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Regio- and Diastereoselective Samarium-Mediated Allylic Sulfone Reductions

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Regio- and Diastereoselective Samarium-Mediated Allylic Sulfone Reductions

By

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

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Master's Thesis

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Cody L. Schwans

Date

June 2nd, 2023

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A Thesis

Presented to

The Faculty of

Western Washington University

In Partial Fulfillment

Of the Requirements for the Degree

Master of Science

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Abstract

A series of allylic sulfones were synthesized containing a stereodirecting group and chelating element and subjected to samarium diiodide reductions in the presence of a proton donor. The resulting products could be obtained with high regioselectivity (no less than 95:5) and high diastereoselectivity (>10:1) that correlated with the size of the stereodirecting group. A mechanism is proposed that includes loss of the sulfone and formation of a chelated organosamarium intermediate followed by intramolecular protonation by a samarium-bound proton source. In this way, both the regioselectivity and absolute stereochemistry of the resulting products are explained.

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Chapter 1: Introduction

1.1 The Significance of Stereochemistry

Stereochemistry is of significant interest to organic chemists, especially in the design of medicinal and therapeutic compounds. The three-dimensional structure of molecules carries great gravity in the function that it provides in biological systems. Asymmetric carbon atoms containing four different groups are fundamental structural components found in many functional organic molecules as they dictate how this three-dimensionality manifests. As a result, having full control of their stereochemistry in the synthesis of pharmaceutical compounds containing these types of stereocenters is an absolute necessity. For even a single set of enantiomers, the minor difference between an *S*-enantiomer and an *R*-enantiomer can radically alter its function in a patient, behaving as a helpful medicine or a detrimental poison in certain cases.

An example of how significant the control of stereochemistry is to the biological activity of organic molecules can be seen in the once over-the-counter drug Thalidomide (Figure 1.1). This drug was initially prescribed as a sedative that could facilitate deep sleep without potential for harmful side effects like hangover or addiction. Over time, Thalidomide become a popular anti-emetic, aiding pregnant women in reducing the effects of morning sickness.[1] It was provided as a racemate, containing both enantiomers in equal mixture. While the *R*-enantiomer satisfies its intended purpose of mitigating nausea, the *S*-enantiomer possesses teratogenic properties. This led to horrid birth defects, commonly seen as limb malformations.[2] This ultimately placed the spotlight on the dire need to test stereocenter-containing pharmaceutical compounds rigorously before they are made available to consumers.[3]

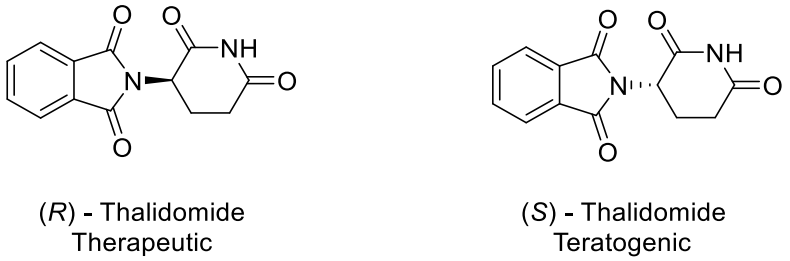


Figure 1.1. (R) and (S) enantiomers of thalidomide.

It is therefore essential that stereochemistry be controlled absolutely in these cases. Many useful natural products contain multiple stereocenters, providing a large obstacle in organic synthesis. Compounds such as Erythromycin, an antibiotic, and Taxol, a cancer therapeutic, possess 18 and 12 stereocenters respectively (Figure 1.2). Needing absolute control of stereochemistry can stymie synthetic routes to common functional groups as well as dramatically reduce yields. Therefore, reactions that allow for direct control of stereochemistry are very important in the synthesis of desired targets.

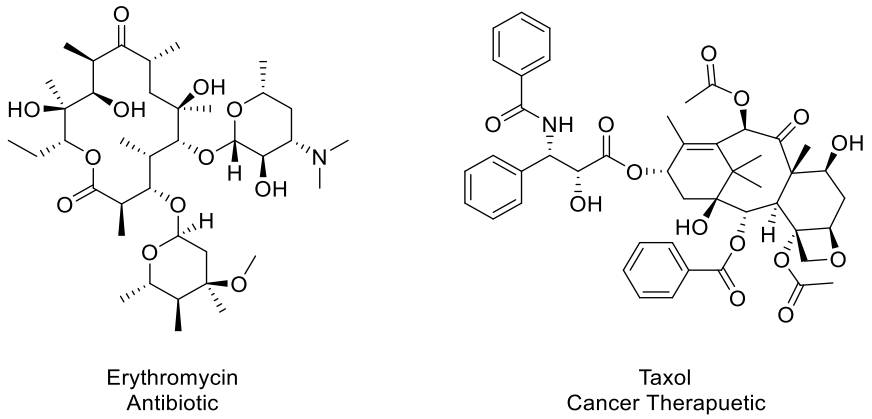


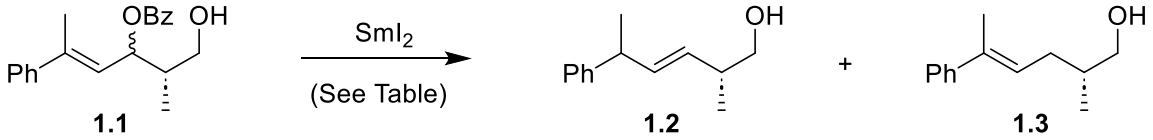
Figure 1.2. Useful natural products with many stereocenters: Erythromycin and Taxol.

1.2 Establishment of $SmI_2(H_2O)_n$ Mediated Trisubstituted Allylic Benzoate Reduction

In 2017, the O'Neil group demonstrated that trisubstituted allylic benzoates could be reduced using $SmI_2(H_2O)_n$ with complete regioselectivity (entries 2 and 4 in table 1.1) and high

diastereoselectivity (up to 76:24) when paired with a cosolvent that could facilitate intramolecular protonation.[4] The best cosolvent was found to be water. This was very advantageous as water is both easily accessible and devoid of toxic properties. In an effort to bolster the diastereoselectivity of this reaction when using water as a cosolvent, the reaction was run at 0°C. However, this ended up lowering the regioselectivity (from 15:1 to 5:1). Despite this result, it was still desirable to have a reduction that could produce this level of regioselectivity and diastereoselectivity with a simple and non-toxic cosolvent at room temperature.

*Table 1.1. Additive effects on SmI_2 reductions of compound **1.1**. Adapted from reference.*[4]



d.r. 70:30

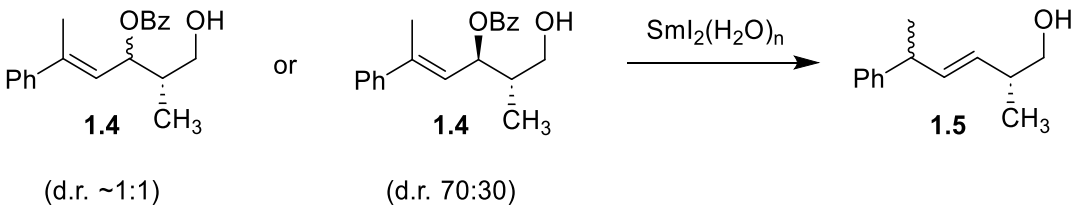
Entry	Additive[a]	1.2 : 1.3[b]	1.2 d.r.[b]
1	DMPU	2:1	75:25
2	*t*-BuOH	1:0[c]	67:33
3	*i*-PrOH	2.3:1	67:33
4	MeOH	1:0[c]	60:40
5	H_2O	15:1	76:24
6	H_2O[d]	5:1	75:25

Notes for Table 1.1: [a]Reactions were performed by adding the additive (16 equiv. DMPU or 1400 equiv. ROH) to SmI_2 (7 equiv.) followed by the substrate and stirring for 30 min. [b]Determined by ^1H NMR. [c]1.3 was not detected by NMR. [d]Performed at 0 °C.

Because the benzoyl group is lost through the reduction, it was hypothesized that the stereochemistry of this group would be inconsequential to the formation of the final products. To test

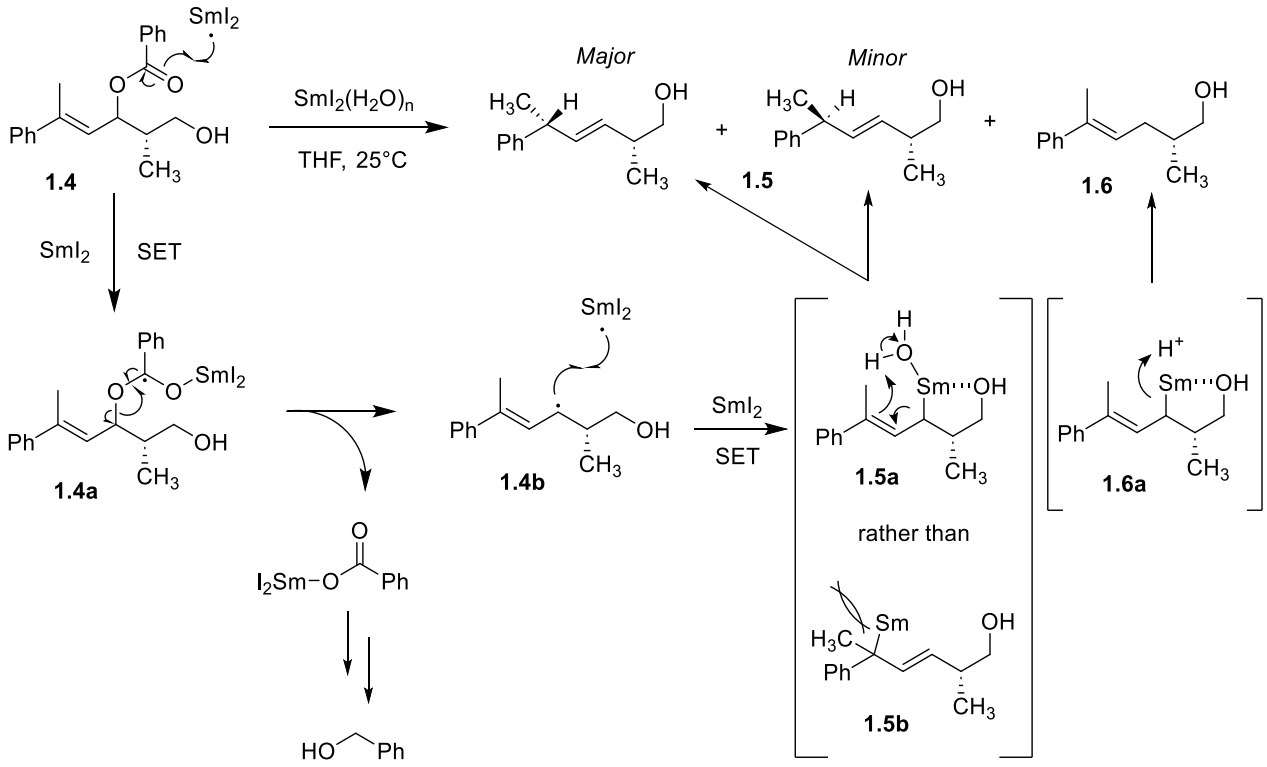
this hypothesis, two differently enriched samples of the same trisubstituted allylic benzoate **1.4** were synthesized and reduced with $SmI_2(H_2O)_n$ (Scheme 1.1). It was found that regardless of benzoyl stereochemistry, the reaction would converge to the same product, supporting the theoretical proposed mechanism (Scheme 1.2). This reduction occurs via single electron transfer (SET).[5] As a result, once the allylic benzoate **1.4a** binds to $SmI_2(H_2O)_n$, a radical may be placed on the allylic carbon atom of **1.4b** by the departed benzoyl group. An additional unit of $SmI_2(H_2O)_n$ will then engage with the lone radical, and through further single electron transfer, bind to the allylic carbon atom of **1.5a**. Due to steric hindrance provided by the phenyl group, it was believed that isomerization to **1.5b** was not favorable. This would result in intramolecular protonation that favors the major stereoisomer **1.5** where the methyl group of the newly formed stereocenter is in the syn configuration relative to the stereodirecting methyl group near the chelating hydroxyl.

Scheme 1.1. Effect of benzoyl stereochemistry on the stereoselectivity of $SmI_2(H_2O)_n$ reductions. Adapted from reference.[6]



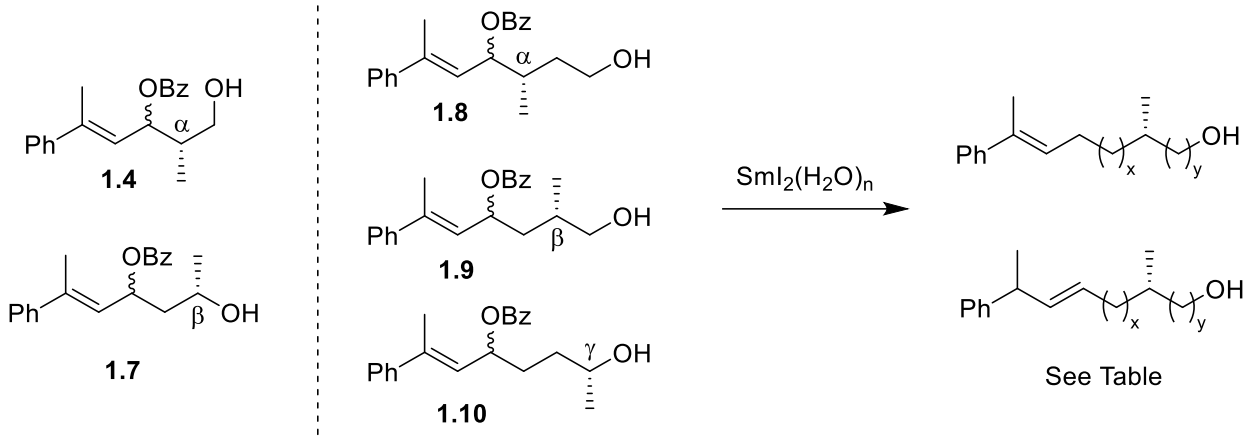
(d.r. ~1:1) (d.r. 70:30)

Scheme 1.2. Theoretical mechanism of $SmI_2(H_2O)_n$ reduction on a trisubstituted allylic benzoate. Adapted from reference.[5]



A logical step to further evaluate this reduction was to see if a different chelating group linker length or stereodirecting group position would impact the resulting diastereoselectivity or regioselectivity. To do this, 5- and 6-membered organosamarium chelates were synthesized, each with different positioning of the stereodirecting methyl group along the linker chain (Table 1.2). Overall, the reduction was the most diastereoselective and regioselective when the distance between the benzoyl group was minimized (x = 0) and when the chelating linker length was minimized (y = 0 or 1). Thus, future substrate design would feature these characteristics to increase the diastereoselectivity and regioselectivity of the reduction.

Table 1.2. Comparison of methyl stereocenter position and chelate linker length on diastereoselectivity and regioselectivity for $SmI_2(H_2O)_n$ allylic benzoate reductions for substrates proceeding through 5- and 6-membered organosamarium chelates. Adapted from reference.[7]

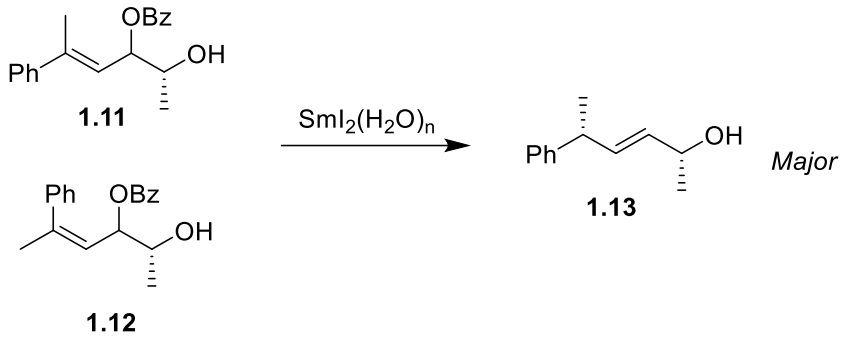


Entry	Starting Material	Product	d.r.[a]	Regioselectivity
1	1.4	(x= 0, y = 1)	75:25	98:2
2	1.7	(x= 1, y = 0)	70:30	100:0
3	1.8	(x= 0, y = 2)	78:22	88:12
4	1.9	(x= 1, y = 1)	57:43[b]	94:6
5	1.10	(x= 0, y = 1)	56:44	83:17

Notes for Table 1.2: All reactions were performed using 105 equiv. of H_2O and 7 equiv. of SmI_2 in degassed THF at rt under N_2. [a]Determined by ^1H NMR and GC-FID. [b]Identical results were obtained when the reaction was performed under Ar.

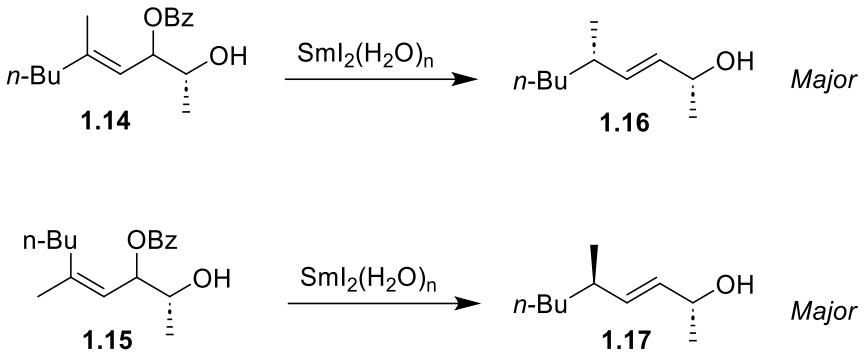
These results left another major question unanswered. What would happen if the alkene geometry of the trisubstituted allylic benzoate was switched? Would a *cis*- or *trans*-configuration alter the reduction in any way? To evaluate this, trisubstituted allylic benzoates **1.11** and **1.12** were reduced with $SmI_2(H_2O)_n$ (Scheme 1.3). Surprisingly, regardless of *cis*- or *trans*-configuration, both starting materials converged to the same major diastereomer. This prompted an investigation of the geminal substituents featured on the alkene.

Scheme 1.3. An alkene phenyl group causes both cis and trans-stereoisomers to stereoselectively favor the major syn product. Adapted from reference.[5]



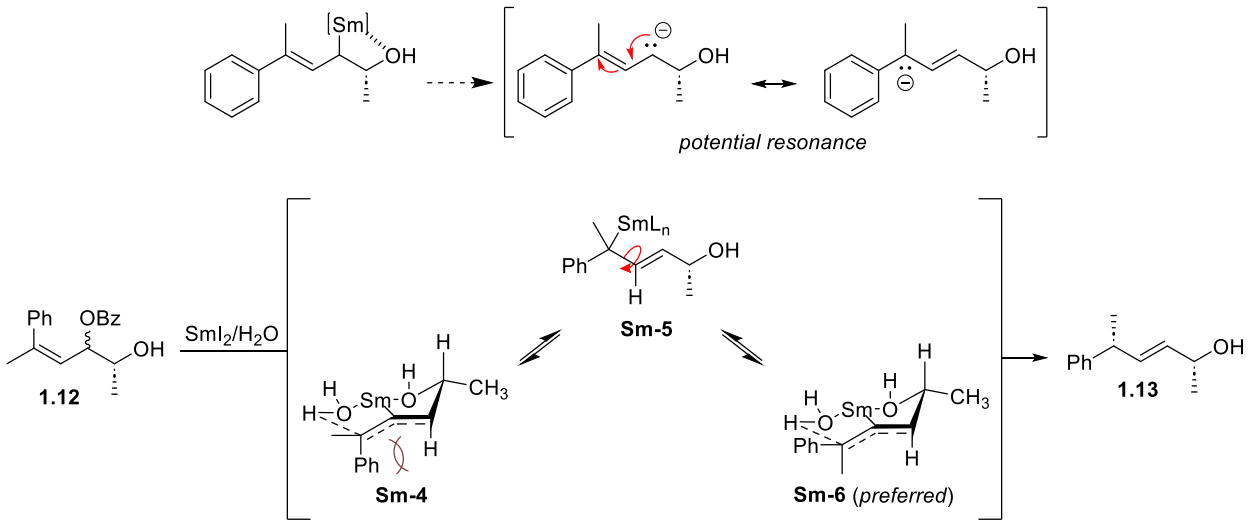
In an effort to address this phenomenon, compounds **1.14** and **1.15** were synthesized, featuring an *n*-butyl group instead of a phenyl group, and reduced with $SmI_2(H_2O)_n$ (Scheme 1.4). In contrast to the phenyl substrates **1.11** and **1.12**, this resulted in an inversion of preference for the syn (**1.16**) or anti product **1.17**, depending on whether the *trans*- or *cis*- stereoisomer was reduced respectively. The results suggested that the phenyl group was in some way responsible for the divergence from this preference based on alkene geometry. To make sense of this, the O'Neil group evaluated a possible mechanism behind the isomerization of the bicyclic intermediate.

Scheme 1.4. The alkene geometry of a non-phenyl (n-butyl) group causes the trans- stereoisomer to favor the syn product while the cis- stereoisomer favors the anti product. Adapted from reference.[5]



When considering interconversions between η^3 and η^1 isomer complexes, this phenomenon becomes much more understandable (Scheme 1.5). Upon reduction of **1.12** with $SmI_2(H_2O)_n$ and formation of bicyclic intermediate **Sm-4**, the phenyl group would be placed in a pseudo-axial position, increasing the steric strain experienced by the complex. Resonance throughout the phenyl ring would reposition the alkene, permitting rotation of the phenyl-bound carbon atom. This would enable the phenyl group to reorient itself to the pseudo-equatorial position while in the η1 complex (**Sm-5**) before reforming to the η3 (**Sm-6**) complex. Altogether, the results compelled us to further investigate substrates that may undergo this reduction as they may provide even greater control over product stereochemistry and provide additional insights to explain this apparent phenyl-effect.

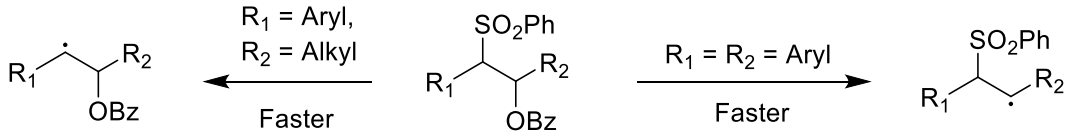
Scheme 1.5. Sterically driven isomerization of trisubstituted allylic benzoates through η3- η1- η3 interconversions. Adapted from reference.[5]

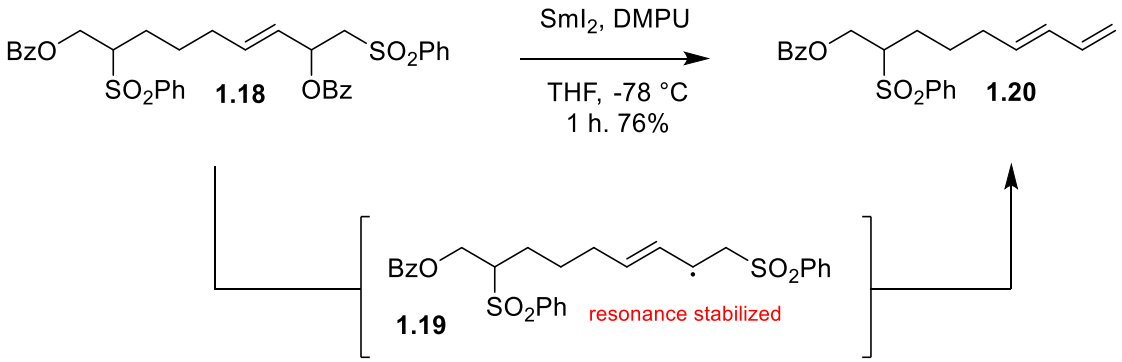


1.3 Sulfone as an Alternative to Benzoyl Group

While the O'Neil group's work on trisubstituted allylic benzoates demonstrated stereoselective synthesis via $SmI_2(H_2O)_n$ was possible, alternative substrates (e.g., containing different single electron acceptors) had yet to be tested. In past studies, it had been shown that both benzoate esters and phenyl sulfones may behave as single electron acceptors when treated with $SmI_2(H_2O)_n$. In fact, compounds that possess both a benzoyl and sulfone group have been shown to compete in elimination rate when subjected to SmI_2.[8] While the benzoyl eliminates faster, if the resulting radical is particularly high in energy, the sulfone may undergo the single electron transfer mechanism in competition. By extension, a bis-benzoyloxysulfone **1.18** has been shown to yield a diene **1.20** still possessing a remaining benzoyloxysulfone, demonstrating this competing single electron transfer pathway (Scheme 1.6). If both trisubstituted allylic benzoates and sulfones are capable of this reduction, what advantages would a sulfone have over a benzoyl group?

Scheme 1.6. The rates in which benzoyl and sulfonyl groups are eliminated by SmI_2 are different based on stability from resonance, but both can be eliminated in the case of bis-benzoyloxysulfones. Adapted from reference.[8]



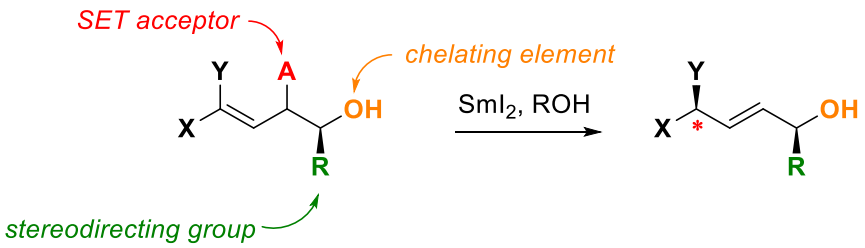


Even though work by the O'Neil group has shown that trisubstituted allylic benzoates are great candidates for the $SmI_2(H_2O)_n$ reduction, establishing all the needed elements within this substrate design has proven challenging. For these benzoates to properly function in the reduction, they must be endowed with a single electron acceptor, a stereodirecting group, and a chelating group (Scheme 1.7). First-generation substrates using a benzoyl group as an electron acceptor have historically required the use of 6-8 total steps for their synthesis, including organometallic addition.[5] It would be ideal if the pathway to suitable substrates could be achieved in fewer steps to increase yield and simplicity. The remainder of this thesis is focused on studies of a second-generation substrate for stereoselective $SmI_2(H_2O)_n$ reductions featuring a sulfone in place of the benzoyl group. Hypothetically, accessing this compound would potentially be much easier than the first-generation benzoyl esters. The sulfone could be leveraged by using a sulfonyl anion aldehyde addition reaction to produce the substrate directly containing the needed stereodirecting and chelating groups of choice. The simplicity of this addition

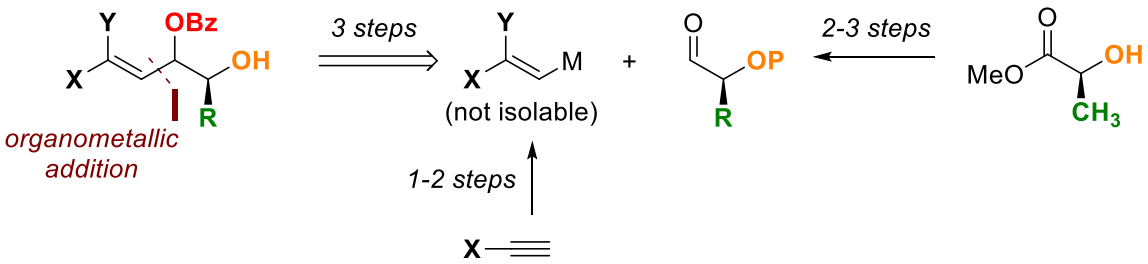
would come with merits of its own, such as enabling easy manipulation of stereodirecting groups by choosing an aldehyde that possesses this group prior to addition. If these substrates were more easily accessible, the potential of the $SmI_2(H_2O)_n$ reduction in modern organic synthesis of sterically complex molecules would be greatly enhanced.

Scheme 1.7. Both first- and second-generation substrates require a SET acceptor, stereodirecting group, and chelating group, but accessing a substrate that features a sulfone as an electron acceptor would be easier to achieve compared to one that features a benzoyl group.

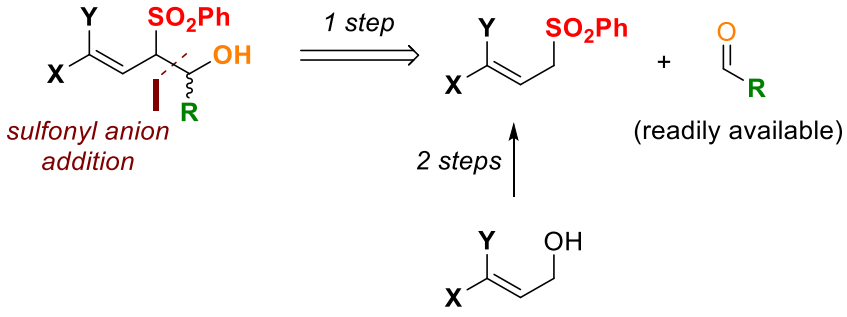
Basic substrate design:



First generation substrates - OBz as the electron acceptor



Proposed second generation substrates - SO_2Ph as the electron acceptor



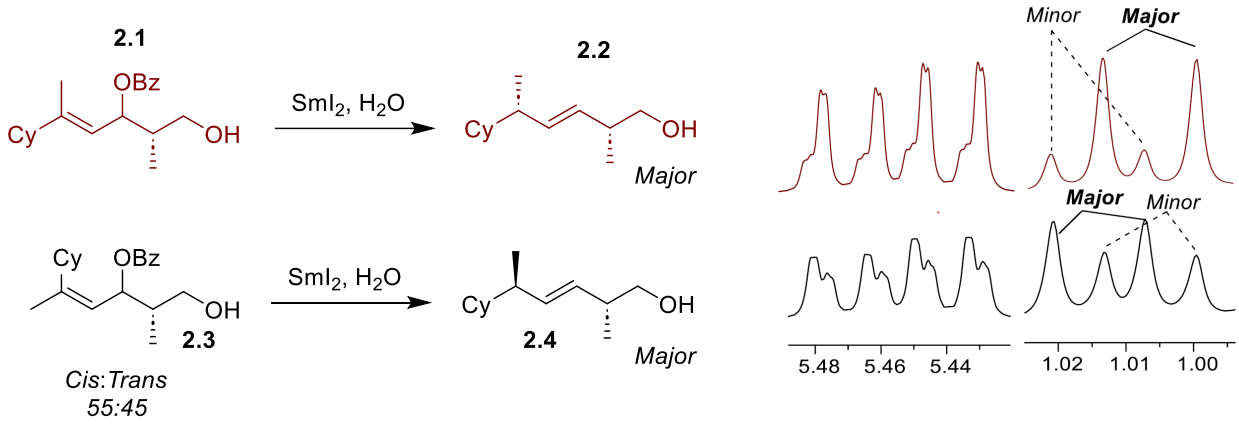
Chapter 2: Allylic Sulfone Synthesis

2.1: Horner-Wadsworth-Emmons Olefination Approach

Our first objective was to synthesize a trisubstituted allylic sulfone that would feature a geminal methyl and phenyl group. In addition to serving as a single electron acceptor in the samarium reduction, the sulfone could also enable our target substrate to be synthesized by sulfonyl anion addition to an electrophile of choice. For instance, addition to an aldehyde would produce an allylic sulfone with the needed chelating and stereodirecting groups for the samarium-mediated reduction conditions we wanted to explore.

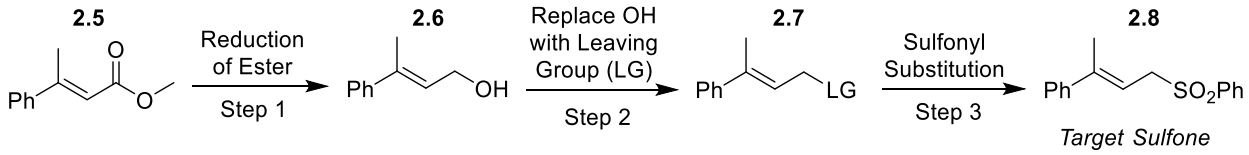
However, an important objective for the synthesis of our standard allylic sulfone was access to both *cis*- and *trans*-stereoisomers for a study of stereospecificity. Past results from the O'Neil group had shown that trisubstituted allylic benzoates under the samarium-mediated reduction conditions can lose stereospecificity depending on the identity of the geminal substituents.[9] Alkyl substituents in the geminal position of the substrate caused a preservation of stereospecificity that persisted through the samarium-mediated reduction as was seen in Scheme 1.4. It was theorized that a more sterically hindering cyclohexyl group present in **2.1** and **2.3** (Figure 2.1) might promote a sterically driven loss of stereospecificity by permitting bond rotation in the organosamarium complex. To our group's surprise, this phenomenon was not observed and stereospecificity was preserved, as **2.2** and **2.4** favored the syn and anti diastereomer respectively. When the cyclohexyl group was replaced with a similarly sterically hindering phenyl group, as was seen in Scheme 1.5, the same samarium-mediated reduction conditions lost preservation of stereospecificity. This indicated that steric hindrance was likely not the culprit behind this phenomenon and electronics were potentially responsible. As a result, we wanted our primary trisubstituted allylic sulfone to feature *cis*- and *trans*-isomers containing both alkyl and phenyl groups so that further exploration of these results would be possible.

Figure 2.1. Usage of a geminal cyclohexyl group preserved stereospecificity, despite providing steric hindrance. Adapted from reference.[8]



In order to synthesize our target sulfone as both *cis*- and *trans*-stereoisomers, a Horner-Wadsworth-Emmons (HWE) olefination was selected as our approach. This olefination reacts aldehydes or ketones with phosphonate carbanions, ultimately resulting in both *cis*- and *trans*- alkenes with a preference for the latter.(10) We believed that if we could synthesize both stereoisomers and separate them, we could gain control over the *E*/*Z* ratio and push the resulting mixture of alkenes towards our desired sulfone. This approach would also permit selection of the geminal substituents based on the choice of aldehyde or ketone. Because we wanted a trisubstituted allylic sulfone, a ketone was chosen to access our desired substrate. If acetophenone could be pushed to the ester **2.5.1** via the HWE olefination, then the desired substate could be accessed in three additional steps (Scheme 2.1).

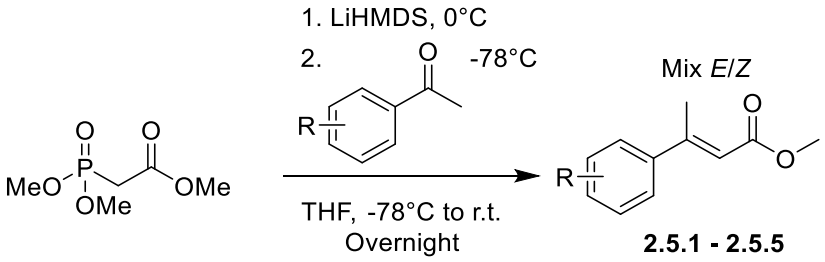
*Scheme 2.1. Pathway to target sulfone from ester **2.5** in three additional reactive steps.*



Additionally, acetophenone derivatives with different aromatic substitutions could potentially be employed as well. We chose to target 3'-chloro, 3'-methoxy, 3'-methyl, and 2'-methylacetopheone for this purpose, as these different functionalizations could enable further investigation into what could

be an electronically driven loss of stereospecificity due to a geminal phenyl group that was seen in past work.

Table 2.1. Horner-Wadsworth-Emmons olefination with different acetophenone derivatives.



Entry	Compound #	Acetophenone Derivative	*E*/*Z* Ratio[a]	Percent Yield
1	**2.5**	Acetophenone	83:17	72
2	**2.5.2**	3'-Chloroacetophenone	82:18	82
3	**2.5.3**	3'-Methoxyacetophenone	86:14	62
4	**2.5.4**	3'-Methylacetophenone	85:15	58
5	**2.5.5**	2'-Methylacetophenone	28:72	13

Notes for Table 2.1: All reactions were performed by adding 1.2 equiv. of trimethylphosphonoacetate to a solution of LiHMDS (1.1 equiv.) in THF at 0°C, allowed to warm to room temp over 30 minutes, chilled to 78°C, then adding the acetophenone derivative (1 equiv.) and let stir overnight. [a]Determined by NMR.

Indeed, deprotonation of trimethylphosphonoacetate using LiHMDS enabled nucleophilic attack of acetophenone, producing the trisubstituted allylic ester **2.5.1** as a mixture of *E*- and *Z*-stereoisomers in 72% yield that, consistent with the HWE olefination, favored the *E*-stereoisomer. The 3'-chloro, 3-methoxy, and 3-methylacetophenone derivatives **2.5.2**, **2.5.3**, and **2.5.4** were also synthesized in comparable yield and featured near identical *E*/*Z* ratios. However, while 2'-methylacetophone was successful in the HWE olefination, the resulting ester **2.5.5** was only achieved in 13% yield and the *Z*-stereoisomer was favored. The heavy toll on yield could have been due to the steric hindrance of the

ortho-substituted methyl group interfering with formation of an oxaphosphetane intermediate. The inversion of preference from the *E*-stereoisomer to the *Z*-stereoisomer was surprising.

Intrigued by the inversion of preference of stereoisomer displayed by the 2'-methylacetophone derivative, we wanted to see if other strong nucleophilic bases could impact the *E*/*Z* ratio of the resulting ester. Keeping in line with the initially chosen LiHMDS, the same reactions that employed standard acetophenone and 2'-methylacetophenone were tested using the similar organosilicon bases NaHMDS and KHMDS.

Table 2.2. Horner-Wadsworth-Emmons reaction using different organosilicon bases.

Entry	Base	Acetophenone Derivative	Percent Trans[a]	Percent Cis[b]	Percent Yield
1	LiHMDS	Acetophenone	83	17	72
2	KHMDS	Acetophenone	72	28	32
3	NaHMDS	Acetophenone	75	25	20
4	LiHMDS	2'-Methylacetophenone	28	72	13
5	KHMDS	2'-Methylacetophenone	32	68	3
6	NaHMDS	2'-Methylacetophenone	40	60	4

Notes for Table 2.2: All reactions were performed by adding 1.2 equiv. of trimethylphosphonoacetate to a solution of LiHMDS (1.1 equiv.) in THF at 0°C, allowed to warm to room temp over 30 minutes, chilled to 78°C, then adding the acetophenone derivative (1 equiv.) and let stir overnight. [a,b]Determined by NMR.

For the standard acetophenone system, LiHMDS not only afforded our target ester in the highest yield of 72% but was the most *trans*-selective. NaHMDS and KHMDS had very similar *cis*/*trans* selectivities, but KHMDS afforded a marginally higher yield. Consistent with the previous result from Table 2.1, when 2'-methylacetophenone was used, the resulting product favored the *cis*-stereoisomer, but with very low yields. LiHMDS afforded the highest yields in this system, as well as the highest

selectivity for the *cis*-stereoisomer. Fortuitously, both stereoisomers of the resulting esters were partially separable by column chromatography on silica.

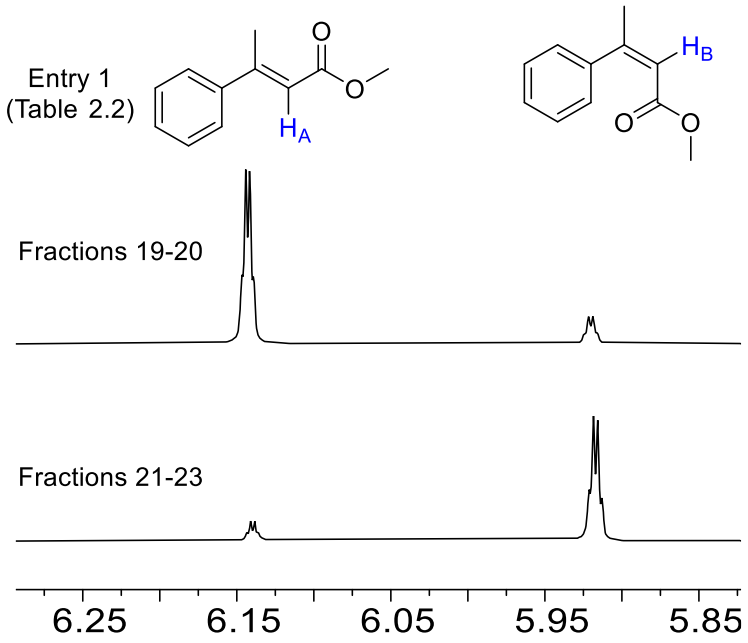


Figure 2.2. Purification of HWE product permit separation of E and Z-stereoisomer samples.

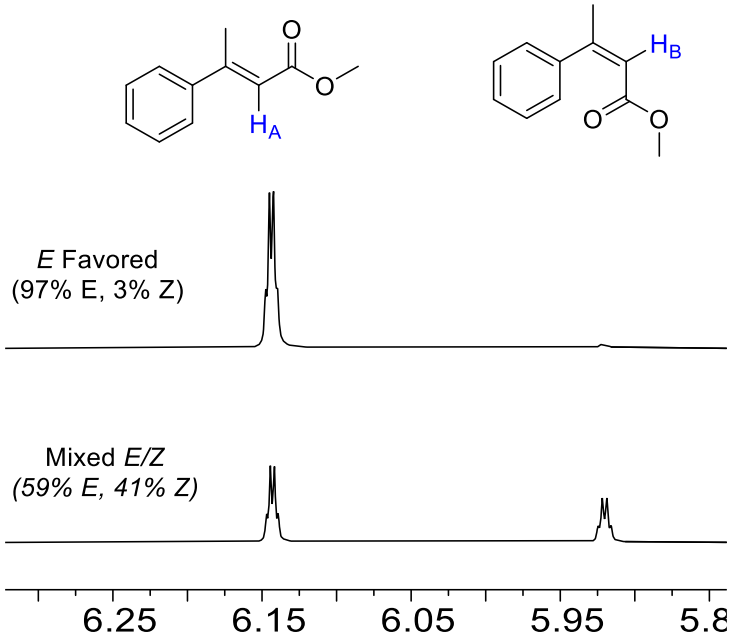
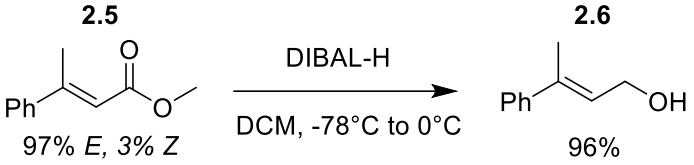


Figure 2.3. Generation of E-favored and mixed E/Z samples of target ester.

The *E*-stereoisomer of the resulting ester was generally found in earlier fractions while the *Z*-stereoisomer followed shortly after (Figure 2.2). Our goal was to synthesize both stereoisomers of this ester and isolate fractions that were either mostly *trans* or mostly *cis*. Selectively mixing these fractions would concentrate samples that consisted predominantly of the *E*-stereoisomer, as well as a mixture of both *E*- and *Z*-stereoisomers. As a result, an *E*-favored (97% *E*, 3% *Z*) and a mixed *E*/*Z* (59% *E*, 41% *Z*) portion of the ester were generated and would be used in our progress towards our allylic sulfone (Figure 2.3).

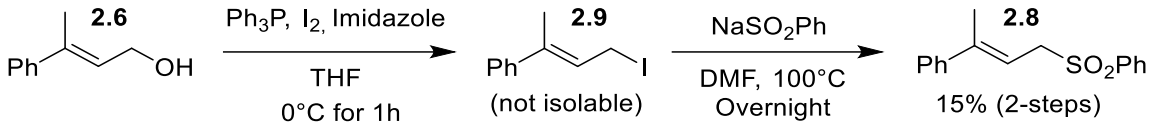
With a trisubstituted allylic alkene established, our next objective was to exchange our ester with a sulfonyl group. We elected to reduce our ester to produce an allylic alcohol as we wanted to remove the carbonyl from the allylic position, and the new hydroxyl group could enable further synthesis.

*Scheme 2.2. DIBAL-H reduction of **2.5** to allylic alcohol **2.6**.*



Reduction of ester **2.5** using DIBAL-H afforded the allylic alcohol **2.6** in excellent yield. We then believed that if our substrate could be provided with a good leaving group, a sulfonyl substitution via nucleophilic attack on the allylic position by a sulfonyl containing species could endow our substrate with the needed sulfonyl group. Our initial choice of leaving group was dependent on two factors: the reactivity of the leaving group and the utility of the conditions that the reaction would require. Alcohols are the most common precursors to alkyl halides, and among them, iodides possess the most reactivity out of the halides.[11] Thus, a halogenation to form an iodide was chosen.

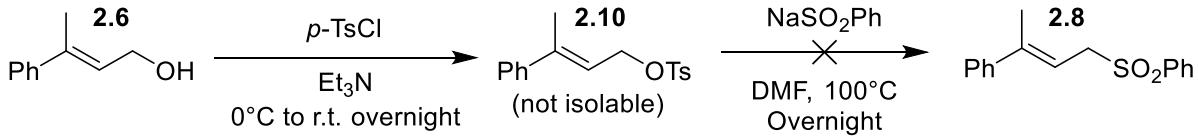
*Scheme 2.3. Synthetic route to allylic sulfone **2.8** via iodide **2.9**.*



Alcohol **2.6** was transformed to iodide **2.9** using a combination of triphenylphosphine, imidazole, and crystalline iodine. Unfortunately, attempts at purification of **2.9** resulted in decomposition on silica, likely due to the reactivity of the iodide. Thus, this compound was taken crude into a substitution using benzenesulfinic acid sodium salt. Excitingly, our target sulfone was able to be isolated, albeit with a very low yield (15%). Such a low yield necessitated we consider alternative synthetic approaches towards our target allylic sulfone **2.8**.

Because the instability of the iodide placed a barrier in our reactive methodology, we looked towards other potential leaving groups so we could avoid decomposition of our intermediate. Rather than a halogenation, it was theorized that a tosylate (OTs) could give us the leaving group we needed for a substitution while faring better through purification via column chromatography on silica.

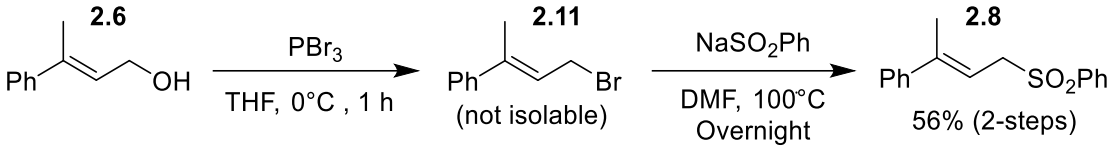
*Scheme 2.4. Synthetic route to allylic sulfone **2.8** via tosylate **2.10**.*



Unfortunately, like the attempted isolation of iodide **2.9**, the tosylated substrate **2.10** also decomposed on silica via column chromatography. Furthermore, efforts to substitute **2.10**'s tosyl group with a sulfonyl group were unsuccessful. We therefore needed to turn our attention once more towards an alternative synthesis. Looking back to our iodide containing substrate **2.9**, we felt that this approach was more promising than the tosylation, but still needed adjustment to avoid decomposition. Thus, we

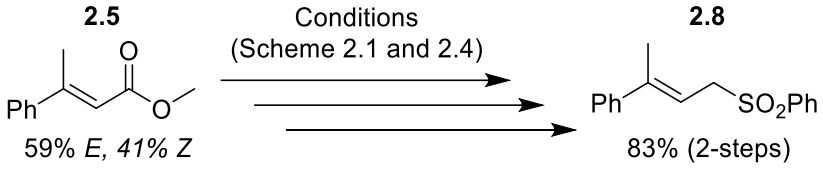
sought a procedure that would halogenate our substrate to a bromide, incorporating the next most reactive halogen for the purpose of our planned sulfonyl substitution.

*Scheme 2.5. Synthetic route to allylic sulfone **2.8** via bromide **2.11**.*



Halogenation of **2.6** using PBr_3 afforded an allylic bromide **2.11**. While this substrate decomposed when passing through silica via column chromatography like iodide **2.9**, it looked better yielding than the iodination via NMR and we believed it would be more stable, so it could reasonably be sulfonylated as a crude mixture. Fortuitously, this substrate was sulfonylated with benzenesulfinic acid sodium salt and afforded our target allylic sulfone **2.8** in 56% yield over two steps, far surpassing the 15% yield of the route using an iodide. Furthermore, with confirmation that this route in synthesis was successful, we repeated the synthesis with ester **2.5** (Scheme 2.6) as a mixture of both *E*- and *Z*-stereoisomers rather than mostly the *E*-stereoisomer. With a mixture of *E*- and *Z*-stereoisomers, the same allylic sulfone **2.8** was achieved in 83% yield from the corresponding alcohol.

*Scheme 2.6. Identical synthetic route with a mixture of E- and Z-stereoisomers of ester **2.5** afforded sulfone **2.8**.*

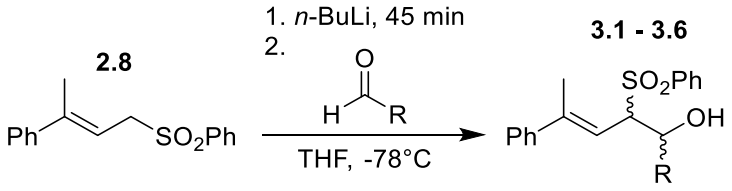


Chapter 3: Metalated Sulfone Anion Addition of Aldehydes

3.1: Aldehyde Additions

The allylic sulfone **2.8** still needed a stereodirecting group and a chelating group for the samarium-mediated reduction. The resonance stabilization provided by the sulfonyl group would make the allylic protons adjacent to the sulfone acidic. This could allow for a deprotonation at this site and convert the allylic sulfone into a nucleophile that could attack an electrophile endowed with a potential chelating and stereodirecting group. Aldehydes would be a good choice for the synthesis of our desired substrates for the samarium-mediated reduction as nucleophilic attack could simultaneously provide the stereodirecting and chelating group while keeping the linker length a small as possible (n = 0). Additionally, a careful selection of aldehyde would allow for control of the identity of the stereodirecting group. We wanted to see how modifying this group might affect the organosamarium intermediate and the resulting diastereoselectivity of the products. To do so, the sulfone **2.8** that was concentrated to its mostly *E*-stereoisomer was reacted with a series of aldehydes of increasing sterically demanding R groups (Table 3.1).

Table 3.1. Metalated sulfone addition using aldehydes with increasingly sterically hindering R groups.



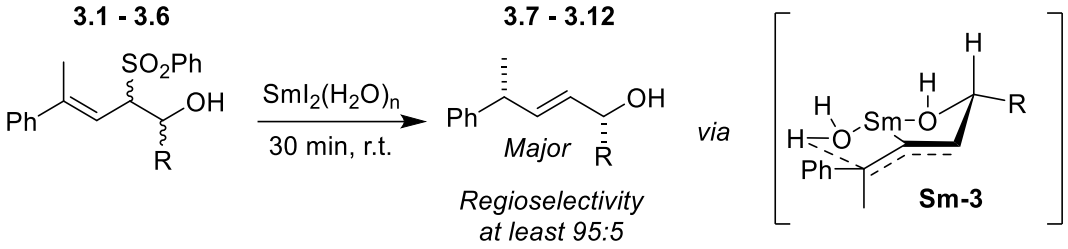
Entry	Compound #	R	Percent Yield
1.	**3.1**[a]	CH_3	82
2.	**3.2**[b]	CH_2CH_3	54
3.	**3.3**[c]	$CH_2CH_2CH_2CH_2CH_3$	26
4.	**3.4**[c]	$CH(CH_3)_2$	31
5.	**3.5**[a]	$CH_2CH(CH_3)_2$	66
6.	**3.6**[b]	$C(CH_3)_3$	60

Notes for Table 3.1: All reactions were performed by adding 1.2 equiv. of n-BuLi to the sulfone in THF at -78°C and left to react for 45 minutes, then adding 2.0 equiv. of the aldehyde. [a]Quenched after 2 hours reacting at -78°C. [b]Quenched after 2 hours reacting at -78°C, then 1 hour at 0°C. [c]Quenched after reacting at -78°C while warming to room temperature overnight.

Yields for the sulfonyl anion aldehyde addition products varied. Notably, the reaction with acetaldehyde had the highest yield at 82% while the hexanal and isobutyraldehyde derivatives **3.3** and **3.4** had significantly lower yields at 26% and 31% respectively. At first glance, it seemed that increasing the steric bulk of the R group hindered the sulfonyl anion aldehyde addition as a methyl group (Table 3.1, entry 1) was the highest yielding while a 5-membered alkyl chain (Table 3.1, entry 3) had a substantially lower yield. However, both the isovaleraldehyde and pivaldehyde derivatives **3.5** and **3.6** had yields of 66% and 60% respectively. The pivaldehyde derivative would be the most sterically hindering, so the steric bulk of the R group may not be the culprit behind the lower yields for the hexanal and isobutyraldehyde derivatives.

These aldehyde addition products **3.1** through **3.6** were then reduced with $SmI_2(H_2O)_n$. All the resulting reduction products **3.7** through **3.12** were not only successfully synthesized but had regioselectivities of at least 95:5. Upon evaluation of the diastereomeric ratio of the resulting diastereomers using deconvolution in MestReNova (see supporting information), a clear trend appeared. As the steric hindrance of the stereodirecting group increased, the diastereomeric ratio of the resulting reduction products increased as well. To explain this phenomenon, we looked to our proposed bicyclic organosamarium intermediate (**Sm-3**) and the impact that steric strain of the stereodirecting group may place on the intermediate. With an increased preference to rest in the pseudo-equatorial position to enter a lower energy state, the stereodirecting group could increase the rigidity of the ringed system. This bias towards a more rigid, energetically favorable ring structure would favor selective intramolecular protonation, increasing the diastereoselectivity of the resulting product.

*Table 3.2. Samarium-mediated reductions of aldehyde addition products via organosamarium intermediate **Sm-3** demonstrated an increasing diastereomeric ratio as the stereodirecting group (R) increased in steric hindrance.*



Entry	Compound #	R	d.r.[a]	Percent Yield
1.	**3.7**	CH_3	6.7 : 1	43
2.	**3.8**	CH_2CH_3	10.5 : 1	59
3.	**3.9**	$CH_2CH_2CH_2CH_2CH_3$	12.1 : 1	59
4.	**3.10**	$CH(CH_3)_2$	12.7 : 1	72
5.	**3.11**	$CH_2CH(CH_3)_2$	13.5 : 1	58
6.	**3.12**	$C(CH_3)_3$	15.1 : 1	59

Notes for Table 3.2: All reactions were performed using 105 equiv. of H_2O and 7 equiv. of SmI_2 in degassed THF at rt under N_2. [a]Determined by ^1H NMR.

In an effort to evaluate the reliability of deconvolution as a means to determine the diastereomeric ratio, the samarium reduction products **3.8**, **3.9**, and **3.11** were analyzed via gas chromatography (GC). Hopefully, if these diastereomers could be separated via GC, a diastereomeric ratio could be generated and compared with that found through deconvolution via NMR. However, despite many different conditions used (see Table 3.3), in the case of **3.8** and **3.9**, separation of diastereomers was not observed (example in Figure 3.1). Fortunately, we were able to see separation in the samarium-mediated reduction product **3.11**. The diastereomeric ratio of the purified version of the product **3.11** via NMR and GC were 9.4 and 8.6 respectively. This supported that our deconvolution methodology in MestReNova was a reasonably accurate tool to evaluate the diastereomeric ratio.

*Table 3.3. Samarium reduction products **3.8**, **3.9**, and **3.11** were analyzed via gas chromatography utilizing varying parameters in an effort to see separation of diastereomers.*

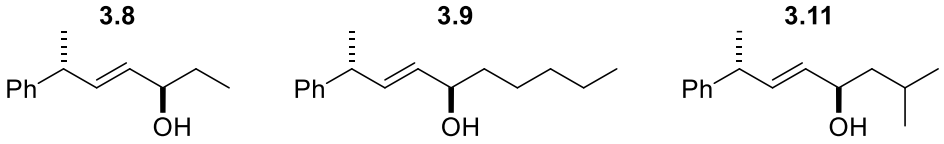


Table 3.3
Entries 1-6

Table 3.3
Entries 1-3

Table 3.3
Entries 1-3

Entry	Temperature Range (°C)	Time Run (min)	Flow Rate (mL/min)	Temperature Ramp (°C/min)
1.	100 - 320	32	0.5	10
2.	100 - 320	32	1.0	10
3.	100 - 320	32	1.5	10
4.	100 - 250	40	1.5	5
5.	100 - 250	70	0.5	2.5
6.	100 - 250	70	1.5	2.5

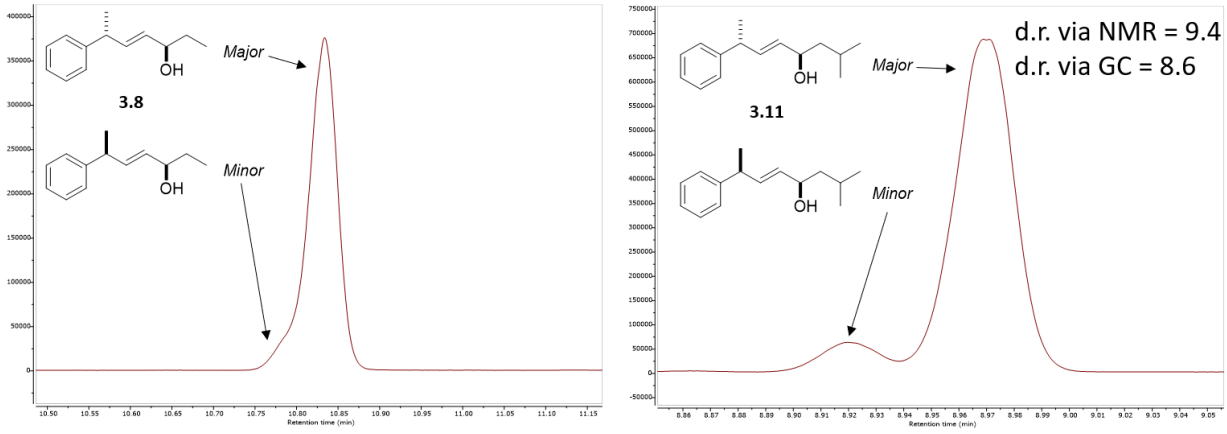


*Figure 3.1. While separation of diastereomers couldn't be seen in most of our samarium reduction products, the samarium reduction product **3.11** was separable via GC and had a diastereomeric ratio comparable to that found via deconvolution in NMR spectra.*

To confirm that the 2nd generation sulfonyl substrates had the same relative stereochemistry compared to the 1st generation benzoyl system, we compared the NMR spectra of the same product **3.7** generated from the samarium-mediated reductions of **3.1'** and **3.1** (Figure 3.2). Both spectra were nearly identical, which indicated that they both formed the same product. Of particular note, a closer inspection of the diastereotopic methyl peak for the reduction product **3.7** (synthesized from both starting materials) favored the same major diastereomer. Substrate **3.7** had already been synthesized from **3.1'** in past work in the O'Neil lab, and it was found through ozonolysis of **3.7** that the syn product was the major diastereomer.[8] This supported that the relative stereochemistry for **3.7** was the same when synthesized from either **3.1'** or **3.1** and thus 2nd generation substrates replicated the formation of the same major syn diastereomer.

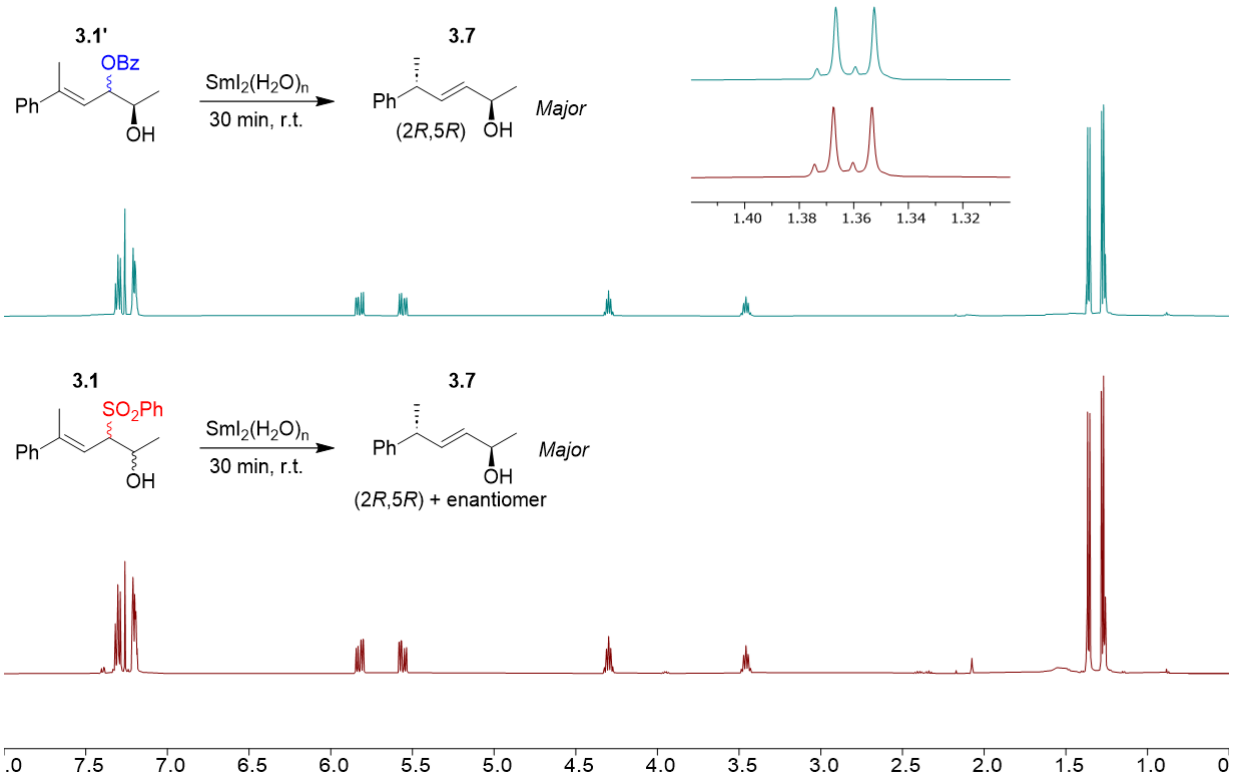
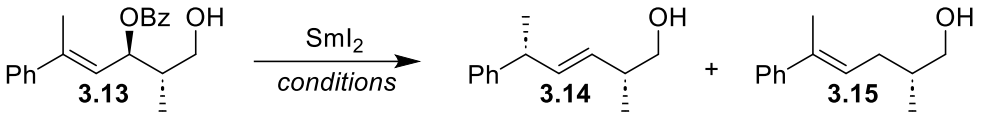


*Figure 3.2. Both the benzoyl substrate **3.1'** and the sulfone substrate **3.1** converged to the same product and favored the same major diastereomer, which supported that the relative stereochemistry of either system was consistent.*

3.2 Modifying the Equivalents of Water

Previous results from the O'Neil group demonstrated that there was an ideal number of equivalents of water relative to the samarium diiodide used in the samarium-mediated reduction to optimize yield and facilitate greater regioselectivity.[4]

Table 3.4. Equivalents of water affected the regioselectivity, diastereoselectivity, and yield of samarium-mediated reduction products. Adapted from reference.[4]



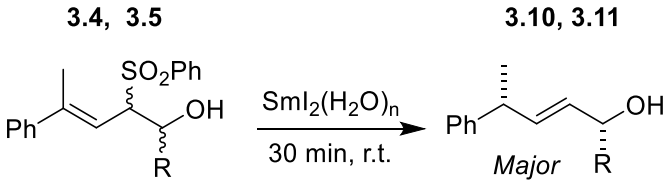
H_2O (equiv)[a]	3.14:3.15[b]	d.r.[b] of 10	Yield[c] of 10
200	86:14	75:25	30%
100	86:14	76:24	60%
50	86:14	75:25	75%
25	91:9	75:25	82%
15	97:3	75:25	90%
10	98:2	76:24	76%
5	98:2	72:28	86%
1	100:0	72:28	66%

Notes for Table 3.4: [a]Relative to SmI_2. [b]Determined by NMR. [c]Isolated yield.

While there was a modest overall increase in diastereoselectivity for the reduction of compound **3.13** as greater than 5 equivalents of water relative to SmI_2 were used, the regioselectivity started to decrease after more than 15 equivalents of water. Additionally, at 15 equivalents of water, the yield of the desired product **3.14** was the highest observed at 90%. Because of these findings, 15 equivalents of

water were chosen as the standard for the samarium-mediated reduction on our allylic sulfone system. However, we were curious if these results would be consistent if we modified the equivalents of water. Thus, we ran two more samarium-mediated reductions on our isovaleraldehyde sulfone derivative **3.5**, using 5 and 154 equivalents of water relative to SmI_2. Overall, the diastereomeric ratio of the products were lowered when fewer or greater than 15 equivalents of water were used (Table 3.5). The greatest decrease in diastereomeric ratio was seen when 5 equivalents of water were used as the yield was substantially lowered to 17%. At 154 equivalents, the diastereomeric ratio only decreased modestly, but the yield was overall similar to the 15 relative equivalent standard. This indicated that 15 equivalents of water was indeed still optimized for our allylic sulfone as was the case with the benzoate system.

Table 3.5. Changing relative equivalents of water for the samarium-mediated reduction of the isovaleraldehyde and isobutyraldehyde substrates revealed different trends in d.r., but similar trends in yield.



Entry	R	Equiv. H_2O[a]	d.r.[b]	Yield (%)
1.	$CH_2CH(CH_3)_2$	5	6.9 : 1	17
2.	$CH_2CH(CH_3)_2$	15	13.5 : 1	58
3.	$CH_2CH(CH_3)_2$	154	11.6 : 1	46
4.	$CH(CH_3)_2$	15	12.7 : 1	72
5.	$CH(CH_3)_2$	50	13.3 : 1	52
6.	$CH(CH_3)_2$	154	13.5 : 1	43

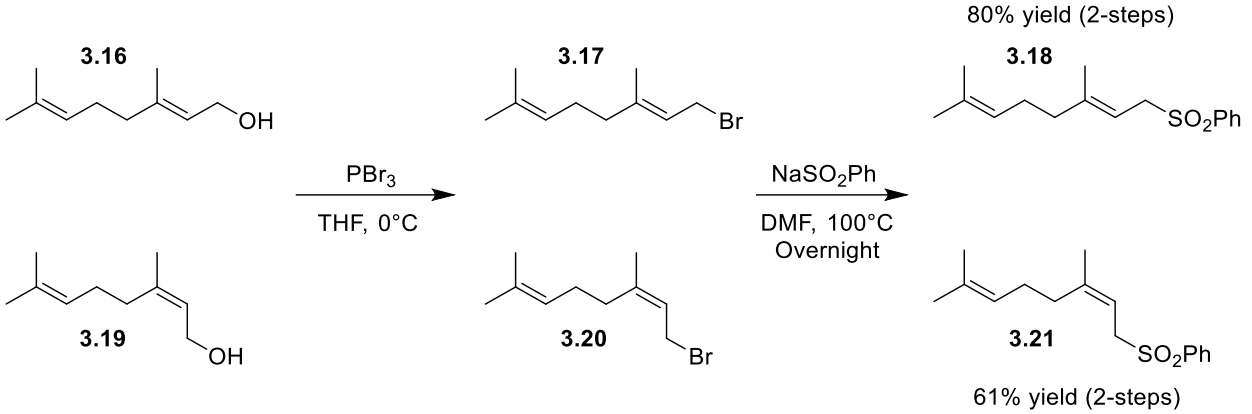
Notes for Table 3.5: All reactions were performed using 7 equiv. of SmI_2 in degassed THF at rt under N_2. [a]Relative to SmI_2. [b]Determined by NMR.

To test if the results regarding water equivalents were sensitive to substrate structure, we also evaluated samarium-mediated reductions on the isobutyraldehyde sulfone derivative **3.4** using different equivalents of water. Since the results from fewer than 15 equivalents of water were very poor, we elected to try 50 and 154 equivalents respectively. At both 50 and 154 equivalents of water, the diastereomeric ratio increased slightly (to 13.3 : 1 and 13.5 : 1 respectively compared to 12.7 : 1 for 15 equivalents). However, yields for both reactions were lower (52% and 43% respectively compared to 72% for 15 equivalents). Again, 15 equivalents of water relative to SmI_2 appeared optimal in terms of balancing yield and the diastereomeric ratio for both the allylic sulfone and benzoyl substrates.

3.3: Geminal Substituents and Stereospecificity

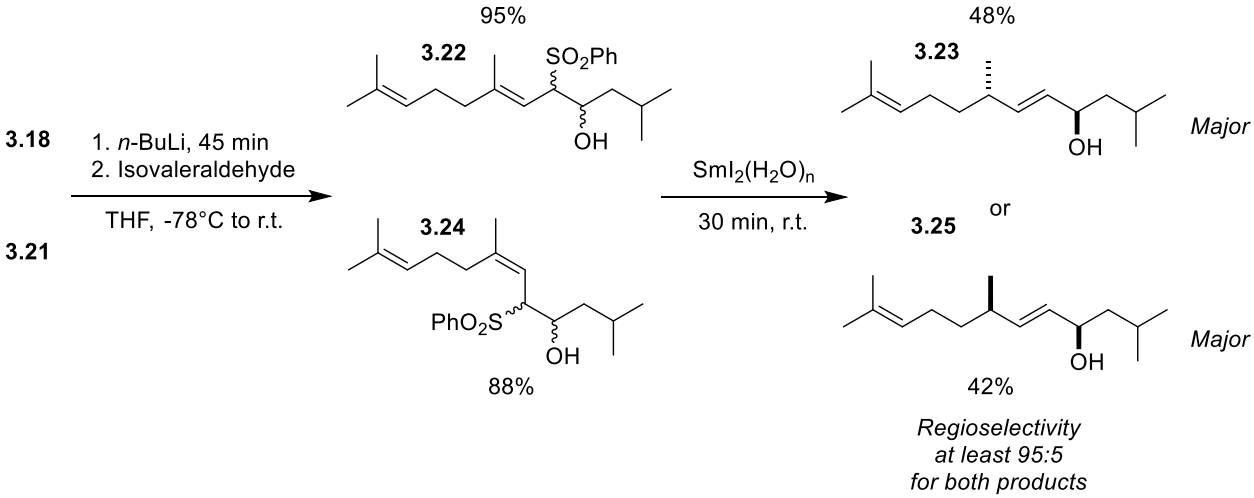
Based on past results from the O'Neil group, it was expected that phenyl substitution of the double bond would result in a non-stereospecific reduction with $SmI_2(H_2O)_n$. We wanted to see if this loss of stereospecificity would be consistent with our 2nd generation sulfone system. To investigate this phenomenon, we elected to synthesize both *cis*- and *trans*-alkyl-based substrates. These resulting compounds could be compared with a mixture of *cis*- and *trans*-substrates post aldehyde addition as these compounds were already designed to include a geminal phenyl group using our HWE olefination-based synthesis. To access the desired *cis*- and *trans*-alkyl substrates, we chose to start with geraniol (**3.16**) and nerol (**3.19**) as these compounds were readily available, are *trans*- and *cis*- respectively, only possess methyl groups in their geminal positions, and have a hydroxyl group that could be converted into a sulfone using the same approach featured in our 2nd generation sulfone synthesis.

*Scheme 3.1. Sulfonylation approach for geraniol and nerol to substrates **3.18** and **3.21**.*



Both alcohols **3.16** and **3.19** were halogenated using PBr_3 and subsequently sulfonylated via benzenesulfinic acid sodium salt. Over two steps, allylic sulfones **3.18** and **3.21** were afforded in 80% and 61% yields respectively. The two resulting sulfones were then subjected to an aldehyde addition with isovaleraldehyde, which afforded the resulting aldehyde addition products **3.22** and **3.24** in 95% and 88% yield respectively (Scheme 3.2). These two substrates were then reduced with $SmI_2(H_2O)_n$.

*Scheme 3.2. Aldehyde addition and subsequent samarium-mediated reduction of **3.18** and **3.21**.*



The samarium-mediated reduction afforded the two stereoisomers **3.23** and **3.25** with regioselectivity of at least 95:5 in 48% and 42% yield respectively. Closer inspection of their NMR spectra revealed great insight into the stereospecificity of the resulting products (Figure 3.3).

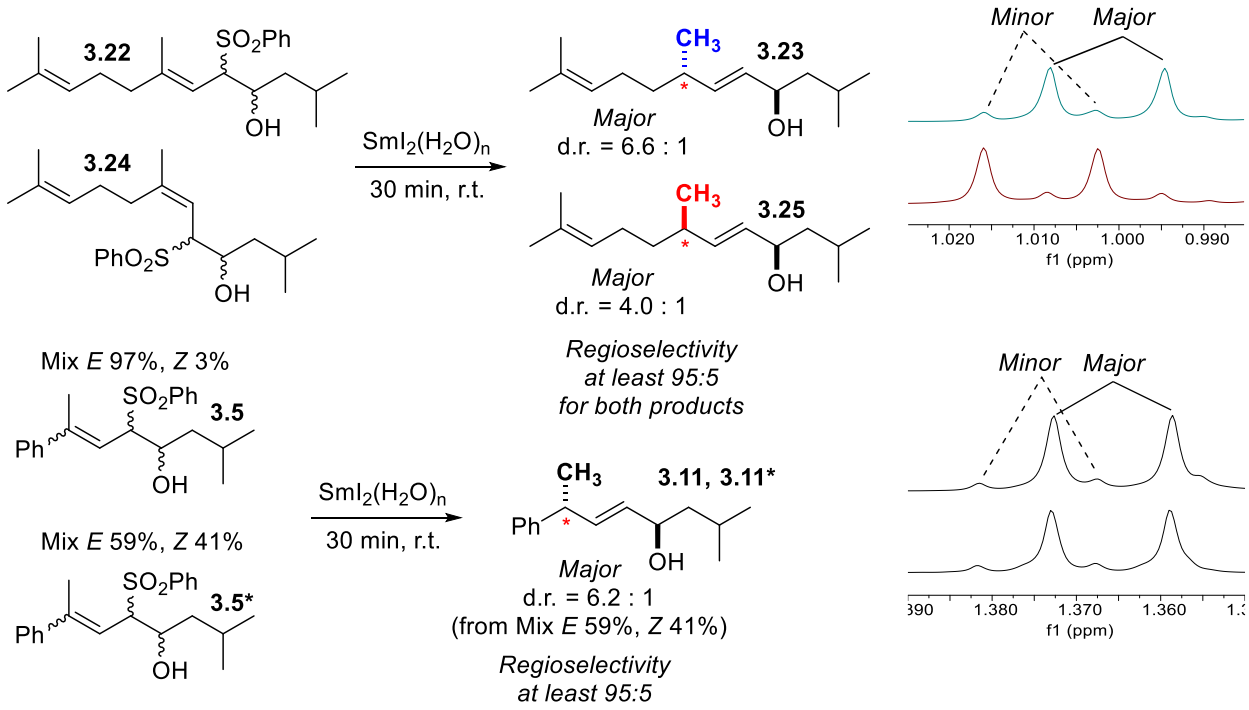
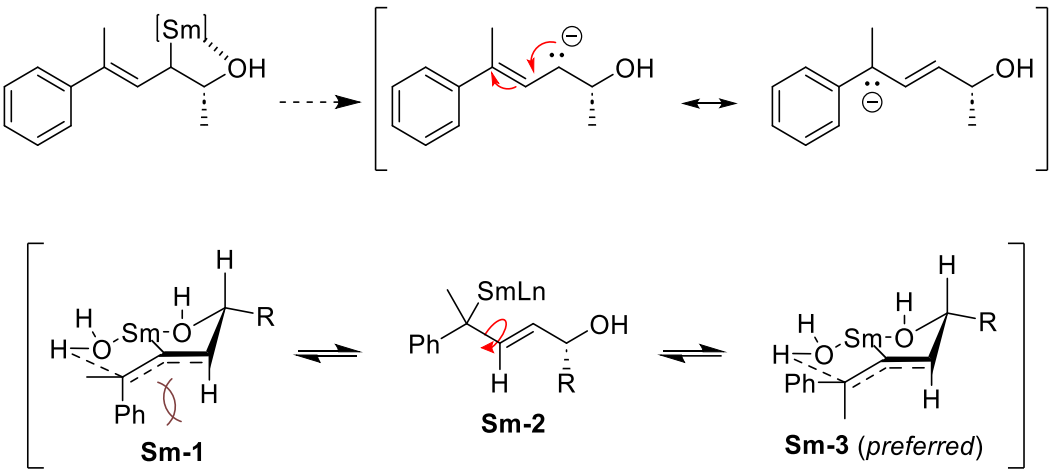


Figure 3.3. A geminal non-phenyl group preserved stereospecificity while a geminal phenyl group caused both stereoisomers to lose stereospecificity and converge to the same product.

As the *trans*-exclusive substrate **3.22** and *cis*-exclusive substrate **3.24** were reduced with $SmI_2(H_2O)_n$, the major diastereomer obtained switched. This was consistent with past results from the O'Neil group with the benzoate system, as geminal alkyl substituents preserved stereospecificity, with *trans*-benzoates favoring the syn product and *cis*-benzoates favoring the anti product. Such stereospecificity could be seen in the NMR spectra in Figure 3.3 as the major and minor product of each reaction was inverted. However, when different *cis*/*trans* mixtures **3.5** (97% *E*) and **3.5*** (59% *E*) that both featured a geminal phenyl group were reduced with $SmI_2(H_2O)_n$, both precursors converged to the same major diastereomer. This too was consistent with past results from the O'Neil group. Thus, our 2nd generation substrate with a sulfone as the single electron acceptor still followed these exciting stereospecific preferences according to geminal functional group and alkene geometry.

To explain such results, a bicyclic organosamarium intermediate could be used. While a geminal alkyl group is incapable of supporting resonance stabilization, a phenyl group could stabilize an anion or radical left behind once $SmI_2(H_2O)_n$ departs from the substrate. The resulting resonance form would translocate the carbon-carbon double bond, permitting free rotation where this double bond was originally locked in place. If such rotation could occur, a sterically driven isomerization from organosamarium intermediate **Sm-1** to **Sm-3** would position the originally pseudo-axial phenyl group to the pseudo-equatorial position. Thus, regardless of precursor alkene geometry, the organosamarium intermediate would still facilitate selective intramolecular protonation that favors the syn product.

*Scheme 3.3. Loss of stereospecificity with a geminal phenyl group could be due to a resonance-promoted movement of the carbon-carbon double bond, which in turn enabled free rotation around the carbon-carbon bond in the proposed bicyclic organosamarium intermediate **Sm-2**.*



Chapter 4. Metalated Sulfone Anion Addition of Epoxides

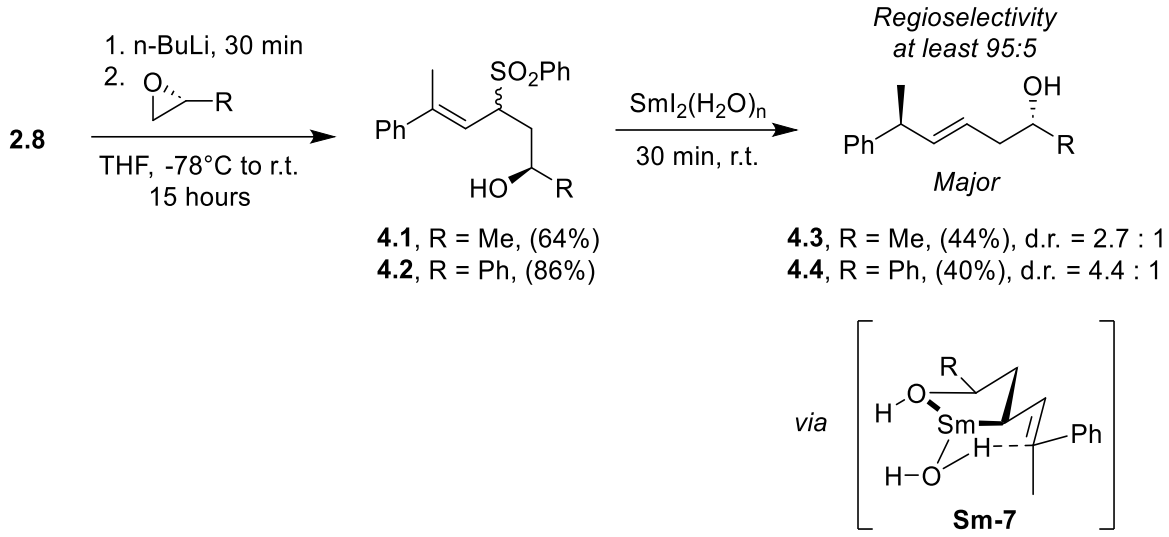
4.1: Epoxide Openings

Akin to aldehydes, epoxides could be good candidates to furnish our allylic sulfone with the required chelating and stereodirecting group. Via metalated sulfone anion addition, epoxides with an R

group of choice could be opened, simultaneously establishing a chelating and stereodirecting group. Furthermore, use of chiral epoxides could enable the reaction sequence to be enantioselective. Using a fixed chiral epoxide would allow the samarium-mediated reduction, which generates a major diastereomer with high selectivity, to also afford a concentration of one enantiomer. Using the *trans*-favored sulfone **2.8** (97% *E*) in a metallated sulfone anion addition, we chose (*R*)-propylene oxide and (*R*)-styrene oxide as our epoxides to open. These two chiral epoxides only differ by a methyl or phenyl group on carbon 2. If we could successfully open these epoxides, we could see how a methyl or phenyl group as the needed stereodirecting group would augment the diastereomeric ratio of the resulting samarium-mediated reduction products. Before we could test this, however, we needed to complete the required metallated sulfone anion addition with each of these epoxides.

To start, we elected to employ similar conditions as were used with our metallated sulfone anion additions of aldehydes, and only changed the amount of time the substrate would react with *n*-butyllithium from 45 minutes to 30 minutes. After running these epoxide openings overnight, we were able to synthesize the sulfone-epoxide addition products **4.1** and **4.2** in 64% and 86% yields respectively. Subsequent reduction with $SmI_2(H_2O)_n$ afforded the expected products **4.3** and **4.4** in 44% and 40% yields respectively. However, we observed a notable difference in the diastereomeric ratio between both products as **4.3** had a lower d.r. of 2.7 : 1 while **4.4** had a higher d.r. of 4.4 : 1. This could be explained through steric hindrance as the phenyl group in **4.4** would cause the resulting organosamarium intermediate **Sm-7** to experience increased ring rigidity, facilitating more selective intramolecular protonation.

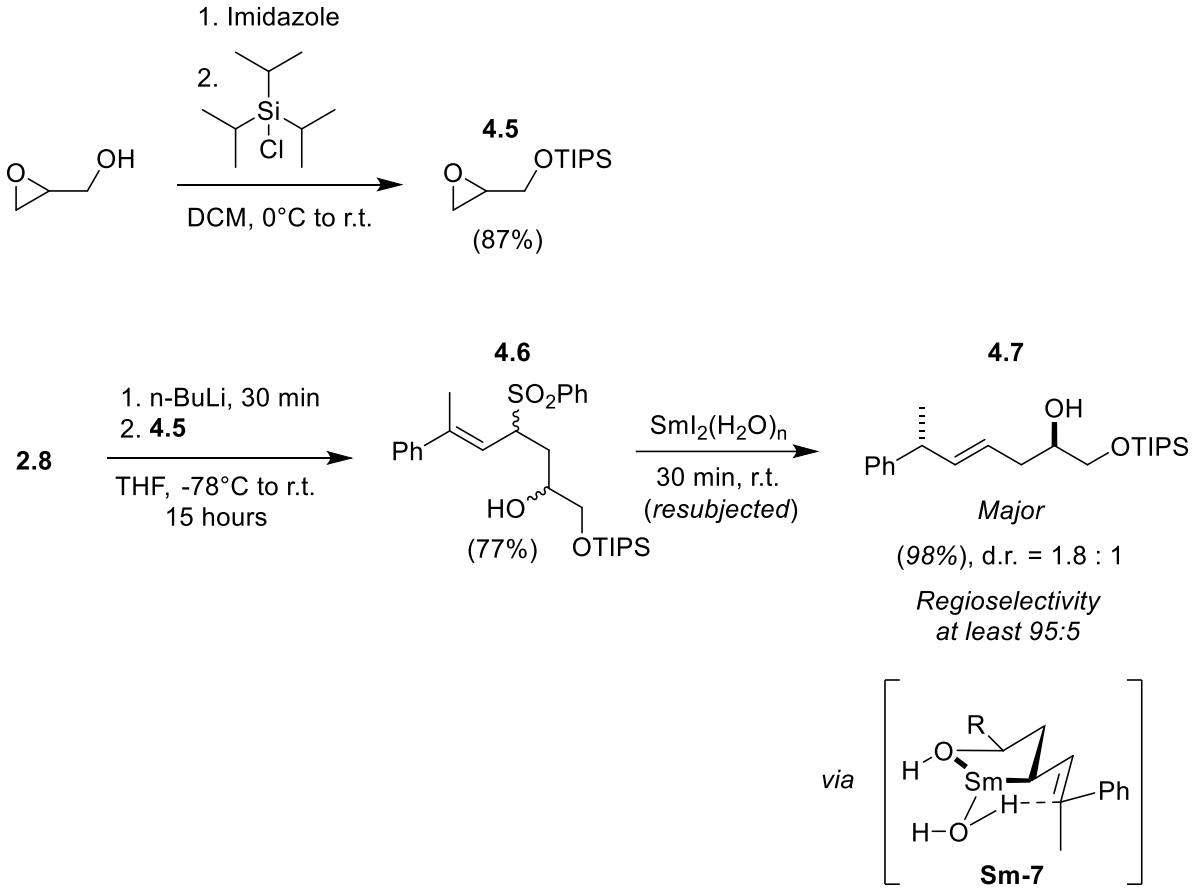
Scheme 4.1. Initial metalated sulfone anion additions of epoxides (R)-propylene oxide and (R)-styrene oxide and subsequent samarium-mediated reductions.



While these results supported a sterically driven increase in diastereomeric ratio as was seen with metallated sulfone anion additions of aldehydes, we were curious if we could simultaneously expand the reactive scope of these epoxide openings while also exploring the impact of steric hindrance on our samarium-mediated reductions. Resultantly, we looked at how sterically hindering protecting groups might impact the reduction. Being able to incorporate protecting groups in precursor substrates prior to the reduction would enhance its utility in synthesis, but due to the chelating nature of the resulting organosamarium intimidate, such a protecting group must not possess the potential to compete in chelation with samarium diiodide. We believed a reasonable choice of a sterically hindered protecting group in this case was a silyl ether as it could provide the needed steric hindrance for our study but wouldn't chelate with samarium. Starting with the racemic epoxide glycidol, protection of the hydroxyl group with triisopropylchlorosilane afforded the protected silyl ether **4.5** in 87% yield (Scheme 4.2). The standard mostly *trans*-sulfone **2.8** was employed in the epoxide opening of **4.5** under the same conditions as substrates **4.1** and **4.2** (Scheme 4.1).

Compounds with silyl ethers vicinal to a hydroxyl group have been reported to undergo 1,4-*O*,*O*-silyl migration.[12] While we were hopeful that the consequent adduct **4.6** would be successfully synthesized, we were cautious that potential silyl migration could occur between the hydroxyl and the TIPS-protecting group where they might rearrange and switch positions. To evaluate if such migration had occurred, we performed an acylation of **4.6**. Doing so would enable an NMR study where the chemical shift of the proton connected to the same carbon as the hydroxyl group would shift significantly if acylation occurred at this position but wouldn't change very significantly if the migration had taken place. After acylation, we were pleased to see that the chemical shift for the proton of interest in **4.6'** shifted from about 4.0 ppm to 5.0 ppm (Figure 4.1). This large shift downfield would be expected if the hydroxyl group remained at its original position, which indicated that the TIPS-protecting group had not migrated. Substrate **4.6** was synthesized in 77% yield and thereafter reduced with $SmI_2(H_2O)_n$. While there was detectable conversion of **4.6** to **4.7**, there was still some of **4.6** left unreacted. Thus, **4.6** was resubjected to the same reduction conditions. The resulting reduction product **4.7** was achieved in 98% yield with regioselectivity of at least 95:5. However, to our surprise, a reduction of diastereomeric ratio relative to products **4.3** and **4.4** was observed, as the reduction product **4.7** had a d.r. of 1.8 : 1. While this didn't follow the trend seen with the samarium reduction products **3.7** through **3.12** as well as **4.3** and **4.4**, where an increase in the size of the stereodirecting group correlated with an increase in d.r., such a reduction in d.r. could be explained by the size of the triisopropylsilyl ether. If the size of this stereodirecting group was too obstructive, it could potentially inhibit the formation of our proposed organosamarium intermediate **Sm-7**. Such an inhibition could explain why a noticeable reduction in d.r. was observed for a substrate utilizing this relatively large triisopropylsilyl ether stereodirecting group.

*Scheme 4.2. Metalated sulfone anion addition of the silyl ether protected epoxide **4.5**.*



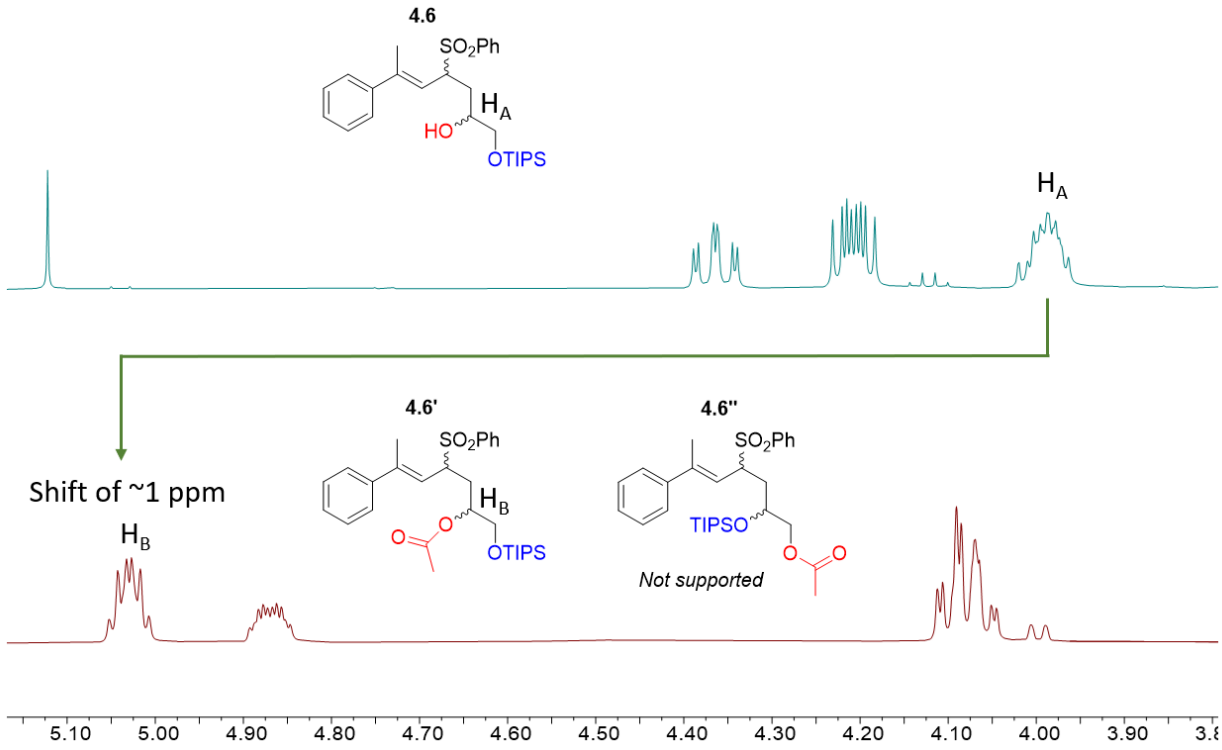


*Figure 4.1. Acylation of **4.6** supported formation of **4.6'** and that no silyl migration had occurred, as the chemical shift of proton H_A adjacent to the hydroxyl group shifted downfield by roughly 1 ppm, leaving the TIPS-protecting group in its original location.*

The epoxide-opened reduction products **4.3**, **4.4**, and **4.7** gave us insight into the feasibility of such a reactive pathway towards diastereoselective samarium-mediated reduction products. The incorporation of an additional carbon atom in the carbon skeleton between the sulfone and the chelating/stereodirecting groups in the sulfone precursors **4.1**, **4.2**, and **4.6** would add to the substrate's linker length. Consistent with results from past research in the O'Neil group (Table 1.2), this would expectedly lower the diastereomeric ratio of the reduction products relative to products that had a shorter linker length, such as our aldehyde addition substrates. For example, the acetaldehyde addition substrate (Table 3.2, entry 1) post samarium-mediated reduction featured a diastereomeric ratio of 6.7 : 1 while product **4.3** only had a diastereomeric ratio of 2.7 : 1. This reduction in diastereomeric ratio could be attributable to the linker length and demonstrated a limitation in an epoxide-opening

approached synthesis. However, because these epoxide-opened substrates when reduced with SmI_2 were still quite diastereoselective, the scope of substrates that could be accessed and subsequently reduced in this methodology were favorably expanded upon.

4.2: Deuterium Study

Because the samarium-mediated reduction featured an intramolecular protonation, we wanted to ensure we were confident that this protonation was occurring in the position consistent with the 1st generation benzoate system. Because water was employed as the proton source, a simple switch to deuterium oxide (D_2O) would enable an NMR study where we could draw comparisons of relevant peaks of interest and investigate the location that intramolecular protonation was taking place. Following our usage of epoxide openings, we repeated the samarium-mediated reduction of substrate **4.1** using identical reaction conditions but used D_2O rather than water. Once this synthesis was completed, the reduction product **4.8** was afforded in excellent yield (84%) and was analyzed via NMR (Figure 4.2).

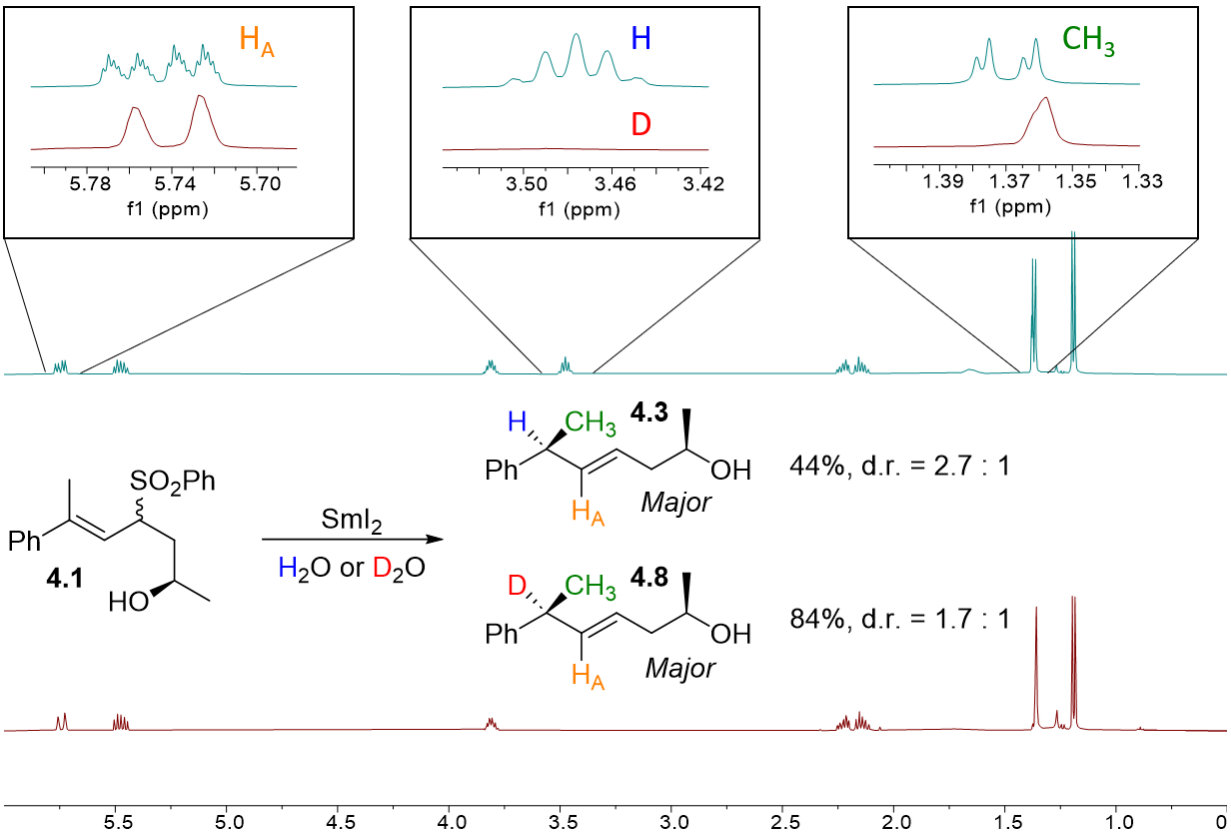


Figure 4.2. Comparison of water and D_2O as the proton donor via NMR confirmed that intramolecular protonation was occurring at the newly formed stereocenter.

The deuterated reduction product **4.8** had reduced splitting complexity compared to the protonated reduction product **4.3**. The alkene proton H_A in **4.3** was a doublet of doublet of doublet of triplets while **4.8** had a doublet of doublet of triplets in the same region. This would be expected if intramolecular protonation occurred at carbon 6 as the alkene proton H_A in **4.8** would not be split by deuterium in proton NMR. Furthermore, the peak for the proton on carbon 6 in **4.3** was not present in **4.8**, which further supported that intramolecular protonation took place at that location. The reduction of splitting complexity for **4.8** compared to **4.3** was also seen in the methyl region of the NMR spectra. While **4.3** had a clear set of doublets (one for each diastereomer), as was consistent with many of our samarium-mediated reduction products, **4.8** appeared to have two singlets that bled into one another.

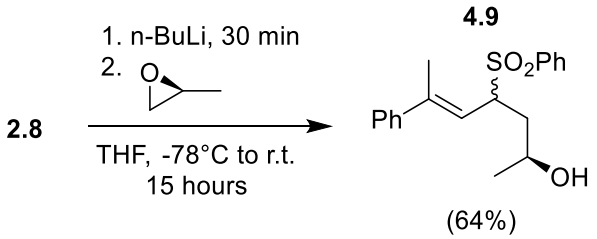
The methyl group connected to carbon 6 would be expected to manifest as a set of doublets if its protons could be split by a proton directly connected to carbon 6, but this was not observed in **4.8**. Overall, these findings supported that the intramolecular protonation/deuteration featured in the samarium-mediated reduction occurred on carbon 6 for both products **4.3** and **4.8**. Interestingly, the yield and diastereomeric ratio for both products were quite different. Product **4.8** was isolated in nearly double the yield of product **4.3** but experienced a lower diastereomeric ratio than its protonated counterpart.

4.3 Alternative Proton Donors

While the samarium-mediated reduction of trisubstituted allylic sulfones had demonstrated promising synthesis towards asymmetric carbon atoms, all these reductions were performed using water as the proton donor. While generally this would be favorable as water is a readily available and non-toxic compound, we were curious if other proton donors could be employed in water's stead to explore the versatility of the conditions in which the samarium-mediated reduction could take place, potentially opening new options in synthesis.

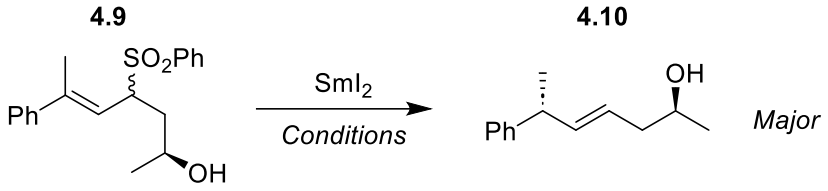
To advance this inquiry, we performed a series of samarium-mediated reductions on epoxide-opened sulfone precursor **4.9**, a trisubstituted allylic sulfone synthesized using (*S*)-propylene oxide rather than (*R*)-propylene oxide as was featured in Scheme 4.1. This allowed us to not only generate the needed substrate **4.9** for samarium-mediated reductions, but also allowed us to exercise the enantioselective synthesis capable of epoxide openings.

*Scheme 4.3. Epoxide opening of (S)-propylene oxide to make trisubstituted allylic sulfone **4.9**.*



Methanol, isopropanol, and *tert*-butanol were chosen as alternative proton donors that would be featured in the following samarium-mediated reductions. These alcohols were selected because they all possessed the needed ability to donate a proton and featured gradually increasing steric bulk, with methanol the least and *tert*-butanol the most sterically hindering. We were interested to see if steric hindrance of the proton donor could impact the resulting diastereomeric ratio the reduction product. Because steric hindrance of the proton donor could possibly impact the coordination sphere of samarium diiodide, it would be interesting to see if these potential alterations would affect the ability for samarium diiodide to facilitate intramolecular protonation in the samarium-mediated reduction system. Employing the trisubstituted allylic sulfone **4.9**, a series of samarium-mediated reductions were performed using these three alcohols as proton donors. Included in these results are products **4.3** and **4.8** as they provide a reference to compare how water and D_2O differed from the three alcohols (Table 4.1).

Table 4.1. Samarium-mediated reduction with methanol, isopropanol, and tert-butanol.



Entry	Proton Source	Equivalents	Color After Adding H Donor	Time Reacted	Color After Reaction Period	Percent Conversion[b]	d.r.[c]
1.[a]	H_2O	105	Red	30 min.	Clear/White	~100	2.7
2.[a]	D_2O	105	Red	30 min.	Clear/White	~100	1.7
3.	MeOH	105	Blue	1 h.	Blue	18.8	1.8
4.	MeOH	105	-	85 h.	Clear/White	53.7	1.8
5.	MeOH	1400	Green	15 h.	Clear/White	12.2	1.7
6.	MeOH	1400	-	65 h.	Clear/White	10.9	2.6
7.	*i*-PrOH	105	Blue	15 h.	Blue	19.4	1.7
8.	*i*-PrOH	1400	Purple	15 h.	Purple	7.6	1.5
9.	*i*-PrOH	1400	-	65 h.	Purple	20.2	1.5
10.	*t*-BuOH	105	Blue	15 h.	Blue	16.6	1.9
11.	*t*-BuOH	1400	Purple	15 h.	Purple	6.7	1.9
12.	*t*-BuOH	1400	-	40 h.	Lavender/Blue	19.5	1.8

Notes: Reactions were performed by adding the degassed proton source (105 or 1400 equiv.) to SmI_2 (7 equiv.), followed by the substrate (1 equiv.). [a]Used **4.1** in place of **4.9**. [b,c]Determined by NMR.

With methanol used as the proton donor for the samarium-mediated reduction at 105 equivalents, we already noticed some similarities and differences compared to the same reaction using water as the proton donor. Samarium diiodide solution in THF is a vibrant, electric blue. Normally, once water has been added to the samarium diiodide, the reaction mixture turns red almost instantly.

Furthermore, when the average 30-minute reaction period is complete, the reaction mixture generally becomes a clear and white solution. In the case of methanol, even after reacting for an hour, such a color change was not observed. Rather, the reaction mixture remained the familiar blue color. Half of this reaction mixture was quenched and extracted, which afforded our intended product **4.10**, but the percent conversion and diastereomeric ratio were markedly lower than seen in the water-based system. Having given the other half of the reaction mixture 85 hours to react, some noticeable differences were observed. The solution became clear and white, like that seen with water as the proton donor that had nearly 100% conversion. While the diastereomeric ratio did not change, the percent conversion was substantially higher. These results led us to believe that the color of the reaction mixture might be a visual indicator that the reaction had completed, as the color changed from its initial color after the proton donor has been added to a clear white, followed by a substantially higher percent conversion.

We were interested to see if significantly increasing the equivalents of the proton donor would have any effect on the color, percent conversion, or diastereomeric ratio. The same reaction was performed using 1400 equivalent of methanol (Table 4.1, entries 5 and 6) instead of the standard 105 the O'Neil group had found to be optimal in the water-based system. It would be intuitive that increasing the concentration of a reactant would increase the reactivity of the reaction, boosting the percent conversion and potentially the diastereomeric ratio. However, these results differed from our expectations. Once the methanol was added to the samarium diiodide solution, the color changed from blue to green. Given 15 hours to react, the solution turned a clear white color as suspected of a completed reaction that would need no further reaction period. However, once half of the reaction mixture was quenched and extracted, the resulting percent conversion and diastereomeric ratio were substantially lower than that of that of the water-based system. These results indicated that increasing the equivalents of the proton donor does not benefit the reaction, and instead, had the opposite effect. A notable exception was found in entry 6, as the diastereomeric ratio was higher while preserving the

low percent conversion. This increase in diastereomeric ratio was believed to be an outlier as further results with the other proton donors would not replicate this increase.

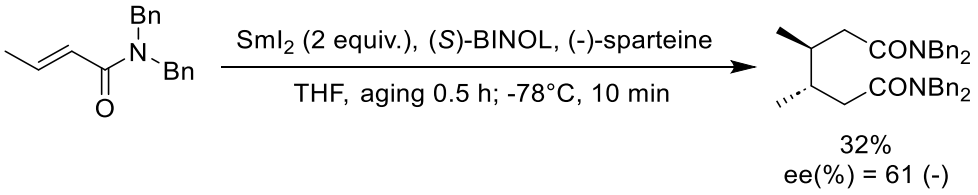
Switching the proton donor to isopropanol, a similar decrease in percent conversion and diastereomeric ratio compared to the methanol system was observed. Despite this, at 105 equivalents of the proton donor and a reaction period of 15 hours, no color change was observed, and the percent conversion remained fairly low. However, the diastereomeric ratio was similar to the methanol system. At 1400 equivalents, the reaction mixture turned purple, rather than the red or green observed prior, and remained purple over its reaction period of 15 hours (Table 4.1, entry 8). This resulted in a very low percent conversion of 7.6% and a diastereomeric radio smaller than that of the methanol system. Given 65 hours, the other half of this reaction mixture remained purple and would feature an increased percent conversion, but no change in diastereomeric ratio.

Using *tert*-butanol as the proton donor, very similar results to the isopropanol system were observed. However, the diastereomeric ratio was higher than the isopropanol system and roughly on par with the methanol system. While we initially had thought that the steric hindrance of the proton donor might play a major role in the diastereoselectivity of the reaction, this did not appear to be the case. Using these three alcohols, regardless of steric hindrance, overall produced less favorable percent conversions and diastereomeric ratios than the water system. Thus, it became apparent that water was uniquely favorable in the samarium-mediated reduction. With a diastereomeric ratio of 2.7 : 1 (Table 4.1, entry 1), the water-based system notably surpassed the other proton donors for percent conversion and diastereomeric ratio. As a result, we decided to investigate other ways to influence samarium diiodide to see if such modifications would lead to improvements of the samarium-mediated reduction.

4.4: Chiral Ligands

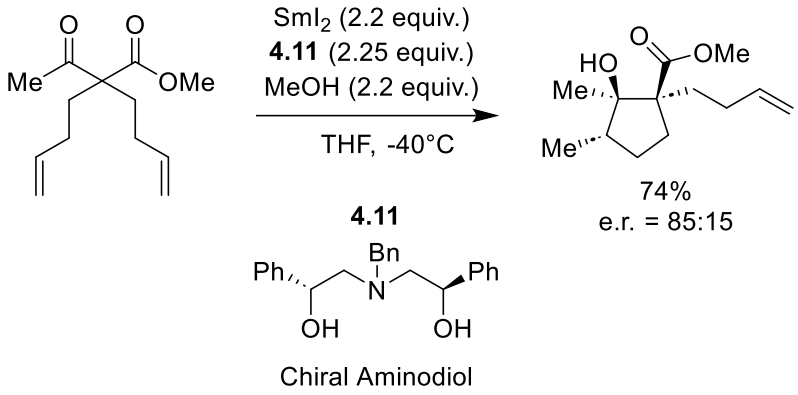
Samarium diiodide is a versatile reagent due to its tunability through additives and their impact on its reduction potential, reaction rate, and chemoselectivity.[13-16] If diastereoselective intramolecular protonation occurs due to a proton source in samarium diiodide's coordination sphere, it would be interesting to see how asymmetric ligands might impact the diastereoselectivity of the reaction. Fortunately, there have been other studies that have investigated the impacts of chiral ligands on samarium diiodide when it is used as a reactant. We looked to the work of Kikukawa et al., who had reported that (*S*)-BINOL, in enantiopure form, when used with (-)-sparteine could facilitate samarium diiodide-promoted reductive homo-coupling of β-substituted acrylic acid amides with high enantiomeric excess, resulting in a diastereoselective and enantioselective formation of carbon-carbon bonds.[17]

Scheme 4.4. Kikukawa et al. demonstrated that samarium diiodide-promoted reductive homo-coupling of β-substituted acrylic acid amides could be synthesized in enantiomeric excess. Adapted from reference.[17]



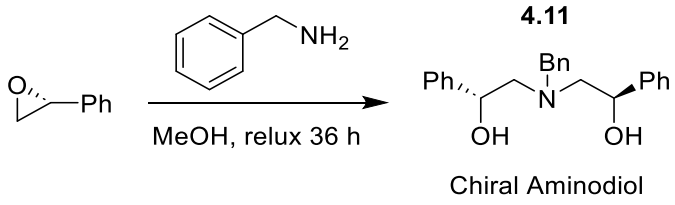
Additionally, Kern et al. had employed the chiral aminodiol **4.11** to facilitate samarium diiodide-mediated radical cyclizations of keto-esters with high enantioselectivity and diastereoselectivity.[18] While not identical reactions to the samarium-mediated reduction in our study, we were curious if usage of enantiopure BINOL or the same chiral aminodiol **4.11** reported by Kern et al. could ligate to samarium diiodide and influence the diastereoselectivity of the samarium-mediated reduction we had been exploring.

*Scheme 4.5. Kern et al. demonstrated that chiral aminodiol **4.11** facilitated samarium diiodide-mediated radical cyclizations of keto-esters. Adapted from reference.*[18]



While we had (*S*)-BINOL on hand, we needed to synthesize the chiral aminodiol reported by Kern et al. Following their work, we employed the same reported reactive methodology to obtain this chiral aminodiol and performed two epoxide openings of (*R*)-styrene oxide using benzylamine (Scheme 4.6).

*Scheme 4.6. Synthesis of chiral aminodiol **4.11**. Adapted from reference.*[18]

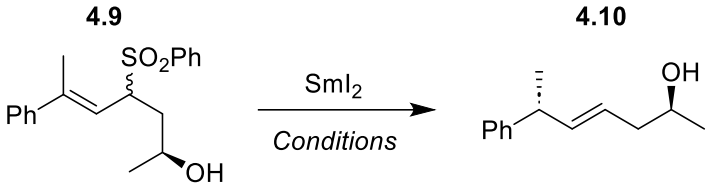


Once both chiral ligands were available, a series of samarium-mediated reductions were performed utilizing these compounds. Kern et al. reported the use of achiral protic additives for their cyclizations and had achieved excellent yields and enantioselectivity by employing methanol as an additive.[18] We wanted to see if such an additive would be necessary in our system, so we ran a control reaction not using the methanol additive (Table 4.2, entry 1). Given 15 hours, the reduction product **4.10** was obtained, but with a low percent conversion of 22%. While the diastereomeric ratio initially looked

promising via deconvolution in MestReNova, we believed that the resulting diastereotopic methyl region of interest was too messy to reliably extrapolate the diastereomeric ratio accurately (Figure 4.3). This was echoed in the subsequent reaction that employed identical conditions, but included the methanol additive (Table 4.2, entry 2). The same diastereomeric ratio of 3.0 : 1 was observed but was similarly met with messy diastereotopic methyl peaks that likely interfered with our ability to accurately determine the diastereomeric ratio using deconvolution. Both of these reactions suffered from low percent conversion as well, limiting the desirability of such a reactive methodology. To see if the reaction period was too small for the chiral ligands to be effective in the samarium-mediated reduction, we tried the reduction again using a 40-hour reaction period. While this led to a near identical low percent conversion, the diastereotopic methyl peak used in our deconvolution procedure was noticeably more resolved. The diastereomeric ratio was determined to be 2.3 : 1, and we were more confident in the reliability of this result. However, because the use of chiral aminodiol **4.11** did not afford a percent conversion anywhere near as good as the water-based system and had a slightly lower diastereomeric ratio as well, we believed that the chiral aminodiol would not lead anywhere promising in our system.

Resultantly, we tried a final samarium-mediated reduction using (*S*)-BINOL. To be confident that the reaction ran to completion, we employed a 65-hour reaction period. Over this period, no color deviation from the usual electric blue of samarium diiodide/THF solution was observed. However, we believed that given more time, the reaction would be unlikely to proceed any further. After this reaction period, the reduction product **4.10** was afforded in an even lower percent conversion of 13.8% than the previous reactions that employed the chiral aminodiol **4.11**, albeit the diastereomeric ratio was strikingly similar. Due to these results, we believed that the potential for these chiral ligands to enhance the diastereoselectivity of the samarium-mediated reduction would not be observed after further experimentation.

Table 4.2. Usage of (S)-BINOL and a chiral aminodiol as chiral ligands for the samarium-mediated reduction.



Entry	Ligand	Additive	Time Reacted	Percent Conversion	d.r.[a]
1.	**4.11**	-	15 hours	22.0	3.0 : 1[b]
2.	**4.11**	MeOH	15 hours	22.1	3.0 : 1[b]
3.	**4.11**	MeOH	40 hours	22.6	2.3 : 1
4.	(*S*)-BINOL	-	65 hours	13.8	2.2 : 1

Notes: Reactions were performed by adding SmI_2 (7 equiv.) to the chiral ligand (7.2 equiv.), followed by the additive (7 equiv.) and then the substrate. [a]Determined by NMR. [b]Tentative result likely not accurate.

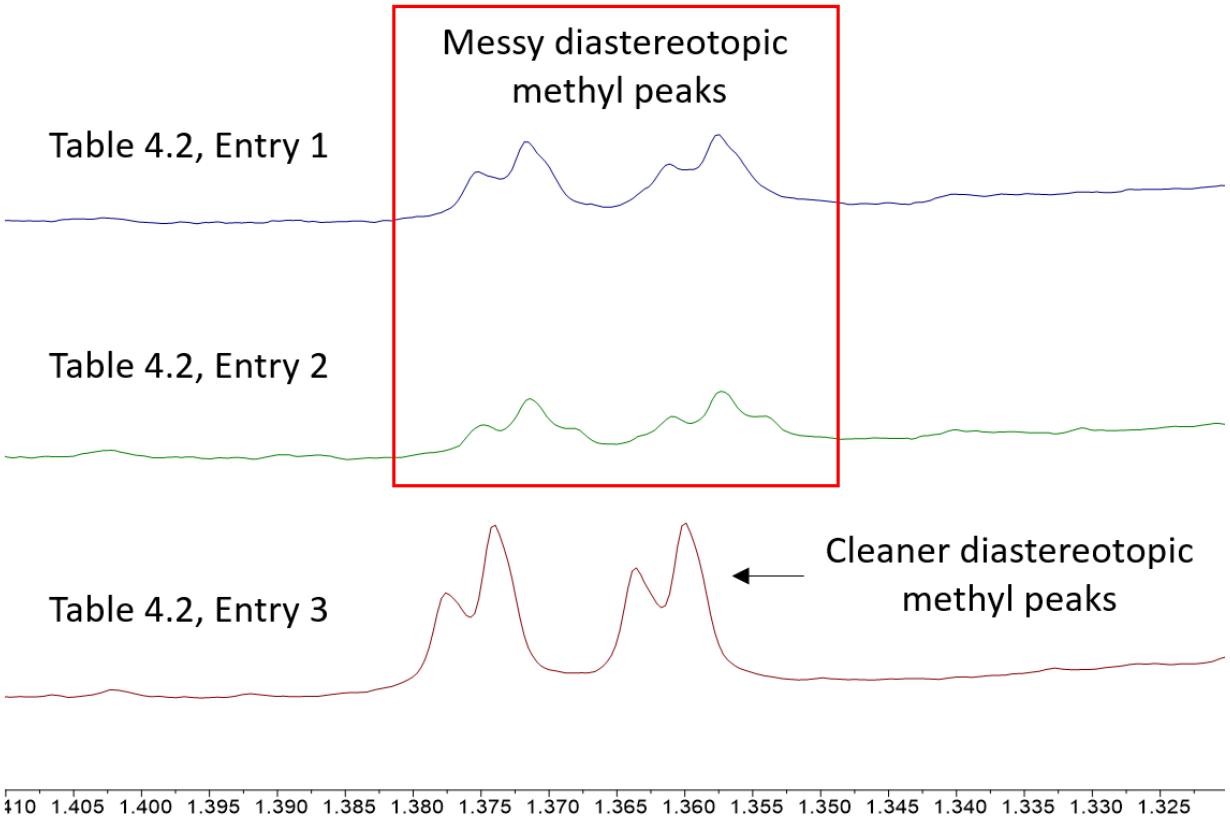


Figure 4.3. Comparison of diastereotopic methyl peaks of entries 1-3 in Table 4.2.

4.5: Comparison of Sulfone and Benzoate Samarium-Mediated Reduction Products

While the 2nd generation sulfone substrates had shown promise and demonstrated reasonable diastereoselectivity for the samarium-mediated reduction when derived from epoxide-opening methodology, we wanted to ensure that these reactions were confidently affording the same desired products as the 1st generation benzoate substrates. Additionally, we needed to confirm the absolute stereochemistry of such products. To evaluate the identities of the products originating from these 1st generation and 2nd generation substates, we employed the same approach as the study we had performed in Figure 3.2 by referencing an existing reduction product the O'Neil group had confirmed the absolute stereochemistry of. Comparing the NMR spectra of the products of the samarium-mediated reduction of substrates **4.1** and **4.12**, it was apparent that both reactions converged to the

same product **4.3** and favored the same major diastereomer. This supported that the 2nd generation sulfonyl substrates and the 1st generation benzoyl substrates both led to samarium-mediated reduction products that had the same absolute stereochemistry.

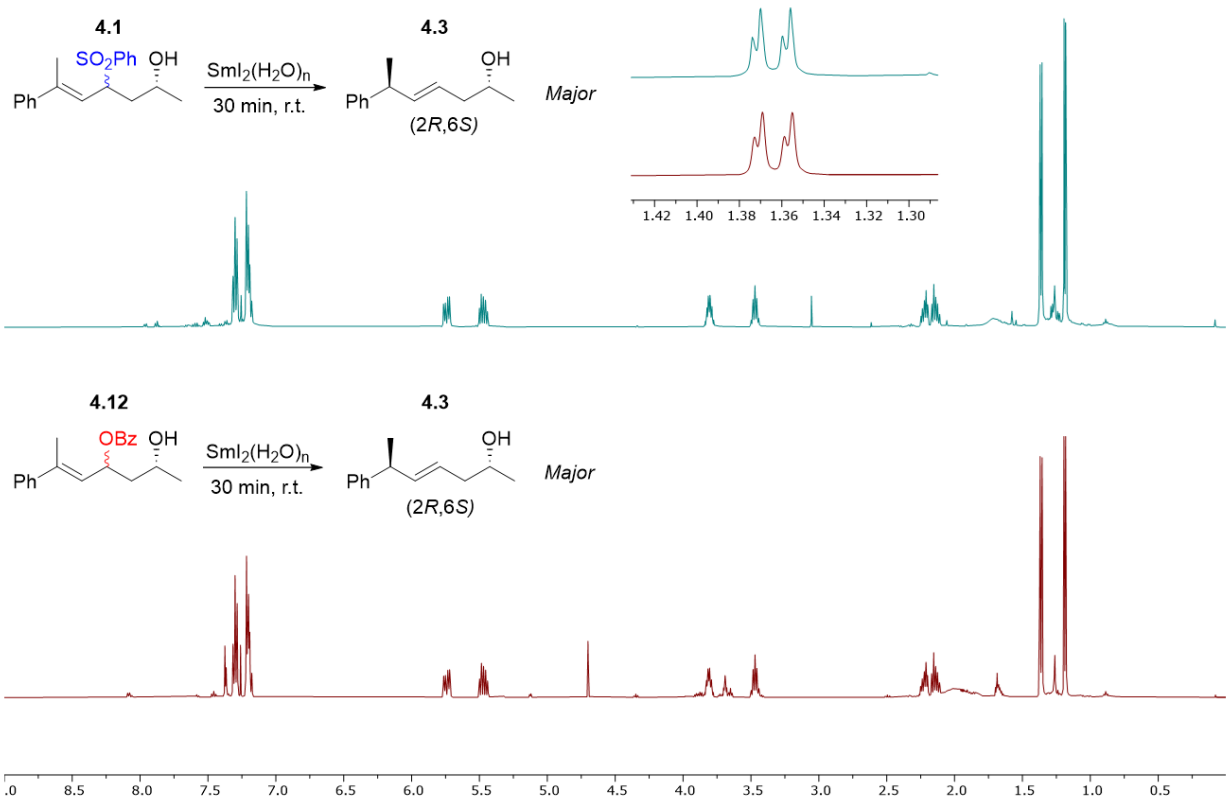


Figure 4.4. Comparison of 1st generation (benzoate) and 2nd generation (sulfone) samarium-mediated reduction products via NMR spectroscopy revealed convergence to the same major diastereomer, and thus had matching absolute stereochemistry.

Chapter 5: Attempted Regioselective Synthesis of Thailandamide Fragment

5.1: Thailandamide A

While the samarium-mediated reduction had the capacity to be quite diastereoselective given short substrate linker lengths (x = 0, y = 0 or 1, see Table 1.2) and sterically hindering stereodirecting groups, another important characteristic of the reaction is that it is very regioselective.[7] Therefore, this

reaction could be useful in the development of natural products that necessitate regioselective synthesis of asymmetric carbon atoms. We looked for natural products that featured asymmetric carbon atoms across an alkene that may be able to be accessed within the required parameters of the samarium-mediated reduction, which could further explore the reaction's usefulness in organic synthesis.

One such substrate that we believed could be a potential candidate for this chemistry was thailandamide A (referred to as thailandamide for the rest of this study). This natural product is a linear polyene, produced as one of the secondary metabolites of the bacillus *Burkholderia thailandensis.* It has been observed to possess activity that is both powerful and selective against Gram-positive and cell wall-weakened Gram-negative bacteria.[19] Synthesis towards this natural product could demonstrate the potential of the samarium-mediated reduction, highlighting the usefulness of the marked regioselectivity of the reaction demonstrated both in past studies by the O'Neil group and this study as well.

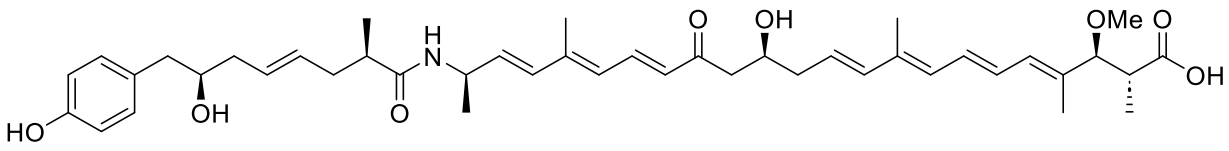


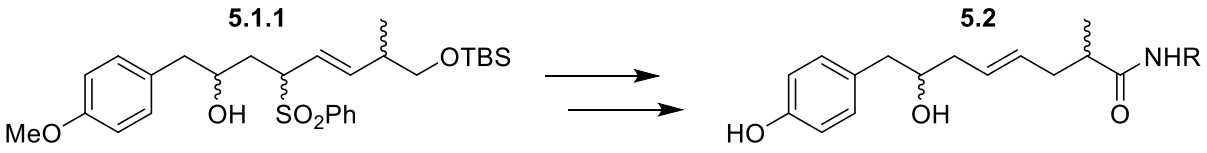
Figure 5.1. Structure of thailandamide A.

5.2. Synthesis Towards Thailandamide Fragment

Thailandamide possesses multiple alkenes, but the single alkene on the left side of its structure as drawn in Figure 5.1 was of particular interest as the samarium-mediated reduction could theoretically be capable of establishing this functional group regioselectively. While the stereochemistry of the final product would be important if trying to synthesize thailandamide A exactly, we were more interested in a proof of concept of regioselective synthesis via the samarium-mediated reduction. Thus, we aimed to

synthesize some analogue of the fragment of thailandamide **5.2** using the allylic sulfone **5.1.1**. If an analogue of **5.1.1** could be successfully synthesized and the samarium-mediated reduction regioselectively establish **5.2**'s desired alkene, only a few subsequent reactive steps could bring us towards our desired thailandamide fragment.

*Scheme 5.1. Thailandamide fragment of interest **5.2** could be synthesized from some analogue of target fragment **5.1.1**.*

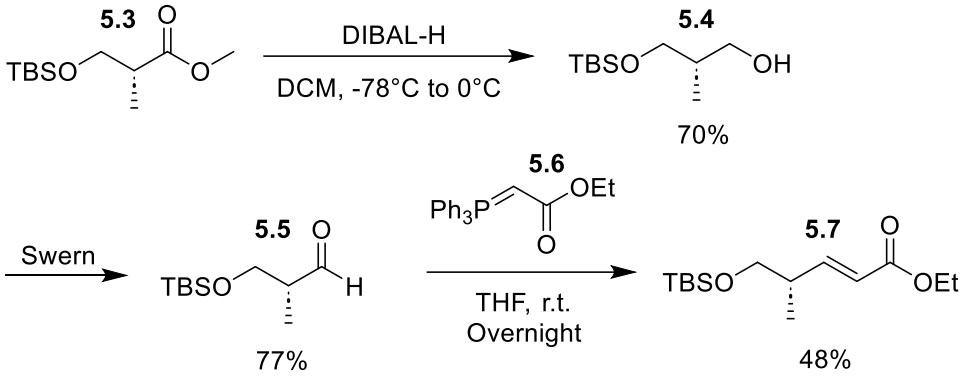


Synthesis towards fragment **5.1.1** provided a strong opportunity to bring multiple elements of the chemistry described in earlier chapters of this study. Akin to our sulfone synthesis efforts in chapter 2, to endow the fragment with the needed sulfonyl group to facilitate single electron transfer, an ester could be reduced with DIBAL-H to an alcohol and subsequently brominated. Given a good leaving group, a sulfonyl substitution with benzenesulfinic acid sodium salt could then form an allylic sulfone. Similar to what we had done in chapter 4, this sulfone could then engage in a metalated sulfone anion addition with an enantiopure chiral epoxide of choice.

To begin our synthesis, we started with the TBS-protected chiral ester **5.3** that we had readily available in lab. This ester was successfully reduced with DIBAL-H, which afforded alcohol **5.4** in 70% yield. This crude alcohol was then taken into a Swern oxidation, providing aldehyde **5.5** in 77% yield. We then employed a Wittig reaction using the Wittig reagent **5.6**, which afforded the allylic ester **5.7** in 48% yield. The noticeable drop in yield was likely due to difficulty extracting **5.7** from the phosphonium salts generated as a byproduct of the Wittig reaction. While both the resultant phosphonium salts and **5.7** were soluble in DCM, only **5.7** was soluble in MTBE. It was likely that even multiple generous rinses of the crude reaction mixture with MTBE must still not have extracted all of **5.7**, which would have led to a

loss in total product prior to purification via column chromatography. Regardless, with a still reasonable amount of **5.7**, our next objective was to convert the allylic ester into an allylic sulfone.

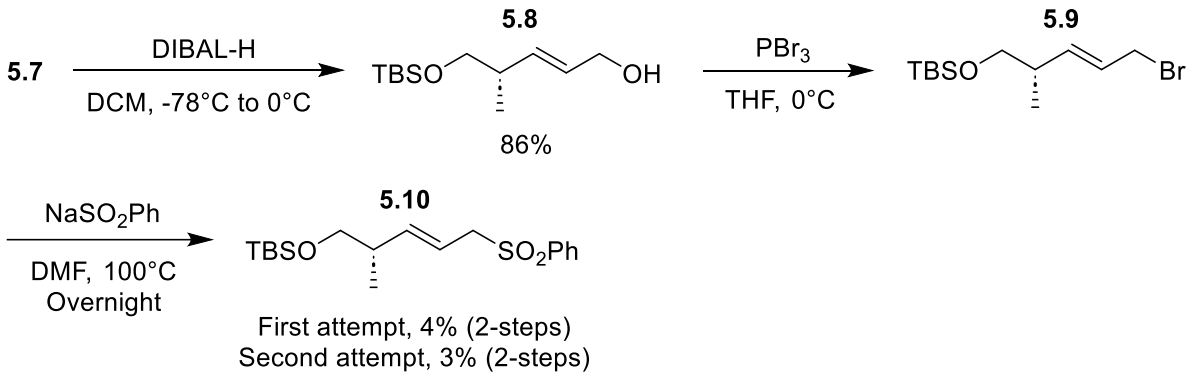
*Scheme 5.2. Synthesis towards ester **5.7** via TBS-protected ester **5.3**.*



A DIBAL-H reduction of **5.7** was employed to access the desired alcohol **5.8**, which was afforded in 86% yield (Scheme 5.3). The resulting alcohol was then brominated with phosphorous tribromide, and the crude product **5.9** was then subjected to a sulfonyl substitution via benzenesulfinic acid sodium salt, which subsequently afforded the allylic sulfone **5.10** in 4% yield over two steps. This low yield was surprising considering the success we experienced with this reactive methodology in chapter 2. As a result, we ran this reaction sequence again, starting with the TBS protected ester **5.3** up to the desired allylic sulfone **5.10**. Unfortunately, a repeat of this synthesis did not afford an improvement in yield and instead **5.10** was obtained in 3% yield. Because these yields were obtained over a two-step synthesis (**5.9** was not purified via column chromatography due to concerns of decomposition on silica), we considered where problems could arise through either the bromination or the sulfonyl substitution. Ultimately, we thought it would be likely that the bromination step was the culprit. Comparing the starting alcohols **5.8** and **2.6**, **5.8** notably had a TBS protecting group while **2.6** did not. It could be possible that the TBS protecting group may have interfered in the bromination step and was targeted by phosphorous tribromide. This could explain the very low yields of both iterations of **5.10**'s synthesis. Even though we only had two portions of **5.10**, one at 11.4 mg and the other at 6.5 mg, we still believed

that a metalated sulfone anion addition to a chiral epoxide would be possible. As a result, we began synthesis of a chiral epoxide that could be opened with **5.10** to achieve our desired thailandamide fragment.

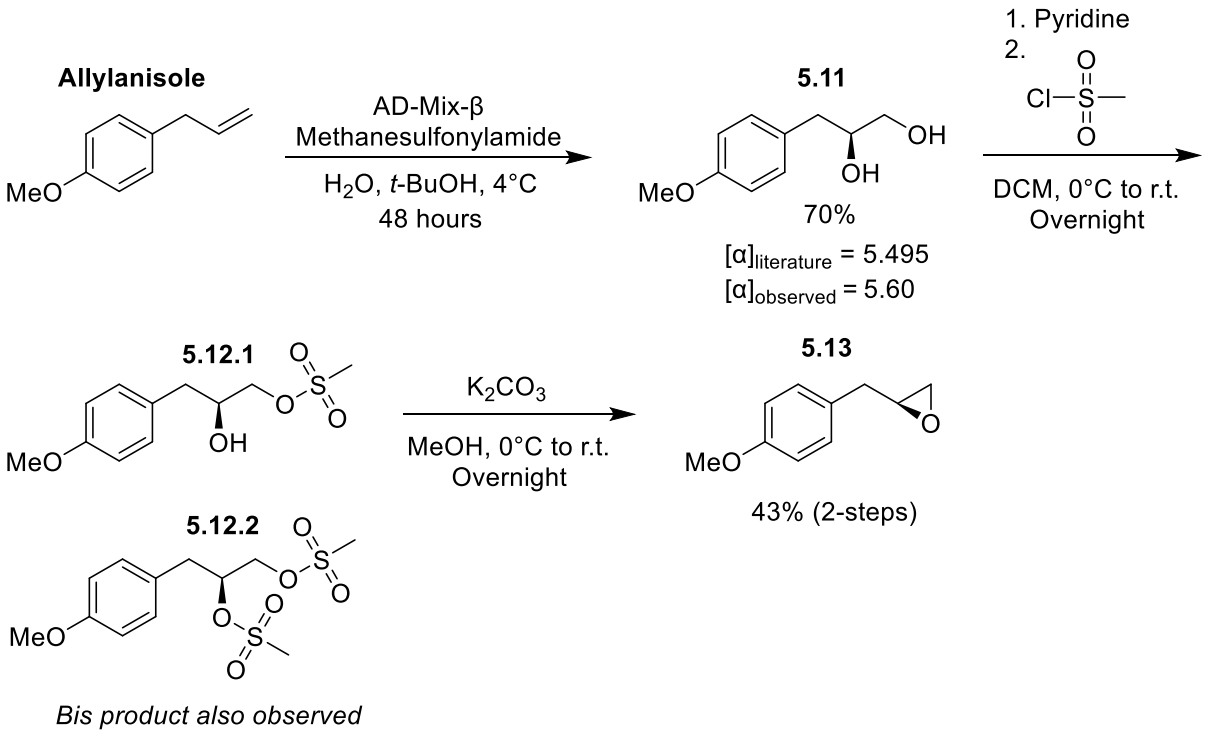
*Scheme 5.3. Synthesis of allylic sulfone **5.10** starting with allylic ester **5.7**.*



In an effort to access our desired chiral epoxide, we employed a Sharpless asymmetric dihydroxylation of allylanisole with AD-Mix-β. This dihydroxylation successfully afforded the chiral diol **5.11** in 70% yield and had an optical rotation that was consistent with literature.[20] This diol was then subjected to methanesulfonyl chloride in pyridine, which afforded the mesylated product **5.12.1**. While it was expected that the primary alcohol of **5.11** would be mostly mesylated, a significant amount of the bis product **5.12.2** was also observed. This was concerning because if both alcohols were significantly mesylated, it could be possible that the subsequent formation of epoxide **5.12.2** would lose preservation of the stereocenter we aimed to achieve with the Sharpless asymmetric dihydroxylation and instead produce the epoxide as a mixture of both enantiomers. To determine if this would be the case, the mixture of **5.12.1** and **5.12.2** was converted to an epoxide using potassium carbonate in methanol. Fortunately, NMR analysis revealed that both the desired chiral epoxide **5.13** and the bis product **5.12.2** were both present in the crude reaction mixture, which indicated that the intended product **5.12.1** was only targeted in the reaction (see Figure 5.2). As a result, the desired chiral epoxide

5.13 was separated from the lingering unreacted bis product and successfully retrieved in 43% yield over two steps.

*Scheme 5.4. Synthetic route to chiral epoxide **5.13** starting with allylanisole.*



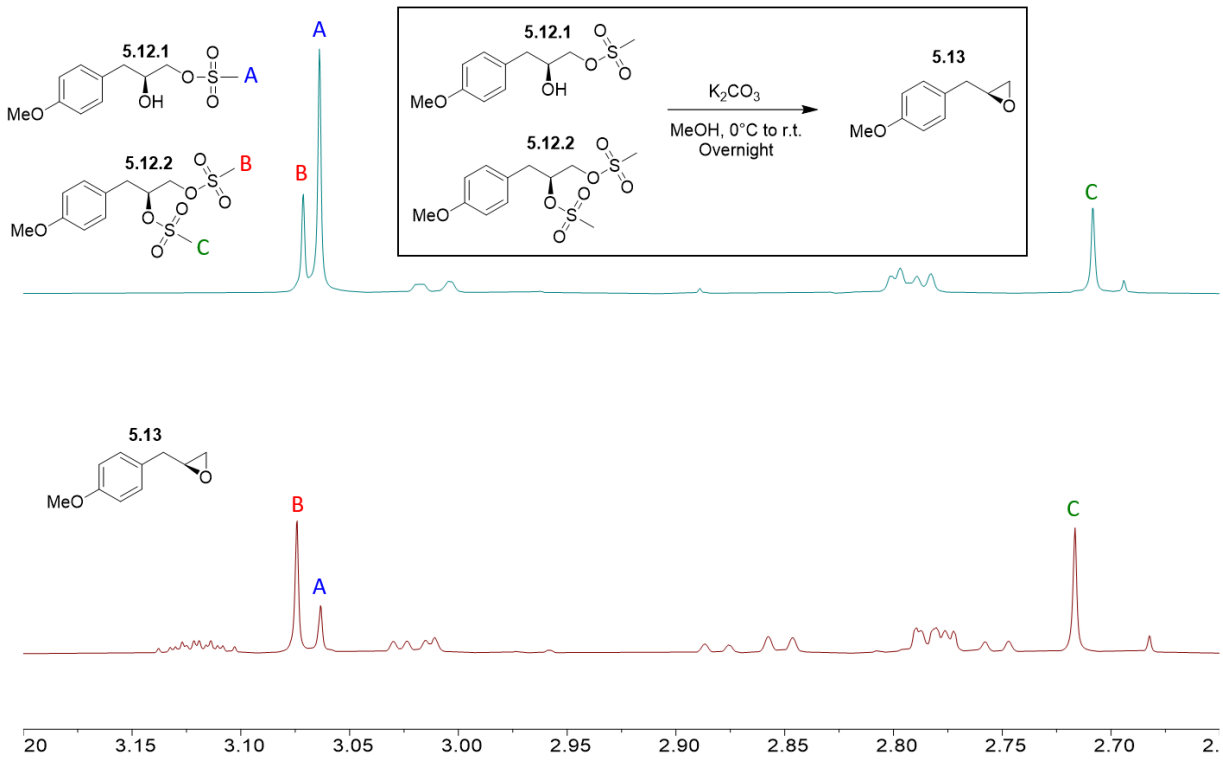


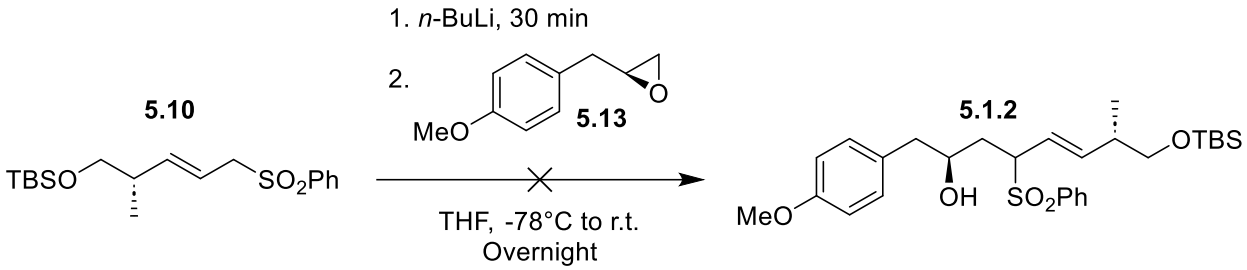
*Figure 5.2. While the bis product **5.12.2** was present alongside **5.12.1** after mesylation, **5.12.2** persisted while **5.12.1** was consumed, which indicated that **5.12.2** was not prone to form an epoxide in this reaction and would not affect the enantioselectivity of the desired chiral epoxide **5.13**.*

With both the allylic sulfone **5.10** and the chiral epoxide **5.13**, we were ready to try the epoxide opening via metalated sulfone anion addition. Using the 11.4 mg portion of **5.10** we had synthesized; we were disappointed to see that the target thailandamide fragment **5.1.2** was not formed (Scheme 5.5). Rather, it appeared that the sulfone had departed from the resultant product. Using the last portion of **5.10** (6.5 mg), the synthesis was attempted again but to no avail. In this case, starting material **5.10** was detected in the NMR spectrum, which indicated that the reaction had mostly left the starting material untouched. Ultimately **5.1.2** was not synthesized in either experiment. While these results were unfortunate, it's difficult to say if the chemistry in these experiments would or would not have worked given different conditions. Having used such small amounts of the starting sulfone **5.10**, a limitation due to the very low yields we observed in our synthesis, minor increases or decreases in the equivalents of

n-butyllithium relative to **5.10** could potentially have caused undesired results. If too many equivalents of *n*-butyllithium were used, possible elimination reactions or disturbance of the TBS protecting group could have occurred. If too few equivalents of *n*-butyllithium were used, the starting material may not have been deprotonated enough to engage in metalated sulfonyl anion addition and open chiral epoxide **5.13**. As such, at such small scale, minor discrepancies in the volume of *n*-butyllithium delivered could have had consequences, and it was very possible that the difficulty of delivering an accurate volume of this base might have been the culprit behind the inability to synthesize **5.1.2**. In the attempt with 11.4 mg of **5.10**, the loss of the sulfone could be due to an excess of *n*-butyllithium being delivered, expelling the sulfone via elimination. On the other hand, when using 6.5 mg of **5.10**, the abundance of leftover starting material likely indicated that not enough *n*-butyllithium was present to cause deprotonation and therefore subsequent attack of epoxide **5.13**. Because our results from chapter 4 would indicate that such epoxide openings would be possible with allylic sulfones, it would be logical to assume that these results may have just been a product of experimental error in lab.

In the future, alteration of the synthesis described in Scheme 5.3 could lead to more definitive results. If **5.10** could be synthesized while bypassing the heavy loss in yield during the bromination and sulfonyl substitution steps, a larger amount of **5.10** could be reacted in the same methodology. If **5.1.2** were successfully synthesized as a result of this, then it would be very likely that experimental error was indeed the reason for the failure of this reaction sequence. However, there was still the possibility that our approach in synthesis from **5.10** to **5.1.2** simply does not work as this reaction failed twice. Ultimately, alternative synthesis towards **5.10** and potentially **5.1.2** will be required in future work to develop more concrete results and hopefully achieve the desired thailandamide fragment.

*Scheme 5.5. Attempted metalated sulfone anion addition of sulfone **5.10** and chiral epoxide **5.13** towards target thailandamide fragment **5.1.2**.*



Conclusions

In summary, the samarium-mediated reduction of 2nd generation allylic sulfones showed promise as a simpler reactive methodology to achieve diastereoselective asymmetric carbon atoms compared to 1st generation allylic benzoate substrates. Synthesis of 2nd generation allylic sulfones required fewer reactive steps than 1st generation benzoates, and both aldehydes and epoxides could be targeted by metalated sulfonyl anion addition to endow the resulting substrates with chelating and stereodirecting groups simultaneously. Both aldehyde addition and epoxide-opened products were readily reduced with $SmI_2(H_2O)_n$, which proved to be both diastereoselective and achieved a regioselectivity of at least 95:5. Of particular note, aldehyde addition products that were reduced with $SmI_2(H_2O)_n$ demonstrated an increase in diastereomeric ratio depending on the steric bulk of the stereodirecting group. Comparison of these reduction products when derived from 1st or 2nd generation substrates indicated that both reactive methodologies led to the same product, favoring the same major diastereomer and thus relative stereochemistry. In agreement with the 1st generation system, samarium-mediated reduction of 2nd generation substrates also featured a loss of stereospecificity when a geminal phenyl group was present, which was likely due to C-C bond rotation in the organosamarium intermediate. Also consistent with past work, this stereospecificity was preserved when the allylic sulfone featured non-phenyl geminal substituents. Usage of water as a proton donor was observed to be uniquely effective in this samarium-mediated reduction, greatly surpassing simple alcohol proton donors in both diastereoselectivity and percent conversion. Furthermore, incorporation of chiral ligands in the reduction did not lead to promising increases in diastereoselectivity. Synthesis towards an analogue of the natural product thailandamide A was not successful, likely due to experimental error that arose from loss of material from limitations when brominating a TBS-protected allylic sulfone. Given the success with epoxide openings in this study, we had reason to believe that regioselective synthesis via

samarium-mediated reduction would still be possible. Future work could seek to remedy this shortcoming by design of an alternative synthesis towards thailandamide A that could bypass the low yields following the bromination and sulfonyl substitution utilized in our synthesis towards 2nd generation allylic sulfones.

Supporting Information

Experimental

General: All reactions were carried out under N_2 in flame-dried glassware unless specified otherwise. The solvents used were dried by passing the solvent through a column of activated alumina under nitrogen immediately prior to use. All reagents were purchased and used as received unless otherwise mentioned. All TLC analysis used 0.25 mm silica layer fluorescence UV254 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 diastereomeric ratios were calculated using MestReNova 14.2.1 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). Analysis by gas chromatography with flame ionization detection (GC-FID). Samples were analyzed on an Agilent 7890 GC-FID. Samples (1 µl) were injected cool-on-column and separated on a 100% dimethyl polysiloxane capillary column (Agilent HP-5, 30 m length, 0.32 mm I.D., 0.25 µm film thickness) with He as the carrier gas at a flow rate and oven temperature according to Table 3.3 followed by GC-FID analysis.

General Experimental Procedures

Procedure A: Horner-Wadsworth-Emmons Olefination

LiHMDS (1.1 equiv. relative to substrate) was added to a dry Schlenk flask, followed by the addition of THF (0.5 M relative to LiHMDS) and the resulting mixture cooled to 0°C. Trimethylphosphonoacetate (1.2 equiv. relative to substrate) was then slowly added. The reaction mixture was allowed to warm to

room temperature and stir over a 30-minute period, then cooled to -78°C. The acetaldehyde substrate (1.0 equiv.) was then added dropwise, and the reaction mixture let stir while warming to room temperature overnight. The reaction mixture was then quenched with aq. NH_4Cl and extracted with MTBE (3x). The combined organic extracts were dried with $MgSO_4$, and subsequently concentrated *in vacuo*.

Procedure B: DIBAL-H reduction

A dry Schlenk flask containing ester (1.0 equiv.) in DCM (0.2 M) was cooled to -78°C. DIBAL-H (2.2 equiv.) was added slowly and let stir for 1 hour while warming to 0°C. The reaction mixture was diluted with ethyl acetate, washed with a 1.0 M solution of HCl, then extracted with ethyl acetate (3x). The combined organic extracts were then washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*.

Procedure C: Bromination

To a dry Schlenk flask charged with THF (1.4 M), alcohol (1.0 equiv.) was added, and the resulting reaction mixture cooled to 0°C. PBr_3 (0.4 equiv.) was added dropwise, and the reaction mixture was stirred for 1 hour. The reaction mixture was then quenched with ice water and extracted with hexanes (3x). The combined organic extracts were then dried with $MgSO_4$ and concentrated *in vacuo*.

Procedure D: Sulfone substitution

To a dry Schlenk flask containing the bromide substrate (1.0 equiv.), DMF (1.0 M) was added, followed by the addition of $NaSO_2Ph$ (1.5 equiv.). The reaction mixture was then stirred at 100°C overnight. After this period, the reaction mixture was diluted with ethyl acetate, washed with H_2O, and extracted with ethyl acetate (3x). The combined organic extracts were then dried with $MgSO_4$ and concentrated *in vacuo*.

Procedure E: Metalated sulfone addition of aldehydes

To a dry Schlenk flask containing sulfone substrate (1.0 equiv.), THF (0.2 M) was added, and the reaction mixture was cooled to -78°C. Once the reaction mixture was cooled, *n*-BuLi (1.2 equiv.) was added, and the reaction mixture was stirred for 45 minutes. After this period, the aldehyde (2.0 equiv.) was added, and the reaction mixture was stirred while warming to room temperature overnight. The reaction mixture was quenched with aq. NH_4Cl, extracted with MTBE (3x). The combined organic extracts were then dried with $MgSO_4$ and concentrated *in vacuo*.

Procedure F: Metallated sulfone addition of epoxides

To a dry Schlenk flask containing sulfone substrate (1.0 equiv.), THF (0.2 M) was added, and the reaction mixture was cooled to -78°C. Once the reaction mixture was cooled, *n*-BuLi (1.2 equiv.) was added and the reaction mixture was stirred for 30 minutes. After this period, the epoxide (1.2 equiv.) was added and the reaction mixture was stirred while warming to room temperature overnight. The reaction mixture was quenched with aq. NH_4Cl and extracted with MTBE (3x). The combined organic extracts were then dried with $MgSO_4$ and concentrated *in vacuo*.

Procedure G: Samarium-mediated reduction with H_2O

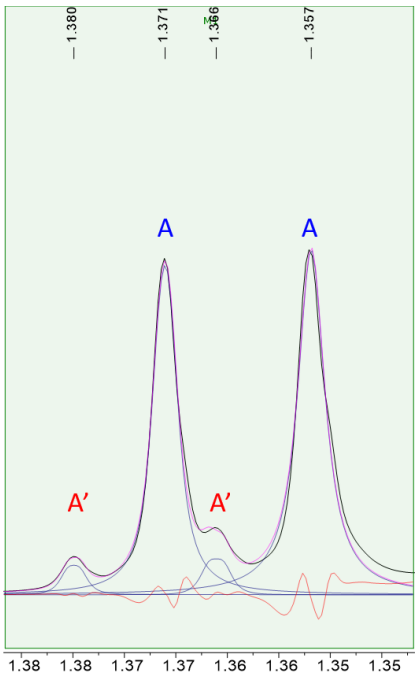
To a dry Schlenk flask, SmI_2 in THF (0.1 M, 7 equiv.) was added degassed distilled H_2O (105 equiv.) turning the solution a deep red color. The metalated sulfone addition product (1.0 equiv.) was then added, and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was then quenched with aq. $NaHCO_3$ and extracted with ethyl acetate (3x). The combined organic extracts were then passed through a silica plug and concentrated *in vacuo*.

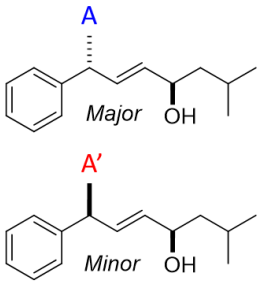
Procedure H: Samarium-mediated reduction with Alcohols (MeOH, i-PrOH, t-BuOH)

To a dry Schlenk flask, SmI_2 in THF (0.1 M, 7 equiv.) was added degassed alcohol (105 equiv. or 1400 equiv.). The metallated sulfone addition product was then added, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then quenched with aq. $NaHCO_3$ and extracted with ethyl acetate (3x). The combined organic extracts were then passed through a silica plug and concentrated *in vacuo*.

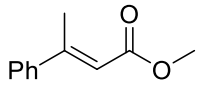
Deconvolution Procedure Via MestReNova

To determine the diastereomeric ratio of the samarium reduction products, deconvolution in MestReNova was employed. To do so, diastereotopic methyl peaks of interest were selected using the "Line Fitting" tool. Once selected, they were then "Fit" using the same tool. Peaks that did not belong to the two doublets of interest were removed from the selection table. That data was then transferred to Excel where the integrations belonging to each peak could be summated to their respective doublet and then compared to determine the diastereomeric ratio. Example seen below.





	Name: M1								
	From: 1.347 ppm								
	To: 1.389 ppm								
	Residual Error:1.31e+05								
	#	ppm	Height	Width(Hz)	L/G	Area			Integration
D1	1	1.3799	745.7	1.36	1.63	8170.356		D1	18854.495
D2	2	1.371	8332.73	1.43	0.58	113438.8		D2	254513.248
D1	3	1.3661	905.78	1.57	2	10684.14			
D2	4	1.3568	8726.91	1.59	0.09	141074.5		d.r.	13.5

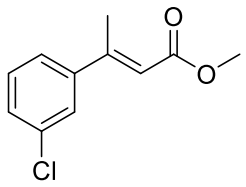


methyl (*E*)-3-phenylbut-2-enoate (**2.5**)

Prepared according to general procedure **A** using acetophenone (2.65 mL, 22.7 mmol). Purification by flash column chromatography on silica gave the oil **2.5.1** (2.88 g, 72%) as a mixture of *cis*- and *trans*-stereoisomers.

Spectral data for trans-stereoisomer in agreement with literature.[21]

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.50 – 7.45 (m, 2H), 7.40 – 7.35 (m, 3H), 6.14 (q, *J* = 1.4 Hz, 1H), 3.76 (s, 3H), 2.59 (d, *J* = 1.4 Hz, 3H).



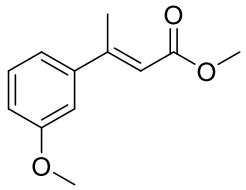
methyl (*E*)-3-(3-chlorophenyl)but-2-enoate (**2.5.2**)

Prepared according to general procedure **A** using 3'-chloroacetophenone (0.267 mL, 2.06 mmol). Purification by flash column chromatography on silica gave the oil **2.5.2** (0.356 g, 82%) as a mixture of *cis*- and *trans*-stereoisomers.

Spectral data for *trans*-stereoisomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.44 (t, *J* = 1.9 Hz, 1H), 7.36 – 7.30 (m, 3H), 6.12 (q, *J* = 1.3 Hz, 1H), 3.76 (s, 3H), 2.55 (d, *J* = 1.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 166.92, 154.21, 143.97, 134.53, 129.76, 128.96, 126.52, 124.45, 117.69, 51.23, 17.89.



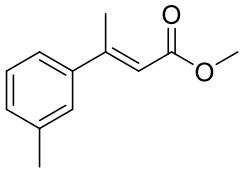
methyl (*E*)-3-(3-methoxyphenyl)but-2-enoate (**2.5.3**)

Prepared according to general procedure **A** using 3'-methoxyacetopheone (0.283 mL, 2.06 mmol). Purification by flash column chromatography on silica gave the oil **2.5.3** (0.261 g, 62%) as a mixture of *cis*- and *trans*-stereoisomers.

Spectral data for *trans*-stereoisomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ =7.29 (t, *J* = 8.0 Hz, 1H), 7.06 (ddd, *J* = 7.7, 1.8, 0.9 Hz, 1H), 6.99 (dd, *J* = 2.6, 1.7 Hz, 1H), 6.91 (ddd, *J* = 8.1, 2.5, 0.9 Hz, 1H), 6.14 (q, *J* = 1.4 Hz, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 2.56 (d, *J* = 1.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 167.21, 159.61, 155.75, 143.68, 129.49, 118.78, 116.83, 114.37, 112.10, 55.30, 51.11, 18.07.



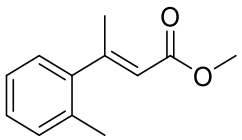
methyl (*E*)-3-(m-tolyl)but-2-enoate (**2.5.4**)

Prepared according to general procedure **A** using 3'-methylacetopheone (0.280 mL, 2.06 mmol). Purification by flash column chromatography on silica gave the oil **2.5.4** (0.228 g, 58%) as a mixture of *cis*- and *trans*-stereoisomers.

Spectral data for *trans*-stereoisomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.30 – 7.24 (m, 3H), 7.21 – 7.15 (m, 1H), 6.13 (q, *J* = 1.4 Hz, 1H), 3.76 (s, 3H), 2.57 (d, *J* = 1.3 Hz, 3H), 2.38 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 167.30, 156.12, 142.18, 138.12, 129.78, 128.39, 127.01, 123.43, 116.47, 51.07, 21.43, 18.02.



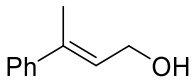
methyl (*E*)-3-(o-tolyl)but-2-enoate (**2.5.5**)

Prepared according to general procedure **A** using 2'-methylacetopheone (0.269 mL, 2.06 mmol). Purification by flash column chromatography on silica gave the oil **2.5.5** (0.052 g, 13%) as a mixture of *cis*- and *trans*-stereoisomers.

Spectral data for *cis*-stereoisomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.24 – 7.15 (m, 3H), 7.09 – 7.05 (m, 1H), 5.77 (q, *J* = 1.5 Hz, 1H), 3.75 (s, 3H), 2.45 (d, *J* = 1.4 Hz, 3H), 2.29 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 167.04, 158.60, 143.82, 133.85, 130.40, 127.71, 127.04, 125.73, 118.95, 51.06, 20.82, 19.68.

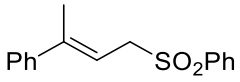


(*E*)-3-phenylbut-2-en-1-ol (**2.6**)

Prepared according to general procedure **B** using ester **2.5.1** (0.500 g, 2.84 mmol), which afforded the oil **2.6** (0.403 g, 96%) as a mixture of *cis*- and *trans*-stereoisomers.

Spectral data for trans-stereoisomer in agreement with literature.[22]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 – 7.40 (m, 2H), 7.36 – 7.31 (m, 2H), 7.30 – 7.23 (m, 1H), 5.98 (tq, *J* = 6.7, 1.4 Hz, 1H), 4.37 (dd, *J* = 6.7, 0.9 Hz, 2H), 2.09 – 2.08 (m, 3H).



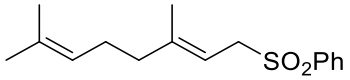
(*E*)-((3-phenylbut-2-en-1-yl)sulfonyl)benzene (**2.8**)

Prepared according to general procedures **C** and **D**, starting with alcohol **2.6** (0.200 g, 1.35 mmol). Purification by flash column chromatography on silica gave the oil **2.8** (0.206 g, 56%) as a mixture of *cis*- and *trans*-stereoisomers over two steps.

Spectral data for trans-stereoisomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.92 – 7.88 (m, 2H), 7.67 – 7.62 (m, 1H), 7.57 – 7.51 (m, 2H), 7.36 – 7.25 (m, 5H), 5.72 (tq, *J* = 8.2, 1.4 Hz, 1H), 4.01 (d, *J* = 8.1 Hz, 2H), 1.70 – 1.67 (m, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 144.56, 142.16, 138.56, 133.68, 129.07, 128.53, 128.35, 127.88, 125.79, 113.20, 56.70, 15.93.

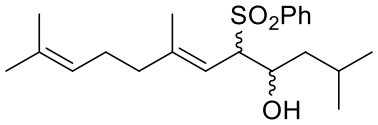


(*E*)-((3,7-dimethylocta-2,6-dien-1-yl)sulfonyl)benzene (**3.18**)

Prepared according to general procedures **C** and **D**, starting with geraniol **3.16** (0.50 mL, 2.9 mmol). Purification by flash column chromatography on silica gave the oil **3.18** (0.64 g, 80%) over two steps.

Spectral data for *trans*-stereoisomer in agreement with literature.[23]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 – 7.83 (m, 2H), 7.66 – 7.60 (m, 1H), 7.56 – 7.50 (m, 2H), 5.18 (tq, *J* = 8.0, 1.2 Hz, 1H), 5.03 (ddh, *J* = 6.8, 4.7, 1.5 Hz, 1H), 3.80 (d, *J* = 7.9 Hz, 2H), 2.06 – 1.95 (m, 4H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.58 (d, *J* = 1.4 Hz, 3H), 1.31 (d, *J* = 1.4 Hz, 3H).



(*E*)-2,7,11-trimethyl-5-(phenylsulfonyl)dodeca-6,10-dien-4-ol (**3.22**)

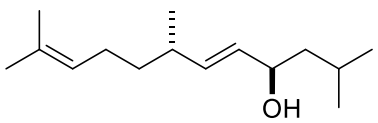
Prepared according to general procedure **E** using sulfone **3.18** (0.094 g, 0.34 mmol) and isovaleraldehyde (0.074 mL, 0.68 mmol). Purification by flash column chromatography on silica gave the oil **3.22** (0.118 g, 95%) as a mixture of diastereomers.

Spectral data for both diastereomers as a mixture:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.86 – 7.82 (m, 4H), 7.66 – 7.62 (m, 2H), 7.55 – 7.51 (m, 4H), 5.45 (dt, *J* = 10.7, 1.4 Hz, 1H), 5.02 – 4.98 (m, 2H), 4.86 (dq, *J* = 11.0, 1.4 Hz, 1H), 4.66 (ddd, *J* = 8.9, 4.7, 1.4 Hz, 1H), 4.35 (ddd, *J* = 10.7, 8.5, 2.6 Hz, 1H), 4.00 (bs, 1H), 3.84 (dd, *J* = 11.0, 8.6 Hz, 1H), 3.68 (dd, *J* = 10.7, 1.4 Hz, 1H), 2.97 (bs, 1H), 2.00 – 1.90 (m, 8H), 1.68 (s, 6H), 1.58 (s, 6H), 1.51 – 1.46 (m, 1H), 1.32 (ddd, *J* = 14.0, 10.5, 3.7 Hz, 2H), 1.19 (ddd, *J* = 14.0, 10.2, 2.6 Hz, 2H), 1.08 – 1.03 (m, 1H), 1.15 (d, *J* = 1.4 Hz, 3H), 1.11 (d, *J* = 1.4 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 6H), 0.90 (d, *J* = 6.7 Hz, 6H).

Spectral data for major diastereomer:

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 145.45, 137.74, 133.77, 132.15, 129.11, 128.81, 123.37, 114.18, 70.90, 67.69, 43.39, 39.64, 25.91, 25.72, 23.93, 23.88, 21.14, 17.67, 16.21.



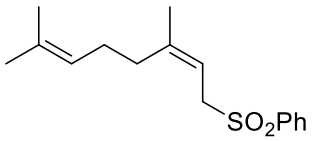
(4R,7S,*E*)-2,7,11-trimethyldodeca-5,10-dien-4-ol (**3.23**)

Prepared according to general procedure **G** using sulfone **3.22** (0.129 g, 0.354 mmol). Purification by flash column chromatography on silica gave the oil **3.23** (0.038 g, 48%) as a mixture of diastereomers.

Spectral data for major diastereomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.53 (ddd, *J* = 15.4, 7.4, 0.9 Hz, 1H), 5.41 (ddd, *J* = 15.4, 7.0, 1.0 Hz, 1H), 5.09 (ddq, *J* = 8.6, 5.7, 1.5 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 1H), 2.12 (p, *J* = 6.9 Hz, 1H), 1.95 (q, *J* = 7.7 Hz, 2H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.59 (s, 3H), 1.46 (ddd, *J* = 13.3, 7.7, 6.6 Hz, 1H), 1.34 – 1.29 (m, 4H), 0.98 (d, *J* = 6.8 Hz, 3H),0.92 (t, *J* = 6.8 Hz, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 137.51, 131.70, 131.32, 124.57, 71.41, 46.54, 36.91, 35.82, 25.74, 25.70, 24.61, 22.90, 22.53, 20.38, 17.68.

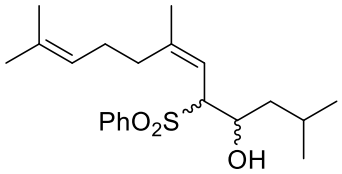


(*Z*)-((3,7-dimethylocta-2,6-dien-1-yl)sulfonyl)benzene (**3.21**)

Prepared according to general procedures **C** and **D**, starting with nerol **3.19** (0.50 mL, 2.9 mmol). Purification by flash column chromatography on silica gave the oil **3.21** (0.485 g, 61%) over two steps.

Spectral data for *cis*-stereoisomer in agreement with literature.[23]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88 – 7.85 (m, 2H), 7.65 – 7.61 (m, 1H), 7.56 – 7.51 (m, 2H), 5.20 (t, *J* = 8.0 Hz, 1H), 4.96 – 4.92 (m, 1H), 3.79 (d, *J* = 7.8, 2H), 1.87 – 1.81 (m, 2H), 1.77 – 1.74 (m, 2H), 1.72 (s, 3H), 1.64 (s, 3H), 1.54 (s, 3H).



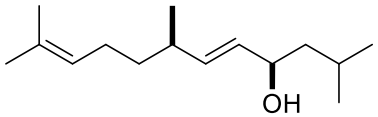
(*Z*)-2,7,11-trimethyl-5-(phenylsulfonyl)dodeca-6,10-dien-4-ol (**3.24**)

Prepared according to general procedure **E** using sulfone **3.21** (0.100 g, 0.359 mmol) and isovaleraldehyde (0.079 mL, 0.72 mmol). Purification by flash column chromatography on silica gave the oil **3.24** (0.115 g, 88%) as a mixture of diastereomers.

Spectral data for mixture of diastereomers:

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.85 – 7.81 (m, 4H), 7.65 – 7.61 (m, 2H), 7.55 – 7.50 (m, 4H), 5.46 (d, *J* = 10.9 Hz, 1H), 4.90 – 4.81 (m, 3H), 4.62 (ddd, *J* = 9.5, 4.2, 1.3 Hz, 1H), 4.33 (ddd, *J* = 10.7, 8.4, 2.4 Hz, 1H), 3.86 (dd, *J* = 11.1, 8.4 Hz, 1H), 3.70 (dd, *J* = 10.8, 1.4 Hz, 1H), 2.26 – 2.17 (m, 1H), 2.20 – 1.88 (m, 2H), 1.86 – 1.73 (m, 4H), 1.70 (d, *J* = 1.4 Hz, 3H), 1.67 – 1.60 (m, 1H), 1.66 (d, *J* = 1.3 Hz, 3H), 1.64 (s, 3H), 1.63 (s, 3H), 1.52 (s, 3H), 1.51 (s, 3H), 1.40 – 1.24 (m, 2H), 1.22 – 1.14 (m, 1H), 1.05 – 0.92 (3H), 0.91 (d, *J* = 7.0 Hz, 6H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.20, 145.56, 137.79, 137.72, 133.80, 133.71, 132.26, 132.22, 129.13, 129.00, 128.80, 123.23, 123.10, 114.70, 112.02, 70.64, 68.39, 67.67, 66.56, 43.60, 43.58, 32.10, 31.71, 25.78, 25.66, 25.64, 25.62, 24.27, 23.99, 23.89, 23.40, 23.32, 23.22, 21.79, 21.07, 17.66.



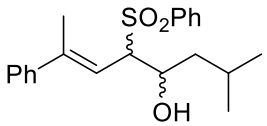
(4R,7R,*E*)-2,7,11-trimethyldodeca-5,10-dien-4-ol (**3.25**)

Prepared according to general procedure **G** using sulfone **3.24** (0.115 g, 0.315 mmol). Purification by flash column chromatography on silica gave the oil **3.25** (0.030 g, 42%) as a mixture of diastereomers.

Spectral data for major diastereomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.50 (ddd, *J* = 15.4, 7.7, 0.8 Hz, 1H), 5.40 (ddd, *J* = 15.4, 7.2, 0.9 Hz, 1H), 5.09 (ddq, *J* = 8.5, 5.7, 1.4 Hz, 1H), 4.12 (q, *J* = 7.0 Hz, 1H), 2.11 (p, *J* = 6.9 Hz, 1H), 1.98 – 1.89 (m, 2H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.59 (s, 3H), 1.46 (ddd, *J* = 13.6, 7.5, 6.9 Hz, 1H), 1.35 (bs, 1H), 1.34 – 1.27 (m, 4H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.91 (dd, *J* = 7.9, 6.6 Hz, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 137.75, 131.79, 131.33, 124.56, 71.55, 46.53, 36.97, 36.05, 25.82, 25.69, 24.61, 22.82, 22.59, 20.53, 17.64.



(*E*)-2-methyl-7-phenyl-5-(phenylsulfonyl)oct-6-en-4-ol (**3.5**)

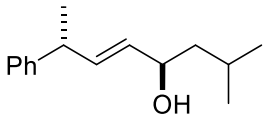
Prepared according to general procedure **E** using sulfone **2.8 (**0.103 g, 0.379 mmol) and isovaleraldehyde (0.083 mL, 0.76 mmol). Purification by flash column chromatography on silica gave the oil **3.5** (0.090 g, 66%) as a mixture of diastereomers.

Spectral data for both diastereomers as a mixture:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.88 – 7.85 (m, 4H), 7.66 – 7.62 (m, 2H), 7.54 – 7.50 (m, 4H), 7.35 – 7.25 (m, 6H), 7.24 – 7.22 (m, 4H), 6.02 (dq, *J* = 10.9, 1.4 Hz, 1H), 5.42 (dq, *J* = 11.2, 1.5 Hz, 1H), 4.81 (ddd, *J* = 9.3, 4.5, 1.4 Hz, 1H), 4.52 (ddd, *J* = 10.8, 8.5, 2.5 Hz, 1H), 4.02 (dd, *J* = 8.5, 2.0 Hz, 1H), 3.87 (dd, *J* = 10.9, 1.4 Hz, 1H), 3.08 (bs, 1H), 1.97 (th, *J* = 10.4, 3.4 Hz, 1H), 1.83 – 1.73 (m, 1H), 1.59 – 1.54 (m, 2H), 1.42 (ddd, *J* = 14.2, 10.5, 3.7 Hz, 2H), 1.51 (d, *J* = 1.4 Hz, 3H), 1.47 (d, *J* = 1.4 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 6H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H).

Spectral data for major diastereomer:

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 145.11, 142.15, 137.78, 133.82, 128.97, 128.93, 128.28, 127.87, 125.81, 114.78, 69.31, 66.74, 43.66, 24.34, 23.10, 21.91, 16.20.



(4R,7R,*E*)-2-methyl-7-phenyloct-5-en-4-ol (**3.11**)

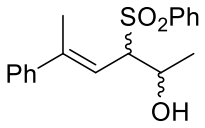
Prepared according to general procedure **G** using sulfone **3.5** (0.078 g, 0.22 mmol). Purification by flash column chromatography on silica gave the oil **3.11** (0.028 g, 58%) as a mixture of diastereomers.

Spectral data for major diastereomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.33 – 7.28 (m, 2H), 7.22 – 7.19 (m, 3H), 5.84 (ddd, *J* = 15.4, 6.6, 1.0 Hz, 1H), 5.50 (ddd, *J* = 15.4, 7.1, 1.4 Hz, 1H), 4.16 (tdd, *J* = 6.9, 5.8, 1.0 Hz, 1H), 3.47 (p, *J* = 7.0 Hz, 1H), 1.73 (dtd, *J* = 13.1, 6.6, 1.1 Hz, 1H), 1.49 (ddd, *J* = 13.6, 7.9, 6.5 Hz, 2H), 1.37 (d, *J* = 7.1 Hz, 3H), 0.93 (dd, *J* = 7.5, 6.6 Hz, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 145.58, 136.13, 132.12, 128.43, 127.15, 126.15, 71.24, 46.42, 41.92, 24.58, 22.94, 22.44, 21.23.

HRMS (ESI+) Calculated for C15H22NaO (M + Na): 241.156286. Found 241.155469.



(*E*)-5-phenyl-3-(phenylsulfonyl)hex-4-en-2-ol (**3.1**)

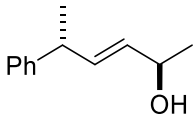
Prepared according to general procedure **E** using sulfone **2.8** (0.090 g, 0.33 mmol) and acetaldehyde (0.037 mL, 0.66 mmol). Purification by flash column chromatography on silica gave the oil **3.1** (0.085 g, 82%).

Spectral data for both diastereomers as a mixture:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.89 – 7.85 (m, 4H), 7.67 – 7.63 (m, 2H), 7.55 – 7.51 (m, 4H), 7.34 – 7.25 (m, 6H), 7.23 – 7.21 (m, 4H), 6.00 (dq, *J* = 10.9, 1.4 Hz, 1H), 5.39 (dq, *J* = 11.0, 1.4 Hz, 1H), 4.87 (qd, *J* = 6.5, 1.6 Hz, 1H), 4.58 (dq, *J* = 8.6, 6.3 Hz, 1H), 4.19 (bs, 1H), 4.01 (dd, *J* = 11.0, 8.6 Hz, 1H), 3.87 (dd, *J* = 10.9, 1.6 Hz, 1H), 3.15 (bs, 1H), 1.54 (d, *J* = 1.4 Hz, 3H), 1.53 (d, *J* = 1.5 Hz, 3H), 1.26 (d, *J* = 5.8 Hz, 3H), 1.24 (d, *J* = 5.8 Hz, 3H).

Spectral data for major diastereomer:

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 143.80, 141.98, 137.52, 134.03, 129.07, 129.05, 128.44, 128.03, 125.72, 116.78, 71.90, 66.28, 20.95, 16.10.



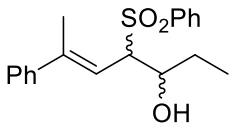
(2R,5R,*E*)-5-phenylhex-3-en-2-ol (**3.7**)

Prepared according to general procedure **G** using sulfone **3.1** (0.080 g, 0.25 mmol). Purification by flash column chromatography on silica gave the oil **3.7** (0.019 g, 43%) as a mixture of diastereomers.

Spectral data for major diastereomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.32 – 7.28 (m, 2H), 7.22 – 7.18 (m, 3H), 5.82 (ddt, *J* = 15.4, 6.6, 1.1 Hz, 1H), 5.56 (ddt, *J* = 15.5, 6.6, 1.1 Hz, 1H), 4.30 (p, *J* = 6.4 Hz, 1H), 3.46 (p, *J* = 7.0 Hz, 1H), 1.55 (bs, 1H), 1.36 (dd, *J* = 7.0, 0.9 Hz, 3H), 1.28 – 1.25 (m, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 145.56, 135.41, 132.87, 128.43, 127.16, 126.16, 68.86, 41.82, 23.40, 21.16.



(*E*)-6-phenyl-4-(phenylsulfonyl)hept-5-en-3-ol (**3.2**)

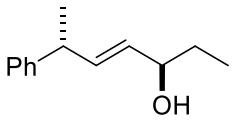
Prepared according to general procedure **E** using sulfone **2.8** (0.089 g, 0.33 mmol) and propionaldehyde (0.049 mL, 0.66 mmol). Purification by flash column chromatography on silica gave the oil **3.2** (0.059 g, 54%).

Spectral data for both diastereomers as a mixture:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.91 – 7.85 (m, 4H), 7.66 – 7.62 (m, 2H), 7.55 – 7.50 (m, 4H), 7.34 – 7.24 (m, 9H), 7.23 – 7.21 (m, 1H), 6.01 (dq, *J* = 10.9, 1.4 Hz, 1H), 5.40 (dq, *J* = 11.1, 1.4 Hz, 1H), 4.60 (ddd, *J* = 8.2, 5.6, 1.5 Hz, 1H), 4.40 (ddd, *J* = 8.8, 7.9, 3.1 Hz, 1H), 4.05 (dd, *J* = 11.0, 8.8 Hz, 1H), 3.93 (dd, *J* = 10.9, 1.4 Hz, 1H), 3.17 (bs, 1H), 1.52 (d, *J* = 1.5 Hz, 3H), 1.51 (d, *J* = 1.5 Hz, 3H), 1.74 – 1.60 (m, 2H), 1.47 – 1.39 (m, 2H), 0.97 (td, *J* = 7.4, 4.4 Hz, 6H).

Spectral data for major diastereomer:

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 145.11, 142.15, 137.76, 133.80, 128.95, 128.91, 128.26, 127.84, 125.77, 114.67, 70.07, 68.77, 27.95, 16.17, 10.06.



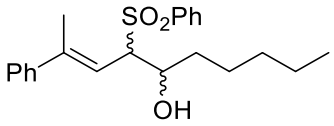
(3R,6R,*E*)-6-phenylhept-4-en-3-ol (**3.8**)

Prepared according to general procedure **G** using sulfone **3.2** (0.059 g, 0.18 mmol). Purification by flash column chromatography on silica gave the oil **3.8** (0.020 g, 59%) as a mixture of diastereomers.

Spectral data for major diastereomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.32 – 7.28 (m, 2H), 7.23 – 7.18 (m, 3H), 5.84 (ddd, *J* = 15.5, 6.6, 1.1 Hz, 1H), 5.50 (ddd, *J* = 15.4, 7.0, 1.4 Hz, 1H), 4.01 (q, *J* = 6.6, 1H), 3.48 (p, *J* = 7.0 Hz, 1H), 1.65 – 1.46 (m, 2H), 1.37 (d, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 145.59, 136.63, 131.48, 128.43, 127.17, 126.15, 74.43, 41.95, 30.15, 21.24, 9.78.



(*E*)-2-phenyl-4-(phenylsulfonyl)dec-2-en-5-ol (**3.3**)

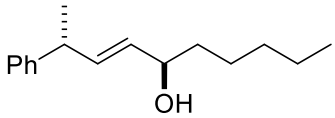
Prepared according to general procedure **E** using sulfone **2.8** (0.105 g, 0.386 mmol) and hexanal (0.093 mL, 0.77 mmol). Purification by flash column chromatography on silica gave the oil **3.3** (0.037 g, 26%) as a mixture of diastereomers.

Spectral data for both diastereomers as a mixture:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1H NMR (500 MHz, CDCl3) δ = 7.89 – 7.85 (m, 4H), 7.67 – 7.62 (m, 2H), 7.56 – 7.49 (m, 6H), 7.34 – 7.24 (m, 7H), 7.23 – 7.20 (m, 1H), 6.01 (dq, J = 11.0, 1.5 Hz, 1H), 5.40 (dq, J = 11.0, 1.4 Hz, 1H), 4.68 (ddd, J = 8.4, 5.1, 1.4 Hz, 1H), 4.45 (td, J = 8.2, 3.0 Hz, 1H), 4.04 (dd, J = 11.0, 8.7 Hz, 1H), 3.90 (dd, J = 10.8, 1.4 Hz, 1H), 3.09 (bs, 1H), 1.65 – 1.55 (m, 4H), 1.51 (d, J = 1.4 Hz, 3H), 1.50 (d, J = 1.4 Hz, 3H), 1.34 – 1.24 (m, 12H), 0.93 – 0.82 (m, 6H).

Spectral data for major diastereomer:

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 145.16, 142.21, 137.82, 133.84, 129.01, 128.96, 128.32, 127.91, 125.84, 114.75, 69.09, 68.70, 34.82, 31.50, 25.26, 22.49, 16.25, 13.94.



(2R,5R,*E*)-2-phenyldec-3-en-5-ol (**3.9**)

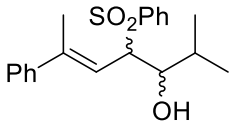
Prepared according to general procedure **G** using sulfone **3.3** (0.058 g, 0.15 mmol). Purification by flash column chromatography on silica gave the oil **3.9** (0.021 g, 59%) as a mixture of diastereomers.

Spectral data for major diastereomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.32 - 7.29 (m, 2H), 7.23 – 7.18 (m, 3H), 5.82 (ddd, *J* = 15.5, 6.6, 1.0 Hz, 1H), 5.51 (ddd, *J* = 15.4, 7.1, 1.4 Hz, 1H), 4.08 (q, *J* = 6.7 Hz, 1H), 3.47 (p, *J* = 7.0 Hz, 1H), 1.63 – 1.44 (m, 4H), 1.36 (d, *J* = 7.0 Hz, 3H), 1.33 - 1.27 (m, 4H), 0.92 – 0.86 (m, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 145.60, 136.35, 131.84, 128.43, 127.17, 126.15, 73.12, 41.92, 37.28, 31.71, 25.17, 22.60, 21.22, 14.00.

HRMS (ESI+) Calculated for C16H24NaO (M + Na): 255.171936. Found 255.170874.



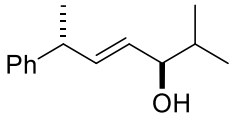
(*E*)-2-methyl-6-phenyl-4-(phenylsulfonyl)hept-5-en-3-ol (**3.4**)

Prepared according to general procedure **E** using sulfone **2.8** (0.085 g, 0.31 mmol) and isobutyraldehyde (0.057 mL, 0.62 mmol). Purification by flash column chromatography on silica gave the oil **3.4** (0.034 g, 31%) as a mixture of diastereomers.

Spectral data for major diastereomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.87 – 7.85 (m, 2H), 7.67 – 7.64 (m, 1H), 7.55 – 7.51 (m, 2H), 7.34 – 7.29 (m, 3H), 7.23 – 7.21 (m, 2H), 5.39 (dq, *J* = 11.0, 1.4 Hz, 1H), 4.34 (dd, *J* = 9.2, 2.2 Hz, 1H), 4.07 (bs, 1H), 4.05 (dd, *J* = 11.1, 9.2 Hz, 1H), 1.78 (pd, *J* = 6.8, 2.1 Hz, 1H), 1.49 (d, *J* = 1.4 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 143.09, 141.94, 137.48, 133.98, 129.25, 129.00, 128.45, 128.02, 125.69, 116.61, 72.74, 70.13, 31.11, 20.03, 15.80, 13.72.



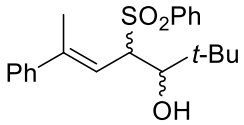
(3R,6R,*E*)-2-methyl-6-phenylhept-4-en-3-ol (**3.10**)

Prepared according to general procedure **G** using sulfone **3.4** (0.034, 0.098 mmol). Purification by flash column chromatography on silica gave the oil **3.10** (0.014 g, 72%) as a mixture of diastereomers.

Spectral data for major diastereomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.32 – 7.28 (m, 2H), 7.23 – 7.18 (m, 3H), 5.83 (ddd, *J* = 15.5, 6.6, 1.0 Hz, 1H), 5.51 (ddd, *J* = 15.5, 7.3, 1.4 Hz, 1H), 3.82 (t, *J* = 6.7, 1H), 3.53 – 3.45 (m, 1H), 1.73 (dq, *J* = 13.4, 6.7 Hz, 1H), 1.37 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 145.63, 137.38, 129.96, 128.43, 127.17, 126.14, 78.18, 42.06, 33.91, 21.28, 18.28, 18.16.



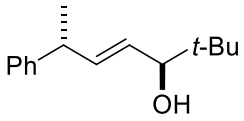
(*E*)-2,2-dimethyl-6-phenyl-4-(phenylsulfonyl)hept-5-en-3-ol (**3.6**)

Prepared according to general procedure **E** using sulfone **2.8** (0.084 g, 0.31 mmol) and pivaldehyde (0.069 mL, 0.62 mmol). Purification by flash column chromatography on silica gave the oil **3.6** (0.067 g, 60%) as the major diastereomer.

Spectral data for major diastereomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.87 – 7.82 (m, 2H), 7.64 (ddt, *J* = 8.7, 7.1, 1.3 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.33 – 7.25 (m, 3H), 7.23 – 7.19 (m, 2H), 6.09 (dq, *J* = 10.6, 1.4 Hz, 1H), 4.46 (s, 1H), 4.11 (dd, *J* = 10.8, 0.9 Hz, 1H), 2.96 (s, 1H), 1.45 (d, *J* = 1.5 Hz, 3H), 0.96 (s, 9H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 142.99, 142.46, 137.23, 133.75, 129.36, 128.82, 128.32, 127.74, 125.70, 116.54, 74.62, 66.64, 35.79, 26.55, 16.29.



(3S,6R,*E*)-2,2-dimethyl-6-phenylhept-4-en-3-ol (**3.12**)

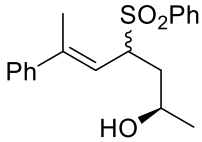
Prepared according to general procedure **G** using sulfone **3.6** (0.033 g, 0.092 mmol). Purification by flash column chromatography on silica gave the oil **3.12** (0.012 g, 59%) as a mixture of diastereomers.

Spectral data for major diastereomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.33 – 7.28 (m, 2H), 7.23 – 7.18 (m, 3H), 5.83 (ddd, *J* = 15.4, 6.6, 1.0 Hz, 1H), 5.57 (ddd, *J* = 15.5, 7.6, 1.4 Hz, 1H), 3.73 (d, *J* = 7.6, 1H), 3.49 (p, *J* = 7.0 Hz, 1H), 1.37 (d, *J* = 7.1 Hz, 3H), 0.91 (s, 9H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 145.65, 138.00, 128.55, 128.43, 127.17, 126.14, 80.97, 42.16, 34.92, 25.75, 21.30.

HRMS (ESI+) Calculated for C15H22NaO (M + Na): 241.156286. Found 241.155235.



(2R,*E*)-6-phenyl-4-(phenylsulfonyl)hept-5-en-2-ol (**4.1**)

Prepared according to general procedure **F**. Purification by flash column chromatography on silica gave the oil **4.1** (64%) as a mixture of diastereomers.

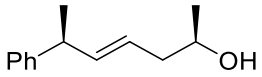
Spectral data for both diastereomers as a mixture:

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.88 – 7.83 (m, 4H), 7.62 – 7.58 (m, 2H), 7.51 – 7.46 (m, 4H), 7.32 – 7.23 (m, 6H), 7.22 – 7.19 (m, 4H), 5.54 (dq, *J* = 10.8, 1.5 Hz, 1H), 5.49 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.35 (td, *J* = 11.0, 2.9 Hz, 1H), 4.19 (ddd, *J* = 10.6, 8.2, 5.4 Hz, 1H), 4.15 – 4.10 (m, 1H), 3.75 (dqd, *J* = 10.5, 6.2, 2.5 Hz, 1H), 2.44 (dt, *J* = 14.0,

5.4 Hz, 1H), 2.34 (ddd, *J* = 13.6, 10.6, 2.8 Hz, 1H), 2.25 (bs, 1H), 1.96 (ddd, *J* = 14.0, 8.2, 7.2 Hz, 1H), 1.89 (ddd, *J* = 13.7, 11.2, 2.5 Hz, 1H), 1.57 (d, *J* = 1.4 Hz, 3H), 1.53 (d, *J* = 1.4 Hz, 3H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.21 (d, *J* = 6.2 Hz, 3H).

Spectral data for major diastereomer:

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 142.94, 141.98, 137.53, 133.57, 129.09, 128.78, 128.27, 127.77, 125.65, 120.35, 65.54, 62.50, 37.30, 23.02, 16.03.



(2R,6S,*E*)-6-phenylhept-4-en-2-ol (**4.3**)

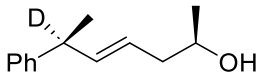
Prepared according to general procedure **G** using sulfone **4.1** (0.110 g, 0.333 mmol). Purification by flash column chromatography on silica gave the oil **4.3** (0.042 g, 44%) as a mixture of diastereomers.

Spectral data for major diastereomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.31 (m, *J* = 8.0, 6.8, 1.3 Hz, 2H), 7.24 – 7.17 (m, 3H), 5.75 (dddt, *J* = 15.3, 6.8, 2.5, 1.3 Hz, 1H), 5.48 (dddd, *J* = 15.7, 8.0, 6.8, 1.3 Hz, 1H), 3.81 (dtdd, *J* = 8.8, 7.4, 5.5, 4.3 Hz, 1H), 3.48 (p, *J* = 6.9 Hz, 1H), 2.26 – 2.19 (m, 1H), 2.18 – 2.10 (m, 1H), 1.65 (s, 1H), 1.37 (dd, *J* = 7.0, 1.9 Hz, 3H), 1.19 (dd, *J* = 6.2, 1.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 145.96, 139.04, 128.41, 127.06, 126.05, 124.71, 67.26, 42.46, 42.33, 22.67, 21.37.

HRMS (ESI+) Calculated for C13H18NaO (M + Na): 213.124986. Found 213.124383.



(2R,6S,*E*)-6-phenylhept-4-en-6-d-2-ol (**4.8**)

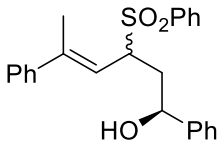
Prepared according to general procedure **G** using sulfone **4.1** (0.050 g, 0.15 mmol) and 105 equiv. D_2O (0.32 mL, 16 mmol). Purification by flash column chromatography on silica gave the oil **4.8** (0.024 g, 84%) as a mixture of diastereomers.

Spectral data for major diastereomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.32 – 7.28 (m, 2H), 7.22 – 7.18 (m, 3H), 5.74 (ddt, *J* = 15.3, 2.4, 1.3 Hz, 1H), 5.47 (dddd, *J* = 15.3, 7.5, 6.6, 0.8 Hz, 1H), 3.81 – 3.78 (m, 1H), 2.23 (dddd, *J* = 12.9, 6.6, 4.9, 1.4 Hz, 1H), 2.14 (dtt, *J* = 13.8, 7.6, 1.3 Hz, 1H), 1.71 (bs, 1H), 1.36 (bs, 3H), 1.19 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 145.92, 139.02, 128.42, 127.04, 126.06, 124.71, 67.26, 42.46, 42.41, 22.67, 21.28.

HRMS (ESI+) Calculated for C13H17DNaO (M + Na): 214.131263. Found 214.130387.



(1S,*E*)-1,5-diphenyl-3-(phenylsulfonyl)hex-4-en-1-ol (**4.2**)

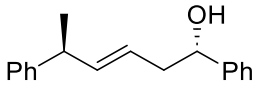
Prepared according to general procedure **F** using sulfone **2.8** (0.200 g, 0.734 mmol) and (*R*)-styrene oxide (0.101 mL, 0.881 mmol). Purification by flash column chromatography on silica gave the oil **4.2** (0.247 g, 86%) as a mixture of diastereomers.

Spectral data for both diastereomers as a mixture:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1H NMR (500 MHz, CDCl3) δ = 7.89 – 7.82 (m, 2H), 7.81 – 7.79 (m, 2H), 7.63 – 7.57 (m, 2H), 7.53 – 7.45 (m, 4H), 7.38 – 7.27 (m, 16H), 7.24 – 7.19 (m, 4H), 5.58 (dq, *J* = 10.5, 1.4 Hz, 1H), 5.49 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.92 (t, *J* = 7.0 Hz, 1H), 4.67 (dd, *J* = 10.7, 2.9 Hz, 1H), 4.43 (td, *J* = 10.8, 3.0 Hz, 1H), 3.87 (ddd, *J* = 10.4, 9.0, 4.7 Hz, 1H), 2.74 (ddd, *J* = 13.7, 7.5, 4.8 Hz, 2H), 2.33 (ddd, *J* = 13.8, 9.0, 6.5 Hz, 2H), 1.60 (d, *J* = 1.4 Hz, 3H), 1.35 (d, *J* = 1.4 Hz, 3H).

Spectral data for major diastereomer:

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 143.65, 142.49, 142.13, 137.55, 133.61, 129.24, 128.85, 128.75, 128.37, 128.21, 127.89, 126.14, 125.76, 119.88, 72.02, 62.33, 37.05, 16.16.



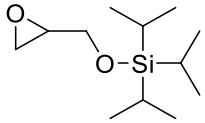
(1S,5S,*E*)-1,5-diphenylhex-3-en-1-ol (**4.4**)

Prepared according to general procedure **G** using sulfone **4.2** (0.143 g, 0.363 mmol). Purification by flash column chromatography on silica gave the oil **4.4** (0.037 g, 40%) as a mixture of diastereomers.

Spectral data for major diastereomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.36 – 7.33 (m, 4H), 7.31 – 7.27 (m, 3H), 7.21 – 7.14 (m, 3H), 5.73 (ddt, *J* = 15.4, 6.7, 1.3 Hz, 1H), 5.51 – 5.39 (m, 1H), 4.73 – 4.70 (m, 1H), 3.45 (p, *J* = 7.0 Hz, 1H), 2.01 (bs, 1H), 2.54 – 2.43 (m, 2H), 1.34 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 145.85, 143.92, 139.39, 128.39, 128.35, 127.44, 127.10, 126.05, 125.86, 124.34, 73.65, 42.65, 42.27, 21.26.



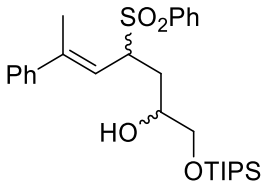
Triisopropyl(oxiran-2-ylmethoxy)silane (**4.5**)

To a dry Schlenk flask containing DCM (0.2 M, 15 mL), glycidol (0.200 mL, 3.00 mmol) was added and the reaction mixture cooled to 0°C. Imidazole (0.408 g, 5.99 mmol) was then added, followed by the addition of triisopropylchlorosilane (0.770 mL, 3.60 mmol), and the reaction mixture was left to react overnight while warming to room temperature. The reaction mixture was then quenched with H_2O, extracted with DCM (3x). The combined organic extracts were dried with $MgSO_4$ and concentrated *in vacuo*, affording the oil **4.5** (0.600g, 87%).

Spectral data:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.91 (dd, *J* = 11.6, 3.2 Hz, 1H), 3.75 (dd, *J* = 11.7, 4.6 Hz, 1H), 3.11 (tt, *J* = 4.4, 2.9 Hz, 1H), 2.77 (dd, *J* = 5.2, 4.0 Hz, 1H), 2.67 (dd, *J* = 5.2, 2.6 Hz, 1H), 1.15 – 1.09 (m, 3H), 1.08 – 1.05 (m, 18H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 63.92, 52.58, 44.47, 17.90, 11.94.



(*E*)-6-phenyl-4-(phenylsulfonyl)-1-((triisopropylsilyl)oxy)hept-5-en-2-ol (**4.6**)

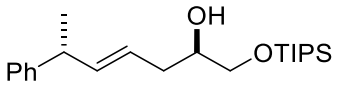
Prepared according to general procedure **F** using sulfone **2.8** (0.222 g, 0.815 mmol) and TIPS protected epoxide **4.5** (0.225 g, 0.977 mmol). Purification by flash column chromatography on silica gave the oil **4.6** (0.315 g, 77%) as a mixture of diastereomers.

Spectral data for both diastereomers as a mixture:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.91 – 7.85 (m, 4H), 7.65 – 7.58 (m, 2H), 7.53 – 7.48 (m, 4H), 7.34 – 7.21 (m, 10H), 5.54 (dq, *J* = 10.5, 1.4 Hz, 1H), 5.51 (dq, *J* = 10.7, 1.4 Hz, 1H), 4.36 (ddd, *J* = 11.6, 10.6, 2.8 Hz, 1H), 4.21 (ddd, *J* = 10.5, 8.0, 5.3 Hz, 1H), 3.99 (tdd, *J* = 7.2, 5.2, 3.6 Hz, 1H), 3.76 – 3.71 (m, 2H), 3.63 (ddd, *J* = 11.7, 5.9, 2.7 Hz, 1H), 3.58 – 3.53 (ddd, *J* = 9.8, 8.1, 6.7 Hz, 2H), 2.60 (bs, 1H), 2.50 (dt, *J* = 14.2, 5.3 Hz, 1H), 2.39 (ddd, *J* = 13.6, 10.8, 2.8 Hz, 1H), 1.93 (dt, *J* = 14.3, 7.8 Hz, 1H), 1.82 (ddd, *J* = 13.7, 11.6, 2.3 Hz, 1H), 1.62 (d, *J* = 1.4 Hz, 3H), 1.56 (d, *J* = 1.4 Hz, 3H), 1.14 – 1.07 (m, 6H), 1.06 – 1.02 (m, *J* = 6.9, 4.3, 2.2 Hz, 36H).

Spectral data for major diastereomer:

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 142.74, 142.20, 137.76, 133.60, 129.27, 128.85, 128.33, 127.80, 125.80, 120.66, 69.89, 66.77, 62.24, 31.74, 17.92, 16.12, 11.84.



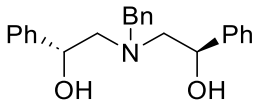
(2R,6R,*E*)-6-phenyl-1-((triisopropylsilyl)oxy)hept-4-en-2-ol (**4.7**)

Prepared according to general procedure **G** using sulfone **4.6** (0.120 g, 0.240 mmol). Purification by flash column chromatography on silica gave the oil **4.7** (0.085 g, 98%) as a mixture of diastereomers (required resubjection).

Spectral data for major diastereomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.31 – 7.27 (m, 2H), 7.21 – 7.17 (m, 3H), 5.73 – 5.67 (m, 1H), 5.53 – 5.46 (m, 1H), 3.73 – 3.67 (m, 2H), 3.55 – 3.50 (m, 1H), 3.46 (p, *J* = 7.0 Hz, 1H), 2.49 (bs, 1H), 2.27 – 2.18 (m, 2H), 1.35 (d, *J* = 7.0 Hz, 3H), 1.15 – 1.08 (m, 3H), 1.07 – 1.04 (m, 18H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 146.03, 138.10, 128.37, 127.11, 126.01, 124.44, 71.64, 66.84, 42.28, 36.28, 21.25, 17.94, 11.89.

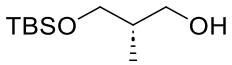


(1R,1'R)-2,2'-(benzylazanediyl)bis(1-phenylethan-1-ol) (**4.11**)

To a 25-mL round-bottom flask equipped with a reflux adapter and charged with methanol (10 mL, 0.5 M), (*R*)-styrene oxide (1.26 mL, 11 mmol) was added, followed by benzylamine (0.55 mL, 5 mmol). The reaction mixture was refluxed at 70°C for 36 hours. Volatiles were removed from the reaction mixture *in vaccuo*. Purification by flash column chromatography on silica gave the oil **4.11** (0.620 g, 36%).

Spectral data in agreement with literature.[18]

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.38 – 7.27 (m, 15H), 4.77 (dd, *J* = 9.7, 3.6 Hz, 2H), 4.00 (d, *J* = 13.6 Hz, 1H), 3.70 (d, *J* = 13.6 Hz, 1H), 3.30 (bs, 2H), 2.82 (dd, *J* = 13.4, 9.7 Hz, 2H), 2.76 (dd, *J* = 13.4, 3.6 Hz, 2H).

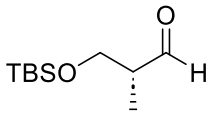


(S)-3-((tert-butyldimethylsilyl)oxy)-2-methylpropan-1-ol (**5.4**)

Prepared according to general procedure **B** using ester **5.3** (1.0 g, 4.3 mmol), which afforded **5.4** (0.61 g, 70%) as an oil.

Spectral data in agreement with literature.[24]

^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.74 (ddd, *J* = 9.9, 4.4, 0.9 Hz, 1H), 3.65 (ddd, *J* = 10.7, 4.2, 0.9 Hz, 1H), 3.60 (dd, *J* = 10.7, 7.4 Hz, 1H), 3.54 (dd, *J* = 9.9, 8.0 Hz, 1H), 2.81 (br s, 1H), 1.99 – 1.89 (m, 1H), 0.90 (s, 9H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.07 (s, 6H).

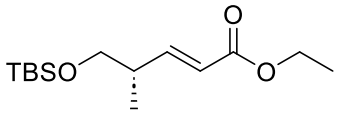


(R)-3-((tert-butyldimethylsilyl)oxy)-2-methylpropanal (**5.5**)

A dried Schlenk flask was charged with DCM (15 mL, 0.2 M) and oxalyl chloride (0.386 mL, 4.5 mmol), then cooled to -78°C. DMSO (0.426 mL, 6.0 mmol) was then added, and the reaction mixture was stirred for 15 minutes. The alcohol **5.4** (0.613 g, 3.0 mmol) was then added and the reaction mixture stirred for 20 minutes, followed by the addition of triethylamine (2.1 mL, 15 mmol) and stirred for 1 hour. The reaction mixture was then quenched with H_2O and extracted with DCM (3x). The combined organic extracts were then dried with $MgSO_4$, pushed through a silica plug, and concentrated *in vacuo*, affording the aldehyde **5.5** (0.469 g, 77%).

Spectral data in agreement with literature.[24]

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.74 (d, *J* = 1.6 Hz, 1H), 3.86 (dd, *J* = 10.1, 5.2 Hz, 1H), 3.81 (dd, *J* = 10.2, 6.4 Hz, 1H), 2.57 – 2.49 (m, 1H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H).

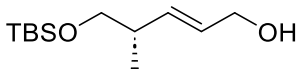


Ethyl (S,*E*)-5-((tert-butyldimethylsilyl)oxy)-4-methylpent-2-enoate (**5.7**)

A dried Schlenk flask was charged with THF (23 mL, 0.1 M) and the aldehyde **5.5** (0.469 g, 2.32 mmol) was then added. The Wittig reagent **5.6** (1.21 g, 3.48 mmol) was then added and the reaction mixture was stirred overnight. The volatiles were removed *in vaccuo* and ester **5.7** was then extracted from residual phosphonium salts using MTBE. The resulting organic extract was then concentrated *in vacuo*. Purification by flash column chromatography on silica gave the oil **5.7** (0.30 g, 48%).

Spectral data in agreement with literature.[25]

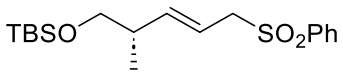
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.93 (dd, *J* = 15.8, 7.2 Hz, 1H), 5.83 (dd, *J* = 15.9, 1.4 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.55 (dd, *J* = 9.8, 6.5 Hz, 1H), 3.51 (dd, *J* = 9.8, 6.4 Hz, 1H), 2.53 – 2.47 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H).



(S,*E*)-5-((tert-butyldimethylsilyl)oxy)-4-methylpent-2-en-1-ol (**5.8**)

Prepared according to general procedure **B** using ester **5.7** (0.291 g, 1.07 mmol), which afforded **5.8** (0.211 g, 86%) as an oil.
Spectral data in agreement with literature.[25]

^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.70 – 5.61 (m, 2H), 4.10 (d, *J* = 4.6 Hz, 2H), 3.50 (dd, *J* = 9.7, 6.2 Hz, 1H), 3.41 (dd, *J* = 9.7, 6.9 Hz, 1H), 2.37 – 2.32 (m, 1H), 1.44 (bs, 1H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H).



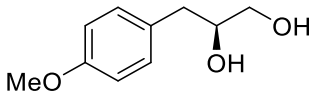
(S,*E*)-tert-butyldimethyl((2-methyl-5-(phenylsulfonyl)pent-3-en-1-yl)oxy)silane (**5.10**)

Prepared according to general procedures **C** and **D**, starting with alcohol **5.8** (0.211 g, 0.917 mmol). Purification by flash column chromatography on silica gave the oil **5.10** (0.011 g, 4%) over two steps.

Spectral data:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.88 – 7.82 (m, 2H), 7.67 – 7.60 (m, 1H), 7.57 – 7.51 (m, 2H), 5.49 – 5.38 (m, 2H), 3.77 – 3.73 (m, 2H), 3.35 (dd, *J* = 9.8, 6.1 Hz, 1H), 3.28 (dd, *J* = 9.8, 6.8 Hz, 1H), 2.32 – 2.23 (m, 1H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.86 (s, 9H), -0.00 (s, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 143.96, 138.22, 133.57, 128.89, 128.62, 115.85, 67.25, 60.23, 39.38, 25.86, 18.29, 16.00, -5.40.



(S)-3-(4-methoxyphenyl)propane-1,2-diol (**5.11**)

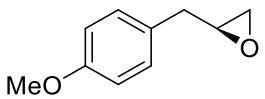
At room temperature, a 25-mL round bottom flask was charged with a 1:1 mixture of water (2.25 mL) and *t*-BuOH (2.25 mL), followed by the addition of AD-mix-β (2.34 g, 3 mmol) and methanesulfonamide (0.285 g, 3 mmol). The reaction mixture was stirred until two clear phases were visible, then cooled to 4°C. 4-allylaniosle (0.47 mL, 3 mmol) was then added and the reaction mixture was left to stir for 48 hours at 4°C. The reaction mixture was then quenched with sulfite and stirred for 1 hour, followed by extraction with ethyl acetate (3x). The combined organic extract was then rinsed with brine, reextracted with ethyl acetate, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography on silica gave the white solid **5.11** (0.385 g, 70%).

Spectral data in agreement with literature.[20]

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.15 – 7.12 (m, 2H), 6.89 – 6.83 (m, 2H), 3.93 – 3.86 (m, 1H), 3.79 (d, *J* = 1.6 Hz, 3H), 3.70 – 3.64 (m, 1H), 3.53 – 3.47 (m, 1H), 2.76 – 2.66 (m, 2H), 2.17 (bs, 2H).

Optical rotation data in agreement with literature.[20]

Reported: $[\alpha]^{26.30}$ = +5.495 (c = 1.8, $CHCl_3$), observed: $[\alpha]^{20.1}$ = +5.60 (c = 2.0, $CHCl_3$).



(S)-2-(4-methoxybenzyl)oxirane (**5.13**)

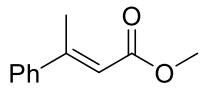
A dried Schlenk flask was delivered a mixture of the mesylated alcohols **5.12.1** and **5.12.2** (0.186 g, 0.715 mmol), followed by the addition of methanol (3.6 mL, 0.2 M). The reaction mixture was cooled to 0°C and potassium carbonate (0.074 g, 0.54 mmol) was added. The reaction mixture was stirred overnight while warming to room temperature, then quenched with H_2O and extracted with ethyl acetate (3x). The combined organic extract was then

dried with $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography on silica gave the oil **5.13** (0.039 g, 43%) over two steps.

Spectral data in agreement with literature.[26]

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.19 – 7.16 (m, 2H), 6.88 – 6.85 (m, 2H), 3.80 (s, 3H), 3.12 (tdd, *J* = 5.5, 3.8, 2.6 Hz, 1H), 2.87 (dd, *J* = 14.6, 5.6 Hz, 1H), 2.79 – 2.75 (m, 2H), 2.53 (dd, *J* = 5.0, 2.7 Hz, 1H).

Spectra



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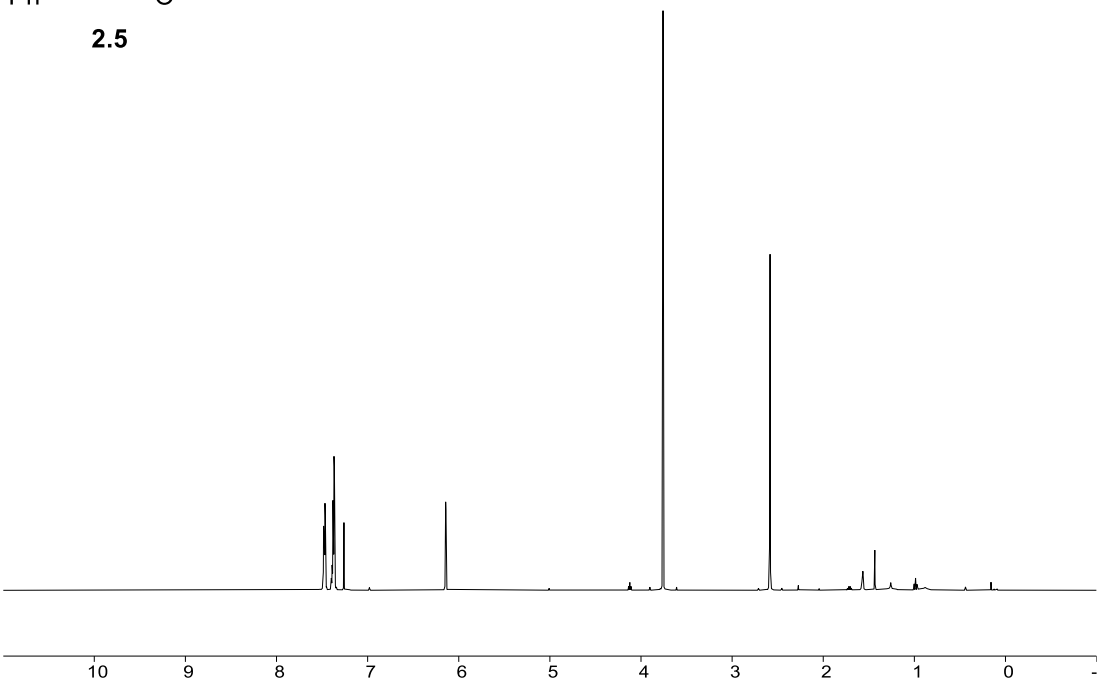

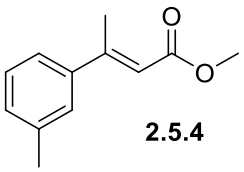
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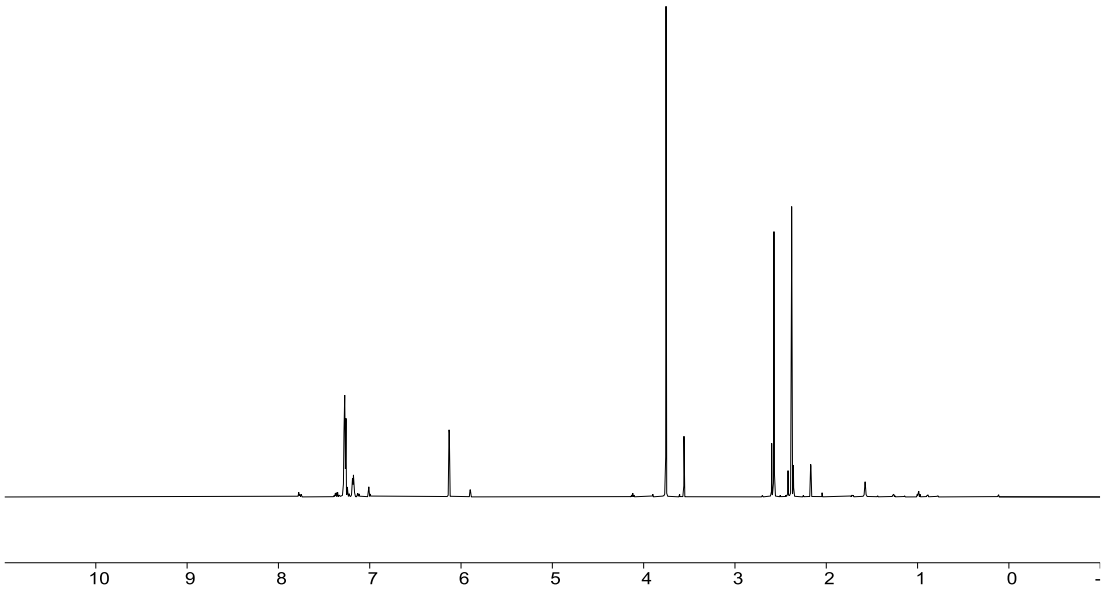
2.5.4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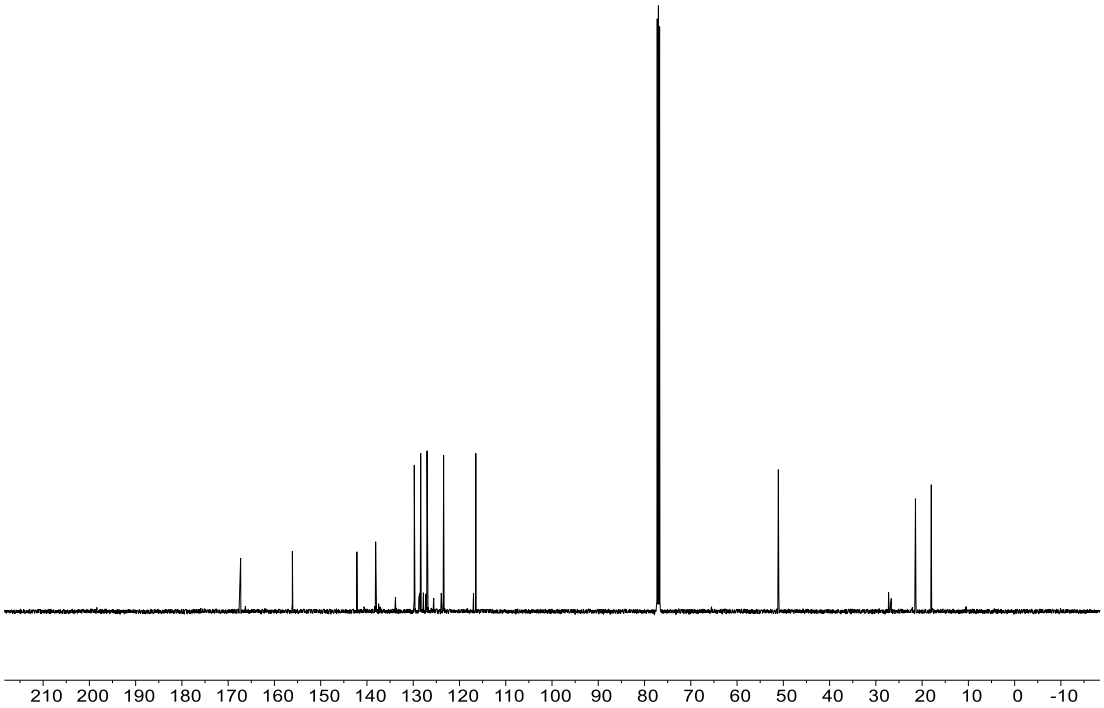
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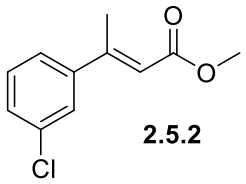
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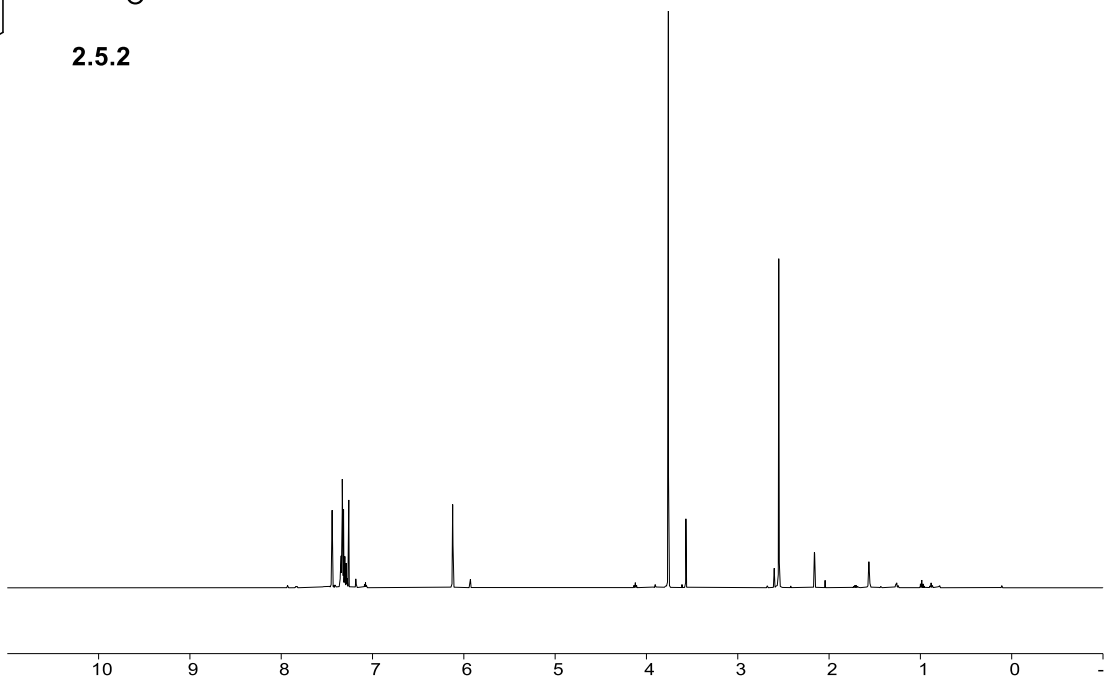
2.5.2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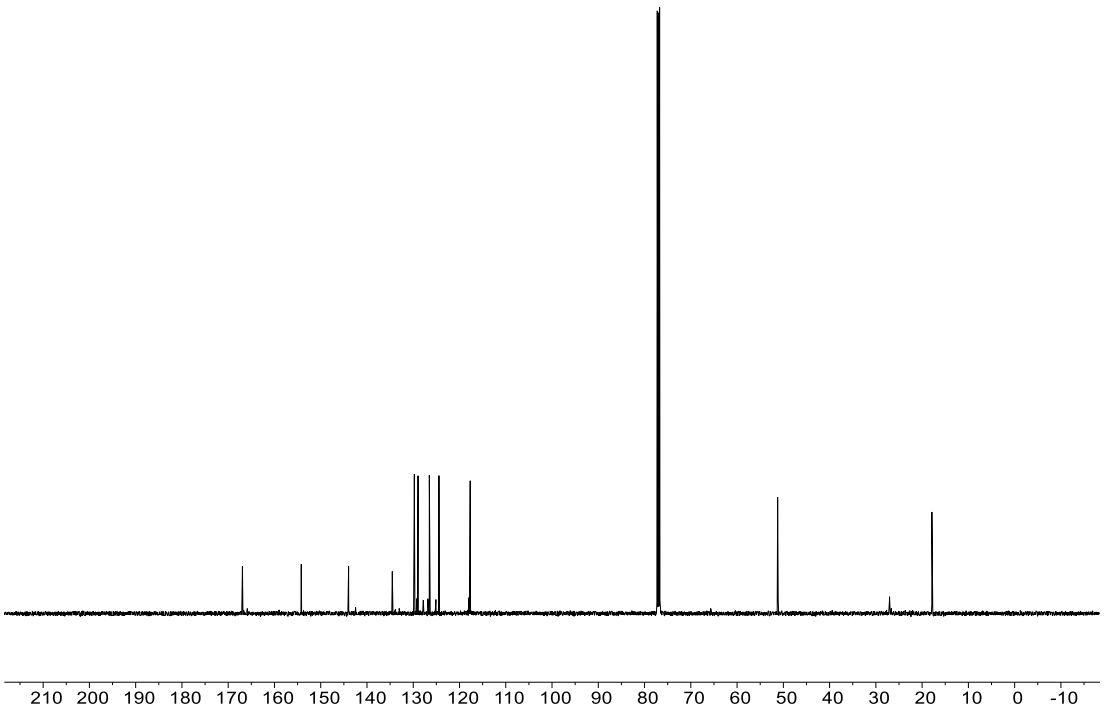
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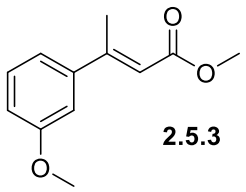

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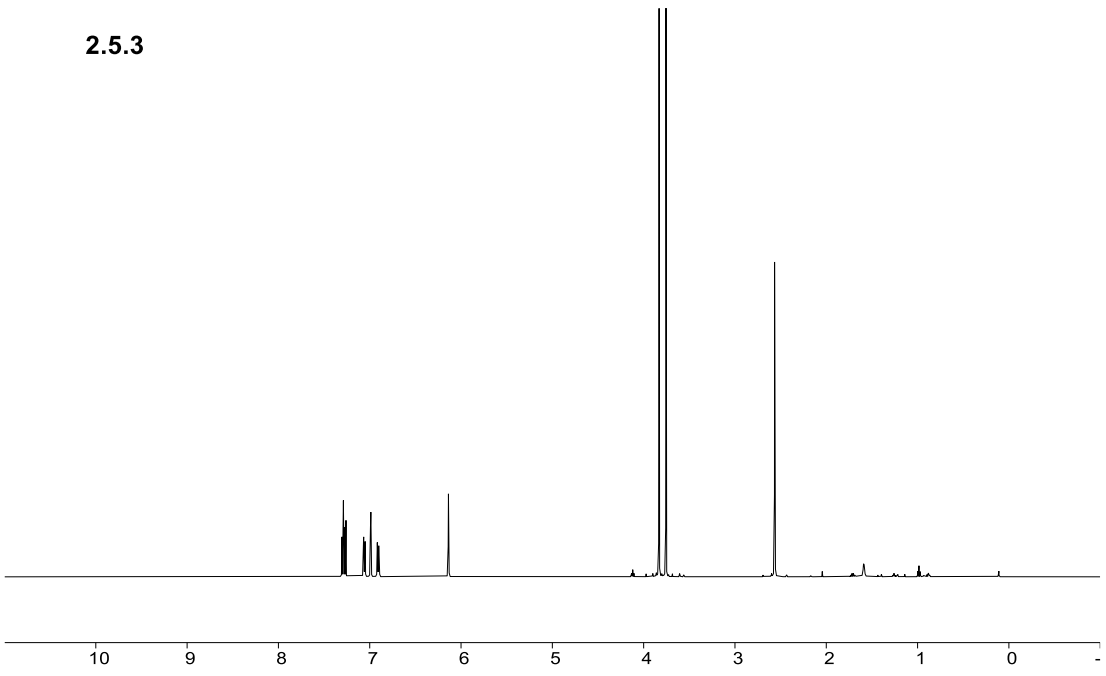
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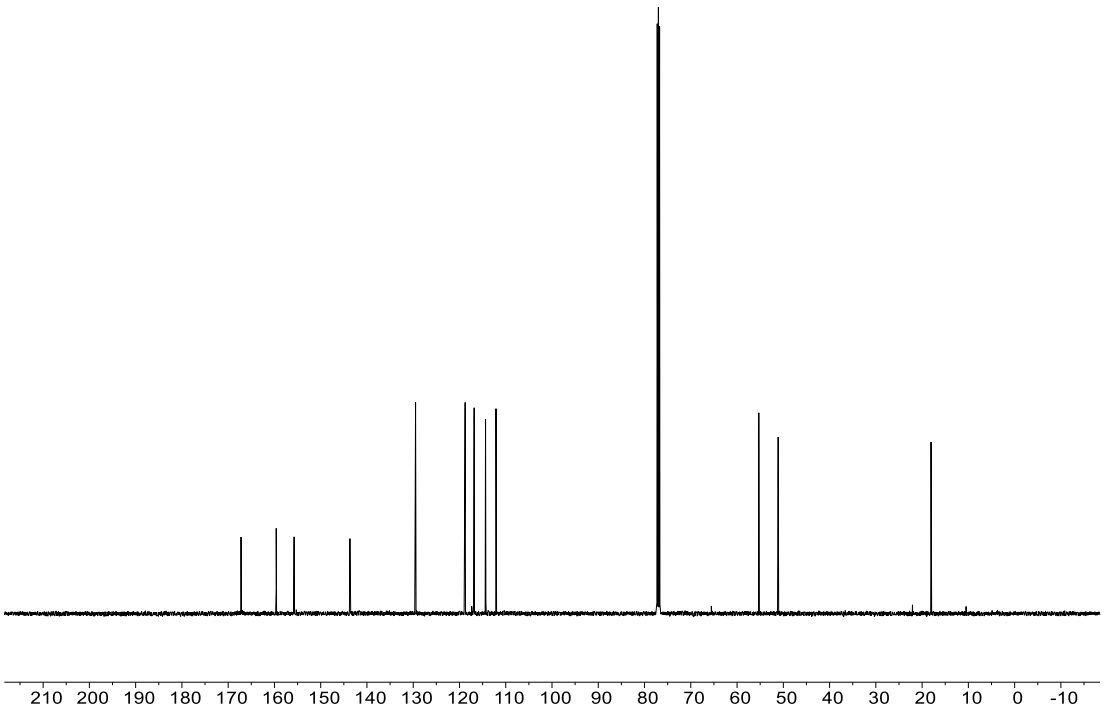
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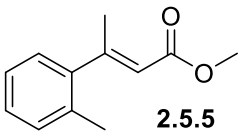

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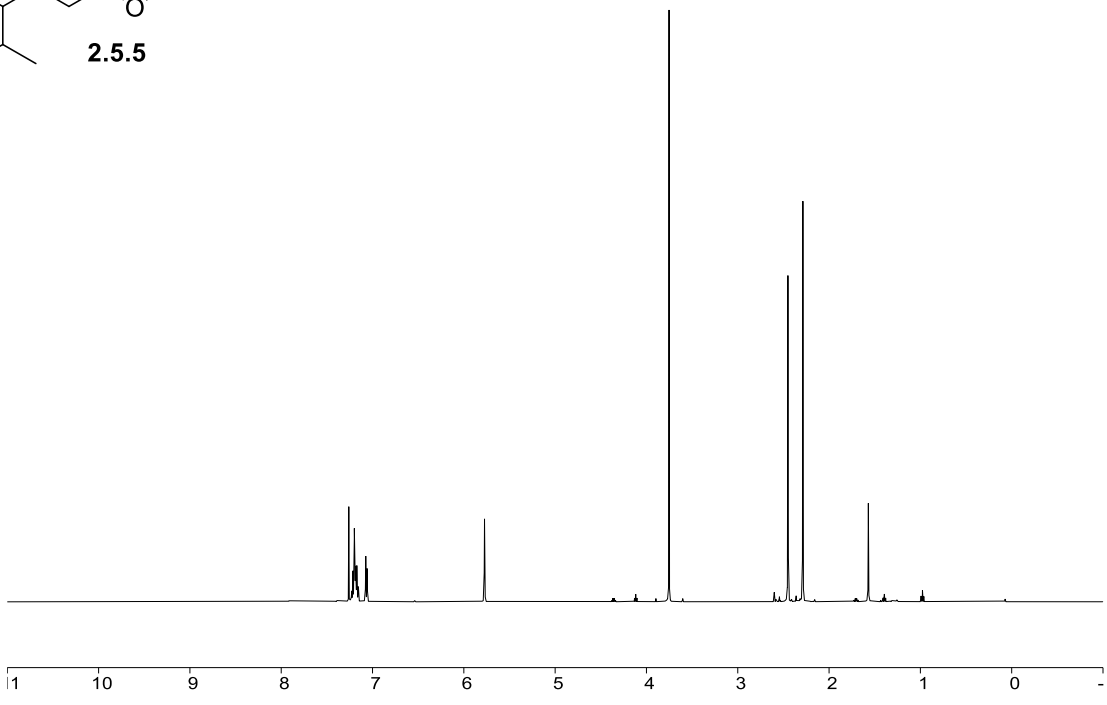
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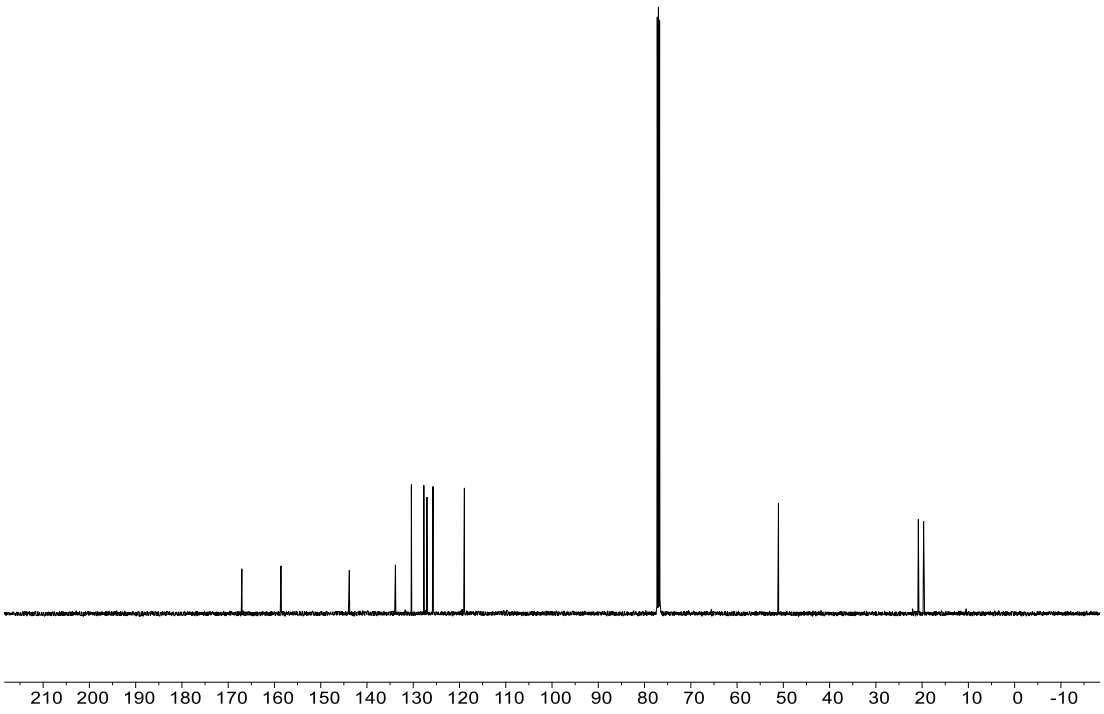
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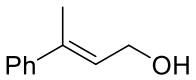

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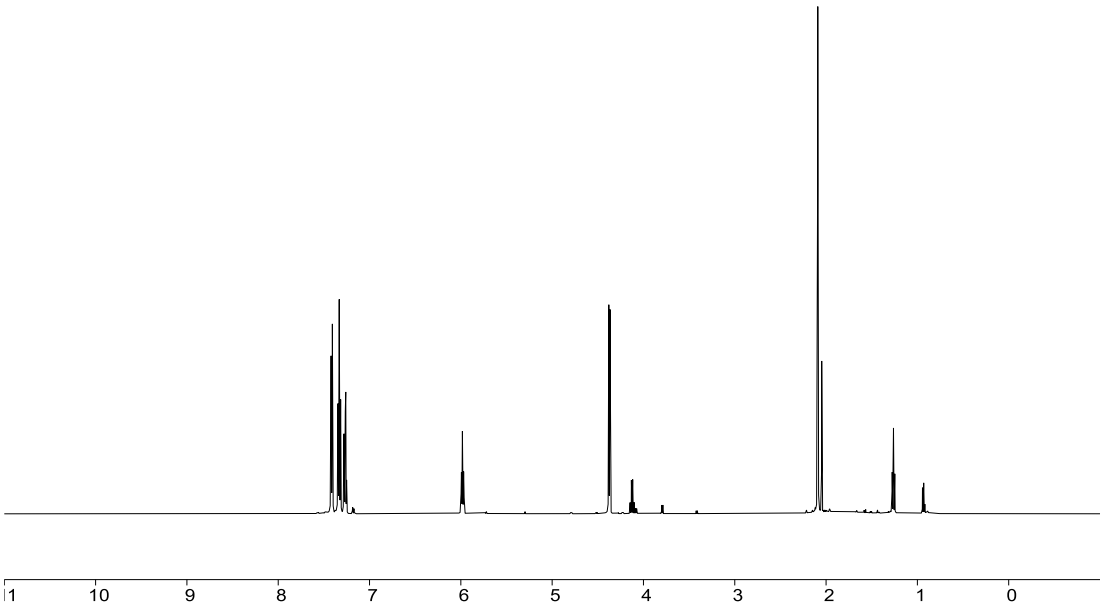

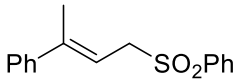
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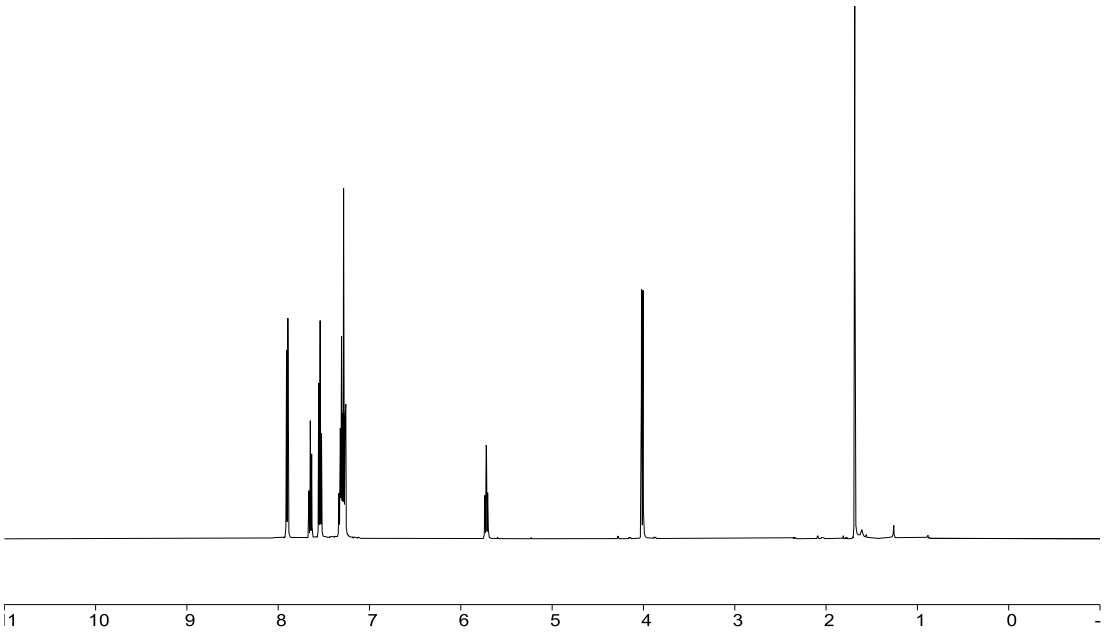
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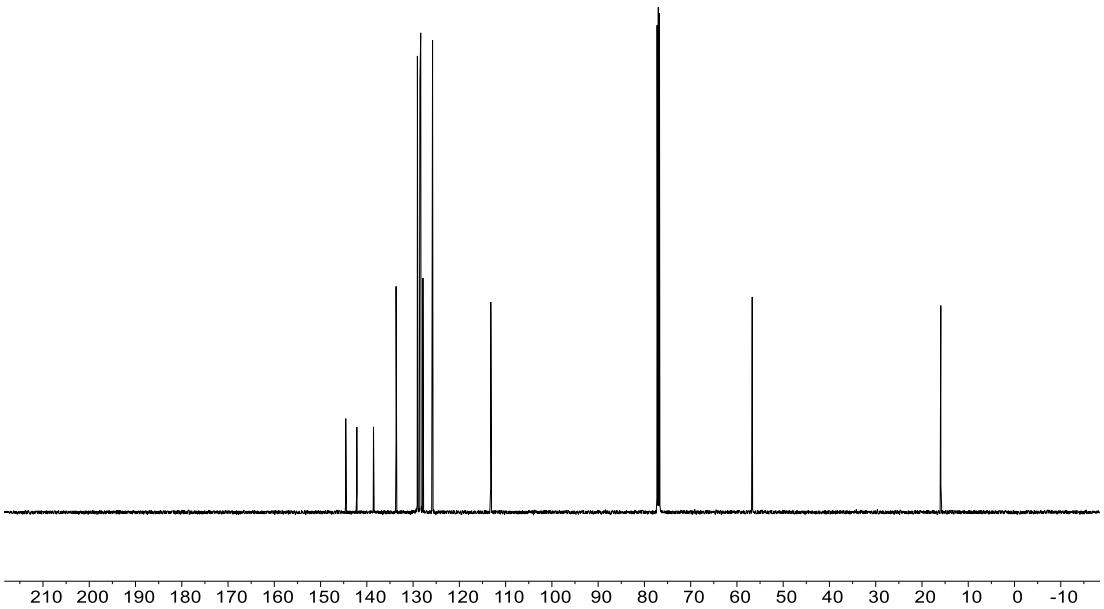
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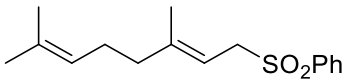

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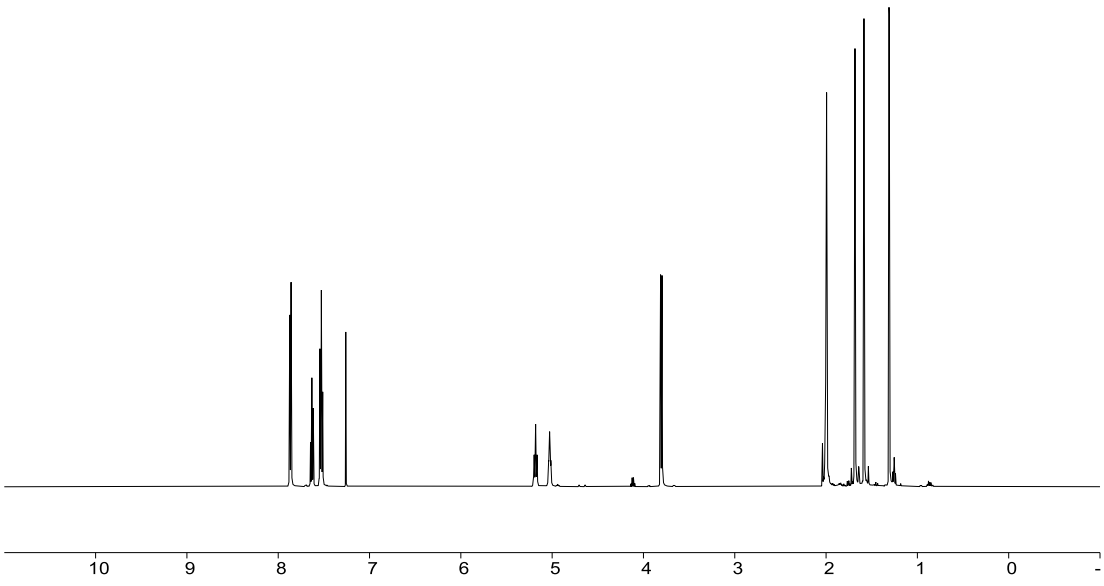

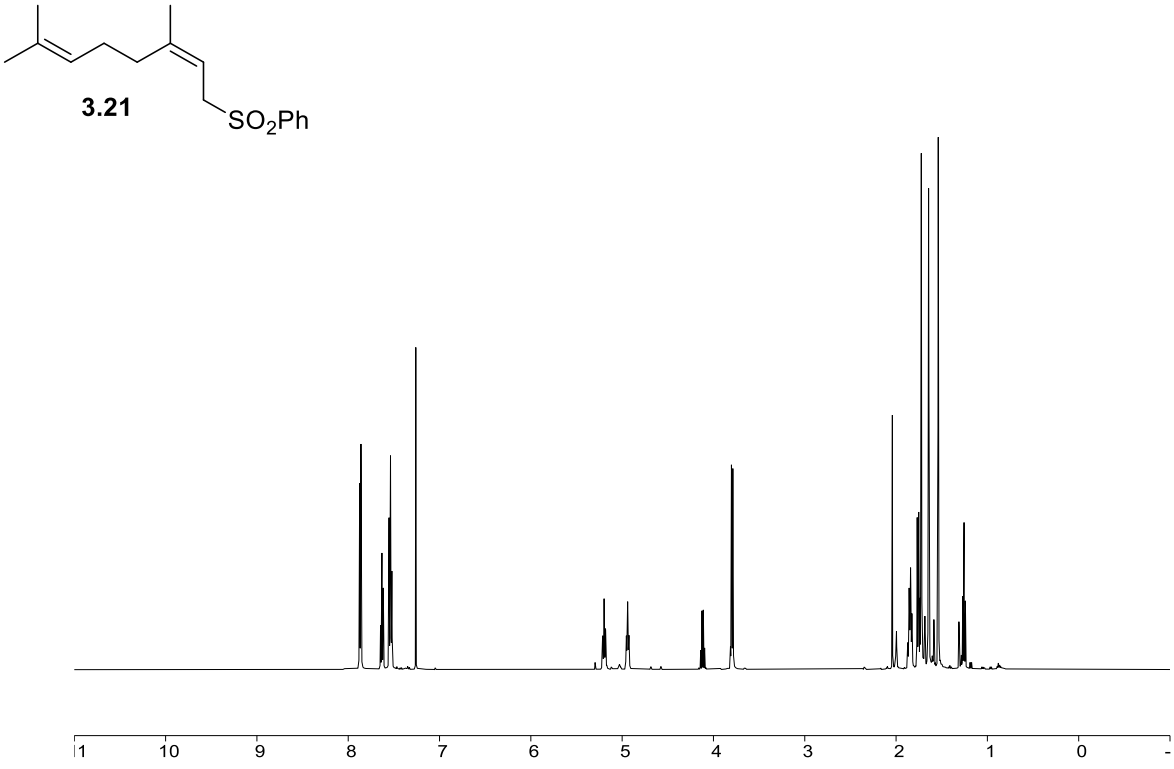
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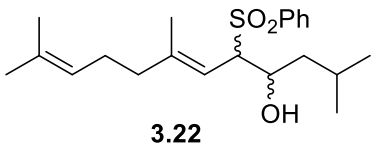

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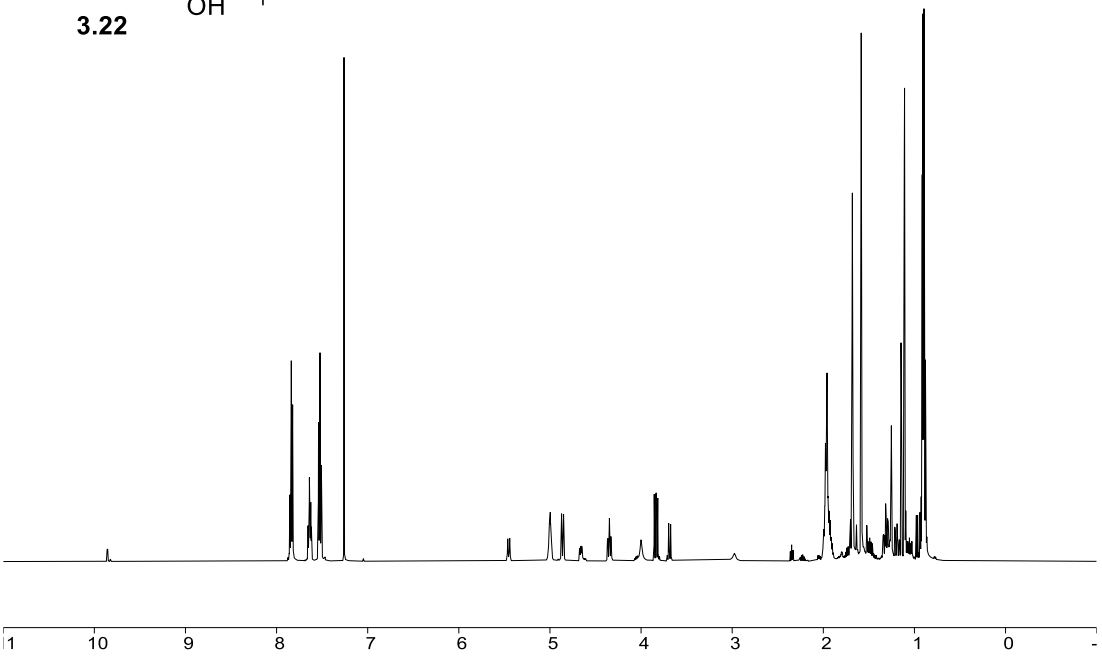

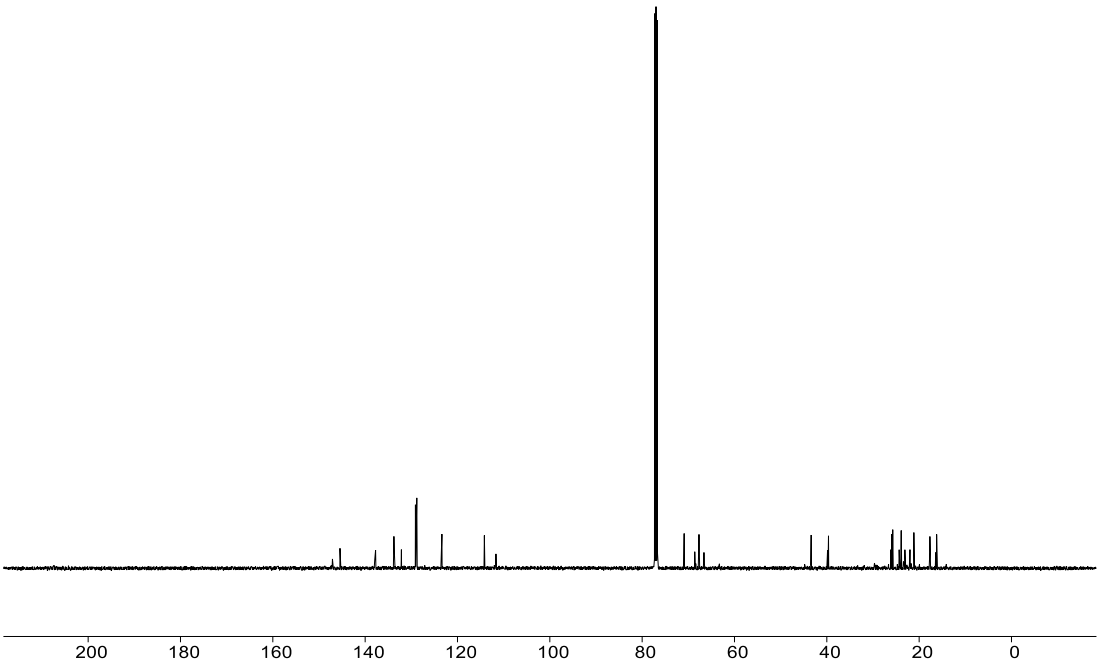

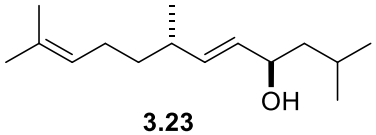

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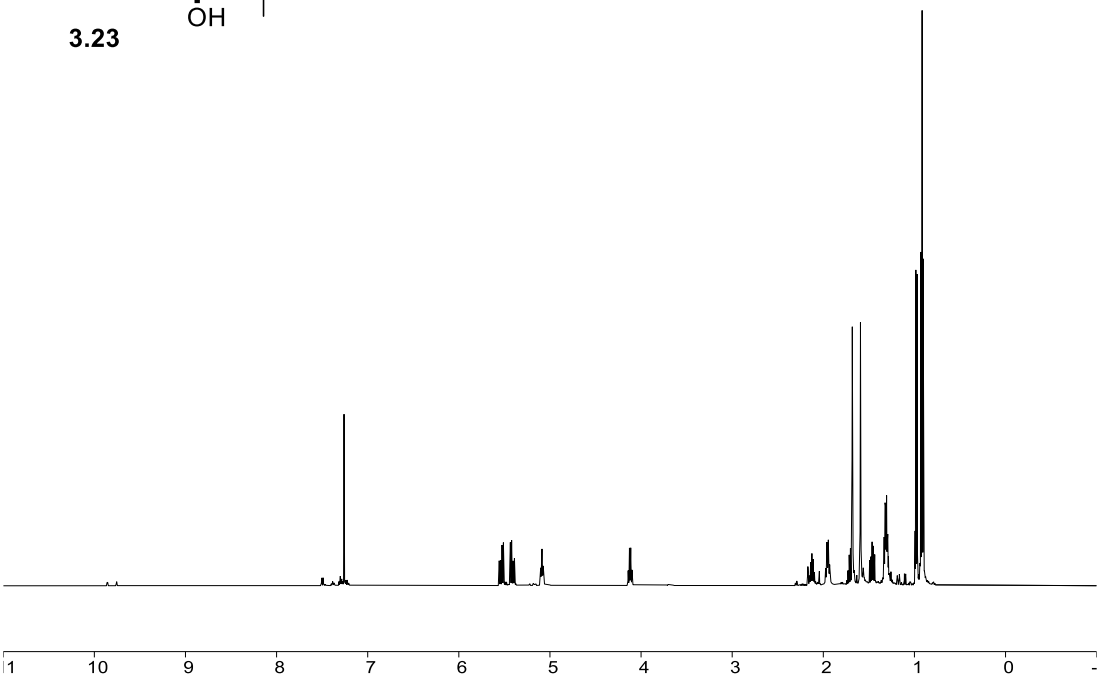

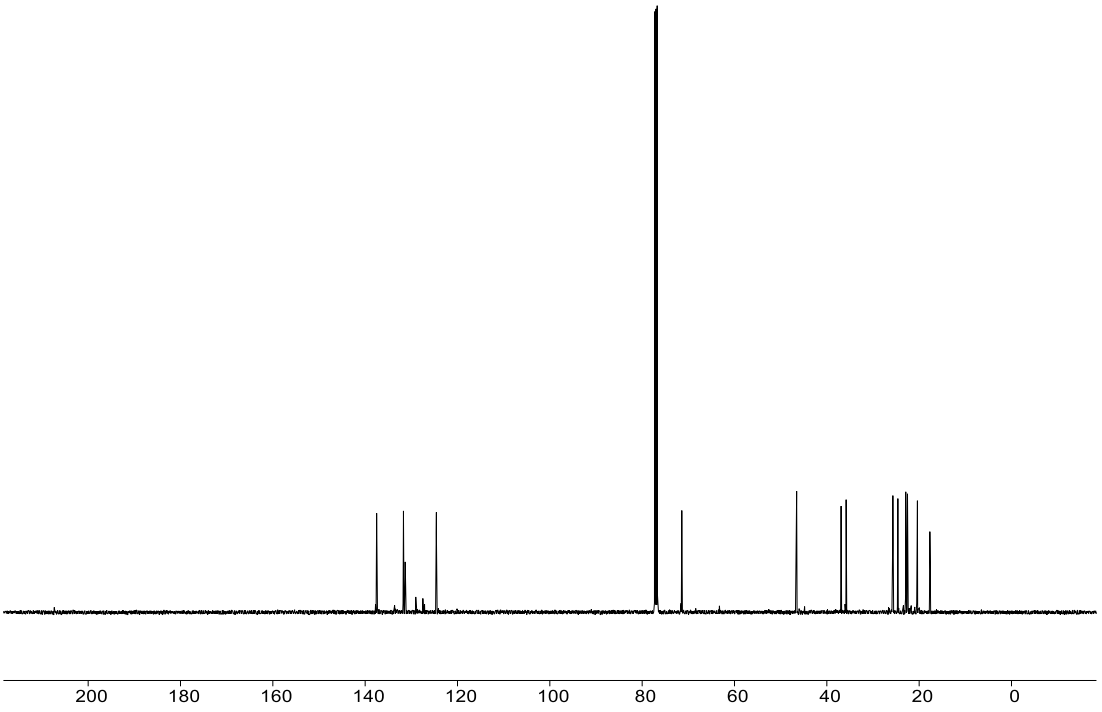

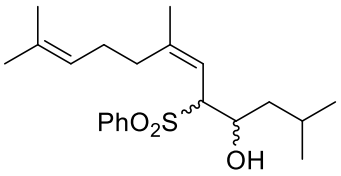

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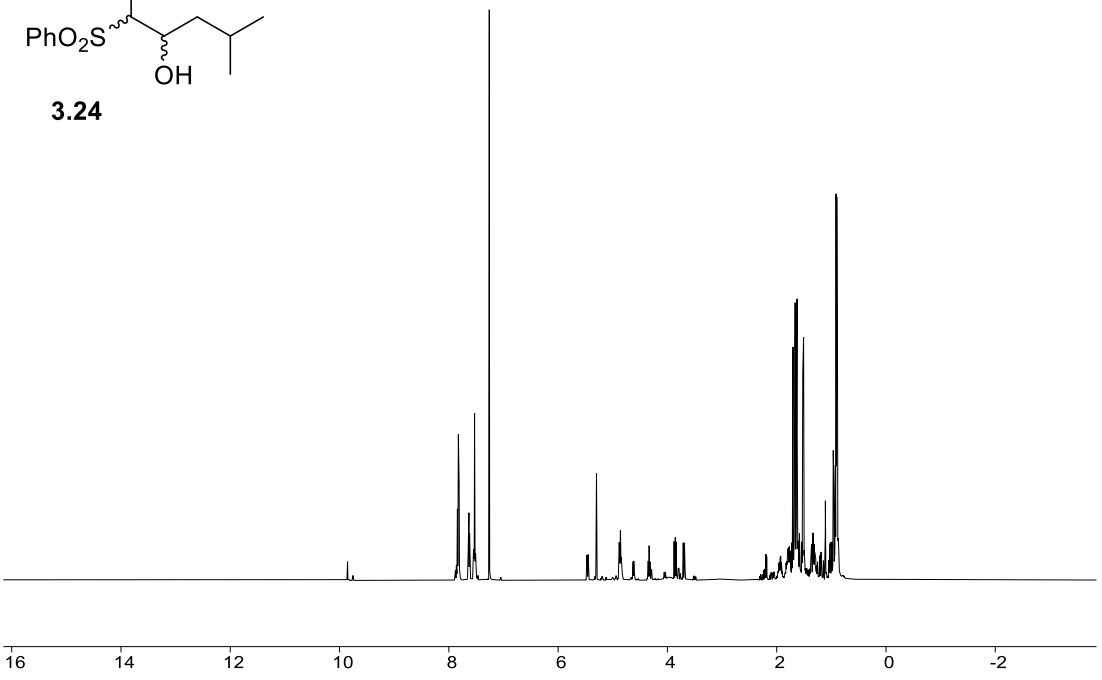

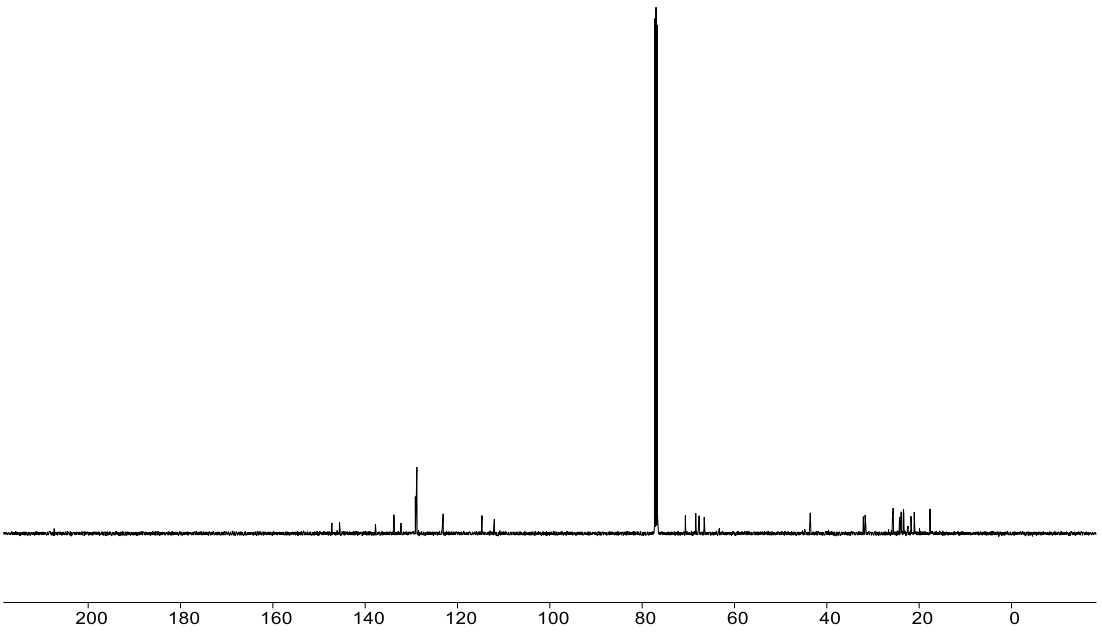

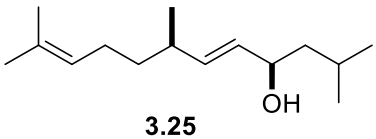

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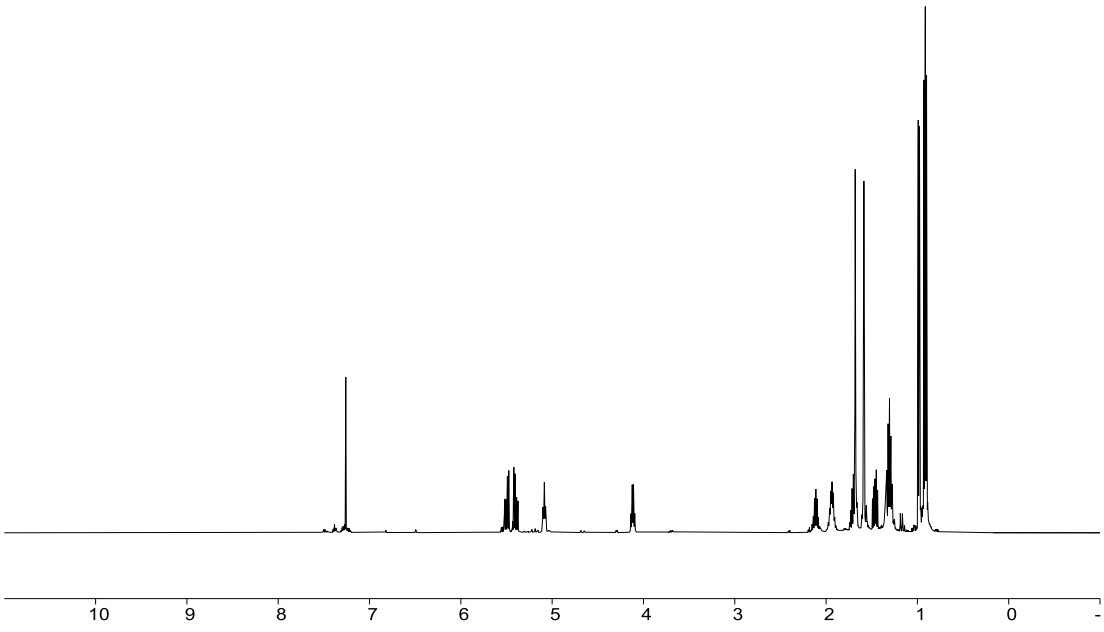

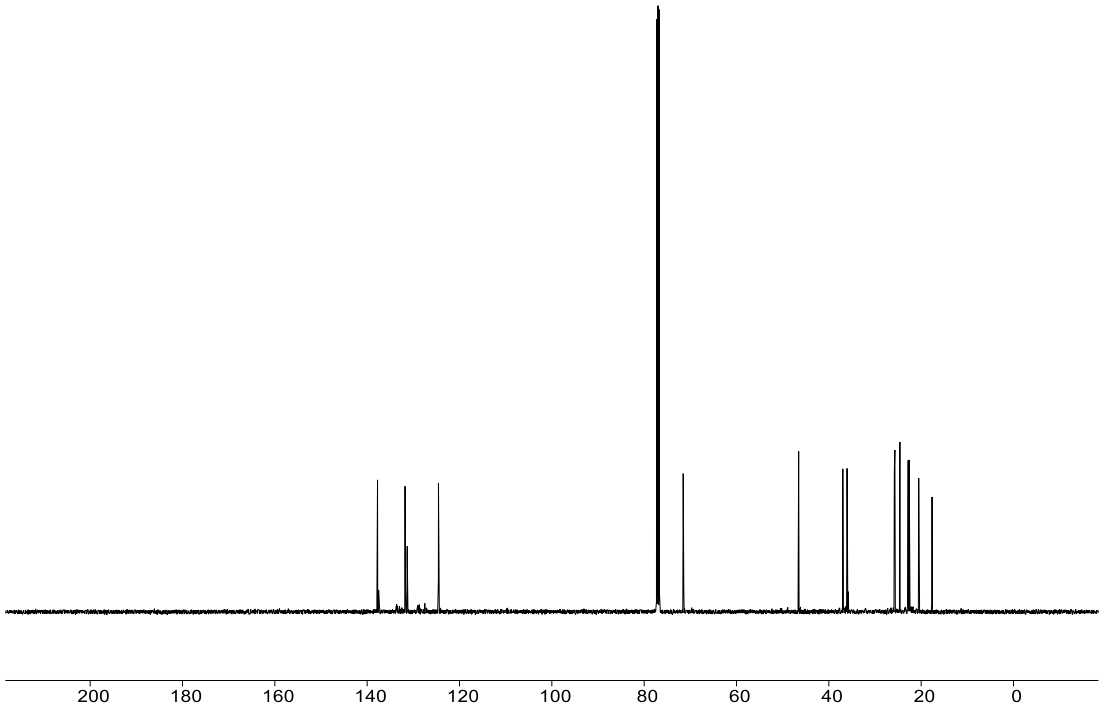

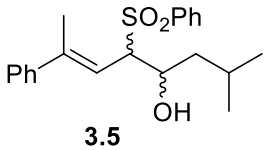
SO2Ph
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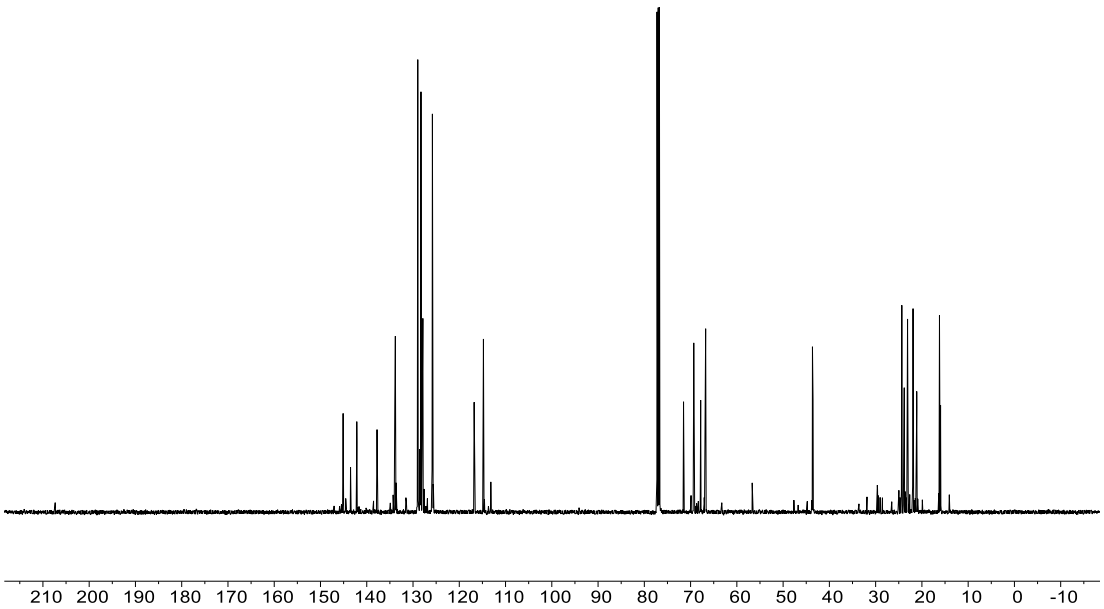
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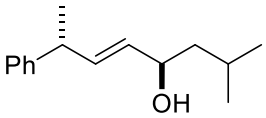
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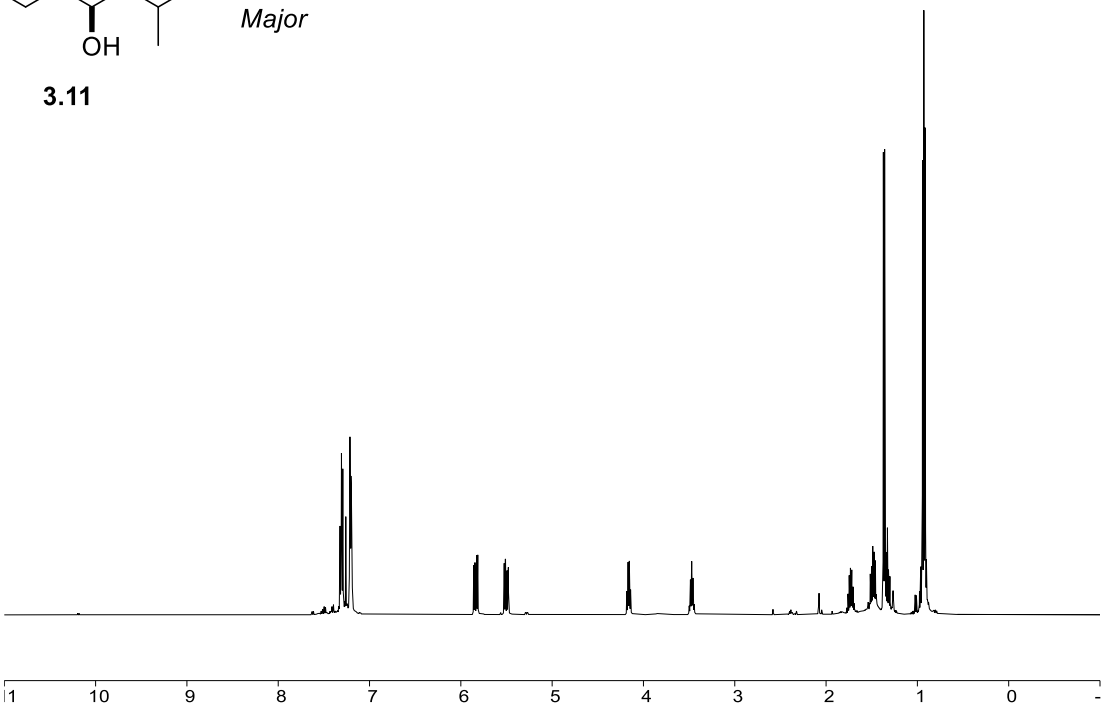
Major

3.11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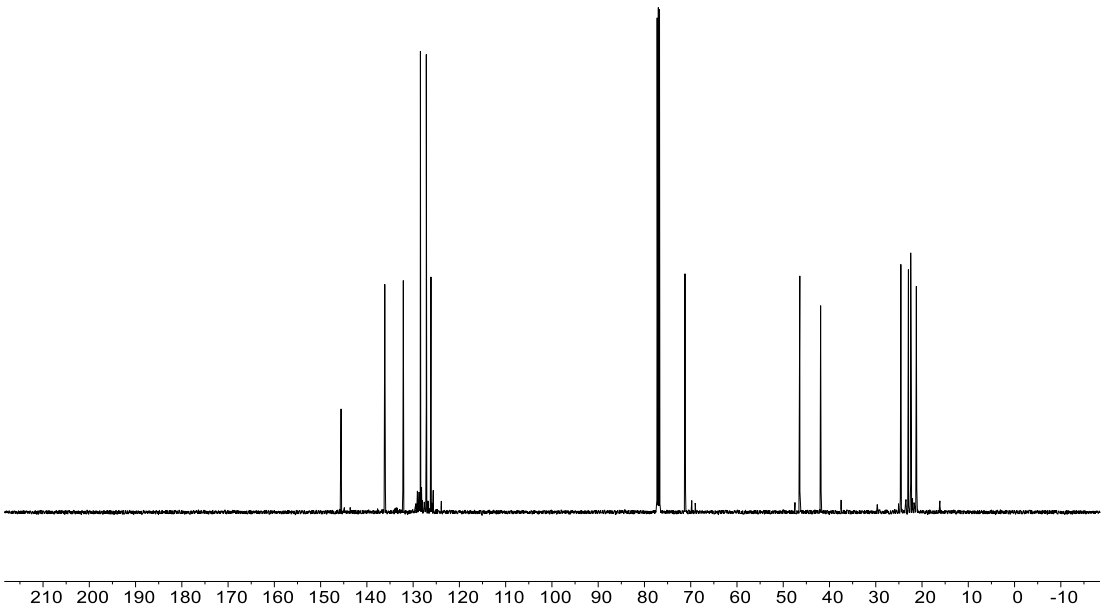
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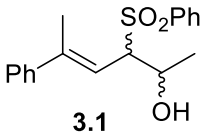
SO2Ph
Ph
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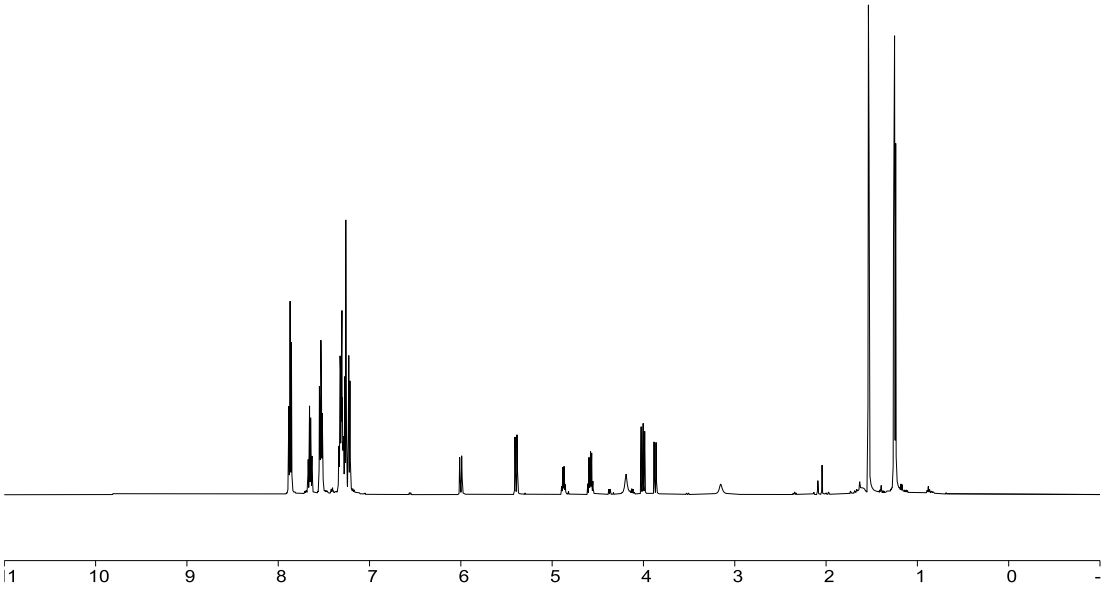
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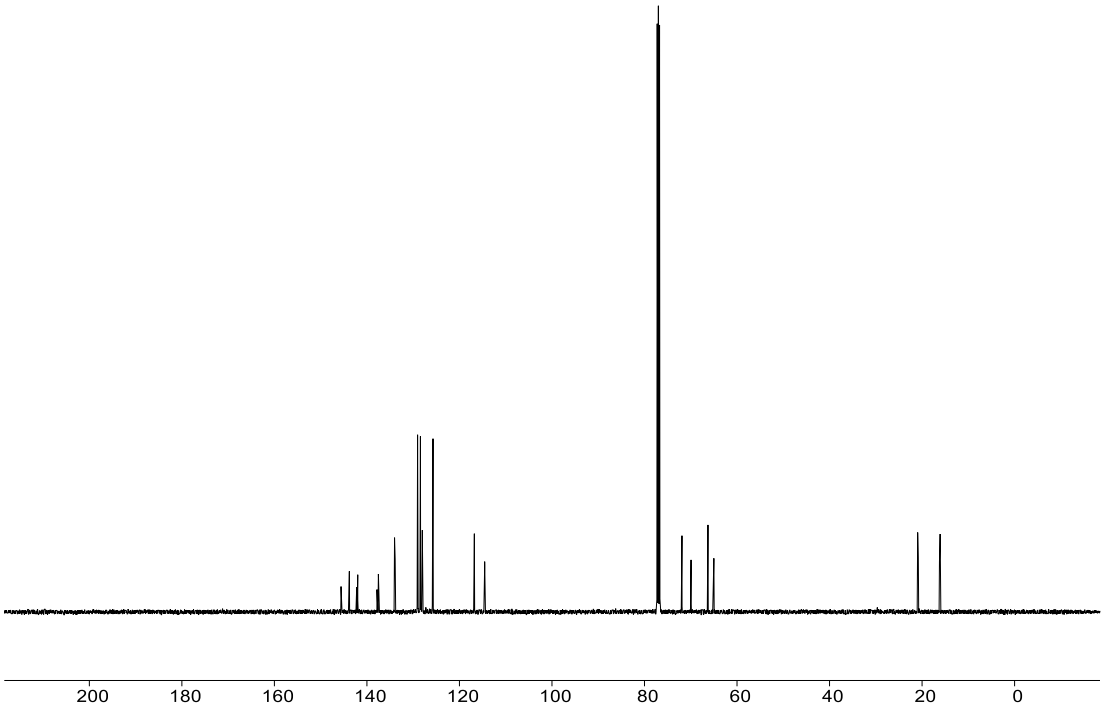
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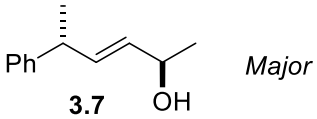

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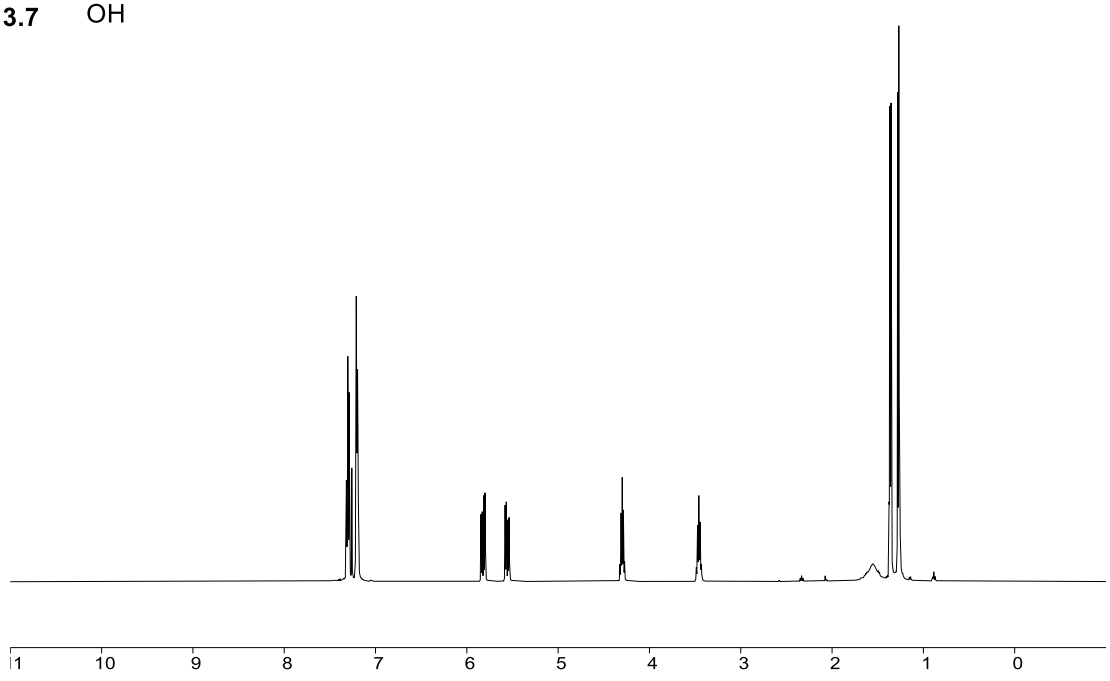

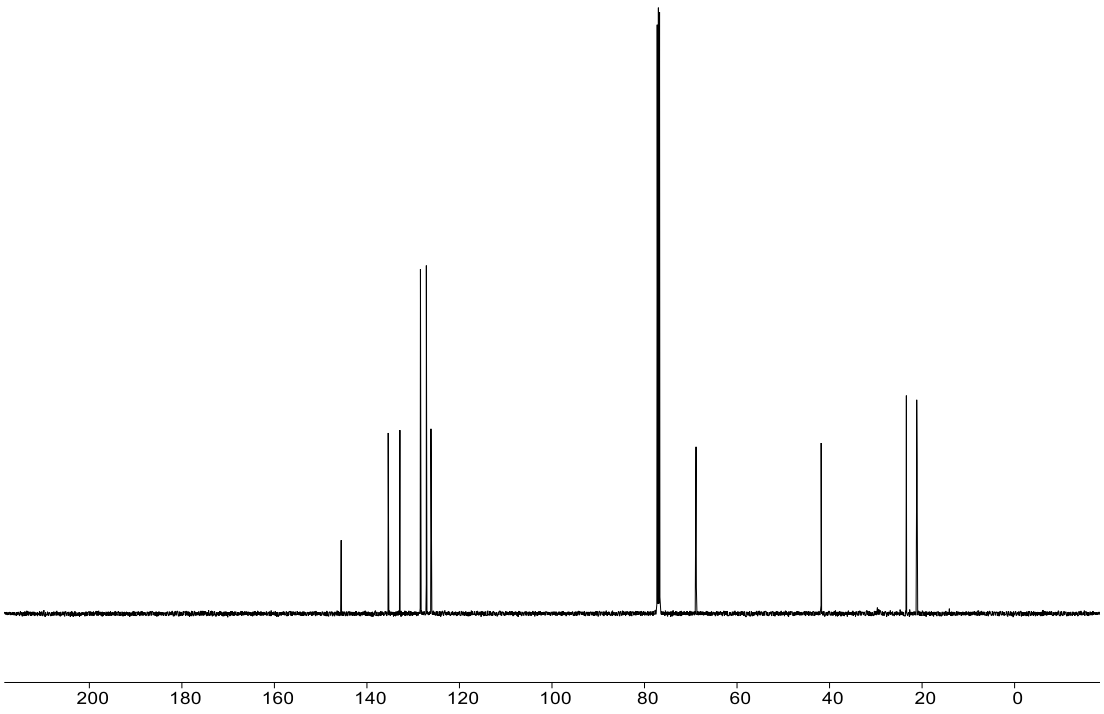

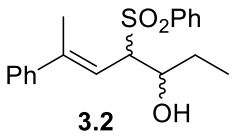

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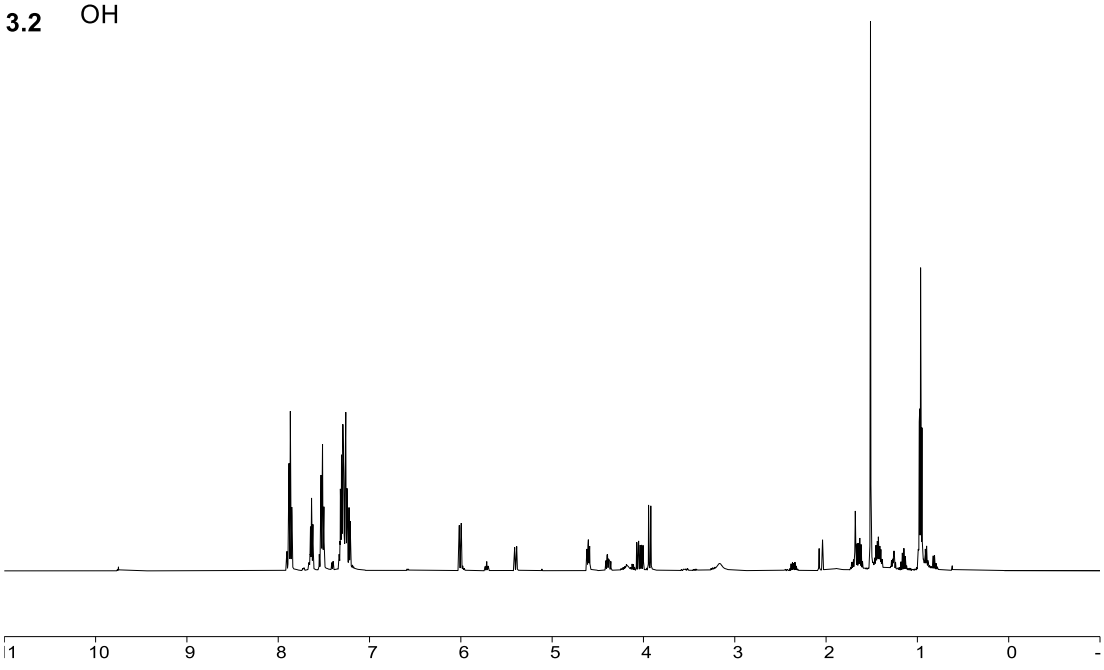

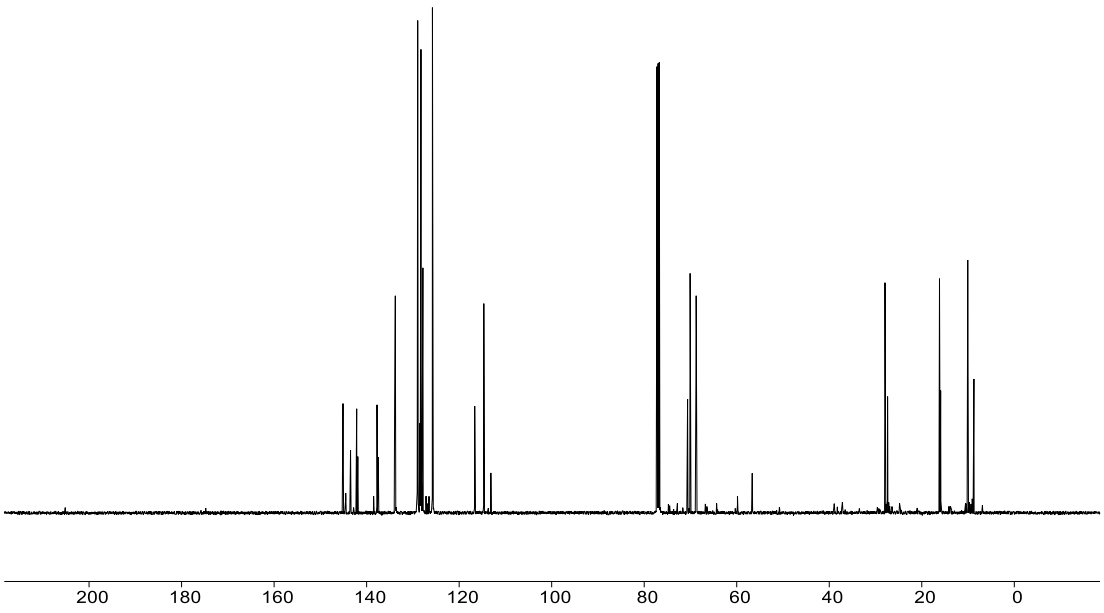

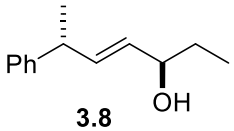
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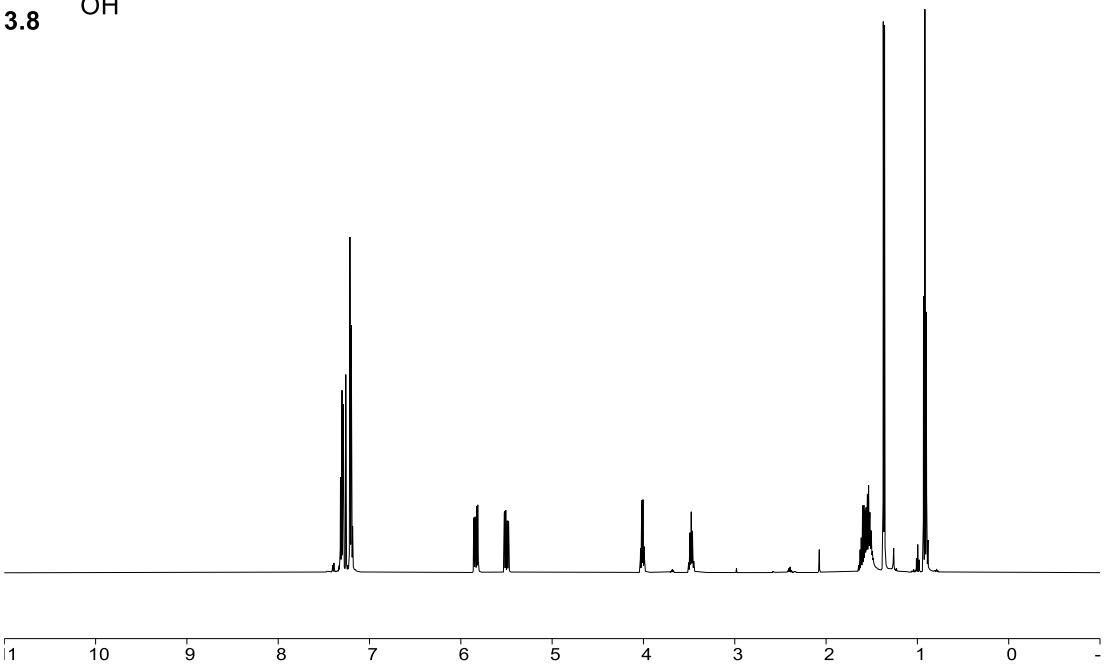
3.8 *Major*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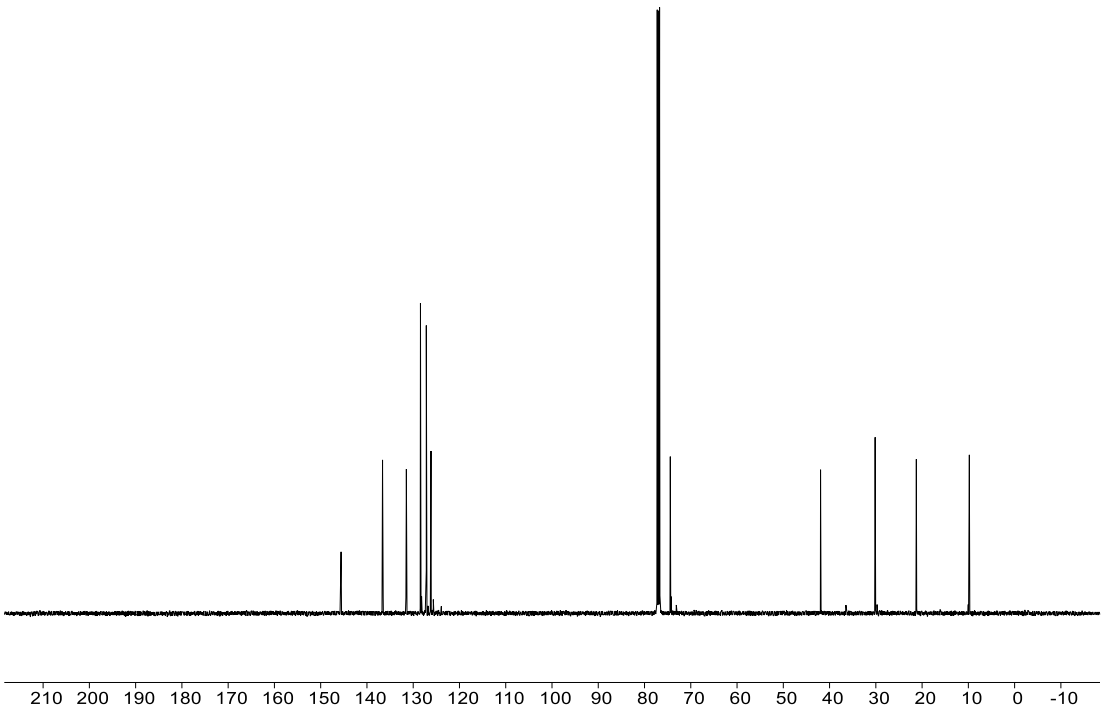
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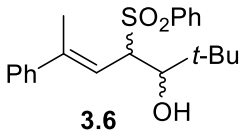
SO2Ph
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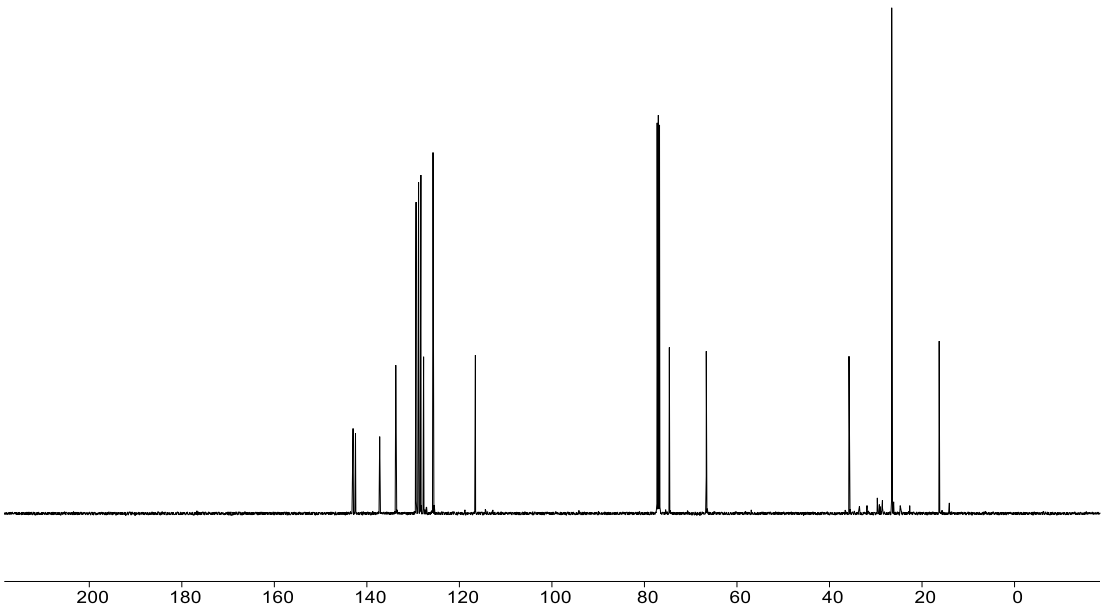
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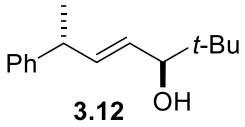
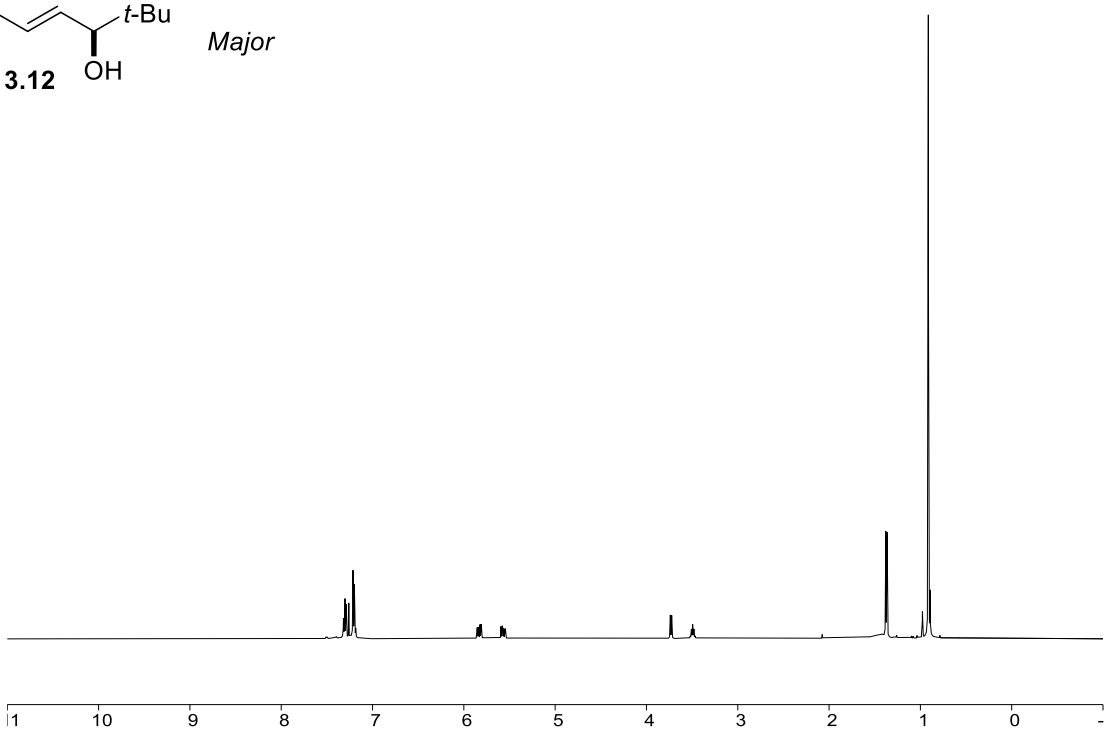
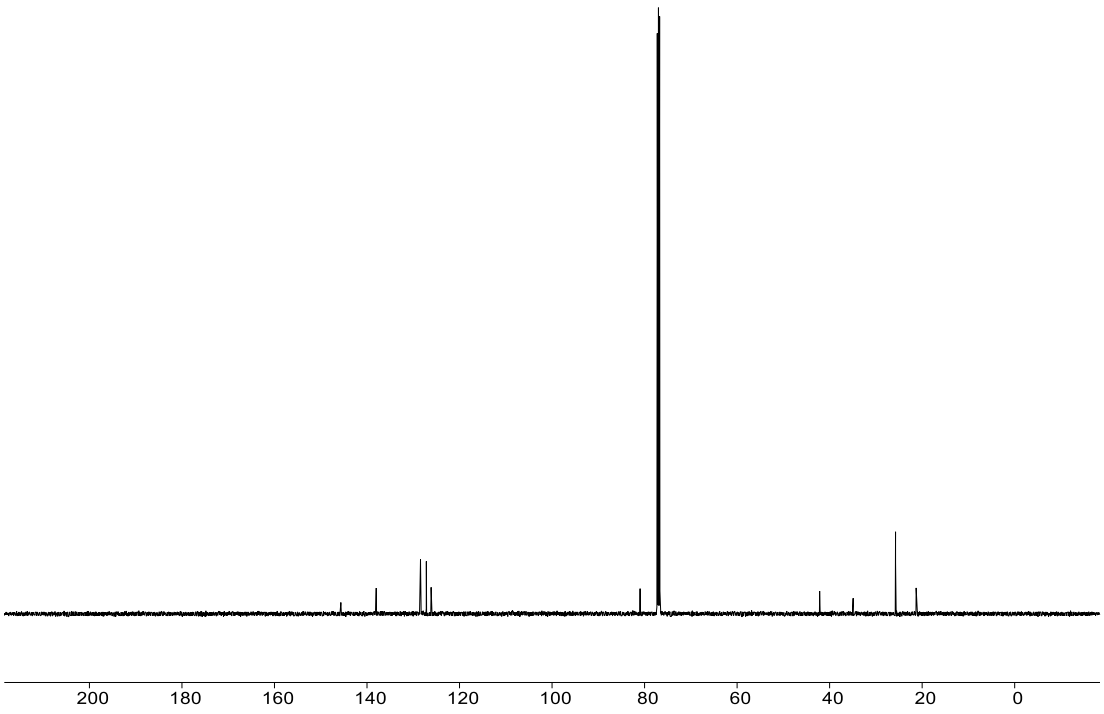
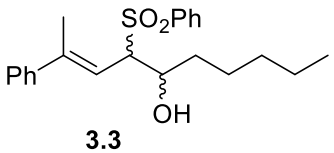


3.12 *Major*






SO2Ph
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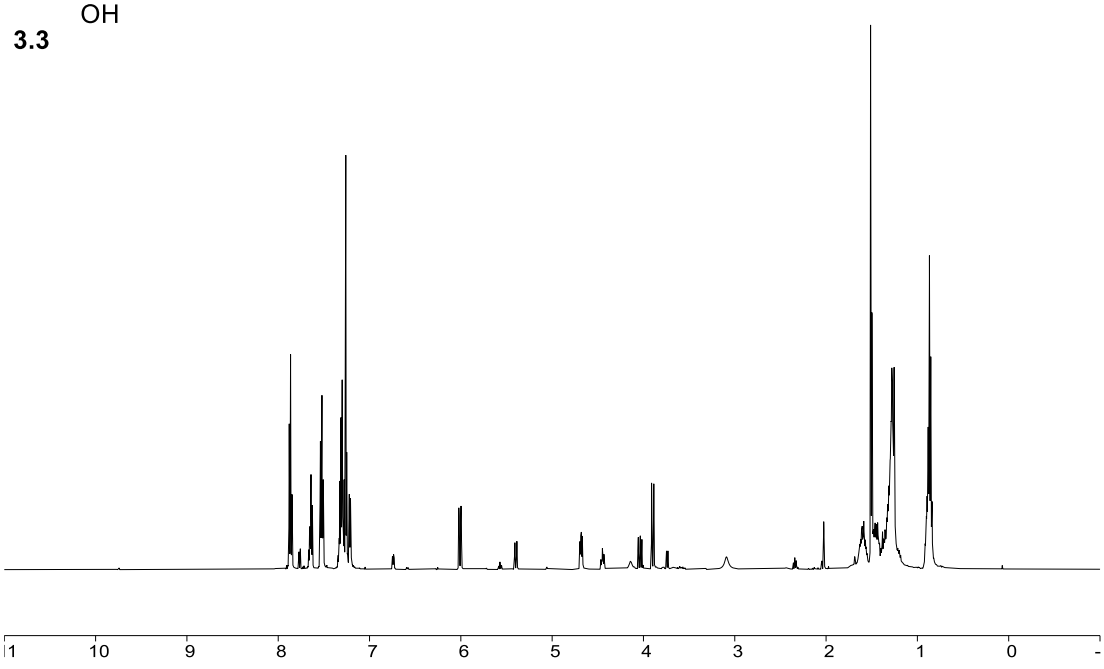
OH

3.3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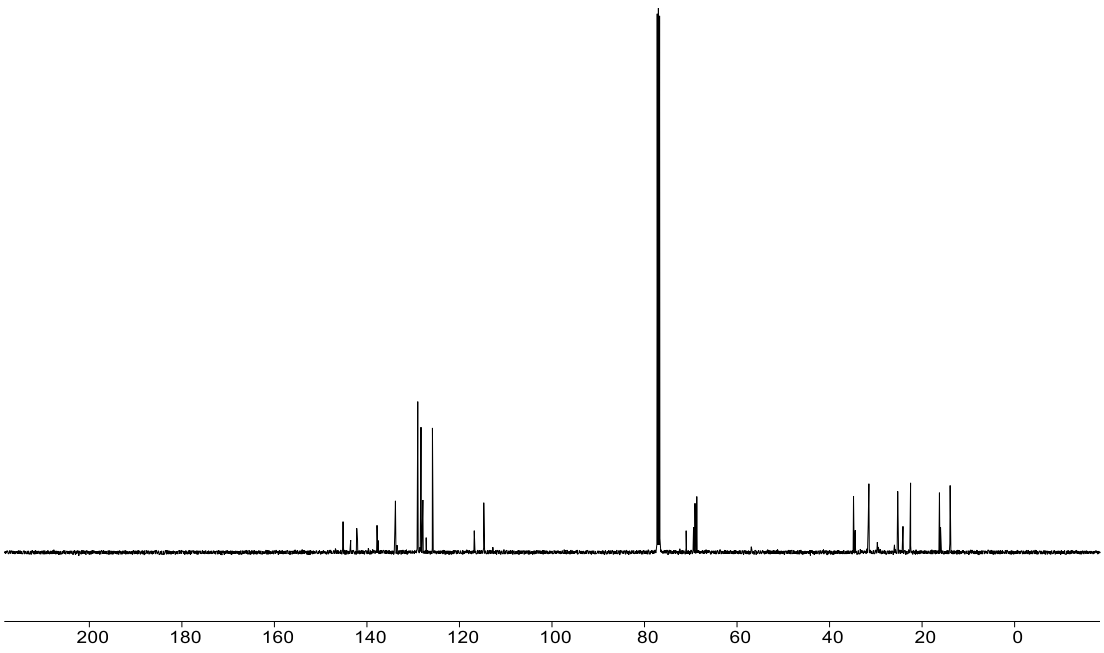
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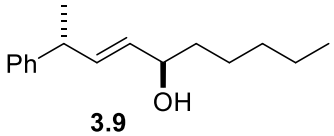
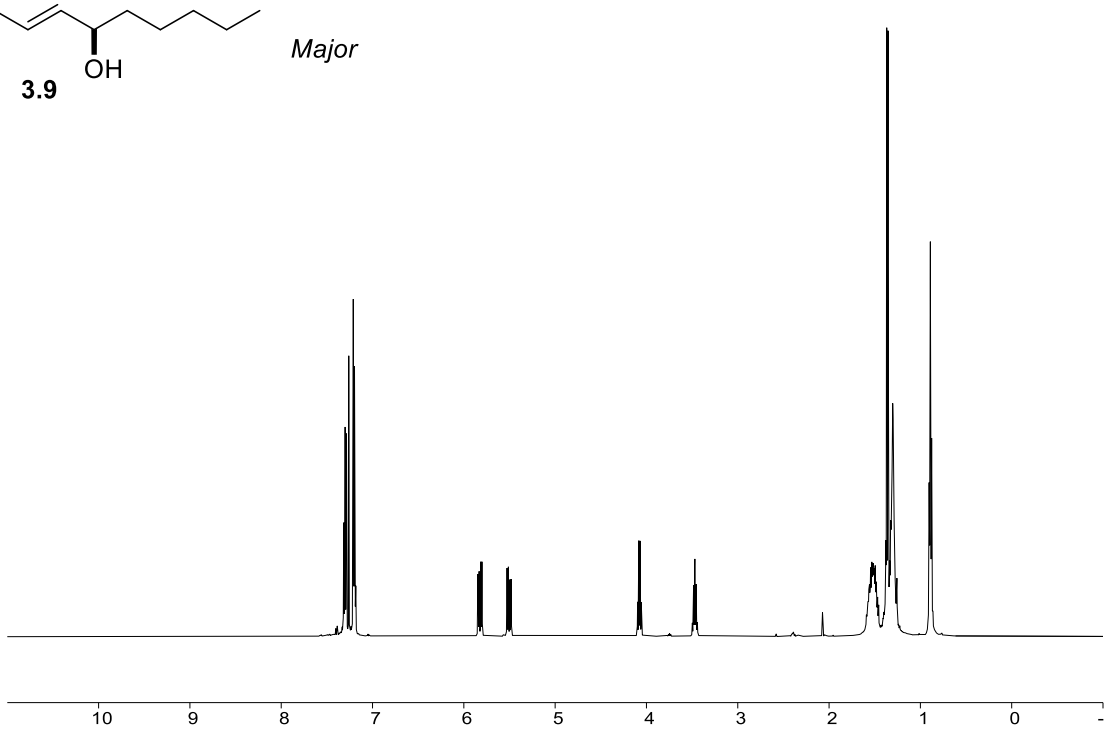
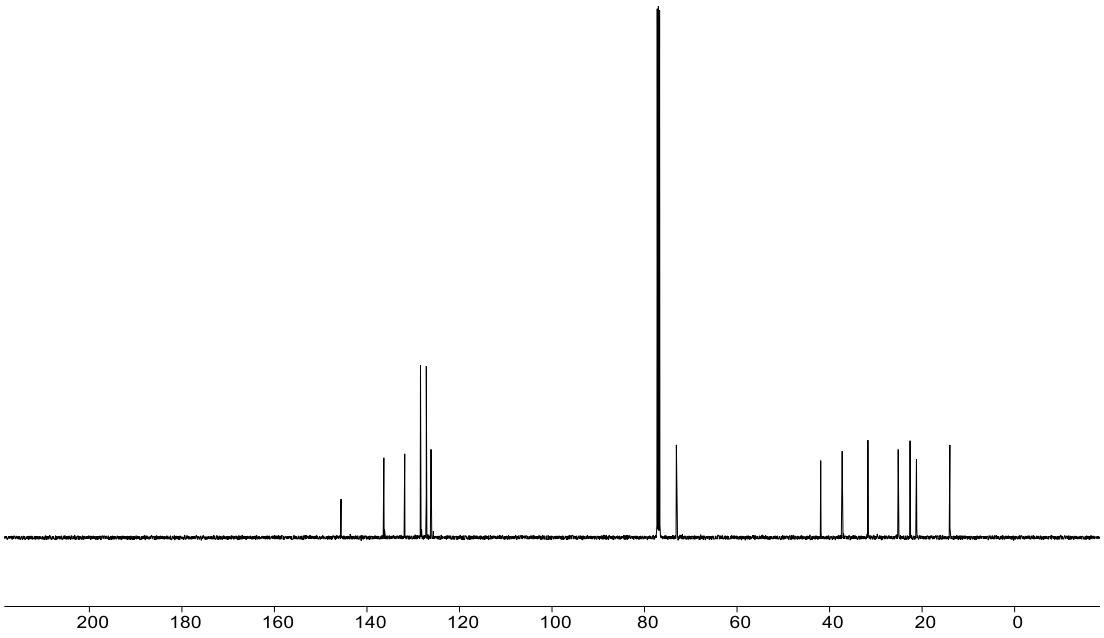
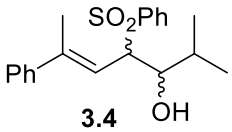


3.9

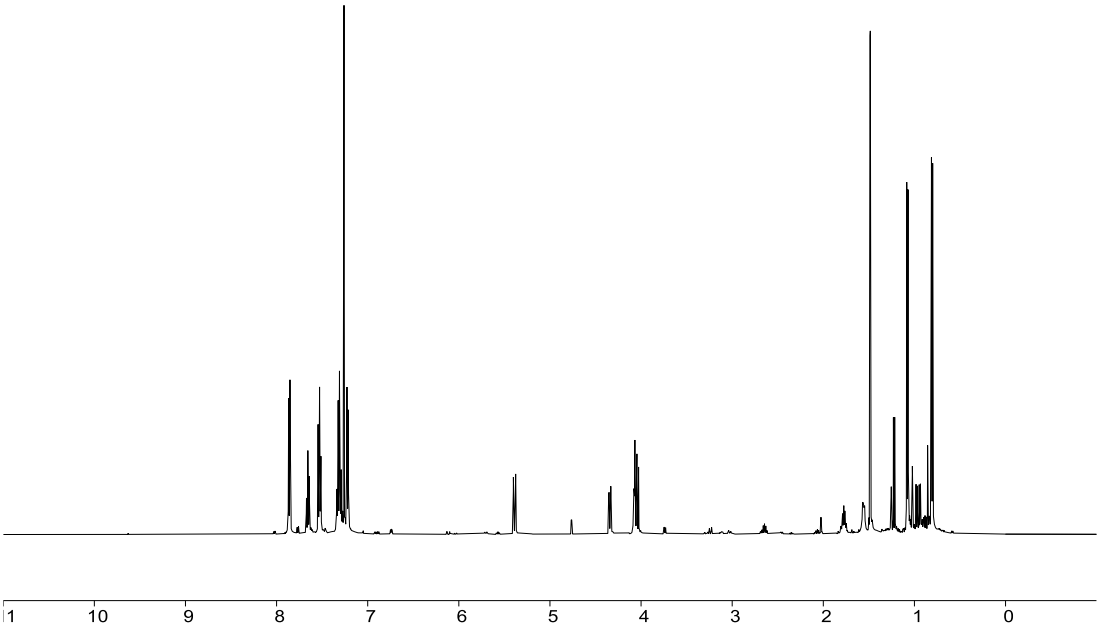
Major






SO2Ph
Ph
OH

3.4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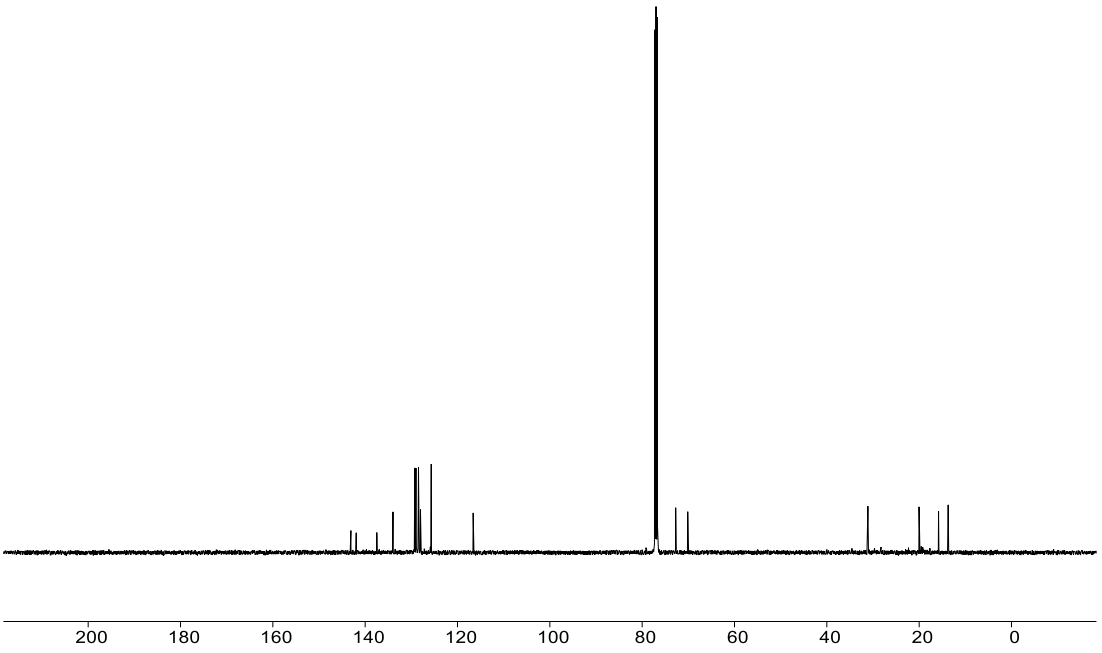
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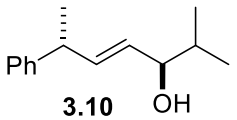
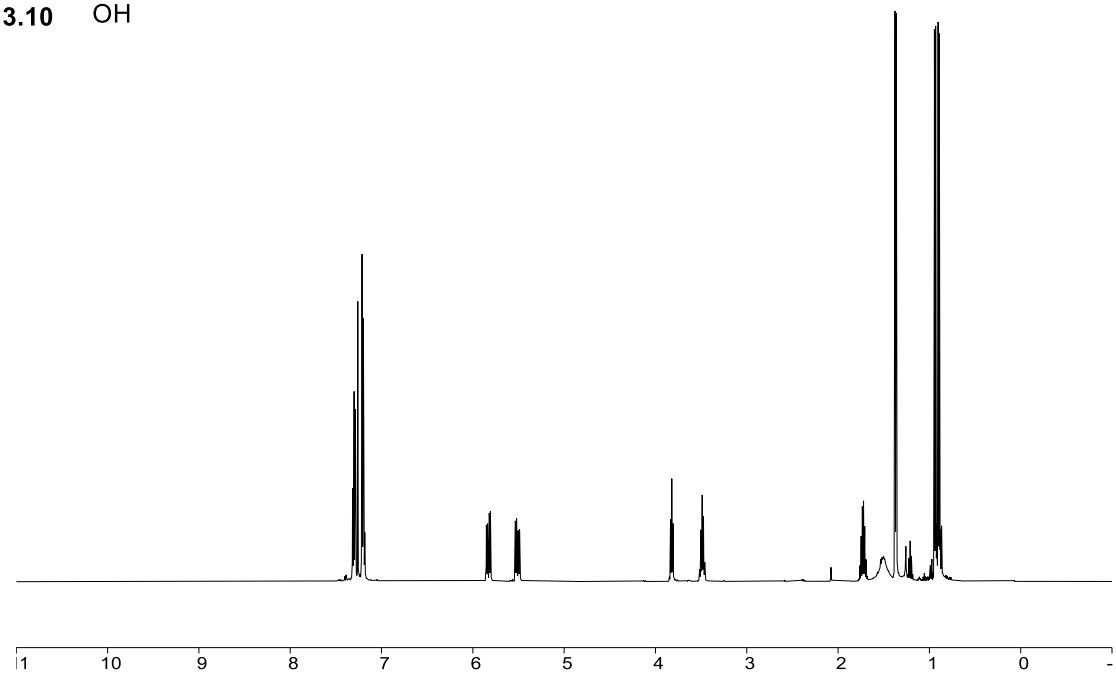
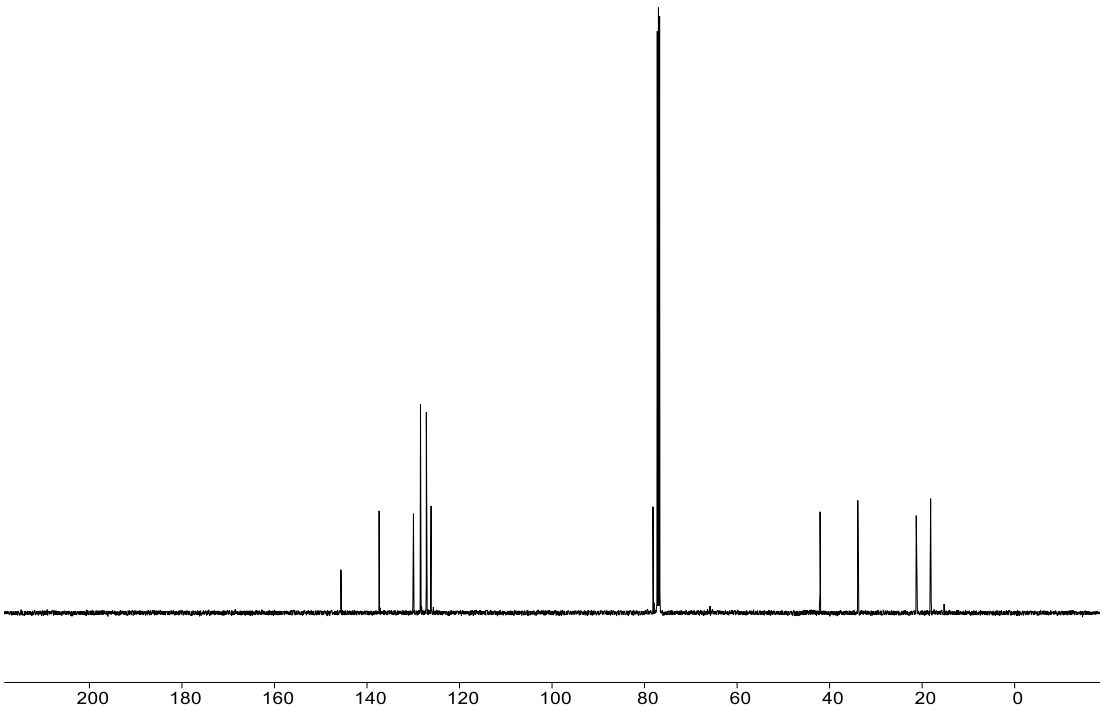
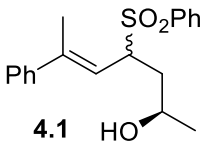


3.10 *Major*






SO2Ph
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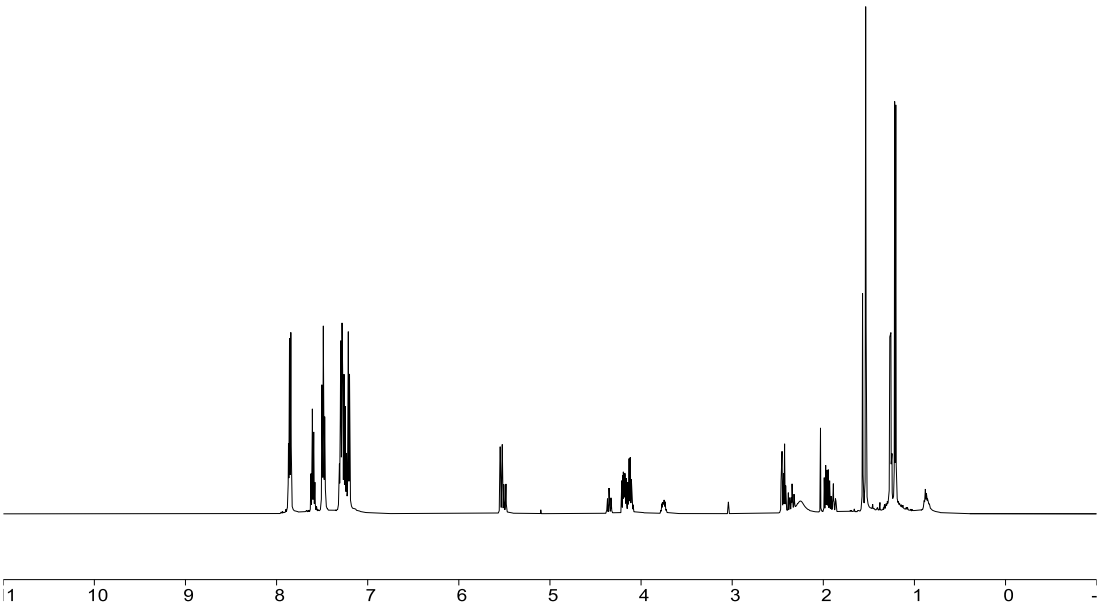
4.1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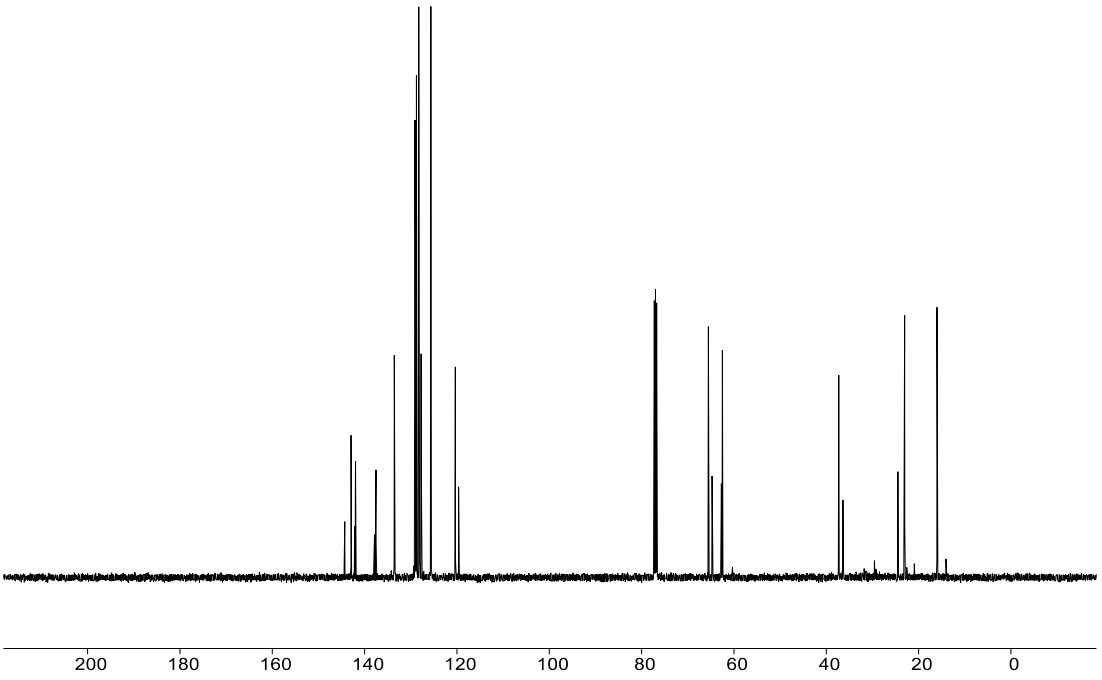
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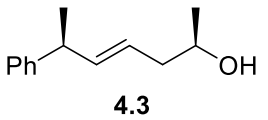
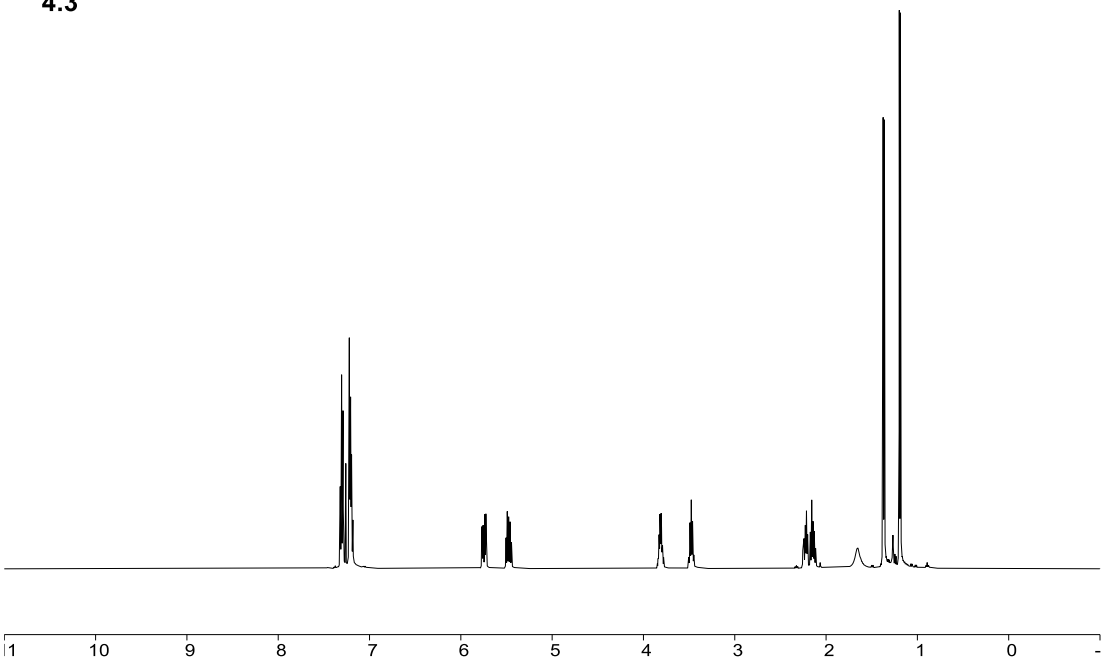
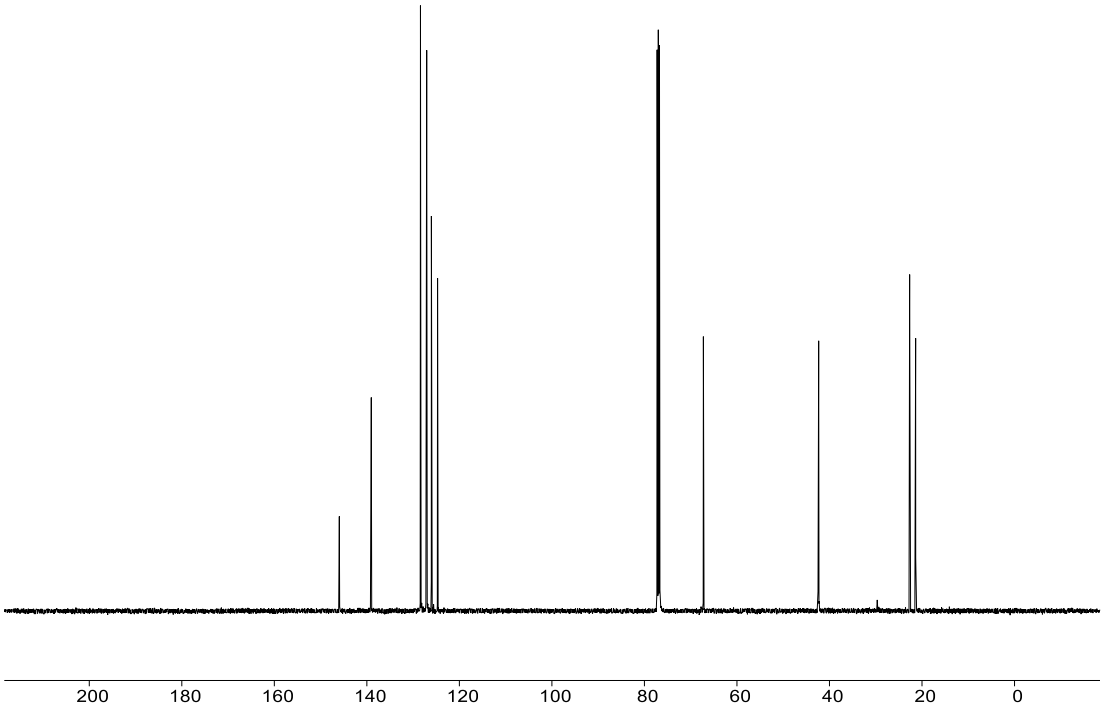
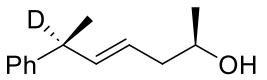


4.3 *Major*

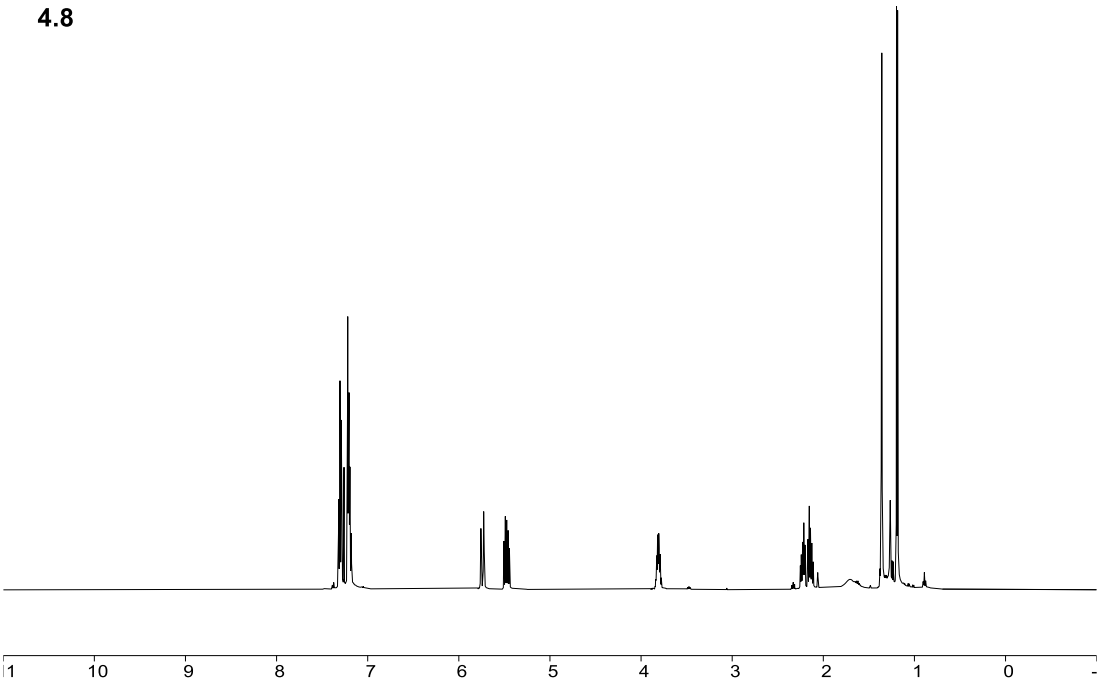


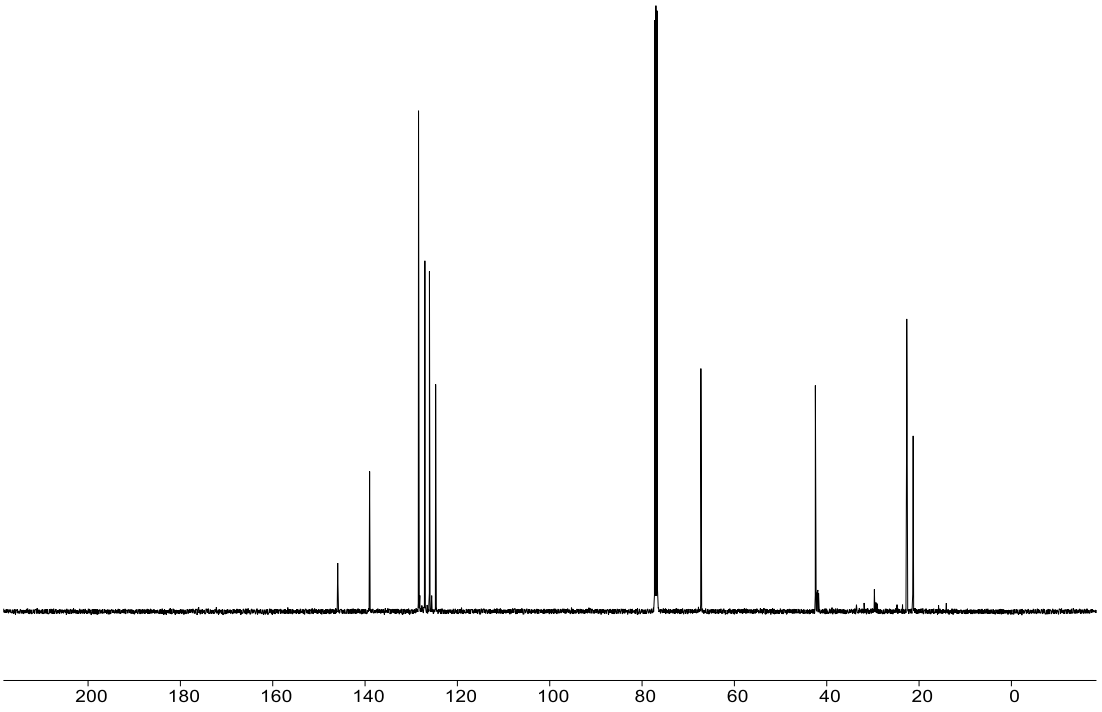


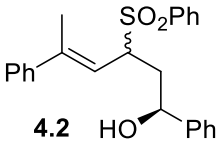


4.8

Major






SO2Ph
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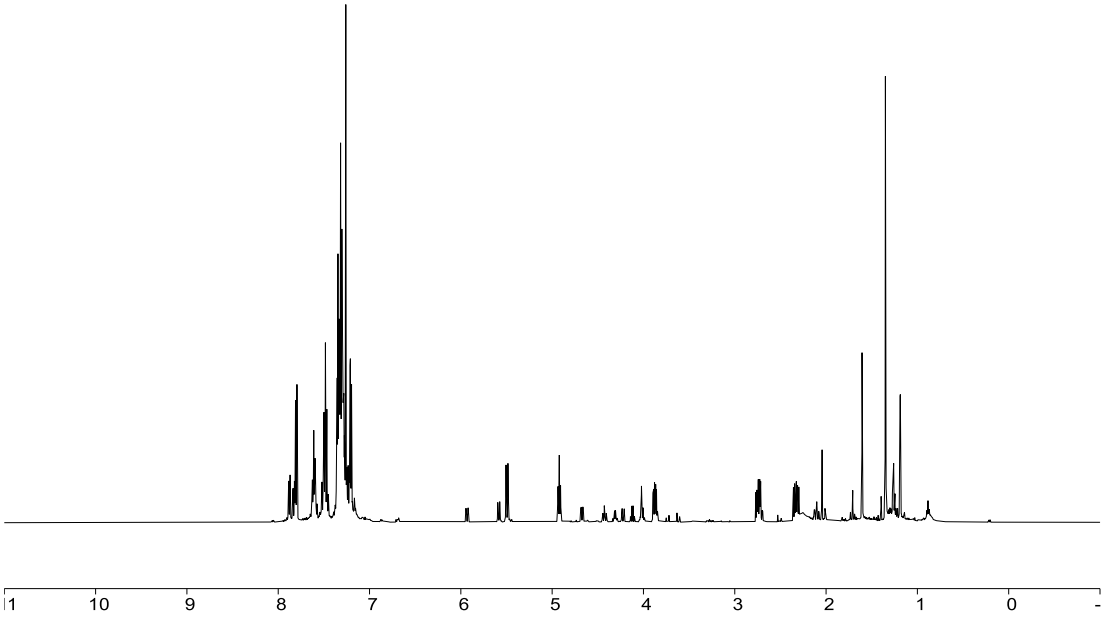
4.2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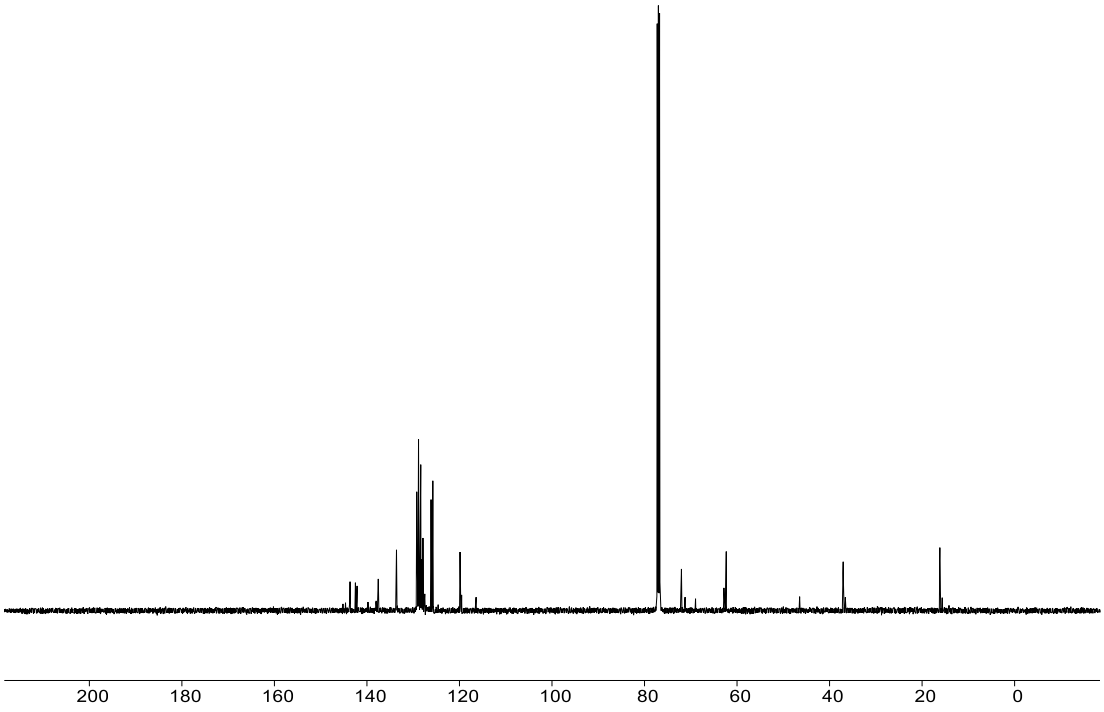
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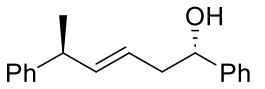
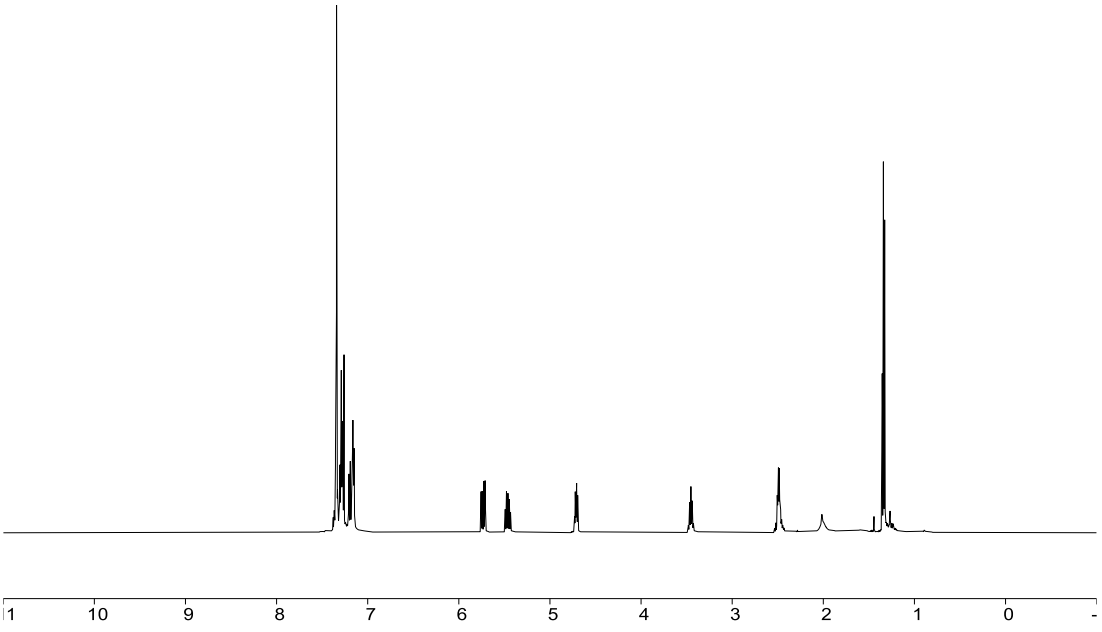

OH
Ph
Ph

4.4

Major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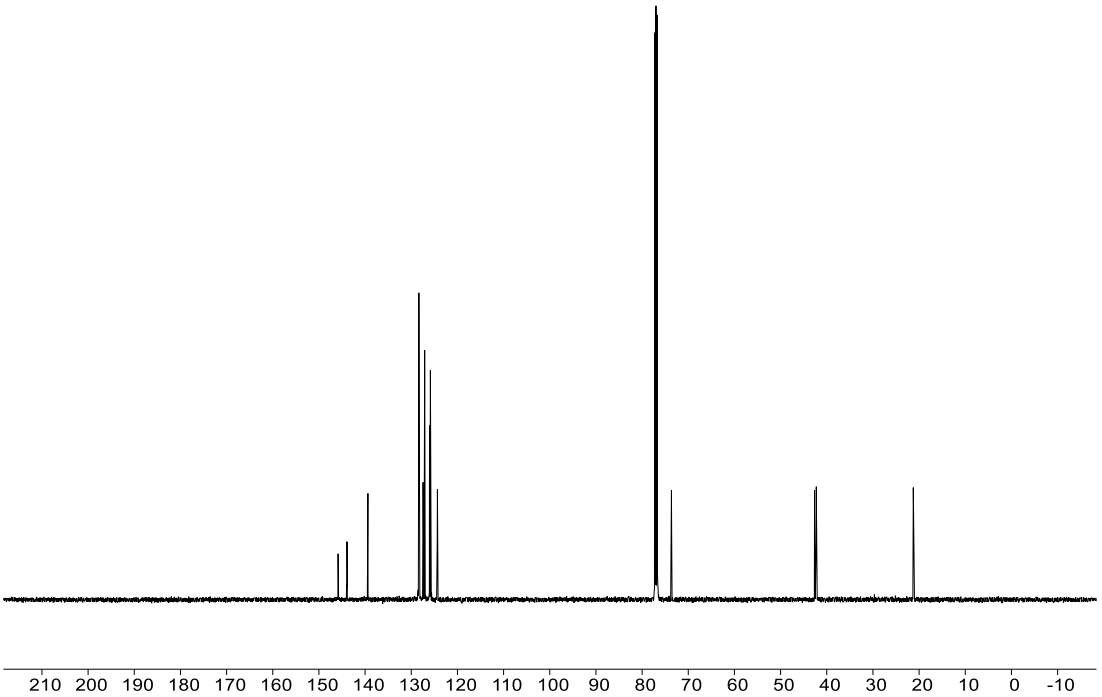
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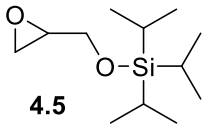

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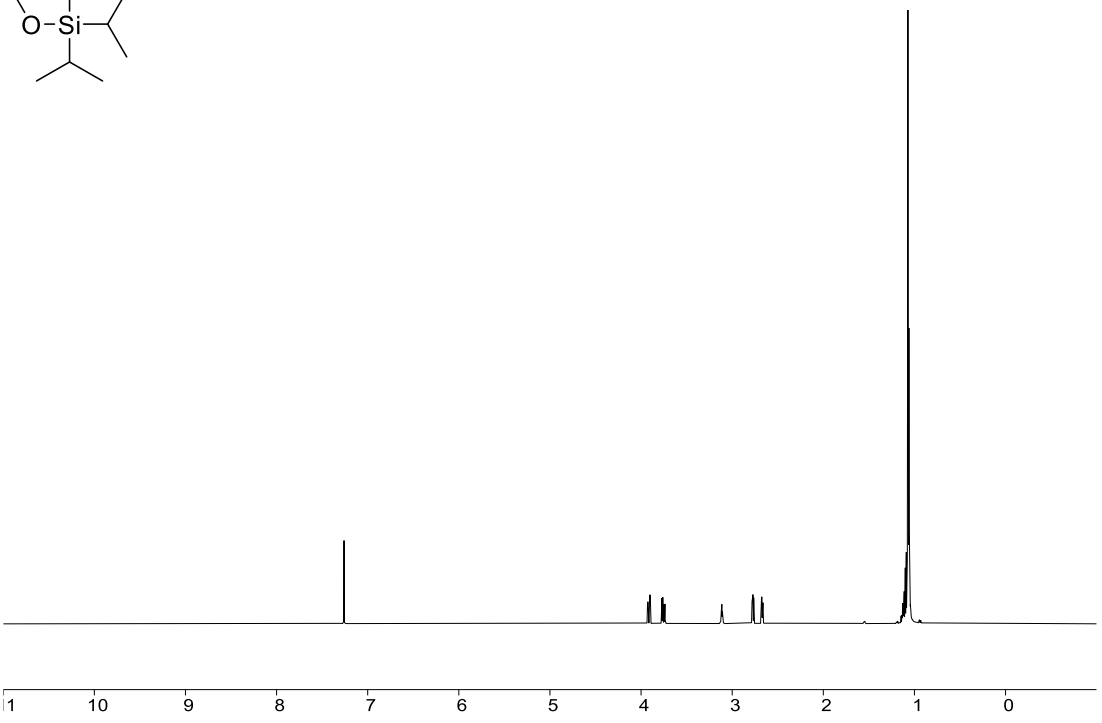

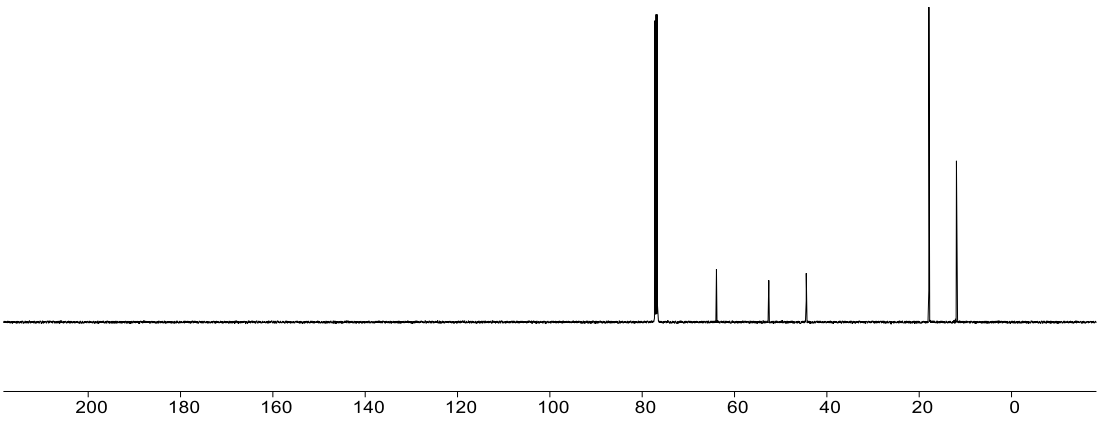

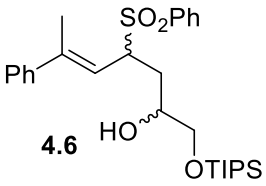
SO2Ph
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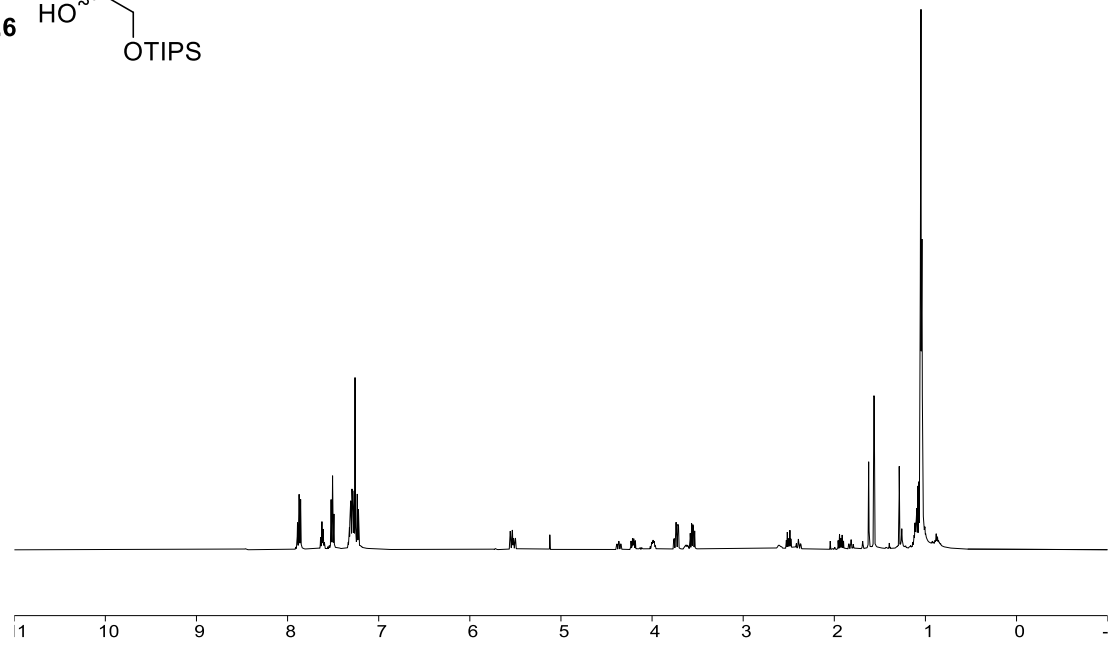
OTIPS

4.6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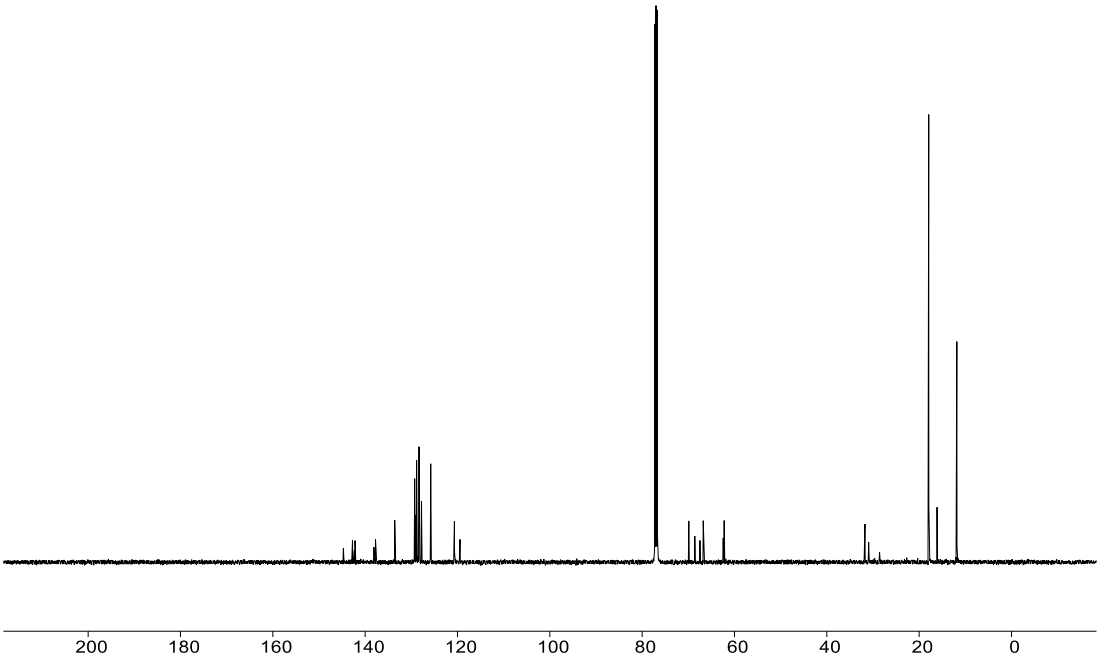
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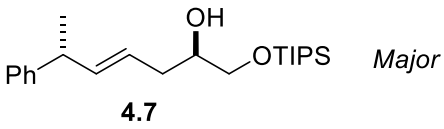
OH
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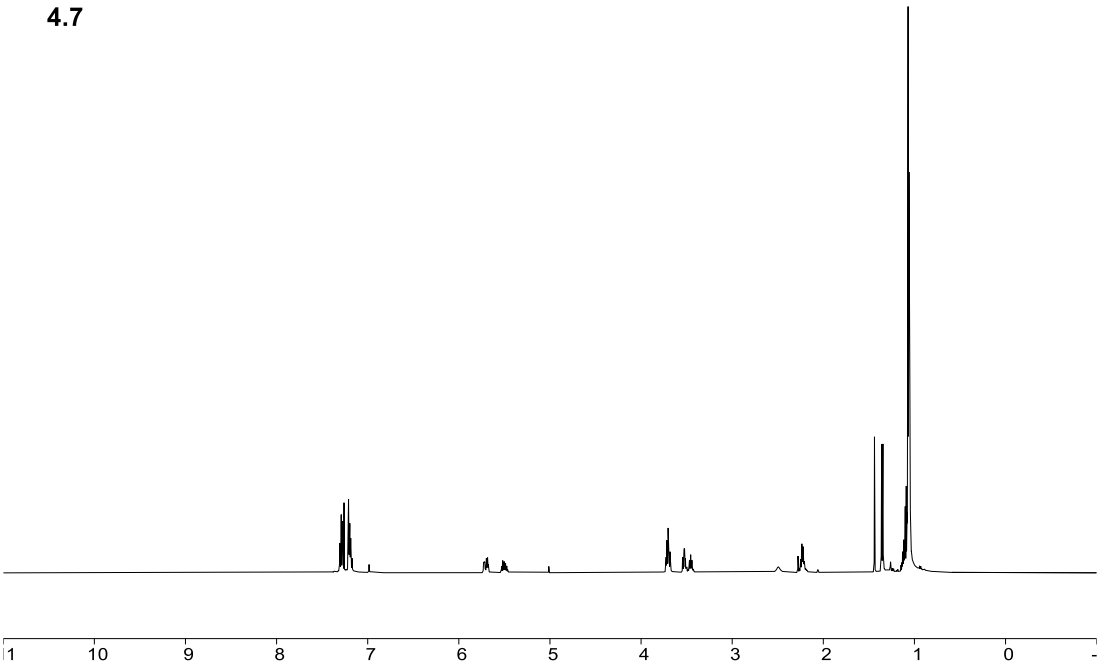
OTIPS

Major

4.7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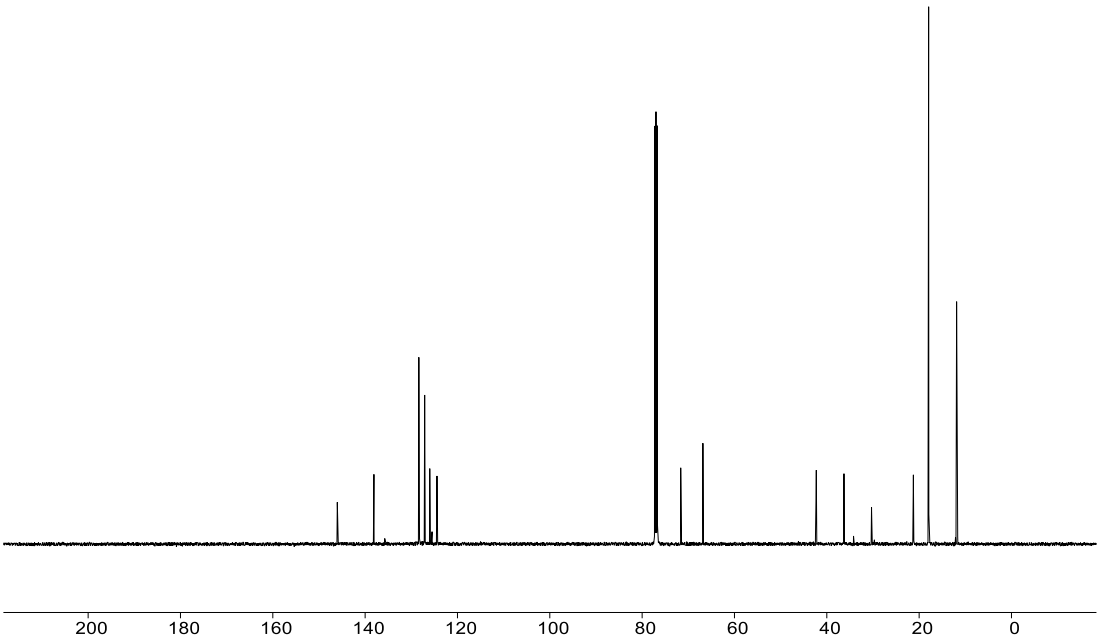
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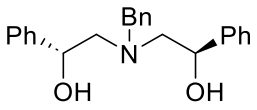

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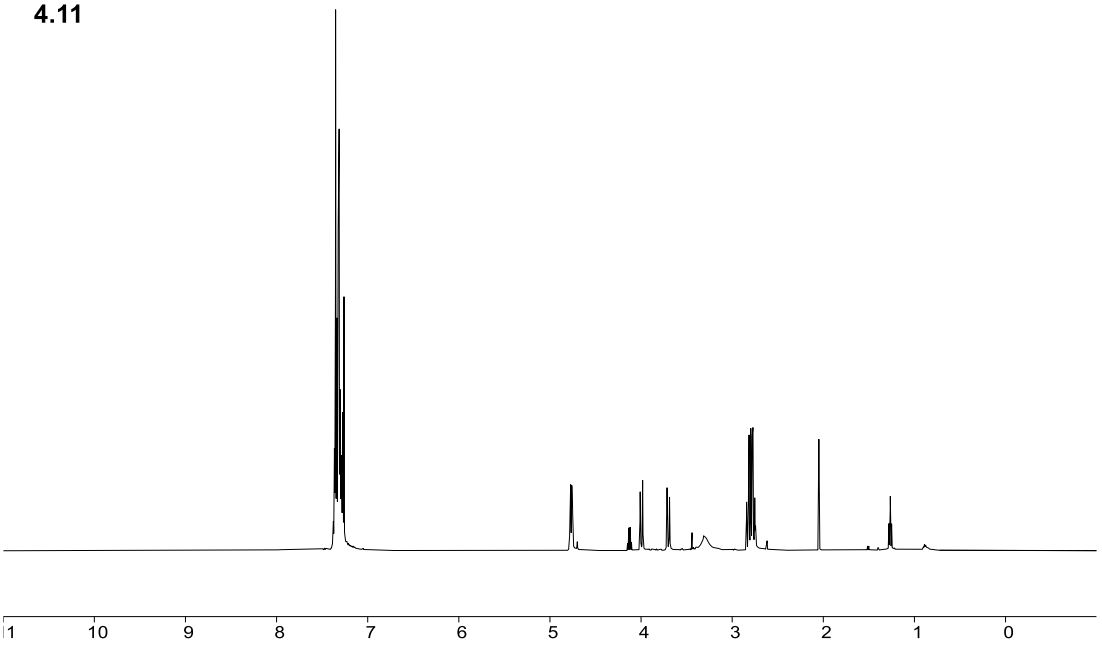

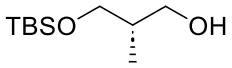

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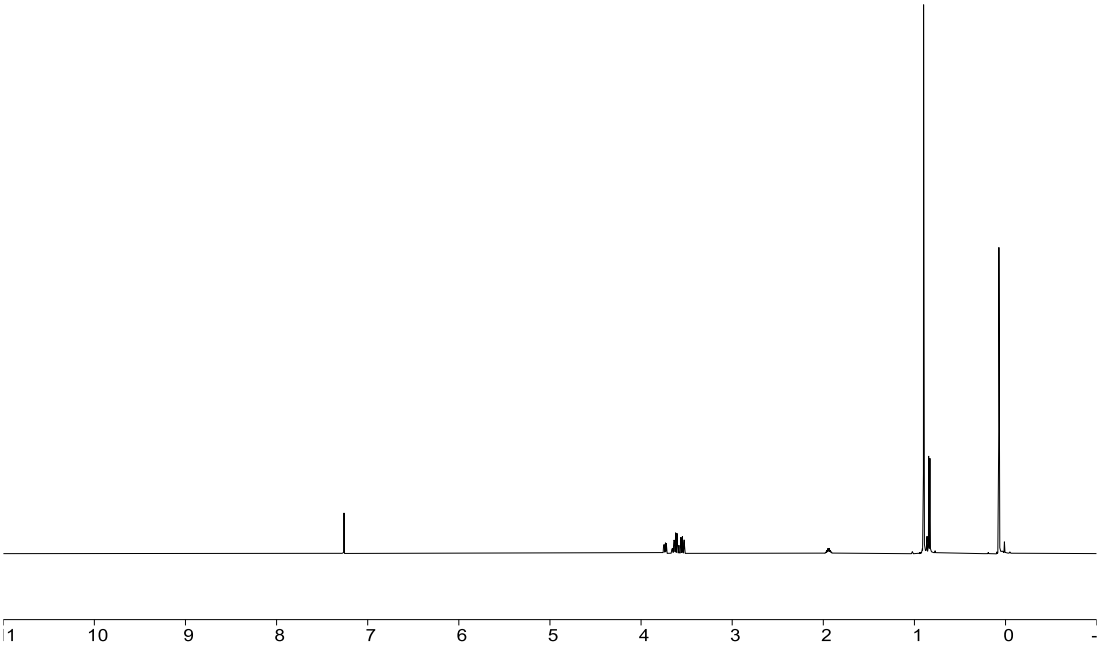

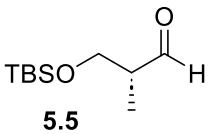

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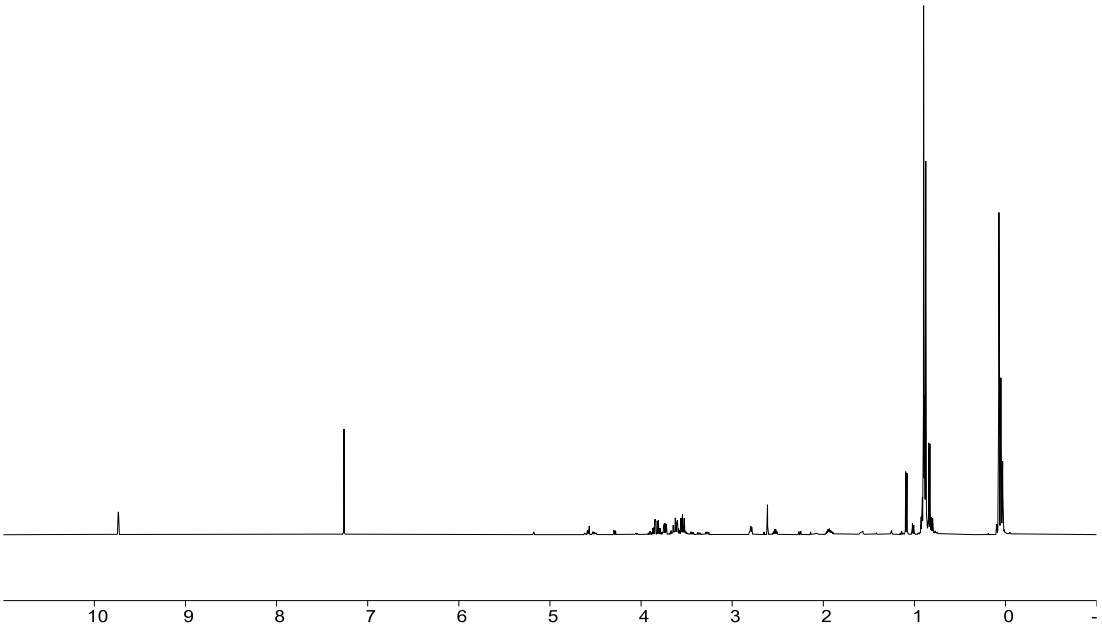

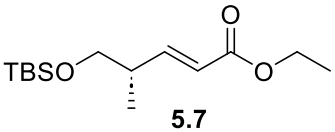

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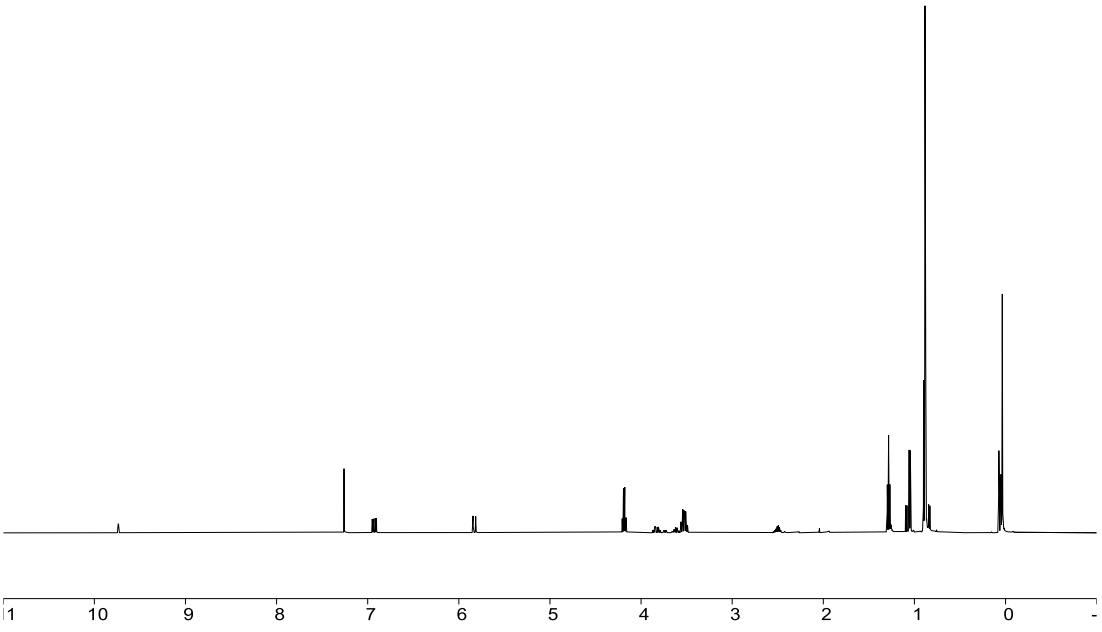

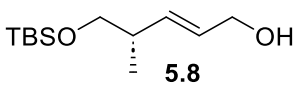

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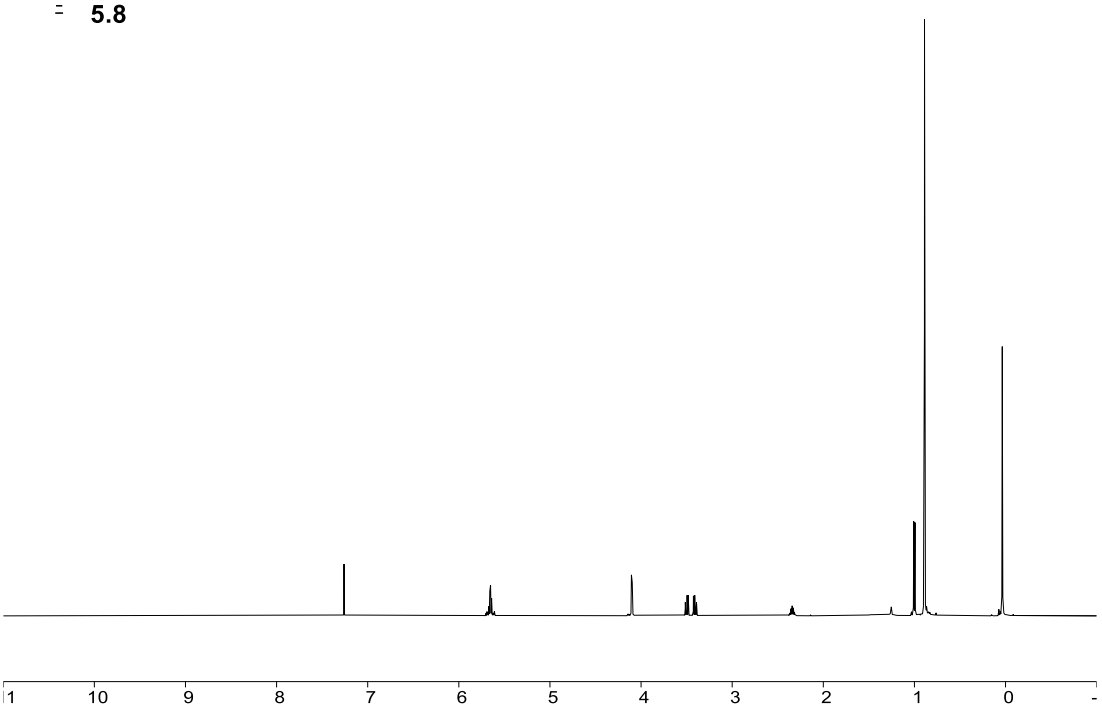

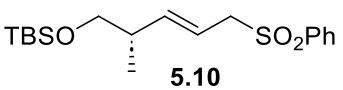
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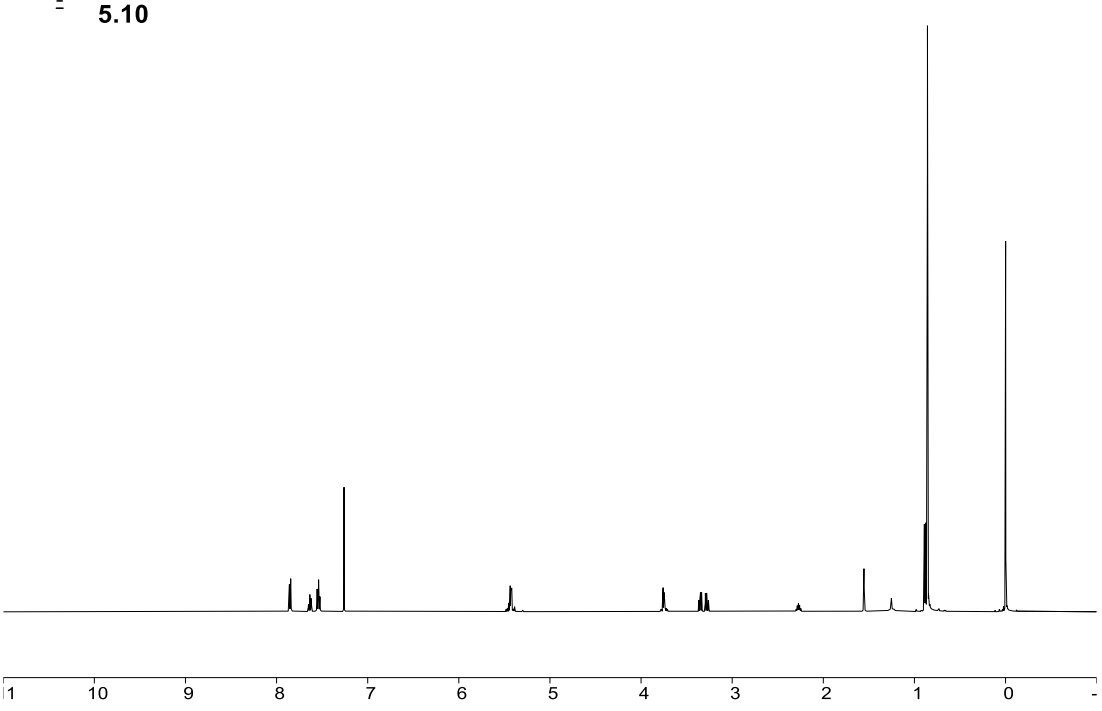
SO2Ph

5.10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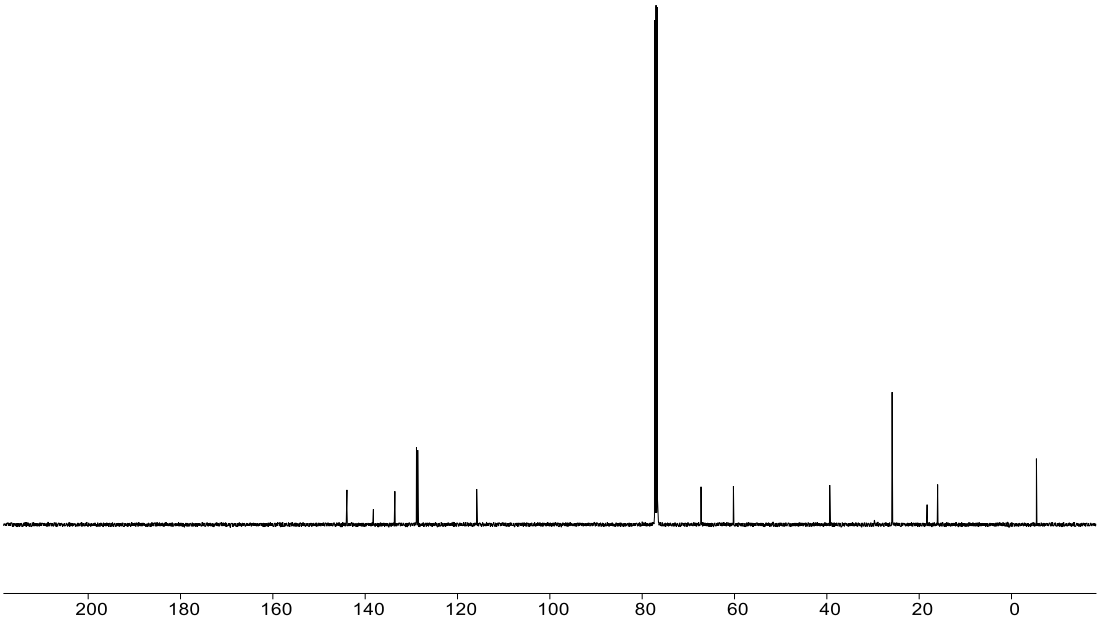
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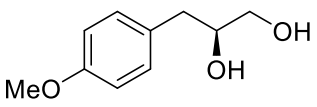
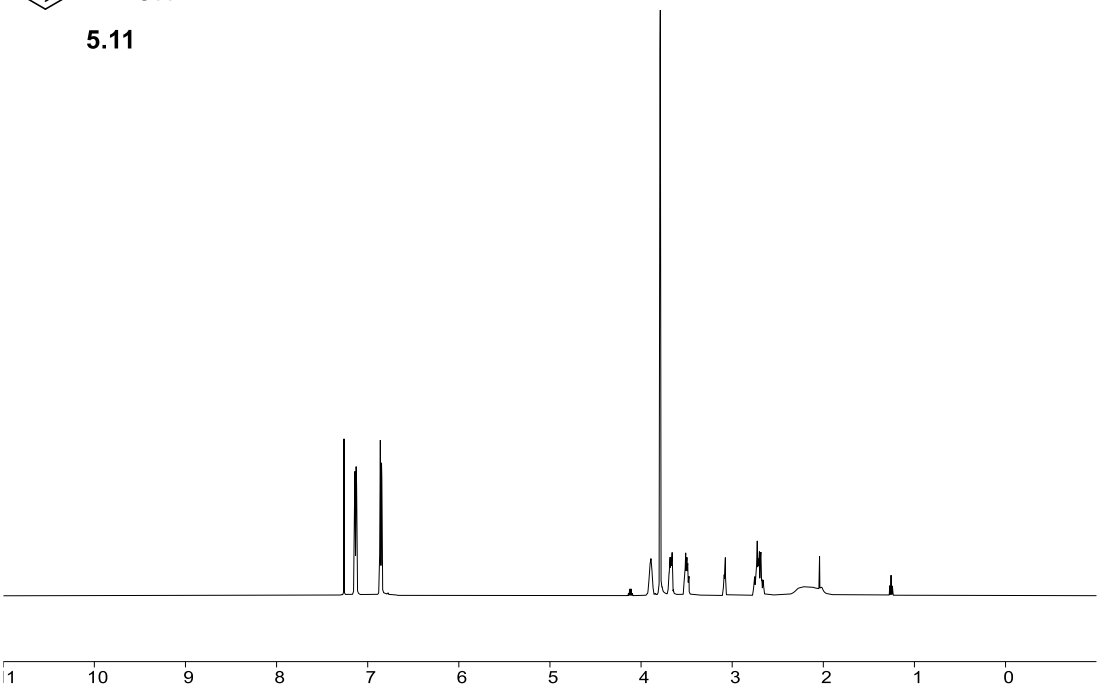
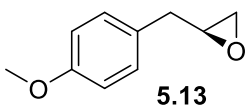


5.11





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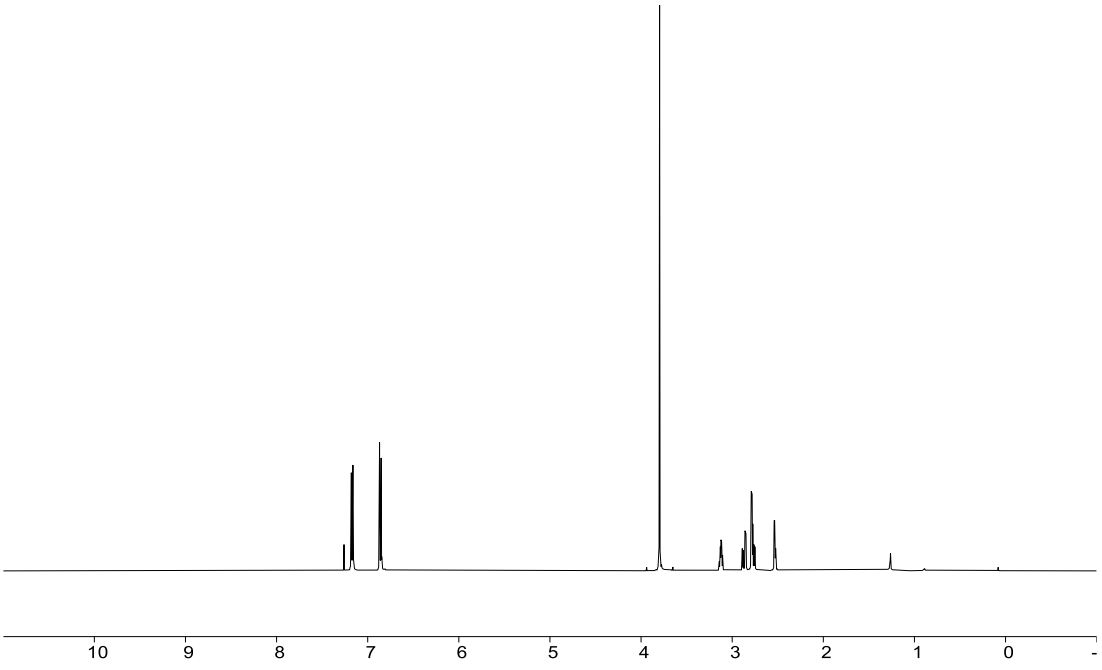

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