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Development of Regio- and Diastereoselective Samarium (II) Iodide Mediated Allylic Benzoate Reductions

Trevor Stockdale
Western Washington University, stockdt1@gmail.com

Development of Regio- and Diastereoselective Samarium (II) Iodide Mediated Allylic Benzoate Reductions.

By

Trevor Stockdale

Accepted in Partial Completion
of the Requirements for the Degree
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ADVISORY COMMITTEE

Dr. Gregory O'Neil, Chair

Dr. James Vyvyan

Dr. John Gilbertson

GRADUATE SCHOOL

Dr. Gautam Pillay, Dean

Master's Thesis

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Trevor Stockdale

6/4/2018

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A Thesis
Presented to
The Faculty of
Western Washington University

In Partial Fulfillment
Of the Requirements for the Degree
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Abstract

Herein, we report a regio- and diastereoselective samarium mediated allylic benzoate reduction. The reaction can achieve high yields, regioselectivity, and diastereoselectivity, however there appear to be many factors influencing the outcome: proton sources, alkene geometry, chelating group length, relative stereocenter positioning, and stereocenter identity. These substrate parameters were looked at in-depth which ultimately led to several conclusions about optimized substrates. For instance, experiments indicate that the reaction proceeds through a bicyclic organosamarium species followed by intramolecular protonation from samarium bound water.

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List of Abbreviations

HMPA	Hexamethylphosphoramide
DMPU	N, N′-Dimethylpropyleneurea
SmI_2	Samarium Diiodide
THF	Tetrahydrofuran
SCE	Standard Calomel Electrode
SET	Single Electron Transfer
NaOH	Sodium Hydroxide
H_2O	Water
Na(Hg)	Sodium Mercury Amalgam
n-BuLi	n-Butyl Lithium
Ac_2O	Acetic Anhydride
SO_2Ph	Sulfone
OBz	Benzoyl
OAc	Acetate
D_2O	Deuterium oxide
$Pd(P(Ph_3)_4$	Palladium tetrakis triphenylphosphine
α	Alpha
β	Beta
γ	Gamma
$OP(O)OEt_2$	Diethyl phosphite
ROH	Generic alcohol
MeOH	Methyl alcohol
t-BuOH	Tertiary butyl alcohol
OBn	Benzyl ether
Ts	Tosyl
Ph	Phenyl
OTBS	Tertiary butyl dimethyl silyl ether
NaOAc	Sodium acetate

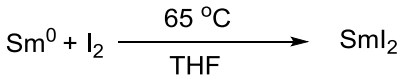
MeCN	Acetonitrile
PhI=O	Iodosobenzene
Boc	Tertiary-butyloxycarbonyl
$AlMe_3$	Trimethyl aluminum
Cp_2ZrCl_2	Zirconocene dichloride
CHO	Aldehyde
OPMB	Para-methoxybenzene ether
i-PrOH	Isopropanol
OH	Hydroxyl
$NaBH_4$	Sodium Borohydride
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
Me_2S	Dimethyl Sulfide
O_3	Ozone
Et	Ethyl
n-Bu	n-Butyl
$TiCl_4$	Titanium tetrachloride
Et_3N or TEA	Triethylamine
NMP	N-Methyl-2-pyrrolidone
$LiBH_4$	Lithium Borohydride
TBSCl	Tertbutyl dimethyl silyl chloride
BzCl	Benzoyl Chloride
HF, pyr	Hydrofloric Acide, pyridine
t-BuLi	tertiary-butyl Lithium
LAH	Lithium Aluminum Hydride
PMB-acet.	Para-methoxybenzene acetimidate
CSA	Camphor sulphonic acid
$(COCl)_2$	Oxalyl chloride
DMSO	Dimethyl sulfoxide
i-Pr	Isopropyl

t-Bu	Tertiary-butyl
Ph	Phenyl
Bn	Benzyl
p-TsOH	Para-toluene sulphonic acid
GC-MS	Gas Chromatography - Mass spectrometry
d.r.	Diastereometric ratio
Et_2O	Diethyl ether
$NaClO_2$	Sodium chlorite
NaH_2PO_4	Sodium phosphate monobasic
t-BuCOCl	Trimethylacetyl chloride
KHMDS	Potassium bis(trimethylsilyl)amide
BnBr	Benzyl Bromide
DiBAl-H	Diisobutylaluminium hydride
DCM	Dichloromethane
EtOAc	Ethyl Acetate
Hex	Hexanes

Chapter 1: Introduction

1.1 Samarium diiodide in synthesis

Samarium diiodide (Kagan's reagents) has become a common place single electron transfer (SET) reagent in many organic laboratories.[1] Uses range from a variety of reductions, eliminations, olefinations, radical cascade reactions, pinacol couplings, as well as in a variety of named reactions such as Barbier, Birch reduction, Julia olefination, and Reformatsky. (Figure 1-1)[2,3] The versatility of samarium diiodide comes from its ease of preparation and use, and the fact that its properties can be manipulated with the addition of co-solvents and proton donors.[4] Additives such as HMPA, DMPU, alcohols, and water change the steric bulk and redox properties of the reagent allowing for both chemo- and regioselective transformations. Reactions utilizing SmI_2 proceed either through a one electron, open shell, or two electron, closed shell pathways. Samarium preferably exists in its +3 oxidation state with the loss of its three outermost electrons ($5d^1$ and $6s^2$) allowing for a Xenon like configuration.[5] Upon conversion to SmI_2, samarium metal gives up its outermost electrons ($6s^2$) leaving the configuration as $[Xe]4f^6 5d^1$. SmI_2 reactions proceed through the now thermodynamically favorable loss of its outermost valance electron $5d^1$ adopting a [Xe] like configuration as the 4f electrons lie closer to nucleus then the valance electrons of xenon. Our lab utilizes Imamoto's method of preparation of SmI_2 which consists of heating samarium metal in THF with I_2 at 65 ^{0}C for 12 hours (Scheme 1-1).[1]



Scheme 1-1. Imamoto's method of preparation of SmI_2

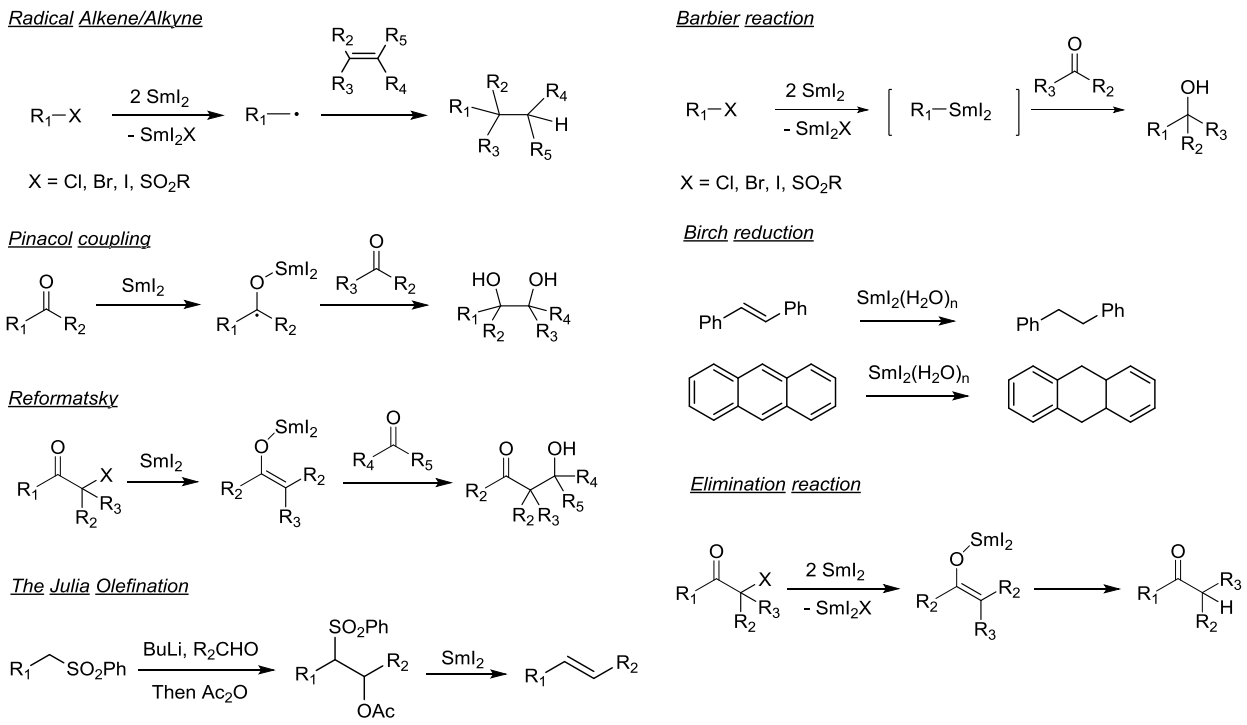


Figure 1-1. Applications of Samarium Diiodide

SmI_2 is typically prepared as a 0.1 M solution in THF. It was shown that when prepared in THF SmI_2 has a coordination number of seven and a pentagonal bipyramidal molecular geometry.[6] The crystal structure shows the iodides present along the z-axis and five THF molecules ligated in a planar fashion (Figure 1-2). Protic solvents such as alcohols have played a key role in many SmI_2 reactions but the use of water as an additive has only been studied in-depth recently. [1] Water acts as a lewis base and proton donor increasing the redox potential (to -1.3 V vs SCE) of SmI_2 close to that of the toxic HMPA (-1.75 V vs SCE). Intriguingly, Procter et al. showed that the effective reduction potential of $SmI_2(H_2O)_n$ is much higher (up to -2.21 V vs SCE) than those determined via electrochemical methods.[3] Procter determined the effective redox potential utilizing a series of aromatic hydrocarbons with gradually increasing redox potentials to correlate with the redox potential of various lanthanide (II) reagents. The large disparity in effective redox potential vs those measured from electrochemical methods is due to the limited solubility, irreversible oxidation, precipitation, and instability of lanthanide reductants to cyclic voltammetry studies. Procter reported $SmI_2(H_2O)_n$ reacts with substrates whose reduction potentials are more positive than -2.21 V vs

SCE and will cleanly mediate Birch reductions of substrates bearing at least two aromatic rings in excellent yields, at room temperature, under very mild reactions conditions, and with selectivity that is not achievable from other SET reductants. In this way, $SmI_2(H_2O)_n$ will effectively reduce a variety of carbonyls such as aldehydes, ketones, lactones, activated esters and amides, and with the help of an activating additive such as NaOH, reduction of benzoic acid will even proceed to the corresponding alcohols.[7]

Figure 1-2. Molecular Configuration of SmI_2 in THF. Iodide = purple, oxygen = red, samarium = gray, carbon = blue.

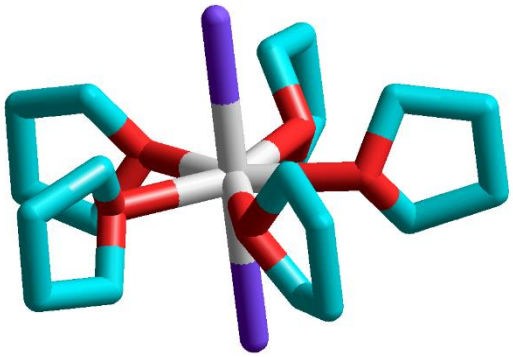
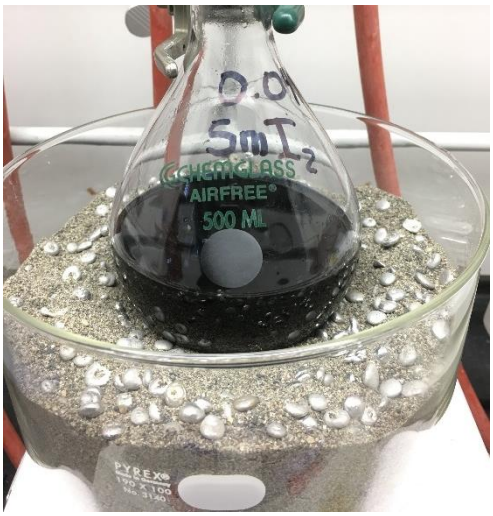


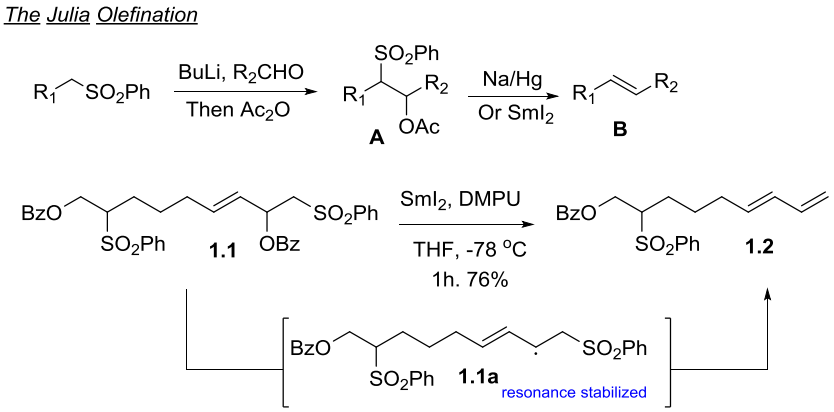
Figure 1-3. Freshly prepared SmI_2



Proton donors coordinated to Sm(II) reside in close proximity to coordinated substrates allowing for selective intramolecular proton delivery through heterolytic cleavage of the O-H bond.[8] The interplay between proton donor acidity (and even stoichiometry) and substrate coordination strength plays an important mechanistic role in reactions involving SmI_2. A study from Flowers et al. showed a direct correlation between the rate of ketone reduction and the pK_a of alcohol proton donors. Water showed the highest affinity for SmI_2, and the onset of coordination led to a change in the mechanism of ketone reduction (*vide infra*).[9] Methanol, ethanol, 2,2,2-trifluoroethanol, and phenol all showed a reaction order of 1. However water provided the highest rate enhancement with a reaction order of 1.4. Further rate enhancement studies showed a kinetic isotope effect k_H/k_D of 2, indicating the rate-limiting step in ketone reduction involved a proton transfer. They reported that for reductions with concentrations less than 8 equivalents of water the reaction order was 0.9 ± 0.1. Increasing equivalents of water above 8 lead to a reaction order above 1, and

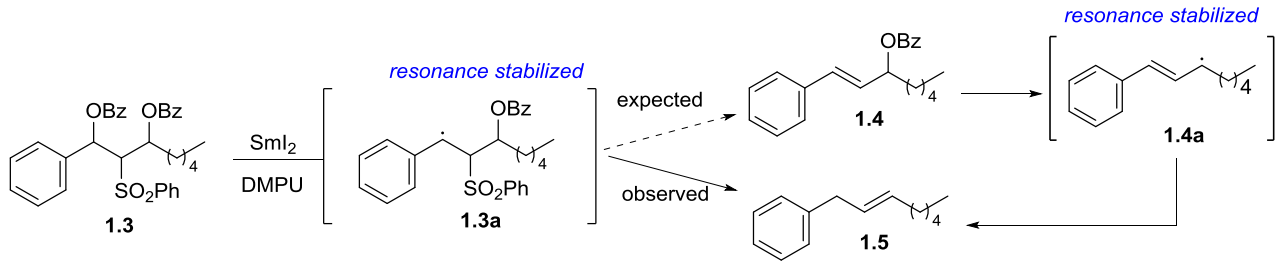
above 80 equivalents the rate was 2.0 ± 0.2 which remained constant up to 130 equivalents of water. Above 130 equivalents the rate was too fast to measure. They concluded that (1) there is a linear relationship with the pK_a of a proton donor and rate of ketone reduction, (2) water has a much higher affinity for SmI_2 then the alcohols studied, and (3) water's complexation with SmI_2 produces a reductant capable of ketone reduction in a mechanistically distinct intramolecular pathway.

The O'Neil group became interested in the use of SmI_2 as part of investigations into interrupted Julia olefinations.[10] Keck had shown that SmI_2 can be used as an alternative to Na(Hg)[11] for reducing acyloxysulfones of type **A** to *trans*-alkenes **B** (Scheme 1-1) It was observed that SmI_2 reduction of compound **1.1** occurred chemoselectively to give **1.2**. This was rationalized by the reaction preferentially proceeding through resonance stabilized intermediate **1.1a.** Conclusions from that study were that SmI_2 SET can occur to both sulfonyl and/or benzoyl groups and is likely reversible.[10] Fragmentation of the initially formed radical into a carbon radical is rate-determining and a difference in carbon radical stabilities allows for chemoselective reductive-eliminations.



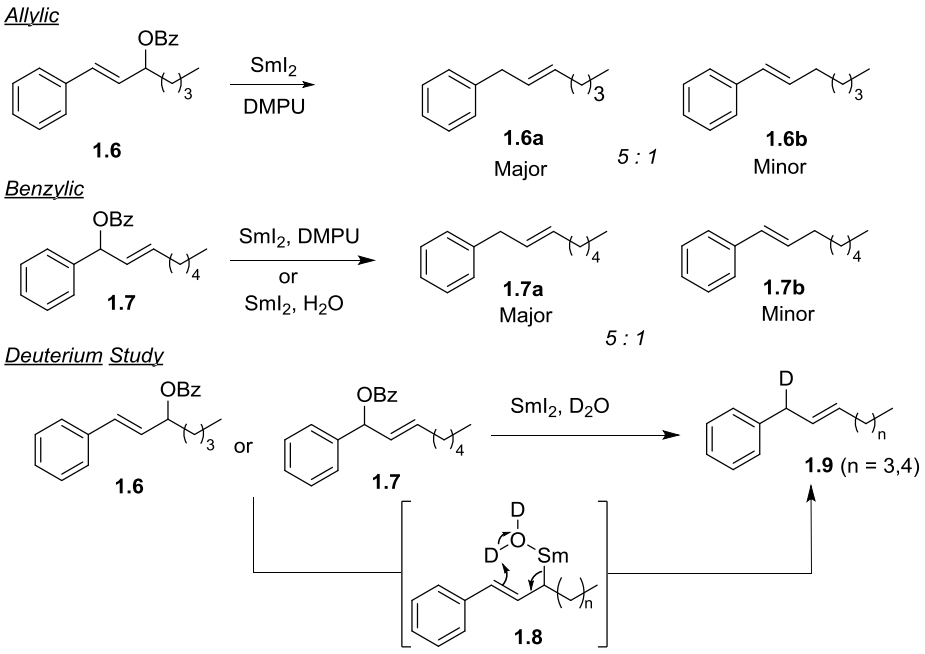
Scheme 1-2. Chemoselective Samarium mediated Julia Olefinations

A similar investigation on bis-benzoyloxysulfone **1.3** using SmI_2 was expected to selectively produce resonance-stabilized intermediate **1.3a**. Further reduction and loss of the sulfone group would then give **1.4**. Surprisingly, it was not allylic benzoate **1.4** that was obtained but rather the fully eliminated product **1.5** (Scheme 1-2).



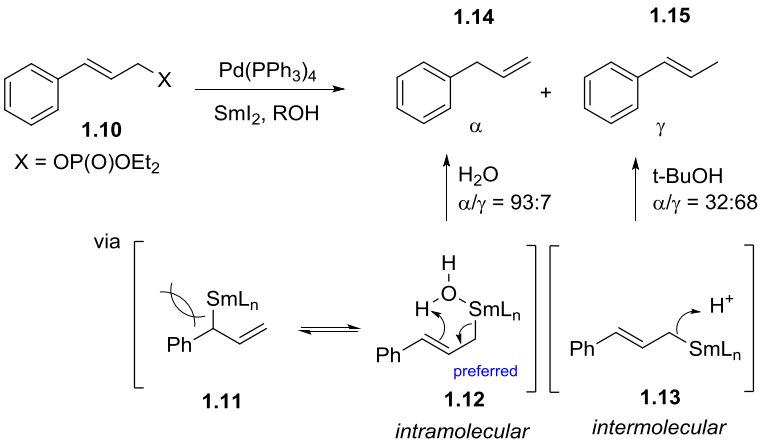
Scheme 1-3. Unexpected elimination of a bis-benzoyloxysulfone.

Upon further consideration this result was perhaps not so surprising. Following reductive elimination reduction and formation of **1.4**, a second SmI_2 mediated reduction could occur through resonance stabilized intermediate **1.4a** giving the unconjugated product **1.5** (Scheme 1-3). To test the intermediacy of allylic benzoate **1.4**, analogous substrate **1.6** was subjected to SmI_2 mediated reductive elimination with DMPU giving products **1.6a** and **1.6b** in the same ratio as the reduction of bis-benzoyloxysulfone **1.3**. Similarly, reductive elimination of benzylic benzoate **1.7** with either SmI_2/DMPU or SmI_2/H_2O gave products **1.7a** and **1.7b** with identical selectivity. Performing the reaction with either **1.6** or **1.7** with D_2O the major product for each was the mono deuterated adduct **1.9** suggesting both substrates converge to the same organo-samarium intermediate **1.8**.



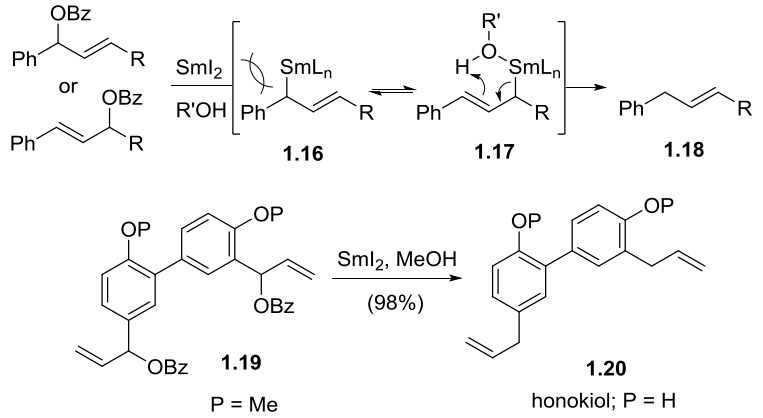
Scheme 1-4. Reduction of allylic and benzylic benzoates **1.6** and **1.7**

Previous work from Yoshida et al. using a $Pd(PPh_3)_4/SmI_2$ system suggested the selectivity for the non-conjugated product is due to steric reasons.[12] They reported the reduction of allylic phosphonate **1.10** was selective for the α-isomer **1.14** resulting from intramolecular proton delivery from the organo-samarium intermediate **1.12**. Changing the proton source to *tert*-butanol resulted in a switch in selectivity giving the γ-isomer **1.15** as the major product presumably proceeding through intermolecular protonation (Scheme 1-5). Applying that rational to our system, we can then explain the selective formation of **1.18** by a steric preference for organosamarium intermediate **1.17** followed by intramolecular protonation.



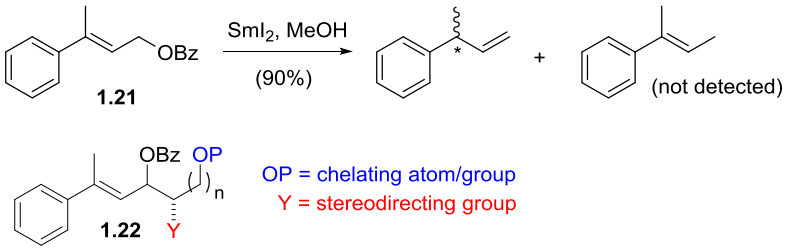
Scheme 1-5. Anagalous work from Yoshida et al.

This methodology then featured in our group's synthesis of the biologically relevant natural product honokiol (**1.20**) to simultaneously install both allyl substituents found in the target compound (Scheme 1-6).[13]



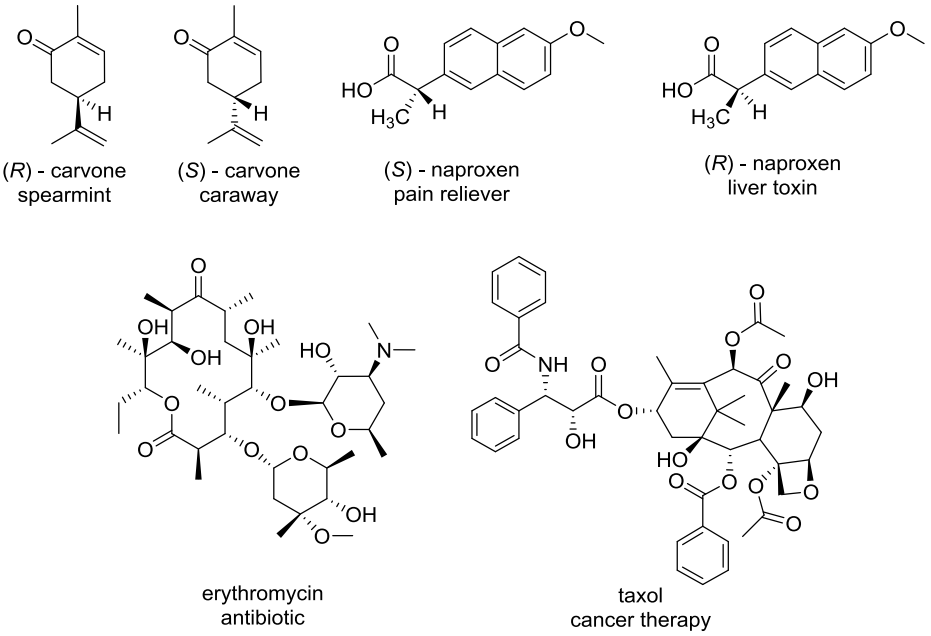
Scheme 1-6. Synthesis of the natural product honokiol

The remainder of this thesis is focused on this reaction applied to tri-substituted alkenes with applications to enantioselective synthesis. More specifically, it was recognized that when applied to tri-substituted alkene substrates, the reaction would produce a new stereocenter. We questioned whether the use of a stereodirecting group and/or tethered chelating atom as in compound **1.22** would render the reaction stereoselective (Scheme 1-7).



Scheme 1-7. Reduction of trisubstituted-alkene allylic benzoate **1.21** and formation of a new stereocenter (*), and proposed model to induce diastereoselectivity **1.22**.

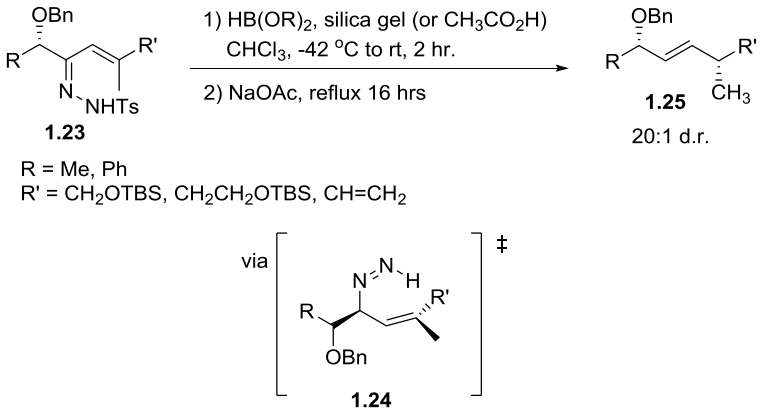
Reactions that are able to generate new stereocenters with high selectivity are valuable tools to organic chemists. Many natural products and medicines we use exist in a very specific geometric configuration which dictates how they will interact with our bodies. For example, the natural product carvone which is produced in nature as both the (*R*) and (*S*) enantiomers interact very differently: the (*R*) enantiomer smells like spearmint while the (*S*) enantiomer smells like caraway seeds despite only differing by the configuration of a single stereocenter (Scheme 1-8) . Similarly, the (*S*) enantiomer of naproxen is a pain reliever while the (*R*) configuration is a liver toxin. Carvone and naproxen are simple chiral molecules with only one stereocenter, however attempting to synthesize much more complicated natural products such as erythromycin[14] or taxol[15] which have 18 and 12 stereocenter respectively with absolute configurational control becomes very difficult. The introduction of a general method for stereoselective stereocenter synthesis could therefore have a significant impact on the field.



Scheme 1-8. Chiral natural products

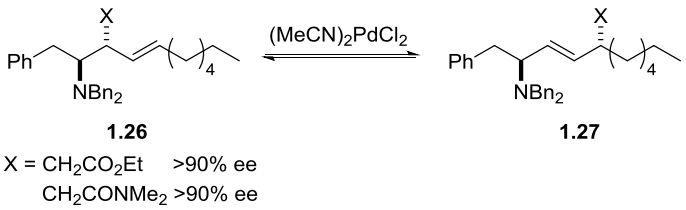
1.2 Examples of 1,4-stereocontrol.

Other groups have published similar diastereoselective olefin migration processes to that proposed in Scheme 1-7. For instance, McIntosh et al reported acyclic 1,4-stereocontrol via an allylic diazene rearrangement (Scheme 1-9).[16] The reaction was proposed to proceed through intermediate **1.24** with intramolecular hydrogen delivery and double bond migration. The authors also noted a change from *E* to *Z* alkene changed the selectivity from *syn*-**1.25** to *anti*-**1.25** in support of their proposed mechanism.



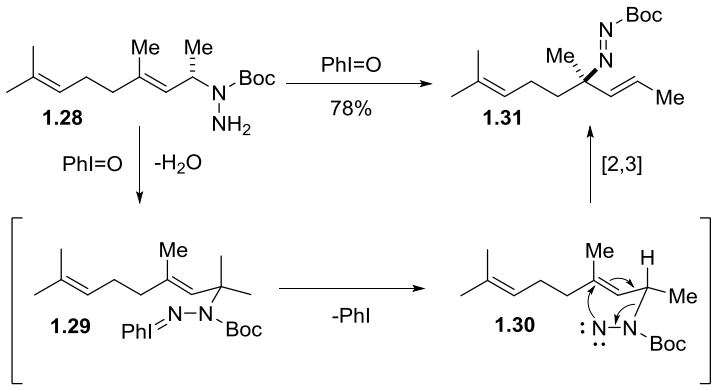
Scheme 1-9. Allylic diazene rearrangement from McIntosh et al.

Some of the best chiral auxiliaries take advantage of a 1,4-relationship to induce high diastereoselectivity, such as chiral oxzolidinones.[17,18] Clayden et al. investigated (*S*)-2-(dibenzylamino)-3-phenylpropanal as a chiral auxiliary for the preparation of β-chiral alcohols.[19] Their method takes advantage of a palladium (II) catalyzed rearrangement of allylic esters proceeding through a [3,3]-sigmatropic rearrangement (Scheme 1-10). They noted the driving force for the reaction is the steric repulsion between the migrating carbonyl and the allylic NBn_2 group. They confirmed enantioselectivity of their reaction via ozonolysis of the newly formed alkene and reduction of the resulting aldehyde followed by ^{1}HNMR analysis via the Mosher ester method.[20]



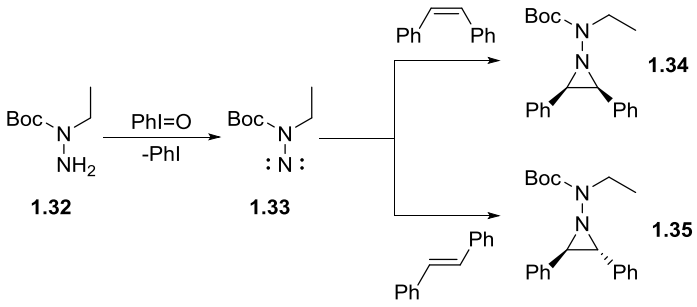
Scheme 1-10. [1,3]-sigmatropic rearrangement of allylic esters from Clayden et al.

Strick et al. reported an oxidative [2,3]-sigmatropic rearrangement of allylic hydrazides (Scheme 1-11).[21] They propose the reaction proceeds through a singlet *N*-nitrene intermediate which proceeded smoothly to form a variety of compounds. Once exposed to iodosobenzene the allylic hydrazide **1.28** would be oxidized to aminoiodinane **1.29**. Elimination of iodobenzene then allows a [2,3] sigmatropic rearrangement of **1.30** giving **1.31** in 78% yield.



Scheme 1-11. Proposed mechanism for oxidative rearrangment from Strick et al.

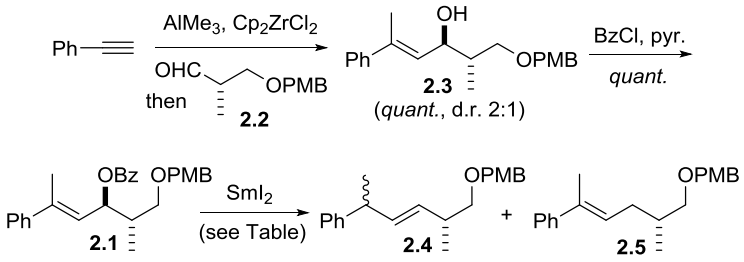
To gain insight into the mechanism, they performed the oxidative [2,3]-sigmatropic rearrangement on hydrazide **1.32** with either *cis*- or *trans*-stilbene (Scheme 1-12). They reported hydrazide **1.32** produced only *cis*-**1.34** when exposed to *cis*-stilbene and *trans*- **1.35** when exposed to *trans*-stilbene. They concluded this rearrangement is stereospecific with regard to alkene geometry.



Scheme 1-12. Impact of alkene geometry on oxidative [2,3]-rearrangement from Strick et al.

Chapter 2. Reductions on Roche- ester Derived Substrates.

Initial investigations into diastereoselective SmI_2 allylic benzoate reductions began with the PMB-*trans*-phenyl compound **2.1.** This was prepared by zirconium-catalyzed carboalumination of phenylacetlyene[22] which upon addition of aldehyde (*S*)-**2.2**[23] gave **2.3** (Scheme 2-1).[24] The stereochemistry of the newly formed hydroxyl in **2.3** was assumed to by (*S*) arising from chelation control,[25,26] however the actual configuration was not determined as it proved unimportant for the reaction (*vide infra*). Benzoylation of **2.3** and treatment with SmI_2/ROH or SmI_2/DMPU resulted in a mixture of regioisomers favoring the unconjugated product **2.4**, with the highest regioselectivity coming from the use of H_2O as a proton source (5:1). Analysis of the ^1H NMR spectra showed no appreciable levels of diastereoselectivity for any of the reactions. The highest diastereomeric ratio (d.r.) was obtained when using *tert*-butanol (*t*-BuOH), however this reaction proceeded with modest regioselectivity and produced what we have tentatively characterized as the homo-dimerization products, presumably arising from a slower protonation event.[27] The SmI_2/H_2O reaction was much cleaner giving a regioselectivity of 5:1 and no dimerization, however the reaction was not diastereoselective (d.r. 1:1). Figure 2-1 shows a representative example of ^1H NMR analysis for determination of diastereoselectivity for reduction of compound **2.1** with SmI_2 and various proton sources.

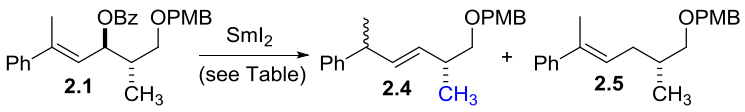


Entry	Additive[A]	**2.4**:**2.5**[B]	**2.4** d.r.[B]
1.	DMPU	1.3:1	60:40
2.	*t*-BuOH	3:1	69:31
3.	MeOH	3:1	60:40
4.	H_2O	5:1	50:50

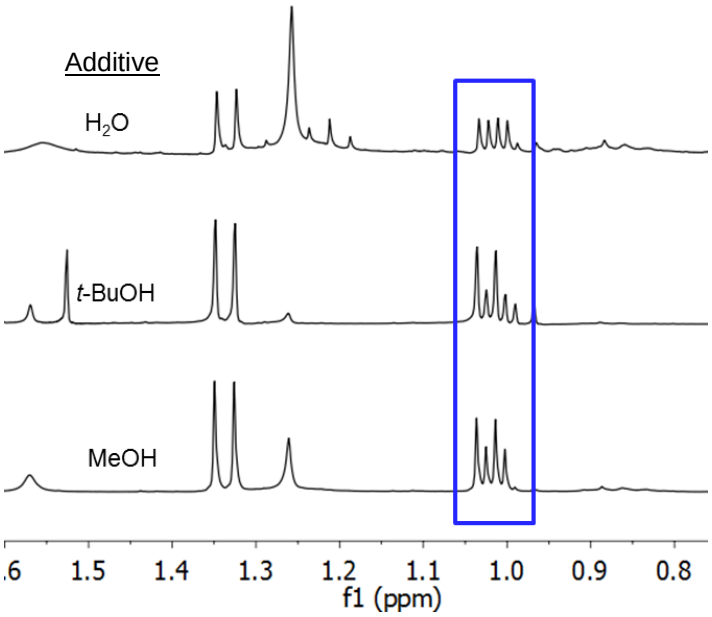
Notes: [A]Reactions were performed by adding the additive (16 equiv. DMPU or 1400 equiv. ROH) to SmI_2 (7 equiv.) followed by the substrate at room temperature. [B]Determined by NMR

Scheme 2-1. Initial screenings of compound **2.1** reductions

Figure 2-1. Example method of quantification of compound **2.1** reductions via ^{1}HNMR analysis. Blue box shows signals from the methyl group of **2.4** highlighted in blue.



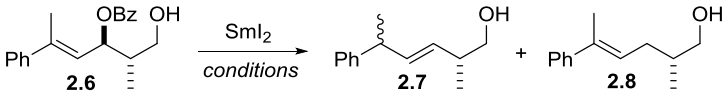
Entry	Additive	**2.4**:**2.5**	**2.4** d.r.
1	H_2O	5:1	50:50
2	*t*-BuOH	3:1	69:31
3	MeOH	3:1	60:40



We proposed removal of the PMB-protecting group and performing the reaction with a primary hydroxyl would give better diastereoselectivity through enhanced samarium chelation (*ref.* Ch. 1 section 1.1). Deprotection of **2.1** with DDQ gave the primary alcohol compound **2.6**. Reduction of **2.6** with SmI_2 gave both improved regio- and diastereoselectivity (up to 75:25). Table 2-1 presents results from our investigation into different proton sources on the reduction of **2.6** with SmI_2 (Table 2-1). The highest, and nearly identical, diastereoselectivities were obtained under anhydrous conditions using DMPU (entry 1) or in the presence of H_2O (entry 5), suggestive against an internal protonation by the hydroxyl group. These reactions both gave a d.r. of 75:25 however the reaction with DMPU gave significantly lower regioselectivity

(2:1 vs 15:1 for H_2O). Running the reaction at 0 ^{0}C showed no improvement to the diastereoselectivity of the reaction but rather an erosion of regioselectivity (entry 6).

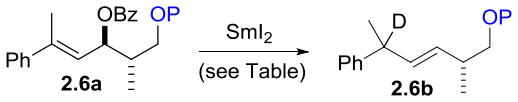
Table 2-1. Regio and diastereoselective reduction of compound **2.7.**



Entry	Additive[A]	2.7 : 2.8[B]	Compound 2.7 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: [A]Reactions were performed by adding the additive (16 equiv. DMPU or 200 equiv. ROH) to SmI_2 (7 equiv.) followed by the substrate and stirring for 30 min. [B]Determined by NMR. [C]**2.9** was not detected by NMR. [D]Performed at 0 °C.

A deuterium study was carried out in which substrate **2.6a** was subjected to either SmI_2/D_2O or anhydrous DMPU followed by a D_2O quench (Scheme 2-2). The results show with both a free hydroxyl and OPMB ether chelating group (entries 1 and 3) we see deuterium incorporation in the product **2.6b**. However reduction with a free hydroxyl using DMPU followed by a D_2O quench we saw no evidence of deuterium incorporation indicating proton transfer from the free hydroxyl. At this stage it is not clear as to whether proton transfer happens intra- or intermolecularly. We can conclude, however, that the rate of internal protonation from premixing D_2O with SmI_2 is faster than proton delivery from the free hydroxyl chelating group.

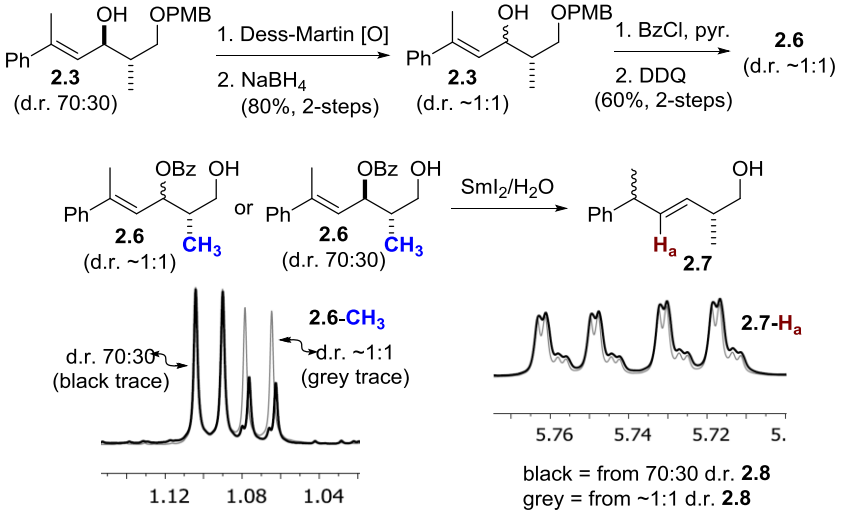


Entry	OP	Additive	Result
1	OH	D_2O	D_2O incorporation
2	OH	DMPU/D_2O	No incorporation
3	OPMB	DMPU/D_2O	D_2O incorporation
4	OPMB	None	Dimerization

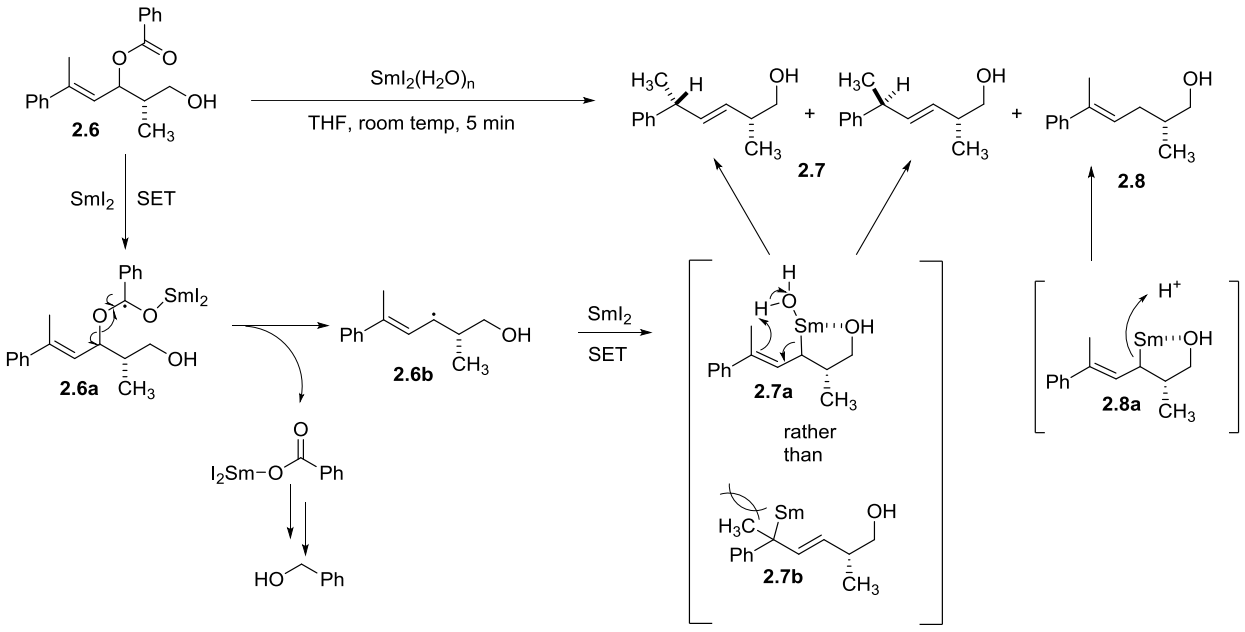
Notes: Reactions were performed by adding the additive (16 equiv. DMPU or 700 equiv. D_2O) to SmI_2 (7 equiv.) followed by the substrate at room temperature. DMPU reactions were reactions were quenched with D_2O at room temp.

Scheme 2-2. Deuterium study probing extent of internal protonation from hydroxyl group

In order to determine if the stereochemistry of the OBz-stereocenter had any impact on the stereoselectivity of the reaction, compound **2.6** was also prepared as a roughly 1:1 mixture of diastereomers via oxidation of the secondary alcohol **2.3** using Dess-Martin followed by reduction of the resulting ketone using $NaBH_4$ (Scheme 2-4). Treatment of **2.6**, now as a 1:1 mixture of diastereomers, with SmI_2 gave **2.7** with the same 75:25 diastereomeric ratio previously obtained when using **2.6** as a 70:30 mixture of diastereomers. This result indicates that regardless of the stereochemistry of the -OBz moiety, the reaction will produce the same diastereoselectivity.[28] In line with these results, our proposed mechanism involves radical species **2.6b** at which point original stereochemistry would be lost (Scheme 2-4).



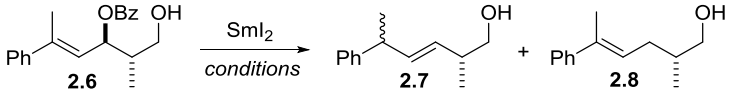
Scheme 2-3 Examining the impact of compound **2.6** -OBz stereochemistry on the stereoselectivity of SmI_2-reductions



Scheme 2-4. Proposed mechanism of samarium mediated allylic benzoate reduction.

Table 2-2 shows our optimization with respect to equivalents of water for the SmI_2/H_2O reduction of **2.6**. Keck et al described diastereoselective reductions of β-hydroxyketones by SmI_2 wherein higher equivalents of water led to a loss of diastereoselectivity.[29] Saturation of the inner coordination sphere was thought to inhibit substrates from coordinating with samarium.[1] Interestingly, our results show that irrespective of equivalents of H_2O, the hydroxyl group of **2.6** is still able to coordinate to samarium. This is consistent with a more recent study from Procter who showed that even high concentrations of H_2O do not fully saturate the inner coordination sphere of samarium.[30] Decreasing the equivalents of water led to an increase in regioselectivity, possibly due to a decreased rate of intermolecular protonation. Yields also increased as equivalents of water decreased, with the exception of 1 equivalent where side products (possibly homodimerization) were observed leading to a lower isolated yield of **2.7** (66% with 1 equivalent).

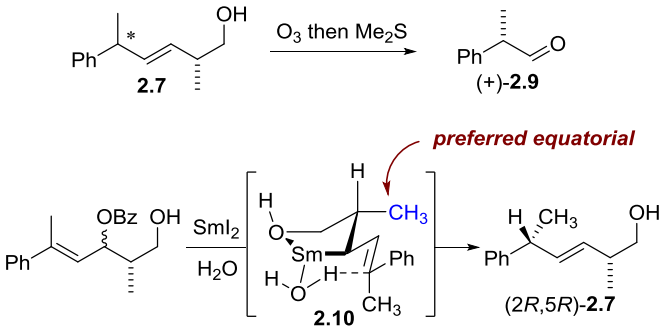
Table 2-2. Impact of water equivalents on regioselectivity, diastereoselectivity, and isolated yield from the SmI_2 reduction of compound **2.7**.



H_2O Equivalents[A]	2.7 : 2.8[B]	2.7 d.r.[B]	2.7 yield[C]
200	86 : 14	75 : 25	30 %
100	86 : 14	76 : 24	60 %
50	86 : 14	75 : 25	75 %
25	91 : 9	75 : 25	82 %
15	97 : 3	75 : 25	90 %
10	98 : 2	76 : 24	76 %
5	98 : 2	72 : 28	86 %
1	100 : 0	72 : 28	66 %

[A]Relative to SmI_2. [B]Determined by NMR. [C]Isolated yield.

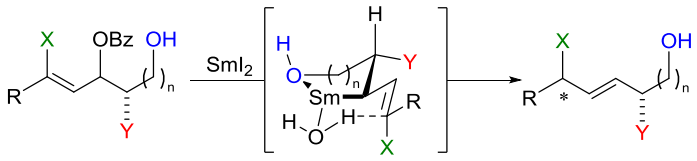
Stereochemical determination of the newly formed stereocenter was determined by ozonolysis of **2.7** giving aldehyde (+)-**2.9** (Scheme 2-5). Comparison of the optical activity of **2.9** with that previously reported[31] revealed the compound was enriched in the (*S*)-enantiomer, indicating the major diastereomer of **2.7** has the (*2R,5R*)-configuration. A potential model that explains this outcome is given in Scheme 2-4. This model is based on the energetics of the fused 5,6-bicyclic intermediate **2.10,**[32] which involves hydroxyl chelation followed by intramolecular protonation by a samarium bound water molecule.



Scheme 2-5. Determination of absolute stereochemistry of the major stereoisomer of **2.7** by ozonolysis

Chapter 3. Reaction Substrate Optimization

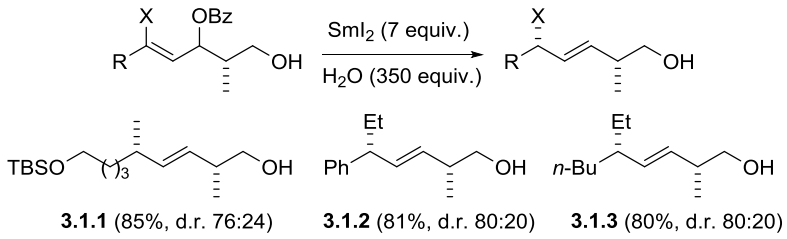
To further examine the generality of the reaction we set out to examine if enhanced selectivity could be obtained by changing: (1) the substituents on the tri-substituted alkene: (R and X; black and green), (2) the steric bulk of stereocenter Y (red) and its position relative to the chelating group (blue), and (3) the distance of the chelating group (e.g. so far n = 1) relative to the OBz stereocenter (Scheme 3-1-1).



Scheme 3-1-1. General substrate type for further reaction investigations

3.1. Effects of alkene substituents

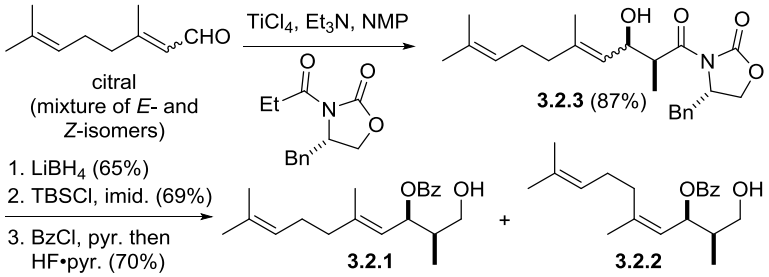
In order to determine the effects of substituents on the tri-substituted alkene, three additional substrates were prepared using the same sequence of reactions previously used to synthesize compound **2.6** including: 1) zirconium catalyzed carboalumination followed by trapping the resulting vinylalane with a Roche ester-based aldehyde, 2) benzoylation, and 3) deprotection of the primary alcohol. After reduction with SmI_2 it was clear this reaction is not only limited to aryl substrates like **2.7**. For example the alkyl TBS-protected compound **3.1.1** was obtained with complete regioselectivity and identical diastereoselectivity to that of phenyl compound **2.7** (~75:25, Table 2-1). Ethyl stereocenters were also prepared using the same protocol involving zirconium-catalyzed carboalumination (in this case using triethylaluminum)[22] followed by the addition of aldehyde **2.2** (*ref*. Scheme 2.2), benzoylation, and deprotection of the primary alcohol for substrate preparation. Compounds **3.1.2** and **3.1.3** were obtained in 81% and 80% yields respectively with a d.r. of 80:20. The stereochemistry of the newly generated stereocenter in each of these products is assumed to be (*R*) in analogy to compound **2.7**.



Scheme 3-1-2. SmI_2 mediated allylic benoate reductions to produce non-aryl and/or non-methyl products

3.2. Effects of alkene geometry

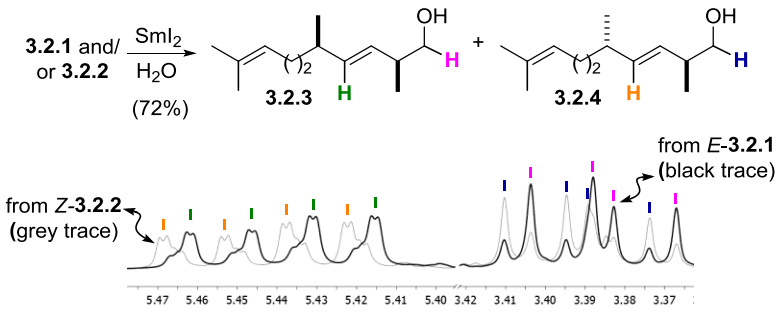
McIntosh et al. showed their ADR rearrangement to be stereospecific with regard to the tri-substituted alkene geometry (*ref.* Scheme 1.8).[16] Our reaction bears similar characteristics such as intramolecular proton delivery followed by alkene rearrangement, such that we set out to similarly examine the role of alkene geometry on stereocenter formation in our reaction with the preparation of compounds **3.2.1** and **3.2.2** (Scheme 3-2-1). We began this five step synthesis utilizing an Evans aldol reaction[33] with a mixture of *cis*- and *trans*-isomers of citral furnishing **3.2.3** in 87% yield. Reduction of the oxazolidinone with $LiBH_4$ proceeded in 65% yield, followed by mono-protection of the newly formed primary alcohol with TBSCl in 69% yield. Benzoylation of the secondary alcohol with benzoyl chloride and deptrotection of the OTBS silyl ether gave the partially separable isomers **3.2.1** and **3.2.2** in 70% over two steps.



Scheme 3-2-1. Preparation of (*E*)- and (*Z*)-isomers **3.2.1** and **3.2.3**

After purification over silica gel three roughly equal mass fractions were obtained containing the isomers: (1) A sample enriched in the *trans*-isomer **3.2.1** (87:13 **3.2.1:3.2.3**), (2) a sample enriched in the *cis*-isomer **3.2.3** (16:84 **3.2.1:3.2.2**), and (3) a roughly equimolar mixture of **3.2.2** and **3.2.3** (42:58

3.2.2:3.2.3). Each sample was subjected to reduction with SmI_2/H_2O (Scheme 3-2). Analysis of the crude ^1H NMR of each sample showed clear sign of the *cis*- and *trans*-isomers giving opposing selectivities. We calculated an expected diastereoselectivity for each sample based on an assumption the reaction is stereospecific to alkene geometry and on the selectivity observed for product **2.7** (~75:25). This led to expected diastereomeric ratios (d.r.) of 68:32, 33:67, and 48:52 from samples 1, 2, and 3 respectively. As shown the d.r. obtained from each sample was nearly identical to the predicted values indicating the reaction is stereospecific with regards to alkene geometry.



Sample	**3.2.1**:**3.2.2**	**3.2.3**:**3.2.4** (expected)	**3.2.3**:**3.2.4**(obtained)
1.	87:13	68:32	70:30
2.	16:84	33:67	35:65
3.	42:58	48:52	47:53

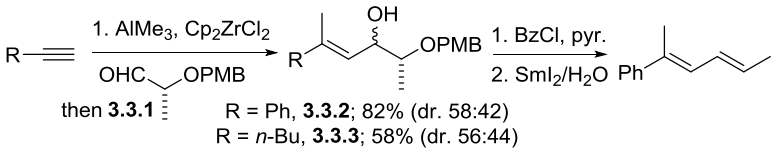
Scheme 3-2-2. Alkene stereospecificity experiments using differentially enriched mixtures of **3.2.1** and **3.2.2**. Colored lines are signals for the same colored hydrogens.

3.3. Effect of chelating group distance.

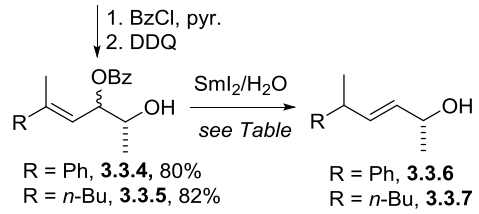
Synthesis of 4-memebred ring chelate.

Having only examined a substrate that proceeds through a 5-membered ring chelate we set out to prepare substrates that would also proceed through a 4-, 6- and 7-membered ring chelates. Synthesis of a 4-member ring chelate was accomplished from lactate aldehyde **3.3.1.**[34] Carboalumination of either phenylacetylene or hex-1-yne followed by addition to **3.3.1** gave alcohols **3.3.2** and **3.3.3** respectively (Scheme 4-1). Treatment of PMB-protected compound **3.3.2** with benzoyl chloride followed by reduction with SmI_2 lead exclusively to beta-elimination. Removal of the PMB-protecting group suppressed this competing elimination to some extent as the hydroxyl is a worse leaving group,[35] allowing compound **3.3.6**

to be obtained in 53% yield from **3.3.4** with 5 equivalents of H_2O. We hypothesized that increasing the amount of water might increase the rate of protonation relative to elimination thus improving the yield. Indeed, the use of 100 equivalents of water gave a higher yield (60% vs 53%). However, further increasing the amounts of water to 200 equivalents resulted in no additional increase to the isolated yield.

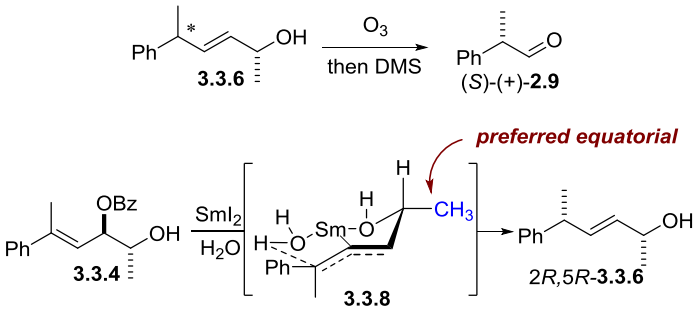


R	H_2O (equiv.)	d.r.	yield%
Ph	5	86:14	53
Ph	100	84:16	60
Ph	200	84:16	60
n-Bu	50	90:10	50
n-Bu	100	88:12	55



Scheme 3-3-1. Synthesis of and reductive elimination results for lactate derived substrates **3.3.4** and **3.3.5**

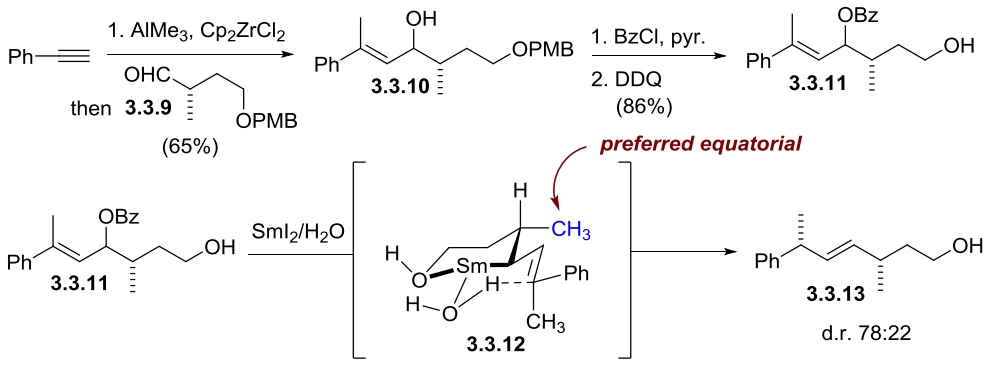
The diastereomeric ratios of compounds **3.3.6** and **3.3.7** were moderately higher (86:14 and 90:10 respectively) then those obtained from the Roche ester derived compounds (~75:25, see Table 2-2). Determination of the absolute stereochemistry of the major diastereomer was obtained by ozonolysis of product **3.3.6** followed by a measurement of the resulting aldehydes optical rotation. Again, we saw an enrichment of (*S*)-(+)-**2.9**, indicating the absolute stereochemistry of the major diastereomer of **3.3.6** is (*2R,5R*). A possible model for the origin of selectivity similar to that of the Roche ester derived substrates (*ref.* scheme 2-4), however for this substratewe propose a η^3-complex **3.3.8** (Scheme 3-3-2). Yet at this stage extended hydrogen bonded networks involving multiple water molecules[36] and/or multiple samarium centers[8] cannot be ruled out.



Scheme 3-3-2. Determination of the absolute stereochemistry of the major stereoisomer of **3.3.6** by ozonolysis.

Synthesis of 6-member ring chelate.

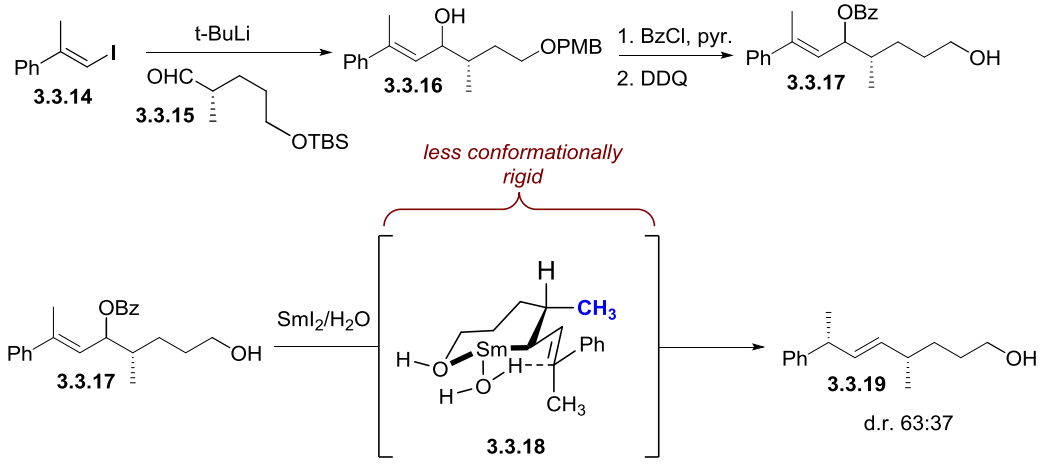
In a similar fashion to the Roche ester and lactate derived substrates, the synthesis of 6-membered chelate substrate **3.3.11** began with carboalumination of phenyl acetylene followed by trapping the resulting vinylalane with aldehyde **3.3.9**[37] to give **3.3.10** in 65% yield (Scheme 3-3-3). Compound **3.3.10** was then treated with benzoyl chloride followed by deprotection of the PMB-protecting group giving **3.3.11** in 86% yield over two steps. Reduction with SmI_2/H_2O resulted in reduced compound **3.3.13** with nearly identical d.r. (78:22) to that obtained for the related 5-membered ring chelate substrate **2.7**. The stereochemistry of the newly generated stereocenter is assumed to be (*R*) in analogy to compound **2.7**. Stereochemistry is proposed to arise from a conformationally biased transition state where the methyl stereocenter (blue) lies equatorial in the 6-6 bicyclic organosamarium intermediate **3.3.12**.



Scheme 3-3-3. Synthesis and reduction of substrate **3.3.11** proceeding through 6-6 bicyclic intermediate **3.3.12** resulting in **3.3.13**

Synthesis of 7-membered ring chelate.

Substrate **3.3.17** was also prepared which when subjected to reductive elimination by SmI_2/H_2O, would proceed through a 7-membered ring-chelate organosamarium intermediate **3.3.18**. It was anticipated that this reaction would give lower yield and diastereoselectivity as the intermediate 7-membered organosamarium ring chelate would be less stable then the 5- and 6- membered chelate substrates due to the ring size chelate effect.[38] Its synthesis began with a lithium halogen exchange on vinyl iodide **3.3.14**,[39] followed by addition of the resulting vinyl lithium to aldehyde **3.3.15**.[40]This gave alcohol **3.3.16** as a 1:1 mixture of diastereomers. Benzoylation of the secondary alcohol in **3.3.16**, and deprotection of the PMB ether gave the desired reduction substrate **3.3.17**. Reduction with SmI_2/H_2O gave **3.3.19** with a d.r. of 63:37 in only 7% isolated yield along with extremely high levels of dimerization. This indicates that the 7-membered ring chelate not only gives a less conformationally locked organosamarium intermediate, but also promotes side reactions like dimerization.

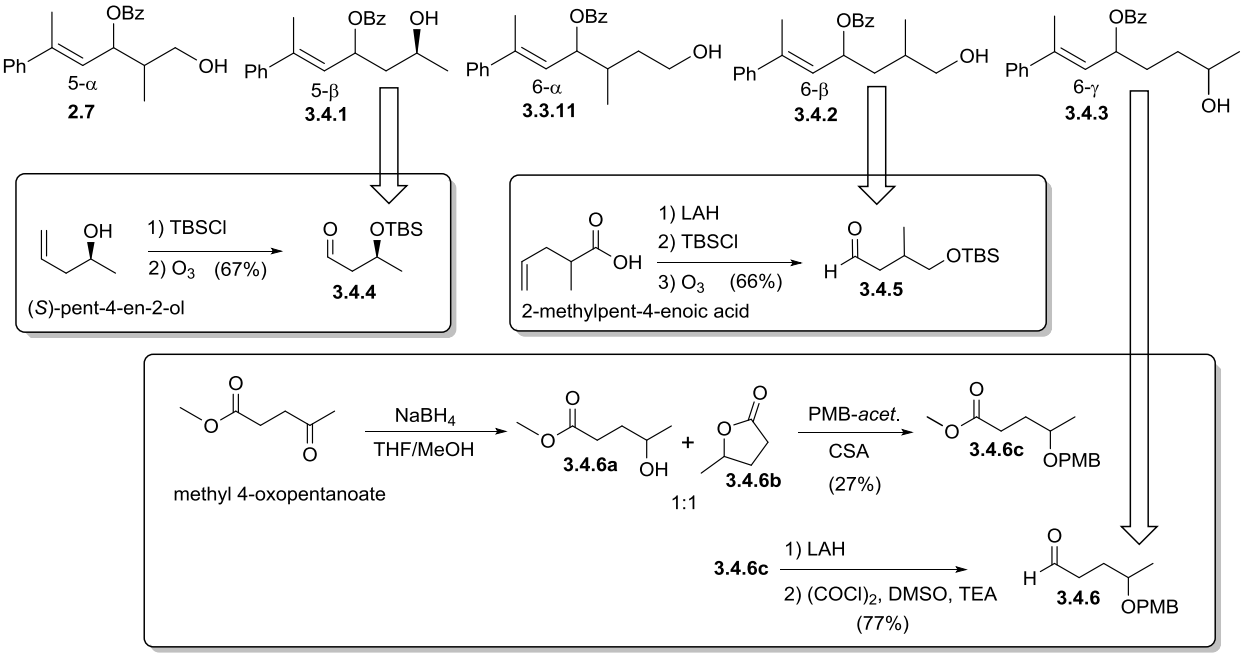


Scheme 3-3-4. Synthesis and reduction of substrate **3.3.17** proceeding through 7-6 bicyclic intermediate **3.3.18** resulting in **3.3.19.**

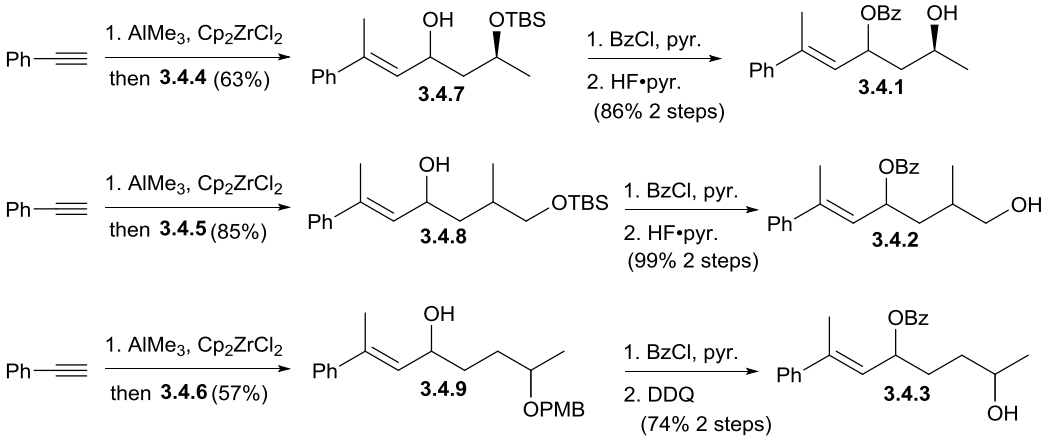
In sum, the distance of the chelating group appears to plays a significant role in this reaction. Diastereoselectivity tends to increase with shorter chain lengths of the chelating group (63:37 vs 90:10 for **3.3.17**:**3.3.5**) however the highest diastereoselectivity obtained (90:10 with **3.3.5**) is hindered by elimination.

3.4. Effects of stereocenter positioning on SmI_2 mediated allylic benzoate reductions.

Scheme 3-4-1 shows substrates we concluded would help elucidate the effect of stereocenter positioning relative to the OBz stereocenter. Compounds **2.7** and **3.1.11** served as models for the 5-α (5-membered ring chelate with stereocenter α to OBz stereocenter) and 6-α systems, however **3.4.1** (5-β), **3.4.2** (6-β) and **3.4.3** (6-γ) would need to be prepared. Using the same sequence of reactions employed previously, we would then need known aldehydes **3.4.4**,[41] **3.4.5**,[42] and **3.4.6**.[43] To that end, compounds **3.4.1**, **3.4.2** and **3.4.3** were synthesized in good yields. The synthesis of **3.4.4** began with (*S*)-pent-4-en-2-ol and TBS protection of the secondary alcohol, followed by ozonolysis of the terminal alkene to give **3.4.4** in 67% yield. The synthesis of **3.4.5** began with LAH reduction of 2-methylpent-4-enoic acid, TBS protection of resulting primary alcohol, followed by ozonolysis of terminal alkene to give **3.4.5** in 66% yield. Synthesis of **3.4.6** began with an attempt to reduce the ketone of methyl 4-oxopentanoate with $NaBH_4$ reduction in the presence of water, however only the over reduced diol was obtained. Switching the proton source from water to methanol produced the desired secondary alcohol in as a 1:1 mixture with the cyclized lactone **3.4.6b** which proved inseparable via column chromatography. However, PMB protection of the secondary alcohol in **3.4.6a** with PMB-acetimidate and CSA allowed for separation from the product from lactone **3.4.6b** in 27% over two steps. Reduction of the resulting ester in **3.4.6c** with LAH, followed by a Swern oxidation gave **3.4.6** in 21% yield. Completion of the syntheses of compounds **3.4.1**, **3.4.2**, and **3.4.3** was accomplished though the sequence of 1) carboalumination/aldehyde addition, 2) benzoylation of the resulting secondary alcohol, and finally deprotection of either an OTBS or OPMB ether using either HF-pyr. or DDQ. Yields for these steps were generally good and similar to that previously obtained for other substrates (*ref.* Scheme 3-4-2).



Scheme 3-4-1. Substrates for determination of the effect of stereocenter position and synthesis of aldehydes **3.4.4**, **3.4.5**, and **3.4.6** from commercial starting materials.



Scheme 3-4-2. Synthesis of compound **3.4.1**, **3.4.2**, and **3.4.3**.

Following reduction of compounds **3.4.1**, **3.4.2**, and **3.4.3** with SmI_2/H_2O a clear trend emerged. Shifting the stereocenter to the beta-position as in a comparison between compounds **2.7** (5-α) and **3.4.1** (5–β) resulted in a slight loss of diastereoselectivity (75:25 for **2.7** vs 70:30 for **3.4.1**) with essentially no change in regioselectivity (Table 3-4-1). This could potentially be explained by the shift from a primary alcohol in **2.7** to a secondary alcohol in **3.4.10**. A more sterically hindered alcohol may result in a loss of samarium chelation, resulting in a less conformationally restricted transition state and ultimately lower

selectivity. However shifting the stereocenter from α to β in the 6-membered chelate systems (i.e. **3.3.13** vs **3.4.11**) we see a significant loss of diastereoselectivity (78:22 for **3.3.13** vs 57:43 for **3.4.11**) (Figure 3-4-1). This cannot be explained by a change in the strength of the chelating group as both **3.3.13** and **3.4.11** contain primary alcohols. However placement of the stereodirecting group closer to the carbon samarium bond must have an effect on the selectivity. More evidence to support this was seen by shifting the stereodirecting group further to the gamma position as in **3.4.12** which gave the same selectivity observed for 6–β compound **3.4.11**. It therefore seems that having the stereodirecting group at the alpha position and closest to the OBz stereocenter (and therefore the carbon-bound samarium) is optimal for maximizing the diastereoselectivity of this reaction.

Table 3-4-1. Effects of stereocenter position on regio- and diastereoselectivity on 5-5 and 5-6 bicyclic systems. Substrates were reduced using 35 equiv. of H_2O and 7 equiv of SmI_2. Values obtained from analysis of crude ^1H NMR.

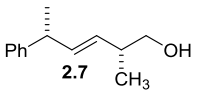
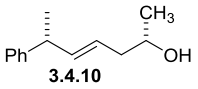
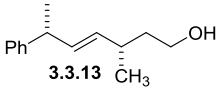
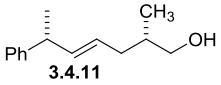
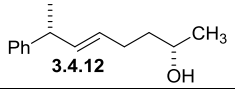
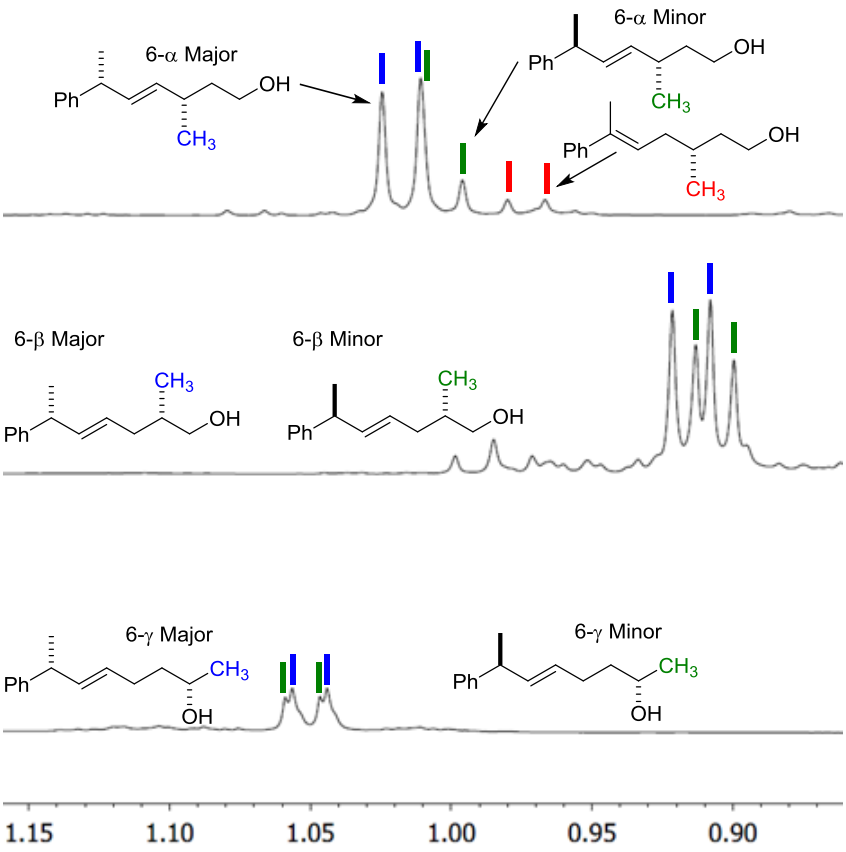
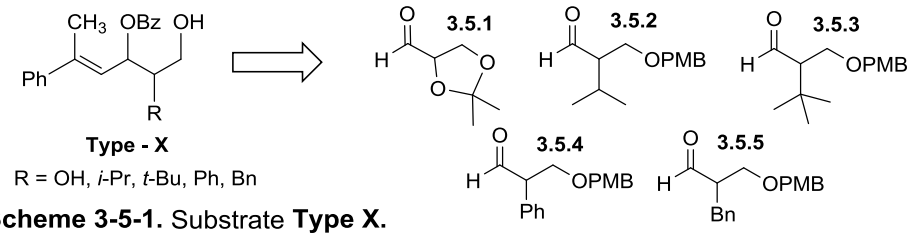
Starting Material	Product	d.r.	conj : nonconj
5-α	 **2.7**	75:25	2:98
5-β	 **3.4.10**	70:30	0:100
6-α	 **3.3.13**	78:22	12:88
6-β	 **3.4.11**	57:43	6:94
6-γ	 **3.4.12**	56:44	17:83

Figure 3-4-1. NMR analysis showing diastereomeric ratios for compounds 6α, 6β, and 6γ. Major diastereomer = blue lines, minor diastereomer = red lines, conjugated product = red lines.



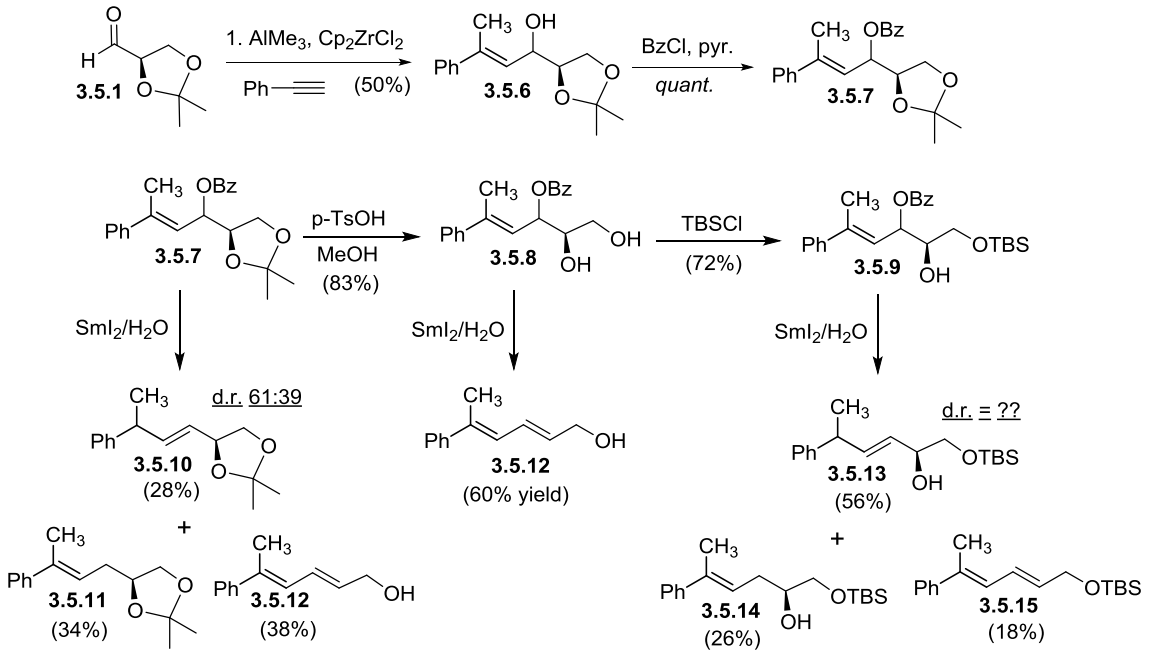
3.5. Effects of stereocenter Identity

We also prepared a series of compounds to determine the effect of the existing stereocenter identity on the reaction. Substrates examined were those of **Type X** with R = OH, *i*-Pr, *t*-Bu, Ph, and Bn. 5-membered chelate substrates were chosen as the previous 5-membered ring chelate **2.7** had already been studied in detail (*ref*. Ch. 2) with respect to proton sources, equiv. of water, and determination of relative stereochemistry, so a more direct comparison could be obtained. A retrosynthetic analysis allowed us to determine we would need aldehydes **3.5.1**, **3.5.2**, **3.5.3**, **3.5.4**, and **3.5.5.** [44,45,46]



Scheme 3-5-1. Substrate **Type X.**

Synthesis of mannitol derived substrate **3.5.8** began with aldehyde **3.5.1** (Scheme 3-5-2). Examination of the synthetic pathway peaked our interests in providing both acetonide **3.5.7** and TBS protected 4-membered ring chelate **3.5.9** as additional reduction substrates to be examined. Substrate **3.5.9** in particular would give us insight to a system analogous to the lactate derived substrate **3.3.5** however with a much bulkier stereocenter (CH_2OTBS vs methyl). Carboalumination of phenylacetylene and addition to **3.5.1** with produced **3.5.6** in 50% yield. Benzoylation of the resulting alcohol gave acetonide ester **3.5.7**. Deprotection of the acetonide group using p-TsOH in MeOH, produced **3.5.8** in 83% yield. Mono-protection of the diol then gave **3.5.9** in 72% yield. Reductive elimination of **3.5.7** gave the elimination product **3.5.12** as the major product (28:34:38 of **3.5.11**:**3.5.10:3.5.12**) and a d.r. of 61:39 for compound **3.5.10**. Upon subjection to SmI_2/H_2O, substrate **3.5.8** produced exclusively the elimination diene product **3.5.12** similar to what was observed for lactate-derived compound **3.3.5**. The mono-protected substrate **3.5.9** produced a crude ^1H NMR showing the non-conjugated product as the major component (56:26:21 of **3.5.13**:**3.5.14**:**3.5.15**). Efforts are ongoing to determine the diastereomeric ratio of compound **3.5.13** which has proved difficult from the mixture obtained.

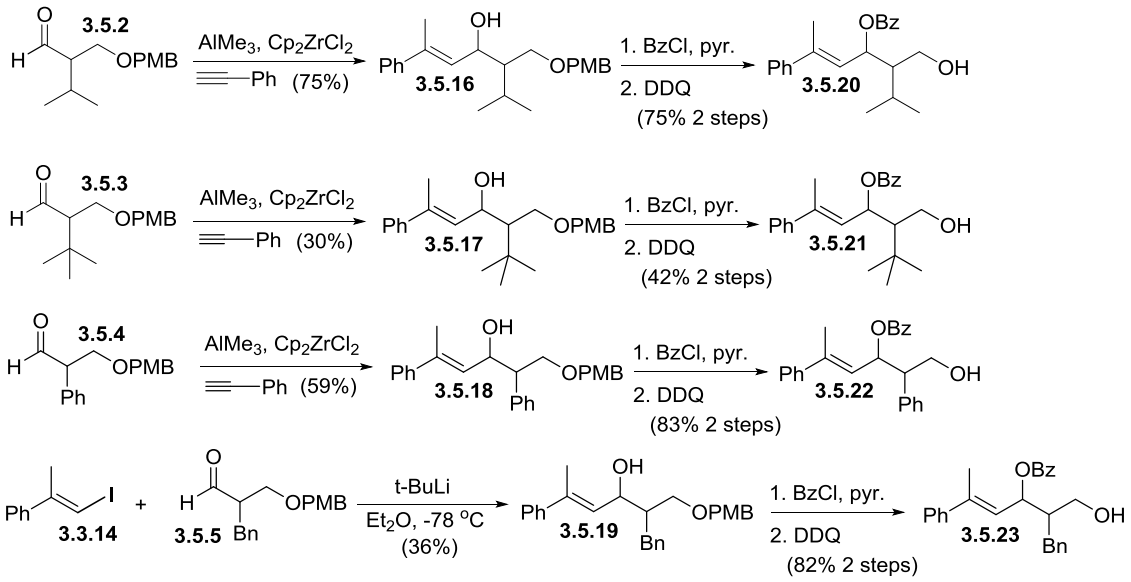


Scheme 3-5-2. Synthesis and reduction of substrates **3.5.7**, **3.5.8** and **3.5.9**. Product percentages are mol% except for 3.5.12 which is an isolated yield. All value taken from cude ^{1}H NMR data.

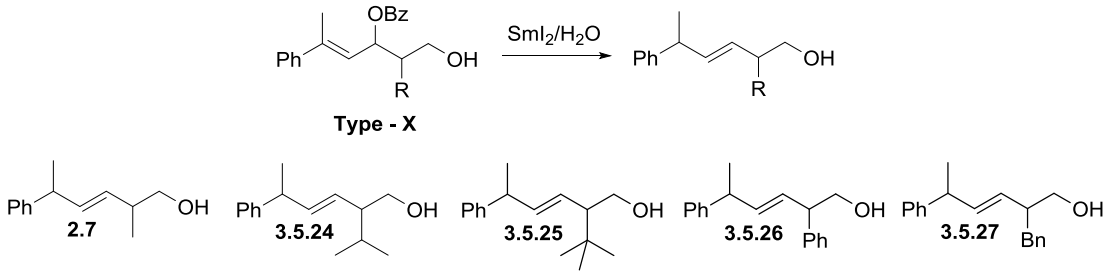
It appears that substrates with an oxygen atom positioned alpha to the OBz stereocenter suffer from elimination, even more so when an additional chelating group is present such as in **3.5.8**. Acetonide **3.5.7** gave low diastereoselectivity (d.r. 61:39) and the major product was from elimination. Additionally, more conjugated isomer then unconjugated was produced possibly due to poor chelation from the acetonide giving rise to a higher level of intermolecular protonation. We were unable to determine a d.r. (via GC-MS or ^{1}H NMR) for substrate **3.5.9** which also produced a moderate amount of both the conjugated isomer and elimination product. Because of the amount of undesired products we decided further pursuit of even a very high d.r. would not compensate for the low yield.

The remainder of the alternate stereocenter substrates were synthesized via carboalumination of phenyl acetylene and addition into aldehydes **3.5.2**, **3.5.3**, and **3.5.4** gave isopropyl-containing **3.5.16**, tert-butyl **3.5.17**, and phenyl substrate **3.5.18** respectively (Scheme 3-5-3). Benzyl compound **3.5.19** was synthesized via lithium-halogen exchange of vinyl iodide **3.3.14** and trapping of the resulting organo-lithium species with aldehyde **3.5.5**. The resulting secondary alcohols **3.5.16**-**3.5.19** were then subjected to benzoylation followed by deprotection of the PMB ether to give compounds **3.5.19**-**3.5.22** containing

different stereodirecting groups. All substrates gave the desired product in good yield with SmI_2/H_2O except for **3.5.18** (R= Ph) and **3.5.8** (R = OH) where excessive elimination was a problem. Results from the reductive eliminations of all compounds of **Type-X** are shown in Scheme 3-5-4. Increasing the size of the stereodirecting group appears to play a modest role in the diastereoselectivity of the reaction however no clear trend emerged. A change in stereocenter identity from methyl to *i*-Pr (**2.7** vs **3.5.24**) resulted in an increase in diastereoselectivity from 75:25 to 83:17, however compound **3.5.21** containing an even larger *t*-Bu group showed no further increase but rather a small drop in diastereoselectivity (80:20). Reduction with a phenyl stereocenter (**3.5.22**) gave a diastereoselectivity similar to that of a methyl group (73:27 **3.5.22** vs 75:25 **2.7**) but with lower yield due to elimination to form a fully conjugated terminal diene. Substrate **3.5.23** with a benzyl stereocenter gave a d.r. similar to that obtained for an *i*-Pr group (81:19). For all reactions, the amount of non-conjugated product exceeded the conjugated isomer (from 7:93 **3.5.20** to 0:100 **3.5.22**) suggestive of a dominant intramolecular protonation pathway.



Scheme 3-5-3. Synthesis of substrates **3.5.20** through **3.5.23**.



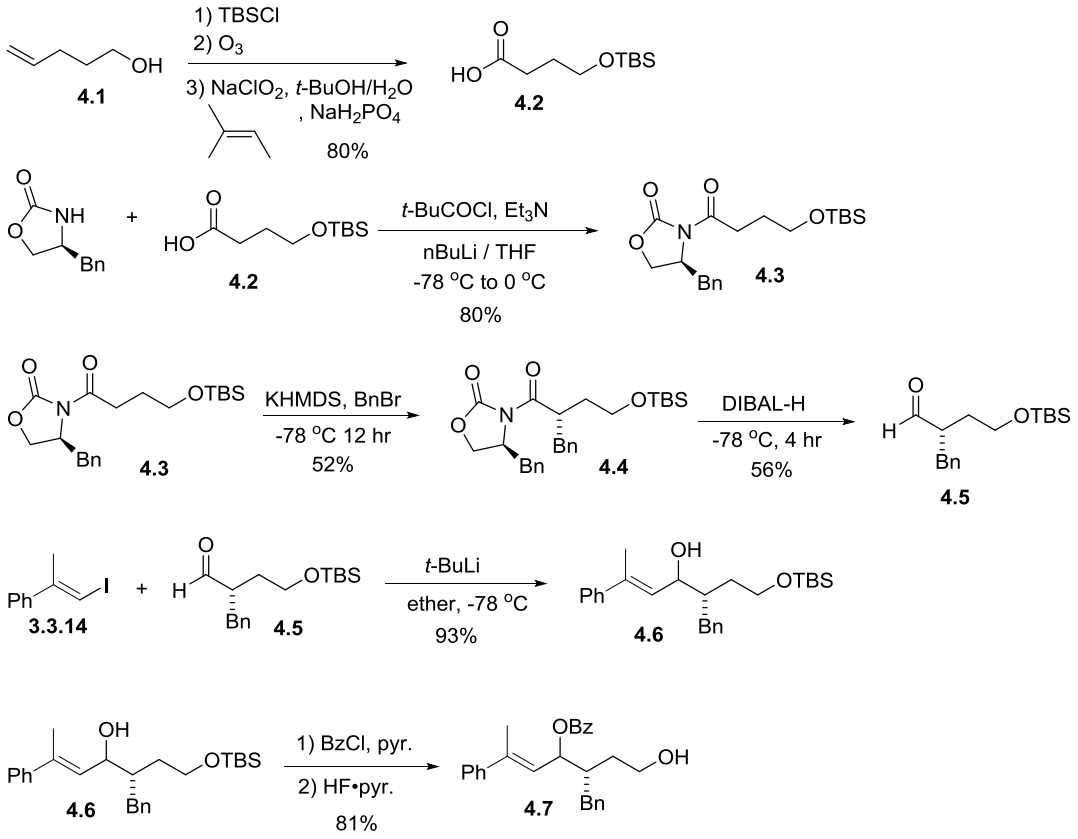
Substrate	R	d.r.	conj.:nonconj.	yield%
2.7	Me	75:25	2:98	90
3.5.24	*i*-Pr	83:17	7:93	80
3.5.25	*t*-Bu	80:20	5:95	83
3.5.26	Ph	73:27	0:100	25
3.5.27	Bn	81:19	4:96	82
3.5.8	OH	*elimination*	-	-

Scheme 3-5-4. Stereocenter identity effects on diastereoselectivity and yield. All reductions took place at room temp using 7 equiv of SmI_2 and 105 equiv of water.

Chapter 4. Synthesis of an optimized substrate.

Based on the previous results, we set out to synthesize an optimized and enantioenriched substrate. We chose a 6-membered ring chelate with a benzyl stereocenter due to the slight d.r. enhancement of the 6-membered ring chelate over the 5- (78:22 vs 75:25). Stereocenter identity came down to either the i-Pr or Bn stereocenter as they had roughly the same and highest d.r. among the groups tested (83:17 vs 81:19). Ultimately we chose the benzyl due to it being more synthetically appealing as we imagined installing the stereocenter with an alkylation, and the primary benzyl bromide would be a much better electrophile than a secondary halide for installing an i-Pr group as the reaction takes place a via a S_n2 pathway.[33] We had seen a rise from 75:25 in the *methyl* 5-membered ring chelate **2.7** to 81:19 for the analogous *benzyl* 5- membered ring chelate **3.5.27**. Additionally, a slight rise from 75:25 in the *methyl* 5-membered chelate 75:25 to 78:22 with the *methyl* 6-membered ring chelate 78:22 was obtained. Combining these effects we hypothesized would give the highest d.r.

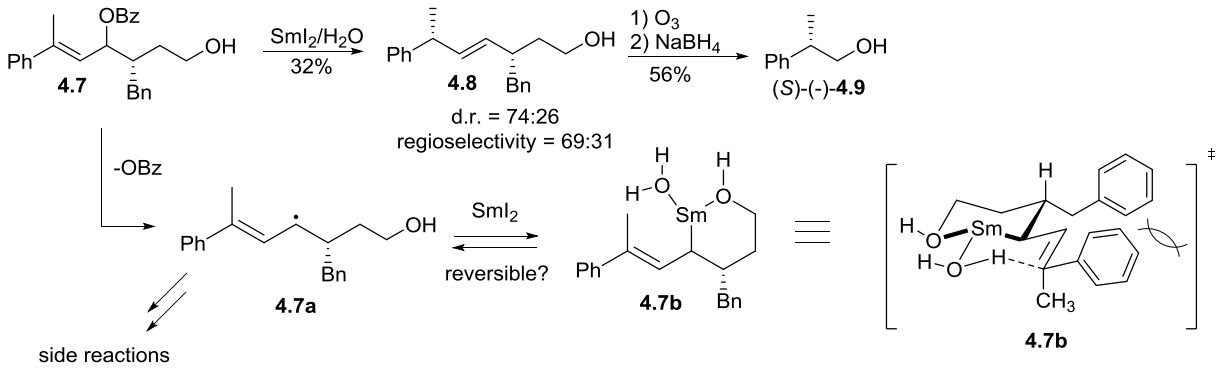
We began with a TBSCl protection of the primary alcohol pent-4-en-1-ol (**4.1**) followed by ozonolysis to the corresponding aldehyde and a Pinnick oxidation to the acid **4.2** in 80% over three steps. Oxzolidinone **4.3**[47] was synthesized in 80% yield by conversion of **4.2** to the mixed anhydride using t-BuCOCl and Et_3N at 0 ºC followed by addition of the lithiated anion of (S)-4-Benzyl-2-oxazolidinone. Alkylation of **4.3** using KHMDS and benzyl bromide produced **4.4** in 52% and 99:1 d.r. DiBAl-H reduction of **4.4** gave aldehyde **4.5** in 56% yield. Lithium halogen exchange on vinyl iodide **3.3.14** at -78 ºC followed by its addition to aldehyde **4.5** gave the secondary alcohol **4.6** as a 62:38 mixture of diastereomers in 93% yield. Benzoylation followed by deprotection of the TBS ether using HF·pyr gave the final allylic benzoate "optimized substrate" **4.7** in 81% over two steps.



Scheme 4-1. Synthesis of optimized substrate **4.7.**

Surprisingly, upon reduction with SmI_2/H_2O we received **4.8** in 32% yield with a d.r. of 74:26 and a 69:31 regioselectivity favoring the unconjugated isomer.. The low yield was in part due to a significant level of dimerization which was observed in the ^1H NMR which may indicate the second electron transfer and formation of the organo samarium species **4.7b** is a reversible process (Scheme 4-2). other studies have shown that larger ions such as samarium prefer smaller ring systems,[48] while smaller ions such as Ni(II) or Cu(III) prefer larger ones.[38] This ultimately boils down to bond distance and angle. Cu(II) and Ni(II), for reference, have an ionic radius of 0.57 and 0.69 Å respectively whereas samarium (II) has a ionic radius of 1.27 Å.[5] This also explains the high diastereoselectivity we saw from the lactate derived substrate (90:10) as it had the smallest ring chelate size (4-membered). Additionally, as the stereodirecting group becomes larger with the 6-membered ring chelate, the stability of the organo samarium species may decrease leading to a slower intramolecular protonation event giving rise to higher levels of intermolecular protonation.

Nonetheless, sufficient amounts of **4.8** were obtained to determine its absolute configuration. Ozonolysis of **4.8** followed by reduction using $NaBH_4$ gave (*S*)-(-)-**4.9**[49] indicating the absolute stereochemistry of the major diastereomer of **4.8** is (*3S,6R*). This is consistent with the model shown in Scheme 4-2 where **4.7** proceeds through a 6-6 bicyclic organosamarium intermediate **4.7b** with a preferred equatorial benzyl stereodirecting group, followed by intramolecular proton delivery from a samarium bound water to give **4.8**.



Scheme 4-2. Reduction of substrate **4.7** proceeding through 6-6 bicyclic intermediate **4.7b** resulting in product **4.8** with conformation of stereochemistry via ozonolysis.

Conclusion

In summary, samarium mediated allylic benzoate reductions can occur diastereoselectively when adjacent to a tri-substituted alkene and flanked by a stereodirecting and chelating group. The reaction can achieve high yields, regioselectivity and good diastereoselectivity, however there appear to be many factors influencing the outcome. The reaction is proposed to proceed through an oxygen chelated bicyclic organosamarium species followed by intramolecular protonation from samarium bound water. Water was shown to be the ideal proton source for these reductions, allowing the reaction to occur within minutes at room temperature. Alkene substitution seems to be general as methyl and ethyl stereocenters were able to be formed. The reaction was also shown to be stereospecific with regards to alkene geometry however not with respect to the OBz stereocenter. Stereocenter position and chelating group length appear to play the most important role with respect to yield and diastereoselectivity, as substrates bearing a stereocenter α to the OBz moiety gave the highest diastereoselectivity. The 4-membered ring chelate produced the highest diastereoselectivity (90:10 with **3.3.5**) while the 7-memebred chelate produced the lowest (63:37), consistent with both ring conformation considerations and metal ion ring chelate size preferences. Stereocenter identity appears to play a modest role, with little change in diastereoselectivity observed as the size of the stereocenter changed (e.g. from a methyl to an *i*-Pr). With regards to our optimized substrate, optimization of the substrate and reaction condition separately and combining the best of each parameter into a single reaction does not appear to work and further studies will be needed. Future experiments may focus on studying substrates with alternate stereodirecting groups as well as other tri-substituted alkenes that will produce a larger variety of stereocenters upon reduction.

Supporting Information

General: All reactions were carried out under N_2 in flame-dried glassware unless specified otherwise. IR: Nicolet iS10 spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. The solvents used were dried by passing the solvent through a column of activated alumina under nitrogen immediately prior to use. Samarium (II) iodide was prepared according to the method of Procter.[1] All other 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). 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

Procedure A: 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 ^{0}C was added trimethyl aluminum (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 min. The reaction was then warmed to room temperature for ten min and then cooled to 0 ^{0}C. Phenyl acetylene (1.0 eq) was added dropwise and the solution was stirred for 40 min at 0 ^{0}C. Aldehyde (0.8 eq) was then added dropwise and the mixture stirred for 1 h at 0 ^{0}C. The reaction was quenched slowly with cold H_2O and then aq. HCl, and extracted with DCM (x3). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*.

[1] Szostak, M. Spain, M.; Procter, D. J. *J. Org. Chem.* **2012**, *77*, 3049

Procedure B: Benzoylation of an alcohol

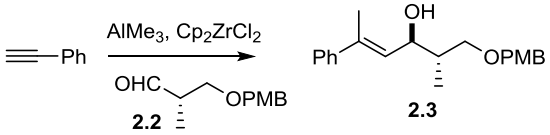
Pyridine (2 equiv.) was added to a schlenk tube containing substrate (1 equiv.) in DCM (0.2 M relative to substrate). The mixture was then cooled to 0 ^{o}C followed by the addition of benzoyl chloride (1.2 equiv.). The reaction was allowed to warm to room temperature for fifteen hours, quenched with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

Procedure C: DDQ removal of PMB protecting group.

Substrate was added to a round bottom containing a 50:50 mixture of DCM:pH 7 buffer (0.1 M relative to substrate). The reaction mixture was cooled to 0 ^{o}C and stirred vigorously at which time DDQ (3 equiv.) was added portion wise over 30 min. The reaction was left to run 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*

Procedure D: SmI_2 reductive elimination with H_2O

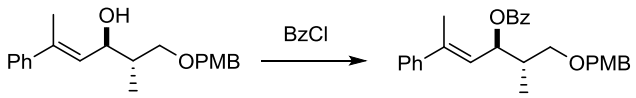
To a dry schlenk tube containing a solution of SmI_2 in THF (0.1 M, 7 equiv.) was added degassed nano pure H_2O (105 equiv.) turning the solution a deep red color. The solution was stirred for 5 min. and the substrate (1 equiv) was then added. After 30 min. the reaction was quenched with aq. $NaHCO_3$,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



Compound 2.3. To a schlenk tube filled with dichloromethane (DCM) (20 mL) and Cp_2ZrCl_2 (0.171 g, 0.587 mmol) at -20 ^{o}C was added trimethyl aluminum (2.0 M in toluene, 5.87 mL, 11.74 mmol) dropwise resulting in a yellow solution which was stirred for 10 minutes. DI H_2O (0.104 mL, 5.87 mmol) was then added dropwise turning the solution a darker shade of yellow which was then stirred for another 10 min. The reaction was then warmed to room temperature for ten min and then cooled to 0 ^{o}C. Phenyl acetylene

(0.644 mL, 5.87 mmol) was added dropwise and the solution was stirred for 40 min at 0 °C. Aldehyde **2.2** (1.0 g, 4.7 mmol) was then added dropwise and the mixture stirred for 1 h at 0 °C. The reaction was quenched slowly with H_2O (1.0 mL) and then aq. HCl (1.0 M, 10 mL), extracted with DCM (2 x 20 mL), and washed with brine (20 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave **2.3** (1.31 g, 85%, R_f = 0.65 in 1:1 Hex:EtOAc) as a clear and colorless oil.

Spectral data for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) 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 (125 MHz, $CDCl_3$) 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 (ESI+): Calcd for $C_{21}H_{26}O_3Na^+$ $[M+Na]^+$: 349.1780. Found 349.1771.

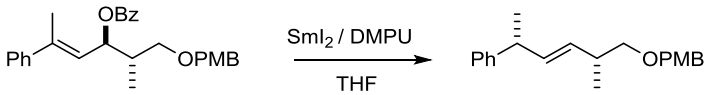


2.3 **2.1**

Compound 2.1. To a solution of **2.3** (1.31 g, 4.00 mmol) in DCM (20 mL) was added pyridine (0.647 mL, 8.00 mmol) at 0°C. Benzoyl chloride (0.557 mL, 4.8 mmol) was then added and the reaction was allowed to warm slowly to room temperature with stirring for 15 hours. The reaction was quenched with aq. $NaHCO_3$ (25 mL), and extracted with DCM (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave **2.1** (1.72 g, *quant*, R_f. = 0.48 in 4:1 Hex:EtOAc) as a clear and colorless oil.

Spectral data for the major diastereomer. IR (ATR): 3063, 3032, 2999, 2962, 2934, 2917, 2851, 1786, 1713, 1611, 1599, 1584, 1450, 1246, 1035, 699. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.0, 1.3 Hz, 2H), 7.54 (dd, *J* = 8.2, 7.6 Hz, 2H), 7.42 (t, *J* = 8.0 Hz, 2H), 7.38 (t, *J* = 7.0 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.25-7.21 (m, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 5.96 (dd, *J* = 9.5, 6.8 Hz, 1H), 5.77 (dq, *J* = 9.5, 1.4 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.40 (d *J* = 11.7 Hz, 1H), 3.77 (s, 3H), 3.49 (t, *J* = 7.0 Hz, 1H), 3.44 (dd, *J* = 6.0, 9.2 Hz, 1H),

2.35 (hept, *J* = 6.9 Hz, 1H), 2.27 (d, *J* = 1.3 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.73, 159.06, 143.00, 140.35, 134.54, 132.73, 130.59, 129.59, 129.24, 128.89, 128.29, 128.21, 127.40, 126.00, 124.06, 113.70, 73.37, 72.79, 71.60, 55.23, 38.33, 16.81, 13.09. HRMS (ESI+): Calcd for $C_{28}H_{30}O_4Na^+$ $[M+Na]^+$: 453.2042. Found 453.2039.



2.1 **2.4**

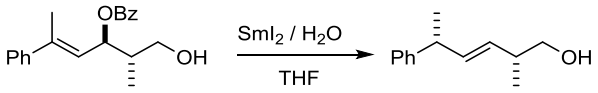
Compound 2.4. To a dry schlenk flask containing a solution of SmI_2 in THF (0.1 M, 16.1 mL) at 0 °C was added DMPU (0.445 mL, 1.61 mmol) resulting in a dark purple solution which was stirred for 1 h. Compound **2.1** (0.100 g, 0.23 mmol) was then added and the solution was stirred for 1 h. The reaction was then quenched with aq. NH_4Cl (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave **2.4** (0.051 g, 70%, R_f. = 0.60 in 10:1 Hex: EtOAc) as a 60:40 mixture of diastereomers.

Spectral Data for the mixture of diastereomers: IR: 3080, 3057, 3025, 2957, 2926, 2850, 1948, 1877, 1804, 1730, 1611, 1511, 1452, 1360, 1245, 1087, 1035, 819, 757, 698. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.5 Hz, 4H), 7.20 (dd, *J* = 11.1, 2.3 Hz, 4H), 7.17 (t, *J* = 6.7 Hz, 2H) 6.87 (d, *J* = 8.5 Hz, 4H), 6.86 (d, *J* = 8.6 Hz, 4H), 5.63 (ddd, *J* = 15.5, 6.7, 1.3 Hz, 2H), 5.39 (ddd, *J* = 15.5, 7.1, 1.4 Hz, 2H), 4.42 (d, *J* = 6.53 Hz, 4H), 3.79 (s, 3H), 3.78 (s, 3H), 3.43 (p, *J* = 7.0 Hz, 2H), 3.32 (dd, *J* = 9.2, 6.2 Hz, 1H) 3.31 (dd, *J* = 9.1, 6.3 Hz, 1H) 3.24 (dd, *J* = 9.2, 6.2 Hz, 1H), 3.23 (dd *J* = 7.1, 4.0 Hz, 1H), 2.48 (hept, *J* = 6.7 Hz, 2H), 1.31 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H). 0.99 (d, *J* = 6.6 Hz, 3H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.04, 134.62, 131.63, 129.13, 129.08, 128.30, 128.10, 127.18, 125.89, 113.70, 75.14, 72.50, 55.23, 42.20, 36.76, 21.48, 17.12. HRMS (ESI+): Calcd for $C_{21}H_{26}O_2Na^+$ $[M+Na]^+$: 333.1830. Found 333.1836.

2.1 **2.6**

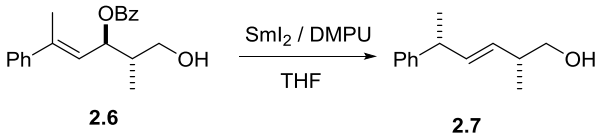
Compound 2.6. Compound **2.1** (1.2 g, 2.78 mmol) was subjected to general procedure **D**. Purification by flash chromatography over silica gave **2.6** (0.604 g, 70%, R_f. = 0.18 in 4:1 Hex:EtOAc) as a clear and colorless oil.

Spectral data for the major isomer. IR (ATR): 3420, 3060, 3032, 2964, 2922, 2880, 1714, 1450, 1268, 1110, 932, 711. ^{1}H NMR (500 MHz, $CDCl_3$) 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 (125 MHz, $CDCl_3$) 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 (ESI+): Calcd for $C_{20}H_{22}O_3Na^+$ $[M+Na]^+$: 333.1467. Found 333.1472.



2.6 **2.7**

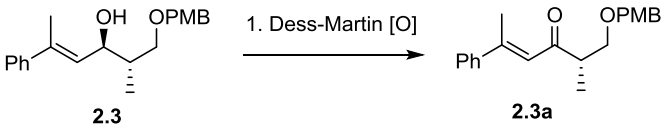
Compound 2.6 reduction with H_2O. To a schlenk tube containing a solution of SmI_2 in THF (0.1 M, 5.6 mL) was added degassed H_2O (0.15 mL, 8.4 mmol) resulting in a deep red solution which was stirred for 5 min. Compound **2.6** (0.025 g, 0.08 mmol) was then added and the solution was stirred for 30 min. The reaction was then quenched with aq. $NaHCO_3$ (15 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo.* Purification by flash chromatography over silica gave **2.7** (0.0135 g, 90%, clear colorless oil, R_f. = 0.31 in 4:1 Hex: EtOAc) as a 76:24 mixture of diastereomers.



2.6 **2.7**

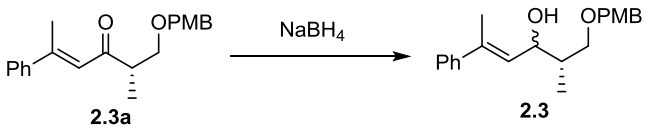
Compound 2.6 reduction with DMPU. To a dry schlenk flask containing a solution of SmI_2 in THF (0.1 M, 5.6 mL) at 0 °C was added DMPU (0.154 mL, 1.28 mmol) resulting in a dark purple solution which was stirred for 1 h. Compound **2.6** (0.025 g, 0.08 mmol) was then added and the solution was stirred for 1 h. The reaction was then quenched with aq. NH_4Cl (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave **2.7** (0.0068 g, 45%, R_f. = 0.31 in 4:1 Hex: EtOAc) as a 75:25 mixture of diastereomers.

Spectral data for the major isomer. IR (ATR): 3360, 3083, 3061, 3025, 2961, 2925, 2871, 1950, 1876, 1803, 1716, 1601, 1492, 1415, 1373, 1272, 1029, 971, 760, 698. ^{1}H NMR (500 MHz, $CDCl_3$) 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 (125 MHz, $CDCl_3$) δ 146.04, 136.89, 131.00, 128.43, 127.07, 126.06, 67.35, 42.27, 39.66, 21.48, 16.60. HRMS (ESI+): Calcd for $C_{13}H_{18}O^+$ $[M]^+$: 190.1358. Found 190.1358.



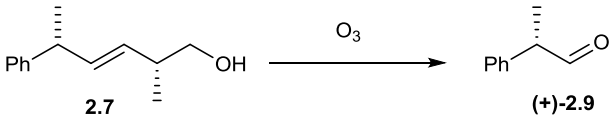
2.3 **2.3a**

Compound 2.3a. To a round bottom flask containing a solution of **2.3** (0.130 g, 0.398 mmol) in DCM (4.0 mL) at 0 °C was added $NaHCO_3$ (0.167 g, 1.99 mmol). Dess-Martin periodinane (0.253 g, 0.597 mmol) was then added portionwise. The reaction was stirred for 1 h., then diluted with DCM (10 mL) and stirred with $Na_2S_2O_3$ (20 mL) for 30 min. The mixture was then extracted with DCM (2 x 15 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo* to afford **2.3a** that was used directly in the next reaction.



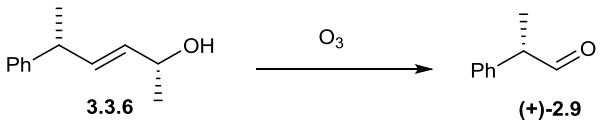
2.3a **2.3**

Compound 2.3. To a round bottom flask containing the crude product **2.3a** (0.398 mmol) in THF:MeOH (1:1, 4 mL total) at 0 °C was added $NaBH_4$ (0.060 g, 3.0 mmol) portion-wise and the reaction was allowed to warm to room temp, and stirred for 1 h. The mixture was quenched with brine (10 mL), extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, concentrated *in vacuo*. Purification by flash chromatography over silica gave **2.3** (0.263 g, 80%, R_f = 0.65 in 1:1 Hex:EtOAc) as ~50:50 mixture of diastereomers.



2.7 **(+)-2.9**

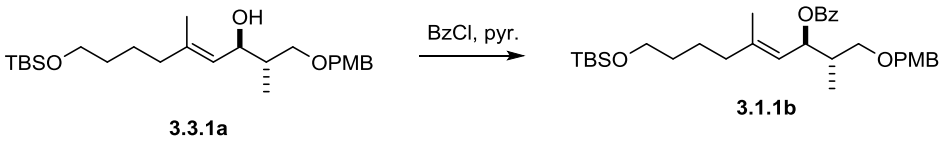
Compound 2.9 from 2.7. To a round bottom flask open to air was added **2.7** (0.050 g, 0.263 mmol) in DCM (2.63 mL). The reaction flask was cooled to -78 °C and O_3 was bubbled into the reaction until the solution turned an electric blue color. The reaction was left to sit for 5 min and then nitrogen was bubbled though the reaction until the solution became colorless. The reaction was quenched with dimethyl sulfide (0.10 mL, 1.31 mmol), warmed to room temperature, and stirred for 1 h. The reaction was washed with brine (15 mL) and extracted with DCM (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography over silica gave **(+)-2.9** (8.2 mg, 23%, R_f = 0.63 in 4:1 Hex:EtOAc) $[\alpha]_D$ = +20° (*c* 0.4, Et_2O).



3.3.6 **(+)-2.9**

Compound 2.9 from 3.3.6. To a round bottom flask open to air was added **3.3.6** (0.130 g, 0.737 mmol) in DCM (7.37 mL). The reaction flask was cooled to -78 °C and O_3 was bubbled into the reaction until the solution turned an electric blue color. The reaction was left to sit for 5 minutes and then nitrogen was bubbled though the reaction until the solution became colorless. The reaction was quenched with dimethyl sulfide (0.26 mL, 3.68 mmol), warmed to room temperature, and stirred for 1 h. The reaction was washed

with brine (15 mL), and extracted with DCM (3 x 15mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography over silica gave **(+)-2.9** (15.4 mg, 15%, R_f = 0.63 in 4:1 Hex:EtOAc) $[\alpha]_D$ = +88.54° (*c* 0.3, $CHCl_3$).



3.3.1a **3.1.1b**

Compound 3.1.1b. Compound **3.1.1a**[2] (1.27 g, 2.908 mmol) was subjected to general procedure **B.** Purification by flash chromatography over silica gave **3.1.1b** (1.068 g, 65%**,** R_f. 0.35 in 10:1 Hex:EtOAc).

Spectral data for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 7.0, 1.1 Hz, 2H), 7.53 (t, *J* = 8.1 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 8.3 Hz, 1H), 6.82 (t, *J* = 7.3 Hz, 2H), 5.76 (dd, *J* = 9.6, 6.9 Hz, 1H), 5.19 (dq, *J* = 9.7, 1.0 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.37 (d, *J* = 11.6 Hz, 1H), 3.77 (s, 3H), 3.63 (t, *J* = 6.0 Hz, 2H), 3.43 (dd, *J* = 9.2, 5.8 Hz, 1H), 3.36 (dd, *J* = 9.2, 6.2 Hz, 1H), 2.22 (hept, *J* = 6.5 Hz, 1H), 2.03 (t, *J* = 6.8 Hz, 2H), 1.80 (d, *J* = 1.3 Hz, 3H), 1.46 (m, 4H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H).

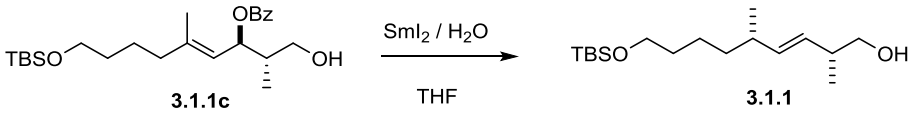
Spectral data for the mixture of diastereomers. IR (ATR): 3061, 2930, 2855, 1715, 1612, 1558, 1512, 1451, 1247, 1096, 1036, 834, 709. ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.68, 162.34, 159.00, 142.08, 141.17, 134.52, 132.56, 130.93, 130.56, 130.53, 129.53, 129.17, 129.09, 128.87, 128.21, 121.65, 120.91, 113.66, 113.65, 73.22, 73.05, 72.76, 72.70, 71.80, 71.75, 62.97, 55.21, 39.44, 39.37, 38.67, 38.09, 32.35, 25.95, 23.93, 23.89, 18.34, 16.88, 16.78, 13.01, 12.81, -5.28. HRMS (ESI+): Calcd for $C_{32}H_{48}O_5SiNa^+$ $[M+Na]^+$: 563.3169. Found 563.3162.

[2] King, B. R.; Swick, S. M.; Schaefer, S. L.; Welch, J. R.; Hunter, E. F.; O'Neil, G. W. *Synthesis* **2014**, *46*, 2927-2936.

3.1.1b 3.1.1c

Compound 3.1.1c. Compound **3.1.1b** (0.500 g, 0.924 mmol) was subjected to general procedure **C.** Purification by flash chromatography over silica gave **3.1.1c** (0.310 g, 80%, R_f. = 0.35 in 4:1 Hex:EtOAc) as a clear and colorless oil.

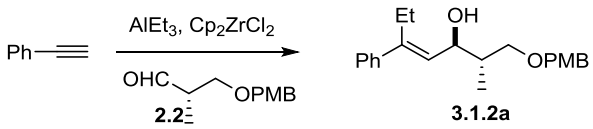
IR (ATR): 3461, 3072, 2926, 2856, 1715, 1698, 1600, 1578, 1257, 1159, 833, 710. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.1, 1.2 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 2H), 5.75 (dd, *J* = 9.3, 8.5 Hz, 1H), 5.28 (dq, *J* = 9.4, 1.3 Hz, 1H), 3.60 (m, 4H), 2.07 (m, 2H), 1.99 (m, 1H), 1.78 (d, *J* = 1.4 Hz, 3H), 1.49 (m, 4H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.03(s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.53, 142.42, 132.95, 129.65, 128.49, 128.35, 121.53, 73.28, 64.20, 62.94, 40.89, 40.41, 39.37, 38.28, 32.34, 25.95, 23.89, 18.34, 16.95, 12.97, -5.28. HRMS (ESI+): Calcd for $C_{24}H_{40}O_4SiNa^+$ [M+Na]$^+$: 443.2594. Found 443.2590.



3.1.1c 3.1.1

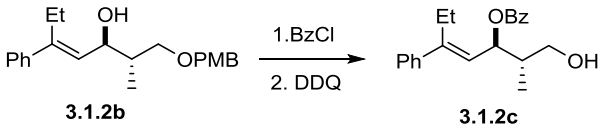
Compound 3.1.1. Compound **3.1.1c** (0.033 g, 0.08 mmol) was then subjected to general procedure **D**. Purification by flash chromatography over silica gave **3.1.1 (**0.0206 g, 85%, R_f = 0.33 in 10:1 Hex:EtOAc) as a 75:25 mixture of diastereomers.

IR (ATR): 3340, 2953, 2927, 2856, 1471, 1462, 1386, 1254, 1097, 1034, 968, 834, 773. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40 (ddd, *J* = 15.5, 7.7, 1.0 Hz, 1H), 5.20 (ddd, *J* = 15.4, 7.8, 1.0 Hz, 1H), 3.59 (t, *J* = 6.6 Hz, 2H), 3.46 (dd, *J* = 10.5, 5.6 Hz, 1H), 3.35 (dd, *J* = 10.5, 7.8 Hz, 1H), 2.29 (hept, *J* = 7.0 Hz, 1H), 2.09 (hept, *J* = 6.61 Hz, 1H), 1.48 (m, 2H), 1.28 (m, 4H), 0.97 (dd, *J* = 6.8, 5.2 Hz, 6H), 0.89 (s, 9H), 0.04 (s, 6H).^{13}C NMR (125 MHz, $CDCl_3$) δ 138.33, 130.34, 67.34, 63.22, 39.71, 36.79, 32.90, 25.98, 23.64, 20.74, 18.37, 16.66, -5.26. Calcd for $C_{17}H_{36}O_2SiNa^+$ [M+Na]$^+$: 323.2382. Found 323.2385.



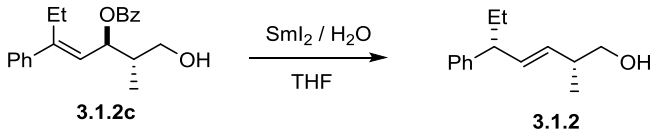
Compound 3.1.2a. To a schlenk tube filled with DCM (5.9 mL) and Cp_2ZrCl_2 (0.052 g, 0.178 mmol) at -20 ^oC was added triethyl aluminum (1.0 M in hexanes, 2.86 mL, 2.86 mmol) dropwise resulting in a yellow solution which was stirred for 10 min. DI H_2O (0.031 mL, 1.78 mmol) was then added dropwise turning the solution a darker shade of yellow which was then stirred for another 10 min. The reaction was then warmed to room temperature for ten minutes and then cooled down to 0 ^oC. Phenyl acetylene (0.196 mL, 1.78 mmol) was added dropwise and the solution was allowed to stir for 40 min at 0 ^oC. Aldehyde **2.2** (0.256 g 1.21 mmol) was then added dropwise and the mixture stirred for 1 hour at 0^oC. The reaction was quenched slowly with H_2O (1 mL) and then aq. HCl (1 M, 10 mL), and extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave **3.1.2a** (0.234 g, 56%, R_f **=** α =0.26; β= 0.31 in 4:1 Hex:EtOAc) as a partially separable mixture diastereomers (dr. 78:21)**.**

Spectral data for the major diastereomer. ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 8.6, 1.6 Hz, 2H), 7.25 (t, *J* = 7.2, 2H), 7.20 (t, *J* = 8.7 Hz 2H), 7.19 (m, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.53 (d, *J* = 9.1 Hz, 1H), 4.44(d, *J* = 11.6 Hz, 1H), 4.41 (d, *J* = 11.7 Hz, 1H), 4.39 (dd, *J* = 9.42, 7.6 Hz, 1H), 3.74 (s, 3H), 3.94 (dd, *J* = 9.3, 4.3 Hz, 1H), 3.46 (dd, *J* = 9.3, 7.5 Hz, 1H), 2.51 (d hept, *J* = 7.4, 2.8, 2H), 1.95 (qd, *J* = 7.2, 4.3 Hz, 1H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.23, 144.45, 142.21, 129.87, 129.30, 129.11, 128.12, 127.00, 126.57, 113.79, 74.41, 73.05, 72.66, 55.20, 39.30, 23.26, 13.74, 13.71. HRMS (ESI+): Calcd for $C_{22}H_{28}O_3Na^+$ $[M+Na]^+$: 363.1936. Found 363.1949.



Compound 3.1.2c. Compound 3.1.2b (0.186 g, 0.58 mmol) was then subjected to procedure **A** which was taken crude into procedure **B.** Purification by flash chromatography over silica gave **3.1.2c** (0.114 g, 51 % 2 steps, R_f = 0.23 in 4:1 Hex:EtOAc).

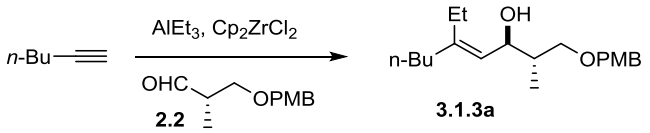
Spectral data for the major isomer. IR (ATR): 3413, 3061, 3030, 2976, 2934, 2876, 1714, 1600, 1584, 1451, 1314, 1270, 1107, 1026, 711. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 8.2 Hz,1.2 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 2H), 7.38 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.33 (t, *J* = 7.1Hz, 2H), 7.29 (dd, *J* = 8.6, 1.4 Hz, 1H), 5.96 (dd, *J* = 9.6, 8.3 Hz, 1H), 5.70 (d, *J* = 9.6 Hz, 1H), 3.69 (dd, *J* = 11.4, 4.5 Hz, 1H), 3.65 (dd, *J* = 11.4, 4.4 Hz, 1H), 2.79 – 2.63 (m, 2H), 2.11 (m, 1H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.00 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.47, 147.61, 141.72, 133.04, 129.68, 128.36, 128.26, 127.47, 126.64, 123.98, 72.88, 63.99, 40.52, 23.66, 13.44, 13.24. HRMS (ESI+): Calcd for $C_{21}H_{24}O_3Na^+$ [M+Na]$^+$: 347.1623. Found 347.1624.



3.1.2c **3.1.2**

Compound 3.1.2. Compound **3.1.2c** (0.054 g, 0.16 mmol) was then subjected to procedure **C**. Purification by flash chromatography over silica gave yielding **3.1.2** (0.0273 g, 81%, (R_f = 0.25 in 4:1 Hex:EtOAc) as a 80:20 mixture of diastereomers.

Spectral data for the major diastereomer. IR (ATR): 3336, 3062, 3026, 2958, 2927, 2871, 1600, 1492, 1451, 1377, 1028, 968, 757, 697. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.7 Hz, 2H), 7.19 (m, 1H) 7.18 (dd, *J* = 8.2, 1.4 Hz 2H), 5.69 (ddd, *J* = 15.4, 7.9, 1.0 Hz, 1H), 5.32 (ddd, *J* = 15.4, 7.8, 1.1 Hz, 1H), 3.46 (dd, *J* = 10.5, 5.6 Hz, 1H), 3.36 (dd, *J* = 10.5, 7.7 Hz, 1H), 3.13 (q, *J* = 7.6 Hz, 1H), 2.34 (hept, *J* = 6.8 Hz, 1H), 1.71 (p, *J* = 7.4 Hz, 2H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.64 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.01, 135.79, 132.03, 128.40, 127.44, 126.02, 67.30, 50.69, 39.73, 28.93, 16.62, 12.20. HRMS (ESI+): Calcd for $C_{14}H_{20}ONa^+$ [M+Na]$^+$: 227.1412. Found 227.1421.

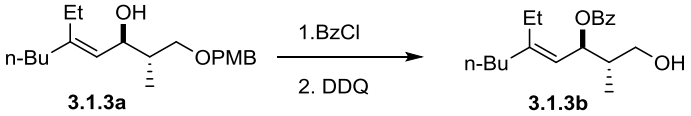


2.2 **3.1.3a**

Compound 3.1.3a. To a schlenk tube filled with DCM (5.9 mL) and Cp_2ZrCl_2 (0.052 g, 0.178 mmol) at -20 ^{o}C was added triethyl aluminum (1.0 M in hexanes, 2.86 mL, 2.86 mmol) dropwise resulting in a yellow solution which was stirred for 10 min. DI H_2O (0.031 mL, 1.78 mmol) was then added dropwise turning the

solution a darker shade of yellow which was then stirred for another 10 min. The reaction was then warmed to room temperature for ten min and then cooled down to 0 °C. 1-hexyne (0.204 mL, 1.78 mmol) was added dropwise and the solution was allowed to stir for 40 min at 0 °C. Aldehyde **2.2** (0.204 mL, 1.78 mmol) was then added dropwise and the mixture stirred for 1 h at 0 °C. The reaction was quenched slowly with H_2O (1.0 mL) and then aq. HCl (1.0 M, 10 mL), extracted with DCM (2 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave **3.1.3a** (0.186 g**,** 48%, R_f = 0.36 in 4:1 Hex:EtOAc) as a 65:35 mixture of diastereomers.

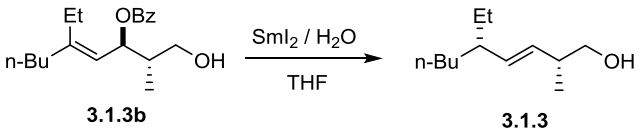
Spectral data for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.11 (dt, *J* = 9.2, 1.1 Hz, 1H), 4.44 (m, 2H), 4.28 (dd, *J* = 9.2, 7.8 Hz, 1H), 3.80 (s, 3H), 3.56 (dd, *J* = 9.3, 4.5 Hz, 1H), 3.46 (dd, *J* = 9.3, 7.6 Hz, 1H), 2.09 (p, *J* = 7.6 Hz, 2H), 2.05 – 1.97 (m, 2H), 1.86 (hd, *J* = 7.2, 4.5 Hz, 1H), 1.38 (p, *J* = 7.1 Hz, 2H), 1.30 (p, *J* = 7.3 Hz, 2H), 0.98 (t, *J* = 7.6 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 159.22, 145.05, 130.02, 129.27, 125.57, 113.79, 74.68, 73.02, 72.31, 55.25, 39.21, 35.93, 30.22, 23.46, 22.52, 13.99, 13.65, 13.50.



3.1.3a **3.1.3b**

Compound 3.1.3b. Compound **3.1.3a** (0.186g, 0.58mmol) was then subjected to general procedure **B** which was taken crude into procedure **C.** Purification by flash chromatography over silica gave **3.1.3b** (0.0979 g, 55% 2 steps, R_f = 0.32 in 4:1 Hex: EtOAc).

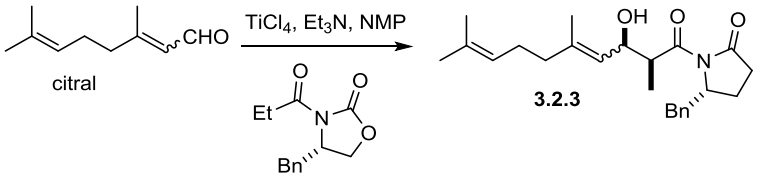
IR (ATR): 3411, 3062, 2690, 2930, 2873, 1715, 1600, 1583, 1451, 1296, 1176, 1160, 1108, 1026, 949, 711.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 2H), 5.79 (dd, *J* = 9.6, 8.4 Hz, 1H), 5.24 (dt, *J* = 9.5, 1.1 Hz, 1H), 3.62 (dd, *J* = 11.4, 4.3 Hz, 1H), 3.57 (dd, *J* = 11.4, 4.0 Hz, 1H), 2.20 (dq, *J* = 7.6, 2.2 Hz, 2H), 2.06 (ddt, *J* = 7.2, 2.5, 1.1 Hz, 2H), 1.96 (m, 1H), 1.40 (p, *J* = 7.2 Hz, 2H), 1.31 (p, *J* = 7.2 Hz, 2H), 1.03 (d, *J* = 7.0 Hz, 3H), 1.00 (t, *J* = 7.6 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 166.56, 148.42, 132.94, 130.43, 129.67, 128.34, 120.73, 72.83, 64.08, 40.44, 35.88, 30.13, 23.80, 22.47, 13.97, 13.23, 13.16. HRMS (ESI+): Calcd for $C_{19}H_{28}O_3Na^+$ $[M+Na]^+$: 327.1936. Found 327.1936.



3.1.3b **3.1.3**

Compound 3.1.3b. Compound **3.1.3a** (0.031 g, 0.098 mmol) was then subjected to procedure **C.** Purification by flash chromatography over silica gave **3.1.3** (0.0121 g, 80% yield (based on recovered starting material), R_f = 0.55 in 4:1 Hex:EtOAc) as a 80:20 mixture of diastereomers.

Spectral data for the major isomer. IR (ATR): 3332, 2956, 2922, 2872, 2857, 1457, 1378, 1033, 969, 728. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (dd, *J* = 15.6, 8.4 Hz, 1H), 5.18 (dd, *J* = 15.7, 7.0 Hz, 1H), 3.47 (dd, *J* = 10.5, 5.6 Hz, 1H), 3.36 (dd, *J* = 10.5, 8.1 Hz, 1H), 2.32 (hept, *J* = 7.0 Hz, 1H), 1.81 (m, 1H), 1.44 – 1.15 (m, 8H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.92, 132.09, 67.32, 44.66, 39.89, 34.69, 29.66, 28.00, 22.77, 16.79, 14.08, 11.70. HRMS (CI+) Calcd for $C_{12}H_{24}ONH_4^+$ $[M+NH_4]^+$: 202.2171. Found 202.2167.

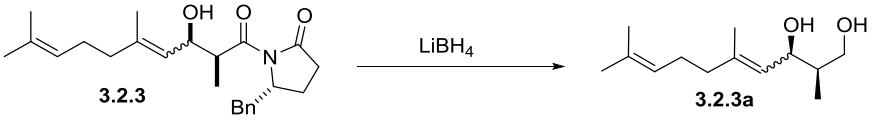


3.2.3

Compound 3.2.3. To a solution of of (S)-4-benzyl-3-propionyloxazolidin-2-one (0.845 g, 3.75 mmol) in DCM (30.0 mL) at 0 °C was added $TiCl_4$ (1.0 M, 3.74 mL, 3.74 mmol) dropwise and the resulting black solution was stirred for 5 min. Et_3N (0.497 mL, 3.57 mmol) was then added dropwise and the resulting dark black/purple was stirred for 20 minutes. The reaction was then cooled down to -78 °C at which point NMP (0.343 mL, 3.57 mmol) was added and the reaction was stirred for 10 min. Citral (0.735 mL, 4.28 mmol) was then added and the reaction stirred for 1 h. The reaction was then warmed to 0 °C turning the color to a light brown orange. After 1 h, the reaction was quenched with aq. NH_4Cl (30 mL), and extracted with DCM (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave **3.2.3** (1.203 g, 87%) as a partially separable mixture of *cis*/*trans*-isomers. (R_f-*cis* = 0.23 in 4:1 hex: EtOAc; R_f-*trans* = 0.16 in 4:1 hex: EtOAc)

Spectral data for the cis isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 6.9 Hz, 2H), 7.26 (t, *J* = 7.7 Hz, 1H), 7.19 (dd, *J* = 6.8, 1.4 Hz, 2H), 5.30 (dd, *J* = 8.9, 1.6 Hz, 1H), 5.11 (m, 1H), 4.67 (m, 2H), 4.18 (d, *J* = 7.1 Hz, 1H), 4.16 (d, *J* = 5.7 Hz, 1H), 3.87 (qd, *J* = 7.0, 4.7 Hz, 1H), 3.24 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.77 (dd, *J* = 13.4, 9.4 Hz, 1H), 2.20 – 2.06 (m, 4H), 1.73 (d, *J* = 1.5 Hz, 3H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.60 (d, *J* = 1.4 Hz, 3H), 1.28 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.24, 153.04, 140.35, 135.05, 132.03, 129.33, 128.83, 127.27, 124.62, 123.85, 68.58, 66.00, 55.12, 43.00, 37.70, 32.27, 26.45, 25.56, 23.35, 17.60, 11.95. HRMS (ESI+): Calcd for $C_{23}H_{31}NO_4Na^+$ $[M+Na]^+$: 408.2151. Found 408.2164.

Spectral data for the trans isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.3 Hz, 2H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.21 (dd, *J* = 8.4, 1.5, 2H), 5.27 (dq, *J* = 8.5, 1.3 Hz, 1H), 5.08 (tp, *J* = 6.9, 1.5 Hz, 1H), 4.72-4.66 (m, 2H), 4.23 – 4.16 (m, 2H), 3.91 (qd, *J* = 7.0, 4.3 Hz, 1H), 3.25 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.79 (dd, *J* = 13.4, 9.4 Hz, 1H), 2.09 (m, 2H), 2.03 (m, 2H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.60 (d, *J* = 1.3 Hz, 3H), 1.29 (d, *J* = 7.0 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 176.56, 153.12, 139.88, 135.06, 131.77, 129.41, 128.94, 127.39, 123.89, 123.80, 69.07, 66.10, 55.18, 43.01, 39.65, 37.81, 26.40, 25.67, 17.67, 16.82, 11.65. Calcd for $C_{23}H_{31}NO_4Na^+$ $[M+Na]^+$: 408.2151. Found 408.2164.

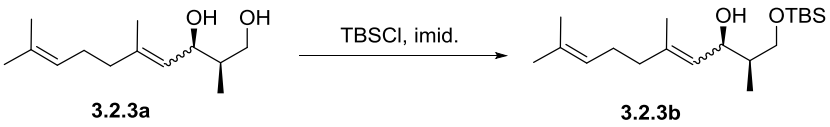


3.2.3 **3.2.3a**

Compound 3.2.3a. To a solution of compound **17** (0.500 g, 1.29 mmol) in THF (21.0 mL) and MeOH (0.114 mL) at 0 °C was added $LiBH_4$ (2.0 M in THF, 1.415 mL, 2.83 mmol) dropwise. The reaction was stirred for 2 h at 0 °C before quenching with aq. NaOH (2.0 M, 4.0 mL) and stirring for 18 hours. The mixture was extracted with EtOAc (3 x 20mL) and the combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave the diol **18a** (0.179 g, 65%, R_f = 0.45 and 0.37 in 1:1 Hex: EtOAc.

Spectral data for mixture of isomers: IR (ATR): 3334, 2964, 2914, 2879, 1444, 1375, 1262, 1081, 1028, 969, 737. ^{1}H NMR (500 MHz,$CDCl_3$) δ 5.37 (d, *J* = 9.4 Hz, 1H), 5.32 (dq, *J* = 9.1, 1.3 Hz, 1H), 5.11 (t hept, *J* = 7.1, 1.4 Hz, 1H) 5.07 (t hept, *J* = 7.0, 1.4 Hz, 1H), 4.52 (dd, *J* = 9.0, 4.3 Hz, 1H), 4.49 (dd, *J* = 9.3, 4.4 Hz, 1H), 3.71 (ddd, *J* = 10.8, 7.3, 0.9 Hz, 2H), 3.61 (ddd, *J* = 10.8, 4.5, 0.9 Hz, 2H), 2.09 (m, 8H), 1.96 (m, 1H) 1.91 (m 1H), 1.77 (d, *J* = 1.4 Hz, 3H), 1.69 (d, *J* = 1.4 Hz, 6H), 1.68 (d, *J* = 1.5 Hz, 3H), 1.61 (d, *J* = 1.5

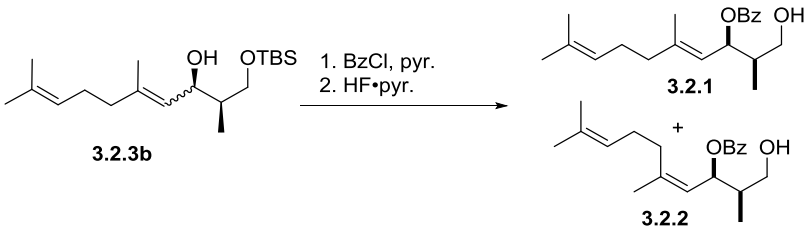
Hz, 6H), 0.91 (d, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.23, 138.51, 132.00, 131.44, 125.36, 124.74, 123.80, 123.77, 71.27, 70.76, 65.83, 65.70, 40.31, 40.08, 39.65, 32.11, 26.37, 26.22, 25.51, 25.46, 23.31, 17.50, 17.47, 16.45, 11.56, 11.53.



3.2.3a **3.2.3b**

Compound 3.2.3b. To a schlenk flask containing DCM (8.43 mL) and imidazole (0.143g, 2.11 mmol) at 0 ^{o}C was added compound **3.2.3a** (0.179, 0.843mmol). TBSCl (0.127g, 0.843 mmol) in DCM (2.0mL) was then added dropwise. The reaction was quenched with aq. NH_4Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave **3.2.3b** (0.1898 g, 69%, R_f. = 0.77 in 4:1 Hex:EtoAc) as a clear and colorless oil.

Spectral data for the cis and trans mixture. IR (ATR) 3442, 2956, 2927, 2856, 1471, 1376, 1252, 1084, 1004, 834, 773. ^{1}H NMR (500 MHz,$CDCl_3$) δ 5.30 (dq, *J* = 8.8, 1.3 Hz, 1H), 5.27 (dq, *J* = 8.8, 1.3 Hz, 1H), 5.10 (m, 2H) 4.47 (dt, *J* = 8.6, 3.9 Hz, 2H), 3.65 (d, *J* = 5.9 Hz, 2H), 3.64 (dd, *J* = 6.4, 2.1 Hz, 2H), 2.10 (m, 4H), 2.05 (m, 4H), 1.89 (m, 1H), 1.82 (m 1H), 1.75 (d, *J* = 1.4 Hz, 3H), 1.68 (s, 6H), 1.66 (d, *J* = 1.4 Hz, 3H), 1.60 (s, 6H), 0.91 (s 9H), 0.90 (s, 9H), 0.89 (d, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 7.1 Hz, 3H), 0.07 (t, *J* = 3.3 Hz, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.38, 137.84, 131.78, 131.37, 126.26, 125.47, 124.04, 124.02, 71.28, 70.39, 66.81, 66.76, 40.54, 39.73, 32.28, 26.60, 26.34, 25.78, 25.62, 25.57, 23.43, 18.08, 18.07, 17.58, 17.57, 16.57, 11.52, 11.37, -5.64, -5.64, -5.68, -5.70.



3.2.3b **3.2.1** **3.2.2**

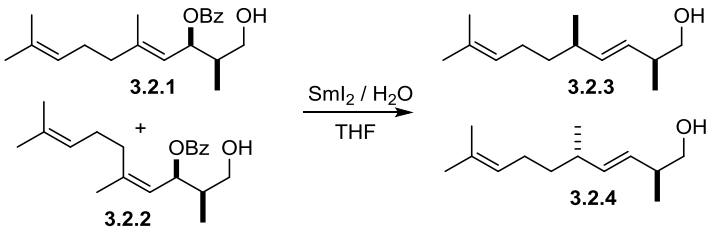
Compounds 3.2.1 and 3.2.2. Compound **3.2.3b** (0.1898 g, 0.58 mmol) was subjected to procedure **A** (0.263 g crude yield). The crude product was then placed into a teflon reaction vessel containing THF (3.0 mL), cooled to 0 ^{o}C, and treated with HF·pyr (70 % HF, 0.100 mL, 3.016 mmol) and left to sit for 18 h at 4

°C without stirring. The reaction was quenched with aq. $NaHCO_3$ and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave **3.2.1** and **3.2.2** (0.088 g, 70 %) as a partially mixture of *cis*/*trans* isomers (R_f-*cis* = 0.29; R_f-*trans* = 0.33 in 4:1 Hex:EtOAc).

IR (ATR) of **3.2.1** and **3.2.1** mixture. 3420, 2966, 2917, 1716, 1601, 1450, 1274, 1114, 1026, 944, 711.

Spectral data for **3.2.1.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.3, 1.3, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 2H), 5.99 (dd, *J* = 9.3, 4.2 Hz, 1H), 5.42 (dd, *J* = 9.4, 1.3 Hz, 1H), 5.15 (tp, *J* = 7.1, 1.4 Hz, 1H), 3.51 (dd, *J* = 11.6, 5.8 Hz, 1H), 3.45 (dd, *J* = 11.5, 8.2 Hz, 1H), 2.27 (m, 1H), 2.17 (m, 1H), 2.13-2.05 (m, 2H), 2.01 (m, 1H), 1.77 (d, *J* = 1.5 Hz, 3H), 1.64 (d, *J* = 1.3 Hz, 3H), 1.59 (d, *J* = 1.2 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.57, 141.61, 132.95, 132.15, 130.37, 129.66, 128.34, 123.66, 121.95, 71.63, 64.63, 41.06, 32.52, 26.46, 25.64, 23.46, 17.62, 11.16.

Spectral data for ***3.2.2****.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.56 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 2H), 5.93 (dd, *J* = 8.9, 4.5 Hz, 1H), 5.36 (dq, *J* = 9.0, 1.3 Hz, 1H), 5.10 (tp, *J* = 6.7, 1.4 Hz, 1H), 3.52 (m, 1H), 3.49 (m, 1H), 2.15 – 1.98 (m, 5H), 1.78 (d, *J* = 1.4 Hz, 3H), 1.66 (d, *J* = 1.3 Hz, 3H), 1.59 (d, *J* = 1.3 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 166.61, 141.04, 132.97, 131.89, 130.37, 129.64, 128.36, 123.72, 121.45, 72.43, 64.62, 40.89, 39.62, 26.22, 25.67, 17.70, 16.87, 11.42.

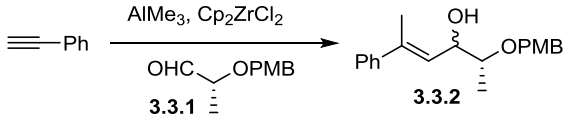


Compounds 3.2.3 and 3.2.4. A mixture of **3.2.1** and **3.2.2** (42:58) (0.026 g, 0.08 mmol) was subjected to procedure **C**. Purification by flash chromatography over silica gave a mixture of **3.2.3** and **3.2.4** (0.0113 g, 72 %, R_f. = 0.53 in 4:1 Hex:EtoAc). See Scheme 8 for dr. values.

IR (ATR) of **3.2.3** and **3.2.4** mixture: 3345, 3022, 2957, 2917, 2869, 2850, 1453, 1376, 1263, 1033, 970.

*Spectral data for **3.2.3**.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41 (ddd, *J* = 15.5, 7.8, 1.0 Hz, 1H), 5.21 (ddd, *J* = 15.4, 7.9, 1.0 Hz, 1H), 5.11 (tp, *J* = 7.1, 1.4 Hz, 1H), 3.47 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.35 (dd, *J* = 10.5, 7.8 Hz, 1H), 2.30 (hept, *J* = 14.0, 7.1 Hz, 1H), 2.10 (p, *J* = 7.0 Hz, 1H), 1.94 (q, *J* = 7.3 Hz, 2H), 1.68 (s, 3H), 1.59 (s, 3H), 1.30 (q, *J* = 7.4 Hz, 2H), 0.99 (d, *J* = 4.2 Hz, 3H), 0.98 (d, *J* = 4.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.41, 131.28, 130.52, 124.62, 67.30, 39.77, 37.12, 36.40, 25.81, 25.71, 20.92, 17.68, 16.76.

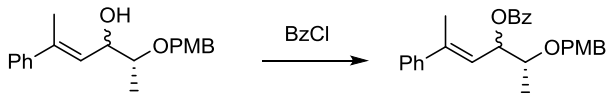
*Spectral data for **3.2.4**.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41 (ddd, *J* = 15.5, 7.7, 1.0 Hz, 1H), 5.21 (ddd, *J* = 15.5, 7.9, 1.0 Hz, 1H), 5.09 (tp, *J* = 7.1, 5.7, 2.8, 1.4 Hz, 1H), 3.47 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.36 (dd, *J* = 10.4, 7.8 Hz, 1H), 2.30 (hept, *J* = 6.6 Hz, 1H), 2.11 (p, *J* = 7.0 Hz, 1H), 1.94 (q, *J* = 7.6 Hz, 2H), 1.68 (s, 3H), 1.59 (s, 3H), 1.30 (q, *J* = 7.7 Hz, 2H), 0.99 (d, *J* = 3.5 Hz, 3H), 0.97 (d, *J* = 3.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.30, 131.32, 130.47, 124.56, 67.34, 39.73, 37.12, 36.40, 25.87, 25.71, 20.74, 17.67, 16.68.



Compound 3.3.2. To a schlenk tube filled with Dichloromethane (DCM) (10.8 mL) and Cp_2ZrCl_2 (0.095 g, 0.325 mmol) at -20 °C, was added trimethyl aluminum (2.0 M in toluene, 3.25 mL, 6.5 mmol) dropwise resulting in a yellow solution which was stirred for 10 min. DI H_2O (0.058 mL, 3.25 mmol) was then added dropwise turning the solution a darker shade of yellow which was then stirred for another 10 min. The reaction was then warmed to room temperature for 10 min and then cooled down to 0 °C. Phenylacetylene (0.356 mL, 3.25 mmol) was added dropwise and the solution was allowed to stir for 40 min at 0 °C. Aldehyde **3.3.1** (0.500 g, 2.6 mmol) was then added dropwise and the mixture stirred for 1 h at 0 °C. The reaction was quenched slowly with H_2O (1.0 mL) and then aq. HCl (1.0 M, 10mL), extracted with DCM (2 x 20 mL), and washed with brine (15 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography over silica gave **3.3.2** (0.688 g, 82 %, (R_f.α = 0.30; R_f.β = 0.20 in 4:1 Hex:EtoAc) as a clear and colorless oil with partially separable diastereomers (d.r = 58:42).

*Spectral data for diastereomer **3.3.2α:*** ^{1}H NMR (500 MHz, $CDCl_3$) 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 (125 MHz, $CDCl_3$) 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 (ESI+): Calcd for $C_{20}H_{24}O_3Na^+$ $[M+Na]^+$: 335.1623. Found 335.1612.

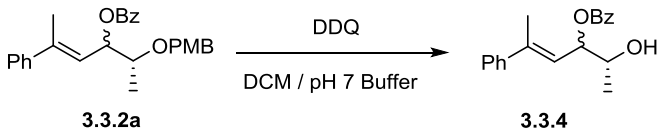
*Spectral data for Diastereomer **3.3.2β:*** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.7, 1.4, 2H), 7.32 (t, *J* = 7.19 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.80 (dq, *J* = 8.4, 1.3 Hz, 1H), 4.62 (dd, *J* = 8.4, 3.6 Hz, 1H), 4.62 (d, *J* = 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 (125 MHz, $CDCl_3$) 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 (ESI+): Calcd for $C_{20}H_{24}O_3Na^+$ $[M+Na]^+$: 335.1623. Found 335.1612.



3.3.2 **3.3.2a**

Compound 3.3.2a. Compound **3.3.2** (0.371 g, 1.18 mmol) was subjected to procedure **A.** Purification by flash chromatography over silica gave **3.3.2a** (0.376 g, 76 %, R_f. = 0.52 in 4:1 Hex:EtOAc)

Spectral data for mixture of diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 8.2, 1.2 Hz, 2H), 8.06 (dd, *J* = 8.2, 1.2 Hz, 2H) 7.56 (t, *J* = 7.2 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 4H), 7.39 (dd, *J* = 8.5, 1.5 Hz, 4H), 7.31 (t, *J* = 7.1 Hz, 4H), 7.27 (m, 4H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 11.2 Hz, 2H), 6.79 (d, *J* = 11.2 Hz, 2H), 6.00 (dd, *J* = 9.1, 3.6 Hz, 1H), 5.98 (dd, *J* = 9.6, 6.3 Hz, 1H), 5.92 (dq, *J* = 8.9, 1.2 Hz, 1H), 5.81 (dq, *J* = 9.2, 1.2 Hz, 1H), 4.64 (d, *J* = 11.6 Hz, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.55 (d, *J* = 11.7, 1H), 3.84 (m, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 2.24 (d, *J* = 1.4 Hz, 3H), 2.20 (d, *J* = 1.4 Hz, 3H), 1.29 (d, *J* = 6.4 Hz, 3H), 1.27 (d, *J* = 6.4 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 165.82, 159.11, 142.79, 141.02, 132.87, 132.81, 130.57, 129.71, 129.28, 128.87, 128.32, 128.28, 128.21, 127.50, 126.00, 125.97, 122.80, 122.65, 113.73, 113.68, 75.82, 75.77, 74.51, 73.93, 71.21, 71.09, 55.24, 16.99, 16.81, 16.23, 16.07.



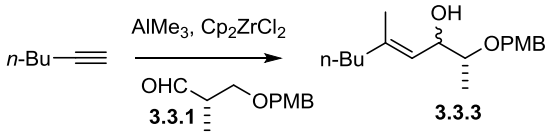
3.3.2a **3.3.4**

Compound 25. Compound **3.3.2a** (0.280 g, 0.672 mmol) was subjected to general procedure **C.** Purification by flash chromatography over silica gave **3.3.4** (0.170 g, 85 %, R_f = 0.24 in 4:1 Hex:EtoAc) as a clear and colorless oil.

Spectral data for mixture of diastereomers. IR (ATR): 3450, 3062, 3031, 2976, 2929, 1712, 1600, 1583, 1450, 1266, 1110, 1025, 963, 909, 709. HRMS (ESI+): Calcd for $C_{19}H_{20}O_3Na^+$ [M+Na]$^+$: 319.1310. Found 319.1314.

*Spectral data for diastereomer **3.3.4α:*** ^{1}H NMR (500 MHz, $CDCl_3$) 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 (125 MHz, $CDCl_3$) 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 **3.3.4β:*** ^{1}H NMR (500 MHz, $CDCl_3$) 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 (125 MHz, $CDCl_3$) 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.

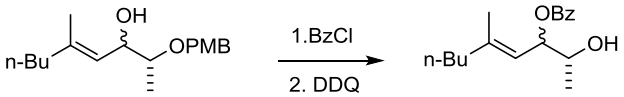


Compound 3.3.3. To a schlenk tube filled with DCM (10.8 mL) and Cp_2ZrCl_2 (0.095 g, 0.325 mmol) at -20 ^{o}C, was added $AlMe_3$ (2.0 M in toluene, 3.25 mL, 6.5 mmol) dropwise resulting in a yellow solution which was stirred for 10 min. DI H_2O (0.058 mL, 3.25 mmol) was then added dropwise turning the solution a darker shade of yellow which was then stirred for another 10 min. The reaction was then warmed to room temperature for 10 min and then cooled down to 0 ^{o}C. 1-hexyne (0.373 mL, 3.25 mmol) was added dropwise

and the solution was allowed to stir for 40 min at 0 °C. Aldehyde **3.3.1** (0.500 g, 2.6 mmol) was then added dropwise and the mixture stirred for 1 h at 0 °C. The reaction was quenched slowly with H_2O (1.0 mL) and then aq. HCl (1.0 M, 10 mL), and extracted with DCM (2 x 20 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave **3.3.3** (0.441 g**,** 58%, (R_f α = 0.38; R_f β = 0.34 in 4:1 Hex:EtoAc) as a clear and colorless oil with partially separable diastereomers (d.r = 56:44).

*Spectral data for diastereomer **3.3.3α:*** ^{1}H NMR (500 MHz, $CDCl_3$) 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 (125 MHz, $CDCl_3$) 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. HRMS (ESI+): Calcd for $C_{18}H_{28}O_3Na^+$ $[M+Na]^+$: 315.1936. Found 315.1944.

*Spectral data for diastereomer **3.3.3β:*** ^{1}H NMR (500 MHz, $CDCl_3$) 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 (125 MHz, $CDCl_3$) 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.

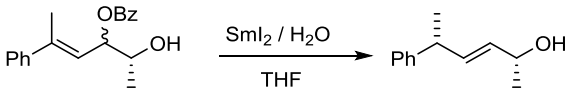


3.3.3 **3.3.5**

Compound 3.3.5. Compound **3.3.3** (0.431 g, 1.3 mmol) was subjected to general procedure **B** and taken crude into procedure **C.** Purification by flash chromatography over silica gave **3.3.5** (0.344 g, 89 % for 2 steps, R_f = 0.32 in 4:1 Hex EtOAc)

Spectral data for mixture of diastereomers. IR (ATR): 3462, 3062, 2956, 2929, 2871, 1714, 1600, 1578, 1450, 1315, 1266, 1111, 1068, 962, 709.^{1}H NMR (500 MHz, $CDCl_3$) 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),

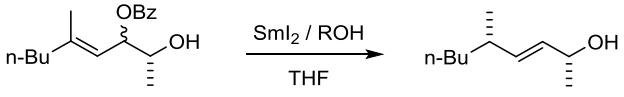
5.32 (dq, *J* = 9.2, 1.3 Hz, 1H), 5.20 (dq, *J* = 9.5, 1.3 Hz, 1H), 4.03 (qd, *J* = 6.3, 4.2 Hz, 1H), 3.97 (p, *J* = 6.6 Hz, 1H), 2.06 (t, *J* = 7.6 Hz, 2H), 2.04 (t, *J* = 7.3 Hz, 2H), 1.84 (d, *J* = 1.4 Hz, 3H), 1.81 (d, *J* = 1.4 Hz, 3H) 1.40 (m, 4H), 1.29 (p, *J* = 7.4 Hz, 4H), 1.24 (d, *J* = 6.5 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 (125 MHz, $CDCl_3$) 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 (ESI+): Calcd for $C_{17}H_{24}O_3Na^+$ $[M+Na]^+$: 299.1623. Found 299.1617.



3.3.4 **3.3.6**

Compound 3.3.6. Compound **3.3.4** (0.030 g, 0.10 mmol) was subjected to procedure **C**. Purification by flash chromatography over silica gave **3.3.6** (0.017g, 60%, R_f. = 0.30 in 4:1 Hex:EtoAc)

Spectral data for major diastereomer. IR (ATR): 3328, 3083, 3060, 3026, 2967, 2925, 2871, 1601, 1493, 1451, 1370, 1274, 1060, 970, 760, 699. ^{1}H NMR (500 MHz, $CDCl_3$) 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 (125 MHz, $CDCl_3$) δ 145.56, 135.41, 132.87, 128.44, 127.16, 126.16, 68.87, 41.83, 23.42, 21.17. HRMS (ESI+): Calcd for $C_{12}H_{15}$ $[M-OH]^+$: 159.1174. Found 159.1175.

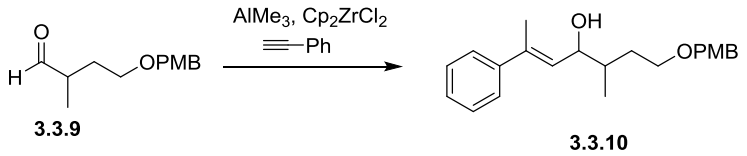


3.3.5 **3.3.7**

Compound 3.3.7. Compound **3.3.5** (0.030 g, 0.108 mmol) was subjected to general procedure **D**. Purification by flash chromatography over silica gave **3.3.7** (0.010 g, 60 %, R_f. = 0.38 in 4:1 Hex:EtOAc) as a 90:10 mixture of diastereomers.

Spectral data for the major diastereomer. IR (ATR): 3347, 2958, 2925, 2871, 2857, 1606, 1457, 1371, 1258, 1150, 1123, 1060, 969, 730. ^{1}H NMR (500 MHz, $CDCl_3$) 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,

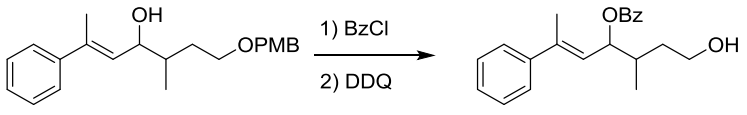
3H), 0.99 (d, J = 6.8 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 136.99, 132.24, 69.03, 36.56, 36.14, 29.48, 23.49, 22.79, 20.40, 14.08. HRMS (CI+): Calcd for $C_{10}H_{19}$ [M-OH]+: 139.1487. Found 139.1482.



3.3.9 **3.3.10**

Compound 3.3.10. Aldehyde **3.3.9** (0.300 g, 1.3 mmol) was subjected to general procedure A. Purification by flash chromatography gave **3.3.10** (0.288 g, 65%, R_f = 0.65 in 1:1 Hex:EtOAc) as a mixture of diastereomers (d.r = 60:40).

Spectral data for the mixture of diastereomers. IR (ATR): 3396, 3102, 3080, 3056, 3028, 2931, 2863, 1611, 1585, 1511, 1493, 1444, 1364, 1301, 1245, 1081, 1032, 909, 820, 757, 731, 696. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.38 (m, 4H), 7.32 (t, 7.32, *J* = 7.3 Hz, 4H) 7.27 (dd, *J* = 5.6, 2.1 Hz, 2H) 7.26 (dd, *J* = 7.0, 2.0 Hz, 2H), 7.25 (tt, *J* = 6.3, 1.3 Hz, 2H), 6.88 (d, *J* = 8.6, 2H), 6.87 (d, *J* = 8.6, 2H), 5.82 (dq, *J* = 8.7, 1.4 Hz, 1H), 5.77 (dq, *J* = 8.9, 1.4 Hz, 1H), 4.47 (s, 2H) 4.47 (d, *J* = 11.5 Hz, 1H), 4.44 (d, 11.5 Hz, 1H), 4.43 (dd, = 9.1, 4.5 Hz, 1H), 4.30 (dd, *J* = 8.8, 6.9 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.63-3.56(m, 2H), 3.54-3.49 (m, 2H), 2.63 (br, OH), 2.40 (br, OH), 2.08 (d, 1.4 Hz, 3H) 2.07 (d, *J* = 1.4 Hz, 3H), 1.92-1.81 (m, 4H), 1.64 (sep, *J* = 6.7 Hz, 1H), 1.50 (sep, *J* = 6.6 Hz, 1H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.23, 143.31, 137.56, 137.26, 130.20, 129.55, 129.39, 129.37, 129.19, 128.20, 127.14, 125.90, 113.84, 113.83, 72.78, 72.77 72.71, 72.20, 68.36, 68.03, 55.28, 37.80, 37.56, 32.96, 32.77, 16.61, 16.51, 16.00, 15.21.

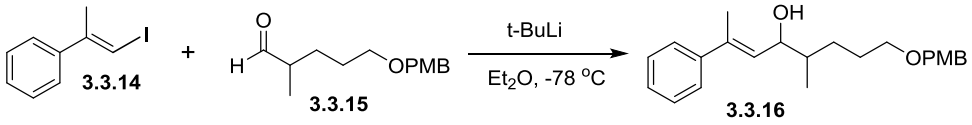


3.3.10 **3.3.11**

Compound 3.3.11. Compound **3.3.10** (0.288 g, 0.845 mmol) was subjected to general procedure **B** and **C**. Purification by flash chromatograph gave compound **3.3.11** (0.238 g, 86 %, R_f = 0.15 in 4:1 Hex:EtOAc).

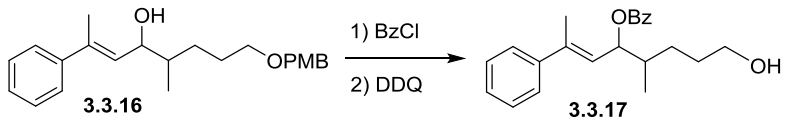
Spectral data for the major diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.4, 2H), 7.40 (d, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.26 (tq, *J* = 7.3, 3.5 Hz, 1H), (5.88 – 5.83, m, 2H), 3.85-3.79 (m, 1H), 3.78-3.70 (m, 1H), 2.24 (s, 3H), 2.22-2.13 (m, 1H), 1.90 (p, 7.2 Hz, 1H), 1.52 (p, *J* = 7.4 Hz, 1H), 1.08 (d, *J* = 7.0 Hz, 3H).

Spectral data for the mixture of diastereomers. IR (ATR): 3047, 3059, 3031, 2967, 2931, 2877 1713, 1600, 1583, 1450, 1314, 1266, 1175, 1108, 1068, 909, 848, 731. ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.33, 166.30, 143.26, 143.23, 140.64, 140.32, 133.21, 130.95, 129.96, 129.95, 128.71, 128.59, 127.82, 127.80, 126.33, 124.91, 124.56, 75.94, 75.78, 61.33, 61.24, 35.77, 35.74, 35.20, 34.97, 17.27, 17.18, 15.78, 15.61.



Compound 3.3.16. To a Schleck flask containing ether (5.2 mL) and t-BuLi (1.7 M, 0.917 mL, 1.56 mL) at -78 ^{0}C was added vinyl iodide **3.3.14** (0.190 g, 0.78 mmol) dropwise. The solution was stirred for 10 min at -78 ^{0}C, aldehyde **3.3.15** (0.123g, 0.520 mmol) was added dropwise, and the reaction was stirred for 1 hour at -78 ^{0}C. The reaction was quenched cold with aq. NH_4Cl (30 mL), and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave alcohol **3.3.16** (0.097 g, 53 %, R_f = 0.64 in 1:1 Hex:EtOAc) as a mixture of diastereomers (d.r = 50:50).

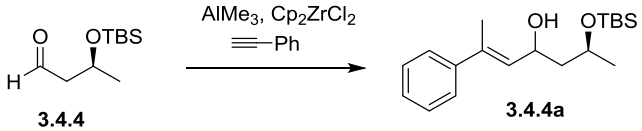
Spectral data for the mixture of diastereomers. IR (ATR): 3412, 3080, 3056, 3031, 2931, 2856, 1611, 1585, 1511, 1493, 1444, 1362, 1301, 1245, 1172, 1092, 1032, 821, 758, 735, 696. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dt, *J* = 8.4, 1.5 Hz, 4H), 7.33 (tt, *J* = 8.3, 1.0, 4H), 7.27 (tt, *J* = 4.1, 1.3 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 4H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.80 (dq, *J* = 8.9, 1.5 Hz, 1H), 5.78 (dq, *J* = 9.0, 1.4 Hz, 1H), 4.44 (s, 2H), 4.43 (s, 2H), 4.38 (dd, *J* = 8.9, 5.7 Hz, 1H), 4.35 (dd, *J* = 8.9, 6.5 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.48-3.42 (m, 4H), 2.10 (d, *J* = 1.4 Hz, 3H), 2.09 (d, *J* = 1.4 Hz, 3H), 1.80-1.59 (m 10H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.09, 143.17, 138.01, 137.65, 130.68, 129.38, 129.24, 129.22, 128.98, 128.24, 127.25, 127.22, 125.86, 113.75, 72.67, 72.65, 72.57, 72.55, 70.38, 70.32, 55.27, 39.51, 39.44, 28.96, 28.93, 27.53, 27.21, 16.59, 16.50, 14.97, 14.95.



3.3.16 3.3.17

Compound 3.3.17. Compound **3.3.16** (0.097 g, 0.273 mmol) was subjected to general procedure **B** and **C**. Purification by flash chromatograph gave compound **3.3.17** (0.065 g, 71 %, R_f = 0.13 in 4:1 Hex:EtOAc) over two steps.

Spectral data for the mixture of diastereomers. IR (ATR): 3400, 3059, 3031, 2931, 2876, 1712, 1600, 1583, 1493, 1450, 1380, 1314, 1266, 1175, 1107, 1068, 1025, 908, 731. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (dt, *J* = 8.4, 1.0 Hz, 4H), 7.55 (tq, *J* = 6.9, 1.3 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 4H), 7.40 (dt, *J* = 8.5, 1.5 Hz, 4H), 7.31 (tt, *J* = 7.38, 1.0 Hz, 4H), 7.26 (tq, *J* = 7.2 Hz, 1.3 Hz, 2H), 5.82 (m, 4H), 3.67 (tt, *J* = 6.5, 2.0 Hz, 4H), 2.24 (d, *J* = 1.0 Hz, 3H), 2.23 (s, 3H),2.04 (m, 1H), 1.97 (m, 1H) 1.77-1.54 (m, 8H), 1.12 (d, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.97, 165.94, 142.93, 142.89, 140.14, 139.65, 132.79, 130.65, 129.57, 128.31, 128.20, 127.40, 127.38, 125.95, 125.94, 124.83, 124.27, 75.53, 75.45, 63.07, 63.06, 38.05, 37.56, 30.45, 30.17, 28.60, 28.56, 16.87, 16.78, 15.30, 15.05.

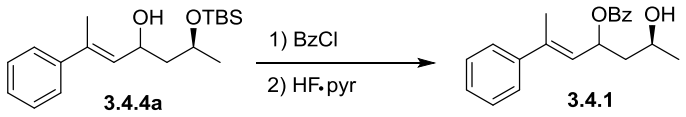


3.4.4 3.4.4a

Compound 3.4.1a. Aldehyde **3.4.4** (0.231 g, 1.15 mmol) was subjected to general procedure A. Purification by flash chromatography gave alcohol **3.4.1a** (0.234 g, 63%, R_f = 0.52 in 4:1 Hex:EtOAc) as a mixture of diastereomers (d.r. = 54:46).

Spectral data for the mixture of diastereomers. IR (ATR): 3413, 3081, 3057, 3027, 2955, 2928, 2855, 1612, 1512, 1494, 1462, 1374, 1248, 1143, 1077, 1001, 834, 807, 774, 756, 731, 695. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.1 Hz, 4H), 7.31 (t, *J* = 7.4 Hz, 4H), 7.24 (t, *J* = 7.2 Hz 2H), 5.83 (dq, *J* = 8.6, 1.3 Hz, 1H), 5.79 (dq, *J* = 8.2, 1.4 Hz, 2H), 4.90 (dt, *J* = 8.9, 3.1 Hz, 1H) 4.72 (dt, *J* = 8.9, 3.1 Hz, 1H), 4.23 (pd, *J* = 6.2, 3.6 HZ 1H), 4.16 (dtd, *J* = 12.2, 6.1, 3.8 Hz, 1H), 3.35 (br, OH), 3.13 (br, OH), 2.10 (d, *J* = 1.4 Hz, 3H), 2.10 (d, *J* = 1.4 Hz, 3H), 1.83 (ddd, *J* = 9.1, 7.0, 3.4, Hz, 1H) 1.80 (ddd, *J* = 9.2, 5.2, 1.6, Hz, 1H) 1.63 (dddd, *J* = 14.3, 6.91, 3.8, 3.2 Hz, 1H) 1.60 (dddd, *J* = 14.3, 8.7, 6.2, 2.6 Hz, 1H) 1.28 (d, *J* = 6.3 Hz, 3H), 1.23 (d, *J* = 6.1 Hz, 3H), 0.93 (s, 18H), 0.14 (d, *J* = 9.1 Hz, 6H). 0.12 (d, *J* = 8.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$)

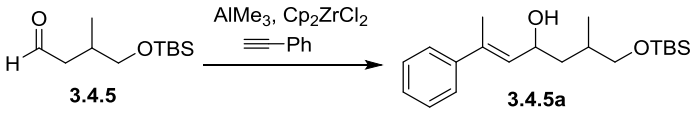
δ 143.24, 143.21, 136.54, 135.96, 131.13, 130.86, 128.33, 127.25, 127.22, 125.99, 125.94, 69.63, 68.69, 67.20, 66.06, 46.31, 45.03, 25.97, 24.71, 23.29, 18.11, 18.07, 16.52, 16.28, -3.66, -4.26, -4.65, -4.83.



3.4.4a **3.4.1**

Compound 3.4.1. Compound **3.4.4a** (0.234g, 0.729 mmol) was subjected to general procedure B. The crude product mixture was placed into a teflon reaction vessel containing THF (7.3 mL), cooled to 0 °C, and treated with HF·pyr (70 % HF, 0.400 mL, 12.064 mmol) and left to sit for 18 h at 4 °C without stirring. The reaction was quenched with aq. $NaHCO_3$ and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave **3.4.1** (0.194 g, 86 % over two steps (R_f-α =0.24; R_f-β = 0.18 in 4:1 Hex:EtOAc) as clear and colorless oil with partially separable diastereomers (d.r. = 54:46).

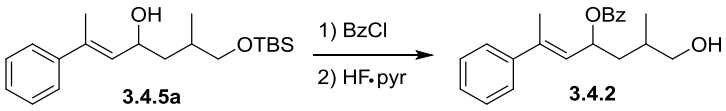
Spectral data for the mixture of diastereomers. IR (ATR): 3428, 3060, 3032, 1713, 1600, 1584, 1450, 1266, 1108, 1068, 1025, 934, 847, 731. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (t, *J* = 9.2 Hz, 4H), 7.58 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.55 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 4H), 7.41 (d, *J* = 7.51 Hz, 4H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.27 (tt, *J* = 5.88, 1.3 Hz, 2H), 6.19 (dd, *J* = 8.8, 3.5 Hz, 1H), 6.10 (dt, *J* = 6.90 Hz, 1H) 5.90 (dq, *J* = 8.7, 1.4 Hz, 1H), 5.80 (dq, *J* = 9.2, 1.2 Hz, 1H), 3.97 (qd, *J* = 6.2, 1.4 Hz, 1H), 3.86 (qd, *J* = 6.2, 2.6 Hz, 1H), 2.26 (d, *J* = 1.2 Hz, 3H), 2.19 (t, *J* = 1.2 Hz, 3H), 2.13 (ddd, *J* =14.0, 8.3, 6.6, 1H), 1.99 (ddd, *J* = 13.3, 10.4, 2.6, 1H), 1.88 (ddd, *J* = 11.5, 7.3, 4.5 Hz, 1H), 1.80 (ddd, *J* = 13.7, 10.0, 3.3 Hz, 1H) 1.29 (d, *J* = 6.2 Hz, 3H), 1.24 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.10, 165.91, 142.66, 142.52, 139.76, 139.26, 133.20, 132.91, 130.52, 130.02, 129.79, 129.60, 128.42, 128.36, 128.30, 128.26, 127.59, 127.53, 125.96, 125.93, 125.87, 125.76, 70.75, 69.88, 65.46, 63.63, 45.08, 44.24, 24.14, 23.08, 16.66.



3.4.5 **3.4.5a**

Compound 3.4.5a. Aldehyde **3.4.5** (0.500 g, 2.31 mmol) was subjected to general procedure A. Purification by flash chromatography gave **3.4.5a** (0.658 g, 85 %, R_f = 0.51 in 4:1 Hex:EtOAc) as a mixture of diastereomers (d.r = 54:46)

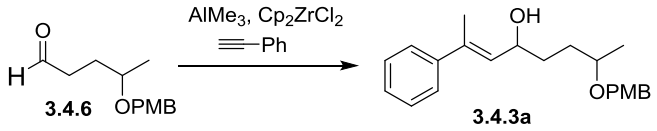
Spectral data for the mixture of diastereomers. IR (ATR): 3347, 3082, 3058, 3028, 2954, 2927, 2855, 1598, 1495, 1471, 1462, 1387, 1360, 1250, 1153, 1089, 1028, 1005, 833, 774, 755, 694. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.8 Hz, 4H), 7.33 (t, *J* = 7.4 Hz, 4H), 7.26 (tq, *J* = 7.4, 1.3 Hz, 2H), 5.83 (tq, *J* = 8.5, 1.4 Hz, 2H), 4.72 (td, *J* = 7.3, 6.2, 1H), 4.64 (td, *J* = 8.8, 3.8 Hz, 1H), 3.60 (dd, *J* = 10, 4.7Hz, 1H) 3.58 (dd, 5.2, 9.9 Hz, 1H), 3.52 (dd, *J* = 9.9, 6.7 Hz 1H), 3.48 (dd, *J* = 10.0, 7.4 Hz, 1H), 3.25 (br, OH), 2.95 (br, OH), 2.12 (d, 1.4 Hz 6H), 1.89 (o, *J* = 6.6 Hz, 2H), 1.72 (ddd, *J* = 14.3, 9.2, 7.1 Hz, 1H), 1.66 (ddd, *J* = 7.2, 6.1, 3.6 Hz, 2H), 1.49 (ddd, *J* = 14.1, 5.9, 3.7 Hz, 1H), 0.98 (d, *J* = 6.8 Hz, 6H), 0.95 (s, 9H) 0.95 (s, 9H), 0.12 (d, *J* = 2.7 Hz, 6H), 0.11 (d, *J* = 2.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.07, 143.05, 136.02, 135.69, 131.58, 131.19, 128.08, 126.97, 126.94, 125.74, 69.01, 68.39, 67.71, 66.58, 43.19, 42.31, 33.90, 32.30, 25.85, 18.26, 18.23, 17.76, 17.38, 16.14, -5.46, -5.51, -5.53.



3.4.5a **3.4.2**

Compound 3.4.2. Alcohol **3.4.5a** (0.250g, 0.747 mmol) was subjected to general procedure **B**. The crude mixture was placed into a teflon reaction vessel containing THF (7.4 mL), cooled to 0 °C, and treated with HF·pyr (70 % HF, 0.400 mL, 12.064 mmol) and left to sit for 18 h at 4 °C without stirring. The reaction was quenched with aq. $NaHCO_3$ and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography over silica gave **3.4.2** (0.240 g, 99 % over two steps (R_f = 0.18 in 4:1 Hex:EtOAc) as clear and colorless oil.

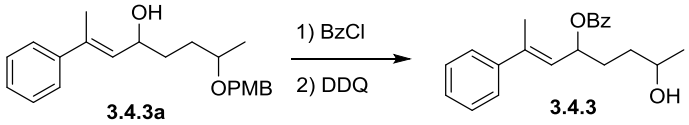
Spectral data for the mixture of diastereomers. IR (ATR): 3429, 3065, 3032, 2962, 2919, 2877, 1712, 1600, 1583, 1450, 1314, 1267, 1108, 1069, 1025, 931, 711. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, 8.0 Hz, 4H), 7.55 (tt, 7.5, 1.1 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 4H) 7.41 (dd, *J* = 7.6, 1.8 Hz, 4H), 7.32 (t, 7.2 Hz, 4H) 7.26 (tt, *J* = 7.3, 1.2 Hz, 2H), 6.06 (dt, *J* = 6.8, 9.1 Hz, 1H), 6.04 (dt, *J* = 8.7, 5.3 Hz, 1H), 5.81 (dq, *J* = 9.0, 1.3, 1H) 5.78 (dq, *J* = 9.2, 1.3 Hz, 1H) 3.57 (dd, *J* = 5.6, 1.8, 4H), 2.24 (d, *J* = 1.3 3H), 2.23 (d, *J* = 1.3 Hz, 3H), 1.98 (m, 2H), 1.94-1.78 (m, 4H), 1.05 (d, *J* = 6.7, 3H) 1.04 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.15, 166.10, 142.72, 142.69, 139.52, 138.98, 132.89, 132.87, 130.60, 130.53, 129.63, 129.62, 128.35, 128.26, 127.50, 127.47, 126.59, 126.35, 125.97, 125.96, 71.00, 70.58, 68.16, 68.02, 38.67, 32.47, 32.37, 17.17, 16.83, 16.71, 16.65.



3.4.6 **3.4.3a**

Compound 3.4.3a. Aldehyde **3.4.6** (0.300 g, 1.3 mmol) was subjected to general procedure **A**. Purification by flash chromatography gave **3.4.3a** (0.254 g, 57 %, R_f = 0.61 in 4:1 Hex:EtOAc) as a mixture of diastereomers (d.r = 50:50).

Spectral data for the mixture of diastereomers. IR (ATR): 3395, 3080, 3056, 3030, 2930, 2861, 1611, 1585, 1512, 1493, 1443, 1374, 1337, 1301, 1172, 1032, 911, 821, 757, 733, 696. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.8 Hz, 4H), 7.33 (t, *J* = 7.3 Hz, 4H), 7.28 (dd, *J* = 8.8, 1.5 Hz, 4H) 7.26 (tt, *J* = 6.5, 1.2 Hz, 2H), 6.88 (dd, *J* = 8.6, 2.0 Hz, 4H), 5.78 (dq, *J* = 5.4, 1.4 Hz, 1H), 5.77 (dq *J* = 5.4, 1.4 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 4H), 4.40 (dd, *J* = 11.3, 2.4 Hz, 2H), 3.80 (s, 6H), 3.57 (hex, 5.9 Hz, 2H) 2.08 (d, *J* = 1.3 Hz, 3H) 2.08 (d, *J* = 1.3 Hz, 3H), 1.81-1.56 (m, 8H), 1.22 (d, *J* = 6.2 Hz, 6H)). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.06, 142.97, 142.95, 136.80, 136.72, 130.86, 130.84, 129.26, 129.24, 128.18, 127.15, 125.78, 113.74, 74.44, 74.43, 70.02, 69.98, 68.96, 68.89, 55.22, 33.67, 33.58, 32.56, 32.51, 19.49, 19.47, 16.29, 16.27.

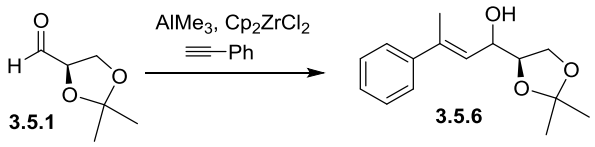


3.4.3a **3.4.3**

Compound 3.4.3. Compound **3.4.3a** (0.288 g, 0.845 mmol) was subjected to general procedure B and C. Purification by flash chromatograph gave compound **3.4.3** (0.180 g, 74 %, R_f = 0.15 in 4:1 Hex:EtOAc) over two steps.

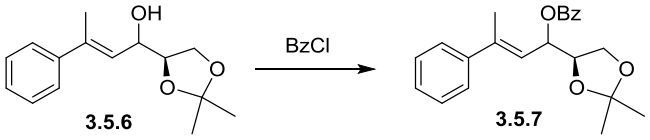
Spectral data for the mixture of diastereomers. IR (ATR): 3411, 3059, 3031, 2967, 2927, 2866, 1712, 1601, 1583, 1493, 1450, 1376, 1314, 1267, 1175, 1109, 1069, 1025, 710. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 8.5, 1.3 Hz, 4H), 7.55 (tt, *J* = 7.4, 1.2 Hz, 2H), 7.44 (t, *J* = 8.0, 4H), 7.41 (dd, *J* = 7.6, 1.6 Hz, 4H), 7.32 (t, *J* = 7.8, 4H), 7.26 (tt, *J* = 7.2, 1.4 Hz, 2H), 5.95 (dt, *J* = 6.9, 6.7 Hz, 1H) 5.94 (dt, *J* = 6.9, 6.7 Hz, 1H), 5.81 (dq, *J* = 9.0, 1.3 Hz, 2H), 3.88 (hex, *J* = 6.5 Hz, 2H), 2.22 (d, *J* = 1.4 Hz, 3H), 2.21 (d, *J* = 1.3 Hz, 3H), 2.05 (qt, *J* = 6.94, 5.49, 1H), 1.95 (dt, *J* =6.8, 6.4 Hz, 1H) 1.93 (dt, *J* = 6.7, 6.5 Hz, 1H), 1.83 (qt, *J* = 6.0, 3.9 Hz, 1H), 1.63-1.54 (m, 4H), 1.23 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.08, 166.03, 142.72, 142.70, 139.39, 139.32, 133.63, 132.86, 132.85, 130.60, 130.17, 129.62, 128.48, 128.33, 128.25,

127.49, 127.47, 126.16, 126.14, 125.96, 72.28, 72.15, 67.93, 67.88, 34.70, 34.56, 31.42, 31.31, 23.70, 23.67, 16.71.



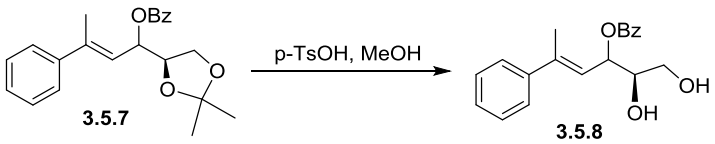
Compound 3.5.6. Compound **3.5.1** (0.500 g, 3.8 mmol) was subjected to general procedure **A**. Purification by flash chromatography gave **3.5.6** (0.586 g, 50 %, R_f = 0.66 in 1:1 Hex:EtOAc) as a mixture of diastereomers (d.r = 74:26).

Spectral data for the major diastereomers. IR (ATR): 3450, 3060, 3034, 2990, 2800, 1665, 1601, 1585, 1501, 1453, 1386, 1310, 1076, 853. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.33 (t, *J* = 7.1 Hz, 2H), 7.27 (tt, *J* = 7.2, 1.4 Hz, 1H), 5.68 (dq, *J* = 8.5, 1.4 Hz, 1H), 4.73 (ddd, *J* = 8.4, 3.9, 2.9 Hz, 1H), 4.20 (td, *J* = 6.9, 4.1 Hz, 1H) 4.02 (dd, *J* = 8.2, 6.6 Hz, 1H), 4.00 (dd, 8.4, 8.2 Hz, 1H), 2.14 (d, *J* = 1.3 Hz, 3H), 1.48 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.57, 139.96, 128.29, 127.55, 125.93, 125.89, 125.05, 109.28, 78.14, 68.35, 64.70, 26.45, 25.22, 16.78.



Compound 3.5.7. Compound **3.5.6** (0.586 g, 2.35 mmol) was subjected to general procedure **B**. Purification by flash chromatograph gave compound **3.5.7** (0.833 g, 100 %, R_f = 0.51 in 4:1 Hex:EtOAc).

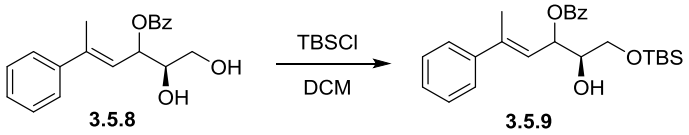
Spectral data for the major diastereomer. IR (ATR): 3509, 3061, 3032, 2986, 2954, 2928, 2883, 2857, 1716, 1600, 1584, 1493, 1450, 1380, 1370, 1315, 1264, 1211, 1107, 1068, 1025, 710. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.56 (tt, *J* = 7.5, 1.4 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 2H), 7.42 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.32 (t, *J* = 7.0 Hz, 2H), 7.27 (tt, *J* = 7.2, 1.4 Hz, 1H), 6.04 dd, *J* = 9.2, 4.6 Hz, 1H), 5.78 (dq, *J* = 9.2, 1.3 Hz, 1H), 4.41 (td, *J* = 6.5, 4.7 Hz, 1H), 4.17 (dd, *J* = 8.4, 6.6 Hz, 1H), 4.04 (dd, *J* = 8.4, 6.3 Hz, 1H), 2.26 (d, *J* = 1.4 Hz, 3H), 1.41 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.68, 142.43, 141.88, 133.04, 130.59, 129.76, 128.89, 128.39, 128.27, 127.70, 126.01, 121.73, 71.51, 65.75, 26.41, 25.31, 16.97.



3.5.7 3.5.8

Compound 3.5.8. To a round bottom flask open to air filled with Methanol (8.5 mL) and **3.5.7** (0.300 g, 0.851 mmol) was added p-Toluenesulfonic acid (0.404 g, 2.128 mmol). The reaction was stirred for 5 min, quenched with aq. $NaHCO_3$, and extracted with DCM (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave **3.5.8** (0.223 g, 83 %, R_f = 0.25 in 1:1 Hex:EtOAc).

Spectral data for the major of diastereomer. IR (ATR): 3389, 3061, 3032, 2926, 2881, 1712, 1600, 1583, 1493, 1450, 1382, 1265, 1176, 1111, 1068, 1025, 907, 710. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.59 (tt, *J* = 7.4, 1.4 Hz, 1H), 7.47 (t, *J* = 8.1 Hz, 2H), 7.45 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.35 (t, *J* = 7.0 Hz, 2H), 7.30 (tt, *J* = 7.15, 1.4 Hz, 1H), 5.99 (dd, *J* = 9.3, 5.8 Hz, 1H), 5.94 (dq, *J* = 9.1, 1.3 Hz, 1H) 4.03 (td, *J* = 5.9, 3.2 Hz, 1H), 3.85 (dd, *J* = 11.7, 3.3 Hz, 1H), 3.76 (dd, *J* = 11.7, 6.1 Hz, 1H), 2.26 (d, *J* = 1.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.22, 142.54, 142.26, 133.30, 129.75, 128.45, 128.29, 127.80, 125.97, 121.93, 73.59, 72.10, 62.78, 16.95.

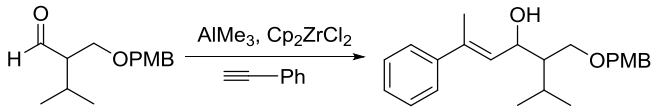


3.5.8 3.5.9

Compound 3.5.9. To a schlenk flask containing DCM (3.2 mL) and imidazole (0.054g, 0.800 mmol) at 0 °C was added compound **3.5.8** (0.100, 0.320mmol). TBSCl (0.053g, 0.352 mmol) in DCM (1.0mL) was then added dropwise. The reaction was quenched with aq. NH_4Cl (10 mL) and extracted with DCM (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave **3.5.9** (0.99 g, 72%, R_f. = 0.42 in 4:1 Hex:EtoAc) as a clear and colorless oil.

Spectral data for the major diastereomer. IR (ATR): 3471, 3061, 3032, 2953, 2927, 2856, 1716, 1601, 1584, 1493, 1450, 1315, 1258, 1097, 937, 834, 733. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.56 (tt, *J* = 7.5, 1.4 Hz, 1H), 7.44 (t, *J* = 8.2 Hz, 2H), 7.43 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.32 (tt, *J* = 7.1, 1.4 Hz, 2H), 7.28 (tt, *J* = 4.5, 1.4 Hz, 1H), 5.99 (dd, *J* = 9.4, 5.8 Hz, 1H), 5.93 (dq, *J* = 9.4, 1.3 Hz, 1H) 4.04 (dq, *J*

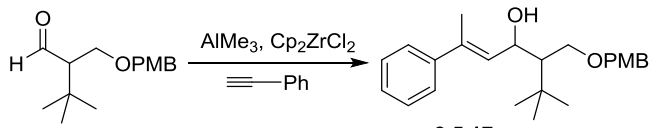
= 6.1, 4.6 Hz, 1H), 3.80 (dd, *J* = 10.2, 4.5 Hz, 1H), 3.73 (dd, *J* = 10.2, 6.3 Hz, 1H), 2.58 (d, *J* = 4.5, OH), 2.26 (d, *J* = 1.3 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.65, 142.64, 141.80, 132.99, 130.29, 129.67, 128.35, 128.20, 127.56, 126.02, 122.05, 73.36, 72.15, 63.35, 25.83, 16.88, -5.44.



3.5.2 **3.5.16**

Compound 3.5.16. Compound **3.5.2** (0.346 g, 1.46 mmol) was subjected to general procedure **A**. Purification by flash chromatography gave 3.5.16 (0.392 g, 75 %, R_f = 0.34 in 4:1 Hex:EtOAc) as a mixture of diastereomers (d.r = 91:9).

Spectral data for the major diastereomer. IR (ATR): 3456, 3080, 3055, 3028, 2956, 2870, 1611, 1585, 1512, 1443, 1418, 1366, 1301, 1246, 1173, 1079, 1032, 987, 909, 819, 757,732,696. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 8.6, 1.4 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.27 (dd, *J* = 8.7, 2.1 Hz, 2H), 7.25 (tt, *J* = 7.3, 2.2 Hz, 1H), 6.89 (dt, *J* = 8.7, 2.1 Hz, 2H), 5.81 (dq, *J* = 8.5, 1.3 Hz, 1H), 4.72 (dt, *J* = 8.6, 5.8 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 3.81 (s, 3H), 3.79 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.68 (dd, *J* = 9.5, 5.7 Hz, 1H), 2.06 (d, *J* = 1.3 Hz, 3H), 2.04 (hex, *J* = 6.8 Hz, 1H), 1.47 (qd, *J* = 6.0, 3.0 Hz, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.34, 143.20, 135.77, 131.06, 129.69, 129.47, 128.13, 126.98, 125.82, 113.86, 73.24, 70.87, 69.43, 55.25, 50.01, 26.35, 21.52, 19.25, 16.12.

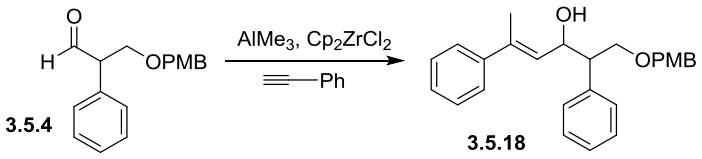


3.5.3 **3.5.17**

Compound 3.5.17. Compound **3.5.2** (0.387 g, 1.54 mmol) was subjected to general procedure **A**. Purification by flash chromatography gave **3.5.17** (0.175 g, 30 %, R_f = 0.43 in 4:1 Hex:EtOAc) as a mixture of diastereomers (d.r = 77:23).

Spectral data for the major diastereomer. IR (ATR): 3445, 3080, 3056, 3027, 2954, 2868, 1611, 1586, 1512, 1493, 1464, 1443, 1363, 1301, 1246, 1206, 1075, 1034, 986, 819, 757, 696. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 8.3, 1.7 Hz, 2H) 7.30 (t, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.24 (tt, *J* = 6.0, 1.6 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.98 (dq, *J* = 8.3, 1.4 Hz, 1H), 4.89 (td, *J* = 8.3, 2.5 Hz, 1H), 4.46 (d, *J* = 11.4 Hz,

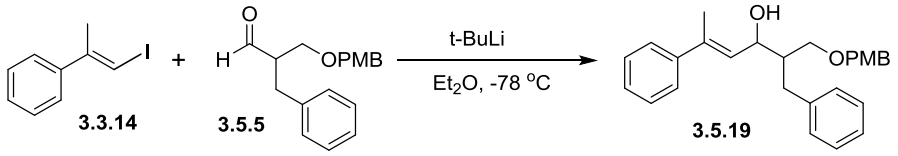
1H) 4.42 (d, *J* = 11.4 Hz, 1H), 3.83 (dd, *J* = 4.1, 1.5 Hz, 2H), 3.80 (s, 3H), 3.32 (d, *J* = 8.3 Hz, 1H), 2.05 (d, *J* = 1.3 Hz, 3H), 1.42 (td, *J* = 4.2, 2.6 Hz, 1H), 1.10 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.26, 143.33, 133.83, 132.89, 129.81, 129.45, 128.10, 126.85, 125.81, 113.81, 73.19, 69.71, 68.84, 55.23, 52.86, 33.39, 29.26, 15.95.



3.5.4 **3.5.18**

Compound 3.5.18. Compound **3.5.4** (0.113 g, 0.42 mmol) was subjected to general procedure **A**. Purification by flash chromatography gave **3.5.18** (0.097 g, 59 %, R_f = 0.19 in 4:1 Hex:EtOAc) as a mixture of diastereomers (d.r = 98:2).

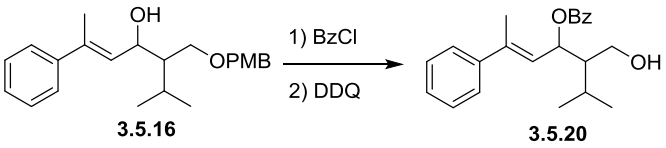
Spectral data for the major diastereomer. IR (ATR): 3419, 3082, 3059, 3028, 2999, 2915, 2858, 1611, 1585, 1512, 1493, 1452, 1362, 1301, 1246, 1173, 1076, 1030, 908, 819, 730, 697. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.27 (m, 2H), 7.26 (d, *J* = 8.7 Hz, 2H) 7.24-7.15 (m, 8H), 6.88 (d, *J* = 8.7, 2H), 5.60 (dq, *J* = 8.9, 1.4 Hz, 1H), 4.88 (td, 8.6, 3.0 Hz, 1H) 4.55 (d, *J* = 11.6 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 3.99 (dd, *J* = 9.4, 8.3 Hz, 1H), 3.88 (dd, *J* = 9.4, 4.7 Hz, 1H), 3.81 (s, 3H), 3.45 (d, *J* = 3.1 Hz, OH), 3.14 (td, *J* = 8.1, 4.6 Hz, 1H), 1.82 (d, *J* = 1.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.35, 143.37, 139.37, 137.61, 129.65, 129.44, 129.06, 128.65, 128.30, 128.03, 126.97, 126.89, 125.90, 113.89, 73.23, 73.11, 72.64, 55.28, 51.75, 16.40.



3.3.14 **3.5.5** **3.5.19**

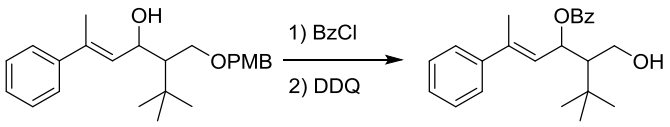
Compound 3.5.19. To a Schleck flask containing ether (3.5 mL) and t-BuLi (1.7 M, 0.905 mL, 1.54 mL) at -78 ^{0}C was added vinyl iodide **3.3.14** (0.171 g, 0.702 mmol) dropwise. The solution was stirred for 10 min at -78 ^{0}C and **3.5.5** (0.100 g, 0.351 mmol) was added dropwise. The reaction was stirred for 1 hour at -78 ^{0}C before being brought to room temperature for 30 min. The reaction was quenched with aq. NH_4Cl (30 mL), and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave **3.5.19** (0.051 g, 36 %, R_f = 0.22 in 4:1 Hex:EtOAc) as a mixture of diastereomers (d.r = 50:50).

Spectral data for the mixture of diastereomers. IR (ATR):3430, 3034, 2917, 2849, 1600, 1594, 1493, 1454, 1442, 1382, 1333, 1244, 1201, 1160, 1033, 968, 919, 836, 745, 687. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.33 (m, 6H), 7.33-7.28 (m, 4H), 7.28-7.24 (m, 8H), 7.23-7.14 (m, 6H), 6.89 (d, *J* = 8.7 Hz, 4H), 5.89 (dq, *J* = 8.9, 1.4 Hz, 1H) 5.87 (dq, *J* = 8.6, 1.3 Hz, 1H), 4.75 (dd, *J* = 8.9, 3.8 Hz, 1H), 4.60 (t, *J* = 7.3 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.41 (d, *J* = 11.5 Hz, 2H), 4.36 (d, *J* = 11.5 Hz, 1H), 3.81 (s, 6H), 3.71 (dd, *J* = 9.4, 3.5 Hz, 1H), 3.51 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.48 (dd, *J* = 9.7, 4.2 Hz, 1H), 3.46 (dd, *J* = 9.4, 5.2 Hz, 1H), 3.26 (br, OH), 3.10 (br, OH), 2.93 (dd, *J* = 13.7, 5.8 Hz, 1H), 2.83 (dd, *J* = 13.7, 5.3 Hz, 1H), 2.70 (dd, *J* = 9.5, 3.5 Hz, 1H) 2.67 (dd, *J* = 9.5, 3.9 Hz, 1H), 2.27 (dtt, *J* = 9.7, 5.8, 4.1 Hz, 1H), 2.08 (d, *J* = 1.4 Hz, 3H), 2.05 (m, 1H), 2.02 (d, *J* = 1.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.30, 159.28, 143.17, 143.09, 140.33, 140.29, 137.46, 136.81, 130.04, 129.86, 129.81, 129.47, 129.43, 129.10, 129.07, 128.36, 128.32, 128.30, 128.18, 128.15, 127.15, 127.10, 125.97, 125.92, 125.86, 125.83, 113.82, 73.12, 73.10, 71.23, 71.22, 70.48, 70.12, 55.23, 46.39, 46.36, 34.74, 32.93, 16.48, 16.27.



3.5.16 **3.5.20**

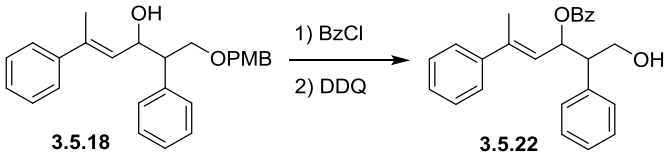
Compound 3.5.20. Compound **3.5.16** (0.392 g, 1.11 mmol) was subjected to general procedure **B** and **C**. Purification by flash chromatograph gave **3.5.20** (0.281 g, 75 %, R_f = 0.50 in 4:1 Hex:EtOAc) over two steps. *Spectral data for the major diastereomer*. IR (ATR): 3459, 3083, 3060, 3080, 2958, 2930, 2884, 1712, 1600, 1583, 1493, 1450, 1387, 1314, 1266, 1176, 1109, 1069, 1025, 920, 710. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.5, 1.3 Hz, 2H), 7.57 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.45 (tt, *J* = 7.9, 1.5 Hz, 2H), 7.41 (dd, *J* = 7.4, 1.5 Hz, 2H), 7.32 (t, *J* = 7.1 Hz, 2H), 7.27 (tt, *J* = 7.3, 1.3 Hz, 1H), 6.19 (dd, *J* = 9.3, 6.7 Hz, 1H), 5.90 (dq, *J* = 9.3, 1.3 Hz, 1H), 3.90 (dd, *J* = 4.5, 3.7 Hz, 2H), 2.26 (d, *J* = 1.4 Hz, 3H), 2.00 (hd, *J* = 6.9, 5.1 Hz, 1H), 1.79 (dtd, *J* = 6.7, 5.0, 4.1 Hz, 1H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.06, 142.67, 139.70, 133.07, 130.29, 129.57, 128.48, 128.26, 127.53, 125.95, 125.46, 73.06, 60.79, 51.30, 27.00, 21.42, 19.50, 16.69.



3.5.17 **3.5.21**

Compound 3.5.21. Compound **3.5.17** (0.144 g, 0.391 mmol) was subjected to general procedure **B** and **C**. Purification by flash chromatograph gave alcohol **3.5.21** (0.060 g, 42 %, R_f = 0.35 in 4:1 Hex:EtOAc) over two steps.

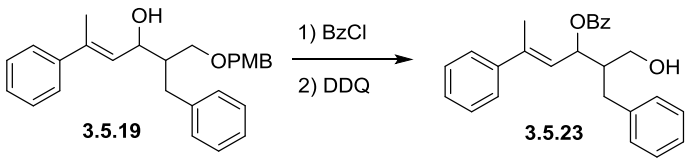
Spectral data for the major diastereomer. IR (ATR): 3459, 3059, 3030, 2958, 2873, 1713, 1600, 1583, 1493, 1476, 1450, 1367, 1269, 1175, 1110, 1040, 910, 711. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.56 (tt, *J* = 7.0, 1.3 Hz, 1H), 7.45 (tt, *J* = 7.7, 1.5 Hz, 2H), 7.40 (dd, *J* = 7.0 Hz, 1.5 Hz, 2H), 7.30 (tt, *J* = 7.1, 1.5 Hz, 2H), 7.24 (tt, *J* = 7.1, 1.3 Hz, 1H), 6.33 (dd, *J* = 9.0, 2.2 Hz, 1H), 6.06 (dq, *J* = 9.0, 1.4 Hz, 1H), 4.18 (dd, *J* = 11.7, 6.1 Hz, 1H), 4.08 (dd, *J* = 11.7, 4.1 Hz, 1H), 2.27 (d, *J* = 1.4 Hz, 3H), 1.72 (ddd, *J* = 6.2, 4.1, 2.2 Hz, 1H) 1.08 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.60, 142.74, 137.24, 132.99, 130.44, 129.47, 128.47, 128.19, 127.33, 127.10, 125.93, 72.25, 60.94, 55.52, 33.20, 28.82, 16.51.



3.5.18 **3.5.22**

Compound 3.5.22. Compound **3.5.18** (0.097 g, 0.249 mmol) was subjected to general procedure **B** and **C**. Purification by flash chromatograph gave **3.5.22** (0.065 g, 83 % based on 92% conversion, R_f = 0.37 in 4:1 Hex:EtOAc) over two steps.

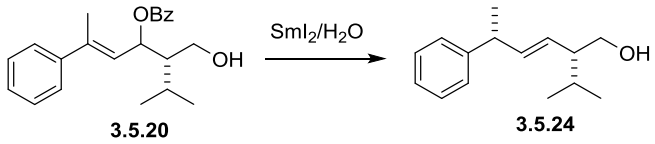
Spectral data for the major diastereomer. IR (ATR): 3460, 3083, 3060, 3029, 2923, 1713, 1600, 1583, 1511, 1493, 1450, 1315, 1266, 1109, 1068, 1025, 907, 710. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.3, 1.2, 2H), 7.49 (tt, 7.0, 1.2 Hz, 1H), 7.37 (tt, *J* = 7.9, 1.5 Hz, 2H), 7.25 (dd, *J* = 4.2, 1.0 Hz, 4H), 7.19-7.16 (m, 2H), 7.16-7.12 (m, 2H), 7.12-7.09 (m, 2H), 6.17 (t, *J* = 9.0 Hz, 1H), 5.56 (dq, *J* = 9.5, 1.4 Hz, 1H), 3.97 (d, *J* = 5.9 Hz, 2H), 3.26 (dt, *J* = 8.7, 5.9 Hz, 1H), 1.93 (d, *J* = 1.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.14, 142.79, 140.52, 138.28, 133.10, 130.13, 129.68, 129.05, 128.56, 128.41, 128.10, 127.38, 127.36, 125.92, 124.40, 72.63, 63.45, 53.03, 16.76.



3.5.19 3.5.23

Compound 3.5.23. Compound **3.5.19** (0.102 g, 0.254 mmol) was subjected to general procedure **B** and **C**. Purification by flash chromatograph gave **3.5.23** (0.081 g, 82 %, R_f = 0.32 in 4:1 Hex:EtOAc) over two steps.

Spectral data for the mixture of diastereomers. IR (ATR): 3467, 3104, 3083, 3061, 3026, 2926, 1713, 1600, 1583, 1493, 1450, 1373, 1314, 1266, 1175, 1111, 1068, 1025, 909, 758, 733, 711. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 8.2, 1.2 Hz, 2H), 8.06 (dd, *J* = 8.1, 1.2 Hz, 2H) 7.59 (m, 1H), 7.58 (m, 1H) 7.47 (t, *J* = 7.6 Hz, 4H), 7.44-7.40 (m, 2H), 7.40-7.32 (m, 6H), 7.32-7.27 (m, 6H), 7.26-7.19 (m, 6H), 6.23 (dd, *J* = 8.9, 4.8 Hz, 1H), 6.10 (dd, *J* = 9.4, 7.6 Hz, 1H), 5.97 (dq, *J* = 6.1, 1.3 Hz, 1H) 5.95 (dq, *J* = 6.5, 1.3 Hz, 1H), 3.71 (dd, *J* = 11.7, 3.5 Hz, 1H), 3.66 (dd, *J* = 11.5, 4.6 Hz, 1H), 3.61-3.55 (m, 2H), 3.05 (dd, *J* = 14.0, 4.9 Hz, 1H), 2.87 (dd, *J* = 13.6, 5.1 Hz, 1H), 2.80 (dd, *J* = 13.6, 9.8 Hz, 1H), 2.69 (dd, *J* = 14.0, 9.5 Hz, 1H), 2.39 (ddq, *J* = 9.6, 7.2, 4.8, 1H), 2.24 (m, 1H), 2.23 (d, *J* = 1.4 Hz, 3H), 2.21 (d, *J* = 1.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.46, 166.45, 142.66, 142.64, 140.96, 139.94, 139.92, 139.91, 133.14, 133.11, 130.16, 130.10, 129.71, 129.69, 129.19, 128.97, 128.53, 128.49, 128.43, 128.29, 128.26, 127.63, 127.54, 126.18, 125.99, 125.93, 124.47, 124.32, 72.31, 61.79, 60.15, 48.05, 47.63, 33.17, 33.04, 16.86, 16.72.

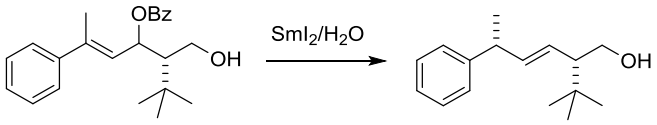


3.5.20 3.5.24

Compound 3.5.24. Compound 3.5.20 (0.050 g, 0.147 mmol) was subjected to general procedure **D**. Purification by flash chromatograph over silica gave **3.5.24** (0.026 g, 80 %, R_f = 0.37 in 4:1 Hex:EtOAc) as a mixture of diastereomers (d.r. = 83:17)

Spectral data for the major diastereomer. IR (ATR): 3352, 3056, 2959, 2926, 2870, 1600, 1580, 1492, 1451, 1367, 1303, 1208, 1108, 1031, 908, 732, 699. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.5 Hz, 2H), 7.22 (dd, *J* = 6.6, 1.6 Hz, 2H), 7.20 (tt, *J* = 6.7, 1.3 Hz, 1H), 5.76 (ddd, *J* = 15.4, 6.7, 0.7 Hz, 1H), 5.28 (ddd, *J* = 15.4, 9.5, 1.4 Hz, 1H), 3.65 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.51 (p, *J* = 6.9 Hz, 1H), 3.41 (dd, *J* = 10.5, 9.0 Hz,

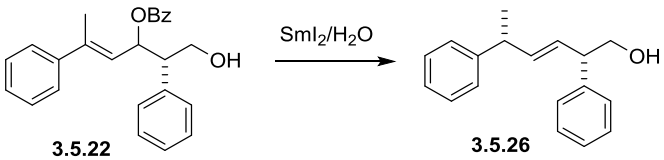
1H), 2.00 (tdd, *J* = 9.6, 6.9, 5.3 Hz, 1H), 1.67 (o, *J* = 6.7 Hz, 1H), 1.38 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.01, 139.51, 128.45, 128.05, 127.04, 126.06, 64.15, 52.46, 42.47, 28.89, 21.54, 20.86, 19.65.



3.5.21 **3.5.25**

Compound 3.5.25. Compound **3.5.21** (0.075 g, 0.212 mmol) was subjected to general procedure **D**. Purification by flash chromatograph over silica gave **3.5.25** (0.027 g, 83 %, R_f = 0.33 in 4:1 Hex:EtOAc) as a mixture of diastereomers (d.r. = 80:20)

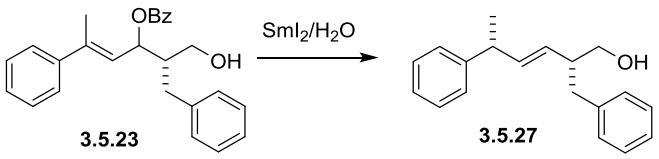
Spectral data for the major diastereomer. IR (ATR): 3436, 3055, 2963, 2873, 1599, 1597, 1512, 1441, 1365, 1255, 1108, 1032, 909, 732. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.65 Hz, 2H), 7.23-7.17 (m, 3H), 5.78 (ddd, *J* = 15.3, 6.8, 0.6 Hz, 1H), 5.36 (ddd, *J* = 15.3, 9.9, 1.4 Hz, 1H), 3.74 (dd, *J* = 10.3, 3.8 Hz, 1H), 3.53 (p, *J* = 6.8 Hz, 1H), 3.36 (t, *J* = 10.3 Hz, 1H), 1.95 (td, *J* = 10.3, 4.0 Hz, 1H), 1.38 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.99, 140.50, 128.51, 127.52, 127.01, 126.12, 61.84, 56.49, 42.55, 32.07, 28.08, 21.54.



3.5.22 **3.5.26**

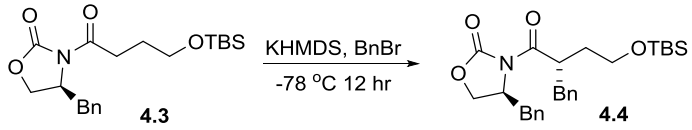
Compound 3.5.26. Compound **3.5.22** (0.066 g, 0.176 mmol) was subjected to general procedure **D**. Purification by flash chromatograph over silica gave **3.5.26** (0.012 g, 80 %, R_f = 0.28 in 4:1 Hex:EtOAc) as a mixture of diastereomers (d.r. = 73:27).

Spectral data for the major diastereomer. IR: 3427, 3026, 2924, 1601, 1492, 1451, 1271, 1031, 758. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.26-7.17 (m, 6H), 5.82 (ddd, *J* = 15.6, 6.7, 0.88 Hz, 1H), 5.66 (ddd, *J* = 15.4, 8.0, 1.3 Hz, 1H), 3.87 (m, 1H), 3.77 (p, *J* = 8.15, 2H), 3.51 (q, *J* = 7.5 Hz, 1H). 1.36 (d, *J* = 7.1 Hz, 3H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.13, 128.73, 128.48, 127.90, 127.12, 126.83, 126.15, 66.51, 51.46, 42.38, 21.40.



Compound 3.5.27. Compound **3.5.23** (0.050 g, 0.147 mmol) was subjected to general procedure **D**. Purification by flash chromatograph over silica gave **3.5.27** (0.030 g, 82 %, R_f = 0.37 in 4:1 Hex:EtOAc) as a mixture of diastereomers (d.r. = 81:19).

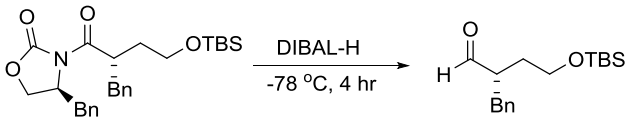
Spectral data for the major diastereomer. IR (ATR): 3352, 3056, 3026, 2964, 2925, 2869, 1600, 1580, 1493, 1452, 1424, 1303, 1208, 1108, 1031, 973, 840, 800, 700. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.1 Hz, 2H), 7.24 (t, *J* = 7.7 Hz, 2H) 7.21 (tt, *J* = 6.2, 2.1 Hz, 1H), 7.19-7.08 (m, 3H), 7.03 (d, *J* = 7.3 Hz, 2H), 5.64 (ddd, *J* = 15.5, 6.4, 0.8 Hz, 1H), 5.31 (ddd, *J* = 15.4, 8.4, 1.4 Hz, 1H), 3.61 (dd, *J* = 10.5, 4.9 Hz, 1H), 3.48 (dd, *J* = 10.5 Hz, 7.5 Hz, 1H), 3.42 (p, *J* = 6.5 Hz, 1H), 2.80 (dd, *J* = 13.1, 6.0 Hz, 1H), 2.60 (dd, *J* = 13.2 Hz, 8.4 Hz, 1H), 2.54 (dtd, *J* = 13.8 Hz, 7.8, 5.0 Hz, 1H), 1.28 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.83, 139.81, 138.48, 129.25, 129.00, 128.36, 128.23, 127.09, 126.01, 125.92, 65.44, 47.45, 42.14, 37.88, 21.31.



Compound 4.4. To a schlenk flask containing oxazolidinone **4.3** (1.56 g, 4.14 mmol) in THF (20.73 mL) at -78 ^{0}C was added KHMDS (1 M in THF, 9.94 mL, 9.94 mmol) dropwise. The reaction was stirred at -78 ^{0}C for 1 hr before freshly distilled Benzyl Bromide (1.22 mL, 9.94 mmol) was added dropwise. The reaction was stirred for 12 hours at -78 ^{0}C, quenched with aq. NH_4Cl, and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave **4.4** (1.01 g, 52 %, R_f. = 0.51 in 4:1 Hex:EtoAc) as a clear and colorless oil.

IR (ATR): 3087, 3064, 3028, 2953, 2927, 2855, 1778, 1697, 1603, 1496, 1384, 1348, 1248, 1205, 1098, 1029, 834, 775, 732, 699. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.4 Hz, 4H), 7.25 (d, *J* = 7.0 Hz, 2H), 7.19 (tt, *J* = 5.9, 2.0 Hz, 2H), 7.07 (d, *J* = 6.8 Hz, 2H) 4.61 (ddt, *J* = 9.7, 7.8, 3.1, 1H), 4.35 (ddd, *J* = 7.7,

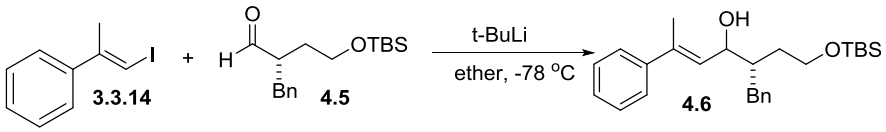
4.6, 4.4 Hz, 1H) 4.09 (ddd, *J* = 8.6, 7.9, 0.8, 1H) 4.04, (dd, *J* = 9.0, 2.9 Hz, 1H), 3.65 (dd, *J* = 5.9, 1.2 Hz, 1H), 3.64 (d, *J* = 5.9 Hz, 1H), 3.07 (dd, *J* = 13.3, 7.8 Hz, 1H) 3.02 (dd, *J* = 13.5, 3.5 Hz, 1H) 2.80 (dd, *J* = 13.3, 7.5 Hz, 1H), 2.36 (dd, *J* = 13.5, 9.7 Hz, 1H) 2.05 (ddt, *J* = 13.6, 9.1, 6.5 Hz, 1H), 1.71 (dtd, *J* = 13.7, 5.8, 4.3 Hz 1H), 0.85 (s, 9H), -0.01 (s, 3H), -0.02 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.83, 152.99, 138.79, 135.42, 130.12, 129.44, 129.34, 128.87, 128.56, 128.47, 128.31, 127.18, 126.42, 65.66, 61.41, 55.12, 41.71, 39.15, 37.67, 34.55, 25.93, 25.85, 18.27, -5.49, -5.50.



4.4 **4.5**

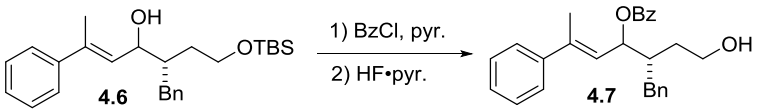
Compound 4.5. To a schlenk flask containing DCM (100 mL) and **4.4** (1.014 g, 2.17 mmol) at -78 ^{0}C was added DiBAl-H (1.15 mL, 6.50 mmol) dropwise. The reaction was stirred at -78 ^{0}C for 4 hr before being warmed to room temperature and quenched with 2M rochelle salt and stirred for 3 hours. The aqueous layer was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave **4.5** (0.358 g, 56 %, R_f. = 0.74 in 4:1 Hex:EtoAc) as a clear and colorless oil.

IR (ATR): 3087, 3064, 30282952, 2927, 2855, 2737, 2713, 1724, 1603, 1496, 1471, 1388, 1252, 1098, 1029, 987, 833, 809, 774, 730, 698. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (d, *J* = 2.1 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.20 (tt, *J* = 6.7, 1.3 Hz, 1H), 7.17 (d, *J* = 6.7 Hz, 2H), 3.67 (ddd, *J* = 10.3, 6.9, 5.1 Hz, 1H), 3.62 (ddd, *J* = 10.3, 6.7, 5.2 Hz, 1H), 3.04 (dd, *J* = 13.4, 6.3 Hz, 1H), 2.77 (dddt, *J* = 12.0, 7.6, 4.1, 2.0 Hz, 1H), 2.71 (dd, *J* = 13.4, 7.7, 1H), 1.89 (dddd, *J* = 14.5, 7.9, 6.7, 5.1 Hz, 1H) 1.72 (dddd, *J* = 14.3, 6.8, 5.2, 4.4 Hz, 1H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.15, 138.87, 128.99, 128.50, 126.35, 60.48, 50.68, 34.69, 31.75, 25.86, 18.22, -5.51.



Compound 4.6. To a Schleck flask containing ether (12.0 mL) and t-BuLi (1.7 M, 2.82 mL, 4.8 mmol) at -78 ^{0}C was added vinyl iodide **3.3.14** (0.190 g, 0.78 mmol) dropwise. The solution was stirred for 5 min at -78 ^{0}C, **4.5** (0.585g, 2.4 mmol) was added dropwise, and the reaction was stirred for 1 hour at -78 ^{0}C. The reaction was quenched at -78 ^{0}C with aq. NH_4Cl (30 mL), and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave **4.6** (0.394 g, 93 %, R_f = 0.44 in 4:1 Hex:EtOAc) as a mixture of diastereomers (d.r = 62:38)

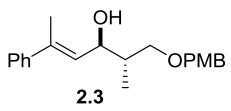
Spectral data for the mixture of diastereomers. IR (ATR): 3396, 3083, 3061, 3021, 2927, 2856, 1601, 1494, 1471, 1445, 1386, 1254, 1084, 1005, 908, 833, 775, 757, 730, 696, 664. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5, 2H), 7.40 (d *J* = 8.0 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.32-7.23 (m, 10H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.17 (t, *J* = 8.2 Hz, 2H), 5.95 (dq, *J* = 8.8, 1.3 Hz, 1H), 5.89 (dq, J = 8.7, 1.4 Hz, 1H), 4.61 (dt, *J* = 8.8, 4.4 Hz, 1H), 4.42 (dt, *J* = 8.7, 5.4 Hz, 1H), 3.80 – 3.73 (m, 2H), 3.62 – 3.56 (m, 2H), 3.55 (d, *J* = 5.2, OH), 3.49 (d, *J* = 5.3 Hz, OH), 2.89 (dd, *J* = 13.7, 6.0 Hz, 1H), 2.83 (dd, *J* = 13.9, 5.5 Hz, 1H), 2.54 (dd, *J* = 13.9, 9.3 Hz, 1H), 2.51 (dd, *J* = 13.7, 9.3 Hz, 1H), 2.21 (oct, *J* = 4.7 Hz, 1H), 2.08 (d, *J* = 1.3 Hz, 3H), 2.04 (m, 1H), 2.01 (d, *J* = 1.3 Hz, 3H), 1.80 (m, 1H), 1.75 (dtd, *J* = 15.3, 7.9, 4.4 Hz, 1H), 1.66 (m, 1H), 1.55 (ddt, *J* = 9.0, 6.5, 4.3 Hz, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.42, 143.35, 140.80, 140.78, 137.38, 136.93, 130.46, 129.13, 128.64, 128.33, 128.28, 128.17, 128.13, 127.09, 127.01, 125.89, 125.87, 125.84, 70.60, 70.53, 62.15, 61.21, 45.27, 45.24, 36.97, 36.87, 32.40, 31.98, 25.90, 25.89, 18.25, 16.59, 16.41, -5.43, -5.46, -5.48.



Compound 4.7. Compound **4.6** (0.394 g, 0.961 mmol) was subjected to general procedure **B**. The resulting crude mixture was dissolved in THF (10 mL) in a Teflon contained at 0 ^{0}C. HF·pyr (70%, 0.400 mL) was added dropwise and the reaction mixture was let to sit without stirring for 18 hours. The reaction

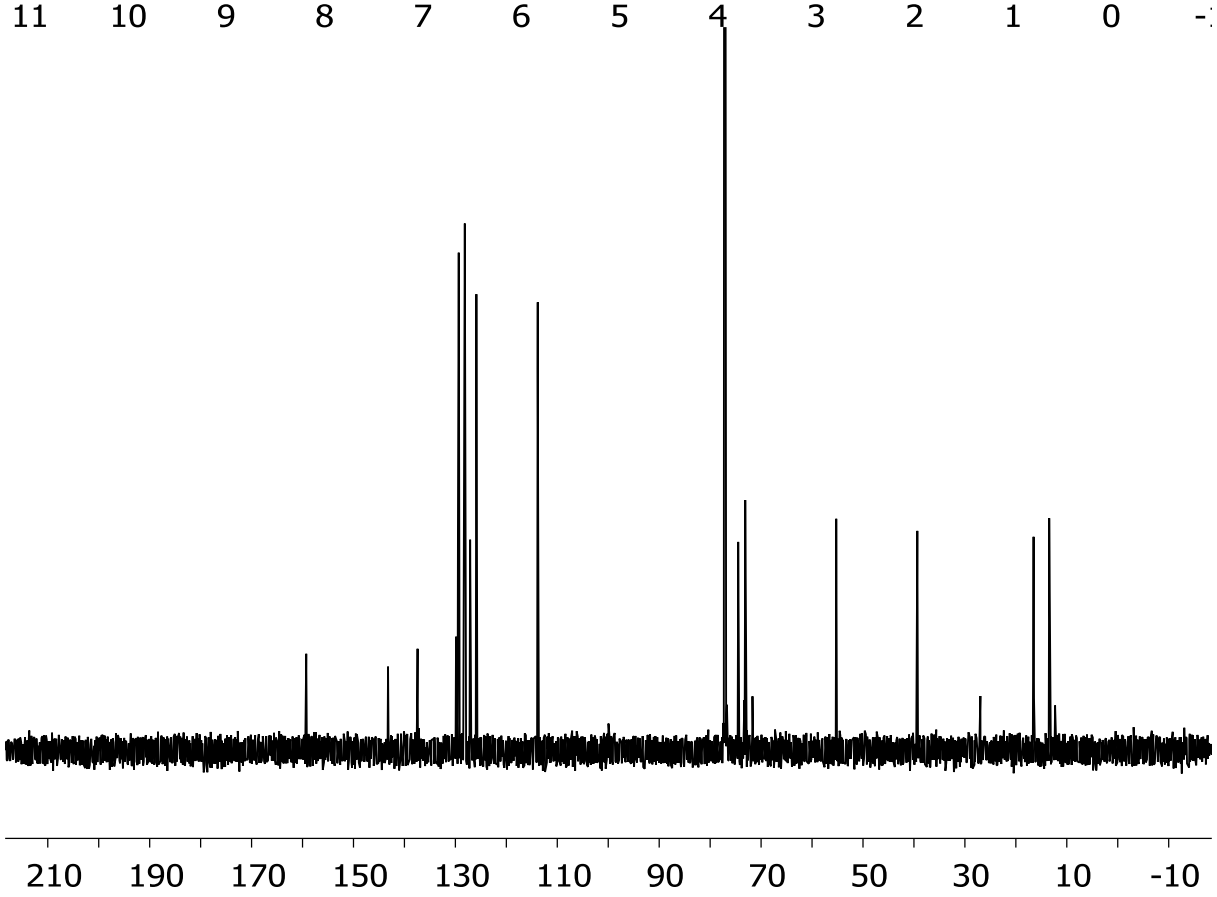
was quenched with aq. $NaHCO_3$, and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gave **4.7** (0.312 g, 81 % over two steps, R_f = 0.63 in 1:1 Hex:EtOAc).

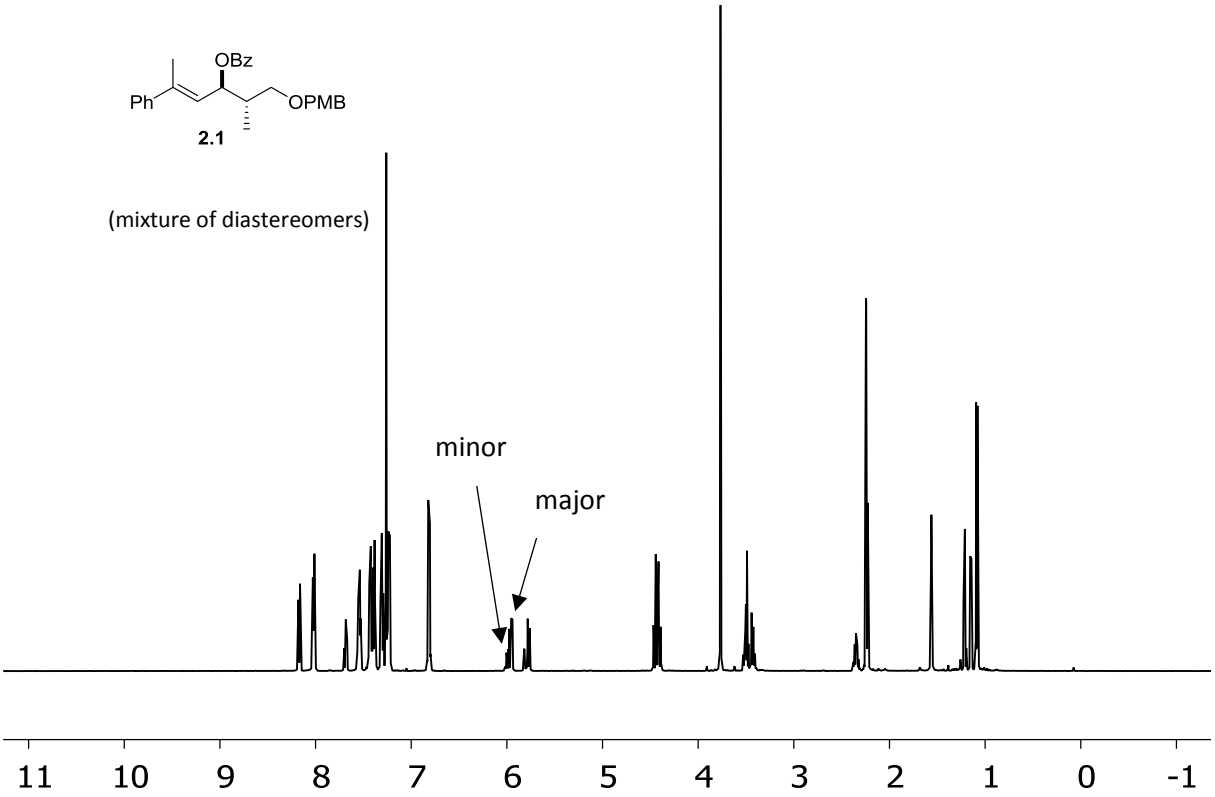
Spectral data for the mixture of diastereomers. IR (ATR): 3411, 3084, 3061, 3026, 2931, 2880, 1712, 1600, 1583, 1494, 1450, 1381, 1314, 1267, 1175, 1111, 1068, 1025, 907, 757, 730, 710, 696. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.0 Hz, 4H), 7.57 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.56 (tt, *J* = 7.4, 1.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 4H), 7.39 (t, *J* = 7.0 Hz, 4H), 7.35-7.27 (m, 10H), 7.24-7.18 (m, 6H), 6.01 (dd, *J* = 9.1, 4.7 Hz, 1H), 5.94 (dd, *J* = 9.2, 4.3 Hz, 1H), 5.91 (dq, *J* = 9.2, 1.4 Hz, 1H), 5.90 (dq, *J* = 9.2, 1.4 Hz, 1H), 3.71 (t, *J* = 6.8 Hz, 4H), 2.98 (dd, *J* = 14.0, 5.8 Hz, 1H), 2.97 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.70 (dd, *J* = 14.0, 8.5 Hz, 1H), 2.67 (dd, *J* = 13.7, 8.2 Hz, 1H), 2.45 (dddd, *J* = 12.6, 8.4, 6.2, 4.9 Hz, 1H), 2.36 (dddd, *J* = 12.5, 8.2, 6.2, 4.6 Hz, 1H), 2.19 (d, *J* = 1.3 Hz, 3H), 2.12 (d, *J* = 1.2 Hz, 3H), 1.88 (dq, *J* = 13.6, 6.8 Hz, 1H), 1.87 (dq, *J* = 13.0, 6.9 Hz, 1H), 1.76 (dq, *J* = 13.5, 6.5 Hz, 1H) 1.66 (dq, *J* = 13.2, 6.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.87, 142.82, 142.78, 140.52, 140.25, 140.13, 132.93, 132.92, 130.46, 129.61, 129.59, 129.10, 129.05, 128.50, 128.49, 128.38, 128.25, 128.23, 127.53, 127.49, 126.17, 125.97, 125.96, 124.23, 123.86, 73.88, 73.71, 61.17, 61.13, 42.22, 41.48, 37.08, 36.92, 32.94, 32.87, 16.86, 16.69.

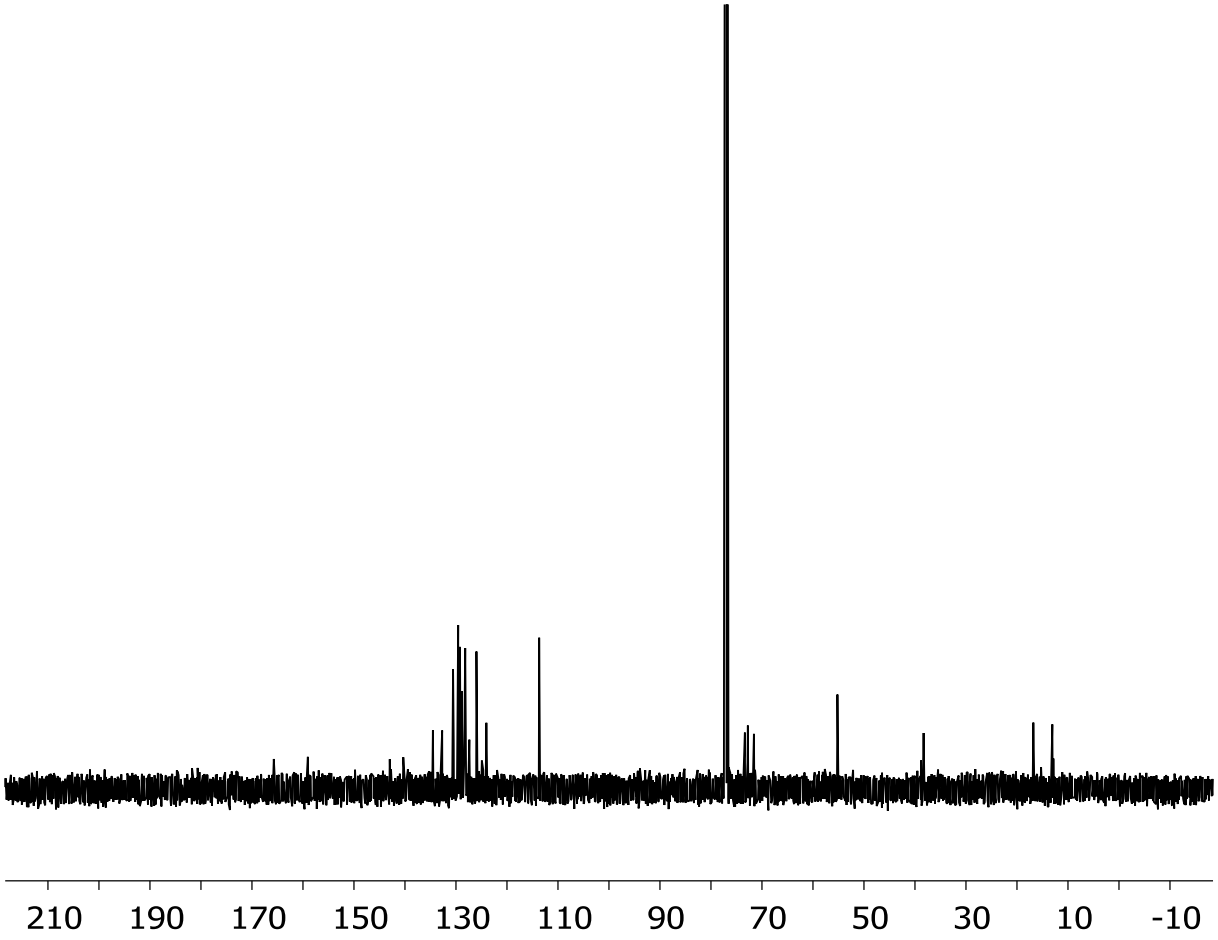


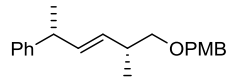
2.3

(mixture of diastereomers)



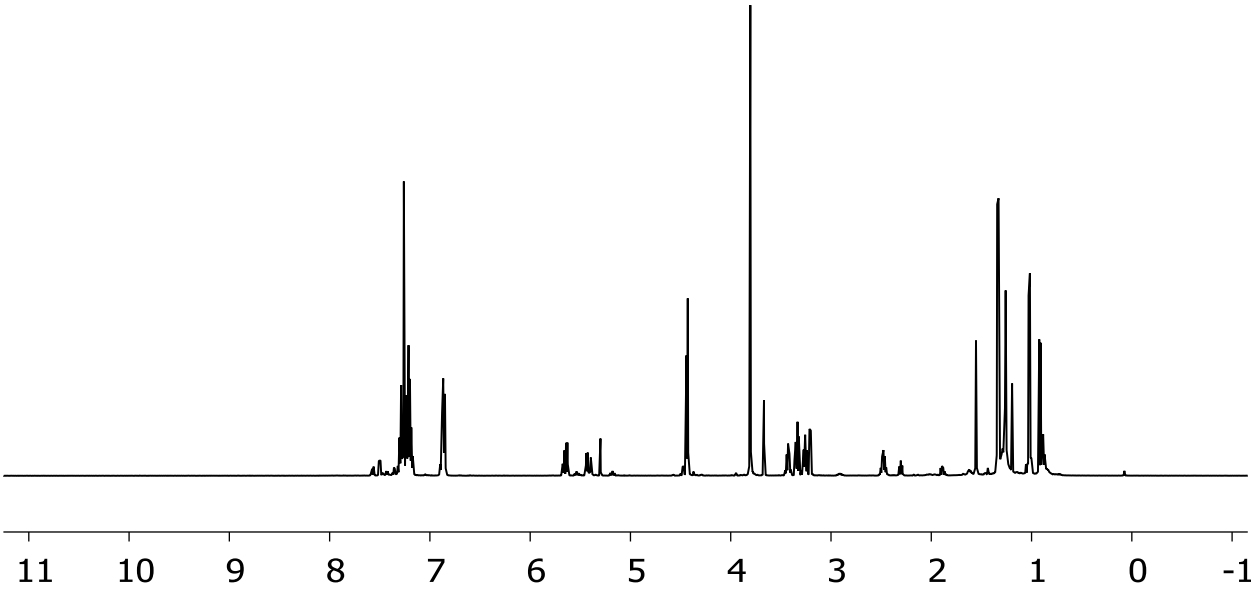

OBz
Ph
OPMB
2.1
(mixture of diastereomers)
minor
major
11
10
9
8
7
6
5
4
3
2
1
0
-1

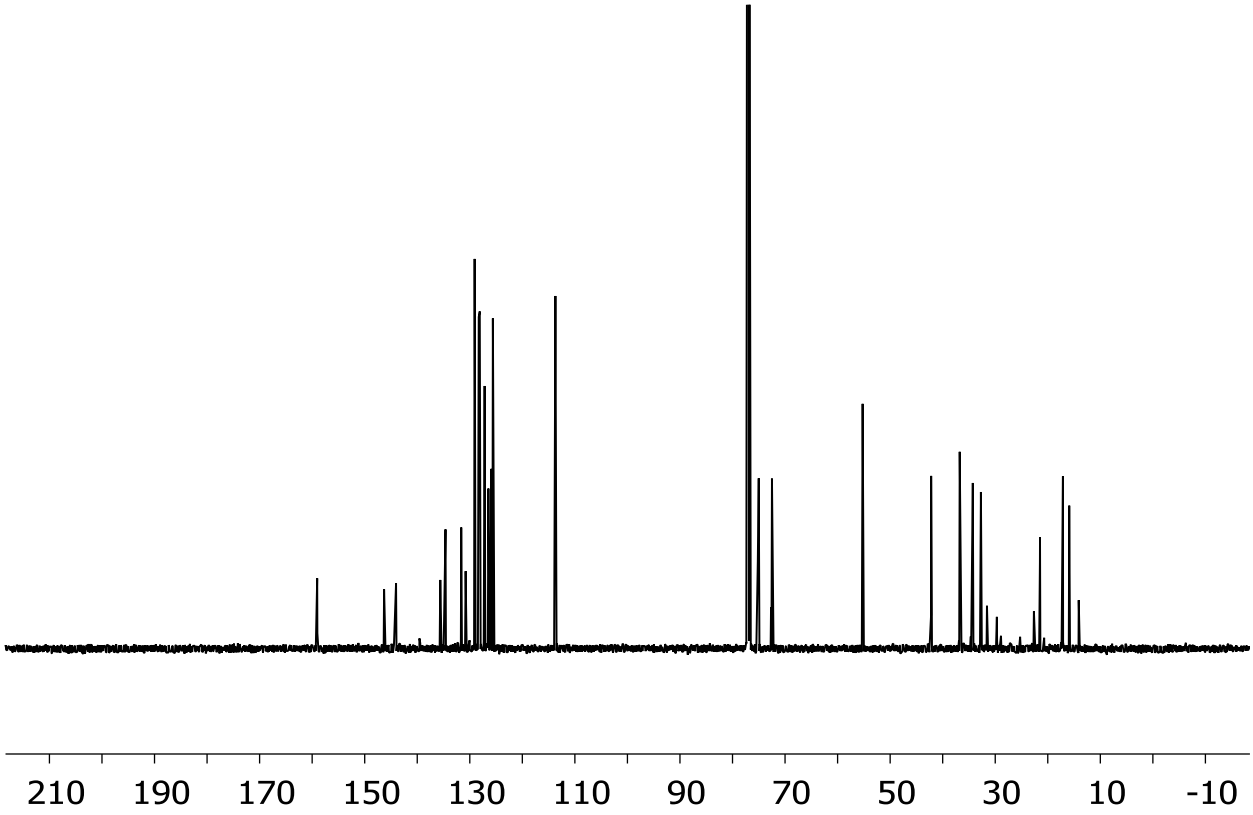

210
190
170
150
130
110
90
70
50
30
10
-10

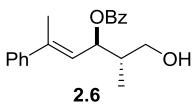


2.4

(mixture of diastereomers)

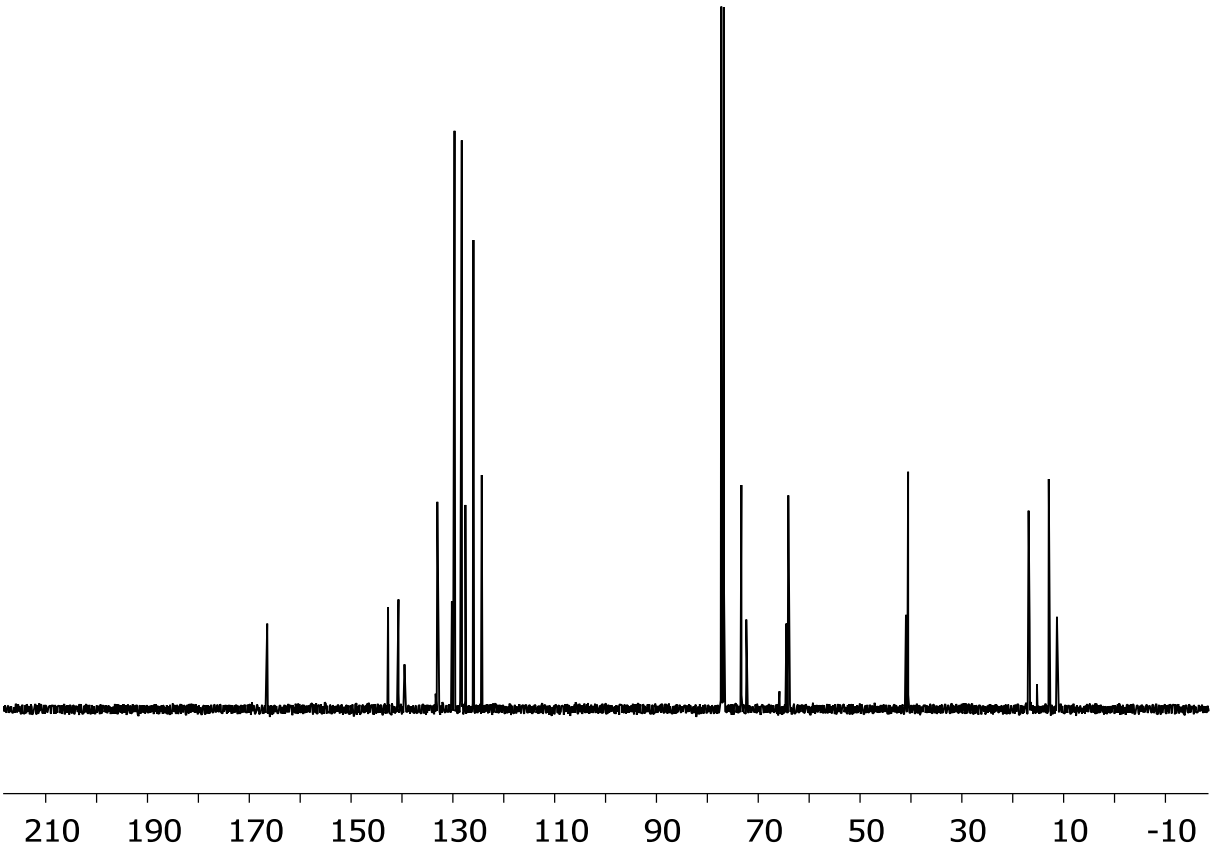


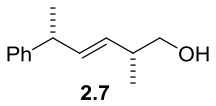




2.6

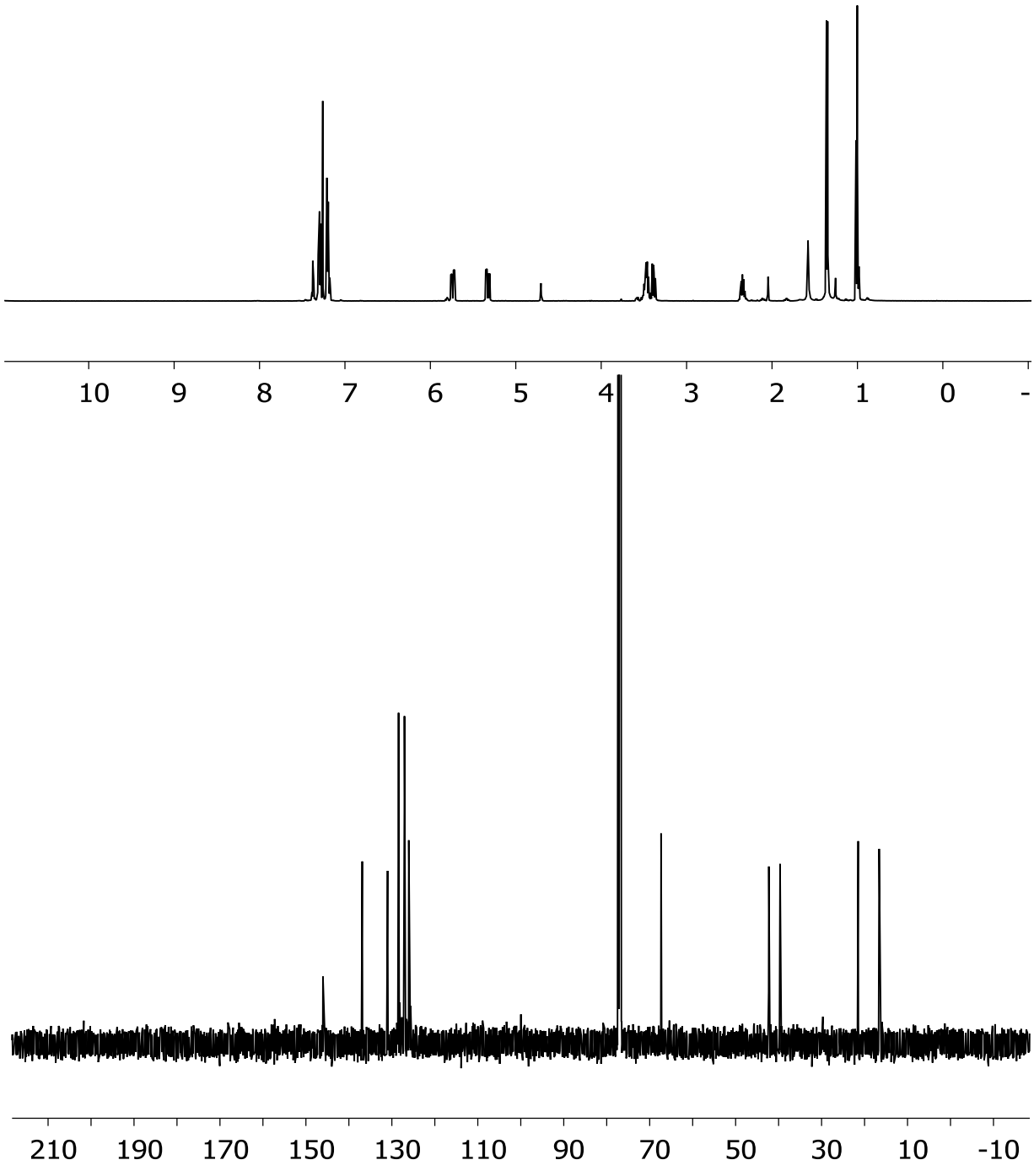
(mixture of diastereomers)

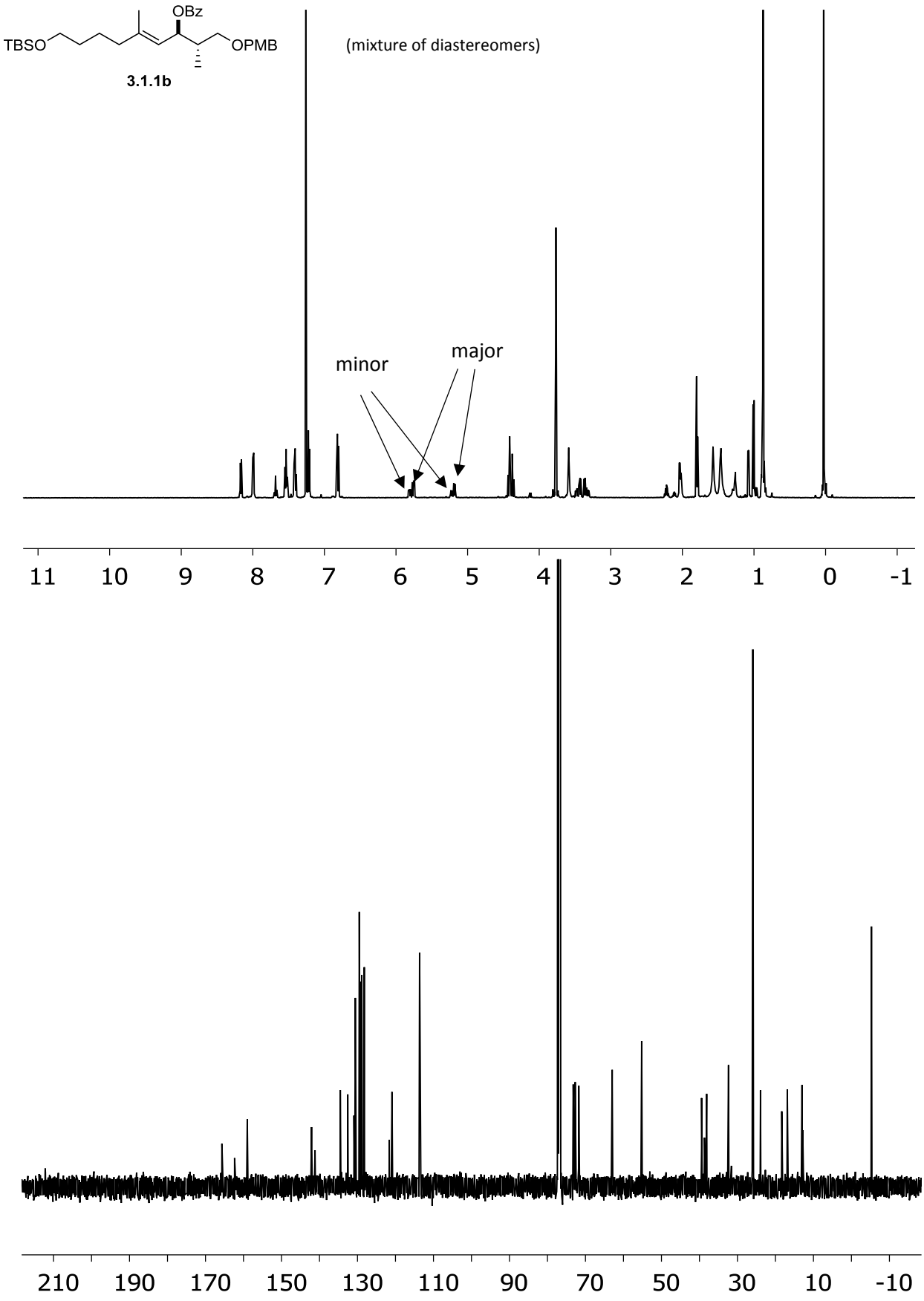


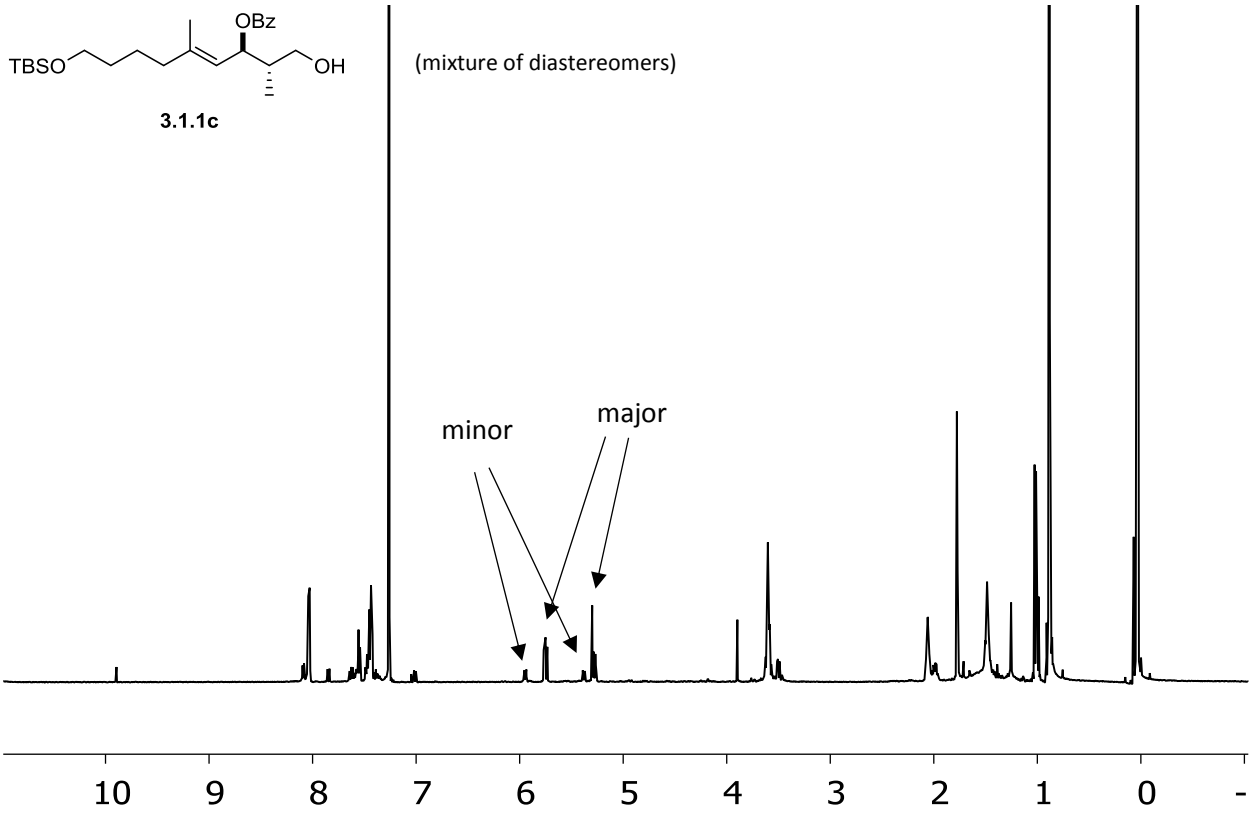


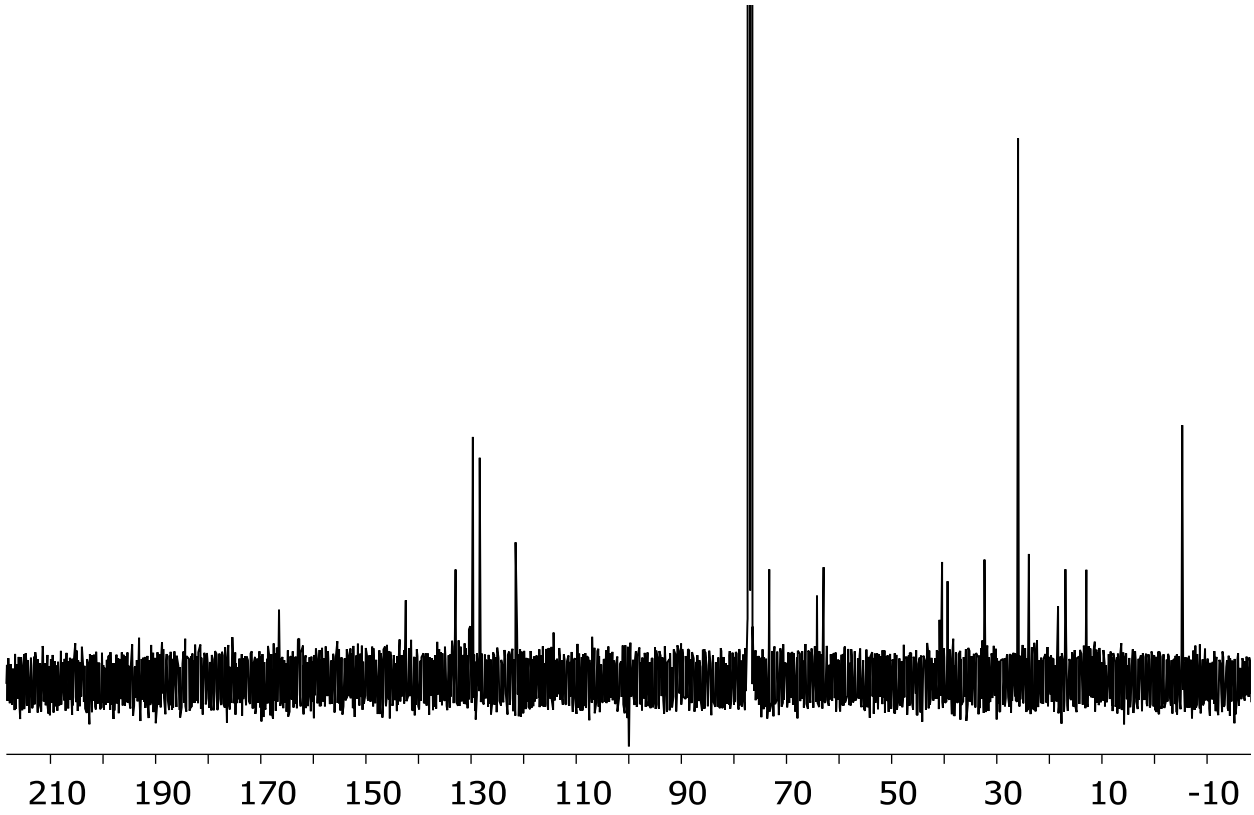
2.7

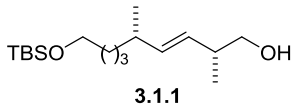
(major diastereomer)




OBz
TBSO
OPMB
3.1.1b
(mixture of diastereomers)
minor
major
11
10
9
8
7
6
5
4
3
2
1
0
-1
210
190
170
150
130
110
90
70
50
30
10
-10

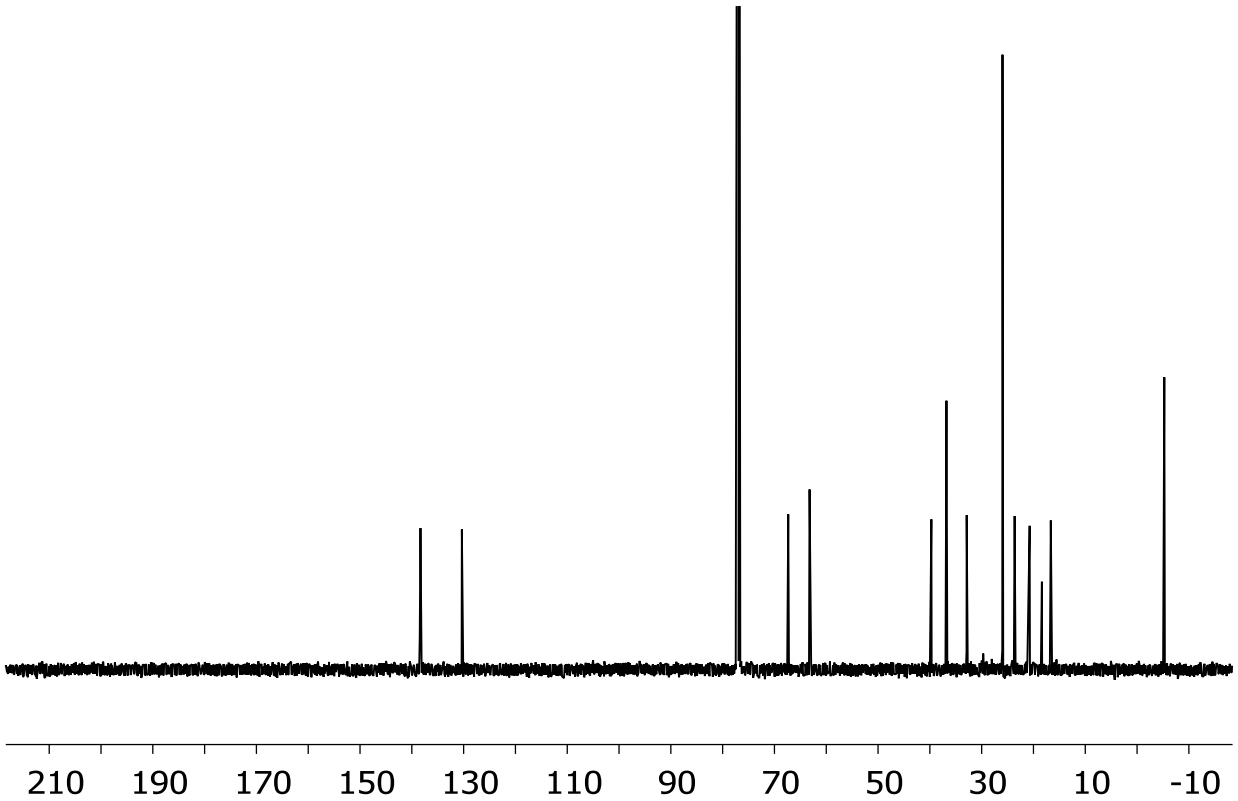

OBz
TBSO
OH
3.1.1c
(mixture of diastereomers)
minor
major
10
9
8
7
6
5
4
3
2
1
0
-

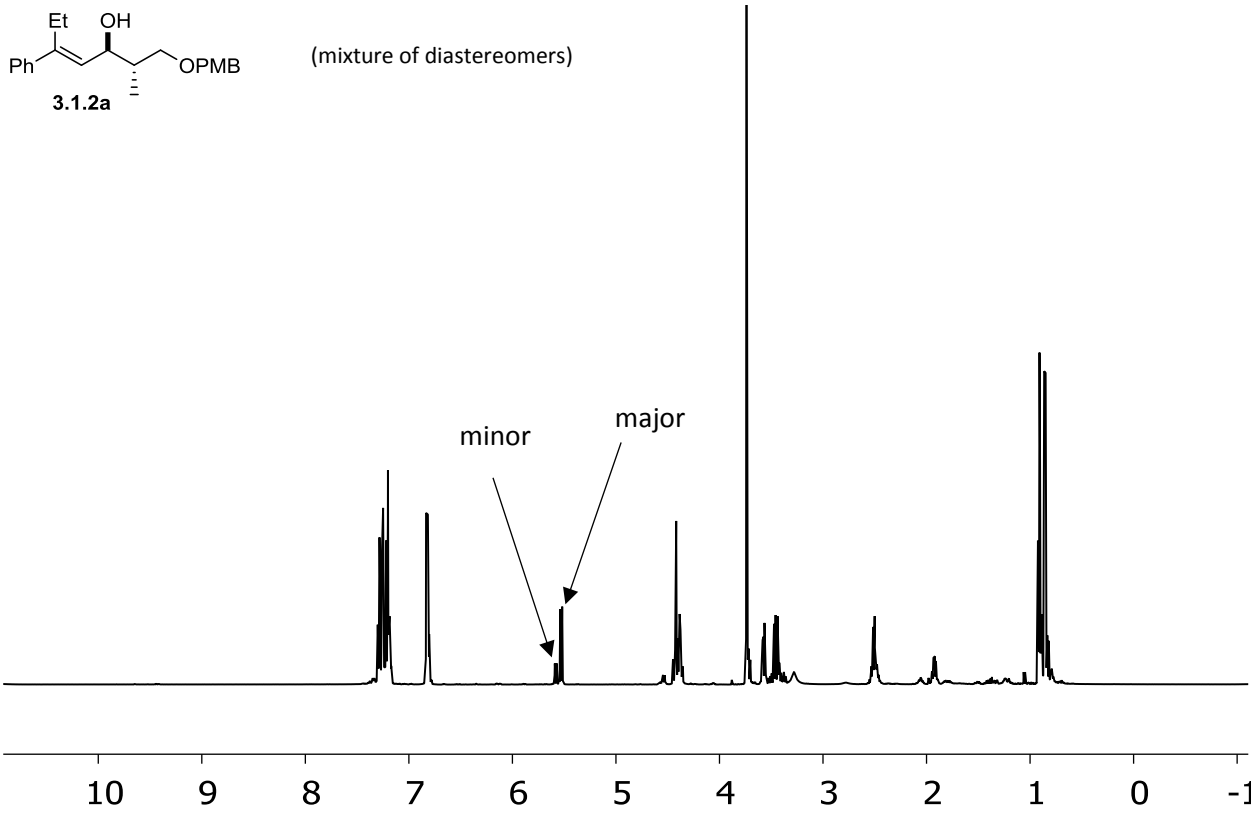

210
190
170
150
130
110
90
70
50
30
10
-10

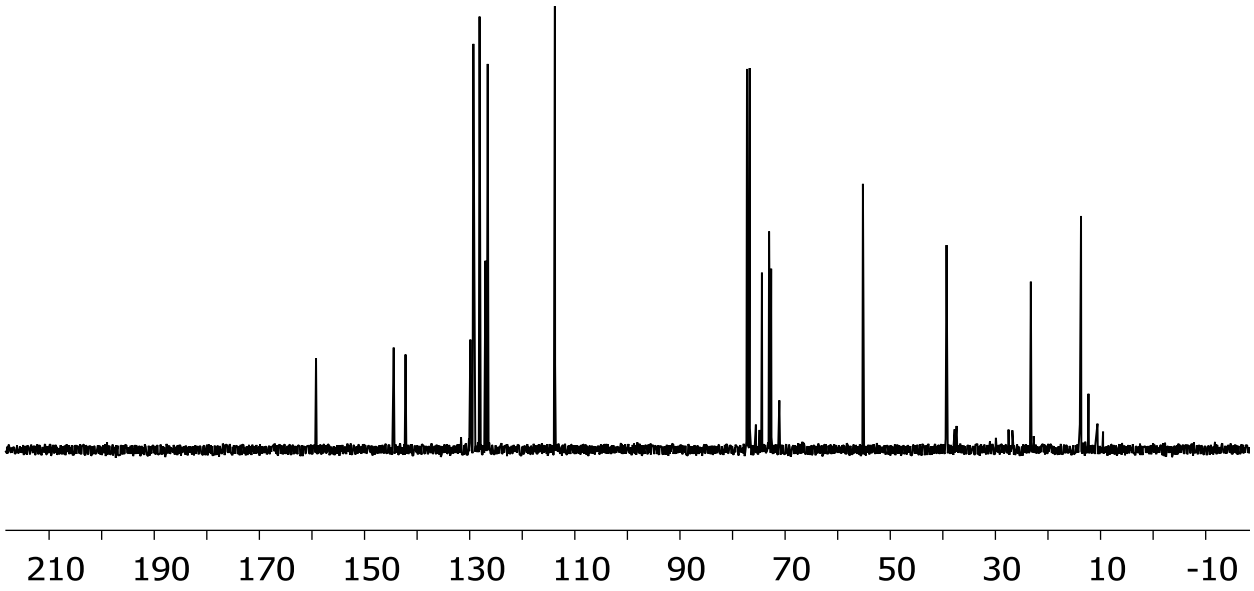


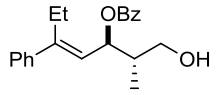
3.1.1

(major diastereomer)



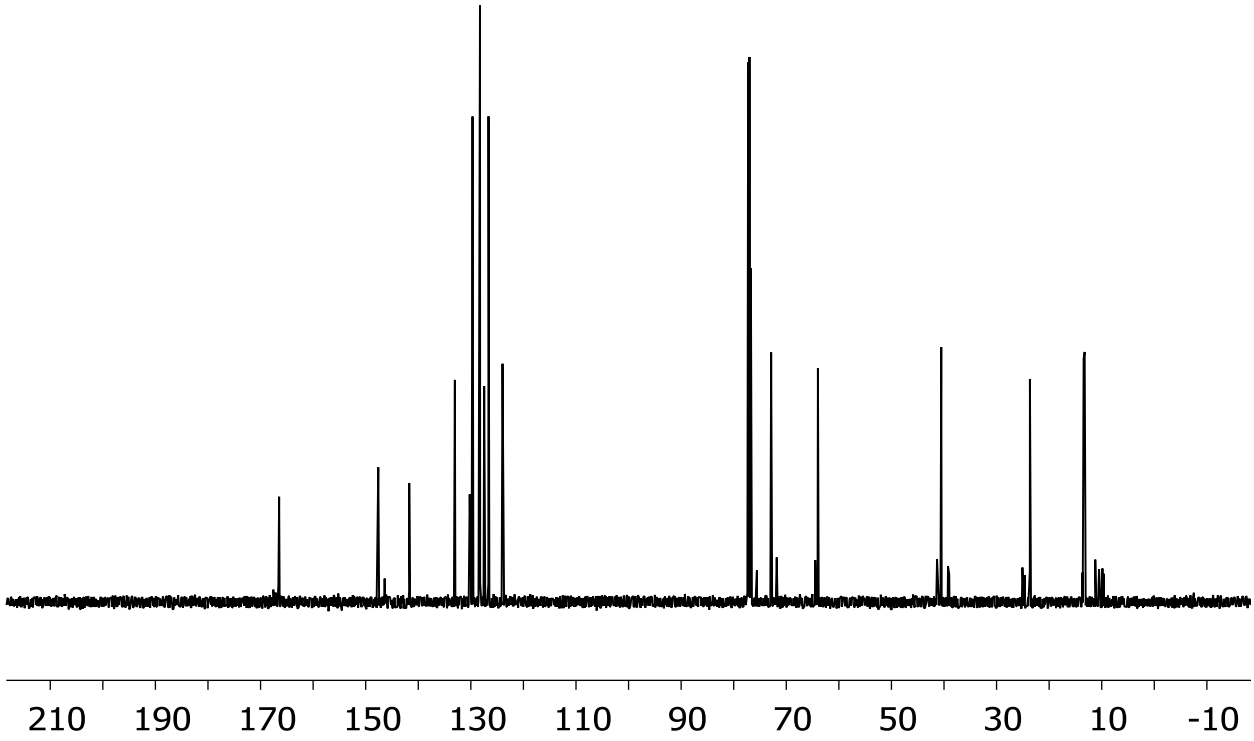

Et
OH
Ph
OPMB
3.1.2a
(mixture of diastereomers)
minor
major
10
9
8
7
6
5
4
3
2
1
0
-1

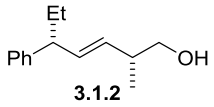

210
190
170
150
130
110
90
70
50
30
10
-10



3.1.2c

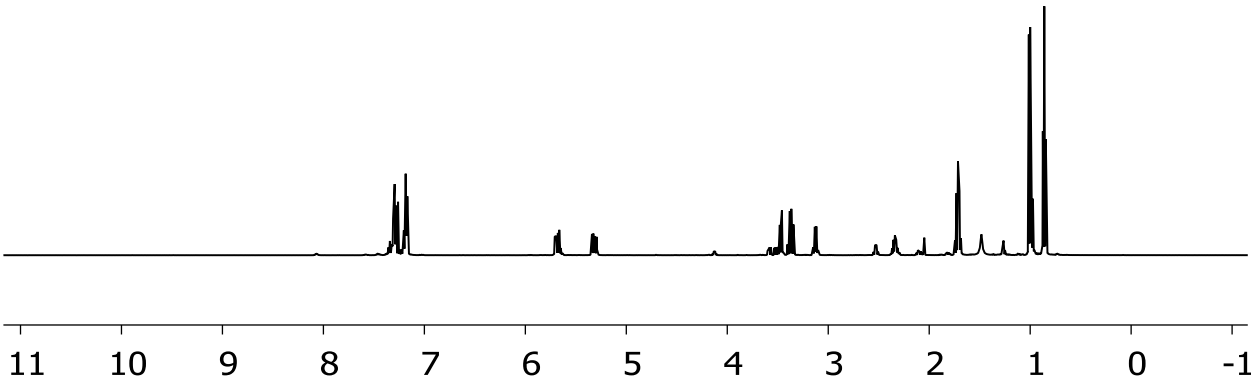
(mixture of diastereomers)

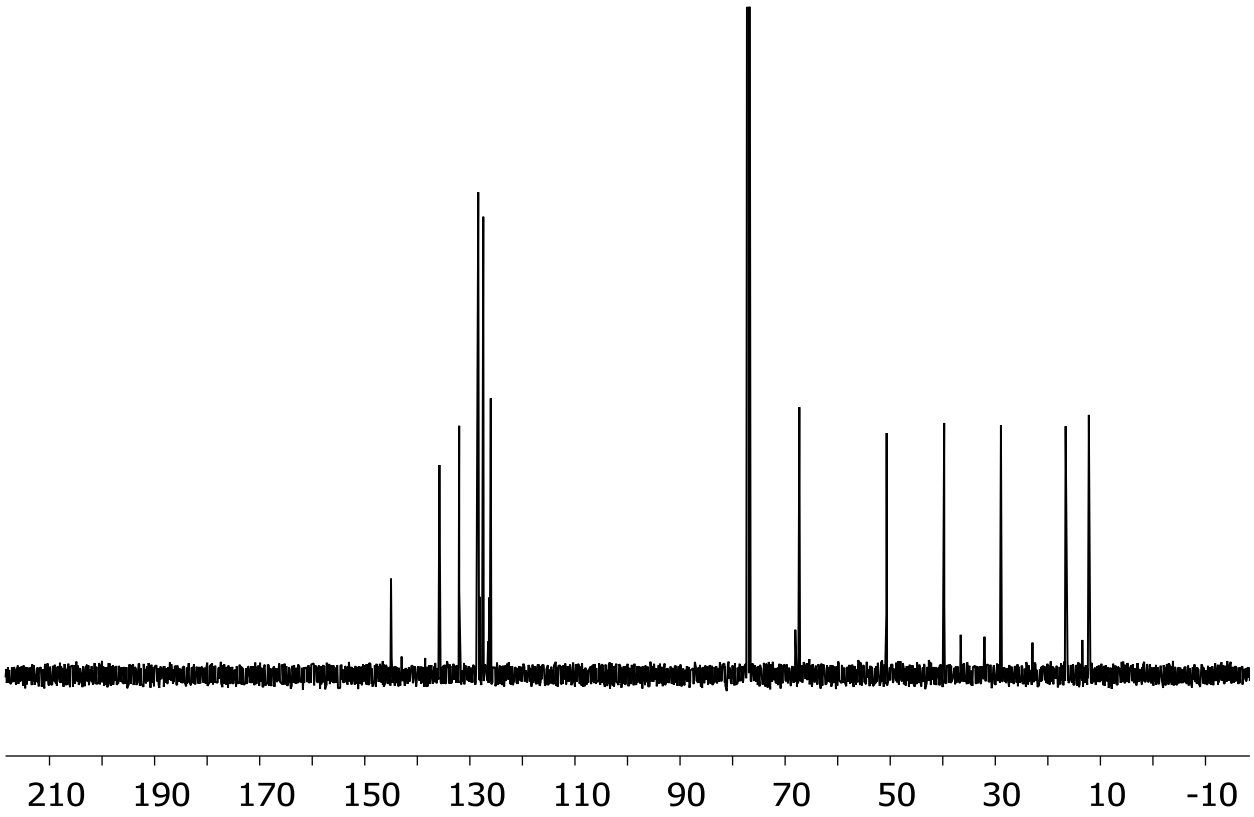


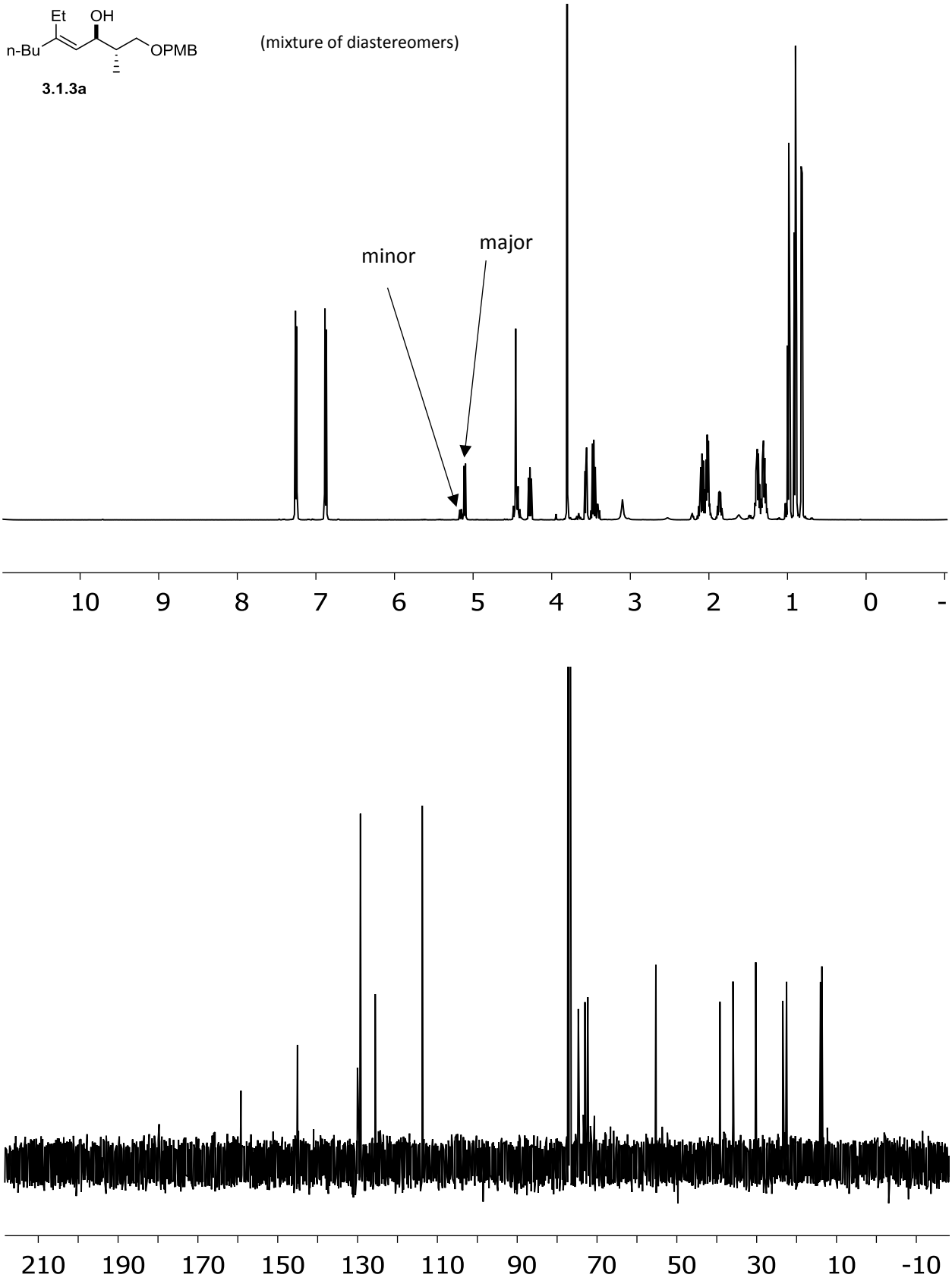


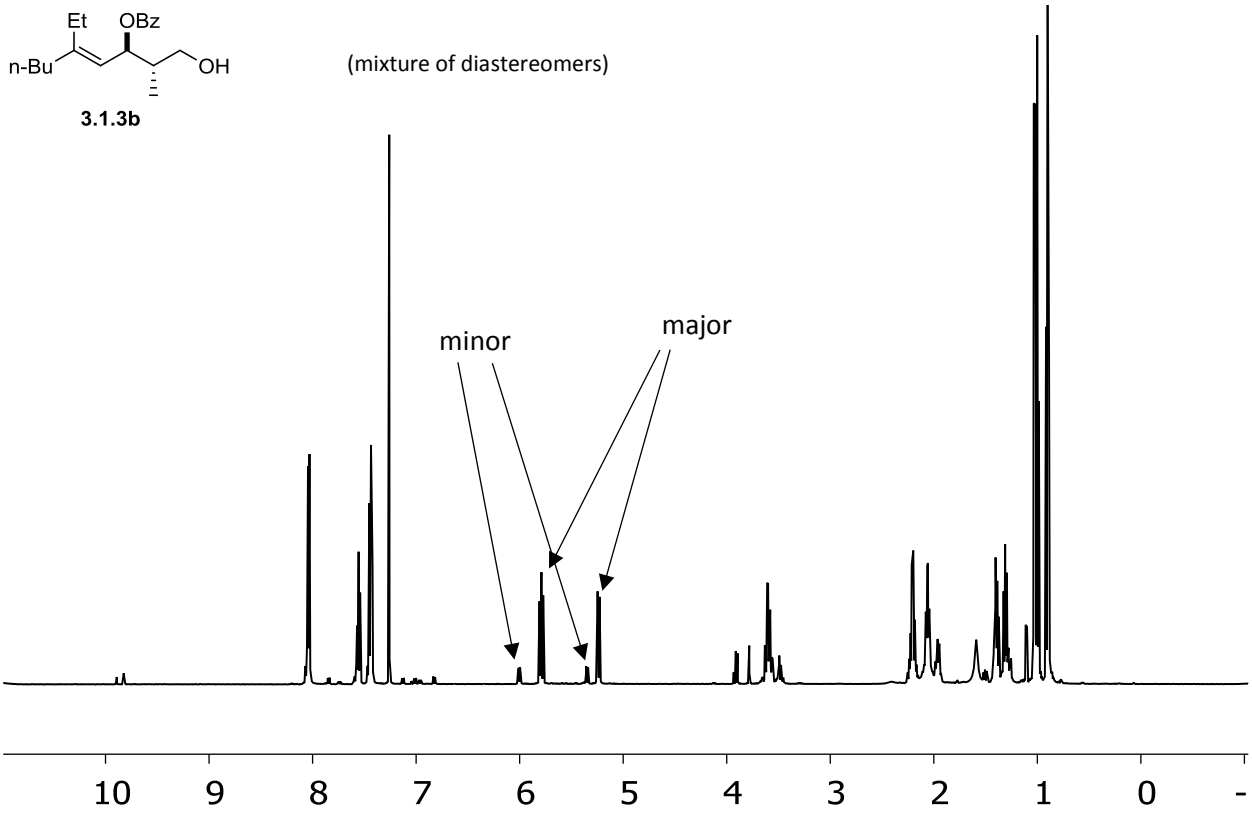
3.1.2

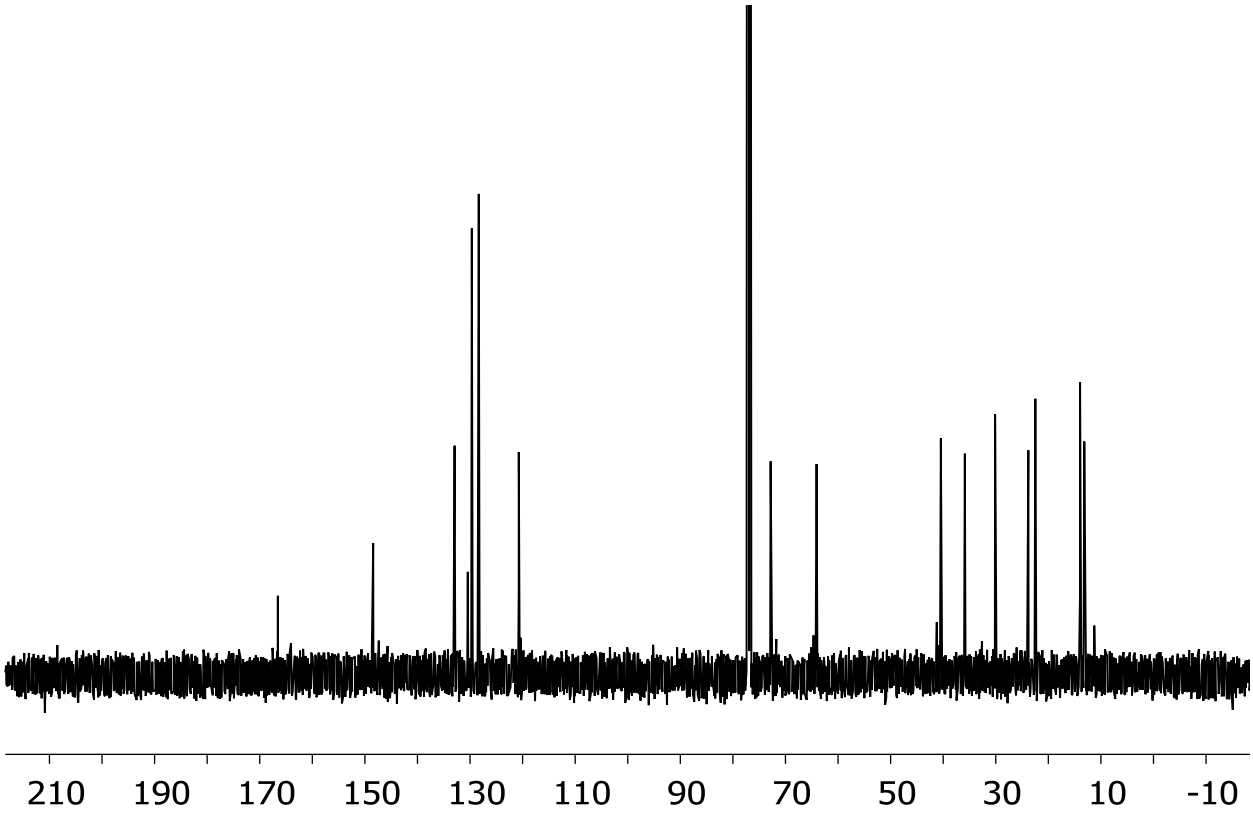
(major diastereomer)

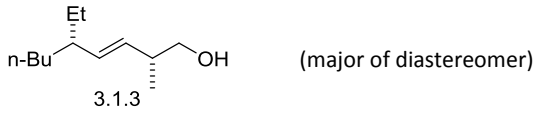





Et
OH
n-Bu
OPMB
3.1.3a
(mixture of diastereomers)
minor
major
10
9
8
7
6
5
4
3
2
1
0
-
210
190
170
150
130
110
90
70
50
30
10
-10

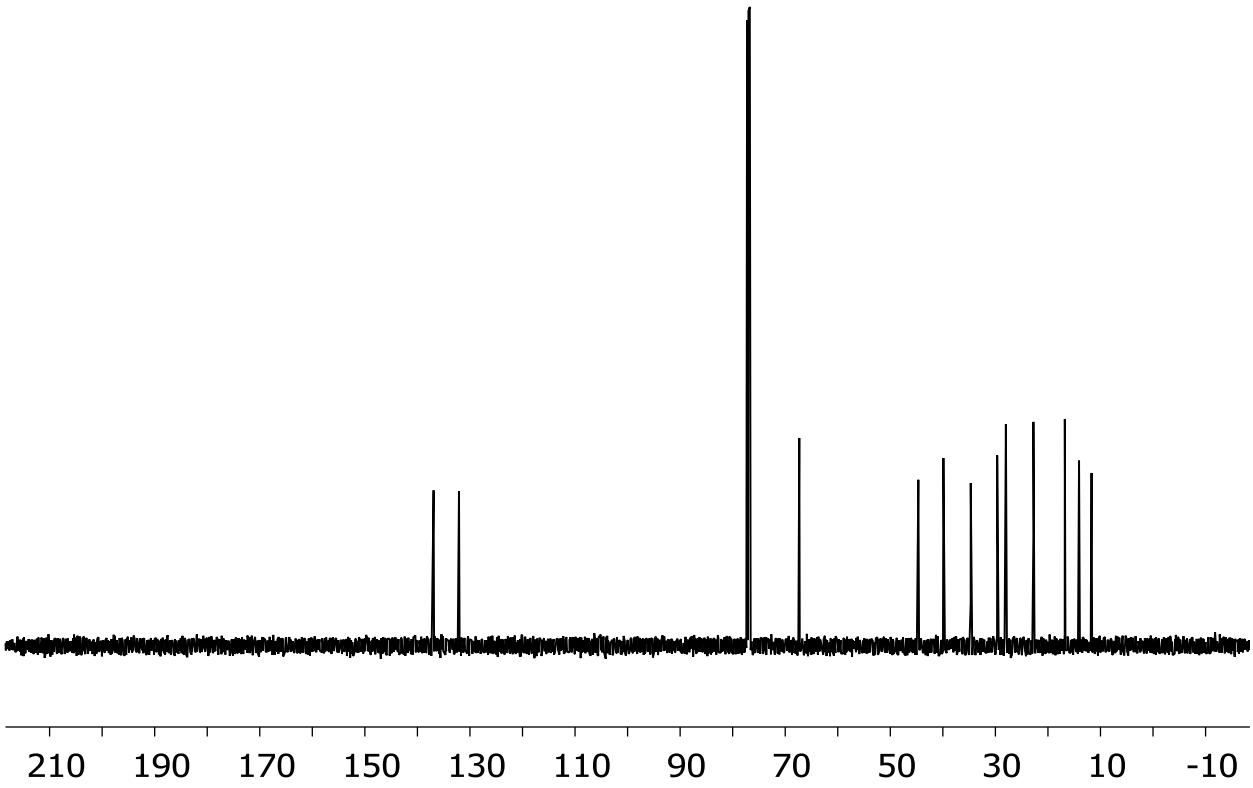

Et
OBz
n-Bu
OH
3.1.3b
(mixture of diastereomers)
minor
major
10
9
8
7
6
5
4
3
2
1
0
-

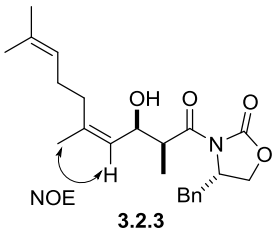

210
190
170
150
130
110
90
70
50
30
10
-10



3.1.3

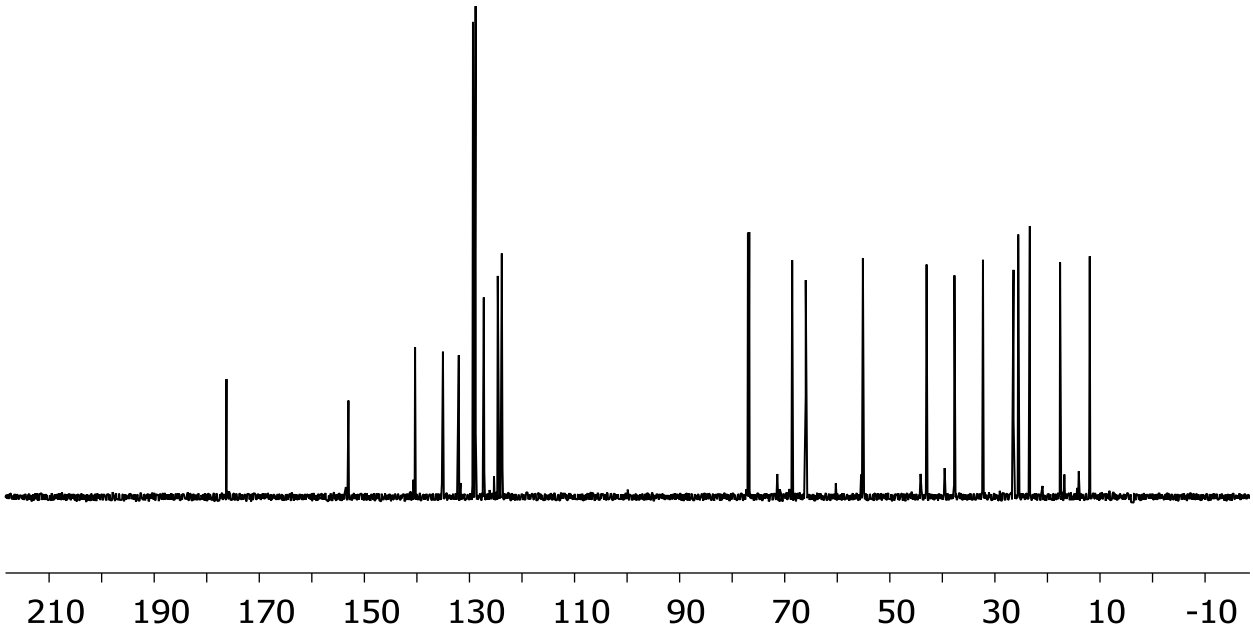
(major of diastereomer)

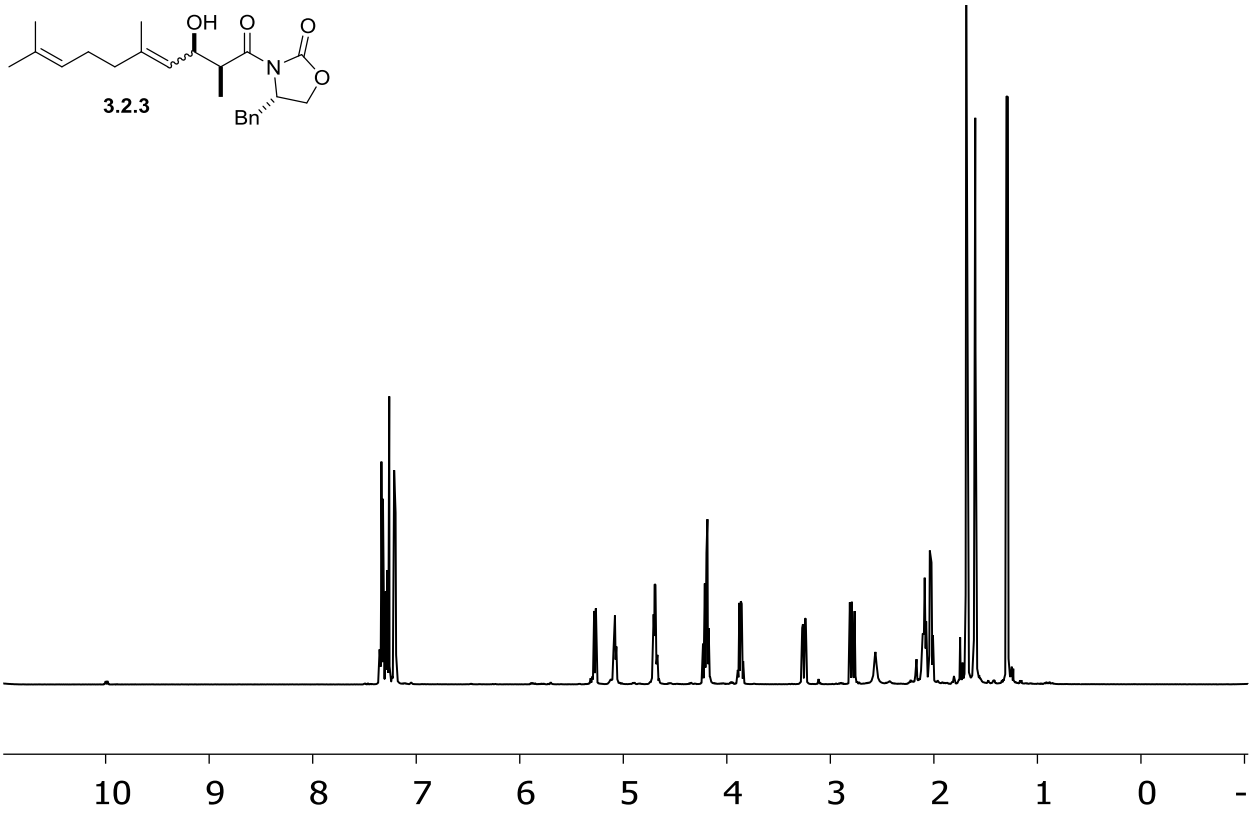


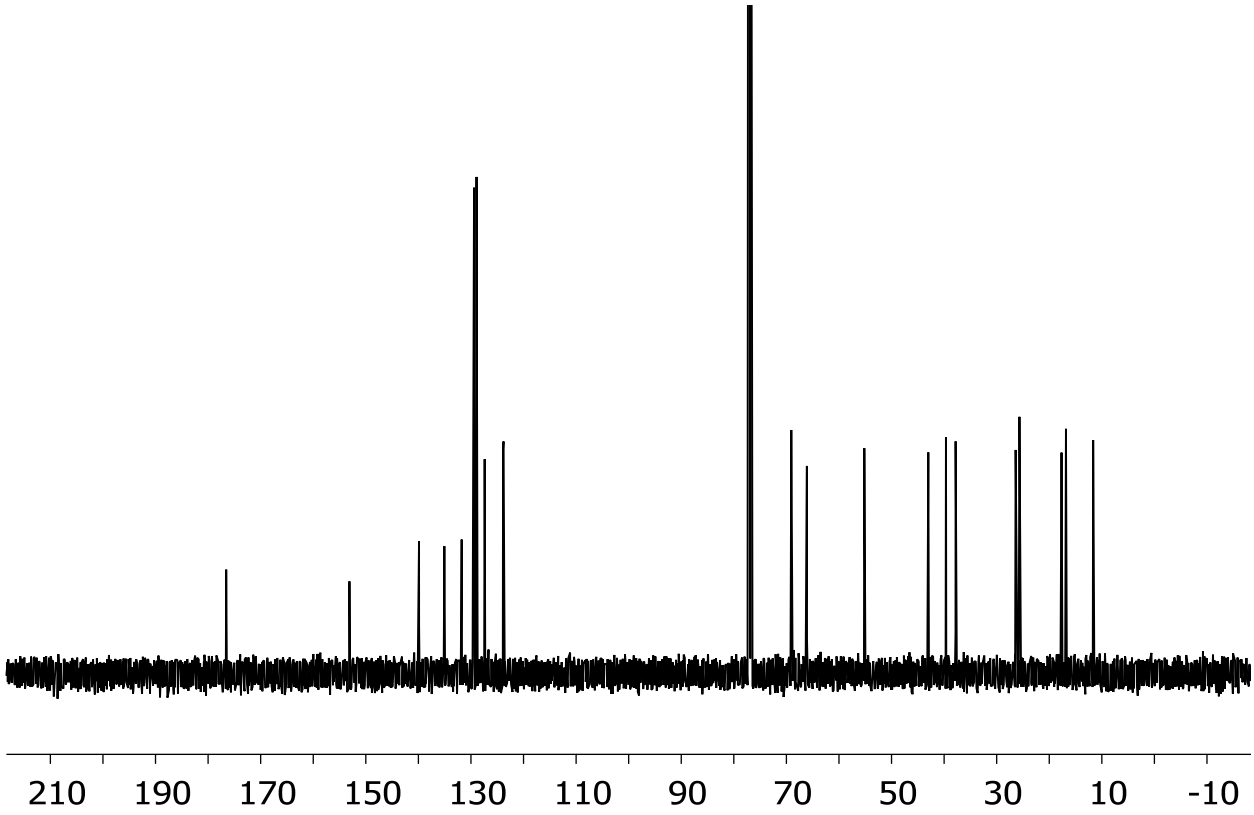

OH
O
O
N
O
H
NOE
Bn

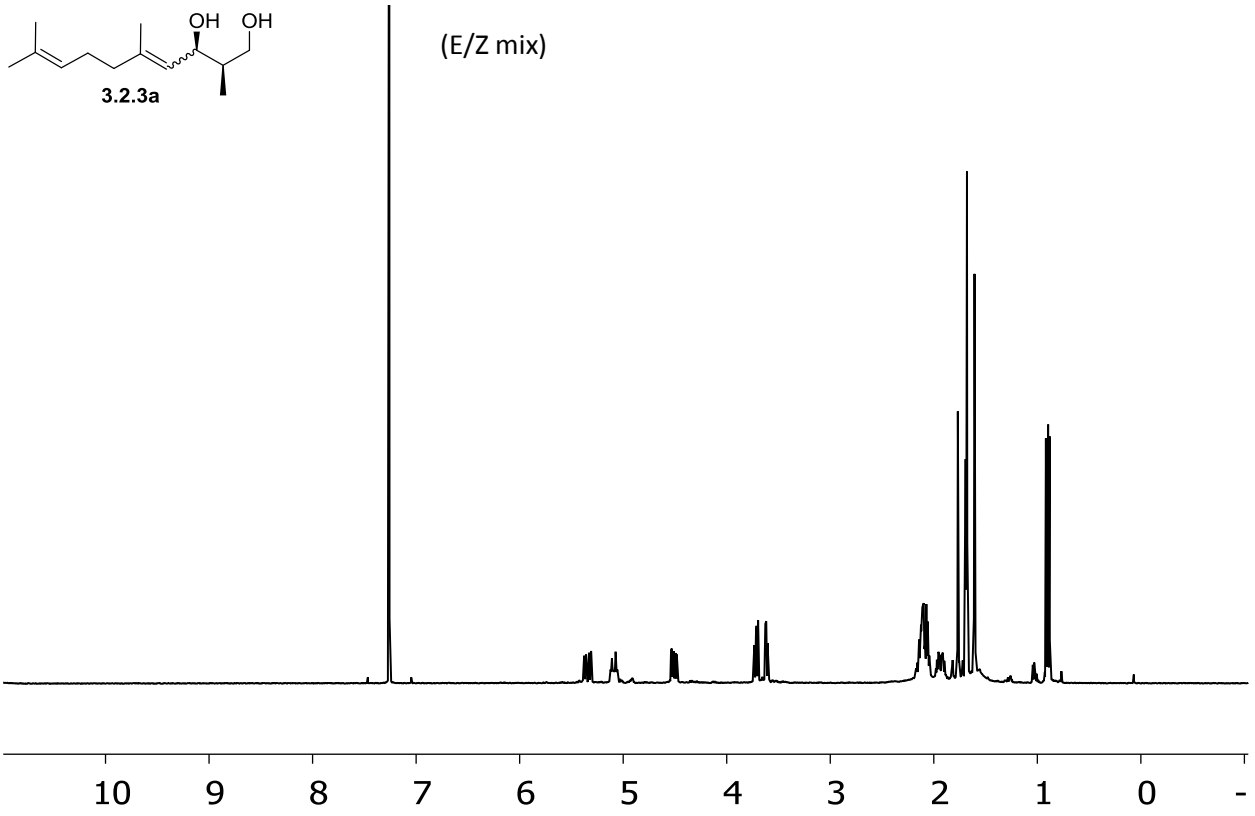
3.2.3

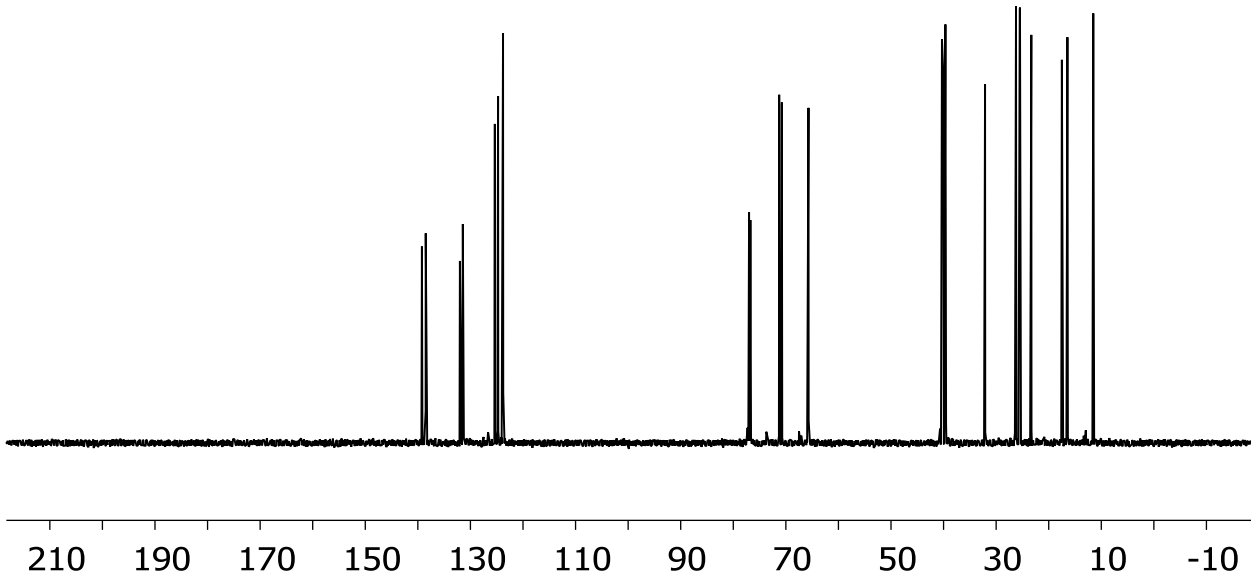
10
9
8
7
6
5
4
3
2
1
0
-

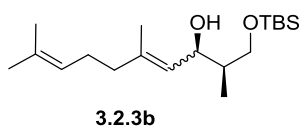

210
190
170
150
130
110
90
70
50
30
10
-10


OH
O
O
N
O
Bn
3.2.3
10
9
8
7
6
5
4
3
2
1
0
-


210
190
170
150
130
110
90
70
50
30
10
-10


OH
OH
3.2.3a
(E/Z mix)
10
9
8
7
6
5
4
3
2
1
0
-

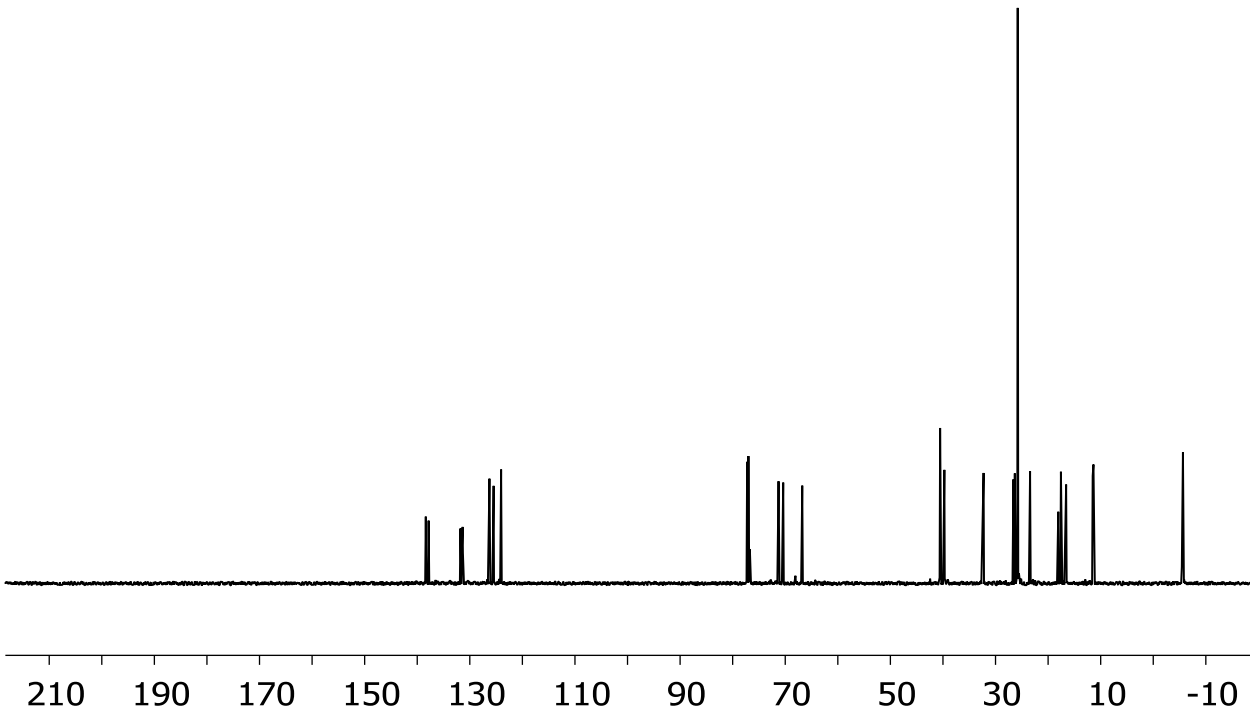

210
190
170
150
130
110
90
70
50
30
10
-10

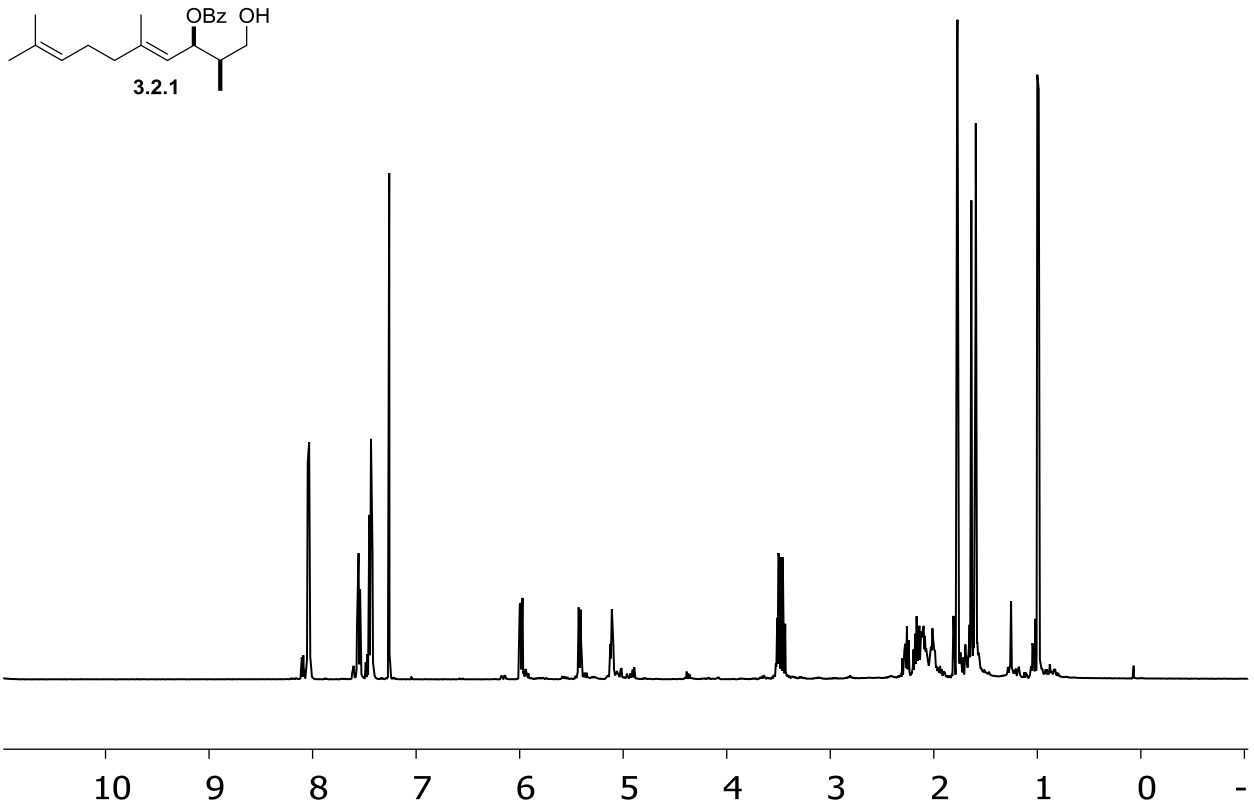

OH
OTBS

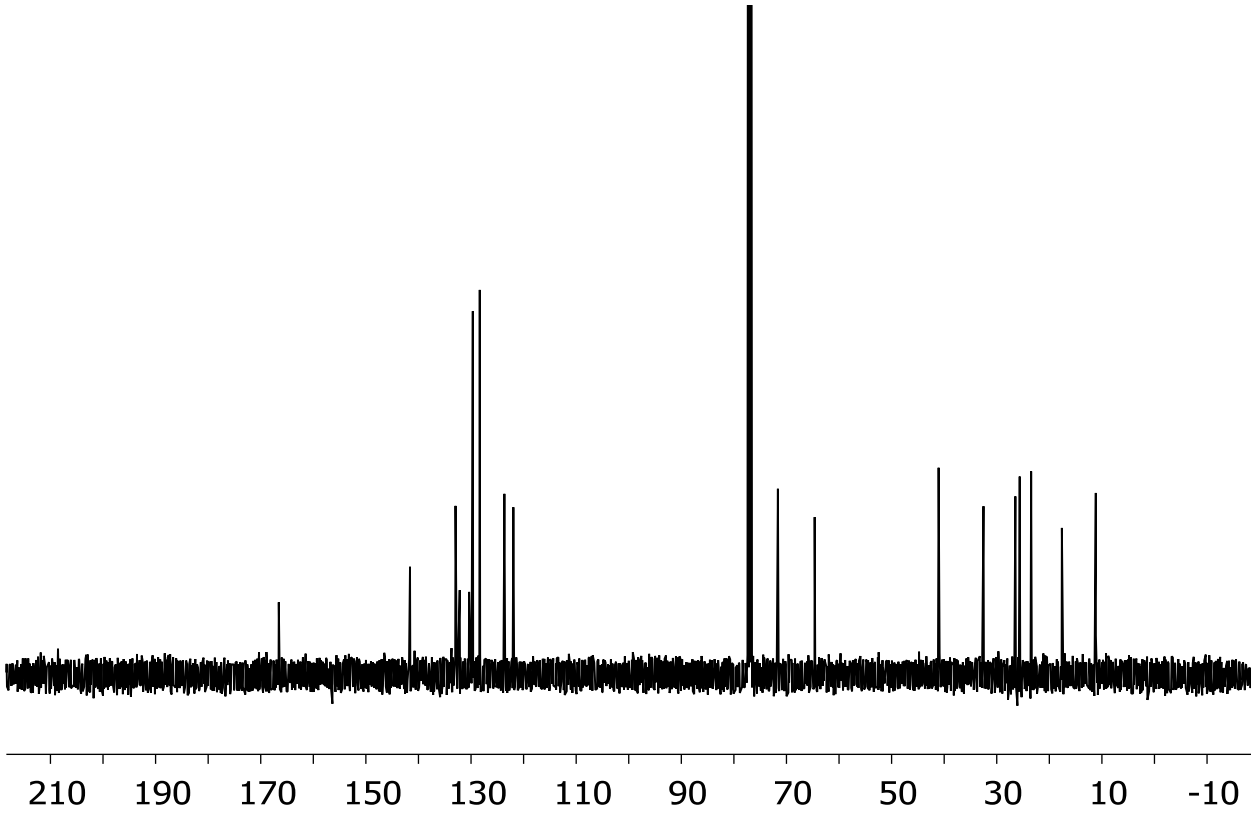
3.2.3b

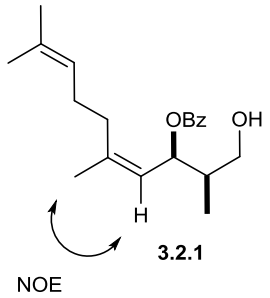
(E/Z mix)

11
10
9
8
7
6
5
4
3
2
1
0
-1


210
190
170
150
130
110
90
70
50
30
10
-10

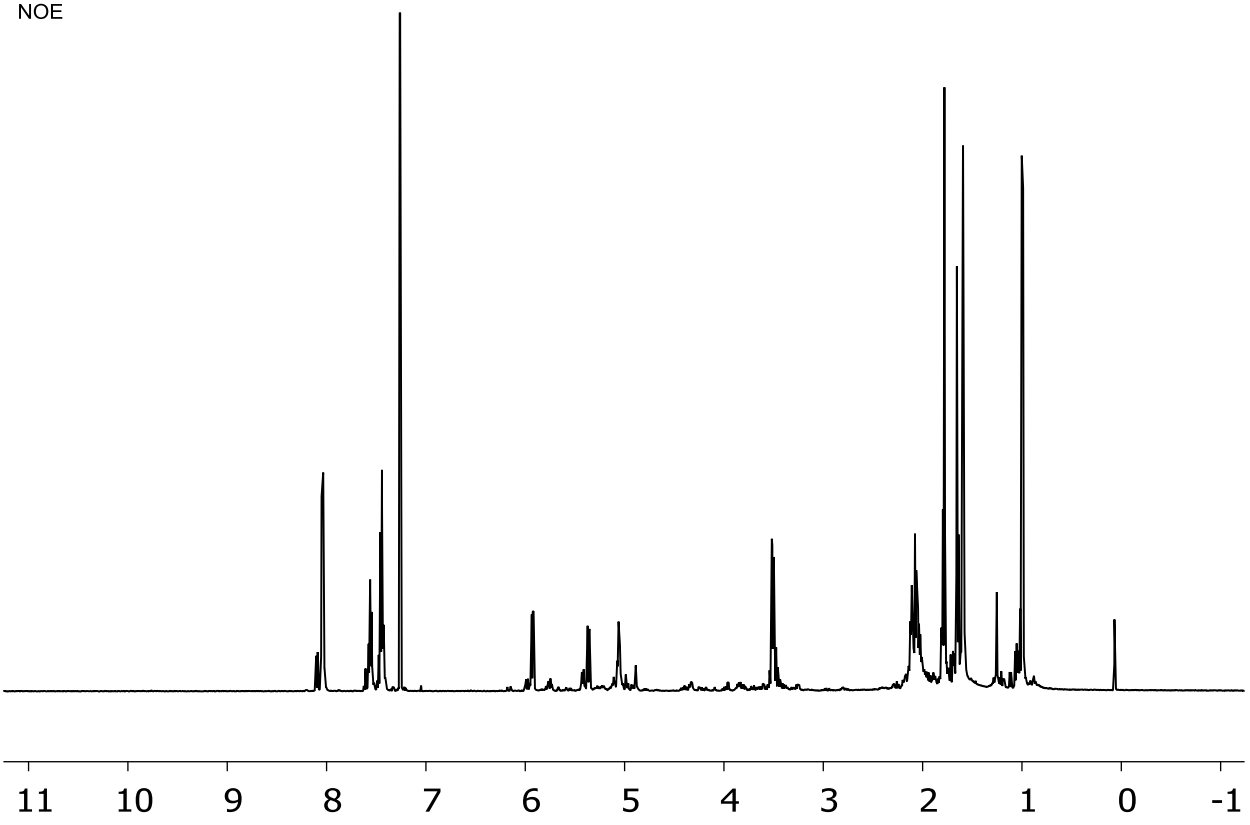

OBz
OH
3.2.1
10
9
8
7
6
5
4
3
2
1
0
-

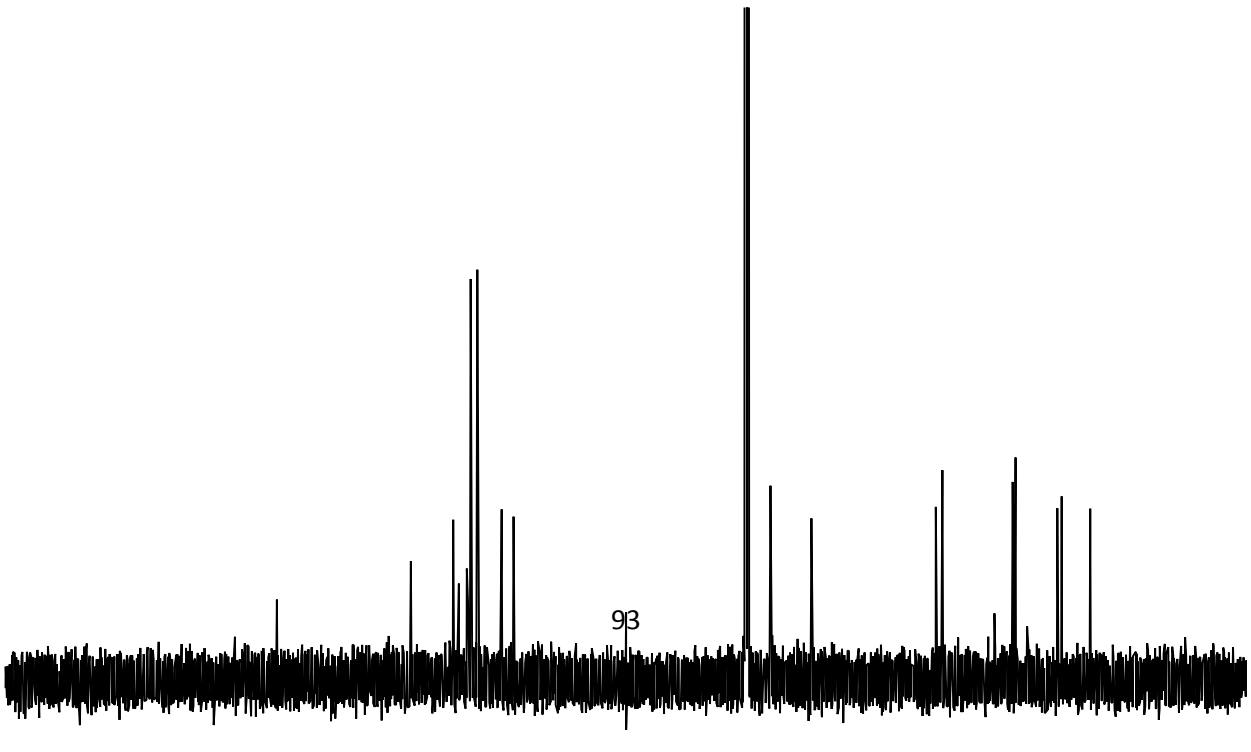

210
190
170
150
130
110
90
70
50
30
10
-10

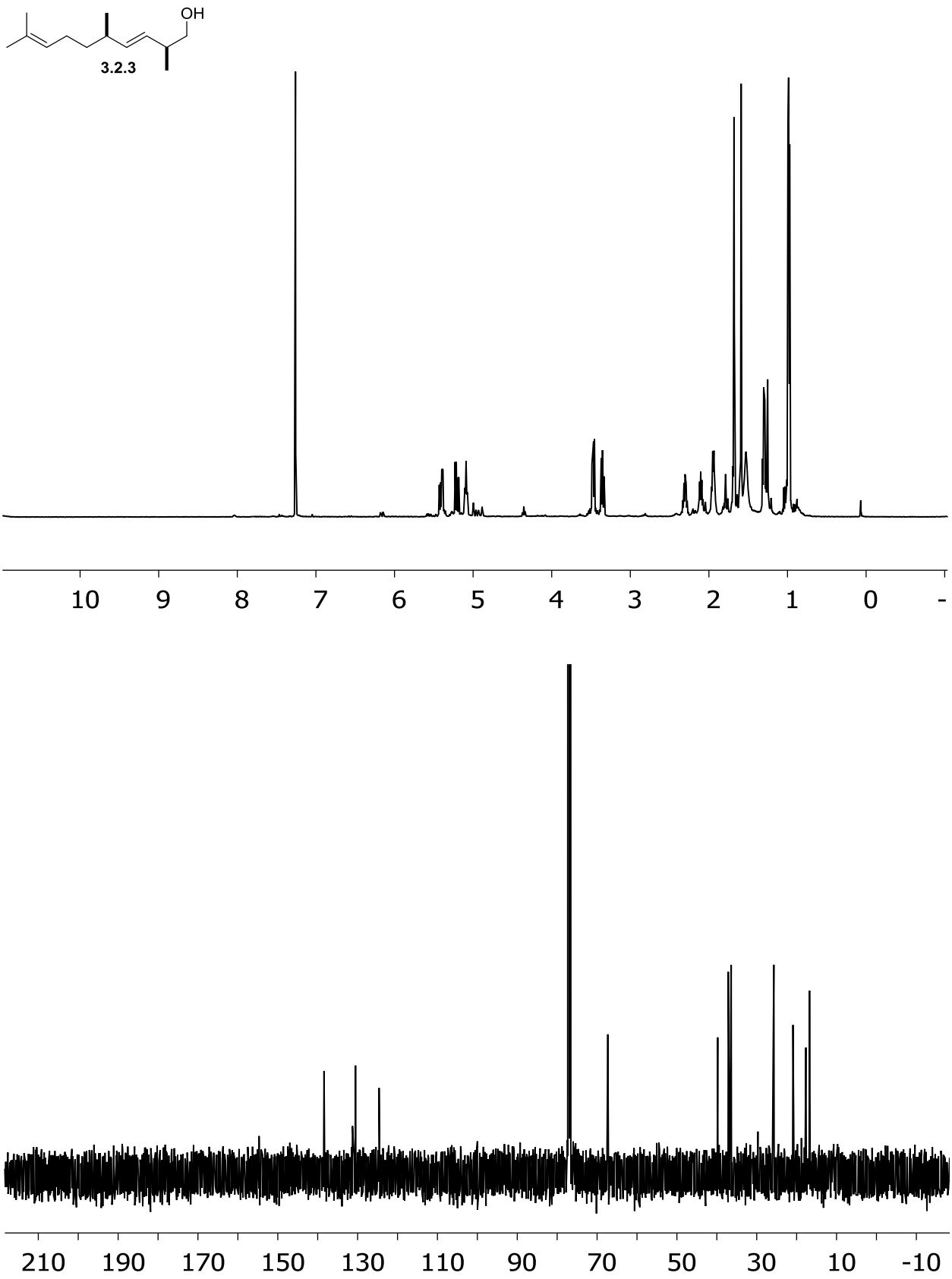


3.2.1

NOE






OH
3.2.3
10
9
8
7
6
5
4
3
2
1
0
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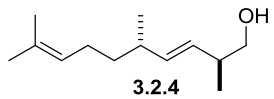
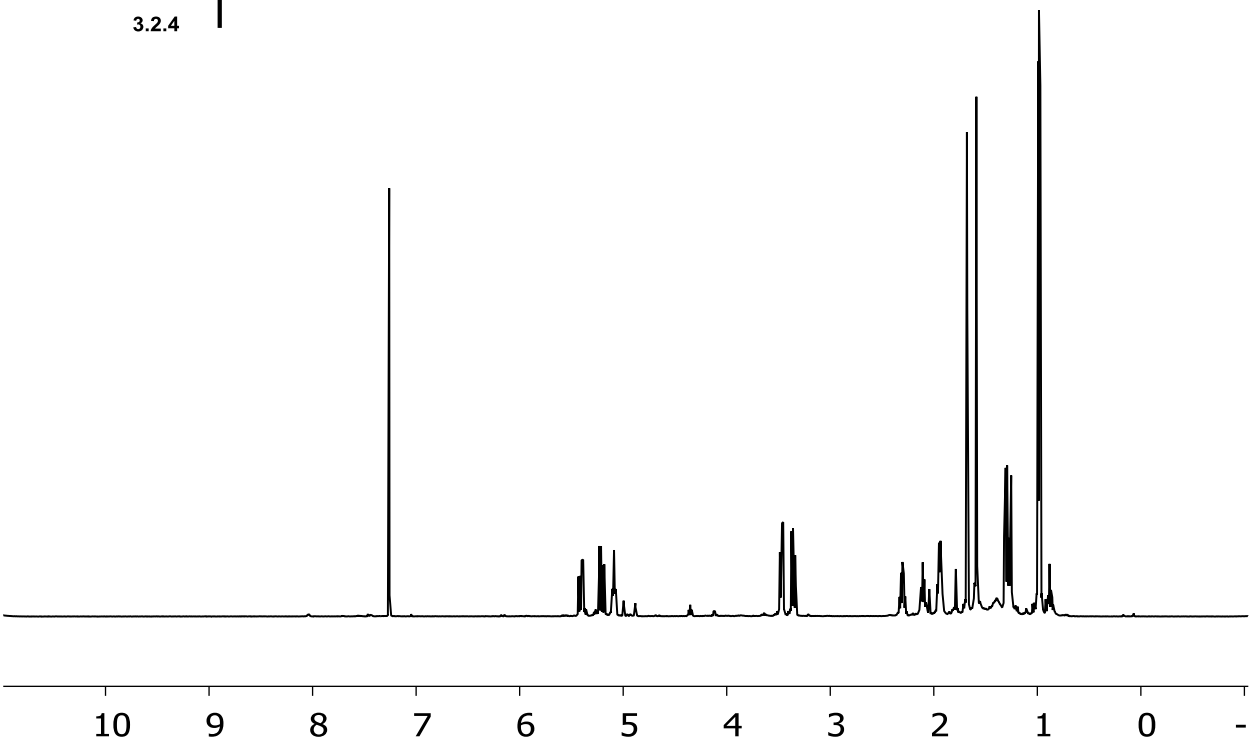
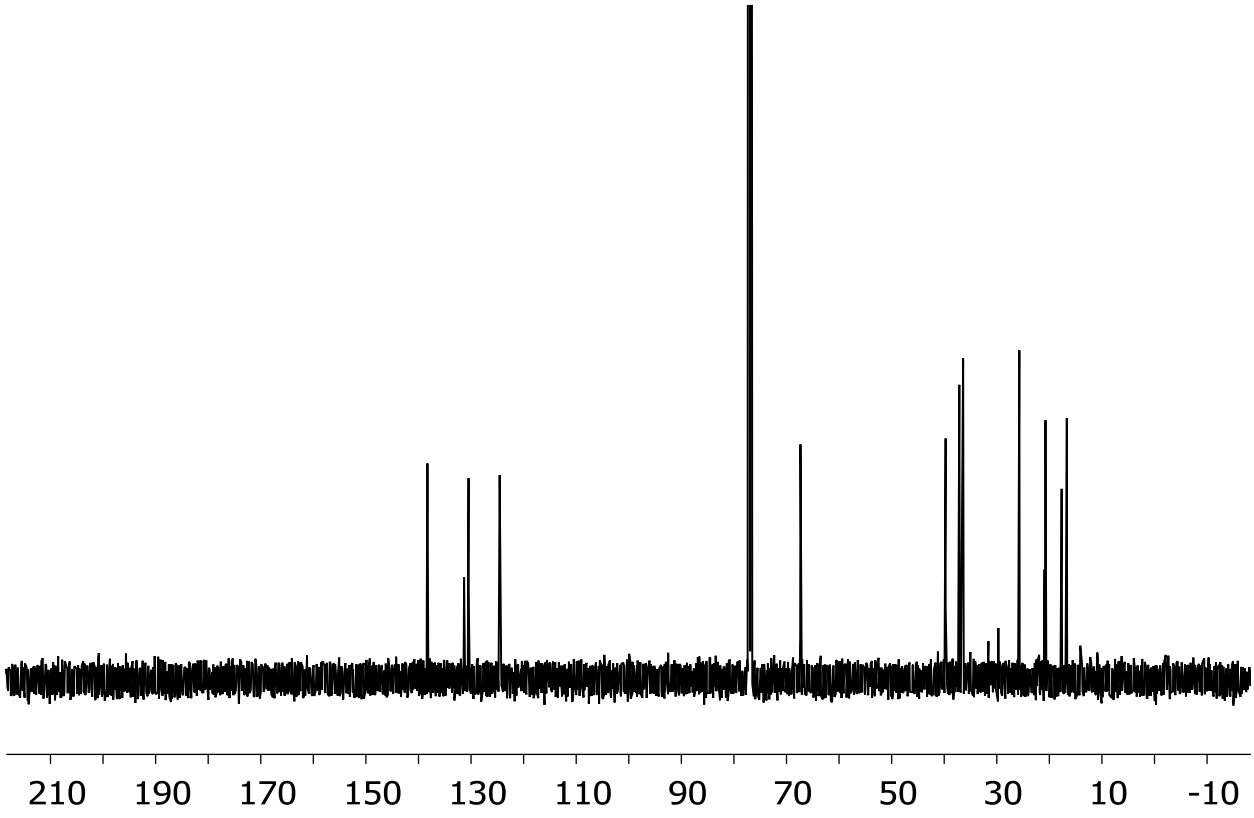
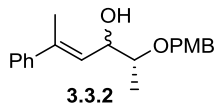
210
190
170
150
130
110
90
70
50
30
10
-10



3.2.4

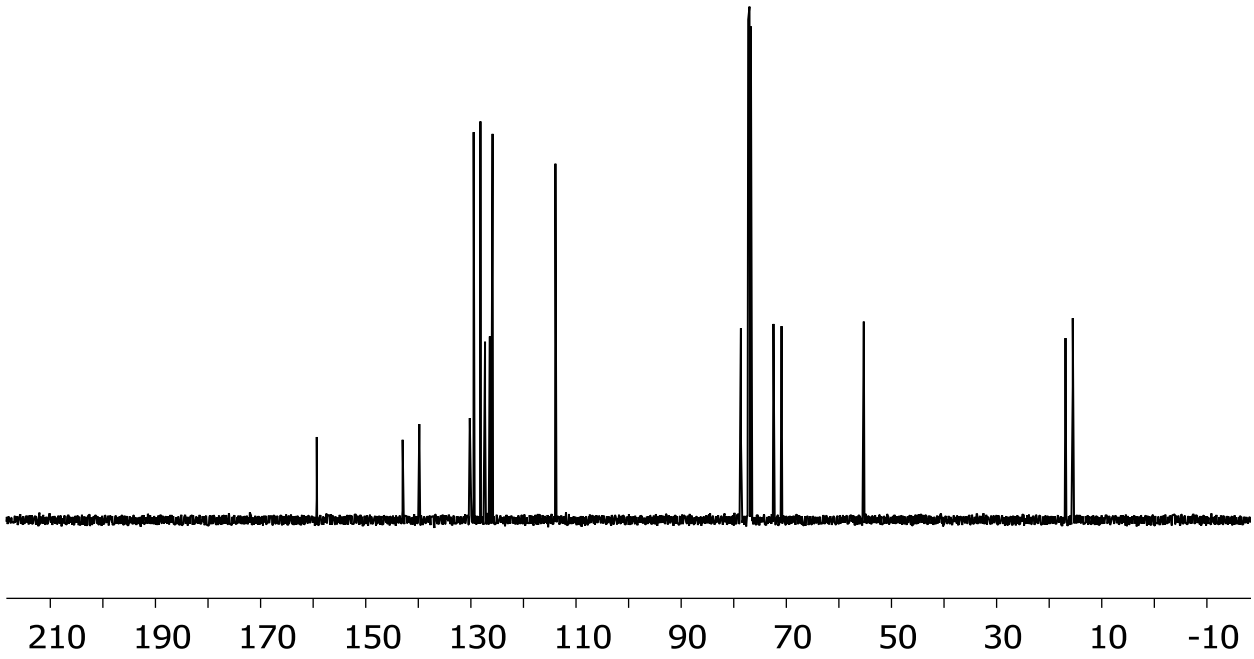


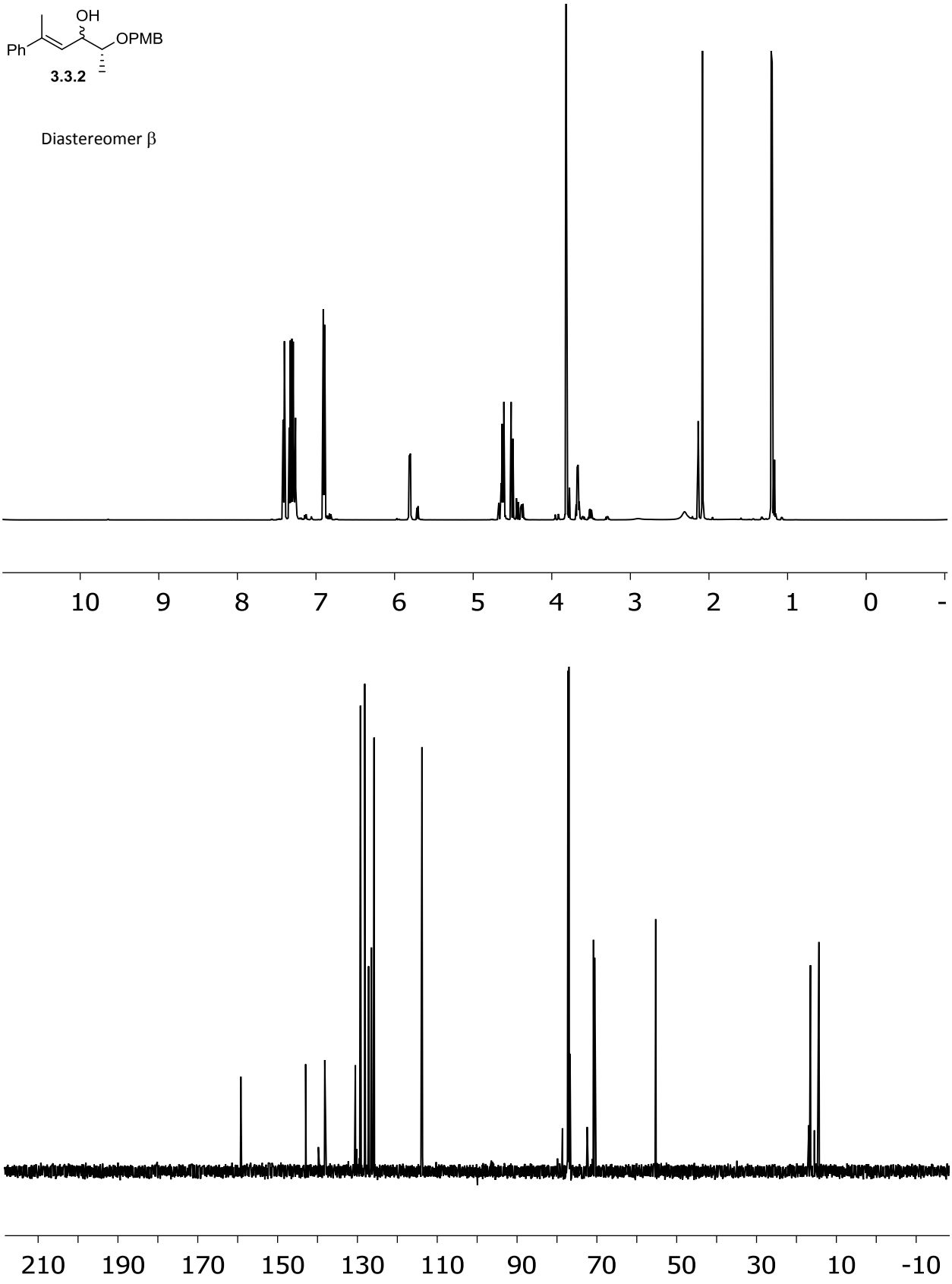




3.3.2

Diastereomer α




OH
Ph
OPMB
3.3.2
Diastereomer β
10
9
8
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5
4
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2
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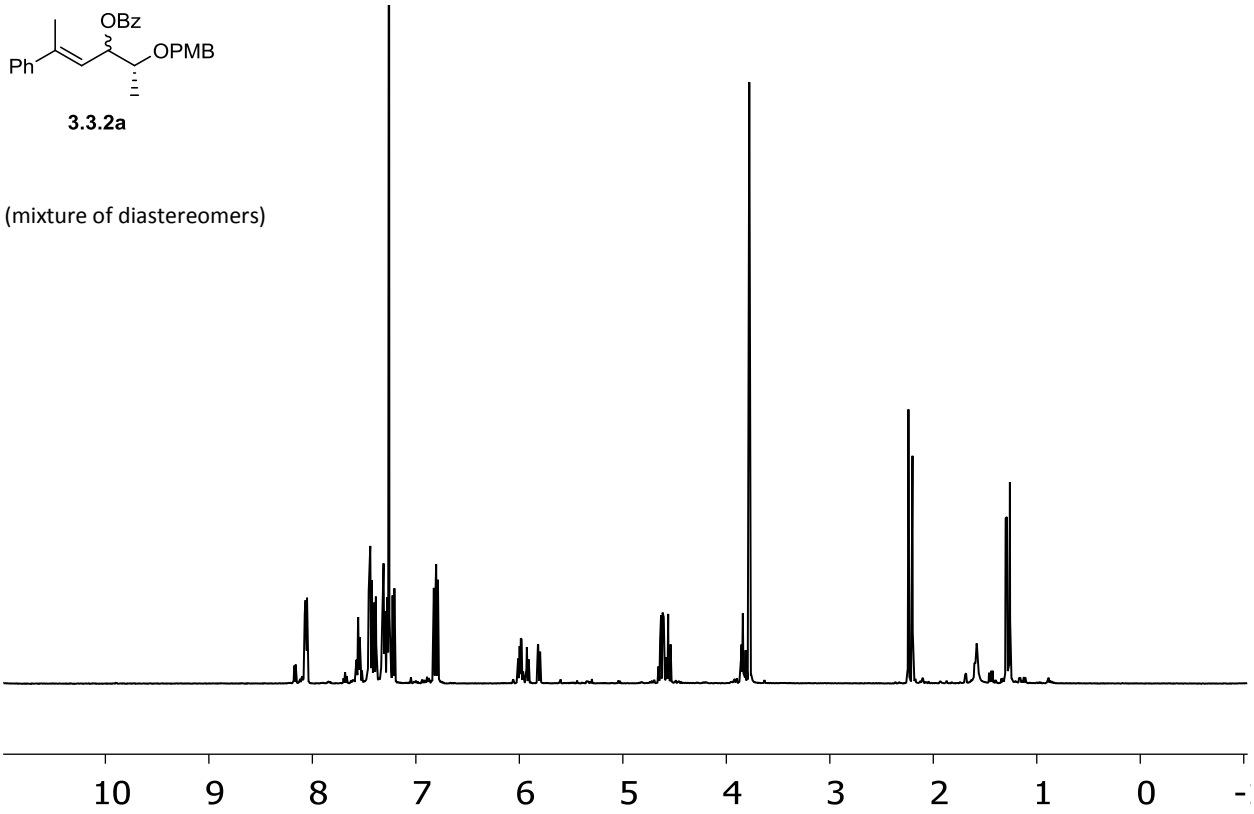
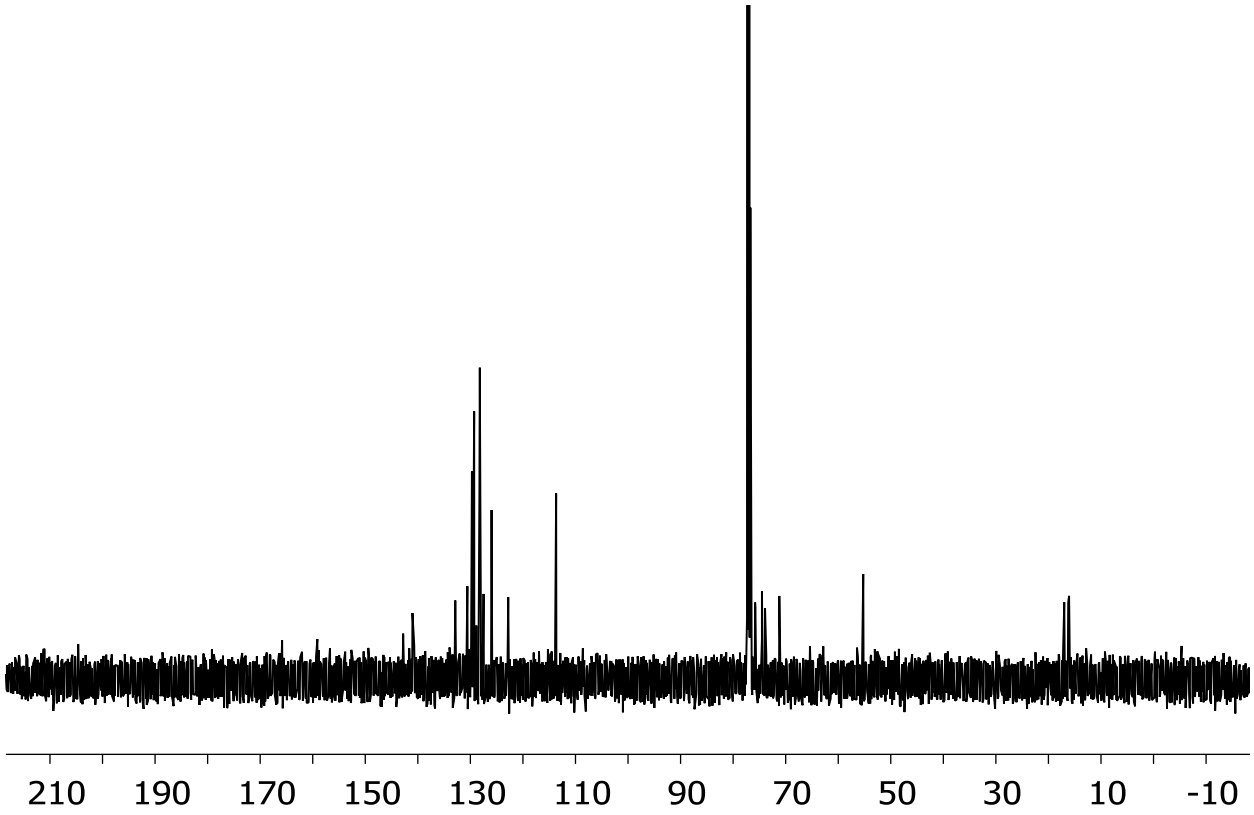
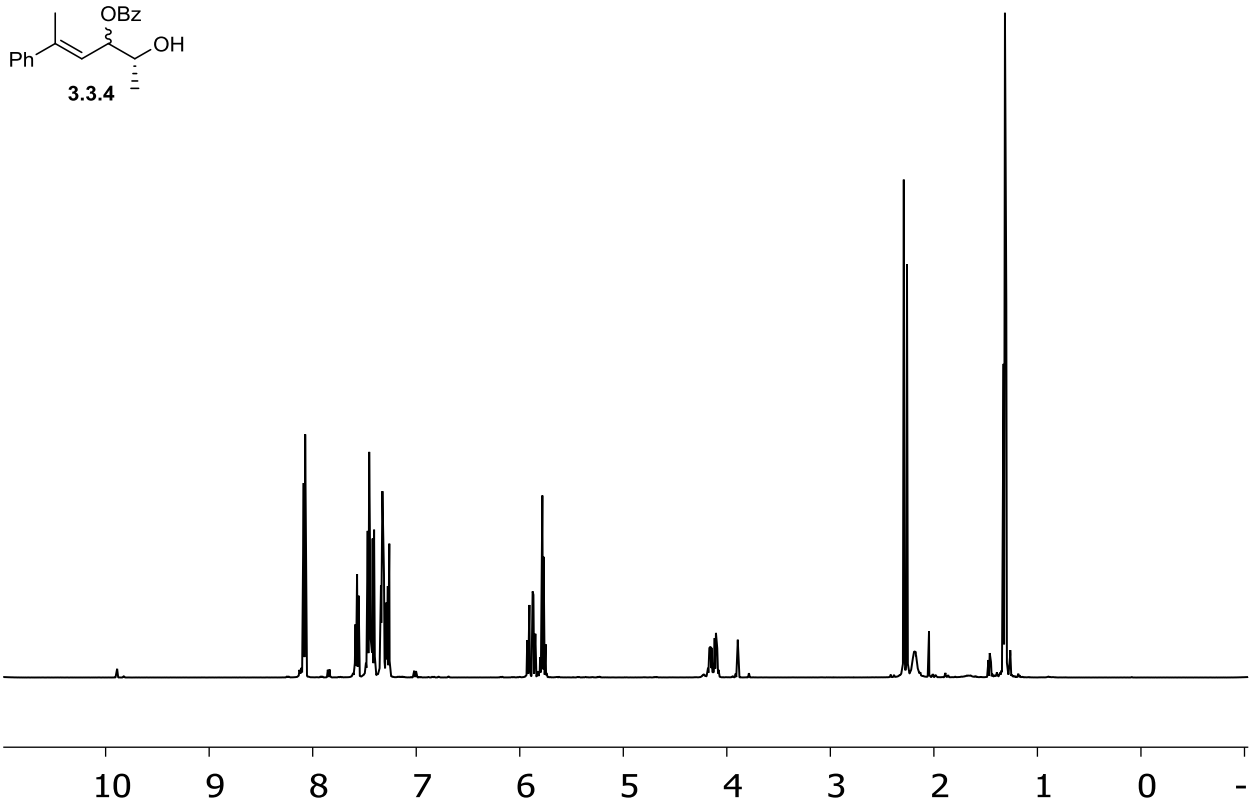
210
190
170
150
130
110
90
70
50
30
10
-10



3.3.2a

(mixture of diastereomers)




OBz
OH
Ph
3.3.4
10
9
8
7
6
5
4
3
2
1
0
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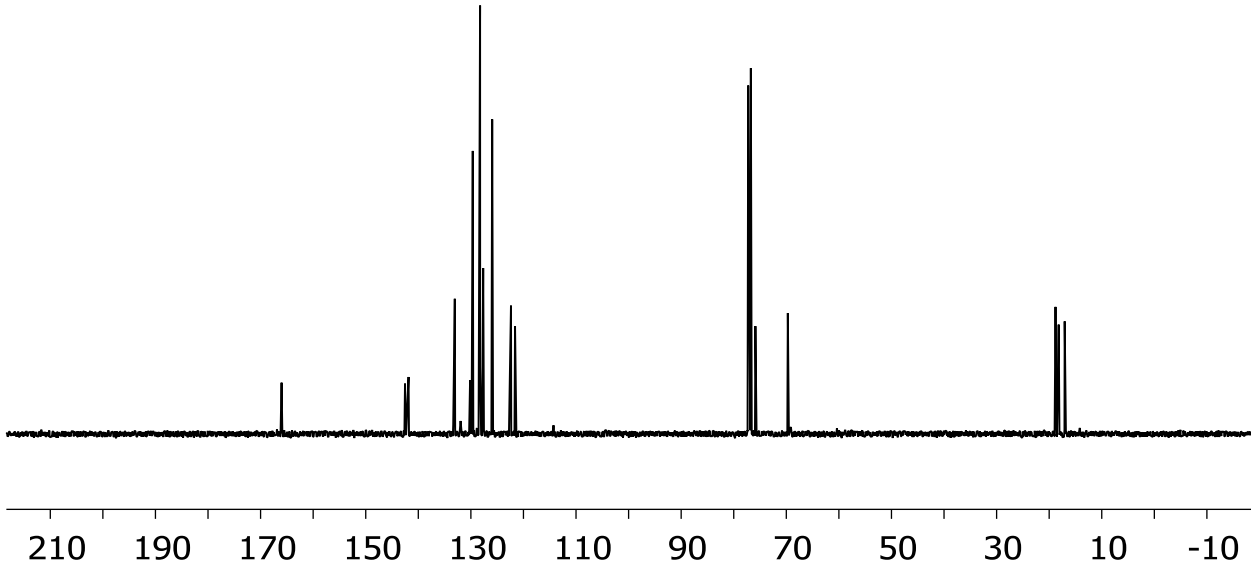
210
190
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10
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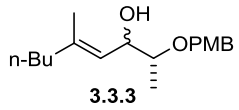
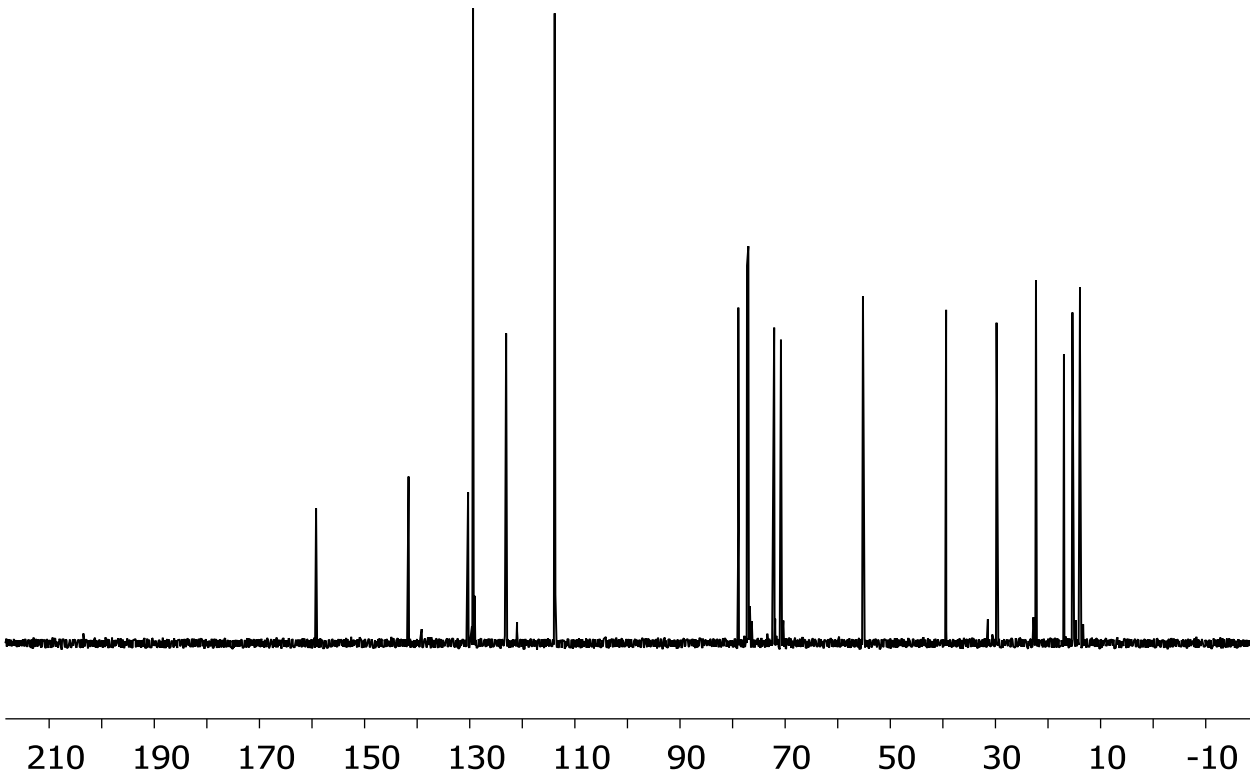
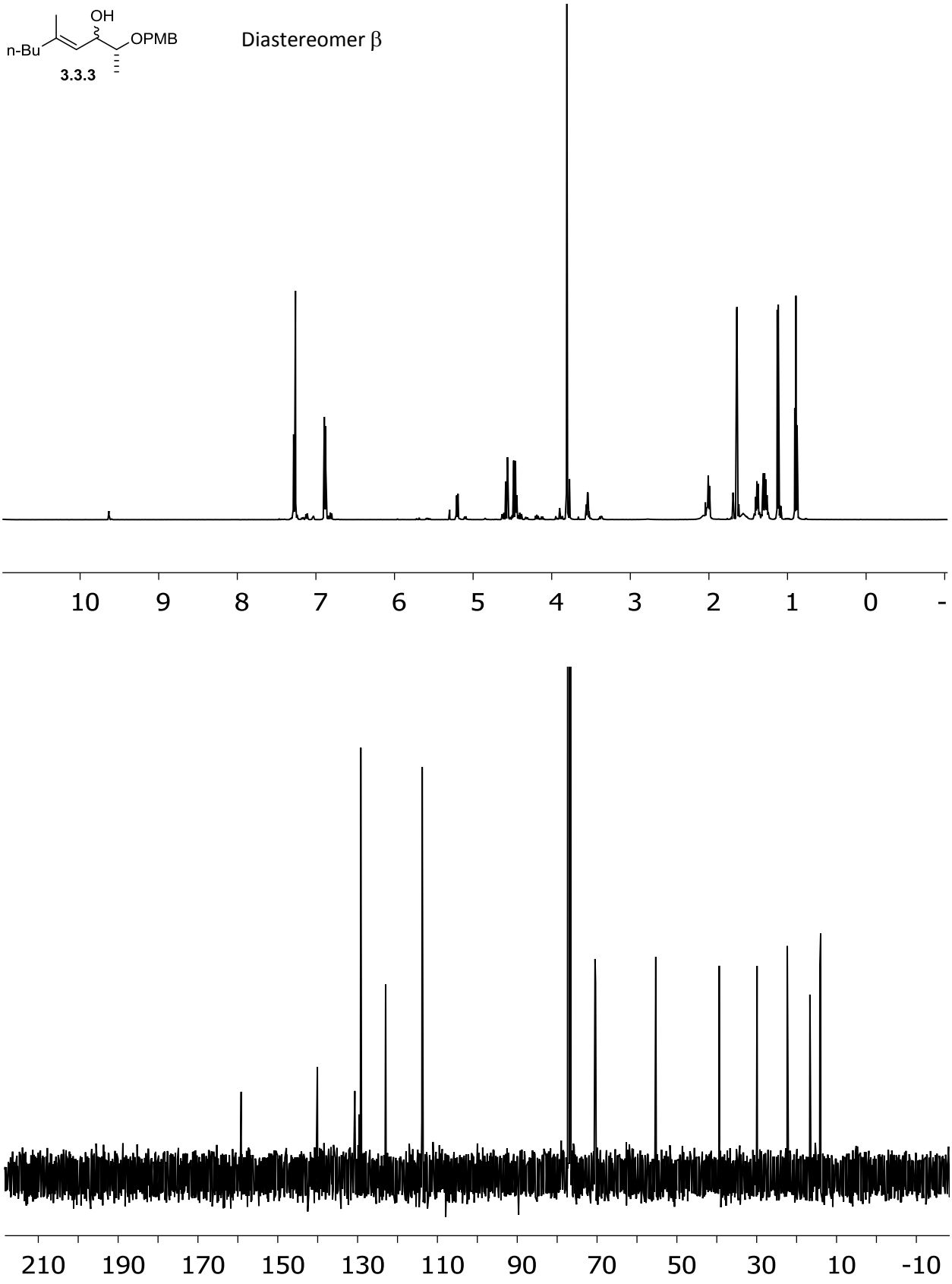


3.3.3

(Diastereomer α)




OH
n-Bu
OPMB
3.3.3
Diastereomer β
10
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210
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130
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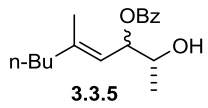
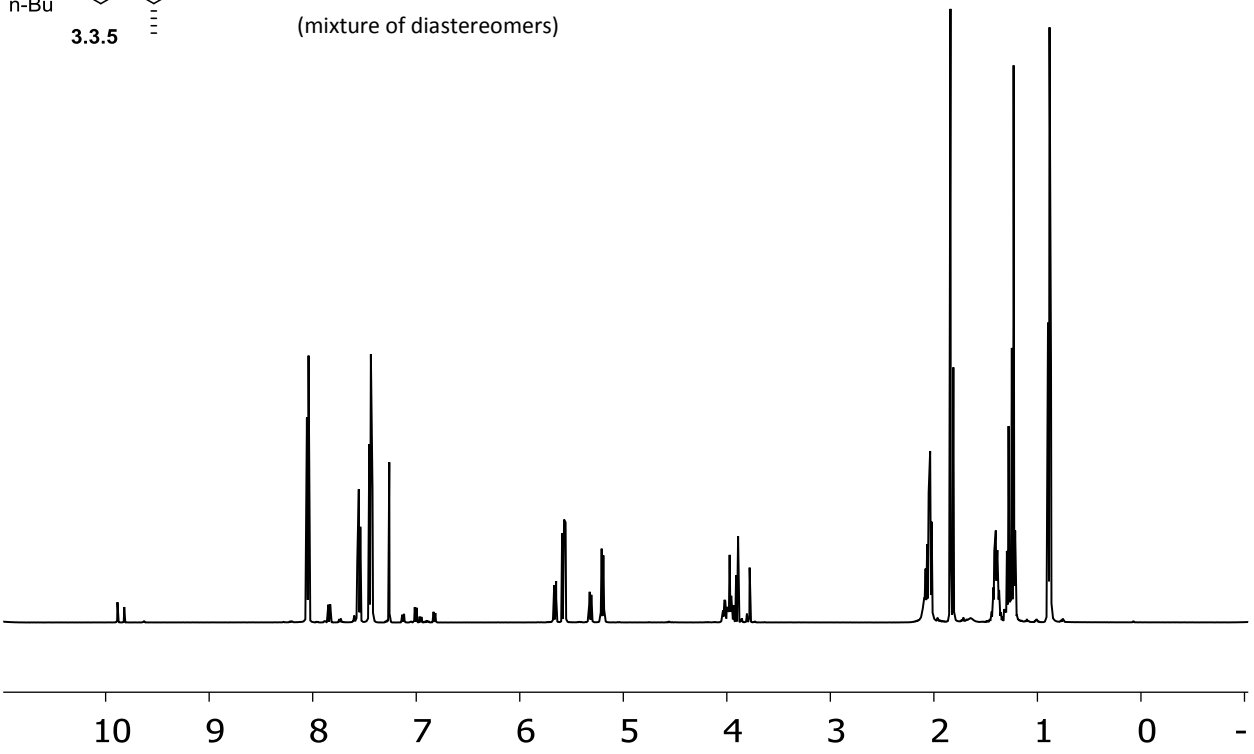
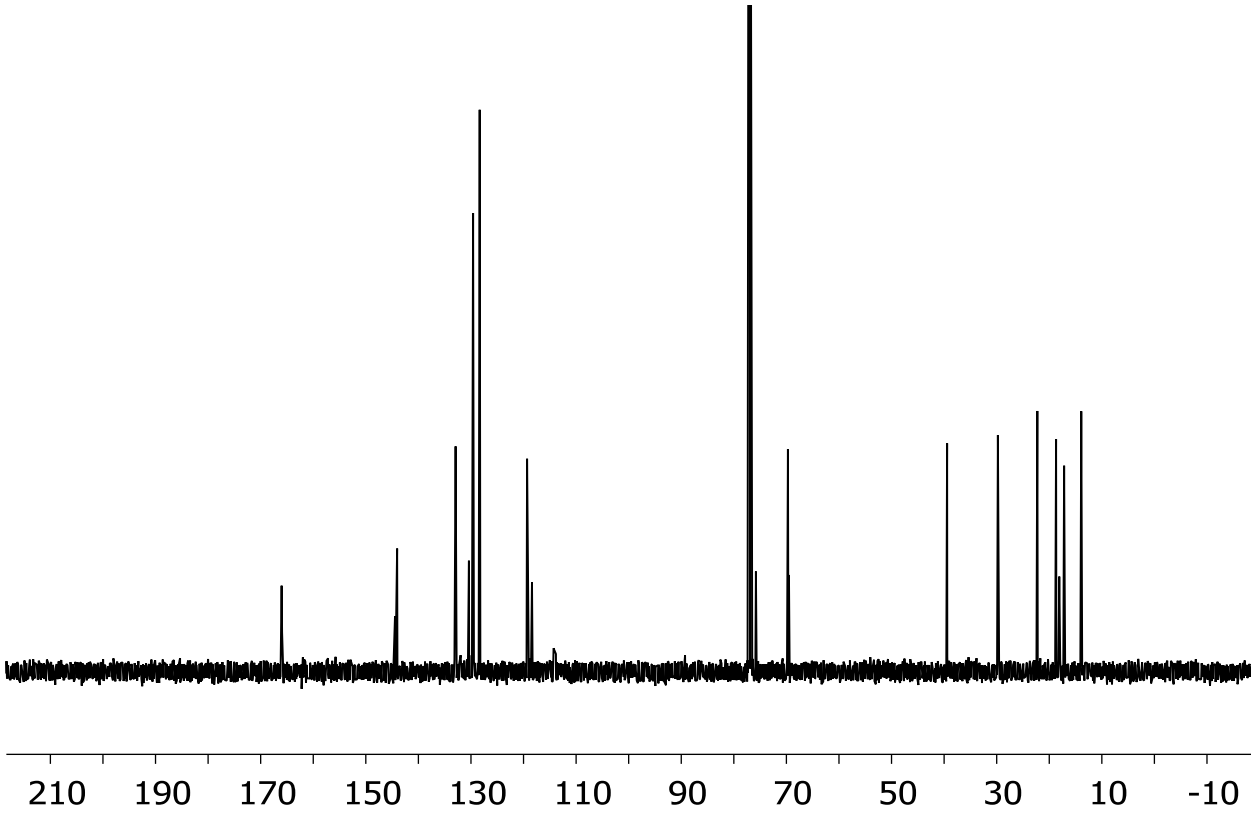
-10

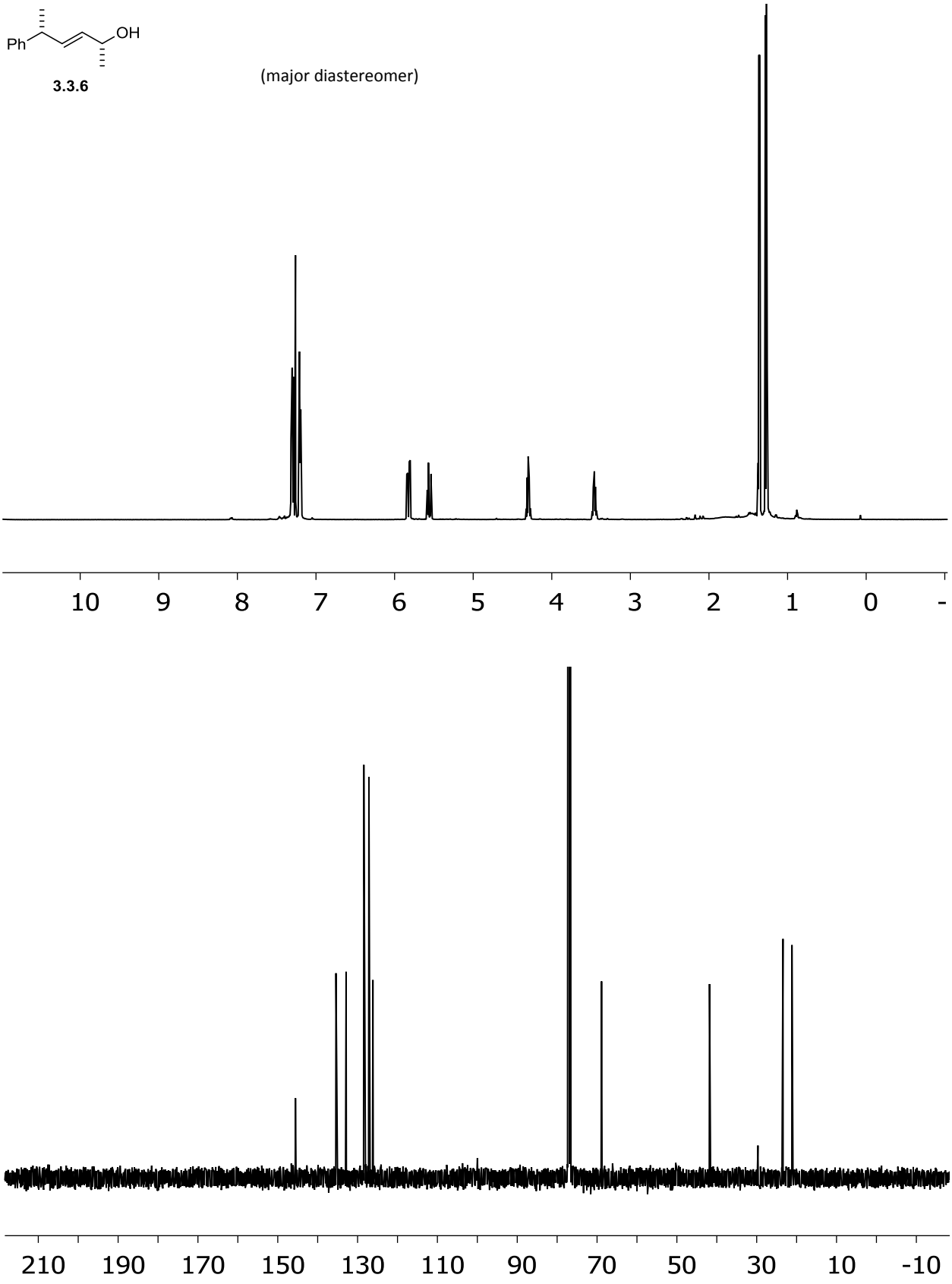


3.3.5

(mixture of diastereomers)






Ph
OH
3.3.6
(major diastereomer)
10
9
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110
90
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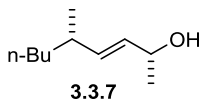
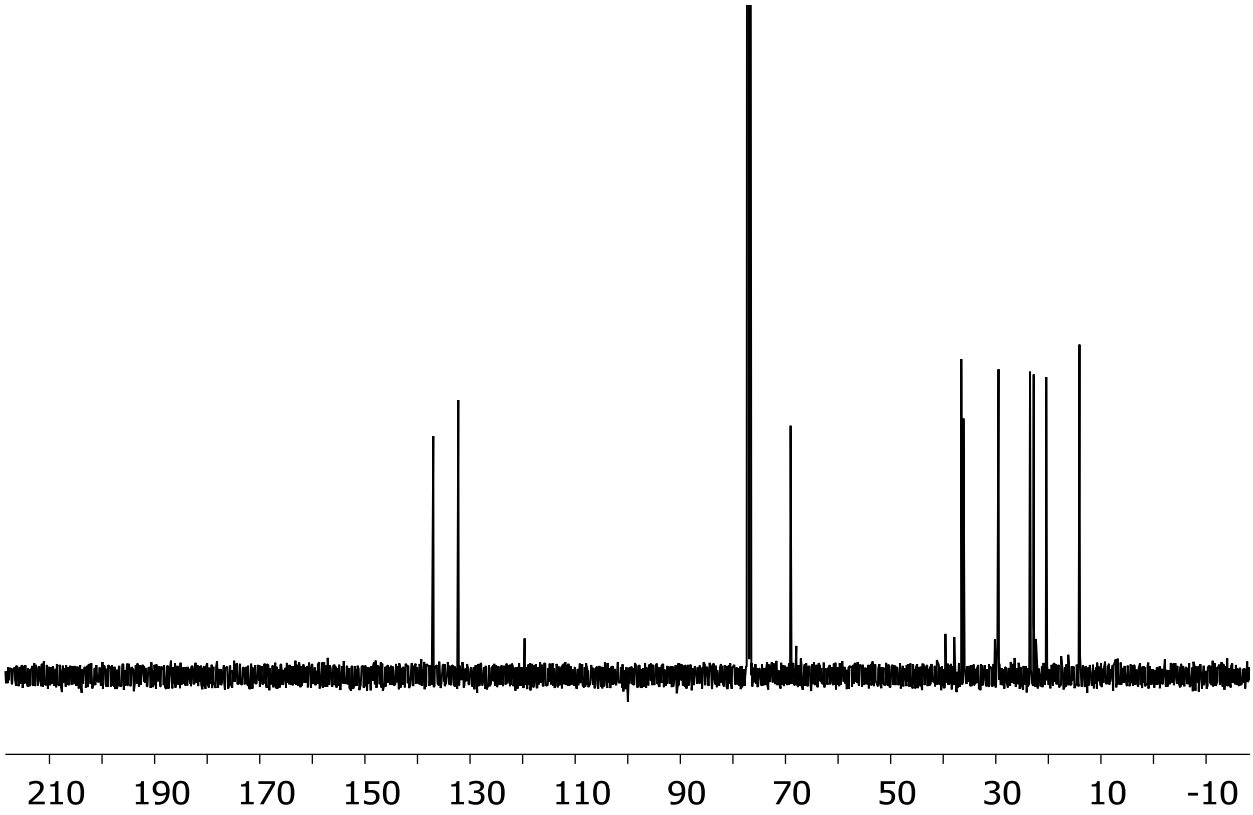
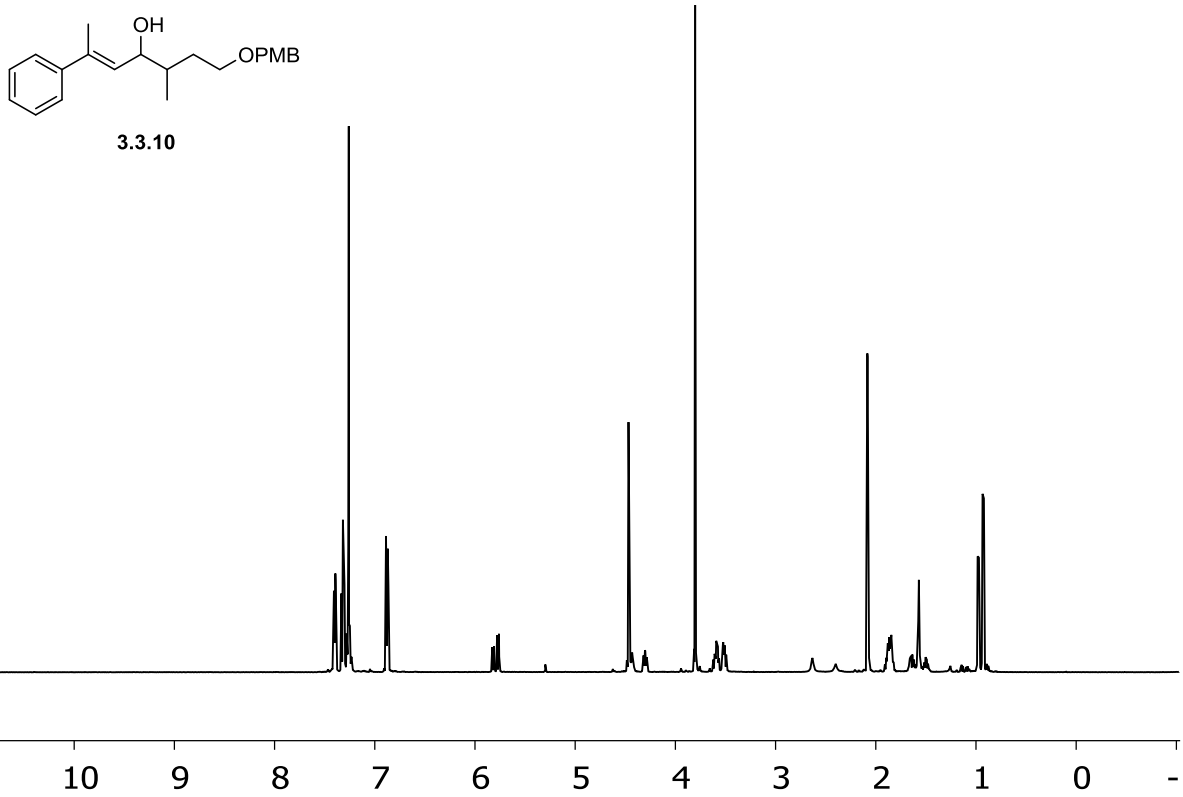
50
30
10
-10



3.3.7

(major diastereomer)





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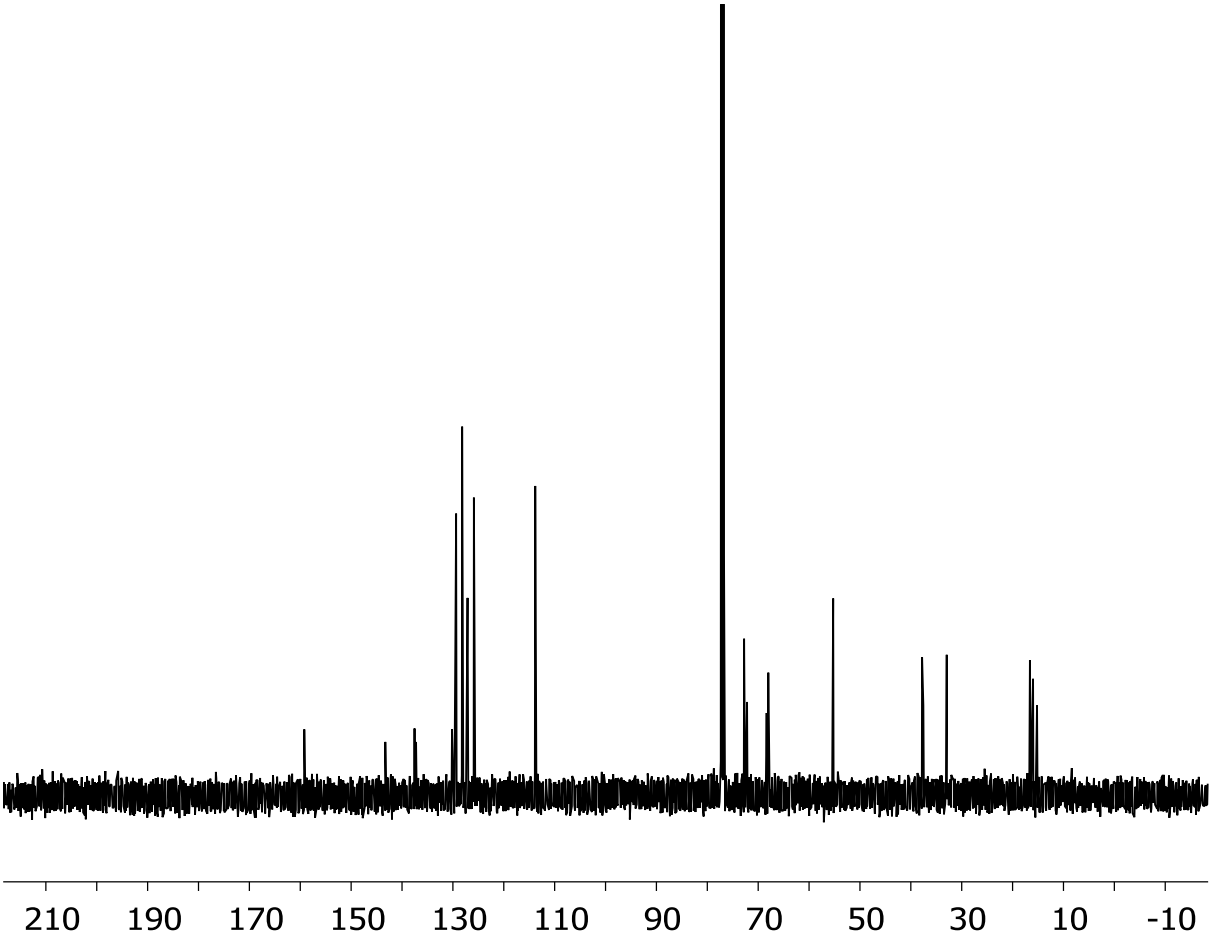
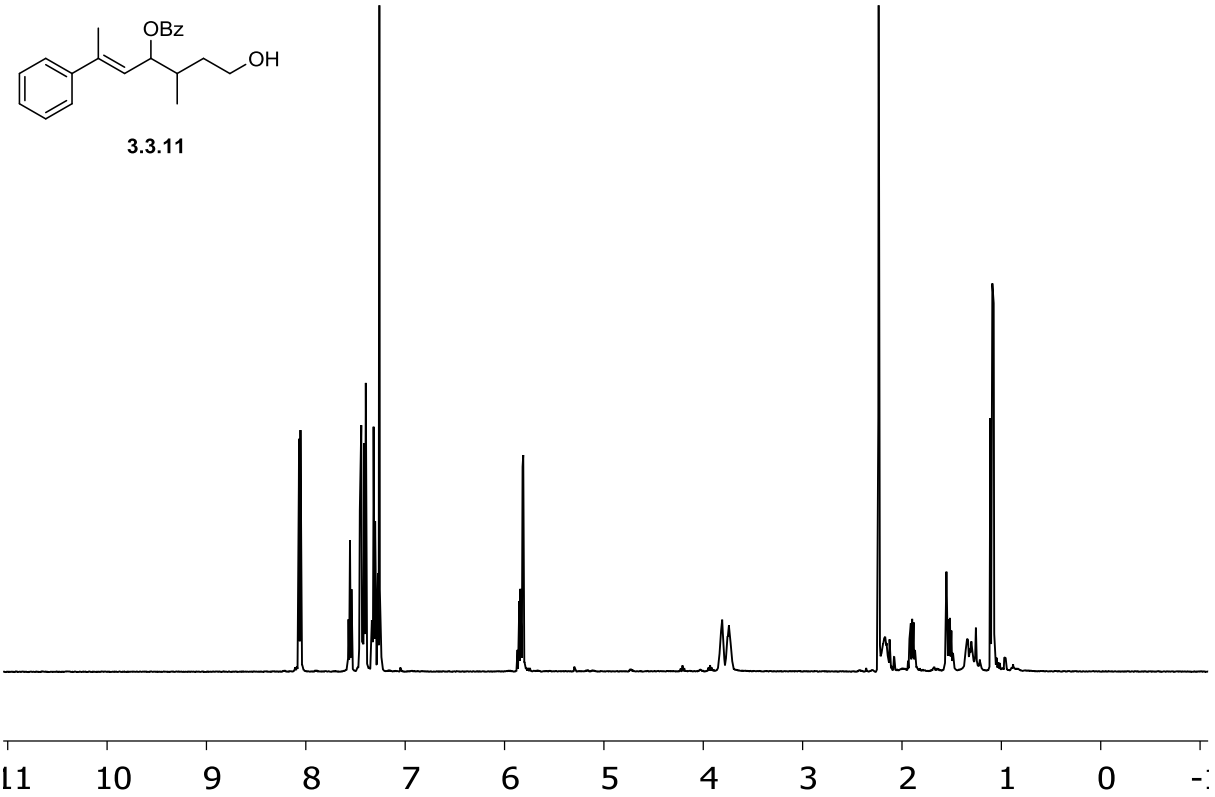
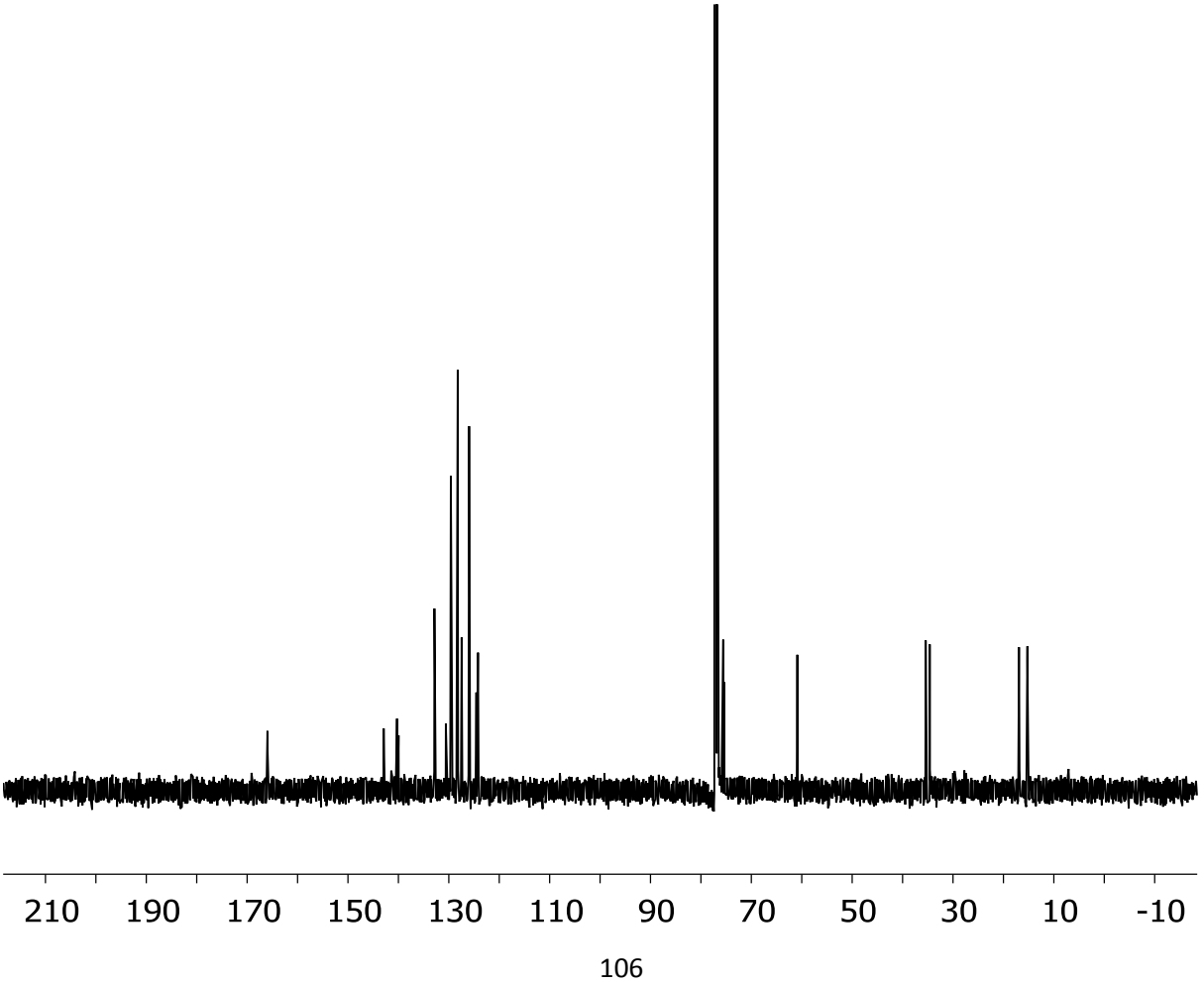
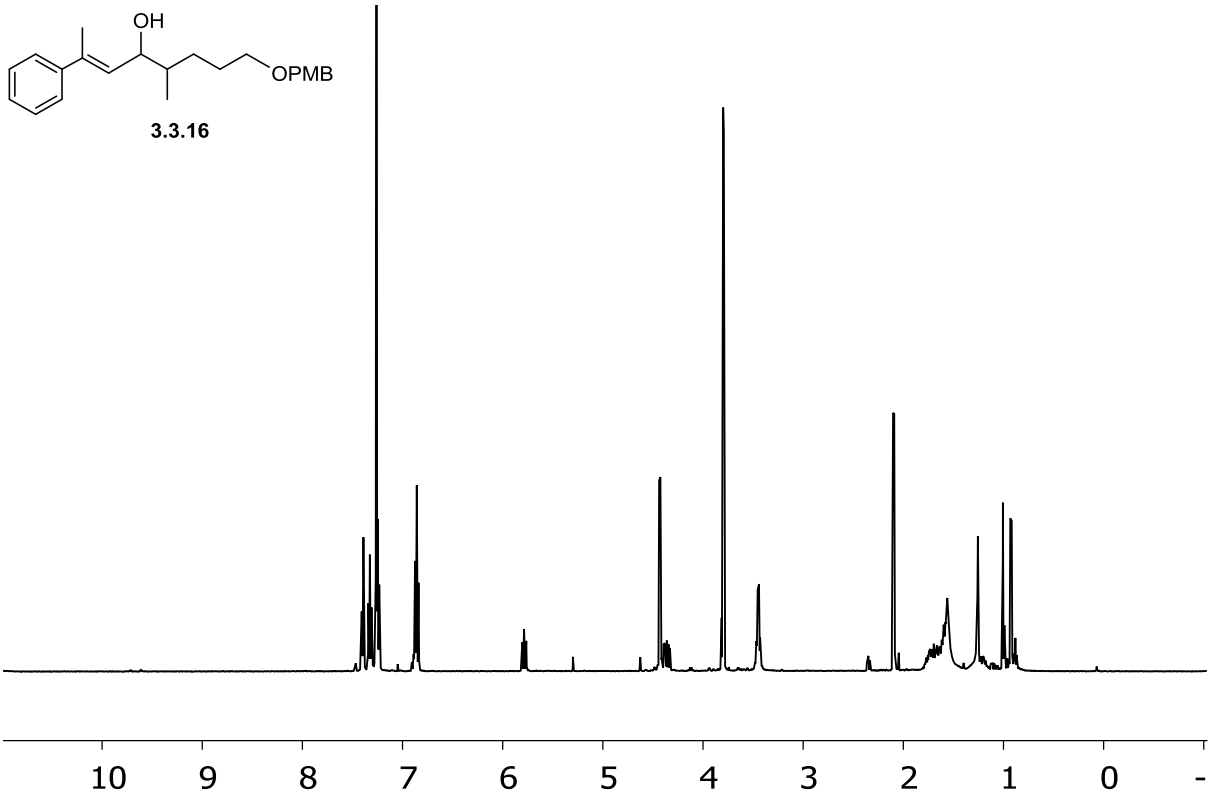




3.3.11





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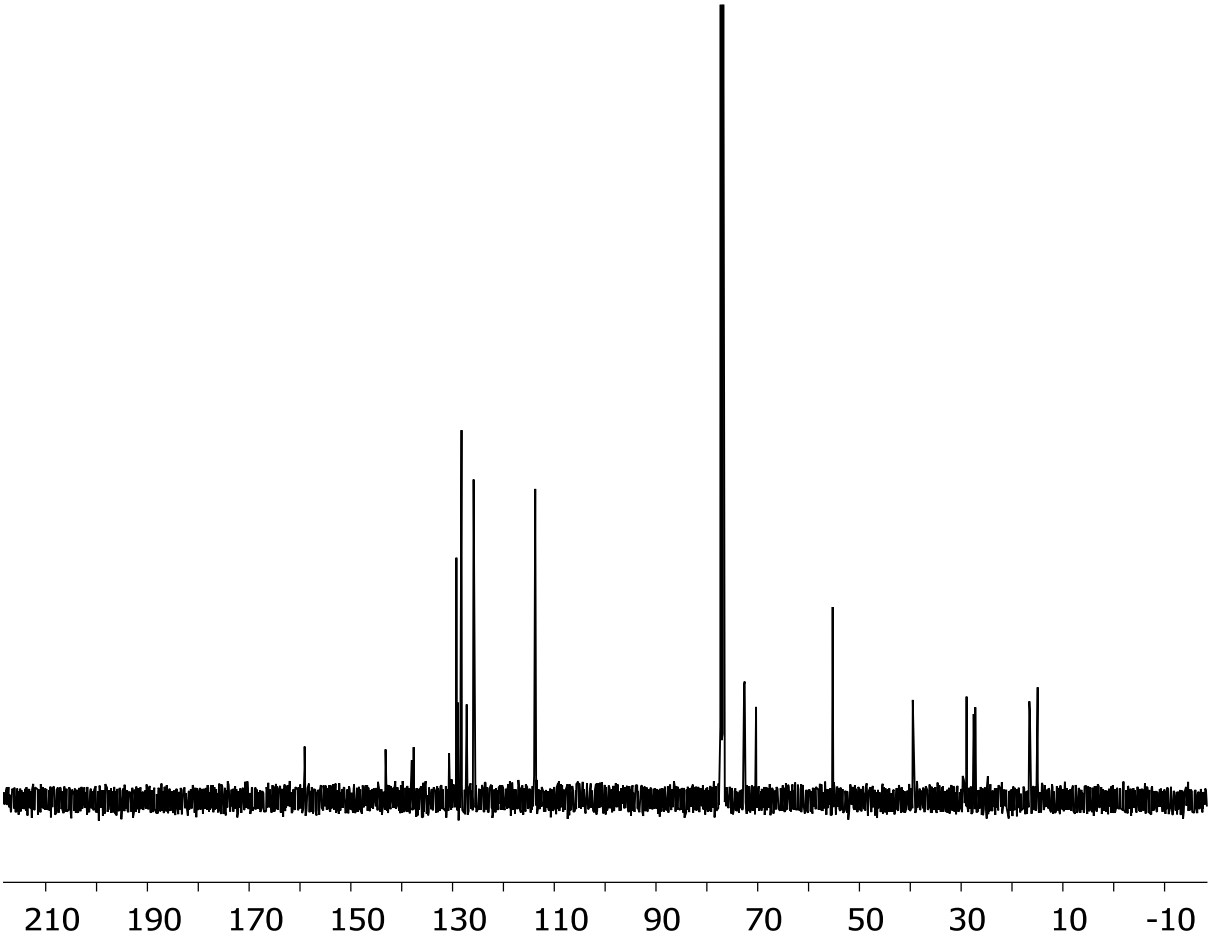
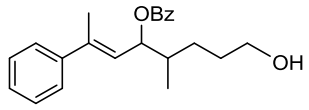
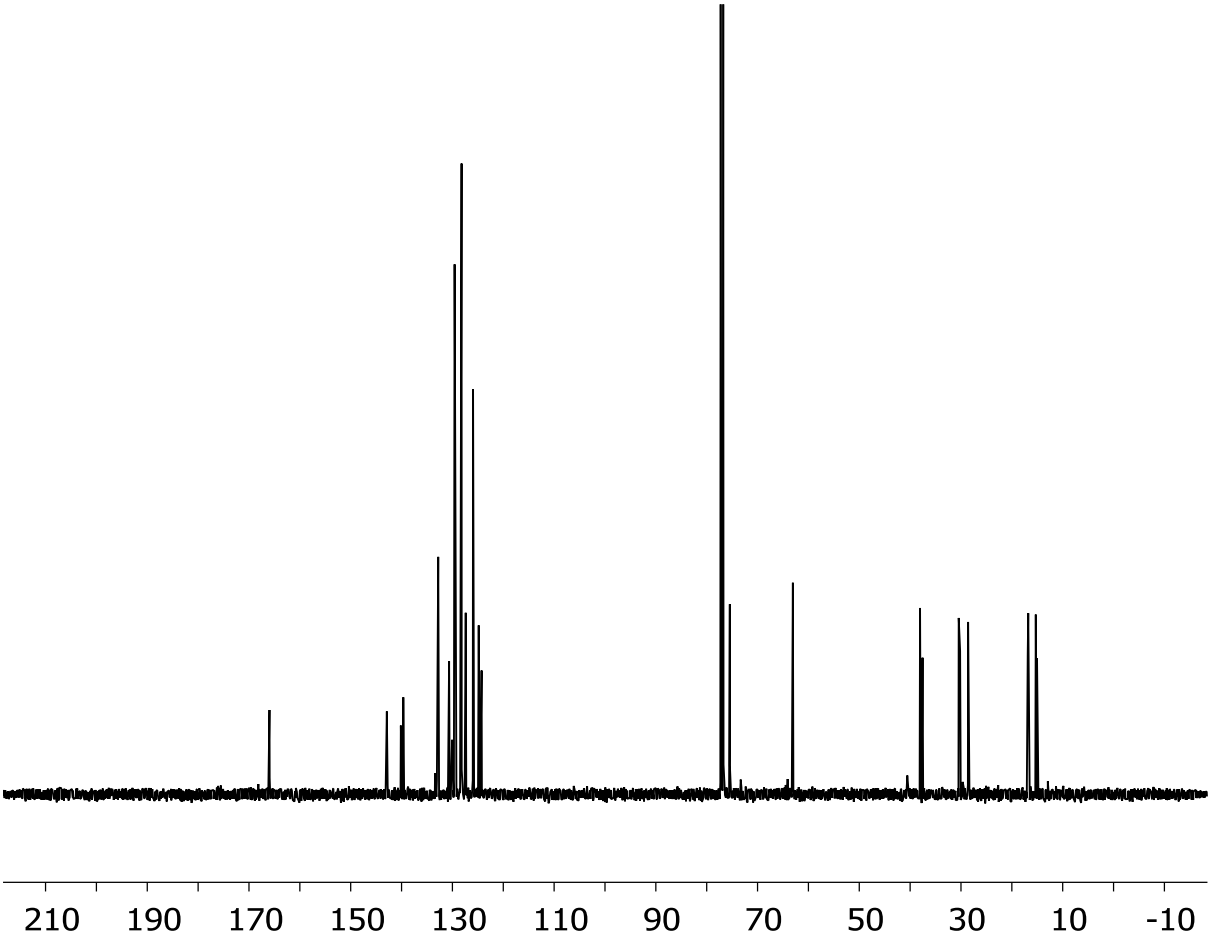
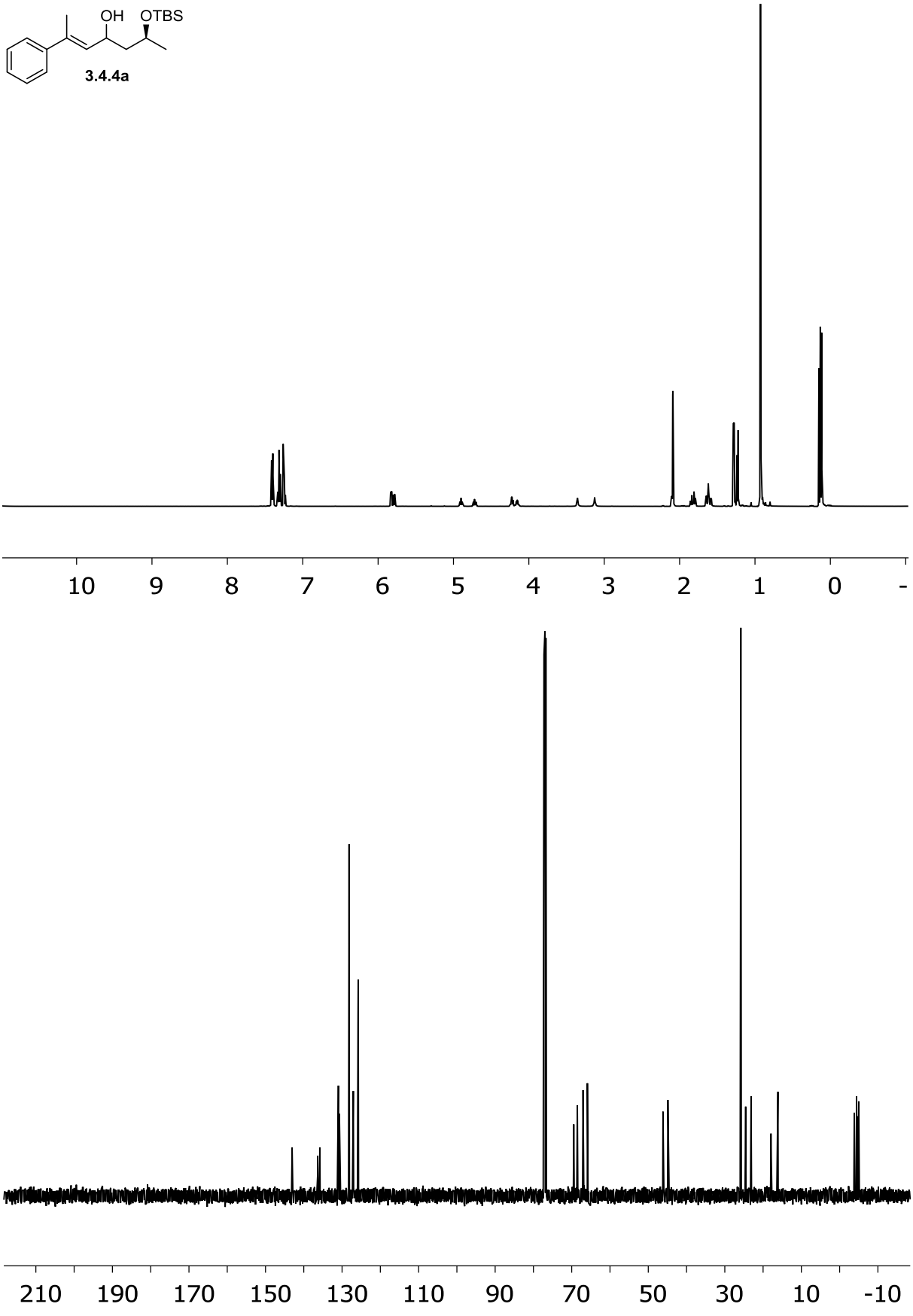




3.3.17




OH
OTBS
3.4.4a
10
9
8
7
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4
3
2
1
0
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210
190
170
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130
110
90
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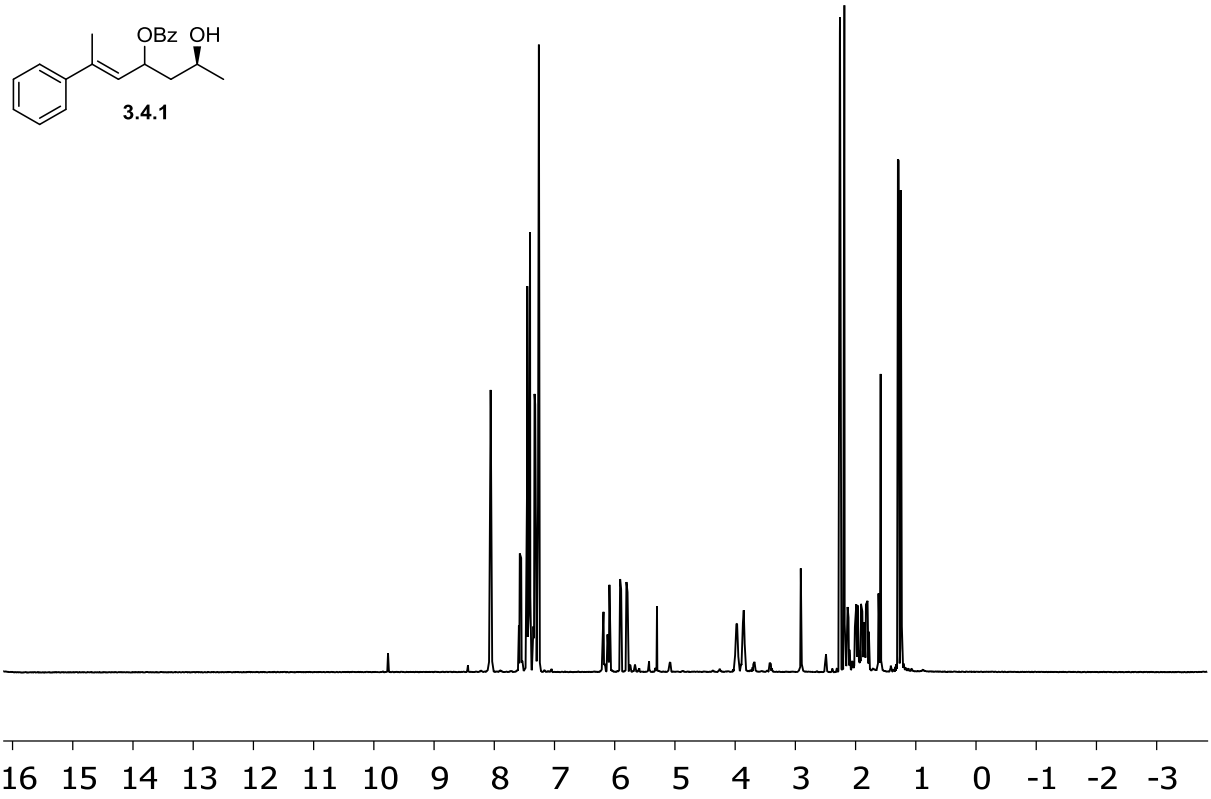
50
30
10
-10


OBz
OH
3.4.1
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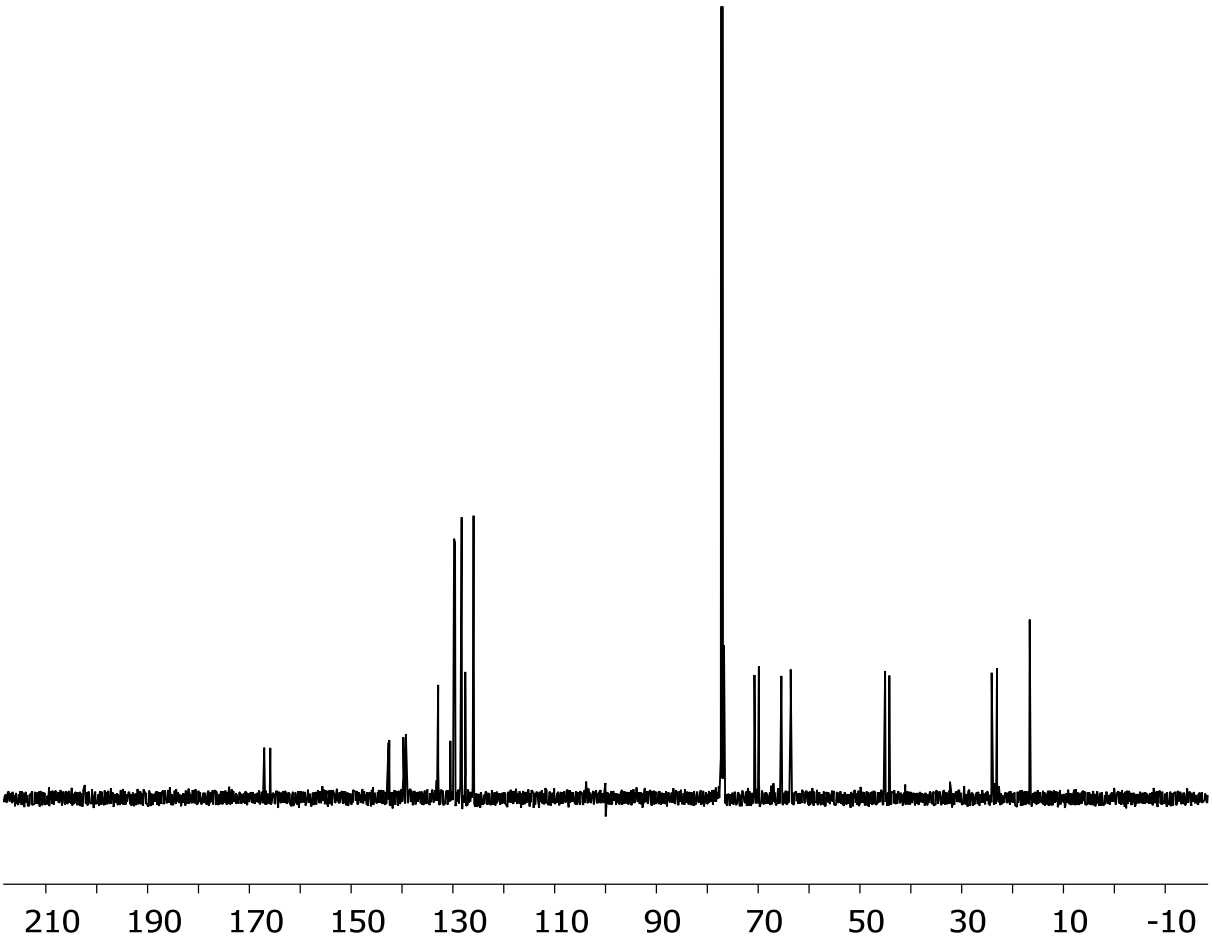
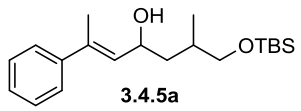
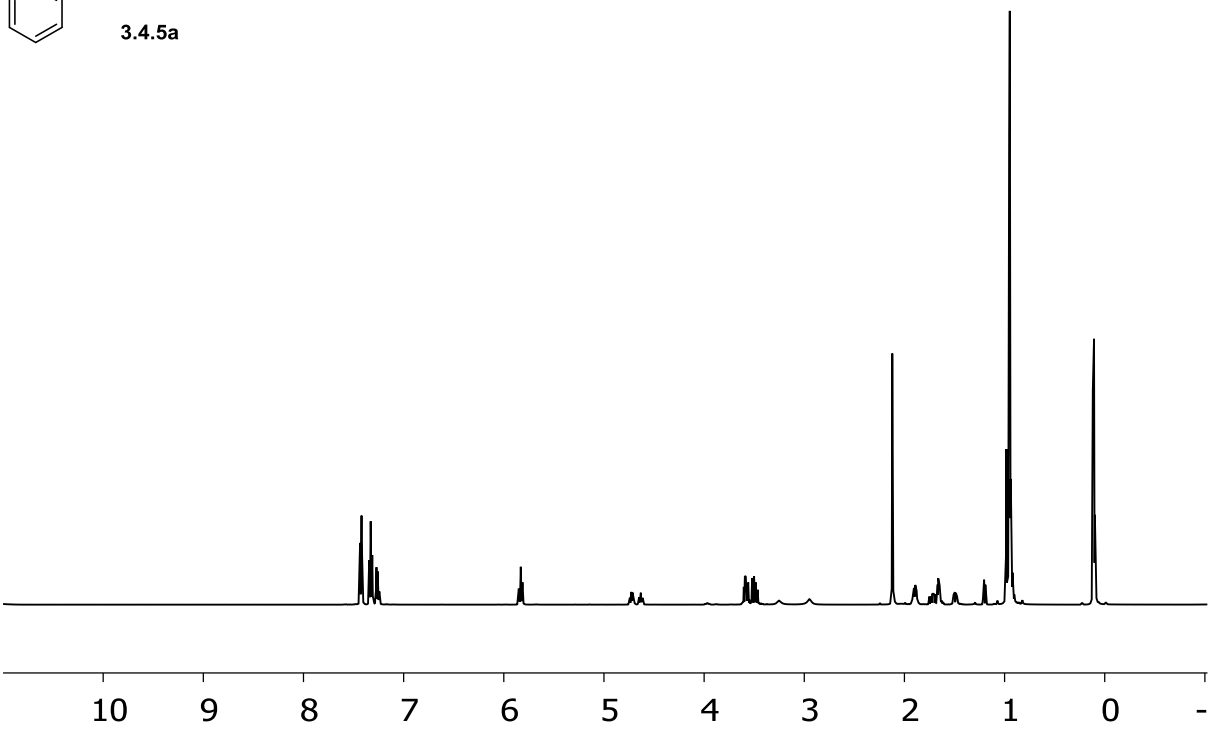
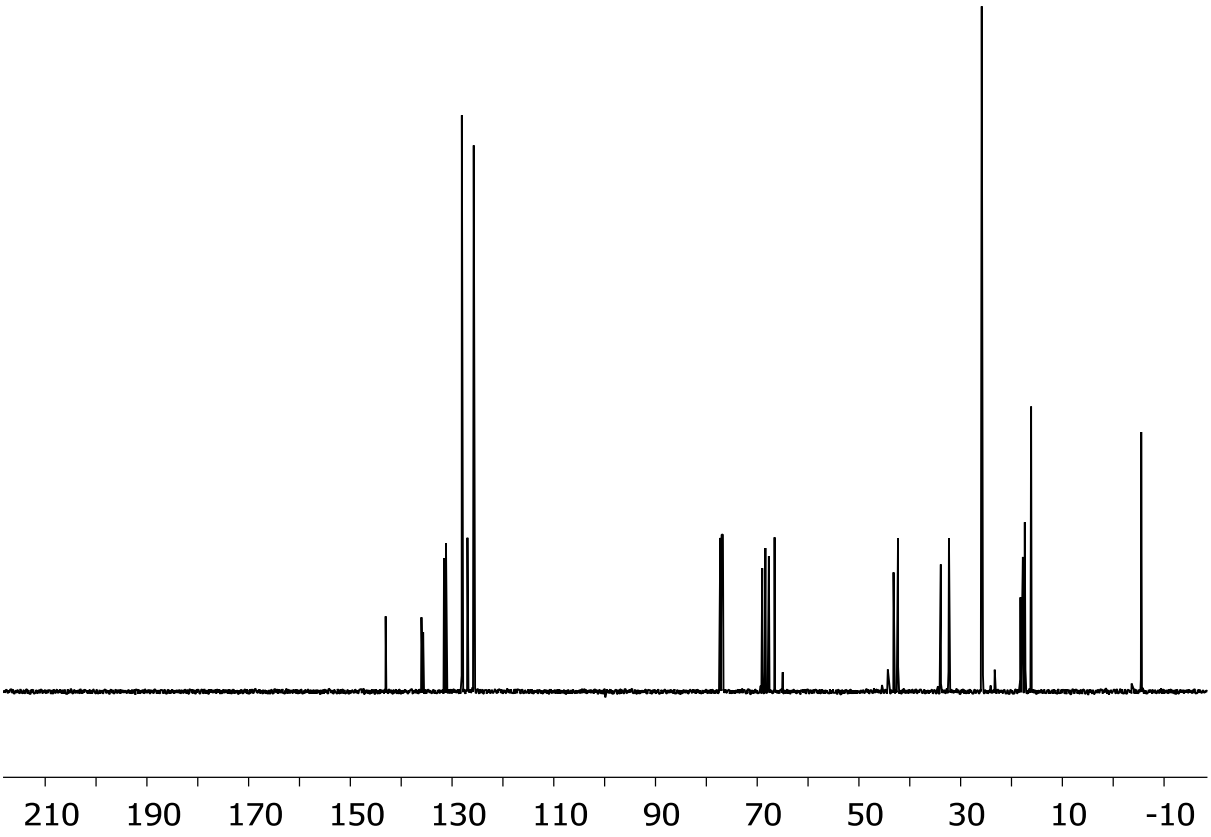
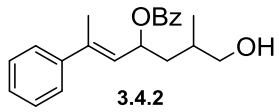

210 190 170 150 130 110 90 70 50 30 10 -10



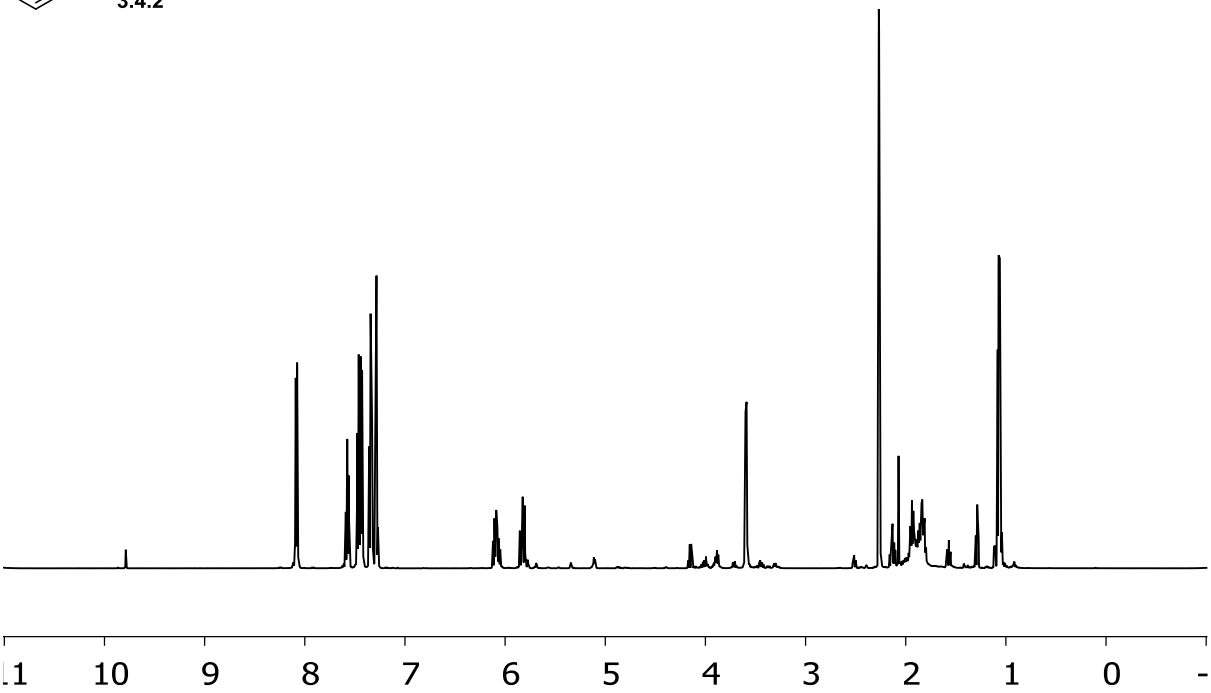
3.4.5a

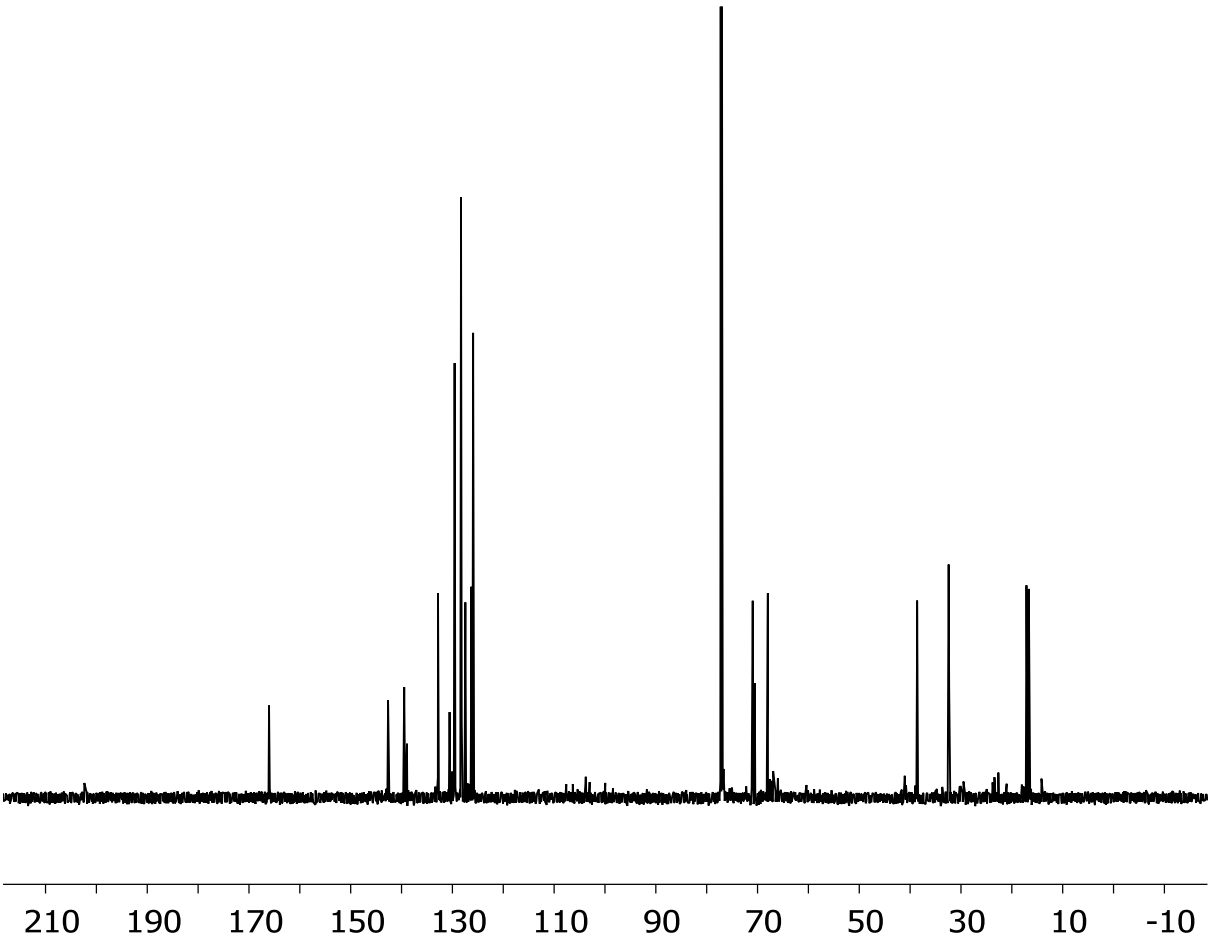


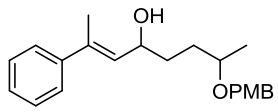




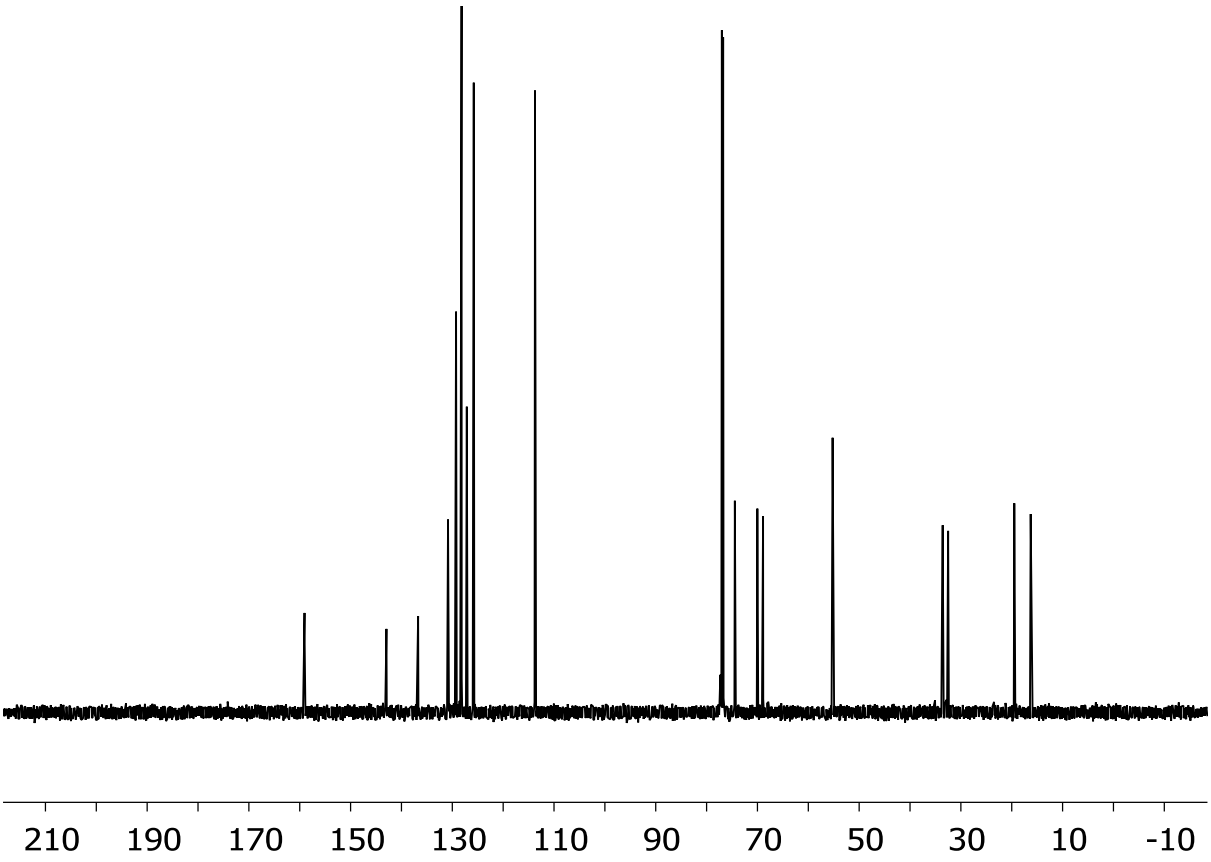
3.4.2

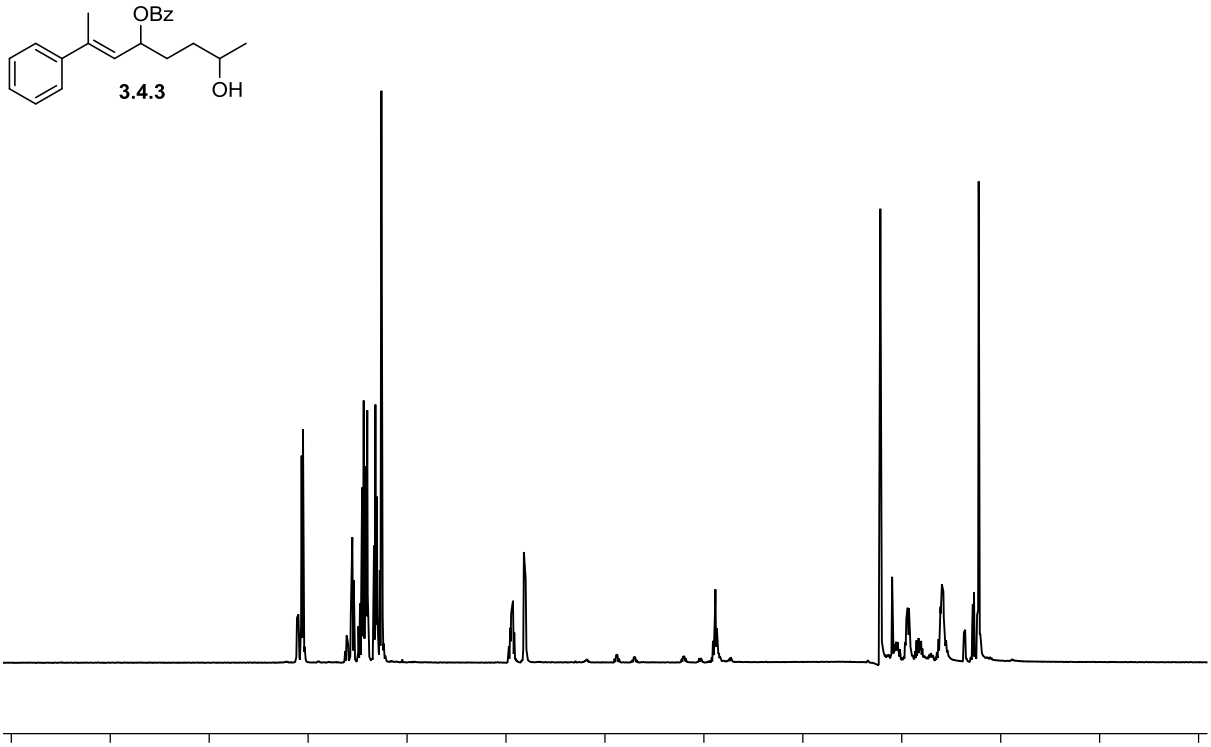






3.4.3a




OBz
OH
3.4.3
11
10
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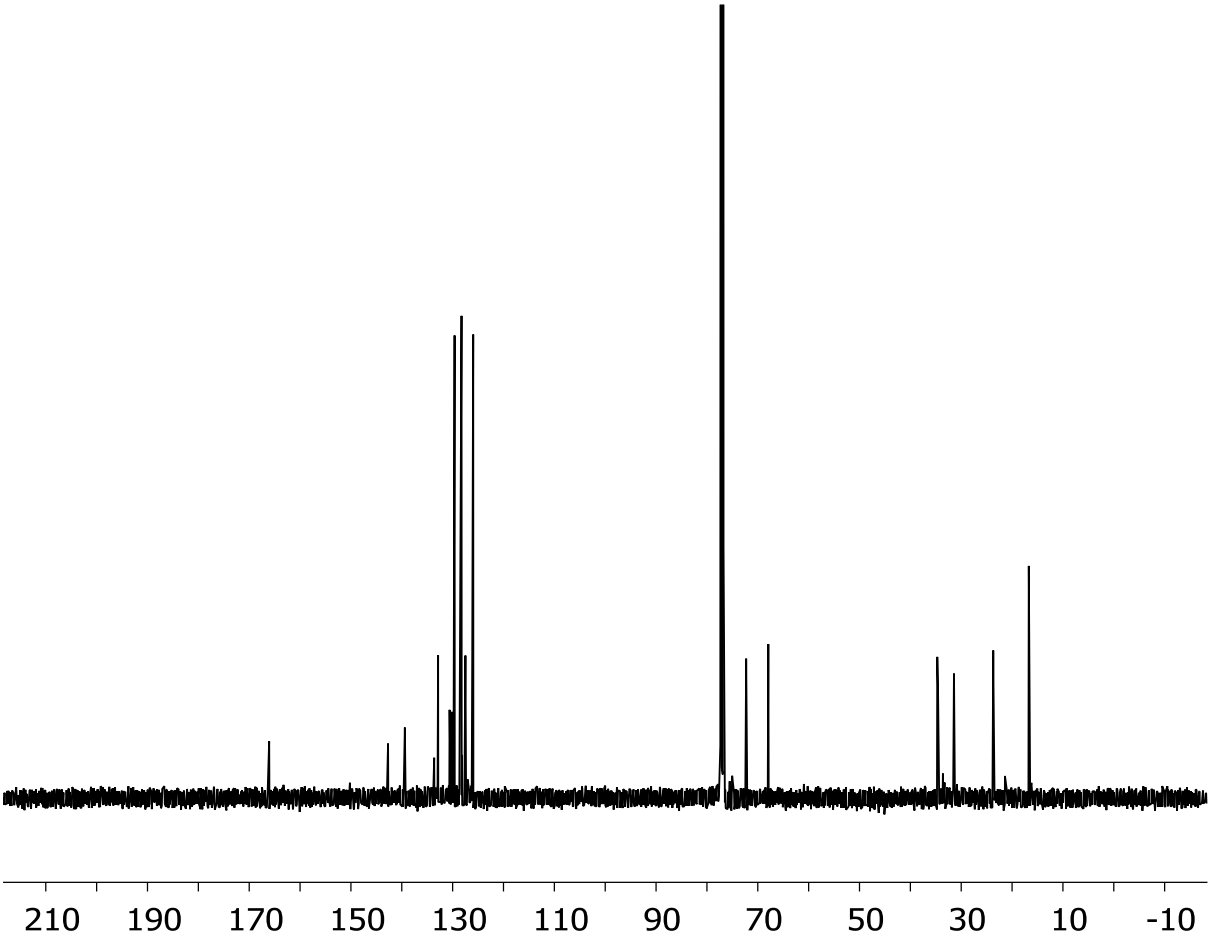
3
2
1
0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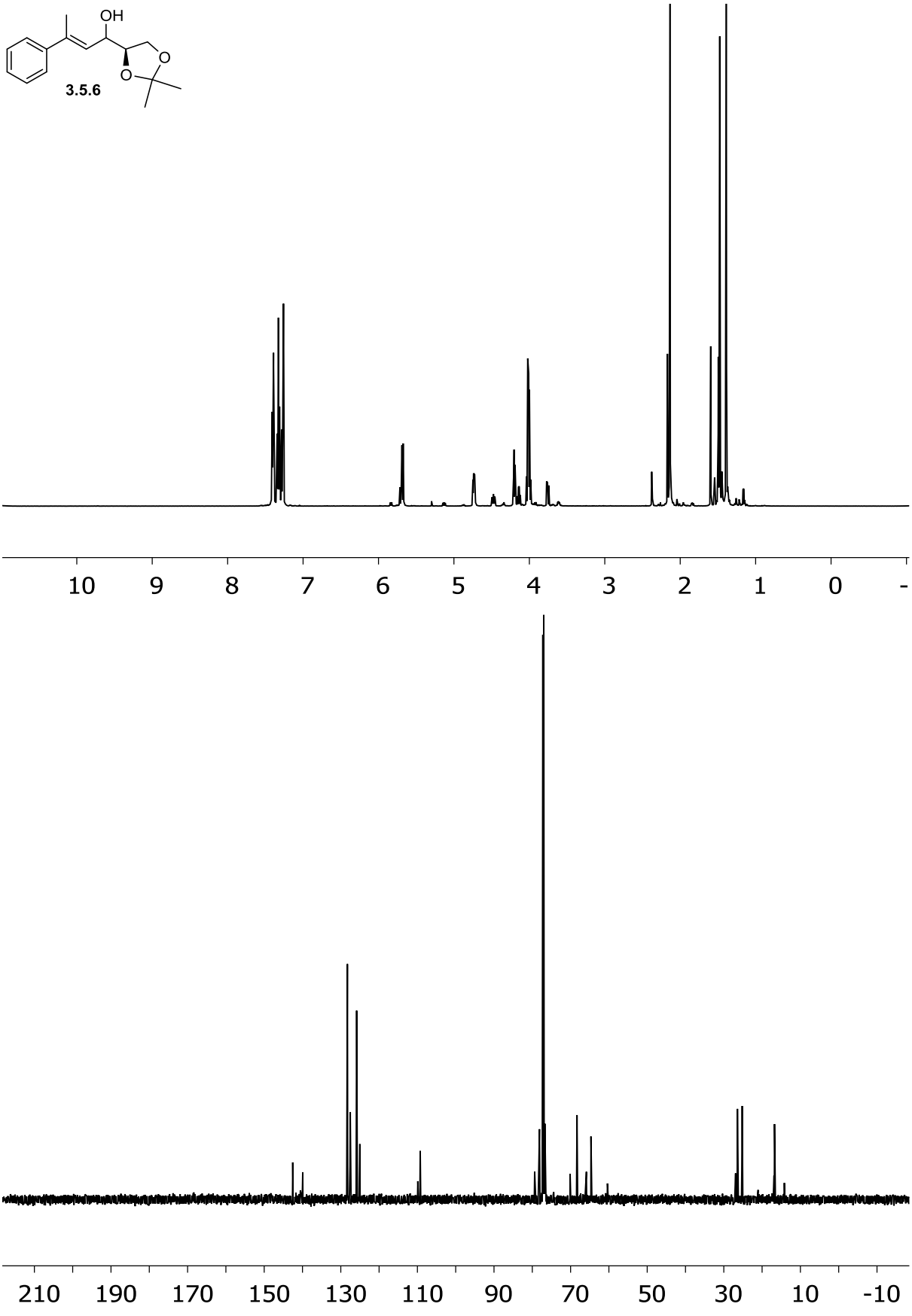
OH
O
O
3.5.6
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210
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170
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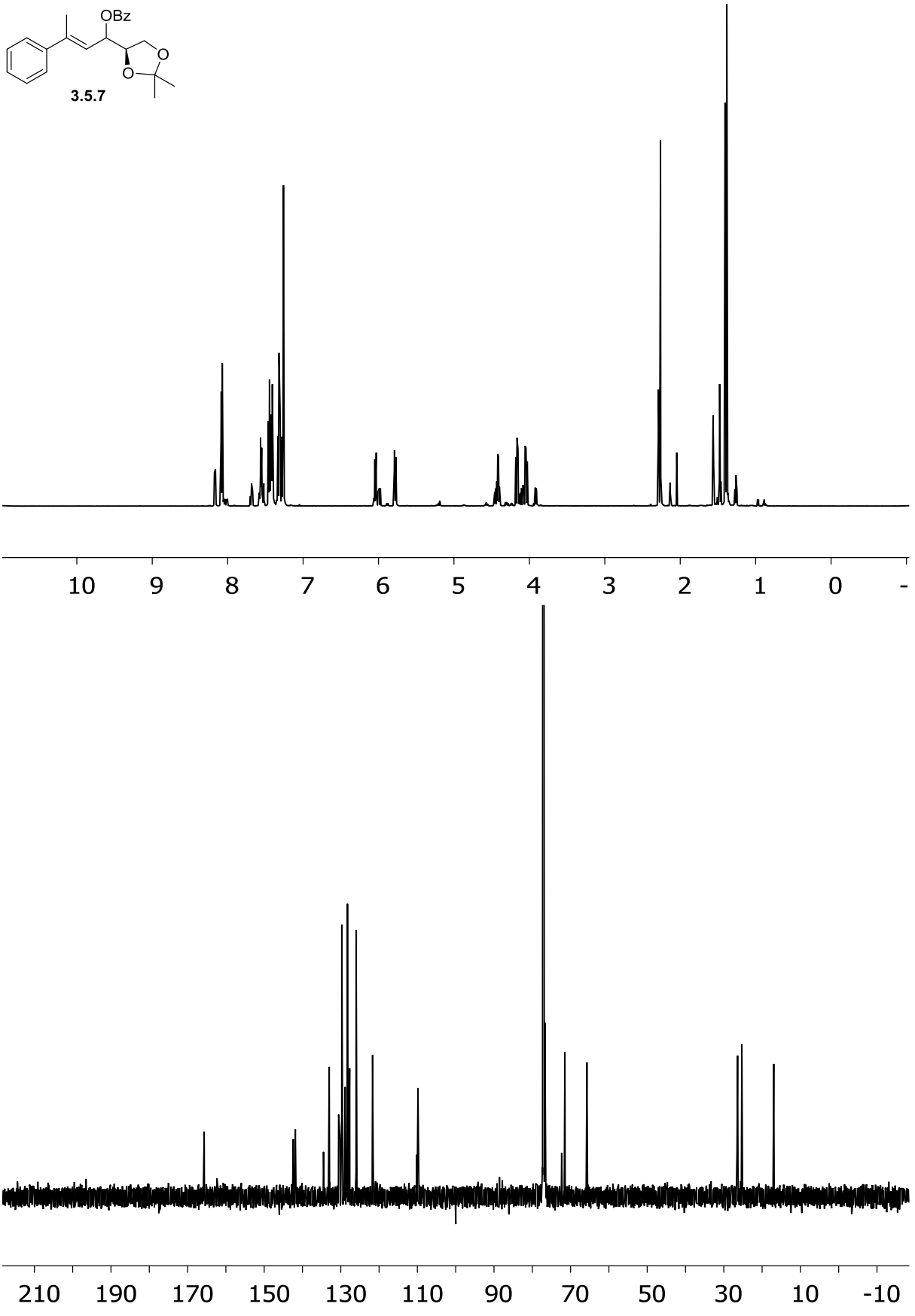
-10


OBz
O
O
3.5.7
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210
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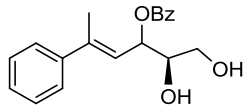
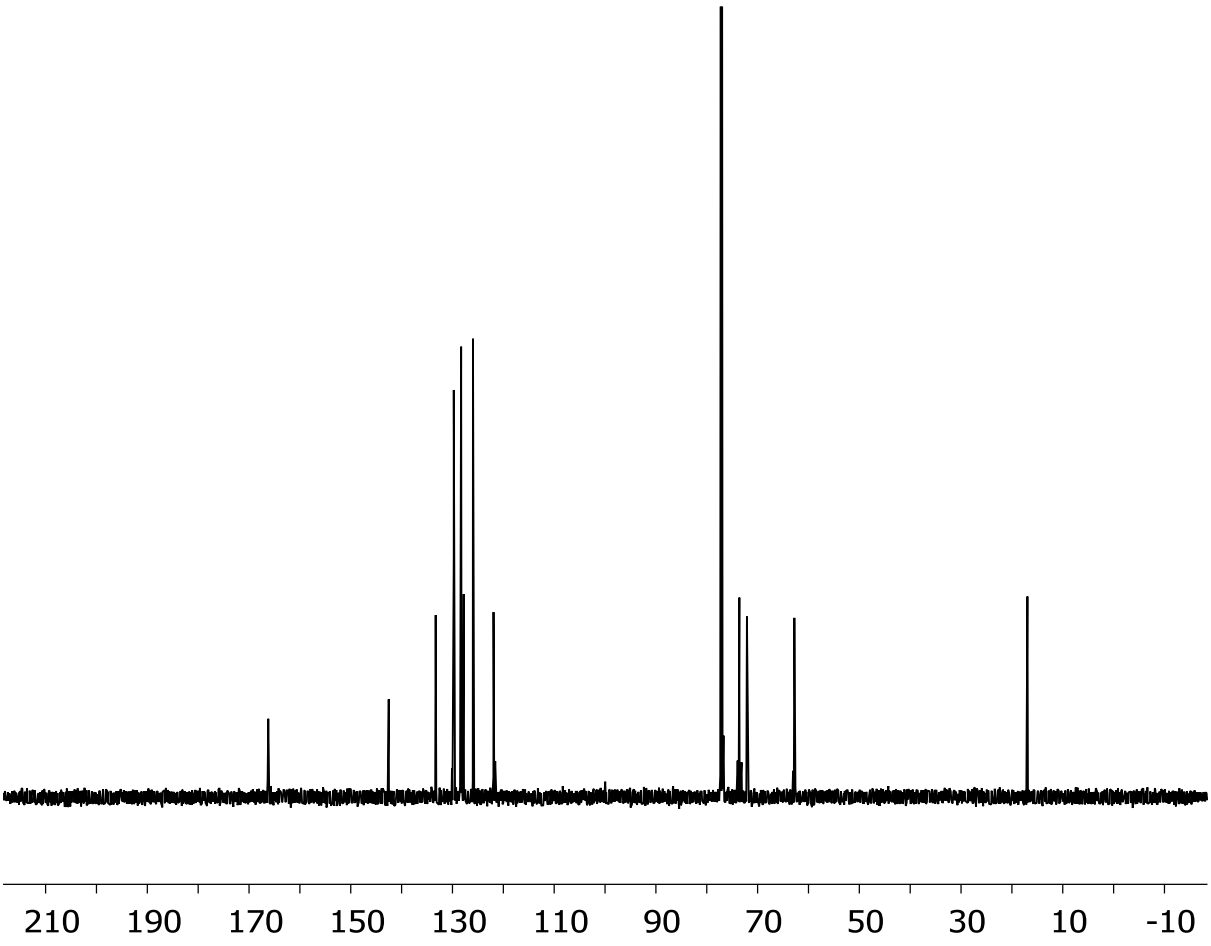
-10



3.5.8




OBz
OTBS
OH

3.5.9

11
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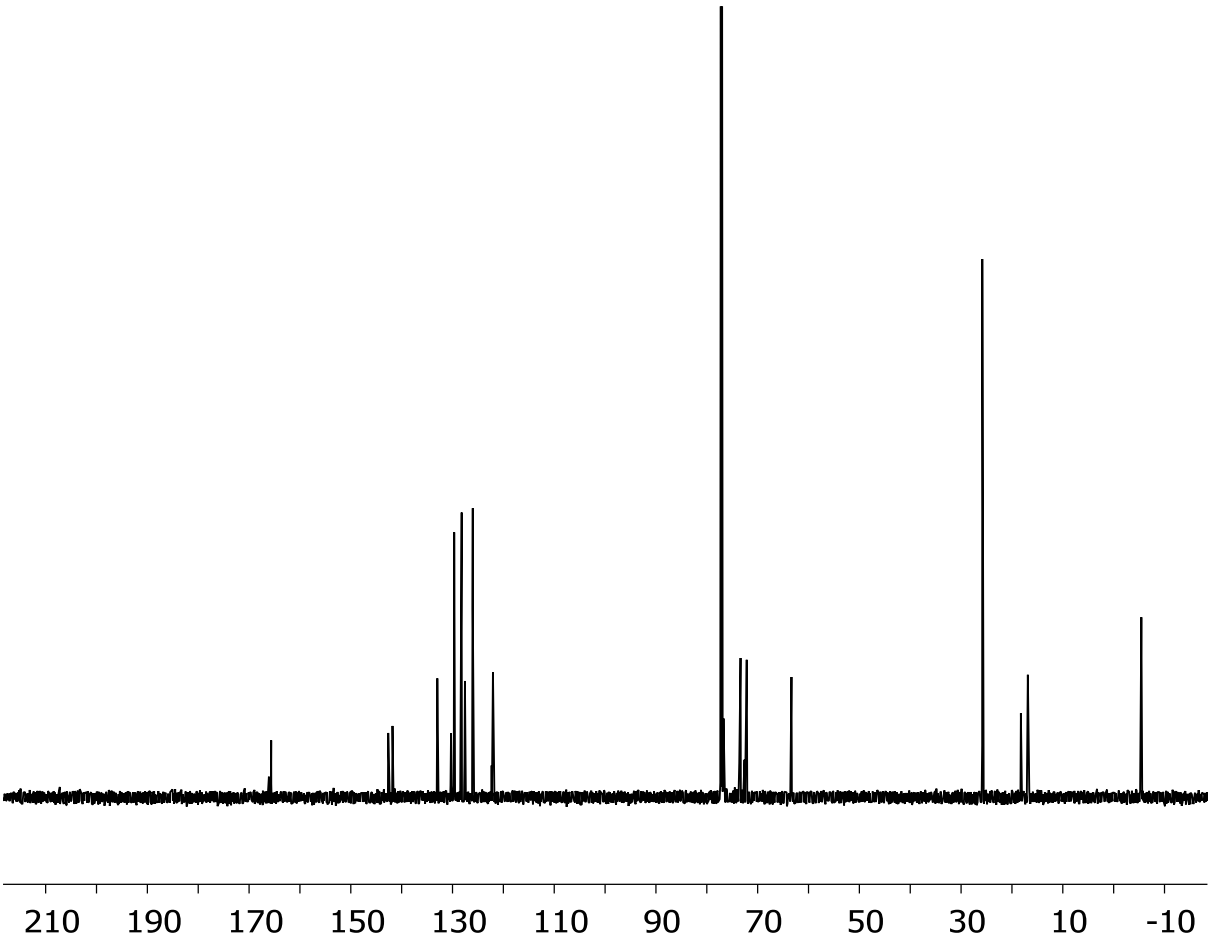
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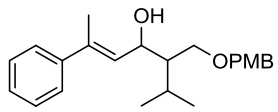

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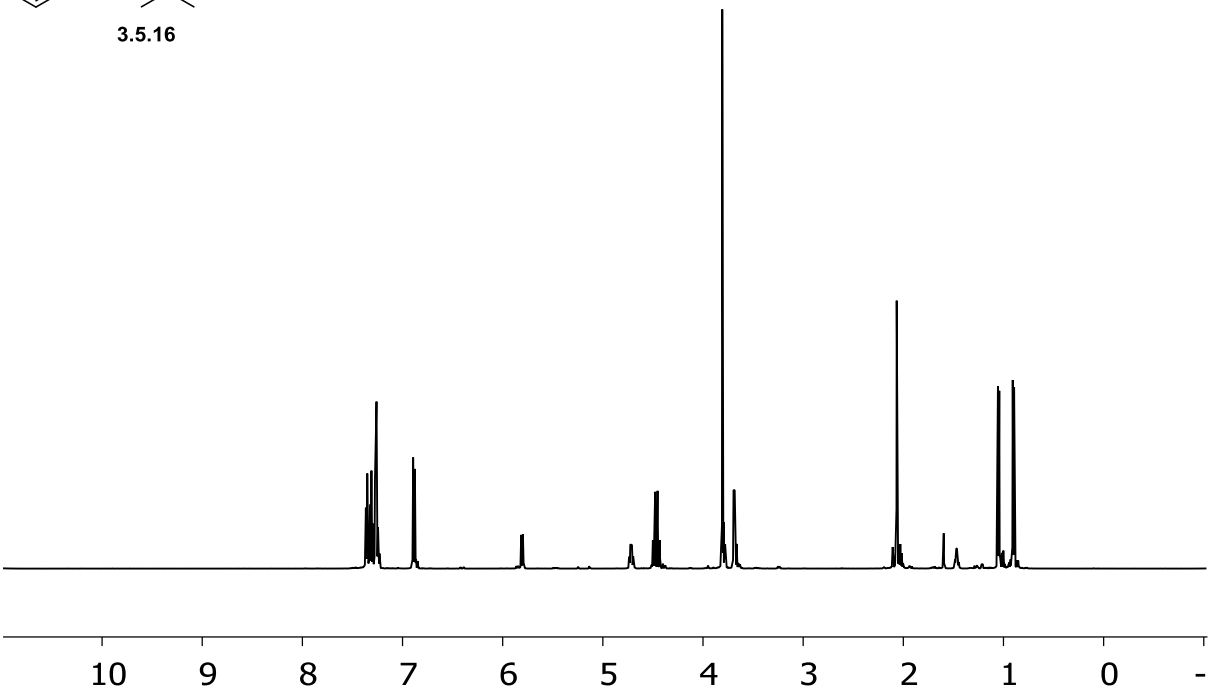

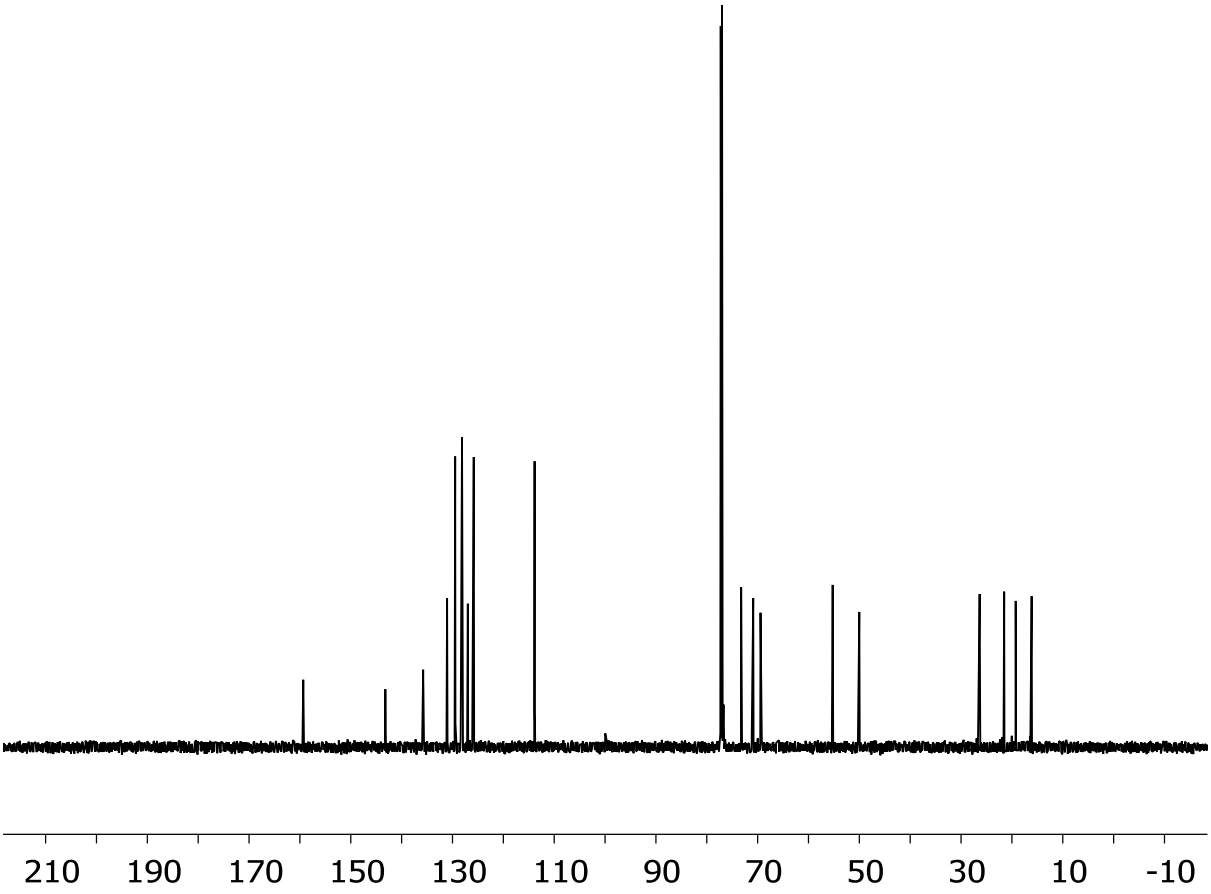

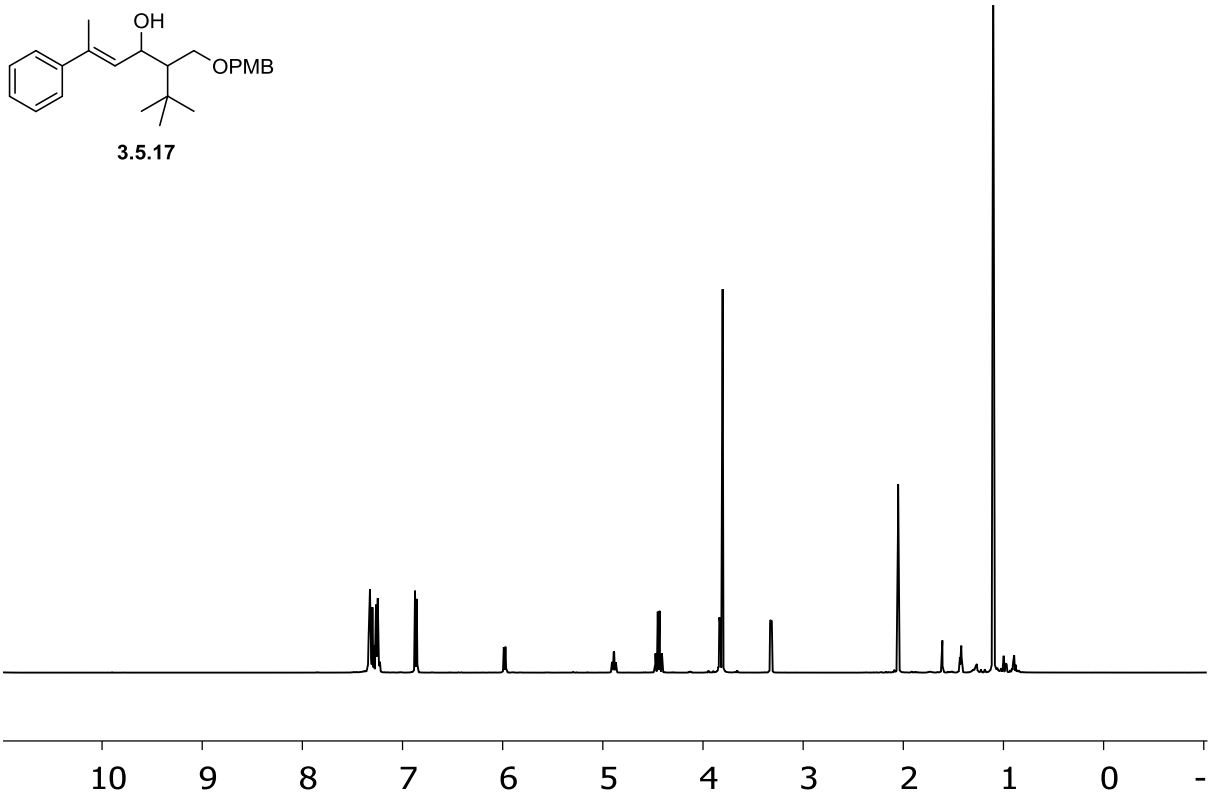
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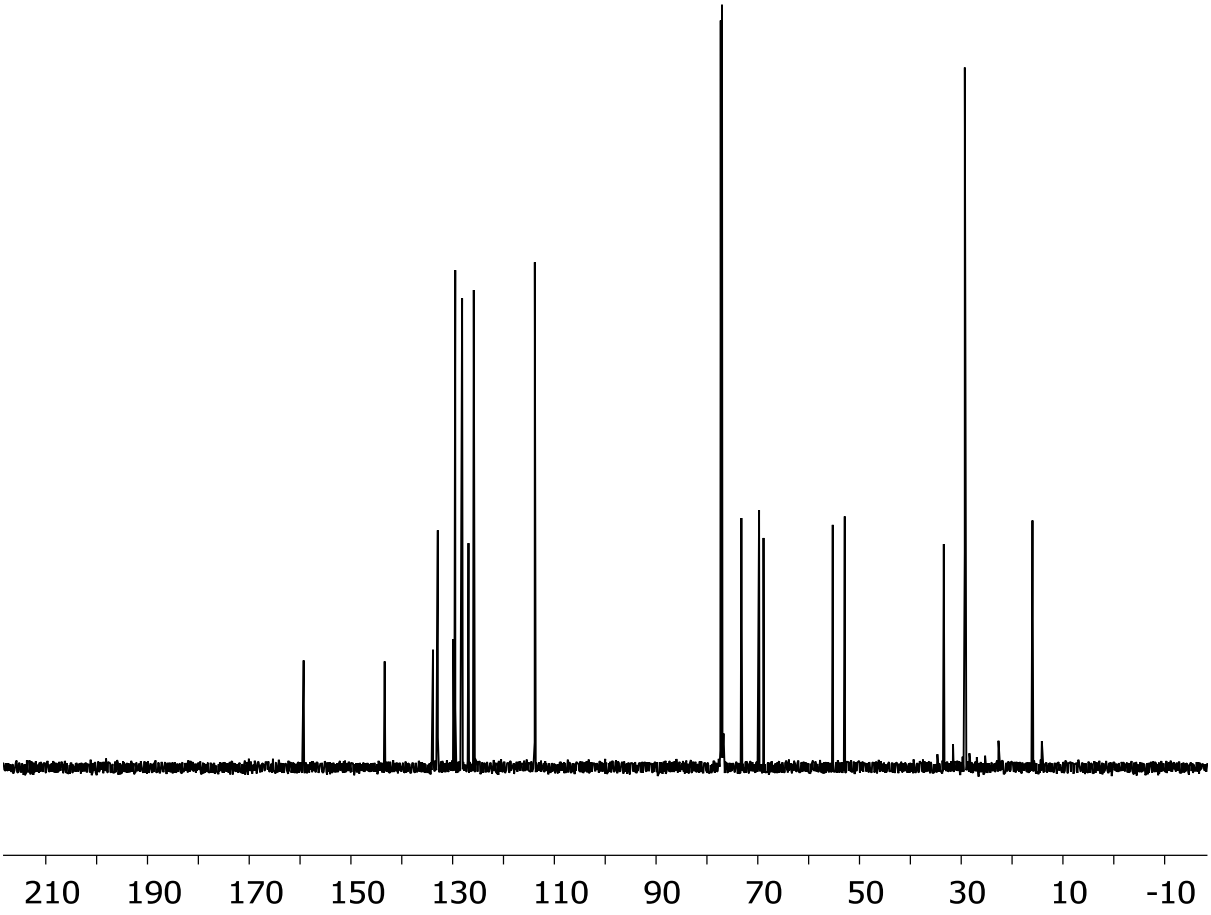
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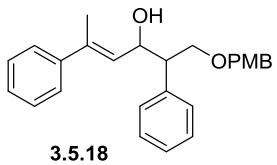

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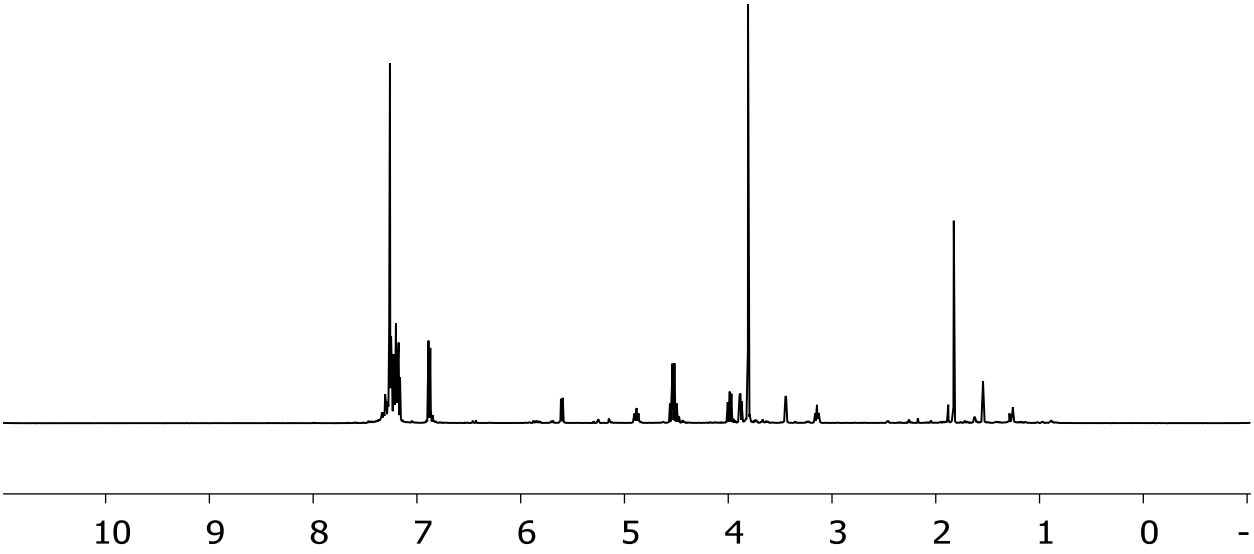

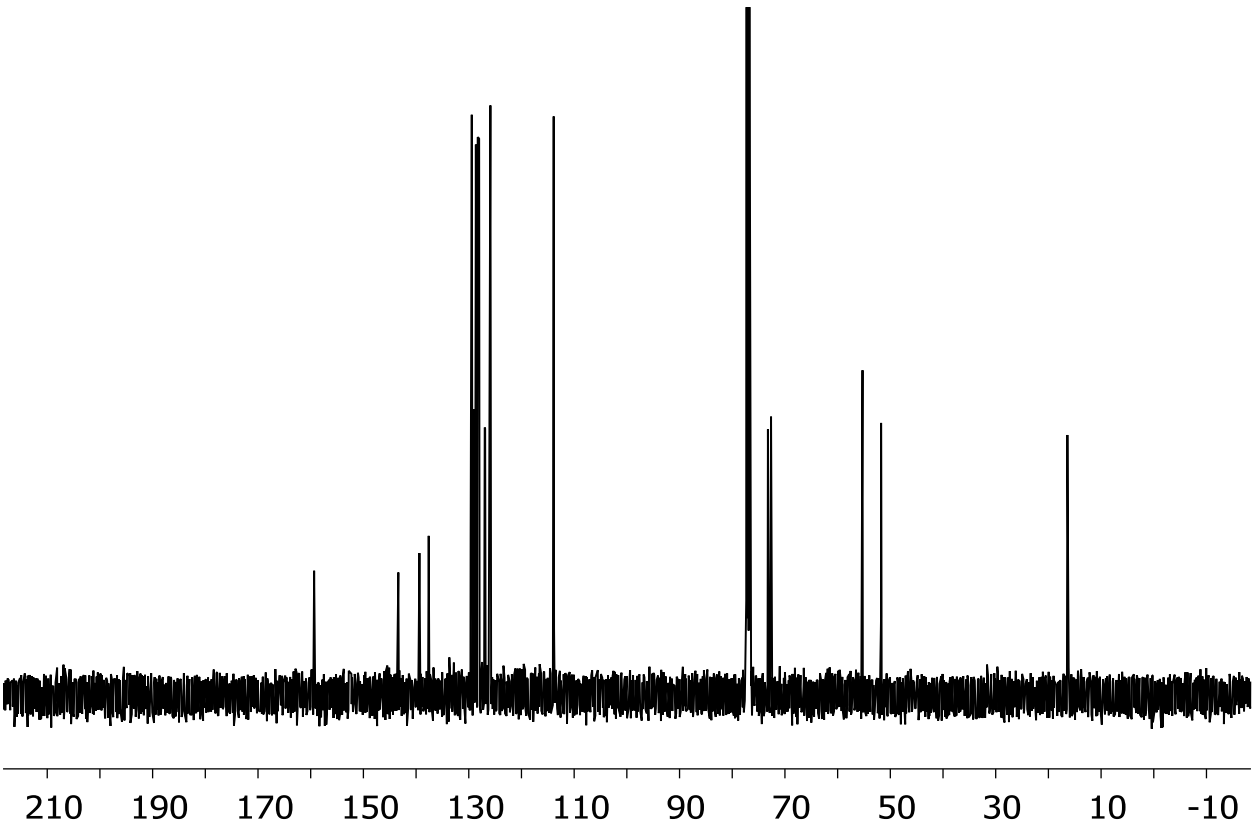

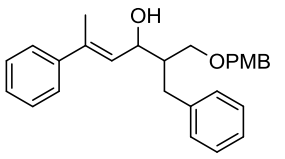

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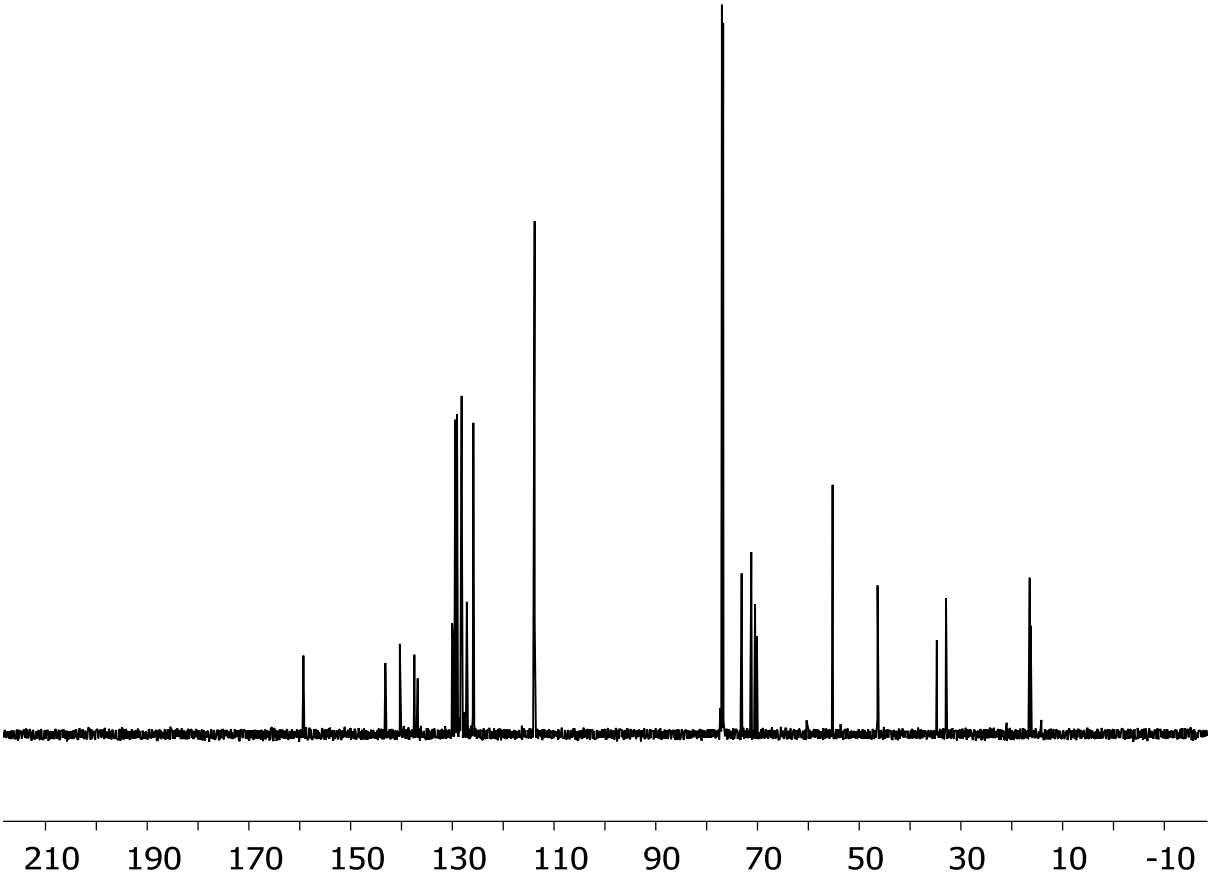

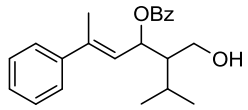

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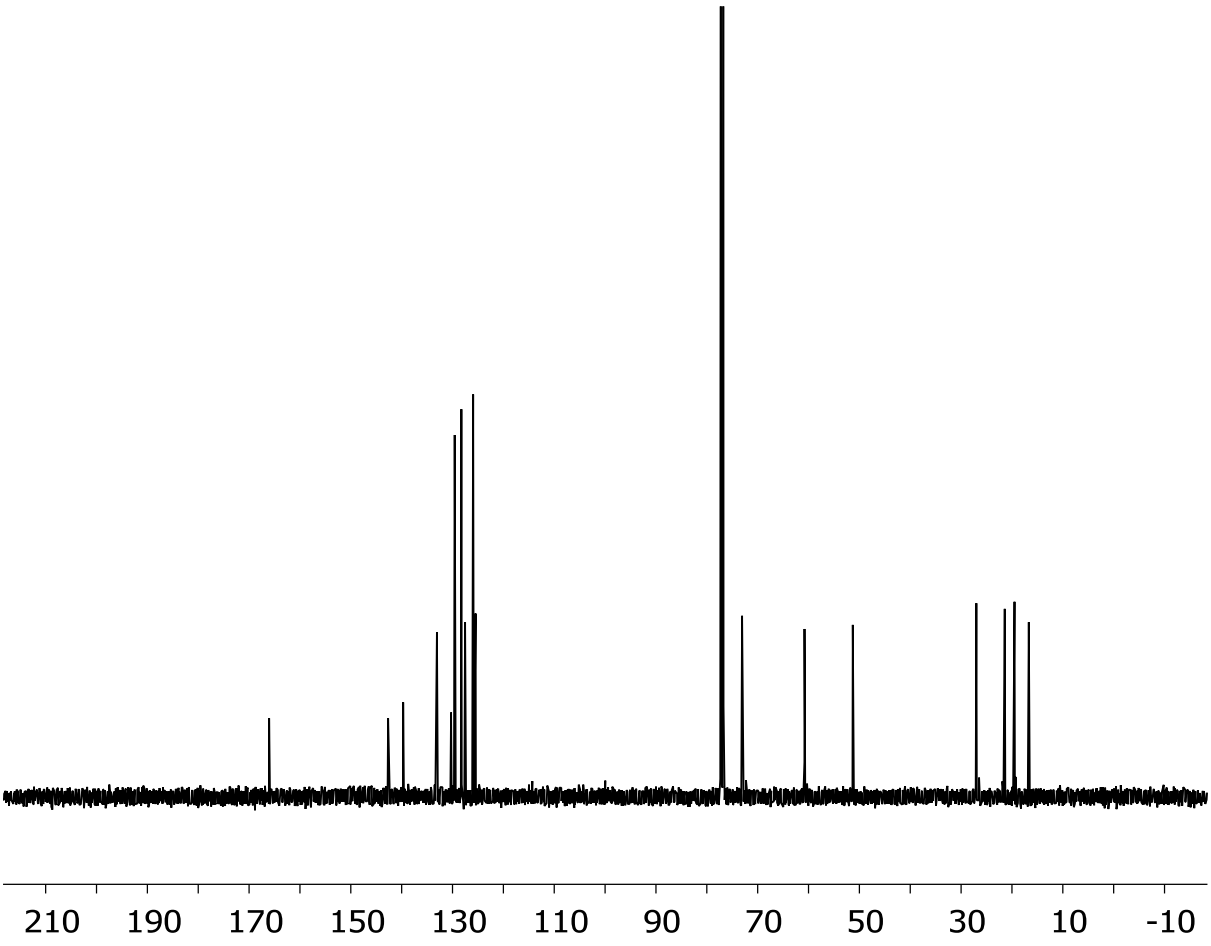

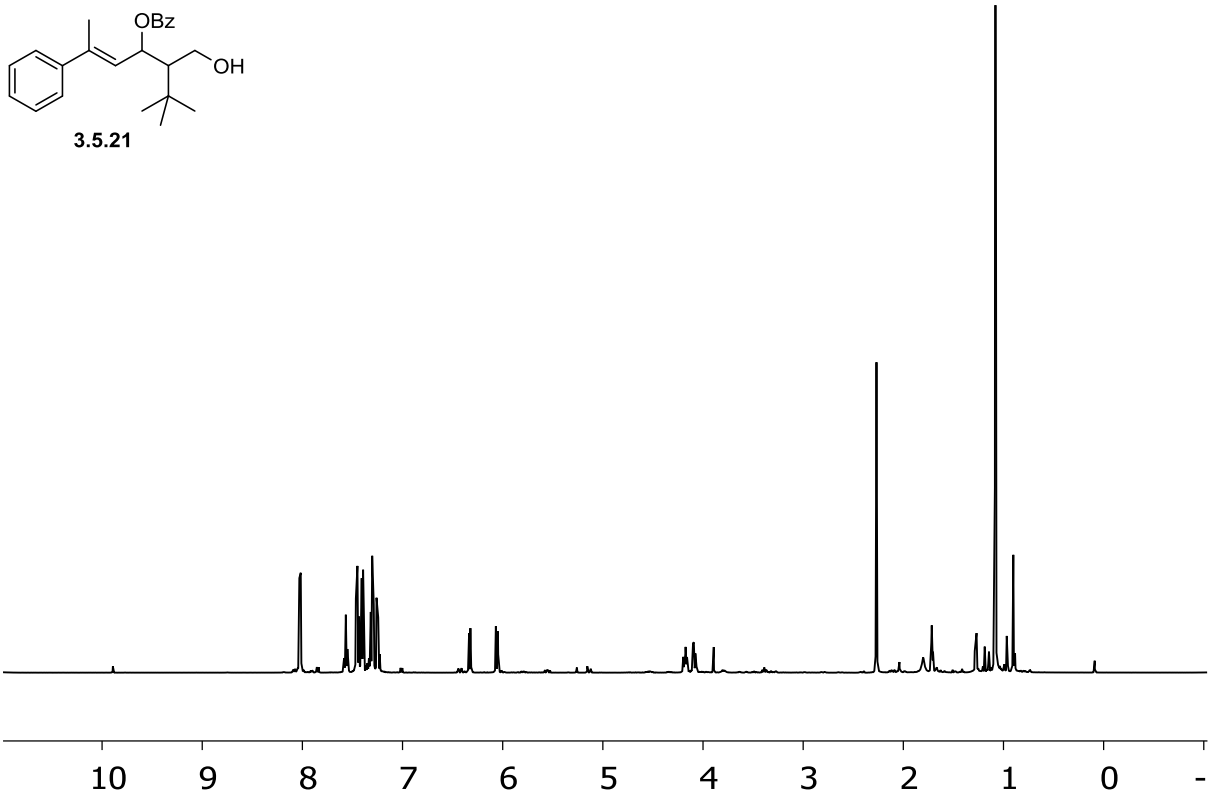
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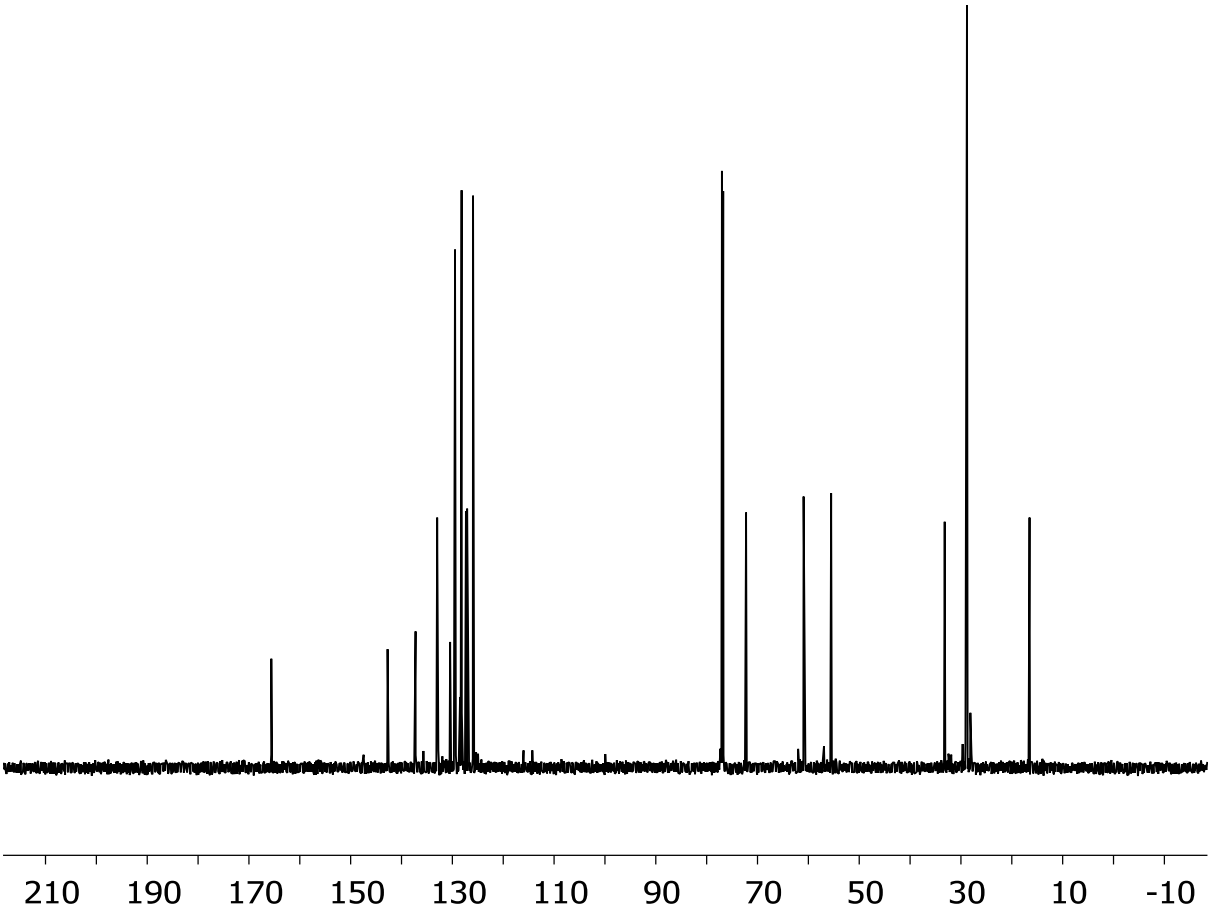
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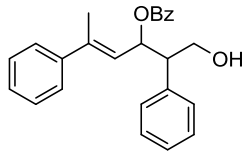

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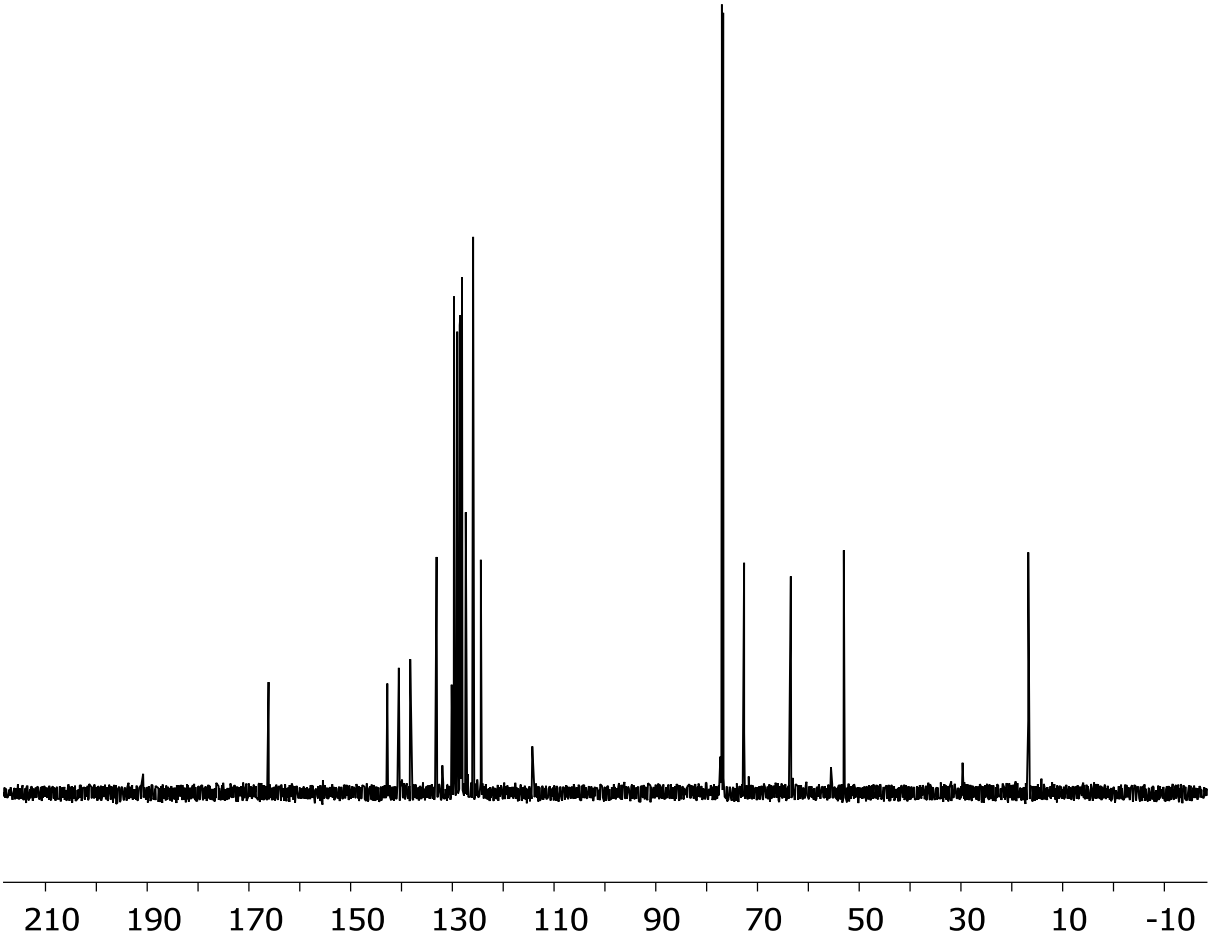

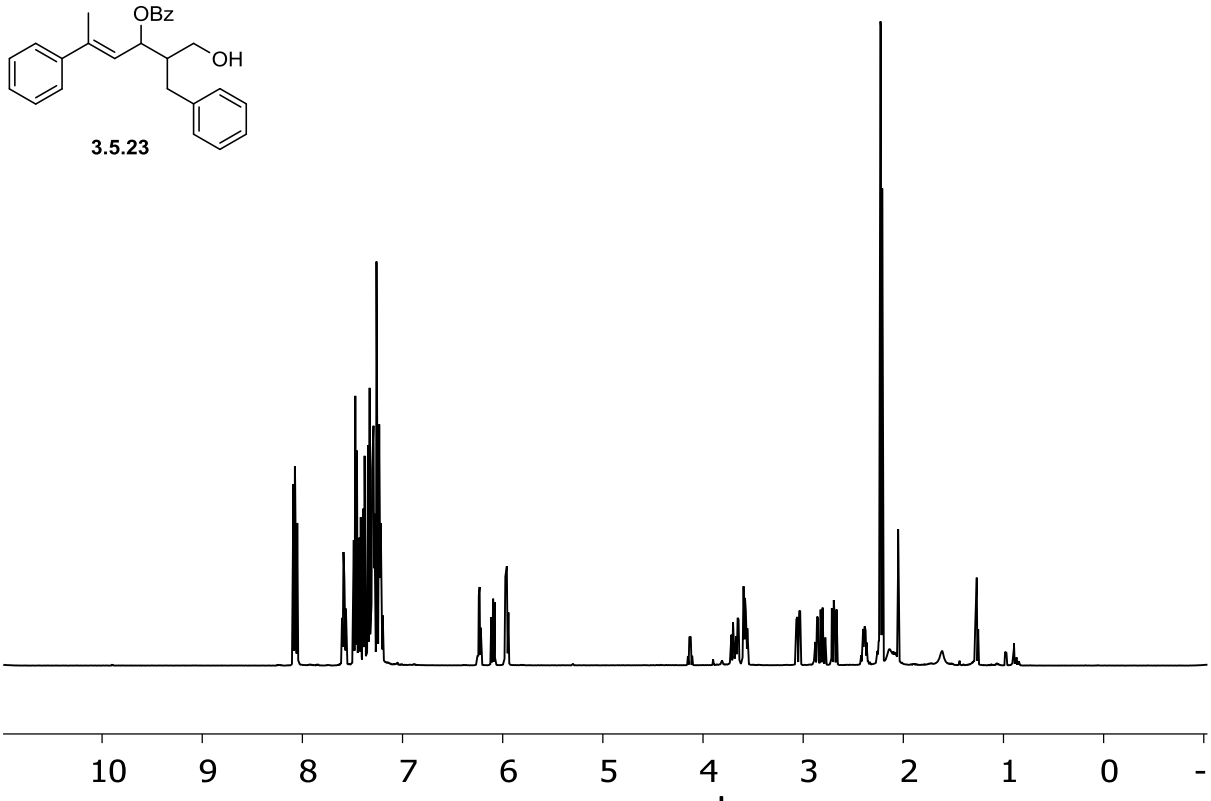
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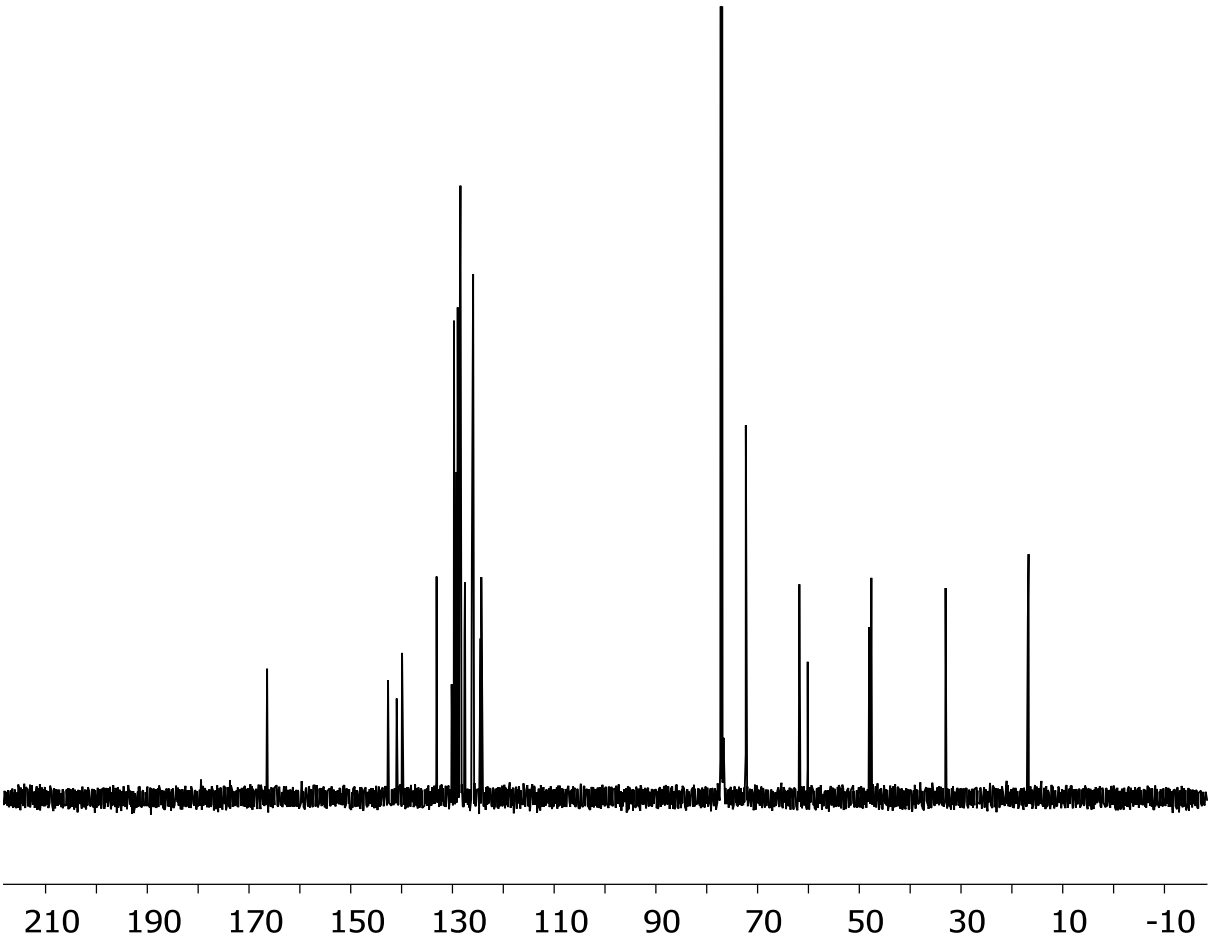
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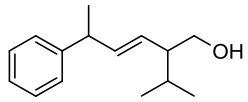

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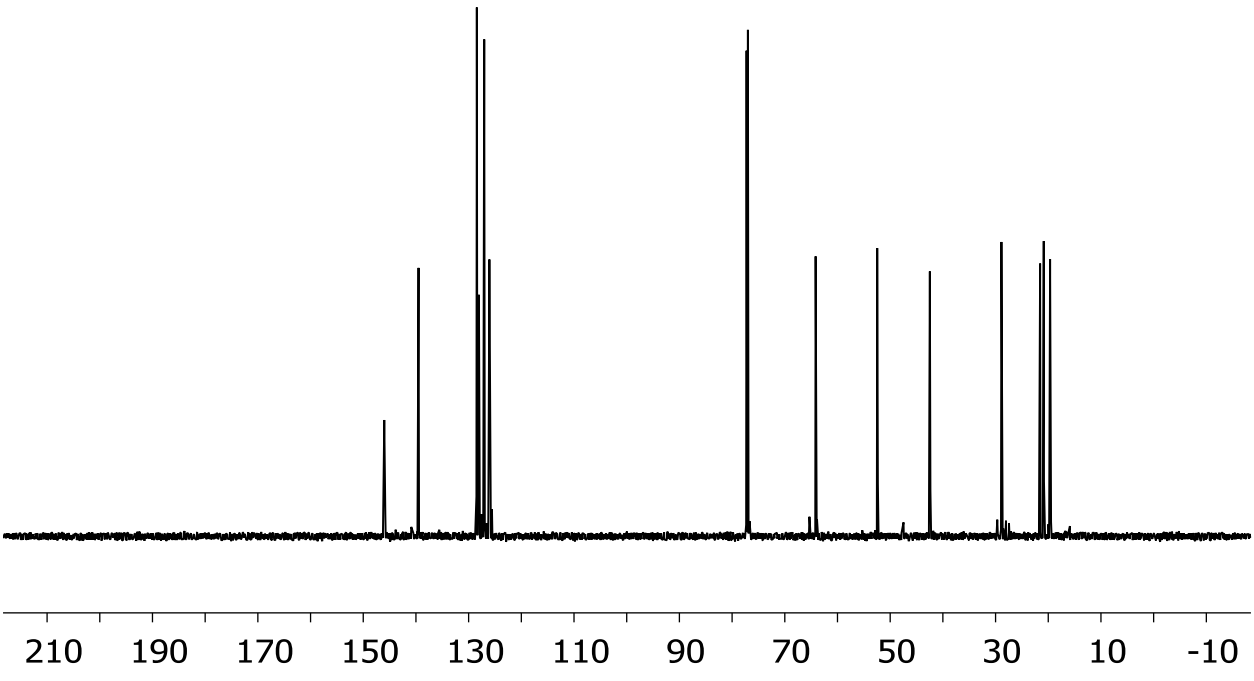

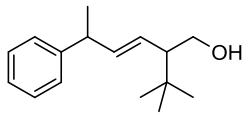

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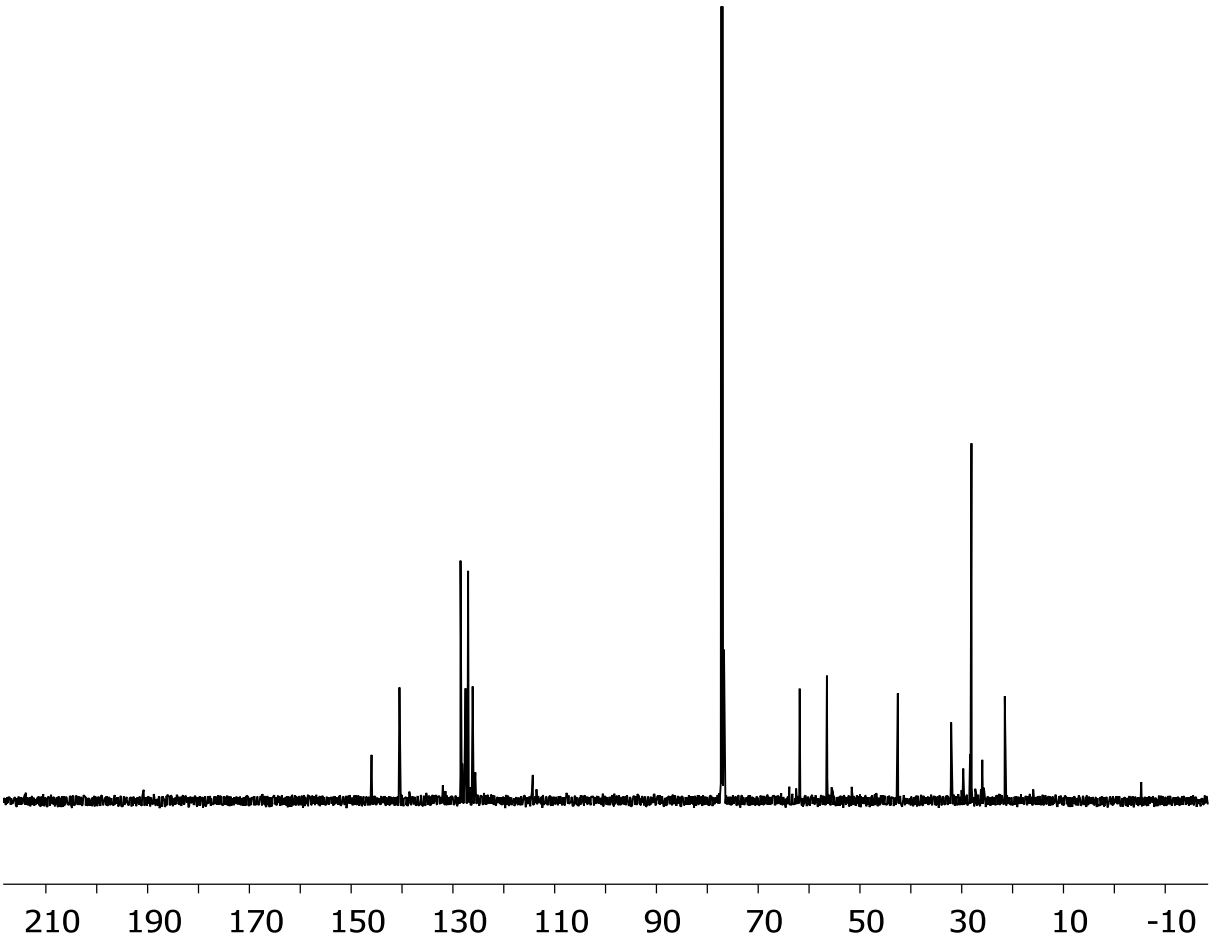

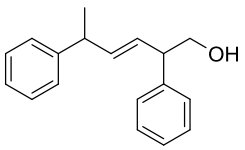

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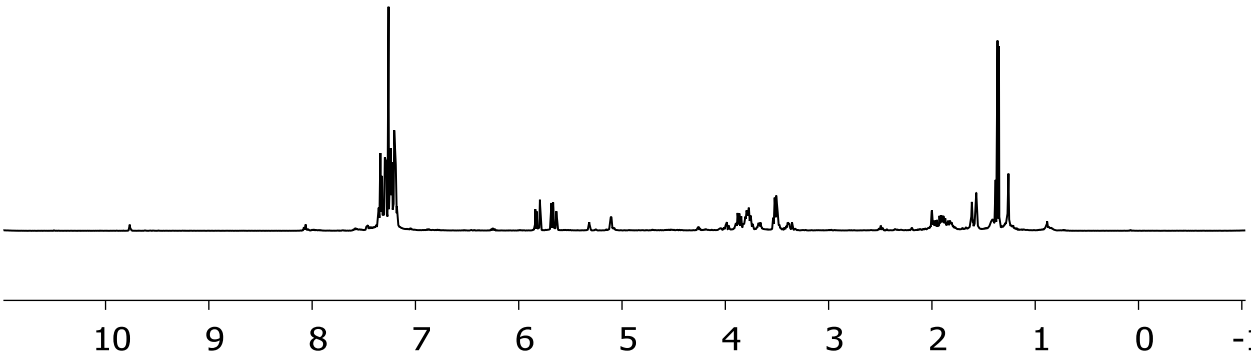

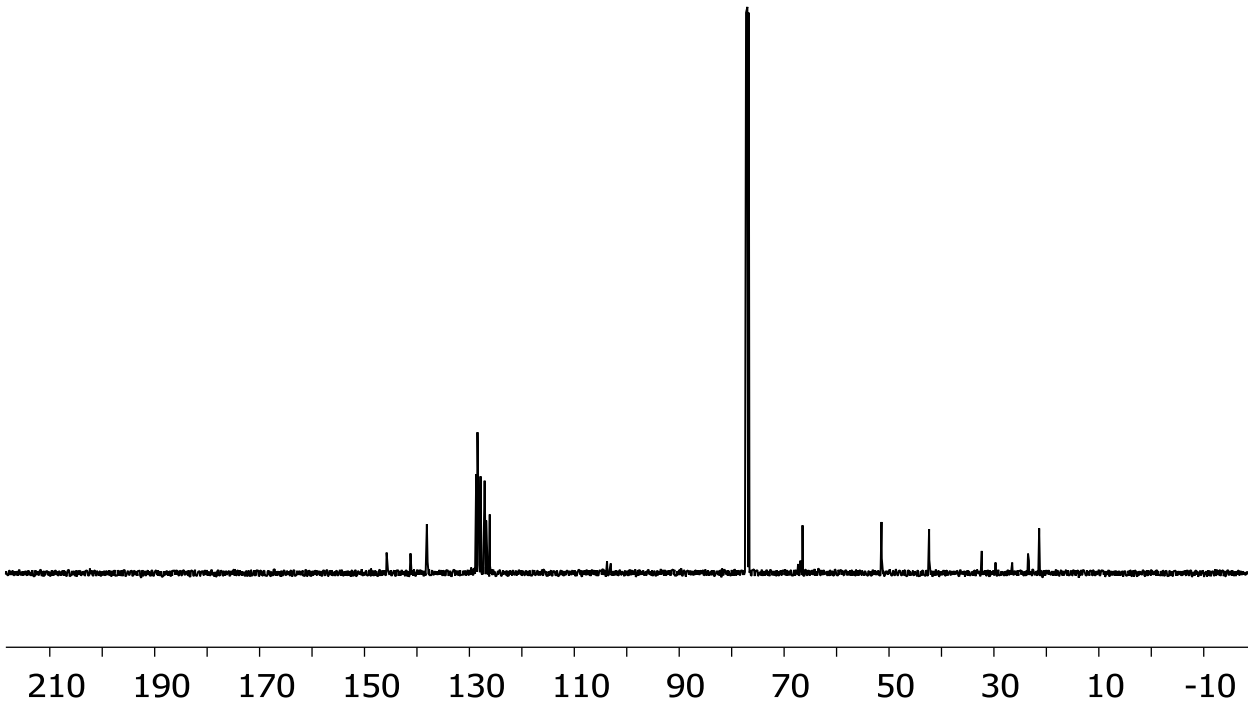

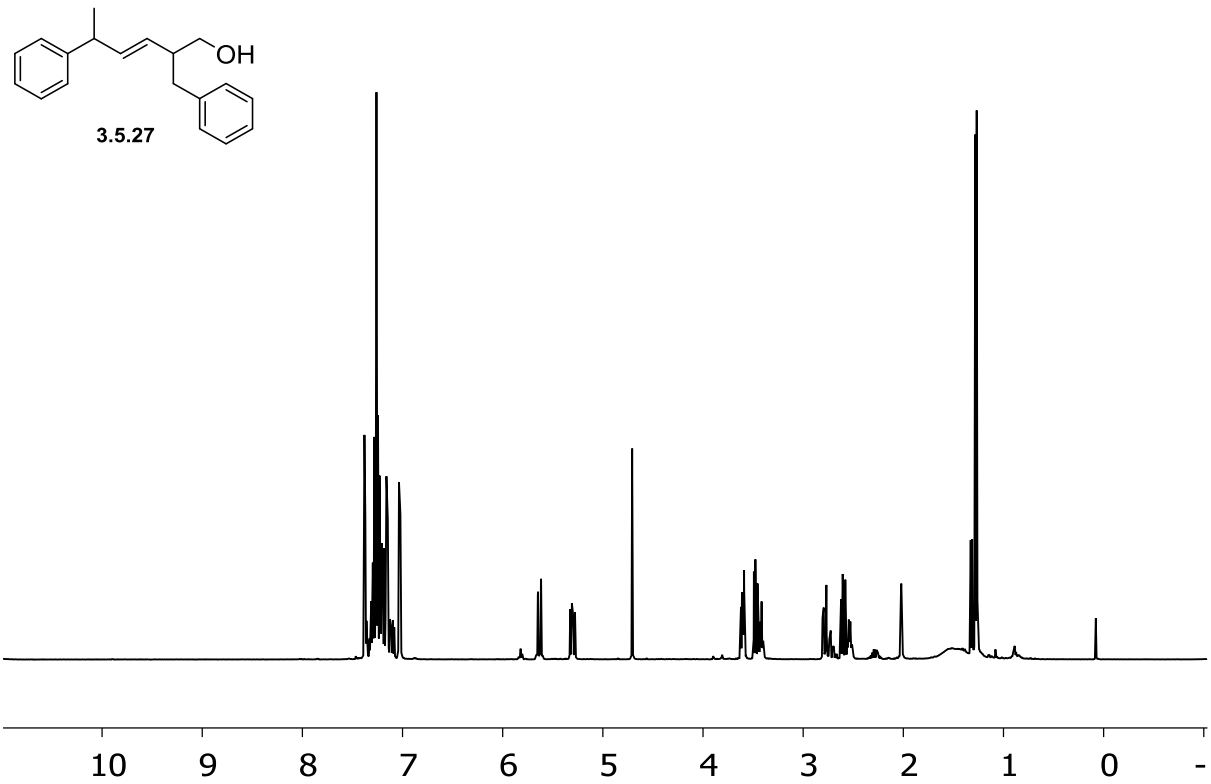
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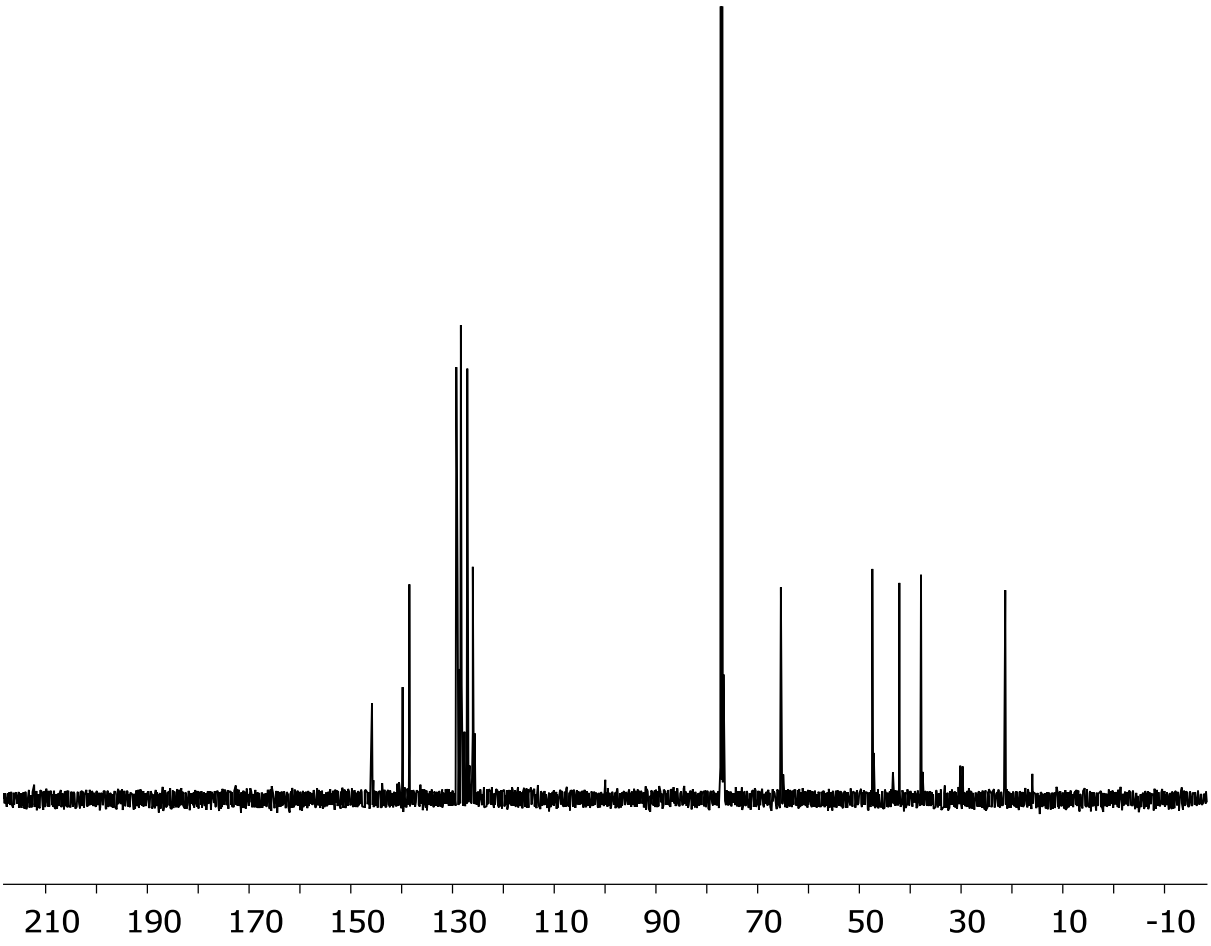
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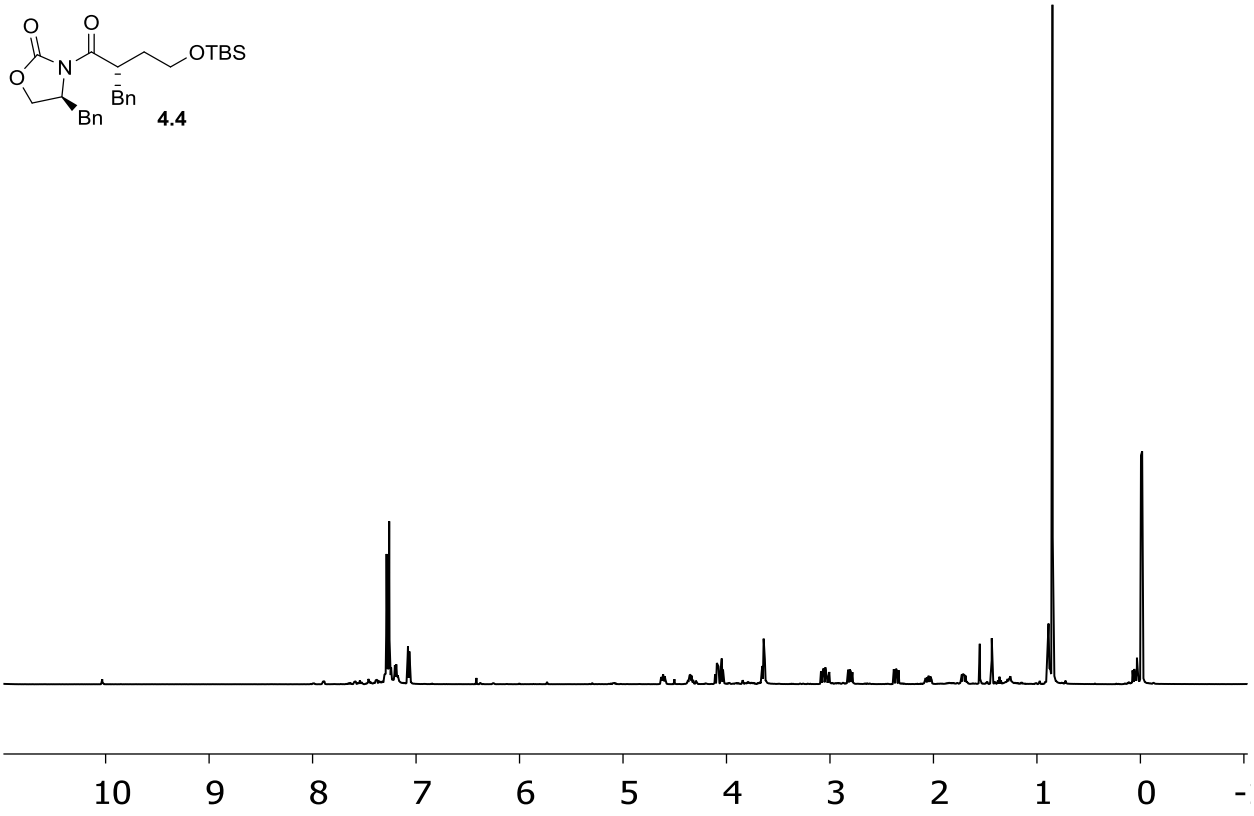
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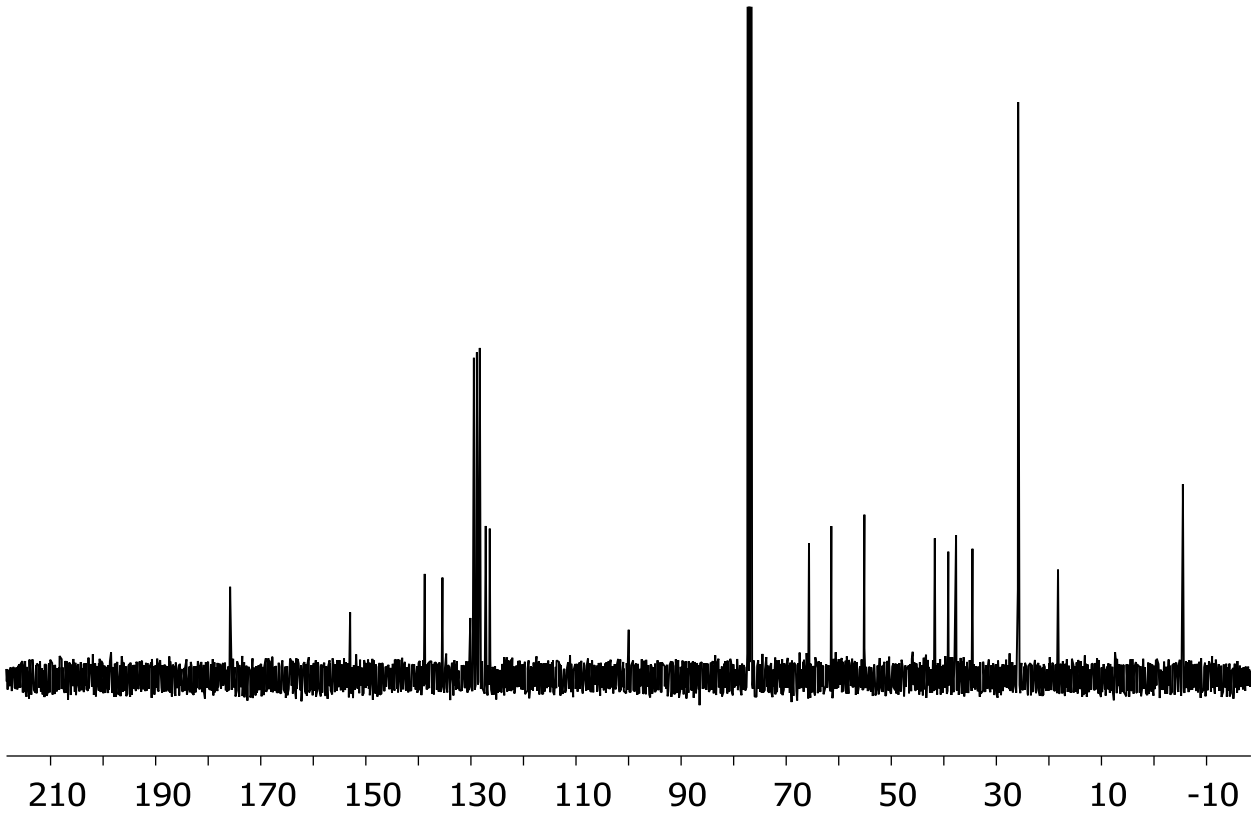
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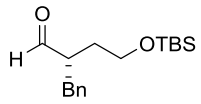
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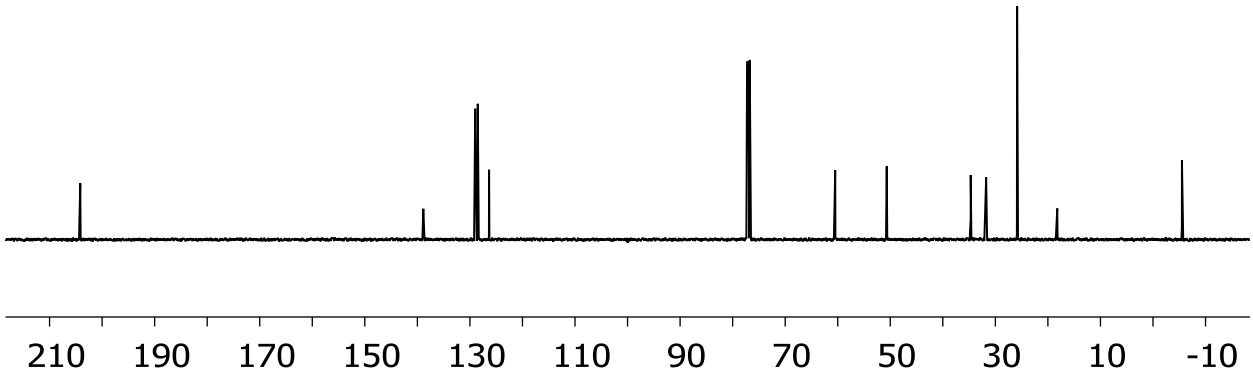
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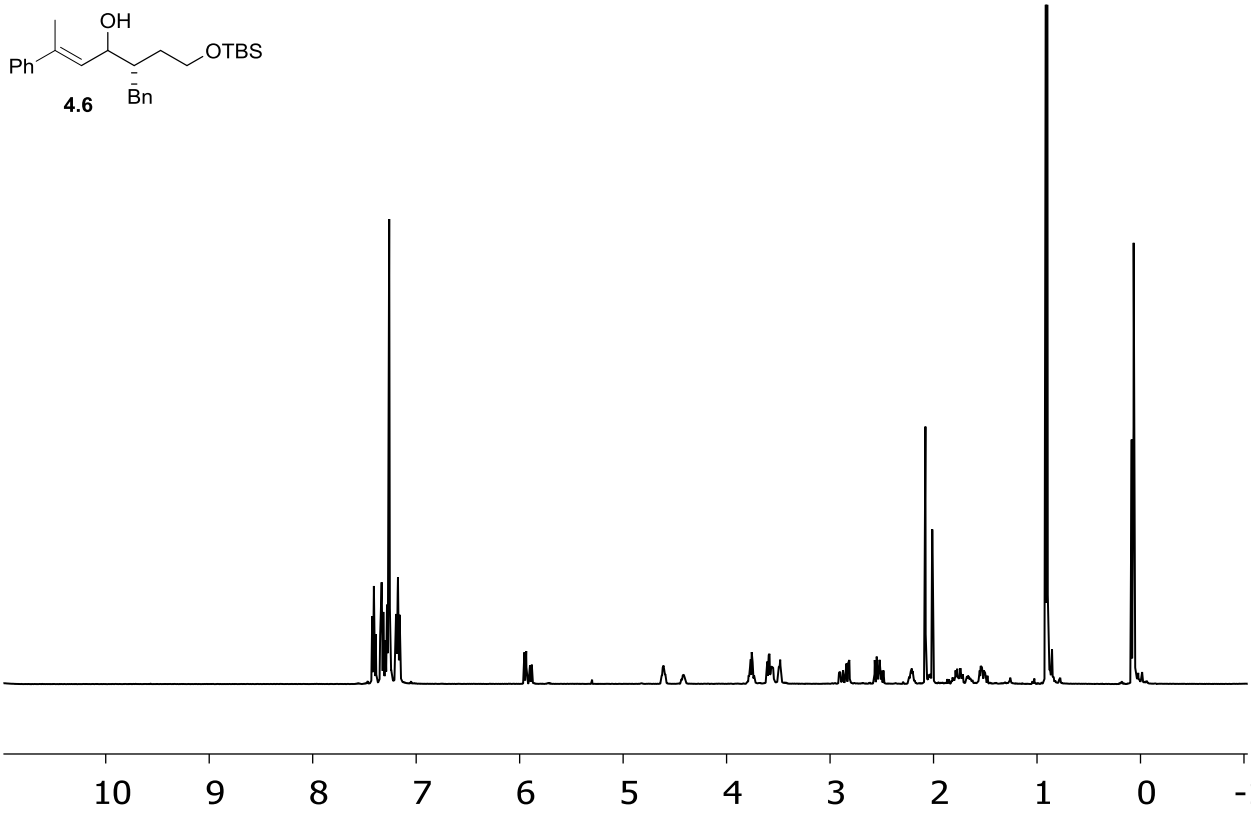
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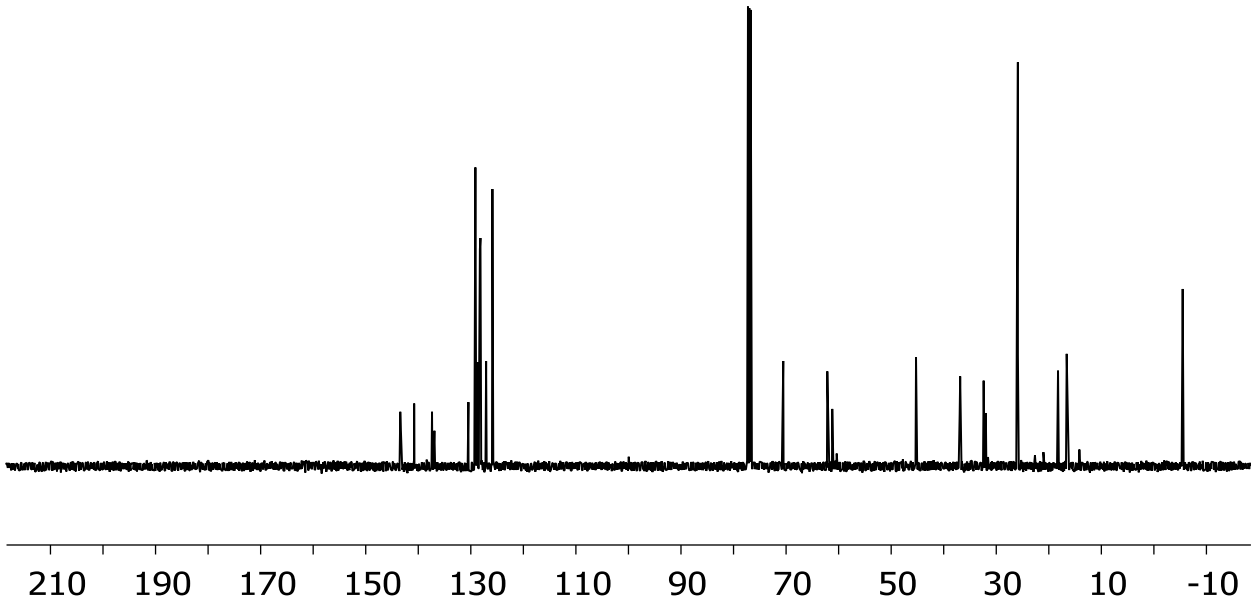
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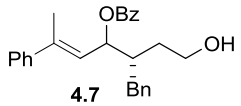
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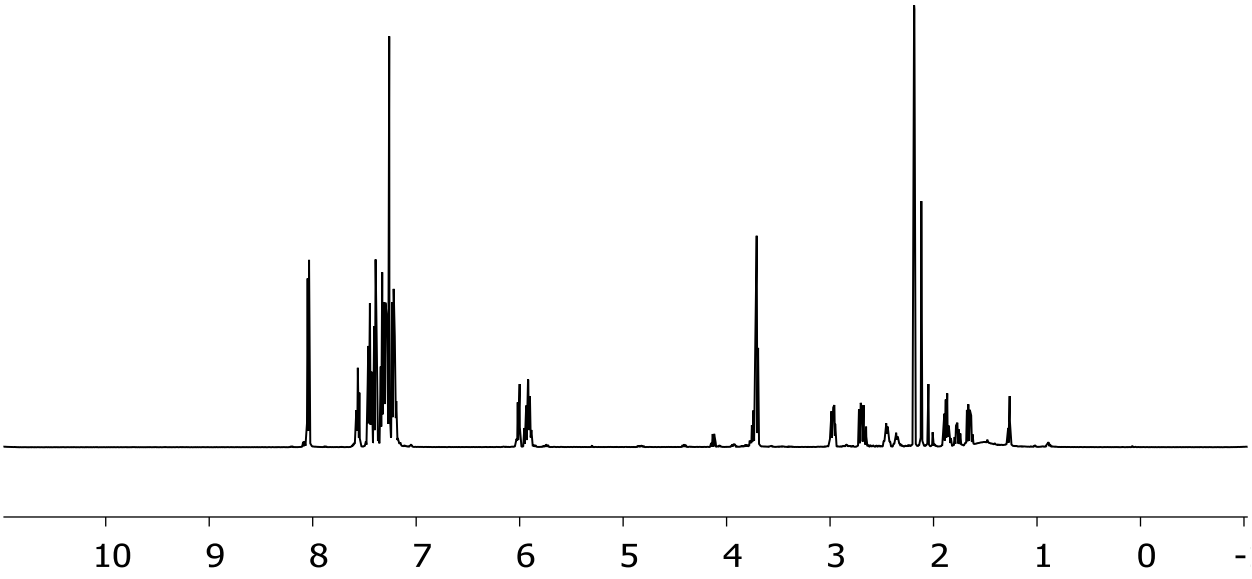
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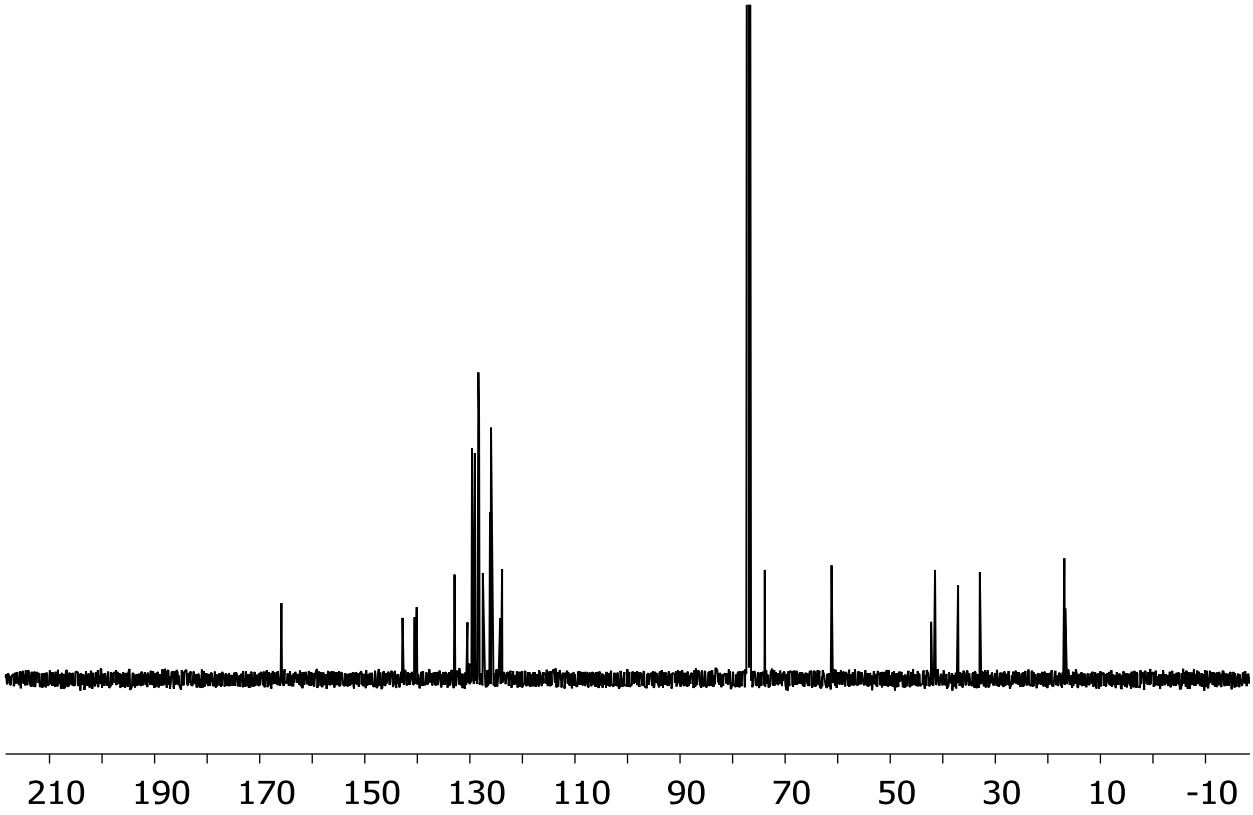
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