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Photo-Induced Remote C-H Functionalization and New Thioglycoside Donor Development for O-Glycosylation

Shaofu Du

Louisiana State University and Agricultural and Mechanical College

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PHOTO-INDUCED REMOTE C-H FUNCTIONALIZATION
AND NEW THIOLYGLYCOSIDE DONOR DEVELOPMENT FOR *O*-GLYCOSYLATION

A Dissertation

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfilment of the
requirements for the degree of
Doctor of Philosophy

in

The Department of Chemistry

by
Shaofu Du
B.S., Lanzhou University, 2014
May 2019

To my family and friends

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LIST OF ABBREVIATIONS

^1H	proton NMR
^{13}C	carbon NMR
CDCl_3	deuterated chloroform
CV.....	cyclic voltammetry
DAST.....	diethylaminosulfur trifluoride
DBU.....	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM.....	dichloromethane
DMF.....	<i>N,N</i> -dimethylformamide
DMT.....	dipole moment theory
DTBMP.....	2,6-di- <i>tert</i> -butyl-4-methylpyridine
EDA.....	electron donor acceptor
EtOAc.....	ethyl acetate
HAT.....	hydrogen atom transfer
HMDS.....	bis(trimethylsilyl)amine
HRMS.....	high resolution mass spectrometry
ICU.....	intensive care unit
IDCP.....	iodonium dicollidine perchlorate
Kdo.....	3-deoxy- <i>D-manno</i> -oct-2-ulosonic acid
LED.....	light emitting diode
LHMDS.....	lithium bis(trimethylsilyl)amide
LOS.....	lipooligosaccharide
LPS.....	lipopolysaccharide
MBTG.....	4-(4-methoxyphenyl)-3-butenylthioglycoside

MHC.....	major histocompatibility complex
MPTG.....	4-(4-methoxyphenyl)-4-pentenylthioglycoside
MOT.....	molecular orbital theory
NBS.....	<i>N</i> -bromosuccinimide
NIS.....	<i>N</i> -iodosuccinimide
NMR.....	nuclear magnetic resonance
PTFA.....	<i>N</i> -phenyltrifluoroacetimidate
SBox.....	<i>S</i> -benzoxazolyl
SCE.....	saturated calomel electrode
SET.....	single electron transfer
TBAF.....	tetra- <i>n</i> -butylammonium fluoride
TBAI.....	tetra- <i>n</i> -butylammonium iodide
TBS.....	<i>tert</i> -butyldimethylsilyl
TCA.....	trichloroacetimidate
TEMPO.....	(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl
TFA.....	trifluoroacetic acid
THF.....	tetrahydrofuran
TLC.....	thin layer chromatography
TMSI.....	trimethylsilyl iodide
TMSOTf.....	trimethylsilyl trifluoromethanesulfonate
Troc-Cl.....	2,2,2-trichloroethyl chloroformate
<i>p</i> -TsOH.....	<i>para</i> -toluenesulfonic acid
Tz ^o Cl.....	<i>o</i> -tosyl triazene chloride

UV.....ultraviolet

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ABSTRACT

This dissertation focuses on the method development of C-H functionalization using photo-redox catalysis and the synthesis of new thioglycoside donors towards *O*-glycosylation. Chapter 1 describes the remote Csp³-H functionalization using photo-redox catalysis. The site-selective and high-yielding conversion of unreactive aliphatic C-H bonds has been a challenge for organic chemists for many years. In this work, inert C-H bonds were successfully converted to more useful C-C, C-N, and C-O bonds via hydrogen atom transfer (HAT), radical translocation and polar crossover. This mechanistic manifold was enacted by visible-light irradiation of *o*-diazoniaphenyl alkyl sulfones in the presence of Ru(bpy)₃Cl₂. Remote hydroxylation, etherification, amidation, and C-C bond formation were all successfully achieved via this transformation.

Chapter 2 provides an overview of sugar chemistry and a mild, acid-catalyzed *O*-glycosylation method with thioglycoside has been developed. Chemical synthesis of oligosaccharide has become a vital alternative way to acquire adequate quantity of pure product to study the function because of the microheterogeneity. Therefore, new glycosyl donors and glycosylation methods have been developed throughout these years. Herein, a newly-developed 4-(4-methoxyphenyl)-3-butenyl thioglycoside (MBTG) has been used to achieve *O*-glycosylation using mild, acid-catalyzed conditions. A number of conditions have been applied to demonstrate the compatibility of the MBTG thioglycoside side chain. Most importantly, a latent-active strategy for multistep synthesis of oligosaccharides has been developed.

Chapter 3 details a new class of thioglycoside development towards *O*-glycosylation. Thioglycosides are often used in oligosaccharide synthesis. Harsh reaction conditions would be applied to activate common thioglycosides due to their high stability. The development of a stable and easily-activated thioglycoside has become an urgent mission for chemists to prosper the carbohydrate community. In this research, I developed a new class of thioglycosides called 4-(4-

methoxyphenyl)-4-pentenyl thioglycoside (MPTG), which has been proven much more effective than MBTGs with respect to yield and reaction with acceptors that are sterically and electronically deactivated.

Chapter 4 centers upon the method development involving synthesis of a core pentasaccharide from an *Acinetobacter baumannii* lipooligosaccharide. *Acinetobacter baumannii*, which is a gram-negative coccobacillus, is a pathogenic bacterium to people with poor immune system. The pentasaccharide synthesized here is widely conserved in *Acinetobacter baumannii* and is a potential vaccine target. Total synthetic efforts are underway in the lab.

CHAPTER 1: VISIBLE-LIGHT-PROMOTED REMOTE C-H FUNCTIONALIZATION OF *O*-DIAZONIAPHENYL ALKYL SULFONES

1.1 Introduction

C-H bonds are the most abundant bonds in nature. Due to the high bond dissociation energy, sp^3 hybridized C-H bonds are hard to break and functionalize. Therefore, seeking more efficient ways to convert C-H bonds to more useful C-C, C-N, and C-O bonds is of great importance. As such, direct C-H functionalization has become one of the most straightforward and valuable methods for the synthesis of value-added compounds, which is also the requirement of sustainable and economic chemistry.¹

The research on functionalization of C-H bonds has been the subject of great interest during the past two decades.²⁻⁶ The strategies often fall into two categories: directed and non-directed.^{7, 8} Non-directed C-H functionalization depends on the innate reactivity of the C-H bonds. Directed C-H functionalization often needs the assistance of metals resulting in the formation of active organometallics. This strategy doesn't require the prior activation of C-H bonds. Another approach to directed C-H functionalization is to produce a radical upon thermal, chemical, or photochemical activation. This radical can further abstract hydrogen from a remote C-H position in the same molecule (often referred as a radical translocation event).⁹

Despite the recent advances in remote C-H functionalization,¹⁰ seeking milder conditions still remains a goal for synthetic chemists. Instead of using high-energy, unsafe ultraviolet light or large amounts of corrosive reagents, visible-light photo-redox catalysis provides an alternate route to solve those problems. In the past few decades, visible-light photo-redox catalysis has become more prosperous due to the mild conditions used for substrate activation.¹¹ Direct C-H bond

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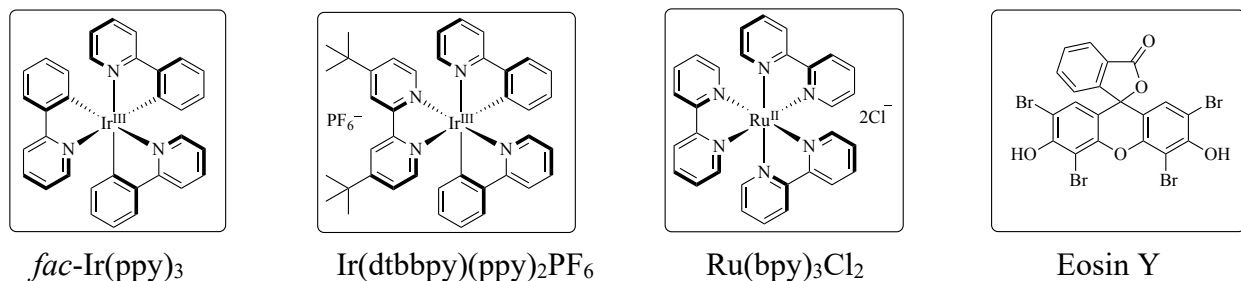


Figure 1.1 Commonly-used Photo-redox Catalysts

replacements with alkyl,¹² vinyl,¹³ CF₃,¹⁴ and aryl groups¹⁵ have been achieved by using visible-light irradiation in the presence of photocatalysts (Figure 1).

The single-electron transfer (SET) processes that excited state photocatalysts undergo with organic molecules gives facile access to radical and radical ionic intermediates. Also, the electronic tunability of ligands coordinated to metal centers means that some photocatalysts can act as both oxidants and reductants depending on the nature of the quenching species that are present. For example, the commonly used photocatalyst *fac*-Ir(ppy)₃ was excited from ground singlet state to excited triplet state via blue LED irradiation ($\lambda_{\text{max}} = 455 \text{ nm}$). After excitation, the photocatalyst *fac*-Ir(ppy)₃^{*} can either reduce an electron acceptor to generate [*fac*-Ir(ppy)₃]⁺ ($E_{1/2}(\text{Ir}^+/\text{Ir}^*) = -1.73 \text{ V}$ vs saturated calomel electrode (SCE)), which then oxidizes the electron donor to close the

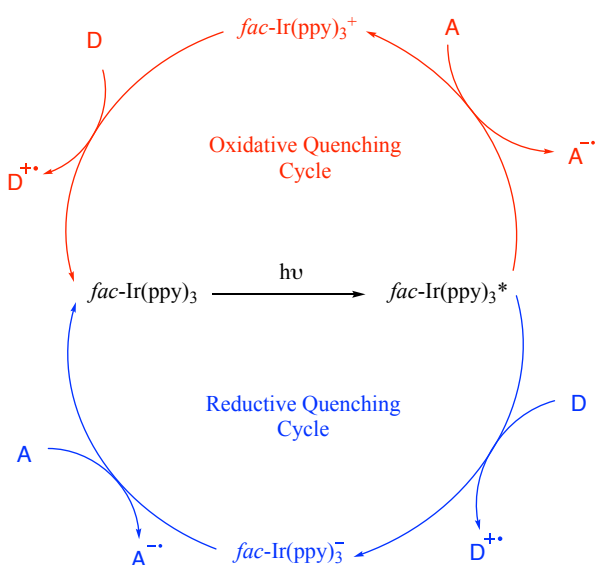


Figure 1.2 *fac*-Ir(ppy)₃ Quenching Cycle

oxidative quenching cycle ($E_{1/2}(\text{Ir}^+/\text{Ir}) = +0.77 \text{ V vs SCE}$), or oxidize the electron donor forming $[\text{fac-Ir}(\text{ppy})_3]^+$ ($E_{1/2}(\text{Ir}^*/\text{Ir}) = +0.31 \text{ V vs SCE}$), followed by oxidation to close the reductive quenching cycle ($E_{1/2}(\text{Ir}/\text{Ir}^+) = -2.19 \text{ V vs SCE}$), (Figure 1.2). This dual photo-redox catalysis capability provides new mechanistic pathways for reaction design.¹⁶

1.2 Representative Examples of Radical Translocation

The first known radical translocation was discovered in the late 1800s by Hofmann, Löffler, and Freytag, and further explored in the early 1900s. However, the mechanism was not understood.¹⁷ In 1950, Wawzonek and Thelen proposed the mechanism (Figure 1.3), which was finally confirmed by the work of Corey and Hertler in the 1960s.¹⁸ For example, one reaction began with *N*-chloro-*N*-methylcyclooctylamine **1a**, which was protonated by sulfuric acid,

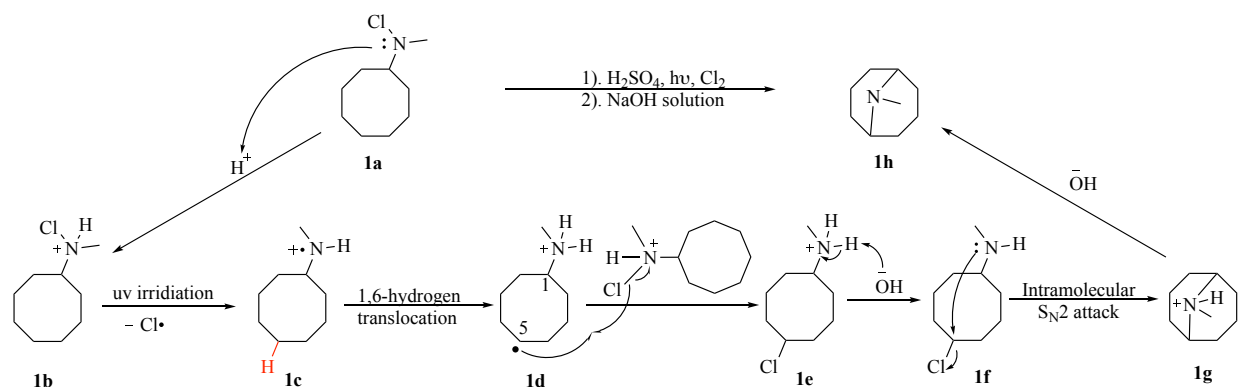


Figure 1.3 Predicted Mechanism for Hoffmann-Löffler-Freytag Reaction

followed by ultraviolet irradiation in the presence of chlorine. The resulting secondary nitrogen centered radical cation **1c** abstracted a hydrogen from a carbon 5 (Figure 1.3) and generated a secondary carbon-centered radical intermediate **1d**, which started a chain reaction to form the amine salt **1e**, followed by the deprotonation with base to obtain the free amine **1f**, which underwent an intramolecular S_N2 attack, followed by deprotonation, to acquire the final product *N*-methylgranatanine **1h**.

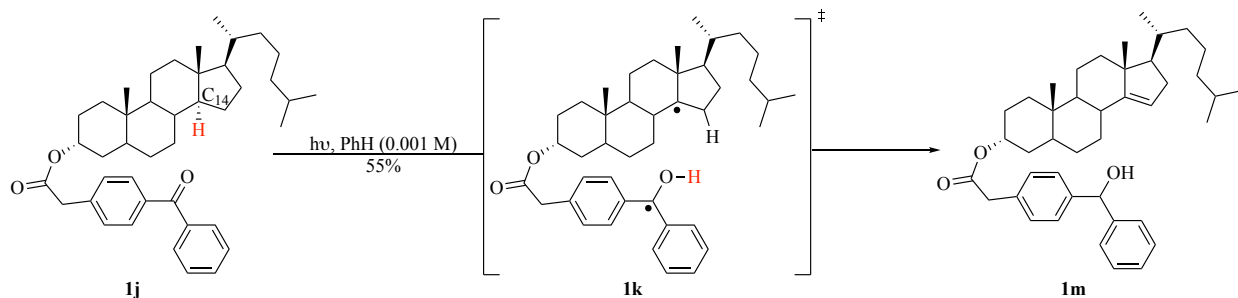
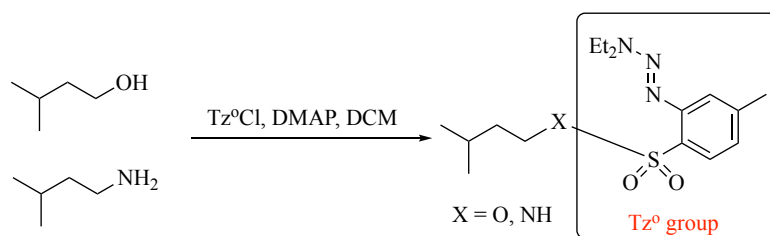


Figure 1.4 Breslow's Photochemical Transfer Hydroenation

In the 1970s, Breslow and co-workers employed a guided radical translocation reaction which they referred to as remote oxidation.¹⁹ Under irradiation with ultraviolet light, the benzophenone was excited and the carbonyl oxygen of the excited benzophenone abstracted the axial hydrogen on carbon 14 to generate the diradical intermediate, which further transferred the hydrogen on carbon 15 to the benzhydryl radical to complete the process (Figure 1.4). This groundbreaking efficient oxidation of inactivated alkanes has led to more interest in remote functionalization reactions.

More recently, a guided remote desaturation of aliphatic carbon chains was developed by Baran and co-workers.²⁰ A special 'portable desaturase', Tz°Cl (Scheme 1.1), was used in this



Scheme 1.1 Installation of Tz° Functionality

transformation (Figure 1.5). *Ortho* to sulfonyl is a *N,N*-diethyl triazene **1n**, which was treated with

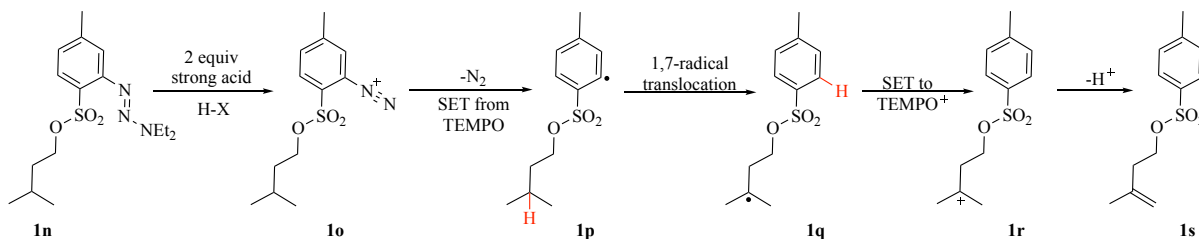


Figure 1.5 Proposed Mechanism for the Desaturation Reaction

acid to produce an aryl diazonium salt **1o**, followed by reduction with 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO) to generate the aryl radical **1p** with the loss of N₂ and concomitant oxidation to TEMPO⁺. Once generated, the aryl radical underwent an unusual 1,7-hydrogen-atom translocation (HAT) to generate a more stable tertiary radical intermediate **1q**, which is oxidized by TEMPO⁺ to generate the corresponding carbocation intermediate **1r**. This process also regenerated TEMPO. At the same time, the elimination led to the alkene product **1s**. Though low yields were obtained, this transformation provides an alternative pathway to explore remote C-H functionalization.

Recently, the Ragains group has developed a remote hydroxylation method proceeding via radical translocation and polar crossover.²¹ This remote hydroxylation used the photo-redox

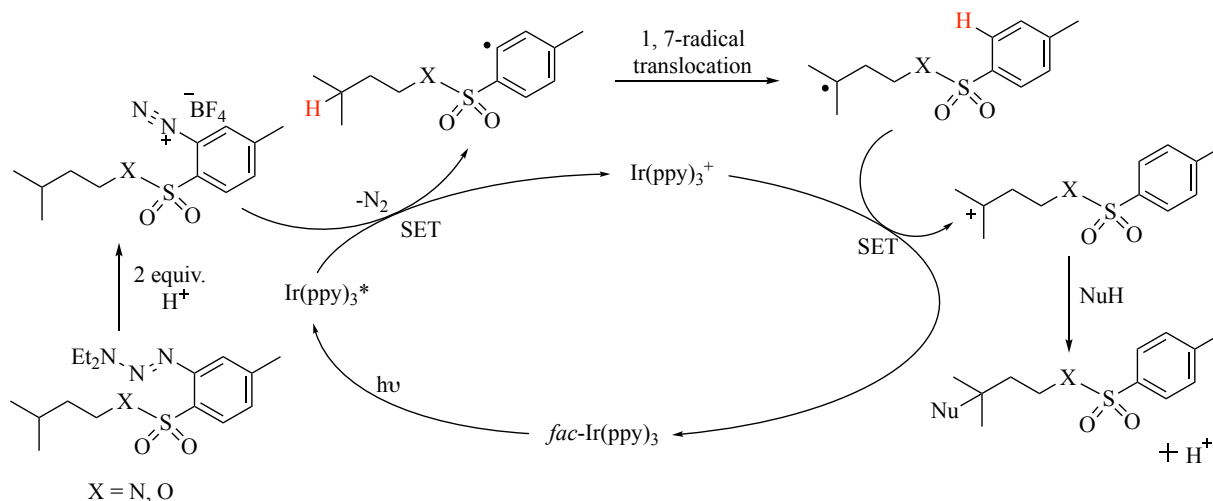
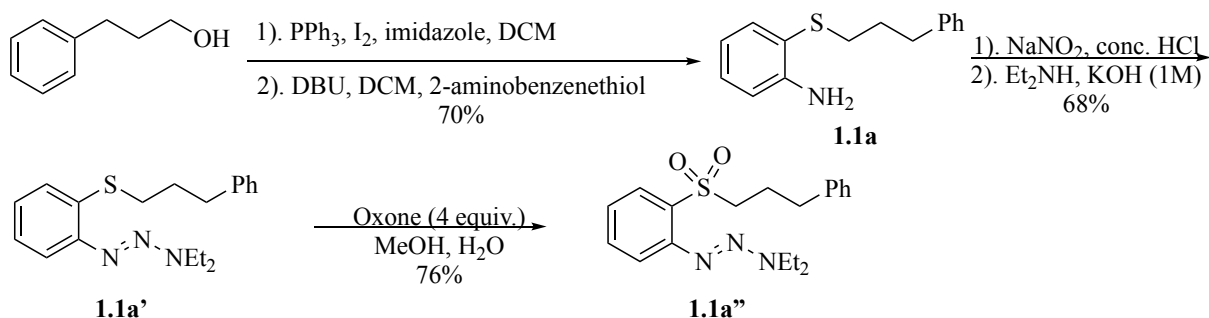


Figure 1.6 Hypothesis for Remote Hydroxylation

catalyst *fac*-Ir(ppy)₃ to achieve a single-electron transfer (SET) process (Figure 1.6). This reaction involved radical translocation, oxidation to carbocation, and nucleophilic trapping to provide various functional groups at the unreactive C-H position. However, when sulfonate ester was applied to standard conditions without photocatalyst, substantial amounts of alcohol and diazonium salt were generated, which suggested the potential decomposition risk of this substrate under acidic conditions.

1.3 Results and Discussion

Inspired by our original work with sulfonate esters and sulfonamides, we wondered if triazene-containing sulfones would give us similar results. In this way, we could eliminate the potential hydrolysis problem of the sulfonate ester/sulfonamide intermediates, increase product yield, and enable further manipulation of the sulfone. En route to our goal of mild conditions, remote C-H functionalization reactions were performed under visible-light irradiation. To begin with, we selected 3-phenyl-1-propanol as our model substrate. In order to synthesize the sulfonyl triazene compound **1.1a''**, the hydroxy group in 3-phenylpropanol was replaced by iodine using triphenylphosphine and iodine with imidazole in dichloromethane. Once the iodide compound was obtained, displacement with 2-aminobenzenethiol generated 2-((3-phenylpropyl)thio)aniline **1.1a**, which further reacted with HNO_2 to generate the diazonium salt followed by nucleophilic trapping with diethylamine to give (*E*)-3,3-diethyl-1-(2-((3-phenylpropyl)thiophenyl)triaz-1-ene **1.1a'**. Then **1.1a'** was oxidized with Oxone to give the final sulfonyltriazene compound (*E*)-3,3-diethyl-1-(2-((3-phenylpropyl)sulfonyl)phenyl)triaz-1-ene **1.1a''** (Scheme 1.2).

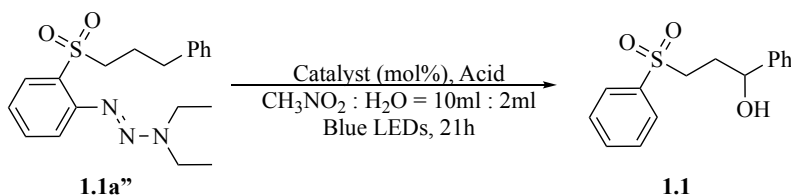


Scheme 1.2 Synthetic Route to Sulfonyltriazene **1.1c**

With the sulfonyltriazene **1.1a''** in hand, reaction conditions were screened. To begin from our previous work, conditions were screened. We began our investigation using **1.1a''** as a model substrate together with 10 mol% *fac*-Ir(ppy)₃ and 48% tetrafluoroboric acid. We obtained 30% hydroxylation product. Later on, I screened additional reaction conditions which are summarized in Table 1.1. The yield increased with larger quantities of acid (entry 2). When triflic acid was

used, the yield increased (entry 3). The temperature dependency of the same reaction conditions as entry 3 were studied (entries 4,5), and we found that the reaction proceeded best at room temperature. When we turned off the light, the reaction could still occur resulting in 17% yield (entry 6). Lowering the amount of catalyst (entry 7) or changing to the more weakly-reducing

Table 1.1 Attempted Optimization of the Reaction Conditions

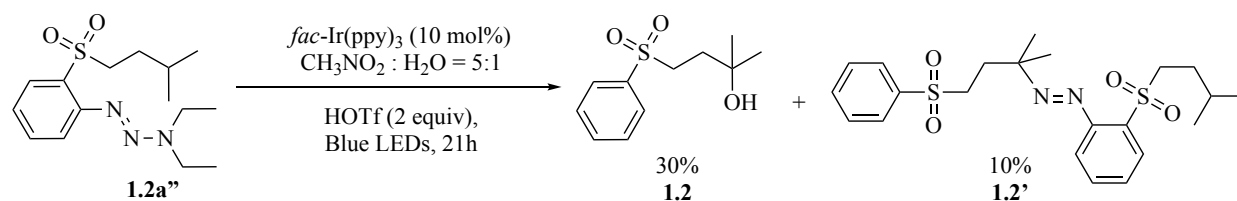


entry	catalyst/ mol%	acid/ equiv.	Yield (%) ^d
1	<i>fac</i> -Ir(ppy) ₃ / 10	48% HBF ₄ / 2	30
2	<i>fac</i> -Ir(ppy) ₃ / 10	48% HBF ₄ / 10	45
3	<i>fac</i> -Ir(ppy) ₃ / 10	triflic acid/ 2	47
4 ^a	<i>fac</i> -Ir(ppy) ₃ / 10	triflic acid/ 2	31
5 ^b	<i>fac</i> -Ir(ppy) ₃ / 10	triflic acid/ 2	25
6 ^c	<i>fac</i> -Ir(ppy) ₃ / 10	triflic acid/ 2	17
7	<i>fac</i> -Ir(ppy) ₃ / 1	triflic acid/ 2	23
8	Ir(dtbbpy)(ppy) ₂ PF ₆ / 5	triflic acid/ 2	13

^aReaction performed at 50 °C for 69 hours. ^bReaction performed at 0 °C for 36 hours. ^cReaction performed without light. ^dIsolated yields.

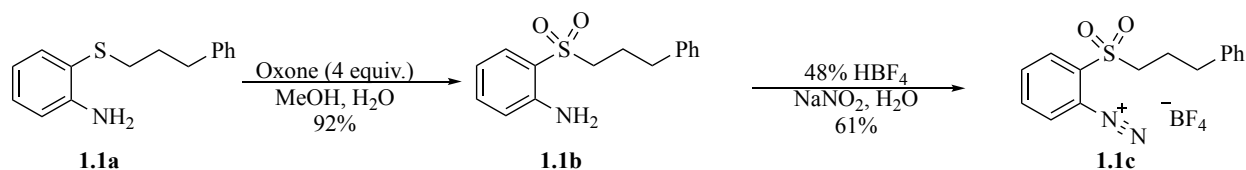
catalyst Ir(dtbbpy)(ppy)₂PF₆ (entry 8) decreased the yield. Based on the screening, we chose entry 2 as our standard reaction conditions. When these conditions were applied to (*E*)-3,3-diethyl-1-(2-(isopentylsulfonyl)phenyl)triaz-1-ene **1.2a''**, the undesired diazene compound **1.2'**, which resulted from the attack of the generated tertiary radical on diazonium ion, was isolated. After 21 hours of

irradiation, the starting **1.2a''** was not fully consumed. Further reactions proved sluggish and low-yielding compared with sulfonate esters or sulfonamides (Scheme 1.3).



Scheme 1.3 Remote Hydroxylation of **1.2a''**

Based on our previously proposed mechanism, we wondered if the direct use of diazonium salts would be more beneficial. Though the diazonium salt is somewhat unstable at room temperature, it has certain merits. For example, acid can be omitted from this transformation, and problems with sluggish conversion of triazene would be avoided. Most importantly, the arenediazonium tetrafluoroborates are not explosive. To acquire the diazonium salt, starting with **1.1a**, oxidation with Oxone in a water and methanol mixture afforded 2-((3-phenylpropyl)sulfonyl)aniline **1.1b** (Scheme 1.4). The reaction was complete in less than 5 minutes. **1.1b** was then converted to the corresponding 2-((3-phenylpropyl)sulfonyl)benzenediazonium tetrafluoroborate **1.1c** using a previously published procedure (Scheme 1.4).

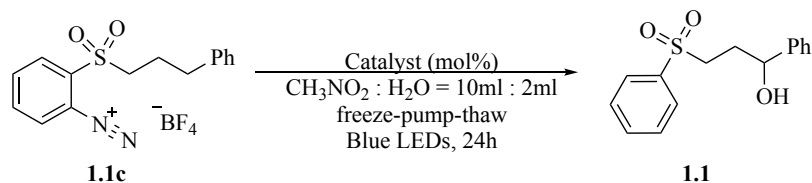


Scheme 1.4 Synthesis of **1.1c**

With the diazonium salt **1.1c** in hand, remote hydroxylation conditions were explored. The initial experiment was performed with 10 mol% *fac*-Ir(ppy)₃. Only 31% of hydroxylation product **1.1** was obtained (Table 1.2). Further optimization found that decreasing catalyst loading could slightly increase the yield (entry 2). Screening the effect of various catalysts showed us that

Ru(bpy)₃Cl₂·6H₂O was the best for this transformation (entries 3-7), giving us the highest yield observed (entry 8). A series of controls established that light, photocatalyst, and exclusion of oxygen are all essential to this transformation (entries 9-11).²²

Table 1.2 Optimization of Remote Hydroxylation^a



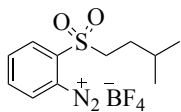
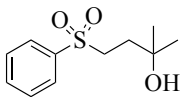
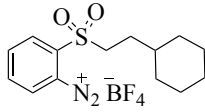
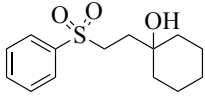
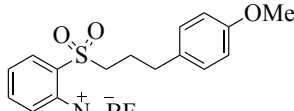
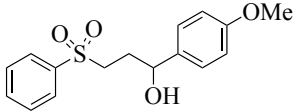
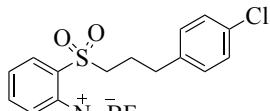
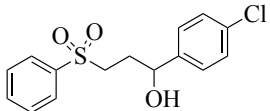
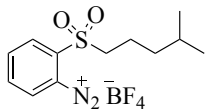
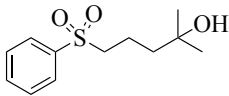
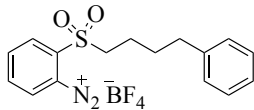
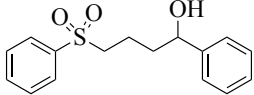
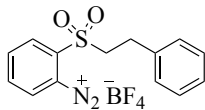
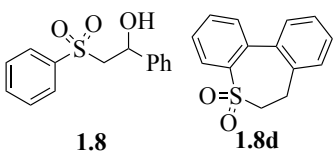
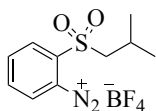
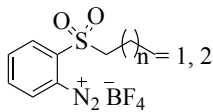
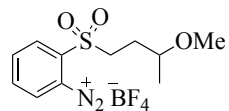
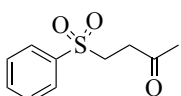
entry	catalyst/ mol%	Yield (%) ^b
1	<i>fac</i> -Ir(ppy) ₃ / 10	31
2	<i>fac</i> -Ir(ppy) ₃ / 1	37
3	Ru(bpy) ₃ Cl ₂ ·6H ₂ O/ 1	58
4	Cu(dap) ₂ Cl/ 1	31
5	Ru(phen) ₃ (Barf) ₂ / 1	60
6	Ir[dF(CF ₃)ppy] ₂ (dtbbpy)PF ₆ / 1	52
7 ^c	Eosin Y/ 1	24
8	Ru(bpy)₃Cl₂·6H₂O/ 0.5	79
9 ^d	Ru(bpy) ₃ Cl ₂ ·6H ₂ O/ 1	33
10	Ru(bpy) ₃ Cl ₂ ·6H ₂ O/ 0	0
11 ^e	Ru(bpy) ₃ Cl ₂ ·6H ₂ O/ 1	0

^aReaction conditions: sulfonyl diazonium salt (**1.1c**, 0.2 mmol), Ru(bpy)₃Cl₂·6H₂O (0.5 mol%, 0.001 mmol), CH₃NO₂ (10 mL), H₂O (2 mL). ^bIsolated yield. ^cReaction was irradiated with green LEDs. ^dReaction performed without freeze-pump-thaw. ^eReaction performed without irradiation.

Encouraged by these results, we next evaluated the substrate scope that could be employed in this remote hydroxylation reaction (Table 1.3). An isoamyl alcohol derivative produced tertiary alcohol **1.2** in 52% yield (entry 1). Cyclohexylethanol derivative **1.3c** gave a relatively low-yielding conversion in 28% yield (entry 2) because of competing elimination. Considering electronic effects, we used *p*-Cl and *p*-OMe phenyl derivatives **1.4c** and **1.5c**, which gave moderate yields (entries 3&4). All the examples above involved 1,6-HAT. We also designed substrates to undergo 1,7- and 1,5-HAT. Aliphatic substrate **1.6c** gave a poor (16%) yield (entry 5) while the corresponding benzylic substrate gave only trace alcohol product as evidenced by crude ¹H NMR (entry 6). All of these results suggested that 1,7-HAT was less favorable than 1,6-HAT for this transformation. Also, substrate **1.8c** was expected to undergo 1,5-HAT. Surprisingly, a mixture of alcohol and intramolecular cyclization product was obtained (entry 7). The aliphatic substrate **1.9c** did not undergo hydroxylation, further demonstrating that 1,5-HAT is not favorable under these conditions. Further studies on aliphatic sulfone substrates **1.10c** and **1.11c** resulted in complex mixtures, where no desired alcohol products were detected. Finally, a methyl ether substrate **1.12c** was converted to ketone **1.12**, likely proceeding by a hydroxylation to a hemiacetal intermediate.

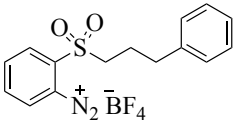
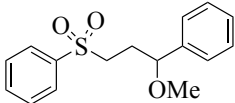
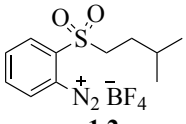
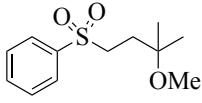
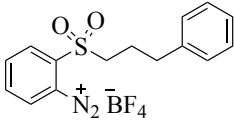
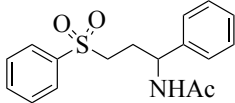
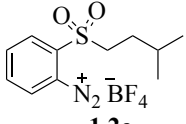
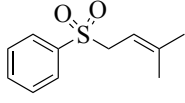
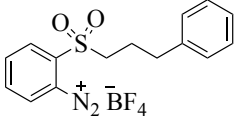
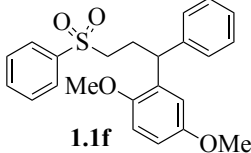
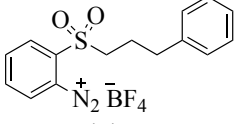
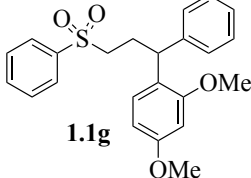
Previous attempts to convert Tz^o sulfonate esters and sulfonamides to methyl ether using methanol as a nucleophile were successful.²¹ With this precedent in mind, we explored more nucleophiles including MeOH, CH₃CN/H₂O, and even 1,3- and 1,4-dimethoxybenzene. All of the results are shown in Table 1.4. Etherification proceeded as expected with aliphatic and benzylic substrates (entries 1&2). A Ritter-type reaction was successful for benzylic substrate (entry 3) while aliphatic substrate gave only elimination product (entry 4). Further, remote C-C bond formation was achieved with dimethoxybenzene nucleophiles.

Table 1.3 Substrate Scope for Remote Hydroxylation^a

entry	substrate	product(s)	yield(%) ^b
1	 1.2c	 1.2	52
2	 1.3c	 1.3	28
3	 1.4c	 1.4	55
4	 1.5c	 1.5	40
5	 1.6c	 1.6	16
6	 1.7c	 1.7	trace
7	 1.8c	 1.8 1.8d	~49 (1:3.45, 1.8/1.8d)
8	 1.9c	no alcohol products isolated	0
9	 1.10c (n = 1), 1.11c (n = 2)	no alcohol products isolated	0
10	 1.12c	 1.12	71

^aReaction conditions: 0.2 mmol of diazonium salt, 10 mL CH₃NO₂, 2 mL H₂O, 0.5 mol% Ru(bpy)₃Cl₂, Temp = 26 - 28 °C, 24 h irradiation with blue LEDs. ^bIsolated yields.

Table 1.4 Etherification, Amidation, and Arylation^a

entry	substrate	product	yield (%) ^b
1 ^c	 1.1c	 1.1d	59
2 ^c	 1.2c	 1.2d	38
3 ^d	 1.1c	 1.1e	51
4 ^d	 1.2c	 1.2e	60
5 ^e	 1.1c	 1.1f	34
6 ^f	 1.1c	 1.1g	19

^aReaction conditions: 0.2 mmol of diazonium salt, 10 mL CH₃NO₂, 2 mL H₂O, 0.5 mol% Ru(bpy)₃Cl₂, temp = 26 - 28 °C, 24 h irradiation with blue LEDs. ^bIsolated yields. ^c100 μL of MeOH added. ^d100 μL of CH₃CN, 0.2 mmol H₂O added. ^e1.0 mmol of 1,4-dimethoxybenzene added. ^f1.0 mmol of 1,3-dimethoxybenzene added.

Based on the results we obtained, a proposed mechanism may proceed as follows (Figure 1.7): ground state Ru(bpy)₃²⁺ is excited by irradiation using blue LEDs ($\lambda_{\text{max}} = 452 \text{ nm}$) to excited state,^{15a} which reduces the diazonium ion **1.1c** to aryl radical **1.13** with the loss of nitrogen gas,²³ followed by a 1,6-HAT generating a more stable benzylic radical **1.14**,^{24,21} which has an oxidation

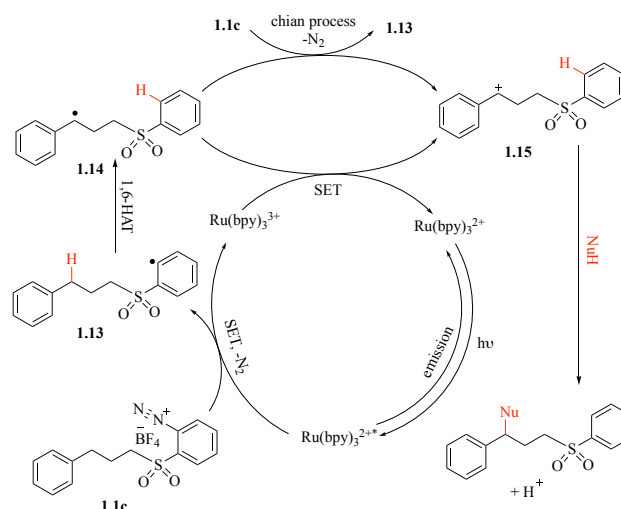


Figure 1.7 Proposed Mechanism for Remote C-H Functionalization

half potential between +0.1 V and +0.4 V (SCE).²⁵ Oxidation with $\text{Ru}(\text{bpy})_3^{3+}$ ($E_{1/2} = +1.29$ V vs SCE) leads to the carbenium ion **1.15**,²⁶ which is further attacked by nucleophiles to generate the final products. At the same time, $\text{Ru}(\text{bpy})_3^{3+}$ is reduced to ground state $\text{Ru}(\text{bpy})_3^{2+}$ to complete the catalytic cycle. Regarding the process **1.14** \rightarrow **1.15**, instead of closing the photoredox cycle via SET, the oxidation of radical **1.14** ($\sim +0.1$ V to +0.4 V vs SCE) by diazonium ion **1.1c** (-0.08 V vs SCE) may also result in the formation of **1.13** and **1.15** through a chain process (Figure 1.7). Irreversible loss of N_2 might be a driving force for such a chain process since, at face value, electron transfer is not favorable based on redox potential.

1.4 Summary

A mild, visible-light-promoted remote aliphatic C-H functionalization has been achieved using low loadings of the photocatalyst $\text{Ru}(\text{bpy})_3\text{Cl}_2$. Intramolecular HAT and SET oxidation of radical to carbocation intermediate are likely. In addition, the well-known 1,5-HAT is not very facile in this system. Transformations including remote hydroxylation, etherification, amidation, and arylation have been demonstrated. This method provides an efficient approach to the elaboration of alkyl iodides to value-added products of C-H functionalization.

1.5 Experimental

1.5.1. General Methods

Reagents were purchased from Sigma-Aldrich, Alfa Aesar, or Fisher Scientific and used as received. Flash column chromatography was performed using 60 Å silica gel purchased from Fisher Scientific. ^1H NMR and ^{13}C NMR spectroscopy were performed on a Bruker AV-400 and AV-500 spectrometer. Mass spectra were obtained using an Agilent 6210 electrospray time-of-flight mass spectrometer. Qualitative TLC was performed on aluminum sheets (Merck, silica gel 60, F254). Compounds were visualized by UV absorption (254 nm) and stained with anisaldehyde. Deuterated solvents were acquired from Cambridge Isotope Labs. All reactions were carried out under an atmosphere of dry nitrogen or, in the case of photochemical reactions, subjected to three cycles of freeze-pump-thaw before irradiation. Remote hydroxylation reactions were conducted in round bottom flasks and irradiated with 4 W blue LEDs (Creative Lighting Solutions, $\lambda_{\text{max}} = 455 \text{ nm}$) which were wrapped around a crystallizing dish as pictured in figure 1.8.

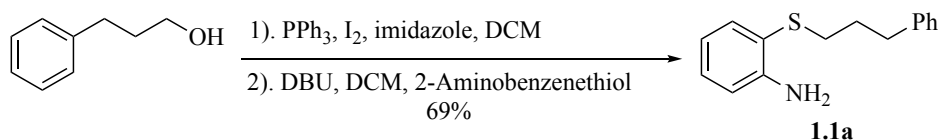


Figure 1.8: Experimental Setup

1.5.2 Procedures and Characterization

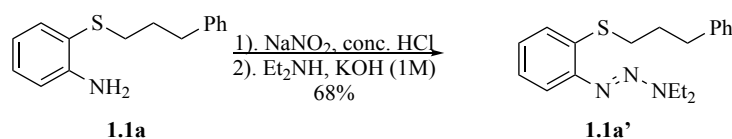
Synthesis and evaluation of *o*-triazenylphenyl alkyl sulfone **1.1c** in remote hydroxylation:

Synthetic procedure for preparation of *o*-triazenylphenyl thioether **1.1a**:



A 250 mL round bottom flask was charged with PPh₃ (30.0 mmol, 7.87 g) and 150 mL dichloromethane. Iodine (30.0 mmol, 7.61 g) was added in small portions under N₂ at room temperature. The reaction was stirred for 10 minutes. Imidazole (49.9 mmol, 3.40 g) was added to the solution in small portions and the reaction was allowed to stir for 10 more minutes. 3-Phenylpropan-1-ol (20.0 mmol, 2.72 mL) was added to the suspension dropwise in 5 minutes and the reaction was stirred for 1 hour at room temperature. 150 mL Sat. Na₂S₂O₅ was added to the reaction mixture and the aqueous layer was extracted with 150 mL dichloromethane twice. The organic layer was dried over MgSO₄ and concentrated in ice bath under low pressure to around 100 mL. The obtained iodide compound was used without further purification. 2-Aminobenzenethiol (24.0 mmol) was added to the alkyl iodide/DCM solution under N₂ and cooled to 0 °C. 1, 8-Diazabicycloundec-7-ene (DBU, 22.7 mmol, 3.40 mL) was added to the reaction dropwise at 0 °C. The reaction was warmed to room temperature and stirred for 2 hours. Water (100 mL) was added to the reaction. The aqueous layer was extracted with 100 mL DCM twice. The organic layer was dried over MgSO₄ and concentrated under vacuum. The resulting oil was purified using gradient silica gel column chromatography (0% - 10% ethyl acetate in hexanes) to give 3.40 g product **1.1a** as a colorless oil.

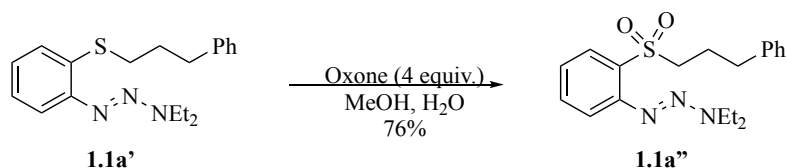
Synthetic procedure for preparation of *o*-triazenylphenyl alkyl sulfide **1.1a'**:



A 25 mL RB flask equipped with a stir bar was charged with 2.43 g (9.98 mmol) **1.1a**, which were then suspended in 10 mL concentrated hydrochloric acid to obtain a white slurry. The resulting mixture was cooled to 0 °C, and 1.035 g (15.00 mmol) sodium nitrite in 5 mL H₂O was added dropwise to the reaction. The resulting yellow solution was stirred at 0 °C for 10 min after which a solution of 1.15 mL (11.1 mmol) diethylamine in 10 mL 1 M KOH was injected to the

reaction flask using a syringe. The reaction was allowed to proceed at 0 °C for 1 hour before it was quenched by dropwise addition of 3 M NaOH until the pH ~ 12. The product was extracted with 40 mL ethyl acetate three times. The combined organic layer was washed with brine and dried over MgSO₄. The resulting crude mixture was purified using silica gel column chromatography to give 2.21 g (68%) product **1.1a'** as a yellow oil. **¹H NMR** (500 MHz, CDCl₃) δ 7.32 (dd, *J* = 7.8, 1.5Hz, 1H), 7.29 – 7.25 (m, 2H), 7.19 – 7.14 (m, 4H), 7.10 – 7.02 (m, 2H), 3.77 – 3.74 (m, 4H), 2.91 (t, *J* = 7.4Hz, 2H), 2.78 (t, *J* = 7.5Hz, 2H), 2.05 – 1.99 (m, 2H), 1.28 (t, *J* = 7.1Hz, 6H). **¹³C NMR** (125 MHz, CDCl₃) δ 148.38, 141.51, 132.27, 128.52, 128.35, 126.33, 125.89, 125.39, 125.30, 116.62, 35.05, 34.65, 32.86, 31.62, 30.83, 30.60, 30.40. **HRMS** (*m/z*): [M+H]⁺ calcd. for C₁₉H₂₆SN₃ 328.1842, found 328.1851.

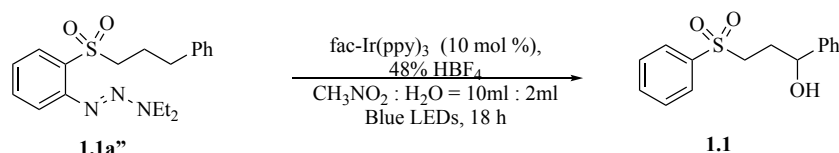
Synthetic procedure for preparation of *o*-triazenylphenyl alkyl sulfone **1.1a''**:



A 100 mL RBF was charged with 1.63 g (4.98 mmol) **1.1a'** and 30 mL methanol at room temperature. 6.15 g (20.0 mmol) Oxone was dissolved in 30 mL water and added to the solution at once. The suspension was stirred for 5 minutes (normally there is a color change from yellow to brown). The reaction was monitored by TLC until starting material had been consumed. The mixture was extracted with 40 mL dichloromethane three times. The combined organic layer was dried with MgSO₄, filtered, and concentrated under vacuum. The resulting oil was purified using gradient silica gel chromatography (0 - 15 % hexanes in ethyl acetate) to give 1.36 g (76 %) product **1.1a''** as a yellow oil. **¹H NMR** (500 MHz, CDCl₃) δ 8.02 (dd, *J* = 7.9, 1.3Hz, 1H), 7.57 (dd, *J* = 8.2, 1.0Hz, 1H), 7.52 – 7.49 (m, 1H), 7.25 – 7.20 (m, 3H), 7.16 (t, *J* = 7.3Hz, 1H), 7.08 (d, *J* = 7.1Hz, 2H), 3.82 – 3.77 (m, 2H), 3.58 – 3.52 (m, 4H), 2.70 (t, *J* = 7.4Hz, 2H), 2.09 – 2.03 (m, 2H), 1.34 (t, *J* = 7.2Hz, 3H), 1.17 (t, *J* = 7.2Hz, 3H). **¹³C NMR** (125 MHz, CDCl₃) δ 149.09, 140.30,

134.09, 131.52, 129.42, 128.47, 128.42, 126.21, 124.49, 117.70, 54.21, 49.58, 42.42, 34.33, 24.04, 14.44, 11.24. **HRMS** (m/z): [M+H]⁺ calcd. for C₁₉H₂₆SN₃O₂ 360.1740, found 360.1747.

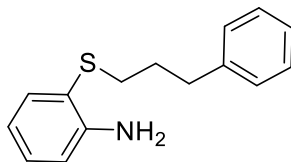
Representative synthetic procedure for remote hydroxylation of *o*-triazenylphenyl alkyl sulfone **1.1a''**:



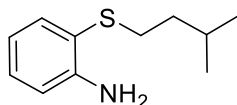
To a vigorously stirred solution of 100.0 mg (0.2781 mmol) triazene **1.1a''** and 18.2 mg (0.0278 mmol) *fac*-Ir(ppy)₃ in 10 mL CH₃NO₂ and 2 mL deionized H₂O was added 50 μ L (0.5568 mmol) 48% HBF₄ via gas-tight syringe. The reaction was subjected to freeze-pump-thaw cycles three times to get rid of oxygen. Irradiation of the solution with blue LEDs (λ_{max} = 455 nm) commenced and the reaction mixture was stirred vigorously for 18 h. 10 mL of 5% NaHCO₃ was then added at once. The aqueous layer was extracted with 10 mL DCM three times. The combined organic layers were dried over Na₂SO₄, filtered and concentrated to 97.6 mg of a yellow oil. Silica gel chromatography (0 - 30 % hexane in ethyl acetate) of the oil residue afforded 23.1 mg (30%) of **1.1** as a pale solid. **¹H NMR** (500 MHz, CDCl₃) δ 7.86 (d, *J* = 7.3Hz, 2H), 7.64 (t, *J* = 7.5Hz, 1H), 7.56 – 7.52 (m, 2H), 7.33 – 7.30 (m, 2H), 7.28 – 7.25 (m, 3H), 4.78 (t, *J* = 5.1Hz, 1H), 3.26 – 3.15 (m, 2H), 2.43 (s, 1H), 2.16 – 2.07 (m, 2H). **¹³C NMR** (125 MHz, CDCl₃) δ 143.02, 138.95, 133.74, 129.32, 128.68, 127.99, 127.98, 125.59, 72.13, 52.82, 31.73. **HRMS** (m/z): [M+Na]⁺ calcd. for C₁₅H₁₆SO₃Na 299.0712, found 299.0719.

Synthesis and evaluation of *o*-diazoniaphenyl alkyl sulfone tetrafluoroborates for remote hydroxylation:

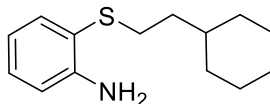
Previously-reported *o*-aminothioethers made using the method described above (isolated yields and references for spectral data in parentheses):



2-((3-phenylpropyl)thio)aniline **1.1a** (3.40 g, yield 70%, starting with 2.72 mL 3-phenyl-1-propanol) colorless oil. **¹H NMR** (500 MHz, CDCl₃) δ 7.34 (d, *J* = 7.7 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 2H), 7.16 – 7.11 (m, 3H), 7.07 (t, *J* = 7.9 Hz, 1H), 6.67 – 6.63 (m, 2H), 4.21 (s, 2H), 2.73 – 2.67 (m, 4H), 1.88 – 1.82 (m, 2H). **¹³C NMR** (125 MHz, CDCl₃) δ 148.17, 141.40, 135.71, 129.50, 128.42, 128.31, 125.85, 118.40, 117.80, 114.82, 34.55, 34.01, 31.04. **HRMS** (*m/z*): [M+H]⁺ calcd. for C₁₅H₁₈NS 244.1154, found 244.1159.

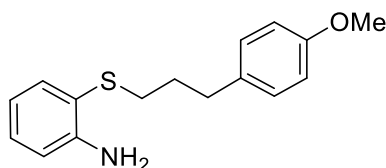


2-(isopentylthio)aniline **1.2a** (2.25 g, yield 57%, starting with 2.20 mL isoamyl alcohol) light yellow oil. **¹H NMR** (500 MHz, CDCl₃) δ 7.36 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.09 (td, *J* = 8.0, 1.5 Hz, 1H), 6.71 – 6.66 (m, 2H), 4.32 (s, 2H), 2.74 (t, *J* = 7.8 Hz, 2H), 1.71 – 1.65 (m, 1H), 1.48 – 1.43 (m, 2H), 0.85 (d, *J* = 6.8 Hz, 6H). **¹³C NMR** (125 MHz, CDCl₃) δ 148.06, 135.48, 129.35, 118.43, 118.36, 114.81, 38.59, 32.92, 27.30, 22.27. **HRMS** (*m/z*): [M+H]⁺ calcd. for C₁₁H₁₈NS 196.1154, found 196.1146.

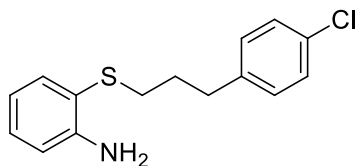


2-((2-cyclohexylethyl)thio)aniline **1.3a** (3.47 g, yield 73%, starting with 2.80 mL 2-cyclohexylethanol) colorless oil. **¹H NMR** (500 MHz, CDCl₃) δ 7.35 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.10 – 7.07 (m, 1H), 6.71 – 6.66 (m, 2H), 4.31 (s, 2H), 2.75 (t, *J* = 7.7 Hz, 2H), 1.68 (s, 2H), 1.66 (s, 3H), 1.48 – 1.44 (m, 2H), 1.39 – 1.32 (m, 1H), 1.24 – 1.08 (m, 3H), 0.90 – 0.82 (m, 2H). **¹³C NMR**

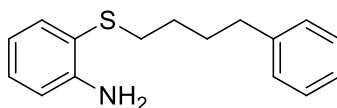
(125 MHz, CDCl₃) δ 148.02, 135.41, 129.30, 118.45, 118.43, 114.80, 37.17, 36.83, 33.01, 32.50, 26.55, 26.23. **HRMS** (m/z): [M+H]⁺ calcd. for C₁₄H₂₂NS 236.1467, found 236.1460.



2-((3-(4-methoxyphenyl)propyl)thio)aniline **1.4a** (4.64 g, yield 85%, starting with 3.20 mL 3-(4-methoxyphenyl)-1-propanol) colorless oil. **¹H NMR** (500 MHz, CDCl₃) δ 7.34 (dd, J = 7.6, 1.5 Hz, 1H), 7.09 – 7.06 (m, 1H), 7.04 (d, J = 8.6 Hz, 2H), 6.80 – 6.78 (m, 2H), 6.68 – 6.64 (m, 2H), 4.30 (s, 2H), 3.74 (s, 3H), 2.71 (t, J = 7.5 Hz, 2H), 2.63 (t, J = 7.8 Hz, 2H), 1.82 (m, 2H). **¹³C NMR** (125 MHz, CDCl₃) δ 157.77, 148.18, 135.68, 133.44, 129.47, 129.31, 118.38, 117.86, 114.80, 113.74, 55.17, 33.96, 33.62, 31.27. **HRMS** (m/z): [M+H]⁺ calcd. for C₁₆H₂₀NSO 274.1260, found 274.1263.

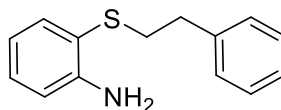


2-((3-(4-chlorophenyl)propyl)thio)aniline **1.5a** (1.327 g, yield 90%, starting with 1.487 g 1-chloro-4-(3-iodopropyl)benzene) colorless oil **¹H NMR** (500 MHz, CDCl₃) δ 7.35 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 8.3 Hz, 2H), 7.10 (t, J = 7.7 Hz, 1H), 7.05 (d, J = 8.3 Hz, 2H), 6.71 (d, J = 8.0 Hz, 1H), 6.67 (t, J = 7.5 Hz, 1H), 4.35 – 4.29 (br, 2H), 2.71 (t, J = 7.3 Hz, 2H), 2.67 (t, J = 7.7 Hz, 2H), 1.83 (quint, J = 7.4 Hz, 2H). **¹³C NMR** (125 MHz, CDCl₃) δ 148.43, 140.05, 136.03, 131.79, 129.99, 129.85, 128.64, 118.68, 117.85, 115.09, 34.05, 34.03, 31.14. **HRMS** (m/z): [M+H]⁺ calc. for C₁₅H₁₇NSCl 278.0765, found 278.0775.

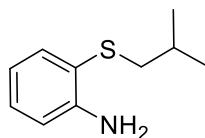


2-((4-phenylbutyl)thio)aniline **1.7a** (2.432 g, yield 99%, starting with 2.493 g (4-iodobutyl)benzene) light yellow oil **¹H NMR** (500 MHz, CDCl₃) δ 7.35 (dd, J = 7.9, 1.3 Hz, 1H),

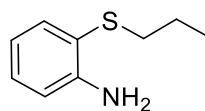
7.29 – 7.25 (m, 4H), 7.27 – 7.22 (m, 2H), 6.73 – 6.67 (m, 2H), 4.37 – 4.26 (br, 2H), 2.77 (t, $J = 7.2\text{Hz}$, 2H), 2.60 (t, $J = 7.6\text{Hz}$, 2H), 1.74 (quint, $J = 7.7\text{Hz}$, 2H), 1.62 (quint, $J = 7.3\text{Hz}$, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 148.37, 142.41, 135.94, 129.69, 128.59, 128.49, 125.93, 118.65, 118.33, 115.03, 35.62, 34.85, 30.60, 29.34. HRMS (m/z): $[\text{M}+\text{H}]^+$ calc. for $\text{C}_{16}\text{H}_{20}\text{NS}$ 258.1311, found 258.1316.



2-(phenethylthio)aniline **1.8a** (1.27 g, yield 28%, starting with 2.40 mL 2-phenylethanol) colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.38 (m, 1H), 7.27 – 7.24 (m, 2H), 7.19 – 7.16 (m, 1H), 7.13 (d, $J = 8.4\text{Hz}$, 2H), 7.11 – 7.08 (m, 1H), 6.70 – 6.66 (m, 2H), 4.18 (s, 2H), 2.99 – 2.96 (m, 2H), 2.84 – 2.81 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 148.36, 140.41, 135.89, 129.76, 128.64, 128.51, 126.40, 118.56, 117.77, 115.01, 36.13, 36.05. HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{16}\text{NS}$ 230.0998, found 230.0999.

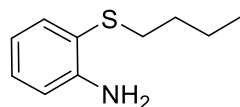


2-(isobutylthio)aniline **1.9a** (0.54 g, yield 15%, starting with 1.85 mL isobutanol) yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.37 – 7.35 (m, 1H), 7.11 – 7.07 (m, 1H), 6.72 – 6.66 (m, 2H), 4.28 (s, 2H), 2.63 (d, $J = 6.9\text{Hz}$, 2H), 1.80 – 1.72 (m, 1H), 1.00 (d, $J = 6.7\text{Hz}$, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 147.90, 135.38, 129.27, 118.28, 118.50, 114.85, 43.95, 28.51, 21.91. HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_{16}\text{NS}$ 182.0998, found 182.1004.

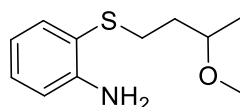


2-(propylthio)aniline **1.10a** (2.02 g, yield 61%, starting with 1.50 mL 1-propanol) colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.36 (dd, $J = 7.7, 1.3\text{Hz}$, 1H), 7.11 – 7.08 (m, 1H), 6.72 – 6.66 (m,

2H), 4.32 (s, 2H), 2.71 (t, $J = 6.8\text{Hz}$, 2H), 1.61 – 1.54 (m, 2H), 0.98 (t, $J = 7.4\text{Hz}$, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 148.14, 135.69, 129.41, 118.42, 118.25, 114.81, 36.85, 22.98, 13.31. Spectral data matched that previously reported in literature.²⁷

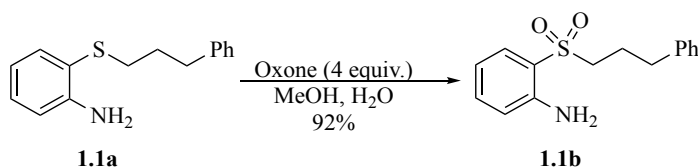


2-(butylthio)aniline **1.11a** (3.18 g, yield 88%, starting with 2.27 mL 1-iodobutane) light purple oil. ^1H NMR (500 MHz, CDCl_3) δ 7.36 (dd, $J = 7.7, 1.4\text{Hz}$, 1H), 7.11 – 7.08 (m, 1H), 6.72 – 6.66 (m, 2H), 4.32 (s, 2H), 2.73 (t, $J = 7.4\text{Hz}$, 2H), 1.57 – 1.51 (m, 2H), 1.44 – 1.37 (m, 2H), 0.89 (t, $J = 7.4\text{Hz}$, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 148.10, 135.58, 129.37, 118.43, 118.35, 114.81, 34.55, 31.74, 21.83, 13.65. Spectral data matched that previously reported in literature.²⁸



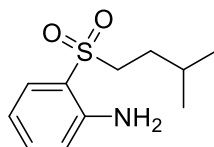
2-((3-methoxybutyl)thio)aniline **1.12a** (2.53 g, yield 61%, starting with 2.22 mL 3-methoxy-1-butanol) colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.36 (dd, $J = 7.7, 1.5\text{Hz}$, 1H), 7.11 – 7.08 (m, 1H), 6.71 – 6.66 (m, 2H), 4.33 (s, 2H), 3.45 – 3.39 (m, 1H), 3.27 (s, 3H), 2.86 – 2.76 (m, 2H), 1.79 – 1.72 (m, 1H), 1.67 – 1.61 (m, 1H), 1.10 (d, $J = 6.2\text{Hz}$, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 148.16, 135.63, 129.50, 118.42, 117.93, 114.84, 75.28, 56.02, 36.40, 30.78, 18.87. HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{18}\text{NSO}$ 212.1104, found 212.1106.

Representative synthetic procedure for sulfonylaniline preparation:

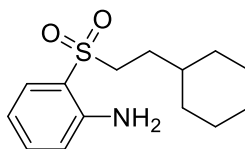


A 250ml round bottom flask was charged with **1.1a** (10.0 mmol, 2.43 g) and 50 mL methanol at room temperature. Oxone (40.0 mmol, 12.3 g) was dissolved in 50 mL water and

added quickly to the solution at once. The suspension was stirred for 5 minutes (normally there is a color change (yellow to brown) meaning the reaction was complete). The resulting mixture was extracted with 3 X 100 mL DCM. The organic layer was dried with MgSO₄, filtered, and concentrated under vacuum. The resulting oil was purified using gradient silica gel column chromatography (0% - 20% ethyl acetate in hexanes) to give 2.53g sulfonylaniline product **1.1b** of a colorless oil. **¹H NMR** (500 MHz, CDCl₃) δ 7.65 (dd, *J* = 8.0, 1.5Hz, 1H), 7.33 – 7.30 (m, 1H), 7.26 – 7.23 (m, 2H), 7.19 – 7.16 (m, 1H), 7.09 (dd, *J* = 8.2, 1.2Hz, 2H), 6.77 (td, *J* = 7.1, 1.0Hz, 1H), 6.70 (dd, *J* = 8.2, 0.75Hz, 1H), 4.91 (s, 2H), 3.14 – 3.10 (m, 2H), 2.67 (t, *J* = 7.5Hz, 2H), 2.06 – 2.00 (m, 2H). **¹³C NMR** (125 MHz, CDCl₃) δ 146.59, 140.08, 135.11, 130.23, 128.54, 128.36, 126.32, 120.23, 117.74, 117.61, 53.34, 34.07, 23.90. **HRMS** (*m/z*): [M+Na]⁺ calcd. for C₁₅H₁₇NSO₂Na 298.0872, found 298.0872.

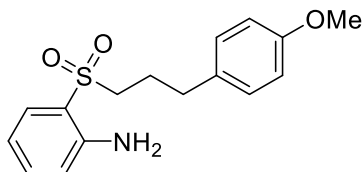


2-(isopentylsulfonyl)aniline **1.2b** (2.03 g, yield 89%, starting with 1.96 g **1.2a**) yellow oil. **¹H NMR** (500 MHz, CDCl₃) δ 7.67 (dd, *J* = 8.0, 1.4Hz, 1H), 7.37 – 7.33 (m, 1H), 6.83 – 6.79 (m, 1H), 6.75 (d, *J* = 8.2Hz, 1H), 5.04 (s, 2H), 3.16 – 3.13 (m, 2H), 1.64 – 1.57 (m, 3H), 0.87 (d, *J* = 6.4Hz, 6H). **¹³C NMR** (125 MHz, CDCl₃) δ 146.54, 135.06, 130.26, 120.36, 117.76, 117.56, 52.44, 30.67, 27.20, 22.06. **HRMS** (*m/z*): [M+H]⁺ calcd. for C₁₁H₁₈NSO₂ 228.1053, found 228.1061.

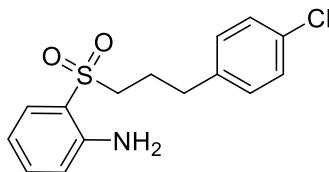


2-((2-cyclohexylethyl)sulfonyl)aniline **1.3b** (2.07 g, yield 78%, starting with 2.35 g **1.3a**) colorless oil. **¹H NMR** (500 MHz, CDCl₃) δ 7.65 (dd, *J* = 8.0, 1.5Hz, 1H), 7.35 – 7.29 (m, 1H), 6.80 – 6.75 (m, 2H), 5.11 (s, 2H), 3.17 – 3.13 (m, 2H), 1.68 – 1.56 (m, 7H), 1.29 – 1.22 (m, 1H), 1.21 – 1.05

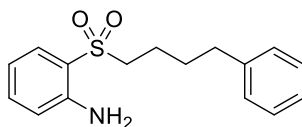
(m, 3H), 0.88 – 0.81 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 146.63, 135.03, 130.11, 120.15, 117.59, 117.56, 51.98, 36.52, 32.74, 29.26, 26.25, 25.98. HRMS (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{14}\text{H}_{21}\text{NSO}_2\text{Na}$ 290.1185, found 290.1190.



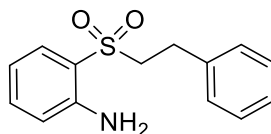
2-((3-(4-methoxyphenyl)propyl)sulfonyl)aniline **1.4b** (2.76 g, yield 90%, starting with 2.73 g **1.4a**) colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.65 (d, $J = 8.0\text{Hz}$, 1H), 7.34 (td, $J = 8.3, 1.2\text{Hz}$, 1H), 7.01 (d, $J = 8.5\text{Hz}$, 2H), 6.81 – 6.77 (m, 3H), 6.71 (d, $J = 8.2\text{Hz}$, 1H), 5.01 (s, 2H), 3.77 (s, 3H), 3.12 (t, $J = 7.8\text{Hz}$, 2H), 2.62 (t, $J = 7.5\text{Hz}$, 2H), 2.00 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 158.10, 146.55, 135.11, 132.08, 130.26, 129.30, 120.20, 117.76, 117.56, 113.95, 55.24, 53.26, 33.18, 24.12. HRMS (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{16}\text{H}_{19}\text{NSO}_3\text{Na}$ 328.0978, found 328.0974.



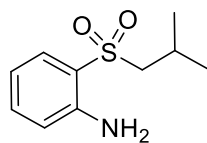
2-((3-(4-chlorophenyl)propyl)sulfonyl)aniline **1.5b** (2.75 g, yield 89%, starting with 2.77 g **1.5a**) colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.66 (dd, $J = 8.0, 1.4\text{Hz}$, 1H), 7.34 (m, 1H), 7.25 – 7.21 (m, 2H), 7.02 (d, $J = 8.4\text{Hz}$, 2H), 6.80 (td, $J = 8.0, 0.7\text{Hz}$, 1H), 6.72 (d, $J = 8.1\text{Hz}$, 1H), 4.99 (s, 2H), 3.12 – 3.10 (m, 2H), 2.66 (t, $J = 7.6\text{Hz}$, 2H), 2.05 – 1.99 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 146.58, 138.54, 135.20, 132.15, 130.25, 129.73, 128.68, 120.27, 117.87, 117.63, 53.11, 33.41, 23.83. HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{17}\text{NSO}_2\text{Cl}$ 310.0663, found 310.0665.



2-((4-phenylbutyl)sulfonyl)aniline **1.7b** (1.56 g, yield 54%, starting with 2.57 g **1.7a**) light yellow oil **¹H NMR** (500 MHz, CDCl₃) δ 7.66 (dd, J = 8.0, 1.5 Hz, 1H), 7.36 – 7.33 (m, 1H), 7.25 – 7.09 (m, 5H), 6.82 – 6.78 (m, 1H), 6.73 (dd, J = 8.3, 0.7 Hz, 1H), 5.04 – 4.97 (br, 2H), 3.15 (t, J = 7.9 Hz, 2H), 2.58 (t, J = 7.5 Hz, 2H), 1.76, (quint, J = 7.2 Hz, 2H), 1.69 (quint, J = 7.2 Hz, 2H). **¹³C NMR** (125 MHz, CDCl₃) δ 146.71, 141.55, 135.28, 130.47, 128.58, 128.51, 126.15, 120.50, 118.02, 117.74, 54.05, 35.46, 30.21, 22.18. **HRMS** (m/z): $[M+H]^+$ calc. for C₁₆H₂₀NO₂S 290.1209, found 290.1215.

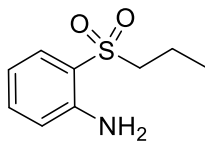


2-(phenethylsulfonyl)aniline **1.8b** (1.85 g, yield 66%, starting with 2.30 g **1.8a**) colorless oil. **¹H NMR** (500 MHz, CDCl₃) δ 7.71 (dd, J = 8.0, 1.4 Hz, 1H), 7.37 – 7.34 (m, 1H), 7.27 – 7.24 (m, 2H), 7.20 – 7.18 (m, 1H), 7.12 (d, J = 7.4 Hz, 2H), 6.82 – 6.80 (m, 1H), 6.74 (d, J = 8.2 Hz, 1H), 5.05 (s, 2H), 3.43 – 3.40 (m, 2H), 3.04 – 3.00 (m, 2H). **¹³C NMR** (125 MHz, CDCl₃) δ 146.63, 137.70, 135.30, 130.33, 128.78, 128.33, 126.84, 120.03, 117.93, 117.66, 55.24, 28.55. **HRMS** (m/z): $[M+H]^+$ calcd. for C₁₄H₁₆NSO₂ 262.0896, found 262.0899.

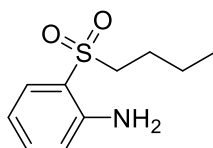


2-(isobutylsulfonyl)aniline **1.9b** (0.31 g, yield 50%, starting with 0.54 g **1.9a**) light yellow oil **¹H NMR** (500 MHz, CDCl₃) δ 7.69 (dd, J = 8.4, 1.4 Hz, 1H), 7.35 (td, J = 7.5, 1.5 Hz, 1H), 6.81 (td, J = 7.6, 0.8 Hz, 1H), 6.74 (d, J = 8.2 Hz, 1H), 5.02 (s, 2H), 3.05 (d, J = 6.4 Hz, 2H), 2.28 – 2.20 (m, 1H), 1.05 (d, J = 6.8 Hz, 6H). **¹³C NMR** (125 MHz, CDCl₃) δ 146.36, 135.01, 129.97, 121.41,

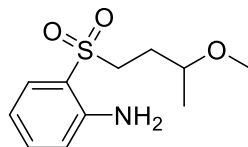
117.86, 117.56, 61.56, 23.91, 22.79. **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{10}H_{16}NSO_2$ 214.0896, found 214.0895.



2-(propylsulfonyl)aniline **1.10b** (1.56 g, yield 78%, starting with 1.67 g **1.10a**) light yellow oil **¹H NMR** (500 MHz, $CDCl_3$) δ 7.6 (d, $J = 8.0$ Hz, 1H), 7.35 (td, $J = 7.7, 1.2$ Hz, 1H), 6.81 (t, $J = 7.6$ Hz, 1H), 6.74 (d, $J = 8.2$ Hz, 1H), 5.03 (s, 2H), 3.14 – 3.11 (m, 2H), 1.78 – 1.71 (m, 2H), 0.99 (t, $J = 7.5$ Hz, 3H). **¹³C NMR** (125 MHz, $CDCl_3$) δ 146.56, 135.07, 130.32, 120.35, 117.79, 117.54, 55.89, 16.24, 12.95. Spectral data matched that previously reported in literature.²⁹



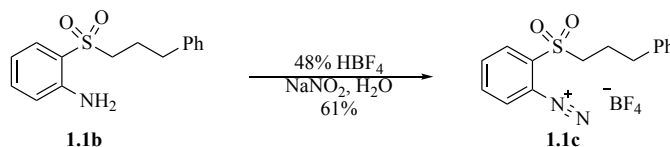
2-(butylsulfonyl)aniline **1.11b** (1.50 g, yield 70%, starting with 1.81 g **1.11a**) light green oil. **¹H NMR** (500 MHz, $CDCl_3$) δ 7.36 (dd, $J = 7.7, 1.4$ Hz, 1H), 7.09 (td, $J = 7.9, 1.2$ Hz, 1H), 6.81 (td, $J = , 2$ Hz), 4.16 (s, 2H), 2.73 (t, $J = 7.4$ Hz, 2H), 1.57 – 1.51 (m, 2H), 1.44 – 1.36 (m, 2H), 0.88 (t, $J = 7.4$ Hz, 3H). **¹³C NMR** (125 MHz, $CDCl_3$) δ 148.10, 135.62, 129.41, 118.49, 118.42, 114.88, 34.59, 31.78, 21.87, 13.69. Spectral data matched that previously reported in literature.²⁹



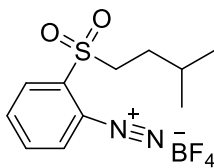
2-((3-methoxybutyl)sulfonyl)aniline **1.12b** (1.46 g, yield 60%, starting with 2.12 g **1.12a**) colorless oil. **¹H NMR** (500 MHz, $CDCl_3$) δ 7.66 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.36 – 7.32 (m, 1H), 6.80 (td, $J = 8.1, 1.0$ Hz, 1H), 6.74 (dd, $J = 8.3, 0.8$ Hz, 1H), 5.08 (s, 2H), 3.56 – 3.40 (m, 1H), 3.29 – 3.27 (m, 1H), 3.23 (s, 3H), 3.22 – 3.17 (m, 1H), 1.95 – 1.88 (m, 1H), 1.83 – 1.76 (m, 1H), 1.10

(d, $J = 6.2$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 146.62, 135.11, 130.16, 120.15, 117.66, 117.58, 74.55, 55.97, 50.43, 28.83, 18.81. **HRMS** (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{18}\text{NSO}_3$ 244.1002, found 244.1006.

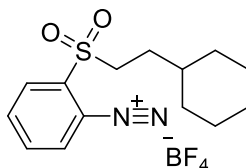
Representative synthetic procedure for *o*-diazoniaphenyl alkyl sulfone tetrafluoroborate synthesis:



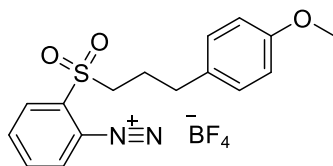
A 50 mL round bottom flask was charged with sulfonylaniline **1.1b** (5.0 mmol, 1.38 g) and cooled to 0 °C. 48% tetrafluoroboric acid (13.5 mmol, 1.80 mL) in 2.5 mL deionized water was added to **1.1b** over the course of 5 minutes with stirring under N_2 . A solution of sodium nitrite (6.45 mmol, 445 mg) in 1 mL deionized water was added dropwise over 2 minutes period to the aqueous solution and the stirring rate was increased. The reaction was stirred for 2 hours at 0 °C. The resulting mixture was filtered and washed with 1 mL cold deionized water. The solid was added to a 250 mL Erlenmeyer flask and dissolved in 15 mL acetone. The remaining solid was filtered out. One hundred milliliters anhydrous diethyl ether was added to the solution. The precipitated diazonium salt was filtered, washed with 50 mL anhydrous diethyl ether, and dried under high vacuum for 1 hour to afford 1.12 g **1.1c** of a light yellow powder. Owing to the instability at room temperature, the freshly made diazonium salt should be used immediately or stored at -2 °C for less than a week prior to use. ^1H NMR (500 MHz, CD_3CN) δ 8.82 (d, $J = 1.0$ Hz, 1H), 8.48 (td, $J = 7.8, 1.2$ Hz, 1H), 8.40 (dd, $J = 8.0, 1.2$ Hz, 1H), 8.31 – 8.27 (m, 1H), 7.34 – 7.31 (m, 2H), 7.26 – 7.22 (m, 3H), 3.56 (m, 2H), 2.78 (t, $J = 7.6$ Hz, 2H), 2.17 – 2.09 (m, 2H). ^{13}C NMR (125 MHz, CD_3CN) δ 143.33, 140.75, 139.75, 137.24, 137.01, 134.53, 129.16, 129.07, 126.99, 113.93, 56.30, 33.92, 24.17. **HRMS** (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{15}\text{H}_{15}\text{SO}_2\text{N}_2^+$ 287.0849, found 287.0840.



2-(isopentylsulfonyl)benzenediazonium tetrafluoroborate **1.2c** (1.35 g, yield 83%, starting with 1.14 g **1.2b**) pale solid. **¹H NMR** (500 MHz, CD₃CN) δ 8.82 (dd, *J* = 8.3, 0.8 Hz, 1H), 8.49 – 8.46 (m, 1H), 8.41 (dd, *J* = 7.9, 1.0 Hz, 1H), 8.29 – 8.25 (m, 1H), 3.53 (t, *J* = 8.0 Hz, 2H), 1.74 – 1.66 (m, 3H), 0.91 (d, *J* = 6.2 Hz, 6H). **¹³C NMR** (125 MHz, CD₃CN) δ 143.30, 139.92, 137.19, 136.98, 134.55, 113.94, 55.49, 30.35, 27.62, 21.71. **HRMS** (*m/z*): [*M*]⁺ calcd. for C₁₁H₁₅SO₂N₂⁺ 239.0849, found 239.0849.

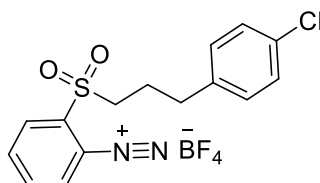


2-((2-cyclohexylethyl)sulfonyl)benzenediazonium tetrafluoroborate **1.3c** (590.1 mg, yield 32%, starting with 1.34 g **1.3b**) light brown solid. **¹H NMR** (500 MHz, CD₃CN) δ 8.81 (dd, *J* = 8.3, 1.0 Hz, 1H), 8.47 (td, *J* = 8.3, 1.1 Hz, 1H), 8.40 (dd, *J* = 7.9, 1.2 Hz, 1H), 8.27 (td, *J* = 8.3, 1.2 Hz, 1H), 3.56 – 3.52 (m, 2H), 1.70 – 1.61 (m, 7H), 1.40 – 1.34 (m, 1H), 1.26 – 1.11 (m, 3H), 0.96 – 0.89 (m, 2H). **¹³C NMR** (125 MHz, CD₃CN) δ 143.29, 139.93, 137.19, 136.99, 134.54, 113.95, 55.17, 36.95, 32.86, 29.05, 26.56, 26.34. **HRMS** (*m/z*): [*M*]⁺ calcd. for C₁₄H₁₉SO₂N₂⁺ 279.1162, found 279.1153.

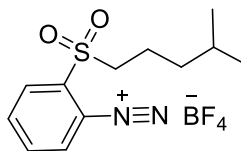


2-((3-(4-methoxyphenyl)propyl)sulfonyl)benzenediazonium tetrafluoroborate **1.4c** (1.87 g, yield 92%, starting with 1.53 g **1.4b**) yellow solid. **¹H NMR** (500 MHz, CD₃CN) δ 8.83 (dd, *J* = 8.3, 1.2 Hz, 1H), 8.48 (td, *J* = 7.8, 0.9 Hz, 1H), 8.39 (dd, *J* = 7.9, 1.0 Hz, 1H), 8.29 (td, *J* = 8.2, 1.0 Hz,

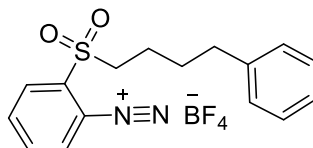
1H), 7.13 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 3.78 (s, 3H), 3.54 (t, $J = 9.2$ Hz, 2H), 2.71 (t, $J = 7.5$ Hz, 2H), 2.11 – 2.04 (m, 2H). ^{13}C NMR (125 MHz, CD_3CN) δ 158.90, 143.31, 139.77, 137.23, 137.02, 134.52, 132.61, 130.11, 114.50, 113.94, 56.27, 55.44, 33.04, 24.35. HRMS (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{16}\text{H}_{17}\text{SO}_3\text{N}_2^+$ 317.0954, found 317.0961.



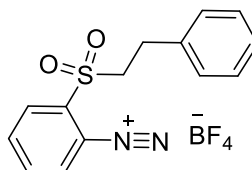
2-((3-(4-chlorophenyl)propyl)sulfonyl)benzenediazonium tetrafluoro-borate **1.5c** (1.01 g, yield 50%, starting with 1.54 g **1.5b**) pale yellow solid. ^1H NMR (500 MHz, CD_3CN) δ 8.83 (dd, $J = 8.3, 0.9$ Hz, 1H), 8.48 (td, $J = 7.8, 1.1$ Hz, 1H), 8.40 (dd, $J = 7.9, 1.2$ Hz, 1H), 8.29 (td, $J = 7.7, 1.2$ Hz, 1H), 7.33 (dd, $J = 6.6, 1.8$ Hz, 2H), 7.22 (d, $J = 8.4$ Hz, 2H), 3.56 – 3.53 (m, 2H), 2.76 (t, $J = 7.6$ Hz, 2H), 2.13 – 2.07 (m, 2H). ^{13}C NMR (125 MHz, CD_3CN) δ 143.32, 139.67, 139.60, 137.26, 137.03, 134.56, 132.19, 130.84, 129.07, 113.94, 56.15, 33.20, 23.99. HRMS (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{15}\text{H}_{14}\text{ClSO}_2\text{N}_2^+$ 321.0459, found 321.0455.



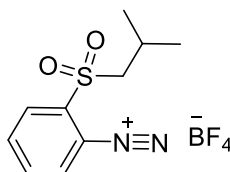
2-((4-methylpentyl)sulfonyl)benzenediazonium tetrafluoroborate **1.6c** (1.05 g, yield 62%, starting with 1.21 g **1.6b**) pale solid. ^1H NMR (500 MHz, CD_3CN) δ 8.85 (d, $J = 8.1$ Hz, 1H), 8.50 (td, $J = 7.8, 0.9$ Hz, 1H), 8.42 (dd, $J = 7.9, 0.9$ Hz, 1H), 8.30 (td, $J = 7.9, 1.1$ Hz, 1H), 3.54 (t, $J = 8.0$ Hz, 2H), 1.84 – 1.78 (m, 2H), 1.62 – 1.57 (m, 1H), 1.35 – 1.31 (m, 2H), 0.90 (d, $J = 6.7$ Hz, 6H). ^{13}C NMR (125 MHz, CD_3CN) δ 143.27, 139.93, 137.19, 137.05, 134.51, 113.96, 56.98, 37.21, 27.84, 22.07, 20.32. HRMS (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{12}\text{H}_{17}\text{SO}_2\text{N}_2^+$ 253.1005, found 253.1004.



2-((4-phenylbutyl)sulfonyl)benzenediazonium tetrafluoroborate **1.7c** (1.08 g, yield 56%, starting with 1.44 g **1.7b**) yellow solid. **¹H NMR** (500 MHz, CD₃CN) δ 8.84 (d, *J* = 8.2Hz, 1H), 8.49 (td, *J* = 7.8, 0.7Hz, 1H), 8.39 (dd, *J* = 8.2, 1.0Hz, 1H), 8.29 (td, *J* = 8.2, 1.1Hz, 1H), 7.33 - 7.30 (m, 2H), 7.23 - 7.21 (m, 3H), 3.58 (t, *J* = 7.7Hz, 2H), 2.66 (t, *J* = 7.4Hz, 2H), 1.86 - 1.80 (m, 2H), 1.79 - 1.74 (m, 2H). **¹³C NMR** (125 MHz, CD₃CN) δ 143.26, 142.27, 139.80, 137.22, 137.03, 134.49, 129.01, 128.96, 126.54, 113.94, 56.61, 35.02, 30.02, 21.80. **HRMS** (*m/z*): [*M*]⁺ calcd. for C₁₆H₁₇SO₂N₂⁺ 301.1005, found 301.1005.

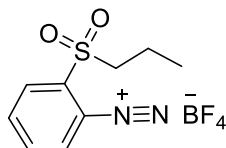


2-(phenethylsulfonyl)benzenediazonium tetrafluoroborate **1.8c** (1.12 g, yield 54%, starting with 1.50 g **1.8b**) pale solid. **¹H NMR** (500 MHz, CD₃CN) δ 8.81 (d, *J* = 8.3Hz, 1H), 8.47 - 8.44 (m, 1H), 8.39 (d, *J* = 7.7Hz, 1H), 8.27 (t, *J* = 7.8Hz, 1H), 7.33 - 7.30 (m, 2H), 7.26 (d, *J* = 7.3Hz, 3H), 3.91 - 3.88 (m, 2H), 3.18 (m, 2H). **¹³C NMR** (125 MHz, CD₃CN) δ 143.27, 139.78, 137.35, 137.22, 137.08, 134.63, 129.40, 129.17, 127.73, 113.75, 57.70, 28.30. **HRMS** (*m/z*): [*M*]⁺ calcd. for C₁₄H₁₃SO₂N₂⁺ 273.0692, found 273.0687.

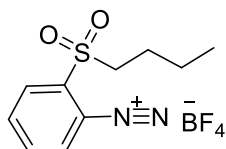


2-(isobutylsulfonyl)benzenediazonium tetrafluoroborate **1.9c** (0.23 g, yield 49%, starting with 0.31 g **1.9b**) **¹H NMR** (500 MHz, CDCl₃) δ 8.84 (d, *J* = 8.2Hz, 1H), 8.50 (t, *J* = 7.7Hz, 1H), 8.44 (d, *J* = 7.6Hz, 1H), 8.29 (t, *J* = 7.9Hz, 1H), 3.47 (d, *J* = 6.6Hz, 2H), 2.43 - 2.38 (m, 1H), 1.15 (d,

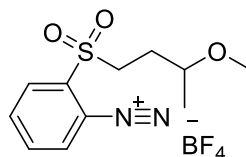
$J = 6.7\text{Hz}$, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 143.32, 140.69, 137.13, 136.88, 134.26, 113.74, 63.92, 24.52, 22.18. HRMS (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{10}\text{H}_{13}\text{N}_2\text{SO}_2$ 225.0692, found 225.0697.



2-(propylsulfonyl)benzenediazonium tetrafluoroborate **1.10c** (950 mg, yield 64%, starting with 1.00 g **1.10b**) yellow solid. ^1H NMR (500 MHz, CD_3CN) δ 8.85 (d, $J = 8.8\text{Hz}$, 1H), 8.50 (td, $J = 7.8$, 1.2Hz, 1H), 8.42 (dd, $J = 7.9$, 1.2Hz, 1H), 8.30 (td, $J = 7.7$, 1.2Hz, 1H), 3.56 – 3.52 (m, 2H), 1.88 – 1.81 (m, 2H), 1.06 (t, $J = 7.4\text{Hz}$, 3H). ^{13}C NMR (125 MHz, CD_3CN) δ 143.44, 140.04, 137.36, 137.22, 134.68, 114.13, 58.50, 16.54, 12.61. HRMS (m/z): $[\text{M}]^+$ calcd. for $\text{C}_9\text{H}_{11}\text{SO}_2\text{N}_2^+$ 211.0536, found 211.0535.



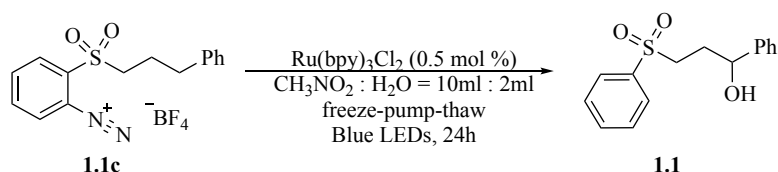
2-(butylsulfonyl)benzenediazonium tetrafluoroborate **1.11c** (1.12 g, yield 73%, starting with 1.05 g **1.11b**) light yellow solid. ^1H NMR (500 MHz, CD_3CN) δ 8.85 (dd, $J = 8.3$, 1.1Hz, 1H), 8.50 (td, $J = 7.8$, 1.2Hz, 1H), 8.43 (dd, $J = 7.9$, 1.2Hz, 1H), 8.30 (td, $J = 8.3$, 1.3Hz, 1H), 3.57 - 3.54 (m, 2H), 1.82 – 1.76 (m, 2H), 1.52 – 1.44 (m, 2H), 0.95 (t, $J = 7.4\text{Hz}$, 3H). ^{13}C NMR (125 MHz, CD_3CN) δ 143.28, 139.90, 137.19, 137.04, 134.52, 113.96, 56.63, 24.19, 21.57, 13.22. HRMS (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{10}\text{H}_{13}\text{SO}_2\text{N}_2^+$ 225.0692, found 225.0693.



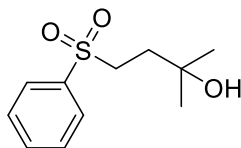
2-((3-methoxybutyl)sulfonyl)benzenediazonium **1.12c** (1.03 g, yield 59%, starting with 1.23 g **1.12b**) pale yellow power. ^1H NMR (500 MHz, CD_3CN) δ 8.81 (d, $J = 8.3\text{Hz}$, 1H), 8.48 (td, $J =$

8.0, 1.0Hz, 1H), 8.42 (dd, $J = 7.9, 1.1$ Hz, 1H), 8.27 (m, 1H), 3.68 – 3.54 (m, 2H), 3.44 – 3.38 (m, 1H), 3.20 (s, 3H), 2.02 – 1.96 (m, 1H), 1.90 – 1.82 (m, 1H), 1.10 (d, $J = 6.1$ Hz, 3H). ^{13}C NMR (125 MHz, CD_3CN) δ 143.33, 139.94, 137.20, 136.91, 134.53, 113.93, 74.72, 55.94, 53.86, 28.74, 18.49. **HRMS** (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{11}\text{H}_{15}\text{SO}_3\text{N}_2^+$ 255.0798, found 255.0794.

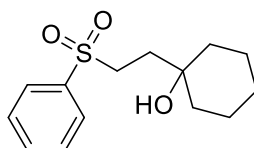
Representative synthetic procedure for remote hydroxylation of *o*-diazoniaphenyl alkyl sulfone tetrafluoroborate:



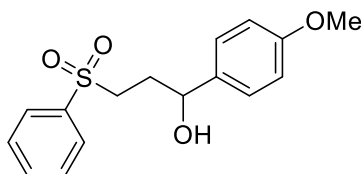
A 50 mL roundbottom flask (RBF) was charged with diazonium salt **1.1c** (0.2 mmol, 74.8 mg) and 0.5 mol % photocatalyst $\text{Ru(bpy)}_3\text{Cl}_2$ (0.001 mmol, 0.75 mg from stock solution). Vacuum-purge-backfill under N_2 atmosphere was applied three times. 10 mL nitromethane and 2 mL deionized water, both under N_2 atmosphere, were added to the flask using a syringe. The solution was deoxygenated three times using freeze-pump-thaw with a dry ice and acetone bath. The reaction was then irradiated with 4 W blue LEDs (455 nm) for 24 hours. 10 mL 5% NaHCO_3 was added to the solution and stirred for 1 minute. The aqueous layer was extracted with 10 mL DCM two times. The organic layer was dried over Na_2SO_4 , filtered, and concentrated under vacuum to afford 95.6 mg of crude material. The residue was purified by gradient column chromatography using silica gel (0% to 30% ethyl acetate in hexanes) to obtain 43.6 mg product **1.1** (79% of a pale yellow solid). ^1H NMR (500 MHz, CDCl_3) δ 7.86 (d, $J = 7.3$ Hz, 2H), 7.64 (t, $J = 7.5$ Hz, 1H), 7.56 – 7.52 (m, 2H), 7.33 – 7.30 (m, 2H), 7.28 – 7.25 (m, 3H), 4.78 (t, $J = 5.1$ Hz, 1H), 3.26 – 3.15 (m, 2H), 2.43 (s, 1H), 2.16 – 2.07 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 143.02, 138.95, 133.74, 129.32, 128.68, 127.99, 127.98, 125.59, 72.13, 52.82, 31.73. **HRMS** (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{15}\text{H}_{16}\text{SO}_3\text{Na}$ 299.0712, found 299.0719.



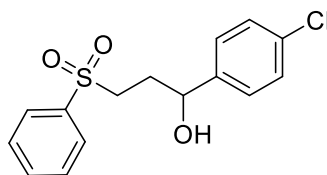
2-methyl-4-(phenylsulfonyl)butan-2-ol, **1.2** (23.7 mg, yield 52%, starting with 65.2 mg **1.2c**) colorless oil. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.93 – 7.91 (m, 2H), 7.68 – 7.65 (m, 1H), 7.59 – 7.56 (m, 2H), 3.26 – 3.23 (m, 2H), 1.90 – 1.86 (m, 2H), 1.22 (s, 6H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 139.16, 133.72, 129.32, 128.01, 69.57, 52.20, 35.50, 29.36. **HRMS** (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{17}\text{SO}_3$ 229.0893, found 229.0902.



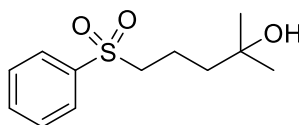
1-(2-(phenylsulfonyl)ethyl)cyclohexan-1-ol **1.3** (15.1 mg, yield 28%, starting with 74.0 mg **1.3c**) yellow oil. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.93 – 7.91 (m, 2H), 7.67 – 7.64 (m, 1H), 7.59 – 7.56 (m, 2H), 3.26 – 3.23 (m, 2H), 1.88 – 1.85 (m, 2H), 1.57 – 1.46 (m, 7H), 1.40 – 1.35 (m, 3H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 139.26, 133.66, 129.29, 127.99, 70.30, 51.33, 37.44, 34.22, 25.49, 21.98. **HRMS** (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{21}\text{SO}_3$ 269.1206, found 269.1205.



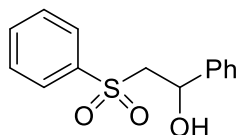
1-(4-methoxyphenyl)-3-(phenylsulfonyl)propan-1-ol **1.4** (33.7 mg, yield 55%, starting with 80.9 mg **1.4c**) pale yellow solid. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.87 (dd, $J = 7.1, 1.2\text{Hz}$, 2H), 7.65 (td, $J = 7.4, 1.0\text{Hz}$, 1H), 7.55 (td, $J = 7.4, 1.0\text{Hz}$, 2H), 7.19 (d, $J = 7.5\text{Hz}$, 2H), 6.85 (dd, $J = 7.5, 1.2\text{Hz}$, 2H), 4.74 (s, 1H), 3.79 (s, 3H), 3.26 – 3.13 (m, 2H), 2.18 (s, 1H), 2.13 – 2.09 (m, 2H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 159.37, 139.03, 135.10, 133.71, 129.31, 128.02, 126.89, 114.06, 71.89, 55.30, 52.95, 31.70. **HRMS** (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{16}\text{H}_{18}\text{SO}_4\text{Na}$ 329.0818, found 329.0829.



1-(4-chlorophenyl)-3-(phenylsulfonyl)propan-1-ol **1.5** (24.8 mg, yield 40%, starting with 81.7 mg **1.5c**) pale solid. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.85 (d, $J = 7.7\text{Hz}$, 2H), 7.65 (t, $J = 7.4\text{Hz}$, 1H), 7.55 (t, $J = 7.7\text{Hz}$, 2H), 7.28 (d, $J = 8.4\text{Hz}$, 2H), 7.20 (d, $J = 8.3\text{Hz}$, 2H), 4.80 (s, 1H), 3.19 (t, $J = 7.7\text{Hz}$, 2H), 2.57 (s, 1H), 2.13 – 2.03 (m, 2H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 141.60, 138.89, 133.86, 133.65, 129.39, 128.82, 127.97, 127.02, 71.39, 52.69, 31.74. **HRMS** (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{16}\text{ClSO}_3$ 311.0503, found 311.0504.

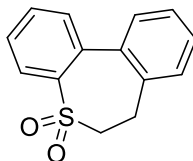


2-methyl-5-(phenylsulfonyl)pentan-2-ol **1.6** (8.0 mg, yield 17%, starting with 68.1 mg **1.6c**) white solid $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.92 (dd, $J = 7.5, 0.8\text{Hz}$, 2H), 7.68 – 7.65 (m, 1H), 7.59 – 7.56 (m, 2H), 3.14 (t, $J = 7.9\text{Hz}$, 2H), 1.88 – 1.82 (m, 2H), 1.54 (t, $J = 8.5\text{Hz}$, 2H), 1.20 (s, 6H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 139.22, 133.70, 129.31, 128.04, 70.59, 56.53, 41.74, 29.34, 17.83. **HRMS** (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{12}\text{H}_{18}\text{SO}_3\text{Na}$ 265.0869, found 265.0870.

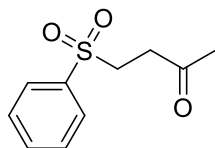


1-phenyl-2-(phenylsulfonyl)ethan-1-ol **1.8** (~5.8 mg, yield 11%, starting with 72.0 mg **1.8c**) white solid. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.96 (d, $J = 8.0\text{Hz}$, 2H), 7.70 – 7.65 (m, 1H), 7.60 (d, $J = 8.0\text{Hz}$, 2H), 7.34 – 7.27 (m, 5H), 5.28 (d, $J = 10.0\text{Hz}$, 1H), 3.60 (br, $J = 2.0\text{Hz}$, 1H), 3.50 (dd, $J = 13.9, 10.1\text{Hz}$, 1H), 3.35 (dd, $J = 14.4, 1.8\text{Hz}$, 1H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 140.63, 139.16,

134.13, 129.47, 128.76, 128.35, 127.97, 125.65, 68.44, 63.93. Spectral data matched that previously reported in literature.³⁰



6,7-dihydrodibenzo[b,d]thiepine 5,5-dioxide **1.8d** (~18.7 mg, yield 38%, starting with 72.0 mg **1.8c**) white solid. **¹H NMR** (500 MHz, CDCl₃) δ 8.14 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.74 (td, $J = 7.6, 1.3$ Hz, 1H), 7.55 (td, $J = 7.7, 1.1$ Hz, 1H), 7.51 (dd, $J = 7.6, 0.9$ Hz, 1H), 7.45 – 7.42 (m, 2H), 7.40 – 7.37 (m, 1H), 7.32 – 7.30 (m, 1H), 3.78 (t, $J = 6.9$ Hz, 2H), 2.99 (br, 2H). **¹³C NMR** (125 MHz, CDCl₃) δ 140.56, 139.45, 137.07, 135.26, 134.24, 130.80, 129.48, 129.15, 129.04, 128.56, 127.98, 125.65, 63.69, 29.60. **HRMS** (m/z): $[M+H]^+$ calcd. for C₁₄H₁₃SO₂ 245.0631, found 245.0635.

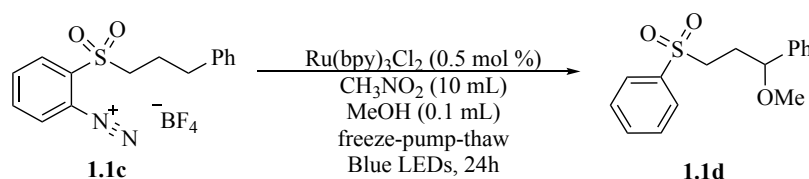


4-(phenylsulfonyl)butan-2-one **1.12** (30.1 mg, yield 71%, starting with 68.3 mg **1.12c**) pale solid. **¹H NMR** (500 MHz, CDCl₃) δ 7.91 (d, $J = 7.6$ Hz, 2H), 7.68 (t, $J = 7.4$ Hz, 1H), 7.58 (t, $J = 7.8$ Hz, 2H), 3.38 (t, $J = 7.3$ Hz, 2H), 2.93 (t, $J = 7.5$ Hz, 2H), 2.18 (s, 3H). **¹³C NMR** (125 MHz, CDCl₃) δ 203.68, 138.98, 133.96, 129.42, 127.97, 50.55, 35.86, 29.88. **HRMS** (m/z): $[M+Na]^+$ calcd. for C₁₀H₁₂SO₃Na 235.0399, found 235.0400.

Procedure for preparation of **1.1** on 1 mmol scale:

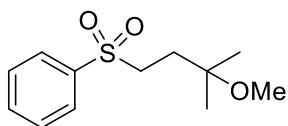
A 100 mL round-bottom flask was charged with diazonium salt **1.1c** (374.1 mg, 1.00 mmol) and 0.5 mol % photocatalyst Ru(bpy)₃Cl₂ (3.7 mg, 0.005 mmol). Vacuum-purge-backfill under N₂ atmosphere was applied three times. 50 mL nitromethane and 10 mL deionized water were

added to the flask under N₂ using a syringe. The solution was deoxygenated three times using freeze-pump-thaw with a dry ice and acetone bath. The reaction was then irradiated with 4 W blue LEDs (455 nm) for 24 hours. 50 mL 5% NaHCO₃ solution was added to neutralize acid and stirring commenced for 1 minute. The aqueous layer was extracted with 25 mL DCM twice. The organic layer was dried over Na₂SO₄, filtered, and concentrated under vacuum to afford 280 mg of crude material. The residue was purified by gradient column chromatography using silica gel (0% to 33% ethyl acetate in hexanes) to obtain 170.0 mg product **1.1** (62% of a pale-yellow solid). Representative procedure for remote etherification using methanol:



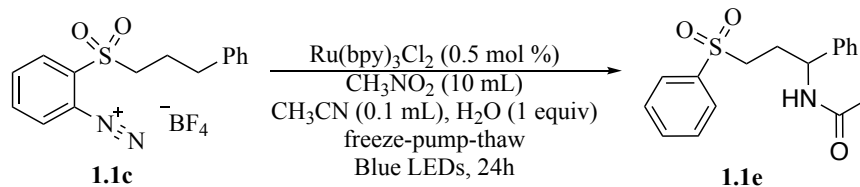
A 50 mL roundbottom flask (RBF) was charged with diazonium salt **1.1c** (0.2 mmol, 74.8 mg) and 0.5 mol % photocatalyst Ru(bpy)₃Cl₂ (0.001 mmol, 0.75 mg from stock solution). Vacuum-purge-backfill under N₂ atmosphere was applied three times. 10 mL nitromethane and 100 uL methanol both under N₂ atmosphere, were added to the flask using a syringe. The solution was deoxygenated three times using freeze-pump-thaw with a dry ice and acetone bath. The reaction was then irradiated with 4 W blue LEDs (455 nm) for 24 hours. 10 mL 5% NaHCO₃ was added to the solution and stirred for 1 minute. The aqueous layer was extracted with 10 mL DCM three times. The organic layer was dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by gradient column chromatography using silica gel (0% to 30% ethyl acetate in hexanes) to obtain 34.2 mg (59%) product **1.1d** as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.87 (d, *J* = 7.9 Hz, 2H), 7.66 – 7.63 (m, 1H), 7.56 – 7.53 (m, 2H), 7.35 – 7.26 (m, 3H), 7.21 (dd, *J* = 8.2, 1.2 Hz, 2H), 4.20 (t, *J* = 6.5 Hz, 1H), 3.27 – 3.16 (m, 2H), 3.16 (s, 3H), 2.10 – 2.06 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 140.48, 139.13, 133.69, 129.31, 128.68, 128.09,

128.05, 126.41, 81.40, 56.72, 52.89, 31.11. **HRMS** (m/z): [M+K]⁺ calcd. for C₁₆H₁₈SO₃K 329.0608, found 329.0611.



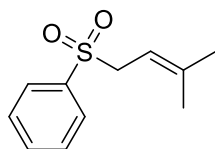
((3-methoxy-3-methylbutyl)sulfonyl)benzene **1.2d** (18.5 mg, yield 38%, starting with 65.2 mg **1.2c**) colorless oil. **¹H NMR** (500 MHz, CDCl₃) δ 7.92 (dd, *J* = 8.3, 0.9 Hz, 2H), 7.68 – 7.65 (m, 1H), 7.59 – 7.56 (m, 2H), 3.17 – 3.14 (m, 2H), 3.08 (s, 3H), 1.89 – 1.86 (m, 2H), 1.13 (s, 6H). **¹³C NMR** (125 MHz, CDCl₃) δ 139.25, 133.66, 129.29, 128.00, 73.16, 51.82, 49.20, 32.02, 24.88. **HRMS** (m/z): [M+K]⁺ calcd. for C₁₂H₁₈SO₃K 281.0608, found 281.0605.

Representative procedure for remote amidation using CH₃CN and H₂O:



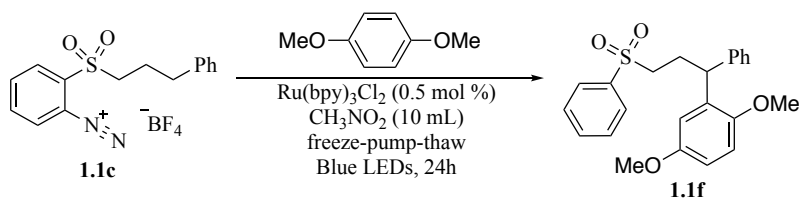
A 50 mL roundbottom flask (RBF) was charged with diazonium salt **1.1c** (0.2 mmol, 74.8 mg) and 0.5 mol % photocatalyst Ru(bpy)₃Cl₂ (0.001 mmol, 0.75 mg from stock solution). Vacuum-purge-backfill under N₂ atmosphere was applied three times. 10 mL nitromethane, 100 μL CH₃CN and 3.6 μL H₂O under N₂ atmosphere, were added to the flask using a syringe. The solution was deoxygenated three times using freeze-pump-thaw with a dry ice and acetone bath. The reaction was then irradiated with 4 W blue LEDs (455 nm) for 24 hours. 10 mL 5% NaHCO₃ was added to the solution and stirred for 1 minute. The aqueous layer was extracted with 10 mL DCM three times. The organic layer was dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by gradient column chromatography using silica gel (0% to 30% ethyl acetate in hexanes) to obtain 34.0 mg (51%) product **1.1e** as a white solid. **¹H NMR** (500 MHz, CDCl₃) δ 7.88 (dd, *J* = 7.3, 1.2 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.58 – 7.55 (m, 2H), 7.34

– 7.31 (m, 2H), 7.29 – 7.27 (m, 1H), 7.23 (d, $J = 7.1$ Hz, 2H), 6.28 (d, $J = 8.4$ Hz, 1H), 5.01 (dd, $J = 14.9, 8.5$ Hz, 1H), 3.18 – 3.14 (m, 1H), 3.12 – 3.06 (m, 1H), 2.35 – 2.27 (m, 1H), 2.24 – 2.17 (m, 1H), 1.95 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 169.66, 140.41, 138.94, 133.91, 129.43, 129.04, 128.04, 127.98, 126.50, 53.52, 51.90, 28.75, 23.27. HRMS (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{17}\text{H}_{19}\text{NSO}_3\text{Na}$ 340.0978, found 340.0983.



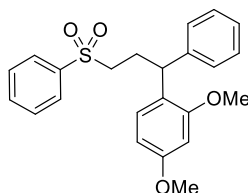
((3-methylbut-2-en-1-yl)sulfonyl)benzene **1.2e** (25.8 mg, yield 60%, starting with 65.5 mg **1.2c**) white solid. ^1H NMR (500 MHz, CDCl_3) δ 7.91 (d, $J = 7.5$ Hz, 2H), 7.66 – 7.63 (m, 1H), 7.59 – 7.53 (m, 2H), 5.20 – 5.18 (m, 1H), 3.78 (d, $J = 7.9$ Hz, 2H), 1.72 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 142.97, 138.73, 133.52, 128.98, 128.49, 110.42, 56.20, 25.83, 17.73. HRMS (m/z): $[\text{M}+\text{K}]^+$ calcd. for $\text{C}_{11}\text{H}_{14}\text{SO}_2\text{K}$ 249.0346, found 249.0346.

Representative procedure for remote arylation:



A 50 mL round-bottomed flask (RBF) was charged with diazonium salt **1.1c** (0.2 mmol, 74.8 mg), 1,4-dimethoxybenzene (1.0 mmol, 138.2 mg), and 0.5 mol % photocatalyst $\text{Ru}(\text{bpy})_3\text{Cl}_2$ (0.001 mmol, 0.75 mg from stock solution). Vacuum-purge-backfill under N_2 atmosphere was applied three times. 10 mL nitromethane was added to the flask using a syringe under N_2 atmosphere. The solution was deoxygenated three times using freeze-pump-thaw and then irradiated with 4 W blue LEDs (455 nm) for 24 hours. 10 mL 5% NaHCO_3 was added to the solution and stirred for 1 minute. The aqueous layer was extracted with 10 mL DCM three times.

The organic layer was dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue (193.2 mg yellow solid crude mixture) was purified by gradient column chromatography using silica gel (0% to 30% ethyl acetate in hexanes) to obtain 26.6 mg (34%) product **1.1f** as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.86 (dd, *J* = 7.4, 1.3Hz, 2H), 7.64 (t, *J* = 7.4Hz, 1H), 7.54 (t, *J* = 7.7Hz, 2H), 7.25 – 7.22 (m, 2H), 7.17 – 7.14 (m, 3H), 6.73 (br, *J* = 8.9Hz, 1H), 6.67 (dd, *J* = 8.8, 3.0Hz, 1H), 6.62 (d, *J* = 3.0Hz, 1H), 4.34 (t, *J* = 8.0Hz, 1H), 3.69 (s, 3H), 3.68 (s, 3H), 3.06 (t, *J* = 7.9Hz, 2H), 2.40 – 2.34 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 153.66, 151.09, 142.42, 139.04, 133.60, 132.60, 129.25, 128.52, 128.06, 127.87, 126.52, 114.49, 111.70, 111.29, 55.97, 55.60, 54.87, 42.24, 27.46. HRMS (m/z): [M+H]⁺ calcd. for C₂₃H₂₅SO₄ 397.1468, found 397.1476.



2,4-dimethoxy-1-(1-phenyl-3-(phenylsulfonyl)propyl)benzene **1.1g** (15.4 mg, yield 19%, starting with 74.8 mg **1.1c**) white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.87 (dd, *J* = 7.4, 1.1Hz, 2H), 7.64 (t, *J* = 7.4Hz, 1H), 7.54 (t, *J* = 7.7Hz, 2H), 7.25 – 7.21 (m, 2H), 7.16 – 7.12 (m, 3H), 6.93 (dd, *J* = 9.0, 1.8Hz, 1H), 6.40 – 6.38 (m, 2H), 4.26 (t, *J* = 8.5Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.04 (t, *J* = 8.1Hz, 2H), 2.43 – 2.31 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 159.49, 157.77, 143.11, 139.12, 133.57, 129.23, 128.44, 128.07, 128.01, 127.79, 126.34, 123.74, 104.29, 98.72, 55.35, 55.30, 54.98, 41.75, 27.55. HRMS (m/z): [M+Na]⁺ calcd. for C₂₃H₂₅SO₄ 397.1468, found 397.1470.

Cyclic Voltammetry:

CV of 1 mM **1.1c** in acetonitrile was performed on an AUTOLAB PGSTAT302 instrument at a scan rate of 0.1 V/s with Ag/Ag⁺ reference electrode, Pt counter electrode and glassy carbon working electrode. Electrodes were mechanically polished then cleaned with acetone. The

electrolyte used was tetrabutylammonium hexafluorophosphate at 0.1 M concentration. Observed E_{red} of **1.1c** vs Ag/Ag⁺ was -0.38 V (-0.28 V measurement – 0.10 V ferrocene calibration offset). Ag/Ag⁺ was converted to SCE by adding 0.30 V to the Ag/Ag⁺ potential. Therefore, we report the E_{red} of **1.1c** as -0.08 V (SCE) in the text of the Communication so that a direct comparison to the (spectro)electrochemistry of Ru(bpy)₃²⁺ can be made.

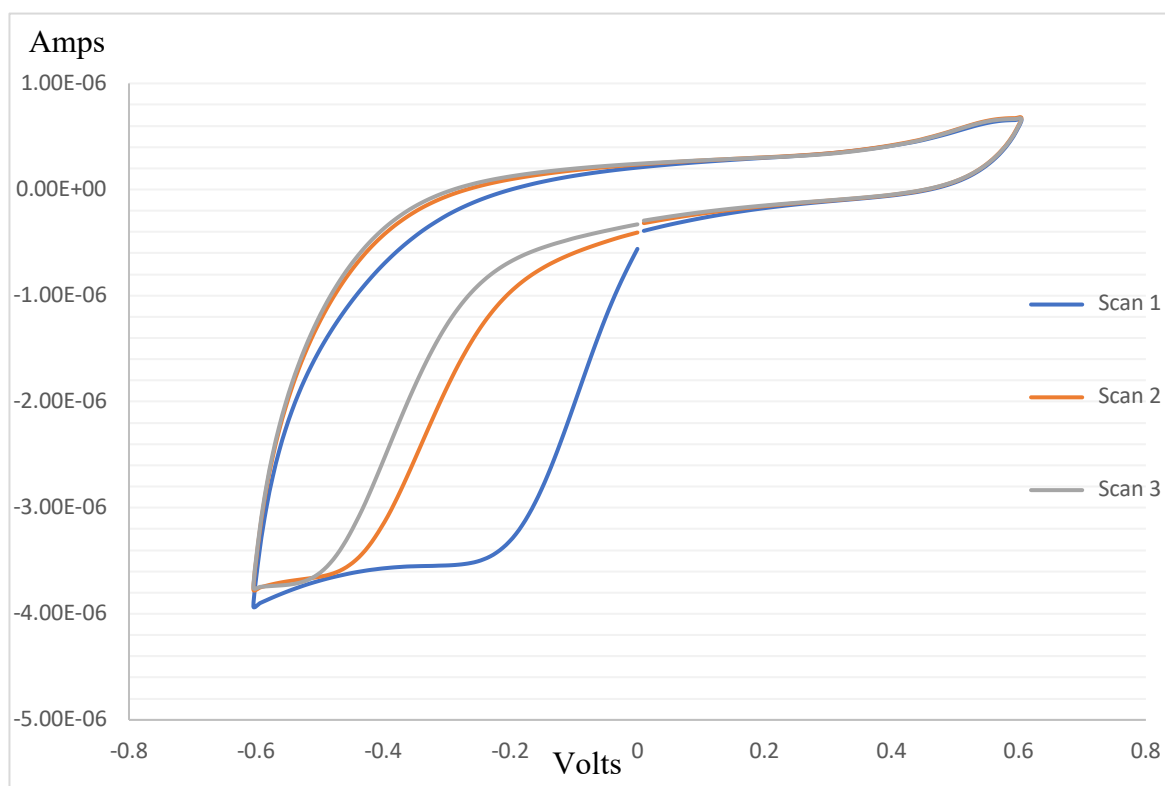


Figure 1.9 CV of Arenediazonium Salt **1.1c**

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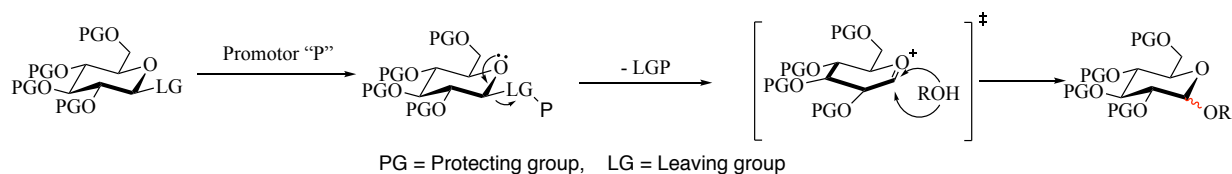
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CHAPTER 2: ACID-CATALYZED *O*-GLYCOSYLATION WITH STABLE THIOGLYCOSIDE DONORS

2.1 Introduction

Carbohydrates play essential roles in biological systems.¹ Over the past few decades, research has revealed the function of carbohydrates in numerous health-related contexts. For example, the pathogenesis of diabetes, AIDS, and cancer are all carbohydrate-related processes.² Understanding the roles of carbohydrates in these processes has facilitated many biological discoveries.³

Oligosaccharides are found in numerous natural products and play significant roles in therapeutics and vaccines.⁴ The interactions between oligosaccharides and proteins, lipids, and other conjugates are critical for cell recognition and differentiation.⁵ Oligosaccharides are ubiquitous on the outside of cells. Therefore, the identification of oligosaccharide composition,⁶ conformation,⁷ and interaction with other molecules⁸ is of great importance. Isolation from natural resources provides easy access to test the biological properties of these molecules. However, due to the microheterogeneity of naturally occurring oligosaccharides,⁹ isolates from natural sources often contain small quantities of contaminants. Therefore, scientists are exploring chemical¹⁰ and enzymatic¹¹ synthesis of oligosaccharides to get enough pure material to study and unambiguously assign the function.



Scheme 2.1 *O*-Glycosylation

Many methods have been developed for the formation of oligosaccharides. Specifically, *O*-glycosylation (Scheme 2.1), a chemical reaction that adds an alcohol to a sugar molecule, plays a very important role in the multistep synthesis of oligosaccharides. In *O*-glycosylation, stereo-

control of glycosidic bond formation is still a challenge in glycosylation reactions. Glycosylation reactions can undergo both S_N1 - and S_N2 -type mechanisms,¹² which can confound the control of anomeric configuration. Factors, like protecting groups, leaving groups, solvents, and additives can be of great importance.

2.2 Mechanistic Pathways

In general, the mechanism of chemical glycosylation falls into two categories: unimolecular S_N1 mechanisms, and bimolecular S_N2 -like mechanisms (Figure 2.1). For the S_N1 pathway, after activation of the glycosyl donors, dissociation results in the oxocarbenium ion intermediate. Attack of glycosyl acceptor from either the top or the bottom face will generate the glycosidic linkage. This pathway normally leads to anomeric mixtures since there is often little or

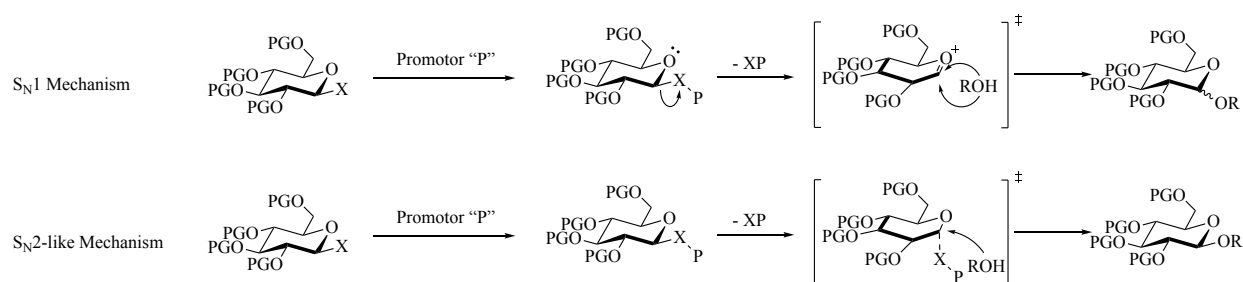


Figure 2.1 Possible Mechanism for Chemical Glycosylation (PG = Protecting Group)

no stereo-control at the anomeric center. The second mechanism is the S_N2 -like pathway. After activation, the leaving group stays close enough to form a contact ion pair with the resulting glycosyl carbocation. As a result, the glycosyl acceptor can only attack from the opposite face, generating a single anomer. There are many other factors that can affect the stereochemical outcome of the glycosylation reactions. Understanding the multiple factors contributing to the mechanism can explain the stereoselectivity of the reaction and provide insights leading to the design of *O*-glycosylation reactions.

2.3 Neighboring Group Participation

The presence of an acyl protecting group at the C₂ position can affect the stereoselectivity of the glycosylation reactions. After generating the oxocarbenium ion intermediate, the carbonyl

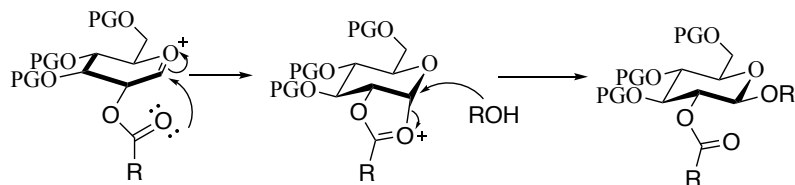


Figure 2.2 Neighboring Group Participation (PG = Protecting Group)

lone pair will interact with the anomeric center resulting in the formation of a dioxolenium ion, which blocks the bottom face of the intermediate (Figure 2.2). As a result, the glycosyl acceptor can only attack from the top face of the intermediate to generate, exclusively, the β anomer. Neighboring group participation is a very important tool to control the stereoselectivity of glycosylation reactions.

2.4 Anomeric Effect

The anomeric effect (also called “Edward-Lemieux Effect”) was first discovered by J. T. Edward and R. U. Lemieux in the 1960s.¹³ Electronegative atom substituents on the anomeric carbon prefer to be axial. Two possible explanations were proposed. According to molecular orbital theory (MOT), hyperconjugation occurs between the lone pair on the oxygen and the σ^*

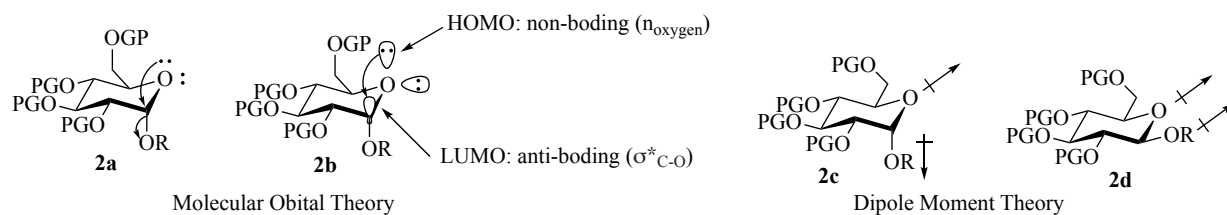


Figure 2.3 MOT and DMT Explanations for Anomeric Effect (PG = Protecting Group)

orbital of the C-OR bond (**2a**, **2b** Figure 2.3).¹⁴ The increased bond length of an axial C-Cl bond (1.819 Å) compared with the equatorial C-Cl bond (1.718 Å) in a glycosyl chloride further

supported this hyperconjugation hypothesis. Another explanation is the dipole moment theory (DMT), which stated that the opposing dipoles (**2c**) were more stabilizing than the aligned dipoles (**2d**) (Figure 2.3).¹³

2.5 Solvent Effects

Another factor to be considered for the stereochemical outcome of glycosylation reactions is solvent. The utilization of solvent to control the stereochemistry of glycosylation is attractive since the solvent can be simply removed under vacuum. Another advantage is avoiding the use of special protecting groups and simplifying the preparation steps for the starting materials. Non-polar solvents like toluene, benzene, and dichloromethane will not participate in the glycosylation process. The purpose of using these solvents is due to temperature and solubility preference of glycosylation reactions. For example, some glycosylation reactions require high temperature to undergo the S_N2-type mechanism. Instead, high boiling point solvents like benzene or toluene can be used. Polar, coordinating solvents, such as diethyl ether, acetonitrile, and *N,N*-dimethylformamide will attack the oxocarbenium ion and direct the stereochemical outcome of the glycosylation. For example, diethyl ether favors the formation of β -oxonium intermediate **2f** (Figure 2.4-A), which undergoes an S_N2-like process to generate α glycoside (**2g**) as the major

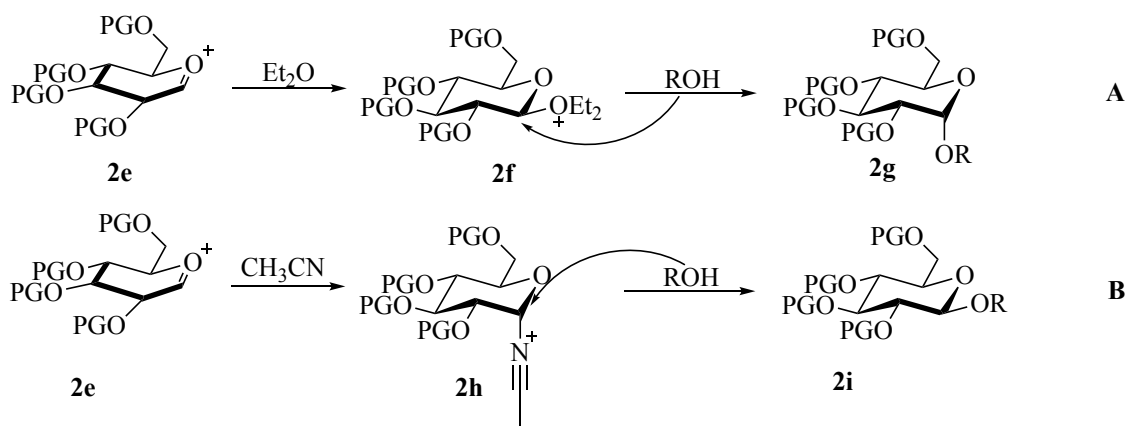


Figure 2.4 Effect of Solvents on Glycosylation (PG = Protecting Group)

product.¹⁵ Acetonitrile, by contrast, prefers to form the α -nitrilium ion **2h** that is attacked by alcohols to generate the β glycoside **2i** (Figure 2.4-B).¹⁶

2.6 Glycosyl Acceptors

A glycosyl acceptor refers to a carbohydrate mono- or oligosaccharide-ligated alcohol which serves as a nucleophile in the formation of glycosidic linkages. The reactivity of glycosyl acceptor is strongly determined by the nucleophilicity of an alcohol in *O*-glycosylation. Some commonly used glycosyl acceptors are shown in Figure 2.5. In general, primary alcohols are more nucleophilic than secondary alcohols. For example, the free hydroxyl group on carbon 6 (**2j**) is more nucleophilic than the hydroxyl groups on carbons 2 (**2k**) to 4 (**2l**). Axial hydroxyl groups (**2m**) are generally less nucleophilic than those at equatorial positions. Protecting groups also have

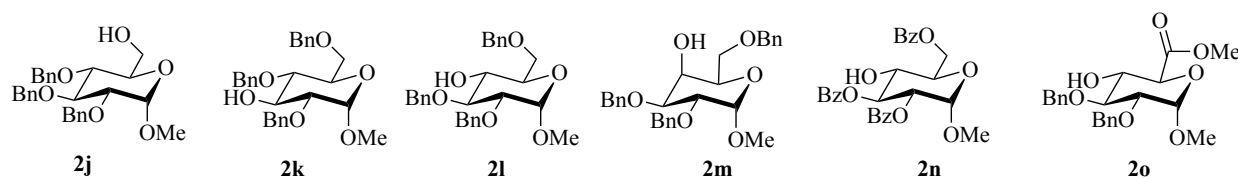


Figure 2.5 Representative Examples of Glycosyl Acceptors

a huge impact on the reactivity of glycosyl acceptors. For example, *O*-benzylated glycosyl acceptors (**2l**) are more reactive than *O*-benzoylated ones (**2n**) due to electron-withdrawing carbonyl groups. Also, the electronic effect is another concern considering the reactivity of glycosyl acceptors. For example, the carbonyl containing glycosyl acceptor (**2o**) is much less reactive than *O*-benzylated glycosyl acceptors (**2l**).

2.7 Glycosyl Donors

A glycosyl donor refers to a carbohydrate mono- or oligosaccharide which serves as an electrophile in the formation of glycosidic linkages and has a leaving group at the anomeric position. For the purposes of this dissertation, the alpha (α) and beta (β) carbohydrate anomers are

defined as follows: α anomer refers to stereoisomers with the *cis* relationship between the C₅-C₆ bond and the C₁-H bond (C₁ is the anomeric carbon); β anomer refers to stereoisomers with the *trans* relationship between the C₅-C₆ bond and the C₁-H bond (Figure 2.1). Selectivity in obtaining the α or β anomer is the key to the synthesis of oligosaccharides, particularly those occurring in complex natural glycans.

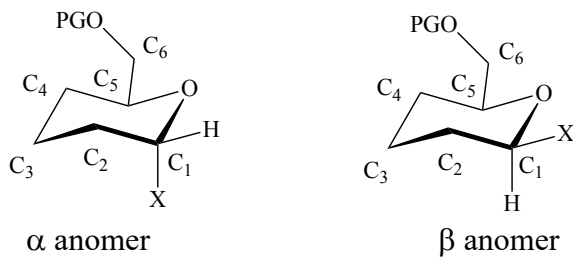


Figure 2.6 General Configuration of α and β Anomers (PG = Protecting Group)

2.7.1 Protecting Groups

Protecting groups are widely used in glycosyl donors as well as glycosyl acceptors. The effects are varying. As the famed carbohydrate chemist Bertram O. Fraser-Reid once said: "protecting groups do more than protect."¹⁷ The best-known effect of protecting groups is neighboring group participation (*vide supra*),¹⁸ which directly controls the stereochemical outcome of the glycosylation reaction. The vast majority of β glycosidic linkages are generated using this effect. In some cases, protecting groups can affect the conformation and electronics of the starting

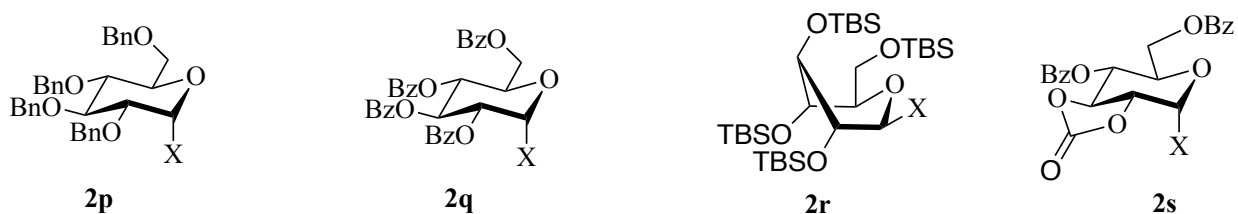


Figure 2.7 Examples of Glycosyl Donors

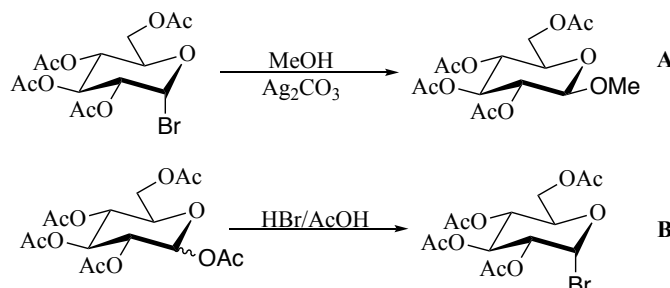
materials, reaction intermediates, and products.¹⁹ For example, the electron withdrawing benzoyl protected glycosyl donor **2q** (Figure 2.7) is less reactive than the electron donating benzyl protected glycosyl donor **2p** (Figure 2.7) because the electron-releasing benzyl groups can better

stabilize the oxocarbenium ion intermediate. The *tert*-butyldimethylsilyl (TBS) protected glycosyl donor **2r** has a twist boat conformation because the C₂-C₄ C-O bonds, protected by bulky TBS groups, occupy the pseudo-axial positions to avoid stereo interaction (Figure 2.7). Though the effects of protecting groups have been studied for decades, a paradigm, namely the armed-disarmed strategy, to distinguish protecting groups' properties was developed by Fraser-Reid and others starting in 1988.²⁰ This strategy is focused on the nucleophilicity of the anomeric heteroatom resulting from the electron-withdrawing effects of the protecting groups. The carbonyl-containing acyl protecting groups (**2q**) withdraw electrons from the anomeric heteroatom, which decreases the reactivity (disarming) of glycosyl donors toward eventual formation of oxocarbenium or ion pairs. To contrast, alkyl substituents (**2p**) increase the reactivity through release of electrons (arming). Benzyl and benzoyl protected donors have become benchmarks for describing armed and disarmed glycosyl donors, respectively. Super armed glycosyl donors (**2r**) are defined as more reactive than the *per-O*-benzylated donors. Super disarmed glycosyl donors like **2s** is much less reactive because the cyclic protecting groups increase the rigidity of the sugar ring to interfere with the flat oxocarbenium ion formation (**2e**, Figure 2.4).

2.7.2 Glycosyl Halides

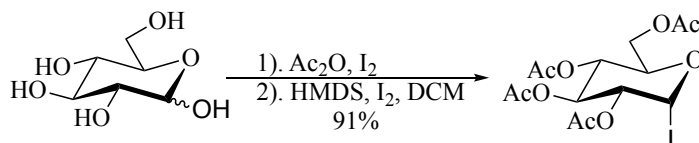
Fisher and Armstrong²¹ as well as Koenigs and Knorr²² independently reported that glycosyl bromides and chlorides could react with alcohols to form glycosidic linkages in the presence of silver or mercury salts in 1901 (Scheme 2.2-A). After that, they extended the preparation procedure to synthesize the glycosyl halides. For example, they treated *per-O*-acetylated monosaccharides with HBr/AcOH to generate glycosyl bromides (Scheme 2.2-B),²³ which is still an efficient method to make glycosyl bromides today. However, the strongly acidic conditions used to make the glycosyl bromide make it incompatible with oligosaccharide synthesis especially with acid-sensitive glycosides. Milder synthetic routes are in demand. Mizuno and

coworkers²⁴ and Xue and coworkers²⁵ performed the synthesis of glycosyl halides using photo-redox catalysis. Regarding glycosyl iodide, most glycosylation reactions used in situ generation



Scheme 2.2 Preparation and Glycosylation with Glycosyl Bromide

because of the short shelf life of glycosyl iodides. Many dependable methods to obtain glycosyl iodide using either trimethylsilyl iodide (TMSI)²⁶ or HI²⁷ have been developed. Instead of using the harsh and reactive TMSI reagent, Field's group developed another activation method combining easily handled hexamethyldisilane and iodine, which generated TMSI in situ as the reactive intermediate. Field's group successfully made acetylated glycosyl iodide using this activation method in good yields (Scheme 2.3).²⁸ In 1981, Mukaiyama *et al.* uncovered the role of



Scheme 2.3 Preparation of Glycosyl Iodide

glycosyl fluoride as glycosyl donor. Glycosyl fluoride could be activated by AgClO_4 and SnCl_2 .²⁹ Because of the stability of the C-F bond compared with other C-X bonds, the utility and synthesis of glycosyl fluoride have been widely developed.³⁰

2.7.3 Alkenyl/Alkynyl Glycosides

The prototype alkenyl glycoside is the *n*-pentenyl glycoside (**2.1**) because of its versatility. The activation of *n*-pentenyl glycoside is shown in Figure 2.8. Employment of *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) results in the bromonium (**2.2**) or iodonium

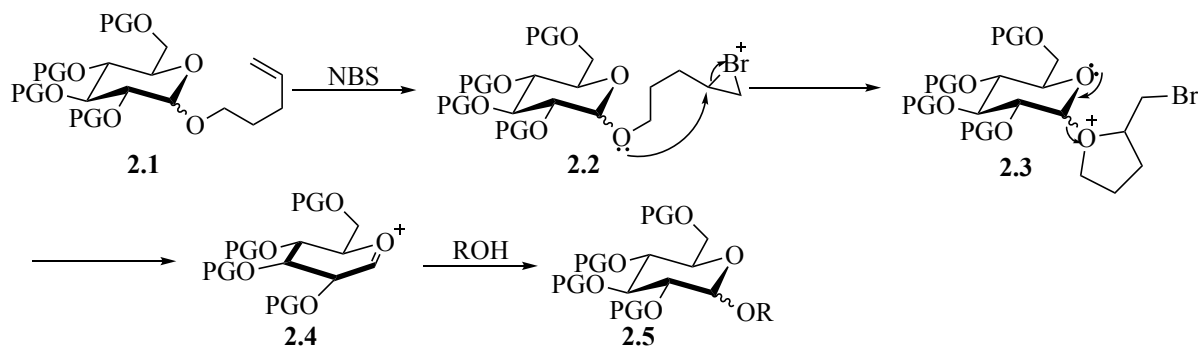


Figure 2.8 Activation of *n*-Pentenyl Glycoside (PG = Protecting Group)

ion by reaction with the alkene. The following cyclization with the exoanomeric oxygen leads to the formation of tetrahydrofuranyl oxonium ion intermediate **2.3**. Collapse of **2.3** generates the oxocarbenium ion **2.4** with a tetrahydrofuran derivative as leaving group. Then, **2.4** is attacked by

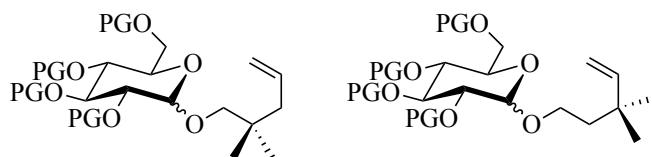


Figure 2.9 *gem*-Dimethyl Analogs of *n*-Pentenyl Glycosides (PG = Protecting Group)

a nucleophile to generate the final glycosylation product. It is worthy to note that the coupling efficiency is higher in *gem*-dimethyl substituted *n*-pentenyl glycosides due to Thorpe-Ingold effect (Figure 2.9).³¹

Propargyl glycosides were the prototype for Au-catalyzed *O*-glycosylation. Because of the alkynophilic property of gold, this class of glycoside can be activated by Au^I or Au^{III} species

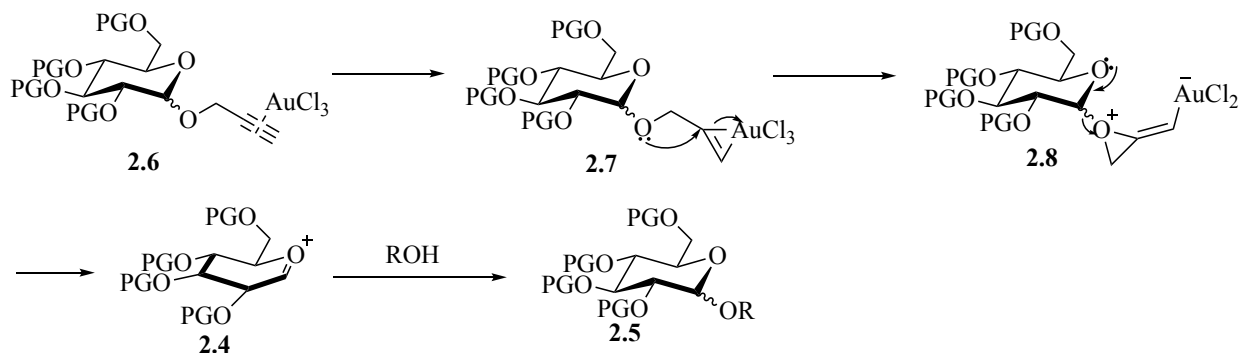


Figure 2.10 Activation of Propargyl Glycoside (PG = Protecting Group)

(Figure 2.10).³² Coordination of AuCl₃ to the propargyl glycoside **2.6** leads to the formation of cyclopropyl gold intermediate **2.7**. The oxocarbenium ion **2.4** is generated by the expulsion of an alkenyl gold complex intermediate **2.8**. Intermediate **2.4** is then attacked by an alcohol to generate

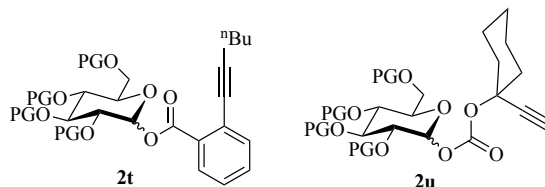


Figure 2.11 Structures of Yu's and Hotha's Alkynyl Glycoside (PG = Protecting Group)

the final product **2.5**. Besides the propargyl glycoside, Yu and coworkers introduced a new class of alkynyl glycoside called *ortho*-alkynyl benzoate glycoside **2t**, (Figure 2.11), which could be activated by gold catalysts and even molecular iodine.^{33a} Hotha and coworkers developed another, more useful alternative alkynyl glycoside called glucosyl ethynylcyclohexyl carbonate **2u** (Figure 2.11). The rigidity of the structure conformation makes it a faster and more efficient glycosyl donor than **2t** in the synthesis of oligosaccharides.^{33b}

2.7.4 Glycosyl Imidates

Since they were first introduced by Schmidt and coworker in 1980,³⁴ glycosyl trichloroacetimidates have been widely used in oligosaccharide synthesis. The preparation of those glycosyl donors involves reacting the anomeric hydroxyl group of a reducing sugar with trichloroacetonitrile under basic conditions. The activation of glycosyl imidates requires strong Lewis acid such as AgOTf,³⁵ BF₃•Et₂O,³⁶ TMSOTf,³⁷ ZnBr₂,³⁸ or protic acid.³⁹ Protonation of nitrogen in the glycosyl trichloroacetimidate **2.9** is followed by the departure of imidoyl group

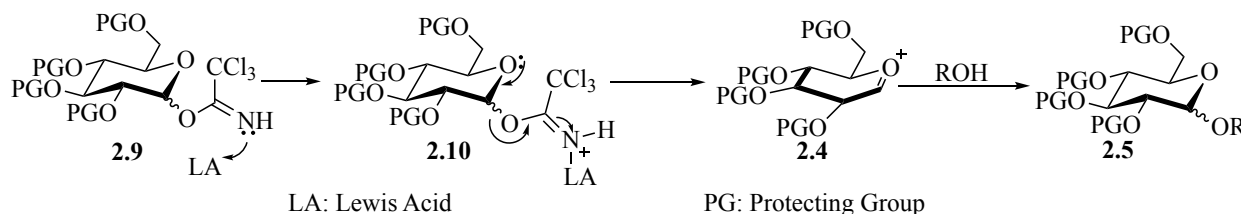
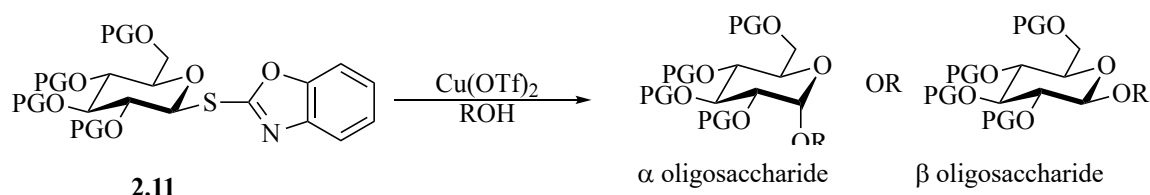


Figure 2.12 Activation of Glycosyl Trichloroacetimidate with Lewis Acid

resulting in the formation of trichloroacetamide and oxocarbenium ion **2.4**, which is further attacked by alcohols to generate the final products **2.5** (Figure 2.12). Yu and coworkers have introduced an alternative called glycosyl *N*-phenyl trifluoroacetimidates. Their synthesis involves combination of anomeric hydroxyl group with (*N*-phenyl)trifluoroacetimidoyl chloride in the presence of K_2CO_3 . Yu's group has demonstrated that the stability and efficacy of these *N*-phenyl trifluoroacetimidates is comparable to that of trichloroacetimidates. Due to the relative instability of glycosyl imidates, long-term storage should be avoided. For the best results, they should be used immediately after preparation.

Thio-imidates have also been introduced as glycosyl donors for oligosaccharide synthesis. Demchenko and coworkers have made important contributions to the development of thioimide glycosyl donors. They introduced a new thioimide donor called the *S*-benzoxazolyl (SBox)



Scheme 2.4 Glycosylation of SBox Glycoside (PG = Protecting Group)

glycoside (**2.11**), which has been reported to undergo both α and β selective *O*-glycosylation (Scheme 2.4).⁴⁰ Typical promoters include Cu(OTf)_2 ,⁴¹ MeOTf ,⁴² and NIS/HOTf for thioimide activation.

2.7.5 Thioglycosides

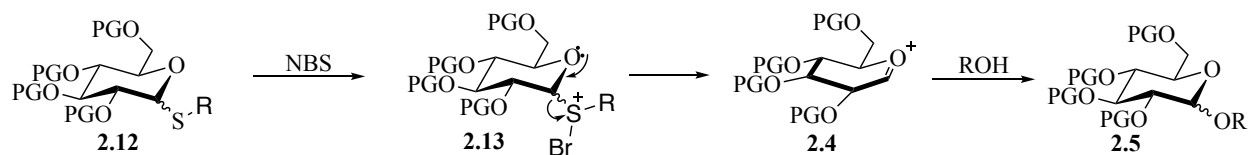


Figure 2.13 Activation of Thioglycoside Using NBS (PG = Protecting Group)

Thioglycosides, first introduced as glycosyl donors by R. J. Ferrier *et al*,⁴³ have become one of the most commonly used glycosyl donors in the synthesis of oligosaccharides and complex

glycoconjugates. This class of glycoside is remarkably stable towards various protecting group manipulations, making them ideal candidates for the orthogonal synthesis of oligosaccharides. However, because of the high stability, harsh promoters like AgOTf, CuOTf, NIS/HOTf, and PhHgOTf are used to activate thioglycosides.⁴⁴ More recently, much milder promoters such as iodonium dicollidine perchlorate (IDCP),⁴⁵ Ipy₂BF₄,⁴⁸ NBS/HOTf,⁴⁵ PhIO/Tf₂O,⁴⁷ and the photosensitizer Ru(bpy)₃²⁺ were applied to activate thioglycosides.⁴⁹ The aim is to use the promoter as an electrophile that can react with or coordinate to sulfur lone pair to convert the sulfide to a more efficient leaving group so as to generate the oxocarbenium intermediate **2.4** (Figure 2.13).

2.7.6 Glycals

Glycals, which are an important precursor for making 3,4-unsaturated glycosides, are of great importance in carbohydrate chemistry. The Ferrier rearrangement (Figure 2.14) is one such process involving glycal substrates.⁵⁰ This transformation takes place in the presence of Lewis acid. The use of glycals as glycosyl donors in glycosylation reactions was expanded by

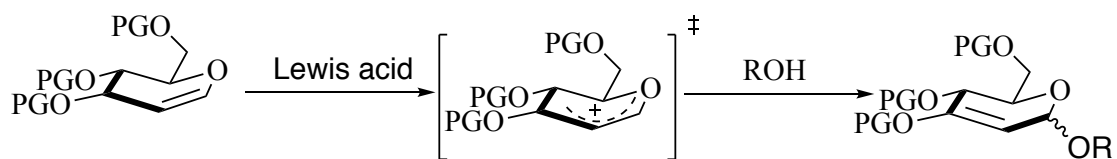


Figure 2.14 Ferrier Rearrangement (PG = Protecting Group)

Danishefsky.⁵¹ Nucleophilic attack of the alkene on electrophiles generates an onium intermediate which can then be attacked by an alcohol to form glycosyl products (Figure 2.15). This method has been extensively used in the stereoselective synthesis of *O*-glycosides. However, the harsh

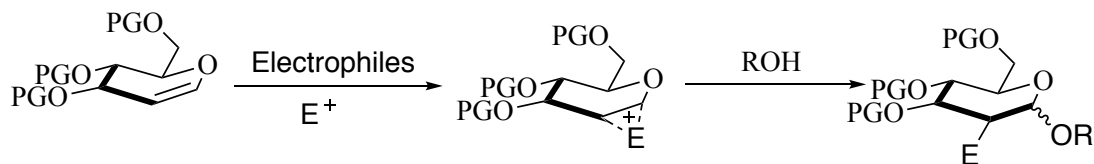


Figure 2.15 Glycosylation of Glycals (PG = Protecting Group)

reaction conditions sometimes limit their use in some glycosylation reactions such as substrates containing acid-labile functionality.⁵²

2.8 Research Significance

Due to the microheterogeneity of natural oligosaccharides, it is often hard to obtain sufficient quantities of pure materials from natural sources. The chemical synthesis of oligosaccharides is a significant tool for deepening our understanding of glycobiology.⁹ In particular, *O*-glycosylation is one of the most important chemical reactions in the multistep synthesis of oligosaccharides. Two of the most commonly used donors in *O*-glycosylation are thioglycosides and glycosyl trichloroacetimidates (TCAs, Figure 2.16). As mentioned earlier, thioglycosides are easily synthesized from glycosyl halides. Due to their high stability, thioglycosides are ideal candidates for multistep synthesis though their activation requires harsh conditions. TCAs are directly synthesized from lactols and are activated under mildly acidic conditions. However, TCAs are not easily carried through multistep synthesis due to their instability in certain systems. *N*-phenyltrifluoroacetimidates (PTFAs, Figure 2.16), which are more stable substituents for TCAs, are still considered unstable and have short shelf life.¹⁰

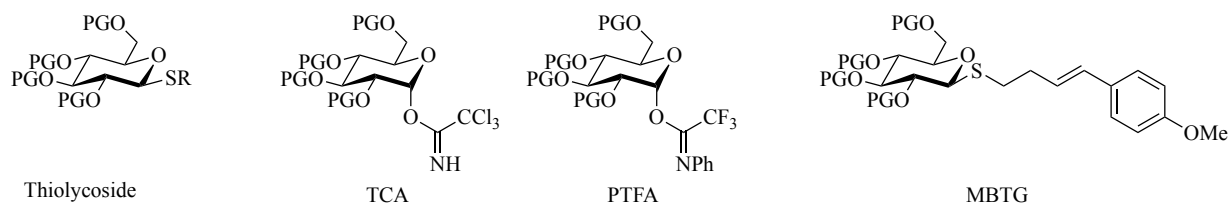
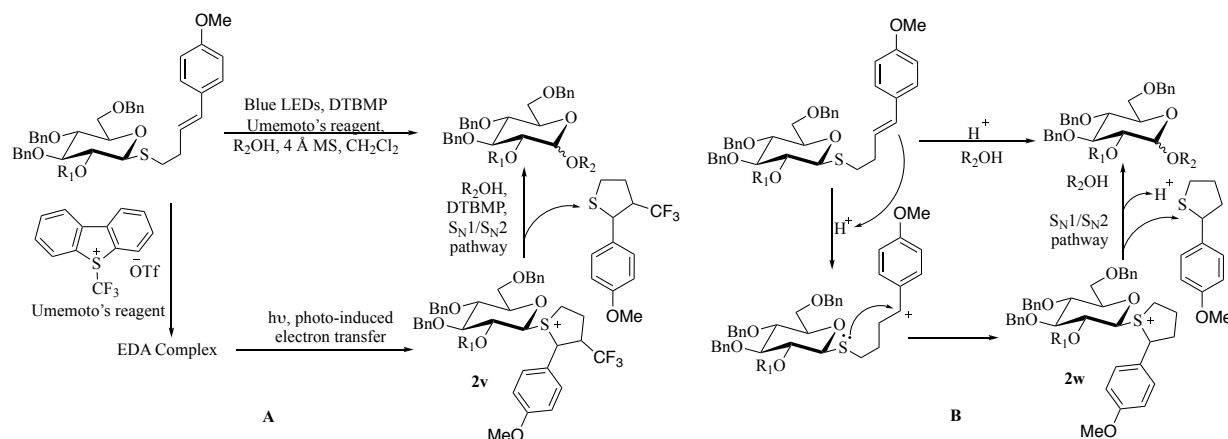


Figure 2.16 Structures of Glycosyl Donors (PG = Protecting Group)

Recently, the Ragains group has developed a new class of thioglycosides: 4-(4-methoxyphenyl)-3-butenylthioglycosides (MBTGs, Figure 2.16). MBTGs were first used in a visible-light-promoted *O*-glycosylation reaction (Scheme 2.5-A).⁴⁹ In this transformation, the electron-rich thioglycoside and Umemoto's reagent formed an electron donor-acceptor (EDA) complex, which was activated by blue LED irradiation to generate a glycosylsulfonium ion

intermediate (**2v**). Subsequent alcohol attack resulted in the formation of glycosidic linkages. In contrast to most thioglycoside activation methods, this photo-induced activation of MBTGs is a



Scheme 2.5 Visible-Light-Promoted and Acid-Catalyzed *O*-Glycosylation

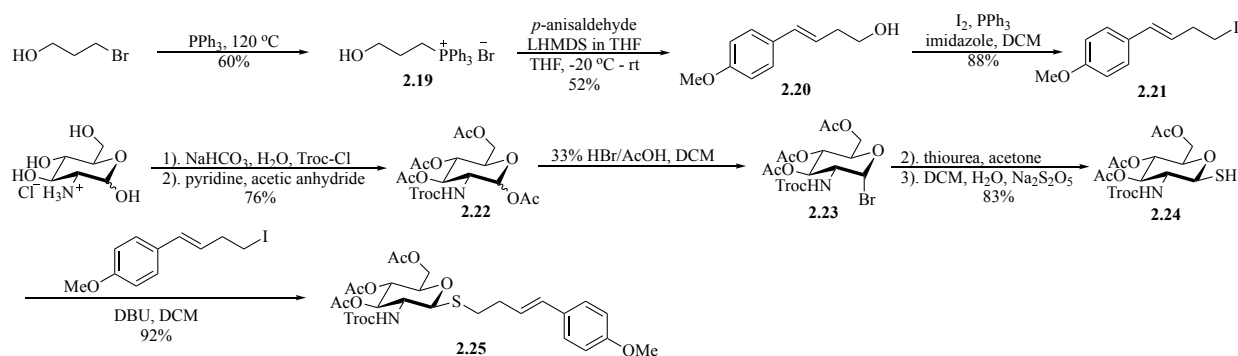
mild approach to *O*-glycosylation that occurs in the absence of photocatalysts. Subsequently, we wondered if the protonation of MBTG would result in a glycosylsulfonium ion intermediate (**2w**) that is similar to **2v** using catalytic amounts of strong acid (Scheme 2.5-B). Herein, I report on my efforts to develop *O*-glycosylation by acid-catalyzed activation of MBTGs.

2.9 Results and Discussion

2.9.1 Synthesis of MBTG Donors

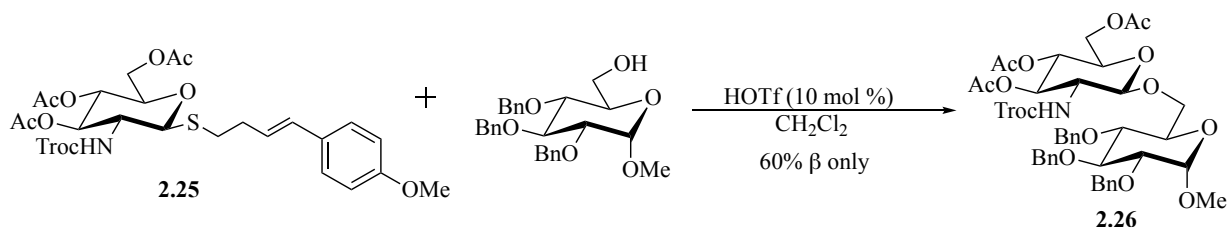
2-Amino-2-deoxy sugar derivatives are widely found in natural sources. They are the very important building blocks for the synthesis of glycopeptides, which are essential for treating gram-positive bacterial infections. The synthesis of 2-amino-2-deoxyglucose MBTG donor was divided into two parts: the synthesis of alkyl iodide **2.21** and the mercapto glucosamine **2.24** (Scheme 2.6). Regarding the synthesis of **2.21**, 3-bromopropanol was treated with melted triphenylphosphine at 120 °C, generating the phosphonium bromide salt **2.19**.⁵³ Wittig reaction of **2.19** with *p*-anisaldehyde in the presence of lithium bis(trimethylsilyl)amide (LHMDS) resulted in the formation of alcohol **2.20**,⁵⁴ which was further treated with iodine, triphenylphosphine, and imidazole in dichloromethane to generate alkyl iodide **2.21**.⁵⁵ For the synthesis of mercapto

glucosamine **2.24**, D-glucosamine hydrochloride was treated with 2,2,2-trichloroethoxycarbonyl chloride under basic conditions, followed by treatment with pyridine and acetic anhydride to afford the protected glucosamine **2.22**.⁵⁶ Conversion to glycosyl bromide **2.23** was achieved using 33% HBr/AcOH in DCM.²³ Glycosyl bromide **2.23** was further reacted with thiourea, followed by hydrolysis to give the mecapto glucosamine **2.24**.⁵⁷ Alkylation of **2.24** with alkyl iodide **2.21** resulted in the formation of the final 2-amino-2-deoxyglucose MBTG donor **2.25**.⁴⁹ Glycosylation



Scheme 2.6 Synthetic Route for 2-Amino-2-deoxyglucose MBTG Donor **2.25**

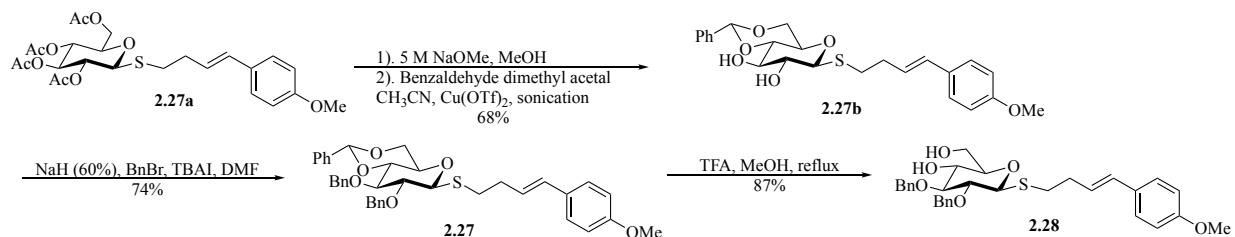
of MBTG donor **2.25** with methyl 2,3,4-tri-*O*-benzyl- α -D-glucopyranoside with 10 mol% triflic acid in DCM provided 60% yield of disaccharide **2.26** (Scheme 2.7), which demonstrated the efficacy of the 2-amino-2-deoxyglucose MBTG donor **2.25** in *O*-glycosylation.



Scheme 2.7 *O*-Glycosylation of **2.25**

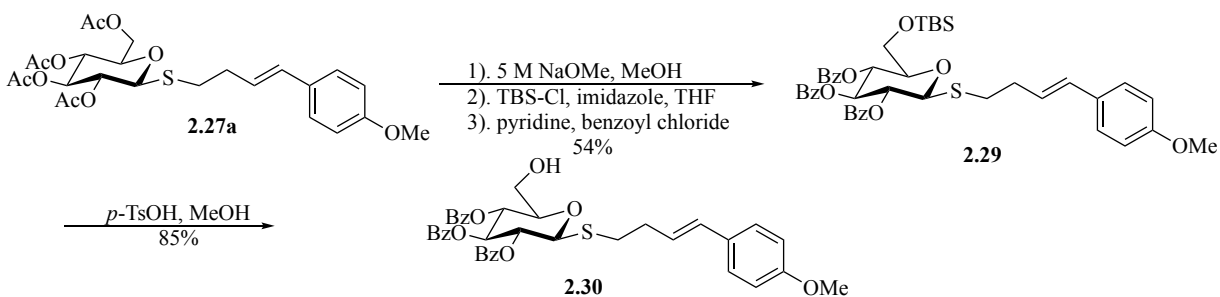
2.9.2 Compatibility, Latent-Active Strategy

Previously, we have demonstrated that the side chain of MBTG donor was stable under methanolysis (NaOMe, MeOH). In order to further demonstrate the robustness of the MBTG thioglycoside side chain, I have conducted a number of experiments which demonstrated the side



Scheme 2.8 Synthesis and Removal of Benzyldiene-Protected MBTG Donor **2.27**

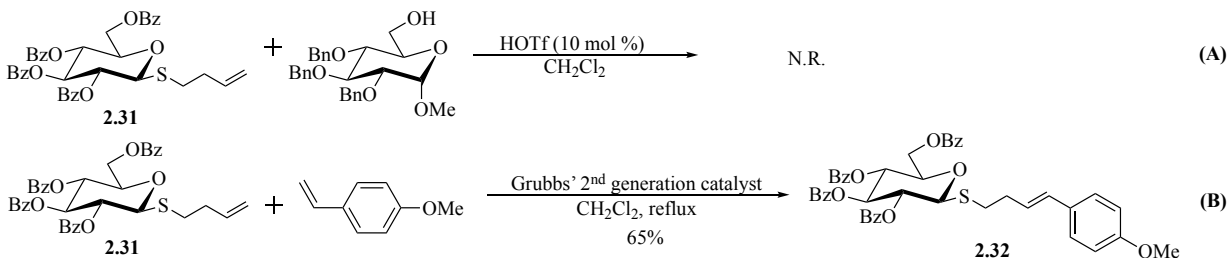
chain could tolerate various conditions. Firstly, I synthesized the benzyldiene protected MBTG donor **2.27**. Starting with **2.27a**, deacetylation followed by benzyldiene protection afforded **2.27b**, which was then protected by benzyl groups to provide **2.27**.⁴⁹ **2.27** was then treated with trifluoroacetic acid (TFA) in methanol under reflux. Benzyldiene removal product **2.28** was observed (Scheme 2.8). Another reaction that I performed was the removal of *tert*-butyldimethylsilyl (TBS) from MBTG thiglycoside **2.29**. The synthesis of **2.29** commenced with **2.27a**, deacetylation, protection of C₆ hydroxyl group with TBS group using imidazole in THF followed by benzoyl protection of the remaining hydroxyl groups affording **2.29** (Scheme 2.9). Instead of using fluoride-containing reagents, *para*-toluenesulfonic acid in MeOH was used for the removal of TBS group, which yielded the product **2.30** in high yield (Scheme 2.9). These two examples demonstrated that the side chain was stable towards mild acids.



Scheme 2.9 Synthesis and Removal of TBS-Protected MBTG Donor **2.29**

Another important contribution to this work was the development of a latent-active strategy for multistep synthesis of oligosaccharides. In this study, I synthesized a 3-butenylthioglycoside

donor **2.31** and demonstrated that it had no reactivity under acid-catalyzed conditions (Scheme 2.10-A). However, the 3-butenylthioglycoside **2.31** could be converted, via cross metathesis, to the reactive MTBG thioglycoside **2.32** (Scheme 2.10-B).



Scheme 2.10 Latent-Active Strategy of **2.31**

2.10 Summary

In this study, I have synthesized a 2-amino-2-deoxyglucose MBTG donor and demonstrated the efficacy of this donor in *O*-glycosylation. I also demonstrated that the MBTG side chain was stable under mild acid conditions, which broadens the potential utility of MBTGs for oligosaccharide synthesis. Further, the latent-active strategy involving cross-metathesis provided another viable pathway for oligosaccharide synthesis.

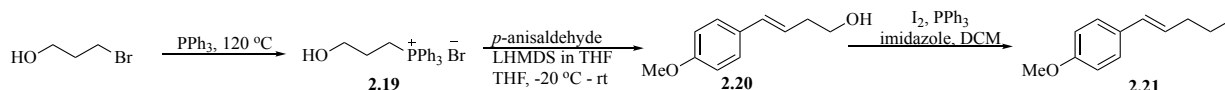
2.11 Experimental

2.11.1 General Methods

Reagents were purchased from Sigma Aldrich and used as received. Flash column chromatography was performed using 60Å silica gel purchased from Sigma Aldrich. ¹H NMR and ¹³C NMR spectroscopy were performed on a Bruker AV-400 or a Bruker AV500 spectrometer. Mass spectra were obtained using an Agilent 6210 electrospray time-of-flight mass spectrometer. Analytical and preparative TLC were conducted on aluminum sheets (Merck, silica gel 60, F254). Compounds were visualized by UV absorption (254 nm) and staining with anisaldehyde. 5 mL Pyrex micro reaction vessels (Supelco) were used in the glycosylation reactions. Deuterated solvents were obtained from Cambridge Isotope Labs. All solvents were purified according to the method of Grubbs.⁵⁸

2.11.2 Procedures and Characterization

Synthesis of **2.21**



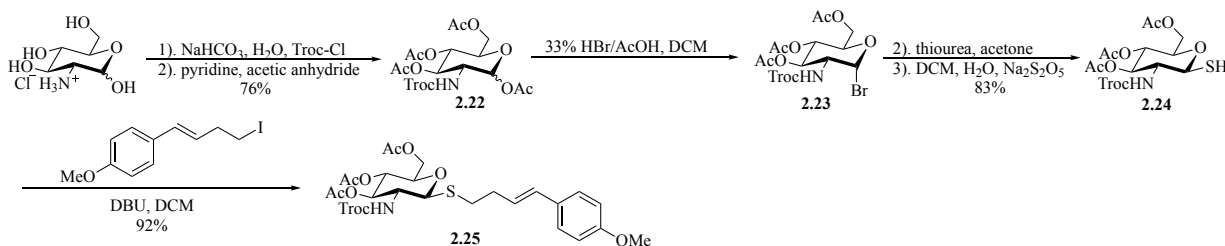
A 250 mL RBF was charged with 5.25 g (20.0 mmol) triphenylphosphine, which was then heated to $120\text{ }^\circ\text{C}$. 1.81 mL (20.0 mmol) 3-Bromo-1-propanol was added slowly over a period of 5 min after the triphenylphosphine was fully dissolved. The reaction was kept at $120\text{ }^\circ\text{C}$ for 15 min before 70 mL EtOH was added to the suspension. The flask was removed from heating until a homogeneous solution was obtained, which was then cooled to $0\text{ }^\circ\text{C}$ until a lot of solid precipitating out of solution. The suspension was filtered, washed with 200 mL hexanes. The resulting crystal **2.19** (4.815 g, 60%) was further dried on high vacuum.

To a mixture of 4.82 g (12.0 mmol) **2.19** in 20 mL dry THF at $-20\text{ }^\circ\text{C}$ was added 25 mL (25 mmol) LHMDs (1 M in THF) dropwise. The mixture was stirred for one hour at $-20\text{ }^\circ\text{C}$, and then 1.25 mL (10.3 mmol) of *para*-anisaldehyde was added dropwise. This resulting mixture was stirred for another hour at $-20\text{ }^\circ\text{C}$ before slowly warming to room temperature, and then stirred overnight. The reaction was quenched using 40 mL sat. NH_4Cl (aq), extracted with 2 X 50 mL EtOAc, then dried over Na_2SO_4 . Silica gel chromatography (20% EtOAc in hexanes) afforded 933 mg (52%) **2.20** of a white solid. Spectral data matched that reported in literature.⁴⁹

1.52 g (5.99 mmol) I_2 was added in three portions to the solution of 1.57 g (5.99 mmol) triphenylphosphine in 20 mL DCM and stirred for 10 minutes at room temperature. 680 mg (9.99 mmol) imidazole was added in one portion and the reaction was stirred for another 10 minutes at room temperature. 712.4 mg (3.997 mmol) **2.20** was added to the reaction and stirred for 1 h. 30 mL sat. $\text{Na}_2\text{S}_2\text{O}_5$ was added and the layers were separated. The aqueous layer was extracted with DCM (2 X 30 mL) and the organic layers were dried over Na_2SO_4 . Silica gel chromatography (5%

EtOAc in hexanes) afforded 1.02 g (88%) of a white solid. Spectral data matched that reported in literature.⁴⁹

Synthesis of **2.25**



8.20 mL (60.0 mmol) 2,2,2-Trichlorethoxycarbonyl chloride was added to a vigorously stirred solution of 10.8 g (50.1 mmol) D-glucosamine hydrochloride and 12.80 g (150.0 mmol) sodium bicarbonate in 100 mL H₂O during a period of 10 min at room temperature (18°C). The reaction was stirred for an additional hour. The resulting mixture was neutralized by slowly adding 2 M HCl (55 mL) and filtered. The filter cake was washed with 100 mL H₂O and the remaining solid material was placed on high vacuum (14 h). The dried solid was dissolved in 50 mL pyridine, and 25.0 mL (264 mmol) acetic anhydride was added to the solution. The reaction was stirred overnight (12 h) and then concentrated. The resulting crude material was purified using silica gel chromatography with an isocratic run of 20% ethyl acetate in hexanes to afford 19.86 g (76%) 1,2,3,6-tri-O-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-D-glucopyranose (**2.22**) as a white solid. Spectral data matched that previously reported in the literature.⁵⁹

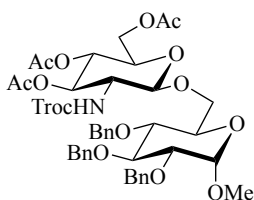
18.75 mL 33% HBr/HOAc was added at once to a solution of 4.18 g (8.0 mmol) **2.22** in 30 mL dichloromethane at 0°C. The reaction was allowed to warm to room temperature (19°C) and stirred for 3 h. 50 mL cold water was added to the reaction. The aqueous layer was extracted with 2 X 30 mL DCM. The combined organic layers were washed with 30 mL sat. NaHCO₃, 30 mL brine, and dried over Na₂SO₄. The resulting solution was concentrated to a white foam (**2.23**) and carried on without further purification. The resulting white foam was dissolved in 15 mL acetone, and 0.91 g (12 mmol) thiourea was then added. The reaction was heated to reflux for 2 h

during which a white precipitate formed in the solution. The suspension was filtered. The residue was kept, and the filtrate was once again heated to reflux. This process was repeated 3 times until there was no more solid precipitate. The combined precipitates were dissolved in 30 mL DCM, and a solution of 1.77 g Na₂S₂O₅ in 15 mL H₂O was added. The resulting mixture was stirred vigorously and heated to 55 °C for 3 h. The resulting aqueous layer was extracted with 2x15 mL DCM. The combined organic layers were dried over Na₂SO₄ and concentrated. The resulting crude material was purified by silica gel chromatography using a gradient solvent system starting at 100% hexanes and ending at 25% ethyl acetate in hexanes to afford 3.3 g (83 %) 3,4,6-tri-*O*-acetyl-2-deoxy-1-mercapto-2-(2,2,2-trichloroethoxycarbonylamino)- α -D-glucopyranose (**2.24**) as a white powder. ¹H NMR (500 MHz, CDCl₃) δ 5.38 (d, *J* = 10.0 Hz, 1H), 5.17 (t, *J* = 10.0 Hz, 1H), 5.11 (t, *J* = 10.0 Hz, 1H), 4.79 (d, *J* = 15.0 Hz, 1H), 4.72 (d, *J* = 15.0 Hz, 1H), 4.65 (t, *J* = 7.5 Hz, 1H), 4.25 (dd, *J* = 10.0, 5.0 Hz, 1H), 4.13 (d, *J* = 15.0 Hz, 1H), 3.78 – 3.71 (m, 2H), 2.48 (d, *J* = 10.0 Hz, 1H), 2.10 (s, 3H), 2.04 (s, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 170.9, 170.7, 169.3, 154.4, 95.3, 80.2, 76.3, 74.6, 73.0, 68.2, 62.1, 59.0, 20.8, 20.64, 20.60. HRMS (*m/z*): [M+Na]⁺ calcd. for C₁₅H₂₀NSO₉Cl₃Na 517.9810, found 517.9816. [α]_D²⁵ = +2.2 (*c*=1, DCM). IR (cm⁻¹): 3325, 2960, 2951, 1739, 1536, 1219, 1084.

338 μ L DBU (2.26 mmol) was added dropwise to a solution of 993.5 mg (2.000 mmol) **2.24** and 605.0 mg (2.100 mmol) 1-iodo-4-(4-methoxyphenyl)-3-butene (**2.21**)⁷ in 10 mL DCM. The reaction was stirred for 1 h and then concentrated. The resulting crude material was purified using silica gel chromatography (100% hexanes to 30% ethyl acetate in hexanes) to afford 1.20 g (92%) 4-(4-methoxyphenyl)-3-butenyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-1-thio- α -D-glucopyranoside (**2.25**) as a white foam. ¹H NMR (500 MHz, CDCl₃) δ 7.27 (d, *J* = 10.0 Hz, 2H.), 6.84 (d, *J* = 10.0 Hz, 2H), 6.38 (d, *J* = 20.0 Hz, 1H), 6.08 – 6.02 (m, 1H), 5.23 – 5.17 (m, 2H), 5.08 (t, *J* = 9.7 Hz, 1H), 4.77 (d, *J* = 12.0 Hz, 1H), 4.66 – 4.63 (m, 2H),

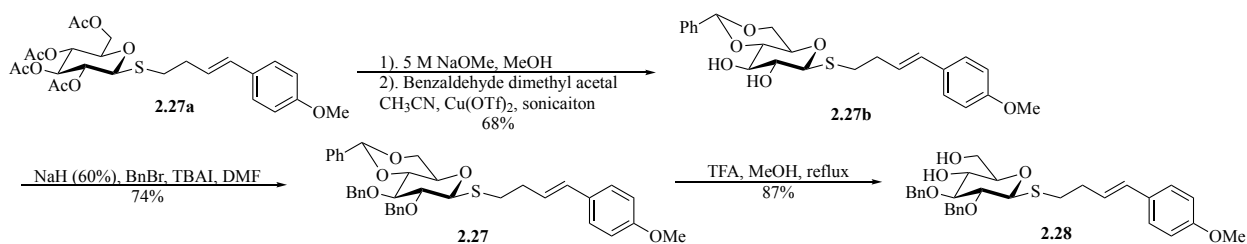
4.25 (dd, $J = 12.4, 5.1$ Hz, 1H), 4.14 (dd, $J = 10.0, 5.0$ Hz, 1H), 3.82 – 3.76 (m, 1H), 3.80 (s, 3H), 3.72 – 3.69 (m, 1H), 2.88 – 2.78 (m, 2H), 2.53 – 2.48 (m, 2H), 2.08 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.7, 169.4, 159.0, 154.0, 131.0, 130.0, 127.2, 125.6, 114.0, 95.3, 84.6, 77.2, 75.9, 74.5, 73.2, 68.5, 62.3, 55.3, 55.3, 33.3, 30.1, 20.7, 20.6, 20.6. HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{33}\text{Cl}_3\text{NSO}_{10}$ 656.0885, found 656.0884. $[\alpha]_{\text{D}}^{25} = -27.0^\circ$ ($c=1$, DCM). IR (cm^{-1}): 3338, 2955, 2837, 1742, 1715, 1537, 1219, 1025.

Synthesis of **2.26**



A reaction vial was charged with 98.5 mg (0.150 mmol) **2.25** and 34.9 mg (0.075 mmol) methyl 2,3,4-tri-*O*-benzyl- α -D-glucopyranoside. Vacuum-purge-backfill under N_2 atmosphere was applied three times. 1 mL DCM and then 1.3 μL (0.015 mmol) HOTf, were added to the vial using a syringe. The reaction was stirred for 1.5 h. 5.0 μL triethylamine was then added to quench the reaction which was concentrated. The resulting crude mixture (180.1 mg) was purified by silica gel using a gradient run (100% hexanes to 30% ethyl acetate in hexanes) to afford 42.4 mg (61%) **2.26** as pale-yellow solid. Spectral data matched that previously reported in the literature.⁶⁰

Synthesis of **2.28**



To a flame-dried 250 mL round bottomed flask equipped with a stir bar was added 2.75 g (5.24 mmol) 4-(4-methoxyphenyl)-3-butenyl-2,3,4,6-tetra-*O*-acetyl-1-thio- β -D-glucopyranoside **2.27a** and 100 mL MeOH. 0.51 mL (2.1 mmol) of a commercial 5 M solution of NaOMe in MeOH

was added at once at room temperature. The resulting solution was stirred magnetically for 10 minutes after which the reaction was judged to be complete by TLC analysis. The resulting solution was concentrated under vacuum. The crude mixture was carried on without further purification.

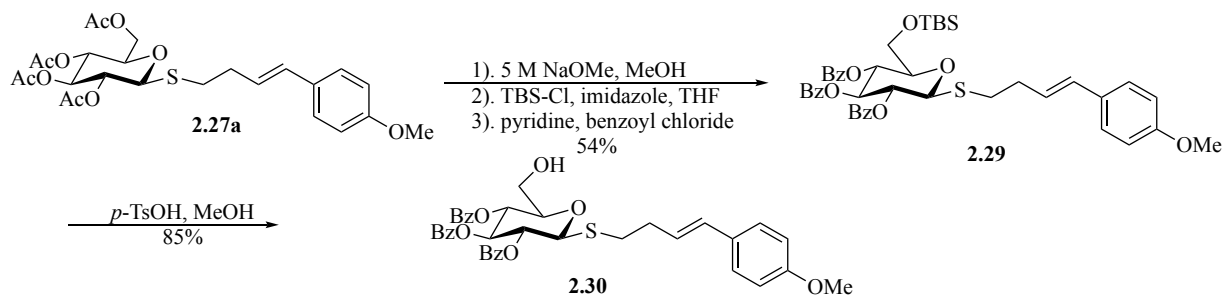
To a flame dried 100 mL round-bottom flask was added 1.069 g (2.999 mmol) of 4-(4-methoxyphenyl)-3-butenyl-1-thio- β -D-glucopyranoside and 0.60 mL (3.6 mmol) of commercial benzaldehyde dimethyl acetal and vacuum-purge-backfilled with N₂ three times. 30 mL of acetonitrile was added under N₂. Then, 58.1 mg (0.166 mmol) of copper (II) trifluoromethanesulfonate was added in one portion. This mixture was sonicated for 30 minutes at room temperature after which the reaction was judged to be complete by TLC analysis. The reaction mixture was concentrated under reduced pressure and a yellow oil was afforded. Silica gel chromatography (isocratic run of 5% MeOH in DCM) afforded 910 mg (68%) **2.27b** as a white foam.

900 mg **2.27b** (2.024 mmol) and 149.7 mg tetrabutylammonium iodide (TBAI) (0.4053 mmol) were dissolved in 10 mL DMF. The solution was cooled to 0 °C, and 60% sodium hydride (404.1 mg, 10.10 mmol) was added portion-wise. The resulting mixture was stirred for 30 min at 0 °C. BnBr (720 μ L, 5.8 mmol) was added dropwise. The reaction was warmed to rt (21 °C) and allowed to stir overnight (12 h). 10 mL Sat. NH₄Cl was added to quench the reaction, which was then extracted with EtOAc (2 X 30 mL). The organic layer was washed with 300 mL brine, dried with Na₂SO₄, and concentrated. The resulting crude material was purified using silica gel (0% to 15% ethyl acetate in hexanes) to afford 940.0 mg (74 %) **2.27** as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.51 – 7.48 (m, 2H), 7.42 – 7.26 (m, 15H), 6.84 (d, *J* = 8.8Hz, 2H), 6.40 (d, *J* = 15.8Hz, 1H), 6.10 (dt, *J* = 6.9, 15.8Hz, 1H), 5.59 (s, 1H), 4.96 (d, *J* = 11.3Hz, 1H), 4.89 (d, *J* = 10.2Hz, 1H), 4.83 (d, *J* = 6.0Hz, 1H), 4.80 (d, *J* = 7.1Hz, 1H), 4.59 (d, *J* = 9.8Hz, 1H), 4.37 (dd, *J*

= 5.0, 10.4Hz, 1H), 3.84 – 3.70 (m, 3H), 3.81 (s, 3H), 3.51 – 3.44 (m, 2H), 2.94 – 2.81 (m, 2H), 2.58 – 2.52 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 158.90, 138.36, 137.90, 137.24, 130.88, 130.07, 128.90, 128.31, 128.31, 128.25, 128.19, 128.00, 127.80, 127.65, 127.16, 125.95, 125.78, 113.91, 101.09, 86.02, 82.74, 81.55, 81.29, 75.93, 75.17, 70.21, 68.67, 55.24, 33.42, 30.94. **HRMS** (m/z): [M+Na]⁺ calcd. for C₃₈H₄₀SO₆Na 647.2438, found 647.2428. [α]_D²⁰ = + 11.2° (c = 1.0, DCM). **IR** (cm⁻¹): 3063, 3031, 2875, 1606, 1508, 1362, 1245, 1073, 1028, 741, 692.

A 25 mL RBF was charged with 208.1 mg **2.27** (0.3331 mmol) and 5 mL MeOH. 0.20 mL trifluoroacetic acid was added. The reaction was heated to reflux which was maintained for 6 h until starting material had been consumed (monitoring with TLC). The reaction mixture was then concentrated. The resulting crude material was purified using silica gel (0% to 40% ethyl acetate in hexanes) to afford 155.6 mg (87 %) **2.28** as a white solid. **¹H NMR** (400 MHz, CDCl₃) δ 7.41 – 7.26 (m, 12H), 6.84 (d, *J* = 8.7Hz, 2H), 6.41 (d, *J* = 15.8Hz, 1H), 6.10 (dt, *J* = 6.9, 15.8Hz, 1H), 4.98 (d, *J* = 6.4Hz, 1H), 4.96 (d, *J* = 5.0Hz, 1H), 4.77 – 4.71 (m, 2H), 4.55 (d, *J* = 9.6Hz, 1H), 3.92 – 3.87 (m, 1H), 3.82 (s, 3H), 3.80 – 3.74 (m, 1H), 3.62 – 3.57 (m, 1H), 3.50 (t, *J* = 8.8Hz, 1H), 3.41 (t, *J* = 9.6Hz, 1H), 3.38 – 3.33 (m, 1H), 2.94 – 2.81 (m, 2H), 2.59 – 2.53 (m, 2H), 2.33 – 2.28 (m, 1H), 2.09 – 2.04 (m, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 158.93, 138.36, 137.75, 130.96, 130.07, 128.70, 128.42, 128.30, 128.04, 127.93, 127.87, 127.20, 125.76, 113.94, 85.88, 85.60, 81.55, 79.05, 75.42, 75.35, 70.55, 62.80, 55.27, 33.46, 31.08. **HRMS** (m/z): [M+Na]⁺ calcd. for C₃₁H₃₆SO₆Na 559.2125, found 559.2129. [α]_D²⁰ = - 18.9° (c = 1.0, DCM). **IR** (cm⁻¹): 3565, 3344, 3030, 2906, 1605, 1510, 1130, 1050, 1022, 738, 695.

Synthesis of **2.30**



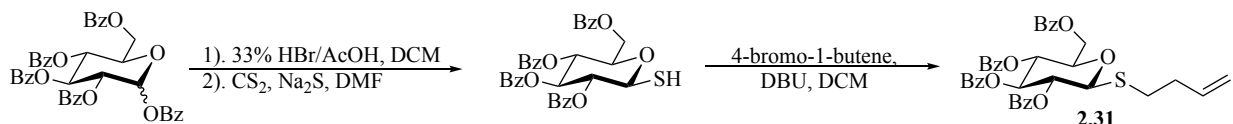
To a flame-dried 250 mL roundbottom flask equipped with a stir bar was added 524.6 mg (1.000 mmol) 4-(4-methoxyphenyl)-3-butenyl-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside **2.27a** and 20 mL MeOH. 0.1 mL (0.5 mmol) of a commercial 5 M solution of NaOMe in MeOH was added at once at room temperature. The resulting solution was stirred magnetically for 10 minutes after which the reaction was judged to be complete by TLC analysis. The resulting solution was concentrated under vacuum and co-evaporated with 10 mL toluene. The crude mixture was carried on without further purification.

The resulting solid was dissolved in 8 mL THF in a 50 mL round-bottomed flask followed by adding 340.4 mg (5.000 mmol) imidazole and 452.2 mg (3.000 mmol) *tert*-butyldimethylsilyl chloride. The reaction was stirred at room temperature for 1 hour. 50 mL Ethyl acetate was added, and the resulting mixture was washed with 20 mL brine twice. The organic layer was dried with Na₂SO₄ and concentrated. The resulting foam oil was dissolved in 5 mL dry pyridine and cooled to 0 °C. Benzoyl chloride (0.53 mL, 4.5 mmol) was added dropwise to the solution. The reaction was stirred overnight (12 h). The resulting mixture was diluted with 20 mL EtOAc. The organic layer was washed sequentially with 2 X 30 mL 1 M HCl, 2 X 30 mL sat. NaHCO₃, 20 mL brine, and then dried with Na₂SO₄. The resulting solution was concentrated and purified by chromatography (0% to 15% EtOAc in hexanes) to afford 423 mg (54%) of **2.29** as a white solid.

A 10 mL RBF was charged with 140.0 mg **2.29** (0.1787 mmol), 0.05 mL H₂O, and 3 mL acetone. *p*-Toluenesulfonic acid (31.3 mg, 0.182 mmol) was added at rt (21 °C) and the reaction

was subsequently stirred for 8 h. The reaction mixture was concentrated, and the resulting crude material was purified by chromatography (0% to 30% EtOAc in hexanes) to afford 101.3 mg (85%) of **2.30** as a white solid.

Synthesis of **2.31**

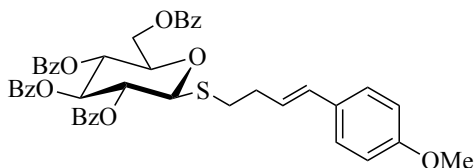


0.46 mL 33% HBr/HOAc was added dropwise to a solution of 1.40 g (2.00 mmol) 1,2,3,4,6-penta-*O*-benzoyl-D-glucopyranose⁶¹ in 8 mL dichloromethane at 0 °C. The reaction was warmed to room temperature (19 °C) and stirred for 12 h. 20 mL cold water was then added to the reaction. The aqueous layer was extracted with 2 X 15 mL DCM. The combined organic layers were washed with 20 mL sat. NaHCO₃, 20 mL brine, and dried over Na₂SO₄. Evaporation of solvent resulted in a material that was carried on without further purification. 180 μ L (3.0 mmol) CS₂ was added dropwise to a suspension of 0.96 g (4.0 mmol) Na₂S·9H₂O in 10 mL DMF at room temperature (19 °C). The unpurified material was dissolved in 2.0 mL DMF and injected into the solution, whose color turned to orange from dark red. The reaction was stirred for 15 min at 19 °C. 30 mL H₂O was added to quench the reaction. The aqueous layer was extracted with 2 X 15 mL ethyl acetate. The combined organic layers were washed with 50 mL brine, dried with Na₂SO₄, and concentrated. Silica gel chromatography (isocratic run of 30% ethyl acetate in hexanes) afforded 0.78 g (65 %) 2,3,4,6-tetra-*O*-benzoyl-1-mercapto- β -D-glucopyranoside as a white foam. Spectral data matched that previously reported in the literature.⁶²

164 μ L (1.10 mmol) DBU was added dropwise to a mixture of 612.6 mg (0.9999 mmol) 2,3,4,6-tetra-*O*-benzoyl-1-mercapto- β -D-glucopyranoside and 203 μ L (2.00 mmol) 4-bromo-1-butene in 5 mL DCM at rt. The reaction was allowed to stir overnight (15 h) and was then concentrated. The resulting crude material was purified using silica gel (100% hexanes to 20%

ethyl acetate in hexanes) to afford 350.6 mg (53 %) **2.31** as a white foam. **¹H NMR** (500 MHz, CDCl₃) δ 8.02 (dd, *J* = 10.0, 5.0 Hz, 2H), 7.95 (dd, *J* = 10.0, 5.0 Hz, 2H), 7.90 (dd, *J* = 10.0, 5.0 Hz, 2H), 7.82 (dd, *J* = 10.0, 5.0 Hz, 2H), 7.56 – 7.47 (m, 3H), 7.44 – 7.32 (m, 7H), 7.28 – 7.25 (m, 2H), 5.93 (t, *J* = 10.0 Hz, 1H), 5.78 – 5.70 (m, 1H), 5.67 (t, *J* = 10.0 Hz, 1H), 5.57 (t, *J* = 10.0 Hz, 1H), 5.03 – 4.95 (m, 2H), 4.88 (d, *J* = 10.0 Hz, 1H), 4.64 (dd, *J* = 10.0, 5.0 Hz, 1H), 4.50 (dd, *J* = 10.0, 5.0 Hz, 1H), 4.20 – 4.16 (m, 1H), 2.87 – 2.75 (m, 2H), 2.39 – 2.34 (m, 2H). **¹³C NMR** (125 MHz, CDCl₃) δ 166.1, 165.8, 165.2, 165.1, 136.1, 133.4, 133.3, 133.2, 133.1, 129.8, 129.8, 129.7, 129.5, 128.7, 128.7, 128.4, 128.3, 128.3, 128.3, 116.2, 84.0, 76.7, 76.3, 74.1, 70.6, 69.6, 63.3, 34.0, 29.7, 29.4. **HRMS** (*m/z*): [M+Na]⁺ calcd. for C₃₈H₃₄SO₉Na 689.1816, found 689.1827. [α]_D²⁵ = 53.9° (*c*=1, DCM). **IR** (cm⁻¹): 3068, 3003, 2958, 2924, 1710, 1360, 1251, 1087.

Synthesis of **2.32**



228 μ L (2.02 mmol) 4-vinylanisole was injected into a mixture of 133.3 mg (0.1999 mmol) **2.31**, and 16.9 mg (0.0199 mmol) 2nd generation Grubbs' catalyst in 6 mL DCM. The reaction was heated to reflux within 5 min and then stirred at reflux for an additional 2 h. The solution was then allowed to cool to rt (19 °C) and then concentrated. The resulting crude mixture (223.0 mg) was purified by silica gel (100% hexanes to 15% ethyl acetate in hexanes) to afford 124.3 mg (80 %) **2.32** as a white foam.

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CHAPTER 3: DEVELOPMENT OF 4-(4-METHOXYPHENYL)-4-PENTENYL THIOLYGLYCOSIDES AS STABLE AND VERSATILE DONORS FOR THE SYNTHESIS OF CHALLENGING GLYCOSIDIC LINKAGES

3.1 Introduction

Thioglycosides, as previously described, have been widely used for the synthesis of oligosaccharides due to their easy synthesis, high stability, and tunable reactivity.¹ These merits have facilitated the exploration of glycosidic linkage formation using these glycosyl donors.² Thioglycosides have proven to be especially useful in the formation of synthetically difficult glycosidic linkages. On the other hand, because of the high stability of thioglycosides, harsh activation conditions are often required. Finding easily activated, bench-top stable thioglycosides and milder activation conditions are of great importance in the development of chemical glycosylation.³

Progress has been made with the development of new thioglycosides and activation methods. For example, the activation of *para*-tolyl thioglycosides **3a** is effected with a range of reagent systems of varying reactivity including *N*-iodosuccinimide with triflic acid (NIS/HOTf),⁴ ultraviolet irradiation with the oxidant Cu(OTf)₂,⁵ and even milder gold catalysis⁶ (Figure 3.1).

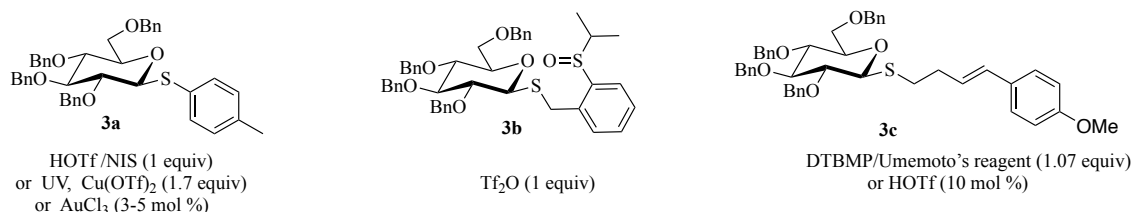


Figure 3.1 Selective Thioglycosides and Activation Methods

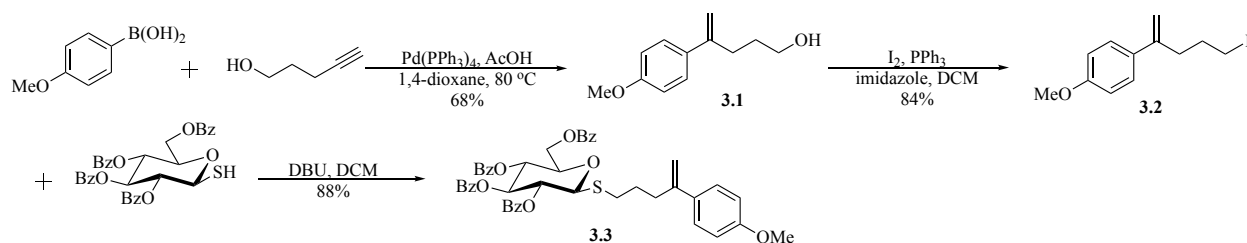
However, these conditions require either stoichiometric or excess amounts of the promoters. Wan and coworkers have developed a new 2-(2-propylsulfinyl)benzyl thioglycoside **3b** (Figure 3.1) which showed great reactivity towards *O*-glycosylation with various glycosyl acceptors using stoichiometric triflic anhydride as activator.⁷ Recently, our group developed another class of thioglycoside called: 4-(4-methoxyphenyl)-3-butenyl thioglycosides (MBTGs) **3c** (Figure 3.1).

We have demonstrated that these newly developed MBTG donors could be activated using visible-light irradiation.⁸ Excess amounts of Umemoto's reagent and the mild base 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) or 4Å molecular sieves were required for this transformation. Further, we found that this MBTG donor could also undergo *O*-glycosylation under mild acid-catalyzed conditions.⁹ Nevertheless, poor reactivity was shown with unreactive glycosyl acceptors.

With our continuing research on acid-catalyzed *O*-glycosylation with thioglycosides, another new class of thioglycoside, called 4-(4-methoxyphenyl)-4-pentenyl thioglycosides (MPTGs), has been developed. The new MPTG thioglycosides showed higher reactivity toward very hindered glycosyl acceptors.

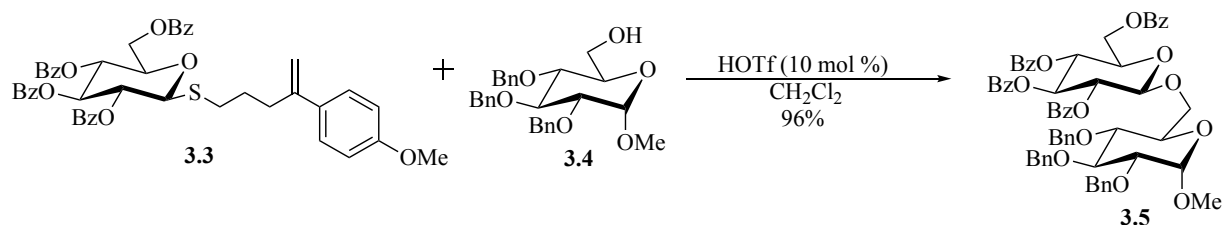
3.2 Results and Discussion

To begin with, I chose the tetra-*O*-benzoyl protected MPTG donor **3.3** as the model substrate. In order to synthesize the model substrate, I developed the following synthetic sequence: alcohol **3.1** was obtained by the reaction of 4-methoxyphenyl boronic acid and pent-4-yn-1-ol under palladium catalysis in dioxane at 80 °C.¹⁰ The alcohol **3.1** was then converted to alkyl iodide **3.2** following treatment with iodine, triphenylphosphine, and imidazole in DCM.¹¹ Alkylation of **3.2** with tetra-*O*-benzoyl mercapto glucoside¹² resulted in the formation of target MPTG donor **3.3** (Scheme 3.1).⁸



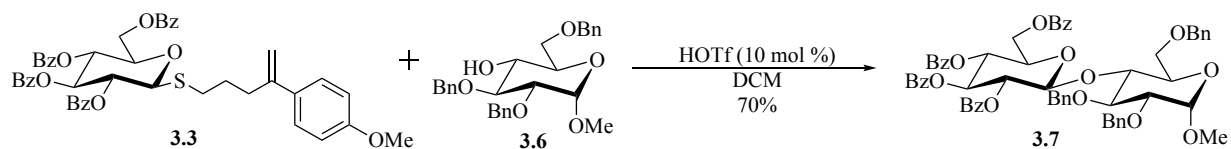
Scheme 3.1 Synthesis of MPTG Donor **3.3**

With **3.3** in hand, reaction conditions were screened. The initial experiment was performed using the same conditions previously reported with C₆-OH glycosyl acceptor **3.4**,¹³ and 96% yield



Scheme 3.2 *O*-Glycosylation of MPTG **3.3** with C₆-OH

of the disaccharide **3.5** was obtained (Scheme 3.2). With such a high yield obtained with C₆-OH **3.4**, we wondered if this MPTG donor would react with more unreactive glycosyl acceptors like C₄-OH (**3.6**) because the previous MBTG donor (**3c**, Figure 3.1) showed low reactivity towards C₄-OH. To our delight, we obtained a 70% yield of the desired disaccharide **3.7** (Scheme 3.3).



Scheme 3.3 *O*-Glycosylation of MPTG **3.3** with C₄-OH

Inspired by these results, reaction conditions were screened for the optimization of this process using glycosyl donor **3.3** and glycosyl acceptor **3.6** (Table 3.1). We found that the concentration and substrate ratio at 0.15 mmol **3.3** and 0.075 mmol **3.6** along with 10 mol% HOTf in 1 mL or 2 mL DCM gave us the best yield (entries 1,2). Decreasing (entry 3) or increasing the reaction concentration (entry 4) or changing the substrate ratio (entries 5-8) resulted in decreasing yields. Replacement of HOTf with TMSOTf produced diminished yields (entry 9). While studying the effects of temperature on this transformation, we found that a complex mixture resulted (as shown by crude NMR spectra) and none of the desired product **3.7** was detected at either 0 °C or -20 °C (entries 10&11). The possible explanation for this phenomenon is that the MPTG donor **3.3** decomposes before glycosyl acceptor attacks because the low temperature results in decreased

overall reactivity of the glycosyl acceptor, especially for unreactive glycosyl acceptors. Regarding the amount of acid, one equivalent of HOTf (entry 12) resulted in traces of product while, when HOTf was eliminated, no reaction occurred (entry 13). Finally, more polar solvents such as CH₃CN and acetone proved inferior to CH₂Cl₂, and no product was obtained in these cases (entries 14, 15). After the screening of various conditions, we chose entry 1 as our standard condition for *O*-glycosylation.

We next studied the substrate scope for this glycosylation reaction (Table 3.2) with a range of alcohol acceptors and an expanded set of MPTG donors. With tetra-*O*-benzoyl donor **3.3**, both primary and secondary alcohol acceptors were effective for the formation of disaccharide in good to excellent yield (entries 1-5). C₂-OH acceptor (**3f**, Figure 3.2) performed well in the glycosylation and provided 81% yield of the desired disaccharide (entry 3). Besides the reaction with relatively unreactive C₄-OH acceptor, it is noteworthy that the MPTG donor **3.3** could even react with the C₄-OH galactosyl acceptor¹³ (**3g**, Figure 3.2, entry 4) and C₄-OH glucuronate acceptor¹⁴ (**3h**, Figure 3.2, entry 5), respectively. These two acceptors are thought to be among the least reactive acceptors in glycosylation reactions because of their steric hindrance

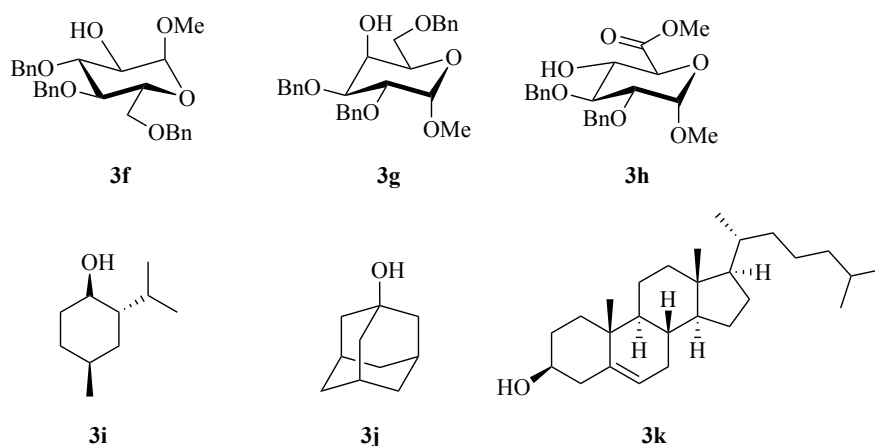
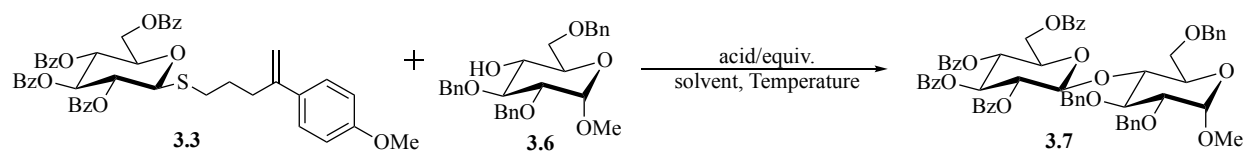


Figure 3.2 Glycosyl Acceptors Used in *O*-Glycosylation

Table 3.1 Reaction Conditions Optimization

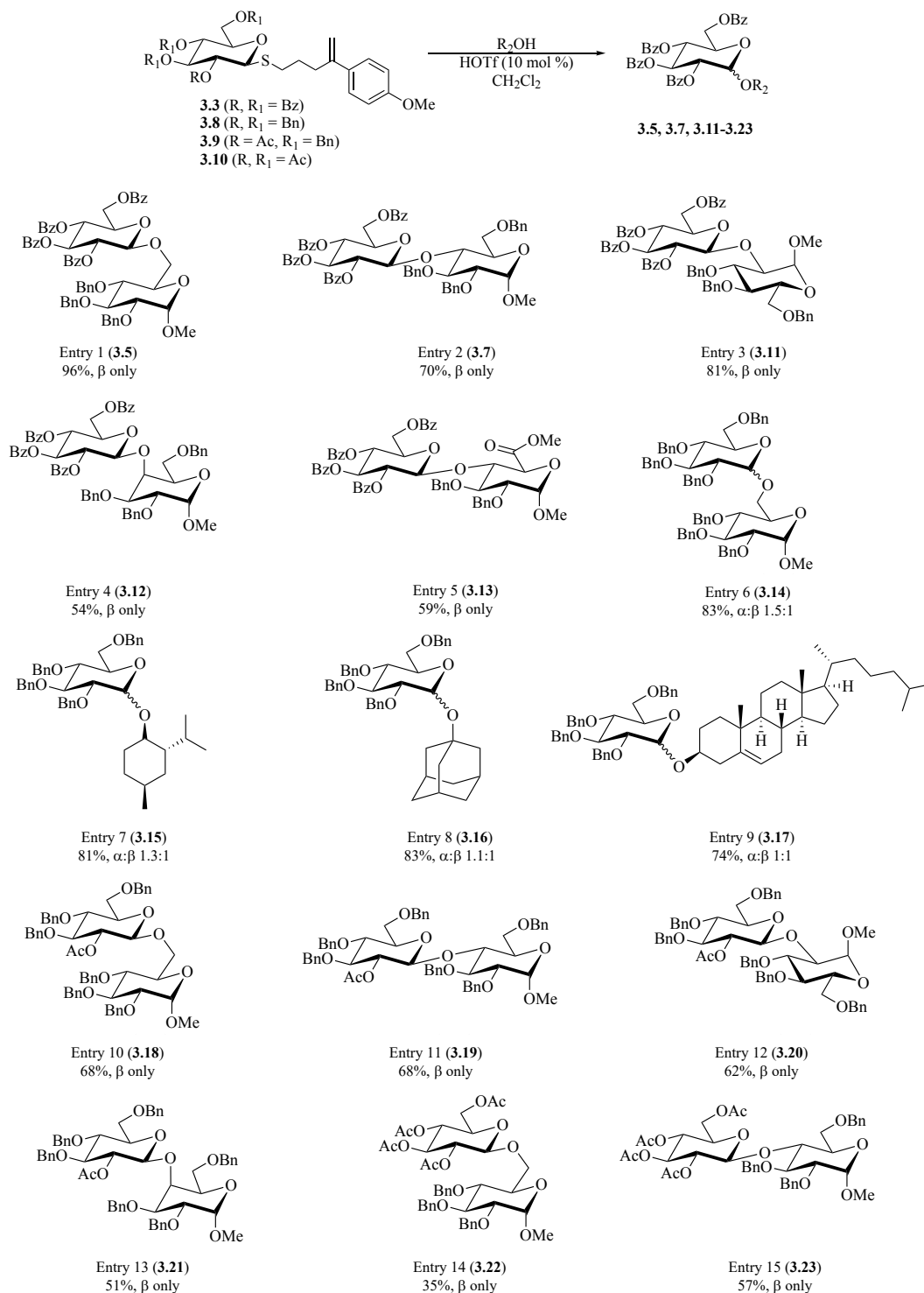


Entry	Donor 3.3 (mmol)	Acceptor 3.6 (mmol)	Solvent ^a	Acid/equiv.	Yield (%) ^b	Temp. (°C)
1	0.15	0.075	DCM	HOTf/0.1	70	20
2	0.15	0.075	DCM/ 2 mL	HOTf/0.1	70	20
3	0.15	0.075	DCM/10 mL	HOTf/0.1	45	20
4	0.38	0.19	DCM	HOTf/0.1	63	20
5	0.075	0.075	DCM	HOTf/0.1	43	20
6	0.075	0.075	DCM/2 mL	HOTf/0.1	37	20
7	0.1	0.1	DCM	HOTf/0.1	44	20
8	0.12	0.1	DCM	HOTf/0.1	46	20
9	0.15	0.075	DCM	TMSOTf/0.1	58	20
10	0.15	0.075	DCM	HOTf/0.1	n.d. ^c	0
11	0.15	0.075	DCM	HOTf/0.1	n.d.	- 20
12	0.15	0.075	DCM	HOTf/1.0	trace	20
13	0.15	0.075	DCM	HOTf/0	n.c. ^d	20
14	0.15	0.075	CH ₃ CN	HOTf/0.1	n.d.	20
15	0.15	0.075	Acetone	HOTf/0.1	n.d.	20

^aUnless otherwise stated, 1 mL solvent was used. ^bIsolated yields. ^cn.d. for none detected. ^dn.c. for no conversion.

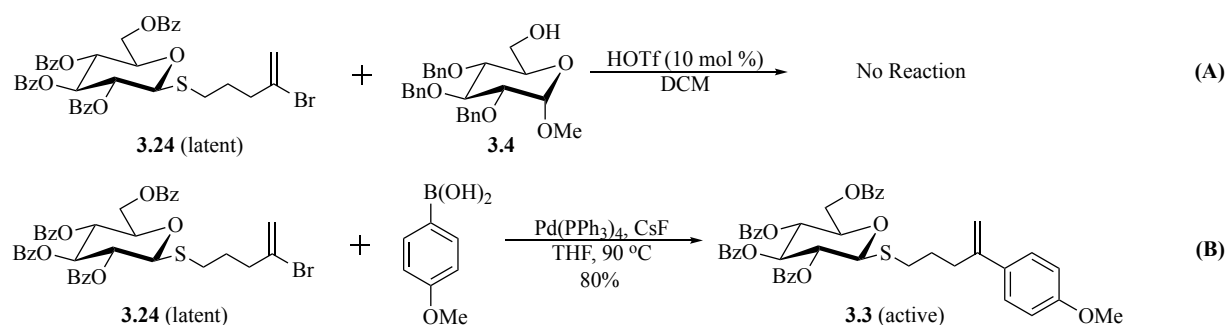
and electronic deactivation. As for tetra-*O*-benzyl MPTG donor **3.8**, high yield was obtained with carbohydrate acceptor (entry 6) and non-carbohydrate acceptors like menthol (**3i**, Figure 3.2, entry 7), 1-adamantanol (**3j**, Figure 3.2, entry 8), and cholesterol (**3k**, Figure 3.2, entry 9). Without the neighboring group participation (no acyl group at the C₂ position), all the disaccharides were obtained as a mixture α and β anomers. I also performed the experiments using tetra-*O*-benzyl donor **3.8** with the above mentioned C₄-OH glycosyl acceptors. The glycosylation proceeded as expected, but an inseparable mixture with both anomers and unidentified side-products was obtained. Next, we examined the glycosyl donor **3.9**, which contained an acetyl group at the C₂ position, resulting in exclusive β linkage formation through neighboring group participation. Primary alcohols like C₆-OH acceptor (entry 10) and secondary alcohols like C₄-OH (**3.6**, entry 11), C₂-OH (**3f**, entry 12), and even with C₄-OH galactosyl acceptor (**3g**, entry 13) afforded the corresponding disaccharides in good yield. Moderate to good yield was obtained with C₆-OH (**3.4**, entry 14) and C₄-OH (**3.6**, entry 15) reacting with *per*-acetylated donor **3.10**. The MBTG analog of **3.10**, by contrast, provided either low yields (with C₄-OH) or substantial by-products (with C₆-OH). This is a reflection of historically poor performance of *per*-acetylated donors. Our results with **3.10**, by contrast, are exciting.

Table 3.2 Substrate Scope^a



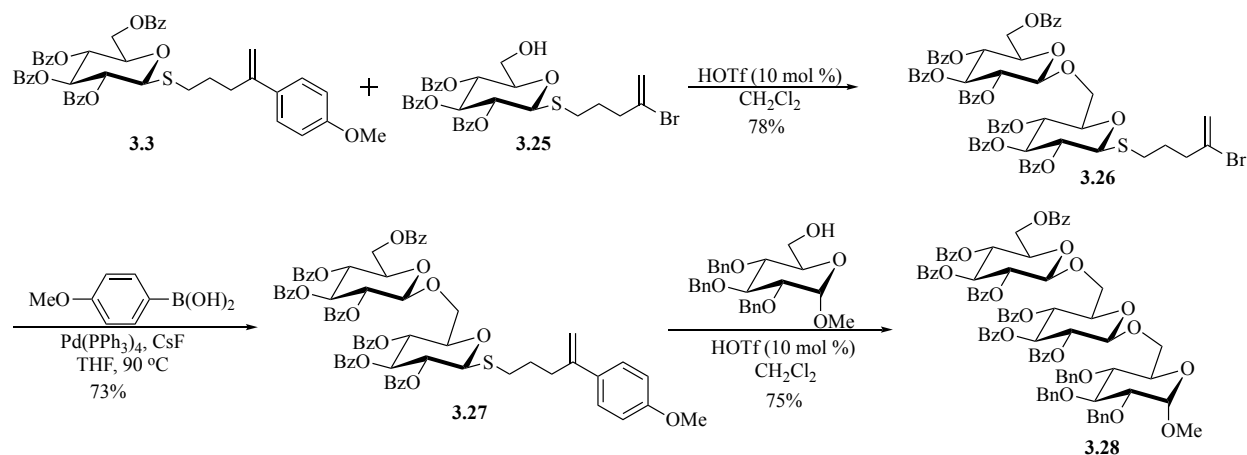
^aAll the reactions were performed using 0.15 mmol donor, 0.075 mmol acceptor, and 10 mol% HOTf in 1 mL DCM at room temperature.

To further demonstrate the utility of MPTG donors as synthetic intermediates, we performed a series of transformations. A latent-active strategy which enabled a successful synthesis of a trisaccharide was developed. First of all, 4-bromo-4-pentenylthioglycoside **3.24** was synthesized by combining mercapto glucose and 2-bromo-5-iodopent-1-ene in the presence of 1,8-



Scheme 3.4 Glycosylation and Suzuki Reaction of Donor **3.24**

diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane. Compound **3.24** then proved to be inert towards *O*-glycosylation with C₆-OH acceptor (Scheme 3.4-A). However, Suzuki reaction of **3.24** with 4-methoxyphenyl boronic acid in the presence of catalytic Pd(PPh₃)₄ and cesium fluoride in THF at elevated temperature resulted in the formation of glycosyl donor **3.3**, which is an effective donor, in high yield (Scheme 3.4-B). This latent-active strategy was further used in the synthesis of trisaccharide **3.28** (Scheme 3.5). Glycosylation of 4-bromo-4-pentenylthioglycoside



Scheme 3.5 Trisaccharide Synthesis

alcohol acceptor **3.25** with MPTG donor **3.3** generated disaccharide **3.26**, followed by the Suzuki coupling of the vinyl bromide side chain to generate new MPTG donor **3.27**, which reacted with C₆-OH generating the trisaccharide **3.28** (Scheme 3.5).

3.3 Summary

I have demonstrated that the newly developed MPTGs are stable thioglycosides that are nevertheless activated by catalytic triflic acid for moderate to high yielding *O*-glycosylation at room temperature. *O*-glycosylation occurs with a range of MBTG donors and alcohol acceptors. Challenging 1 → 4 glycosidic linkages are formed with a sterically hindered C₄-OH galactosyl acceptor and a sterically hindered and electronically deactivated C₄-OH glucuronate acceptor. In addition, a latent-active strategy involving Suzuki reaction has been developed, and efforts towards trisaccharide synthesis have been successful.

3.4 Future Work

As previously reported by Codée,¹⁵ additives like DMF and triphenylphosphine oxide were used to control the stereoselectivity to obtain exclusively the α anomer using *N*-phenyl trifluoroacetimidates. We wonder if this new MPTG donor could undergo similar process (Figure 3.3). Several reaction conditions have been screened. When DMF was added, the reaction was shut down and starting materials were recovered. When triphenylphosphine oxide was added, starting

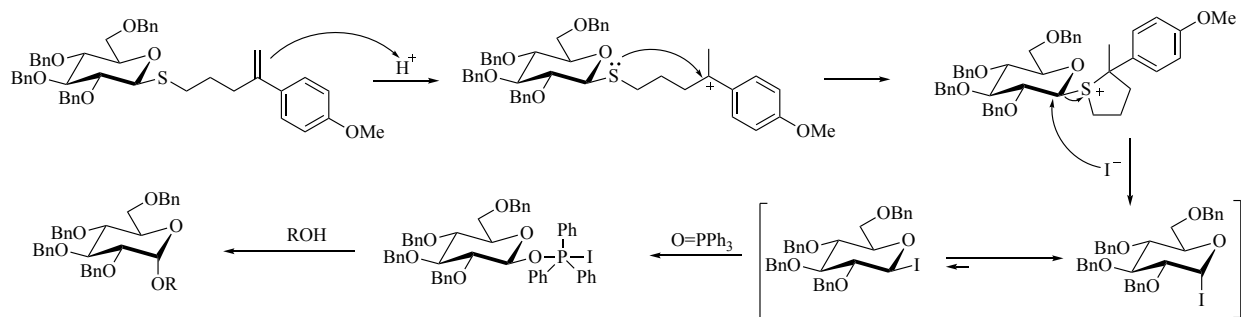


Figure 3.3 Proposed Mechanism for α Selectivity

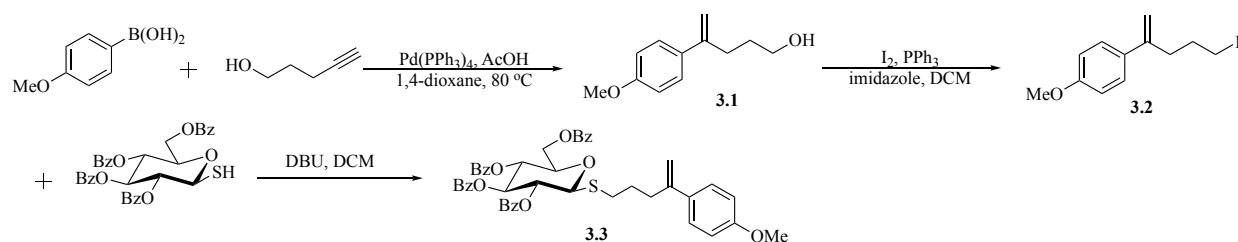
substrate was consumed but resulted in complex mixtures. More reaction conditions and various additives will be screened in the future.

3.5 Experimental

3.5.1 General Methods

Reagents were purchased from Sigma Aldrich, Alfa Aesar and used as received. Flash column chromatography was performed using 60Å silica gel purchased from Sigma Aldrich. ^1H NMR and ^{13}C NMR spectroscopy were performed on a Bruker AV-400 or a Bruker AV-500 spectrometer. Mass spectra were obtained using an Agilent 6210 electrospray time-of-flight mass spectrometer. Optical Rotation were obtained from JASCO P-2000 polarimeter. Analytical and preparative TLC were conducted on aluminum sheets (Merck, silica gel 60, F254). Compounds were visualized by UV absorption (254 nm) and staining with anisaldehyde. 5 mL Pyrex micro reaction vessels (Supelco) were used in the glycosylation reactions. Deuterated solvents were obtained from Cambridge Isotope Labs. Solvents (purified according to the method of Grubbs¹⁶) included Et_2O , DCM, CH_3CN , DMF, and THF and were used directly from a PureSolv 400-5 solvent system. Other solvents were used as received from a commercial vendor.

3.5.2 Procedures and Characterization

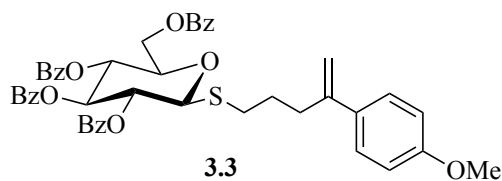


Synthesis of 3.2

A 100 mL round bottom flask was charged with PPh_3 (8.85 mmol, 2.32 g) and 10.0 mL dichloromethane. Iodine (8.86 mmol, 2.25 g) was added in small portions under N_2 at room temperature (20 °C). The reaction was stirred for 10 minutes. Imidazole (14.7 mmol, 1.00 g) was added to the solution in small portions and the reaction was allowed to stir for 10 more minutes.

3.1 (5.72 mmol, 1.10 g), which was synthesized according to a previously reported method,¹⁷ was added to the suspension in one portion and the reaction was stirred for 1 hour at room temperature. 10 mL Sat. Na₂S₂O₅ was added to the reaction mixture and the aqueous layer was extracted with 10 mL dichloromethane twice. The organic layer was dried over Na₂SO₄ and concentrated. The resulting crude mixture was purified using silica gel column chromatography to afford 1.45 g (84%) product **3.2** as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.35 – 7.32 (m, 2H), 6.88 – 6.85 (m, 2H), 5.25 (d, *J* = 1.4Hz, 1H), 5.03 (d, *J* = 1.3Hz, 1H), 3.81 (s, 3H), 3.18 (m, 2H), 2.60 (m, 2H), 1.97 – 1.91 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 159.18, 145.74, 132.89, 127.21, 113.75, 111.96, 55.30, 35.85, 31.67, 6.67. HRMS (*m/z*): [M+H]⁺ calcd. for C₁₂H₁₆OI 303.0246, found 303.0234.

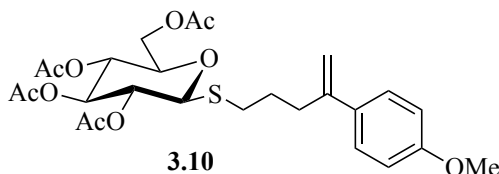
Synthesis of **3.3**



240 μL (1.60 mmol) DBU was added dropwise to a mixture of 612.6 mg (1.001 mmol) 2,3,4,6-tetra-*O*-benzoyl-1-mercapto-β-D-glucopyranoside¹² and 362.0 mg (1.198 mmol) **3.2** in 10 mL DCM at 20 °C. The reaction was allowed to stir 15 min and then concentrated. The resulting crude material was purified using silica gel (0% to 30% ethyl acetate in hexanes) to afford 690.0 mg (88 %) **3.3** as a white foam. ¹H NMR (500 MHz, CDCl₃) δ 8.02 (dd, *J* = 1.4, 9.4Hz, 2H), 7.95 (dd, *J* = 1.4, 9.7Hz, 2H), 7.90 (dd, *J* = 1.4, 8.3Hz, 2H), 7.82 (dd, *J* = 1.5, 8.3Hz, 2H), 7.57 – 7.48 (m, 3H), 7.45 – 7.33 (m, 7H), 7.31 – 7.25 (m, 4H), 6.83 (d, *J* = 8.8Hz, 2H), 5.89 (t, *J* = 9.6Hz, 1H), 5.65 (t, *J* = 9.8Hz, 1H), 5.54 (t, *J* = 9.8Hz, 1H), 5.16 (d, *J* = 1.5Hz, 1H), 4.91 (d, *J* = 1.4Hz, 1H), 4.76 (d, *J* = 10.0Hz, 1H), 4.60 (dd, *J* = 3.1, 12.2Hz, 1H), 4.46 (dd, *J* = 5.4, 12.1Hz, 1H), 4.12 – 4.08 (m, 1H), 3.81 (s, 3H), 2.79 – 2.68 (m, 2H), 2.54 – 2.49 (m, 2H), 1.79 – 1.73 (m, 2H). ¹³C

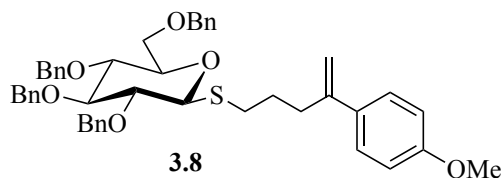
NMR (126 MHz, CDCl₃) δ 166.09, 165.81, 165.20, 165.18, 159.11, 146.42, 133.47, 133.32, 133.26, 133.15, 129.89, 129.87, 129.85, 129.74, 129.71, 129.15, 128.81, 128.78, 128.43, 128.39, 128.34, 128.31, 127.22, 126.67, 113.70, 111.57, 84.20, 76.27, 74.12, 70.67, 69.63, 63.33, 55.29, 34.01, 29.72, 27.98. **HRMS** (*m/z*): [M+K]⁺ calcd. for C₄₆H₄₂SO₁₀K 825.2136, found 825.2141. **[α]_D²⁰** = + 13.3° (*c* = 1.00, DCM). **IR** (cm⁻¹): 3066, 3037, 2945, 1721, 1368, 1246, 1086.

Synthesis of **3.10**



A solution of 2,3,4,6-tetra-*O*-acetyl-1-mercapto- β -D-glucopyranoside¹⁸ (728.6 mg, 2.000 mmol) and 635.5 mg **3.2** (2.103 mmol) in 10 mL of DCM, 350 μ L DBU (2.3 mmol) was added to the solution dropwise at rt (20 °C). After fifteen minutes, the solution was concentrated. Purification of the resulting crude material by gradient silica gel chromatography (0% to 40% ethyl acetate in hexanes) gave 870.3 mg (81%) **3.10** of a yellow oil. **¹H NMR** (400 MHz, CDCl₃) δ 7.34 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.23 (d, *J* = 1.6 Hz, 1H), 5.20 (t, *J* = 9.4 Hz, 1H), 5.07 (d, *J* = 11.7 Hz, 1H), 5.04 – 4.99 (m, 2H), 4.42 (d, *J* = 10.0 Hz, 1H), 4.21 (dd, *J* = 12.4, 4.9 Hz, 1H), 4.08 (dd, *J* = 12.4, 2.4 Hz, 1H), 3.82 (s, 3H), 3.65 – 3.61 (m, 1H), 2.74 – 2.63 (m, 2H), 2.61 – 2.56 (m, 2H), 2.06 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.79 – 1.74 (m, 2H). **¹³C NMR** (126 MHz, CDCl₃) δ 170.6, 170.1, 169.3, 169.3, 159.1, 146.5, 133.1, 127.2, 113.7, 111.5, 83.74, 75.82, 73.90, 69.91, 68.31, 62.13, 55.25, 34.14, 29.61, 28.09, 20.68, 20.58, 20.55. **HRMS** (*m/z*): [M+Na]⁺ Calcd. for C₂₆H₃₄O₁₀SNa 561.1770, found 561.1768. **[α]_D²⁰** = - 67.0° (*c* = 1.02, DCM). **IR** (cm⁻¹): 3062, 3030, 2909, 2864, 1745, 1510, 1226, 1054, 1035, 737, 697.

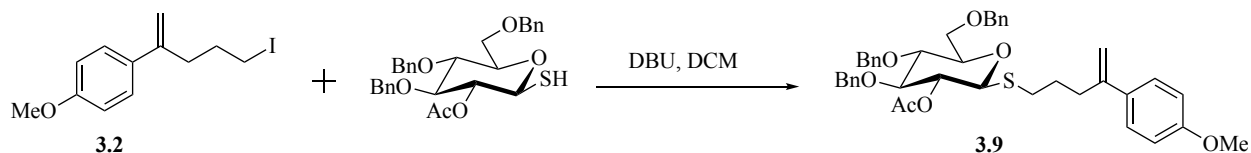
Synthesis of **3.8**



A 100 mL round bottom flask was charged with 1.52 g **3.10** (2.82 mmol) and 28 mL of methanol under a nitrogen atmosphere. 5 M solution of NaOMe in MeOH (280 μ L, 1.40 mmol) was added at once to the reaction solution at rt (25 °C). The resulting mixture was stirred for 15 min. The solvent was evaporated and further co-evaporated with 30 mL toluene yielding crude “tetra-ol”. The residue was then diluted with 30 mL DMF followed by the addition of tetra-*n*-butylammonium iodide (416.6 mg, 1.128 mmol), and placed under a stream of nitrogen. The solution was cooled to 0 °C. 60% Sodium hydride (1.13 g, 28.3 mmol, in mineral oil) was added in three portions to the solution at 0°C and the suspension was stirred for 30 minutes. Benzyl bromide (2.00 mL, 16.8 mmol) was then added dropwise to the suspension at 0 °C. The suspension was then allowed to warm to room temperature and stirred overnight (12 h). The reaction was then quenched with 40 mL of saturated ammonium chloride at 0 °C followed by extraction with 40 mL Et₂O twice. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting crude material was purified by gradient silica gel chromatography (0% to 15% EtOAc in hexanes) to give 1.36 g (66% over two steps) **3.8** of a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.39 - 7.17 (m, 22H), 6.84 (d, J = 8.8 Hz, 2H), 5.22 (d, J = 1.4 Hz, 1H), 5.00 (d, J = 1.4 Hz, 1H), 4.93 (d, J = 2.1 Hz, 1H), 4.90 (d, J = 1.7 Hz, 1H), 4.85 (m, 2H), 4.74 (d, J = 10.2 Hz, 1H), 4.62 - 4.52 (m, 3H), 4.40 (d, J = 9.7 Hz, 1H), 3.80 (s, 3H), 3.73 - 3.59 (m, 4H), 3.46 - 3.40 (m, 2H), 2.82 - 2.70 (m, 2H), 2.64 - 2.59 (m, 2H), 1.84 (quint, J = 7.4 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 159.0, 146.7, 138.5, 138.2, 138.1, 138.0, 133.2, 128.36, 128.34, 128.32, 128.29, 128.26, 128.23, 127.9, 127.8, 127.70, 127.66, 127.6, 127.5, 127.2, 113.6, 111.3, 86.61,

85.19, 81.73, 79.06, 77.91, 75.67, 75.42, 74.95, 73.40, 69.03, 55.19, 34.25, 30.26, 28.27. **HRMS** (**m/z**): [M+Na]⁺ Calcd. for C₄₆H₅₀O₆SNa 753.3226, found 753.3232. [α]_D²⁰ = - 36.1° (*c* = 1.02, DCM). **IR** (cm⁻¹): 3061, 3030, 2903, 2861, 1510, 1246, 1063, 1029, 734, 695.

Synthesis of **3.9**



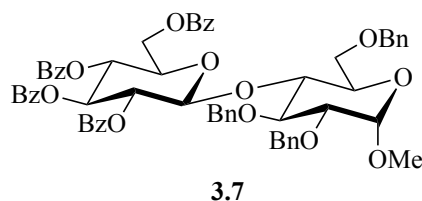
A solution of 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-1-mercapto- β -D-glucopyranoside⁸ (350.0 mg, 0.6881 mmol) and 225.7 mg **3.2** (0.7470 mmol) in 5 mL of CH₂Cl₂, 120 μ L DBU (0.80 mmol) was added to the solution dropwise at rt (20 °C). After fifteen minutes, the solution was concentrated. Purification of the resulting crude material by gradient silica gel chromatography (0% to 30% ethyl acetate in hexanes) gave 382.0 mg (81%) **3.9** of a yellow syrup. ¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.17 (m, 17H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.19 (d, *J* = 1.5 Hz, 1H), 5.06 – 4.93 (m, 1H), 4.96 (d, *J* = 1.5 Hz, 1H), 4.82 – 4.76 (m, 2H), 4.70 – 4.63 (m, 1H), 4.62 – 4.49 (m, 3H), 4.29 (d, *J* = 10.0 Hz, 1H), 3.76 (s, 3H), 3.70 – 3.61 (m, 4H), 3.45 – 3.41 (m, 1H), 2.80 - 2.61 (m, 2H), 2.60 – 2.49 (m, 2H), 1.96 (s, 3H), 1.81 - 1.67 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 169.5, 158.9, 146.6, 138.11, 138.10, 137.9, 133.2, 128.34, 128.32, 128.26, 127.9, 127.74, 127.67, 127.63, 127.58, 127.5, 127.1, 113.6, 111.3, 84.31, 83.48, 79.38, 77.77, 75.10, 74.97, 73.37, 71.69, 68.75, 55.14, 34.18, 29.16, 28.14, 20.88. **HRMS** (**m/z**): [M+Na]⁺ Calcd. for C₄₁H₄₆O₇SNa 705.2862, found 705.2870. [α]_D²⁰ = - 61.0° (*c* = 0.995, DCM). **IR** (cm⁻¹): 3062, 3030, 2909, 2864, 1745, 1226, 1054, 1035, 737, 697.

Representative procedure/optimized glycosylation conditions (0.0752 mmol scale):

A 5 mL Pyrex reactor vial was charged with 0.150 mmol glycosyl donor, 0.0750 glycosyl acceptor and 1 mL of dry dichloromethane. TfOH (1.4 μ L, 0.015 mmol) was added via gas-tight

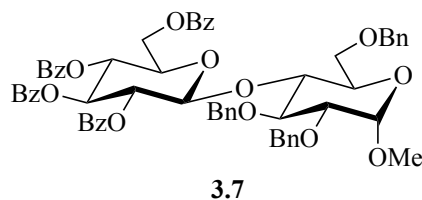
syringe. The reaction was stirred at room temperature for 70 min or until consumption of alcohol acceptor was observed via TLC. Triethylamine (4.20 μ L, 0.0300 mmol) was then added to the reaction mixture and the crude products were concentrated and then purified by gradient silica gel chromatography to afford the desired glycosides. Determination of anomeric ratios: The anomeric ratio (α : β) was determined based on the integration of key resonances identified with the assistance of published ^1H NMR data. In the cases where spectral data was unavailable, the anomeric products were separated with silica gel chromatography or preparative TLC.

1 mmol scale glycosylation (synthesis of **3.7** at 1 mmol scale):



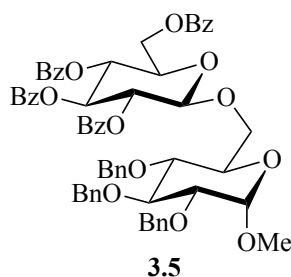
A flame-dried 25 mL round bottom flask was charged with **3.3** (1.18 g, 1.50 mmol) and methyl-2,3,6-tri-*O*-benzyl- α -D-glucopyranoside (0.465g, 1.00 mmol) at 20 $^{\circ}\text{C}$. Anhydrous CH_2Cl_2 (7.0 mL) was then added to the solution, followed by TfOH (13 μ L, 0.14 mmol). After stirring for 3 hours, triethylamine (42 μ L, 0.30 mmol) was added to the reaction solution which was allowed to stir for an additional 5 minutes. Solvents were then removed in vacuo to afford 1.7 g crude material. Purification by silica gel chromatography (0% to 20% EtOAc in hexanes) yielded 750.8 mg, (72%, β only) of **3.7** as a white foam. Spectral data matched that previously reported in literature.¹⁹

Synthesis of **3.7**



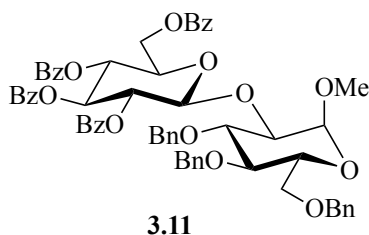
A reaction vial was charged with 118.5 mg (0.1506 mmol) **3.3** and 35.0 mg (0.0753 mmol) methyl 2,3,6-tri-*O*-benzyl- α -D-glucopyranoside. 1 mL DCM and then 1.3 μ L (0.014 mmol) HOTf were added to the vial using a syringe at 20 °C. The reaction was stirred for 50 min. 5.0 μ L triethylamine was then added to quench the reaction which was concentrated. The resulting crude mixture (190.2 mg) was purified with silica gel chromatography using a gradient run (0% to 30% ethyl acetate in hexanes) to afford 55.0 mg (70%) **3.7** as white foam. Spectral data matched that previously reported in the literature.¹⁹

Synthesis of **3.5**



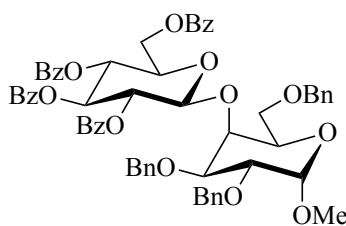
A reaction vial was charged with 118.5 mg (0.1506 mmol) **3.3** and 38.2 mg (0.082 mmol) methyl 2,3,4-tri-*O*-benzyl- α -D-glucopyranoside. 1 mL DCM and then 1.3 μ L (0.014 mmol) HOTf were added to the vial using a syringe at 20 °C. The reaction was stirred for 30 min. 5.0 μ L triethylamine was then added to quench the reaction which was then concentrated. The resulting crude mixture (167.2 mg) was purified with silica gel chromatography using a gradient run (0% to 20% ethyl acetate in hexanes) to afford 82.1 mg (96%) **3.5** as a white foam. Spectral data matched that previously reported in the literature.²⁰

Synthesis of **3.11**



A reaction vial was charged with 118.2 mg (0.1502 mmol) **3.3** and 34.9 mg (0.0751 mmol) methyl 3,4,6-tri-*O*-benzyl- α -D-glucopyranoside. 1 mL DCM and then 1.3 μ L (0.014 mmol) HOTf were added to the vial using a syringe at 20 °C. The reaction was stirred for 30 min. 5.0 μ L triethylamine was then added to quench the reaction which was then concentrated. The resulting crude mixture (167.8 mg) was purified with silica gel chromatography using a gradient run (0% to 20% ethyl acetate in hexanes) to afford 63.6 mg (81%) **3.11** as a white foam. Spectral data matched that previously reported in the literature.²⁰

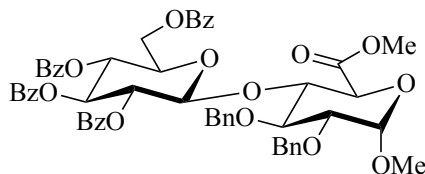
Synthesis of **3.12**



3.12

A reaction vial was charged with 117.8 mg (0.1497 mmol) **3.3** and 34.9 mg (0.0751 mmol) methyl 2,3,6-tri-*O*-benzyl- α -D-galactopyranoside. 1 mL DCM and then 1.3 μ L (0.014 mmol) HOTf were added to the vial using a syringe at 23 °C. The reaction was stirred for 70 min. 5.0 μ L triethylamine was then added to quench the reaction which was then concentrated. The resulting crude mixture (172.3 mg) was purified with silica gel chromatography using a gradient run (0% to 20% ethyl acetate in hexanes) to afford 42.4 mg (54%) **3.12** as a white foam. Spectral data matched that previously reported in the literature.⁷

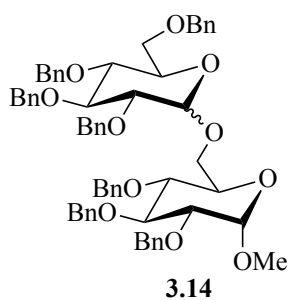
Synthesis of **3.13**



3.13

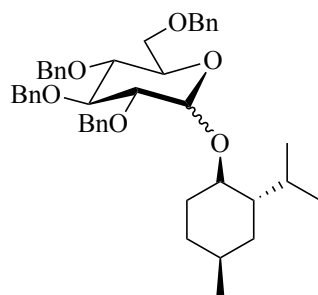
A reaction vial was charged with 118.5 mg (0.1506 mmol) **3.3** and 30.1 mg (0.0748 mmol) 1-*O*-methyl-2,3-di-*O*-benzyl- α -D-glucopyranuronic acid methyl ester. 1 mL DCM and then 1.3 μ L (0.014 mmol) HOTf were added to the vial using a syringe at 20 °C. The reaction was stirred for 70 min. 5.0 μ L triethylamine was then added to quench the reaction which was then concentrated. The resulting crude mixture (194.4 mg) was purified with silica gel chromatography using a gradient run (0% to 20% ethyl acetate in hexanes) to afford 43.5 mg (59%) **3.13** as a white foam. **¹H NMR** (400 MHz, CDCl₃) δ 7.99 – 7.94 (m, 4H), 7.87 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.80 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.55 – 7.20 (m, 22H), 5.85 (t, *J* = 9.6 Hz, 1H), 5.64 (t, *J* = 9.6 Hz, 1H), 5.48 (dd, *J* = 9.7, 3.9 Hz, 1H), 5.13 (d, *J* = 8.0 Hz, 1H), 5.10 (d, *J* = 10.9 Hz, 1H), 4.88 (d, *J* = 11.4 Hz, 1H), 4.74 (d, *J* = 12.1 Hz, 1H), 4.56 (d, *J* = 12.2 Hz, 1H), 4.53 (d, *J* = 4.0 Hz, 1H), 4.41 (dd, *J* = 12.1, 3.4 Hz, 1H), 4.29 (dd, *J* = 12.1, 4.7 Hz, 1H), 4.11 (dd, *J* = 9.6, 1.2 Hz, 1H), 4.05 – 3.96 (m, 3H), 3.51 – 3.46 (m, 1H), 3.47 (s, 3H), 3.36 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 169.7, 165.9, 165.8, 165.2, 165.0, 139.0, 138.0, 133.3, 133.15, 133.08, 132.9, 129.8, 129.74, 129.73, 129.65, 129.60, 129.5, 129.0, 128.80, 128.78, 128.4, 128.3, 128.23, 128.20, 128.11, 128.07, 127.9, 127.20, 127.15, 100.7, 99.95, 98.76, 79.41, 78.85, 78.60, 75.41, 73.69, 73.11, 72.38, 72.09, 69.60, 63.00, 55.66, 52.38. **HRMS (m/z):** [M+Na]⁺ Calcd. for C₅₆H₅₂O₁₆Na 1003.3153, found 1003.3172. **$[\alpha]_D^{20}$** = +13.3° (*c* = 0.990, DCM). **IR** (cm⁻¹): 2952, 2920, 2851, 1724, 1451, 1263, 1249, 1093, 1040, 707.

Synthesis of **3.14**



A reaction vial was charged with 105.3 mg (0.1440 mmol) **3.8** and 34.8 mg (0.0749 mmol) methyl 2,3,4-tri-*O*-benzyl- α -D-glucopyranoside. 1 mL DCM and then 1.3 μ L (0.014 mmol) HOTf were added to the vial using a syringe at 19 °C. The reaction was stirred for 70 min. 5.0 μ L triethylamine was then added to quench the reaction which was then concentrated. The resulting crude mixture (147.3 mg) was purified with silica gel chromatography using a gradient run (0% to 20% ethyl acetate in hexanes) to afford 61.0 mg (83%, 1.5:1 α : β) **3.14** as a white foam. Spectral data matched that previously reported in the literature.²¹

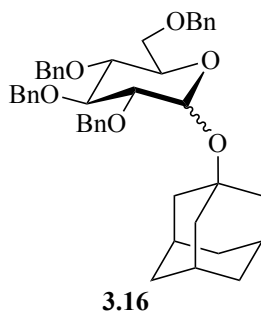
Synthesis of **3.15**



3.15

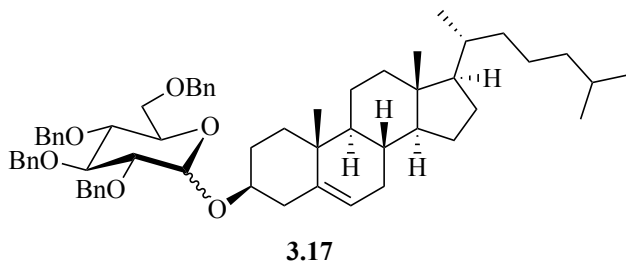
A reaction vial was charged with 109.7 mg (0.1501 mmol) **3.8** and 11.8 mg (0.0755 mmol) menthol. 1 mL DCM and then 1.3 μ L (0.014 mmol) HOTf were added to the vial using a syringe at 21 °C. The reaction was stirred for 70 min. 5.0 μ L triethylamine was then added to quench the reaction which was then concentrated. The resulting crude mixture (147.8 mg) was purified with silica gel chromatography using a gradient run (0% to 20% ethyl acetate in hexanes) to afford 41.5 mg (81%, 1.3:1 α : β) **3.15** as a colorless oil. Spectral data matched that previously reported in the literature.²²

Synthesis of **3.16**



A reaction vial was charged with 109.7 mg (0.1501 mmol) **3.8** and 11.4 mg (0.0749 mmol) 1-adamantanol. 1 mL DCM and then 1.3 μ L (0.014 mmol) HOTf were added to the vial using a syringe at 21 °C. The reaction was stirred for 70 min. 5.0 μ L triethylamine was then added to quench the reaction which was then concentrated. The resulting crude mixture (143.2 mg) was purified with silica gel chromatography using a gradient run (0% to 20% ethyl acetate in hexanes) to afford 42.0 mg (83%, 1.1:1 α : β) **3.16** as a colorless oil. Spectral data matched that previously reported in the literature.²³

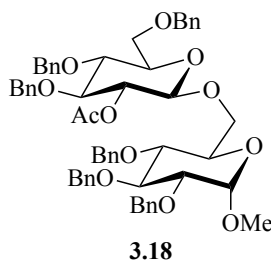
Synthesis of **3.17**



A reaction vial was charged with 109.7 mg (0.1501 mmol) **3.8** and 29.0 mg (0.0750 mmol) cholesterol. 1 mL DCM and then 1.3 μ L (0.014 mmol) HOTf were added to the vial using a syringe at 21 °C. The reaction was stirred for 70 min. 5.0 μ L triethylamine was then added to quench the reaction which was then concentrated. The resulting crude mixture (159.6 mg) was purified with silica gel chromatography using a gradient run (0% to 20% ethyl acetate in hexanes) to afford 50.3

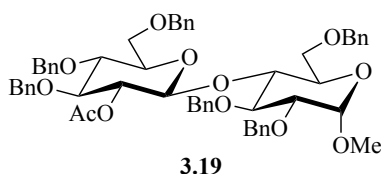
mg (74%, 1:1 α : β) **3.17** as a colorless oil. Spectral data matched that previously reported in the literature.²⁴

Synthesis of **3.18**



A reaction vial was charged with 103.2 mg (0.1511 mmol) **3.9** and 34.9 mg (0.0751 mmol) methyl 2,3,4-tri-*O*-benzyl- α -D-glucopyranoside. 1 mL DCM and then 1.3 μ L (0.014 mmol) HOTf were added to the vial using a syringe at 19 °C. The reaction was stirred for 70 min. 5.0 μ L triethylamine was then added to quench the reaction which was then concentrated. The resulting crude mixture (137.2mg) was purified with silica gel chromatography using a gradient run (0% to 20% ethyl acetate in hexanes) to afford 48.2 mg (68%) **3.18** as a colorless oil. Spectral data matched that previously reported in the literature.²⁵

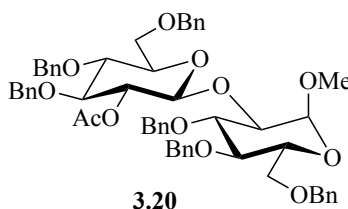
Synthesis of **3.19**



A reaction vial was charged with 103.2 mg (0.1511 mmol) **3.9** and 35.0 mg (0.0753 mmol) methyl 2,3,6-tri-*O*-benzyl- α -D-glucopyranoside. 1 mL DCM and then 1.3 μ L (0.014 mmol) HOTf were added to the vial using a syringe at 19 °C. The reaction was stirred for 70 min. 5.0 μ L triethylamine was then added to quench the reaction which was then concentrated. The resulting crude mixture (153.1mg) was purified with silica gel chromatography using a gradient run (0% to 20% ethyl acetate in hexanes) to afford 47.9 mg (68%) **3.19** as a colorless oil. Spectral data

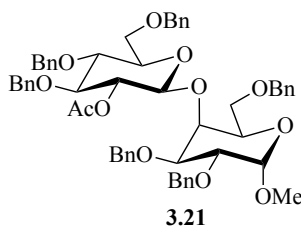
matched that previously reported in the literature.²⁶

Synthesis of **3.20**



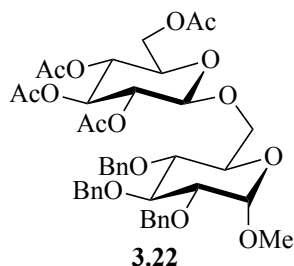
A reaction vial was charged with 102.5 mg (0.1501 mmol) **3.9** and 34.8 mg (0.0749 mmol) methyl 3,4,6-tri-*O*-benzyl- α -D-glucopyranoside. 1 mL DCM and then 1.3 μ L (0.014 mmol) HOTf were added to the vial using a syringe at 20 °C. The reaction was stirred for 70 min. 5.0 μ L triethylamine was then added to quench the reaction which was then concentrated. The resulting crude mixture (169.3 mg) was purified with silica gel chromatography using a gradient run (0% to 20% ethyl acetate in hexanes) to afford 43.4 mg (62%) **3.20** as a white solid. Spectral data matched that previously reported in the literature.⁸

Synthesis of **3.21**



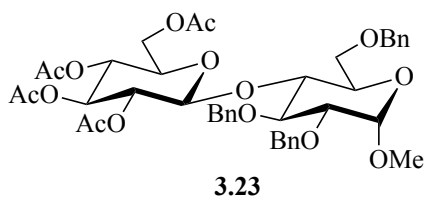
A reaction vial was charged with 101.7 mg (0.1489 mmol) **3.9** and 34.0 mg (0.0732 mmol) methyl 2,3,6-tri-*O*-benzyl- α -D-galactopyranoside. 1 mL DCM and then 1.3 μ L (0.014 mmol) HOTf were added to the vial using a syringe at 20 °C. The reaction was stirred for 120 min. 5.0 μ L triethylamine was then added to quench the reaction which was then concentrated. The resulting crude mixture (170.7 mg) was purified with silica gel chromatography using a gradient run (0% to 20% ethyl acetate in hexanes) to afford 35.1 mg (51%) **3.21** as a white solid. Spectral data matched that previously reported in the literature.²⁷

Synthesis of **3.22**



A reaction vial was charged with 85.8 mg (0.1593 mmol) **3.10** and 34.4 mg (0.0741 mmol) methyl 2,3,4-tri-*O*-benzyl- α -D-glucopyranoside. 1 mL DCM and then 1.3 μ L (0.014 mmol) HOTf were added to the vial using a syringe at 20 °C. The reaction was stirred for 70 min. 5.0 μ L triethylamine was then added to quench the reaction which was then concentrated. The resulting crude mixture (150.3 mg) was purified with silica gel chromatography using a gradient run (0% to 20% ethyl acetate in hexanes) to afford 20.6 mg (35%) **3.22** as a colorless oil. Spectral data matched that previously reported in the literature.²⁸

Synthesis of **3.23**



A reaction vial was charged with 85.8 mg (0.1593 mmol) **3.10** and 35.0 mg (0.0753 mmol) methyl 2,3,6-tri-*O*-benzyl- α -D-glucopyranoside. 1 mL DCM and then 1.3 μ L (0.014 mmol) HOTf were added to the vial using a syringe at 20 °C. The reaction was stirred for 70 min. 5.0 μ L triethylamine was then added to quench the reaction which was then concentrated. The resulting crude mixture (130.1 mg) was purified with silica gel chromatography using a gradient run (0% to 20% ethyl acetate in hexanes) to afford 34.0 mg (57%) **3.23** as a colorless oil. Spectral data matched that previously reported in the literature.²⁹

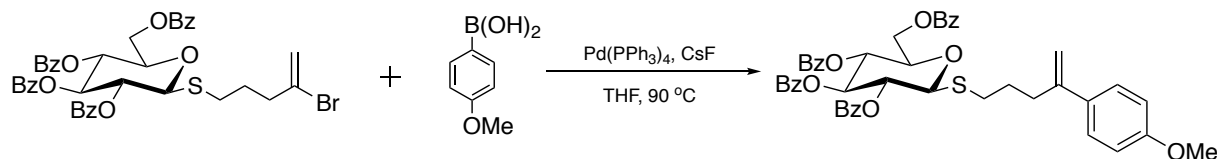
Additional Transformations with MPTGs

Synthesis of **3.24**

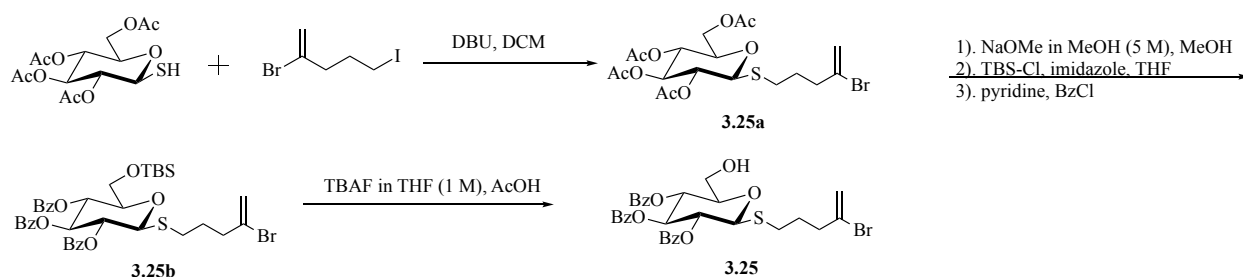


180 μ L (1.20 mmol) DBU was added dropwise to a mixture of 612.6 mg (1.000 mmol) 2,3,4,6-tetra-*O*-benzoyl-1-mercapto- β -D-glucopyranoside and 329.9 mg (1.200 mmol) 2-bromo-5-iodopent-1-ene³⁰ in 10 mL DCM at 20 °C. The reaction was allowed to stir 15 min and then concentrated. The resulting crude material was purified using silica gel (0% to 30% ethyl acetate in hexanes) to afford 630.0 mg (83 %) **3.24** as a white foam. **¹H NMR** (400 MHz, CDCl₃) δ 8.04 (dd, J = 8.2, 1.4 Hz, 2H), 7.96 (dd, J = 8.6, 1.4 Hz, 2H), 7.91 (dd, J = 8.5, 1.4 Hz, 2H), 7.82 (dd, J = 8.5, 1.4 Hz, 2H), 7.58 - 7.48 (m, 3H), 7.46 - 7.33 (m, 7H), 7.31 - 7.26 (m, 2H), 5.94 (t, J = 9.5 Hz, 1H), 5.68 (t, J = 9.8 Hz, 1H), 5.57 (t, J = 9.7 Hz, 1H), 5.50 (d, J = 1.5 Hz, 1H), 5.34 (d, J = 1.3 Hz, 1H), 4.86 (d, J = 9.9 Hz, 1H), 4.64 (dd, J = 11.0, 3.0 Hz, 1H), 4.50 (dd, J = 12.2, 5.5 Hz, 1H), 4.21 - 4.17 (m, 1H), 2.83 - 2.77 (m, 1H), 2.73 - 2.66 (m, 1H), 2.48 - 2.43 (m, 2H), 1.92 - 1.84 (m, 2H). **¹³C NMR** (126 MHz, CDCl₃) δ 166.0, 165.7, 165.12, 165.10, 133.4, 133.3, 133.2, 133.12, 133.09, 133.0, 129.78, 129.75, 129.6, 129.5, 129.0, 128.70, 128.66, 128.3, 128.23, 128.21, 117.5, 84.00, 81.29, 76.28, 74.02, 70.55, 69.53, 63.20, 39.73, 28.68, 27.72. **HRMS (m/z):** [M+K]⁺ calcd. for C₃₉H₃₅SO₉BrK 797.0822, found 797.0808. **[α]_D²⁰** = +96.2° (c = 0.490, DCM). **IR (cm⁻¹):** 2951, 1721, 1257, 1066, 705.

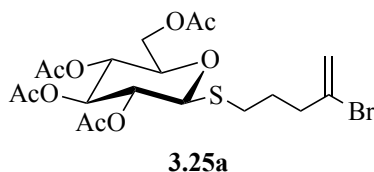
Suzuki-Coupling of **3.24**/*p*-Methoxyphenylboronic acid:



A vial was charged with 102.1 mg (0.1344 mmol) **3.24**, 61.2 mg (0.403 mmol) *p*-methoxyphenyl boronic acid, 7.8 mg (0.0067 mmol) Pd(PPh₃)₄ and 102 mg (0.672 mmol) cesium fluoride. Vacuum-purge-backfill was performed three times. 2 mL THF was added under N₂. The vial was then sealed with a cap. The resulting mixture was heated to 90 °C for 3 h. The reaction was cooled to rt and 3 mL water was added. The reaction mixture was extracted with 3 X 10 mL ethyl acetate. The combined organic layer was dried with sodium sulfate and then concentrated. The resulting crude mixture (230.0 mg) was purified by silica gel (100% hexanes to 10% ethyl acetate in hexanes) to afford 85.0 mg (80 %) **3.3** as a white foam.



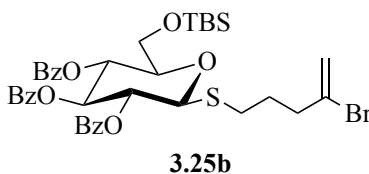
Synthesis of **3.25a**



A solution of 2,3,4,6-tetra-*O*-acetyl-1-mercapto-β-D-glucopyranoside (700.0 mg, 1.921 mmol) and 550.1 mg (2.001 mmol) 2-bromo-5-iodopent-1-ene in 10 mL DCM at rt. 350 μL DBU (2.19 mmol) was added to the solution dropwise at rt (20 °C). The reaction was allowed to stir 15 min and then concentrated. The resulting crude material was purified using silica gel (0% to 30% ethyl acetate in hexanes) to afford 790.2 mg (80 %) **3.25a** as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 5.60 (d, *J* = 1.5 Hz, 1H), 5.42 (d, *J* = 1.7 Hz, 1H), 5.21 (t, *J* = 9.4 Hz, 1H), 5.07 (t, *J* = 9.8 Hz, 1H), 5.02 (t, *J* = 9.7 Hz, 1H), 4.48 (d, *J* = 10.0 Hz, 1H), 4.22 (dd, *J* = 12.4, 5.0 Hz, 1H), 4.12 (dd, *J* = 12.4, 2.4 Hz, 1H), 3.72 – 3.68 (m, 1H), 2.74 - 2.69 (m, 1H), 2.66 – 2.59 (m, 1H), 2.55

– 2.50 (m, 2H), 2.07 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.92 – 1.84 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 170.5, 170.1, 169.32, 169.30, 133.1, 117.5, 83.62, 75.87, 73.81, 69.80, 68.27, 62.11, 39.89, 28.60, 27.74, 20.68, 20.65, 20.54, 20.52. HRMS (m/z): $[\text{M}+\text{Na}]^+$ Calcd. for $\text{C}_{19}\text{H}_{27}\text{O}_9\text{SBrNa}$ 533.0457, found 533.0467. $[\alpha]_{\text{D}}^{20} = +10.7^\circ$ ($c = 1.10$, DCM). IR (cm^{-1}): 2962, 2945, 1739, 1368, 1219, 1032, 898.

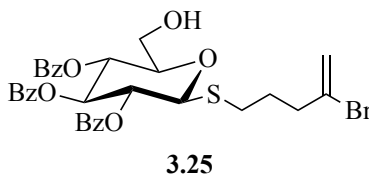
Synthesis of **3.25b**



A 100 mL RBF was charged with 670.0 mg (1.310 mmol) **3.25a** and 30 mL MeOH. 0.13 mL 5 M sodium methoxide in methanol was added to the solution and stirred for 15 min at 21 °C. The solution was evaporated to yield the deacetylated thioglycoside which was then co-evaporated with 30 mL toluene to remove any remaining volatile compounds. The resulting tetra-ol was dissolved in 20 mL THF followed by sequential addition of TBS-Cl (590.7 mg, 3.919 mmol) and imidazole (446.0 mg, 6.551 mmol). After 1 hour, EtOAc (70 mL) was added and the resulting solution was washed with H_2O (2 x 40 mL). The organic layer was dried over Na_2SO_4 , concentrated, and placed on high vacuum for 2 h. The resulting white solid was dissolved in 5 mL pyridine. 760 μL (6.54 mmol) benzoyl chloride was added dropwise to the solution over a period of 2 min at rt (21 °C). The reaction was stirred for 3 h at 21 °C. 20 mL water and 40 mL DCM were added. The organic layer was washed with 30 mL 1 M HCl three times, followed by 50 mL sat. NaHCO_3 , dried with Na_2SO_4 , and concentrated. The resulting crude mixture (768.3 mg) was purified by silica gel (0% to 30% ethyl acetate in hexanes) to afford 620.0 mg (61 % two-step yield) **3.25b** as a white foam. ^1H NMR (400 MHz, CDCl_3) δ 7.95 (dd, $J = 8.5, 1.4$ Hz, 2H), 7.92 (dd, $J = 8.5, 1.4$ Hz, 2H), 7.81 (dd, $J = 8.4, 1.4$ Hz, 2H), 7.54 - 7.50 (m, 2H), 7.45 - 7.36 (m, 5H),

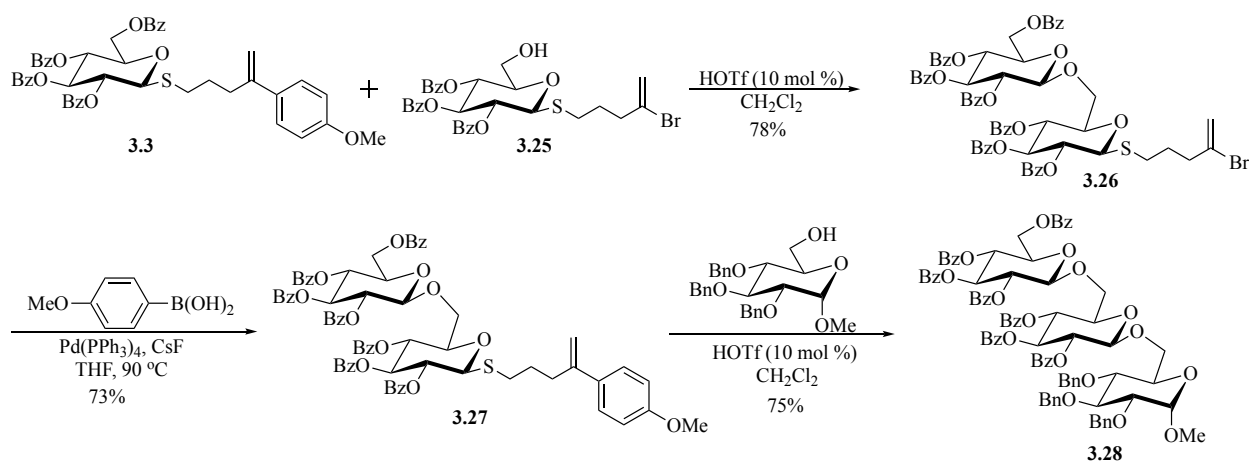
7.30 - 7.26 (m, 2H), 5.86 (t, $J = 9.5$ Hz, 1H), 5.56 (d, $J = 1.6$ Hz, 1H), 5.56 - 5.51 (m, 2H), 5.41 (d, $J = 1.6$ Hz, 1H), 4.77 (d, $J = 9.9$ Hz, 1H), 3.89 - 3.81 (m, 3H), 2.87 - 2.80 (m, 1H), 2.77 - 2.70 (m, 1H), 2.52 (t, $J = 7.1$ Hz, 2H), 1.96 - 1.86 (m, 2H), 0.88 (s, 9H), 0.034 (s, 3H), 0.029 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.8, 165.1, 165.0, 133.2, 133.13, 133.05, 129.8, 129.68, 129.65, 129.2, 129.1, 128.9, 128.34, 128.30, 128.2, 117.4, 83.48, 79.50, 74.42, 70.64, 69.37, 62.72, 39.95, 28.20, 27.63, 25.78, 18.25, -5.39, -5.44. HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{38}\text{H}_{46}\text{SO}_8\text{BrSi}$ 769.1866, found 769.1841. $[\alpha]_{\text{D}}^{20} = -22.0^\circ$ ($c = 1.11$, DCM). IR (cm^{-1}): 2928, 2855, 1725, 1249, 1066, 834, 704.

Synthesis of **3.25**

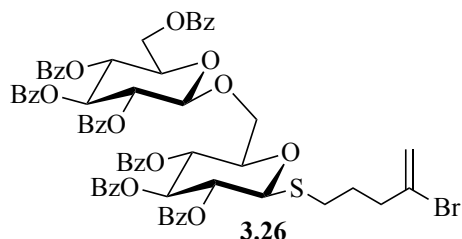


3 mL of tetra-*n*-butylammonium fluoride (1M in THF) was acidified to pH 6 by dropwise addition of acetic acid and careful monitoring with pH paper. 3.0 mL of the premixed AcOH/TBAF solution was added to **3.25b** (450.0 mg, 0.5846 mmol) in a 10 mL round bottom flask at 21 °C. After 6 hours, the reaction solution was diluted with EtOAc (15 mL). The organic layer was washed with sat. NH_4Cl (aq.) (3 mL) and sat. NaCl (aq.) (10 mL) then dried over Na_2SO_4 and concentrated. Silica gel chromatography (0% to 30% EtOAc in hexanes) yielded 283.2 mg (74%) **3.25** as a white foam. ^1H NMR (400 MHz, CDCl_3) δ 7.97 - 7.94 (m, 4H), 7.83 (dd, $J = 8.5, 1.4$ Hz, 2H), 7.56 - 7.51 (m, 2H), 7.46 - 7.37 (m, 5H), 7.30 - 7.24 (m, 2H), 5.95 (t, $J = 9.6$ Hz, 1H), 5.56 (d, $J = 1.8$ Hz, 1H), 5.54 - 5.48 (m, 2H), 5.41 (d, $J = 1.7$ Hz, 1H), 4.82 (d, $J = 10.0$ Hz, 1H), 3.90 - 3.81 (m, 2H), 3.77 - 3.73 (m, 1H), 2.87 - 2.80 (m, 1H), 2.77 - 2.71 (m, 1H), 2.54 - 2.49 (m, 3H), 1.95 - 1.87 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 165.8, 165.7, 165.0, 133.5, 133.2, 133.1, 133.0, 129.8, 129.7, 129.5, 129.0, 128.7, 128.4, 128.3, 128.2, 117.4, 83.82, 78.85, 73.89, 70.46,

69.27, 61.40, 39.74, 28.54, 27.67. **HRMS (m/z):** $[M+H]^+$ calcd. for $C_{32}H_{32}SO_8Br$ 655.1001, found 655.0993. $[\alpha]_D^{20} = +21.0^\circ$ ($c = 1.03$, DCM). **IR (cm⁻¹):** 3526, 3064, 2940, 2871, 1722, 1176, 1066, 1024, 704.



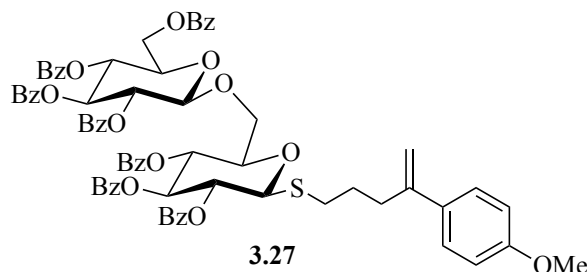
Synthesis of **3.26**



A reaction vial was charged with 118.3 mg (0.1503 mmol) **3.3** and 48.0 mg (0.0732 mmol) **3.25**. 1 mL DCM and then 1.3 μL (0.014 mmol) HOTf were added to the vial using a syringe at 20°C . The reaction was stirred for 70 min. 5.0 μL triethylamine was then added to quench the reaction which was then concentrated. The resulting crude mixture (180.0 mg) was purified with silica gel chromatography using a gradient run (0% to 20% ethyl acetate in hexanes) to afford 72.3 mg (86%) **3.26** as a white foam. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.04 - 8.00 (m, 4H), 7.94 - 7.81 (m, 8H), 7.76 (dd, $J = 8.5, 1.4$ Hz, 2H), 7.58 - 7.24 (m, 21H), 5.89 (t, $J = 9.6$ Hz, 1H), 5.81 (t, $J = 9.6$ Hz, 1H), 5.63 (t, $J = 9.7$ Hz, 1H), 5.54 (d, $J = 1.5$ Hz, 1H), 5.51 (dd, $J = 9.7, 7.7$ Hz, 1H), 5.40 (d, $J = 1.5$ Hz, 1H), 5.40 (t, $J = 9.2$ Hz, 1H), 5.33 (t, $J = 9.4$ Hz, 1H), 4.98 (d, $J = 7.8$ Hz, 1H), 4.61

(d, $J = 9.8$ Hz, 2H), 4.42 (dd, $J = 12.1, 5.0$ Hz, 1H), 4.14 – 4.09 (m, 1H), 4.05 (dd, $J = 11.9, 2.1$ Hz, 1H), 4.00 (dt, $J = 10.4, 2.8$ Hz, 1H), 3.86 (dd, $J = 11.5, 7.0$ Hz, 1H), 2.67 - 2.62 (m, 1H), 2.54 – 2.43 (m, 3H), 1.84 – 1.70 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 166.0, 165.7, 165.6, 165.3, 165.10, 165.06, 165.0, 133.42, 133.37, 133.23, 133.16, 133.11, 129.83, 129.77, 129.76, 129.71, 129.68, 129.6, 129.5, 129.2, 129.1, 128.78, 128.75, 128.72, 128.65, 128.4, 128.33, 128.31, 128.23, 128.18, 117.5, 101.3, 83.36, 78.07, 73.96, 72.84, 72.26, 71.83, 70.40, 69.62, 69.53, 68.55, 62.86, 39.70, 28.20, 27.56. **HRMS** (m/z): $[\text{M}+\text{K}]^+$ calcd. for $\text{C}_{66}\text{H}_{57}\text{SO}_{17}\text{BrK}$ 1271.2137, found 1271.2108. $[\alpha]_{\text{D}}^{20} = +84.6^\circ$ ($c = 0.505$, DCM). **IR** (cm^{-1}): 1721, 1450, 1249, 1066, 1024, 704.

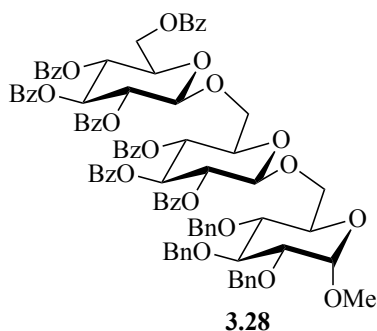
Synthesis of **3.27**



A vial was charged with 130.7 mg (0.1059 mmol) **3.26**, 49.3 mg (0.325 mmol) *p*-methoxyphenylboronic acid, 11.7 mg (0.0101 mmol) $\text{Pd}(\text{PPh}_3)_4$ and 79.7 mg (0.526 mmol) cesium fluoride. Vacuum-purge-backfill was performed three times. 2 mL THF was added under N_2 . The vial was then sealed with a cap. The resulting mixture was heated to 90 °C and kept for 3 h. The reaction was cooled to rt and 3 mL water was added. The reaction was extracted with 10 mL ethyl acetate three times. The combined organic layer was dried with sodium sulfate and then concentrated. The resulting crude mixture (221.4 mg) was purified by silica gel (0% 20% ethyl acetate in hexanes) to afford 101.2 mg (76 %) **3.27** as a white foam. ^1H NMR (400 MHz, CDCl_3) δ 8.01 (dd, $J = 8.2, 1.4$ Hz, 2H), 7.98 (dd, $J = 8.3, 1.4$ Hz, 2H), 7.91 (dd, $J = 8.4, 1.4$ Hz, 2H), 7.87 (m, 4H), 7.81 (dd, $J = 8.5, 1.4$ Hz, 2H), 7.77 (dd, $J = 8.4, 1.4$ Hz, 2H), 7.54 - 7.25 (m, 23H), 6.87 (d, $J = 8.8$ Hz, 2H), 5.86 (t, $J = 9.6$ Hz, 1H), 5.78 (t, $J = 9.4$ Hz, 1H), 5.61 (t, $J = 9.7$ Hz, 1H), 5.49

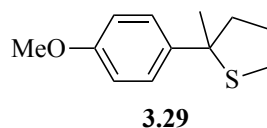
(dd, $J = 7.8, 9.8$ Hz, 1H), 5.39 (t, $J = 9.8$ Hz, 1H), 5.31 (t, $J = 9.4$ Hz, 1H), 5.22 (d, $J = 1.4$ Hz, 1H), 4.95 (m, 2H), 4.59 (dd, $J = 12.2, 3.2$ Hz, 1H), 4.55 (d, $J = 9.9$ Hz, 1H), 4.40 (dd, $J = 12.2, 5.4$ Hz, 1H), 4.10 - 4.06 (m, 1H), 4.03 (dd, $J = 12.0, 2.0$ Hz, 1H), 3.96 - 3.92 (m, 1H), 3.85 - 3.77 (m, 1H), 3.80 (s, 3H), 2.66 - 2.60 (m, 1H), 2.54 - 2.47 (m, 3H), 1.69 - 1.60 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 166.0, 165.7, 165.6, 165.3, 165.11, 165.08, 165.0, 159.1, 146.6, 133.41, 133.36, 133.3, 133.17, 133.15, 133.1, 133.08, 129.83, 129.80, 129.71, 129.69, 129.6, 129.5, 129.24, 129.18, 128.9, 128.80, 128.76, 128.71, 128.38, 128.34, 128.3, 128.23, 128.19, 127.2, 113.7, 111.3, 101.3, 83.52, 78.06, 74.02, 72.87, 72.22, 71.84, 70.48, 69.67, 69.56, 68.57, 62.90, 55.21, 33.79, 29.23, 27.89. **HRMS (m/z):** $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{73}\text{H}_{64}\text{SO}_{18}\text{Na}$ 1283.3711, found 1283.3728. $[\alpha]_{\text{D}}^{20} = +43.6^\circ$ ($c = 1.04$, DCM). **IR (cm $^{-1}$):** 1721, 1451, 1245, 1065, 1024, 704.

Synthesis of **3.28**



A reaction vial was charged with 100.1 mg (0.07936 mmol) **3.27** and 18.5 mg (0.0398 mmol) methyl 2,3,4-tri-*O*-benzyl- α -D-glucopyranoside. 1 mL DCM and then 0.7 μL (0.008 mmol) HOTf were added to the vial using a syringe. The reaction was stirred for 70 min. 2.5 μL triethylamine was then added to quench the reaction which was then concentrated. The resulting crude mixture (152.3 mg) was purified with silica gel chromatography using a gradient run (0% to 20% ethyl acetate in hexanes) to afford 45.3 mg (75%) **3.28** as a white foam. Spectral data matched that previously reported in the literature.³¹

Tetrahydrothiophene by-product **3.29**



The compound was purified from early-eluting column chromatography fractions from *O*-glycosylation procedures. **¹H NMR:** (500 MHz, CDCl₃) δ 7.47 – 7.44 (m, 2H), 6.85 – 6.82 (m, 2H), 3.79 (s, 3H), 3.09 – 3.03 (m, 2H), 2.32 – 2.27 (m, 1H), 2.18 – 2.08 (m, 3H), 1.74 (s, 3H). **¹³C NMR:** (125 MHz, CDCl₃) δ 157.92, 140.42, 127.43, 113.33, 59.68, 55.29, 45.71, 33.36, 32.88, 29.63. **HRMS (m/z):** [M+H]⁺ calcd. for C₁₂H₁₇SO 209.1000, found 2209.0986.

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CHAPTER 4: STUDIES TOWARD THE TOTAL SYNTHESIS OF AN *ACINETOBACTER BAUMANNII* LIPOOLIGOSACCHARIDE CORE PENTASACCHARIDE

4.1 Introduction

Acinetobacter baumannii (*A. baumannii*) is a pathogenic bacteria prone to infecting people with poor immune systems, especially ICU patients.¹ It can cause wounded skin infections, bacteremia, pneumonia, and urinary tract infections.² It is a non-fermenting, Gram-negative, aerobic coccobacillus, which has become increasingly resistant to most antibiotics.³ It has been listed as one of the 6 top-priority dangerous microorganisms by the Infectious Disease Society of America. Multidrug-resistant strains have made *A. baumannii* less susceptible to treatment with antibiotic therapy. Therefore, developing novel treatments and prevention strategies is of great importance.

Currently, there is no licensed vaccine for the prevention of *A. baumannii* infections. Potential vaccine candidates include outer membrane complexes (OMCs),⁴ outer membrane vesicles (OMVs),³ a whole cell vaccine,⁵ single outer membrane proteins like OmpA, Ata, and Bap,⁶ and the K1 capsular polysaccharide (K1 CPS).⁷ Vaccine formulations with the aforementioned antigens have been proven effective to some degree in preventing *A. baumannii* infections in animal models.

Carbohydrates on the cell surface play a significant role in biological processes. Nearly every protein on the cell surface is modified by glycosylation with a complex carbohydrate. Studying bacterial cell surface carbohydrates may provide alternative pathways for the prevention of bacterial infections. Therefore, development of synthetic carbohydrate vaccines has great promise for the prevention of *A. baumannii* infections. Particularly, vaccines based on bacterial lipopolysaccharide (LPS) and lipooligosaccharide (LOS) are attractive. Lipopolysaccharides and lipooligosaccharides are highly immunogenic cell-surface antigens found on Gram-negative

bacteria. Their use as immunogens in vaccines is precluded, however, due to their toxicity. Chemical synthesis of certain portions of these molecules including the so-called core oligosaccharides may circumvent this problem by “leaving out” the toxic lipid A portion (Figure 4.1). As such, conjugation of core oligosaccharides from the *A. baumannii* lipooligosaccharide is a potentially effective and unexplored approach to the development of an *A. baumannii* vaccine. Chemical synthesis of core oligosaccharide also allows control of the structure being recognized by immune receptors and enables us to determine whether this could result in a strongly or weakly-neutralizing antibodies.⁸ With regard to lipopolysaccharide-based vaccines, Van Boom and coworker⁹ and Boons and coworker¹⁰ both demonstrated that synthetic oligosaccharides derived from the core LPS oligosaccharide (of *Neisseria meningitidis* and *Francisella tularensis*, respectively) could be conjugated to protein carrier molecules. As a result, oligosaccharides that cannot typically be complexed to major histocompatibility complex II (MHC II) could, in fact, be complexed to T cells and triggering of adaptive immunity. This is because oligosaccharide generally cannot complex to MHC II whereas peptides and glycopeptides conjugates can.

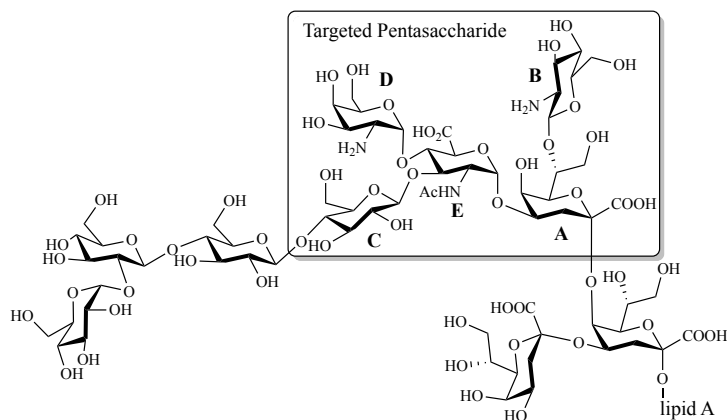


Figure 4.1 LOS Structure of *A. baumannii*

The structure of the LOS of *A. baumannii* (Figure 4.1) contains a central pentasaccharide, a lipid A moiety attached to two 3-deoxy-D-manno-oct-2-ulosonic acid (Kdo), and a trisaccharide which consists of three D-glucoses.¹¹ The central oligosaccharide has a highly complex nature,

containing five different sugar molecules that include Kdo (**A**), glucosamine (**B**), glucose (**C**), galactosamine (**D**), and *N*-acetyl glucosaminuronic acid (**E**, Figure 4.2). The development of our proposed LOS-based vaccine conjugate needs well-defined conjugation to carrier molecules for

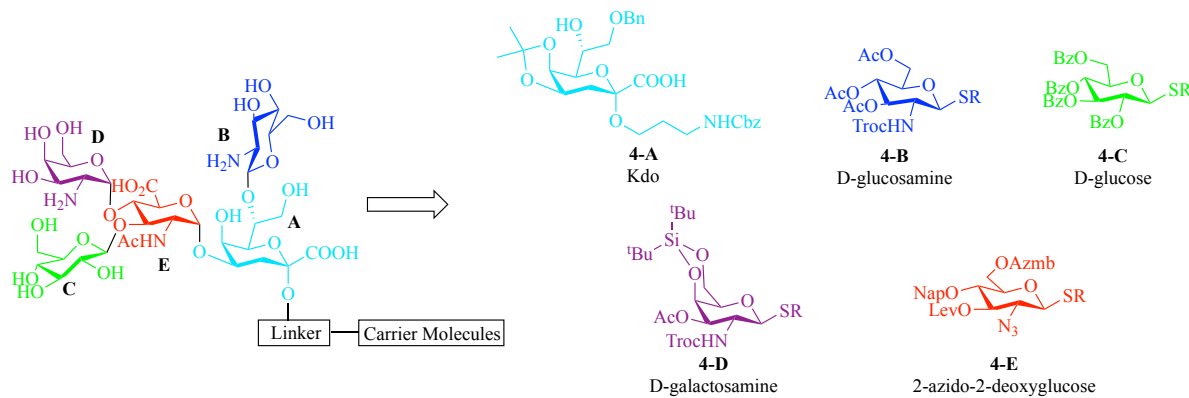
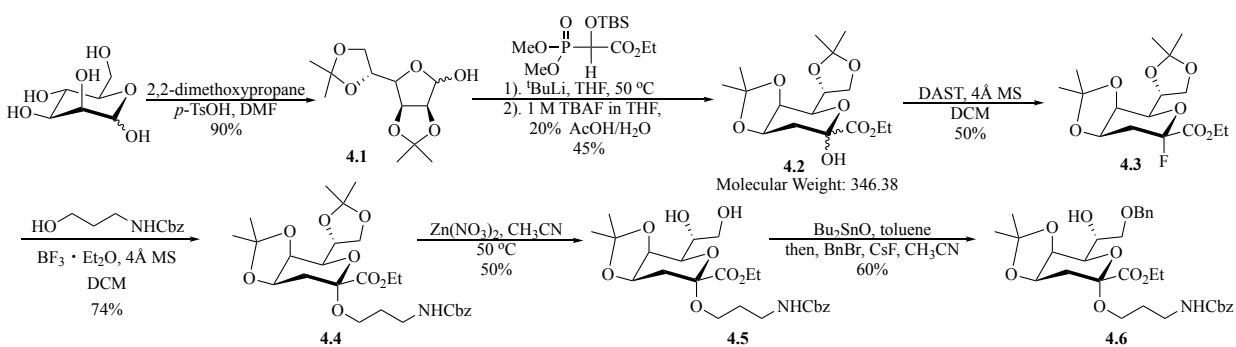


Figure 4.2 Building Blocks for the Synthesis of Core Pentasaccharide

immunizations that can prevent infection with *A. baumannii*. Herein, a chemical synthesis of the *A. baumannii* core pentasaccharide is being developed, and a potentially safe and effective vaccine for the prevention of infection by *A. baumannii* is a long-term goal of this work.

4.2 Results and Discussion

Chemical synthesis of the targeted pentasaccharide is challenging due to its highly branched structure, and furthermore, the β -glucosamine **4-B** (Figure 4.2), α -linked galactosamine **4-D** (Figure 4.2), and α -*N*-acetyl glucosaminuronic acid **4-E** (Figure 4.2) are all difficult to install. Moreover, this molecule contains multiple free amino and carboxylic acid groups, which makes the synthesis even more difficult. It is also noteworthy that the glucosaminuronic acid **4-E** contains three different *O*-linkages, which need to be differentiated by orthogonal protecting groups in the course of the synthesis so that compatible reaction intermediates can be provided. Currently, I'm working on the synthesis of a Kdo acceptor, a glucosamine donor, and a disaccharide portion of the core pentasaccharide.



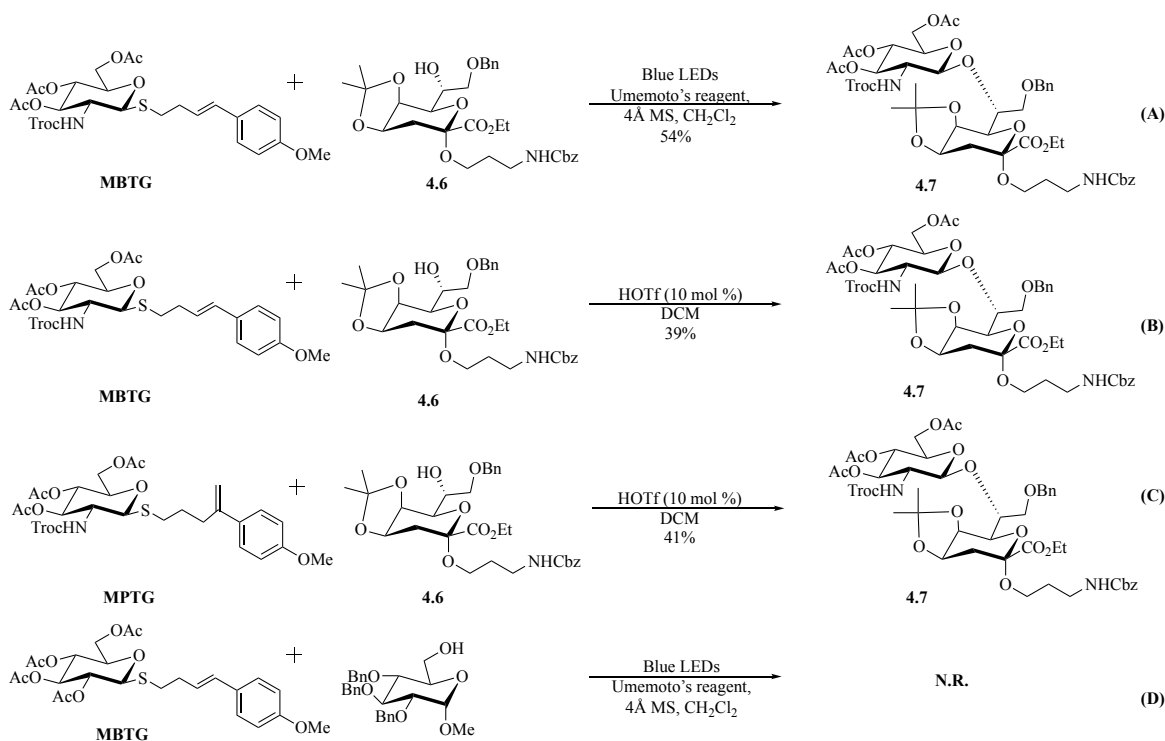
Scheme 4.1 Synthesis of Kdo

The preparation of Kdo **4-A** commenced with D-mannose, which was protected with 2,2-dimethoxypropane to generate the protected mannose **4.1**, which further underwent the Horner-Wadsworth-Emmons reaction with a phosphonate ester, followed by desilylation resulting in the formation of Kdo ethyl ester **4.2**.¹² The ethyl ester intermediate **4.2** was then treated with diethylaminosulfur trifluoride (DAST) to afford the glycosyl fluoride **4.3**. *O*-glycosylation of **4.3** with benzyl (3-hydroxypropyl) carbamate promoted by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ afforded **4.4** as a single (α) diastereomer.¹¹ Selective removal of the C₇, C₈ acetonide using zinc nitrate in acetonitrile generated diol **4.5**. The C₈ alcohol was then selectively protected with benzyl group in the presence of dibutyltin oxide via a stannyl acetal intermediate, followed by treatment with benzyl bromide and cesium fluoride to afford the desired C₈-benzylated acceptor **4.6**.¹³

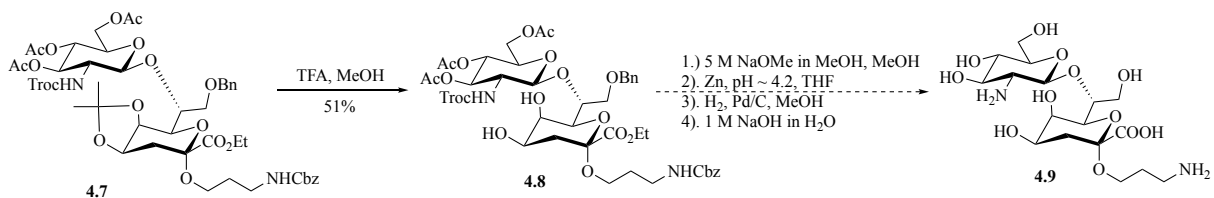
The previously synthesized glucosamine donor **4-B** was prepared and utilized for synthesis of a disaccharide intermediate (*vide infra*).¹⁴

With the donor and acceptor in hand, disaccharide synthesis was performed using either photo-induced or acid-catalyzed *O*-glycosylation (Scheme 4.2).¹⁴ Somewhat surprisingly, the photo reaction gave us the best yield (Scheme 4.2-A). Previous results indicated that the related tetra-*O*-acetyl MBTG donor **4.10** was not reactive in the photo-induced reaction (Scheme 4.2-D). Acid-catalyzed glycosylation with MBTG (**4.8**)/MPTG (**4.9**) donors afforded lower yield possibly because the isopropylidene acetal was reactive under the acidic conditions. Deprotection of

disaccharide **4.7** to generate a simplified analog of the target pentasaccharide is currently underway in the laboratory (Scheme 4.3).



Scheme 4.2 Glycosylation of Kdo **4.6** with MBTG/MPTG Donors



Scheme 4.3 Deprotection of **4.7**

4.3 Future Work

Synthesis of D-galactosamine donor **4-D** and *N*-acetyl-D-glucosaminuronic acid donor **4-E** are currently underway in the laboratory. Conditions for the synthesis of trisaccharide using donor **4-E** with disaccharide acceptor **4.8** will be explored. Various hydroxyl protecting groups on **4-E** which can be specifically deprotected for later site selective *O*-glycosylation for the synthesis of tetrasaccharide and pentasaccharide are being installed. Conditions for deprotecting the

protected pentasaccharide will be studied. Eventually, this chemically synthesized pentasaccharide will be conjugated to carrier molecules and tested in an animal model for immunogenicity.

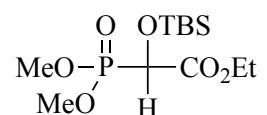
4.4 Experimental

4.4.1 General Methods

Reagents were purchased from Sigma Aldrich, Alfa Aesar, TCI and used as received. Flash column chromatography was performed using 60Å silica gel purchased from Sigma Aldrich. ^1H NMR and ^{13}C NMR spectroscopy were performed on a Bruker AV-400 or a Bruker AV-500 spectrometer. Mass spectra were obtained using an Agilent 6210 electrospray time-of-flight mass spectrometer. Optical Rotation was obtained from a JASCO P-2000 polarimeter. Analytical and preparative TLC were conducted on aluminum sheets (Merck, silica gel 60, F254). Compounds were visualized by UV absorption (254 nm) and staining with anisaldehyde. 5 mL Pyrex micro reaction vessels (Supelco) were used for the glycosylation reactions. Deuterated solvents were obtained from Cambridge Isotope Labs. Solvents included Et_2O , DCM, CH_3CN , DMF, and THF and were used directly from a PureSolv 400-5 solvent system. Other solvents were used as received from a commercial vendor.

4.4.2 Procedures and Characterizations

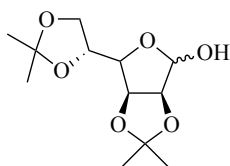
Synthesis of Ethyl ester α -(dimethoxyphosphinyl) glycolate t-Butyldimethylsilyl Ether **4.11**



Ethyl glyoxylate (48 mL of a ~50% solution in toluene, 240 mmol) was heated to reflux, maintained at reflux for 1 h, and cooled to rt (18 °C). To a solution of dimethyl phosphite (22 mL, 240 mmol) in dry toluene (120 mL) was added Et_3N (96 mL, 690 mmol) at 0 °C. After 15 min, the cooled solution of ethyl glyoxylate was added at 0 °C at once. The mixture was allowed to stir at room temperature for 3 h. After TLC showed the reaction was complete, volatiles were removed under reduced pressure and the resulting crude mixture was used directly for the next step without

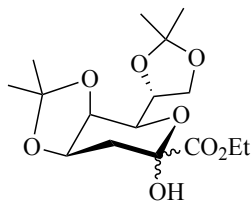
further purification. Dry DMF (220 mL) was added to the solution, and imidazole (31.20 g, 458.3 mmol) mixture, followed by adding TBS-Cl (51.8 g, 344 mmol). After the reaction mixture was allowed to stir overnight (12 h). EtOAc (400 mL) was added to dilute the reaction which was then washed with 2X500 mL brine. The combined aqueous layer was extracted with 200 mL EtOAc. The combined organic layer was then washed with 300 mL sat. aqueous NaHCO₃. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel column chromatography (0% to 60% EtOAc in Hexanes) to give 39.2 g (50%) product of a colorless oil. Spectral data matched that previously reported in the literature.¹³

Synthesis of **4.1**



To a solution of D-mannose (14.40 g, 79.93 mol) and TsOH•H₂O (921 mg, 4.84 mmol) in dry DMF (100 mL) was added 2,2-dimethoxypropane (16 mL, 130 mmol). After 6 h, additional 2,2-dimethoxypropane (14 mL, 110 mmol) was added and the mixture was allowed to stir at room temperature overnight. The solution was diluted with 200 mL EtOAc, and then poured into 200 mL sat. NaHCO₃, and extracted with 100 mL EtOAc twice. The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo to give 17.7 g (85%) **4.1** of a white solid which was used directly for the next step without further purification.

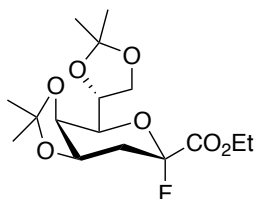
Synthesis of **4.2**



To a suspension of ^tBuOLi (2.502 g, 31.26 mmol) in dry THF (20 mL) was added a solution of ethyl ester α-(dimethoxyphosphinyl) glycolate t-butyldimethylsilyl ether **4.11** (9.29 g, 28.5

mmol) in dry THF (10 mL). After stirring for 15 min, 4.48 g (17.2 mmol) **4.1** was added at once. The mixture was gradually heated to 50 °C and kept stirring for 1 h. After the solution was cooled to room temperature, 10 mL of sat. NH₄Cl was added to the reaction mixture, followed by adding 100 mL EtOAc. The organic layers were washed with 50 mL brine twice, and then dried over Na₂SO₄, filtered, and concentrated in vacuo to give a pale-yellow oil. The crude product was used immediately for the next step without further purification. 20% AcOH/H₂O (36 mL) was added to a solution of the crude Horner-Emmons product in THF (30 mL) at 0 °C, followed by the addition of 1 M tetrabutylammonium fluoride (TBAF) in THF (27 mL). After 3 h, the mixture was neutralized with 200 mL sat. NaHCO₃, followed by adding 200 mL EtOAc. The organic layer was washed with 100 mL sat. NaHCO₃, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0% to 25% EtOAc in Hexanes) to give 2.68 g (7.74 mmol) **4.2** (45%, three step yield) as a colourless oil. Spectral data matched that previously reported in the literature.¹³

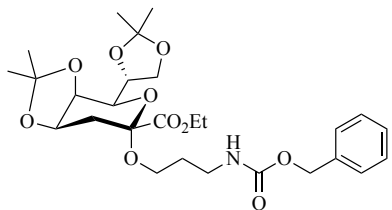
Synthesis of **4.3**



A flame-dried round-bottomed flask was charged with 1.73 g (4.99 mmol) Ethyl [3-deoxy-4,5-7,8-di-*O*-isopropylidene- α -D-manno-octulopyranosid] onate¹ **4.2** and 5.0 g activated 4Å MS. 80 mL DCM was added under N₂. The resulting suspension was then cooled to -50 °C, followed by adding 800 μ L (6 mmol) diethylaminosulfur trifluoride dropwise over a period of 4 min. The reaction was then stirred for 15 min at -50 °C. MeOH (1 mL) and sat. NaHCO₃ (20 mL) were added. The organic layer was dried with Na₂SO₄, filtered, and concentrated. The resulting crude mixture (1.99 g) was purified by chromatography (0% to 20% EtOAc in hexanes) to afford 800.0

mg (2.30 mmol, 46%) **4.3** of a white solid. **¹H NMR** (400 MHz, CDCl₃) δ 4.59 – 4.56 (m, 1H), 4.43 - 4.38 (m, 2H), 4.28 (q, *J* = 7.1Hz, 2H), 4.17 (dd, *J* = 9.0, 6.1Hz, 1H), 4.09 (dd, *J* = 9.0, 3.9Hz, 1H), 3.69 (dd, *J* = 8.4, 2.2Hz, 1H), 3.07 (dd, *J* = 15.5, 3.6Hz, 1H), 2.03 – 1.94 (m, 1H), 1.45 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 1.35 – 1.31 (m, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ 170.5, 170.1, 169.32, 169.30, 133.1, 117.5, 83.62, 75.87, 73.81, 69.80, 68.27, 62.11, 39.89, 28.60, 27.74, 20.68, 20.65, 20.54, 20.52. **HRMS (m/z):** [M+Na]⁺ Calcd. for C₁₆H₂₅O₇FNa 371.1477, found 371.1486

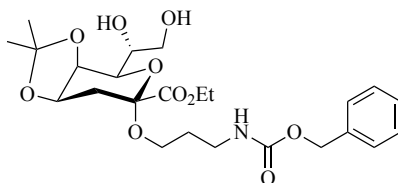
Synthesis of **4.4**



A flame-dried round-bottomed flask was charged with 130.8 mg (0.3755 mmol) **4.3**, 156.8 mg (0.749 mmol) *N*-benzyloxycarbonyl-3-amino-propanol and 200 mg activated 4Å MS. 4 mL DCM was added under N₂. The resulting suspension was then cooled to 0 °C, followed by adding 50 µL (0.41 mmol) BF₃•Et₂O at once. The reaction was then stirred for 1 h at 0 °C before 0.1 mL Et₃N was added to quench the reaction. The resulting mixture was concentrated. The resulting crude mixture (0.99 g) was purified by chromatography (0% to 25% EtOAc in hexanes) to afford 157.0 mg (0.2920 mmol, 78%) **4.4** of a colorless oil. **¹H NMR** (500 MHz, CDCl₃) δ 7.35 – 7.29 (m, 5H), 5.25 (t, *J* = 5.7Hz, 1H), 5.09 (s, 2H), 4.49 – 4.46 (m, 1H), 4.35 (q, *J* = 6.1Hz, 1H), 4.27 – 4.17 (m, 3H), 4.14 – 4.10 (m, 1H), 4.03 (dd, *J* = 8.8, 5.4Hz, 1H), 3.77 – 3.73 (m, 1H), 3.63 (dd, *J* = 6.7, 1.9Hz, 1H), 3.31 – 3.21 (m, 3H), 2.76 (dd, *J* = 15.6, 3.9Hz, 1H), 1.82 (dd, *J* = 15.5, 3.0Hz, 1H), 1.77 – 1.67 (m, 2H), 1.42 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 1.30 (s, 3H), 1.28 – 1.24 (m, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ 168.7, 156.4, 136.7, 128.5, 128.1, 128.0, 109.6, 109.0, 97.40,

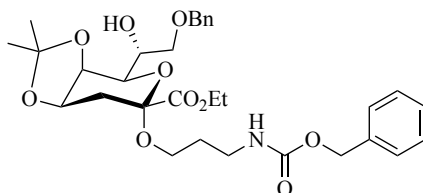
74.29, 72.04, 71.06, 70.13, 66.57, 66.51, 61.65, 60.57, 38.36, 32.94, 29.33, 26.70, 25.56, 25.45, 24.95, 14.14. **HRMS (m/z):** $[M+H]^+$ Calcd. for $C_{27}H_{40}O_{10}N$ 538.2647, found 538.2646.

Synthesis of **4.5**



270.0 mg (0.5022 mmol) **4.4** was dissolved in 5 mL CH_3CN , followed by adding 500.0 mg (1.681 mmol) $Zn(NO_3)_2 \cdot 6H_2O$. The resulting suspension was then heated to 50 °C. The reaction was then stirred for 30 min at 50 °C. The reaction was concentrated. The resulting crude mixture (1.02 g) was purified by chromatography (0% to 5% MeOH in DCM) to afford 124.9mg (0.2510 mmol, 50%) colorless oil. **1H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 5H), 5.47 (s, 1H), 5.10 (s, 2H), 4.51 – 4.47 (m, 1H), 4.32 (d, $J = 7.6$ Hz, 1H), 4.29 – 4.19 (m, 2H), 4.02 – 4.00 (m, 1H), 3.94 (d, $J = 10.7$ Hz, 1H), 3.85 – 3.78 (m, 2H), 3.74 – 3.69 (m, 1H), 3.65 (s, 1H), 3.34 – 3.21 (m, 3H), 2.70 (dd, $J = 15.4, 4.4$ Hz, 1H), 1.86 (dd, $J = 15.6, 3.2$ Hz, 1H), 1.76 (s, 1H), 1.43 (s, 3H), 1.32 (s, 3H), 1.29 – 1.26 (m, 3H). **HRMS (m/z):** $[M+H]^+$ Calcd. for $C_{24}H_{36}O_{10}N$ 498.2334, found 498.2337.

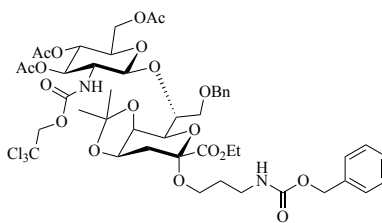
Synthesis of **4.6**



110 mg (0.22 mmol) **4.5** was dissolved in 3 mL dry toluene in a flame-dried RBF, followed by adding 88.0 mg (0.353 mmol) dibutyltin oxide. The resulting suspension was then heated to reflux. The reaction was then refluxed for 3 h, cooled to rt, and about half of the toluene was evaporated. Benzyl bromide (40 μ L, 0.3 mmol), cesium fluoride (50.1 mg, 0.330 mmol), and 1.5 mL CH_3CN were added to the reaction. The resulting mixture was heated to 70 °C overnight (12

h). The resulting suspension was filtered through a celite cake, washed with 10 mL CH₃CN, and concentrated. The crude mixture (400 mg) was purified by chromatography (0% to 50% EtOAc in hexanes) to afford 75mg (59%) white foam. ¹H NMR (500 MHz, CDCl₃) δ 7.35 – 7.28 (m, 10H), 5.16 (t, *J* = 6.3Hz, 1H), 5.08 (s, 2H), 4.56 (s, 2H), 4.48 – 4.45 (m, 1H), 4.34 (dd, *J* = 7.4, 2.1Hz, 1H), 4.26 – 4.11 (m, 3H), 3.78 – 3.69 (m, 3H), 3.61 – 3.58 (m, 1H), 3.23 – 3.17 (m, 3H), 2.63 – 2.59 (m, 2H), 1.86 (dd, *J* = 15.1, 3.4Hz, 1H), 1.68 – 1.64 (m, 2H), 1.42 (s, 3H), 1.31 (s, 3H), 1.29 – 1.24 (m, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 168.7, 156.4, 137.8, 136.7, 128.5, 128.4, 128.1, 128.0, 127.8, 109.5, 97.70, 73.59, 71.87, 71.04, 70.08, 69.14, 66.49, 61.67, 60.75, 38.36, 33.22, 29.14, 26.00, 25.22, 14.14. HRMS (*m/z*): [M+H]⁺ Calcd. for C₃₁H₄₂O₁₀N 588.2803, found 588.2805.

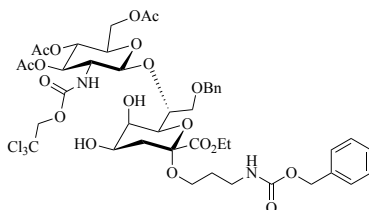
Synthesis of **4.7**



A flame-dried 5 mL Pyrex reactor vial was charged with the **MBTG** donor (81.3 mg, 0.124 mmol), Umemoto's reagent (54.0 mg, 0.134 mmol), glycosyl acceptor **4.7** (36.0 mg, 0.0613 mmol), 150 mg of freshly activated powdered 4 Å molecular sieves and 1 mL of dry dichloromethane under nitrogen atmosphere. The reactor vial was placed 1-2 cm away from a blue LEDs strip and irradiated from the side for 24 hours. The reaction maintained a temperature of ~ 28 °C due to adventitious heating from the light source. The reaction mixture was then filtered to remove molecular sieves, washed with 5 mL DCM, and the crude products were concentrated and then purified by gradient silica gel chromatography to afford disaccharide **4.7** (34.7 mg, 0.0330 mmol, 54%). ¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.27 (m, 10H), 5.53 (s, 1H), 5.21 (s, 1H), 5.15 – 5.02 (m, 4H), 4.85 (d, *J* = 8.5Hz, 1H), 4.76 (dd, *J* = 9.8, 3.1Hz, 1H), 4.70 – 4.60 (m, 3H), 4.50 (d, *J* =

11.6 Hz, 1H), 4.42 – 4.39 (m, 1H), 4.32 (dd, $J = 7.4, 1.8$ Hz, 1H), 4.27 – 4.08 (m, 6H), 3.96 (d, $J = 10.5$ Hz, 1H), 3.78 – 3.55 (m, 6H), 3.23 – 3.16 (m, 3H), 2.55 (dd, $J = 15.2, 4.4$ Hz, 1H), 2.05 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 1.35 (s, 3H), 1.25 (s, 3H), 1.30 – 1.21 (m, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 170.5, 170.3, 169.4, 168.5, 156.4, 154.4, 137.8, 136.7, 128.6, 128.5, 128.40, 128.36, 127.98, 127.93, 127.88, 127.86, 109.0, 97.65, 95.53, 74.33, 73.48, 72.60, 71.81, 71.22, 69.94, 68.55, 66.39, 61.97, 61.65, 61.53, 60.91, 56.32, 38.46, 33.05, 29.11, 26.52, 25.74, 24.79, 20.64, 20.56, 20.53, 14.04. **HRMS (m/z):** $[\text{M}+\text{Na}]^+$ Calcd. for $\text{C}_{46}\text{H}_{59}\text{O}_{19}\text{Cl}_3\text{N}_2\text{Na}$ 1071.2670, found 1071.2684.

Synthesis of **4.8**



A 25 mL round-bottomed flask was charged with a solution of 68.2 mg (0.0649 mmol) **4.7** in 5 mL MeOH, followed by adding 25 μL (0.33 mmol) trifluoroacetic acid at room temperature (20 $^{\circ}\text{C}$). The reaction was stirred for 2 h at 20 $^{\circ}\text{C}$ and concentrated under vacuum. The crude mixture was purified by column chromatography to afford 33.4 mg (0.0331 mmol, 51%) **4.8** as a white foam. **^1H NMR** (400 MHz, CDCl_3) δ 7.40 – 7.31 (m, 10H), 5.32 (brs, 1H), 5.13 – 5.05 (m, 2H), 5.10 (s, 2H), 5.00 (t, $J = 9.6$ Hz, 1H), 4.81 (d, $J = 8.5$ Hz, 1H), 4.72 (d, $J = 12.0$ Hz, 1H), 4.64 – 4.50 (m, 3H), 4.33 (d, $J = 12.7$ Hz, 1H), 4.25 – 4.20 (m, 3H), 4.07 – 3.98 (m, 3H), 3.86 (d, $J = 10.2$ Hz, 1H), 3.76 – 3.62 (m, 3H), 3.52 (d, $J = 9.5$ Hz, 1H), 3.38 – 3.36 (m, 1H), 3.30 – 3.24 (m, 3H), 2.11 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.85 (t, $J = 12.1$ Hz, 1H), 1.69 (m, 2H), 1.26 (t, $J = 7.1$ Hz, 3H).

4.5 References

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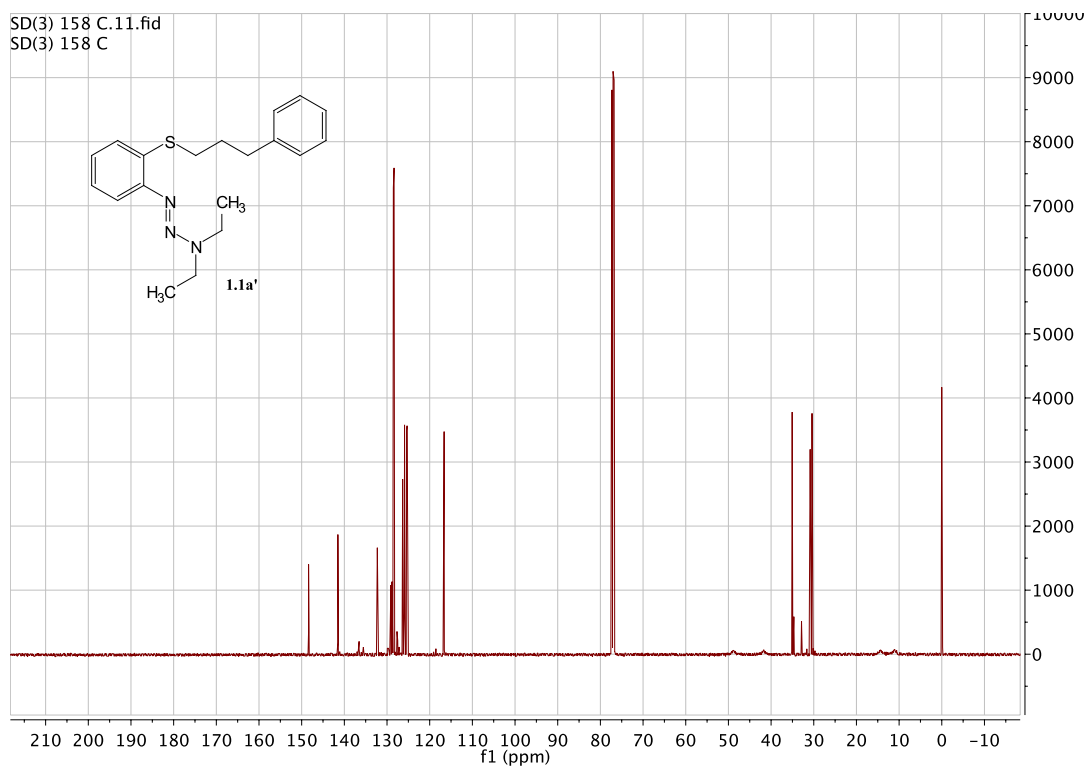
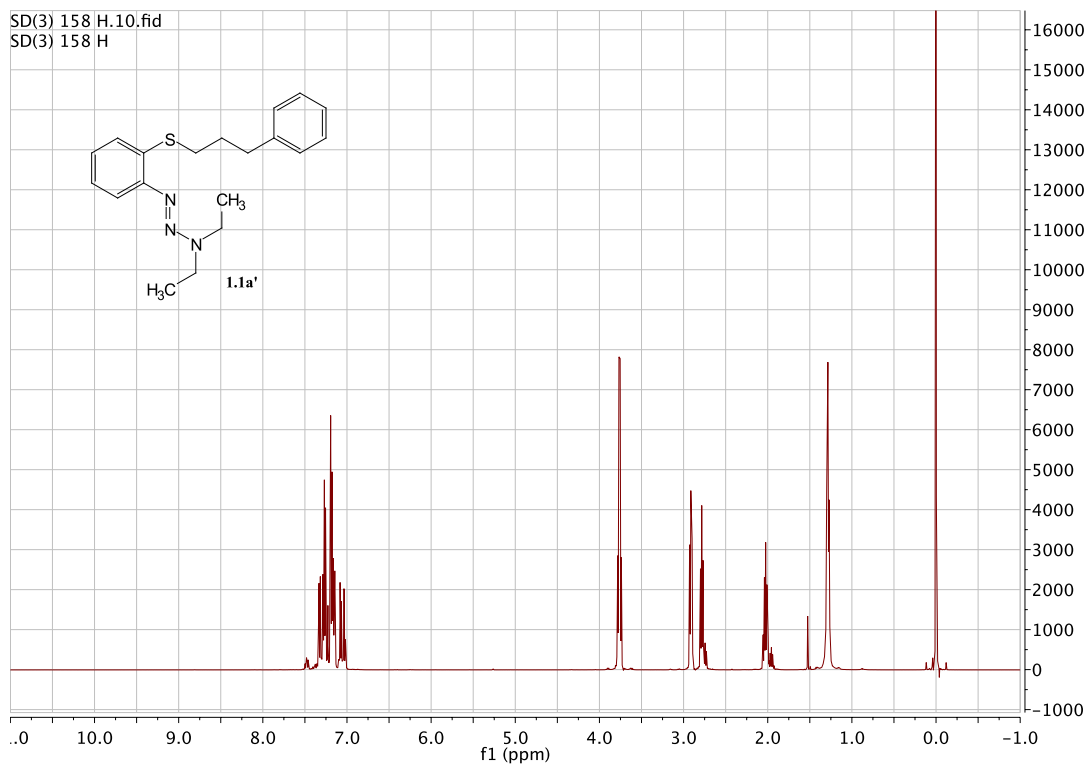
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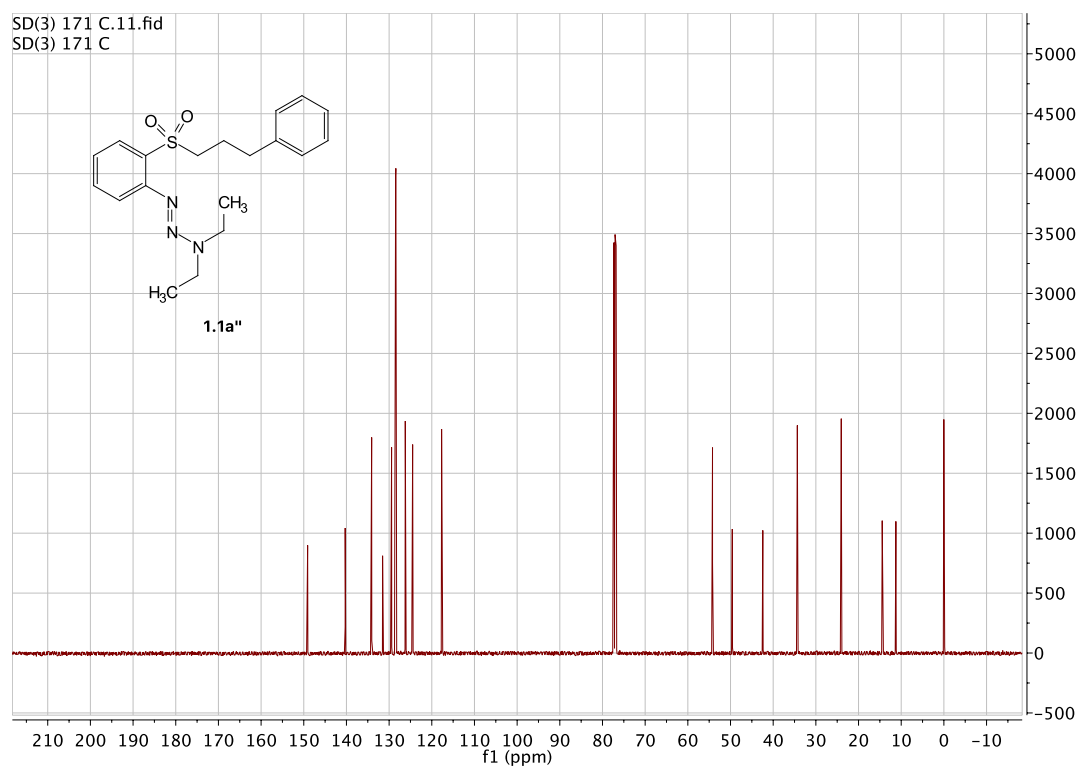
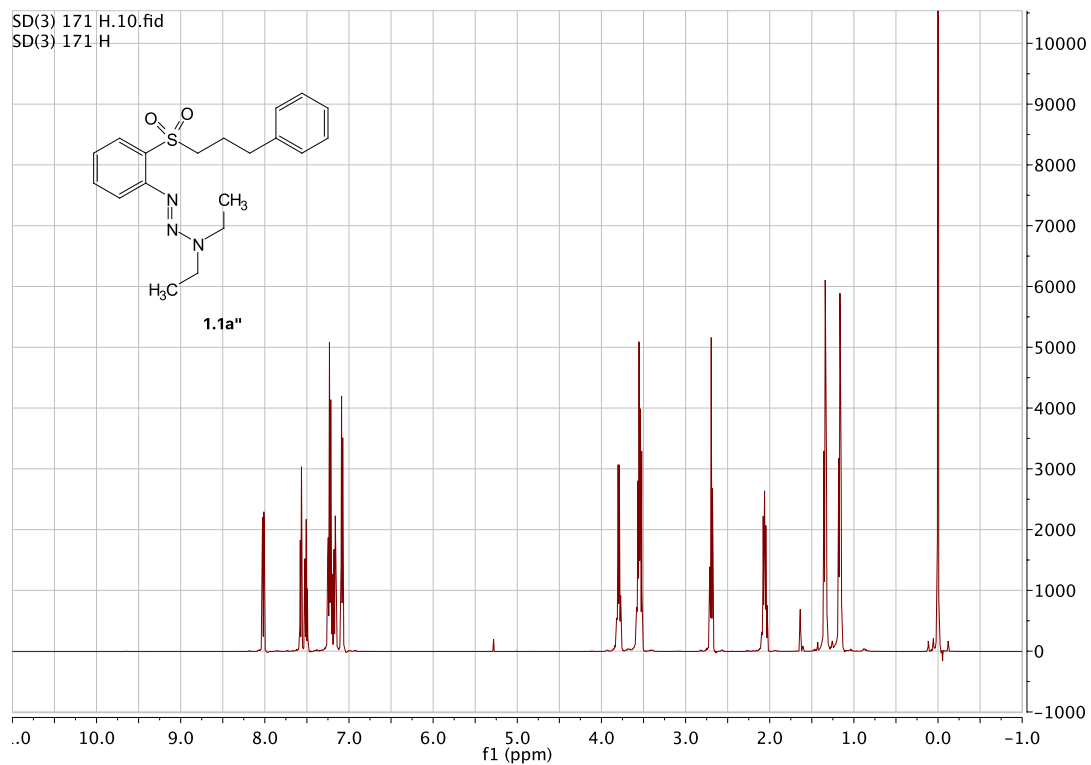
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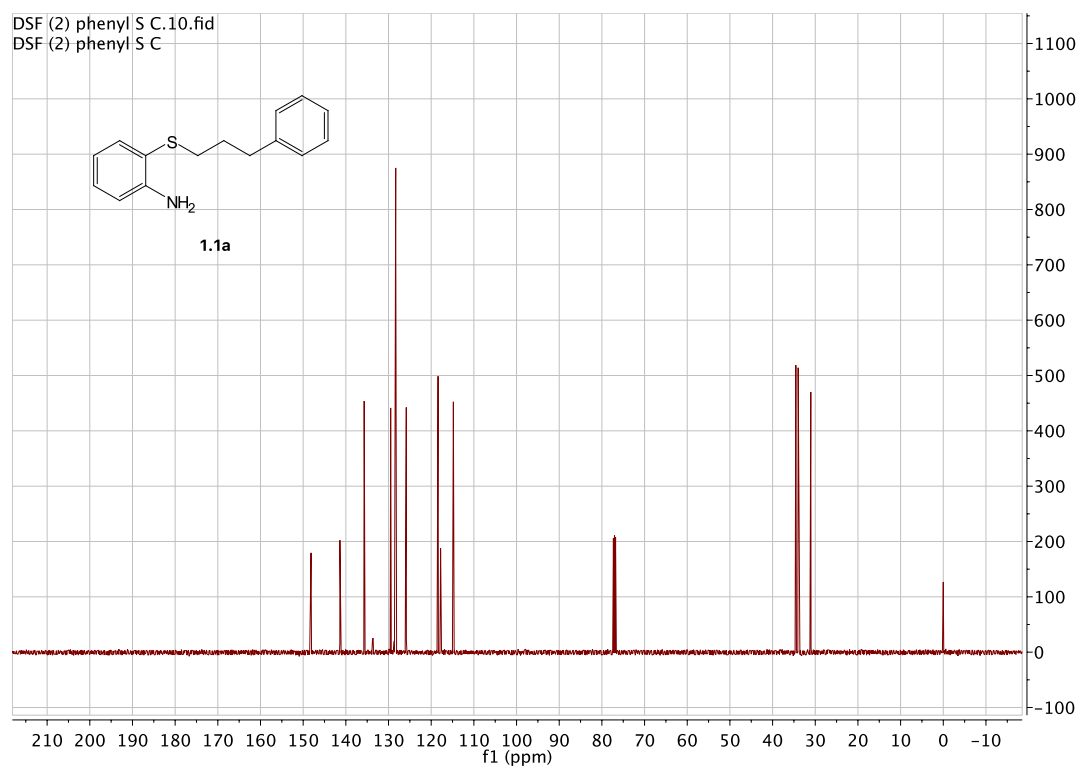
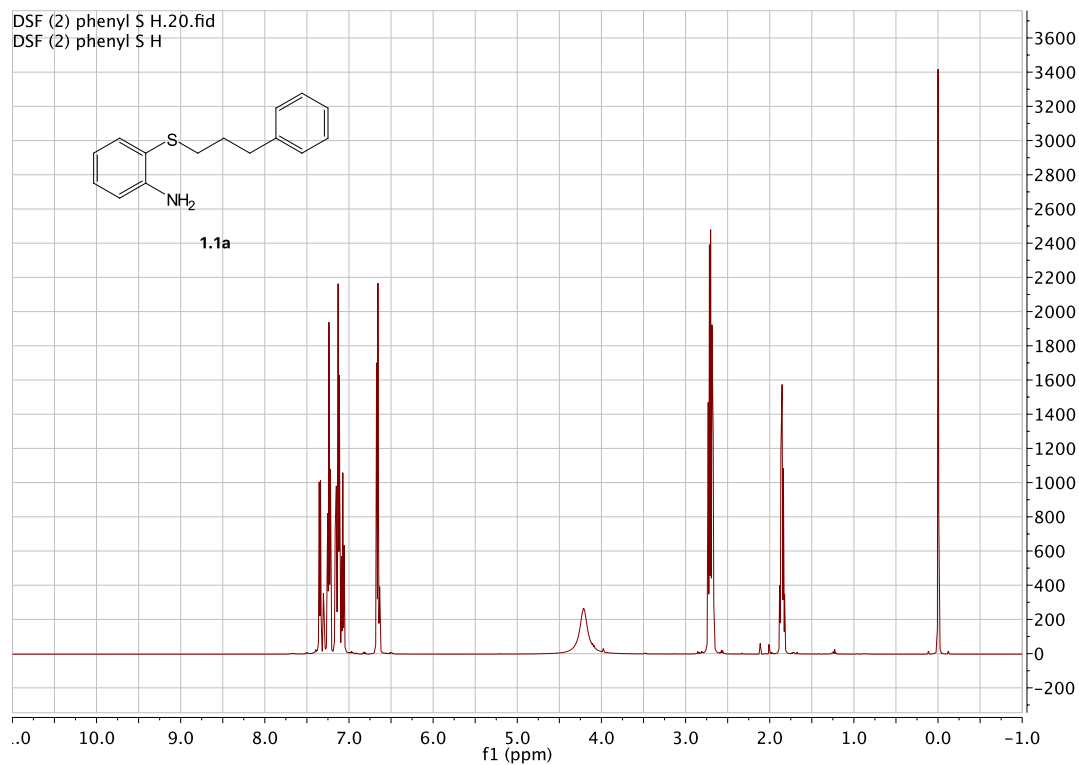
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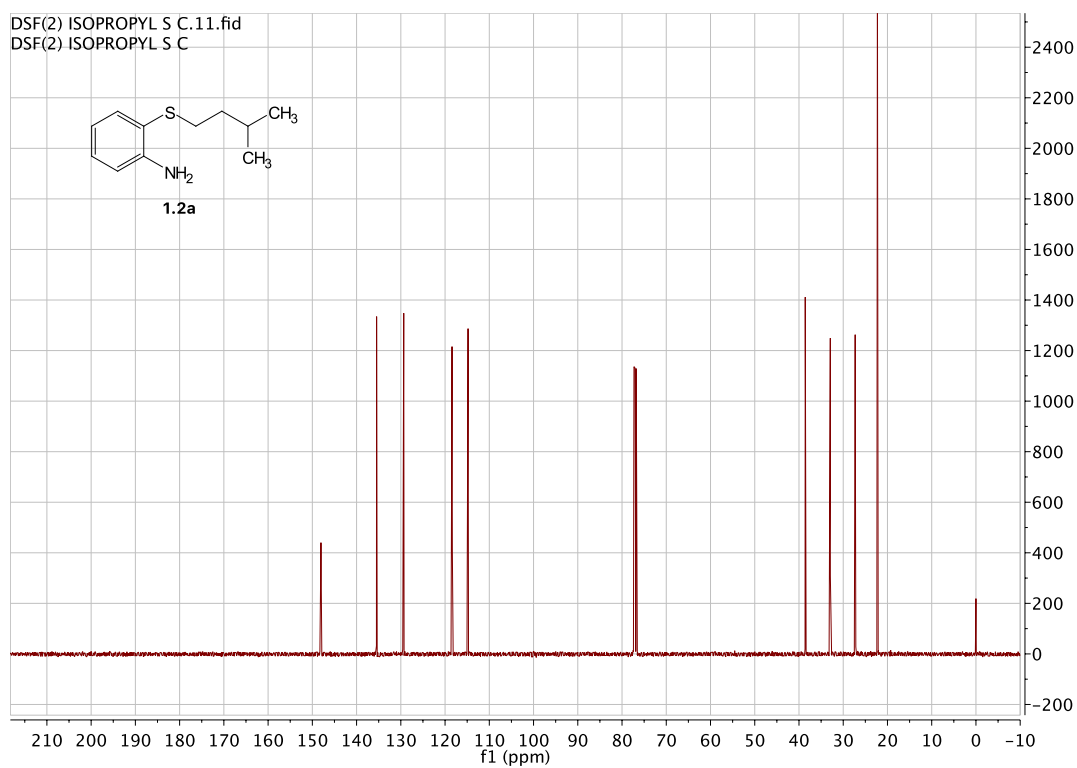
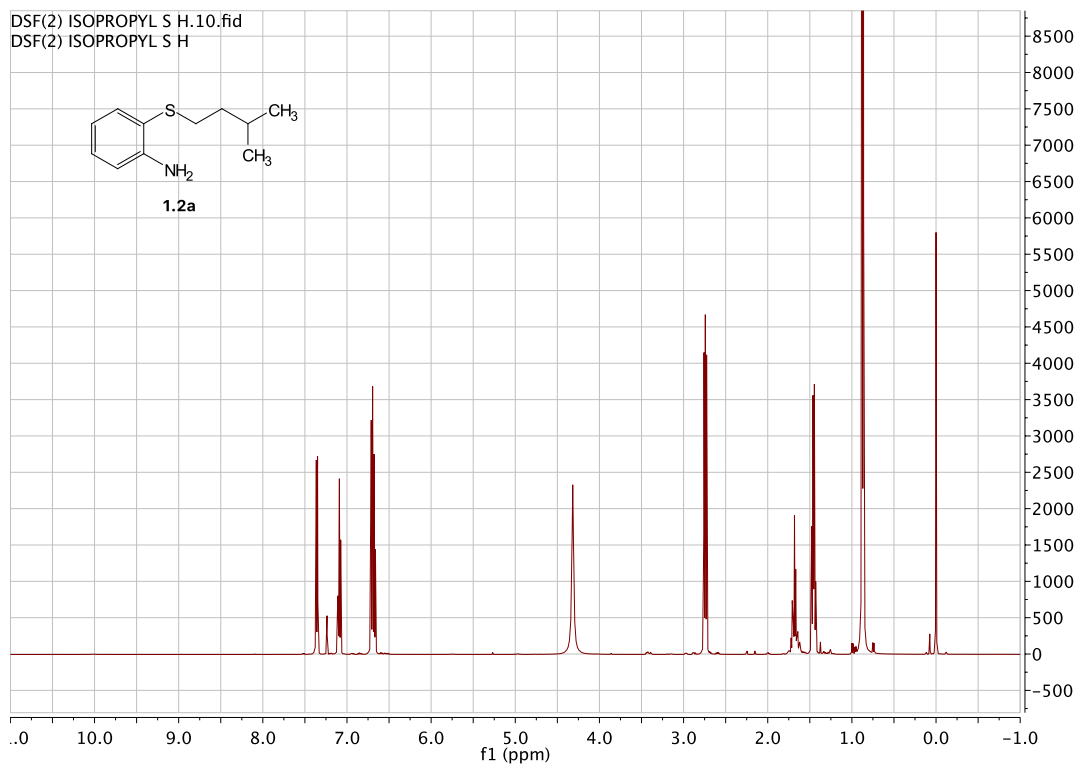
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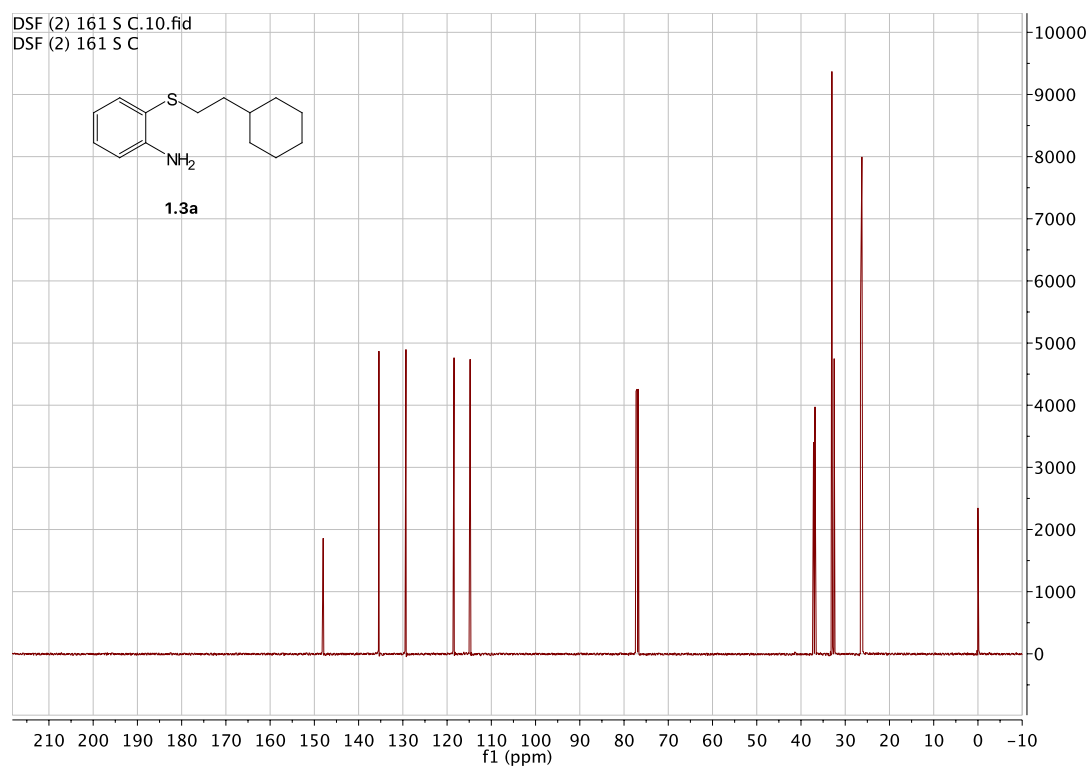
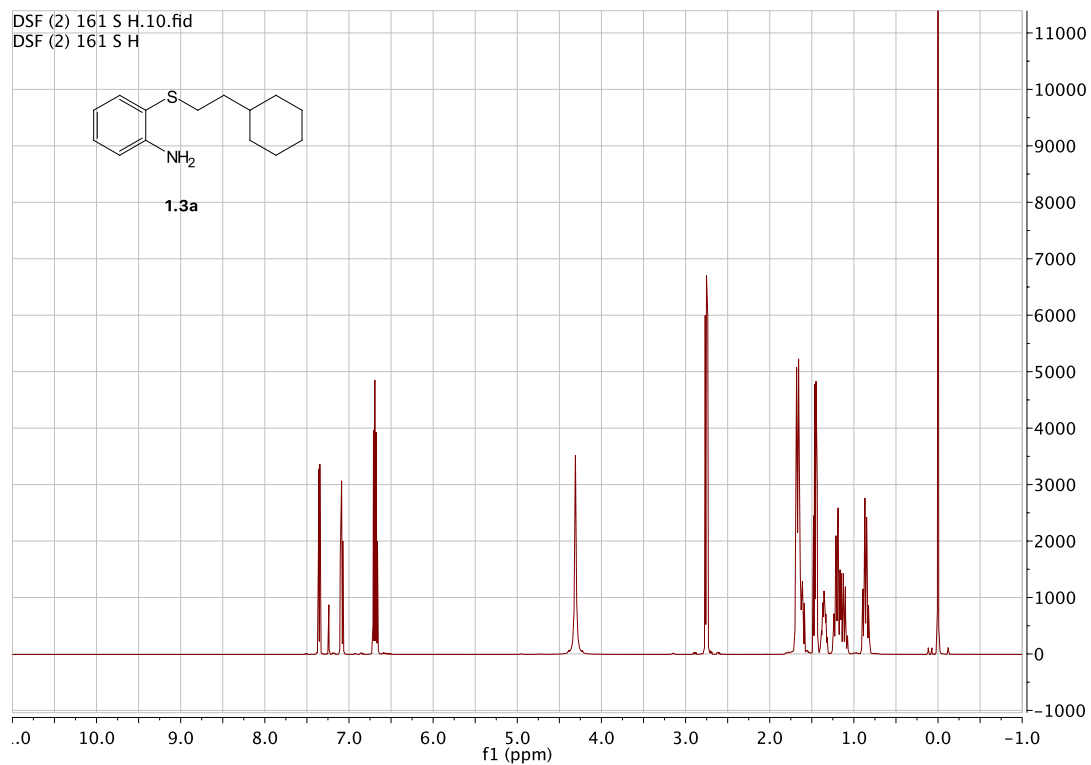
APPENDIX B. NMR SPECTRA OF COMPOUNDS FOUND IN CHAPTER 1

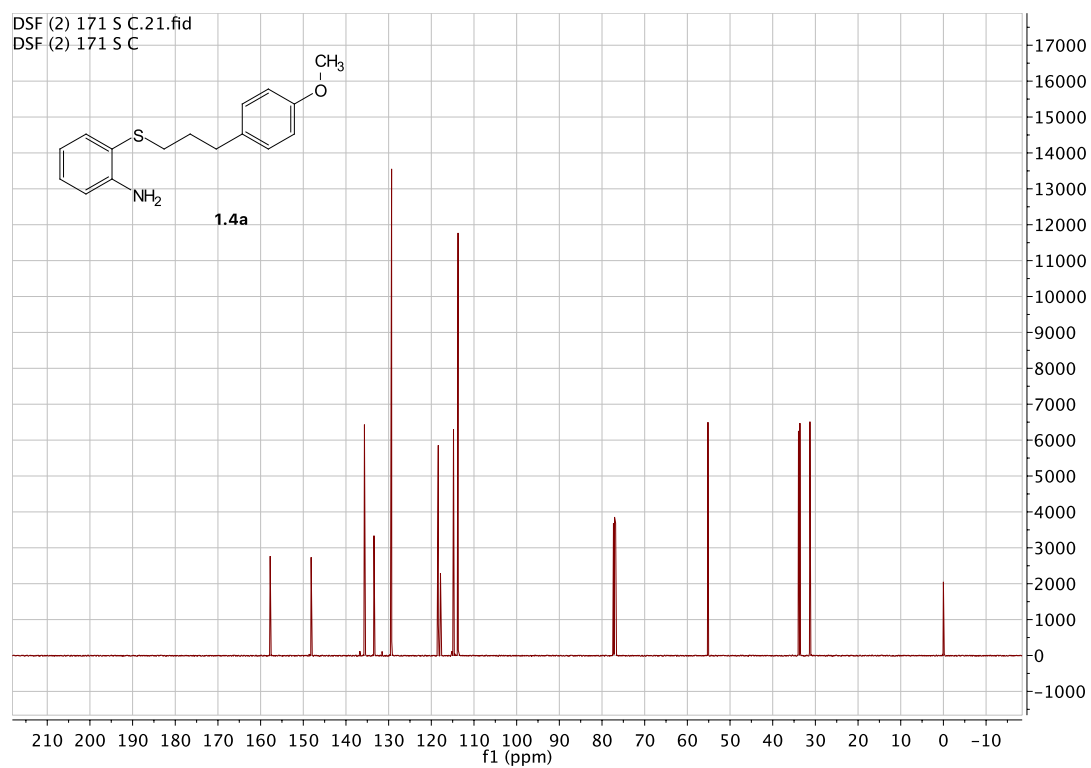
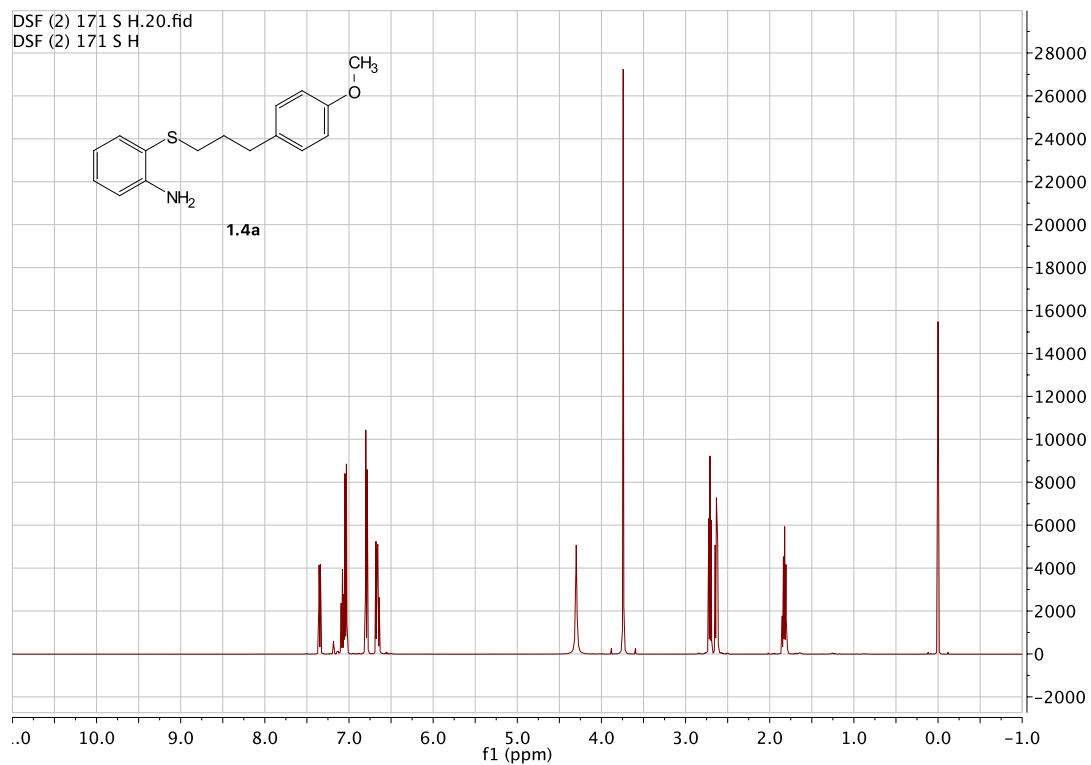


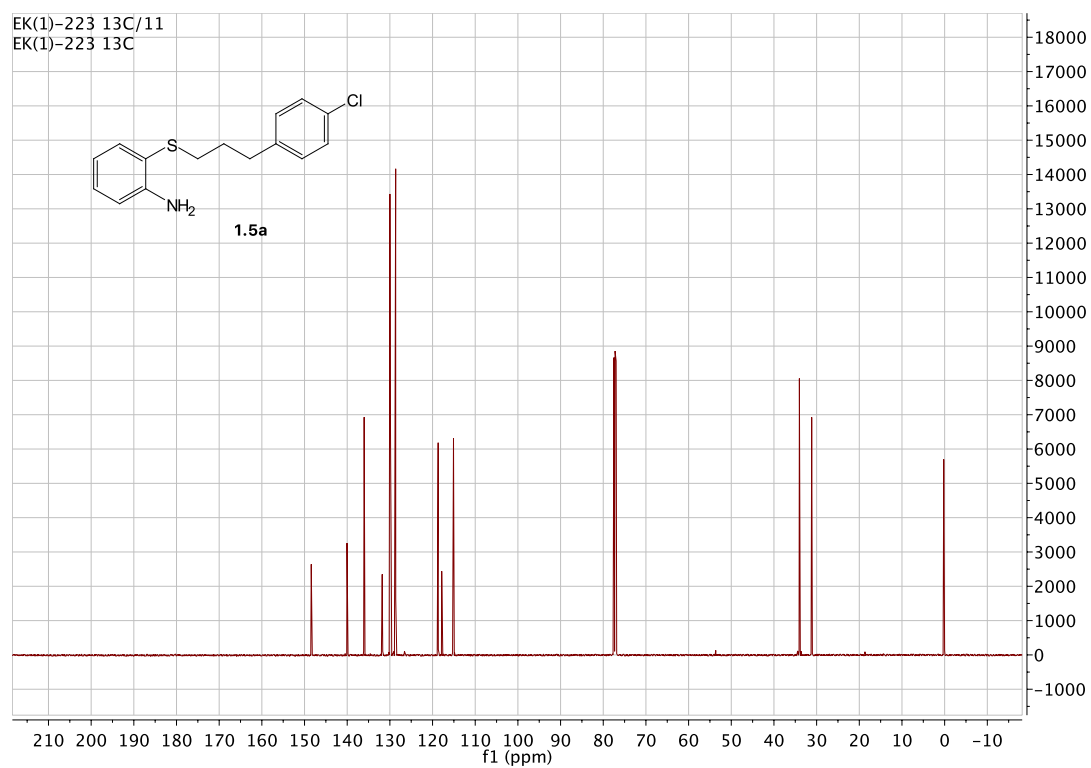
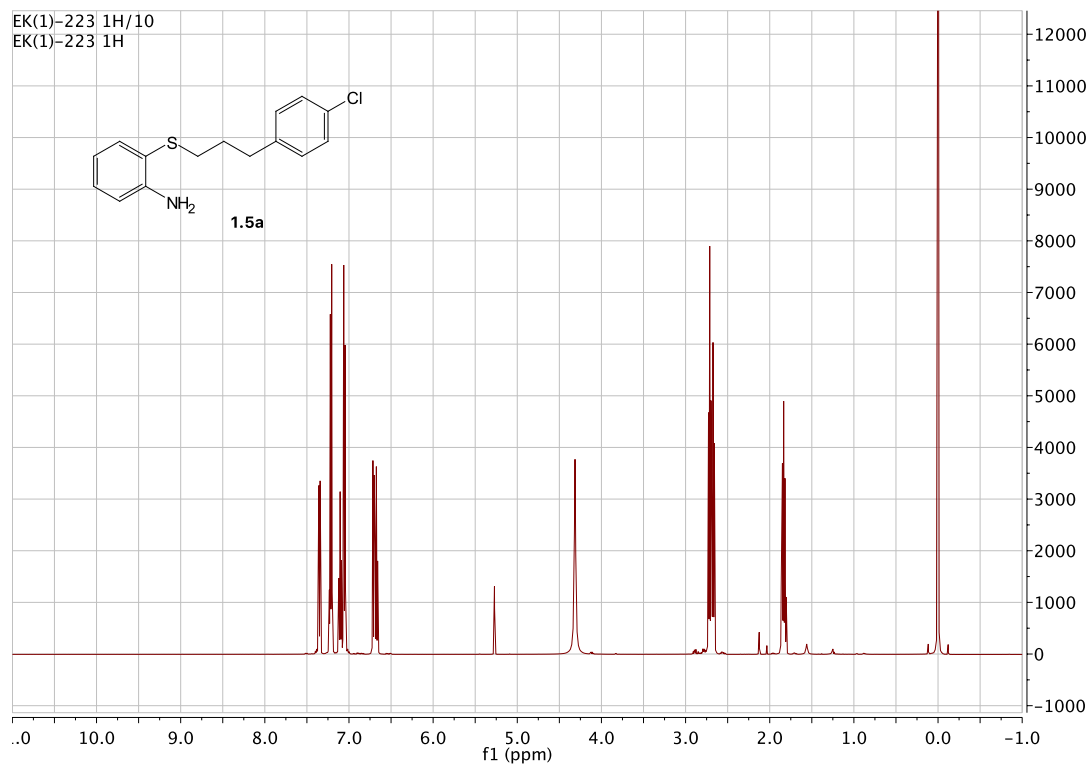


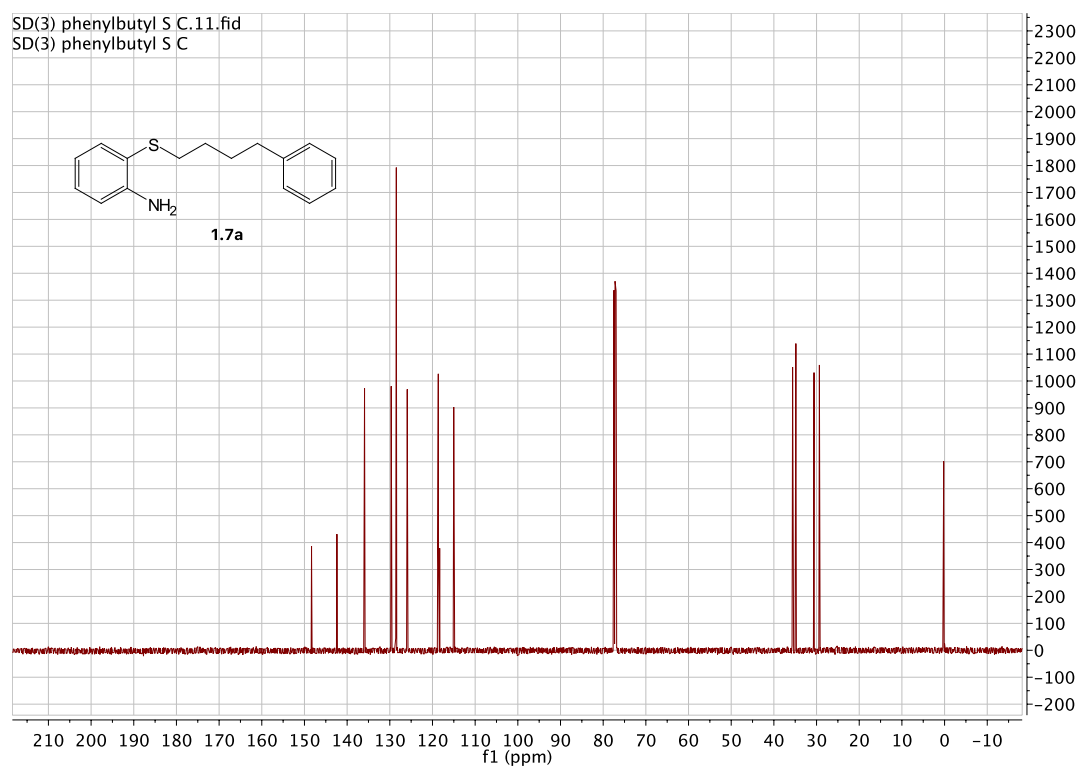
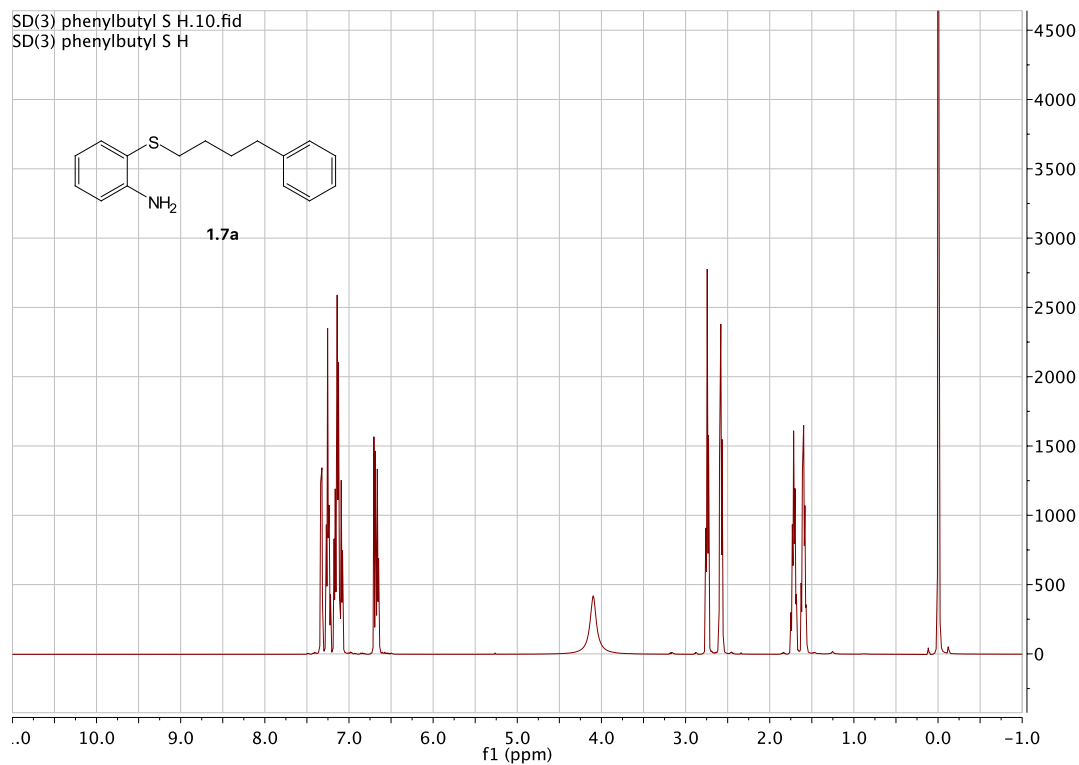


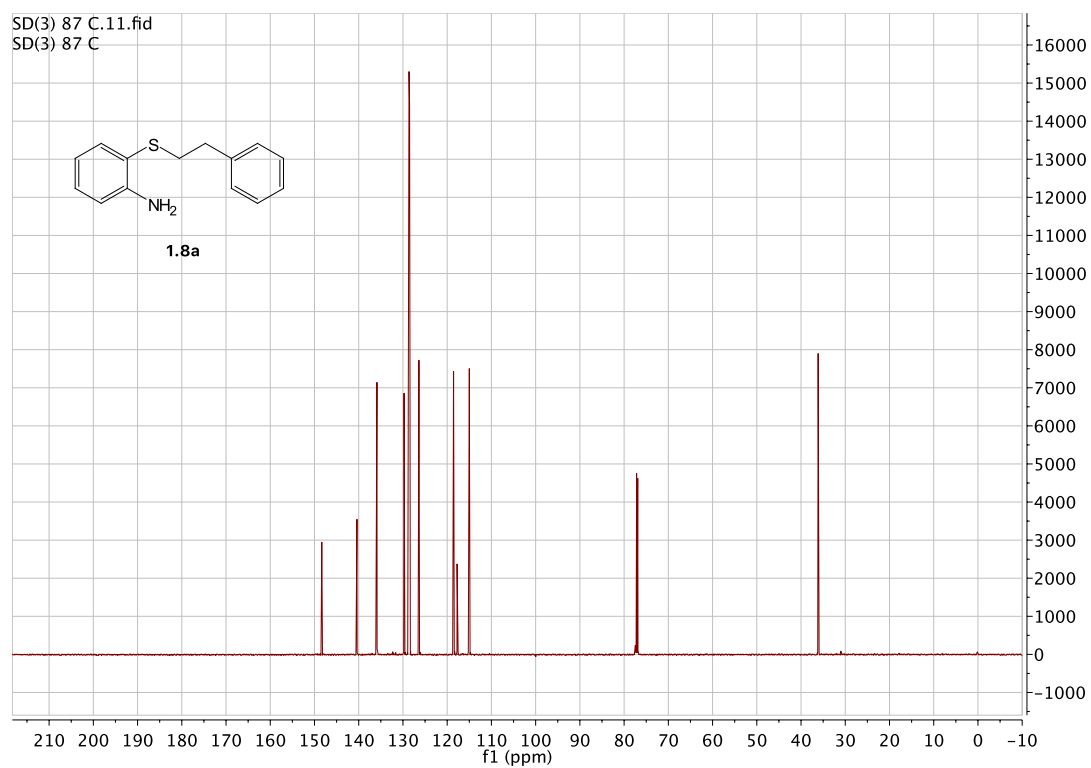
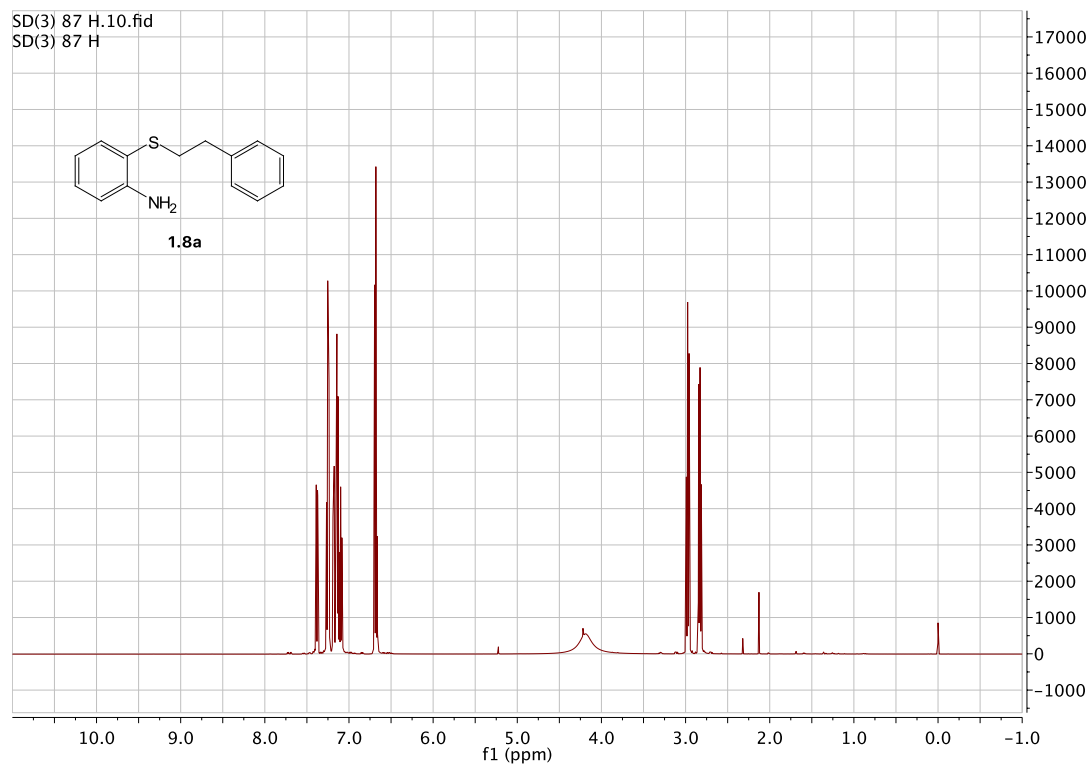


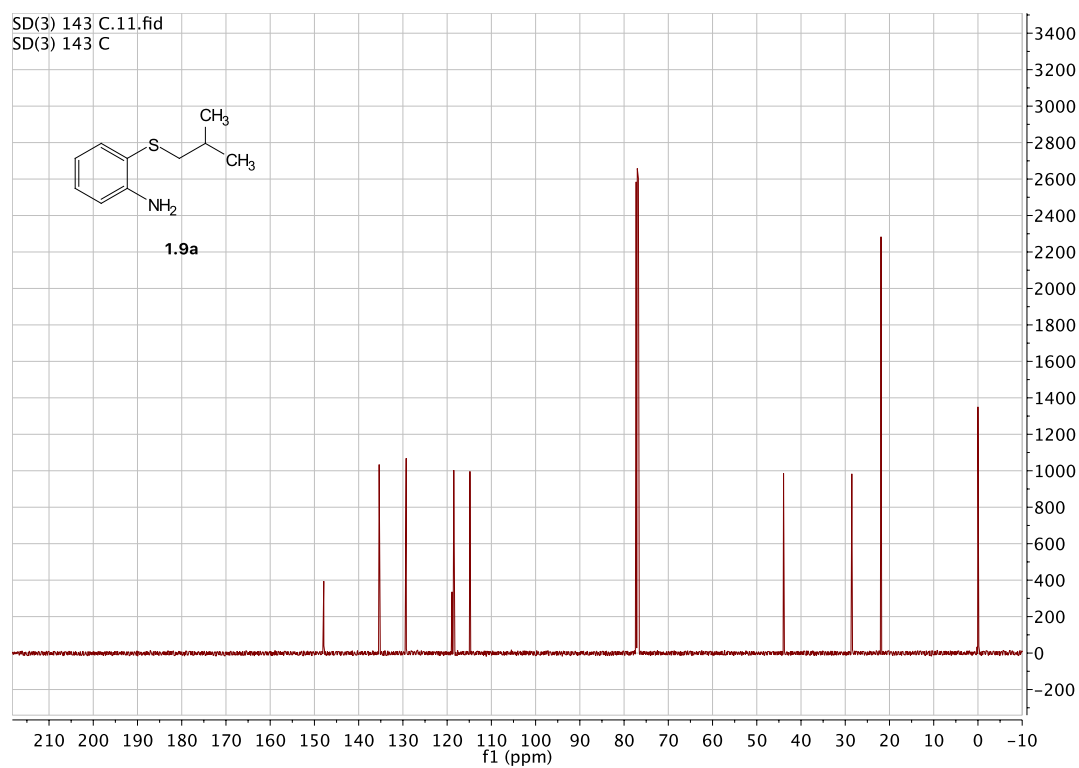
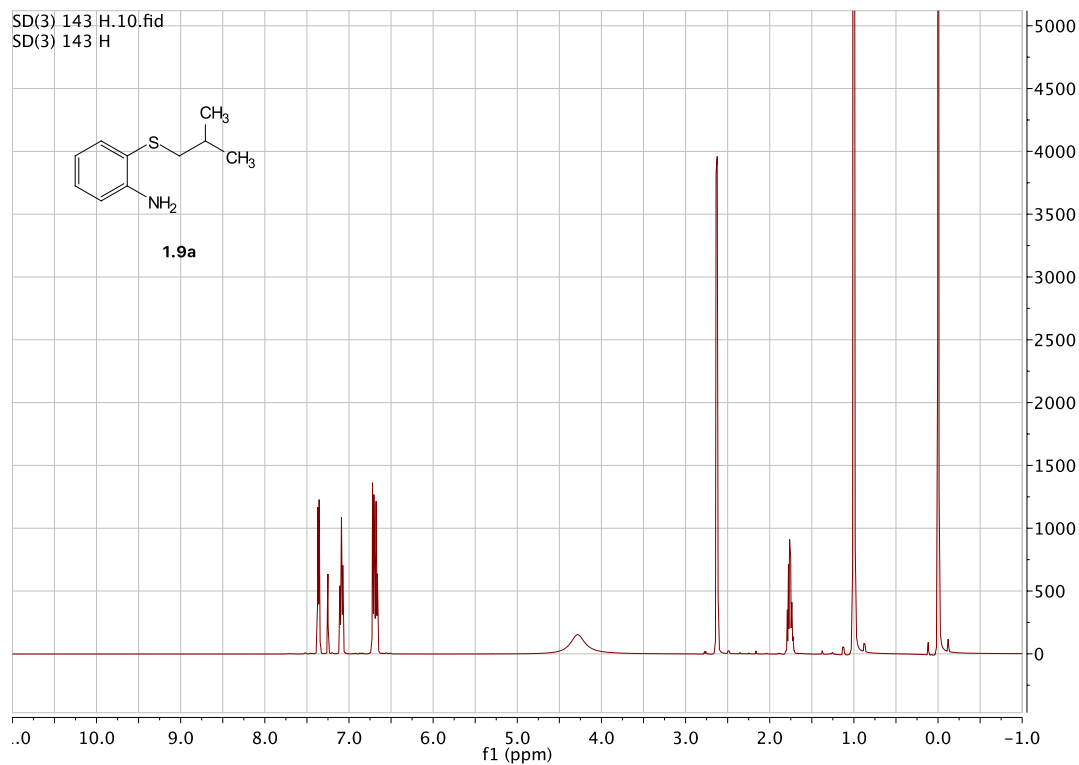


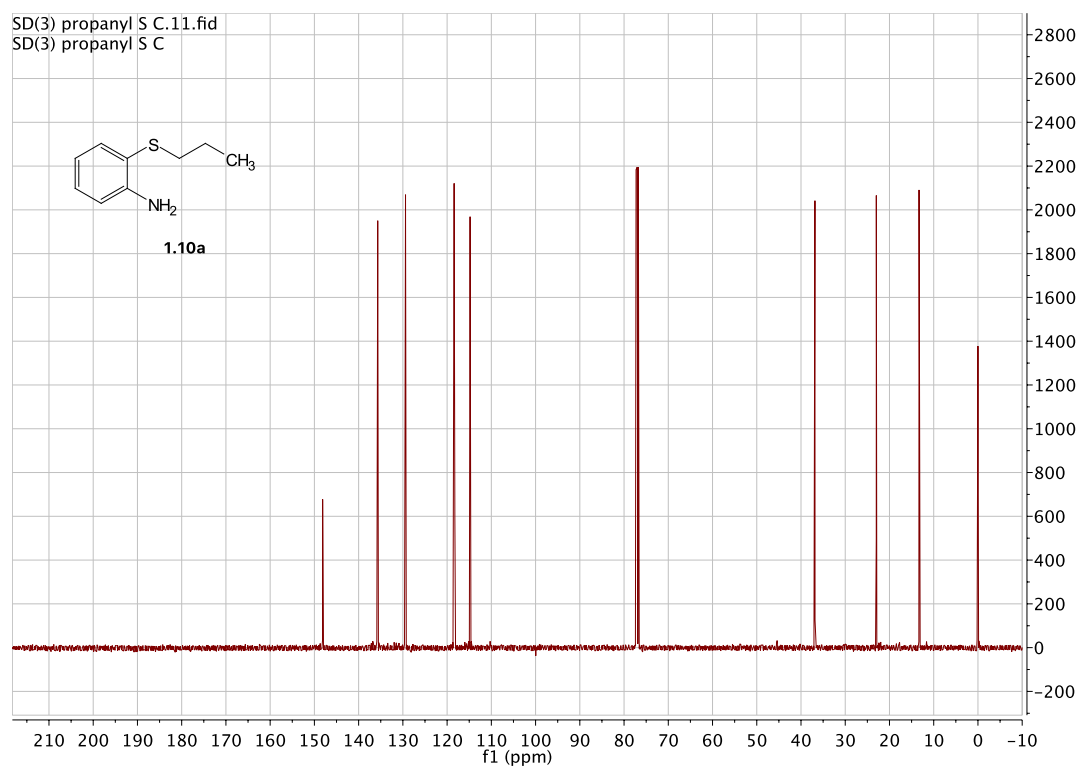
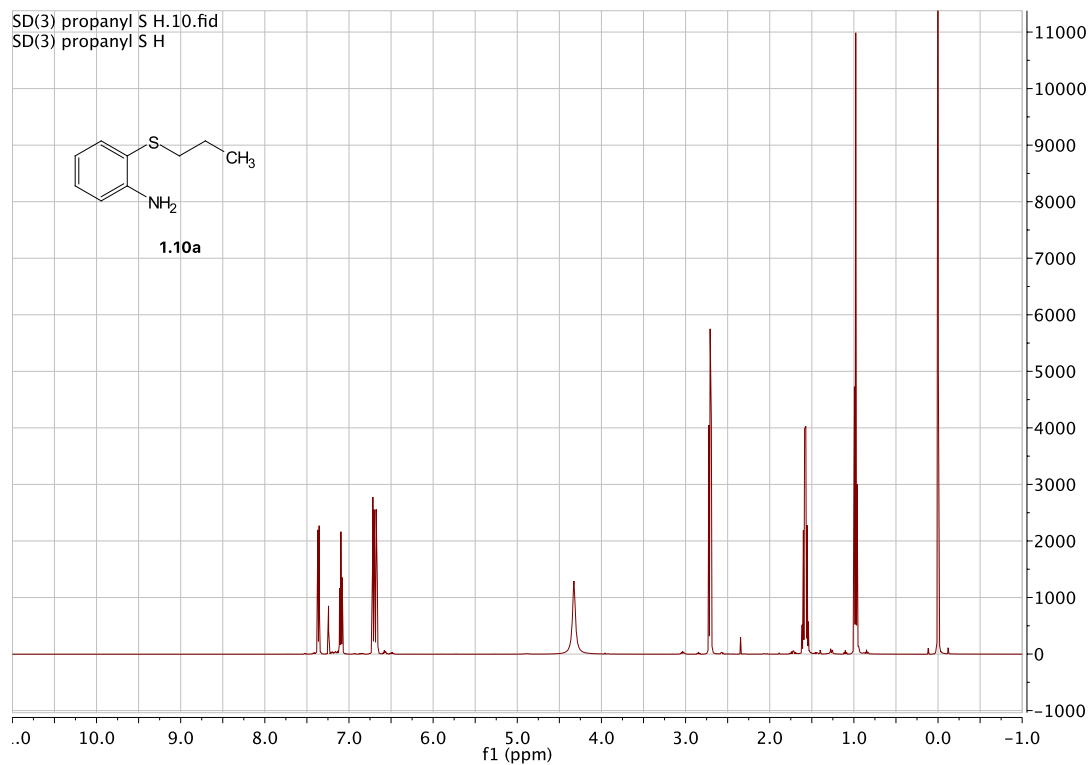


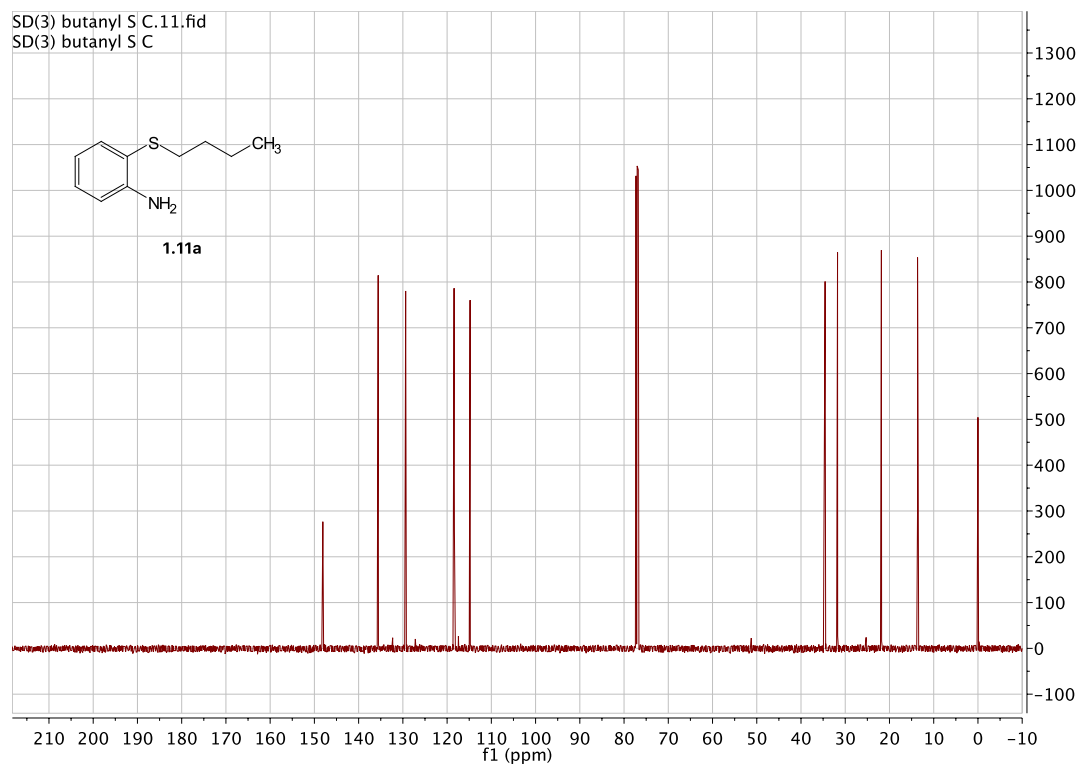
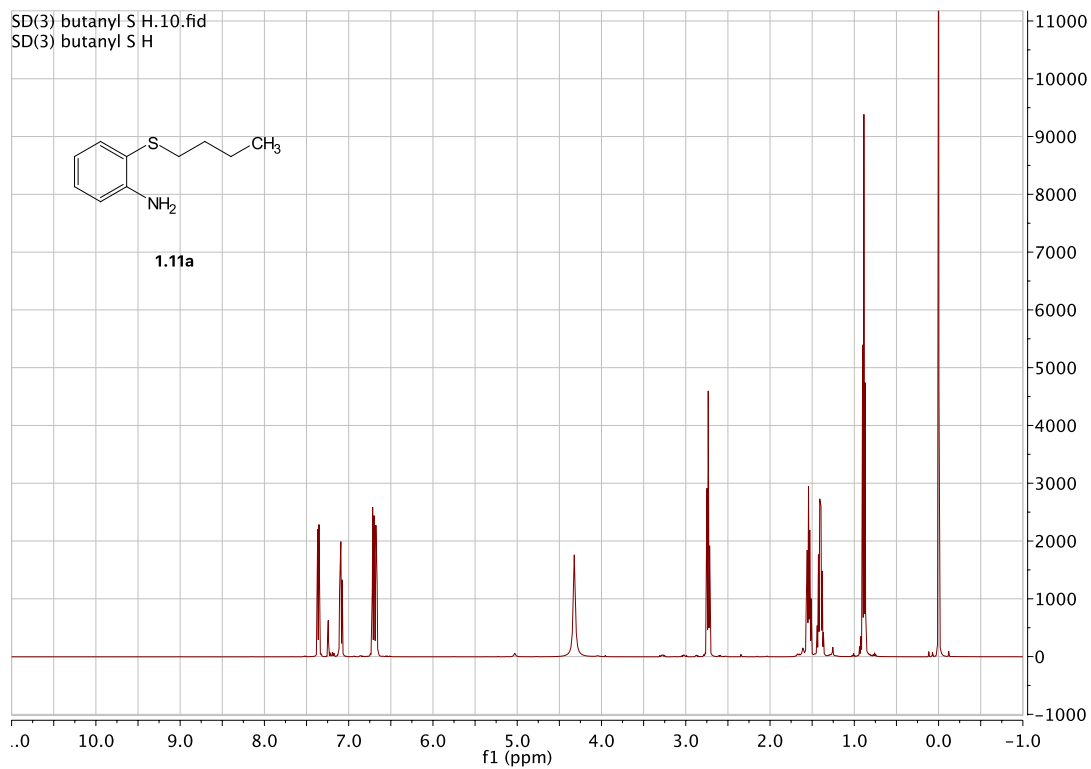


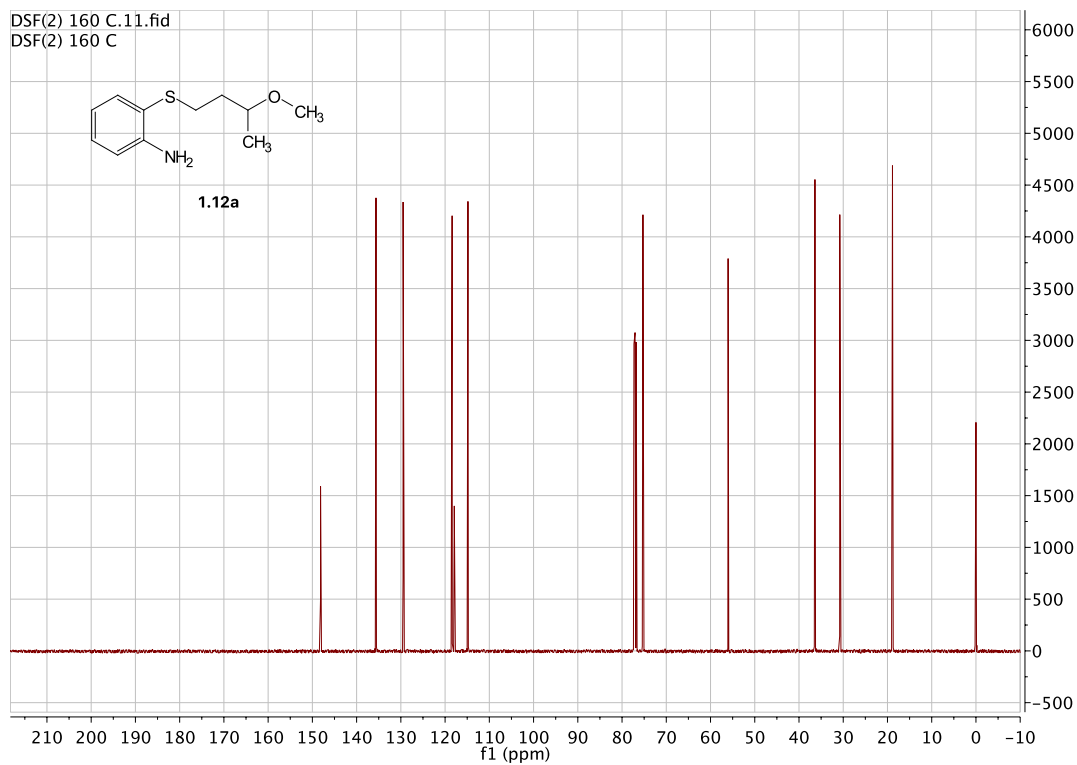
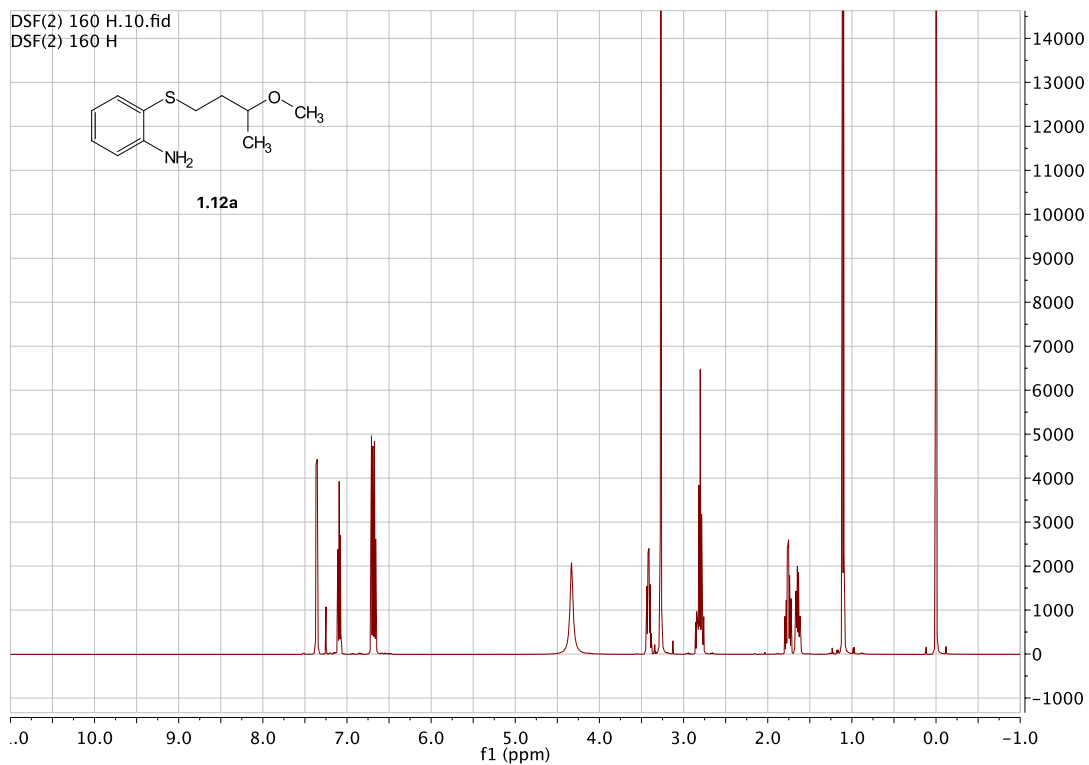


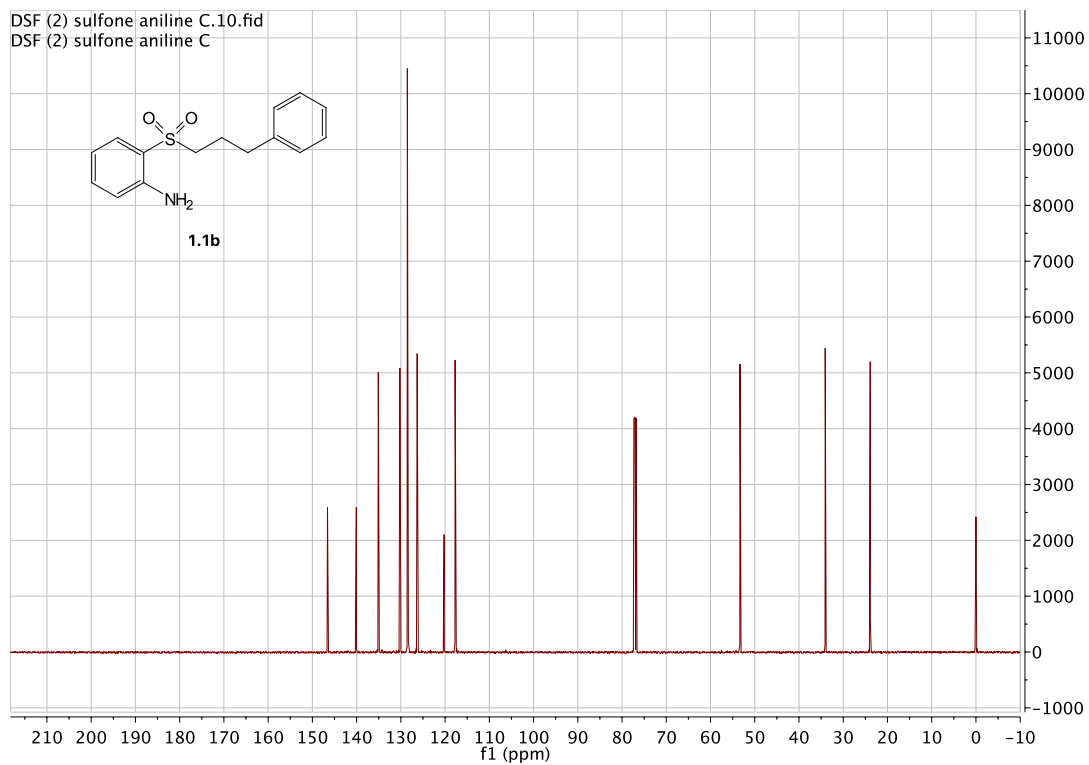
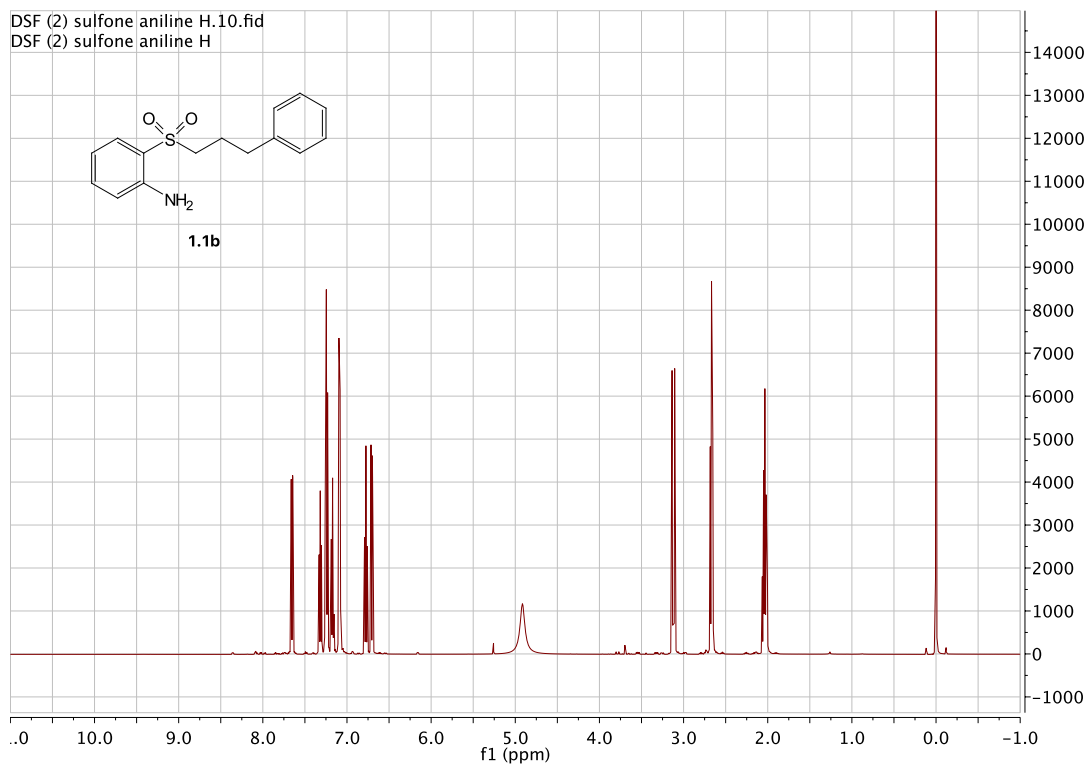


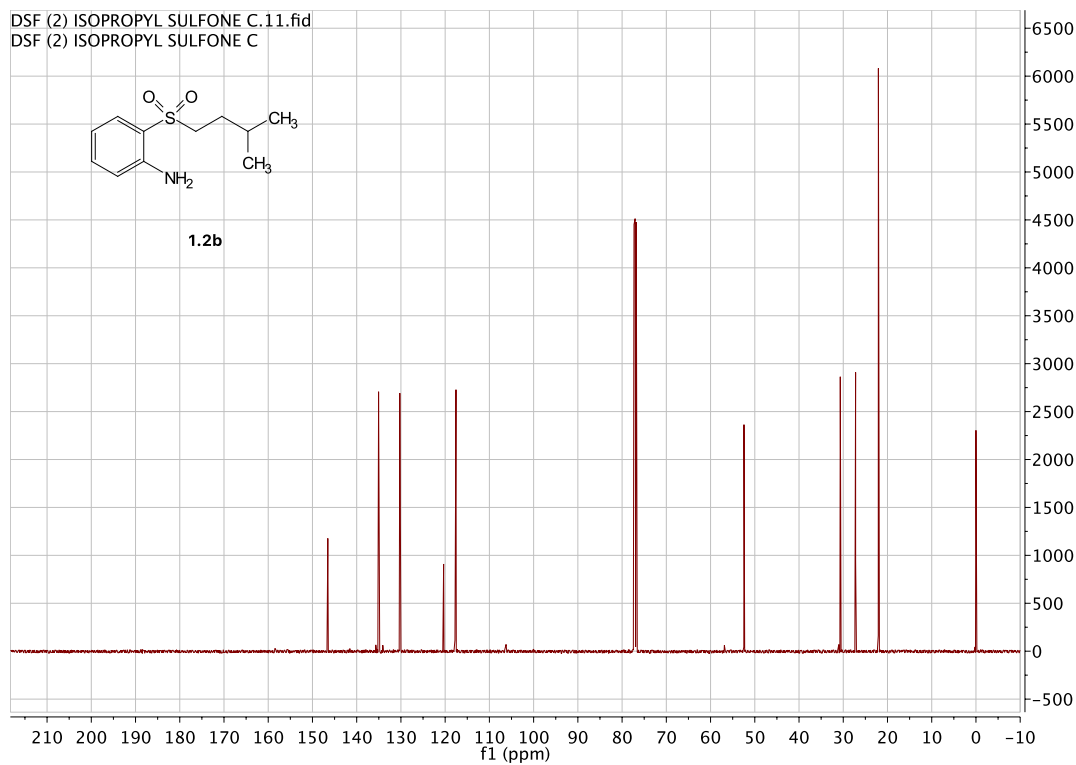
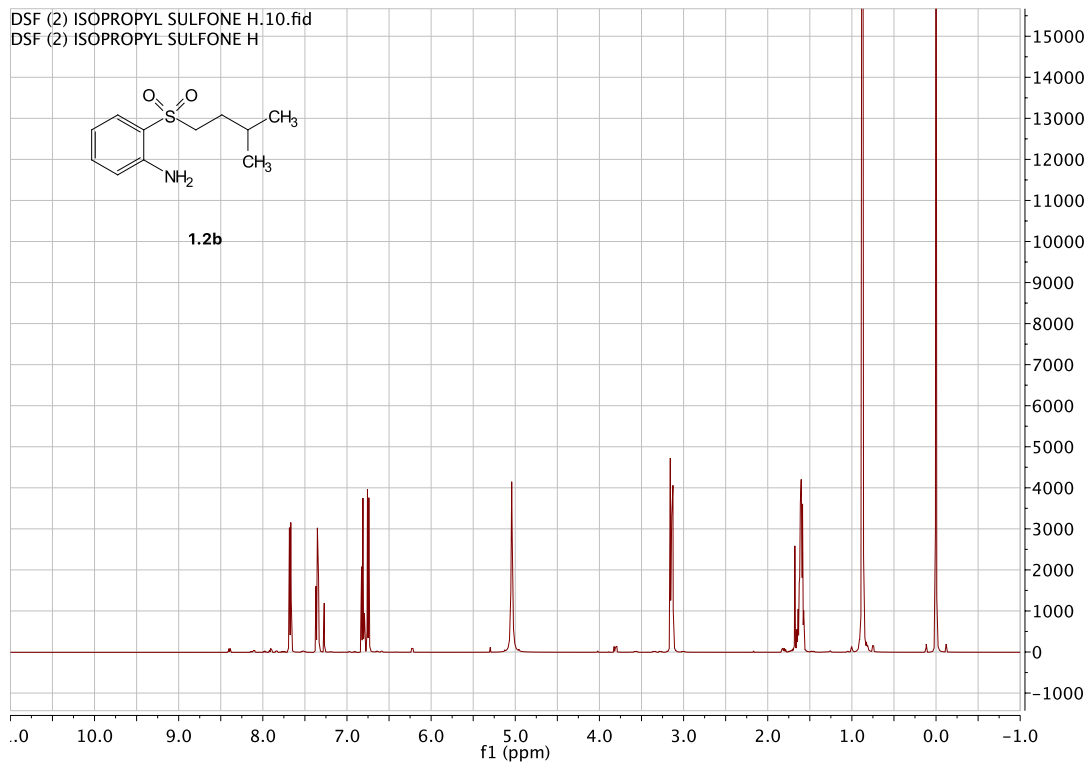


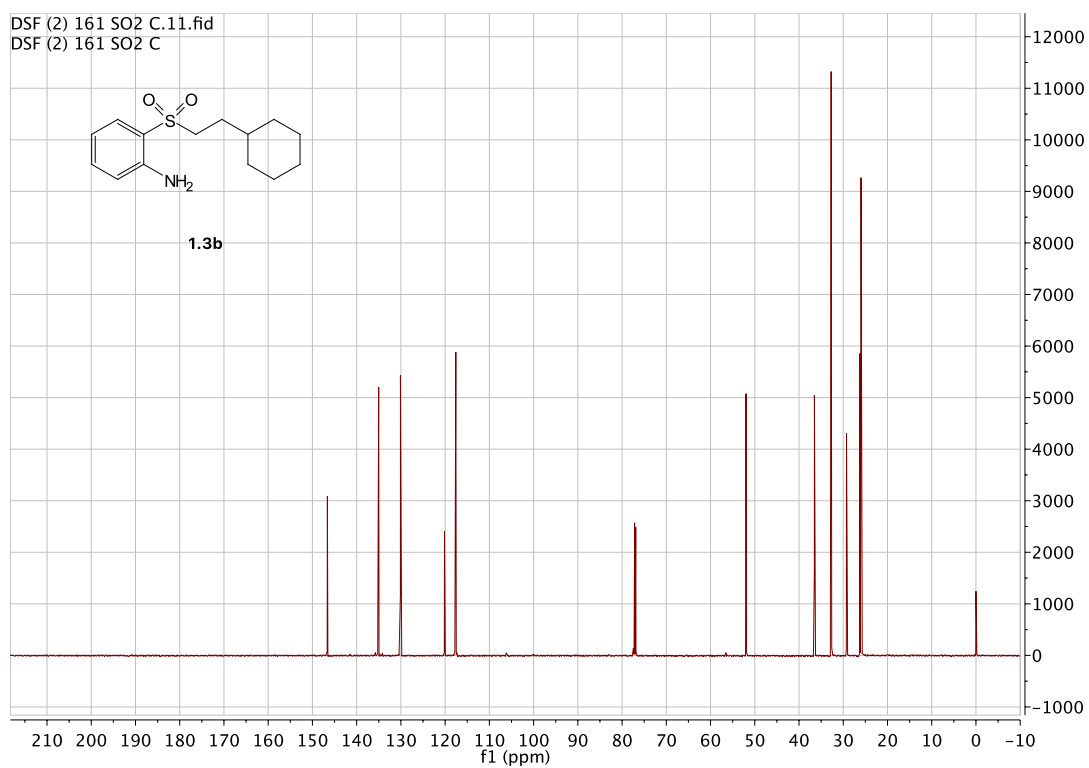
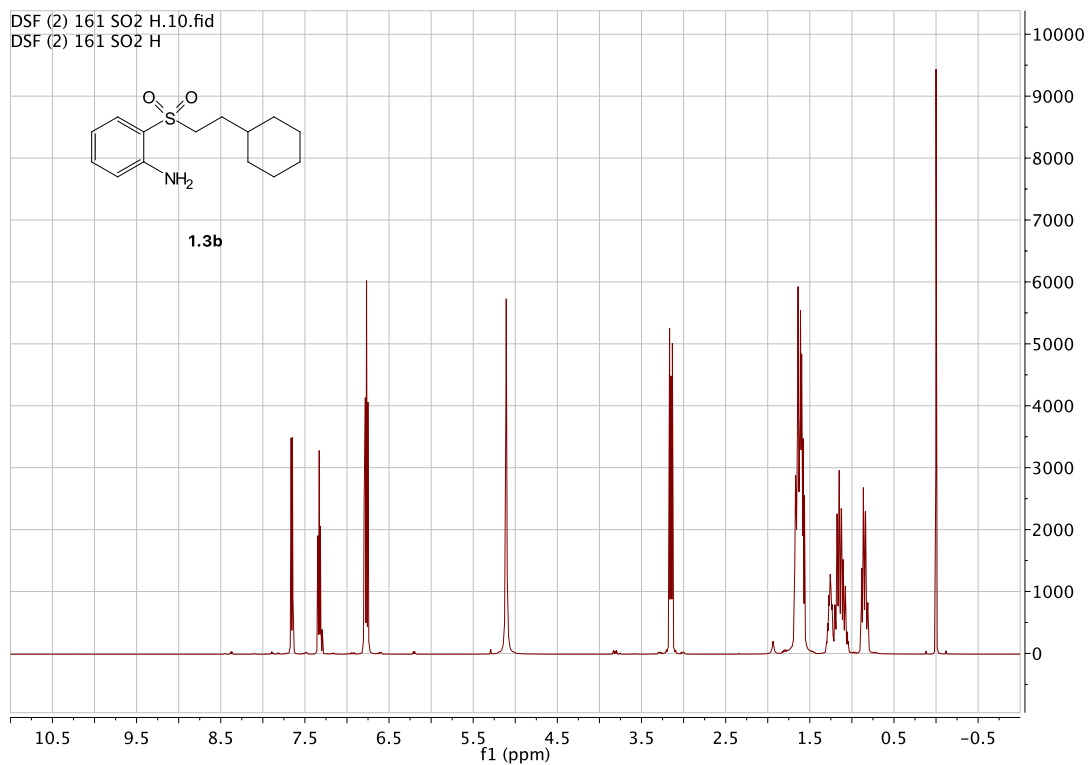


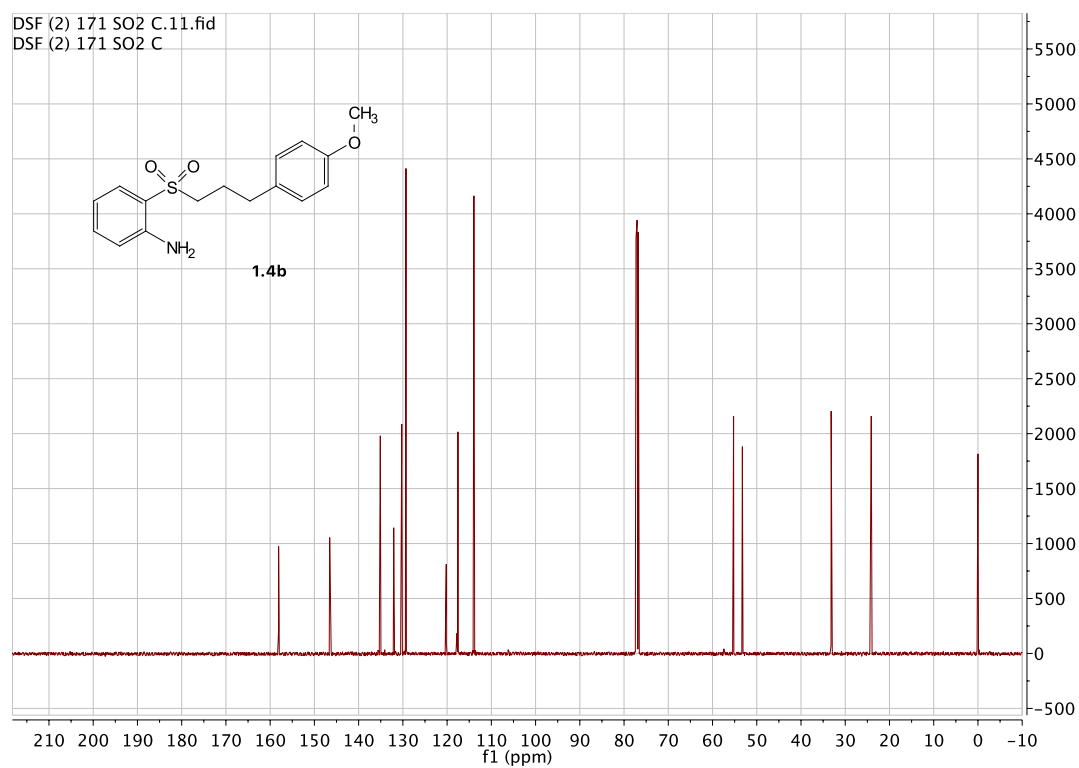
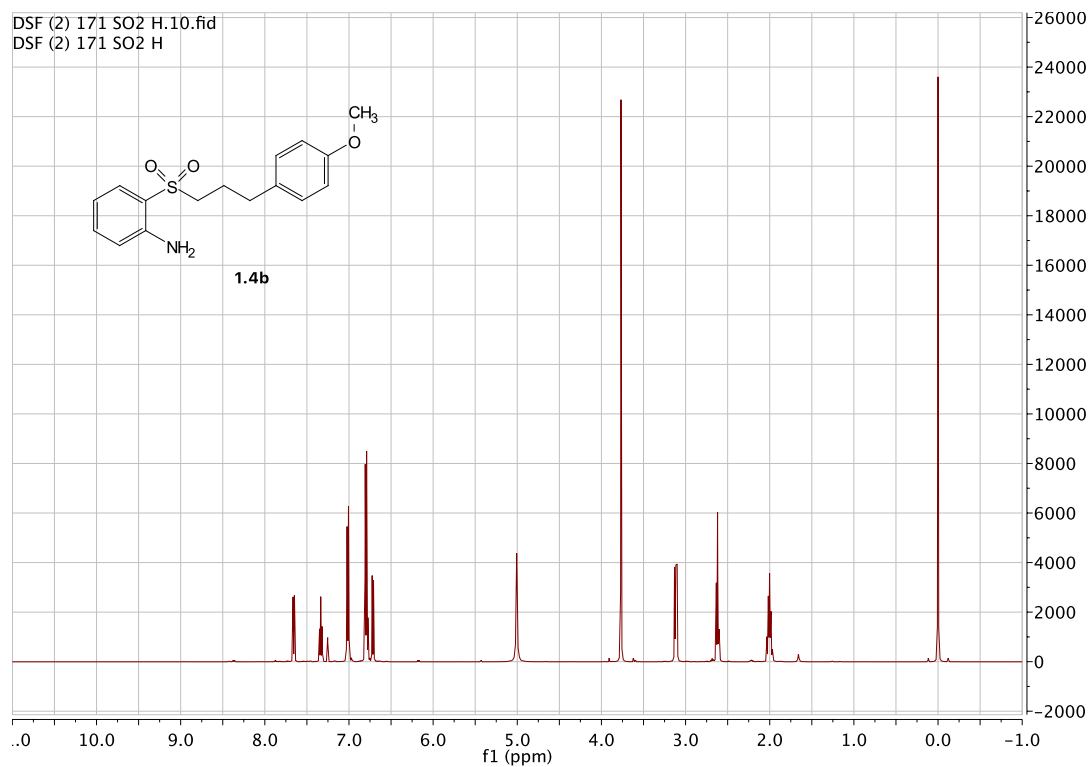


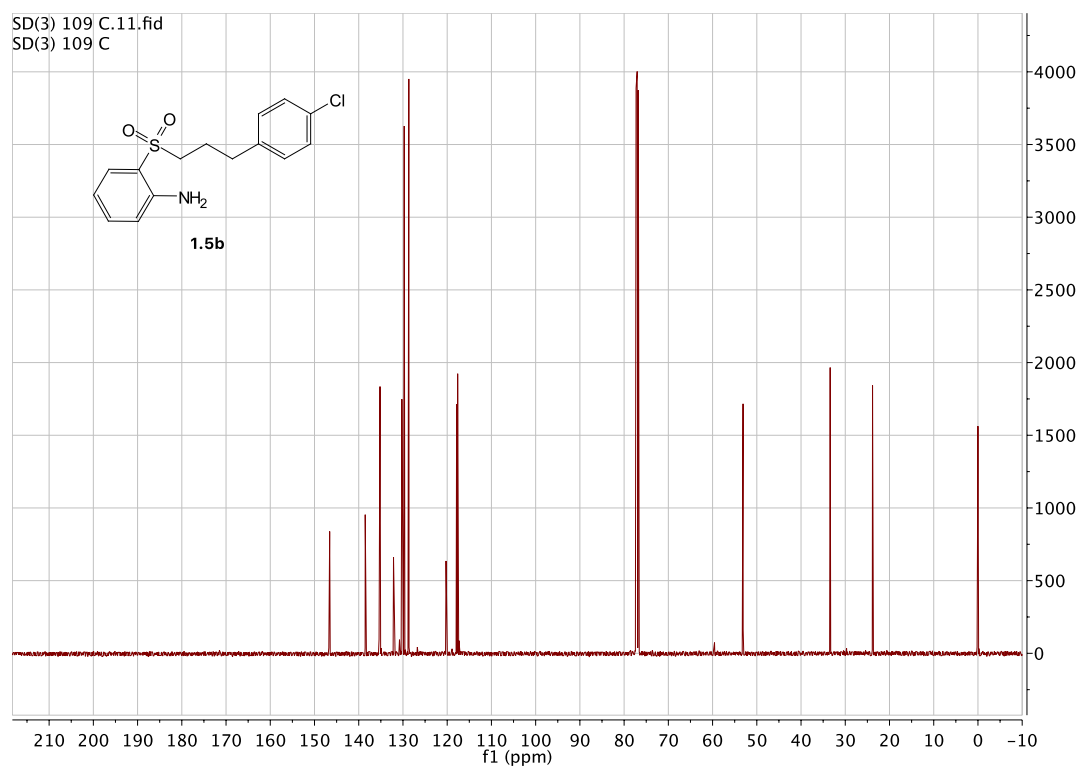
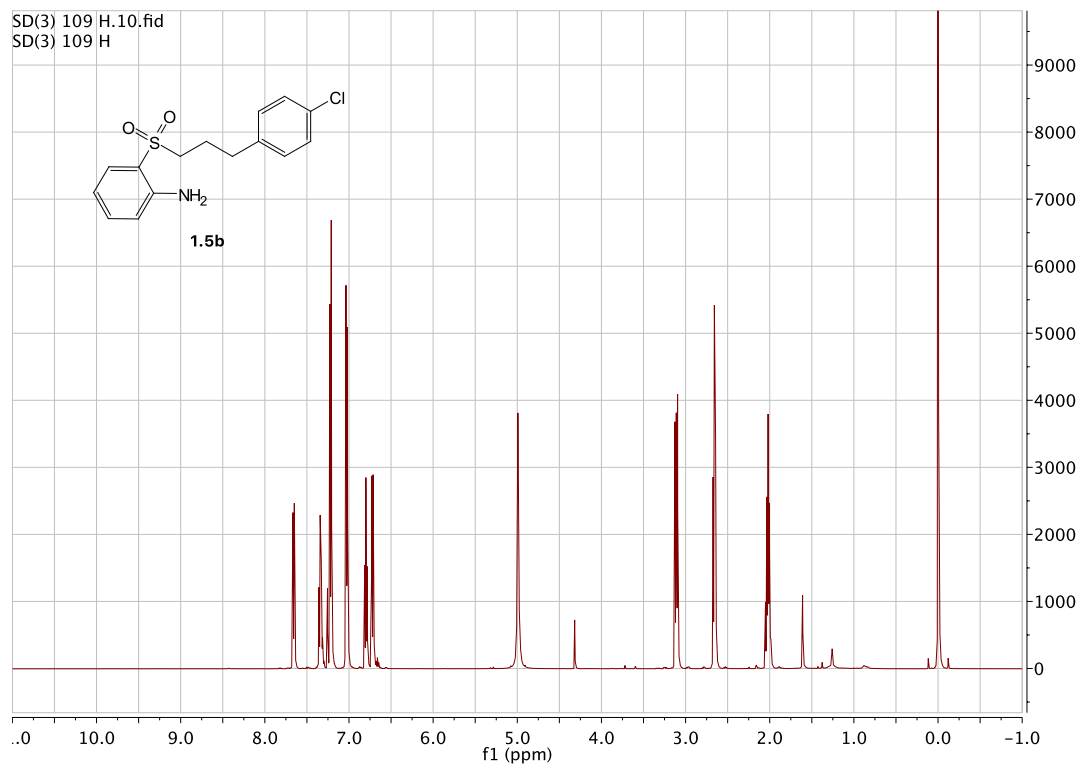




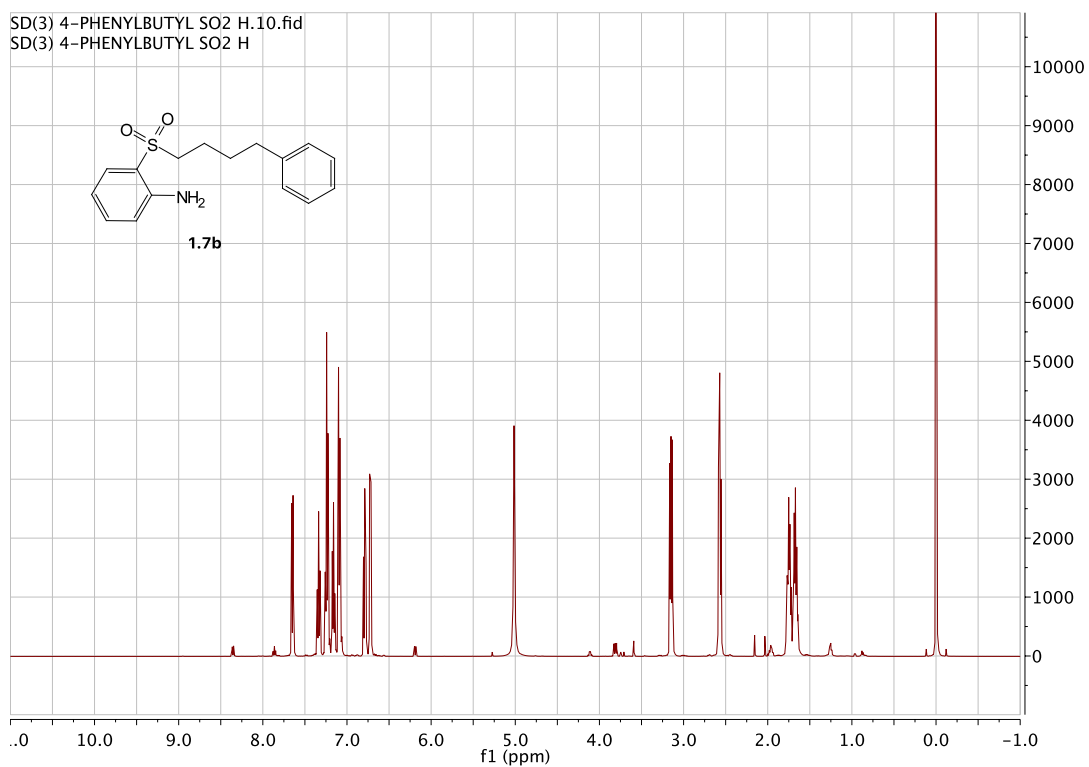




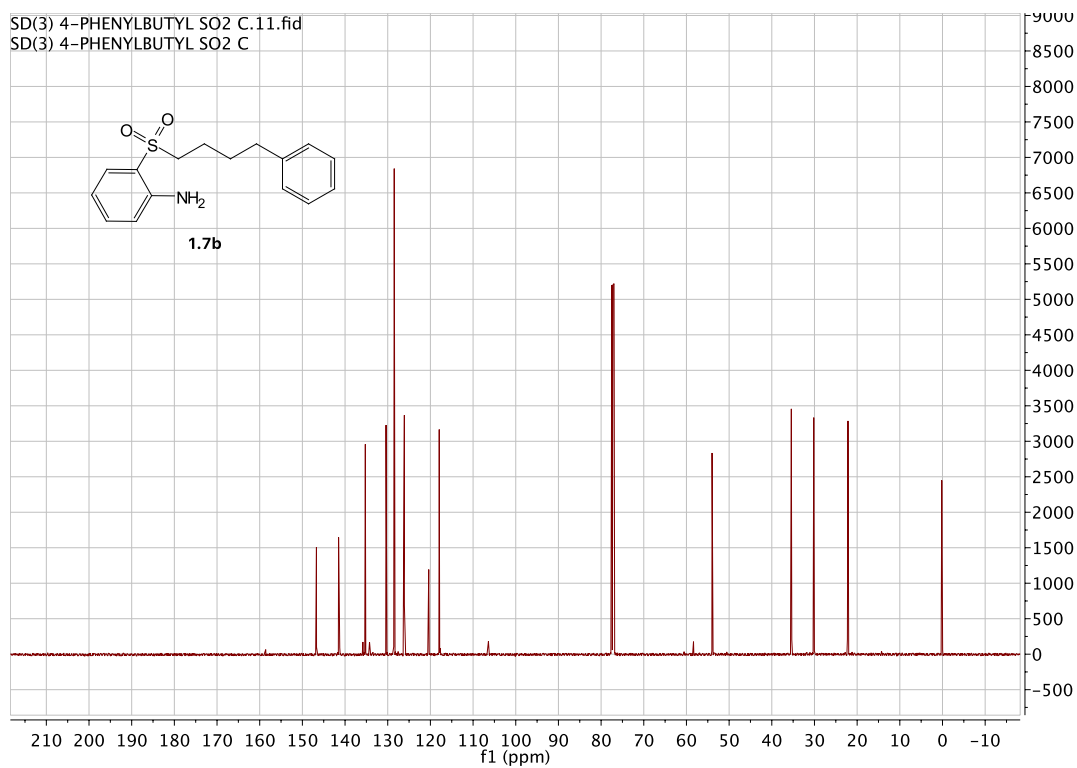


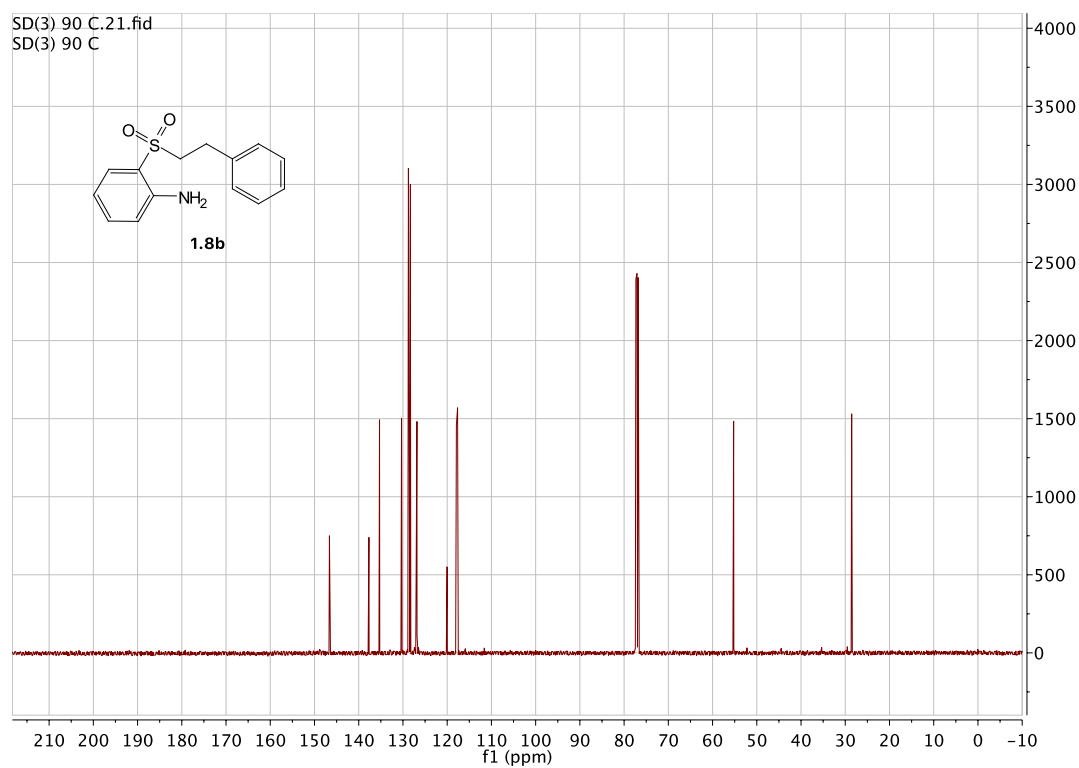
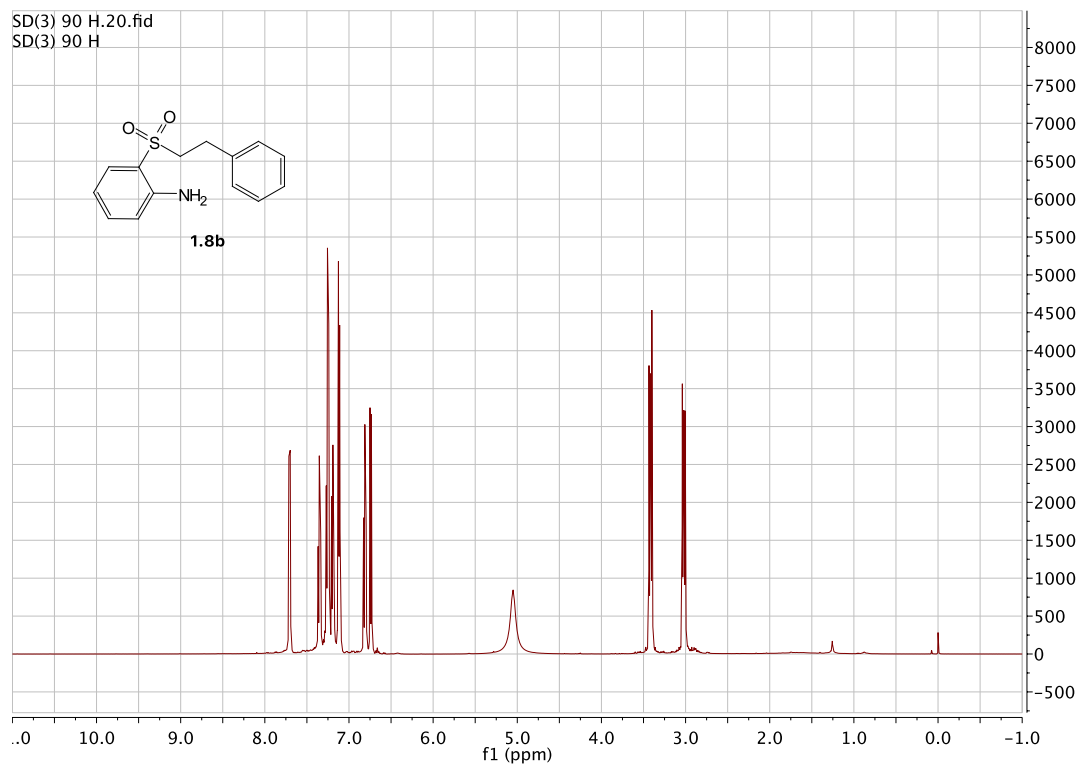


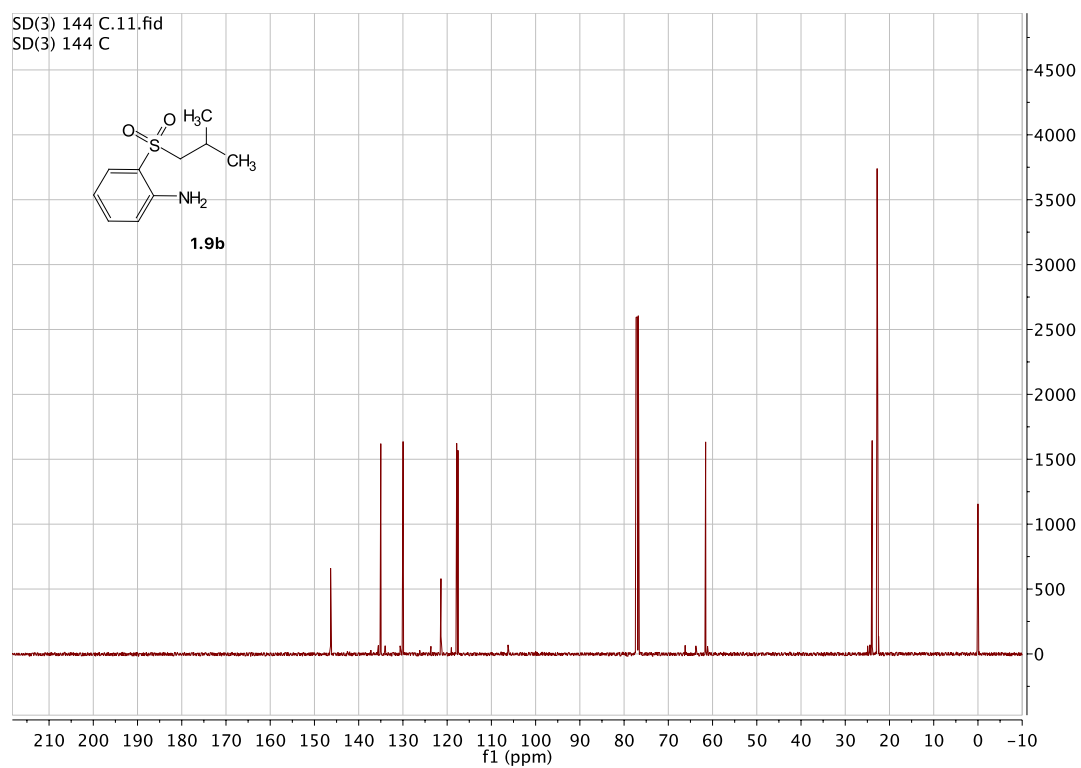
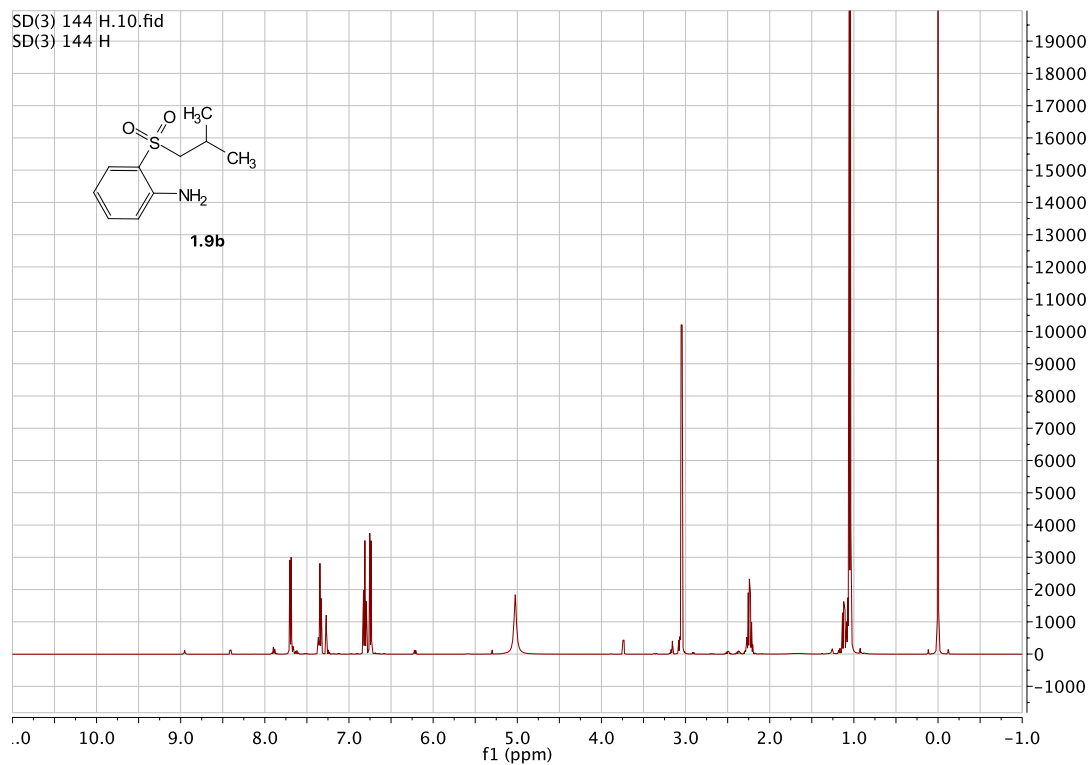
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SD(3) 4-PHENYLBUTYL SO2 H

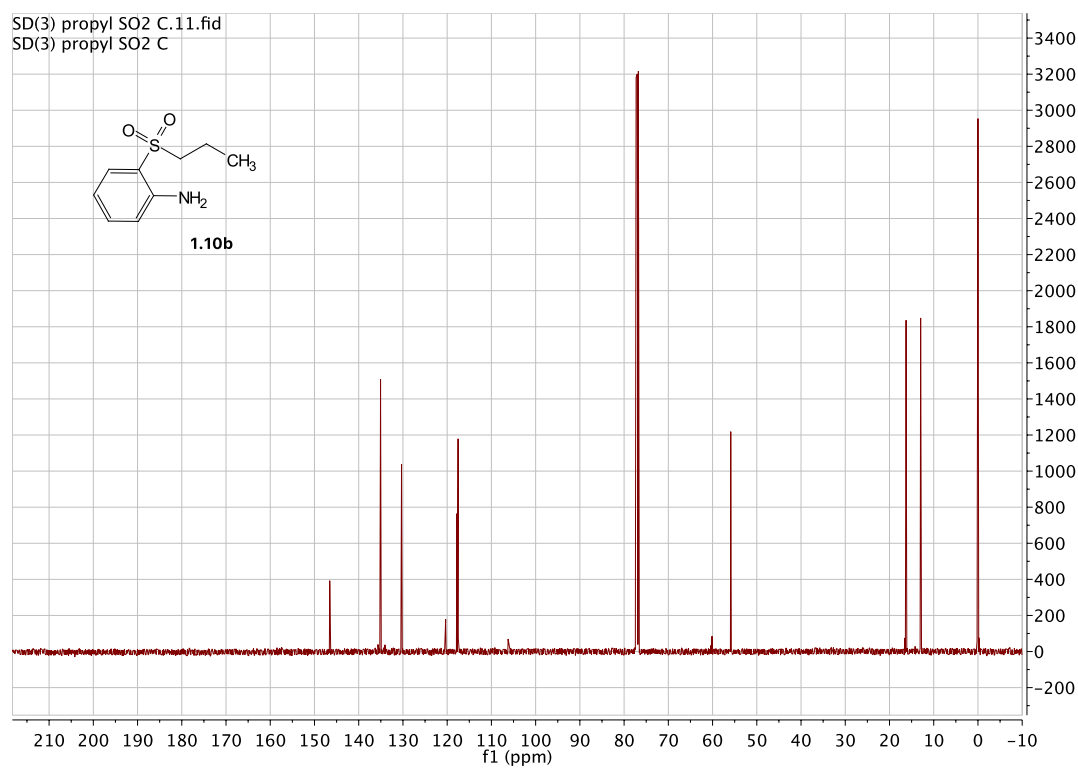
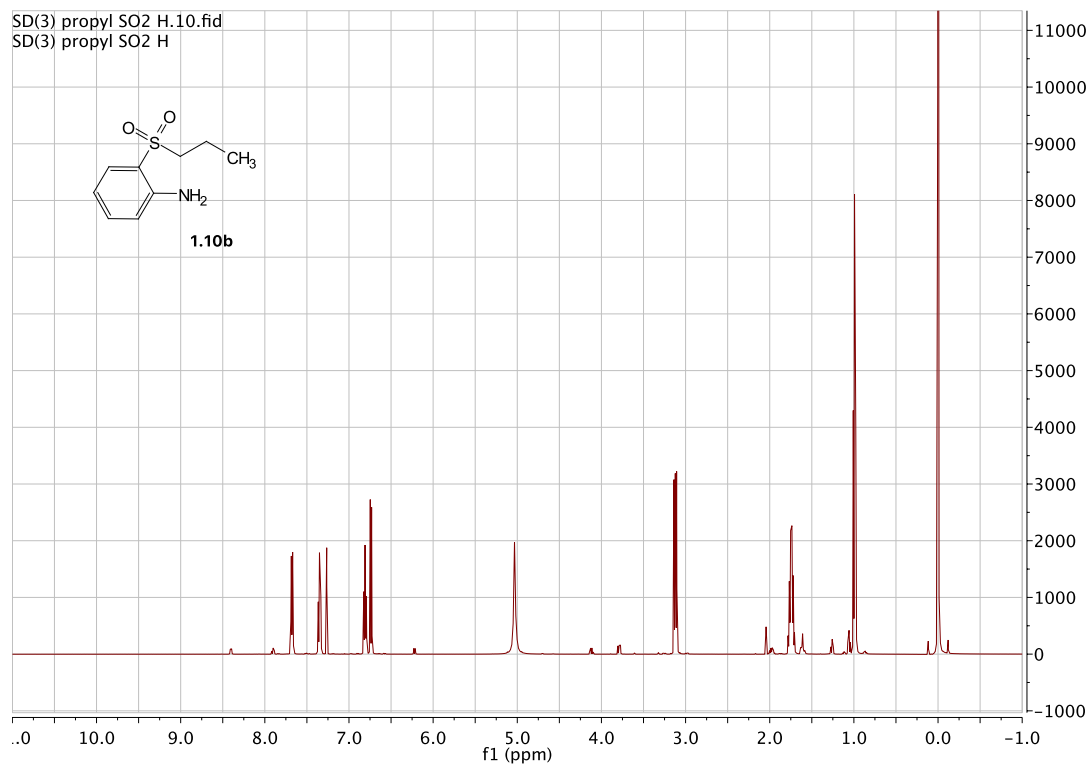


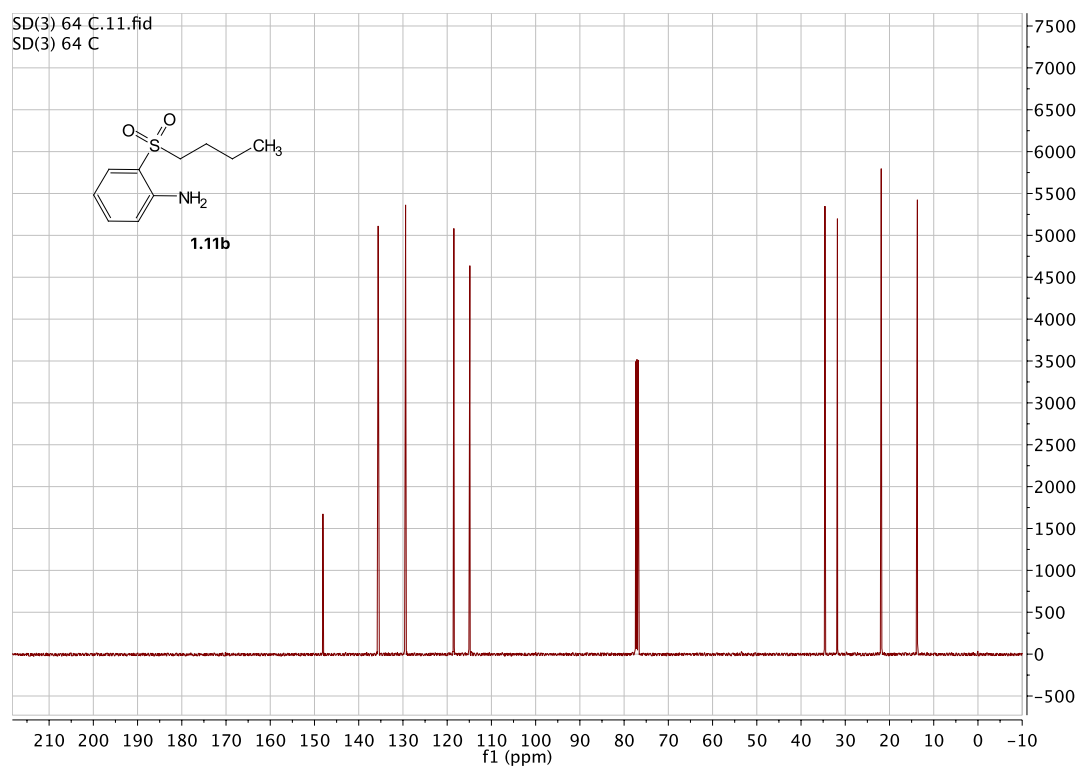
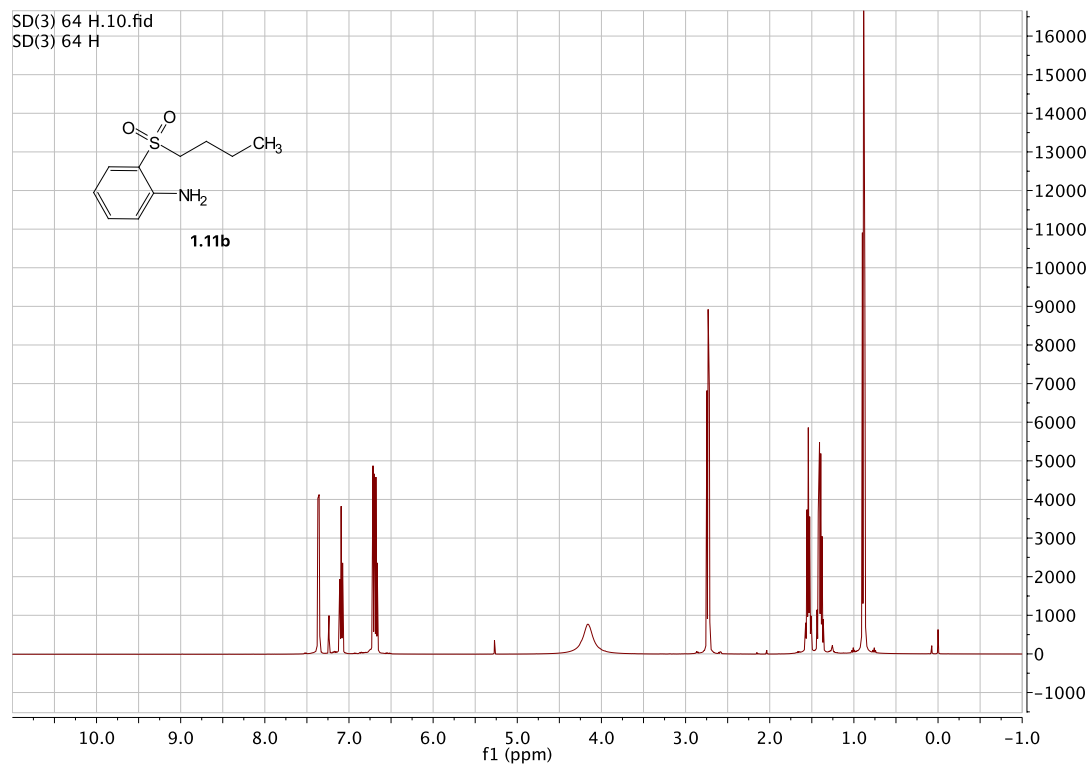
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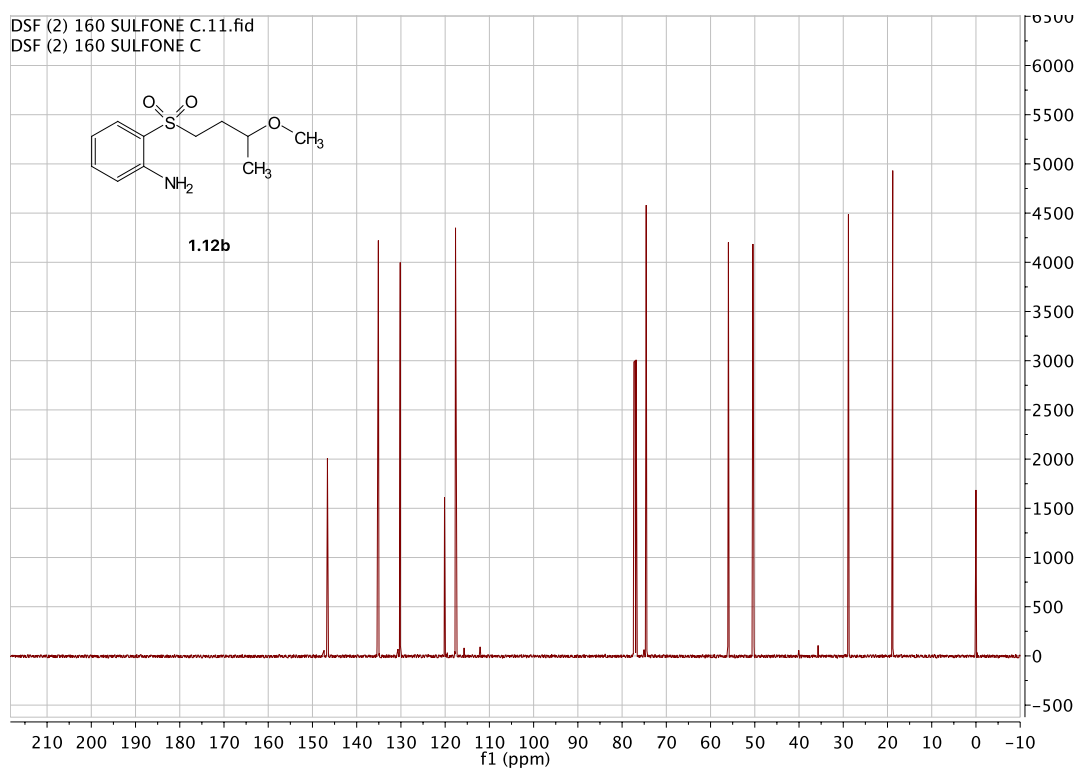
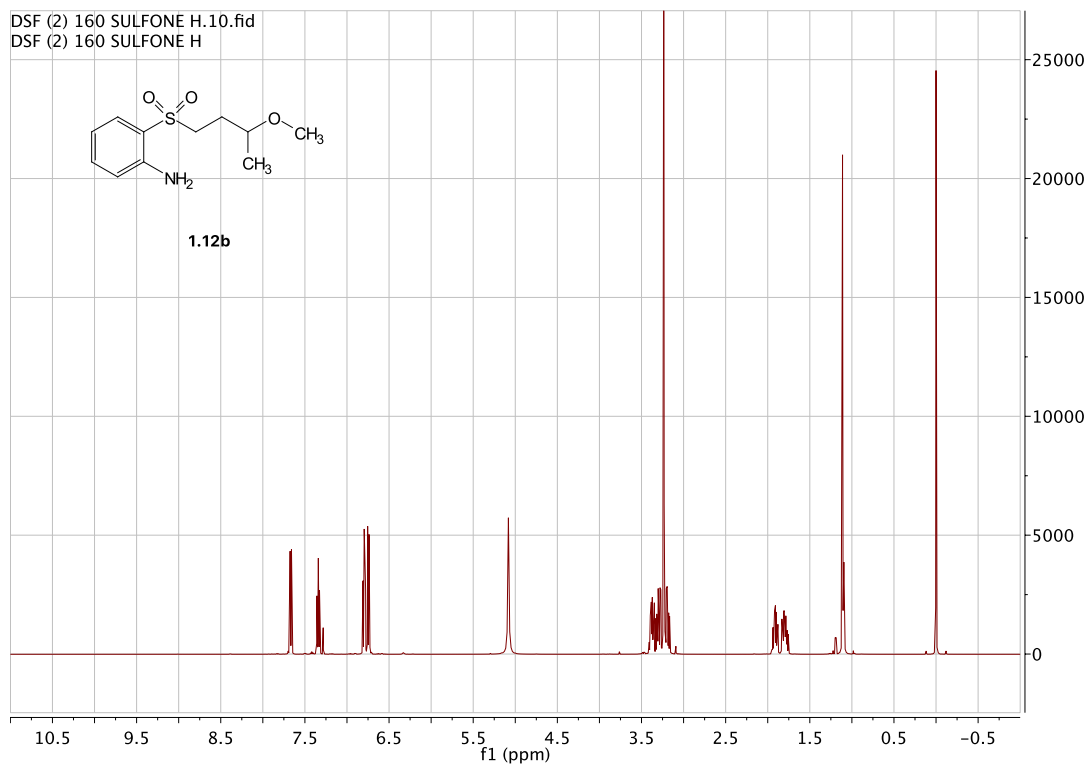




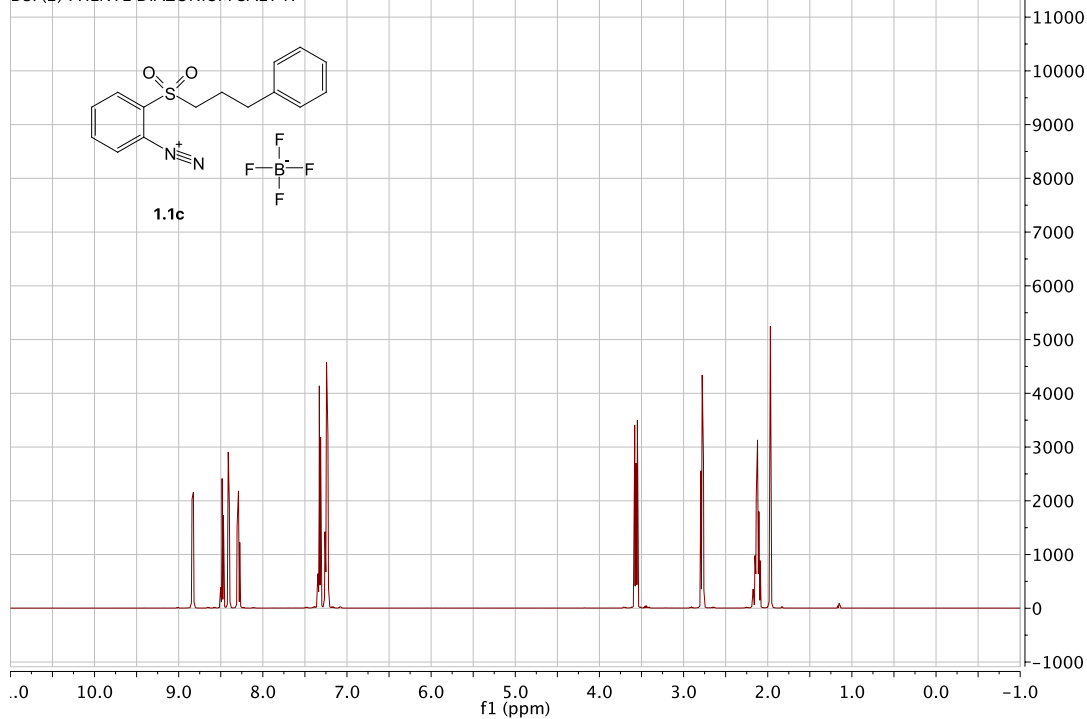




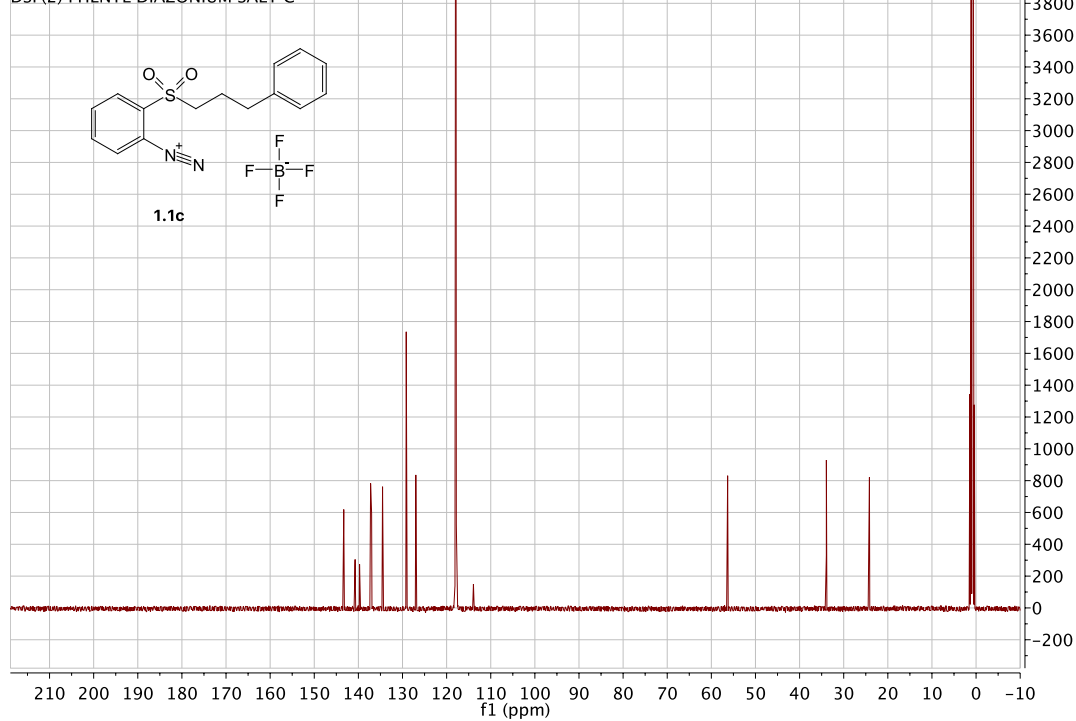


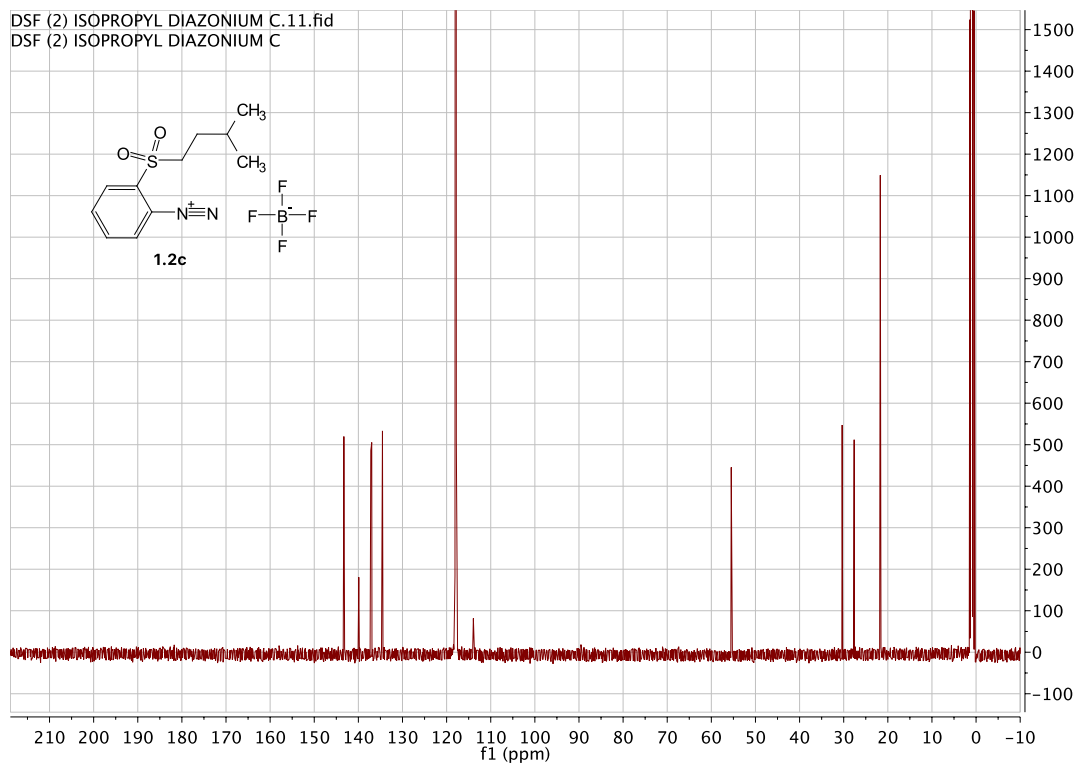
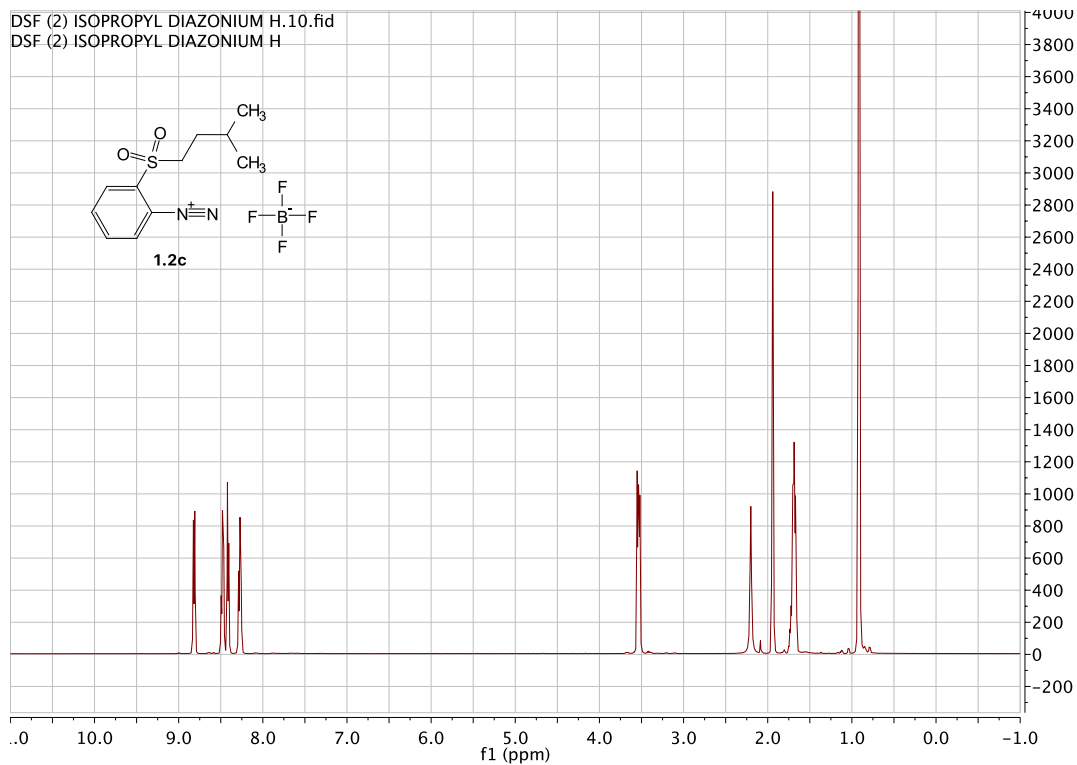


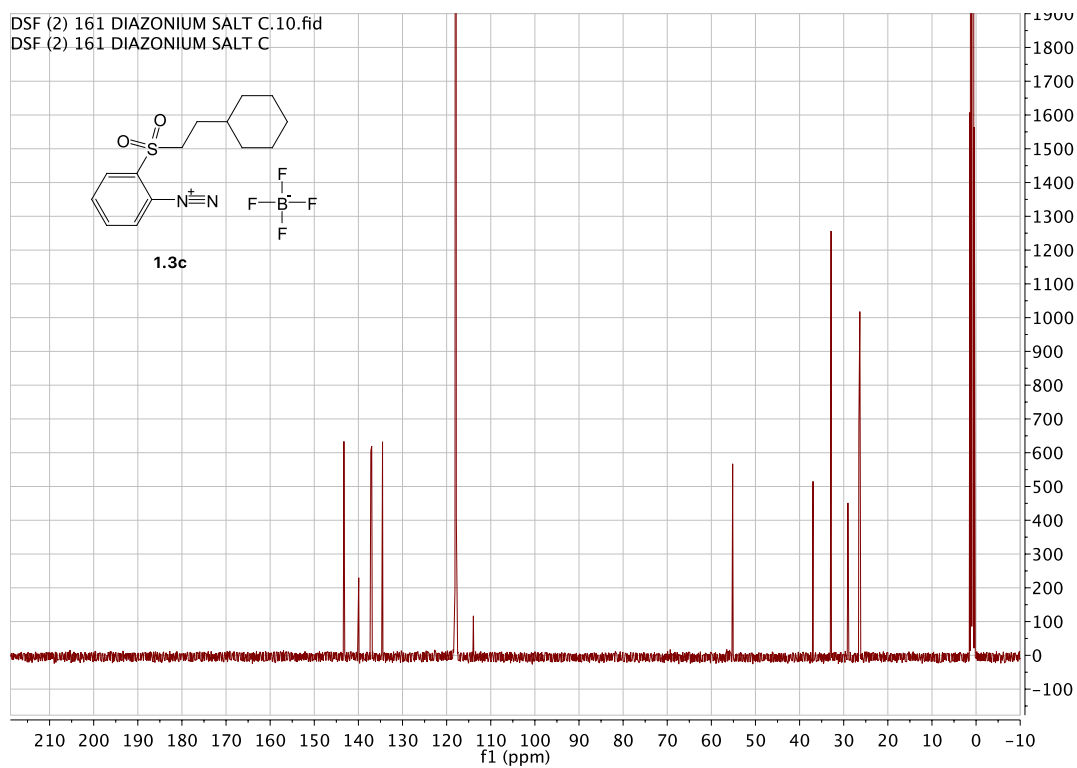
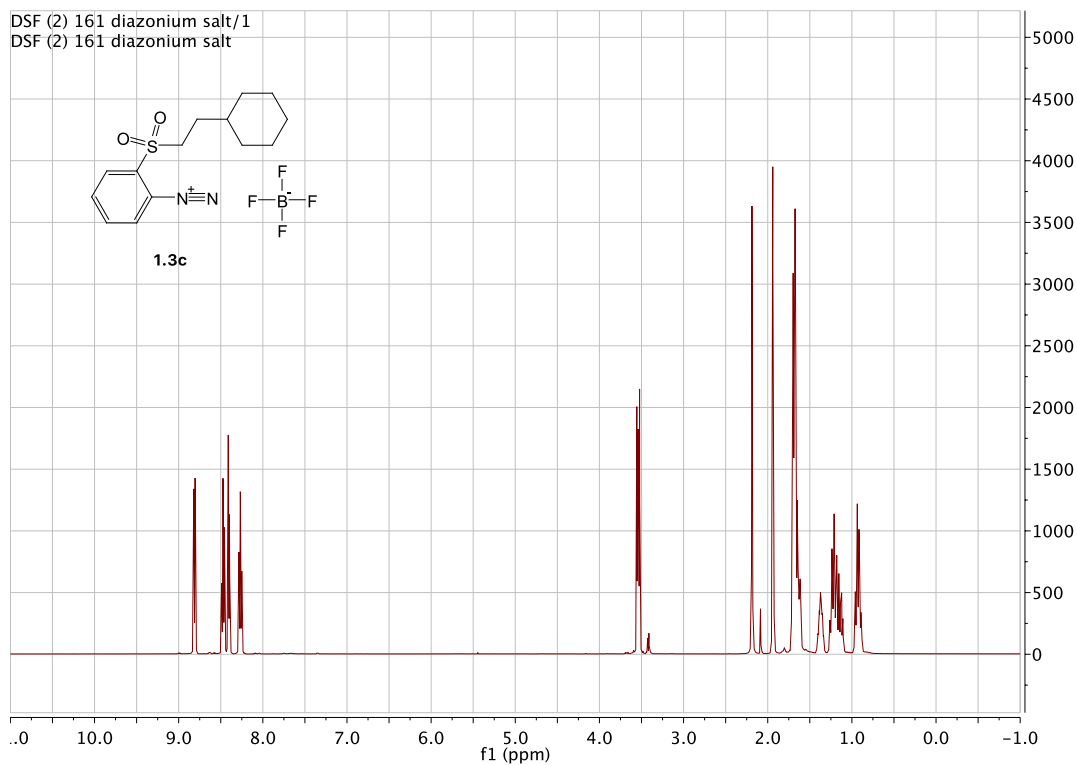
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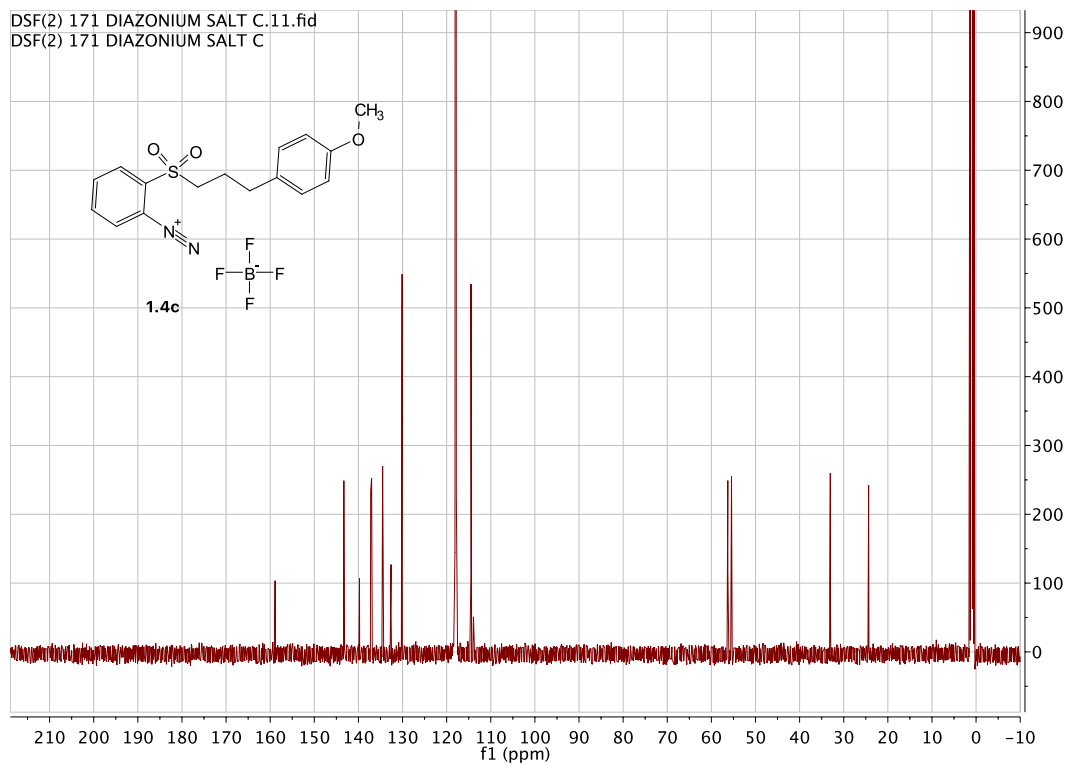
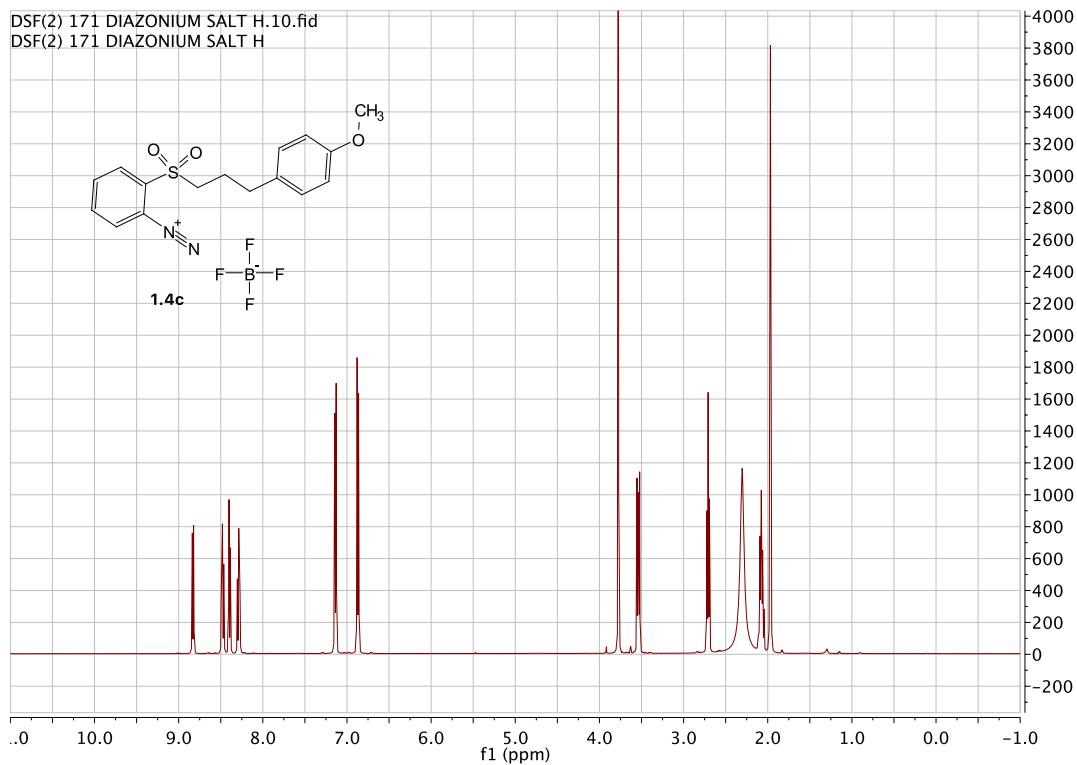


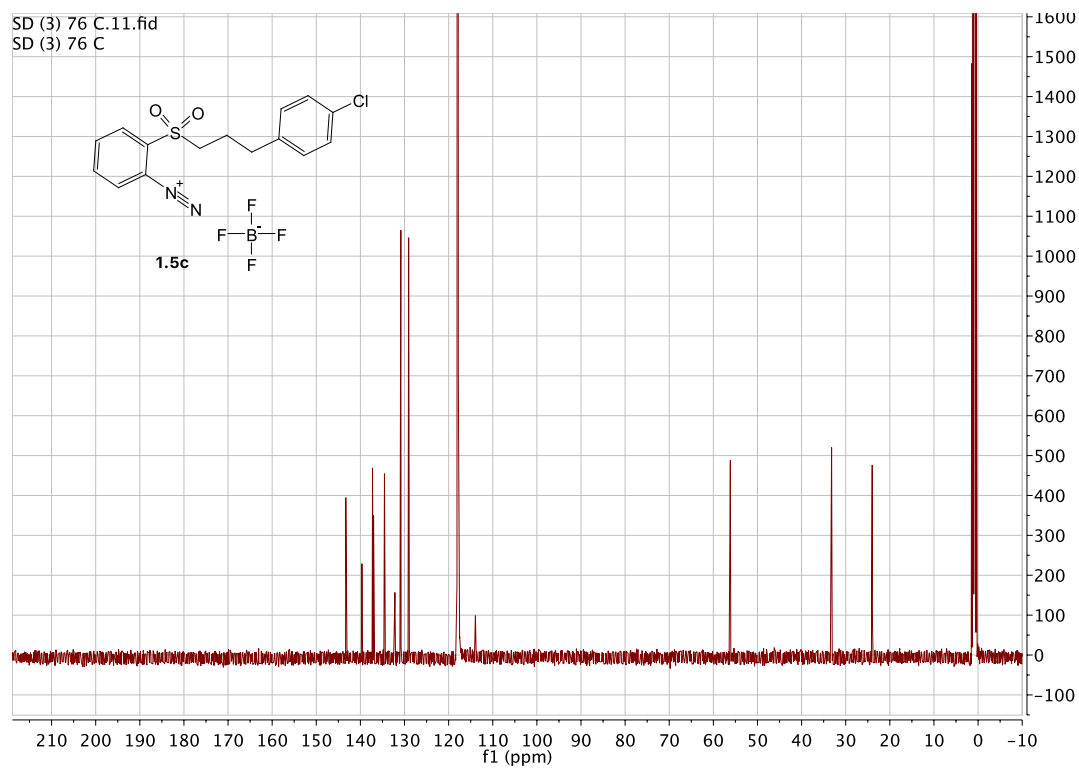
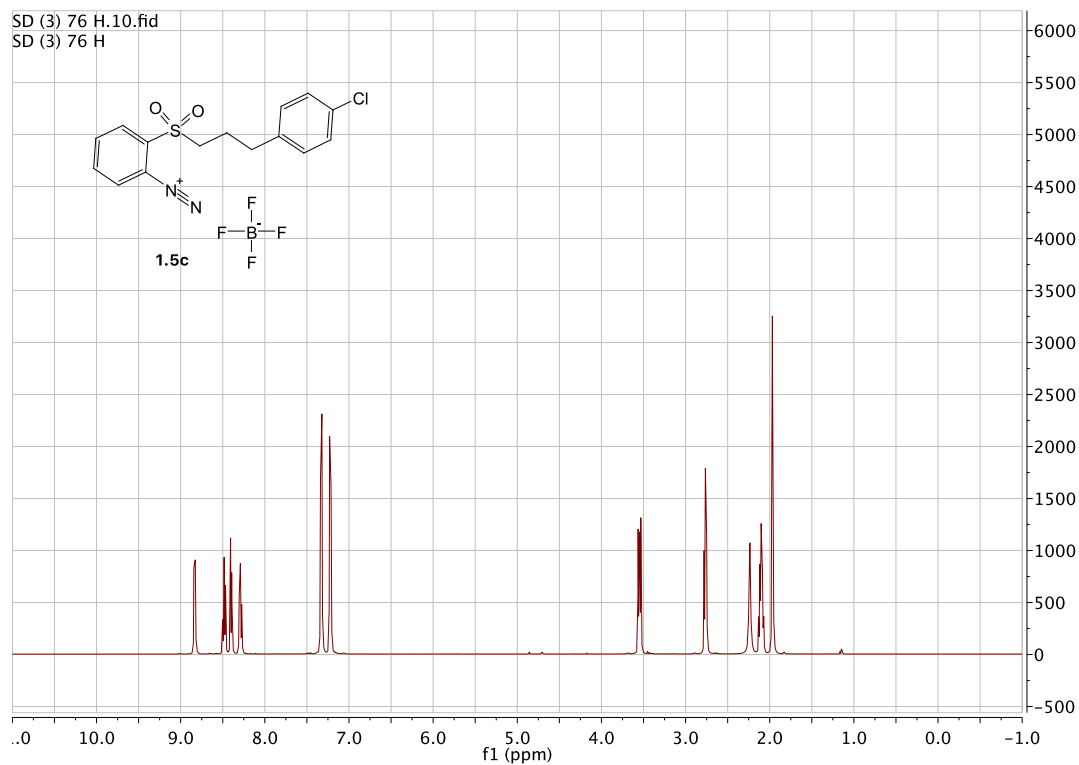
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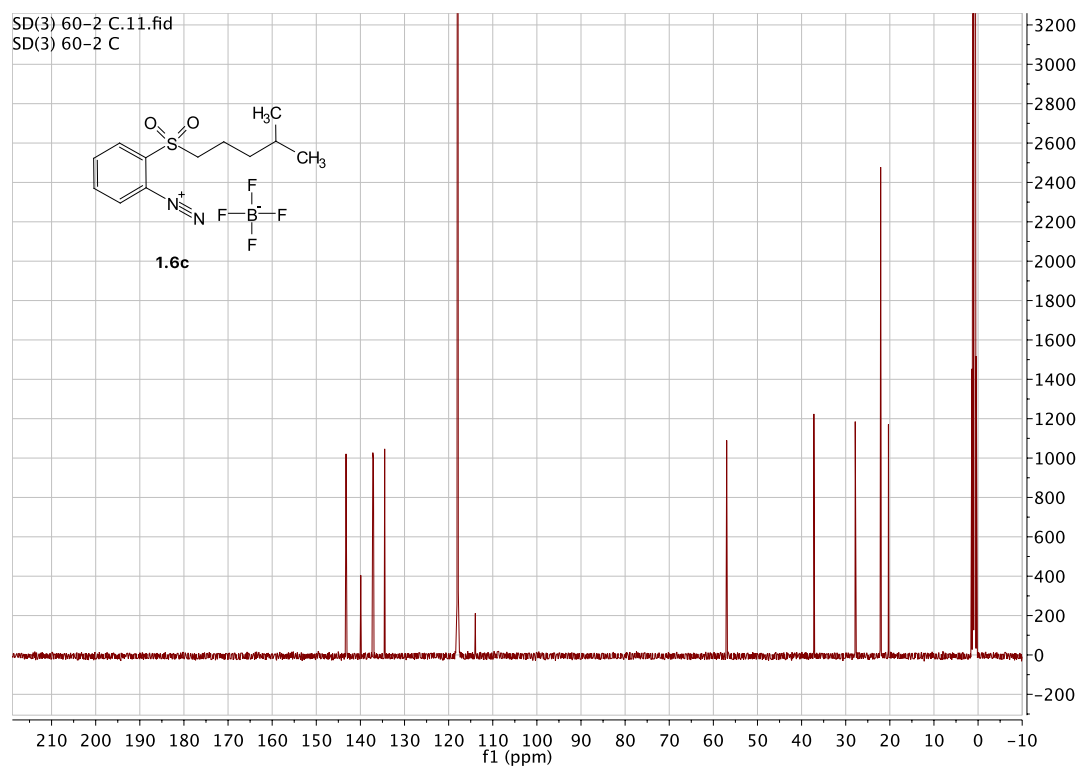
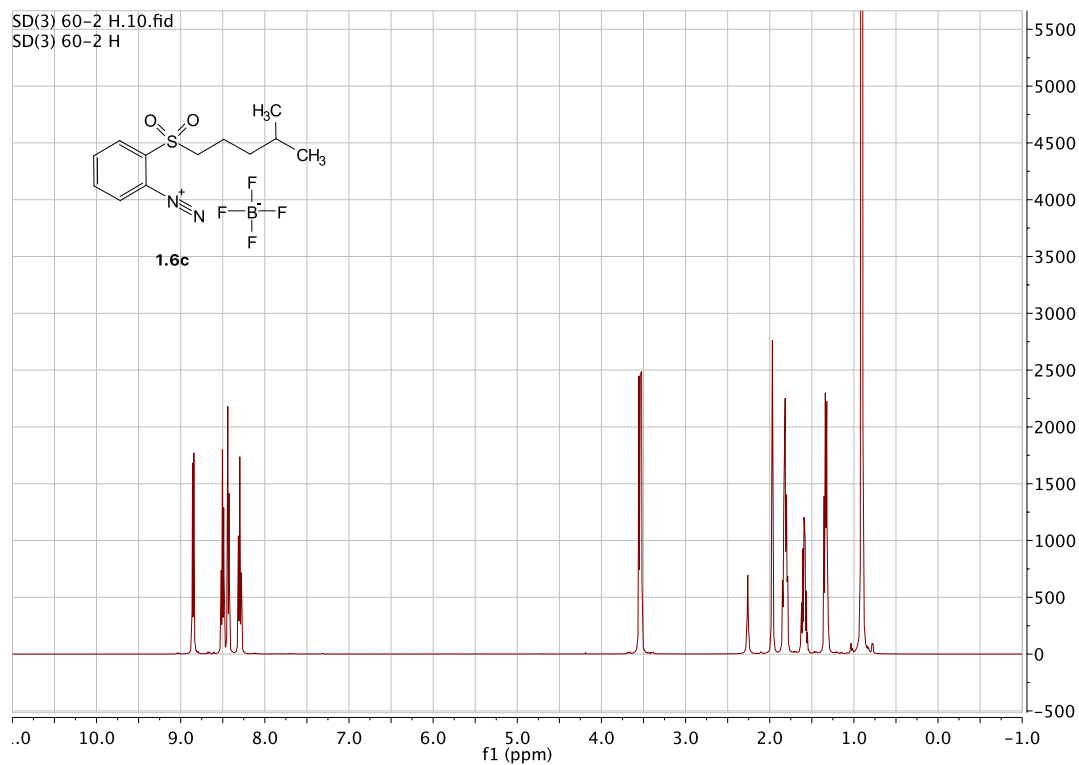


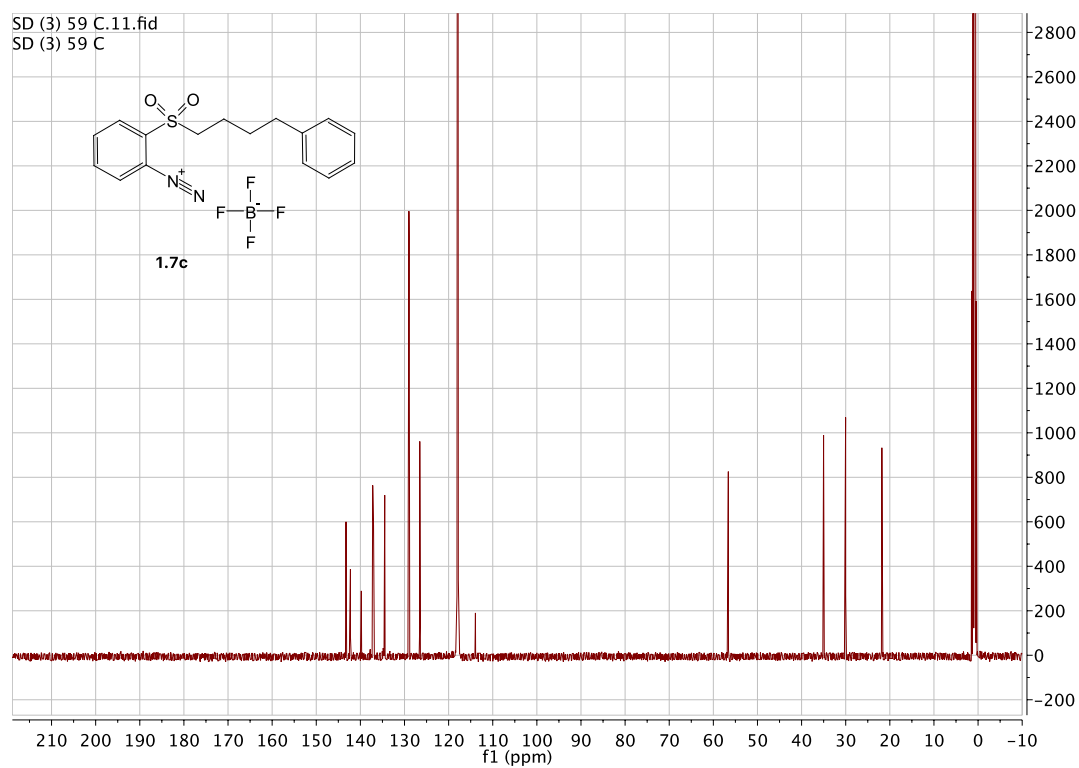
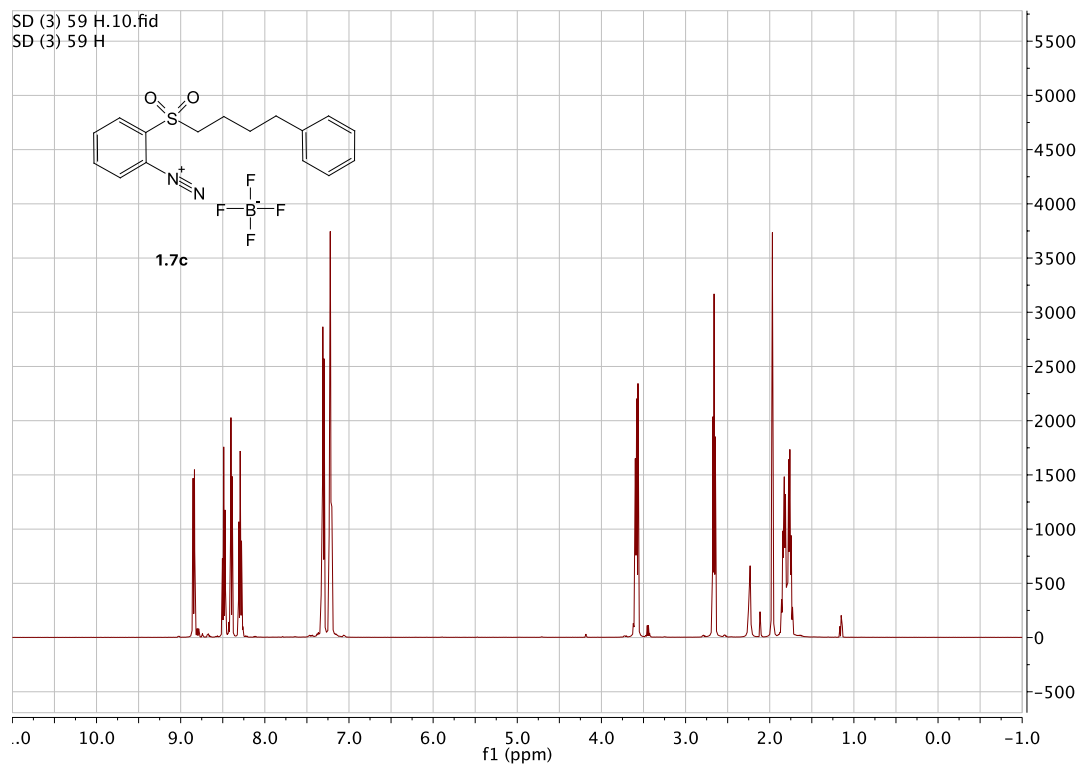


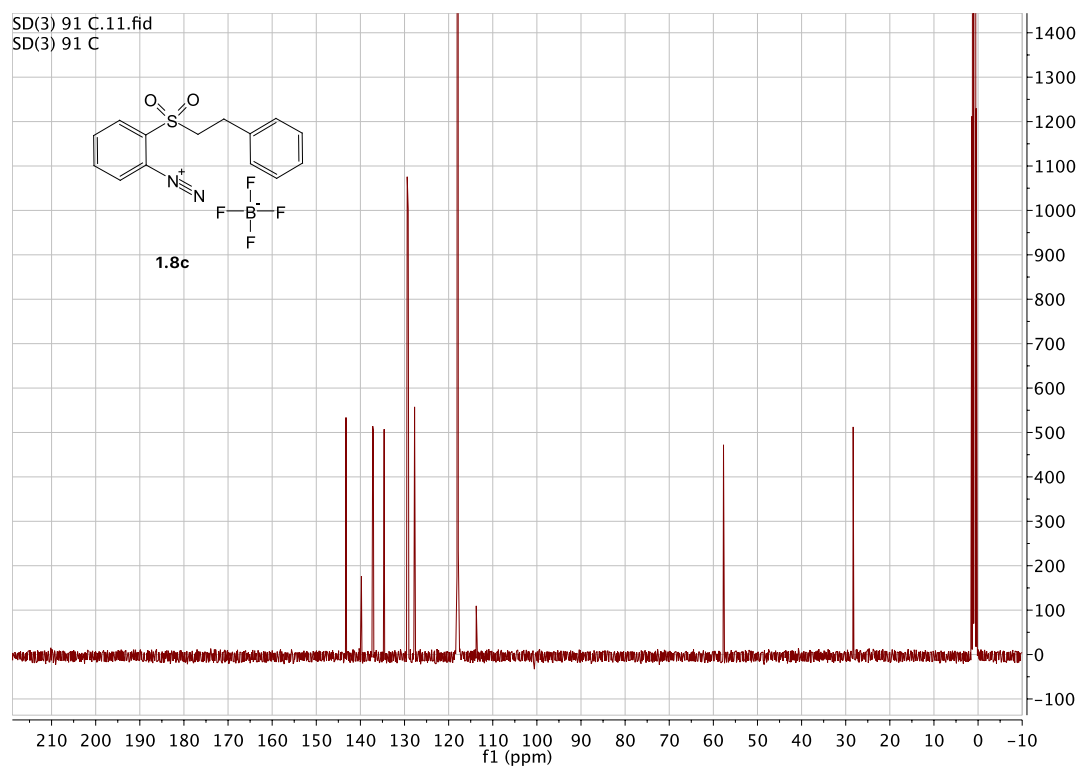
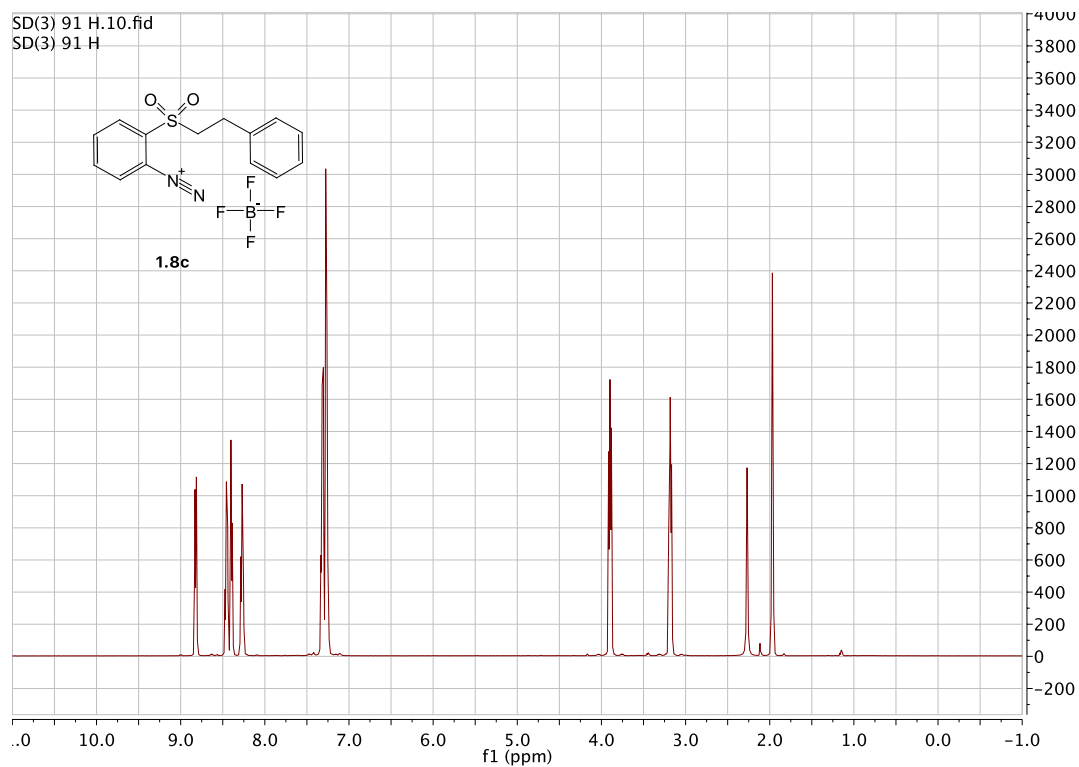


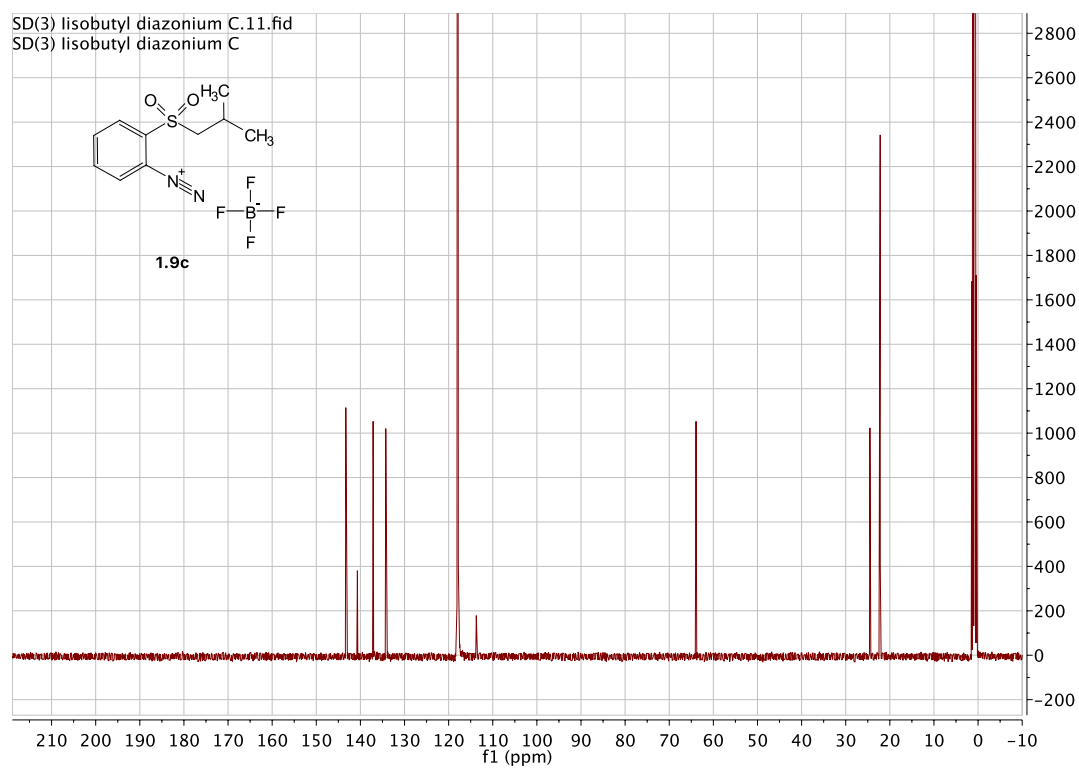
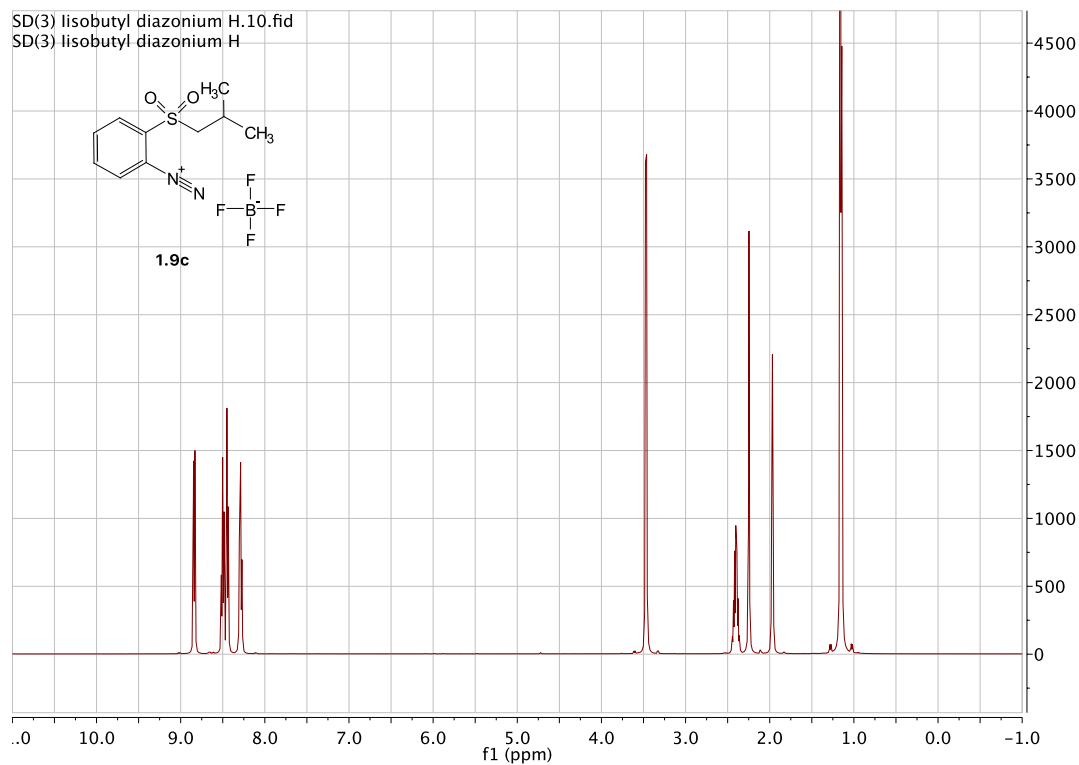


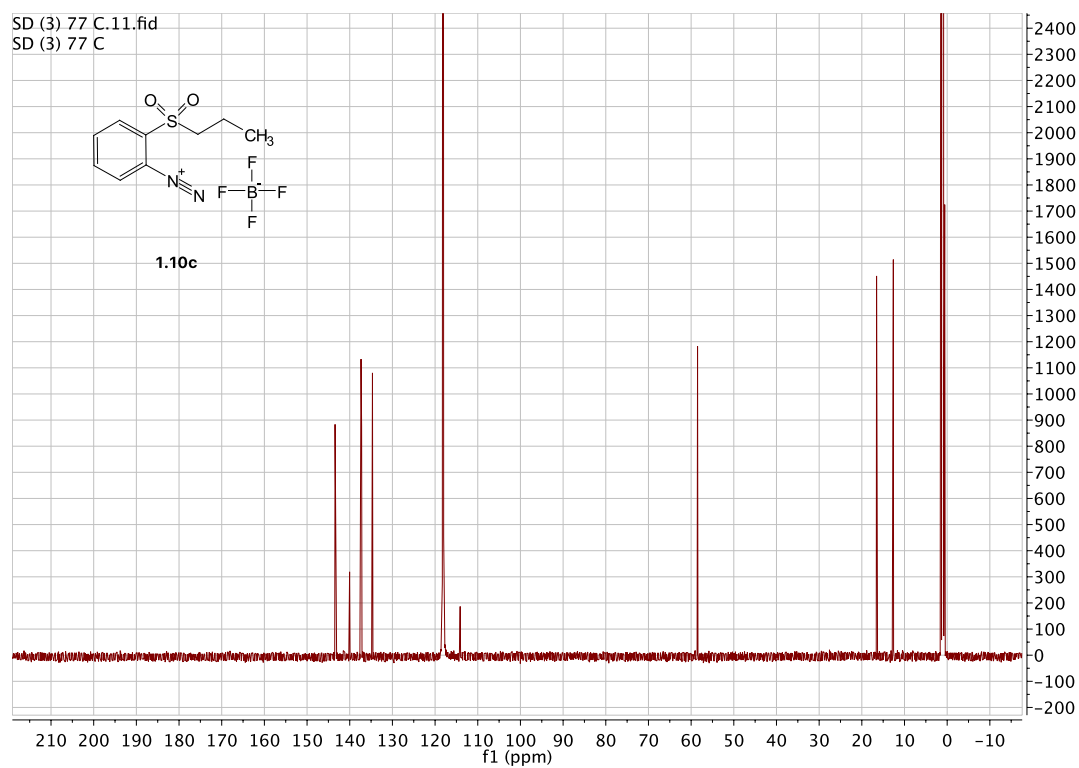
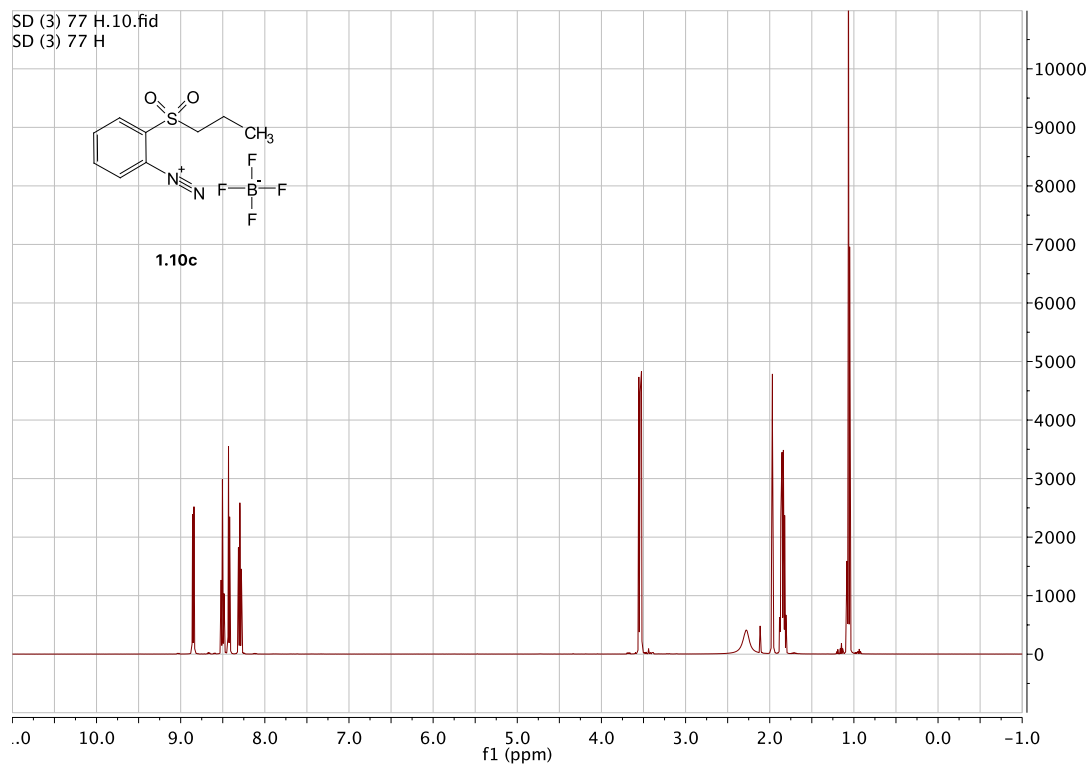


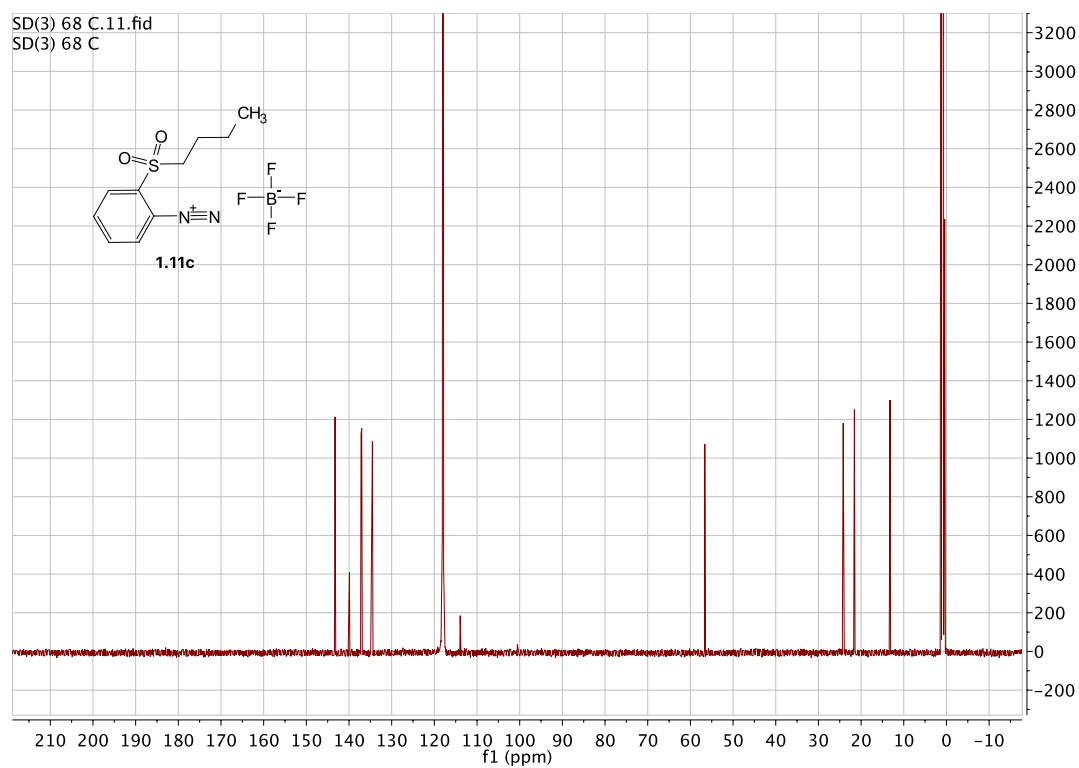
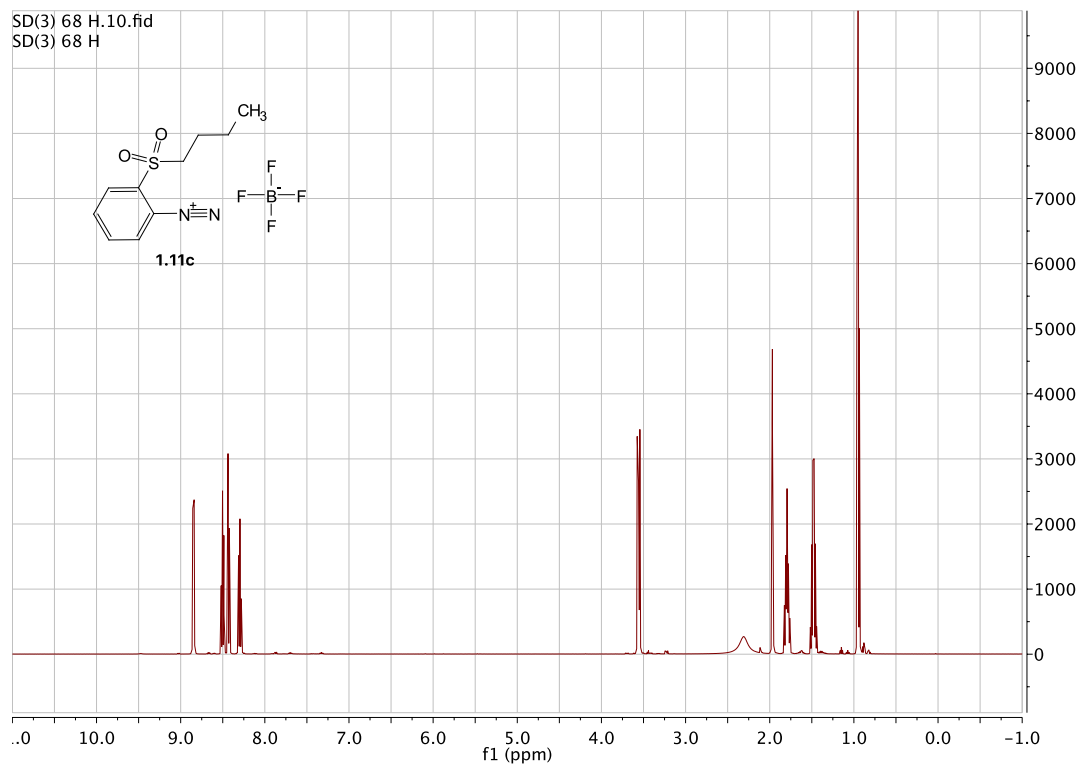


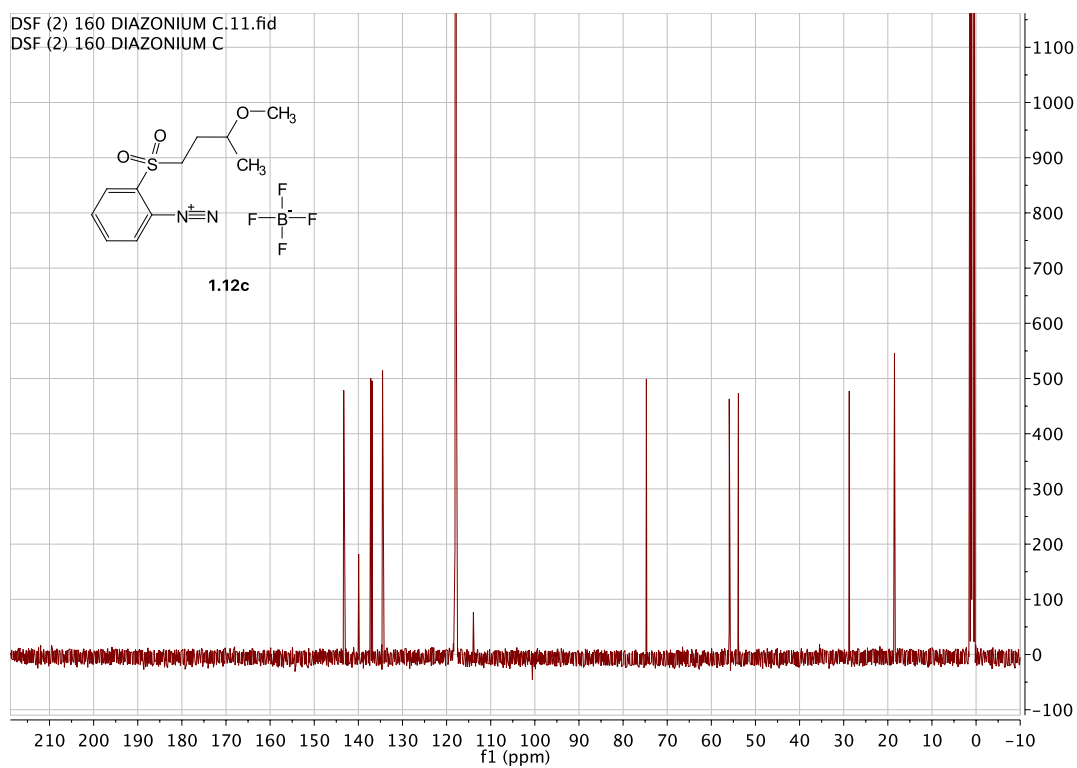
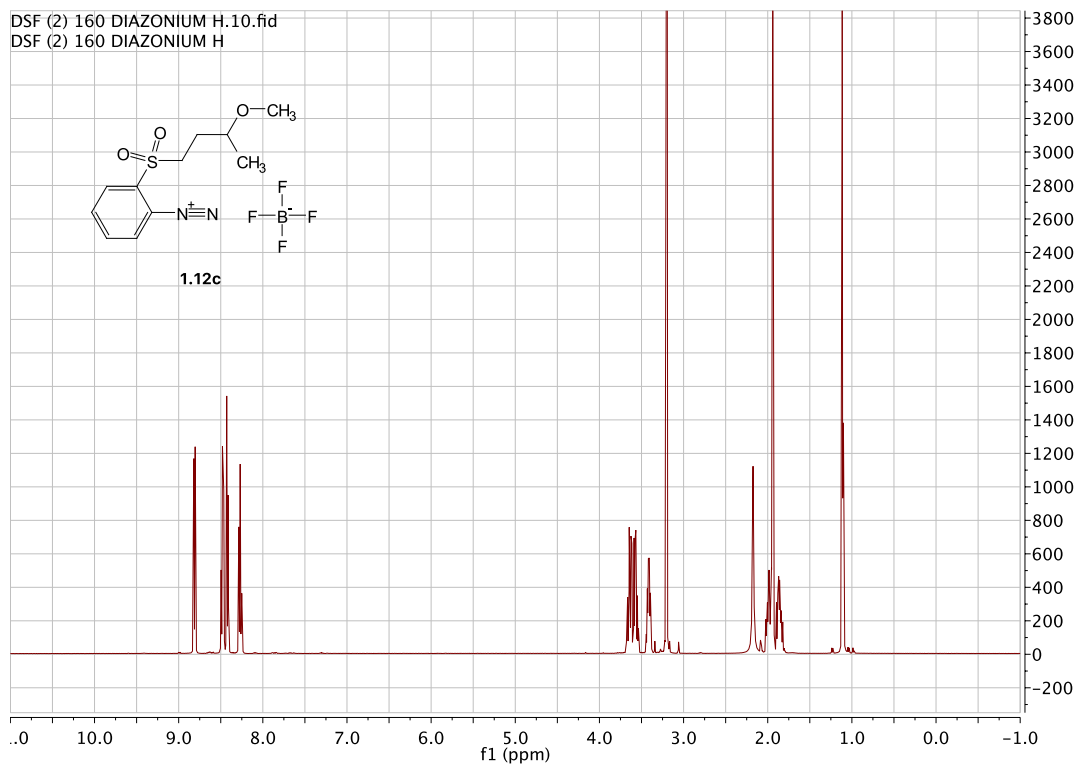


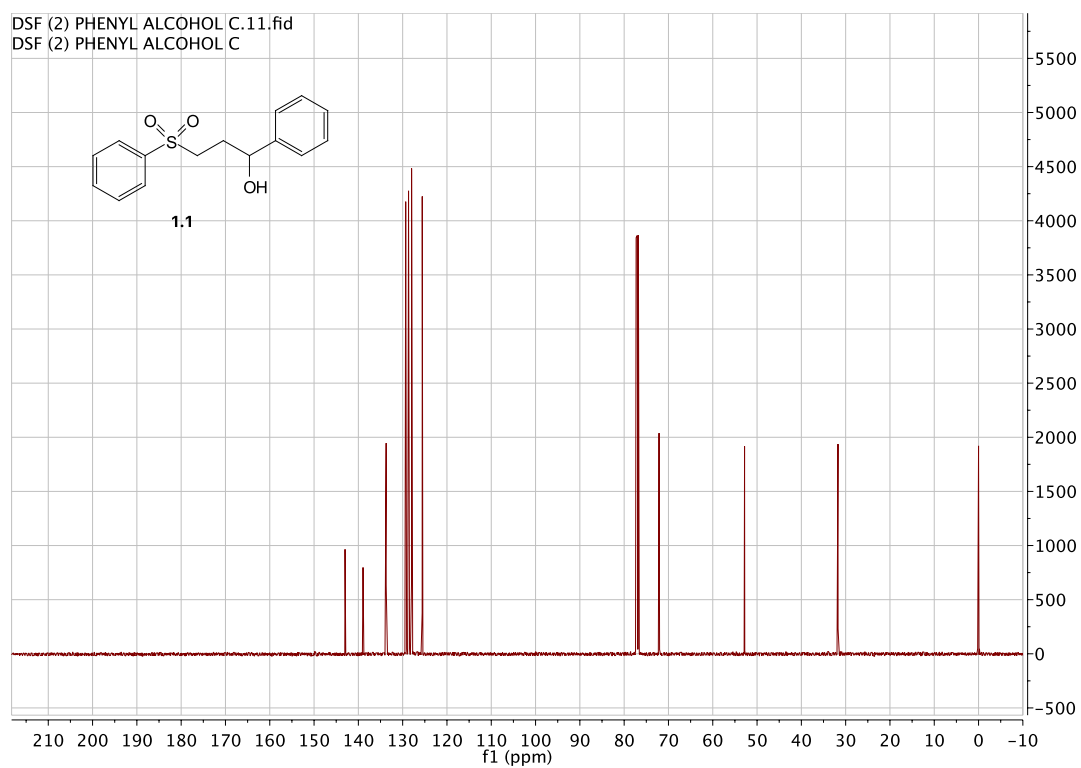
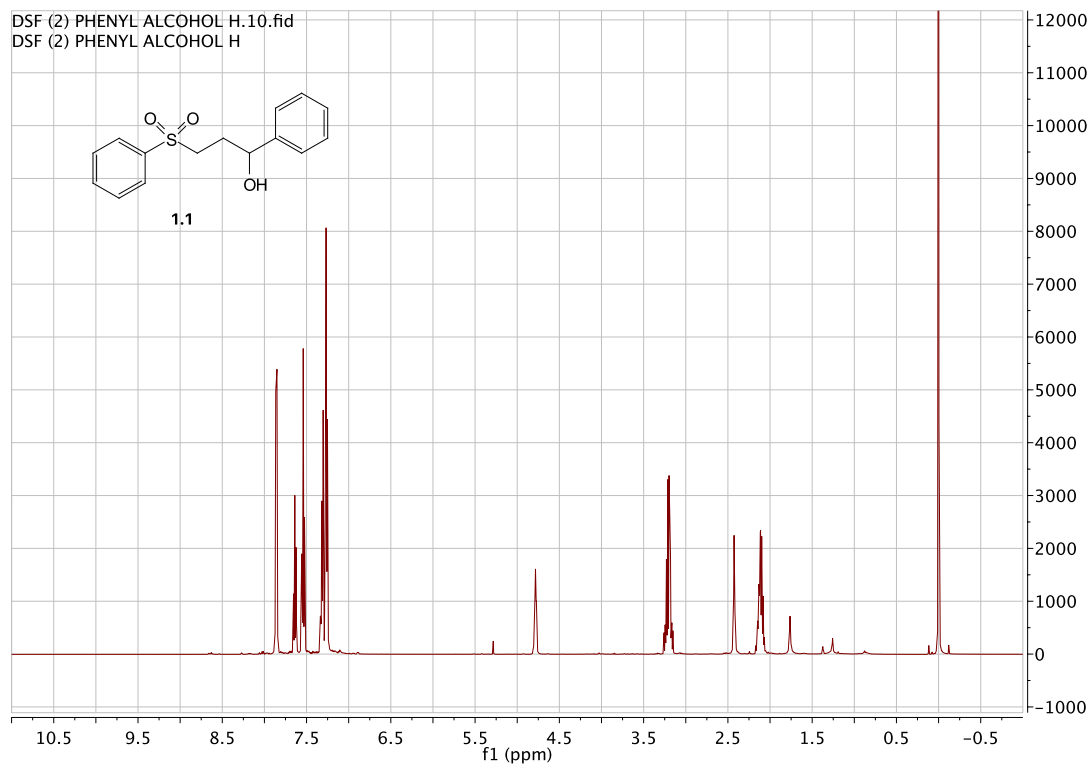


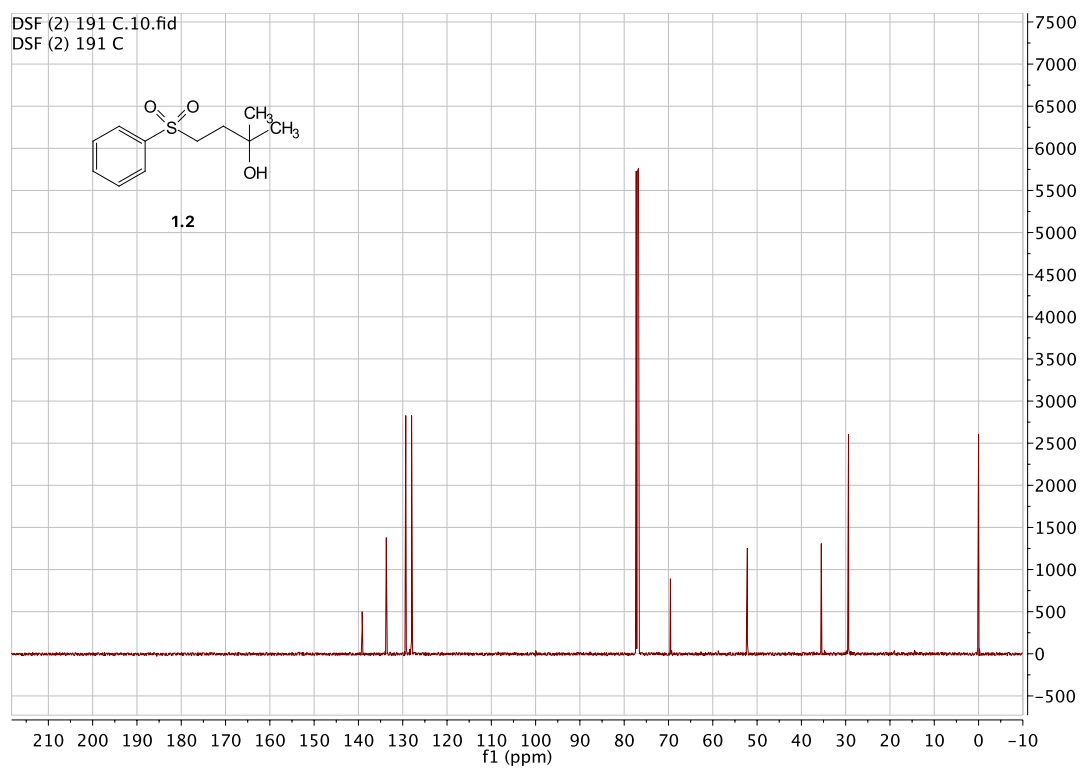
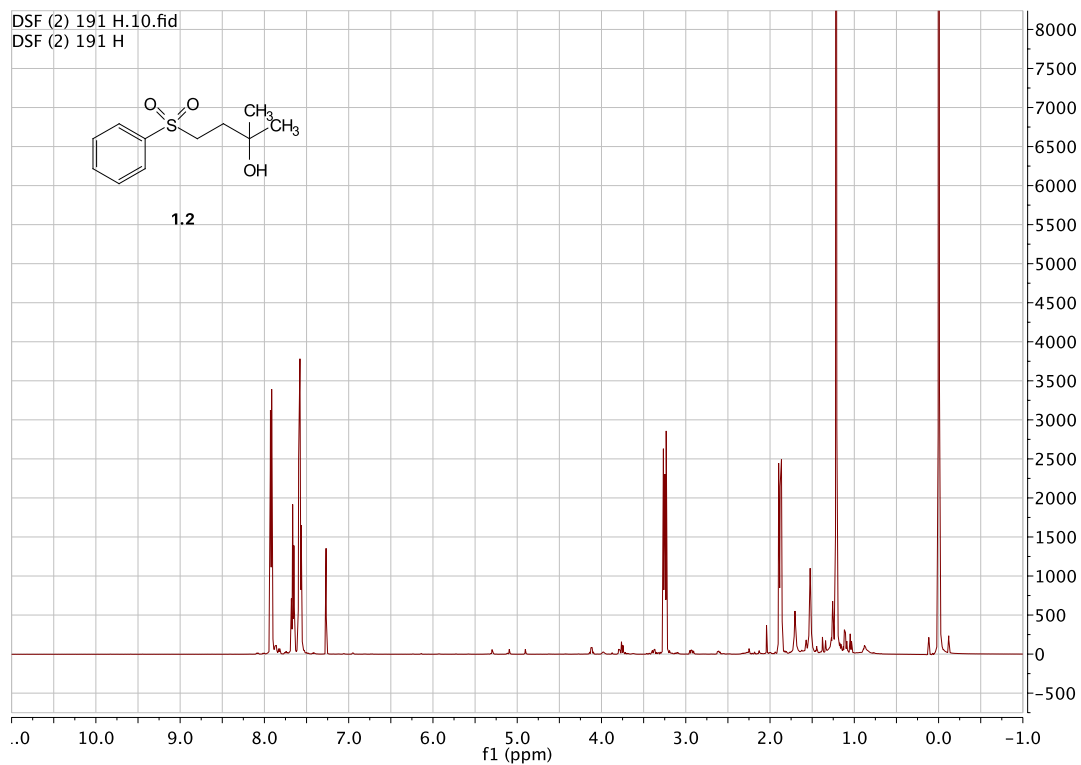


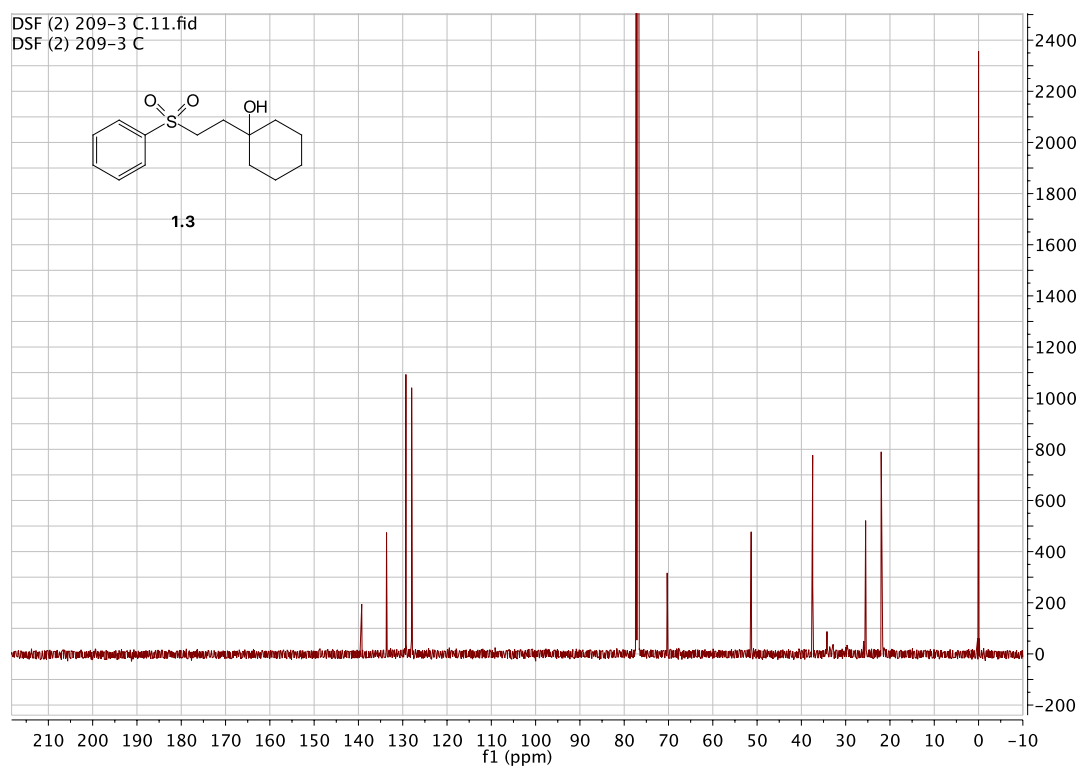
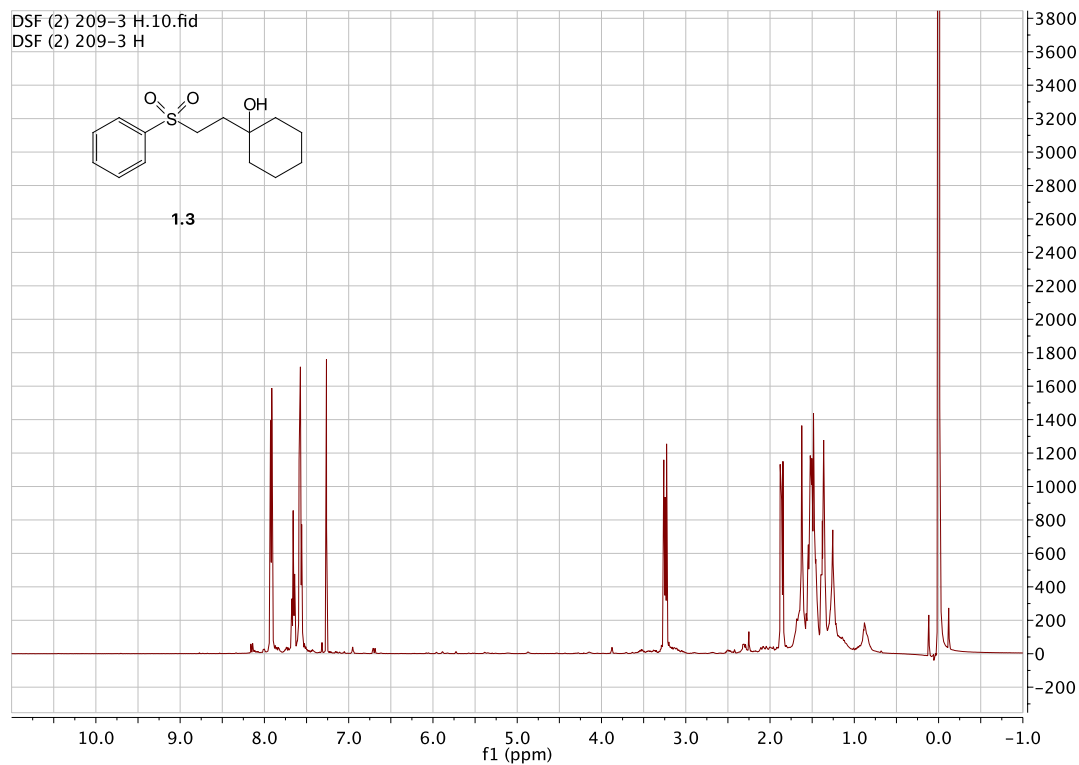


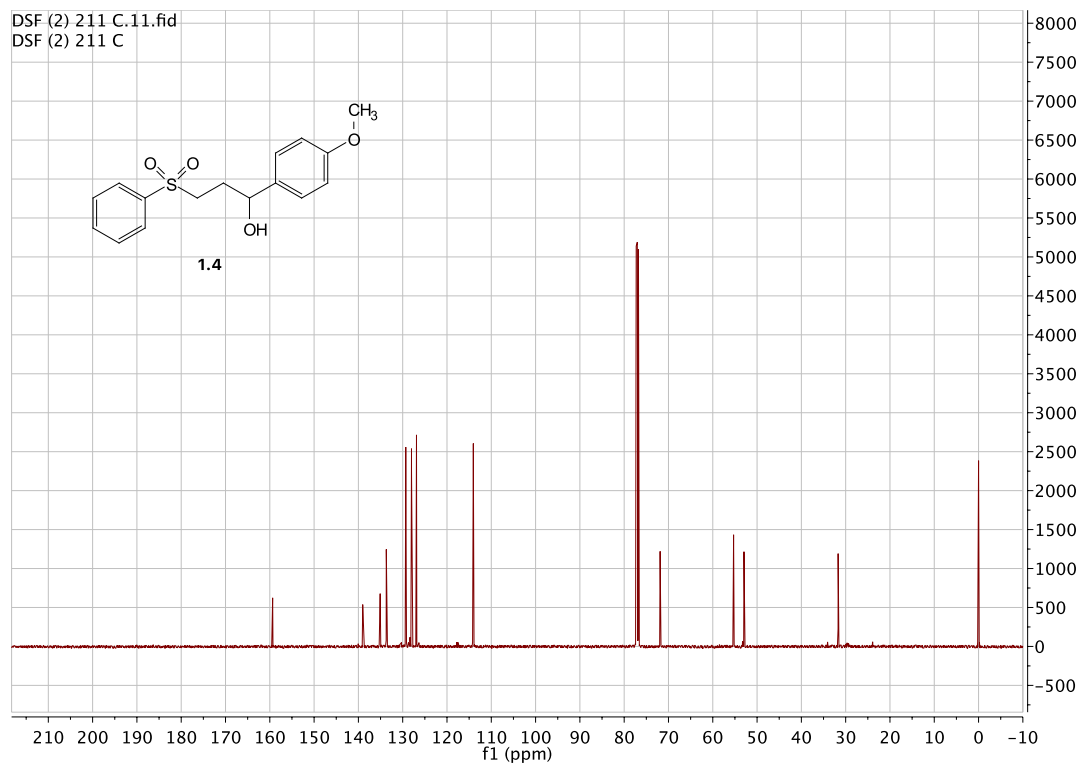
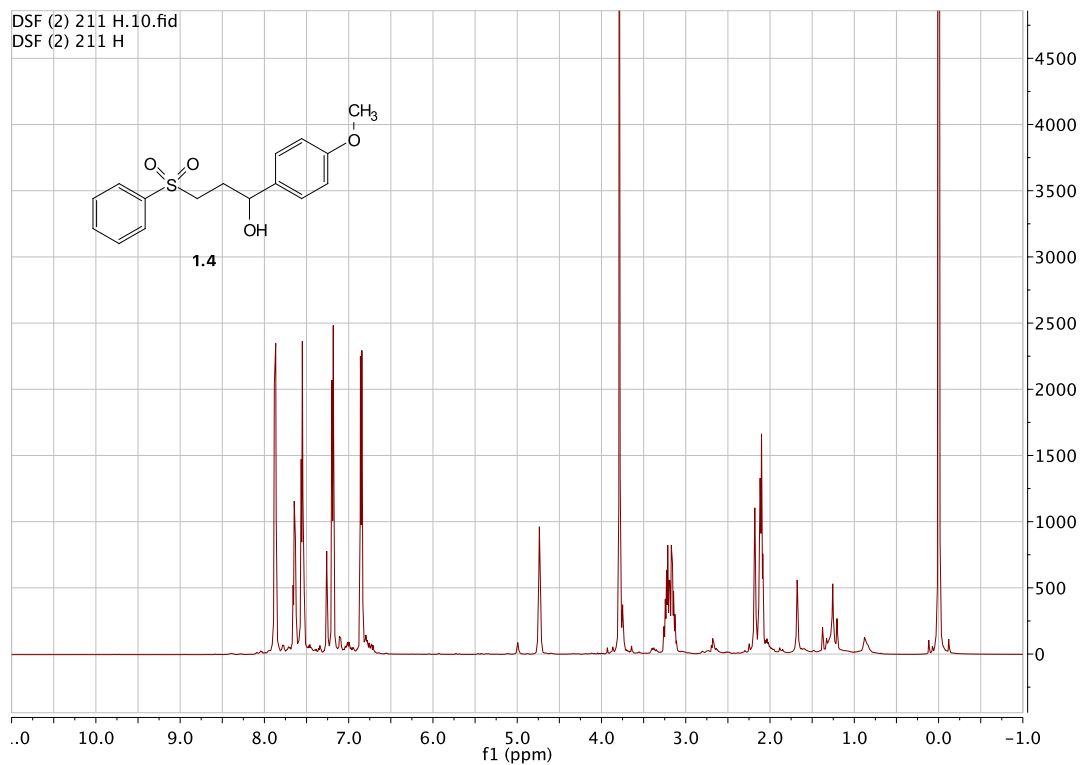


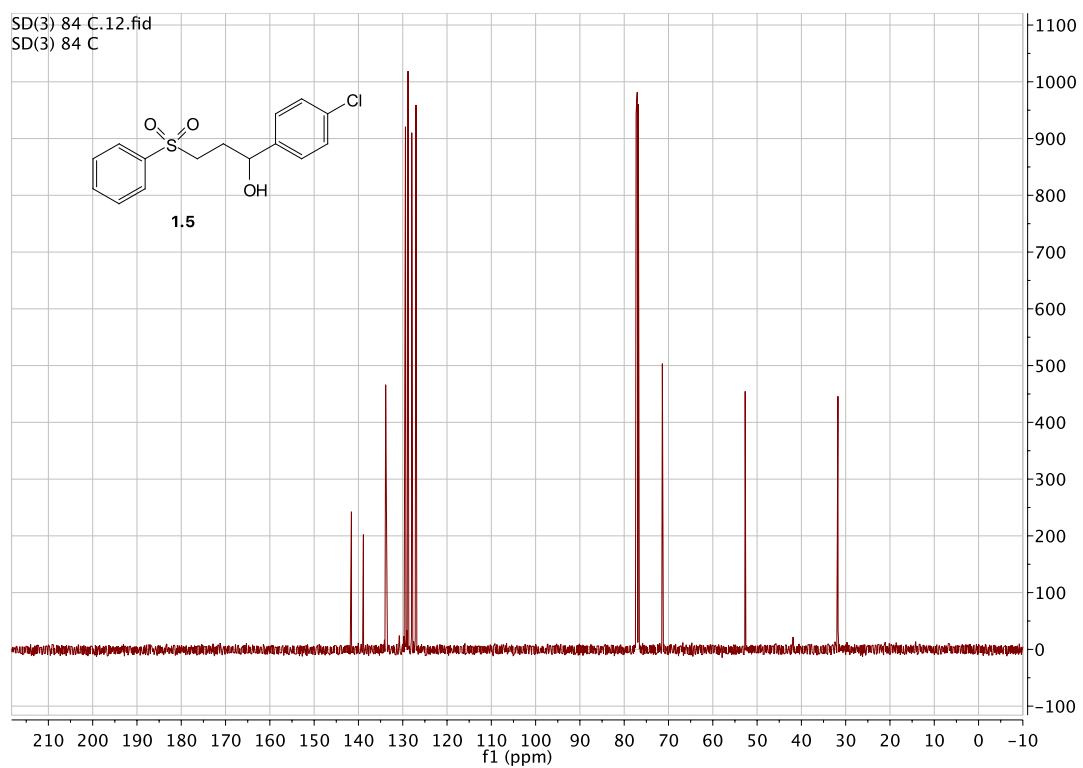
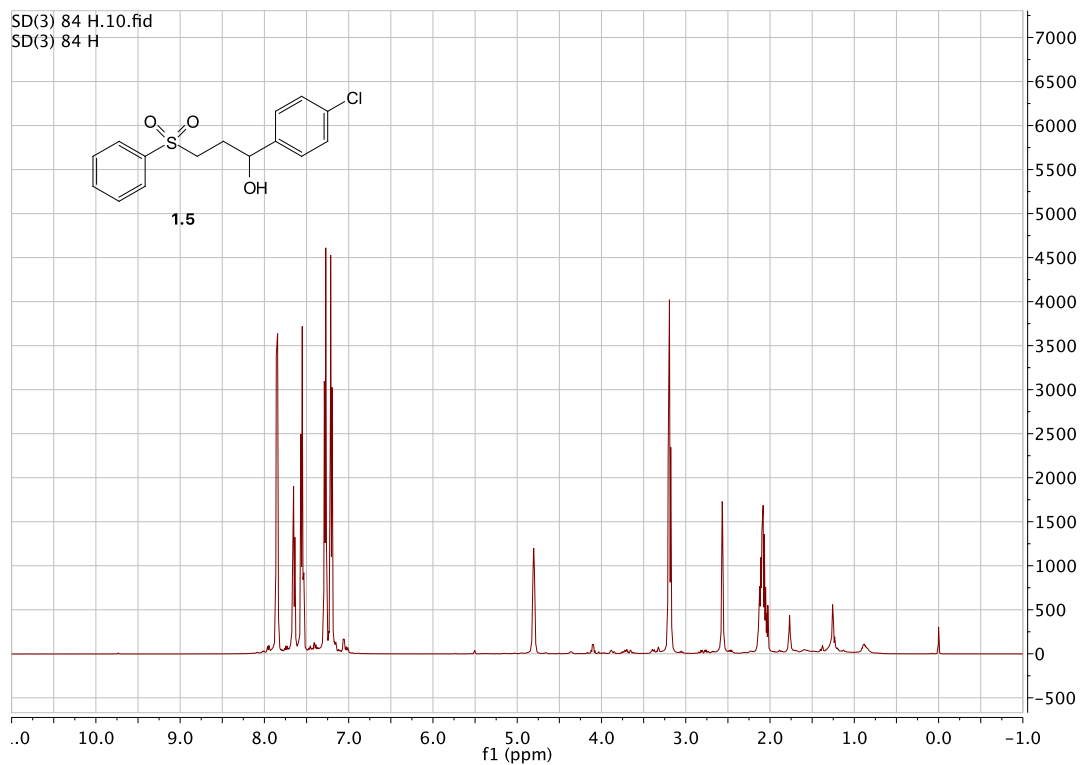


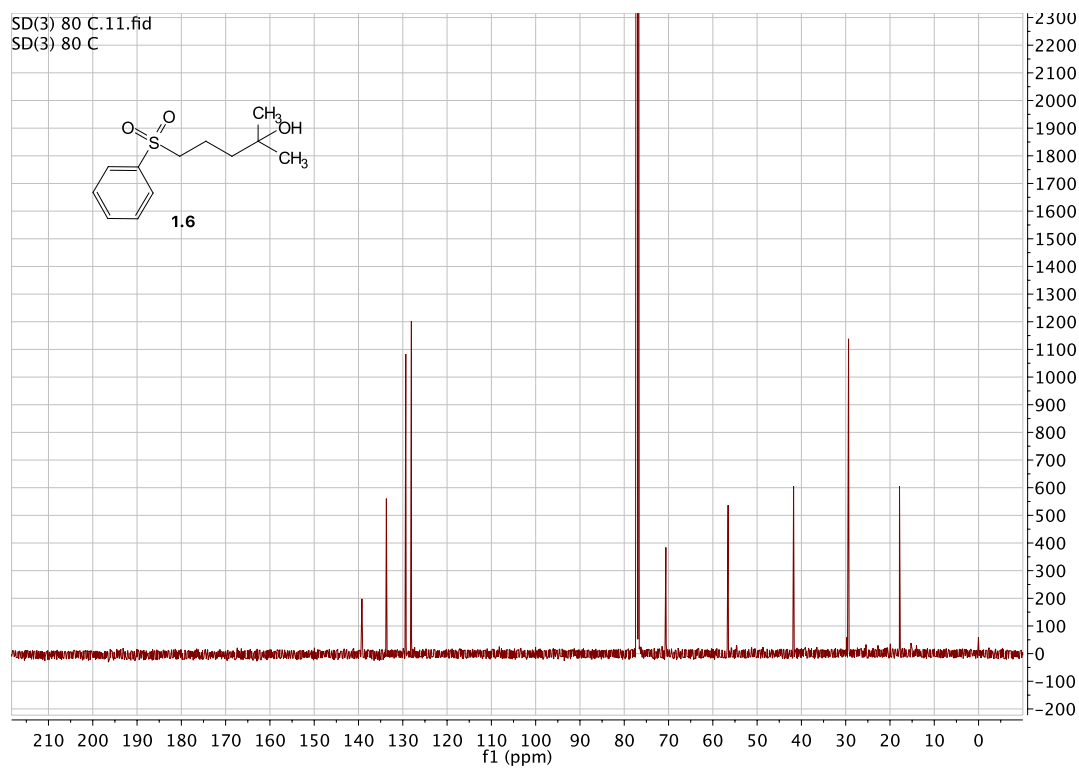
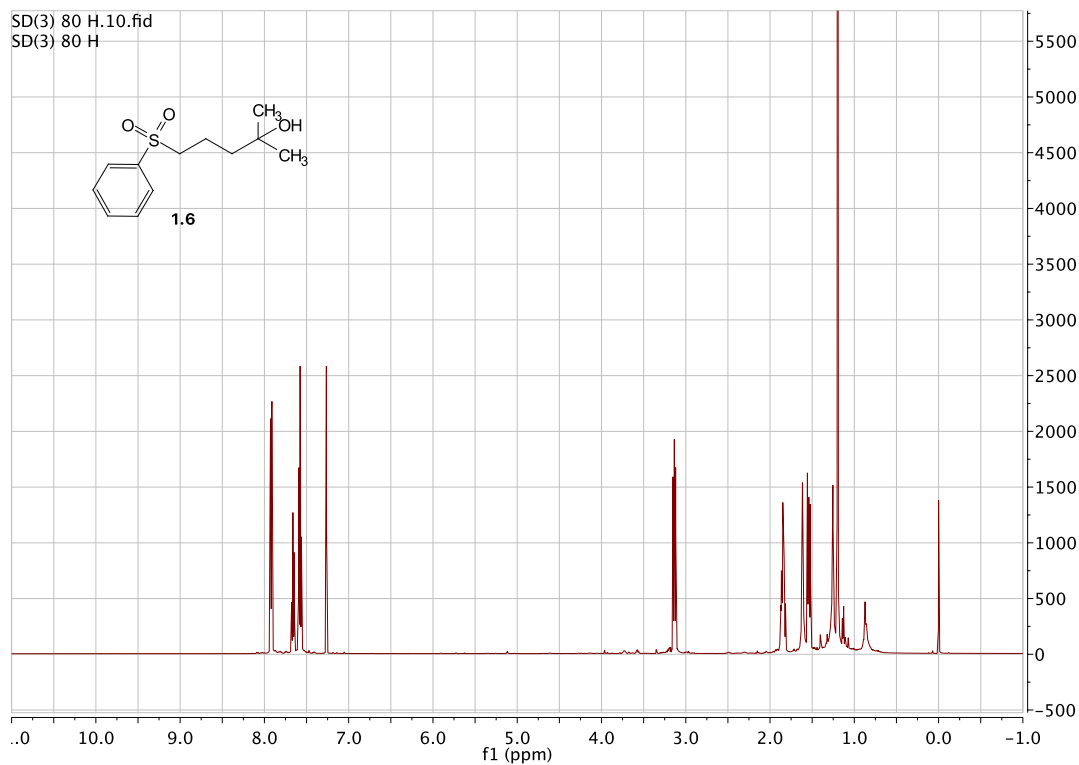


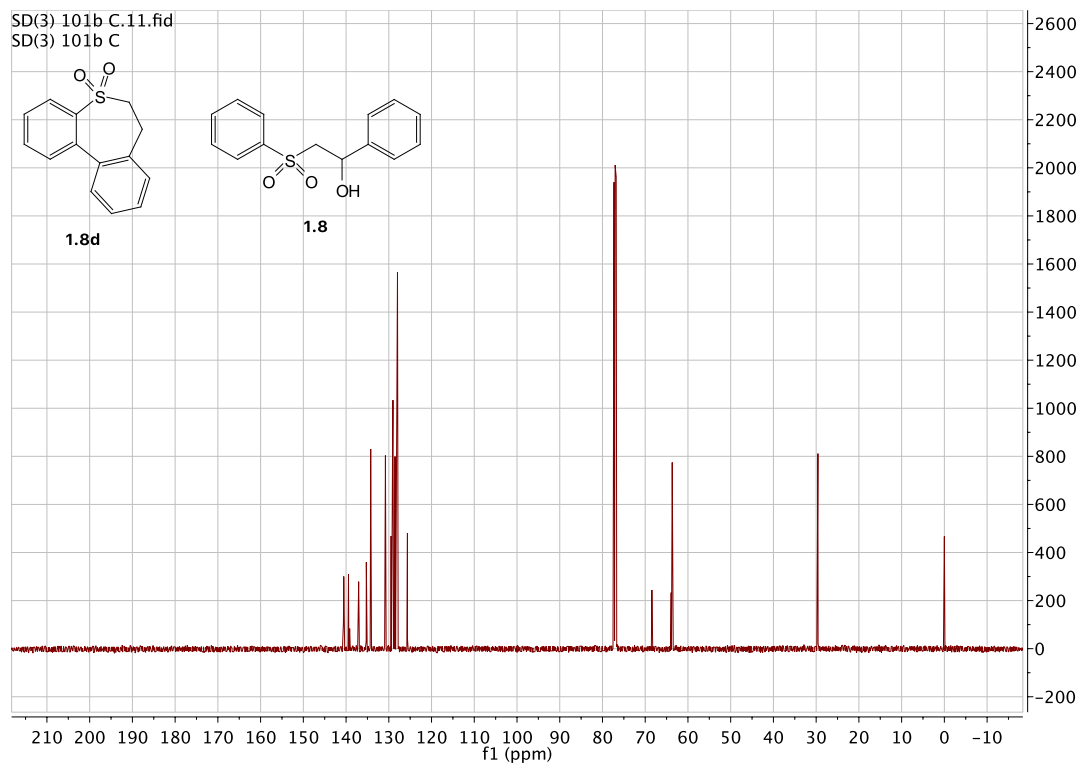
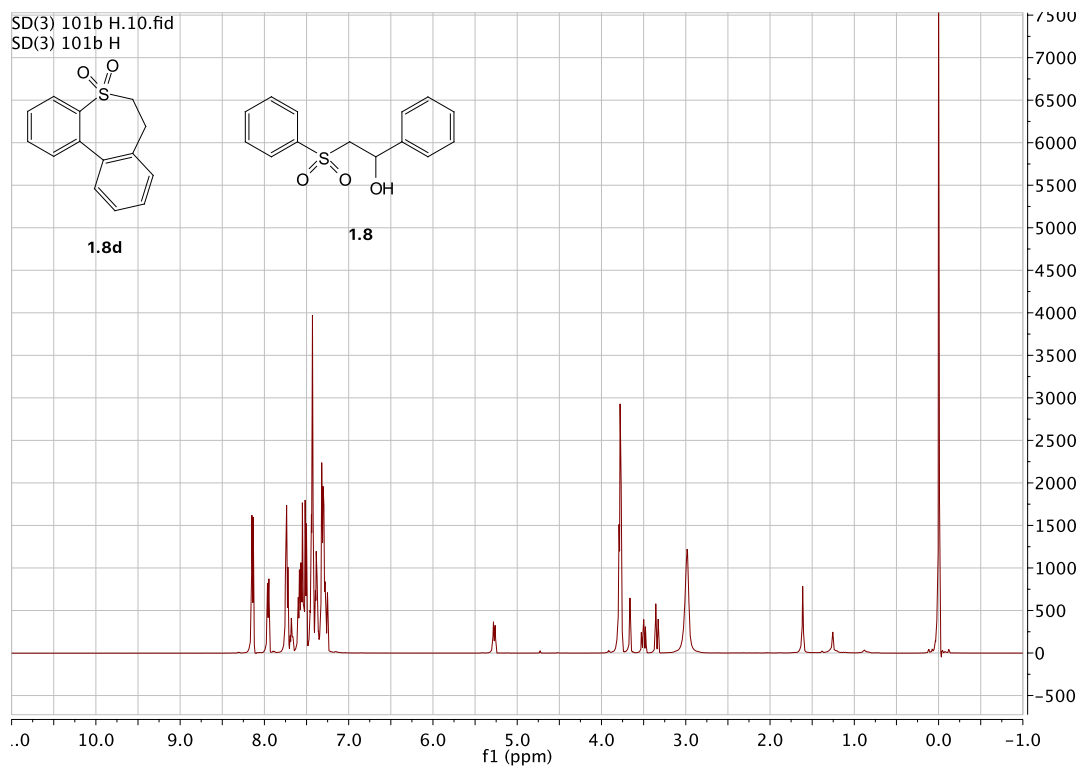


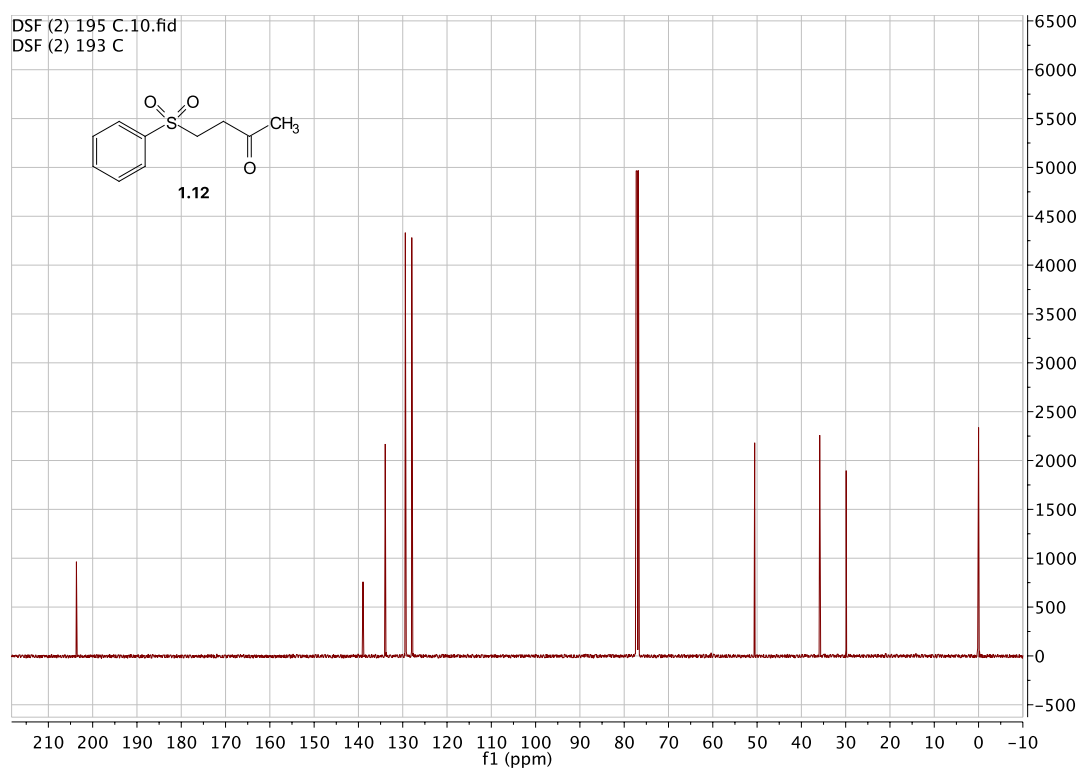
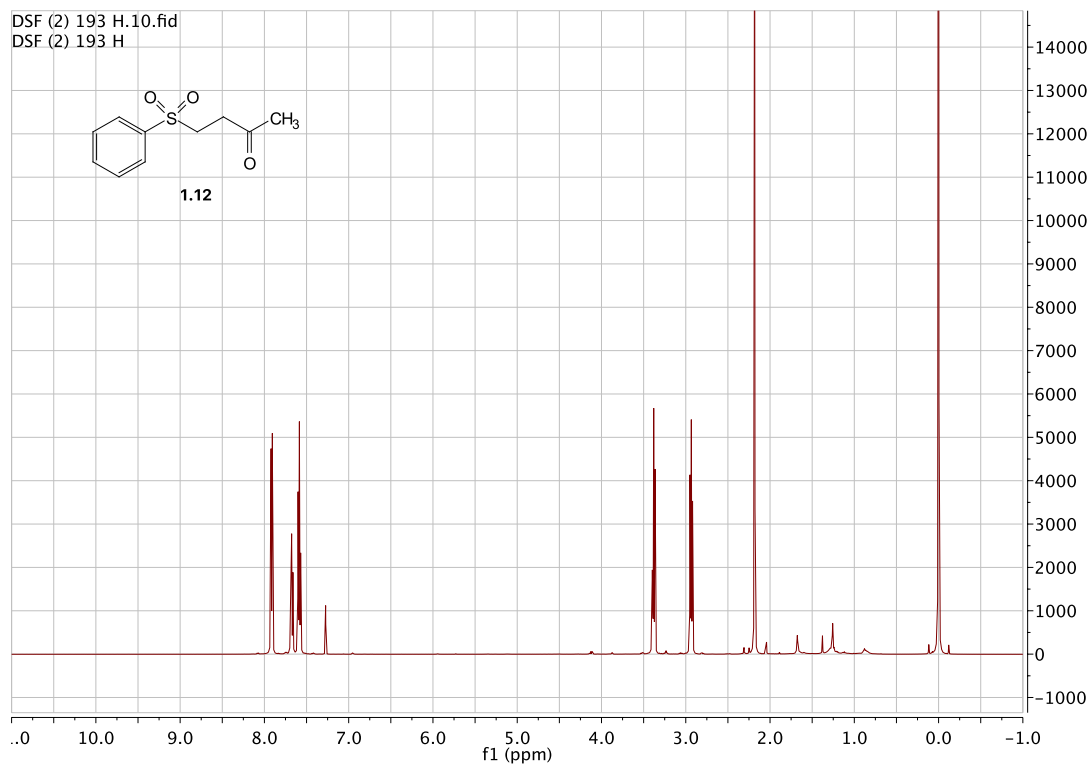


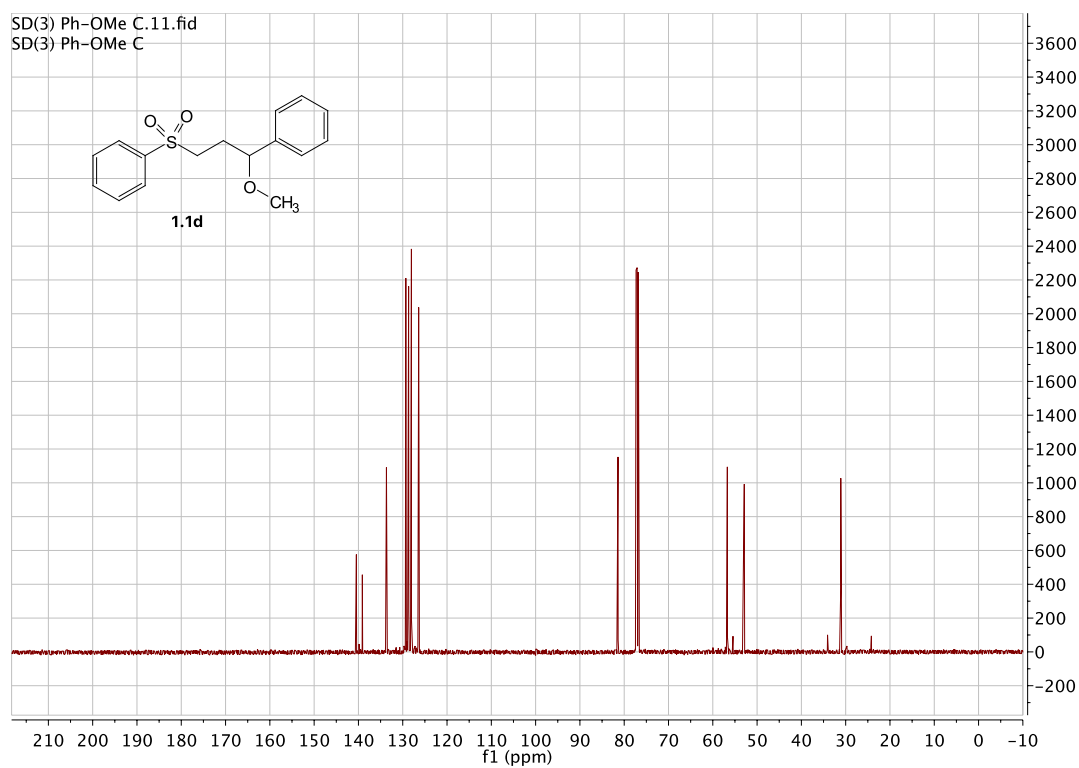
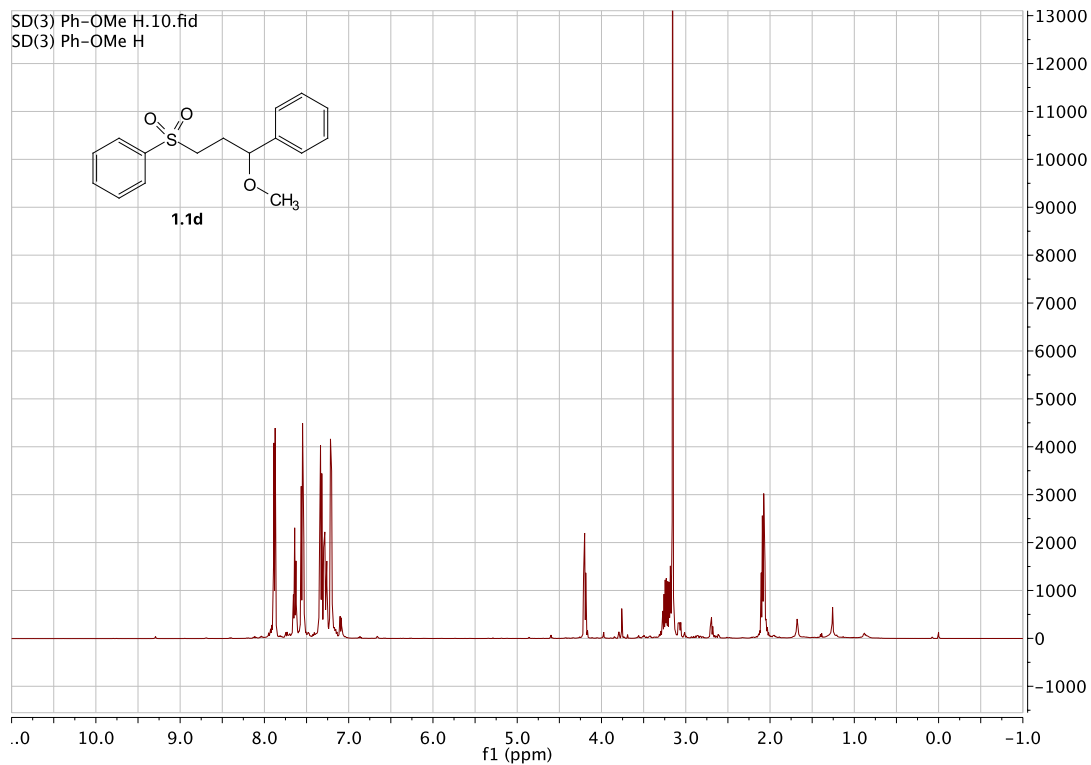


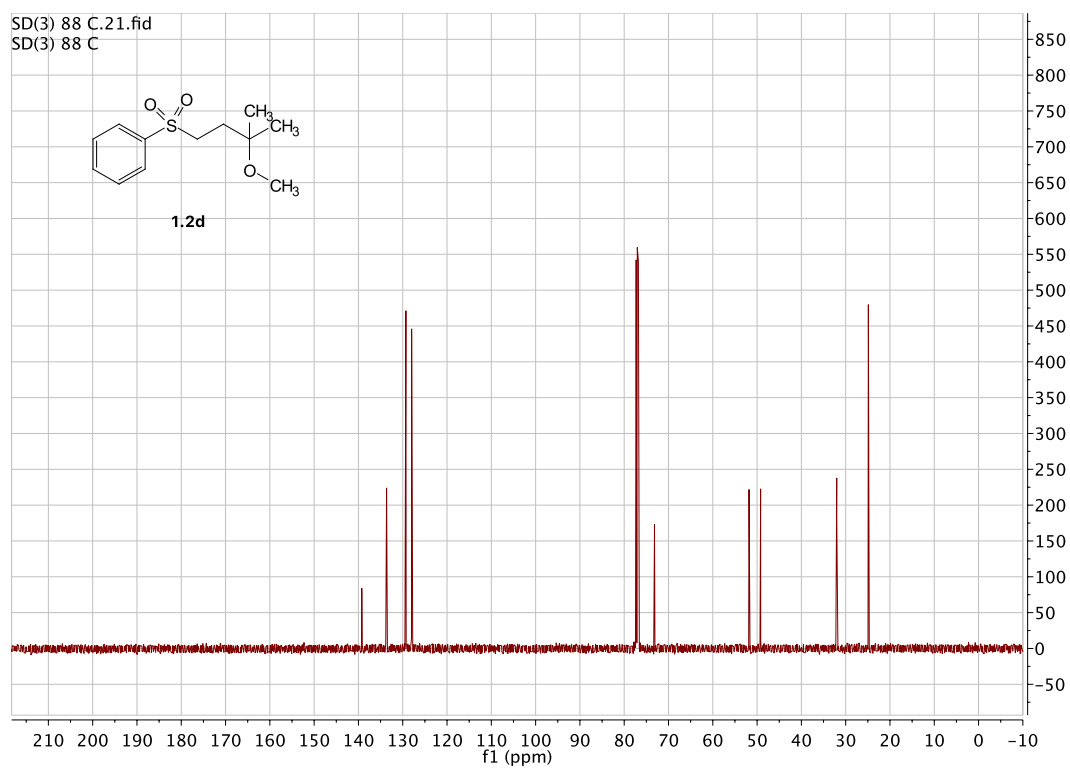
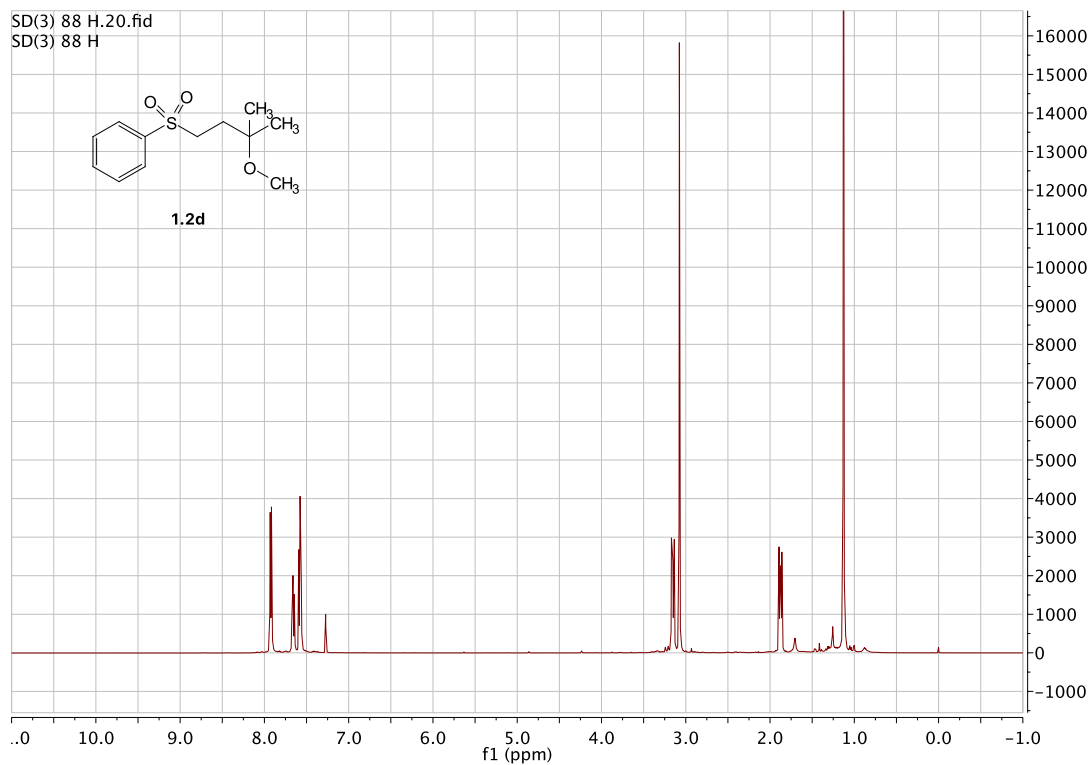


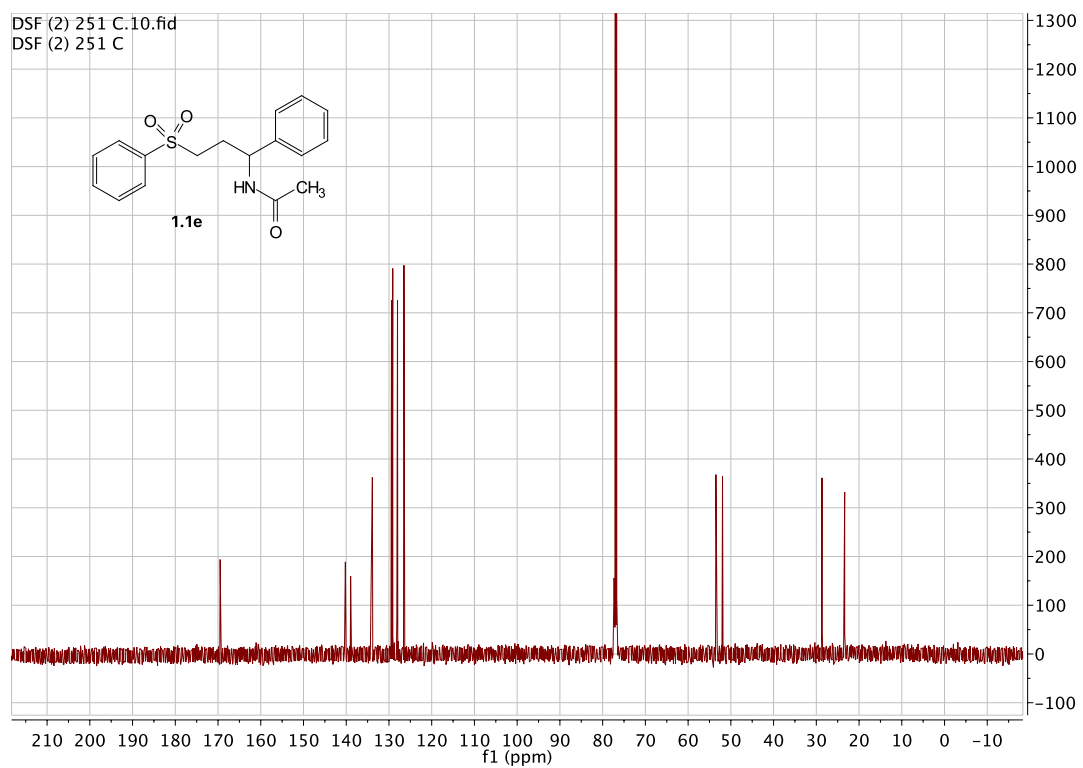
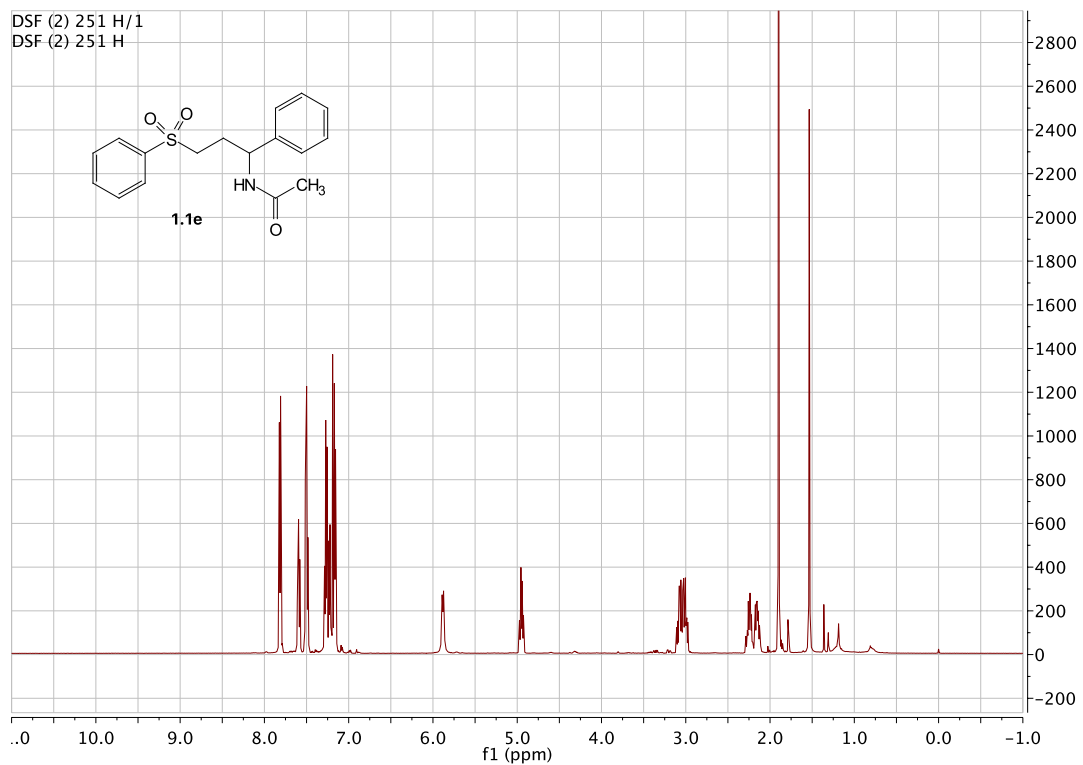


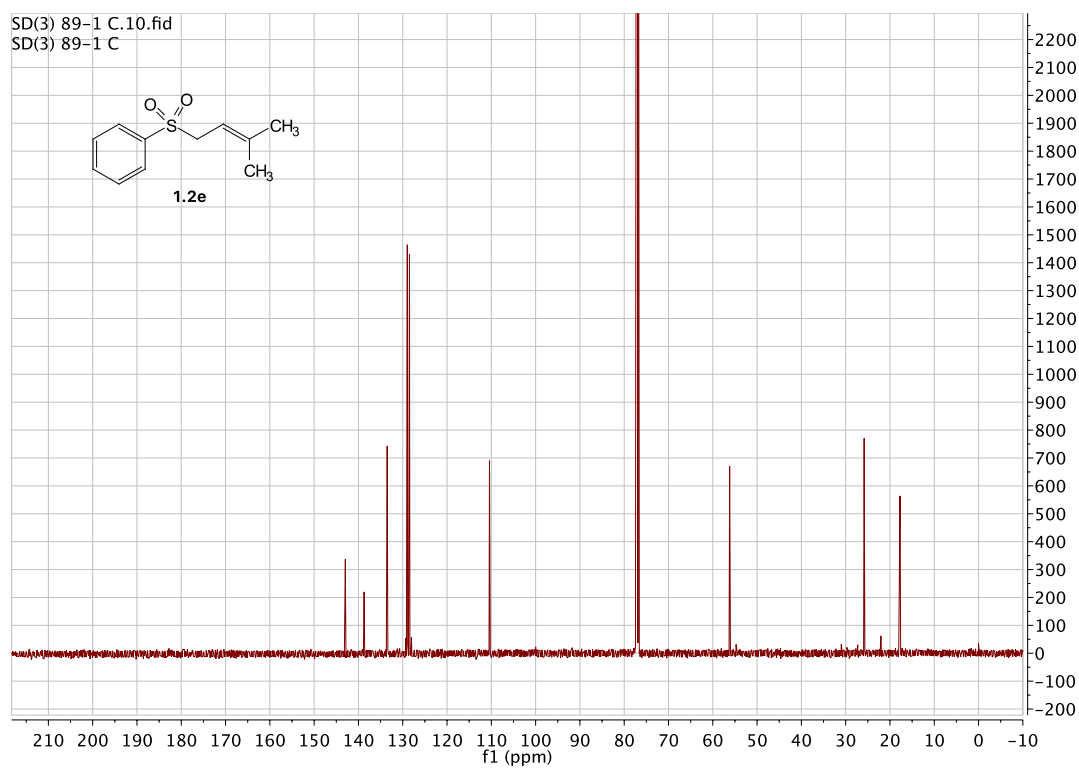
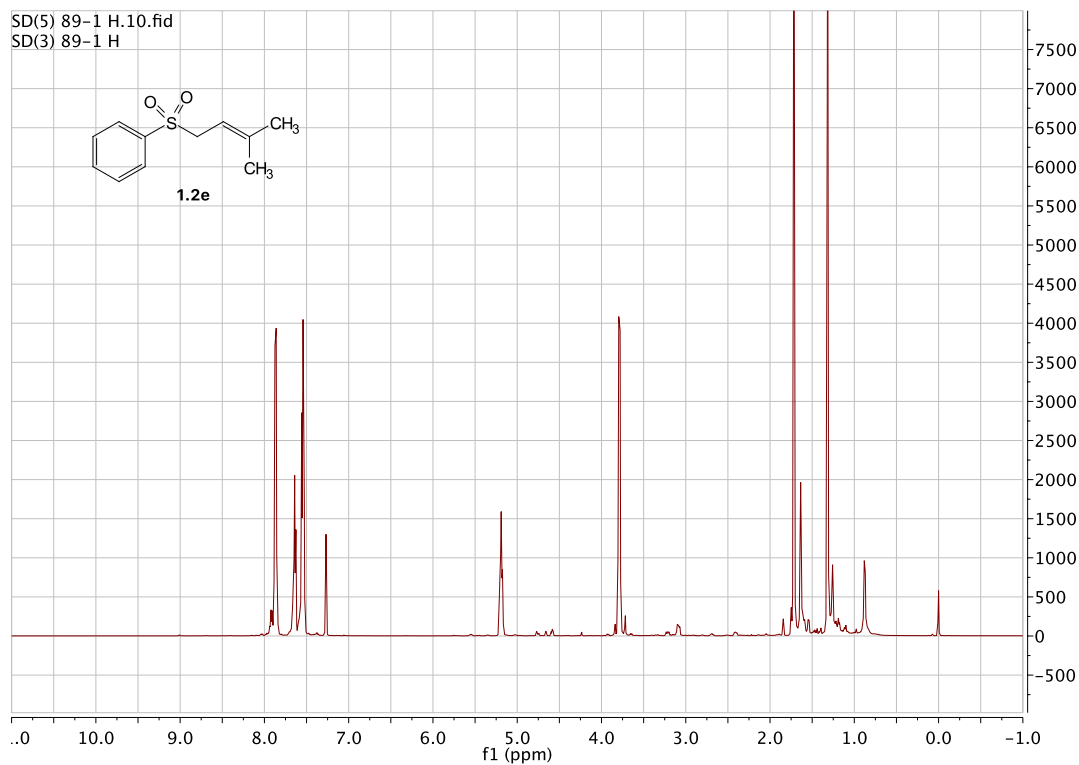


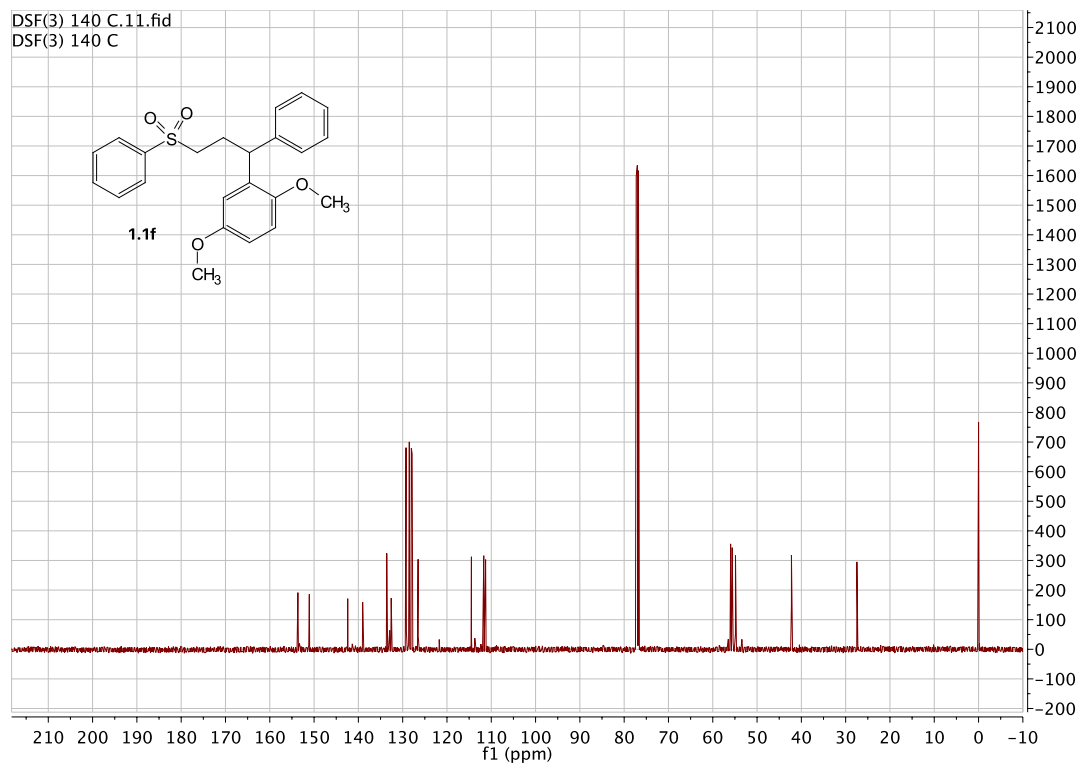
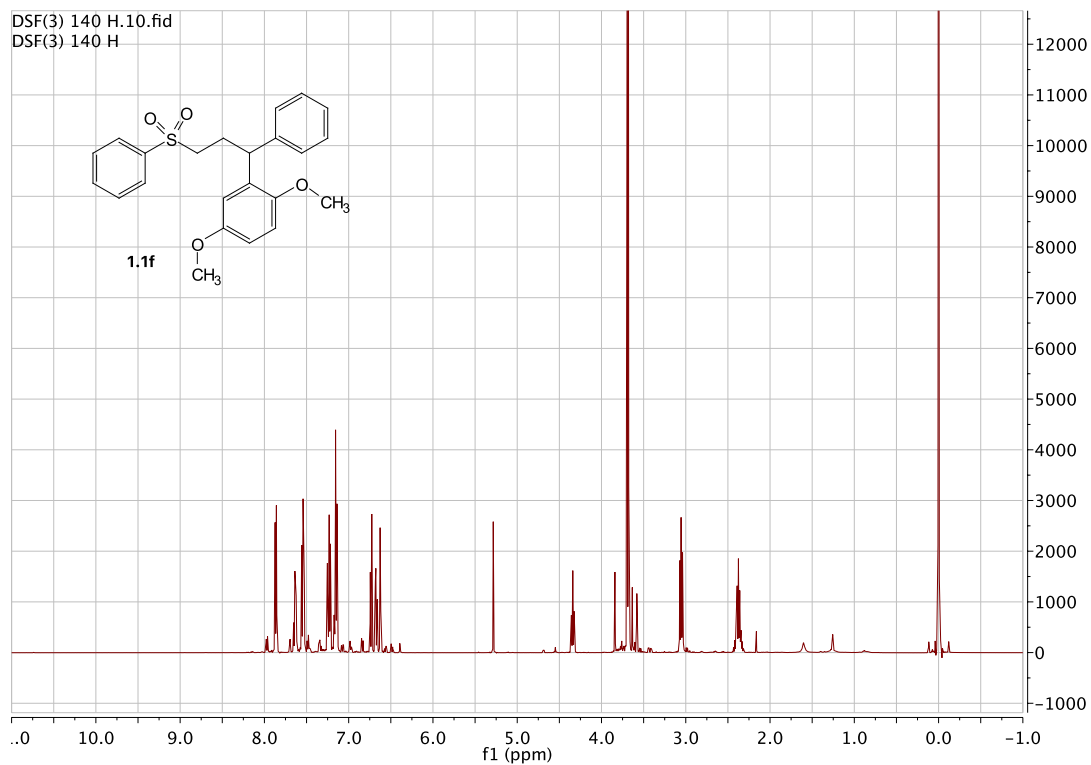


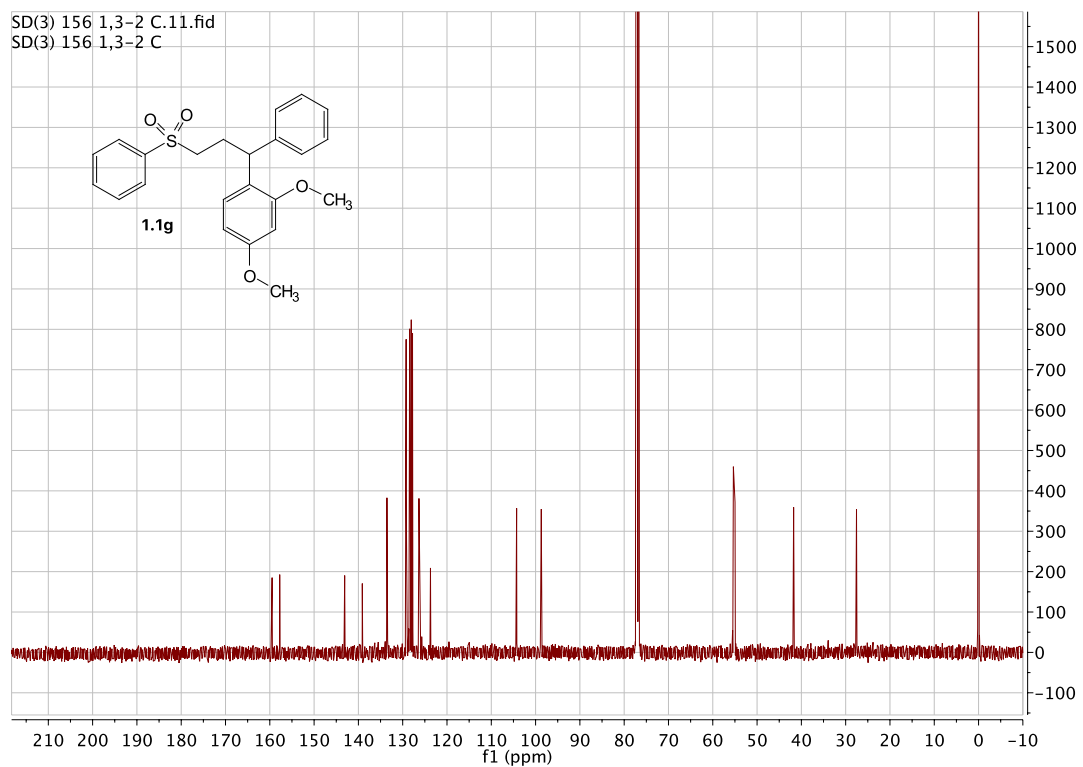
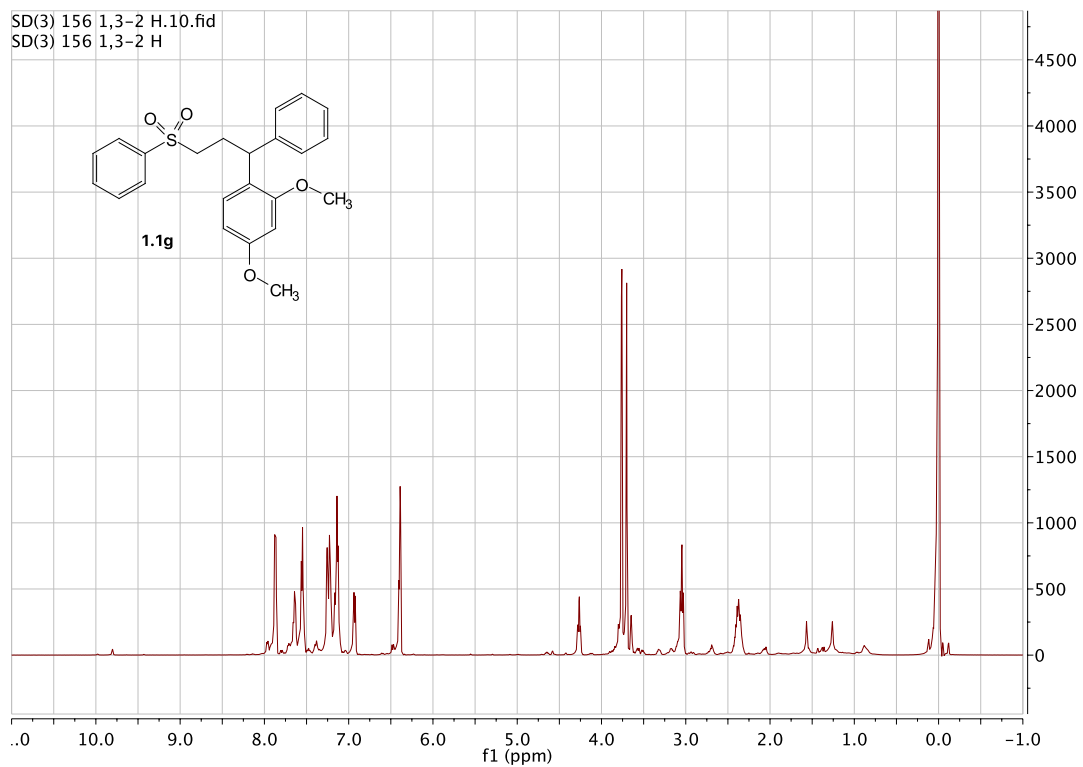




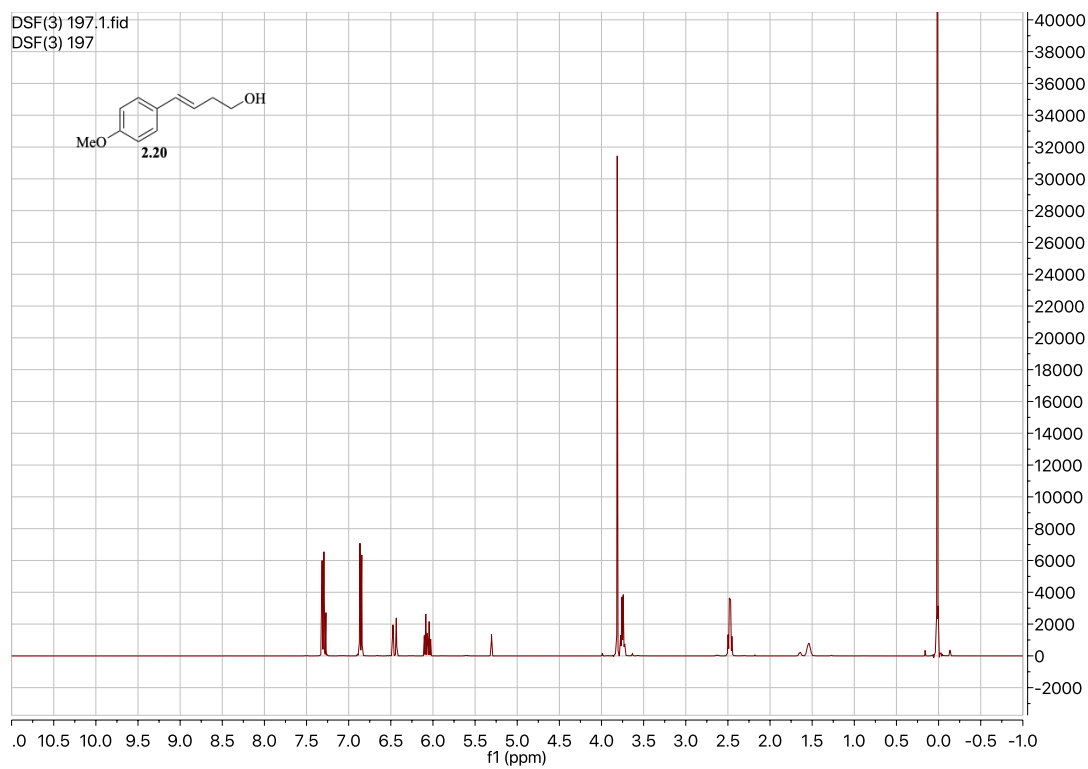
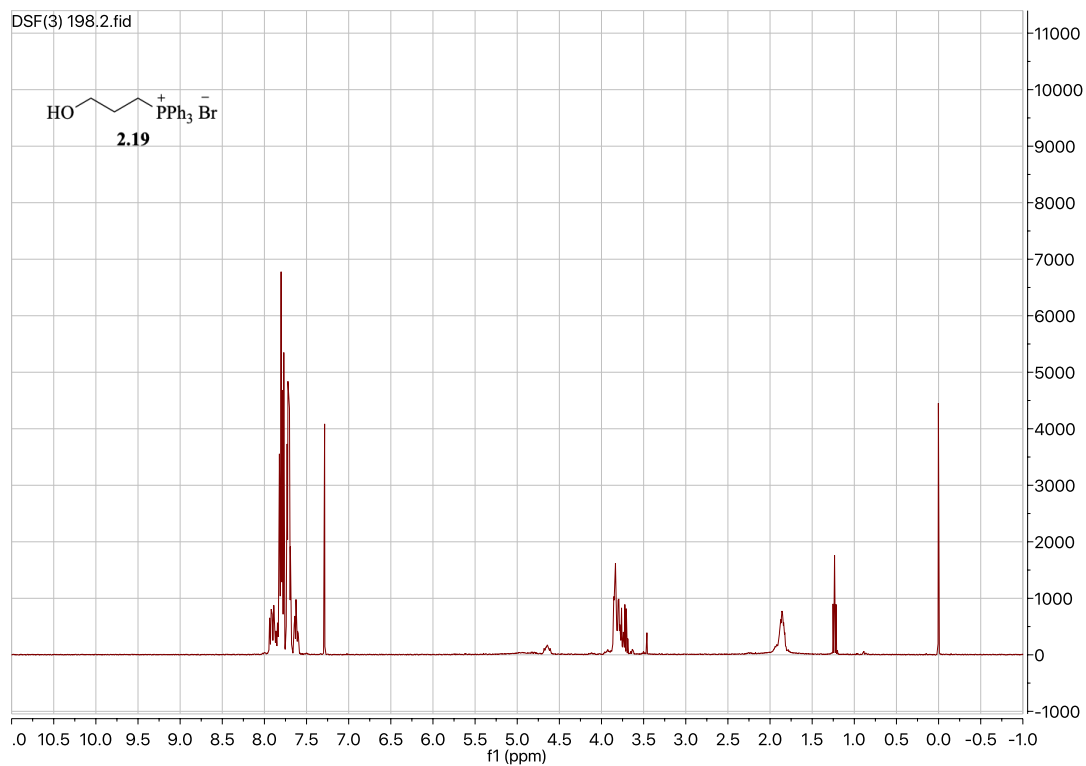


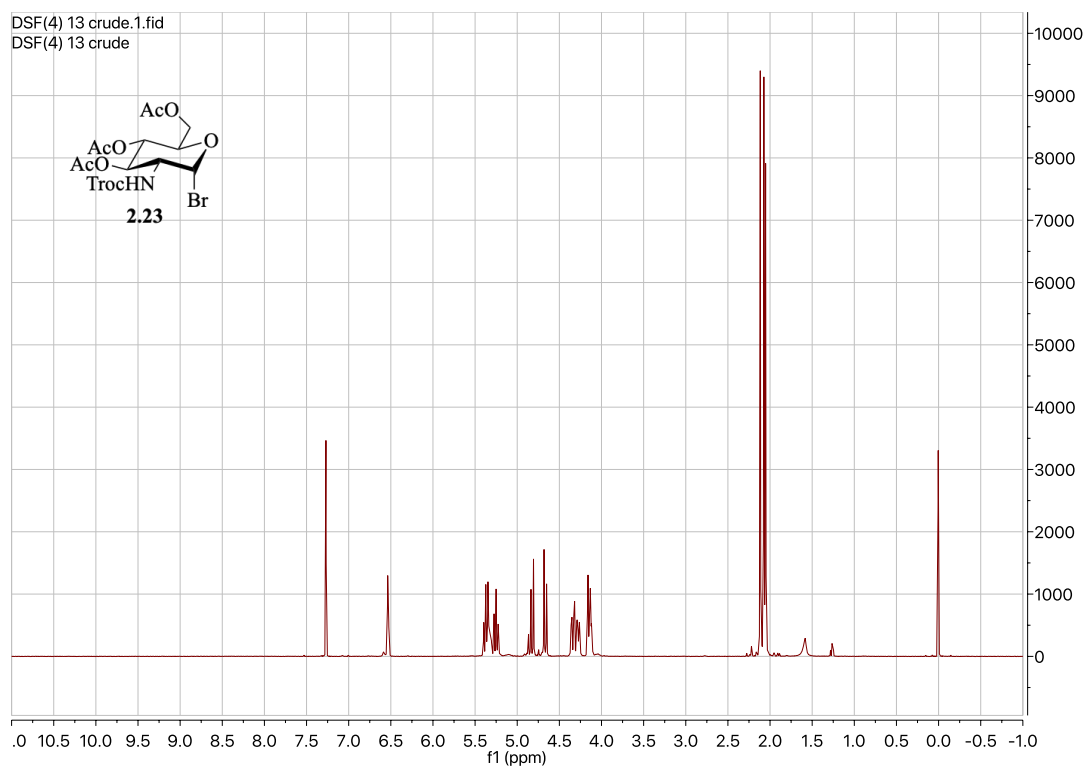
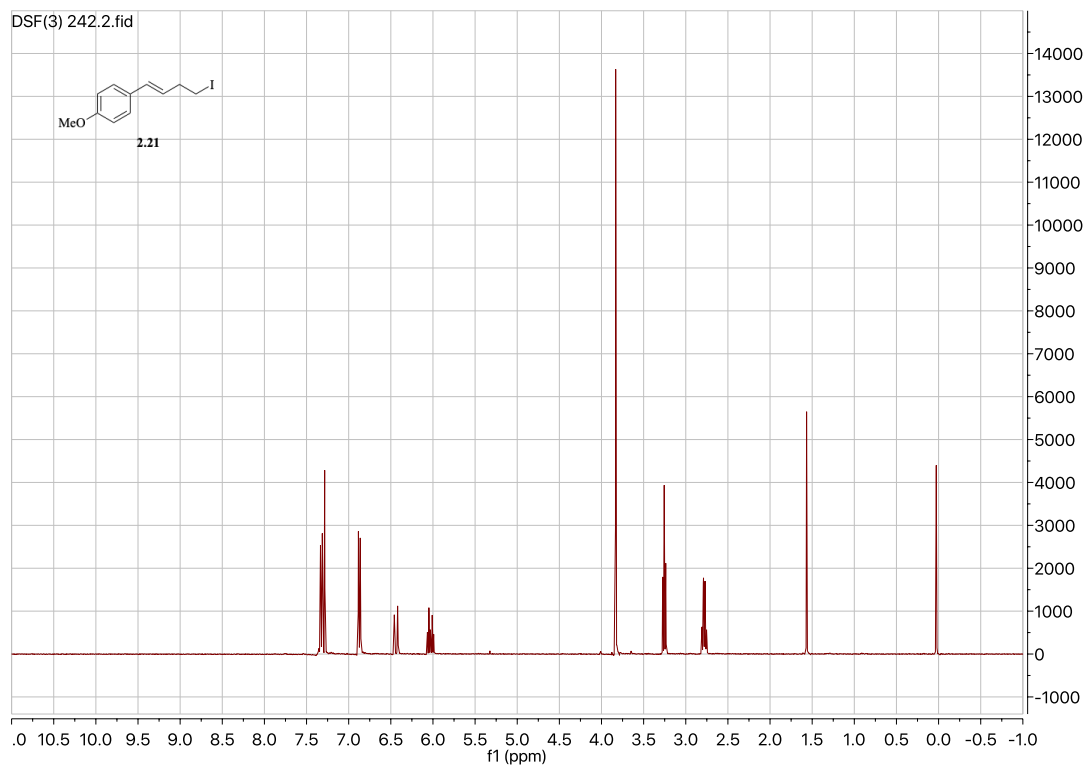


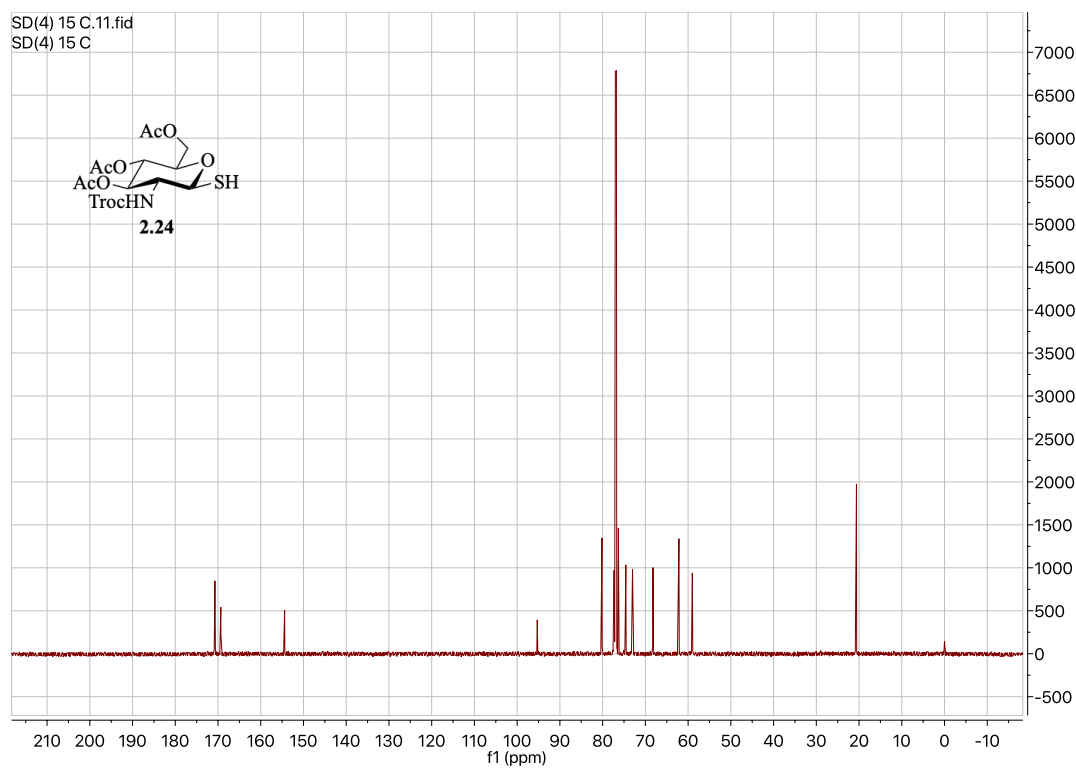
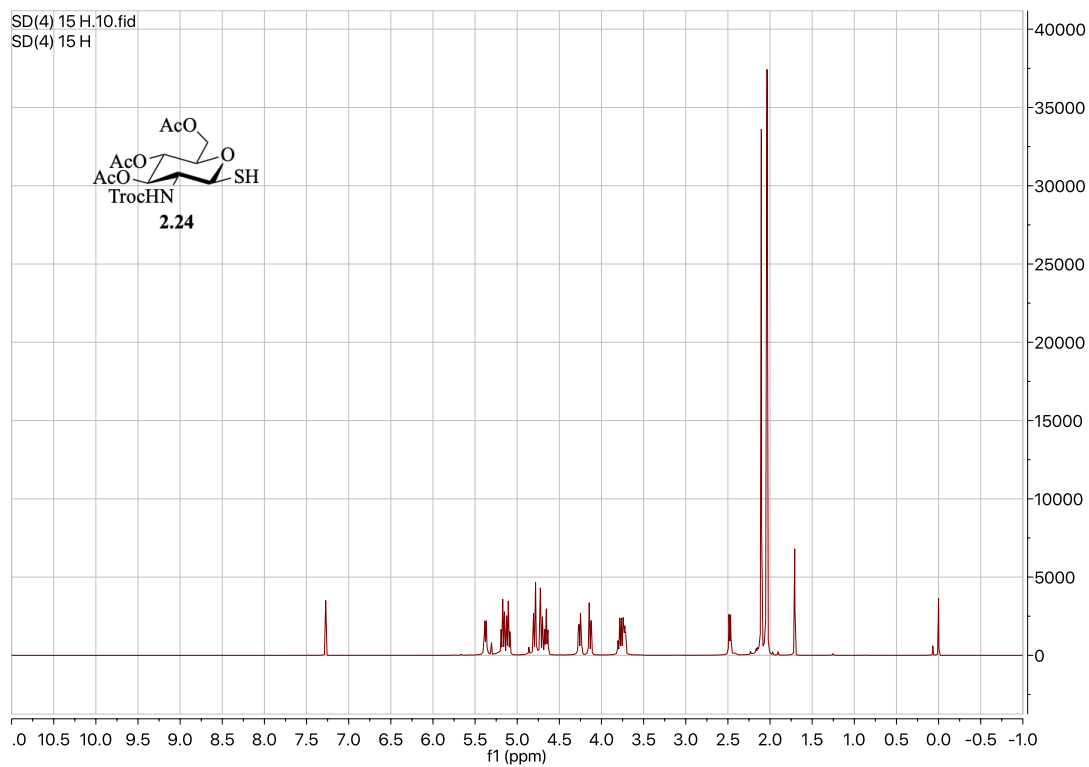


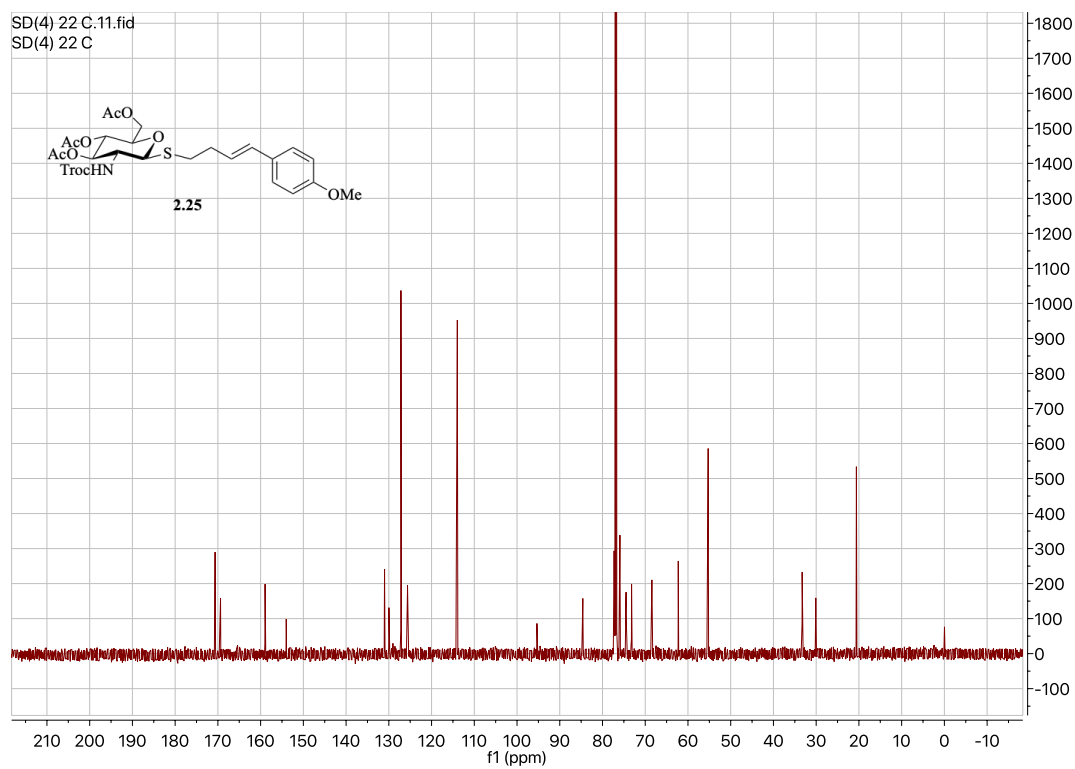
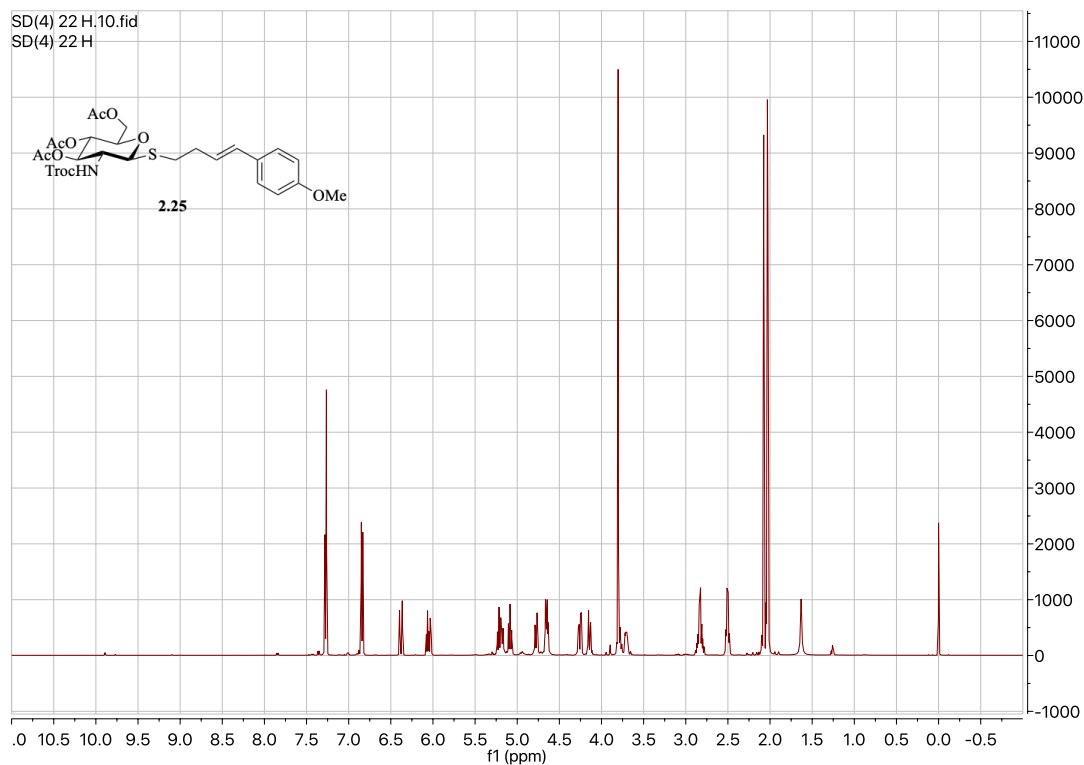


APPENDIX C. NMR SPECTRA OF COMPOUNDS FOUND IN CHAPTER 2

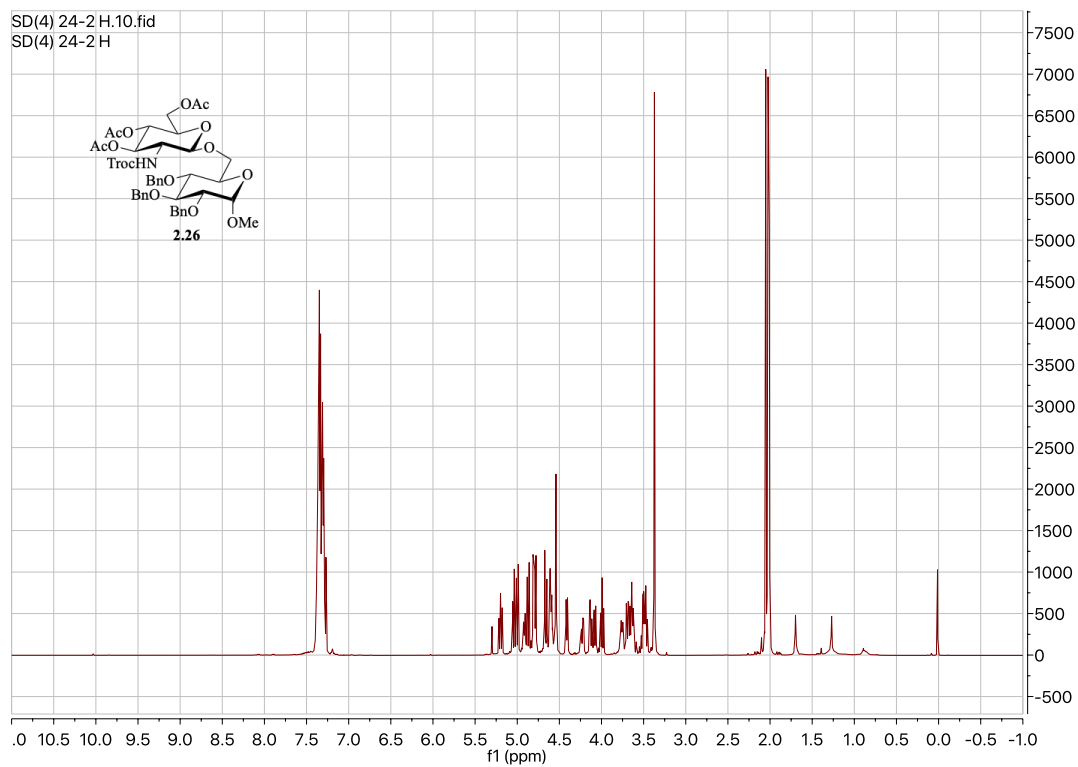




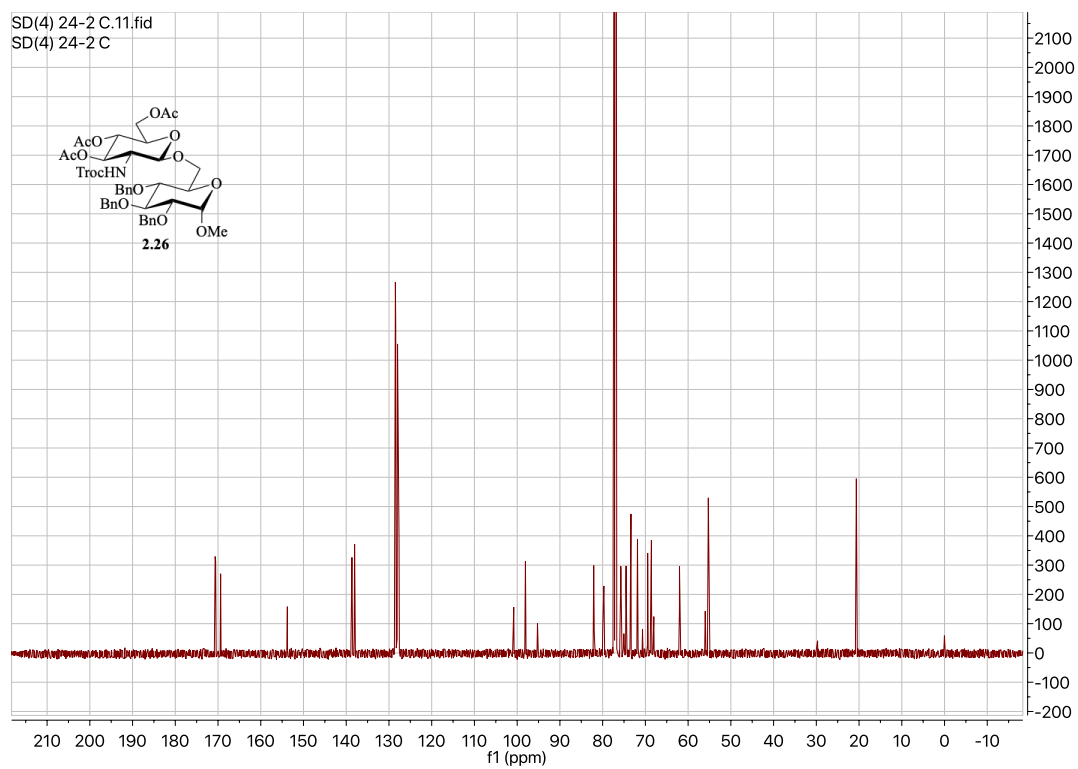


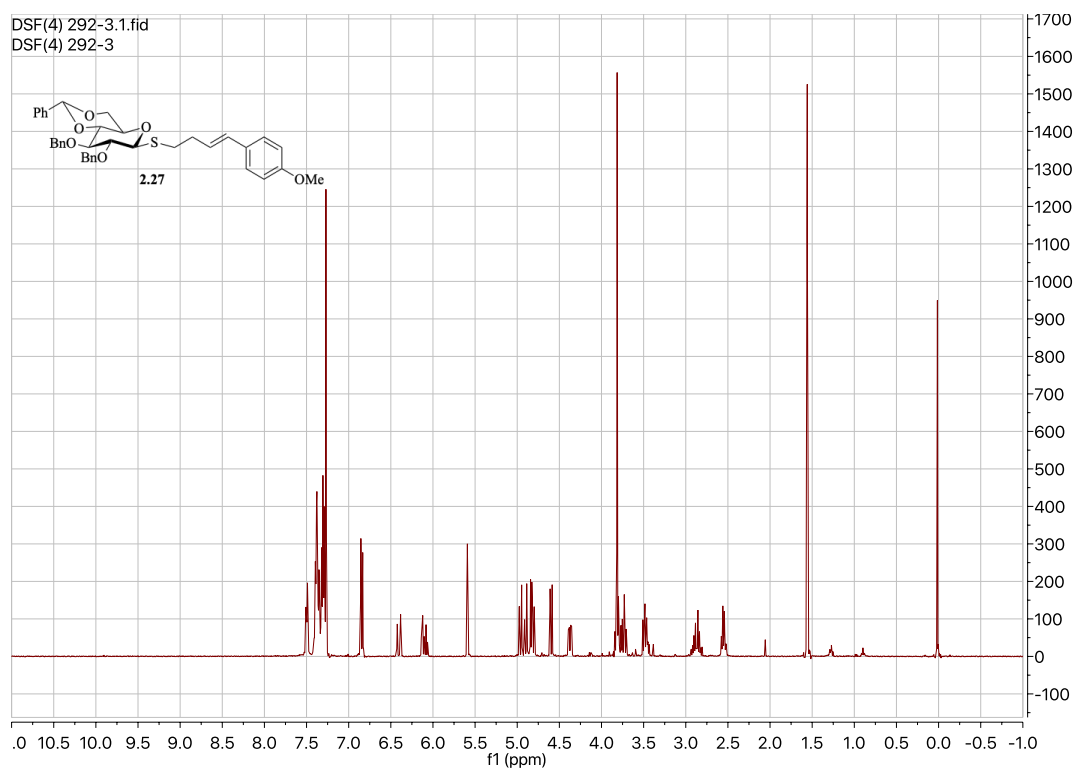
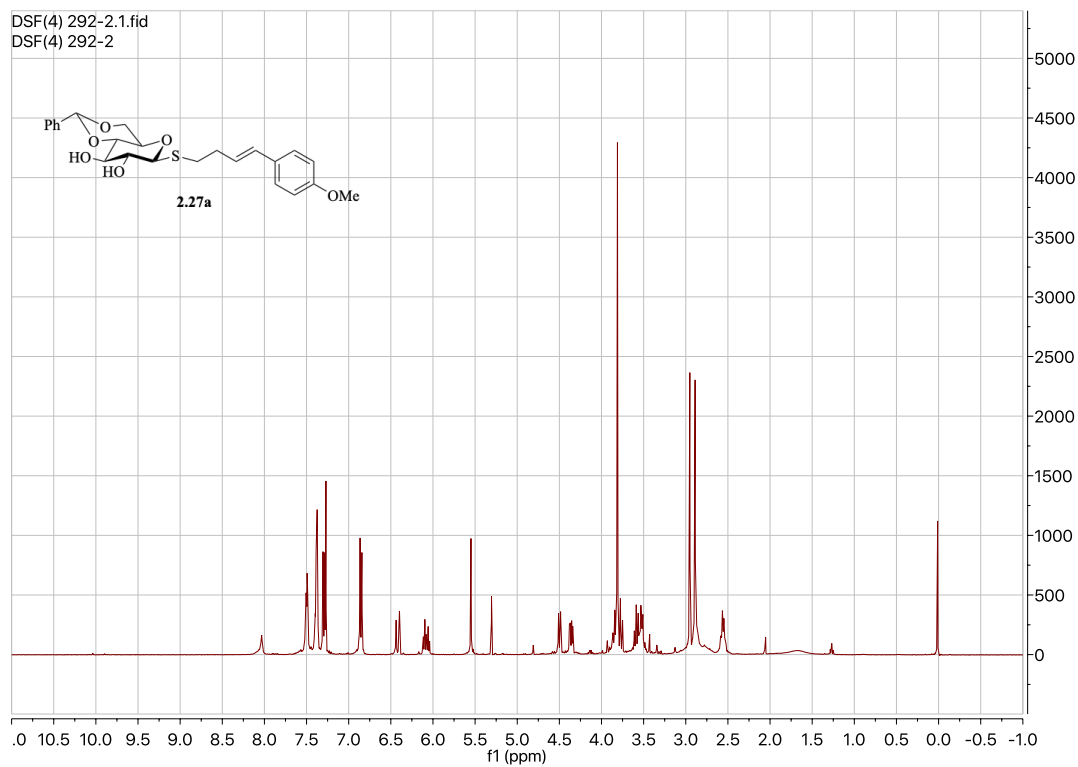


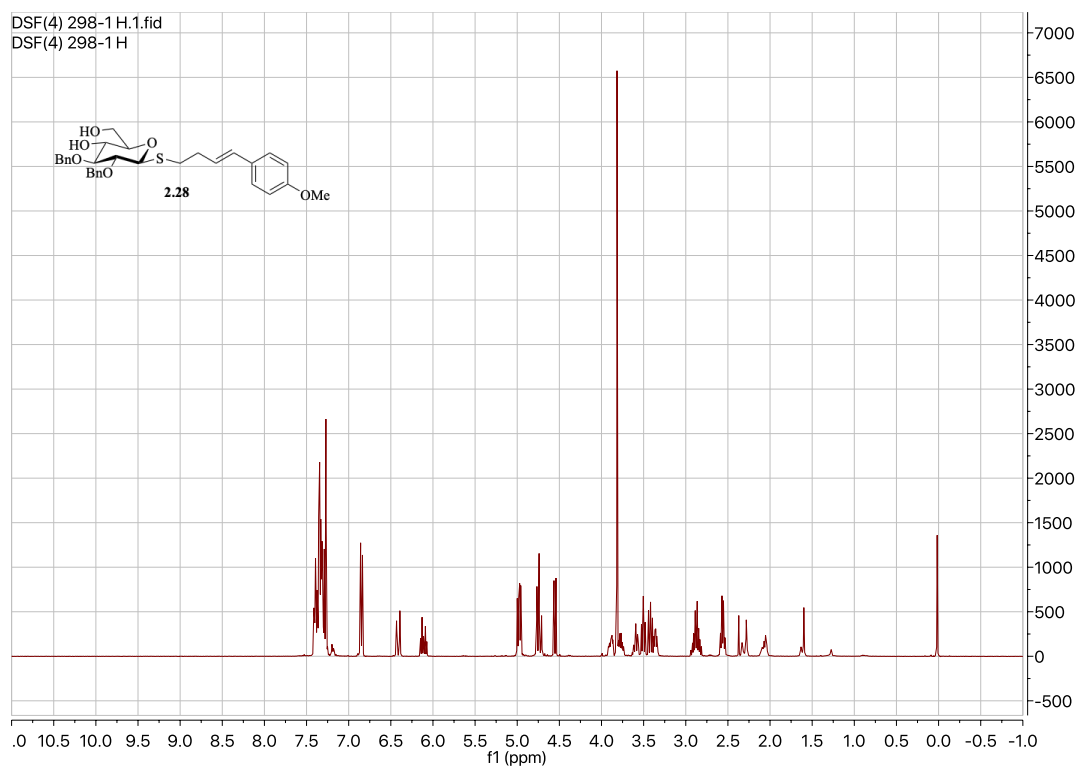
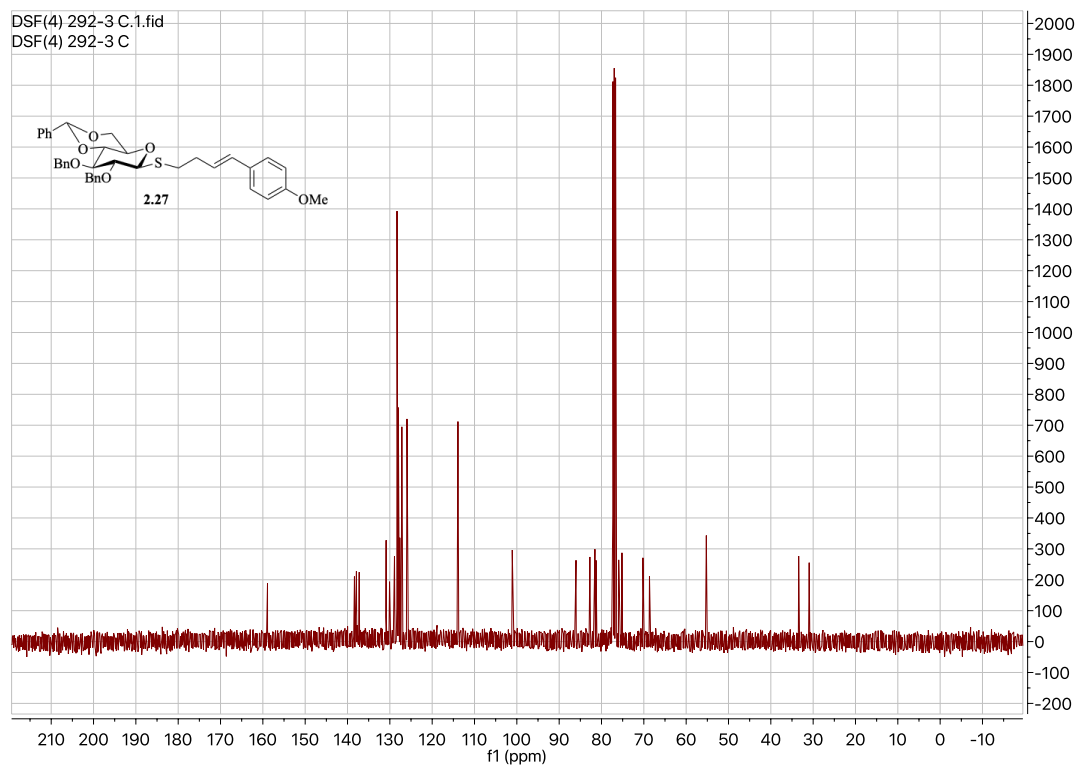
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SD(4) 24-2 H

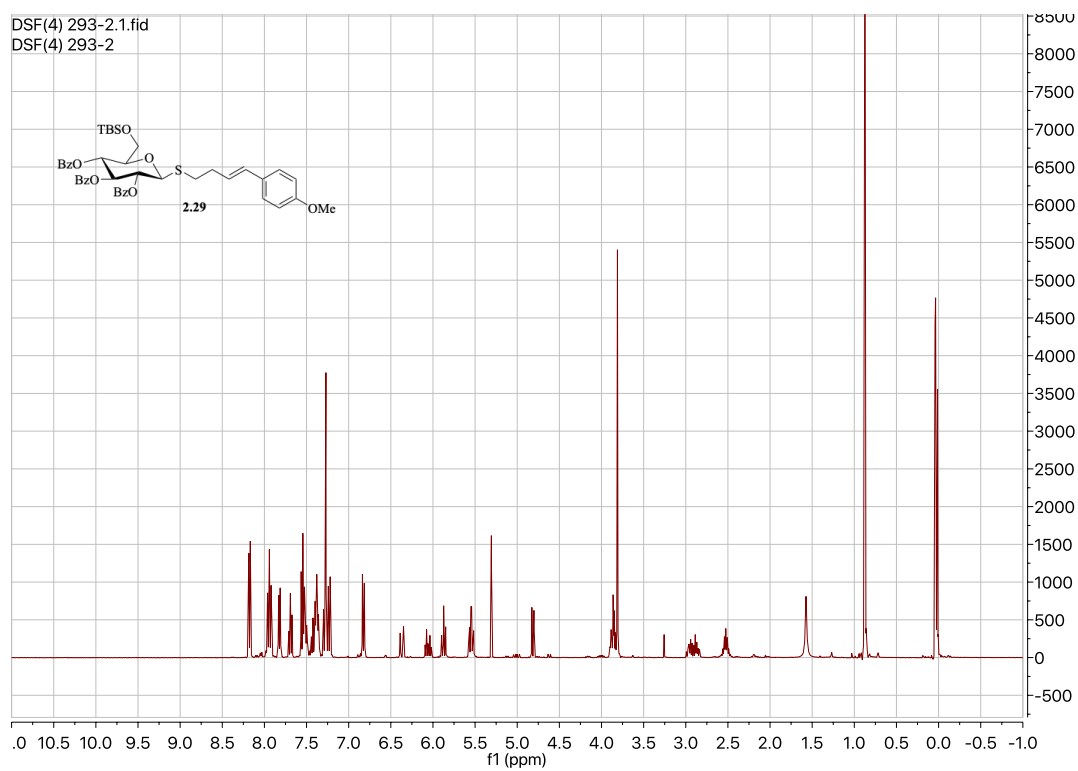
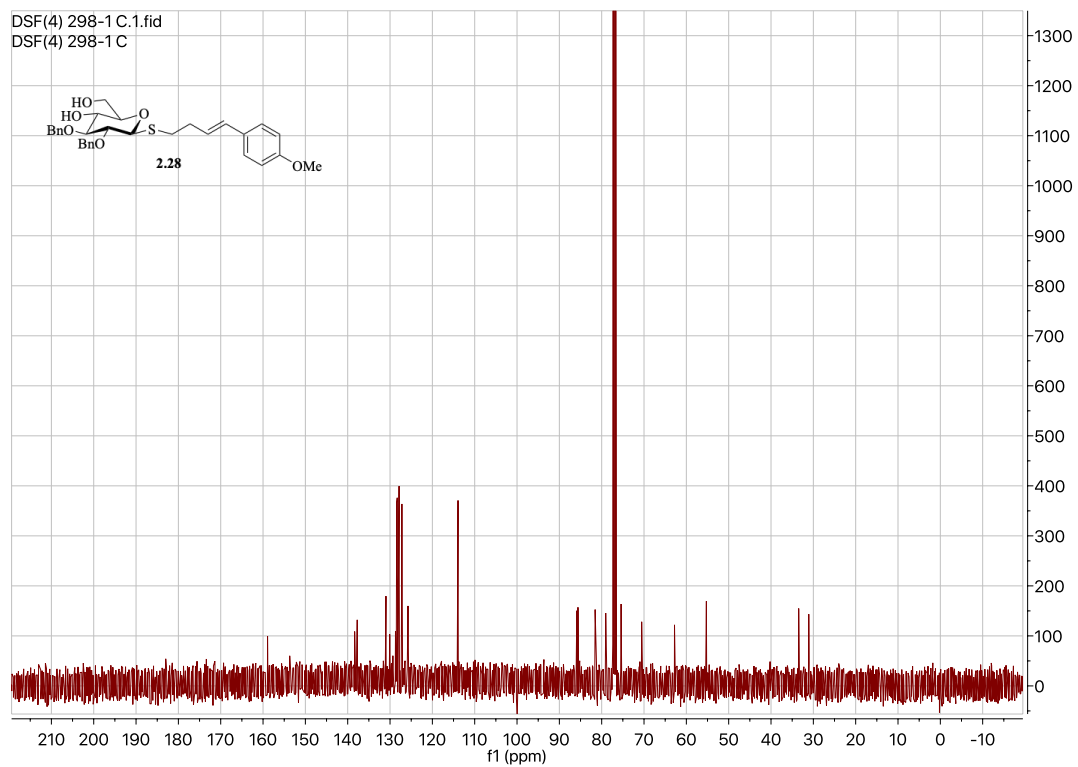


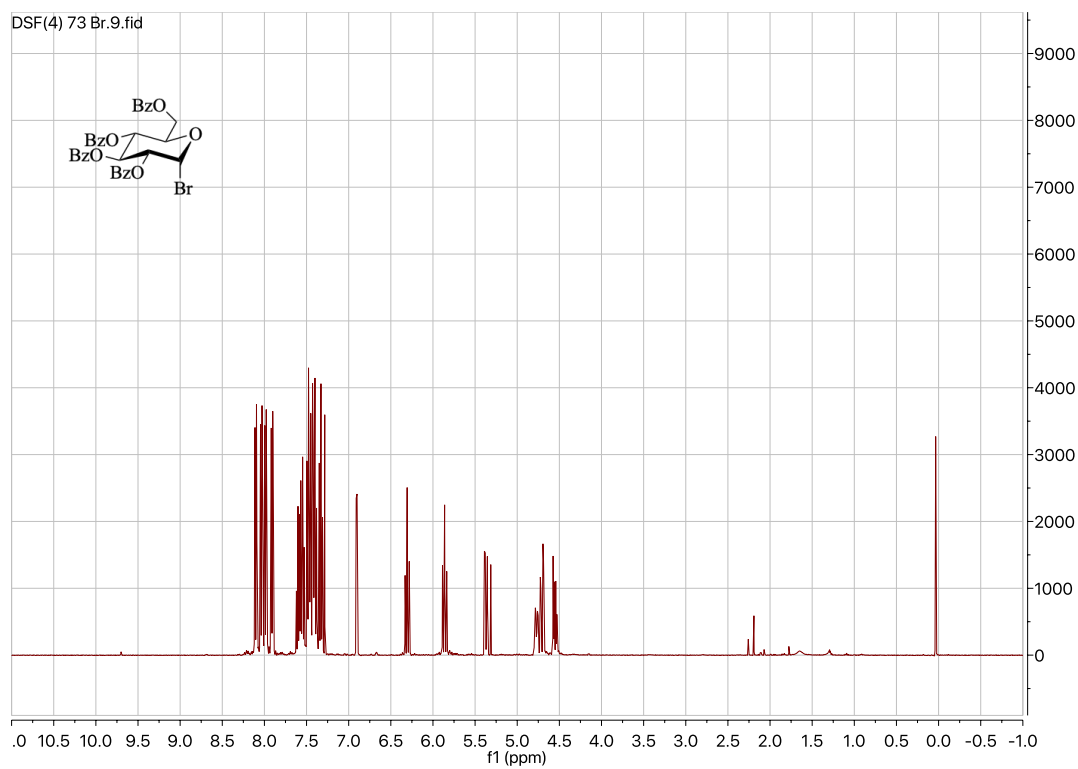
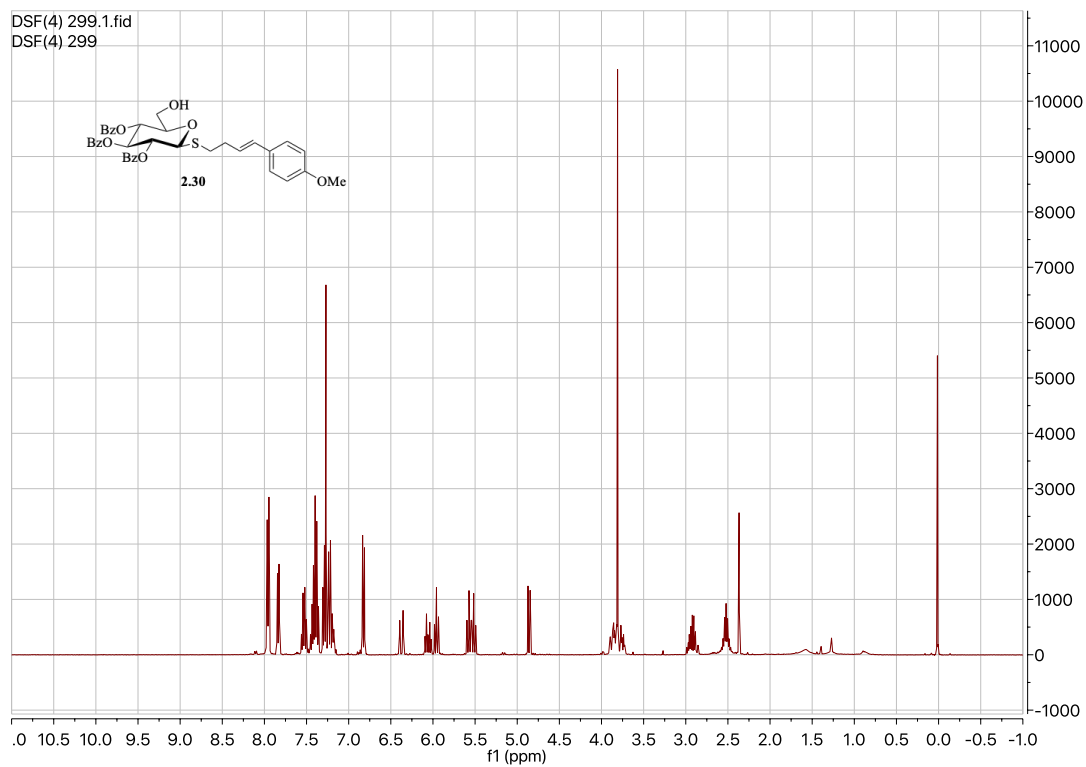
SD(4) 24-2 C.11.fid
SD(4) 24-2 C

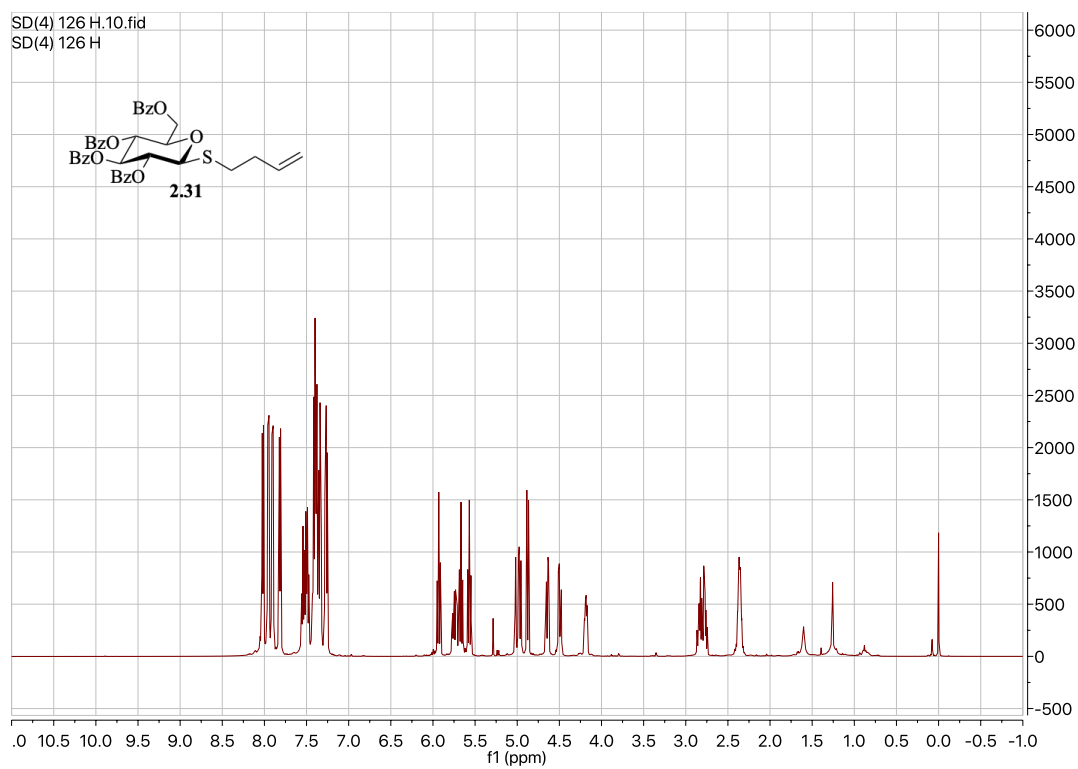
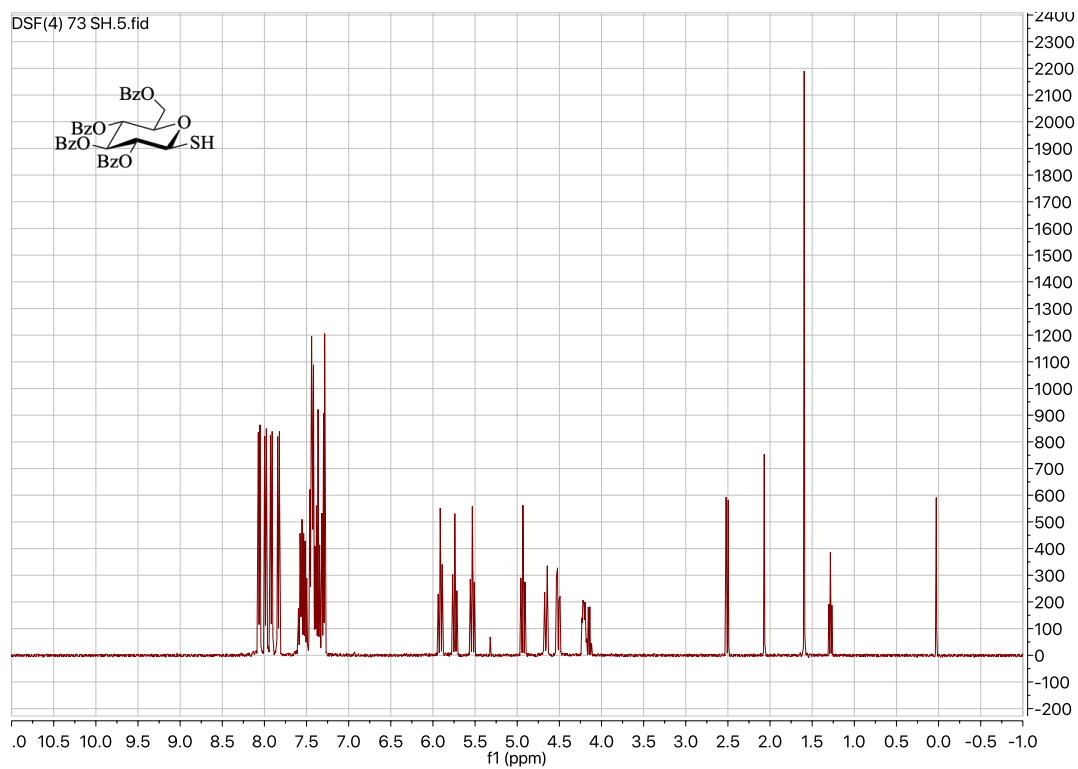


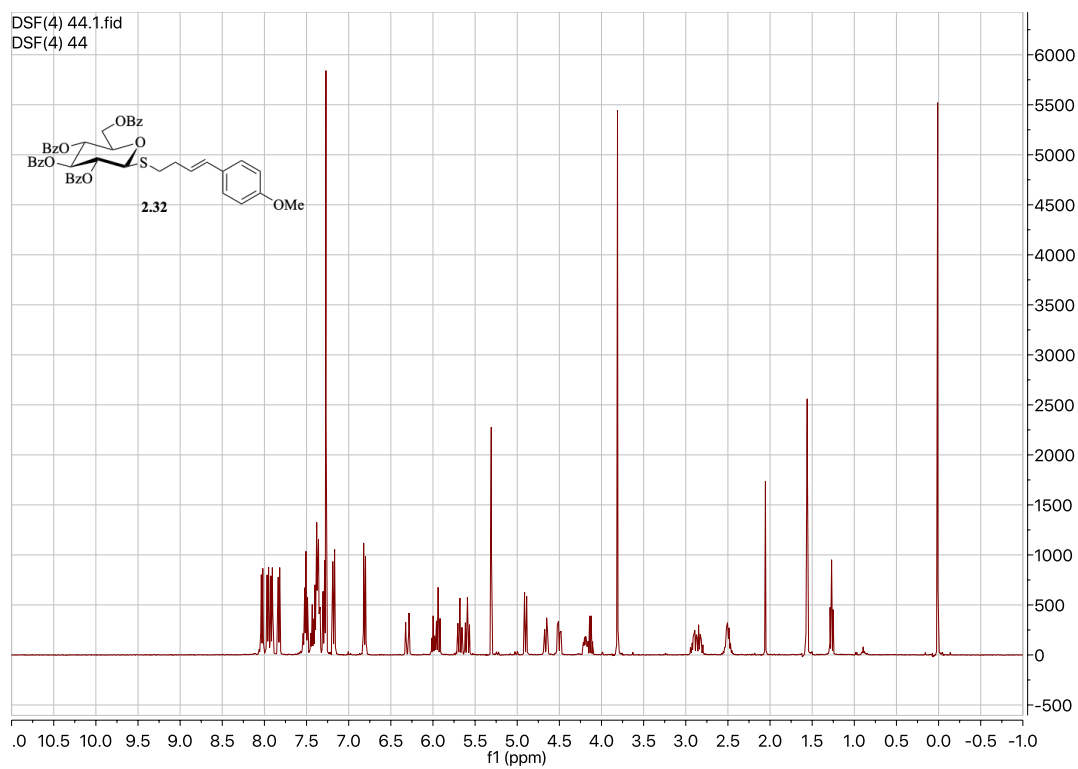
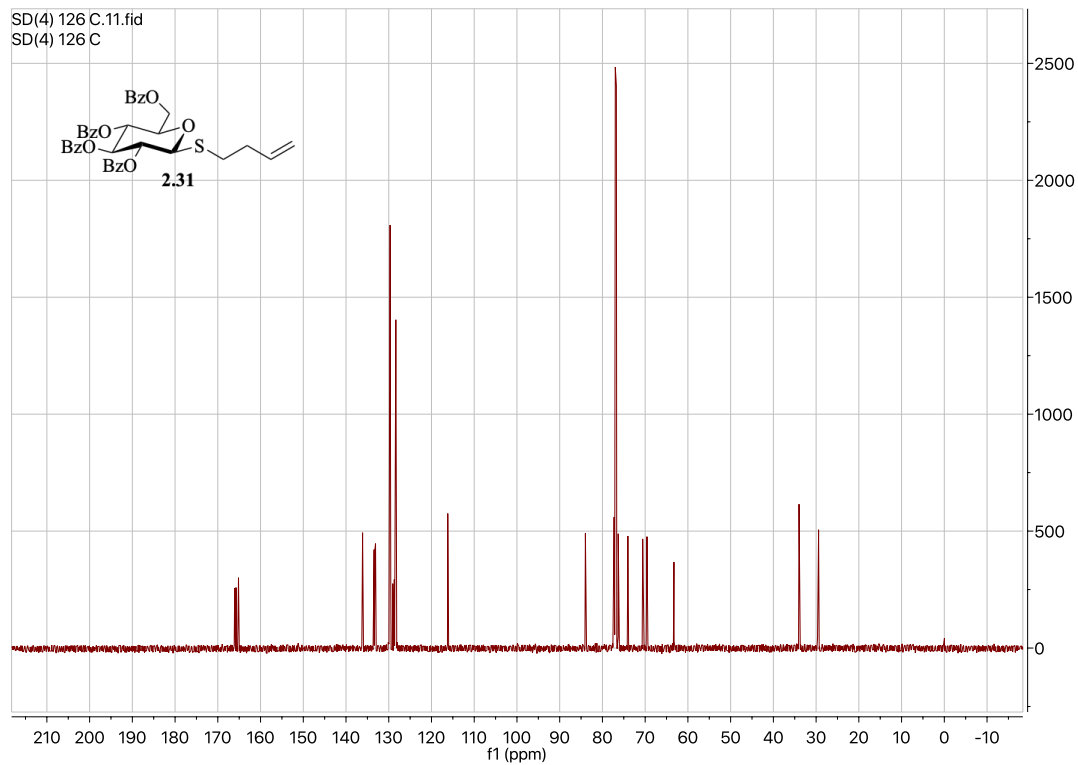




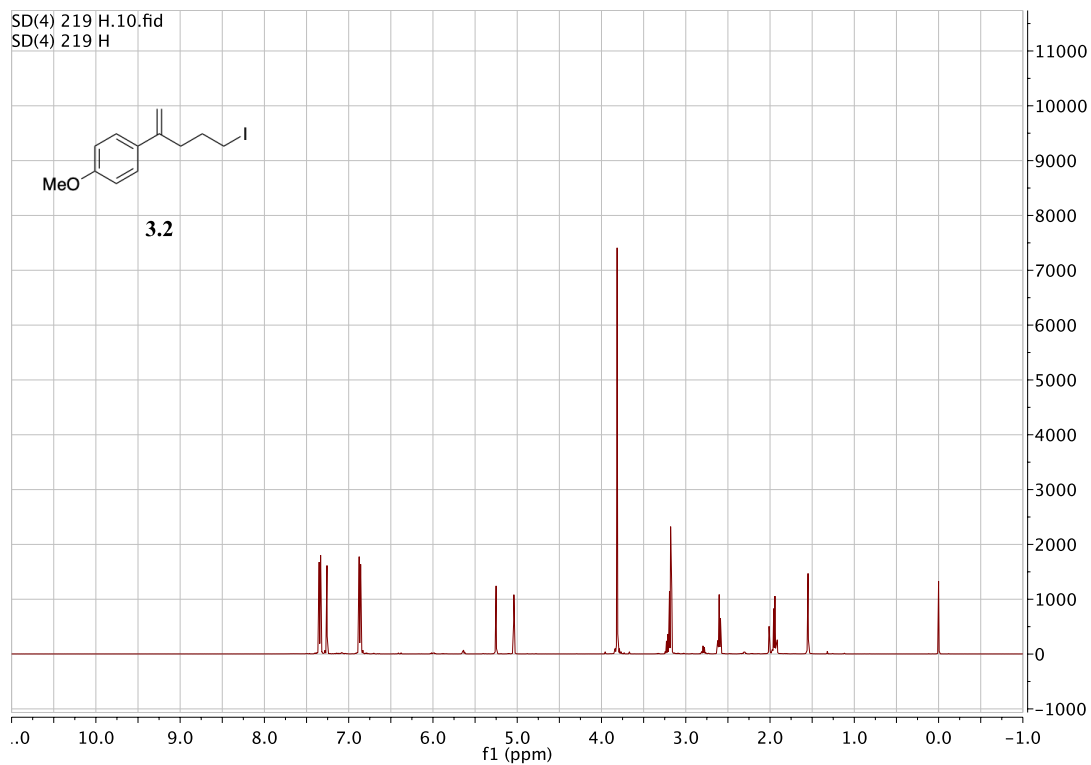
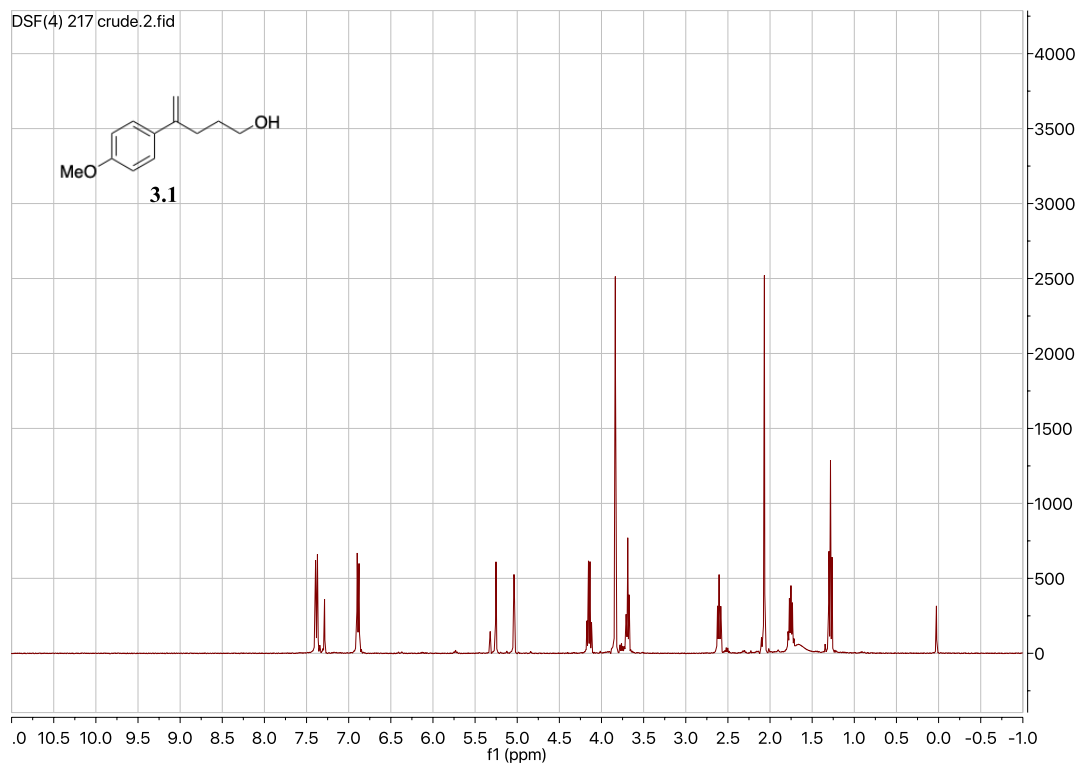


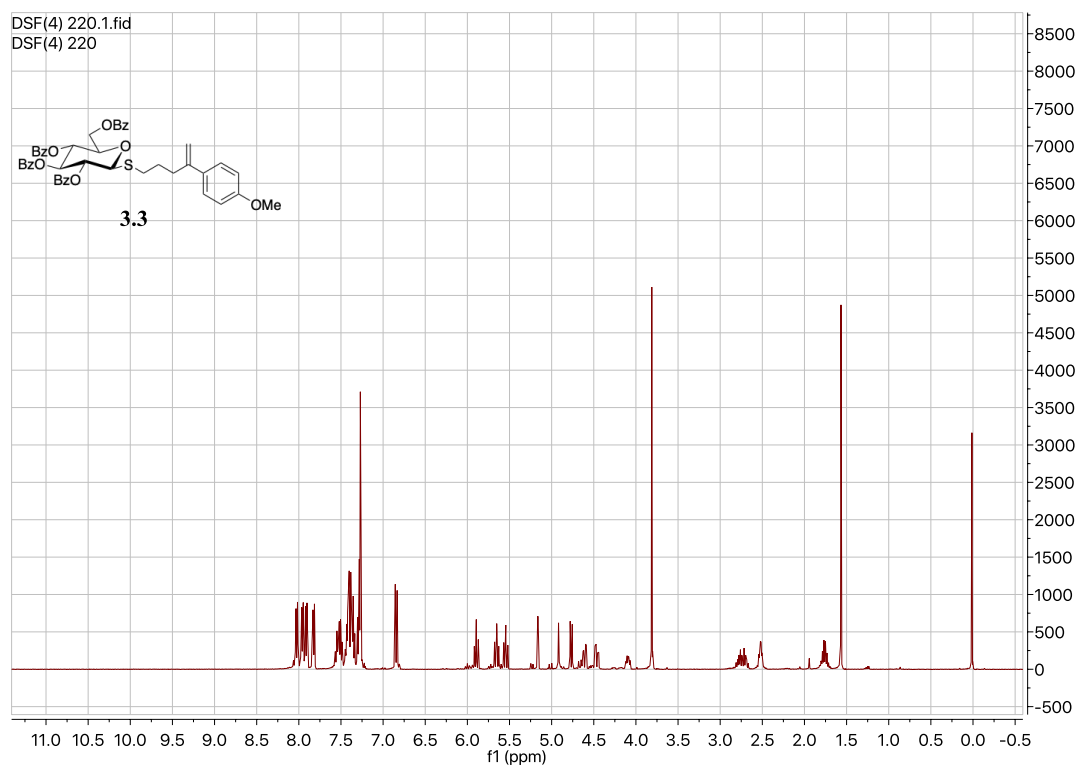
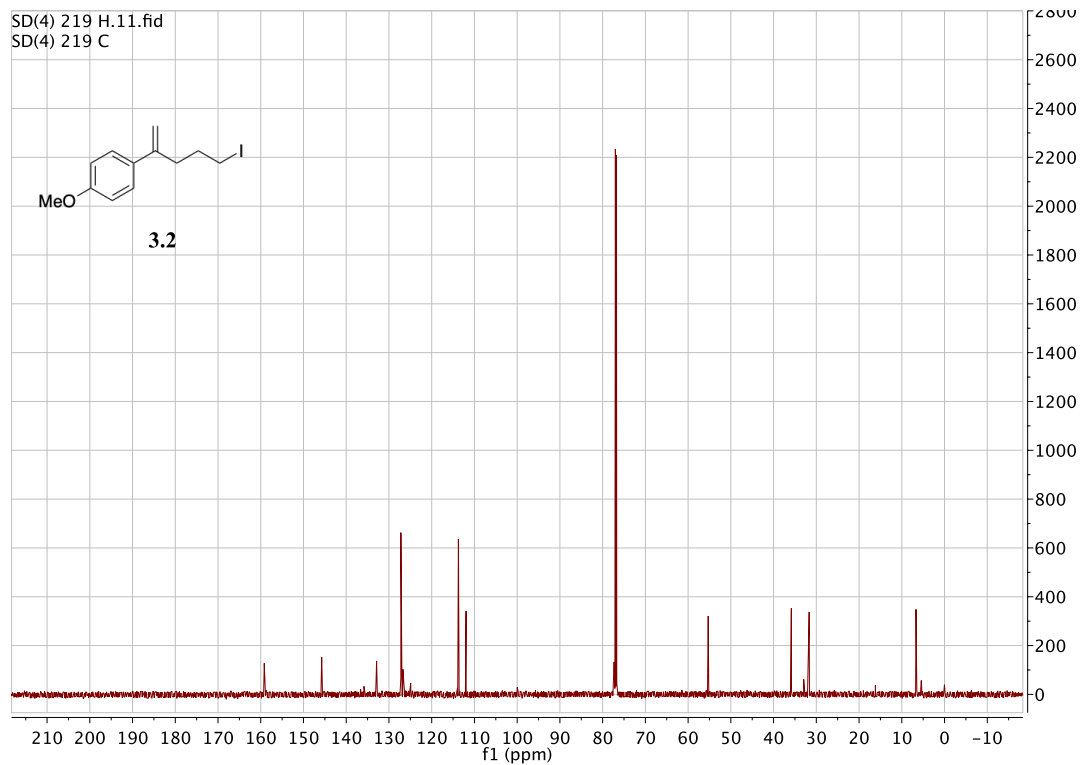


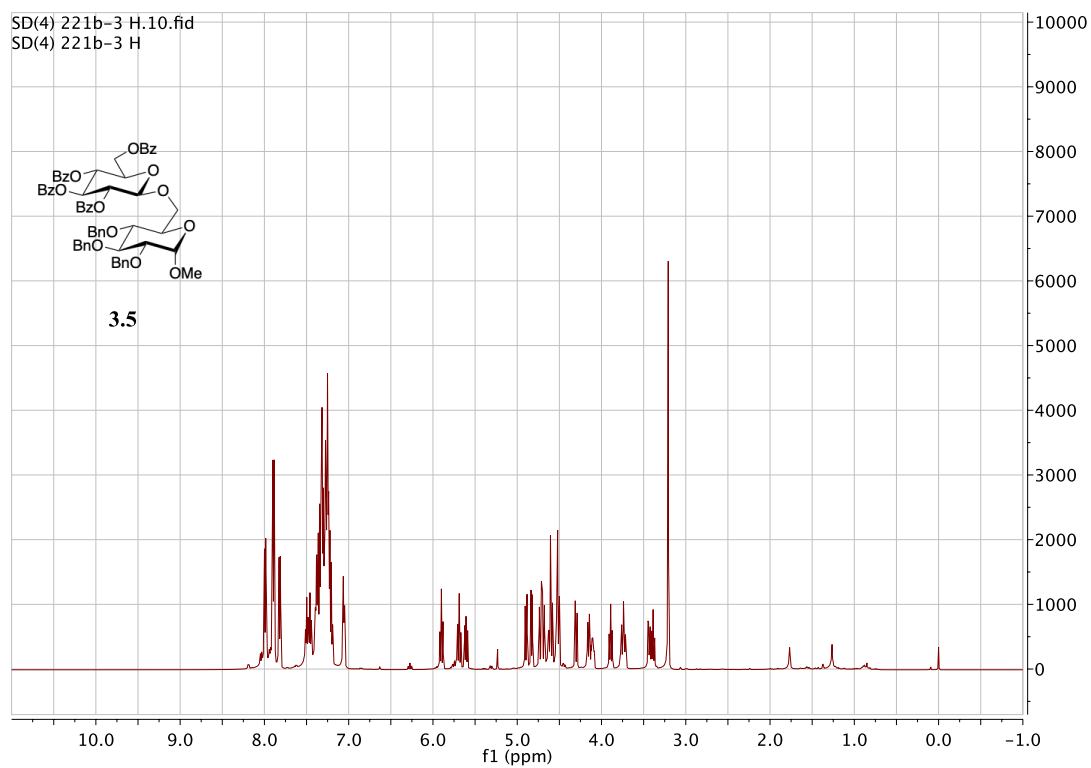
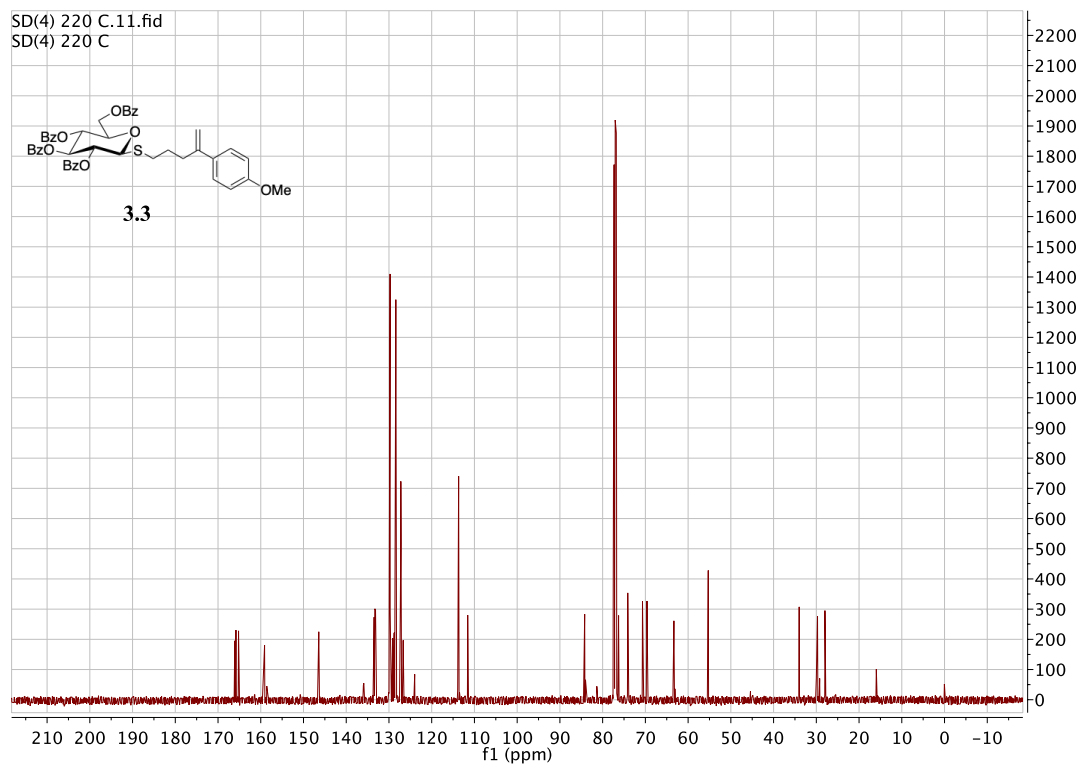


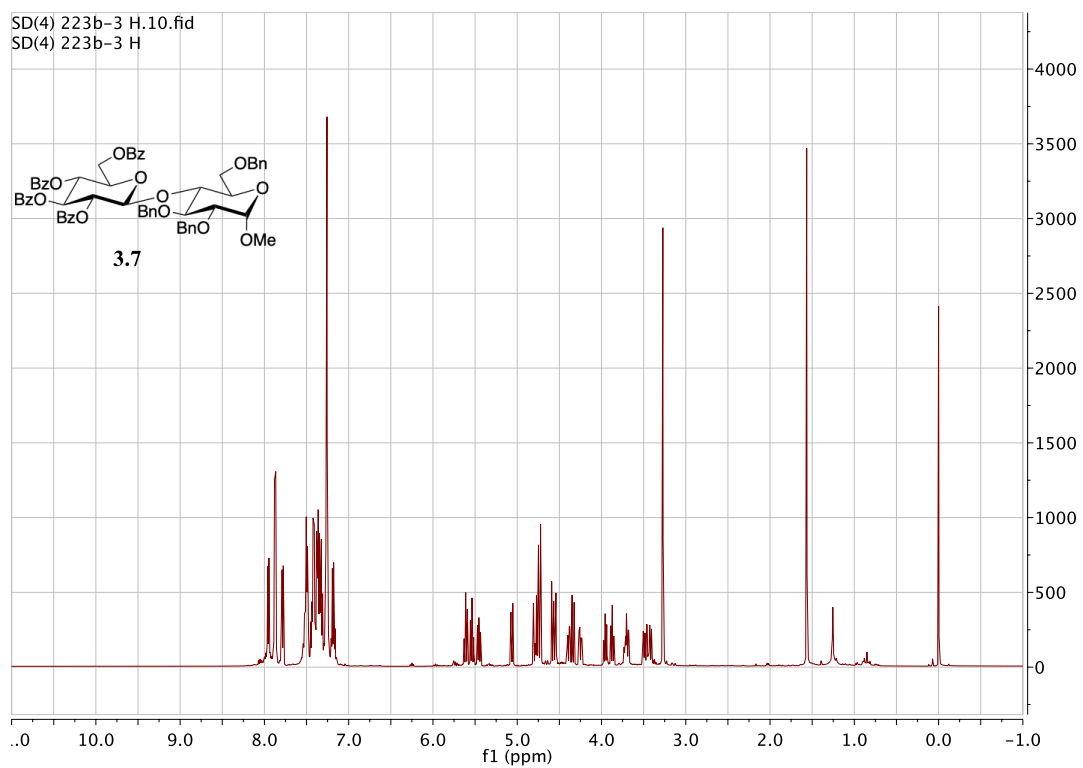
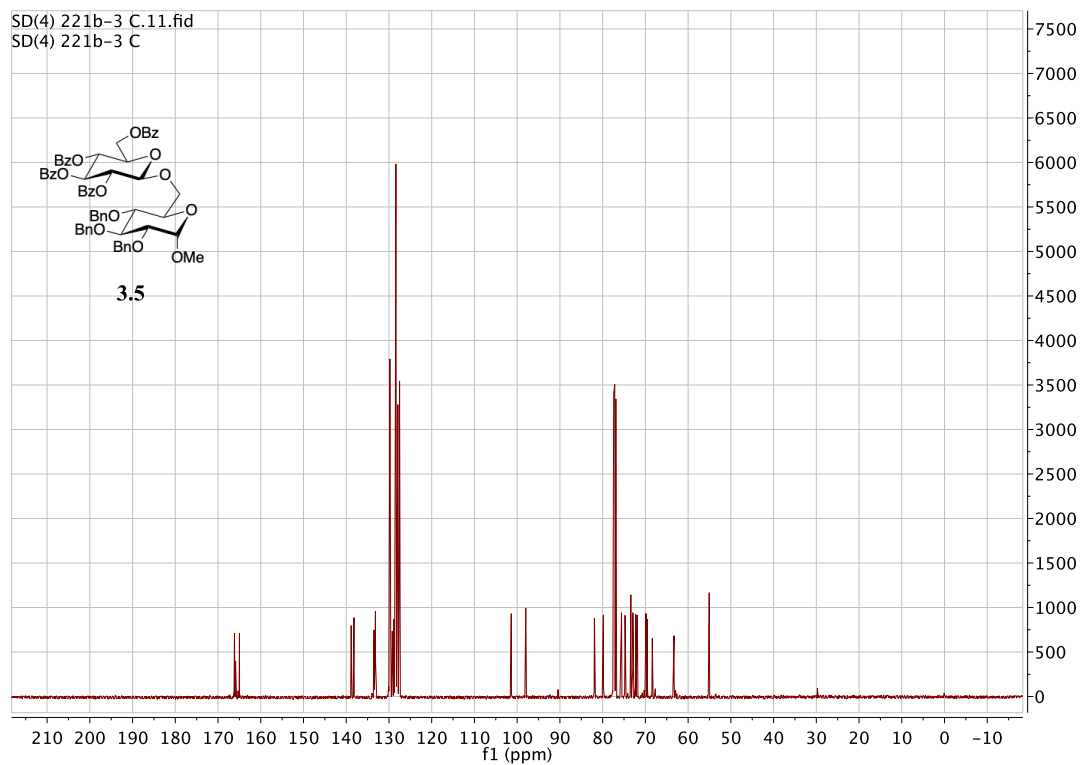


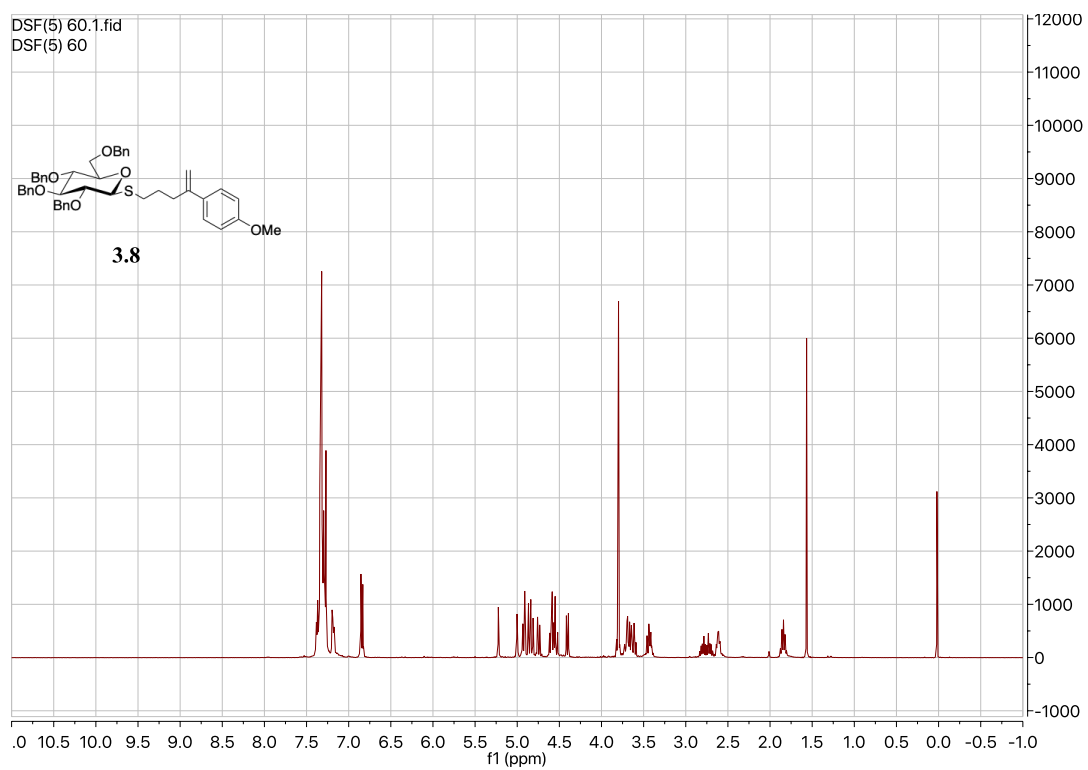
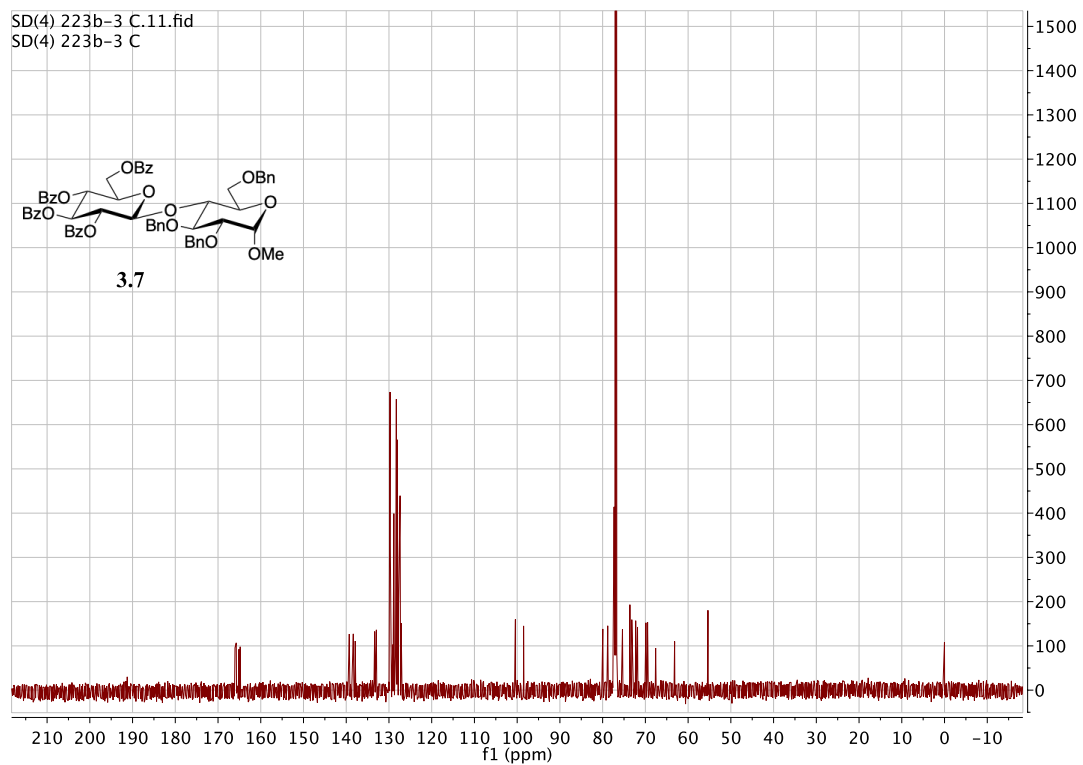
APPENDIX D. NMR SPECTRA OF COMPOUNDS FOUND IN CHAPTER 3

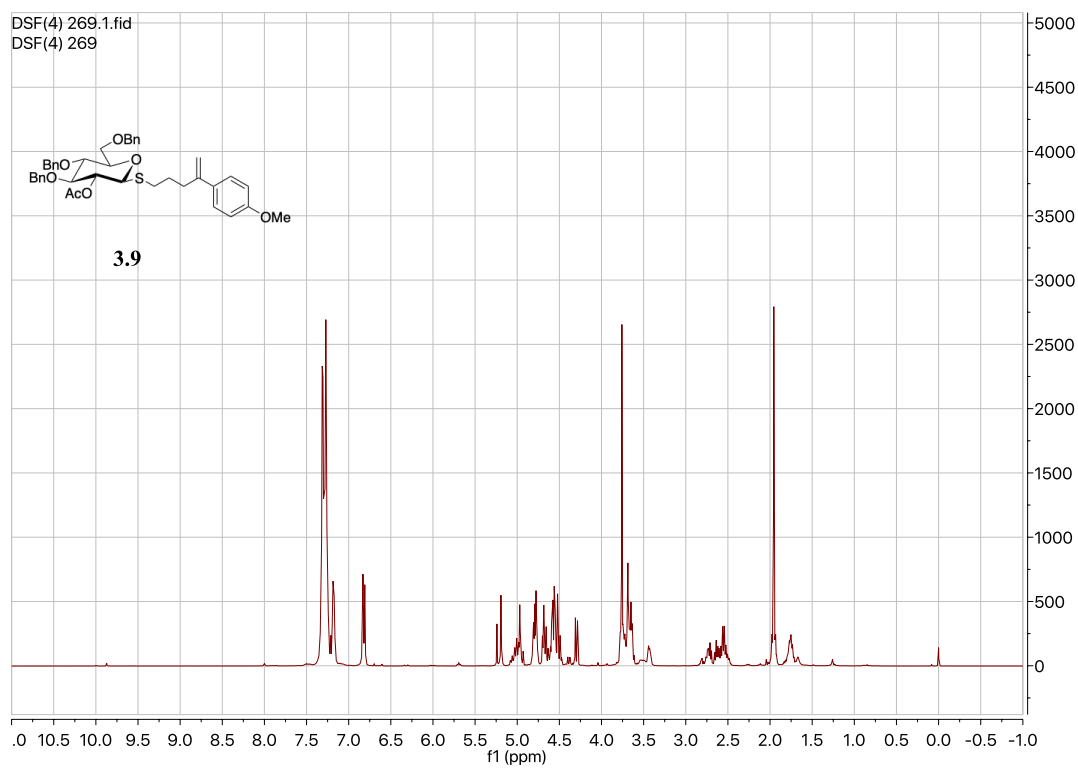
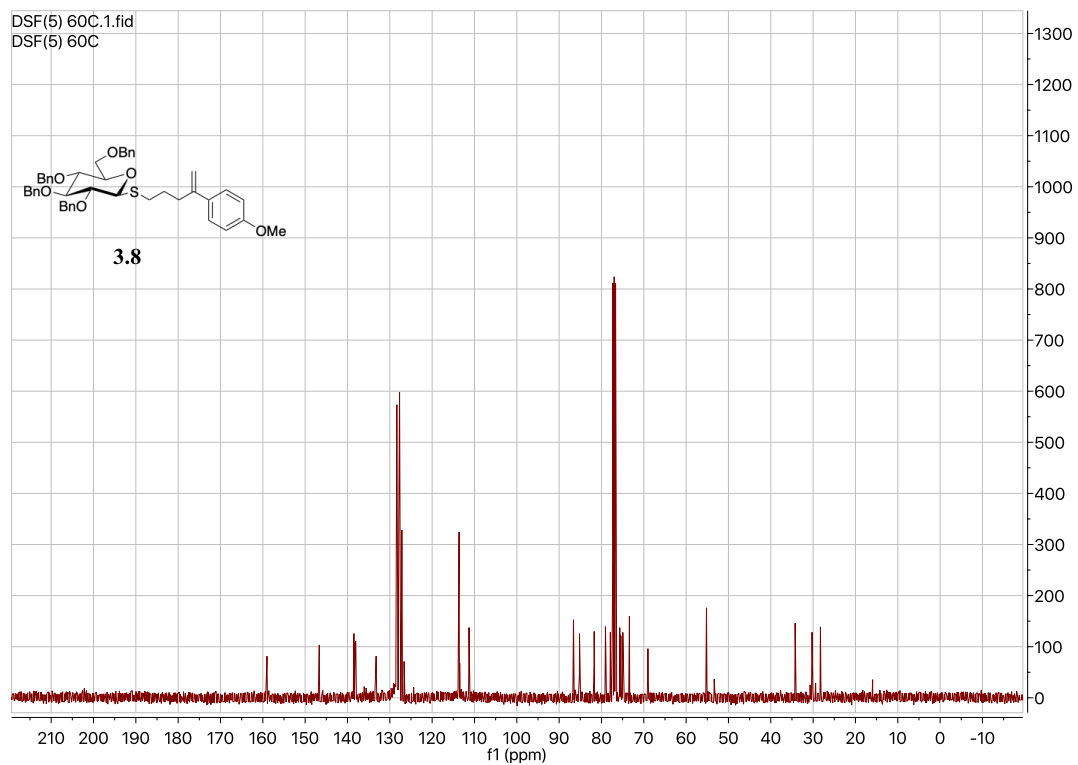


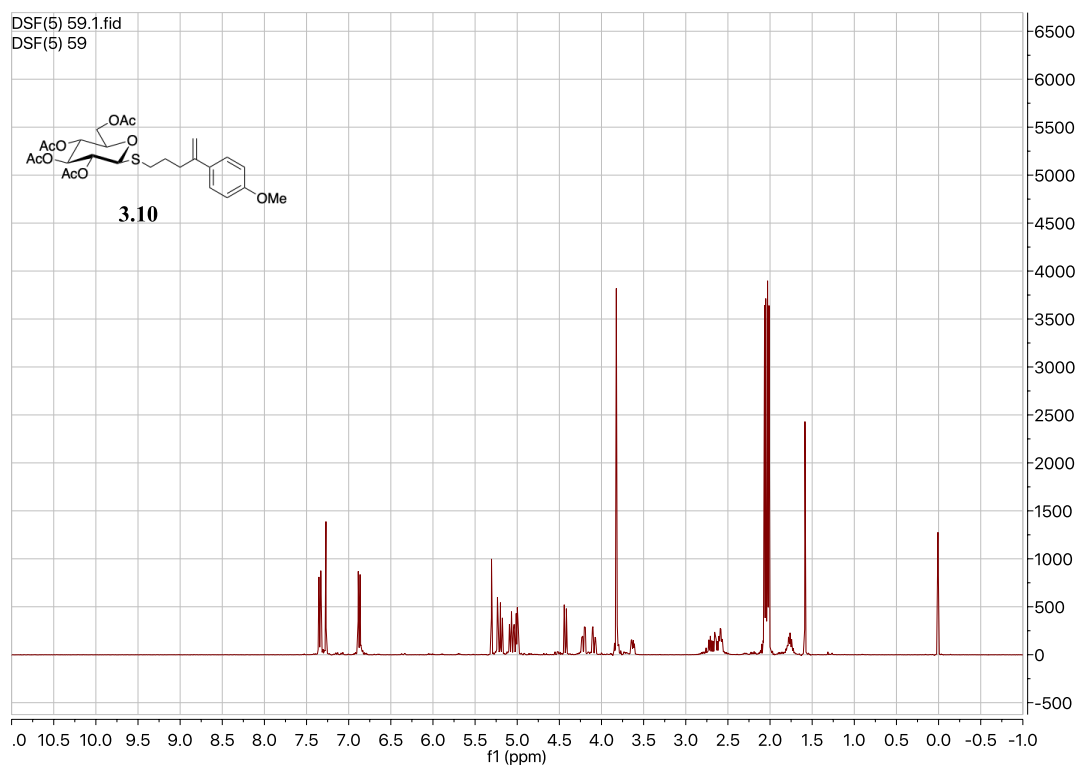
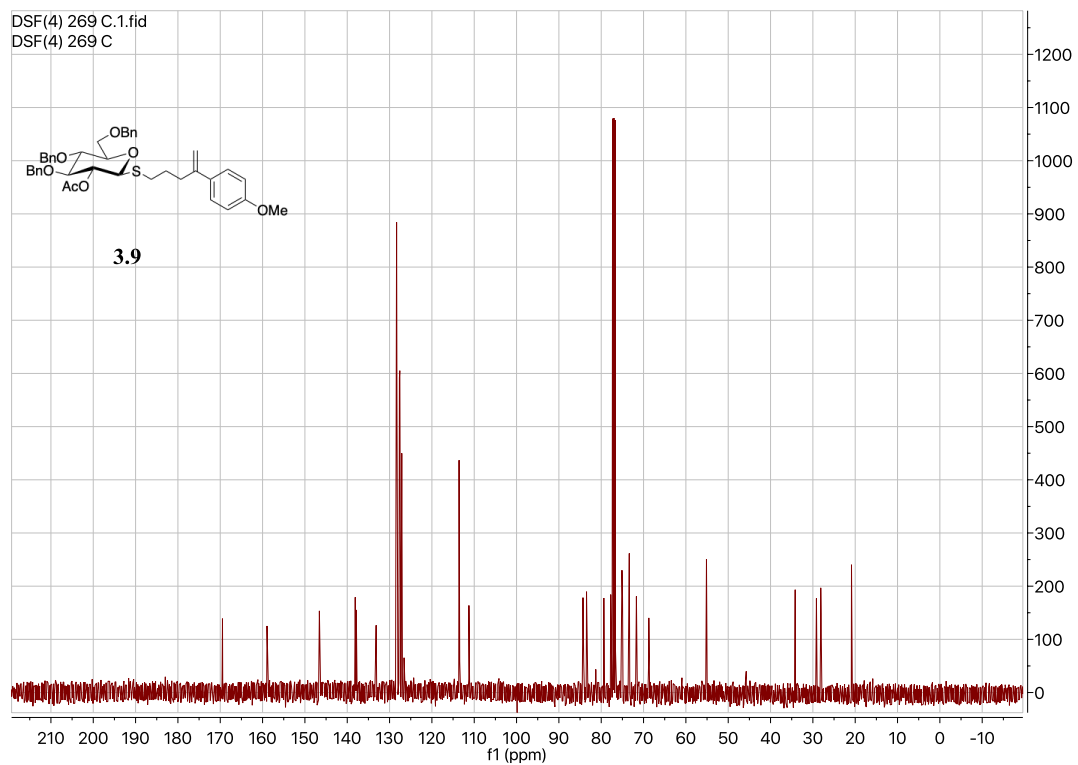


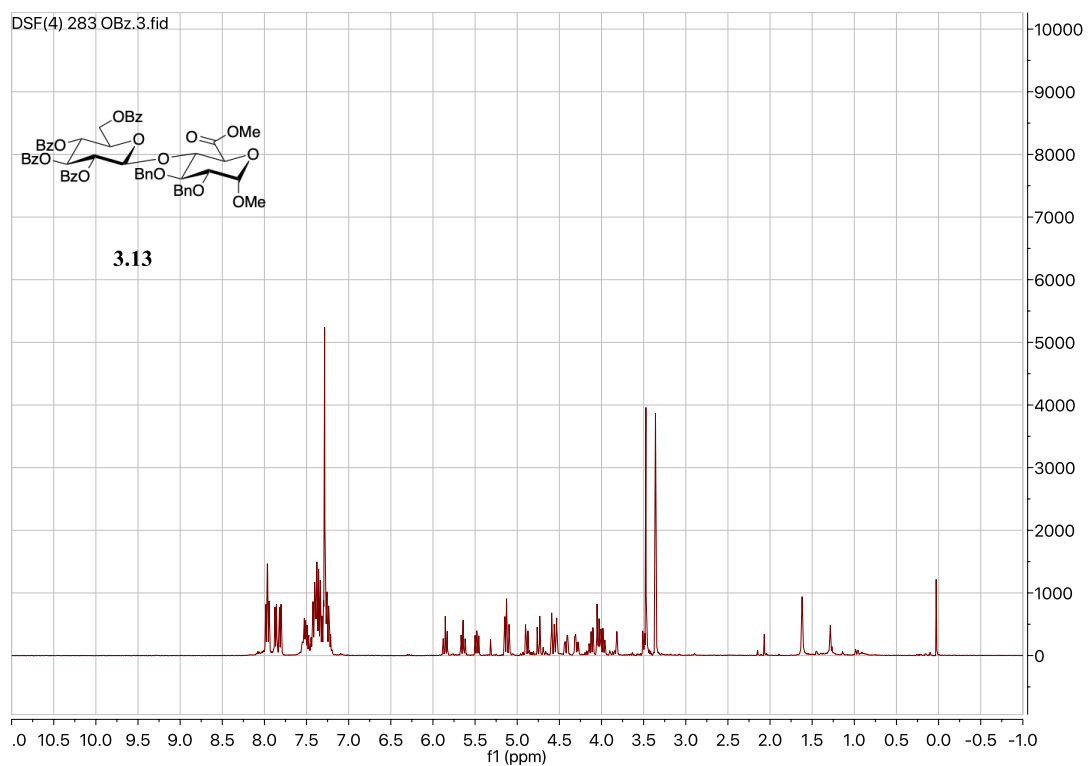
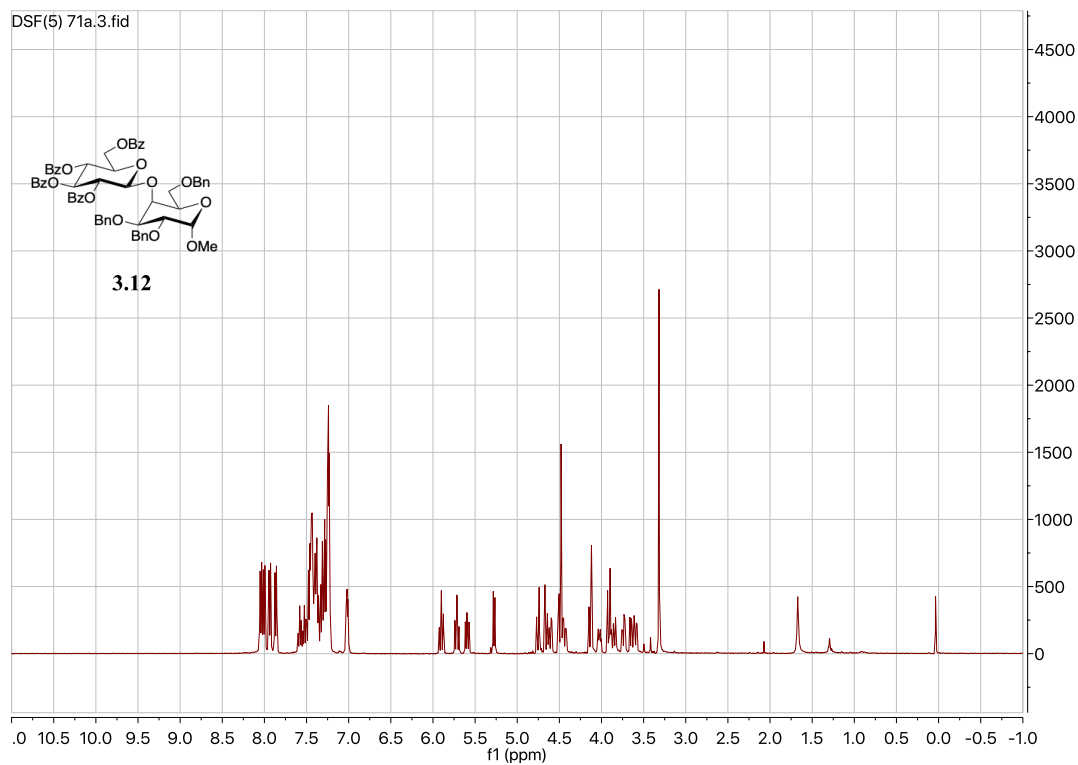


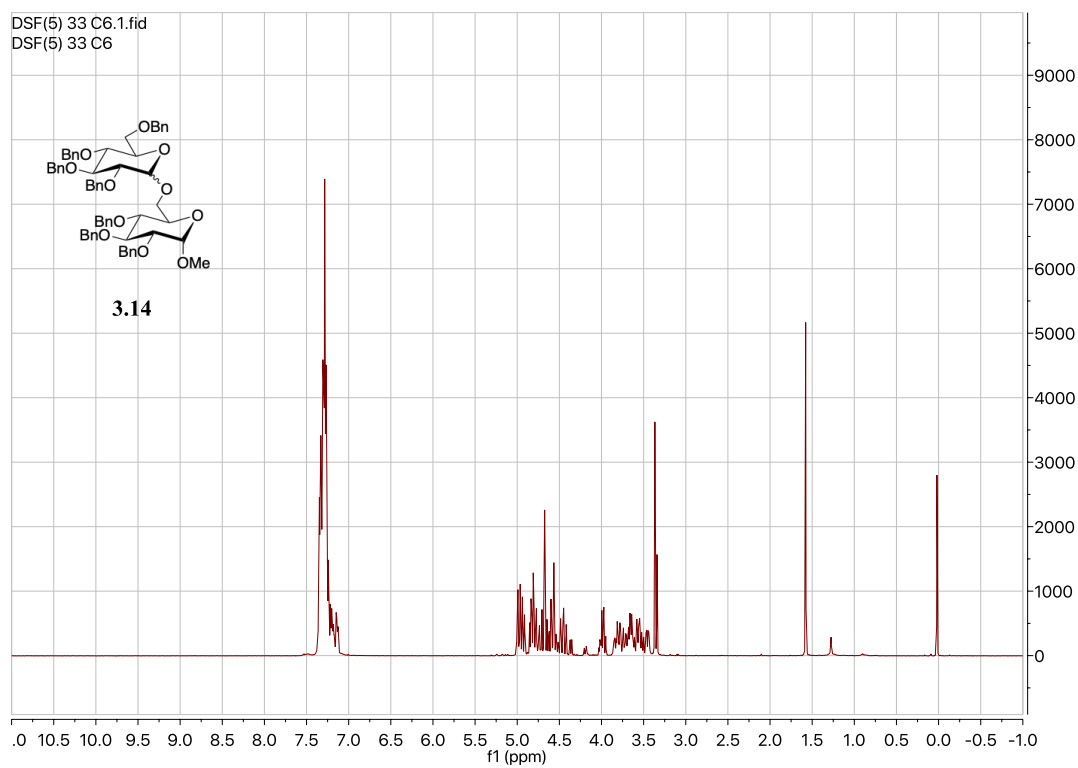
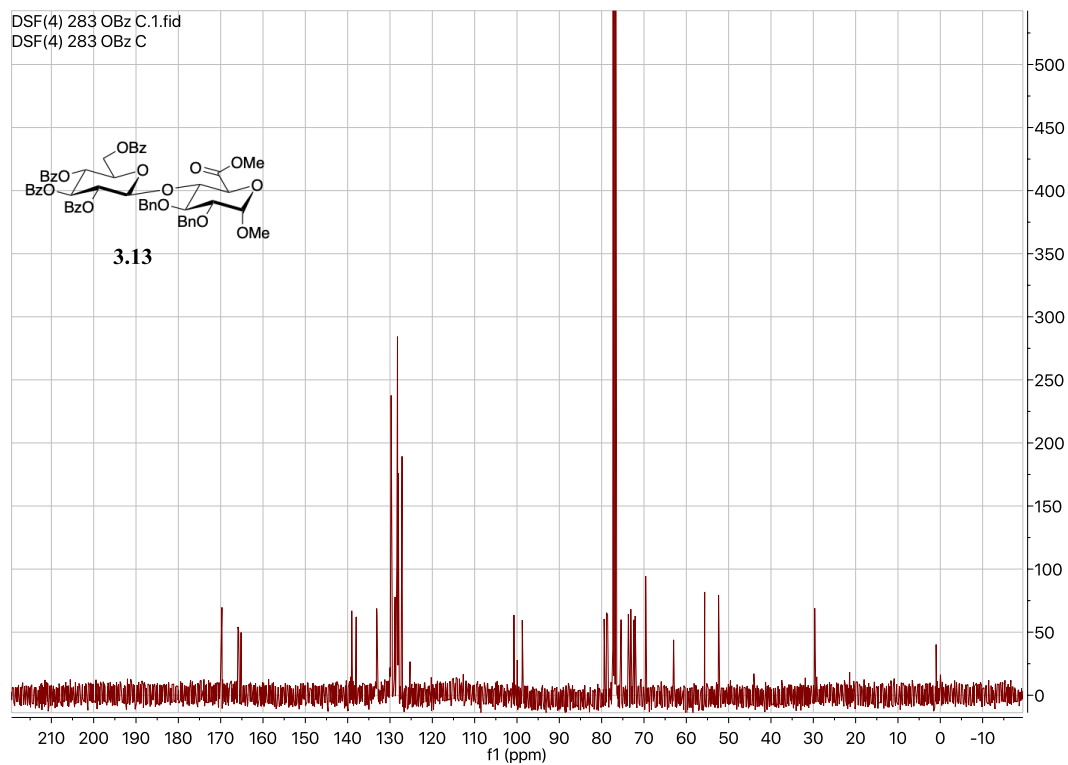


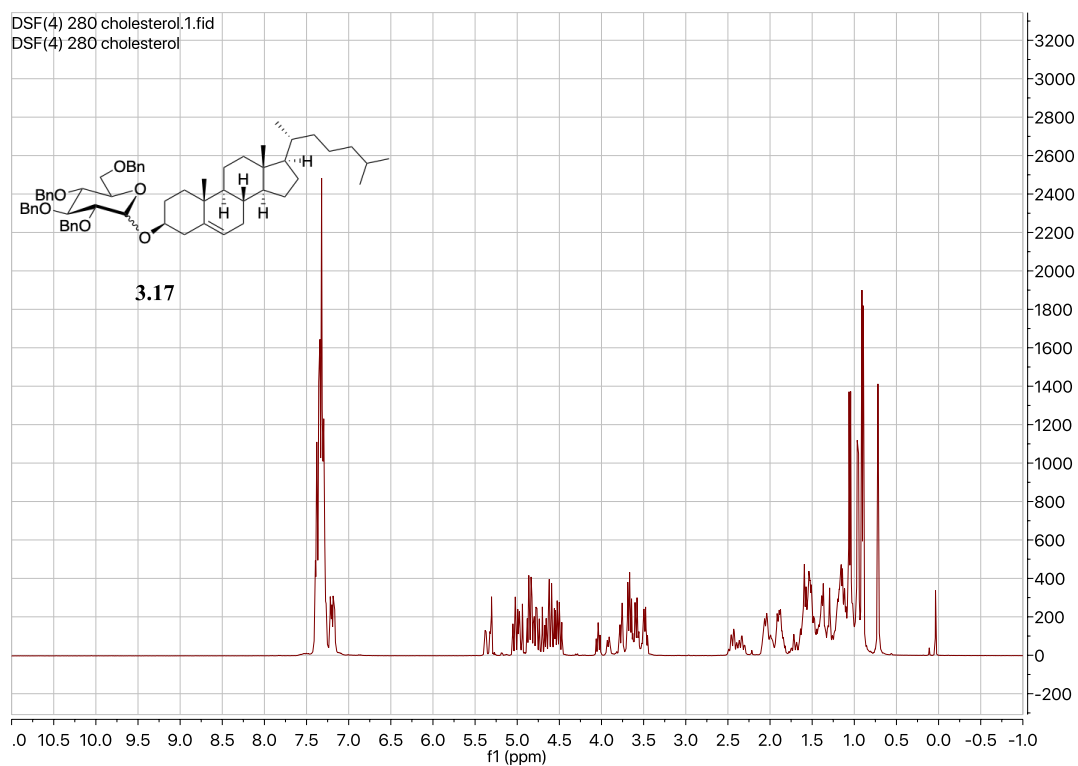
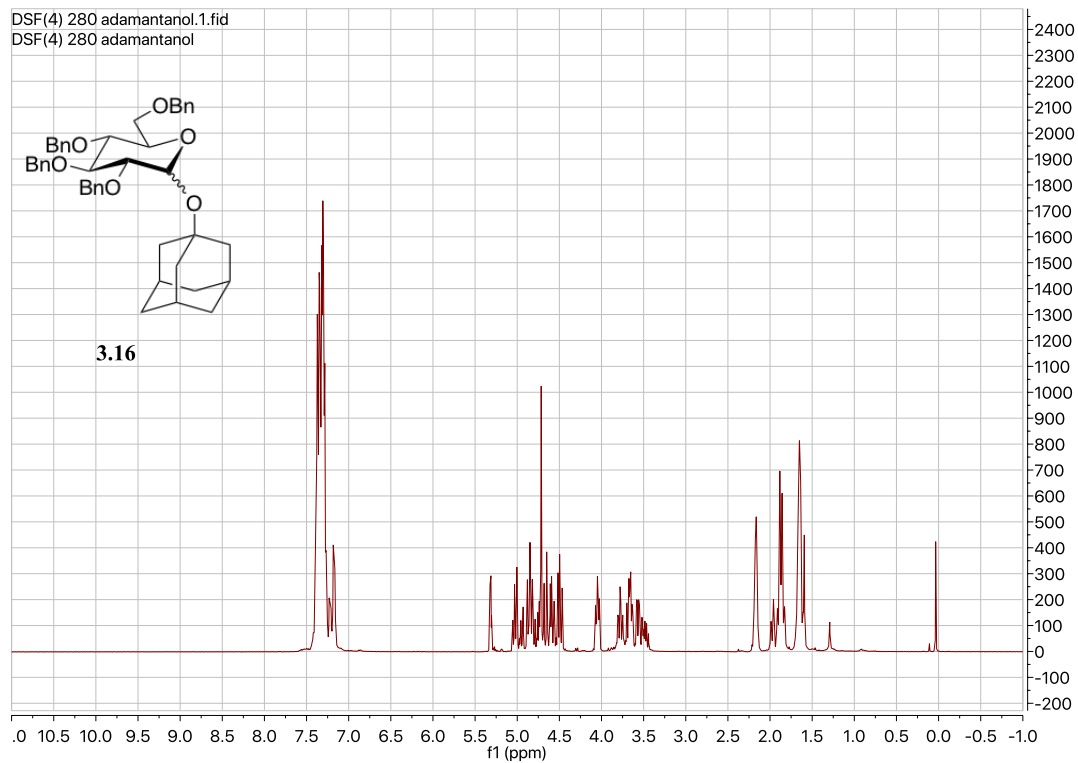


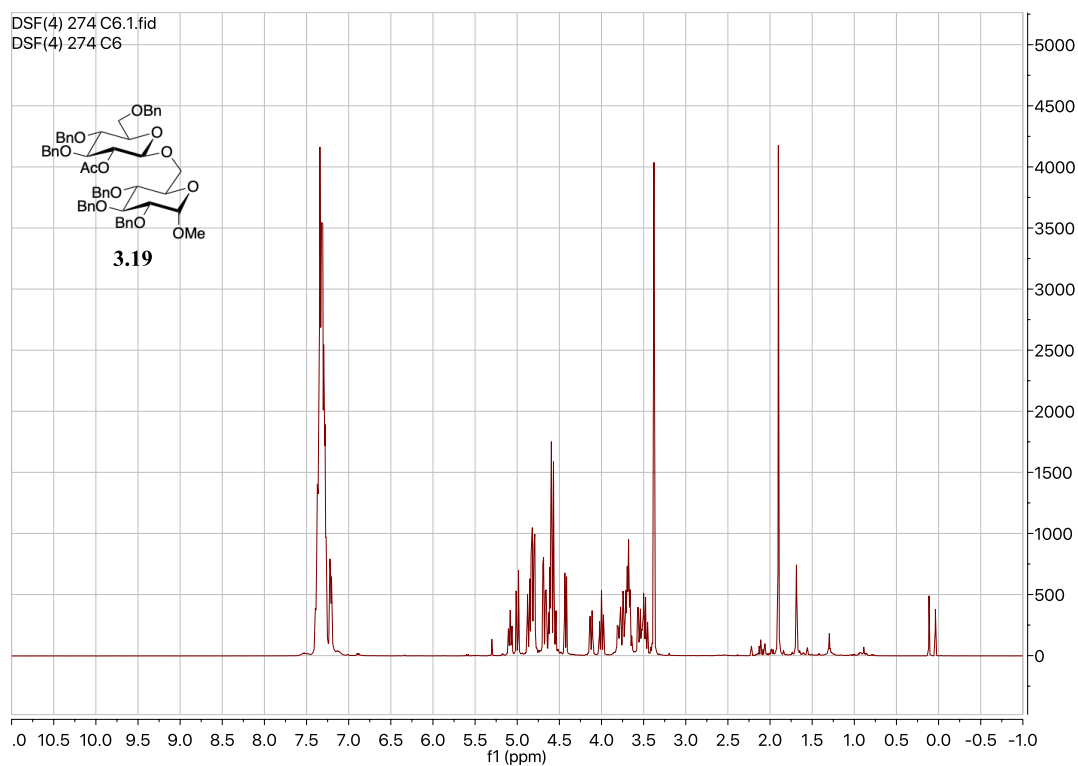
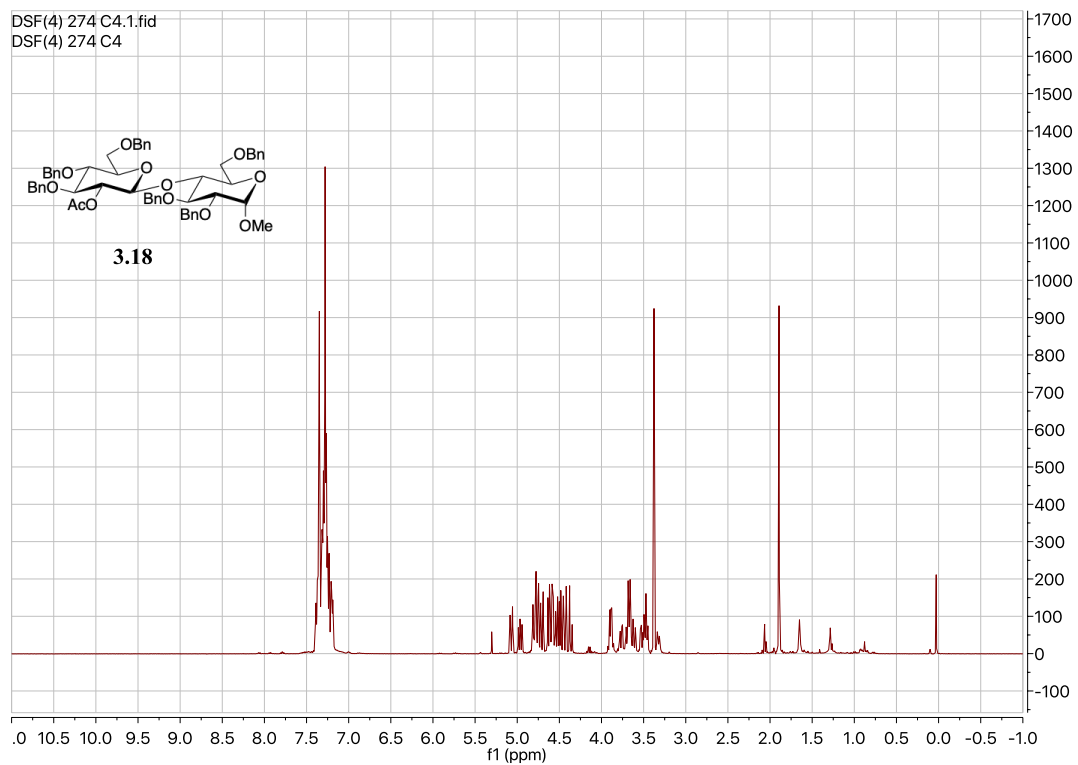


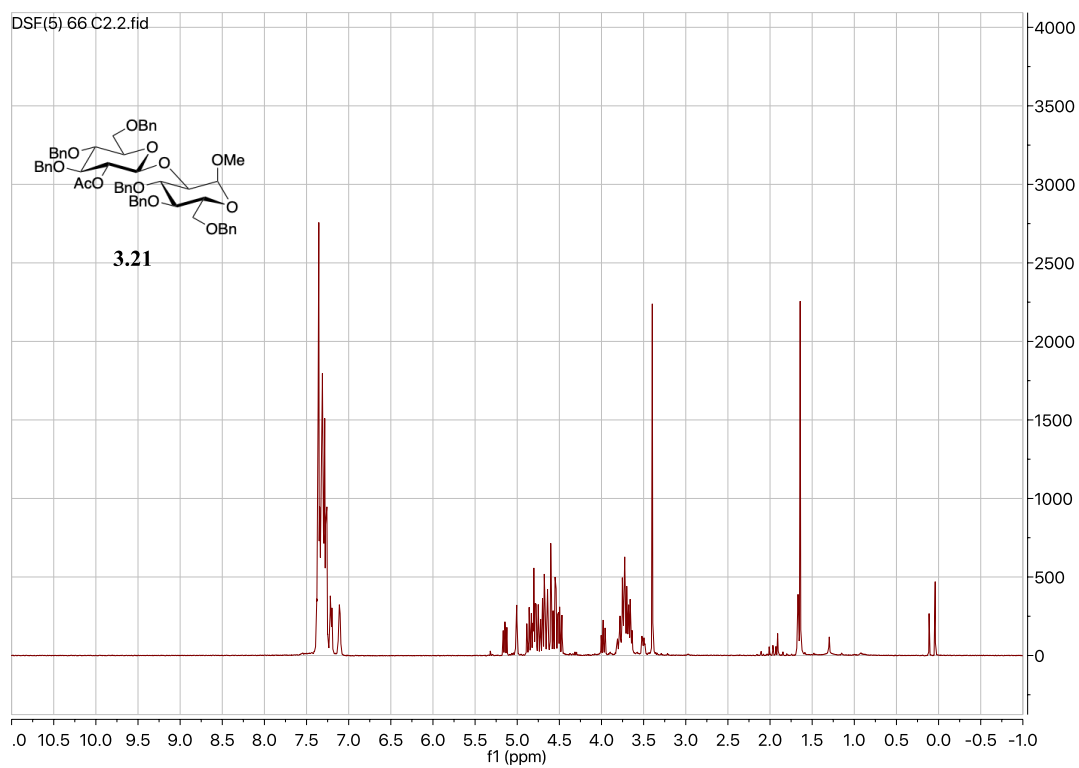
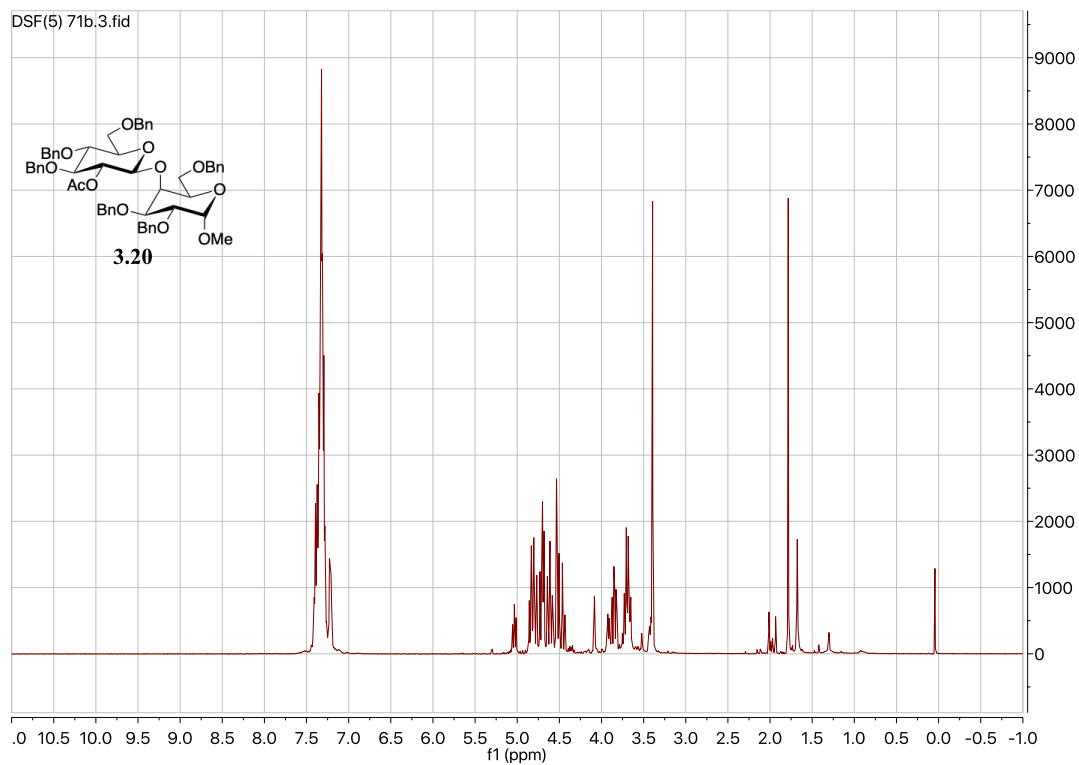


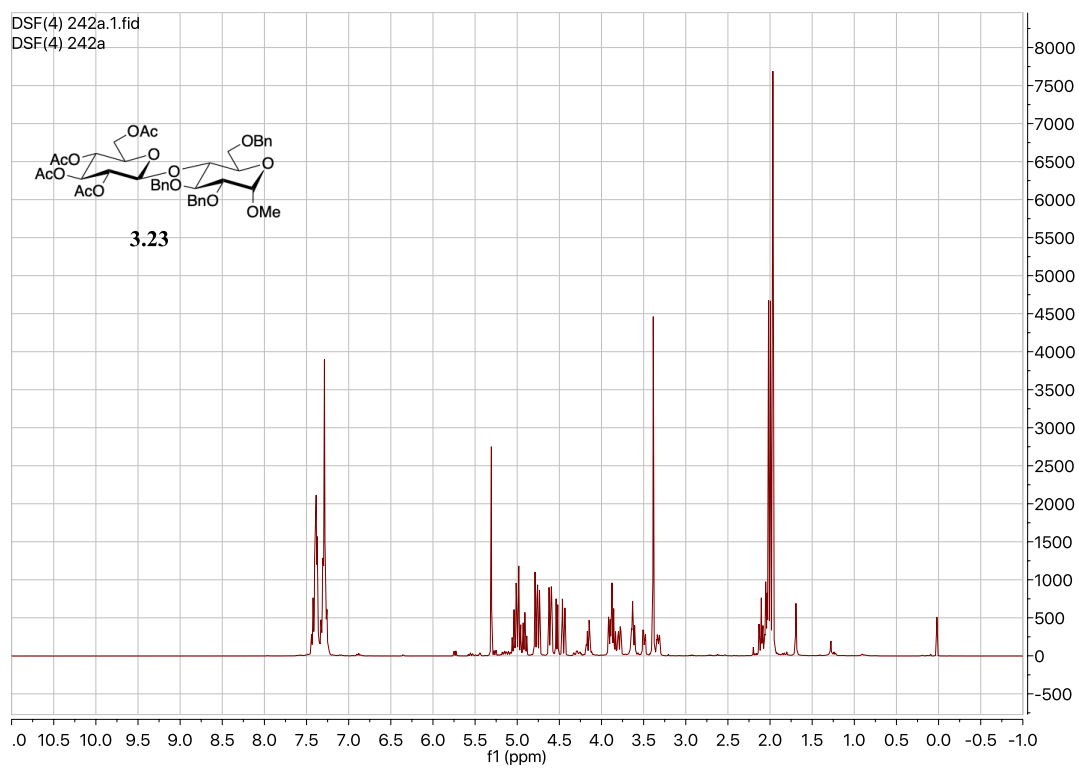
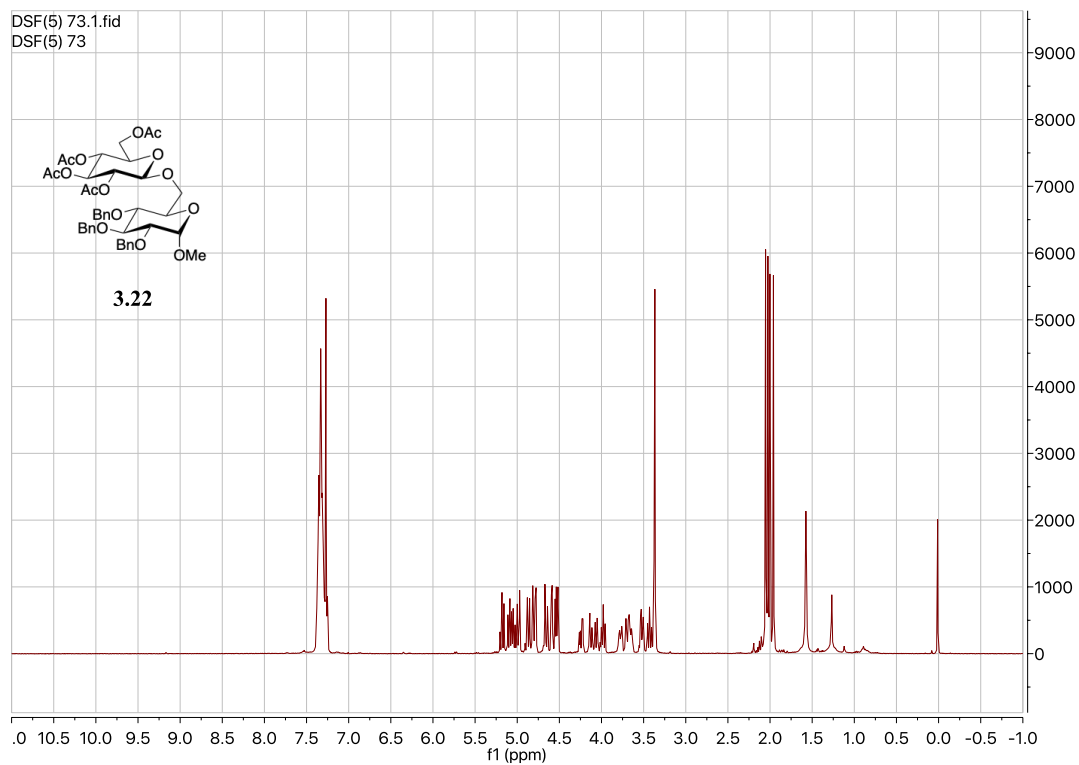


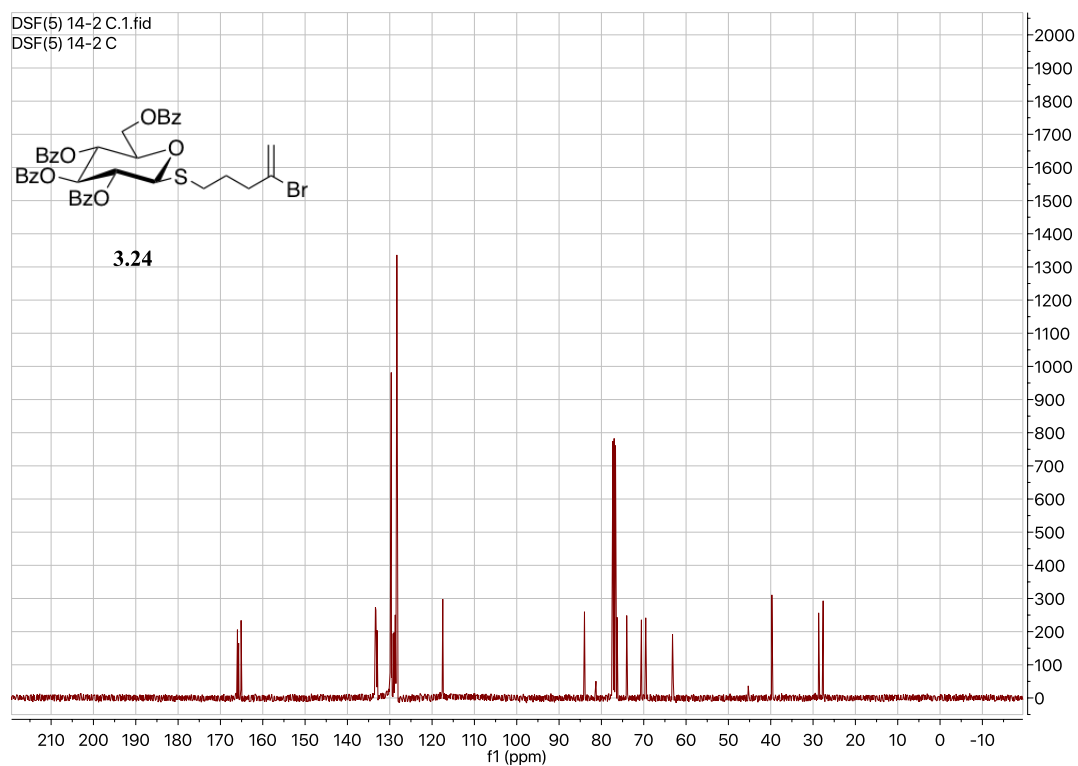
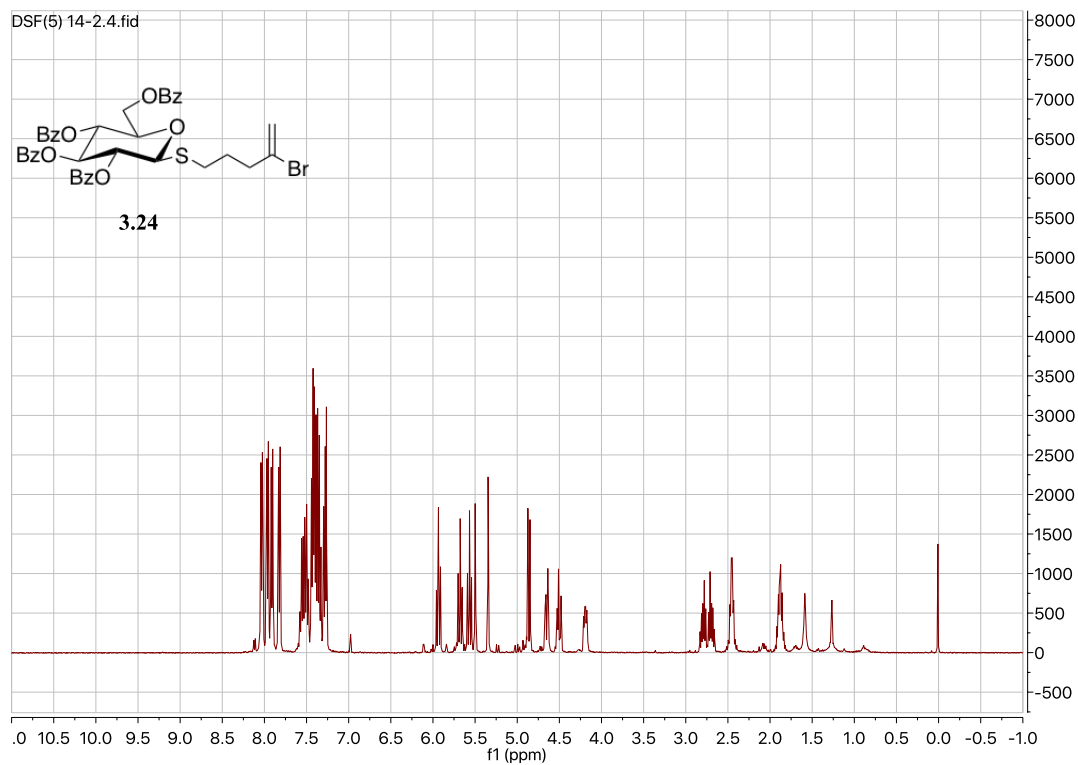


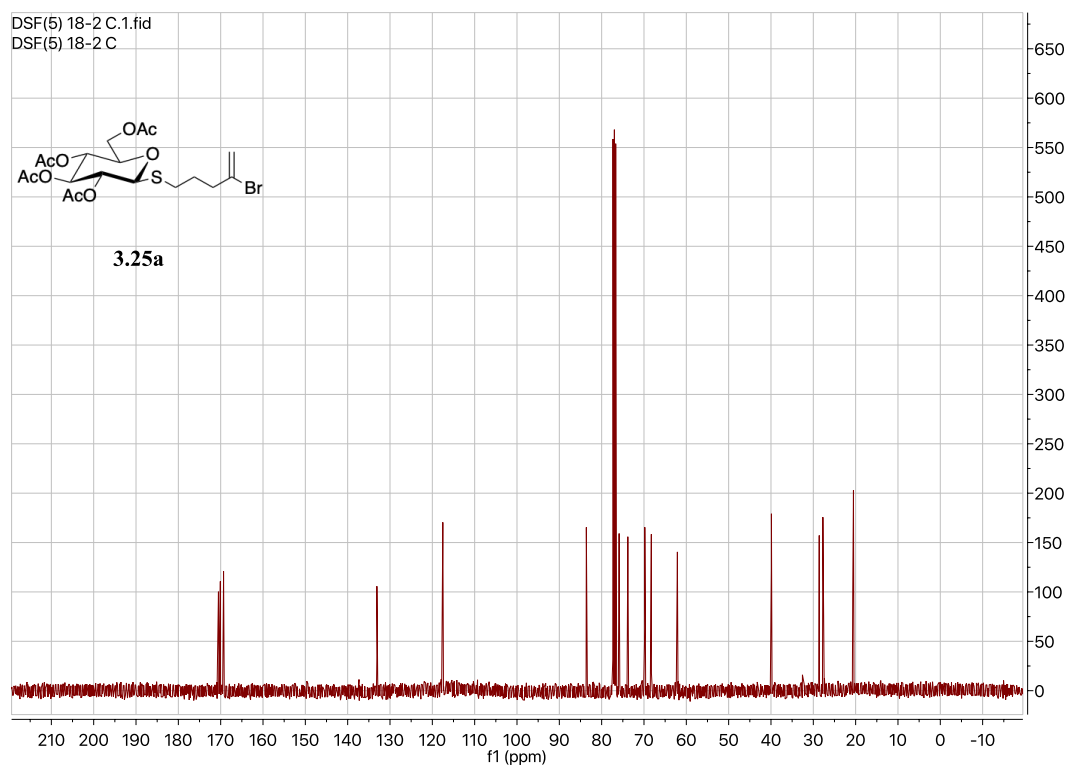
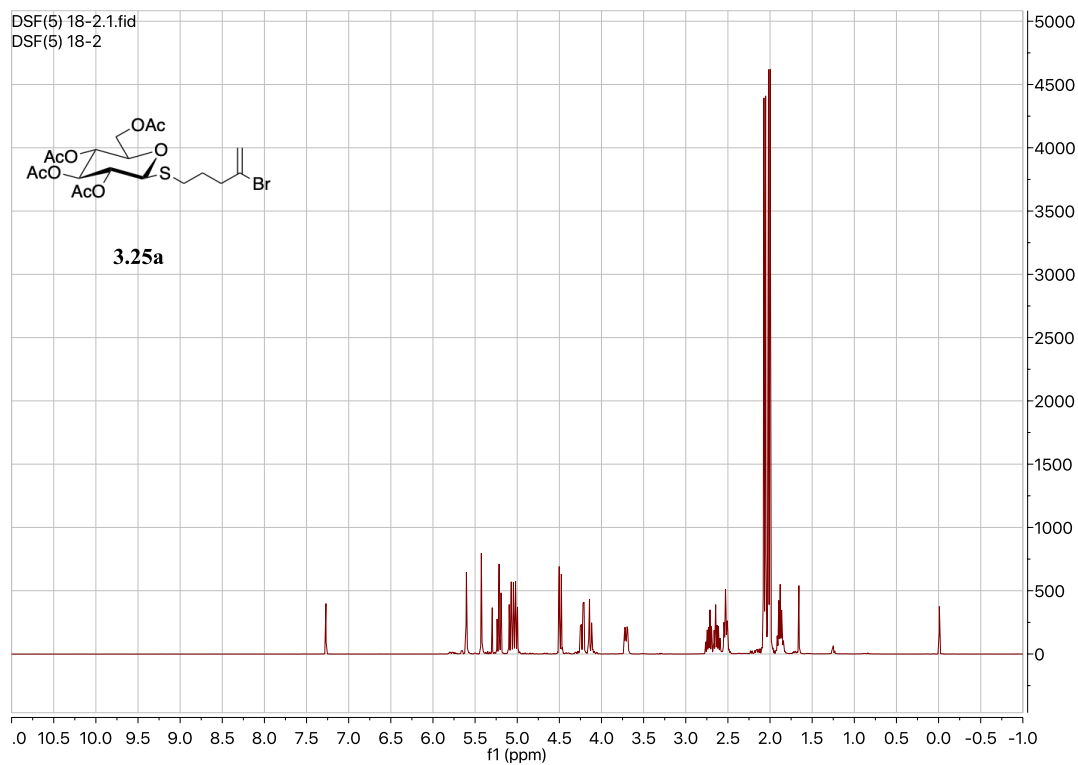


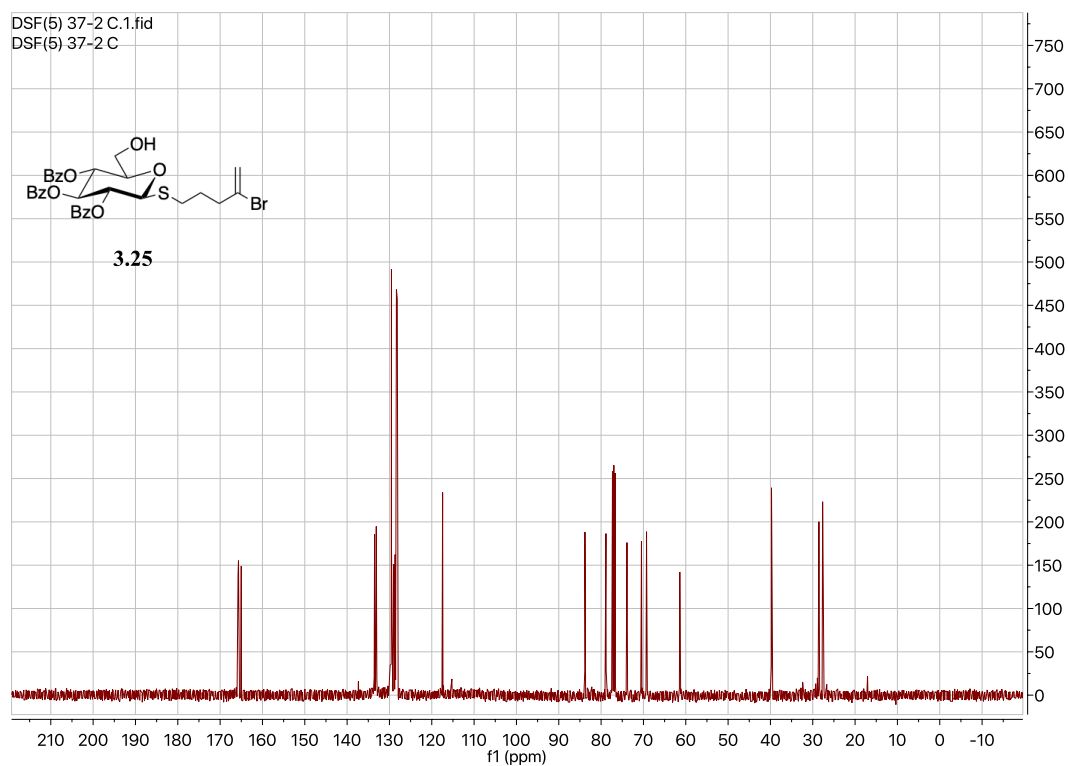
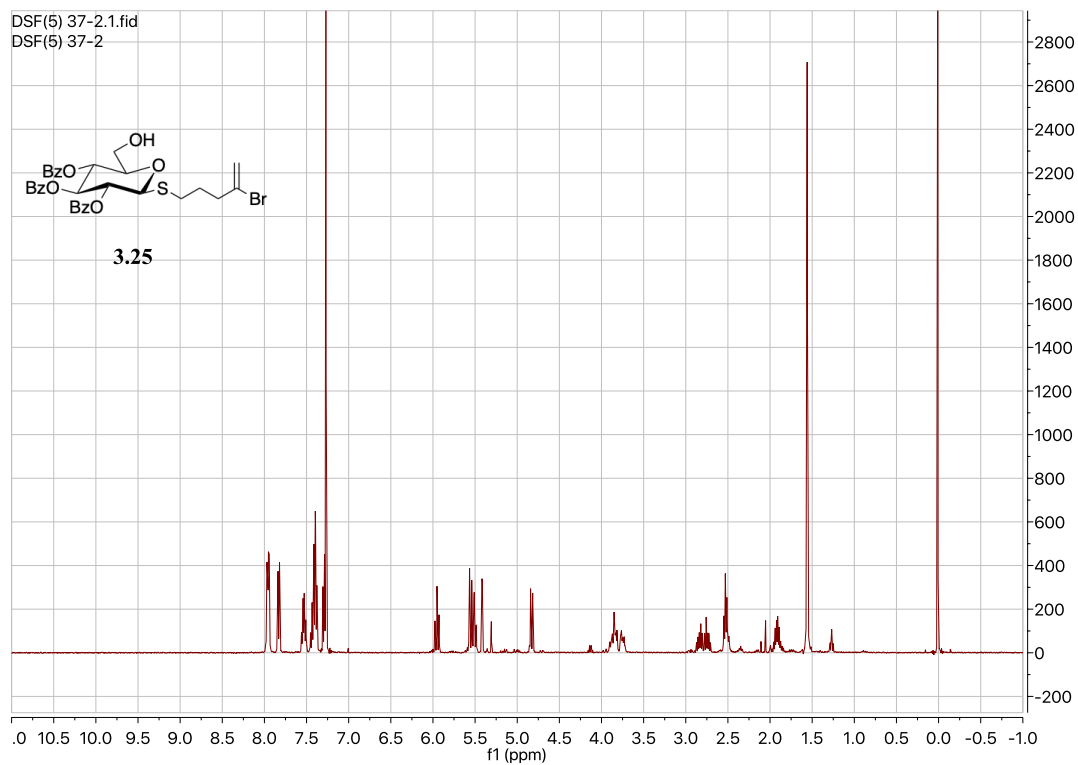


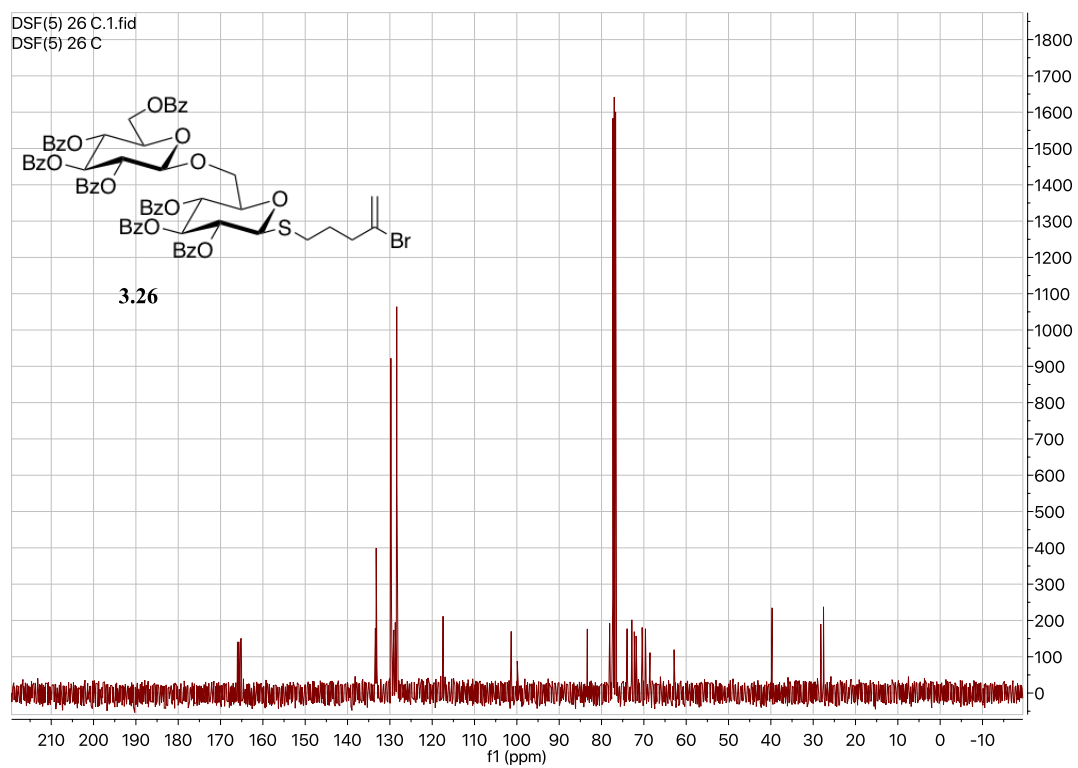
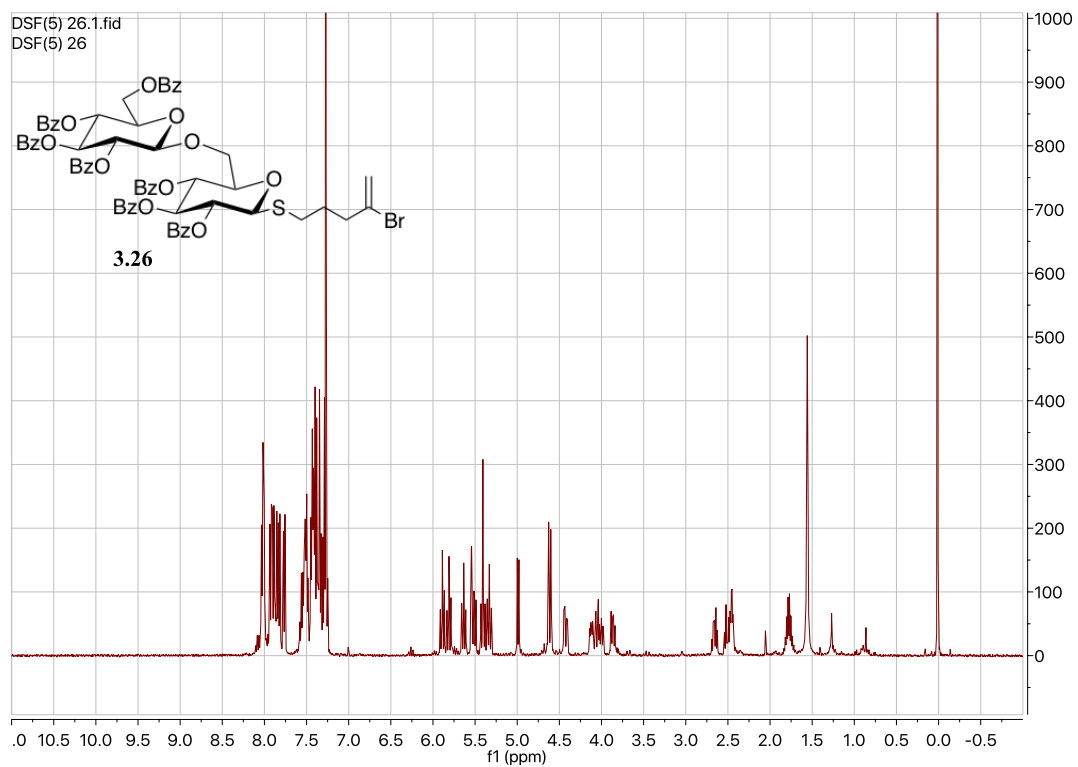


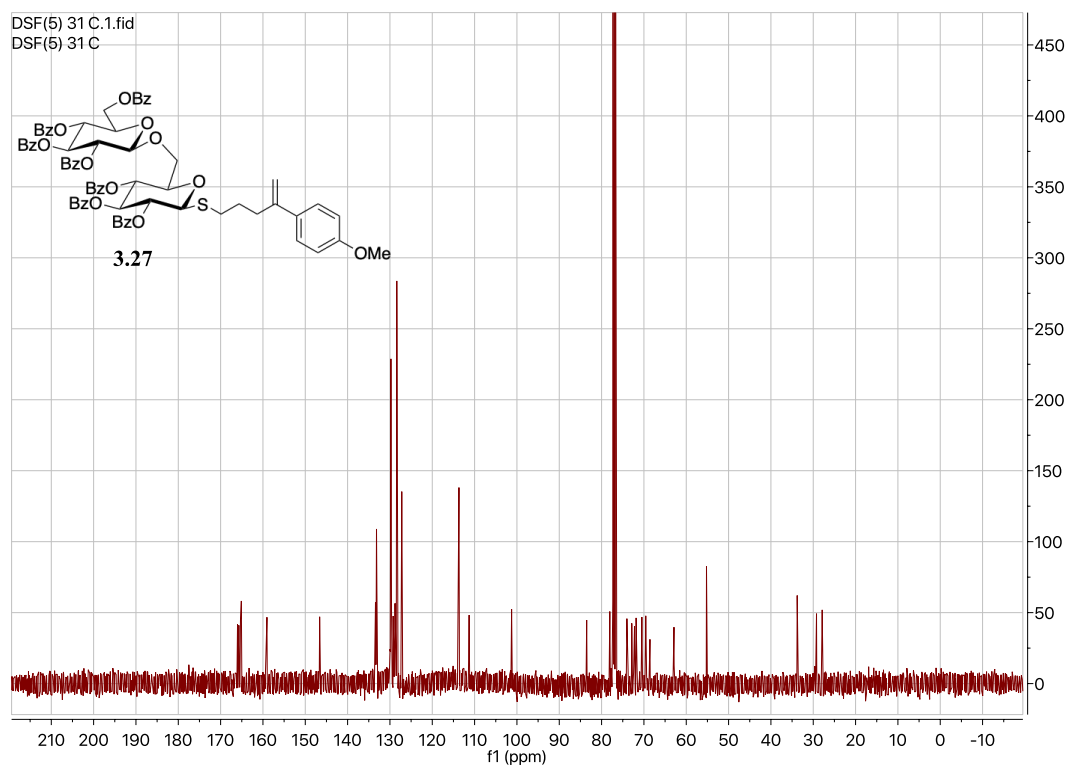
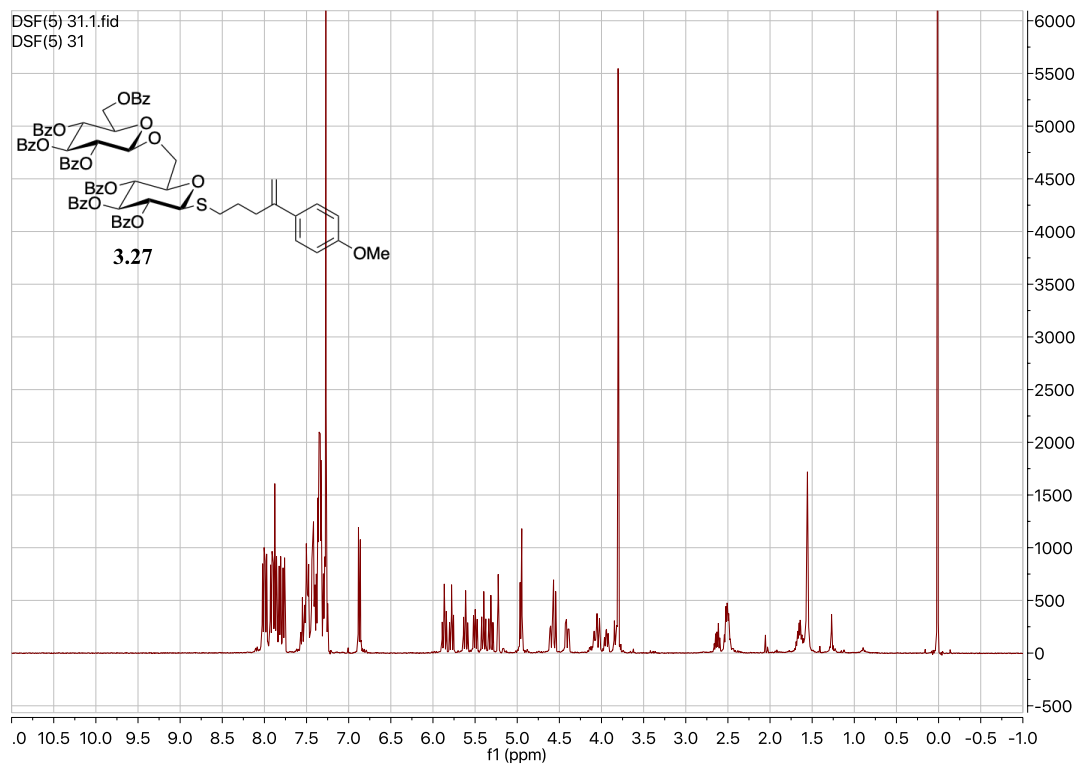


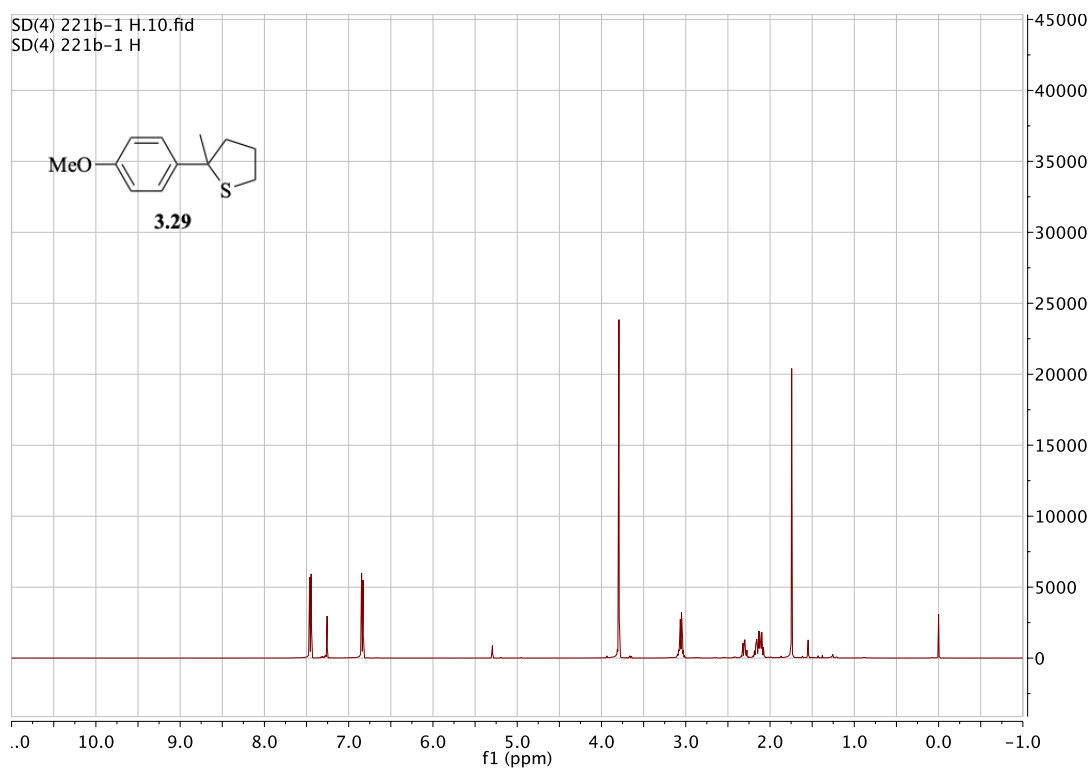
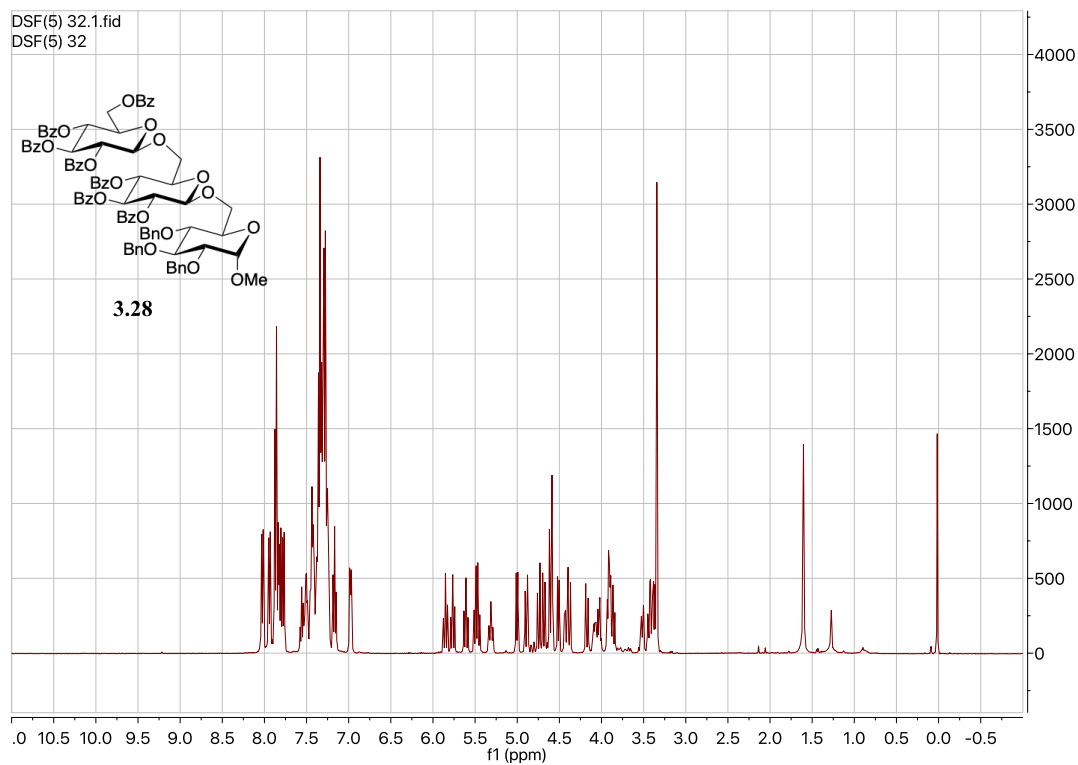




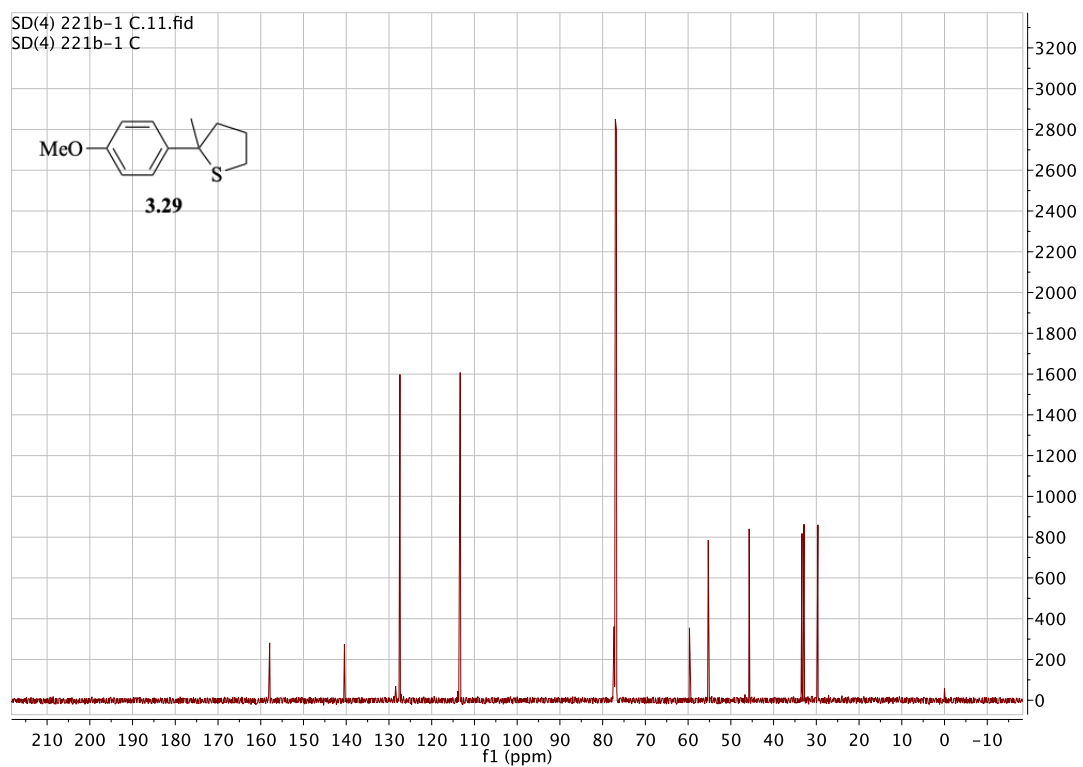




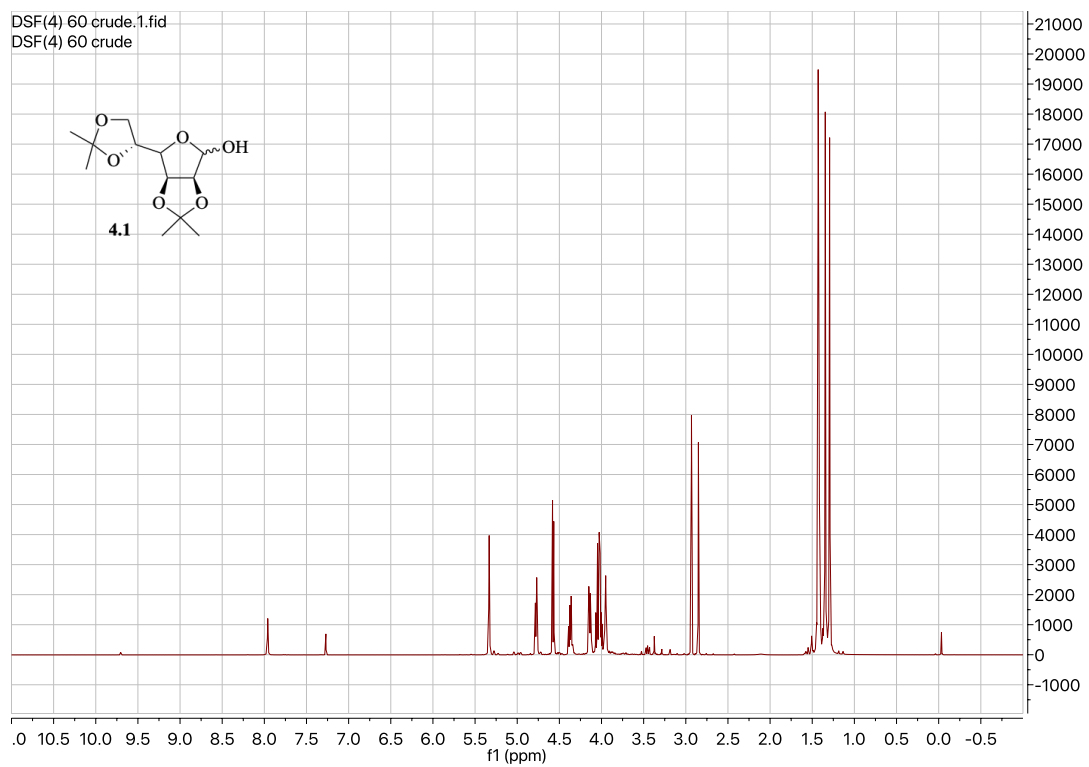
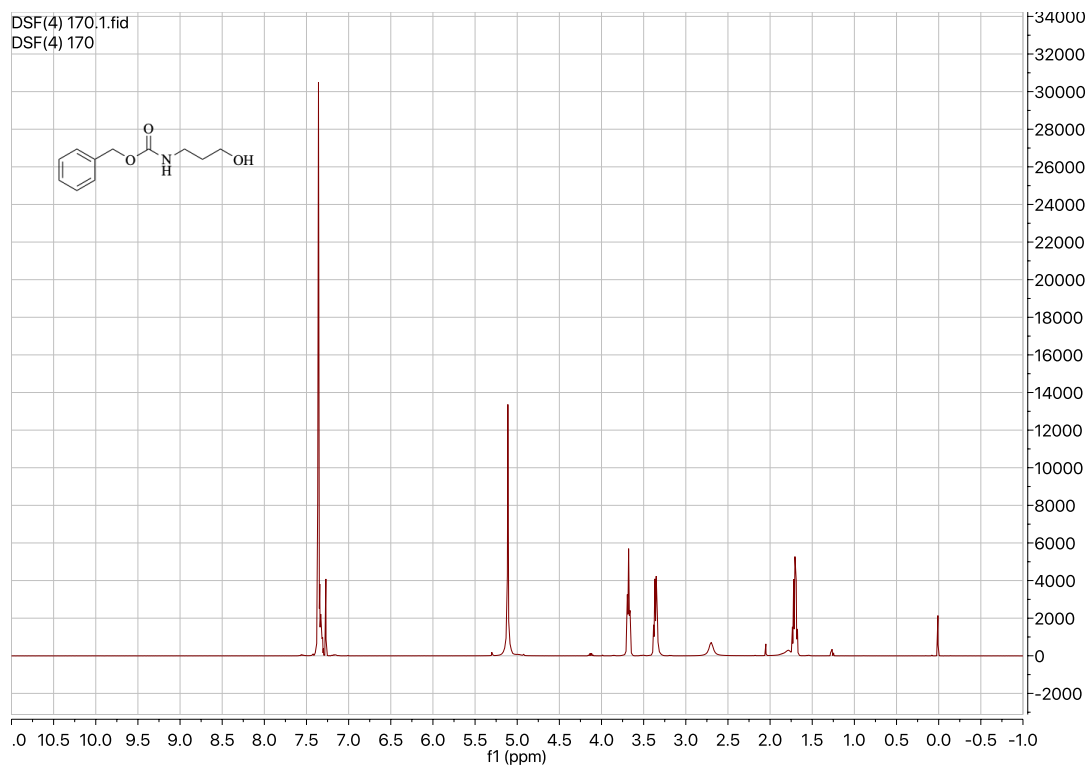


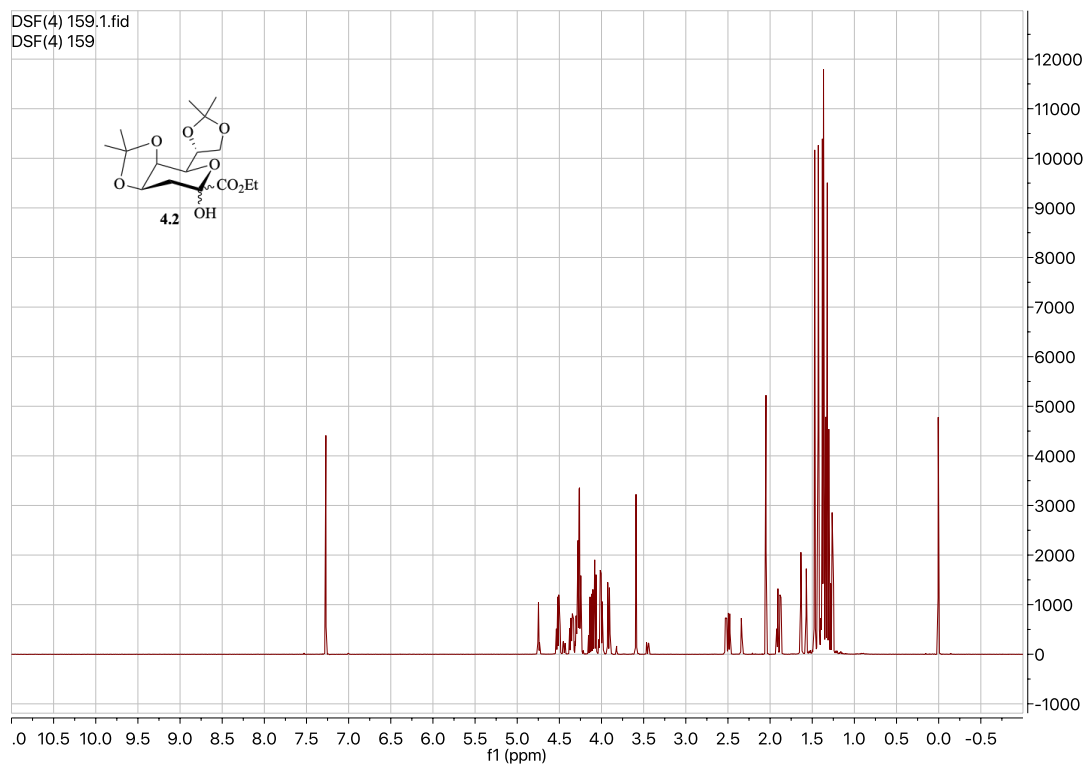
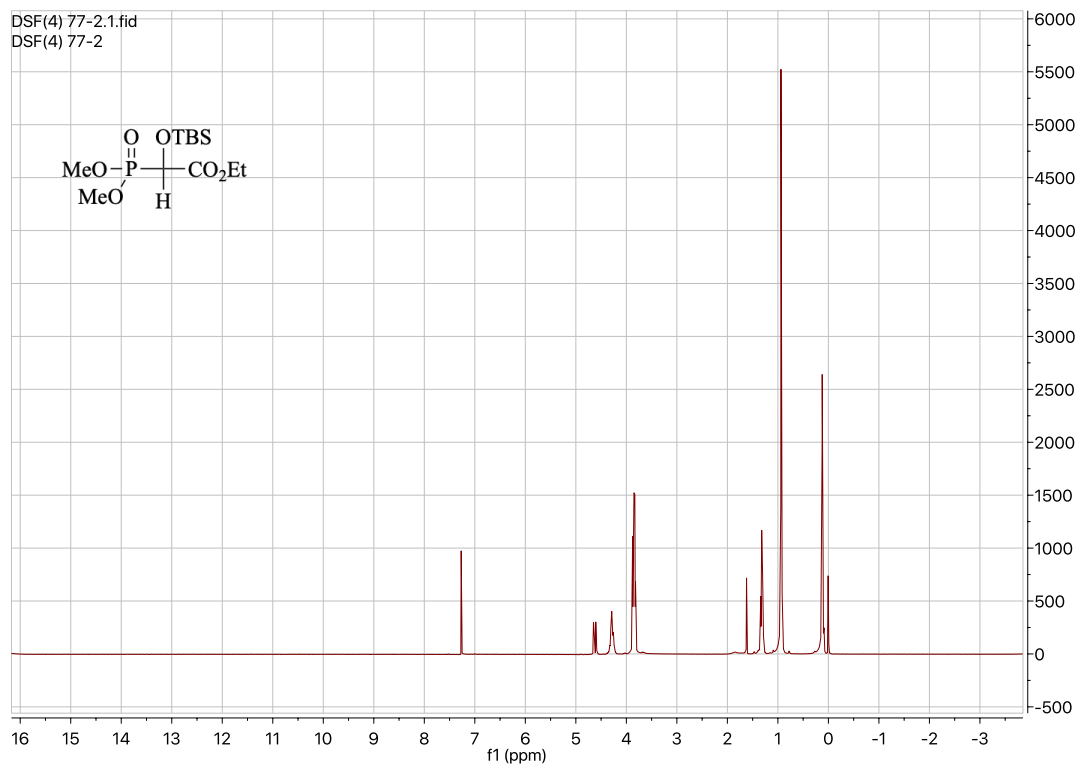


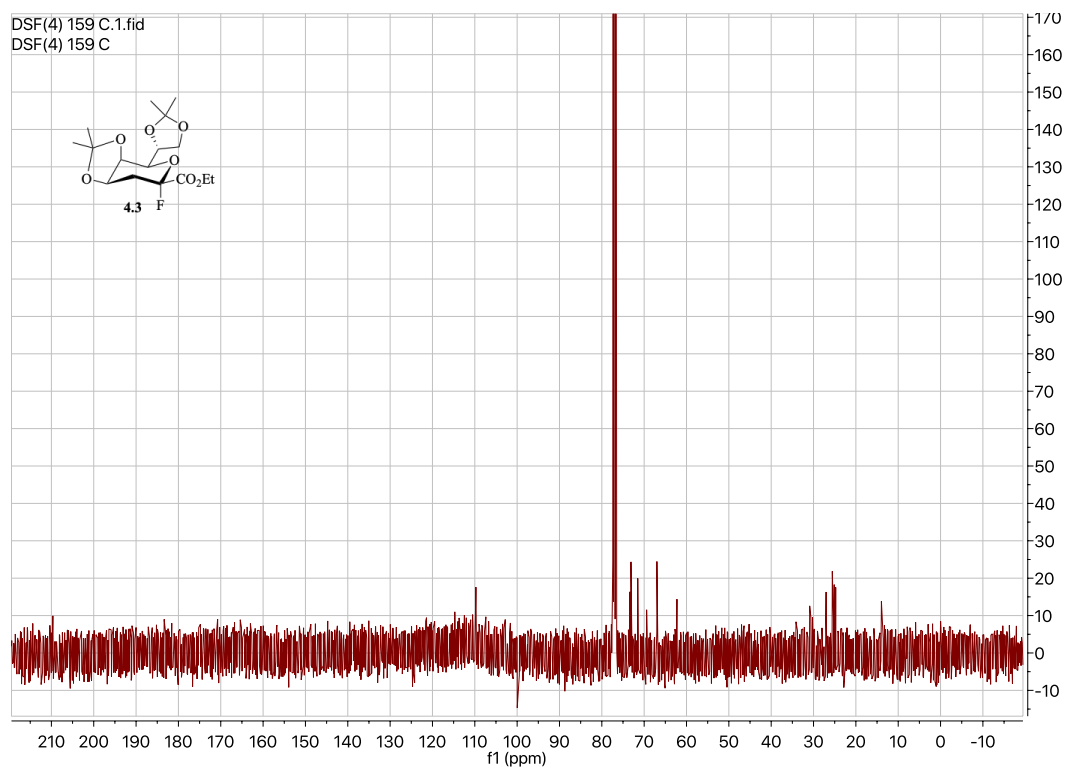
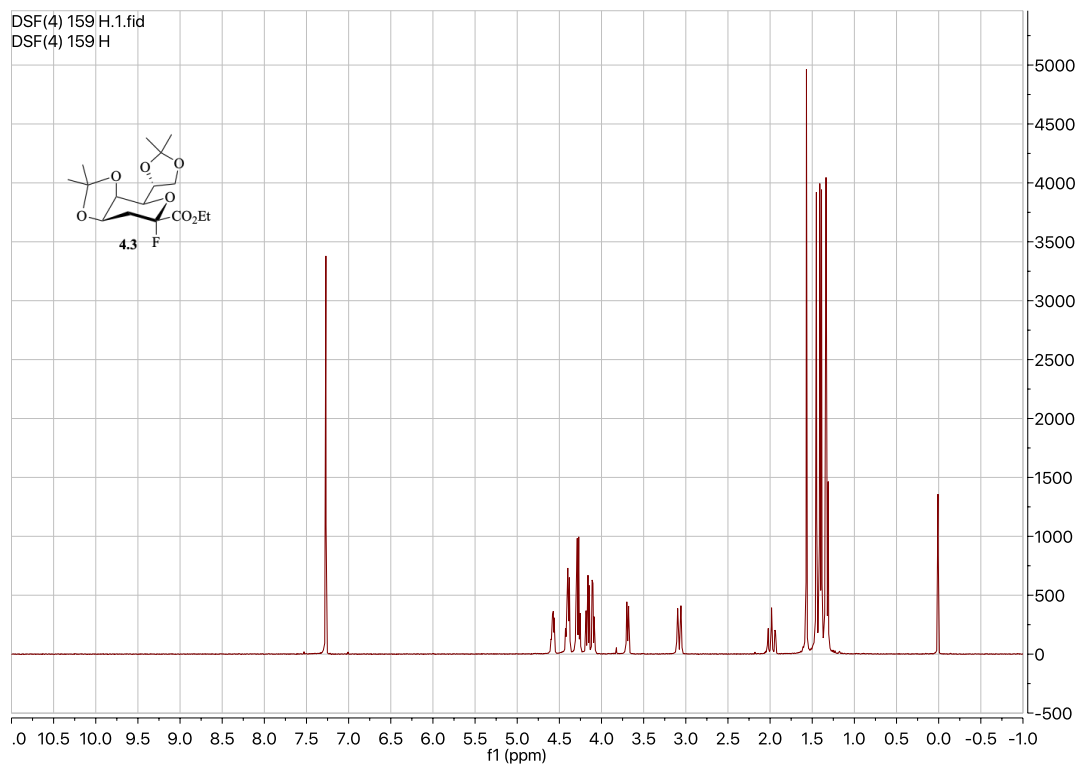
SD(4) 221b-1 C.11.fid
SD(4) 221b-1 C

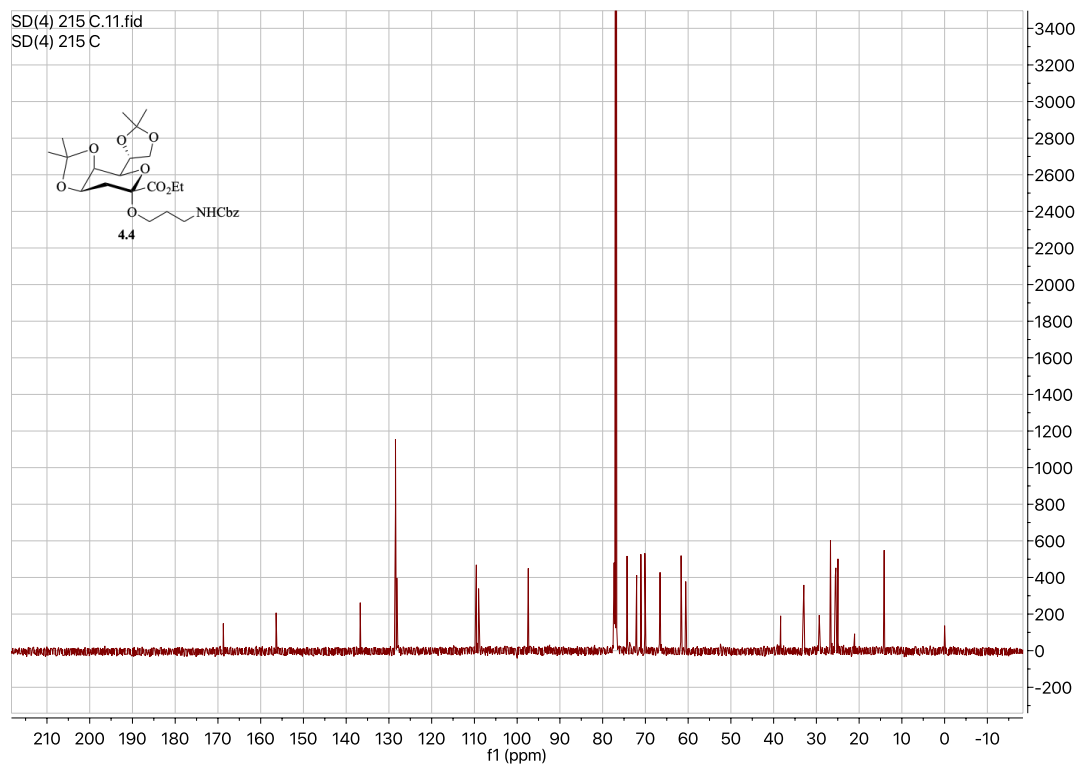
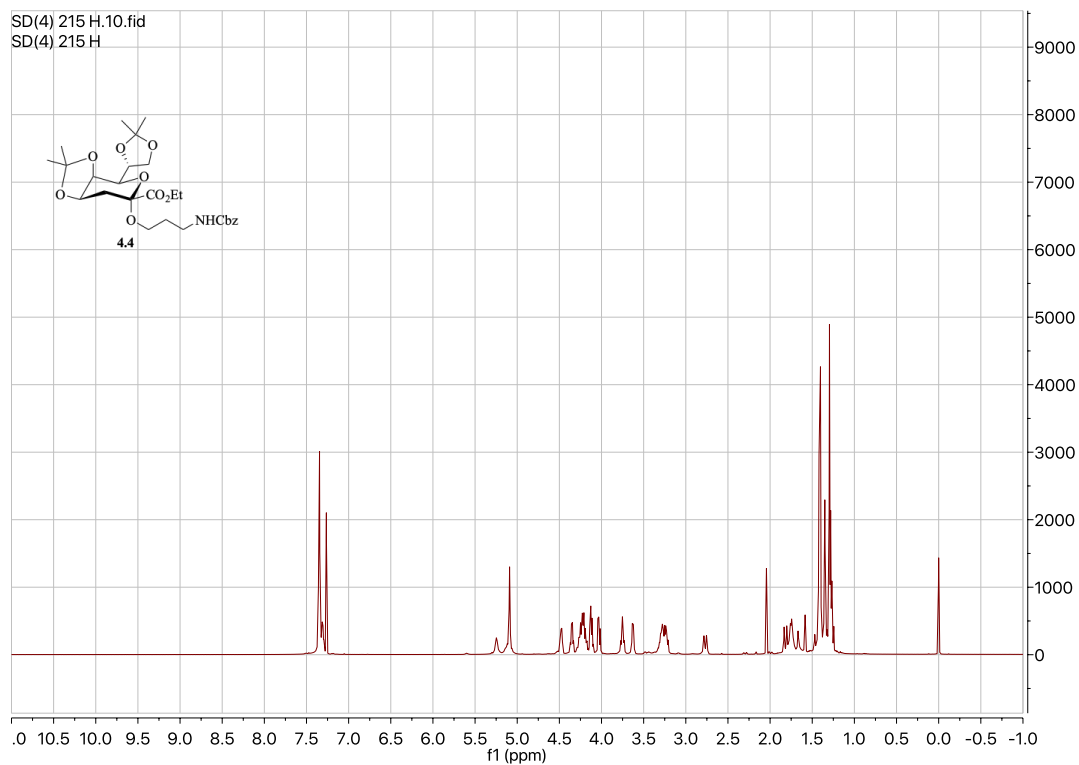


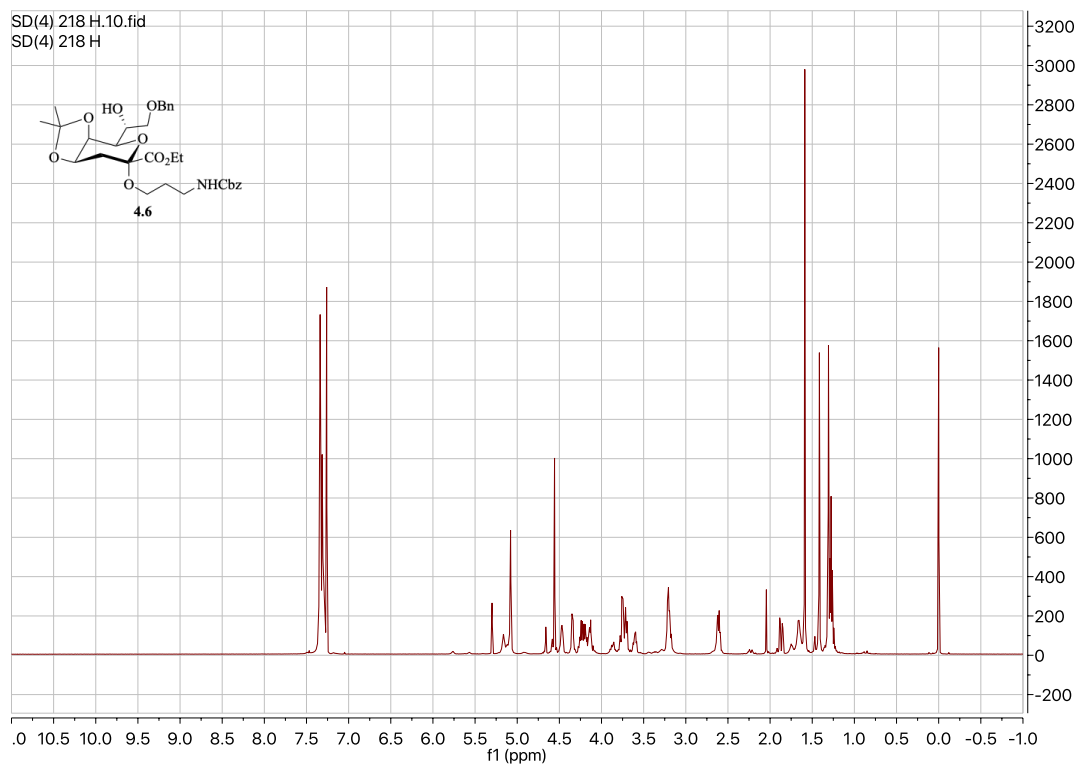
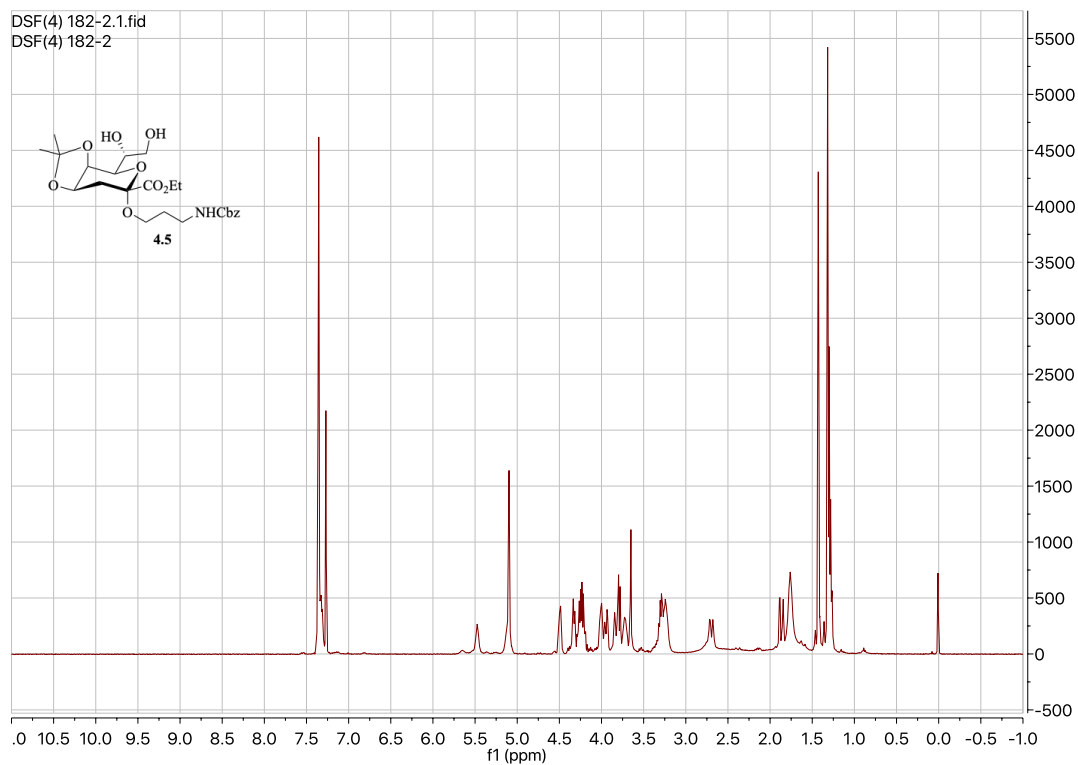
APPENDIX E. NMR SPECTRA OF COMPOUNDS FOUND IN CHAPTER 4

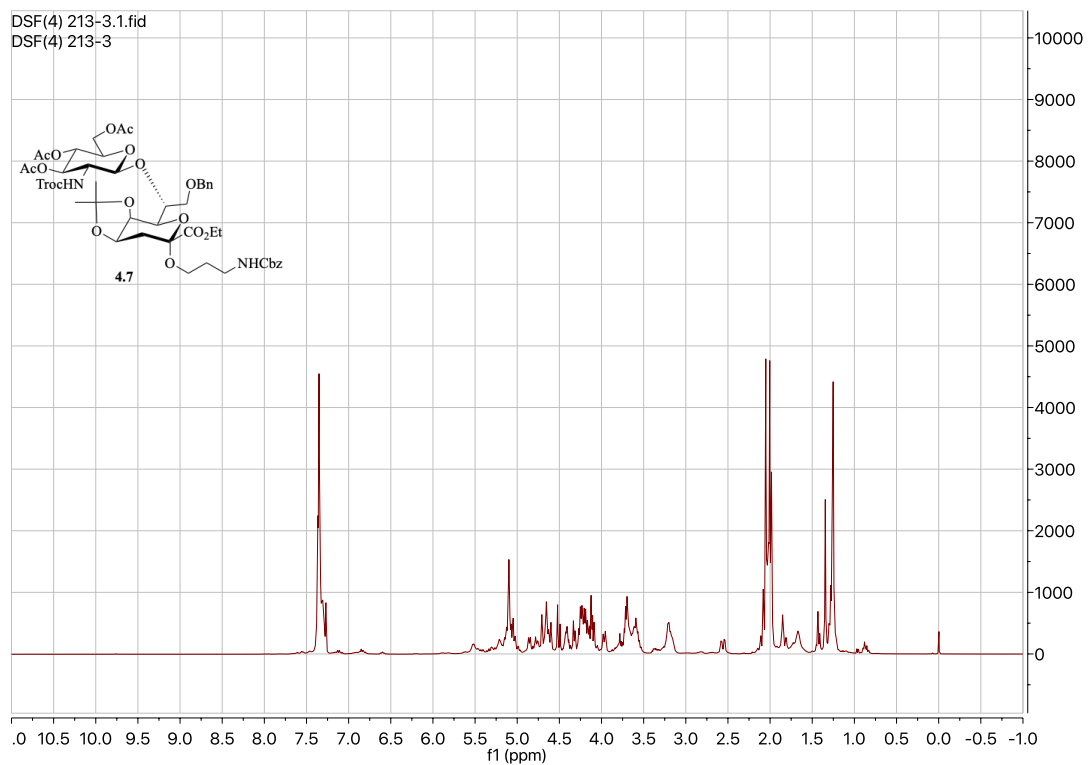
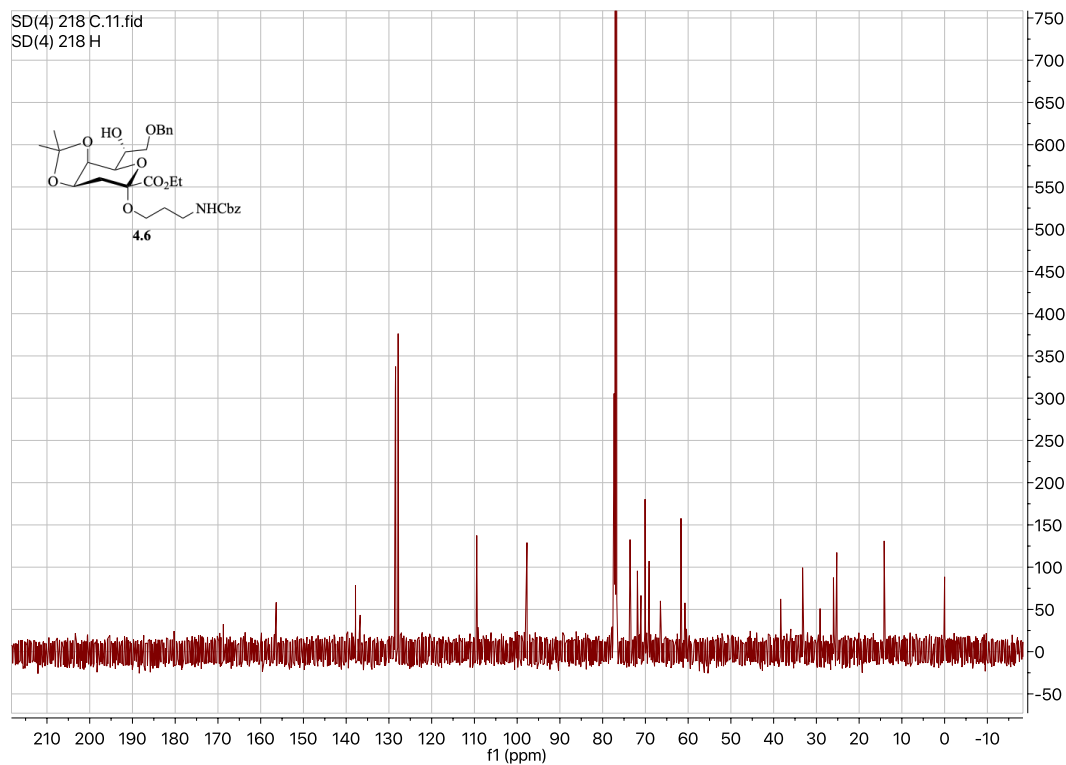


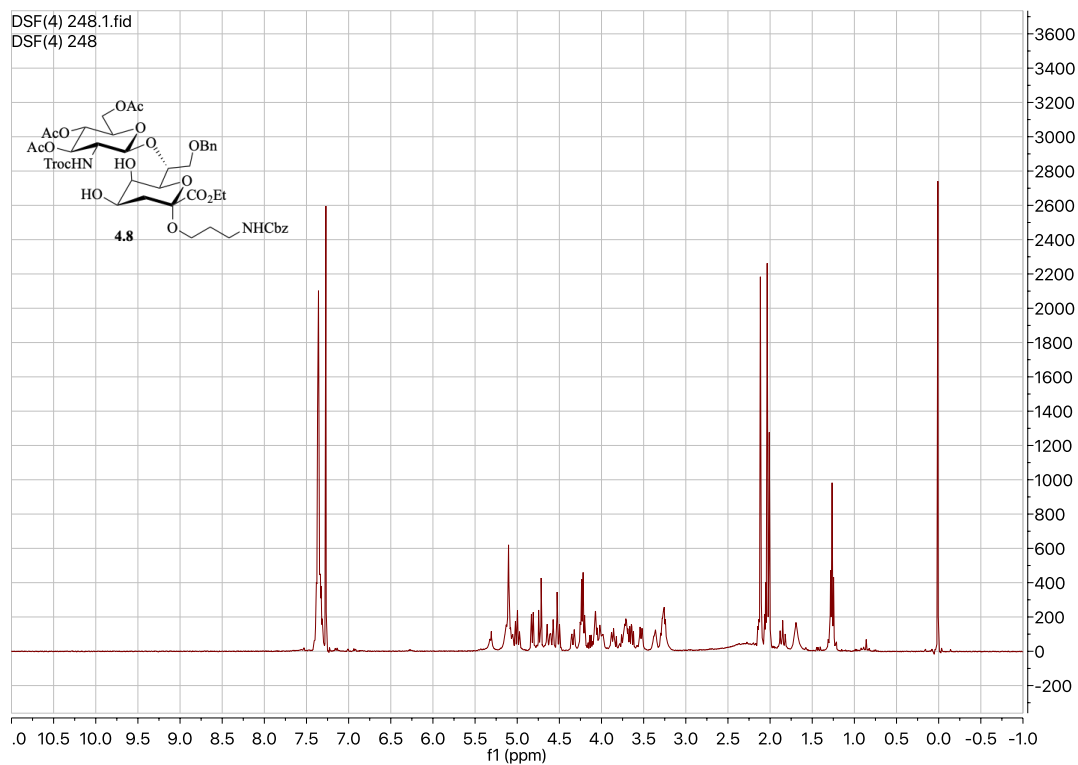
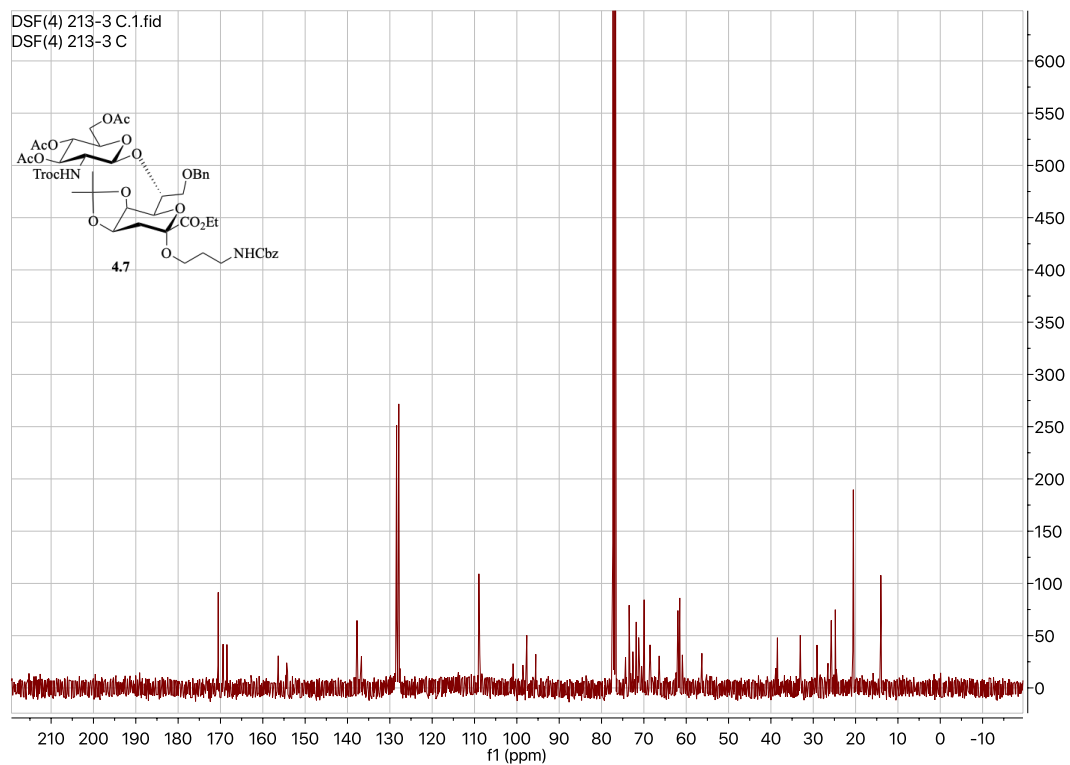












VITA

Shaofu Du was born in Xuchang, China to Changwei Du and Xia Yang in 1992. After graduation from Xuchang High School, he began his undergraduate study in Lanzhou University and obtained the Bachelor of Science degree in summer, 2014. After that, he traveled to United States of America and joined in Louisiana State University to pursue his doctorate degree in chemistry. In the fall of 2014, he joined Dr. Justin R. Ragains research group to study photochemistry and carbohydrate chemistry. Shaofu is currently a Ph.D. candidate and plans to receive a Ph.D. in chemistry in spring 2019.