chem. Int. Ed*. **2014**, *53*, 9334–9338.

12. Li, C.; Li, X.; Hong, R. *Org. Lett*. **2009**, *11*, 4036–4039.

13. Weaver, M. G.; Bai, W. J.; Jackson, S.; Pettus, T. R. R. *Org. Lett*. **2014**, *16*, 1294–1297.

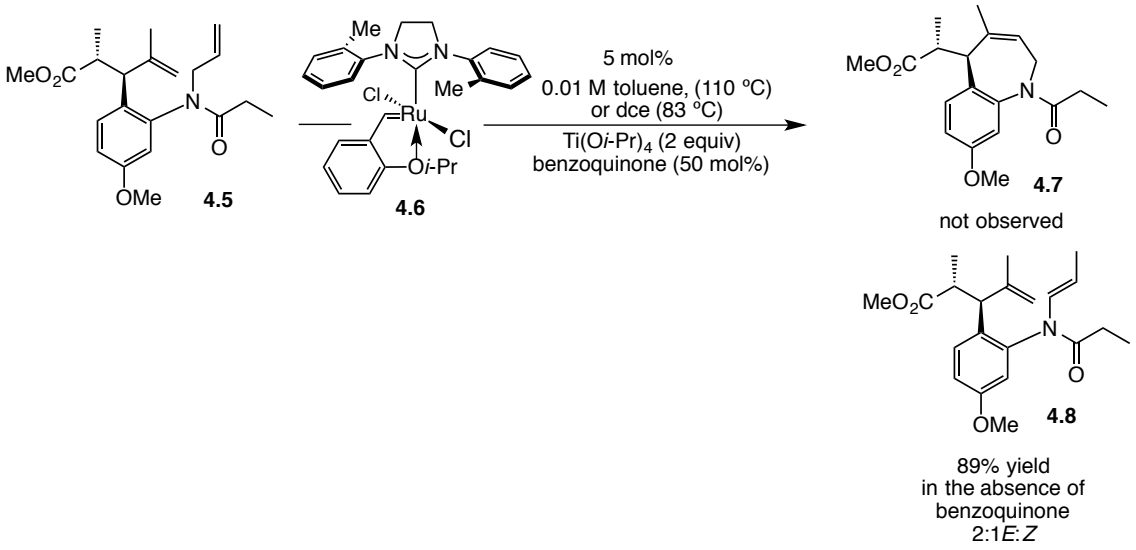
Scheme 4.1. Porco's Attempt at Tetrapetalone A



Porco produced the first major publication in tetrapetalone synthesis. His strategy relied on an oxidative ring forming reaction as shown in scheme 4.1.[14] The proposed reaction was that the trisubstituted alkene would attack the iodine-activated phenol (structure **I**), leaving an allylic carbocation (intermediate **II**) onto which the amide would cyclize leading to **4.3**. While this reaction was initially reported to be a success, a further correction indicated that in fact they had only oxidized the phenol to quinone **4.4**. Careful comparison of **4.3** and **4.1** reveals an additional problem. Even if the oxidative cyclization had succeeded, the resulting quinol (highlighted with "*" in **4.3**) must necessarily be of the stereochemistry indicated in **4.3**, which is opposite to that required for **4.1**, and this inverted stereochemistry would be quite difficult to correct.

14. a) Wang, X.; Porco, J. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3067–3071. b) Wang, X.; Porco, J. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 6607.

Scheme 4.2. Wood's RCM Towards Tetrapetalone



The Wood group had devoted substantial synthetic efforts towards tetrapetalone A,[15] although these efforts did not result in publications, only a Ph.D. thesis. This work will be discussed because the synthetic plans were thwarted by failed ring-closing metathesis reactions, and so is particularly relevant to our study. In their first failed metathesis route (scheme 4.2), they subjected **4.5** to 5 mol % of ruthenium based metathesis complex **4.6**[16] hoping to form the seven membered ring **4.7**. No conversion to the desired product was observed, instead, only the olefin isomerization product **4.8** was obtained. While addition of benzoquinone[17] completely suppresses this ruthenium hydride catalyzed olefin isomerization event, still none of **4.7** is obtained. Chelation of carbonyls to Ru catalysts is detrimental to olefin metathesis and Ti(*i*-OPr)$_4$ is known to suppress this chelation by binding to the carbonyl more tightly than the Ru complex. Addition of Ti(*i*-OPr)$_4$, both with and without benzoquinone, did not allow the Wood group to access **4.7**. Wood's subsequent synthetic strategy was less obvious and requires some explanation. As shown in scheme 4.3, **4.1** could, in principle, derive from glycosylation, phenolic oxidation and Friedel-Crafts reaction of aldehyde **4.9**. This

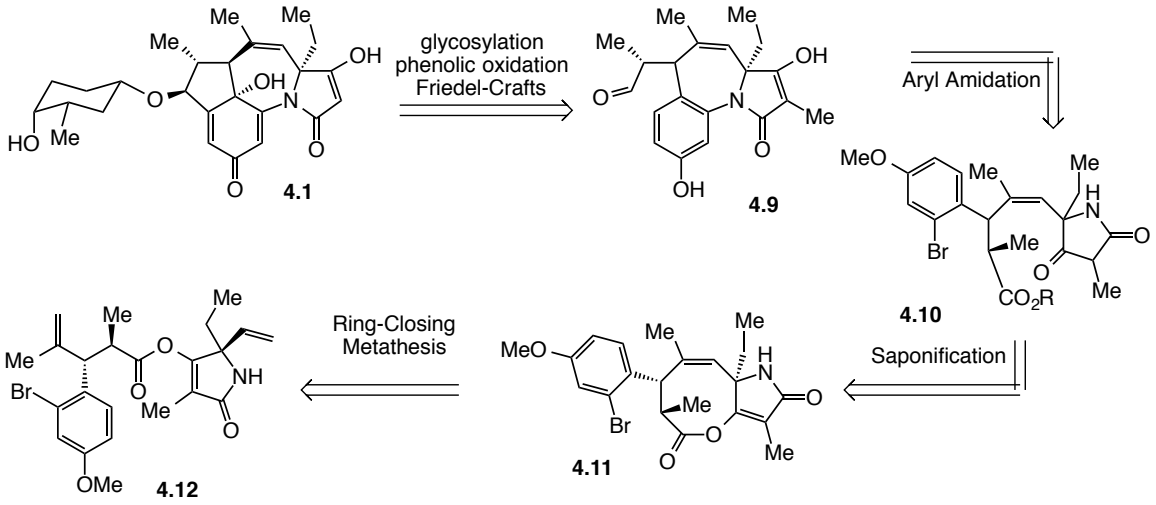
15. Howell, J. M. *Ph.D. Thesis* Colorado State University, Fort Collins, CO, **2012**.

16. Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589–1592.

17. Hong, S.-H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.

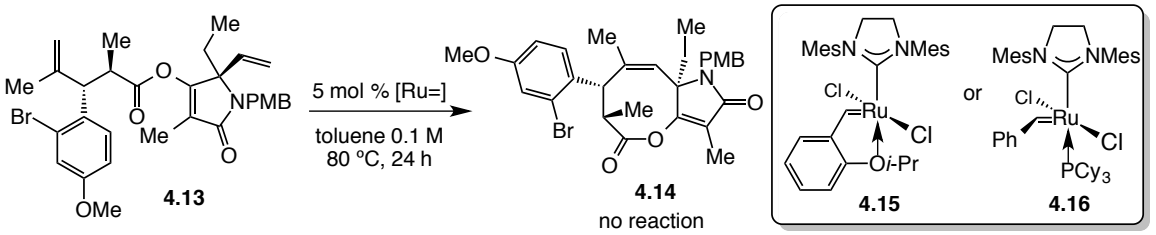
aldehyde could be obtained from an intramolecular C-N coupling of tetramic acid-bromide **4.10**, which would be generated from lactone **4.11**. This lactone could be obtained from RCM, and this where their efforts failed.

Scheme 4.3. Wood's Revised RCM Strategy



There are several challenges inherent in this metathesis reaction. Any metathesis to form the central double bond of tetrapetalone, will necessarily involve the formation of a trisubstituted olefin adjacent to a quarternary carbon. To the best of our knowledge, there are two examples of this in the literature[18] one of which is our successful synthesis of tetrapetalone A me-agylcon.[11] Additionally, the Wood plan contained an ester moiety that could chelate to the Ru catalyst, and all his efforts contained a protecting group on the adjacent nitrogen, which placed further bulk near the reaction site.

Scheme 4.4. Failed RCM towards Tetrapetalone



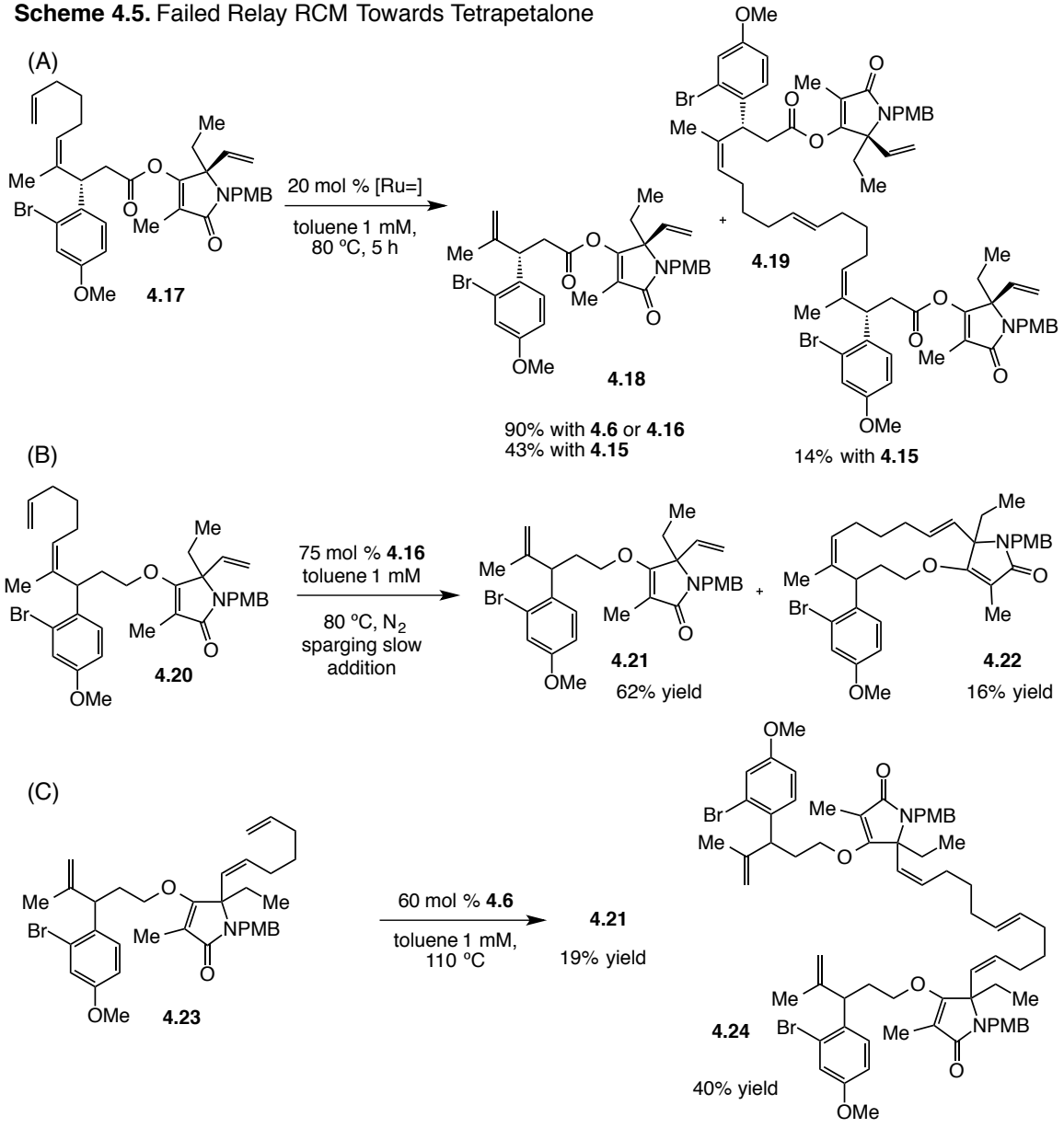
18. Enquist, J. A.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231.

The RCM of **4.13** failed with both **4.15** and **4.16**. This strategy requires the metathesis catalyst to initiate onto an olefin adjacent to a quaternary carbon, a step that may be problematic especially for stryrene-ether containing **4.15**. This initiation step was apparently also of concern to the Wood group, as they spent the remainder of their efforts trying to employ a relay-RCM strategy as summarized in scheme 5. Relay metathesis[19] is a well-established protocol for dealing with difficult substrates, wherein an initial RCM releases cyclopentene, and results in the metathesis catalyst loaded onto a particular olefin in the hope that it will now be capable of performing the desired metathesis reaction. Relay methods circumvent difficulties with the initiation step, but are not without their drawbacks, which Wood's failed reactions illustrate. Treatment of relay substrate **4.17** with catalysts **4.6** and **4.16** resulted in only truncated product **4.18**, where the catalyst performed the initial RCM, releasing the portion installed for the relay, but then failed to effect the desired RCM. With catalyst **4.15**, 43%-truncated product **4.18** was obtained, along with 14% of **4.19**, which arose from a self-metathesis of two molecules of **4.17**. They next tried relay RCM with **4.20** where the ester had been deleted and replaced with an ether linkage, to remove the possibility of chelation. Although they only report a reaction with **4.16**, this substrate fared no better and they obtained 62% yield of truncated product **4.21**, and 16% yield of RCM product **4.22** where the relay linker was incorporated into the ring. With **4.23** they redesigned the relay in order to place the Ru on the α-olefin. With the unhindered Ru catalyst **4.6**, this metathesis reaction gave only truncated **4.21** and the self-metathesis product **4.24**. Wood's efforts in this area appear to have ceased.

---

19. Hoye, T. R.; Jeffery, C. S.; Tannakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, 126, 10210–10211.

Scheme 4.5. Failed Relay RCM Towards Tetrapetalone



Other than our successful efforts, Sarpong's.[20] were the closest to affording tetrapetalone. His work began with a Nazarov[21] cyclization on **4.25** to close the five-

20. a) Marcus, A. P.; Sarpong, R. *Org. Lett.* **2010**, *12*, 4560–4563. b) Marcus, A. P.; Sarpong, R. *Org. Lett.* **2014,** *16*, 3420. c) Marcus, A. P.; Lee, A. S.; Davis, R. L.; Tantillo, D. J.; Sarpong, R. *Angew. Chem. Int. Ed.* **2008**, *47*, 6379–6383.

21. For the initial report, see: a) Nazarov, I. N.; Zaretskaya, I. I. *Izv. Akad. Nauk SSSR Ser. Khim* **1941**, 211–224. For some reviews, see: b) Vaidya, T.; Frontier, A. J. *ChemCatChem*, **2011**, *3*, 1531-1548. c) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577–7606. d) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479–6517.

membered ring, followed by epimerization of the methyl group affording **4.26** in 73% yield and 4:1 d.r.. Reduction of the carbonyl, silyl protection, and replacement of the bromine with an azide gave **4.27**. One should note that the initial reports by the Sarpong group misassigned the stereochemistry of the carbinol set by the reduction.[20b] The azide was reduced to an amine, and then subjected to Paal-Knorr conditions to install a pyrrole, hydroboration-oxidation of the olefin resulted in **4.28**. Oxidation of the alcohol with 2.5 equiv of Dess-Martin periodinane resulted in a cyclization of the pyrrole onto the transient aldehyde and further oxidation of the resulting secondary alcohol into a ketone. Extending a literature preceedent[22] this molecule was then subjected to dissolving metal conditions, allowing the pyrrole to be alkylated with ethyl iodide. Subsequent oxidation of the pyrrole with H_2O_2 catalyzed by $Mn(OAc)_3 \bullet H_2O$[23] afforded the tetracyclic amide **4.29**. Methylation of **4.29** was achieved with lithium diisopropyl amide and methyl iodide, the enelactam was then oxidized following a conjugate boration with NHC **4.30** and CuCl.[24] The resulting molecule was then oxidized to a tetramic acid under Swern conditions affording Saprong's final intermediate **4.31.** It is unlikely that the phenol could be oxidized to the requisite quinone with the tetramic acid moiety in place, a successful synthesis would certainly have to perform this step earlier. Additionally troubling for the Sarpong route, is the regioselectivity in the methylation of **4.29**. The authors explain this molecule probably does not deprotonate adjacent to the ketone due to bad orbital overlap between the C-H and the C-O π^*. As this α-methyl ketone needs to be transformed into a double bond, this alone might lead to a failure of this route.

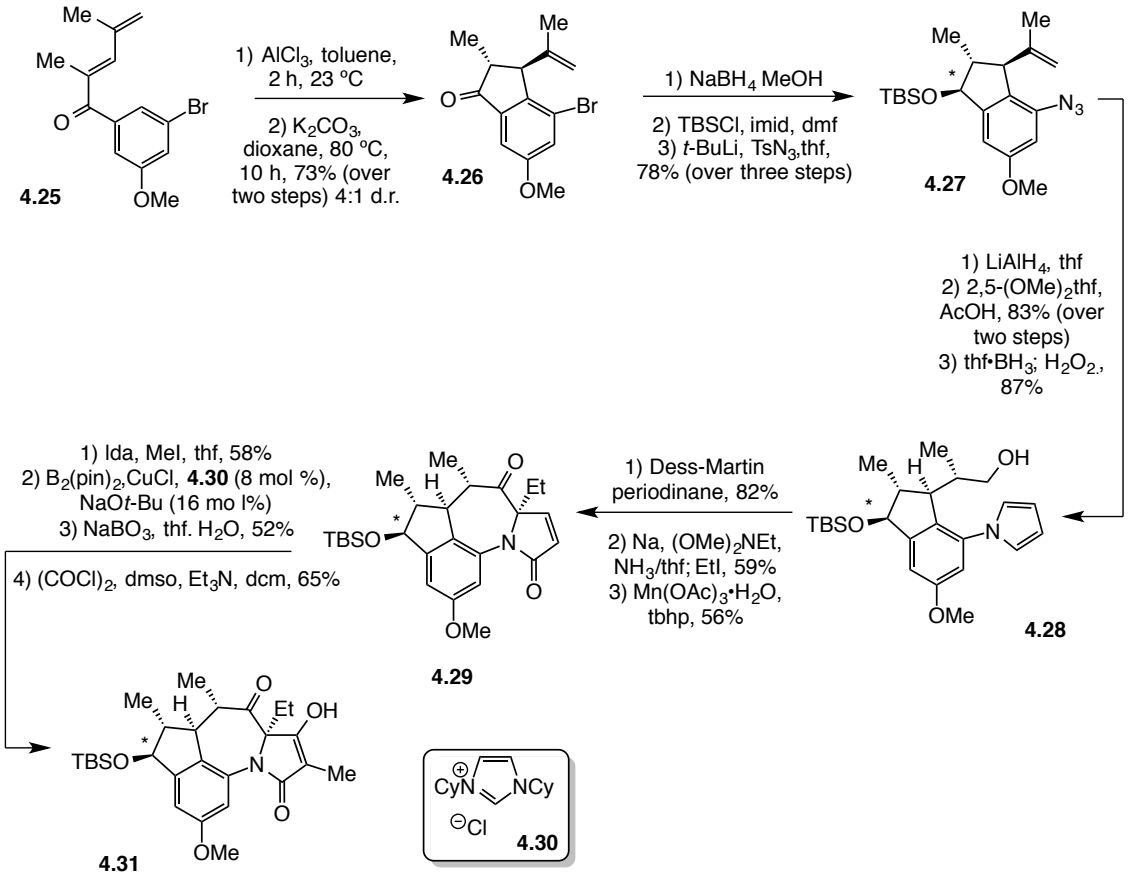
---

22. a) Donohoe, T. J.; Guyo, P. M.; Beddoes, R. L.; Helliwell, M. *J. Chem. Soc. Perkin Trans. I* **1998**, 667–676. b) Donohoe, T. J.; Harji, R. R.; Cousins, R. P. C. *Tetrahedron Lett.* **2000**, *41*, 1331–1334.

23. Shing, T. K. M.; Yeung, Y.-Y.; Su, P. L. *Org. Lett.* **2006**, *8*, 3149–3151.

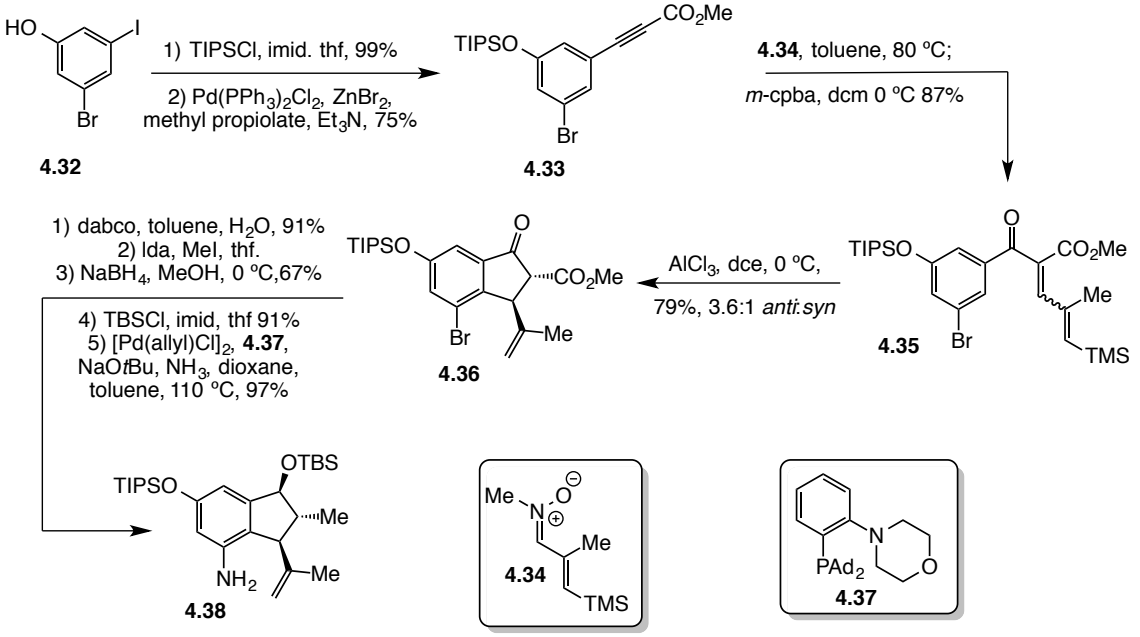
24. Lee, K.-s.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253–7255. (The Sarpong report differs from the literature conditions by the addition of copper).

Scheme 4.6. Sarpong's Progress Towards Tetrapetalone



4.3. Preparation of an RCM Substrate Towards Tetrapetalone

Scheme 4.6. Frontier's Initial Steps Towards Tetrapetalone A



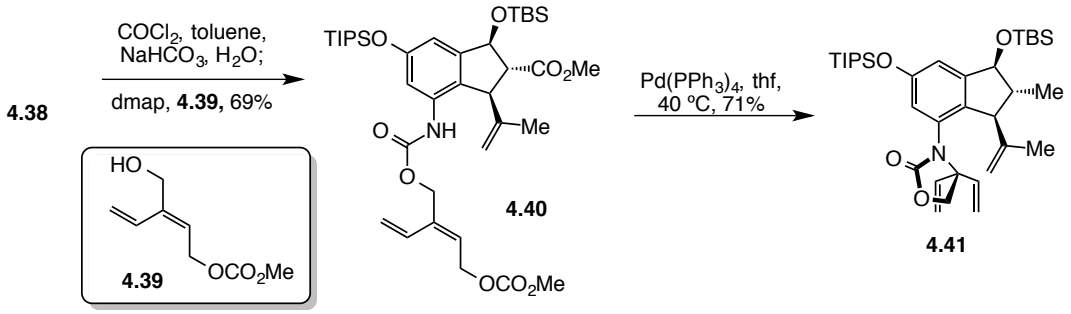
The Frontier synthesis began with phenol **4.32**, which was silylated and then the iodine selectively cross-coupled in a Sonogashira reaction producing alkyne **4.33**. Nazarov cyclization substrate **4.35** was obtained by a [3+2] cycloaddition between nitrosamine **4.34** and alkyne **4.33** followed by an oxidative ring opening with *meta*-chloroperbenzoic acid. The Nazarov reaction proceeded almost exactly the same as the closely related cyclization reported by Sarpong (*vide supra*) affording **4.36** in 79% yield and 3.6:1 diastereomeric ratio. This bicyclic ketone was subjected first to a Krapcho[25] decarboxylation, followed by methylation, reduction and TBS protection. The resulting bromide was aminated by a palladium catalyzed cross-coupling with ammonia, using Mor-DalPhos **4.37**[26]. The use of other amines resulted in no conversion to product, presumably due to steric hindrance. The Frontier group arrived at intermediate **4.38** in

[25] a) Jiricek, J.; Blechert, S. *J. Am. Chem. Soc.* **2004,** *126*, 3534–3538. b) Krapcho, A. P.; Mundy, B. P. *Tetrahedron* **1970**, *26*, 5437–5446.

[26] Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 4071–4074.

eight steps, which was similar to Sarpong's **4.27** after reduction (obtained in seven steps) except that **4.38** contained a more readily removable TIPS group on the phenol. The RCM substrate was completed by conversion of amine **4.38** into an isocyanate followed by trapping with alcohol **4.39** to give oxazolidinone **4.40**. Exposure of **4.40** to catalytic $Pd(PPh_3)_4$ resulted in an intramolecular allylic substitution to give the *gem*-divinyl containing RCM substrate **4.41**.

Scheme 4.7. Synthesis of a Ring-Closing Metathesis Substrate



4.4. Diastereoselective RCM Towards Tetrapetalone

With **4.41** in hand we set about devising conditions under which RCM could occur (table 4.1, and figure 4.2). Treating **4.41** with 25 mol % of Ru catalyst **4.15** at 80 ºC resulted in no conversion to product after 24 h (entry 1). Rather than abandon this route, a reaction was attempted in which **4.15** was added in 5 mol % increments every 30 min. In this reaction 89% of the substrate was consumed, and 58% yield of RCM products **4.42** and **4.43** were obtained, although in a poor diastereomeric ratio of 2.4:1. These diastereomers were not separable at this stage, but could be resolved after exhaustive reduction of the oxazolidone with super hydride, as shown in scheme 4.8. The reduction gives 80% yield, so the two-step yield of the desired isomer works out to 35%. For a reaction in the middle of a synthesis, this yield is unacceptable. This is where our group became involved with the project.

Figure 4.2. Mo-Alkylidene Complexes Used in the RCM Towards Tetrapetalone A

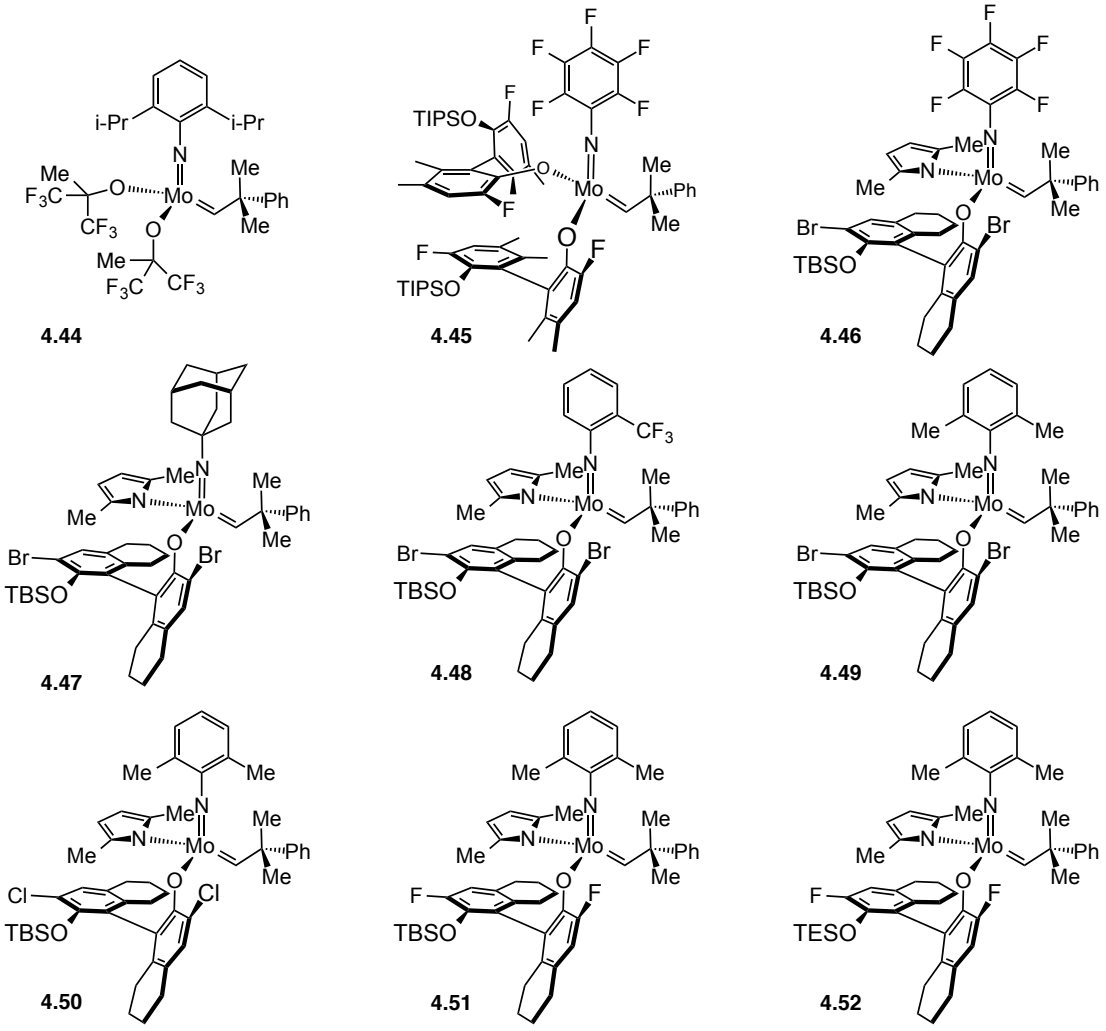
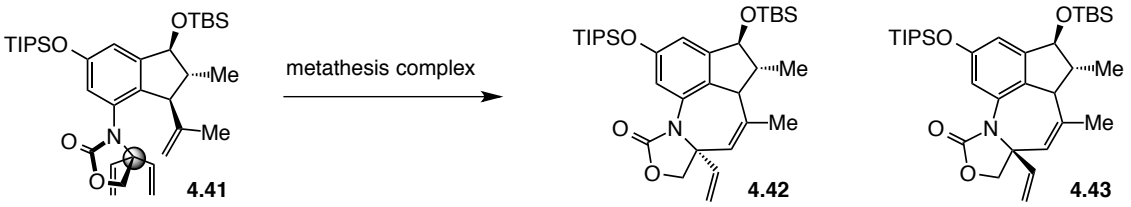


Table 4.1. Diastereoselective Ring-Closing Metathesis Towards Tetrapetalone A



4.41 **4.42** **4.43**

Entry	Complex (mol %)	T [°C]	t [h]	Conv. [%][b]	Yield [%][c]	Ratio **4.42:4:43**[b]
1	**4.15** (25)	80	24	<2	na	na
2	**4.15** (90)[d]	85	9	89	58	2.4:1
3	**4.44** (25)	22	25	12	nd	1:5
4	**4.45** (12.5)	22	25	98	90	1:3
5	**4.46** (25)	22	25	<2	na	na
6	**4.47** (25)	22	25	<2	na	na
7	**4.48** (25)	22	25	49	40	1:1
8	**4.49** (25)	22	25	28	nd	>25:1
9	**4.50** (25)	22	25	46	nd	>25:1
10	**4.51** (25)	22	25	50	40	>25:1
11	**4.51** (25)	40	25	63	63	>25:1
12	**4.52** (25)	22	25	58	nd	>25:1
13	**4.52** (25)	65	20	83	82	>25:1

a) Reactions performed under N_2 in toluene 0.015-0.0015 M (entries 1 and 2) or benzene 0.1 M (entries 3-13). b) Determined by ^1H NMR analysis of the crude reaction mixture. c) Determined by isolation and purification of products. d) Initial loading was 5 mol % with an additional 5 mol % added every 30 min. na = not applicable; nd = not determined.

We began our studies into the Mo-catalyzed RCM, with the highly active bishexafluoro-*tert*-butanol complex **4.44**[27]. We were encouraged that some reaction occurred, even though only 12% conv to product was observed and the d.r. was 1:5 favoring the undesired **4.43**. We next evaluated the activity of bisaryloxide **4.45**, which has shown high activity and selectivity in the RCM formation of the macrocyclic *Z*-

27. Murdzek, J. S.; Schrock, R. R. *Organometallics* **1987**, *6*, 1373–1374.

trisubstituted olefin of epothiolone.[28] Fortunately, just 12.5 mol % of this catalyst provided almost complete (98%) conversion to product, and 90% yield. Unfortunately, **4.43** was the major product, and the two-step yield would be no better than **4.14**.

With no clear plan on how to improve the diastereoselectivity with bisoxide catalysts such as **4.44** and **4.45**, but having demonstrated Mo based catalysis of this RCM was possible, we moved on to monoaryloxide monopyrrolide (MAP) containing catalysts. Both perfluoroimido containing MAP complex **4.46**, and adamantylimido complex **4.47** gave no conversion to product. Fortunately, the more active **4.48** provided 49% conversion to an equimolar mixture **4.42** and **4.43**. The less active and less Lewis acidic (vs. **4.48**) dimethylphenylimido complex **4.49**, provided low conversion of 28%, but only **4.42** was observed. As only the imido has changed between complexes **4.48** and **4.49**, we believed this dimethylphenylimido ligand to be critical for achieving high diastereoselectivity. Then, in an attempt to improve our low reactivity, we swapped the bromine of the aryloxide ligand for smaller and more electron withdrawing halides. Chlorine containing **4.50** improved the conversion to 46% without sacrificing the diastereoselectiviy. A further, albeit small, increase in conversion to 50% was obtained with a fluorinated ligand (complex **4.51**, entry 11). We were mostly satisfied with this result, as we could achieve similar overall two-step yield as **4.14**, but with lower catalyst loading and better selectivity. However, we were particularly unhappy with 25 h as the required time for the reaction, so we explored the application of heat to the RCM (entries 11 and 13). While we were not able to decrease the reaction time, there was an increase in conversion to 63%, allowing us to obtain **4.42**, uncontaminated with **4.43**, in 63% yield. Further improvement was seen when complex **4.52**, bearing a smaller silyl-protecting group on the ligand was employed, (58% conv. vs 50% conv. at 22 ºC, entries 10 and 12). With our final conditions (entry 13), using 25 mol % of **4.52**, at 65 ºC, 82% of **4.42** was obtained. This reaction was employed three times on 0.5g of material in order to obtain sufficient quantities of **4.42** to complete the synthesis.

This is a rare example of ring-closing metathesis to form a trisubsituted olefin immediately adjacent to an all carbon quarternary center. We are not aware of any other

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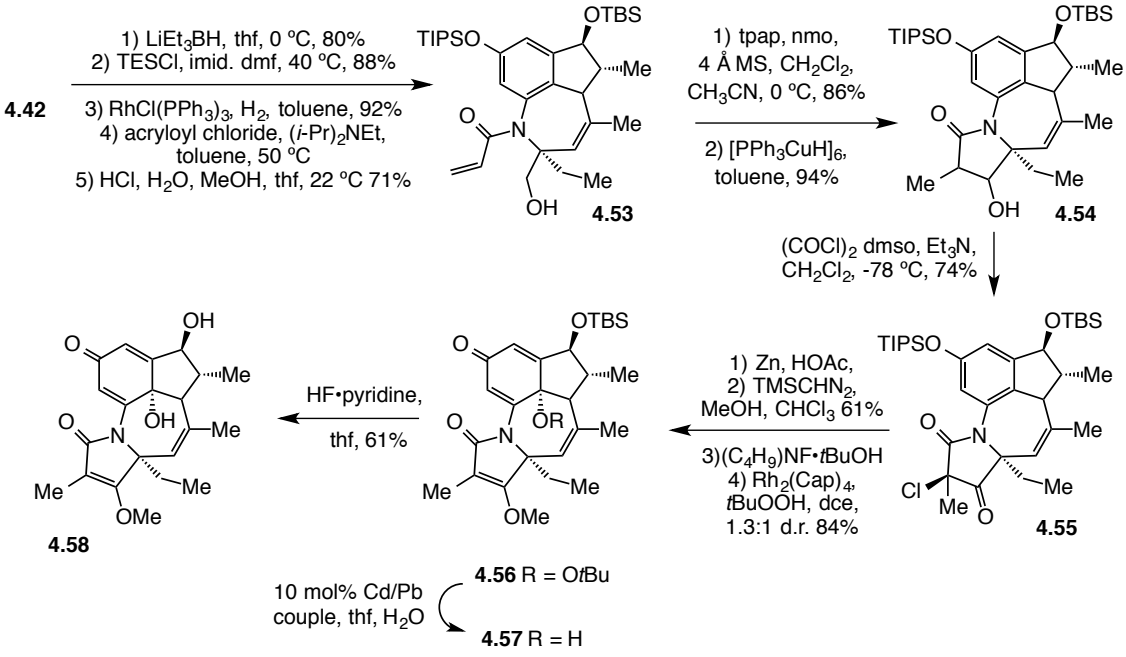
28. Wang, C.; Haeffner, F.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 1939–1943.

examples where this occurs in a seven membered ring. Another, feature of this RCM is the use of a chiral catalyst to control diastereoselectivity[29] we believe this is the first example of this within the context of olefin metathesis.

4.5 Completion of Tetrapetalone A-Me Aglycon

Scheme 4.8. Completion of Tetrapetalone A Me-Aglycon



The Frontier group's completion of the synthesis is described for completeness (scheme 4.8). Treatment of tetracyclic **4.42** with Super-Hydride® resulted in complete reduction of the carbamate to an amino alcohol. This alcohol was protected, and then the vinyl group was selectively reduced with Wilkinson's catalyst.[30] Acryloyl chloride reacted readily with the amine, and deprotection of the primary TES group gave **4.53**. The final five membered ring was installed by first oxidizing the primary alcohol to an aldehyde, with catalytic tetrapropylammonium perruthinate and *N*-methylmorpholine

29. Hoveyda, A. H. *J. Org. Chem.* **2014**, *79*, 4763–4792.

30. Ireland, R. E.; Bey, P. *Org. Synth.* **1973**, *53*, 63.

oxide.[31] Next, the α-β unsaturated amide was reduced in a 1,4 fashion with Stryker's reagent[32] forming a Cu-enolate which was able to engage in an aldol reaction with the adjacent aldehyde to form **4.54**. When **4.54** was exposed to Swern oxidation conditions the expected oxidation to the tetramic acid[14a] occurred concomitantly with incorporation of a chlorine atom.[33] Fortunately, Zn in acetic acid readily reduced the halide. For the remainder of the operations, the sensitive tetramic acid was protected as the methyl ether, by exposure to trimethylsilyldiazomethane. After removal of the TIPS group, with tetrabutylammonium fluoride *tert*-butanol complex, the stage was set for oxidation of the phenol to the final quinol. Iodine based oxidants failed to react, but dirhodium caprolactamate was able to catalyze the oxidation with *tert*-butyl hydrogen peroxide, although with only 1.3:1 d.r. These diastereomers could be separated, and while common reduction methods such as Zn/HOAc, Mg/MeOH and Al/Hg failed to provide **4.57**, they did regenerate the phenol. This enabled recycling of the undesired diastereomer. Successful reduction to the quniol was obtained with 10 mol % Cd/Pb couple in thf/H_2O. Finally, removal of the TBS group with HF•pyridine gave the methyl-ester of tetrapetalone A-agylcon **4.58**. As this was a racemic synthesis, the β-rhodinose[34] moiety, was not appended since this could only provide a 1:1 mixture of diastereomers. Additionally, the tetramic acid has been irreversibly masked with a methyl group. A synthesis of **4.1** would probably necessitate revising the order of operations and forming the tetramic acid after the oxidative dearomatization of the phenol.

Ultimately the Frontier group arrived at racemic tetrapetalone A Me-aglycon **4.58**, in 25 linear steps. While this sequence was quite long, it was ultimately successful, whereas all other routes have, so far, ended in failure. The diastereoselective RCM enabled by stereogenic-at-Mo MAP complexes proved critical for the endeavor.

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31. Ley, S. V.; Norman, J.; Griffith, W. P. Marsden, S. P. *Synthesis* **1994**, 639–666.

32. Schwartz, K. D.; White, J. D. *Org. Lett.* **2010**, *13*, 248–251.

33. Smith, A. B. III; Leenay, T. L.; Liu, H.-J.; Nelson, L. A. K.; Ball, R. G. *Tetrahedron Lett.* **1988**, *29*, 49–52.

34. Kelly, T. R.; Kaul, P. N. *J. Org. Chem.* **1983**, *48*, 2775–2777.

4.6 Enantioselectivie RCM Towards Aspidosperma Alkaloids: Background

We first developed MAP catalysts for the enantioselective RCM of **4.59**, in the synthesis of quebrachamine **4.62**[35] (scheme 4.9). This synthesis was designed to specifically feature the challenging RCM of **4.59** to **4.61**, where existing chiral diolate containing Mo catalysts, and chiral NHC based Ru catalysts[36] failed to provide any enantioselectivity, in the cases where they reacted at all. One complicating factor in the RCM of **4.59**, is the tendancy of Lewis basic moieties such as amines and amides to coordinate to metathesis promoting complexes[37] and inhibit their reactivity. Another issue is that **4.59** contains a very sterically demanding *gem*-divinyl unit, reaction with which can be very slow. Furthermore, while it was reasonable to imagine enantioselective formation of **4.61** would be possible, it did not fit our model of enantio-induction in RCM[38]. Even after we developed MAP catalysts such as **4.60** to overcome these challenges and provide a highly efficient and selective transformation, we still have no model explaining the selectivity in this case.

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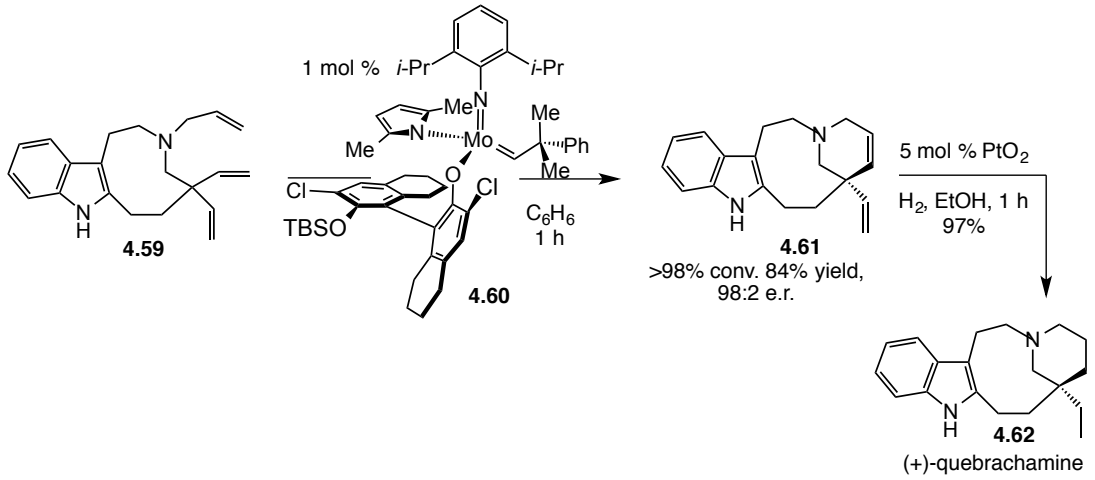
35. Malcolmson, S. J.; Meek, S. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *456*, 933–937. b) Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R. Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 943–953.

36. Van Veldhuizen, J. J.; Campbell, J. E. Guidici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877–6882.

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

38. Jernelius, J. A.; Schrock, R. R.; Hoveyda, A. H. *Tetrahedron,* **2004**, *60*, 7345–7351.

Scheme 4.9. RCM in the Synthesis of Quebrachamine



4.7 Enantioselective RCM Towards Aspidosperma Alkaloids

Based on our success towards quebrachamine, and their longstanding interest in aspidosperma alkaloids[39], we began a collaboration with the Movassaghi group in order to assist with the enantioselective RCM of **4.63** *en route* to (—)-deoxoapodine **4.65**[40]. As **4.63** is very similar to **4.59**, differing only by a carbonyl unit, and PMB protection on the indole nitrogen, we began our endeavors with **4.60**, the same catalyst that was optimal for **4.59**. While there was high conversion to product, the enantioselectivity was only 82:18, vs. 98:2 in the RCM of **4.59**. Furthermore, we have recently discovered, that **4.64** was obtained with the opposite sense of enantioselectivity vs. **4.61**. Although we desire the (*S*)-enantiomer, in order to obtain (—)-deoxoapodine **4.65**, most catalyst screening reactions were performed with catalysts that afford the (*R*)-enantiomer of **4.64** (as shown in tables **4.2** and **4.3**).

Having determined that a selective reaction was possible, but would require identification of a different catalyst than **4.60**, we first decided to vary the imido group of

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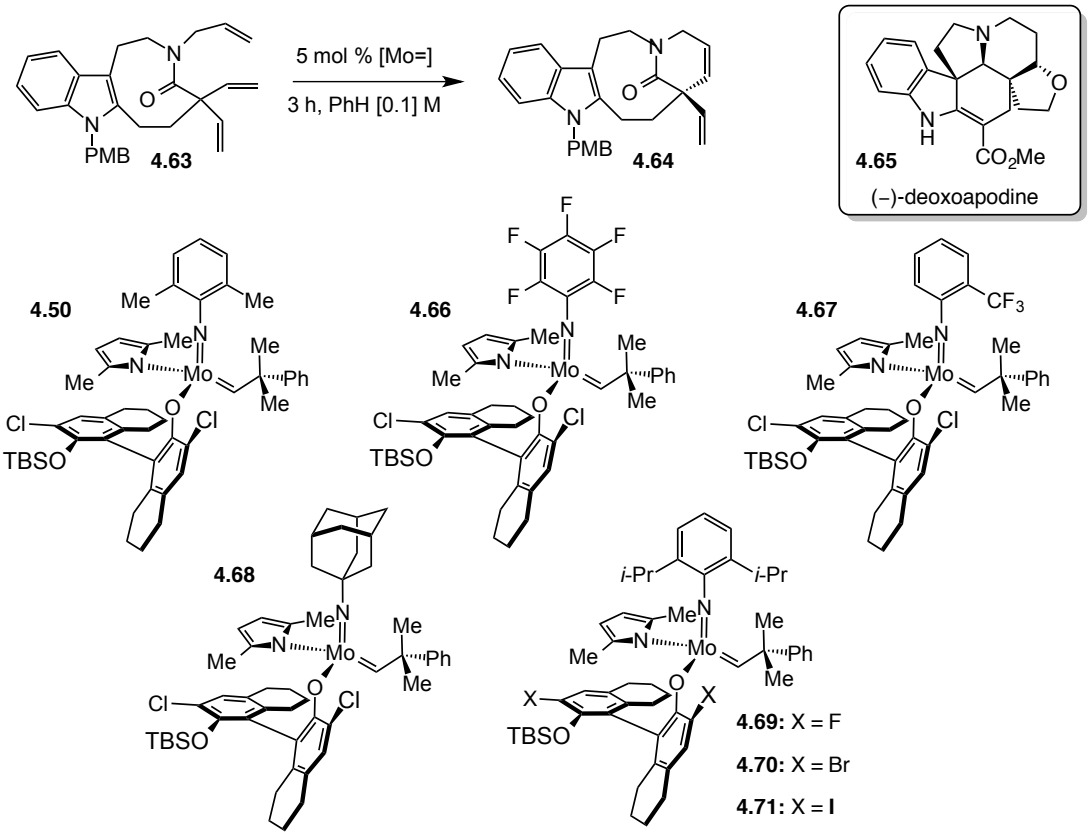
39. a) Mewald, M.; Medley, J. W.; Movassaghi, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 11634–11639. b) Mewald, M.; Movassaghi, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 4572–4576.

40. For isolation reports, see: a) Inglesias, R.; Diatta, L. *Rev. CENIC Cience. Fis.* **1975**, *6*, 135. b) Bui, A. M.; Das, B. C.; Potier, P. *Phytochemistry* **1980**, *19*, 1473–1475 For previous syntheses, see: c) Lee, K.; Boger, D. L. *J. Am. Chem. Soc.* **2014**, *136*, 3312–3317. d) Overman, L. E.; Robertson, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 2598–2610.

the Mo-complex (entries 2-5) as changes to the imido are often the most important for reactivity and selectivity of a Mo complex. Smaller imidos than the diisopropylphenyl moiety (complex **4.60**) all gave nearly racemic products (e.r. less than 63:37), expect for pentafluoroimido **4.66**, which failed to react at all. We determined that the solution to our selectivity problem must lie with a catalyst containing a diisopropylphenyl imido unit, and a different aryl oxide ligand. We tested the complexes derived from different halides at the *ortho* position of the phenol. A catalyst containing a more diminutive F unit **4.69** resulted in nearly racemic product (e.r. = 58:42). Fortunately, enantioselectivity improved to 91:9 when the more sizable and less electron withdrawing Br was placed on the phenol. Further improvement to 93:7 was seen with catalyst **4.71** with iodine in the crucial *ortho* position. We have so far found no better Mo-complex or conditions for this reaction.

Table 4.2. RCM Towards Aspidosperma Alkaloids[a]



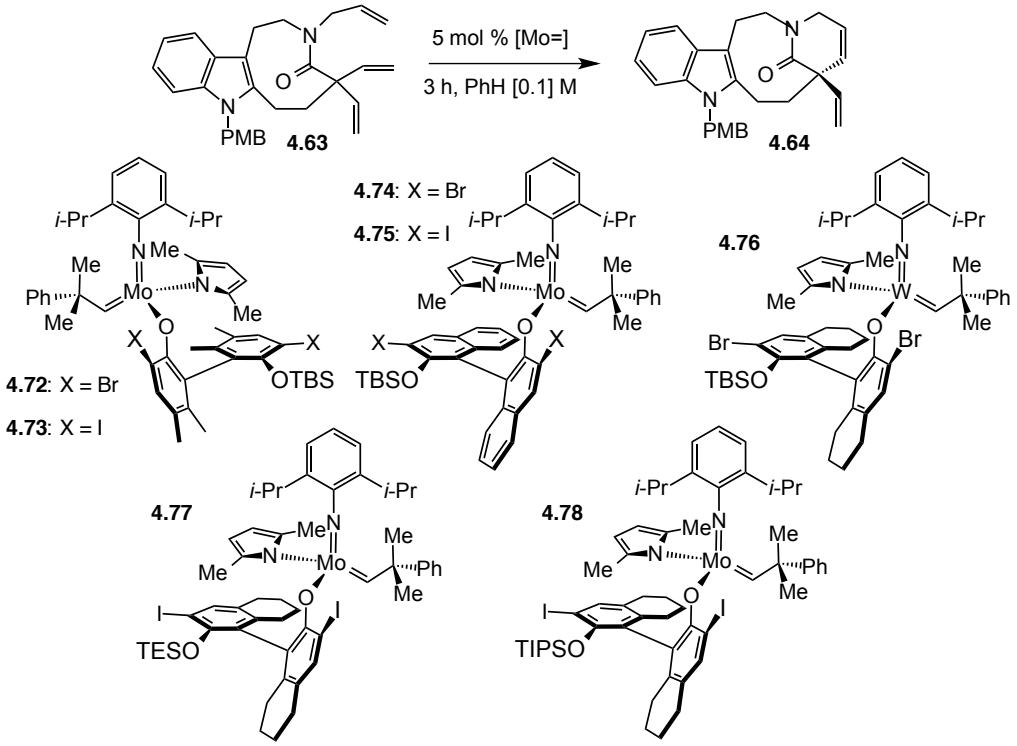
Entry	complex	conv.[b]	e.r.[c]
1	**4.60**	>95	82:18
2	**4.50**	57	38:62
3	**4.66**	<10	na
4	**4.67**	29	46:54
5	**4.68**	>98	61:39
6	**4.69**	53	58:42
7	**4.70**	>95	91:9
8	**4.71**	>98	93:7

a) Reactions performed under N_2 in a dry box in benzene (0.1 M.)
b) Determined by ^{1}H NMR analysis of the crude reaction mixture.
c) Determined by HPLC analysis of isolated and purified material.
na = not applicable.

As we were not completely satisfied with 93:7 enantioselectivity we took additional efforts to improve the reaction including adjusting the reaction conditions while keeping complex **4.71** constant (table 4.3 entires 1-3). As addition of Lewis bases is known to improve selectivity of Mo-catalyzed olefin metathesis reactions[41] we hoped thf could increase our enantioselectivity, but we saw only a decrease in selectivity (entry 1). We also attempted to lower the reaction temperature. This presented some operational difficulties; the reaction had, like all our other Mo-catalyzed olefin metathesis reactions, been developed in benzene, but as benzene freezes at 5 ºC lower temperature reactions demanded a different reaction solvent. Unfortunately, the substrate was not completely soluble in toluene at the concentrations employed. We attempted the reaction, at extended reaction times at -15 ºC and 4 ºC. At -15 ºC no reaction was observed, and no difference in e.r. was detected at 4 ºC.

41. Teng, X.; Cefalo, D. R.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 10779–10784.

Table 4.3 Additional Catalyst Screening Towards Aspidosperma Alkaloids



Entry	complex	time (h)	temp (°C)	conv (%)[b]	e.r.[c]
1[d]	**4.71**	3	22	>98	91:9
2	**4.71**	12	-15	<2	na
3	**4.71**	12	4	>98	92:8
4	**4.72**	3	22	>98	18:82
5	**4.73**	3	22	>98	10:90
6	**4.74**	3	22	<5	na
7	**4.75**	3	22	11	63:37
8	**4.76**	3	22	<5	na
9	**4.77**	3	22	>98	91:9
10	**4.78**	3	22	20	84:26

a) Reactions performed under N_2 in a dry box in benzene (0.1 M) b) Determined by ^{1}H NMR analysis of the crude reaction mixture. c) Determined by HPLC analysis of isolated and purified material. d) Reaction conducted in the presence of 30 equiv thf. na = not applicable.

Related but distinct catalysts were ineffective at improving the enantioselectivity (table 4.3 entries 4-10). We started by investigating the other biphenyl[7], and binol[42] scaffolds commonly used in Mo based metathesis. As the difference between bromine and iodine containing catalysts **4.70** and **4.71** were slight, we decided to investigate both bromine and iodine versions of these new complexes. The biphenyl catalysts were just as reactive as the octahydrobinaphthol versions, but enantioselectivity was slightly lower (entries 4 and 5). The binol based catalysts performed very poorly, **4.74** failed to react at all, and **4.75** gave only 11% conversion with an enantiomeric ratio of 63:37. As tungsten complexes are often more selective than their molybdenum-based analogues[43] we employed the W based complex **4.76**, which could serve as a direct comparison with **4.70**, unfortunately, no conversion to **4.64** was achieved. We were now convinced that iodooctahydrobinaphol was the correct ligand framework, and only one position was left to modify, that of the silyl unit on the second aryl oxide. Triethylsilyl containing complex **4.77** showed slightly lower e.r. at 91:9, and TIPS catalyst **4.78**, was much worse giving only 84:26 e.r.. Having obtained these additional data, we were convinced to utilize ***ent*-4.71** as the optimal catalyst for the synthesis.

We have currently successfully increased the scale of the RCM using ***ent*-4.71** to afford up to 115 mg of ***ent*-4.64** in a single batch.

Stabilization of sensitive catalysts by encapsulation in paraffin wax is a common procedure[44] especially in patent literature. Our sensitive MAP catalysts have recently become commercially available as a 5 wt % formulation in paraffin from Aspira Scientific, in collaboration with XiMo AG. We have successfully utilized a wax tablet of **4.70** in the formation of **4.64** outside of a glovebox, using common laboratory techniques (scheme 4.10). The yield and selectivity were both slightly higher than the analogous reaction performed in the glovebox using a solution of *in situ* generated catalyst (c.f. table 4.2, entry 7). This could either be an experimental error, or due to the slow release of the

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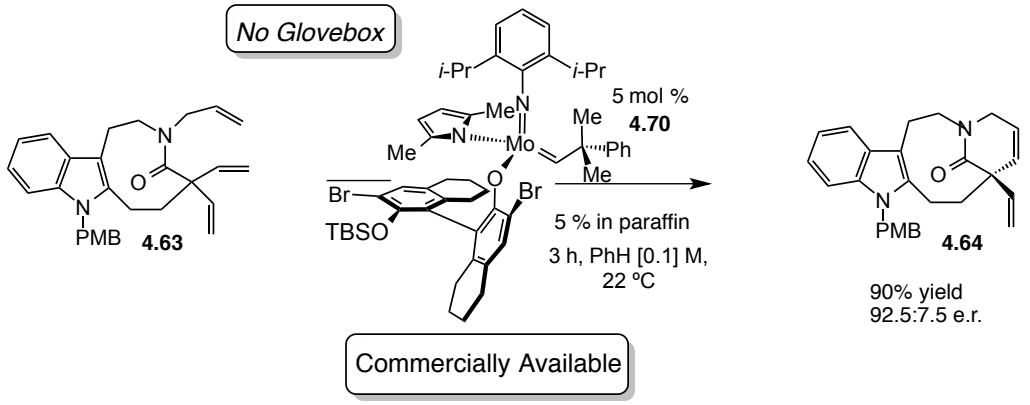
42. Zhu, S. S.; Cefalo, D. R.; La. D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251–8259.

43. Jiang, A. J.; Zhao, Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 16630–16631, b) Zhao, Y.; Hoveyda, A. H.; Schrock, R. R. *Org. Lett.* **2011**, *13*, 784–787.

44. Taber, D. F.; Frankowski, K, J. *J. Org. Chem.* **2003**, *68*, 6047–6048.

catalyst, which could increase the enantioselectivity of RCM reactions.[45] Unfortunately, our optimal catalyst **4.71** was not currently available, and **4.70** is the opposite enantiomer from the one we required. Never the less, we hope this serves as an important proof of principle, and will encourage use of our catalysts as they become more widely available.

Scheme 4.10. Enantioselective Ring-Closing Metathesis Inside the Fume Hood



4.8 Conclusions

We have demonstrated the ability of Mo based MAP catalysts to effect two critical RCM reactions with high stereoselectivity not available with other metathesis complexes. The diversity of available catalysts, and their ability to be rapidly and logically modified was key to these efforts, and enabled the stereoselective synthesis of molecules not otherwise obtainable. We have also demonstrated one of our RCM reactions without the use of a glovebox and with commercially available catalyst. We hope these successes of these collaborative endeavors will lead to more widespread use of our modular and easily obtained Mo catalysts in the future.

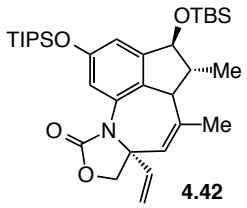
4.9 Experimental

General: All reactions were carried out in oven-dried (135 °C) or flame-dried glassware under an inert atmosphere of dry N_2 unless otherwise stated. Thin layer chromatography (TLC) analysis was accomplished on 250 μm SiliCycle plates, with visualization

45. Meek, S. J.; Malcolmson, S. J.; Li, B.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 16407–16409.

provided by potassium permanganate, anisaldehyde or UV fluorescence quenching. Compounds were purified by silica gel chromatography on SiliCycle SilaFlash 230-400 mesh silica gel. All substrates were dried by azeotropic distillation with C_6H_6 prior to use in reactions with Mo- based complexes, or distilled under vacuum from CaH_2. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance (^{13}C) or the solvent resonance resulting from incomplete deuteration (^{1}H) as the internal reference (7.26 ppm for ^{1}H, 77.16 ppm for ^{13}C). Benzene (Alfa Aesar) was purged with Ar and purified under a positive pressure of dry Ar by a modified Innovative Technologies purification system, and further dried over activated 4 Å molecular sieves (Aldrich).

Complexes **4.44**[27], **4.45**[28], **4.47**[46], **4.48**[47], **4.49**[48], **4.60**[35a], **4.69**[35b], **4.70**[35b], **4.71**[35b] and **4.76**[43a] were prepared according to literature procedure. Complexes **4.46**, **4.50**, **4.51**, **4.52**, **4.66**, **4.67**, **4.68**, **4.69, 4.72**, **4.73**, **4.74**, **4.75**, **4.77**, **4.78** were prepared by procedures analogous to those for **4.60**[35]. CatPac-3 was purchased from Aspira and used as received.



4.42

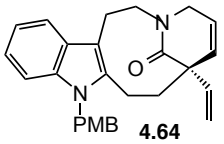
(*rac*)-(1*S,2*R**,4a*S**)-1-((*tert*-butyldimethylsilyl)oxy)-2,3-dimethyl-10-((triisopropylsilyl)oxy)-4a-vinyl-2,2a,4a,5-tetrahydro-1*H*,7*H*-indeno[1,7-*ef*]oxazolo[3,4-*a*]azepin-7-one** (**4.42**)**:** It is recommended that **4.41** be purified by recrystallization from boiling hexanes. In a N_2 filled glovebox, an oven dried 4-mL vial equipped with stir bar, was charged with **4.41**, (10.3 mg, 0.0168 mmol), followed by a benzene solution of **4.52** (168 uL, 0.00421 mmol, 25 mol %). The vial was capped, heated to 65 ºC and the solution allowed to stir for 25 h. The reaction was quenched by

46. Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3844–3845.

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. Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461–466.

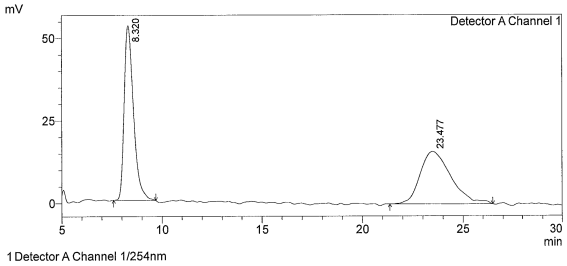
removal from the glovebox and addition of diethyl ether. The mixture was concentrated, and percent conversion and diastereoselectivity were determined by ^{1}H NMR of the crude mixture. The mixture was purified by silica gel chromatography (2% diethyl ether in hexanes) to afford **4.42** as an off-white solid (7.8 mg, 0.0134 mmol, 80% yield). **IR (neat):** 2947 (s), 2928 (s), 2893 (m), 2866 (s), 2361 (s), 2342 (m), 1755 (s), 1609 (m), 1582 (m), 1470 (s), 1380 (s), 1366 (s), 1257 (s), 1227 (m), 1200 (w), 1150 (m), 1103 (s), 1069 (m), 1009 (m), 907 (m), 872 (s), 837 (s), 760 (m), 733 (s), 683 (m); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.50 (d, *J* = 1.6 Hz, 1H), 6.58 (s, 1H), 5.98 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.74 (s, 1H), 5.26 (d, *J* = 3.0 Hz, 1H), 5.23 (d, *J* = 3.0 Hz, 1H), 4.50 (d, *J* = 8.1 Hz, 1H), 4.22 (d, *J* = 8.2 Hz, 1H), 4.01 (d, *J* = 8.2 Hz, 1H) 3.76 (d, *J* = 9.9 Hz, 1 H), 2.37 – 2.22 (m, 1H), 1.90 (s, 3H), 1.38 – 1.20 (m, 6H), 1.10 (dd, *J* = 7.3, 1.4 Hz, 18H), 0.97 (s, 9), 0.20 (s, 4H), 0.16 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 155.82, 155.33, 146.81, 146.03, 136.17, 134.95, 126.74, 120.55, 117.42, 113.78, 111.63, 81.33, 75.26, 65.21, 49.01, 47.87, 25.99, 21.37, 18.56, 18.10, 18.02, 12.79, –3.74, –3.87. **HRMS (ESI+):** Calculated for C33H54NO4Si2 ([M+H]+): m/z 584.3591, found: 584.3589.



4.64

(8*S*)-11-(4-methoxybenzyl)-8-vinyl-1,2,3,5,8,9,10,11-octahydro-4,8-methano[1]azacyclododecino[6,5-*b*]indol-16-one (4.64): In a N_2 filled glovebox, an oven dried 4-mL vial equipped with stir bar, was charged with **4.63**, (7.7 mg, 0.018 mmol), benzene (131 μL) was then added, followed by a [0.02] M benzene solution of *ent*-**4.71** (43.7 μL, 8.7 * 10^-4 mmol, 5 mol %). The vial was capped, and the solution allowed to stir for 3 h. The reaction was quenched by removal from the glovebox and addition of diethyl ether. The mixture was concentrated, and percent conversion was determined by analysis of the ^{1}H NMR spectrum of the crude mixture. The mixture was chromatagraphed on SiO_2 (gradient of 10% EtOAc/hexanes to 20% EtOAc/hexanes) to afford tetracycle **4.64** (7.0 mg 0.016 mmol, 90% yield) as off white solid. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.59 – 7.49 (m, 1H), 7.13 – 7.00 (m, 3H), 6.89 – 6.81 (m, 2H), 6.81 – 6.73 (m, 2H), 6.15 (dd, *J* = 17.7, 10.7 Hz, 1H), 5.87 (s, 1H), 5.64 (d, *J* = 10.1 Hz, 1H), 5.32 (d, *J* = 17.0 Hz, 1H), 5.14 (d, *J* = 17.0 Hz, 1H), 5.07 (dd, *J* = 10.7, 0.9 Hz, 1H), 5.02

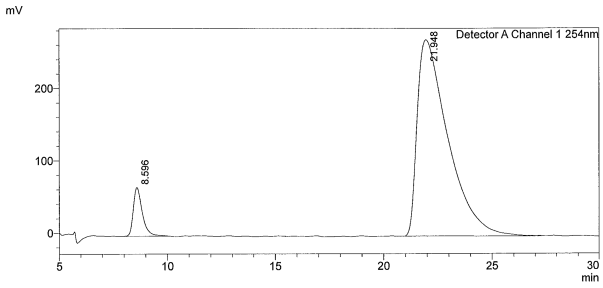
(dd, *J* = 17.7, 0.9 Hz, 1H), 4.57 – 4.46 (m, 1H), 4.18 – 4.08 (m, 1H), 3.97 – 3.86 (m, 1H), 3.74 (s, 3H), 3.12 (d, *J* = 14.7 Hz, 1H), 2.90 (ddd, *J* = 14.4, 10.8, 3.2 Hz, 1H), 2.78 (d, *J* = 8.5 Hz, 1H), 2.74 (ddd, *J* = 13.0, 4.5, 3.2 Hz, 1H), 2.66 (ddd, *J* = 15.8, 9.6, 1.4 Hz, 1H), 2.33 (ddd, *J* = 13.6, 9.5, 1.5 Hz, 1H), 1.88 (ddd, *J* = 13.5, 9.1, 1.4 Hz, 1H), 2.08 – 2.02 (m, 1H), Other characterization data (^{13}C NMR, IR, optical rotation and were collected at MIT and will be reported in due course.) Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiracel® OJ-H 70:30 hexanes:*i*-PrOH, 1.0 mL/min, 254 nm) t_R of **4.64** 8 min (minor) and 22 min (major).



Peak Table

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	8.320	1703619	52907	50.113		M
2	23.477	1695936	15906	49.887		M
Total		3399555	68813			



<Peak Table>

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
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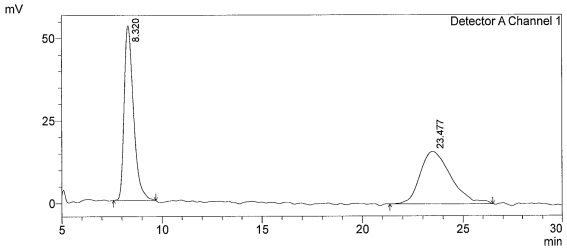
2	21.948	26721473	271873	93.178		M	
Total		28677727	339302				

Peak #	Ret. Time	Area %	Peak #	Ret. Time	Area %
1	8.3	50.113	1	8.6	6.822
2	23.5	49.887	2	21.9	93.178

Procedure using CatPac-3 tablet:

To an oven dried Schlenk tube equipped with stir bar, triene **4.63** (7.0 mg, 0.016 mmol, 1 equiv) was added under a stream of Ar. A CatPac-3® tablet was cut to the appropriate weight (17.1 mg, 7.9 *10 ^-4 mmol, 5 mol %) and introduced into the Schlenk tube under a stream of Ar. Benzene (160 μL) was added, the flask was stoppered and closed to Ar, and the mixture allowed to stir for 3 h. The reaction was then quenched by exposure to air and the addition of Et_2O, the mixture was concentrated, and percent conversion was determined by analysis of the ^{1}H NMR spectrum of the crude mixture. The mixture was purified by silica gel chromatography (gradient 10% EtOAc/hexanes to 20% EtOAc/hexanes) to afford tetracycle **4.64** (6.4 mg, 0.015 mmol, 94% yield) as off white solid. Enantiomeric purity was determined by HPLC analysis in comparison with

authentic racemic material (Chiracel® OJ-H 70:30 hexanes:*i*-PrOH, 1.0 mL/min, 254 nm) t_R of **4.64** 8 min (major) and 25 min (minor).

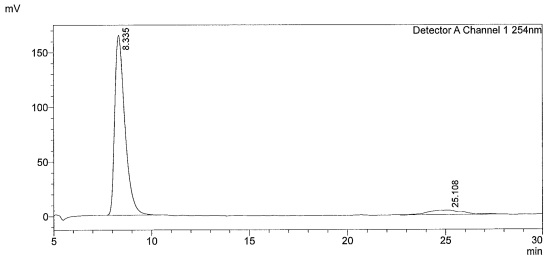


1 Detector A Channel 1/254nm

Peak Table

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	8.320	1703619	52907	50.113		M
2	23.477	1695936	15906	49.887		M
Total		3399555	68813			



<Peak Table>

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
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2	25.108	485914	3934	7.594		M	
Total		6398894	168422				

Peak #	Ret. Time	Area %	Peak #	Ret. Time	Area %
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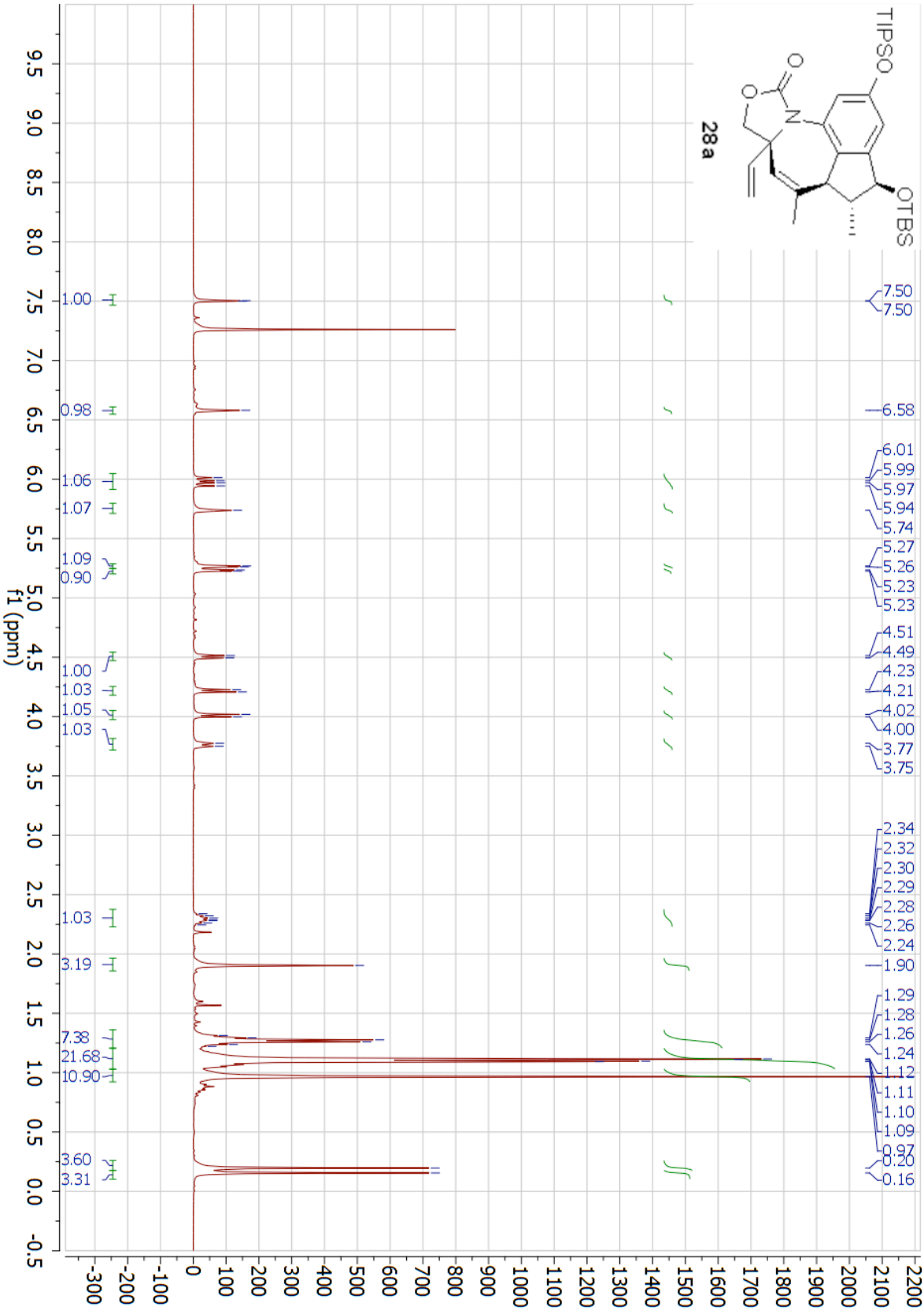
2	23.5	49.887	2	25.1	7.594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1.07
1.09
0.90
1.00
1.03
1.05
1.03
1.03
3.19
7.38
21.68
10.90
3.60
3.31
7.50
7.50
6.58
6.01
5.99
5.97
5.94
5.74
5.27
5.26
5.23
5.23
4.51
4.49
4.23
4.21
4.02
4.00
3.77
3.75
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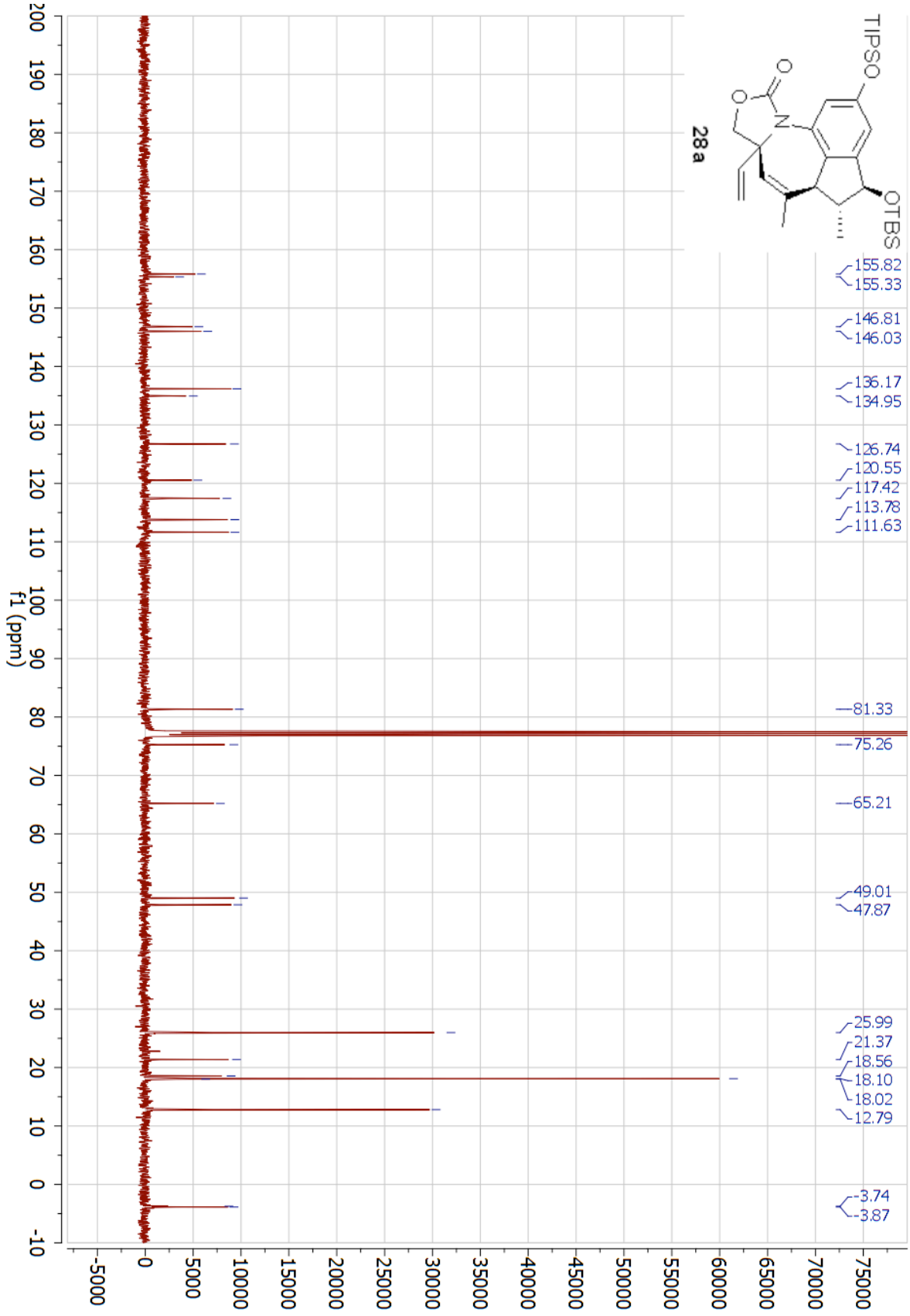
28a
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OTBS
O
O
N
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155.33
146.81
146.03
136.17
134.95
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111.63
81.33
75.26
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18.02
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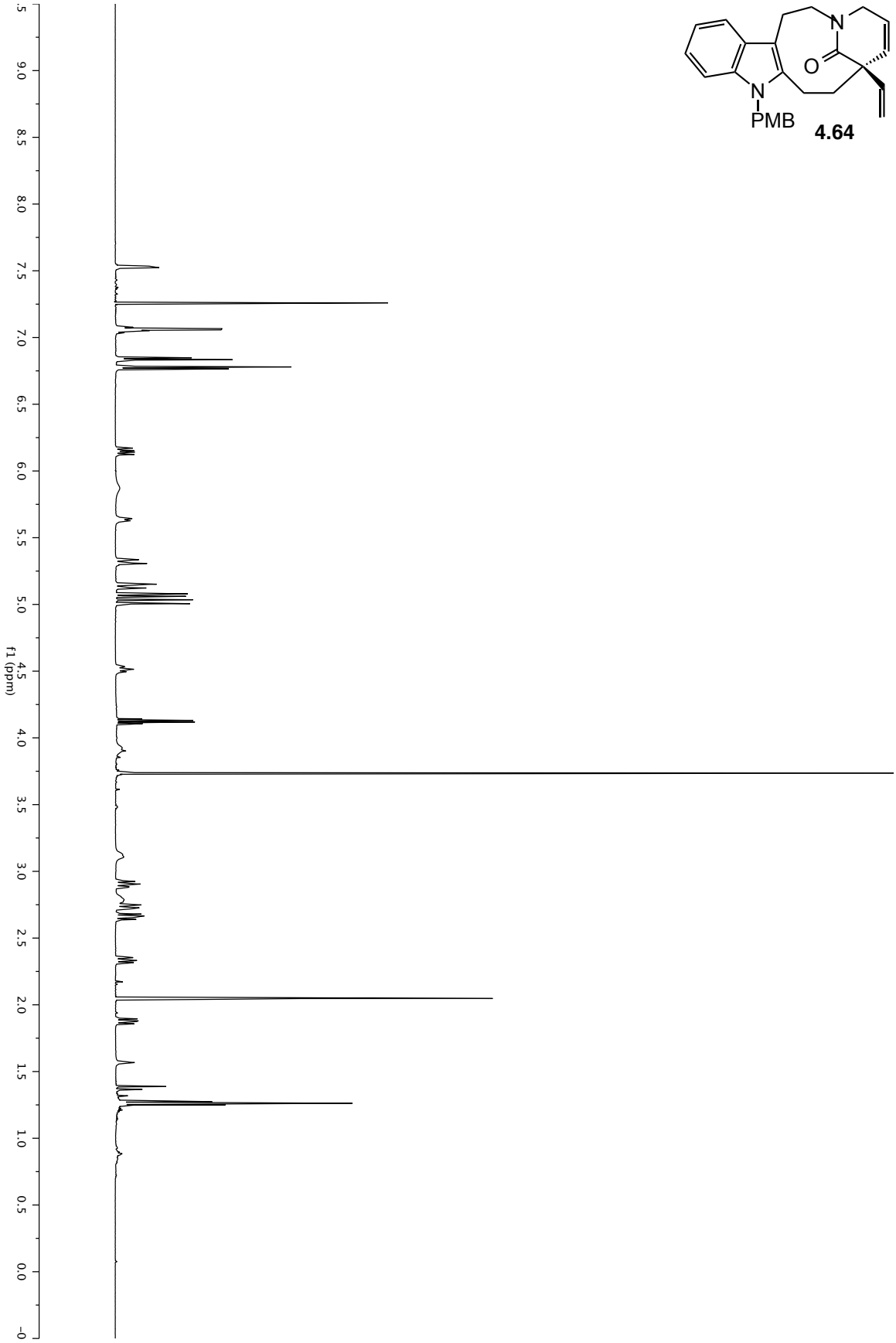
-3.87
f1 (ppm)


N
O
N
PMB
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f1 (ppm)