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# Thioetherification and Etherification Utilizing Trichloroacetimidates Under Thermal Conditions & Progress Towards an Efficient Synthesis of AQX-1125

Brian C. Duffy  
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**Thioetherification and Etherification**  
**Utilizing Trichloroacetimidates Under Thermal Conditions**  
**&**  
**Progress Towards an Efficient Synthesis of AQX-1125**

Brian C. Duffy, M.S.

Syracuse University, 2016

**Abstract of the Dissertation**

The synthesis of ethers and thioethers is necessary as the motifs are ubiquitous in natural products, pharmaceuticals, and are quite useful in numerous synthetic applications. While common methodologies exist to prepare simple ether and thioether substrates, the harsh conditions of these techniques make them unsuitable for complex molecules. The requirement for facile and efficient means has led to an investigation into *O* - and *S* - alkylations occurring solely under thermal conditions utilizing trichloroacetimidates without the addition of a strong acid or base promoter.

The alkylation of thiols by the direct displacement of trichloroacetimidates has been accomplished under thermal conditions (heating in refluxing THF). These reactions proceed to the corresponding thioetherification product without the requirement of an added acid, base, or metal catalyst. This facile procedure provides the sulfide in excellent yields with only the formation of the neutral trichloroacetamide as the side product. Formation of the trichloroacetimidate *in situ* has also been studied, which provides a convenient method for the formation of sulfides from alcohols in a single flask.

A similar methodology towards obtaining etherification products has also been investigated. *O* – Diphenylmethyl and *para*-methoxybenzyl trichloroacetimidates in refluxing solvent has shown to effectively convert a variety of alcohols to their corresponding ether without disturbing pre-existing functionality. This methodology provides the subsequent etherification products in moderate to excellent yields with only the formation of the neutral trichloroacetamide as the side product.

Additionally, the development of a more efficient and concise total synthesis towards the SHIP1 activator AQX-1125 from *trans*-dehydroandrosterone has been studied. The synthetic approach features an allylic oxidation of the C7 position and ozonolysis to generate key intermediates. Alternative routes have also been proposed and future investigations will aim to complete this project in the future.

**Thioetherification and Etherification**  
**Utilizing Trichloroacetimidates Under Thermal Conditions**  
**&**  
**Progress Towards an Efficient Synthesis of AQX-1125**

by

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Dissertation

Submitted to the Graduate Faculty of

Arts & Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

Syracuse University

July 2016



SYRACUSE UNIVERSITY

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*"Never give in...never...in nothing great or small or large or petty...except to convictions of honour...never yield to force...never yield to the apparently overwhelming might of the enemy."*

-Winston Churchill

*"Nothing in this world that's worth having comes easy"*

## PREFACE

This thesis has been adapted from the following published articles:

Howard, K.T.; Duffy, B.C.; Linaburg, M.R.; Chisholm, J. D., Formation of DPM Ethers Using *O'*-Diphenylmethyl Trichloroacetimidate Under Thermal Conditions. *Org. Biomol. Chem.* **2016**, 14, 1623.

Duffy, B.C; Howard, K.T.; Chisholm, J. D., Alkylation of Thiols with Trichloroacetimidates under Neutral Conditions. *Tetrahedron Lett.* **2015**, 56, 3301.

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## List of Symbols/Abbreviations

°C – degree Celsius .....	
µg - microgram.....	
µL - microliter.....	
µM - micromolar.....	
δ - chemical shift (ppm).....	
AcOH – acetic acid.....	
AgOTf – silver trifluoromethanesulfonate.....	
AIDS – acquired immune deficiency syndrome.....	
BF <sub>3</sub> •OEt <sub>2</sub> -boron trifluoride diethyl etherate.....	
BH <sub>3</sub> – borane .....	
Bn – benzyl.....	
BnBr – benzyl bromide.....	
br s – broad singlet.....	
Btk – Bruton’s tyrosine kinase.....	
CaCO <sub>3</sub> – calcium carbonate.....	
Cb – cyclobutyl.....	
CDCl <sub>3</sub> – deuterated chloroform, used for calibrating NMR.....	
CeCl <sub>3</sub> – cerium (III) chloride.....	
COP - cobalt oxazoline palladacycle.....	
Cpm – cyclopropylmethyl.....	
CSA – camphorsulfonic acid.....	
d – day(s).....	

d - doublet.....

DBU - 1,8-diazabicyclo[5.4.0]undec-7-ene.....

DCE – 1,2-dichloroethane.....

DCM – dichloromethane.....

DEAD – diethyl azodicarboxylate.....

DIAD – diisopropyl azodicarboxylate.....

DMAP – 4-dimethylaminopyridine.....

DMF – *N,N*- dimethylformamide.....

DMP – 2,2-dimethoxypropane.....

DPM – diphenylmethyl.....

DPT-BM - 4-(4,6-diphenoxy-1,3,5-triazin-2-yl)-4-benzylmorpholinium  
trifluoromethanesulfonate.....

EDCI -1-ethyl-3-(30dimethylaminopropyl)carbodiimide.....

eq. – equivalent(s).....

Et<sub>3</sub>N – triethylamine.....

g – gram(s).....

Ga(OTf)<sub>3</sub> – gallium (III) triflate.....

h – hour(s).....

Ha – homoallyl.....

Hz - hertz .....

J – coupling constant.....

LAH – lithium aluminium hydride.....

M - molar.....

m – multiplet.....

mCPBA – meta-chloroperoxybenzoic acid.....

MeOTf – methyl trifluoromethanesulfonate.....

MgO – magnesium oxide.....

MHz - megahertz.....

mL - milliliter.....

(m)mol – (milli)mole.....

mp – melting point.....

MS – molecular sieves.....

NaBH<sub>4</sub> – sodium borohydride.....

NaCl – sodium chloride.....

NaH – sodium hydride.....

NaIO<sub>4</sub> – ammonium periodate.....

NH<sub>4</sub>BF<sub>4</sub> – ammonium tetrafluoroborate.....

NH<sub>4</sub>Cl – ammonium chloride.....

NIS – *N*-iodosuccinimide.....

PDK1 – phosphoinositide kinase I.....

Ph – phenyl.....

PH – pleckstrin domains.....

PhCF<sub>3</sub> –  $\alpha, \alpha, \alpha$ -trifluorotoluene.....

PI – Phosphoinositide.....

PI(3,4)P<sub>2</sub> – phosphatidylinositol (3,4)-bisphosphate.....

PI(3,4,5)P<sub>3</sub> – phosphatidylinositol (3,4,5)-triphosphate.....

PI(4,5)P<sub>2</sub> – phosphatidylinositol (4,5)-bisphosphate.....  
 PI3K – phosphoinositide 3-kinase(s).....  
 PIP – phosphatidylinol 3-phosphate.....  
 PMB – *para*-methoxybenzyl.....  
 pTsOH – *para* –toluene sulfonic acid.....  
 q - quartet.....  
 rt – room temperature.....  
 RTK – receptor tyrosine kinase.....  
 RuCl<sub>3</sub> \* H<sub>2</sub>O– ruthenium trichloride hydrate.....  
 s - singlet.....  
 sat'd - saturated.....  
 SHIP1 – SH 2-containing inositol-5'-phosphatase 1 .....  
 SHIP2 – SH 2-containing inositol-5'-phosphatase 2 .....  
 SmCl<sub>3</sub> – samarium (III) chloride.....  
 SmI<sub>3</sub> – samarium (III) iodide.....  
 Sn(OTf)<sub>2</sub> - tin(II) trifluoromethanesulfonate.....  
 t - triplet.....  
 TBAF – tetra-n-butylammonium fluoride.....  
 TBS – *tert*-butyldimethylsilyl.....  
 tBuOOH – *tert*-Butyl hydroperoxide.....  
 TCAN – trichloroacetonitrile.....  
 TfOH – Trifluoromethanesulfonic acid.....  
 THF – tetrahydrofuran.....



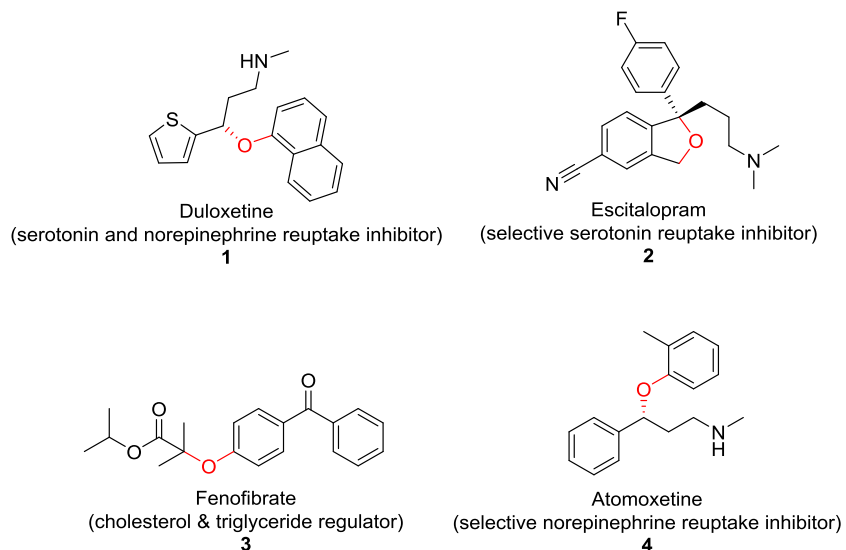
TMS – tetramethylsilane, used for calibrating NMR.....

TMSOTf - Trimethylsilyl trifluoromethanesulfonate.....

## Chapter 1. Trichloroacetimidates in Etherification and Thioetherification

### 1.1 Introduction

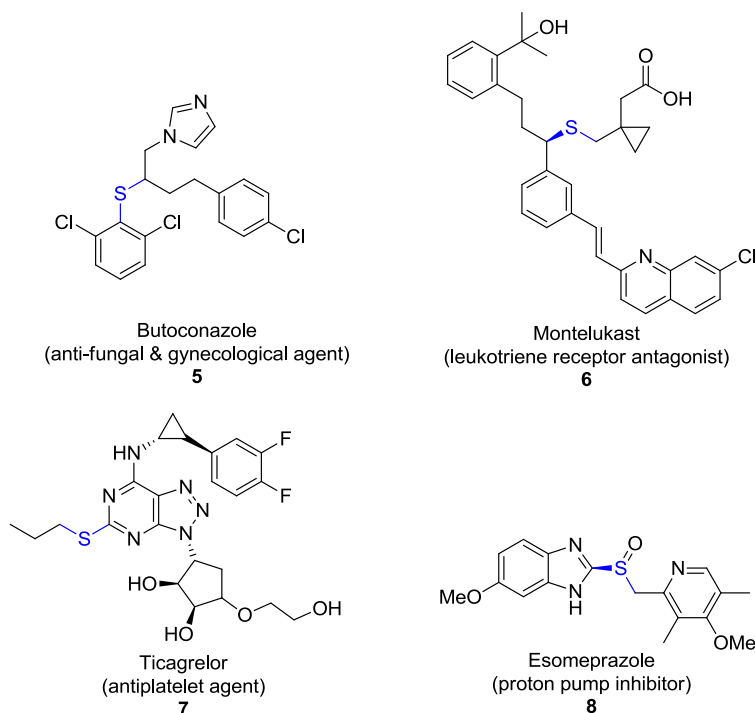
The ether motif is ubiquitous throughout organic chemistry, being common in numerous natural products, pharmaceuticals, and agrochemicals.<sup>1-9</sup> The generation of an ether plays an important role in synthetic organic chemistry as oxygen is one of the most abundant heteroatoms in organic products. Ether formation also plays a key role in the protection of alcohols, another common organic functional group. For example, benzyl ethers are among the most common protecting groups in utilized in organic synthesis. Ethers are also commonly found in pharmaceuticals, such as those shown in Figure 1 below.<sup>8-79</sup>



**Figure 1: Selected Pharmaceuticals that Contain Ethers**

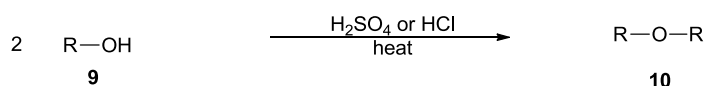
The sulfur analogs of ethers, thioethers or sulfides, also play an important role in modern medicinal chemistry. Recent data mining efforts have shown that 48% of all new drugs approved between 2000 and 2010 contain sulfur.<sup>80</sup> Organosulfur compounds are in clinical use for numerous medical conditions, such as cancer, diabetes, depression, AIDS, and arthritis, and have

also found use in antibacterial and anti-inflammatory applications.<sup>80-86</sup> Some examples include Ticagrelor, a blood thinner, and Montelukast, which is used for the treatment of asthma (Figure 2).<sup>80</sup> Sulfides are also the precursors to sulfoxides and sulfones, which are useful functional groups in their own right, as demonstrated by the proton pump inhibitor Esomeprazole.



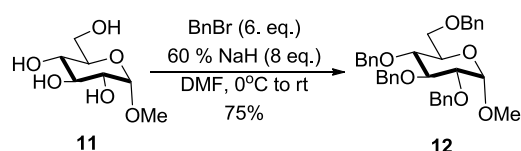
**Figure 2: Selected Organosulfur Pharmaceuticals**

Development of effective and practical methodology for the formation of ethers has received enormous attention. One of the earliest examples of a simple ether formation is via an acid-catalyzed condensation of alcohols; although primitive, it established a means to synthesize a symmetrical ether which is still widely used in industrial settings, frequently utilizing inexpensive primary alcohols. Secondary or tertiary alcohol substrates often yield elimination products instead of the desired ethers.<sup>77,87,88</sup>



**Scheme 1: Acid Mediated Etherification**

Perhaps the most utilized methodology in ether and thioether syntheses takes advantage of base-mediated alkylation. Most commonly these reactions are variations on the Williamson ether synthesis, which occurs via a  $S_N2$  displacement of an alkyl halide or sulfonate by the respective alkoxide or thiolate.<sup>77,87,88</sup> A stereotypical example is the anionic benzylation of  $\alpha$ -D-methyl-glucoside **11** with benzyl bromide and sodium hydride. This reaction has also been adapted to take place under near-neutral conditions utilizing barium oxide or silver oxide.<sup>10,11,88</sup> Additionally, there are well known examples of ether formation via transition-metal-catalyzed reactions, which include Ullmann<sup>49-52</sup> and Buchwald-Hartwig reactions.<sup>53-67</sup>

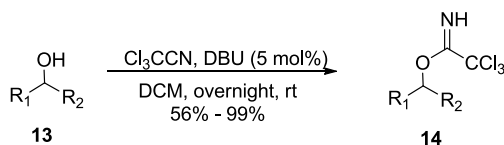


**Scheme 2: Anionic Benzylation of  $\alpha$ -D-methyl-glucoside**

These common methods are all valuable methodologies towards ether synthesis; although each has their respective disadvantages, like the requirement for expensive catalysts or that harsh reaction conditions that often limit the substrate scope.<sup>79</sup> For example, the Williamson ether synthesis requires an alkoxide ion formation in the presence of a strong base<sup>78,87,88</sup> and the Ullmann condensation towards etherification requires a copper catalyst in high-boiling solvent.<sup>49-52</sup> These conditions are often not compatible with sensitive functional groups in polyfunctional molecules, and complex substrates often do not survive and/or multiple side products are generated. These limitations are especially relevant in the total synthesis of natural products, as these complex molecules often contain alcohols that need to be protected as ethers but the standard Williamson conditions lead to degradation and poor yields.

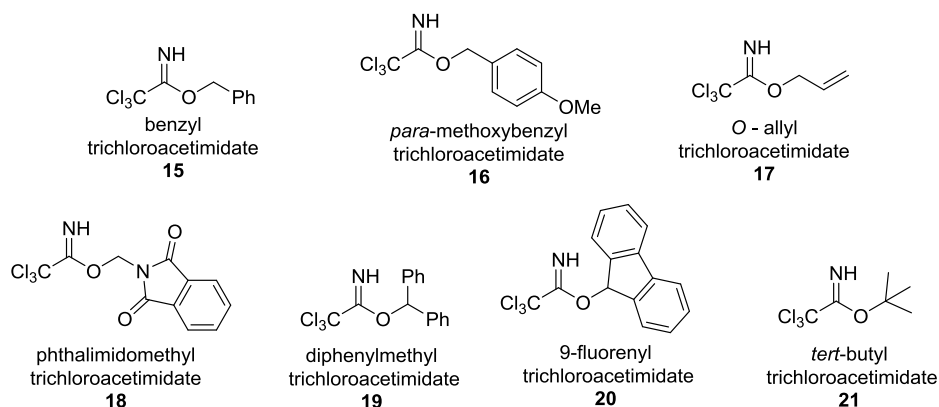
## 1.2 Trichloroacetimidates

Trichloroacetimidates have emerged as useful alternative etherification reagents as they can be used in etherifications without the need for a strong base. Trichloroacetimidates are usually prepared by reaction of the inexpensive trichloroacetonitrile with an alkoxide ion, a method that was reported by Steinkopf and Malinowski<sup>89, 90</sup> and later popularized by Cramer in the late 1950's by his inclusion of benzylic imidates.<sup>91,92</sup> Notably, Overman and Schmidt have since modernized the method to prepare more complex trichloroacetimidates in polyfunctional molecules, using DBU and other amine bases instead of metal hydrides (Scheme 3).<sup>10-12,78</sup> Trichloroacetimidates typically require activation by an external promoter, commonly a Lewis or Brønsted acid like TfOH or TMSOTf, to undergo ether formation and therefore care must be exercised in their utilization in the presence of acid-sensitive functionality.<sup>10,11,14</sup>



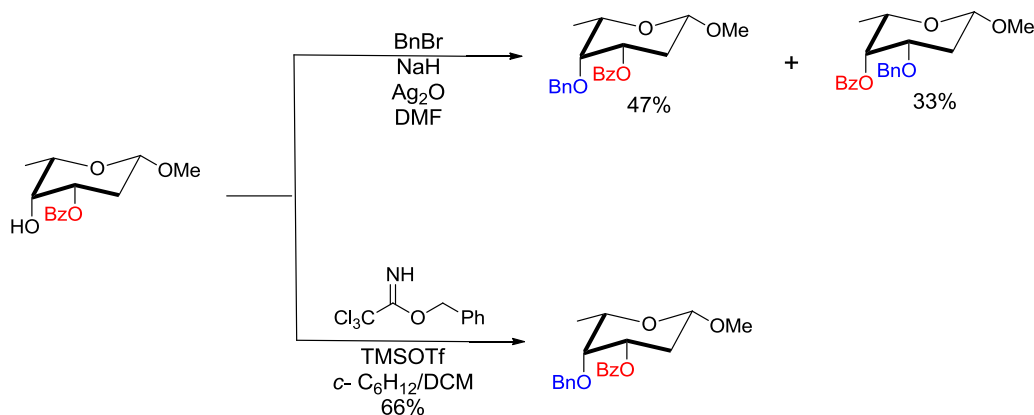
**Scheme 3: Synthesis of Trichloroacetimidates**

Trichloroacetimidates have become known as a reliable means of installing benzyl, allyl and *tert*-butyl ethers, especially in base sensitive substrates.<sup>93-95</sup> Additionally, numerous imidate-type reagents have been developed, which include new trifluoroacetimidate<sup>96, 97</sup> and phosphinimidate-based reagents.<sup>98</sup>



**Figure 3: Commonly Used Trichloroacetimidates for Alcohol Protection**

The versatility of imidates in the installation of benzyl ethers is illustrated in the protection of benzoate **22** (Scheme 4). The *O*-benzoyl group rapidly migrates under basic conditions, leading to a mixture of products, while the trichloroacetimidate provides a single isomer of the carbohydrate derivative **23**.<sup>99,100</sup> Several other examples of the use of trichloroacetimidates in the protection of base sensitive substrates may also be found in the literature.<sup>99</sup>

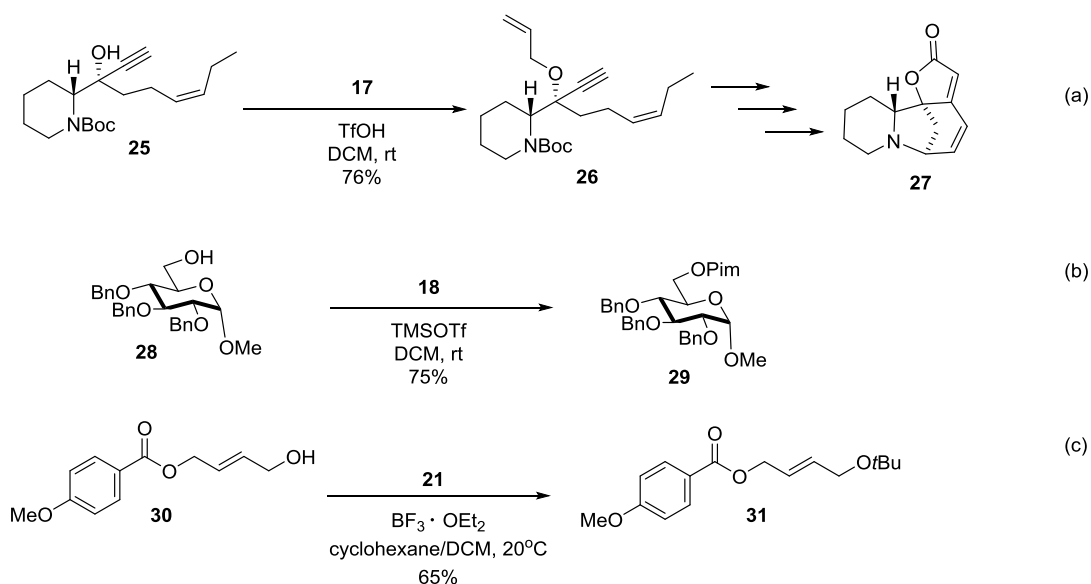


**Scheme 4: Mild Benzylation Utilizing Benzyl Trichloroacetimidate**

Although PMB and Bn imidate are two of the more well known examples, numerous trichloroacetimidates have been developed for use in etherification. Common imidates in etherification include: *O*-allyl, *tert*-butyl, phthalimidomethyl, diphenylmethyl, and 9-fluorenyl

trichloroacetimidates. All of these imidates may be used to install the corresponding ethers under mild reaction conditions in high yields in the presence of sensitive functionality.<sup>10-12,79</sup> The advantage to using different types of ethers is that they may be removed under mild and/or orthogonal conditions, which makes them useful protecting groups for alcohols and facilitates complex synthetic pathways.

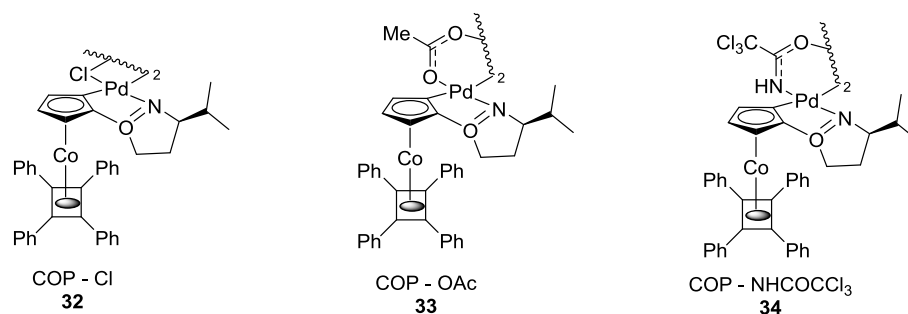
Recent applications of imidates include the use of allylic imidate **17** in the protection of a key intermediate in the synthesis of securinine,<sup>101</sup> the use of phthalimidyl imidate **18** in the protection of glucose derivative **29**,<sup>102,103</sup> as well as the use of *tert*-butyl trichloroacetimidate **21**, to synthesize the differentially protected diol **31** (Scheme 5).<sup>104</sup>



**Scheme 5: Selected Examples of Mild Alkylations Utilizing Trichloroacetimidates**

Trichloroacetimidates have also been used in the asymmetric synthesis of ethers. Overman has developed methodology utilizing palladium (II) catalysts, the cobalt oxazoline palladacycles (COP), to form some allylic ethers enantioselectively. These catalysts were originally developed for enantioselective imidate rearrangements to form allylic amines of high

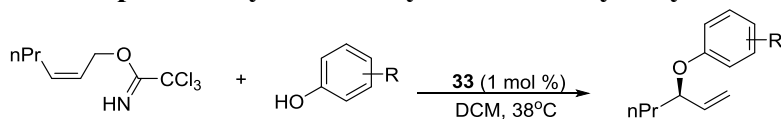
enantiopurity.<sup>105-115</sup> These catalysts have also shown facility at enantioselective allylic substitution reactions with phenols and carboxylic acids.



**Figure 4: COP Catalysts**

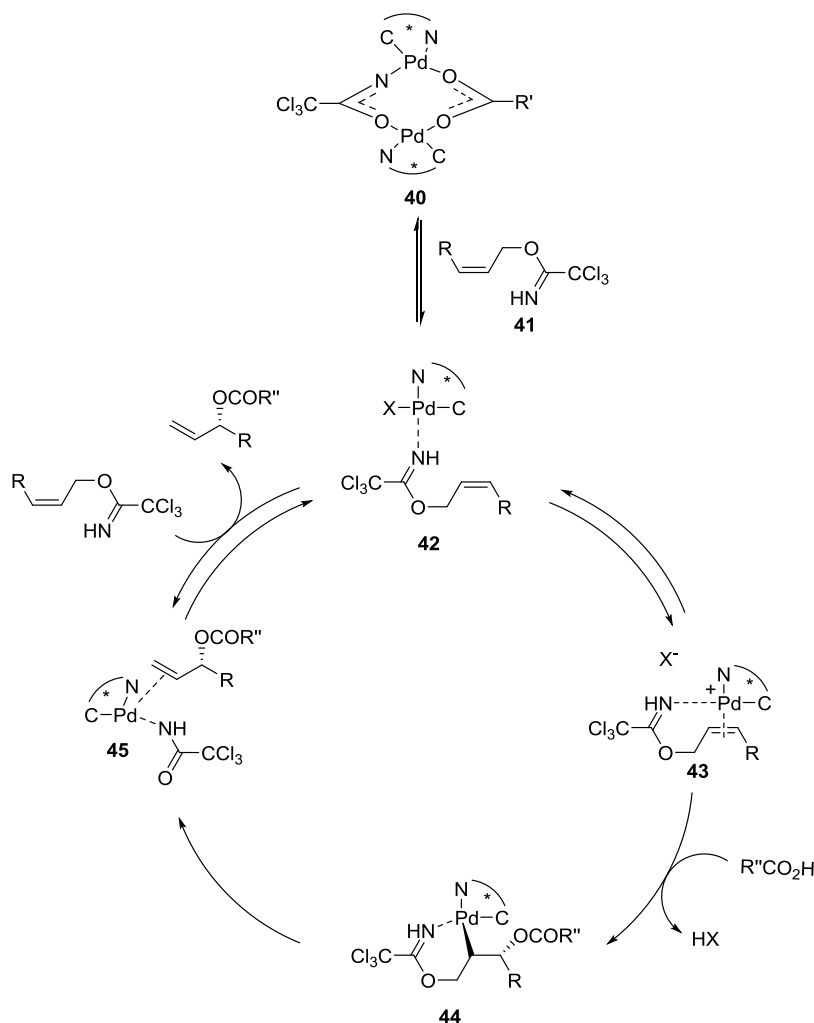
More specifically, Overman and co-workers have investigated the enantioselective allylic esterifications and etherifications, commonly utilizing COP-catalyst **33**. Branched allyl esters are obtained in moderate to high yields with excellent enantiomeric purity and substrates bearing ester, ether, and silyl ether functionality tolerate this reaction well. Additionally, phenolic substrates were examined and obtained in good to excellent yields with high enantiomeric excesses. Both electron-donating and electron-withdrawing phenols participated in these reactions; however reaction times were noticeably longer than substitutions with carboxylic acids.<sup>110-115</sup>



**Table 1: Selected Examples of Asymmetric Synthesis of Allyl Aryl Ethers**

ArOH	Time (h)	Yield (%)	ee (%)
R = H, <b>35</b>	36	86	92
R = 4-OMe, <b>36</b>	96	63	90
R = 4-Cl, <b>37</b>	36	96	91
R = 2-Br, <b>38</b>	24	87	90
R = 2-OAc, <b>39</b>	36	90	90

Overman also performed kinetic and computational investigations into the likely mechanism of ether formation using COP catalysts. These studies found that the chelation of the basic imidate nitrogen to palladium(II) (as shown in **42** below), is critical for the selective C-O forming transformation (Scheme 6). Once complex **42** is formed, it is followed by alkene coordination to form chelated-cationic palladium (II) intermediate **42**. Anti-acyloxypalladation by external nucleophilic attack at C3 generates intermediate **44**. Subsequent syn-deoxypalladation forms the alkene imidate complex **45**. This complex then reacts with imidate **41** and liberates the respective product and acetamide and allows for the regeneration of intermediate **42**.<sup>115</sup>



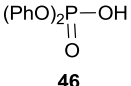
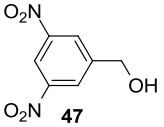
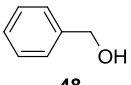
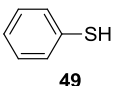
**Scheme 6: Catalytic Cycle for Pd<sup>II</sup>-catalyzed Allylic Esterification**

In contrast to etherification, thioetherification with trichloroacetimidates is almost completely unknown outside of carbohydrate chemistry as only two examples of thioetherification has been recorded with trichloroacetimidates and these reactions only demonstrate the viability of the reaction with thiophenol.<sup>116,117</sup>

Schmidt's studies on the reactivity of the *O*-cyclopropylmethyl trichloroacetimidate were one of the first reports of sulfide formation with imidates and thiols outside the carbohydrate sphere. The *O*-cyclopropylmethyl trichloroacetimidate may form cyclopropylmethyl (Cpm), cyclobutyl (Cb), and/or homoallyl (Ha) products as all these structures may result from the rearrangement and trapping of the cyclopropylcarbinyl cation intermediate. Product formation in

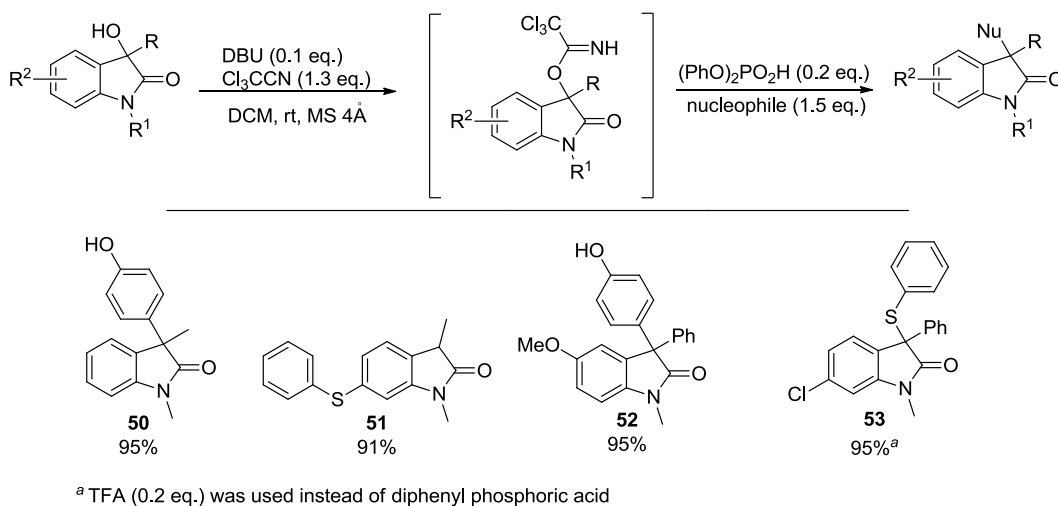
these cases appears to be dependent on the nucleophilicity and steric demand of the reacting partner. Schmidt explains the results in Table 2 by rationalizing that the enhanced reactivity of thiol **49** results in a more rapid substitution reaction, providing only the cyclopropylmethyl alkylated product. In other cases when alcohols were used (like **47** and **48**) significantly more rearrangement products were isolated (Table 2).<sup>116</sup>

**Table 2: Selected Examples of Alkylation with O-cyclopropylmethyl trichloroacetimidate**

Acceptor	Cpm (%)	Cb (%)	Ha (%)	Yield (%)
 <b>46</b>	33	23	16	72
 <b>47</b>	42	47	-	89
 <b>48</b>	-	85	-	85
 <b>49</b>	91	-	-	91

A second example of thioether formation was mentioned by Zhu and co-workers in their studies of the hydroxyindole system shown below in Scheme 7. This imidate was formed *in situ* to provide a useful method to vary the structures at C-3 with different nucleophiles (Scheme 7). This alkylation is proposed to go through a stabilized cationic intermediate. Alcohols, phenols, amines, anilines, indoles, pyrroles, allyltin, and enol ether nucleophiles were effective in accessing the desired products, for example the *para*-Friedel-Craft products **50** and **52** were isolated in excellent yields. When thiophenol was utilized, however, a deviation in regioselectivity was seen in the case of compound **51**, with substitution on the aromatic ring

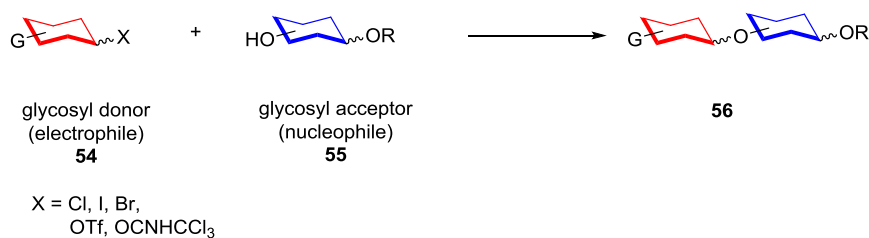
being derived from distal attack of the thiophenol on the aromatic ring. Blocking the site of attack with a chlorine resulted in the more common direct substitution product **53** (Scheme 9).<sup>117</sup> This variation in reactivity is likely due to the increased nucleophilicity of sulfur in comparison to oxygen.



## Scheme 7: Selected Examples of Nucleophilic Substitution of 3-Hydroxyindoles

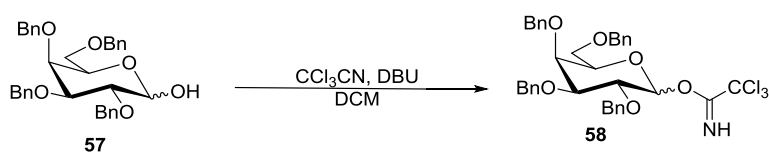
### 1.3 Glycosylation

Trichloroacetimidates have also been heavily utilized in the synthesis of glycosidic bonds, a reaction that has become very popular in oligosaccharide synthesis.<sup>118-137</sup> Glycosyl trichloroacetimidates in carbohydrate synthesis were popularized by Schmidt after his disclosure in 1980 that they may function as a new type glycosyl donor (Scheme 8).<sup>126-128</sup>



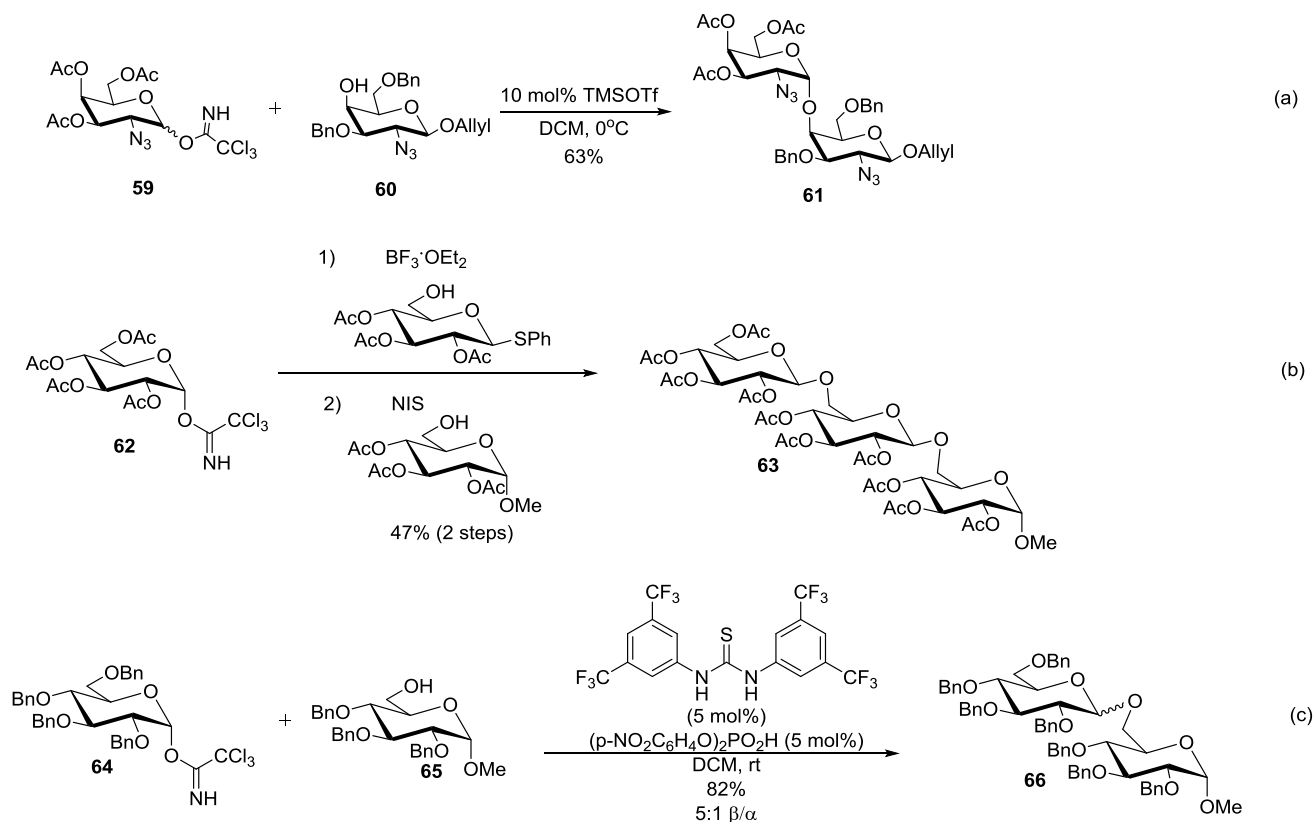
## Scheme 8: Chemical Glycosylation

Typically the glycosyl imidates are formed by the reaction of the pyranose with trichloroacetonitrile and an added base.<sup>128,130</sup> The advantage of utilizing trichloroacetimidates towards glycosidic bond formation is the facile nature of their preparation and the ease of their displacement, which often occurs with predictable selectivity for the  $\alpha$ - or  $\beta$ - anomer.



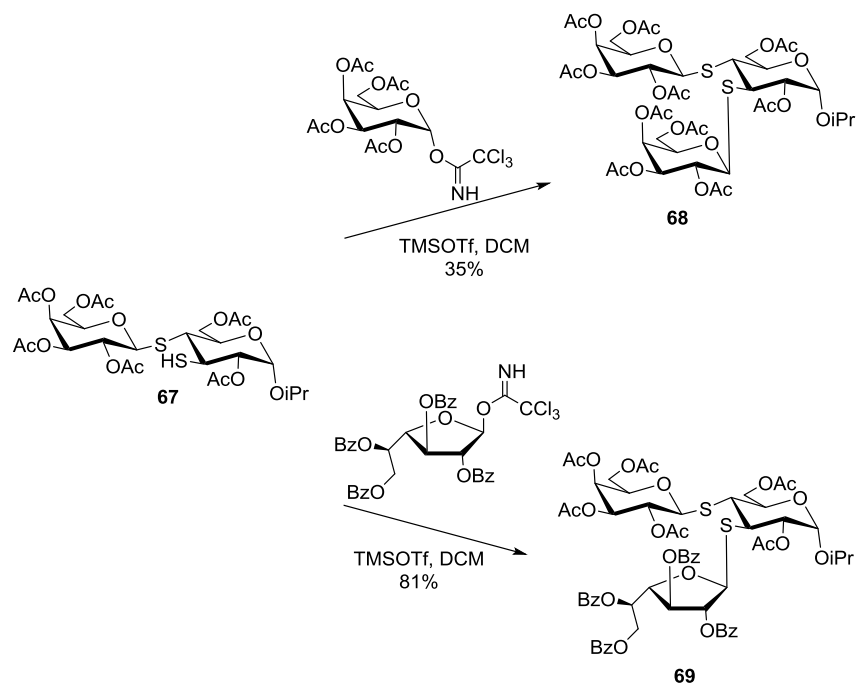
### Scheme 9: *O* - Glycosyl Trichloroacetimidate Formation

The stereochemistry of the glycosylation reaction has been widely studied and is found to be dependent on the structure of the starting imidate; in many cases the reaction proceeds with inversion, although depending on the substrate, mixtures may also be observed (Scheme 12).<sup>130</sup> Typical promoters for utilizing trichloroacetimidates for glycosylation reactions are strong Lewis Acids, commonly  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{AgOTf}$ ,  $\text{ZnCl}_2$ ,  $\text{Sn}(\text{OTf})_2$ , or  $\text{TMSOTf}$ .<sup>118-133</sup> However, more recently Brønsted acids have also been utilized towards oligosaccharide syntheses.<sup>134-137</sup>



### Scheme 10: Oligosaccharide Synthesis Utilizing Trichloroacetimidates

In addition to *O*-alkylation towards oligosaccharide syntheses, Schmidt and numerous other groups have also investigated thioglycoside synthesis.<sup>132,137-158</sup> Thioglycosides themselves are valuable intermediates in carbohydrate synthesis as they are considerably more stable to a wide range of reaction conditions, act as protecting groups, and can act as either a glycosyl donor or acceptor depending on reaction conditions.<sup>133,138-159</sup> Varela and co-workers have recently depicted the versatility of imidates as glycosyl donors towards thiooligosaccharide synthesis using TMSOTf in hindered substrates, as depicted in Scheme 11.<sup>159</sup>

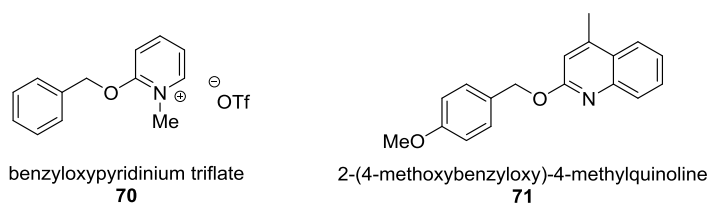


**Scheme 11: Thiooligosaccharide Synthesis Utilizing Trichloroacetimidates**

#### 1.4 Specialized Etherification Reagents

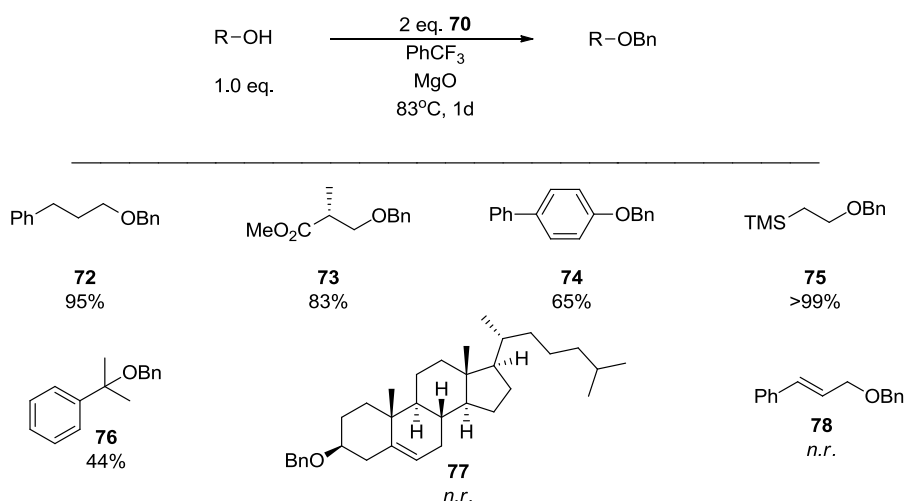
While trichloroacetimidates may be used to form ethers under mild conditions, the requirement of an acid catalyst may still be an issue with some very sensitive substrates. Consequently, several groups have investigated new *O*-alkylation methods that may occur under mild and near-neutral conditions.<sup>10,11</sup> A special focus of this work has been in the installation of benzyl and substituted benzyl ethers, as these systems are commonly used to mask alcohols during complex synthetic schemes. Dudley and co-workers recently developed two alkylating agents for the protection of alcohols and carboxylic acids, benzyloxypyridinium triflate, **70**, and 2-(4-methoxybenzyloxy)-4-methylquinoline, **71**.<sup>14-21</sup> Reagent **70** is a bench stable solid that is synthesized from the corresponding pyridine and methyl triflate. Compound **70** reacts with alcohols to form benzyl ethers in good yields without the need to add strong acid or

base. The lepidine derivative **71** is also effective at installing 4-methoxybenzyl ethers, but must first be activated *in situ* by the addition of methyl triflate.



**Figure 5: Dudley's Alkylating Agents**

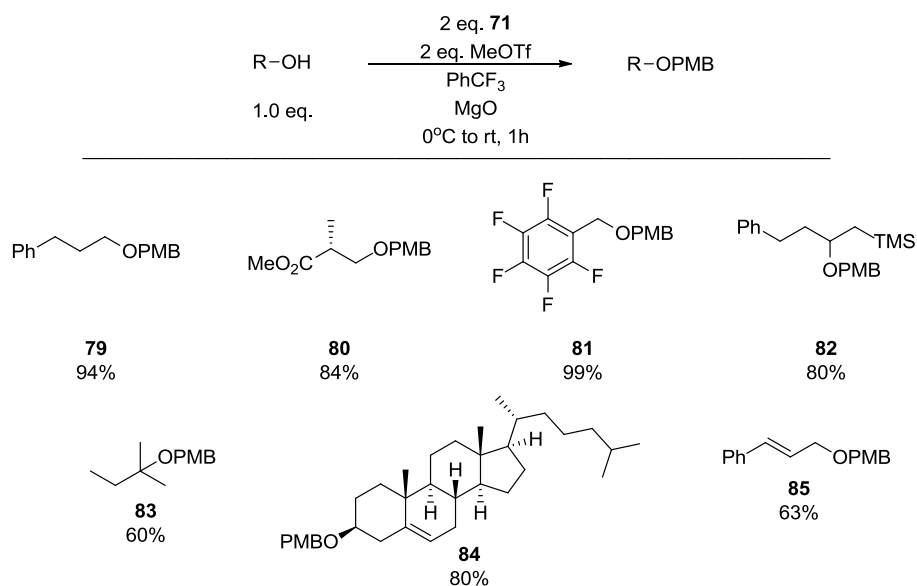
Some examples of the use of benzylating reagent **70** are shown below in Scheme 12.<sup>14</sup> Primary, secondary and tertiary alcohols are benzylated under these reaction conditions. Phenols have also been shown to provide good yields of ether products. The formation of ethers **73** and **75** are also notable, as **73** is known to undergo a facile retroaldol when treated with strong base, which precludes the formation of the benzyl ether under Williamson conditions, and **75** is subject to Peterson elimination. Previous attempts to form **75** employing imidate **15** and TfOH did not provide the desired ether. However this methodology did have limitations as seen with the more hindered tertiary substrate **76**, which observed a significant decrease in yield and cholesterol **77** and cinnamyl alcohol **78** did not yield any product.



**Scheme 12: Formation of Benzyl Ethers Using Benzyloxypyridinium triflate**



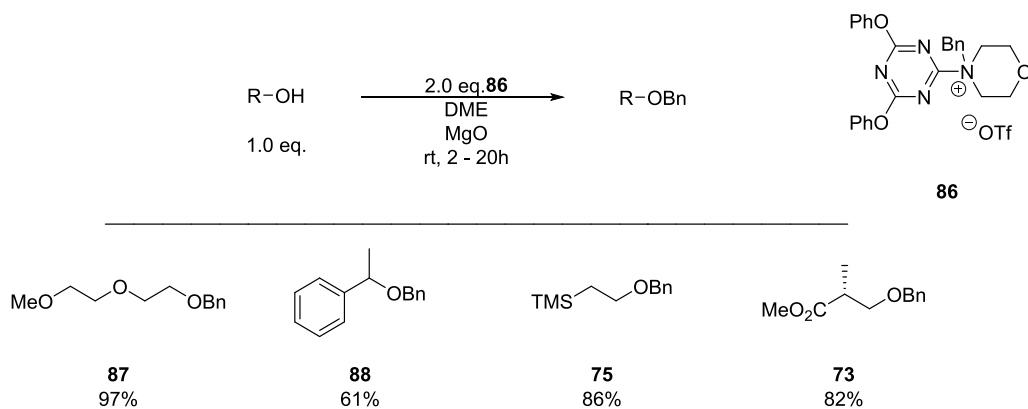
Dudley has also developed lepidine ether **71** for the formation of PMB ethers, which is reported to be significantly more stable than other PMB transfer reagents like PMB chloride and PMB trichloroacetimidate. When alcohols are treated with **71** and methyl triflate in refluxing  $\alpha,\alpha,\alpha$ -trifluorotoluene, the respective PMB ethers were formed in moderate to high yields; however tertiary and allylic alcohols were considerably less reactive (Scheme 13).<sup>15</sup> Paquette and co-workers used a similar PMBO-lepidine derivative and conditions to serve as a surrogate for generating PMB ethers, commenting on the formation *N*-methyl-2-lepidone.<sup>160</sup>



**Scheme 13: Formation of PMB Ethers Using 2-(4-methoxybenzyloxy)-4-methylquinoline**

Recently, the Kunishima group has developed triazinylammonium salts, more specifically 4-(4,6-diphenoxy-1,3,5-triazin-2-yl)-4-benzylmorpholinium trifluoromethanesulfonate (DPT-BM) **86**, to install benzyl ethers at room temperature.<sup>161</sup> However, it should be noted that the Dudley, Paquette, and Kunishima reagents required the addition of MgO to function optimally as it acts as a mild base and desiccant for acid and/or trace amounts of water. Again, this reagent provides good yields for benzyl ether **73**, which may undergo a facile retroaldol reaction under basic conditions. Also notable is the formation of

benzyl ether **75**, as  $\beta$ -silyl alcohols are sensitive to both acidic and basic etherification conditions.



**Scheme 14: Formation of Benzyl Ethers Using DPT-BM**

### 1.5 Summary

Although the literature contains expansive investigations towards *O*-alkylation using trichloroacetimidates and imidate-based reagents, prior to this work<sup>86</sup> no known investigation reported sulfide formation using trichloroacetimidates without the addition of a Brønsted or Lewis acid catalyst. The work<sup>79,86</sup> described in the subsequent chapters illustrates that trichloroacetimidates can alkylate both thiols and alcohols efficiently solely under thermal conditions, providing new ways to form ethers and sulfides and protect alcohols and thiols under mild conditions.

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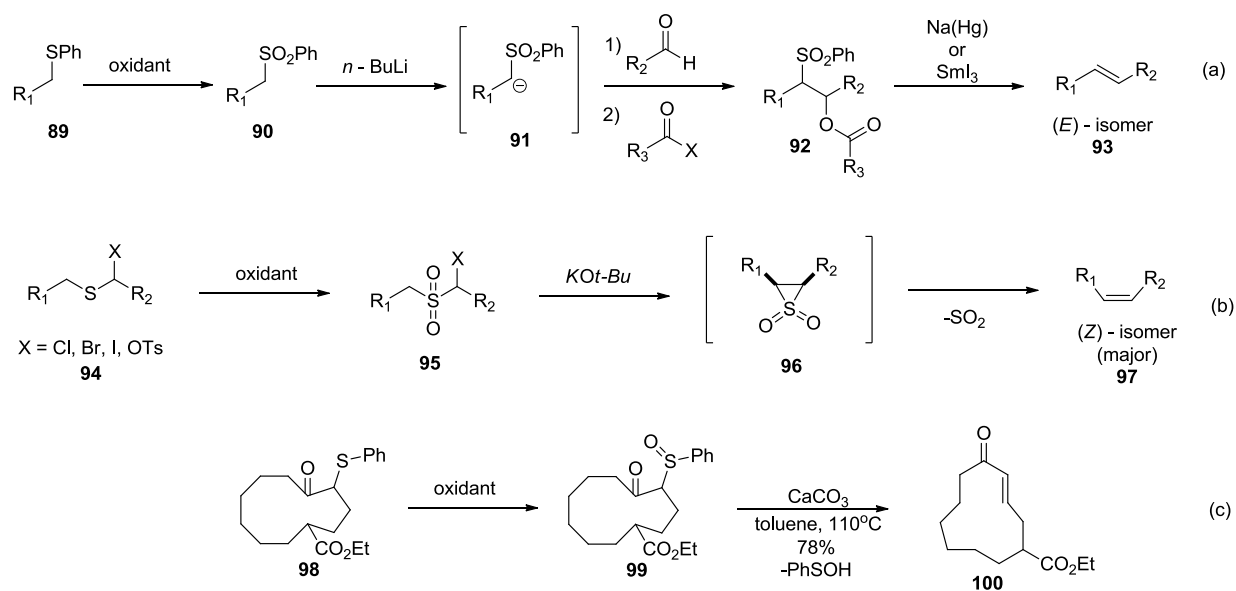
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## Chapter 2. Thioetherification Utilizing Trichloroacetimidates Under Thermal Conditions

### 2.1 Introduction

In addition to being of great medicinal and pharmaceutical importance (see Chapter 1, Figure 2),<sup>1-11</sup> thioethers are commonly found in molecules with diverse structures and functions, including secondary metabolites,<sup>4,12-16</sup> enzyme cofactors,<sup>5,17</sup> and pesticides.<sup>18,19</sup> Thioethers are also a the precursors to sulfoxides and sulfones, which are versatile synthons with numerous synthetic applications, including the Julia – Lythgoe olefination, the Ramberg – Bäcklund rearrangement, and the formation of unsaturated ketones from  $\alpha$ -thio ketones (Scheme 15).<sup>20-31</sup>

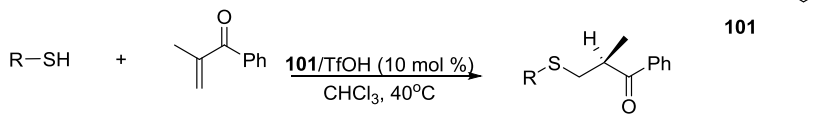


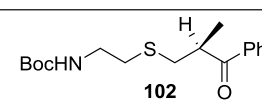
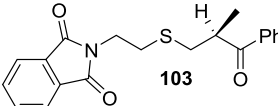
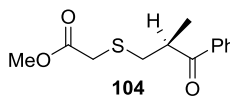
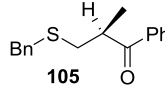
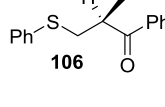
**Scheme 15: Selected Examples of Olefination Reactions Utilizing Sulfones and Sulfoxides**

## 2.2 Common Methods for the Synthesis of Sulfides

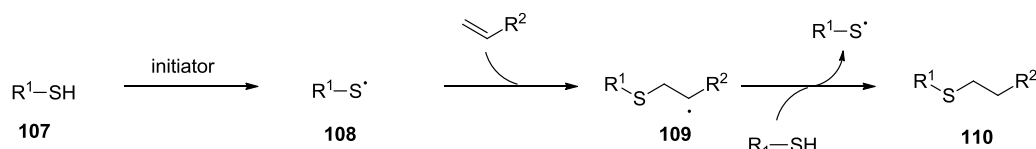
Due to their importance, the literature contains numerous methods to form sulfides from a variety of precursors. The most stereotypical route towards thioether formation is via an  $S_N2$  displacement of an alkyl halide and metal thiolate; however this requires a strong base and generates an inherent byproduct: an equimolar amount of metal halide.<sup>32-39</sup> While still often employed, researchers often prefer to utilize more mild conditions to form sulfides.

The addition of thiols to alkenes has also been explored as a means to form sulfides. For example, asymmetric sulfa-Michael additions to electron-deficient alkenes with thiol nucleophiles are considered a reliable methodology for the synthesis of chiral thioethers; however this method usually requires chiral catalysts like thioureas,<sup>43</sup> squaramides,<sup>44</sup> or strongly basic guanidine derivatives.<sup>45</sup> Substrates may also be limited as the carbonyl is required to activate the alkene for the addition reaction.<sup>43-46</sup> A recent example of this type of methodology is the system of Luo and co-workers (Table 3). This reaction effects an efficient conjugate addition-protonation reaction of thiols to  $\alpha$ -substituted vinyl ketones by a chiral primary amine catalyst **101** and TfOH.<sup>46</sup>

**Table 3: Selected Examples of Asymmetric Synthesis of Thioethers**<sup>46</sup>


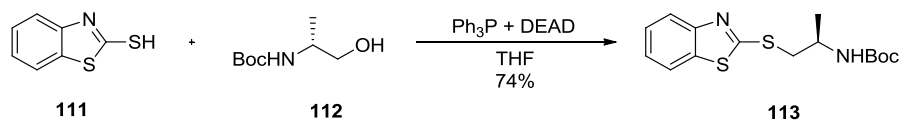
Product	Time (h)	Yield (%)	ee (%)
 <b>102</b>	24	82	81
 <b>103</b>	24	85	87
 <b>104</b>	12	95	86
 <b>105</b>	12	72	19
 <b>106</b>	7	88	76

In addition to sulfa-Michael additions, thiols can also add to unactivated olefins in an anti-Markovnikov manner,<sup>47-57</sup> commonly via the thiol-ene reaction.<sup>47,53-57</sup> Initially reported by Posner in 1905,<sup>47</sup> the thiol-ene reaction is widely applicable in polymer and synthetic chemistry. This reaction requires a photoinitiator, such as benzophenone or dimethyloxyphenyl acetophenone,<sup>48-52</sup> or more recently, ruthenium polypyridyl complexes.<sup>57</sup>

**Scheme 16: General Mechanism of Radical Thiol-Ene Reaction**

The direct displacement of alcohols with thiols has also been explored. Commonly the Mitsunobu reaction may be employed, which is an effective method for the synthesis of sulfides

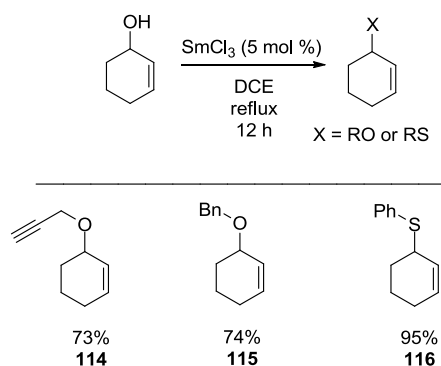
from alcohols. Unfortunately this reaction generates large amounts of waste byproducts in the form of triphenylphosphine oxide and reduced azodicarboxylates byproducts, which limits its utility to small scale reactions.<sup>40-42</sup>



**Scheme 17: An Example of the Mitsunobu Reaction in the Synthesis of a Sulfide**

Other direct displacement reactions towards sulfides, generally employing acetates or alcohols as leaving groups for thiol nucleophiles, have been investigated to reduce the waste products generated in the Mitsunobu reaction. These reactions usually require a promoter like a Lewis or Brønsted acid or transition metal catalyst. In many cases these reactions proceed through  $\text{S}_{\text{N}}1$  type mechanisms, which limit the substrate scope.<sup>39,58-88</sup>

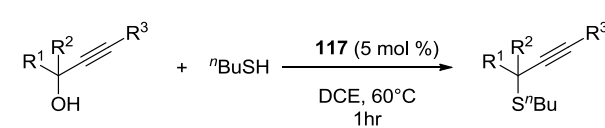
One early example of thioether formation via alcohol displacement was reported by Kagan and co-workers. This work described thioether formation from a limited series of allylic alcohols and thiols in which they used  $\text{SmCl}_3$  as a catalyst.<sup>60</sup> The authors propose that the displacement occurs via a stabilized allylic cation and hence loses any inherent stereochemical information present in the alcohol. Numerous groups have since investigated transition-metal catalyzed allylic substitution to form thioethers.<sup>60,65-70,84-88</sup> While these systems perform well, they are typically limited to allylic substrates.

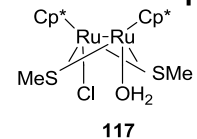


**Scheme 18: Selected Examples of Samarium (III) Trichloride Allylic Ether Formation**

More recently, Hidai and Uemura have demonstrated the displacement of propargyl alcohols with thiols using a novel cationic methanethiolate-bridged diruthenium complex, **117**. Complex **117** itself can be prepared by stirring AgOTf with  $[\text{Cp}^*\text{Ru}(\text{SMe})_2\text{RuCp}^*(\text{OH}_2)]$ , which is quite expensive and difficult to prepare. This displacement has been reported to generate the desired sulfide in the presence of a catalytic amount of a  $\text{NH}_4\text{BF}_4$ .<sup>84</sup>

**Table 4: Selected Examples of Ruthenium-Catalyzed Propargylic Sulfides** 

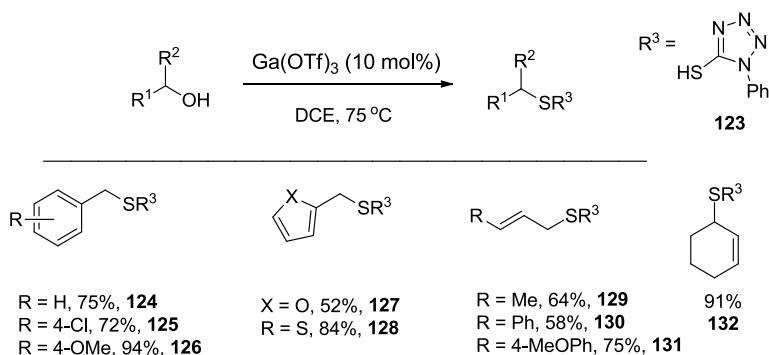




**117**

Propargyl Alcohol	Yield (%)
$\text{R}^1 = \text{Ph}_2\text{C}=\text{CH}$ , $\text{R}^2 = \text{H}$ , $\text{R}^3 = \text{Ph}$ , <b>118</b>	96
$\text{R}^1 = \text{Ph}_2\text{C}\equiv\text{CH}$ , $\text{R}^2 = \text{H}$ , $\text{R}^3 = \text{Ph}$ , <b>119</b>	trace
$\text{R}^1 = \text{Ph}$ , $\text{R}^2 = \text{H}$ , $\text{R}^3 = n\text{hexyl}$ , <b>120</b>	83
$\text{R}^1 = \text{Ph}$ , $\text{R}^2 = \text{H}$ , $\text{R}^3 = t\text{Bu}$ , <b>121</b>	86
$\text{R}^1 = p\text{-MeC}_6\text{H}_4$ , $\text{R}^2 = \text{H}$ , $\text{R}^3 = \text{Ph}$ , <b>122</b>	90

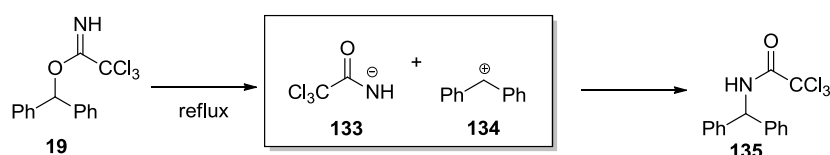
Additionally, Wu and co-workers recently disclosed that a catalytic amount of  $\text{Ga}(\text{OTf})_3$  can promote displacement of alcohols with sulfur nucleophiles.<sup>64</sup> The yields of these processes are good to excellent depending on the substrates, although this method was limited to activated allylic and benzylic alcohols as it also proceeds by an  $\text{S}_{\text{N}}1$  mechanism.



**Scheme 19: Selected Examples of Gallium (III) Triflate Catalyzed Sulfide Formation**

### 2.3 Reaction Development

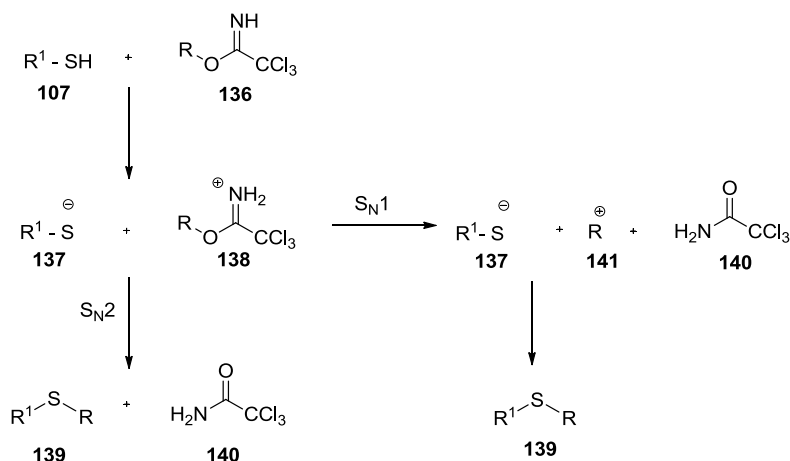
Researchers in the Chisholm laboratory noted that trichloroacetimidate **19** would rearrange to the corresponding acetamide **133** when heated in refluxing solvent, usually toluene<sup>89</sup> (Scheme 20), without any added Brønsted or Lewis acid catalyst. The typical [3,3]-sigmatropic rearrangement that transforms allylic imidates to allylic acetamides<sup>90</sup> is not available to imidate **19**, so this rearrangement was unexpected.



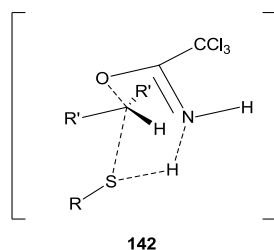
**Scheme 20: Proposed Generation of the DPM Acetamide in Absence of Nucleophile**

Mechanistically, it was hypothesized that the imidate ionizes to form the stable diphenylmethyl cation **134** and, should no nucleophile be present, the trichloroacetamide anion (a weak base with a pKa of 11 in DMSO)<sup>91</sup> adds and forms the corresponding trichloroacetamide **135**. However, in the presence of a more effective external nucleophile like a thiol, it may be possible to trap the cation, leading to the formation of sulfide **139** and trichloroacetamide **140** without the use of an acid or base promoter, as seen in Scheme 21. This could provide a method to generate sulfides under essentially neutral conditions without a catalyst, where the strongest base present is the trichloroacetamide anion **133**.





**Scheme 21: Possible Mechanistic Pathway of Sulfide Generation**

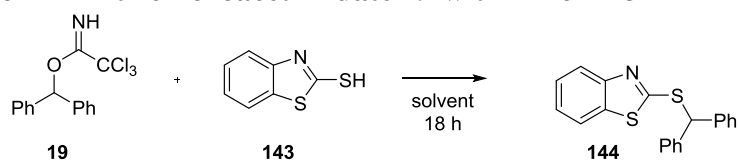


**Figure 6: Possible Concerted Transition State of Sulfide Generation**

As described in Scheme 21, we suspect that the substitution reaction may occur through either an  $S_{\text{N}}1$  or  $S_{\text{N}}2$  pathway (stepwise proton transfer) or through a highly ordered six-membered transition state (concerted proton transfer) where the C-O bond breaking and C-S bond formation are simultaneous as shown in Figure 6. The reaction also may be dependent on the pK<sub>a</sub> of the thiol nucleophile (which may first protonate the imidate). The substitution would obviously proceed much more rapidly if protonation occurs first, activating the imidate before displacement and accelerating either an  $S_{\text{N}}1$  or  $S_{\text{N}}2$  pathway. To our knowledge, there have been no attempts at sulfide formation using trichloroacetimidates without the addition of a Brønsted or Lewis acid catalyst.<sup>92,93</sup> In this report, we have investigated the scope of these trichloroacetimidate displacements to generate sulfides. The rest of this chapter is focused on

investigations into the reactivity of alkyl, allylic/propargylic, electron-poor and electron-rich trichloroacetimidates with several thiols having different acidities.<sup>94</sup>

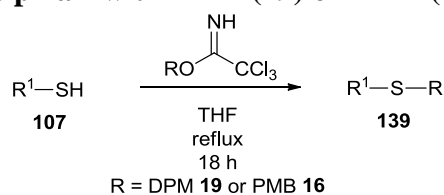
All trichloroacetimidates discussed in this chapter were generated using typical reaction conditions for their formation, as shown in Scheme 3. *O*-Diphenylmethyl (DPM) trichloroacetimidate **19** was used as an initial substrate since previous publications from the Chisholm laboratory<sup>89</sup> have shown that this imidate is particularly reactive, and therefore may be an excellent precursor for DPM sulfides. As DPM is a useful protecting group for thiols this reaction would have utility regardless of any other limitations to the substrate scope.<sup>95</sup> Previous experiments in the Chisholm laboratory defined the optimal conditions for etherification with the DPM trichloroacetimidate as refluxing in toluene solvent without a catalyst for 18 hours.<sup>89</sup> As such, these conditions were initially explored to generate the desired sulfide. Refluxing DPM imidate **19** with thiol **145** in toluene provided sulfide **146** in 76% yield, confirming our hypothesis that thiols can be alkylated with trichloroacetimidates without an added catalyst or promoter (Table 5, Entry 1). As thiols are typically better nucleophiles than alcohols, lower reaction temperatures were explored to determine if the reaction could proceed under even more mild conditions. Lowering the reaction temperature to 23 °C provided no product, while performing the displacement at 65 °C gave a significantly decreased yield, indicating that an elevated temperature was necessary. A variety of solvents were screened, as seen in Table 1, and THF emerged as the optimal solvent, providing an 88% yield of product after refluxing the reactants for 18 h. THF proved to be a much better medium for the substitution, as even at room temperature 70% of sulfide **146** could be isolated after 18 h.

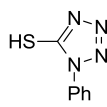
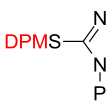
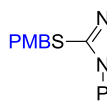
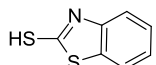
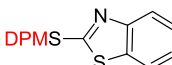
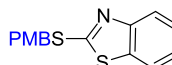
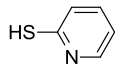
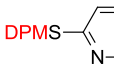
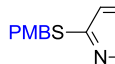
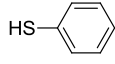
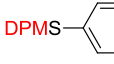
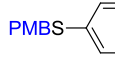
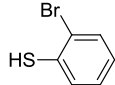
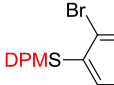
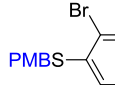
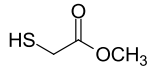
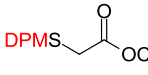
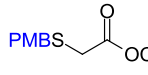
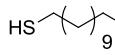
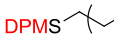
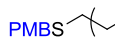
**Table 5: Reaction of DPM trichloroacetimidate **19** with Thiol **143**<sup>a</sup>**

Entry	Solvent	Temperature	Yield <sup>b</sup>
1	toluene	111 °C	76%
2	toluene	23 °C	0
3	toluene	65 °C	45%
4	dichloromethane	40 °C	48%
5	THF	23 °C	70%
<b>6</b>	<b>THF</b>	<b>66 °C</b>	<b>88%</b>
7	2-butanone	80 °C	Trace
8	acetonitrile	82 °C	52%
9	DMF	100 °C	18%

<sup>a</sup>All reactions were performed at 0.1M for 18 h in the noted solvent. <sup>b</sup>Isolated yields.

A number of different thiol substrates were then explored to determine if they would participate in the imidate displacement. The initial hypothesis that the sulfide formation may be dependent on the pKa of the thiol was also tested by utilizing thiols with different acidities. The range of nucleophilic thiols were chosen with respect to the 2-mercaptobenzthiazole, which has a pKa of 1.4 in DMSO (Table 6).<sup>96</sup> This investigation was performed in the context of evaluating the installation of both the DPM and PMB protecting group, and so two imidates that may be used to install thiol protecting groups, diphenylmethyl trichloroacetimidate (**19**) and 4-methoxybenzyl-2,2,2-trichloroacetimidate (**16**), were chosen as alkylation reagents.<sup>97</sup>

**Table 6: Varying Nucleophile pKa<sup>96</sup> with DPM (19) or PMB (16) imidate**

Thiol	pKa in DMSO <sup>84</sup>	Product	Yield	Product	Yield
 <b>123</b>	~1 <sup>a</sup>	 <b>145</b>	94%	 <b>126</b>	84%
 <b>143</b>	1.4	 <b>144</b>	88%	 <b>146</b>	89%
 <b>147</b>	5.5	 <b>148</b>	85%	 <b>149</b>	81%
 <b>150</b>	6.4	 <b>151</b>	78%	 <b>152</b>	79%
 <b>153</b>	8.9	 <b>154</b>	71%	 <b>155</b>	59%
 <b>156</b>	13.0	 <b>157</b>	66%	 <b>158</b>	67%
 <b>159</b>	17.5	 <b>160</b>	64%	 <b>161</b>	40%

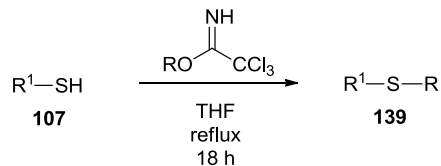
<sup>a</sup>calcd via pKa(DMSO) = 2.55 pKa(water) - 6.26

Generally, the yields of the thiol alkylation were higher with DPM imidate **19** than with PMB imidate **16**, likely due to the enhanced electrophilicity of this reagent. The aromatic thiols investigated proved to be excellent substrates for this alkylation reaction, providing the sulfide in high yields. Alkyl thiols provided more moderate yields of the desired sulfide; we suspect the

lower acidity of these thiols leads to a slower proton transfer to the imidate nitrogen, resulting in a less rapid displacement of the imidate.

Conveniently, when the reaction mixtures were washed with 2M aqueous NaOH solution to remove any unreacted thiol, it was noticed that the trichloroacetamide byproduct was also removed. Trichloroacetamide is insoluble in water, and aforementioned, has a pKa of 11.<sup>91</sup> The deprotonated acetamide should be much more soluble in water, however, and therefore could be removed via the aqueous washing. This discovery provides a convenient purification method for the thioetherification and other alkylation reactions with trichloroacetimidates by the removal of the major byproduct, further enhancing the usefulness and applicability of this methodology.

Variation of the trichloroacetimidate electrophile, the imidate alkylating reagent, was then explored. Experiments were performed in THF at reflux with 1-phenyl-1H-tetrazole-5-thiol **123**, as this thiol not only provided high yields, the reaction products may be transformed into sulfones that are useful for stereoselective Julia-Lythgoe olefination reactions.<sup>21-26</sup> Table 7 depicts the reaction of benzylic trichloroacetimidates with thiol **123**. The trichloroacetimidates varied from phenyl, methyl and hydrogen at the alpha position, and the yields did not vary greatly based on substitution, 94%, 87%, and 87% respectively. This demonstrates the versatility of trichloroacetimidates to generate sulfides as the substitution at the alpha position of the benzylic trichloroacetimidates does not affect the yield significantly.

**Table 7: Reaction of Benzylic Imidates with Thiol 123**

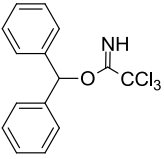
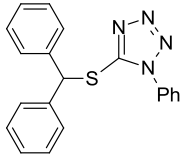
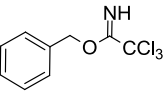
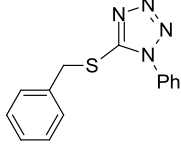
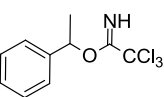
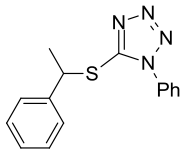
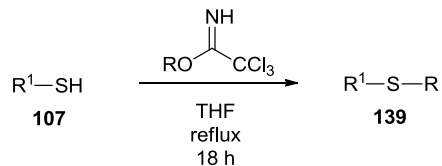
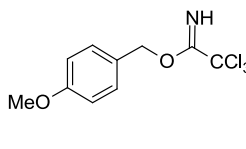
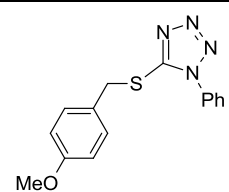
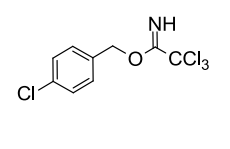
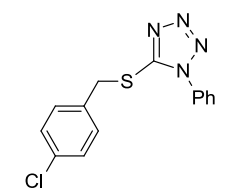
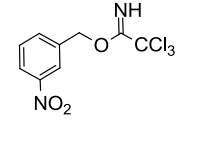
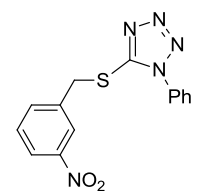
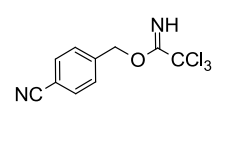
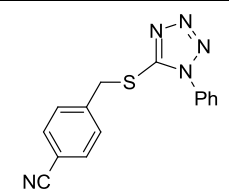
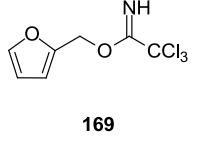
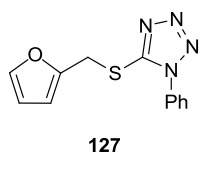
Entry	Imidate	Product	Yield
1			94%
2			87%
3			87%

Table 8 demonstrates that electron-withdrawing benzylic trichloroacetimidates are just as capable in generating sulfides as electron-donating ones. More specifically, the electron-rich PMB imidate **16** afforded alkylated thiol **126** in 84% yield while the electron-poor imidate **167** provided alkylated thiol **168** in 72% yield. The high reactivity with these groups supports the hypothesis that the reaction may proceed through the  $S_N2$  pathway, although Friedel Crafts reactions of similar electron poor imidates have been observed under Lewis-acid mediated conditions at high temperature.<sup>97</sup> Another possibility is that the reaction may proceed under either an  $S_N1$  or an  $S_N2$  pathway depending on the structure of the trichloroacetimidate.

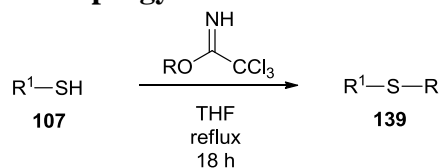
**Table 8: Reaction of Benzylic Imidates with Thiol 123**

Entry	Imidate	Product	Yield
1			84%
	<b>16</b>	<b>126</b>	
2			88%
	<b>164</b>	<b>125</b>	
3			80%
	<b>165</b>	<b>166</b>	
4			72%
	<b>167</b>	<b>168</b>	
5			69%
	<b>169</b>	<b>127</b>	

Tables 9 and 10 show that allylic and propargylic trichloroacetimidates have improved reactivity with thiol **123** when compared to benzylic trichloroacetimidates. No products of  $S_N2'$

addition was observed with the allylic and propargylic imidates. The highest yielding reaction used prenyl imidate **171** which afforded alkylated thiol **172** in 98% yield, Entry 2.

**Table 9: Reaction of Allylic and Propargylic Imidates with Thiol 123**



Entry	Imidate	Product	Yield
1			96%
2			98%
3			95%
4			91%

Table 10 further illustrates the versatility of trichloroacetimidates to generate sulfides as observed with geraniol trichloroacetimidate, **175**, and nerol trichloroacetimidate, **177**, as no apparent isomerization of the trisubstituted alkene geometry occurred and the sulfide products were isolated in 83% and 88% yield, respectively. No isomerization of the trisubstituted alkenes seems to implicate an  $S_N2$  mechanism in these cases, as the formation of an allylic cation (which



occur in an  $S_N1$  process) may lead to isomerization of the alkene. The phthalimidomethyl system also proved capable in generating the desired sulfide **181** in 78% yield (Table 10, Entry 4).

**Table 10: Reaction of Allylic and Propargylic Imidates with Thiol **123****

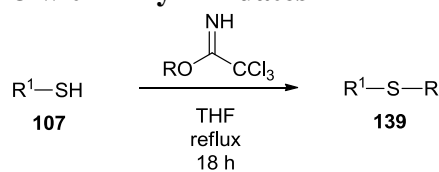
Entry	Imidate	Product	Yield
1			83%
2			88%
3			96%
4			78%

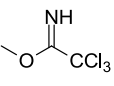
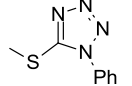
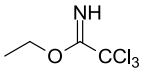
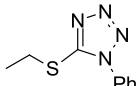
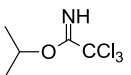
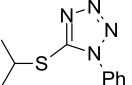
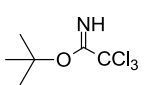
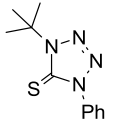
Thiol additions to alkyl trichloroacetimidates were also investigated (Table 11).

Unhindered methyl and ethyl trichloroacetimidates provided the corresponding sulfides in moderate yields, 75% and 81%, respectively. No reaction was observed with the isopropyl imidate **186** in refluxing THF, but switching to the higher-boiling toluene as the solvent yielded the desired product in a moderate yield of 38%. The yield of **187** could be increased to 51% by using 5 equivalents of the imidate. Reaction of thiol **123** with *tert*-butyl imidate did not provide

the desired sulfide product, however, but yielded the tetrazolothione **189** as the major product instead in 32% yield. The yield could be increased to 55% by using 5 equivalents of imidate. We suspect that steric interaction between the bulky *tert*-butyl group and the adjacent N-phenyl ring on thiol **123** may favor alkylation of the nitrogen, leading to the tetrazolothione. Recently Wu and co-workers found sulfides could be rearranged to the tetrazolothione thermodynamically by heating in DCE with catalytic Ga(OTf)<sub>3</sub>,<sup>64</sup> so it is possible that after initial *S*-alkylation the *tert*-butyl migrates to generate the tetrazolothione. Given that both methyl and *tert*-butyl imidates react under these conditions, both an S<sub>N</sub>1 or S<sub>N</sub>2 mechanism is available to this reaction; however, as yields are higher with primary imidates, an S<sub>N</sub>2 pathway seems preferred.

**Table 11: Reaction of Thiol 123 with Alkyl Imidates**



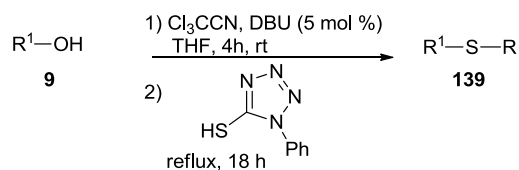
Entry	Imidate	Product	Yield
1	 <b>182</b>	 <b>183</b>	75%
2	 <b>184</b>	 <b>185</b>	81%
3	 <b>186</b>	 <b>187</b>	38% <sup>a,b</sup>
4	 <b>188</b>	 <b>189</b>	32%

<sup>a</sup> The reaction was performed in toluene at reflux.

<sup>b</sup> A 51% isolated yield was obtained when 5 equivalents of imidate was used in toluene at reflux

While addition of the thiol to the trichloroacetimidate provides a powerful method for the formation of new sulfides under near neutral conditions, one must still prepare the trichloroacetimidate from the alcohol before substitution, as seen in Scheme 3. Attempts were therefore made to streamline the process into a one-pot procedure by forming the trichloroacetimidate *in situ*. *In situ* formation of the imidate has been used to form allylic trichloroacetimidates for use in the Overman rearrangement,<sup>90</sup> and similar procedures have been used for substitution reactions in some isatin derivatives.<sup>92</sup> Alcohols were first subjected to imidate formation conditions in anhydrous THF followed by addition of the thiol and simple heating. This procedure has provided the sulfides without the need for isolation of the trichloroacetimidate intermediate further streamlining this methodology. Table 12 depicts the generation of benzylic sulfides in respectable yields from the commercially available alcohols, 1-phenylethanol and benzyl alcohol, 64% and 78%, respectively.

**Table 12: One-pot Conversion of Benzylic Alcohols to Sulfides**



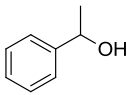
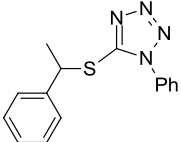
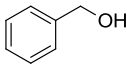
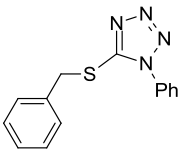
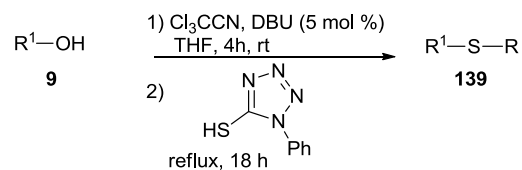
Entry	Alcohol	Product	Yield
1	 <b>190</b>	 <b>124</b>	64%
2	 <b>191</b>	 <b>163</b>	78%

Table 13 illustrates the versatility of this one-pot process as multiple allylic examples were completed in addition to one alkyl example, 1-butanol. All yields are slightly lower than the displacement with purified imidate (which is to be expected as two reactions are being performed) with prenyl alcohol being the highest yielding, 82%.

**Table 13: One-pot Conversion of Alcohols to Sulfides**

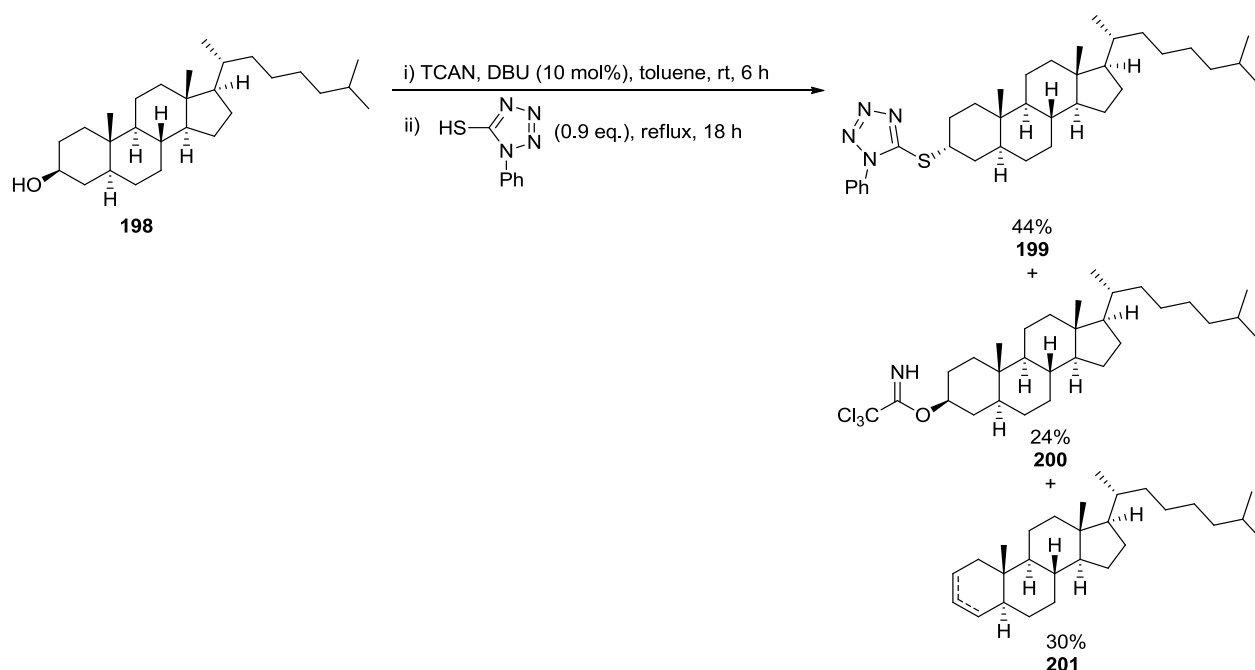


Entry	Alcohol	Product	Yield
1			67%
2			82%
3			79%
4			77%
5			63%

We hypothesized the moderate yield of the isopropyl sulfide generation in Table 11, entry 3, may be due to competing elimination reactions to form the volatile alkene as a side product, as the substitution reaction may be sluggish due to sterics. The alkene formed in this case would be

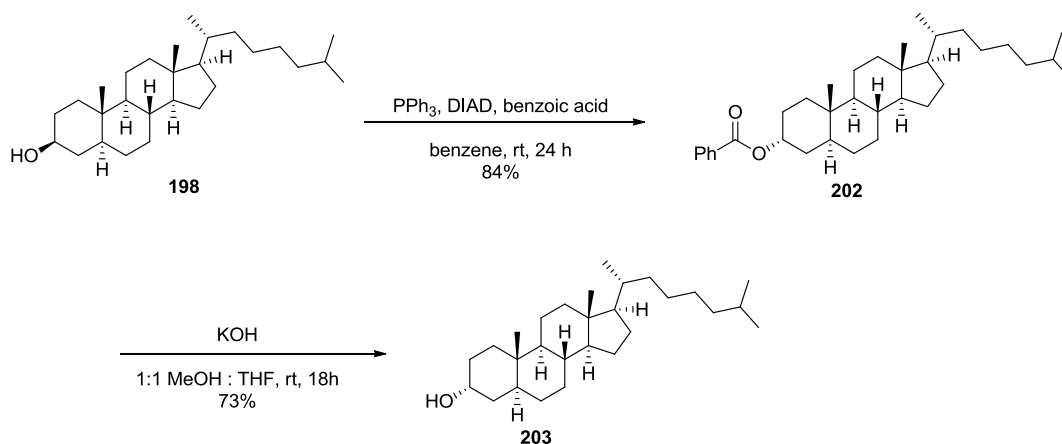
a gas, however, so it would be difficult to prove this hypothesis. To further explore this idea, we subjected  $\beta$ -dihydrocholesterol **198** with thiol **123** to the *in situ* substitution conditions. Any alkenes formed from the reaction should be isolable in the higher molecular weight steroid skeleton. In addition, this would provide some evidence of the mechanistic pathway, as the stereocenter on the steroid will provide information on the displacement proceeding with retention or inversion.

Exposing steroid **198** to *in situ* substitution conditions in refluxing THF did not yield product, and starting thiol **123** and the steroidal imidate were recovered from the reaction. This result is consistent with the reaction of isopropyl trichloroacetimidate, which required heating the reaction in toluene to generate the desired sulfide **187**. Formation of steroid imidate in toluene followed by addition of thiol led to generation of desired sulfide **199** in 44% yield. None of the  $\beta$ -isomer was observed in the crude  $^1\text{H}$  NMR, with the remaining material being unreacted imidate, 24% yield, and a mixture of alkenes in 30% yield. This process was also completed in a two-pot method, which yielded similar results in both yield and of materials.



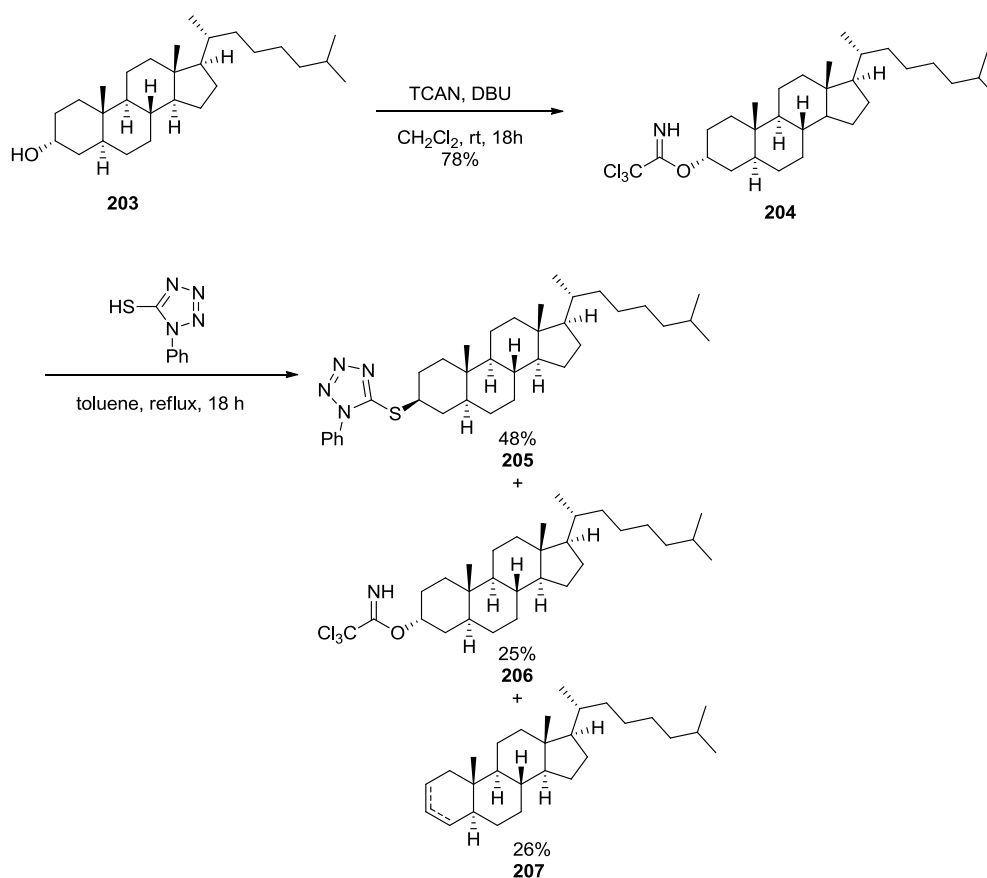
**Scheme 22: One-pot Conversion of  $\beta$ -dihydrocholesterol to  $\alpha$ -sulfide**

The low yield of the displacement may be due to the thiol having to attack from an axial position and therefore it must negotiate the axial hydrogens at C1 and C5 of the steroid, so it was theorized that the opposite alcohol diastereomer may be a better substrate for displacement. To investigate this possibility, steroid imidate **204** was generated by subjecting alcohol **199** to Mitsunobu conditions followed by hydrolysis of the benzoate to generate the corresponding  $\alpha$ -alcohol **203** (Scheme 23).



**Scheme 23: Generation of  $\alpha$ -dihydrocholesterol**

$\alpha$ -Alcohol **203** was used to generate the corresponding imidate **204** and subjected to the two-pot method, as shown in Scheme 29. Addition of thiol **123** in refluxing toluene led to generation of desired sulfide **205** in 48% yield. None of the  $\alpha$ -isomer was observed in the crude  $^1\text{H}$  NMR, with the remaining material being unreacted imidate, 25% yield, and a mixture of alkenes in 26% yield. The moderate yield of these displacements is therefore most likely due to the unreactive nature of the secondary imidate, and not due to any steric factors derived from the steroid core. As complete inversion was observed with no retention product, these reactions must proceed through an  $\text{S}_{\text{N}}2$  manifold.



**Scheme 24: Conversion of  $\alpha$ -dihydrocholesterol to  $\beta$ -sulfide**

## 2.4 Summary

In summary, we have developed a new method<sup>94</sup> of alkylating thiols under thermal conditions without the need of an acid, base, or transition metal catalyst by utilizing a trichloroacetimidate as an electrophile. Using thiols as substrates, we have shown that the reaction tolerates considerable variation of nucleophiles. In addition, we have shown the versatility of the trichloroacetimidate electrophile with alkyl, allylic/propargylic, and benzylic trichloroacetimidates with both electron-donating and –withdrawing groups providing good yields with 1-phenyl-1H-tetrazole-5-thiol, **123**.

We propose that this displacement precedes either by S<sub>N</sub>2 or S<sub>N</sub>1 pathway depending on the nature of the electrophile. Support for an S<sub>N</sub>2 pathway was found with the generation of chiral steroid alcohols **198** and **203** proceeding solely to the respective inverted sulfide. Additionally, support for S<sub>N</sub>2 preference is apparent as yields are higher with methyl and primary alkyl imidates and no isomerization of the trisubstituted alkene geometry of geraniol **175** and nerol **177** imidates. Support for an S<sub>N</sub>1 pathway comes from the ability to generate sulfide **145** from DPM imidate, as previous work<sup>89</sup> has shown that addition to this substrate typically proceeds through an S<sub>N</sub>1 manifold, and the ability for *tert*-butyl imidate to react, as this is strictly limited to an S<sub>N</sub>1 pathway.



## 2.5 Experimental

**General Methods:** All anhydrous reactions were run under a positive pressure of argon or nitrogen. All syringes, needles, and reaction flasks required for anhydrous reactions were dried in an oven and cooled under an N<sub>2</sub> atmosphere or in a desiccator. Dichloromethane and THF were dried by passage through an alumina column following the method of Grubbs (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518). Triethylamine was distilled from CaH<sub>2</sub>. All other reagents and solvents were purchased from commercial sources and used without further purification.

**Analysis and Purification.** Analytical thin layer chromatography (TLC) was performed on precoated glass backed plates (silica gel 60 F<sub>254</sub>; 0.25 mm thickness). The TLC plates were visualized by UV illumination and by staining. Solvents for chromatography are listed as volume:volume ratios. Flash column chromatography was carried out on silica gel (40-63 μm). Melting points were recorded using an electrothermal melting point apparatus and are uncorrected. Elemental analyses were performed on an elemental combustion system ECS 4010 analyzer with a thermal conductivity detector and 2 meter GC column maintained at 50 °C.

**Identity.** Proton (<sup>1</sup>H NMR) and carbon (<sup>13</sup>C NMR) nuclear magnetic resonance spectra were recorded at 300 or 400 MHz and 75 or 100 MHz respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. Coupling constants are reported in hertz (Hz). The spectra were recorded in solutions of deuterated chloroform (CDCl<sub>3</sub>), with residual chloroform (δ 7.26 ppm for <sup>1</sup>H NMR, δ 77.23 ppm for <sup>13</sup>C NMR) or tetramethylsilane (δ 0.00 for <sup>1</sup>H NMR, δ 0.00 ppm for <sup>13</sup>C NMR) as the internal reference. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; td = triplet of doublets; tt = triplet of triplets; qd = quartet of doublets; ddd = doublet of doublet of

doublets; br s = broad singlet). Where applicable, the number of protons attached to the corresponding carbon atom was determined by DEPT 135 NMR. Infrared (IR) spectra were obtained as thin films on NaCl plates by dissolving the compound in  $\text{CH}_2\text{Cl}_2$  followed by evaporation or as KBr pellets.

### **1) General Procedure for Preparing Trichloroacetimidates:**

Benzhydrol (10.125 g, 54.9 mmol) was added to a 250 mL flame dried round-bottom flask. 55 mL of dry DCM was added to dissolve the alcohol while under an argon atmosphere. 1,8-diazabicyclo[5.4.0]undec-7-ene (0.83 mL, 5.5 mmol) and trichloroacetonitrile (6.1 mL, 82.4 mmol) were then added to the reaction. This reaction mixture was allowed to stir for 20 hours at room temperature. The reaction mixture was concentrated under reduced pressure then pre-adsorbed on silica gel, and purified by silica gel column chromatography using 20% ethyl acetate/ 75% hexanes/ 5% triethylamine. This provided desired trichloroacetimidate as a white solid (9.99 g, 56%).

### **2) General Procedure for Generating Sulfides:**

1-phenyl-1H-tetrazole-5-thiol (0.203 g, 1.14 mmol) was placed into a 25 mL flame dried round-bottom flask and was dissolved in 6 mL of dry THF. Diphenyl-methyl trichloroacetimidate (0.44 g, 1.35 mmol) was added to the stirring reaction flask. The reaction mixture was heated to reflux while under an argon atmosphere for 18 hours. The reaction mixture was allowed to cool to room temperature, and was concentrated under reduced pressure. This was then pre-adsorbed on silica gel and purified by column chromatography using 30% ethyl acetate /70% hexanes. This provided desired sulfide as a white colored solid (0.127g, 94%).

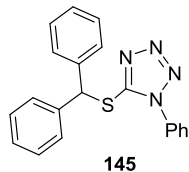
**3) General One-pot Conversion Procedure:**

Propargyl Alcohol (0.08 g, 1.43 mmol) was placed into a 25 mL flame dried round-bottom flask and was dissolved in 6 mL of dry THF. 1,8-diazabicyclo[5.4.0]undec-7-ene (122  $\mu$ L, 0.82 mmol) and trichloroacetonitrile (1.23 mL, 12.3 mmol) were then added to the reaction. This reaction mixture was allowed to stir for 6 hours at room temperature. 1-phenyl-1H-tetrazole-5-thiol (0.203 g, 1.14 mmol) was added and the reaction mixture was heated to reflux while under an argon atmosphere for 18 hours. The reaction mixture was allowed to cool to room temperature, and was concentrated under reduced pressure, pre-adsorbed on silica gel, and purified by column chromatography using 20% ethyl acetate/ 80% hexanes. This provided desired sulfide as a brown colored solid (0.190 g, 77%).

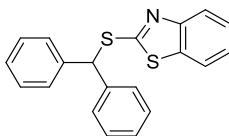
**General Procedures for the Purification of Sulfides:**

**Method A.** The reaction mixture was pre-adsorbed on silica gel and purified by silica gel chromatography using the listed solvent system.

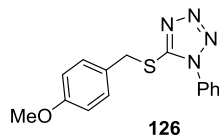
**Method B.** The reaction mixture was cooled to room temperature, concentrated under reduced pressure and dissolved in 50 mL of ethyl acetate. The organic layer was washed five times with 25 mL of 2M NaOH and then with 25 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to provide the desired sulfide.



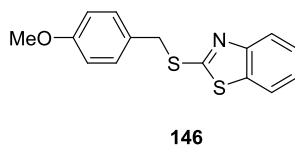
**5-[(Diphenylmethyl)thio]-1-phenyl-1H-Tetrazole (145).** Prepared by General Procedure 2 from the known imidate.<sup>95</sup> Purified by Method A (30% ethyl acetate /70% hexanes solvent system). White colored solid (0.127g, 94%). mp = 104.5-105.7°C; TLC  $R_f$  = 0.45 (30% ethyl acetate /70% hexanes); IR (neat) 3061, 3029, 2927  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58-7.41 (m, 10H), 7.38-7.21 (m, 5H), 3.40 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  152.9, 139.0, 133.4, 130.0, 129.6, 128.6, 128.3, 127.8, 123.9, 56.4. Anal. calcd for  $\text{C}_{20}\text{H}_{16}\text{N}_4\text{S}$ : C, 67.74; H, 4.68; N, 16.27. Found: C, 69.99; H, 4.50; N, 16.00.



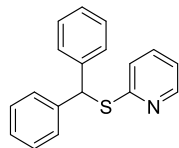
**2-[(Diphenylmethyl)thio]-benzothiazole (144).** Prepared by General procedure 2 from the known imidate.<sup>95</sup> Purified by Method A (10% acetone /90% hexanes solvent system). Cream colored solid (0.290 g, 88%). mp = 129.5-131°C; TLC  $R_f$  = 0.44 (10% acetone /90% hexanes); IR (neat) 3059, 3026, 2923  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.88 (d,  $J$  = 1.6 Hz, 1H), 7.71 (d,  $J$  = 1.6 Hz, 1H), 7.48-7.36 (m, 2H), 7.45-7.25 (m, 10H), 6.30 (s, 1H), 1.56 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  165.5, 152.9, 139.8, 135.4, 128.7, 128.5, 127.7, 126.0, 124.3, 121.8, 120.9, 56.3. Anal. calcd for  $\text{C}_{20}\text{H}_{15}\text{NS}_2$ : C, 72.03; H, 4.53; N, 4.20. Found: C, 72.06; H, 4.39; N, 4.15.



**5-((4-Methoxybenzyl)thio)-1-phenyl-1H-tetrazole (126).**<sup>64</sup> Prepared by General Procedure 2 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by Method A (30% ethyl acetate /70% hexanes solvent system). Cream colored solid (0.286 g, 89%). TLC  $R_f = 0.42$  (30% ethyl acetate /70% hexanes);  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.48-7.36 (m, 5H), 7.34 (d,  $J = 8.7$  Hz, 2H), 6.84 (d,  $J = 8.7$  Hz, 2H), 4.58 (s, 2H), 3.78 (s, 3H);  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  159.5, 154.1, 133.6, 130.5, 130.1, 129.8, 127.1, 123.8, 114.2, 55.3, 37.3.

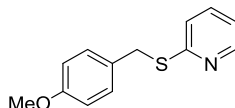


**2-[[4-(4-Methoxyphenyl)methyl]thio]-benzothiazole (146).**<sup>64</sup> Prepared by General Procedure 2 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by Method A (20% acetone /80% hexanes solvent system). Yellow colored solid (0.291 g, 89%). TLC  $R_f = 0.55$  (20% acetone /80% hexanes);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.88 (d,  $J = 1.2$  Hz, 1H), 7.71 (d,  $J = 2.0$  Hz, 1H), 7.48-7.36 (m, 2H), 6.86 (d,  $J = 2.4$  Hz, 2H), 4.58 (s, 2H), 3.78 (s, 3H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  163.8, 159.4, 153.9, 133.5, 130.4, 129.9, 129.6, 126.9, 123.6, 114.1, 55.2, 53.2, 37.2.



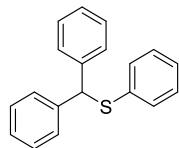
148

**2-[(Diphenylmethyl)thio]pyridine (148).** Prepared by General Procedure 2 from the known imidate.<sup>95</sup> Purified by Method A (10% ethyl acetate/90% hexanes solvent system). White colored solid (0.269 g, 85%). TLC  $R_f = 0.38$  (10% ethyl acetate/90% hexanes). mp = 66.4-67.3°C; IR (neat) 3060, 3027, 2961, 2923, 1600, 1576  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.38 (m, 1H), 7.50-7.08 (m, 12 H), 6.97 (m, 1H), 6.41 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  158.3, 149.4, 141.3, 136.1, 128.5, 127.5, 127.0, 122.3, 119.8, 52.6. Anal. calcd for  $\text{C}_{18}\text{H}_{15}\text{NS}$ : C, 77.94; H, 5.45; N, 5.05. Found: C, 78.24; H, 5.49; N, 4.90.



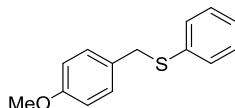
149

**2-[[4-Methoxyphenyl)methyl]thio]pyridine (149).**<sup>64</sup> Prepared by General Procedure 2 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by Method A (5% acetone /95% hexanes solvent system). Cream colored solid (0.214 g, 81%). TLC  $R_f = 0.32$  (5% acetone /95% hexanes);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.42 – 8.41 (m, 1H), 7.41 (m, 3H), 7.28 (d,  $J = 8.7$  Hz, 2H), 7.11 (d,  $J = 7.5$  Hz, 1H), 6.83-6.80 (m, 1H), 6.78 (d,  $J = 8.7$  Hz, 2H), 4.37 (s, 2H), 3.71 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  159.1, 158.8, 149.4, 135.9, 130.1, 129.9, 122.1, 119.6, 113.9, 55.3, 33.9.



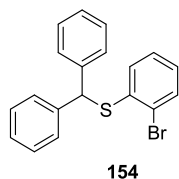
151

**1,1'-[(Phenylthio)methylene]bis-benzene (151).** Prepared by General Procedure 2 from the known imidate.<sup>95</sup> Purified by Method A (30% DCM /70% hexanes solvent system). White colored solid (0.127 g, 94%). mp = 61.8-63.4°C; TLC  $R_f$  = 0.45 (30% DCM /70% hexanes); IR (neat) 3060, 3027, 3004, 2961, 2923, 1599  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.48-7.13 (m, 15H), 5.54 (s, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  141.0, 136.1, 130.5, 129.1, 128.7, 128.5, 127.5, 127.2, 127.2, 126.6, 57.4. Anal. calcd for  $\text{C}_{19}\text{H}_{16}\text{S}$ : C, 82.56; H, 5.83. Found: C, 82.62; H, 5.58.

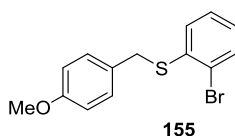


152

**1-Methoxy-4-[(phenylthio)methyl]-benzene (152).** Prepared by General Procedure 2 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by Method A (30% DCM /70% hexanes solvent system). Cream colored solid (0.208 g, 79%). TLC  $R_f$  = 0.44 (20% acetone /80% hexanes); mp = 76.1-77.8°C; IR (neat) 3047, 3003, 2959, 2912, 2837, 1250  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31-7.19 (m, 6H), 6.82 (d,  $J$  = 8.8 Hz, 2H), 4.08 (s, 2H), 3.79 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  158.7, 136.5, 129.9, 129.8, 128.8, 126.2, 113.8, 113.8, 55.2, 38.4. Anal. calcd for  $\text{C}_{14}\text{H}_{14}\text{OS}$ : C, 73.01; H, 6.13. Found: C, 72.97; H, 6.07.

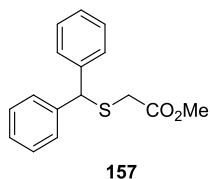


**1-Bromo-2-[(diphenylmethyl)thio]benzene (154).** Prepared by General Procedure 2 from the known imidate.<sup>95</sup> Purified by Method A (30% DCM /70% hexanes solvent system). Yellow colored oil (0.343 g, 85%). TLC  $R_f$  = 0.81, 0.71 (30% DCM /70% hexanes); IR (neat) 3084, 3061, 3027, 2961, 650  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.50-6.91 (m, 14 H), 5.66 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  140.0, 137.4, 132.8, 130.2, 129.6, 128.5, 128.4, 127.5, 126.9, 124.1, 55.9. Anal. calcd for  $\text{C}_{19}\text{H}_{15}\text{BrS}$ : C, 64.23; H, 4.26. Found: C, 64.52; H, 4.45.

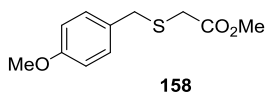


**1-Bromo-2-[1-methoxy-4-(phenylthio)methyl]benzene (155).** Prepared by General Procedure 2 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by Method A (20% acetone /80% hexanes solvent system). Cream colored solid (0.208 g, 59%). mp = 121.2-122.7°C; TLC  $R_f$  = 0.44 (20% acetone /80% hexanes); IR (neat) 3074, 3033, 3003, 2957, 1249  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 (d,  $J$  = 8.4 Hz, 2H), 7.51-7.21 (m, 3H), 7.04-6.84 (m, 1H), 6.84 (d,  $J$  = 8.8 Hz, 2H), 4.11 (s, 2H), 3.79 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  158.9, 138.1, 132.9, 130.1, 128.8, 127.9, 127.7, 126.8, 123.6, 114.0, 55.3, 37.4. Anal. calcd for  $\text{C}_{14}\text{H}_{13}\text{BrOS}$ : C, 54.38; H, 4.24. Found: C, 54.21; H, 4.22.

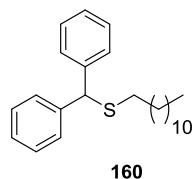




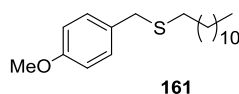
**Methyl 2-(benzhydrylthio)acetate (157).** Prepared by General Procedure 2 from the known imidate.<sup>95</sup> Purified by Method B. Yellow colored oil (0.202 g, 65%). TLC  $R_f = 0.46$  (10% ethyl acetate/90% hexanes); IR (neat) 3084, 3060, 3027, 3003, 2950, 2843, 1735;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44-7.22 (m, 10H), 5.39 (s, 1H), 3.65 (s, 3H), 3.08 (s, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.7, 140.3, 128.6, 128.4, 127.4, 54.2, 52.3, 33.5; Anal. calcd for  $\text{C}_{16}\text{H}_{16}\text{O}_2\text{S}$ : C, 70.56; H, 5.92. Found: C, 70.55; H, 5.92.



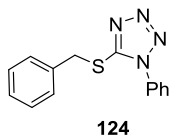
**Methyl 2-((4-methoxybenzyl)thio)acetate (158).** Prepared by General Procedure 2 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by Method B. Yellow colored oil (0.132 g, 51%). TLC  $R_f = 0.34$  (10% ethyl acetate/90% hexanes); IR (neat) 3030, 3000, 2952, 2836, 1744;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (d,  $J = 6.3$  Hz, 2H), 6.85 (d,  $J = 6.6$  Hz, 2H), 3.79-3.78 (m, 5H), 3.72 (s, 3H), 3.07 (s, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  170.9, 158.8, 130.3, 129.1, 113.9, 55.3, 52.3, 35.8, 31.9; Anal. calcd for  $\text{C}_{11}\text{H}_{14}\text{O}_3\text{S}$ : C, 58.38; H, 6.24. Found: C, 58.30; H, 6.28.



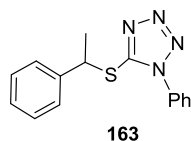
**Benzhydryl dodecyl sulfide (160).**<sup>100</sup> Prepared by General Procedure 2 from the known imidate.<sup>95</sup> Purified by Method A (30% DCM /70% hexanes solvent system). Colorless oil (0.273 g, 64%). TLC  $R_f = 0.57$  (30% DCM/70% hexanes);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43-7.18 (m, 10H), 5.14 (s, 1H), 2.37 (t, 2H,  $J = 5.7$  Hz), 1.58-1.49 (m, 2H), 1.32-1.23 (m, 12H), 0.88 (t, 3H,  $J = 5.1$  Hz);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  142.2, 141.6, 129.3, 128.6, 127.4, 54.1, 32.3, 31.9, 29.6, 29.5, 29.4, 29.3, 29.1, 28.9, 28.8, 22.7, 14.1.



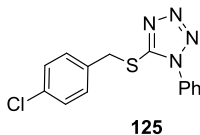
**Dodecyl 4-methoxybenzyl sulfide (161).**<sup>100</sup> Prepared by General Procedure 2 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by Method A (20% DCM /80% hexanes solvent system). Colorless oil (0.149 g, 40%). TLC  $R_f = 0.38$  (20% DCM /80% hexanes);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.22 (d,  $J = 6.6$  Hz, 2H), 6.84 (d,  $J = 6.6$  Hz, 2H), 3.80 (s, 3H), 3.66 (s, 2H), 2.40 (t,  $J = 5.7$  Hz, 2H), 1.56-1.49 (m, 2H), 1.31-1.23 (m, 12H), 0.88 (t,  $J = 5.1$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  158.5, 130.7, 129.8, 113.8, 55.3, 35.6, 31.9, 31.3, 29.7, 29.6, 29.59, 29.5, 29.3, 29.2, 28.9, 22.7, 14.1.



**5-(Benzylthio)-1-phenyl-1H-tetrazole (124).**<sup>64</sup> Prepared by General Procedures 2 and 3 from the commercially available benzyl alcohol or benzyl-2,2,2-trichloroacetimidate. Purified by Method A (30% ethyl acetate /70% hexanes solvent system). Cream colored solid (0.193g, 87%). mp = 68.8-69.7°C (ethyl acetate), lit = 69-70°C; TLC R<sub>f</sub> = 0.55 (30% ethyl acetate /70% hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.58-7.50 (m, 5H), 7.45-7.22 (m, 5H), 4.62 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 153.8, 135.2, 133.6, 130.1, 129.7, 129.2, 128.8, 128.2, 123.8, 37.6.

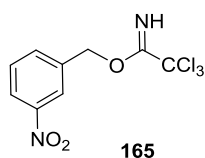


**1-Phenyl-5-[(1-phenylethyl)thio]-1H-tetrazole (163).**<sup>64</sup> Prepared by General Procedure 2 from the known imidate.<sup>102</sup> Purified by Method A (30% ethyl acetate /70% hexanes solvent system). Yellow colored oil (0.141 g, 87%). TLC R<sub>f</sub> = 0.65 (30% ethyl acetate /70% hexanes); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.54-7.49 (m, 5H), 5.29 (q, *J* = 7.2 Hz, 1H), 1.88 (d, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 153.5, 140.7, 133.4, 129.9, 129.5, 128.6, 128.0, 127.1, 123.8, 47.8, 22.1.

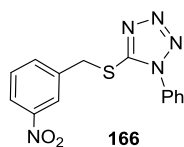


**5-[[4-Chlorophenyl)methyl]thio]-1-phenyl-1H-tetrazole (125).**<sup>64</sup> Prepared by General Procedure 2 from the known imidate.<sup>99</sup> Purified by Method A (20% ethyl acetate /80% hexanes solvent system). White colored solid (0.271 g, 88%). mp = 102-104°C; TLC R<sub>f</sub> = 0.368 (20% ethyl acetate /80% hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.61-7.55 (m, 5H), 7.39-1.36 (m,

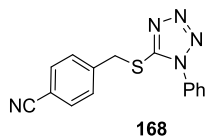
2H), 7.30-7.26 (m, 2H), 4.58 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  153.3, 133.8, 133.7, 133.2, 130.3, 129.9, 129.5, 128.7, 123.5, 36.5.



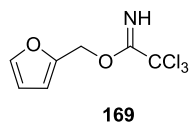
**3-Nitrobenzyl 2,2,2-trichloroacetimidate (165).** Prepared by General Procedure 1. Purified by Method A (20% ethyl acetate/ 75% hexanes/ 5% triethylamine solvent system). Light orange colored solid (2.19 g, 90%). TLC  $R_f$  = 0.50 (20% ethyl acetate/ 75% hexanes/ 5% triethylamine). mp = 32.4-32.9°C; IR (neat) 3340, 3090, 3077, 1646, 1530, 1352  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.51 (br s, 1H), 8.33 (s, 1H), 8.20 (d,  $J$  = 9.2 Hz, 1H), 7.79 (d,  $J$  = 8.0 Hz, 1H), 7.58 (t,  $J$  = 8.0 Hz, 1H), 5.44 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  162.1, 148.4, 137.5, 133.5, 129.6, 123.2, 122.5, 90.9, 69.0; Anal. calcd for  $\text{C}_9\text{H}_7\text{Cl}_3\text{N}_2\text{O}_3$ : C, 36.33; H, 2.37; N, 9.42. Found: C, 36.25; H, 2.22; N, 9.18.



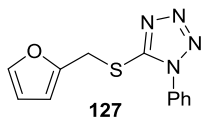
**5-[[3-Nitrophenyl)methyl]thio]-1-phenyl-1H-tetrazole (166).** Prepared by General Procedure 2 from the prepared imidate **84**. Purified by Method A (50% DCM /50% hexanes solvent system). White colored solid (0.247 g, 80%). TLC  $R_f$  = 0.36 (50% DCM /50% hexanes); mp = 119.8-120.9°C; IR (neat) 3091, 3077, 3059, 2996, 1527, 1353  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.32-8.31 (m, 1H), 8.16 (d,  $J$  = 8.1 Hz, 1H), 7.87 (d,  $J$  = 8.1 Hz, 1H), 7.58-7.49 (m, 5H), 7.28-7.15 (m, 2H), 4.69 (s, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  153.0, 148.4, 137.8, 135.4, 133.4, 130.3, 129.9, 129.7, 124.1, 123.7, 123.1, 36.3. Anal. calcd for  $\text{C}_{14}\text{H}_{11}\text{N}_5\text{O}_2\text{S}$ : C, 53.66; H, 3.54; N, 22.35. Found: C, 53.55; H, 3.67; N, 22.37.



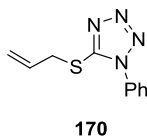
**4-[[1-(1-Phenyl-1H-tetrazol-5-yl)thio]methyl]-benzonitrile (168).** Prepared by General Procedure 2 from the known imidate.<sup>102</sup> Purified by Method A (20% ethyl acetate /80% hexanes solvent system). Cream colored solid (0.298 g, 72%). TLC  $R_f = 0.24$  (20% ethyl acetate /80% hexanes); mp = 102.8-104.1°C; IR (neat) 2956, 2925, 2854, 2229  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61-7.49 (m, 10H), 4.63 (s, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  153.1, 141.1, 133.3, 132.5, 130.3, 129.8, 129.2, 123.9, 118.4, 111.9, 36.6. Anal. calcd for  $\text{C}_{15}\text{H}_{11}\text{N}_5\text{S}$ : C, 61.42; H, 3.78; N, 23.87. Found: C, 61.68; H, 3.68; N, 23.48.



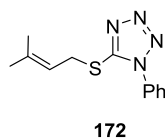
**Furfuryl 2,2,2-trichloroacetimidate (169).** Prepared by General Procedure 1. Purified by Method A (20% ethyl acetate/ 75% hexanes/ 5% triethylamine solvent system). Yellow colored oil (1.98 g, 99%). TLC  $R_f = 0.75$  (20% ethyl acetate/ 75% hexanes/ 5% triethylamine);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.42 (br s, 1H), 7.45 (s, 1H), 6.49 (m, 1H), 6.38 (m, 1H), 5.29 (s, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  162.1, 148.6, 143.3, 111.1, 110.4, 91.1, 62.5; Anal. calcd for  $\text{C}_7\text{H}_6\text{Cl}_3\text{NO}_3$ : C, 34.67; H, 2.49; N, 5.78. Found: C, 34.72; H, 2.42; N, 5.85.



**5-[(2-Furanylmethyl)thio]-1-phenyl-1H-tetrazole (127).**<sup>64</sup> Prepared by General Procedures 2 and 3 from the commercially available alcohol or prepared imidate. Purified by Method A (20% acetone /80% hexanes solvent system). Yellow colored oil (0.332 g, 69%). TLC  $R_f = 0.42$  (20% acetone /80% hexanes);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.96 – 7.94 (m, 2H), 7.58-7.51 (m, 5H), 7.36 (s, 1H), 6.61 (d,  $J = 3.0$  Hz, 1H), 6.39 (d,  $J = 3.9$  Hz, 2H), 4.24 (s, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  153.5, 148.3, 142.9, 133.5, 130.2, 129.8, 123.8, 110.8, 109.8, 30.1.

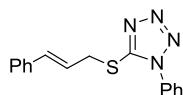


**1-Phenyl-5-(2-propen-1-ylthio)-1H-tetrazole (170).**<sup>88</sup> Prepared by General Procedure 2 from the commercially available *O*-allyl 2,2,2-trichloroacetimidate. Purified by Method A (20% ethyl acetate /80% hexanes solvent system). Yellow colored oil (0.201 g, 81%). TLC  $R_f = 0.60$  (30% ethyl acetate /70% hexanes); IR (neat) 3069, 3010, 2981, 2928  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61-7.55 (m, 5H), 6.08-5.87 (m, 1H), 5.39 (d,  $J = 2.4$  Hz, 1H), 5.17 (d,  $J = 1.2$  Hz, 1H), 4.01 (d,  $J = 9.0$  Hz, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  153.6, 133.4, 131.3, 130.0, 129.6, 123.7, 119.9, 35.7.



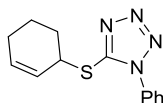
**5-[(3-Methyl-2-butenyl)thio]-1-phenyl-1H-tetrazole (172).** Prepared by General Procedures 2 and 3 from the commercially available alcohol or known imidate.<sup>98</sup> Purified by Method A (30% ethyl acetate /70% hexanes solvent system). Cream colored solid (0.250 g, 98%). mp = 38-39°C;

TLC  $R_f = 0.72$  (30% ethyl acetate /70% hexanes); IR (neat) 3062, 3015, 2981, 2928, 2895  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61-7.55 (m, 5H), 5.44-7.37 (m, 1H), 4.04 (d,  $J = 8.0$  Hz, 2H), 1.73 (s, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  154.3, 139.8, 133.7, 129.9, 129.7, 123.7, 116.8, 31.6, 25.6, 17.9. Anal calcd for  $\text{C}_{12}\text{H}_{14}\text{N}_4\text{S}$ : C, 58.51; H, 5.73, N, 22.74. Found: C, 58.29; H, 5.54; N, 22.39.



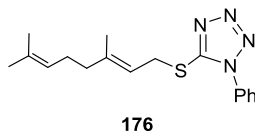
130

**1-Phenyl-5-[[2E]-3-phenyl-2-propen-1-yl]thio-1H-tetrazole (130).**<sup>64</sup> Prepared by General Procedure 2 from the known imidate.<sup>103</sup> Purified by Method A (30% ethyl acetate /70% hexanes solvent system). Yellow colored oil (0.264 g, 95%). TLC  $R_f = 0.63$  (30% ethyl acetate /70% hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61-7.55 (m, 5H), 7.39-7.27 (m, 5H), 6.72 (d,  $J = 15.6$  Hz, 1H), 6.41-6.31 (m, 1H), 4.23 (d,  $J = 8.8$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  153.6, 135.7, 134.9, 133.3, 129.9, 129.6, 129.5, 128.4, 128.3, 127.9, 126.3, 123.6, 122.2, 35.6.

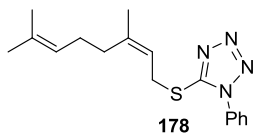


132

**2-Cyclohexen-1-yl-1-phenyl-1H-tetrazole-5-thiol (132).**<sup>64</sup> Prepared by General Procedure 2 from the known imidate.<sup>104</sup> Purified by Method A (20% ethyl acetate /80% hexanes solvent system). Yellow colored oil (0.104 g, 91%). TLC  $R_f = 0.65$  (20% ethyl acetate /80% hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61-7.55 (m, 5H), 6.01-5.78 (m, 2H), 4.78-4.72 (m, 1H), 2.24-1.67 (m, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  154.1, 133.0, 129.9, 129.7, 124.8, 123.8, 44.7, 28.9, 24.8, 19.1.

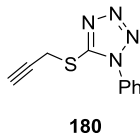


**(E)-[(3,7-Dimethyl-2,6-octadienyl)thio]-1-phenyl-1H-tetrazole (176).**<sup>88</sup> Prepared by General Procedures 2 and 3 from the commercially available alcohol or known imidate.<sup>104</sup> Purified by Method A (30% ethyl acetate /70% hexanes solvent system). Light yellow colored oil (0.292 g, 83%). TLC  $R_f = 0.74$  (30% ethyl acetate /70% hexanes); IR (neat) 3061, 2925, 1503, 1454, 1384  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61-7.52 (m, 5H), 5.43-5.38 (m, 1H), 5.06-5.01 (m, 1H), 4.07 (d,  $J = 8.0$  Hz, 2H), 2.15-2.01 (m, 2H), 1.69 (s, 3H), 1.58 (s, 3H), 1.26 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  154.3, 143.1, 133.7, 131.8, 130.0, 123.6, 117.4, 116.7, 39.5, 31.9, 26.4, 25.6, 23.4, 17.7, 16.3.

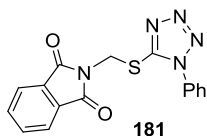


**(Z)-5-[(3,7-Dimethyl-2,6-octadienyl)thio]-1-phenyl-1H-tetrazole (178).**<sup>88</sup> Prepared by General Procedure 2 from the known imidate.<sup>104</sup> Purified by Method A (30% ethyl acetate /70% hexanes solvent system). Clear colored oil (0.292 g, 88%). TLC  $R_f = 0.57$  (30% ethyl acetate /70% hexanes); IR (neat) 3052, 2967, 2857, 1500, 1448, 1383  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.66-7.50 (m, 5H), 5.45-5.41 (m, 1H), 5.13-5.08 (m, 1H), 4.06 (d,  $J = 8.0$  Hz, 2H), 2.18-2.07 (m, 4H), 1.75 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  154.3, 143.2, 133.6, 132.1, 129.9, 129.6, 123.6, 123.4, 117.3, 31.9, 31.3, 26.3, 25.5, 23.3, 17.6.

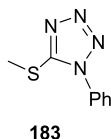




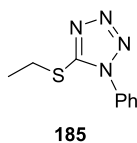
**1-Phenyl-5-(2-propyn-1-ylthio)-1H-tetrazole (180).**<sup>88</sup> Prepared by General Procedures 2 and 3 from the commercially available alcohol or known imidate.<sup>105</sup> Purified by Method A (20% ethyl acetate /80% hexanes solvent system). Brown colored solid (0.250 g, 96%). mp = 78-79°C, lit = 97-98°C; TLC  $R_f$  = 0.421 (20% ethyl acetate /80% hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.61-7.55 (m, 5H), 4.17 (d,  $J$  = 2.8 Hz, 2H), 2.18 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 153.1, 133.6, 130.6, 130.1, 123.9, 73.3, 22.0.



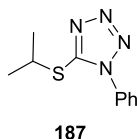
**2-(((1-Phenyl-1H-tetrazol-5-yl)thio)methyl)isoindoline-1,3-dione (181).** Prepared by General Procedure 2 from the known imidate.<sup>98</sup> Purified by Method A (40% acetone /60% hexanes solvent system followed by trituration with methanol and filtered). White colored solid (0.256 g, 78%). mp = 84.3-85.6°C; TLC  $R_f$  = 0.45 (40% acetone /60% hexanes); IR (neat) 3064, 3015, 1777, 1722 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.88-7.86 (m, 2H), 7.77-7.75 (m, 2H), 7.57-7.49 (m, 5H), 5.47 (s, 2H) ; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 166.3, ,134.6, 131.7, 130.3, 127.7, 124.2, 123.9, 39.9, 30.9. Anal. calcd for C<sub>16</sub>H<sub>11</sub>N<sub>5</sub>O<sub>2</sub>S: C, 56.96; H, 3.29; N, 20.76. Found: C, 56.87; H, 3.26; N, 20.81.



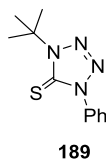
**5-(Methylthio)-1-phenyl-1H-tetrazole (183).**<sup>106</sup> Prepared by General Procedure 2 from the commercially available methyl 2,2,2-trichloroacetimidate. Purified by Method A (25% ethyl acetate /75% hexanes solvent system). White colored solid (0.081 g, 75%). mp = 77.2-77.8°C, lit = 81-82°C; TLC R<sub>f</sub> = 0.31 (25% ethyl acetate /75% hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.51-7.47 (m, 5H), 2.75 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 155.1, 133.8, 130.3, 129.9, 123.8, 15.5.



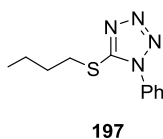
**5-(Ethylthio)-1-phenyl-1H-tetrazole (185).**<sup>108</sup> Prepared by General Procedure 2 from the commercially available ethyl 2,2,2-trichloroacetimidate. Purified by Method A (20% ethyl acetate /80% hexanes solvent system). Yellow colored oil (0.225 g, 81%). TLC R<sub>f</sub> = 0.33 (20% acetone /80% hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.58-7.51 (m, 5H), 3.42 (q, *J* = 7.2 Hz, 2H), 1.50 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 154.3, 133.7, 130.0, 129.8, 123.8, 22.5, 14.5.



**5-(Isopropylthio)-1-phenyl-1H-tetrazole (187).**<sup>107</sup> Prepared by General Procedure 2 from the known imidate.<sup>106</sup> Purified by Method B (35% DCM /65% hexanes). Yellow colored oil (0.689 g, 38%). TLC  $R_f$  = 0.64, 0.62 (35% DCM /65% hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58-7.52 (m, 5H), 4.16-4.09 (m, 1H), 1.51 (d,  $J$  = 6.8 Hz, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  154.1, 133.7, 130.1, 129.7, 124.0, 39.8, 23.3.

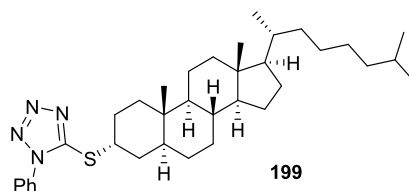


**1-(tert-butyl)-4-phenyl-1H-tetrazole-5(4H)-thione (189).**<sup>64</sup> Prepared by General Procedure 2 from the commercially available *tert*-butyl 2,2,2-trichloroacetimidate. Purified by Method A (10% ethyl acetate /90% hexanes solvent system). Cream colored solid (0.043 g, 16%). mp = 92-94°C; TLC  $R_f$  = 0.80 (10% ethyl acetate /90% hexanes); IR (neat) 3070, 2960, 2925  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61-7.55 (m, 5H), 1.65 (s, 9H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  152.9, 133.4, 130.0, 129.6, 124.7, 50.6, 30.7. Anal calcd for  $\text{C}_{11}\text{H}_{14}\text{N}_4\text{S}$ : C, 56.38; H, 6.02; N, 23.91. Found: C, 56.45; H, 5.91; N, 24.18.

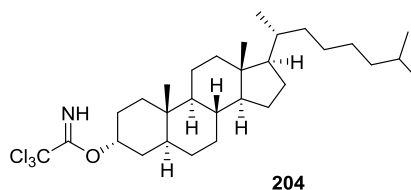


**5-(Butylthio)-1-phenyl-1H-tetrazole (197).**<sup>26</sup> Prepared by General Procedure 3 from the commercially available alcohol. Purified by Method A (10% acetone /90% hexanes solvent system). Light Yellow oil (0.199 g, 63%). TLC  $R_f$  = 0.22 (10% acetone /90% hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.60-7.53 (m, 5H), 3.33 (t,  $J$  = 7.6 Hz, 1H), 1.75-1.85 (m, 2H), 1.41-

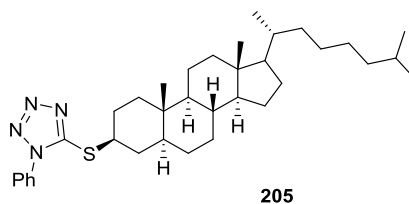
1.54 (m, 2H), 0.88 (t,  $J = 7.6$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  154.5, 133.7, 130.0, 129.7, 123.9, 33.0, 31.0, 21.7, 13.4.



**5-[( $\alpha$ -Cholestan-3 $\alpha$ )thio]-1-phenyl-1H-tetrazole (199).** Prepared by General Procedures 2 and 3 from the known imidate<sup>109</sup> or alcohol (in toluene). Purified by Method A (10% ethyl acetate /90% hexanes solvent system). Yellow solid (0.303 g, 48%). mp = 127.7-128.4°C; TLC  $R_f$  = 0.51 (10% ethyl acetate /90% hexanes); IR (neat) 2929, 2865, 1642, 1597  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61-7.52 (m, 5H), 4.57 (br s, 1H), 2.12-0.78 (m, 42H), 0.64 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  154.7, 133.8, 129.9, 129.7, 124.1, 56.5, 56.3, 54.1, 47.9, 42.6, 41.8, 39.9, 39.5, 36.4, 36.2, 35.8, 35.4, 33.8, 31.8, 28.3, 28.2, 28.0, 27.3, 24.1, 23.9, 22.8, 22.6, 20.8, 18.7, 12.1, 11.9; Anal. calcd for  $\text{C}_{34}\text{H}_{52}\text{N}_4\text{S}$ : C, 74.40; H, 9.55; N, 10.21. Found: C, 74.41; H, 9.52; N, 10.11.



**5 $\alpha$ -Cholestan-3 $\alpha$ -2,2,2-trichloroacetimidate (204).**<sup>109</sup> Prepared by General Procedure 1 from commercially available alcohol. Purified by Method A (10% ethyl acetate/ 80% hexanes/ 5% triethylamine solvent system). White colored solid (0.849 g, 91%). TLC  $R_f$  = 0.58 (10% ethyl acetate /80% hexanes/ 5% triethylamine);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.18 (br s, 1H), 5.13 (s, 1H) 1.98 – 0.73 (m, 42H), 0.66 (s, 3H).



**5-[( $\alpha$ -Cholestan-3 $\beta$ )thio]-1-phenyl-1H-tetrazole (205).**<sup>109</sup> Prepared by General Procedure 2 from the starting imidate **204** (in toluene). Purified by Method A (5% ethyl acetate /95% hexanes solvent system.) Light yellow colored solid (0.226 g, 42%). TLC  $R_f$  = 0.46 (10% ethyl acetate /90% hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58 – 7.51 (m, 5H), 3.95 – 3.84 (m, 1H), 2.14 – 2.09 (m, 1H), 1.99 – 0.73 (42H), 0.72 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  153.9, 133.8, 129.9, 129.7, 123.9, 56.4, 56.3, 54.2, 47.3, 46.9, 42.6, 39.9, 39.5, 38.7, 36.1, 35.8, 35.5, 35.4, 31.9, 29.0, 28.5, 28.2, 28.0, 24.2, 23.9, 22.8, 22.6, 21.0, 18.7, 12.2, 12.1.

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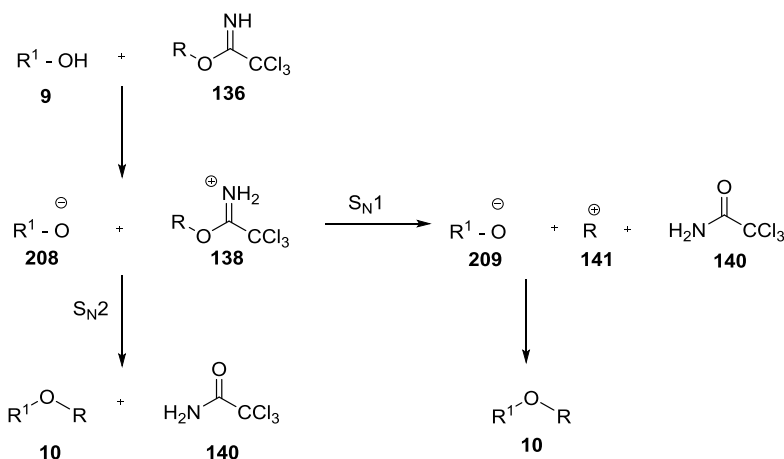
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## Chapter 3. Etherification Utilizing Trichloroacetimidates Under Thermal Conditions

### 3.1 Introduction

As mentioned in Chapter 1, the literature contains numerous methods to introduce ether and ester protecting groups by alkylation; however it comes with the caveat of the requirement of an external promoter or harsh conditions.<sup>1-100</sup> Trichloroacetimidates are a facile method to introduce ether and ester protecting groups and are easily formed from alcohols (Scheme 3). Many trichloroacetimidates are also commercially available. Previous literature typically requires that the imidate be activated by an external promoter for etherification; these promoters usually are Brønsted acids, Lewis acids or transition metal catalysts.<sup>1-9,24-27,70,75,76,78</sup> Recently within the Chisholm group it was found that *S*-alkylation<sup>101</sup> and esterifications<sup>102,103</sup> utilizing trichloroacetimidates could occur without the addition of an added catalyst. Therefore it was theorized that ether formation might be possible under similar reaction conditions. This would provide a mild alternative for the conversion of alcohols to ethers without an external promoter and expand the applicability of trichloroacetimidate alkylations to substrates containing acid-sensitive functionality. To our knowledge, no precedent has shown that ether formation with trichloroacetimidates may be performed solely under thermal conditions without an added catalyst,<sup>73</sup> and this improvement on the known methodology could be quite useful in complex substrates. As proposed in Scheme 25, we suspect that the substitution reaction may occur in a similar manner as the thioetherification, which is through either an  $S_N1$  or  $S_N2$  pathway (stepwise proton transfer). Obviously, the proton transfer step will be more difficult, as alcohols are less acidic than thiols or carboxylic acids. Still, under more vigorous reaction conditions the

etherification may be possible. This chapter focuses on defining the limits of this new etherification procedure, particularly on the reactivity of both diphenylmethyl and 4-methoxybenzyl trichloroacetimidates in these reactions.



**Scheme 25: Possible Mechanistic Pathway of Ether Generation**

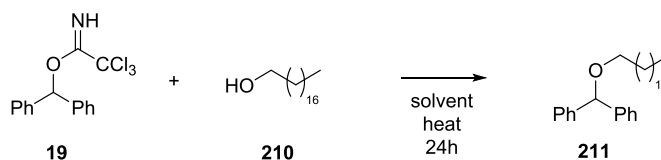
### 3.2 Reaction Development

*O*-Diphenylmethyl (DPM) trichloroacetimidate **19** was utilized as the initial electrophile in the etherification. As diphenylmethyl is a common protecting group used in organic synthesis (often as a surrogate for benzyl) the installation of this group would be useful in organic synthesis.<sup>3</sup> Additionally, the DPM imidate **19** is a conveniently handled white solid that can be stored for long periods of time at 0°C,<sup>5,102</sup> so it may be a practical "on-demand" etherification reagent. When 1-octadecanol **210** and 1.2 equivalents of **19** were combined in toluene and heated to 50 °C for 24 hours, only 24% of the desired ether **211** could be isolated (Table 14, Entry 1). A significant amount of starting material was also recovered. While the yield was low this result provided evidence for the initial hypothesis that this etherification could occur solely under thermal conditions. We then increased the temperature to refluxing in toluene (111 °C), which provided the desired ether in a much more desirable 85% yield. Several other solvents were also



investigated, including THF, which proved to be ideal for thioetherifications; however the yield did not improve significantly. Therefore, toluene at reflux for 24 hours (Entry 2) was chosen as the standard reaction conditions to generate the desired etherification products.

**Table 14: Reaction of DPM trichloroacetimidate with 1-octadecanol**



Entry	Solvent	Temperature	Yield <sup>b</sup>
1	toluene	50 °C	24%
<b>2</b>	<b>toluene</b>	<b>111 °C</b>	<b>85%</b>
3	$\alpha, \alpha, \alpha$ - trifluorotoluene	102 °C	62%
4	THF	66 °C	36%
5	dichloromethane	40 °C	18%
6	1,2-dichloroethane	83 °C	66%
7	1,4-dioxane	101 °C	60%
8	acetonitrile	82 °C	28%
9	DMF	110 °C	33%


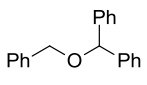

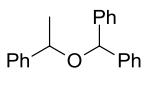
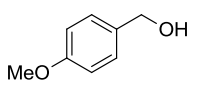
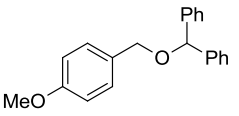
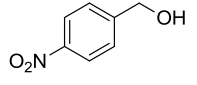
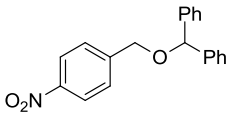
<sup>a</sup>All reactions were performed at 0.25M for 24 h in the noted solvent. <sup>b</sup>Isolated yields.

With reaction conditions in hand, we then investigated the scope of this etherification methodology with regard to the alcohol reaction partner. Benzylic alcohols were excellent substrates, generating DPM ethers under essentially neutral conditions very efficiently regardless if an electron - withdrawing or – donating group is present. More specifically, the 4-nitrobenzyl alcohol afforded ether **218** in 88% yield while the 4-methoxybenzyl alcohol provided ether **216** in 71% yield.

**Table 15: Reaction of DPM Imidate with Benzylic Alcohols**

$$\text{R}^1 - \text{OH} \xrightarrow[\text{toluene, reflux, 24 h}]{\mathbf{19}} \text{R}^1 - \text{O} - \text{C}(\text{Ph})_2$$

**9**  **212**

Entry	Alcohol	Product	Yield
1	 <b>192</b>	 <b>213</b>	88%
2	 <b>191</b>	 <b>214</b>	92%
3	 <b>215</b>	 <b>216</b>	71% <sup>a</sup>
4	 <b>217</b>	 <b>218</b>	88%

<sup>a</sup> Performed by Kyle Howard

This methodology was also extended towards simple primary and secondary alcohols to obtain the desired ethers in respectable yields. Propargyl alcohol proved to be an exceptional substrate, providing the corresponding DPM ether in nearly quantitative yields. Additionally cinnamyl alcohol **218**, which has consistently been a challenging substrate for some other etherification reagents,<sup>8</sup> gave an 88% yield of the desired ether.

**Table 16: Reaction of DPM Imidate with Alkyl and Allylic Alcohols**

$$\text{R}^1\text{-OH} \xrightarrow[\text{toluene, reflux, 24 h}]{\text{19}} \text{R}^1\text{-O-C(Ph)}_2$$

**9**  **212**

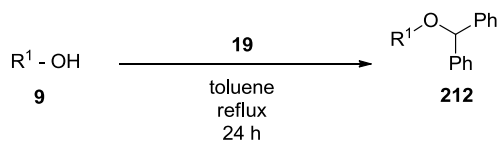
Entry	Alcohol	Product	Yield
1			85% <sup>a</sup>
2			85% <sup>a</sup>
3			93% <sup>a</sup>
4			53% <sup>a</sup>
5			97%
6			88% <sup>a</sup>

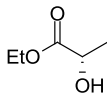
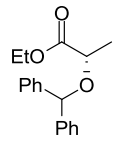
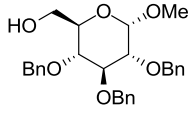
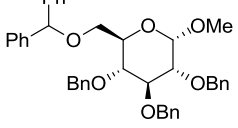
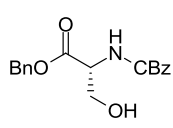
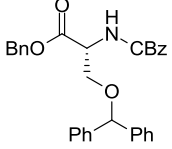
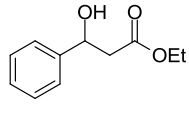
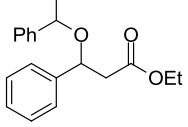
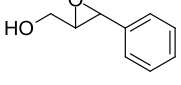
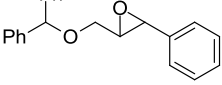
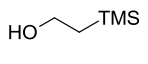
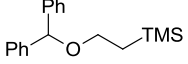
<sup>a</sup> Performed by Kyle Howard

Table 17 further demonstrates the general nature of this methodology with DPM imidate with acid/base labile compounds, and even chiral alcohols could tolerate this transformation without degradation, racemization, isomerization, or elimination. Most notably, epoxide **227** as well as  $\beta$  – trimethylsilylethanol, **229**, which can undergo Peterson elimination<sup>104</sup> successfully yielded the desired products in 65% and 79% yield, respectively. We have established that carbohydrate alcohols were just as capable of generating the desired DPM ether, with the

formation of ether **222** in 73% yield. This demonstrates the versatility of trichloroacetimidates as well as verifies the initial hypothesis that *O*-alkylation may occur in multiple substrates without an added catalyst with the DPM trichloroacetimidate.

**Table 17: Reaction of DPM Imidate with Acid-Sensitive Alcohols**



Entry	Alcohol	Product	Yield
1	 <b>219</b>	 <b>220</b>	90% <sup>a</sup>
2	 <b>221</b>	 <b>222</b>	73%
3	 <b>223</b>	 <b>224</b>	91% <sup>a</sup>
4	 <b>225</b>	 <b>226</b>	96% <sup>a</sup>
5	 <b>227</b>	 <b>228</b>	65% <sup>a</sup>
6	 <b>229</b>	 <b>230</b>	79%

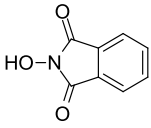
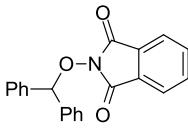
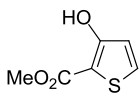
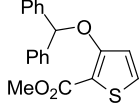
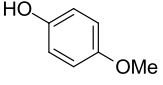
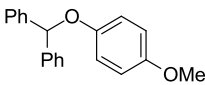
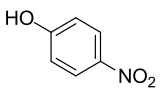
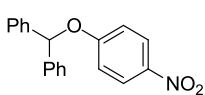
<sup>a</sup> Performed by Kyle Howard

We then continued to investigate more complex alcohols in the form of phenolic and phenolic-like substrates (Table 18). More specifically, the electron-poor thiophene provided ether **233** in 53% yield, the base sensitive *N*-hydroxyphthalimide afforded the etherification product in **232** 80% yield, and the 4-nitro and 4-methoxy phenols in 61% and 91% yield, respectively.

**Table 18: Reaction of DPM Imidate with Phenols and Phenol-Like Alcohols**

$$\text{R}^1\text{-OH} \xrightarrow[\text{toluene, reflux, 24 h}]{\mathbf{19}} \text{R}^1\text{-O-CH(Ph)}_2$$

$$\mathbf{9} \qquad \qquad \qquad \mathbf{212}$$

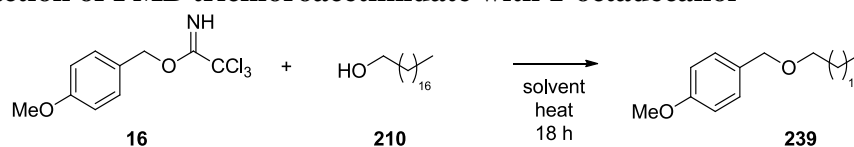
Entry	Alcohol	Product	Yield
1	 $\mathbf{231}$	 $\mathbf{232}$	80% <sup>a</sup>
2	 $\mathbf{233}$	 $\mathbf{234}$	53%
3	 $\mathbf{235}$	 $\mathbf{236}$	91% <sup>a</sup>
4	 $\mathbf{237}$	 $\mathbf{238}$	61%

<sup>a</sup> Performed by Kyle Howard

With the completion of our expansive investigation into ether formation with DPM imidate,<sup>5</sup> we then changed the imidate electrophile to a more commonly used protecting group,

4-methoxybenzyl (PMB).<sup>9,11,18,24,83</sup> Given the previous ideal conditions for our etherification methodology with DPM was toluene at refluxing conditions, we presumed this could be a high-yielding set of conditions for etherification utilizing PMB imidate; however, this was not the case. Although toluene yielded the desired etherification product in 70% yield (Table 19, Entry 1), which is respectable and proves that this alkylation can be completed without an exogenous catalyst, we observed a considerable amount of starting materials and also some Friedel-Crafts products between the PMB imidate and the toluene. The elevated temperatures were decreased in an attempt to minimize the formation of Friedel-Crafts products, however the yield of the desired ether significantly decreased. Switching the solvent to the less activated  $\alpha,\alpha,\alpha$ -trifluorotoluene was also explored, as the electron-withdrawing trifluoromethyl group should inhibit the formation of Friedel-Crafts alkylation products. This resulted in a slightly higher yielding etherification product, 73%; however there were still some starting materials present. Other modifications to the reaction conditions such as varying temperatures, varying reaction concentration, and the addition of drying agents like MgO were also investigated, however no further improvement to the yield was found.

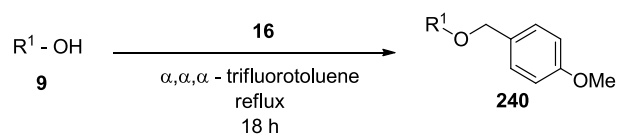
**Table 19: Reaction of PMB trichloroacetimidate with 1-octadecanol**



Entry	Solvent	Temperature	Yield <sup>b</sup>
1	toluene	111 °C	70%
2	toluene	50 °C	23%
3	$\alpha, \alpha, \alpha$ - trifluorotoluene	102 °C	73%
4	THF	66 °C	40%
5	dichloromethane	40 °C	17%
6	1,4-dioxane	101 °C	25%
7	acetonitrile	82 °C	18%
8	DMF	110 °C	11%

<sup>a</sup>All reactions were performed at 1.0M for 18 h in the noted solvent. <sup>b</sup>Isolated yields.

The generality of this methodology with the PMB imidate was then investigated. The benzylic alcohols in Table 20 were varied from phenyl, methyl and hydrogen at the alpha position with PMB imidate **16**, and the yields did not vary greatly based on substitution between methyl and phenyl, 68%, and 67% respectively, but when a primary benzyl alcohol was used a significantly higher yield was obtained (81% to form ether **244**). The less reactive PMB imidate seemed to be more significantly affected by the steric environment near the reactive alcohol. Additionally functionalized benzylic substrates afforded the desired ether in good yield; more specifically, the 4-methoxybenzyl and 4-nitrobenzyl alcohols afforded ethers **245** and **246** in 78% and 85% yield.

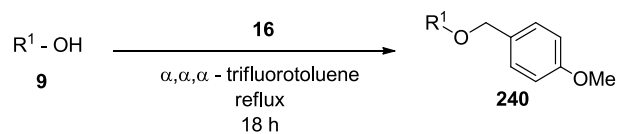
**Table 20: Reaction of PMB Imidate with Benzylic Alcohols**

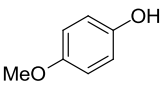
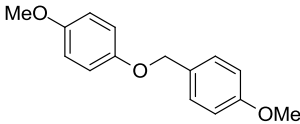
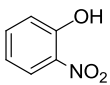
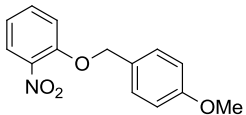
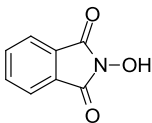
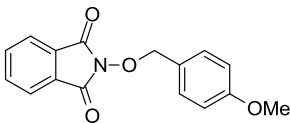
Entry	Alcohol	Product	Yield
1			68%
2			67% <sup>a</sup>
3			81%
4			78%
5			85%

<sup>a</sup> Performed by Dan Wallach

Phenols and an hydroxy imide alcohol were just as capable of generating the desired ether as benzylic alcohols, as shown in Table 21. Electron poor phenols proved to be good substrates, but the electron rich 4-methoxyphenol gave a decreased yield. This may indicate that the acidity of the alcohol plays a more significant role in the rate of the etherification reaction with the less reactive PMB imidate.

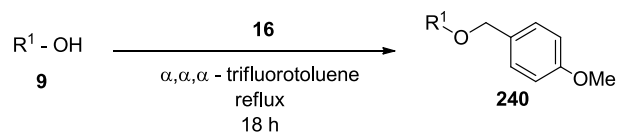


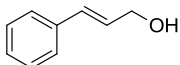
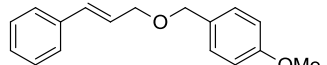
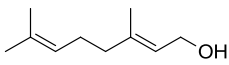
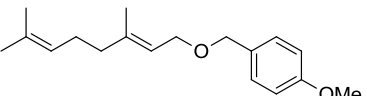
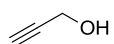
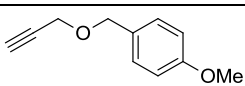
**Table 21: Reaction of PMB Imidate with Phenols and Hydroxy Imide**

Entry	Alcohol	Product	Yield
1	 <b>235</b>	 <b>247</b>	39%
2	 <b>248</b>	 <b>249</b>	76% <sup>a</sup>
3	 <b>231</b>	 <b>250</b>	58%

<sup>a</sup> Performed by Kyle Howard

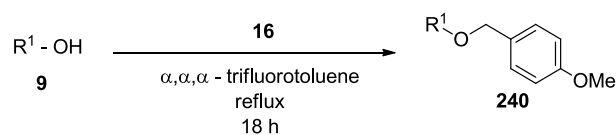
Although preliminary, similar to our DPM investigation we found our methodology could be expanded to simple and complex allylic and propargylic substrates (Table 22). We have shown the difficult cinnamyl alcohol substrate could be isolated in 52% yield while propargyl alcohol again proved to be an excellent substrate yielding 82% of the desired ether, **253**.

**Table 22: Reaction of PMB Imidate with Allylic Alcohols**

Entry	Alcohol	Product	Yield
1	 217	 251	52% <sup>a</sup>
2	 195	 252	45%
3	 196	 253	82% <sup>a</sup>

<sup>a</sup> Performed by Kyle Howard

Some more complex substrates were then investigated (Table 23). Specifically, **254** and **255** have shown that we can isolate the  $\beta$  – trimethylsilylethanol and cyclohexanol etherification products in the absence of an exogenous catalyst, 68% and 47%, respectively.

**Table 23: Reaction of PMB Imidate with Alkyl Alcohols**

Entry	Alcohol	Product	Yield
1	 <b>210</b>	 <b>239</b>	74% <sup>a</sup>
2	 <b>229</b>	 <b>254</b>	68%
3	 <b>212</b>	 <b>255</b>	47%

<sup>a</sup> Performed by Kyle Howard

### 3.3 Summary

In summary, we have developed a method for the protection of alcohols as their corresponding DPM<sup>5</sup> and PMB ethers solely under thermal conditions without the need of an acid, base, or transition metal catalyst by utilizing a trichloroacetimidate. Using various alcohols as substrates, we have shown that the reaction tolerates considerable variation of alcohol nucleophiles. A wide-range of acid and/or base sensitive substrates was investigated yielding the respective etherification products in moderate to high yields. These mild reaction conditions for the installation of common protecting groups have shown compatibility with numerous polyfunctional molecules as no racemization or elimination products were observed. Typically only the inert trichloroacetamide and trace amounts of respective ether dimer (DPM-O-DPM and

PMB-O-PMB) were isolated as side products. These mild conditions for the thermal protection of alcohols as DPM or PMB ethers provides a general method and could expand their relevance to sensitive substrates in synthetic applications. The yields of the DPM ethers are significantly greater than the PMB ethers in many cases. Currently, on-going investigations within the Chisholm group are underway to improve the overall yields of the PMB etherification methodology.

### 3.4 Experimental

**General Methods:** All anhydrous reactions were run under a positive pressure of argon or nitrogen. All syringes, needles, and reaction flasks required for anhydrous reactions were dried in an oven and cooled under an N<sub>2</sub> atmosphere or in a desiccator. Dichloromethane and THF were dried by passage through an alumina column following the method of Grubbs (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518). Triethylamine was distilled from CaH<sub>2</sub>. All other reagents and solvents were purchased from commercial sources and used without further purification.

**Analysis and Purification.** Analytical thin layer chromatography (TLC) was performed on precoated glass backed plates (silica gel 60 F<sub>254</sub>; 0.25 mm thickness). The TLC plates were visualized by UV illumination and by staining. Solvents for chromatography are listed as volume:volume ratios. Flash column chromatography was carried out on silica gel (40-63 μm). Melting points were recorded using an electrothermal melting point apparatus and are uncorrected. Elemental analyses were performed on an elemental combustion system ECS 4010 analyzer with a thermal conductivity detector and 2 meter GC column maintained at 50 °C.

**Identity.** Proton (<sup>1</sup>H NMR) and carbon (<sup>13</sup>C NMR) nuclear magnetic resonance spectra were recorded at 300 or 400 MHz and 75 or 100 MHz respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. Coupling constants are reported in hertz (Hz). The spectra were recorded in solutions of deuterated chloroform (CDCl<sub>3</sub>), with residual chloroform (δ 7.26 ppm for <sup>1</sup>H NMR, δ 77.23 ppm for <sup>13</sup>C NMR) or tetramethylsilane (δ 0.00 for <sup>1</sup>H NMR, δ 0.00 ppm for <sup>13</sup>C NMR) as the internal reference. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; td = triplet of doublets; tt = triplet of triplets; qd = quartet of doublets; ddd = doublet of doublet of

doublets; br s = broad singlet). Where applicable, the number of protons attached to the corresponding carbon atom was determined by DEPT 135 NMR. Infrared (IR) spectra were obtained as thin films on NaCl plates by dissolving the compound in  $\text{CH}_2\text{Cl}_2$  followed by evaporation or as KBr pellets.

### **1) General Procedure for Preparing Trichloroacetimidates:**

Benzhydrol (10.125 g, 54.9 mmol) was added to a 250 mL flame dried round-bottom flask. 55 mL of dry DCM was added to dissolve the alcohol while under an argon atmosphere. 1,8-diazabicyclo[5.4.0]undec-7-ene (0.83 mL, 5.5 mmol) and trichloroacetonitrile (6.1 mL, 82.4 mmol) were then added to the reaction. This reaction mixture was allowed to stir for 20 hours at room temperature. The reaction mixture was concentrated under reduced pressure then pre-adsorbed on silica gel, and purified by silica gel column chromatography using 20% ethyl acetate/ 75% hexanes/ 5% triethylamine. This provided desired trichloroacetimidate as a white solid (9.99 g, 56%).

### **2) General Procedure for Generating DPM Etherification Product:**

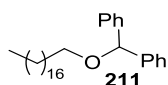
4-nitrobenzyl alcohol (0.251 g, 1.64 mmol) was placed into a 25 mL flame dried round-bottom flask and was dissolved in 4 mL of dry toluene. Diphenylmethyl 2, 2, 2 - trichloroacetimidate (0.648 g, 1.97 mmol) was added to the stirring reaction flask. The reaction mixture was heated to reflux while under an argon atmosphere for 18 hours. The reaction mixture was allowed to cool to room temperature, and was concentrated under reduced pressure. This was then pre-adsorbed on silica gel and purified by column chromatography using 40% dichloromethane /60% hexanes. This provided desired ether as a cream-colored solid (0.462 g, 88%).

### 3) General Procedure for Generating PMB Etherification Product:

Benzhydrol (0.737 g, 4 mmol) was placed into a 25 mL flame dried round-bottom flask and was dissolved in 4 mL of anhydrous  $\alpha,\alpha,\alpha$  - trifluorotoluene. 4 - methoxy benzyl 2,2,2 - trichloroacetimidate (2.268 g, 8 mmol) was added to the stirring reaction flask. The reaction mixture was heated to reflux while under an argon atmosphere for 18 hours. The reaction mixture was allowed to cool to room temperature, and was concentrated under reduced pressure. This was then pre-adsorbed on silica gel and purified by column chromatography using 20% ethyl acetate /80% hexanes. This provided desired ether as a clear- colored oil (0.791 g, 68%).

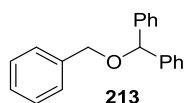
### General Procedures for the Purification of Ethers:

The reaction mixture was pre-adsorbed on silica gel and purified by silica gel chromatography using the listed solvent system. In some cases the trichloroacetamide was difficult to remove chromatographically. When this occurred, the reaction mixture was cooled to room temperature, concentrated under reduced pressure and dissolved in 50 mL of ethyl acetate. The organic layer was washed three times with 25 mL of 2M NaOH and then once with 25 mL of saturated NaCl. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure.

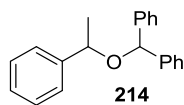


**Octadecyloxydiphenylmethane (211).** Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 10% ethyl acetate /90% hexanes solvent system. White colored solid (0.273 g, 85%). mp = 47-48 °C; TLC  $R_f$  = 0.80 (10% ethyl acetate/hexanes); IR (solid film from  $\text{CH}_2\text{Cl}_2$ ) 3027, 2923, 2852, 1493, 1453, 1097  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.21-7.37 (m,

10H), 5.33 (s, 1H), 3.44 (t,  $J = 6.6$  Hz, 2H), 1.60-1.67 (m, 2H), 1.26 (m, 30H), 0.88 (t,  $J = 6.3$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  142.9, 128.5, 127.5, 127.2, 83.8, 69.4, 32.2, 30.1, 29.94, 29.91, 29.87, 29.85, 29.7, 29.6, 26.5, 22.9, 14.3 (several signals in the aliphatic region were not resolved). Anal calcd for  $\text{C}_{31}\text{H}_{48}\text{O}$ : C, 85.26; H, 11.08. Found: C, 85.18; H, 11.13.

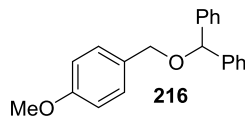


**Benzyloxymethane (213).**<sup>85</sup> Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 25% ethyl acetate /75% hexanes solvent system. Clear colored oil (0.238 g, 94%). TLC  $R_f = 0.92$  (25% ethyl acetate/hexanes);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.24-7.42 (m, 15H), 5.46 (s, 1H), 4.56 (s, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  142.4, 138.6, 128.6, 128.6, 127.9, 127.72, 127.65, 127.3, 82.7, 70.7.

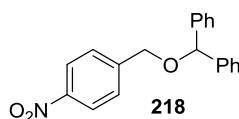


**((1-Phenylethoxy)methylene)dibenzene (214).**<sup>86</sup> Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 10% ethyl acetate /90% hexanes solvent system. Clear colored oil (0.434 g, 92%). TLC  $R_f = 0.85$  (10% acetone/hexanes);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.20-7.41 (m, 15H), 5.31 (s, 1H), 4.51 (q,  $J = 6.6$  Hz, 1H), 1.53 (d,  $J = 6.3$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  143.9, 143.0, 142.2, 128.7, 128.4, 128.3, 127.73, 127.70, 127.67, 127.3, 127.1, 126.7, 80.2, 75.1, 24.5.

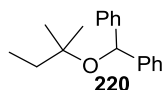




**(4-Methoxybenzyloxy)diphenylmethane (216).**<sup>87</sup> Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 10% ethyl acetate /90% hexanes solvent system. Clear colored oil (0.314 g, 71%). TLC  $R_f = 0.50$  (10% ethyl acetate/hexanes);  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.24-7.41 (m, 12H), 6.91 (d,  $J = 8.7$  Hz, 2H), 5.45 (s, 1H), 4.50 (s, 2H), 3.83 (s, 3H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.3, 142.4, 130.6, 129.5, 128.5, 127.6, 127.3, 113.9, 82.2, 70.3, 55.4.

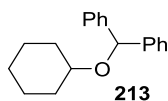


**(((4-Nitrobenzyl)oxy)methylene)dibenzene (218).** Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 40% DCM/60% hexanes solvent system. Off-white colored solid (0.460 g, 88%). mp = 62-64 °C; TLC  $R_f = 0.59$  (40% DCM/60% hexanes); IR (solid film from  $\text{CH}_2\text{Cl}_2$ ) 3062, 3028, 2922, 2857, 1493, 1347, 1288  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.19 (d,  $J = 8.7$  Hz, 2H), 7.52 (d,  $J = 8.1$  Hz, 2H), 7.25-7.40 (m, 10H), 5.46 (s, 1H), 4.62 (s, 2H);  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  147.4, 146.1, 141.6, 128.6, 127.8, 127.7, 127.0, 123.6, 83.5, 69.5. Anal calcd for  $\text{C}_{20}\text{H}_{17}\text{NO}_3$ : C, 77.22; H, 5.37; N, 3.49. Found: C, 77.20; H, 5.31; N, 3.44.

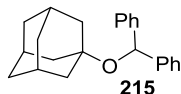


**(((tert-Pentyloxy)methylene)dibenzene (220).**<sup>88</sup> Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 10% ethyl acetate /90% hexanes solvent system. Clear colored oil (0.489 g, 85%). TLC  $R_f = 0.92$  (10% ethyl acetate/hexanes);  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 (d,  $J = 6.9$  Hz, 4H), 7.33 (t,  $J = 7.2$  Hz, 4H), 7.20-7.26 (m, 2H), 5.60 (s, 1H), 1.62 (q,  $J = 7.5$  Hz,

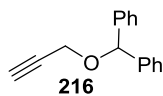
2H), 1.17 (s, 6H), 0.91 (t,  $J = 7.5$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  145.6, 128.3, 127.0, 126.9, 76.9, 75.6, 34.8, 26.1, 8.9.



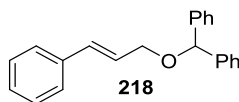
**((Cyclohexyloxy)methylene)dibenzene (213).**<sup>89</sup> Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 10% ethyl acetate /90% hexanes solvent system. Clear colored oil (0.494 g, 93%). TLC  $R_f = 0.68$  (10% ethyl acetate/hexanes);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.24-7.40 (m, 10H), 5.58 (s, 1H), 3.35-3.44 (m, 1H), 1.93 (dd,  $J = 9.0, 6.0$  Hz, 2H), 1.76-1.82 (m, 2H), 1.41-1.58 (m, 3H), 1.26 (q,  $J = 8.3$  Hz, 3H);  $^{13}\text{C}$  NMR (75MHz,  $\text{CDCl}_3$ )  $\delta$  143.3, 128.4, 127.31, 127.26, 80.1, 75.1, 32.5, 26.0, 24.2.



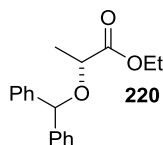
**1-(Benzhydryloxy)adamantine (215).** Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 10% ethyl acetate /90% hexanes solvent system. Orange colored solid (0.383 g, 92%). mp = 64-66 °C; TLC  $R_f = 0.71$  (10% ethyl acetate/hexanes); IR (solid film from  $\text{CH}_2\text{Cl}_2$ ) 3025, 2905, 2850, 1492, 1451, 1354, 1082  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.20-7.39 (m, 10H), 5.80 (s, 1H), 2.14 (s, 3H), 1.83 (bs, 6H), 1.62 (bs, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  145.3, 128.2, 127.2, 126.9, 74.4, 73.8, 43.0, 36.6, 30.8. Anal calcd for  $\text{C}_{23}\text{H}_{26}\text{O}$ : C, 86.75; H, 8.23. Found: C, 86.72; H, 8.18.



**Diphenyl(prop-2-ynyloxy)methane (216).**<sup>90</sup> Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 10% ethyl acetate /90% hexanes solvent system. Yellow colored oil (0.384 g, 97%). TLC  $R_f = 0.86$  (10% ethyl acetate/hexanes);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.24-7.40 (m, 10H), 5.68 (s, 1H), 4.17 (d,  $J = 2.4$  Hz, 2H), 2.46 (t,  $J = 2.4$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  141.3, 128.6, 127.9, 127.5, 81.8, 79.9, 74.8, 56.0.

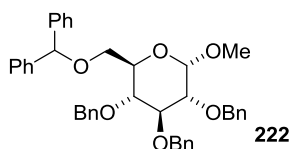


**Cinnamyloxydiphenylmethane (218).**<sup>91</sup> Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 10% ethyl acetate /90% hexanes solvent system. White colored solid (0.395 g, 88%). mp = 55-57 °C; TLC  $R_f = 0.58$  (25% ethyl acetate/hexanes);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.23-7.42 (m, 15H), 6.63 (d,  $J = 15.9$  Hz, 1H), 6.32-6.41 (m, 1H), 5.51 (s, 1H), 4.20 (dd,  $J = 6.0, 1.5$  Hz, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  142.3, 136.9, 132.3, 128.6, 128.5, 127.7, 127.5, 127.1, 126.6, 126.3, 82.8, 69.4.

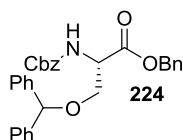


**(R)-Ethyl 2-(benzhydryloxy)propanoate (220).**<sup>92</sup> Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 10% ethyl acetate /90% hexanes solvent system. Clear colored oil (0.434 g, 90%).  $[\alpha]_D^{21.6} -103.8$  ( $c$  1.04, DCM); TLC  $R_f = 0.57$  (10% ethyl acetate/hexanes);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26-7.41 (m, 10H), 5.57 (s, 1H), 4.16-4.28 (m, 2H), 4.08 (q,  $J = 6.0$  Hz, 1H), 1.49 (d,  $J = 9.0$  Hz, 3H), 1.30 (t,  $J = 9.0$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.6,

142.1, 141.1, 128.7, 128.4, 128.0, 127.7, 127.6, 127.5, 82.8, 72.7, 61.0, 19.0, 14.4. Chiral HPLC analysis: Chiralcel OD (heptane/2-PrOH = 99/1, 1.0 mL/min, 254 nm, 25 °C):  $t_{(R \text{ enantiomer})} = 5.3$  min,  $t_{(S \text{ enantiomer})} = 5.8$  min.

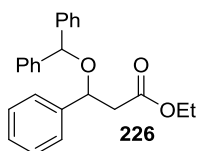


**Methyl 2,3,4-Tri-O-benzyl-6-O-diphenylmethyl- $\alpha$ -D-glucopyranoside (222).**<sup>7</sup> Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 15% ethyl acetate /85% hexanes solvent system. Clear colored oil (0.750 g, 73%). TLC  $R_f = 0.43$  (15% ethyl acetate/85% hexanes); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.55-7.18 (m, 25 H), 5.50 (s, 1H), 5.13 (d,  $J = 10.8$  Hz, 1H), 4.98 (t,  $J = 11.1$  Hz, 2H), 4.93 (d,  $J = 12.0$  Hz, 1H), 4.82 (d,  $J = 11.7$  Hz, 1H), 4.80 (d,  $J = 3.6$  Hz, 1H), 4.68 (d,  $J = 11.1$  Hz, 1H), 4.16 (t,  $J = 9.3$  Hz, 1H), 3.89-3.99 (m, 1H), 3.77-3.84 (m, 3H), 3.72 (dd,  $J = 3.6, 9.6$  Hz, 1H), 3.49 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  142.2, 142.1, 138.8, 138.3, 138.2, 128.5, 128.4, 128.36, 128.1, 127.9, 127.8, 127.7, 127.5, 127.4, 127.2, 126.9, 98.1, 84.1, 82.3, 80.1, 78.0, 75.9, 75.1, 73.4, 70.3, 67.9, 55.1.

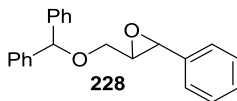


**(S)-Benzyl 3-(benzhydryloxy)-2-(((benzyloxy)carbonyl)amino)propanoate (224).** Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 10% ethyl acetate /90% hexanes solvent system. Clear colored oil (0.273 g, 91%).  $[\alpha]_D^{21.6} -12.5$  ( $c$  1.26, CHCl<sub>3</sub>); TLC  $R_f = 0.18$  (10% ethyl acetate/hexanes); IR (solid film from CH<sub>2</sub>Cl<sub>2</sub>) 3434, 3341, 3062, 3030, 2949, 2876, 1722, 1498, 1339, 1197, 1067 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.07-7.30 (m, 20H), 5.63 (d,  $J = 12.0$  Hz, 1H), 5.19 (s, 1H), 5.12 (d,  $J = 4.0$  Hz, 2H), 5.04 (s, 2H), 4.49 (dt,  $J = 2.8$  Hz, 1H),

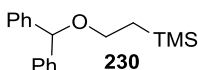
3.84 (dd,  $J = 9.4, 2.8$  Hz, 1H), 3.60 (dd,  $J = 9.4, 3.1$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 156.1, 141.6, 141.4, 136.4, 135.4, 128.7, 128.65, 128.6, 128.5, 128.4, 128.3, 128.2, 127.7, 127.0, 126.9, 84.2, 69.0, 67.4, 67.2, 54.8 . (note: two signals in the aromatic region were not resolved.) Anal calcd for  $\text{C}_{31}\text{H}_{29}\text{NO}_5$ : C, 75.13; H, 5.90; N, 2.83. Found: C, 74.94; H, 5.97; N, 3.00. Chiral HPLC analysis: Chiralcel OD (heptane/2-PrOH = 90/10, 1.0 mL/min, 254 nm, 25 °C):  $t_{(S \text{ enantiomer})} = 16.7$  min,  $t_{(R \text{ enantiomer})} = 23.9$  min.



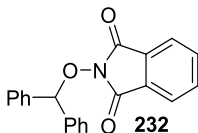
**Ethyl 3-(benzhydryloxy)-3-phenylpropanoate (226).** Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 10% ethyl acetate /90% hexanes solvent system. White colored solid (0.178 g, 96%). mp = 73-74 °C; TLC  $R_f = 0.53$  (10% ethyl acetate/hexanes); IR (solid film from  $\text{CH}_2\text{Cl}_2$ ) 3061, 3028, 2980, 1736, 1493, 1453, 1268, 1172, 1052  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.19-7.40 (m, 15H), 5.24 (s, 1H), 4.81 (ddd,  $J = 1.3, 4.9, 9.0$  Hz, 1H), 4.00-4.23 (m, 2H), 2.96 (ddd,  $J = 1.4, 9.0, 14.7$  Hz, 1H), 2.65 (ddd,  $J = 1.2, 4.9, 14.7$  Hz, 1H), 1.21 (td,  $J = 1.1, 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.8, 142.8, 141.3, 140.7, 128.8, 128.6, 128.3, 128.2, 128.0, 127.9, 127.24, 127.16 126.7, 80.11, 75.7, 60.6, 44.0, 14.3. Anal calcd for  $\text{C}_{24}\text{H}_{24}\text{O}_3$ : C, 79.97; H, 6.71. Found: C, 79.96; H, 6.88.



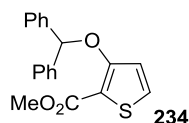
**2-((Benzhydryloxy)methyl)-3-phenyloxirane (228).**<sup>93</sup> Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 10% ethyl acetate /90% hexanes solvent system. Clear colored oil (0.255 g, 65%) TLC  $R_f = 0.50$  (10% ethyl acetate/hexanes);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25-7.44 (m, 15H), 5.53 (s, 1H), 3.86 (dd,  $J = 11.5, 3.1$  Hz, 1H), 3.80 (d,  $J = 2.0$  Hz, 1H) 3.66 (dd,  $J = 5.3, 11.5$  Hz, 1H), 3.29-3.32 (m, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  141.99, 141.94, 137.1, 128.7, 128.6, 128.4, 127.8, 127.77, 127.5, 127.3, 127.2, 125.9, 84.1, 68.9, 61.4, 56.1.



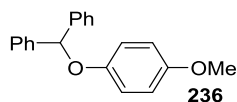
**(2-(Benzhydryloxy)ethyl)trimethylsilane (230).** Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 15% DCM/5% triethylamine/ 80% hexanes solvent system. Pale yellow colored oil (0.368 g, 79%). TLC  $R_f = 0.56$  (15% DCM/5% triethylamine/ 80% hexanes); IR (solid film from  $\text{CH}_2\text{Cl}_2$ ) 3087, 3063, 3029, 2953, 2892, 1452, 1317, 1249  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36 (dd,  $J = 6.3, 1.2$  Hz, 4H), 7.30 (t,  $J = 6.6$  Hz, 4H), 7.22-7.25 (m, 2H), 5.35 (s, 1H), 3.56 (t,  $J = 6.0$  Hz, 2H), 1.03 (t,  $J = 6.0$  Hz, 2H), 0.00 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  144.0, 129.6, 128.5, 128.2, 84.6, 67.6, 19.7, 0.0; Anal calcd for  $\text{C}_{18}\text{H}_{24}\text{OSi}$ : C, 76.00; H, 8.50; Found: C, 75.77; H, 8.62.



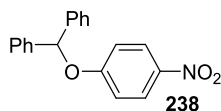
**2-(Benzhydryloxy)isoindoline-1,3-dione (232).**<sup>94</sup> Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 10% ethyl acetate /90% hexanes solvent system. Yellow colored solid (0.323 g, 80%). mp = 160-162 °C; TLC  $R_f$  = 0.29 (10% acetone/hexanes); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.66-7.76 (m, 4H), 7.52-7.56 (m, 4H), 7.29-7.39 (m, 6H), 6.53 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 163.8, 137.9, 134.4, 128.9, 128.8, 128.5, 128.4, 123.4, 89.7.



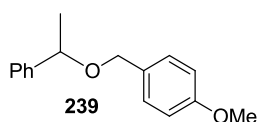
**Methyl 3-(benzhydryloxy)thiophene-2-carboxylate (234).** Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 10% ethyl acetate /90% hexanes solvent system. White colored solid (0.280 g, 53%). mp = 105-106 °C; TLC  $R_f$  = 0.3 (10% ethyl acetate/90% hexanes); IR (solid film from CH<sub>2</sub>Cl<sub>2</sub>) 3061, 3028, 2948, 1711, 1538, 1228, 1062 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.53 (d,  $J$  = 7.6 Hz, 4H), 7.35 (t,  $J$  = 7.2 Hz, 4H), 7.25–7.28 (m, 3H), 6.74 (d,  $J$  = 5.6 Hz, 1H), 6.27 (s, 1H), 3.90 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 162.4, 160.1, 141.2, 130.4, 128.9, 128.1, 126.7, 118.7, 111.6, 85.0, 51.8. Anal calcd for C<sub>19</sub>H<sub>16</sub>O<sub>3</sub>S: C, 70.35; H, 4.97; Found: C, 70.26; H, 5.02.



**((4-Methoxyphenoxy)methylene)dibenzene (236).**<sup>95</sup> Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 10% acetone /90% hexanes solvent system. Orange colored solid (0.424 g, 91%). mp = 84-85 °C; TLC  $R_f$  = 0.42 (10% acetone/hexanes); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.26-7.43 (m, 10H), 6.88 (d,  $J$  = 9.1 Hz, 2H), 6.75 (d,  $J$  = 9.2 Hz, 2H), 6.11 (s, 1H), 3.73 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 154.2, 152.4, 141.7, 128.7, 127.8, 127.1, 117.4, 114.7, 82.8, 55.7.



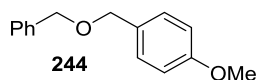
**((4-Nitrophenoxy)methylene)dibenzene (238).**<sup>18</sup> Prepared by General Procedure 2 from the known imidate.<sup>6</sup> Purified by 10% ethyl acetate /90% hexanes solvent system. Pale yellow colored solid (0.310 g, 61%). mp = 157-158 °C; TLC  $R_f$  = 0.36 (10% ethyl acetate/90% hexanes); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.13 (d,  $J$  = 9.0 Hz, 2H), 7.28-7.42 (m, 10H), 7.02 (d,  $J$  = 9.3 Hz, 2H), 6.31 (s, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 162.9, 141.6, 139.8, 128.8, 128.3, 126.7, 125.8, 115.9, 82.5.



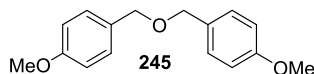
**1-methoxy-4-((1-phenylethoxy)methyl)benzene (239).**<sup>23</sup> Prepared by General Procedure 3 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by 10% ethyl acetate /90% hexanes solvent system. Clear colorless oil (0.649 g, 67%). TLC  $R_f$  = 0.52 (10% ethyl acetate/90% hexanes); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.35-7.33 (m, 4H), 7.31-7.20 (m, 3H), 6.85 (d,  $J$  = 8.7 Hz, 2H), 4.46 (q,  $J$  = 6.6 Hz, 1H), 4.23 (dd,  $J$  = 11.4, 46.8 Hz, 2H), 3.75



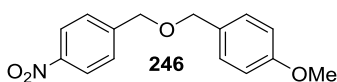
(s, 3H), 1.45 (d,  $J = 6.3$  Hz, 3H);  $^{13}$  C NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  159.2, 143.9, 130.8, 129.4, 128.6, 127.5, 126.4, 113.9, 77.0, 70.0, 55.3, 24.3.



**1-(benzyloxymethyl)-4-methoxybenzene (244).**<sup>67</sup> Prepared by General Procedure 3 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by 20% ethyl acetate/80% hexanes solvent system. Clear colored oil (0.739 g, 81%). TLC  $R_f = 0.54$  (20% ethyl acetate/80% hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34-7.23 (m, 7 H), 6.87 (d,  $J = 8.4$  Hz, 2 H), 4.51 (s, 2 H), 4.48 (s, 2 H), 3.77 (s, 3 H);  $^{13}$  C NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.1, 138.3, 130.3, 129.3, 128.3, 127.7, 127.5, 113.7, 71.6, 55.2.

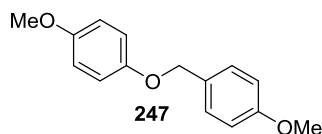


**bis(4-methoxybenzyl)ether (245).**<sup>20</sup> Prepared by General Procedure 3 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by 20% acetone /80% hexanes solvent system. Clear colored oil (0.899 g, 78%). TLC  $R_f = 0.50$  (20% acetone/80% hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27 (d,  $J = 8.8$  Hz, 4 H), 6.87 (d,  $J = 8.8$  Hz, 4 H), 4.50 (s, 4 H), 3.78 (s, 6 H);  $^{13}$  C NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.1, 130.4, 129.3, 113.7, 71.4, 55.2.

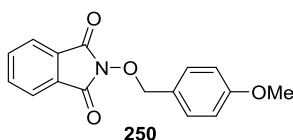


**1-methoxy-4-(4-nitrobenzyloxymethyl)benzene (246).** Prepared by General Procedure 3 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by 10% acetone/90% hexanes solvent system. Dark yellow colored oil (0.929 g, 85%). TLC  $R_f = 0.45$  (10% acetone/90% hexanes); IR (neat) 3109, 3076, 3003, 2935, 2838, 1561, 1342, 1302, 1246;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21 (d,  $J = 2$  Hz, 2 H), 7.51 (d,  $J = 8.8$  Hz, 2 H), 7.26 (d,  $J = 2$  Hz, 2 H), 6.90 (d,  $J = 8.8$  Hz, 2 H), 4.61 (s, 2 H), 4.55 (s, 2 H), 3.81 (s, 3 H);  $^{13}$  C NMR (100

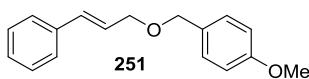
MHz, CDCl<sub>3</sub>)  $\delta$  159.5, 147.3, 146.1, 129.6, 129.5, 129.3, 127.8, 123.6, 114.4, 113.9, 72.5, 70.5, 55.3, 44.9; Anal. Calcd for C<sub>15</sub>H<sub>15</sub>NO<sub>4</sub>: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.80, H, 5.41, N, 5.00.



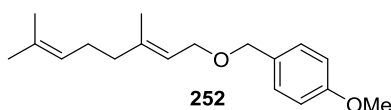
**1-methoxy-4-((4-methoxybenzyl)oxy)benzene (247).**<sup>97</sup> Prepared by General Procedure 3 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by 10% ethyl acetate/90% hexanes solvent system. Light yellow colored oil (0.381 g, 39%). TLC  $R_f$  = 0.56 (10% ethyl acetate/90% hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.08 (d,  $J$  = 8.8 Hz, 4H) 6.82 (d,  $J$  = 8.8 Hz, 4H), 3.86 (s, 2H), 3.77 (s, 6 H); <sup>13</sup> C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  157.9, 135.8, 129.8, 113.9, 55.3, 40.2.



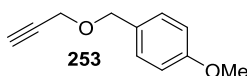
**N-(4-methoxybenzyloxy)phthalimide (250).**<sup>97</sup> Prepared by General Procedure 3 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by 20% ethyl acetate/80% hexanes solvent system. White colored solid (0.657 g, 58%). mp = 134.9-136.3°C; TLC  $R_f$  = 0.28, 0.57 (20% ethyl acetate/80% hexanes); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.82-7.71 (m, 4 H) 7.45 (d,  $J$  = 8.4 Hz, 2 H), 6.88 (d,  $J$  = 8.4 Hz, 2 H), 5.15 (s, 2 H), 3.80 (s, 3 H); <sup>13</sup> C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  163.5, 160.4, 134.3, 131.6, 128.8, 125.8, 123.4, 113.9, 79.4, 55.2.



**(*E*)-1-((cinnamyloxy)methyl)-4-methoxybenzene (251).** Prepared by General Procedure 3 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by 25% ethyl acetate/75% hexanes solvent system. Yellow colored oil (0.516 g, 52%). TLC  $R_f$  = 0.70 (25% ethyl acetate/75% hexanes);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 (d,  $J$  = 7.2 Hz, 2H), 7.34–7.30 (m, 4H), 7.25 (d,  $J$  = 6.3 Hz, 1H), 6.90 (d,  $J$  = 8.6 Hz, 2H), 6.63 (d,  $J$  = 16.0 Hz, 1H), 6.33 (dt,  $J$  = 6.0, 15.9 Hz, 1H), 4.52 (s, 2H), 4.18 (dd,  $J$  = 1.4, 6.0 Hz, 2H), 3.82 (s, 3H).

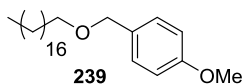


**(*E*)-1-(((3,7-Dimethylocta-2,6-dien-1-yl)oxy)methyl)-4-methoxybenzene (252).**<sup>98</sup> Prepared by General Procedure 3 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by 10% ethyl acetate/90% hexanes solvent system. Clear colored oil (0.498 g, 45%).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 (d,  $J$  = 8.8 Hz, 2H), 6.93 (d,  $J$  = 8.8 Hz, 2H), 5.49 – 5.46 (m, 1H), 5.20 – 5.17 (m, 1H), 5.16 (s, 2H), 4.07 (d,  $J$  = 7.2 Hz, 2H), 3.81 (s, 3H), 2.22 – 2.18 (m, 2H), 2.17 – 2.10 (m, 2H), 1.76 (s, 3H), 1.71 (s, 3H), 1.68 (s, 3H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  157.9, 135.8, 129.8, 113.9, 55.3, 40.2.  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.2, 140.2, 129.43, 124.1, 120.9, 113.8, 71.6, 66.3, 55.3, 39.6, 26.4, 25.7, 17.7, 16.5.

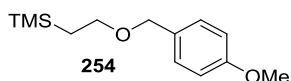


**1-methoxy-4-((prop-2-yn-1-yloxy)methyl)benzene (253).**<sup>99</sup> Prepared by General Procedure 3 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by 10% ethyl acetate/90% hexanes solvent system. Clear colored oil (0.578 g, 82%). TLC  $R_f$  = 0.41 (10% Ethyl acetate/90% hexanes);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32 (d,  $J$  = 8.4 Hz, 2H), 6.93 (d,  $J$  =

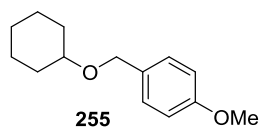
1.8 Hz, 2 H), 4.57 (s, 2 H), 4.17 (d,  $J = 2.4$  Hz, 2 H), 3.82 (s, 3 H), 4.55 (s, 2 H), 2.52 (d,  $J = 2.4$  Hz, 1 H).



**1-methoxy-4-((octadecyloxy)methyl)benzene (239).**<sup>100</sup> Prepared by General Procedure 3 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by 10% ethyl acetate/90% hexanes solvent system. White colored solid (0.844 g, 96%). mp = 45.6-46.5°C. TLC  $R_f = 0.82$  (10% ethyl acetate/90% hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.26 (d,  $J = 8.8$  Hz, 2H), 6.87 (d,  $J = 8.7$  Hz, 2H), 4.42 (s, 2H), 3.79 (s, 3H), 3.43 (t,  $J = 6.7$  Hz, 2H), 1.63-1.56 (m, 2H), 1.36-1.25 (m, 34H), 0.88 (t,  $J = 6.6$  Hz, 3H).



**(2-((4-methoxybenzyl)oxy)ethyl)trimethylsilane (254).**<sup>79</sup> Prepared by General Procedure 3 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by 10% ethyl acetate/90% hexanes solvent system. Red colored oil (0.558 g, 68%). TLC  $R_f = 0.76$  (10% ethyl acetate/90% hexanes); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.25 (d,  $J = 8.4$  Hz, 2H), 6.86 (d,  $J = 8.1$  Hz, 1H), 4.40 (s, 2H), 3.78 (s, 3H), 3.54 (td,  $J = 0.9, 8.1$  Hz, 2H), 0.97 (td,  $J = 0.9, 8.1$  Hz, 2H), 0.00 (s, 9H).



**1-((cyclohexyloxy)methyl)-4-methoxybenzene (255).**<sup>89</sup> Prepared by General Procedure 3 from the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate. Purified by 10% ethyl acetate/90% hexanes solvent system. Yellow colored oil (0.414 g, 47%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.26 (d, *J* = 8.4 Hz, 2H) 6.86 (d, *J* = 8.7 Hz, 2H), 4.46 (s, 2H), 3.77 (s, 3H), 3.36 – 3.28 (m, 1H), 1.95 – 1.90 (m, 2H), 1.75 – 1.70 (m, 2H), 1.55 – 1.48 (m, 1H), 1.39 – 1.28 (m, 5H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 157.9, 135.8, 129.8, 113.9, 55.3, 40.2. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 159.0, 131.5, 129.0, 113.7, 69.3, 55.3, 32.3, 25.9, 24.2.

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Total Synthesis of Bongkreki Acid and Apoptosis Inhibitory Activity of its Analogues.

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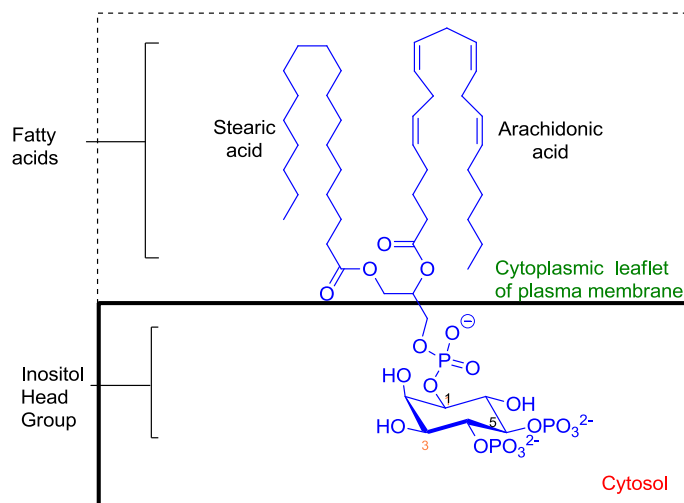
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## Chapter 4. Progress Towards an Efficient Synthesis of AQX-1125

### 4.1 Introduction

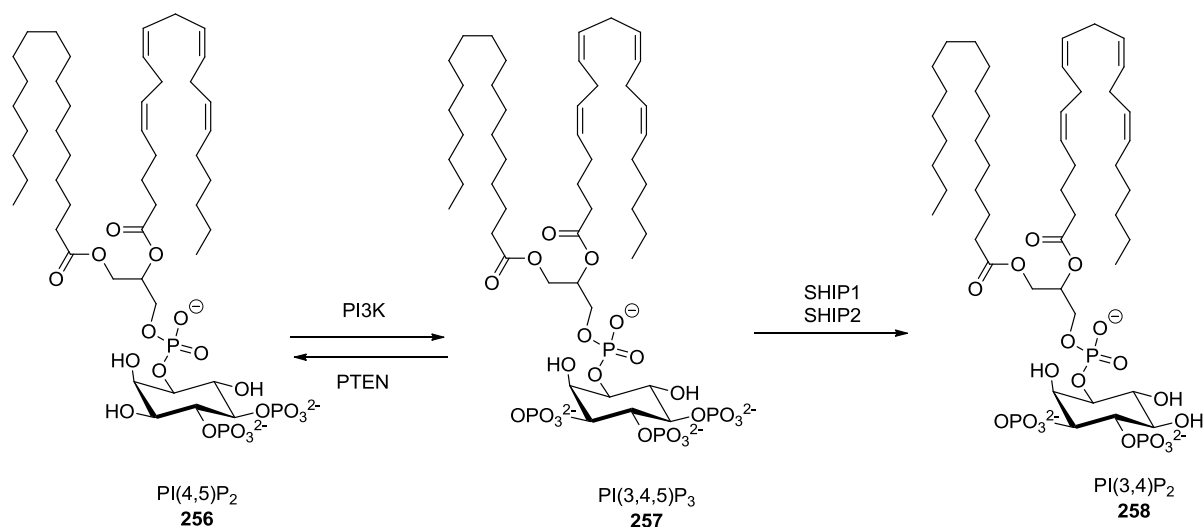
Phosphoinositides (PIs) are important signaling molecules that make up only a small fraction of cellular phospholipids<sup>1</sup> yet play an integral role in the regulation of many cellular processes, including cell proliferation and survival, vesicular trafficking by recruitment of effector proteins, and cytoskeletal reorganization. These molecules act as important secondary messengers, which are regulated by numerous enzymes, including kinases, phosphatases, and phospholipases.<sup>1-17</sup> The phosphorylation pattern on the inositol plays a critical role in signal transduction, so inositol phosphorylation is tightly regulated by inositol kinases and phosphatases with aberrant regulation being implicated in numerous human diseases.<sup>18-25</sup>

The structure of the PIs typically contains a glycerol backbone esterified to two fatty acid chains and a phosphate which is attached to a polar inositol head group. The polar inositol extends into the cytoplasm, while the long alkyl chains intercalate into the cell membrane, depicted by PI(4,5)P<sub>2</sub> in Figure 7, a common phosphoinositide. The inositol head group is typically phosphorylated with the phosphorylation pattern tightly regulated by cytoplasmic lipid kinases.<sup>26</sup>



**Figure 7: Structure of PI(4,5)P<sub>2</sub>**

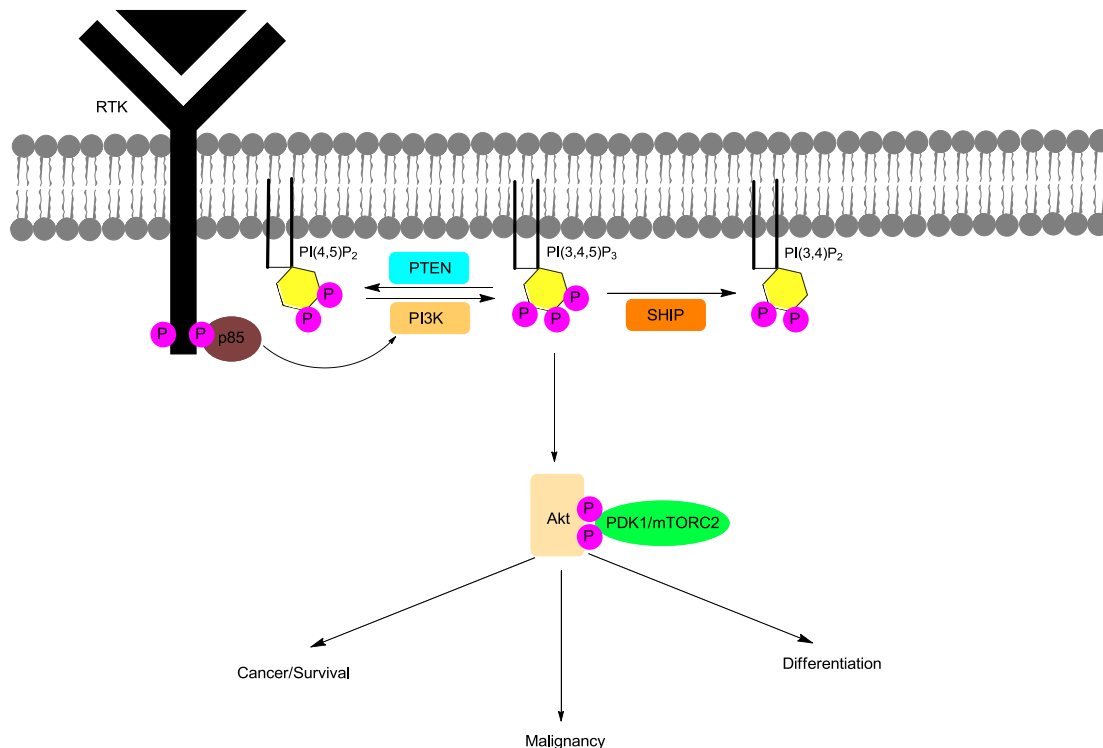
Several enzymes are known to functionalize PIs, and one of the most studied are the phosphatidylinositol 3-kinases (PI3K).<sup>14</sup> PI3K is an essential class of lipid kinases which are characterized by their ability to phosphorylate the inositol ring at the 3'-OH group on PIs (Scheme 26).<sup>27</sup> The enzyme PI3K (phosphatidylinositol 3-kinase) catalyzes the production of the lipid second messenger phosphatidylinositol-3,4,5-triphosphate (PI(3,4,5)P<sub>3</sub>) at the cell membrane (Scheme 32). Once PI3K is activated by a nearby receptor tyrosine kinase (RTK) it rapidly forms PI(3,4,5)P<sub>3</sub> from PI(4,5)P<sub>2</sub>.<sup>12,23,28,36</sup> PI(3,4,5)P<sub>3</sub> is normally maintained at a low concentration, however, upon external stimuli, PI3K can rapidly synthesize its key secondary messenger from phosphatidylinositol-4,5-diphosphate (PI(4,5)P<sub>2</sub>).<sup>13</sup> This formation leads to the recruitment of the pleckstrin homology (PH) domains to the cell membrane, more specifically, serine-threonine protein kinases, which include protein kinase B (Akt) and phosphoinositide kinase I (PDK1), in addition to Btk, Src and others, initiating signals of the growth-factor response pathway.<sup>12,23,28,35-</sup>



### Scheme 26: Enzymatic Synthesis and Degradation of PI(3,4,5)P<sub>3</sub>

Focusing on the PI3K-Akt signaling pathway, it is deeply rooted in the regulation of numerous cellular functions that include survival, adhesion, proliferation, differentiation, movement, and end-cell activation and has been extensively investigated as they are implicated in various human diseases.<sup>14-16,23,28,36</sup> The identification of this pathway began in earnest in the early 1980s with attempts to characterize insulin receptor signaling;<sup>12,35</sup> however, with the discovery of this highly conserved, tightly regulated pathway its potent contribution to tumorigenesis became apparent, and most modern investigations are focused on developing cancer treatments.<sup>35</sup>





### Scheme 27: Signaling from the PI3K pathway through Akt

Phosphatases also regulate the phosphorylation pattern on inositols in the PI3K signaling pathway. The phosphatase and tensin homolog (PTEN) and SH2-containing inositol-5'-phosphatase (SHIP1 and SHIP2) are common inositol phosphatases involved in processing PIP<sub>3</sub>.<sup>41,42</sup> PTEN reverses the PI3K reaction, removing a phosphate from the 3' position of the inositol, transforming PI(3,4,5)P<sub>3</sub> back to PI(4,5)P<sub>2</sub>. PTEN is well known as a tumor suppressor gene<sup>41-43</sup> that consists of a 403 amino acid protein located on human chromosome 10q23.<sup>23,44,45</sup> Complete loss of PTEN is associated with cancer and metastasis, with PTEN knockout mice rapidly developing tumors. In PTEN knockouts, there is no enzyme to facilitate the hydrolysis of PIP<sub>3</sub> to PI(4,5)P<sub>2</sub>, allowing Akt to become hyperactivated. With hyperactivation, PTEN-deficient cells are prevented from undergoing their normal apoptotic stimuli which leads to the abnormal growth.<sup>43,46</sup>

In contrast to PTEN, SHIP knockout mice are viable and do not develop cancer, although they do possess a modified immune system<sup>47</sup> and have shortened lifespans. Conversely to PTEN, SHIP converts PI(3,4,5)P<sub>3</sub> to PI(3,4)P<sub>2</sub> and is therefore classified as inositol phospholipid 5'-phosphatase.<sup>14,23</sup> Hydrolysis of PI(3,4,5)P<sub>3</sub> blocks PI3K effector pathways and thereby inhibits additional proteins, including Akt, to increase in concentration. Alternatively, SHIP can also promote activation of Akt due to increased affinity of the Akt PH domain for PI(3,4)P<sub>2</sub>. Therefore, SHIP can both negatively and positively influence cellular pathology. Nevertheless, blocking either signaling pathway provides a promising approach for treating several types of cancer.<sup>48-50</sup> Additionally, SHIP has an SH2 protein-protein recognition domain, which allows the protein to act as a docking partner for a number of other soluble proteins, recruiting their enzymatic activity to the plasma membrane.<sup>51,52</sup>

Two major isoforms of SHIP are directly associated with the PI3K pathway, SHIP1 and SHIP2. Although these enzymes share a high level of amino acid conservation, they differ considerably in tissue distribution and cell signaling.<sup>14,41,42</sup> SHIP1 is predominantly confined to hematopoietic cells,<sup>53</sup> but is also expressed by osteoblasts and mesenchymal stem cells.<sup>25,53</sup> SHIP1 functions as a negative controller in immunoreceptor signaling and hematopoietic progenitor cell proliferation/survival, as well as an inducer of cellular apoptosis.<sup>41,43</sup>

In contrast, SHIP2 is more ubiquitous as it is expressed across all cell and tissue types;<sup>14</sup> especially high levels of SHIP2 are found in human heart and skeletal muscle cells as well as in the placenta.<sup>54</sup> SHIP2 has been reported to act as a significant negative regulator of the insulin-signaling pathway and this is apparent in SHIP2 knockout mice where they have shown a reduced body weight despite increased food intake.<sup>55,56</sup>

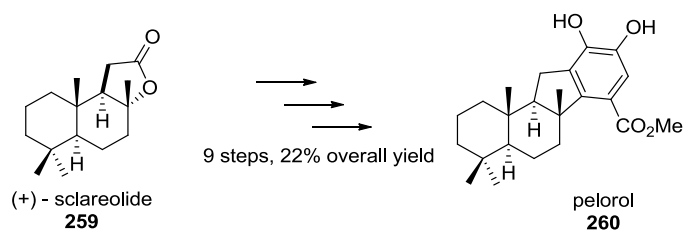
## 4.2 SHIP1 Agonists

Since a small variation in the concentration of PI(3,4,5)P<sub>3</sub> at the cell membrane plays a critical role in signal transduction, the enzymes controlling inositol phosphorylation in the PI3K pathway (PI3K, PTEN and SHIP) have become appealing targets for pharmaceutical intervention towards finding treatments for a number of disease states.<sup>6,14,57-59</sup> Inhibition of PI3K has been the most hotly pursued approach, with a number of pharmaceutical companies competing heavily in this area.<sup>59-61</sup> In contrast, the phosphatases PTEN and SHIP have received less attention. Recently there have been reports of several investigations,<sup>15,17,24</sup> including several within the Chisholm group,<sup>63-66</sup> that have been completed on SHIP1 antagonists and their effects on the PI3K pathway.<sup>68,69</sup> However, the remainder of this chapter will focus solely on SHIP1 agonists, their activity, and respective literature syntheses.

SHIP1 is known to be an allosterically activated enzyme, with the product of the SHIP1 phosphatase activity, PI(3,4)P<sub>2</sub>, binding to the enzyme and accelerating the hydrolysis of the 5'-phosphate.<sup>14,17,67</sup> In theory, this binding site may be occupied by other small molecules which can accelerate the rate of hydrolysis of PI(3,4,5)P<sub>3</sub>. Therefore SHIP agonists may provide a novel method for the degradation of PI(3,4,5)P<sub>3</sub> which could be used to influence signaling associated with the PI3K pathway. The acceleration of SHIP would provide a new method for degradation of PI(3,4,5)P<sub>3</sub> which may be influenced by pharmacological intervention with a small molecule. The exploration for small molecule SHIP1 agonists became of particular interest as the hyperactivity associated with the PI3K pathway has been shown to facilitate tumor growth as well as aggravate conditions related to inflammation and osteoporosis.<sup>14,59</sup>

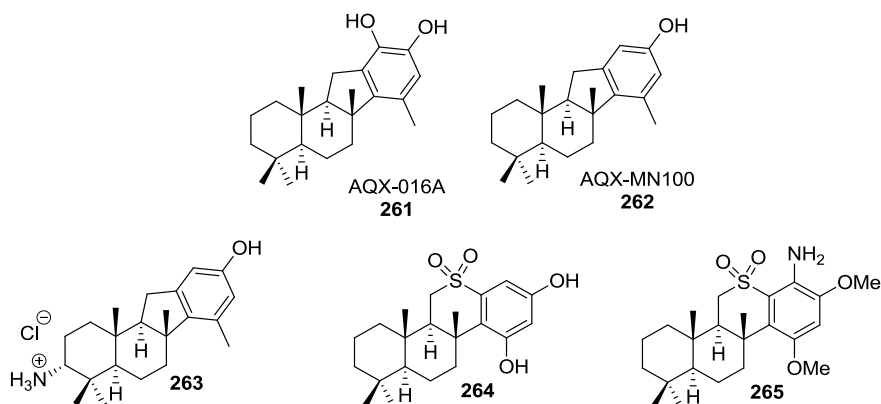
In an attempt to find new small molecule SHIP1 agonists, Andersen and co-workers<sup>59</sup> screened crude extracts of marine invertebrates. They found that the naturally occurring

sesquiterpene pelorol **260** (found in an extract from *Dactylospongia elegans* harvested in Papua New Guinea), was able to enhance SHIP1 phosphatase activity. The first total synthesis of pelorol was also developed by the Andersen group, requiring only 9 steps from (+) – sclareolide.<sup>59</sup> Pelorol **260** had been previously isolated by independently by König<sup>70</sup> and Schmitz<sup>71</sup> in 2000 from *D. elegans* and the Micronesian sponge *Petrosadpongia metachromia*, but the enzymatic target was not previously reported. Also notable is a second synthesis of pelorol by Baran, which required 11 steps and proceeded in 8.5% overall yield.<sup>72</sup>



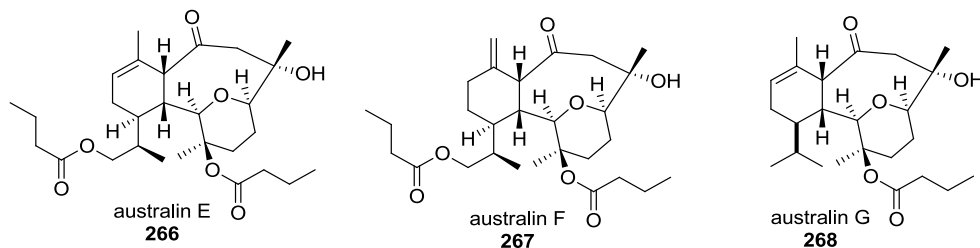
### Scheme 28: Pelorol Synthesis

Since the determination of pelorol's SHIP1 agonist activity, numerous analogs of **260** have been synthesized and tested for SHIP1 activity. Some of these are seen in Figure 8 below.<sup>59,68</sup> Toly analogue **261** was synthesized by Yang in six steps from **259**. Catechol **261** was shown to inhibit degranulation and TNF $\alpha$  production in SHIP1 as well as show anti-inflammatory effects similar to that of dexamethasone (a known reference standard).<sup>59</sup> As catechols are typically undesired in pharmaceuticals due to the likely production of unwanted side effects like metal chelation and the associated toxicity, **262** was synthesized.<sup>14,17,71-75</sup> Similarly to **261**, this analogue showed comparable potency, preference to SHIP1 over SHIP2, and was tolerated well by cells.<sup>17,66</sup> The pelorol analogs all suffered from poor water solubility however, which limited their use in *in vivo* assays, and clinical development of this class of SHIP1 agonists was discontinued for this reason.



**Figure 8: Pelorol Analogs**

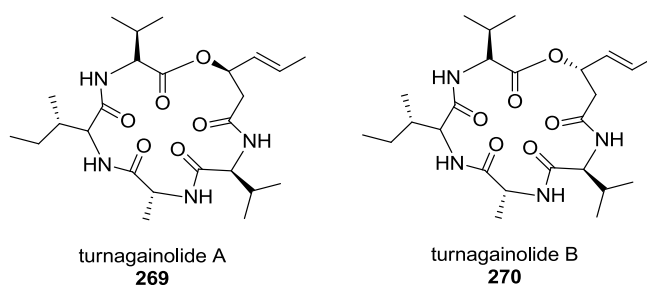
In addition to pelorol and its analogues, Anderson's group was able to find a number of other, structurally distinct natural products which act as SHIP1 agonists. For example, Andersen and co-workers<sup>73</sup> isolated and elucidated the structure of australin E (**266**) from the soft coral *Cladiella sp.* This molecule belongs to the eunicellin diterpenoids and is the first example of a SHIP1 agonist from this class of natural products (even though they have previously shown *in vitro* cytotoxicity against cancer cell lines).<sup>76</sup> Other australin analogs (F and G) were also identified in the initial isolate but did not show SHIP1 agonist activity.



**Figure 9: Australin E, F, and G**

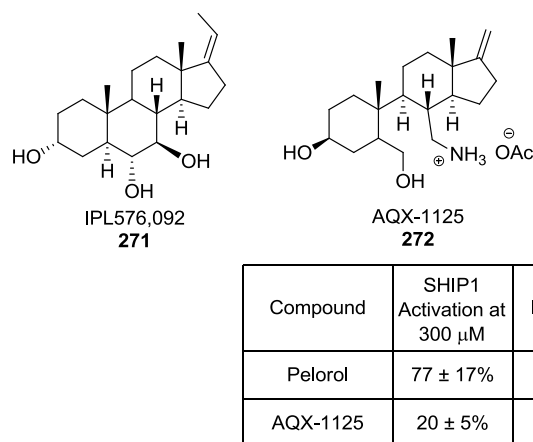
Another structural class of SHIP1 agonists found by the Anderson group is the cyclic depsipeptides (Figure 10). These agonists were isolated from a strain of *Bacillus sp.* and the structures were verified by the synthesis of the linear seco acids followed by macrocyclization with a carbodiimide reagent. Turnagainolide B **270** was found to have similar potency as **262**,

yet **269**, which only differs in stereochemistry of the lactone, was found to have no SHIP1 agonist activity.<sup>77</sup>



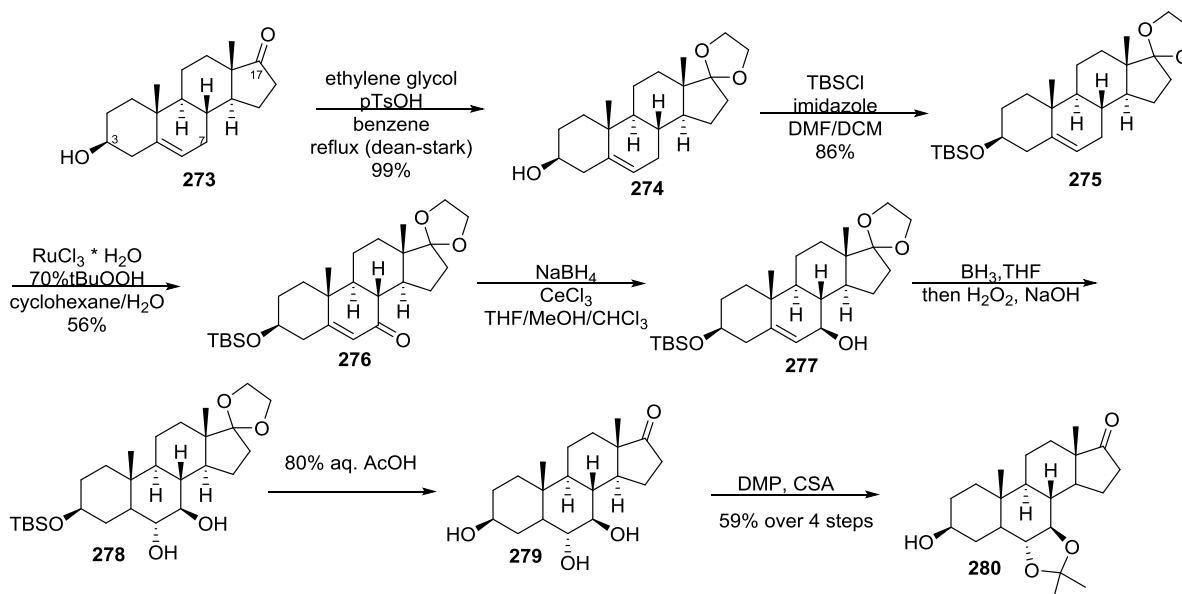
**Figure 10: Turnagainolides A and B**

Aquinox Pharmaceuticals developed an aminosteroid derivative with an open B ring, AQX-1125 (Figure 11, **272**),<sup>78</sup> which was likely found by screening a number of indene derivatives that were synthesized by Inflazyme Pharmaceuticals.<sup>79</sup> Aquinox describes a number of preclinical studies with AQX-1125, as well as its advancing to the clinic as an anti-asthmatic agent.<sup>80,81</sup> While AQX-1125 was not as effective a SHIP1 agonist as pelorol **260**, the significantly better water solubility of AQX-1125 led to its advancement to the clinic. In 2015, **272** made it to Phase 2 clinical trials to treat asthma, however it recently was unable to demonstrate efficacy in patients with mild to moderate atopic dermatitis, not showing statistical significance in the study.<sup>82</sup> As of January 2016, AQX-1125 has undergone plans with the FDA for a Phase 3 clinical trial to be used for the treatment of patients with bladder pain syndrome/interstitial cystitis (BPS/IC), which is a chronic inflammatory bladder disease.<sup>83</sup> AQX-1125 is the first pharmaceutical agent that specifically targets SHIP1 to reach clinical trials.



**Figure 11: IPL576,092 & AQX-1125 with SHIP Activation and logP Comparison to 260**

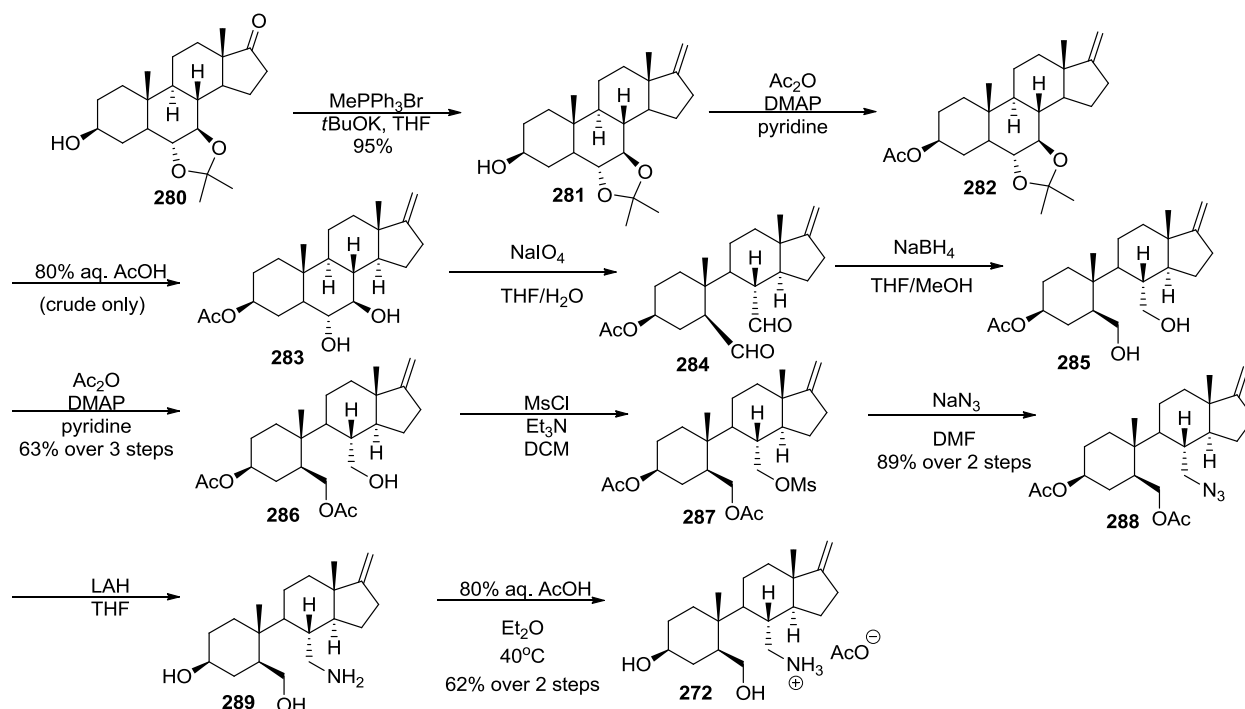
Aquinox has disclosed only a single synthesis of AQX-1125 through patent literature,<sup>78</sup> and also reports a similar intermediate and synthetic route as IPL576,092 (Figure 11, **271**).<sup>79</sup> As seen in Scheme 29, the synthetic route begins from trans-dehydroandrosterone **273**. Treatment of **273** with ethylene glycol in the presence of pTsoH provided the ketal **274**. The hydroxy group at C3 was then protected as a TBS ether. Allylic oxidation of this ether using ruthenium catalysis provided enone **276** in 56% overall yield. The authors also employed chromium-trioxide-dimethylpyrazole which they report obtained a higher yield of 65%; however this uses a 10-fold excess of chromium trioxide and therefore is not practical for large-scale work. Stereoselective 1,2-reduction of the enone using Luche conditions followed by a hydroboration-oxidation of the C5-C6 alkene gave an intermediate steroid diol **278**. Both the ketal and TBS ether protecting groups were then deprotected in a one-step process by treatment of 80% aq. AcOH followed by protection of 6 $\alpha$ OH and 7 $\beta$ OH as an acetonide, yielding steroid **280**.<sup>78</sup>



### Scheme 29: Literature Synthesis of AQX-1125

Installation of the C17 alkene was then performed with treatment of ketone **280** with the corresponding Wittig reagent to obtain exocyclic olefin **281**, which was followed by protection of the C3 alcohol as the acetate to provide **282**. Hydrolysis of the acetone to form diol **283** followed by treatment with NaIO<sub>4</sub> in THF to oxidatively cleave the diol provided the open B ring dialdehyde **284**. The dialdehyde was quickly reduced using NaBH<sub>4</sub> and protected as the respective monoacetate **286**. This protection was reported to be somewhat selective but the yield of undesired monoprotected acetate isomer was not given. Amine synthesis resulted from an azide displacement of the respective mesylate **287** followed by subsequent reduction employing lithium aluminum hydride, **289**. To finish the synthesis, they carefully prepared the acetate salt to complete the first synthesis of AQX-1125 in 17 steps and 13% overall yield (Scheme 30).<sup>78</sup>





**Scheme 30: Literature Synthesis of AQX-1125**

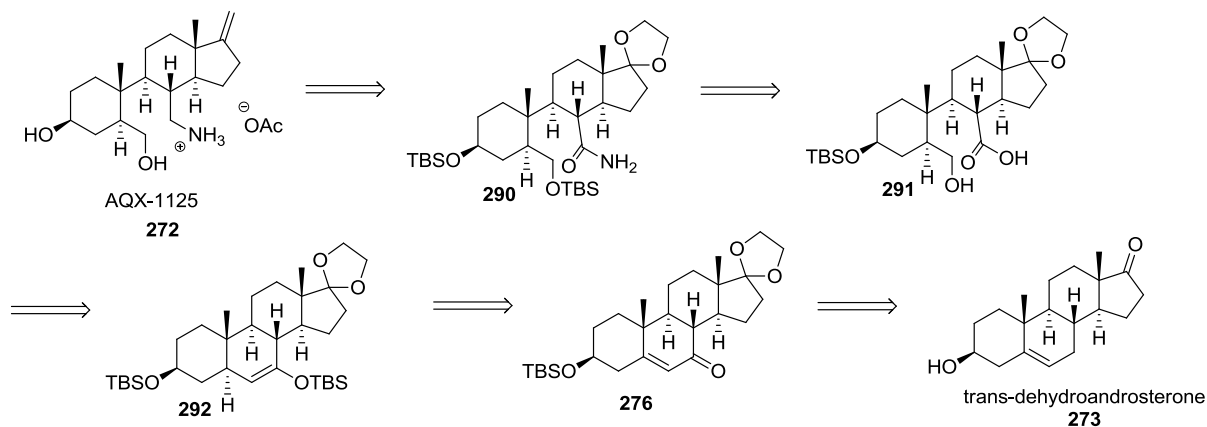
### 4.3 Synthetic Route

During our recent studies on the SHIP enzyme some biochemical experiments were proposed that would require access to a small molecule SHIP agonist. Attention was then turned to the above synthesis of AQX-1125 to determine if it would be feasible to generate enough of the agonist to facilitate the biochemical studies. While the synthesis of AQX-1125 certainly has proven useful in exploring the interesting chemical space and synthesizing compounds for screening, this synthetic route is quite long and involved.<sup>78</sup> The synthesis seen above in Schemes 29 and 30 also generates an intermediate (diol **285**), which is difficult to selectively manipulate resulting in an avoidable loss of material. Efforts were therefore directed to develop a more streamlined approach to AQX-1125 that could be used to provide material for biological evaluation.

Examining the structure of AQX-1125, a new retrosynthetic approach was envisioned.

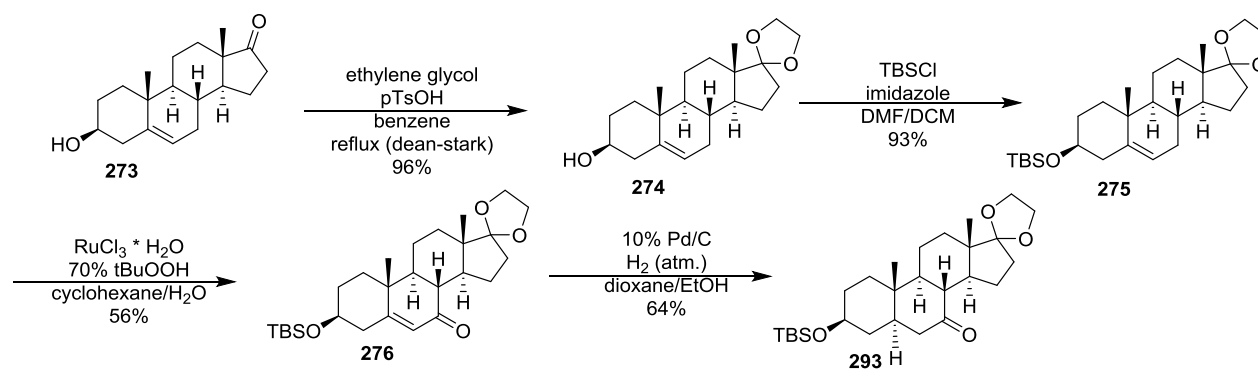
The major feature differentiating this route would be the focus on intermediates like **290** and **291**

which have the C6 and C7 carbons in different oxidation states. This would allow for a selective manipulation that was not available in the aforementioned synthesis. The retrosynthetic plan anticipated the key intermediates would be generated from an allylic oxidation of the C7 position, ozonolysis of the respective silyl enol ether, an EDCI – mediated amide coupling followed by LAH reduction of the amide, and a late stage Wittig (Scheme 31).



### Scheme 31: Retrosynthetic Analysis of AQX-1125 **272**

The new synthetic route begins with trans-dehydroandrosterone, **273**. Dioxolane protection of the ketone at C17 and TBS protection of the C3 alcohol both proceeded in excellent yields to generate intermediate **275**. Allylic oxidation at C7 on alkene **276** was then performed, providing a 56% yield of the desired product. While this yield was moderate it was comparable to many literature examples.<sup>78,79,84</sup> A recent report by the Baran group notes that this transformation may be performed electrochemically in higher yield, and these conditions may be investigated in the future.<sup>85</sup>



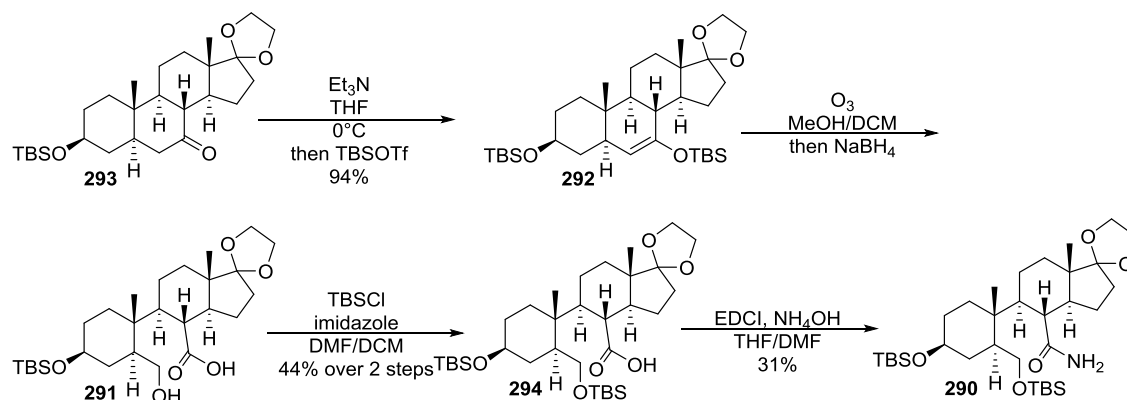
### Scheme 32: Synthesis of Ketone 293

Various attempts were made to complete the olefin reduction of **276** to obtain **293**. Initial conditions used magnesium in methanol, unfortunately after multiple attempts (Table 24, entries 1-3) only reduction of the ketone was observed. Transfer hydrogenation utilizing Pd/C and ammonium formate was then attempted (entry 4) since the literature showed examples with similar steroid substrates;<sup>86</sup> however, only starting material was obtained. Utilizing catalytic hydrogenation (10% Pd/C under one atmosphere of H<sub>2</sub> gas) provided the desired product **293** (entry 7) in 64% yield as the only compound isolated. Literature has shown to yield the *trans* – decalin product selectively in similar steroid systems.<sup>84</sup> As the C5 hydrogen signal is obscured in the <sup>1</sup>H NMR by other signals, we tentatively assign the product as the *trans* – decalin. Verification of this assignment will be the subject of future work.

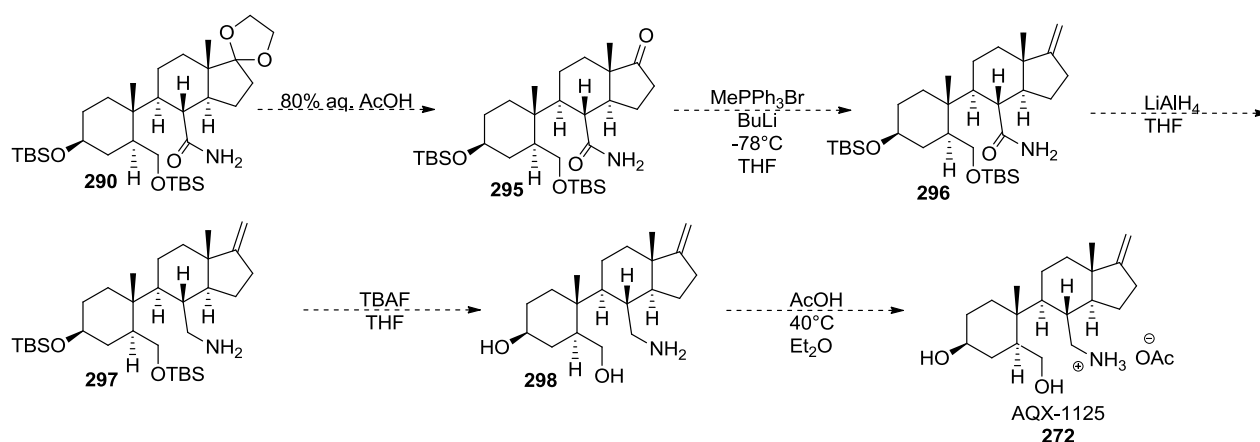
**Table 24: Reduction Attempts of Substrate 276 to 293**

Entry	Reduction Conditions	Result
1	Mg, MeOH	Starting Material
2	Mg, MeOH/THF	Starting Material
3	Mg, EtOH/THF	Reduction of Ketone
4	10% Pd/C, ammonium formate, EtOH/THF, reflux	Starting Material
5	10% Pd/C, H <sub>2</sub> , EtOAc	Starting Material
6	10% Pd/C, H <sub>2</sub> , dioxane	Starting Material
7	10% Pd/C, H <sub>2</sub> , EtOH	Starting Material
8	10% Pd/C, H <sub>2</sub> , dioxane/EtOH	64% of desired product

The silyl enol ether **292** was then generated from the reduced steroid **293**. Ozonolysis using a reductive work-up was then utilized to obtain hydroxy-acid **291**; this material was immediately brought forward to the TBS protected intermediate **294**. Key intermediate **290** was then accessed by an EDCI – mediated amide coupling using ammonium hydroxide; although this reaction proved capricious (giving product only twice despite multiple attempts) and purification of **290** proved to be difficult.

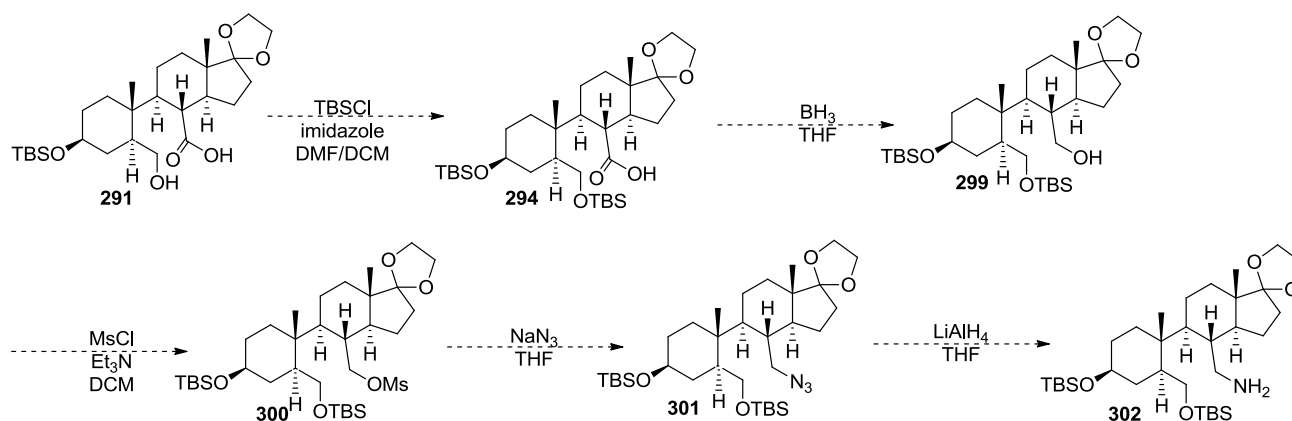
**Scheme 33: Synthesis of Amide 290**

To complete the synthesis of AQX-1125, the synthetic route would require deprotection of the dioxolane utilizing 80% aq. AcOH to regenerate the ketone at C17; however, every time this reaction was attempted, degradation occurred and no product or starting materials was isolated. This may be due to the loss of the C6 silyl ether, which then facilitates amide hydrolysis. The corresponding acid generated from this reaction is likely difficult to separate or recover from AcOH. Nevertheless, we can still report our proposed end-game towards **272**, which would include a Wittig reaction to obtain the methylene at C17. An  $\text{LiAlH}_4$  reduction to the amine **297**, deprotection of the silyl enol ether utilizing TBAF and generation of the acetate salt would complete the synthesis of AQX-1125 **272**.



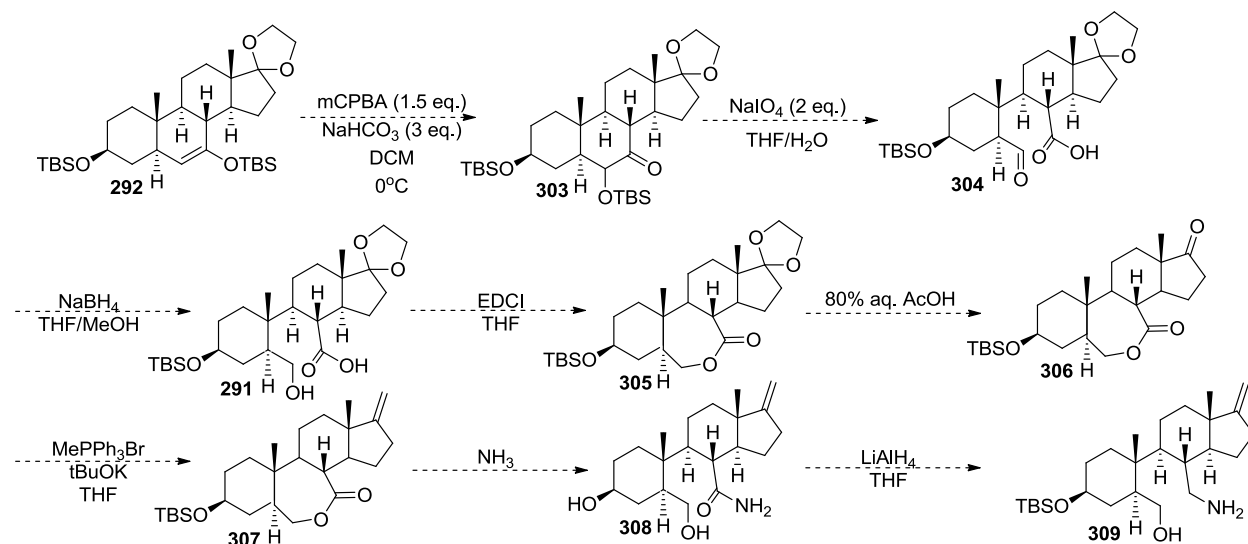
**Scheme 34: Proposed End-Game Towards Synthesis of AQX-1125**

Due to the consistently low yields in the formation of the amide and difficulties in deprotection of C17, two alternative syntheses to our original route have been proposed. The first features an alternative method to obtain the required amine **302**, seen in Scheme 35. This route still proceeds through ozonized **291** but after subsequent protection of the hydroxyl group, the manipulation to the amine would result from reduction of the ensuing azide displacement of the mesylate.



### Scheme 35: Proposed Alternate Synthesis Towards Amine 302

We could imagine deprotection at C17 would still prove difficult in this substrate, so we envision that lactone intermediate **305** may be more suitable towards such conditions and yield the desired unprotected ketone (Scheme 36). This would be obtained from a new route to the respective hydroxy-acid **291** via a Rubottom oxidation, followed by NaIO<sub>4</sub> in THF to oxidatively cleave to yield the open B ring, and selective reduction of the aldehyde utilizing NaBH<sub>4</sub>. Subsequent lactonization of **291** using EDCI would then yield **305**. We chose to propose an alternate route to **291** as ozonolysis may not be scalable. Once **305** was obtained, the alkene could be installed at C17 and the lactone could be opened with ammonia to directly access the corresponding amide. The amide can then be reduced to the amine, accessing AQX-1125 after deprotection of the silyl ether.



**Scheme 36: Proposed Alternate Synthesis Towards Protected Exocyclic Olefin 309**

#### 4.4 Summary

The PI3K pathway is a major signaling axis and since its identification there have been numerous efforts made to develop a targeted therapy, specifically PI3K inhibitors or SHIP agonists/antagonists; however most have limited efficacy. Of these agents, only a single small molecule SHIP modulator has been advanced to clinical trials, AQX-1125. The illustrated synthetic route Aquinox Pharmaceuticals took to develop AQX-1125 is quite long and not very efficient.<sup>78</sup> The route generates a pseudosymmetrical intermediate **285** with two primary alcohols that require selective manipulation. A new synthetic route to AQX-1125 was investigated to develop a more concise process proceeding through a more manageable intermediate as a key intermediate. This proposed synthesis, once complete, would require 13 steps to obtain AQX-1125, which is significantly more efficient. Although some portions of this synthesis proved difficult, specifically the amine formation and ketal deprotection, alternative routes have been proposed and the Chisholm group will continue to explore these alternatives.

## 4.5 Experimental

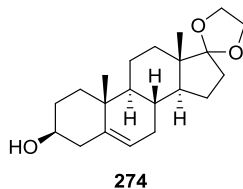
**General Methods:** All anhydrous reactions were run under a positive pressure of argon or nitrogen. All syringes, needles, and reaction flasks required for anhydrous reactions were dried in an oven and cooled under an N<sub>2</sub> atmosphere or in a desiccator. Dichloromethane and THF were dried by passage through an alumina column following the method of Grubbs (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518). Triethylamine was distilled from CaH<sub>2</sub>. All other reagents and solvents were purchased from commercial sources and used without further purification.

**Analysis and Purification.** Analytical thin layer chromatography (TLC) was performed on precoated glass backed plates (silica gel 60 F<sub>254</sub>; 0.25 mm thickness). The TLC plates were visualized by UV illumination and by staining. Solvents for chromatography are listed as volume:volume ratios. Flash column chromatography was carried out on silica gel (40-63 μm). Melting points were recorded using an electrothermal melting point apparatus and are uncorrected. Elemental analyses were performed on an elemental combustion system ECS 4010 analyzer with a thermal conductivity detector and 2 meter GC column maintained at 50 °C.

**Identity.** Proton (<sup>1</sup>H NMR) and carbon (<sup>13</sup>C NMR) nuclear magnetic resonance spectra were recorded at 300 or 400 MHz and 75 or 100 MHz respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. Coupling constants are reported in hertz (Hz). The spectra were recorded in solutions of deuterated chloroform (CDCl<sub>3</sub>), with residual chloroform (δ 7.26 ppm for <sup>1</sup>H NMR, δ 77.23 ppm for <sup>13</sup>C NMR) or tetramethylsilane (δ 0.00 for <sup>1</sup>H NMR, δ 0.00 ppm for <sup>13</sup>C NMR) as the internal reference. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; td =

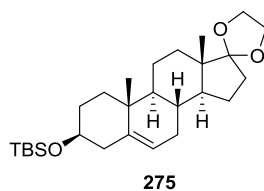


triplet of doublets; tt = triplet of triplets; qd = quartet of doublets; ddd = doublet of doublet of doublets; br s = broad singlet). Where applicable, the number of protons attached to the corresponding carbon atom was determined by DEPT 135 NMR. Infrared (IR) spectra were obtained as thin films on NaCl plates by dissolving the compound in CH<sub>2</sub>Cl<sub>2</sub> followed by evaporation or as KBr pellets.



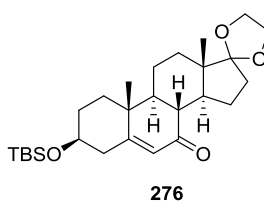
### 5-androsten-3β-ol-17-ethylene ketal, **274**<sup>79</sup>

Trans-dehydroandrosterone **273** (0.504 g, 1.73 mmol) was added to a 50 mL flame dried round-bottom flask. 5 mL of dry Benzene was added to suspend the trans-dehydroandrosterone. p-Toluene sulfonic acid monohydrate (0.013 g, 0.066 mmol) and ethylene glycol (0.5 mL) were then added to the reaction. This reaction mixture was heated to reflux under a Dean-Stark trap for 4.5 hours under argon. The mixture was removed from heat and allowed to cool to rt. The excess benzene was removed under reduced pressure. The remaining contents were diluted with diethyl ether (50 mL) and washed successively with saturated NaHCO<sub>3</sub> (2 x 25 mL) and saturated NaCl (25 mL). The organic layer was dried with anhydrous NaSO<sub>4</sub> and removed under reduced pressure to yield a white colored solid (0.558 g, 96%). TLC R<sub>f</sub> = 0.28 (30% ethyl acetate /70% hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.36 – 5.34 (m, 1H), 3.95 – 3.84 (m, 4H), 3.57 – 3.49 (m, 1H), 2.33 – 2.19 (m, 2H), 2.04 – 1.98 (m, 2H), 1.88 – 1.78 (m, 3H), 1.77 – 1.28 (m, 12H), 1.22 (m, 2H), 1.01 (s, 3H), 0.86 (s, 3H).



**5-androsten-3β-ol-17-ethylene ketal tert-butyldimethylsilyl ether, 275<sup>79</sup>**

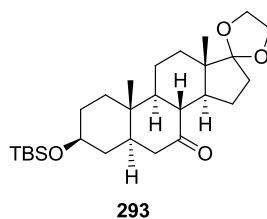
5-androsten-3β-ol-17-one ethylene ketal **274** (0.501 g, 1.50 mmol) was added to a 50 mL flame dried round-bottom flask. 2.7 mL of DMF and 2.7 mL of CH<sub>2</sub>Cl<sub>2</sub> were added to dissolve the ketal. Imidazole (0.255 g, 3.67 mmol) and tert-butyl (chloro) dimethyl silane (0.347 g, 2.32 mmol) were then added to the reaction. This reaction mixture was allowed to stir at rt for 6 hours under argon. The excess solvent was removed under reduced pressure. The remaining contents were diluted with diethyl ether (50 mL) and washed successively with 5% aqueous HCl (2 x 100 mL), saturated NaHCO<sub>3</sub> (2 x 25 mL) and saturated NaCl (25 mL). The organic layer was dried with anhydrous NaSO<sub>4</sub> and removed under reduced pressure to yield a white colored solid (0.624 g, 93%). TLC R<sub>f</sub> = 0.74 (30% ethyl acetate /70% hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.36 – 5.34 (m, 1H), 3.95 – 3.84 (m, 4H), 3.57 – 3.49 (m, 1H), 2.33 – 2.04 (m, 2H), 2.02 – 1.88 (m, 2H), 1.79 – 1.76 (m, 3H), 1.76 – 1.22 (m, 12H), 1.22 (m, 2H), 1.01 (s, 3H), 0.86 (s, 9H), 0.00 (s, 3H).



**5-androsten-7-one-3β-ol 17-ethylene ketal tert-butyldimethylsilyl ether, 276<sup>79</sup>**

5-androsten-3β-ol-17-one ethylene ketal tert-butyldimethylsilyl ether **275** (0.252 g, 0.55 mmol) was added to a 25 mL flame dried round-bottom flask. 1.0 mL of cyclohexane and 0.15 mL of water were added to dissolve the ketal. Ruthenium trichloride hydrate (0.001 g, catalytic) was

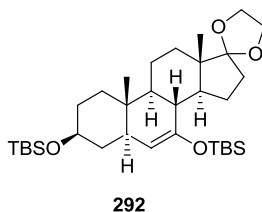
then added to the reaction. 70% tert-Butyl hydroperoxide (0.65 mL) was added dropwise at 0°C. This reaction mixture was allowed to come to rt and stir for 18 hours under argon. Then an additional 1.0 mL of cyclohexane was added and this was allowed to stir at rt for 2 additional hours. The mixture was diluted with ethyl acetate (50 mL) and washed successively with 25% aqueous Na<sub>2</sub>SO<sub>4</sub> (2 x 50 mL) and saturated NaCl (25 mL). The organic layer was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and removed under reduced pressure to yield a white colored solid (0.142 g, 56%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.60 (s, 1 H), 3.95 – 3.84 (m, 4 H), 3.59 – 3.49 (m, 1 H), 2.46 – 2.42 (m, 3H), 2.29 – 2.18 (m, 1H), 1.66 – 1.34(m, 13 H), 1.12 (s, 3 H), 0.83 (s, 9 H), 0.80 (s, 3 H), 0.00 (s, 3 H).



### **5-androsta-7-one-3β-ol 17-ethylene ketal tert-butyldimethylsilyl ether, 293**

To a 25 mL flame-dried round bottom flask, 0.048 g of 10% Pd/C was added and dissolved in 6.0 mL of dioxane and 2.0 mL of ethanol. This was placed under vacuum until bubbling occurred in which a hydrogen balloon was added and deflated under vacuum. The vacuum was then removed and a hydrogen balloon was placed. In a separate flame dried conical flask, 5-androsten-7, 17-dione-3β-ol 17-ethylene ketal tert-butyldimethylsilyl ether **276** was dissolved in 9.0 mL of dioxane. This was placed under vacuum and a hydrogen balloon was added. This mixture was then transferred under hydrogen to the initial mixture. This was allowed to stir for 7 hours at rt. This was then filtered through celite, rinsing with ethyl acetate. This was concentrated under reduced pressure and subjected to column chromatography (10% ethyl acetate/90% hexanes) to yield a white colored solid (0.312 g, 64%). mp = 198.5 – 200.3°C; TLC

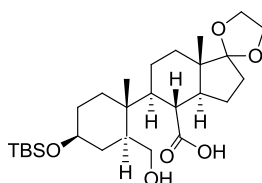
$R_f = 0.67$  (15% ethyl acetate /85% hexanes); IR (neat) 2950, 2857, 1703  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) 3.91 – 3.77 (m, 4 H), 3.59 – 3.47 (m, 1 H), 2.32 – 2.19 (m, 3 H), 1.99 – 1.31 (m, 15 H), 0.99 (s, 3 H), 0.84 (s, 9 H), 0.79 (s, 3 H), 0.00 (s, 3 H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  211.4, 118.7, 71.4, 65.2, 64.4, 55.3, 50.1, 46.6, 45.9, 45.7, 43.4, 38.4, 36.3, 35.9, 34.1, 31.5, 29.7, 25.8, 23.8, 21.3, 18.2, 14.4, 11.8, -4.66.



**5-androsta -7 – tert-butyldimethyl oxysilane -3 $\beta$ -ol 17-ethylene ketal tert-butyldimethylsilyl ether, 292**

1.2 mL of triethylamine (8.8 mmol) and 0.5 mL of  $\text{CH}_2\text{Cl}_2$  were placed in a 50 mL flame dried round-bottom flask and was placed at  $0^\circ\text{C}$ . 5-androsta-7-one-3 $\beta$ -ol 17-ethylene ketal tert-butyldimethylsilyl ether, **293** (0.104 g, 0.22 mmol) was dissolved in 1.5 mL of  $\text{CH}_2\text{Cl}_2$  and was then added dropwise to the stirring solution. This was allowed to stir at this temperature for 15 minutes. Tert-butyldimethylsilyl trifluoromethane sulfonate (0.8 mL, 15.1 mmol) was then added to the reaction, maintaining  $0^\circ\text{C}$ . This reaction mixture was placed at rt and allowed to stir for 4 hours under argon. This was re-placed at  $0^\circ\text{C}$  and isopropyl alcohol (0.40 mL) was then added. This was then filtered through celite, rinsing with  $\text{CH}_2\text{Cl}_2$ . This was concentrated under reduced pressure and subjected to column chromatography (10% ethyl acetate/90% hexanes) to yield a pale yellowish-white colored solid (0.120 g, 94%). TLC  $R_f = 0.58$  (10% ethyl acetate /90% hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.36 (s, 1H), 3.93 – 3.79 (m, 4H), 3.61 – 3.53 (m, 1H), 1.95 – 1.85 (m, 4 H), 1.84 – 1.45 (m, 11 H), 1.14 – 1.39 (m, 4 H), 1.16 - 0.89 (m, 45 H), 0.79 (s, 3 H), 0.00 (s, 12 H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  152.2, 118.7, 108.4, 72.1, 65.2, 64.5, 53.9,

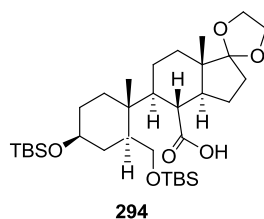
48.6, 47.5, 43.4, 42.0, 39.4, 34.9, 34.5, 34.3, 31.9, 30.8, 26.1, 25.9, 25.7, 25.70, 20.9, 18.3, 18.2, 18.1, 14.7, 11.3, -2.9, -3.9, -4.8, -4.6, -4.57.



291

**(7a'S)-5'-((1R,4S)-4-((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl)-1-methylcyclohexyl)-7a'-methyloctahydrospiro[[1,3]dioxolane-2,1'-indene]-4'-carboxylic acid, 291**

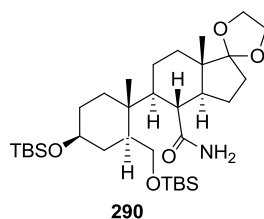
5-androsta -7 – tert-butyldimethyl oxysilane -3 $\beta$ -ol 17-ethylene ketal tert-butyldimethylsilyl ether, **292** (2.58 g, 4.46 mmol) was dissolved in methanol (25 mL) and CH<sub>2</sub>Cl<sub>2</sub> (25 mL) and was treated with excess O<sub>3</sub> at -78 °C until the solution turned blue. After purging with argon, the blue color dissipated. This was placed at 0 °C and sodium borohydride (1.781 g, 26.9 mmol) was added. This was then placed at rt and allowed to stir for 4 hours. After the solvent was evaporated on a rotary evaporator, the residue was stirred with 10% aq. HCl (20 mL) for 10 minutes and was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  50 mL), saturated NH<sub>4</sub>Cl (50 mL) and saturated NaCl (50 mL). The organic layer was dried with anhydrous NaSO<sub>4</sub> and removed under reduced pressure to yield a cream colored foam (1.04 g, 47%). TLC R<sub>f</sub> = 0.46 (5% DCM /95% MeOH). This was used in the next reaction without further purification.



**(4'R,7a'S)-5'-((1R,4S)-4-((tert-butyl dimethylsilyl)oxy)-2-(((tert-butyl dimethylsilyl)oxy)methyl)-1-methylcyclohexyl)-7a'-methyloctahydrospiro[[1,3]dioxolane-2,1'-indene]-4'-carboxylic acid, 294**

(7a'S)-5'-((1R,4S)-4-((tert-butyl dimethylsilyl)oxy)-2-(hydroxymethyl)-1-methylcyclohexyl)-7a'-methyloctahydrospiro[[1,3]dioxolane-2,1'-indene]-4'-carboxylic acid, **291**

(0.770 g, 1.55 mmol) was added to a 50 mL flame dried round-bottom flask. 3.0 mL of DMF and 3.0 mL of CH<sub>2</sub>Cl<sub>2</sub> were added to dissolve the carboxylic acid. Imidazole (0.268 g, 3.77 mmol) and tert-butyl (chloro) dimethyl silane (0.362 g, 2.52 mmol) were then added to the reaction. This reaction mixture was allowed to stir at rt for 6 hours under argon. The excess solvent was removed under reduced pressure. The remaining contents were diluted with diethyl ether (50 mL) and washed successively with 5% aqueous HCl (2 x 100 mL), saturated NaHCO<sub>3</sub> (2 x 25 mL) and saturated NaCl (25 mL). The organic layer was dried with anhydrous NaSO<sub>4</sub> and removed under reduced pressure to yield a whit colored solid (0.878 g, 93%). mp = 79.5 – 81.1°C; TLC R<sub>f</sub> = 0.33 (30% ethyl acetate /70% hexanes); IR (neat) 3390, 2929, 2857, 1808, 1736, 1703 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.91 – 3.79 (m, 4 H), 3.64 – 3.61 (m, 1 H), 3.43 – 3.38 (m, 1 H), 3.12 (t, *J* = 9.2 Hz, 1 H), 2.29 (t, *J* = 10.8 Hz, 1 H), 1.98 – 1.03 (m, 25 H), 0.88 – 0.83 (m, 29 H), 0.06 – 0.02 (m, 12 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 181.5, 118.6, 108.4, 72.1, 65.2, 64.5, 62.5, 47.6, 46.0, 45.0, 44.9, 42.5, 37.7, 34.5, 33.6, 31.5, 30.4, 29.8, 25.96, 25.94, 22.9, 30.6, 19.3, 18.3, 18.2, 13.7, -4.6, -5.32, -5.34.



**(4'R,7a'S)-5'-((1R,4S)-4-((tert-butyldimethylsilyl)oxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)-1-methylcyclohexyl)-7a'-methyloctahydrospiro[[1,3]dioxolane-2,1'-indene]-4'-carboxamide, 290**

(4'R,7a'S)-5'-((1R,4S)-4-((tert-butyldimethylsilyl)oxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)-1-methylcyclohexyl)-7a'-methyloctahydrospiro[[1,3]dioxolane-2,1'-indene]-4'-carboxylic acid, **294** was dissolved in 10.0 mL of DMF. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.827 g, 1.35 mmol) was then added. This was allowed to stir at rt for 1 hour. The reaction was placed at 0 °C and ammonium hydroxide (0.7 mL) dissolved in 2.0 mL of DMF was added dropwise. This was allowed to stir at rt for 4 hours. The excess solvent was removed under reduced pressure. The remaining contents were diluted with diethyl ether (50 mL) and washed successively with saturated NaHCO<sub>3</sub> (2 x 25 mL), 20% aqueous HCl (2 x 50 mL), and saturated NaCl (25 mL). The organic layer was dried with anhydrous NaSO<sub>4</sub> and removed under reduced pressure to yield a pale yellow colored oil (0.257 g, 31%). TLC R<sub>f</sub> = 0.15 (30% ethyl acetate /70% hexanes); IR (neat) 3342, 3178, 2952, 2930, 2883, 2558, 1730 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.93 – 3.79 (m, 4 H), 3.64 – 3.61 (m, 1 H), 3.44 – 3.38 (m, 1 H), 3.12 (t, *J* = 9.2 Hz, 1 H), 2.29 (t, *J* = 11.2 Hz, 1 H), 1.98 – 1.79 (m, 4 H), 1.51 – 1.42 (m, 10 H), 1.41 – 1.39 (m, 6 H), 1.22 – 1.18 (m, 2 H), 0.85 – 0.78 (m, 25 H), 0.015 – 0.011 (m, 12 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 182.8, 118.7, 108.4, 72.1, 65.2, 64.5, 62.5, 47.6, 46.0, 45.0, 44.9, 42.5, 37.7, 34.5, 33.6, 31.5, 30.4, 29.8, 25.96, 25.94, 22.9, 30.6, 19.3, 18.3, 18.2, 13.7, -4.6, -5.32, -5.35.

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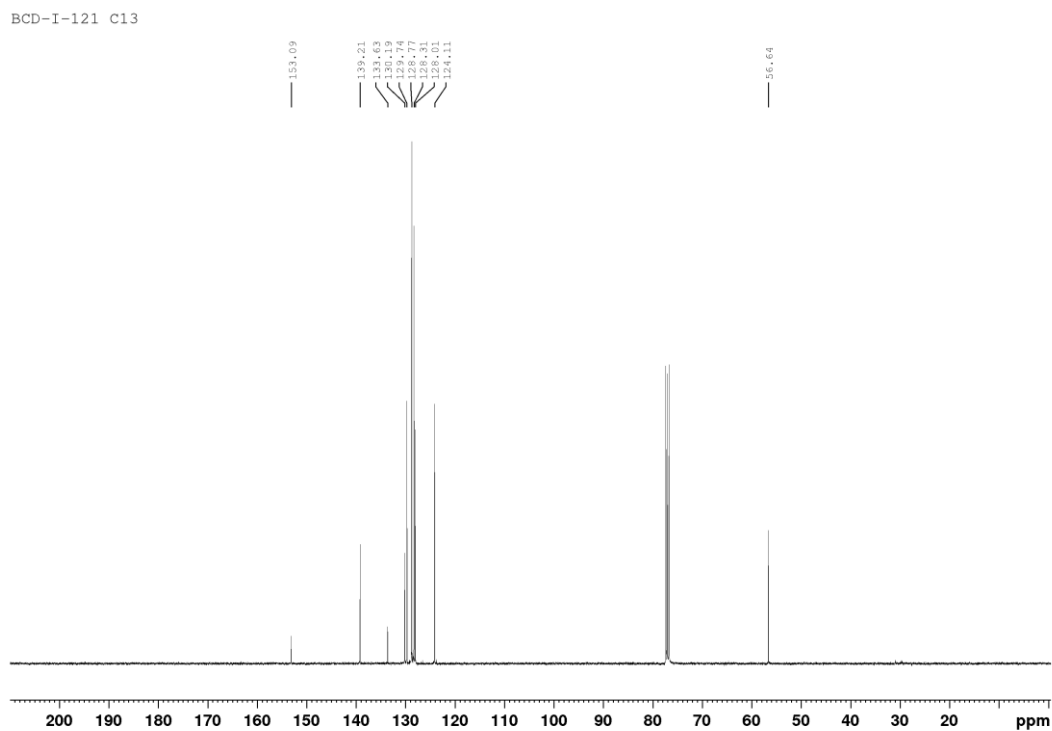
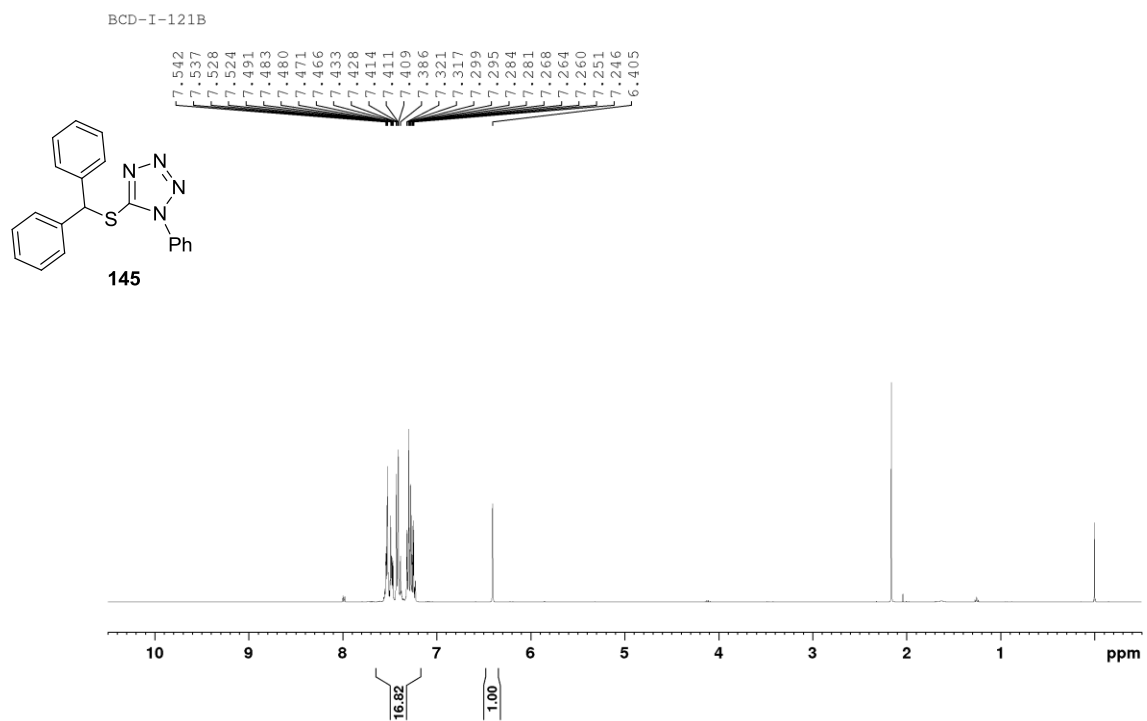
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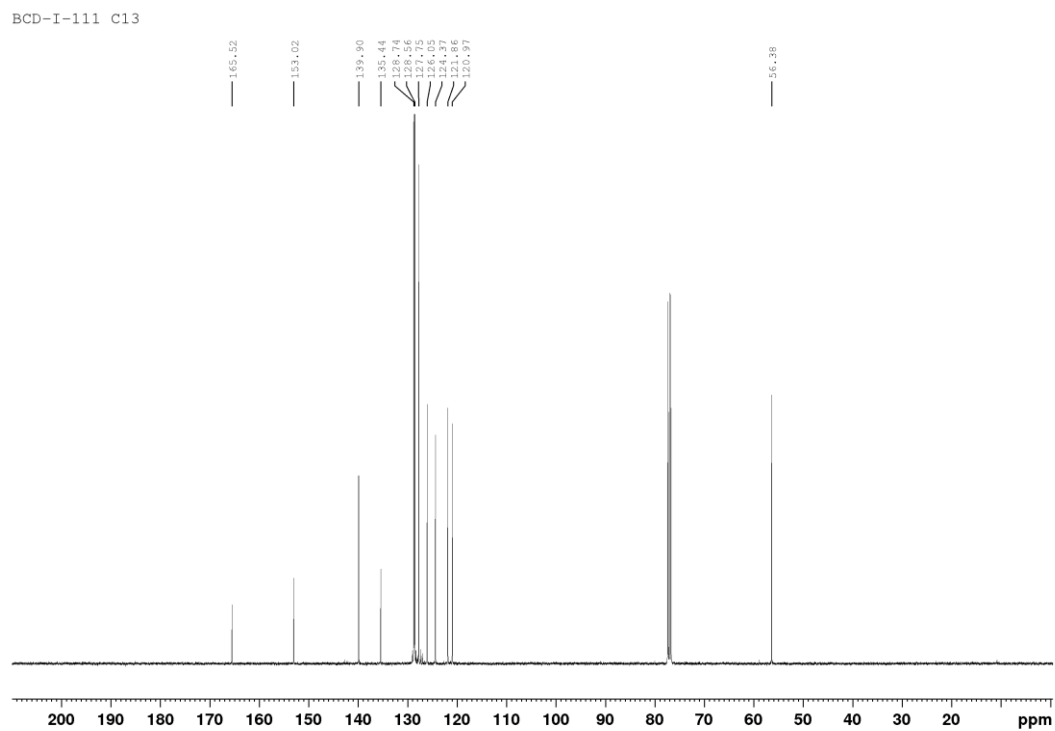
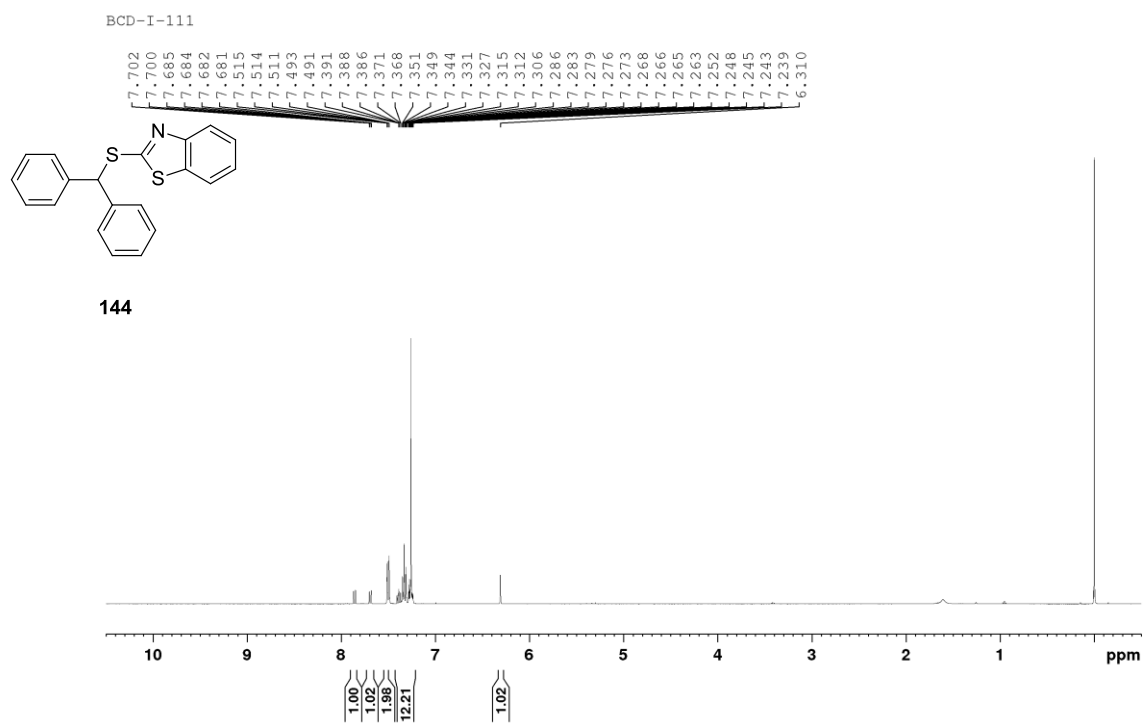
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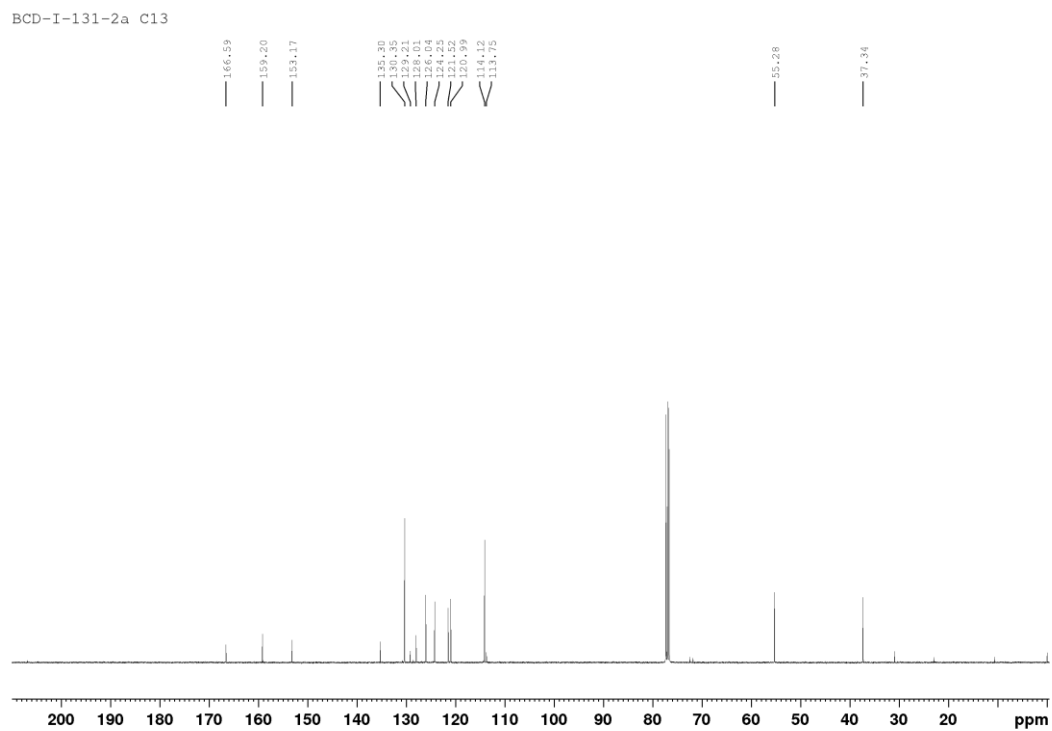
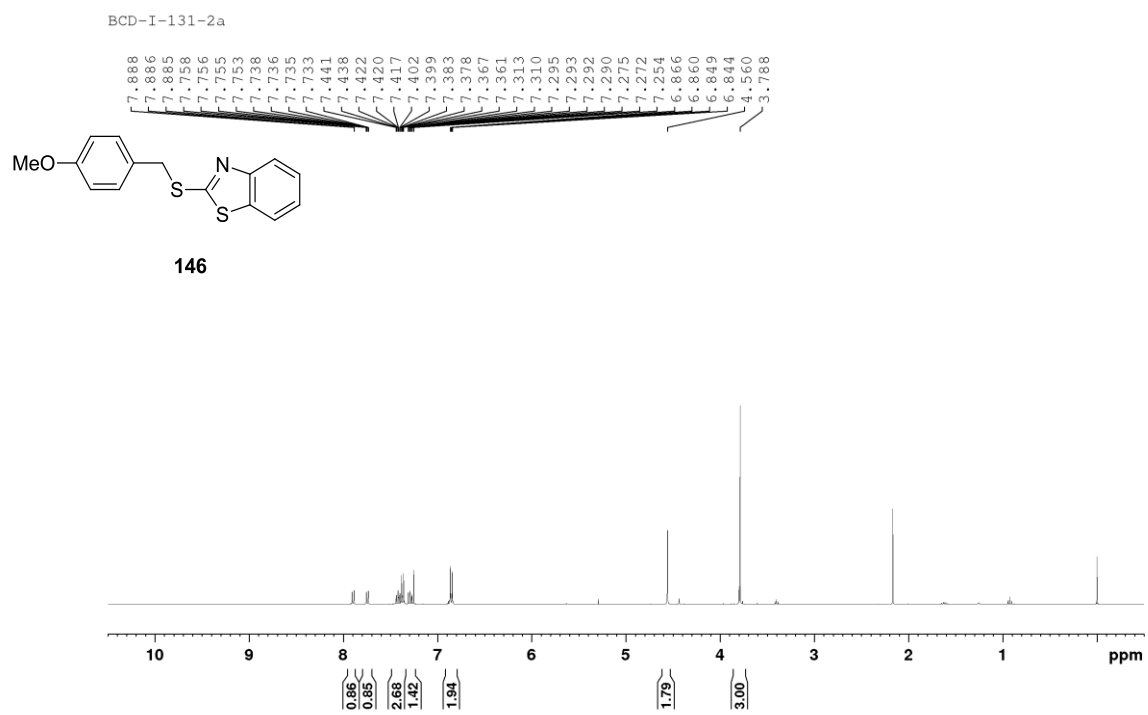
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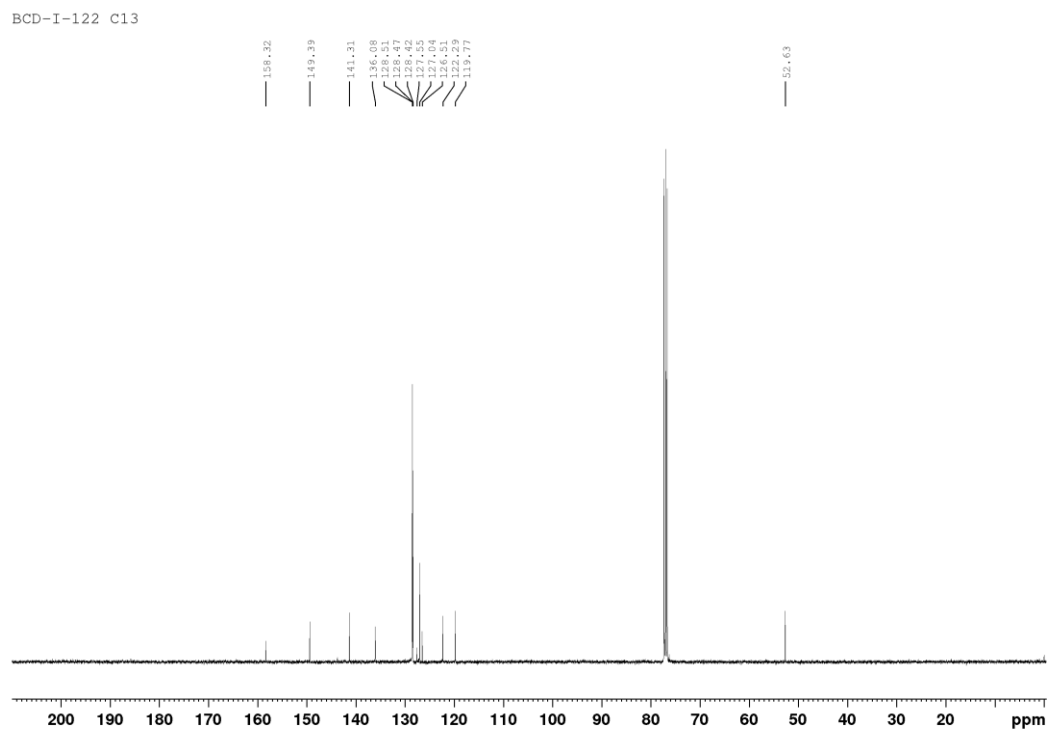
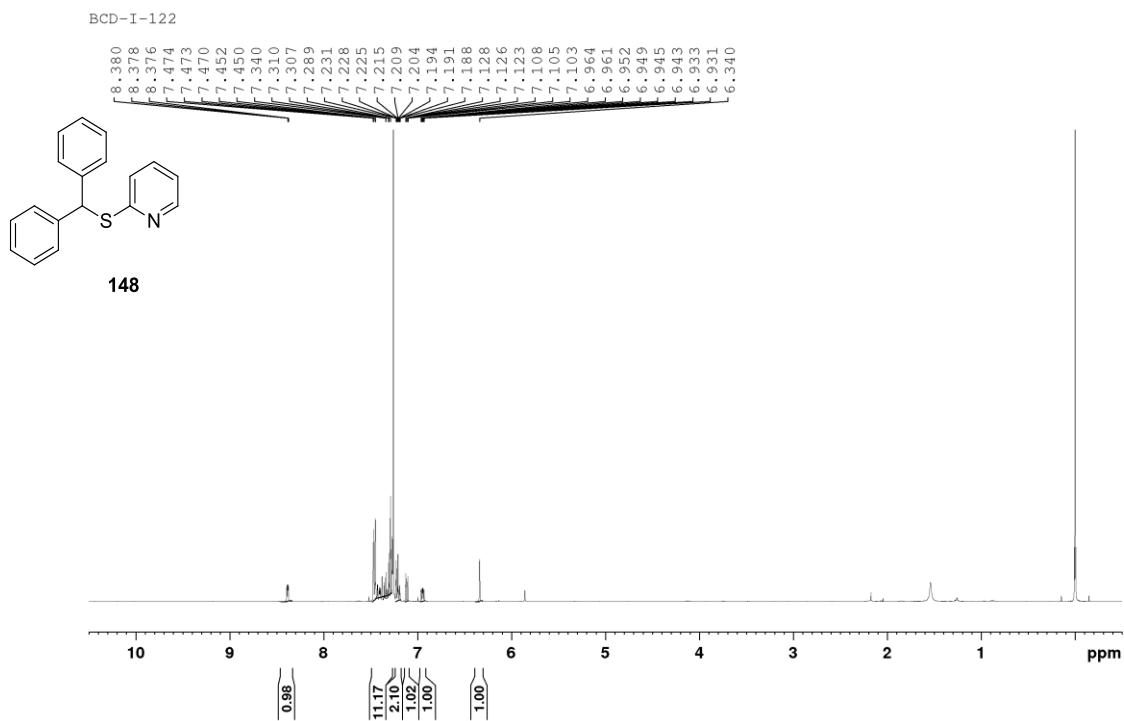
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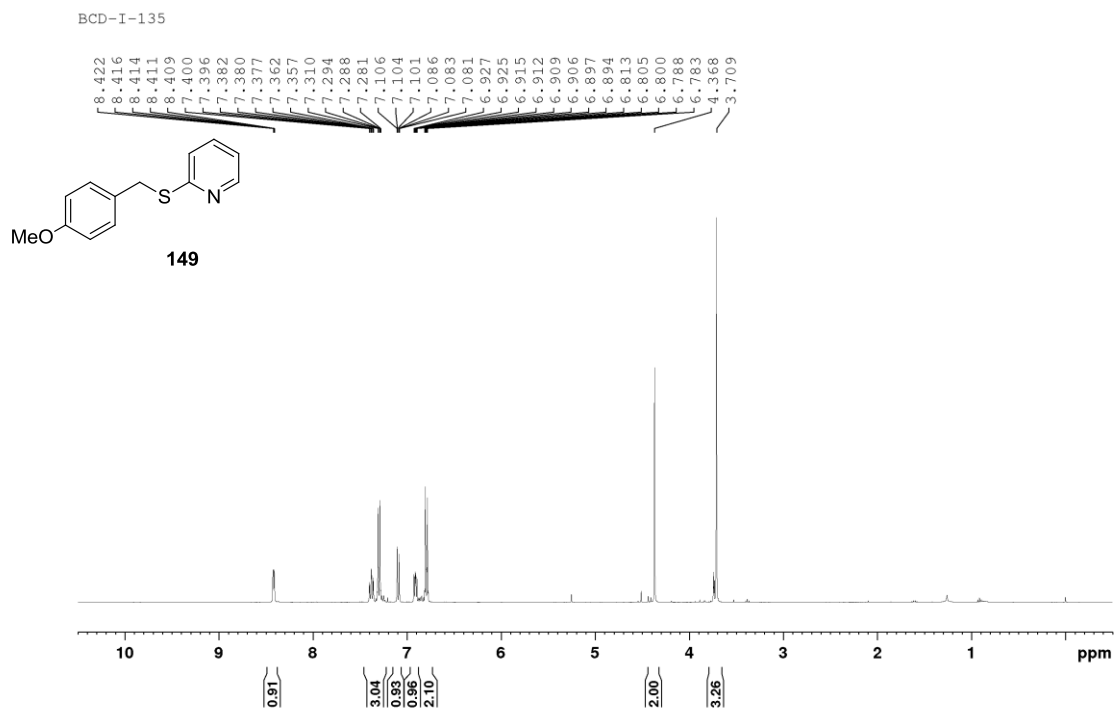
Appendix –  $^1\text{H}$  and  $^{13}\text{C}$  NMR Spectra



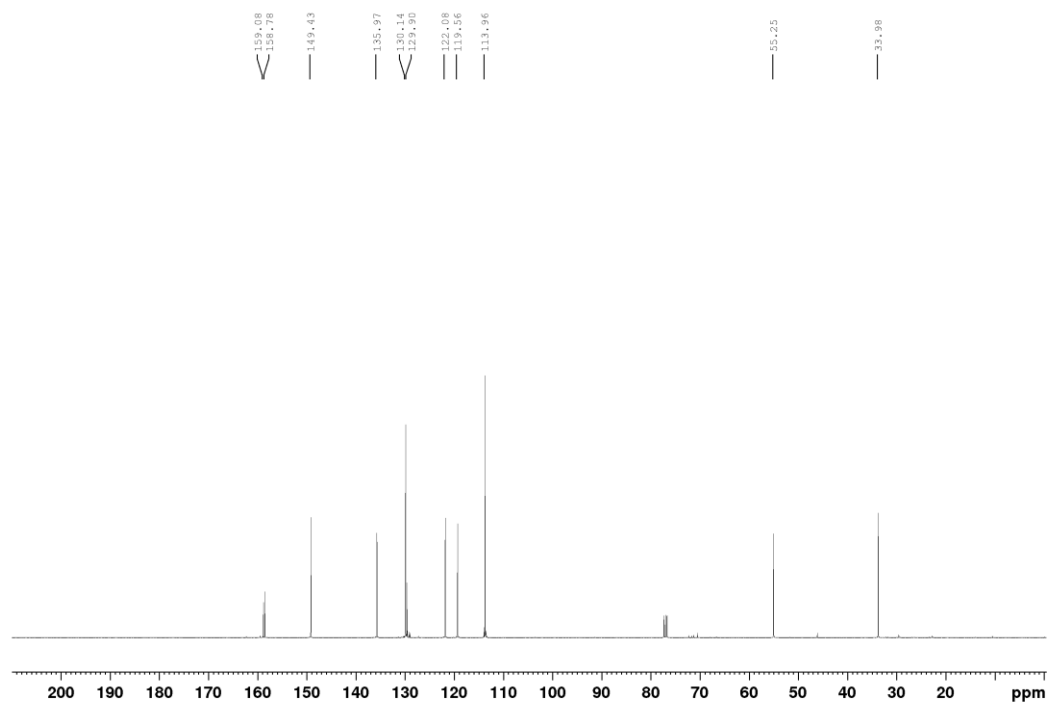


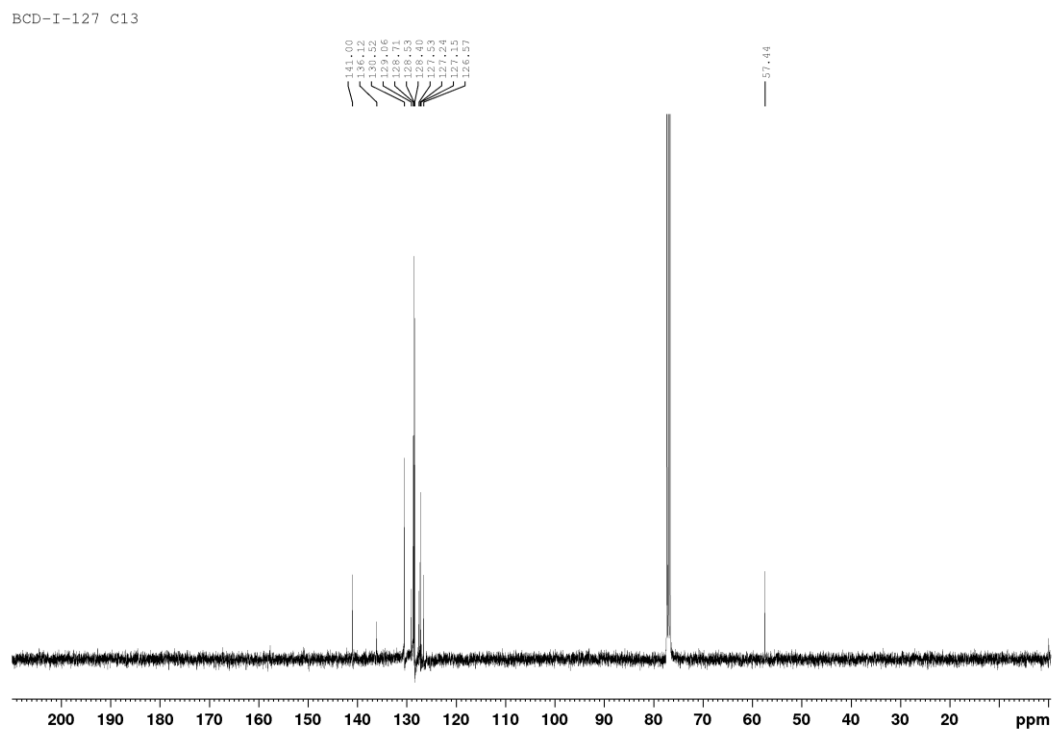
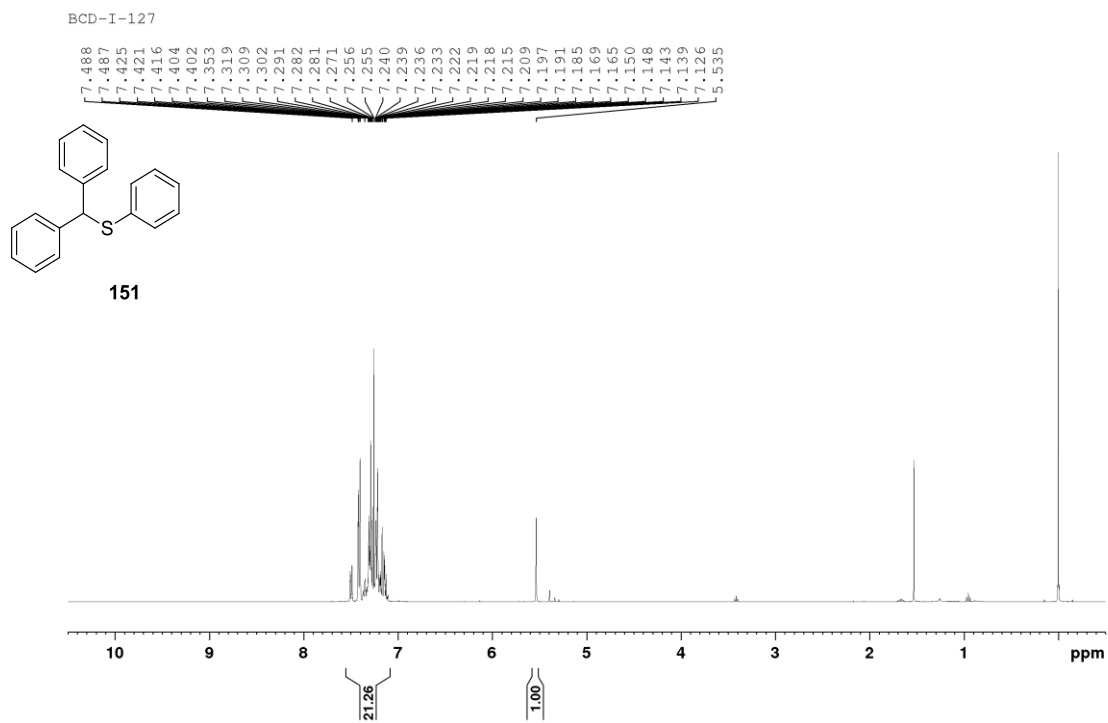


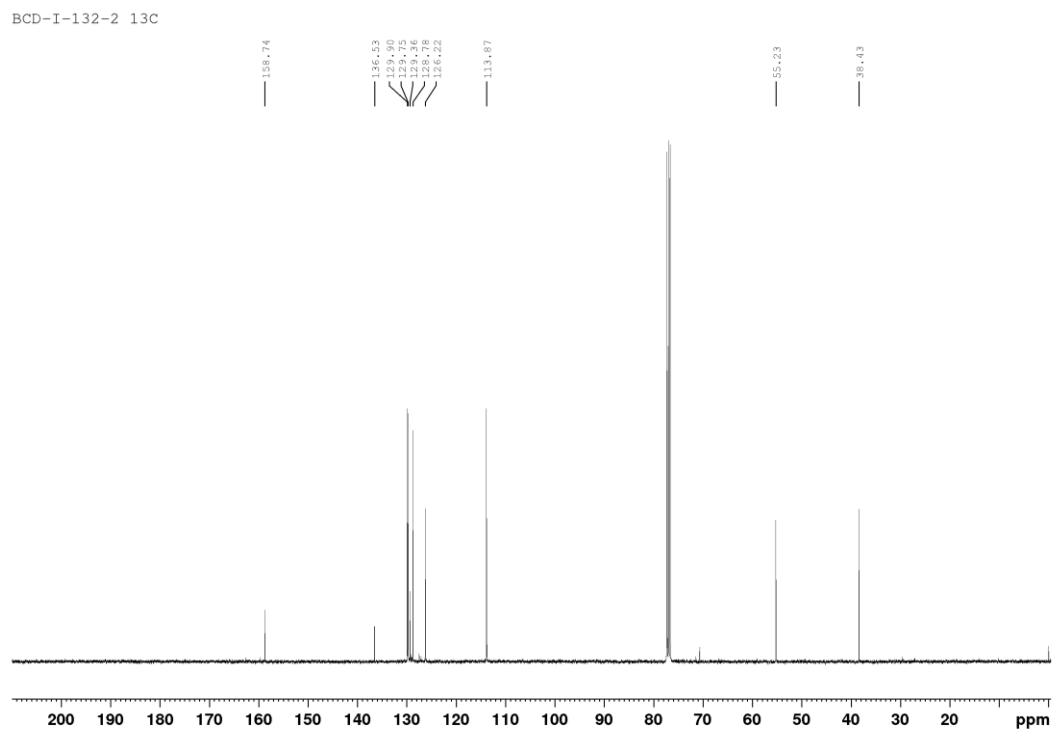
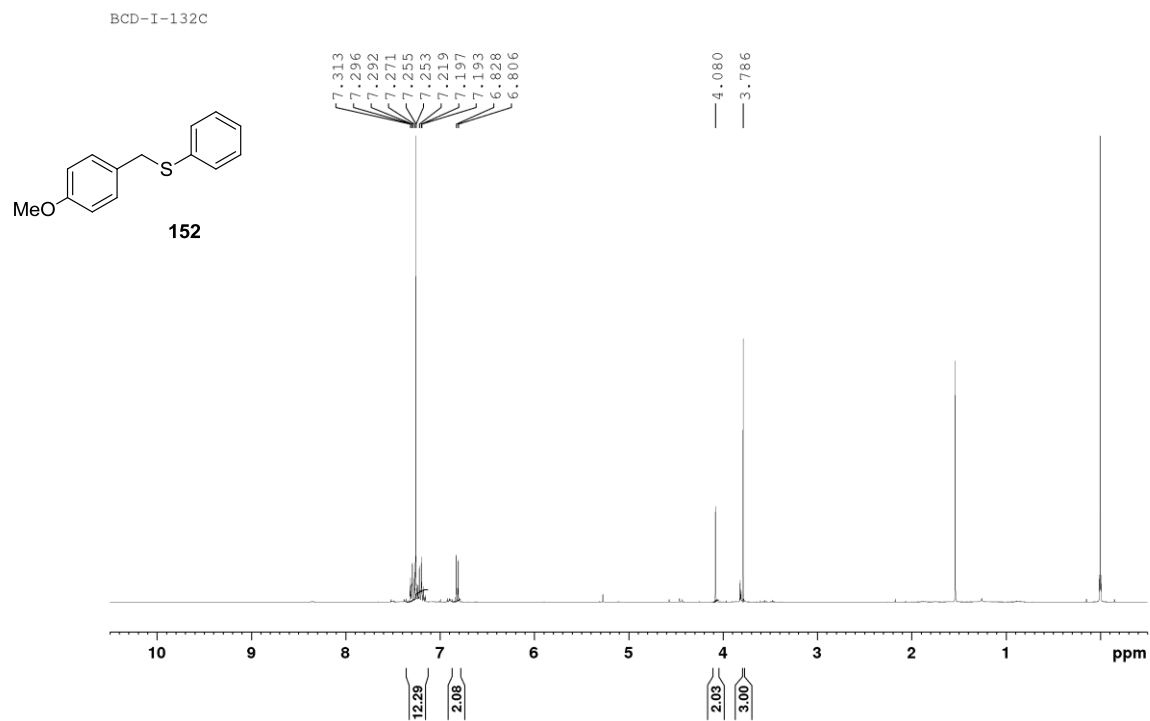


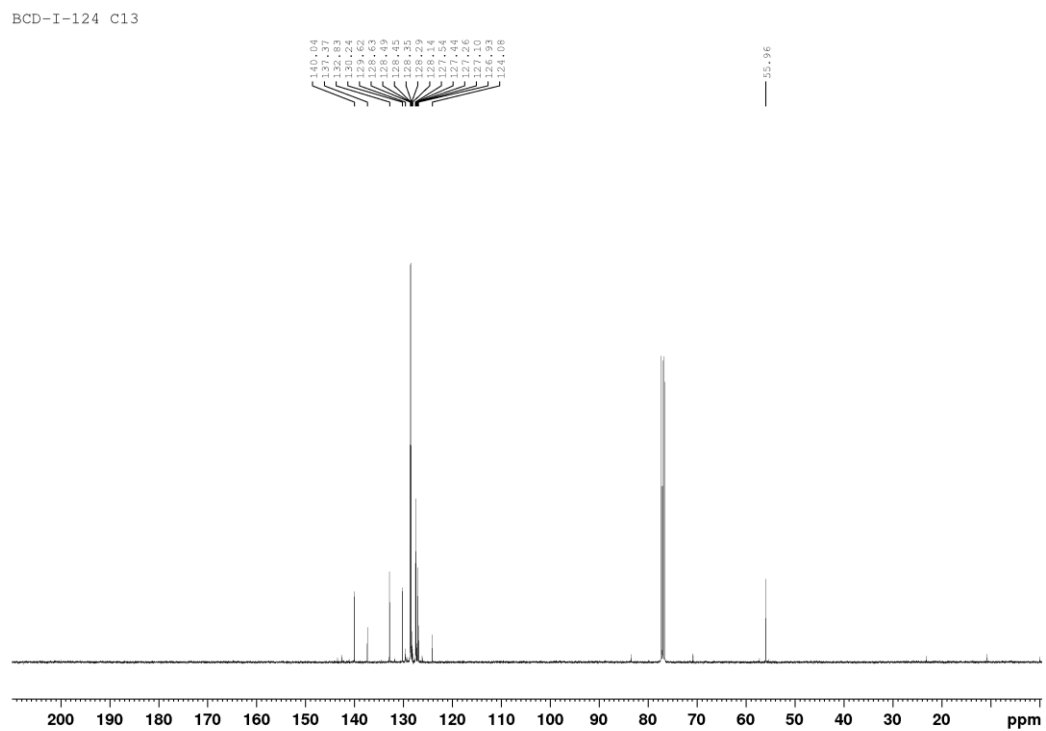
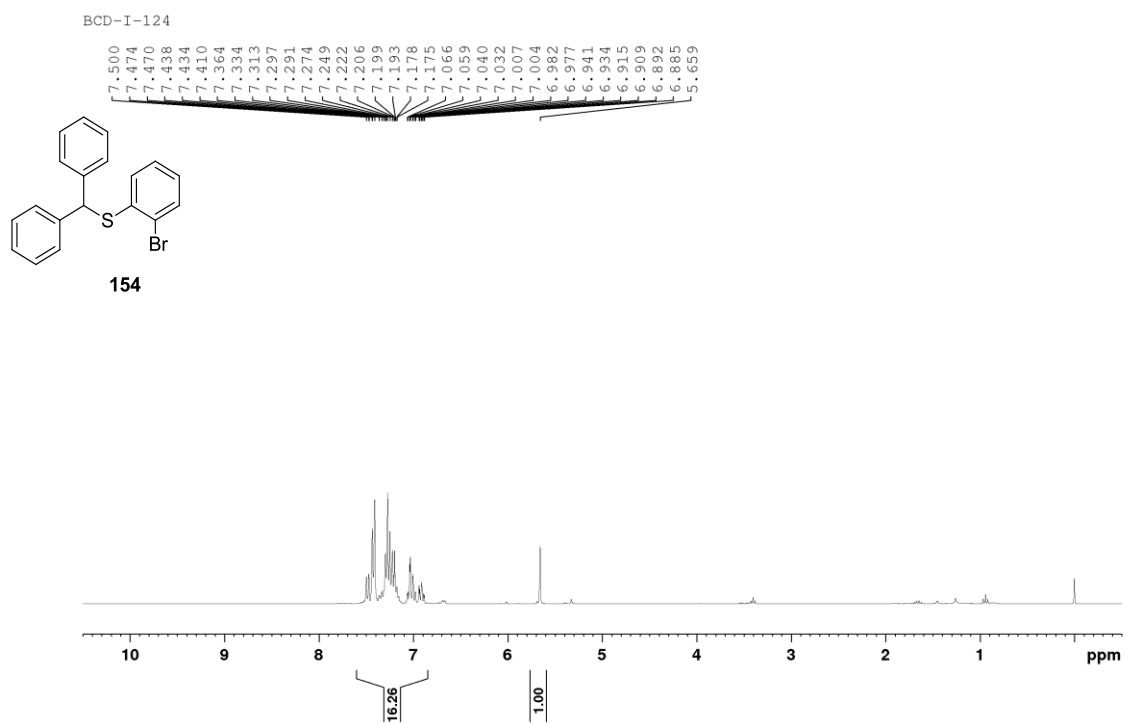


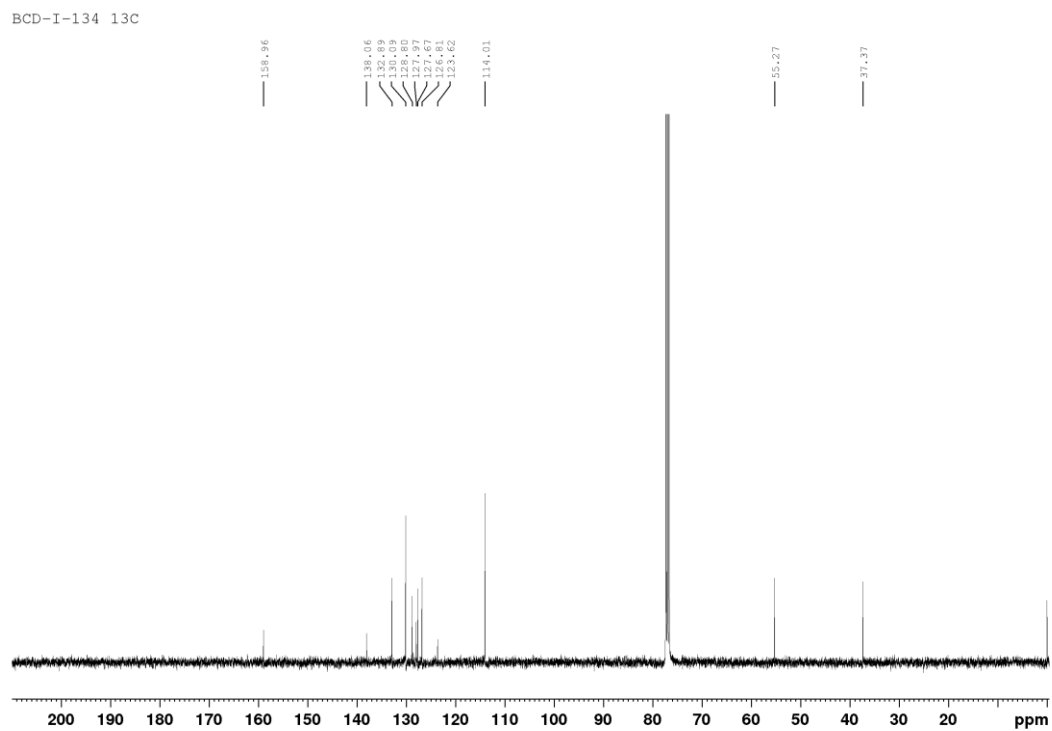
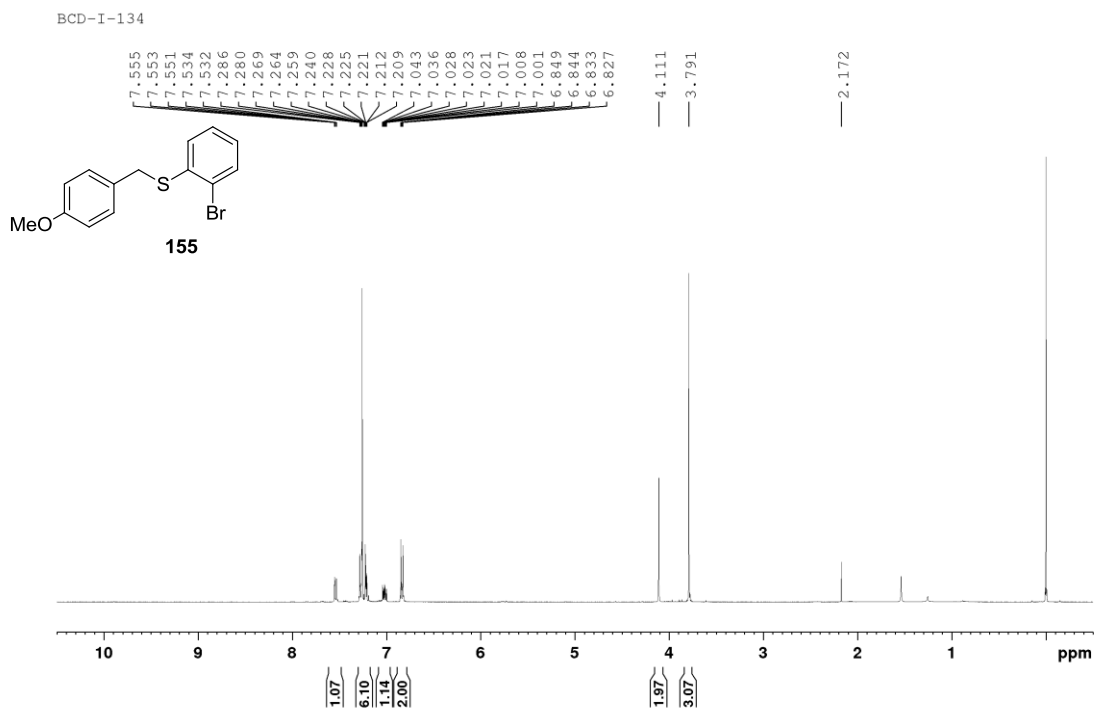
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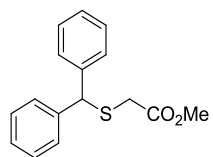




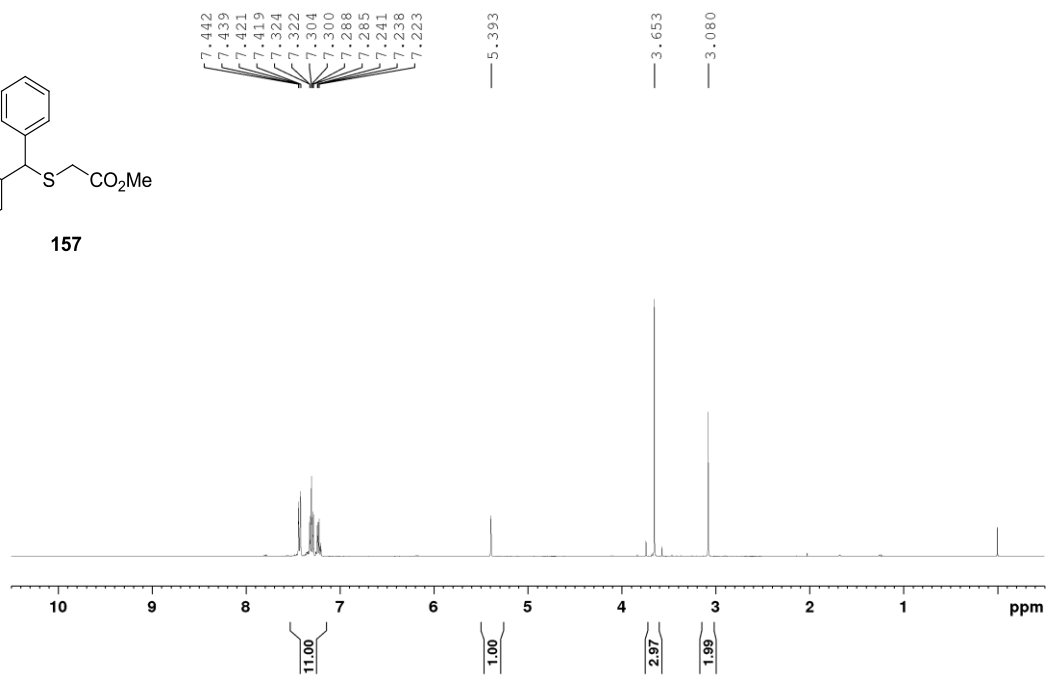




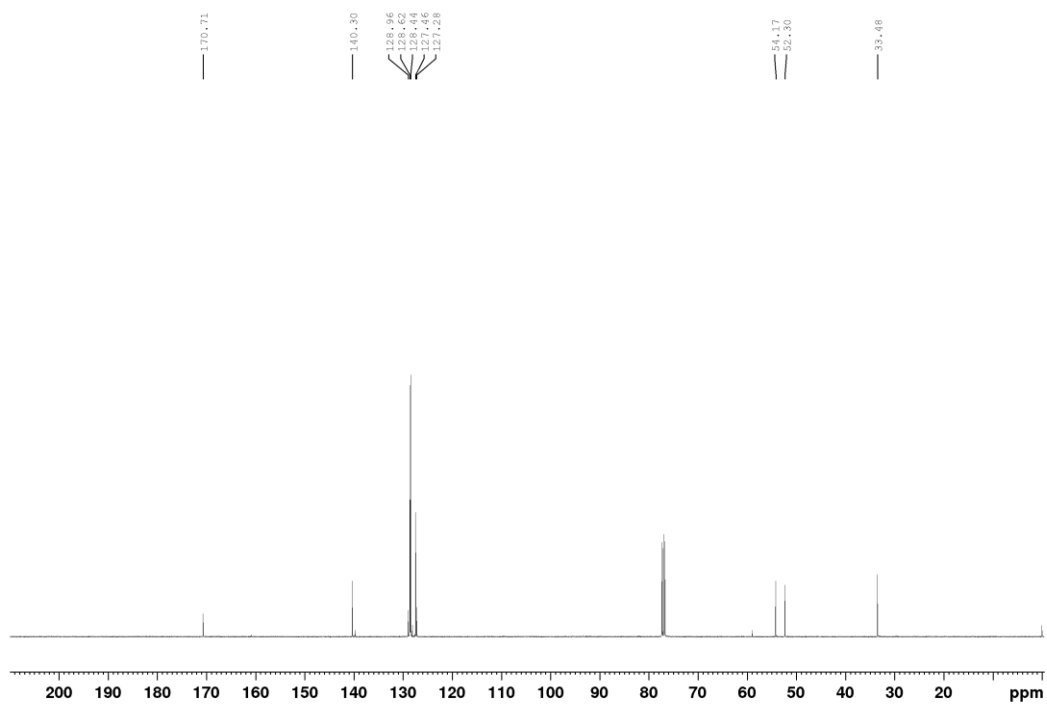
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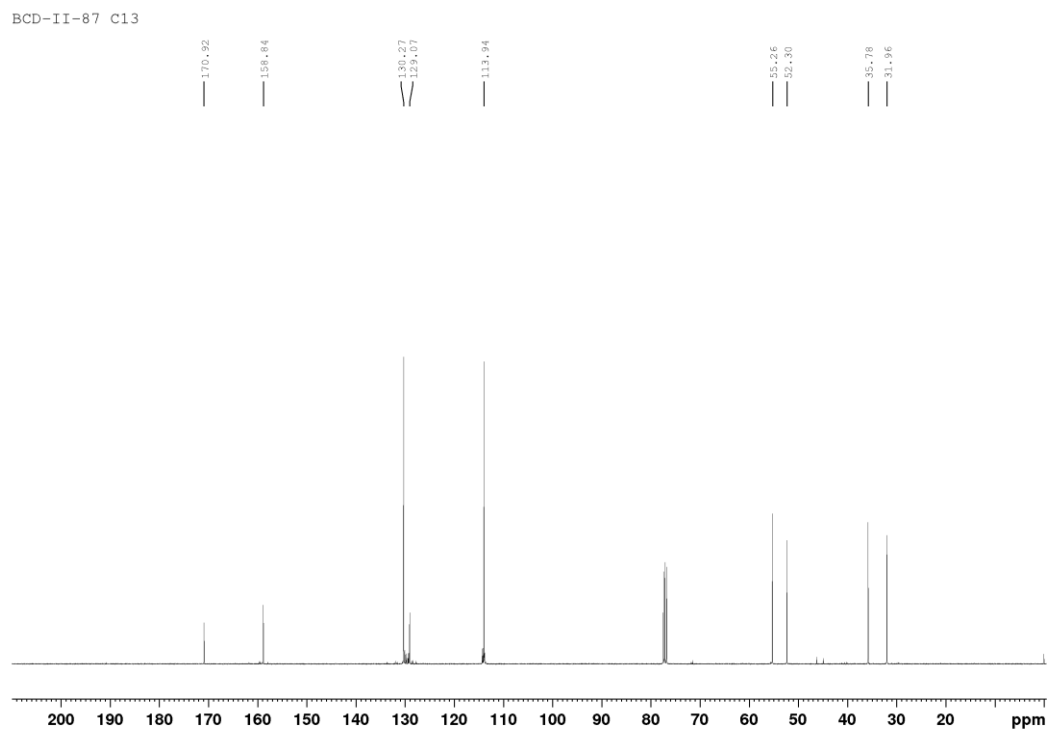
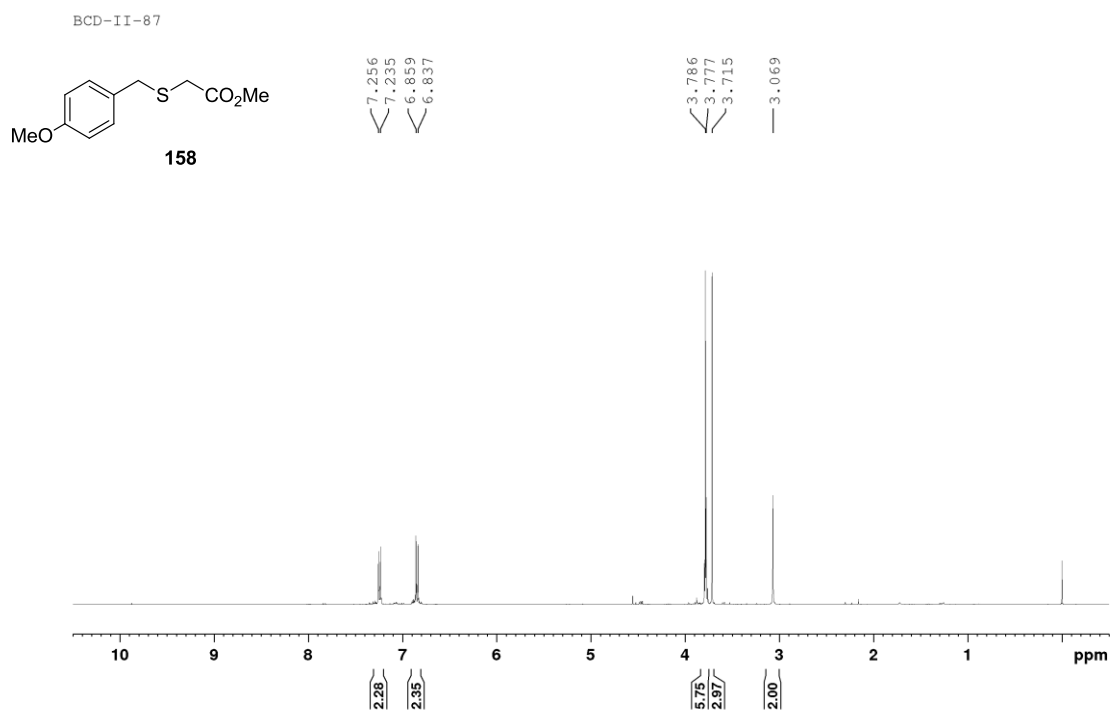


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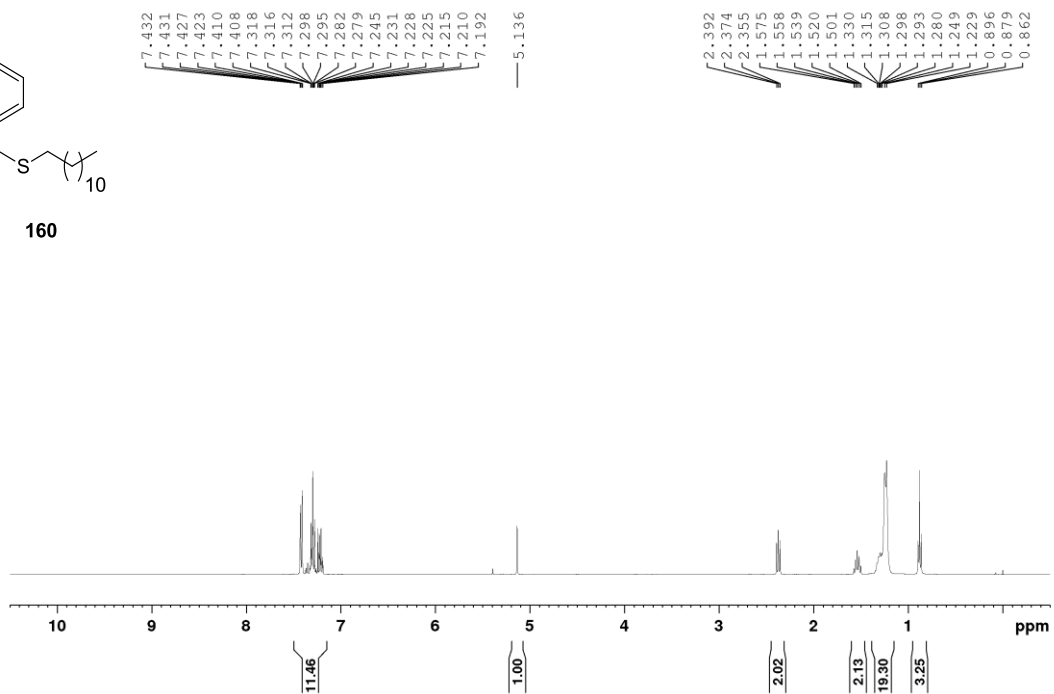
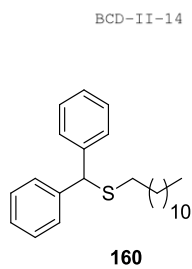


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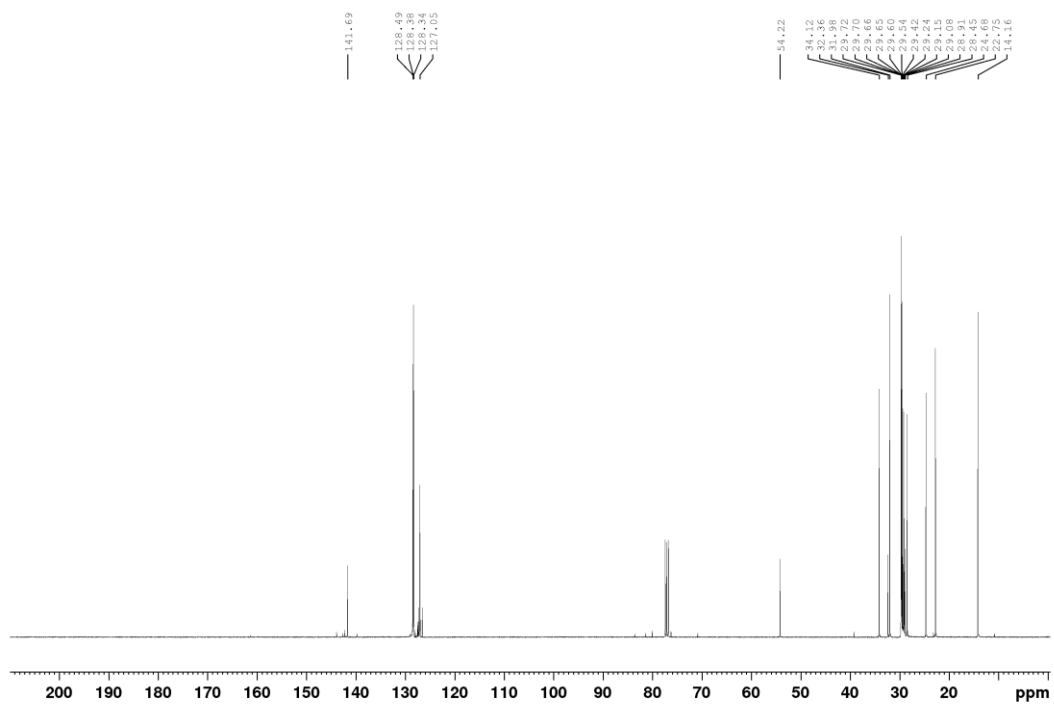




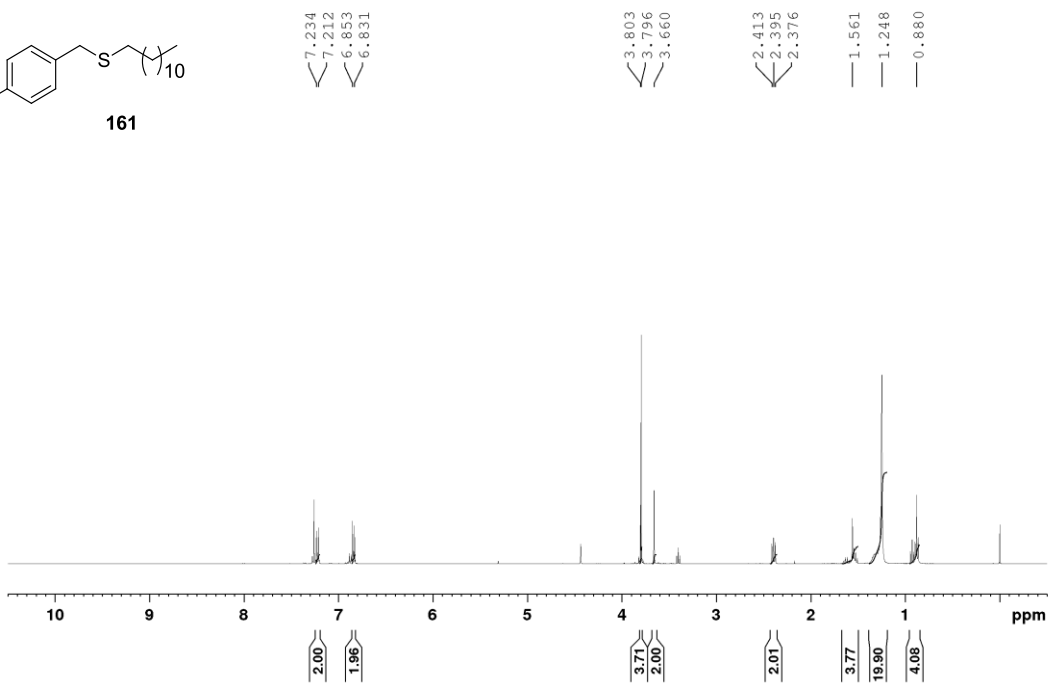
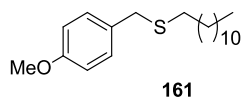




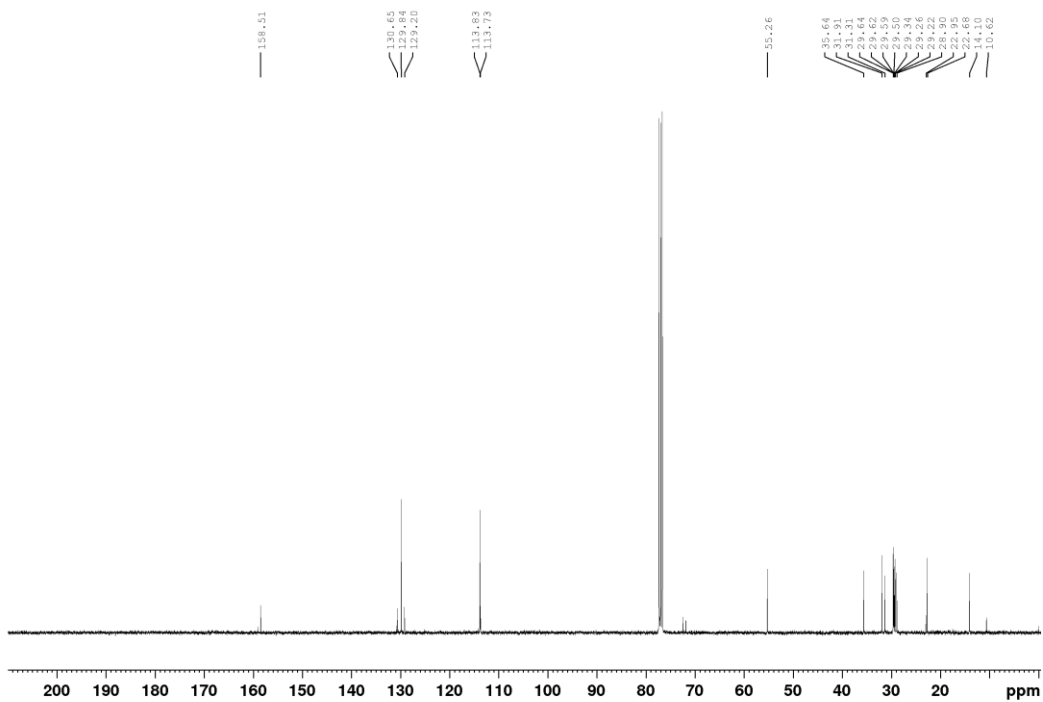
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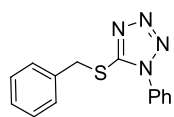
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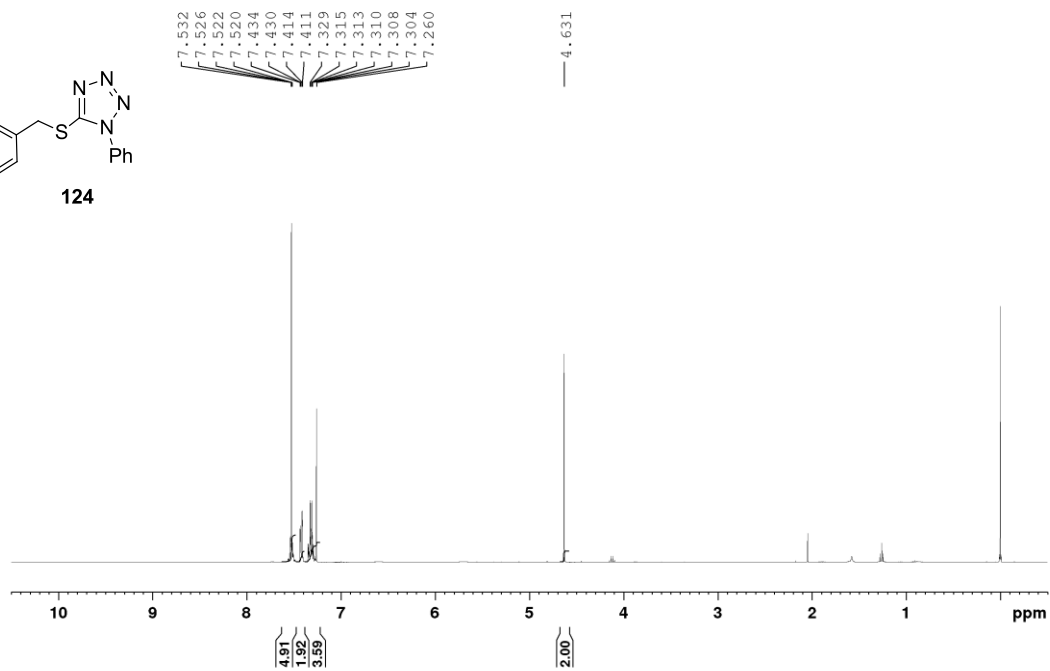
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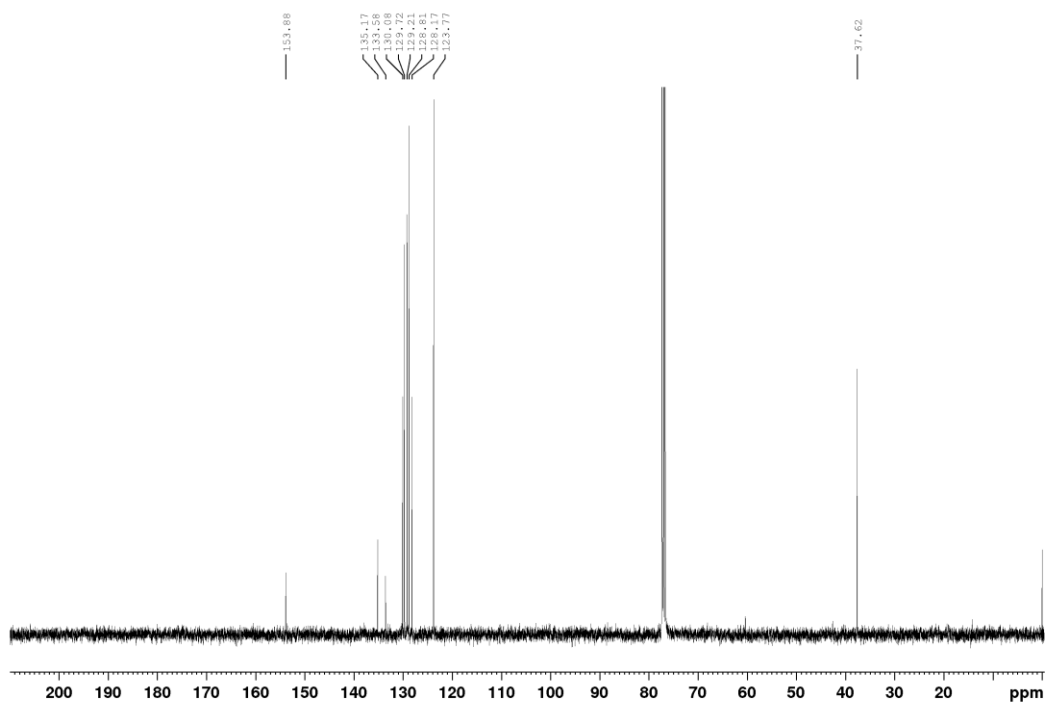
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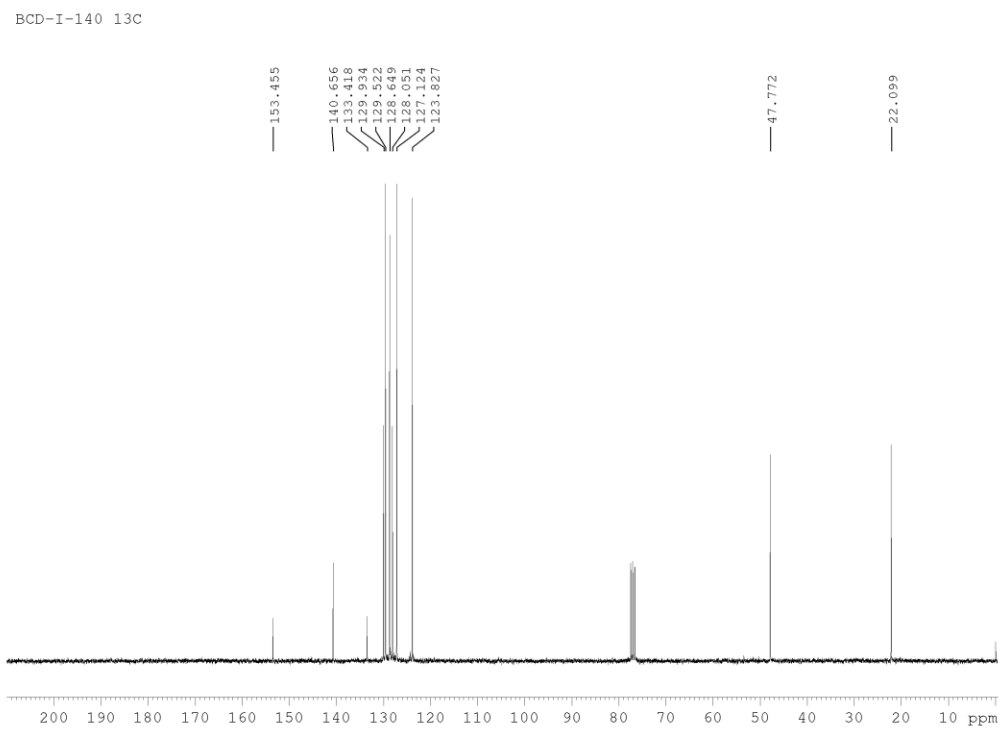
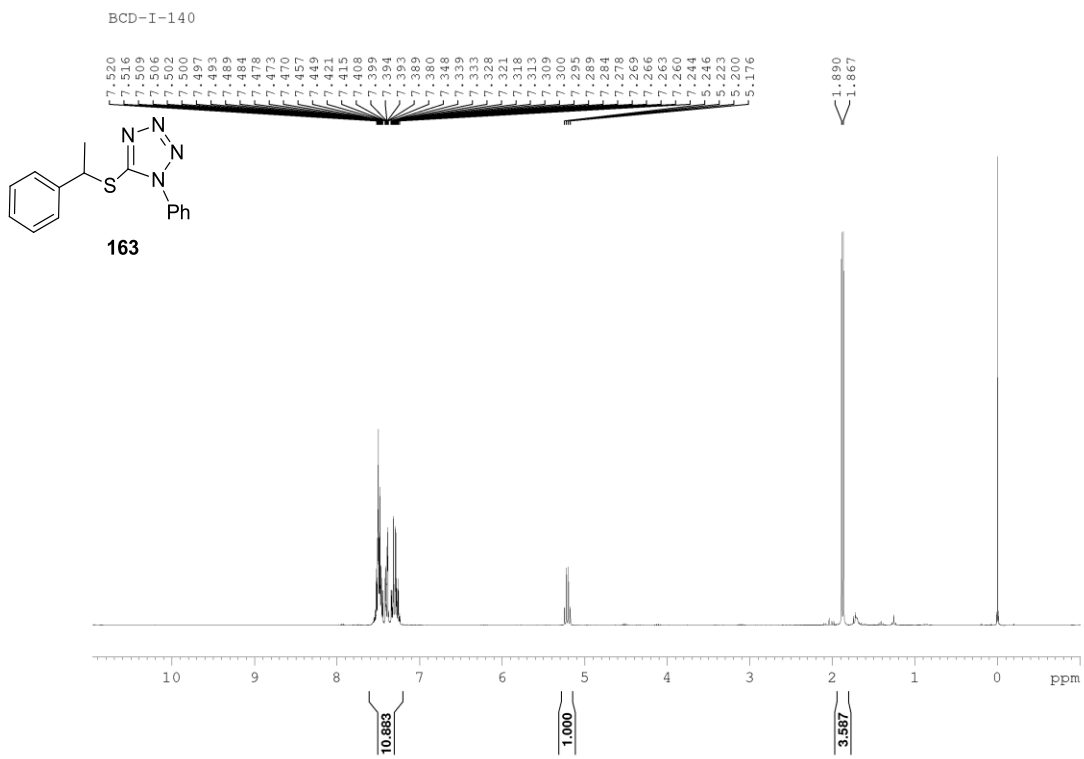


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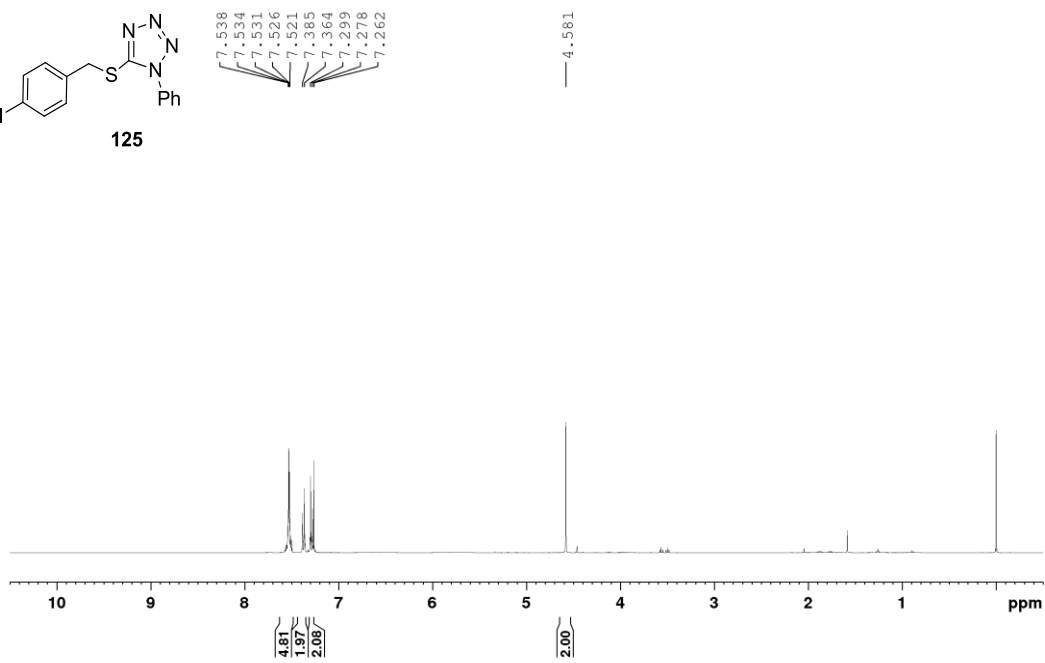
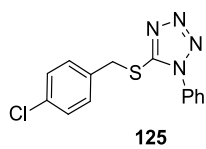


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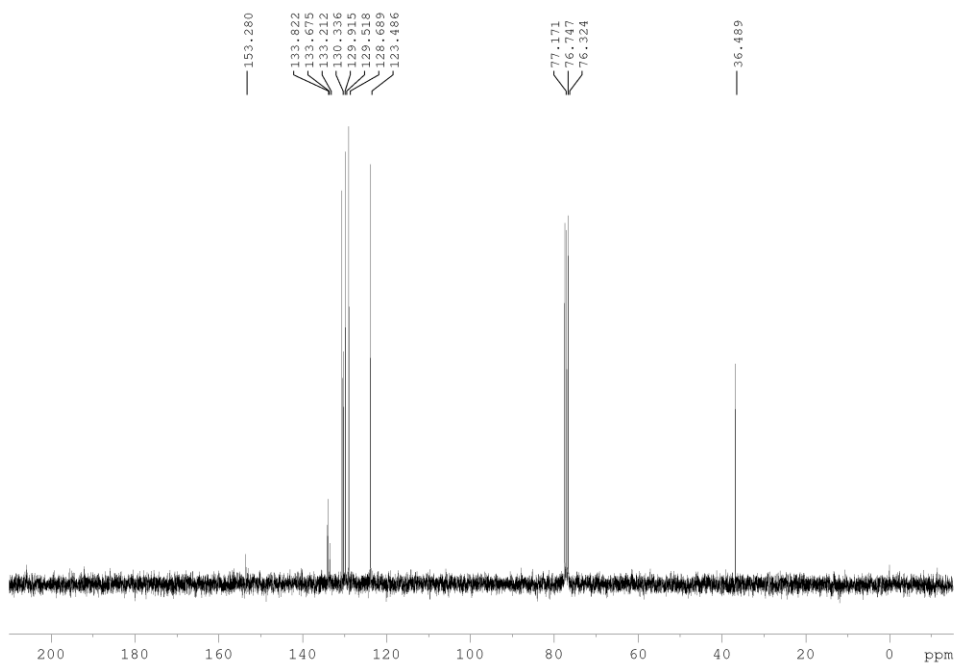


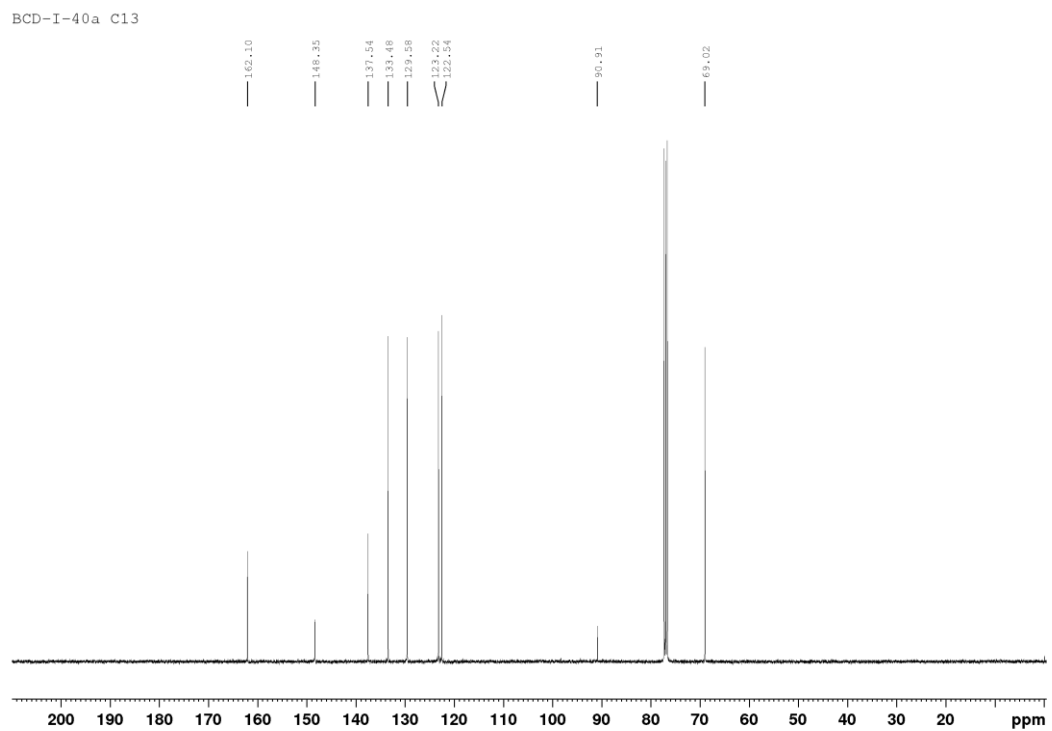
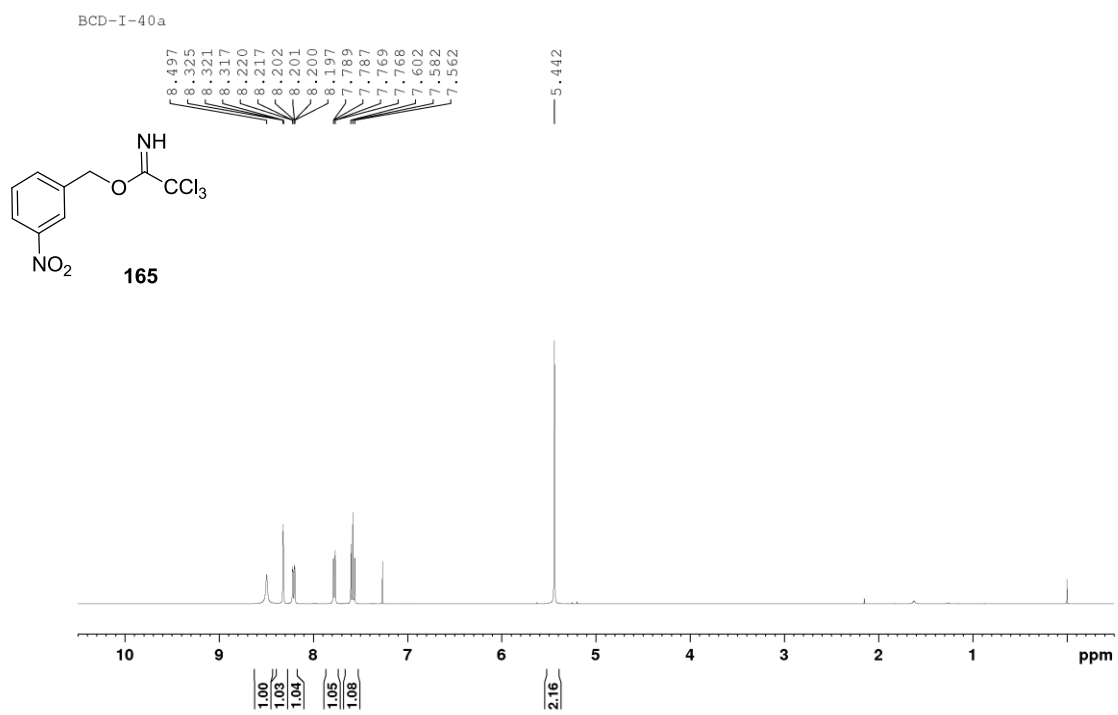


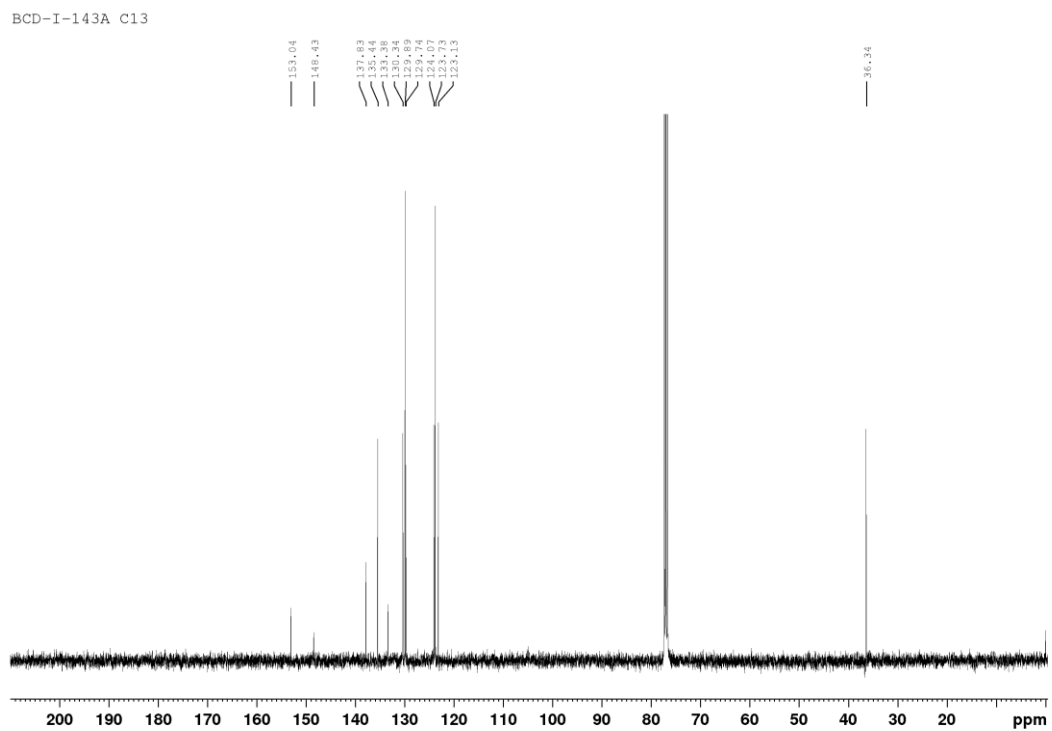
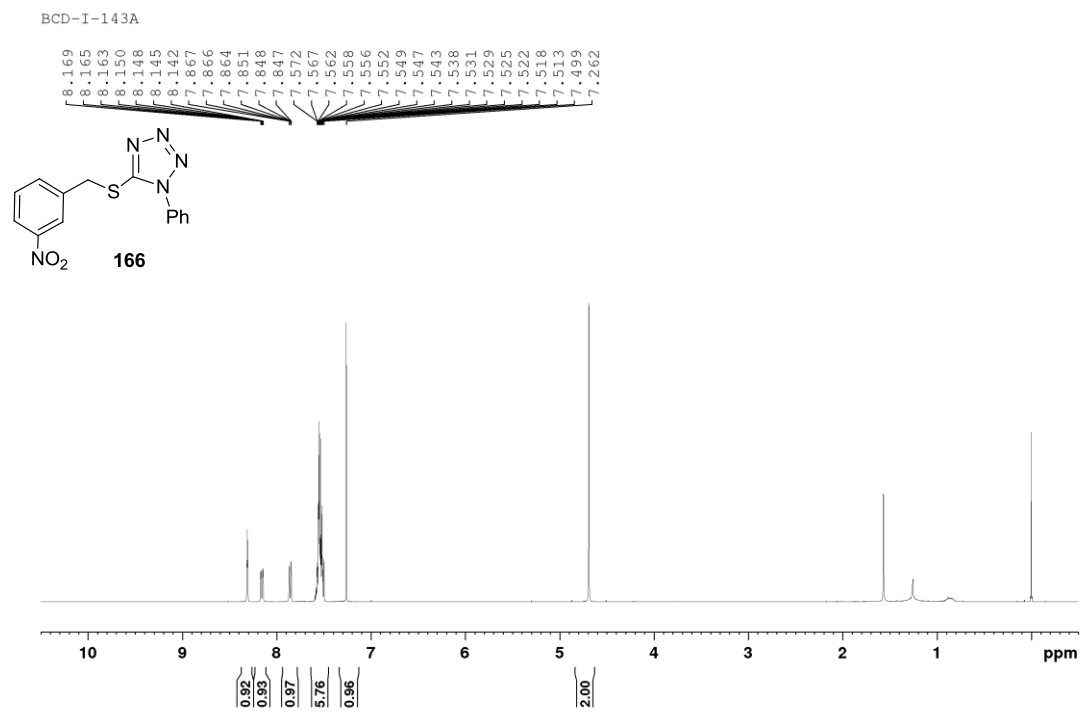
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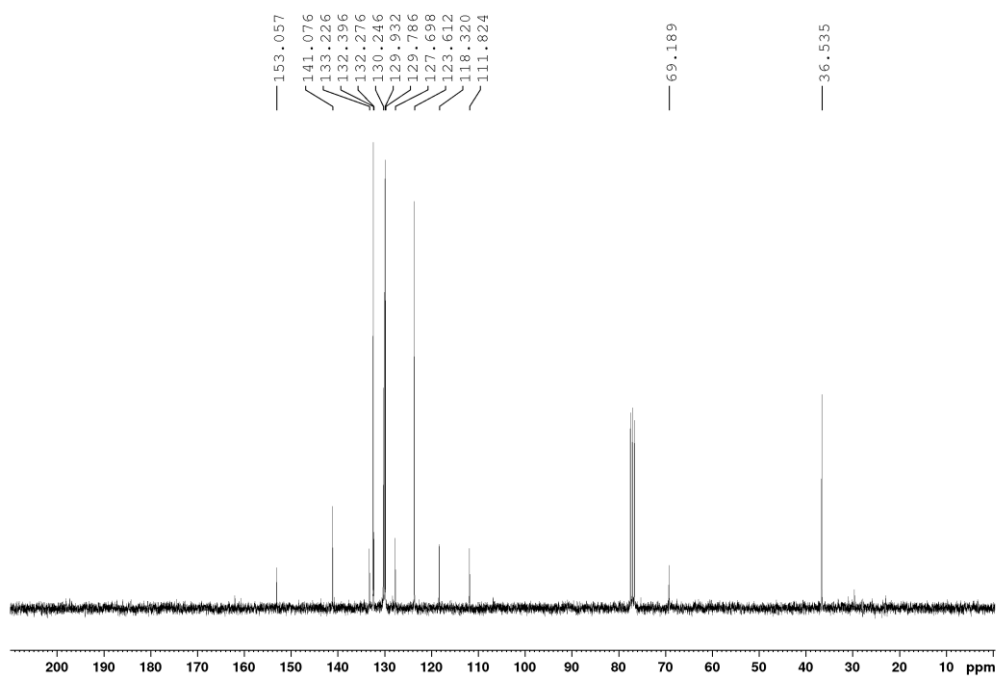
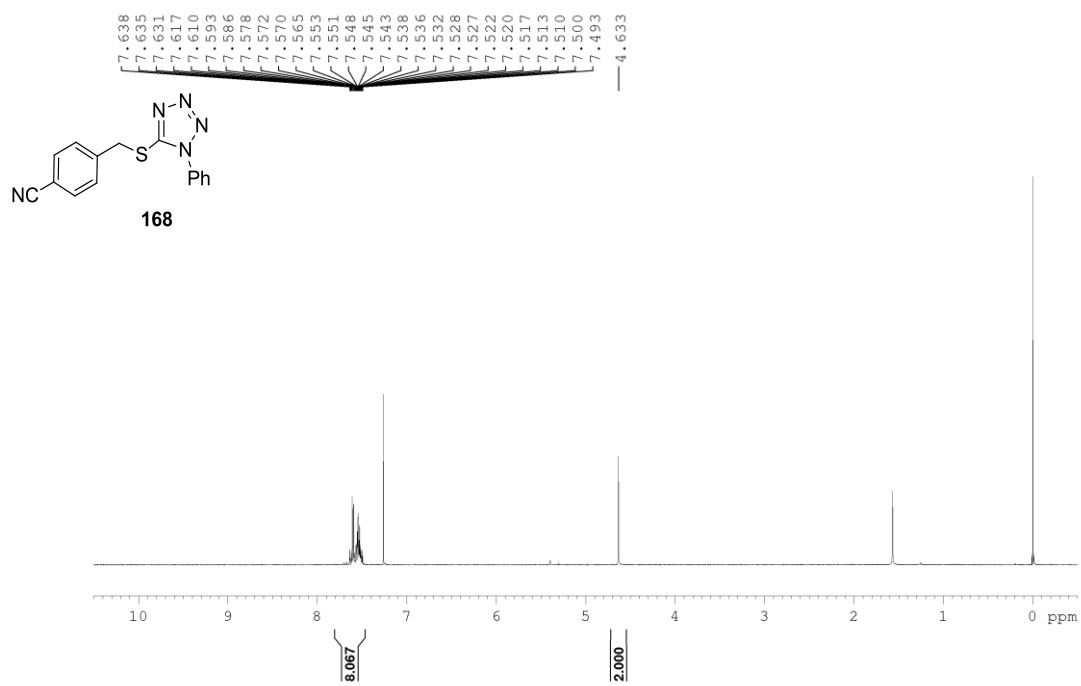


3CD-I-142 13C

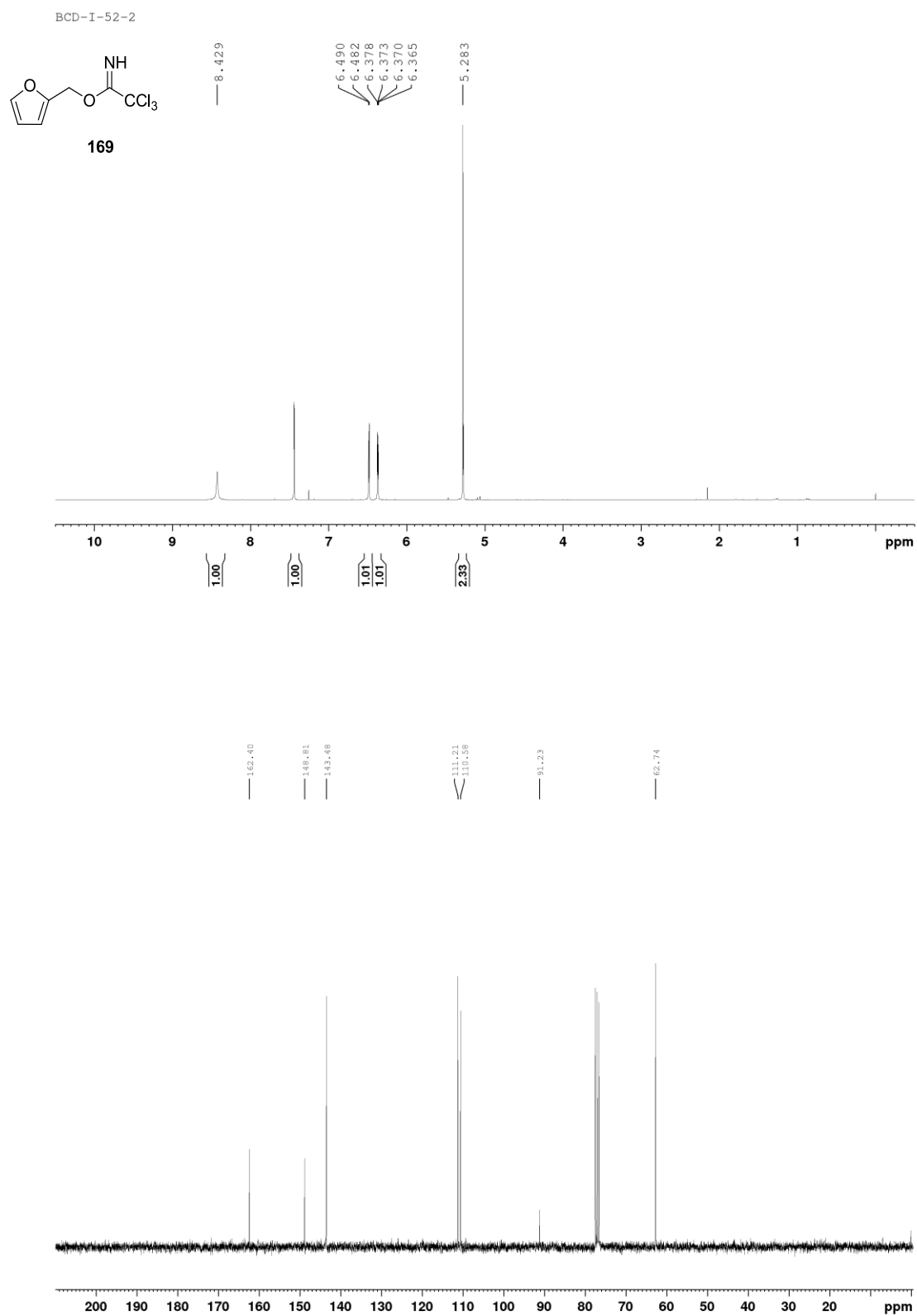




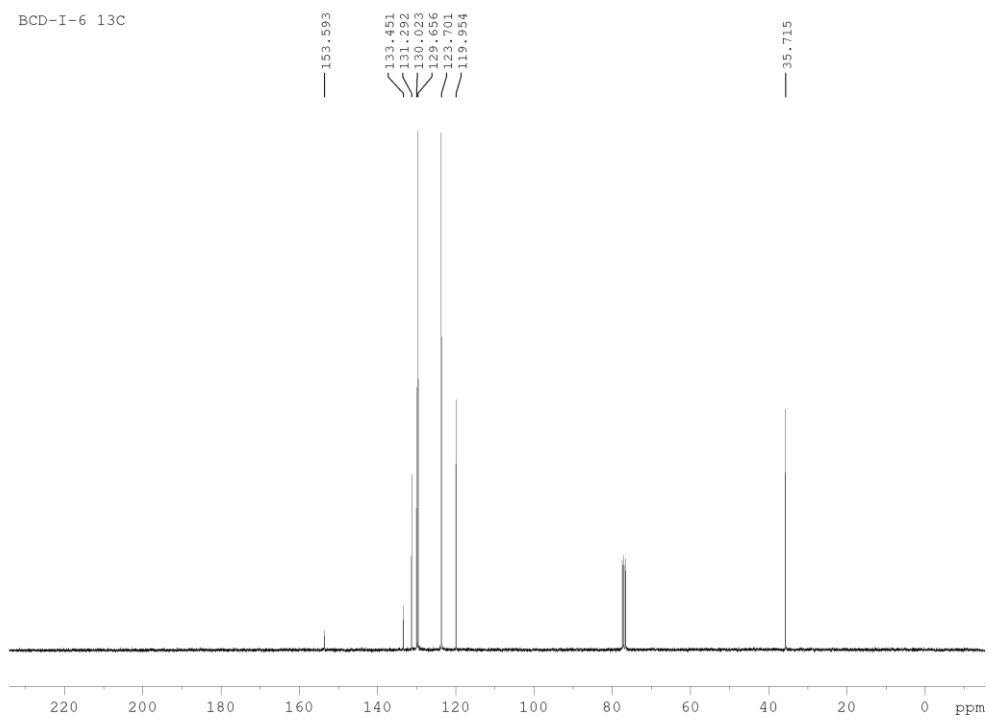
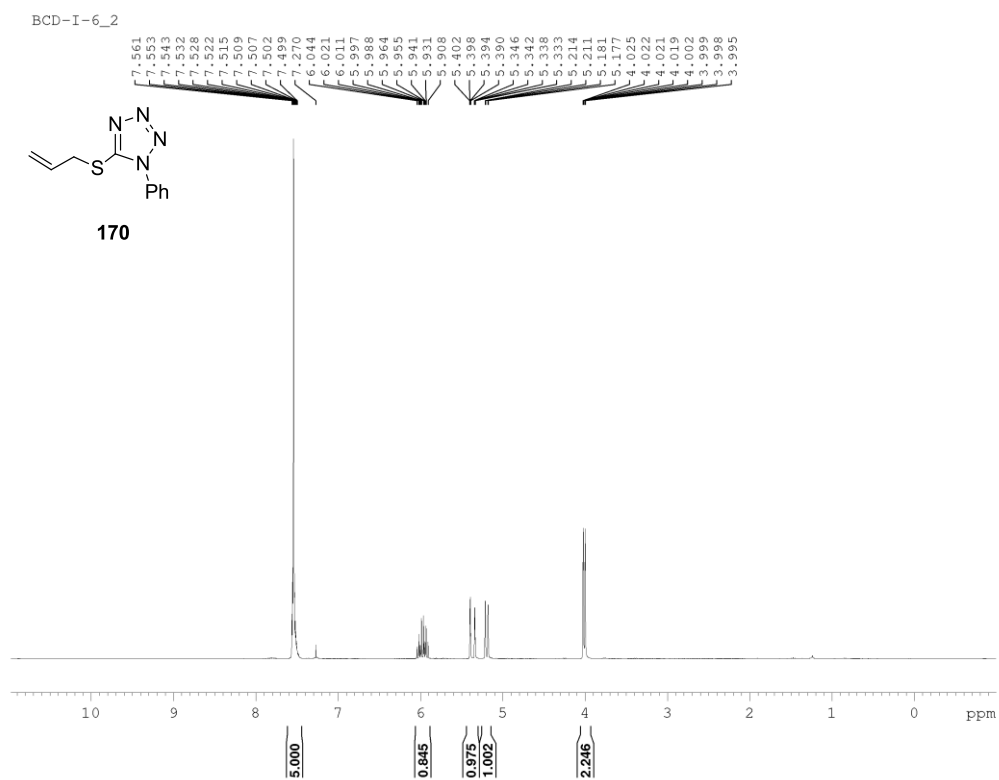




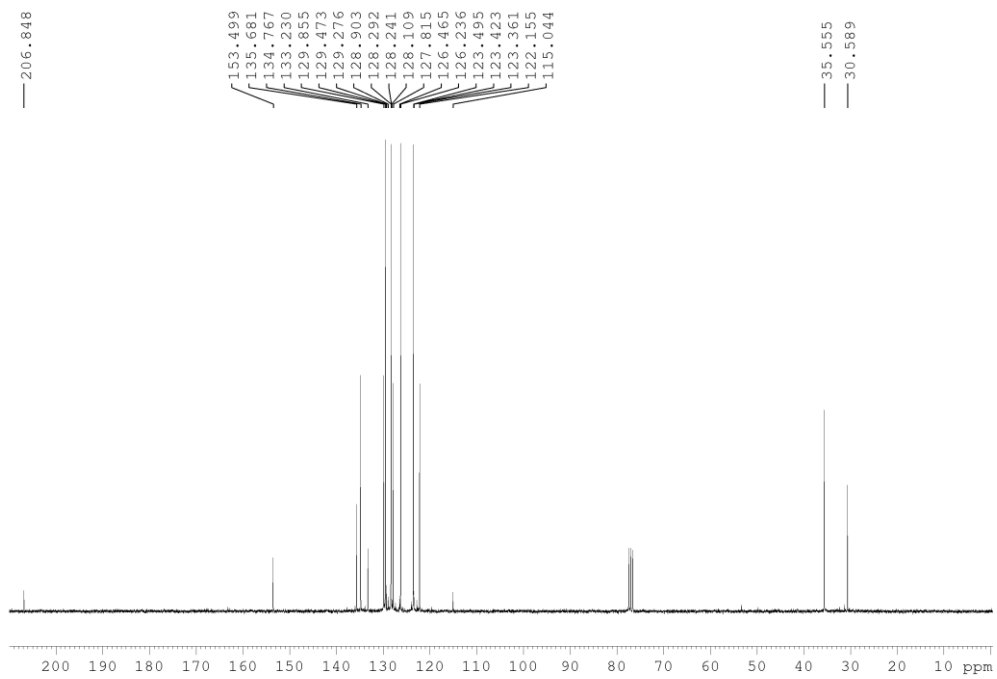
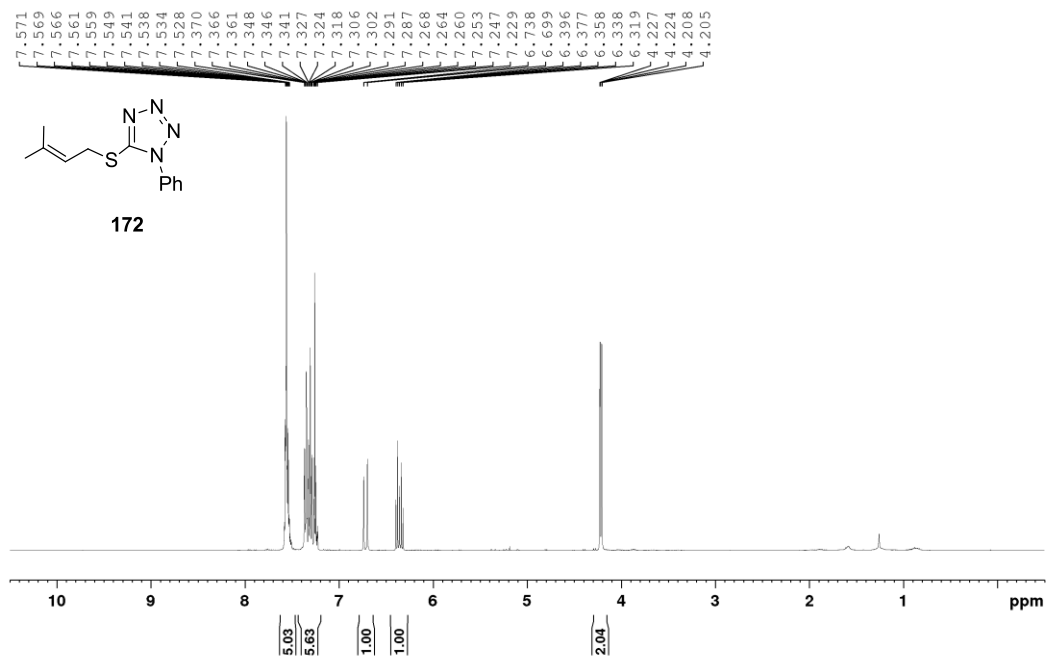


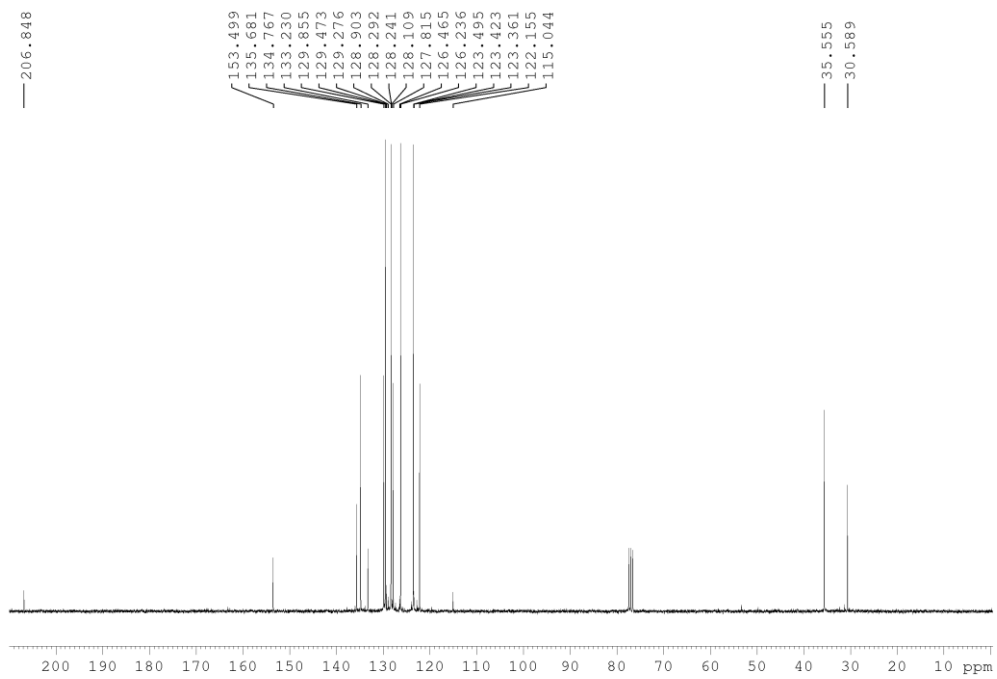
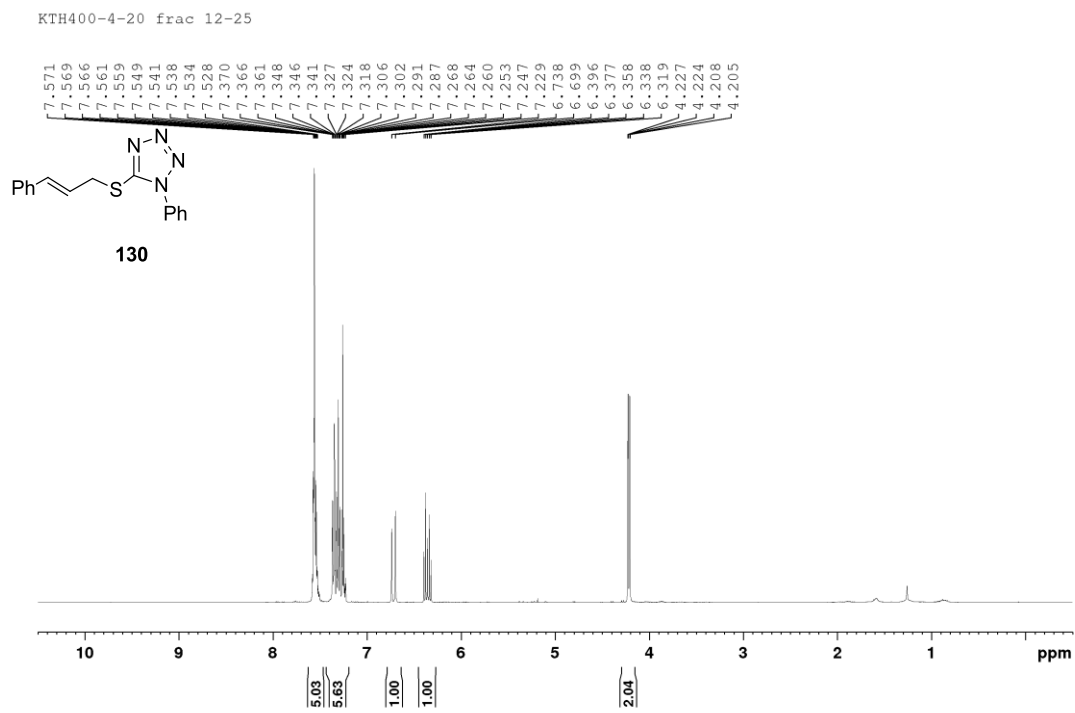


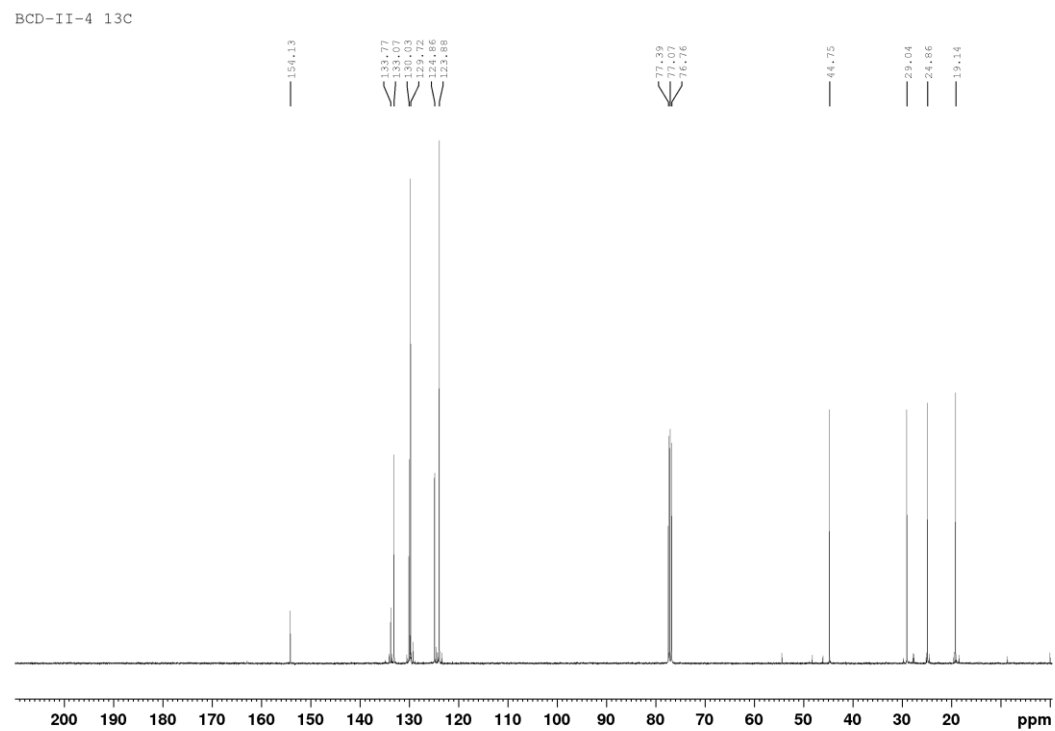
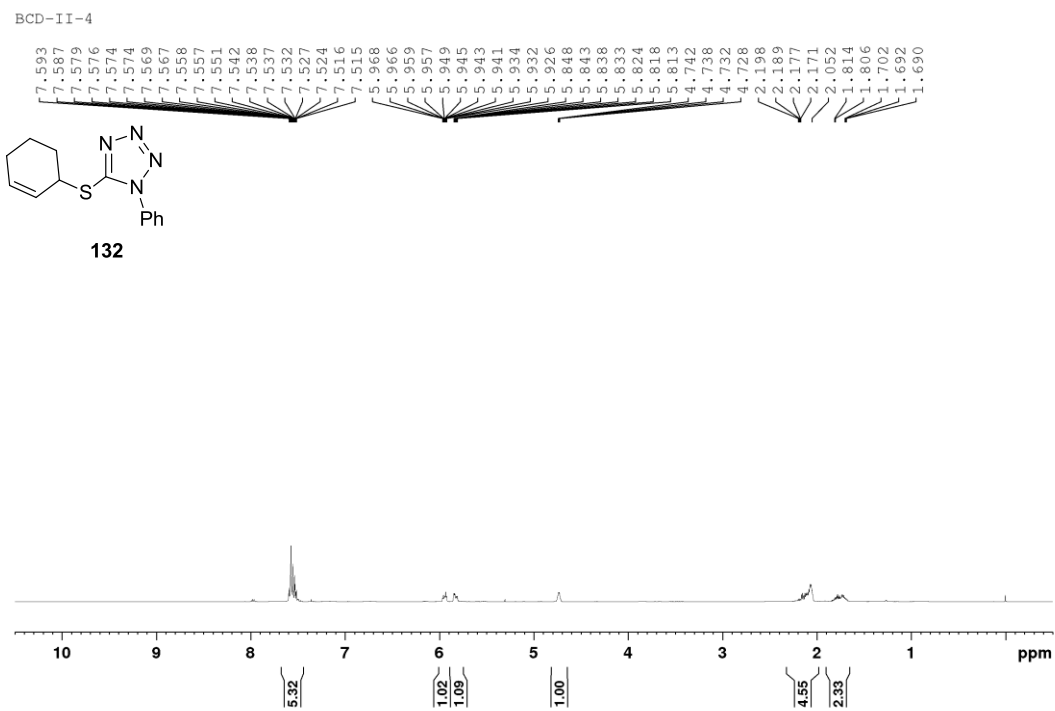


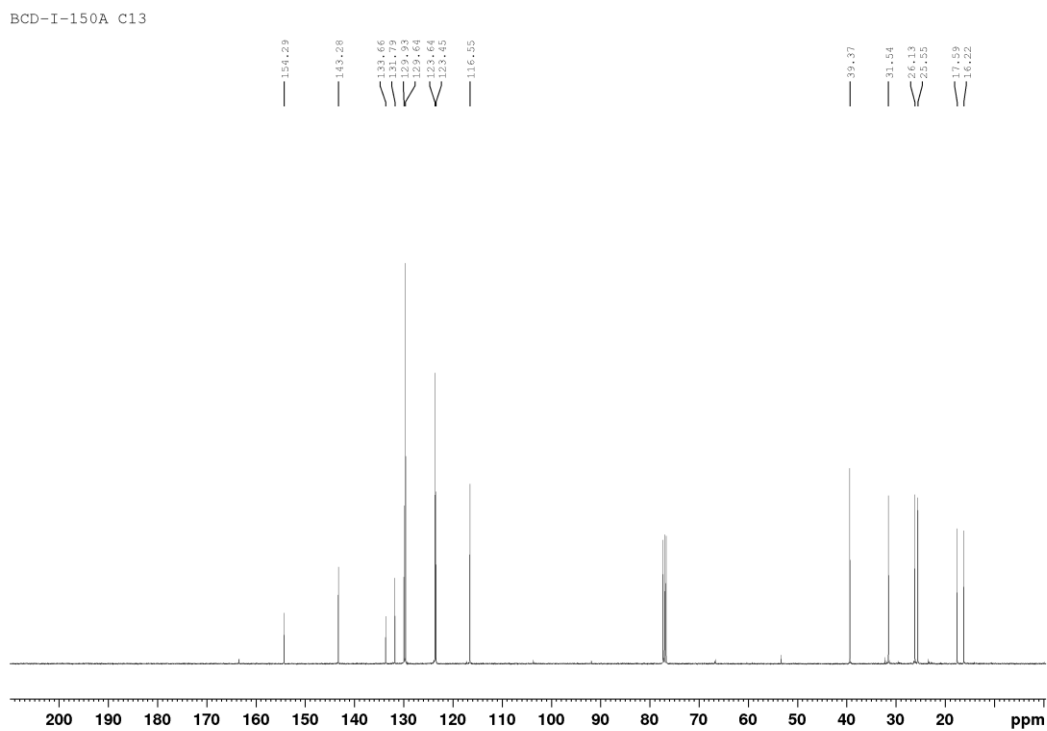
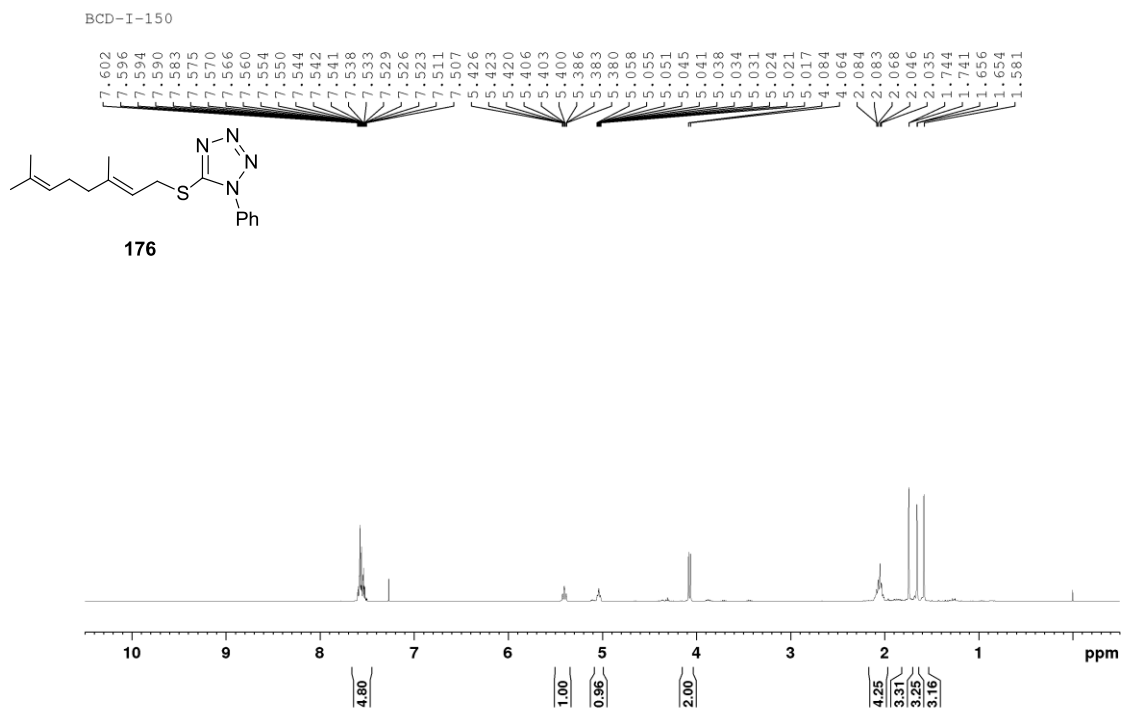


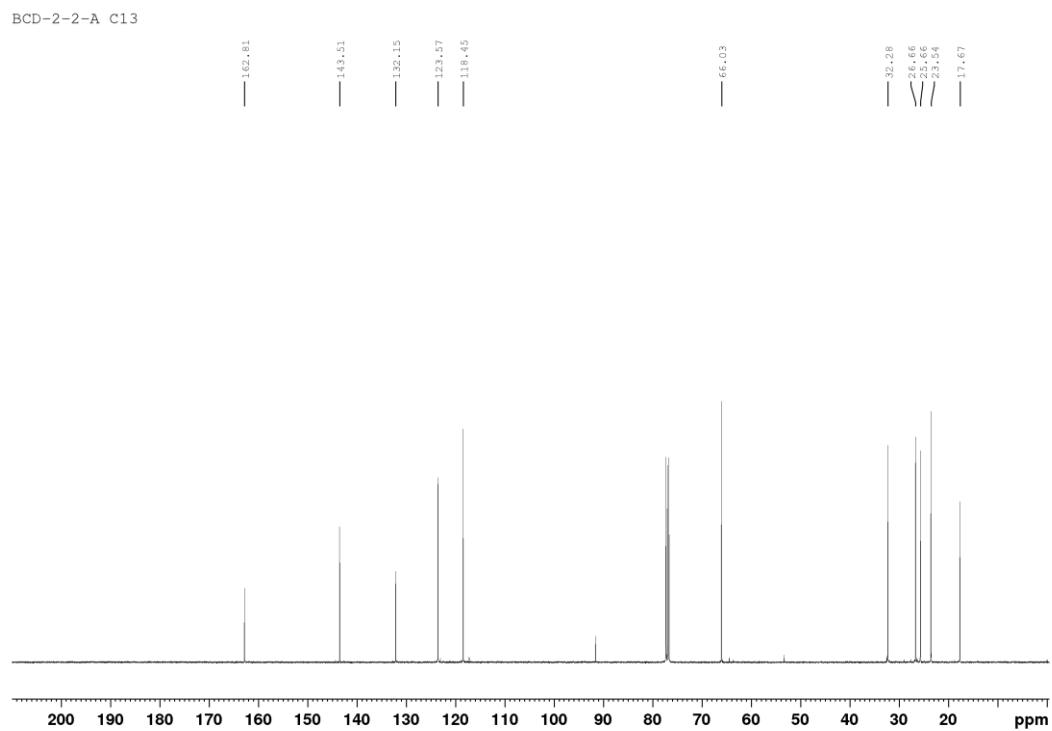
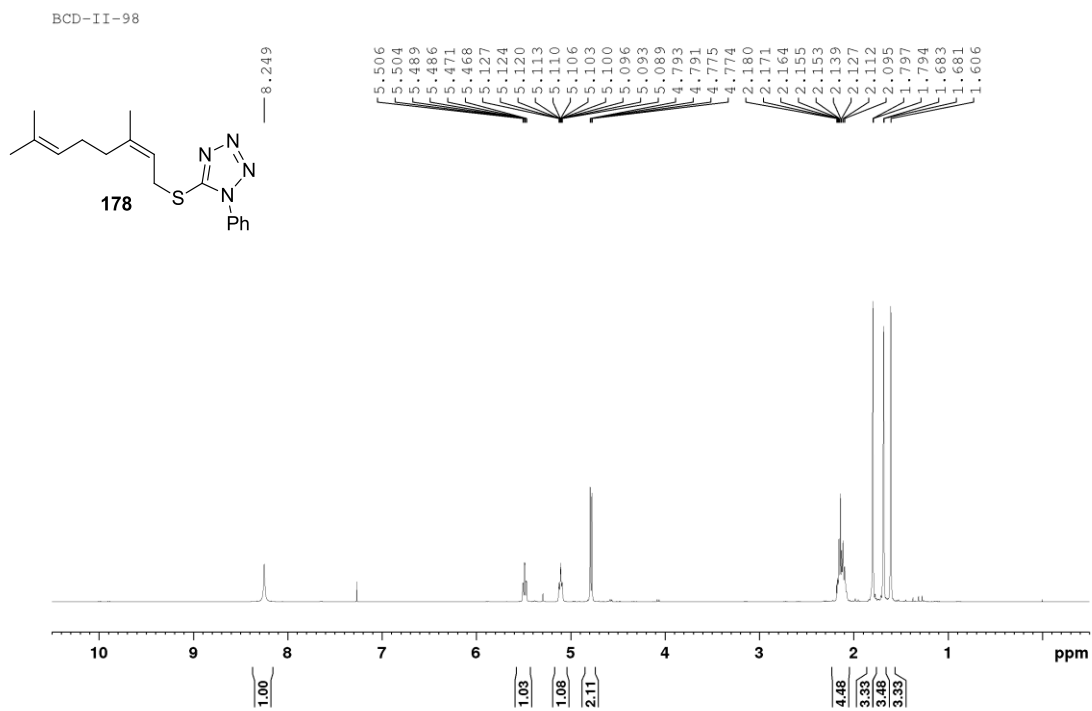
KTH400-4-20 frac 12-25





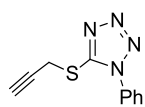




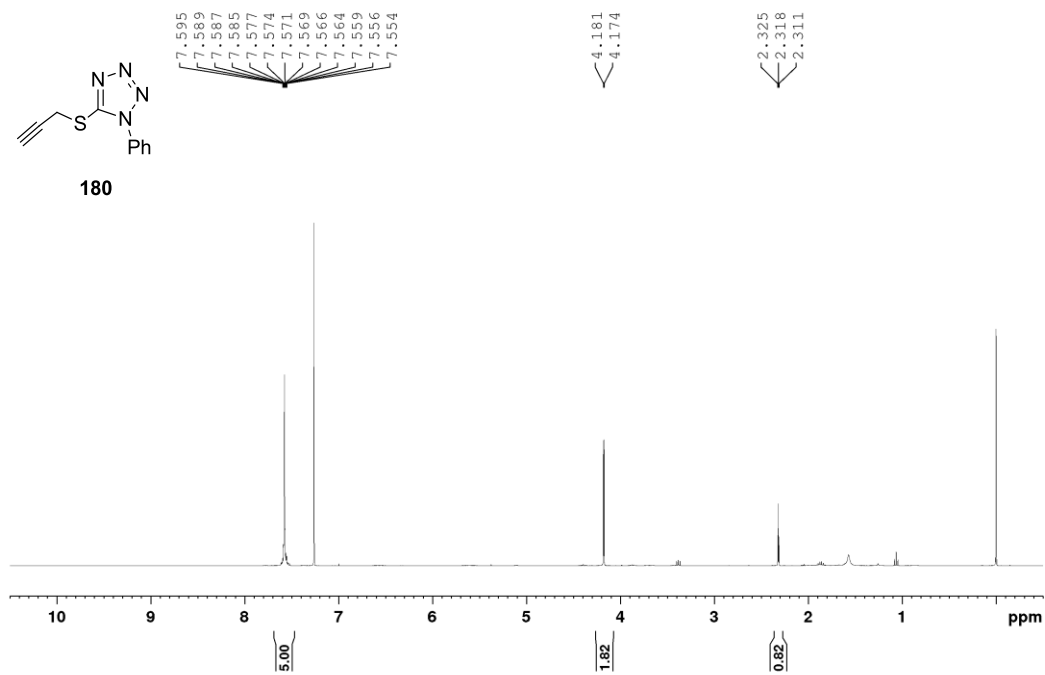




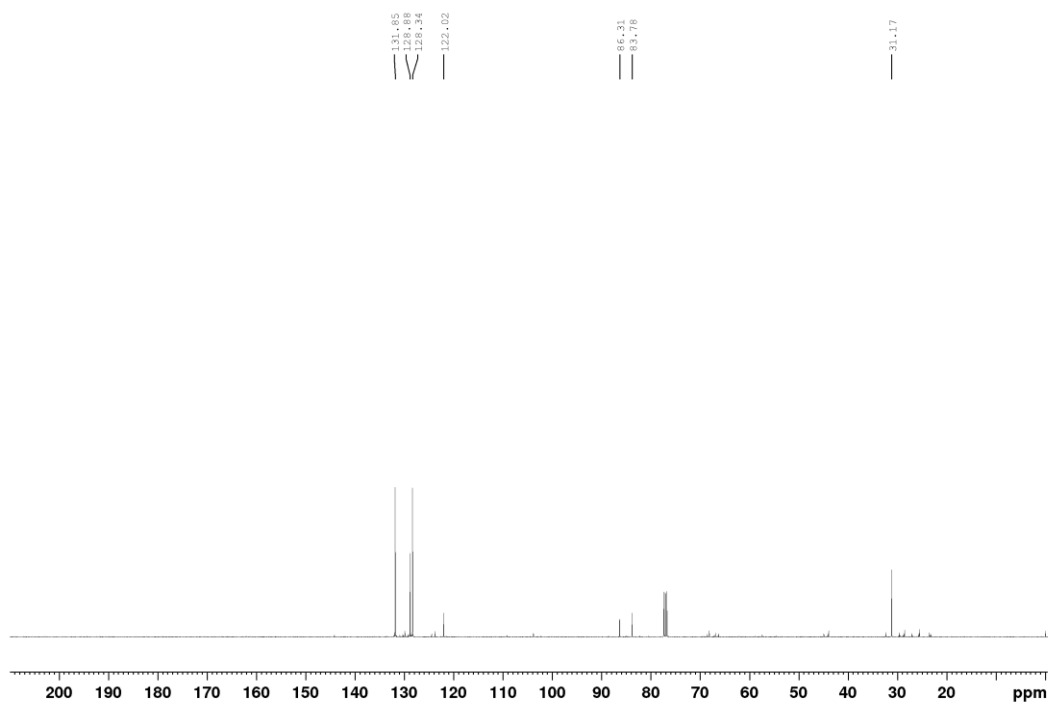
BCD-II-5

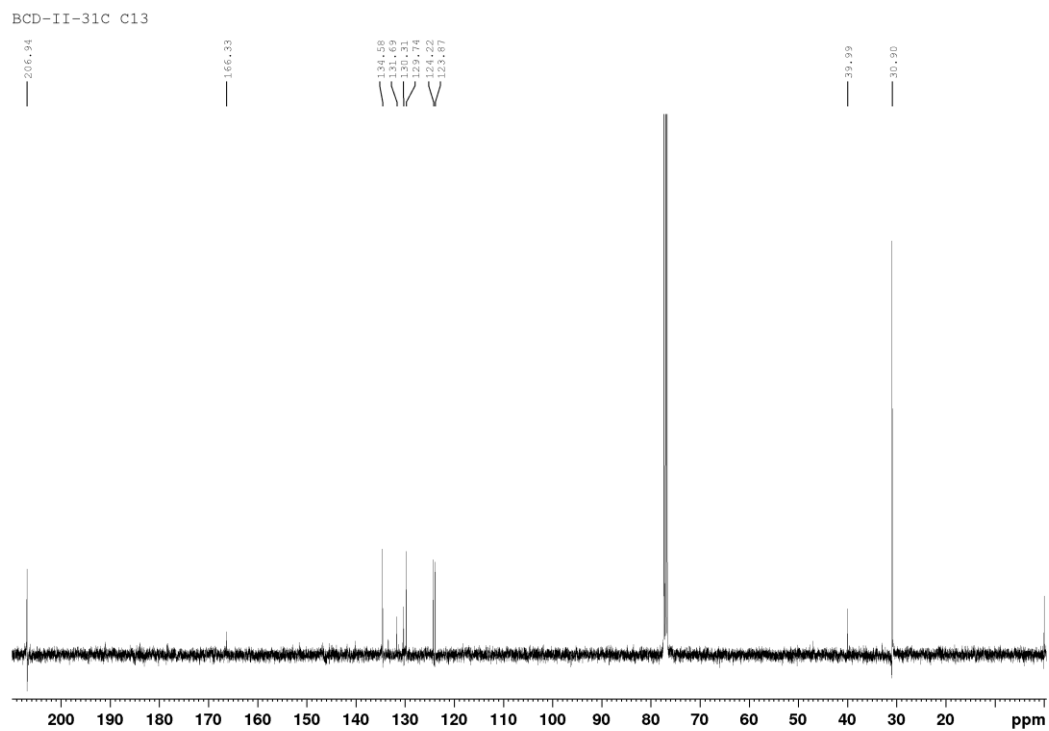
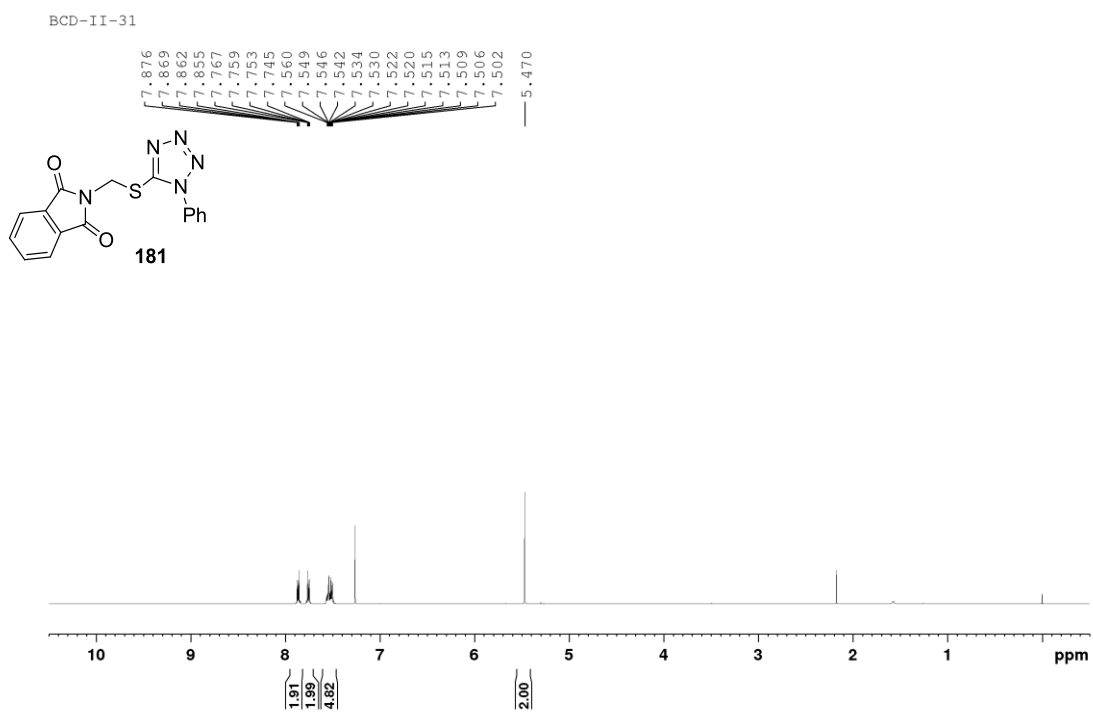


180

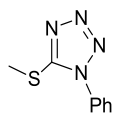
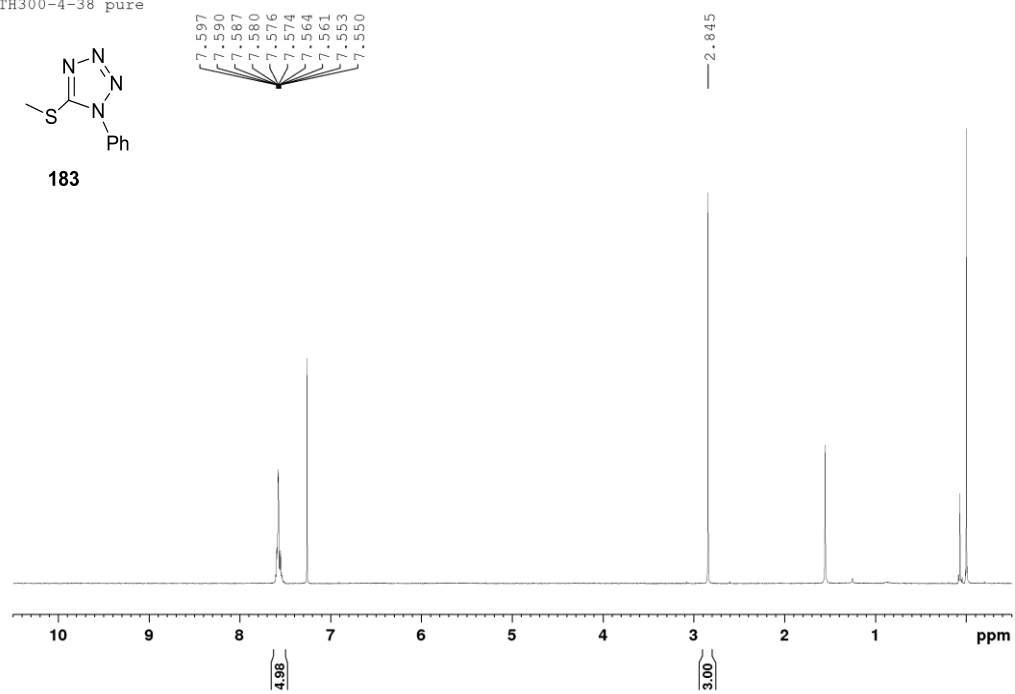


BCD-II-5 C13

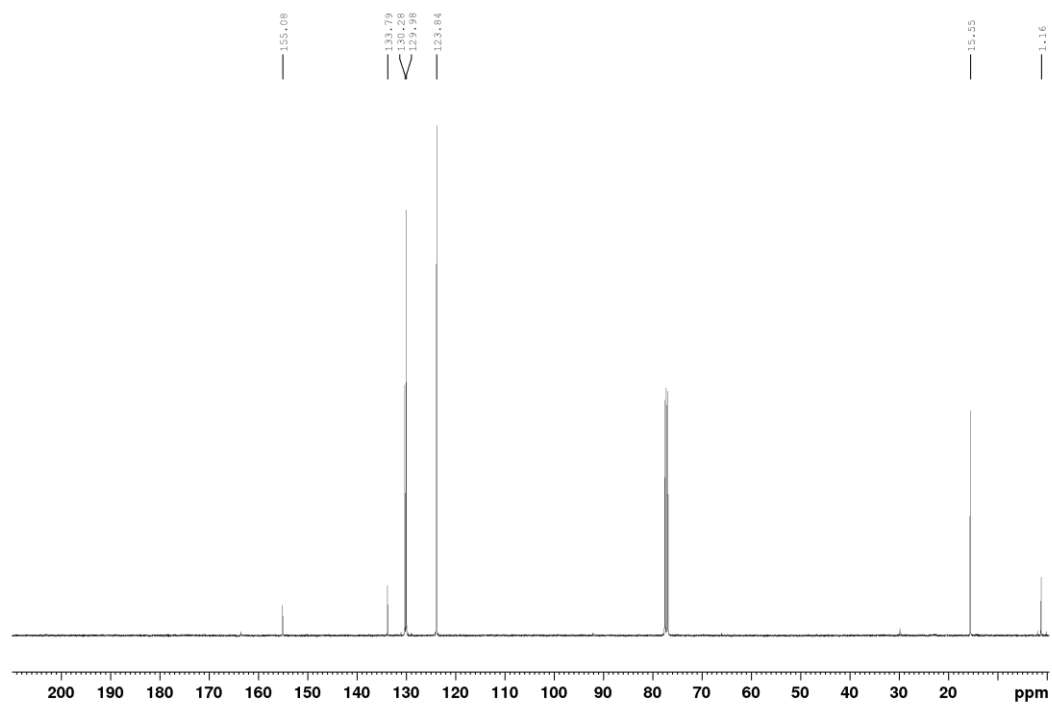




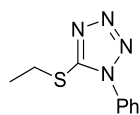
KTH300-4-38 pure

**183**

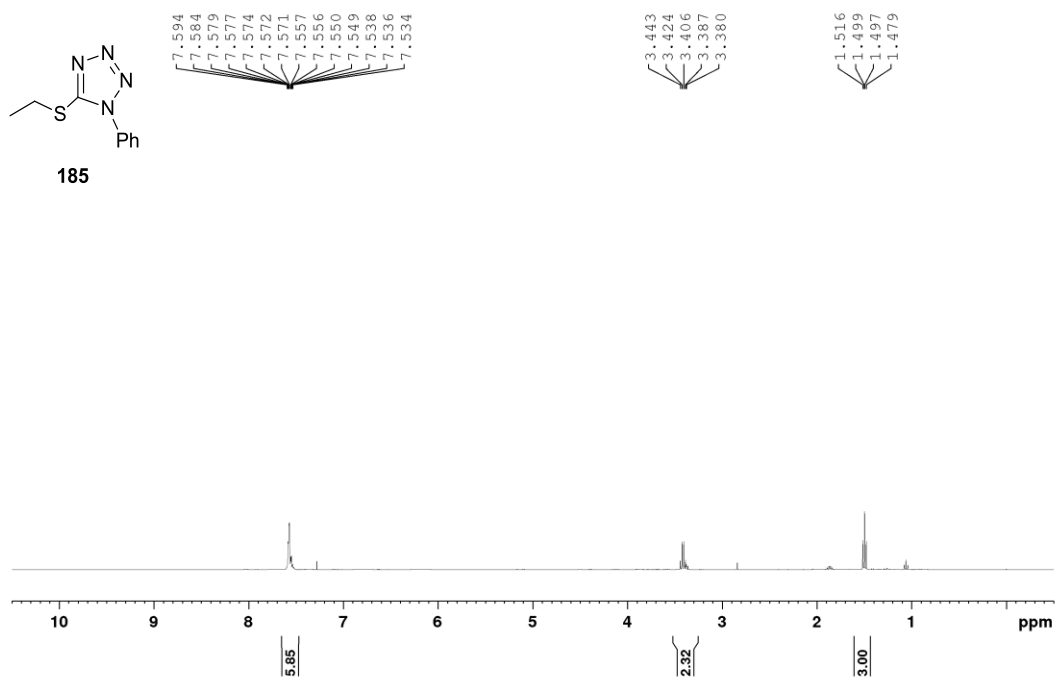
KTH400-4-38 13C



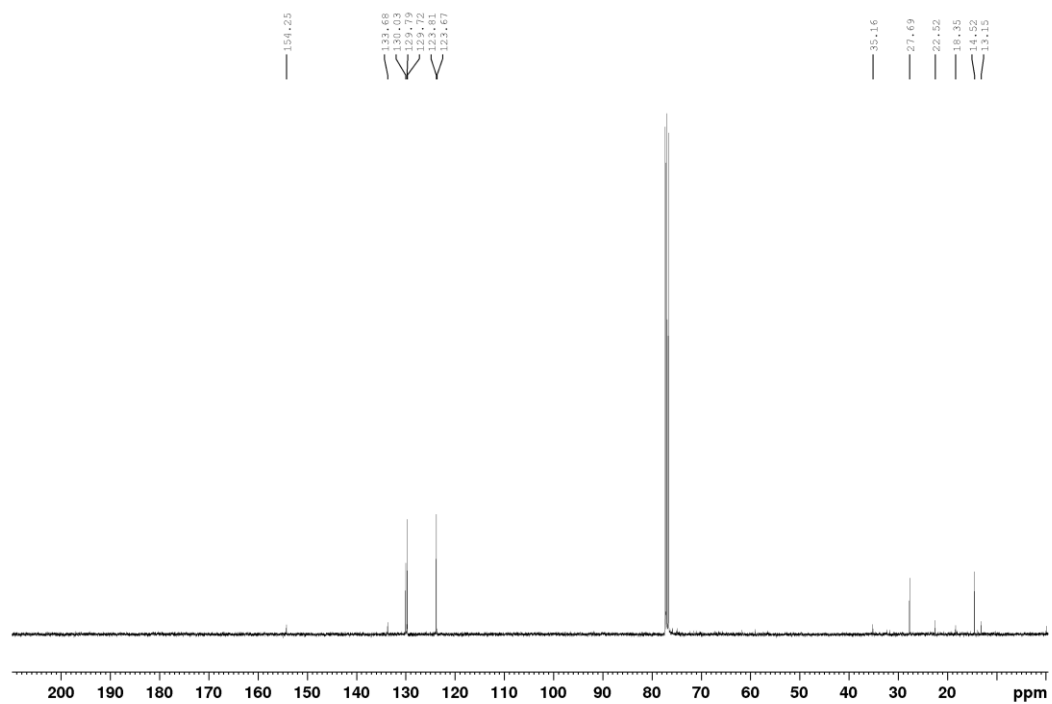
BCD-II-8



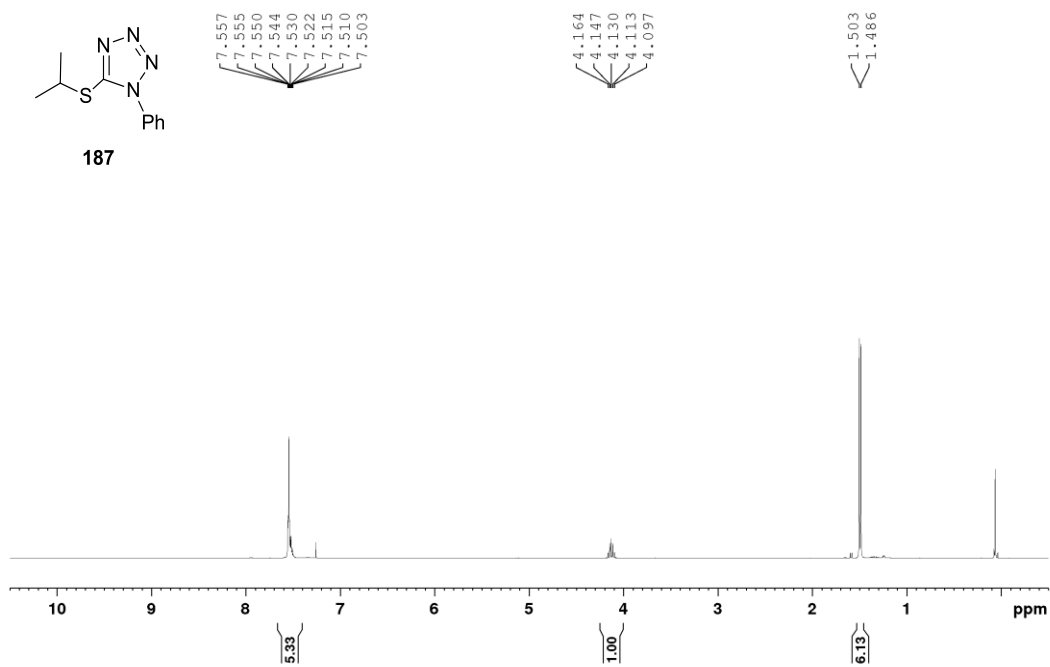
185



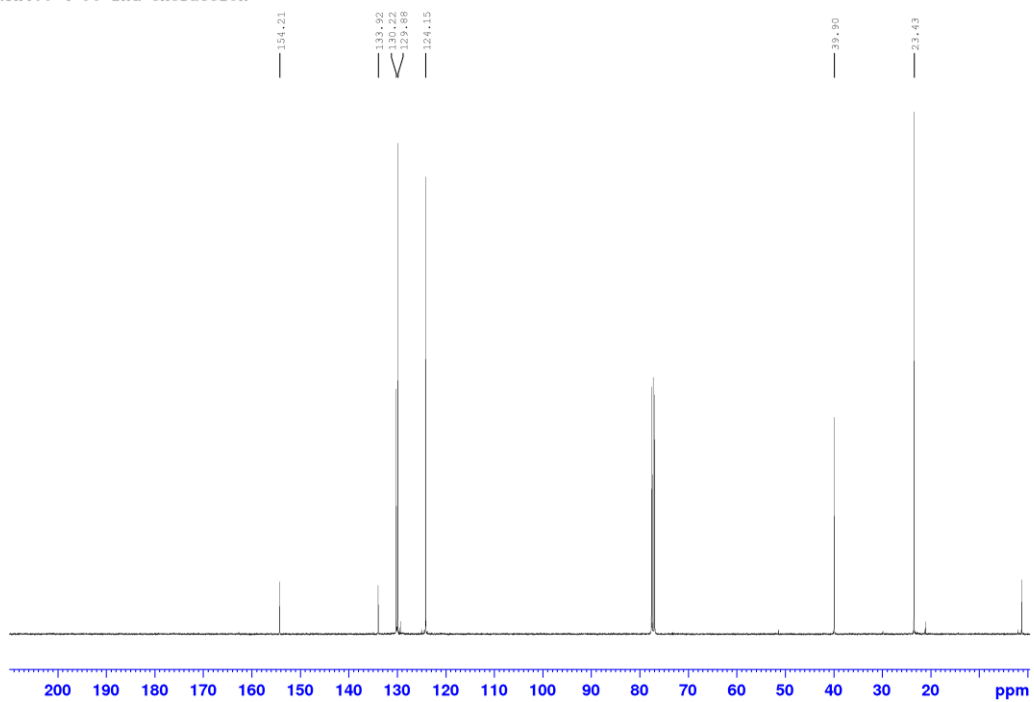
BCD-II-8 C13



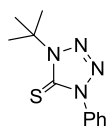
KTH400-4-98 2nd extraction



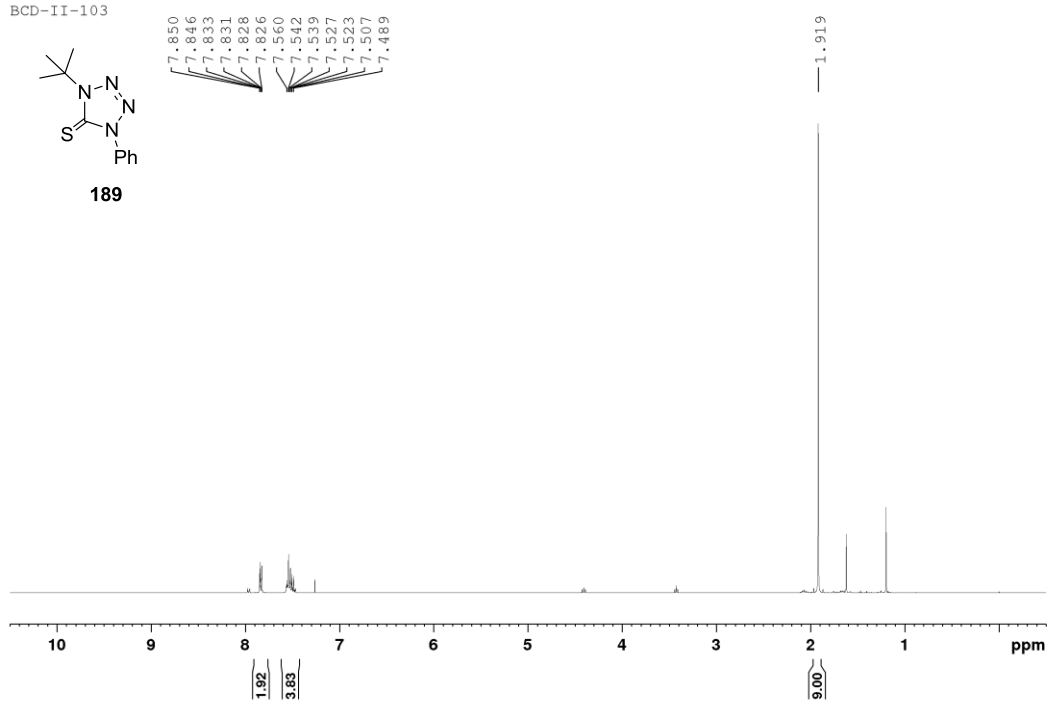
KTH400-4-98 2nd extraction



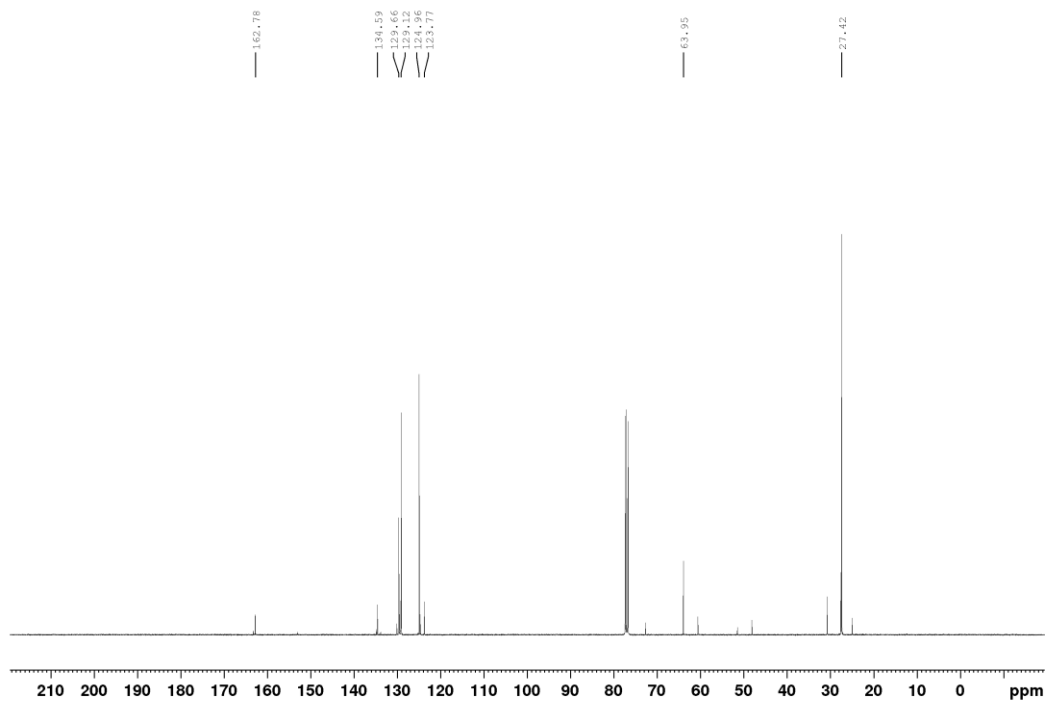
BCD-II-103



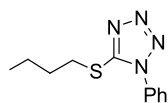
189



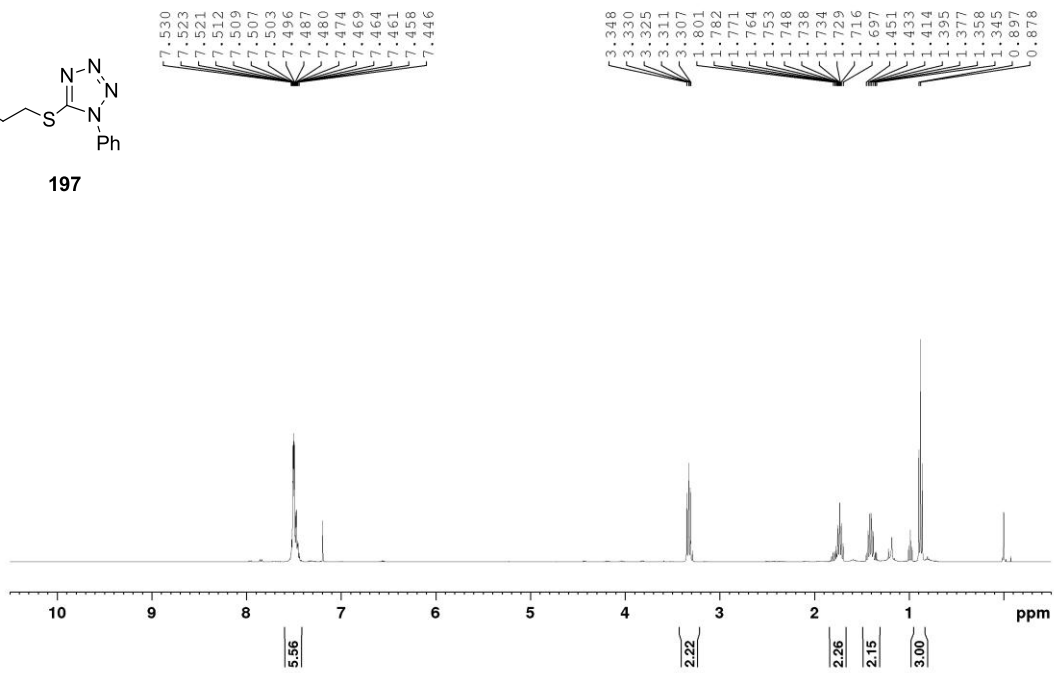
BCD-II-103 C13



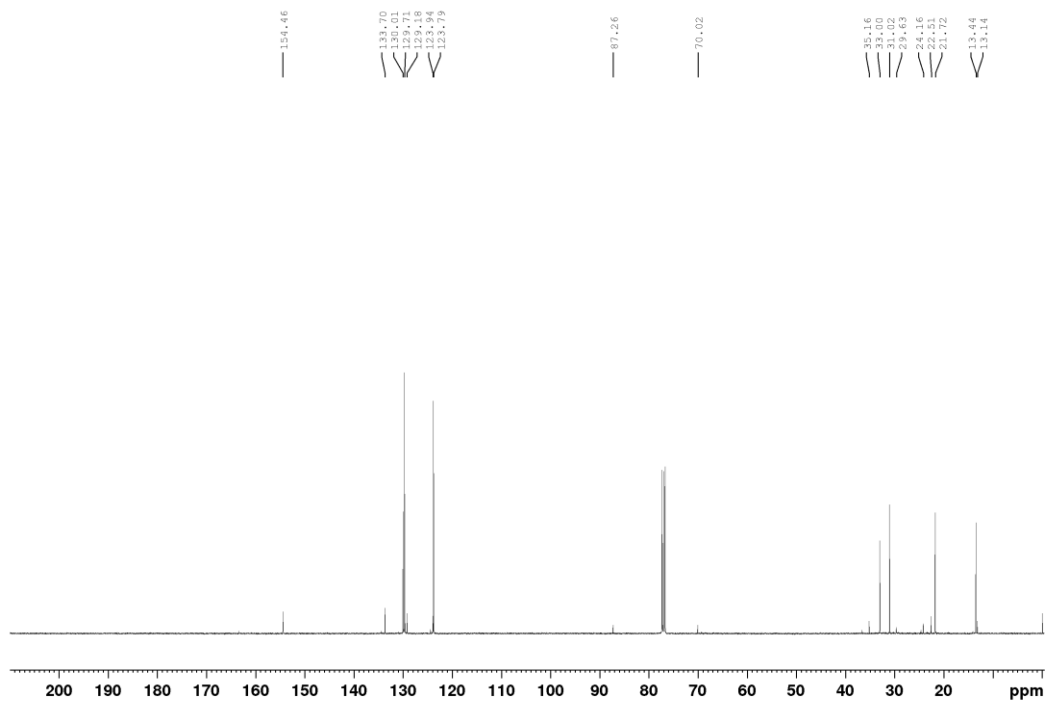
BCD-II-53



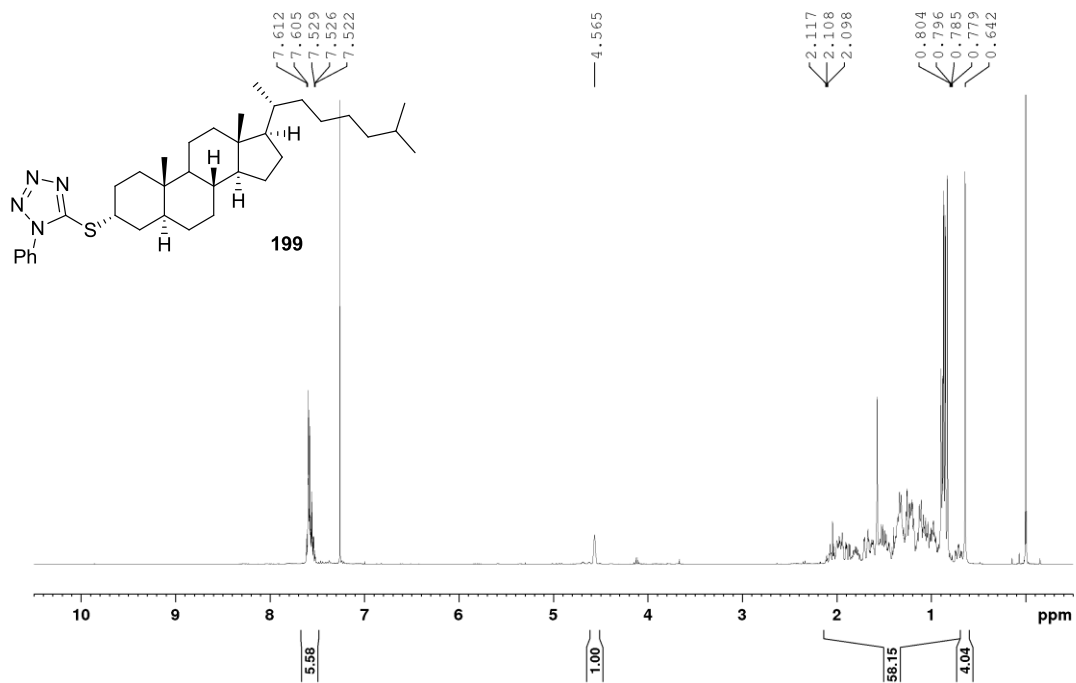
197



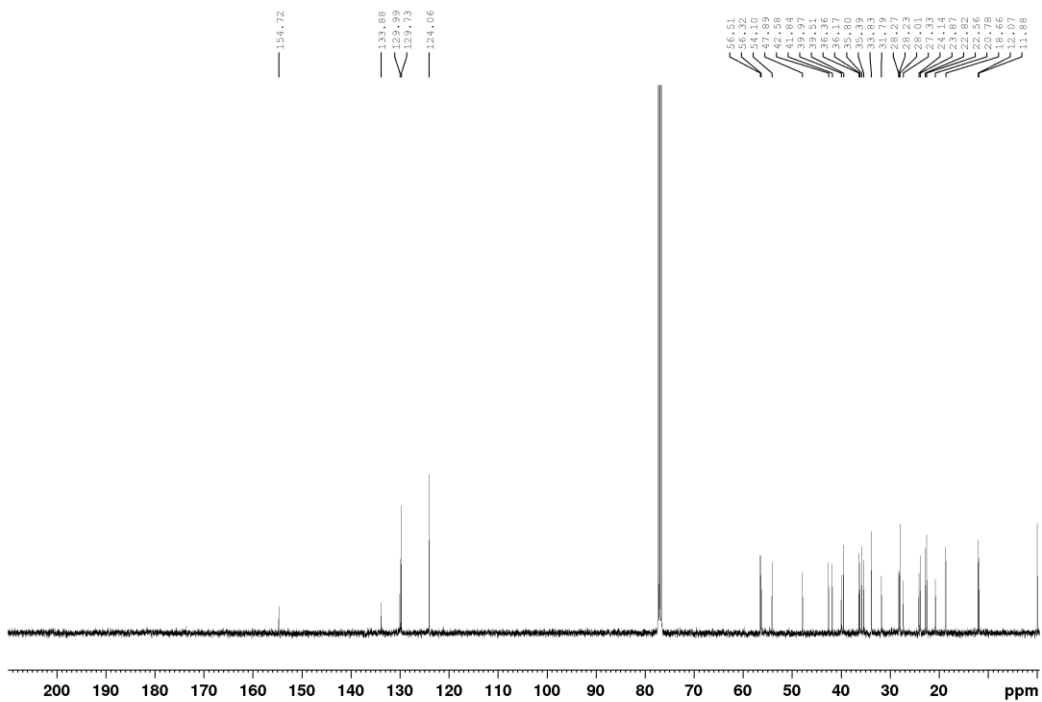
BCD-II-53-2 C13



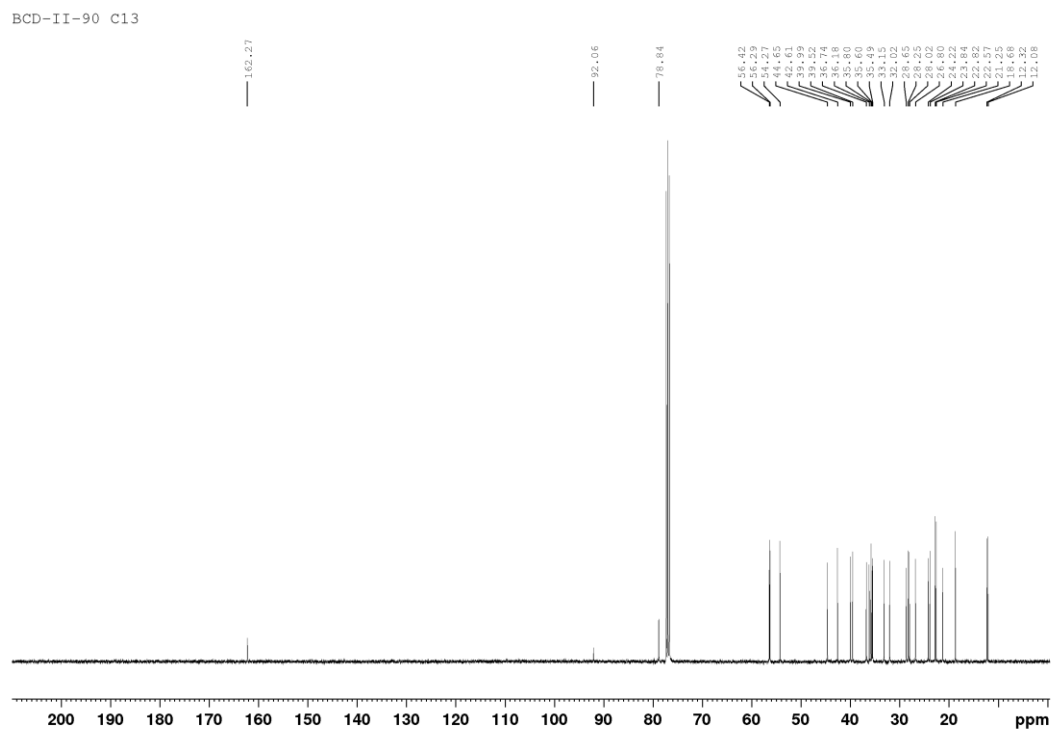
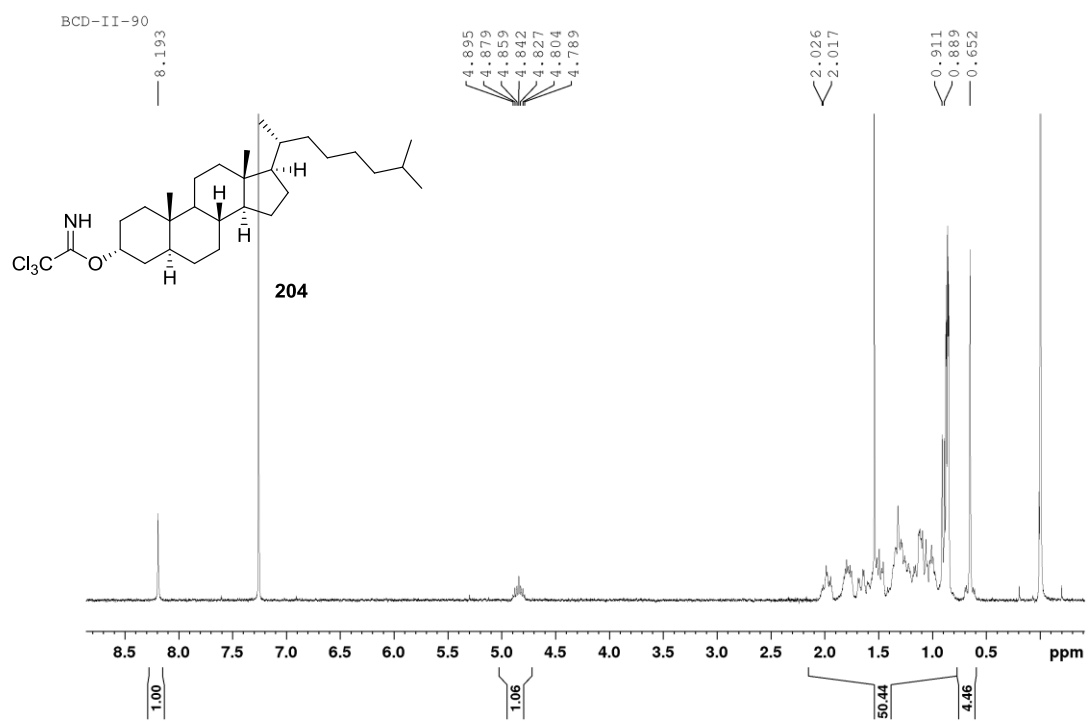
BCD-II-85

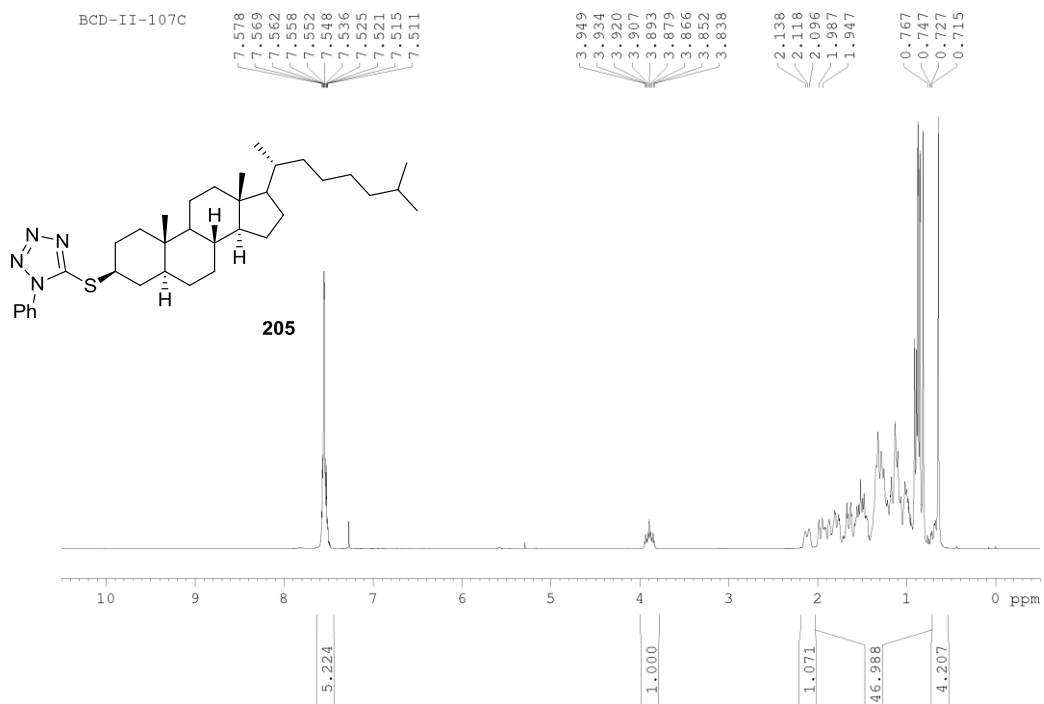


BCD-II-85 C13

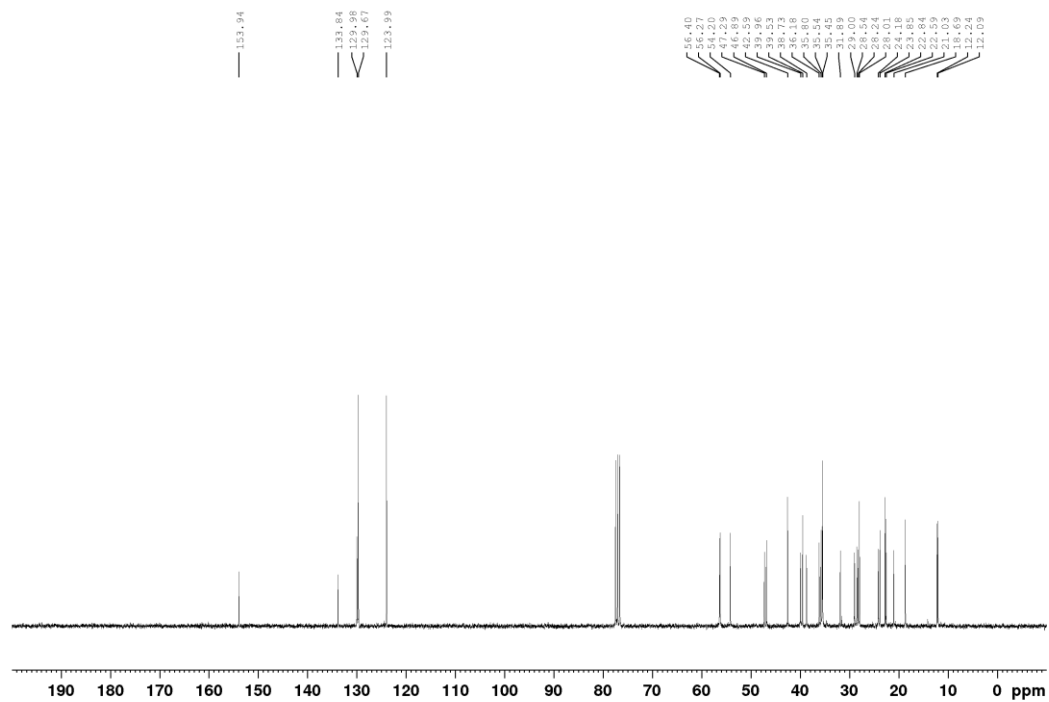


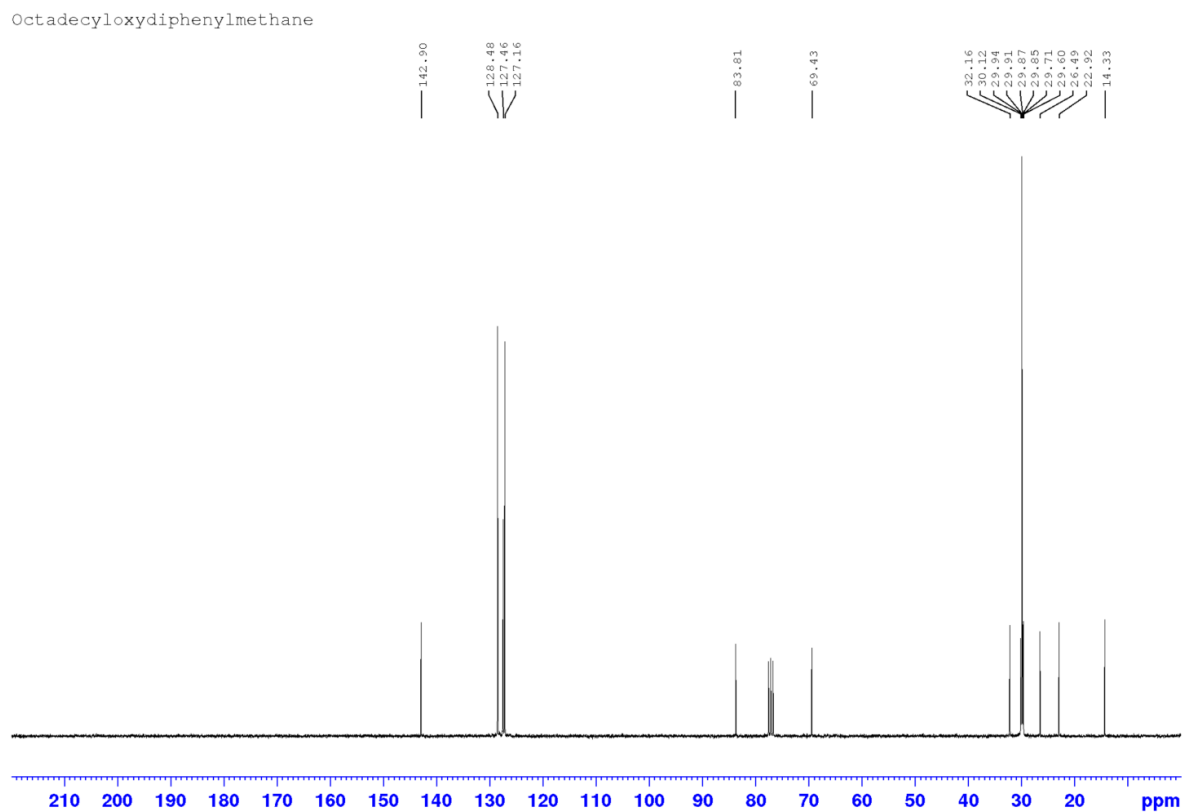
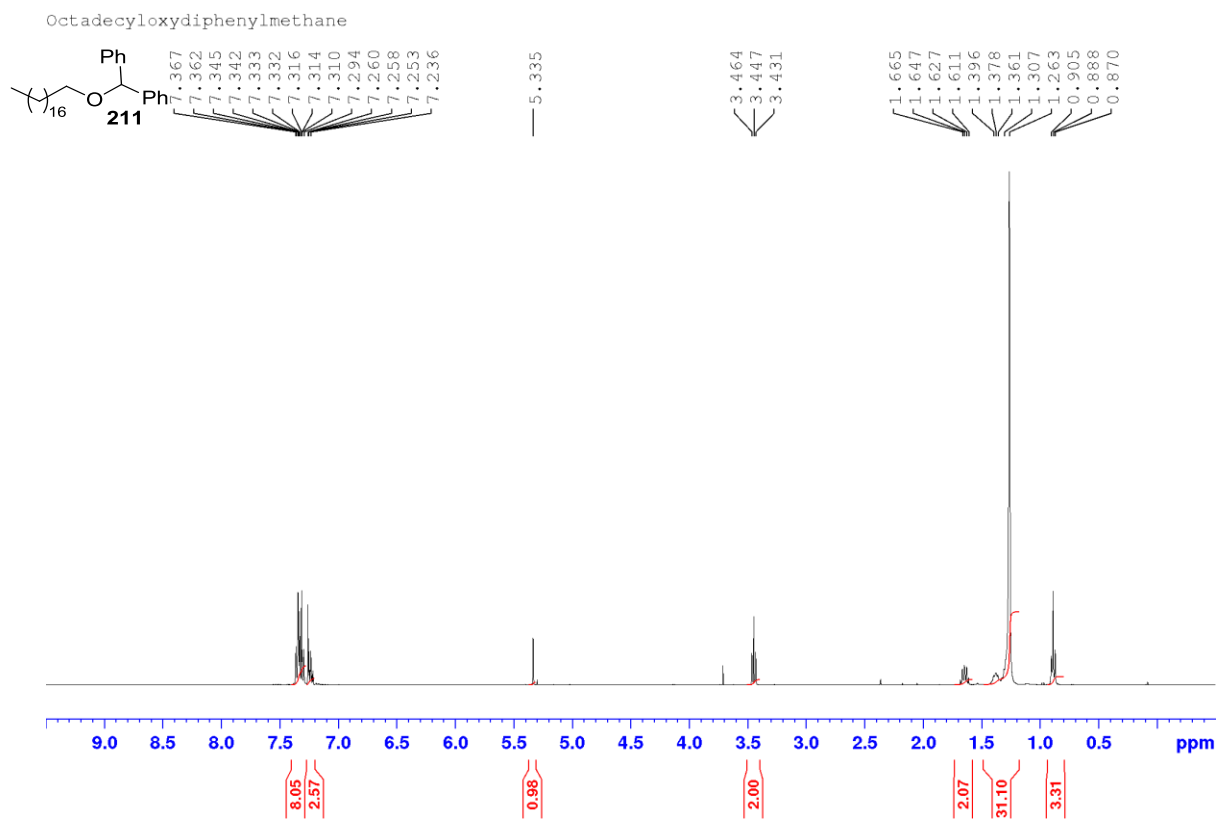




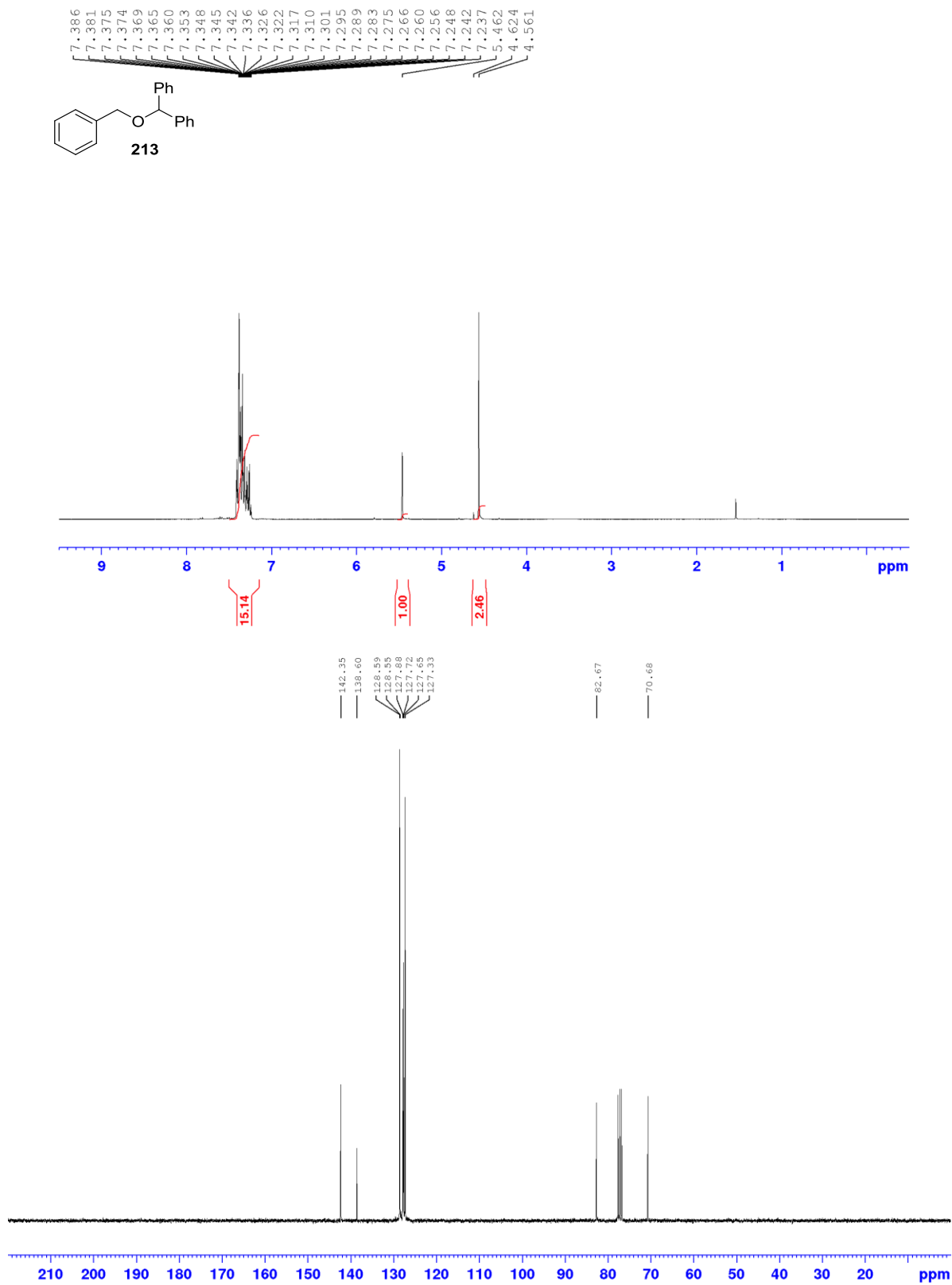
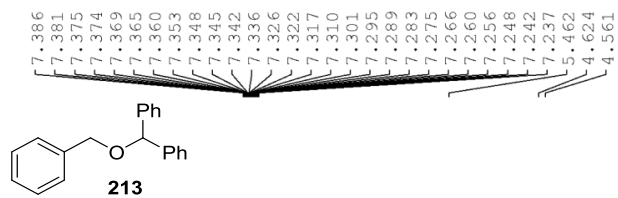


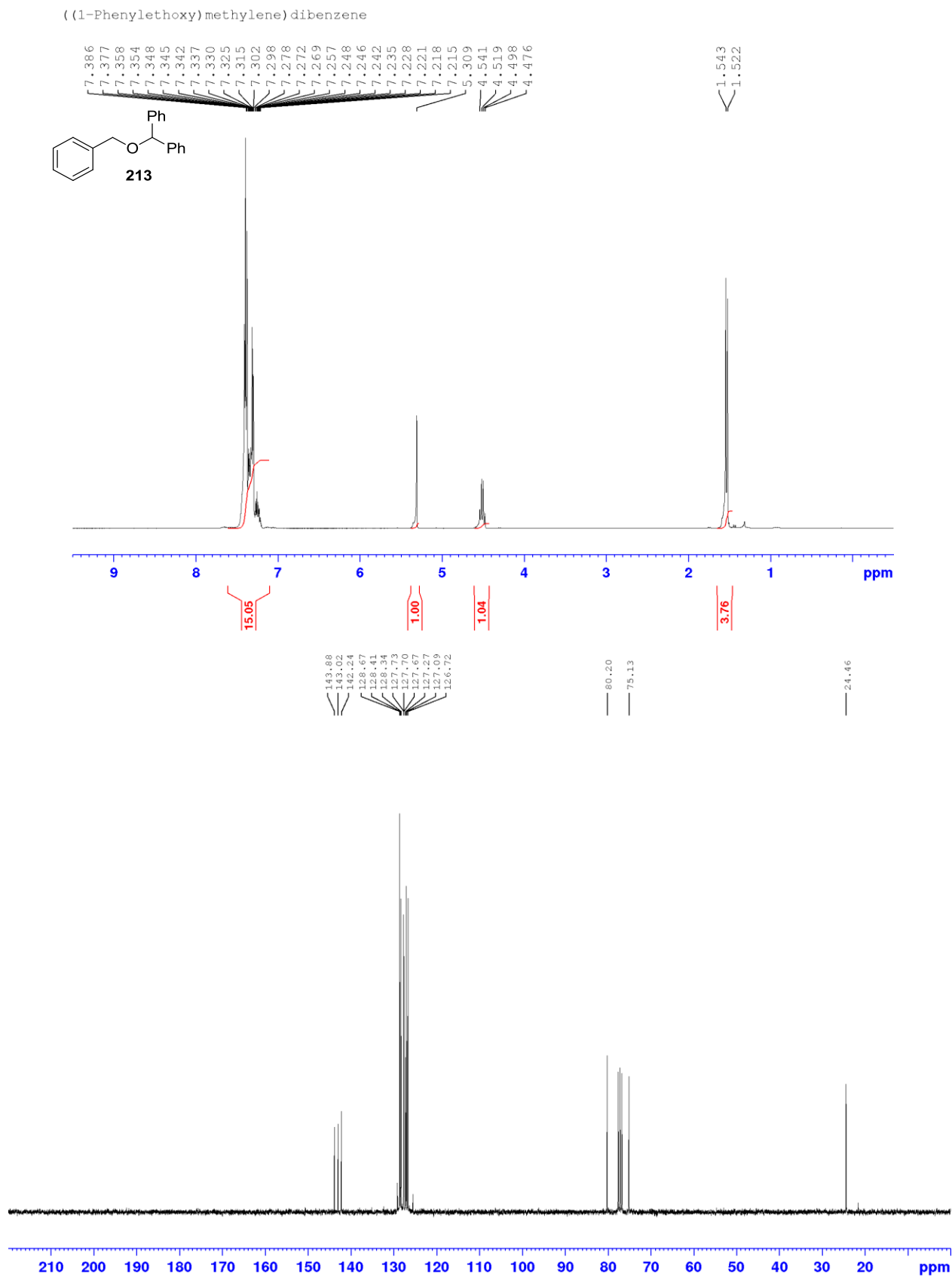
BCD-II-107C C13



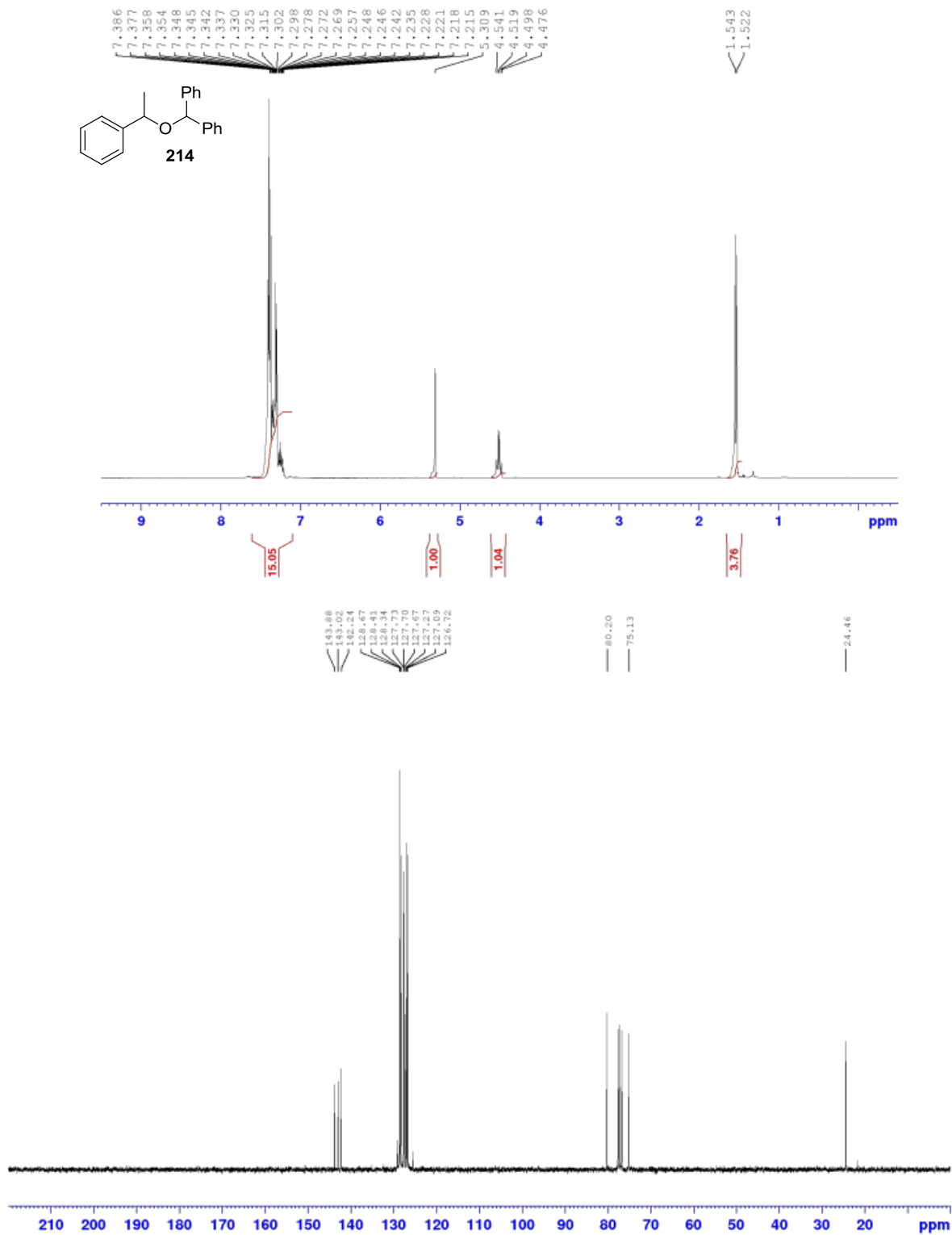


Benzyloxydiphenylmethane

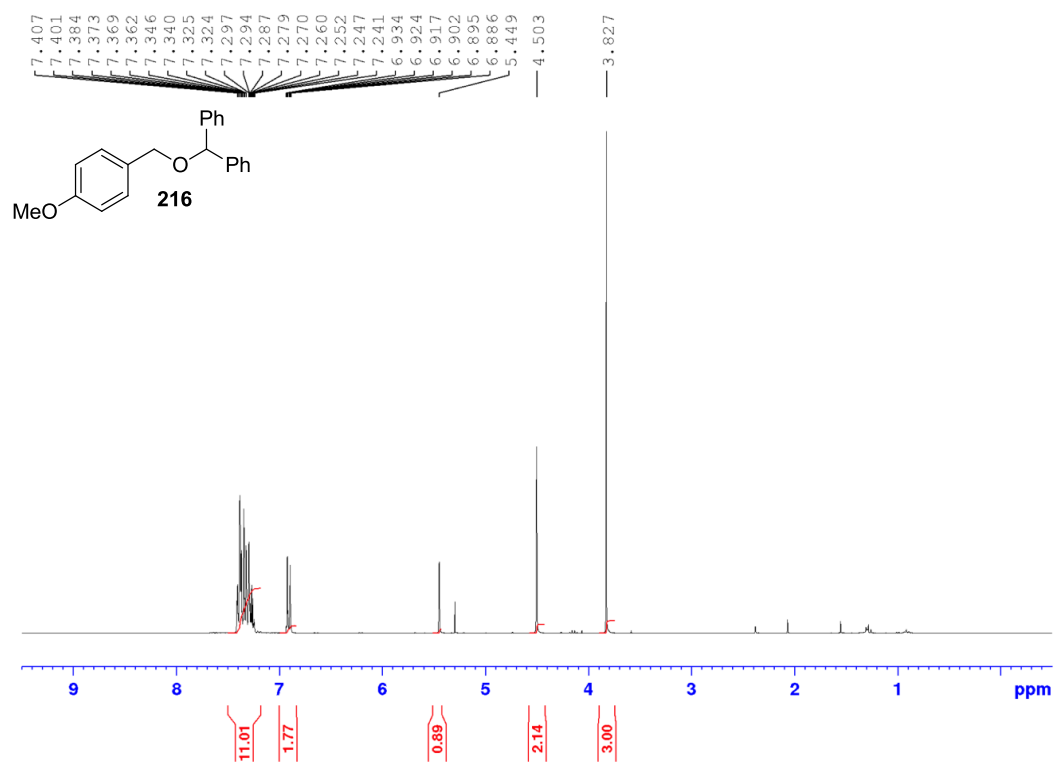




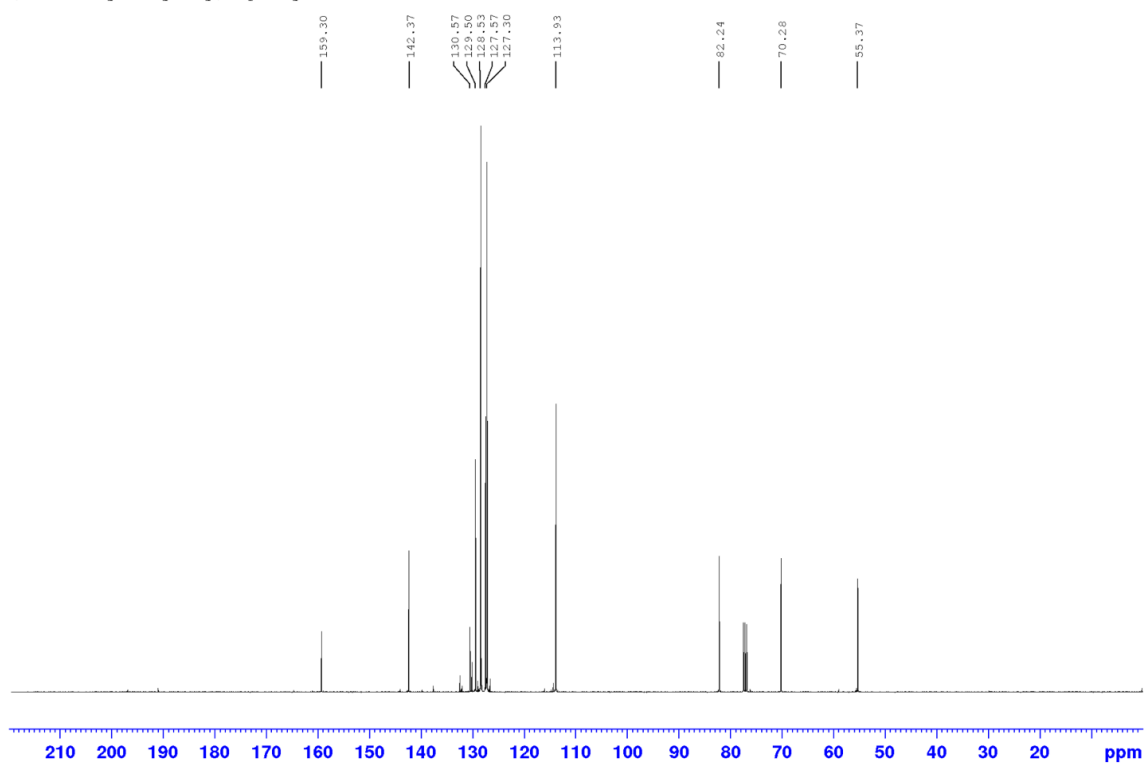
(1-Phenylethoxy)methylene)dibenzene

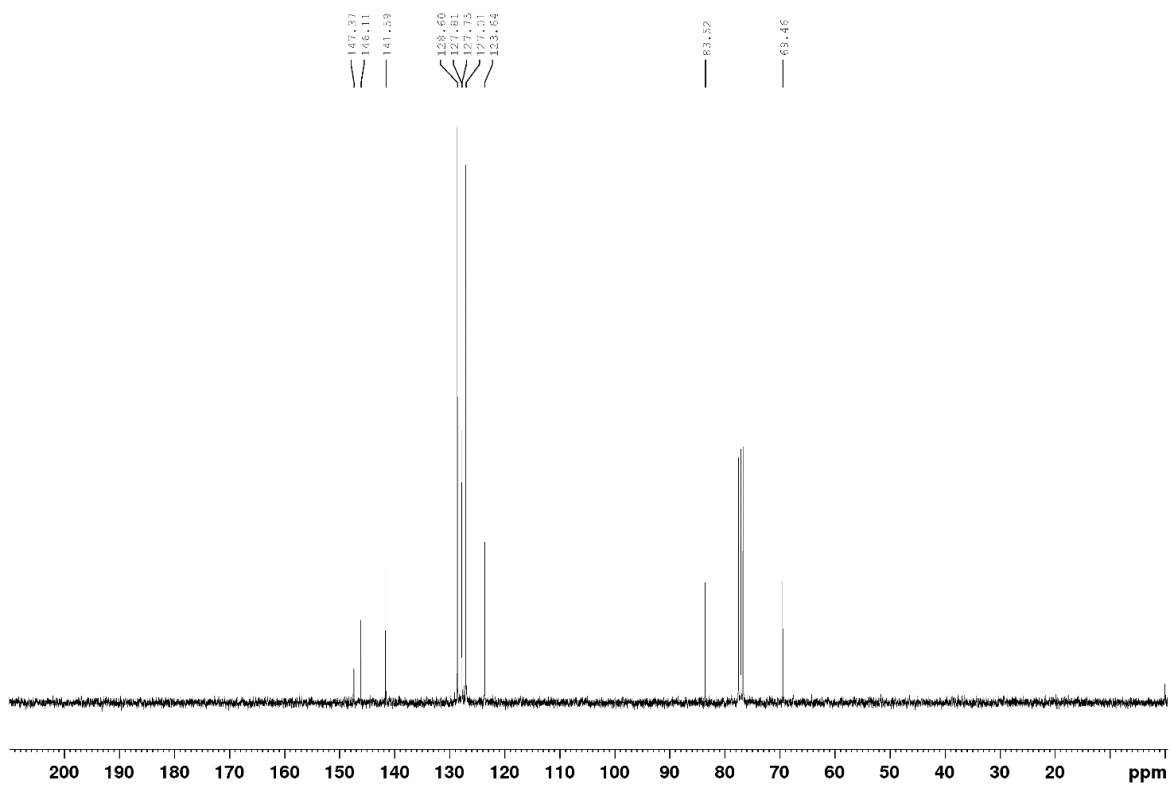
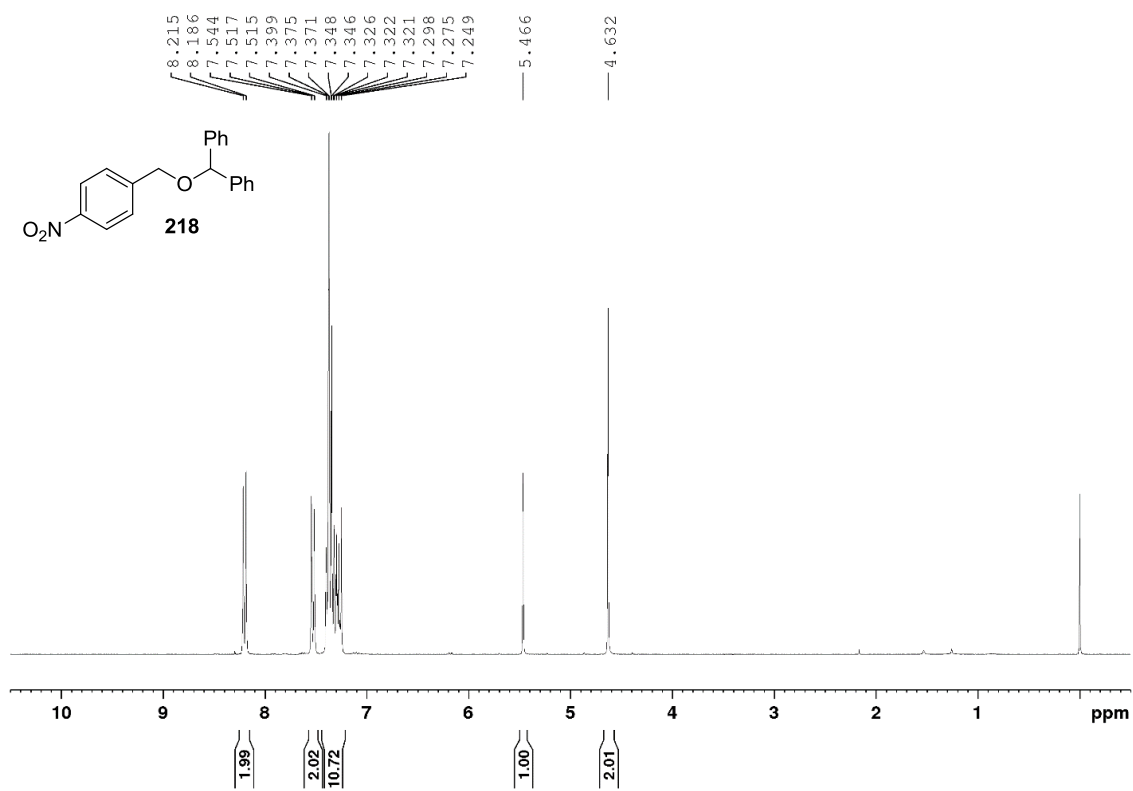


(4-Methoxybenzyloxy) diphenylmethane



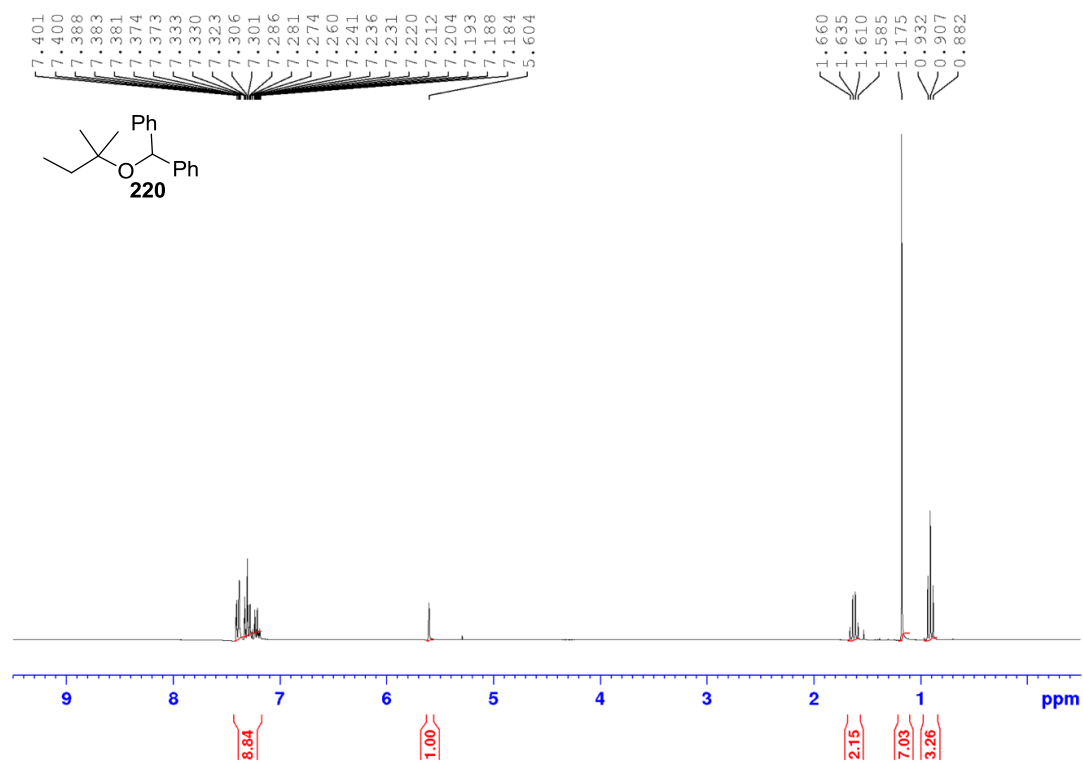
(4-Methoxybenzyloxy) diphenylmethane



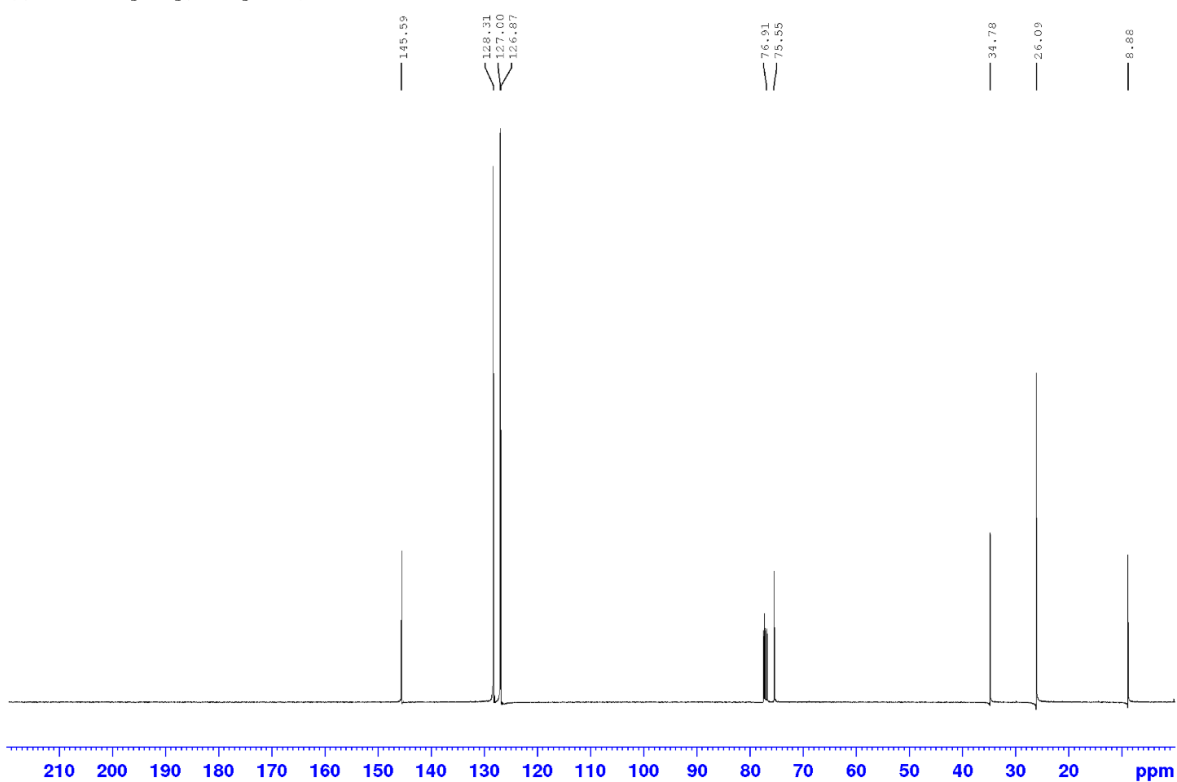




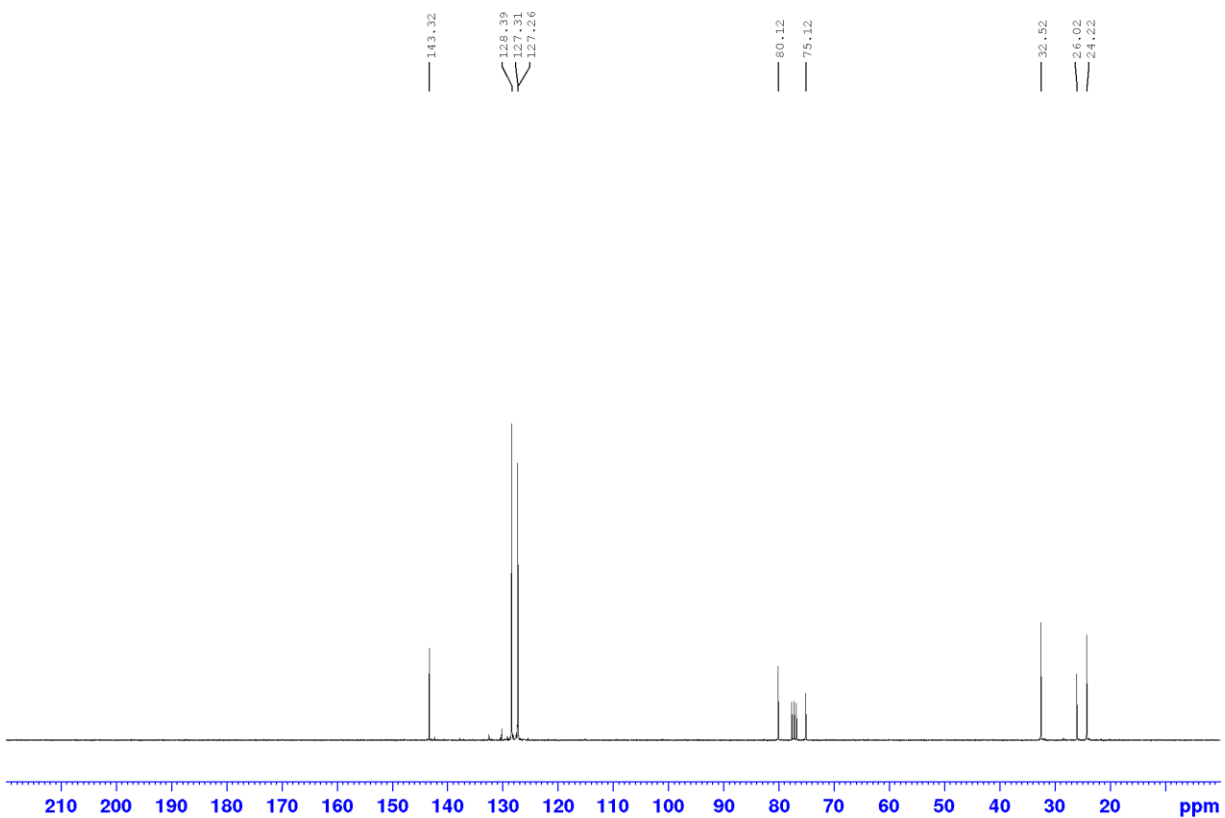
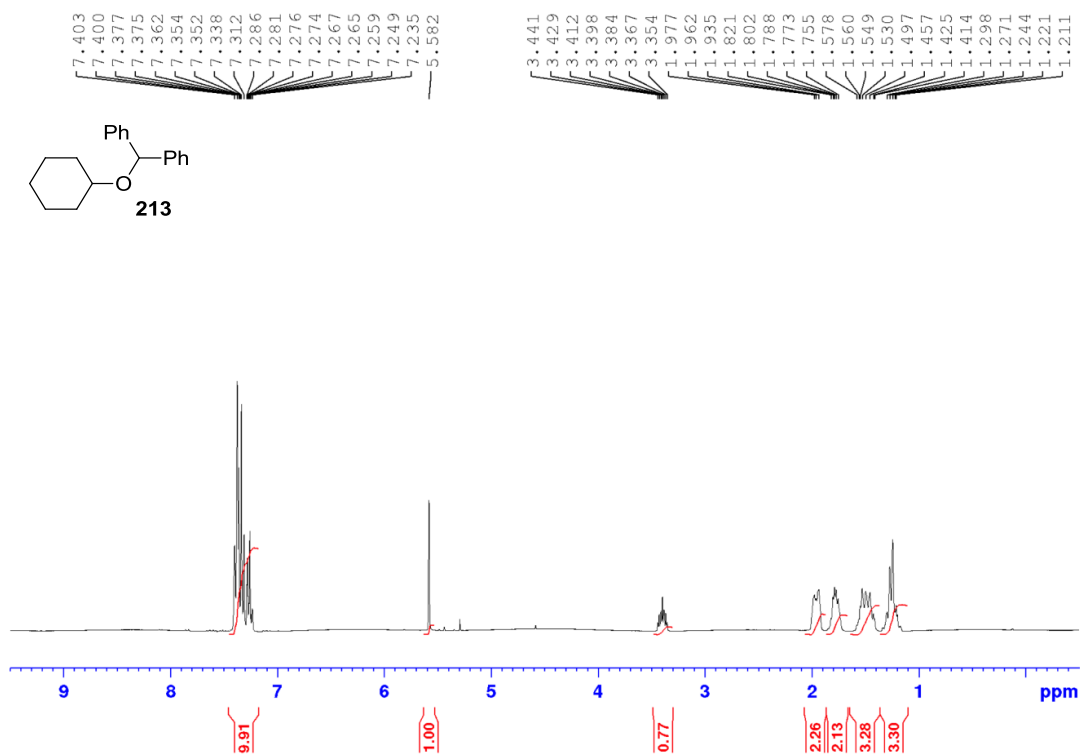
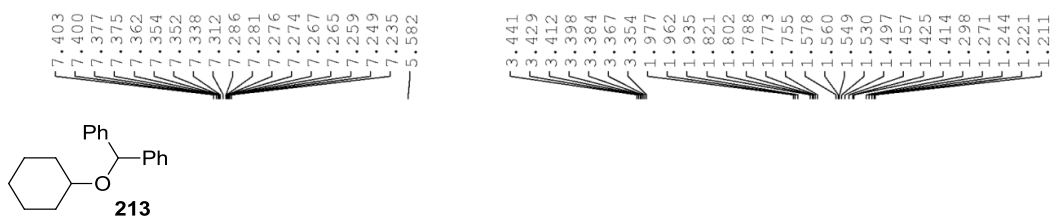
((tert-Pentyloxy)methylene)dibenzene

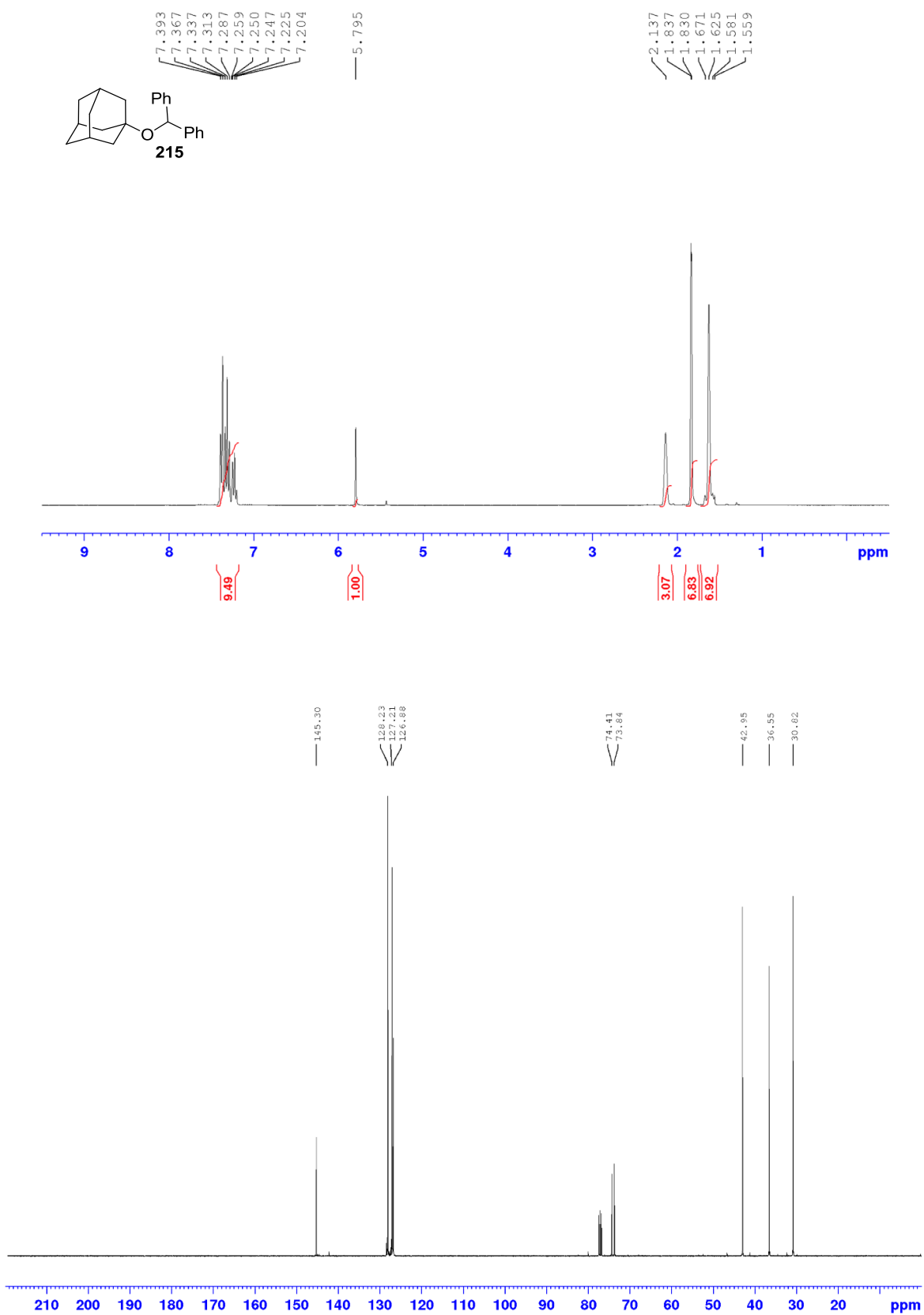


((tert-Pentyloxy)methylene)dibenzene

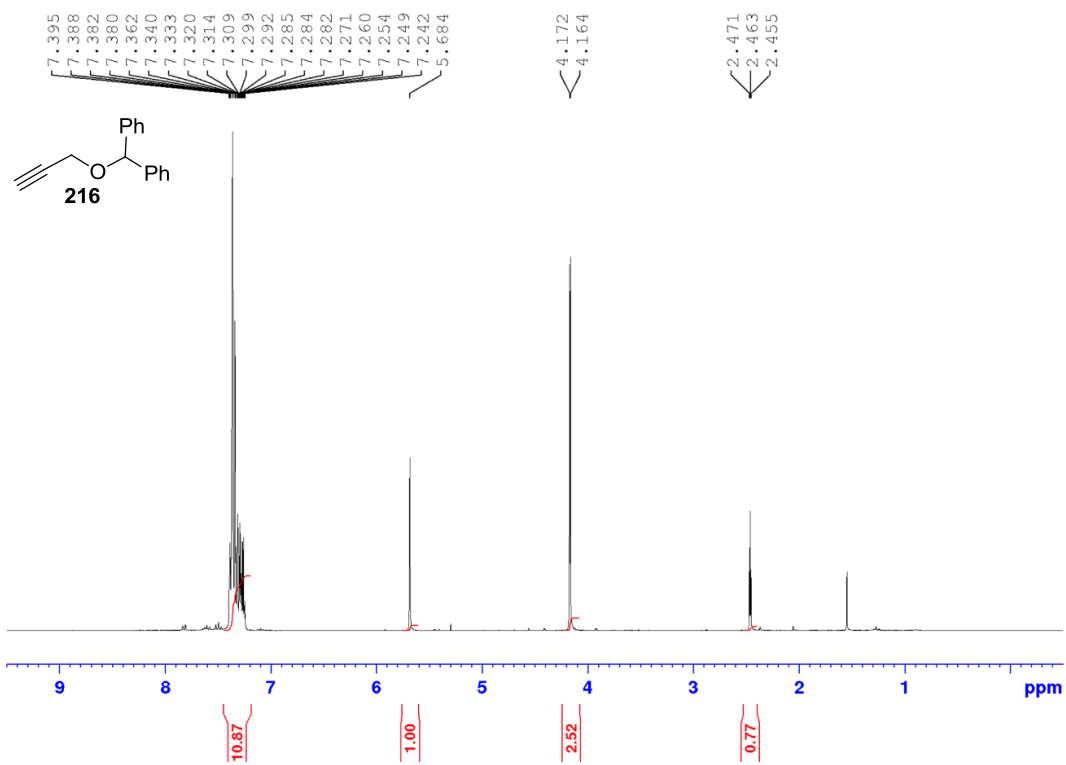


((Cyclohexyloxy)methylene)dibenzene

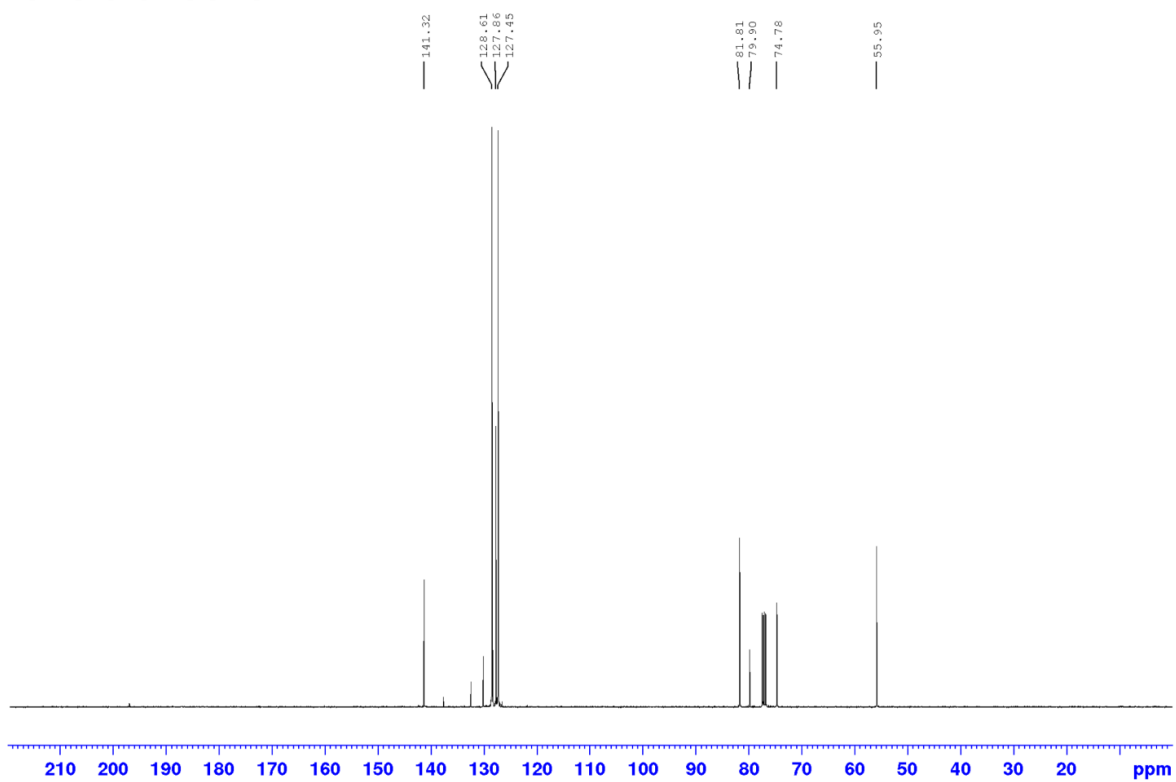




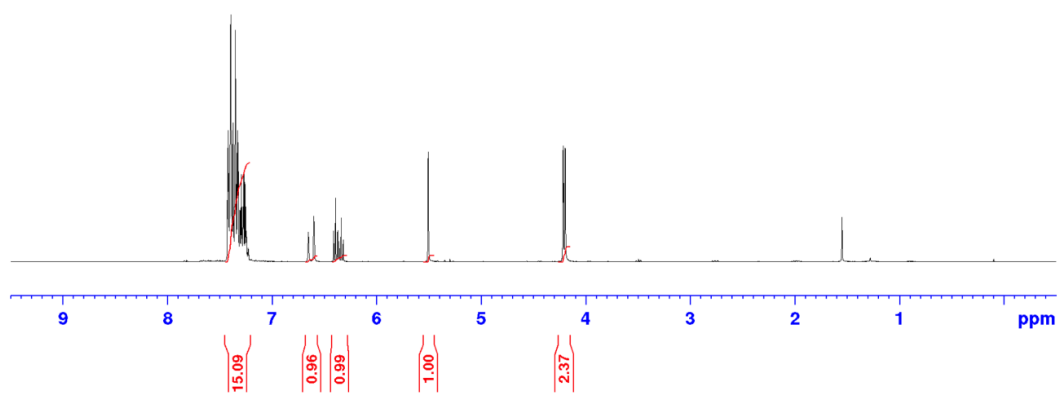
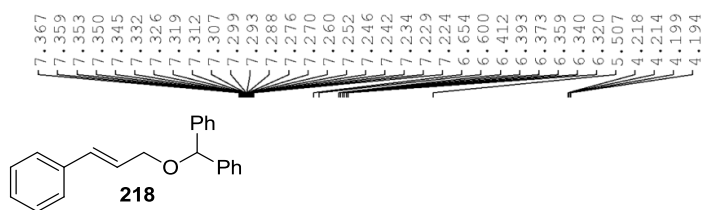
Diphenyl (prop-2-ynoxy) methane



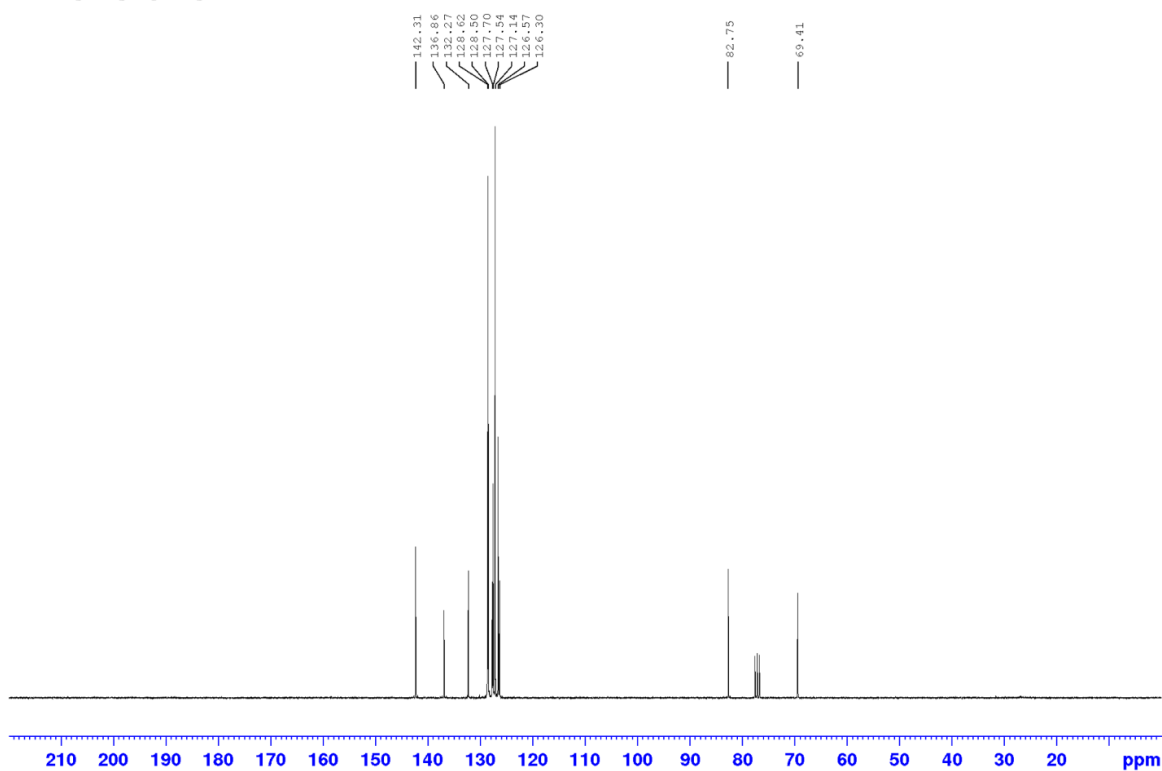
Diphenyl (prop-2-ynoxy) methane



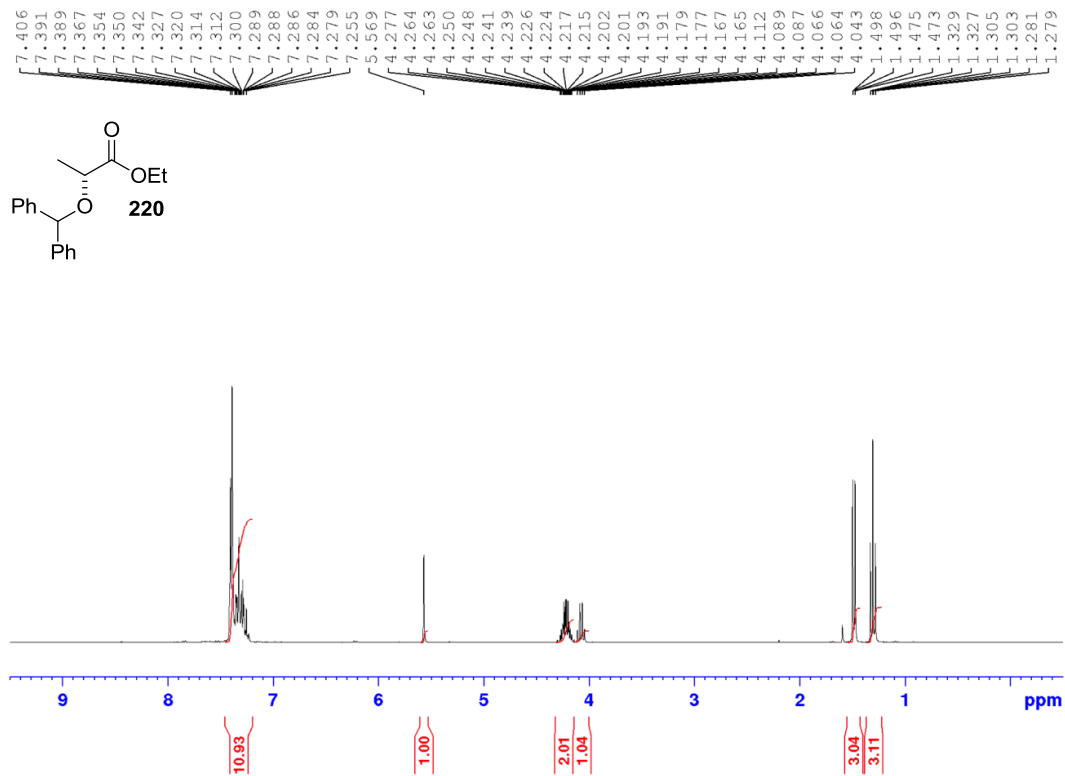
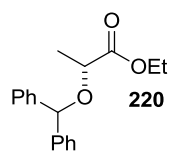
Cinnamyloxydiphenylmethane



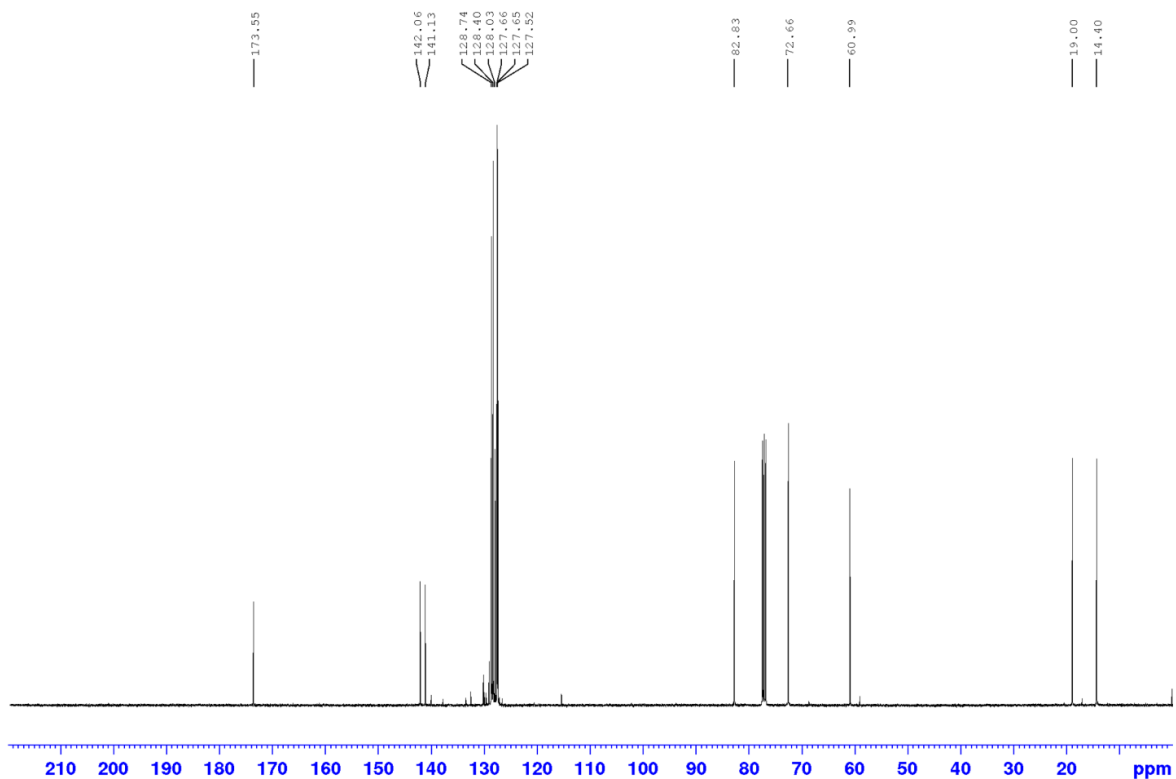
Cinnamyloxydiphenylmethane

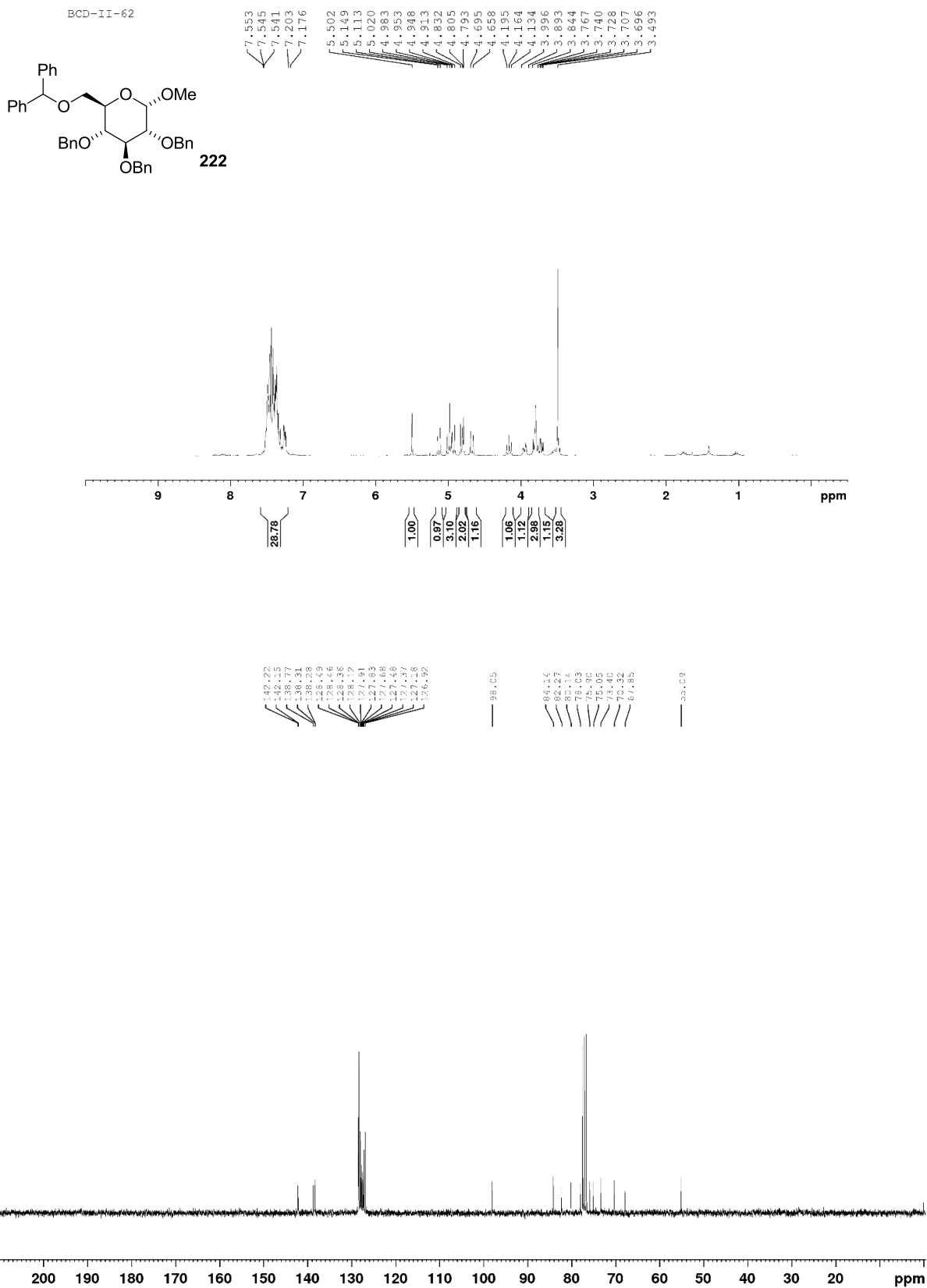


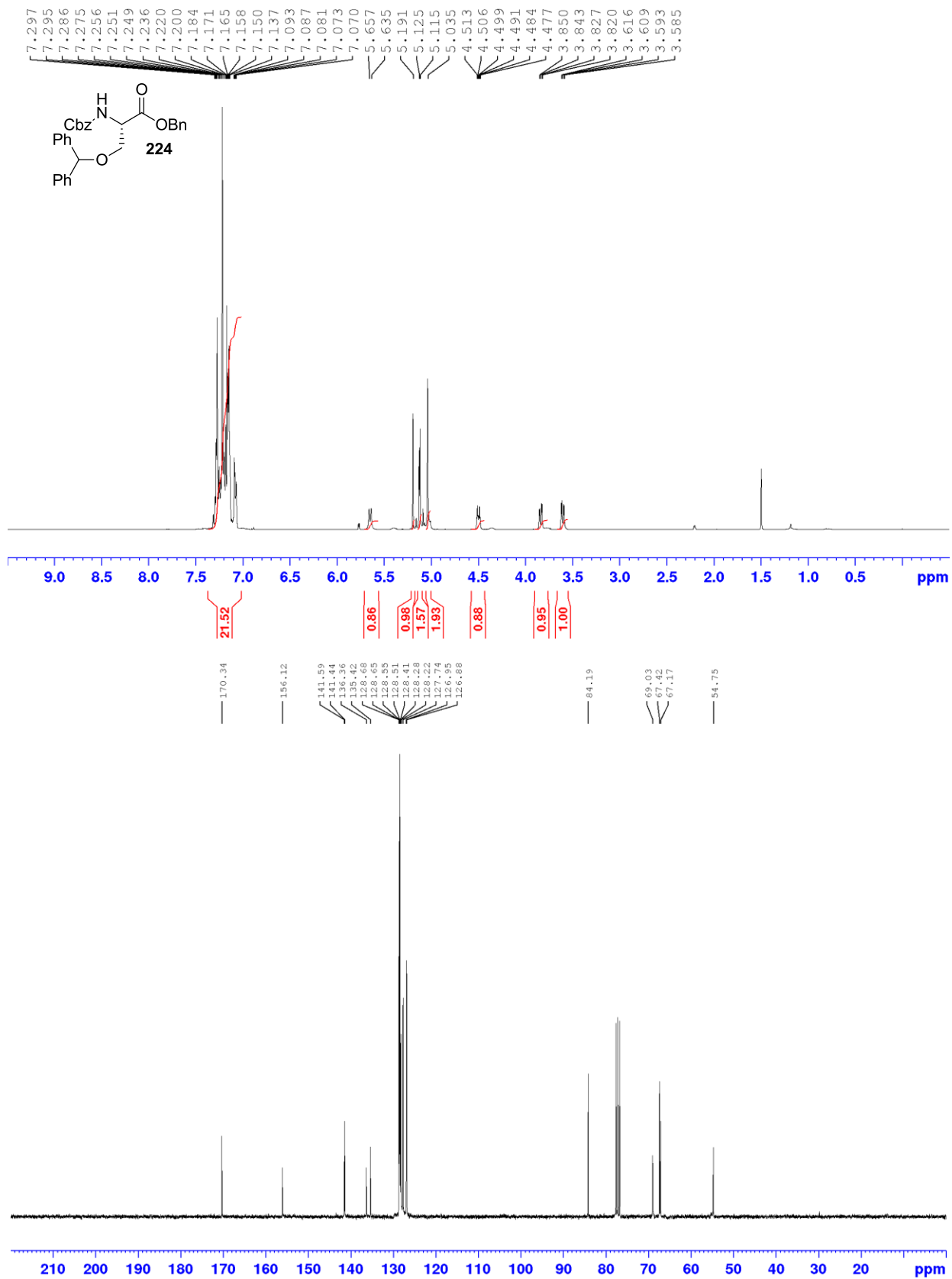
(R)-Ethyl 2-(benzhydryloxy)propanoate



(R)-Ethyl 2-(benzhydryloxy)propanoate

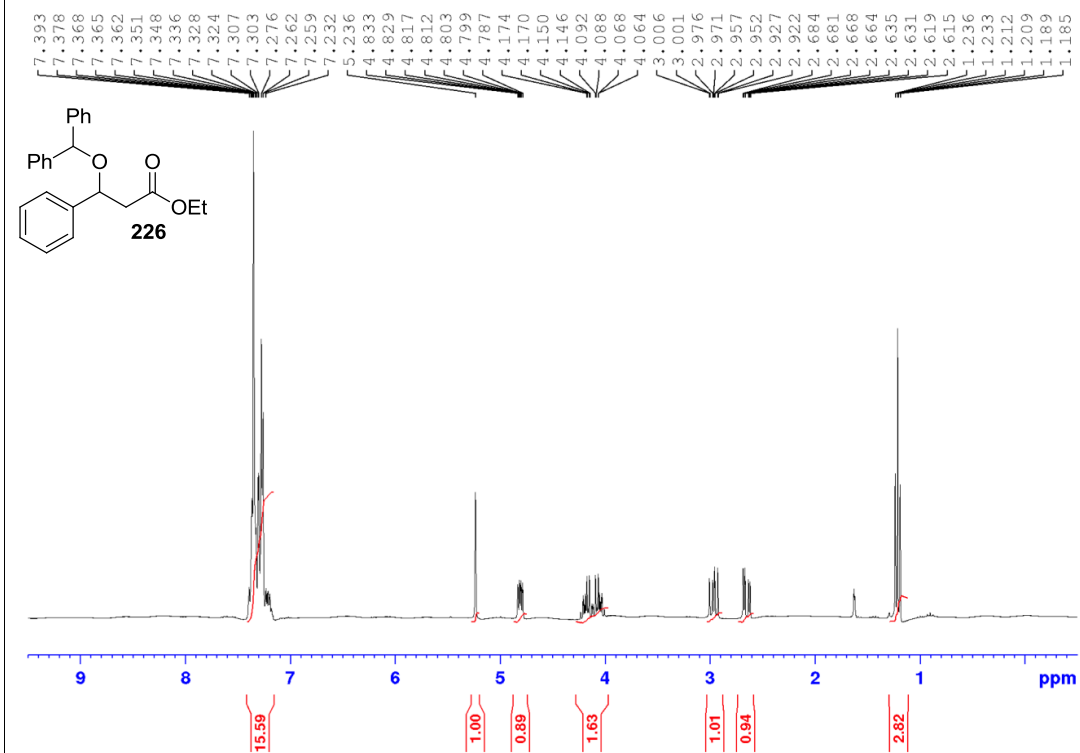




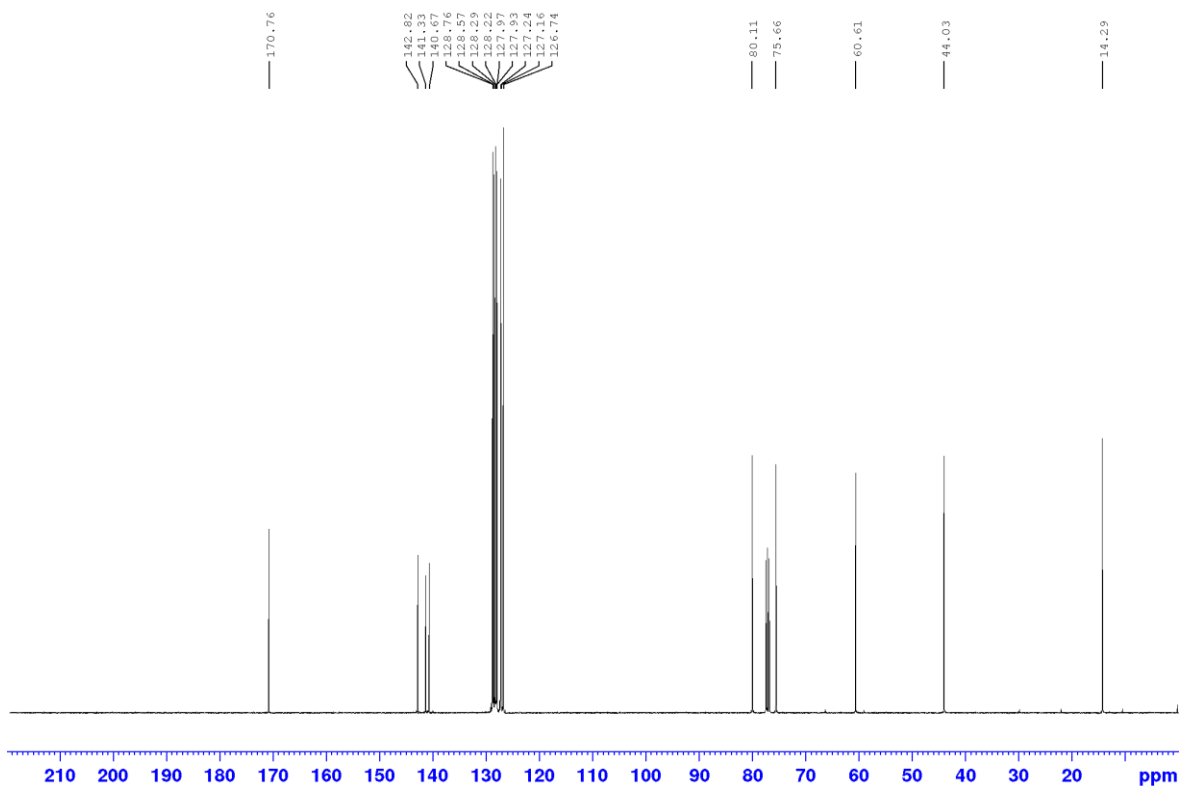




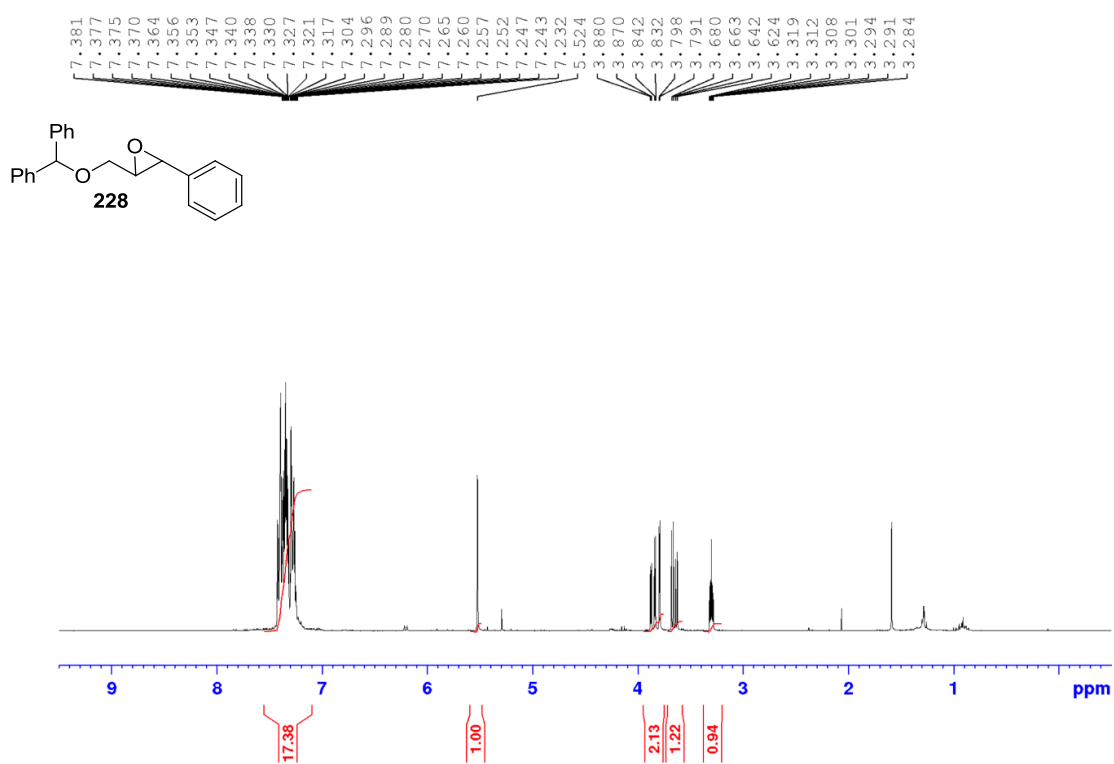
Ethyl 3-(benzhydryloxy)-3-phenylpropanoate



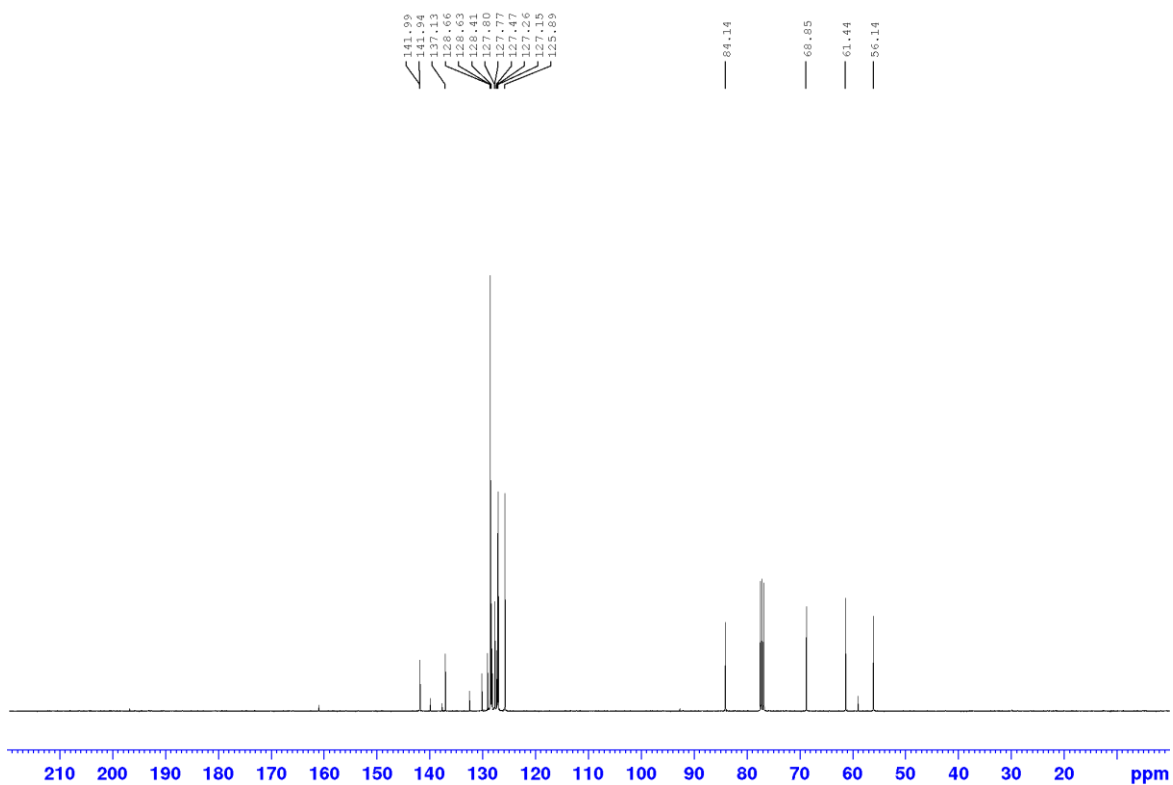
Ethyl 3-(benzhydryloxy)-3-phenylpropanoate

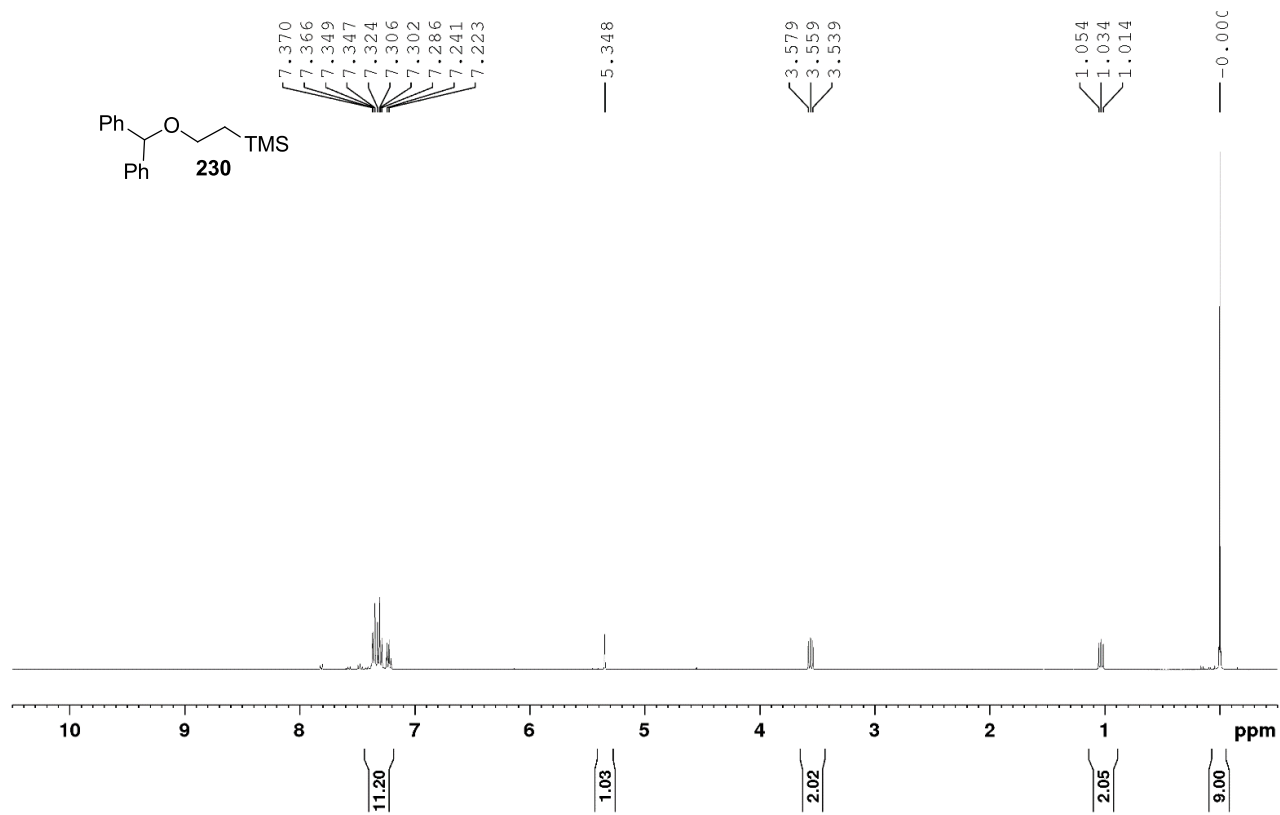


2-((Benzhydryloxy)methyl)-3-phenyloxirane

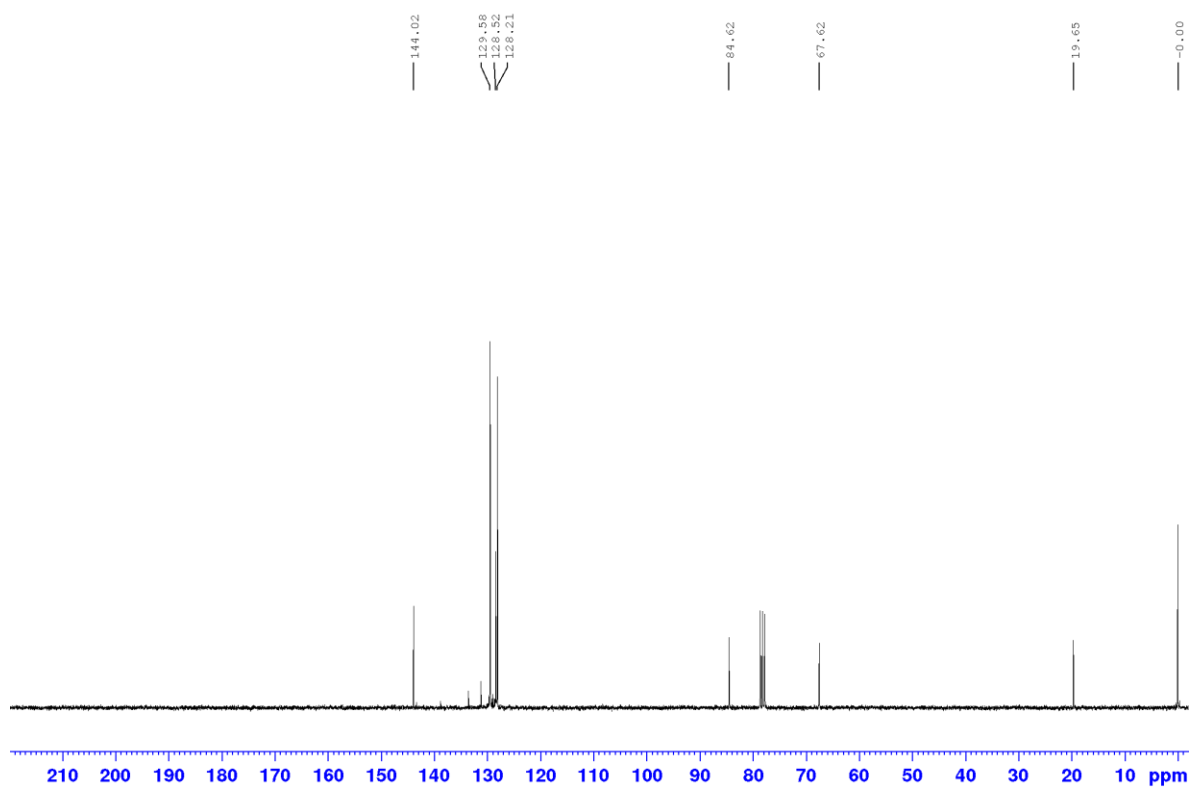


2-((Benzhydryloxy)methyl)-3-phenyloxirane

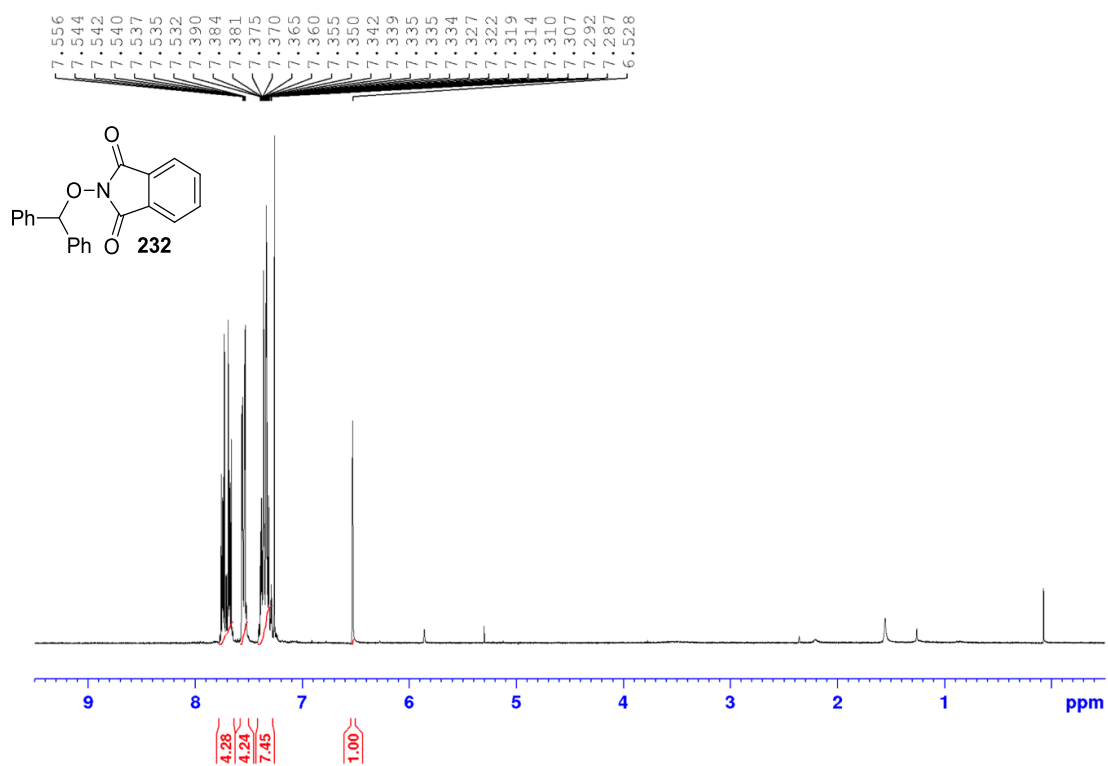




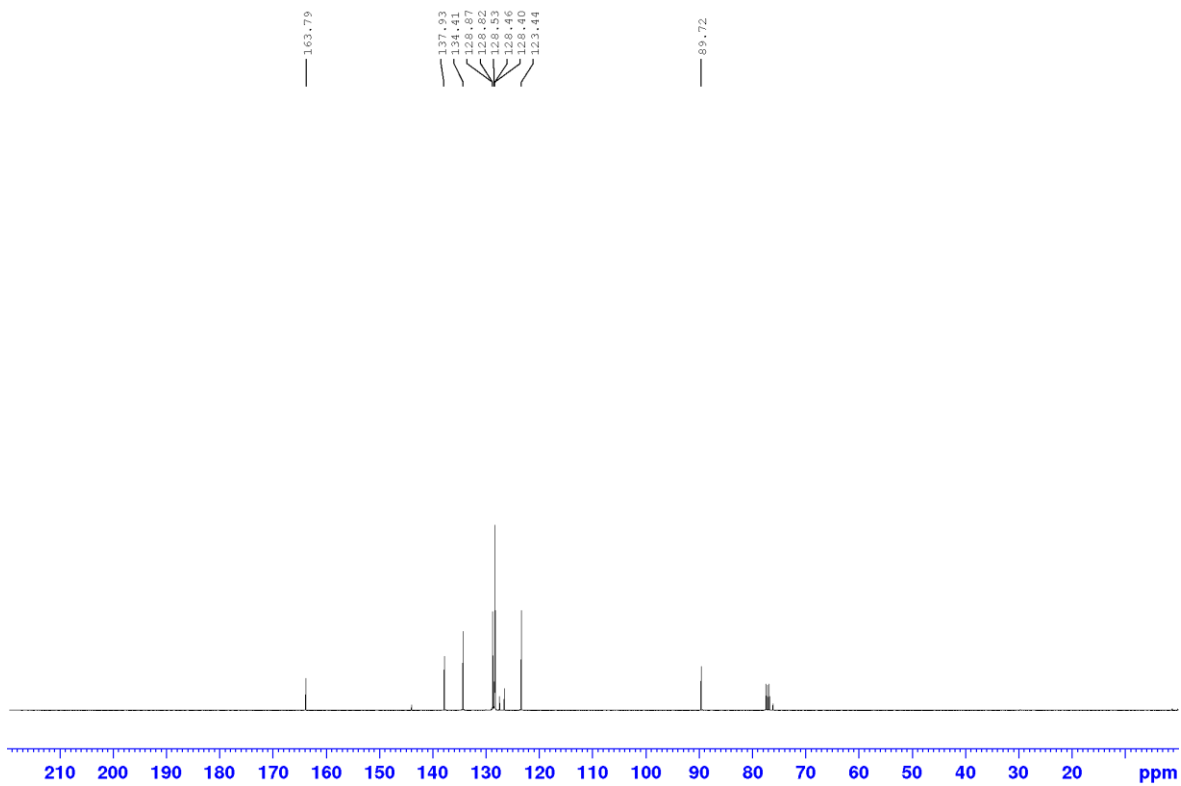
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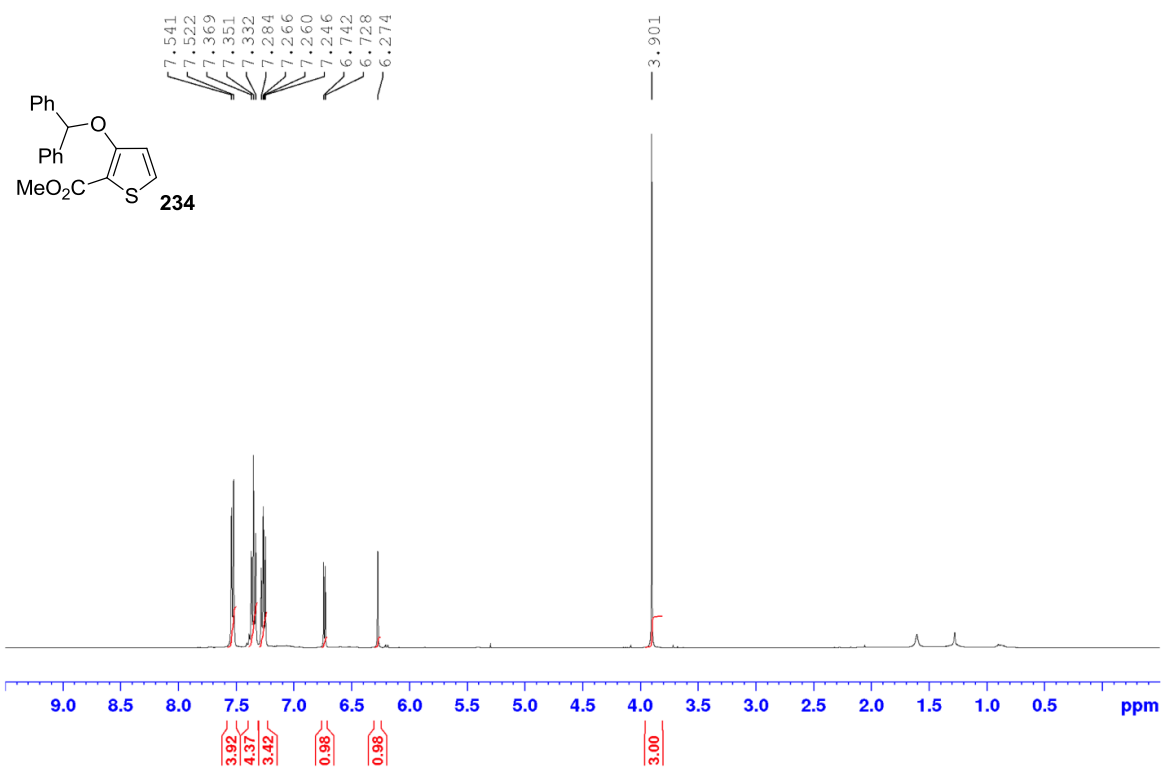
2-(Benzhydryloxy)isoindoline-1,3-dione



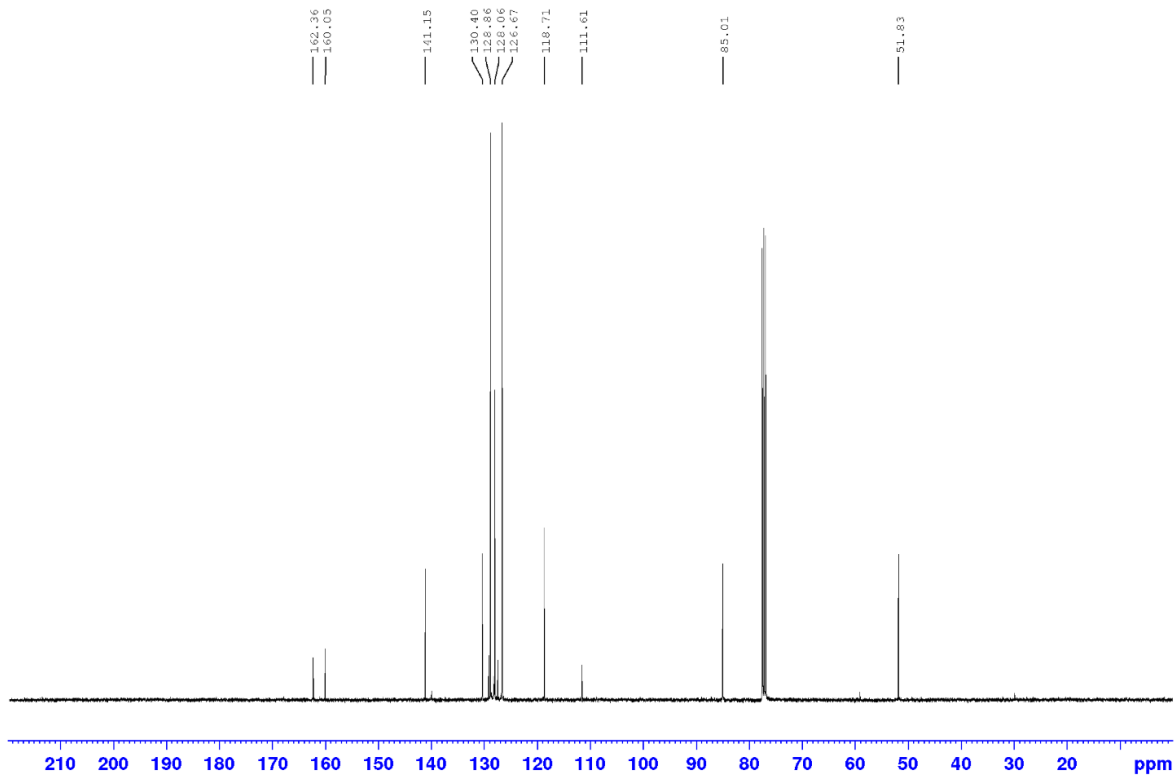
2-(Benzhydryloxy)isoindoline-1,3-dione



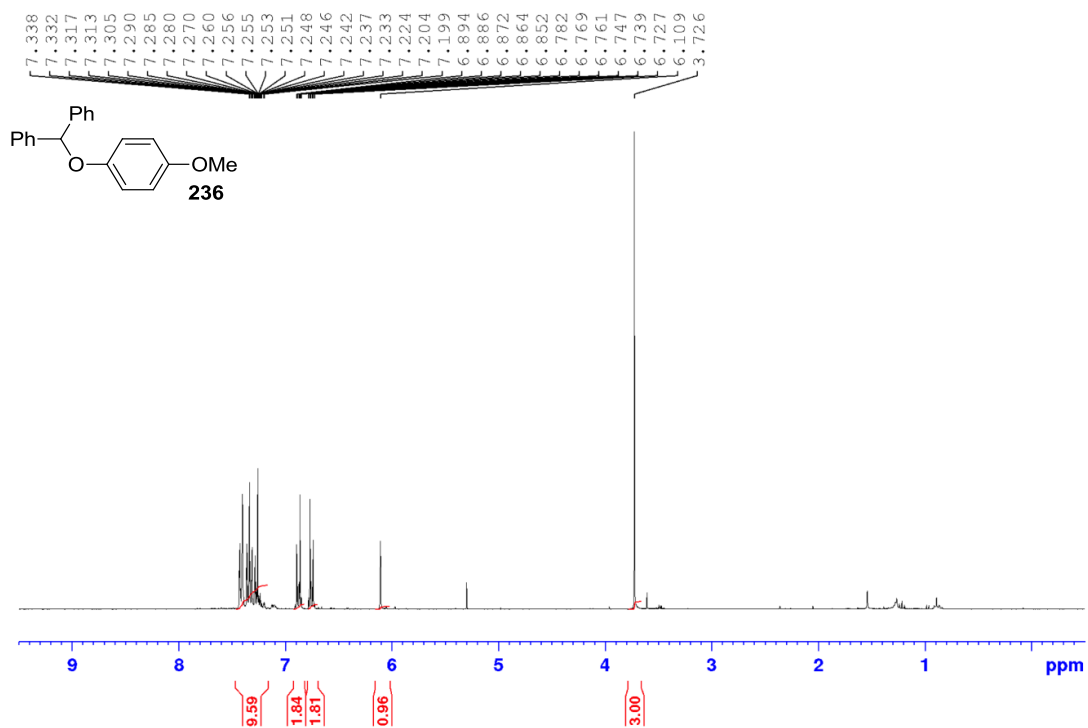
Methyl 3-(benzhydryloxy)thiophene-2-carboxylate



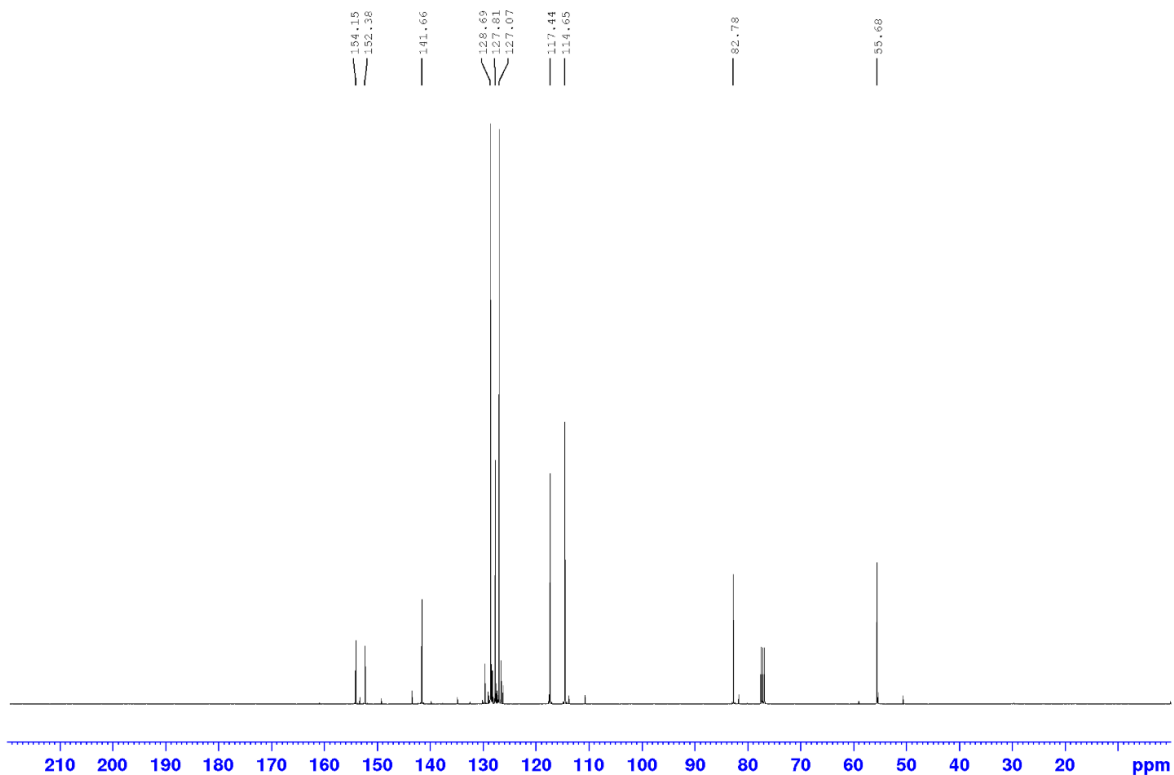
Methyl 3-(benzhydryloxy)thiophene-2-carboxylate

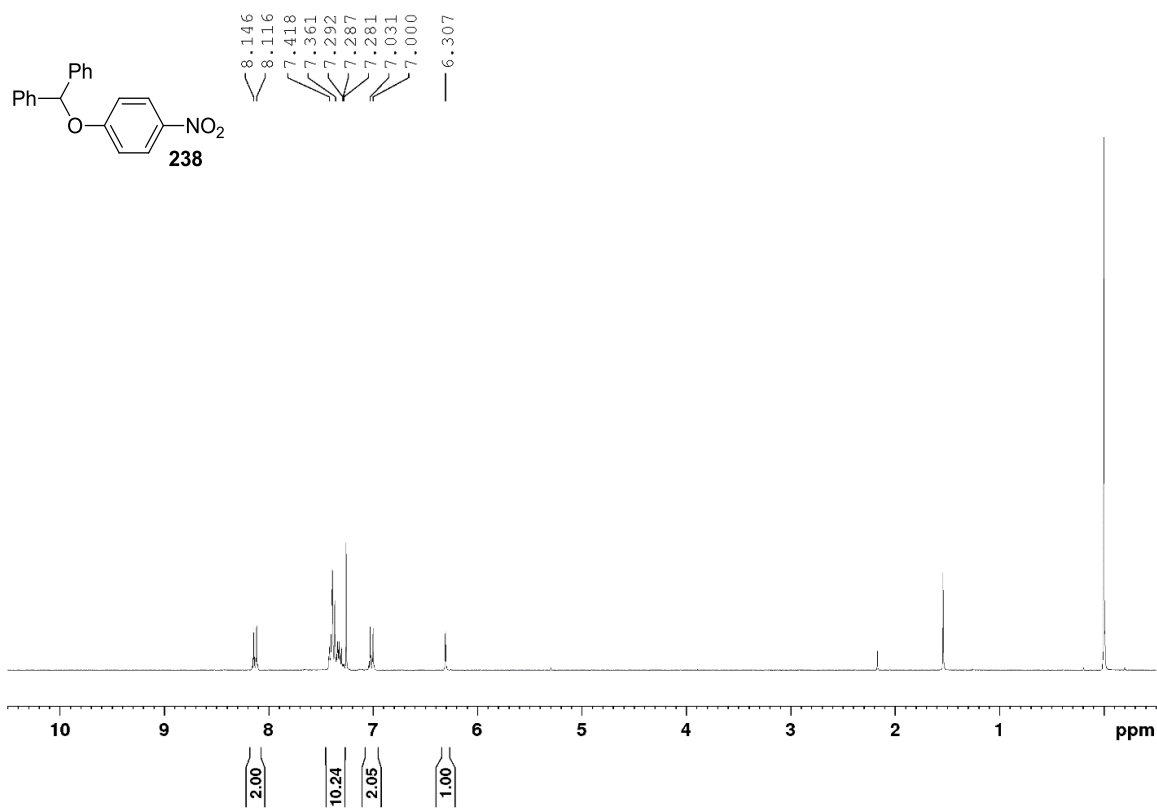


((4-Methoxyphenoxy)methylene)dibenzene

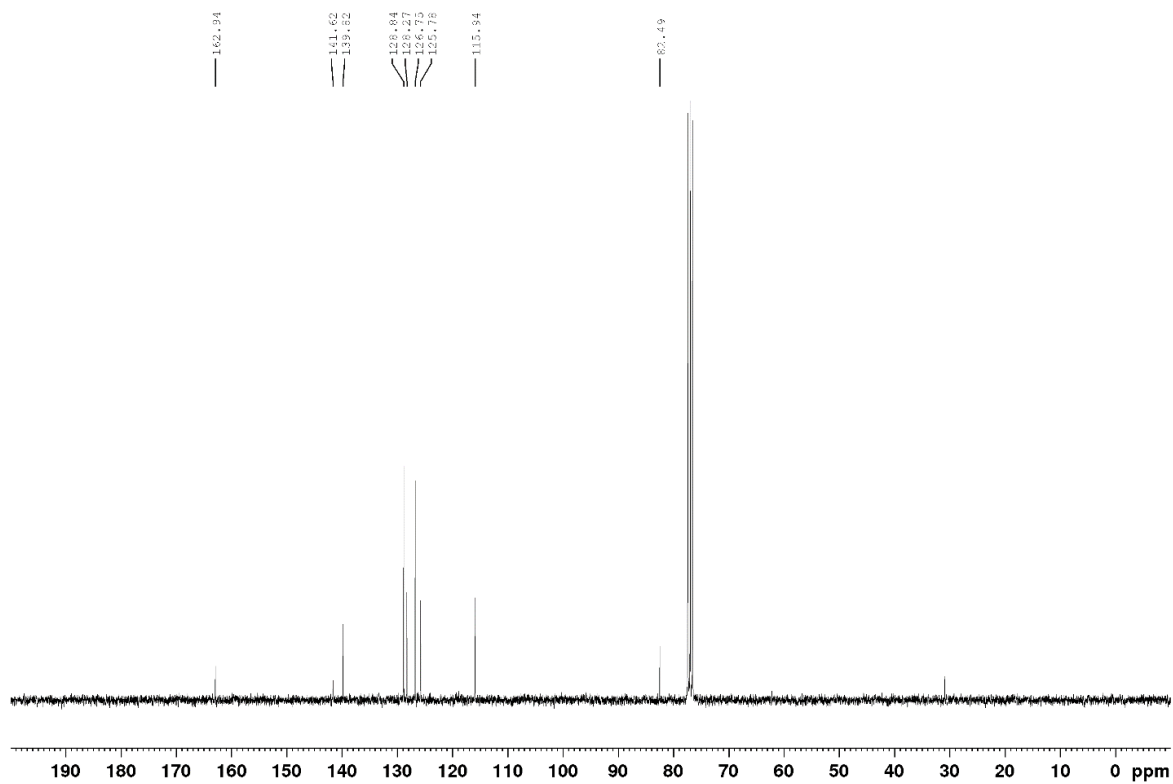


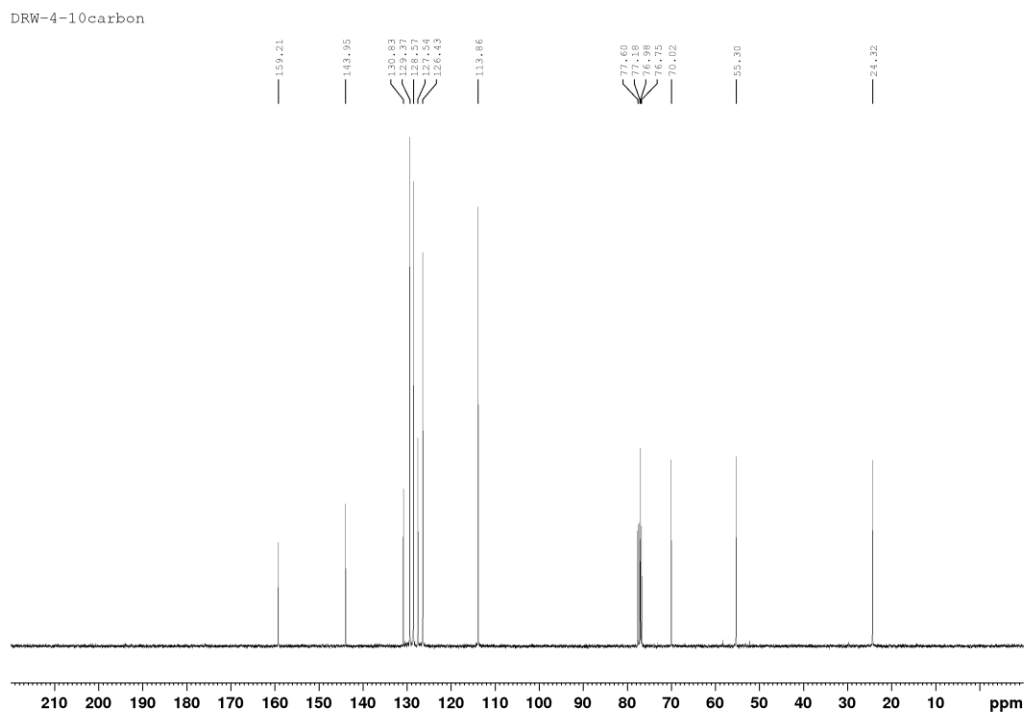
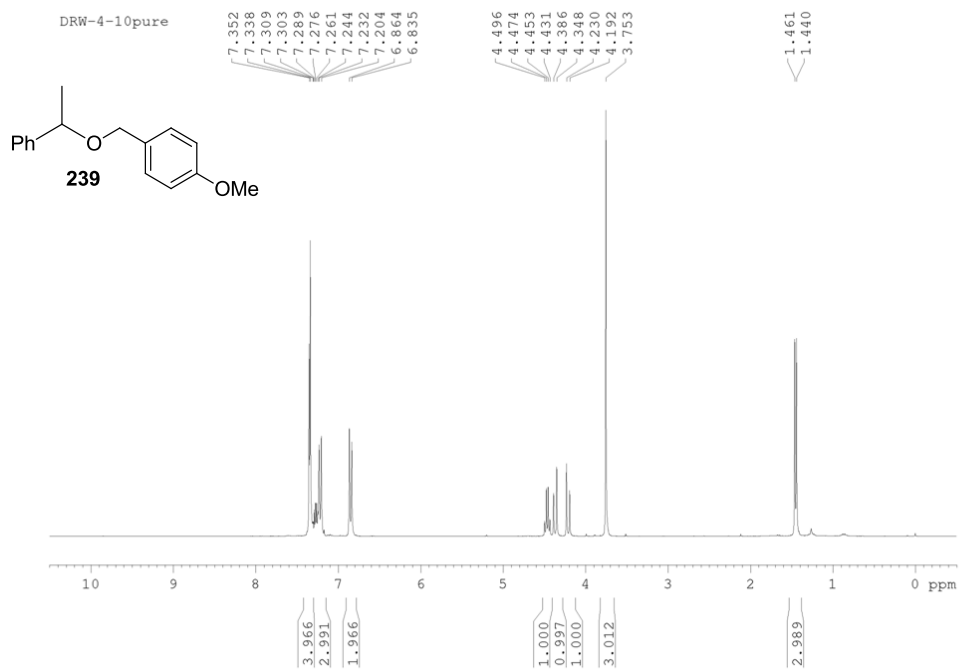
((4-Methoxyphenoxy)methylene)dibenzene



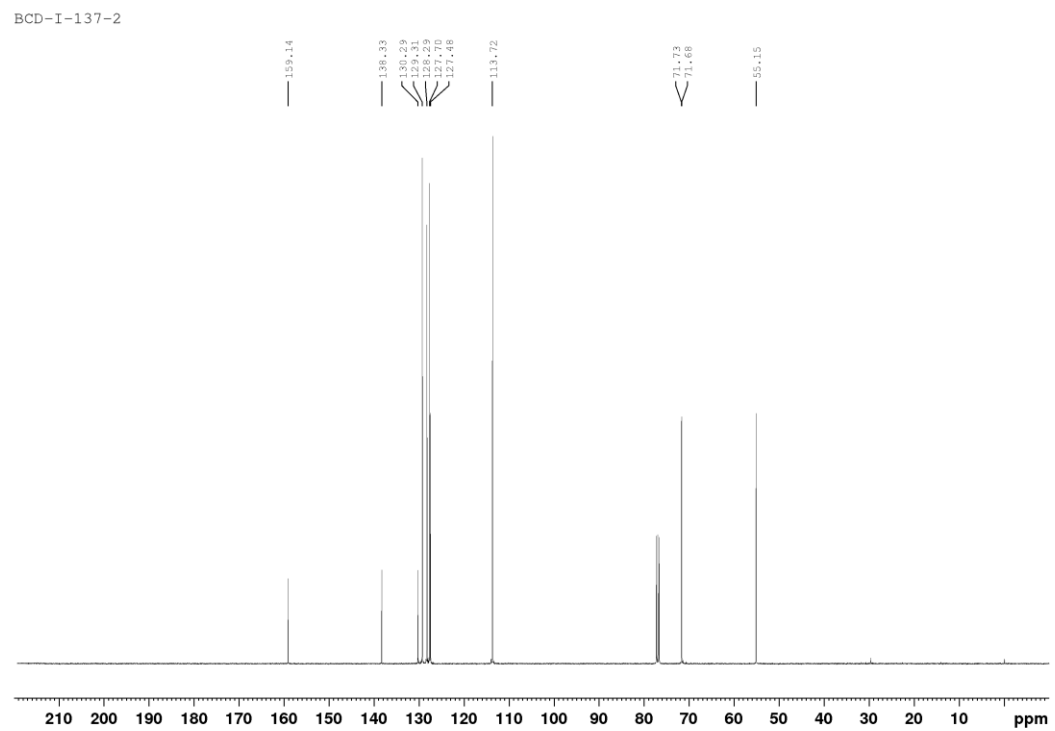
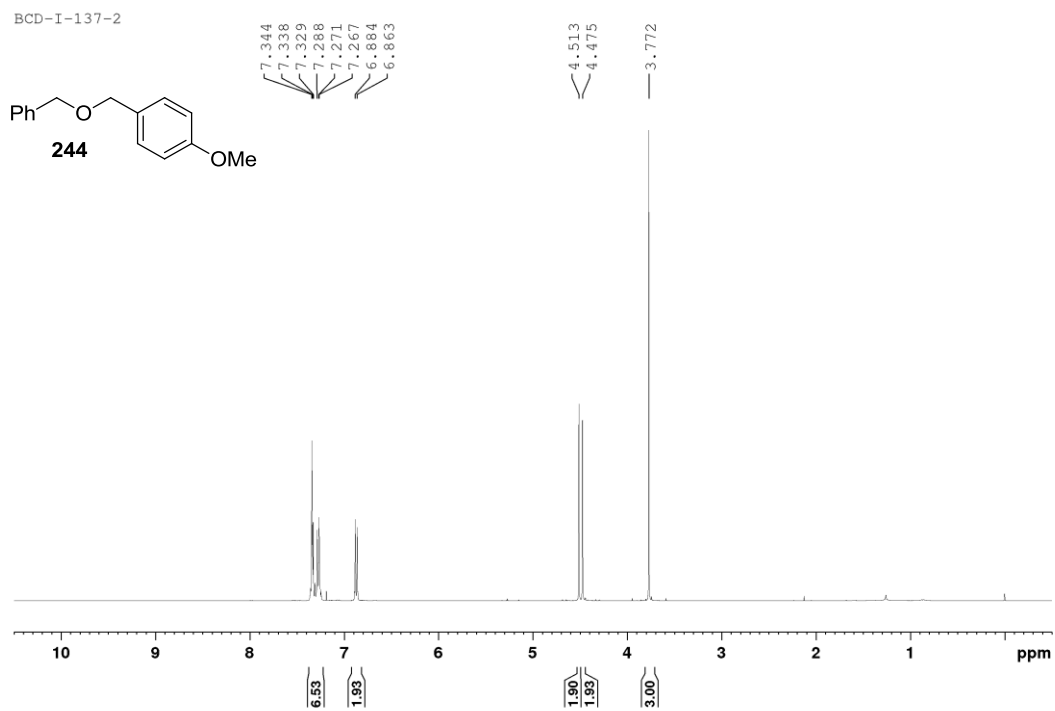


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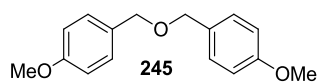




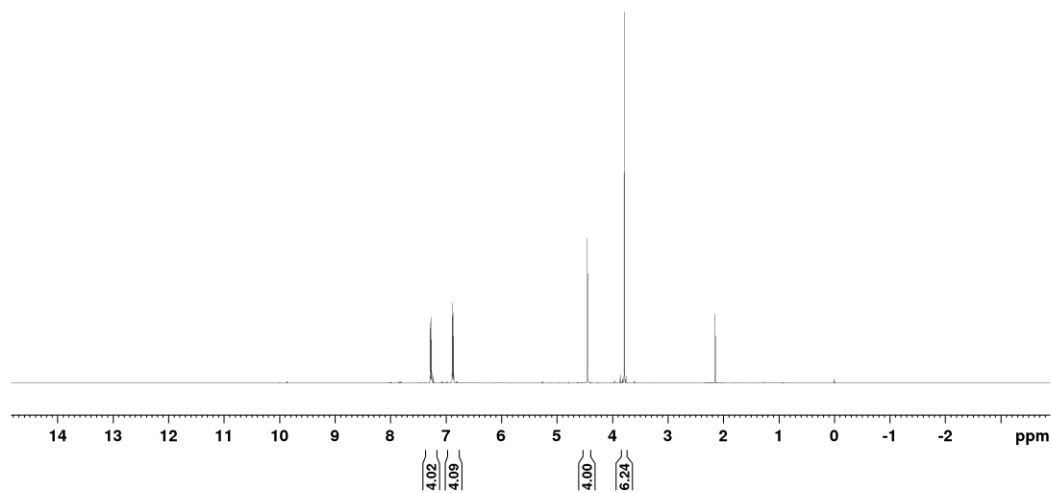




BCD-I-146

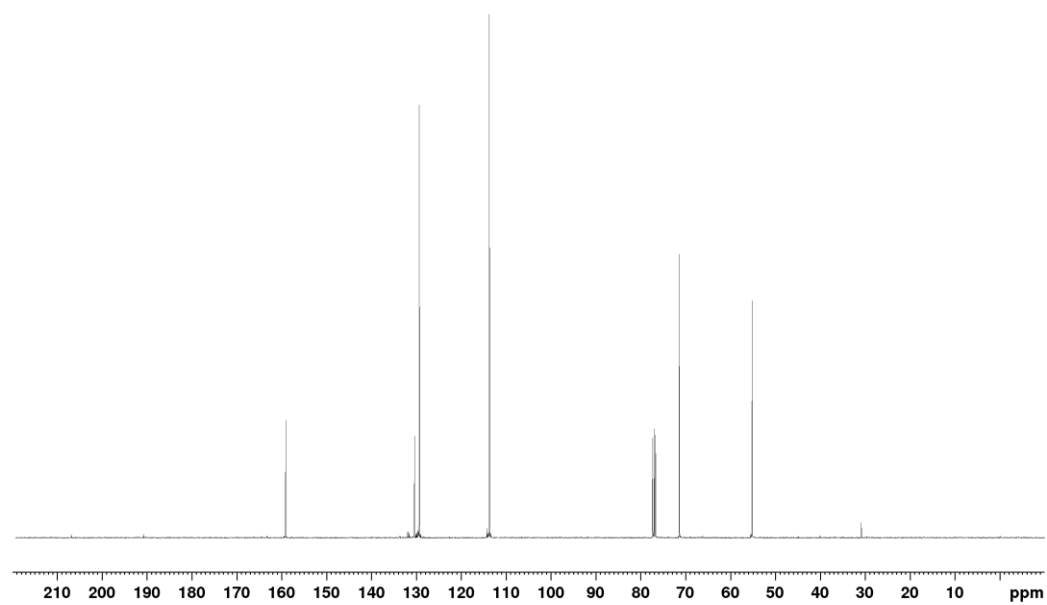


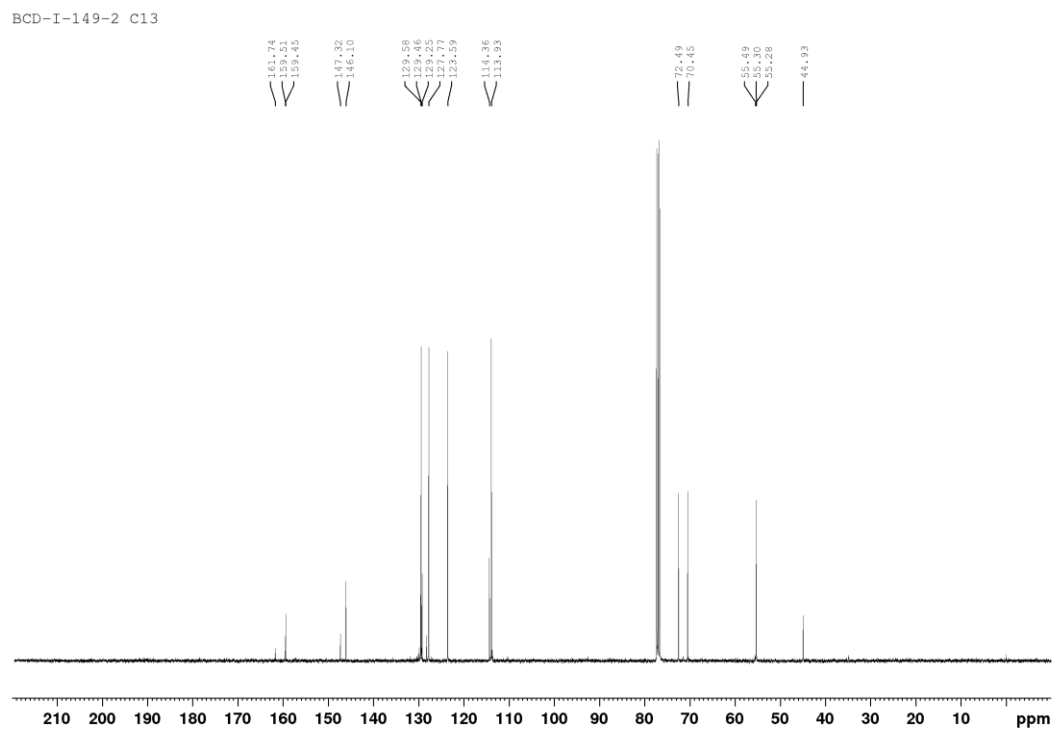
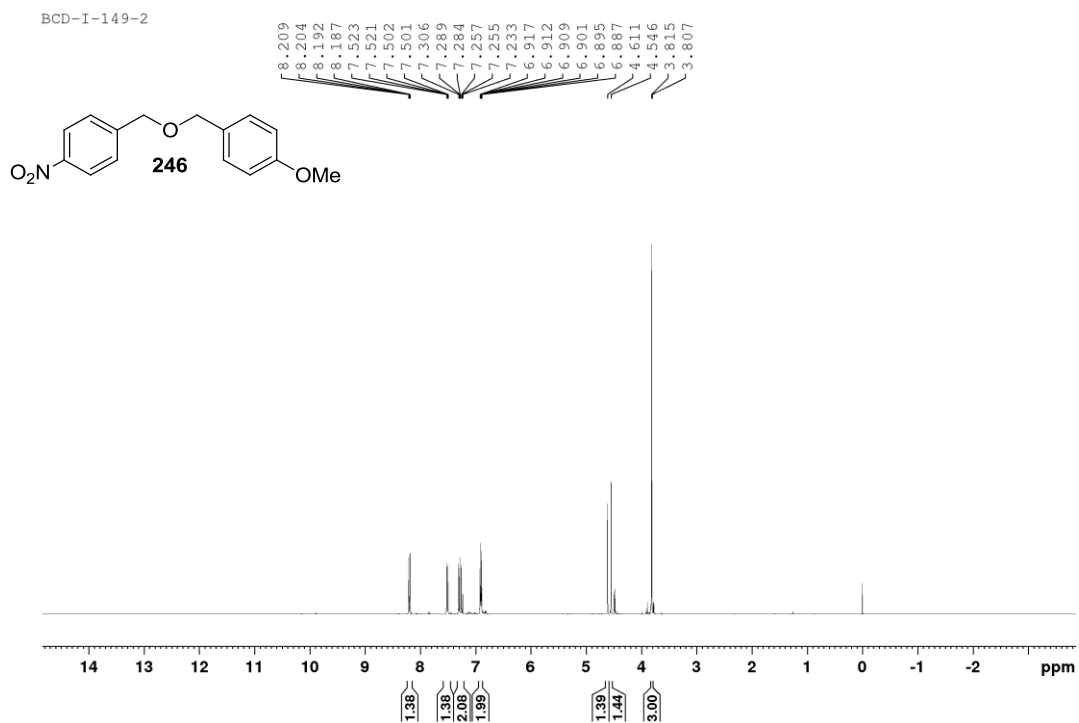
7.282  
7.260  
6.885  
6.863  
4.450  
3.785

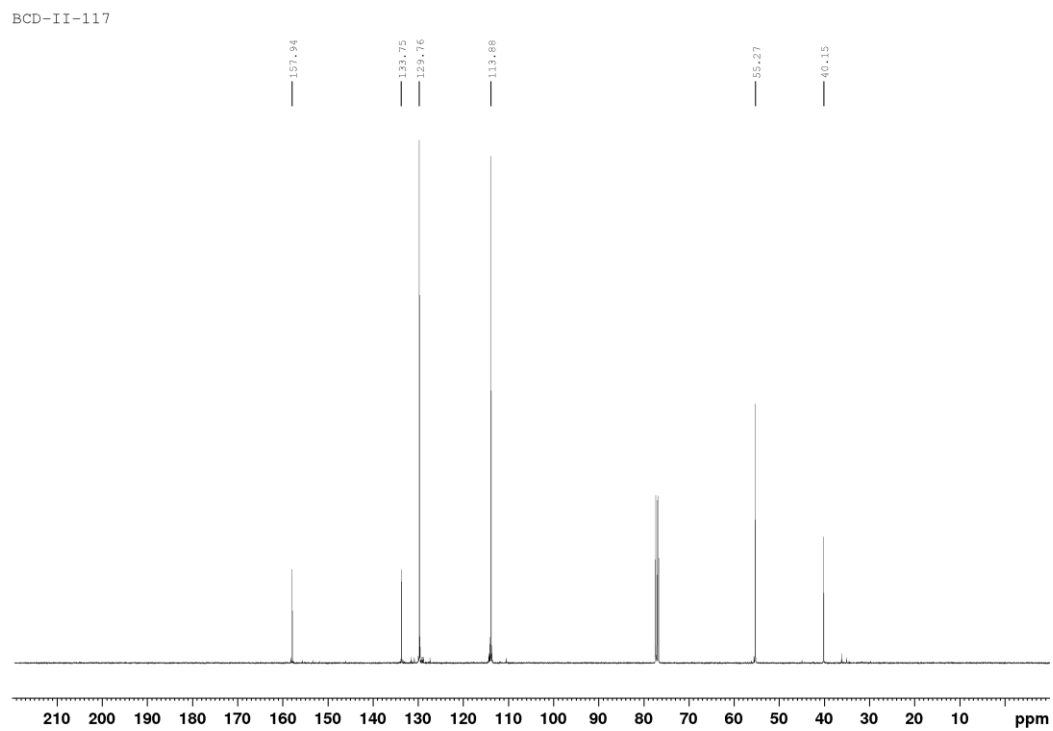
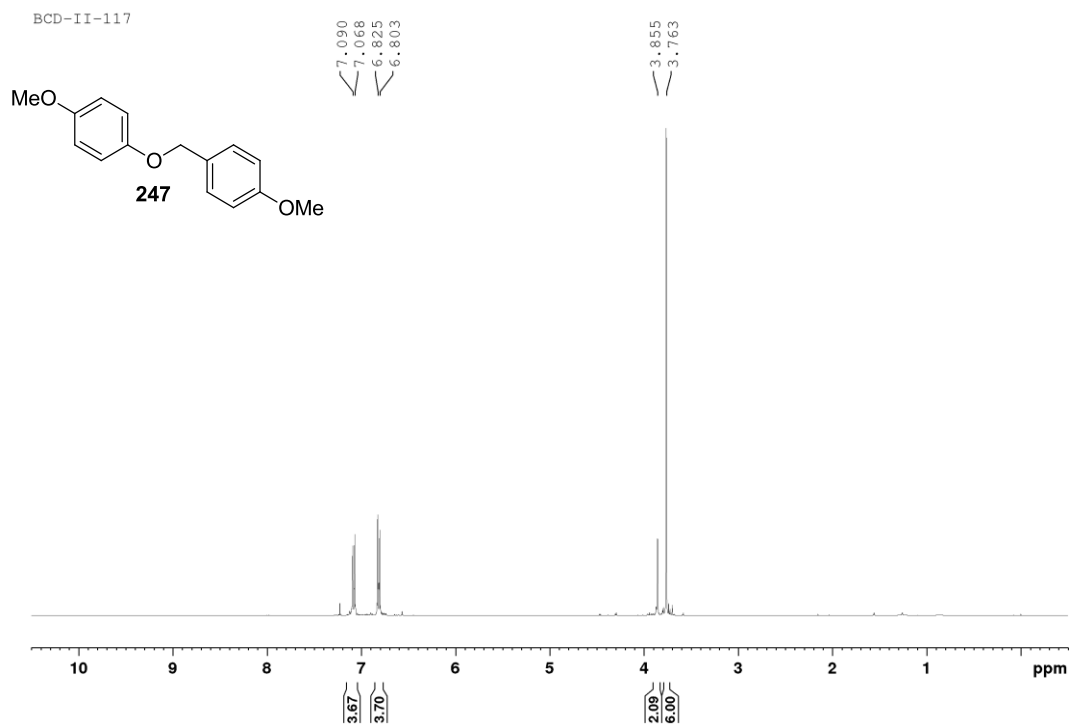


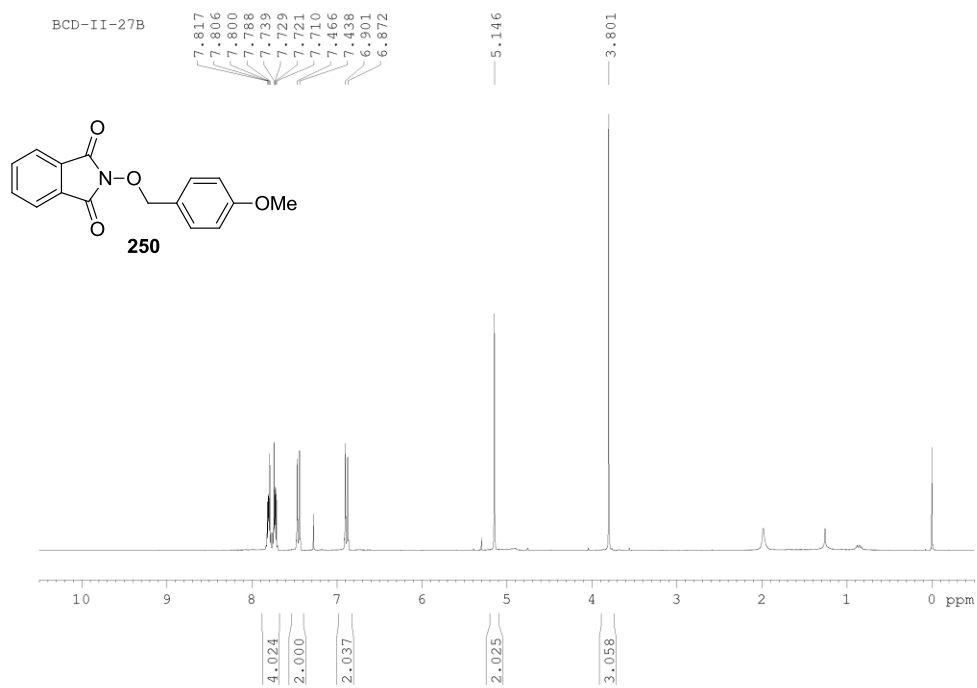
BCD-I-146 C13

159.11  
130.39  
129.34  
113.71  
71.39  
55.18

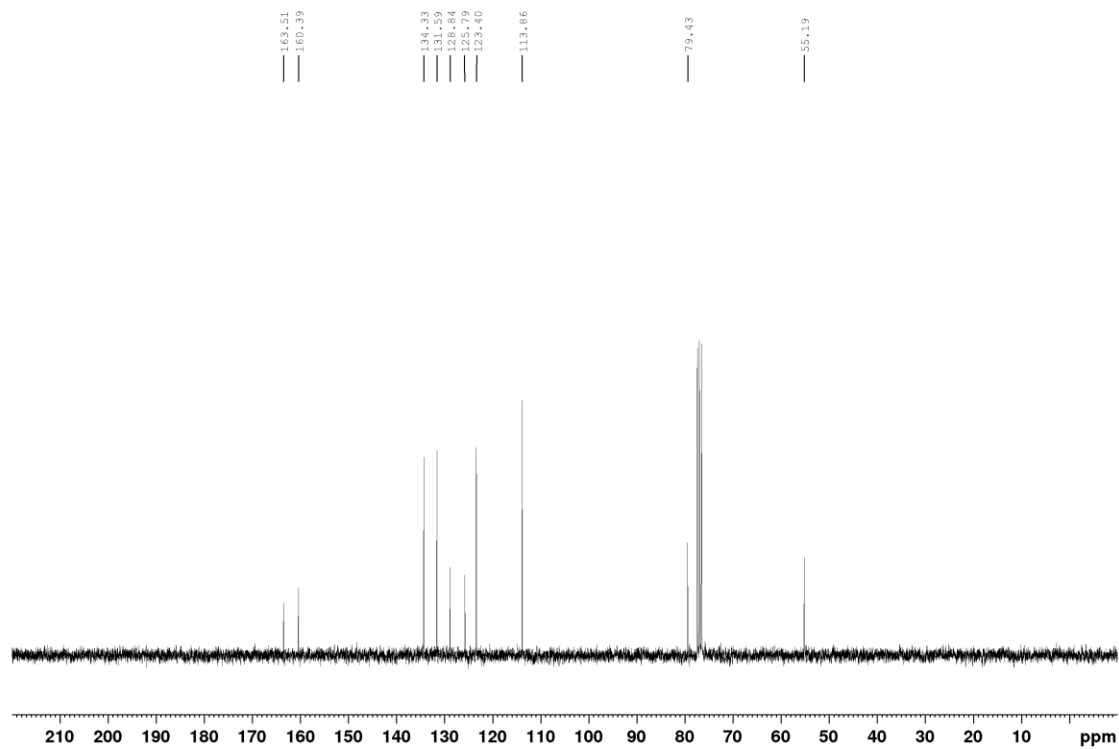




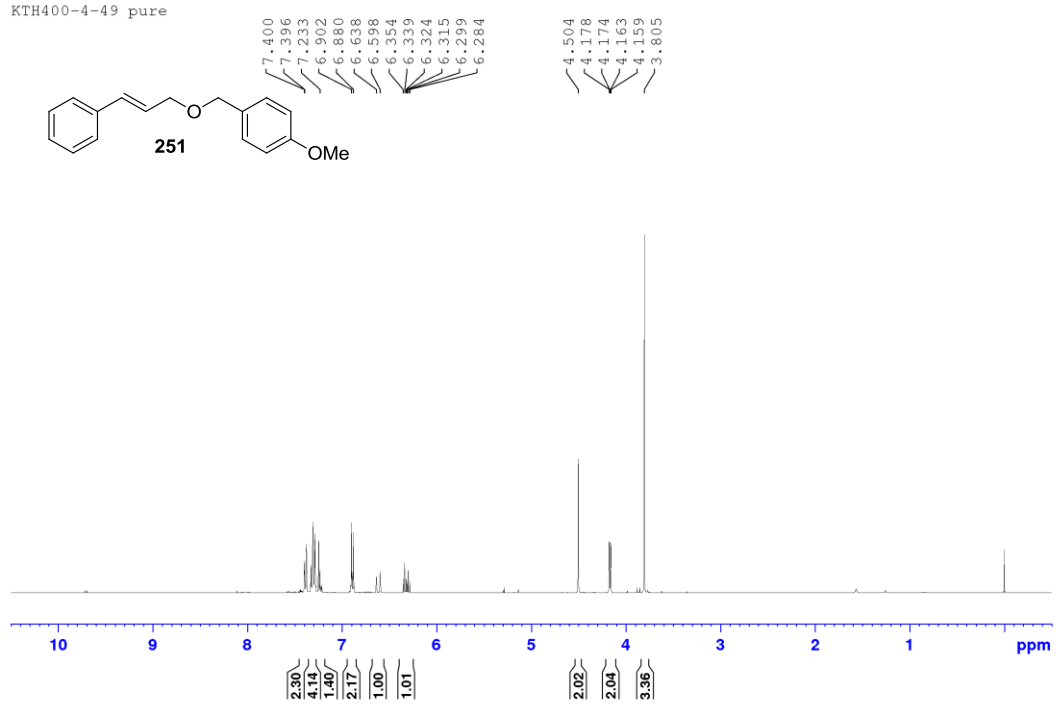




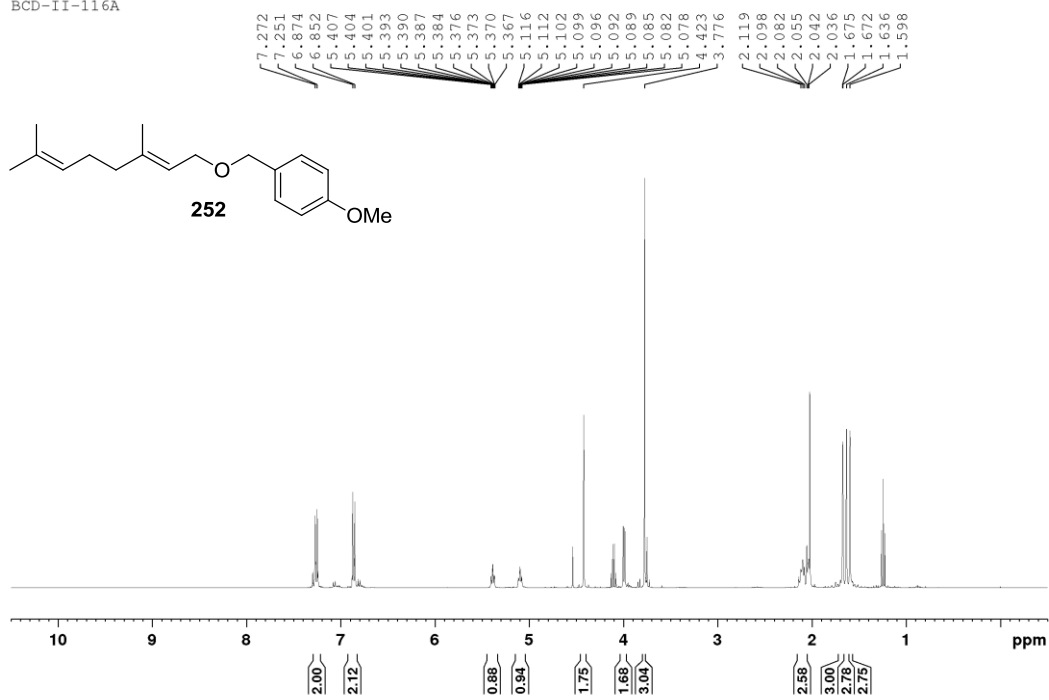
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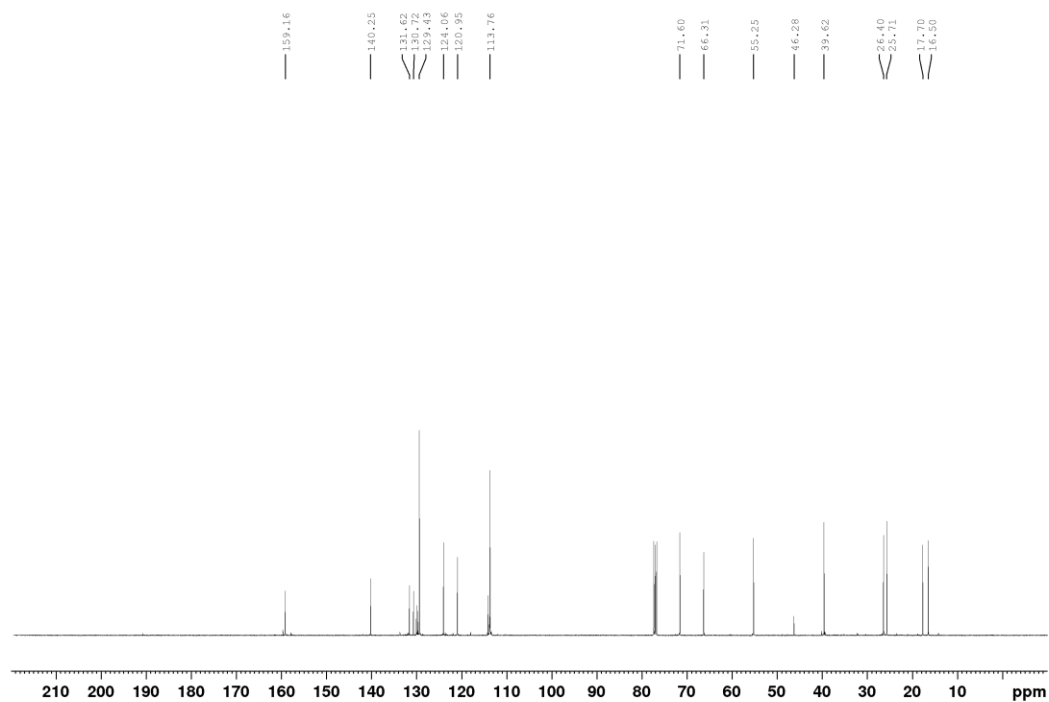
KTH400-4-49 pure

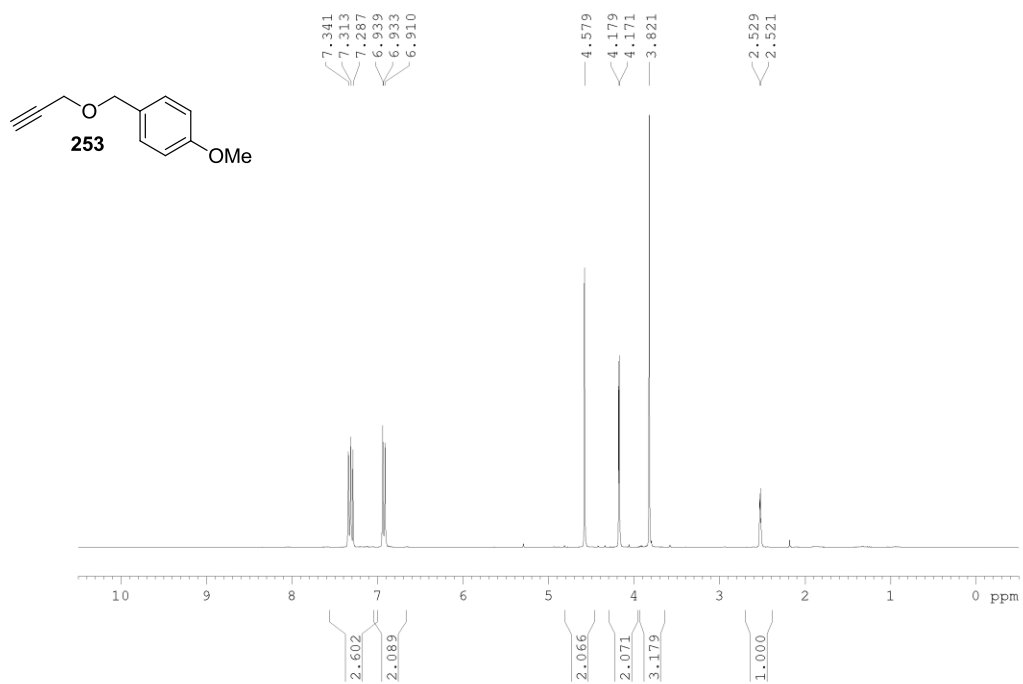


BCD-II-116A



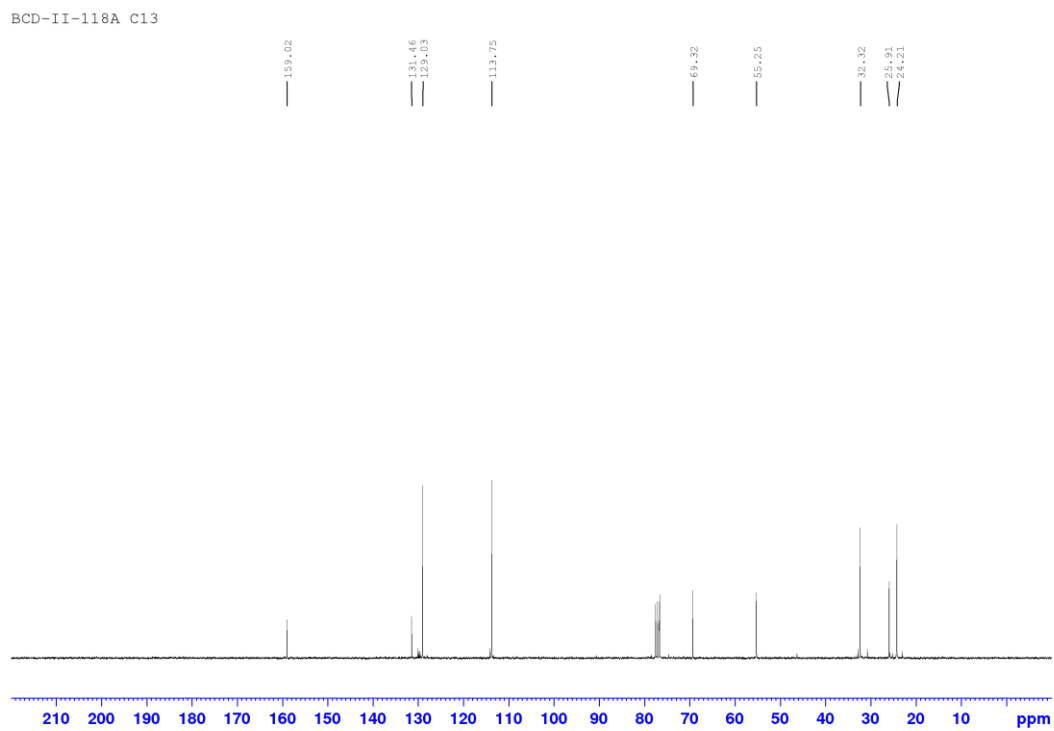
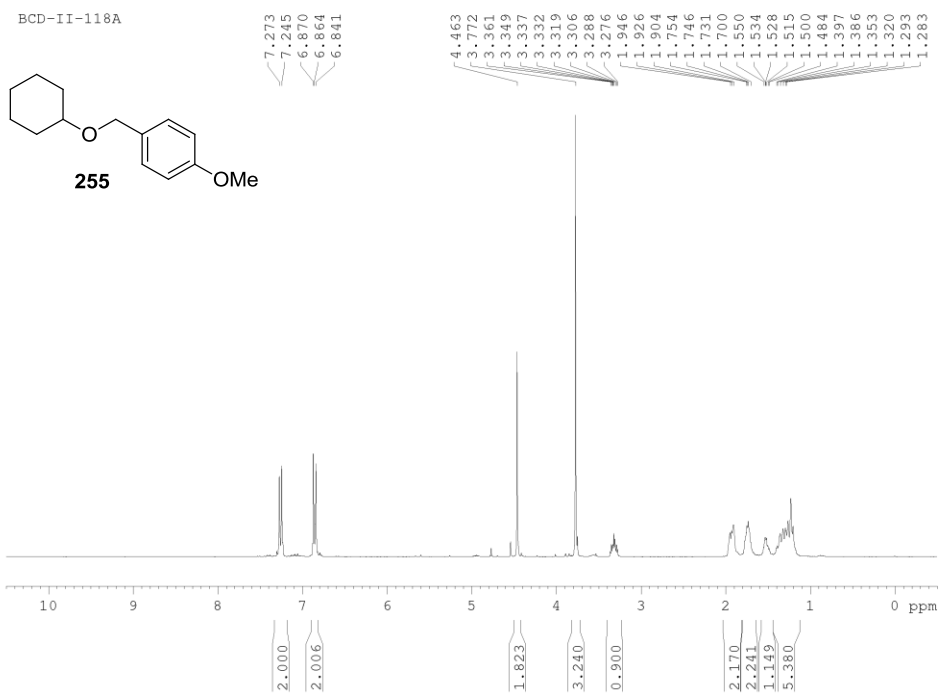
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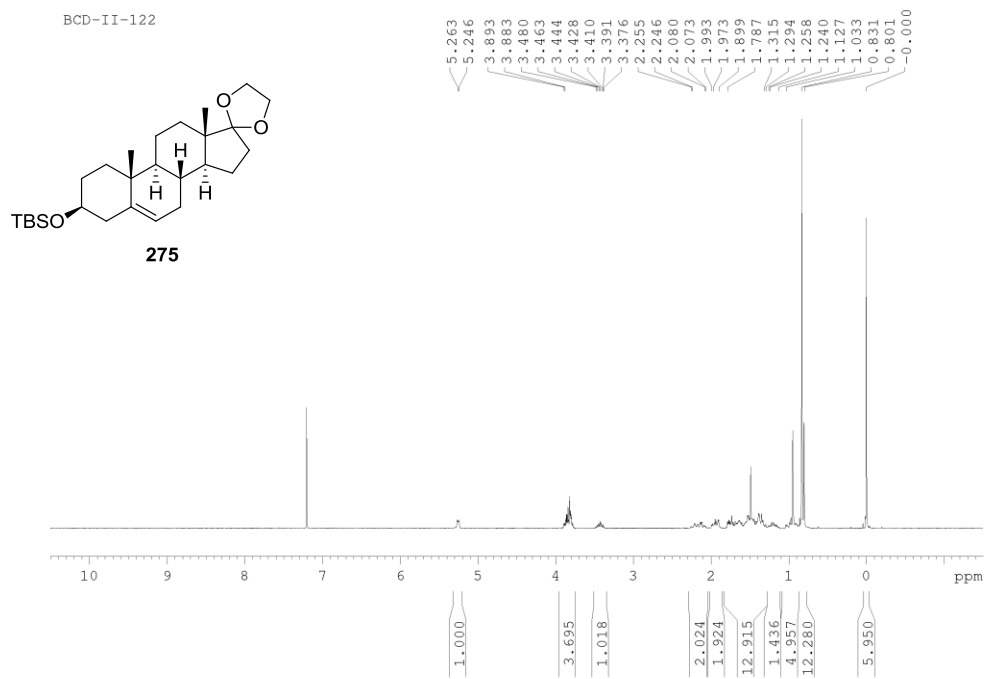
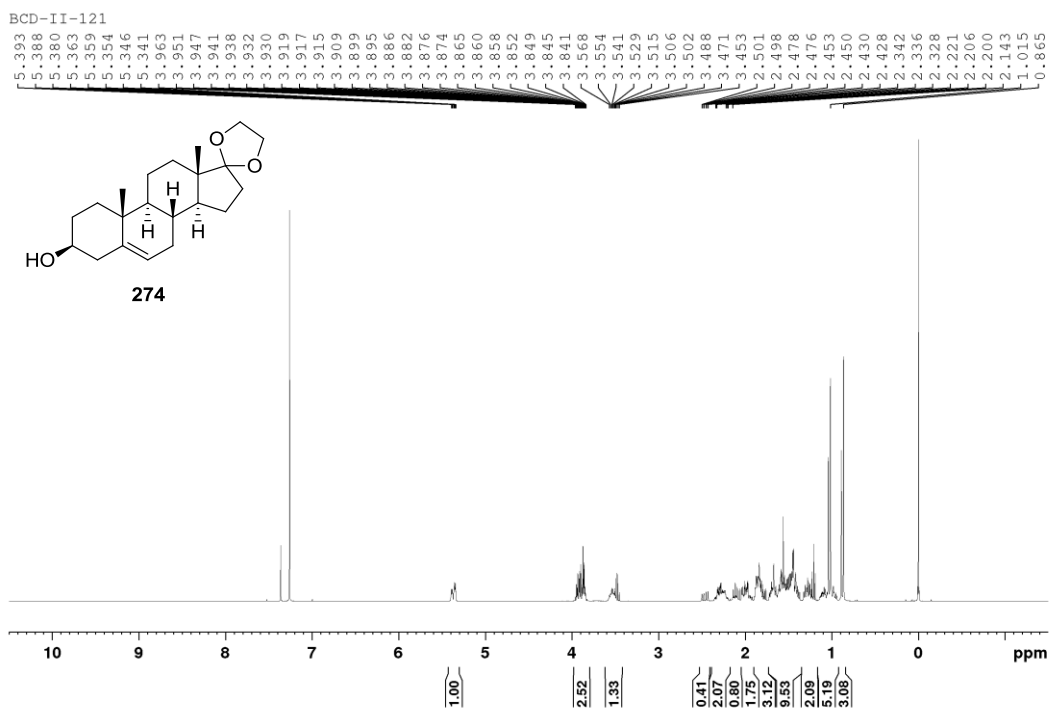


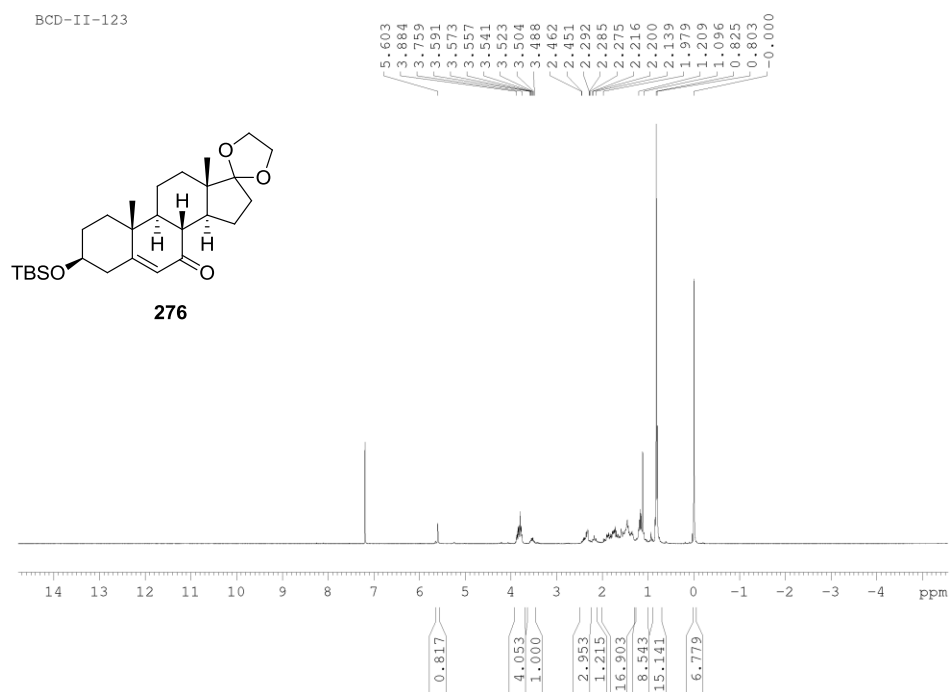




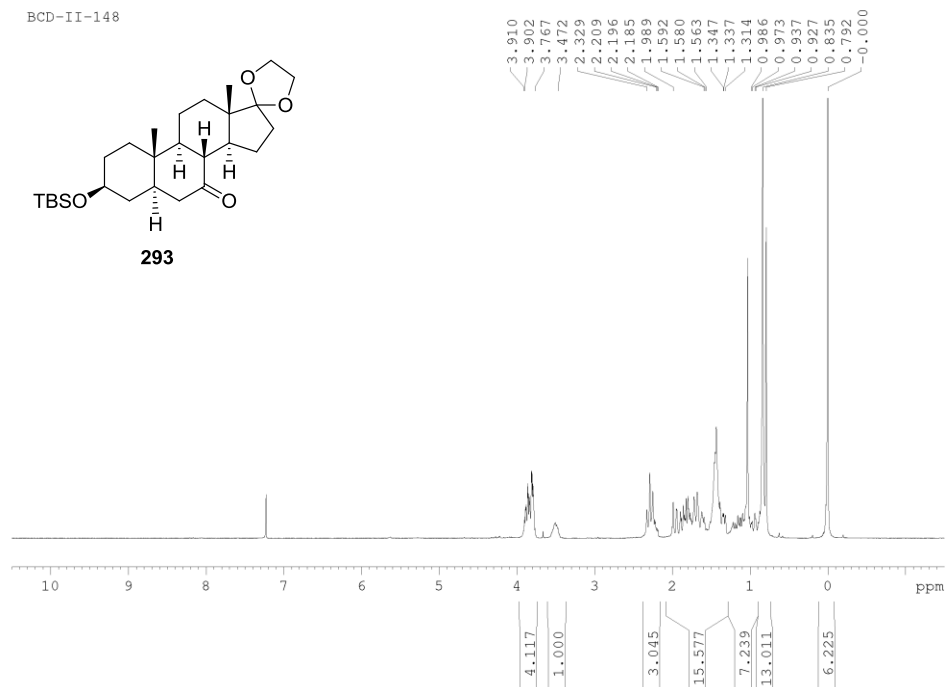
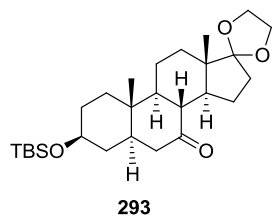




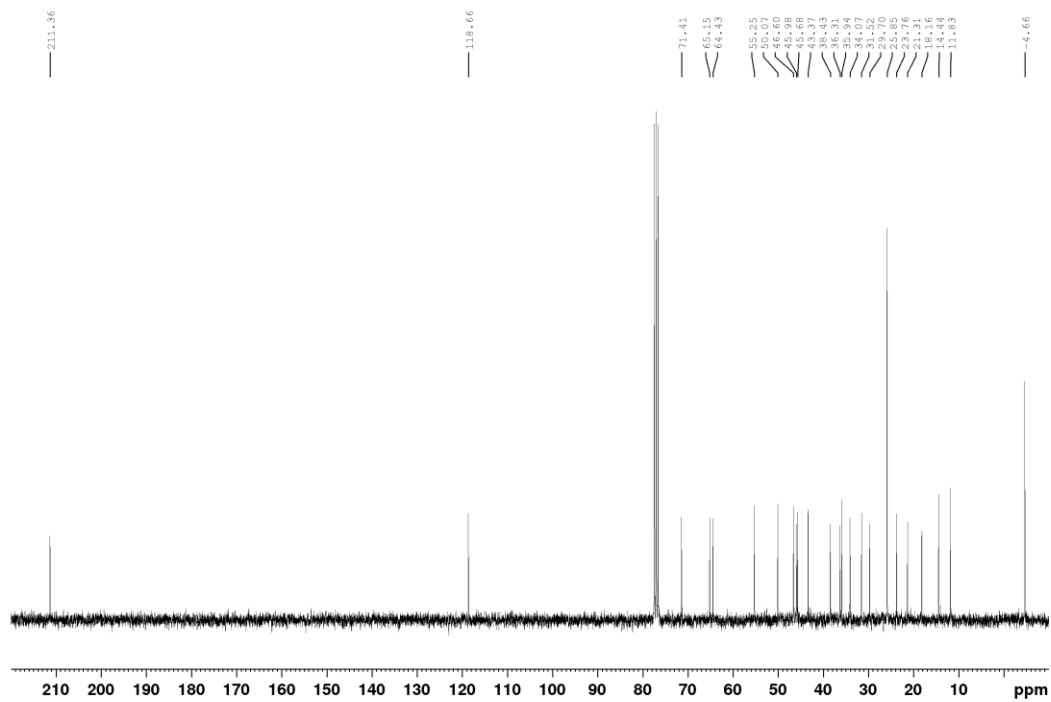




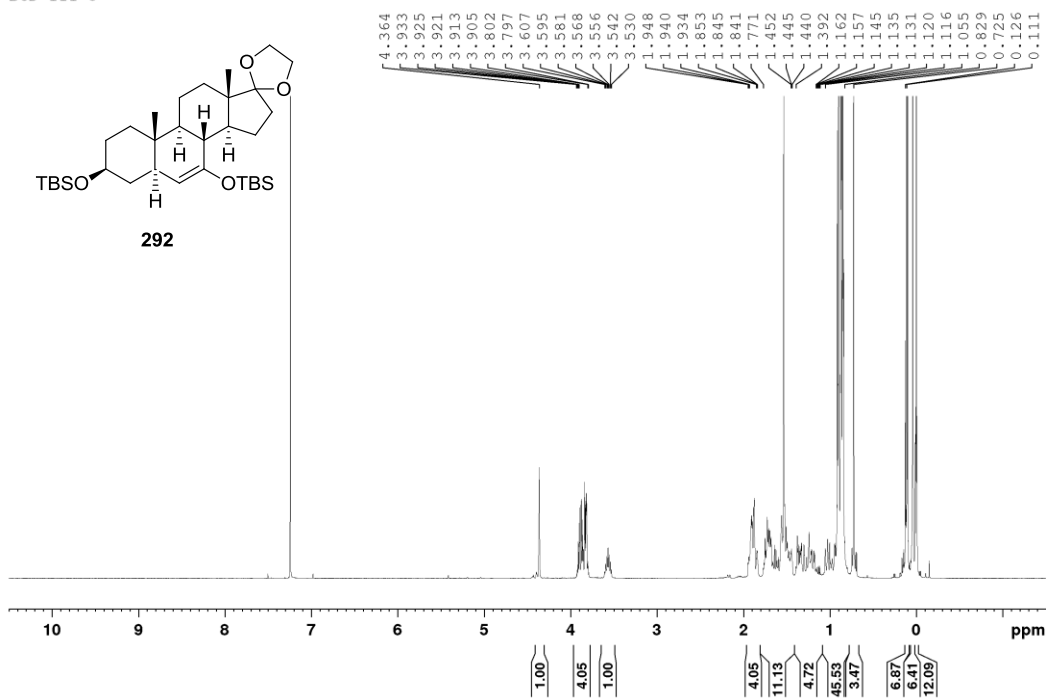
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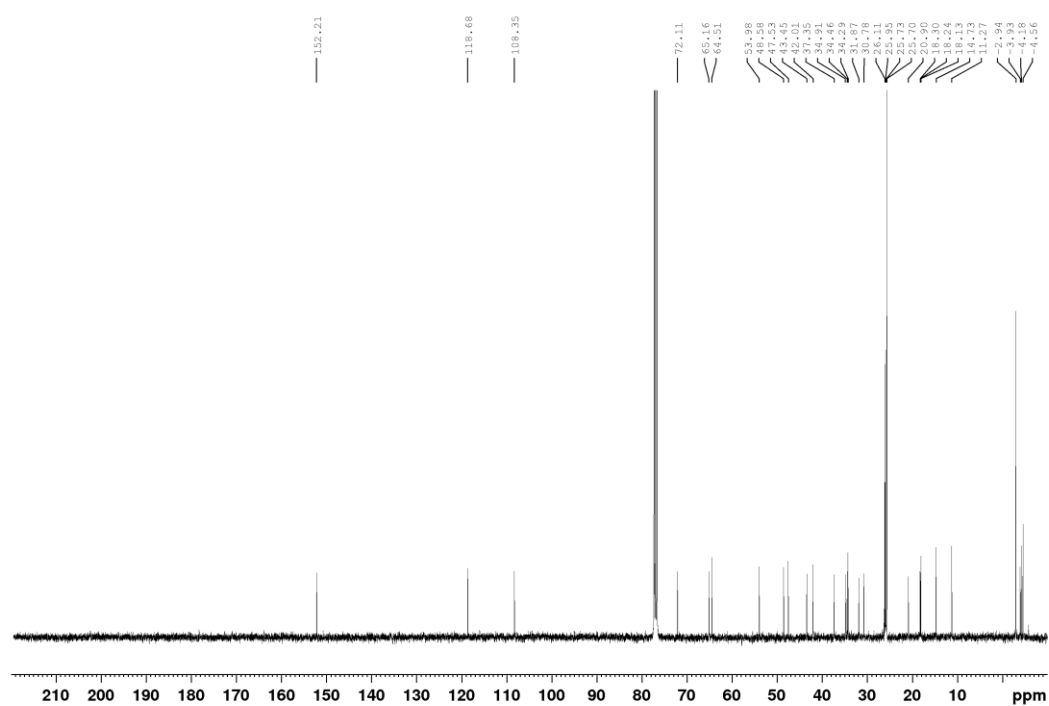
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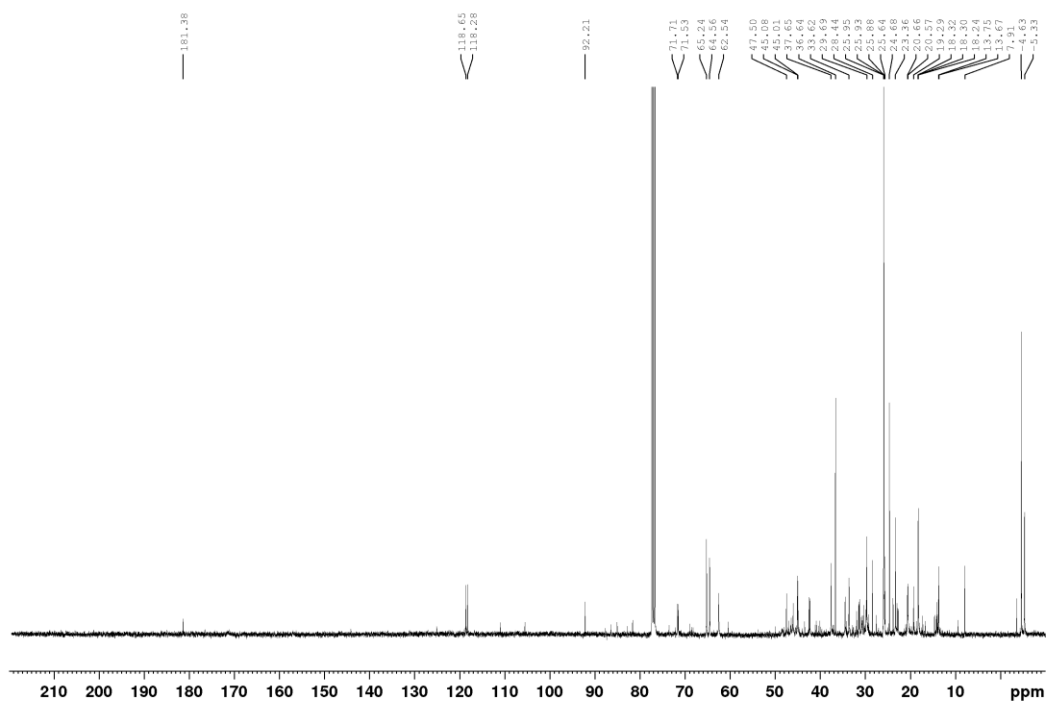
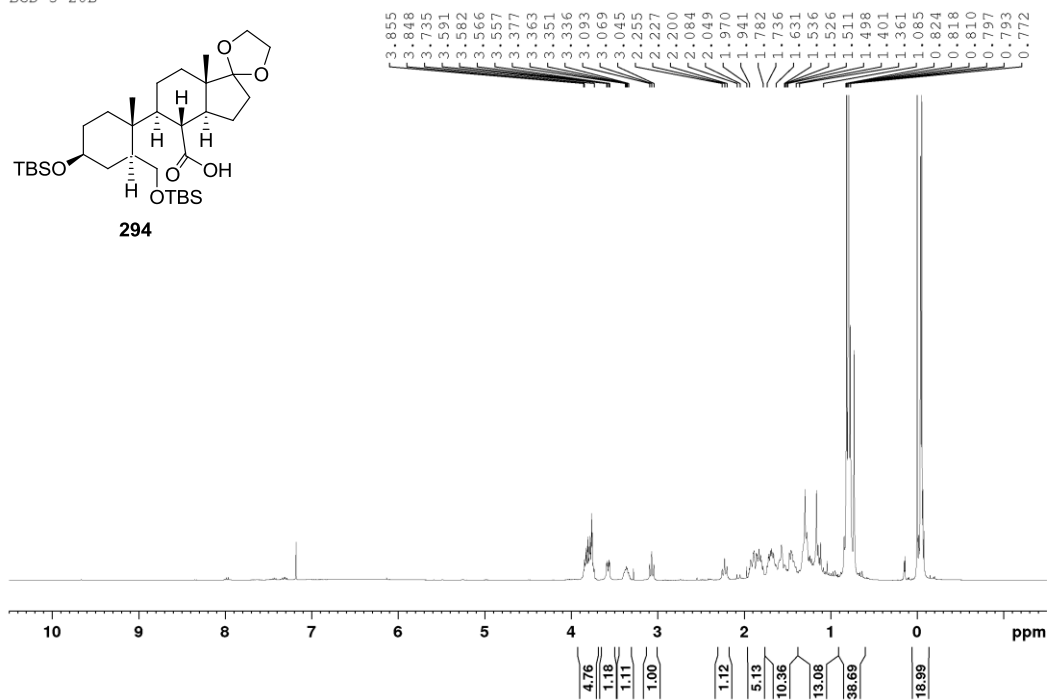
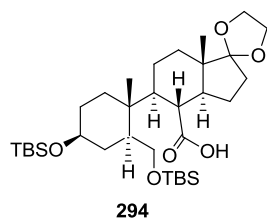
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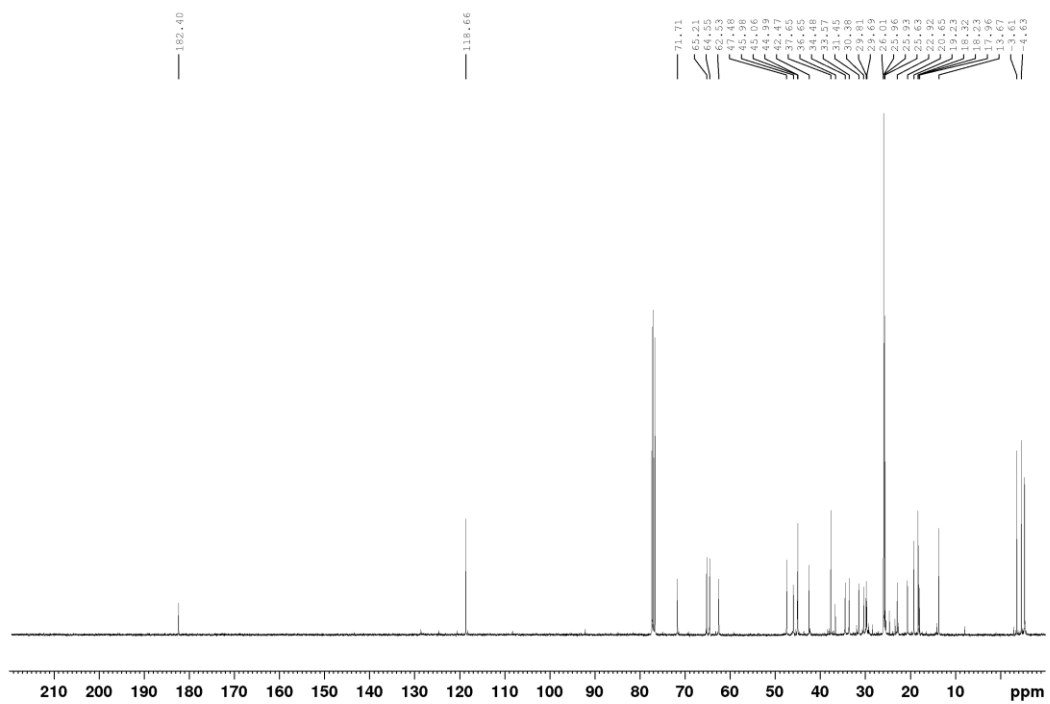
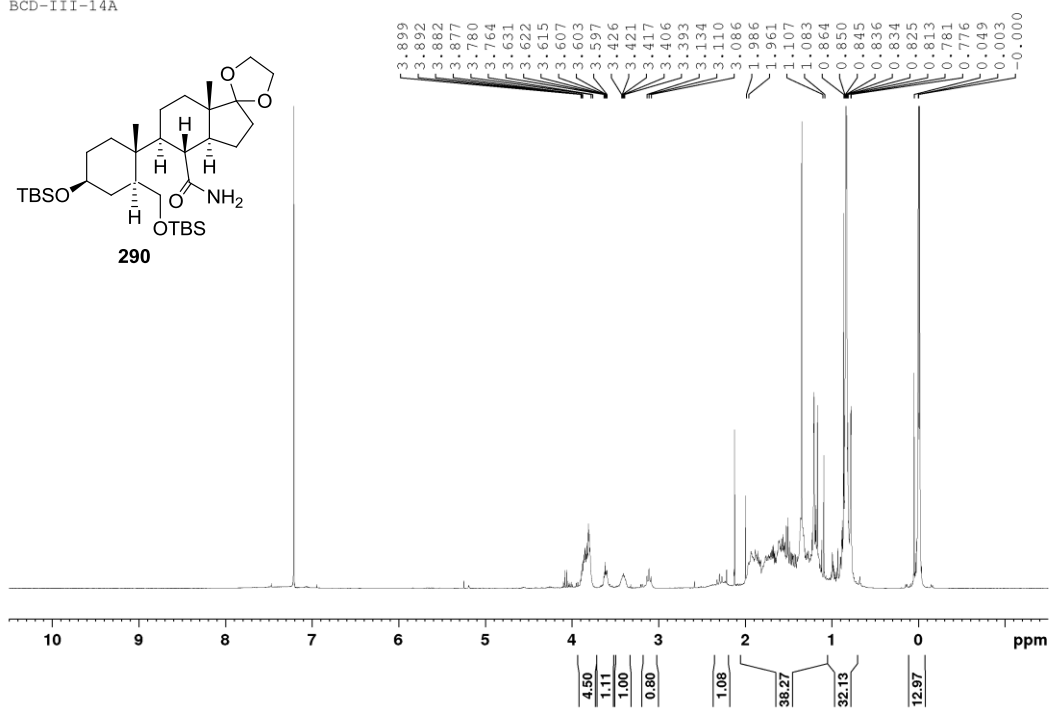
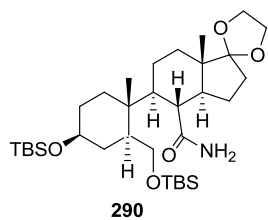
BCD-III-5



BCD-3-20B



BCD-III-14A







## Brian C. Duffy

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919-922-0446

[bduffy@syr.edu](mailto:bduffy@syr.edu)

### Educational Background:

- Doctor of Philosophy: Chemistry  
GPA: 3.7/4.0  
Thesis: *Thioetherification and Etherification Utilizing Trichloroacetimidates Under Thermal Conditions & Progress Towards an Efficient Synthesis of AQX-1125* Defended: June 2016  
Advisor: John Chisholm, Ph.D.  
Syracuse University, Syracuse, NY 13244  
August 2012 – July 2016
- Master of Science: Chemistry  
GPA: 3.6/4.0  
Thesis: *Solvent and Solubility Effects on Quinone Ratios* Defended: June 2012  
Advisor: Brian Love, Ph.D.  
East Carolina University, Greenville, NC 27850  
Graduated: July 2012
- Bachelor of Science: Biochemistry  
East Carolina University, Greenville, NC 27850  
Graduated: July 2009

### Teaching Experience:

- Instructor: Summer Session II - *Organic Chemistry II Lab*  
Syracuse University, July 2015 – August 2015
- Lead Graduate Teaching Assistant- *Organic Chemistry I and II Lab*  
Syracuse University, December 2013 – July 2015
- Graduate Teaching Assistant - *Organic Chemistry I and II Lab*  
Syracuse University, August 2012 - July 2015  
East Carolina University, January 2011-May 2012
- Undergraduate Teaching Assistant - *General Chemistry II Lab*  
East Carolina University, August 2007 – June 2009

### Research Experience:

#### *Doctoral Research:*

- Investigated and developed methodology to obtain thioethers and ethers under essentially neutral conditions from a variety of thiols and alcohols utilizing trichloroacetimidates.
- Developed and implemented a new and more efficient synthetic route towards known SHIP1 agonist, AQX-1125 from trans-dehydroandrosterone utilizing an Ruthenium catalyzed allylic oxidation and an ozonolysis to generate key intermediates.

#### *Masters' Research:*

- Investigated and developed methodology towards finding reaction conditions which allowed formation of either the quinone or corresponding diquinone as the major product upon treatment of 2-alkyl-1,4-dimethoxybenzenes with ceric ammonium nitrate.

Professional Memberships, Certifications, and Awards:

Certificate in College Teaching  
Syracuse University Summer Fellowship  
National Science Teacher Association (NSTA)  
Graduate Teaching Award in Chemistry

Received TBD  
June 2015

May 2012 (East Carolina University)

Presentations:

1. **Duffy, B.C**; Howard, K.T.; Chisholm, J. D., Synthetic Thioetherification and Etherification Under Neutral Conditions Using Trichloroacetimidates. 250<sup>th</sup> ACS National Meeting & Exposition – Boston: Research Poster Session; August 2015
2. **Duffy, B.C**; Howard, K.T.; Chisholm, J. D.; Catalyst-free Generation of Sulfides Utilizing Trichloroacetimidates. 44<sup>th</sup> National Organic Chemistry Symposium - University of Maryland, College Park: Research Poster Session; June 2015
3. **Duffy, B.C.**; Chisholm, J. D., Synthetic Studies on Small-Molecule SHIP1 Agonists; 2015 Northeast Regional Meeting – Ithaca College: Research Poster Session; June 2015
4. Howard, K.T.; **Duffy, B.C**; Chisholm, J. D., Convenient formation of PMB and DPM ethers with trichloroacetimidates under thermal conditions. 248<sup>th</sup> ACS National Meeting & Exposition – San Francisco: Research Poster Session; August 2014
5. **Duffy, B.C**; Howard, K.T.; Chisholm, J. D; Direct Alkylation of Thiols with Trichloroacetimidates Under Neutral Conditions. University of Buffalo - Chemistry Graduate Student Symposium: Research Poster Session; May 2014
6. **Duffy, B.C**; Love, B.; Solvent and Solubility Effects on Quinone Ratios; East Carolina University: Research Oral Session; March 2012

Publications:

1. Howard, K.T.; **Duffy, B.C.**; Linaburg, M.L.; Chisholm, J. D., Formation of DPM Ethers Using *O'*-Diphenylmethyl Trichloroacetimidate Under Thermal Conditions. *Org. Biomol. Chem.* **2016**, 14, 1623-1628.  
doi: 10.1039/C5OB02455B
2. **Duffy, B.C**; Howard, K.T.; Chisholm, J. D., Alkylation of Thiols with Trichloroacetimidates under Neutral Conditions. *Tetrahedron Lett.* **2015**, 56, 3301-3305. doi.org/10.1016/j.tetlet.2014.12.042
3. Love, B. and **Duffy, B.C.**, A One-Pot Synthesis of Blattellaquinone. *The Chemical Educator*, **2014**, 19, 287-288. doi: 10.1333/s00897142576a
4. Love, B.; **Duffy, B.C.**; Simmons, A., Effects of reaction conditions on quinone/diquinone product ratios in the oxidation of 1,4-dimethoxybenzene derivatives with ceric ammonium nitrate. *Tetrahedron Lett.* **2014**, 12, 1994-1997. doi: 10.1016/j.tetlet.2014.02.017
5. **Duffy, B.C.**; Chisholm, J. D., Synthetic Studies on Small-Molecule SHIP1 Agonists. *Manuscript in Progress.*
6. Howard, K.T.; **Duffy, B.C.**; Chisholm, J. D., Formation of PMB Ethers with Trichloroacetimidates under Thermal Conditions *Manuscript in Progress.*