Stereoselective Olefin Cross-Metathesis of α,β,γ,δ-Unsaturated Phenyl Esters

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STEREOSELECTIVE OLEFIN CROSS-METATHESIS OF α,β,γ,δ-UNSATURATED PHENYL ESTERS

A thesis

by

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Abstract

Chapter 1. Catalytic olefin metathesis has developed into a powerful tool in the arsenal of the synthetic chemist as a quick and reliable method to build complexity in biologically active molecules. One particular subset of this class of reactions, catalytic olefin cross-metathesis, has seen great strides within the last decade. Using recently reported well-defined catalysts, chemists have been able to synthesize olefins in a stereoselective fashion via this reaction in a laboratory setting. While many classes of *Z* olefins have succumbed to this transformation, one class of olefins that has not been synthesized in a selective manner is that of *Z*-unsaturated esters, precious motifs found in a myriad of natural products. Traditional preparations of *Z*-acrylates and *Z*-dienoates are presented drawing examples from both total syntheses as well as method development reports.

Chapter 2. A catalytic olefin cross-metathesis reaction utilizing *E*-dienoates as substrates is presented. A large variety of functionalized (*E,Z*)-dienoates are prepared in high yields and high stereoselectivities. This method has many advantages over more common

methods of making these motifs, such as a wider substrate scope and the ability to be performed at ambient temperature.

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I would like to thank all members of the Hoveyda group for providing a pleasant and jovial atmosphere to learn organic chemistry. I would especially like to thank Mr. Tyler Mann and Ms. Elsie Yu. Tyler taught me the ropes of working on olefin metathesis when I first started in the lab and has always been a constant source of information and advice for me. Elsie has always been a valuable source of advice and has been a fantastic partner and mentor on the unsaturated carbonyl cross-metathesis project. These two are also gratefully acknowledged for proofreading this thesis.

I would lastly like to thank those outside of Boston College who have stood by me through my journey through graduate school. My parents, my brother, Brendan, and the rest of my family members have served as constant sources of support and have been

nothing but encouraging to me. None of what I have accomplished in this thesis would have been possible without them.

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LIST OF ABBREVIATIONS

%	percent
Ag_2CO_3	silver carbonate
Al_2O_3	aluminum oxide
app	apparent
B(cat)	catecholboron
B(pin)	pinacolatoboron
Boc	tert-butoxycarbonyl
br	broad
Bz	benzyl
$CaCO_3$	calcium carbonate
CF_3	trifluoromethyl
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
conv	conversion
Cp	cyclopentadiene
CuTC	Copper(I)-thiophene-2-carboxylate
d	doublet
DART	direct analysis in real time
DIBAL	diisobutylaluminum hydride
dma	N,N-dimethylacetamide
dmf	N,N-dimethylformamide
DMSO	dimethyl sulfoxide

dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
equiv	equivalence
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
h	hour
HMTO	hexamethylterphenoxide
HOAc	acetic acid
i-Bu	isobutyl
K_2CO_3	potassium carbonate
KHMDS	potassium bis(trimethylsilyl)amide
M	molar
m	multiplet
Me	methyl
MeOH	methanol
min	minute
MOM	methoxymethyl
n-Bu	*n*-butyl

n-BuLi	*n*-butyllithium
n-Hex	*n*-hexyl
NBu_4Cl	tetra-*n*-butylammonium chloride
$(n\text{-Bu})_4NF$	tetra-*n*-butylammonium fluoride
nmp	N-methyl-2-pyrrolidone
o-BrC_6H_4	*ortho*-bromostyrene
o-MeC_6H_4	*ortho*-methylstyrene
OAc	Acetate
OMe	methoxide
PEPPSI	pyridine-enhanced precatalyst preparation stablization and initiation
PMB	*para*-methoxybenzyl
PPh_3	triphenylphosphine
q	quartet
rt	room temperature
s	singlet
$SiMe_3$	trimethylsilane
t	triplet
t-BuLi	*tert*-butyllithium
t-BuOK	potassium *tert*-butoxide
TBDPS	*tert*-butyldiphenylsilane
TBS	*tert*-butyldimethylsilyl
thf	tetrahydrofuran
TIPS	triisopropylsilyl

wt %	weight %

1. Traditional Preparation of *Z*-Acrylates and *Z*-Dienoates

1.1 Introduction

Olefins are some of the most widely used functional groups in organic synthesis. In many cases, alkenes are used as building blocks towards greater complexity and are key structures in some of the most prominent reactions in organic chemistry, such as catalytic cross couplings[1] and dihydroxylation.[2] Olefins are often utilized as valuable precursors to biologically active molecules, in both the *cis* and *trans* forms. However, in many cases, olefins are part of the final molecule as well, often with one isomeric form having significantly higher biological activity over the other.[3] While nature has found means of generating olefins in a stereoselective fashion, chemists in the laboratory have found this challenge more difficult to overcome due to the fact that, in general, *Z* olefins are energetically higher than their corresponding *E* isomer.

One area of stereoselective synthesis that has achieved great strides within the last decade is catalytic olefin metathesis.[4] Through the rationalized design of catalysts,[5] chemists have been able to overcome the barrier to *Z* olefin formation for a large group of *Z* olefins in a stereoslective manner using various metathetic processes, including ring-opening/cross-metathesis (ROCM),[6] ring-closing metathesis (RCM),[7] and cross-

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[1] Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146–151.

[2] Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2024–2032.

[3] Gaukroger, K.; Hadfield, J. A.; Hepworth, L. A.; Lawrence, N. J.; McGown, A. T. *J. Org. Chem.* **2001**, *66*, 8135–8138.

[4] For recent reviews on olefin metathesis see: (a) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592–4633. (b) Samojlowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev.* **2009**, *109*, 3708–3742. (c) Hoveyda, A. H.; Malcolmson, S. J.; Meek, S. J.; Zhugralin, A. R. *Angew. Chem. Int. Ed.* **2010**, *49*, 34–44.

[5] Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 943–953.

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

metathesis (CM).[8] While significant progress has been made towards developing *Z*-selective metathesis processes, there are still several challenges and classes of olefins that remain unsolved.

One particular class of olefins that continues to be a challenge in olefin CM is *Z*-α,β- and α,β,γ,δ-unsaturated esters. These olefins are found in a large variety of biologically active molecules (see Scheme 1.1 for representative examples),[9] making methods that allow their generation in a stereoselective fashion important to further advance synthetic chemistry. While *Z*-selective RCM of these motifs has been very recently accomplished,[10] *Z*-selective cross-metathesis of these architectures remains a challenge. In the first chapter of this thesis, traditional methods for the preparation of both *Z*-α,β- as well as (*E,Z*)- and (*Z,E*)-α,β,γ,δ-unsaturated ester olefins will be presented, drawing examples from both total syntheses and method development reports. The first chapter will then conclude with the most advanced metathesis reactions of these motifs. The second chapter of this work will describe our contribution to this field by using catalytic olefin cross-metathesis to generate these molecules in high stereoselectivity.

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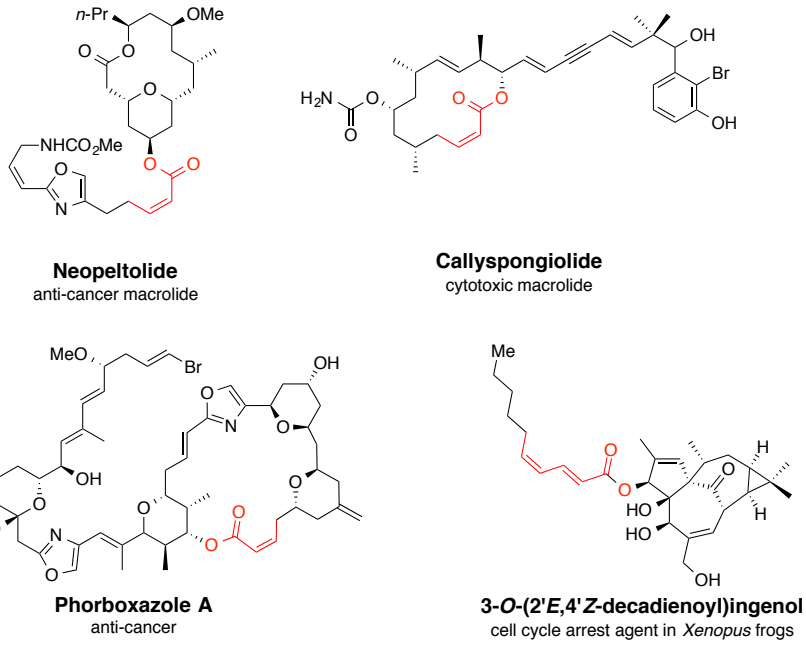
[7] Wang, C.; Yu, M.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Chem. Eur. J.* **2013**, *19*, 2726–2740.

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

[9] (a) Ghosh, A.K.; Shurrush, K. A.; Dawson, Z. L. *Org. Biomol. Chem.* **2013**, *11*, 7768–7777. (b) Pham, C.-D.; Hartmann, R.; Böhler, P.; Stork, B.; Wesselborg, S.; Lin, W.; Lai, D.; Proksch, P. *Org. Lett.* **2014**, *16*, 266–269. (c) Smith, A. B.; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942–10953. (d) Enders, D.; Prokopenko, O. F. *Liebigs Ann.* **1995**, 1185–1191. (e) Wang, L.-Y.; Wang, N.-L.; Yao X.-S.; Miyata, S.; Kitanaka, S. *J. Nat. Prod.* **2001**, *65*, 1246–1251.

[10] Zhang, H.; Yu, E. C.; Torker, S.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 16493–16496.

Scheme 1.1. *Z*-Unsaturated Esters in Biologically Active Natural Products



1.2 Traditional Preparation of *Z*-Acrylates

The majority of procedures to prepare *Z*-α,β-unsaturated ester olefins reported in the literature can be classified into two categories: (i) Those prepared via the Lindlar hydrogenation of an alkyne and (ii) Those prepared by the Still-Gennari modification of the Horner-Wadsworth-Emmons reaction.

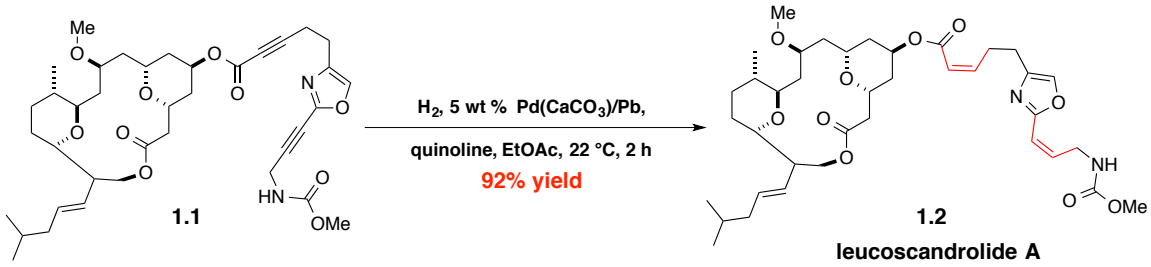
1.2.1 Preparation of *Z*-Acrylates via Lindlar Hydrogenation Alkynes

As mentioned above, one of the notable methods for the preparation of *Z*-α,β-unsaturated enoates is through the Lindlar hydrogenation of an alkyne. This method differs slightly from the more traditional palladium on carbon hydrogenation reaction in that this catalyst is palladium deposited on $CaCO_3$ with a lead poison (often lead acetate). Along with this lead poison, the reaction is also often run with an additive, such as

quinoline, to prevent complete reduction down to the alkane from the alkyne.[11] It is postulated that the *Z* selectivity is derived from the *syn* delivery of the two hydrogen atoms to the alkyne unit after splitting of the hydrogen molecule on the surface of the palladium catalyst.[12]

One example of a Lindlar reduction in a total synthesis to generate a *Z*-acrylate was done by the Paterson group in their synthesis towards (+)-leucoscandrolide A (Scheme 1.2).[13] After generating the di-alkyne intermediate **1.1**, they subjected this macrocycle to H_2 and Lindlar's catalyst to obtain the *Z*-acrylate in exceptional yield and, as expected, all one isomer to complete the synthesis of the natural product (**1.2**).

Scheme 1.2. Use of Lindlar Hydrogenation in the Paterson Synthesis of (+)-Leucoscandrolide A



Another prominent example of this reaction being used in a synthesis setting was done by the Wender group during their campaign towards (−)-laulimalide, a potent anti-cancer agent.[14] Upon using the Yamaguchi Macrolactonization protocol[15] to generate intermediate **1.3**, they subjected this macrocycle to H_2 and Lindlar's catalyst to obtain intermediate **1.4** in 91% yield as one isomer at the acrylate olefin (Scheme 1.3).

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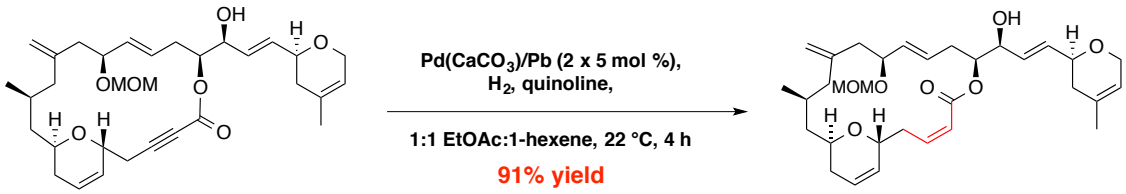
[11] Siau, W.-Y.; Zhang, Y.; Zhao, Y. *Top. Curr. Chem.* **2012**, *327*, 33–58.
[12] Mattson, B.; Foster, W.; Greimann, J.; Hoett, T.; Le, N.; Mirich, A.; Wankum, S.; Cabri, A.; Reichenbacher, C.; Schwanke, E. *J. Chem. Educ.* **2013**, *90*, 613–619.
[13] Paterson, I.; Tudge, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 343–347.
[14] Wender, P. A.; Hedge, S. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 4956–4957.
[15] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

Following deprotection of the alcohol and Sharpless asymmetric epoxidation, the target compound was obtained in 3.5% yield with the longest linear sequence being 36 steps. This same synthetic sequence was also used by Ghosh in his synthesis of (−)-laulimalide.[16] After failing to obtain the target molecule through another route (which will be touched upon in the next section), he was able to obtain a similar intermediate as Wender in 94% yield, which was then carried through to the final target.

Scheme 1.3. Use of Lindlar Hydrogenation in the Wender Synthesis of (−)-Laulimalide



1.3 **1.4**

While the Lindlar reduction appears to be a reliable method to obtain *Z*-acrylates in high stereoselectivity, there are certain problems associated with this method that must be addressed. The first problem associated with this reaction is the need to synthesize the alkyne moiety in the preceding intermediate to the *Z* olefin. Alkynes are not as readily available from commercial sources, requiring added steps in the overall synthesis to construct them and, in most cases, may need to be protected (due to their higher acidity/higher reactivity profile than alkenes), placing more time demands on the chemist. A second issue when using this method is the need to use toxic lead additives. As mentioned above, Lindlar's catalyst is poisoned with a lead additive to tune down its reactivity. Lead is known to be toxic and requires more careful handling in order to prevent significant exposure. A third, and yet more significant problem, with the Lindlar

[16] Ghosh, A. K.; Wang, Y.; Kim, J. T. *J. Org. Chem.* **2001**, *66*, 8973-8982.

reduction is that since the catalyst used in this reduction is a heterogenous catalyst, the quality of the catalyst may vary from batch to batch and may not give the same reproducibility from one batch to the next.[11] Furthermore, the amount of catalyst used needs to be exactly right to reduce the alkyne to the alkene. If too little catalyst is used, the alkyne will not be fully consumed. If too much of the catalyst is used, then over reduction to the alkane is a significant possibility. This could be very detrimental to the synthesis as the alkane is often very difficult to oxidize back to the alkene and would require significantly more steps to obtain the desired alkene.[11]

1.2.2 Preparation of *Z*-Acrylates Via the Still-Gennari Modification of the Horner-Wadsworth-Emmons Reaction

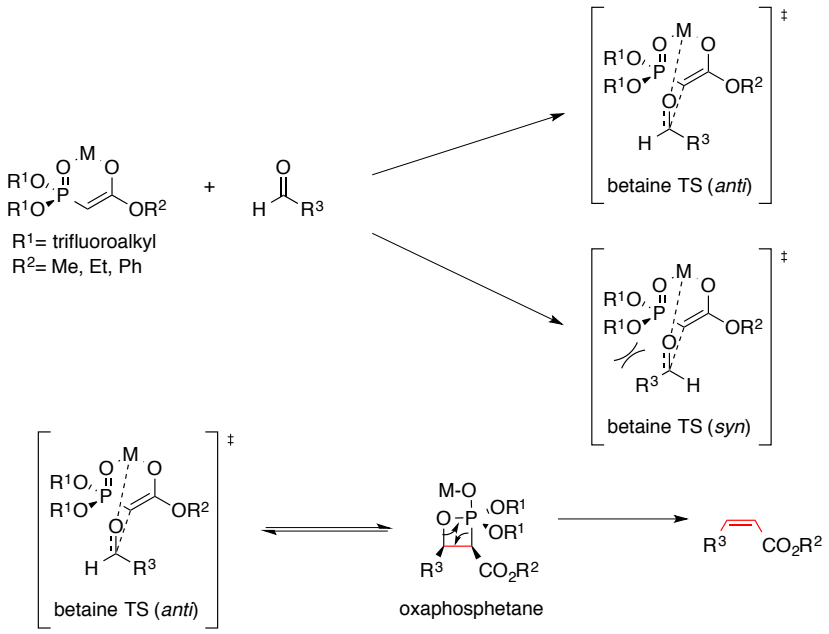
As mentioned above, the second strategy most commonly used to prepare *Z*-α,β-unsaturated esters is through a modified version of the Horner-Wadsworth-Emmons (HWE) Reaction. The HWE reaction was developed as an easier way to prepare α,β-unsaturated carbonyl olefins as an alternative to the widely used Wittig reaction.

The use of phosphonate esters in the HWE reaction allows for easier purification of the product than the Wittig reaction. The phosphonate side chain generated is soluble in water and can be removed through an aqueous workup, whereas the phosphine oxide of the Wittig reaction cannot. Also, the HWE reaction provides a much broader scope.[11] However, this reaction usually provides the *E* product as the major stereoisomer.

In 1983, Still and Gennari introduced a modified HWE reaction in which they synthesized bis(trifluoroethyl) phosphonate esters from a trialkylphosphonate ester and trifluoroethanol and allowed them to react with aldehydes in the presence of a strong base

to generate the corresponding *Z* olefin in high, to relatively high, *Z* selectivity.[17] It is believed that the *Z* selectivity observed in these reactions is due to the addition of the deprotonated trifluoroalkyl phosphonate ester to the aldehyde favoring the *anti* mode of addition due to steric clash incurred in the *syn* mode of addition (Scheme 1.4). The resulting oxaphosphetane collapses quickly to give the desired *Z* alkene and prevent equilibration at the addition step.[18]

Scheme 1.4. Proposed Mechanism of the Still-Gennari Modification of the HWE Reaction



The Still-Gennari modification of the HWE reaction has been applied in several total syntheses to make a *Z*-acrylate. One example of this strategy was shown by Forsyth and coworkers in their synthesis of phorboxazole A, an anticancer agent.[19] After subjecting intermediate **1.5** (Scheme 1.5) to potassium carbonate and 18-crown-6, they were able to affect the intramolecular Still-Gennari olefination to generate intermediate

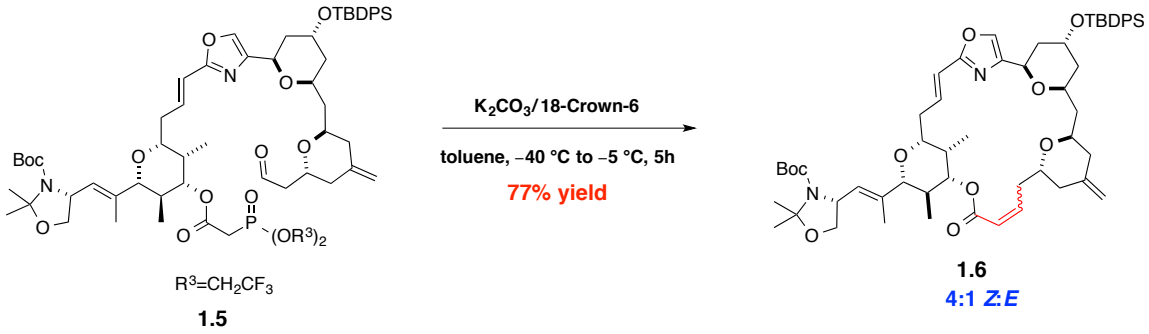
[17] Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.

[18] (a) Drawing recreated from: *Strategic Applications of Named Reactions in Organic Synthesis* (Kürti, L.; Czakó, B.), Elsevier Academic Press, Burlington, MA, **2005**. (b) For additional material concerning the mechanism of the Still-Gennari reaction see: Maryanoff, B. E., Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.

[19] Forsyth, C. J.; Ahmed, F.; Cink, R. D., Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597–5598.

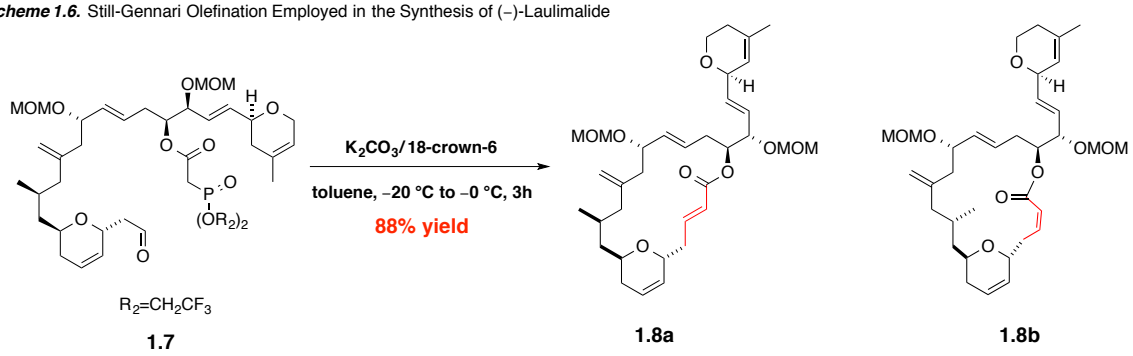
1.6 in a 4:1 *Z*:*E* ratio and 77% yield. When the R^3 group of intermediate **1.5** was just an ethyl group, they noted that the reaction gave roughly the same selectivity and yield. However, they observed that the reaction time was markedly faster using the trifluoroethyl phosphonate ester so the synthesis proceeded using the trifluoroethyl-substituted ester. After this step, the target molecule was then accessed through further functional group manipulation and an amide coupling in a longest linear sequence of 34 steps.

Scheme 1.5. Intramolecular Still-Gennari Reaction Performed in the Synthesis of Phorboxazole A



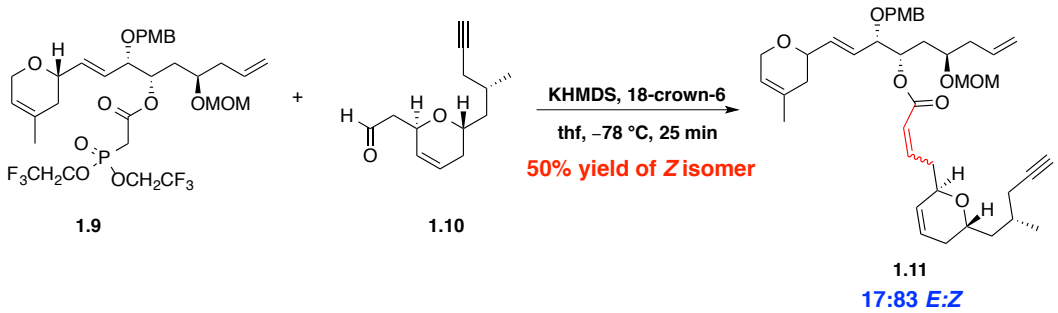
Another example of this reaction being used to prepare *Z*-acrylates comes from the synthesis of (–)-laulimalide by Ghosh and coworkers.[16] As mentioned above, the final strategy used to complete this synthesis was, in the end, a Lindlar reduction of an alkyne. Before they implemented this strategy, however, they attempted to make the acrylate moiety of the natural product through a Still-Gennari olefination. As shown in Scheme 1.6, the best result the Ghosh group was able to obtain from the Still-Gennari reaction was a 1:1.5 *cis*:*trans* ratio of intermediate **1.8**. They were able to separate the two isomers and attempted to isomerize the *trans* isomer. However, the lack of *Z* selectivity lead them to pursue the macrolactonization/Lindlar reduction strategy.

Scheme 1.6. Still-Gennari Olefination Employed in the Synthesis of (−)-Laulimalide



Following on from the Ghosh group's synthesis of (−)-laulimalide, the Trost group attempted a total synthesis towards that natural product. They implemented a different strategy than Ghosh by attempting to make the *Z*-acrylate moiety first and closing the macrocycle at a later point in the synthesis (as opposed to closing the macrocycle through the Still-Gennari reaction as Ghosh did). Unfortunately they ran into the same problem as the Ghosh group encountered in that the best result they could obtain gave the desired alkene, **1.11** in an 83:17 *Z*:*E* ratio (Scheme 1.7).[20] The isomers were separable from each other by column chromatography and so the synthesis was carried forward using the isolated *Z* isomer.

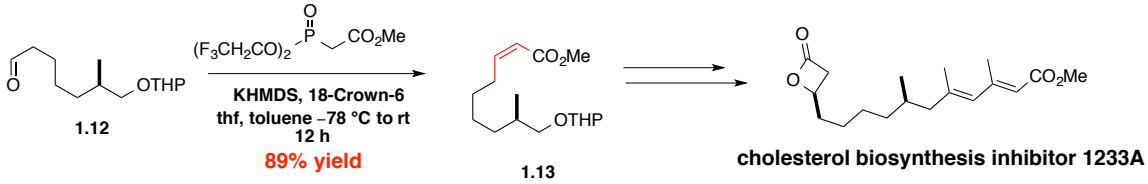
Scheme 1.7. Still-Gennari Olefination Employed in the Synthesis of (−)-Laulimalide by the Trost group



[20] Trost, B. M.; Amans, D.; Seganish, W. M.; Chung, C. K. *Chem. Eur. J.* **2012**, *18*, 2961-2971.

While all of the examples shown above have given less than desirable *Z*:*E* ratios in a synthesis setting, there are examples in the literature where the Still-Gennari olefination is a reliable reaction and gives high selectivity. For example the Ley group group found the reaction as an efficient way to give them the desired *Z*-acrylate in their synthesis of cholesterol biosynthesis inhibitor 1233A (Scheme 1.8).[21] Intermediate **1.13** was obtained in 89% yield after subjection of intermediate **1.12** to the standard Still-Gennari reaction conditions. **1.13** was then used to set the stereochemistry of the oxetane dione stereogenic center in the target molecule in a later step.

Scheme 1.8. Still-Gennari Olefination Employed in the Synthesis of Cholesterol Biosynthesis Inhibitor 1233A



As the above examples show, there are significant drawbacks to using the Still-Gennari olefination reaction for *Z*-acrylate synthesis. In a total synthesis setting it is highly desirable to have as stereoselective of a reaction as possible to prevent side products in future steps if separation of the two stereoisomers is not possible. While the Still-Gennari reaction does provide the desired *Z* isomer in relatively high selectivity in the cases shown above considering the molecular complexity involved, the reaction does not always provide one isomer exclusively and further purification may be needed to separate the stereoisomers. While in the above cases it was possible to separate the stereoisomers from each other, this will not always be the case.

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[21] Bates, R. W.; Fernández-Megía, E.; Ley, S. V.; Rück-Braun, K.; Tilbrook, D. M. G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1917-1925.

Another significant drawback to the Still-Gennari olefination is the reagents needed for the reaction. In order for the reaction to occur, the metal of the base needs to be sequestered. In almost all cases this means adding a chelating agent such as 18-crown-6. These reagents are toxic and precautions need to be taken before their use. Strong base is also required for the reaction, which mandates careful planning to avoid having base-sensitive functionality in the starting material.

Along with all of the above-mentioned challenges with this reaction, the reaction also requires preparation of the phosphonate ester starting material, which adds more steps towards the target molecule if the reaction is being done in a total synthesis setting. Synthetic chemists generally desire the shortest synthesis possible. While it is easily prepared from simple starting materials, it is expensive in terms of time for the synthetic chemist to perform this reaction.

One last drawback to this method has to do with the waste generated. From an atom economy standpoint, it is not advantageous to install such a large amount of mass onto a molecule such as the phosphonate ester only to lose it one step later. Chemists desire to build complexity into their molecules instead of building complexity then removing it later on.

The two methods described above are the overwhelmingly favored methods in the literature for making 1,2-di-substituted acrylates in a *cis* fashion. While the two methods are stereoselective and offer different disconnections, they both have significant drawbacks that warrant consideration before their use. They are, however, currently the most utilized methods for the synthesis of *Z*-α,β-unsaturated esters. Further research

efforts should be aimed at designing reactions that mitigate these limitations and deliver the *Z* olefin in high stereoselectivity while offering different disconnections.

1.3 Traditional Preparation of (*E,Z*)-and (*Z,E)*-Dienoates

Dienoates and their derivatives are found in several naturally occurring biologically active molecules.[22] As with the two strategies to construct *Z*-α,β-unsaturated esters (see part A), there are also two major strategies that the synthetic community has used to construct (*E*,*Z*)- and (*Z*,*E*)-α,β,γ,δ-unsaturated esters: the Still-Gennari reaction, and catalytic cross-coupling. While these reactions are the favorites, there are several other reactions that have been developed to generate these motifs that have not been examined to date in a synthesis setting.

1.3.1 Generation of (*Z,E*)-Dienoates Through Still-Gennari Olefination

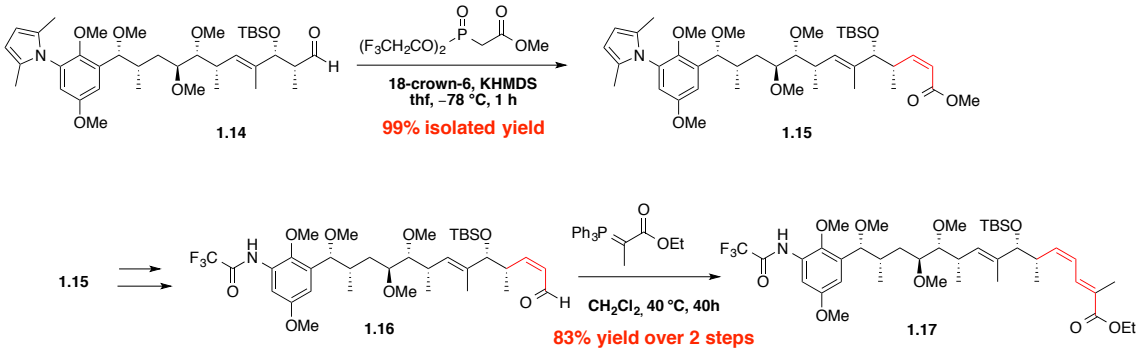
One of the first examples of preparing the (2*E*,4*Z*)-dienoate architecture by Still-Gennari olefination reported in the literature was in the campaign towards the antitumor agent, (+)-macbecin I by scientists at Merck Sharp and Dohme Research.[23] As shown in Scheme 1.9, the group at Merck first prepared the *Z*-acrylate in intermediate **1.15** through this reaction. Following this and several functional group manipulations to aldehyde **1.16**, the final (*E*,*Z*)-dienoate architecture of the natural product was furnished following a Wittig olefination to generate **1.17** in 83% yield over two steps. This same strategy

[22] For representative examples of dienoates and dienoate derivatives in naturally occurring biologically active molecules, see: Wang, G.; Mohan, S.; Negishi, E. *Proc. Nat. Acad. Sci. U.S.A* **2011**, *108*, 11344–11349 and Woerly, E. M.; Struble, J. R.; Palyam, N.; O'Hara, S. P.; Burke, M. D. *Tetrahedron* **2011**, *67*, 4333–4343.

[23] Baker, R.; Castro, J. L. *J. Chem. Soc. Perkin Trans. I* **1990**, 47–65. See also *J. Chem. Soc., Chem. Comm.* **1989**, 378–381.

towards the dienoate motif in (+)-macbecin was used by the Panek group. In their synthesis, the *Z*-acrylate was furnished by a Still-Gennari olefination with a final ratio of 15:1 *Z*:*E*. The *E* olefin of the dienoate was then prepared via Wittig olefination.[24]

Scheme 1.9. Preparation of (2*E*,4*Z*)-Dienoate Via Sequential Still-Gennari/Wittig Olefination Reactions Towards (+)-Macbecin I

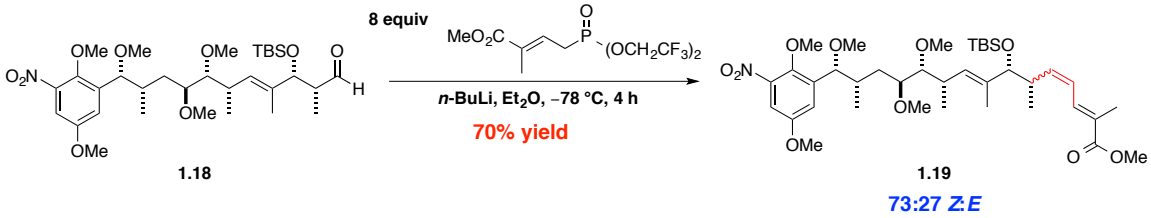


Following the Merck synthesis of (+)-macbecin, the Evans group had identified this synthesis as one that could be improved upon with the latest developments in the field.[25] In particular, they were interested in synthesizing the dienoate moiety in one step as opposed to the two shown in the Merck synthesis above. They rationalized that by using the sterically demanding, activated phosphonate ester that they could achieve kinetic selectivity and therefore generate the (*E*,*Z*)-dienoate in high stereoselectivity in one step. The best result from their model studies showed that they would only be able to achieve a 60% *Z* selectivity, nothing near what was desired. However, when they switched to the natural product system (Scheme 1.10) and increased the equivalents of the phosphonate ester (to 8 equivalents), they achieved a surprising selectivity of 73:27 (*E*,*Z*):(*E*,*E*) obtained in 70% yield. With lower equivalents of the phosphonate ester they

[24] Panek, J. S.; Xu, F. *J. Am. Chem. Soc.* **1995**, *117*, 10587–10588.
[25] Evans, D. A.; Miller, S. J.; Ennis, M. D. *J. Org. Chem.* **1993**, *58*, 471–485.

were only able to achieve selectivity values near to what they observed from their model studies.

Scheme 1.10. Still-Gennari Olefination in the Evans Synthesis of (+)-Macbecin



Inspired by the work done by the Evans Group on (+)-macbecin, the Roush group decided to re-examine their previously published synthesis of (+)-damavirucin.[26] The original route used to make that target involved a similar strategy described above by the Merck group en route to (+)-macbecin, involving making the *Z* olefin of the dienoate through a Still-Gennari olefination followed by an HWE olefination to make the *E* olefin. They attempted to improve the synthesis by cutting down the steps to the dienoate moiety as well as improving the *Z* selectivity, if possible. As shown in Scheme 1.11, as opposed to making the dienoate through sequential Still-Gennari followed by HWE olefination, they synthesized intermediate **1.22** as a 60% yield of a 4:1 mixture of the (*E*,*Z*):(*E*,*E*) isomers, which upon isolation of the *Z* isomer by preparative HPLC gave a final yield of 47% for the *Z* isomer. In total, the route to the dienoate using the new sequence was 5 steps and provided **1.22** in 30% overall yield. This new route negated the need to have three additional functional group manipulations and allowed the bypass of the non-trivial DIBAL reduction shown in the original route to **1.22** in Scheme 1.11.[27]

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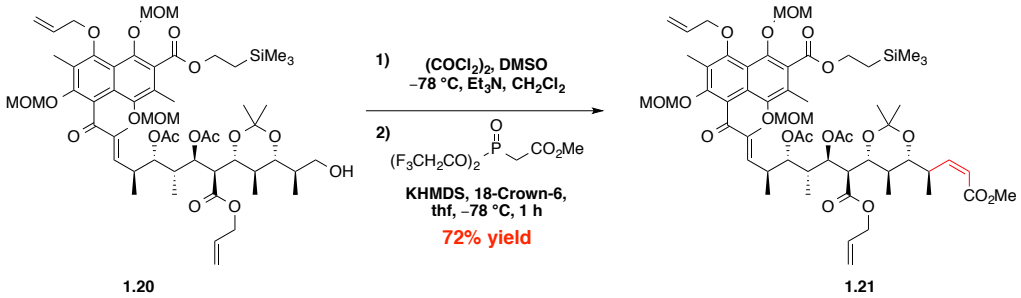
[26] Roush, W. R.; Coffey, D. S.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 11331–11332.

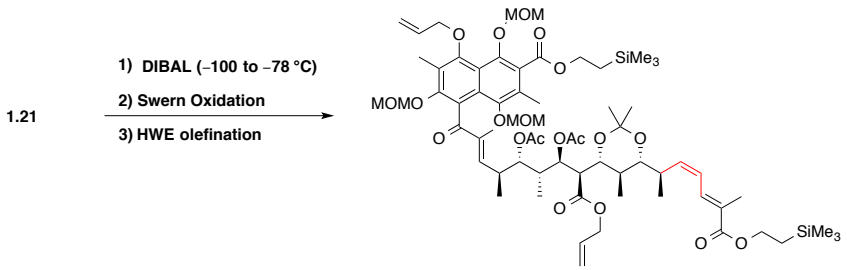
[27] Chemler, S. R.; Coffey, D. S.; Roush, W. R. *Tetrahedron Lett.* **1999**, *40*, 1269–1272.

Scheme 1.11. Comparison Between Old Route and Improved Route to Install the Dienoate Motif of (+)-Damavaricin D

Original route to dienoate motif (1997):

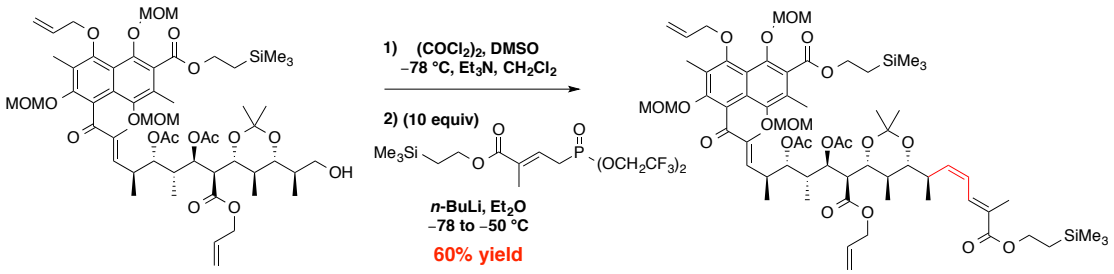


1.20 **1.21**



8 steps overall to 1.22.
24% overall yield

Improved route to dienoate motif (1999):



1.20 **1.22**

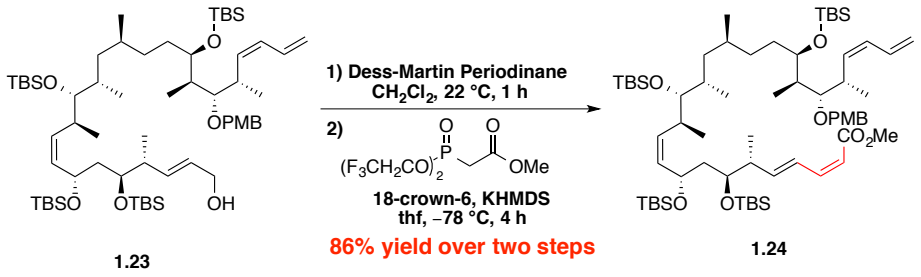
4:1 (*E*,*Z*):(*E*,*E*)
5 step sequence, 30% overall yield

While the previous examples used the Still-Gennari reaction to generate the olefin at the 4 position of the dienoate scaffold stereoselectively, there have been reports in the literature of using the same strategy to make the *Z* olefin at the 2 position. One such example comes from Curran's synthesis of (−)-dictyostatin, a known anticancer agent, to make the (2*Z*,4*E*)-dienoate.[28] As shown in Scheme 1.12, following Dess-Martin periodinane oxidation of the alcohol in intermediate **1.23** to the aldehyde and subjecting

[28] Shin, Y.; Fournier, J.-H.; Fukui, Y.; Brückner, A. M.; Curran, D. P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4634–4637.

that intermediate to the deprotonated phosphonate ester under Still-Gennari conditions, Curran was able to isolate intermediate **1.24** with the (2*Z*,4*E*)-dienoate scaffold in 86% yield over the two steps. Further deprotection and cyclization would afford the target compound in 1% yield with a longest linear sequence of 34 steps.

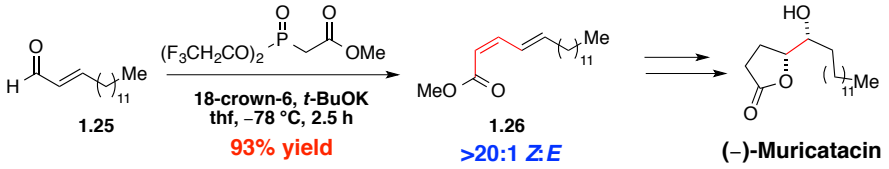
Scheme 1.12. Still-Gennari Olefination Generating the Internal *Z* Olefin of the Dienoate Scaffold of (+)-Dictyostatin



Working on a less complex natural product, O'Doherty and coworkers were able to synthesize the (2*Z*,4*E*)-dienoate **1.26** from aldehyde **1.25** in high yield and exceptionally high stereoselectivity (Scheme 1.13).[29] Two additional steps provided the natural product (–)-muricatacin, a potent cytotoxic compound in 66% yield and a synthesis of six steps. While the olefins are not preserved in the final product, the geometry of the olefin is essential to set the stereochemistry of the dihydroxylation in the next step. The O'Doherty group also carried out studies using the Still-Gennari olefination to synthesize a variety of (2*Z*,4*E*)-dienoates with very similar substrates as those in Scheme 1.13 and they were able to report a variety of these motifs in high stereoselectivity on their way to the synthesis of analogues for the antimicrobial natural product protoanemonin.[30]

[29] Ahmed, M. M.; Cui, H. O'Doherty, G. A. *J. Org. Chem.* **2006**, *71*, 6686–6689.
[30] Ahmed, M. M.; Akhmedov, N. G.; Cui, H.; Friedrich, D.; O'Doherty, G. A. *Heterocycles* **2006**, *70*, 223–233.

Scheme 1.13. Synthesis of the Dienoate Motif in (–)-Muricatacin



1.3.2 Preparation of (*E*,*Z*)-Dienoates via Cross-Coupling Reactions

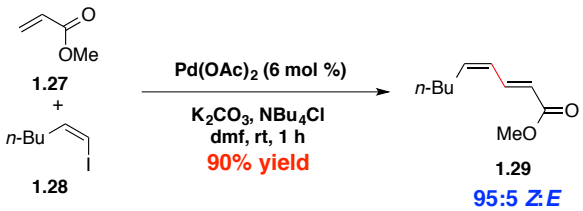
Another powerful approach to the synthesis of conjugated dienoates is metal-catalyzed cross-coupling. Suzuki, Negishi, and Heck coupling reactions have been used to prepare dienoates in a stereoselective fashion. Cross-coupling conquered the coupling of dienes from some of the very first disclosures of these reactions. As early as 1975, Heck reported one of the first disclosures of *Z*-dienoate synthesis using traditional Heck coupling conditions by synthesizing dimethyl (*E*,*Z*)-2,4-nonadienoate with several different Z-alkenes and methyl acrylate.[31] The following year, Negishi reported the cross-coupling of alkenes to make a variety of dienes.[32] However, while only one dienoate example was shown in this disclosure, it was a (2*E*,4*E*)-dienoate.

Following on from these reports, a stereoselective cross-coupling reaction for the synthesis of conjugated dienes was published by Tûyet in 1985 when he disclosed the Heck coupling of several vinylic carbonyls with alkenyl halides using what he termed "Solid-Liquid Phase Transfer Conditions."[33] The single dienoate example from the molecules reported in this paper is shown in Scheme 1.14. Using vinylic ester **1.27** in slight excess, he subjected both this olefin and the *Z*-alkenyl halide (**1.28**) to 6 mol % of $Pd(OAc)_2$ with potassium carbonate and tetrabutylammonium chloride in dmf and

[31] Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083–1090.
[32] Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729–6731.
[33] Tûyet, J. *Tetrahedron Lett.* **1985**, *26*, 2667–2670.

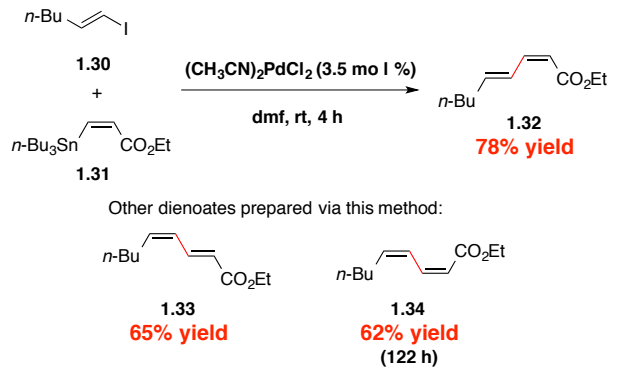
allowed the reaction to proceed for 1 h under N_2 (as opposed to 12.5 h needed by Heck to make the same product). From this reaction he was able to obtain the product in 90% isolated yield with a *Z*:*E* ratio of 95:5. Recently, Mori used this method to prepare similar dienoates.[34]

Scheme 1.14. Cross-Coupling of a *Z*-Alkenyl Halide and a Vinylic Carbonyl by Tûyet



After Tûyet's report, Stille and coworkers reported the cross-coupling of alkenyl halides with alkenyl tin reagents under the influence of a palladium catalyst in 1987.[35] The three (*E*,*Z*)-dienoates synthesized in the paper along with the general conditions required to achieve reaction are shown in Scheme 1.15. Using the *E*-alkenyl iodide **1.30** they were able to cross-couple the *Z*-alkenyl tin reagent **1.31** to generate the (2*Z*,4*E*)-ethyl dienoate in high yield and with complete selectivity. Using the corresponding *Z*-alkenyl iodide and coupling this with alkenyl tin reagents such as **1.31** or its corresponding *E* isomer provided products **1.34** and **1.33**, respectively, with complete stereoretention and moderate yield.

Scheme 1.15. Stereoselective Cross-Coupling to Generate Dienoates by Stille

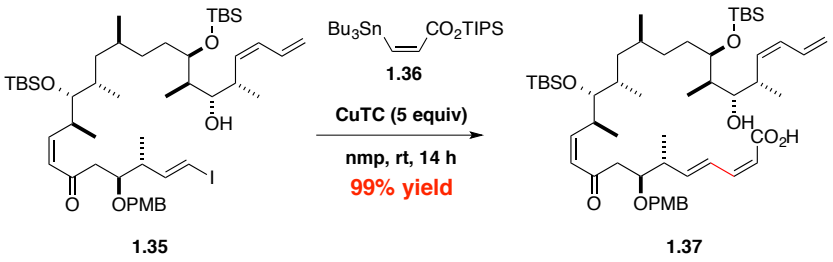


[34] Mori, K. *Tetrahedron* **2012**, *68*, 1936–1946.

[35] Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813–817.

In 2010, Paterson and coworkers reported using a similar strategy on their way to the molecule (–)-dictyostatin.[36] As shown in Scheme 1.16, after preparing alkenyl iodide intermediate **1.35** and subjecting that to alkenyl stannane **1.36** and excess of CuTC, they were able to obtain the desired dienoic acid **1.37** in 99% isolated yield. They go on to say that this product was contaminated with tin residues but was used with these residues regardless without any adverse effects seen. While not a catalytic transformation, this example serves to illustrate that this strategy can be applied in a synthesis setting for the synthesis of dienoates and dienoic acids in a stereoselective fashion.

Scheme 1.16. Use of Stille Coupling to Generate Diene Framework in Paterson's (–)-Dictyostatin Synthesis

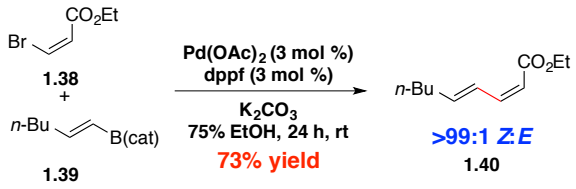


Suzuki and coworkers also reported their own reaction towards the synthesis of 2,4-dienoic esters in a stereoselective fashion in 1985[37] and later on in 1989.[38] Using both *E*- and *Z*-alkenyl bromides, they were able to couple these to alkenyl boronates using a standard palladium catalyst and phosphine ligand to generate a variety of (2,4)-dienoic ester products in high yields and high stereoselectivity, one of which (**1.40**) is shown in Scheme 1.17. All of the dienoates reported are substituted with aliphatic chains at the 4-position. No other functionalized molecules are reported. Suzuki notes that significant optimization needed to occur before high stereoselectivities were achieved. In some cases

[36] Paterson, I.; Britton, R.; Delgado, O.; Gardner, N. M.; Meyer, A.; Naylor, G. J.; Poullennec, K. G. *Tetrahedron* **2010**, *66*, 6534–6545.
[37] Suzuki, A. *Pure Appl. Chem.* **1985**, *57*, 1749.
[38] Yanagi, T.; Miyaura, O. N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3892–3895.

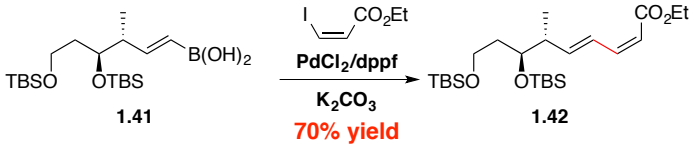
they saw stereoscrambling when starting with a *Z*-alkenyl bromide and using conditions other than those reported to effect the coupling.

Scheme 1.17. Stereoselective Cross-Coupling to Generate Dienoates by Suzuki



The strategy of constructing dienoates via Suzuki coupling has been used in a different route towards the anticancer agent (−)-dictyostatin. In 2007, Ramachandran and coworkers used a very similar method to that reported by Suzuki in 1989 to construct the *Z* olefin of the dienoate in that molecule.[39] As shown in Scheme 1.18, after obtaining intermediate **1.41** through hydroboration of the corresponding alkyne, they then subjected the resulting boronic acid to the palladium catalyst and the *Z*-alkenyl iodide shown to obtain the desired product, **1.42**, in 70% yield and as one isomer.

Scheme 1.18. Suzuki Coupling Strategy Employed in the Synthesis of (−)-Dictyostatin

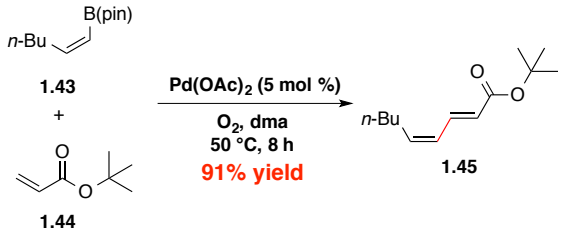


In 2006, Jung and coworkers also reported a stereoselective synthesis of nona-(2*E*,4*Z*)-*tert*-butyl dienoate using a similar strategy as Suzuki. However, they were able to affect the cross-coupling with the alkenyl boronate **1.43** and the unsubstituted *tert*-butyl acrylate **1.44**, instead, to obtain the product (**1.45**) in exceptional yield and

[39] Ramachandran, P. V.; Srivastava, A.; Hazra, D. *Org. Lett.* **2007**, *9*, 157–160.

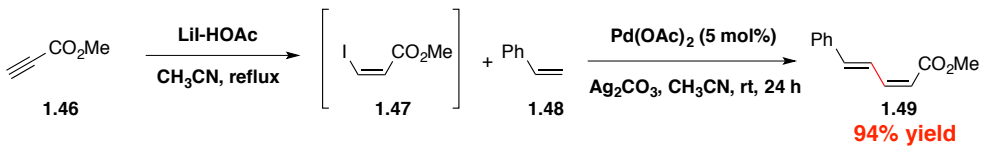
stereoselectivity (Scheme 1.19).[40] This is the only example of an (*E*,*Z*)-dienoate in this disclosure.

Scheme 1.19. Oxidative Palladium Catalysis to Generate Dienoates

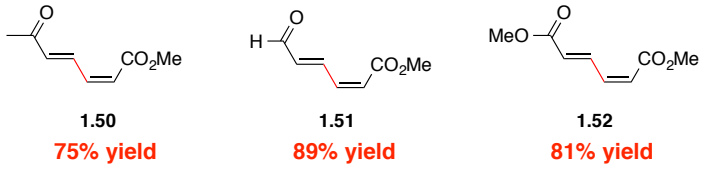


Along with the traditional cross-coupling approaches described above, there have been a handful of disclosures describing sequential, one-pot preparations to afford dienoates in a stereoselective fashion. In 1992 Lu and coworkers reported a one-pot alkyne halogenation/Heck reaction to generate (2*Z*,4*E*)-dienoic acid derivatives.[41] As shown in Scheme 1.20, a variety of dicarbonyl molecules were made and isolated in high yield and with complete stereoselectivity using this procedure.

Scheme 1.20. Sequential Halogenation/Heck Reaction



Other dienoates prepared:

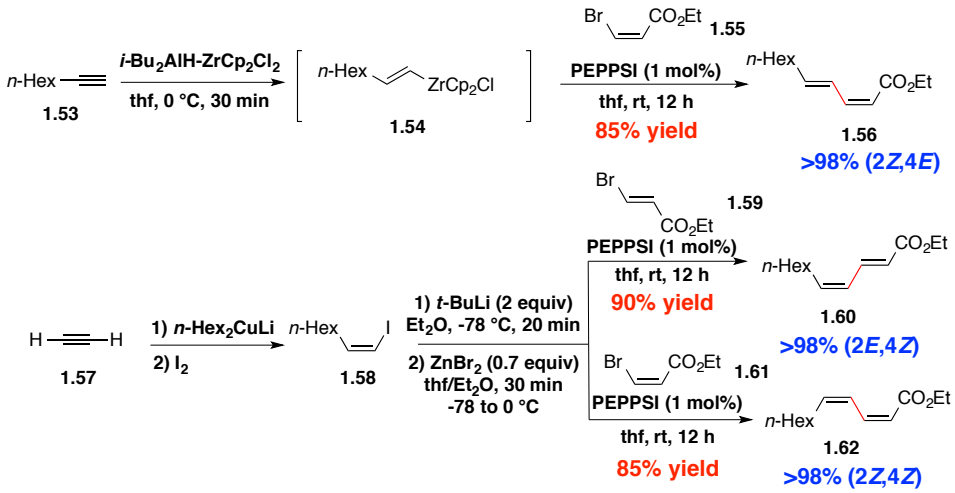


One of the more recent developments in transition-metal catalyzed reactions to stereodefined dienoates came in 2011 from Negishi and coworkers.[42] In this disclosure

[40] Yoo, K. S.; Yoon, C. H.; Jung, K. W. *J. Am. Chem. Soc.* **2006**, *128*, 16384–16393.
[41] Lu, X.; Huang, X.; Ma, S. *Tetrahedron Lett.* **1992**, *33*, 2535–2538.
[42] Wang, G.; Mohan, S.; Negishi, E. *Proc. Nat. Acad. Sci. U.S.A* **2011**, *108*, 11344–11349.

they were able to prepare all four stereoisomers of ethyl undeca-(2,4)-dienoate via alkyne elementometalation followed by cross-coupling using a palladium catalyst. Using a strategy very similar to that reported by Lu above, after performing hydrozirconation on *n*-hexyl acetylene and subjecting that to standard Negishi cross-coupling conditions (Scheme 1.21), undeca-(2*Z*,4*E*)-dienoate **1.56** was isolated in exceptional yield and stereoselectivity (85% yield, >98% 2*Z*,4*E*). To prepare the other stereoisomers of the same dienoate, they first allowed acetylene to undergo carbocupration followed by iodination to generate the *Z*-alkenyl iodide. They then subjected this alkenyl iodide to two different cross-coupling partners, the *E*-alkenyl bromide (**1.59**) and the *Z*-alkenyl bromide (**1.61**) along with Negishi cross-coupling conditions to obtain their respective products, undeca-(2*E*,4*Z*)-dienoate **1.60** and undeca-(2*Z*,4*Z*)-dienoate **1.62** both in high yield and exceptional stereoselectivity.

Scheme 1.21. Dienoate Synthesis Via Alkyne Elementometalation/Pd Cross-Coupling



Before accepting the palladium-catalyzed cross-coupling reactions as the gold standard for preparing *Z*-dienoates, there are several drawbacks to these reactions that must be mentioned. The first is cost. Palladium is an expensive metal and it may not be

feasible to perform such reactions on a large scale due to cost. Another significant problem with these reactions concerns the limited scope for these types of reactions in the literature. Almost every example discussed applies only a straight-chain aliphatic coupling partner. When working on a more complex molecule than the examples shown above, this is not the greatest precedent to go by when deciding how to make the *Z*-dienoate scaffold. These reactions also need to have the geometry of the olefin coupling partner set before the cross-coupling event and even then it is possible that isomerization may occur during the coupling. In order to prepare the olefin containing the *Z* geometry, it will require more steps and time for the chemist to prepare the substrate (such as the last example from Negishi shown above). Lastly, these reactions have modest functional group tolerance. If chelating moieties exist in the substrate, this may affect catalyst activity. While these reactions may appear to be reliable options, caution must be considered before attempting to use them. They do offer an alternative disconnection to the strategies discussed above, however.

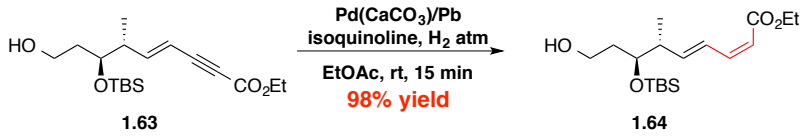
1.3.3 Alternative Strategies to Preparing *Z*-Dienoates

While Still-Gennari olefination and palladium-catalyzed cross-coupling reactions are the two biggest methods by which *Z*-dienoates are prepared, there are several other reports in the literature of strategies to prepare these motifs that must be considered. Although they are rarely used in a synthesis setting, they are still viable options to consider if the alternatives fail. The remainder of this section for this chapter will examine these reported, but not often considered, alternatives.

1.3.3a Lindlar Reduction

Although a popular choice when making *Z*-acrylates, the Lindlar reduction is not used as frequently to generate *Z*-dienoates as the strategies mentioned above. However, there are still several examples in the literature that should be addressed. In their synthesis towards (−)-dictyostatin, Yadav and coworkers reported a Lindlar reduction on intermediate **1.63** (Scheme 1.22), which had been prepared through cross-coupling of the alkyne to the corresponding alkenyl iodide.[43] Following reaction for 15 minutes and purification, the (2*Z*,4*E*)-dienoate **1.64** was obtained in 98% yield. This fragment was then combined with a larger fragment through macrolactonization to afford the target molecule.

Scheme 1.22. Lindlar Reduction Reported in the Synthesis of (−)-Dictyostatin

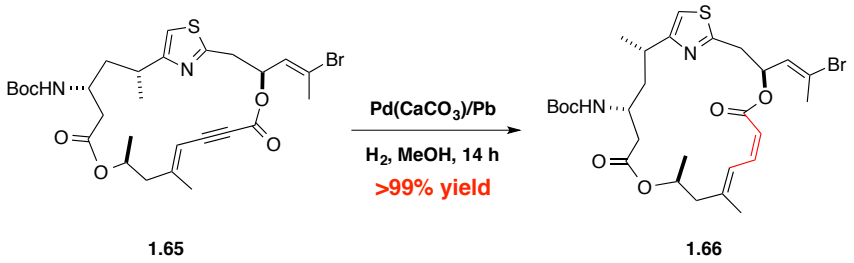


Another example of preparing a *Z*-dienoate in a synthesis setting via a Lindlar reduction comes from the synthesis of the immunosuppressant (−)-pateamine A by Liu and coworkers.[44] After preparing enyne **1.65** (Scheme 1.23), they subjected the macrocycle to Lindlar reduction conditions and were able to obtain **1.66** in >99% yield after 14 hours of reaction. This intermediate was then carried through to the completion of the synthesis.

[43] Yadav, J. S.; Rajender, V. *Eur. J. Org. Chem.* **2010**, 2148–2156.

[44] Romo, D.; Rzasa, R.; Shea, H. A.; Park, K.; Langenhan, J. M.; Sun, L.; Akhiezer, A.; Liu, J. O. *J. Am. Chem. Soc.* **1998**, *120*, 12237–12254.

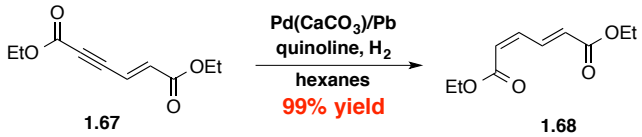
Scheme 1.23. Lindlar Reduction Reported in the Synthesis of (–)-Pateamine A



1.65 **1.66**

In a short report from 2005, Ramachandran and coworkers reported the synthesis of an (*E*,*Z)*-diene dioate through Lindlar reduction on the way to an (*E*,*Z*)-muconic acid diester.[45] After obtaining the enyne dioate **1.67** (Scheme 1.24) and subjecting it to Lindlar reduction conditions, they were able to obtain the diene dioate **1.68** in quantitative yield. This was the only dienoate they generated from the Lindlar reduction in this report.

Scheme 1.24. Lindlar Reduction by Ramachandran



1.67 **1.68**

One final example comes from a report in 2008 from Micalizio and coworkers from their synthesis of the antitumor agent (+)-macbecin I.[46] After performing the Lindlar reduction on alkyne **1.69**, they were able to obtain the desired product **1.70** in 93% yield. It was then taken forward to complete the synthesis. Working on a natural product in the same class as (+)-macbecin, Panek and coworkers used the same strategy to obtain a *Z*-dienoate. However, the Lindlar reduction they performed was on an enyne-acid on their way to the anticancer agent geldanamycin.[47]

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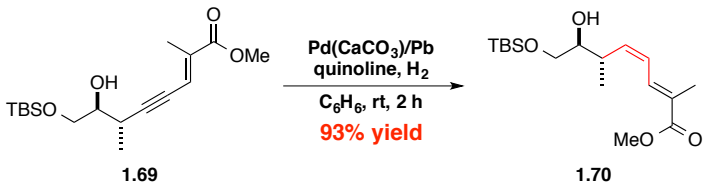
[45] Ramachandran, P. V.; Rudd, M. T.; Reddy, M. V. R. *Tetrahedron Lett.* **2005**, *46*, 2547–2549.

[46] Belardi, J. K.; Micalizio, G. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 4005–4008.

[47] Qin, H.-L.; Panek, J. S. *Org. Lett.* **2008**, *10*, 2477–2479.

Scheme 1.25. Lindlar Reduction Reported by Micalizio in the Synthesis of (+)-Macbecin



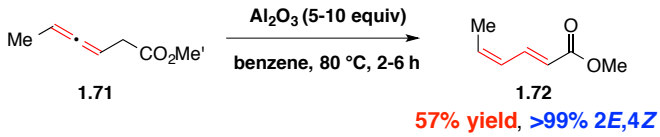
1.69 **1.70**

1.3.3b Synthesis of Dienoates From Allenes

Another alternative to the above mentioned procedures to stereoselective dienoate preparation came from the Takeda group in 1982 in which they were able to prepare several (2*E*,4*Z*)-dienoates in high stereoselectivity and high yield after subjecting a variety of allenes they had prepared to several equivalents of aluminum oxide (Scheme 1.26).[48] This method has not seen widespread use in the literature for two important reasons. The first being that this reaction requires the preparation of allenes, which are not commercially available and require even more steps to prepare than the alkyne methodologies mentioned previously. The second reason this method has not seen widespread use is due to the limited scope they show in the paper. The only substrates shown in this report are aliphatic allenes. No functionality was added to the allenes to broaden the scope of the reaction, perhaps due to the limited synthetic technology at the time.

[48] Tsuboi, S.; Masuda, T.; Makino, H.; Takeda, A. *Tetrahedron Lett.* **1982**, *23*, 209-212.

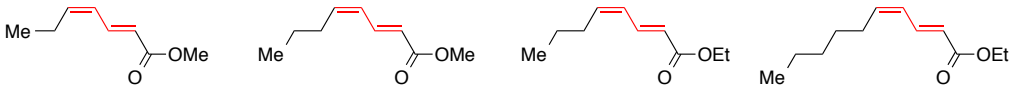
Scheme 1.26. Synthesis of Dienoates From Aliphatic Allenes



1.71 **1.72**

57% yield, >99% 2*E*,4*Z*

Other dienoates prepared in this report:



1.73 **1.74** **1.75** **1.76**

82% yield, 96% 2*E*,4*Z* **80% yield, 96% 2*E*,4*Z*** **69% yield, 93% 2*E*,4*Z*** **82% yield, >99% 2*E*,4*Z***

1.3.3c Cuprate Additions to Alkynes

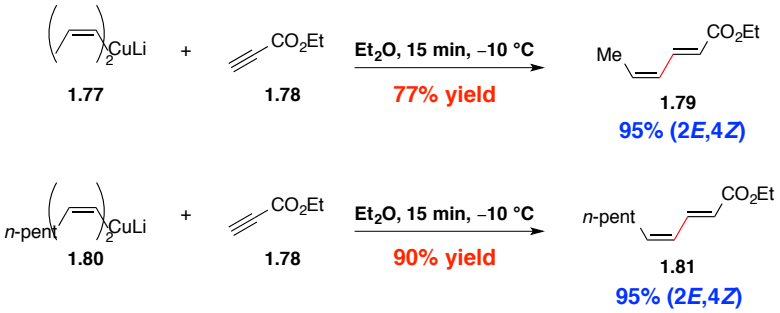
One last method that was developed in the early 1970s deals with the stereoselective synthesis of (*E,Z*)-dienoates through vinyl cuprate additions to α,β-unsaturated carbonyls, specifically alkynes. This method of dienoate synthesis was first reported by Degen and coworkers in 1971.[49] Using a method disclosed by Whitesides[50] to generate *Z*-alkenyl cuprates **1.77** and **1.80** (Scheme 1.27), they then subjected these alkenyl cuprates to ethyl propiolate (**1.78**) to generate dienoates **1.79** and **1.81** in high yield and high stereoselectivity. In all cases, even those that did not involve generating a dienoate, they saw 95% or greater retention of stereochemistry in the final product.

Normant and coworkers studied the synthesis of similar dienoates using the method developed by Degen in 1981.[51] However, as with the products obtained by Degen, these products were exclusively aliphatic dienoates. With a limited scope explored for this type of reaction, it has not been used to a great extent in a synthesis

[49] Näf, F.; Degen, P. *Helv. Chim. Acta* **1971**, *54*, 1939–1949.
[50] Whitesides, G. M.; San Filippo Jr., J.; Casey, C. P.; Panek, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 5302–5303.
[51] Alexakis, A.; Cahiez, G.; Normant, J. F. *Tetrahedron* **1981**, *36*, 1961–1969.

setting, as more developed and explored techniques of preparing dienoate architectures are available.

Scheme 1.27. Vinyl Cuprate Addition to α,β-Unsaturated Esters



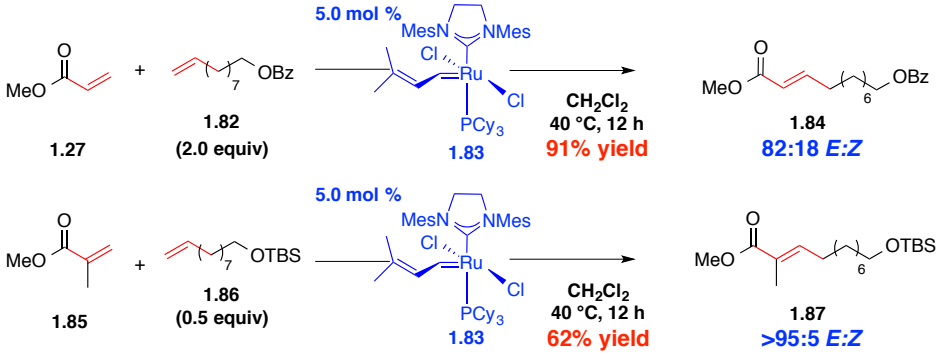
1.4 Traditional Preparation of Acrylates and Dienoates by Olefin Cross-Metathesis

There have been several disclosures in the literature regarding generating α,β- as well as α,β,γ,δ-unsaturated ester compounds via olefin cross-metathesis (coupling two olefins from separate molecules into one) using well-defined catalysts. These catalysts, such as the Schrock bis-alkoxide molybdenum complex,[52] Grubbs' second-generation ruthenium complex,[53] and the Hoveyda-Grubbs phosphine-free complex,[54] generally give the thermodynamic ratio of *Z* and *E* isomers (in some cases even high *E* selectivity), in the final product mixture from the cross-metathesis event. One of the earliest examples of cross-metathesis to generate *Z*-acrylates was reported by Grubbs and coworkers in 2000.[55] Using methyl acrylate **1.27** and subjecting it to 2.0 equivalents of the benzylated alcohol **1.82** and a modified version of the Grubbs second generation complex **1.83**, they were able to obtain the cross product **1.84** in high yield but selectivity proved to be an

[52] Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886.
[53] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956.
[54] Garber, S. B.; Kingsbury. J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
[55] Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784.

issue, giving a thermodynamic ratio of the *E*- and *Z*-acrylate olefin (Scheme 1.28). Among a variety of other unsaturated carbonyl cross products they showed, they also obtained **1.87** in decent yield and in high selectivity in favor of the *E* cross product. All of the products they obtained from the reaction are almost all exclusively *E*-selective; highlighting how the *E* isomer is energetically preferred.

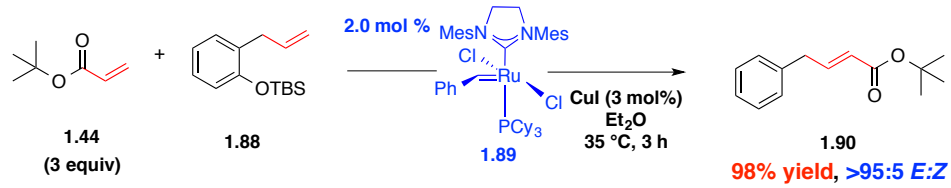
Scheme 1.28. Ru-Catalyzed Cross-Metathesis of α,β-Unsaturated Esters



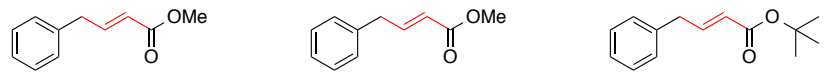
Another example of unsaturated ester cross-metathesis comes from the Lipshutz group in 2011.[56] In this report they perform a cross-metathesis with acrylate **1.44** and the corresponding methyl acrylate with a variety of aryl olefins under the influence of the Grubbs second-generation ruthenium complex **1.89** and, as shown in Scheme 1.29, they obtained every cross product in very high *E* selectivity. Every product they disclose is less than 5% of the corresponding *Z* isomer.

[56] Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. *J. Org. Chem.* **2011**, *76*, 4697–4702.

Scheme 1.29. Ru-Catalyzed Acrylate Cross-Metathesis



Other dienoates prepared in this report:



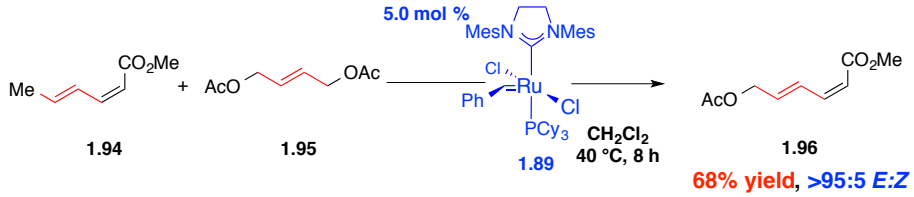
1.91 93% yield, >98:2 *E:Z*

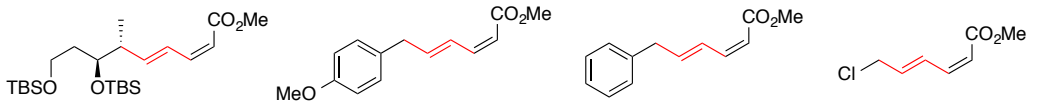
1.92 94% yield, >98:2 *E:Z*

1.93 84% yield, >95:5 *E:Z*

There are fewer reports of dienoate cross-metathesis in the literature. However, one notable paper from the Curran group detailed a cross-metathesis protocol to generate (2*Z*,4*E*)-dienoates.[57] As shown in Scheme 1.30, they were able to prepare a large variety of these products in moderate yields with high *E* selectivity using the Grubbs second-generation ruthenium catalyst **1.89**. They were looking to functionalize the *E* olefin of the dienoate by crossing a large variety of 1,2-disubstituted *E* olefins with dienoate **1.94**. This gave them high *E* selectivity due to the original *E* geometry of the cross partner as well as the general preference from the catalyst towards the *E* isomer.

Scheme 1.30. Ru-Catalyzed Cross-Metathesis of Dienoates





1.97 58% yield, >95:5 *E:Z*

1.98 69% yield, >95:5 *E:Z*

1.99 76% yield, 91:9 *E:Z*

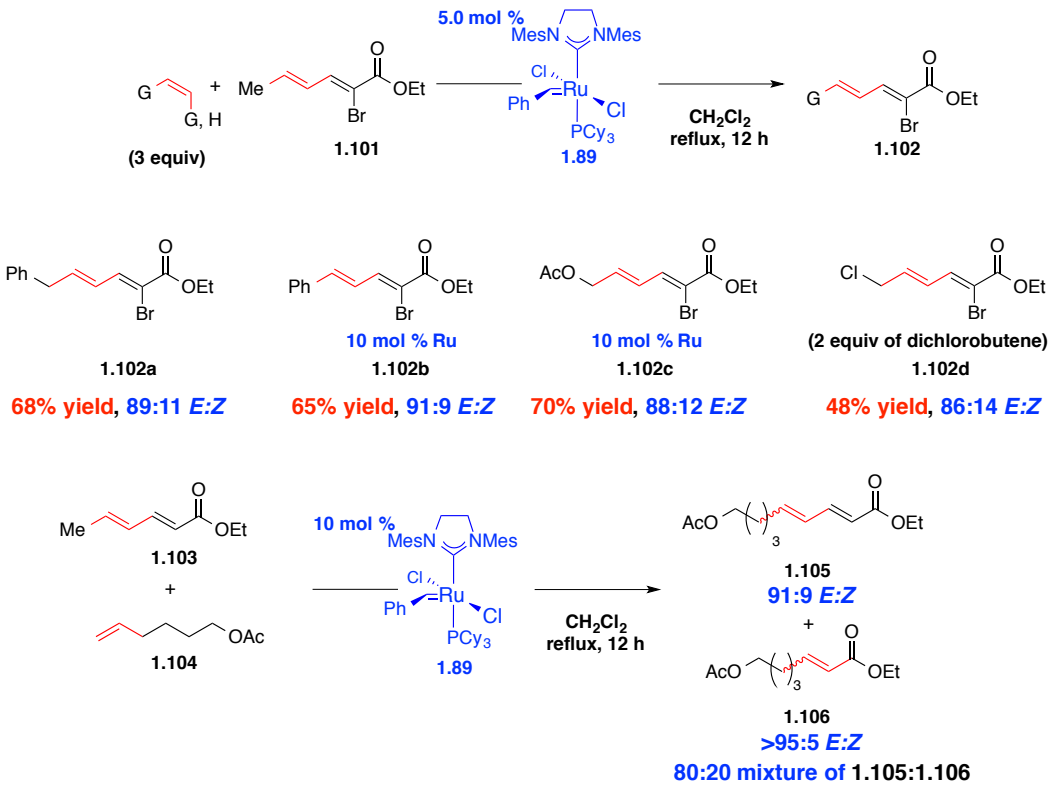
1.100 63% yield, >95:5 *E:Z*

[57] Moura-Letts, G.; Curran, D. P. *Org. Lett.* **2007**, *9*, 5–8.

Another known disclosure of cross-metathesis to generate dienoates was published by the Grubbs group in 2005 with their second-generation ruthenium complex **1.89**.[58] Using this protocol they were able to synthesize a variety of (*E*,*E*)-dienoates in moderate yield and varying selectivities (Scheme 1.31). In some cases, the catalyst loading had to be raised to 10 mol % to achieve high conversion (such as to generate products **1.102b** and **1.102d**). Even when they use a *cis* olefin to undergo the cross-metathesis with dienoate **1.101**, they still obtain the *trans* product as the major product (**1.102c** and **1.102d**), albeit with a slightly lower preference for that isomer. They also show the example of performing a cross-metathesis with **1.103** and alkenyl acetate **1.104** with the same catalyst and observing that the catalyst does perform metathesis with the internal olefin of the dienoate moiety and gives an 80:20 mixture of **1.105**:**1.106**. No yield was given for this reaction. Cossy and coworkers also reported a variety of (*E,E*)-dienoates in 2006 using the Hoveyda-Grubbs phosphine-free complex.[59]

[58] Funk, T. W.; Efskind, J.; Grubbs, R. H. *Org. Lett.* **2005**, *7*, 187-190.
[59] Ferrié, L.; Amans, D.; Reymond, S.; Bellosta, V.; Capdevielle, P.; Cossy, J. *J. Organomet. Chem.* **2006**, *691*, 5456–5465.

Scheme 1.31. Cross-Metathesis of Dienoates Reported by Grubbs

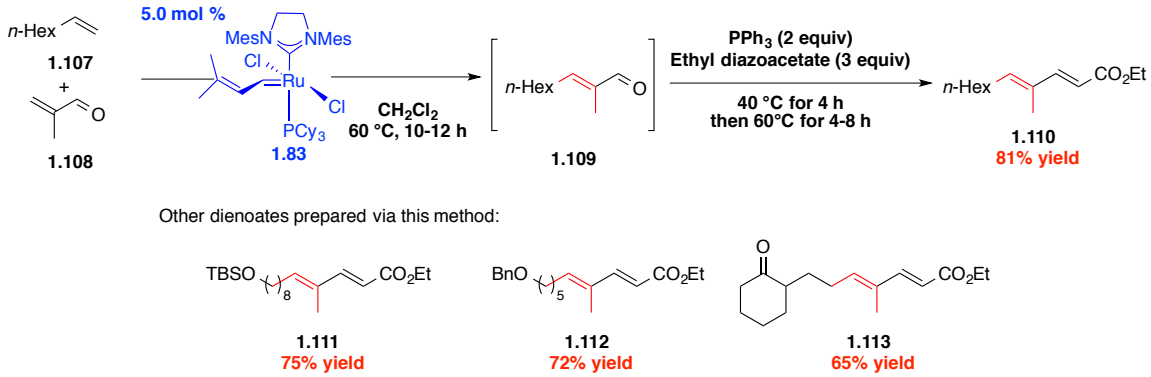


There have also been several tandem approaches to the synthesis of dienoic esters disclosed that should be mentioned involving metathesis processes. One of which, by Snapper and coworkers in 2007, reported a tandem cross-metathesis (using the modified Grubbs second generation complex **1.83**) followed by subsequent Wittig olefination to generate a variety of (*E*,*E*)-dienoates, several of which are shown below (Scheme 1.32).[60] That same year, Andrade and coworkers published a very similar study as that by the Snapper group using the same transformations to synthesize (*E,E*)-dienoic esters.[61]

[60] Murelli, R. P.; Snapper, M. L. *Org. Lett.* **2007**, *9*, 1749–1752.

[61] Paul, T.; Andrade, R. B. *Tetrahedron Lett.* **2007**, *48*, 5367–5370.

Scheme 1.32. Tandem Cross-Metathesis/Wittig Olefination by Snapper



1.5 Research Goals

Virtually all of the methodologies shown above for the synthesis of *Z*-α,β- and (*E*,*Z*)-α,β,γ,δ-unsaturated esters have drawbacks and challenges associated with performing them. Some are limited by cost, while others are limited by how stereoselective they can be; yet others require multiple steps to achieve the desired starting material. The ability to make conjugated unsaturated esters in a *Z*-selective fashion is of great importance to those in the synthetic community, yet the most advanced reactions for these transformations are often found lacking when it comes to delivering the desired product with the desired stereoselectivity. We saw this as an opportunity to use our latest olefin metathesis catalysts to develop the first *Z*-selective olefin cross-metathesis of acrylates. If this was successful, we then would look to pursue development of the first *Z*-selective cross-metathesis of dienoates.

2. Development of a Stereoselective Olefin Cross-Metathesis of Unsaturated Esters

As stated in chapter 1 of this thesis, acyclic *Z* olefins are generally higher in energy than their corresponding *E* isomer. This makes methods that can stereoselectively prepare *Z* olefins of great importance to the chemistry community at large. Before exploring how we developed the protocol for *Z*-selective cross-metathesis (CM) of acrylates and conjugated dienoates, it is important to discuss the foundation for this project. This includes the challenges associated with developing a stereoselective olefin metathesis catalyst and how our group overcame these challenges in recent years.

2.1 Background

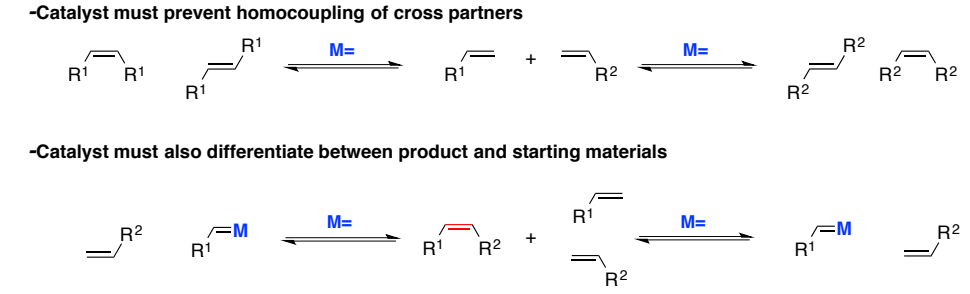
There are two big challenges to overcome when attempting to design a stereoselective olefin cross-metathesis catalyst. The first is that the catalyst must be able to access the kinetic *Z* product over the thermodynamic *E* product. In general, the *Z* isomer is roughly 1.0 kcal/ mol higher in energy than its corresponding *E* isomer (for acyclic olefins).[62] This generally gives a thermodynamic ratio of roughly 83:17 *E*:*Z* at room temperature. Without the desired kinetic selectivity, the catalyst would be just as efficient as the catalysts already reported and would be of no benefit, assuming no control is placed upon the selectivity from the substrate itself.

The second challenge, as shown in Scheme 2.1, associated with developing a stereoselective olefin metathesis catalyst concerns chemoselectivity. In order to prevent significant homocoupling of one olefin, the catalyst must be able to differentiate between

[62] Turner, R. B.; Jarrett, A. D.; Goebel, P.; Mallon, B. J. *J. Am. Chem. Soc.* **1973**, *95*, 790−792.

the two olefins and prefer to perform the cross-metathesis as opposed to homocoupling of the same olefin. Finally, to ensure that *Z* selectivity does not erode once the *Z* product has been formed, the catalyst must be able to differentiate between the product and the two starting material olefins. While kinetic selectivity is vital when designing a stereoselective metathesis catalyst, chemoselectivity is just as important, as kinetic selectivity could be erased through post-metathesis isomerization.

Scheme 2.1. Chemoselectivity Challenges in Stereoselective Catalyst Design

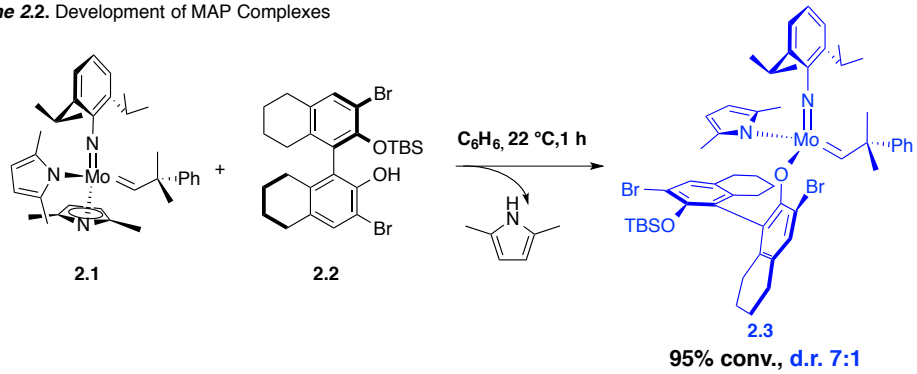


As little as a decade ago, synthetic chemists had to find alternative ways of synthesizing *Z* olefins stereoselectively as the most advanced olefin metathesis catalysts at the time could not achieve the needed kinetic selectivity (as exemplified in the examples in chapter 1 of this thesis). While chemoselectivity was not an issue for these catalysts, there was no answer to the challenge of overcoming the thermodynamic preference for the *E* isomer. The catalysts at the time could only deliver the thermodynamic ratio of *Z*:*E* olefins for many transformations and, in most cases, were highly *E*-selective.

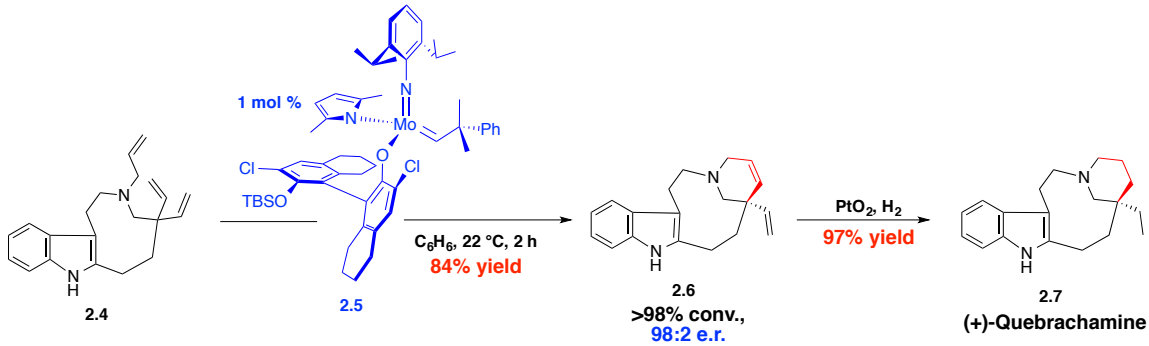
This all changed in 2008 when our group disclosed the development of stereogenic-at-Mo monoaryloxide monopyrrolide (MAP) complexes. In this report, we show that these MAP complexes (**2.3**), are generated *in situ* from a molybdenum bis-

pyrrolide complex (**2.1**) and a monoprotected diol (**2.2**) in high conversion and in high diastereoselectivity (Scheme 2.2).[63] These complexes were originally developed for enantioselective ring-closing metathesis (RCM) of the potent vasodilator (+)-quebrachamine. After obtaining triene **2.4** (Scheme 2.3), we subjected this intermediate to 1.0 mol % of the MAP complex **2.5** and were able to affect the RCM of the triene to generate **2.6** in high enantioselectivity and in high yield. Following hydrogenation we were able to obtain the final natural product (**2.7**) in exceptional yield. It should be noted that prior to the development of the MAP complexes, the most advanced molybdenum and ruthenium metathesis catalysts at the time were ineffective at performing the necessary ring closure.

Scheme 2.2. Development of MAP Complexes



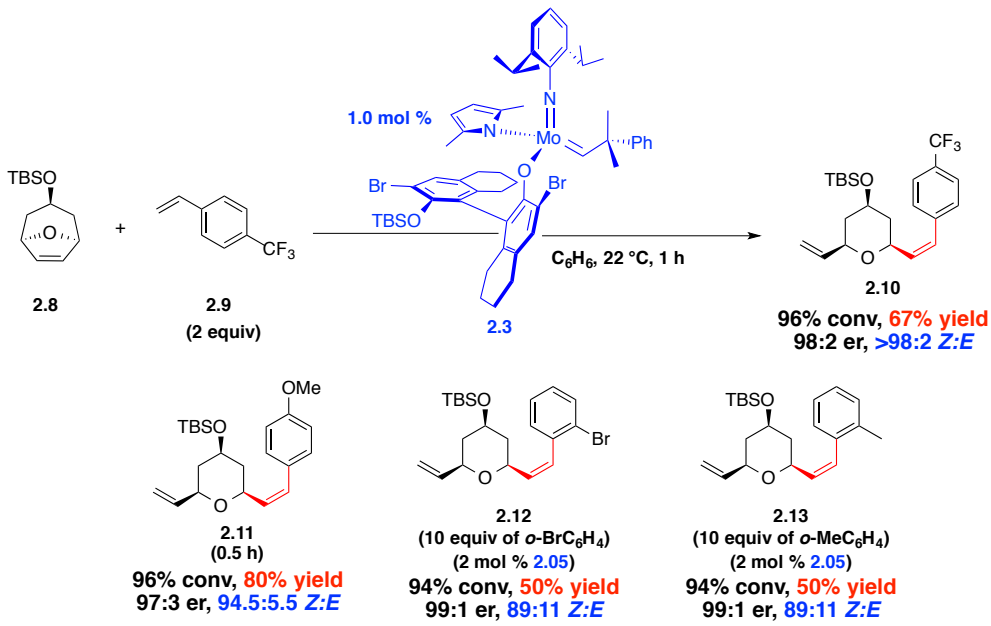
Scheme 2.3. Application of MAP Complexes to the Enantioselective RCM of (+)-Quebrachamine



[63] Malcolmson, S. J.; Meek, S. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *456*, 933–937.

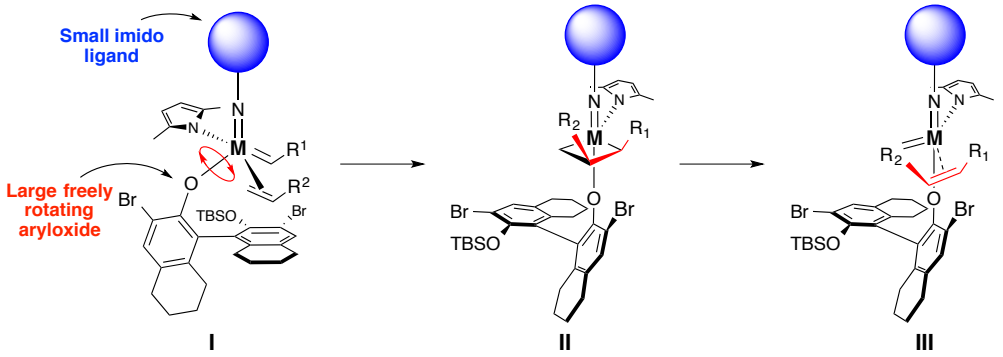
Following on from our studies on enantioselective RCM, we then were able to show these catalysts were effective at another transformation, enantioselective ring-opening/cross-metathesis (ROCM).[64] By subjecting a strained oxabicycle such as **2.8** (Scheme 2.4), and 2 to 10 equivalents of a substituted styrene to MAP complex **2.3**, a large variety of pyrans (**2.10–2.13**) could be generated in moderate to high yield and high enantioselectivity. However, it was the discovery that these products were also formed in exceptionally high *Z* selectivity that was very intriguing. From this study, we proposed that the *Z* selectivity from these complexes arises from the size differential between the small imido ligand and the large, freely rotating aryloxide ligand (Scheme 2.5). This rotating aryloxide ligand sweeps out a large steric space that prevents the incoming olefin substituents from pointing down towards the aryloxide (**I**), instead orienting itself towards the smaller imido group to minimize steric interactions (**II**). Following metallocyclobutane collapse, the desired *Z* olefin is released and the catalytic cycle continues (**III**).

Scheme 2.4. Application of MAP Complexes to Enantioselective ROCM



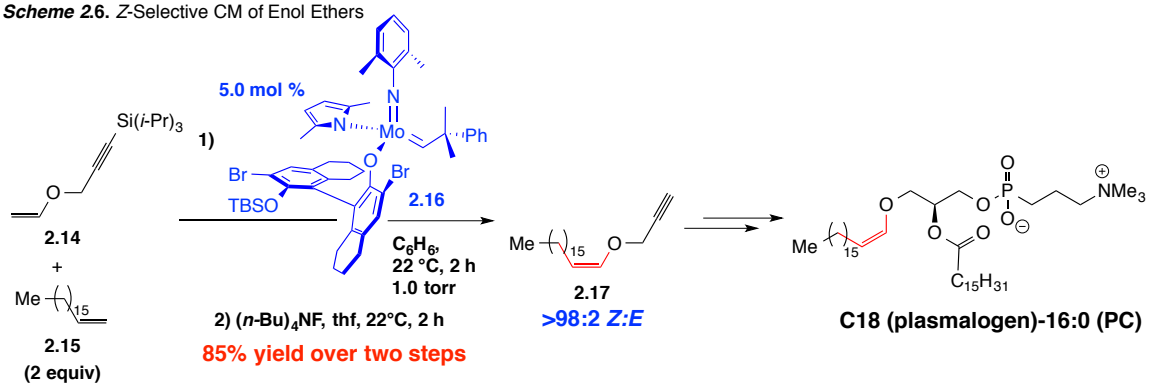
[64] Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3844–3845.

Scheme 2.5. Proposed Model for Stereoselectivity for MAP Complexes



Upon finishing the ROCM project and using what we had learned from that study, our group then began to explore developing a *Z*-selective transformation for the more difficult cross-metathesis reaction. In 2011, we disclosed the cross-metathesis of enol ethers with a variety of terminal cross partners to generate products such as **2.17** in high yield and exceptionally high *Z* selectivity (Scheme 2.6).[65] Product **2.17** was eventually carried forth as an intermediate to the synthesis of the potent anti-oxidant C18 (plasmalogen)-16:0 (PC).

Scheme 2.6. *Z*-Selective CM of Enol Ethers



Following our development of the *Z*-selective cross-metathesis of enol ethers, we then explored developing stereoselective CM reactions for other commonly used

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

substrates in organic synthesis. These studies lead to publications on the *Z*-selective cross-metathesis of allylic ethers,[66] followed closely by allyl and vinyl pinacol boronic esters (B(pin)).[67] The latter of the two studies showed that metathesis combined with cross coupling could be a powerful tool towards rapidly building complexity in synthesis.

After these studies, we became interested in developing metathesis protocols for unsaturated ester olefins. From our initial investigations into the metathesis of these motifs came a report in 2014 on the *Z*-selective RCM of both macrocyclic acrylates and dienoates. Using a recently developed pentafluorophenyl imido molybdenum complex[68] containing a hexamethylterphenoxide ligand (**2.18**), our group synthesized a large variety of macrocyclic *Z*-acrylates and macrocyclic (*E*,*Z*)- and (*Z*,*E*)-dienoates in relatively high *Z* selectivity and isolated these macrocycles in moderate to high yield (Scheme 2.7).[69]

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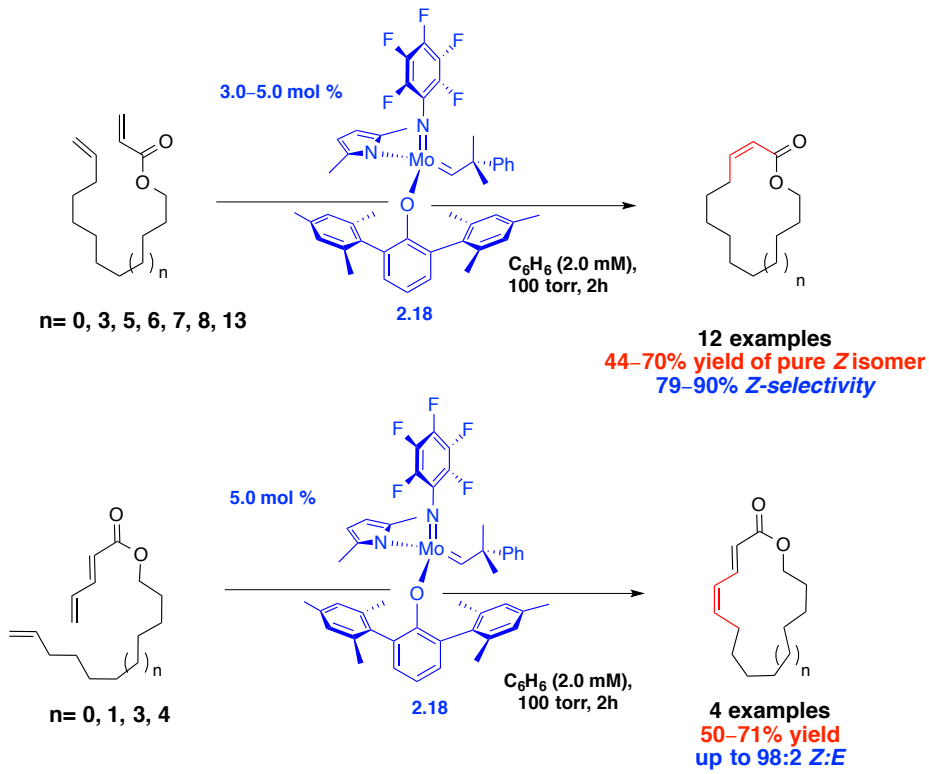
[66] Mann, T. J.; Speed, A. W. H.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 8395–8400

[67] 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.

[68] Yuan, J.; Schrock, R. R.; Gerber, L. C. H.; Müller, P.; Smith, S. *Organometallics* **2013**, *32*, 2983–2992.

[69] Zhang, H.; Yu, E. C.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 16493–16496.

Scheme 2.7. *Z*-Selective RCM of Macrocyclic Acrylates and Dienoates

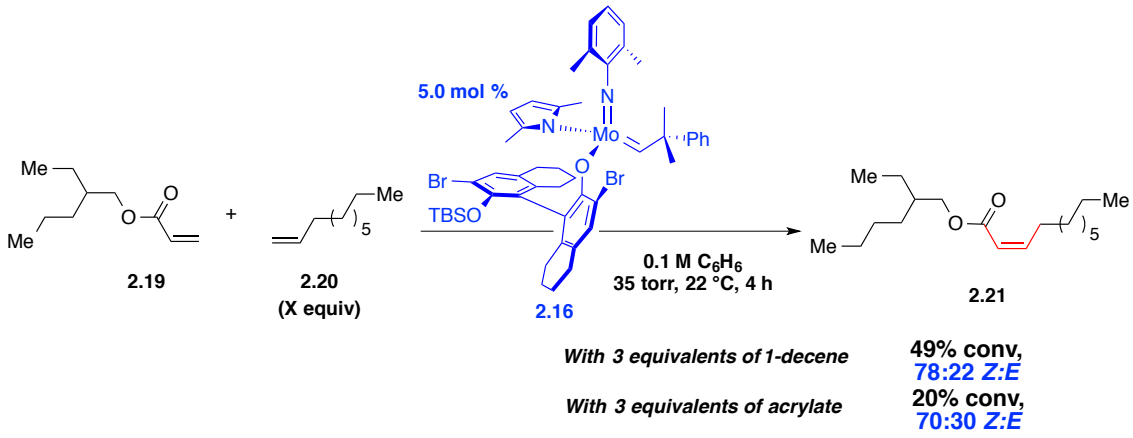


2.2 Development of the *Z*-Selective Cross-Metathesis of Acrylates

While the RCM reaction of macrocyclic acrylates and dienoates was being pursued, we began investigating the development of a separate CM protocol for acyclic unsaturated esters. While RCM and CM are somewhat similar reactions, the conditions used for both reactions are vastly different. RCM reactions require high dilution (as shown in the RCM in Scheme 2.7) to avoid homocoupling of the macrocycle, while CM requires high concentrations to facilitate the two olefins finding each other in a sea of both solvent and the other olefin cross partner. In RCM there is only one substrate added to the reaction, while in CM there are two cross partners, allowing for easy alteration of stoichiometry for optimization. With this in mind, we initiated our studies on optimizing the reaction conditions for the acrylate CM using acrylate **2.19** and attempting to cross

that with 1-decene (**2.20**) under the influence of the MAP complex shown in Scheme 2.8 (**2.16**).[70] When three equivalents of 1-decene were used with one equivalent of acrylate **2.19**, the reaction proceeded to near 50% conversion to product with a *Z*:*E* ratio of 78:22 after 4 hours. When the stoichiometry was reversed and three equivalents of acrylate were added to one equivalent of 1-decene, the conversion did not proceed to even half of that with the other stoichiometry in the same amount of time. This lead to the hypothesis that the Lewis basic carbonyl oxygen of the acrylate was possibly coordinating with the Lewis acidic molybdenum center of the MAP complex, shutting down its reactivity. Moving forward, the non-acrylate cross partner would be used in excess.

Scheme 2.8. Optimization of Acrylate CM Stoichiometry



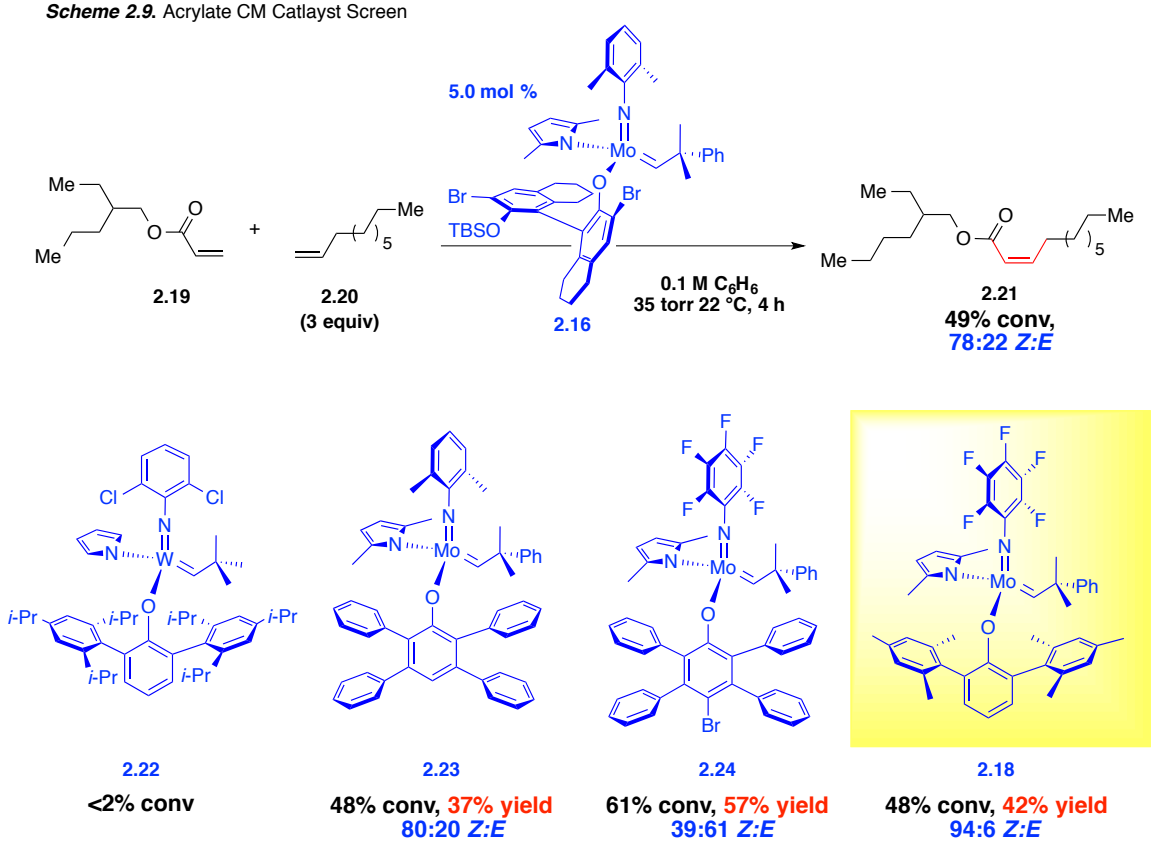
Moving on with the conditions screen for the acrylate CM reaction, using the stoichiometry established from the above-described study, a variety of catalysts were screened to find the optimal catalyst for this transformation. As shown in Scheme 2.9, starting out with the less reactive tungsten complex (**2.22**), no conversion to product was observed after 4 h. Moving to the molybdenum dimethylphenylimido complex **2.23**, similar conversion to **2.21** as when attempting to make the product with the TBS-

[70] Yu, E. C. unpublished results.

protected bromo binol derived dimethylphenylimido complex **2.16** was observed. We then hypothesized that we needed to perhaps make the catalyst more reactive by increasing the Lewis acidity of the molybdenum center. To do this we made the para-bromo substituted tetraphenyl phenol ligand shown in complex **2.24** and we also swapped the imido groups, from the dimethylphenylimido of **2.23** to the pentafluorophenylimido. While this catalyst gave higher conversion, the *Z* selectivity of the reaction suffered, perhaps due to post-metathesis isomerization. Tuning down the reactivity by adding the less electron-withdrawing hexamethylterphenoxide (HMTO) ligand to the pentafluorophenylimido molybdenum (complex **2.18**), conversion again was lower than expected, however the *Z* selectivity was what we desired. We speculated that perhaps acrylate **2.19** was too big of a cross partner for the catalyst to give both high conversion and *Z* selectivity so we began pursuing other acrylates. However, we decided to continue the development of the acrylate CM with complex **2.18**, coincidentally the same catalyst used for the RCM of macrocyclic acrylates and dienoates.[71]

[71] Yu, E. C. unpublished results.

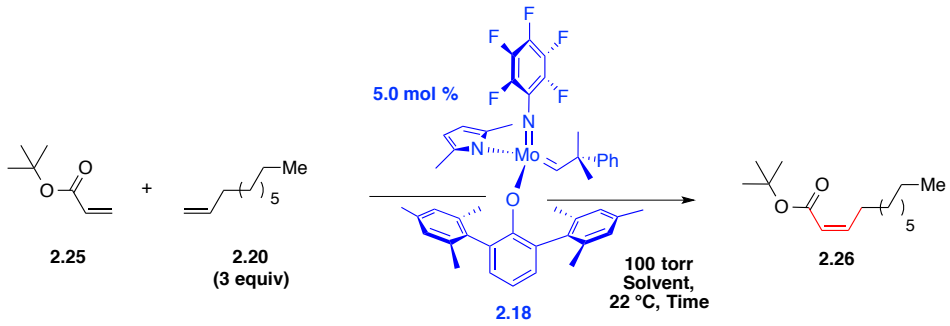
Scheme 2.9. Acrylate CM Catlayst Screen



Having determined the optimal catalyst and stoichiometry for our CM reaction of acrylates, we then investigated the proper solvent for the reaction. As shown in Table 2.1, using *tert*-butyl acrylate **2.25,** instead of acrylate **2.19**, and crossing it with 1-decene (**2.20**) using 5.0 mol % of the pentafluorophenylimido HMTO complex **2.18**, a variety of solvents were screened to determine which gave product **2.26** in the best yield and *Z* selectivity. When the reaction was performed in benzene (catalyst 0.1 M in benzene), conversion to product was 79% after 5 minutes although, as shown in the table, selectivity suffers. As the reaction time is increased to 15 minutes, conversion to product does not increase while *Z* selectivity erodes to virtually 63:35 due to post-metathesis isomerization. When the reaction was performed in thf, conversion after 5 minutes is near

what it was at 5 minutes using benzene, yet with significantly higher *Z* selectivity. As the reaction time was increased, we saw the *Z* selectivity again erode, not nearly as quickly as with benzene, however. Moving to the more Lewis basic solvent acetonitrile, the reaction proceeded at a much slower rate than with benzene and thf but the *Z* selectivity was high even after one hour, indicating there is slower post-metathesis isomerization in acetonitrile. Looking at the data, it may appear that thf is the most optimal solvent for this reaction due to the fact that it produces the same results in acetonitrile after 1 hour as it takes 5 minutes to accomplish in thf. However, we pursued different stoichiometries in acetonitrile and found that the acrylate could be used in excess and the reaction gives a better result than when the other cross partner was used in excess.[72] We decided to pursue the scope of the reaction in acetonitrile.

Table 2.1. Solvent Screening for Acrylate CM



Entry	Solvent	time (min)	conc. (M)	conv (%)	Yield (%)	*Z*:*E*
1	C_6H_6	5	0.1	79	62	79:21
2	C_6H_6	15	0.1	79	65	65:35
3	thf	5	0.025	71	53	93:7
4	thf	15	0.025	89	75	85:15
5	CH_3CN	5	0.1	<2	ND	ND
6	**CH_3CN**	**60**	**0.1**	**70**	**54**	**93:7**

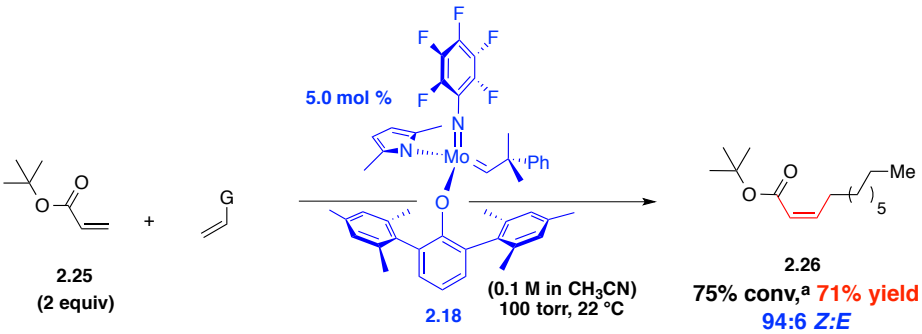
ND= Not determined

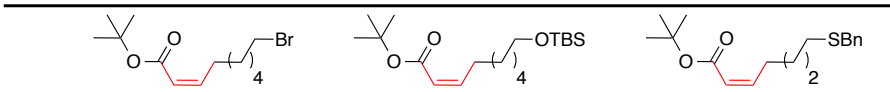
[72] Yu, E. C. unpublished results.

Since the acrylate was the less expensive cross partner in this reaction, we sought to develop the scope using the acrylate in excess with the conditions described above. As shown in Scheme 2.10, a variety of cross partners underwent cross-metathesis with *tert*-butyl acrylate **2.25** in acetonitrile with varying degrees of success. Products **2.26**, **2.27**, **2.28**, and **2.29** were isolated in moderate to high yields and high *Z*:*E* ratios. Shorter chain substrates such as the homoallylic TES ether, allyl benzene, and the para-methoxy benzyl ether (products **2.30**, **2.31**, and **2.32**, respectively) gave high *Z* selectivity and were isolated in decent yield. These substrates were slower to react and required longer reaction times to achieve higher conversion, however. Significant reaction optimization needed to be undertaken to optimize the results from the cross-metatheses of products **2.33** and **2.34**. It is believed that the α–branched substrate to generate product **2.33** (vinyl cyclohexane) imparts greater steric pressure on the catalyst that makes it slower for catalyst turnover to occur. Product **2.34** may be slower to form due to the terminal diene substrate forming a stabilized alkylidene with the catalyst.[73]

[73] Yu, E. C. unpublished results.

Scheme 2.10. Scope of the Acrylate CM Reaction in Acetonitrile

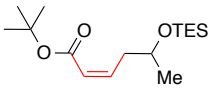




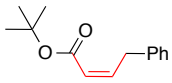
2.27
66% conv,[a] 65% yield
94:6 *Z:E*

2.28
76% conv,[a] 71% yield
93:7 *Z:E*

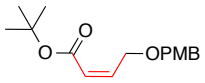
2.29
64% conv,[a,b] 57% yield
>98:2 *Z:E*



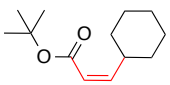
2.30
71% conv,[c] 69% yield
98:2 *Z:E*



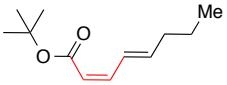
2.31
56% conv,[c] 40% yield
>98:2 *Z:E*



2.32
69% conv,[c] 62% yield
>98:2 *Z:E*



2.33
66% conv,[d] 64% yield
94:6 *Z:E*



2.34
60% conv,[d] 33% yield
93:7 *Z:E*

[a] Reactions were performed for 1 h. [b] A solution of 0.05 M of **2.18** was used. [c] Reactions were performed for 4 h. [d] Reaction was performed for 12 h under ambient pressure.

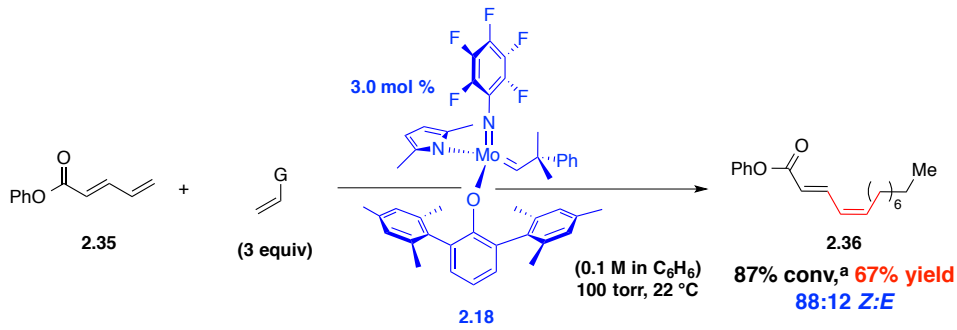
2.3 Development of the *Z*-Selective Cross-Metathesis of Dienoates

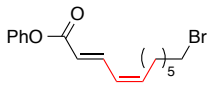
While looking into the scope development of the acrylate CM reaction we were pondering developing a reaction that could allow easy access to (2*E*,4*Z*)-dienoates, inspired from our attempts to synthesize diene **2.34**. Chapter 1 details the significance of dienoate products and, seeing as there was enough of a need for such a reaction, we initiated our studies into the cross-metathesis of dienoates.

As we had already developed a RCM protocol for macrocyclic dienoates and acrylates (see above) as well as a CM reaction of acrylates using the pentafluorophenylimido molybdenum complex **2.18**, we decided to initiate our studies of the CM of dienoates using this catalyst.[74] Looking into the scope of the cross-metathesis of phenyl dienoate **2.35** using three equivalents of the non-dienoate cross partner in benzene, we discovered that the products of the dienoate CM reaction did not isomerize as easily as the acrylates had. In fact, the dienoates could be run using 3.0 mol % of complex **2.18** and still give high conversion after 1 minute under 100 torr vacuum with several long-chain cross partners (see **2.36**, **2.37**, and **2.38** in Scheme 2.11). These substrates could be isolated in moderate to high yield, albeit with slightly lower selectivities than we were hoping for. While the homoallylic TES ether gave nice reactivity (see product **2.40**) with slightly higher *Z* selectivity than the long-chain products described above, when the substrates were made allylic (products **2.42** and **2.43**), the conversion and yield suffered. When the non-dienoate cross partner was made vinylic (vinyl B(pin) of product **2.41**), conversion to product was exceptional as was selectivity, however due to what we believe to be hydrolysis of the pinacol boronic ester (B(pin)) group to the boronic acid on silica gel, the yield was slightly lower than desired. This reaction also required more time to complete (18 h). We believe this to be a result of the formation of a stabilized alkylidene between the vinyl B(pin) and the active catalyst.

[74] Our initial screening data prior to initiating our studies into the scope of the dienoate reaction showed that this was also the optimal catalyst, we later discovered that the dienoate used for these screening reactions was actually a mixture of stereoisomers and the data was not usable.

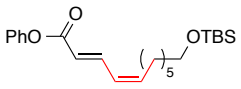
Scheme 2.11. Scope of the Dienoate CM With Complex **2.18**





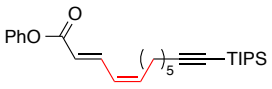
2.37

73% conv,[a] 64% yield
87:13 *Z:E*



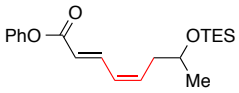
2.38

83% conv,[a] 74% yield
86:14 *Z:E*



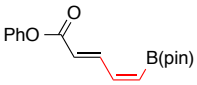
2.39

68% conv,[b] 42% yield
87:13 *Z:E*



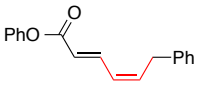
2.40

88% conv,[c] 79% yield
91:9 *Z:E*



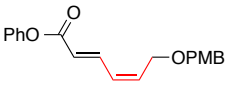
2.41

>98% conv,[d] 72% yield
>98:2 *Z:E*



2.42

57% conv,[e] 52% yield*
92:8 *Z:E*



2.43

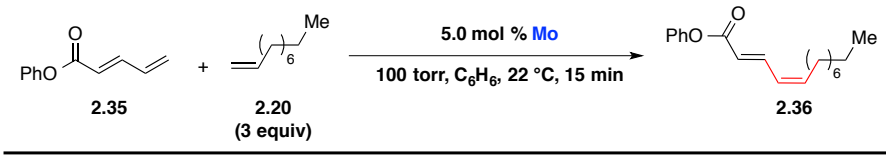
63% conv,[e] 50% yield
92:8 *Z:E*

[a] Reactions were performed for 1 min.
[b] Reaction was performed for 4 h.
[c] Reaction was performed for 30 min.
[d] Reaction was performed for 18 h under ambient pressure with 5:1 B(pin):dienoate stoichiometry.
[e] Reactions were performed for 15 min.
* Isolated with ligand.

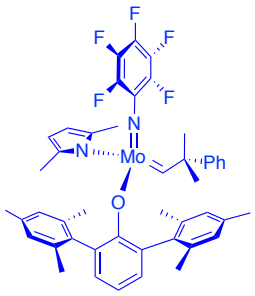
After completing our initial substrate scope with complex **2.18** we began to wonder if this complex was indeed the optimal catalyst for this reaction due to the lower than desired selectivities we observed. As shown in Scheme 2.12, using phenyl dienoate **2.35** and three equivalents of 1-decene **2.20** we began to screen a variety of our older generation MAP complexes for this transformation. When lowering the Lewis acidity of the molybdenum metal by making the *o*-CF_3 phenylimido complex **2.44**, little conversion to product (21%) was seen. Moving towards more electron-rich imido groups we subjected the olefins to complex **2.16** and saw a significant increase in conversion from

complex **2.44**. Moving towards the slightly more electron-rich complex **2.3**, the reaction proceeded to 82% conversion and gave the product in a 97:3 *Z*:*E* ratio. In the hopes of attaining even higher conversion we subjected the olefins to adamantylimido complex **2.45** and saw 90% conversion to product with a *Z*:*E* ratio of 97:3 which provided the product in 83% yield. Having found the optimal imido group, we then sought to look at the ligand of the molybdenum complex in greater detail. Switching the TBS-protected bromo-binol derivative to the corresponding chloro-binol derivative (complex **2.46**), we saw conversion to product increase slightly to 93% conversion, however both yield and *Z* selectivity were lower than when using molybdenum complex **2.45** (73% yield and 95:5 *Z*:*E*). Seeing as the TBS-protected bromo-binol derivative gave slightly higher *Z* selectivity and was more practical to make than the corresponding chloro-binol derivative, we decided to pursue the dienoate CM reaction using complex **2.45**.

Scheme 2.12. Dienoate CM Catalyst Screen



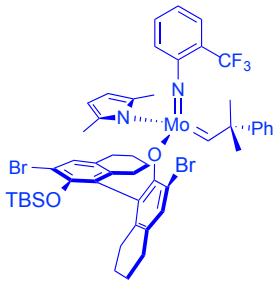
2.35 + **2.20** (3 equiv) → **2.36**



2.18

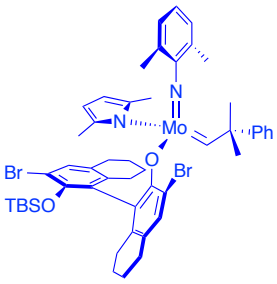
93% conv, 56% yield
87:13 *Z:E*

73% conv[a],
91:9 *Z:E*



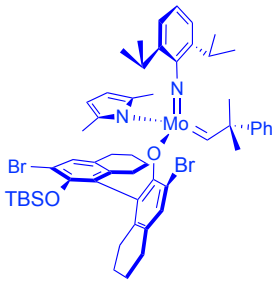
2.44

21% conv
>98:2 *Z:E*



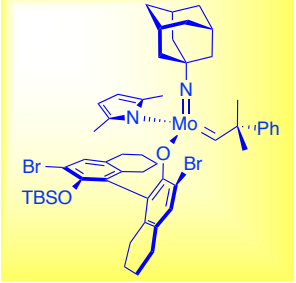
2.16

63% conv
97:3 *Z:E*



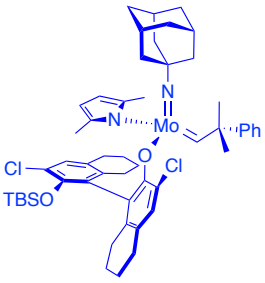
2.3

82% conv, 71% yield
97:3 *Z:E*



2.45

90% conv, 83% yield
97:3 *Z:E*



2.46

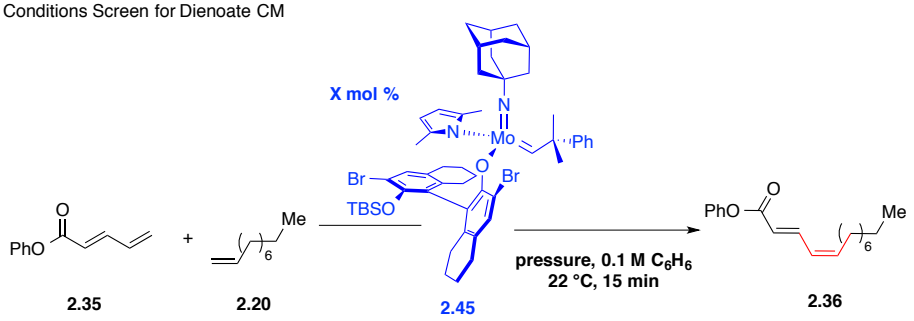
93% conv, 73% yield
95:5 *Z:E*

[a] Reaction run with 3.0 mol % **2.18** (0.1 M in CH_3CN) for 3 h at 100 torr

Having found the optimal catalyst for the transformation, we then looked into screening conditions for the dienoate CM reaction. When the stoichiometry of the reaction was switched from 3:1 to 1:3 **2.20**:**2.35** and the reaction was placed under a vacuum of 100 torr, only 9% conversion to product was observed, indicating excess of the dienoate leads to early catalyst decomposition (Table 2.2, Entry 2). Switching the stoichiometry to 1:1 and using a 100 torr vacuum, the reaction proceeded to 62% conversion to product, however homocoupling of the 1-decene limited conversion to

product. Using the 3:1 **2.20**:**2.35** stoichiometry and sealing the vial lead to 79% conversion with a *Z*:*E* ratio of 97:3 and provided the desired product in 74% yield (Entry 4). Using the optimal 3:1 **2.20**:**2.35** stoichiometry and lowering the catalyst loading to 3 mol % using a 100 torr vacuum provided the product in 81% conversion with a high *Z*:*E* ratio and lead to the isolation of the desired product in 74% yield (Entry 5).

Table 2.2. Conditions Screen for Dienoate CM



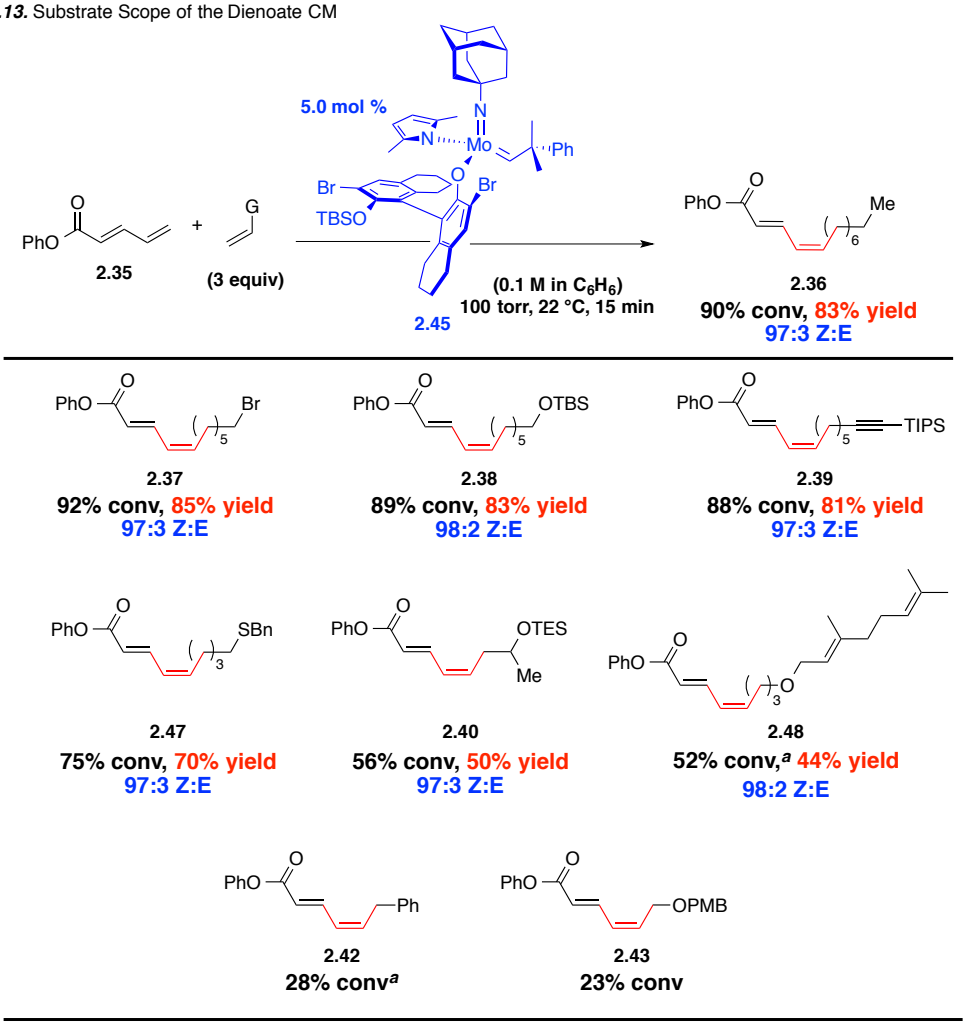
Entry	Equiv 2.35	Equiv 2.20	mol %	Conditions	Conv. (%)	*Z*:*E*	Yield (%)
1	1	3	5.0	100 torr	90	97:3	83
2	3	1	5.0	100 torr	9	>98:2	ND
3	1	1	5.0	100 torr	62	97:3	ND
4	1	3	5.0	sealed vial	79	97:3	74
5	1	3	3.0	100 torr	81	97:3	74

ND= not determined

Having screened a variety of conditions, we concluded that the acceptable conditions for this reaction were in fact the conditions used for the catalyst screening shown in entry 1. With the optimal conditions known we then moved on to developing the scope of the reaction.

The scope of the reaction using the new conditions is shown in Scheme 2.13. A variety of long-chain products (**2.36**, **2.37**, **2.38**, **2.39**, and **2.47**) were able to be isolated in high yield and the reaction provided them in *Z* selectivities of all 97:3 *Z*:*E* or higher.

Scheme 2.13. Substrate Scope of the Dienoate CM



[a] Reaction performed for 30 minutes

2.40 was slower to form than the longer-chain products and only proceeded to 56% conversion in 15 minutes. When attempting to raise the conversion by running the reaction for 30 minutes, no significant increase in conversion was seen. However, virtually only one isomer was formed in this reaction and the product was isolated in

relatively high yield considering the lower conversion. Geraniol-derived ether was able to undergo efficient cross-metathesis with the dienoate, however it required 30 minutes to proceed to decent conversion. **2.48** was, however, able to be isolated in 44% yield and was afforded as one isomer. Reactions to generate both allylic dienoates **2.42** and **2.43** did not afford the product in high enough conversion. No increase in conversion to these products was seen when the reaction was allowed to proceed for a longer time. However, as seen above in Scheme 2.11, complex **2.18** was able to generate both products in decent yield and *Z* selectivity.

2.4 Conclusion

In conclusion, we used the latest in molybdenum metathesis catalysts to develop the first *Z*-selective CM of acrylates. Using the pentafluorophenylimido molybdenum complex **2.18** and performing the cross-metathesis between the two cross partners in acetonitrile, a large variety of *Z*-acrylates could be prepared in high stereoselectivity. Following on from our studies on acrylates we then developed the first stereoselective cross-metathesis of dienoates using adamantylimido molybdenum complex **2.45**. Using these conditions several (2*E*,4*Z*)-dienoates were formed in high stereoselectivity. It is hoped that these two reactions will allow easy access to *Z*-unsaturated esters and shorten the routes to biologically active molecules containing these precious motifs.

2.5 Experimental section

^{1}H NMR spectra were measured using a Varian Unity Inova 400 MHz and 600 MHz spectrometers. Chemical shifts are reported in ppm with the residual solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet, app = apparent), coupling constants (Hz) and assignment. Proton-decoupled ^{13}C NMR spectra were recorded on Varian Unity Inova 400 (100 MHz) and 600 (150 MHz) spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.16 ppm). Infrared (IR) spectra were recorded on a Bruker FTIR Alpha (ATR Mode) spectrometer, λ in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). High-resolution mass spectrometry was performed on a Micromass LCT ESI-MS (positive mode) and a JEOL AccuTOF DART (positive mode) at the Boston College Mass Spectrometry Facility, Chestnut Hill, MA.

Chromatography was performed using flash chromatography on silica gel (SiO_2, 40-63 μm (230-400 mesh)) purchased from Silicycle. Visualization was performed using ultraviolet light (254 nm) as well as potassium permanganate ($KMNO_4$). Melting points were obtained on a Thomas Hoover Capillary Melting point Apparatus of Arthur H. Thomas Company, Philadelphia, PA and are uncorrected.

Vacuum Pumps

KNF Laboport N840.3FTP diaphragm vacuum pump connected to a Welch Labaid vacuum controller generates a vacuum of 100 torr at point of connection to the reaction vessel.

Solvents

Solvents were purged with argon and purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: diethyl ether (Aldrich), and dichloromethane (Aldrich) were passed through activated alumina columns. Benzene (Aldrich) was passed successively through Cu and activated alumina columns. *N*-Pentane was allowed to stir over concentrated H_2SO_4 for three days and two washings with H_2SO_4, washed with H_2O, followed by a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, and filtered. The resulting olefin-free *n*-pentane was then distilled over CaH_2. Tetrahydrofuran (thf; Aldrich) was distilled from sodium benzophenone ketyl.

Metal complex preparation

Molybdenum bis-alkoxide **1** was prepared according to a known procedure.[75] Ru carbene **2** was purchased from Sigma-Aldrich. Ru carbenes **3** and **4** were purchased from Materia, Inc. Mo-monoaryloxide-monopyrrolide complexes **2.3**,[76] **2.16**,[77] **2.18**,[78] **2.44**,[79] **2.45**,[71]

[75] Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; Regan, M. *J. Am. Chem. Soc.* **1990,** *112*, 3875–3886.
[76] Malcolmson, S. J.; Meek, S. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *456*, 933–937.
[77] Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature*, **2011**, *471*, 461–466.
[78] Zhang, H.; Yu, E. C.; Torker, S.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 16493–16496.

2.46[80] were prepared *in situ* according to previously reported procedures. The Mo and Ru complexes were handled in an inert N_2-filled dry box.

Reagents: All reagents were purchased from commercial vendors and used as received unless noted below.

Allyl Benzene: Purchased from Aldrich and distilled over CaH_2 prior to use.

1-((allyloxy)methyl)-4-methoxybenzene: Prepared according to a known procedure.[81]

Alumina (activated, basified): Purchased from Sigma Aldrich and used as received.

Benzene-d_6: Purchased from Cambridge Isotope Laboratories and distilled over sodium-benzophenone ketal before use.

Benzyl(hex-5-en-1-yl)sulfane: Prepared according to a known procedure with a minor modification using 6-bromo-1-hexene.[82]

Benzyl Mercaptan: Purchased from Aldrich and used as received.

8-bromo-1-octene: Purchased from Oakwood Chemicals and distilled over CaH_2 prior to use.

5-bromo-1-pentene: Purchased from Aldrich and used as received.

Chloroform-*d*: Purchased from Cambridge Isotope Laboratories and used as received.

Chlorotriethylsilane: Purchased from Aldrich and used as received.

1-decene: Purchased from Aldrich and distilled over CaH_2 prior to use.

Geraniol: Purchased from Aldrich and used as received.

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[79] 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.
[80] Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3844–3845.
[81] Harada, N-a.; Nishikata, T.; Nagashima, H. *Tetrahedron* **2012**, *68*, 3243–3252.
[82] Lin, Y. A.; Chalker, J. M.; Floyd, N.;Bernardes, G. J. L.; Davis, B. G. *J. Am. Chem. Soc.* **2008**, *130*, 9642–9643.

Imidazole: Purchased from Oakwood and used as received.

***n*-Butyllithium:** Purchased from Strem as a 1.6 M solution in hexanes and used as received.

7-Octen-1-ol: Purchased from TCI and used as received.

2,4-Pentadienoic acid: Purchased from Aldrich and used as received.

4-Penten-2-ol: Purchased from Alfa Aesar and used as received.

Triethylamine: Purchased from Aldrich and distilled over CaH_2 prior to use.

Triisopropylsilyl Acetylene: Purchased from GFS chemicals and used as received.

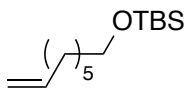
Trimethylacetyl Chloride: Purchased from Aldrich and used as received.

Sodium Phenoxide: Purchased from Fischer and used as received.

Sodium Sulfate (anhydrous): Purchased from Fischer and used as received.

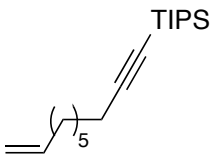
Vinylboronic acid pinacol ester: Purchased from Aldrich and purified by flash chromatography using 10% Et_2O/pentane. It was then distilled over CaH_2 prior to use.

Olefin Metathesis Substrates:



***tert*-Butyldimethyl(oct-7-en-1-yloxy)silane (S1):** To a solution of 7-Octen-1-ol (2.08 g, 16.2 mmol) in dichloromethane (54 mL) was added *tert*-Butyldimethylsilyl chloride (2.94 g, 19.5 mmol) followed by imidazole (1.33 g, 19.5 mmol) and the mixture was allowed to stir for 12 hours. The reaction was then quenched by addition of 10% $NaHCO_3$ and extracted with dichloromethane (3 x 30 mL). The combined organics were then washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting oil was then purified by silica gel chromatography (hexanes/EtOAc, 100:0-98:2), which afforded the desired product as a clear, colorless oil

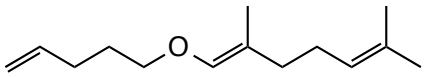
(3.70g, 15.3 mmol, 94% yield). The reagent was then dried by azeotropic distillation with benzene prior to its use in the olefin metathesis reaction. Spectral data are in agreement with the literature.[83]



Dec-9-en-1-yn-1-yltriisopropylsilane (S2): Prepared according to a known procedure with minor modifications.[84] To a flame-dried round bottom flask with a magnetic stir bar triisopropylacetylene (5.0 mL, 22.3 mmol) was added, followed by thf (25 mL). The solution was cooled to 4 °C and *n*-butyl lithium (1.6 M in hexanes, 13.9 mL, 22.3 mmol) was added. The reaction was allowed to warm to 22 °C with stirring over the course of 1 h. To the light yellow solution was added dropwise 8-bromo-1-octene (1.9 mL, 11 mmol). The mixture was heated to reflux for 12 h then allowed to cool to 22 °C and the reaction was then quenched by the addition of H_2O. The aqueous layer was then washed with dicholoromethane. The combined organics were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude oil was distilled in a Kugelrohr apparatus (1 h, 100 °C, 0.75 torr) to afford yellow oil. The oil was then distilled from CaH_2 under vacuum with heating and brought into the glove box to afford **S2** as clear, colorless oil (658 mg, 2.25 mmol, 20% yield). **IR (neat):** 2927 (br), 2863 (s), 2172 (m), 1462 (m), 994 (m), 909 (m), 882 (s), 771 (m), 675 (s), 659 (s), 619 (br). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 5.81 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H), 4.99 (ddt, *J* = 17.1, 2.3, 1.6 Hz, 1H), 4.93 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1H), 2.24 (t, *J* = 7.0 Hz, 2H), 2.07 – 2.02 (m, 2H), 1.56 – 1.50 (m, 2H), 1.46 – 1.29 (m, 6H), 1.09 – 1.04 (m, 21H);

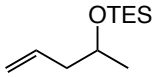
[83] Brimble, M. A.; Flowers, C. L.; Hutchinson, J. K.; Robinson, J. E.; Sidford, M. *Tetrahedron* **2005**, *61*, 10036–10047.
[84] Meek, S.J.; O'Brien, R.V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461–466.

^{13}C NMR (151 MHz, $CDCl_3$): δ 139.3, 114.3, 109.4, 80.2, 33.9, 29.0, 28.9, 28.7, 28.7, 20.0, 18.8, 11.5; **HRMS (DART) $[M+H]^+$** calcd for $C_{19}H_{37}Si$: 293.2664, found: 293.2678.

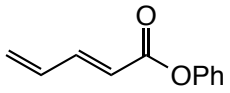


(*E*)-3,7-Dimethyl-1-(pent-4-en-1-yloxy)octa-2,6-diene (S3): In an N_2-filled dry box dry sodium hydride (324 mg, 13.5 mmol 2.0 equiv.) was weighed into an oven-dried flask with a magnetic stirbar. The flask was then sealed and brought out of the dry box then dimethylformamide was then added (11 mL) and the mixture was allowed to stir under N_2 at 4° C. A cooled solution of geraniol (2.08 g, 13.5 mmol 2.0 equiv) in dmf (4 mL) was added by cannula and the resulting mixture was then allowed to warm to room temperature and to stir under N_2 for one hour at which time 5-bromo-1-pentene (0.800 mL, 6.75 mmol) was then added and the mixture was warmed to 60 °C with stirring for 12 h, at which point the reaction was quenched by addition of H_2O. The aqueous layer was washed with three 30 mL portions of Et_2O. The combined organic layers were then washed once with brine and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting yellow oil was purified by silica gel chromatography (Pentane:Et_2O, 100:0-99:1) which afforded the title compound as pale yellow oil (675 mg, 3.03 mmol, 45% yield). The reagent was then further purified by distillation over CaH_2 prior to its use in the olefin metathesis reaction. **IR (neat):** 2967 (m), 2917 (m), 2853 (m), 1641 (w), 1443 (m), 1376 (m), 1104 (s), 1040 (w), 991 (m), 910 (s); **^{1}H NMR (600 MHz, CDCl)**: δ 5.81 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H), 5.35 (ddq, *J* = 6.7, 5.4, 1.3 Hz, 1H), 5.09 (dddd, *J* = 7.0, 5.6, 2.8, 1.4 Hz, 1H), 5.02 (ddt, *J* = 17.1, 1.7 Hz, 1H), 4.95 (ddt, *J* = 10.2, 2.1, 1.2 Hz, 1H), 3.97 (ddq, *J* = 6.7, 5.3, 0.8 Hz, 2H), 3.41 (t, *J* = 6.6 Hz,

2H), 2.15 – 2.01 (m, 8H), 1.71 – 1.64 (m, 10H), 1.61 – 1.58 (m, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 140.0, 138.5, 131.7, 124.2, 121.2, 114.8, 69.6, 67.4, 39.7, 30.5, 29.1, 26.5, 25.8, 17.8, 16.6; **HRMS (DART) $[M+H]^+$** calcd for $C_{15}H_{27}O$: 223.2062, found: 223.2062.



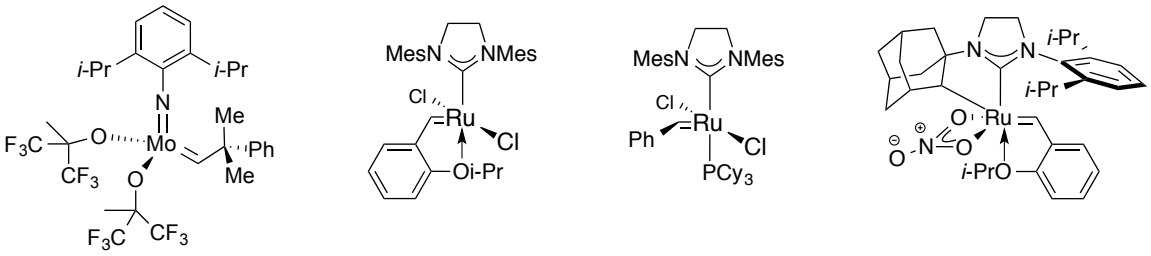
Triethyl(pent-4-en-2-yloxy)silane (S4): Into a flask was added a stir bar, 4-penten-2-ol (711 mg, 8.30 mmol), and dichloromethane, (28 mL). Chlorotriethylsilane (1.70 mL, 9.90 mL) was then added followed by imidazole (674 mg, 9.90 mmol) and the reaction mixture was allowed to stir at 22º C for 12 h under an atmosphere of nitrogen. The reaction was then quenched by addition of H_2O and the aqueous layer was washed with three 30 mL portions of dichloromethane. The combined organic layers were then washed once with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting oil was then purified by chromatography on basic alumina using hexanes, which afforded the title compound as colorless oil (976 mg, 60% yield). The oil was then distilled over CaH_2 prior to use in the olefin metathesis reaction. **IR (neat):** 2954 (s), 2938 (w), 2911 (m), 2876 (s), 1414 (w), 1237 (m), 1128 (m), 1128 (br), 1003 (s), 739 (s); **^{1}H NMR (400 MHz, $CDCl_3$-*d*):** δ 5.81 (ddt, *J* = 17.3, 10.2, 7.2 Hz, 1H), 5.09 – 5.00 (m, 2H), 3.84 (septet, *J* = 6.1 Hz, 1H), 2.30 – 2.11 (m, 2H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.59 (q, *J* = 7.9 Hz, 6H); **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 135.7, 116.7, 68.4, 44.5, 23.6, 7.0, 5.1; **HRMS (DART) $[M+H]^+$** calcd for $C_{11}H_{25}OSi$: 201.1675, found: 201.1677.



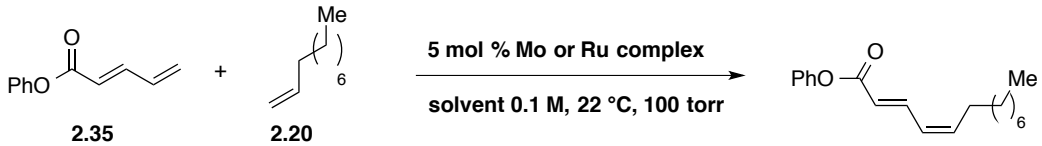
Phenyl-(*E*)-penta-2,4-dienoate (2.35): To a flask containing 2,4-pentadienoic acid (824 mg, 8.40 mmol) was added thf (53 mL). The flask was placed under an N_2 atmosphere and then cooled to -78 °C. Trimethylacetyl chloride (1.03 mL, 8.40 mmol) followed by triethylamine (1.29 mL, 9.24 mmol) were then added and the mixture was stirred at -78 °C for 15 minutes, then allowed to warm to room temperature with stirring over 45 minutes. A -78º C solution of sodium phenoxide (1.07g, 9.24mmol) in tetrahydrofuran (20 mL) was then transferred by cannula into this mixture. The resulting mixture was then allowed to warm to room temperature, with stirring, for 12 h. The reaction was then quenched by the addition of 2 M $KHSO_4$ in H_2O. The aqueous layer was washed with three 30 mL portions of EtOAc and the combined organic layers were washed once with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting brown oil was then purified by silica gel chromatography (hexanes:Et_2O 100:0-99:1) to afford the title compound as a colorless oil (1.0 g, 5.74 mmol, 68% yield). **IR (neat):** 3043 (w), 1728 (s), 1638 (m), 1589 (m), 1487 (m), 1415 (w), 1304 (m), 1186 (s), 1120 (s), 1006 (s); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.45 (ddt, *J* = 15.4, 11.0, 0.8 Hz, 1H), 7.41 – 7.37 (m, 2H), 7.25 – 7.22 (m, 1H), 7.14 – 7.12 (m, 2H), 6.55 (dddd, *J* = 17.0, 11.0, 10.1, 0.8 Hz, 1H), 6.11 (br d, *J* = 15.4 Hz, 1H), 5.70 (apparent d, *J* = 17.0 Hz, 1H), 5.58 (apparent d, *J* = 10.1 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 165.3, 150.9, 146.7, 134.7, 129.5, 126.8, 125.9, 121.7, 121.4; **HRMS (DART) $[M+H]^+$** calcd for $C_{11}H_{11}O_2$: 175.0759, found: 175.0765.

Catalytic Cross-Metathesis with "Traditional" Complexes

Table 2.3. Catalytic CM with 1-Decene and Phenyl Dienoate with "Traditional" Mo Alkylidenes and Ru Carbenes



1 **2** **3** **4**



2.35 **2.20 (3 equiv)** **5 mol % Mo or Ru complex** **solvent 0.1 M, 22 °C, 100 torr** **2.36**

Entry	Solvent	Complex	conv (%)	*Z:E*[b]	yield (%)
1	C_6H_6	**1**	<5	N/D	N/D
2	C_6H_6	**2**	95	8:92	87%*
3	C_6H_6	**3**	19	13:87	N/D
4	thf (ambient)	**4**	<5	N/D	N/D

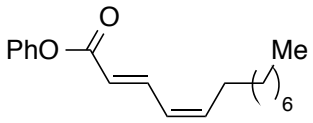
* Isolated as a mixture of the internal olefin cross partner and the desired product

[a] Reactions performed under N_2 atm. [b] Determined by analysis of ^{1}H NMR spectra of unpurified mixtures and refer to consumption of the limiting substrate (**2.35**) (±2%).

General Procedure: Cross-Metathesis with Phenyl Dienoate 2.35

In an N_2-filled dry box, an oven-dried 8 mL vial equipped with a magnetic stir bar was charged with phenyl dienoate (1 equiv). To this oil was then added 3 equiv of neat terminal cross-partner. A septum containing a needle was then placed on the vial. A solution of complex **2.45** or **2.18** (0.1 M in benzene) was then added to the vial, which was quickly connected to a 100-torr vacuum generated from a diaphragm vacuum pump.

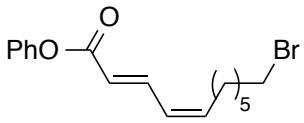
The resulting solution was allowed to stir for 15 minutes, at which time the reaction was taken from the dry box and quenched by exposure to air and addition of wet perdeutero-benzene. The percent conversion and *Z:E* ratio of the resulting mixture was determined by ^{1}H NMR analysis. Purification of the mixture by silica gel chromatography provided the target dienoate.



Phenyl (2*E*,4*Z*)-trideca-2,4-dienoate (2.36)

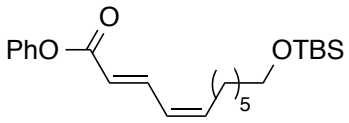
Following the general procedure, to a vial containing phenyl dienoate **2.35** (13.5 mg, 0.0774 mmol), 1-decene (32.6 mg, 0.232 mmol, 3 equiv) was added followed by a solution of **2.45** (38 μL, 0.0038 mmol, 0.05 equiv). The mixture was allowed to stir under a vacuum of 100 torr for 15 minutes; To the resulting mixture was added 250 μL of tetrahydrofuran, followed by a 1 M solution of tetra-*n*-butylammonium fluoride (8 μL 0.007 mmol, 0.1 equiv.). The resulting mixture was allowed to stir for 10 minutes then diluted with hexanes and filtered through a pad of Celite. The resulting pale brown oil was then purified by silica gel chromatography (hexanes:Et_2O, 100:0-99:1) which afforded the title compound as colorless oil (18.6 mg, 0.0649 mmol, 84% yield, 96:4 *Z:E*). **IR (neat):** 2923 (s), 2853 (m), 1730 (s), 1633 (m), 1592 (w), 1492 (m), 1457 (w), 1411 (w), 1194 (s), 1071 (s); **^{1}H NMR (600 MHz, $CDCl_3$), *Z* isomer:** δ 7.79 (ddd, *J* = 15.3, 11.7, 1.1 Hz, 1H), 7.41 – 7.37 (m, 2H), 7.25 – 7.22 (m, 1H), 7.15 – 7.12 (m, 2H), 6.25 – 6.17 (m, 1H), 6.06 (d, *J* = 15.3, 1H), 5.95 (dtt, *J* = 9.7, 7.8, 1.1, 1H), 2.34 (m, 2H), [diagnostic signal for the *E* isomer: 1.48 – 1.41 (m, 2H), 1.35 – 1.24 (m, 10H), 0.91 – 0.86 (m, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 165.8, 151.0, 143.1, 141.6, 129.5, 126.5,

125.8, 121.8, 120.3, 32.0, 29.6, 29.5, 29.4, 29.4, 28.6, 22.8, 14.2; **HRMS (DART) [M+H]$^+$** calcd for $C_{19}H_{27}O_2$: 287.2011, found: 287.2025.



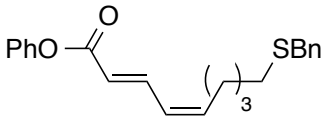
Phenyl (2*E*,4*Z*)-11-bromoundeca-2,4-dienoate (2.37)

Following the general procedure, to a vial containing phenyl dienoate **2.35** (11.4 mg, 0.0774 mmol), 8-bromo-1-octene (37.5 mg, 0.196 mmol, 3 equiv) was added followed by a solution of **2.45** (32 µL, 0.0032 mmol, 0.05 equiv). The mixture was allowed to stir under a vacuum of 100 torr for 15 minutes; purification of the resulting residue by silica gel chromatography (hexanes:Et_2O, 100:0-98:2) which afforded the title compound as colorless oil (19.3 mg, 0.0572 mmol, 87% yield, 94:6 *Z*:*E*). **IR (neat):** 2929 (m), 2855 (m), 1728 (s), 1633 (m), 1591 (w), 1492 (m), 1456 (w), 1259 (br), 1195 (s), 1128 (s), 1128 (s); **^{1}H NMR (400 MHz, $CDCl_3$), *Z* isomer:** δ 7.78 (ddd, *J* = 15.2, 11.7, 0.9 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.26 – 7.21 (m, 1H), 7.16 – 7.11 (m, 2H), 6.22 (m, 1H), 6.07 (d, *J* = 15.2, 1H), 5.93 (m, 1H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.35 (qd, *J* = 7.3, 1.5 Hz, 2H), [diagnostic signal for the *E* isomer: 2.22 (qd, *J* = 6.8 Hz)], 1.92 – 1.81 (m, 2H), 1.52 – 1.32 (m, 6H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.8, 150.9, 142.6, 141.4, 129.5, 126.7, 125.8, 121.8, 120.5, 34.0, 32.8, 29.3, 28.5, 28.4, 28.1; **HRMS (DART) [M+H]$^+$** calcd for $C_{17}H_{22}O_2Br$: 337.0803, found: 337.0813.



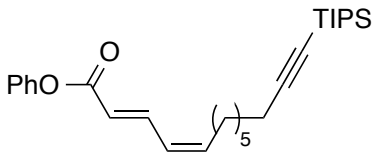
Phenyl (2*E*,4*Z*)-11-((*tert*-butyldimethylsilyl)oxy)undeca-2,4-dienoate (2.38)

Following the general procedure, to a vial containing phenyl dienoate **2.35** (14.7 mg, 0.0843 mmol), octenyl-OTBS **S1** (61.3 mg, 0.253 mmol, 3 equiv) was added followed by a solution of **2.45** (42 μL, 0.0042 mmol, 0.05 equiv). The mixture was allowed to stir under a vacuum of 100 torr for 15 minutes; purification of the resulting residue by silica gel chromatography (hexanes:Et_2O, 100:0-98:2) afforded the title compound as colorless oil (27.8 mg, 0.0715 mmol, 85% yield, 96:4 Z:E). **IR (neat):** 2928 (m), 2855 (m), 1730 (s), 1633 (m), 1592 (m), 1492 (m), 1252 (br), 1194 (s), 1120 (s), 1098 (br); **^{1}H NMR (400 MHz, $CDCl_3$), *Z* isomer:** δ 7.79 (ddd, *J* = 15.2, 11.7, 0.9 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.26 – 7.21 (m, 1H), 7.15 – 7.12 (m, 2H), 6.21 (m, 1H), 6.06 (d, *J* = 15.2 Hz, 1H), 5.95 (m, 1H), 3.60 (t, *J* = 6.6 Hz, 2H), 2.39 – 2.29 (m, 2H), [diagnostic signal for the *E* isomer: 2.21 (qd, *J* = 6.9 Hz)], 1.57 – 1.29 (m, 8H), 0.89 (s, 9H), 0.05 (s, 6H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.8, 151.0, 143.0, 141.5, 129.5, 126.5, 125.8, 121.8, 120.4, 63.3, 32.9, 29.5, 29.2, 28.5, 26.1, 25.8, 18.5, -5.1; **HRMS (DART) $[M+H]^+$** calcd for $C_{23}H_{37}O_3Si$: 389.2512, found: 389.2509.



Phenyl (2*E*,4*Z*)-9-(benzylthio)nona-2,4-dienoate (2.47)

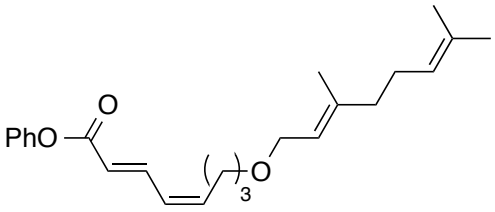
Following the general procedure, to a vial containing phenyl dienoate **2.35** (13.4 mg, 0.0769 mmol), benzyl(hex-5-en-1-yl)sulfane (47.6 mg, 0.231 mmol, 3 equiv) was added followed by a solution of **2.45** (38 μL, 0.0038 mmol, 0.05 equiv). The mixture was allowed to stir under a vacuum of 100 torr for 15 minutes; purification of the resulting residue by silica gel chromatography (hexanes:Et_2O, 100:0-95:5) afforded the title compound as colorless oil (18.5 mg, 0.0524 mmol, 68% yield, 98:2 *Z*:*E*). **IR (neat):** 2922 (m), 1725 (s), 1631 (s), 1591 (m), 1491 (s), 1453 (m), 1239 (br), 1192 (s), 1128 (s), 995 (w), 961 (m), 699 (br), 565 (w), 499 (w); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.76 (ddd, *J* = 15.2, 11.7, 0.9 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.31 (d, *J* = 4.3 Hz, 4H), 7.28 – 7.21 (m, 2H), 7.17 – 7.11 (m, 2H), 6.27 – 6.17 (m, 1H), 6.07 (d, *J* = 15.3 Hz, 1H), 5.95 – 5.85 (m, 1H), 3.71 (s, 2H), 2.43 (t, *J* = 7.1 Hz, 2H), 2.32 (qd, *J* = 7.4, 1.5 Hz, 2H), 1.68 – 1.46 (m, 6H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 165.7, 150.9, 142.2, 141.3, 138.7, 129.5, 129.0, 128.6, 127.1, 126.8, 125.8, 121.8, 120.7, 36.5, 31.3, 28.8, 28.6, 28.1; **HRMS (DART) [M+H]$^+$** calcd for $C_{22}H_{25}O_2S$: 353.1575, found: 353.1589.



Phenyl (2*E*,4*Z*)-13-(triisopropylsilyl)trideca-2,4-dien-12-ynoate (2.39)

Following the general procedure, to a vial containing phenyl dienoate **2.35** (12.8 mg, 0.0734 mmol), dec-9-en-1-yn-1-yltriisopropylsilane **S2** (64.4 mg, 0.220 mmol, 3 equiv) was added followed by a solution of **2.45** (36 μL, 0.0036 mmol, 0.05 equiv). The

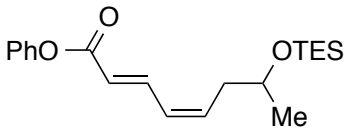
mixture was allowed to stir under a vacuum of 100 torr for 15 minutes; purification of the resulting residue by silica gel chromatography (hexanes:Et_2O, 100:0-99.5:0.5) afforded the title compound as colorless oil (26.3 mg, 0.0599 mmol, 82% yield, 98:2 *Z*:*E*). **IR (neat):** 2926 (m), 2862 (s), 2169 (w), 1731 (s), 1633 (m), 1592 (w), 1461 (m), 1411 (m), 1194 (s), 659 (m); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.78 (ddd, *J* = 15.2, 11.7, 0.9 Hz, 1H), 7.42 – 7.37 (m, 2H), 7.26 – 7.21 (m, 1H), 7.16 – 7.11 (m, 2H), 6.21 (ddtd, *J* = 11.7, 10.7, 1.5, 0.9 Hz, 1H), 6.07 (d, *J* = 15.2, 1H), 5.94 (dtt, *J* = 10.7, 7.8, 0.9 Hz, 1H), 2.34 (qd, *J* = 7.8, 1.5 Hz, 2H), 2.25 (t, *J* = 6.9 Hz, 2H), 1.59 – 1.33 (m, 8H), 1.06–1.08 (m, 21H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 165.8, 151.0, 142.9, 141.5, 129.5, 126.6, 125.8, 121.8, 120.4, 109.2, 80.3, 29.4, 28.9, 28.8, 28.7, 28.5, 19.9, 18.8, 11.5; **HRMS (ESI) [M+H]$^+$** calcd for $C_{28}H_{43}O_2Si$: 439.3032, found: 439.3034.



Phenyl (2*E*,4*Z*)-8-(((*E*)-3,7-dimethylocta-2,6-dien-1-yl)oxy)octa-2,4-dienoate (2.48)

Following the general procedure, to a vial containing phenyl dienoate **2.35** (14.0 mg, 0.0803 mmol), (*E*)-3,7-dimethyl-1-(pent-4-en-1-yloxy)octa-2,6-diene **S3** (53.1 mg, 0.240 mmol, 3 equiv) was added followed by a solution of **2.45** (40 µL, 0.0040 mmol, 0.05 equiv). The mixture was allowed to stir under a vacuum of 100 torr for 15 minutes; purification of the resulting residue by silica gel chromatography (hexanes:Et_2O, 100:0-95:5) afforded the title compound as colorless oil (13.1 mg, 0.0355 mmol, 44% yield, 98:2 *Z*:*E*). **IR (neat):** 2919 (m), 2853 (m), 1729 (s), 1633 (m), 1592 (w), 1492 (m), 1454 (w), 1194 (s), 1117 (s), 499 (w); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.80 (ddd, *J* = 15.2, 11.6, 1.1 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.26 – 7.21

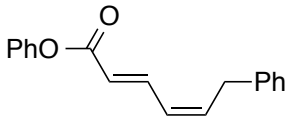
(m, 1H), 7.15 – 7.11 (m, 2H), 6.26 – 6.20 (m, 1H), 6.07 (d, J = 15.2 Hz, 1H), 5.95 (dt, J = 10.7, 7.9 Hz, 1H), 5.35 (m, 1H), 5.08 (m, 1H), 3.98 (d, J = 6.7 Hz, 2H), 3.44 (t, J = 6.4 Hz, 2H), 2.47 – 2.41 (m, 2H), 2.13 – 2.06 (m, 2H), 2.02 (dd, J = 9.3, 6.1 Hz, 2H), 1.78 – 1.70 (m, 2H), 1.70 – 1.65 (m, 6H), 1.59 (s, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 165.7, 151.0, 142.1, 141.4, 140.2, 131.7, 129.5, 127.0, 125.8, 124.2, 121.8, 121.0, 120.7, 69.2, 67.5, 39.7, 29.5, 26.5, 25.8, 25.3, 17.8, 16.6; **HRMS (DART) $[M+NH_4]^+$** calcd for $C_{24}H_{36}NO_3$: 386.2695, found: 386.2694.



Phenyl (2*E*,4*Z*)-7-((triethylsilyl)oxy)octa-2,4-dienoate (2.40)

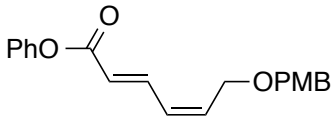
Following the general procedure, to a vial containing phenyl dienoate **2.35** (13.3 mg, 0.0763 mmol), triethyl(pent-4-en-2-yloxy)silane **S4** (45.9 mg, 0.229 mmol, 3 equiv) was added followed by a solution of **2.45** (38 μL, 0.0038 mmol, 0.05 equiv). The mixture was allowed to stir under a vacuum of 100 torr for 15 minutes; purification of the resulting residue by silica gel chromatography (hexanes:Et_2O, 100:0-97:3) afforded the title compound as colorless oil (13.3 mg, 0.0383 mmol, 50% yield, 96:4 *Z*:*E*). **IR (neat):** 2954 (m), 2875 (m), 1730 (s), 1634 (m), 1592 (m), 1492 (m), 1194 (s), 1117 (s), 1002 (s), 720 (br)**; ^{1}H NMR (400 MHz, $CDCl_3$), *Z* isomer:** δ 7.77 (ddd, J = 15.3, 11.6, 1.1 Hz, 1H), 7.43 – 7.35 (m, 2H), 7.26 – 7.20 (m, 1H), 7.16 – 7.10 (m, 2H), 6.35 – 6.26 (m, 1H), 6.07 (m, 1H), 6.04 – 5.97 (m, 1H), 3.94 (sextet, J = 6.0 Hz, 1H), 2.48 (m, 2H), [diagnostic signal for the *E* isomer: 2.38 – 2.31 (m)], 1.18 (d, J = 6.0 Hz, 3H), 1.00 – 0.93 (m, 9H), 0.65 – 0.56 (m, 6H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 165.9, 151.0, 141.6, 139.0, 129.5,

128.1, 125.8, 121.8, 120.8, 68.0, 38.5, 23.9, 7.0, 5.1; **HRMS (ESI) [M+H]$^+$** calcd for $C_{20}H_{31}O_3Si$: 347.2043, found: 347.2035.



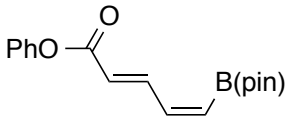
Phenyl (2*E*,4*Z*)-6-phenylhexa-2,4-dienoate (2.42)

Following the general procedure, to a vial containing phenyl dienoate **2.35** (13.4 mg, 0.0769 mmol), allyl benzene (27.3 mg, 0.231 mmol, 3 equiv) was added followed by a solution of **2.18** (23 μL, 0.0023 mmol, 0.03 equiv). The mixture was allowed to stir under a vacuum of 100 torr for 15 minutes; purification of the resulting residue by silica gel chromatography (hexanes:Et_2O, 100:0-99:1) afforded the title compound contaminated with 2% by weight of the phenol ligand as colorless oil (9.7 mg, 0.036 mmol, 48% yield, 90:10 *Z*:*E*). **IR (neat):** 3027 (w), 2920 (w), 1725 (s), 1632 (m), 1590 (m), 1454 (w), 1408 (w), 1244 (m), 1192 (s), 1142 (s), 1108 (s); **^{1}H NMR (600 MHz, $CDCl_3$), *Z* isomer:** δ 7.92 (ddd, *J* = 15.2, 11.7, 1.3 Hz, 1H), 7.42 – 7.38 (m, 2H), 7.34 – 7.30 (m, 2H), 7.26 – 7.23 (m, 2H), 7.22 – 7.19 (m, 2H), 7.16 – 7.14 (m, 2H), 6.34 (m, 1H), 6.16 (d, *J* = 15.2 Hz, 1H), 6.09 (dtt, *J* = 9.9, 7.9, 0.9 Hz, 1H), 3.70 (d, 2H), [diagnostic signal for the *E* isomer: 3.55 (d)]; **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.6, 150.9, 140.9, 140.2, 139.2, 129.5, 128.8, 128.6, 127.1, 126.6, 125.9, 121.8, 121.6, 34.6. **HRMS (ESI) [M+H]$^+$** calcd for $C_{18}H_{17}O_2$: 265.1228, found: 265.1238.



Phenyl (2*E*,4*Z*)-6-((4-methoxybenzyl)oxy)hexa-2,4-dienoate (2.43)

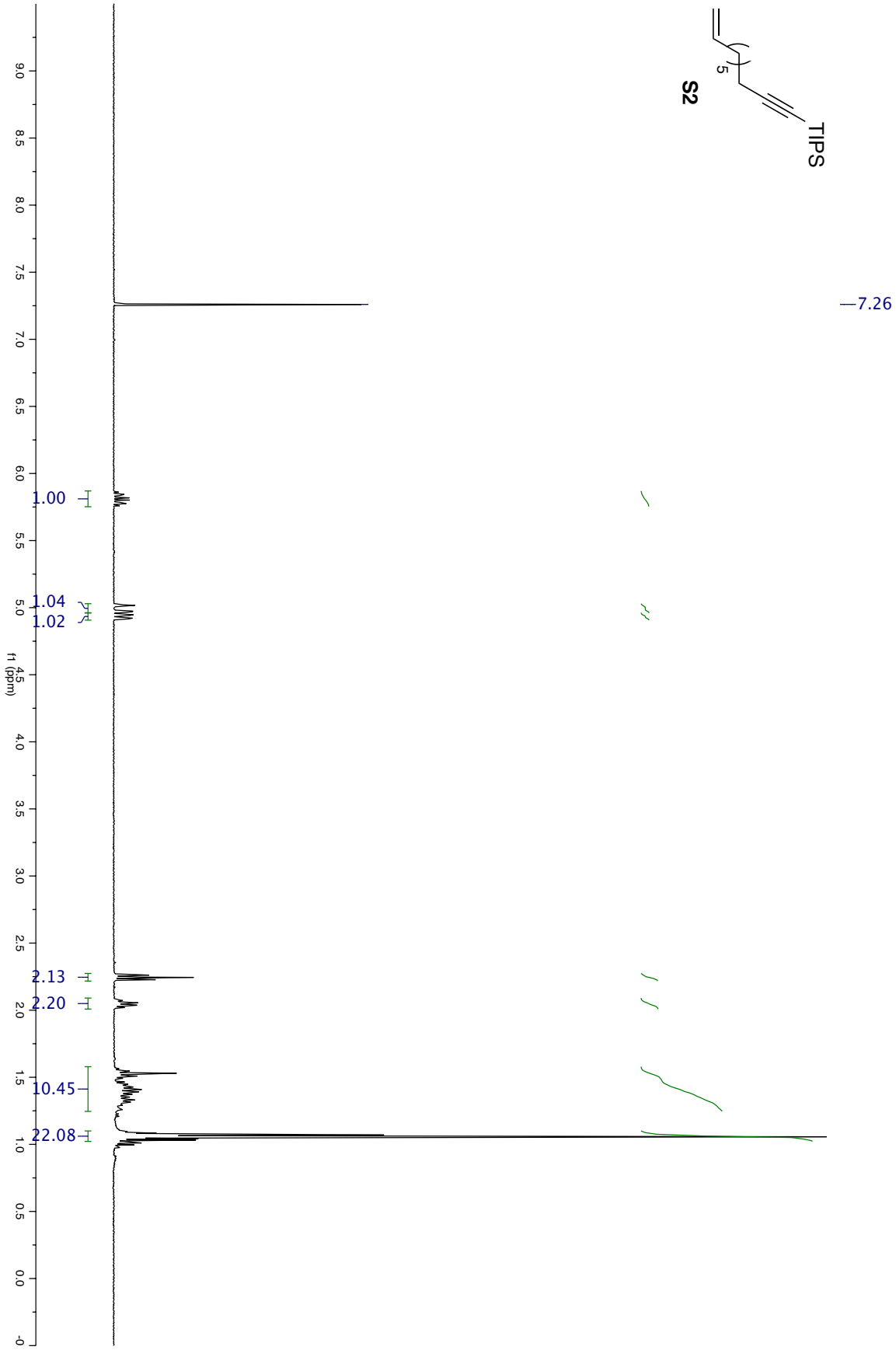
Following the general procedure, to a vial containing phenyl dienoate **2.35** (13.1 mg, 0.0752 mmol), 1-((allyloxy)methyl)-4-methoxybenzene (40.2 mg, 0.226 mmol, 3 equiv) was added followed by a solution of **2.18** (22 μL, 0.0022 mmol, 0.03 equiv). The mixture was allowed to stir under a vacuum of 100 torr for 15 minutes; purification of the resulting residue by silica gel chromatography (hexanes:Et_2O, 100:0-96:4) afforded the title compound as yellow oil (11.7 mg, 0.0360 mmol, 48% yield, 94:6 *Z*:*E*). **IR (neat):** 2922 (m), 1725 (s), 1611 (m), 1511 (s), 1491 (m), 1244 (s), 1192 (s), 1155 (s), 1116 (s), 817 (s); **^{1}H NMR (600 MHz, $CDCl_3$), *Z* isomer:** δ 7.74 (ddd, *J* = 15.3, 11.7, 0.9 Hz, 1H), 7.43 – 7.38 (m, 2H), 7.31 – 7.26 (m, 2H), 7.24 (ddt, *J* = 7.8, 7.1, 1.2 Hz, 1H), 7.14 – 7.12 (m, 2H), 6.89 – 6.85 (m, 2H), 6.32 (m, 1H), 6.11 (d, *J* = 15.3 Hz, 1H), 6.05 (m, 1H), 4.49 (s, 2H), 4.29 (dd, *J*=6.5, 1.6 Hz, 2H), [diagnostic signal for the *E* isomer: 4.14 (dd, *J* = 5.3, 1.6 Hz)], 3.78 (s, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 165.3, 159.5, 150.9, 140.7, 137.4, 130.0, 129.7, 129.6, 128.4, 125.9, 122.3, 121.7, 114.0, 72.6, 65.9, 55.4; **HRMS (DART) $[M+NH_4]^+$** calcd for $C_{20}H_{24}NO_4$: 342.1705, found: 342.1719.

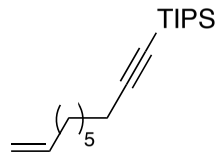


Phenyl (2*E*,4*Z*)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-2,4-dienoate (2.41)

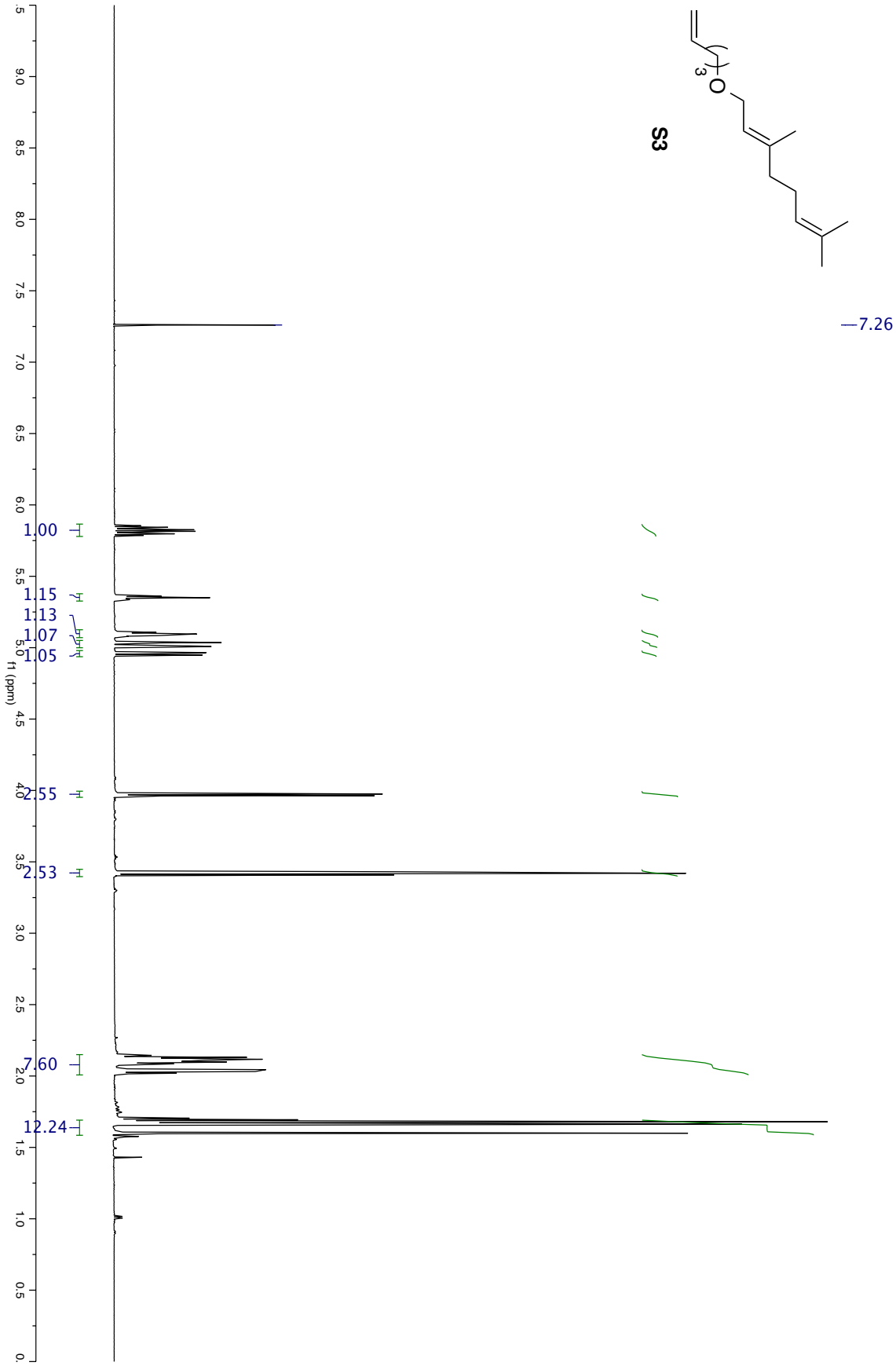
In an N_2-filled dry box an oven-dried 8 mL vial equipped with a magnetic stir bar was charged with phenyl dienoate **2.35** (12.7 mg, 0.0729 mmol), vinylboronic acid pinacol ester (56.1 mg, 0.365 mmol, 5 equiv) was added followed by a solution of **2.18** (21 μL,

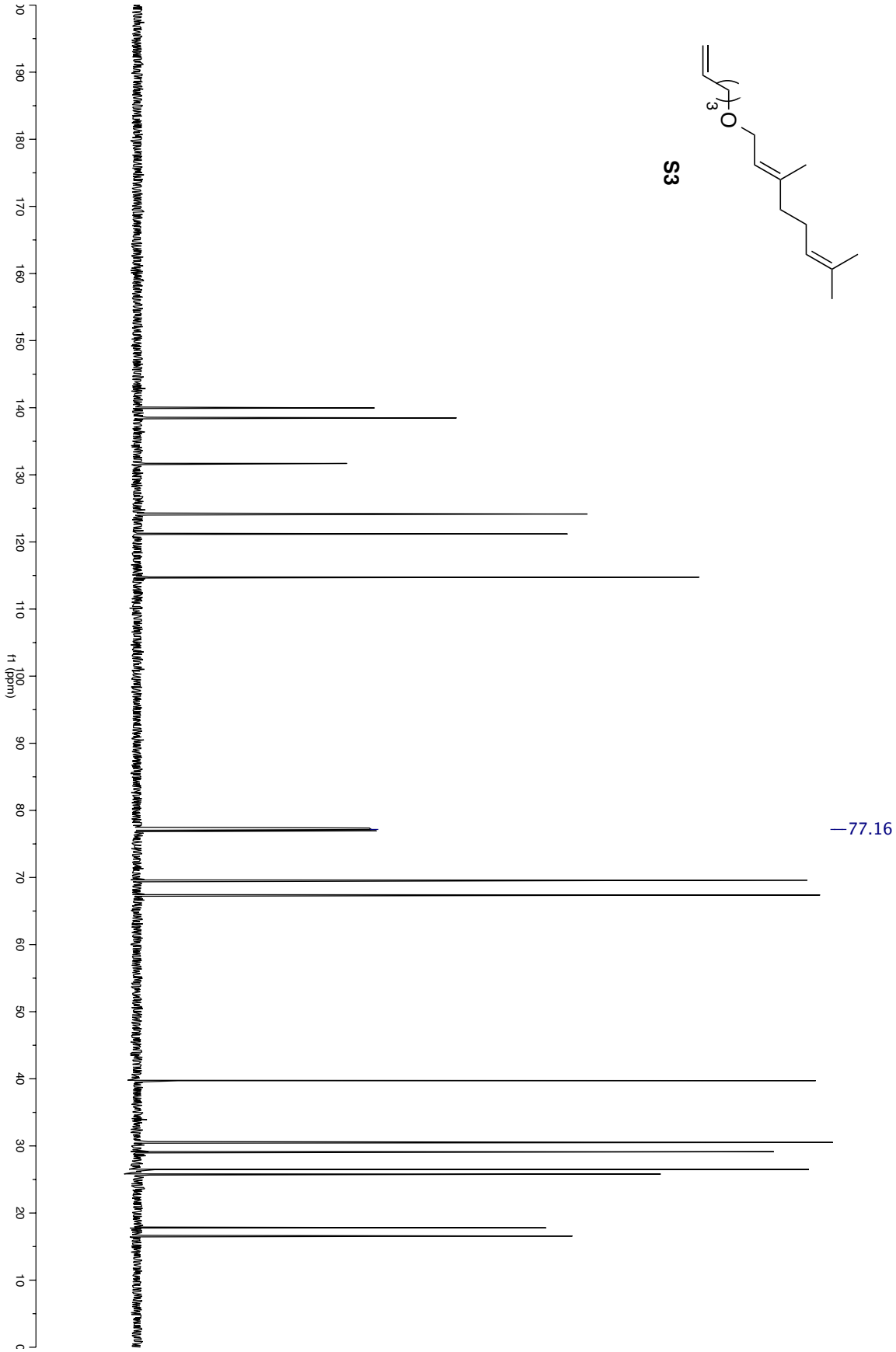
0.0021 mmol, 0.03 equiv). The vial was then sealed and allowed to stir for 18 hours. The reaction vial was removed from the dry box and exposed to air, then concentrated *in vacuo* and the mixture was purified by silica gel chromatography (hexanes:EtOAc, 100:0-96:4) which afforded the title compound as a colorless solid (16.8 mg, 0.0559 mmol, 77% yield). **IR (neat):** 2922 (m), 1724 (s), 1632 (m), 1583 (s), 1382 (m), 1341 (s), 1259 (s), 1135 (s), 963 (s), 492 (w); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.24 (ddd, *J* = 15.4, 11.5, 0.8 Hz, 1H), 7.42 – 7.37 (m, 2H), 7.25 – 7.22 (m, 1H), 7.16 – 7.13 (m, 2H), 7.03 – 6.97 (m, 1H), 6.17 (dt, *J* = 15.4, 0.8 Hz, 1H), 5.90 (dt, *J* = 13.3, 0.8 Hz, 1H), 1.30 (s, 12H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.5, 151.0, 146.5, 145.7, 129.5, 125.8, 124.0, 121.7, 83.9, 25.0; **HRMS (DART) $[M+H]^+$** calcd for $C_{17}H_{22}BO_4$: 301.1611, found: 301.1612; **Melting point:** 141 °C (decomp.).

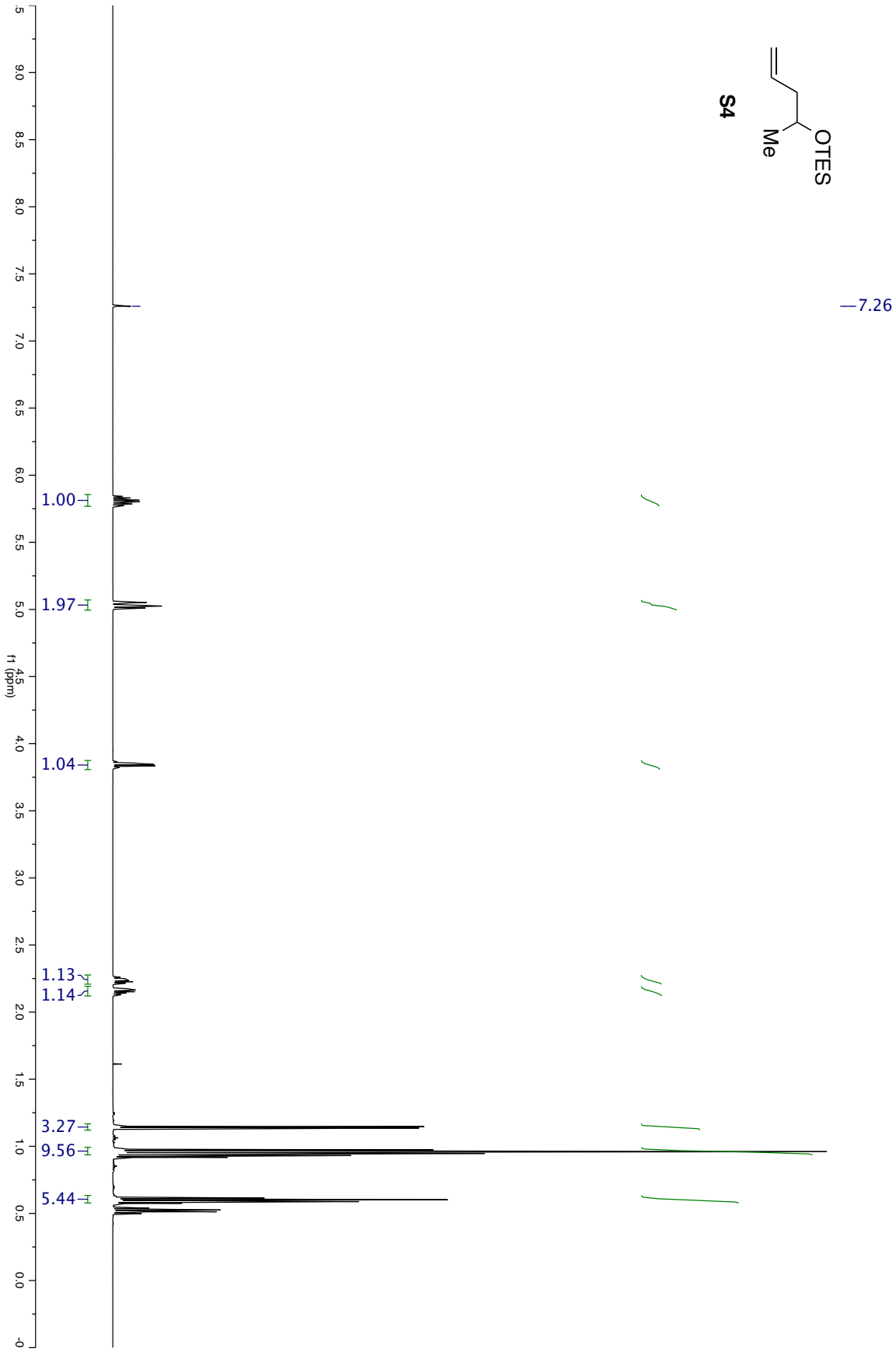

S2
5
TIPS
7.26
1.00
1.04
1.02
2.13
2.20
10.45
22.08
f1 (ppm)

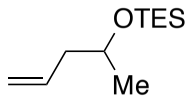


S2


S3
7.26
1.00
1.15
1.13
1.07
1.05
2.55
2.53
7.60
12.24
f1 (ppm)

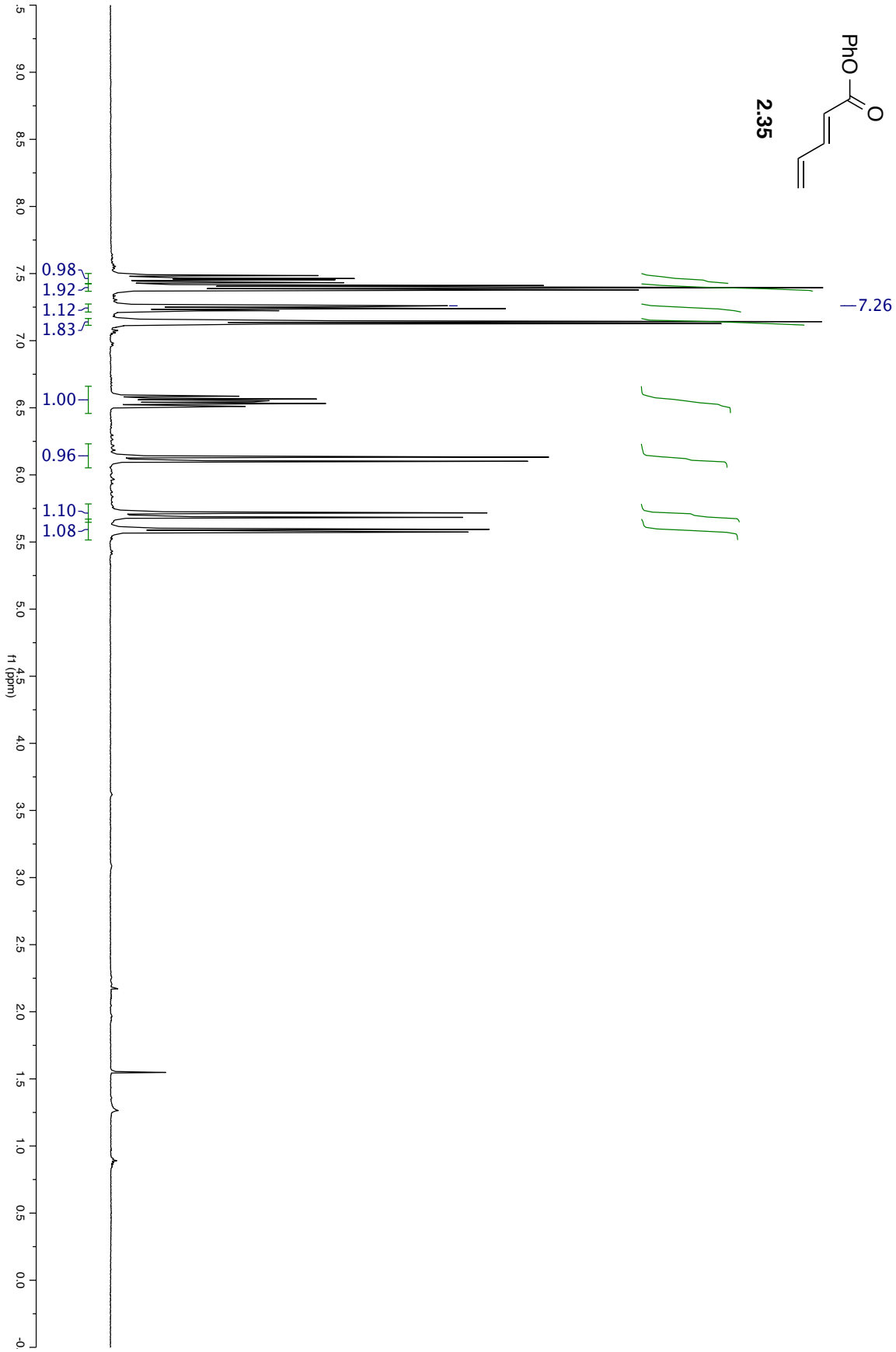

S3
O
3
77.16
f1 (ppm)

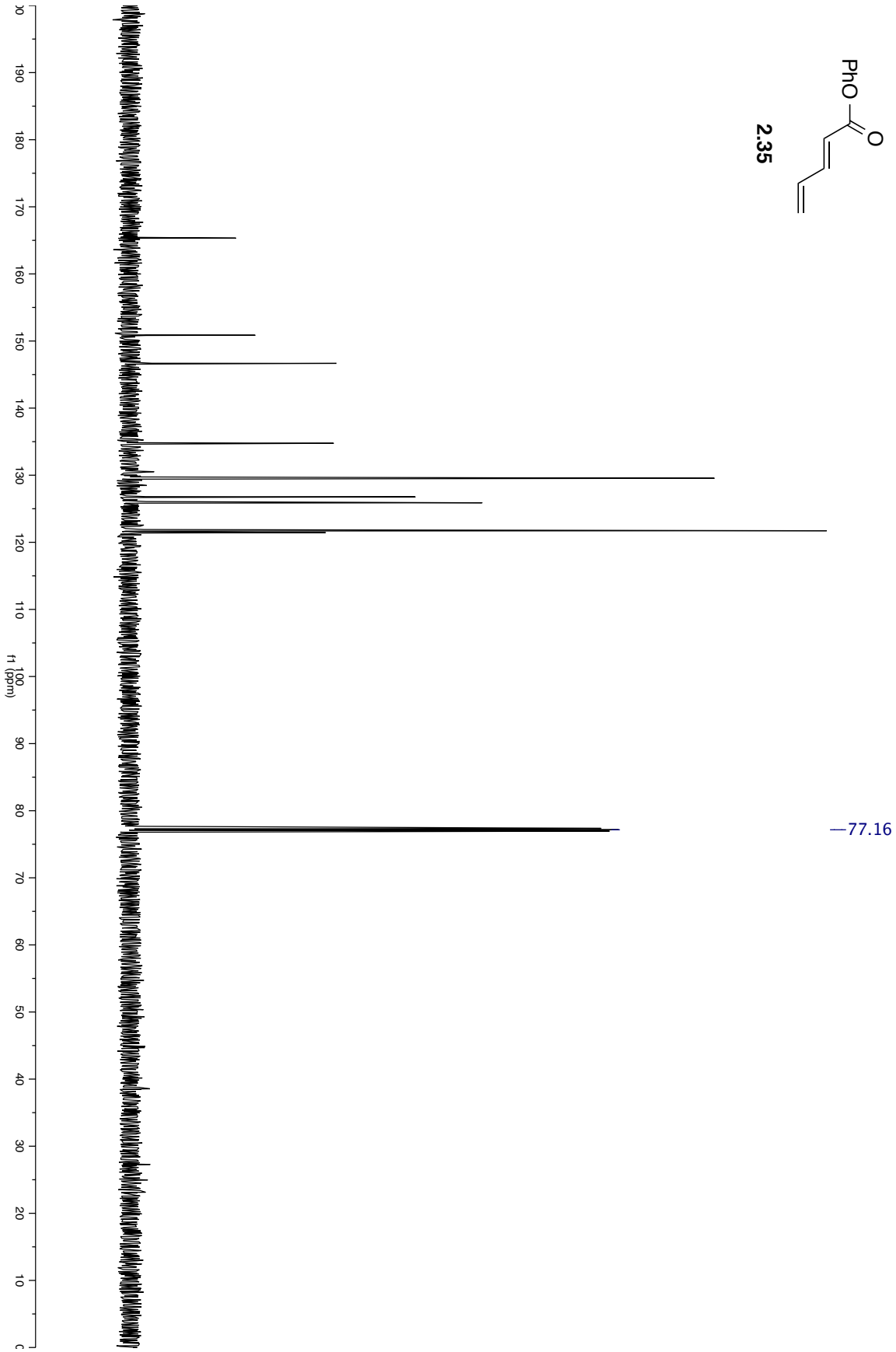

S4
OTES
Me
7.26
1.00
1.97
1.04
1.13
1.14
3.27
9.56
5.44
f1 (ppm)

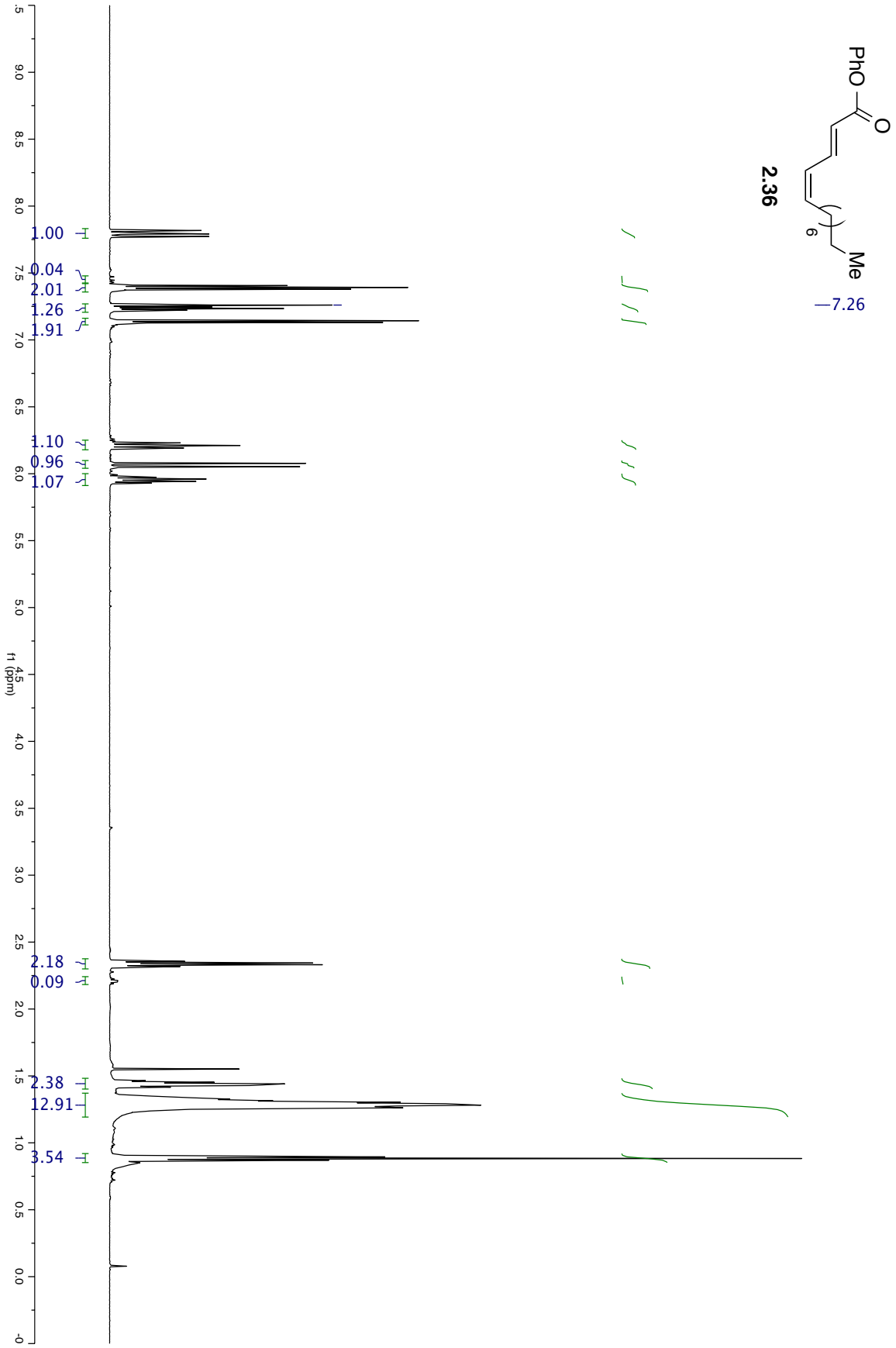

OTES
Me

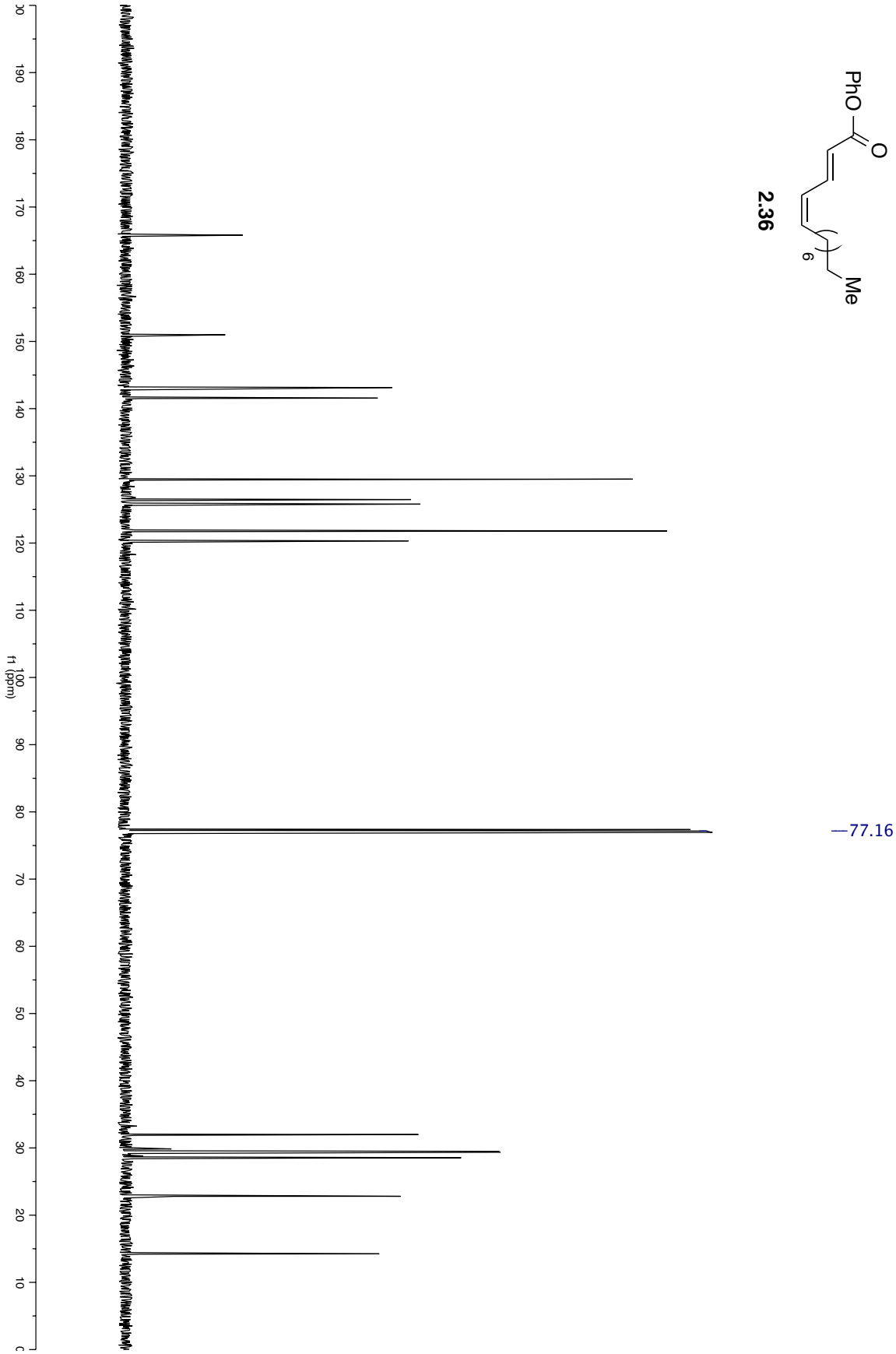
S4

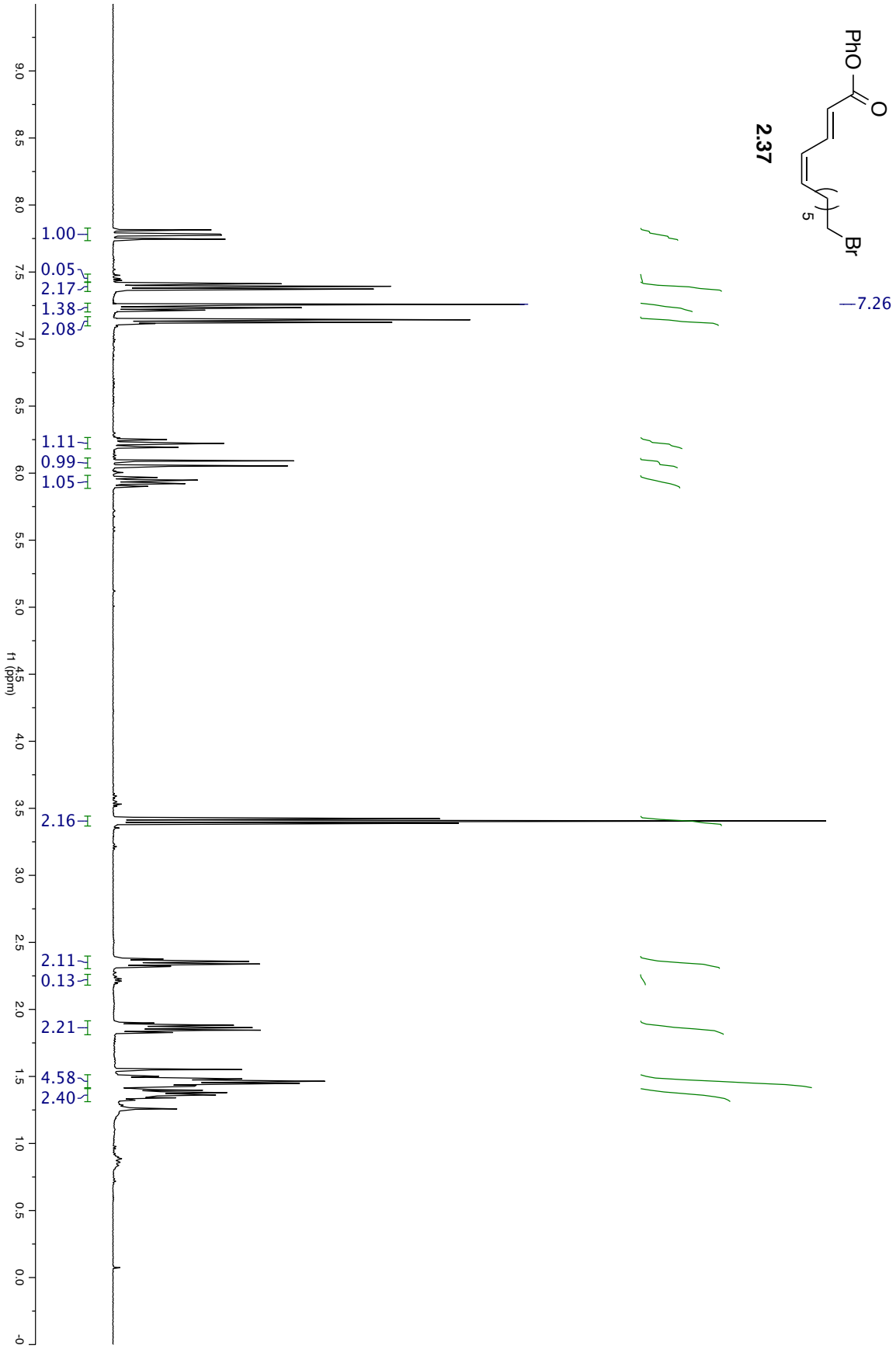
77.16
77
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

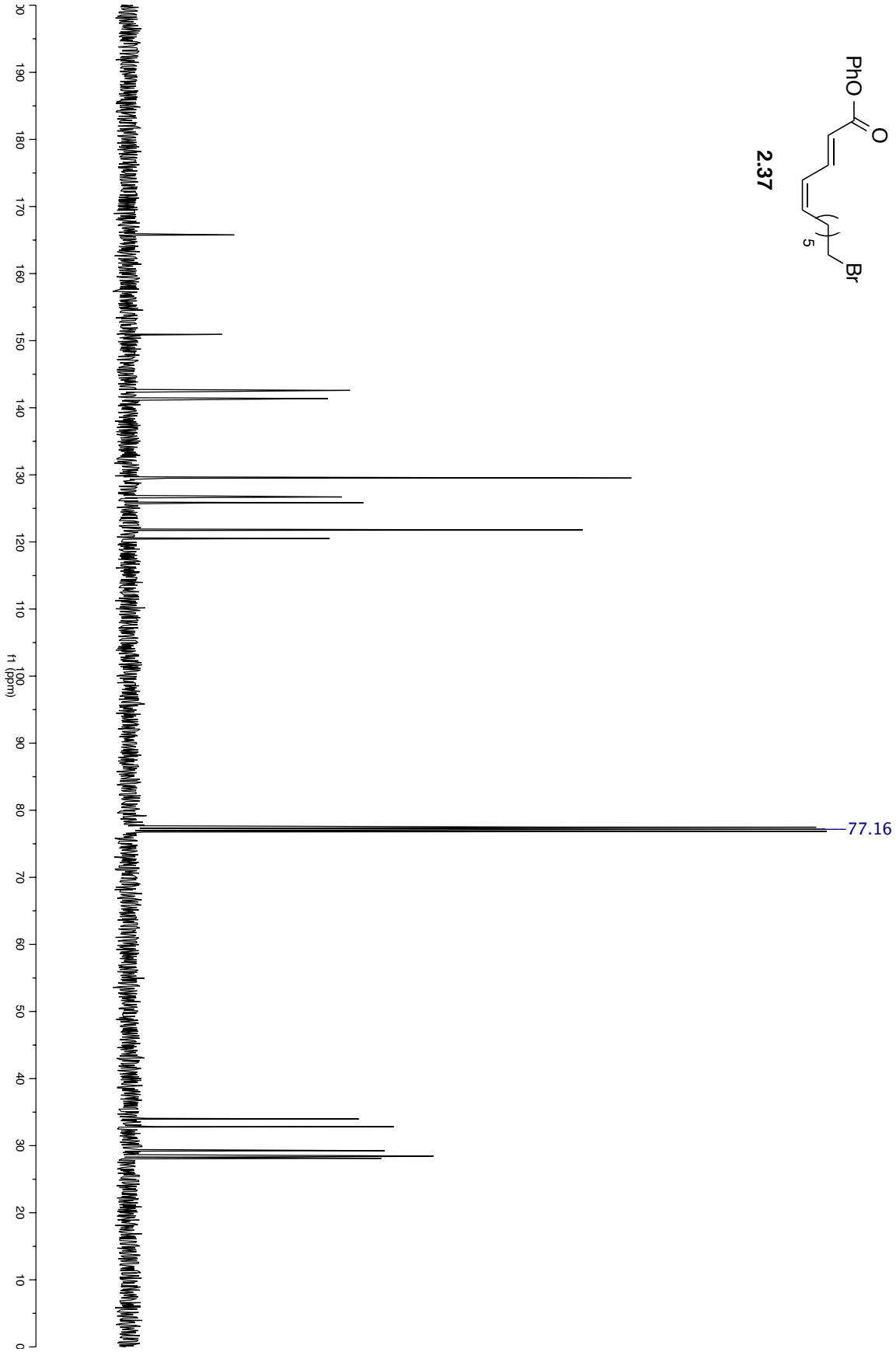

2.35
PhO
O
0.98
1.92
1.12
1.83
1.00
0.96
1.10
1.08
7.26
f1 (ppm)

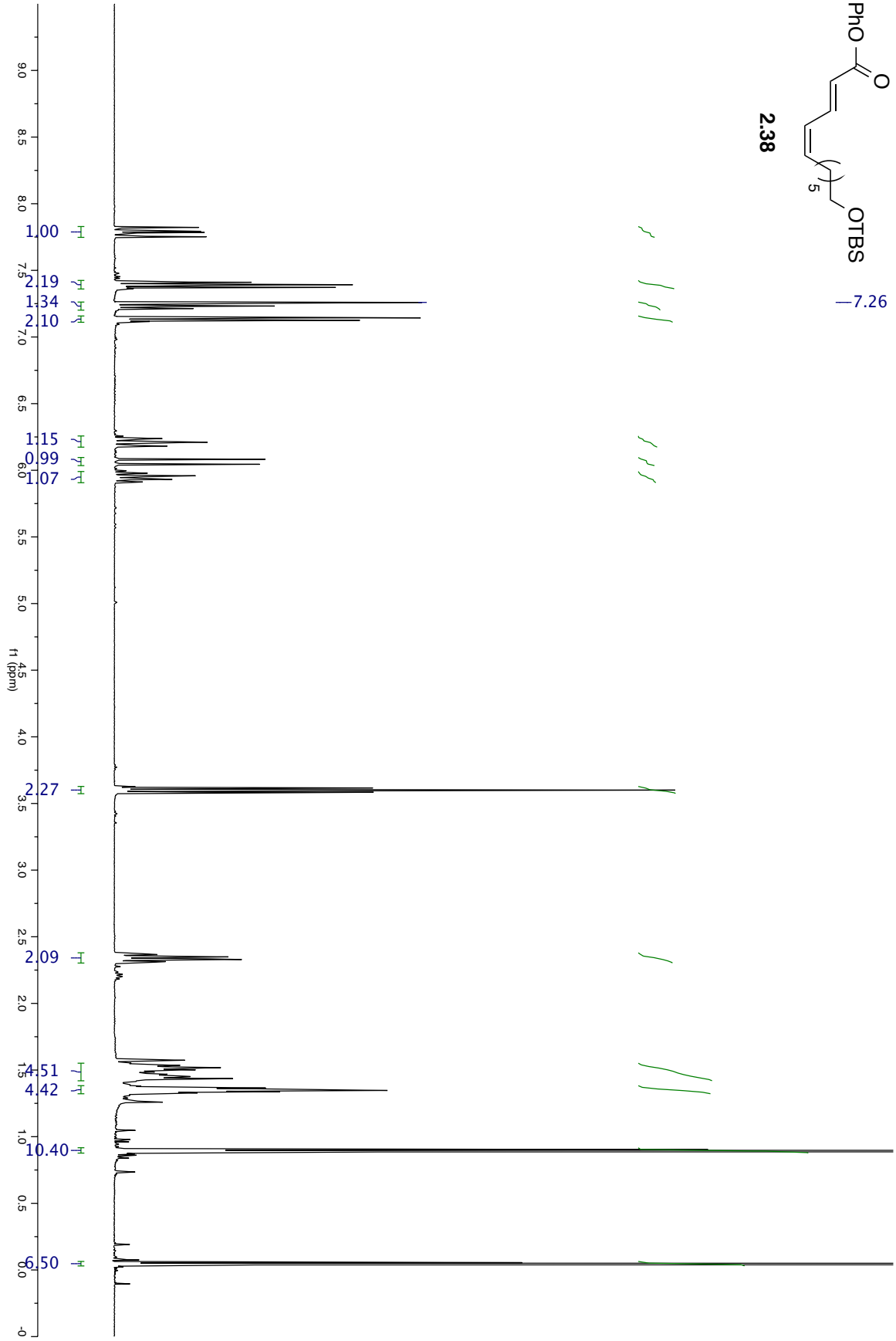

PhO
O
2.35
77.16
f1 (ppm)

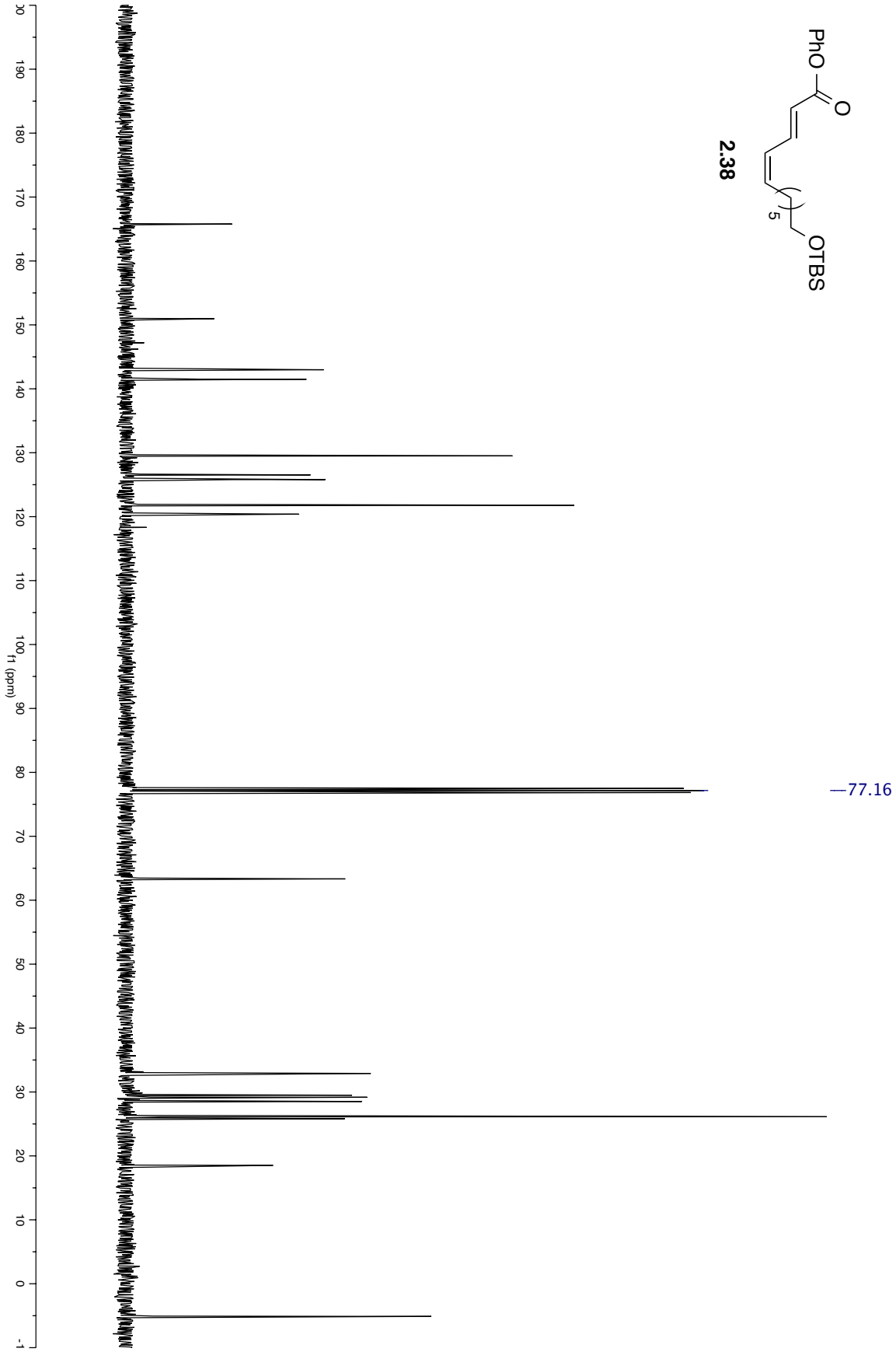

PhO
O
Me
6
2.36
7.26
1.00
0.04
2.01
1.26
1.91
1.10
0.96
1.07
2.18
0.09
2.38
12.91
3.54
f1 (ppm)

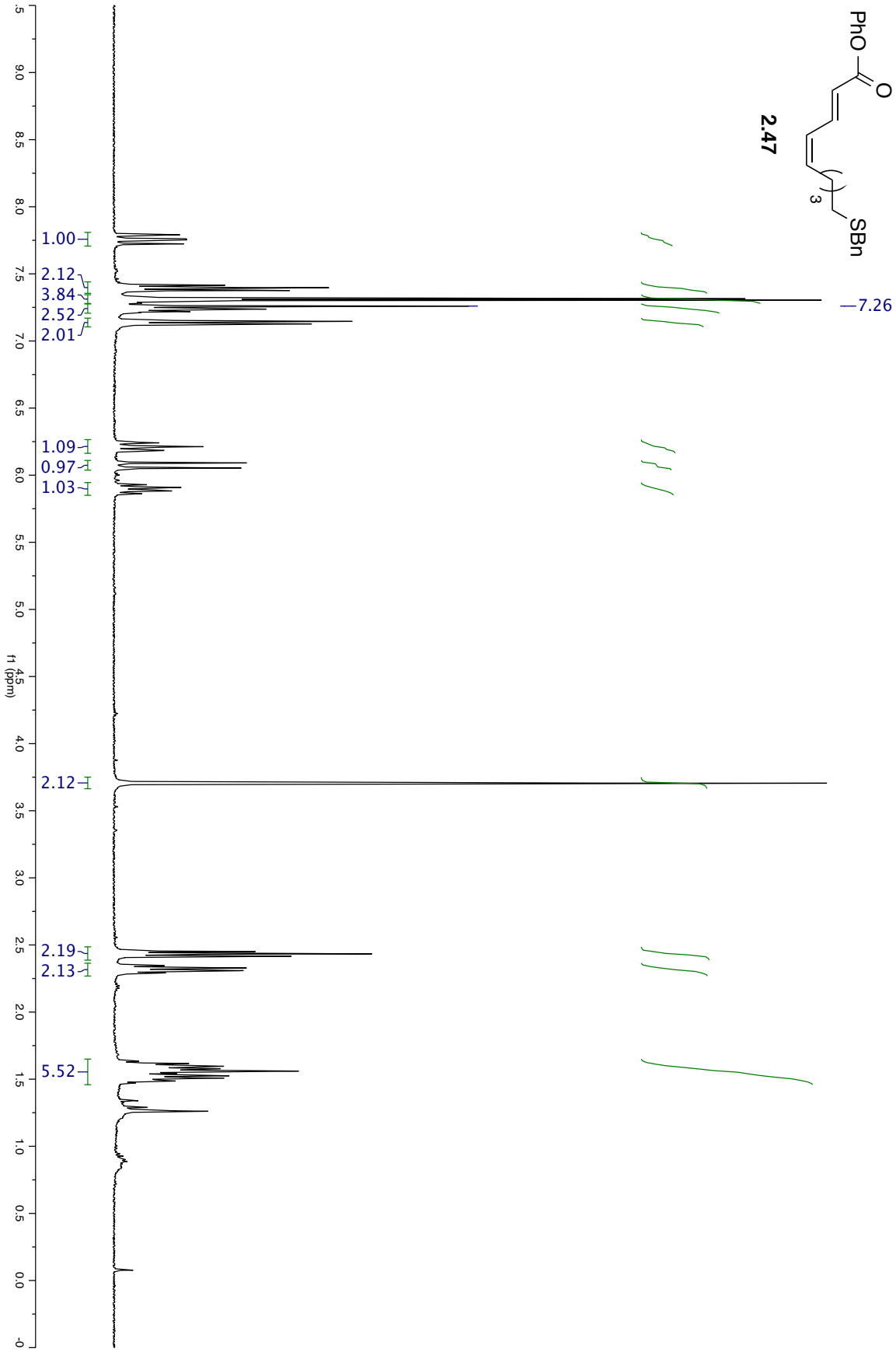

PhO
O
6
Me
2.36
77.16
f1 (ppm)

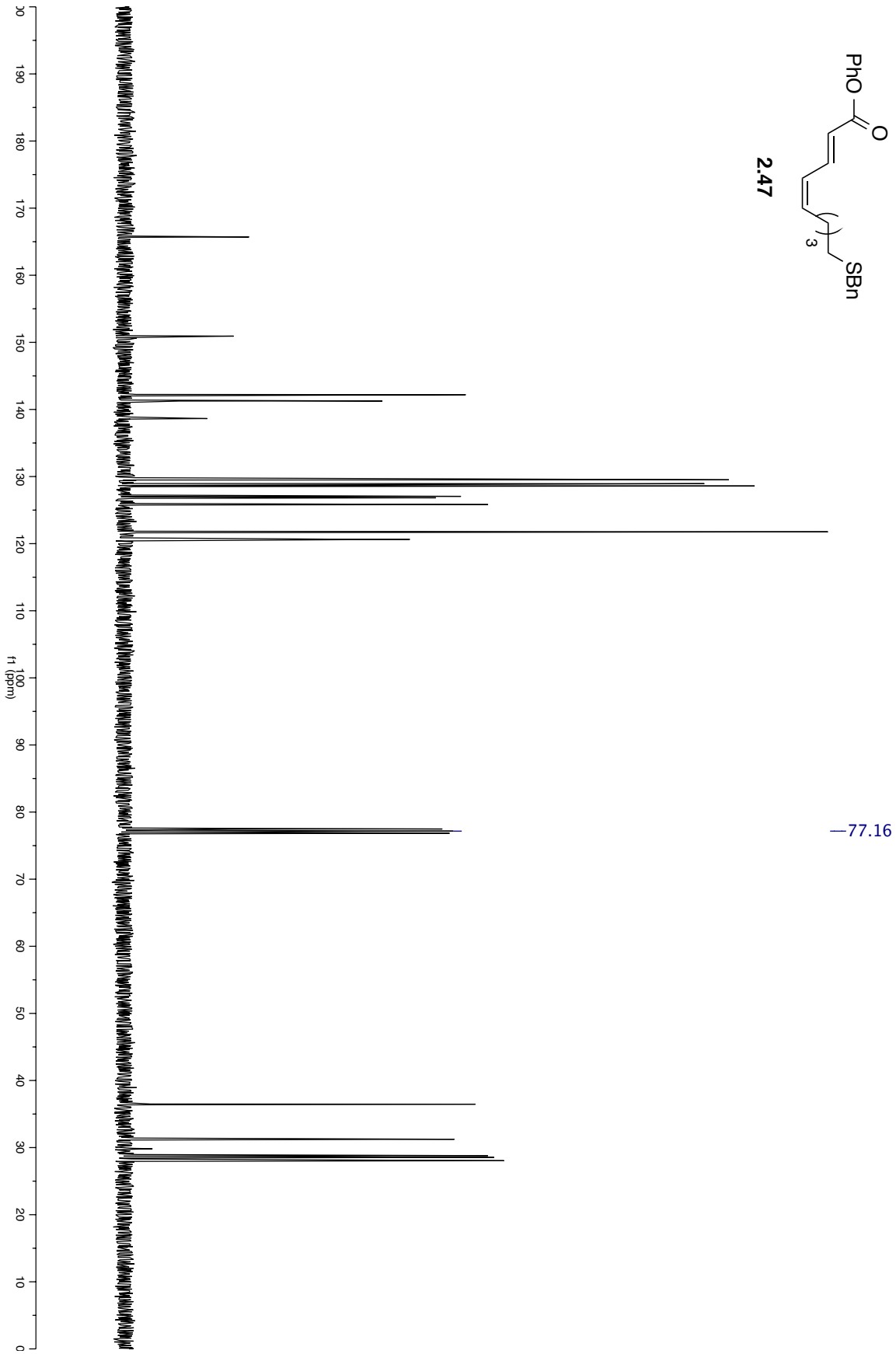

PhO
O
5
Br
2.37
7.26
1.00
0.05
2.17
1.38
2.08
1.11
0.99
1.05
2.16
2.11
0.13
2.21
4.58
2.40
f1 (ppm)

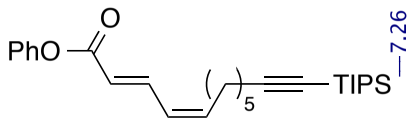

PhO
O
5
Br
2.37
77.16
f1 (ppm)


PhO
O
5
OTBS
2.38
7.26
1.00
2.19
1.34
2.10
1.15
0.99
1.07
2.27
2.09
4.51
4.42
10.40
6.50
f1 (ppm)

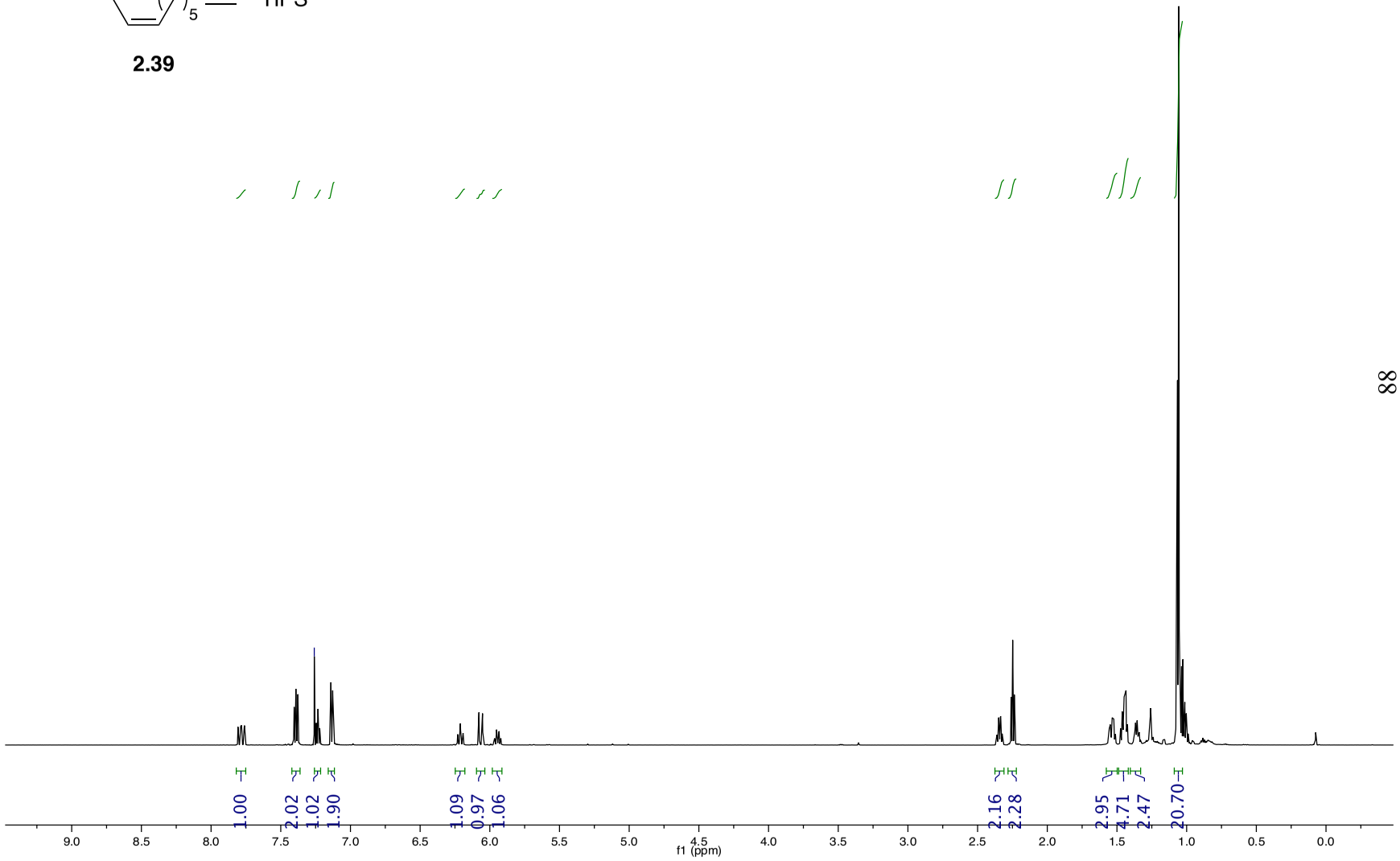

PhO
O
5
OTBS
2.38
77.16
f1 (ppm)

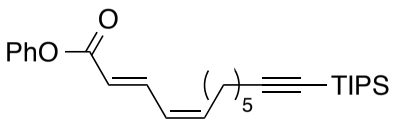

PhO
O
3
SBn
2.47
1.00
2.12
3.84
2.52
2.01
1.09
0.97
1.03
2.12
2.19
2.13
5.52
7.26
f1 (ppm)


PhO
O
3
SBn
2.47
77.16
f1 (ppm)

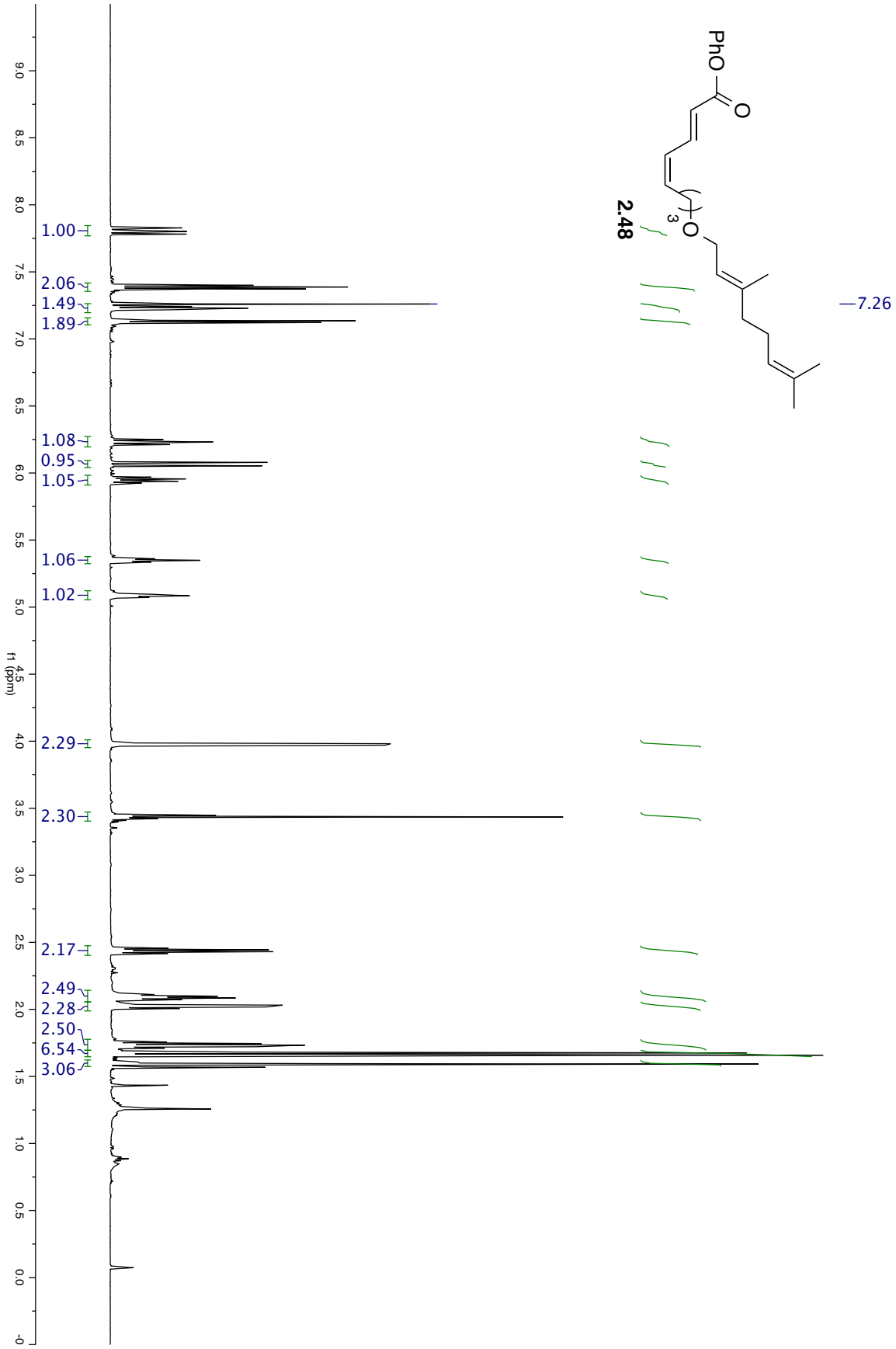

O
PhO
5
TIPS
7.26

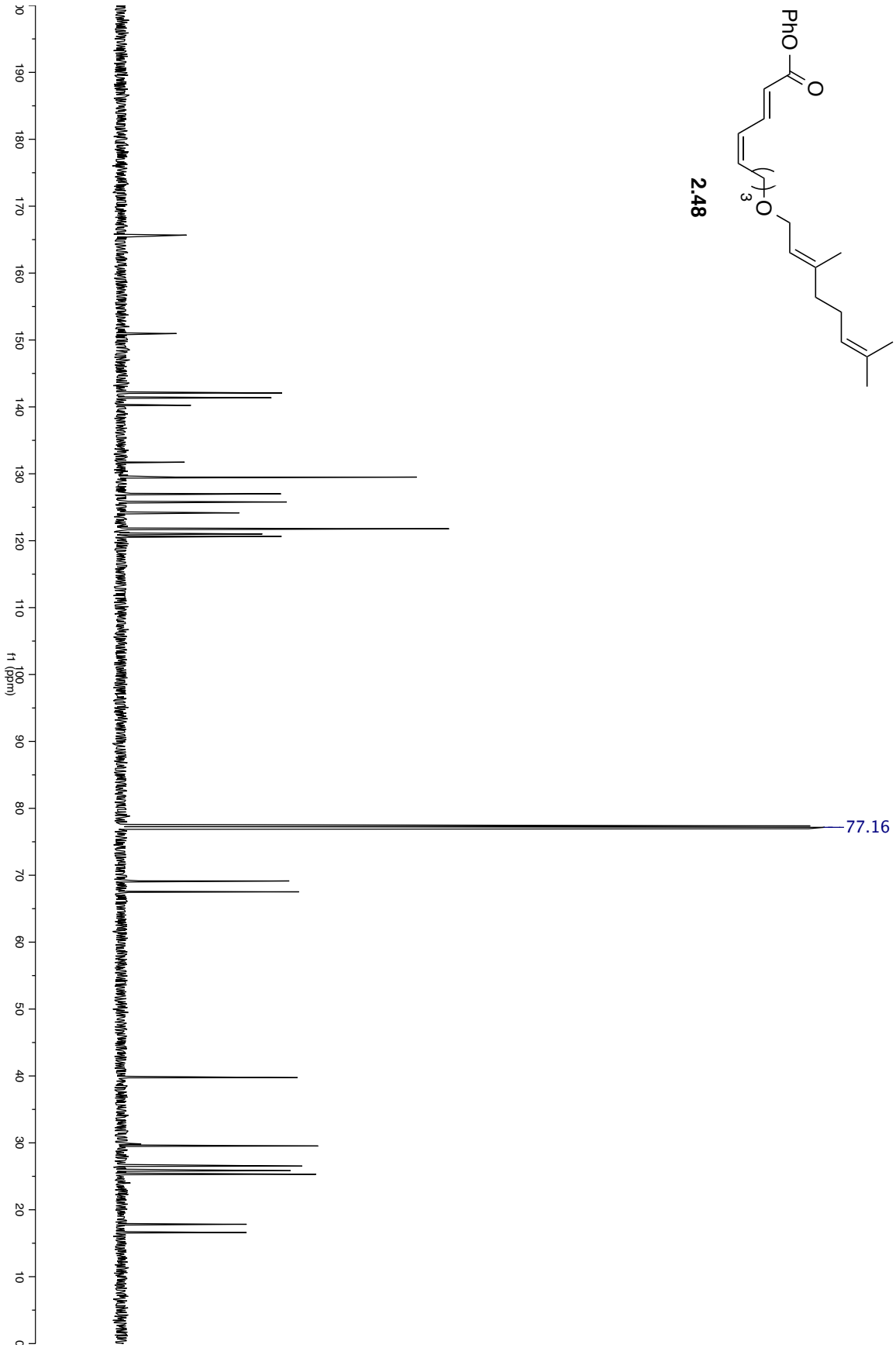
2.39

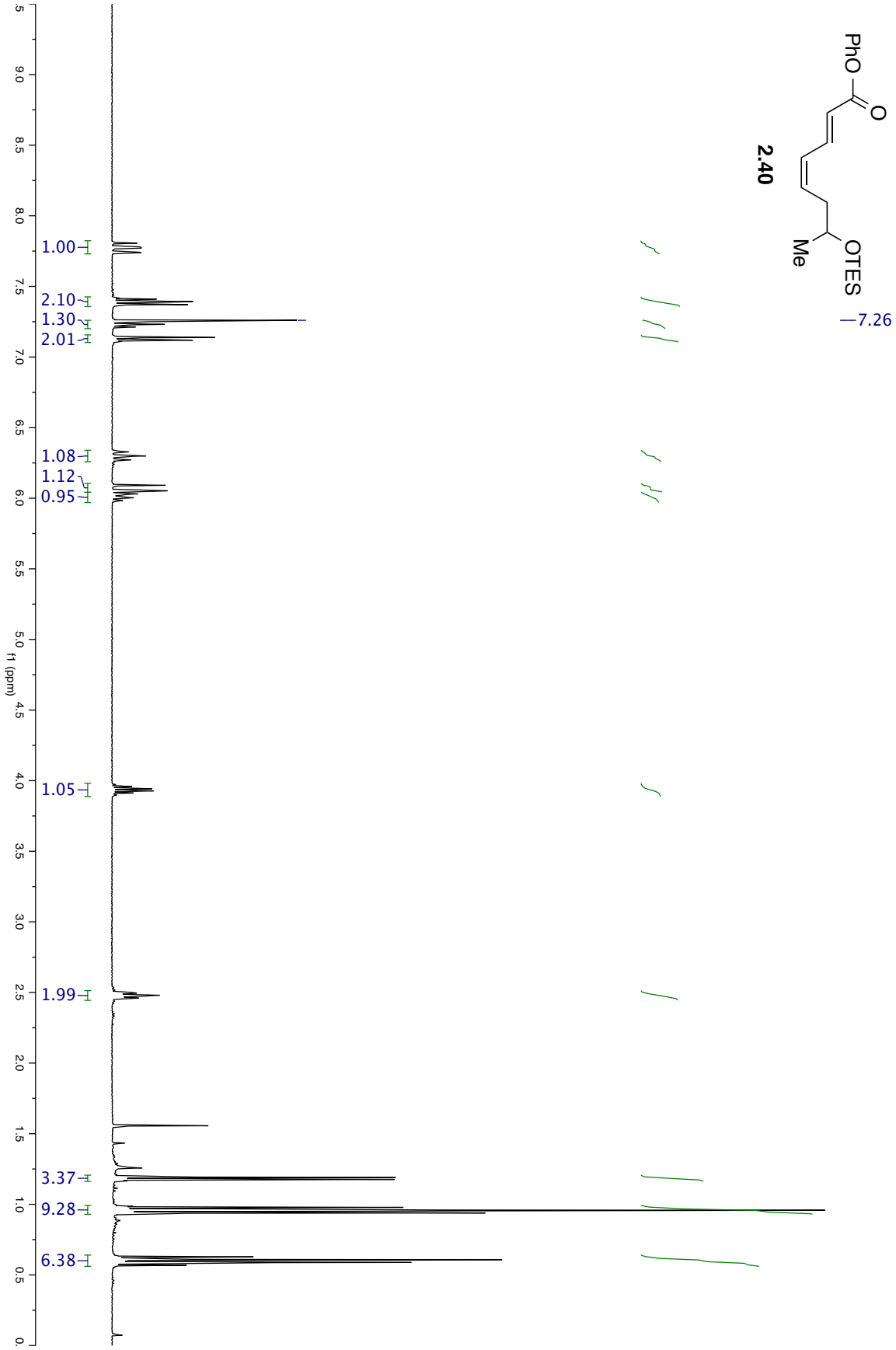

1.00
2.02
1.02
1.90
1.09
0.97
1.06
2.16
2.28
2.95
4.71
2.47
20.70
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

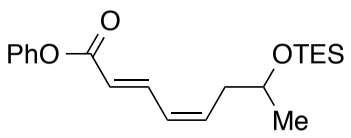


2.39

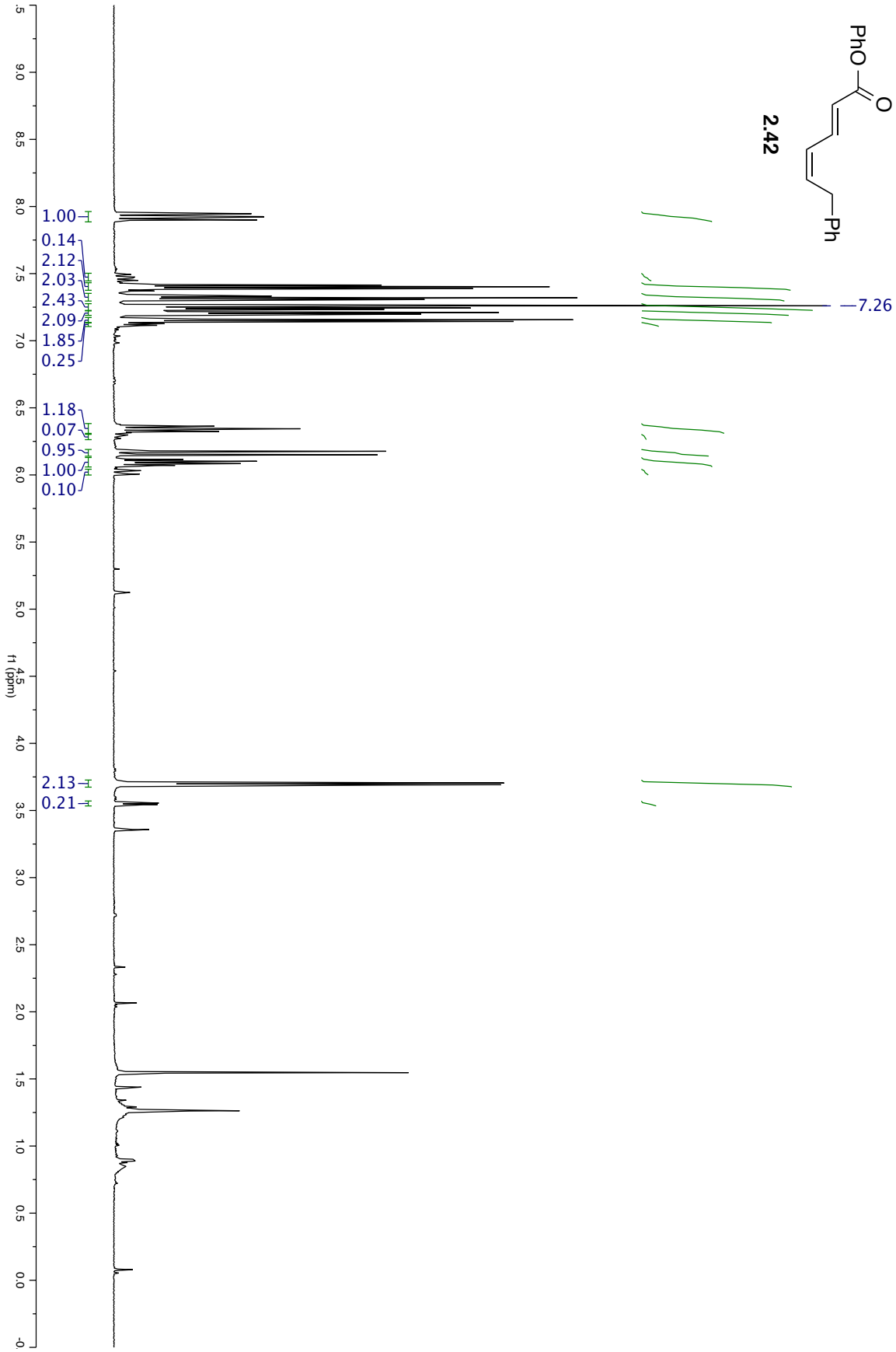

PhO
O
O
3
O
2.48
7.26
1.00
2.06
1.49
1.89
1.08
0.95
1.05
1.06
1.02
2.29
2.30
2.17
2.49
2.28
2.50
6.54
3.06
f1 (ppm)

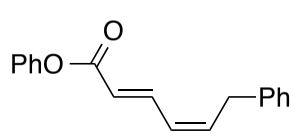

PhO
O
O
3
2.48
77.16
f1 (ppm)


PhO
O
OTES
Me
2.40
7.26
1.00
2.10
1.30
2.01
1.08
1.12
0.95
1.05
1.99
3.37
9.28
6.38
f1 (ppm)



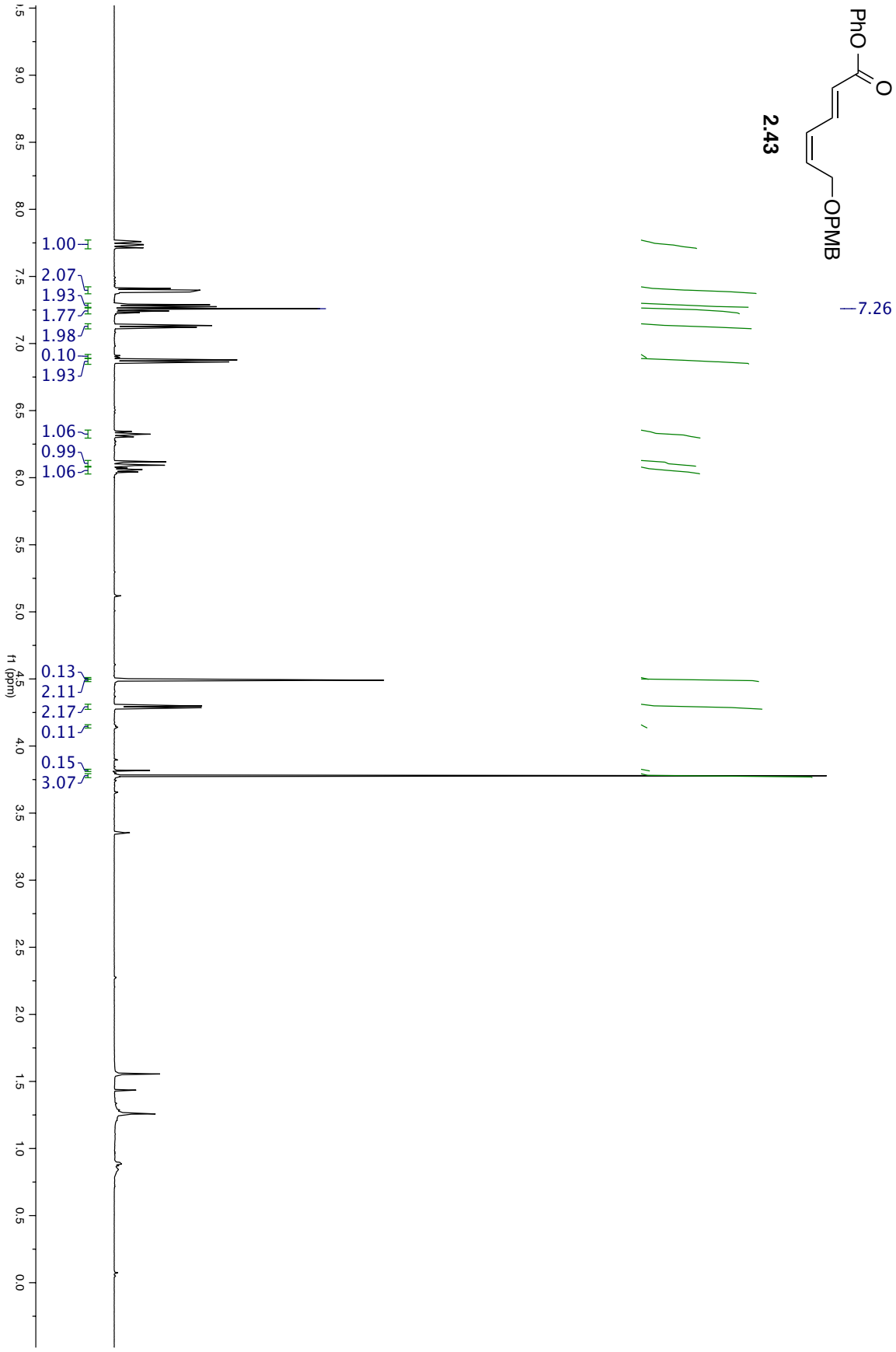
2.40

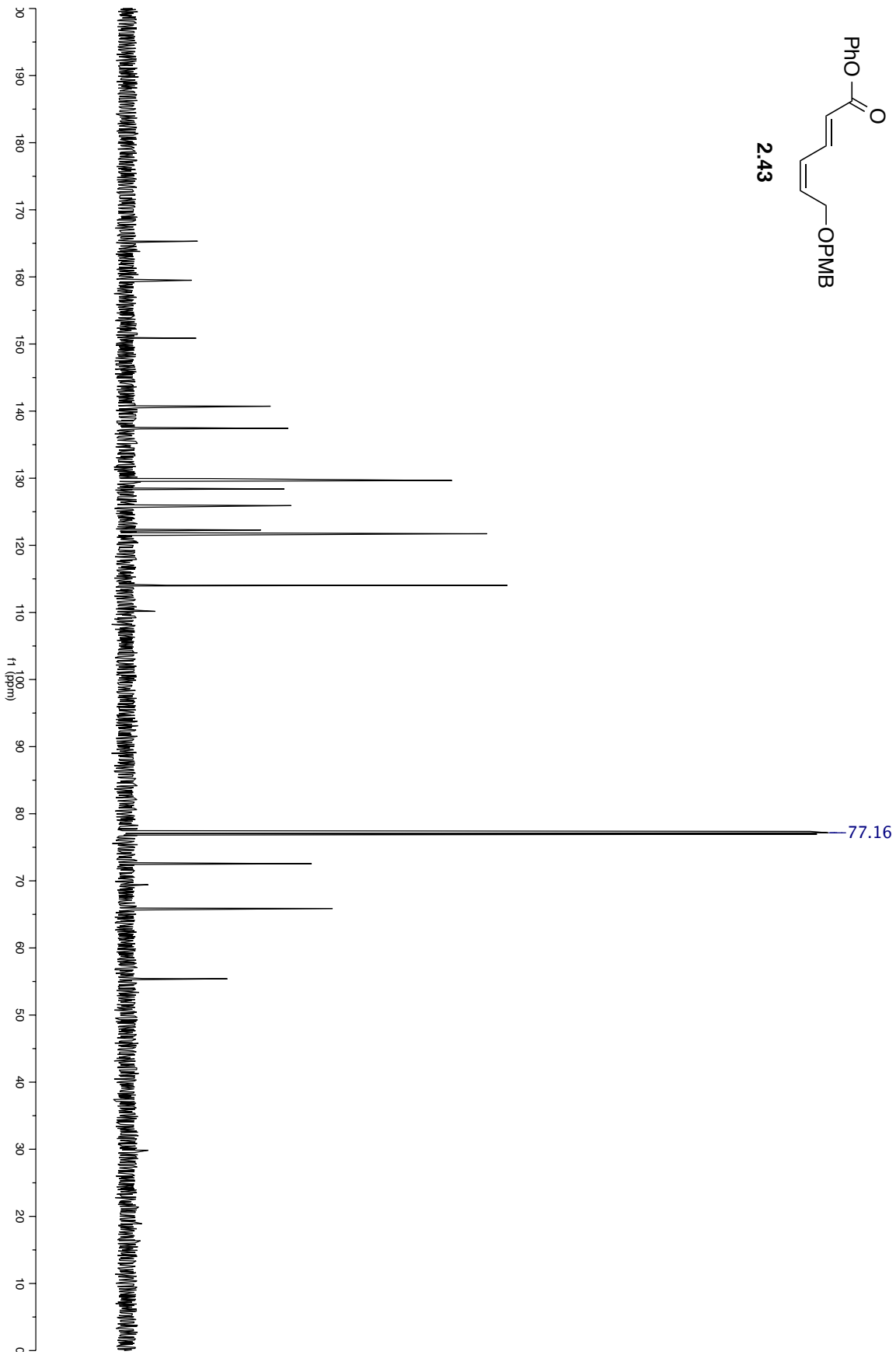

PhO
O
Ph
2.42
1.00
0.14
2.12
2.03
2.43
2.09
1.85
0.25
1.18
0.07
0.95
1.00
0.10
2.13
0.21
7.26
f1 (ppm)

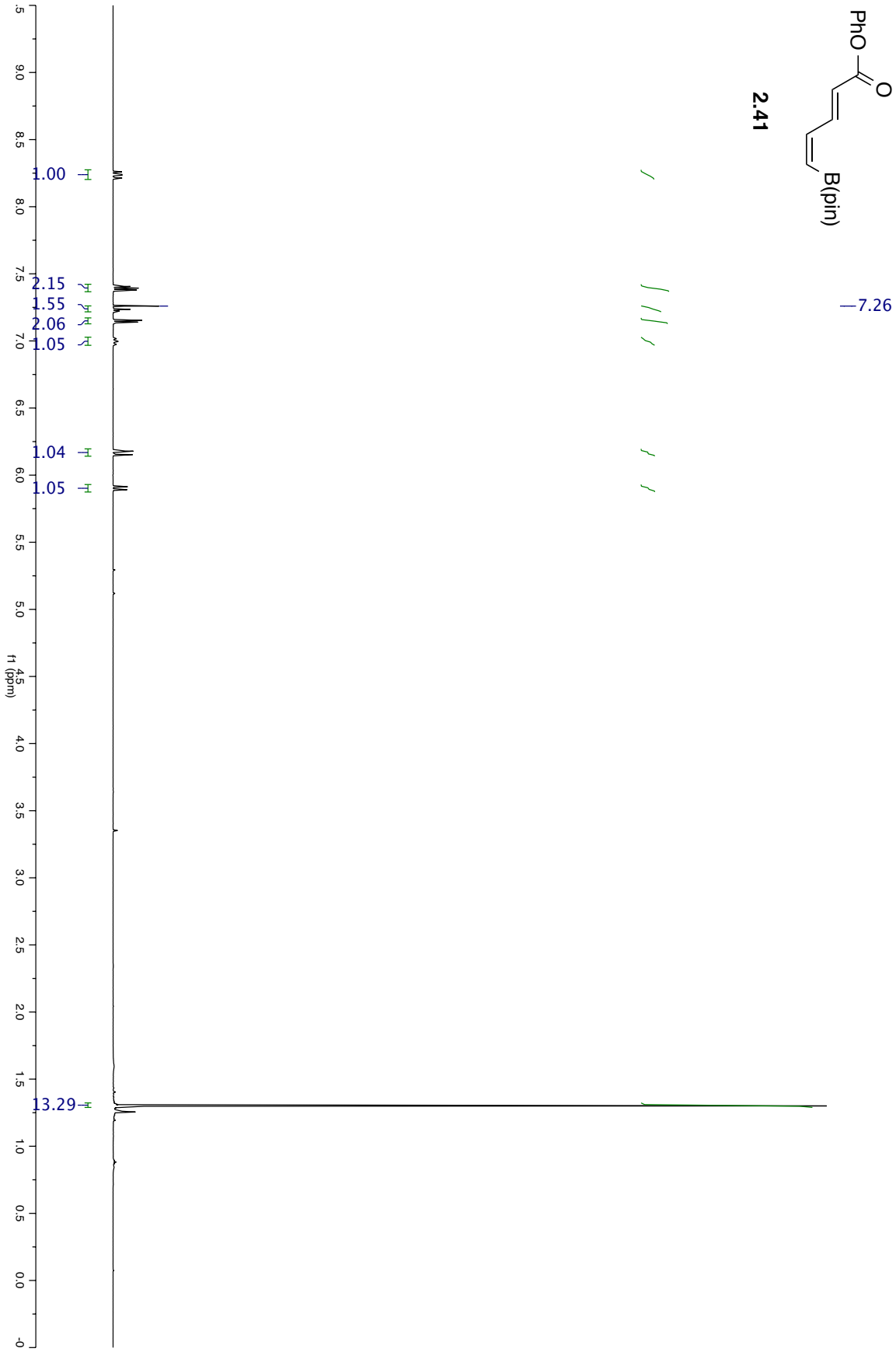

O
PhO
Ph

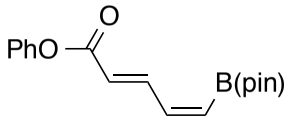
2.42

77.1601
190
180
170
160
150
140
130
120
110
100
f1 (ppm)
90
80
70
60
50
40
30
20
10


PhO
O
OPMB
2.43
7.26
1.00
2.07
1.93
1.77
1.98
0.10
1.93
1.06
0.99
1.06
0.13
2.11
2.17
0.11
0.15
3.07
f1 (ppm)


PhO
O
OPMB
2.43
77.16
f1 (ppm)


PhO
O
B(pin)
2.41
1.00
2.15
1.55
2.06
1.05
1.04
1.05
13.29
7.26
f1 (ppm)


O
PhO
B(pin)

2.41

77.16
190
180
170
160
150
140
130
120
110
100
f1 (ppm)
90
80
70
60
50
40
30
20
10