Spring 2020

Allylic Benzoate Reductions: A Study on Stereospecificity

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Allylic Benzoate Reductions:
A Study on Stereospecificity

By

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Accepted in Partial Completion
of the Requirements for the Degree
Master of Science

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Master's Thesis

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Michael A. Leitch

Date

May 29th, 2020

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A Thesis
Presented to
The Faculty of
Western Washington University

In Partial Fulfillment
Of the Requirements for the Degree
Master of Science

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Abstract

Herein we report results from experiments aimed at better understanding $SmI_2(H_2O)_n$ reductions of allylic benzoates adjacent to a trisubstituted alkene. When flanked by both a chelating group and stereodirecting group, these reactions can occur with complete regioselectivity and good diastereoselectivity (up to 90:10). Initial experiments suggested that the reaction was stereospecific to alkene geometry. However, further experimentation has revealed that the alkene stereospecificity is substrate dependent. For instance, if the geminal alkene substituents are alkyl, results show the reaction to be stereospecific, but if one of the substituents is a phenyl group the reaction is still stereoselective but not stereospecific. This was demonstrated through the synthesis and subsequent $SmI_2(H_2O)_n$ reduction of a series of *cis*- and *trans*-allylic benzoate isomers followed by careful analysis of the product mixtures by ^{1}H NMR. To explain these results our current working hypothesis is based on formation of an η^3-organosamarium bicyclic intermediate. In some cases, C-C bond rotation in the pi-allyl intermediate relieves steric strain, leading to a loss in stereospecificity.

Acknowledgements

Research Advisor

Dr. Gregory W. O'Neil

Thesis Committee

Dr. James Vyvyan

Dr. John Gilbertson

Instrumentation

Dr. Hla Win-Piazza

Sam Danforth

And to my family who helped me succeed so far in life as it would have been impossible without them.

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Chapter 1: Introduction

1.1 The Importance of Stereocenters and Enantioselectivity.

The biological function of many organic molecules is strongly related to their three-dimensional structure. Stereocenters comprised of a central carbon atom with four different substituents play an important role in dictating the three-dimensional shape of the organic molecules. By swapping two of the substituents, the three-dimensional space of the molecules is changed. Stereocenters are a key structural component, making up the sugars and proteins that create organic life and the way they interact with other molecules is intrinsically tied to their stereochemistry.

In the synthesis of pharmaceutical compounds stereochemistry is monitored meticulously. If stereochemistry is ignored, it could lead to drastic effects such as in the case of the over-the-counter drug Naproxen. Originally synthesized in 1970 by Harrison et al. they reported *(S)*-Naproxen (Figure 1) as the major enantiomer with anti-inflammatory activity.[1] Since then it has become widely known that the *(R)*-enantiomer holds little therapeutic effect and instead acts as a liver toxin. Contamination of the therapeutic *(S)*-Naproxen with *(R)*-Naproxen could cause needless liver injury, making the synthesis and isolation of *(S)*-Naproxen imperative. Many of the original syntheses of *(S)*-Naproxen involved making a 50:50 mixture of *(S)*-Naproxen and *(R)*-Naproxen. These 50:50 mixtures of enantiomers are known as a racemate or a racemic mixture. The Naproxen racemic mixture is then resolved using cinchonidine or *n*-alkylglucamine.[2] Then as time progressed, enantioselective syntheses were introduced as they avoid purification costs and improve yield.[3]

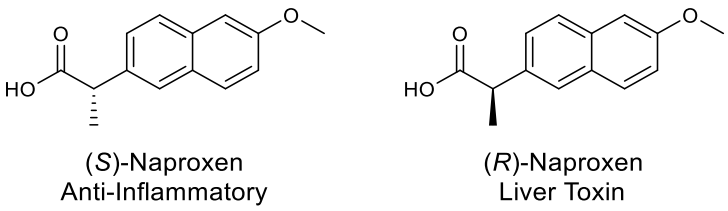


Figure 1. Structure of Naproxen enantiomers

Another example of how important stereochemistry is in medicine is the drug Thalidomide (Figure 2). Thalidomide was prescribed as a racemate and seen as a relatively safe drug with no confirmed deaths from overdose even with an observed 14 gram overdose where the patient made a full recovery.[4] Thalidomide was available for pregnant women as a treatment for morning sickness and recalled in 1961 after over 5000 cases of birth-defects were reported with pregnant women taking Thalidomide.[5] It was later found by Blaschke *et al.* that the S-enantiomer of Thalidomide was the teratogen responsible for the terrifying birth defects.[6] Blaschke et al. also supported the idea that *(R)*-Thalidomide was safe but later it would be determined that *(R)*-Thalidomide readily isomerizes to the *(S)*-isomer under biological conditions.[7,8] After this catastrophe, the United States Food and Drug Administration introduced a new amendment that required drug manufacturers prove that their medicines were safe and effective at what they claimed.[9]

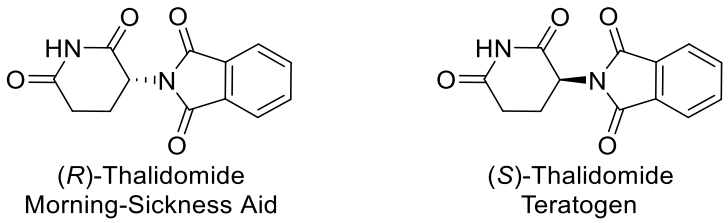


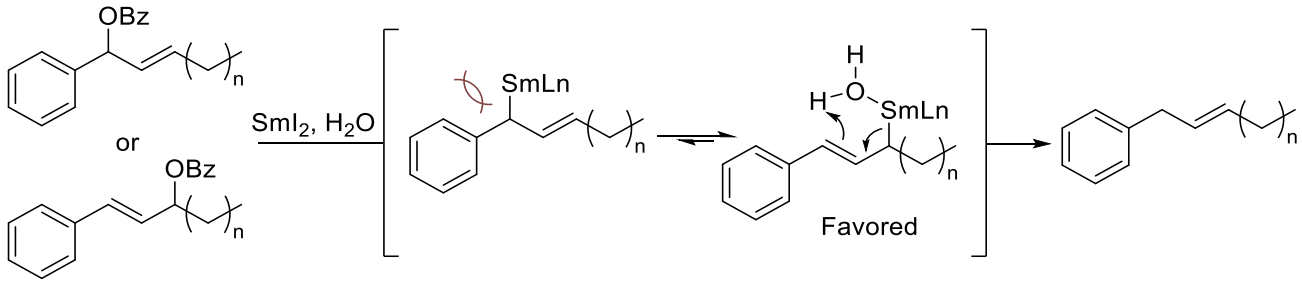
Figure 2. Structure of Thalidomide enantiomers

1.2 Development of Samarium Di-Iodide Mediated Allylic Benzoate Reductions

In 1977, samarium diiodide was discovered as a novel reagent with synthetic utility for its reducing and coupling abilities.[10,11] Since then, samarium diiodide has been found to have wide applications in enantioselective synthesis, in part due to the tunability of the reagent. With various additives such as hexamethylphosphoramide (HMPA), N,N′-dimethylpropyleneurea (DMPU), and alcohols the reduction potential, chemoselectivity, and rate of the reaction can be manipulated.[12–15] Samarium diiodide is popular for its use in the Barbier and Reformatsky reactions as well as radical cyclization reactions,[16,17] and has been used extensively in total synthesis.[18–26] Samarium diiodide is also known for being less toxic and safer to use than other SET reagents such as tributyl tin hydride or sodium amalgam.[27,28]

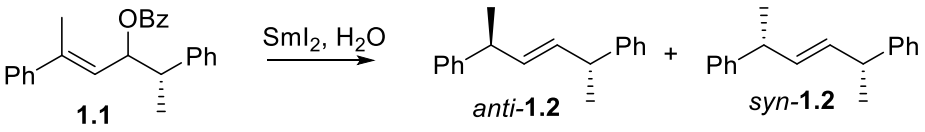
In 2013, the O'Neil group began investigating samarium diiodide reductions of allylic benzoates. Specifically, they showed that aromatic allylic benzoates could be selectively eliminated and isomerized with samarium diiodide (SmI_2) to form non-conjugated alkene products.[29] The regioselectivity of SmI_2 allylic benzoate reductions is rationalized through steric hindrance of a theorized organosamarium intermediate that undergoes a pericyclic protonation as seen in Scheme 1. This work also showed that swapping the positions of the alkene and benzoyl group leads to the same products, suggesting that both converge to the same organo-samarium intermediate seen below.

Scheme 1. Reductions of aromatic allylic benzoates and the proposed intermediate by O'Neil. Adapted from reference.[29]



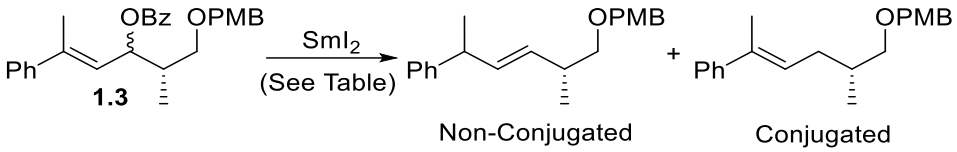
The O'Neil group saw the possible application of this reaction for the creation of a new stereocenter. If the starting material contained a tri-substituted alkene such as compound **1.1**, then subsequent reduction with SmI_2 would lead to a new stereocenter. Indeed, when treated with SmI_2, compound **1.1** gave the expected product **1.2** containing a new stereocenter, however a 1:1 mixture of diastereomers was obtained (Scheme 2).[30] With this result it was theorized that introducing a chelating atom would facilitate facial preference of proton delivery from the proposed organosamarium intermediate.

Scheme 2. Reduction of a substrate without a chelating group leads to no stereoselectivity.



To test this idea, compound **1.3** was synthesized and its reduction with SmI_2 was performed with various additives (Table 1).[31] Results showed some enhancement in the diastereoselectivity (up to 69:31), supportive of this hypothesis, and okay regioselectivity (< 5:1). It was hypothesized that the low chelating ability of the PMB-protected alcohol prevented higher d.r., consistent with a previous report from Keck and Wager who reported a loss in samarium chelation when reducing β-alkoxy ketones with a benzyl ether protecting group (Scheme 3).[32]

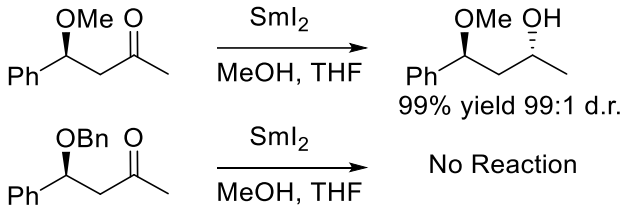
*Table 1. Initial screening of **1.3** reduction with SmI_2 in the presence of various additives. Adapted from reference.*[31]



Additive[a]	Non-Conjugated:Conjugated	Non-conjugated d.r.[b]
DMPU	1.3:1	60:40
t-BuOH	3:1	69:31
MeOH	3:1	60:40
H_2O	5:1	50:50

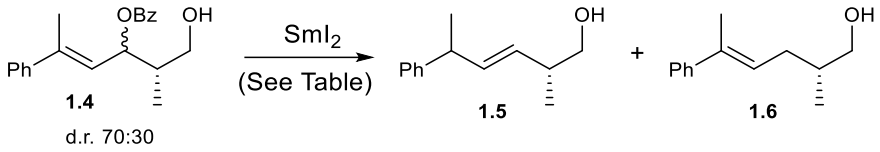
Notes for Table 1: [a]Reactions were performed by adding the additive (16 equiv. DMPU or 1400 equiv. ROH) to SmI2 (7 equiv.) followed by the substrate at room temperature. [b]Determined by NMR.

Scheme 3. Keck and Wager's reductions of β-alkoxy ketones also had low reactivity with benzyl ethers. Adapted from reference.[32]



Analogous to Keck and Wager's work, after the removal of the PMB protecting group and production of the free hydroxyl as a chelator, the O'Neil group was able to achieve complete regioselectivity (entries 2 and 5 in Table 2) and increase the d.r. up to 76:24 (Entries 5 and 7) for reductions of compound **1.4.**[31] Water as an additive gave the highest d.r. (76:24) and only made a nominal amount of the regioisomer. This was very desirable as water is readily available and non-toxic. In an attempt to improve the diastereoselectivity of the reaction further, the reaction was performed at 0 °C (Entry 6), however no significant change in d.r. was observed and there was a significant drop in regioselectivity (15:1 to 5:1).

*Table 2. Additive effects on SmI_2 reductions of compound **1.4**. Adapted from reference.*[31]



Entry	Additive[a]	**1.5 : 1.6**[b]	**1.5** d.r.[b]
1.	DMPU	2:1	75:25
2.	*t*-BuOH	1:0[c]	67:33
3.	*i*-PrOH	2.3:1	67:33
4.	MeOH	1:0[c]	60:40
5.	H_2O	15:1	76:24
6.	H_2O[d]	5:1	75:25

Notes for Table 2: [a]Reactions were performed by adding the additive (16 equiv. DMPU or 1400 equiv. ROH) to SmI_2 (7 equiv.) followed by the substrate and stirring for 30 min. [b]Determined by ^1H NMR. [c]1.6 was not detected by NMR. [d]Performed at 0 °C. [e]Compound 1.4 was used as a 1:1 mixture of diastereomers.

Since the hypothesized intermediate involves loss of the benzoyl group, it was predicted that the stereochemistry of the benzoyl group was inconsequential to the final products. To be sure, a comparison of two differently enriched diastereomeric starting materials were tested (Figure 3).[33] The results gave identical results, supporting the proposed mechanism (Scheme 4). As seen in the proposed mechanism, the formation of the allylic radical **1.4b** eliminates stereochemistry at this position. The allylic radical formation of **1.4b** is also thought to be the rate limiting step (RLS).[29]

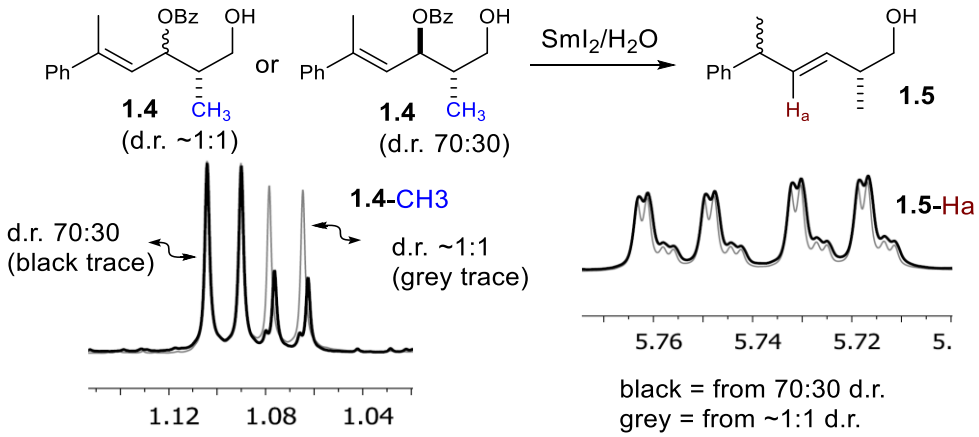
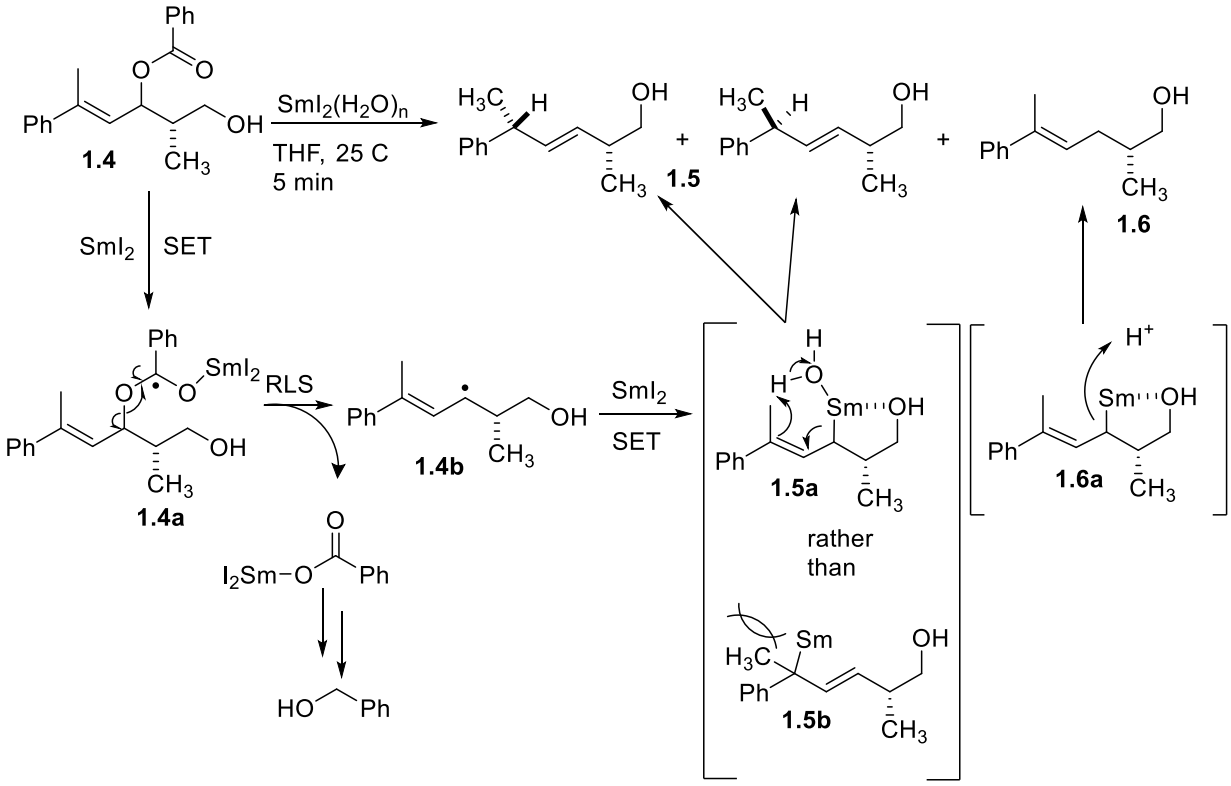


Figure 3. Effect of benzoyl stereochemistry on the stereoselectivity of $SmI_2(H_2O)_n$ reductions. Adapted from reference.[33]

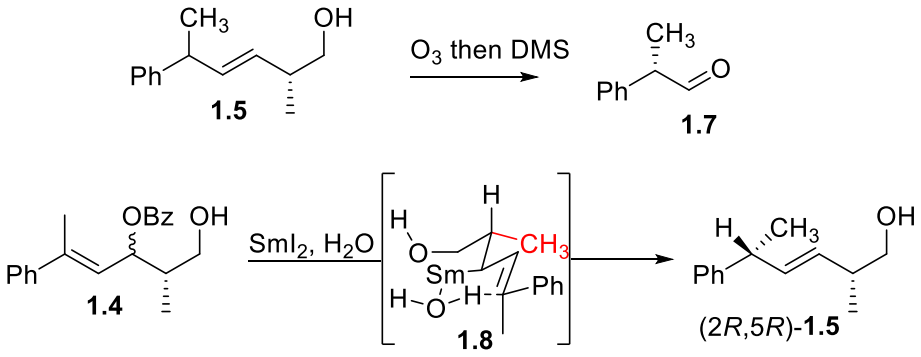
Scheme 4. Proposed mechanism of $SmI_2(H_2O)_n$ allylic benzoate reductions. Adapted from reference.[33]



To determine the absolute stereochemistry of the new stereocenter formed from this reaction, compound 1.**5** was subjected to ozonolysis to make 1.**7** (Scheme 5).[31] By comparing the optical rotation of purified 1.**7** to the literature value[34] it was determined to be enriched in the *S*-

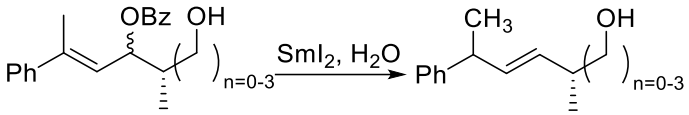
enantiomer. This indicated that the main product of the reaction is the (2*R*,5*R*)-**1.5**, consistent with bicyclic intermediate **1.8** where the methyl group occupies a preferred pseudo-equatorial position.

*Scheme 5. Determination of absolute stereochemistry of **1.5** and proposed bi-cyclic intermediate. Adapted from reference.*[31]



With evidence for a proposed 5-membered chelate, the question emerged how does chelate size affect diastereoselectivity in this reaction? To answer this question the O'Neil group synthesized a series of analogous compounds with differing linker lengths.[30] The longest linker length would theoretically have a 7-membered chelate ring size. As shown in Table 3 (Entry 4), this less conformationally rigid substrate led to a lower d.r. and suffered from a variety of competing side reactions. Reducing the ring size down to a more rigid 6-membered chelate (Entry 3) gave comparable stereoselectivity as was previously seen for a 5-membered chelate (Entry 2). By shrinking the linker length even further (Entry 1) the O'Neil group was able to achieve the highest d.r. yet of 86:14, albeit with a decrease in yield due to competing β-elimination of the hydroxyl forming a diene. Increasing equivalents of water increased the yield for this reaction marginally (53 % to 60 %), presumably by allowing for faster protonation.

Table 3. Effects of linker length on diastereoselectivity. Adapted from reference.[30]



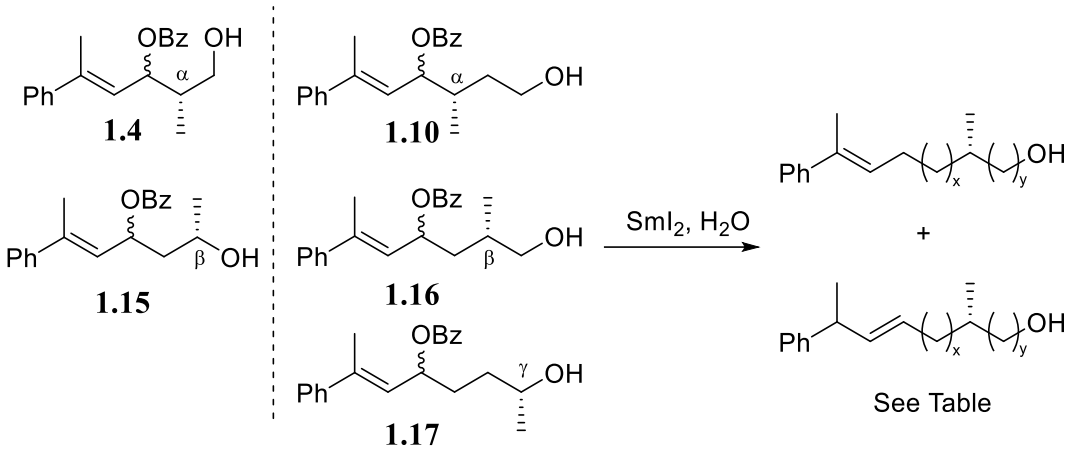
1.4, 1.9-11 **1.5, 1.12-14**

Entry	Starting Material	Product	d.r.[a]
1.	**1.9**	**1.12** (n=0)	86:14
2.	**1.4**	**1.5** (n=1)	76:24
3.	**1.10**	**1.13** (n=2)	78:22
4.	**1.11**	**1.14** (n=3)	63:37

Notes for Table 3: [a]Determined by NMR.

Within the five and six-membered chelate sizes it is also possible to move the stereodirecting methyl group along the carbon chain and see if it would play a role in diastereoselectivity. To probe this, a series of compounds were synthesized by the O'Neil group and reduced with SmI_2 (Table 4).[30] The resulting reduced compounds were then subjected to ozonolysis to confirm stereochemistry. All results were consistent with formation of a bicyclic transition state with the stereodirecting methyl group in a preferred equatorial position. In general, the highest diastereoselectivities were observed when this methyl group was closest to the newly formed stereocenter.

Table 4. Comparison of methyl stereocenter position and the effect on regio- and diastereoselectivity for $SmI_2(H_2O)_n$ allylic benzoate reductions for substrates proceeding through 5- and 6-membered organosamarium chelates. Adapted from reference.[30]

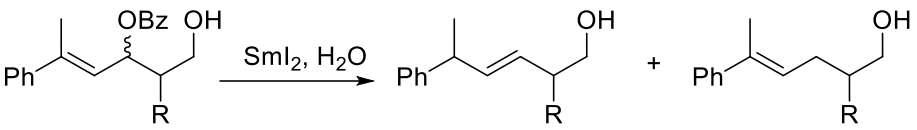


Entry	Starting Material	Product	d.r.[a]	Regioselectivity[a]
1.	**1.4**	**1.5** (x = 0, y = 1)	75:25	98:2
2.	**1.15**	**1.18** (x = 1, y = 0)	70:30	100:0
3.	**1.10**	**1.13** (x = 0, y = 2)	78:22	88:12
4.	**1.16**	**1.19** (x = 1, y = 1)	57:43[b]	94:6
5.	**1.17**	**1.20** (x = 2, y = 0)	56:44	83:17

Notes for Table 4: All reactions were preformed using 105 equiv. of H_2O and 7 equiv. of SmI_2 in degassed THF at rt under N_2. [a]Determined by ^1H NMR and GC-FID. [b]Identical results were obtained when the reaction was performed under Ar.

As mentioned, all the results were consistent with an intermediate featuring an equatorial stereodirecting group. Increasing the steric demand of this stereodirecting group was therefore expected to lead to higher diastereoselectivity. To test this, another series of compounds were synthesized and reduced (Table 5). Increasing the steric bulk of the stereodirecting group from methyl to an isopropyl or benzyl group increased the d.r. of the reaction moderately, however this came at the cost of yield. Both phenyl and hydroxyl stereodirecting groups (Entries 4 and 6) suffered greatly from elimination, suggesting this position is sensitive to both acidic hydrogens and good leaving groups.

Table 5. Stereodirecting group identity effects on regio- and diastereoselectivity for $SmI_2(H_2O)_n$ allylic benzoate reductions. Adapted from reference.[30]



1.4, 1.21-25 *See table*

Entry	R	d.r.[a]	Regioselectivity[a]	Yield%[b]
1.	Me (**1.4**)	75:25	98:2	90
2.	*i*-Pr (**1.21**)	83:17	93:7	80
3.	*t*-Bu (**1.22**)	80:20	95:5	73
4.	Ph (**1.23**)	73:27	100:0	25
5.	Bn (**1.24**)	81:19	96:4	82
6.	OH (**1.25**)	-	-	0

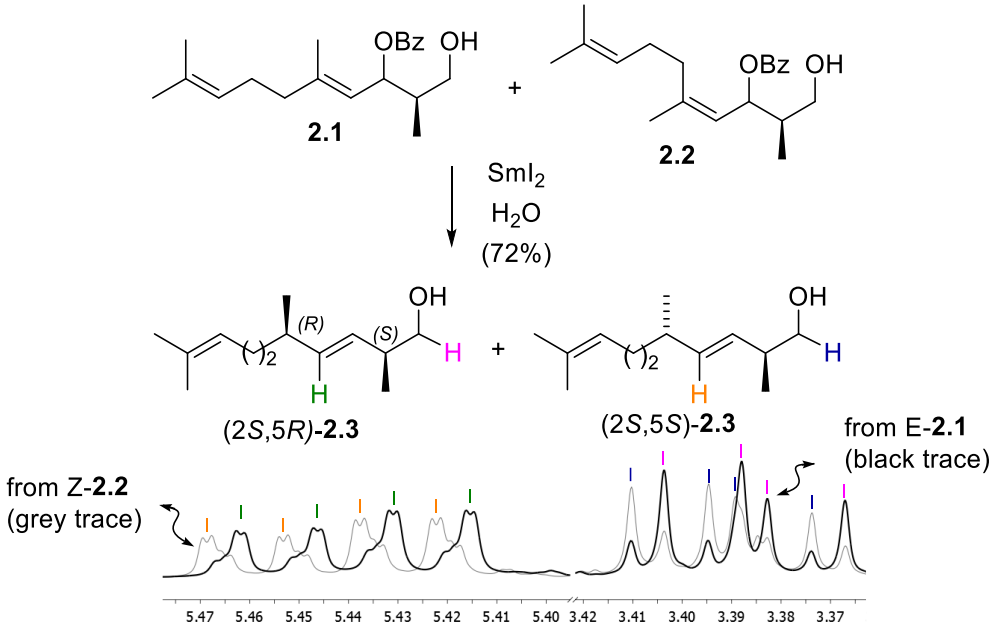
Notes for Table 5: Reductions were performed at room temp. using 7 equiv of SmI_2 and 105 equiv of water. [a]Determined by ^1H NMR. [b]Isolated yield.

Chapter 2

2.1 Initial Diastereoselectivity Study

With a better understanding of the parameters that effect diastereoselectivity in these reactions, the O'Neil group wanted to further explore and test their proposed mechanism. The proposed transition state suggests that switching the alkene geometry should also switch the configuration of the resulting stereocenter (i.e. the reaction should be stereospecific to alkene geometry). To test this, compounds **2.1** and **2.2** were synthesized as a partially separable mixture of *cis*- and *trans*-stereoisomers. Reduction of the differentially enriched samples gave the opposite diastereoselectivity, indicating that in this case the reaction was stereospecific to alkene geometry as predicted. (Scheme 6). These results further support formation of the proposed bi-cyclic intermediate and a pericyclic protonation mechanism to illustrate how the reaction is stereospecific with respect to alkene geometry.

*Scheme 6. Alkene stereospecificity experiments using differentially enriched mixtures of **2.1** and **2.2**. Colored lines are signals for the same colored hydrogens. Adapted from reference.*[33]

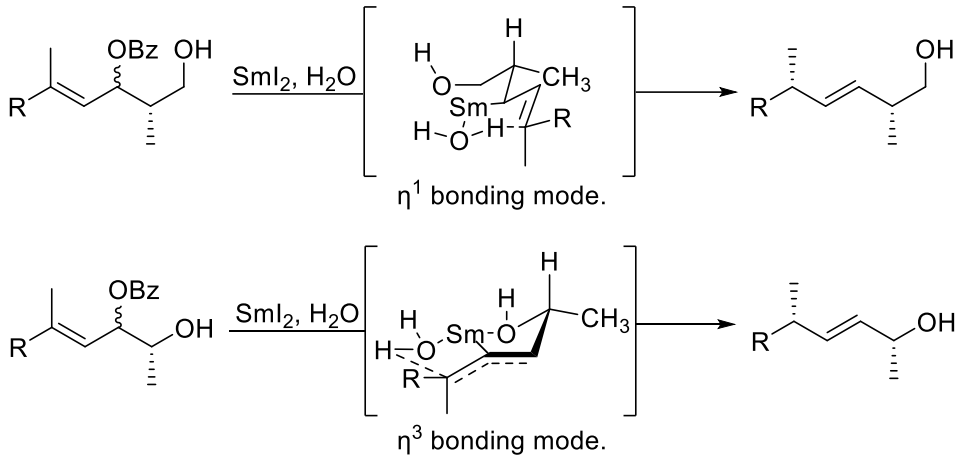


Sample	2.1 : 2.2	5*R* : 5*S* (expected)	5*R* : 5*S* (obtained)
1.	87:13	68:32	70:30
2.	16:84	33:67	35:65
3.	42:58	48:52	47:53

2.2 Comparing Different Chelate Sizes

Previously, the O'Neil group had proposed two different samarium binding modes that were thought to be dependent on chelate size. The first of which can be seen in Scheme 7, where the proposed organosamarium species is shown using an η^1 bonding mode as part of a 5,6-fused bicyclic transition state. The other proposed transition state uses an η^3 bonding mode and can also be seen in Scheme 7. This intermediate was theorized for compounds with smaller linker length (e.g. compound **1.9**) that would otherwise give a 4-membered ring chelate if considered as η^1.

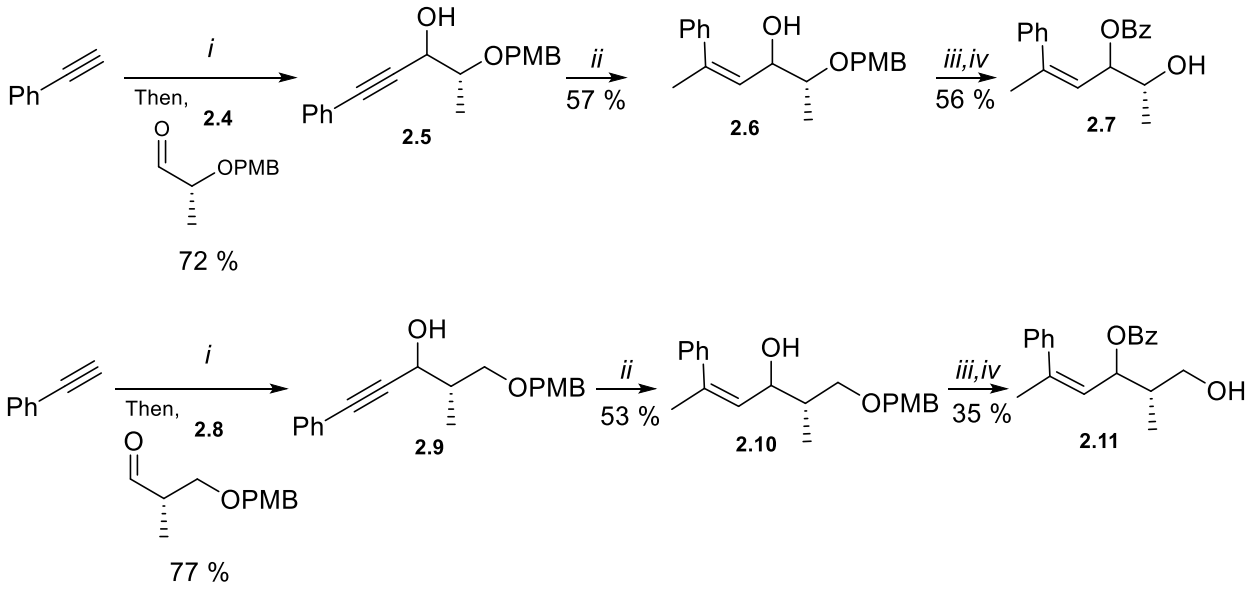
Scheme 7. Proposed bicyclic organosamarium species that utilizes either an η^1 or an η^3 bonding mode.



To test if there were any effects of chelate size on stereospecificity, two more *cis* compounds were synthesized to compare to their *trans* counterparts. These pairs of *cis*/*trans* isomers were investigated featuring different hydroxyl group linker lengths that should theoretically control formation of an η^1or η^3 organosamarium intermediate. The synthesis of the *cis* compounds started with acetylide addition to aldehydes **2.4** or **2.8**, derived from commercially available lactate and Roche esters, respectively (Scheme 8). An iron-catalyzed carbometalation of propargylic alcohols developed by Zhang and Ready was then performed on compounds **2.5** and **2.9**.[35] This procedure gave no reaction if allowed to warm above 0 ºC, likely be due to the decomposition of the iron catalyst to produce lower oxidation state species that are unreactive.[36] However, at 0 ºC the reaction was sluggish, producing only small amounts (23-30%) of the desired product that were inseparable from the starting material. Arguably, the propargylic position in our substrate is much more sterically hindered compared to the compounds presented by Zhang and Ready suggesting that this reaction could be sensitive to sterically hindered alkynes. Ultimately by using higher amounts of reagents, the *cis*-trisubstituted alkene **2.6** and **2.10** was obtained in 57 % and 53 % yield, respectively, albeit with small amounts of starting material. After an overnight benzoylation and subsequent deprotection of the

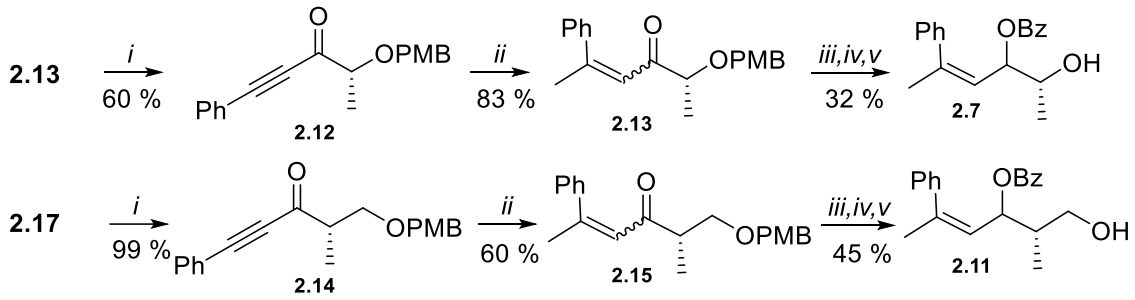
PMB group, *cis* compounds **2.7** and **2.11** were obtained in 56 % and 35 % yield, respectively for the two steps.

*Scheme 8. Synthesis of cis compounds **2.7** and **2.11**. Reagents: i, n-BuLi, THF; ii, $Fe(acac)_3$, dppe, MeMgBr, THF; iii, BzCl, pyridine, DCM; iv, DDQ, DCM, pH 7 buffer.*



Since the iron-catalyzed carbometallation produced an inseparable mixture of starting material and product, an alternative synthesis was investigated to reduce impurities. To do this, the previously made propargylic alcohols **2.5** and **2.9** were oxidized to their corresponding ynones using Dess-Martin periodinane (Scheme 9). Conjugate addition of a Gilman reagent to the α,β-ynones **2.12** and **2.14** gave tri-substituted alkenes **2.13** and **2.15** as an equal mixture of *cis*/*trans* isomers. These mixtures were reduced, benzoylated, deprotected, and purified by column chromatography on silica to yield partially separable mixtures of *cis/trans* isomers **2.15** and **2.19** without the alkyne impurities seen in the previous iron-catalyzed synthesis.

*Scheme 9. Synthesis of cis compounds **2.7** and **2.11**. Reagents: i, Dess-Martin Periodinane, $NaHCO_3$, DCM; ii, MeLi, CuI, THF; iii, $NaBH_4$;iv, MeOH BzCl, pyridine, DCM; v, DDQ, DCM, pH 7 buffer.*



Samarium reductions of compounds **2.7** and **2.11** were performed and the crude mixtures were analyzed by proton NMR. Comparison to results obtained from their *trans* isomers revealed that the reductions of these compounds was non-stereospecific to alkene geometry (i.e. the *cis*- and *trans*- isomers produced the same major stereoisomer (Figure 4).

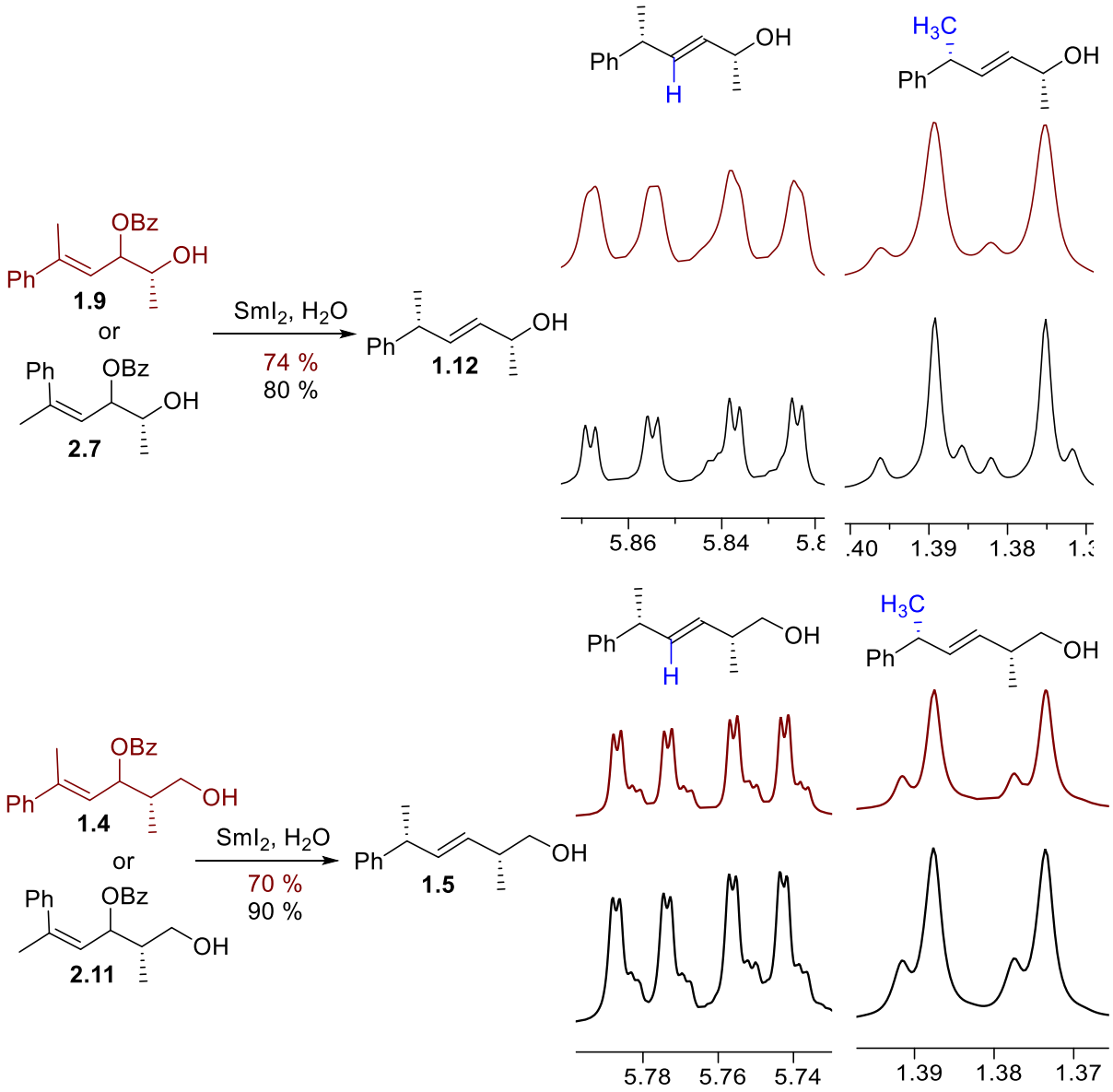
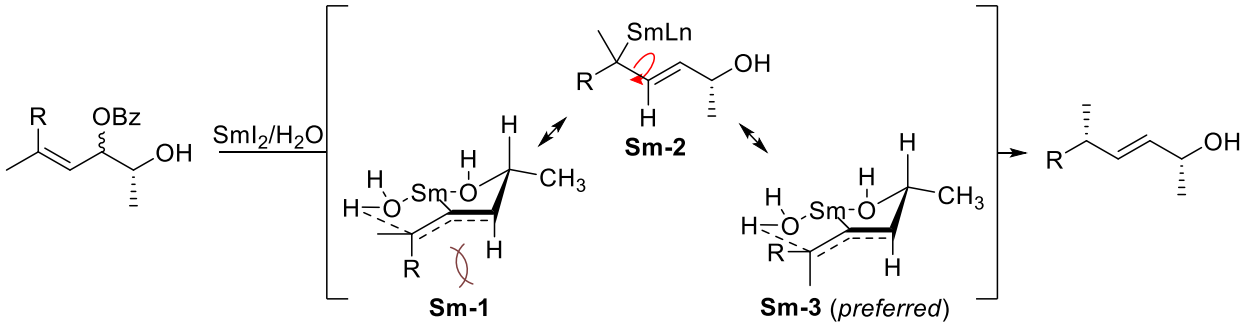


*Figure 4. Reductions of cis substrates **2.7** and **2.11** compared to their trans counterparts show by NMR that these compounds are stereoselective under $SmI_2(H_2O)_n$ conditions.*

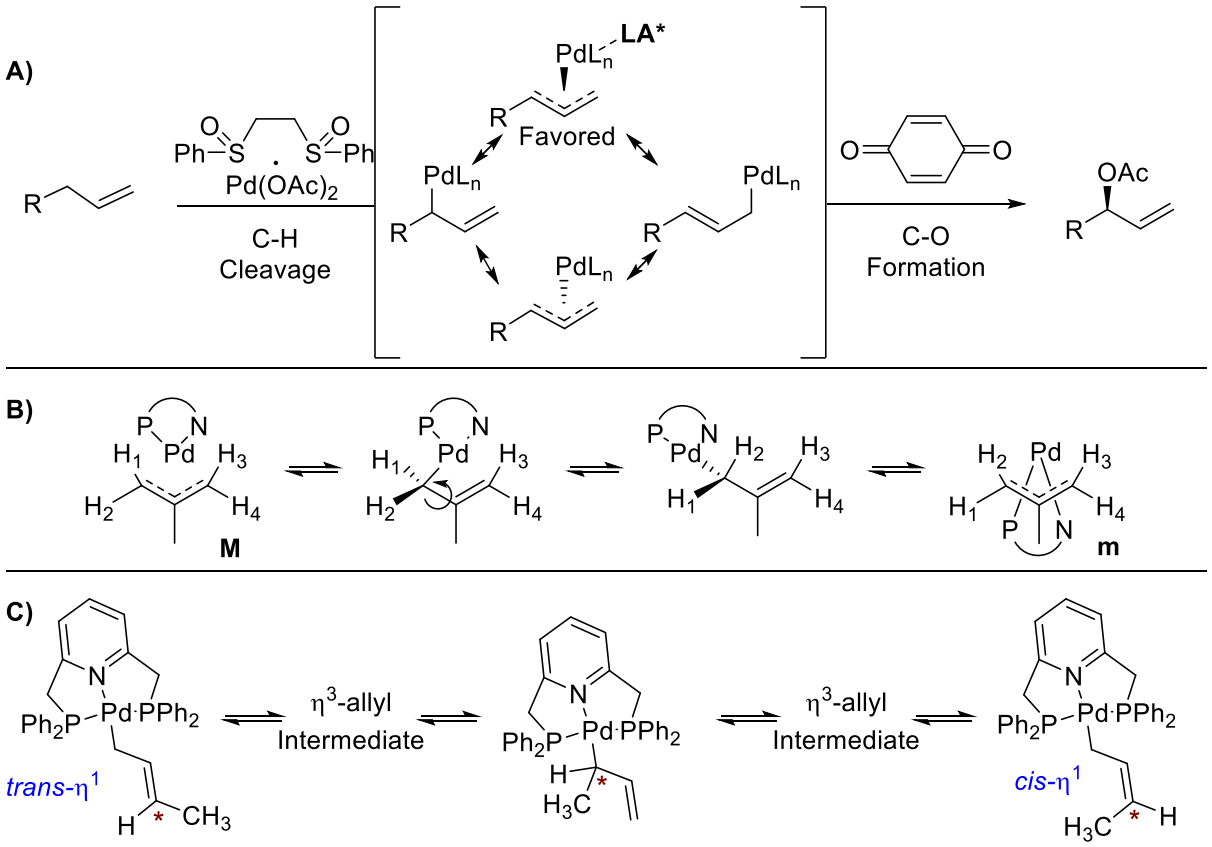
These results could be explained by rotation around the pi-allyl bond after formation of the organosamarium intermediate. For this to happen, the η^3-complex would have to isomerize to an η^1-complex **Sm-2** (Scheme 10). Rotation could then occur around the carbon-carbon bond. Isomerization into the alternative η^1 complex would then give an organosamarium intermediate **Sm-3** with different alkene geometry.

Scheme 10. Isomerization of alkene geometry could arise from a series of η^3- η^1- η^3 interconversions.



This type of carbon-carbon bond rotation for η^3/η^1 complexes has been observed for other organometallic intermediates.[37–45] A few reported examples for palladium are shown in Scheme 11. During their characterization and analysis of allyl-palladium (aminoferrocenyl) phosphine ligands, Rafael Fernández-Galán et. al. observed two isomers **M** and **m** for the major and minor isomer, respectively (Scheme 11 B). It was determined that the palladium complex was isomerizing from the η^3 complex to the η^1 complex s*yn* to phosphorus selectively. This selective isomerization has been observed with chiral ferrocene complexes[46,47] and other heterobidentate palladium ligands.[48,49] These examples caused Fernandez-Galan to postulate steric demand and the kinetic *trans* effect as the origin of selective η^1 isomerization. For our system, however, this η^1 position is very sterically hindered, and it is hard to imagine how the organosamarium complex would form the octahedral or square planar geometry required for the kinetic *trans* effect.

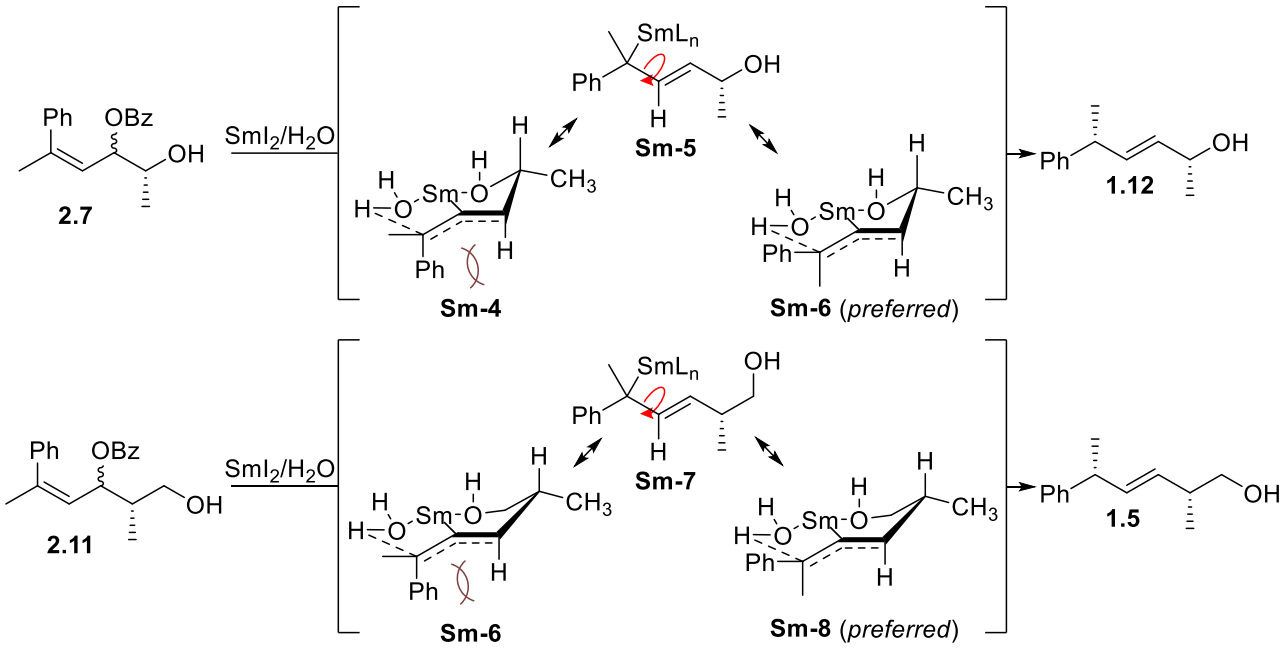
Scheme 11. Examples of palladium η^3- η^1- η^3 isomerizations. ***A)*** *A chiral Lewis acid (LA*) imparts facial selectivity to the rapidly isomerizing palladium intermediate leading to enantioselectivity[50].* ***B)*** *the formation of a selective σ-allyl intermediate cis to phosphorus, rotation around the carbon-carbon bond, and reformation of the η^3 complex explained the interconversion, and rotation observed with allyl-pladdium (Aminoferrocenyl)phosphine ligands[37].* ***C)*** *Palladium when attached to the specialized "PNP" ligand primarily sits in the η^1 bonding mode but can isomerize the alkene geometry during η^3- η^1- η^3 interconversions[38].*



The η^3 bonding mode has been recorded as the primary bonding mode for bis-cyclopentadienyl samarium allyl complexes.[51–53] Since the samarium bonding is largely ionic, the bonding mode will largely be controlled by sterics.[54,55] Such was the case during Procter's et. al. synthesis of δ-lactones where bulky $SmCp^R_2$ reagents showed evidence of η^1 bonding to allyl intermediates.[56] Since the organosamarium intermediates produced from compounds **2.7** and **2.11** have similar steric environments, and no discernable difference in stereospecificity, this could mean that both chelate sizes use the same η^3 bonding mode. More specifically, reduction of **2.15** and **2.19** could lead initially to the formation of η^3 organosamarium intermediates **Sm-4** and

Sm-6 which place the larger substituent (Ph) in a pseudo-axial position. Isomerization of these η^3 complexes to the corresponding η^1 complexes would give **Sm-5** and **Sm-7**, respectively. Rotation could then occur followed by isomerization into the energetically preferred η^3 complexes **Sm-8** and **Sm-9**, allowing the *cis*- and *trans*- substrates to converge to the same organosamarium intermediate and ultimately the same major diastereomer product (Scheme 12).

*Scheme 12. Proposed rotation around the proposed bicyclic intermediate leading to the stereoselective reduction of **2.7** and **2.11**.*

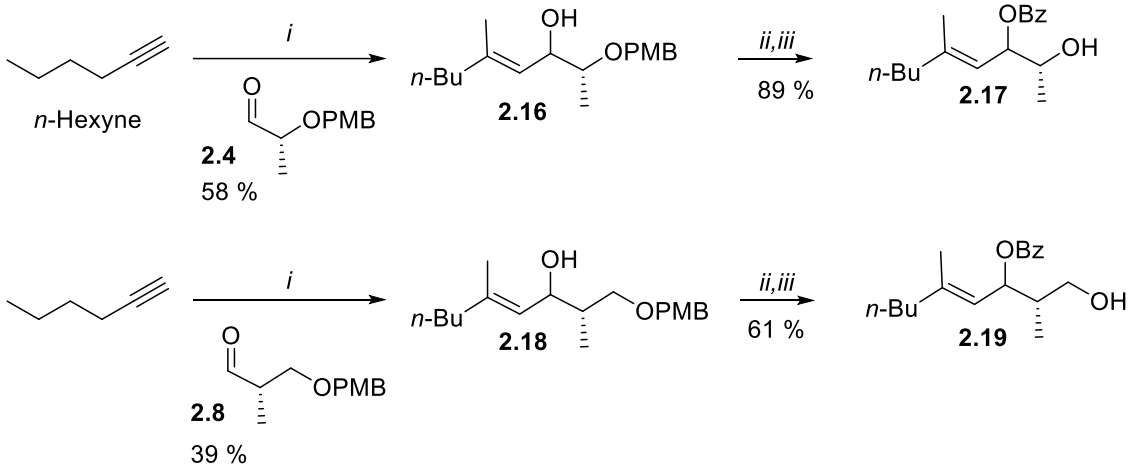


2.3 Comparing *n*-Butyl vs Phenyl Substituents

We hypothesized that if the steric difference between the two alkene substituents is small enough (e.g. for compounds **2.1** and **2.2**) perhaps there is insufficient steric preference to cause a rotation around the pi allyl intermediate. To test this theory, three sets of *cis/trans* isomers containing methyl and *n*-butyl alkene substituents were synthesized and tested. The synthesis of the three *trans* isomers used zirconium-catalyzed carboalumination of *n*-hexyne followed by addition to the corresponding aldehyde (Scheme 13). The resulting secondary alcohols (**2.16** and

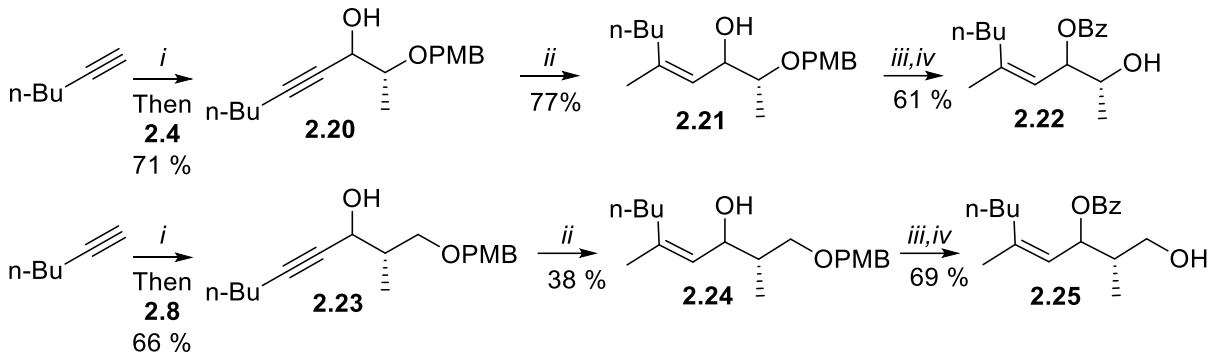
2.18) were acylated with benzoyl chloride and subsequently deprotected affording the desired *trans* substrates **2.17** and **2.19**.

*Scheme 13. Synthesis of trans n-butyl compounds **2.23**, **2.25**, and **2.27**. Reagents: i, $AlMe_3$,Cp_2ZrCl_2; ii, BzCl, pyridine, DCM; iii, DDQ, DCM, pH 7 buffer; iv, p-TsOH, MeOH; v, TBSCl, imidazole, DCM.*



The *cis* isomers were all synthesized by starting with *n*-hexyne, forming the corresponding acetylide by deprotonation with *n*-BuLi, and addition to aldehyde **2.4** or **2.8** (Scheme 14). The resulting secondary alcohols were subjected to iron-catalyzed carbometalation conditions to yield the *cis* alkenes **2.21** and **2.24.** The less sterically demanding propargylic alcohols **2.20** and **2.23** reacted more readily to iron-catalyzed carbometallation conditions, resulting in complete consumption of starting material as determined by proton NMR analysis, supporting the theory that this chemistry is sensitive to sterically demanding alkynes. The resulting *cis*-alkene-containing secondary alcohols were then benzoylated and the PMB group was removed to yield the desired *cis* substrates **2.22** and **2.25**.

*Scheme 14. Synthesis of cis n-butyl compounds **2.30** and **2.33**. Reagents: i, n-BuLi, THF; ii, Fe(acac)$_3$, dppe, MeMgBr, THF; iii, BzCl, pyridine, DCM; iv, DDQ, DCM, pH 7 buffer; v, p-TsOH, MeOH; vi, TBSCl, imidazole, DCM.*



The three pairs of *cis/trans* butyl isomers were all reduced using 7 equivalents of SmI_2 for all substrates, 100 equivalents of H_2O for substrates **2.17** and **2.22**, and 15 equivalents of H_2O for substrates **2.19** and **2.25**. The resulting product mixtures were analyzed by NMR to determine diastereoselectivity (Figure 5). Gratifyingly, these compounds containing sterically similar alkene substituents proved stereospecific with respect to alkene geometry, as predicted.

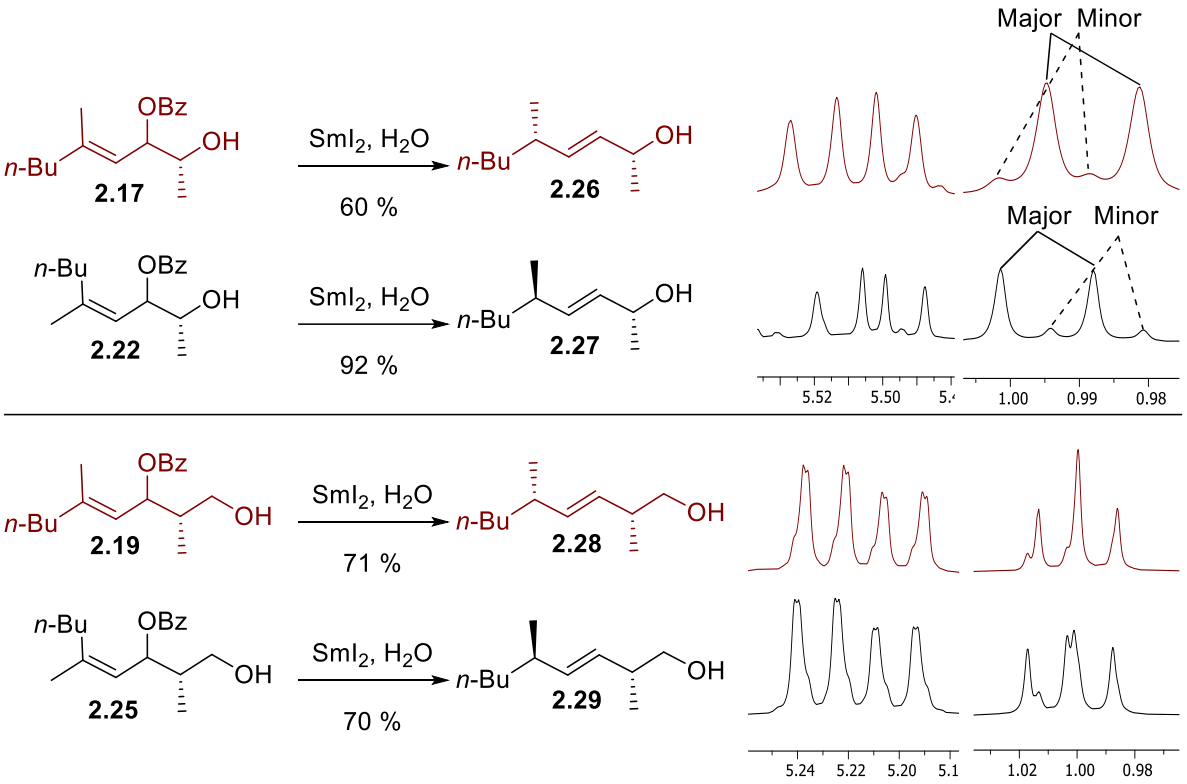


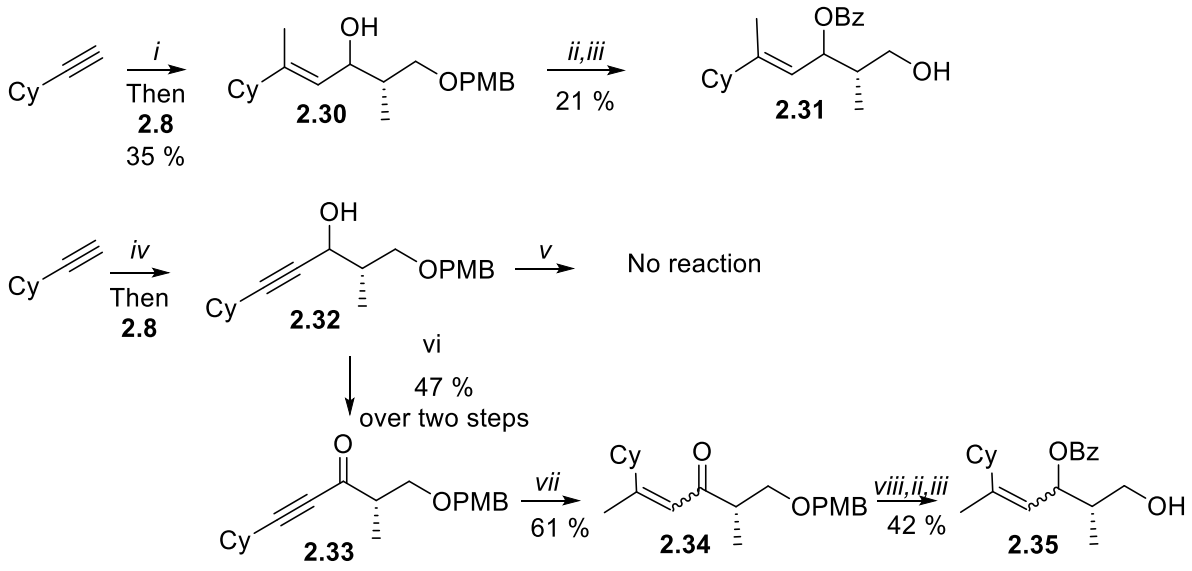
Figure 5. $SmI_2(H_2O)_n$ reductions of butyl compounds are stereospecific with respect to alkene geometry. Notice the switching of major diastereomer in the spectra as alkene geometry is flipped from trans to cis.

2.4 Bulky Alkyl Substituent

With these results it was predicted that placing a large, sterically demanding alkyl group in place of the *n*-butyl group would in turn cause a loss in stereospecificity with respect to alkene geometry by inducing bond rotation upon formation of the organosmarium complex. To test this, a pair of *cis/trans* isomers were made where instead of an *n*-butyl group a cyclohexyl group would be introduced. To make these compounds similar methods were attempted. The synthesis of the *trans* substrate started with zirconium catalyzed hydroalumination of cyclohexyl acetylene followed by addition to aldehyde **2.8** to form the secondary alcohol **2.30** (Scheme 15). The secondary alcohol was then benzoylated and the crude product was treated with DDQ to remove the PMB group and yield the cyclohexyl/methyl *trans* substrate **2.31** in 21% yield for the two

steps. To synthesize the *cis*-isomer, cyclohexyl acetylene was deprotonated using *n*-BuLi to form the corresponding acetylide followed by the addition to the same aldehyde **2.8** to form the propargylic alcohol **2.32**. This propargylic alcohol was then subjected to iron-catalyzed carbometallation. Unfortunately, even with increased equivalents of reagents and reaction time no reaction was observed. This result further supports our theory that sterically demanding alkynes are less reactive and sterically small substrates are optimal to these conditions.

*Scheme 15. Synthesis of sterically demanding cis/trans cyclohexyl/methyl substrates **2.31** and **2.35**. Reagents: i, $AlMe_3$,Cp_2ZrCl_2; ii, BzCl, pyridine, DCM; iii, DDQ, DCM, pH 7 buffer; iv, n-BuLi, THF; v, $Fe(acac)_3$, dppe, MeMgBr, THF; vi, Dess-Martin Periodinane, $NaHCO_3$, DCM; vii, MeLi, CuI, THF; viii, $NaBH_4$, MeOH.*



To circumvent this result, our previous alternative synthesis was employed. This involved oxidizing the already made propargylic alcohol **2.32** to the corresponding ketone (**2.33**) with Dess-Martin periodinane. Conjugate addition of a Gilman reagent to the α,β-ynone **2.33** gave alkene **2.34** in 29% yield over the two steps as an equal mixture of *cis/trans* isomers. This mixture was reduced, benzoylated, deprotected, followed by purification by column chromatography on silica to yield the partially separable mixture of *cis/trans* isomers **2.35**.

Surprisingly, reduction of both isomers **2.31** and **2.35** (Figure 6) revealed that these substrates are stereospecific with respect to alkene geometry! Comparing *cis/trans*-isomers **1.4** and **2.11** (for which the reaction was non-stereospecific) to isomers **2.31** and **2.35** (reaction is stereospecific), the only difference is a phenyl group vs. a cyclohexyl. Flowers had reported a drastic change in diastereoselective β-hydroxyketone reductions with a $SmI_2/H_2O/Et_3N$ mixture for substrates containing phenyl groups.[57] Flowers postulated the electron deficient Sm^{3+} was interacting with the pi system of a nearby benzene ring leading to a different major diastereomer (Figure 7).

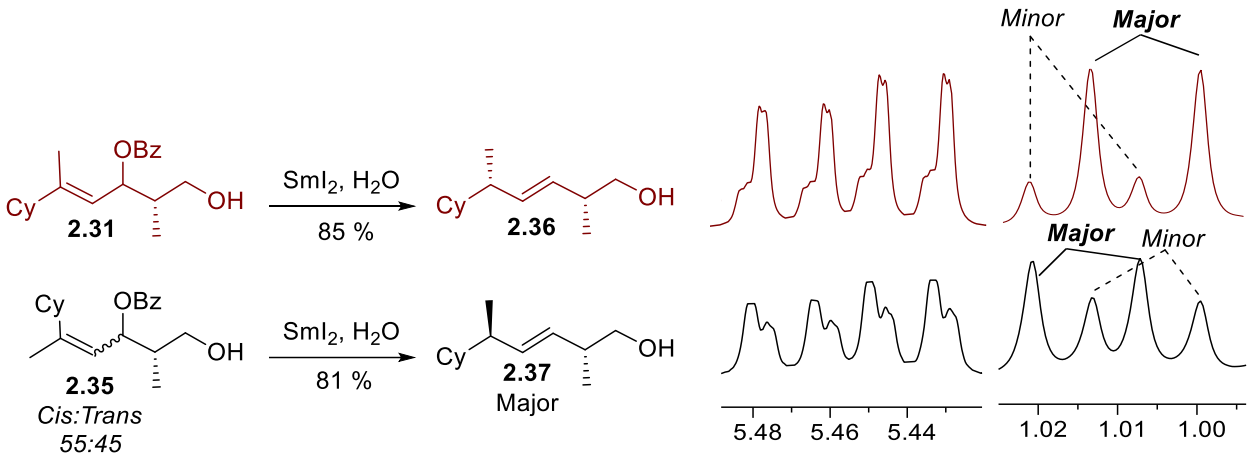


*Figure 6. $SmI_2(H_2O)_n$ reductions of sterically demanding cyclohexyl/methyl compounds cis/trans isomers **2.31** and **2.35** are also stereospecific with respect to alkene geometry. Whereas pure trans-**2.31** gave a d.r. of 76:24 by ^1H NMR analysis, when performed on a ~1:1 mixture with cis-**2.35**, we see a mixture of diastereomers produced.*

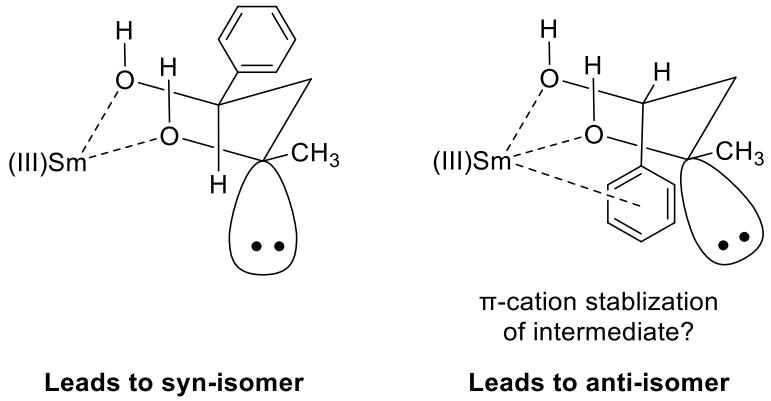


Figure 7. Depiction of possible intermediate leading to poor stereoselectivity or reversal of stereoselectivity when a phenyl group is α to the hydroxyl starting material. Adapted from Flowers et. al.[57]

For our particular system, however, it is difficult to imagine a similar interaction that could lead to a loss in stereospecificity for these allylic benzoate reductions. From our previous work, we showed that the stereochemistry of the major product obtained from reduction of compound **1.4** was the 2*R*,5*R*-diastereomer (Scheme 5). This is consistent with a model wherein the phenyl group is not in close proximity to the bound samarium. Alternatively, for those substrates containing phenyl substituents, it may be that the η^1 isomer Sm-**5** and Sm-**7** (*ref.* Scheme 12) wherein rotation can occur, has a greater contribution to the overall structure of the organosamarium intermediate. This could be rationalized by stabilization of the samarium-bound carbanion by the phenyl ring, or some type of interaction of the phenyl ring with samarium (an interesting reaction has been reported with Cp*2Sm(THF)$_2$ and diazobenzene that forms an agostic bond to the *ortho* C-H bonds of the benzene[58]). While it has yet to be determined what exactly is causing this change in alkene stereospecificity, it appears nearby benzene rings can affect samarium-based reactions.

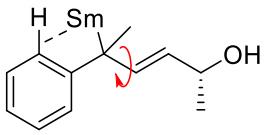


Figure 8. Potential agostic bond to the ortho C-H bond, stabilizing the η^1 bonding mode, allowing free rotation, and leading to a loss in stereospecificity.

In a computational study done by Solin and Szabó, they found that allyl η^1 palladium complexes are destabilized by alkyl substitution at the metal-bonded carbon (Figure 9, **6b-d**).[59] They also found that adding the electron withdrawing group -CF_3 (**9b-d**) to the metal bonded carbon significantly stabilized the η^1 complex when compared to the methyl substituted analogue. In a similar fashion, phenyl substituents in our substrates might act as resonance electron-withdrawing and stabilize the η^1 organosamarium complex, allowing for rotation and a loss of stereospecificity. While on the other hand, alkyl substituents destabilize formation of the tertiary η^1 complex, preventing rotation from occurring, and leading to a stereospecific reaction. Solin and Szabó also found that ligands can affect an η^1 complex's ability to rotate around the C-C bond, as electron donating ligands allow for stronger hyperconjugative interactions between the d_σ(Pd-C) and π^*(C=C) molecular orbitals. For our substrates with phenyl substituents however, the η^1 samarium complex has two different π^*(C=C) molecular orbitals that can be interacted with. One from the alkene moiety and the one from the benzene ring. This could possibly lower the energy barrier for C-C bond rotation as the d_σ(Sm-C) molecular orbital can still be stabilized through hyperconjugative interactions with the phenyl's π^*(C=C) molecular orbital as the alkene's hyperconjugative interaction is broken during rotation.

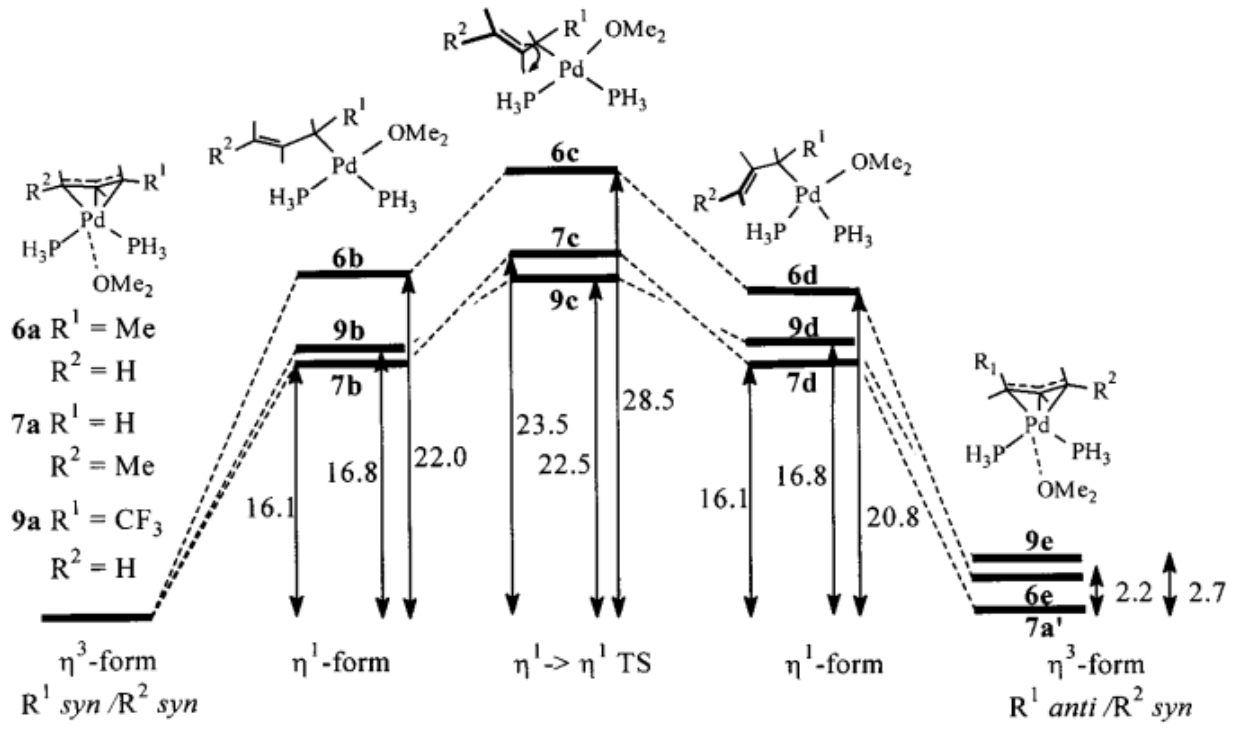


Figure 9. Effects of monosubstitution of the allyl moiety (energies in kcal mol^{-1}). All energies are zero-point energy-corrected. For the sake of clarity, the hydrogens are represented by sticks. Figure from reference[59]

Currently, there appears to be few mechanistic computational studies of samarium (II) reactions. Those that have been conducted include cyclopropanations,[60,61] reductive cyclizations,[62–65] and Barbier reactions.[66] all of which are interesting and valuable to understanding the regio- and diastereoselectivity complex samarium-based reactions. For instance, Zhou and coworkers developed a samarium-catalyzed alkyne−azide cycloaddition that was thought to go through an unprecedented tandem anionic cascade cyclization and anti-addition across the C≡C triple bond.[67] To study this claim, Zhi-Ming et. al. studied several possible mechanistic pathways of these cylcoadditions.[62] From this study they found how samarium influences the electrostatic potential of the starting materials which in turn affects regioselectivity, the most favored pathway in their study confirmed the proposed mechanism by Zhou, and how toluene as a solvent facilitates the intramolecular [1,3]-shift reaction.

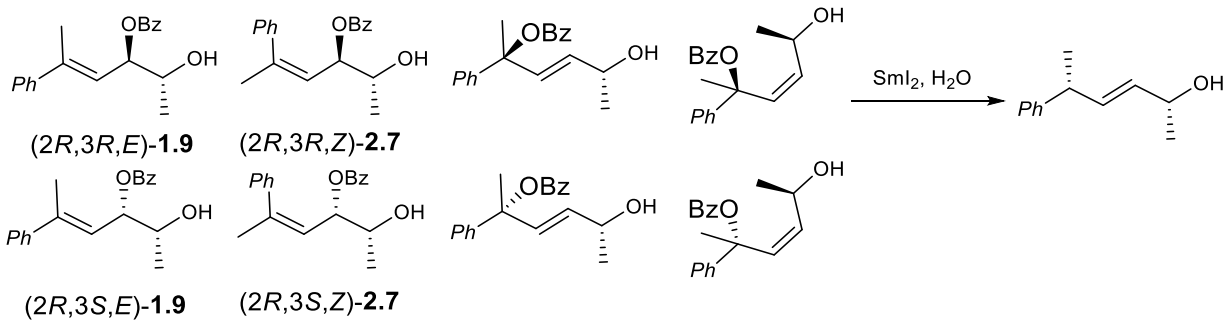
Unfortunately, there appears to be a lack of information on samarium allyl-complexes of the type we have proposed. Further study is needed to understand allyl samarium complexes and what properties control the stereospecificity of allylic benzoate reductions. Computation offers the potential to do so without excessive experimental testing.

Chapter 3

3.1 Tertiary Substrates – Preliminary Results

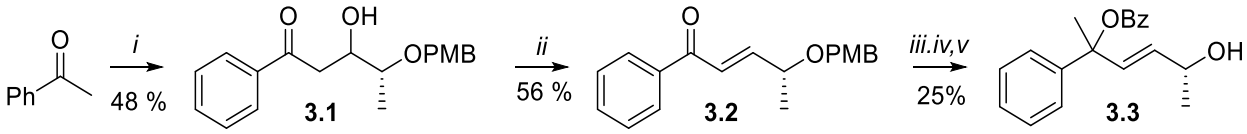
Current results show *cis*- or *trans*-phenyl substituted substrates lead to the same major product in similar yields and diastereoselectivity. It is thought that this lack of alkene stereospecificity arises from an η^1- η^3- η^1 isomerization of the organosamarium complex that allows for rotation and convergence which is promoted through stabilization by the phenyl ring. Previously we had shown that two different benzoyl ester isomers converge to the same organosamarium intermediate (*ref.* Scheme 1). This suggested that swapping the alkene and benzoate positions for substrates containing a phenyl substituent will have no effect on the diastereoselectivity of the reaction, as ultimately these compounds lead to the same intermediate. Combined with our experiments showing that benzoate stereochemistry has no effect on the resulting stereochemistry (Figure 3), this would mean that any of the 8 isomers in Scheme 16 would all lead to the same major product.

Scheme 16. Any of these allylic benzoate isomers should theoretically lead to the same major product.



To test this theory, a tertiary benzoate isomer was synthesized as shown in Scheme 17. The synthesis started with an aldol addition of acetophenone to aldehyde **2.4** to form the β-hydroxy ketone **3.1**. The free hydroxyl was acylated with acetic anhydride and eliminated to form the α,β-enone **3.2** in 56% yield for the two steps. Methyl Grignard addition, acylation of the resulting alkoxide with benzoyl chloride, and deprotection of the secondary PMB-protected alcohol gave the tertiary benzoate substrate **3.3** in 25% yield (3-steps).

*Scheme 17. Synthesis of tertiary benzoate substrate **3.3**. Reagents: i, LDA, THF, **2.4**; ii, Ac_2O, DMAP, DBU, THF; iii, MeMgBr, THF; iv, BzCl; v, DDQ, DCM, pH 7 buffer.*



As predicted, samarium reduction of the tertiary benzoate **3.3** gave identical results to compounds **1.9** and **2.7** (Figure 10). In future work, we plan to synthesize the *cis* isomer of the tertiary substrate **3.3** and test if this isomer also leads to the same major diastereomer **1.12** as predicted.

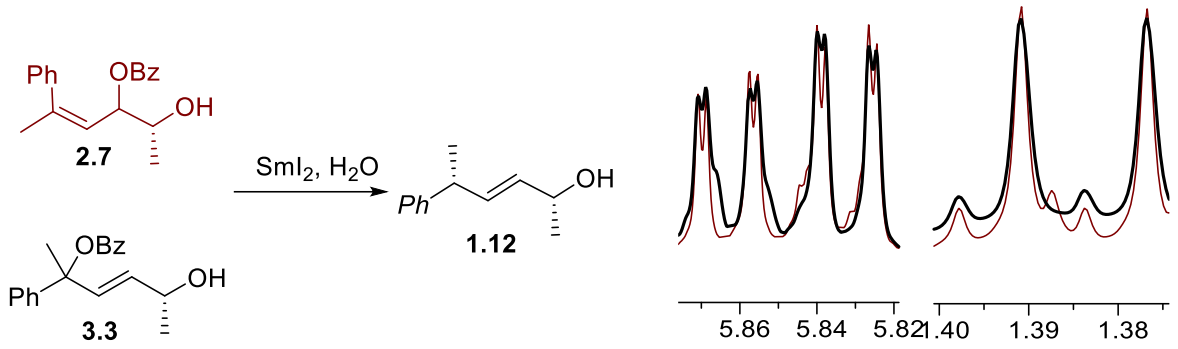
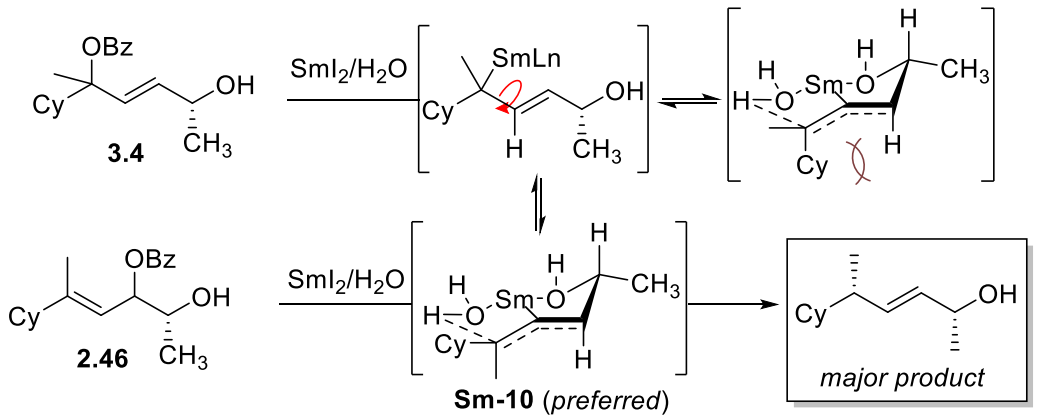


*Figure 10. Reduction of structural isomer **3.3** results in the same major product as **2.15**.*

Another future test involves making an *n*-butyl substituted (instead of phenyl) tertiary benzoate substrate, essentially "forcing" samarium to form an η^1 complex where rotation is possible. This might lead to no diastereoselectivity, or at least lower than what was observed for compounds **2.17** and **2.22** (88:12 d.r.) since there is little steric differentiation between the methyl and *n*-butyl groups. On the other hand, a substrate containing a tertiary benzoate and a sterically demanding alkyl group (e.g. a cyclohexyl group) might be stereoselective in a similar fashion as the phenyl substrates. In this way, both compounds **2.31** and **3.4** would be expected to lead to the same major diastereomer (Scheme 18).

*Scheme 18. Predicted convergence of compounds **2.31** and **3.4** to the same major diastereomer due to the presence of a sterically demanding alkyl group leading to a preference for formation of complex Sm-**10**.*



Conclusions

To summarize, the stereospecificity of samarium diiodide mediated allylic benzoate reductions appears to be sensitive to the electronics of the substrate. When one of the substituents is a benzene ring the reaction is non-stereospecific. Different phenyl-substituted alkene isomers converge to same major diastereomer, with the resulting stereochemistry arising from a bicyclic-organosamarium intermediate that can rotate around the pi-allyl bond to place the benzene ring pseudo-equatorial. If the substituents are both alkyl, then the reaction is stereospecific to alkene geometry. It appears that regardless of steric demand, alkyl substituted substrates have restricted rotation and diastereoselectivity is controlled by the proposed bicyclic intermediate. This change in stereospecificity could be explained by the difference in the substrates ability to stabilize an η^1 intermediate that is required for C-C bond rotation and subsequently isomerization of alkene geometry. As stereospecificity does not appear to change with chelate size, it is likely that the samarium bonding mode is the same regardless of chelate size.

Supporting Information

Experimentals

General: All reactions were carried out under N_2 in flame-dried glassware unless specified otherwise. The solvents used were dried by passing the solvent through a column of activated alumina under nitrogen immediately prior to use. All reagents were purchased and used as received unless otherwise mentioned. All TLC analysis used 0.25 mm silica layer fluorescence UV_{254} plates. Flash chromatography: SilaCycle silica gel P60 (230-400 mesh). IR: Nicolet iS10 spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. NMR: Spectra were recorded on a Unity Inova 500 MHz FT-NMR Spectometer in the solvents indicated; chemical shifts (δ) are given in ppm, coupling constants (*J*) in Hz. Determination of diasteromeric ratios were calculated using MestreNova 10.0 software (example below). The solvent signals were used as references ($CDCl_3$: $\delta_C \equiv 77.00$ ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H \equiv 7.26$ ppm).

General Experimental Procedures

Acetylide formation and addition to aldehydes:

To a Schlenk tube filled with tetrahydrofuran (THF) (0.2 M relative to alkyne) and terminal alkyne (1.0 eq) at -78 ºC was added a solution of *n*-butyllithium (1.2 eq) dropwise and stirred for 30 minutes. Aldehyde (0.8 eq) was then added dropwise and stirred at -78 ºC for one hour. The cold reaction mixture was poured to a seporatory flask containing saturated aq. ammonium chloride and extracted using ethyl acetate (3×). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*.

Iron-catalyzed carbometalation of propargylic alcohols:

Methylmagnesium bromide (25 equiv) was added dropwise to a solution of iron(III) acetylacetonate (1.0 eq), 1,2-bis(diphenylphosphino)ethane (1.0 eq), alkyne (1.0 eq) and THF(0.08 M relative to alkyne) at -78 ºC. The resulting brown mixture was warmed to -20 ºC and stirred for seven hours at this temperature. After cooling to –78 ºC, the reaction was quenched slowly with isopropyl alcohol then saturated aq. Ammonium chloride, and extracted with ethyl acetate (3×). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*.

Benzoylation of an alcohol:

Pyridine (2 equiv.) was added to a Schlenk tube containing substrate (1 equiv.) in DCM (0.2 M relative to substrate). The mixture was then cooled to 0 ^oC followed by the addition of benzoyl chloride (1.2 equiv.). The reaction was allowed to warm to room temperature for 15 hours, quenched with aq. $NaHCO_3$, and extracted with DCM (3x). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*.

DDQ removal of PMB protecting group:

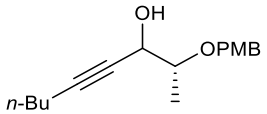
The Substrate was added to a round bottom flask containing a 50:50 mixture of DCM:pH 7 buffer (0.1 M relative to substrate). The reaction mixture was cooled to 0 ^oC and stirred vigorously at which time DDQ (3 equiv.) was added portionwise over 30 min. The reaction was left for 1 hour, quenched with aq. NaOH (1.0 M), extracted with DCM (3x). The combined organic extracts were washed with brine (2x), dried over $MgSO_4$, and concentrated *in vacuo*

SmI_2 reductive elimination with H_2O:

To a dry Schlenk tube containing a solution of SmI_2 in THF (0.1 M, 7 equiv.) was added degassed Nanopure H_2O (105 equiv.) turning the solution a deep red color. The solution was stirred for 5 minutes and the substrate (1 equiv) was then added. After 30 minutes the reaction was quenched with aq. $NaHCO_3$, and extracted with ethyl acetate (3x). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*.

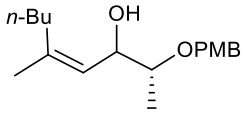
Zirconium catalyzed carboalumination:

To a Schlenk tube filled with dichloromethane (DCM) (0.3 M relative to alkyne) and Cp_2ZrCl_2 (0.1 eq) at -20 ºC was added trimethylaluminum (2.0 eq) dropwise resulting in a yellow solution which was stirred for 10 minutes. DI H_2O (1.0 eq) was then added dropwise turning the solution a darker shade of yellow which was then stirred for another 10 minutes. The reaction was then warmed to room temperature for ten minutes and then cooled to 0 ºC. Phenylacetylene (1.0 eq) was added dropwise and the solution was stirred for 40 minutes at 0 ºC. Aldehyde (0.8 eq) was then added dropwise and the mixture stirred for 1 hour at 0 ºC. The reaction was quenched slowly with cold H_2O and then aq. HCl (1 M), and extracted with DCM (3×). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*.



(2R)-2-((4-methoxybenzyl)oxy)non-4-yn-3-ol (**2.20**)

Prepared according to procedure by Maezaki et al.[68]

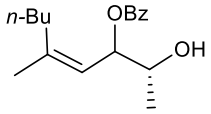


(2R,Z)-2-((4-methoxybenzyl)oxy)-5-methylnon-4-en-3-olol (**2.21**).

Prepared according to the general procedure for iron-catalyzed carbometalation of propargylic alcohols using propargylic alcohol **2.20** (0.100 g, 0.362 mmol). Purification by flash column chromatography on silica gave **2.21** (0.082 g, 77 %) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.23 – 5.16 (m, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.44 (dd, *J* = 8.8, 3.3 Hz, 1H), 3.80 (s, 3H), 3.52 (qd, *J* = 6.4, 3.3 Hz, 1H), 2.10 – 1.96 (m, 2H), 1.72 (d, *J* = 1.4 Hz, 3H), 1.44 – 1.35 (m, 1H), 1.34 – 1.23 (m, 3H), 1.13 (d, *J* = 6.4 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.34, 140.91, 130.82, 129.37, 123.58, 113.96, 77.48, 70.62, 70.09, 55.41, 32.33, 30.63, 23.67, 22.91, 14.26, 14.17.



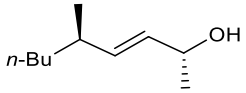
(2R,Z)-2-hydroxy-5-methylnon-4-en-3-yl benzoate (**2.22**)

Prepared according to the general benzoylation procedure using **2.21** (0.10 g, 0.35 mmol). The crude mixture was then subjected to the general procedure for removal of a PMB group with DDQ. Purification by flash column chromatography on silica gave **2.22** (0.058 g, 61 % over two steps) as a colorless oil.

IR (ATR): 3477, 2956, 2926, 2857, 1717, 1715, 1700, 1696, 1694, 1684, 1601, 1585, 1457, 1451, 1376, 1314, 1268, 1176, 1110, 1068, 1025, 997, 958, 804, 709, 687 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (dt, *J* = 8.4, 1.7 Hz, 2H), 7.56 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 5.69 (dd, *J* = 9.5, 4.3 Hz, 1H), 5.32 (dd, *J* = 9.3, 1.5 Hz, 1H), 4.00 (qd, *J* = 6.4, 4.2 Hz, 1H), 2.30 (ddd, *J* = 13.4, 10.0, 5.3 Hz, 1H), 2.14 (ddd, *J* = 13.4, 9.7, 5.7 Hz, 1H), 1.79 (d, *J* = 1.4 Hz, 3H), 1.52 – 1.29 (m, 4H), 1.25 (d, *J* = 6.5 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.02, 145.18, 133.05, 130.51, 129.73, 128.44, 119.05, 75.44, 69.65, 32.61, 30.55, 23.74, 22.91, 18.24, 14.08.



(2R,5R,E)-5-methylnon-3-en-2-ol (**2.27**).

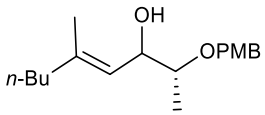
Prepared according to the general procedure for $SmI_2(H_2O)_n$ reductions using **2.22** (0.0109 g, 0.0398 mmol). Purification by flash column chromatography on silica gave **2.27** (0.0057 g, 92 %) as a colorless oil.

Spectral data for the major of diastereomer.

IR (ATR): 3380, 3066, 2917, 2859, 1633, 1593, 1567, 1468, 1439, 1373, 1354, 1297, 1251, 1119, 986, 935, 842, 780, 748, 729, 697, 654 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53 (dd, *J* = 15.4, 6.7 Hz, 1H), 5.48 (dd, *J* = 15.4, 5.8 Hz, 1H), 5.48 (dq, *J* = 5.8ff, 2.5 Hz, 1H), 2.11 (dtq, *J* = 6.7, 6.4, 3.6 Hz, 1H), 1.29 (m, 6H), 1.28 (d, *J* = 6.4, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.08, 132.29, 69.11, 36.58, 36.21, 29.50, 23.57, 22.78, 20.46, 14.10.



(2R,E)-2-((4-methoxybenzyl)oxy)-5-methylnon-4-en-3-ol (**2.16**)

Prepared according the general zirconium-catalyzed carboalumination using 1-hexyne (0.373 mL, 3.25 mmol) and aldehyde **2.4** (0.500 g, 2.6 mmol). Purification by flash chromatography on silica gave **2.16** (0.441 g**,** 58%), as a colorless oil and partially separable mixture of diastereomers (d.r = 56:44). R_f diastereomer$_\alpha$ = 0.38; R_f diastereomer$_\beta$ = 0.34 in 4:1 Hex:EtoAc.

Spectral data for diastereomer α:

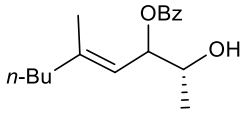
IR (ATR): 3420, 2980, 2928, 1614, 1570, 1265, 1110, 932, 886, 711 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.29 (d, *J* = 8.3 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.13 (dq, *J* = 9.0, 1.3 Hz, 1H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.42 (d, *J* = 11.3 Hz, 1H) 4.21 (dd, *J* = 9.0, 8.0 Hz, 1H), 3.82 (s, 3H), 3.39 (dq, *J* = 8.0, 6.2 Hz, 1H), 2.04 (t, *J* = 7.7 Hz, 2H), 1.71 (d, *J* = 1.4 Hz, 3H), 1.42 (m, 2H), 1.31 (h, *J* = 7.3 Hz, 2H), 1.13 (d, *J* = 6.2 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ = 159.22, 141.64, 130.31, 129.37, 123.08, 113.84, 78.91, 72.09, 70.80, 55.20, 39.38, 29.79, 22.29, 16.97, 15.36, 13.92.

Spectral data for diastereomer β:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.27 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.20 (dq, *J* = 8.5, 1.3 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.1 Hz, 1H) 4.46 (dd, *J* = 8.3, 3.9 Hz, 1H), 3.81 (s, 3H), 3.55 (qd, *J* = 6.4, 3.4 Hz, 1H), 2.01 (t, *J* = 7.0 Hz, 2H), 1.64 (d, *J* = 1.4 Hz, 3H), 1.39 (p, *J* = 7.5 Hz, 2H), 1.29 (m, 2H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 159.17, 140.08, 130.70, 129.20, 122.97, 113.81, 77.32, 70.50, 70.37, 55.28, 39.39, 29.91, 22.34, 16.66, 14.17, 13.97.
HRMS (ES+): *m/z* $[315.1936]^+$ calcd for $C_{18}H_{28}O_3Na^+$ $[M+Na]^+$; found: 315.1944.



(2R,E)-2-hydroxy-5-methylnon-4-en-3-yl benzoate (**2.17**).

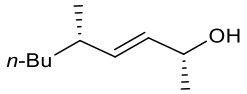
Prepared according to the general benzoylation procedure using **2.16** (0.431 g, 1.3 mmol). The crude mixture was then subjected to the general procedure for removal of a PMB group with DDQ. Purification by flash column chromatography on silica gave **2.17** (0.344 g, 89 % over two steps) as an oil.

Spectral data for the mixture of diastereomers:

IR (ATR) 3462, 3062, 2956, 2929, 2871, 1714, 1600, 1578, 1450, 1315, 1266, 1111, 1068, 962, 709 cm-1.

^{1}H NMR (CDCl3, 500 MHz): δ = 8.05 (dd, *J* = 8.5, 1.3 Hz, 4H), 7.55 (t, *J* = 7.4 Hz, 2H), 7.44 (t, *J* = 7.7 Hz, 4H), 5.66 (dd, *J* = 9.2, 4.4 Hz, 1H), 5.57 (dd, *J* = 9.5, 7.2 Hz, 1H), 5.32 (dq, *J* = 9.2, 1.3 Hz, 1H), 5.20 (dq, *J* = 9.5, 1.3 Hz, 1H), 4.03 (qd, *J* = 6.3, 4.2 Hz, 1H), 3.97 (p, *J* = 6.6 Hz, 1H), 2.06 (t, *J* = 7.6 Hz, 2H), 2.04 (t, *J* = 7.3 Hz, 2H), 1.84 (d, *J* = 1.4 Hz, 3H), 1.81 (d, *J* = 1.4 Hz, 3H) 1.40 (m, 4H), 1.29 (p, *J* = 7.4 Hz, 4H), 1.24 (d, *J* = 6.5 Hz, 3H), 1.22 (d, *J* = 6.5 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (CDCl3, 126 MHz): δ = 166.05, 165.96, 144.48, 144.07, 132.97, 132.95, 130.44, 130.42, 129.64, 129.63, 128.37, 119.36, 118.42, 76.80, 75.83, 69.74, 69.54, 39.50, 39.46, 29.86, 29.80, 22.32, 22.30, 18.73, 18.12, 17.20, 17.09, 13.94.
HRMS (ES+): *m/z* [319.1310]+ calcd for C19H20O3Na+ [M+Na]+; found: 319.1314.



(2R,5S,E)-5-methylnon-3-en-2-ol (**2.26**).

Prepared according to the general procedure for $SmI_2(H_2O)_n$ reductions using **2.17** (0.030 g, 0.11 mmol). Purification by flash column chromatography on silica gave the colorless oil **2.26** (0.010 g, 60 %) as a mixture of diastereomers (d.r. 90:10).

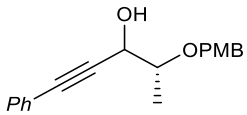
Spectral data for the major diastereomer:

IR (ATR) 3347, 2958, 2925, 2871, 2857, 1606, 1457, 1371, 1258, 1150, 1123, 1060, 969, 730 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.54 (dd, *J* = 15.4, 6.9 Hz, 1H), 5.48 (dd, *J* = 15.4, 6.0 Hz, 1H) 4.28 (p, *J* = 6.3 Hz, 1H), 2.11 (p, *J* = 6.6 Hz, 1H), 1.29 (m, 6H), 1.28 (d, *J* = 6.3 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 136.99, 132.24, 69.03, 36.56, 36.14, 29.48, 23.49, 22.79, 20.40, 14.08.

HRMS (ES+): *m/z* $[139.1487]^+$ calcd for $C_{10}H_{19}$ [M-OH]$^+$; found: 139.1482.



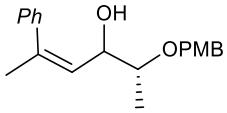
(4R)-4-((4-methoxybenzyl)oxy)-1-phenylpent-1-yn-3-ol (**2.5**)

Prepared according to the general procedure for acetylide formation and attack of aldehyde using phenyl acetylene (0.10 mL, 1.03 mmol) and aldehyde **2.4** (0.150 g, 0.77 mmol). Purification by flash chromatography on silica gave **2.5** (0.165 g**,** 72%), as a clear yellow oil and a mixture of diastereomers (d.r = 82:18).

Spectral data for the major of diastereomer.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.47 (m, 2H), 7.33 (td, *J* = 4.7, 3.0 Hz, 5H), 6.93 (m, 2H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 3.83 (s, 3H), 3.78 (qd, *J* = 6.3, 3.7 Hz, 1H), 2.56 (d, *J* = 5.9 Hz, 1H), 1.37 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.33, 131.79, 130.21, 129.42, 128.45, 128.26, 122.59, 113.91, 87.06, 86.04, 76.63, 70.79, 65.55, 55.31, 14.77.

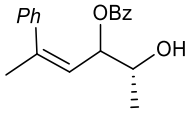


(2R,Z)-2-((4-methoxybenzyl)oxy)-5-phenylhex-4-en-3-ol (**2.6**)

Prepared according to the general procedure for iron-catalyzed carbometalation of propargylic alcohols using propargylic alcohol **2.5** (0.100 g, 0.338 mmol). Purification by flash column chromatography on silica gave **2.6** (0.060 g, 57 %) as a yellow oil.

Spectral data for the major diastereomer:

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.38 – 7.30 (m, 5H), 7.25 – 7.19 (m, 3H), 6.94 – 6.85 (m, 3H), 5.56 (dd, *J* = 9.3, 1.5 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 4.37 (dd, *J* = 11.2, 1.6 Hz, 1H), 3.83 (s, 3H), 3.52 (qd, *J* = 6.5, 3.4 Hz, 1H), 2.09 (d, *J* = 1.6 Hz, 3H), 1.14 (d, *J* = 6.4 Hz, 3H).



(2R,Z)-2-hydroxy-5-phenylhex-4-en-3-yl benzoate (**2.7**)

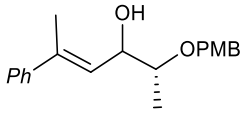
Prepared according to the general benzoylation procedure using **2.6** (0.060 g, 0.192 mmol). The crude mixture was then subjected to the general procedure for removal of a PMB group with DDQ. Purification by flash column chromatography on silica gave **2.7** (0.0317 g, 56 % over two steps) as an oil.

Spectral data for major diastereomer.

IR (ATR): 3455, 3057, 2974, 2926, 1718, 1715, 1700, 1696, 1694, 1685, 1652, 1600, 1584, 1492, 1457, 1451, 1375, 1314, 1266, 1177, 1109, 1069, 1025, 997, 961, 916, 853, 904, 765, 709, 702, 668, 667, 661, 655, 652 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.57 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.36 (tt, *J* = 7.7, 1.5 Hz, 2H), 7.31 – 7.27 (m, 3H), 5.66 (dq, *J* = 9.6, 1.5 Hz, 1H), 5.42 (dd, *J* = 9.6, 3.7 Hz, 1H), 3.99 (qd, *J* = 6.4, 3.7 Hz, 1H), 2.12 (d, *J* = 1.5 Hz, 3H), 1.17 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.29, 144.68, 140.99, 133.16, 130.52, 129.82, 128.53, 127.66, 127.49, 122.21, 121.04, 77.36, 69.14, 26.51, 17.22.



(2R,E)-2-((4-methoxybenzyl)oxy)-5-phenylhex-4-en-3-ol

Prepared according to the general procedure for zirconium-catalyzed carboaluminations using aldehyde **2.4** (0.500 g, 2.6 mmol). Purification by flash chromatography over silica gave the corresponding secondary alcohol (0.688 g, 82%, as a clear oil and partially separable mixture of diastereomers (d.r = 58:42).

R_f diastereomer$_\alpha$ = 0.30; R_f diastereomer$_\beta$ = 0.20 in 4:1 Hex:EtoAc.

Spectral data for diastereomer α:

IR (ATR): 3328, 3058, 3016, 2928, 1268, 1110, 932, 711 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.40 (dd, *J* = 8.6, 1.5 Hz, 2H), 7.33 (t, *J* = 7.1 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.27 (t, *J* = 7.3, 1H) 6.90 (d, *J* = 8.7 Hz, 2H), 5.70 (dq, *J* = 8.9, 1.4 Hz, 1H), 4.66 (d, *J* = 11.3 Hz, 1H), 4.43 (d, *J* = 11.3 Hz 1H), 4.38 (dd, *J* = 8.9, 7.7 Hz, 1H), 3.82 (s, 3H), 3.50 (dq, *J* = 7.7, 6.2 Hz, 1H), 2.13 (d, *J* = 1.4 Hz, 3H), 1.20 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 159.32, 142.98, 139.81, 130.21, 129.48, 128.18, 127.30, 126.40, 125.88, 113.92, 78.64, 72.44, 70.91, 55.26, 16.90, 15.52.

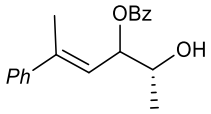
HRMS (ES+): *m/z* $[335.1623]^+$ calcd for $C_{20}H_{24}O_3Na^+$ $[M+Na]^+$; found: 335.1612.

Spectral data for diastereomer β:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.40 (dd, *J* = 8.7, 1.4, 2H), 7.32 (t, *J* = 7.19 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.80 (dq, *J* = 8.4, 1.3 Hz, 1H), 4.62 (dd, *J* = 8.4, 3.6 Hz, 1H), 4.62 (d, *J* = 11.7, 1H), 4.50 (d, *J* = 11.7, 1H), 3.81 (s, 3H), 3.66 (qd, *J* = 6.4, 3.5 Hz, 1H), 2.08 (d, *J* = 1.4 Hz, 3H), 1.20 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 159.26, 143.03, 138.24, 130.57, 129.53, 129.31, 128.23, 127.26, 126.55, 125.89, 113.88, 77.19, 70.92, 70.62, 55.31, 16.56, 14.42.

HRMS (ES+): *m/z* $[335.1623]^+$ calcd for $C_{20}H_{24}O_3Na^+$ $[M+Na]^+$; found: 335.1612.



(2R,E)-2-hydroxy-5-phenylhex-4-en-3-yl benzoate (**1.9**).

Prepared according to the general benzoylation procedure using (2R,E)-2-((4-methoxybenzyl)oxy)-5-phenylhex-4-en-3-ol (0.371 g, 1.18 mmol). The general procedure for DDQ removal of the PMB was then performed on the crude benzoylation product mixture obtained. Purification by flash chromatography on silica gave **1.9** (0.281 g, 80% over two steps) as an oil.

R_f = 0.24 in 4:1 Hex:EtoAc.

Spectral data for diastereomer α:

IR (ATR) 3450, 3062, 3031, 2976, 2929, 1712, 1600, 1583, 1450, 1266, 1110, 1025, 963, 909, 709 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.07 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 8.1 Hz, 2H), 7.41 (dd, *J* = 8.4, 1.5 Hz, 2H), 7.32 (t, *J* = 7.1 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 1H), 5.77 (m, 2H), 4.10 (p, *J* = 6.3 Hz, 1H), 2.29 (d, *J* = 1.2 Hz, 3H), 1.30 (d, *J* = 6.4 Hz, 3H).

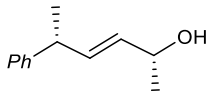
^{13}C NMR ($CDCl_3$, 126 MHz): δ = 166.01, 142.54, 141.90, 133.09, 130.16, 129.66, 128.41, 128.27, 127.68, 125.96, 122.37, 69.74, 18.81, 17.07.

Spectral data for diastereomer β:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.07 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 8.1 Hz, 2H), 7.43 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.33 (t, *J* = 7.1 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H), 5.91 (dq, *J* = 9.3, 1.3 Hz, 1H), 5.85 (dd, *J* = 9.3, 4.0 Hz, 1H), 4.15 (qd, *J* = 6.5, 4.1 Hz, 1H), 2.25 (d, *J* = 1.3 Hz, 3H), 1.31 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 165.94, 142.47, 142.03, 133.06, 130.15, 129.64, 128.39, 128.25, 127.66, 125.95, 122.37, 121.60, 76.73, 75.88, 69.59, 18.19, 16.90.

HRMS (ES+): *m/z* $[319.1310]^+$ calcd for $C_{19}H_{20}O_3Na^+$ $[M+Na]^+$; found: 319.1314.



(2R,5R,E)-5-phenylhex-3-en-2-ol (**1.12**)

To a dry Schlenk tube containing a solution of SmI_2 in THF (0.1 M, 7.0 mL, 7 equiv.) was added degassed nano pure H_2O (2.5 mL, 1400 equiv.) turning the solution a deep red color. The solution was stirred for 5 minutes before compound **1.9** (0.030 g, 0.10 mmol) was then added. After 30 minutes the reaction was quenched with aq. $NaHCO_3$ and extracted with EtOAc (3x). The combined organic extracts were dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude product mixture by flash chromatography on silica gave **1.12** (0.011 g, 60%) as a mixture of diastereomers (d.r. 84:16).

R_f = 0.30 in 4:1 Hex:EtoAc.

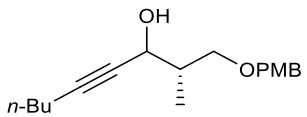
Spectral data for the major diastereomer:

IR (ATR) 3462, 3062, 2956, 2929, 2871, 1714, 1600, 1578, 1450, 1315, 1266, 1111, 1068, 962, 709 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 – 7.18 (m, 3H), 5.82 (ddd, *J* = 15.4, 6.7, 1.1 Hz, 1H), 5.56 (ddd, *J* = 15.5, 6.6, 1.4 Hz, 1H), 4.30 (p, *J* = 6.4 Hz, 1H), 3.46 (p, *J* = 7.0, 6.4 Hz, 1H), 1.36 (d, *J* = 7.0 Hz, 3H), 1.28 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 145.56, 135.41, 132.87, 128.44, 127.16, 126.16, 68.87, 41.83, 23.42, 21.17.

HRMS (ES+): *m/z* $[159.1174]^+$ calcd for $C_{12}H_{15}$ $[M-OH]^+$; found: 159.1175.



(2S)-1-((4-methoxybenzyl)oxy)-2-methylnon-4-yn-3-ol (**2.23**)

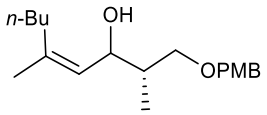
Prepared according to the general procedure for acetylide formation and attack of aldehyde using 1-hexyne (0.132 mL, 1.15 mmol) and aldehyde **2.8** (0.200 g, 0.960 mmol). Purification by flash chromatography on silica gave **2.23** (0.183 g**,** 66%), as a clear yellow oil and a mixture of diastereomers (d.r = 72:28).

Spectral data for major diastereomer.

IR (ATR): 3434, 2957, 2932, 2871, 1612, 1586, 1512, 1464, 1375, 1302, 1245, 1173, 1085, 1032, 819, 754 cm^{-1}.

^{1}H NMR (500 MHz, CDCl3) δ 7.28 (td, *J* = 6.1, 2.6 Hz, 2H), 6.90 (dd, *J* = 8.3, 1.6 Hz, 2H), 4.49 (d, *J* = 11.3 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.43 – 4.38 (m, 1H), 3.82 (s, 3H), 3.66 (dd, *J* = 9.3, 4.5 Hz, 1H), 3.46 (dd, *J* = 9.3, 6.9 Hz, 1H), 3.06 (d, *J* = 5.0 Hz, *O*H), 2.23 (td, *J* = 7.0, 2.0 Hz, 2H), 2.05 (dqd, *J* = 13.7, 6.9, 4.4 Hz, 1H), 1.53 – 1.46 (m, 2H), 1.43 (p, *J* = 7.1 Hz, 2H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.93 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.30, 129.93, 129.37, 113.83, 86.31, 79.00, 73.33, 73.17, 67.08, 55.28, 38.71, 30.87, 21.95, 18.42, 13.60, 12.89.

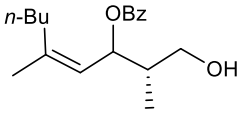


(2S,Z)-1-((4-methoxybenzyl)oxy)-2,5-dimethylnon-4-en-3-ol (**2.24**)

Prepared according to the general procedure for iron-catalyzed carbometalation of propargylic alcohols using propargylic alcohol **2.23** (0.183 g, 0.629 mmol). Purification by flash column chromatography on silica gave **2.24** (0.072 g, 38 %) as a colorless oil. Spectral data for major diastereomer.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.28 (dd, *J* = 7.3, 1.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.24 (dd, *J* = 9.1, 1.4 Hz, 1H), 4.51 – 4.43 (m, 3H), 3.83 (s, 3H), 3.51 (dd, *J* = 9.8, 6.5 Hz, 1H), 3.43 (dd, *J* = 9.1, 5.2 Hz, 1H), 2.09 (dd, *J* = 16.8, 8.3 Hz, 2H), 2.00 (tdd, *J* = 7.0, 5.2, 3.9 Hz, 1H), 1.74 (d, *J* = 1.4 Hz, 3H), 1.54 – 1.26 (m, 4H), 0.96 – 0.88 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 159.26, 159.22, 139.75, 139.58, 130.27, 130.06, 129.36, 129.30, 129.26, 126.79, 125.48, 113.83, 113.79, 74.68, 73.44, 73.04, 72.98, 72.37, 70.62, 55.28, 39.19, 39.18, 32.04, 32.01, 30.51, 30.48, 23.59, 23.49, 22.83, 22.81, 14.05, 14.03, 13.68, 12.21.



(2S,Z)-1-hydroxy-2,5-dimethylnon-4-en-3-yl benzoate (**2.25**)

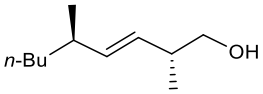
Prepared according to the general benzoylation procedure using **2.24** (0.072 g, 0.24 mmol). The crude mixture was then subjected to the general procedure for removal of a PMB group with DDQ. Purification by flash column chromatography on silica gave **2.25** (0.058 g, 69 % over two steps) as a colorless oil.

Spectral data for major diastereomer.

IR (ATR): 3432, 2958, 2930, 2872, 1714, 1601, 1584, 1451, 1377, 1314, 1269, 1176, 1097, 1068, 1025, 987, 908, 848, 804, 709, 686 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.06 (dt, *J* = 8.8, 1.7 Hz, 2H), 7.58 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 6.02 (dd, *J* = 9.1, 4.0 Hz, 1H), 5.43 (dd, *J* = 9.1, 1.8 Hz, 1H), 3.67 – 3.42 (m, 2H), 2.46 (d, *J* = 7.3 Hz, *O*H), 2.25 (ddd, *J* = 13.5, 9.4, 5.8 Hz, 1H), 2.15 (ddd, *J* = 13.3, 9.3, 5.9 Hz, 1H), 2.04 (dddd, *J* = 13.3, 8.8, 6.8, 2.9 Hz, 1H), 1.78 (d, *J* = 1.5 Hz, 3H), 1.48 – 1.26 (m, 4H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.68, 142.37, 132.99, 130.39, 129.68, 128.38, 121.50, 71.58, 64.66, 41.11, 32.30, 30.31, 23.52, 22.77, 14.00, 11.13.



(2R,5R,E)-2,5-dimethylnon-3-en-1-ol (**2.29**).

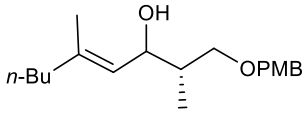
Prepared according to the general procedure for $SmI_2(H_2O)_n$ reductions using **2.25** (0.023 g, 0.079 mmol). Purification by flash column chromatography on silica gave **2.29** (0.010 g, 70 %) as a colorless oil.

IR (ATR): 3339, 2956, 2923, 2871, 2856, 1456, 1377, 1260, 1096, 1071, 1031, 968, 803, 728, 697, 661 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.44 (ddd, *J* = 15.6, 7.7, 1.1 Hz, 1H), 5.22 (ddd, *J* = 15.5, 7.9, 1.1 Hz, 1H), 3.50 (ddd, *J* = 10.6, 7.5, 5.4 Hz, 1H), 3.37 (ddd,

J = 10.5, 7.9, 3.2 Hz, 1H), 2.32 (dddd, *J* = 14.6, 7.9, 5.5, 1.2 Hz, 1H), 2.11 (hept, *J* = 6.4 Hz, 1H), 1.39 (dd, *J* = 8.0, 4.2 Hz, *O*H), 1.34 – 1.23 (m, 6H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 138.74, 130.19, 67.30, 39.75, 36.77, 36.76, 29.57, 22.78, 20.91, 16.75, 14.11.



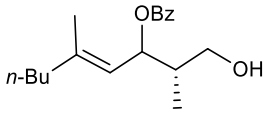
(2S,E)-1-((4-methoxybenzyl)oxy)-2,5-dimethylnon-4-en-3-ol (**2.18**)

Prepared according the general zirconium-catalyzed carboalumination using 1-hexyne (0.069 mL, 0.60 mmol) and aldehyde **2.8** (0.100 g, 0.48 mmol). Purification by flash chromatography on silica gave **2.18** (0.058 g**,** 39%), as a colorless oil and partially separable mixture of diastereomers (d.r = 86:14). Spectral data for major diastereomer.

IR (ATR): 3439, 2957, 2928, 2857, 1669, 1612, 1586, 1512, 1456, 1442, 1373, 1361, 1301, 1245, 1172, 1089, 1034, 1009, 819, 756, 708 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.28 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.18 (dq, *J* = 9.1, 1.4 Hz, 1H), 4.48 (s, 2H), 4.30 (td, *J* = 8.4, 1.0 Hz, 1H), 3.83 (s, 3H), 3.58 (dd, *J* = 9.3, 4.5 Hz, 1H), 3.48 (dd, *J* = 9.3, 7.7 Hz, 1H), 3.16 (d, *J* = 2.5 Hz, 1H), 2.03 (p, *J* = 7.7 Hz, 2H), 1.91 (hd, *J* = 7.2, 4.4 Hz, 1H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.41 (hd, *J* = 7.5, 2.2 Hz, 2H), 1.31 (h, *J* = 7.2 Hz, 2H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 159.27, 139.21, 130.04, 129.32, 126.15, 113.84, 74.76, 73.06, 72.78, 55.28, 39.43, 39.27, 29.97, 22.37, 16.68, 14.00, 13.39.



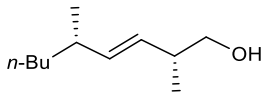
(2S,E)-1-hydroxy-2,5-dimethylnon-4-en-3-yl benzoate (**2.19**)

Prepared according to the general benzoylation procedure using **2.18** (0.058 g, 0.19 mmol). The crude mixture was then subjected to the general procedure for removal of a PMB group with DDQ. Purification by flash column chromatography on silica gave **2.19** (0.034 g, 61 % over two steps) as a colorless oil.

IR (ATR): 3435, 2957, 2928, 2872, 2859, 1714, 1601, 1584, 1491, 1451, 1382, 1315, 1269, 1176, 1098, 1069, 1025, 987, 949, 932, 852, 805, 732, 709, 687 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.06 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.58 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 5.78 (dd, *J* = 9.4, 8.3 Hz, 1H), 5.29 (dq, *J* = 9.4, 1.3 Hz, 1H), 3.64 (dd, *J* = 11.4, 4.5 Hz, 1H), 3.60 (dd, *J* = 11.4, 4.5 Hz, 1H), 2.07 (tt, *J* = 7.1, 1.0 Hz, 2H), 2.02 (pt, *J* = 8.3, 7.0, 4.5 Hz, 1H), 1.80 (d, *J* = 1.3 Hz, 3H), 1.43 (dddd, *J* = 11.0, 9.3, 5.2, 2.4 Hz, 2H), 1.31 (dddd, *J* = 15.8, 14.4, 7.3, 1.8 Hz, 2H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.55, 142.68, 132.96, 130.88, 129.67, 128.01, 121.31, 73.35, 64.25, 40.43, 39.41, 29.88, 22.31, 16.99, 13.96, 12.96.



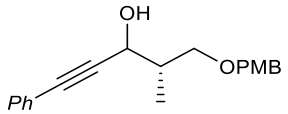
(2R,5S,E)-2,5-dimethylnon-3-en-1-ol (**2.28**)

Prepared according to the general procedure for $SmI_2(H_2O)_n$ reductions using **2.19** (0.034 g, 0.12 mmol). Purification by flash column chromatography on silica gave **2.28** (0.014 g, 71 %) as a colorless oil.

IR (ATR): 3339, 2957, 2924, 2871, 2858, 1457, 1377, 1033, 968 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.43 (ddd, *J* = 15.5, 7.7, 1.1 Hz, 1H), 5.21 (ddd, *J* = 15.4, 7.9, 1.2 Hz, 1H), 3.50 (ddd, *J* = 10.4, 8.0, 5.5 Hz, 1H), 3.37 (ddd, *J* = 10.5, 7.9, 4.2 Hz, 1H), 2.32 (tddd, *J* = 7.9, 6.7, 5.5, 1.1 Hz, 1H), 2.10 (h, *J* = 6.7 Hz, 1H), 1.39 (dd, *J* = 8.1, 4.3 Hz, 1H), 1.35 – 1.21 (m, 6H), 1.00 (t, *J* = 6.8 Hz, 6H), 0.90 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 138.70, 130.21, 67.33, 39.77, 36.80, 36.77, 29.67, 22.78, 20.80, 16.68, 14.10.



(2S,Z)-1-((4-methoxybenzyl)oxy)-2-methyl-5-phenylhex-4-en-3-ol (**2.9**)

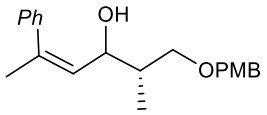
IR (ATR): 3406, 2961, 2909, 2860, 1735, 1612, 1512, 1489, 1463, 1443, 1302, 1245, 1173, 1082, 1030, 911, 818, 756, 733, 791, 667 cm^{-1}.

Prepared according to the general procedure for acetylide formation and attack of aldehyde using phenyl acetylene (0.13 mL, 1.15 mmol) and aldehyde **2.8** (0.200 g, 0.96 mmol). Purification by flash chromatography on silica gave **2.9** (0.228 g**,** 77%), as a clear yellow oil and a mixture of diastereomers (d.r = 55:45).

Spectral data for mixture of diastereomers:

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.44 – 7.40 (m, 4H), 7.35 – 7.29 (m, 10H), 6.88 (t, *J* = 8.5 Hz, 4H), 4.70 – 4.62 (m, 2H), 4.55 – 4.47 (m, 4H), 3.81 (s, 3H), 3.79 (s, 3H), 3.77 (dq, *J* = 7.1, 2.4, 1.9 Hz, 2H), 3.57 (dd, *J* = 9.1, 4.3 Hz, 1H), 3.52 (dd, *J* = 9.3, 6.8 Hz, 1H), 3.25 (dd, *J* = 5.6, 1.9 Hz, 1H), 2.43 – 2.34 (m, 1H), 2.19 (hd, *J* = 6.9, 4.2 Hz, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 131.75, 131.73, 129.43, 129.32, 128.28, 128.25, 128.23, 113.88, 113.86, 73.35, 73.31, 73.29, 73.14, 67.51, 66.99, 55.26, 55.24, 39.50, 38.74, 13.36, 12.99.



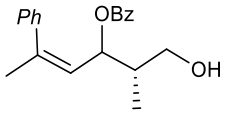
(2S,Z)-1-((4-methoxybenzyl)oxy)-2-methyl-5-phenylhex-4-en-3-ol (**2.10**)

Prepared according to the general procedure for iron-catalyzed carbometalation of propargylic alcohols using propargylic alcohol **2.9** (0.125 g, 0.402 mmol). Purification by flash column chromatography on silica gave **2.10** (0.069 g, 53 %) as a yellow oil. Spectral data for major diastereomer:

IR (ATR): 3425, 2907, 1729, 1617, 1611, 1586, 1512, 1493, 1463, 1442, 1361, 1302, 1245, 1173, 1076, 1033, 910, 818, 765, 729, 701, 668 cm^{-1}.

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.37 – 7.33 (m, 2H), 7.30 – 7.25 (m, 3H), 7.25 – 7.22 (m, 2H), 6.93 – 6.85 (m, 2H), 5.50 (dq, *J* = 9.7, 1.5 Hz, 1H), 4.43 (d, *J* = 8.3 Hz, 2H), 3.98 (dd, *J* = 9.6, 8.0 Hz, 1H), 3.82 (s, 3H), 3.53 (dd, *J* = 9.3, 4.3 Hz, 1H), 3.38 (dd, *J* = 9.3, 8.0 Hz, 1H), 2.09 (d, *J* = 1.5 Hz, 3H), 1.92 (dddd, *J* = 12.4, 7.9, 4.9, 2.7 Hz, 1H), 0.78 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 159.28, 141.51, 140.32, 129.86, 129.40, 129.33, 129.30, 129.26, 128.68, 128.24, 128.21, 128.18, 128.16, 127.90, 127.84, 127.18, 126.88, 126.85, 113.87, 113.83, 113.80, 74.99, 73.84, 73.04, 72.95, 55.28, 39.05, 26.08, 25.88, 13.78, 12.07.



(2S,Z)-1-hydroxy-2-methyl-5-phenylhex-4-en-3-yl benzoate (**2.11**)

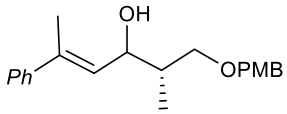
IR (ATR): 3398, 3061, 2693, 2924, 1718, 1716, 1700, 1696, 1692, 1685, 1652, 1601, 1584, 1557, 1539, 1506, 1492, 1457, 1451, 1374, 1314, 1269, 1176, 1110, 1069, 1025, 912, 805, 765, 742, 700, 685, 668, 652 cm^{-1}.

Prepared according to the general benzoylation procedure using **2.10** (0.0693 g, 0.212 mmol). The general procedure for DDQ removal of the PMB was then performed on the crude benzoylation product mixture obtained. Purification by flash chromatography on silica gave **1.9** (0.0233 g, 35% over two steps) as an oil.

Spectral data for mixture of diastereomers:

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.13 (dd, *J* = 8.4, 1.3 Hz, 2H), 8.05 (ddd, *J* = 14.0, 8.4, 1.4 Hz, 2H), 7.66 – 7.55 (m, 2H), 7.52 – 7.43 (m, 6H), 7.40 – 7.35 (m, 4H), 7.28 (m, 4H), 5.74 (d, *J* = 2.1 Hz, 2H), 5.63 (dq, *J* = 9.6, 1.4 Hz, 2H), 5.52 (dd, *J* = 9.6, 7.7 Hz, 2H), 3.49 (t, *J* = 4.6 Hz, 2H), 3.46 (dd, *J* = 11.6, 5.7 Hz, 1H), 3.39 (dd, *J* = 11.6, 8.1 Hz, 1H), 2.13 (d, *J* = 1.5 Hz, 3H), 2.13 (d, *J* = 0.7 Hz, 3H), 2.06 – 1.93 (m, 2H), 1.00 (dd, *J* = 7.0, 3.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.24, 143.00, 142.06, 140.93, 133.69, 133.02, 130.37, 130.19, 129.72, 129.68, 129.53, 129.01, 128.51, 128.47, 128.43, 128.39, 128.37, 128.27, 127.61, 127.49, 127.47, 127.35, 127.32, 123.85, 123.59, 74.11, 72.79, 64.49, 63.86, 41.08, 40.67, 26.20, 12.98, 11.08.



(2S,E)-1-((4-methoxybenzyl)oxy)-2-methyl-5-phenylhex-4-en-3-ol

Prepared according to the general zirconium-catalyzed carboalumination using aldehyde **2.8**[16] (1.0

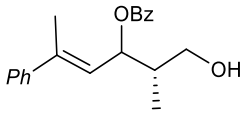
g, 4.7 mmol). Purification by flash chromatography on silica gave (2S,E)-1-((4-methoxybenzyl)oxy)-2-methyl-5-phenylhex-4-en-3-ol (1.31 g, 85%) as a colorless oil.
R_f = 0.65 in 1:1 hexanes:EtOAc.

IR (ATR): 3320, 3028, 2986, 2962, 2851, 1713, 1611, 1595, 1576, 1440, 1246, 1035, 699 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.43 (d, *J* = 7.1 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 2H), 7.29 (t, *J* = 8.7 Hz 3H), 6.91 (d, *J* = 8.6 Hz, 2H), 5.78 (dq, *J* = 8.9, 1.4 Hz, 1H), 4.50 (d, *J* = 11.7, 1H), 4.51 (m, 1H), 4.47 (d, *J* = 11.7Hz, 1H), 3.83 (s, 3H), 3.66 (dd, *J* = 9.3, 4.3 Hz, 1H), 3.51 (dd, *J* = 9.3, 7.6 Hz, 1H), 2.12 (d, *J* = 1.4 Hz, 3H), 2.03 (qd, *J* = 7.4, 4.3 Hz, 1H). 0.93 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 159.27, 143.22, 137.42, 129.87, 129.50, 129.34, 128.15, 127.10, 125.88, 113.84, 74.49, 73.11, 73.10, 55.25, 39.34, 16.52, 13.45.

HRMS (ES+): *m/z* $[349.1780]^+$ calcd for $C_{21}H_{26}O_3Na^+$ $[M+Na]^+$; found: 349.1771.



(2S,E)-1-hydroxy-2-methyl-5-phenylhex-4-en-3-yl benzoate (**1.4**).

Prepared according to the general procedure for removal of a PMB group with DDQ using (2S,E)-1-((4-methoxybenzyl)oxy)-2-methyl-5-phenylhex-4-en-3-ol (1.2 g, 2.78 mmol). Purification by flash chromatography on silica gave **1.4** (0.6 g, 70%) as an oil.

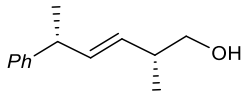
R_f = 0.18 in 4:1 hexanes:EtOAc.

IR (ATR): 3420, 3060, 3032, 2964, 2922, 2880, 1714, 1450, 1268, 1110, 932, 711 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 8.07 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.42 (dd, *J* = 7.2, 1.3 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 5.95 (dd, *J* = 9.4, 8.1 Hz, 1H), 5.84 (dq, *J* = 9.4, 1.4 Hz, 1H), 3.68 (qd, *J* = 11.3, 4.6 Hz, 2H), 2.23 (d, *J* = 1.4 Hz, 3H), 2.15 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 166.48, 142.73, 140.69, 133.05, 130.20, 129.67, 128.38, 128.25, 127.54, 125.96, 124.33, 73.31, 64.09, 40.55, 16.88, 12.92.

HRMS (ES+): *m/z* $[333.1467]^+$ calcd for $C_{21}H_{26}O_2Na^+$ $[M+Na]^+$; found: 333.1472.



(2R,5R,E)-2-methyl-5-phenylhex-3-en-1-ol (**1.5**)

Prepared according to the general procedure for $SmI_2(H_2O)_n$ reductions using compound **1.4** (0.025 g, 0.08 mmol). Purification of the crude product mixture by flash chromatography on silica gave **1.5** (0.0135 g, 90%) as an oil.

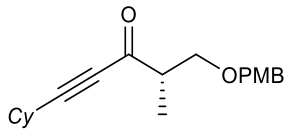
R_f = 0.31 in 4:1 hexanes:EtOAc.

IR (ATR): 3360, 3083, 3061, 3025, 2961, 2925, 2871, 1950, 1876, 1803, 1716, 1601, 1492, 1415, 1373, 1272, 1029, 971, 760, 698 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.38 (t, *J* = 4.7 Hz, 1H), 7.30 (t, *J*=6.9 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.74 (ddd, *J* = 15.5, 6.8, 1.1 Hz, 1H), 5.33 (ddd, *J* = 15.5, 7.9, 1.4 Hz, 1H), 3.47(m, 2H), 3.38 (dd, *J* =10.6, 8.1, 1H) 2.36 (hept, *J* = 7.0 Hz, 1H), 1.36 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 146.04, 136.89, 131.00, 128.43, 127.07, 126.06, 67.35, 42.27, 39.66, 21.48, 16.60.

HRMS (ES+): *m/z* $[190.1358]^+$ calcd for $C_{13}H_{18}O^+$ $[M]^+$; found: 190.1358.



(S)-1-cyclohexyl-5-((4-methoxybenzyl)oxy)-4-methylpent-1-yn-3-one (**2.33**).

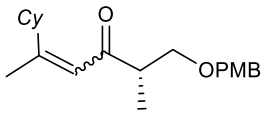
Prepared according to the general procedure for acetylide formation and attack of aldehyde using cyclohexyl acetylene (0.110 mL, 0.842 mmol) and aldehyde **2.8** (0.153 g, 0.926 mmol). The crude oil product was then dissolved in 4 mL of DCM and the flask was placed into a room temp water bath. To the flask, sodium bicarbonate (353 mg, 4.2 mmol) and Dess-Martin periodinane (537 mg, 1.27 mmol) was added. The solution was stirred at room temp for 1 hour. The reaction was washed with 1M NaOH (5mL) and extracted with MTBE (3 x 5 mL). The

combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography on silica gave **2.33** (0.123 g**,** 47%), as an oil.

IR (ATR): 2931, 2854, 2203, 1669, 1611, 1511, 1449, 1300, 1245, 1172, 1089, 1032, 943, 918, 819, 743 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ = 7.28 – 7.25 (m, 2H), 6.92 – 6.87 (m, 2H), 4.47 (s, 2H), 3.83 (s, 3H), 3.76 (dd, *J* = 9.3, 6.8 Hz, 1H), 3.56 (dd, *J* = 9.3, 5.7 Hz, 1H), 2.87 (h, *J* = 6.8 Hz, *O*H), 2.57 (tt, *J* = 9.1, 3.9 Hz, 1H), 1.87 – 1.80 (m, 2H), 1.76 – 1.68 (m, 2H), 1.52 (dtt, *J* = 12.2, 8.7, 3.2 Hz, 3H), 1.42 – 1.32 (m, *J* = 3.7 Hz, 3H), 1.21 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 190.13, 159.20, 130.22, 129.27, 113.74, 99.02, 79.69, 72.88, 71.14, 55.27, 49.06, 31.61, 29.14, 25.63, 24.63, 13.35.



(S)-5-cyclohexyl-1-((4-methoxybenzyl)oxy)-2-methylhex-4-en-3-one (**2.34**).

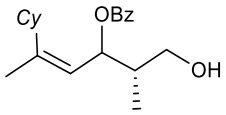
A Schlenk tube was charged with copper (I) iodide (0.112 g, 0.588 mmol) and THF (2 mL). The solution was cooled to -30 °C and a 1.6M solution of MeLi in ether was added dropwise. After stirring for 30 minutes at -30 °C the solution was cooled to -78 °C and **2.33** (0.123 g, 0.392 mmol) was added dropwise turning the solution yellow. The reaction was left for 1 hour at -78 °C, quenched with saturated aq. NH_4Cl (5 mL) and separated with DCM (3 x 5 mL).). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gave the oil **2.34** (0.079 g**,** 61%), as a 50:50 cis/*trans* mixture.

Spectral data for the cis isomer:

IR (ATR): 2926, 2851, 1738, 1679, 1608, 1511, 1448, 1370, 1301, 1244, 1171, 1093, 1033, 915, 892, 819, 771, 757, 732 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ = 7.25 (dd, *J* = 8.7, 2.3 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.12 (t, *J* = 1.2 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 3.82 (s, 3H), 3.68 (dd, *J* = 9.3, 7.3 Hz, 1H), 3.43 (ddd, *J* = 9.2, 6.1, 3.0 Hz, 1H) 2.86 (m, *J* = 6.4 Hz, 1H), 2.13 (d, *J* = 1.2 Hz, 3H), 1.98 (tt, *J* = 11.3, 3.4 Hz, 1H), 1.79 – 1.67 (m, 4H), 1.45 – 1.13 (m, 6H),1.11 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 203.28, 202.34, 164.95, 164.24, 159.13, 130.47, 129.33, 129.21, 122.92, 121.06, 113.80, 113.72, 72.87, 72.85, 72.09, 72.04, 55.27, 49.06, 47.56, 47.46, 40.54, 31.41, 30.95, 30.91, 26.43, 26.24, 26.22, 26.12, 21.21, 18.03, 13.97, 13.95.



(2S,Z)-5-cyclohexyl-1-hydroxy-2-methylhex-4-en-3-yl benzoate (**2.35**)

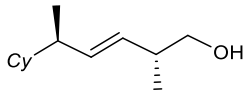
The ketone **2.34** (0.607 g, 0.184 mmol) was dissolved with methanol (1 mL) in an open air flask. Sodium borohydride was added to the stirring mixture. The reaction was left for 1 hour at room temperature, quenched with saturated aq. NH_4Cl (5 mL) and separated with ethyl acetate (3 x 5 mL).). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. The crude reaction mixture was then subjected to the general benzoylation procedure and subsequently the general procedure for removal of a PMB group with DDQ. Purification by flash column chromatography on silica gave a partially separable mixture of cis/*trans* isomers **2.50** (0.052 g, 42 % over three steps) as a colorless oil.

Spectral data for the major diastereomer of the *cis*-isomer:

IR (ATR): 3427, 2925, 2852, 1711, 1602, 1584, 1513, 1450, 1378, 1314, 1272, 1176, 1113, 1097, 1069, 1025, 985, 906, 847, 731, 710, 687 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ = 8.07 (ddd, *J* = 8.5, 2.4, 1.3 Hz, 2H), 7.63 – 7.53 (m, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 6.08 (dd, *J* = 8.9, 4.2 Hz, 1H), 5.34 (dq, *J* = 9.0, 1.5 Hz, 1H), 3.52 (t, *J* = 7.9, 5.9 Hz, 1H), 3.50 (dd, *J* = 7.9, 4.6 Hz, 1H), 2.60 (tq, *J* = 11.1, 3.2 Hz, 1H), 2.43 (dd, *J* = 8.2, 5.0 Hz, 1H), 2.04 (m, 1H), 1.79 (m, 1H), 1.71 (d, *J* = 1.5 Hz, 3H), 1.72 – 1.67 (m, 1H), 1.60 – 1.49 (m, 2H), 1.41 – 1.26 (m, 4H), 1.20 – 1.12 (m, 2H), 1.02 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.62, 166.48, 147.49, 146.66, 132.97, 132.94, 130.47, 130.43, 129.67, 128.37, 121.21, 120.81, 72.26, 71.15, 64.68, 64.14, 41.16, 40.60, 40.40, 31.11, 30.99, 30.94, 26.39, 26.30, 26.14, 26.12, 19.68, 19.65, 13.24, 11.23.



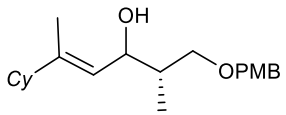
(2R,5R,E)-5-cyclohexyl-2-methylhex-3-en-1-ol (**2.37**)

Prepared according to the general procedure for $SmI_2(H_2O)_n$ reductions using compound **2.35** (0.0068 g, 0.021 mmol). Purification of the crude product mixture by flash chromatography on silica gave **2.37** (0.0034 g, 81 %) as an oil.

IR (ATR): 3335, 2957, 2922, 2851, 2360, 2342, 1448, 1373, 1032, 989, 969, 678, 668 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ = 5.46 (ddd, *J* = 15.3, 8.2, 0.7 Hz, 1H), 5.19 (ddd, *J* = 15.4, 8.0, 0.7 Hz, 1H), 3.50 (dt, *J* = 11.1, 6.0 Hz, 1H), 3.37 (t, *J* = 9.3 Hz, 1H), 2.33 (heptq, *J* = 6.7, 1.1 Hz, 1H), 1.96 (h, *J* = 6.9 Hz, 1H), 1.77 – 1.62 (m, 4H), 1.38 (O**H**, 1H), 1.28 (s, 1H), 1.22 (tq, *J* = 12.7, 3.2 Hz, 2H), 1.15 (dt, *J* = 11.3, 2.5 Hz, 2H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.98 (dd, *J* = 6.8, 0.7 Hz, 3H), 0.93 (ddd, *J* = 12.0, 8.4, 4.0 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 137.28, 130.98, 67.33, 43.06, 42.48, 39.86, 30.42, 30.38, 26.65, 17.94, 16.79.



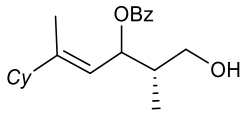
(2S,E)-5-cyclohexyl-1-((4-methoxybenzyl)oxy)-2-methylhex-4-en-3-ol (**2.30**)

Prepared according to the general zirconium-catalyzed carboalumination using cyclohexyl acetylene (0.078 mL, 0.60 mmol) and aldehyde **2.8** (0.100 g, 0.480 mmol). Purification by flash chromatography on silica gave **2.30** (0.116 g, 35%) as a colorless oil.

IR (ATR): 3444, 2924, 2851, 1611, 1586, 1512, 1448, 1420, 1362, 1301, 1246, 1172, 1082, 1034, 1004, 908, 846, 819, 730 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ = 7.30 – 7.26 (m, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.17 (d, *J* = 9.0 Hz, 1H), 4.48 (s, 2H), 4.31 (t, *J* = 8.3 Hz, 1H), 3.83 (s, 3H), 3.58 (dd, *J* = 9.2, 4.5 Hz, 1H), 3.47 (dd, *J* = 9.3, 7.6 Hz, 1H), 1.94 – 1.83 (m, 2H), 1.81 – 1.73 (m, 2H), 1.73 – 1.67 (m, 2H), 1.66 (d, *J* = 1.3 Hz, 3H), 1.28 (dddt, *J* = 19.9, 16.5, 7.5, 3.9 Hz, 3H), 1.18 (tdd, *J* = 14.3, 6.1, 2.5 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 159.40, 144.17, 129.45, 124.59, 113.97, 74.85, 73.18, 72.78, 55.42, 47.51, 39.47, 32.04, 31.94, 26.84, 26.51, 15.33, 13.51.



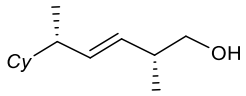
(2S,E)-5-cyclohexyl-1-hydroxy-2-methylhex-4-en-3-yl benzoate (**2.31**)

Prepared according to the general benzoylation procedure using **2.30** (0.116 g, 0.349 mmol). The general procedure for DDQ removal of the PMB was then performed on the crude benzoylation product mixture obtained. Purification by flash chromatography on silica gave **2.31** (0.024 g, 21% over two steps) as an oil.

IR (ATR): 3434, 2924, 2852, 1714, 1601, 1584, 1491, 1449, 1375, 1314, 1269, 1216, 1175, 1111, 1097, 1069, 1036, 1025, 987, 934, 892, 847, 805, 777, 737, 709, 686 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ = 8.06 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.59 (m, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 5.79 (dd, *J* = 9.4, 8.4 Hz, 1H), 5.29 (dt, *J* = 9.4, 1.3 Hz, 1H), 3.64 (dd, *J* = 11.3, 4.4 Hz, 1H), 3.61 (d, *J* = 12.0 Hz, 1H), 2.03 (m, 1H), 1.92 (ddd, *J* = 13.7, 10.8, 2.6 Hz, 1H), 1.79 (d, *J* = 1.4 Hz, 3H), 1.76 (d, *J* = 2.6 Hz, 2H), 1.74 – 1.66 (m, 2H), 1.35 – 1.11 (m, 6H), 1.04 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.57, 132.96, 129.69, 128.37, 119.65, 73.31, 64.24, 47.43, 40.55, 31.80, 31.79, 26.62, 26.59, 26.30, 15.51, 12.96.



(2R,5S,E)-5-cyclohexyl-2-methylhex-3-en-1-ol (**2.36**)

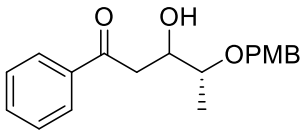
Prepared according to the general procedure for $SmI_2(H_2O)_n$ reductions using compound **2.31** (0.0068 g, 0.0214 mmol)**.** Purification of the crude product mixture by flash chromatography on silica gave **2.36** (0.0034 g, 81 %) as an oil.

IR (ATR): 3331, 2957, 2921, 2850, 1448, 1371, 1030, 989, 969, 965, 889 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ = 5.45 (ddd, *J* = 15.4, 8.3, 1.0 Hz, 1H), 5.19 (ddd, *J* = 15.4, 8.0, 1.0 Hz, 1H), 3.50 (dd, *J* = 10.0, 5.7 Hz, 1H), 3.37 (dd, *J* =

10.4, 8.0 Hz, 1H), 2.34 (pp, *J* = 6.7, 1.2 Hz, 1H), 1.96 (h, *J* = 6.8 Hz, 1H), 1.77 – 1.63 (m, 4H), 1.40 (m, 1H), 1.27 – 1.08 (m, 4H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.97 – 0.87 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 137.09, 130.91, 67.27, 42.92, 42.41, 39.79, 30.38, 30.35, 26.53, 17.71, 16.61.



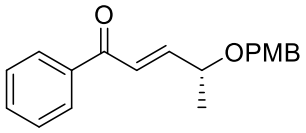
(4R)-3-hydroxy-4-((4-methoxybenzyl)oxy)-1-phenylpentan-1-one (**3.1**)

To a dried Sclenck flask, dry THF (3.2 mL) and diisopropyl amine (0.203 mL, 1.45 mmol) were added under nitrogen. The mixture was cooled to -78 °C and an *n*-BuLi solution (0.463 mL, 2.5M) was added dropwise. The solution was then *trans*ferred to an ice water bath and allowed to stir for 10 minutes. The mixture was then cooled to -78 °C and acetophenone (0.116g, 0.965 mmol) was added dropwise. The reaction mixture was allowed to stir for 1 hour at -78 °C. Then the aldehyde **2.4** (0.138 g, 0.772 mmol) was added dropwise and the reaction mixture was allowed to stir for another hour at -78 °C, quenched with saturated aq. NH_4Cl (5 mL) and separated with DCM (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gave the oil **3.1** (0.108 g**,** 48 %), as a 50:50 *cis*/*trans* mixture.
Spectral data for the major diastereomer

IR (ATR): 3059, 2974, 2932, 2863, 2836, 1735, 1676, 1670, 1652, 1636, 1623, 1613, 1597, 1579, 1512, 1464, 1447, 1353, 1302, 1244, 1208, 1173, 1147, 1079, 1032, 1011, 976, 820, 774, 755, 696, 667, 661 cm^{-1}.

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.95 (dt, *J* = 8.4, 1.2 Hz, 2H), 7.61 – 7.55 (m, 1H), 7.47 (td, *J* = 7.8, 7.4, 1.5 Hz, 2H), 7.30 – 7.25 (m, 2H), 6.88 (t, *J* = 8.5 Hz, 2H), 4.63 (d, *J* = 11.4 Hz, 1H), 4.41 (d, *J* = 11.4 Hz, 1H), 4.28 – 4.23 (m, 1H), 3.81 (s, 3H), 3.64 (qd, *J* = 6.3, 4.4 Hz, 1H), 3.16 (d, *J* = 5.2 Hz, 1H), 1.30 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 200.12, 159.26, 137.00, 133.34, 130.49, 129.49, 128.61, 128.21, 113.84, 76.05, 70.71, 70.47, 55.26, 41.14, 15.15.



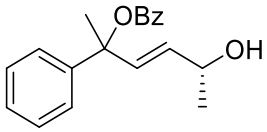
(R,E)-4-((4-methoxybenzyl)oxy)-1-phenylpent-2-en-1-one (**3.2**).

IR (ATR): 2974, 1931, 2936, 1676, 1670, 1669, 1622, 1613, 1597, 1512, 1505, 1448, 1324, 1302, 1279, 1267, 1245, 1207, 1172, 1147, 1076, 1031, 1012, 977, 845, 820, 773, 755, 731, 695, 667, 662 cm^{-1}.

To a dried flask containing THF (3.2 mL) and **3.1** (0.0483 g, 0.159 mmol), DMAP (0.175 g, 1.43 mmol) and acetic anhydride (0.150 mL, 1.59 mmol) was added at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 40 minutes. Then DBU was added at room temperature, stirred for 1 hour quenched with a brine solution (5 mL) and separated with MTBE (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gave the oil **3.2** (0.025 g**,** 56 %), as a 50:50 *cis*/*trans* mixture.
Spectral data for the major diastereomer

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.86 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.53 – 7.46 (m, 1H), 7.40 (dd, *J* = 8.3, 7.0 Hz, 2H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.00 (dd, *J* = 15.6, 1.2 Hz, 1H), 6.90 (dd, *J* = 15.5, 5.6 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.48 (d, *J* = 11.5 Hz, 1H), 4.37 (d, *J* = 11.5 Hz, 1H), 4.20 – 4.11 (m, 1H), 3.73 (s, 3H), 1.29 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 190.70, 159.29, 149.65, 137.71, 132.92, 130.29, 129.29, 128.64, 128.62, 124.90, 113.91, 74.08, 70.63, 55.31, 20.83.



(5R,E)-5-hydroxy-2-phenylhex-3-en-2-yl benzoate (**3.3**)

IR (ATR): 3376, 2974, 2930, 1735, 1701, 1699, 1602, 1584, 1558, 1493, 1450, 1371, 1314, 1274, 1174, 1109, 1069, 1025, 1001, 969, 936, 909, 850, 805, 761, 732, 709, 698, 667 cm^{-1}.

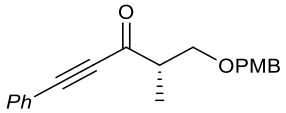
A dried flask containing **3.2** (0.0222 g, 0.0749 mmol) and THF (1 mL) was cooled to 0 °C and a solution of methyl magnesium bromide was added dropwise (0.037 mL, 3M). The reaction was allowed to stir at 0

°C for one hour before addition of BzCl (0.017 mL, 0.15 mmol). The mixture was warmed to room temperature and stirred overnight. The crude mixture was quenched with saturated aq. NH_4Cl (5 mL) and separated with DCM (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The Crude reaction mixture was then subjected to the general procedure for DDQ removal of PMB protecting group. Purification by flash chromatography on silica gave the oil **3.3** (0.0055 g**,** 25 %).

Spectral data for the major diastereomer

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.15 – 8.11 (m, 2H), 8.10 – 8.06 (m, 2H), 7.66 – 7.60 (m, 1H), 7.60 – 7.54 (m, 1H), 7.52 – 7.42 (m, 10H), 7.37 (ddd, *J* = 8.0, 6.3, 1.2 Hz, 2H), 7.31 – 7.26 (m, 2H), 6.26 (dd, *J* = 15.7, 1.2 Hz, 2H), 5.90 (ddd, *J* = 15.8, 6.2, 1.3 Hz, 2H), 4.44 (pdd, *J* = 6.3, 2.3, 1.3 Hz, 2H), 2.05 (s, 3H), 2.04 (s, 3H), 1.35 (d, *J* = 6.4 Hz, 3H), 1.33 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 171.21, 164.91, 143.96, 134.36, 134.27, 133.71, 133.47, 133.40, 132.88, 132.86, 131.32, 130.29, 130.20, 129.61, 129.36, 128.71, 128.58, 128.49, 128.44, 128.38, 128.31, 127.35, 126.01, 125.19, 125.15, 124.65, 83.27, 68.46, 68.40, 26.17, 26.11, 23.31, 23.27.



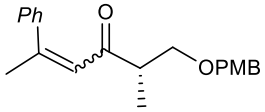
(S)-5-((4-methoxybenzyl)oxy)-4-methyl-1-phenylpent-1-yn-3-one (**2.14**).

To an open air flask **2.9** (0.228 g, 0.735 mmol) and DCM (4 mL) was added and placed into a room temp water bath. To the flask, sodium bicarbonate (308 mg, 3.67 mmol) and Dess-Martin periodinane (467 mg, 1.10 mmol) was added. The solution was stirred at room temp for 1 hour. The reaction was washed with 1M NaOH (5mL) and extracted with MTBE (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography on silica gave **2.14** (0.225 g**,** 99%), as an oil.

IR (ATR): 2935, 2858, 2197, 1666, 1611, 1585, 1511, 1489, 1454, 1442, 1361, 1301, 1283, 1245, 1172, 1059, 1033, 997, 907, 819, 757, 728, 688 cm^{-1}.

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.58 – 7.53 (m, 2H), 7.51 – 7.45 (m, 1H), 7.44 – 7.35 (m, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.51 (s, 2H), 3.83 (dd, *J* = 9.4, 7.0 Hz, 1H), 3.78 (s, 3H), 3.65 (dd, *J* = 9.4, 5.5 Hz, 1H), 3.01 (pd, *J* = 7.0, 5.5 Hz, 1H), 1.29 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 189.81, 159.19, 133.10, 130.69, 130.08, 129.32, 128.60, 120.05, 113.76, 91.73, 86.91, 72.93, 70.98, 55.23, 49.09, 13.27.



(S)-1-((4-methoxybenzyl)oxy)-2-methyl-5-phenylhex-4-en-3-one (**2.15**).

A Schlenk tube was charged with copper (I) iodide (0.209 g, 1.103 mmol) and THF (4 mL). The solution was cooled to -30 °C and a 1.6M solution of MeLi in ether was added dropwise. After stirring for 30 minutes at -30 °C the solution was cooled to -78 °C and **2.14** (0.225 g, 0.731 mmol) was added dropwise turning the solution yellow. The reaction was left for 1 hour at -78 °C, quenched with saturated aq. NH_4Cl (5 mL) and separated with DCM (3 x 5 mL).). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gave the oil **2.15** (0.143 g**,** 60%), as a 50:50 *cis*/*trans* mixture.

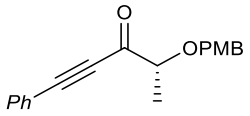
Spectral data for mixture of *cis*/*trans* isomers.

IR (ATR): 2932, 2855, 1680, 1610, 1567, 1573, 1511, 1492, 1442, 1360, 1301, 1244, 1172, 1084, 1032, 965, 917, 818, 762, 697 cm^{-1}

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.52 – 7.47 (m, 2H), 7.40 (dd, *J* = 5.0, 1.9 Hz, 3H), 7.38 – 7.32 (m, 3H), 7.30 – 7.20 (m, 6H), 6.89 (dd, *J* = 12.9, 8.7 Hz, 4H), 6.60 (d, *J* = 1.4 Hz, 1H), 6.26 (d, *J* = 1.4 Hz, 1H), 4.51 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.74 (dd, *J* = 9.3, 7.3 Hz, 1H), 3.60 (dd, *J* = 9.2, 7.0 Hz, 1H), 3.52 (dd, *J* = 9.2, 5.7 Hz, 1H), 3.39 (dd, *J* = 9.3, 6.1 Hz, 1H), 3.01 (pd, *J* = 7.1, 5.7 Hz, 1H), 2.84 – 2.75 (m, 1H), 2.58 (d, *J* = 1.3 Hz, 3H), 2.21 (d, *J* = 1.5 Hz, 3H), 1.18 (d, *J* = 7.1 Hz, 3H), 1.04 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 203.37, 203.04, 159.18, 159.16, 154.42, 152.56, 142.70, 140.87, 130.40, 130.35, 129.28, 129.24, 129.07, 128.54, 128.19, 128.03, 127.18, 126.55, 126.00, 123.94,

113.77, 113.74, 72.94, 72.78, 72.06, 72.02, 55.29, 55.26, 47.96, 46.30, 29.23, 27.12, 18.57, 13.84.



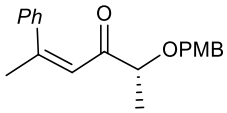
(R)-4-((4-methoxybenzyl)oxy)-1-phenylpent-1-yn-3-one (**2.12**)

To an open air flask **2.5** (0.165 g, 0.556 mmol) and DCM (3 mL) was added and placed into a room temp water bath. To the flask, sodium bicarbonate (223 mg, 2.78 mmol) and Dess-Martin periodinane (353 mg, 0.834 mmol) was added. The solution was stirred at room temp for 1 hour. The reaction was washed with 1M NaOH (5mL) and extracted with MTBE (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography on silica gave **2.12** (0.0982 g**,** 60 %), as an oil.

IR (ATR): 2981, 2934, 2835, 2195, 1670, 1611, 1585, 1511, 1489, 1463, 1442, 1392, 1367, 1301, 1282, 1245, 1172, 1099, 1069, 1031, 996, 973, 846, 821, 756, 688 cm^{-1}.

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.66 – 7.56 (m, 2H), 7.52 – 7.46 (m, 1H), 7.46 – 7.38 (m, 2H), 7.38 – 7.33 (m, 2H), 6.89 (s, 2H), 4.73 (d, *J* = 11.2 Hz, 1H), 4.50 (d, *J* = 11.2 Hz, 1H), 4.14 (q, *J* = 6.9 Hz, 1H), 3.83 (s, 3H), 1.51 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 190.08, 159.45, 133.30, 130.98, 129.70, 129.62, 128.67, 119.86, 113.89, 94.08, 86.25, 80.61, 71.91, 55.31, 17.95.



(R)-2-((4-methoxybenzyl)oxy)-5-phenylhex-4-en-3-one (**2.13**)

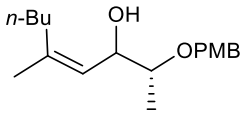
A Schlenk tube was charged with copper (I) iodide (0.095 g, 0.50 mmol) and THF (2 mL). The solution was cooled to -30 ºC and a 1.6M solution of MeLi in ether was added dropwise. After stirring for 30 minutes at -30 ºC the solution was cooled to -78 ºC and **2.12** (0.0982 g, 0.334 mmol) was added dropwise turning the solution yellow. The reaction was left for 1 hour at -78 ºC, quenched with saturated aq. NH_4Cl (5 mL) and separated with DCM (3 x 5 mL).). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gave the oil **2.13** (0.0858 g**,** 83 %), as a 50:50 *cis*/*trans* mixture.

Spectral data for mixture of *cis*/*trans* isomers.

IR (ATR): 2932, 1687, 1610, 1596, 1573, 1512, 1492, 1442, 1370, 1301, 1245, 1173, 1091, 1031, 956, 910, 820, 760, 731, 696 cm^{-1}.

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.53 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.42 (q, *J* = 2.9 Hz, 3H), 7.36 (qd, *J* = 7.6, 6.4, 3.6 Hz, 3H), 7.31 – 7.25 (m, 4H), 7.23 – 7.18 (m, 2H), 6.94 – 6.86 (m, 5H), 6.56 (d, *J* = 1.8 Hz, 1H), 4.57 (d, *J* = 11.3 Hz, 1H), 4.52 (d, *J* = 11.2 Hz, 1H), 4.46 (d, *J* = 11.4 Hz, 1H), 4.35 (d, *J* = 11.3 Hz, 1H), 4.02 (q, *J* = 6.9 Hz, 1H), 3.85 (t, *J* = 7.2 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 2.63 – 2.60 (m, 3H), 2.24 (d, *J* = 1.4 Hz, 3H), 1.40 (d, *J* = 6.9 Hz, 3H), 1.33 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 203.14, 201.41, 159.40, 156.73, 155.80, 142.52, 140.89, 129.95, 129.88, 129.66, 129.58, 129.37, 128.59, 128.14, 128.05, 126.98, 126.59, 121.22, 119.35, 113.91, 113.89, 81.42, 80.42, 71.72, 71.53, 55.31, 53.48, 29.73, 27.78, 18.65, 18.27, 17.93.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OH
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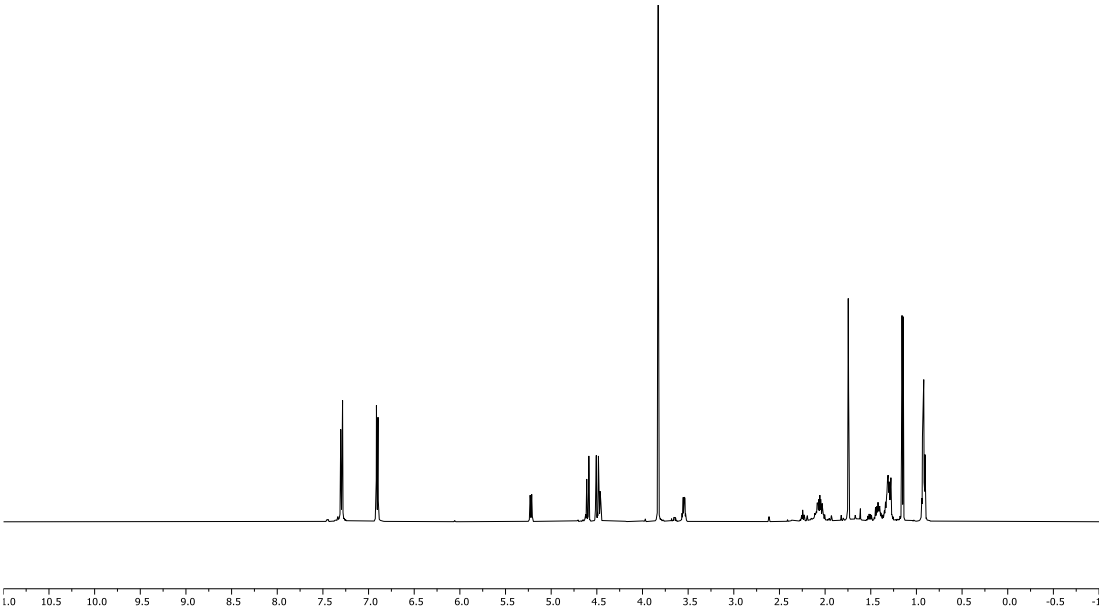
Spectra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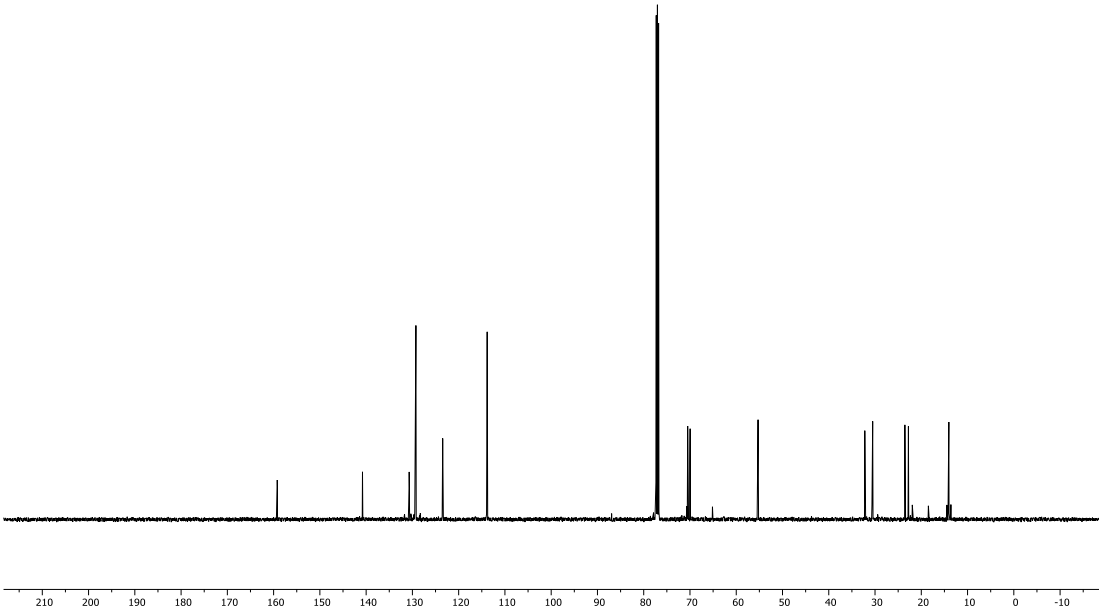
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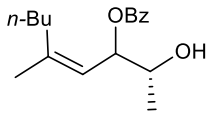
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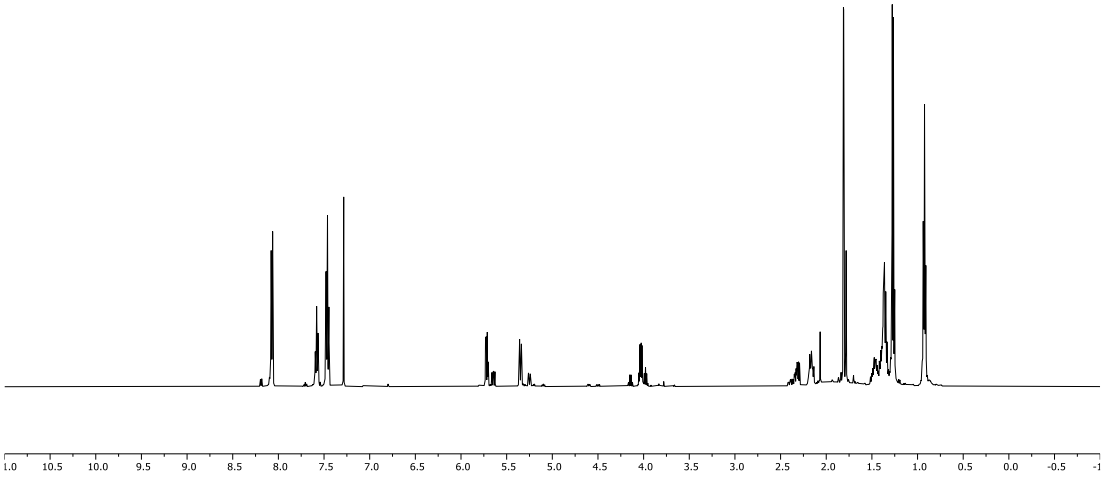
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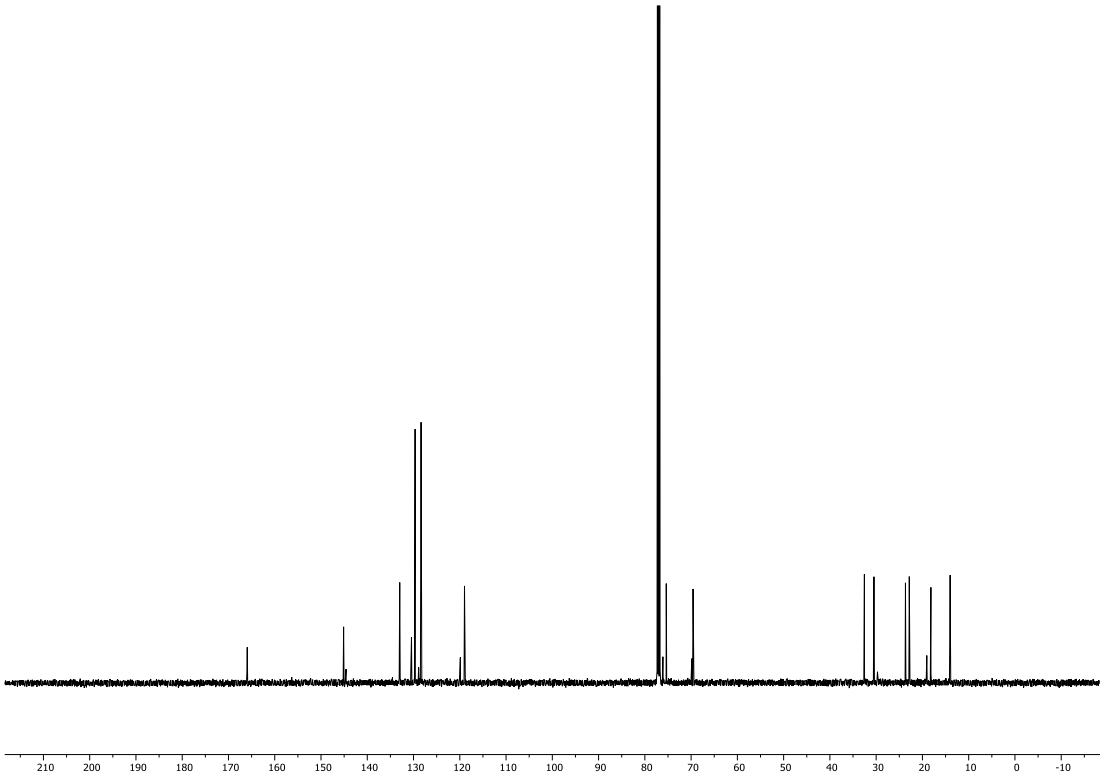
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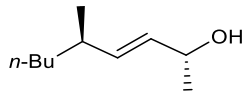
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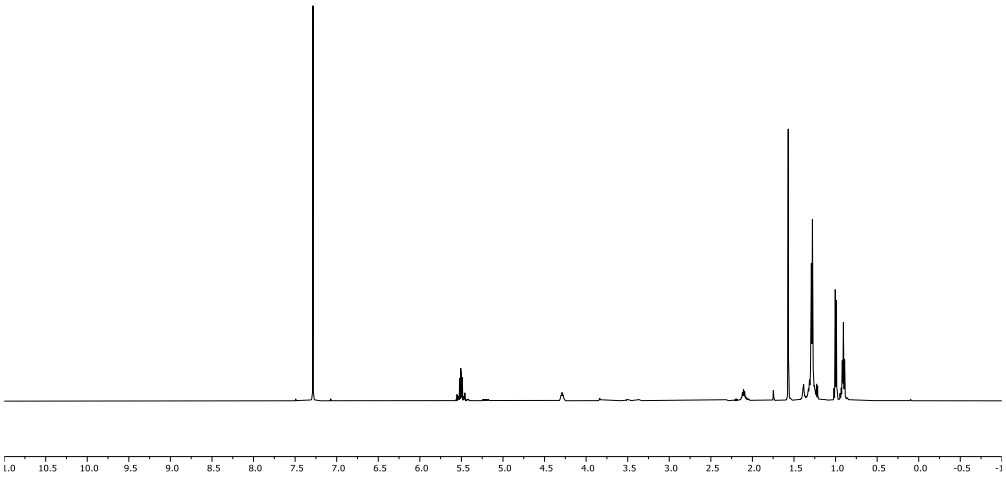
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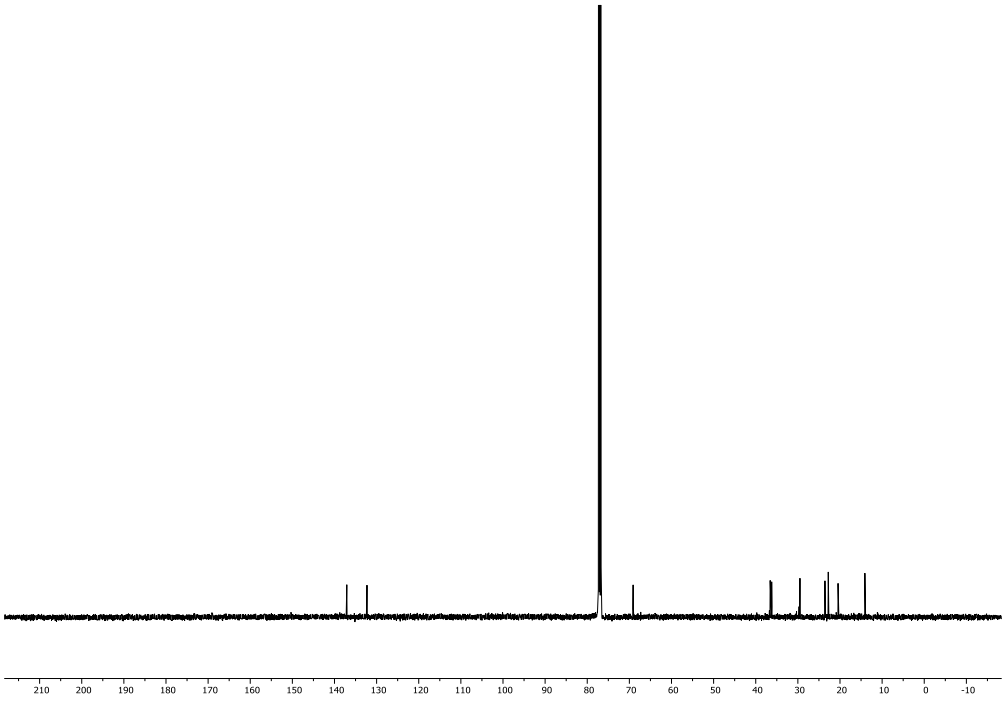
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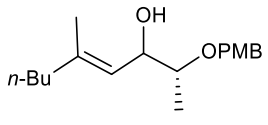
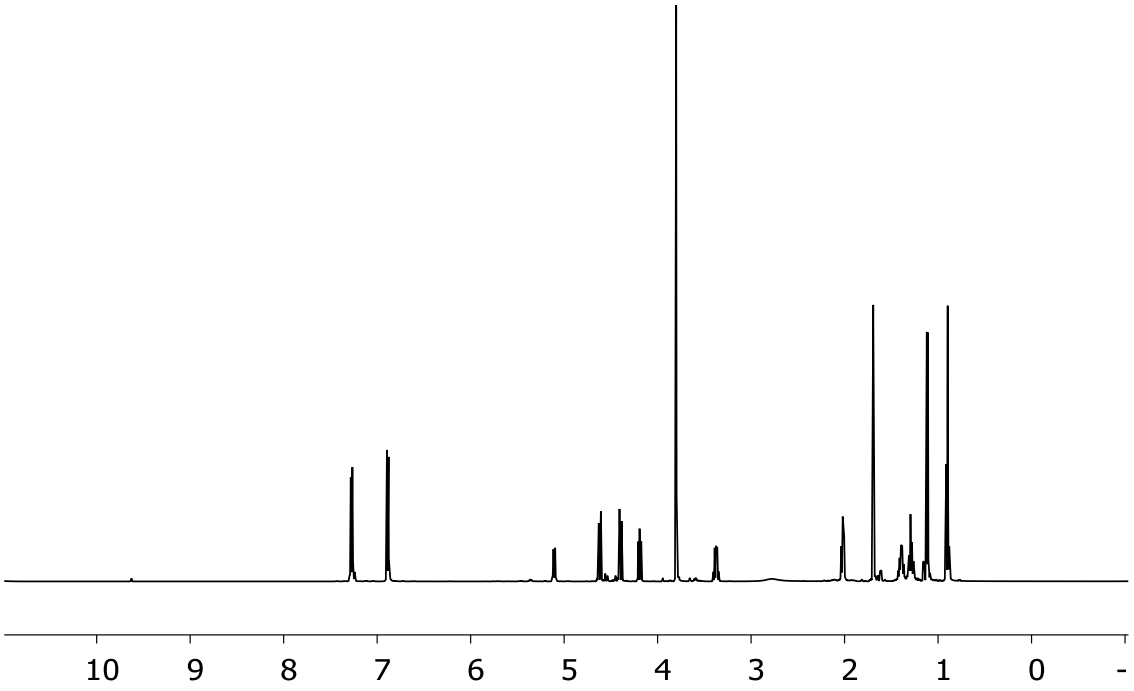
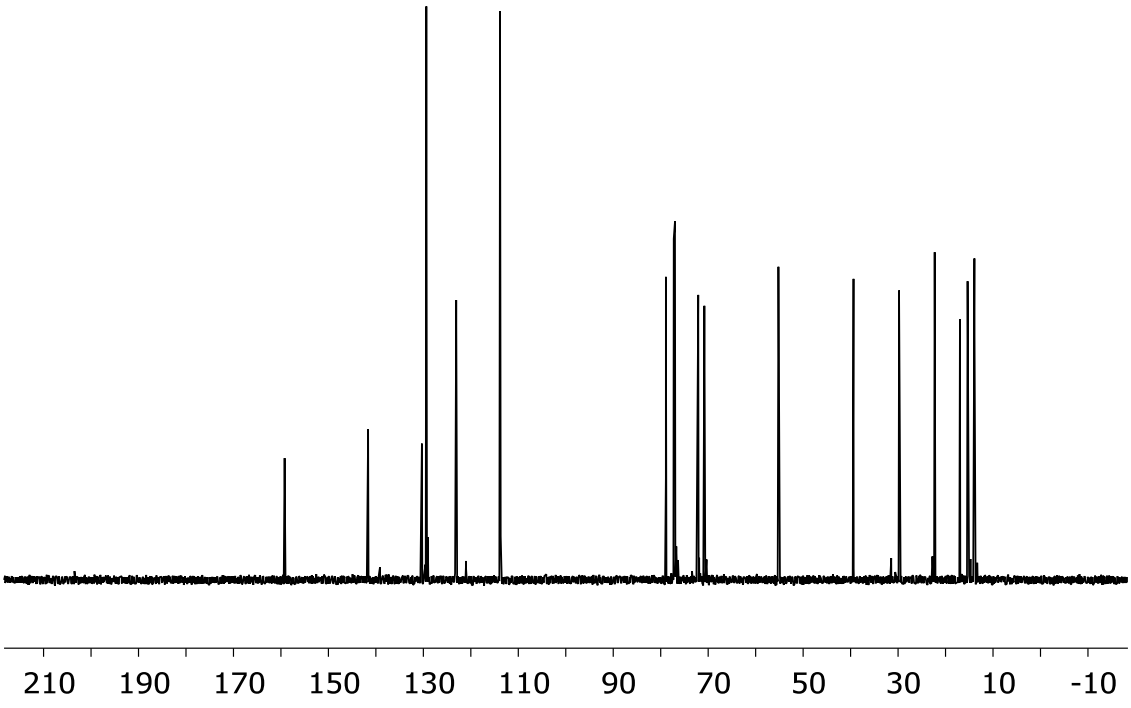
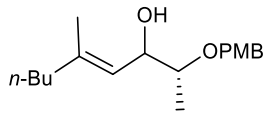


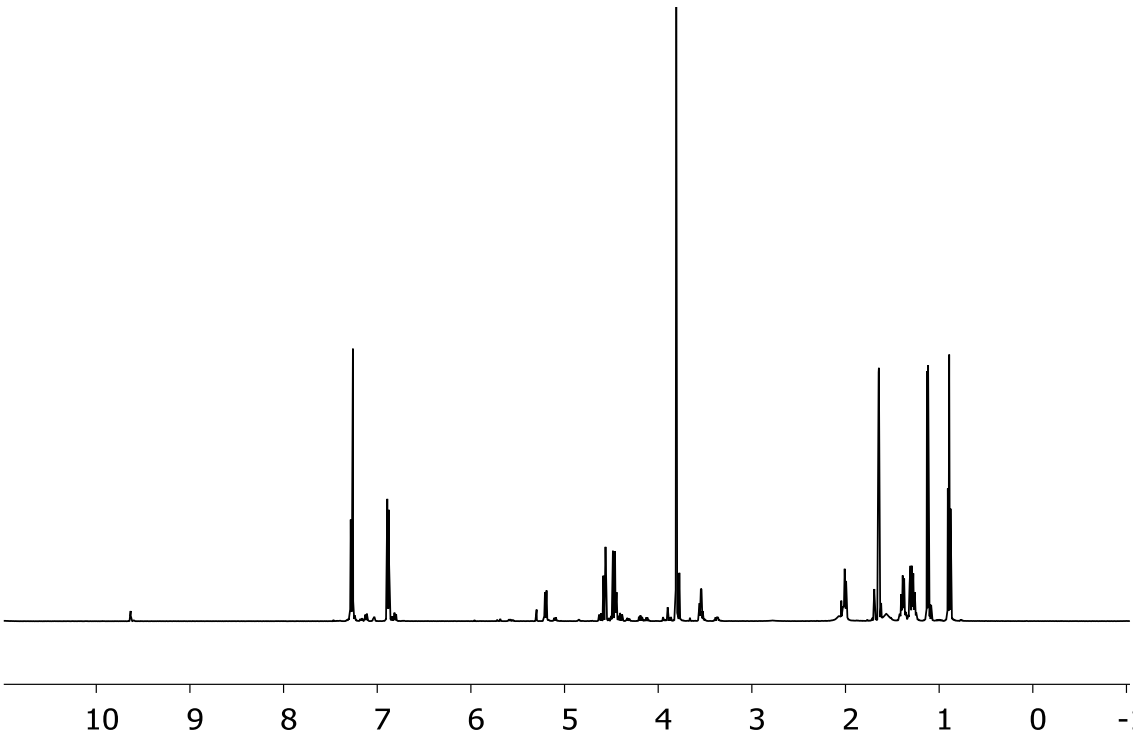
(diastereomer α)

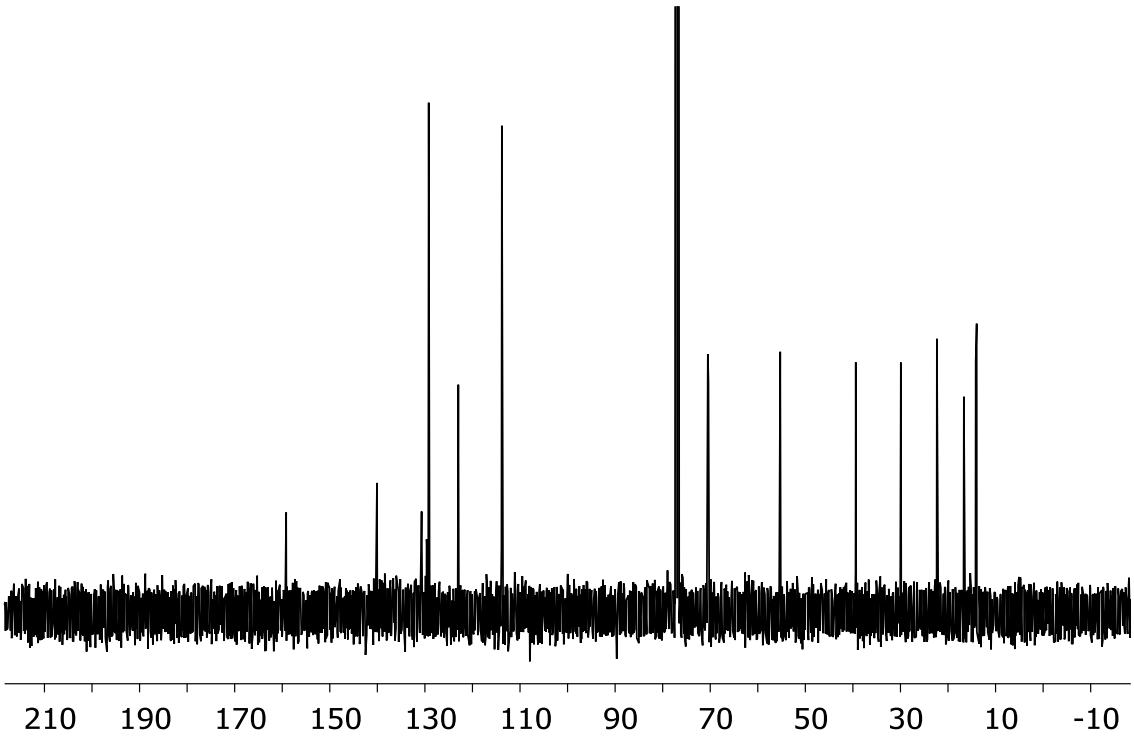


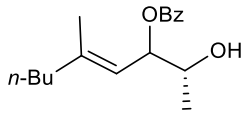




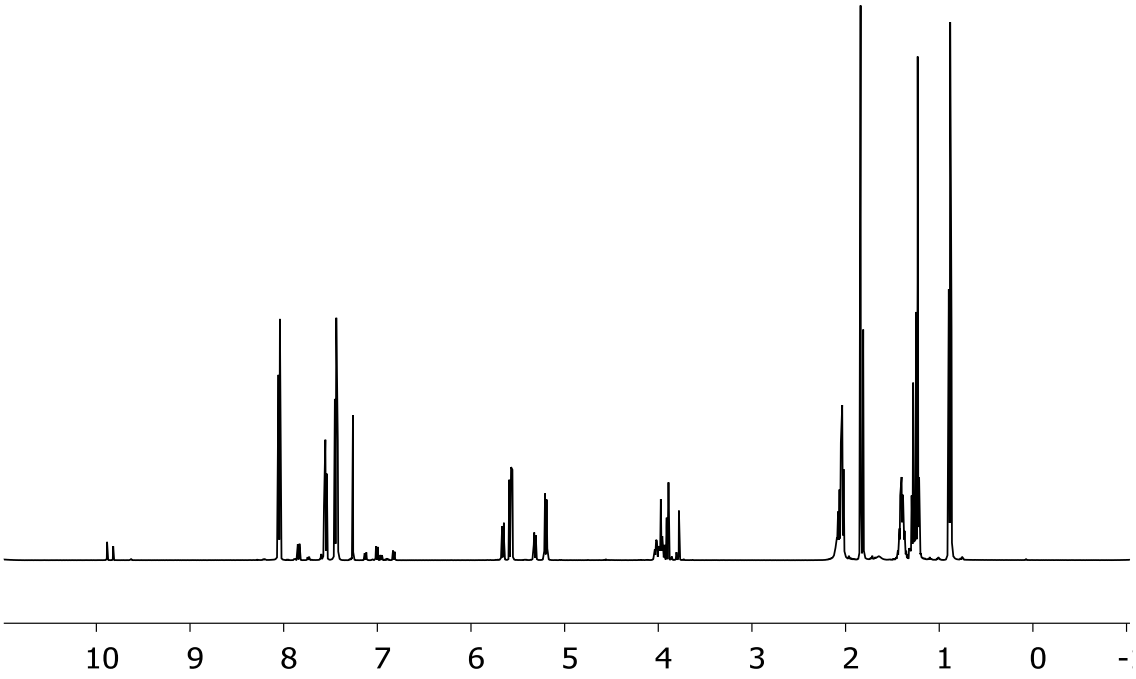
(diastereomer β)

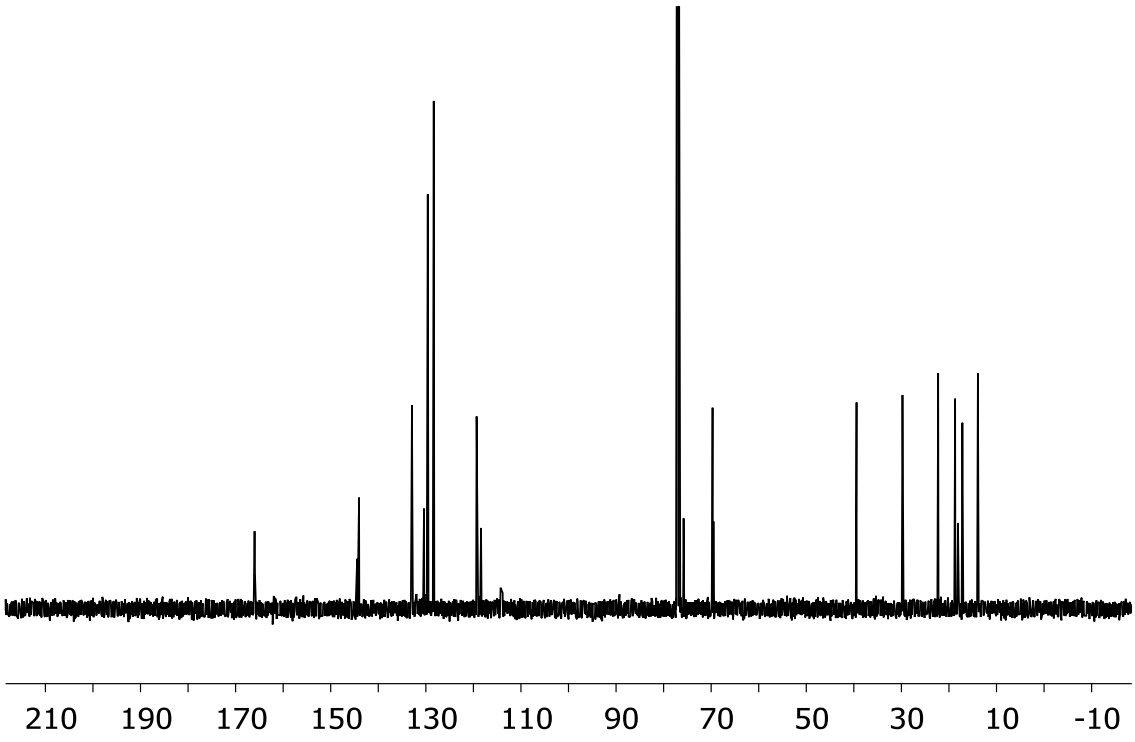


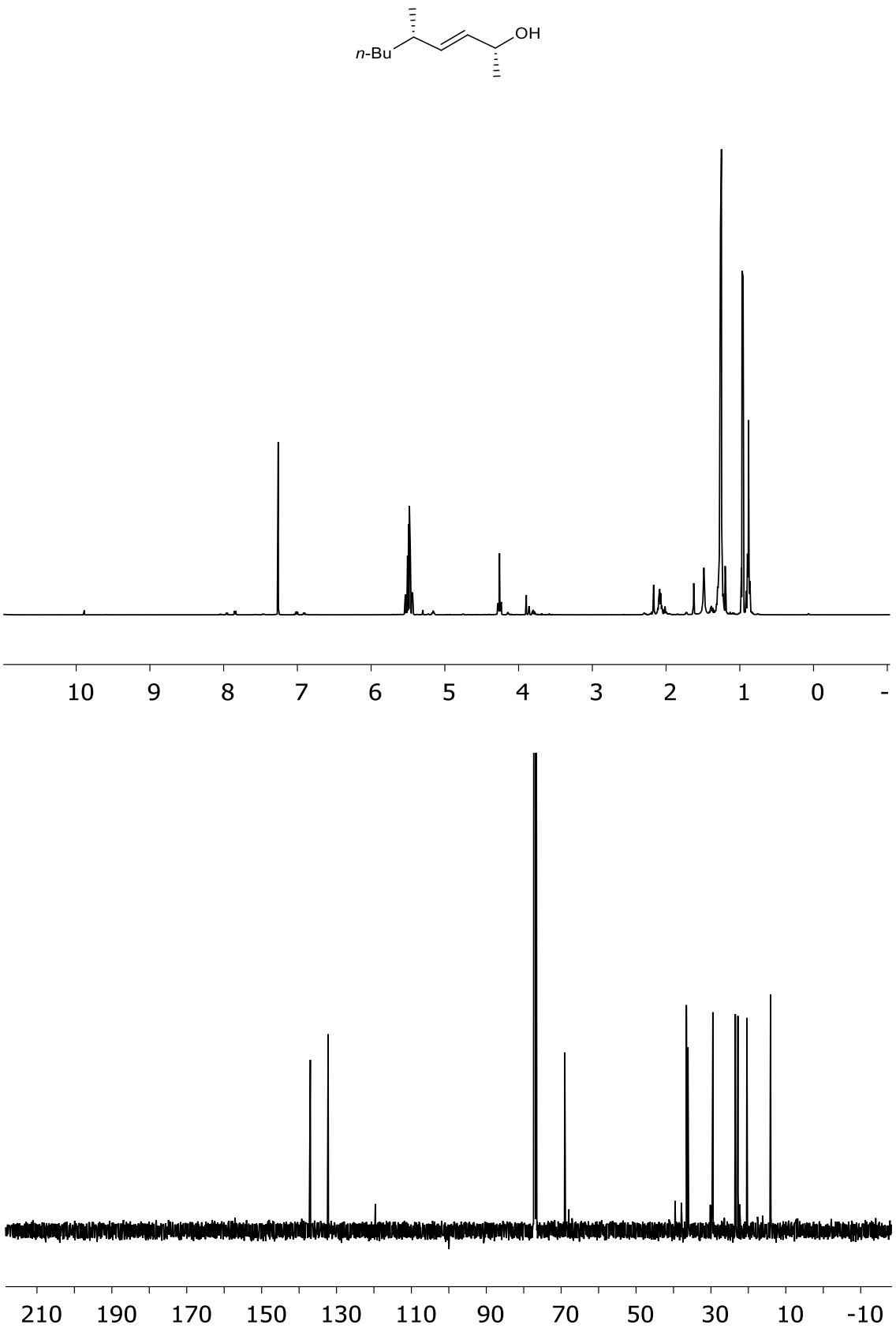




(mixture of diastereomers)






n-Bu
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OH
OPMB
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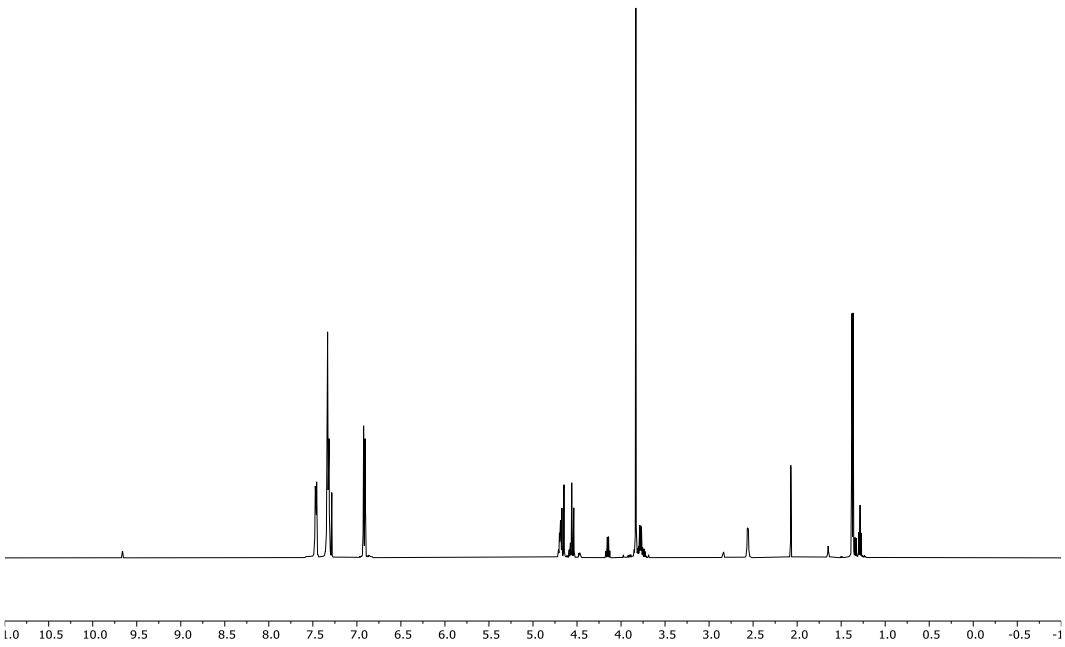
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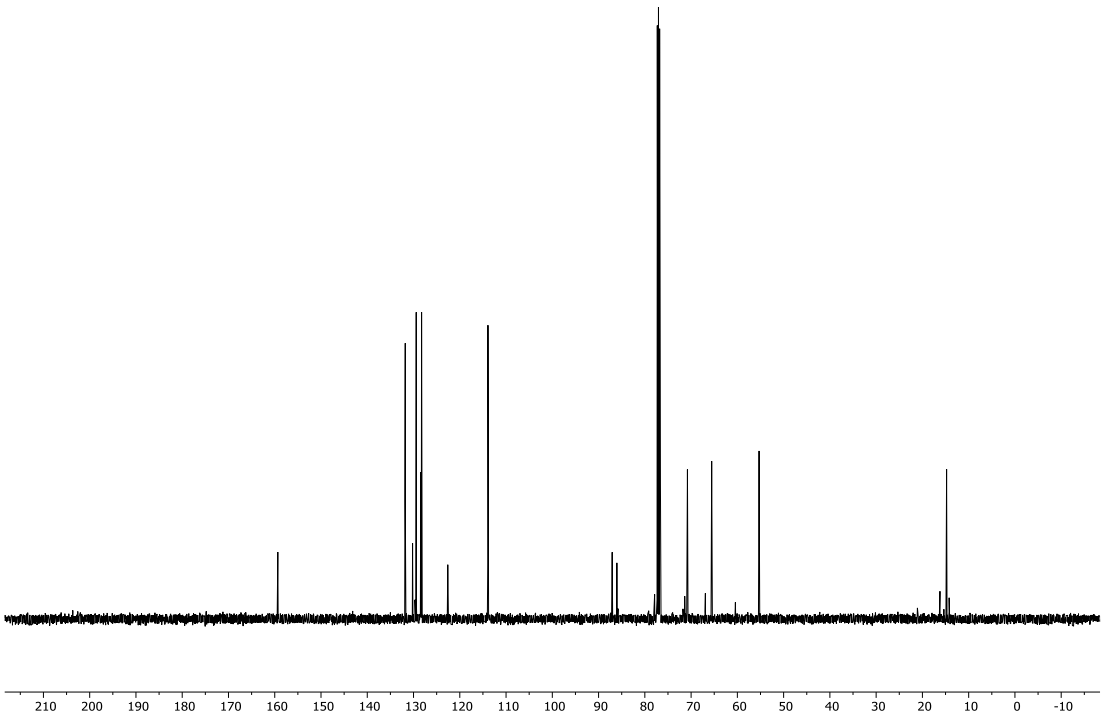
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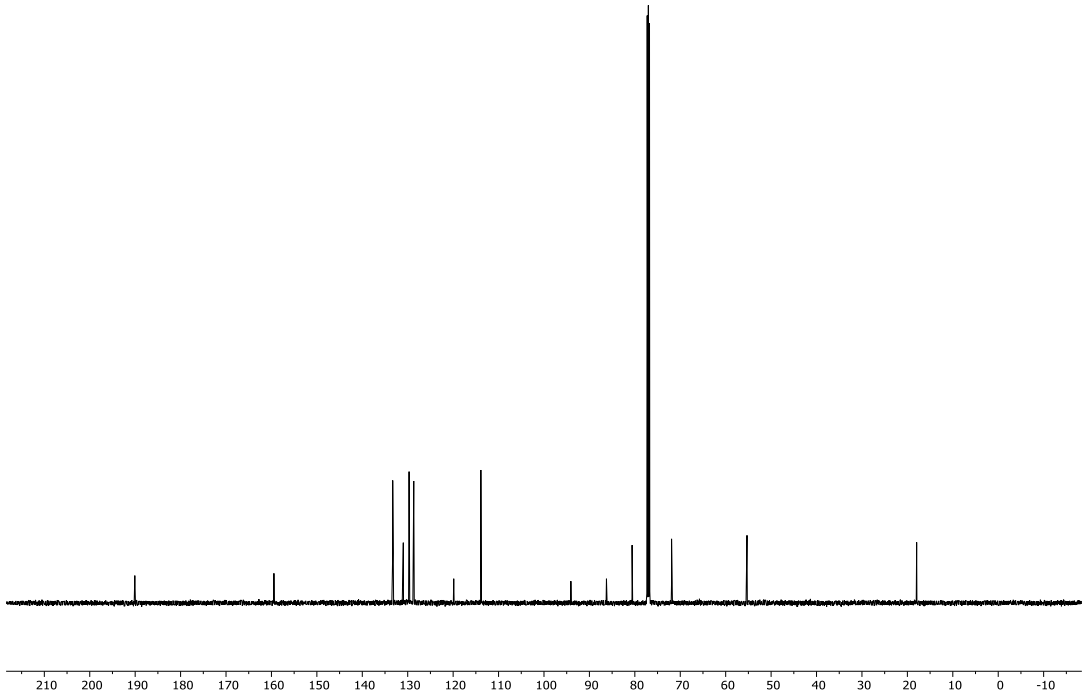
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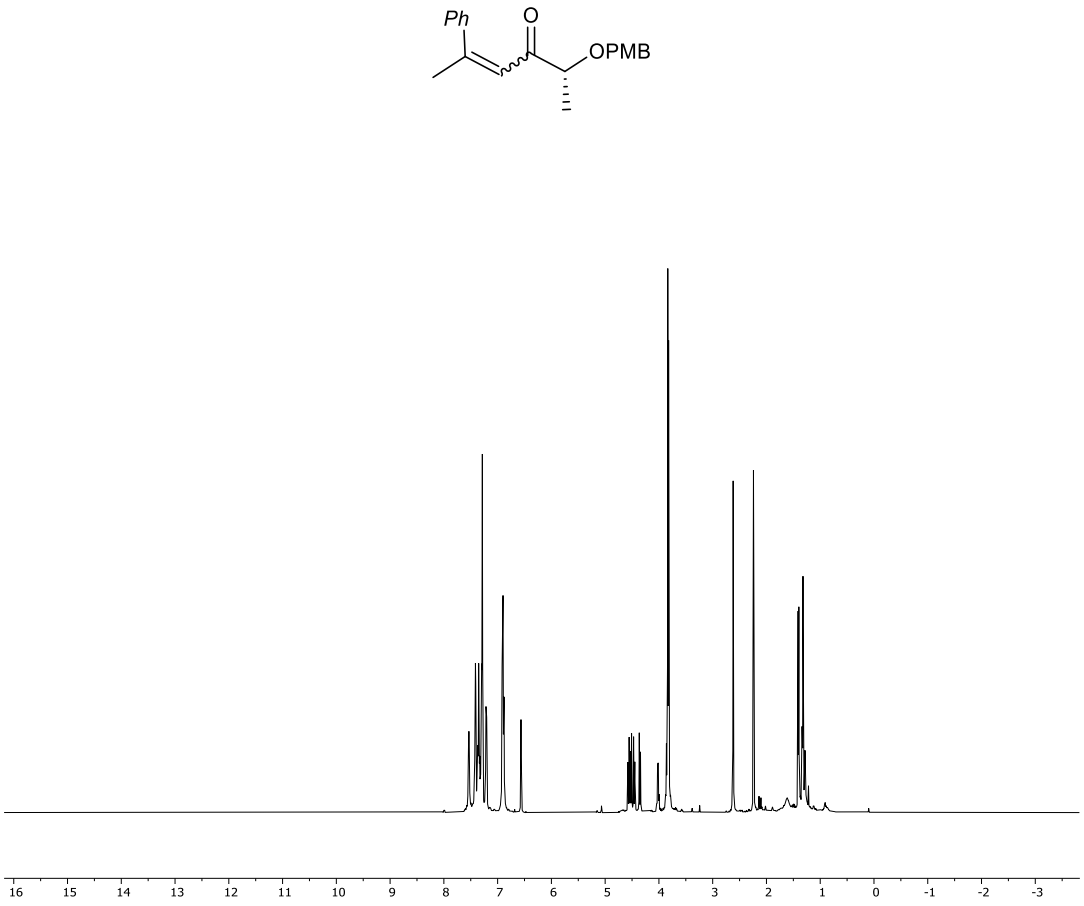
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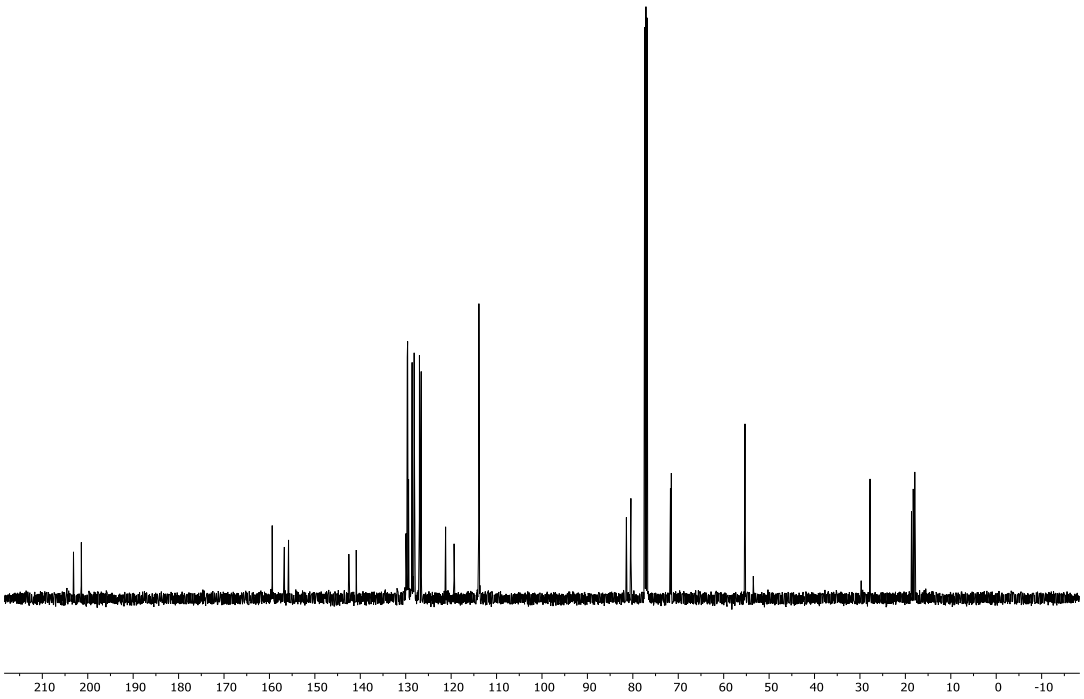
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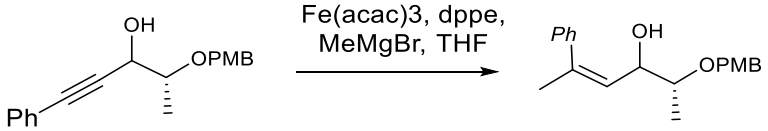
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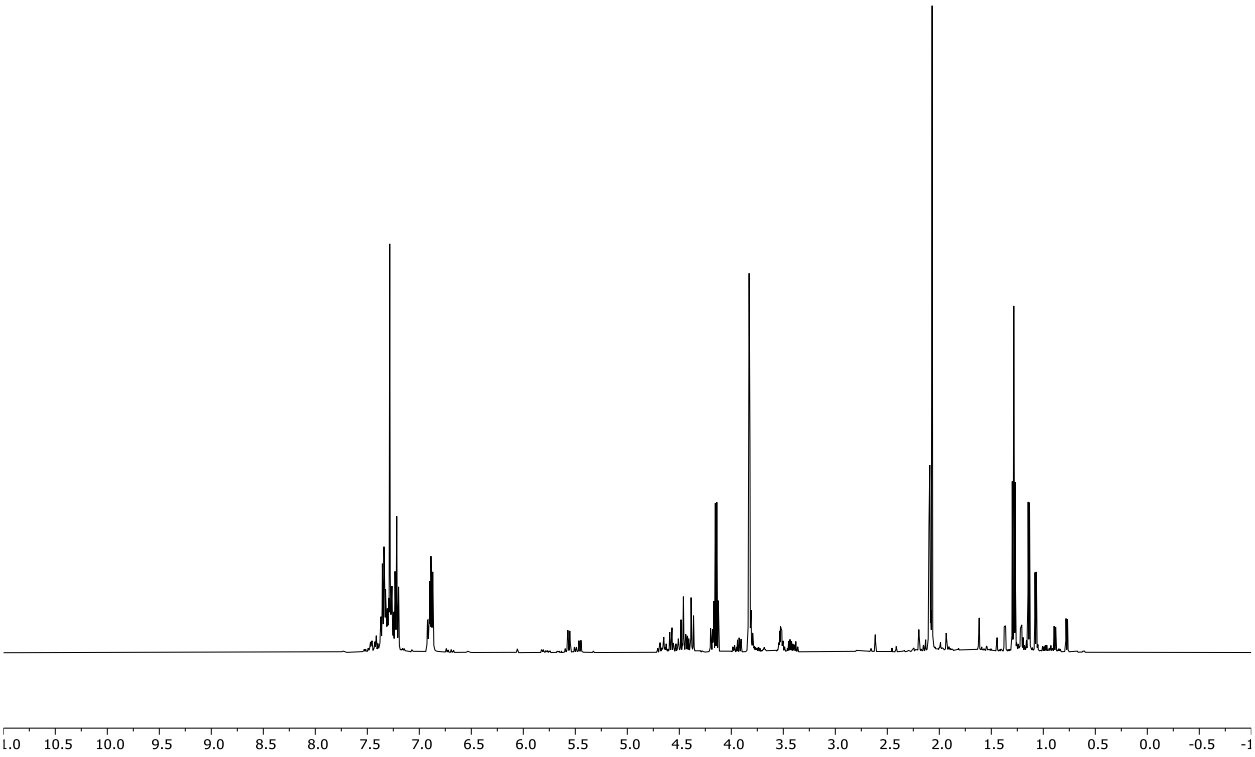
Ph
Fe(acac)3, dppe,
MeMgBr, THF
Ph
OH
OPMB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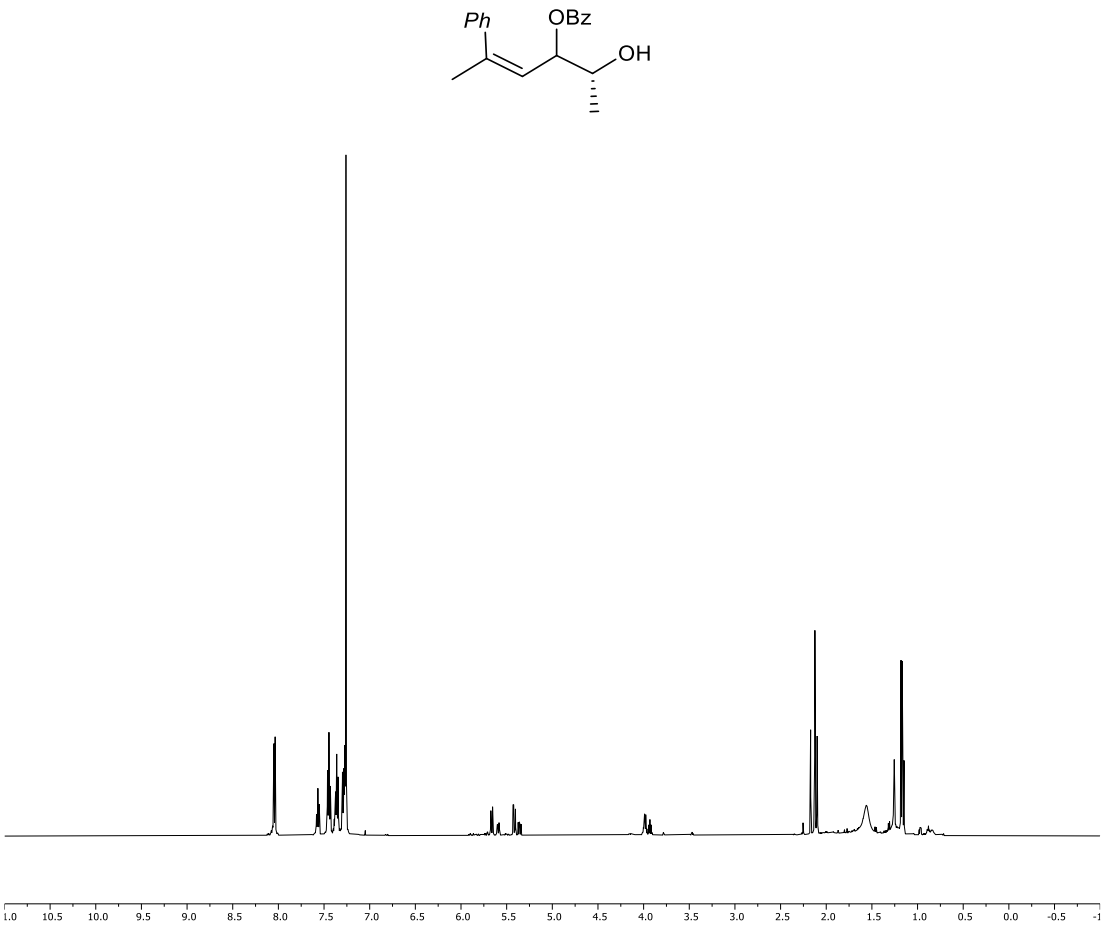
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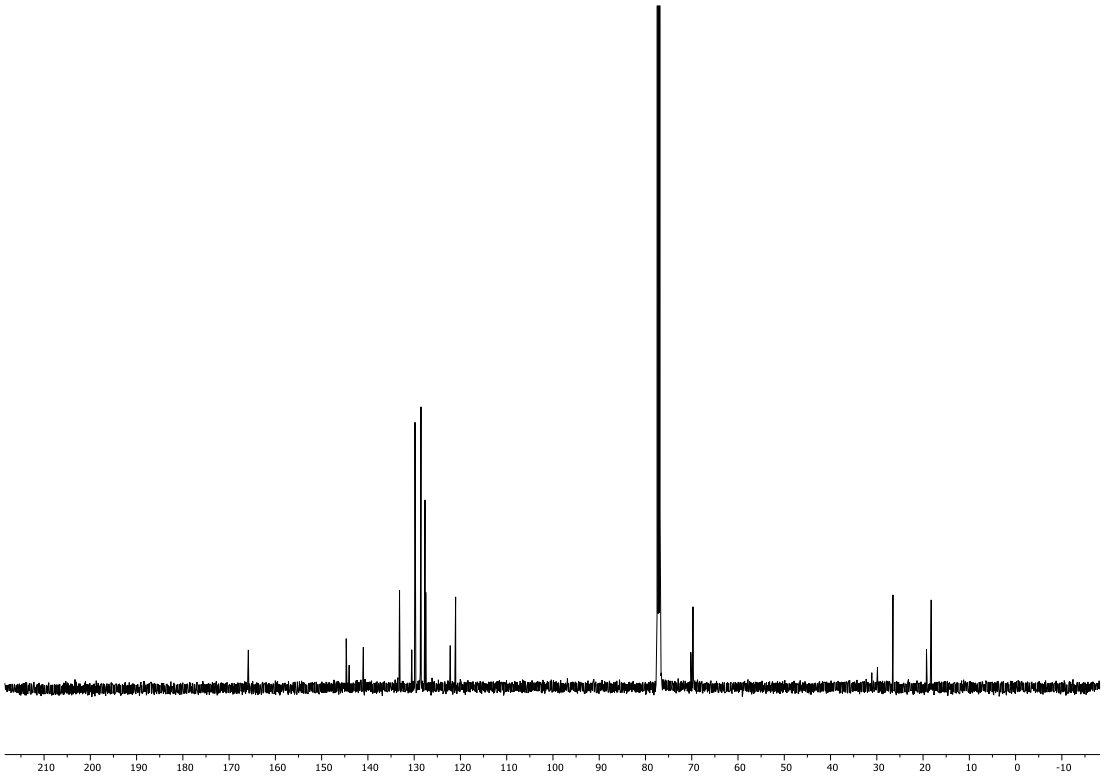
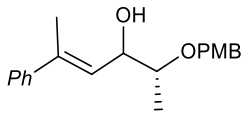
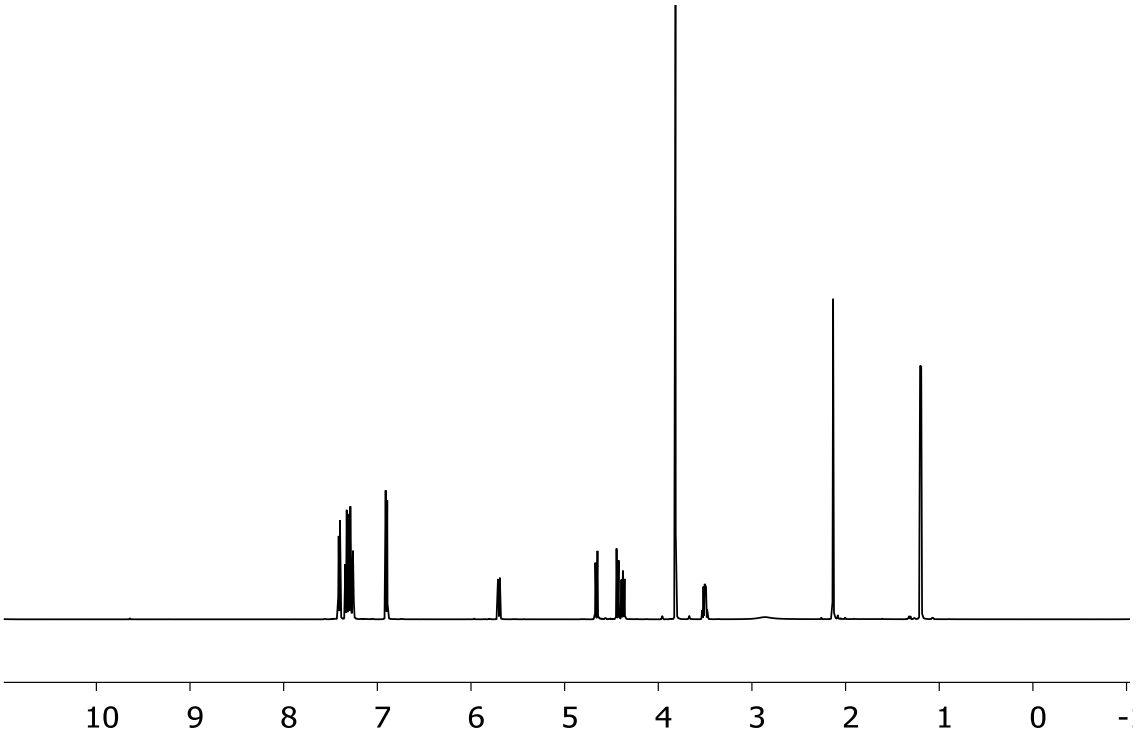
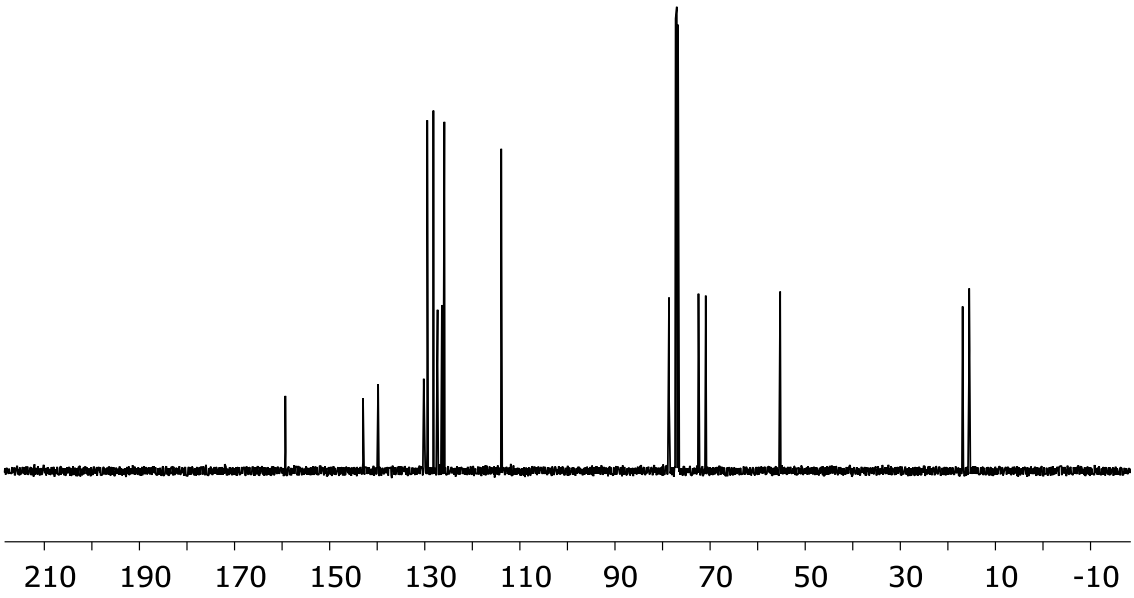
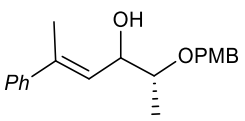




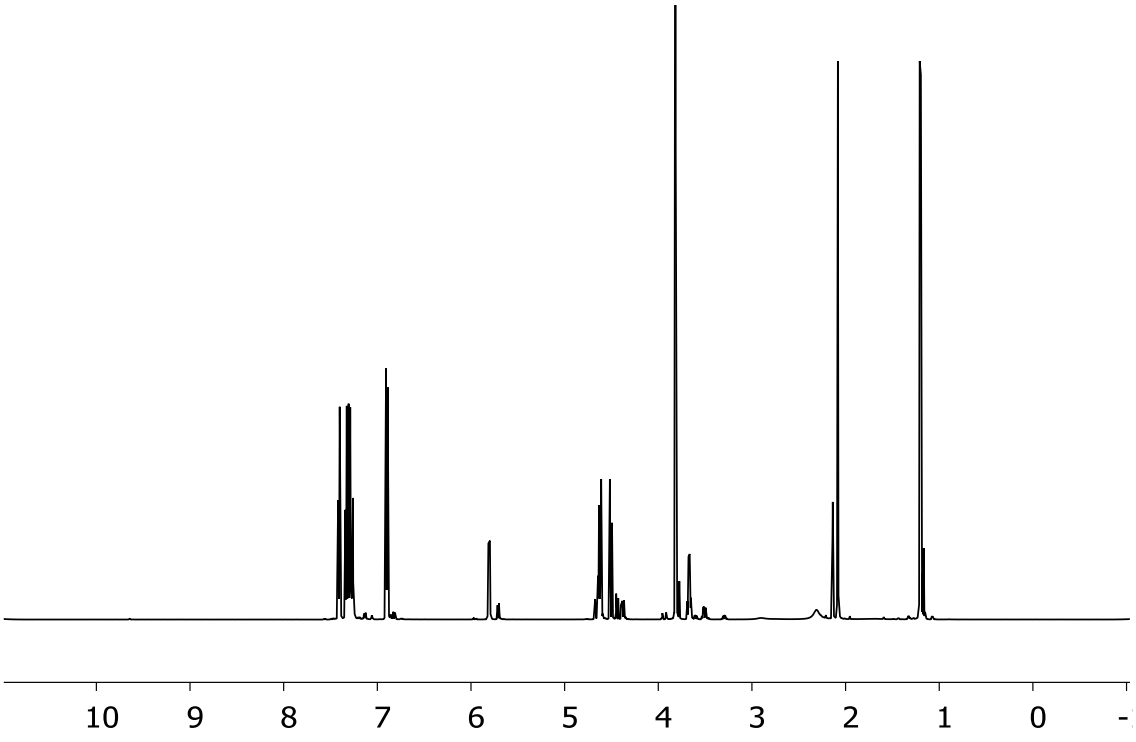
diastereomer α

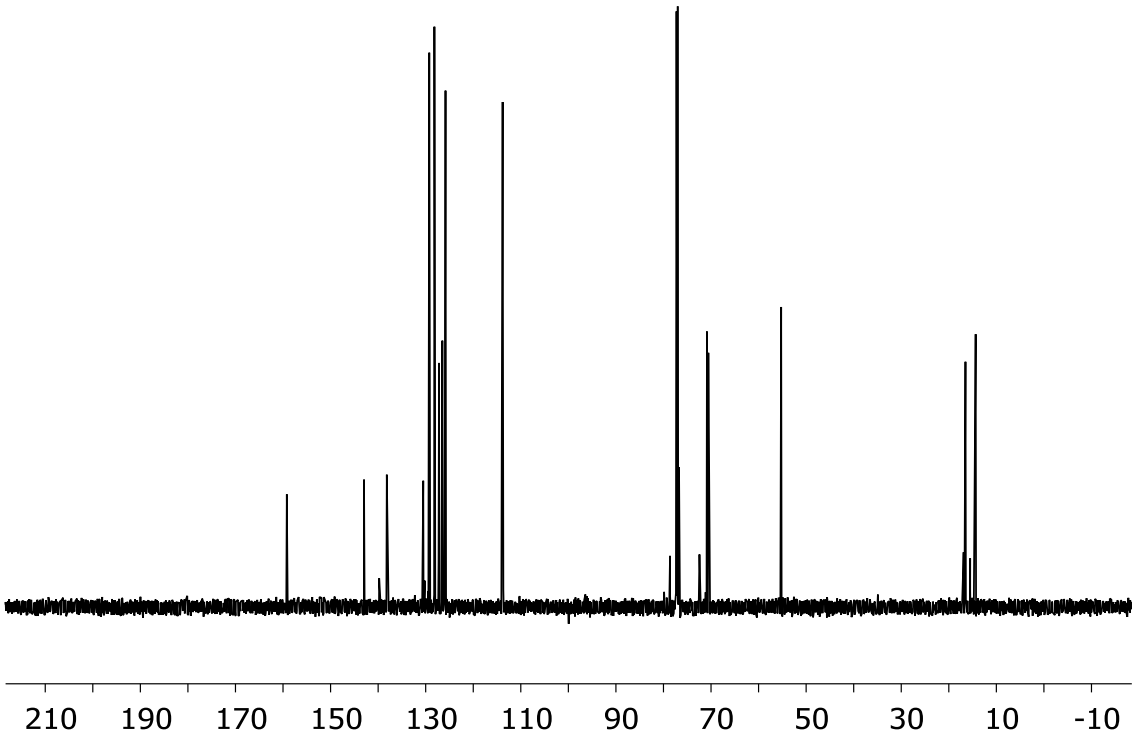


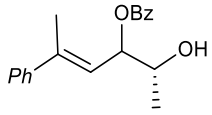




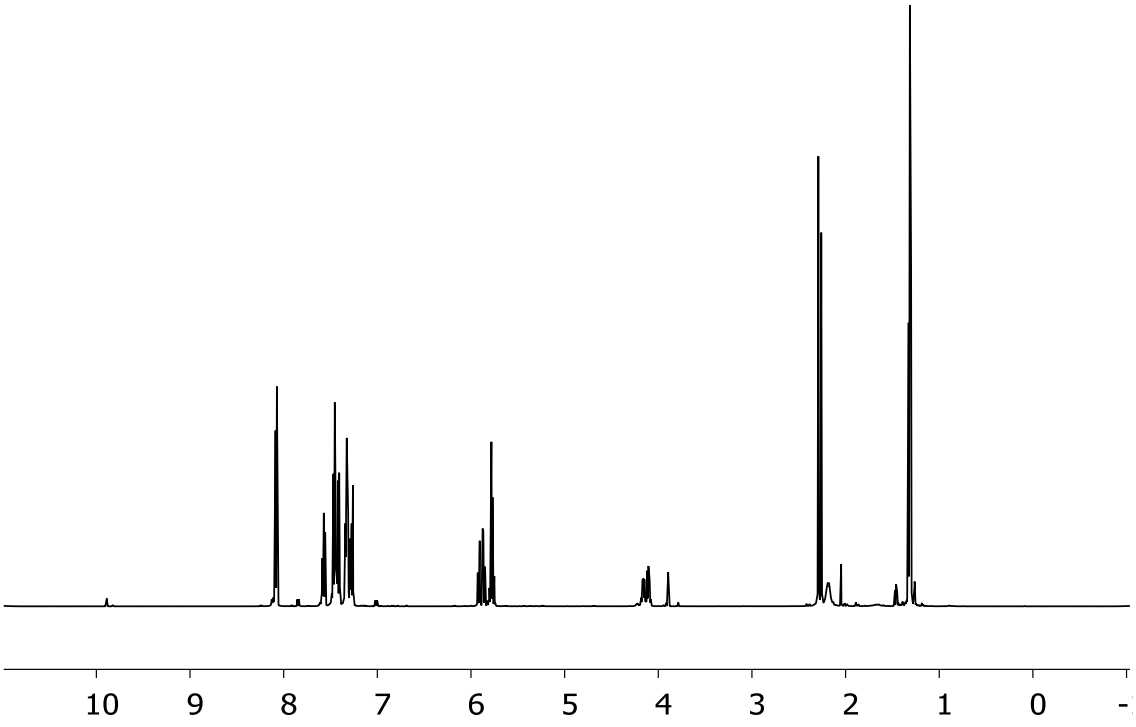
diastereomer β







(mixture of diastereomers)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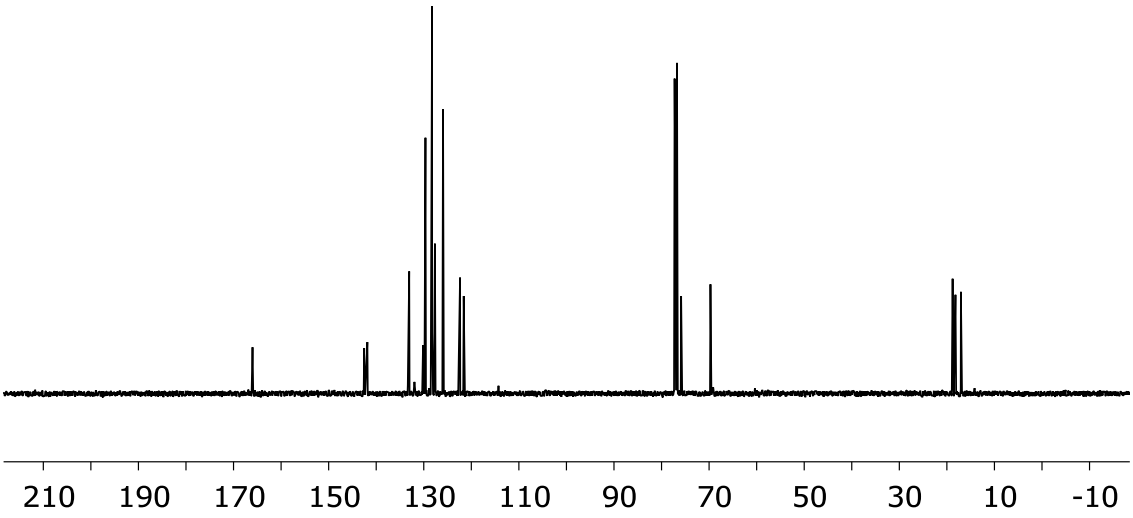
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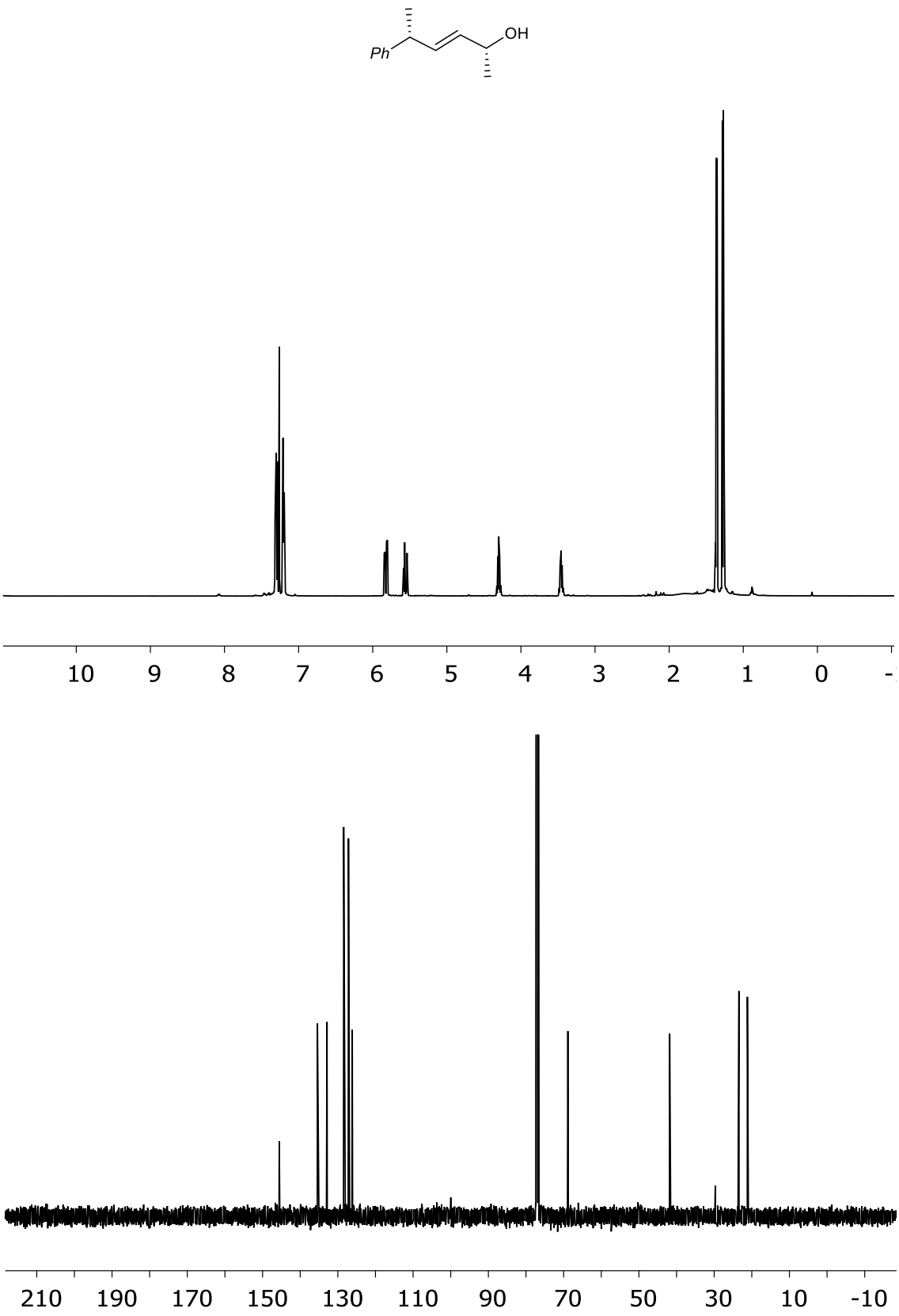
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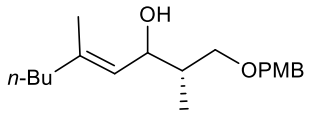
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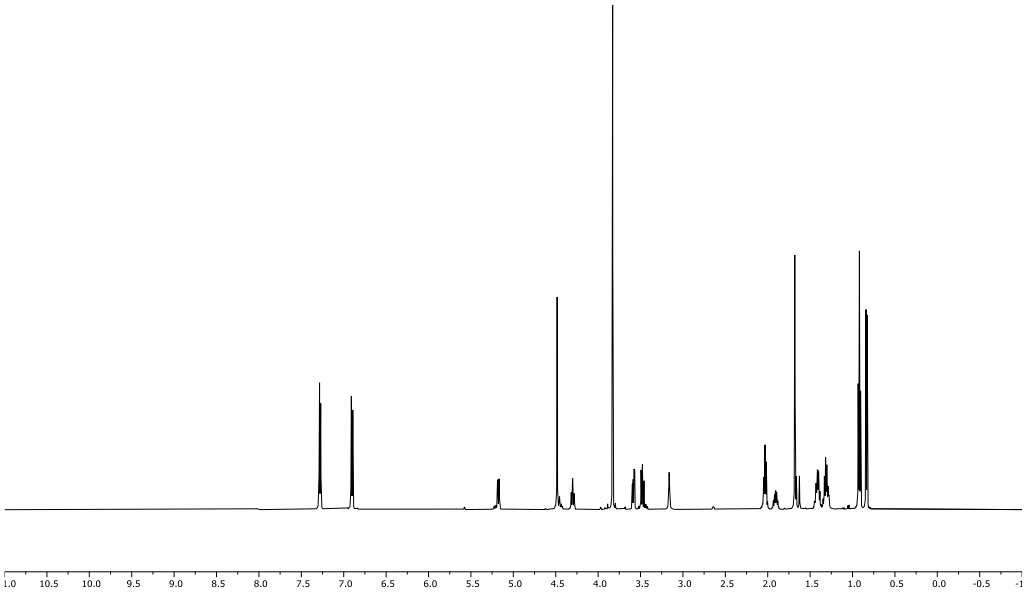
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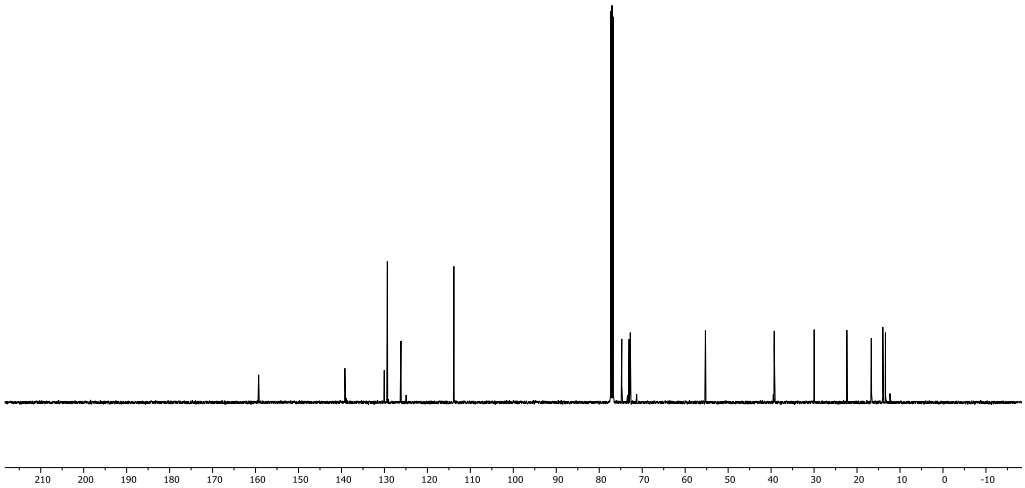
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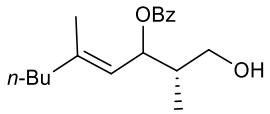
OBz
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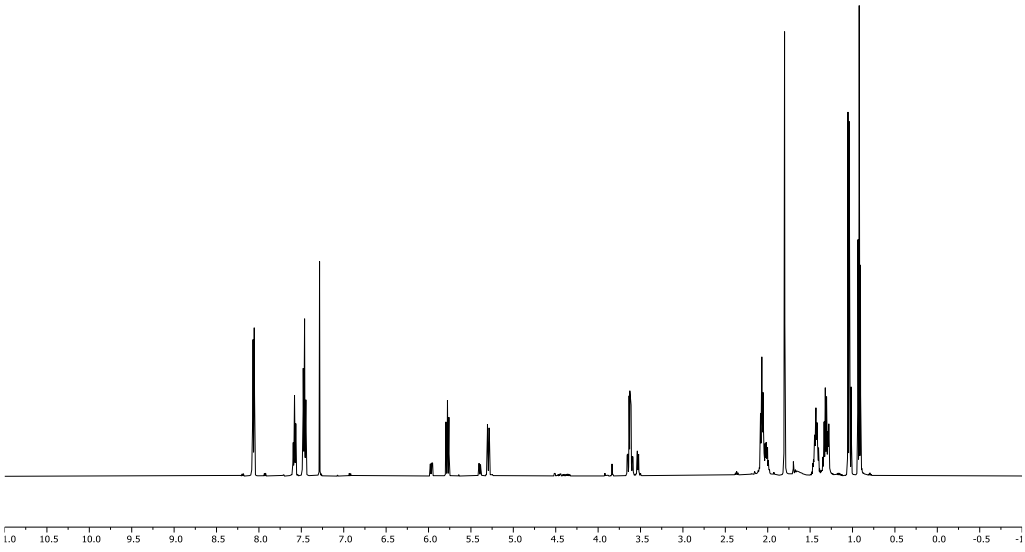
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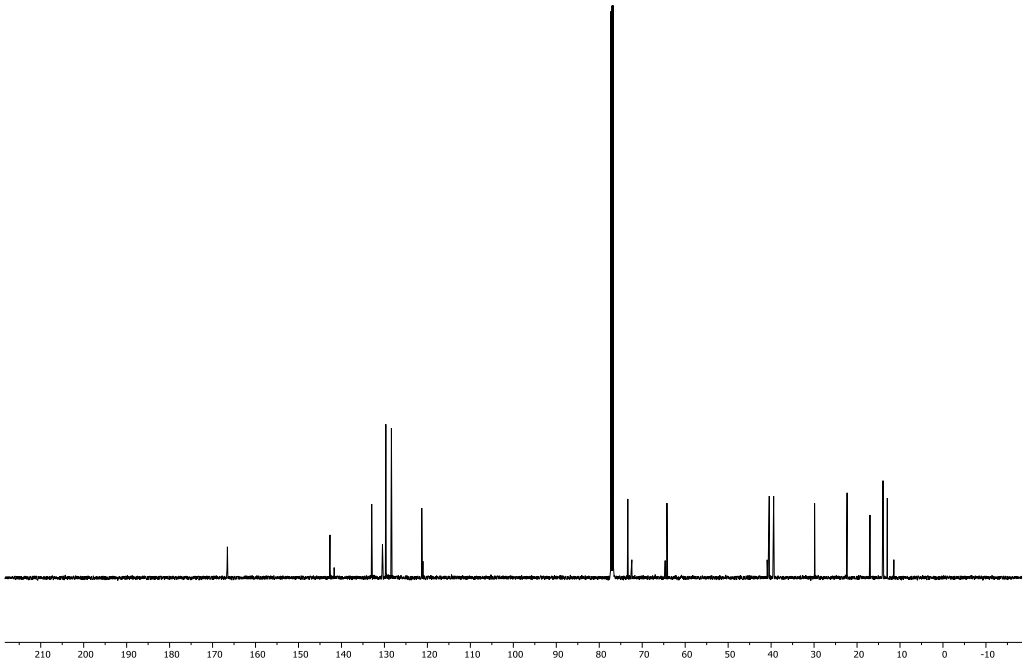
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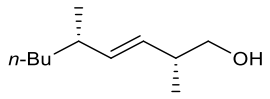
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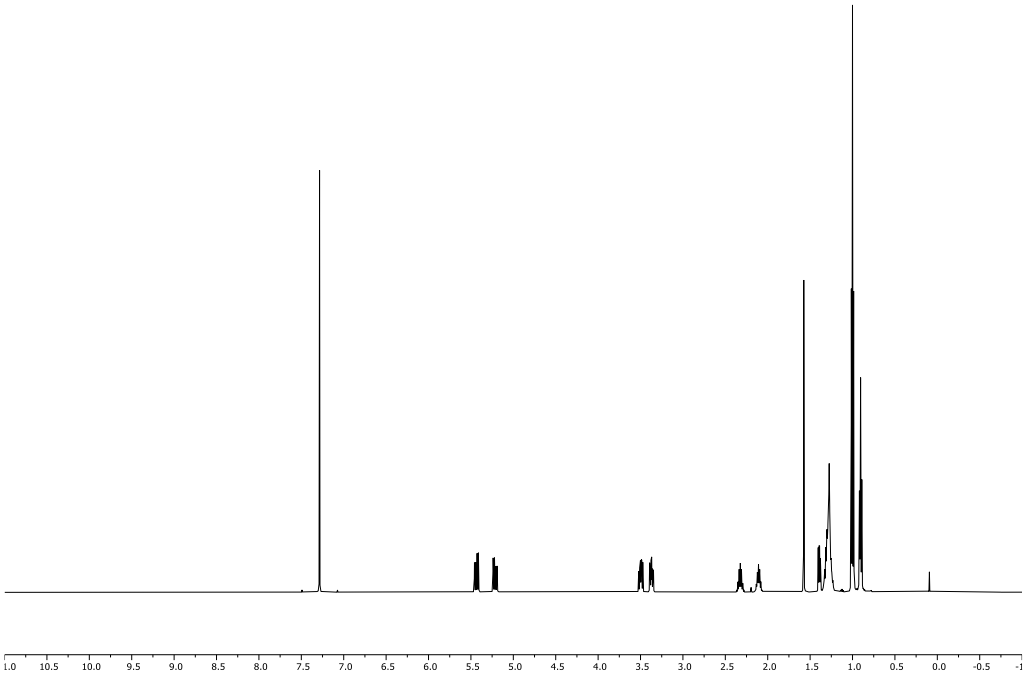
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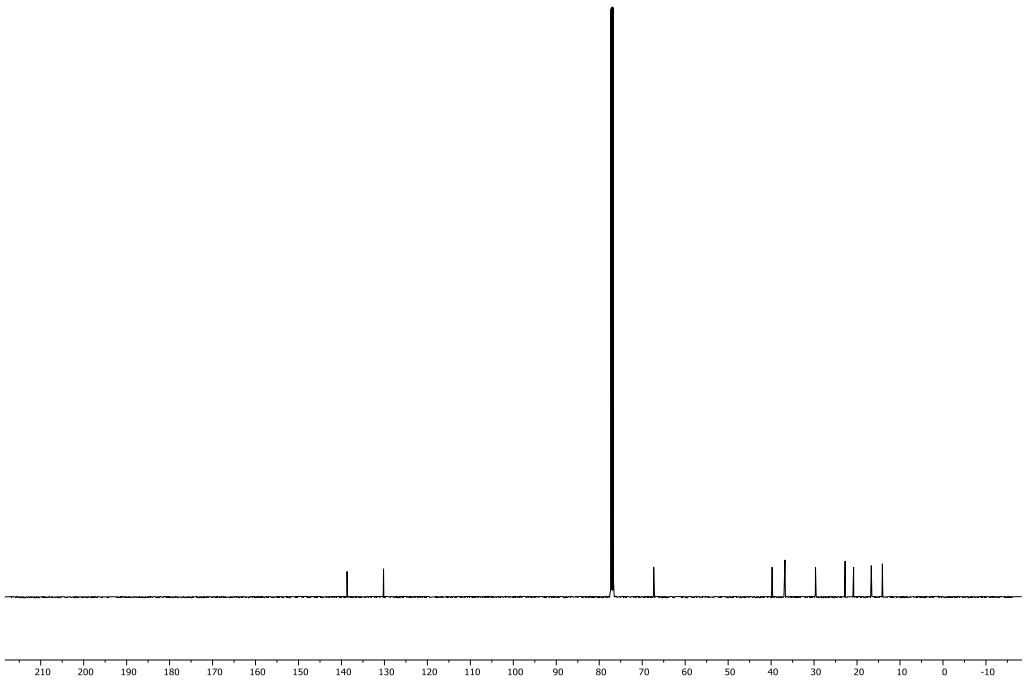
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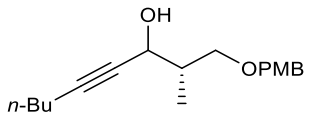
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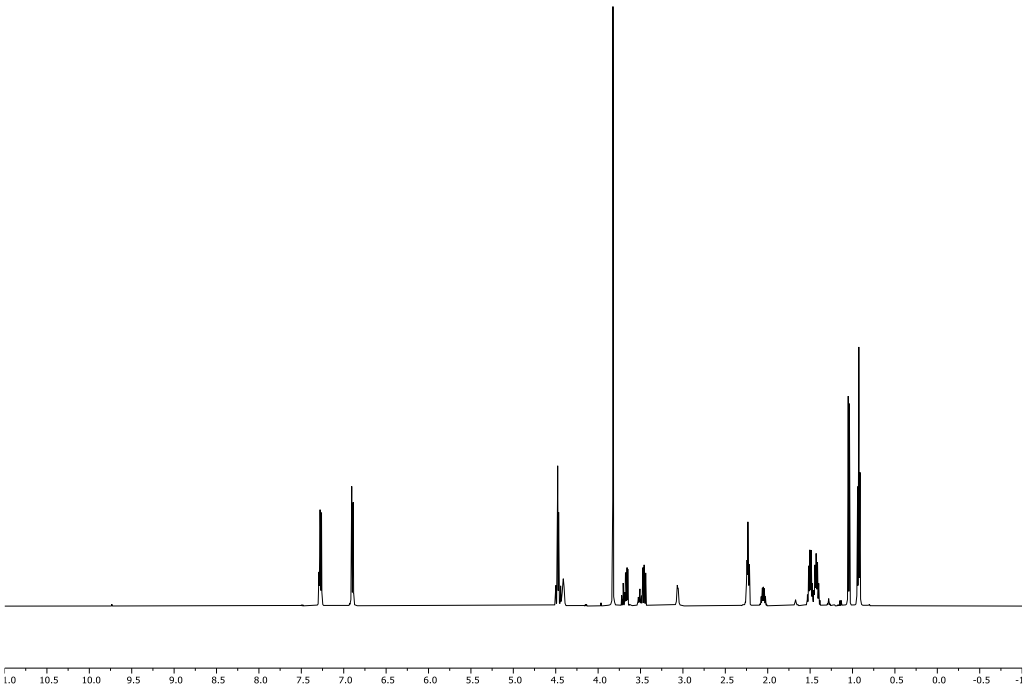
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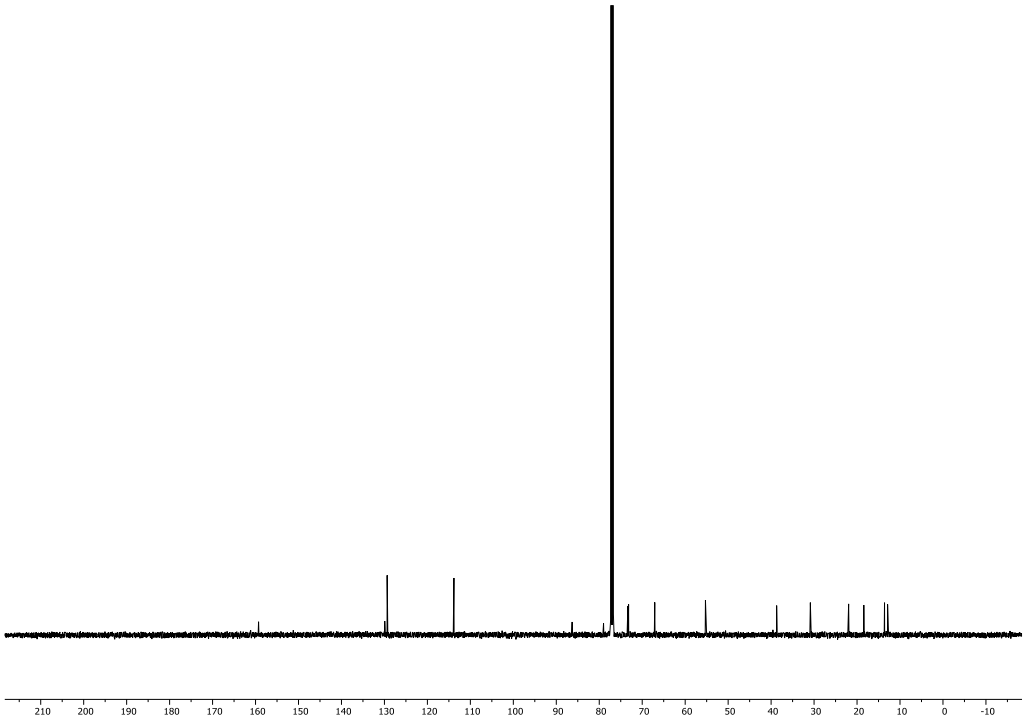
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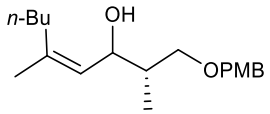
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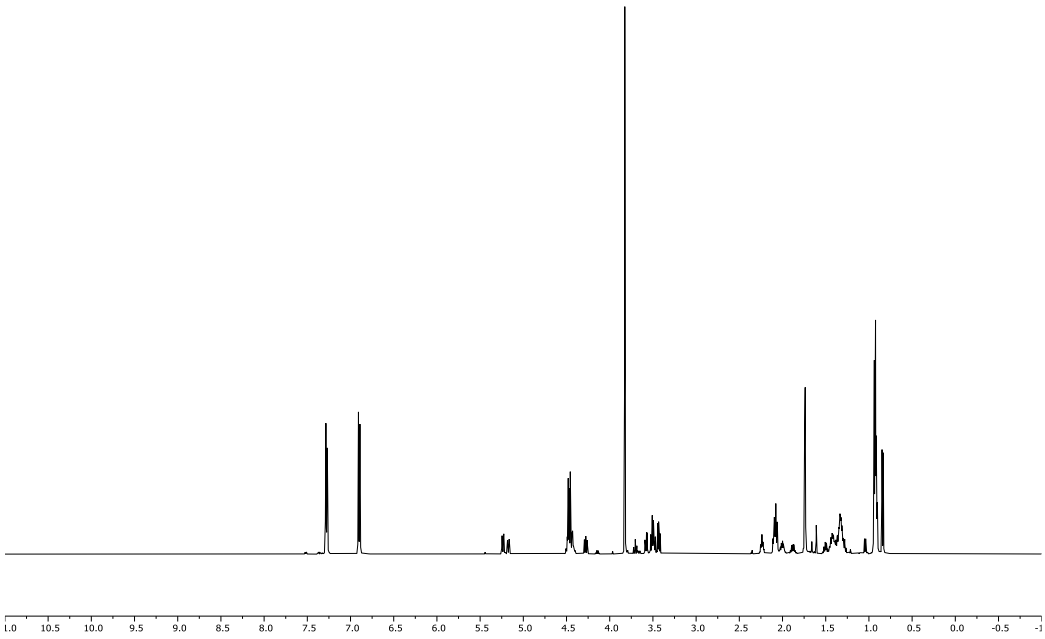
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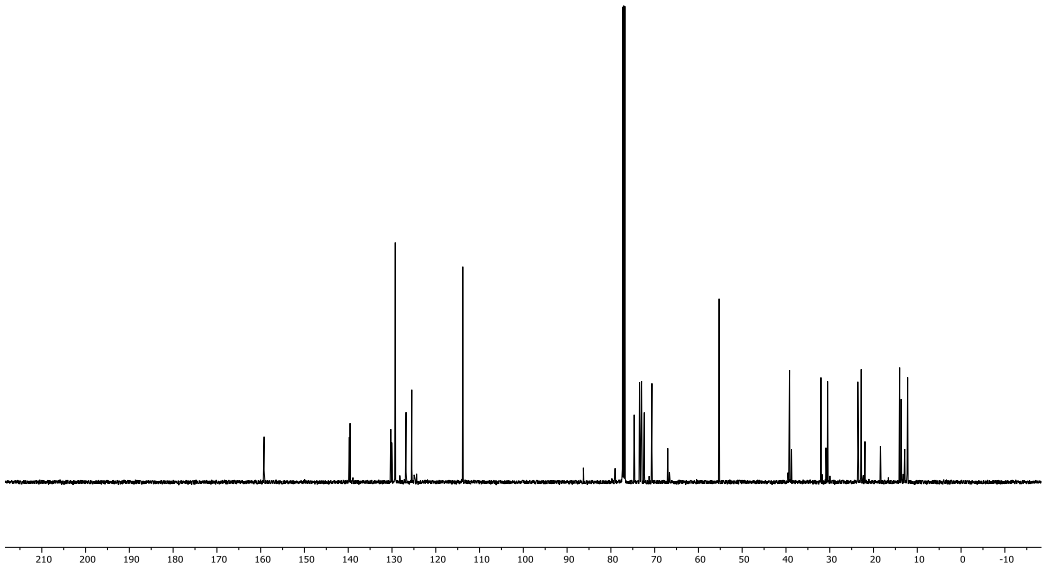
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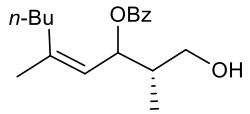
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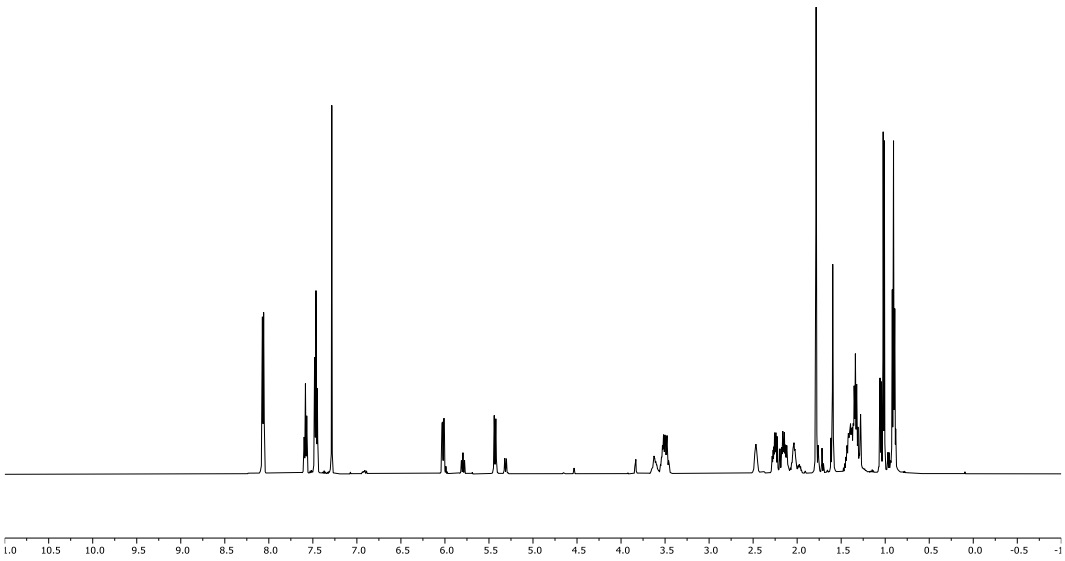
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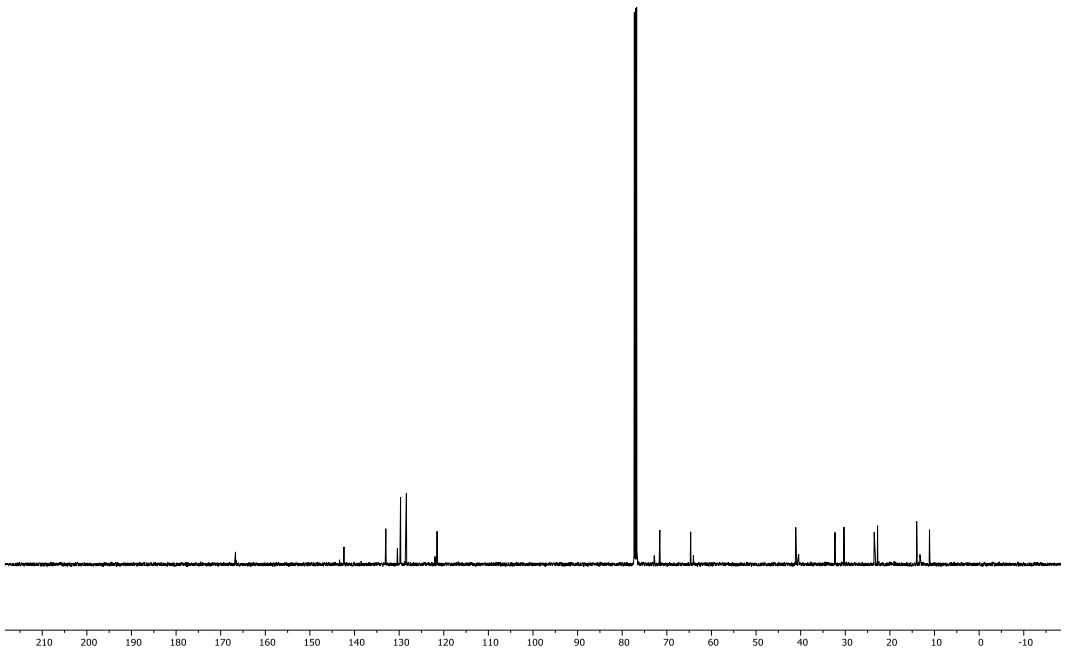
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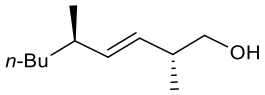
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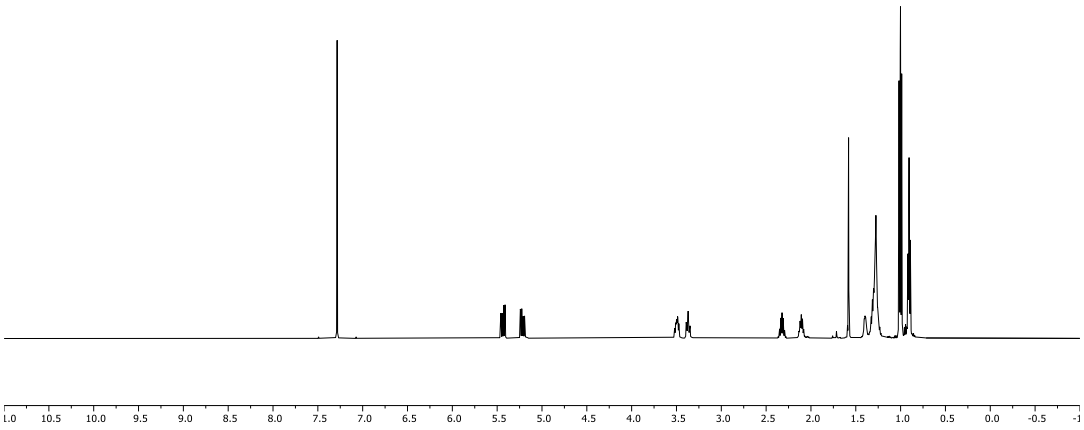
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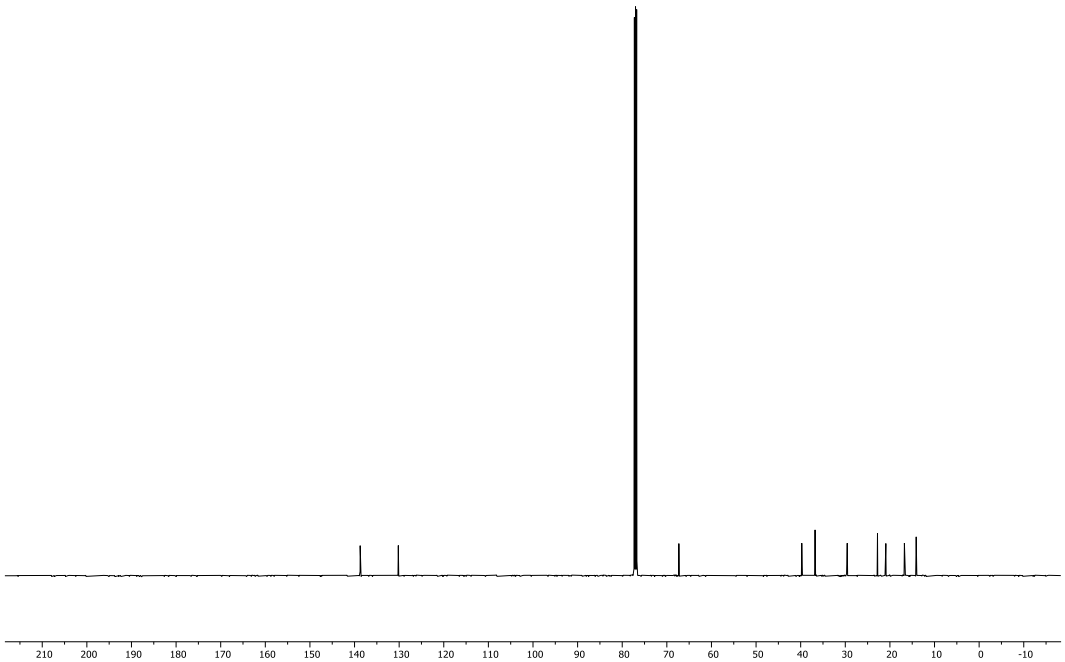
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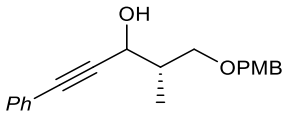
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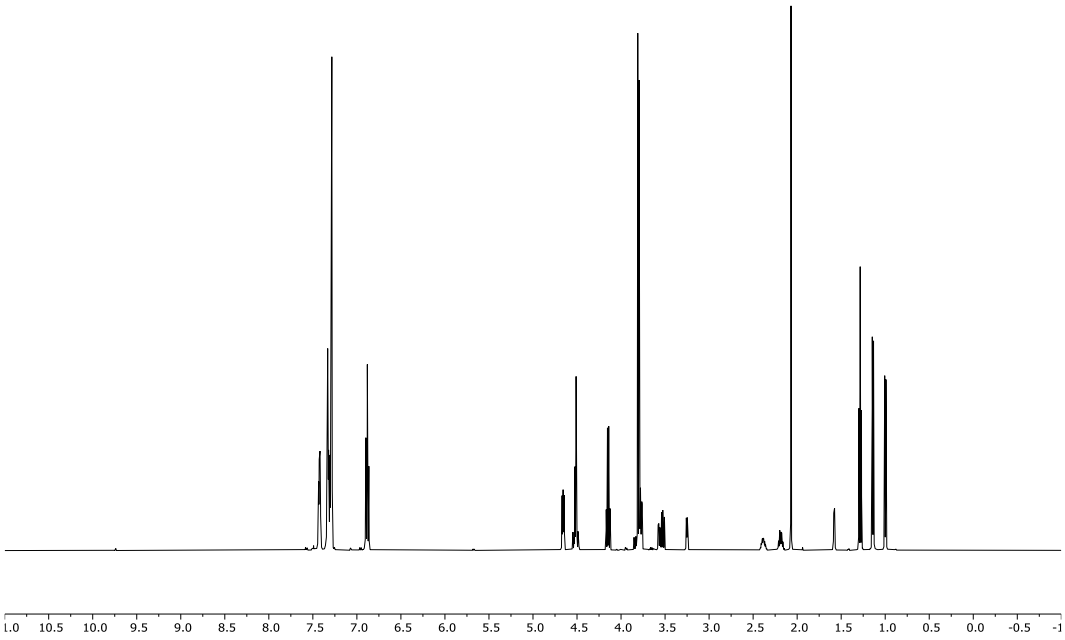
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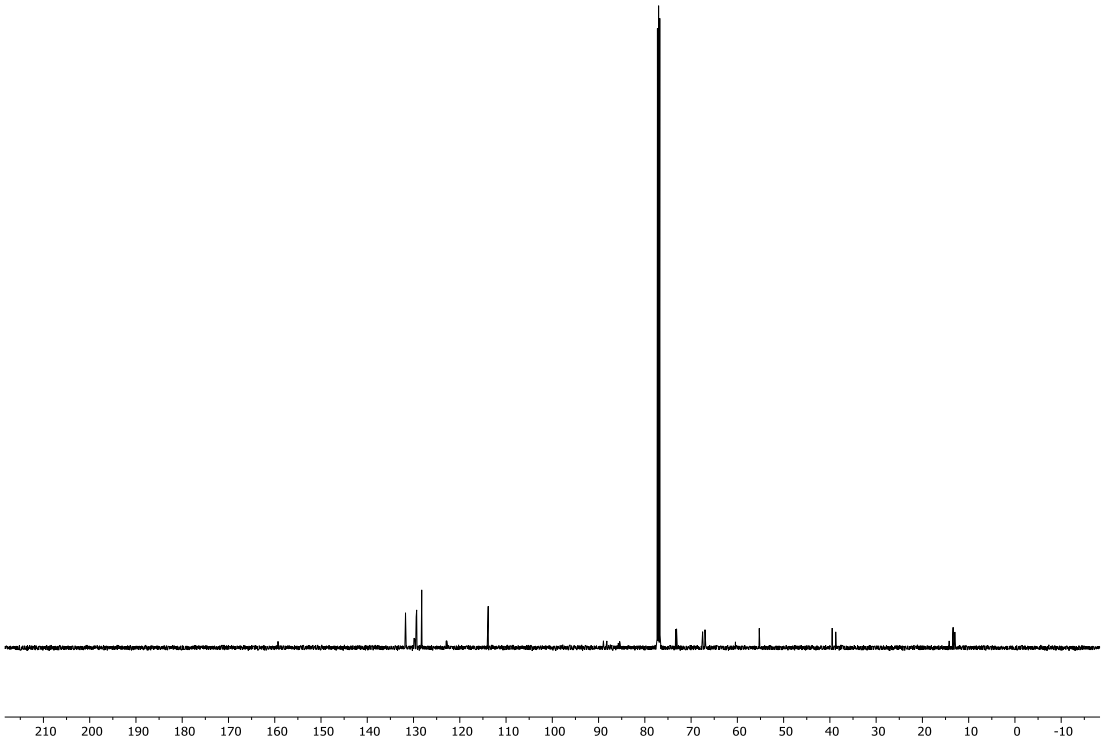
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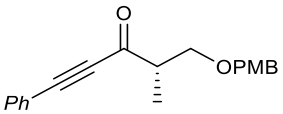
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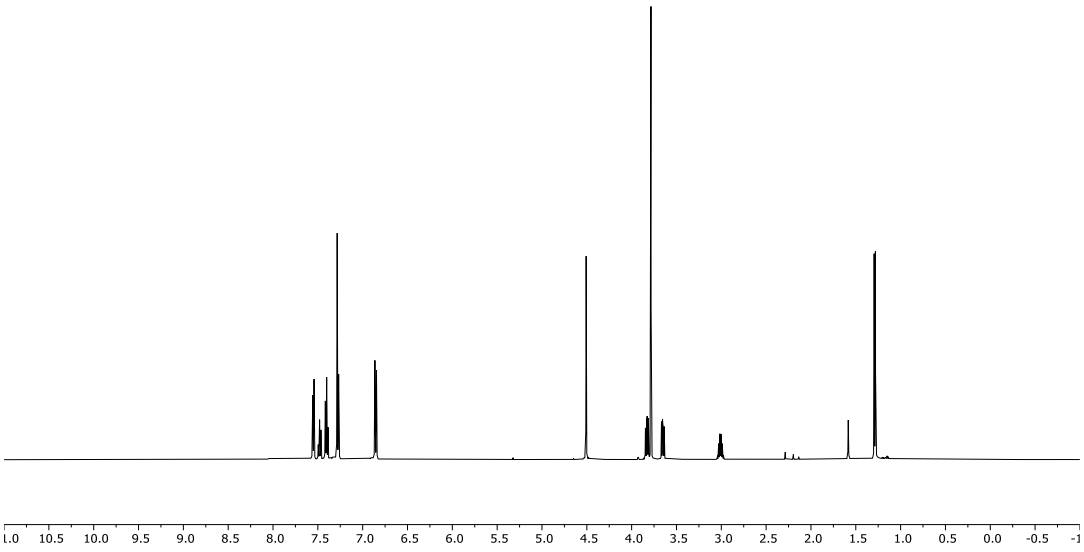
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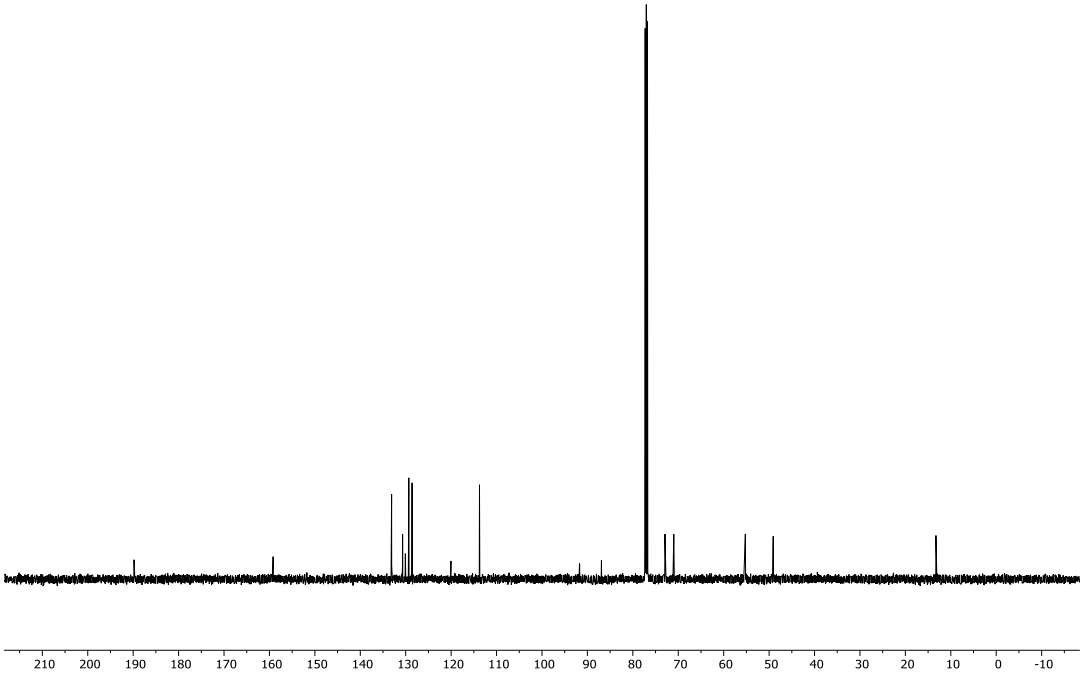
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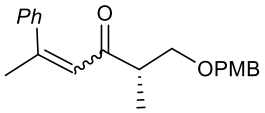
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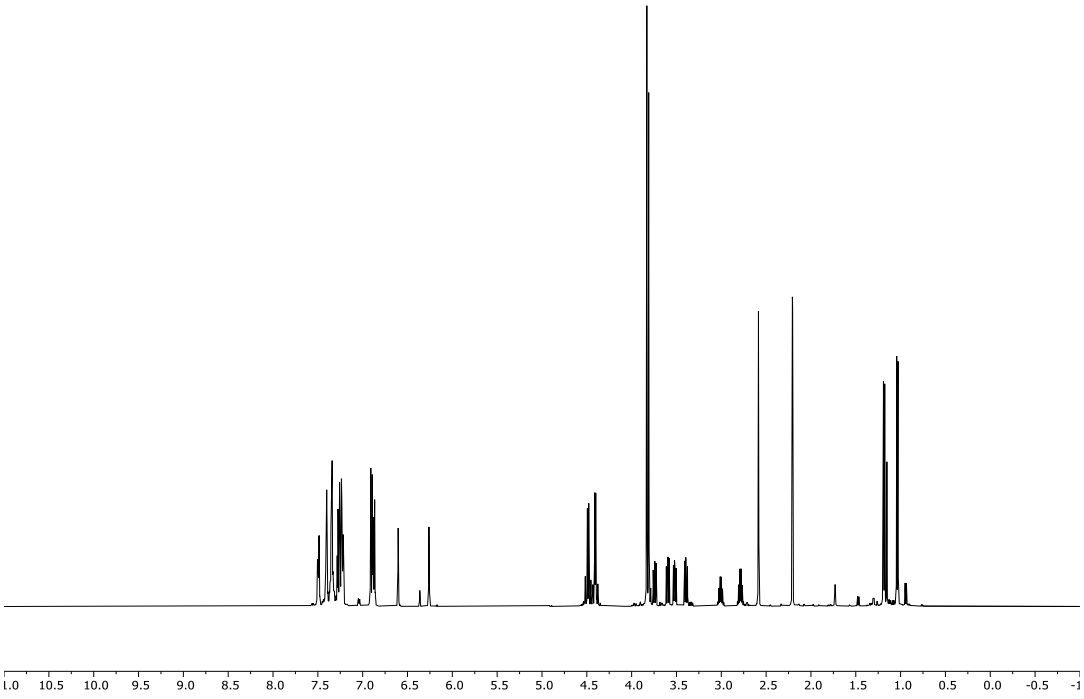
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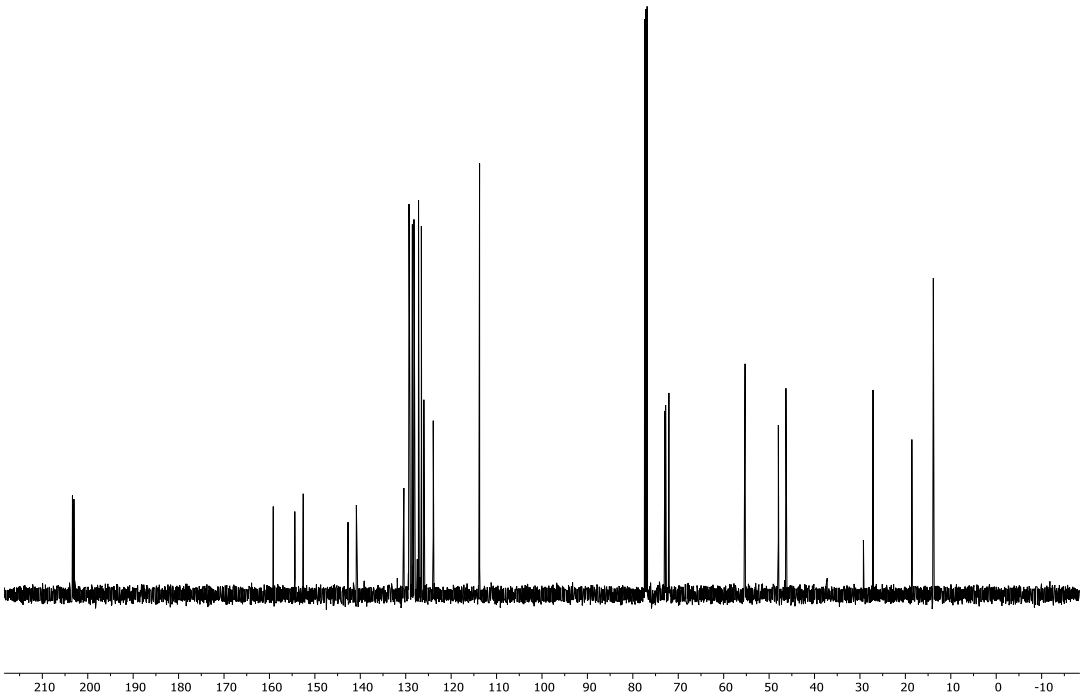
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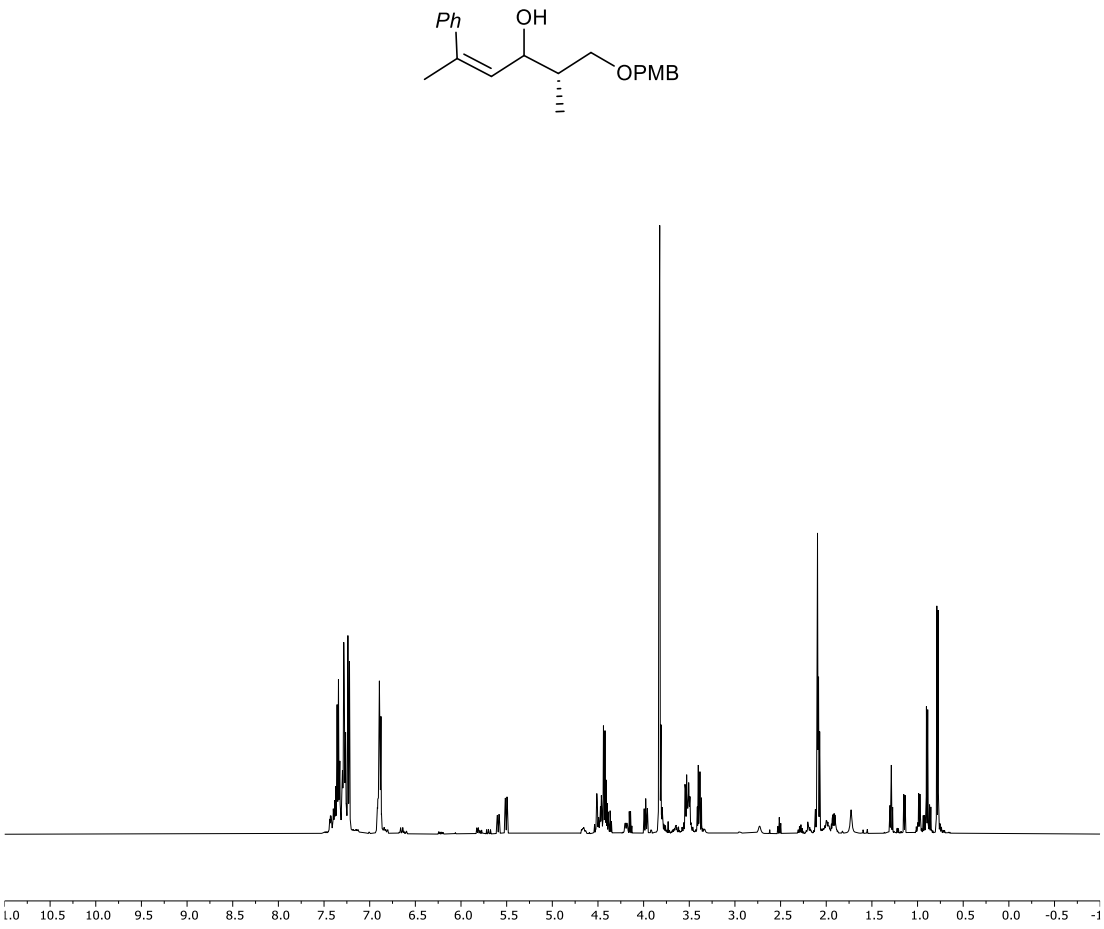
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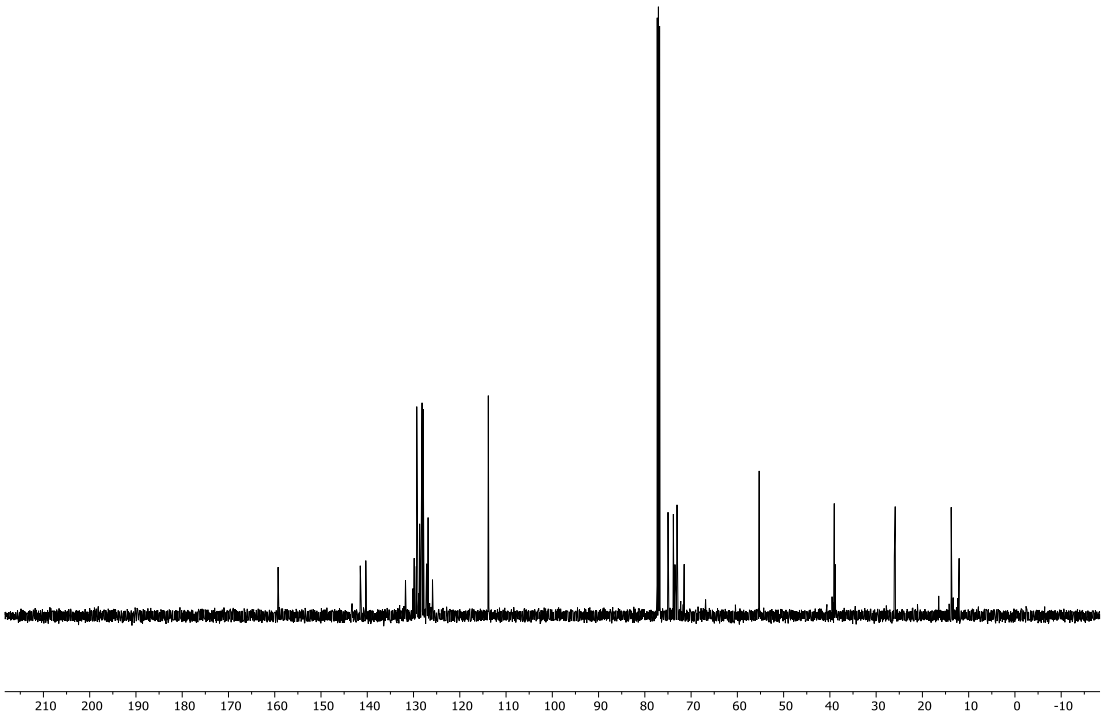
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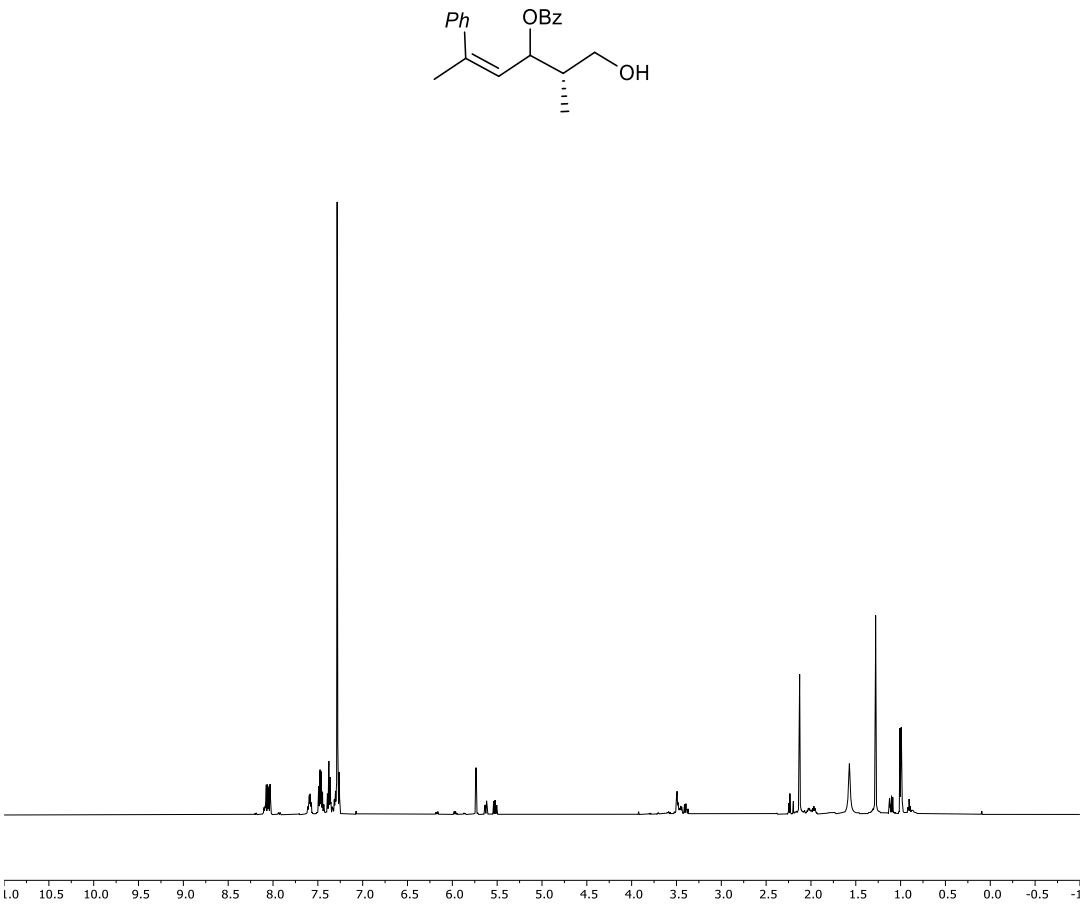
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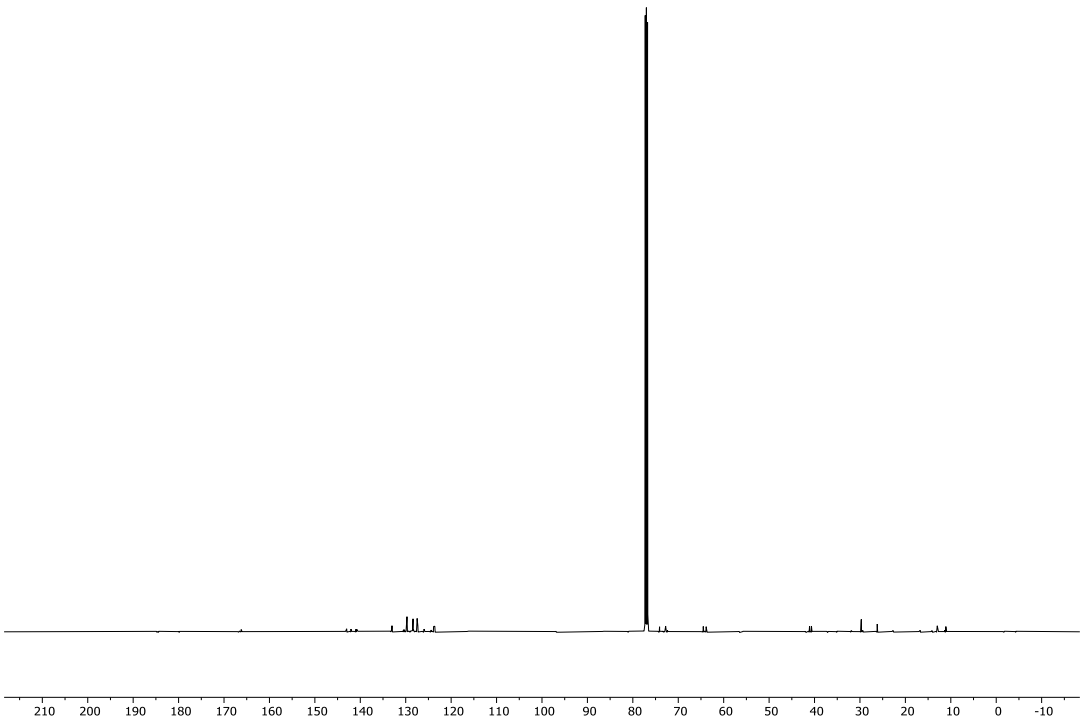
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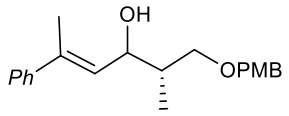
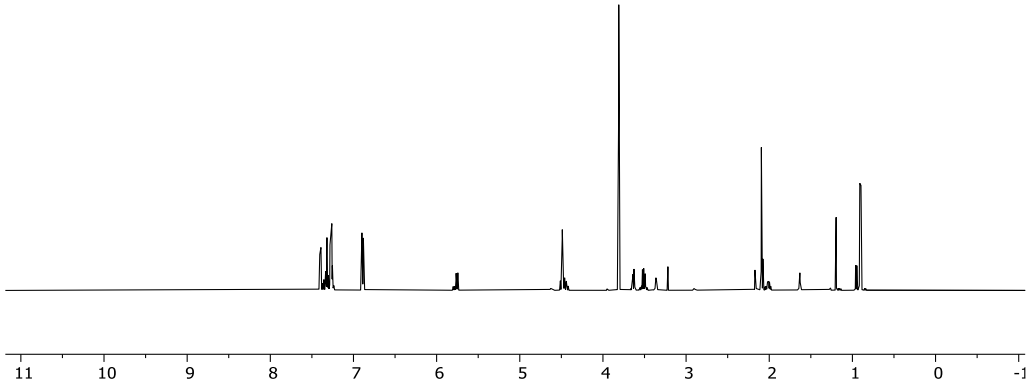
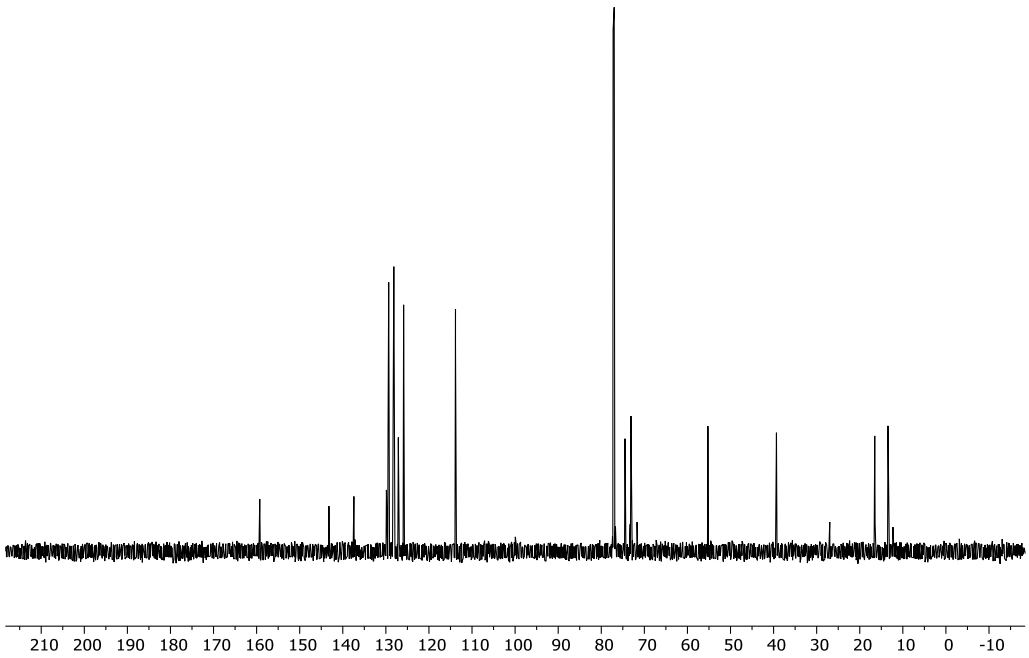
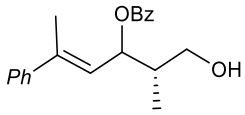


(mixture of diastereomers)







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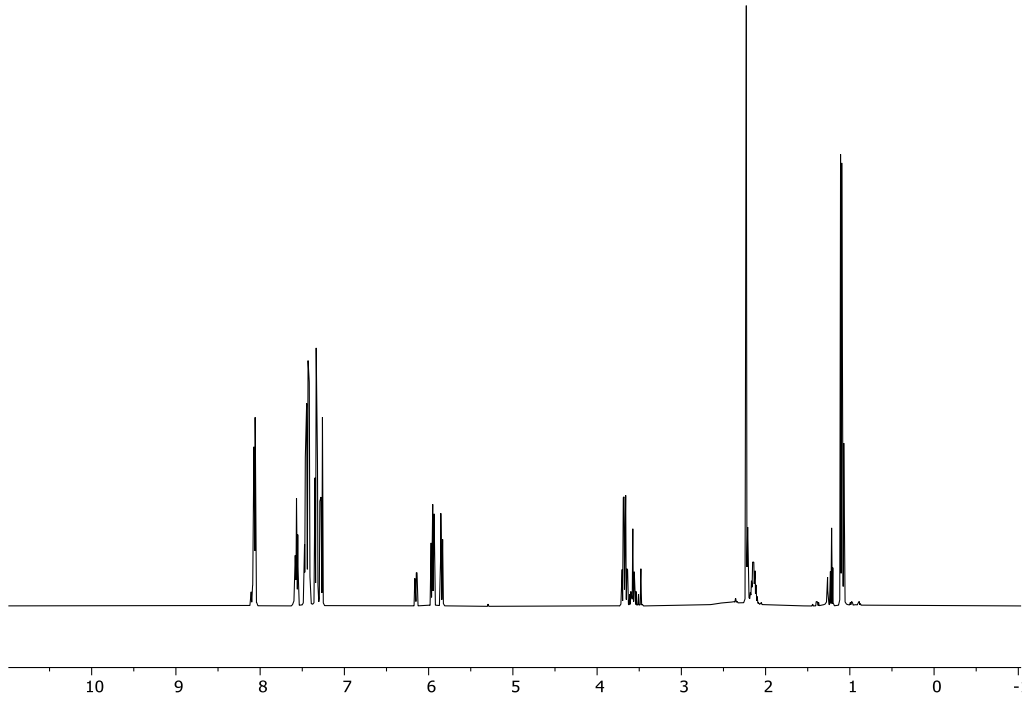

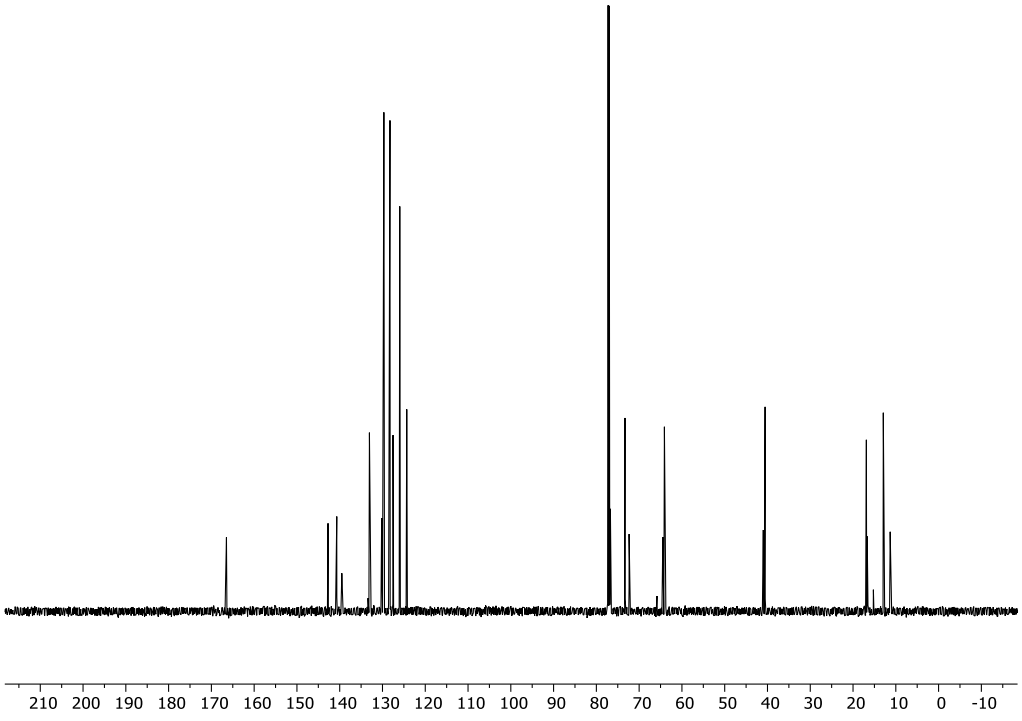

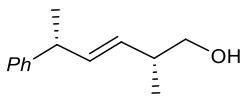

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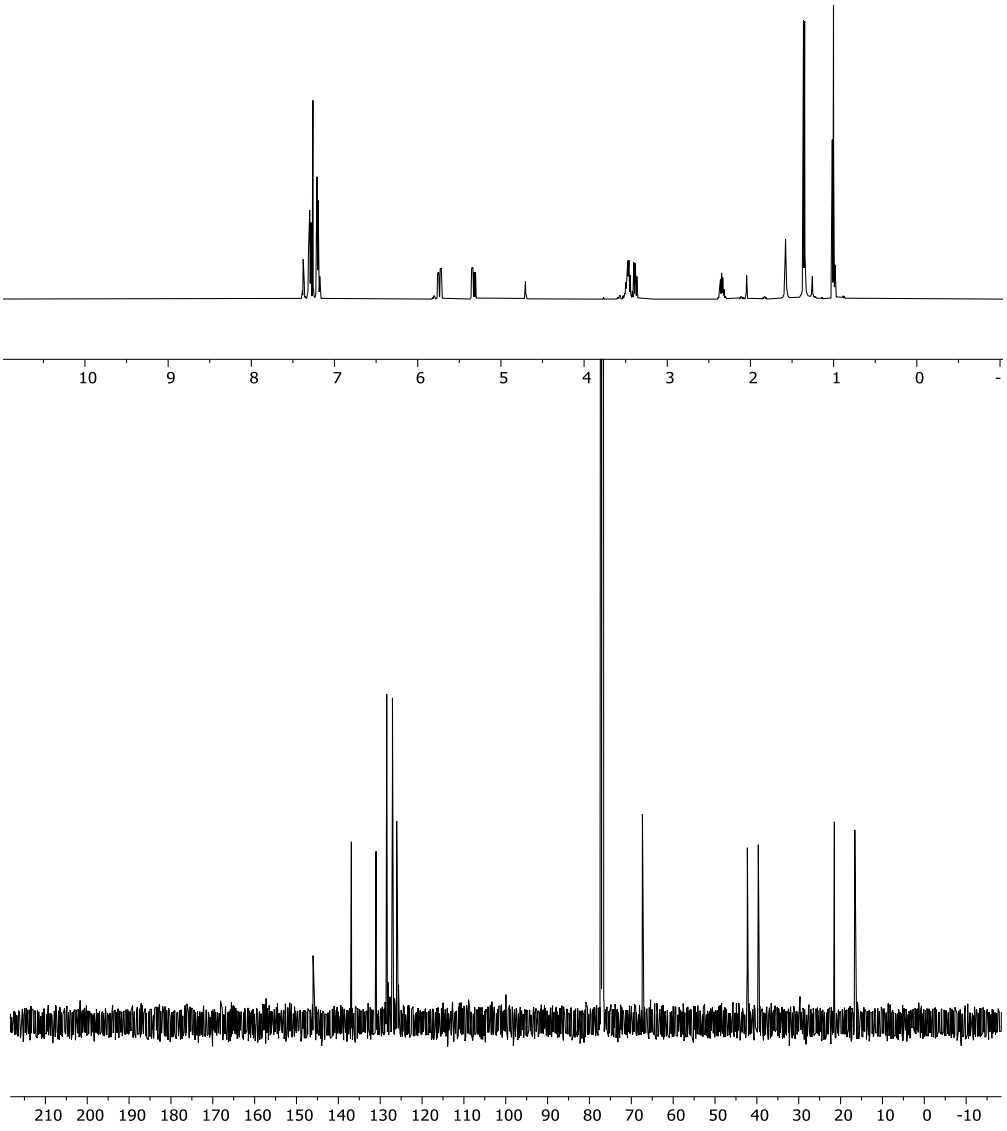
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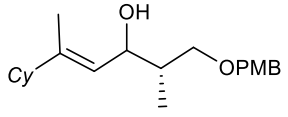
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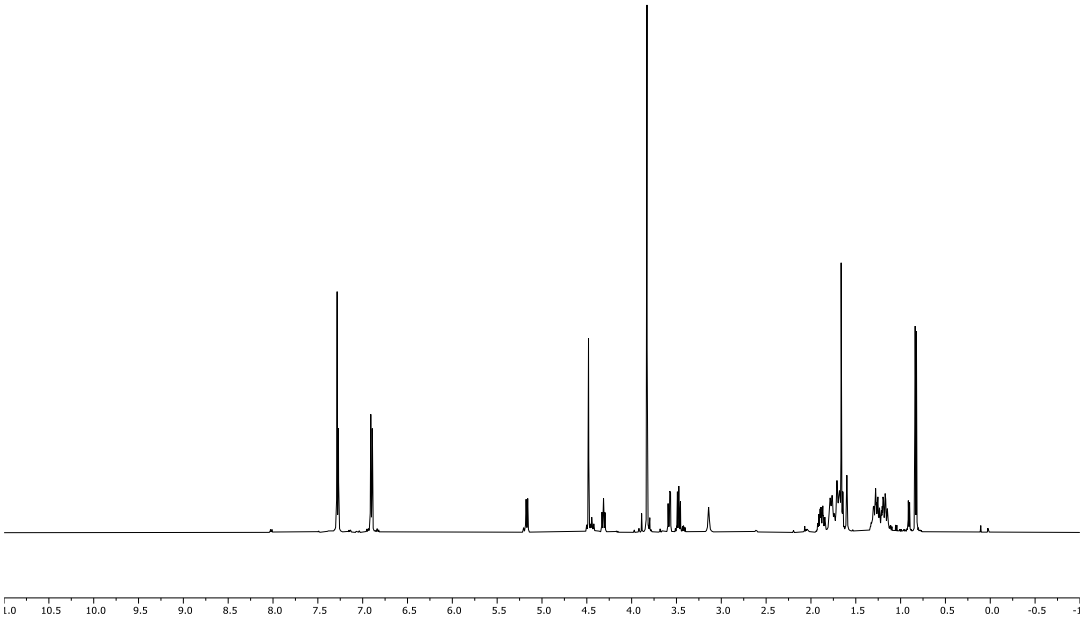
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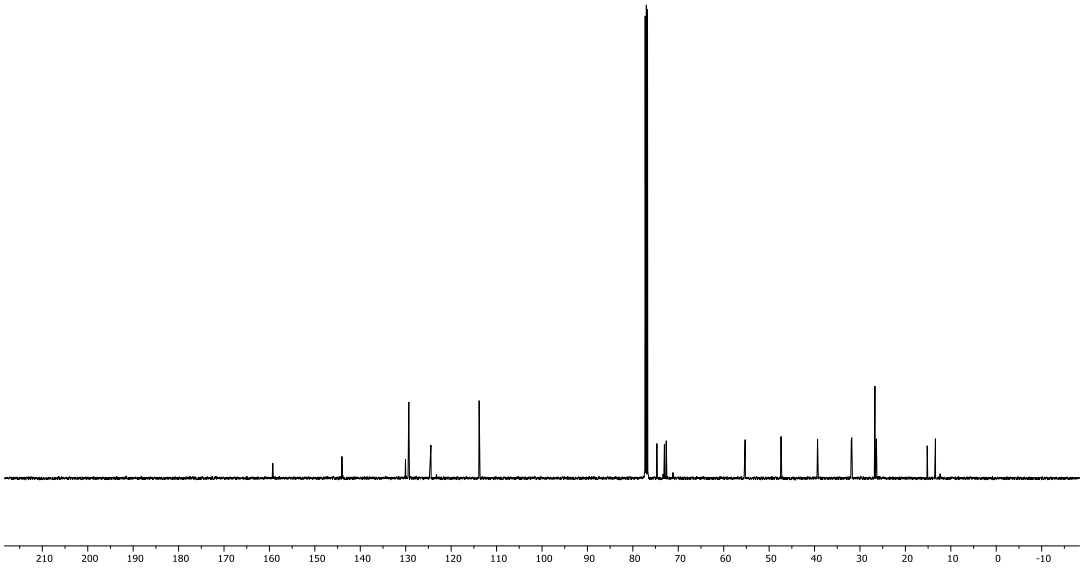
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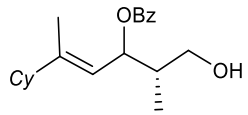
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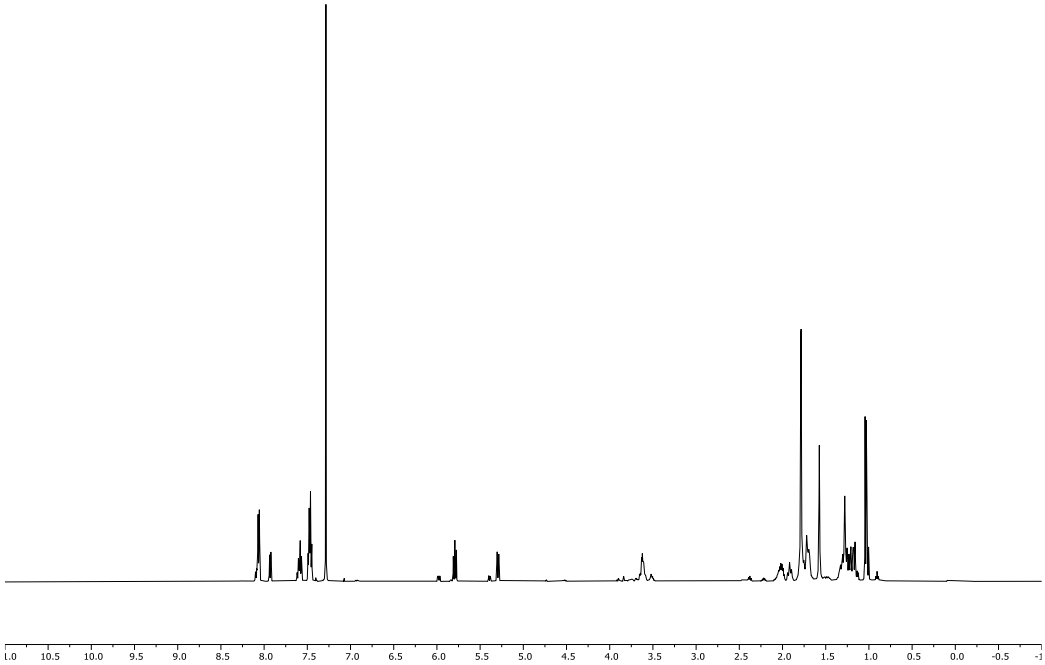
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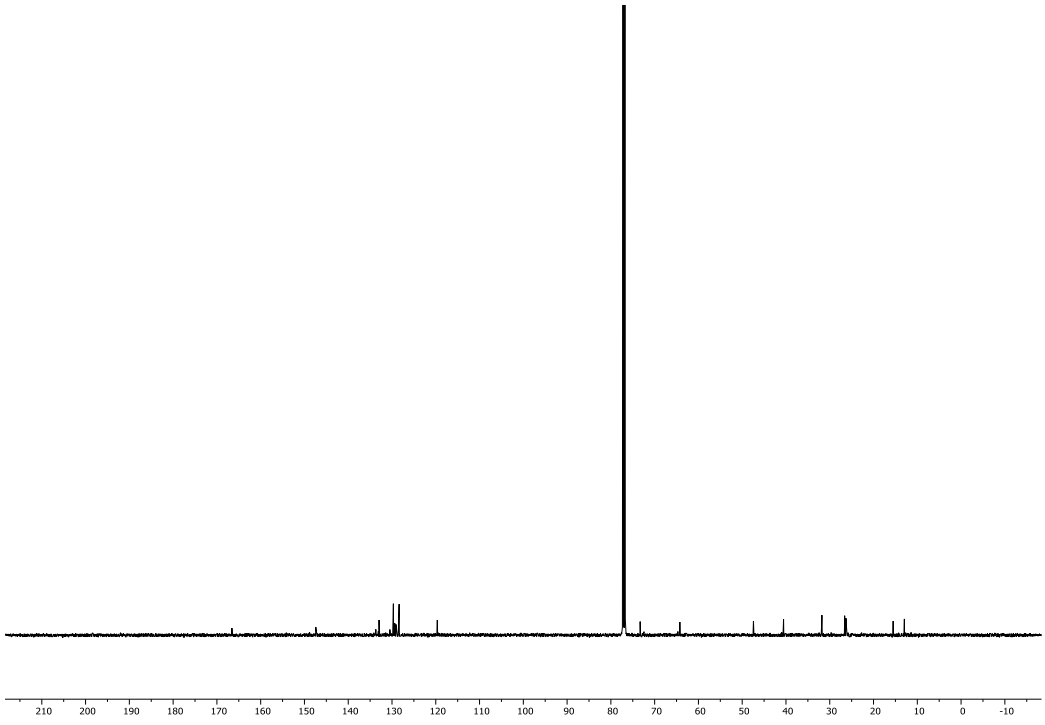
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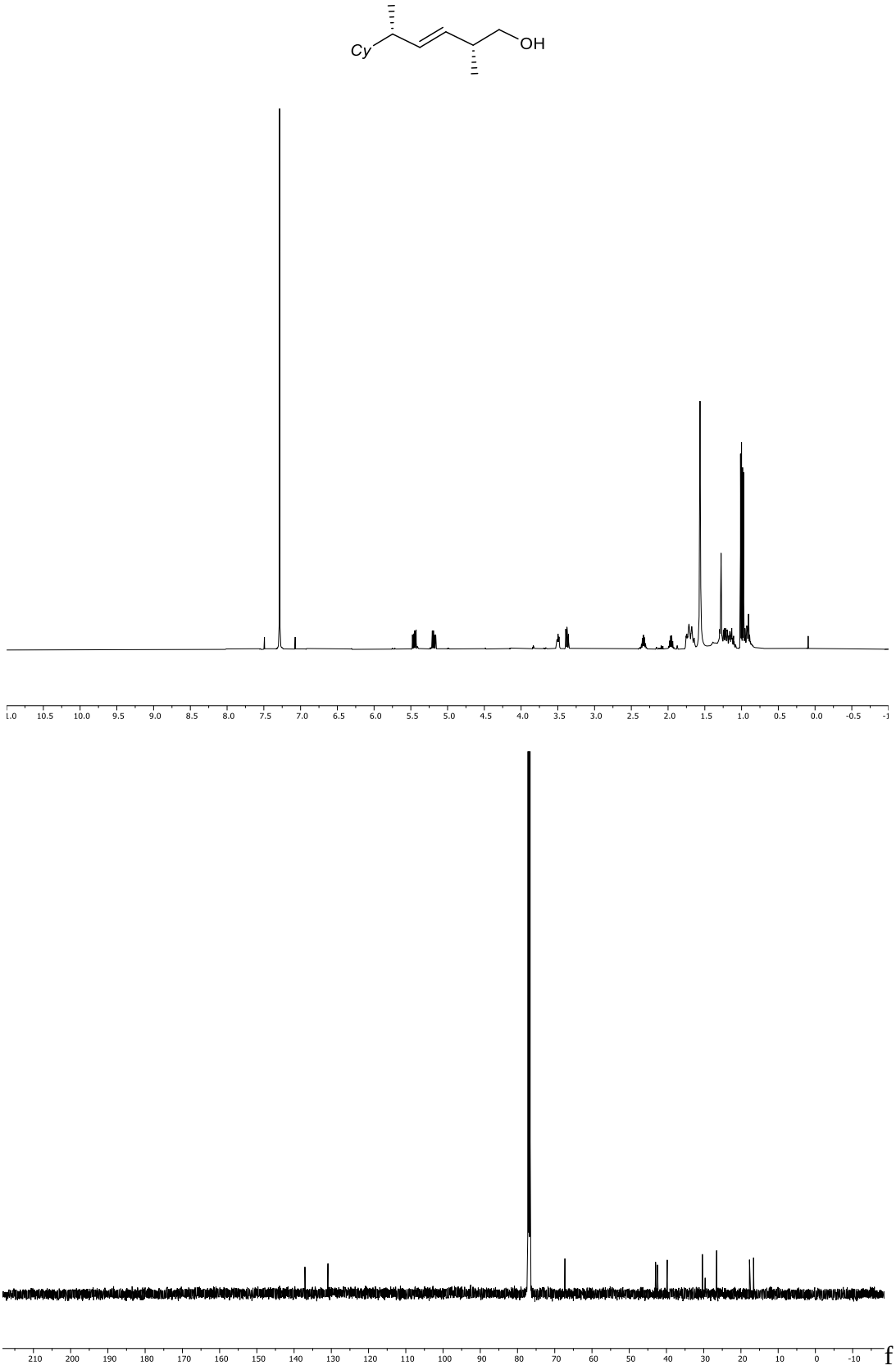
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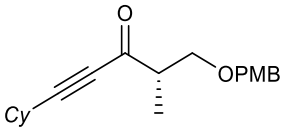
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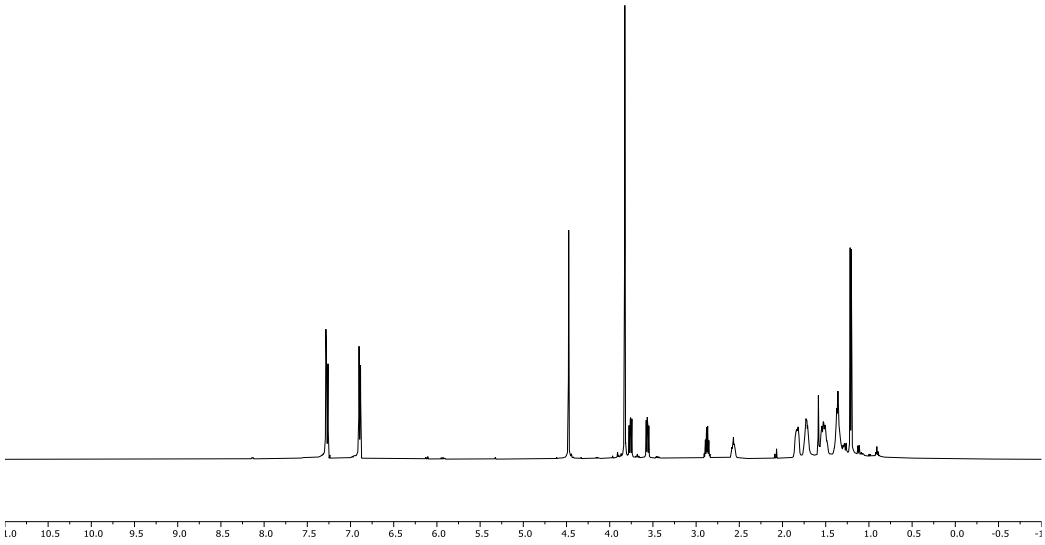
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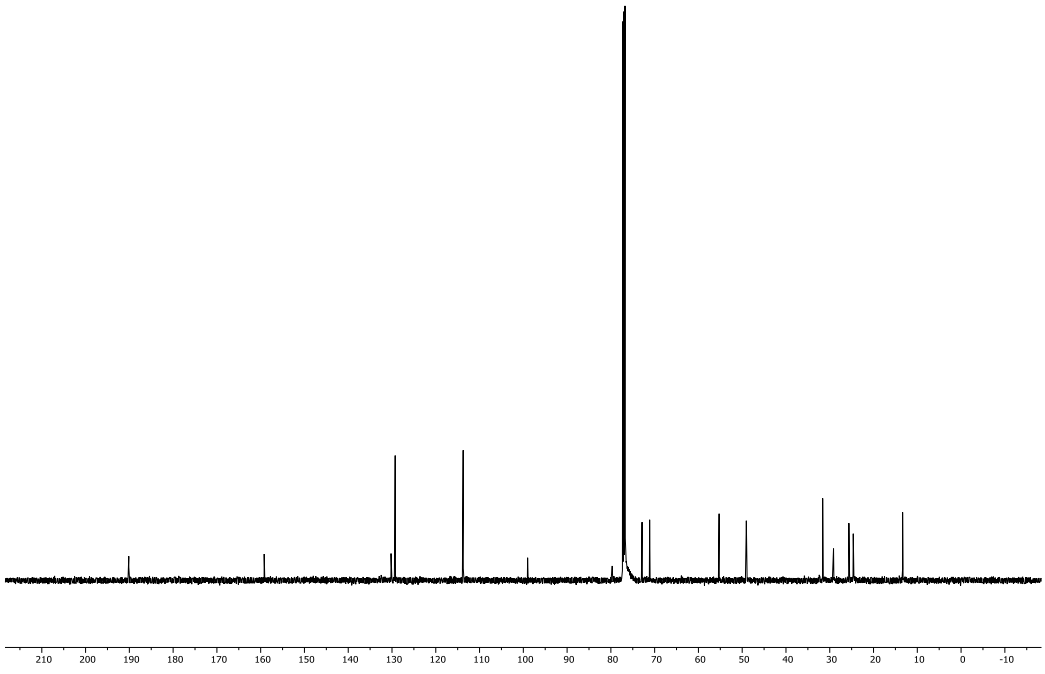
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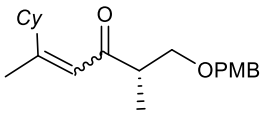
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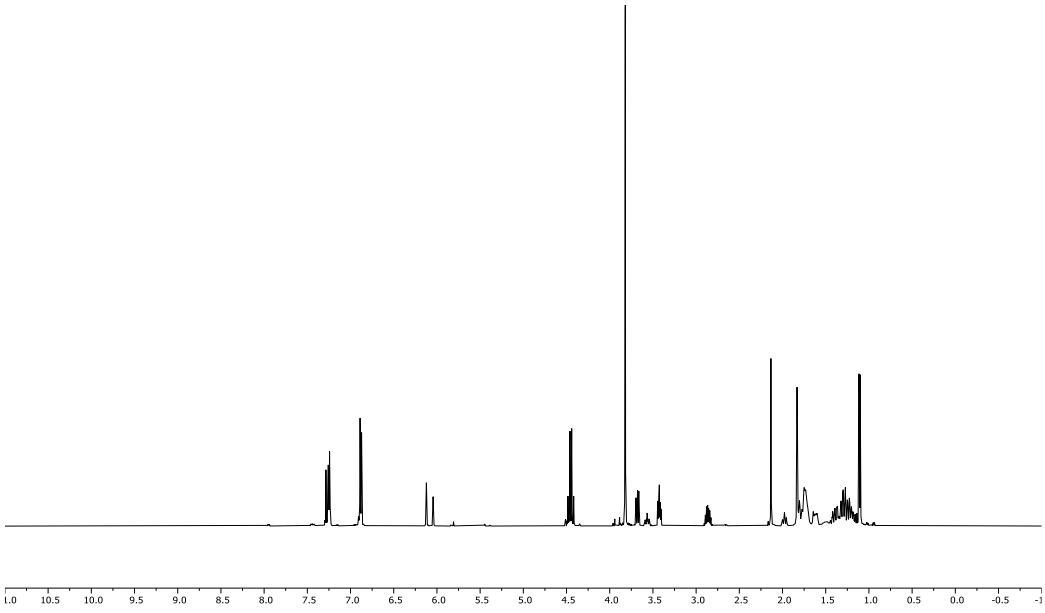
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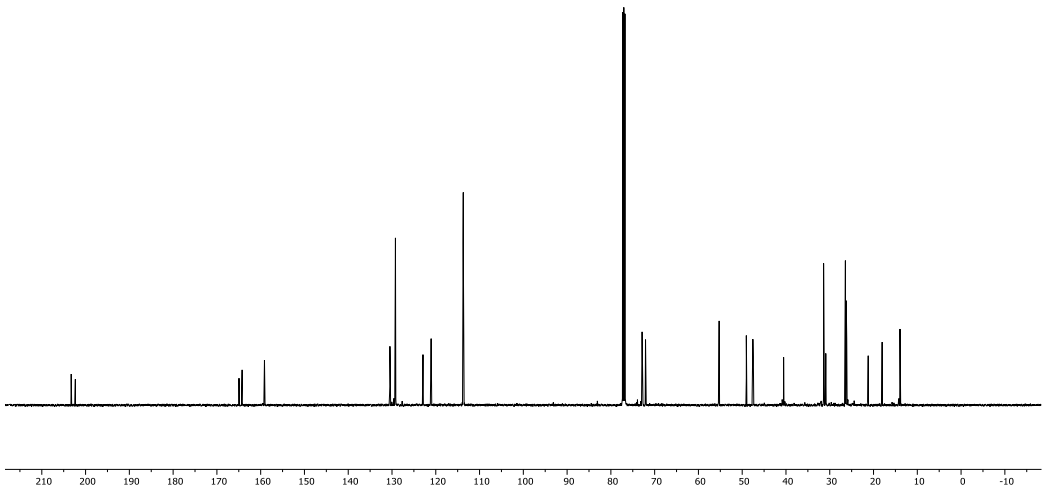
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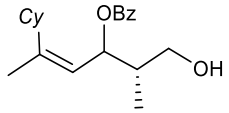
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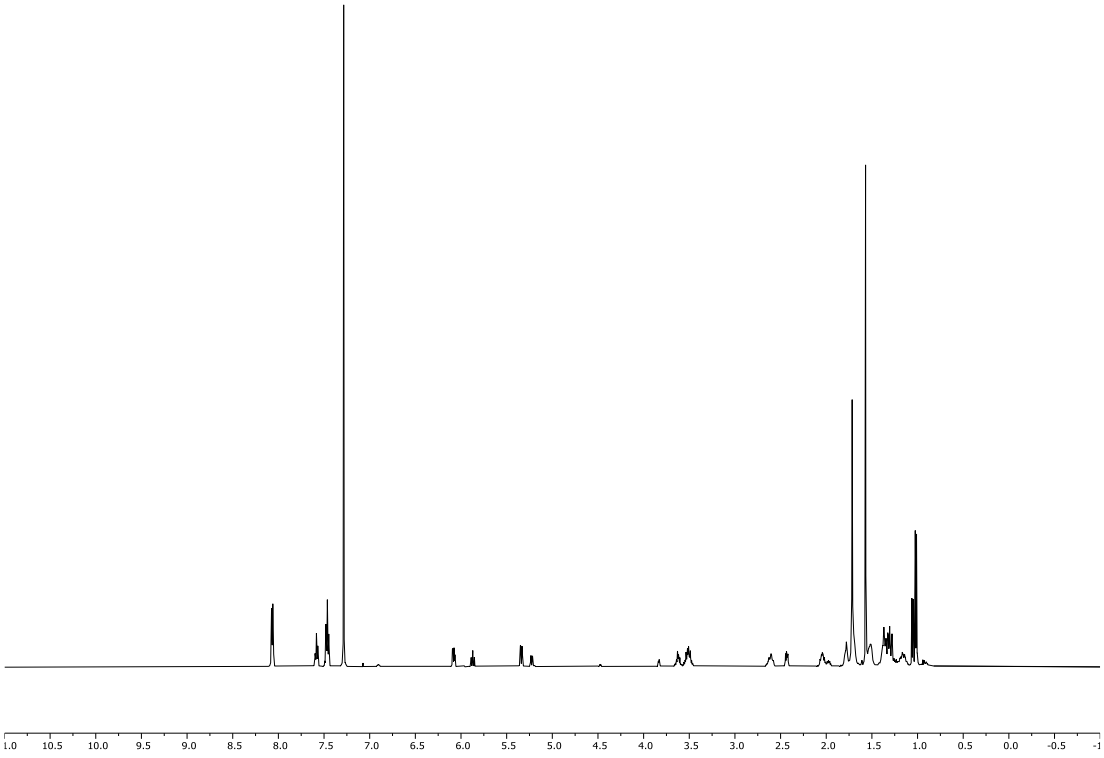
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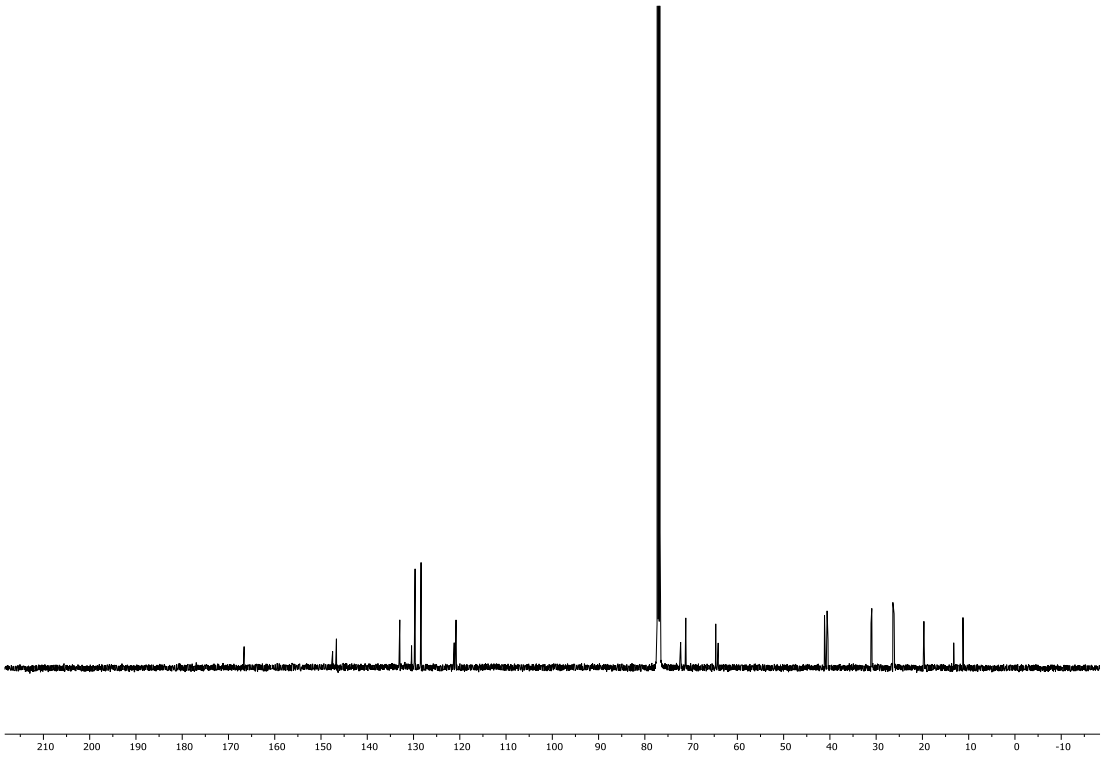
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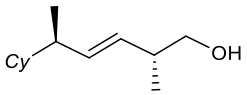
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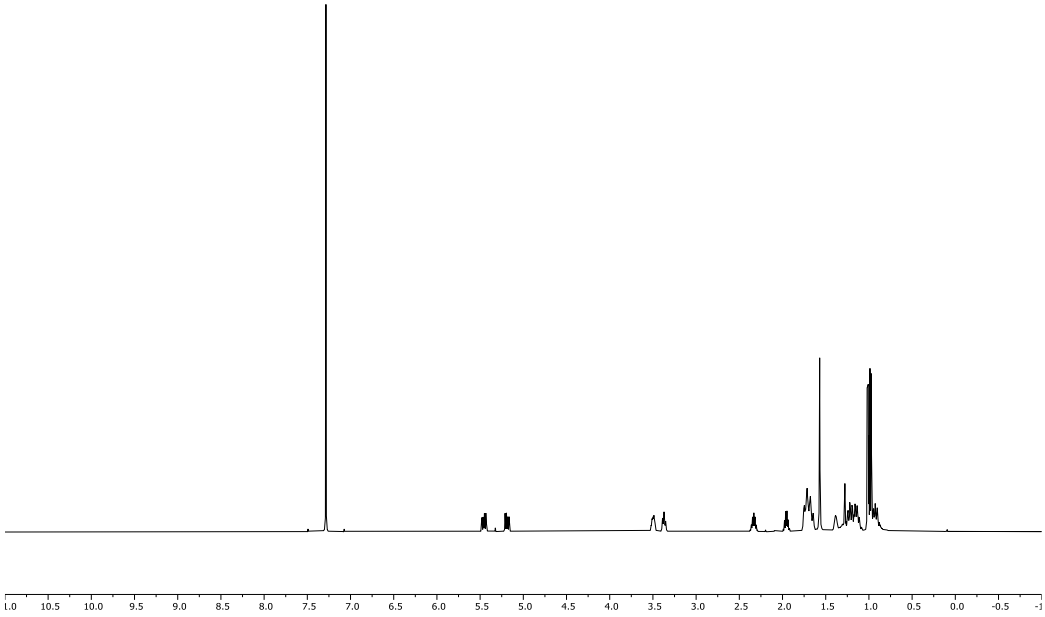
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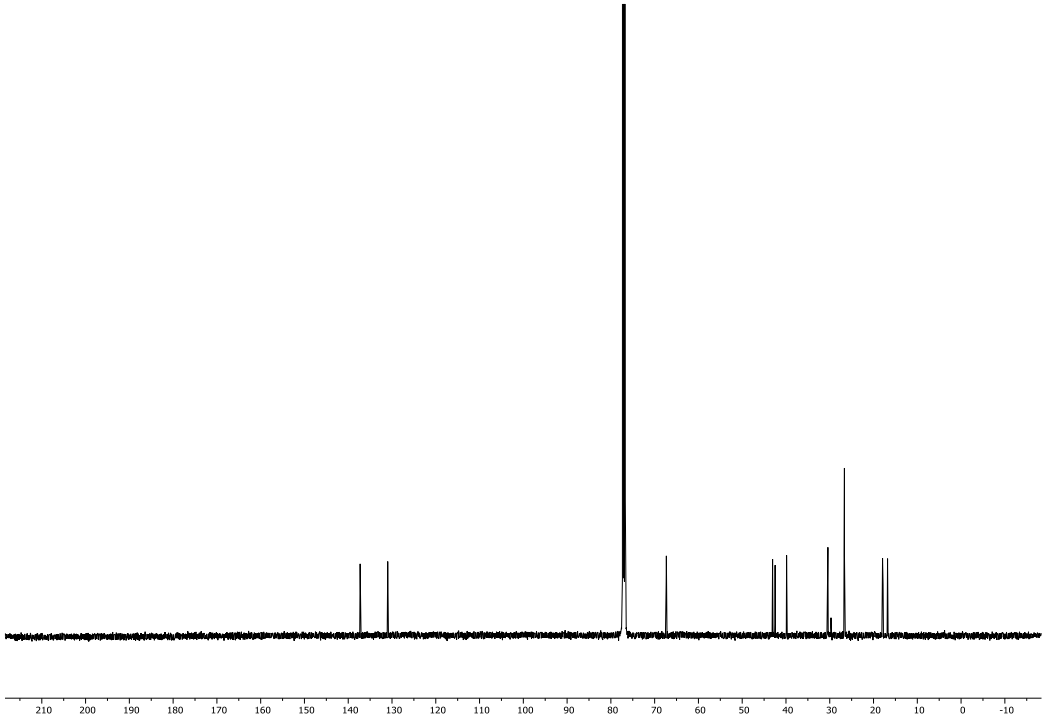
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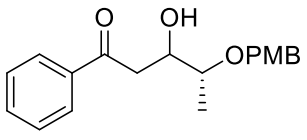
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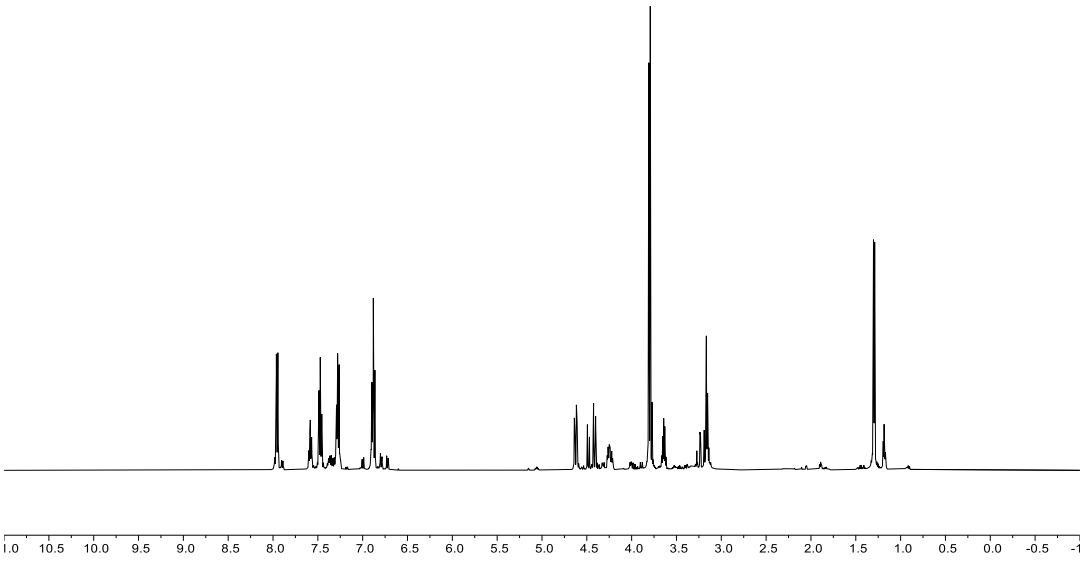
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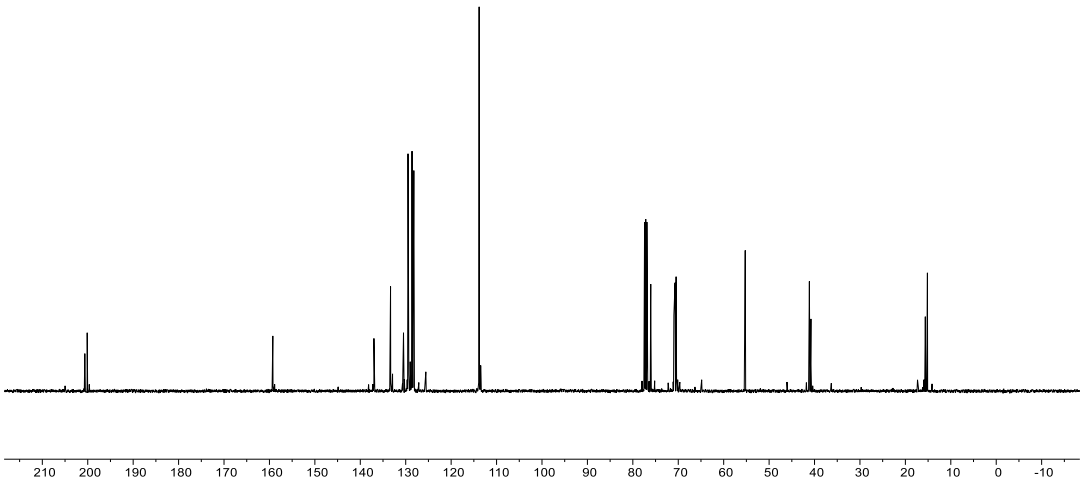
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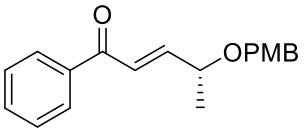
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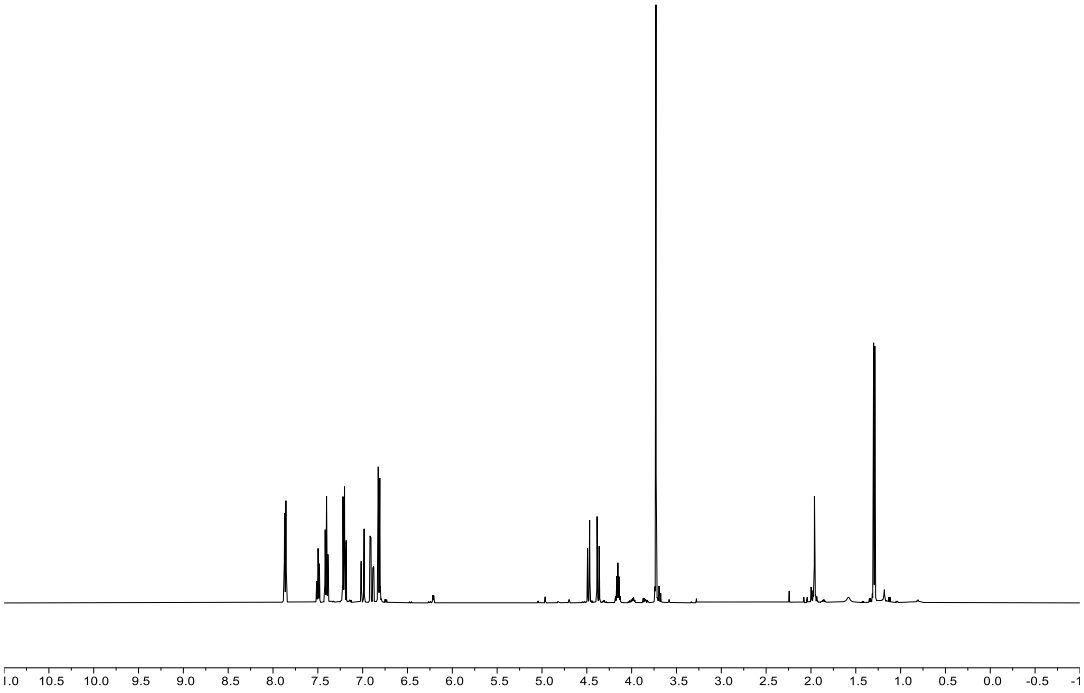
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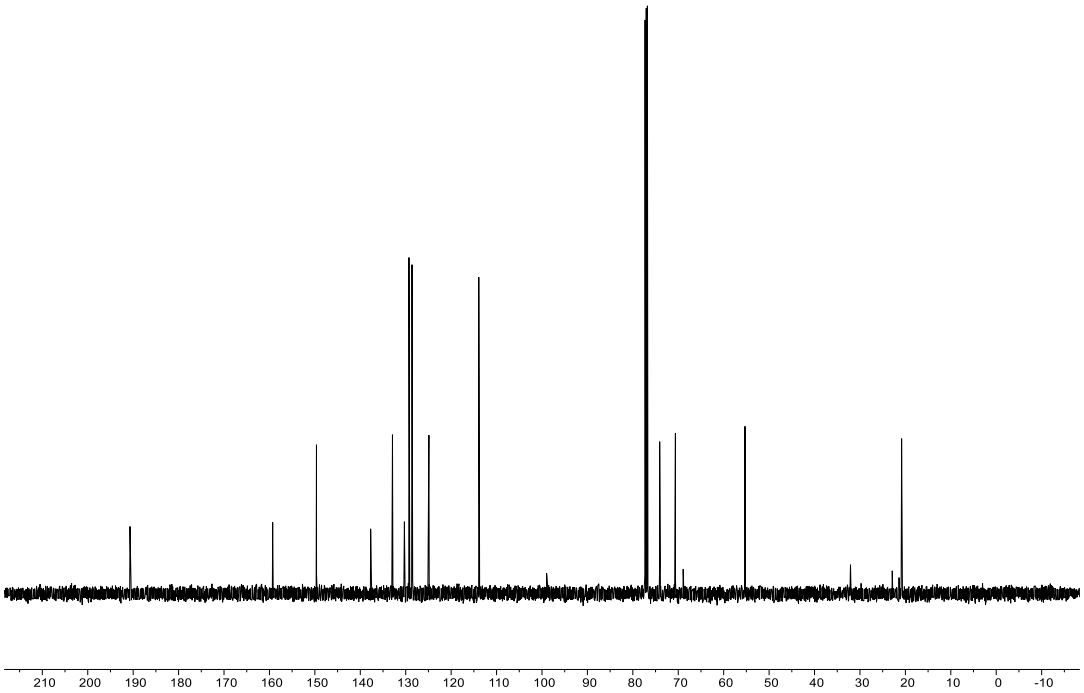
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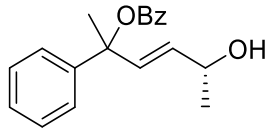
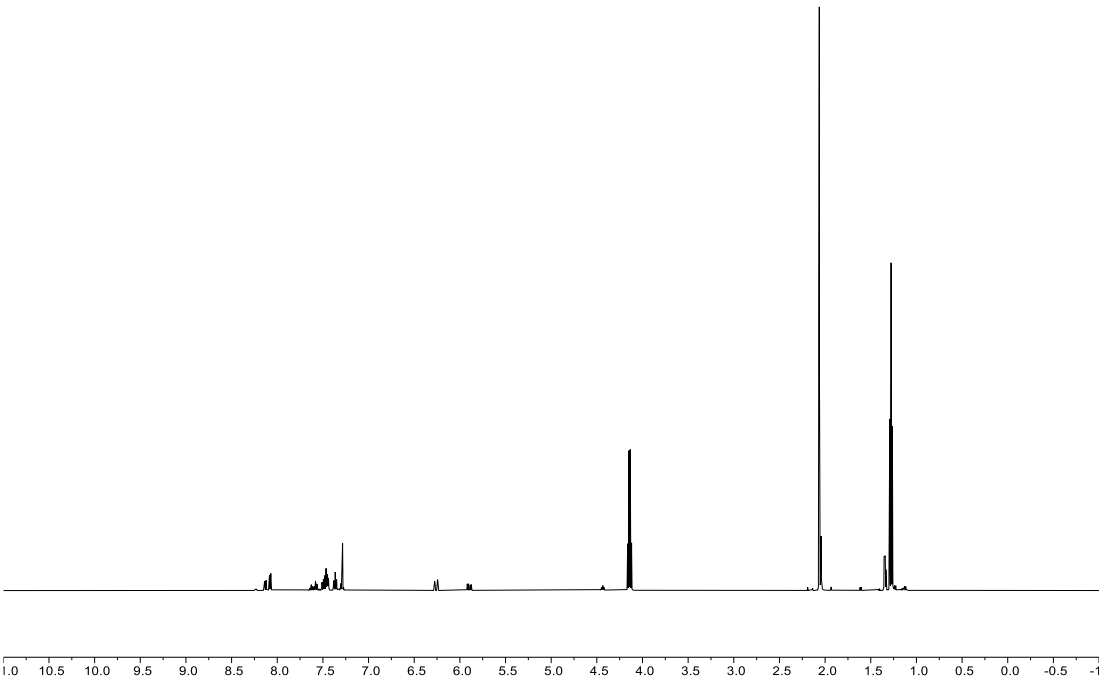

OBz
OH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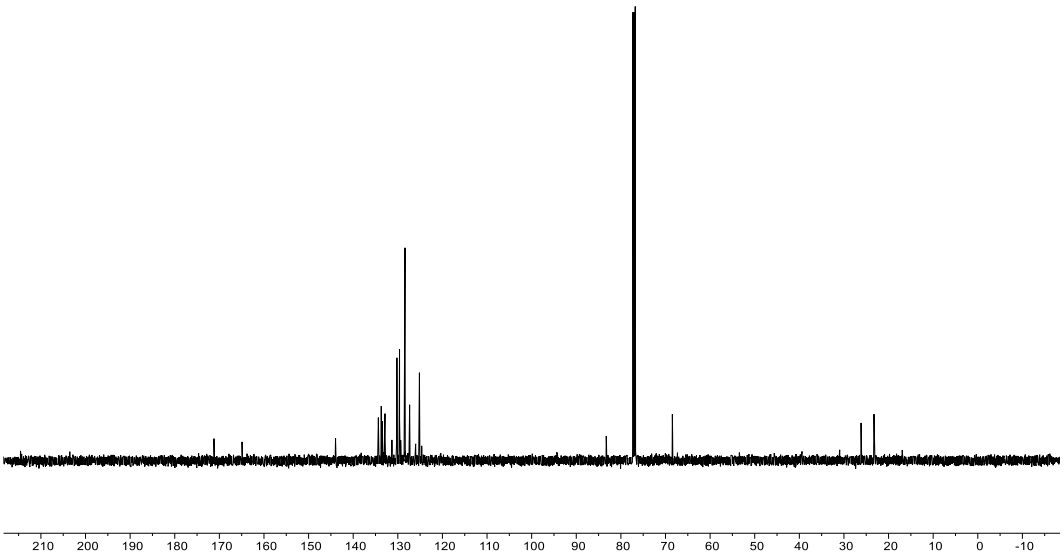
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