Selective Reductions Directed by Rehydrated Alumina and Thiomethylation Using Dimethylsulfoxide

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by

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Authorization to Submit Dissertation

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Abstract

This dissertation describes the development of two synthetic methods based on alumina and dimethylsulfoxide. Chapter 1 describes the 1,2-regioselective reduction of α,β-unsaturated ketones to their corresponding allylic alcohols with $NaBH_4$ in the presence of acidic activated alumina rehydrated to the Brockmann II grade by adding 3% w/w water. The substrate scope includes eight ketones reduced in high regio- and diastereoselectivity to their corresponding allylic alcohols. This is a first application of the general strategy of systematically tuning the surface chemistry of alumina via partial rehydration in order to modulate selectivity in a chemical reaction.

Chapter 2 describes a unique synthesis of aryl methyl sulfides via reduction of dimethylsulfoxide to dimethylsulfide at elevated temperature in the presence of Hunig's base followed by nucleophilic aromatic substitution and demethylation. In this reaction, dimethylsulfoxide serves as a simple and inexpensive formal source of the thiomethyl moiety. Activated aryl fluorides, chlorides, and nitrobenzenes are all suitable substrates with twelve examples demonstrated.

Chapter 3 gives an account of progress made in the effort to develop an efficient synthesis of the methicillin-resistant *staphylococcus aureus* (MSRA)-active antibiotic tetarimycin A. The chapter describes our failed efforts to prepare a key intermediate that would potentially enable a powerful new cyclization reaction that we envisioned could generate the two central rings of the tetracyclic target via combined Knoevenagel and Friedel-Crafts transformations.

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Dedication

"Then Samuel took a stone, and set it *between Mizpeh and Shen, and called the name of it* ***Ebenezer****, saying, Hitherto hath the LORD helped us". This dissertation is dedicated to the glory of God, my parents (Julius and Doris), my only sister Josephine Jones-Mensah and my lovely and beautiful wife Mrs. Laudina Jones-Mensah.*

Table of Contents

List of Tables

List of Figures

List of Schemes

List of Abbreviations

Ac	acetyl
Aq.	aqueous
B	Brockmann
Bn	benzyl
Bz	benzoyl
t-Bu	*tert*-butyl
9-BBN	9-Borabicyclo[3.3.1]nonane
cat.	catalytic amount
CoA	Coenzyme A
d	doublet
DCM	dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
Et	ethyl
Equiv	equivalents
FTIR	fourier transform infrared

gem	geminal
h	hours
HMBC	heteronuclear multiple bond correlation
HRMS	high resolution mass spectrometry
Hz	Hertz
IR	infrared
KCN	potassium cyanide
KS	ketoacyl synthase
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
mL	milliliter
m	multiplet
M	molar
Me	methyl
MRSA	methicillin-resistant *Staphylococcus aureus*
m	*meta*
m.p	melting point
N	normal
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
OTf	trifluoromethanesulfonate
p	para
PG	unspecified protecting group

Ph	phenyl
PKS	Polyketide synthase
PPA	polyphosphoric acid
i-Pr	isopropyl
q	quartet
R_f	relative to front
s	singlet
r.t	Room temperature
SEM	scanning electron microscopy
SM	starting material
S_NAr	nucleophilic aromatic substitution reaction
t	triplet
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSCN	trimethylsilyl cyanide
Ts	*p*-toluenesulfonyl (tosyl)
TsOH	*p*-toluenesulfonic acid
w/w	weight per weight

Chapter 1: Cerium-Free Luche Reduction Directed by Rehydrated Alumina

Chapter 1 is an adapted version of a manuscript in press. Changes include minor modifications to schemes and tables as well as some minor additions.

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Abstract

A 1,2-regioselective reduction of *α,β*-unsaturated ketones to their corresponding allylic alcohols is accomplished with $NaBH_4$ in the presence of acidic activated alumina rehydrated to the Brockmann II grade by adding 3% w/w water. The substrate scope includes eight ketones reduced in high regio- and diastereoselectivity to their corresponding allylic alcohols. This is the first demonstration of this strategy of systematically tuning the surface chemistry of alumina via partial rehydration in order to modulate selectivity in a reaction. Alumina is an appealing alternative to the common Luche reduction additive, $CeCl_3$, from the perspective of cost and procedural simplicity.

Keywords: Alumina, 1,2-reductions, Enones, Allylic alcohols, Rehydration

Section 1.1. Introduction

Transition aluminas (γ-, δ-, κ-, χ-, and η-Al_2O_3), often broadly termed 'activated' aluminas, are the products of thermal dehydration of various polymorphs of aluminum hydroxide $Al(OH)_3$.[1, 2] The structural and surface characteristics of transition aluminas have been extensively studied.[3-6] With high-surface areas, Lewis Acid, Brønsted Acid, and basic

sites, activated aluminas have found use as catalysts and catalyst supports for both industrial processes[1] and laboratory-scale organic chemistry.[7-13]

In 1941 Brockmann and Schodder altered the chromatographic behavior of activated alumina by adding water and equilibrating in a closed vessel at room temperature.[14] The resulting 'Brockmann Scale' (numbered I-V and corresponding to approximately 0, 3, 6, 10, and 15 % w/w water added to activated alumina) now serves as general terminology used to crudely quantify and standardize the degree of dehydration/rehydration (or activation/deactivation) of some activated aluminas.[15] Activated aluminas are typically sold at the Brockmann I grade which corresponds to a water content of 1-1.5 % as determined by Karl Fisher titration (or $Al_2O_3 \cdot nH_2O$ where n = 0.06 - 0.08).[15]

The apparent simplicity of Brockmann's hydration scale is starkly contrasted by the complex and multi-faceted relationships that exists between degree of hydration and the surface properties, particularly Lewis acidity, of aluminas which continue to be elucidated.[16] While a number of chemo-, regio-, and stereoselective reactions at alumina surfaces have been reported,[17-21] the degree of hydration of aluminas has not been generally considered as a variable with a potential impact on reaction selectivity. Schuchardt and co-workers have published a series of reports describing the use of aqueous H_2O_2 in the presence of alumina to epoxidize olefins.[22-25] The authors investigated the role of water in the context of catalytic activity of alumina surfaces. They correlated the amount of water per unit of surface area of alumina to the hydrophilicity of the alumina surfaces and concluded that the epoxidations proceeded best with an optimal level of hydrophilicity that was high enough to promote rapid interaction of the alumina surface with hydrogen peroxide but also low enough to avoid impeding the approach of olefin substrates to the active sites.[23]

The concept of "wet alumina" (water added to commercially available alumina), has appeared several times in synthetic literature primarily in the context oxidations of a variety of substrates using chromium (VI) oxide,[26-28] potassium peroxymonosulfate (Oxone®),[29-32] and other oxidants,[33, 34] supported on wet alumina. As part of our broader efforts to develop heterogeneous tools that reduce the environmental footprint, cost, and procedural complexity of synthesis,[35, 36] we recently began looking closer at the rehydration of activated aluminas as practical strategy for modulating reactivity and selectivity.

Wet alumina was first used to effect a synthetic transformation by Morinoto and co-workers in 1991.[32] The authors described a Baeyer-Villiger Oxidation of several ketones in the presence of Oxone and wet alumina in dichloromethane. The alumina was prepared by adding 20 % w/w water to a commercial alumina followed by vigorous shaking. The word 'wet' did not imply the presence of a slurry as the alumina remains a free-flowing powder after addition of water. As the authors did not report whether studies were conducted that led them to choose 20 % as a suitable amount of water, we decided to conduct a brief experiment of our own to investigate this issue. The results of our study are illustrated in Figure 1.1. We used commercially available acidic, activated alumina, Brockmann I grade, with water added in eight sequential increments from 0 to 28 % w/w. These rehydrated aluminas were combined with Oxone, and 4-*tert*-butylcyclohexanone in ethyl acetate and the mixtures stirred for eight hours at room temperature followed by filtration and analysis of the crude reaction mixtures by ^{1}H NMR. We found the yield of the Baeyer-Villiger Oxidation product, γ-*tert*-butyl-ε-caprolactone, to be dependent on the amount of water that been added to the alumina. The maximum NMR yield of 68 % was observed with 16% w/w water. At 8 % water and below, we observed less than 5 % of the lactone.

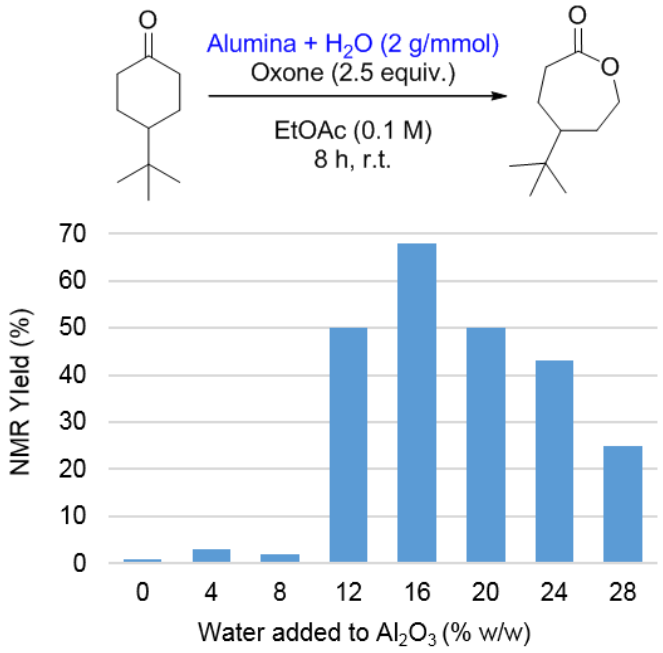
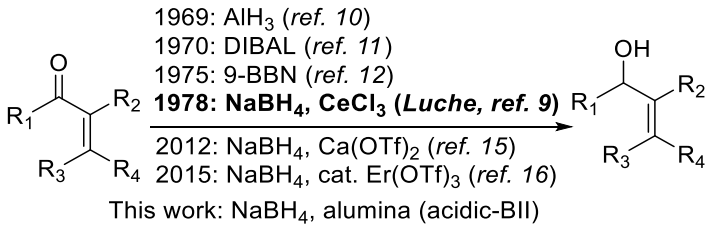


Figure 1.1. Effect of water content of alumina on the yield of the Bayer-Villiger Oxidation of 4-tert-butylcyclohexanone with Oxone and wet alumina.

(Product yields were determined via ^{1}H NMR with anisole used as an internal standard.)

We considered the above result to be a clear demonstration that the degree of rehydration of alumina is a significant and potentially valuable variable in the context of new reaction development that employs alumina as a support or catalyst. Consequently, we have begun an effort to investigate new potential applications of rehydrated aluminas. As our first original contribution in this area, herein we describe a simple and inexpensive process that employs partially rehydrated activated acidic alumina (3% w/w water added; Brockmann II) to promote the regioselective 1,2-reduction of α,β-unsaturated ketones with sodium borohydride ($NaBH_4$) in ethyl acetate (EtOAc).

Section 1.1.1. A brief history of 1,2-Reductions of α,β-Unsaturated Ketones.



Scheme 1.1. Timeline of 1,2-Reductions of α,β-Unsaturated Ketones.

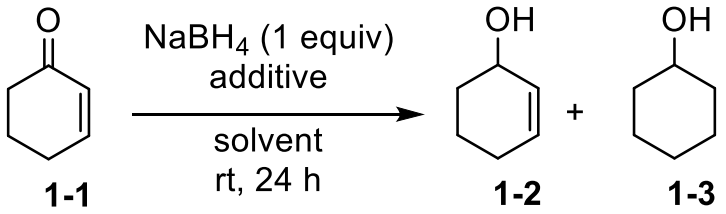
The Luche reduction of α,β-unsaturated ketones to allylic alcohols with $NaBH_4$ in the presence of stoichiometric $CeCl_3$ in methanol was reported in 1978.[37, 38] This mild protocol was preferable to previous approaches with AlH_3,[39] DIBAL,[40] or 9-BBN[41, 42] and has remained the primary method of choice for more than 35 years with few others reported.[43] In 2012, Fuchter and co-workers, seeking alternatives to lanthanides and expanding upon work by Utimoto,[44] found that $Ca(Otf)_2$ was a suitable substitute for $CeCl_3$.[45] In 2015, Nardi used catalytic $Er(Otf)_3$ to achieve selective reductions in 2-MeTHF.[46] Relative to all previous strategies, the use of $NaBH_4$ paired with alumina is preferable in terms of low cost, procedural simplicity, and low environmental impact (Scheme 1.1).

Gemal and Luche attributed the 1,2-selectivity of their $NaBH_4/CeCl_3$/MeOH system to two factors: 1) Brønsted acid coordination of MeOH (enhanced by $CeCl_3$) to the enone, and 2) the conversion of $NaBH_4$ to $NaB(OMe)_nH_{4-n}$ species more selective for 1,2-hydride delivery.[38] Nardi's recent protocol used an aprotic solvent (2-MeTHF) which could neither react with $NaBH_4$ nor engage in Brønsted-type coordination to the substrate, leaving Lewis Acid coordination by $Er(OTf)_3$ to the enone as the sole rationale for selectivity.[46] One might consider $Er(OTf)_3$ to be ideally suited to predispose α,β-enones toward reaction with $NaBH_4$

in a 1,2-fashion. With these studies in mind we decided to investigate the strategy of 'tuning' alumina acidity via rehydration in the context of $NaBH_4$-mediated reduction of enones.

Section 1.2. Results and discussion

We began by treating 2-cyclohexenone (**1-1**) with $NaBH_4$ in the presence of a series of aluminas (Table 1.1). A control reaction with $NaBH_4$ in methanol in the absence of an additive resulted in a 1:1 mixture of alcohols **1-2** and **1-3** (entry 1) while Luche conditions gave exclusively the allylic alcohol (**1-2**, entry 2). Treatment of **1-1** with $NaBH_4$ (1 equiv.) in the presence of activated neutral alumina Brockmann Grade I (Al_2O_3-neutral-B1, 1 g/mmol) in MeOH yielded primarily the dimethylacetal of **1-1** (entry 3) in accordance with previous reports of alumina-mediated carbonyl acetylations.[47, 48] When a series of non-alcoholic solvents were evaluated, most were found to yield an unfavorable ratio of **2** to **3**. Ethyl acetate, which offered a 54:46 ratio in favor of the allylic alcohol **1-2,** was selected as a suitable solvent for further optimization of the alumina additive (entry 4).



Entry	Additive	Solvent	Ratio (1-2 : 1-3)[b]
1	None	MeOH	50 : 50
2	$CeCl_3$ [c]	MeOH	> 99 : 1
3	Al_2O_3-neutral-B1 [d]	MeOH	n/a[e]
4	Al_2O_3-neutral-B1	EtOAc	54 : 46
5	Al_2O_3-neutral-B2	EtOAc	75 : 25
6	Al_2O_3-neutral-B3	EtOAc	68 : 32
7	Al_2O_3-neutral-B4	EtOAc	65 : 35
8	Al_2O_3-basic-B1	EtOAc	46 : 54
9	Al_2O_3-basic-B2	EtOAc	70 : 30
10	Al_2O_3-basic-B3	EtOAc	69 : 31
11	Al_2O_3-acidic-B1	EtOAc	57 : 43
12	Al_2O_3-acidic-B2	EtOAc	79 : 21
13	Al_2O_3-acidic-B3	EtOAc	71 : 29

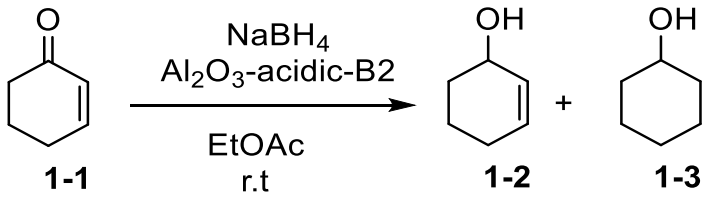
[a.] Reaction conditions for entries 3-13: 2-cyclohexenone (1 mmol), $NaBH_4$ (1 mmol), alumina (1 g), solvent (5 mL), rt, 24 h. [b.] Ratio determined using ^1H NMR after filtration. [c.] Luche conditions were employed (*see ref. 9*). [d.] Neutral, basic, and acidic Brockmann I activated aluminas (Aldrich) were used as purchased (B1) or pre-modified by addition of water (B2-B4, *see experimental section*). [e.] The dimethyl acetal of **1-1** was the major reaction product.

Table 1.1. Optimization of Alumina Additive for the Reduction of 2-Cyclohexenone.[a]

Brockmann II neutral activated alumina (Al_2O_3-neutral-B2) was prepared by adding 3% w/w water to commercially available neutral activated alumina, briefly shaking, and allowing the mixture to equilibrate at room temperature in a sealed vial overnight. The effect of this altered alumina on the selectivity of the reduction was considerable yielding a product ratio 75:25 in favor of 1,2-reduction (entry 4). When the alumina was further rehydrated to Brockmann III (6 % water added) and IV (10 % water added) the selectivity dropped to 68:32 and 65:35 respectively (entries 5 and 6). Commercial suppliers typically offer neutral, basic, acidic versions of activated alumina. This terminology corresponds to the pH of a 5% aqueous suspensions of the aluminas which is approximately 9.5, 7.5, and 4.5 for basic, neutral and acidic aluminas respectively.[15] Aluminas initially obtained by thermal activation of aluminum hydroxide are 'basic' and are subsequently neutralized and acidified by acid treatment under conditions which are proprietary with the degree of hydration remaining at Brockmann I for all three commercially available acidities. We evaluated basic and acidic activated aluminas at the Brockmann I, II, and III water content levels (entries 8-13). In all cases Brockmann II aluminas (3% w/w water) gave a higher selectivity for 1,2-reduction than Brockmann I and III aluminas. Overall, acidic activated Brockmann II alumina (Al2O3-acidic-B2, entry 12) gave the most favorable 2 to 3 ratio of 79:21. Reaction workup in this study consisted of filtration, washing with EtOAc, and removal of solvent. Analysis of the crude filtrate residues by ^{1}H NMR showed primarily compounds 2 and 3 with no major impurities evident. No evidence of boron byproducts was observed via ^{11}B NMR of the crude reaction mixture after filtration. Furthermore, the mass of alumina recovered after filtration and drying at room temperature was higher than the initial mass suggesting presence of adsorbed boron species.

Using the most effective alumina, Al_2O_3-acidic-B2, additional variables were optimized (Table 1.2). Increasing the amount of alumina from 1 to 3 grams per mmol of substrate corresponded to enhancement of selectivity to 84:16 with no further improvement observed at 4 g/mmol (entries 1-4). The reaction rate increased substantially with the substrate consumed in 1 hour and a small drop in selectivity when the amount of $NaBH_4$ was doubled to 2 equiv. (entry 5). All of the above reactions were performed as follows: a slurry of $NaBH_4$ and alumina in ethyl acetate was stirred for 10 minutes before addition of the cyclohexenone. When the $NaBH_4$/alumina pre-stirring time was increased from 10 minutes to 4 hours the reaction rate slowed and selectivity fell to 59:41 (Entry 6) while 8 hours of pre-stirring inhibited the reaction entirely (entry 7). These two experiments were interpreted to indicate that under these reaction conditions, in the absence of a substrate, $NaBH_4$ is converted to substances that are both less reactive and less 1,2-selective toward the reduction of enones. Consequently, we altered the order of addition by combining the substrate and alumina in EtOAc for ten minutes prior to addition of $NaBH_4$. This resulted in a further increase of selectivity to 90:10 (entry 8). A sixty minute delay offered no additional benefit (entry 9). Two acidic aluminas purchased from different suppliers (*see chapter 1 experimental section*) and rehydrated to Brockmann II offered comparable results to those of our original activated alumina (Entries 10-11). Finally, replacement of $NaBH_4$ with $NaCNBH_3$ as the hydride source corresponded to a dramatic decrease in reaction rate and selectivity (entry 12) while $NaBH(OAc)_3$ did not react with 2-cyclohexenone under these conditions resulting only in recovery of unreacted substrate (entry 13). The most favorable ratio of 1,2-reduction to 1,4-reduction of cyclohexenone was 90:10 (Table 1.2, entry 8). Although this procedure constitutes a practically simple and inexpensive approach to 1,2-selective reduction of

unsaturated ketones, it is inferior to the Luche conditions in terms of selectivity in the case of 2-cyclohexenone (Table 1.1, entries 2).



Entry	Al_2O_3[b] (g/mmol)	$NaBH_4$ (equiv.)	Order of Addition	Time (h)	Ratio (**1-2**:**1-3**)[c]
1	1	1	Al_2O_3+ $NaBH_4$ (10 min) then **1-1**	24	79 : 21
2	2	1	Al_2O_3 + $NaBH_4$ (10 min) then **1-1**	24	77 : 23
3	3	1	Al_2O_3 + $NaBH_4$ (10 min) then **1-1**	24	84 : 16
4	4	1	Al_2O_3 + $NaBH_4$ (10 min) then **1-1**	24	84 : 16
5	3	2	Al_2O_3 + $NaBH_4$ (10 min) then **1-1**	1	80 : 20
6	3	2	Al_2O_3 + $NaBH_4$ (4 h) then **1-1**	18	59 :41
7	3	2	Al_2O_3 + $NaBH_4$ (8 h) then **1-1**	24	NR[d]
8	3	2	Al_2O_3 + **1-1** (10 min) then $NaBH_4$	1	90 : 10
9	3	2	Al_2O_3 + **1-1** (60 min) then $NaBH_4$	1	90 : 10
10	3 [e]	2	Al_2O_3 + **1-1** (10 min) then $NaBH_4$	1	88 : 12
11	3 [f]	2	Al_2O_3 + **1-1** (10 min) then $NaBH_4$	1	90 : 10
12	3	2	Al_2O_3 + **1-1** (10 min) then $NaCNBH_3$	24	34 : 66
13	3	2	Al_2O_3 + **1-1** (10 min) then $NaBH(OAc)_3$	24	NR

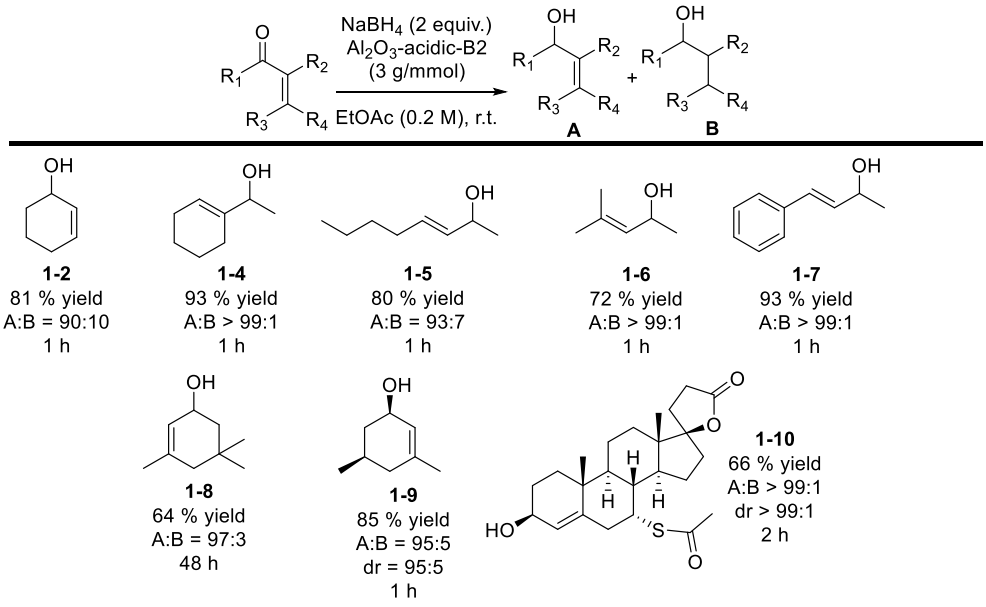
[a.] Reaction conditions: cyclohexenone (1 mmol), alumina, $NaBH_4$, EtOAc (10 mL), r.t. Workup: filtration, washing with EtOAc, and removal of solvent; [b.] Al_2O_3-acidic-B2 prepared from: aluminum oxide, activated, acidic, Brockmann I (Sigma-Aldrich #199966); [c.] Ratio determined via ^{1}H NMR after filtration; [d.] No reaction observed.; [e.] Al_2O_3-acidic-B2 prepared from: aluminum oxide, activated, acidic, Brockmann I (Alfa Aesar #11501); [f.] Al_2O_3-acidic-B2 prepared from: aluminum oxide, activated, acidic, gamma (Strem Chemicals #93-1329).

Table 1.2. Optimization of Reduction in the presence of Al_2O_3-Acidic-B2.a

Section 1.2.1. Substrate scope

The protocol was applied to seven additional α,β-unsaturated ketones as summarized in Table 1.3. We were pleased to observe that in all cases the selectivity was higher than that of our initial substrate with 4 of 8 enones reduced with very high selectivity to their corresponding allylic alcohols (>99 : 1 based on analysis of crude ^{1}H NMR spectra prior to

purification). The reductions of 2-cyclohexenone, 3-octene-2-one, isophorone, and 3,5-dimethylcyclohexenone to their corresponding allylic alcohols **1-2**, **1-5**, **1-8** and **1-9** yielded mixtures with saturated alcohols in ratios of 90:10, 93:7, 97:3 and 95:5 respectively. In these cases the reported yields correspond to mixtures of alcohols. We found that acetone was preferable to EtOAc for washing the alumina residue during filtration resulting in higher isolated yields which ranged from 64 to 93 %. Most of the reductions were complete in 1 or 2 hours with the exception of isophorone which failed to react completely after 48 h. Alcohol **1-8** was obtained in just 64 % in addition to some unreacted isophorone recovered. Allylic alcohols **1-9** and **1-10** were prepared in high diastereomeric ratios (*see chapter 1 experimental section*).



a. Reaction conditions: substrate (2 mmol), Al_2O_3-acidic-B2 (6.0 g), EtOAc (10 mL), r.t. 10 min, then $NaBH_4$ (4 mmol), r.t.; Workup via filtration with acetone wash; Ratios of A:B and diastereomeric products were determined via ^1H NMR prior to chromatography

Scheme 1.2. Substrate Scope for $NaBH_4/Al_2O_3$-acidic-B2 Reduction of Enones.[a]

Delineating a mechanistic rationale for the observed selectivity under these reaction conditions presents a daunting challenge which is complicated not only by the heterogeneity of alumina but also by the low solubility of $NaBH_4$ in ethyl acetate. A few additional practical considerations are as follows: Spent alumina, which contains adsorbed boron byproducts, could not be re-used effectively. The selectivity in the reduction of 2-cyclohexanone decreased from 90:10 to 64:36 (**1-2**:**1-3**) upon reuse of spent alumina and the ratio continued to decrease with repeated use. The 1,2-reduction of 2-cyclopentenone, which is acknowledged to be especially prone to undergo 1,4-additions,[9] does not occur under these conditions with only cyclopentanol formed. In the interest of familiarity to readers, we chose to employ the Brockmann numbering system throughout this initial study, however, there is no inherent reason for hydration corresponding to the arbitrary Brockmann I-V scale to be distinguished from any other intermediate values. In this reaction, Brockmann 1.5 and 2.5 aluminas (corresponding to 1.5 and 4.5 % w/w water) did not offer any improvement in selectivity over Brockmann II.

Nonetheless, as we continue our work in this area we have transitioned to a more systematic nomenclature that explicitly states the % water added, acidity level, and alumina polymorph where available; for example γ-Al_2O_3-acidic+3%H_2O.

From a practical perspective, given the ubiquity of activated aluminas in chemistry laboratories, it is surprising that their 'rehydration' has remained unexplored in the context of reactivity and selectivity in laboratory-scale organic synthesis. Interest is perhaps hampered by the proprietary and opaque nature of the industrial production of aluminas. In addition, adsorbed substrates do not interact with surface sites via consistent and well-defined transition states which would aid in the rationalization and prediction of selectivity.

Furthermore, a methodology that relies on a well-defined degree of hydration of alumina must address the fact that activated aluminas can adsorb water upon long term storage. This concern can be resolved by adoption of a standard dehydration protocol such as heating under vacuum at 350-400 °C,[49, 50] prior to re-hydrating. Future work from our lab will address this issue in depth. Notably, the water content of alumina can be accurately measured via Karl Fischer titration.[51]

Section 1.3. Summary and conclusions

In summary, we have demonstrated the selective reduction of α,β-unsaturated ketones in a 1,2-fashion by $NaBH_4$ in EtOAc in the presence of activated acidic Brockmann II aluminas (Al_2O_3-acidic-B2) prepared simply by adding 3% water to the corresponding commercially available Brockmann I alumina. Alumina is a potentially desirable replacement for $CeCl_3$ and other homogeneous Lewis Acids which are more expensive and more difficult to separate from reaction products. In this case, eight substrates were reduced with selectivity for 1,2- over 1,4-reduction ranging from 90:10 to >99:1.

More generally, with our disclosure of this reaction we hope to draw attention to rehydration of activated alumina as a variable that may have a significant impact on reactivity and selectivity in synthetic chemistry. Activated aluminas are already present in many organic laboratories where they are used as chromatographic media and catalyst supports. They should also now be considered surfaces with acid/base properties that can be finely tuned by simple addition of water to impact reactivity and selectivity.

Section 1.4. Experimental

General experimental details. Infrared spectra were obtained on a Thermo Scientific Nicolet 380 FT-IR spectrometer as thin films on ZnSe disks and peaks are reported in cm^{-1}. ^{1}H and ^{13}C NMR experiments were performed on a Bruker AVANCE 500 MHz instrument and samples were obtained in $CDCl_3$ (referenced to 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). Coupling constants (J) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, br s = broad singlet, d = doublet, t = triplet, dd = doublet of doublets, dq = doublet of quartets, dsep = doublet of septets; tt = triplet of triplets, m = multiplet, app = apparent. MALDI-HRMS of compounds were recorded on a Q-TOF mass spectrometer. Reaction progress was monitored by thin-layer chromatography on silica gel plates (60-F254), observed under UV light and plates were stained using *p*-anisaldehyde. Column chromatography was performed using silica gel (particle size 40-63μm). Ketone substrates were purchased from commercial suppliers AKScientific, VWR, Aldrich, and used without further purification. Activated aluminas (Brockmann I) were purchased from Sigma-Aldrich, Alfa-Aesar, and Strem Chemicals and were rehydrated to Brockmann II, III, and IV levels as described below.

Procedure for rehydration of activated aluminas to Brockmann II, III, & IV grade. Example: Activated acidic alumina Brockmann II (acidic-Al_2O_3-B2): To a 100 mL round bottomed flask was added activated acidic alumina Brockmann I (10.0 g) and deionized H_2O (0.30 mL, 3.0 % w/w). The flask was capped tightly and shaken until visible clumps were broken apart. The capped flask was allowed to sit at room temperature for a minimum of 12 hours before use. Analogous procedures were used to make Brockmann III aluminas using

0.60 mL (6.0 % w/w) of water and Brockmann IV aluminas using 1.0 mL (10 % w/w) of water.

Experimental procedure used in Figure 1. Baeyer-Villiger oxidation of 4-*tert*-butylcyclohexanone: To an oven dried reaction vial containing a magnetic stir bar was added acidic, activated alumina, Brockmann I (Sigma-Aldrich, 1.0 g, 2.0 g per mmol of substrate) and deionized H_2O (80.0 μL, 16% w/w). The vial was capped and tightly and shaken to obtain a free flowing powder. The rehydrated activated alumina was left to stand for at least 12 hours before use. After allowing the alumina to equilibrate, potassium peroxymonosulfate (Oxone®, 769 mg, 2.5 equiv.), ethyl acetate (5 mL, 0.1M) and 4-*tert*-butylcyclohexanone (65.1 μL, 0.50 mmol, 1.0 equiv.) were added to the reaction vial. The reaction vial was capped and the mixture was stirred vigorously to produce a suspension. After 8 hours of stirring at room temperature, the suspension was filtered through filter paper (Fisher P5) and the solids washed with acetone (approximately 5 x 5 mL). The filtrate was concentrated *in vacuo*. To the resulting crude mixture was added anisole (54.3 μL, 0.5 mmol, 1.0 equiv.) to serve as an internal standard for ^{1}H NMR. The yield of lactone was measured by comparing the relative intensity of the anisole signal at 3.78 ppm (3.00H, s) to that of one of the carboxylate protons of γ-*tert*-butyl-ε-caprolactone at 4.30 ppm (0.68H, ddd, J = 13, 5.8, 1.8 Hz) = 68% yield.

General procedure for 1,2-reduction of α,β-unsaturated ketones to allylic alcohols. To a reaction vial equipped with a stir bar were added: activated acidic alumina Brockmann II (acidic-Al_2O_3-B2, 6 g), EtOAc (10 ml), and the α,β-unsaturated ketone substrate (2 mmol). The vial was capped and the mixture was stirred at room temperature for 10 minutes before $NaBH_4$ (152 mg, 2.0 mmol) was added in one portion. The reaction vial was capped and the mixture was stirred at room temperature and monitored by TLC and/or ^{1}H NMR until

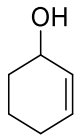
complete disappearance of starting material was observed. The reaction mixture was filtered through filter paper (Whatman, 42 Ashless) and the solids washed with acetone (approximately 3 x 20 mL). The filtrate was concentrated *in vacuo* and the residue purified via flash column chromatography on silica gel (EtOAc/hexanes with gradient elution).

Structural characteristics of purchased activated aluminas

	Sigma-Aldrich [a]			Alfa Aesar	Strem Chemicals
	Activated, neutral, Brockmann I	Activated, basic, Brockmann I	Activated, acidic, Brockmann I	Activated, acidic, Brockmann I	Activated, acidic, Gamma
Catalog #	199974	199443	199966	11501	93-1329
Lot #	STBC4825V	MKBL7881V	BCBL9083V	61401064	24113400
pH (5% stirred aq. suspension)	7.5 ± 0.5	9.5 ± 0.3	4.5 ± 0.5	4.0-5.0	-
Approx. particle size (mesh)	150	150	150	60	60
Surface area (m^2/g)	150	150	150	150	150
Pore diameter (Å)	58	58	58	58	-
Cl^- (mval/g)	0.03	-	0.14		-
Na_2O (%)	0.4	0.4	0.4	-	-
Fe_2O_2 (% max.)	0.02	0.02	0.02	-	-
SiO_2(% max.)	0.02	0.02	0.02	-	-
H_2O (%, approx.)	1.5	1.5	1.5	-	-

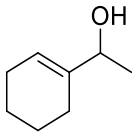
a. Mineral Adsorbents, Filter Agents and Drying Agents (Aldrich Technical Information bulletin AL-143), Aldrich Chemical Co., Milwaukee, WI, USA, 1993. http://www.sigmaaldrich.com/chemistry/chemical-synthesis/learning-center/technical-bulletins/al-1430/activated-alumina.html

Characterization of allylic alcohols 1-2, 1-4 to 1-10



1-2

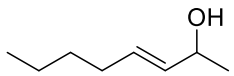
2-cyclohexenol (1-2): The general procedure was used with 2-cyclohexen-1-one (193.6 µL, 2.0 mmol). After 1 hour the reaction mixture was filtered and purified as described above to yield a mixture of **2-cyclohexenol** and cyclohexanol (90:10 ratio, 159 mg, 81% yield corresponding to both alcohols); pale yellow oil; R_f = 0.36 (hexanes/EtOAc 70:30 v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 – 5.77 (m, 1H), 5.73 – 5.69 (m, 1H), 4.18 – 4.13 (m, 1H), 2.09 – 1.48 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.53, 130.11, 65.60, 32.13, 25.19, 19.14. This NMR data is consistent with an authentic sample from Sigma Aldrich. **cyclohexanol:** ^{1}H NMR δ 3.60 – 3.53 (m, 1H, C<u>H</u>OH); this resonance was consistent with an authentic sample and was used to determine product ratio.



1-4

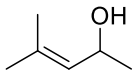
1-(cyclohexen-1-yl) ethanol (1-4): The general procedure was used with 2-cyclohexen-1-one (258.7 µL, 2.0 mmol). After 1 hour the reaction mixture was filtered and purified as described above to yield **1-(cyclohexen-1-yl) ethanol** (234 mg, 93% yield); colorless oil; R_f = 0.51 (hexanes/EtOAc 70:30 v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 – 5.62 (m, 1H), 4.13 (q, *J* = 6.5 Hz, 1H), 2.03 – 1.92 (m, 4H), 1.77 (s, 1H), 1.66 – 1.50 (m, 4H), 1.22 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.38, 121.53, 72.20, 24.99, 23.78, 22.77, 22.71, 21.60. This NMR data is consistent with previously reported values.[52]



1-5

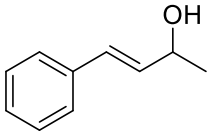
Oct-3-en-2-ol (1-5): The general procedure was used with 3-octen-2-one (296.9 µL, 2.0 mmol). After 1 hour the reaction mixture was filtered and purified as described above to yield a mixture of **oct-3-en-2-ol** and 2-octanol (93:7 ratio, 205 mg, 80% yield corresponding to both alcohols); colorless oil; R_f = 0.66 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (dt, *J* = 15.4, 6.7 Hz, 1H), 5.54 – 5.48 (m, 1H), 4.28 – 4.22 (m, 1H), 2.02 (q, *J* = 7.4 Hz, 2H), 1.47 (br s, 1H), 1.37 – 1.28 (m, 4H), 1.21 (d, *J* = 6.3 Hz, 3H), 0.93 – 0.86 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.28, 131.29, 69.12, 31.92, 31.49, 23.60, 22.34, 14.05. This NMR data is consistent with previously reported values.[53] **2-octanol:** ^{1}H NMR δ 3.82 – 3.75 (m, 1H, C<u>H</u>OH); this resonance was consistent with an authentic sample and was used to determine product ratio.



1-6

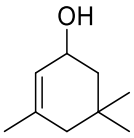
4-methylpent-3-en-ol (1-6): The general procedure was used with mesityl oxide (228.79 µL, 2.0 mmol). After 1 hour the reaction mixture was filtered and purified as described above to yield **4-methylpent-3-en-ol** (144 mg, 72% yield); colorless liquid; R_f = 0.42 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (app dsep, *J* = 8.4, 1.4 Hz, 1H), 4.56 (dq, *J* = 8.5, 6.2 Hz, 1H), 1.71 (d, *J* = 1.4 Hz, 3H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.23 (d, *J* = 6.2 Hz, 3H);^{13}C

NMR (125 MHz, $CDCl_3$) δ 134.37, 129.54, 65.00, 29.85, 25.81, 23.80, 18.17. This NMR data is consistent with previously reported values.[54]



1-7

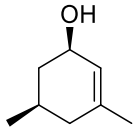
4-Phenyl-3-buten-2-ol (1-7): The general procedure was used with 4-phenyl-3-buten-2-one (292 mg, 2.0 mmol). After 48 hours, the reaction mixture was filtered and purified as described above to yield **4-Phenyl-3-buten-2-ol** (276 mg, 93% yield); colorless oil; R_f = 0.59 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.1 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H), 6.57 (d, *J* = 15.9 Hz, 1H), 6.27 (dd, *J* = 15.9, 6.4 Hz, 1H), 4.50 (app pd, *J* = 6.3, 1.2 Hz, 1H), 1.56 (br s, 1H), 1.38 (d, *J* = 6.4 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 136.87, 133.73, 129.58, 128.73, 127.79, 126.61, 69.10, 23.59. This NMR data is consistent with previously reported values.[54]



1-8

3,5,5-trimethylcyclohex-2-en-1-ol (1-8): The general procedure was used with isophorone (299 µL, 2.0 mmol). After 48 hours, the reaction mixture was filtered and purified as described above to yield mixture of **3,5,5-trimethylcyclohex-2-en-1-ol** and *cis*-3,3,5-trimethylcyclohexanol (97:3 ratio; 179 mg, 64% yield corresponding to both alcohols); colorless oil; R_f = 0.45 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41 (dq, *J* = 2.5, 1.2 Hz, 1H), 4.24 – 4.18 (m, 1H), 1.87 – 1.79 (m, 1H), 1.78 – 1.71 (m, 1H), 1.66 (s,

3H), 1.62 – 1.56 (m, 1H), 1.21 (dd, *J* = 12.4, 9.0 Hz, 1H), 0.98 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.09, 123.80, 66.95, 45.37, 44.28, 31.34, 31.18, 26.35, 23.63. This NMR data is consistent with previously reported values.[52] ***cis*-3,3,5-trimethylcyclohexanol:** ^{1}H NMR δ 3.78 – 3.71 (m, 1H, C<u>H</u>OH); this resonance was consistent previously reported data and was used to determine product ratio.[55]

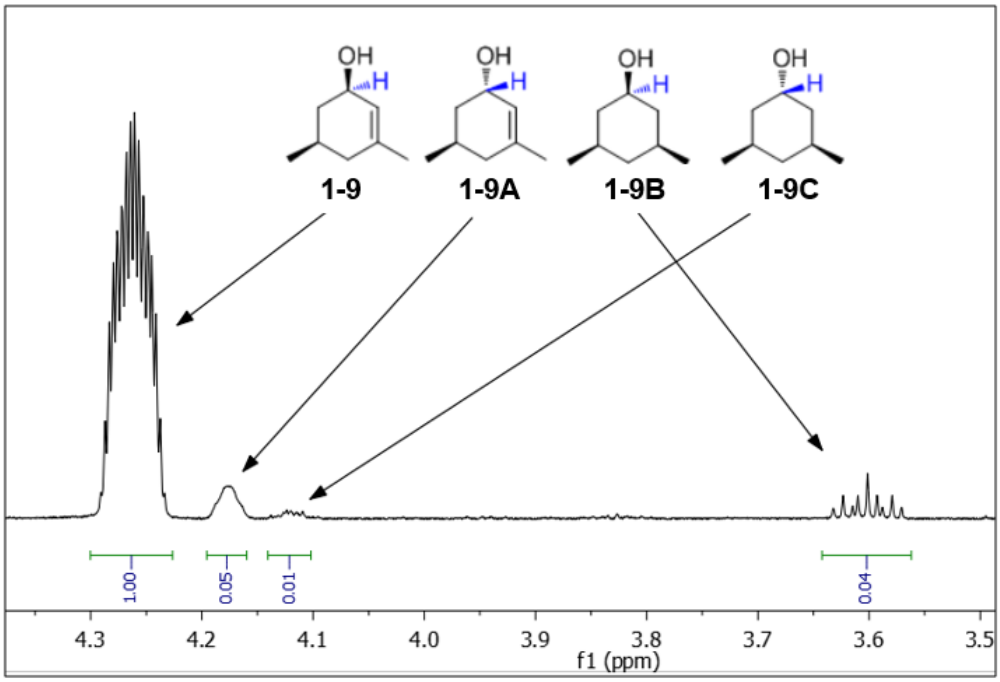


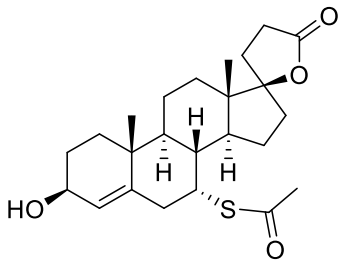
1-9

***cis*-3,5-dimethylcyclohex-2-enol (1-9):** The general procedure was used with 3,5-dimethylcyclohexenone (248 mg, 2.0 mmol). After 1 hour, the reaction mixture was filtered and purified as described above to yield a mixture of ***cis*-3,5-dimethylcyclohex-2-enol** and three minor byproducts: *trans*-3,5-dimethylcyclohex-2-enol (**9A**), 3,5-*cis*-dimethyl-1-*cis*-cyclohexanol (**9B**), and 3,5-*cis*-dimethyl-1-*trans*-cyclohexanol (**9C**). (**9** : **9A** : **9B** : **9C** ratio of 100 : 5 : 4 : 1 *see below*; 214 mg, 85% yield corresponding to all four alcohols); colorless oil; R_f = 0.56 (Hexanes/EtOAc 70:30 v/v); ***cis*-3,5-dimethylcyclohex-2-enol (11):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (dq, *J* = 2.3, 1.2 Hz, 1H), 4.30 – 4.23 (m, 1H), 2.04 – 1.99 (m, 1H), 1.90 (dd, *J* = 17.2, 4.7 Hz, 1H), 1.77 – 1.68 (m, 1H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.64 – 1.56 (m, 1H), 1.08 – 0.99 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$,) δ 137.02, 125.63, 68.67, 41.58, 39.03, 28.38, 23.27, 22.03. ***trans*-3,5-dimethylcyclohex-2-enol (9A):** ^{1}H NMR δ 4.18 (br s, 1H, C<u>H</u>OH); **3,5-*cis*-dimethyl-1-*cis*-cyclohexanol (9B):** ^{1}H NMR δ 3.60 (tt, *J* = 11.1, 4.3 Hz, 1H, C<u>H</u>OH); **3,5-*cis*-dimethyl-1-*trans*-cyclohexanol (9C):** ^{1}H NMR δ 4.13 – 4.10 (m, 1H, C<u>H</u>OH); The ratio of unsaturated to saturated alcohols = 95:5 and the

ratio of *cis*:*trans* allylic alcohol diastereomers (**9**:**9A**) = 95:5. (S*ee Section with Supporting Information*) The above NMR resonances are consistent with previously reported data.[56]

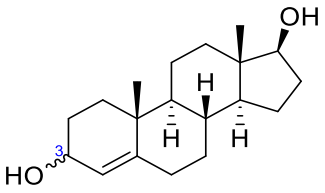
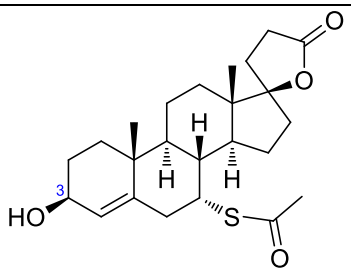
^{1}H NMR analysis of the mixture of: *cis*-3,5-dimethylcyclohex-2-enol (**1-9**), *trans*-3,5-dimethylcyclohex-2-enol (**1-9A**), 3,5-*cis*-dimethyl-1-*cis*-cyclohexanol (**1-9B**), and 3,5-*cis*-dimethyl-1-*trans*-cyclohexanol (**1-9C**). Based on the integrations shown below the ratio of unsaturated to saturated alcohols = 95:5 and the ratio of *cis*:*trans* allylic alcohol diastereomers (**9**:**1-9A**) = 95:5.





1-10

Compound 1-10: The general procedure was used with spironolactone (209 mg, 0.5 mmol), acidic-Al_2O_3-B2 (1.5 g), EtOAc (5 ml) and $NaBH_4$ (38 mg, 1.0 mmol). After 2 hours the reaction mixture was filtered and purified as described above to yield **compound 10** (137 mg, 66 % yield); colorless oil; R_f = 0.7 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 – 5.28 (m, 1H), 4.20 (dddd, *J* = 10.0, 6.0, 2.1, 2.1 Hz, 1H), 3.90 (app q, *J* = 3.7 Hz, 1H), 2.67 (dddd, *J* = 14.3, 4.0, 2.0 Hz, 1H), 2.57 – 2.41 (m, 2H), 2.39 – 2.30 (m, 1H), 2.32 (s, 3H), 2.23 – 2.16 (m, 1H), 2.09 (dd, *J* = 14.3, 2.7 Hz, 1H), 1.99 – 1.86 (m, 3H), 1.82 – 1.69 (m, 2H), 1.64 (br s, 1H), 1.61 – 1.31 (m, 8H), 1.28 – 1.20 (m, 2H), 1.08 (s, 3H), 1.03 – 0.94 (m, 1H), 0.94 (s, 3H), 0.80 (td, *J* = 11.8, 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.91, 176.78, 142.09, 127.91, 95.88, 67.62, 50.03, 46.22, 46.12, 45.64, 39.36, 39.34, 37.46, 35.42, 35.34, 31.39, 31.36, 31.27, 29.35, 29.24, 22.52, 20.46, 19.22, 14.66; IR (cm^{-1}): 3435, 2938, 1767, 1683, 1177; HRMS calculated for $C_{24}H_{34}O_4S$ $(M+H)^+$ 419.22506; found 419.2249. Stereochemistry at C-3 (β-epimer) was inferred via comparison of ^{1}H NMR resonance C_3-H to a similar compound.[57]

 Previously reported data [7] 3α = $\delta_{H\text{-}3}$ 4.075 (ddd, *J* = 5/5/3 Hz) 3β = $\delta_{H\text{-}3}$ 4.122 (dddd, *J* = 7.5/6/2/2 Hz) (Parr, M. K.; Zapp, J.; Becker, M.; Opfermann, G.; Bartz, U.; Schänzer, W. *Steroids* **2007**, *72*, 545.)	 Our product: 3β = $\delta_{H\text{-}3}$ 4.20 (dddd, *J* = 10.0, 6.0, 2.1, 2.1 Hz, 1H)

Section 1.5. References

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Chapter 2: Aryl methyl sulfides via S_NAr using DMSO as the source of the thiomethyl moiety[1]

The Chapter 2 is primarily an adaptation of a published manuscript:

Jones-Mensah, E.; Magolan, J. *Tetrahedron Lett.* ***2014****, 55, 5323.*

Notes: I have adapted the content of this manuscript in a number of ways including modification of some schemes and tables as well as some additions.

The introduction to Chapter 2 is based on a portion of a submitted review manuscript:

Jones-Mensah, E.; Karki, M.; Magolan, J. Dimethylsulfoxide as a Synthon in Organic Chemistry *Synthesis*, **2016** (In Press)

Abstract

A unique synthesis of aryl methyl sulfides is reported proceeding via reduction of dimethylsulfoxide to dimethylsulfide at elevated temperature in the presence of Hunig's base followed by nucleophilic aromatic substitution and demethylation. Activated aryl fluorides, chlorides, and nitrobenzenes are suitable substrates with 12 examples provided. Dimethylsulfoxide serves as a simple and inexpensive formal source of the thiomethyl moiety.

Keywords: Dimethylsulfoxide, Nucleophilic aromatic substitution, Methyl sulfides, Thiomethyl, Hunig's base

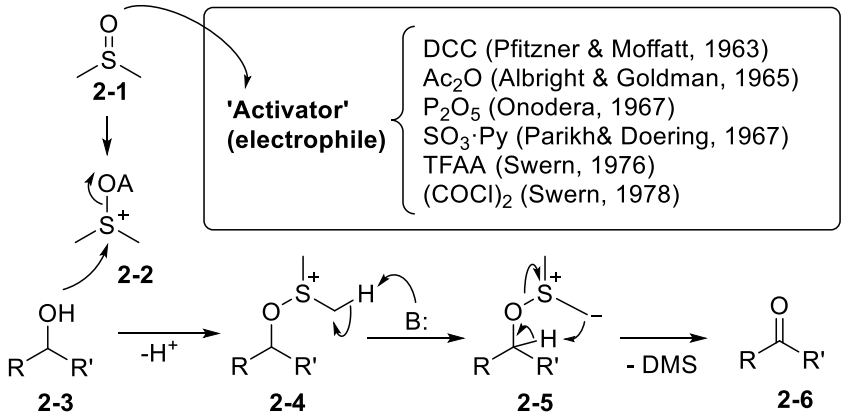
Section 2.1. Introduction

In the context of synthetic chemistry, dimethylsulfoxide (DMSO) is primarily utilized as a high-boiling polar aprotic solvent[2] with a secondary role as a mild and inexpensive oxidant.[3] DMSO is not often thought of as a substrate, building block, or synthon in organic transformations. However, in the past few years an abundance of reports have appeared that

demonstrate DMSO serving in this role. In the last generation, there have been reports of examples in synthetic transformations that have utilized dimethylsulfoxide as a building block for functionalities containing the 'C-S-C', 'C', and 'C-S' fragments of DMSO. This section discusses the applications of DMSO for thiomethylation and a brief insight into the history and recent highlights on DMSO-based oxidations.

Section 2.1.1. History and recent highlights of DMSO-based oxidations

The first review discussing the DMSO as an oxidant was written by Epstein and Sweat in 1967.[3a] It was published during the first years of an intense fifteen-year period of development that saw the emergence of "activated" DMSO as a valuable synthetic tool for the oxidation of primary and secondary alcohols to aldehydes and ketones (Scheme 2.1).



Scheme 2.1. DMSO-based oxidations of alcohols

In 1963, Pfitzner and Moffatt reported an oxidation of alcohols to ketones and aldehydes by treatment with dicyclohexylcarbodiimide (DCC) and mild acid in DMSO.[4] In contrast to many previous oxidations, this new procedure required no stoichiometric heavy metal oxidant, did not suffer from any over-oxidation of primary alcohols, and was suitable for sensitive substrates. The mechanisms of this and other DMSO-based alcohol oxidations

have been thoroughly investigated (Scheme 2.1).[5] The reactions proceed via nucleophilic attack of the DMSO oxygen onto an electrophilic activator (i.e., DCC) to yield an "activated" species **2-2** which subsequently undergoes leaving group displacement by the alcohol substrate **2-3** to give an alkoxydimethylsulfonium salt **2-4**. This species loses a proton forming sulfur ylide **2-5** which undergoes an intramolecular elimination that results in the formation of a carbonyl compound **2-6** and dimethylsulfide (DMS). Soon after Pfitzner and Moffatt's initial report, a number of other electrophiles were found to be suitable alternatives to DCC for the "activation" of DMSO. Albright and Goldman used acetic anhydride,[6] Onodera employed phosphorus pentoxide,[7] and Parikh and Doering reported the use of a SO_3·pyridine complex.[8] A focused search for improved activators led Swern and coworkers to identify trifluoroacetic anhydride (TFAA) in 1976,[9] and oxalyl chloride in 1978. [5c,10] Activation of DMSO with oxalyl chloride (the "Swern Oxidation") is now the most common DMSO-based oxidation employed in synthetic chemistry. Two comprehensive reviews of all of these reactions and their many applications to diverse substrates were provided by Tidwell in 1990.[3b,3c] Two later overviews have also appeared as book chapters.[3d,3e]

A practical advancement to this field was reported in 2005 by Yoshida and workers who demonstrated the oxidation of alcohols with DMSO and trifluoroacetic acid at room temperature using a microscale flow reactor.[10] New electrophilic activators of DMSO have routinely appeared in the literature and will undoubtedly continue to do so. These have included: phosphonitrilic chloride,[11] polyoxomolybdates,[12] triphenylphosphine dibromide and dichloride,[13] cyanuric chloride,[14] bis(trichloromethyl)carbonate,[15] phosgene,[16] and phosphorus pentoxide/trimethylamine.[17]

A number of research groups have recently developed innovative sulfoxide reagents that are odorless and potentially recyclable alternatives to DMSO for alcohol oxidations. These include the odorless 6-(methylsulfinyl)hexanoic acid reported by Liu Vederas,[18] and methyl 6-morpholinohexyl sulfoxide reported by Nishide, Node and coworkers,[19] ion-supported or 'ionic liquid-anchored' sulfoxides from the research groups of Chan[20] and Togo,[21] polystyrene-bound sulfoxides reported by Choi and Toy,[22] and fluorous sulfoxide reagents reported by Crich and Neelamakavil.[23]

An aspect of DMSO-based oxidation chemistry that was omitted from Tidwell's review articles[3b,3c] and has seen considerable recent activity, is the oxidation of functionalities other than the hydroxyl moiety. In 1957, even before the first examples of DMSO-based alcohol oxidations, Kornblum and coworkers used DMSO and triethylamine to convert primary alkyl chlorides to aldehydes.[24] Activated DMSO has been repeatedly shown to oxidize thiols to disulfides[25] and alkynes to 1,2-diketones.[26] It has also been employed for oxidative dealkylation of quaternary ammonium salts to tertiary amines,[27] oxidation of tetraphenylchlorins to porphyrins,[28] conversion of hydrazones to diazo compounds,[29] and oxidation of isonitriles to isocyanates.[30] In 1999, Vankar and coworkers used a combination of trimethylsilylnitrate and DMSO to convert olefins directly to α-nitro ketones.[31] A number of interesting DMSO-based oxidative transformations of complex substrates have appeared recently including the conversion of hydroxyl-β-thiolactams to oxazolethiones,[32] substituted indoles to chlorooxindoles,[33] and functionalized allenols to ethynyl or chlorovinyl alkenoates.[34] In 2014, Koike, Akita and coworkers prepared α-trifluoromethyl ketones from styrenes using an approach that paired photoredox-catalysis with DMSO-based oxidation.[35] In 2011, Yoshida and coworkers oxidized methylene and vinyl carbon atoms directly to

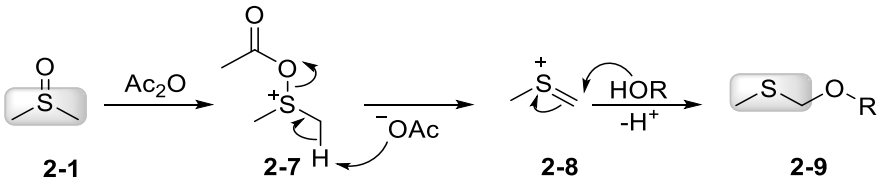
ketones using a unique combination of anodic electrochemical oxidation paired with DMSO oxidation.[36] Dimethylsulfoxide has been routinely paired with HBr giving mild protocol for the *in situ* formation of bromodimethylsulfonium bromide (BDMS), a well-known electrophilic brominating reagent commonly prepared from Br_2 and dimethylsulfide.[37] In 2015, Jiao and coworkers used this approach to develop an exceptionally mild and robust protocol for electrophilic bromination of electron rich arenes and heteroarenes using HBr/DMSO in ethyl acetate.[38] Jiao's conditions were an improvement over previous analogous efforts.[39] The authors also identified the combination NH_4I, H_2SO_4, DMSO for electrophilic iodination chemistry.[38] Jiao's team has also recently developed a protocol for the α-hydroxylation of ketones using *N*-bromosuccinimide (NBS) and DMSO.[40] A number of reports have demonstrated the use of HBr/DMSO for α-oxidation of ketones to 1,2-dicarbonyl derivatives.[41] In 2015, Jiao[42] and our research group[43] independently reported the application of HBr/DMSO for the bromination of olefins. The pairing of catalytic I_2 and stoichiometric DMSO (which re-oxidizes I^- to I_2) has been employed to accomplish oxidative aromatic sulfenylations,[45] selenations,[44a] as well as a report of 1,3-diaryl ketones converted 1,2-diarylketones by excision of a carbon atom via proposed reverse benzylic rearrangement-type mechanism.[45]

Since the flurry of activity in the 1960's and 1970's that brought "activated" DMSO to the forefront of alcohol oxidation chemistry, continued development in this field has yielded many valuable synthetic applications. There is no doubt that further useful DMSO-based oxidations await discovery in the coming years. In addition to the aforementioned applications, DMSO has also recently begun to gain prominence in an entirely different role.

This includes the use of DMSO as a synthon in organic transformations such methylthiomethylation and thiomethylations.

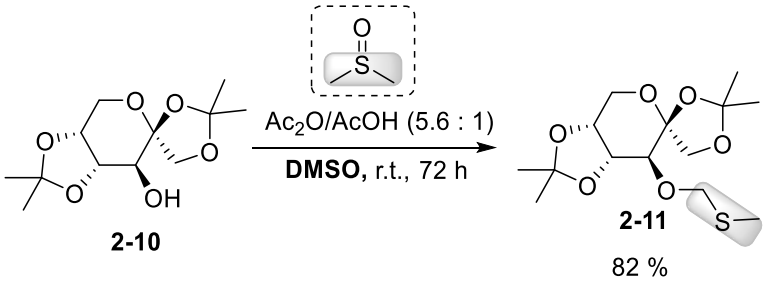
Section 2.1.2. DMSO-based methylthiomethylations (-CH_2SCH_3)

The first major reports of a fragment of dimethylsulfoxide serving as a building block in a synthetic transformation date back to the methylthiomethyl (MTM) ethers (**2-9**) isolated as unwanted byproducts of DMSO-based oxidations of alcohols by Pfitzner and Moffatt (DMSO-DCC) as well as Albright and Goldman (DMSO-Ac_2O) in 1965. [4b,6] These ethers (**2-9**) are formed via a Pummerer-type mechanism[46] involving nucleophilic attack of the alcohol substrate onto the methyl(methylene)sulfonium cation **2-8** that results from an elimination reaction of the species **2-7** as illustrated in Scheme 2.2.



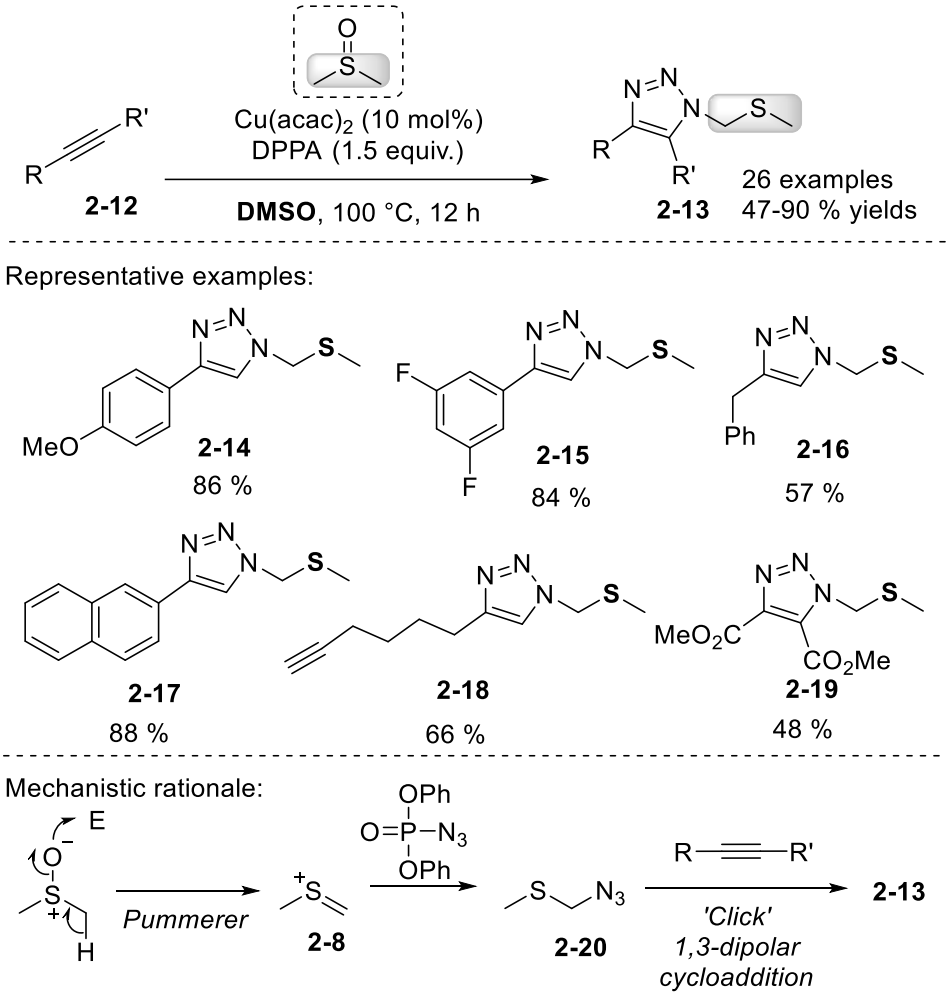
Scheme 2.2. Mechanism of the formation of methylthiomethyl ethers with DMSO.

The production of these undesired ethers during DMSO-based oxidations can be minimized by careful selection of reaction conditions particularly with respect to reaction temperature and solvent.[2a,2c] MTM ethers have been employed as alcohol protecting groups. In this context they are typically prepared by treatment of alcohols with chloromethyl methyl sulfide and can be removed under a variety of conditions.[47]



Scheme 2.3. Protection of an alcohol as an MTM ether using DMSO

In 1976, Yamada used DMSO and Ac_2O to protect tertiary (non-oxidizable) alcohols as MTM ethers in high yields.[48] Pojer and Anygal later demonstrated that in the presence of acetic acid good yields can also be obtained for primary and secondary alcohols as exemplified by the protection of fructopyranose derivative **2-10** as its corresponding MTM ether **2-11**, which was accomplished on an eight gram scale in 82 % yield (Scheme 2.3).[49] This approach has also been generally applied to the hydroxyl protection of nucleosides.[50]



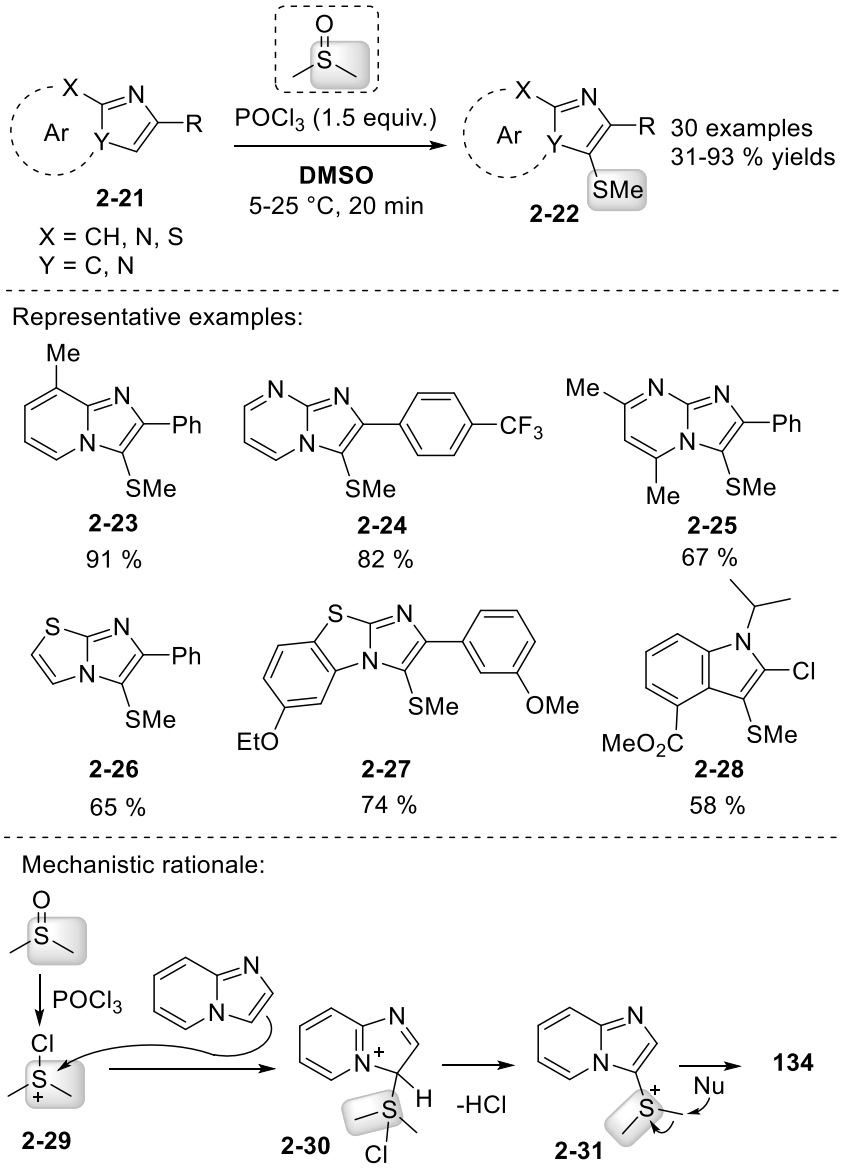
Scheme 2.4. Jiao's synthesis of *N*-methylthiomethyl triazoles using DMSO

Jiao and coworkers recently reported an interesting application of this general strategy with their synthesis of *N*-methylthiomethyl triazoles (**2-13**) in good yields from alkynes, diphenylphosphoryl azide (DPPA), and DMSO under copper catalysis (Scheme 2.4).[51] The reaction tolerated a wide variety of alkynes as exemplified by triazole products **(2-14)-(2-19)**. The authors found that *α,β*-unsaturated ketones reacted analogously to alkynes, enabled by a proposed Cu-air oxidation, and the transformation was also successful when DMSO was replaced with other methyl sulfoxides. A proposed mechanism involved a preliminary reaction between DPPA and DMSO, via the methyl(methylene)sulfonium ion (**2-8,** *previously*

discussed, see Scheme 2.2), to yield a methylthiomethyl azide intermediate (**2-20**) that subsequently undergoes a 1,3-dipolar cycloaddition reaction to yield the triazole products. The reaction was not inhibited by radical scavengers.

Section 2.1.3. DMSO-based thiomethylation (–SCH_3)

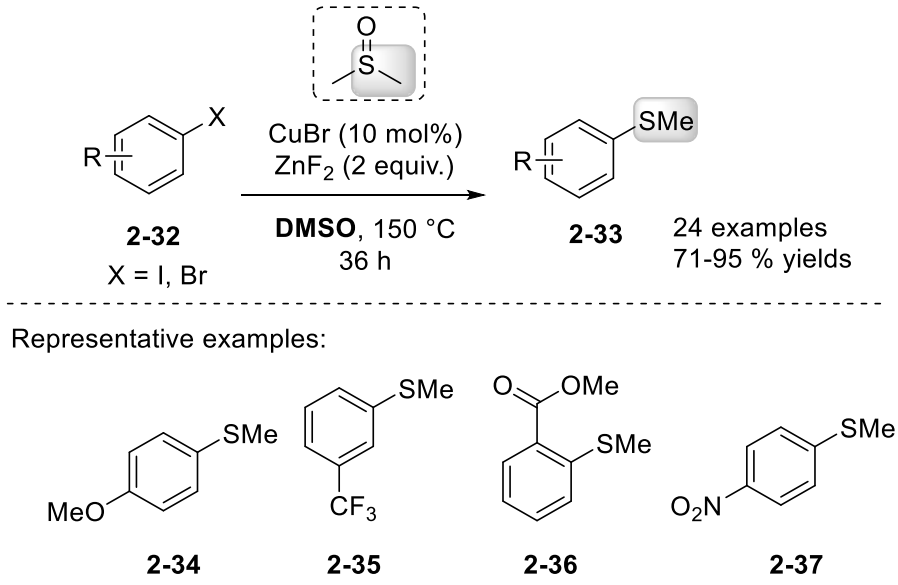
In recent times, DMSO has also been employed as a synthon for 'S-C' functionalities. A few examples are discussed below.



Scheme 2.5. Roychowdhury's C-H thiomethylation of imidazo-fused heterocycles with DMSO

Roychowdhury and coworkers recently disclosed an unusual thiomethylation reaction of imidazo- fused aromatic heterocycles (**2-22**) using phosphoryl chloride ($POCl_3$) in DMSO with the source of the thiomethyl moiety being the solvent (Scheme 2.5).[52] The authors demonstrated thirty examples of this reaction, as exemplified by the preparation of **(2-23)** to **(2-28)**, which was effective on a variety of substrates with variable yields. They proposed the

formation of chlorodimethylsulfonium intermediate **2-29** which was thought to act as a Me_2S-electrophile undergoing an electrophilic aromatic substitution process to yield the aryl sulfonium ion **2-31** before nucleophilic demethylation to produce the thiomethyl products.



Scheme 2.6. Cheng's thiomethylation of aryl halides with DMSO

In 2011, Cheng and coworkers accomplished a copper-mediated thiomethylation of aryl halides using DMSO as the thiomethyl source (Scheme 2.6).[53] The procedure, utilizing catalytic copper(I) bromide and excess zinc(II) fluoride, was suitable for a variety of substituents and yielded twenty-four thiomethyl arenes including **(2-34)** to **(2-37)** from the corresponding bromo- or iodo-arenes in good yields. The mechanism of this reaction is unclear. The authors observed the formation of disulfide byproducts and suggested their involvement in the process.

In 2014, we contributed to this field by disclosing the synthesis of aryl methyl sulfides from electron-poor aryl fluorides, chlorides, and nitroarenes via what we believe is likely to be an S_NAr process.

Section 2.2.0. Relevance of aryl methyl sulfides, sulfoxide and sulfone.

Aryl methyl sulfide, sulfoxide and sulfone functionalities are commonplace in pharmaceutical and agrochemical discovery programs.[54] Examples include the FDA approved antipsychotic (**2-38**)[55] anti-inflammatory (**2-39**),[56] and antibiotic (**2-40**)[57] drugs and the pesticide (**2-41**)[58] illustrated in (Figure 2.1)

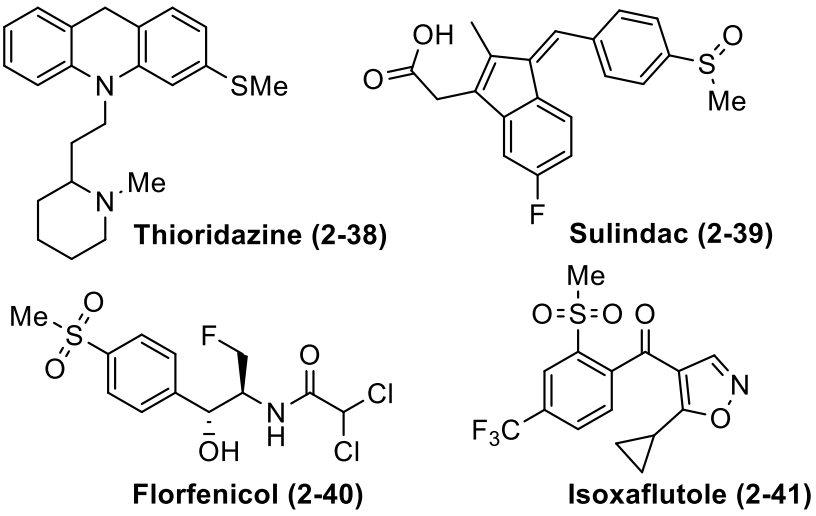
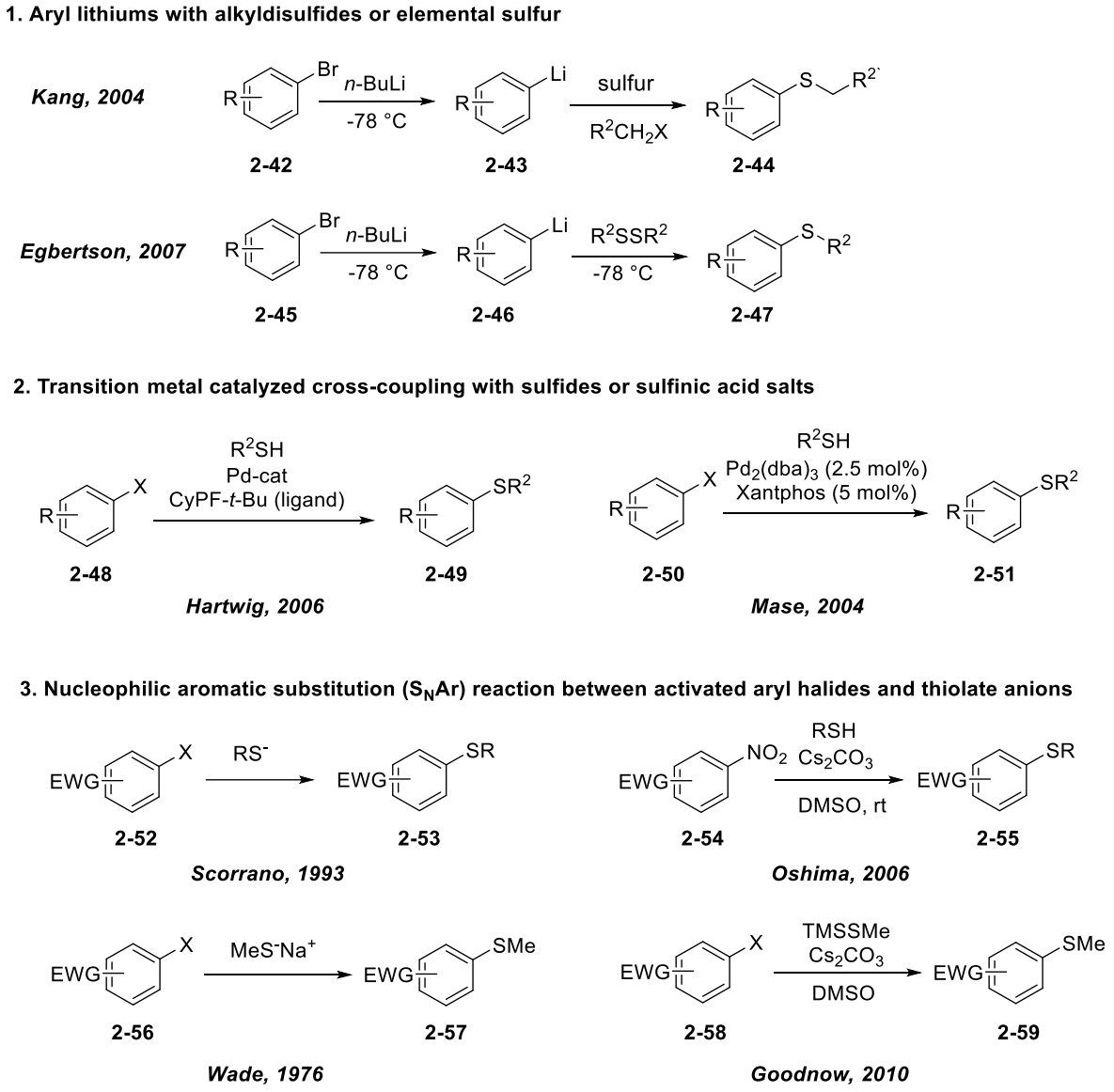


Figure 2.1. Aryl methyl sulfides, sulfoxides, and sulfones of pharmaceutical and agrochemical relevance.

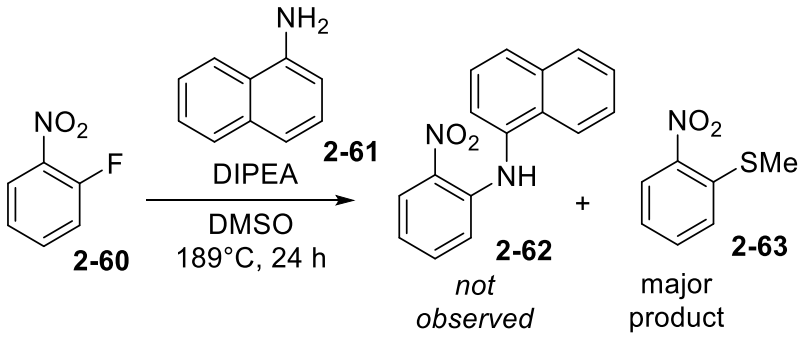
In general, the aryl C-S bond can be accessed via reaction of aryl lithiums with alkyldisulfides or elemental sulfur,[59] transition metal catalyzed cross-coupling with sulfides or sulfinic acid salts,[60] or nucleophilic aromatic substitution (S_NAr) reaction between activated aryl halides and thiolate anions.[61] Thiols have also been used directly as S_NAr substrates in the presence of cesium carbonate.[62] Access to aryl methyl sulfides via S_NAr requires non-volatile derivatives of toxic and malodorous methanethiol gas: sodium methylthiolate (NaSMe),[63] or (methylthio)trimehtylsilane (TMSSMe).[64] (Scheme 2.7)



Scheme 2.7. General approaches to C-S bond formation

Herein we report an alternative, and relatively inexpensive, route to aryl methyl sulfides by means of an atypical S_NAr-type reaction characterized by the unprecedented role of dimethylsulfoxide (DMSO) as a formal source of the thiomethyl moiety.

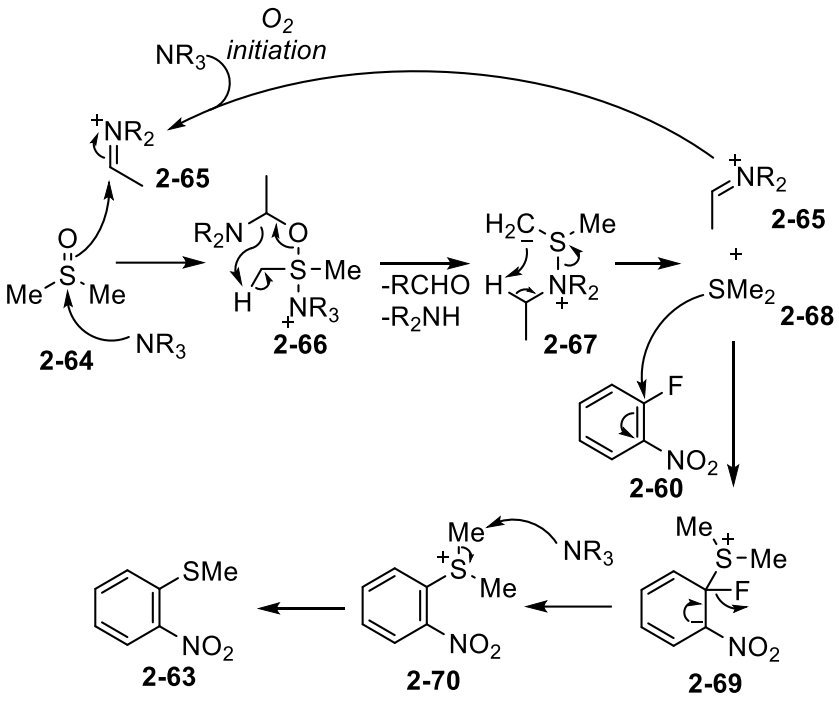
Section 2.2.1. Reaction discovery



Scheme 2.8 Unanticipated formation of sulfide **2-63**.

This work was initiated by the serendipitous observation illustrated in Scheme 2.8. As part of our synthetic methodology development in the area of polycyclic aromatic scaffolds, we attempted to prepare biarylamine **2-62** via S_NAr reaction between 1-fluoro-2-nitrobenzene (**2-60**) and 1-naphthalenamine (**2-61**). This reaction was previously accomplished by McComas and co-workers by treatment with diisopropylethylamine (DIPEA) in refluxing dimethylformamide (DMF).[65] Our brief optimization included a trial reaction in dimethylsulfoxide which, surprisingly, failed to yield **2-62** but rather resulted in substantial recovery of 2-(methylthio)nitrobenzene (**2-63**) in addition to unreacted 1-naphthalenamine (**2-61**).

The only potential source of the sulfur atom incorporated in sulfide **2-63** was the solvent. We thus hypothesized that the formation of sulfide **2-63** was a result of redox chemistry between DMSO and Hunig's base to produce dimethyl sulfide which then served as the nucleophilic partner in a nucleophilic aromatic substitution reaction. A potential mechanism is illustrated in (Scheme 2.9).



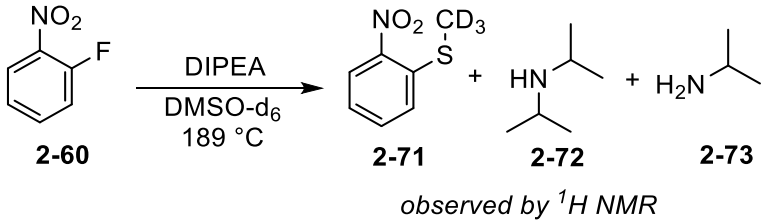
Scheme 2.9. A proposed mechanism

At elevated temperature, activation of DMSO **2-64** by reaction with an electrophilic iminium **2-65**, some of which may be formed via air oxidation, can result in intermediate **2-66** which may undergo intramolecular proton transfer (via 6-membered transition state) as shown to liberate an aldehyde, an amine, and zwitterionic species **2-67**. A subsequent fragmentation with intramolecular proton transfer as illustrated would yield an iminium species **2-65** and dimethylsulfide (DMS, **2-68**). At this point, S_NAr reaction between DMS and aryl fluoride **2-60** can yield **2-70** via the Meisenheimer intermediate **2-69**. Nucleophilic demethylation of **2-70** leads to the observed aryl methyl sulfide product **2-63**.

Section 2.2.2. Mechanistic Insight

Some support for our proposed mechanism was obtained when this reaction was performed in deuterated DMSO and monitored by ^{1}H NMR. In addition to the formation of

the trideuteromethyl sulfide **2-71** as expected, we observed amines **2-72** and **2-73** which are indicators of oxidation of Hunig's base as predicted by our mechanistic hypothesis.



Scheme 2.10. Result of reaction in deuterated DMSO.

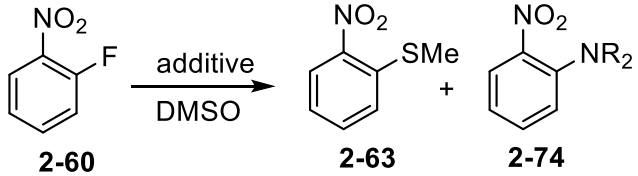
Dimethylsulfoxide, in the presence of various activating additives, is a common terminal oxidant for the oxidation of alcohols[3b] and various other substrates.[66] To our knowledge the dimethylsulfide byproduct that results from all DMSO-based oxidations has not yet been made useful as a substrate in a subsequent transformation.

Section 2.2.3. Reaction Optimization

We sought to optimize the observed transformation into a suitable synthetic tool as summarized in Table 2.1. In the absence of DIPEA no reaction is observed (entry 1). Furthermore, when the temperature is decreased to 100 °C or 150 °C no reaction takes place with only starting materials recovered (entries 2 and 3). With 2.0 equiv. of DIPEA in refluxing DMSO, conversions of 26, 47, and 100 percent are observed at 12, 16, and 22 hours respectively. With diisopropylamine (DIPA) as additive (entry 7) we observe some formation of the diisopropylaniline resulting from nucleophilic substitution of DIPA (compound **2-74**, R = *i*Pr). Similarly, reaction with piperidine yields exclusively the N-substitution product (entry 8, compound **2-74**, NR_2 = piperidine). Triethylamine is also a suitable additive (entry 9). The reaction also proceeds to complete conversion in 22 hours when the amount of DIPEA is reduced to 1.0 equiv. (entry 11) and to 95 % conversion in 22 hours with just 0.5 equiv.

When the amount of amine is reduced to 0.1 equiv. conversion falls to 20 % (entry 12). Given that for each mole of tertiary amine, 3 moles of DMSO can potentially be reduced to DMS, we assume that a minimum of 0.33 equiv. of DIPEA is required for complete substrate consumption. Indeed, complete conversion is observed with 0.4 equiv. of DIPEA after prolonged reaction time (3 days). Finally, addition of 1.0 equiv. of water along with 1.0 equiv of the DIPEA increases the rate of reaction relative to base alone with complete conversion in just 12 hours and a yield of 80 % after workup and chromatography (entry 14). The specific role of water in this process remains unclear. Addition of greater volumes of water does not further improve the reaction rate.

Table 2.1. Reaction optimization.



2-60 **2-63** **2-74**

Entry	Additive (equiv.)	Temp (° C)	Time (h)	Conversion (%)[1]	Ratio (8:19)[1]
1	None	189	24	0	n/a
2	DIPEA (2.0)	100	22	0	n/a
3	DIPEA (2.0)	150	22	0	n/a
4	DIPEA (2.0)	189	12	26	1 : 0
5	DIPEA (2.0)	189	16	47	1 : 0
6	DIPEA (2.0)	189	22	100	1 : 0
7	DIPA (2.0)	189	22	100	1 : 0.3
8	piperidine	189	22	100	0 : 1
9	Et_3N (2.0)	189	22	100	1 : 0
10	DIPEA (1.0)	189	22	100	1 : 0
11	DIPEA (0.5)	189	22	95	1 : 0
12	DIPEA (0.1)	189	22	20	1 : 0
13	DIPEA (0.4)	189	72	100	1 : 0
14	DIPEA (1.0) + H_2O (1.0)	189	12	100	1 : 0 [2]

1. Determined by NMR. 2. Isolated yield of compound **2-63** was 80 %.

Section 2.2.4. Substrate Scope

To explore the substrate scope of this transformation, we applied our preferred reaction conditions (DIPEA 1.0. equiv.; water 1.0 equiv.; refluxing DMSO) to a series of substrates as

shown in Figure 2.2. Reaction of 4-fluoronitrobenzene results in 4-(methylthio)nitrobenzene **2-76** in 81 % yield after 12 hour reaction time. As expected, the p-chloro derivative is less reactive yielding only 49 % of the same sulfide product **2-76** after a prolonged 3-day reaction. We were pleased to find that *p*-dinitrobenzene is also readily converted to **2-76** with complete consumption of starting material after just 6 hours and 80 % isolated yield. Aryl cyanides are also suitable substrates however isolated yields are lower than with their analogous nitrobenzenes. 4-(methylthio)benzonitrile **2-77** is prepared from the corresponding aryl fluoride and chloride substrates in 66 % and 21 % yield respectively. In addition, reaction of 2-fluorobenzonitrile results in 2-(methylthio)benzonitrile **2-78** in 62 % yield. 2-fluorobenzaldehyde and 4-fluorobenzaldehyde are suitable precursors for the corresponding 4- and 2-(methylthio)benzaldehydes **2-79** and **2-80** in 60 % and 64 % yield respectively.

We found that 2-(methylthio)benzaldehyde **2-80** can also be readily obtained from 2-nitrobenzaldehyde in 56 % isolated yield with complete substrate consumption observed after 15 hours . Finally, 2,6-difluorobenzonitrile and 2,6-dichlorobenzonitrile both react to give the mono-substitution products **2-81** and **2-82** in 63 % and 52 % yield respectively.

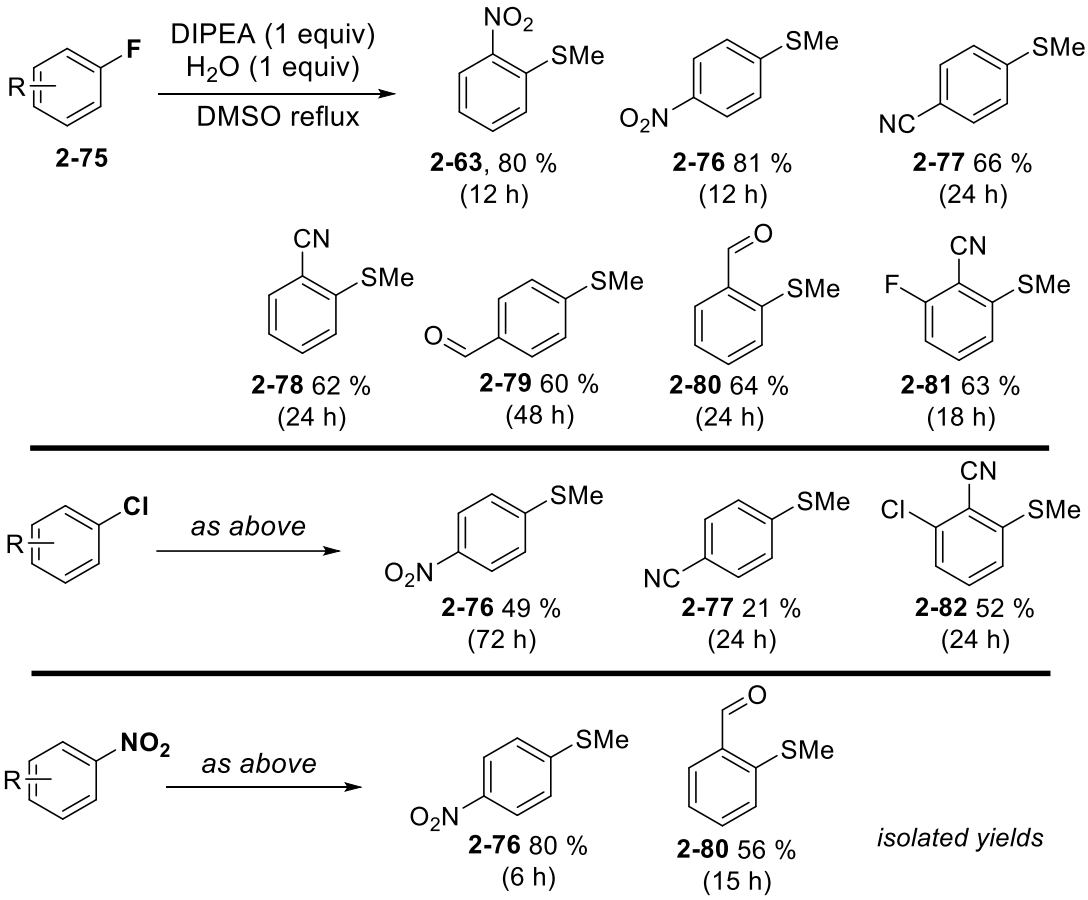
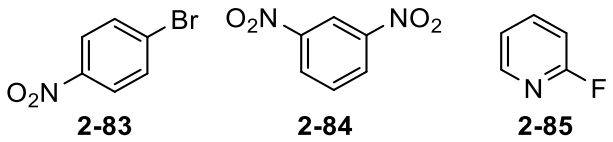


Figure 2.2. Reaction Scope.

Three substrates found unsuitable for this transformation are illustrated in Figure 2.3. Two traditionally poor S_NAr substrates, 4-bromonitrobenzene (**2-83**) and *m*-dinitrobenzene (**2-84**), failed to yield methylthio ethers using our procedure. We observed mainly unreacted starting material with some decomposition after prolonged reaction times. Regrettably, 2-fluoropyridine (**2-85**) is also an unsuitable substrate with only apparent decomposition evident under these reaction conditions.



2-83 **2-84** **2-85**

Figure 2.3. Substrates found to be unsuitable for this chemistry.

Section 2.2.5. Summary

In summary, we disclose an unusual transformation that yields aryl methyl sulfides from activated fluro-, chloro, and nitrobenzenes via an unprecedented nucleophilic aromatic substitution process that relies on the in situ reduction of DMSO to DMS at elevated temperature in the presence of a tertiary amine. As a formal source of the thiomethyl moiety, DMSO is preferable in terms of cost efficiency to NaSMe or TMSSMe. We hope that our convenient alternative to these traditional nucleophiles may find use in medicinal chemistry efforts. We presently continue to explore methodologies based on in situ reduction of sulfoxides to sulfides further synthetic applications forthcoming.

Section 2.2.6. Experimental Section

General Methods

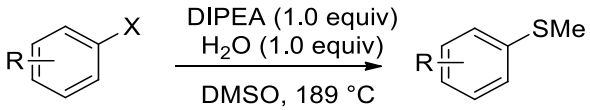
Melting points were determined using a Mel-Temp II apparatus and are uncorrected. Infrared spectra were obtained on a Thermo Scientific Nicolet 380 FT-IR Spectrometer as thin films on ZnSe disks. NMR experiments were performed on a Bruker AVANCE 500 MHz instrument and samples were obtained in $CDCl_3$ (referenced to 7.26 ppm for ^1H and 77.0 ppm for ^{13}C) Coupling constants (J) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. All substrates, reagents, and solvents were obtained from commercial suppliers and used as purchased without further purification. All reactions were open to the atmosphere

unless otherwise stated. Reaction progress was monitored by thin-layer chromatography (TLC, EMD Chemicals Inc, Silica Gel 60 F254), visualized under UV light, and plates were developed using p-anisaldehyde.

Flash chromatography was performed using silica gel (Sorbent Technologies, particle size 40-63 μm).

Synthesis and Characterization of Compounds

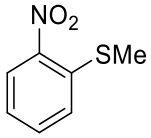
General reaction procedure:



To a round bottomed flask equipped with magnetic stir bar and reflux condenser were added: the aryl halide (2.0 mmol), dimethylsulfoxide (10 mL), *N*,*N*-diisopropylethylamine (0.35 mL, 2.0 mmol), and water (approximately 0.04 mL, 2.0 mmol). The reaction was heated to reflux temperature (189 °C) in a sand bath and stirred for the specified time. Reaction progress was monitored by TLC and/or ^{1}H NMR analysis. When complete consumption of the starting material was evident, the reaction was cooled to room temperature extracted with ethyl acetate (x3) and the combined organic extracts were washed with 2 M HCl, brine, and dried over $MgSO_4$. The solvent was removed *en vacuo* and the crude product was purified by column chromatography on silica gel (Hexanes/EtOAc, gradient elution).

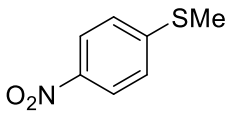
SAFETY NOTE: Although this work was completed without any safety-related problems, we were conscious of the potential for expulsion of gas resulting from generation of dimethyl sulfide (b.p. = 37° C) in a solution of refluxing DMSO (189°C). Care was taken to make

certain that the reaction was performed behind safety glass, inside a fumehood, with the top of the reflux condenser always left open to the atmosphere.



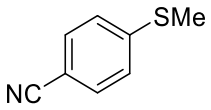
2-63

Methyl(2-nitrophenyl)sulfane (2-63): The general procedure was used with 1-fluoro-2-nitrobenzene (2.0 mmol) as substrate. After 12 h reaction time, workup, and chromatography as described above, compound **2-63** was isolated as yellow crystals; yield: 270 mg, 80 %; mp = 55 - 58 ºC; R_f = 0.51 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.26 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.59 (ddd, *J* = 8.1, 7.2, 1.5 Hz, 1H), 7.43 – 7.35 (m, 1H), 7.29 – 7.21 (m, 1H), 2.51 (s , 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 145.8, 139.5, 133.8, 126.4, 125.9, 124.4, 16.2. These spectral data are in agreement with previously reported literature values.[67]



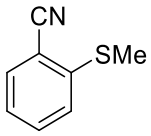
2-76

Methyl(4-nitrophenyl)sulfane (2-76): The general procedure was used with 4-fluoro-2-nitrobenzene (2.0 mmol) as substrate. After 12 h reaction time, workup, and chromatography as described above, compound **2-76** was isolated as yellow crystals; yield: 274 mg, 81 %; mp = 62 - 66 ºC; R_f = 0.71 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.12 (d, J = 9.0 Hz, 2H), 7.29 (d, J = 8.9 Hz, 2H), 2.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 149.1, 145.1, 125.3, 124.1, 15.1. These spectral data are in agreement with previously reported literature values.[68]



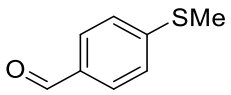
2-77

4-(methylthio)benzonitrile (2-77): The general procedure was used with 4-fluorobenzonitrile (2.0 mmol) as substrate. After 24 h reaction time, workup, and chromatography as described above, compound **2-77** was isolated a pale yellow solid; yield: 197 mg, 66 %; mp = 58 - 60 ºC; R_f = 0.67 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.51 (d, J = 8.6 Hz, 2H), 7.28- 7.21 (m, 2H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 146.3, 132.4, 125.8, 119.2, 108.0, 14.9. These spectral data are in agreement with previously reported literature values.[69]



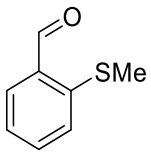
2-78

2-(methylthio)benzonitrile (2-78): The general procedure was used with 2-fluorobenzonitrile (2.0 mmol) as substrate. After 24 h reaction time, workup, and chromatography as described above, compound **2-78** was isolated as a clear yellow oil; yield: 185 mg, 62 %; R_f = 0.53 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.59 (ddd, J = 7.7, 1.5, 0.5 Hz, 1H), 7.52 (ddd, J = 8.1, 7.5, 1.5 Hz, 1H), 7.34 – 7.30 (m, 1H), 7.22 (td, J = 7.6, 1.1 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 143.8, 133.7, 133.1, 126.6, 125.4, 117.1, 112.0, 16.0. These spectral data are in agreement with previously reported literature values.[70]



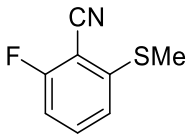
2-79

4-(methylthio)benzaldehyde (2-79): The general procedure was used with 4-fluorobenzaldehyde (2.0 mmol) as substrate. After 48 h reaction time, workup, and chromatography as described above, compound **2-79** was isolated as a yellow oil; yield: 183 mg, 60 %; R_f = 0.61 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.93 (s, 1H), 7.83 – 7.71 (m, 2H), 7.39 – 7.27 (m, 2H), 2.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 191.3, 148.1, 133.3, 130.2, 125.5, 14.9. These spectral data are in agreement with previously reported literature values.[71]



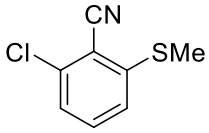
2-80

2-(methylthio)benzaldehyde (2-80): The general procedure was used with xxxxxx (2.0 mmol) as substrate. After 24 h reaction time, workup, and chromatography as described above, compound **2-80** was isolated as a yellow oil; yield: 195 mg, 64 %; R_f = 0.67 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 10.28 (s, 1H), 7.81 (dd, J = 7.6, 1.6 Hz, 1H), 7.53 (ddd, J = 7.9, 7.3, 1.6 Hz, 1H), 7.35 (dd, J = 8.1, 1.0 Hz, 1H), 7.31 – 7.26 (m, 1H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 191.5, 143.6, 134.1, 133.4, 133.2, 125.8, 124.6, 15.8. These spectral data are in agreement with previously reported literature values.[72]



2-81

2-fluoro-6-(methylthio)benzonitrile (2-81): The general procedure was used with 2,6-difluorobenzonitrile (2.0 mmol) as substrate. After 18 h reaction time, workup, and chromatography as described above, compound **2-81** was isolated as an off-white solid; yield: 211 mg, 63 %; mp = 61 - 64 ºC; R_f = 0.47 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.61-7.41 (m, 1H), 7.07 (d, J = 8.1 Hz, 1H), 7.01-6.86 (m, 1H), 2.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 164.2 (d, $^1J_{CF}$ = 258 Hz), 146.5, 134.4 (d, $^3J_{CF}$ = 10 Hz), 121.4, 112.3 (d, $^2J_{CF}$ = 20 Hz), 100.8 (d, $^2J_{CF}$ = 16.2 Hz), 15.9; IR: 3091, 2916, 2224, 1431, 1198; HRMS: 168.0275 (Calculated for $C_8H_8FNS+H^+$ = 168.0283).



2-82

2-chloro-6-(methylthio)benzonitrile (2-82): The general procedure was used with 2,6-dichlorobenzonitrile (2.0 mmol) as substrate. After 24 h reaction time, workup, and chromatography as described above, compound **2-82** was isolated as a light yellow solid; yield: 271 mg, 52 %; mp = 108 - 112 ºC; R_f = 0.44 (Hexanes/EtOAc 70:30 v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.43 (t, J = 8.1 Hz, 1H), 7.30 – 7.22 (m, 1H), 7.18 (dd, J = 8.1, 0.9 Hz, 1H), 2.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 146.8, 138.3, 133.3, 125.9, 123.9, 114.3, 112.2, 16.0; IR: 3091, 2916, 2224, 1431, 1198; HRMS: 183.9987 (Calculated for $C_8H_6ClNS+H^+$ = 183.9988).

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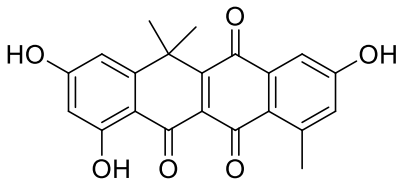
Chapter 3. Progress towards the total synthesis of tetarimycin A

Section 3.1. Introduction

Section 3.1.1 Outline of this Chapter

The subject of this chapter is our progress toward the synthesis of the antibiotic natural product tetarymicin A. This compound is introduced in Section 3.2. Prior to this we review antibiotic drug resistance, the early role of chemical synthesis in antibacterial drug discovery, tetracyclic antibiotics and previous synthetic approaches to tetracyclic antibiotics under Section 3.1.



Tetarimycin A (**3-1**)

Figure 3.1. Structure of tetarimycin A

Section 3.1.2. Antibiotic Drug Resistance

The continued development of novel antibiotics has garnered renewed attention due to the emergence of antibiotic resistance which has become an issue of major public health concern.[1] In the 2013 Global Risks report of the World Economic Forum, antibiotic resistance was identified as a key threat to human health.[2,3] Over 70 % of pathogenic bacteria are resistant to most antibiotics on the market. The mortality rate of most multi-resistant infections currently ranges between 50 and 80 %. An estimated two million Americans acquire bacterial infections in health facilities, resulting in almost 100,000 deaths per year. Globally, more than two million medical conditions per year are due to bacterial infections.[4] The lack of industrial antibacterial research and development has led to an alarming decline in the number of new

antibiotics entering the market in the last 30 years.[2] Pharmaceutical companies are abandoning antibacterial research and development due to the relatively low financial return on investment in antibiotic research. This slowing trend in the discovery of new antibiotics has brought society to what is arguably a crisis point. This has resulted in a renewed academic interest in the research and development of antibiotics.

The serendipitous discovery of Alexander Fleming in the twentieth century marked a revolutionary transition in medicine.[3] Prior to this, many infections were deemed fatal and treated by surgery and many infections led to amputation. Many lives have been saved through the use of antibiotics. Unfortunately, the widespread use of these drugs has contributed to the evolution of resistant strains. Reports have predicted the existence of over 20,000 potential resistance genes (r genes) of more than 400 different types from available bacterial genome sequence.[5] *Staphylococcus* is among the top ten most dangerous bacteria in the world today. It belongs to one of the largest bacterial groups with more than forty subspecies. A large number of antibiotic-resistant strains have been observed.[6]

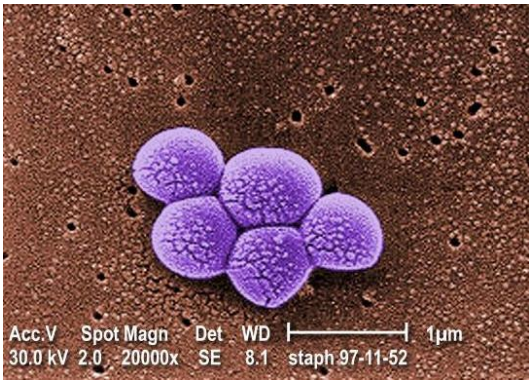


Figure 3.2. An image of *Staphylococcus aureus*

(Photo credit: Public Health Image Library)

Methicillin-resistant *Staphylococcus aureus* (MRSA) is classified as any strain of *Staphylococcus aureus* that has emerged by virtue of natural selection and has developed resistance to traditional *β*-Lactam antibiotics, such as the penicillins: Methicillin **3-2**, Dicloxacillin **3-3**, Nafcillin **3-4**, Oxacillin **3-5** (Figure 3.3). Methicillin was introduced in 1959 as treatment for infections caused by Penicillin-resistant *Staphylococcus aureus* (PRSA). Two years after, there were records of Staphylococcus *aureus* isolates that had acquired resistance to methicillin in the United Kingdom.[7] Since then, MRSA has increasingly contributed to the difficulty in treating infections in humans. [8] MRSA was initially detected as a hospital-acquired infection which caused a life-threatening bloodstream infection, pneumonia, and surgical site infections. It soon became prevalent in Europe, Australia, and many Asian countries. [9] Today, MRSA is a complication in hospitals all over the world. The bacterium has also been found in other facilities such as prisons and nursing homes. It is particularly troublesome for patients with open wounds and weakened immune systems, who have a greater risk to infection than the general public. [10] In the United States, methicillin-resistant *Staphylococcus aureus* (MRSA) is estimated to cause more deaths than HIV. [11] MRSA is a significant global medical concern. Estimates by the Center for Disease Control and Prevention indicates that there are 80,461 invasive MRSA infections and 11, 285 deaths due to MRSA annually. [12]

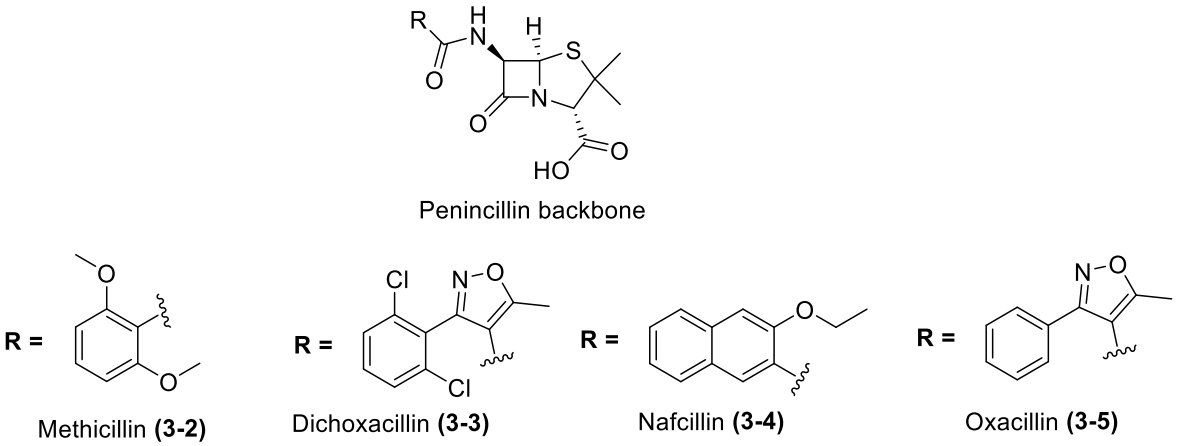


Figure 3.3. Known β-Lactam antibiotics

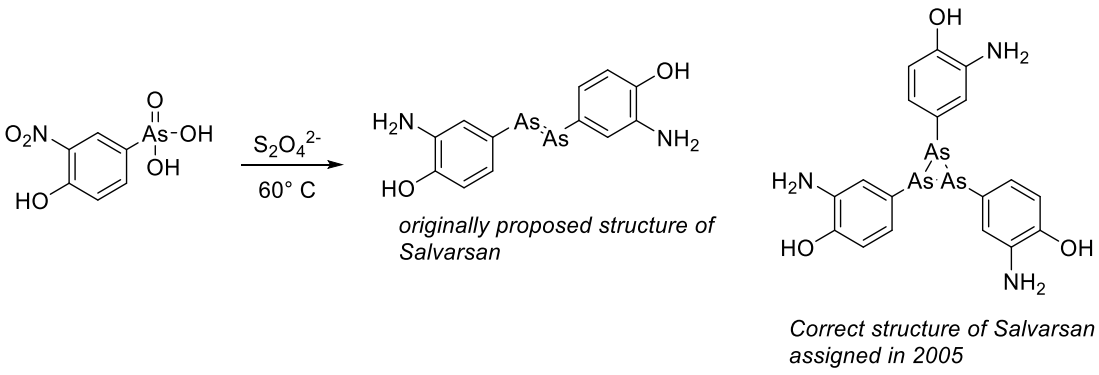
Section 3.1.3. The Early Role of Chemical Synthesis in Antibacterial Drug Discovery

All antibiotics used in human medicine can be grouped into the following three categories:

1. Natural products (manufactured by fermentation of bacteria or fungi)
2. Semisynthetic antibacterials (manufactured by chemical modification of natural products)
3. Synthetic antibacterials (manufactured via synthesis from simple substrates).

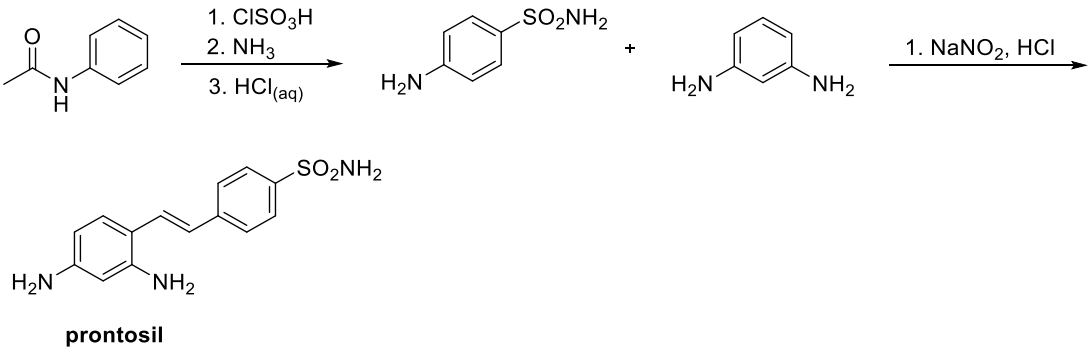
One hundred years ago, the pioneer founder of chemotherapy, Paul Ehrlich was awarded the Nobel Prize for Physiology and Medicine for his "magic bullet" hypothesis, the establishment of the first treatment for African sleeping sickness, and the early synthesis of aniline marked the beginning of therapy for bacterial infection. [8] In 1854, Antoine Bechamp's reduction of nitrobenzene to aniline with Fe/HCl created the platform in the dye industry that led to other lifesaving discoveries. [13] Attempts to derivatize aniline with arsenic acid led to the discovery of wrongly assigned atoxyl, a structure that was subsequently reassigned by Alfred Bertheim in 1907. [14] Further work in the derivatization of atoxyl resulted in the discovery of Salvarsan,

which is the first effective treatment for the sexually transmitted infection syphilis, and the first antibacterial drug. [15]



Scheme 3.1. Synthesis of salvarsan from atoxyl (1909)

Continual research in the dye industry years after the discovery of Salvarsan led to the discovery of prontosil, a sulfanilamide that saved the lives of many including the lead researcher's own 6-year-old daughter. By 1982, chemists had synthesized more than 5000 structural variants of sulfanilamide many of which were approved and used as drugs. [16]



Scheme 3.2. Chemical synthesis of protonsil (1932)

Some of these early sulfur containing dugs are still in use for treatment of bacterial infections. Chemical synthesis has been a significant part of antibacterial drug discovery. It is of great

significance to note that the first two classes of antibiotics employed for clinical purposes were entirely synthetic compounds.

Section 3.1.4. Tetracyclic antibiotics

The synthetic target that will be the focus of this chapter, Tetarimycin A, resembles the tetracycline class of FDA-approved antibiotics but is more closely related to the Tetracenomycin and Elloramycin natural products (Figure 3.4). It is a promising addition to the existing class of tetracycline and tetracenomycin families of aromatic polyketides due to their antibiotic activity. [17] In general, members of these classes have four linearly-connected six-membered rings (Figure 3.4) that are diversely functionalized. Tetracyclines have long been known to inhibit protein synthesis in bacteria by binding to the 30S subunit of the bacterial ribosome. [18] Tetracenomycins are believe to act by intercalation with bacterial DNA. [19] Previous efforts towards isolation, purification, and structural characterization of members of this class have shown that they have diverse bioactivity such as antitumor, antimicrobial activity, as well as cytotoxicity. [20] They are attractive targets for synthetic and medicinal chemistry research and, in the past fifty years, there has been sustained interest within the synthetic community to synthesize tetracyclic antibiotics and their analogs not only due to their promising bioactivities but also due to their challenging structural complexity. [21]

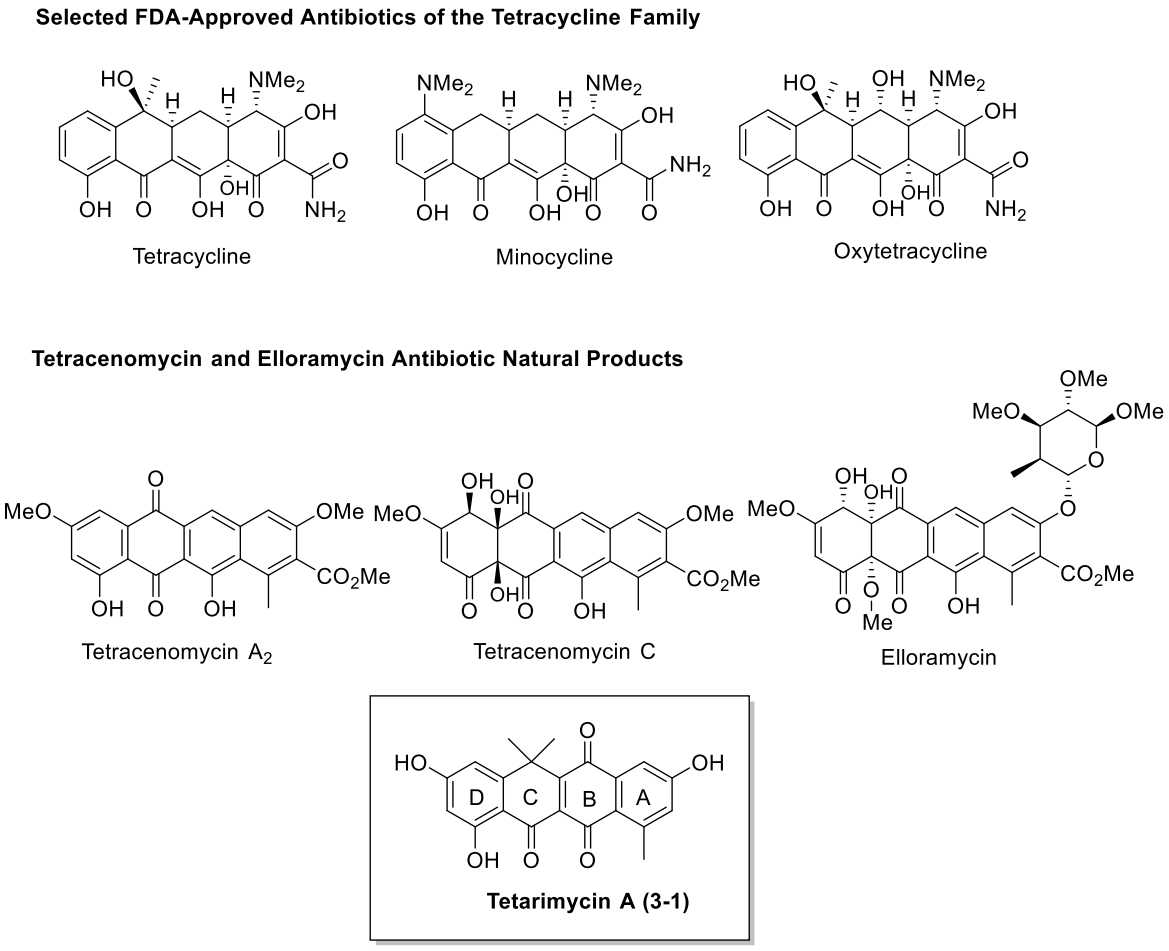
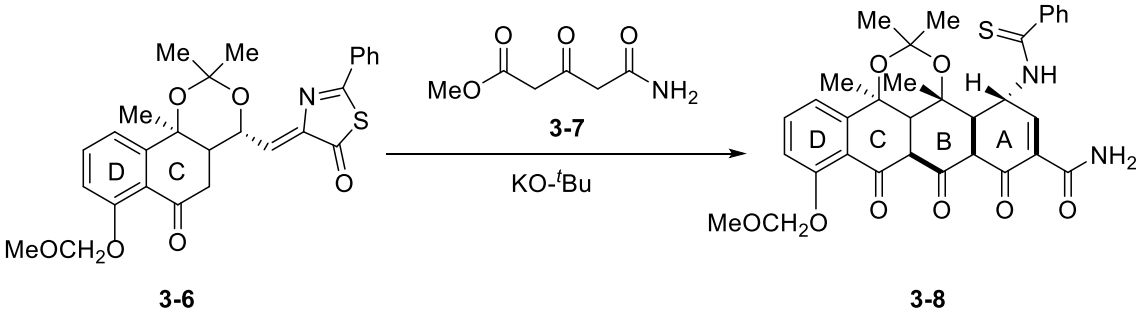


Figure 3.4. Selected tetracyclic antibiotics

Tetracyclines and the tetracenomycin class are characterized by four linearly aligned, six-membered carbon rings conventionally labeled A to D as shown in Figure 3.4. [22] This tetracyclic scaffold forms the basis of many antibiotics including: Tetracenomycin A_2, Tetracenomycin C, Elloramycin, (-)-Tetracycline, Minocycline and Oxytetracycline. The potent activity of these class of compounds has enabled their application in both human and veterinary medicine.

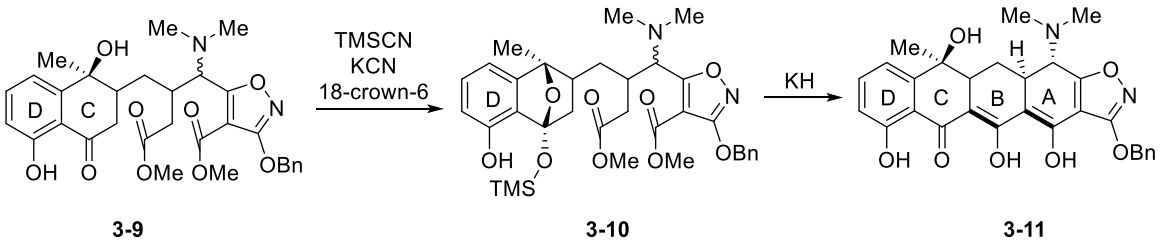
Section 3.1.5. Previous synthetic approaches to tetracyclic antibiotics

In 1968, Woodward *et al.* reported the first synthesis of a tetracycline antibiotic, (±)-6-demethyl-6-deoxytetracycline in 25 steps with 0.002 % yield. [23] Muxfeldt *et al.,* in 1979 accomplished, the total synthesis of (±)-terramycin utilizing an approach that began with a CD ring precursor and construction of the B and A ring using a Michael reaction followed by a Dieckman cyclization with the glutamate derivative **3-7**. [24] Their approach resulted in the creation of three new C-C bonds in one step (scheme 3.3).



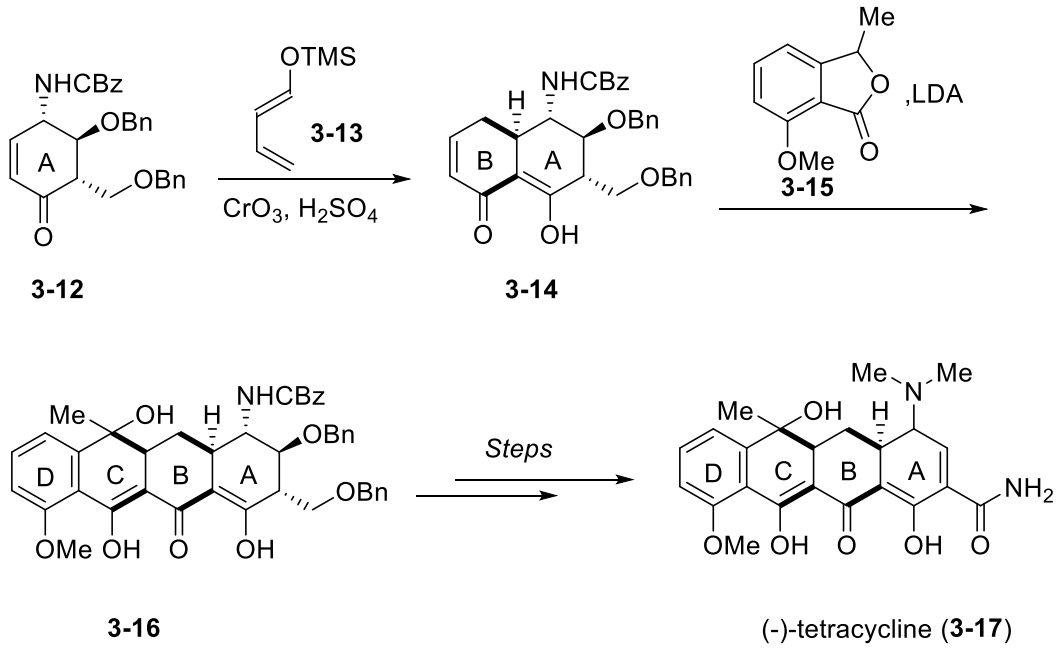
Scheme 3.3. Muxfeldt's 1979 synthesis of (±)-terramycin

Stork *et al.* [25] approached the core of (±)-12a-deoxytetracycline with a CD ring precursor and a double Claisen cyclization to assemble the A and B ring of the tetracyclic core (Scheme 3.4). The hydroxyl group on the C ring was involved in the formation of ketal **3-10**, followed by a deprotonation at the *α*-position to induce the double Claisen cyclization cascade.



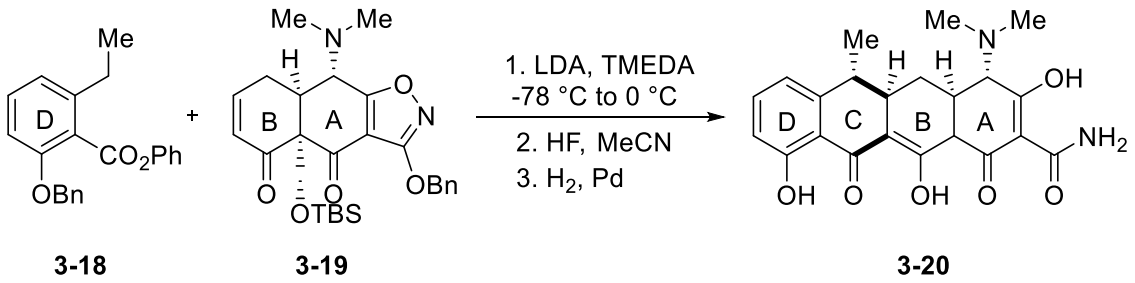
Scheme 3.4. Stork's 1996 synthesis of (±)-12a-deoxytetracycline.

In the last decade, two new unique approaches to this structural scaffold have been introduced. The first was Tatsuta's synthesis of (-)-Tetracycline in 2000 (Scheme 3.5).[26] The authors began with an A ring-containing substrate and synthesized the AB-rings via regio-selective Diels-Alder cycloaddition between enone **3-12** and diene **3-13**. Next, an isobenzofuran derivative **3-15** was added via Michael-Dieckmann cyclization to form the tetracyclic intermediate **3-16**.



Scheme 3.5. Tatsuta's synthesis of (-)-tetracycline (2000)

Meyers and co-workers employed an AB ring precursor strategy which involves the coupling of the AB ring precursor with a D ring-containing partner to generate the C-ring in the process (Scheme 3.6). [27] This efficient approach enabled the preparation of various synthetic analogs.



Scheme 3.6. Myers's synthesis of (-)-6-deoxytetracycline

Section 3.2. Introduction to Tetarimycin A

Tetarimycin A is a Gram-positive specific antibiotic that was originally isolated from the culture-broth extract of *Streptomyces albus*.[28] It has a tetracyclic core with three methyl substituents, three phenols, and a quinone (Figure 3.5).

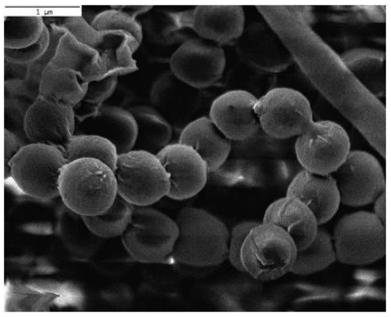


Figure 3.5. A scanning electron micrograph of *Streptomyces albus*[29]

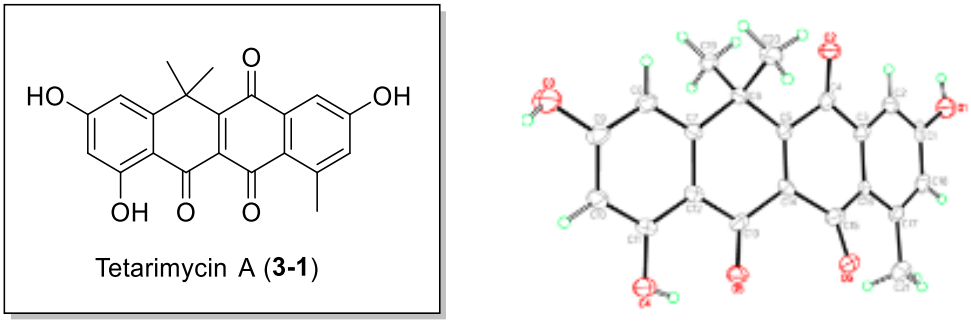
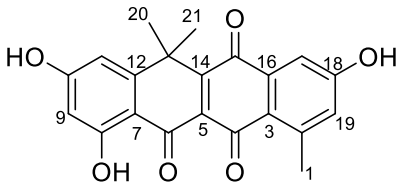


Figure 3.6. Structure of Tetarimycin A (left) and crystal structure of Tetarimycin A (right)

Bioactivity screening has shown that Tetarimycin A possesses potent activity in minimal inhibitory concentrations of 0.39 μg/mL against methicillin-resistant *Staphylococcus aureus* (MRSA). [28] Its structure was determined by NMR and mass spectrometry. The ^{1}H NMR data obtained in Professor Brady's laboratory is shown below (Table 3.1). [28] Chemical shift values in both carbon and proton NMR indicate the presence of aromatic rings. In the ^{1}H NMR spectrum, the four signals at δ 6.32, 6.74, 7.37 and 7.07 ppm with coupling constants of 2.0, 2.0, 2.1 and 2.1 respectively belong to four aromatic protons. Two upfield singlets were assigned as the A-ring methyl, (δ 2.62 ppm) and the C-ring *gem*-dimethyls (δ 2.62 ppm). HMBC correlations were also observed as indicated in Table 3.1.

Table 3.1. ^{1}H (600 MHz), ^{13}C (150 MHz) Chemical shift and HMBC correlations for tetarimycin A in acetone-d_6



	NMR chemical shift values in acetone-d_6			
	δ_C[a,c]	δ_H[b,c]	mult. (*J* in Hz)	HMBC
1	21.6	2.62	s	2, 3, 19
2	143.2			
3	124.8			
4	183.9			
5	136.9			
6	186.4			
7	110.6			
8	166.1[d]			
9	101.9	6.32	d (2.0)	6,[e] 7, 10, 11
10	166.3[d]			
11	106.4	6.74	d (2.0)	6,[e] 7, 9, 10, 13
12	155.6			
13	39.9			
14	156.1			
15	186.6			
16	137.7			
17	112.1	7.37	d (2.1)	3, 15, 16, 18, 19
18	162.1			
19	124.8	7.07	d (2.1)	1, 3, 17, 18
20	30.4			
21		1.82	1.82 s	12, 13, 14, 20, 21

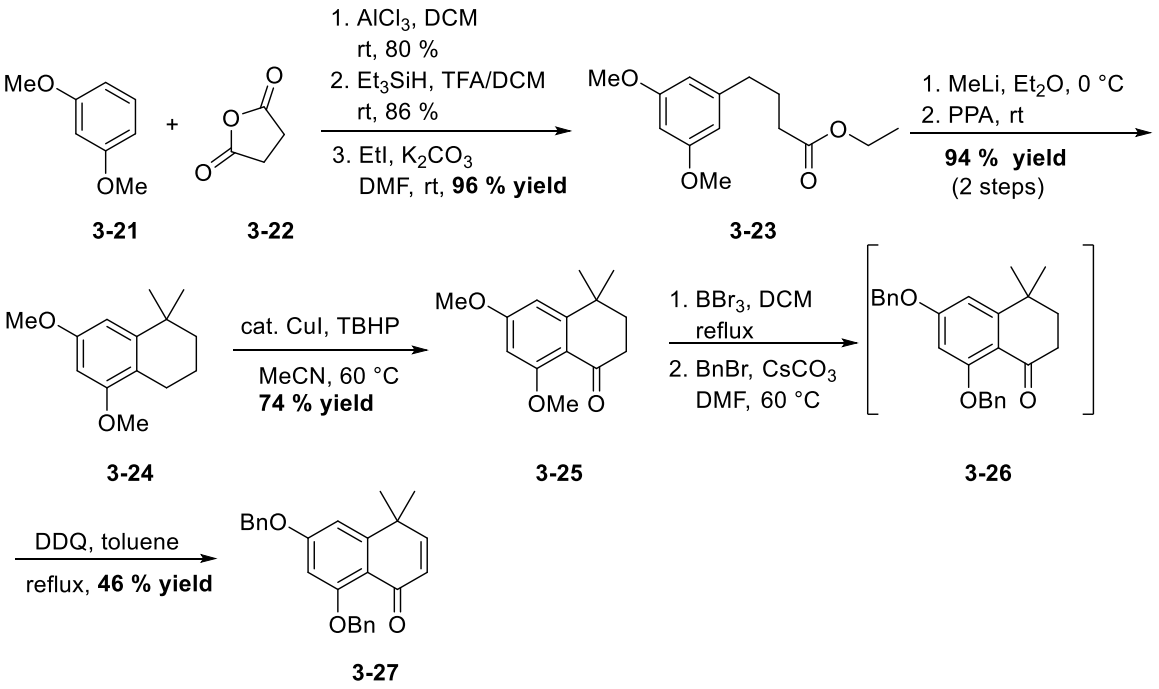
[a] record at 150 MHz, [b] recorded at 600 MHz, chemical shifts referenced to the solvent signal, [d] interchangeable, [e] weak correlations.

Section 3.2.1. Previous synthesis of Tetarimycin A

The first total synthesis of Tetarimycin A was reported in 2015 by Shia *et al.* [30] The authors employed a Hauser-Kraus annulation as the key step to access the B ring from a Michael acceptor DC-ring precursor **3-27** and a donor with an inherent A ring **3-34**. The two precursors required to construct the tetracyclic core we both accessed via Friedel-Crafts

acylation of **3-21** and **3-22** and Diels-Alder cycloaddition of diene **3-28** (2-pyrone) and DMAP as the dienophile.

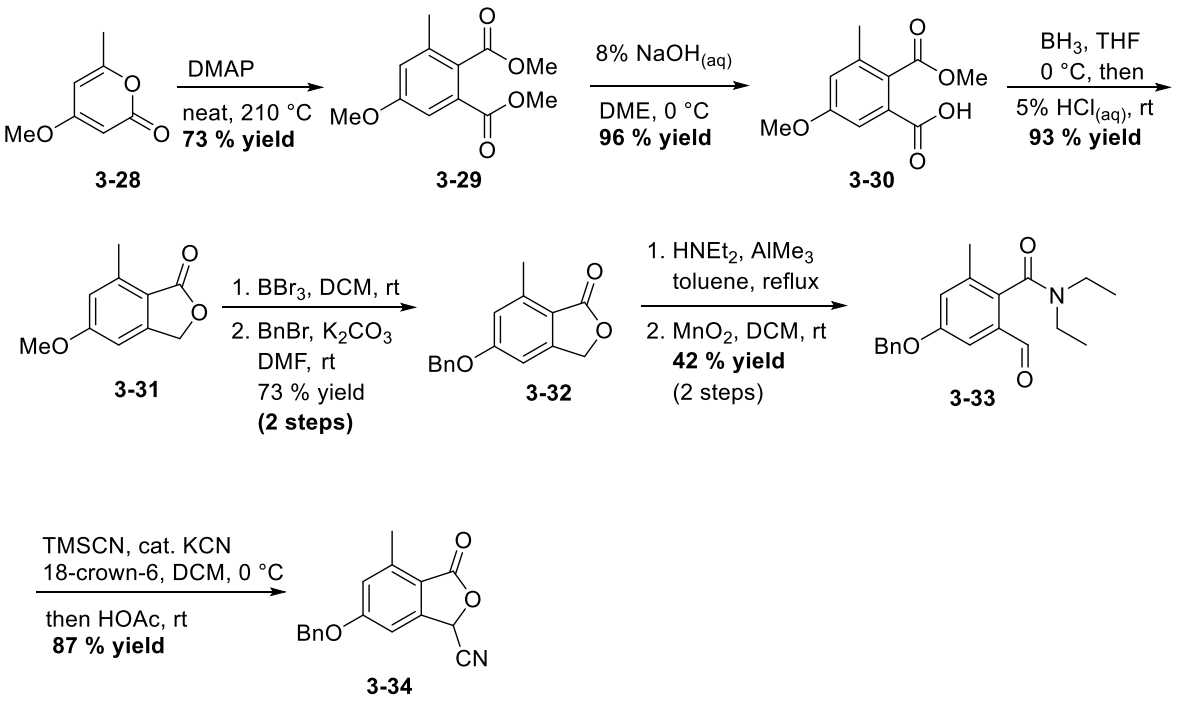
Towards the synthesis of the DC-ring precursor, ester **3-23** (Scheme 3.7) was afforded from succinic anhydride **3-22** and 1,3-dimethoxybenzene **3-21** over 3 steps using Friedel-Crafts acylation. This ester **3-23** was converted to tetralin **3-24** over 2 steps in 94 % yield through intramolecular Friedel-Crafts alkylation mediated by PPA. The carbonyl functionality on the C ring was installed via CuI mediated oxidation with *tert*-butyl hydroperioxide to obtain **3-25**. After protection group manipulations, benzyl protected tetralone **3-26** was subsequently converted to the Michael acceptor DC-ring precursor **3-27** via oxidation with DDQ.



Scheme 3.7. Shia's synthesis of compound **3-27**

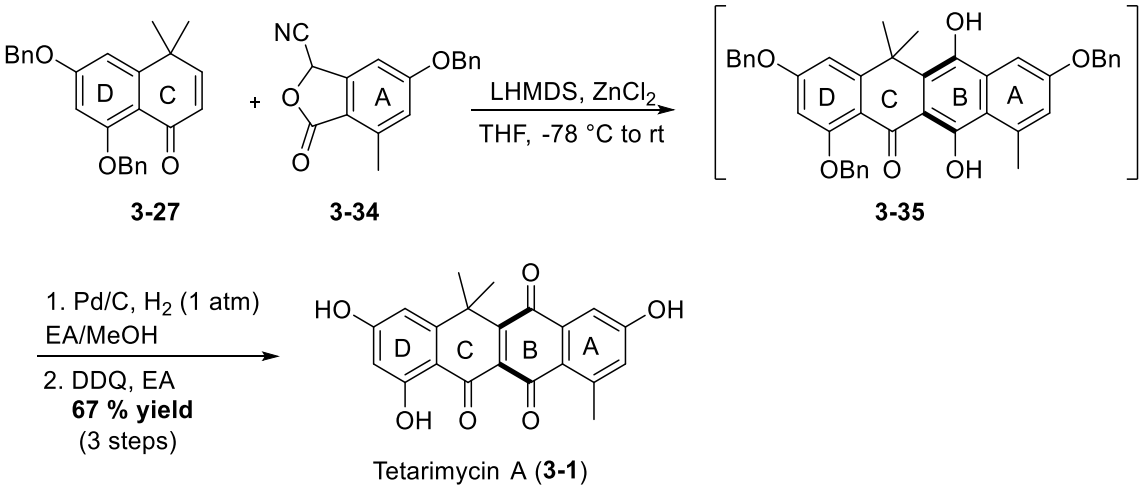
The A ring component **3-34** was obtained by converting 2-pyrone **3-28** to diester **3-29 v**ia a Diels-Alder cycloaddition to DMAP. The isobenzofuran derivative **3-31** was obtained in 93 % yield from the Diels-Alder adduct after hydrolysis of diester **3-29** and chemoselective

reduction of monoester **3-30**. After a change of protection group from the methoxy to benzyl groups, the isobenzofuran derivative **3-32** was transformed to amide aldehyde **3-33** over 2 steps in 45 % yield. The amide was converted to the desired isobenzofuran intermediate **3-34** via a cyano alcohol intermediate that cyclized under acidic conditions. (Scheme 3.8)



Scheme 3.8. Shia's synthesis of compound **3-34**

Shia *et al* successfully constructed the tetracyclic core by coupling benzyl protected donor **3-34** and acceptor **3-27** using LHMDS and $ZnCl_2$ to obtain a mixture of Hauser-Krus product **3-35** and corresponding autoxidized product (Scheme 3.9). The final product was obtained after 22 steps in 67% yield after debenzylation with $Pd/C/H_2$ followed by oxidation with DDQ. Preliminary structural activity relationship studies by the authors confirmed the potent activity of tetarimycin A against MRSA and VRE at low minimum inhibitory concentrations. The hydroxyl group *meta* to the *gem*-dimethyl moiety was identified to be essential for antibacterial activities.

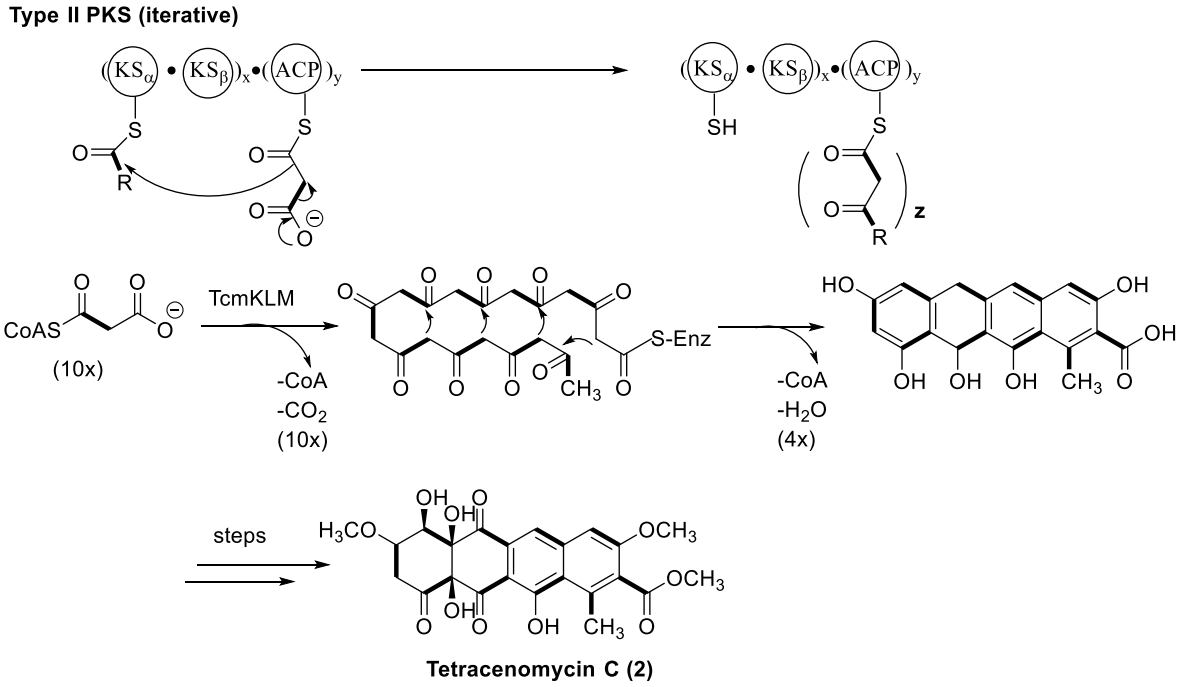


Scheme 3.9. Shia's completion of tetarimycin A

Section 3.3. Results and Discussion

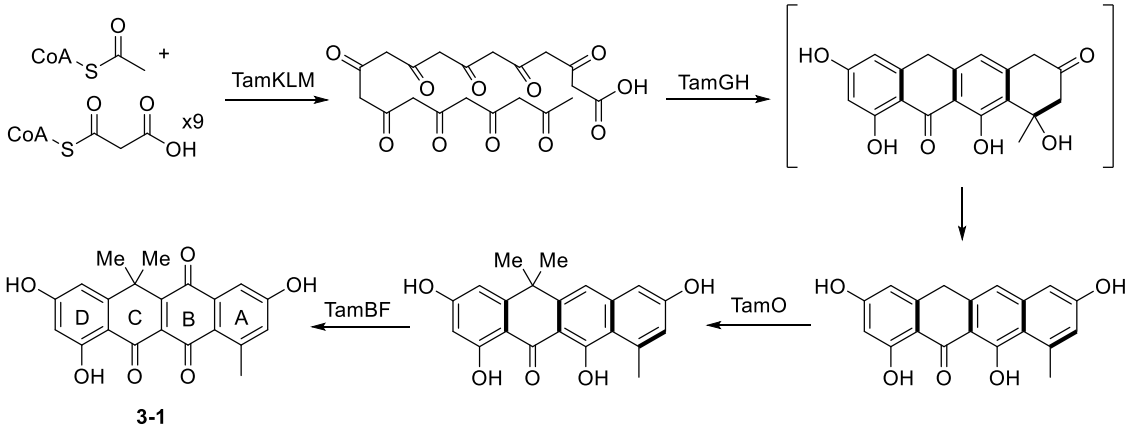
Section 3.3.1. Inspiration for our Retro-Synthetic Approach

Our proposed retrosynthetic approach is inspired by the proposed polyketide condensation mechanism in the enzyme-catalyzed biosynthesis of the tetracenomycin class of compounds. [31] For example, the biosynthetic assembly of the carbon skeleton of the anticancer antibiotic tetracenomycin C is believed to be carried out by a catalyzed addition of acetyl-CoA units to malonyl-CoA to form a polyketide chain using minimal Type II PKS, composed of two ketosynthases, KS_α and KS_β, followed by a stepwise enzyme-catalyzed condensation of polyketide (Scheme 3.10). [31]



Scheme 3.10. Proposed biosynthesis of tetracenomycin C

Following the isolation of tetarimycin A, Brady *et al.* proposed a similar biosynthetic path in which the minimal PKS (TamKLM) generates a polyketide that undergoes a condensation cyclization catalyzed by TamG as shown in (Scheme 3.11). [28] They proposed an oxidation of the tetracyclic intermediate by either or both of the oxidoreductases TamF and TamB to yield the intermediate quinone. Installation of the *gem*-dimethyl group is predicted to be accomplished by the methyl transferase TamO to afford tetarimycin A **3-1**.



Scheme 3.11. Proposed biosynthesis of Tetarimycin A

Section 3.3.2. Our Primary Retrosynthetic Diconnections for Tetarimycin A

Inspired by the biosynthetic assemblies above, we envisioned a strategic approach involving the coupling of two partners via a condensation cascade designed to assemble the central B and C rings as shown in Figure 3.7.

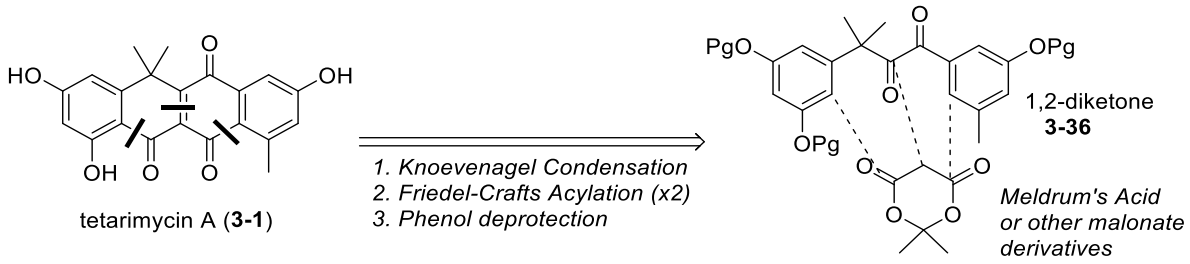
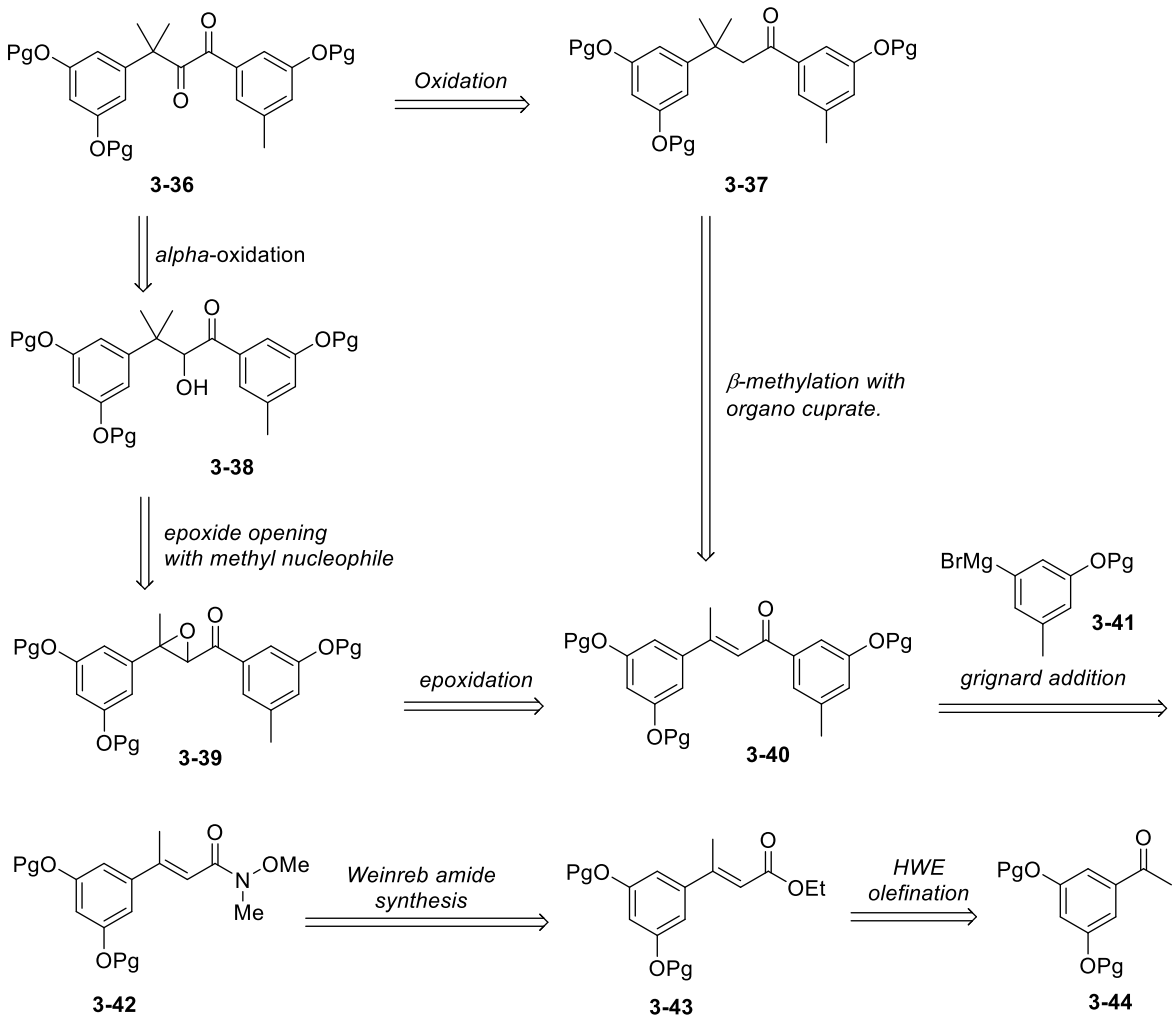


Figure 3.7. General retro-synthetic approach to tetarimycin A

The proposed transformation involves one Knoevenagel condensation and two Friedel-Crafts acylations. The B and C rings of the scaffold are thus formed via condensations of an appropriate 1,2-diketone **3-36** and a malonate derivative such as Meldrum's acid. We believed this to be a strategically efficient approach to this target and an innovative strategy toward this family of compounds. It would be the first approach to such compounds that assembles the B and C rings from a DA precursor in a tandem process.

Section 3.3.3. First generation retro-synthetic approach to 1,2-diketone intermediate

In order to test this cyclization strategy, we first needed to prepare 1,2-diketone **3-36**. From a retrosynthetic viewpoint, we envisioned forming 1,2-diketone **3-36** via α-oxidation of the ketone **3-37** or oxidation of the α-hydroxyl ketone **3-38** (Scheme 3.12). The *gem*-dimethyl moiety on DA ring precursor would be installed via nucleophilic epoxide opening of **3-39** which could be acquired from enone **3-40**. Alternatively, the *gem*-dimethyl moiety could be installed by conjugate addition of a methyl cuprate to enone **3-40**. We believed the epoxide **3-39** could be synthesized from enone **3-40**, which could be afforded via Grignard addition of **3-41** to Weinreb amide **3-42**. The requisite Weinreb amide could be elaborated from *α,β*-unsaturated ester **3-43** using *N,O*-dimethylhydroxylamine hydrochloride. Our initial approach to phenol group protection was to use benzyl ethers. 3,5-dibenzyloxyacetophenone **3-44** would be initially subjected to Horner-Wadsworth-Emmons olefination to afford the corresponding *α,β*-unsaturated ester **3-43**.

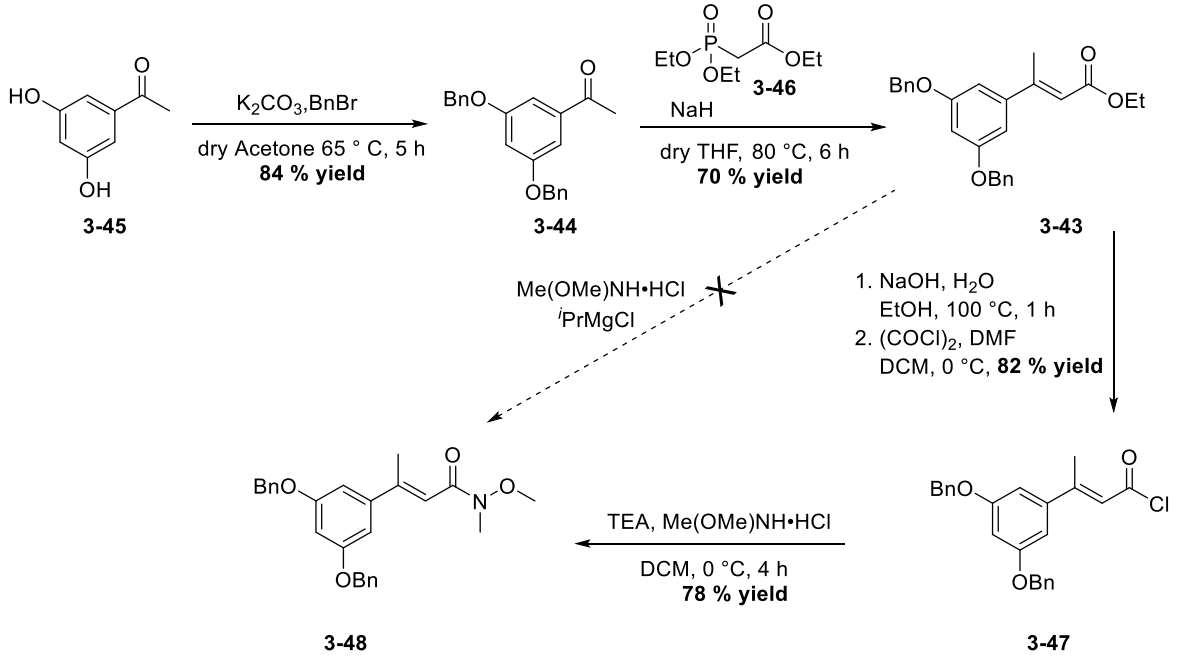


Scheme 3.12. Our first retro-synthetic approach to 1,2-diketone **3-36**

3.3.4. Model Study 1

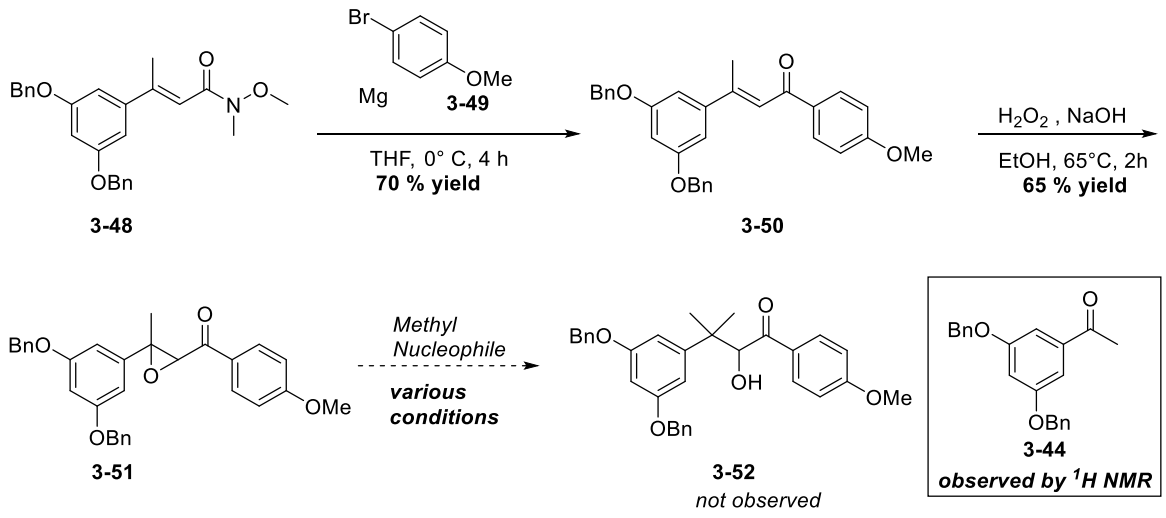
Initial synthetic studies towards the construction of 1,2-diketone **3-36** commenced with benzyl protection of readily available 3,5-dihydroxyacetophenone **3-45** in 84% yield (Scheme 3.13). A Horner-Wadsworth-Emmons olefination[32] of the benzylated product with triethyl phosphonoacetate afforded 70% of the desired *α,β*-unsaturated ester **3-44**. We were unable to synthesize Weinreb amide **3-48** directly from **3-43** using previously reported conditions for analogous transformations using *N,O*-dimethylhydroxylamine hydrochloride and isopropyl magnesiumbromide.[33] We converted the ester to an acyl chloride via hydrolysis

of the ester to the carboxylic acid and subsequent chlorination with oxalyl chloride catalyzed by *N*,*N*-dimethylformamide afforded the acyl chloride **3-47**. Next, treatment with *N*,*O*-dimethylhydroxylamine gave the desired Weinreb amide **3-48** in 78 % yield.



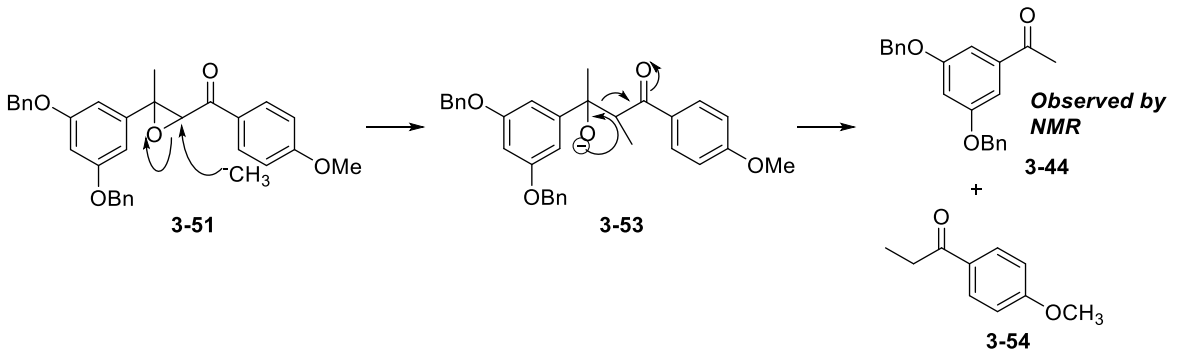
Scheme 3.13. Synthesis of Weinreb amide **3-48**

With **3-48** in hand, we turned our attention to installing the A ring of the proposed precursor via Grignard addition (Scheme 3.14). As it was available in the laboratory, we began with 4-bromoanisole as a model A ring component. Amide **3-48** was elaborated to enone **3-50** in a single step by addition of 4-bromomagnesium anisole.[34] Next the olefin of **3-50** was converted to the corresponding epoxide **3-51** in 68 % yield. We reasoned that the addition of a methyl nucleophile could result in the *gem*-dimethyl moiety if the epoxide could be regioselectively opened at the *β*-position. Ring-opening of epoxides can proceed via S_N2 or S_N1 mechanism depending on the nature of epoxide in the reaction.



Scheme 3.14. Epoxidation of enone **3-50** and failed epoxide ring opening

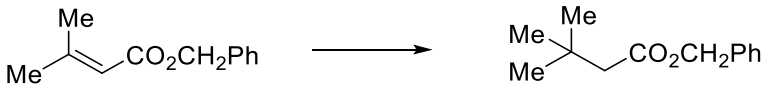
We were disappointed to see that treatment of the epoxide with trimethyaluminium[35] yielded only starting material. Lithium dimethylcuprate addition resulted in an unexpected fragmentation to give 3,5-dibenzylatedhydroxyacetophenone **3-44**. It is likely that lithium dimethycuprate attacked the epoxide from the less hindered side with subsequent cleavage of the C-C bond via a retro-aldol type fragmentation leading to **3-44** (Scheme 3.15). In retrospect, this approach was unwise given that literature precedent dictated that alkyl nucleophiles would open the epoxide with the undesired regiochemistry. Such transformations are more common with intramolecular expoxide-ring openings. [36] Unfortunately, no reagent system is known that offers a nucleophilic methyl under acidic conditions (which would potentially reverse the regiochemistry of this reaction). At this point, we abandoned the strategy of regioselective methylation of an epoxyketone.



Scheme 3.15. Proposed mechanistic path via retro-aldol fragmentation of epoxyketone **3-51**

The second strategy proposed in (Scheme 3.16) involved the use of a 1,4-conjugate addition of a methyl nucleophile to enone **3-50** for installation of the *gem*-dimethyl moiety. [37] It seemed reasonable that this sequence would facilitate the eventual conversion of enone **3-50** to an analog of ketone **3-37**, which could be elaborated to the α-hydroxyketone via a Rubottom oxidation sequence. Unfortunately, our efforts to install the gem-dimethyl moiety via conjugate addition of lithium dimethylcuprate to enone **3-50** also proved ineffective. Conjugate additions of organocuprates to enones and other related *α,β*-unsaturated carbonyl compounds are valuable C-C bond formation reactions, [38] however additions directed to sterically congested *β*-positions are difficult. [39] We briefly studied this problem using a model ester **3-43**. In 2003, Yamamoto *et al.* used lithium dimethylcuprate/TMSCl in dichloromethane as a powerful methylating reagent for conjugate addition to sterically congested α,β-unsaturated esters (Table 3.2, entry 6). [40]

Table 3.2. Conjugate addition to **3-55** using methyl nucleophiles



3-55 **3-56**

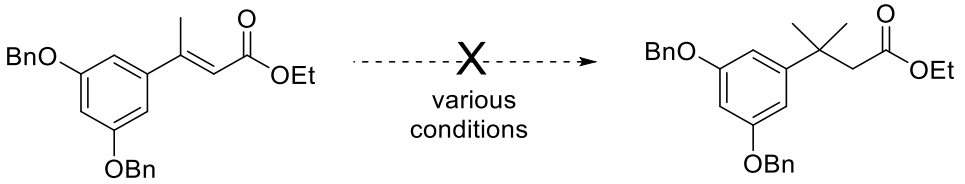
Entry	Conditions	Yield (%)[1]
1	$Me_2CuLi{\cdot}TMSCl/Et_2O$	0 %[a]
2	$Me(Th)CuLi{\cdot}TMSCl/Et_2O$	0 %[a]
3	$Me_2CuLi{\cdot}TMSCl$/toluene	0 %[a]
4	Me_2CuLi only/CH_2Cl_2	0 %[a]
5	$MeCuLi{\cdot}TMSCl/CH_2Cl_2$	75 %
6	$Me_2CuLi{\cdot}TMSCl/CH_2Cl_2$	96 %

[1] Based on crude ^1H NMR

[a] The starting material was recovered

The choice of solvent used in Yamamoto's methylation reagent system was based on findings reports by Nilson *et al*.[41] In 1988, Nilson's group established that the addition of MeCu·TMSI to enolates in dichloromethane gave higher yields than in diethyl ether.[42] Further studies conducted by Ullenius *et al* also demonstrated that diastereoselectivities in the conjugate addition of lithium dimethylcuprate to α,β-unsaturated systems were higher in non-coordinating solvents such as dichloromethane. We surveyed several conditions for 1,4-additions to ester **3-43** (Table 3.3). Unfortunately, all our attempts to apply this strategy failed. Even the pretreatment of *α,β*-unsaturated ester **3-43** with a Lewis acid additive such as $BF_3{\cdot}Et_2O$,[43] prior to the introduction of methylating reagent led to recovery of only the starting material. The reaction in tetrahydrofuran also led primarily to recovered starting material.

Table 3.3 Attempted conjugate additions to enone **3-43**



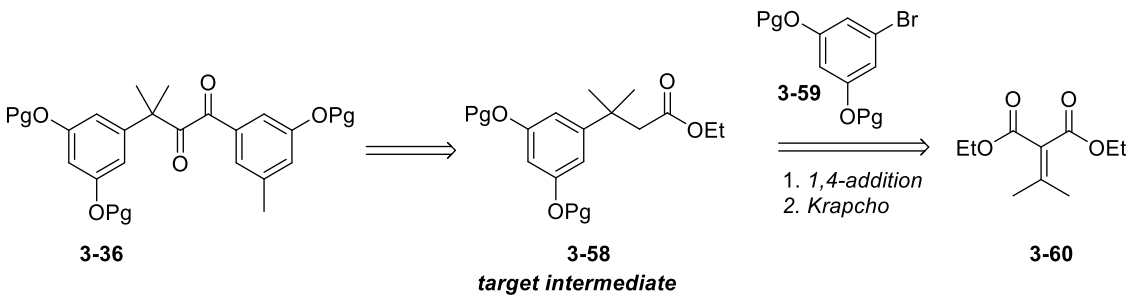
3-43 **3-57**

Entry	Conditions	Yield (%)
1	Me_2CuLi/Et_2O (0-78 °C, 24 h)	0 %[a]
2	$MeCuLi{\cdot}TMSCl/CH_2Cl_2$ (0-78 °C, 48 h)	0 %[a]
3	$Me_2CuLi{\cdot}TMSCl/THF$ (0-78 °C, 48 h)	0 %[a]
4	$Me_2CuLi{\cdot}BF_3EtO_2/Et_2O$ (0-78 °C, 24 h)	0 %[a]

[a] The starting material was recovered

Our lack of success in installing the *gem*-dimethyl moiety at the requisite location by both epoxide-ring opening and conjugate addition led us to revise our retro-synthetic strategy to the synthesis of the target 1,2-diketone **3-36**. Our aim in the next approach was to employ a conjugate addition strategy that could install the *gem*-dimethyl moiety in a single early step.

Section 3.3.5. Model Study 2A



3-36 **3-58** ***target intermediate*** **3-60**

Scheme 3.16. Second generation retro-synthetic approach to 1,2-diketone intermediate

Retro-synthetically, we envisioned that the ester **3-58**, with the requisite *gem*-dimethyl moiety, could be formed via a Krapcho dealkoxycarbonylation of the 1,4-conjugate addition product of diethyl isopropylidenemalonate **3-60** and the organocuprate of an appropriate aryl bromide **3-59**. To test the viability of this approach, we pursued a model 1,2-diketone **3-61**, which is a simplified version of 1,2-diketone **3-36** (Figure 3.8)

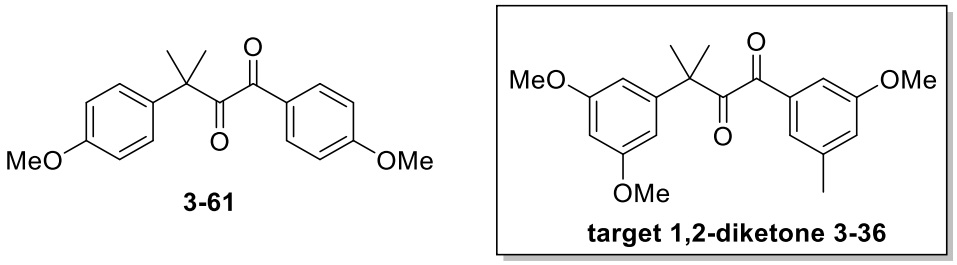
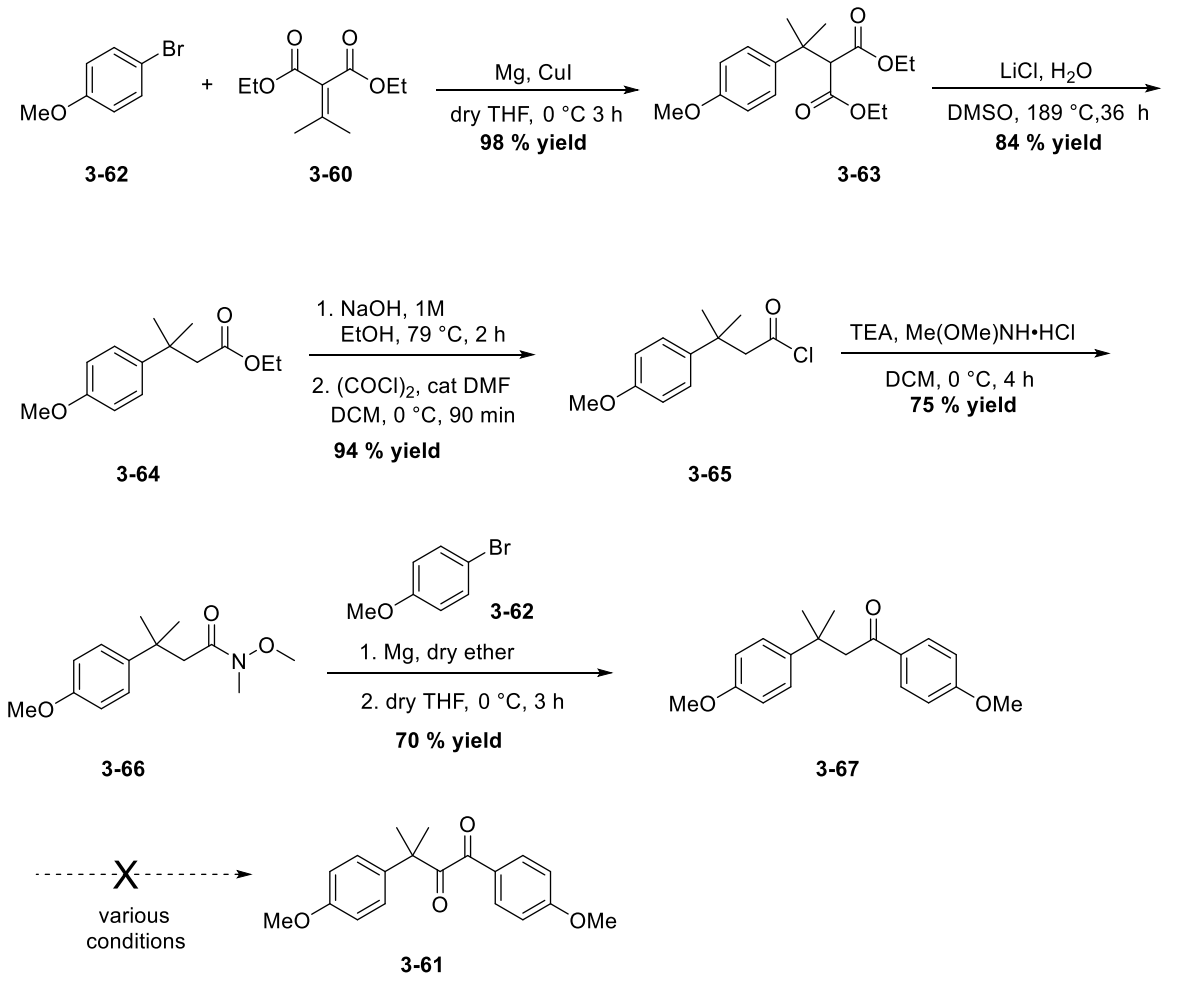


Figure 3.8. 1,2-diketone **3-61**, a simplified Version of 1,2-diketone **3-36**

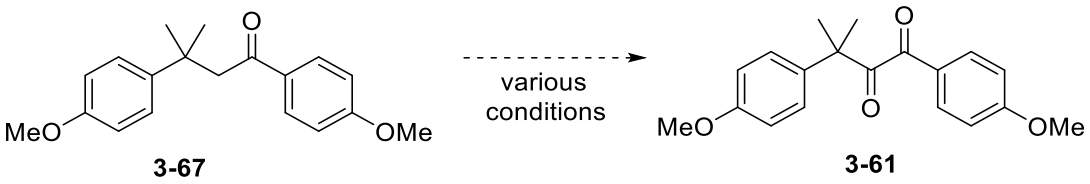
As illustrated in Scheme 3.17, a copper mediated 1,4-conjugate addition[44] of 4-bromoanisole **3-62** to diethyl isopropylidenemalonate **3-60** installed the *gem*-dimethyl moiety in almost quantitative yield of 98 % of diester **3-63**. Next, a Krapcho dealkoxycarbonylation[45] of this diester yielded the monoester **3-64**, which was subsequently hydrolyzed and converted to the acid chloride (**3-65**) with oxalyl chloride. [46] With this in hand, the stage was set for a Weinreb amide formation. Amide **3-66** was obtained from the reaction of the acyl chloride with *N,O*-dimethylhydroxylamine. This was further converted to the ketone **3-67** via a Grignard addition of 4-bromomagnesium anisole **3-62** to the amide. [34]



Scheme 3.17. Synthesis of ketone **3-67**

Having synthesized ketone **3-67**, we tried to install an α-hydroxyl group via a Rubottom oxidation.[47] Surprisingly, we were not able to convert **3-67** to its corresponding trimethylsilyl enol ether under standard conditions for this transformation, presumably due to steric hindrance of the dimethyl moiety blocking deprotonation of the ketone (Table 3.4, entries 1-4). Attempts to employ other α-oxidation strategies using selenium dioxide,[48] *N*-bromosuccimide in DMSO[49] and other methods[50] also proved unsuccessful. A list of the conditions tried are listed in (Table 3.4).

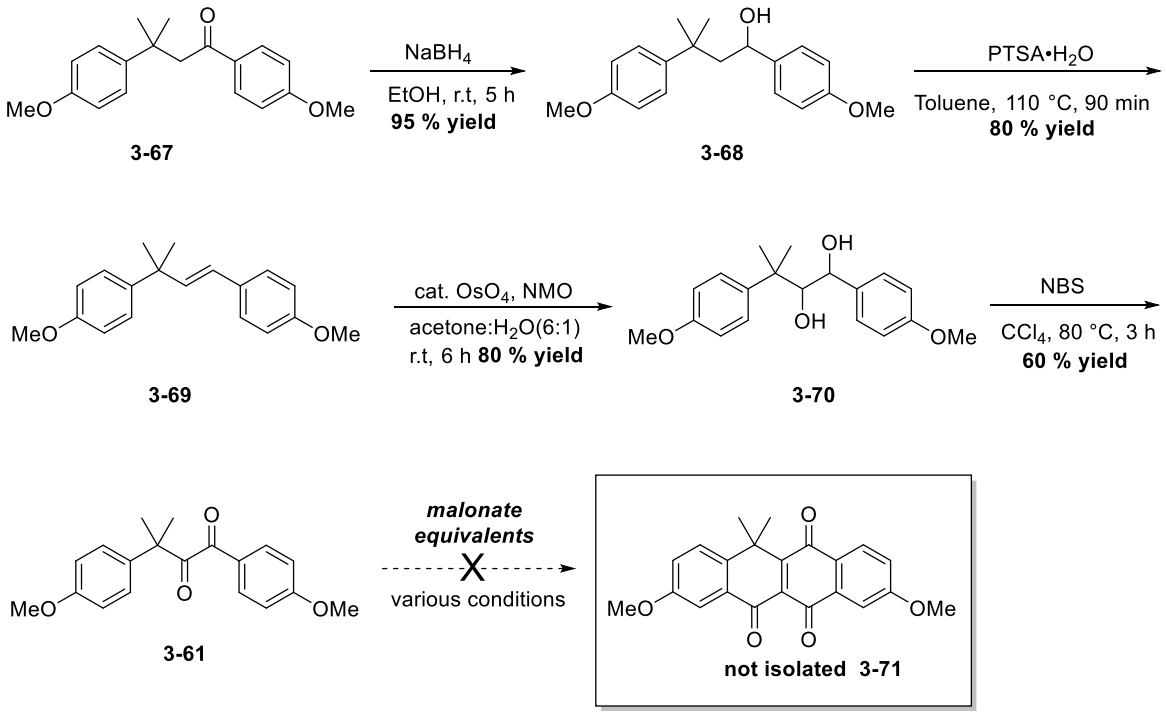
Table 3.4. Attempted α-oxidations of ketone **3-67**



Entry	Conditions	Conversion (%)
1	LDA (1.2 equiv), TMSCl (1.1 equiv), THF, 0 °C, 18 h	0 %[a]
2	LDA (1.5 equiv), TMSCl (2 equiv), THF, 0 °C, 18 h	0 %[a]
3	NaH (1.5 equiv), TMSCl (2 equiv), THF, -78 °C, 18 h	0 %[a]
4	TEA (3 equiv), TMSCl (2 equiv), DCM, -78 °C, 10 h	0 %[a]
5	SeO_2 (5 equiv), reflux AcOH, 24 h	0 %[a]
6	SeO_2 (2 equiv), cat. ^tBuOOH, DCM, r.t, 6 h	0 %[a]
7	SeO_2 (2 equiv), cat. AcOH , cat. H_2O, reflux(Dioxane), 6 h	0 %[a]
8	NBS (1.2 equiv), DMSO, 24 h	0 %[a]
9	$NaNO_2$ (1.5 equiv), THF, r.t, 20 h	0 %[a]

[a] The starting material was recovered

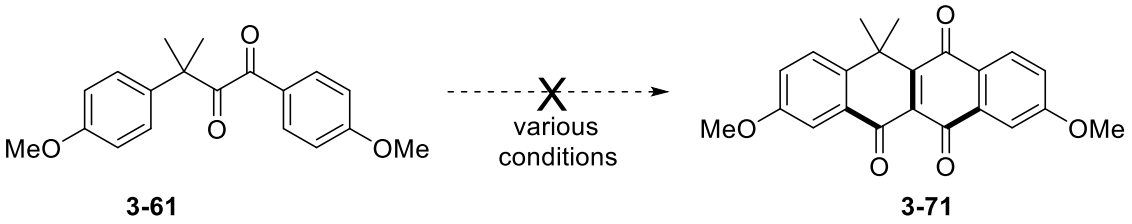
We decided to pursue an alternative approach to 1,2-diketone **3-61** from ketone **3-67** as illustrated in Scheme 3.18. We first reduced ketone **3-67** with a stoichiometric amount of $NaBH_4$ to the corresponding alcohol **3-68**, and then performed an elimination by treatment with *p*-toluenesulfonic acid monohydrate to access the olefin **3-69**.[51] Dihydroxylation[52] of the olefin **3-69** with osmium tetraoxide furnished the vicinal diol **3-70**, which was readily oxidized to the 1,2-diketone **3-61** using Kandpal's protocol with NBS in tetrachloromethane.[53]



Scheme 3.18. Synthesis of 1,2-diketone **3-61** and failed cyclization

After a synthesis of 1,2-diketone **3-61**, we attempted to induce the proposed Knoevenagel/Friedel-Crafts cascade cyclization of 1,2-diketone **3-61** to **3-71** by reacting the diketone with diethyl malonate and Meldrum's acid. Unfortunately none of the desired tetracyclic product was observed. Table 3.5 summarizes the reaction conditions that were employed to try out proposed key cyclization.

Table 3.5. Friedel-Crafts/Knoevanegal condensation of malonate equivalents with 1,2-diketone **3-61**



3-61 **3-71**

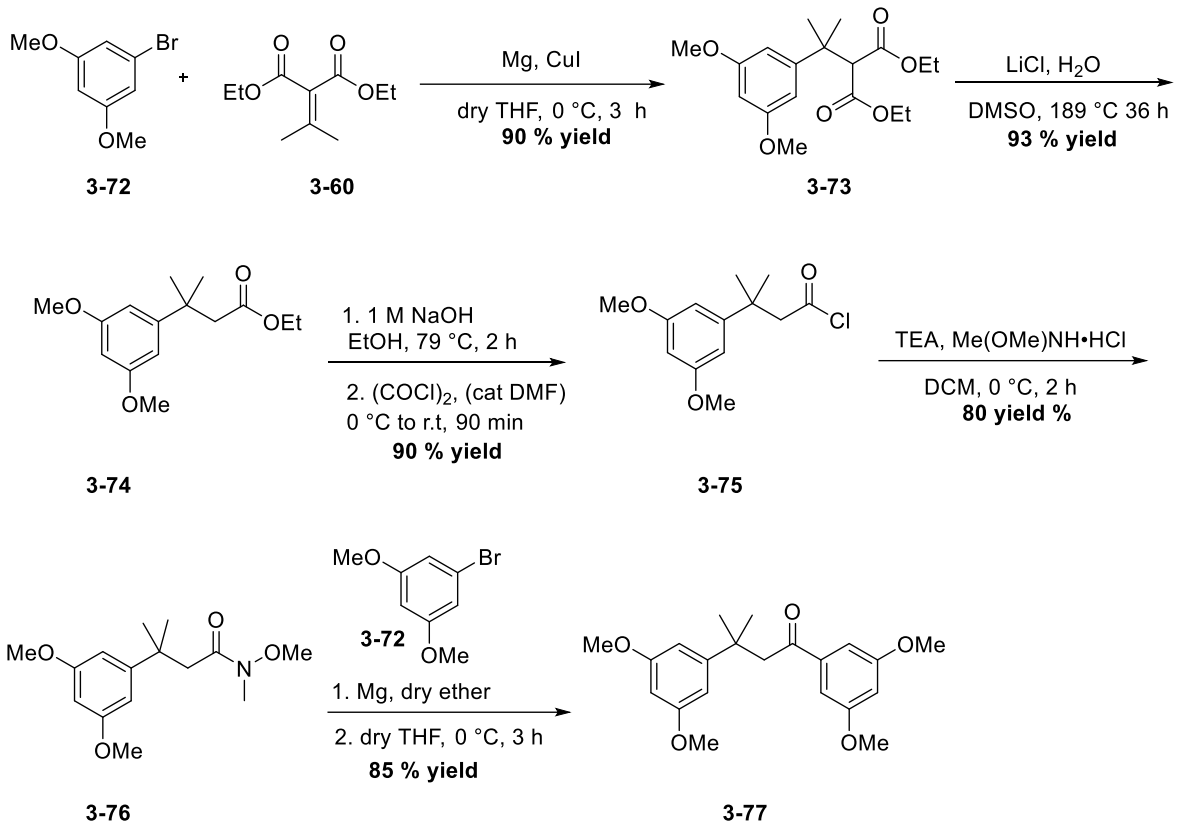
Entry	Conditions	Conversion (%)
1	Diethyl malonate (1 equiv), 10 % $ZnCl_2$, reflux acetic anhydride, 24 h	0 %[a]
2	Diethyl malonate (1 equiv), reflux nitrobenzene, 24 h	0 %[a]
3	Meldrum's acid (1 equiv), TEA (1 equiv), r.t, 24 h	0 %[a]
4	Meldrum's acid (1 equiv), $TiCl_4$ (2.2 equiv), pyridine (2 equiv), THF, r.t, 18 h	0 %[a]
5	Meldrum's acid (1 equiv), $TiCl_4$ (2.5 equiv), pyridine (5 equiv), THF, r.t, 18 h	0 %[a]

[a] The starting material was recovered

Unfortunately, the aromatic rings of substrate 1,2-diketone **3-61** were not appropriately electronically directed for the proposed cyclization reaction. Electrophilic-aromatic substation at positions *meta* relative to methoxy groups was unlikely to occur. The synthesis of 1,2-diketone **3-61** allowed us to develop an effective synthetic route to the desired gem-dimethyl-functionalized 1,2-diketone. The next task was to repeat an analogous sequence of steps with a different model system.

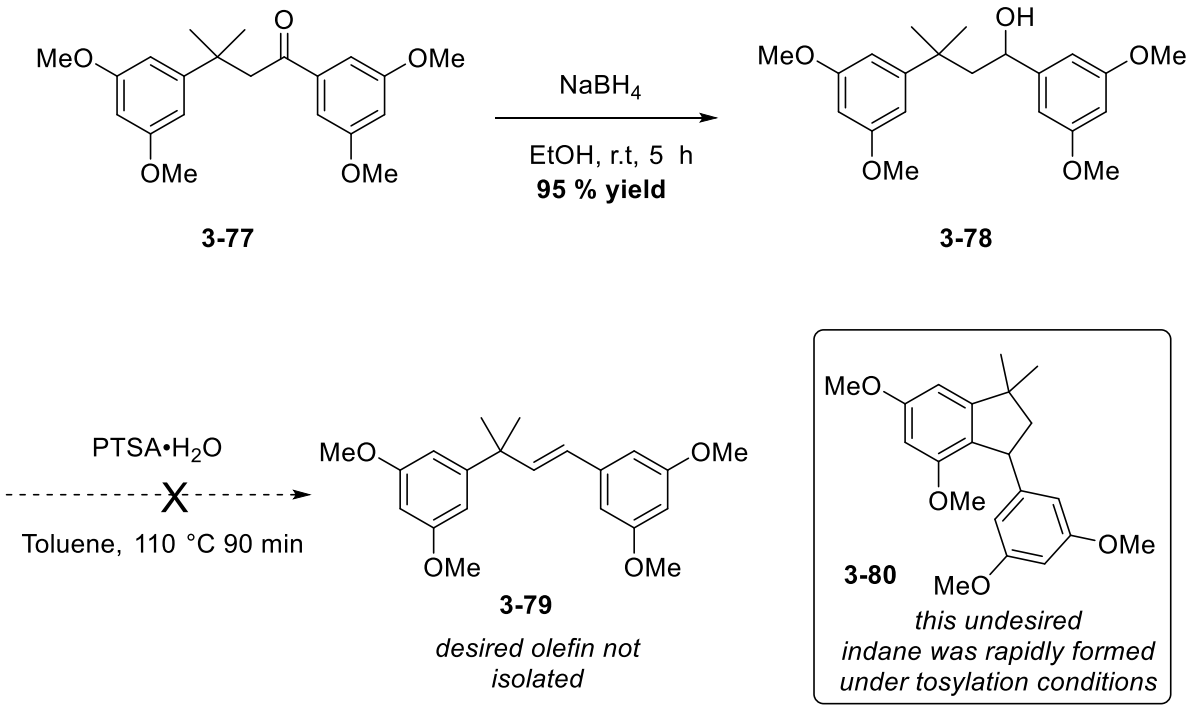
Section 3.3.6. Model Study 2B

The next target was a 1,2-diketone analogous to **3-36** but with 3,5-dimethoxy substituents on both aromatic rings. This 1,2-diketone is still a simplified model of the natural product but it contains a very similar substitution pattern and one that would be more likely to undergo the desired key double cyclization step. Ketone **3-78** was prepared using the same sequence of reactions that was described in the previous section (Scheme 3.18). Namely, the 1,4-conjugate addition of 3,5-dimethoxymagnesium bromide **3-72** to diethyl isopropylidenemalonate **3-60** afforded diester **3-73** in 90 % yield, which was followed by Krapcho dealkoxycarbonylation to give ester **3-74**. Hydrolysis with sodium hydroxide and treatment with oxalyl chloride proceeded smoothly to give acyl chloride (**3-75**). This was converted to Weinreb amide **3-76** in 80 % yield after purification by column chromatography. The 3,5-dimethoxymagnesium bromide **3-72** was added to the Weinreb amide to afford the targeted ketone **3-77**.



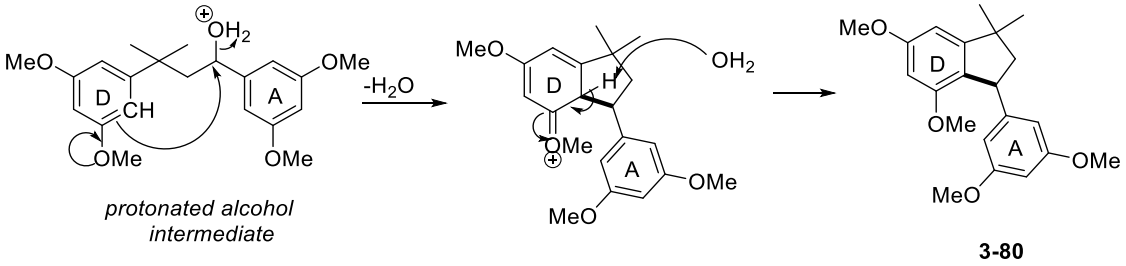
Scheme 3.19. Synthesis of ketone **3-77**

At this point we encountered an unanticipated problem. Ketone **3-77** was effectively reduced to the corresponding alcohol **3-78** but the subsequent attempted elimination with *p*-toluenesulfonic acid failed to yield the desired alkene as it did with the previous model study (Scheme 3.20). Instead, we observed rapid formation of indane **3-80**.



Scheme 3.20. Cyclization of **3-79** to indane **3-80**

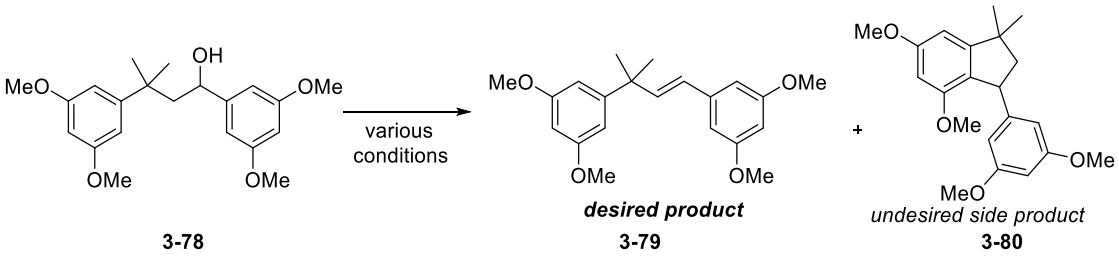
This indane formation occurred via an intramolecular Fridel-Crafts reaction, as reported for similar substrates by other authors. [54] This reaction was favored due to the electronic nature of ring D of ketone **3-77** (Scheme 3.21). The methoxy substituents on the *ortho* and *para* positions are strongly electron donating and promote the Friedel-Crafts cyclization.



Scheme 3.21. Proposed cyclization mechanism to indane **3-80**

Furthermore, the formation of the indane ring **3-80** is thermodynamically favored due to the Thorpe-Ingold effecf[55] enhanced by the *gem*-dimethyl functionality on the intermediate carbocation formed when protonated alcohol losses water. This effect dictates that substituents promote ring-forming reaction. The presence of the two methyl groups makes the intermediate carbocation closer in energy to its conformation in the transition state towards ring formation, hence moving the intermediate carbocation to its transition states involves a small loss of entropy, this makes the transition state entropy change less negative so change in Gibbs free energy is more negative and the ring forms faster. [56] We turned our attention to other ways of dehydrating alcohols to olefins. The use of hydrochloric acid, [57] Martin's sulfurane, [58] and the Burgess reagent[59] all failed to afford the olefin. A summary of procedures employed in the attempted synthesis of olefin **3-79** from the alcohol **3-78** is provided in Table 3.6. The final section on this chapter describes another alternative strategy toward 1,2-diketone **3-36** and the progress made to date.

Table 3.6. Attempted dehydration of alcohol **3-78** to olefin **3-79**

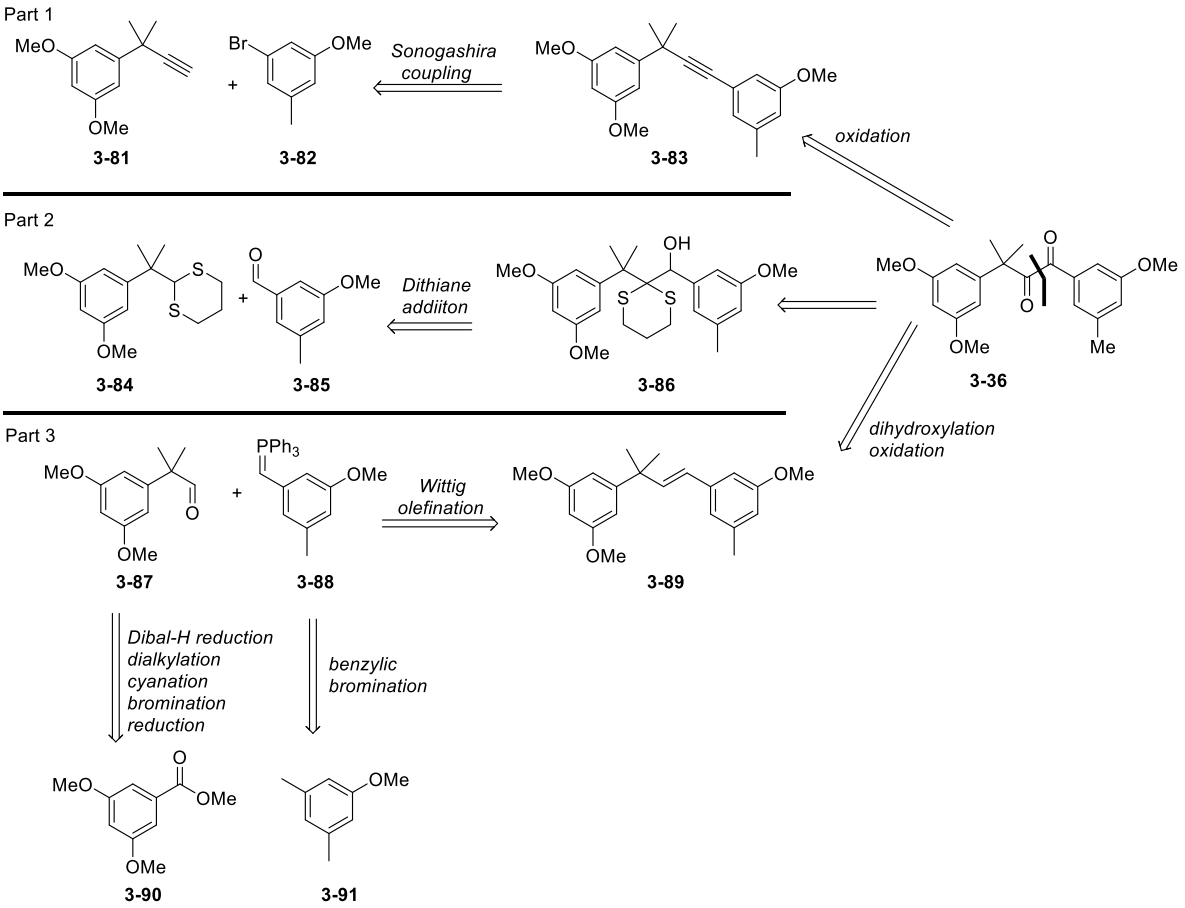


3-78 **3-79** **3-80**

Entry	Conditions	Yield of desired product
1	PTSA·H_2O (0.2 equiv), toluene, 100 °C, 2 h	0
2	HCl (1 M), MeOH, 60 °C, 24 h	0
3	Martin sulfurane (3 equiv), 1 mL TEA, reflux toluene, 2 h	0
4	Burgess (3 equiv), reflux toluene, 2 h	0
5	P_2O_5 (2 equiv), r.t, 16 h	0

Section 3.3.7. Third retrosynthetic strategy to 1,2-diketone 3-36

As an alternative strategy to 1,2-diketone **3-36**, we envisioned a disconnection of the C-C between the two carbonyl carbons of (Scheme 3.22). Three different synthetic paths were proposed based on this retrosynthetic disconnection. The first is based on a Sonogashira cross-coupling between alkyne **3-82** and aryl bromide **3-83** to furnish the C-C triple bond in alkyne **3-84**, which can potentially be oxidized to the 1,2-diketone **3-36**. [60]



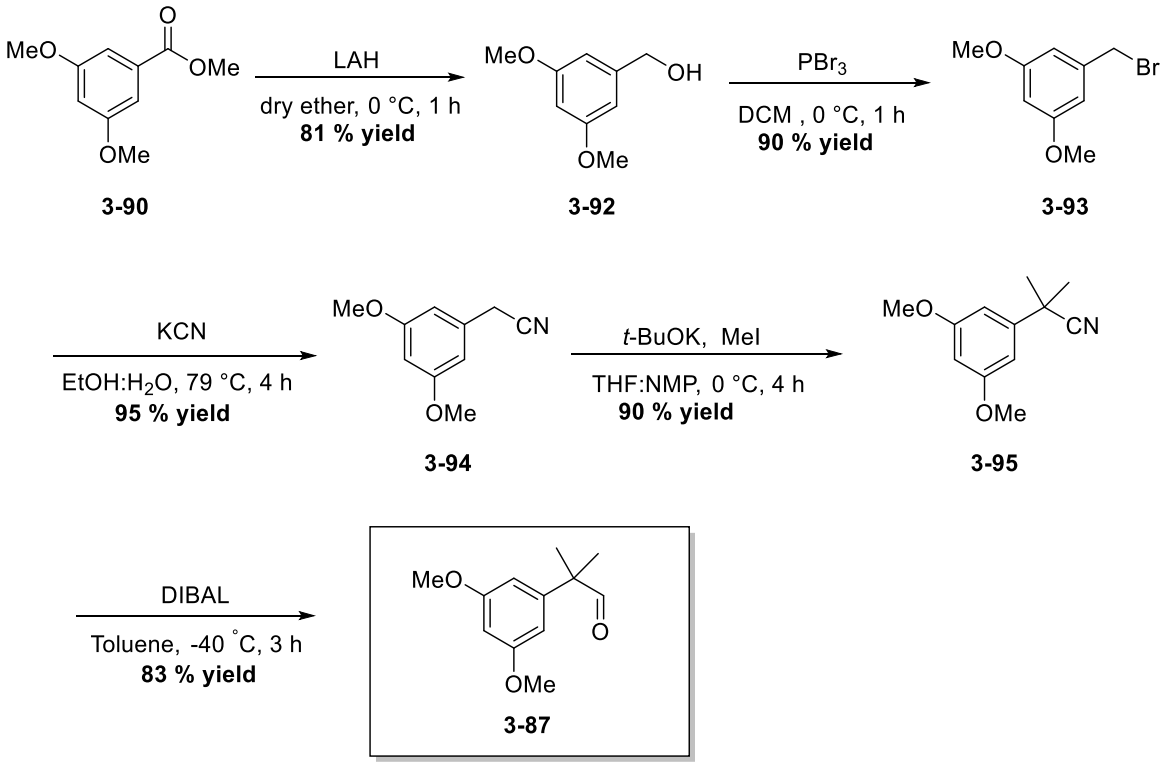
Scheme 3.22. A three-way retro-synthetic approach to 1,2-diketone **3-36**

The second path is based on a dithiane alkylation strategy in which 1,3-dithiane **3-84** is used to alkylate aldehyde **3-85**. The resulting product can be treated with mercuric chloride to afford an α-hydroxyketone which could be oxidized to the 1,2-diketone **3-36**. The third proposed path is based on the synthesis of olefin **3-89** via Wittig olefination between *gem*-dimethyl aldehyde **3-87** and triphenyl phosphonium ylide **3-88**. Each of the three proposed paths share a common aldehyde precursor, **3-87**, which can be afforded from a five-step synthesis from methyl 3,5-dimethoxybenzoate **3-90**. Aldehyde **3-87** can be elaborated to alkyne **3-81** and 1,3-dithaine **3-84** using Corey-Fuchs and 1,3-dithaine synthesis respectively. The idea of a one starting point that leads to three possible paths presents several opportunities

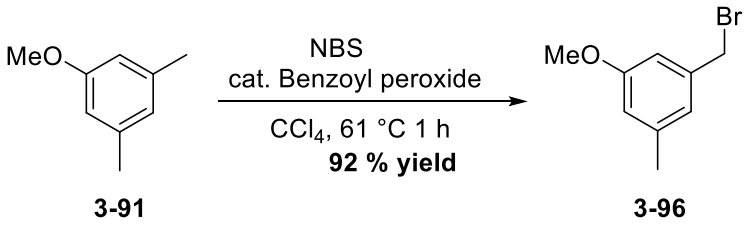
to explore ways to obtain the targeted 1,2-diketone **3-36**. Prior to the submission of this dissertation, we have successfully achieved the proposed 5 step sequence conversion of 3,5-dimethoxybenzoate **3-90** to aldehyde **3-87**.

Section 3.3.8. Model Study 3A

Our synthesis commenced with lithium aluminium hydride reduction[61] of 3,5-dimethoxybenzoate **3-90** to furnish benzyl alcohol **3-92** in 81% yield. The primary alcoholic functionality was converted to the benzyl nitrile **3-94** by two successive nucleophilic substitutions with PBr_3 and KCN in excellent yields. [62] Dimethyl alkylation[63] of the nitrile with iodomethane afforded **3-95** which subsequently was subjected to a DIBAL-H reduction to furnish aldehyde **3-87** in 83 % yield. We have also prepared the A ring component of path 2 via a benzylic bromination[64] of 3,5-dimethylanisole **3-91** with *N*-bromosuccinimide and benzoyl perioxide in chloroform to give the brominated product **3-96** in 92 % yield. (Scheme 3.23). We are currently working our way through the proposed path illustrated above (Scheme 3.22) to the target 1,2-diketone **3-36**.



Scheme 3.23. 5-step sequence synthesis of aldehyde **3-87**



Scheme 3.24. Benzylic bromination of 3,5-dimethylanisole

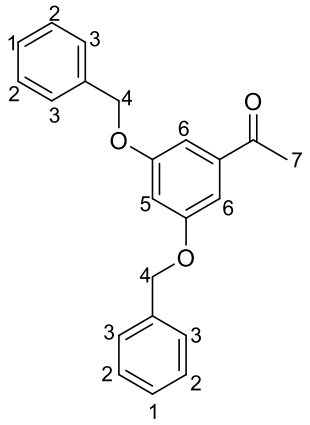
Section 3.4. Conclusion

This work is on-going in the Magolan group. We are optimistic that our new approach can afford the target 1,2-diketone as proposed (Scheme 3.22). Our aim is to install the B and C rings of the tetracyclic core by a unique methodology that will constitute an integral part of our efforts to develop an efficient route to the tetracyclic core of the tetracycline and tetracenomycin class of antibiotics. It of great importance to state that target-directed total

synthesis is well-known to typically proceed with unexpected hurdles and surprises. Irrespective of the enormous work done to this point, we are still motivated to pursue our synthetic target due to the worth of knowledge and experience many group members who contributed to this work have gained. These challenges offer a unique opportunity for us to demonstrate some creativity in synthesis whilst acquiring more knowledge and experience in synthesis.

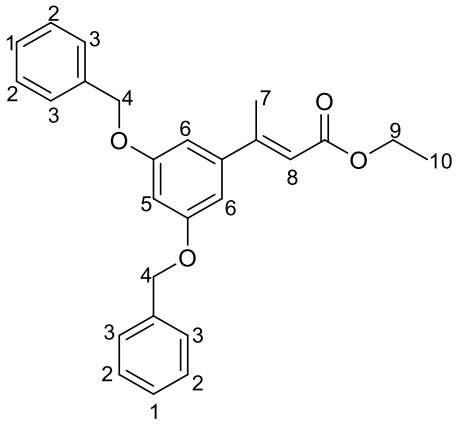
Section 3.5. Experimental Section

All reagents and solvents were obtained from commercial suppliers and used as purchased without further purification. All reactions were open to the atmosphere unless otherwise stated. Melting points were determined using a Mel-Temp II apparatus and are uncorrected. Infrared spectra were obtained on a Thermo Scientific Nicolet 380 FT-IR Spectrometer as thin films on ZnSe disks. NMR experiments were performed on a Bruker AVANCE 500 MHz instrument and samples were obtained in $CDCl_3$ (referenced to 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C coupling constants (J) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. Reaction progress was monitored by thin-layer chromatography (TLC, EMD Chemicals Inc, Silica Gel 60 F254), visualized under UV light, and plates were developed using *p*-anisaldehyde stain. Flash chromatography was performed using silica gel (Sorbent Technologies, particle size 40-63 μm).



Compound 3-44

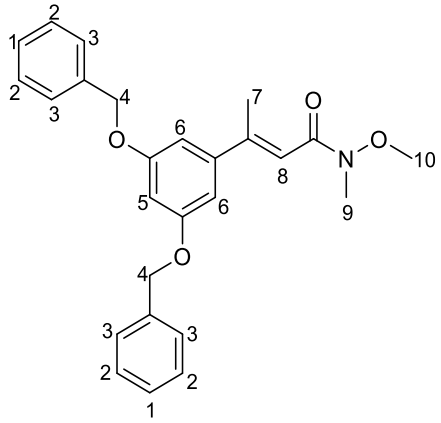
1-(3,5-bis(benzyloxy)phenyl)ethanone (3-44): A mixture of 3,5-dihydroxyacetophenone (2.0 g, 13.14 mmol, 1 equiv) and benzyl bromide (3.90 mL, 32.86 mmol, 2.5 equiv) was stirred with potassium carbonate (5.3 g, 39.42 mmol, 3 equiv) in anhydrous acetone (100 mL) at 65 °C for 5 hours. After cooling the reaction mixture to room temperature, the entire reaction is dissolved in diethyl ether and the potassium carbonate removed by filtration and further extracted with diethyl ether (3 x 100 mL). The crude extract was washed with brine (100 mL) and dried with $MgSO_4$. The solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography with hexane/ethyl acetate as elution solvents to yield compound **3-44** as a white solid crystal (3.6g, 11. 04 mmol, 84 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.45 – 7.42 (m, 4H, **H$_3$**), 7.40 (ddd, *J* = 7.9, 6.8, 0.9 Hz, 4H, **H$_2$**), 7.36 – 7.32 (m, 2H, **H$_1$**), 7.20 (d, *J* = 2.3 Hz, 2H, **H$_6$**), 6.82 (t, *J* = 2.3 Hz, 1H, **H$_5$**), 5.08 (s, 4H, **H$_4$**), 2.56 (s, 3H, **H$_7$**).^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.58, 160.02, 139.13, 136.43, 128.65, 128.17, 127.58, 107.43, 106.93, 70.40, 26.70. These spectral data are in agreement with previously reported literature values. [65]



Compound 3-43

(*E*)-ethyl 3-(3,5-bis(benzyloxy)phenyl)but-2-enoate (3-43): A 100ml round bottom flask was charged with NaH (1.32 g, 55.2 mmol, 5 equiv, 60% mineral dispersion) and washed once with hexane. The hexanes were removed by decanting and the washed sodium hydride was then dried under vacuum for 45 minutes. Triethyl phosphonoacetate (4.38 mL, 22.08 mmol, 2 equiv) in dry THF (10 mL) was added dropwise at 0 °C under argon balloon and stirred. After 30 minutes, the benzyl protected compound **3-44** (3.6 g, 11.04 mmol, 1 equiv) dissolved in THF (30 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and heated at 80 °C for 6 hours. Upon completion as monitored by thin layer chromatography, the mixture was cooled to room temperature. A saturated solution of ammonium chloride (30 mL) was then added. The organic phase was extracted with diethyl ether (3 x 50 mL) and the combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-43** as a clear oil (3.11 g, 7.73 mmol, 70 %). ^{1}H NMR (500 MHz, $CDCl_3$ δ 7.45 – 7.42 (m, 4H, $\mathbf{H_3}$), 7.42 – 7.38 (m, 4H, $\mathbf{H_2}$), 7.36 – 7.32 (m, 2H, $\mathbf{H_1}$), 6.72 (d, *J* = 2.2 Hz, 2H, $\mathbf{H_6}$), 6.63 (t, *J* = 2.2 Hz, 1H, $\mathbf{H_5}$), 6.12 (q, *J* = 1.3 Hz, 1H, $\mathbf{H_8}$), 5.08 (s, 4H, $\mathbf{H_4}$), 4.22 (q, *J* = 7.1 Hz, 2H, $\mathbf{H_9}$), 2.53 (d, *J* = 1.3 Hz, 3H,

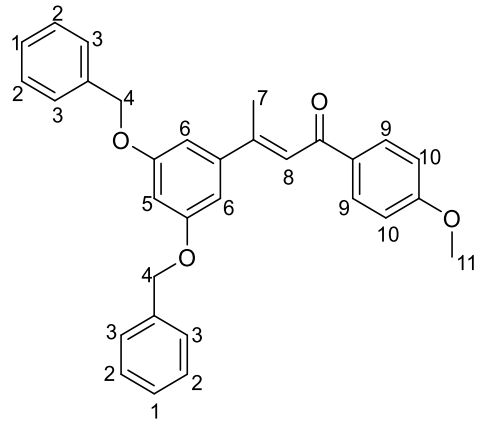
H7), 1.33 (t, *J* = 7.1 Hz, 3H, **H10**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.01, 160.15, 155.50, 144.73, 136.90, 128.86, 128.32, 127.79, 117.70, 106.18, 102.72, 70.50, 60.12, 18.30, 14.58. HRMS (ESI) *m/z* calculated for $C_{26}H_{26}O_4$ ($[M+H]^+$) 403.1909, found 403.1899.



Compound 3-48

(*E*)-3-(3,5-bis(benzyloxy)phenyl)-N-methoxy-N-methylbut-2-enamide(3-48): NaOH (0.93g, 23.19 mmol, 3 equiv) in 5 mL water was added to compund **3-43** (3.11 g, 7.73 mmol, 1equiv) in 50 mL of ethanol and stirred at 100 °C for 60 minutes. The reaction was monitored by thin layer chromatography to see complete disappearance of ester **3-43**. The ethanol was removed *in vacuo* and the aqueous solution was acidified to pH 1 with 1 M aqueous HCl and extracted with diethyl ether (3 x 100 mL). The combined layer was washed with brine and dried with Na_2SO_4 to get a white powder carboxylic acid (2.78 g, 7.42 mmol, 96 %). The product was used in the next step without further purification. Oxalyl chloride (1.91 mL, 22.26 mmol, 3 equiv) was added to the carboxylic acid at 0 °C in dichloromethane (15 mL). After initiation with 3 drops of DMF, the reaction was stirred at 0 °C for 2 hours and allowed to cool to room temperature for 20 minutes. The dichloromethane was removed *in vacuo* and allowed to stay on the high vacuum for an hour to give acyl chloride **3-47** (2.39g, 6.08 mmol, 82 %). The acyl chloride **3-47** was dissolved in dichloromethane (12 mL), cooled to 0 °C and

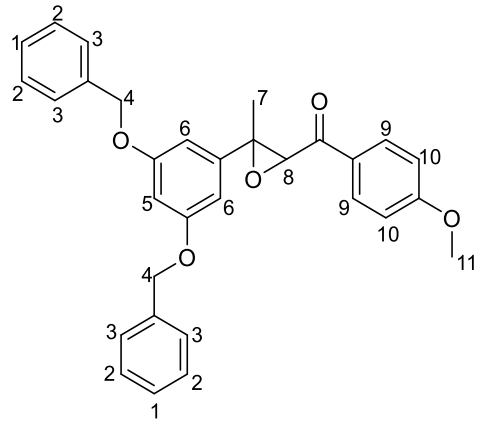
N,*O*-dimethylhydroxylamine (1.78 g, 18.24 mmol, 3 equiv) was added. To this mixture, triethylamine (2.54 mL, 18.24 mmol, 3 equiv) was added drop-wise at 0 °C and the reaction was stirred at this temperature for 4 hours. Upon completion of reaction, the entire mixture was quenched with 100 mL of 1 M aqueous HCl solution and extracted with ethyl acetate (3 x 50 mL), the organic phase was washed with brine and dried over Na_2SO_4. The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-48** as a light yellow oil (1.98 g, 4.74 mmol, 78 %) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 4H, **H$_3$**), 7.42 – 7.38 (m, 4H, **H$_2$**), 7.36 – 7.32 (m, 2H, **H$_1$**), 6.72 (d, *J* = 2.3 Hz, 2H, **H$_6$**), 6.63 (t, *J* = 2.2 Hz, 1H, **H$_5$**), 6.53 (s, 1H, **H$_8$**), 5.07 (s, 4H, **H$_4$**), 3.68 (s, 3H, **H$_{10}$**), 3.27 (s, 3H, **H$_9$**), 2.48 (s, 3H, **H$_7$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.79, 159.83, 151.92 145.22, 136.68, 128.59, 128.03, 127.49, 116.28, 105.97, 101.89, 70.20, 61.55, 23.29, 18.08. HRMS (ESI) *m/z* calculated for $C_{26}H_{27}NO_4$ ([M+H]$^+$) 418.2018, found 418.2029



Compound 3-50

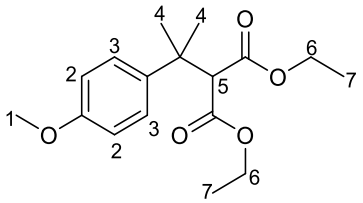
(*E*)-3-(3,5-bis(benzyloxy)phenyl)-1-(4-methoxyphenyl)but-2-en-1-one (3-50): All the glassware used in this reaction were oven dried. A 100 mL oven dried round-bottom flask was charged with magnesium turnings (0.346 g, 14.22 mmol, 3 equiv) kept under argon

atmosphere. 4-bromoanisole (2.66 g, 14.22 mmol, 3 equiv) in anhydrous THF (15 mL) was added dropwise using a flame dried syringe under argon balloon. The mixture is immediately refluxed for 2 hours and allow to cool to room temperature under argon atmosphere**.** The prepared Grignard reagent was added dropwise to the compound **3-48** (1.98 g, 4.74 mmol, 1 equiv) using a dropping funnel and the reaction mixture stirred at 0 °C for 6 hours. On completion, the mixture was quenched with a 1 M aqueous HCl (30 mL) solution and the aqueous phase was extracted with ethyl acetate (3 x 50 mL).The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-50** as a pale yellow oil (1.54 g, 3.32 mmol, 70 %) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.94 (d, *J* = 9.0 Hz, 2H, **H$_9$**), 7.45 (ddt, *J* = 7.6, 1.4, 0.6 Hz, 4H, **H$_3$**), 7.42 – 7.38 (m, 4H, **H$_2$**), 7.37 – 7.32 (m, 2H, **H$_1$**), 7.06 (q, *J* = 1.3 Hz, 1H, **H$_8$**), 6.97 – 6.93 (d, *J* = 8.9 Hz, 2H, **H$_{10}$**), 6.78 (d, *J* = 2.2 Hz, 2H, **H$_6$**), 6.66 (t, *J* = 2.2 Hz, 1H, **H$_5$**), 5.08 (s, 4H, **H$_4$**), 3.88 (s, 3H, **H$_{11}$**), 2.50 (d, *J* = 1.3 Hz, 3H, **H$_7$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.57, 163.22, 159.94, 153.37, 145.15 136.69, 132.18, 130.61, 128.65, 128.10, 127.55, 122.48, 113.71, 106.13, 102.30, 70.30, 55.46, 18.80. HRMS (ESI) *m/z* calculated for $C_{31}H_{28}O_4$ ($[M+H]^+$) 465.2066, found 465.2081



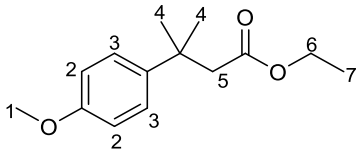
Compound 3-51

(3-(3,5-bis(benzyloxy)phenyl)-3-methyloxiran-2-yl)(4-methoxyphenyl)methanone(3-51): Hydrogen peroxide (30 %, 4 mL) and aqueous sodium hydroxide (1N, 2 mL) were added with syringe to a solution of compound **3-50** (1.54 g, 3.32 mmol, 1 equiv) in ethanol (20 mL) and the mixture was stirred at 60 °C for 60 minutes. On completion, the mixture was allowed to cool to room temperature and 1 M aqueous sodium bicarbonate (50 mL) was added and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-51** as light yellow solid material (1.12 g, 2.32 mmol, 70 %) ^{1}H NMR (500 MHz, $CDCl_3$) 7.96 – 7.92 (d, *J* = 8.9 Hz, 2H, **H$_9$**), 7.46 – 7.43 (m, 4H, **H$_3$**), 7.40 (ddd, *J* = 7.7, 6.7, 1.3 Hz, 4H, **H$_2$**), 7.37 – 7.32 (m, 2H, **H$_1$**), 6.98 – 6.94 (d, *J* = 8.9 Hz, 2H, **H$_{10}$**), 6.73 (d, *J* = 2.3 Hz, 2H, **H$_6$**), 6.63 (t, *J* = 2.3 Hz, 1H, **H$_5$**), 5.07 (s, 4H, **H$_4$**), 4.05 (s, 1H, **H$_8$**), 3.88 (s, 3H, **H$_{11}$**), 1.57 (s, 3H, **H$_7$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.16, 163.15, 159.32, 142.15, 135.61, 129.59, 127.71, 127.61, 127.08, 126.59, 113.14, 103.52, 100.52, 69.24, 65.54, 61.46, 54.53, 16.01. ($[M+Na]^+$) 481.2015, found 481.2011



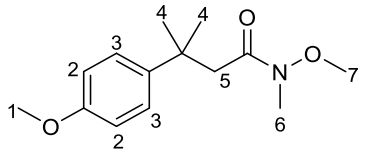
Compound 3-63

Diethyl 2-(2-(4-methoxyphenyl)propan-2-yl)malonate (3-63): A flamed dried round-bottom flask was charged with a stir bar and magnesium turnings (1.76 g, 75 mmol, 3 equiv) under argon atmosphere. A solution of 4-bromoanisole (14.03 g, 75 mmol, 3 equiv) in (15 mL) anhydrous THF was added dropwise. The mixture was refluxed under argon atmosphere for 2 hours and allowed to cool to room temperature. CuI (714 mg, 3.75 mmol, 0.15 equiv) was added and the reaction mixture was stirred for 20 minutes on an ice bath. A solution of diethyl isopropylidenemalonate **3-60** (5.0 g, 25.00 mmol, 1 equiv) in anhydrous THF (25 mL) was added drop wise and the reaction mixture was stirred at 0 °C for 3 hours. On completion, 100 mL saturated NH_4Cl solution was added dropwise to quench the reaction and the aqueous layer was extracted with diethyl ether (3 x 200 mL). The organic layer was washed with water (200 mL), brine (200 mL) and dried with Na_2SO_4. The solution was concentrated *in vacuo* and the crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-63** as pale yellow oil. (7.56 g, 24.5 mmol, 98 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.28 (d, *J* = 9.0 Hz, 2H, **H$_3$**), 6.85 – 6.79 (d, *J* = 8.9 Hz, 2H, **H$_2$**), 4.06 – 4.01 (q, *J* = 7.1 Hz, 3H, **H$_6$**), 3.77 (s, 3H, **H$_1$**), 3.74 (s, 1H, **H$_5$**), 1.55 (s, 6H, **H$_4$**), 1.12 (t, *J* = 7.1 Hz, 6H, **H$_7$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.88, 157.81, 139.00, 127.02, 113.26, 62.05, 60.77, 55.12, 39.50, 26.40, 13.89 with unidentified resonance at 53.36 and 30.82. These spectral data are in agreement with previously reported literature values. [66]



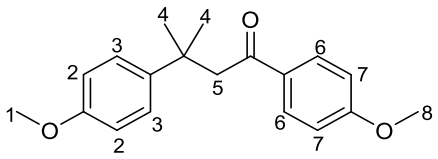
Compound 3-64

Ethyl 3-(4-methoxyphenyl)-3-methylbutanoate (**3-64):** Lithium chloride (4.15 g, 98 mmol, 4 equiv) and water (0.88 mL, 49 mmol, 2 equiv) were added to a solution of the compound **3-63** (7.56g, 24.5 mmol, 1 equiv) in DMSO (40 mL) and refluxed for 36 hours. The reaction was monitored by thin layer chromatography. On completion of the reaction, the mixture was allowed to cool to room temperature. 500 mL of water was added and the aqueous phase was extracted with diethyl ether (3 x 200 mL). The organic layer was washed with brine (200 mL) and dried with Na_2SO_4. The solution was concentrated *in vacuo* and the crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-64** as a pale yellow oil (4.86 g, 20.6 mmol, 84 %) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (d, *J* = 8.9 Hz, 2H, **H$_3$**), 6.88 – 6.82 (d, *J* = 9.0 Hz, 2H, **H$_2$**), 3.99 (q, *J* = 7.1 Hz, 2H, **H$_6$**), 3.79 (s, 3H, **H$_1$**), 2.58 (s, 2H, **H$_5$**), 1.44 (s, 6H, **H$_4$**), 1.11 (t, *J* = 7.1 Hz, 3H, **H$_7$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.56, 157.61, 140.32, 126.51, 113.35, 59.82, 55.15, 48.61, 36.59, 29.01, 14.08. These spectral data are in agreement with previously reported literature values. [67]



Compound 3-66

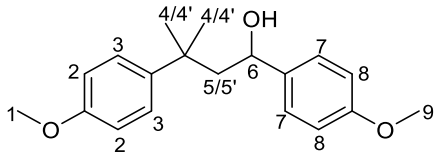
N-methoxy-3-(4-methoxyphenyl)-N,3-dimethylbutanamide (3-66): The procedure used in the synthesis of compound **3-48** was employed to synthesize compound **3-66**. Quantities used were as follows: Acyl chloride **3-65** (4.16 g, 18.33 mmol, 1 equiv), DCM (12 mL), *N*,*O*-dimethylhydroxylamine (5.36 g, 54.99 mmol, 3 equiv), triethylamine (7.68 mL, 54.99 mmol, 3 equiv). The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-66** as a white oil (3.46 g, 13.75 mmol, 75 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.29 (d, *J* = 8.9 Hz, 2H, **H$_3$**), 6.86 – 6.82 (d, *J* = 8.9 Hz, 2H, **H$_2$**), 3.78 (s, 3H, **H$_1$**), 3.54 (s, 3H, **H$_7$**), 3.07 (bs, 3H, **H$_6$**), 2.71 (bs, 2H, **H$_5$**), 1.47 (s, 6H, **H$_4$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.57, 157.43, 141.29, 126.48, 113.30, 60.84, 55.08, 44.24, 36.84, 31.76, 29.04. HRMS (ESI) *m/z* calculated for $C_{14}H_{21}NO_3$ ($[M+H]^+$) 252.1600 found 252.1600.



Compound 3-67

1,3-bis(4-methoxyphenyl)-3-methylbutan-1-one (3-67): The procedure used in the synthesis of compound **3-50** was employed in the synthesis of this compound **3-67**. Quantities used were as follows: Magnesium turnings (1.01 g, 41.25 mmol, 3 equiv), 4-bromoanisole

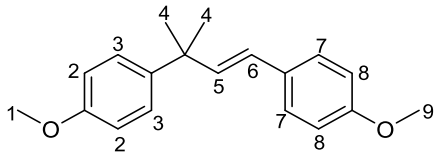
(7.72 g, 41.25 mmol, 3 equiv) in THF (20 mL) and (3.46 g, 13.75 mmol, 1 equiv) in THF (20 mL). The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-67** as a light yellow oil (2.87 g, 9.63 mmol, 70 %) that contained a small amount of unidentified impurities. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 – 7.79 (d, *J* = 9.0 Hz, 2H, **H$_6$**), 7.32 – 7.28 (d, *J* = 8.9 Hz, 2H, **H$_3$**), 6.88 – 6.81 (m, 4H, **H$_2$**/**H$_7$**), 3.84 (s, 3H, **H$_8$**), 3.77 (s, 3H, **H$_1$**), 3.21 (s, 2H, **H$_5$**), 1.48 (s, 6H, **H$_4$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.64, 163.07, 157.43, 141.19, 131.32, 130.33, 126.89, 113.42, 113.39, 55.34, 55.12, 50.61, 36.99, 29.23. HRMS (ESI) *m/z* calculated for $C_{19}H_{22}O_3$ ($[M+H]^+$) 299.1647, found 299.1640



Compound 3-68

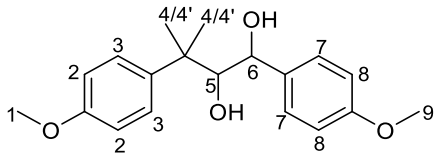
1,3-bis(4-methoxyphenyl)-3-methylbutan-1-ol (3-68): Compound **3-67** (2.87 g, 9.63 mmol, 1 equiv) was dissolved in ethanol (40 mL) in a round-bottomed flask. $NaBH_4$ (1.46 g, 38.52 mmol, 4 equiv) was added and the mixture was stirred at room temperature for 5 hours. On completion of the reaction as monitored by thin layer chromatography, a 5% aqueous NaOH solution (50 mL) was added to the mixture and the aqueous phase was extracted with diethyl ether (2 x 50 mL). The combined organic layer was washed with brine (100 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-68** as a light yellow oil (2.75 g, 9.14 mmol, 95 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (d, *J* = 9.0 Hz, 2H, **H$_7$**), 7.17 – 7.08 (d, *J* = 8.3 Hz, 2H, **H$_3$**), 6.91 – 6.86 (d, *J* = 8.9 Hz, 2H, **H$_8$**), 6.85 – 6.80 (d, *J* = 8.7 Hz, 2H, **H$_2$**), 4.53 (dd, *J* = 8.4, 3.4 Hz, 1H, **H$_6$**) 3.81 (s, 3H, **H$_9$**),

3.79 (s, 3H, **H$_1$**), 2.16 (dd, *J* = 14.5, 8.4 Hz, 1H, **H$_{5/5'}$**), 1.97 (dd, *J* = 14.5, 3.3 Hz, 1H, **H$_{5/5'}$**), 1.41 (s, 3H, **H$_{4/4'}$**), 1.34 (s, 3H, **H$_{4/4'}$**).^{13}C NMR (125 MHz, $CDCl_3$) δ 158.78, 157.61, 140.66, 138.08, 127.01, 126.85, 113.73, 113.69, 71.93, 55.25, 55.21, 53.92, 36.84, 30.35, 29.16. HRMS (ESI) *m/z* calculated for $C_{19}H_{24}O_3$ ([M+Na]$^+$) 323.1623, found 323.1609



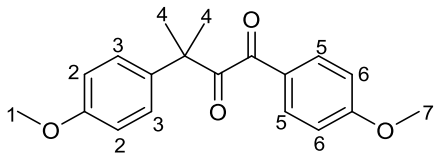
Compound 3-69

(*E*)-4,4'-(3-methylbut-1-ene-1,3-diyl)bis(methoxybenzene) (3-69): Compound **3-68** (2.75 g, 9.14 mmol, 1 equiv) was dissolved in toluene (40 mL) in a round-bottomed flask. *p*-Toluenesulfonic acid monohydrate (174 mg, 0.91 mmol, 0.1 equiv) was added. The mixture was stirred under reflux conditions for 90 minutes and cooled to room temperature. On completion as monitored by thin layer chromatography, the reaction was quenched with water (100 mL) and the aqueous phase was extracted with diethyl ether (3 x 100 mL), washed with water (100 mL) and brine (100 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-69** as light yellow crystals (2.06 g, 7.31 mmol, 80 %) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 4H, **H$_{3/7}$**), 6.88 – 6.81 (m, 4H, **H$_{2/8}$**), 6.34 (d, *J* = 16.2 Hz, 2H, **H$_{5/6}$**), 6.27 (d, *J* = 16.2 Hz, 2H, **H$_{5/6}$**) 3.81 (s, 3H, **H$_9$**), 3.80 (s, 3H, **H$_1$**), 1.49 (s, 6H, **H$_4$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.78, 156.65, 140.09, 137.45, 129.56, 126.25, 126.21, 124.20, 112.94, 112.45, 54.30, 54.23, 39.06, 27.99. HRMS (ESI) *m/z* calculated for $C_{19}H_{22}O_2$ 305.1517, found 305.1510.



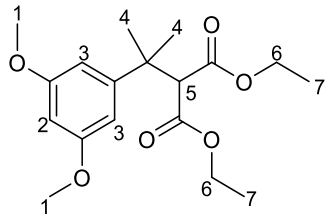
Compound 3-70

1,3-bis(4-methoxyphenyl)-3-methylbutane-1,2-diol (3-70): Compound **3-69** (2.06 g, 7.31 mmol, 1 equiv) was dissolved in acetone-water (6:1) (40 mL) in a round-bottom flask. Osmium tetraoxide (186 mg, 0.731 mmol, 0.1 equiv) and *N*-Methylmorpholine-*N*-oxide (0.942 g, 8.041 mmol, 1.1 equiv) were added at room temperature. The reaction mixture was stirred for 6 hours and the then quenched with saturated aqueous $Na_2S_2O_3$ (60 mL) solution and extracted with ethyl acetate (3 x 100 mL). The combined organic extract was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-70** as a light yellow oil (1.85 g, 5.85 mmol, 80 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.9 Hz, 2H, **H$_7$**), 7.12 (d, *J* = 8.2 Hz, 2H, **H$_3$**), 6.88 (d, *J* = 8.9 Hz, 2H, **H$_8$**), 6.82 (d, *J* = 8.8 Hz, 2H, **H$_2$**), 4.56 (s, 1H, **H$_6$**), 3.81 (s, 1H, **H$_5$**), 3.78 (s, 3H, **H$_9$**), 3.7 (s, 3H, **H$_1$**), 2.48 (s, 1H, **OH**), 2.13 (s, 1H, **OH**), 1.39 (s, 3H, **H$_{4/4'}$**), 1.38 (s, 3H, **H$_{4/4'}$**).^{13}C NMR (125 MHz, $CDCl_3$) δ 157.96, 157.00, 137.34, 134.74, 126.65, 126.12, 112.77, 112.76, 81.05, 70.35, 54.26, 54.23, 40.78, 24.74, 23.27.HRMS (ESI) *m/z* calculated for $C_{19}H_{24}O_4$ ($[M+Na]^+$) 339.1672, found 339.1563.



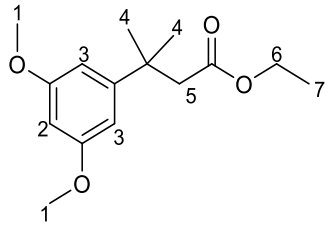
Compound 3-61

1,3-bis(4-methoxyphenyl)-3-methylbutane-1,2-dione (3-61): An oven dried round-bottom flask was charged with a magnetic stir bar. The compound **3-70** (1.85 g, 5.85 mmol, 1 equiv) and *N*-bromosuccinimide (2.082 g, 11.7 mmol, 2 equiv) were dissolved in anhydrous carbon tetrachloride (40 mL). The mixture was refluxed and the progress of the reaction was monitored by thin layer chromatography using benzene/ethyl acetate (90:10) as elution solvent. On completion of the reaction after 3 hours, 100 mL water was added and the organic layer separated. The remaining aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-61** as a dark brown oil (0.91 g, 2.93 mmol, 50 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 9.0 Hz, 2H, **H$_5$**), 7.28 (d, *J* = 9.0 Hz, 2H, **H$_3$**), 6.83 (dd, *J* = 17.5, 9.0 Hz, 4H, **H$_2$/H$_6$**), 3.84 (s, 3H, **H$_7$**), 3.75 (s, 3H, **H$_1$**), 1.69 (s, 6H, **H$_4$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.97, 192.91, 164.38, 158.60, 133.78, 131.92, 127.86, 126.03, 113.96, 113.94, 55.51, 55.18, 49.37, 25.56. HRMS (ESI) *m/z* calculated for $C_{19}H_{20}O_4$ ($[M+H]^+$313.1440, found 313.1430.



Compound 3-73

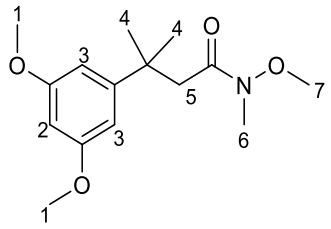
Diethyl 2-(2-(3,5-dimethoxyphenyl)propan-2-yl)malonate (3-73): The procedure used in the synthesis of compound **3-63** was employed in the synthesis of compound **3-73**. Quantities used were as follows: Magnesium turnings (1.76 g, 75 mmol, 3 equiv), 1-bromo-3,5-dimethoxybenzene (16.30 g, 75 mmol, 3 equiv) in anhydrous THF (15 mL), CuI (714 mg, 3.75 mmol, 0.15 equiv) and diethyl isopropylidenemalonate (5.0 g, 25.00 mmol, 1 equiv) in anhydrous THF (25 mL). The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield **3-73** as a light yellow oil (7.61 g, 22.5 mmol, 90 %) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (d, *J* = 2.2 Hz, 2H, **H$_3$**), 6.31 (t, *J* = 2.2 Hz, 1H, **H$_2$**), 4.07 (qd, *J* = 7.1, 1.1 Hz, 4H, **H$_6$**), 3.79 (s, 1H, **H$_5$**), 3.78 (s, 6H, **H$_1$**), 1.53 (s, 6H, **H$_4$**), 1.14 (t, *J* = 7.1 Hz, 6H, **H$_7$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.87, 160.46, 149.74, 104.72, 97.71, 61.75, 60.88, 55.25, 40.29, 26.35, 13.93.HRMS (ESI) *m/z* calculated for $C_{18}H_{26}O_6$ ($[M+Na]^+$) 361.1627, found 361.1620.



Compound 3-74

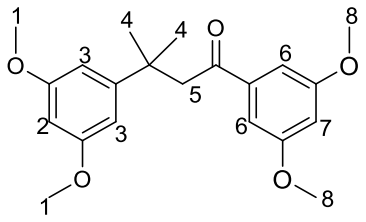
Ethyl 3-(3,5-dimethoxyphenyl)-3-methylbutanoate (3-74): The procedure used in the synthesis of compound **3-64** was employed in the synthesis of compound **3-74**. Quantities

used were as follows: Lithium chloride (3.82 g, 90 mmol, 4 equiv), water (0.81 mL, 45 mmol, 2 equiv) and compound **3-73** (7.61 g, 22.5 mmol, 1 equiv). The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-74** as a pale yellow oil (5.57 g, 20.93 mmol, 93 %) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (d, *J* = 2.2 Hz, 2H, **H$_3$**), 6.31 (t, *J* = 2.2 Hz, 1H, **H$_2$**), 4.02 (q, *J* = 7.1 Hz, 2H, **H$_6$**), 3.78 (s, 6H, **H$_1$**), 2.58 (s, 2H, **H$_5$**), 1.43 (s, 6H, **H$_4$**), 1.13 (t, *J* = 7.2 Hz, 3H, **H$_7$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.39, 160.48, 150.96, 104.28, 97.27, 59.84, 55.15, 48.21, 37.35, 28.74, 14.07. HRMS (ESI) *m/z* calculated for $C_{15}H_{22}O_4$ ($[M+H]^+$) 267.1596, found 267.1586



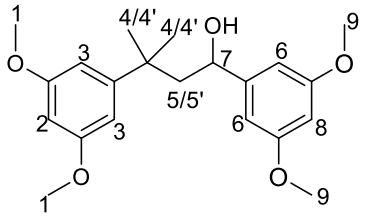
Compound 3-76

3-(3,5-dimethoxyphenyl)-N-methoxy-N,3-dimethylbutanamide (3-76): The procedure used in the synthesis of compound **3-66** was employed in the synthesis of compound **3-76**. Quantities used were as follows: Acyl chloride **3-75** (4.84 g, 18.84 mmol, 1 equiv), DCM (12 mL), *N*,*O*-dimethylhydroxylamine (5.51 , 56.52 mmol, 3 equiv), triethylamine (7.88 mL, 56.52 mmol, 3 equiv). The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-76** as a white oil (4.24 g, 15.07 mmol, 80 %) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (d, *J* = 2.3 Hz, 2H, **H$_3$**), 6.30 (t, *J* = 2.2 Hz, 1H, **H$_2$**), 3.77 (s, 6H, **H$_4$**), 3.56 (s, 3H, **H$_7$**), 3.09 (s, 3H, **H$_6$**), 2.71 (s, 2H, **H$_5$**), 1.45 (s, 6H, **H$_4$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.44, 160.42, 152.00, 104.23, 97.07, 60.87, 55.11, 43.88, 37.67, 31.79, 28.80. HRMS (ESI) *m/z* calculated for $C_{15}H_{23}NO_4$ ($[M+H]^+$) 282.1705, found 282.1700.



Compound 3-77

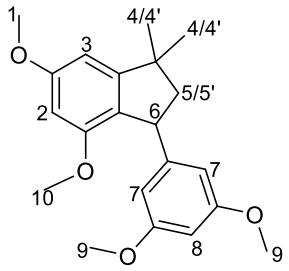
1,3-bis(3,5-dimethoxyphenyl)-3-methylbutan-1-one (3-77): The procedure used in the synthesis of compound **3-67** was employed in the synthesis of compound **3-77**. Quantities used were as follows: Magnesium turnings (1.06 g, 45.21 mmol, 3 equiv), 1-bromo-3,5-dimethoxybenzene (8.37 g, 45.21 mmol, 3 equiv) in THF (20 mL) and Weinreb amide **3-#** (4.24 g, 15.07 mmol, 1 equiv) in THF (20 mL). The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-77** as a light yellow oil (4.60 g, 12.81 mmol, 85 %) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (d, *J* = 2.3 Hz, 2H, **H$_6$**), 6.59 (t, *J* = 2.3 Hz, 1H, **H$_7$**), 6.51 (d, *J* = 2.2 Hz, 2H, **H$_3$**), 6.27 (t, *J* = 2.2 Hz, 1H, **H$_2$**), 3.79 (s, 6H, **H$_8$**), 3.75 (s, 6H, **H$_1$**), 3.22 (s, 2H, **H$_5$**), 1.46 (s, 6H, **H$_4$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.59, 160.68, 160.55, 151.53, 140.18, 105.89, 105.09, 104.38, 97.12, 55.52, 55.18, 50.93, 37.84, 29.06. HRMS (ESI) *m/z* calculated for $C_{21}H_{26}O_5$ ($[M+H]^+$) 359.1858, found 359.1841.



Compound 3-78

1,3-bis(3,5-dimethoxyphenyl)-3-methylbutan-1-ol (3-78): The procedure used in the synthesis of compound **3-68** was employed in the synthesis of compound **3-78**. Quantities

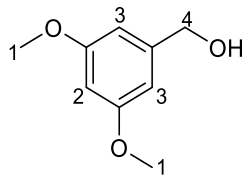
used were as follows: Compound **3-77** (4.60 g, 12.81 mmol, 1 equiv) in ethanol (50 mL) and $NaBH_4$ (1.94 g, 51.24 mmol, 4 equiv). The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-78** as a gray white oil (4.36 g, 12.17 mmol, 95 %) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (d, *J* = 2.2 Hz, 2H, **H$_3$**), 6.38 (dd, *J* = 2.3, 0.5 Hz, 2H, **H$_6$**), 6.33 (t, *J* = 2.2 Hz, 1H, **H$_8$**), 6.31 (t, *J* = 2.3 Hz, 1H, **H$_2$**), 4.53 (dd, *J* = 8.5, 4.3 Hz, 1H, **H$_7$**), 3.80 (s, 6H, **H$_9$**), 3.76 (s, 6H, **H$_1$**), 2.12 (dd, *J* = 14.6, 4.3 Hz, 1H, **H$_{5/5'}$**), 1.99 (dd, *J* = 14.6, 3.1 Hz, 1H, **H$_{5/5'}$**), 1.57 (d, *J* = 4.3 Hz, 1H, **OH**), 1.42 (s, 3H, **H$_{4/4'}$**), 1.35 (s, 3H, **H$_{4/4'}$**).^{13}C NMR (125 MHz, $CDCl_3$) δ 160.79, 160.75, 151.26, 148.47, 104.86, 103.48, 99.23, 97.25, 72.37, 55.28, 55.23, 53.79, 37.83, 29.68, 29.34. HRMS (ESI) *m/z* calculated for $C_{21}H_{28}O_5$ ($[M+H]^+$) 361.2015, found 361.2002.



Compound 3-80

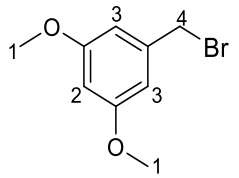
3-(3,5-dimethoxyphenyl)-4,6-dimethoxy-1,1-dimethyl-2,3-dihydro-1H-indane (3-80): This compound is an undesired side product. The procedure used in the synthesis of compound **3-69** was employed in the synthesis of compound **3-80**. Quantities used were as follows: Compound **3-79** (4.36 g, 12.17 mmol, 1 equiv) in toluene (50 mL) and *p*-Toluenesulfonic acid monohydrate (231 mg, 1.22 mmol, 0.1 equiv). The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-80** as a pale yellow material (4.08 g, 11.93 mmol, 98 %) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.36 (d, *J* = 2.1 Hz, 1H, **H$_3$**), 6.30 (d, *J* = 2.1 Hz, 1H, **H$_2$**), 6.28 (d, *J* = 0.5 Hz, 3H, **H$_{7/8}$**), 4.35 (dd,

J = 8.8, 5.8 Hz, 1H, **H6**), 3.84 (s, 3H, **H1/10**), 3.74 (s, 6H, **H9**), 3.61 (s, 3H, **H1/10**), 2.45 (dd, *J* = 12.8, 8.9 Hz, 1H, **H5/5'**), 1.92 (dd, *J* = 12.8, 5.8 Hz, 1H, **H5/5'**), 1.24 (d, *J* = 2.0 Hz, 6H, **H4/4'**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.23, 160.44, 157.09, 155.97, 149.32, 123.18, 105.62, 98.61, 97.49, 97.02, 55.47, 55.26, 55.20, 52.26, 46.42, 44.16, 29.87, 29.61. HRMS (ESI) *m/z* calculated for $C_{21}H_{26}O_4$ ($[M+H]^+$) 343.1909, found 343.1919.



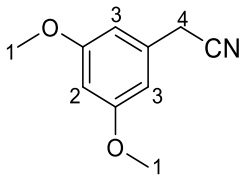
Compound 3-92

(3,5-dimethoxyphenyl)methanol (3-92): Methyl 3,5-dimethoxybenzoate **3-90** (5.0 g, 25.48 mmol, 1 equiv) was added at 0 °C to a stirred suspension of lithium aluminium hydride (775 mg, 25.48 mmol, 1 equiv) in anhydrous ether (100 mL). The mixture was stirred at 0 °C for 1 hour and the reaction mixture was then carefully quenched with aqueous 1 M HCl solution (100 mL). The aqueous layer was extracted with diethyl ether (3 x 100 mL), washed with water (100 mL) and brine (100 mL) and dried with Na_2SO_4. The organic phase was concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-92** as a colorless oil (3.47 g, 20.64 mmol, 81 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (dd, *J* = 2.3, 0.7 Hz, 2H, **H3**), 6.37 (t, *J* = 2.3 Hz, 1H, **H2**), 4.60 (s, 2H, **H4**), 3.77 (s, 6H, **H1**), 2.14 (s, 1H, **OH**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.92, 143.38, 104.53, 99.58, 65.18, 55.27. These spectral data are in agreement with previously reported literature values. [61]



Compound 3-93

1-(bromomethyl)-3,5-dimethoxybenzene (3-93): PBr_3 (2.55 mL, 26.83 mmol, 1.3 equiv) was added dropwise to a stirred solution of compound **3-92** (3.47 g, 20.64 mmol, 1 equiv) in DCM (100 mL) at 0 °C. The reaction mixture was slowly allowed to warm to room temperature and was stirred for 1 hour. The crude mixture was quenched with a saturated solution of aqueous $NaHCO_3$ (100 mL) and allowed to stir at room temperature for another 1 hour. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 100 mL). The organic layers were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-93** as pale white crystals (4.30 g, 18.58 mmol, 90 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (d, *J* = 2.3 Hz, 2H, **H$_3$**), 6.39 (t, *J* = 2.3 Hz, 1H, **H$_2$**), 4.42 (s, 2H, **H$_4$**), 3.80 (s, 6H, **H$_1$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.15, 139.96, 107.21, 100.86, 55.62, 33.80. These spectral data are in agreement with previously reported literature values. [62]

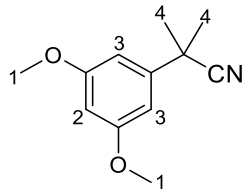


Compound 3-80

2-(3,5-dimethoxyphenyl)acetonitrile (3-94): Compound **3-93** (4.30 g, 18.58 mmol, 1 equiv) was dissolved in a mixture of ethanol (50 mL) and water (50 mL) and potassium cyanide (1.81 g, 27.87 mmol, 1.5 equiv) was added slowly. The mixture was refluxed for 4 hours. On

completion of the reaction as monitored by thin layer chromatography, the reaction was poured into ice-cold water and extracted with ethyl acetate (3 x 75 mL). The extract was concentrated *in vacuo* to afford compound **3-94** (3.13 g, 17.65 mmol, 95 %) as pale yellow crystals which was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (d, *J* = 2.2 Hz, 2H, **H$_3$**), 6.41 (t, *J* = 2.3 Hz, 1H, **H$_2$**), 3.80 (s, 6H, **H$_1$**), 3.68 (s, 2H, **H$_4$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.34, 131.93, 117.64, 106.07, 99.95, 55.44, 23.78. These spectral data are in agreement with previously reported literature values. [68]

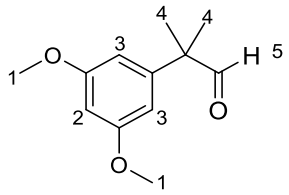
Caution: Potassium cyanide is highly toxic. Its moist form produces hydrogen cyanide. All reaction procedures were conducted inside a fume hood. Aqueous waste was disposed in a separately labelled bottle after treatment with sodium hypochlorite to detoxify all potassium cyanide remains.



Compound 3-95

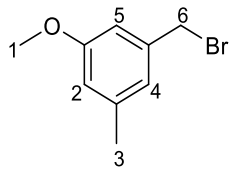
2-(3,5-dimethoxyphenyl)-2-methylpropanenitrile (3-95): A solution of potassium *tert*-butoxide (7.92 g, 70.6 mmol, 4 equiv) in 1-methyl-2-pyrrolidinone/THF (1:1 v/v 100 mL) was cooled to 0 °C on an ice bath. Compound **3-94** (3.13 g, 17.65 mmol, 1 equiv) was added and the reaction mixture stirred for 10 minutes, after which methyl iodide (4.40 mL, 70.6 mmol, 4 equiv) was added dropwise at the same temperature. The mixture was stirred for 4 hours and upon completion as monitored by thin layer chromatography, the reaction mixture was diluted with 1 M aqueous HCl (100 mL) and toluene (100 mL). The organic layer was separated, washed with $NaHCO_3$, brine and dried over Na_2SO_4 and concentrated *in vacuo.*

The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-95** as pale yellow crystals (3.26 g, 15.89 mmol, 90 %) with some minor impurities. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (d, *J* = 2.2 Hz, 2H, **H$_3$**), 6.40 (t, *J* = 2.2 Hz, 1H, **H$_2$**), 3.81 (s, 6H, **H$_1$**), 1.70 (s, 6H, **H$_4$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.11, 143.81, 124.38, 103.64, 99.16, 55.40, 37.31, 29.04. These spectral data are in agreement with previously reported literature values. [69]



Compound 3-87

2-(3,5-dimethoxyphenyl)-2-methylpropanal (3-87): Compound **3-95** (3.26 g, 15.89 mmol, 1 equiv) was dissolved in toluene (40 mL) and cooled to -78 °C. DIBAL-H (1.5 M in toluene, 1.2 equiv) was added dropwise over a period of 10 minutes. The mixture was stirred at -78 °C for 4 hours. On completion, 2 M aqueous HCl solution (50 mL) was added to the reaction and stirred for 30 minutes at room temperature. The organic layer was separated and washed with $NaHCO_3$ (50 mL), brine (50 mL) and dried with Na_2SO_4. The organic phase was concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-87** as a colorless oil. (2.65 g, 12.71 mmol, 80 %) with some minor unidentified impurities. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.46 (s, 1H, **H$_5$**), 6.40 (d, *J* = 2.2 Hz, 2H, **H$_3$**), 6.38 (dd, *J* = 2.4, 1.9 Hz, 1H, **H$_2$**), 3.78 (s, 6H, **H$_1$**), 1.43 (s, 6H, **H$_4$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.74, 161.10, 143.63, 105.15, 98.63, 55.26, 50.52, 22.31. These spectral data are in agreement with previously reported literature values. [70]



Compound 3-96

1-(bromomethyl)-3-methoxy-5-methylbenzene (3-96): To a magnetically stirred solution of the 3,5-dimethyl (3.0 g, 22.30 mmol, 1.05 equiv) in CCl_4 (40 mL) was added NBS (4.17 g, 23.42 mmol, 1.05 equiv) and benzoyl peroxide (60 mg, 0.248 mmol, 0.011 equiv). After refluxing for 1 hour, the reaction mixture was filtered and the filtrate was successively washed with (3 N) aqueous HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL), H_2O (100 mL) and brine (100 mL). The organic layer was dried with Na_2SO_4 and the solvent was concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, gradient elution) to yield compound **3-96** as white crystals. (4.56 g, 21.19 mmol, 95 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (s, 1H, **H$_5$**), 6.74 (s, 1H, **H$_4$**), 6.66 (s, 1H, **H$_2$**), 4.43 (s, 2H, **H$_6$**), 3.80 (s, 3H, **H$_1$**), 2.32 (s, 3H, **H$_3$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.80, 139.96, 138.86, 122.20, 115.07, 111.49, 55.25, 33.65, 21.40. These spectral data are in agreement with previously reported literature values. [64]

Section 3.6. References

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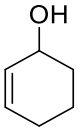
Appendix I

^{1}H and ^{13}C NMR Spectra

Chapter 1



Compound 1-2

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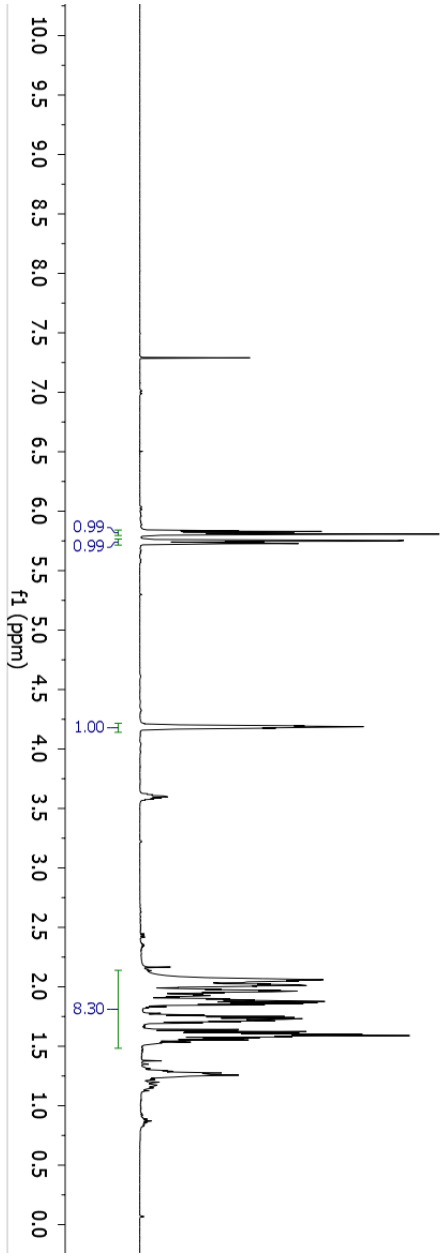

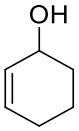

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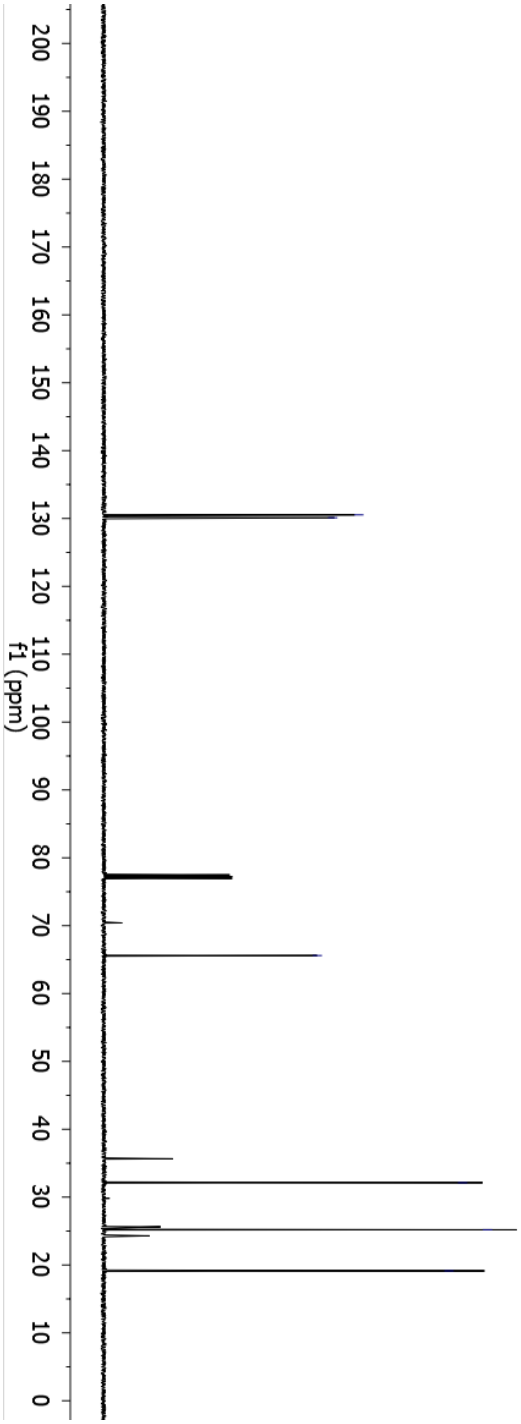

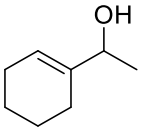

Compound 1-4

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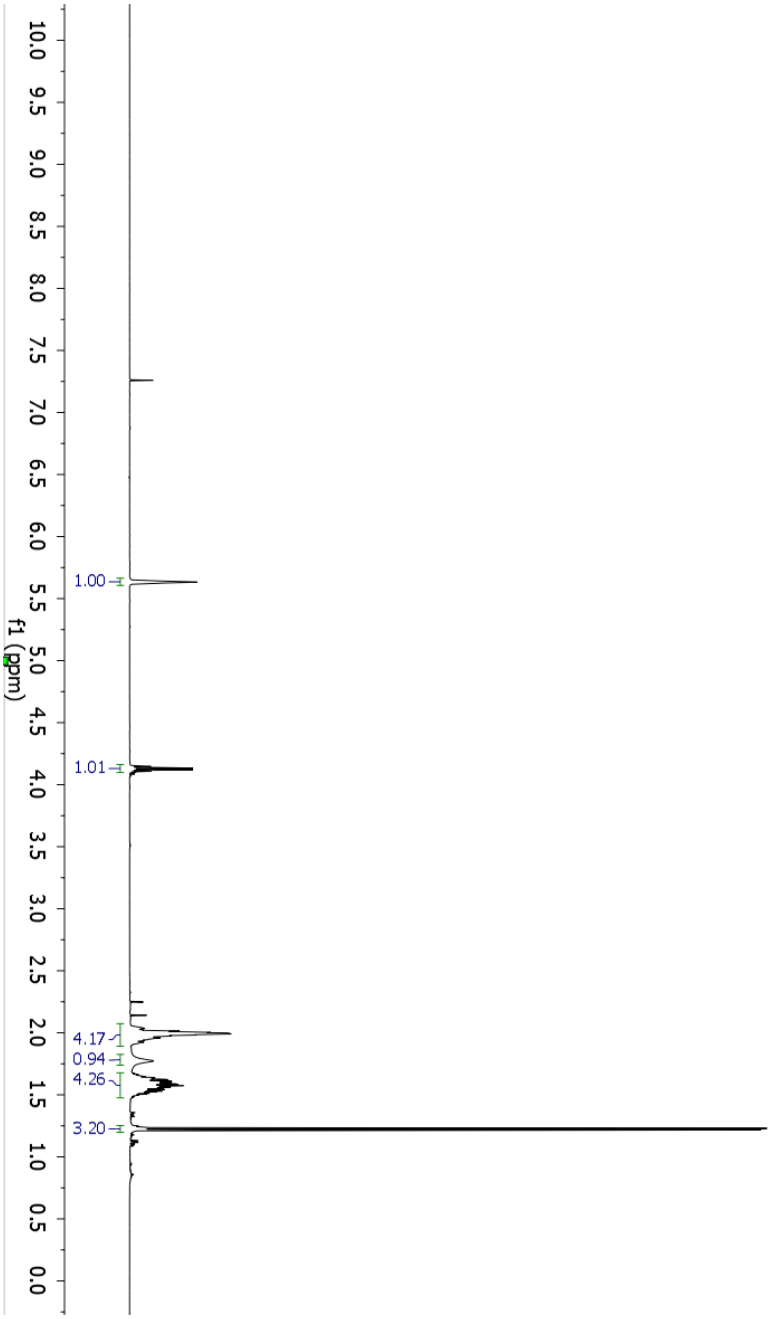

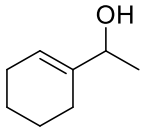

Compound 1-4

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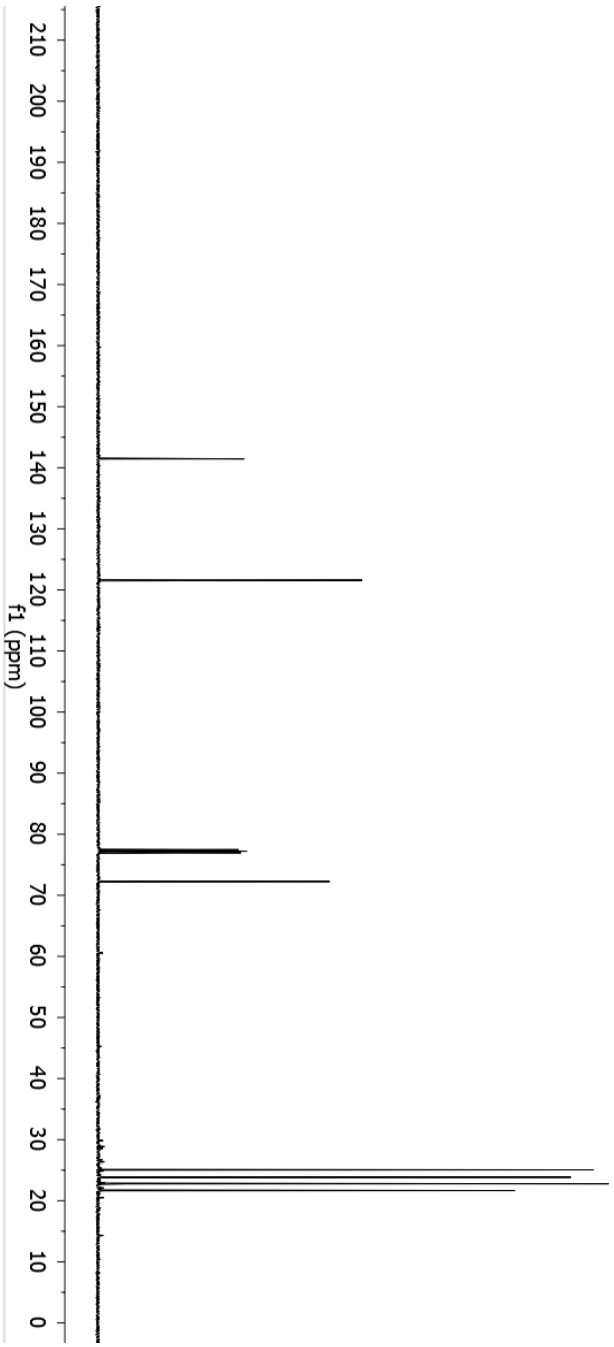

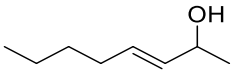

Compound 1-5

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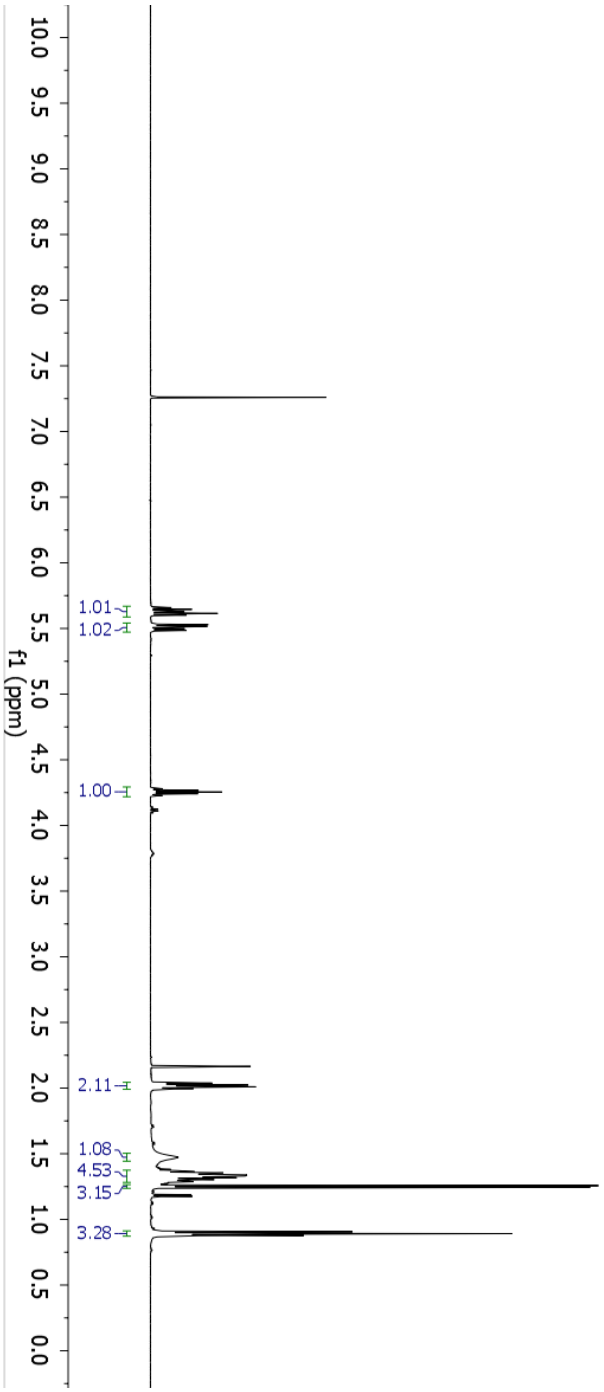

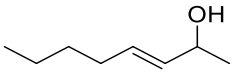

Compound 1-5

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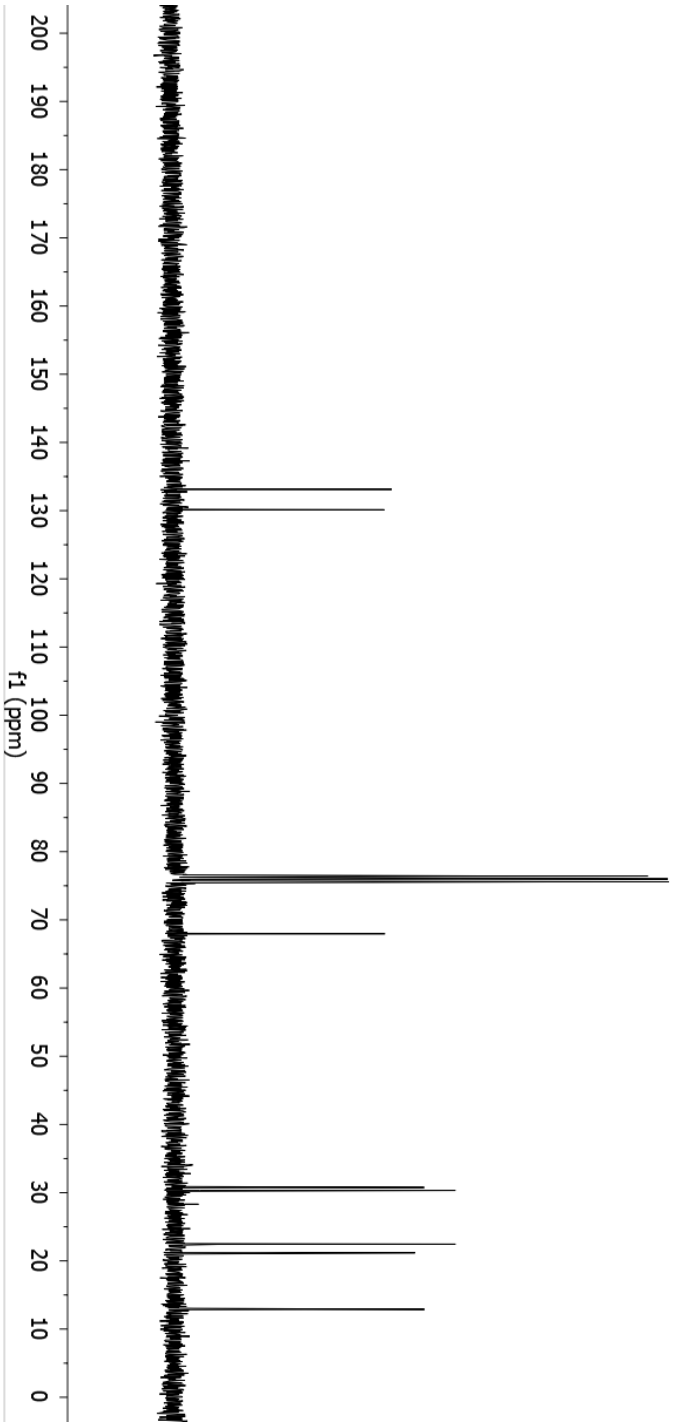
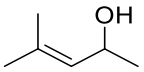
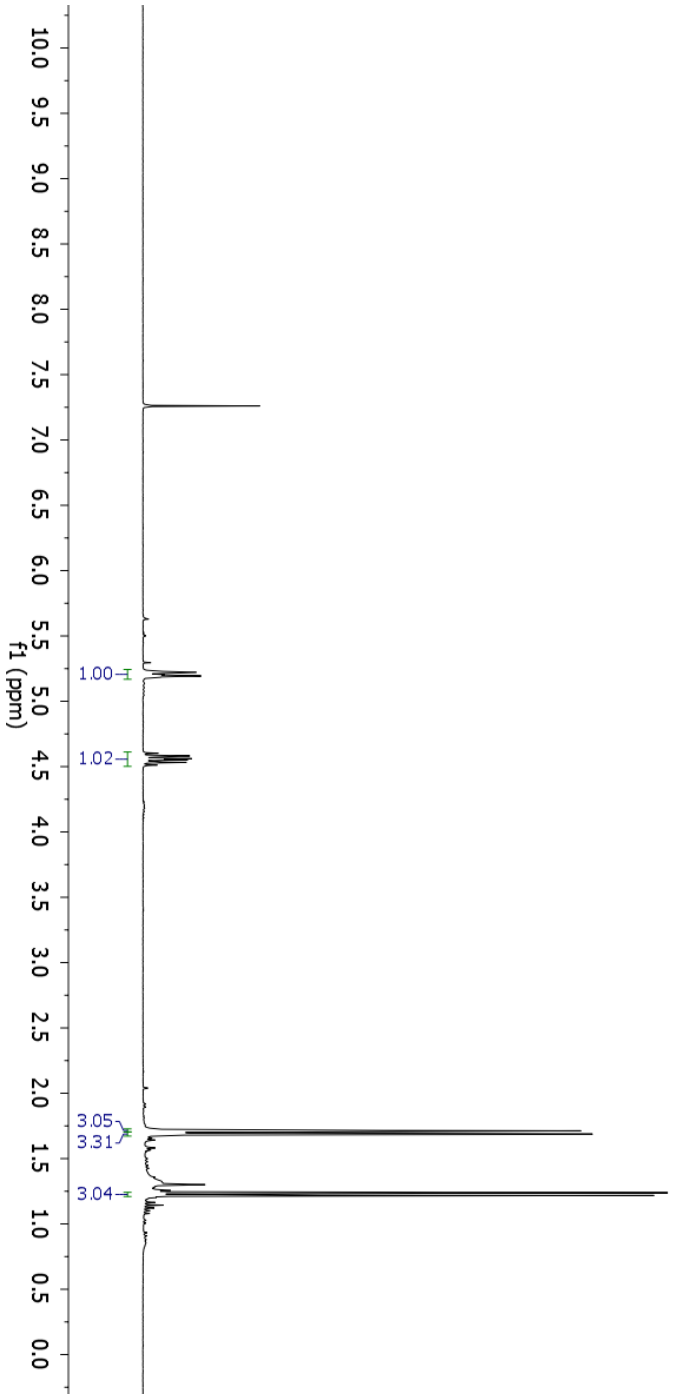
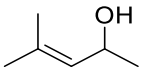




Compound 1-6

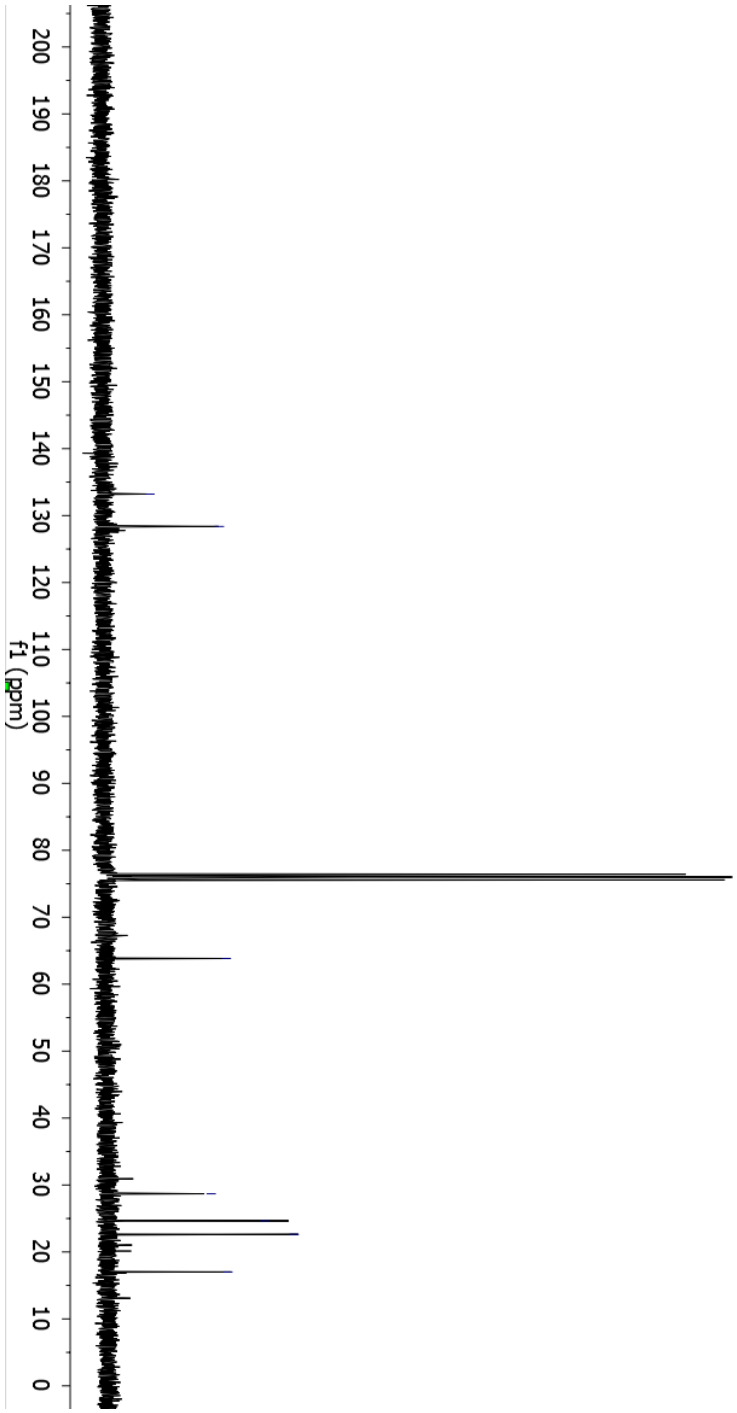
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

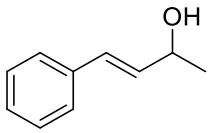




Compound 1-6

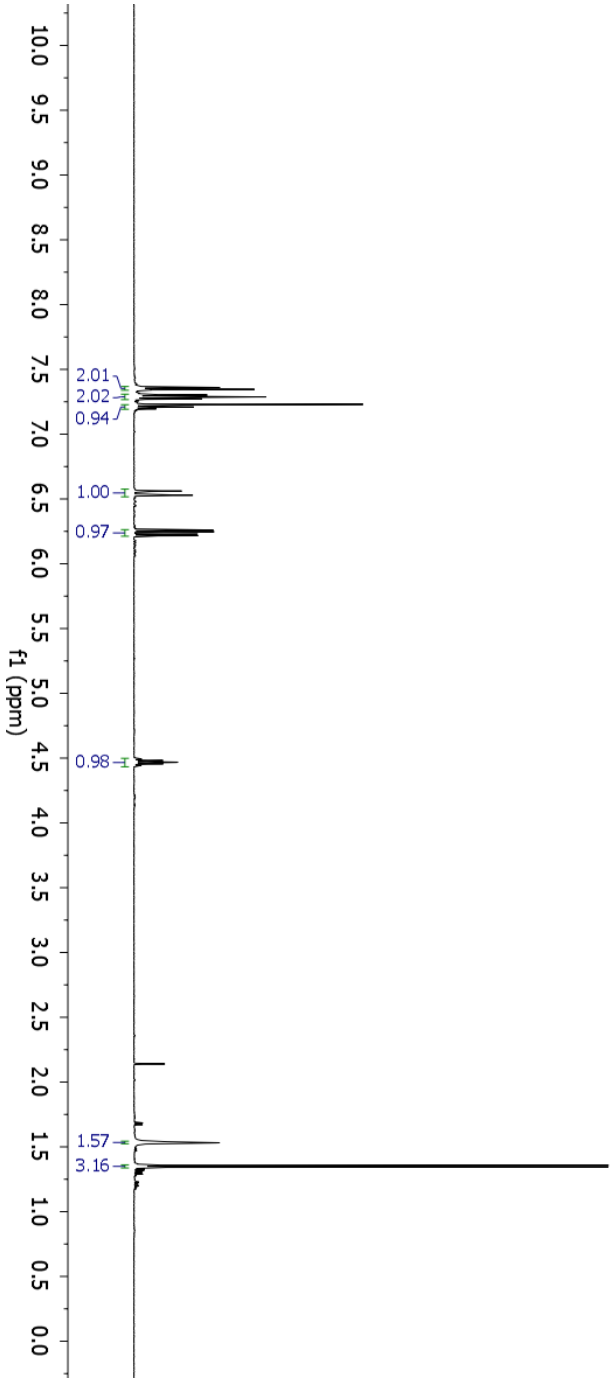
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

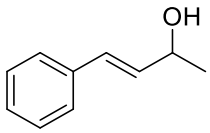




Compound 1-7

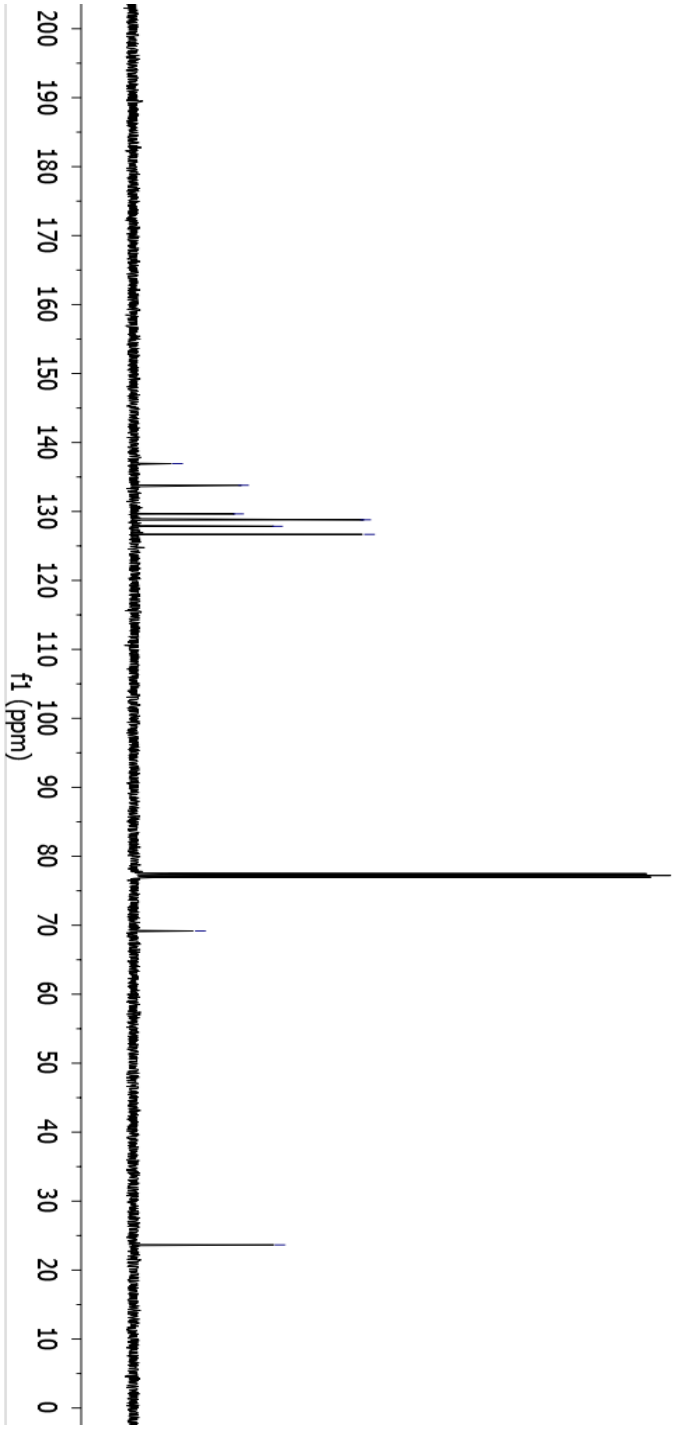
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

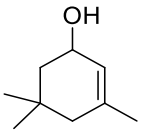




Compound 1-7

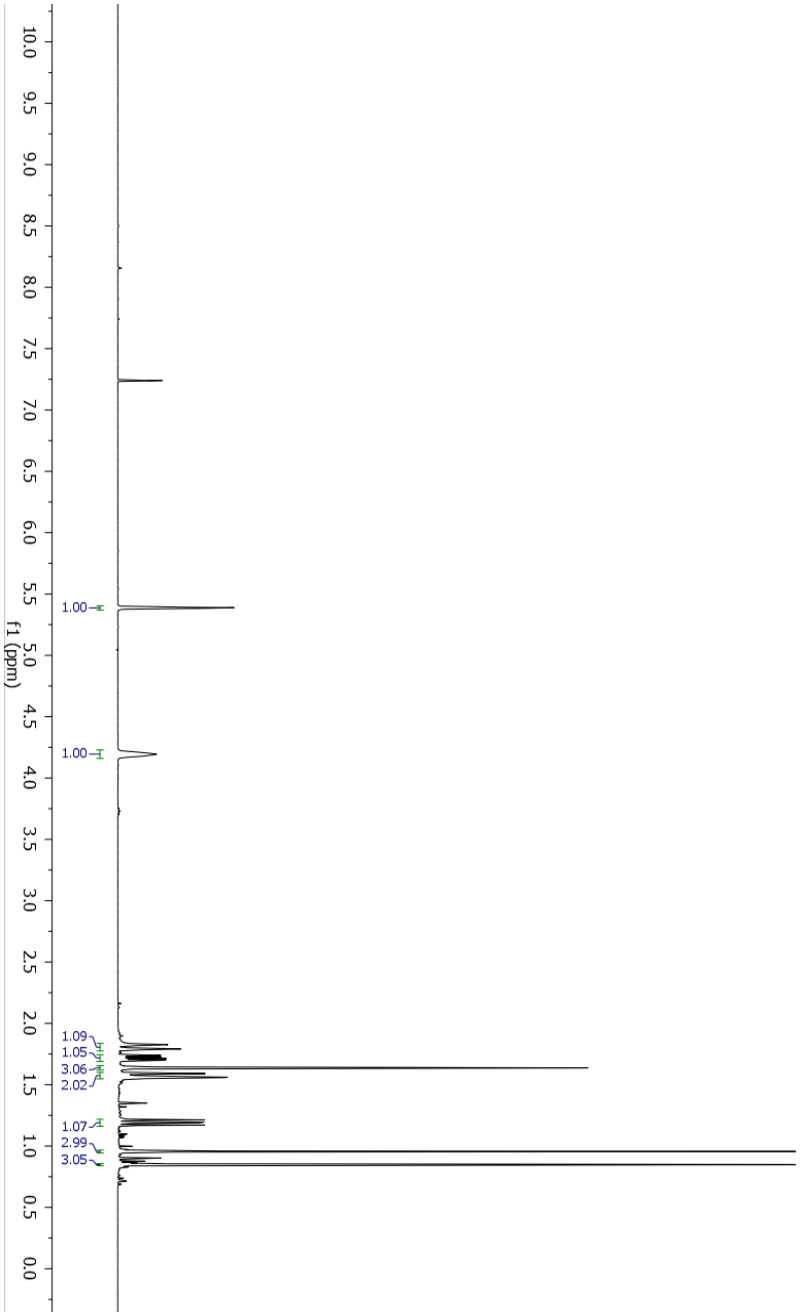
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

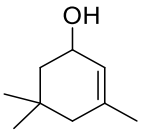




Compound 1-8

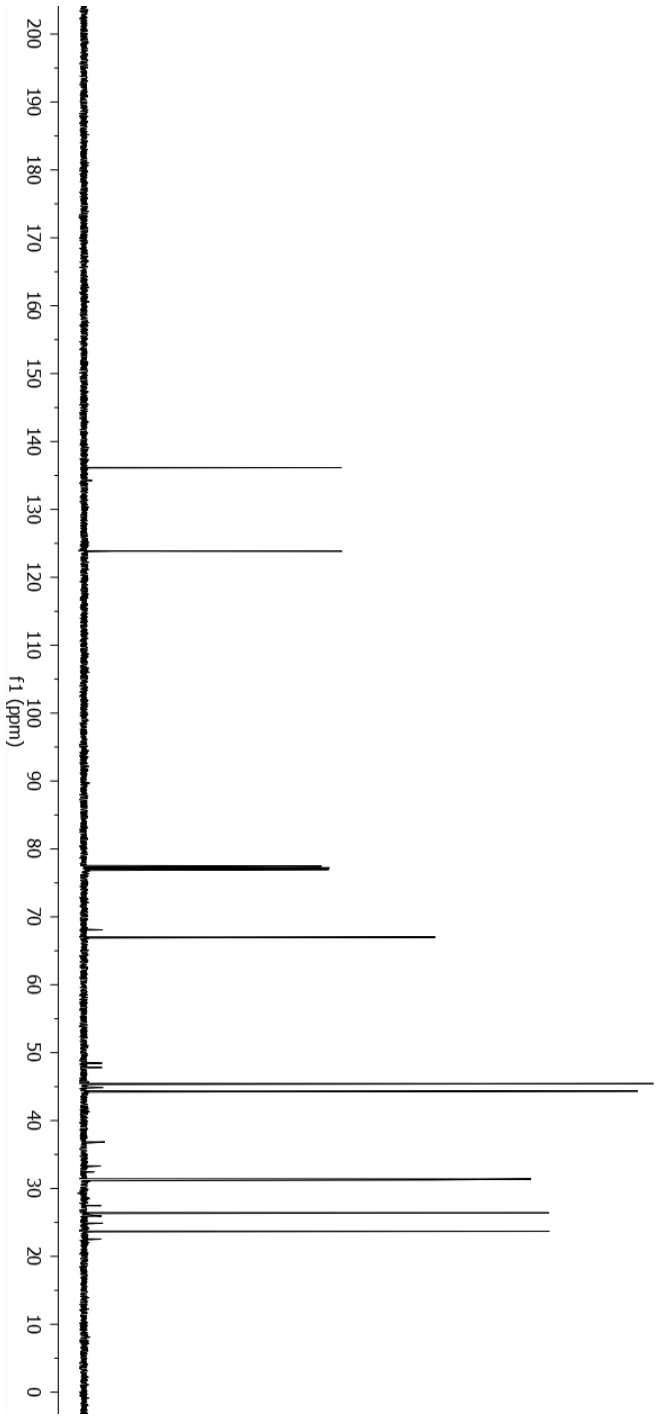
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

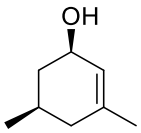




Compound 1-8

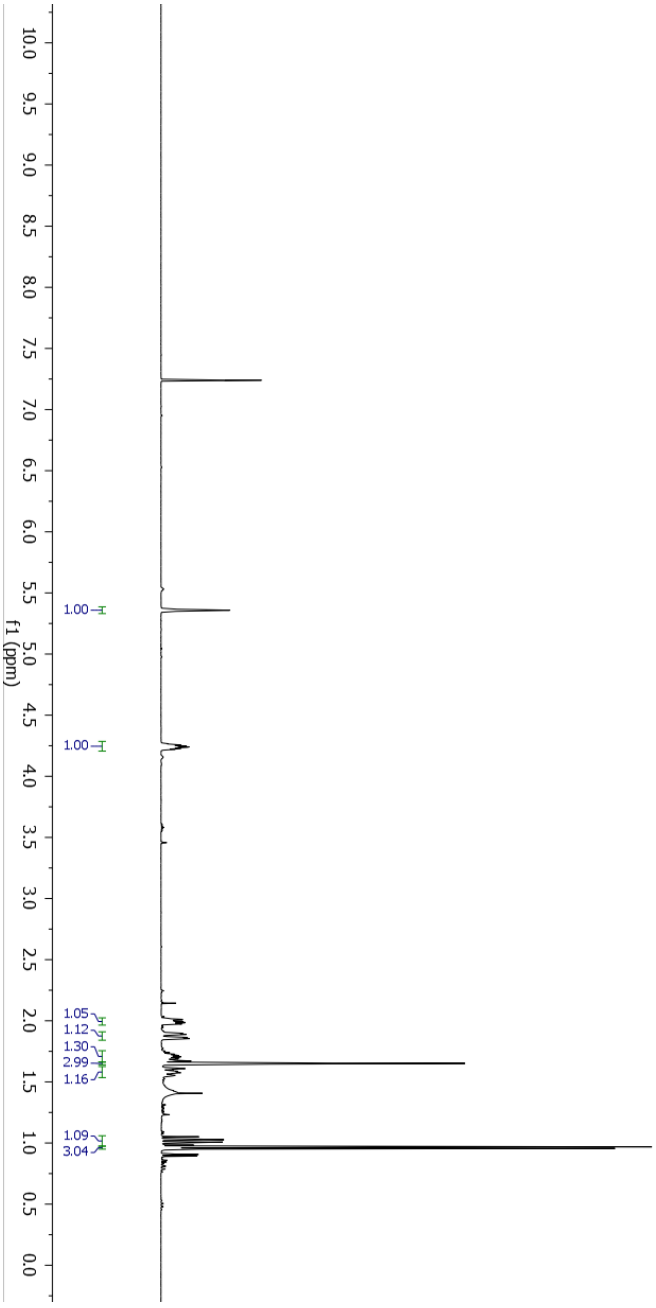
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

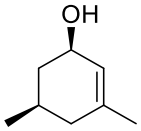




Compound 1-9

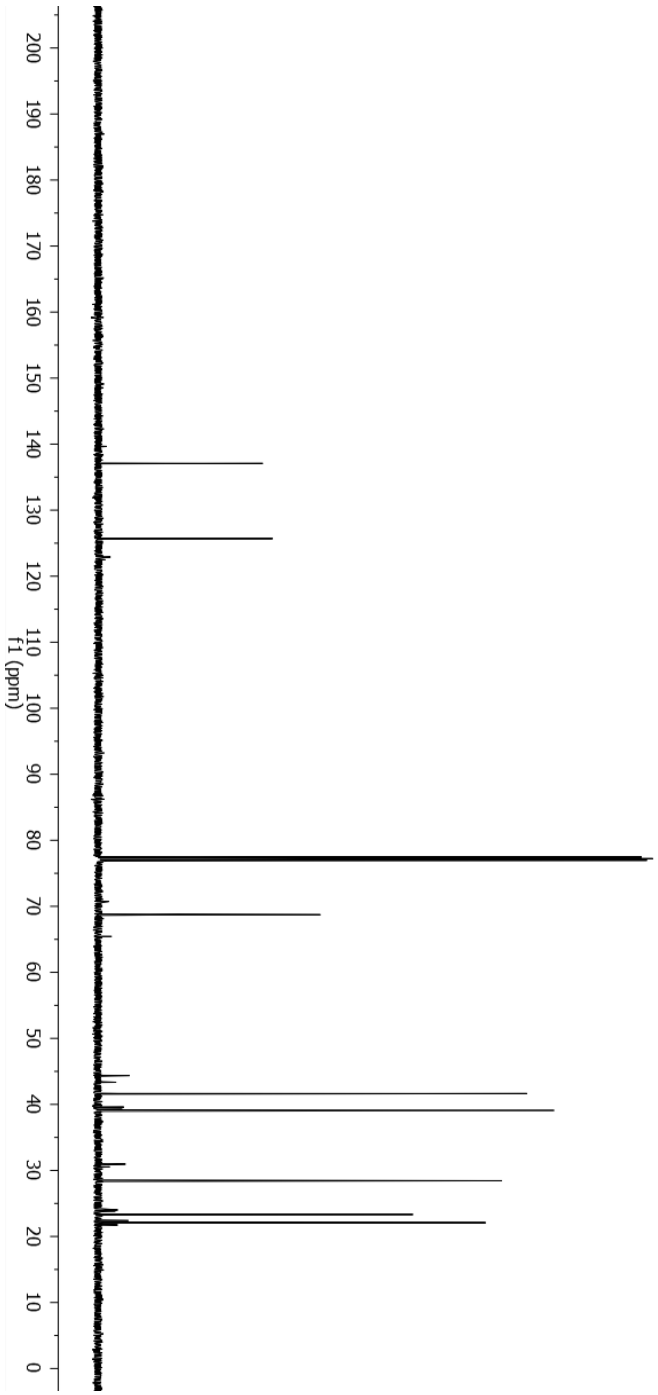
^{1}H NMR spectrum ($CDCl_3$, 300 MHz)

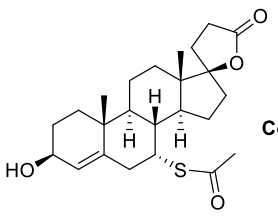




Compound 1-9

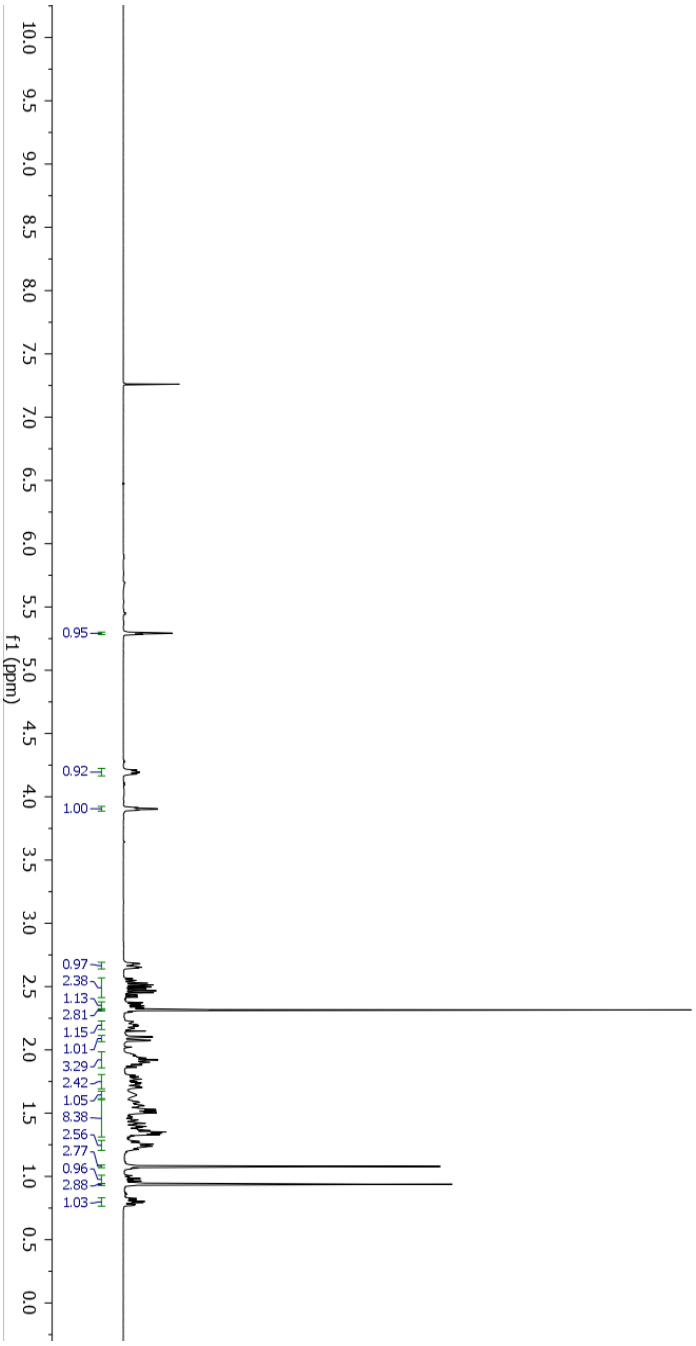
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

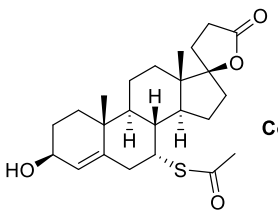




Compound 1-10

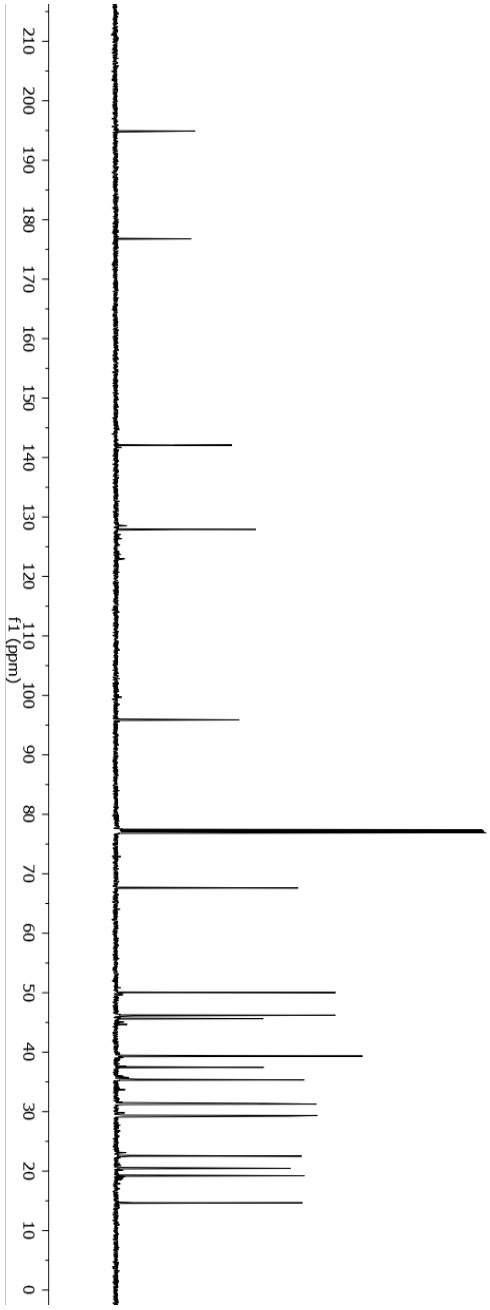
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)





Compound 1-10

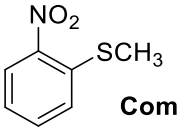
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)



Appendix II

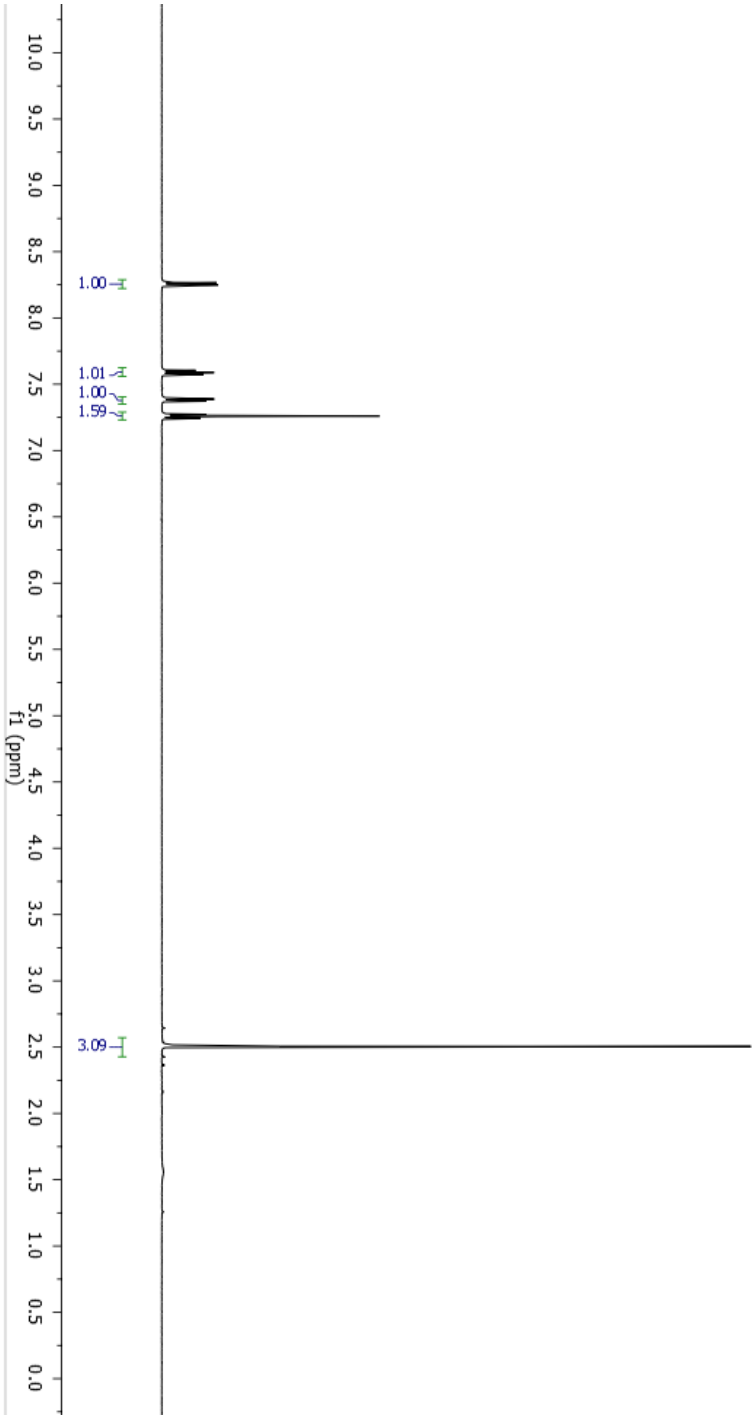
^{1}H and ^{13}C NMR Spectra

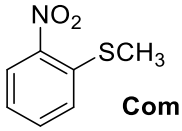
Chapter 2



Compound 2-63

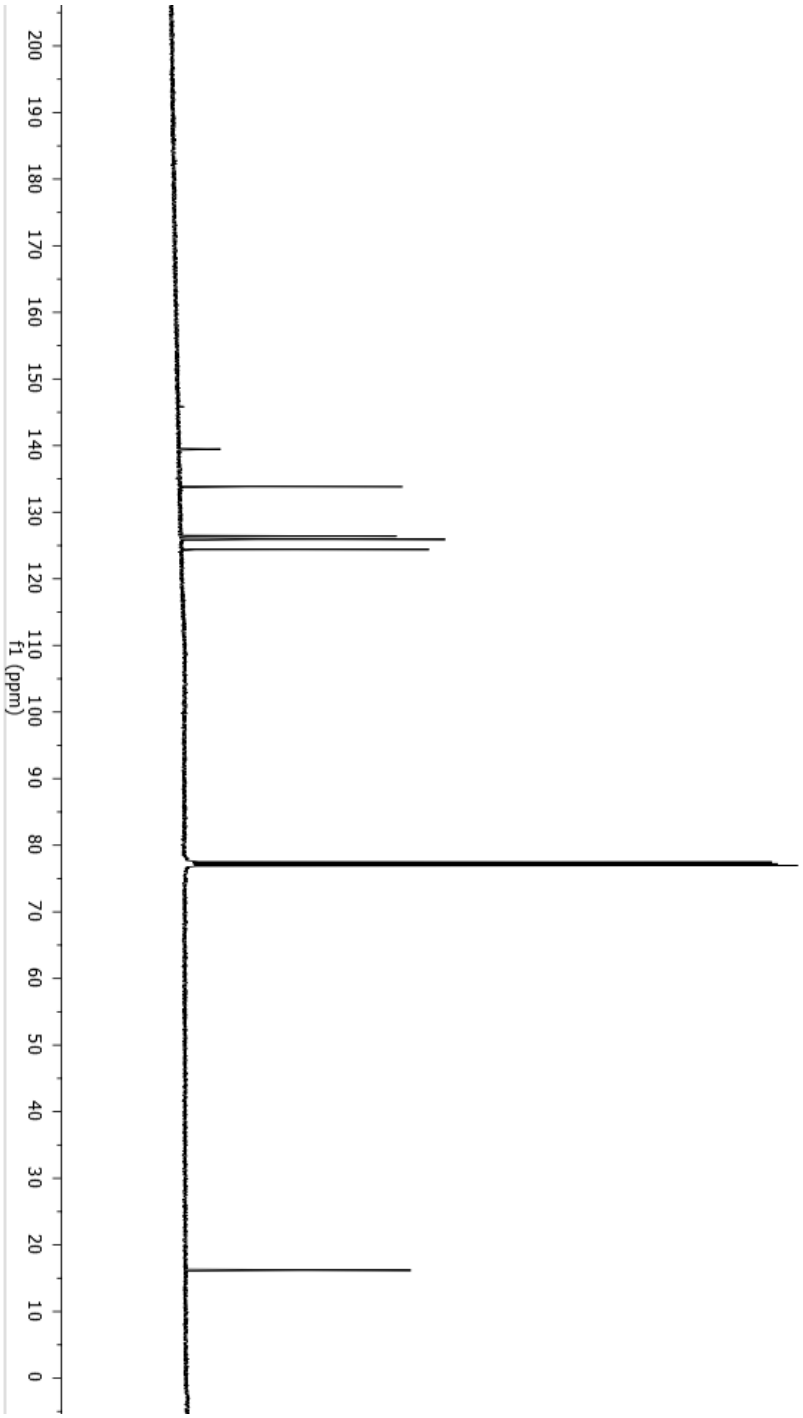
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

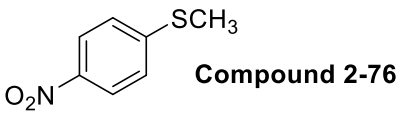




Compound 2-63

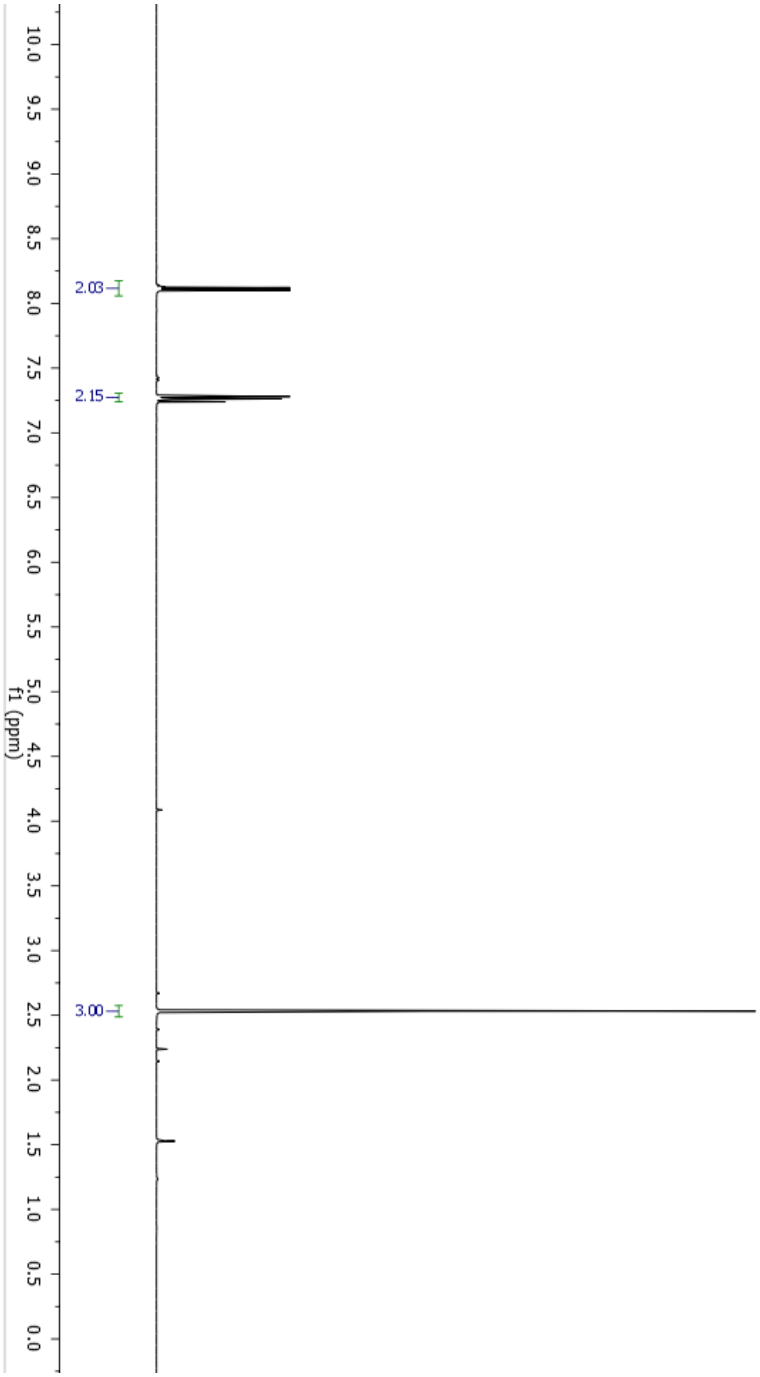
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

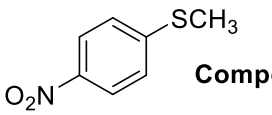




Compound 2-76

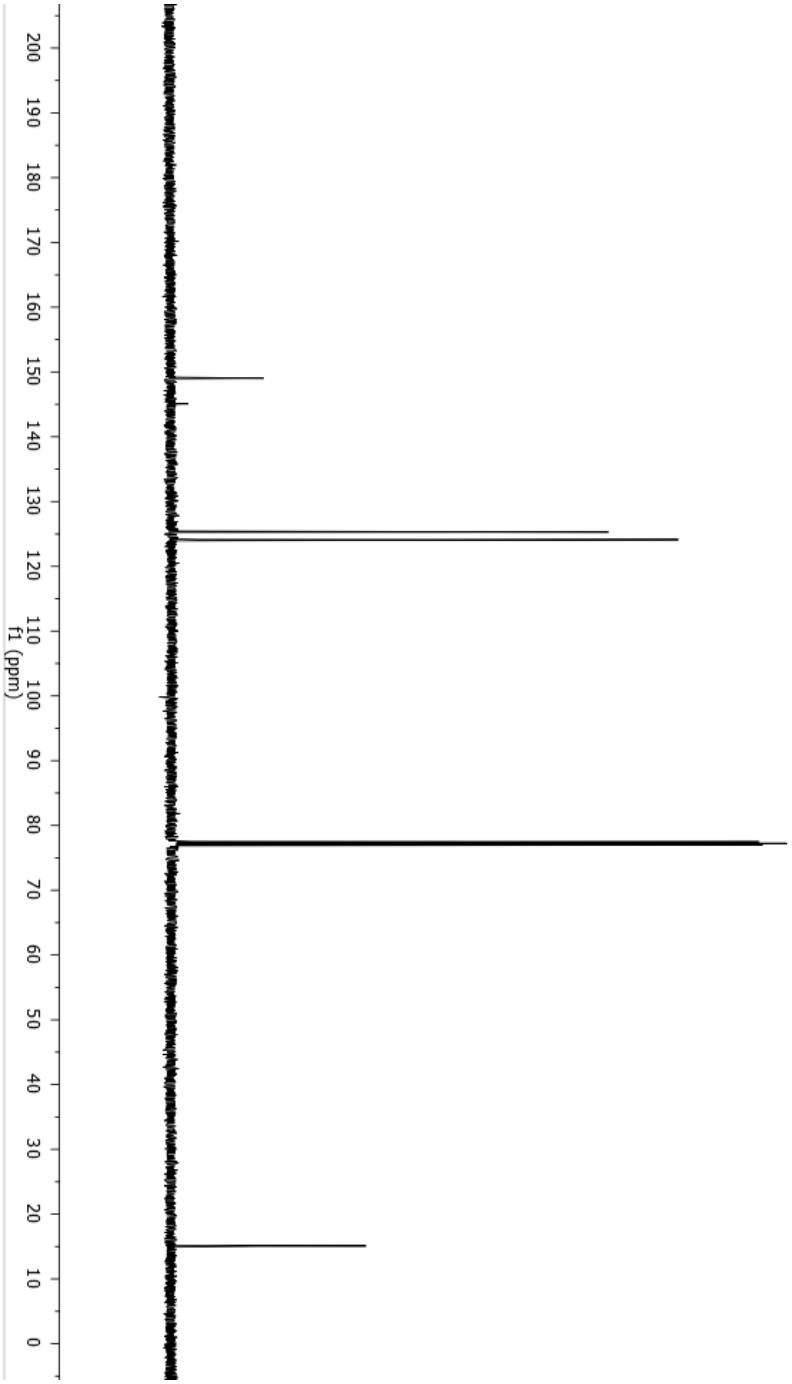
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

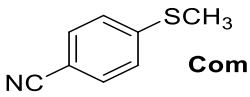




Compound 2-76

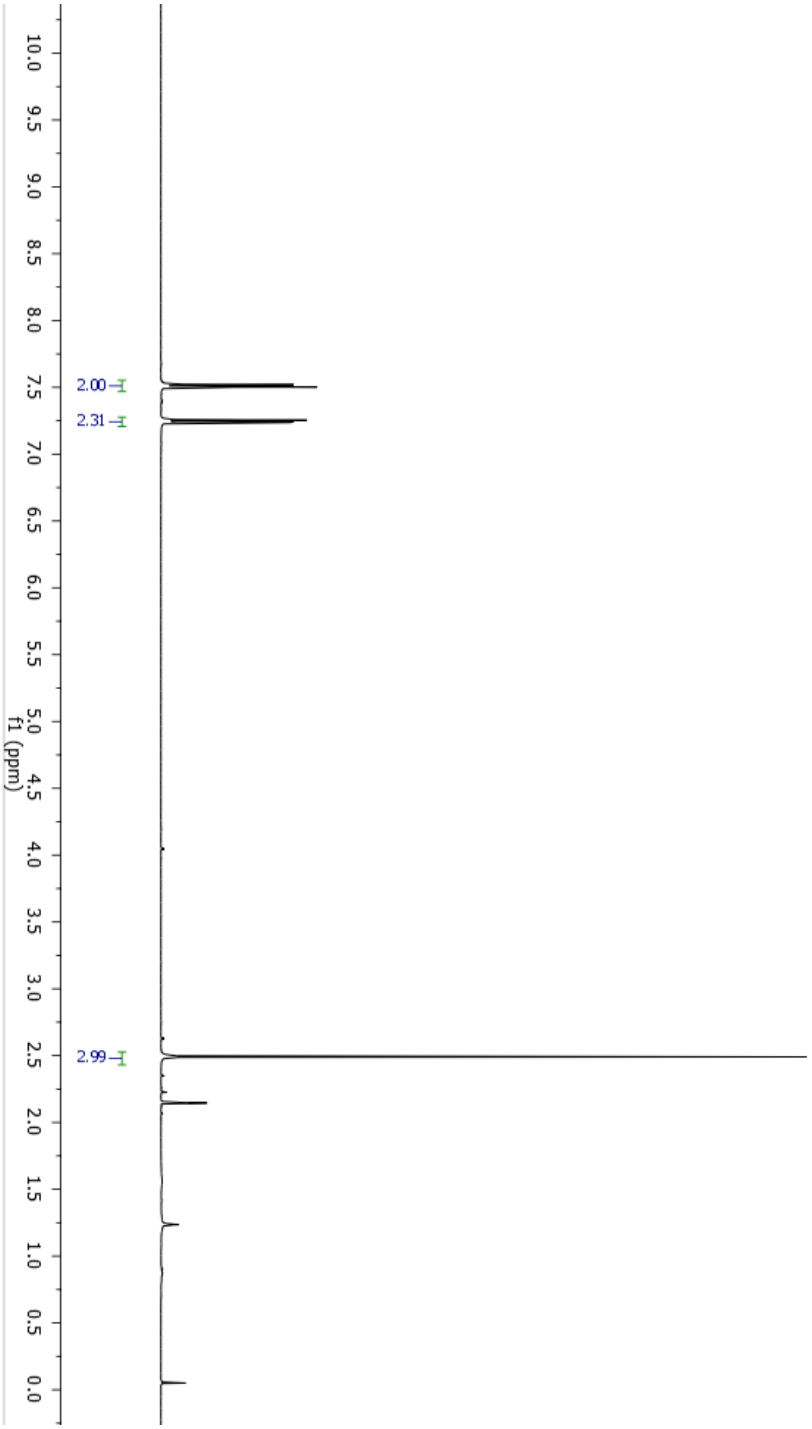
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

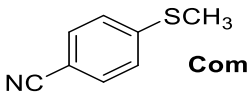




Compound 2-77

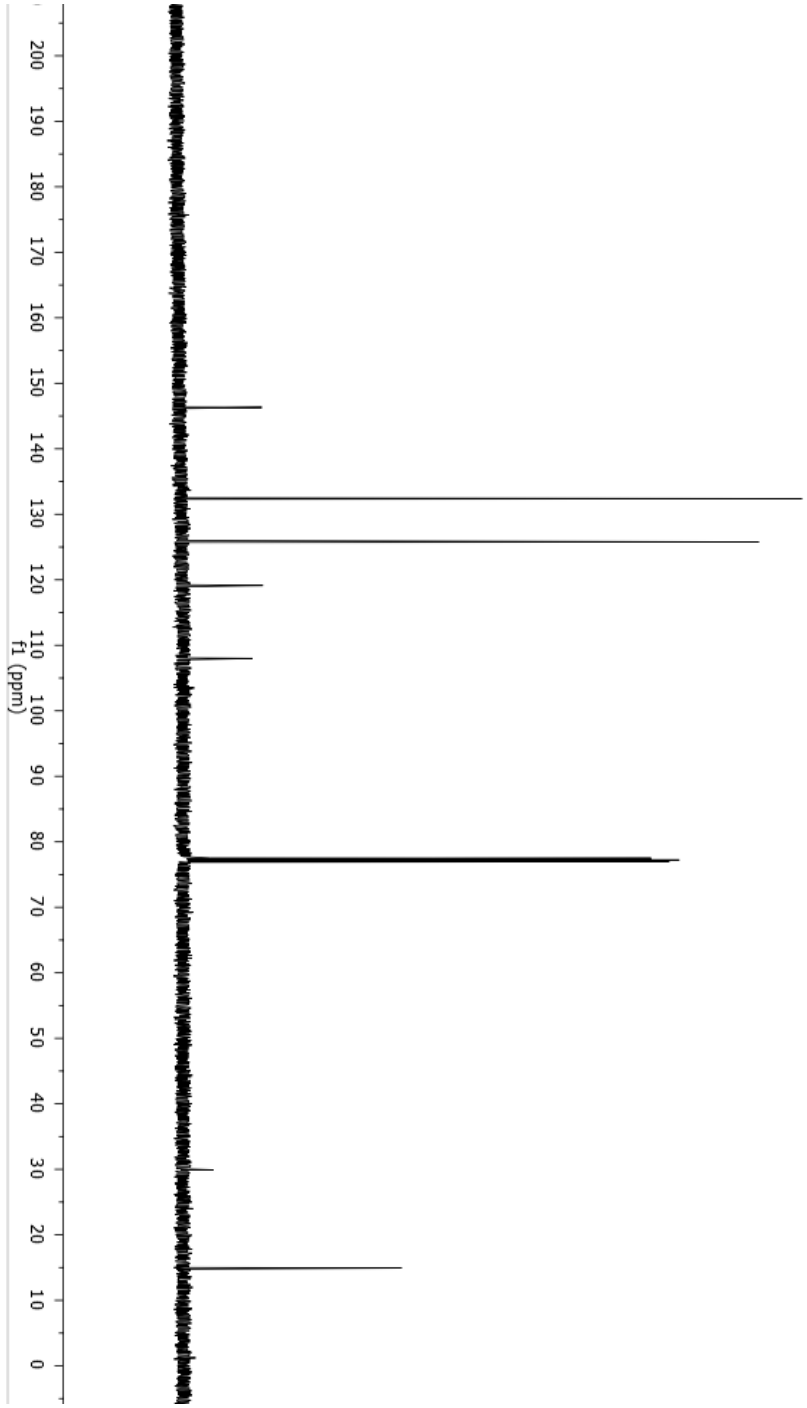
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

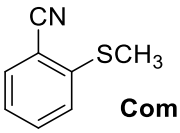




Compound 2-77

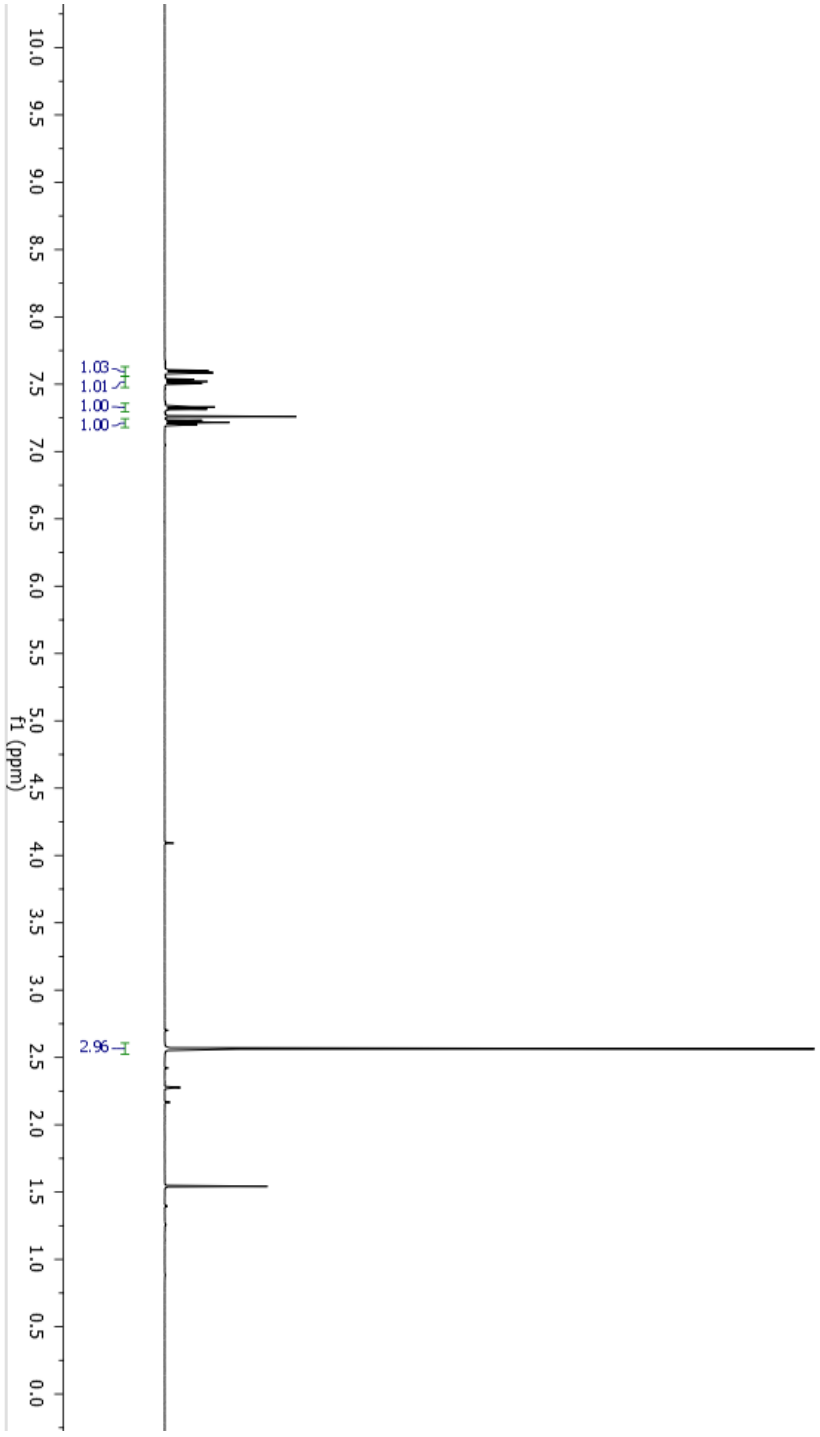
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

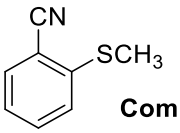




Compound 2-78

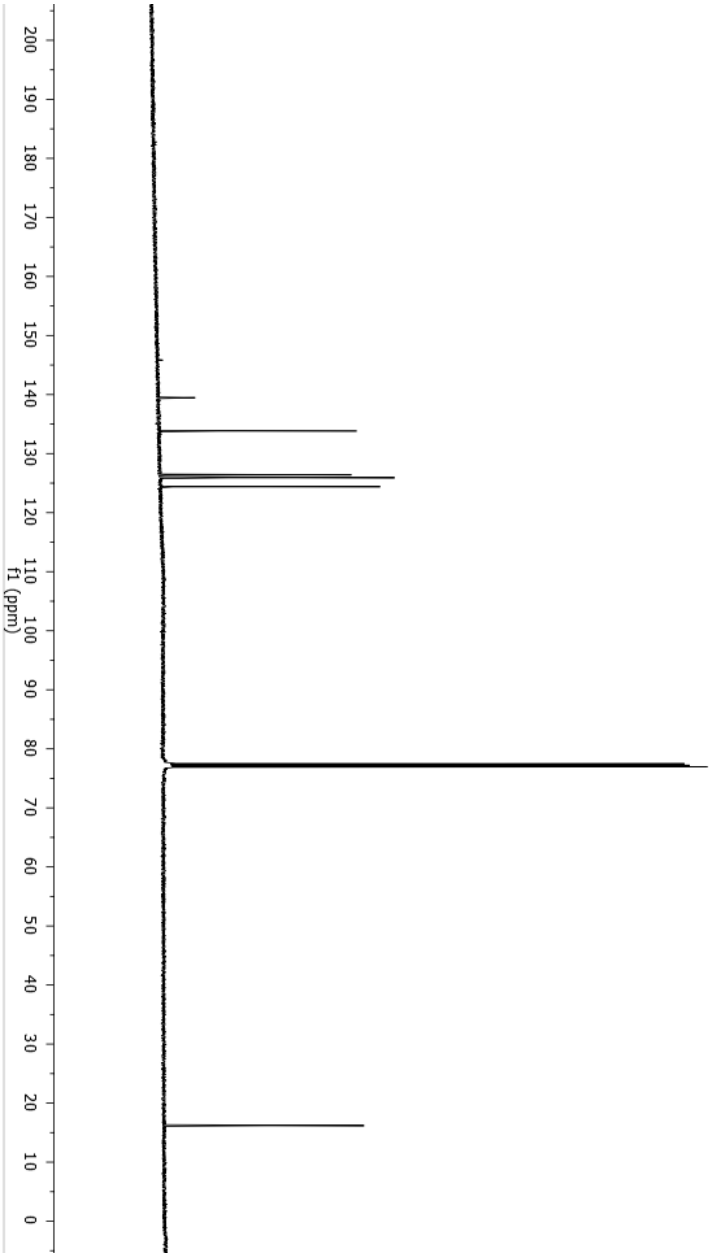
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

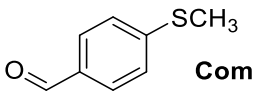




Compound 2-78

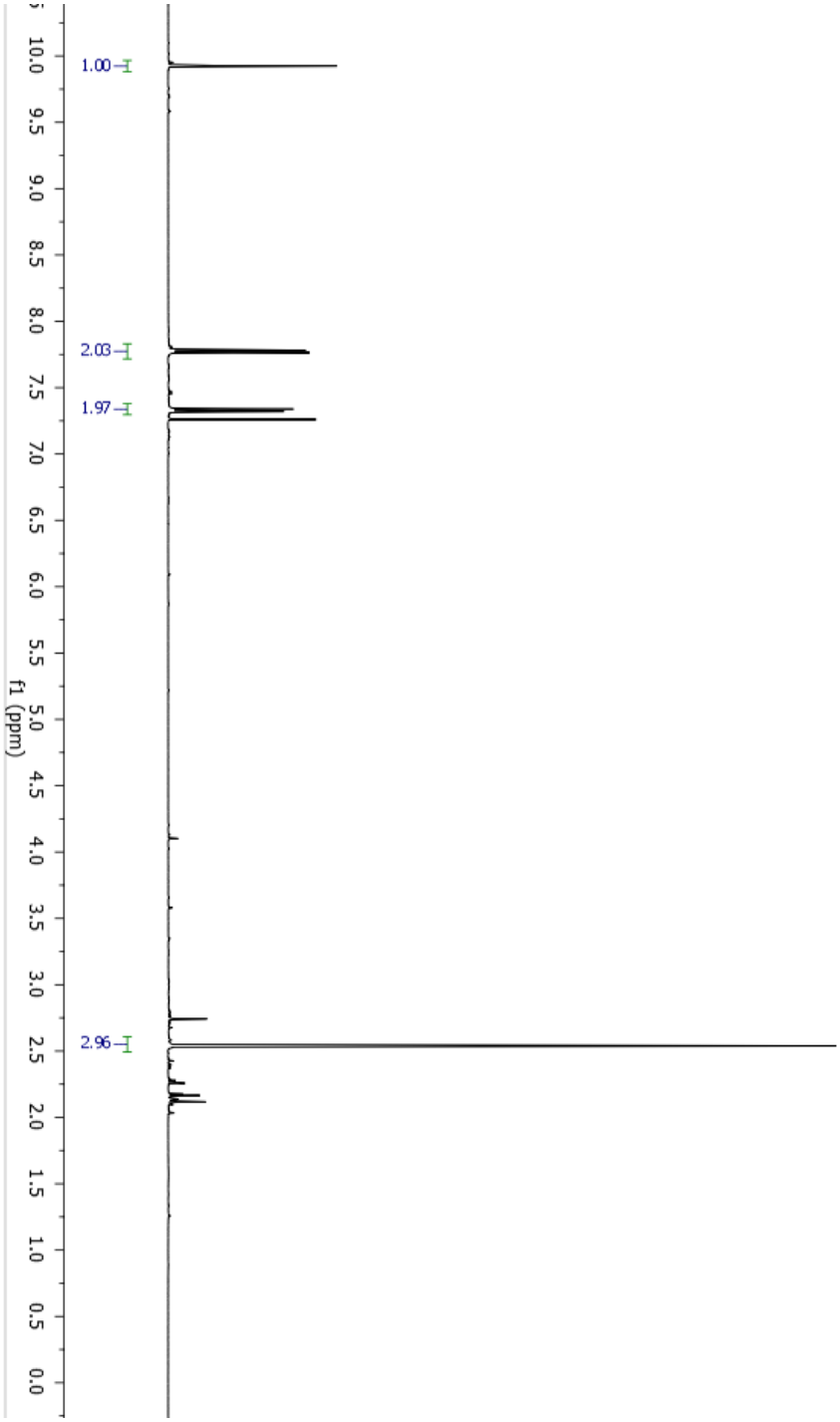
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

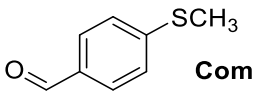




Compound 2-79

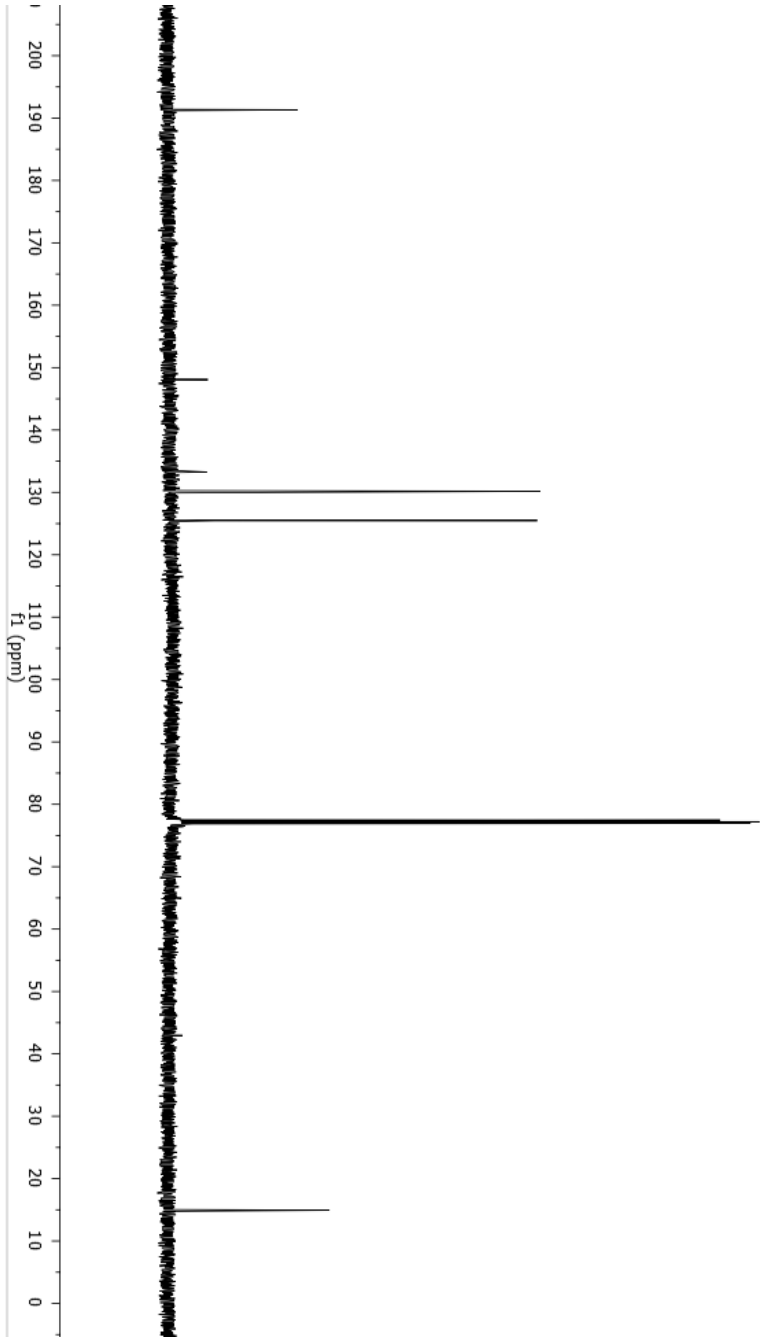
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

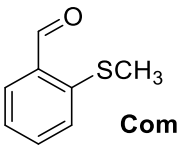




Compound 2-79

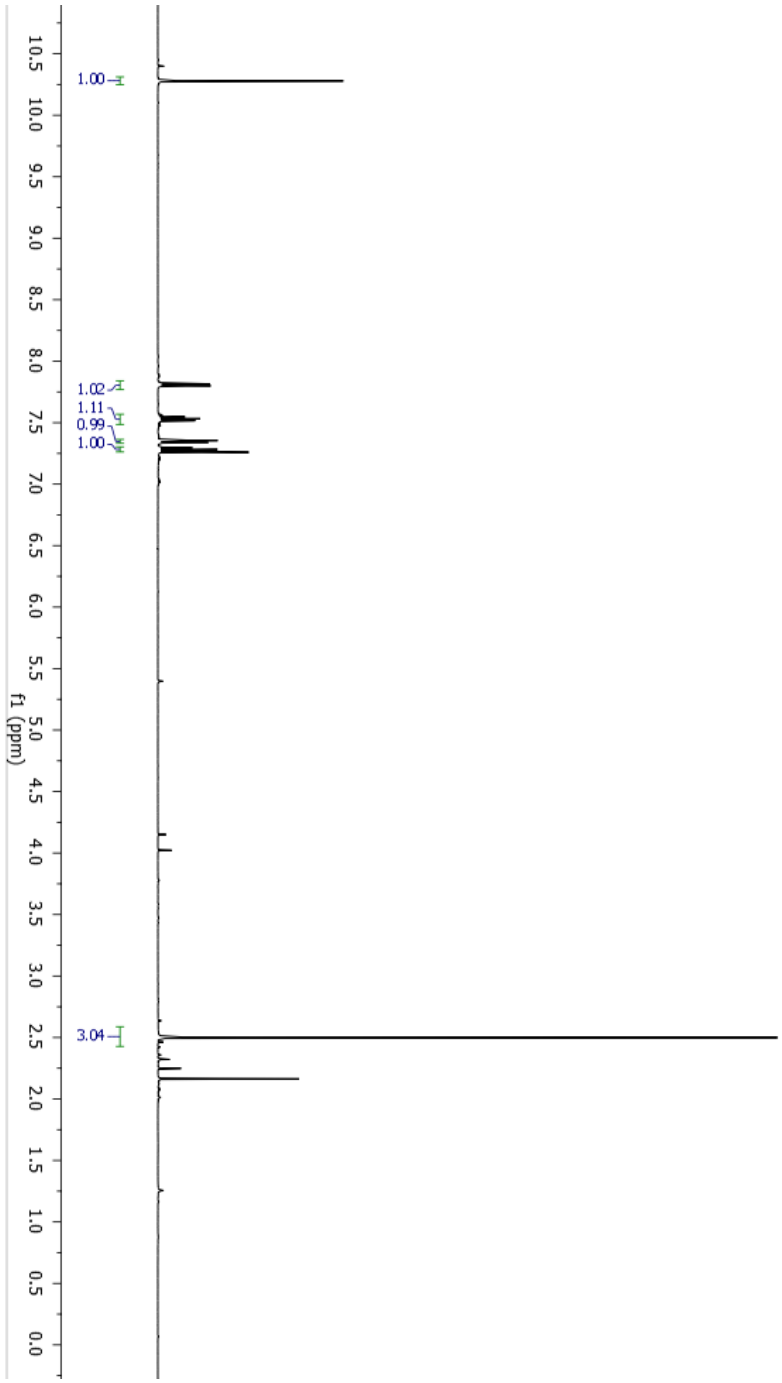
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

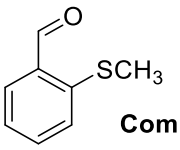




Compound 2-80

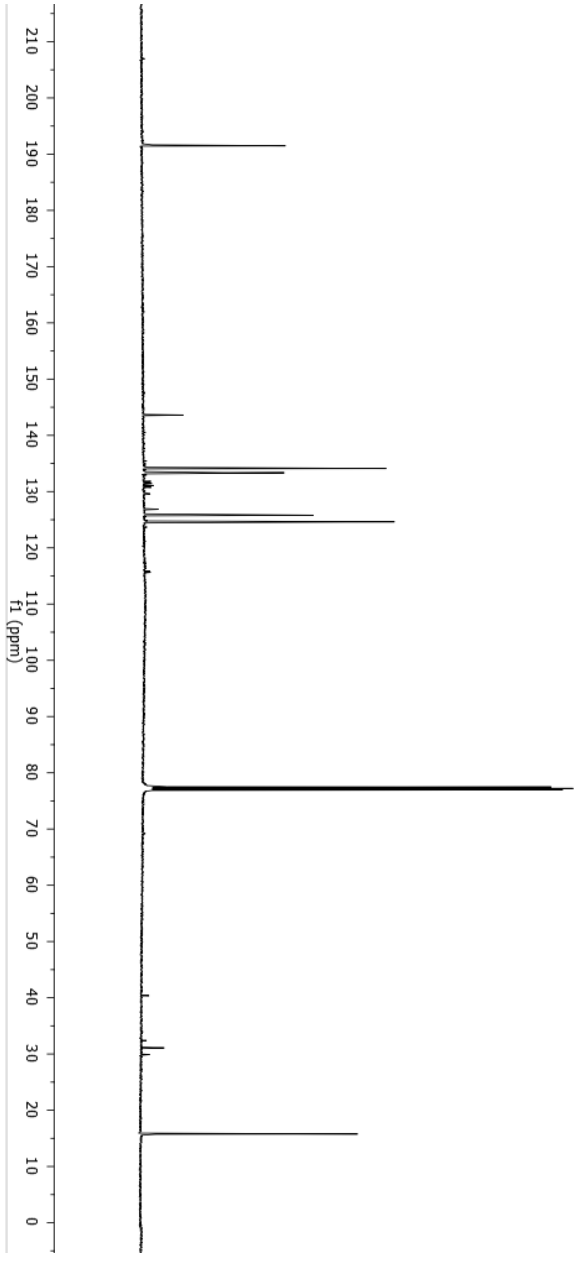
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

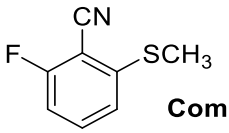




Compound 2-80

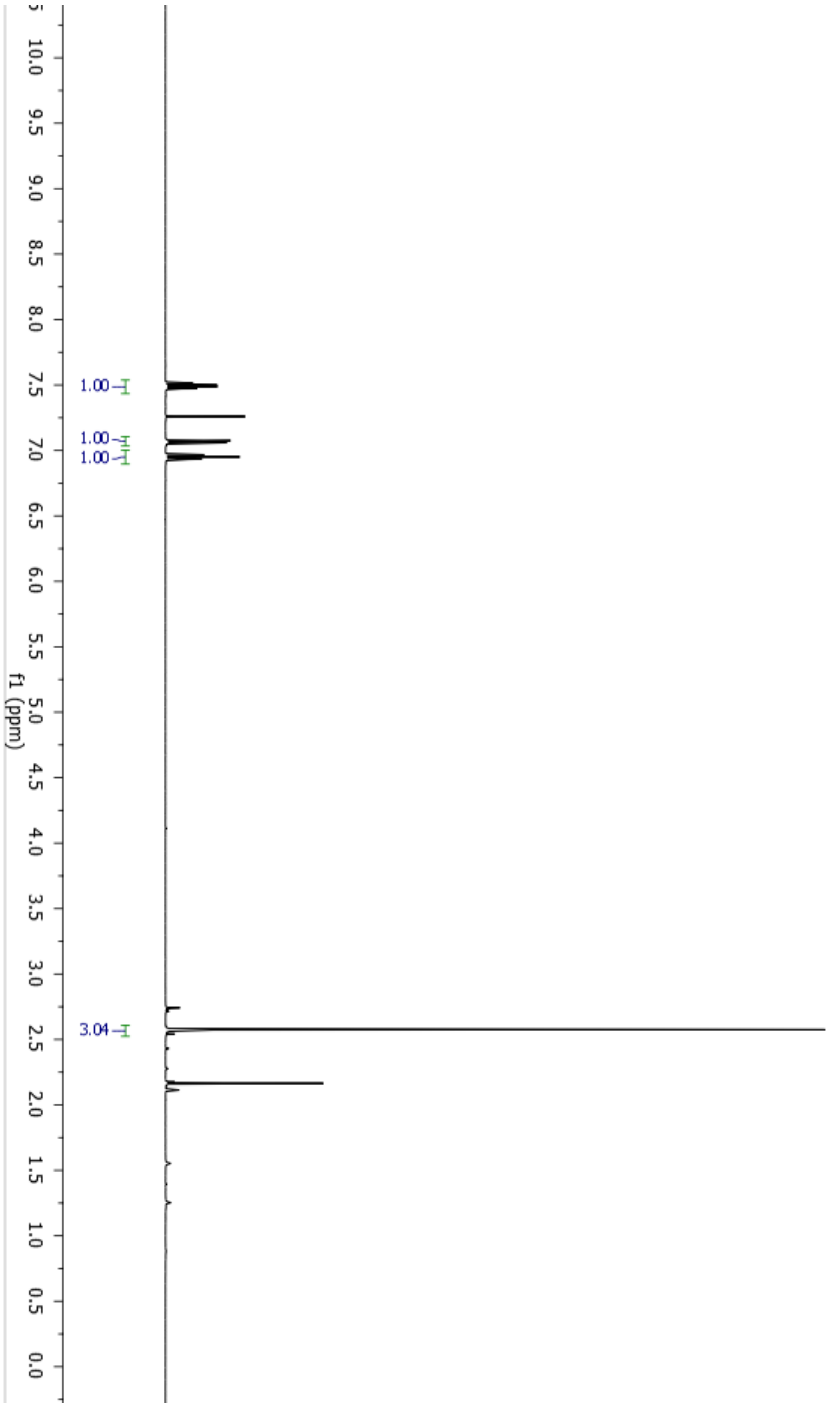
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

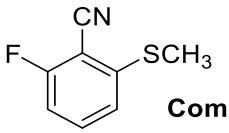




Compound 2-81

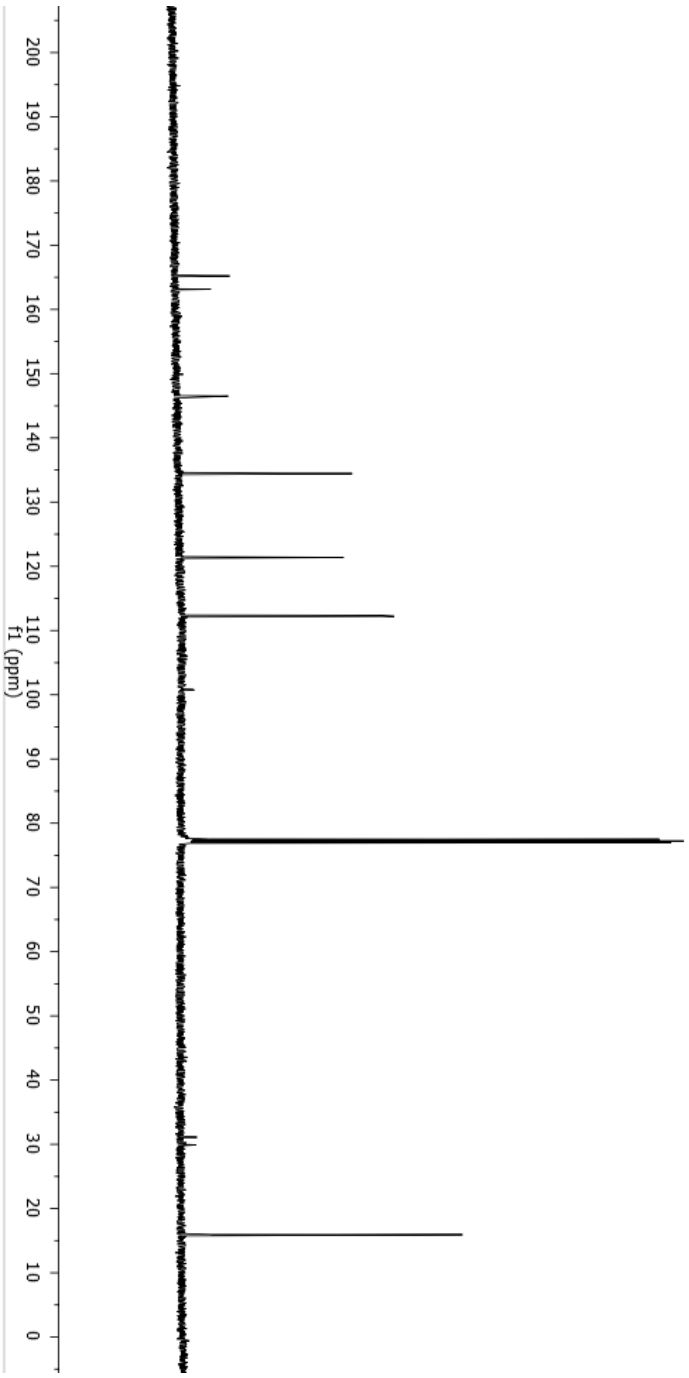
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

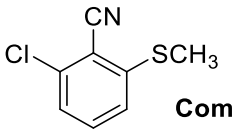




Compound 2-81

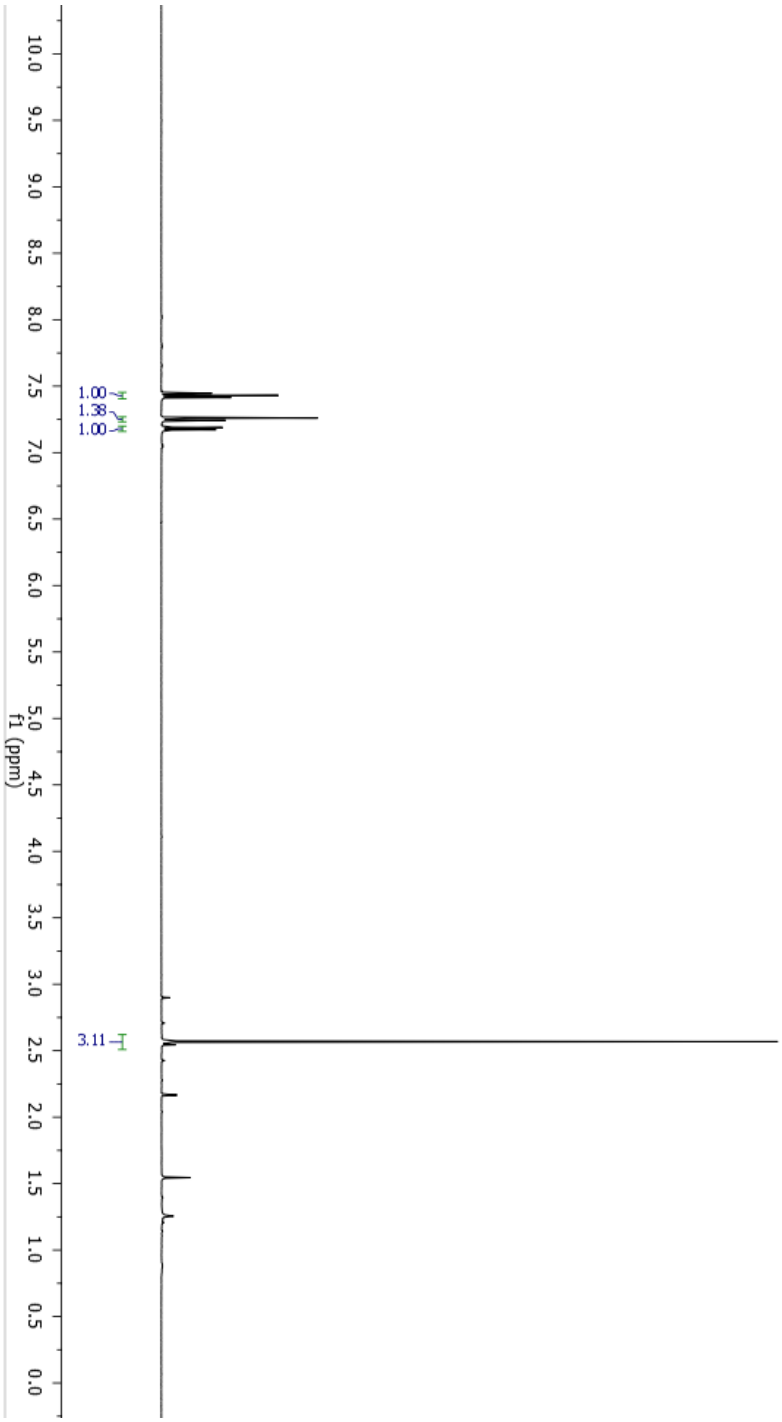
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

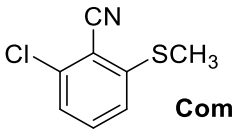




Compound 2-82

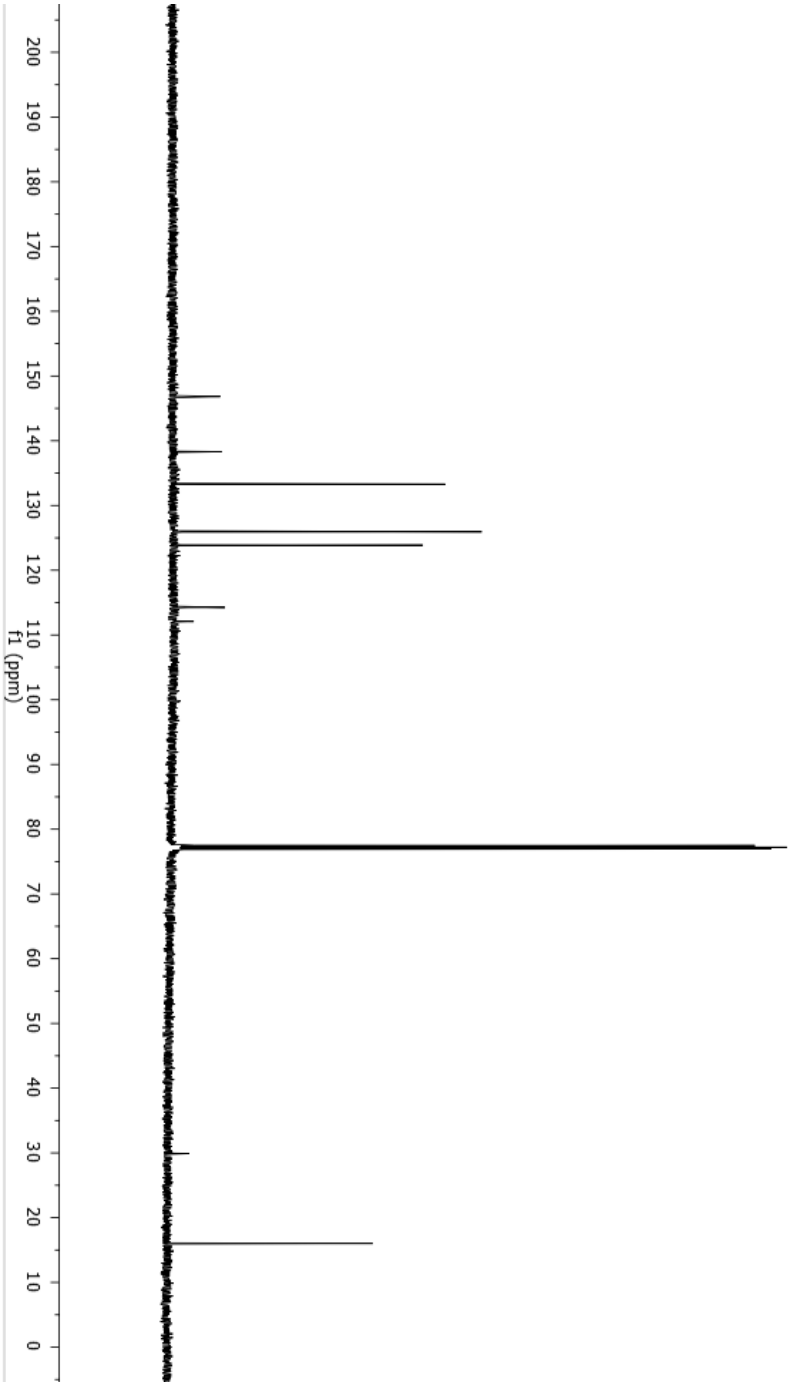
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)





Compound 2-82

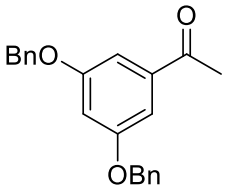
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)



Appendix III

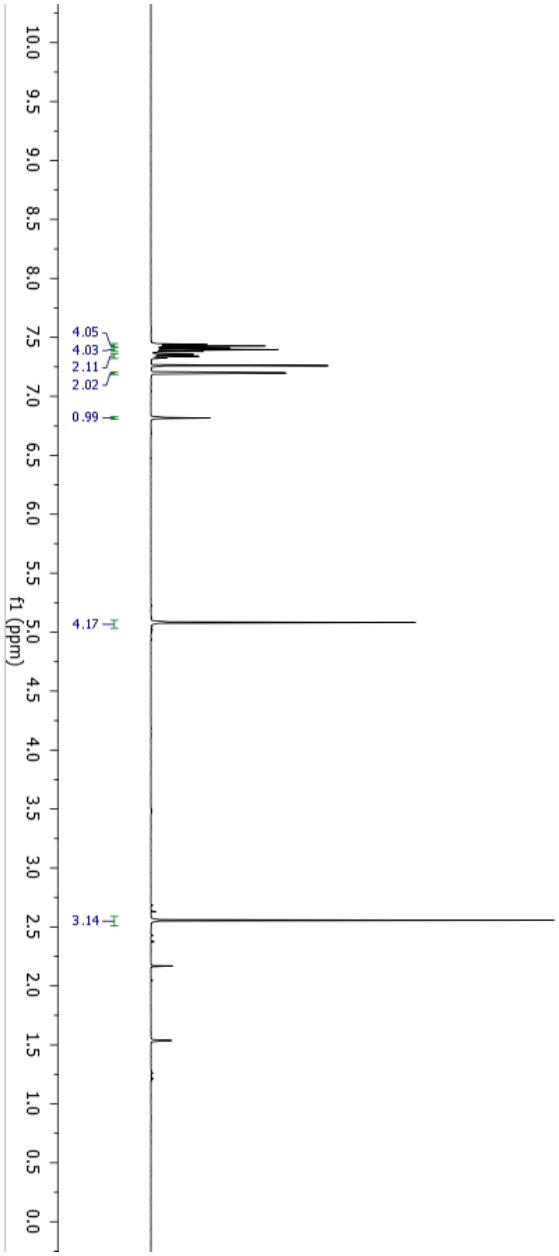
^{1}H and ^{13}C NMR Spectra

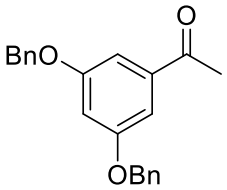
Chapter 3



Compound 3-44

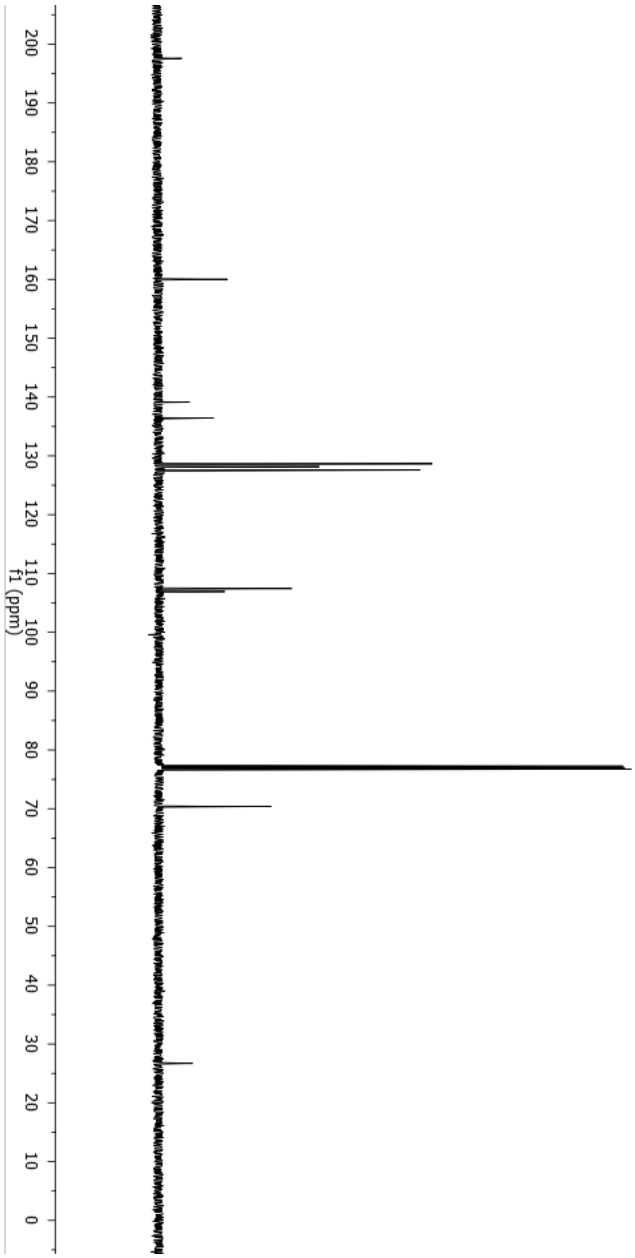
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

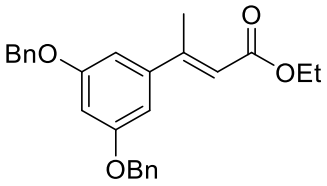




Compound 3-44

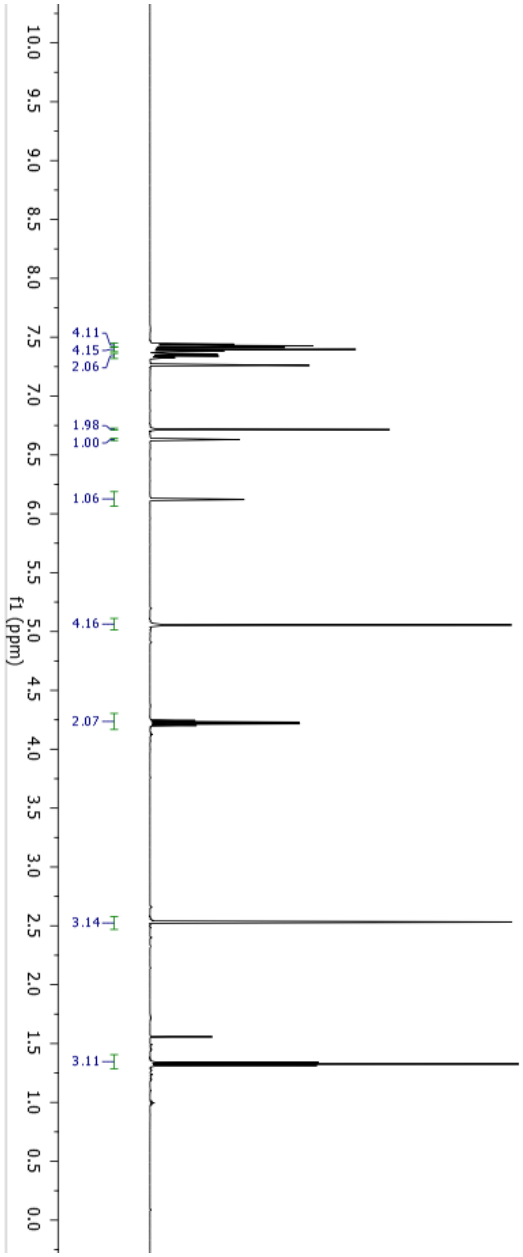
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

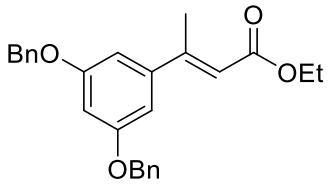




Compound 3-43

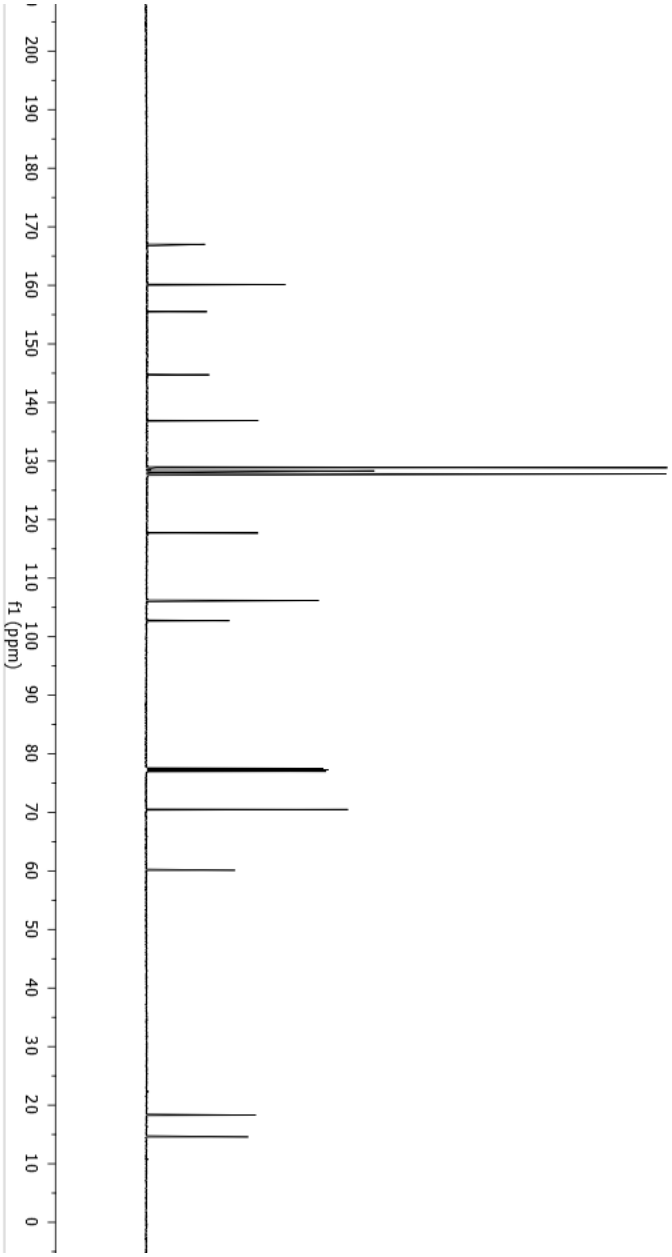
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

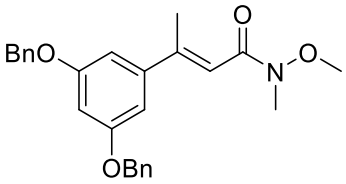




Compound 3-43

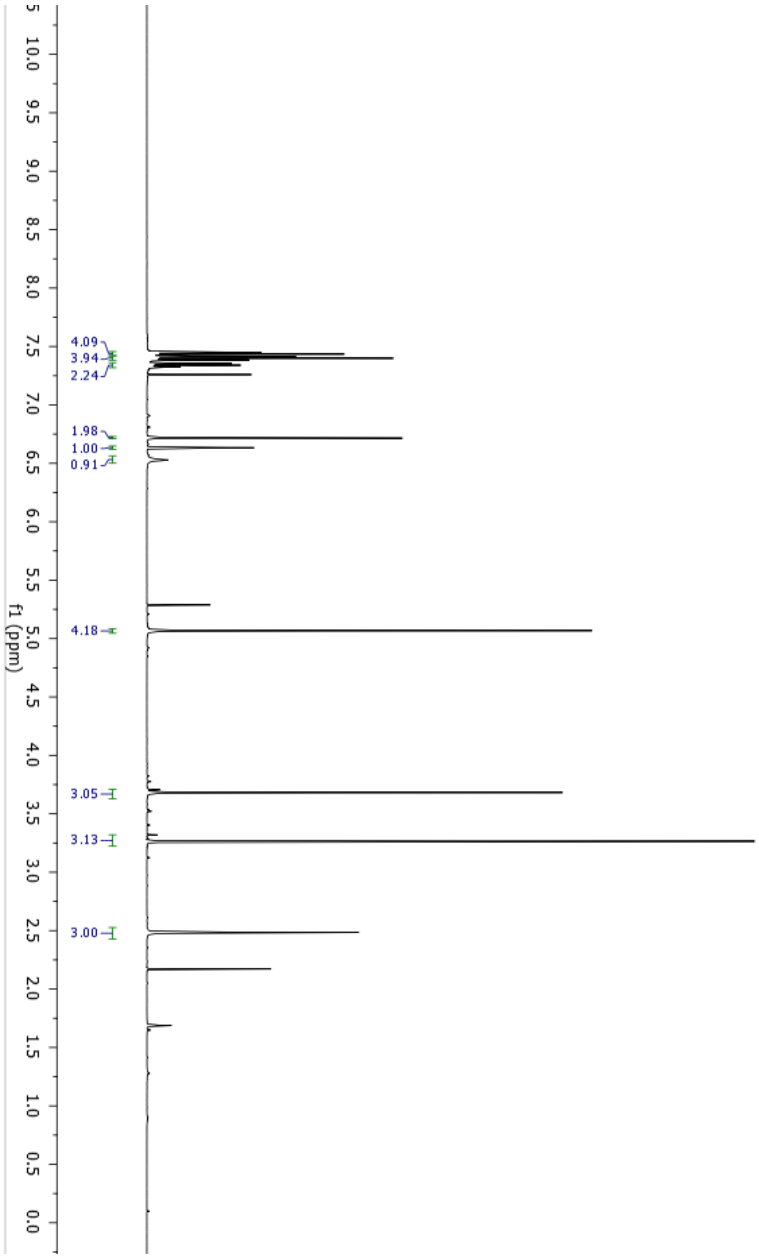
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

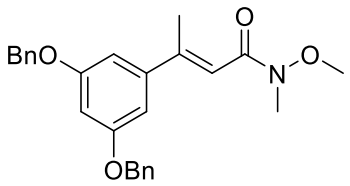




Compound 3-48

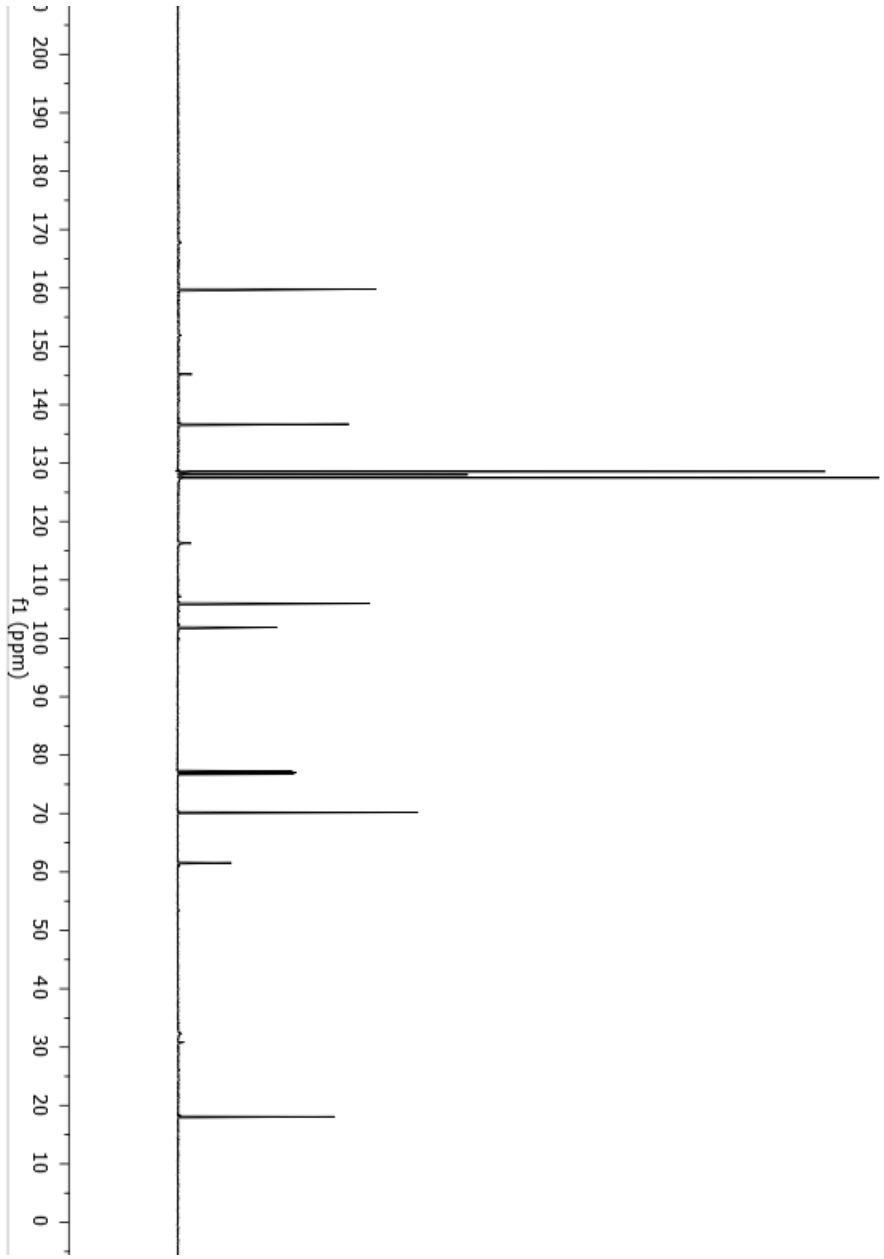
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

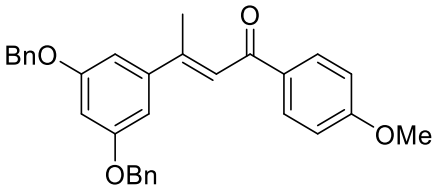




Compound 3-48

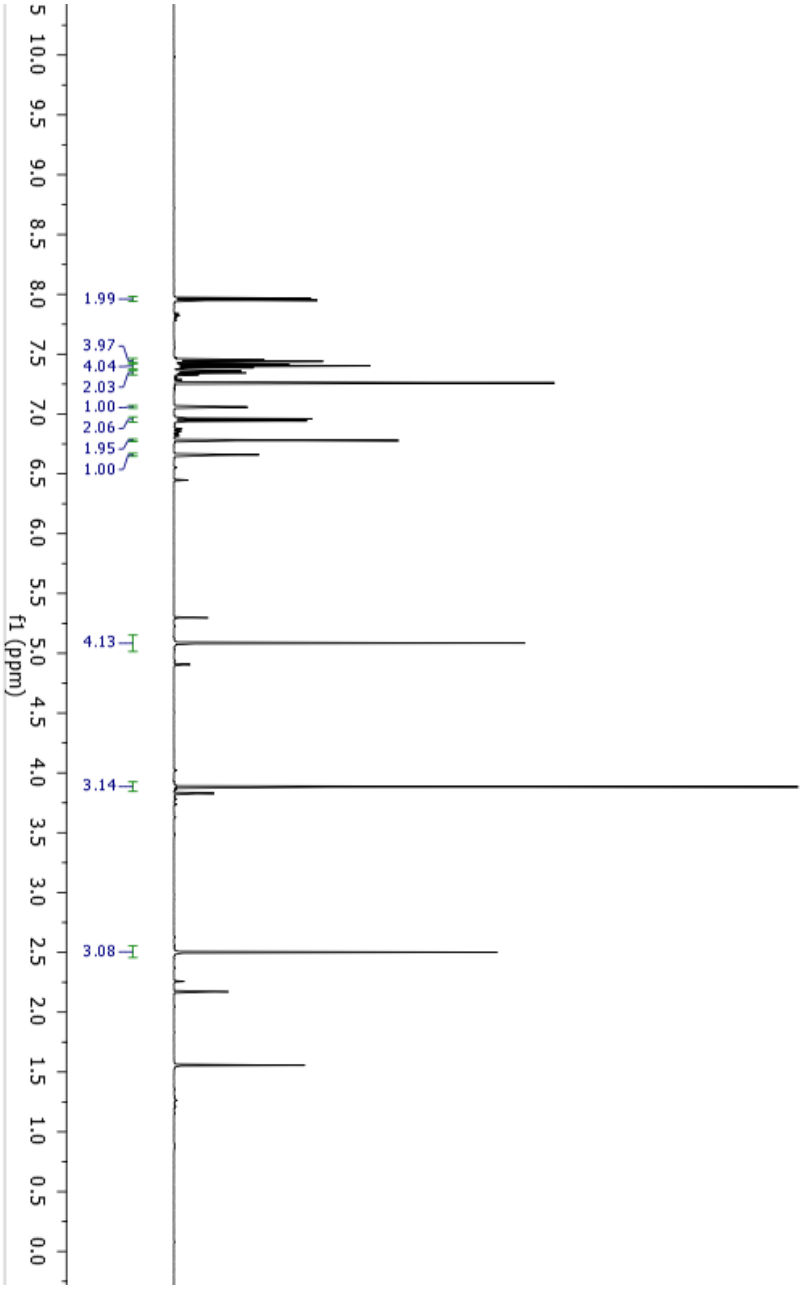
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

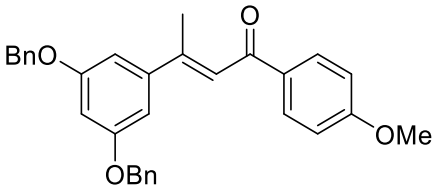




Compound 3-50

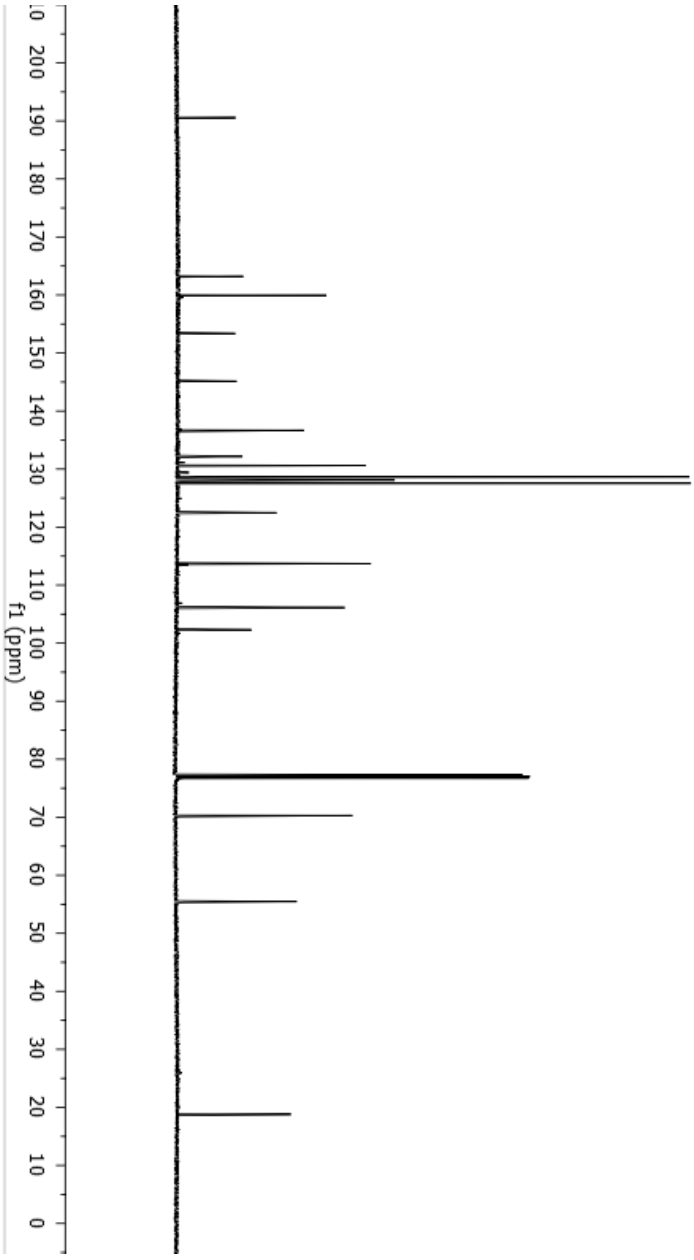
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

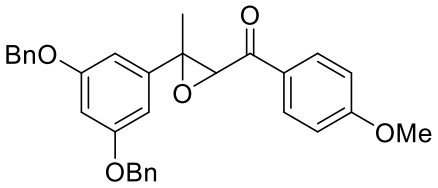




Compound 3-50

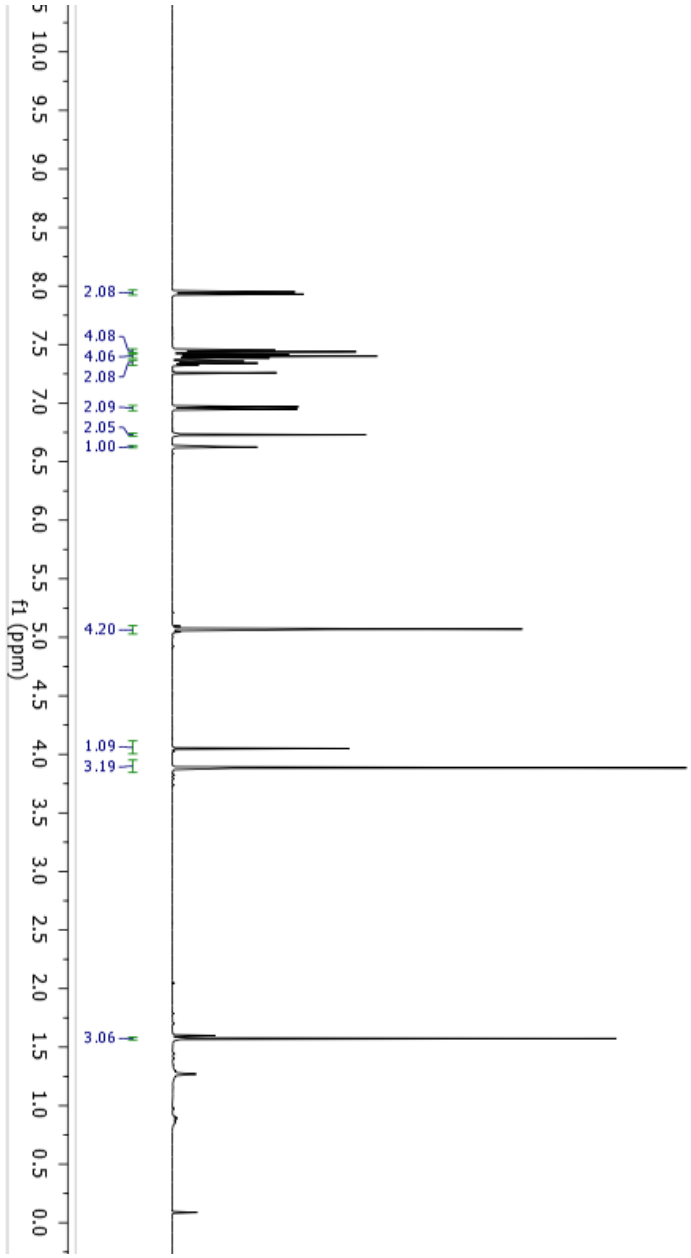
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

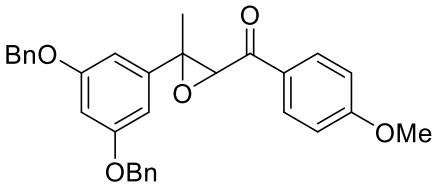




Compound 3-51

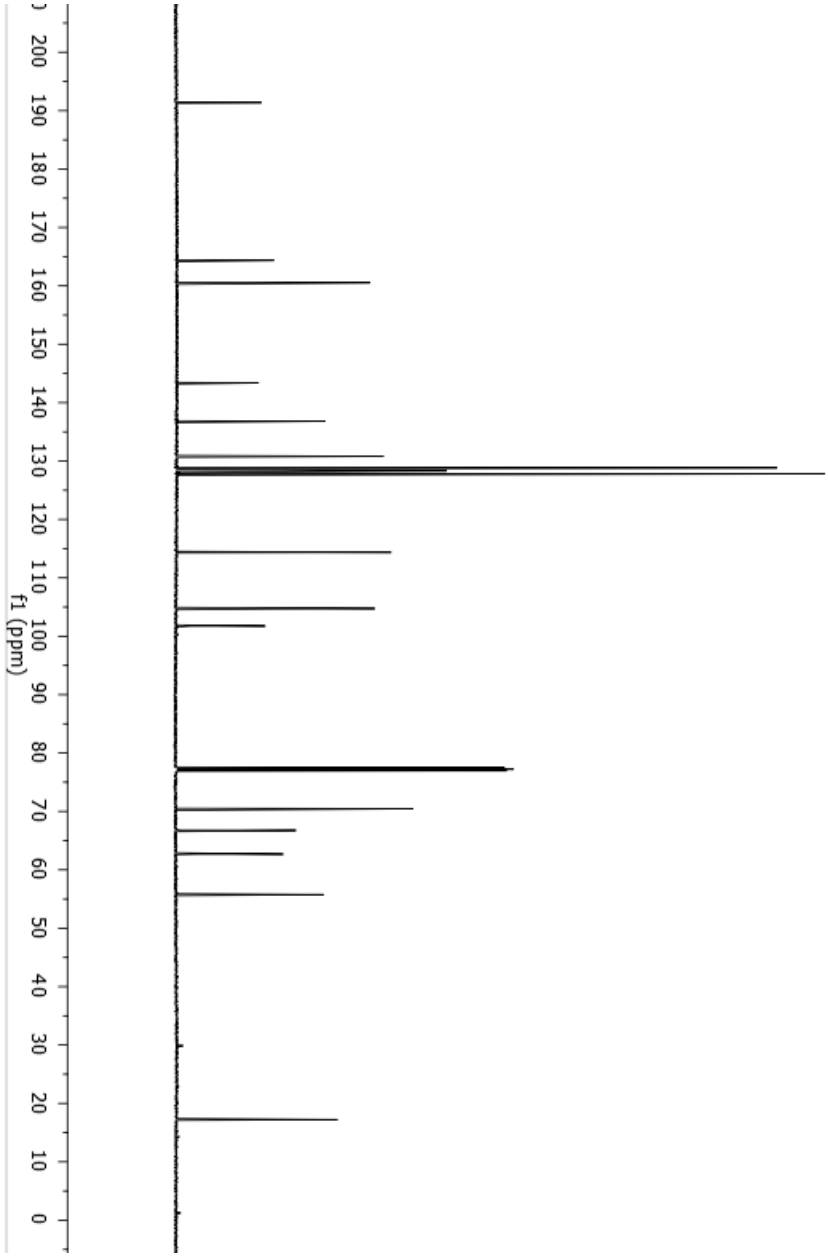
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

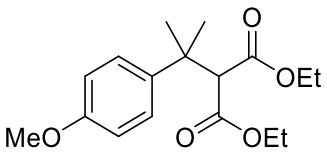




Compound 3-51

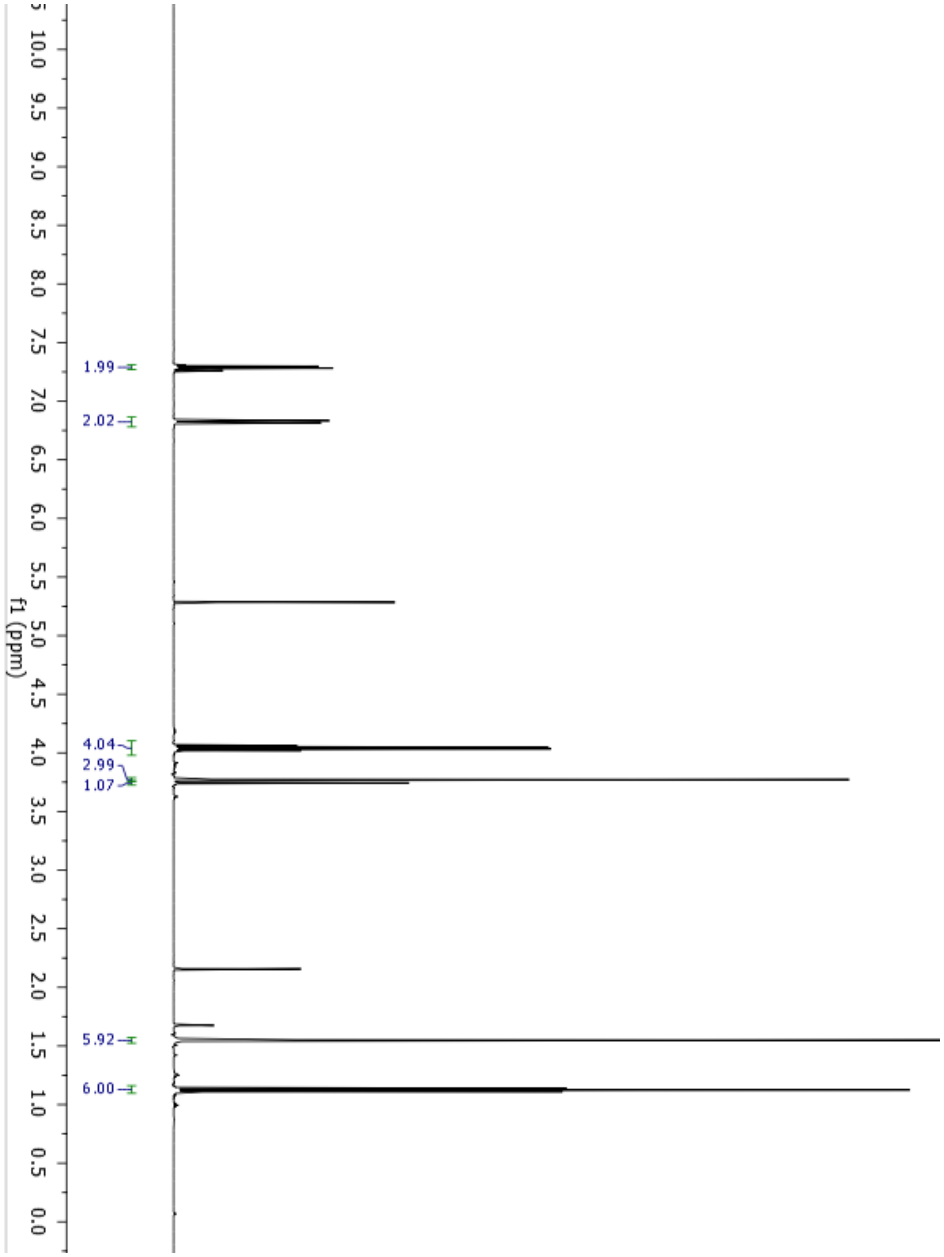
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

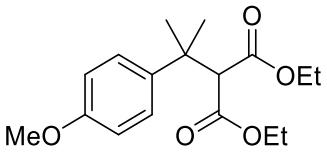




Compound 3-63

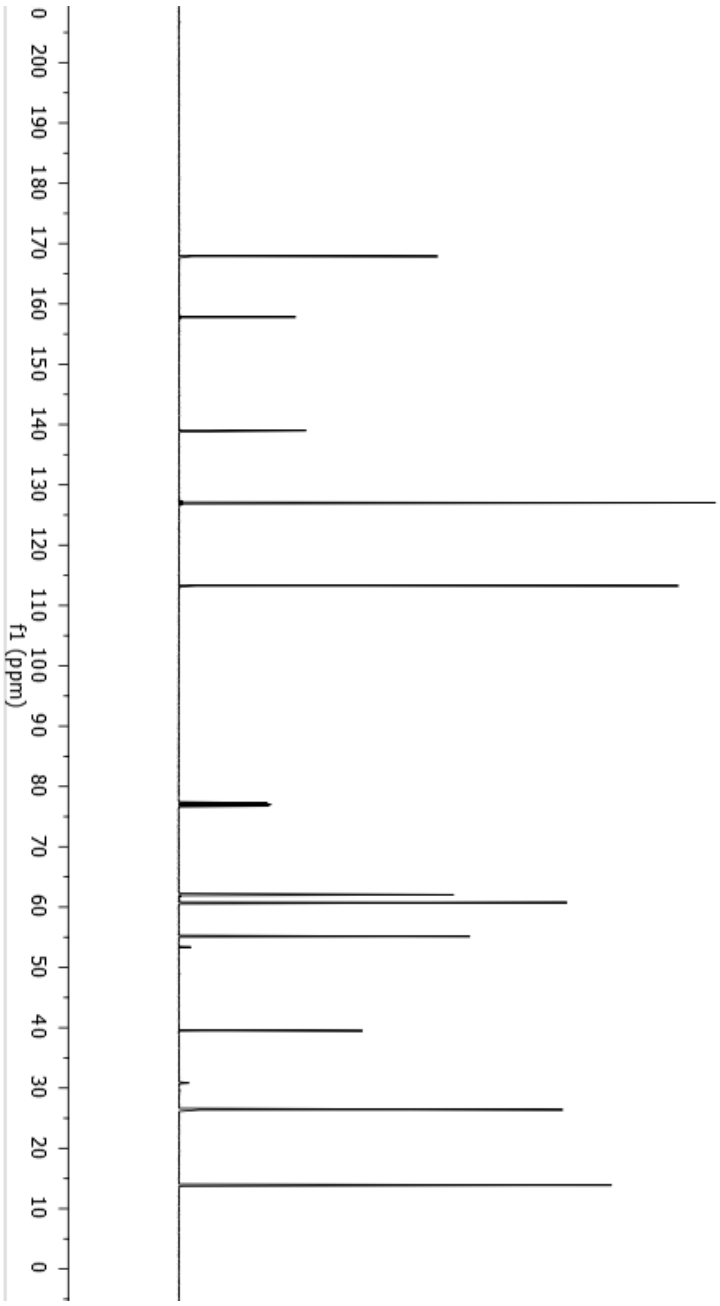
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

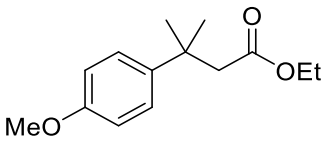




Compound 3-63

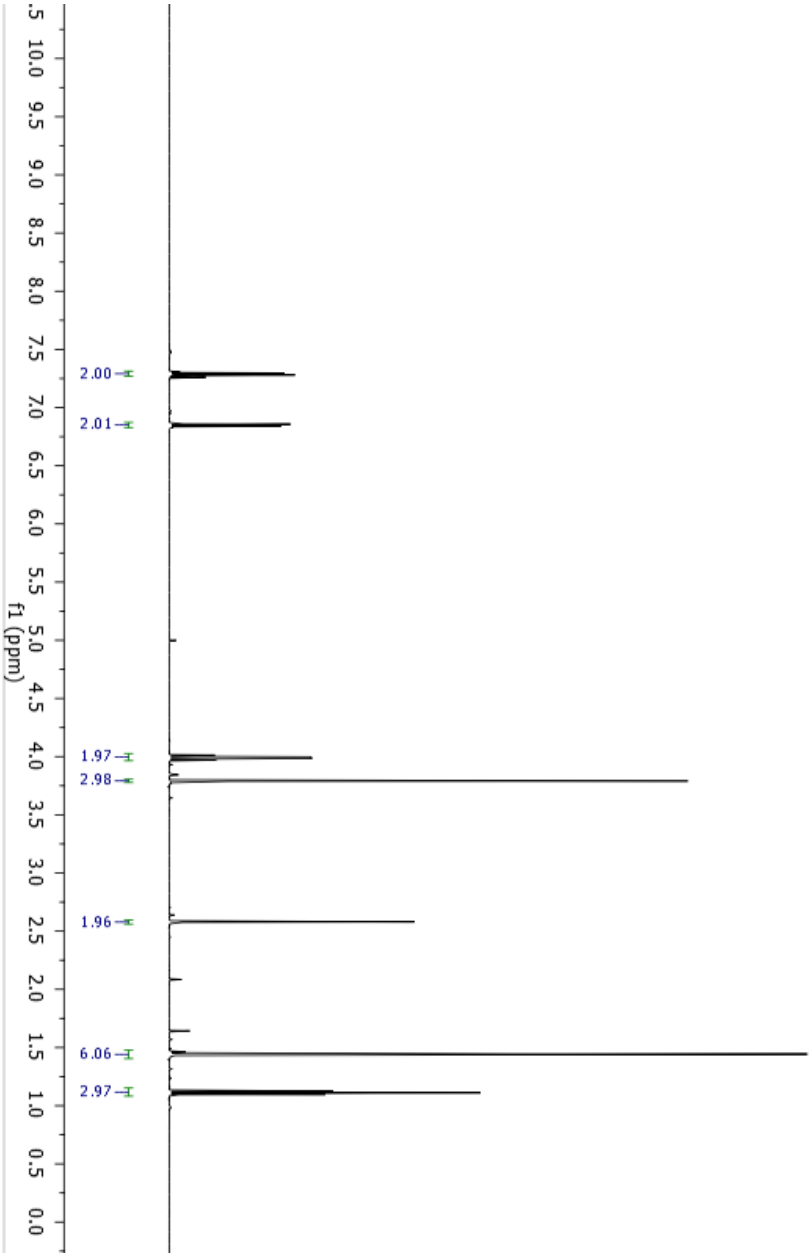
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

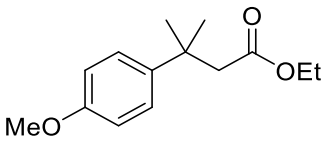




Compound 3-64

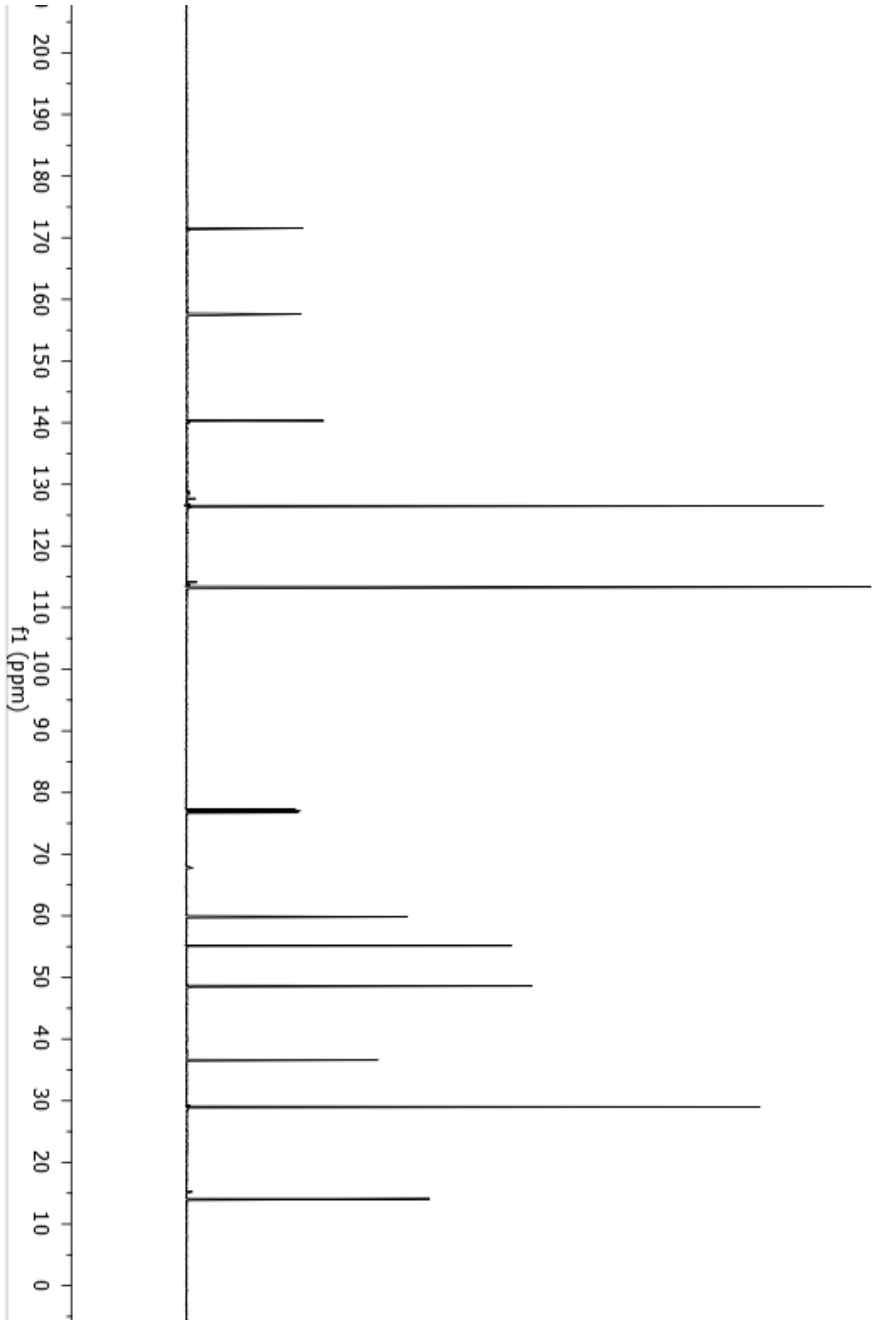
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

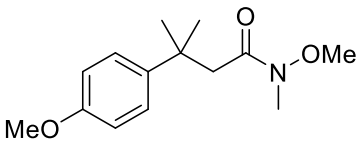




Compound 3-64

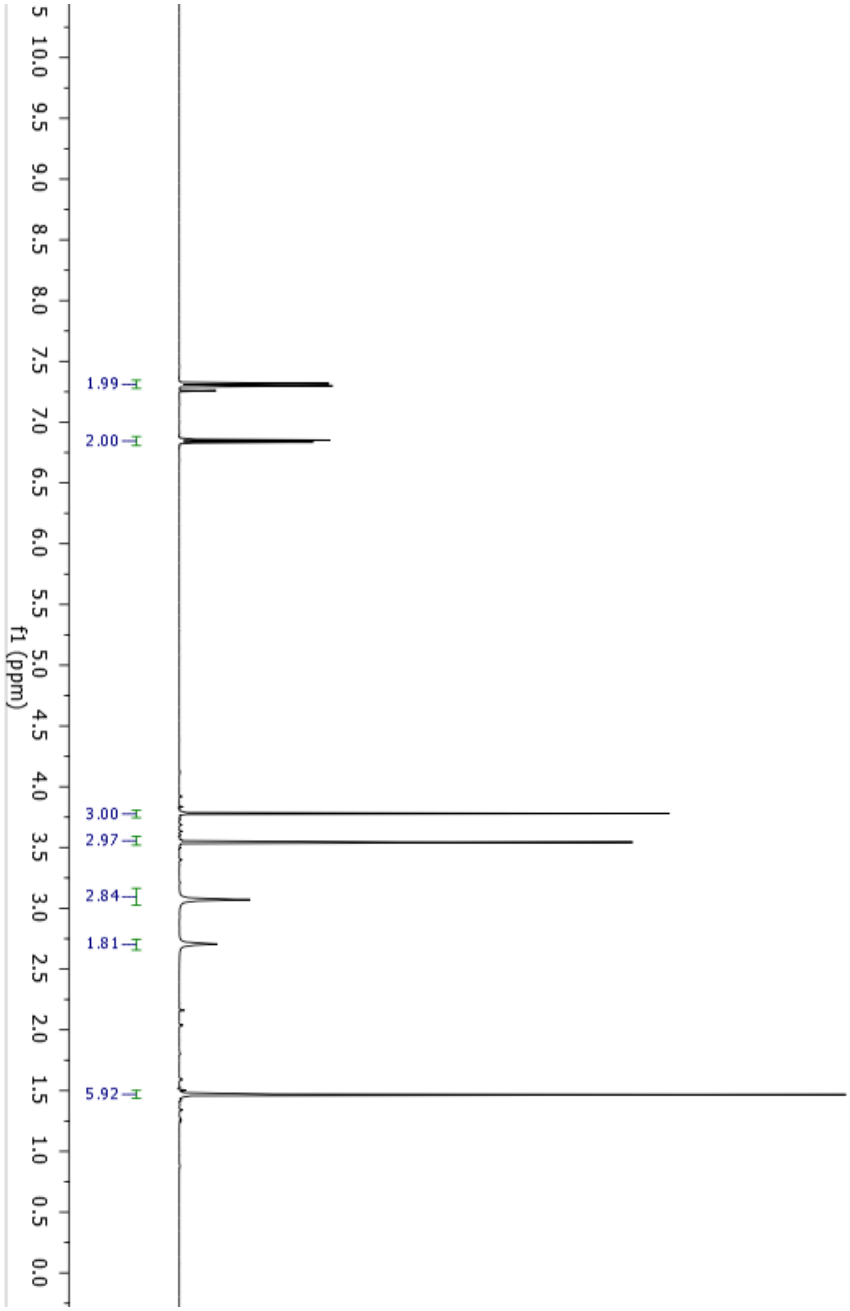
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

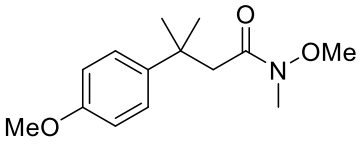




Compound 3-66

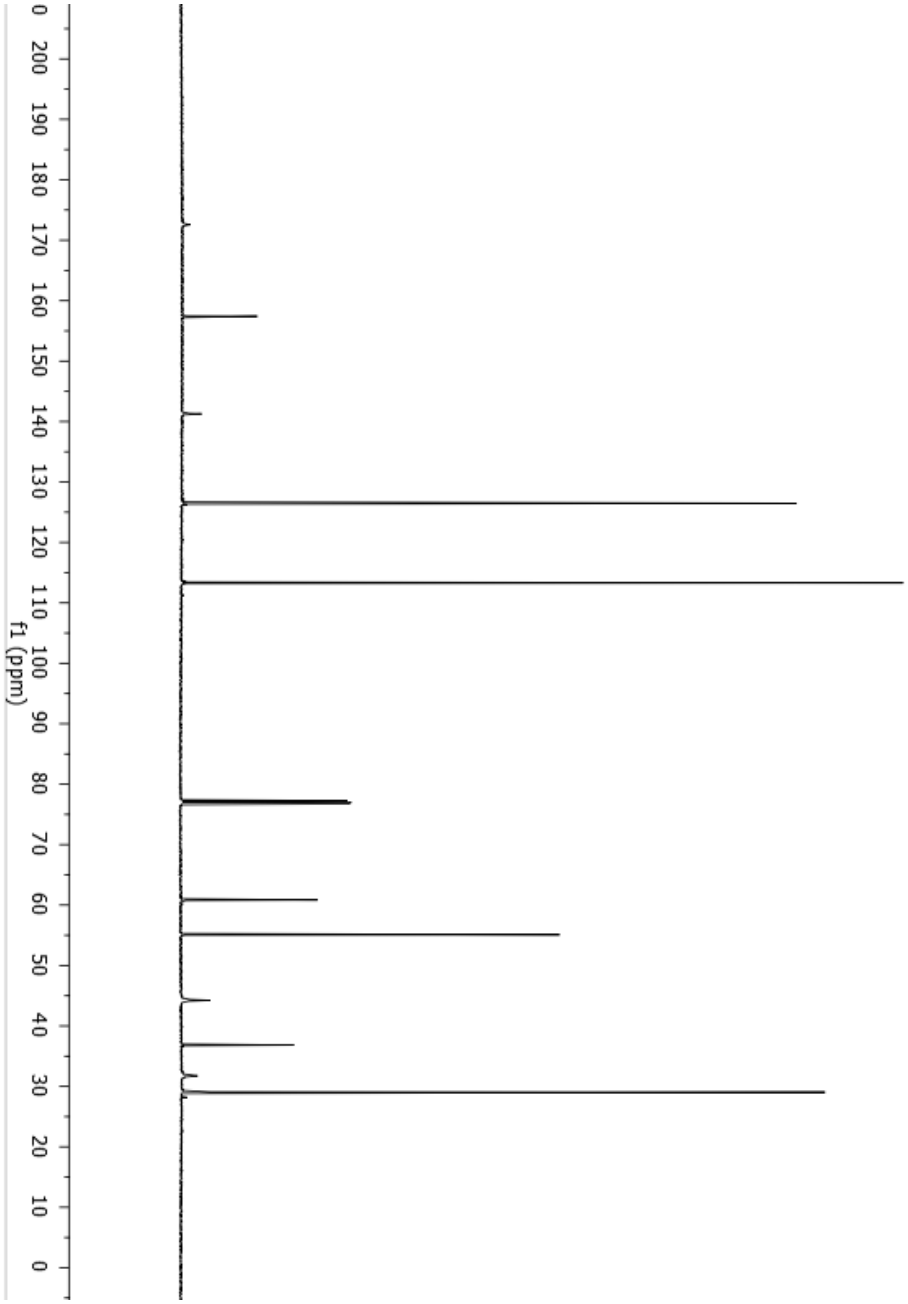
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

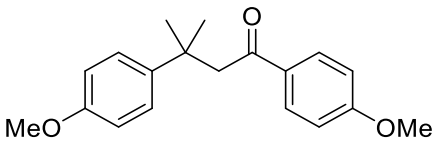




Compound 3-66

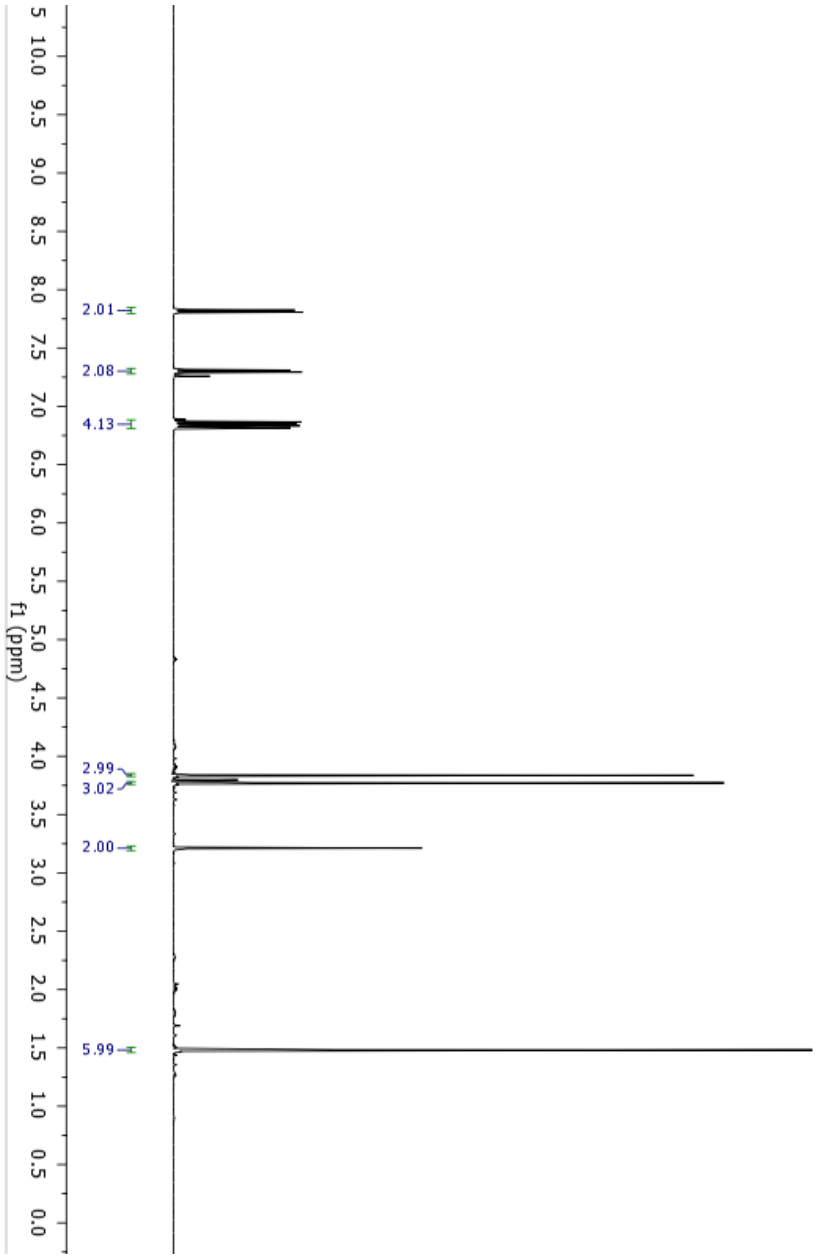
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

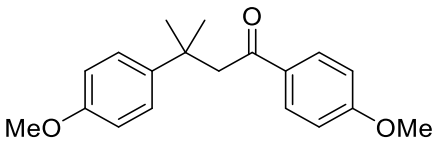




Compound 3-67

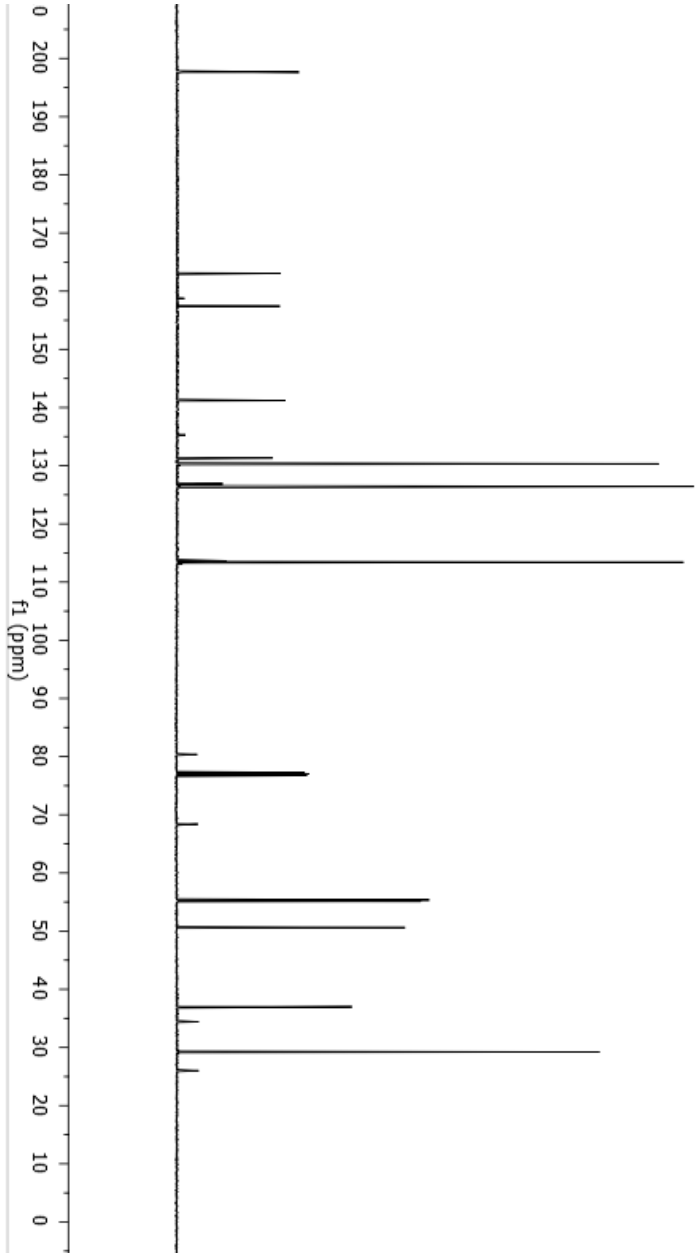
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

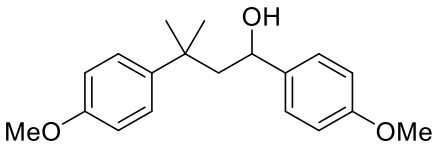




Compound 3-67

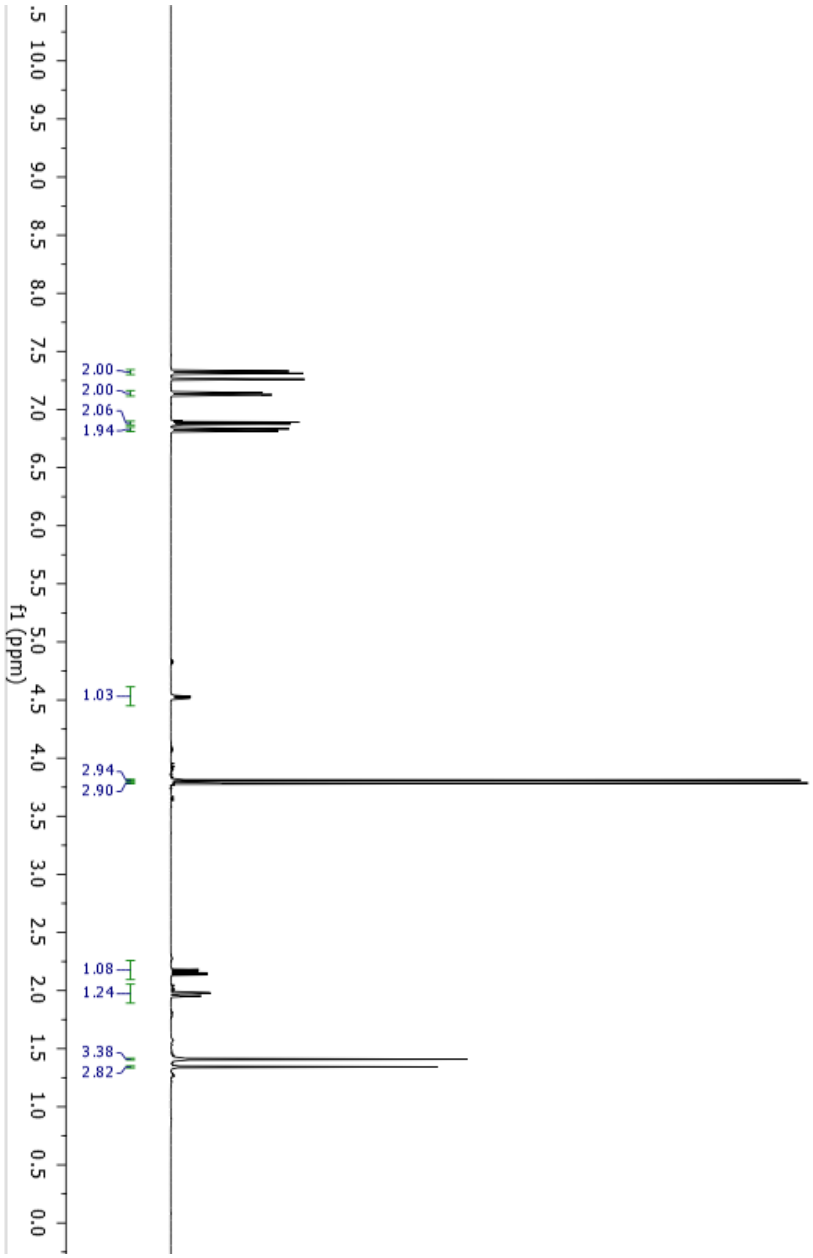
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

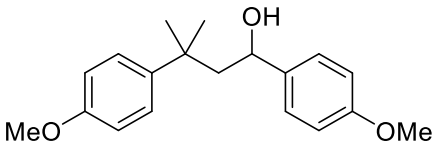




Compound 3-68

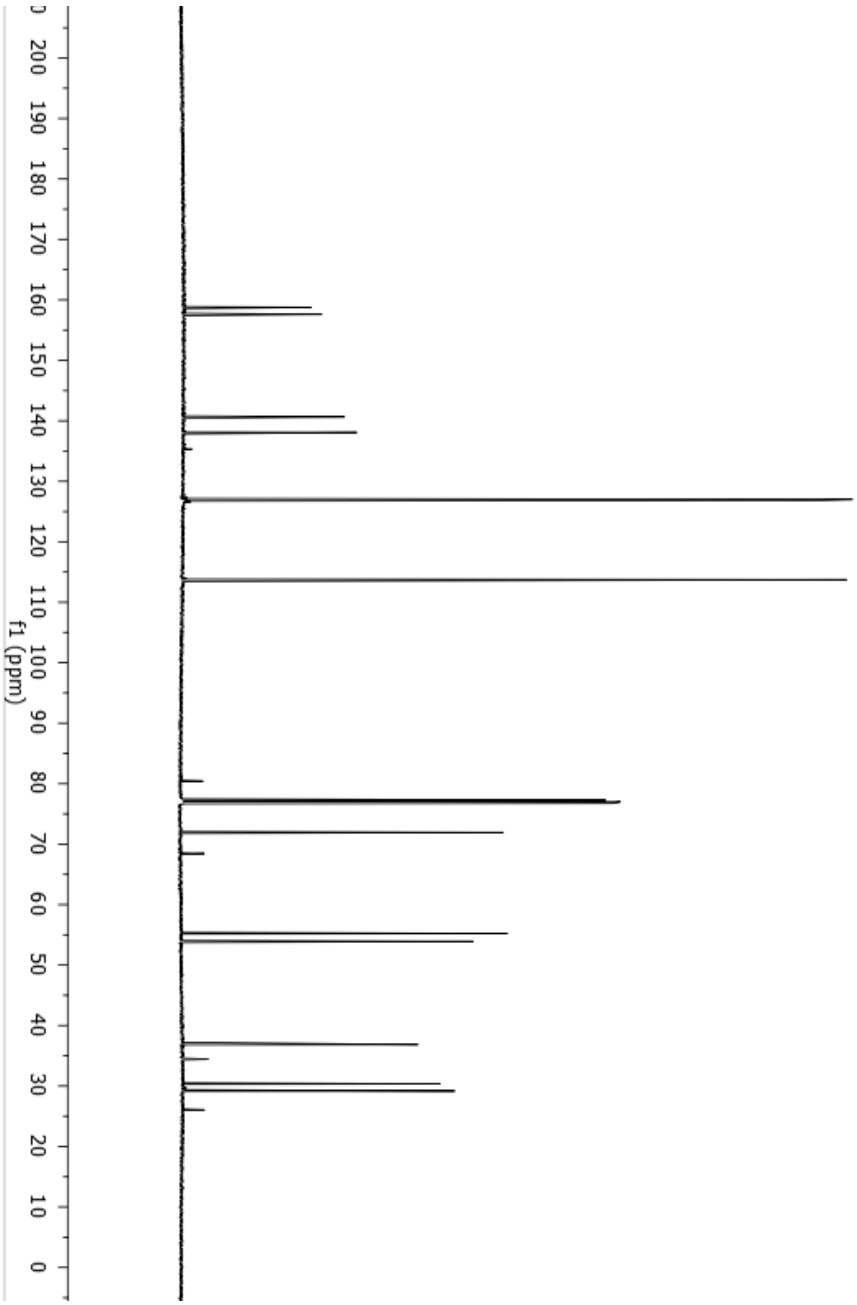
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

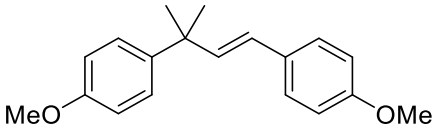




Compound 3-68

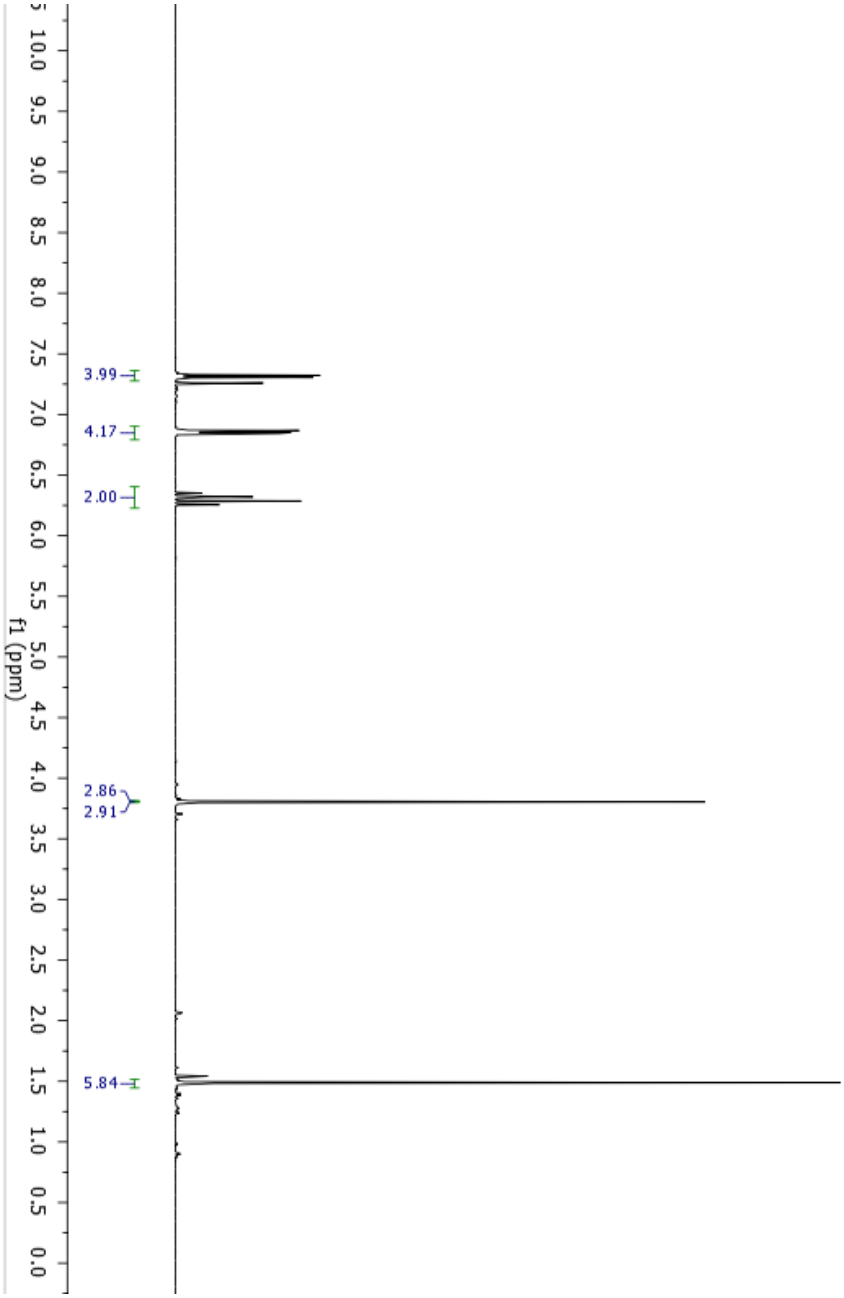
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

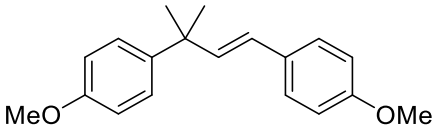




Compound 3-69

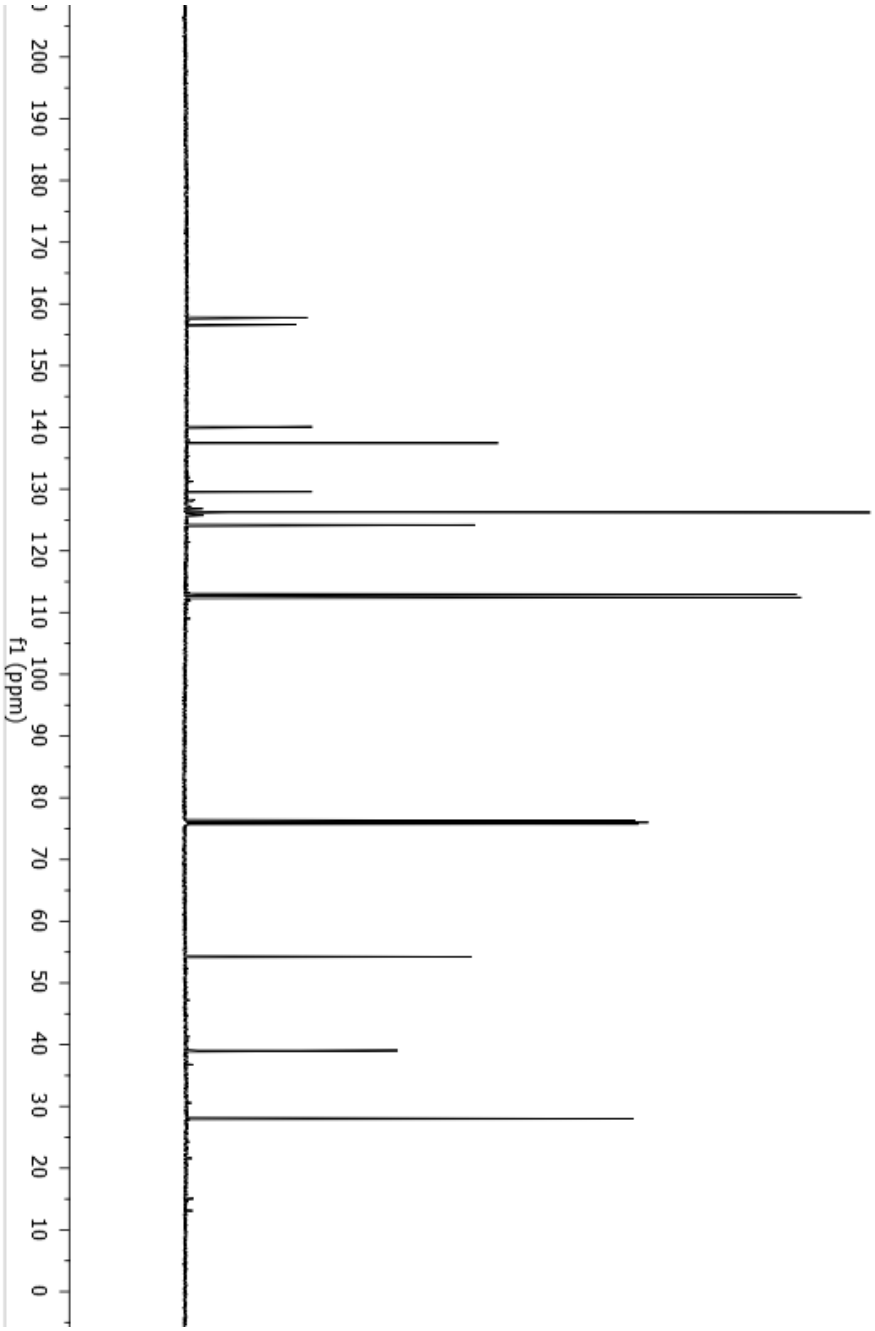
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

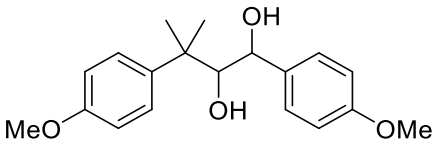




Compound 3-69

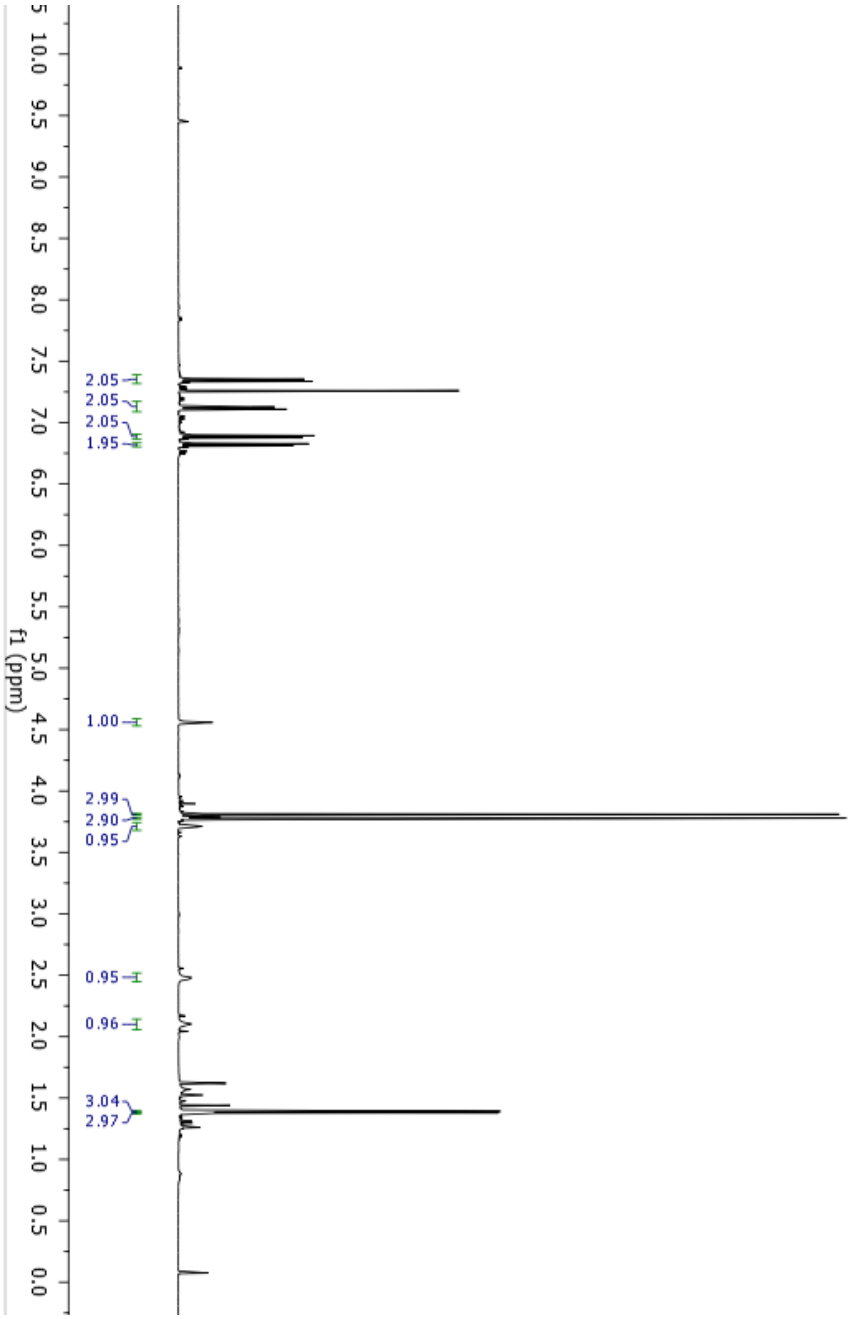
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

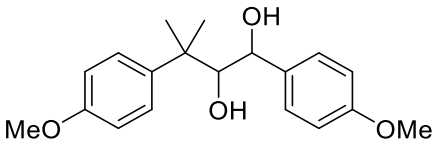




Compound 3-70

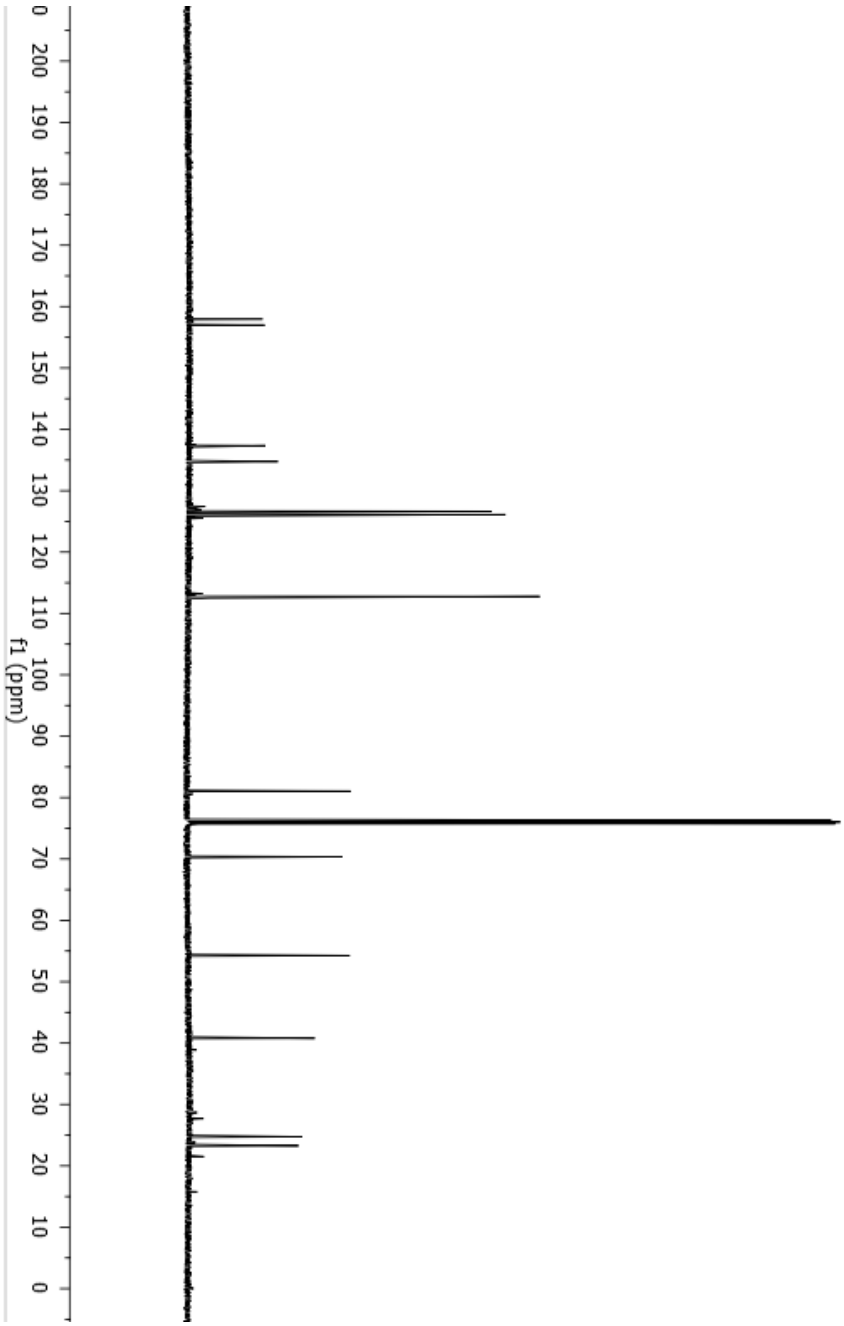
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

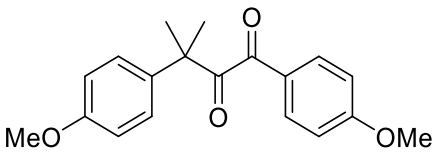




Compound 3-70

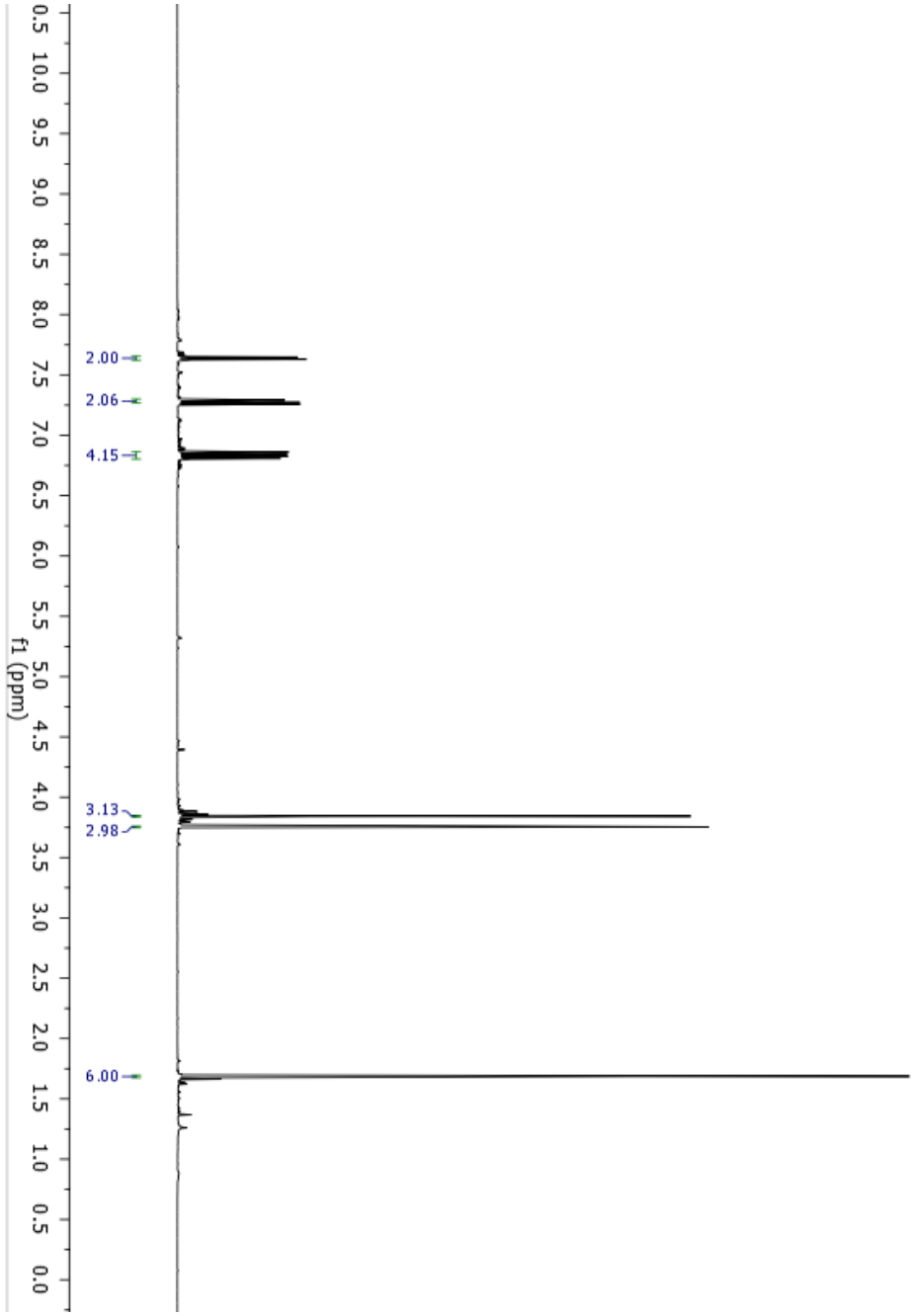
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

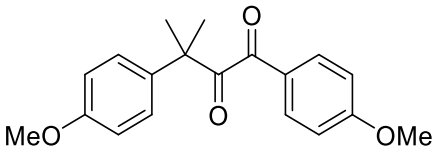




Compound 3-61

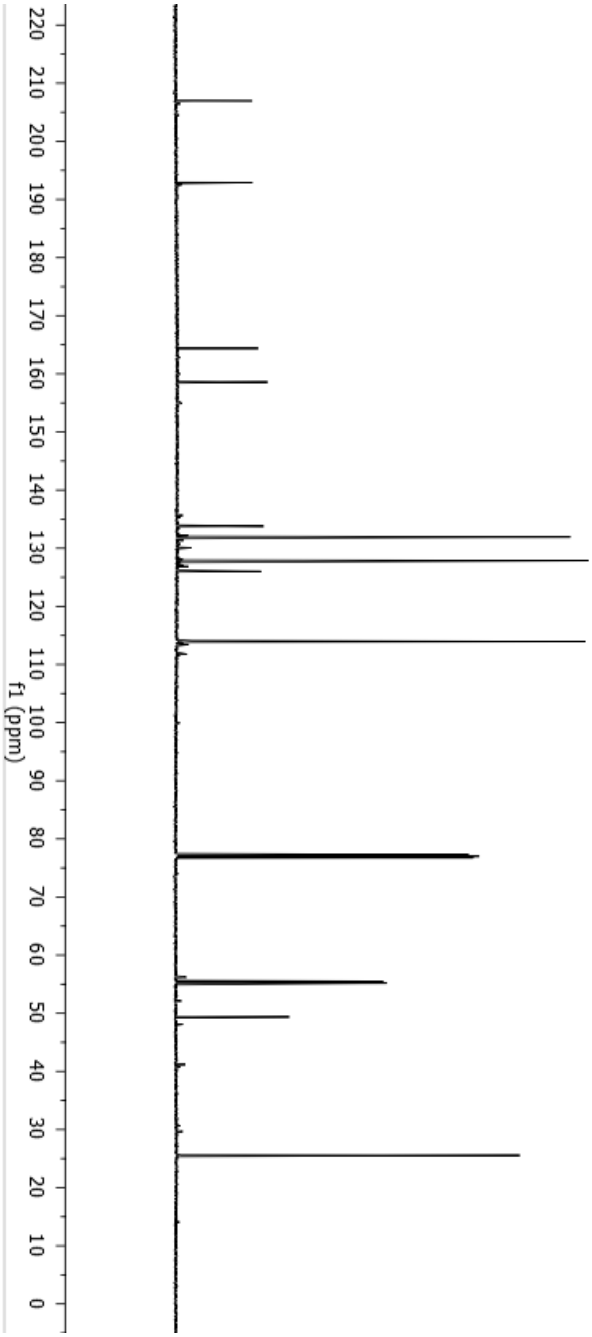
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

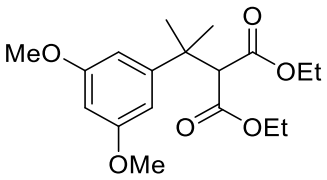




Compound 3-61

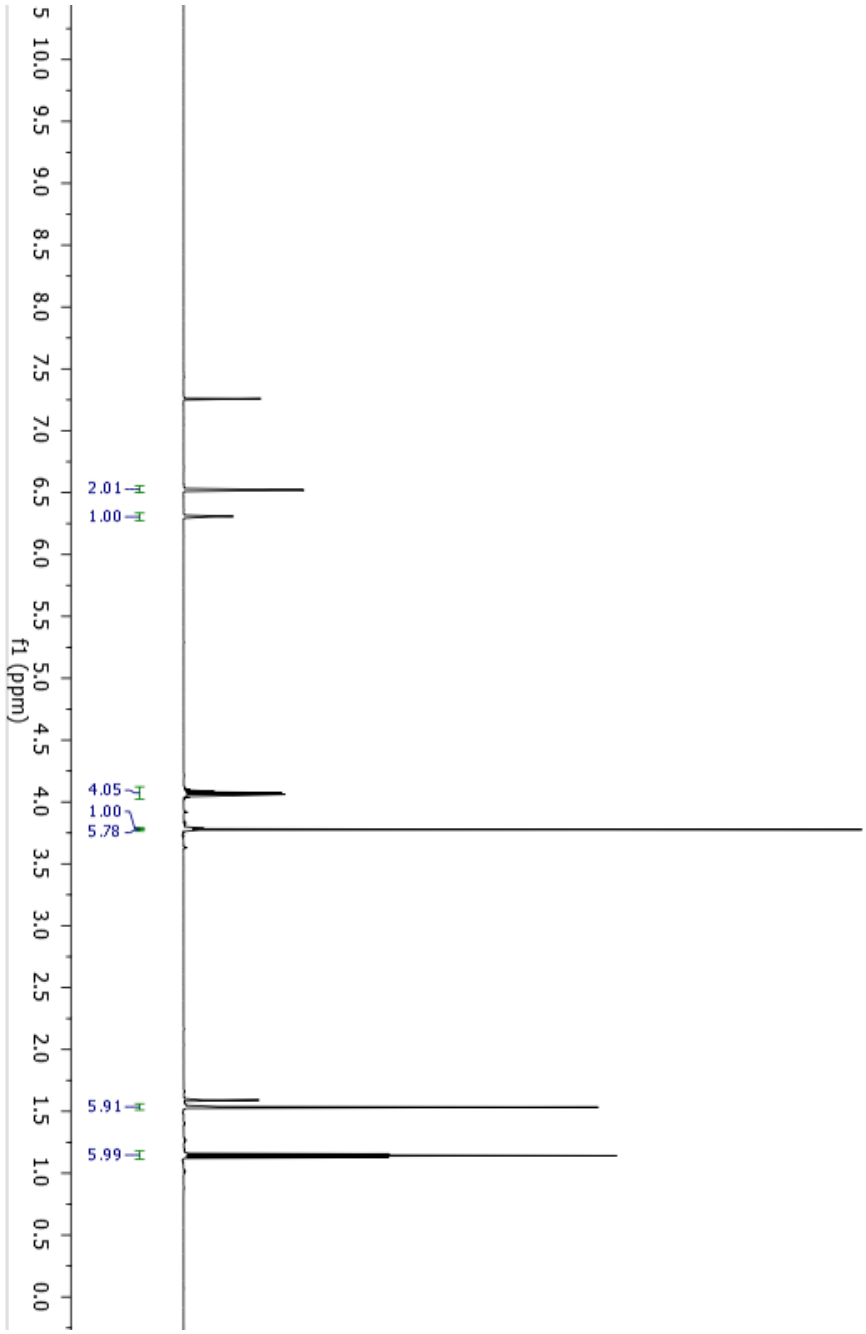
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

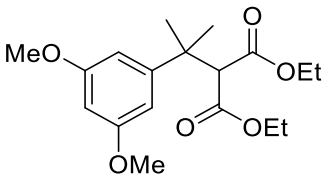




Compound 3-73

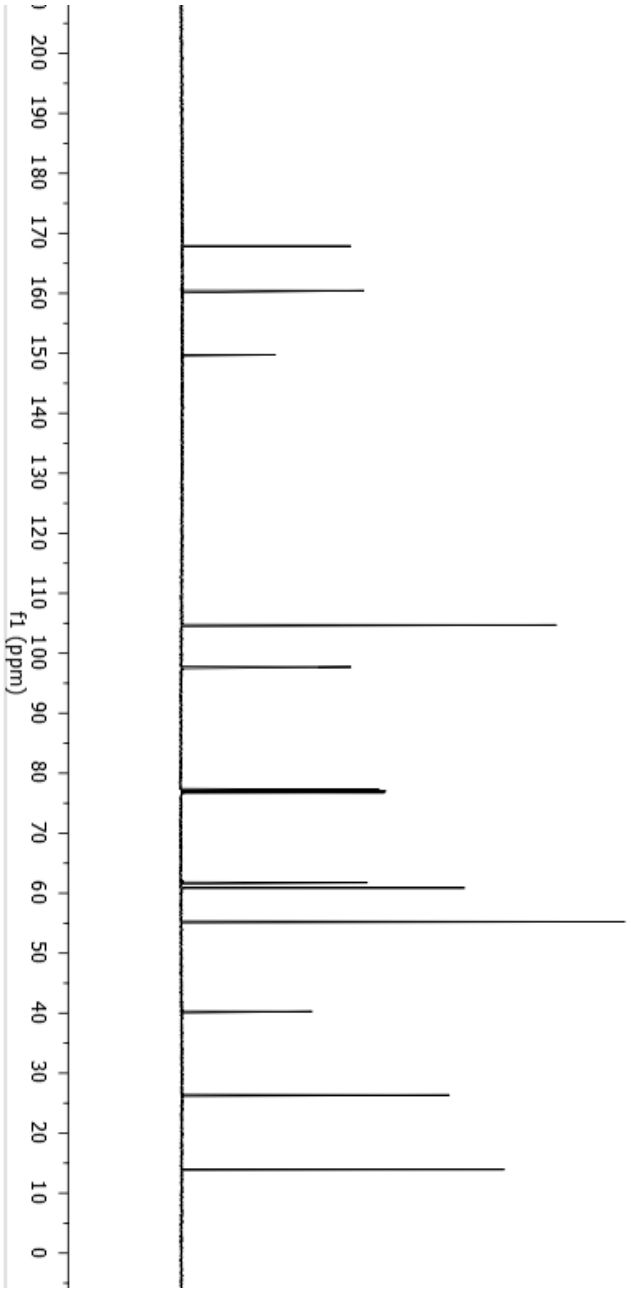
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

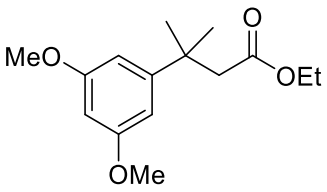




Compound 3-73

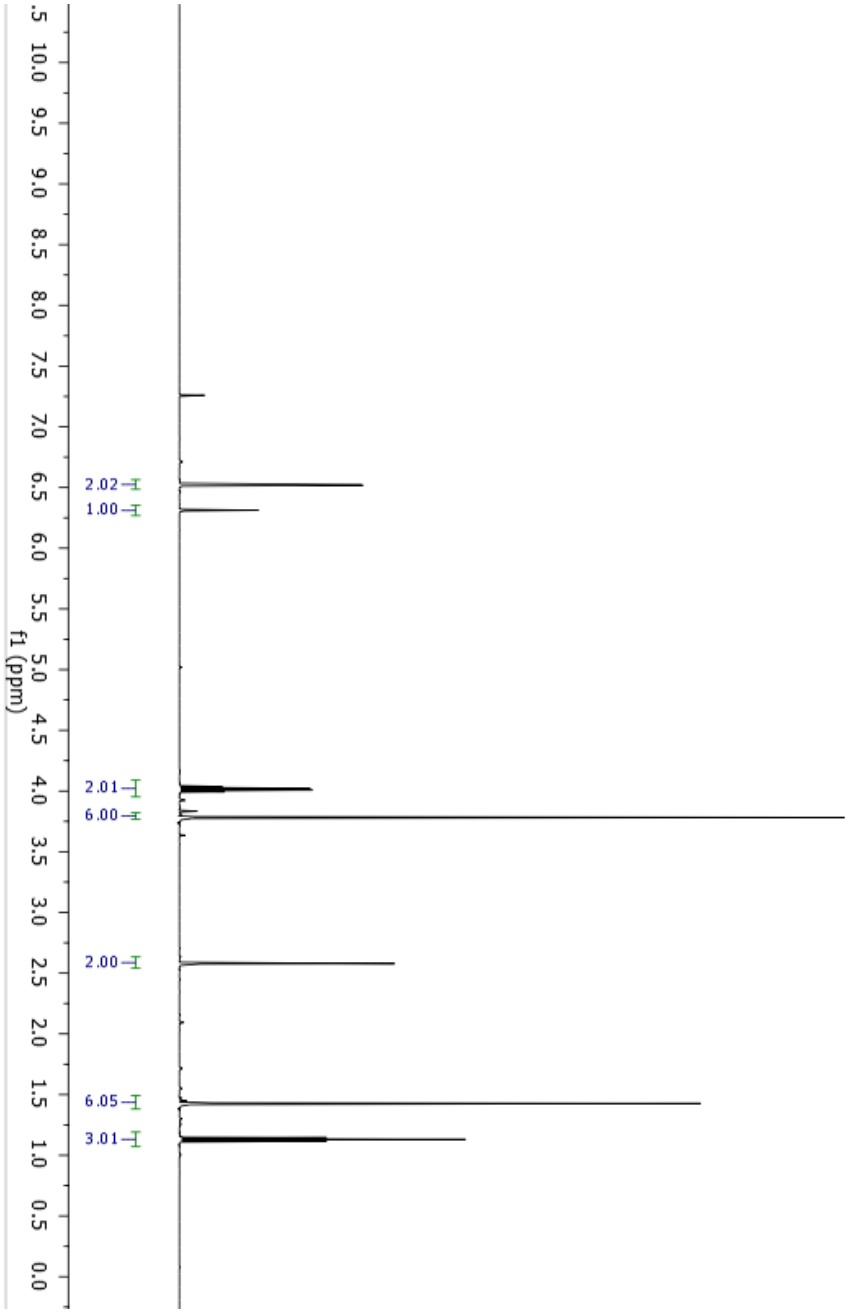
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

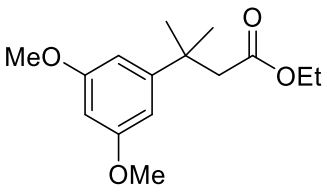




Compound 3-74

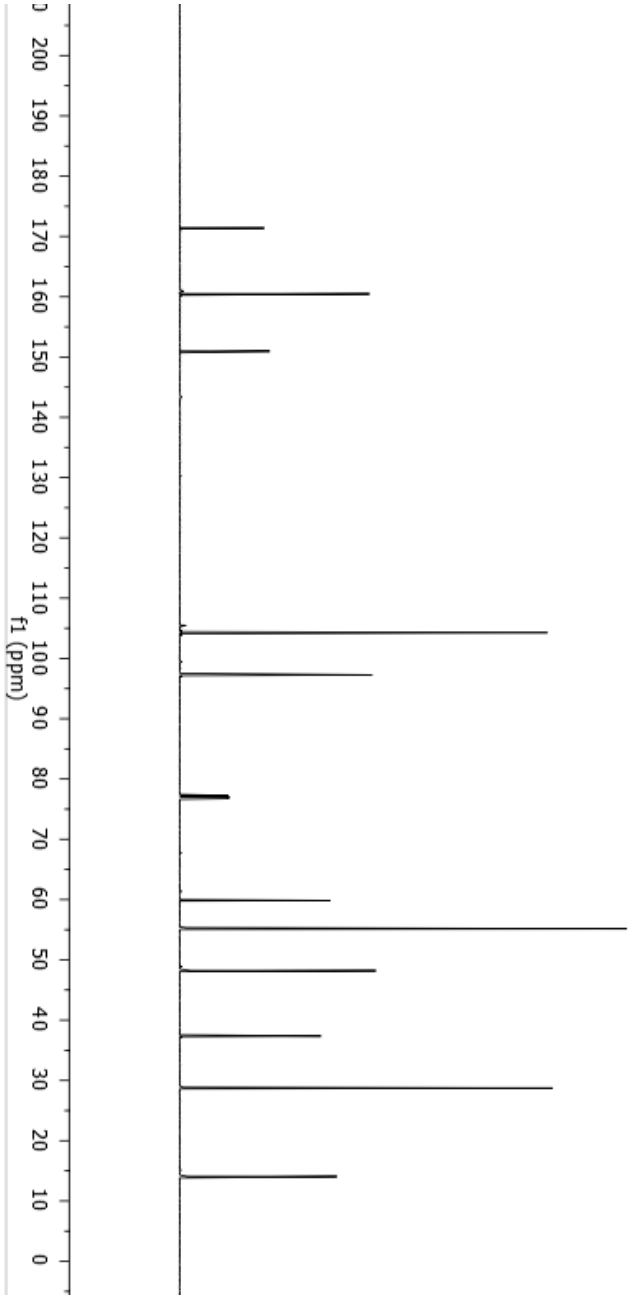
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

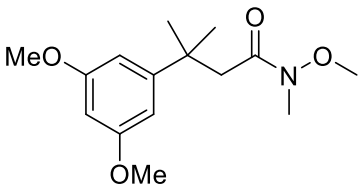




Compound 3-74

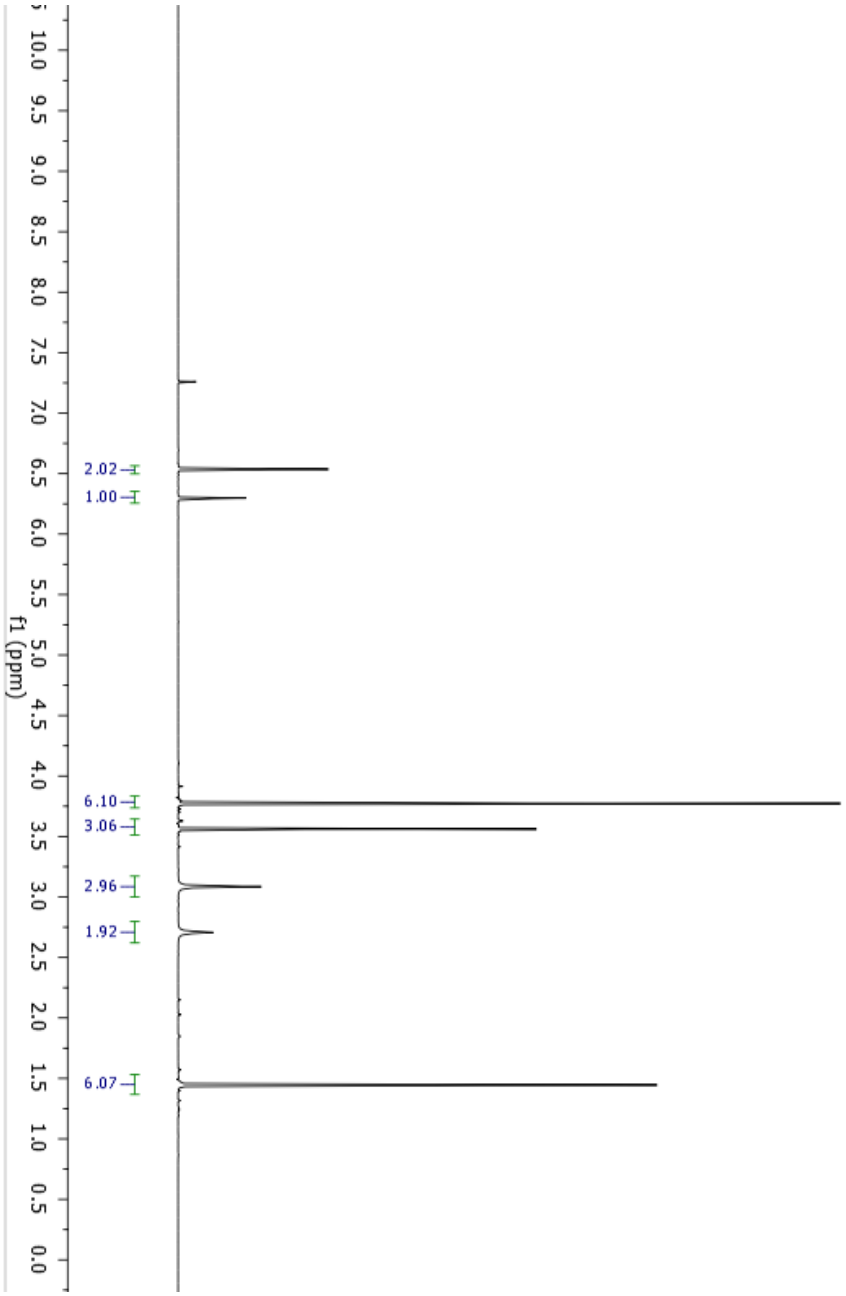
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

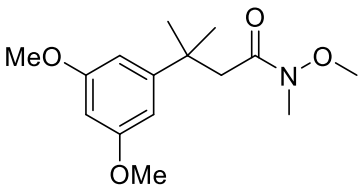




Compound 3-76

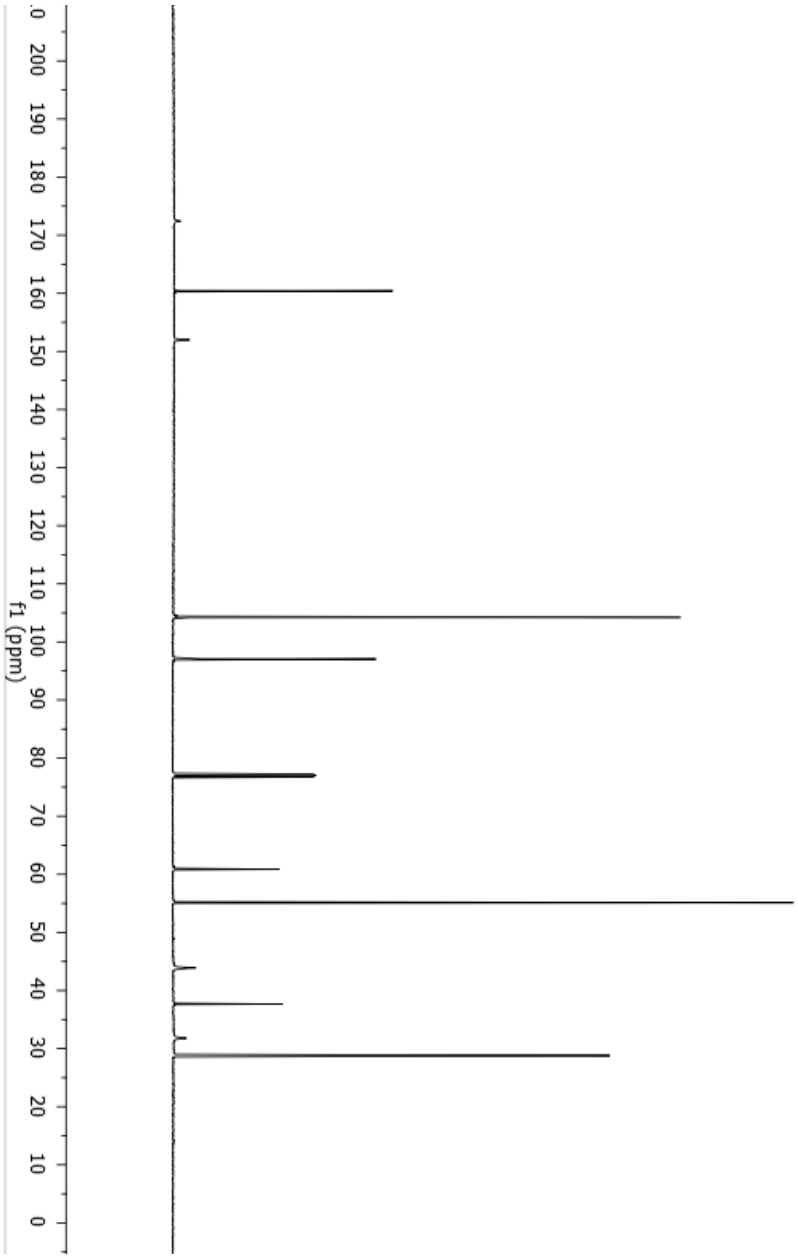
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

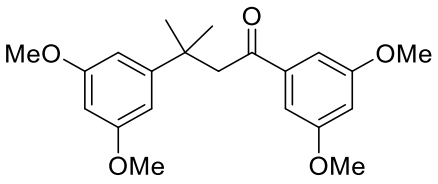




Compound 3-76

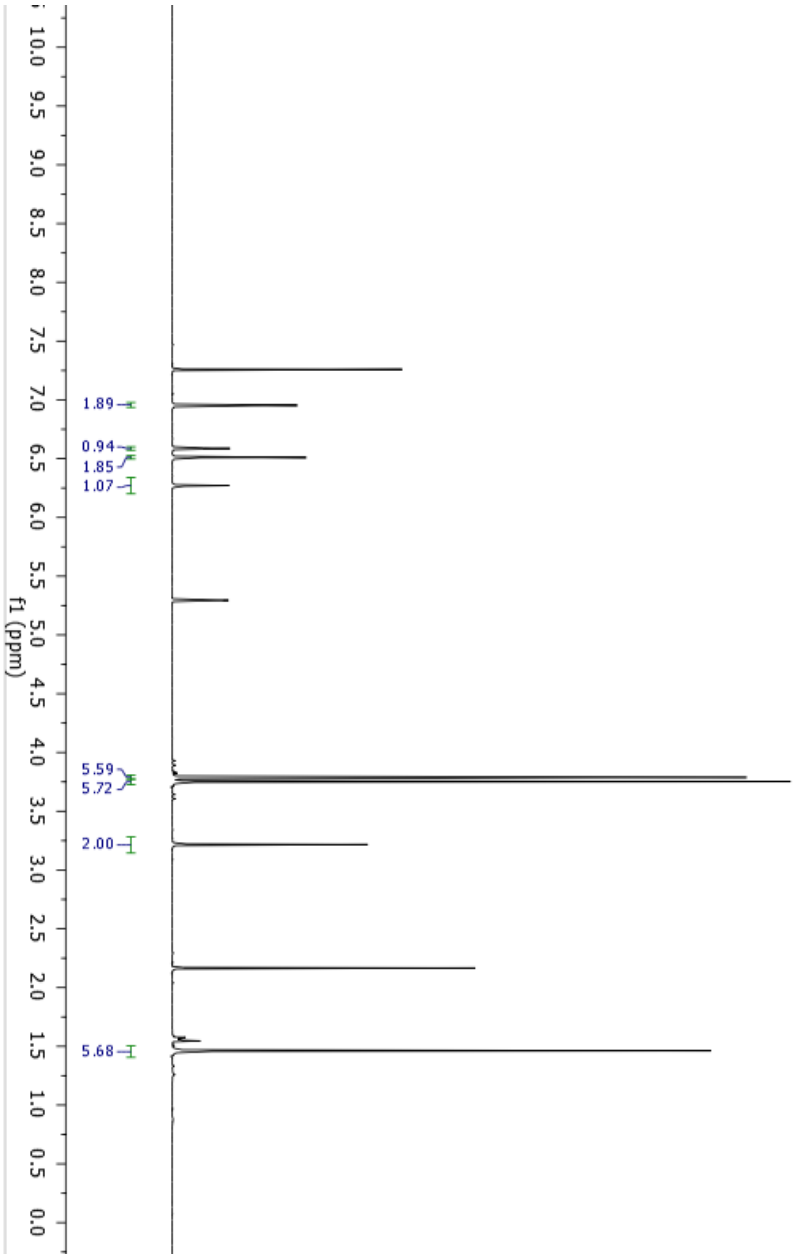
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

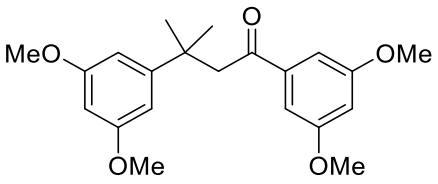




Compound 3-77

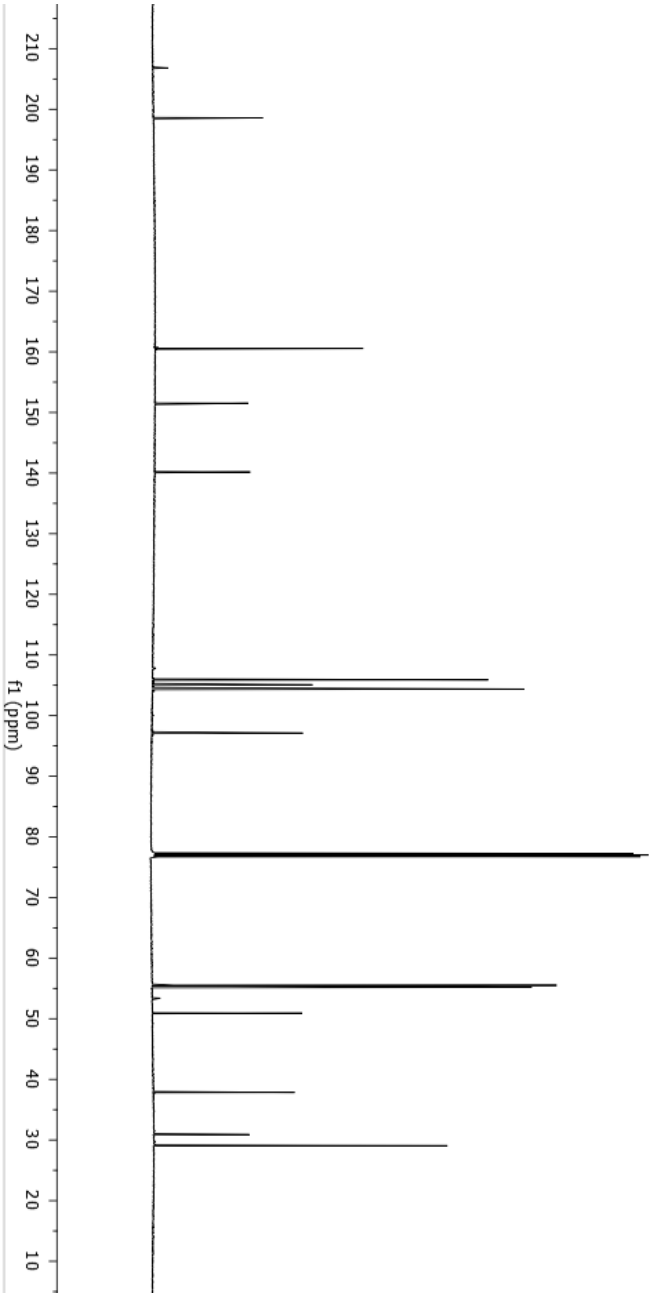
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

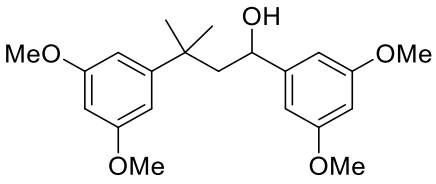




Compound 3-77

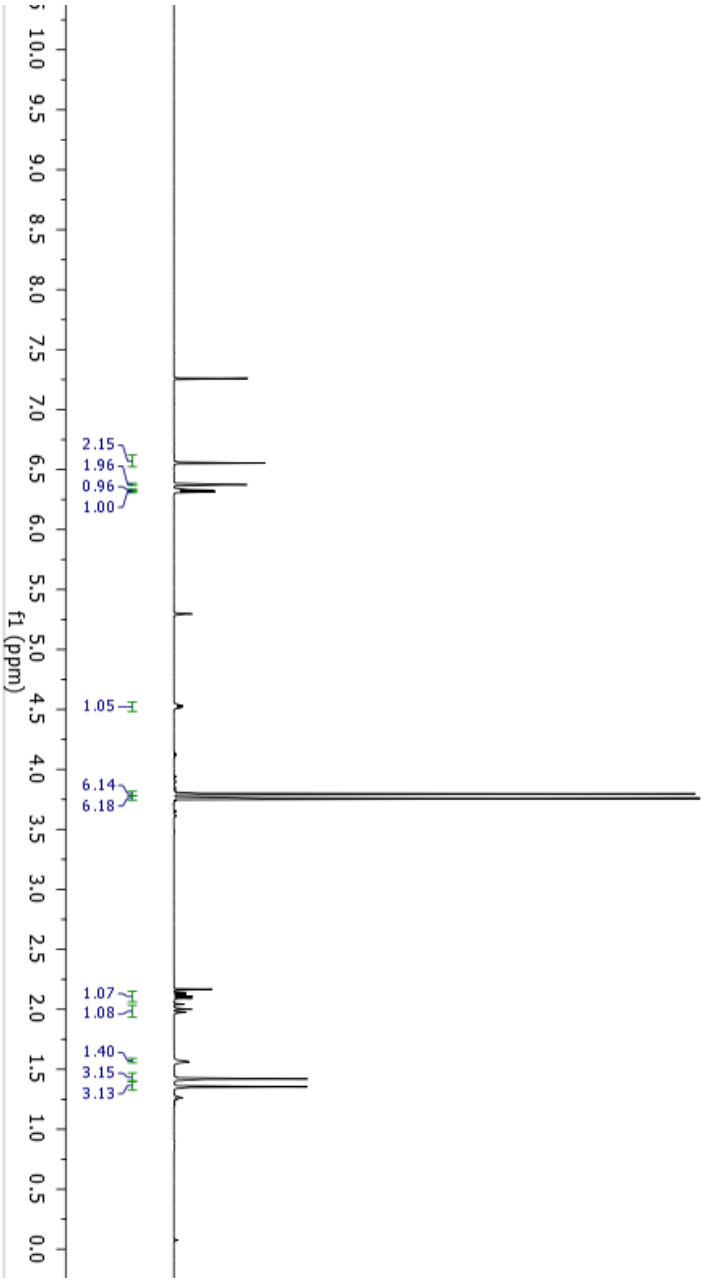
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

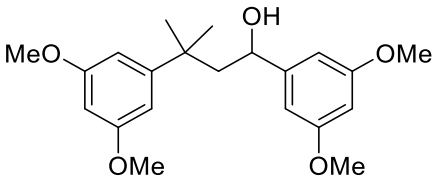




Compound 3-78

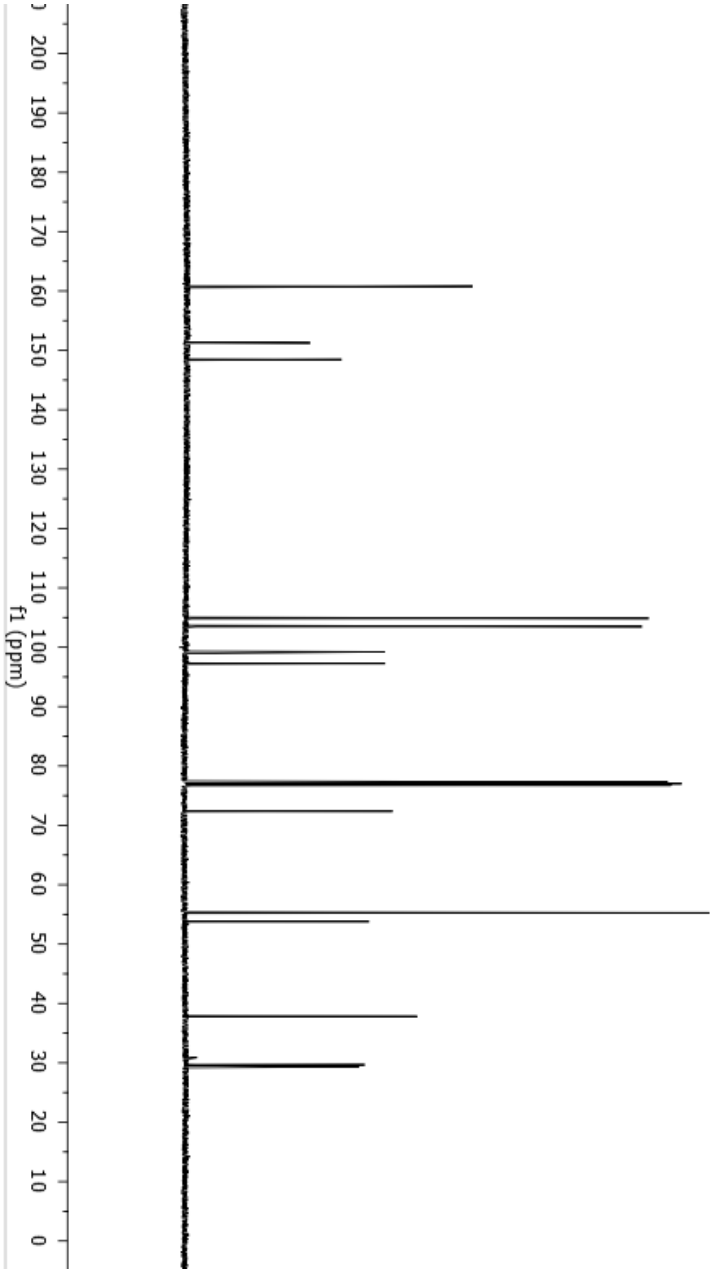
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

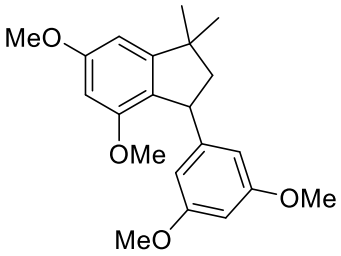




Compound 3-78

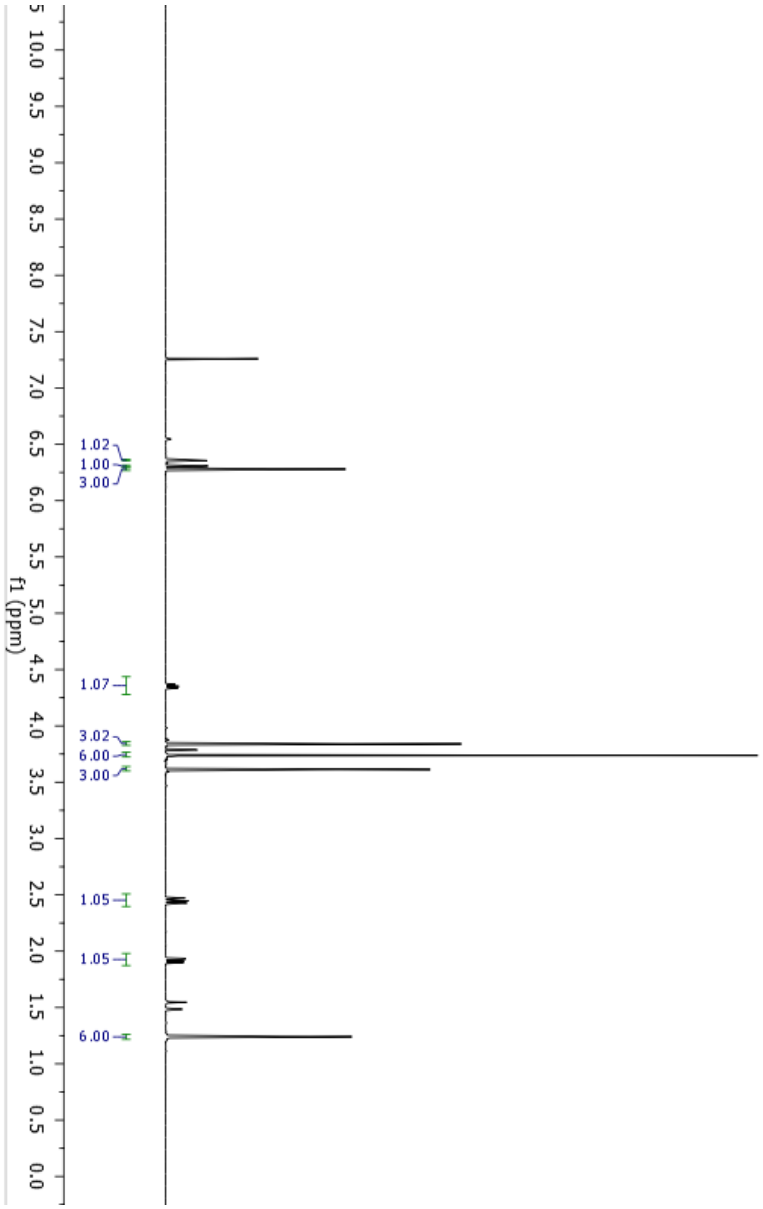
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

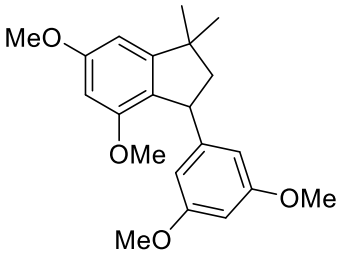




Compound 3-80

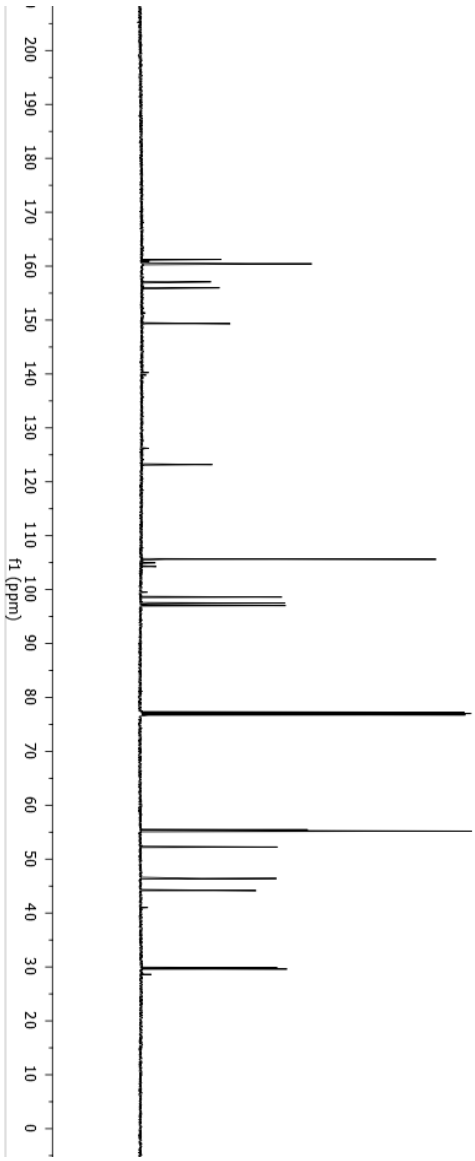
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

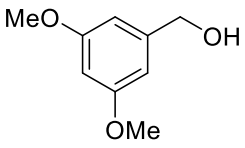




Compound 3-80

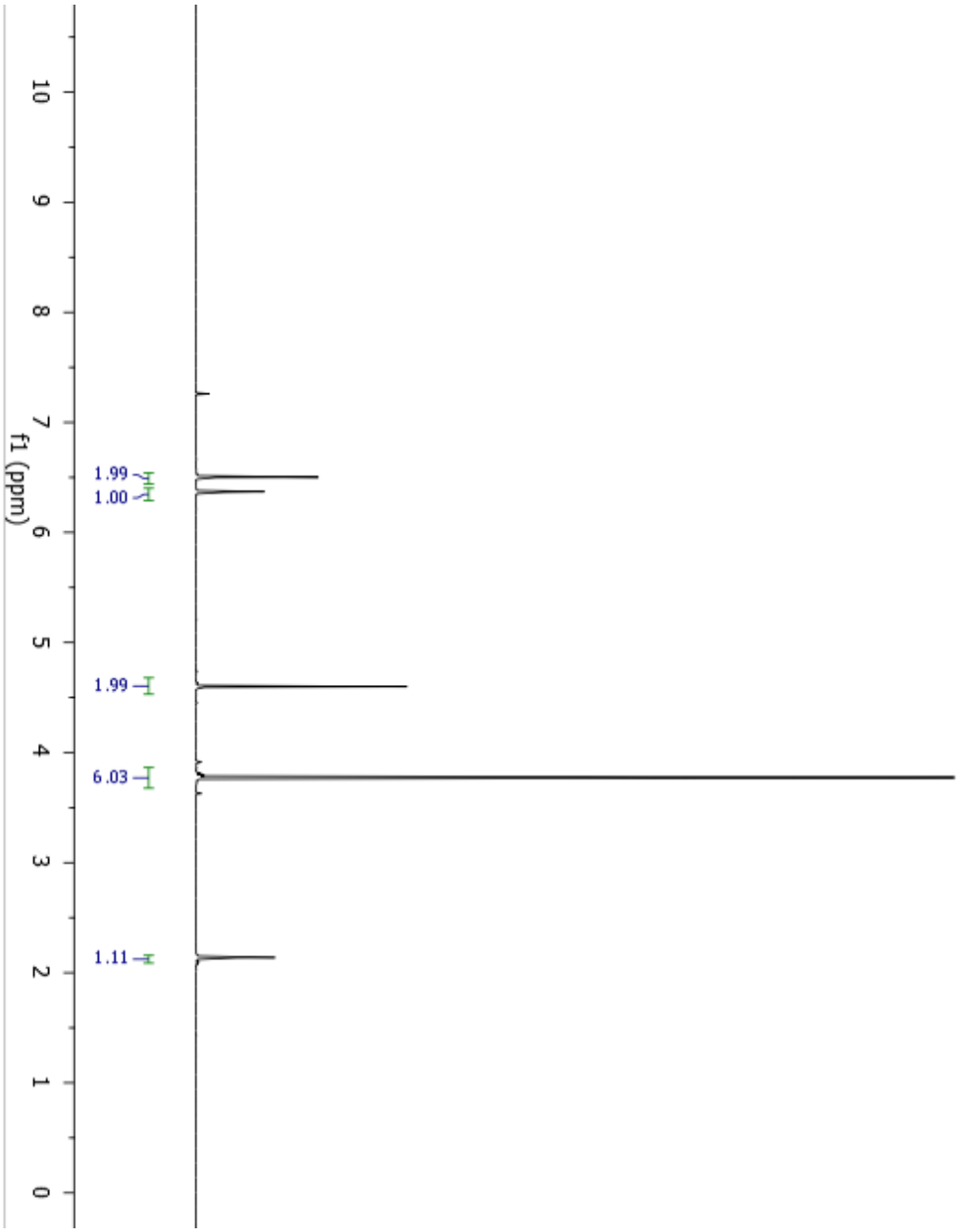
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

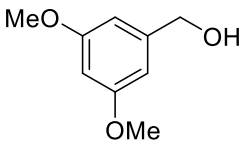




Compound 3-92

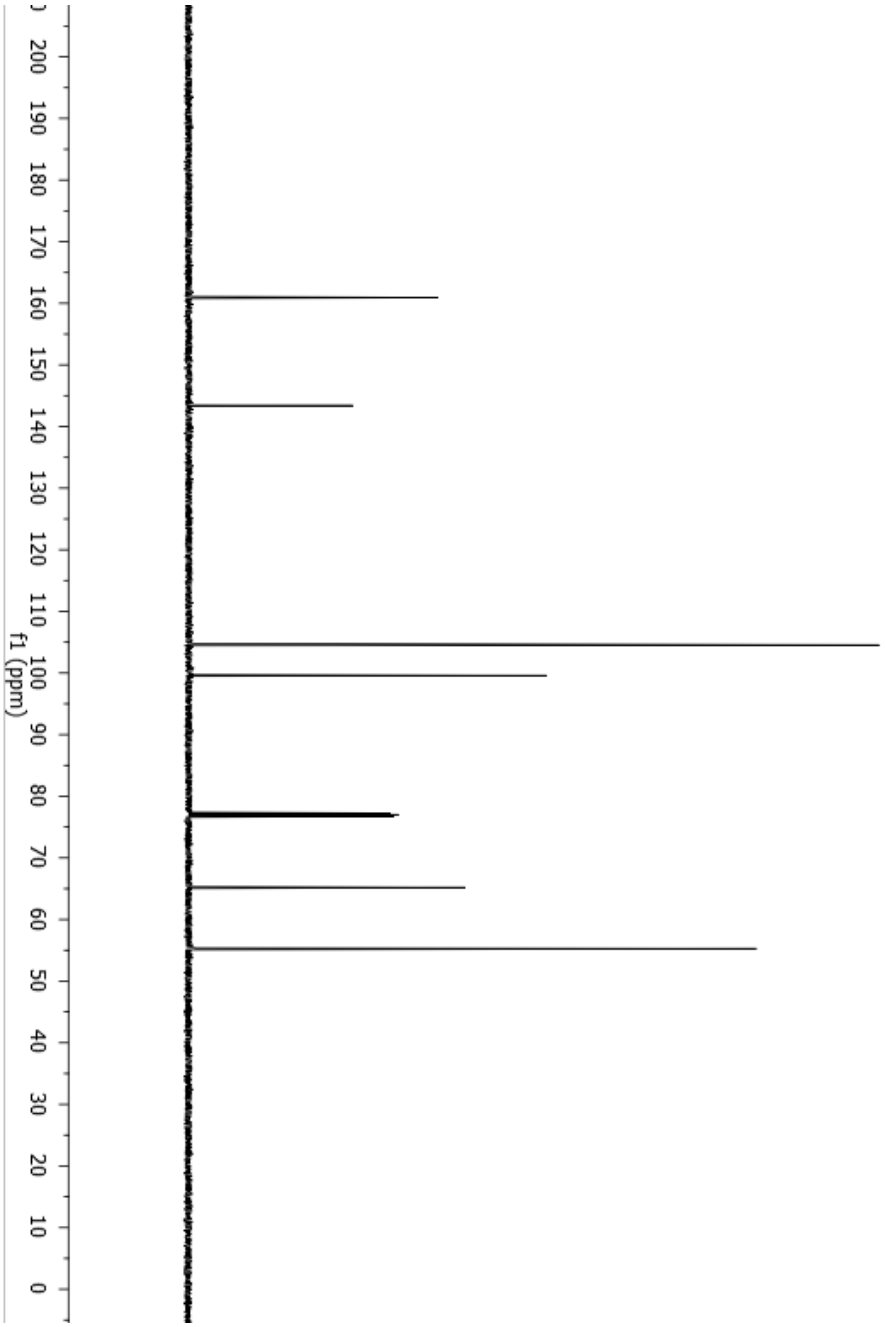
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

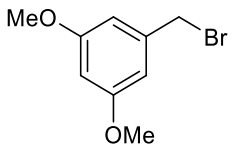




Compound 3-92

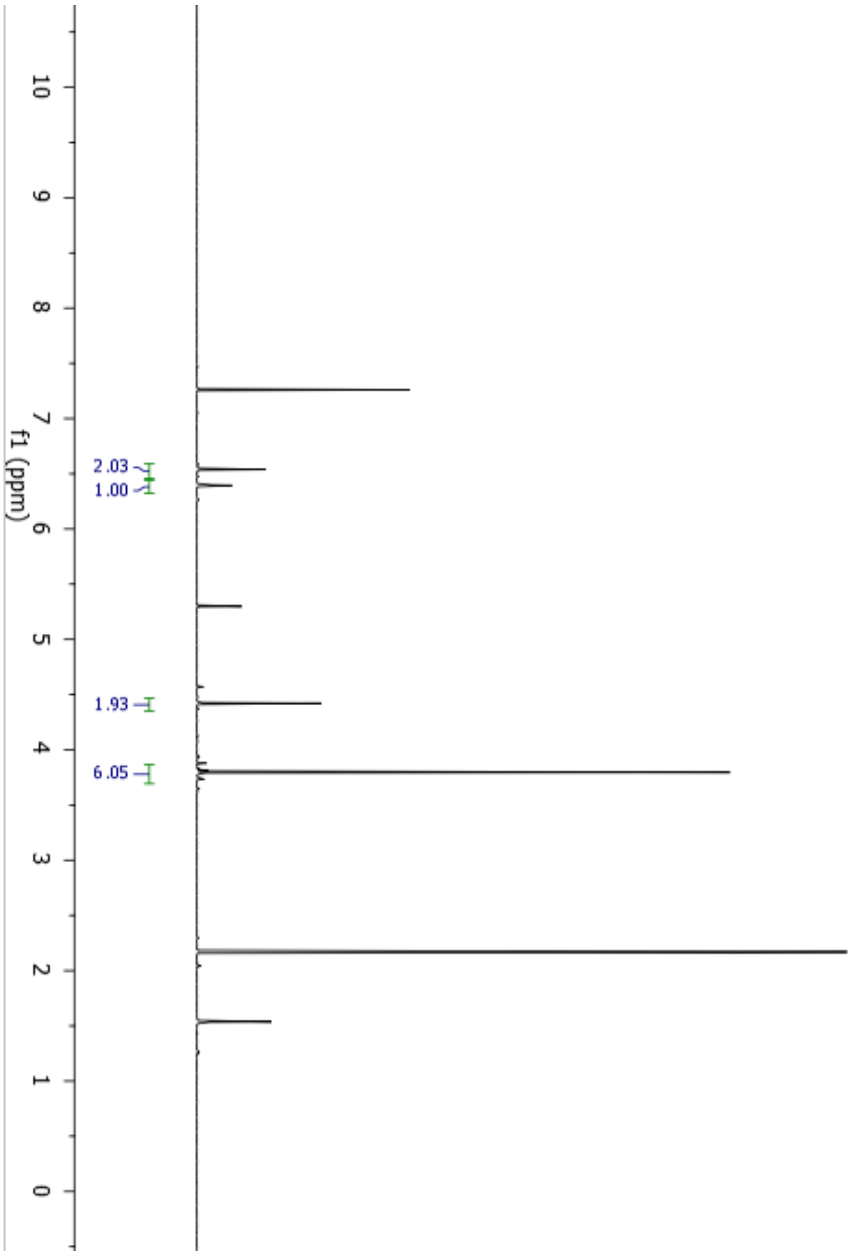
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

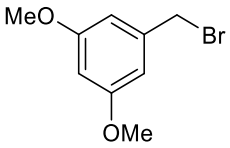




Compound 3-93

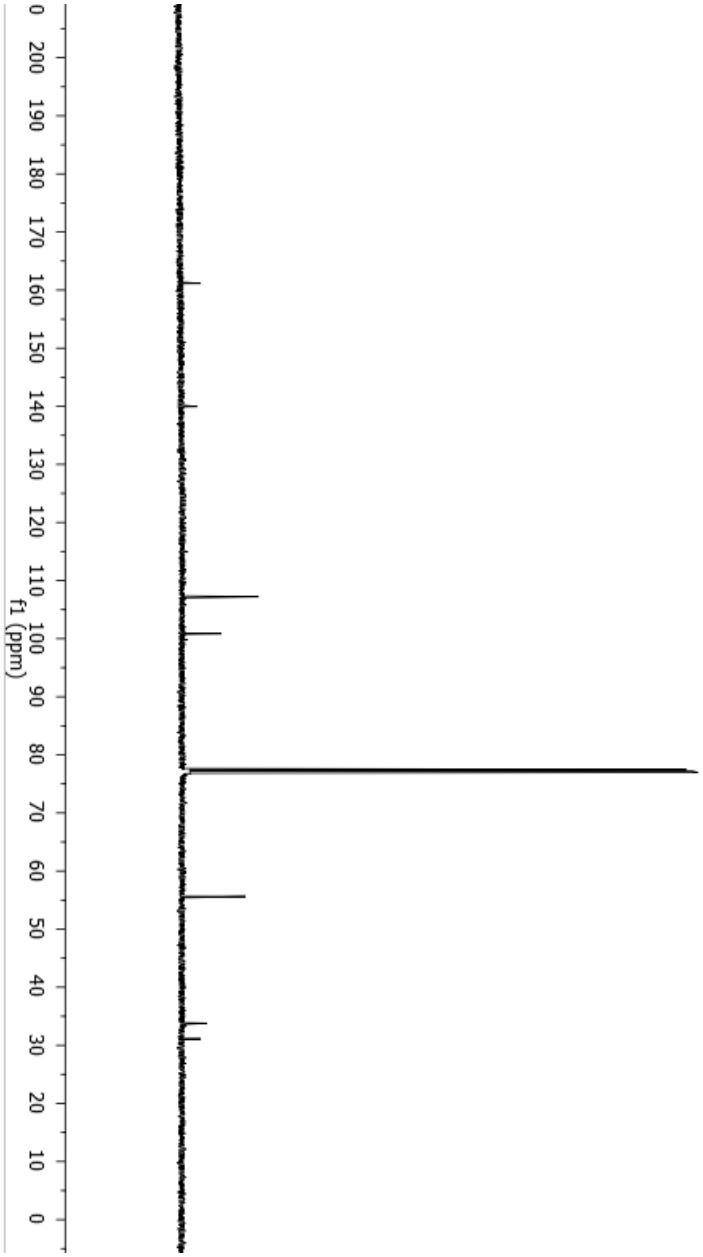
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

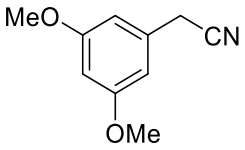




Compound 3-93

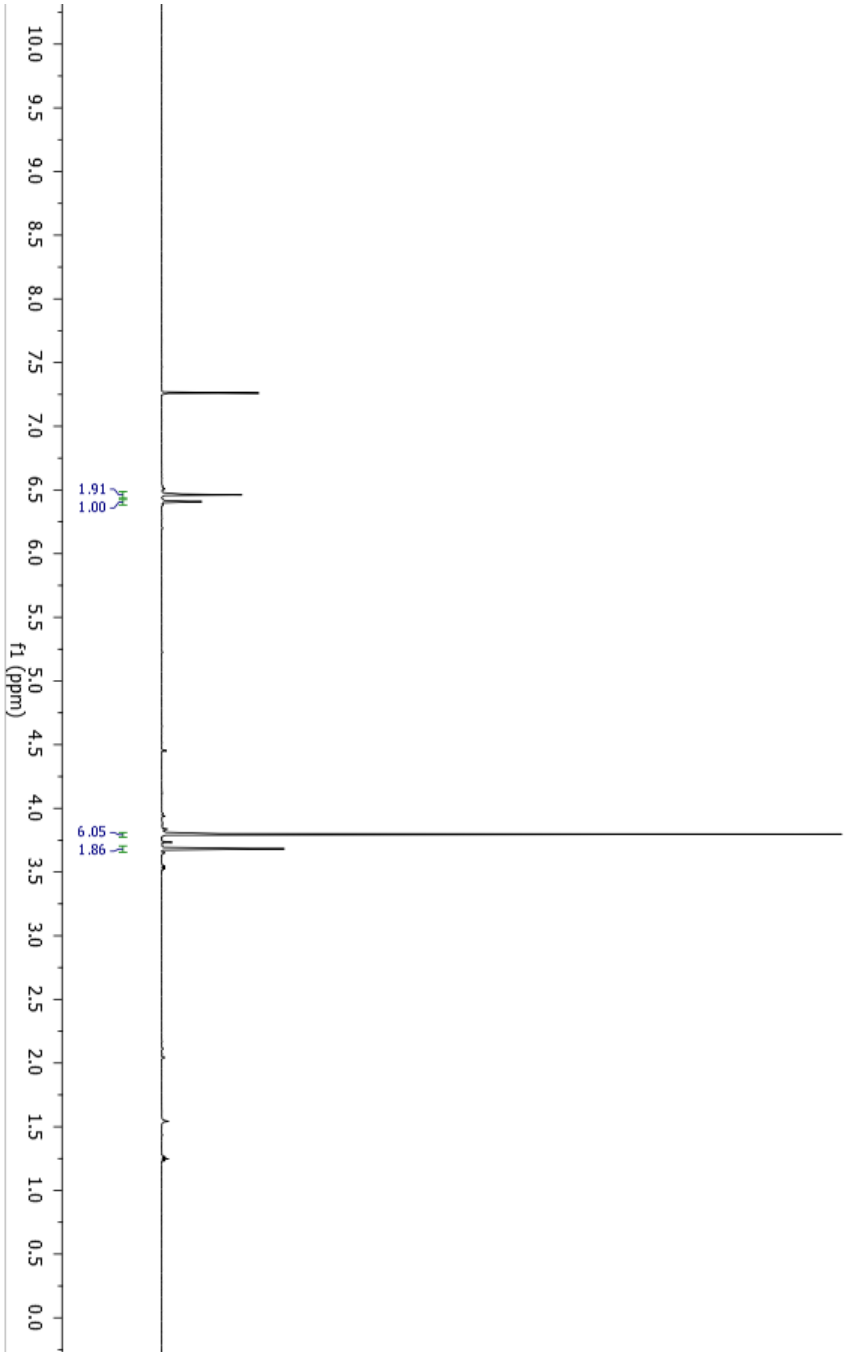
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

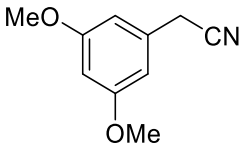




Compound 3-94

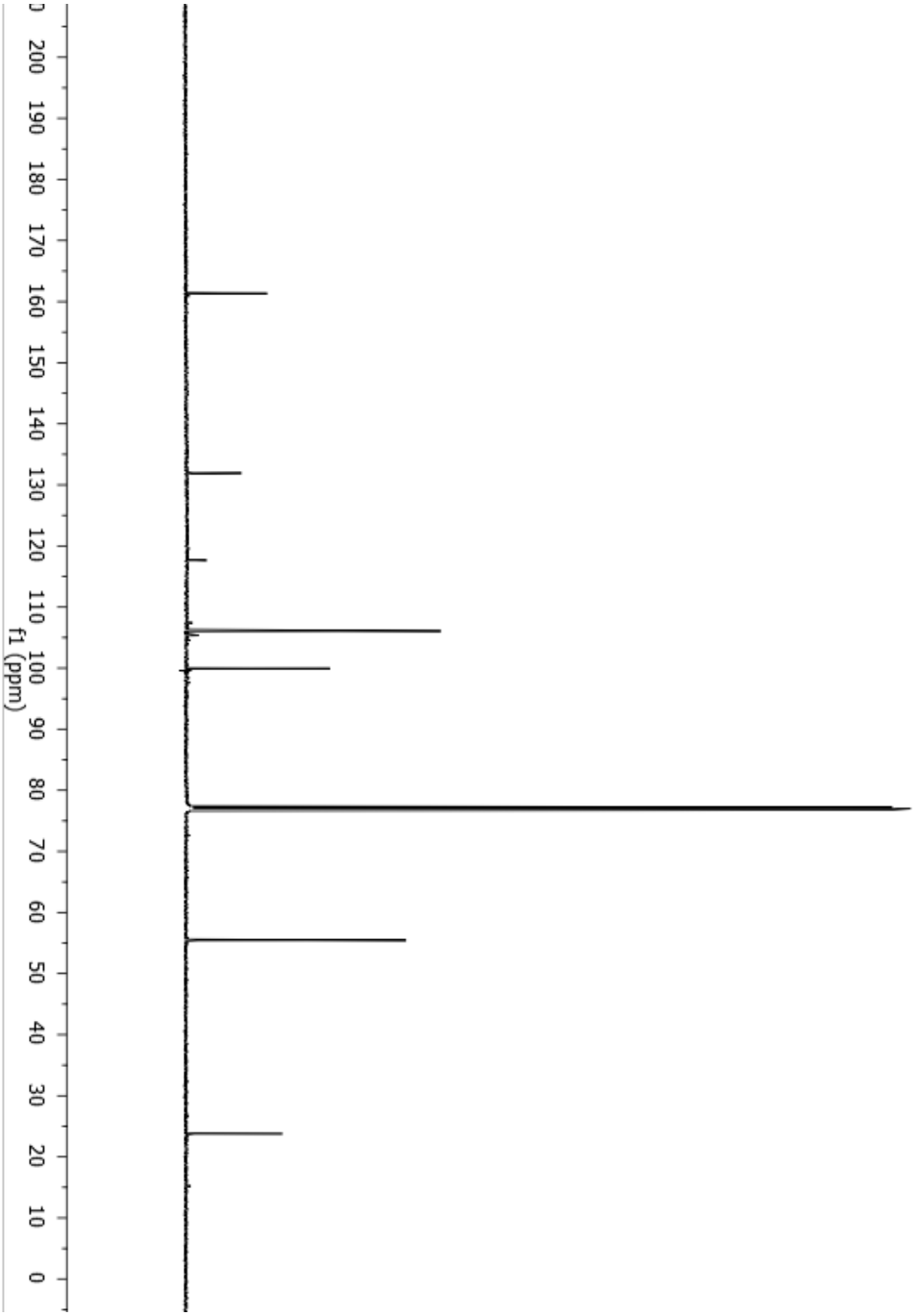
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)



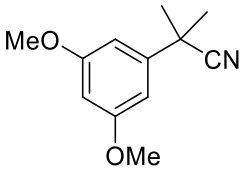


Compound 3-94

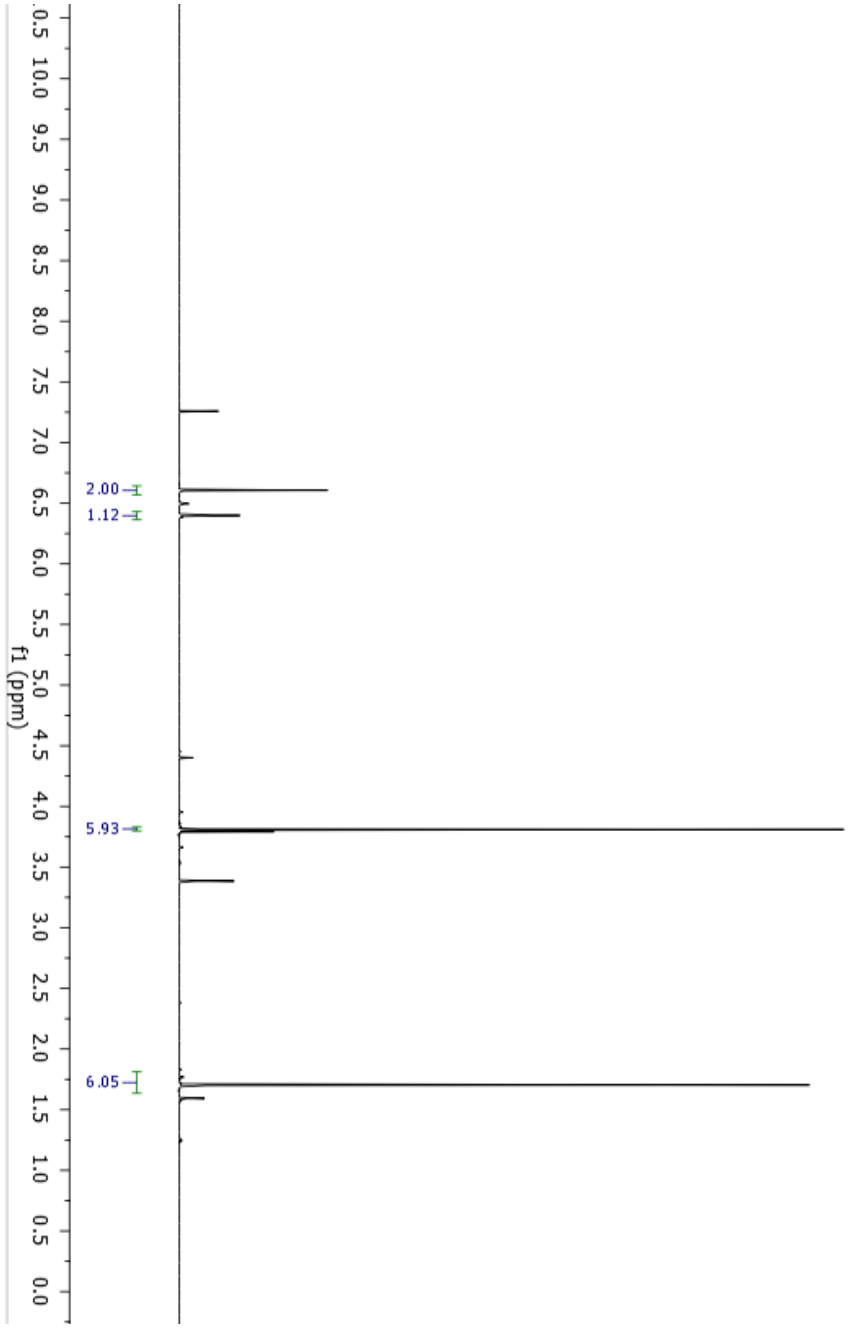
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

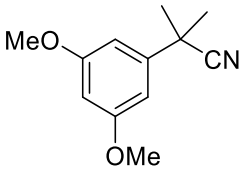


^{1}H NMR spectrum ($CDCl_3$, 500 MHz)



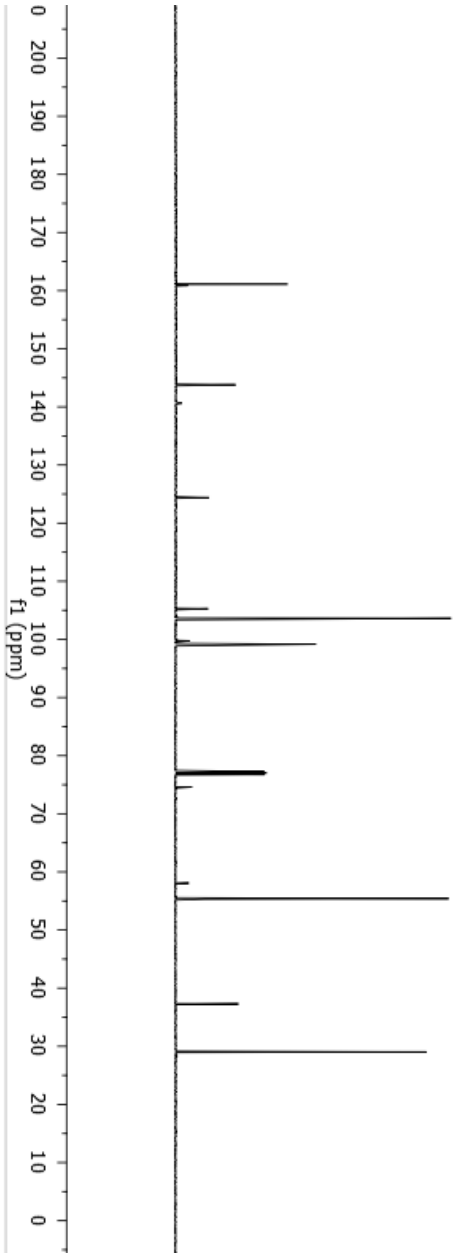
Compound 3-95

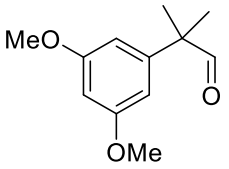




Compound 3-95

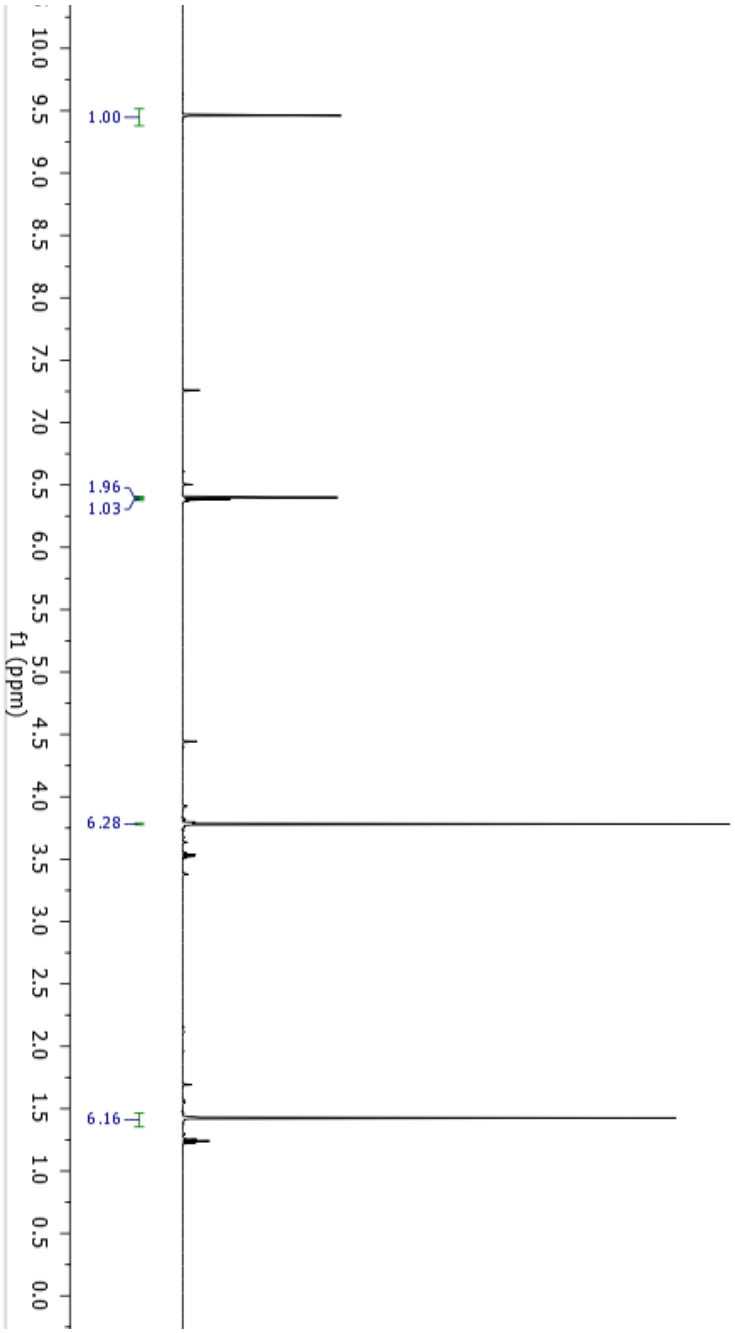
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

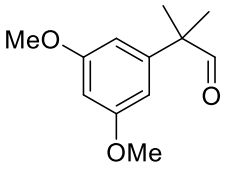




Compound 3-87

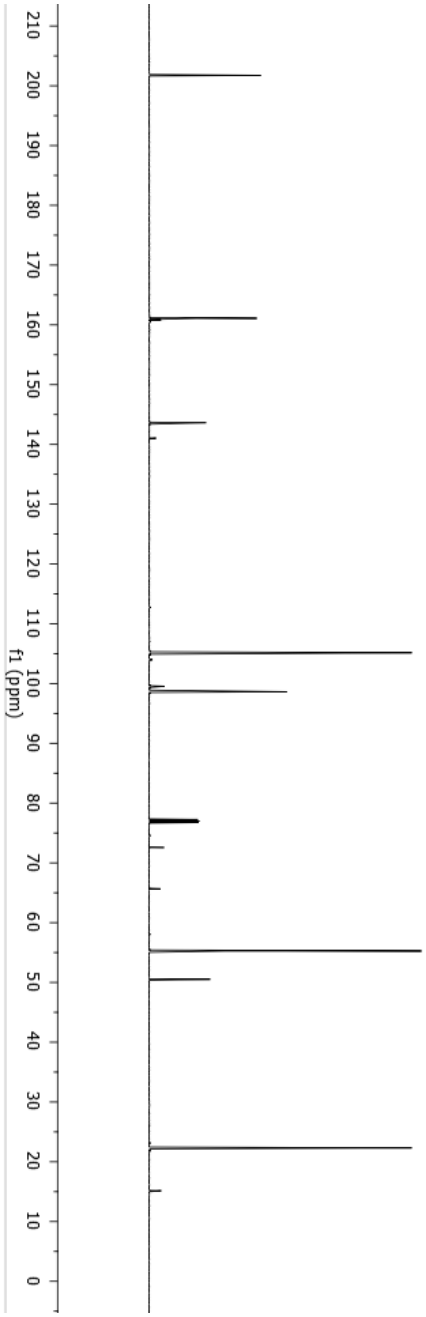
^{1}H NMR spectrum ($CDCl_3$, 500 MHz)

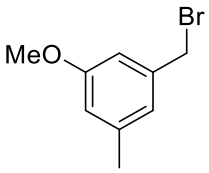




Compound 3-87

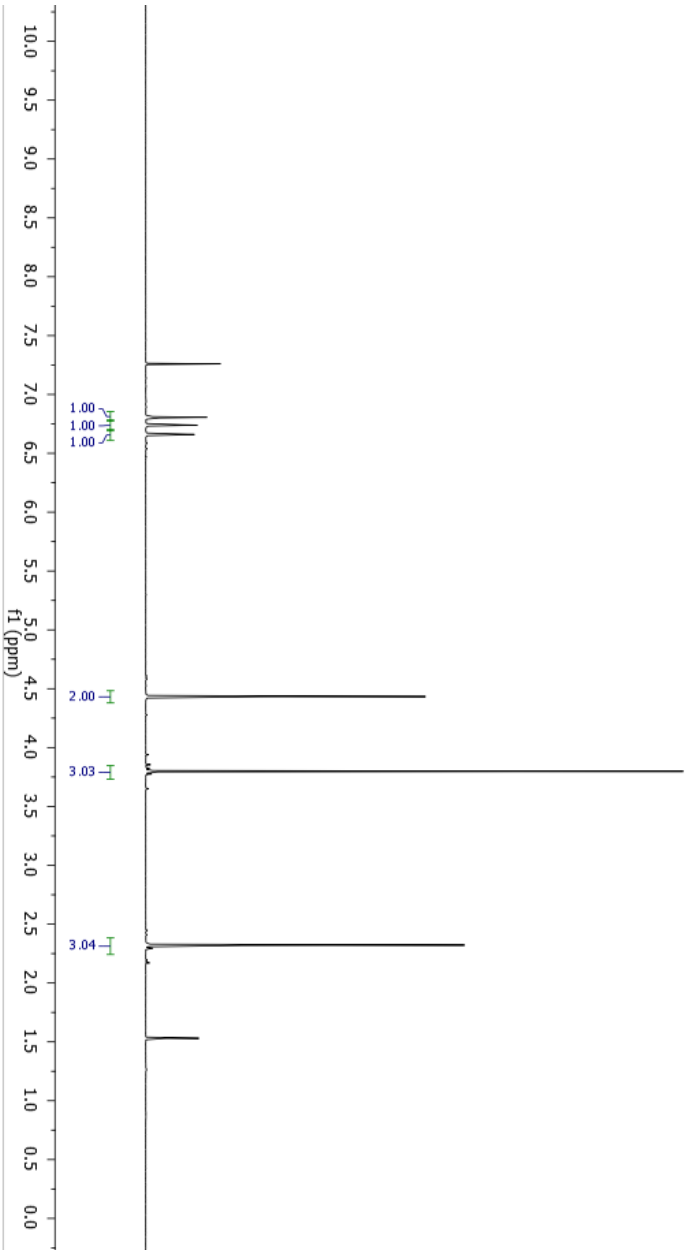
^{13}C NMR spectrum ($CDCl_3$, 125 MHz)

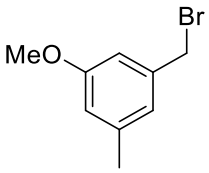




Compound 3-96

^{1}H NMR spectrum ($CDCl_3$, 500 MHz)





Compound 3-96

^{13}C NMR spectrum ($CDCl_3$, 125 MHz)