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Studies Toward the Synthesis of Celastrol
and
The Late-Stage Hydroxylation of Arenes Mediated by 4,5-Dichlorophthaloyl Peroxide

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Studies Toward the Synthesis of Celastrol
and
The Late-Stage Hydroxylation of Arenes Mediated by 4,5-Dichlorophthaloyl Peroxide

by

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Dedication

For Grandpa

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Studies Toward the Synthesis of Celastrol

And

The Late-Stage Hydroxylation of Arenes Mediated by 4,5-Dichlorophthaloyl Peroxide

Andrew Michael Camelio, Ph.D.

The University of Texas at Austin, 2014

Supervisor: Dionicio R. Siegel

The natural product celastrol (**1**) possesses a wide array of promising biological activities related to diseases characterized by protein misfolding including those associated with neuronal degradation, inflammation, and cancer. Relevant to cancer, celastrol functions as a non-ATP-competitive inhibitor of heat shock protein-90, providing a potential lead for the development of new inhibitors with improved pharmacology. A laboratory preparation of the small molecule was undertaken to provide access to the unnatural enantiomer of celastrol. The lack of understanding of the chemistry and biology of the growing class of celastroids is attributed to the incompatibility of biologically inspired polyene cyclization strategies to assemble friedelin triterpenoids. As a result of these problems residing at the interface of chemistry and biology, a purely synthesis-based strategy for polyene cyclizations to rapidly construct the pentacyclic core of the friedelin and celastroid natural products has been developed. This efficient strategy is gram scalable culminating in the first total synthesis of wilforic acid (**127**) and an advanced intermediate capable of delivering celastrol (**1**) as well as numerous celastroid natural products.

Phenols possess broad utility serving as key materials in all facets of chemical industries, especially the pharmaceutical industry. The ideal synthesis of a phenolic compound entails the direct oxidation of an aryl C-H bond remains to be a difficult synthetic challenge. Following our initial report describing the hydroxylation of arenes using phthaloyl peroxide, new peroxide derivatives were investigated to probe their reactivity in an effort to hydroxylate aromatics which were previously unreactive. Electronically poor to moderately rich arenes were successfully hydroxylated with a broad functional group tolerance using 4,5-dichlorophthaloyl peroxide. This protocol has been applied toward the rapid synthesis of phenolic analogs and metabolites of current pharmaceuticals as well as biocides. Mechanistic studies using kinetic isotope effect, competition, and benzylic oxidation experiments indicate that a novel diradical reverse-rebound mechanism is the likely pathway. Further examination of the transition-state using linear free energy relationships with σ vs. σ^+ values established a linear trend with a low negative *rho* value (- 3.92) corresponding best using σ values supporting a diradical reverse-rebound addition.

Table of Contents

List of Tables

List of Schemes

List of Figures

Abbreviations

2D-NMR	two dimensional nuclear magnetic resonance
9-BBN	9-borabicyclononane
Å	angstrom
Ac_2O	acetic anhydride
AcOH	acetic acid
ADH	asymmetric dihydroxylation
ALS	amyotrophic lateral sclerosis
atm	atmosphere
ATP	adenosine triphosphate
BF_3-OEt_2	boron trifluoride diethyl etherate
BHT	butylated hydroxytoluene
BQ	1,4-benzoquinone
Bu	butyl
Cdc37	cell division cycle control protein-37
^{13}C-NMR	carbon nuclear magnetic resonance
CI	chemical ionization
cis	*L.* on the same side
cm^{-1}	inverse centimeters
CO	carbon monoxide
COSY	correlation spectroscopy
CYP450	cytochrome P450
D	dextrorotatory
DABCO	1,4-diazobicyclooctane

DBU	1,8-diazobicycloundecene
DCE	1,2-dichloroethane
DCPP	4,5-dichlorophthaloyl peroxide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement polarization transfer
DFT	density functional theory
DIBAL	diisobutylaluminum hydride
DMA	dimethylacetamide
DMAP	*N*,*N*-dimethylamino pyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMM	dimethoxymethane
DMP	Dess-Martin Periodinane
DMSO	dimethylsulfoxide
dppf	1,1’-bis(diphenylphosphino)ferrocene
d.r.	diastereomeric ratio
E	*Ger.*, entgegen
EAS	electrophilic aromatic substitution
ee	enantiomeric excess
Enz-H^+	proton in the active site of an enzyme
eq.	equivalent
equiv	equivalent
ESI	electrospray ionization
Et	ethyl

EtOAc	ethyl acetate
FDA	Federal Drug Administration
FG	functional group
FMO	Frontier molecular orbital theory
g	gram
^{1}H-NMR	proton nuclear magnetic resonance
HFIP	1,1,1,3,3,3,-hexafluoro-2-propanol
HMPA	hexamethylphosphoramide
HMBC	heteronuclear multi-bond correlation
HOMO	highest occupied molecular orbital
hr	hour
HRMS	high resolution mass spectrometry
HSF-1	heat shock transcription factor-1
HSQC	heteronuclear single quantum correlation
HSP90	heat shock protein-90
HSR	heat shock response
HWE	Horner-Wadsworth-Emmons
Hz	hertz
IKKβ	inhibitor of nuclear factor kappa-β-kinase
imid.	imidazole
INADEQUATE	incredible natural-abundance double-quantum transfer experiment
i-Pr	isopropyl
IR	infrared spectroscopy
J	coupling constant

KIE	kinetic isotope effect
KiHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropyl amide
LiHMDS	lithium hexamethyldisilazide
M	molar
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Me_2CO	acetone
MeCN	acetonitrile
MeLi	methyllithium
mg	milligram
MHz	megahertz
mL	milliliter
mmol	millimole
mol	mole
MsCl	methanesulfonyl chloride
MS	mass spectrometry
N	normal
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
n-BuLi	normal butyllithium
NIH	National Institutes of Health
nM	nanomolar
nm	nanometer
NMR	nuclear magnetic resonance

NOE	nuclear Overhauser effect
OAc	acetate
OBz	benzoate
p23	prostaglandin E synthase-23
p	*para*
PAH	polyaromatic hydrocarbons
PPO	phthaloyl peroxide
p-TsOH	*para*-toluenesulfonic acid monohydrate
PDC	pyridinium dichromate
Pd-C	palladium on carbon
Ph	phenyl
PhH	benzene
PhMe	toluene
Pin	pinacol
PPA	polyphosphoric acid
ppm	parts per million
pyr.	pyridine
R_f	retention factor
s-BuLi	*sec*-butyllithium
SET	single electron transfer
Sia_2BH	diisosiamylborohydride
SM	starting material
SOMO	singly occupied molecular orbital
t-Am	*tert*-amyl
t-Bu	*tert*-butyl

TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydrogen peroxide
TBSCl	*tert*-butyldimethylsilyl chloride
TBSOTf	*tert*-butyldimethyltrifluoromethane sulfonate
TEG	triethylene glycol
NTf	trifluoromethane sulfonimide
OTf	trifluoromethane sulfonate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
TfOH	trifluoromethane sulfonic acid
Tf_2O	trifluoromethane sulfonic anhydride
TGA	thermogravimetric analysis
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TIPSOTf	triisopropylsilyl trifluoromethane sulfonate
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethane sulfone
trans	*L*., across
µM	micromolar
Z	*Ger*., zusammen

Chapter 1 – Significance of Celastrol and Evolution of the Polyene Cyclization

Molecular chaperones play an integral role in maintaining proteostasis, in particular, protein folding and conformation.[1] Chaperone malfunction triggers several diseases which includes cancers as well as those associated with neurodegeneration such as Huntington's, Parkinson's, Alzheimer's, and amyotrophic lateral sclerosis (ALS).[2,3] Quintessential to the proper folding of various proteins is the heat-shock transcription factor-1 (HSF-1). Activation of HSF-1 by external stresses, either physiological or environmental, induces the rapid manufacture of heat shock proteins (HSPs) which serve as molecular chaperones procuring a surveillance role in maintaining protein homeostasis.[4-11] Suppression of neurodegenerative diseases, lysosomal storage diseases (Gaucher and Tay-Sachs), and cancers (i.e. pancreatic, breast, leukemia, and hepatic) has been observed through the upregulation of molecular chaperones including HSP90. Modulation of the heat shock response (HSR) and HSPs through the use of small molecules and natural products has gained enormous pharmacological focus due to the potential therapeutic modalities in human diseases.[1,2,12-19]

The small molecule celastrol (**1**), which belongs to the friedelin family of natural products, possesses a potent, broad array of promising biological activities in the diseases triggered by malfunctioning chaperones.[2] One of the protein targets of celastrol is HSP90, but unlike other small molecules that target this protein, celastrol acts as a non-ATP-competitive inhibitor. This provides a different avenue for the development of new inhibitors with improved pharmacology.[17,20] Celastrol also induces neuronal and tissue regeneration by invoking an immunosuppressant response during refractory periods.[21] *In vitro* analyses has found that the various biological effects are caused through covalent modification via conjugate addition of biological nucleophiles, such as cysteine residues, into the quinone methide.[2,22-26] Since other molecules that possess quinone methides do not interact with HSP90 or provoke HSR, celastrol possesses special structural features that facilitate the induction of HSR and cause the reaction with certain proteins. These features are unknown, and the true mechanism by which celastrol interacts with its targets in their native environment also remains elusive.[2]

The development of a scalable concise synthetic approach could help solve these issues. A platform that constructs celastrol, its unnatural enantiomer, a variety of celastroid natural products as well as their antipodes, and structural derivatives inaccessible through semi-synthesis provides a new biological tool to investigate the mechanisms of action of this natural product. Developing a synthetic platform is, however, not easily accomplished as the molecule's complex topology is comprised of several all-carbon quarternary stereocenters including angular methyls. Despite the evolution of triterpenoid synthesis and the cationic polyene cascades used to access a variety of pentacyclic triterpenes, there remain difficult synthetic problems in regards to constructing the friedelin family of natural products. Therefore, the laboratory synthesis of celastrol and its enantiomer could provide an important tool to investigate its biological mode of action affording valuable information regarding HSP90 while simultaneously solving longstanding synthetic problems.

Isolation, Characterization, Biological Activity

For centuries extracts of the *Tryptergium wilfordii* Hook F. vine (Thunder of God or lei gong teng) have provided remedies used in chinese traditional medicine for various ailments including adema, fever, chills, joint pain, inflammation, and rheumatoid arthritis.[2,27] In 1930 cultivation of the vines' roots was requested to be forbidden in the Chekiang province. Resistant local farmers argued that they were unable to successfully harvest their crops without using the powdered roots as an insecticidal agent. These disputes inspired entomologists to extract the natural products from the vine; culminating in 1936 when Chou and Mei published their findings concluding that the major constituent of the orange extract is β-carotene. This was proven to be incorrect in 1939 by the work of Gisvold, but the actual structure remained elusive for 36 years. Over this time period, structural characterization of celastrol and the methyl ester pristimerin (**2**) indicated the presence of the distinct quinone methide chromophore (425 nm and 255 nm). IR spectroscopy showed the presence of a chelated hydroxyl (3380 cm^{-1}), ester carbonyl (1740 cm^{-1}), and the quinone methide (1607 cm^{-1}). The extract also proved to be chiral as the observed optical rotation of pristimerin is $[\alpha]D\ -168°$. The limited NMR studies of celastrol and pristimerin had shown six methyls represented as singlets, two coupled olefinic protons, and unresolved aliphatic protons suggesting a natural product belonging to the friedelin family.[27] Then in a landmark publication in 1972 Ham and Whiting extracted pristimerin (**2**), performed a conjugate reduction with $NaBH_4$, and subsequently esterified the catechol to afford the *p*-bromobenzoate (**3**). After several recrystallization attempts, they discovered that rapidly cooling a hot benzene/ethanol solution of **3** produced crystals suitable for X-ray diffraction which unambiguously confirmed the structure of **3** and as a result celastrol (**1**) as well as pristimerin (**2**).[28] The absolute configuration revealed the sterically encumbered friedelanyl triterpenoid core possessing the *trans*-angular disposed methyls residing in the C-D ring juncture, three other all-carbon quaternary stereocenters, and the discrete quinone methide functionality which ultimately provides the red-orange color of celastrol. The isolation and purification process to extract celastrol has been extensively examined and perfected so that starting from 15 kg of raw dry roots, 798 mg of celastrol (**1**) is isolated in 99.5% purity.[29]

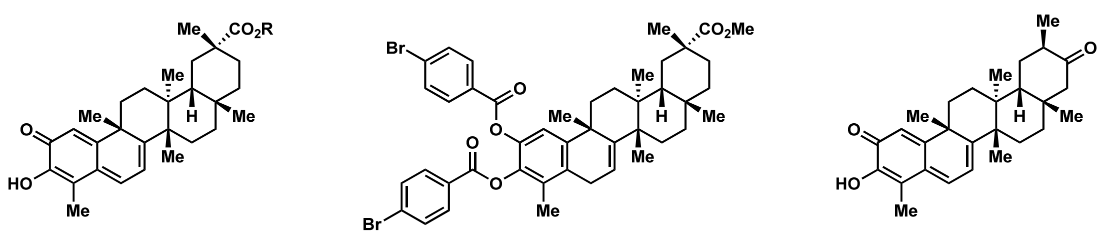


Figure 1.1. Celastrol, pristimerin, tingenone, and the *p*-bromobenzoate of pristimerin.

Celastrol exhibits a broad array of potent biological activities. Diseases associated with cancers, neurodegeneration, and inflammation can be reversed, either *in vitro* or *in vivo*.[2-27] A major protein target of celastrol is HSP90, but it can also act as an antioxidant provoking an autoimmune response which induces neural and tissue regeneration during dormant periods at potencies as low as 50 nM in tadpoles.[21] Other members of the celastroid family of natural products (i.e. tingenone (**4**)) also exhibit cytotoxicity towards skin, stomach, uterine, and lymphoepithelioma cancers in clinical trials with minimal side effects.[27,30,31] The therapeutic effects of the whole extracts from *Tryptergium wilfordii* are also being examined in over 20 clinical trials ranging from

HIV, Lupus, Crohn's disease, kidney disease, and rheumatoid arthritis which are at various stages of completion.[32]

Despite the spectrum of biological activity, the mode of action of celastrol and the related natural products remains elusive.[2] Recently, *in vitro* analysis has shown that biological nucleophiles, such as cysteine residues, add conjugately in a 1,6-Michael-like fashion into the quinone-methide (Figure 1.2).[24] Silverman and co-workers showed that this addition is stereospecific with β–facial selectivity, potentially leading to specificity.[23] Covalent modification of biological targets has also been studied in the context of celastrol and tingenone interacting with DNA as well as modifying cysteine residues of protein targets.[22,23,33,34] Researchers have discovered that the signaling pathways and proteins affected by celastrol include HSP90, Cdc37, p23, NF-κB, and IKK*β*.[2] In regards to HSP90, unlike other small molecule quinone and quinone methide modulators, celastrol does not act as an ATP-competitive inhibitor. Binding to the C-terminus, not the N-terminus like other modulators, causes a conformational change which inhibits the docking of Cdc37. This enhances client protein degradation inducing cellular apoptosis.[20] Despite their potency, no ATP-competitive inhibitor of HSP90 has been FDA approved because of low selectivity which leads to undesirable side effects. Therefore, celastrol represents a new class of inhibitors as therapeutic targets, especially in a variety of cancers including pancreatic cancer due to the high expression of HSP90 in tumor cells.[17]

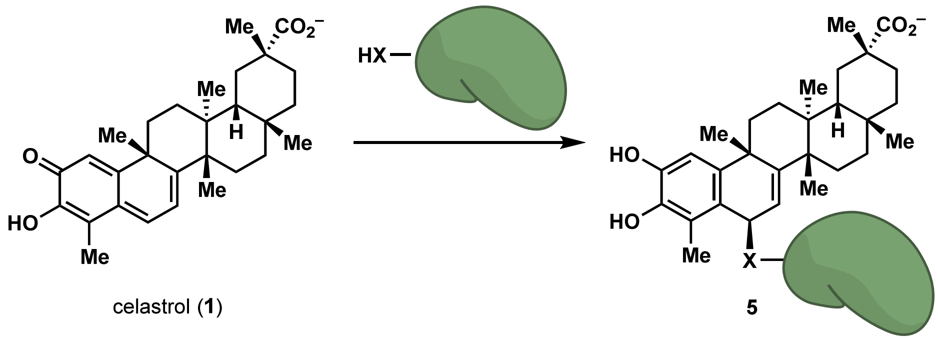


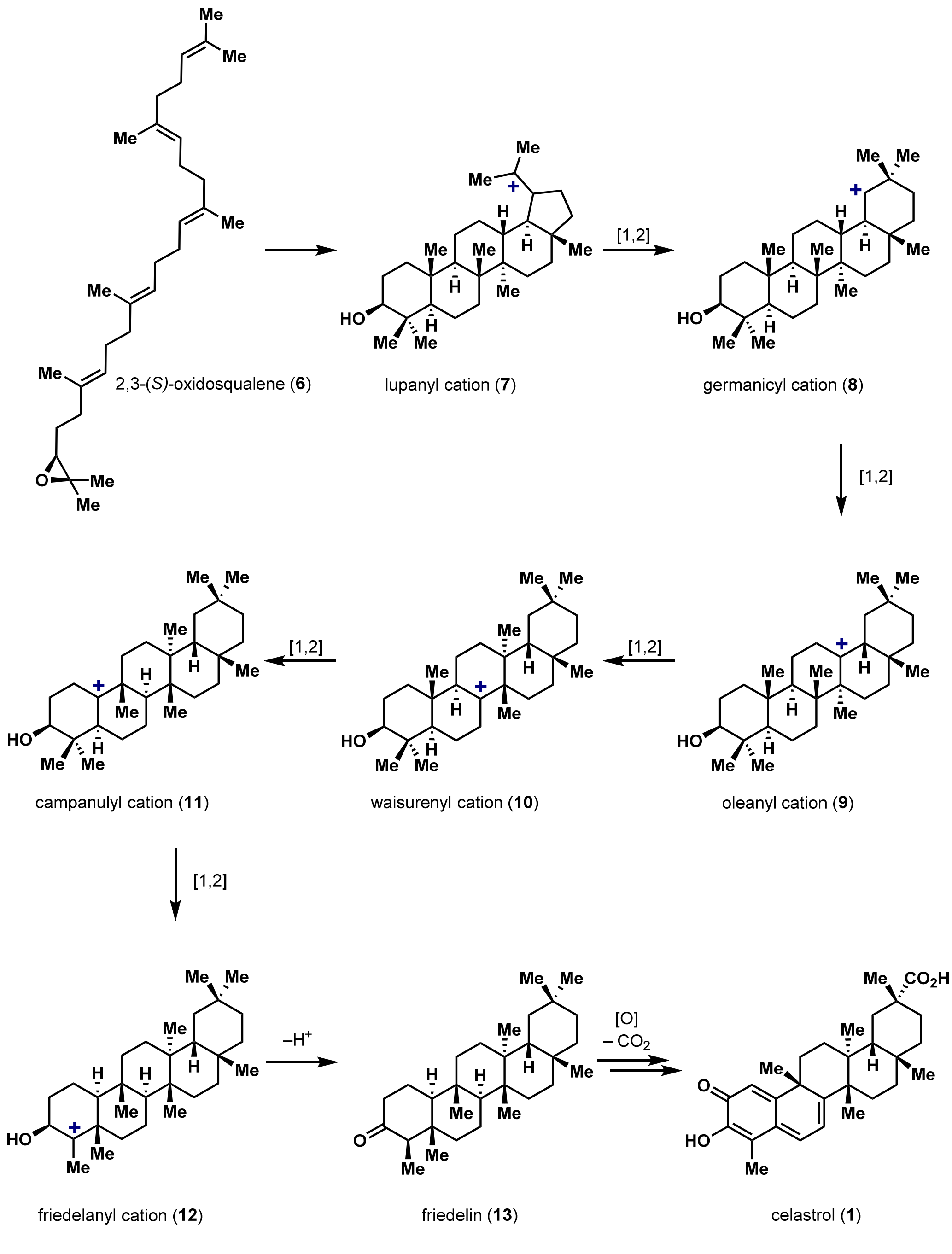
Figure 1.2. Stereospecific formation of celastrol/protein adducts through conjugate addition reactions of nucleophiles into the quinone methide.[23]

There are inherent structural features that celastrol possesses besides the quinone methide functionality which facilitate the small molecule's interaction with its protein targets. These features are still unknown and therefore many questions regarding the biological mode of action, native protein targets, how celastrol affects these numerous targets, the relationship between the varied biological effects, and if the small molecule is a specific alkylating agent remain unanswered.[2] Synthetic access to the enantiomer would provide a tool to further study the small molecule's mode of action through determining if the effects are promoted by specific covalent modification. This in turn reveals the important structural features for future potential therapeutics which are non-ATP competitive inhibitors of HSP90 as well as provide a strategic direction for the synthesis of celastroid analogs.

Biosynthesis

Celastrol is a triterpenoid belonging to the D:A-friedo-nor-oleananes, a subgroup of the friedelin family of natural products.[27] The celastroids bear structurally similar characteristics, but differ mainly in oxygenation states in the A, B, and E rings. Friedelins are characterized by the fused pentacyclic framework, and more distinctly, the vicinal *trans*-angular methyl groups positioned in the C-D ring juncture. Severe 1,3-diaxial strain occurs between both methyls and their adjacent sterically condensed environment. For this reason, as well as the number of stereocenters and all-carbon quaternary centers, there is a lack of synthetic routes to the perpetually growing class of celastroid natural products which has limited the understanding of their chemistry and biology. The absence of a synthesis can in part be attributed to the incompatibility of biologically inspired polyene cyclization strategies to assemble the celastroid or friedelin natural products.[35] The implementation of these reactions for the syntheses of polycyclic triterpenoids is highly desirable as they provide rapid access to relatively large molecules with multiple stereogenic centers in a single transformation.[36,37] Due to the vast number of friedelin natural products that are co-isolated with celastrol it has been postulated that celastrol is biosynthetically derived from friedelin.[27] Unfortunately, the polyene cyclization leading to friedelin is exceedingly challenging to reproduce in the laboratory due to a set of complex, energetically unfavorable methyl and hydride shifts (Scheme 1.1).[35]

Scheme 1.1. Proposed biosynthesis of celastrol.[27,35]

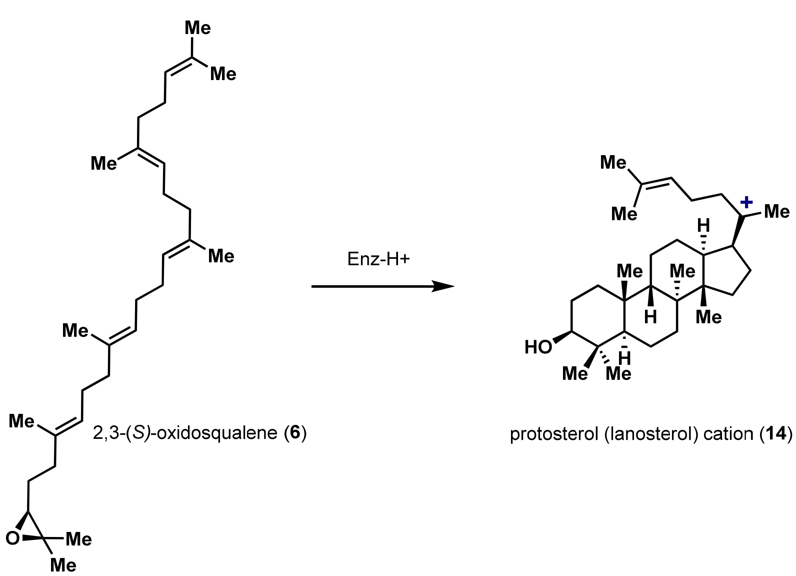


The biosynthesis of celastrol commences in the friedelin cyclase enzyme which converts 2,3-(S)-oxidosqualene (**6**) into the lupanyl cation (**7**). The epoxide is initially ionized by a proton transfer from an aspartic acid residue in the active site. The lupanyl cation then undergoes a series of [1,2] hydride and methyl shifts in a suprafacial manner to arrive at the friedelanyl cation (**12**) (Scheme 1.1). Next, an oxidative hydride migration affords friedelin, which is oxidized in the A, B, and E rings to generate celastrol. The energetics of the suprafacial [1,2]-shifts proceeding from the lupanyl cation (**7**) have been examined by E. J. Corey. The friedelanyl cation is the highest energy species as determined by B3LYP 6-31 G* DFT and *ab initio* Hartree-Fock (6-31* or 3-21(*) levels) calculations. This calls into question if the friedelin-based natural products are derived from other pentacyclic triterpenes. The formation of the friedelanyl cation is thermodynamically unfavored by ~20 kcal/mol. Corey and co-workers propose that the same cyclase enzyme which induces the cyclization of 2,3-(*S*)-oxidosqualene also promotes the subsequent rearrangements driving the reaction forward. Friedelin cyclase uses the exothermicity of the cyclization to perform a nonstop sequence of cyclization and multistep [1,2] rearrangements. The energy gained in the formation of the pentacyclic framework from 2,3-(*S*)-oxidosqualene (~30 kcal/mol) compensates for the high-energy friedelanyl cation (**12**). They also propose that the other natural products (i.e. lupeanes, oleananes, and ursanes) are not generated in the friedelin cyclase due to the lack of correctly positioned proton acceptors in the catalytic site which would facilitate elimination or diversion to the other cations.[35]

The Evolution of Cationic Polyolefin Cyclizations and Polyprenoid Synthesis

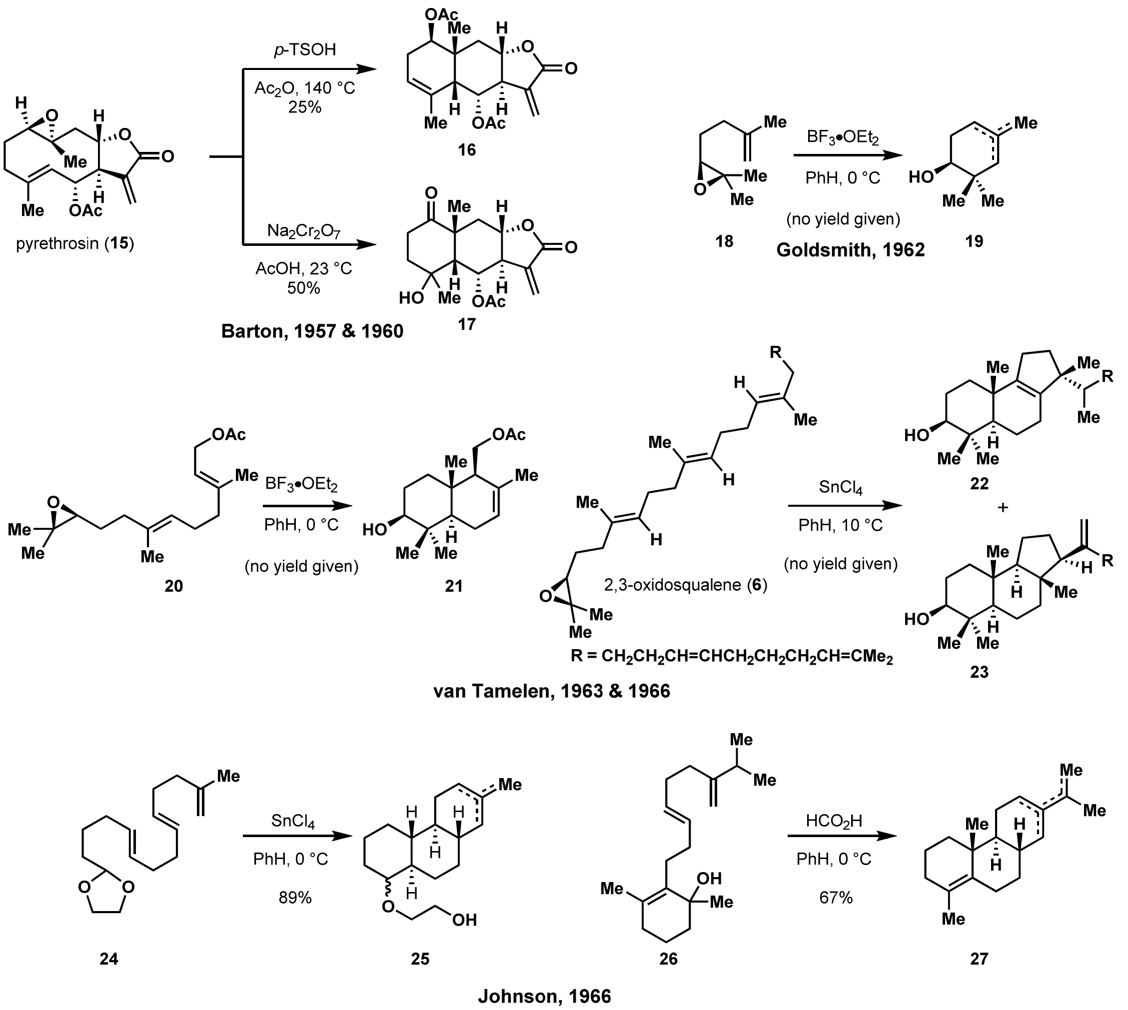
Extensive investigation in the biosynthesis of lanosterol and cholesterol ultimately led to the finding that 2,3-(S)-oxidosqualene (**6**) was cyclized upon acid activation to generate the lanosterol cation (**14**) through a cationic polyolefin cyclization or polyene cascade (Scheme 1.2). Stork and Eschenmoser postulated that upon activation of the epoxide in the active site, the tethered alkenes engage in a concerted manner producing a highly delocalized cation in the transition state. This results in the formation of several carbon-carbon bonds in a single diastereoselective operation to afford the protosterol cation **14**. The landmark insight of these findings is that the reaction is stereospecific. The configuration of the alkene, either *cis* or *trans*, leads to different cyclized products.[38,39]

Scheme 1.2. Biosynthesis of the protosterol cation (**14**) from 2,3-(S)-oxidosqualene.



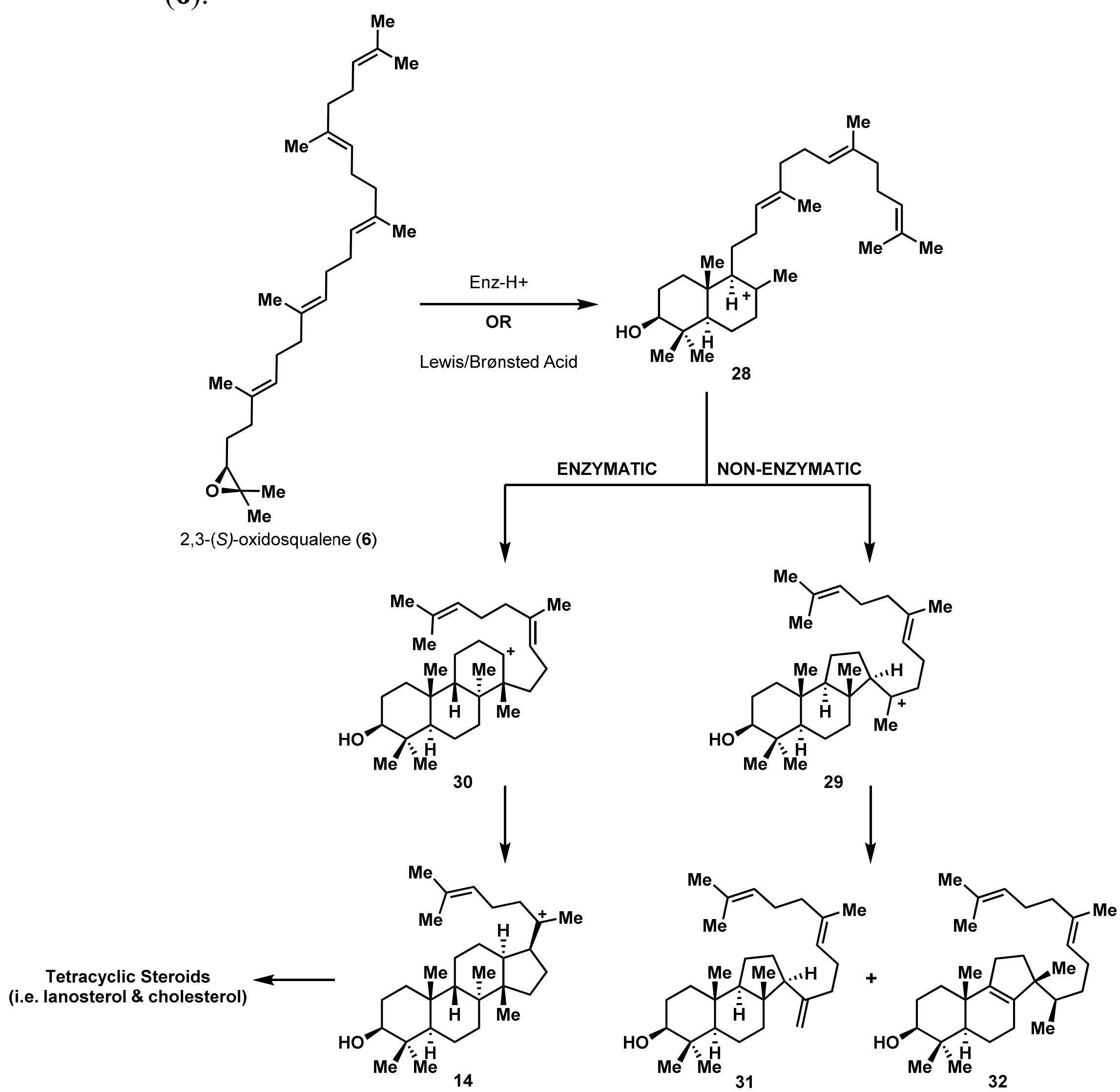
Early pioneers in steroid synthesis examined the synthetic plausibility of this theory to rapidly construct a variety of terpenoids in a biomimetic fashion starting from the readily accessible linear precursors. During the course of elucidating the structure of the sesquiterpenoid pyrethrosin (**15**) Barton discovered that under mild acidic conditions the activated epoxide underwent a transannular ene-cyclization to rapidly generate the fused tricyclic lactones **16** and **17** (Scheme 1.3).[40,41] The viability of this strategy towards steroid synthesis was then investigated by Goldsmith, van Tamelen, and Johnson through the syntheses of various mono-, di-, and tri-terpenoids. They examined several initiators (i.e. epoxides, acetals, and allylic alcohols), the optimal acid promoters (i.e. BF_3-OEt_2, $SnCl_4$, and HCO_2H), and solvents (i.e. PhH or CH_2Cl_2).[42-46] These original accounts are exceedingly important because they set the precedent for utilizing these types of cation initiated polyolefin cyclizations in a non-enzymatic environment. The experiments also provide significant information regarding the use of BF_3-OEt_2 and solvent comparisons between methylene chloride and benzene. BF_3-OEt_2 proved to be a poor Lewis acid for these cyclizations because it prompted the formation of byproducts such as rearranged ketones, fluorohydrins, and fluorination adducts of the subsequent carbonium ions formed after the initial cyclization.

Scheme 1.3. Early examples of ene-cascade cyclizations in terpenoid synthesis.



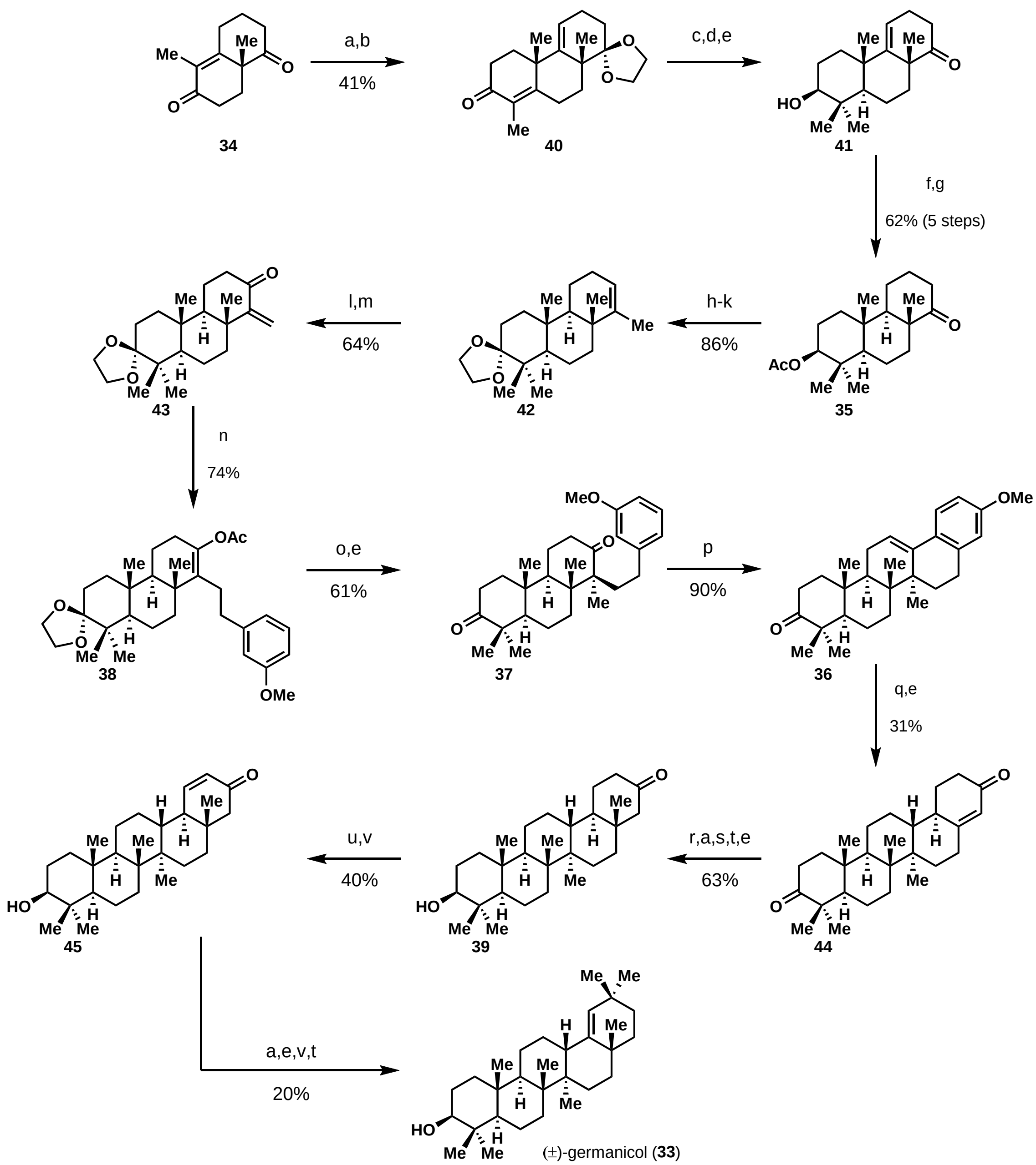
Using polyene cascade strategies to access natural pentacyclic triterpenoids is capricious in the laboratory setting as compared to the controlled enzymatic environment. The challenges reside in the construction of the polyprenoid precursors and successfully performing the cationic cyclizations to provide advanced intermediates in appreciable yields and adequate scalabality. The pentacycles possess strain energy due to the steric constraints of the angular methyls and the distortion of the cyclic backbone which make these cyclizations a daunting task (See Scheme 1.1). Early studies by van Tamelen on the cyclization of oxidosqualene (**6**) proved vital illustrating that upon activation **6** folds preferentially to form a 5-member ring over the desired 6-member ring after the initial cyclization to provide the *trans*-decalin adduct **28** (Scheme 1.4.).[46] The second annulation generates the carbonium intermediate **29** which possesses a more stable tertiary carbocation as compared to the 6-membered tricyclic adduct **30** which possesses the less stable secondary carbocation. The cation **29** can then undergo elimination or a combination of [1,2] methyl and hydride shifts with a subsequent elimination to afford the trienes **31** and **32**.

Scheme 1.4. Enzymatic and non-enzymatic cyclizing pathways for 2,3-(S)-oxidosqualene (**6**).



This finding prompted the joint efforts of the Ireland and Johnson laboratories to conduct the total synthesis of (±)-germanicol (**33**) in a non-biomimetic linear strategy (Scheme 1.5).[47] Commencing from diketone **34**, the tricyclic acetate **35** was synthesized in 7 steps with an overall yield of 25% using a Robinson annulation approach. Compound **35** was elaborated through a low yielding 11 step sequence culminating with the ene-cyclization generating pentacycle **36** from arene **37**. Another highlight of this sequence is the conjugate Grignard addition and trapping of the insipient enolate to construct the tetrasubstituted enol acetate **38**. This was used to deliver the angular methyl in a diastereoselective fashion using an *in situ* acetate cleavage/alkylation protocol to afford **37**. The total synthesis of racemic germanicol (**33**) was then concluded in a 13 step sequence highlighted by the installation of the last angular methyl in the D-E ring juncture through a novel hydrocyanation/reduction protocol developed by Nagata to arrive at ketone **39**.[48,49] The 31 step synthesis afforded racemic germanicol with an overall yield of 0.001% starting from the enone **34**. This underscores the power of the cyclase enzyme and the disparity between the biosynthetic, single step operation versus the multi-step conventional synthesis required to construct these complex terpenoids.

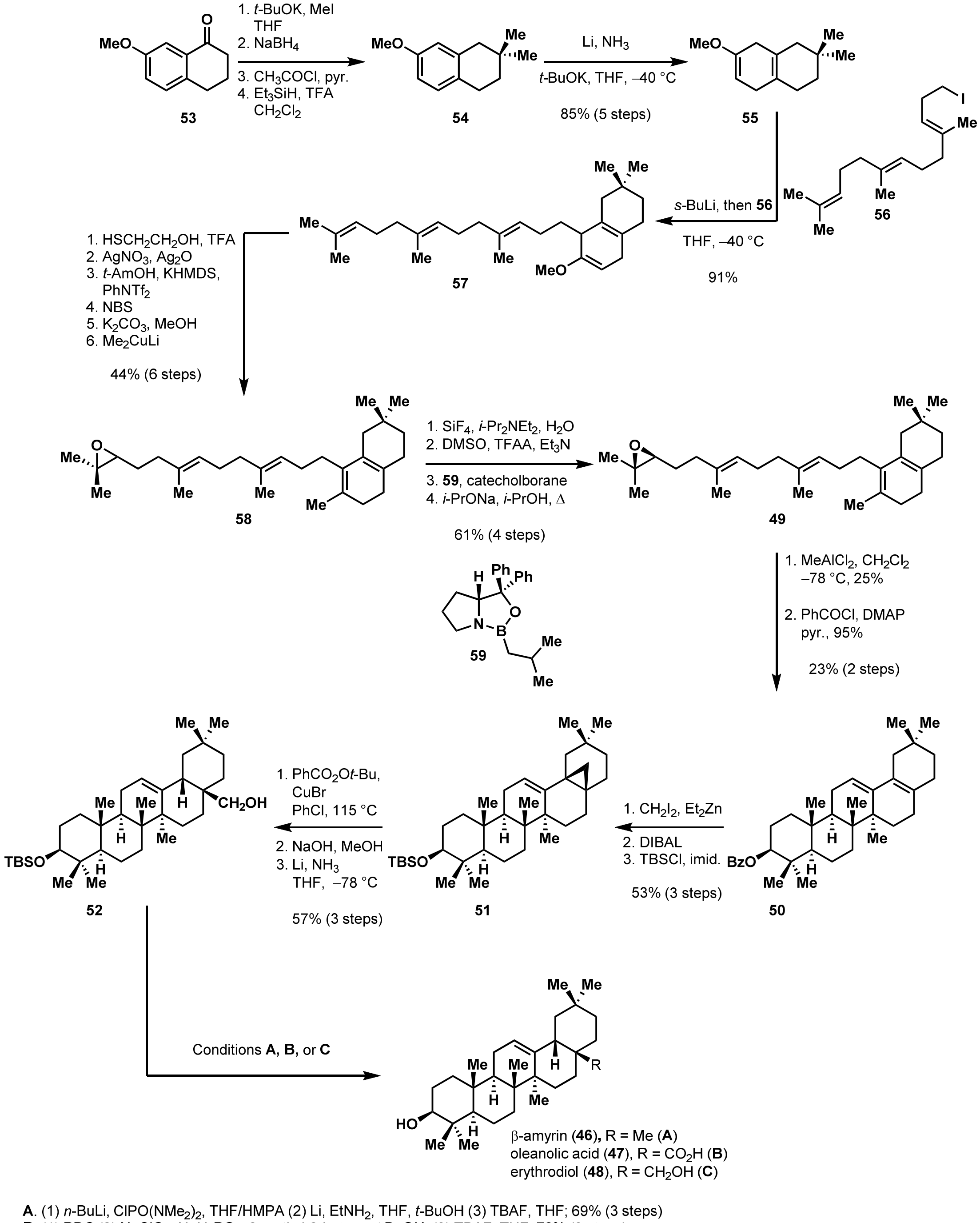
Scheme 1.5. Ireland and Johnson's collaborative total synthesis of (±)-germanicol.[47]



(**a**) $(CH_2OH)_2$, H^+ (**b**) $C_2H_5COCH{=}CH_2$, NaOMe, MeOH (**c**) Li, NH_3, *t*-BuOH, MeI (**d**) $LiAl(Ot\text{-}Bu)_3H$ (**e**) H_3O^+ (**f**) Ac_2O, pyr. (**g**) H_2, Pd-C, AcOH (**h**) MeLi, DME (**i**) 8 N H_2CrO_4, Me_2CO (**j**) $SOCl_2$, pyr. (**k**) *p*-TSOH, PhH, $(CH_2OH)_2$ (**l**) O_2, *hv*, sensitizer, pyr. $LiAlH_4$ (**m**) CrO_3, pyr. (**n**) *m*-$MeOC_6H_4CH_2MgCl$, Ac_2O (**o**) MeLi, DME, MeI (**p**) PPA (**q**) Li, NH_3, EtOH (**r**) $AlEt_3$, HCN, THF (**s**) $(i\text{-}Bu)_2AlH$, PhH (**t**) N_2H_4, OH-, TEG (**u**) Br_2, AcOH (**v**) $CaCO_3$, DMA (**v**) KO*t*-Bu, *t*-BuOH, MeI

Ireland and Johnson's synthesis of germanicol represents a landmark in terpenoid synthesis. This single ring annelation strategy as well as van Tamelen's tactic to construct the A,B,C rings through an epoxide activated cascade proved optimal to access these highly complex pentacyclic targets.[50] Overriding the inherent selectivity with the polyolefin cyclization to deliver these natural products in a more efficient, higher yielding fashion remained an elusive problem for some time. Corey, in 1993, provided a unique solution in the total syntheses of β-amyrin (**46**), oleanolic acid (**47**), and erythrodiol (**48**) from polyene **49** in a strategy reminiscent of the biosynthesis of these natural products. Corey and Lee used a highly stabilized tertiary allylic carbocation to force the desired 6-member ring formation under very mild conditions ($MeAlCl_2$ in CH_2Cl_2 at −78 °C) to access the pentacycle **50** in a modest yield of 25% (Scheme 1.6).[51] The low yield is superseded by the ability to construct the polyene **49** rapidly on multigram scale as well as the number of stereocenters and angular methyls installed in a single operation. This synthesis also highlights the utility of a stereoselective cyclopropanation strategy to install the angular methyl from intermediate **51**. This was a strategy originally developed by Wenkert and then exploited by Ireland in the total synthesis of (±)-shionone.[52,53] The cyclopropane was then opened using a Kharasch free radical chain oxygenation. Then, a dissolving metal reduction delivered a proton with the desired β-facial selectivity due to an internal proton transfer from the free hydroxyl to a π-radical anion to form the alcohol **52**. From this intermediate, varying the set of reaction conditions completed the total syntheses of oleanolic acid, erythrodiol, and β-amyrin in 24, 24, and 27 steps respectively with a 0.01% overall yield.

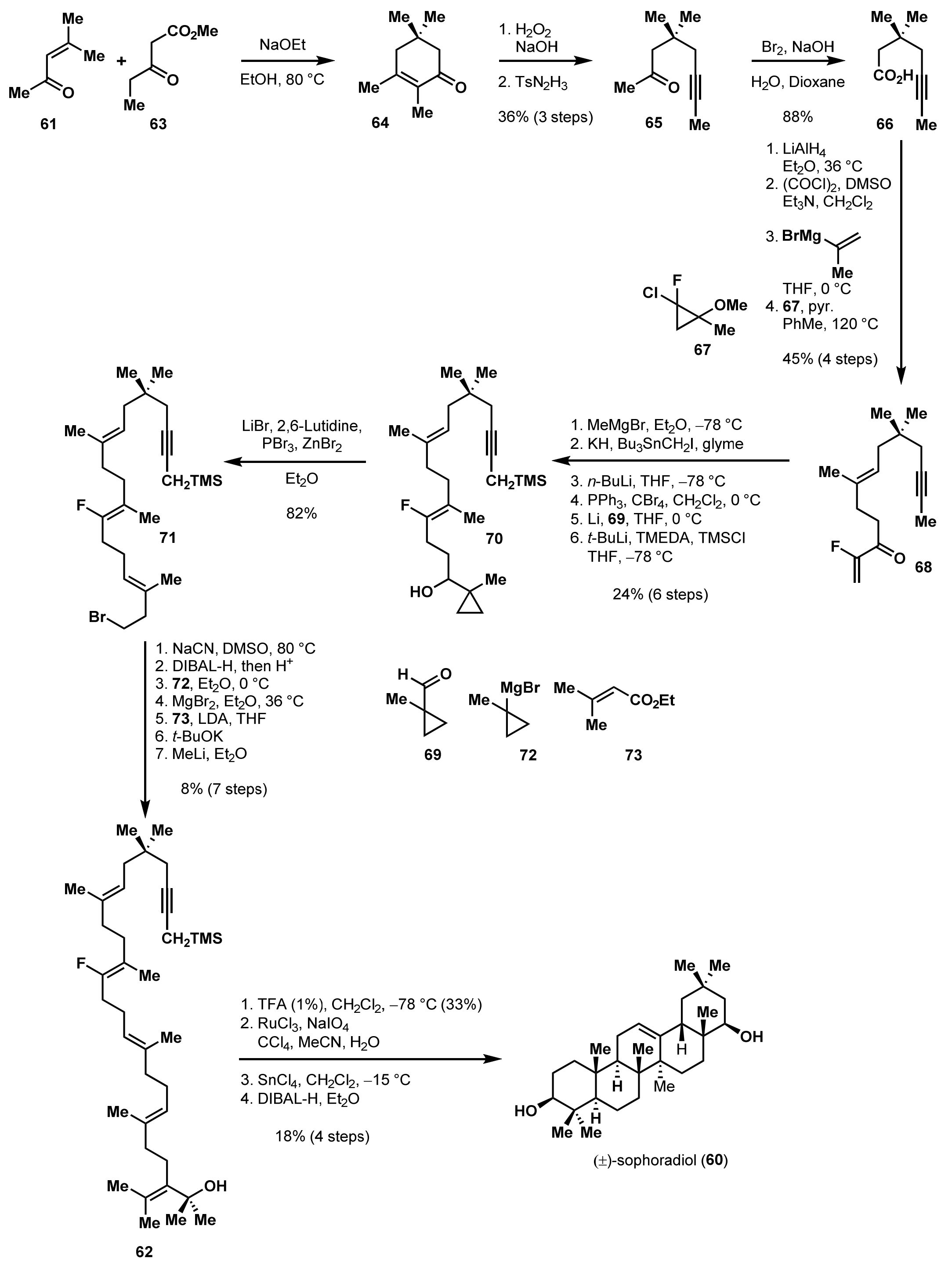
Scheme 1.6. Corey's total syntheses of oleanolic acid, erythrodiol, and β-amyrin.[50]



A. (1) n-BuLi, ClPO(NMe$_2$)$_2$, THF/HMPA (2) Li, EtNH$_2$, THF, t-BuOH (3) TBAF, THF; 69% (3 steps)
B. (1) PDC (2) NaClO$_2$, NaH$_2$PO$_4$, 2-methyl-2-butene, t-BuOH (3) TBAF, THF; 76% (3 steps)
C. TBAF, THF; 95%

Still a biomimetic approach could cut down the number of synthetic steps to deliver a more economic, ideal strategy. However, due to the intrinsic nature of following a Markovnikov pathway outside of enzymatic control, the cyclization of squalene-type precursors to form pentacyclic triterpenoids remained an elusive problem until 1994. Johnson and co-workers developed the first non-enzymatic, biomimetic pentacyclization using fluorine as an auxiliary to stabilize carbocations. The formal synthesis of (±)-β-amyrin (**46**) and the total synthesis of (±)-sophoradiol (**60**) utilizing a polyolefin cascade showcases the first example of constructing these complex natural products in a single diastereoselective operation from completely acyclic precursors (Scheme 1.7).[54,55] Commencing from mesityl oxide (**61**), **62** was constructed in a scalable 22 step sequence highlighted by the utilization of an Ireland-Claisen rearrangement and three separate cyclopropane-mediated rearrangements to ultimately deliver the polyene **62** with excellent selectivity. Under mild conditions the tertiary allylic carbinol was ionized with TFA in CH_2Cl_2 at −78 °C to initiate the polyolefin cascade to generate the pentacycle in 33% yield. After a ruthenium-mediated oxidation, stannic chloride facilitated the elimination of the fluoride to provide the desired alkene. Lastly, a stereoselective double reduction provided the natural product sophoradiol (**60**) in 26 steps with an overall yield of 0.004%. Johnson's biomimetic strategy represents a large advancement in terpenoid synthesis; showcasing the plausibility of accessing these pentacyclic targets in a single diastereoselective operation from completely acyclic precursors utilizing a functional group stabilized cation to promote the desired Markovnikov cyclization pathway.

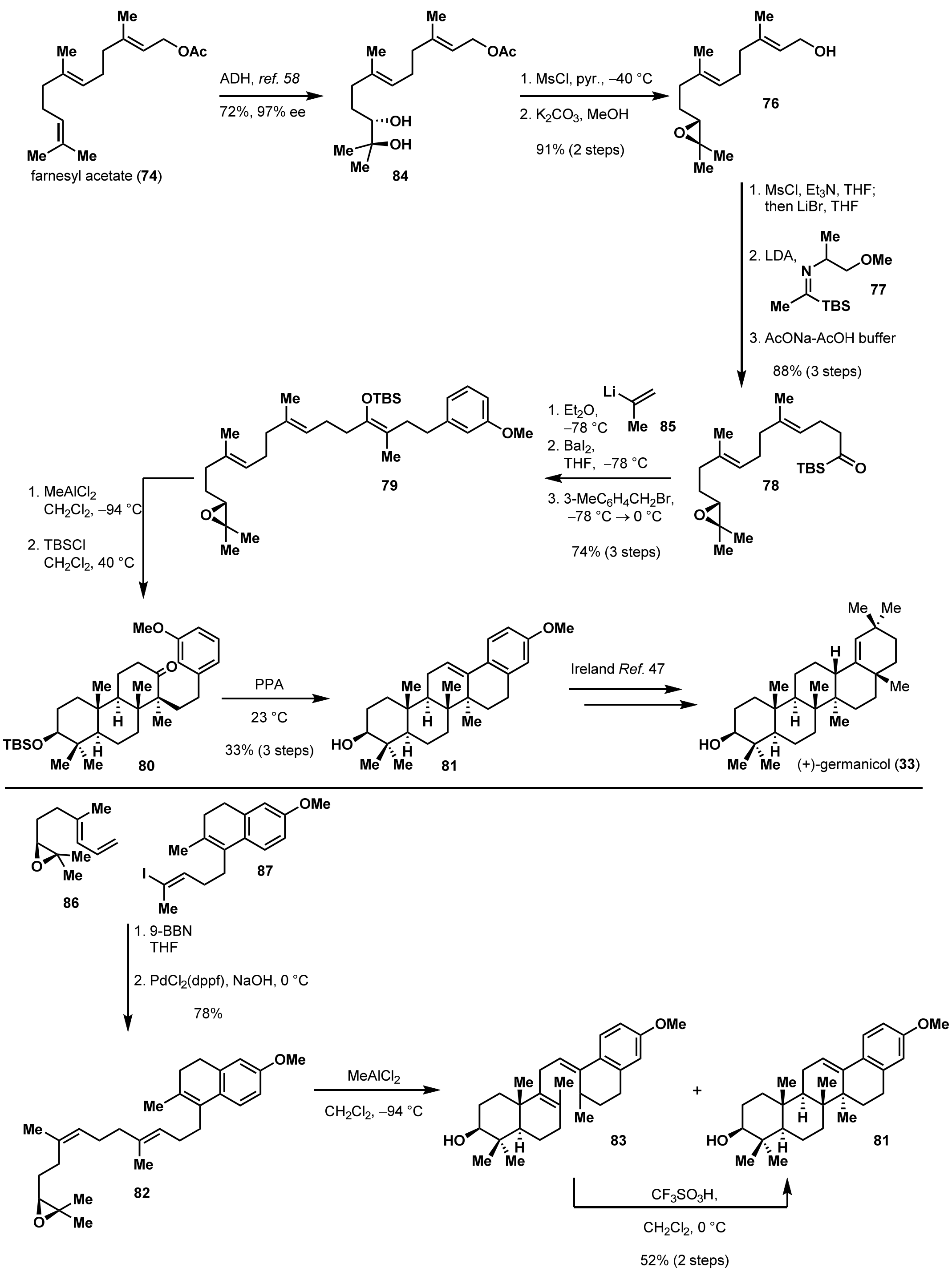
Scheme 1.7. Johnson's total synthesis of sopharadiol.



The major drawbacks of Johnson's strategy are the length (22 steps) and complexity of the synthesis of the polyene **62**. This warranted further development of shorter, more efficient approaches to construct these precursors and ultimately the natural products in appreciable yields. Recently, in two elegant syntheses Corey solved these problems by constructing the polyolefin precursor in only nine steps. Starting from farnesyl acetate (**74**), a rapid enantioselective formal synthesis of (+)-germanicol (**33**) and the total synthesis of (+)-lupeol (**75**) were conducted utilizing biomimetic polyolefin cascades (Scheme 1.8).[56,57] An asymmetric dihydroxylation provided the chiral epoxide **76** in a three step sequence.[58] Alkylation of the silyl imine **77** followed by hydrolysis delivered the acyl silane **78**. The desired oxirane **79** was then assembled in a three step, single flask operation. Beginning with the addition of 2-propenyllithium followed by a [1,2]-Brook rearrangement facilitated by BaI_2, the corresponding allyl lithium species was alkylated by 3-methoxybenzyl bromide to provide the polyene. Enol ether **79** was then cyclized using $MeAlCl_2$ to afford the ketone **80**, which after silylation underwent a smooth annulation promoted by polyphosphoric acid to generate the pentacycle **81**.[56] This advanced intermediate could be used to finish the total synthesis of (+)-germanicol (**33**) using the known procedures originally developed by Ireland.[47]

The epoxy triene **82** was synthesized in an alternative strategy employing a Suzuki-Miyaura cross-coupling, and then cyclized using $MeAlCl_2$ at −94 °C to produce the pentacycle **81**. Similar to the total synthesis of (+)-oleanolic acid (**47**), a benzyl-tetrasubstituted olefin was utilized to direct the desired cyclization. This reaction produced a 7:3 mixture of the diene **83** and the desired pentacycle **81** which was subsequently treated with triflic acid (5 equiv.) to convert the diene into **81**. The formation of **83** under the reaction conditions warranted further investigation. After significant probing, they discovered that the polyene **82** undergoes a rare intramolecular 1,5-migration of a ***proton*** to form a highly stabilized benzylic cation which elimination produced the byproduct **83**.[56]

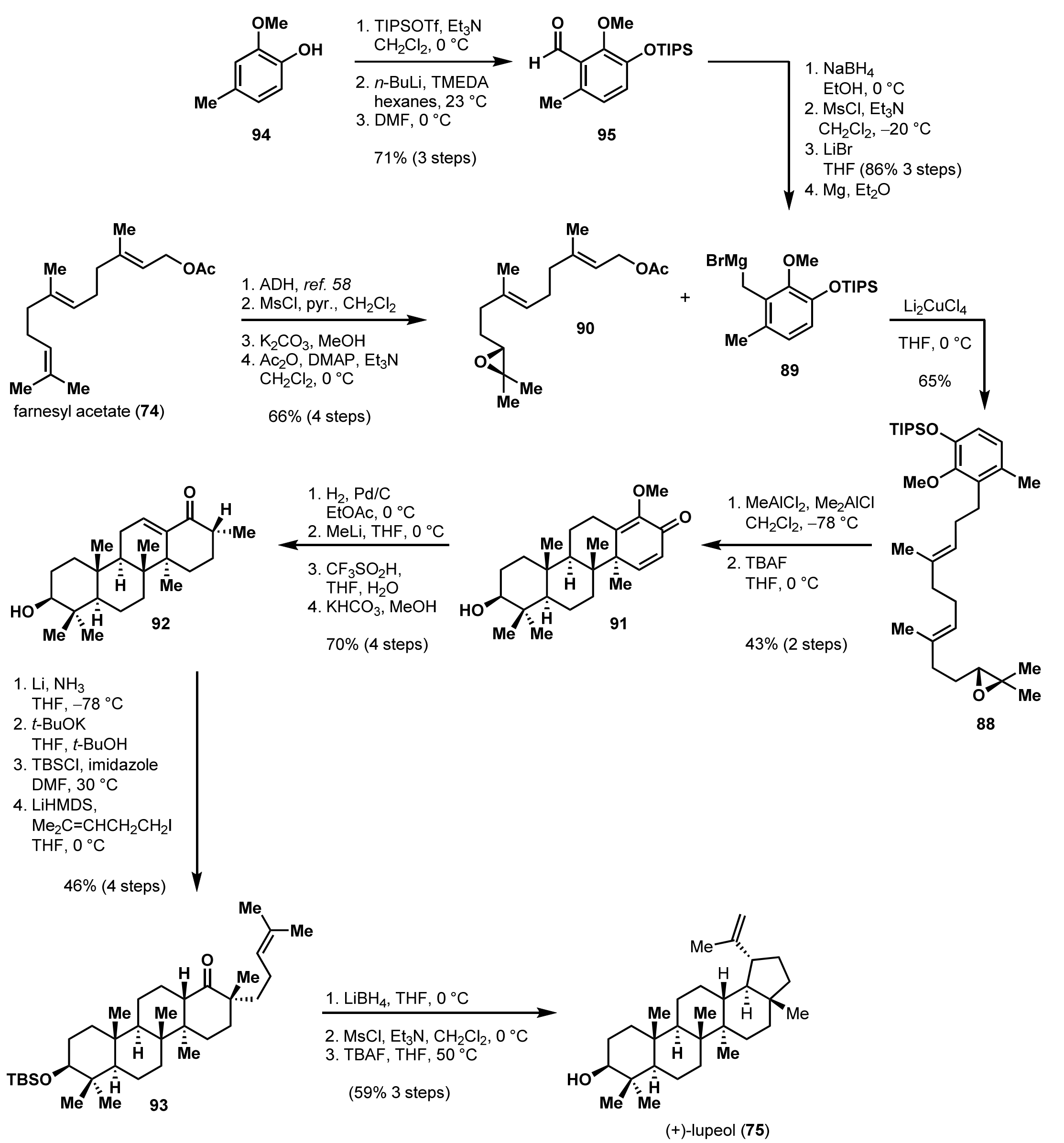
Scheme 1.8. Corey's formal synthesis of (+)-germanicol.[56]



The efficiency of the biosynthesis of the natural triterpenoid lupeol (**75**) is truly remarkable. Chemical emulation of these biosynthetic transformations has been a major synthetic challenge existing since Stork and Eschenmoser first postulated lupeol's native synthesis.[38,39] Recently, the evolution of the synthetic success and overall efficiency of not only the polyene cascade, but also the polyolefin precursors culminated in the enantioselective total synthesis of (+)-lupeol.[57] Corey and Surendra devised a seven step synthesis of the epoxy-triene **88**, the shortest to date. The natural product is accessed in a scalable 20 step synthesis (Scheme 1.9).

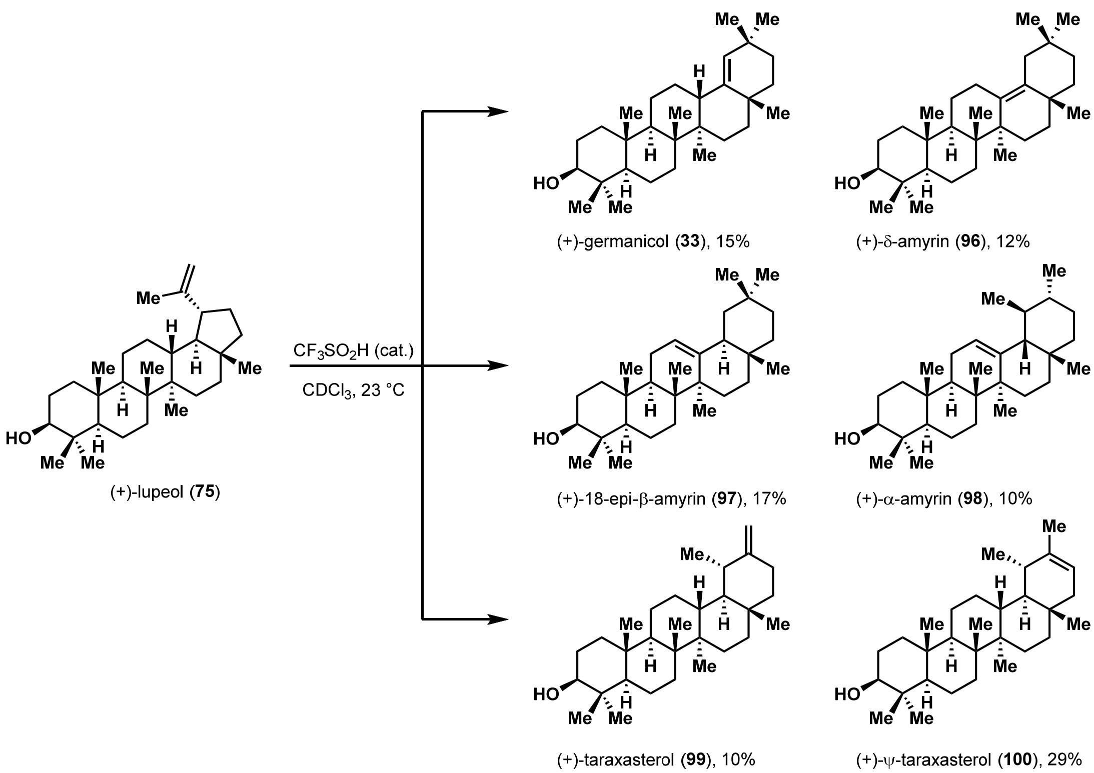
Polyene **88** was assembled using a copper-mediated coupling of Grignard **89** and the epoxy-acetate **90**. Grignard **89** was generated in a 6 step sequence, whereas acetate **90** was constructed in 4 steps. Polyene cyclization of the activated epoxide, followed by desilylation yielded tetracyclic dienone **91** in 43% yield. Reduction, addition of methyl lithium, isomerization mediated by trifluoromethane sulfonic acid, and subsequent epimerization furnished the enone **92** in good yield over four steps. A dissolving metal reduction using the Birch protocol followed by a second epimerization and a TBS protection yielded the silyl ether. Alkylation of the insipient enolate generated the ketone **93,** which after reduction, the activated alcohol was cyclized and deprotected to complete the total synthesis of lupeol.[57]

Scheme 1.9. Corey's total synthesis of (+)-lupeol.[57]



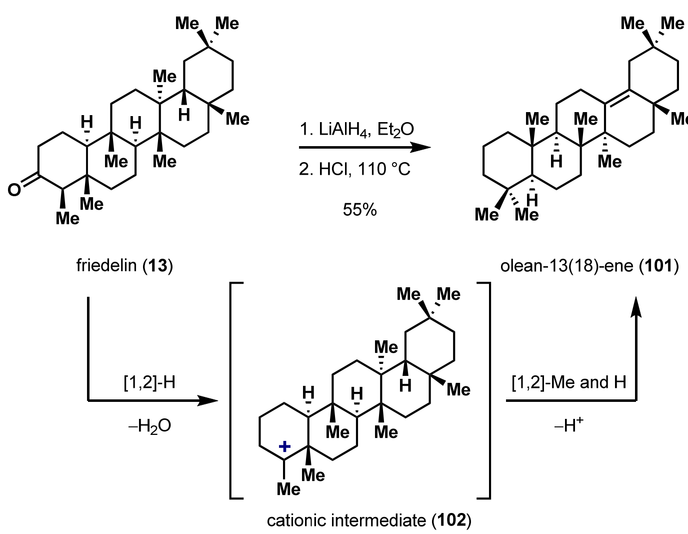
With adequate material in hand, chemically emulating the biosynthesis of various triterpenoids from lupeol through cationic rearrangements was investigated. This reaction is postulated to occur in the active site of various cyclase enzymes due to the exact positioning of a proton accepting group which channels the synthesis of various pentacyclic triterpenes.[35] At equilibrium, carbocation formation was promoted by catalytic trifluoromethane sulfonic acid at 23 °C in deuterated chloroform. Observed by ^{1}H-NMR, lupeol rearranged to six different pentacyclic natural products: (+)-germanicol (**33**), (+)-δ-amyrin (**96**), (+)-18-epi-β-amyrin (**97**), (+)-α-amyrin (**98**), (+)-taraxasterol (**99**), and (+)-ψ-taraxasterol (**100**) (Scheme 1.10).[57] This illustrates the capacity at which lupeol can be diverted to various natural triterpenoids. However, further backbone rearrangement to reveal friedelin was not observed due to the high energy associated with the strain of the conformation primarily caused by the steric encumbrance of the angular methyls. Enzymatically this rearrangement can occur as previously discussed, but outside of enzymatic control this has not been observed indicating that alternative strategies must be developed in order to construct these triterpenoids.

Scheme 1.10. Natural products accessed via cationic rearrangements of (+)-lupeol.[57]



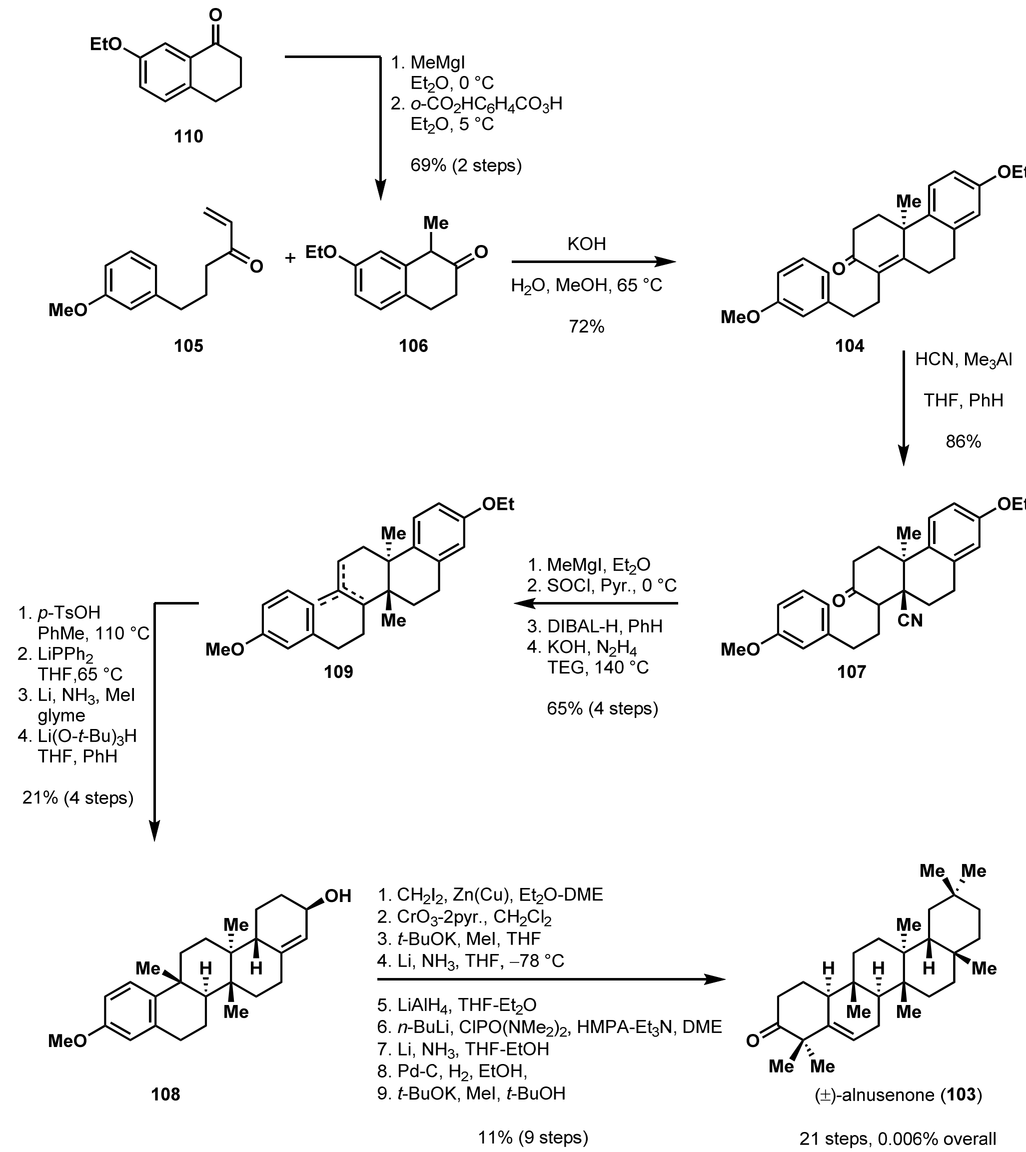
The lack of synthetic routes to the growing class of friedelin natural products, including celastroids, has limited the understanding of their chemistry and biology. Unlike other terpenoids, the absence of a synthesis is attributed to the incompatability of biologically inspired polyene cyclization strategies to efficiently assemble the pentacyclic core. Implementation of these reactions is highly desirable as it provides rapid access to relatively large molecules possessing a complex topology including several stereogenic centers and the angular methyls in a single transformation. The biological polyene cyclization leading to friedelin (**13**), however, is exceedingly challenging to reproduce chemically due to a set of complex energetically unfavorable methyl and hydride shifts (see Scheme 1.1).[35] In a non-enzymatically controlled environment the friedelin-based cationic intermediate **12** undergoes remarkable reversion to the more stable oleanyl cation (**9**).[59,60] In structural elucidation studies of friedelin, (**13**) Corey and Ursprung reduced the natural product with $LiAlH_4$ and heated the alcohol in acid which induced a deep-seated rearrangement. The shifts proceeded in the reverse direction of the biosynthesis to provide olean-13(18)-ene (**101**) in a single operation showcasing the instability of the carbocyclic core under cation promoting conditions (Scheme 1.11).

Scheme 1.11. Rearrangement of friedelin in the reverse direction promoted by acid.[59,60]



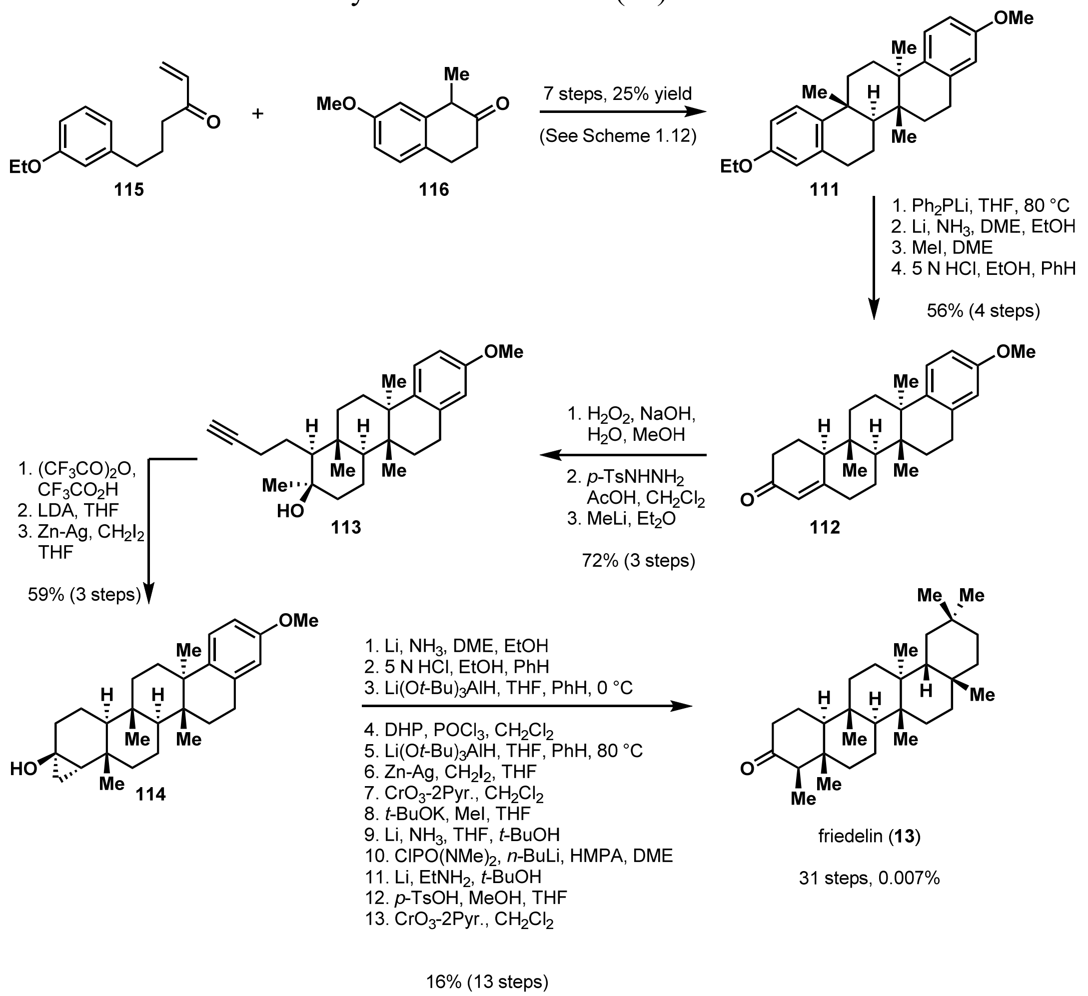
Ireland's total syntheses of (±)-alnusenone (**103**) and (±)-friedelin (**13**) fully delineate the synthetic challenges that this class of triterpenoids possess.[59-61] Alnusenone was constructed in 21 linear steps beginning with a Robinson annulation to generate the tricycle **104** from the enone **105** and ethoxytetralone **106** (Scheme 1.12). After intense investigation, a modified Nagata hydrocyanation protocol was developed to afford the nitrile **107**. This served as a functional handle to install the *trans*-vicinal angular methyls at the C-D ring juncture. Acid mediated annulation, selective methyl ether cleavage, chemoselective Birch reduction, and then a diastereoselective reduction generated the alcohol **108**. The alcohol directed the cyclopropanation which was employed to install the last angular methyl positioned in the E-ring. After oxidation manipulations and a double alkylation of the thermodynamic enolate, the total synthesis of alnusenone was completed in an overall 0.006% yield.[59,60]

Scheme 1.12. Ireland's total synthesis of (±)-alnusenone (**103**).[59,60]



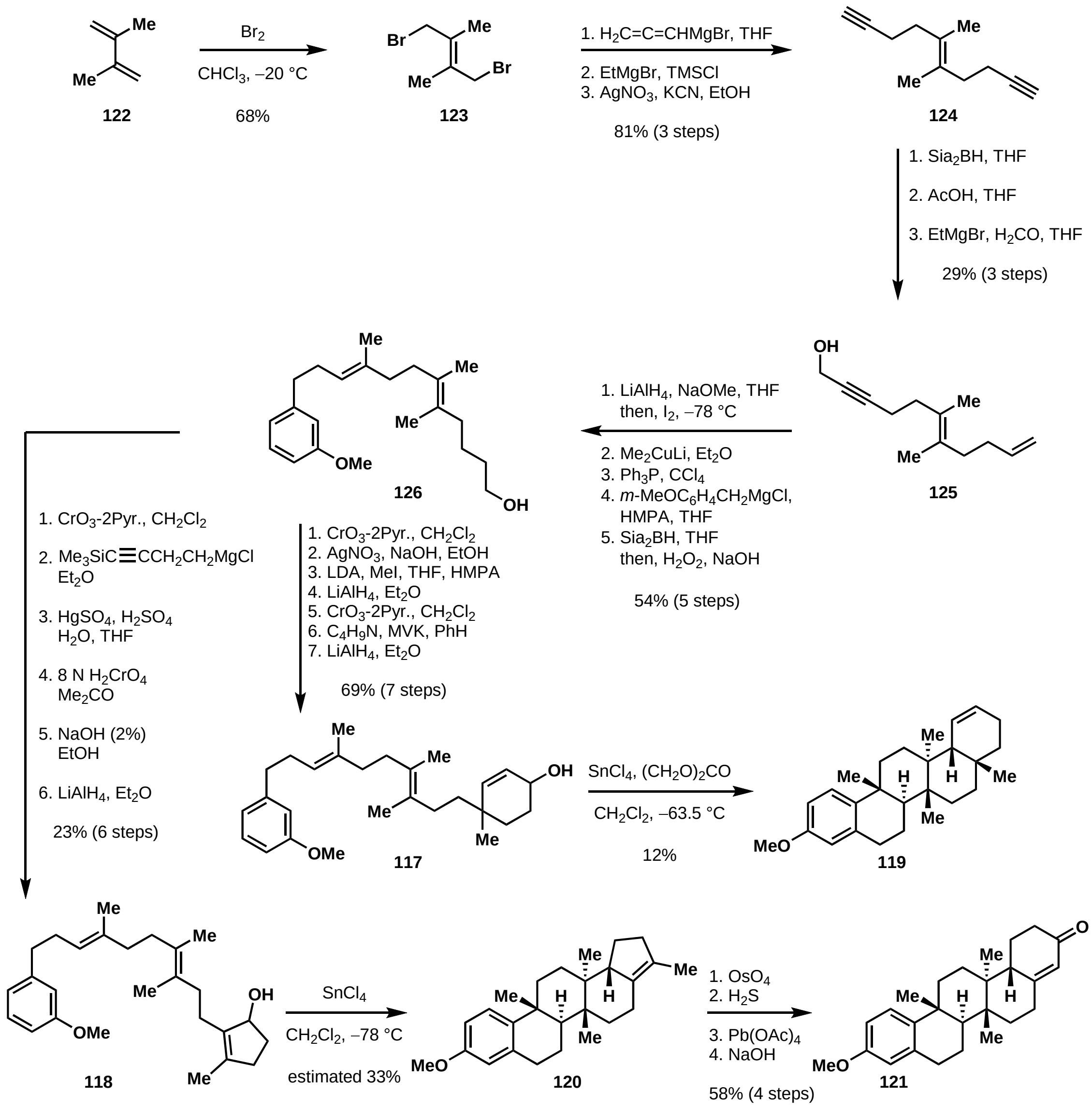
The total synthesis of (±)-friedelin (**13**) was completed in a similar fashion where the pentacyclic diether **111** was accessed in an analogous seven step sequence beginning with the Robinson annulation depicted in Scheme 1.12 (Scheme 1.13).[61] The only difference was the methyl and ethyl groups were swapped to functionalize the A ring prior to the E ring thereby circumventing backbone rearrangement which proved to be an insurmountable issue. Selective deprotection and Birch reduction followed by re-etherification and hydrolysis generated the enone **112** which underwent epoxidation and then Eschenmoser fragmentation. Addition of methyl lithium to the insipient ketone provided the alkynol **113** in seven steps from **111**. Cationic annulation promoted by trifluoroacetic acid followed by cyclopropanation afforded the desired alcohol **114**. This installed the angular methyl in the A-B ring juncture where cuprate addition strategies generated the undesired *cis*-fused decalin.[62] The synthesis was concluded through a 13 step sequence involving several oxidation manipulations to provide (±)-friedelin (**13**) in 31 steps with an overall yield of 0.007%.[61]

Scheme 1.13. Ireland's total synthesis of friedelin (**13**).[61]



In addition to the annulation strategies presented in schemes 1.12 and 1.13, a series of attempts were made to implement polyene cyclizations to provide a faster, more efficient synthesis of (±)-alnusenone (**103**).[63-65] These cyclizations proceeded in the opposite direction of the biosynthesis, where the E-ring bore the initial cation. The polyolefin cascades were initiated through ionizing the allylic alcohols of the cyclohexenol **117** or the cyclopentenol **118**. These transformations provided the pentacyclic adducts in low yield, either 12% in the case of the cyclohexenol or an estimated 33% for the cyclopentenol (Scheme 1.14). The low yields in the cyclization forming the pentacycle **119** prevented this advanced intermediate from being converted to alnusenone (**103**) or any of the synthetic intermediates in the previous synthetic route. Conversion of the cyclopentene **120** to cyclohexenone **121** permitted a formal synthesis of (±)-alnusenone (**103**), although this approach did not improve upon the group's existing route due to lower yields and scalability. Both approaches utilized tetrasubstituted olefins to engage the initial cation to form the *trans*-fused C-D decalin core thereby installing the angular methyls in a single transformation. This approach was inferior, however, to the linear annulation strategies since the syntheses of the polyenes **117** and **118** were not higher yielding, as scalable, or more efficient.

Scheme 1.14. Ireland's polyene cyclization approaches toward (±)-alnusenone.[63-65]



Conclusion

Since the initial postulate regarding (+)-lupeol's biosynthesis, intense research has been conducted to provide strategies that chemically emulate the biosyntheses of various natural tetracyclic and pentacyclic triterpenoids. The polyene cyclization has evolved into a new successful, efficient strategy to access these natural products substantiated by the recent work of Corey and Surendra.[56,57] However, there has not been significant progress utilizing this strategy to access the friedelin natural products thereby alternative approaches have been required to synthesize this class of terpenes. These strategies are longer, inefficient syntheses that implement a high number of oxidation manipulation steps.[59-61] This warrants in-depth investigation to develop a more efficient, scalable route to provide access to these small molecules in a manner which maximizes C-C bond formation, and installs the angular methyls as well as the all-carbon quaternary centers in a stereoselective fashion while minimizing protecting group and oxidation steps. The polyene cascade provides this solution, but minimal success has been observed utilizing this strategy.[63-65] Developing a novel polyolefin cyclization employing new initiators as well as milder Lewis or Brønsted acid promoters could change these outcomes ultimately providing a successful protocol to rapidly access this class of natural products. This would allow the synthesis of celastrol (**1**), its enantiomer, and other celastroids in appreciable amounts. On the biological front, access to these small molecules would provide tools to investigate their modes of action thereby providing answers to important biological questions and directing the future development of this growing class of compounds.

Chapter 2 – Studies Toward the Synthesis of Celastrol

Retrosynthetic Analysis

The optimal synthetic strategy to construct (±)-celastrol (**1**) was planned with the goal of installing the reactive quinone methide functionality in the last step through oxidation of (±)-wilforic acid (**127**), which in turn could be derived from the permethylated pentacycle **128** (Figure 2.1). Introduction of the fully substituted carbon center at C-20 from a ketone simplified the molecule providing the pentacycle **129** as a subtarget accessed through the polyene cyclization of an achiral cyclohexadienone (**130**). The polyolefin cascade rapidly constructs the friedelin core installing each angular methyl and six contiguous stereocenters in a single diastereoselective operation. Strategic use of a chiral Lewis or Brønsted acid could impart stereoinduction to provide access to either enantiomer of celastrol (**1**) making this strategy highly desirable. The electron rich tetrasubstituted arene provides a trap for the cyclization, and due to substitution it is forced to react at a single position. The cyclization precursor was envisioned to be assembled in a convergent manner using three separate fragments: the arene, the tetrasubstituted olefin fragment, and the dienone. The crux of the strategy relied on a precedented olefination protocol to provide the tetrasubstituted alkene **131**.[65] The dienone was to be synthesized through a Birch reduction/alkylation sequence using benzoic acid (**132**) followed by a Wolff-Kishner reduction and a site-selective allylic oxidation.[59,66-72] Olefin **131** was foreseen to be derived from the ketone **133** which is accessed through the copper-mediated coupling of arene **134** to acetate **135**.[57] The arene was to be derived from the cheap, commercially available vanillin (**136**), while **135** could be synthesized from geraniol acetate (**137**) through a simple selective oxidation approach.[73,74]

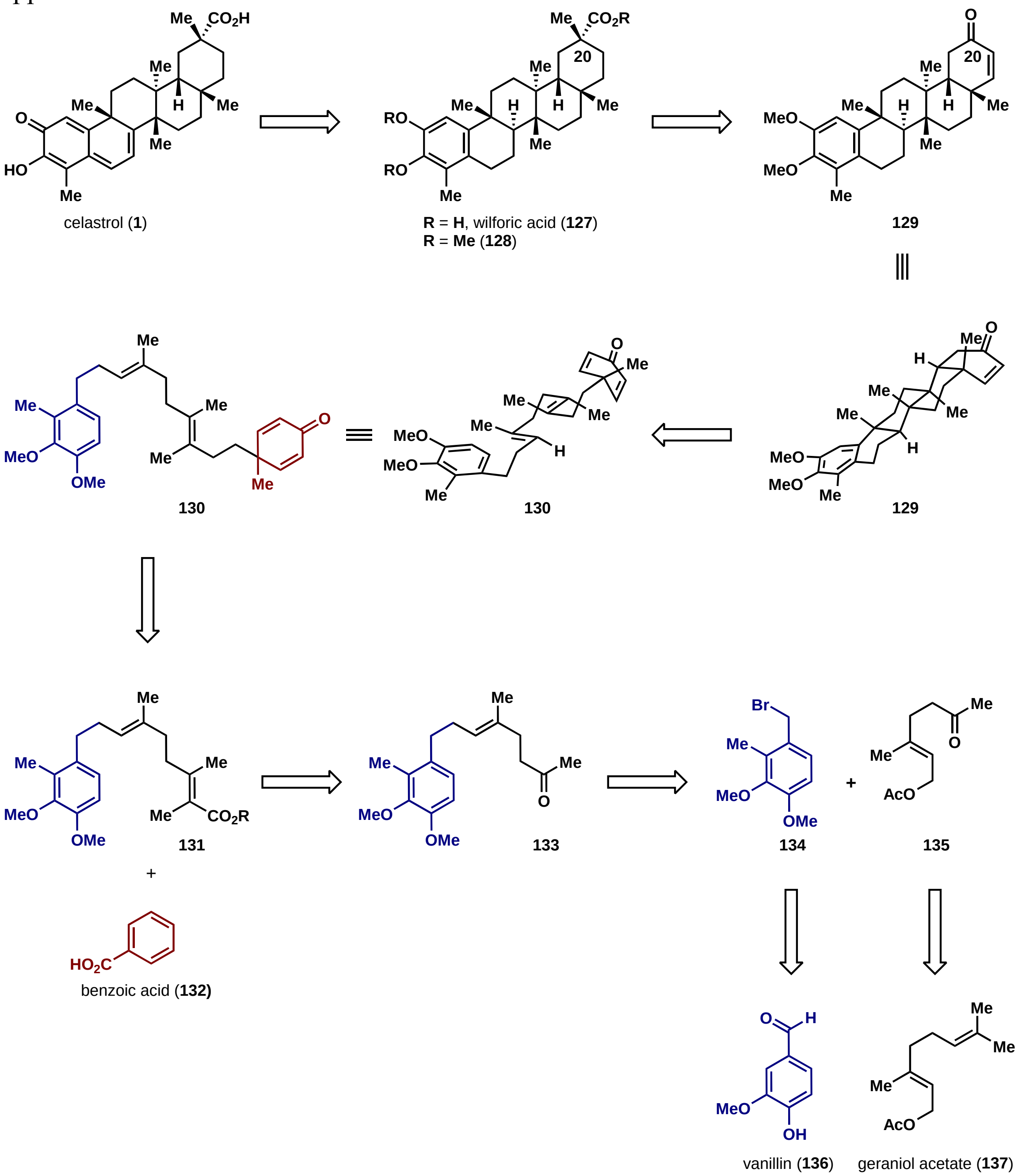
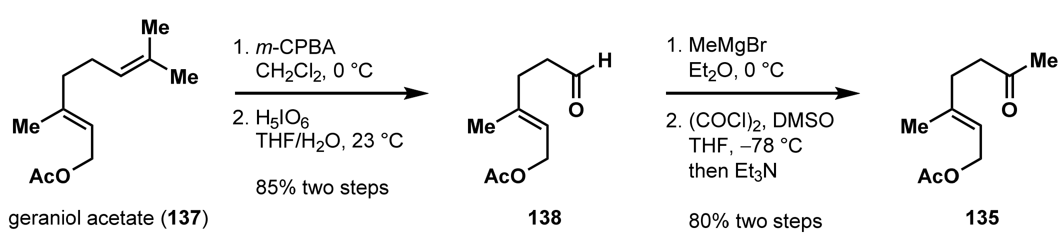


Figure 2.1. Key disconnections of celastrol and the linear precursors for the polyene cyclization.

Forward Synthesis

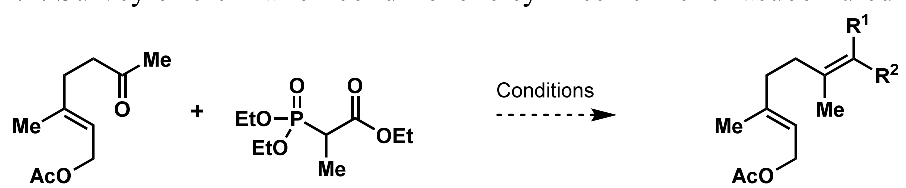
Starting from geraniol acetate, selective oxidation of the exterior olefin by treatment with *m*-CPBA in methylene chloride at 0 °C provided the epoxide; which underwent smooth oxidative cleavage with periodic acid in THF/water to provide the aldehyde **138** in good yield over two steps (Scheme 2.1).[73] This provided the aldehyde cleanly with no purification required. Ozonolysis also generated the aldehyde in a single step, but suffered from long reaction times and poor scalability. Addition of a 3 M solution of methylmagnesium bromide in diethyl ether at 0 °C provided the alcohol which was then subjected to a Swern oxidation in THF at −78 °C to provide the desired ketone **135** in four scalable steps.[74]

Scheme 2.1. Synthesis of the ketone fragment.[73,74]



The main synthetic challenge was selectively installing the tetrasubstituted alkene in appreciable yield. Bestmann demonstrated that Horner-Wadsworth-Emmons (HWE) olefinations were a viable approach to access tetrasubstituted olefins.[65] To test the plausibility of this transformation, **135** was submitted to a number of conditions. Initially, the HWE olefination between **135** and the phosphonate **139** was examined to access the desired alkene **140**. The ketone, however, was recalcitrant toward olefination using HWE, Wittig, Julia, or even Corey-Fuchs protocols.[65,75-78] The use of different bases, counter ions, additives, solvents, and temperatures did not affect any appreciable conversion of the starting ketone; only unreacted starting material was returned (Table 2.1). The Corey-Fuchs reaction would have provided the tetrasubstituted dibromo-olefin **141** which would have served as a functional handle for selective cross-coupling reactions. Literature precedence in the total syntheses of FR182877 by Evans and kedarcidin by Myers illustrated that 1,1-dibromo-alkenes can be differentiated using cross-couplings mitigated by palladium catalysis.[79,80]

Table 2.1. Survey of olefination conditions to synthesize the tetrasubstituted alkene **140**.



135 **139**

140, R^1 = Me, R^2 = CO_2Et
141, R^1, R^2 = Br
142, R^1 = Me, R^2 = $CH_2CH{=}CH_2$

Bases = NaH, LiHMDS, NaHMDS, or KHMDS

Solvent	Additives	Temperature (°C)	SM Conversion	Product E/Z Ratio
THF	----------	23 → 65	----------	----------
PhMe	----------	110	trace	1:1
xylenes	----------	140	< 5%	1:1
diglyme	----------	165	< 5%	1:1
MeCN	LiCl / DBU	77	trace	----------
MeCN	LiCl / *i*-Pr_2NEt	77	trace	----------
CH_2Cl_2	PPh_3, CBr_4, Et_3N	0 → 40	trace	----------
CH_2Cl_2	PPh_3, CBr_4, Zn	0 → 40	trace	----------
THF	$PhSO_2Et$	0 → 65	trace	----------
THF	$PhSO_2CH_2CH{=}CH_2$	0 → 65	trace	----------

An alternative approach to the polyene utilizing a B-alkyl Suzuki-Miyaura cross coupling was devised to construct the tetrasubstituted olefin from the iodo-enoate **143** and the alkyl boronate **144** (Figure 2.2).[81,82] Subjecting the aldehyde **145** to a Seyferth-Gilbert homologation followed by lithiation and trapping with ethyl chloroformate affords the ynoate.[83,84] Addition of Gilman's reagent and trapping the insipient copper allenolate with iodine would provide the enoate **143** using a landmark protocol developed by Corey and Katzenellenbogen.[85,86] The boronate **144** could be generated from benzoic acid through a sequence utilizing a Birch reduction/alkylation, selective reductions as well as oxidations, and then a selective hydroboration.[66-71,87-89]

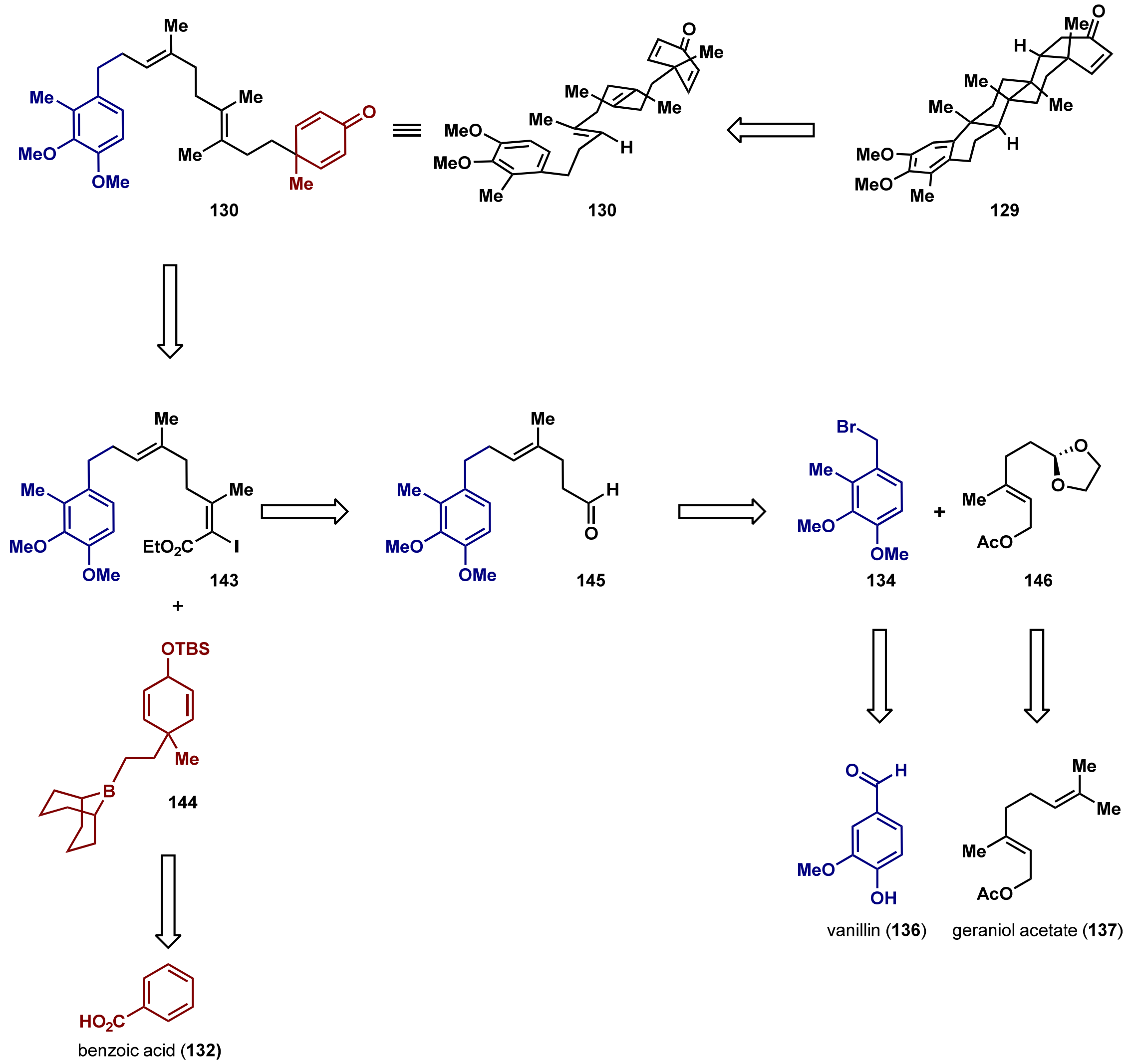
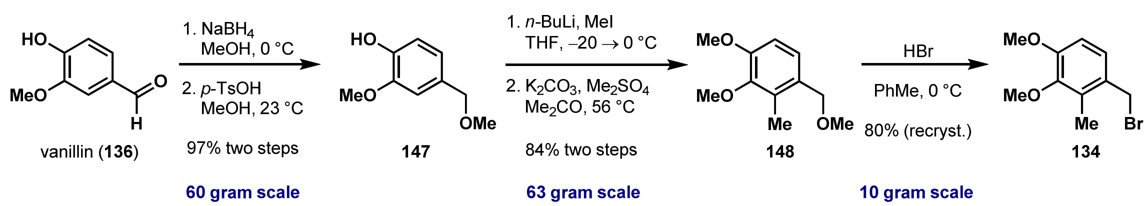


Figure 2.2. New bond disconnections to construct the desired tetrasubstituted olefin.

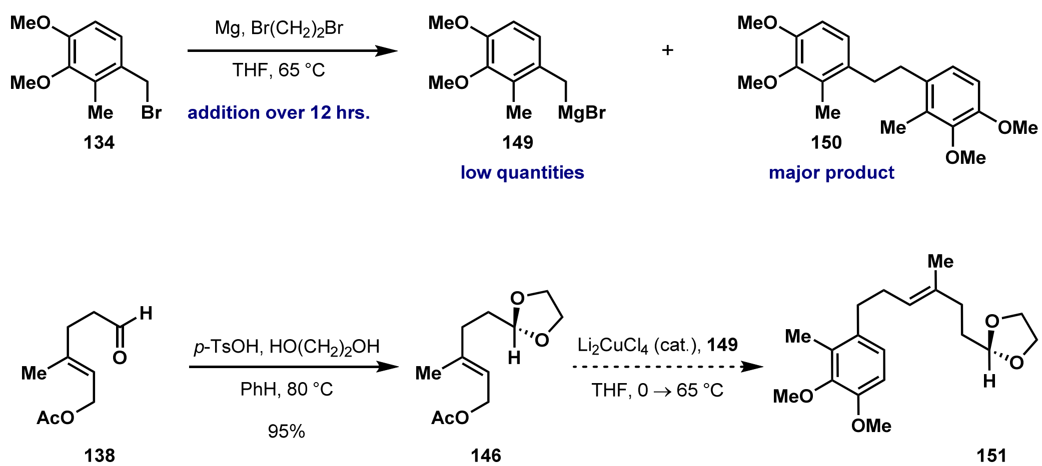
Accessing the key diene **143** required the synthesis of the aryl fragment which was conducted in a highly scalable, five step sequence (Scheme 2.2). Reduction of vanillin with $NaBH_4$ in methanol at 0 °C furnished the diol. Selective protection using catalytic *p*-toluenesulfonic acid in methanol provided the ether **147** in 97% yield over two steps on 60 gram scale. The ether was then subjected to a directed *ortho*-metallation protocol using *n*-butyllithium in THF at −20 °C. After 2.5 hours iodomethane was added to the resultant red-orange colored solution alkylating the dianion to install the tolyl methyl. The crude phenol was then etherified using dimethyl sulfate and potassium carbonate in acetone heated to reflux to generate the arene **148** in an 84% yield over two steps on 63 gram scale.[72] Unfortunately, the dianion could not be alkylated and etherified in a single operation thus requiring the two separate steps. Bromide **134** was then accessed through a reaction using concentrated hydrobromic acid in toluene at 0 °C. The biphasic mixture was stirred vigorously for two hours, and after an aqueous work-up the crude brown solid was recrystallized from hexane to afford **134** as a white crystalline solid in 80% yield.

Scheme 2.2. Synthesis of the aryl fragment.



The aryl fragment was ready to be installed through a copper mediated coupling of the Grignard **149** and the allylic acetate.[57] This warranted protection of the aldehyde therefore the dioxolane **146** was synthesized in 95% yield using catalytic *p*-toluenesulfonic acid and ethylene glycol in benzene heated to reflux (Scheme 2.3). Unfortunately, the coupling of the two fragments failed due to the inability to form the Grignard. After surveying a variety of conditions to generate the Grignard (**149**), only minimal quantities could be generated due to extensive Wurtz coupling which formed the dimer **150**. This occurred despite the slow addition of the bromide as a solution in THF over 12 hours to activated magnesium.[90] After titration, the freshly prepared green colored solution of the Grignard **149** was subjected to acetate **146** in the presence of Kochi's catalyst in THF at a range of temperatures.[57] This reaction did not render the desired coupled adduct **151**, however, only the benzyl dimer and the unreacted acetate **146** were isolated warranting a new coupling strategy.

Scheme 2.3. Attempted Grignard formation and fragment coupling.

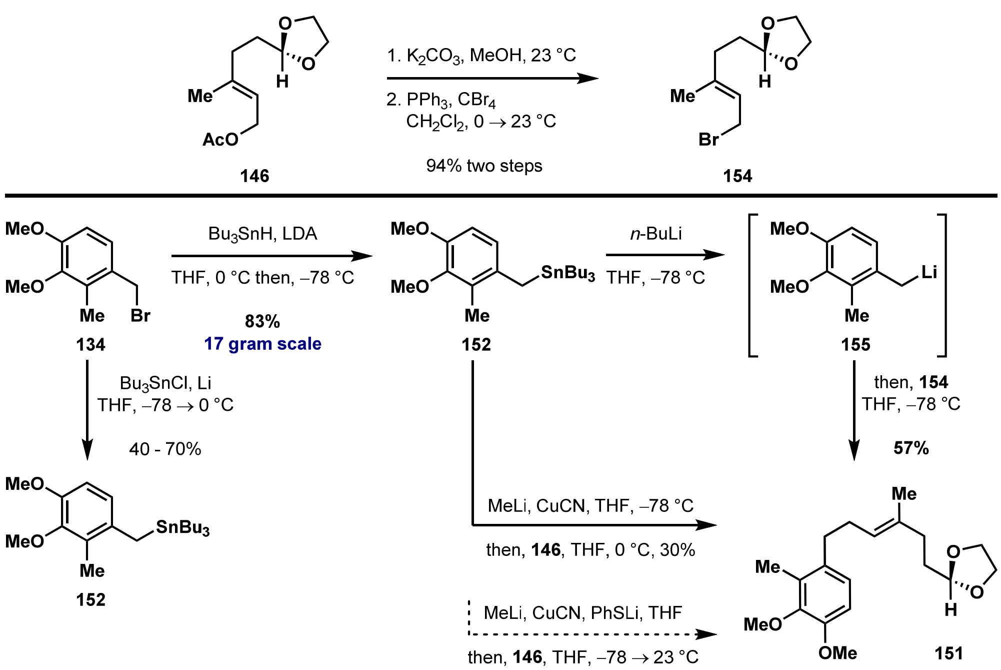


With problematic Grignard formation, tin was installed to provide a functional handle to couple the fragments avoiding significant Wurtz coupling. Stannane **152** was synthesized in the variable yields of 40-70% by alkylating lithium tri-*n*-butylstannane in THF with the benzyl bromide (Scheme 2.4). The stannyl lithium reagent was initially generated by stirring a heterogeneous mixture of lithium metal and tri-*n*-butylstannyl chloride in THF at 0 °C.[91] However, use of this green mixture afforded **152** in variable yields (40-70%) due to Wurtz coupling. After experimentation, I discovered that freshly preparing the lithium tri-*n*-butylstannane proved optimal. Deprotonating tri-*n*-butyltin hydride with freshly prepared LDA at 0 °C in THF and then slowly adding a 0.2 M solution of the bromide **134** in THF at −78 °C over three hours afforded the desired product in 83% yield.[92]

Using palladium or zinc catalysis the dioxolane **151** was inaccessible through a Stille coupling approach. However, treating two equivalents of the stannane with the freshly prepared higher order cuprate $Me_2CuCNLi_2$ in THF at −78 °C followed by warming the golden-yellow solution to 0 °C afforded the desired benzyl cuprate. Slowly adding the allylic acetate to the cuprate successfully coupled the fragments together to provide the arene **151** in 30% yield. The yields of this reaction varied, and using excess stannane was not ideal. Attempts to improve the reaction by using one equivalent of the benzyl tin reagent or a thio-cuprate unfortunately failed to provide the coupled product. It is important to note that this is a modification of the established protocol developed by Lipshutz, representing an extension of his work in the coupling of allylic acetates and alkyl halides to allylic stannanes.[93-95]

Despite successful coupling, the low variable yields and the required use of excess stannane proved inadequate to generate sufficient material. So, a new coupling strategy was devised employing a hard alkylation of the lithiated arene which was generated through a tin-lithium exchange. Treating the benzyl stannane with *n*-butyllithium in deoxygenated THF at −78 °C provided an orange colored solution containing the benzyl lithium species. The bromide **154** was then added to this solution to afford the desired coupled product in 57% yield. It is imperative that deoxygenated THF was used and the bromide was added slowly over the course of 1 hour or else significant Wurtz coupling was observed. Bromide **154** was prepared in two steps by treating the acetate with a mixture of potassium carbonate in methanol and then subjecting the allylic alcohol to an Appel reaction to generate the bromide using carbon tetrabromide and triphenylphosphine in methylene chloride. The byproduct, triphenylphosphine oxide, complicated the purification because the crude bromide rapidly decomposed on silica gel, basic alumina, and during distillation. However, triturating the mixture with cold pentane delivered the bromide after filtration as a pale yellow oil in >95% purity and 94% yield.

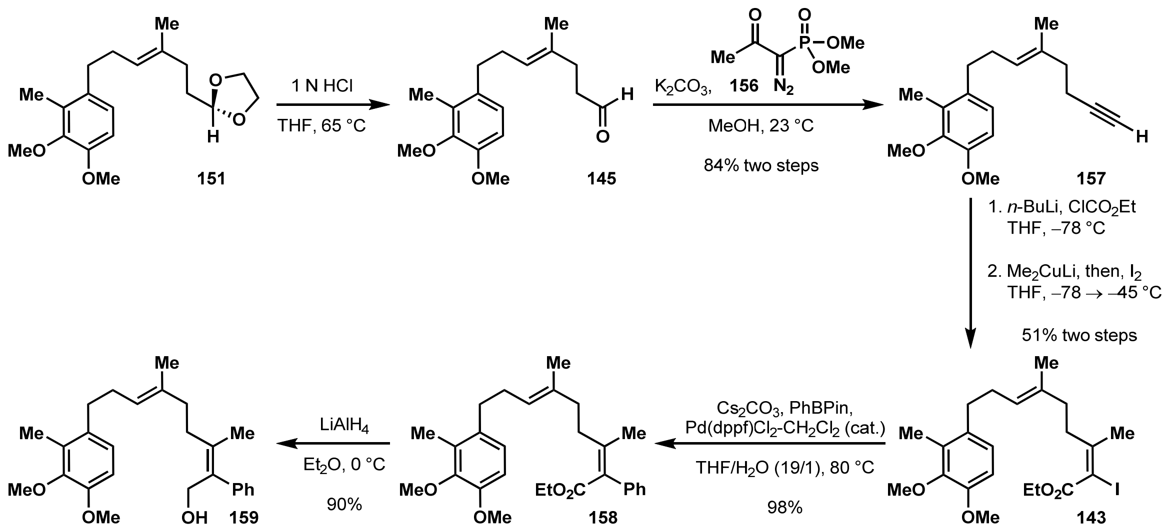
Scheme 2.4. Synthesis of aryl dioxolane **151**.



The dioxolane was hydrolyzed using a solution of 1 N HCl and THF heated to 65 °C to deliver the aldehyde **145** (Scheme 2.5). Treatment with the Bestmann-Ohira reagent (**156**) and potassium carbonate in methanol generated the terminal acetylene **157** through a Seyferth-Gilbert homologation.[83,84] The alkyne was then metalated using *n*-butyllithium in THF at −78 °C, and the resultant lithium acetylide was trapped with ethyl chloroformate to afford the ynoate in 83% yield. Conjugate addition using freshly prepared Gilman's reagent in THF at −78 °C generated the copper allenolate which was iodinated to provide the tetrasubstituted iodo-enoate **143** in 61% yield using the protocol developed by Corey and Katzenellenbogen.[85,86] The observed side products were over addition of Me_2CuLi and those associated with adducts of halo-ene cyclizations. It was imperative that this reaction be conducted at temperatures lower than −45 °C as isomerization of the copper allenolate would occur to provide the undesired *cis*-vinyl iodide.[85] Unfortunately, the copper allenolate could not be alkylated using alkyl halides thereby eliminating the potential to assemble the polyene in a single operation.

The capability of **143** to participate in a Suzuki-Miyaura cross-coupling was then examined. Subjection to catalytic palladium(dppf) dichloride and cesium carbonate in a THF/water mixture heated to 80 °C, the iodide could be coupled to the pinacolate ester of phenyl boronic acid in near quantitative yield to afford the styrene **158**.[96,97,82] At this point the ester was reduced with lithium aluminum hydride in ether to access the allylic alcohol **159** in 90% yield with the desired *trans*-alkene confirmed by NOE spectroscopy.

Scheme 2.5. Synthesis of iodo-enoate fragment.

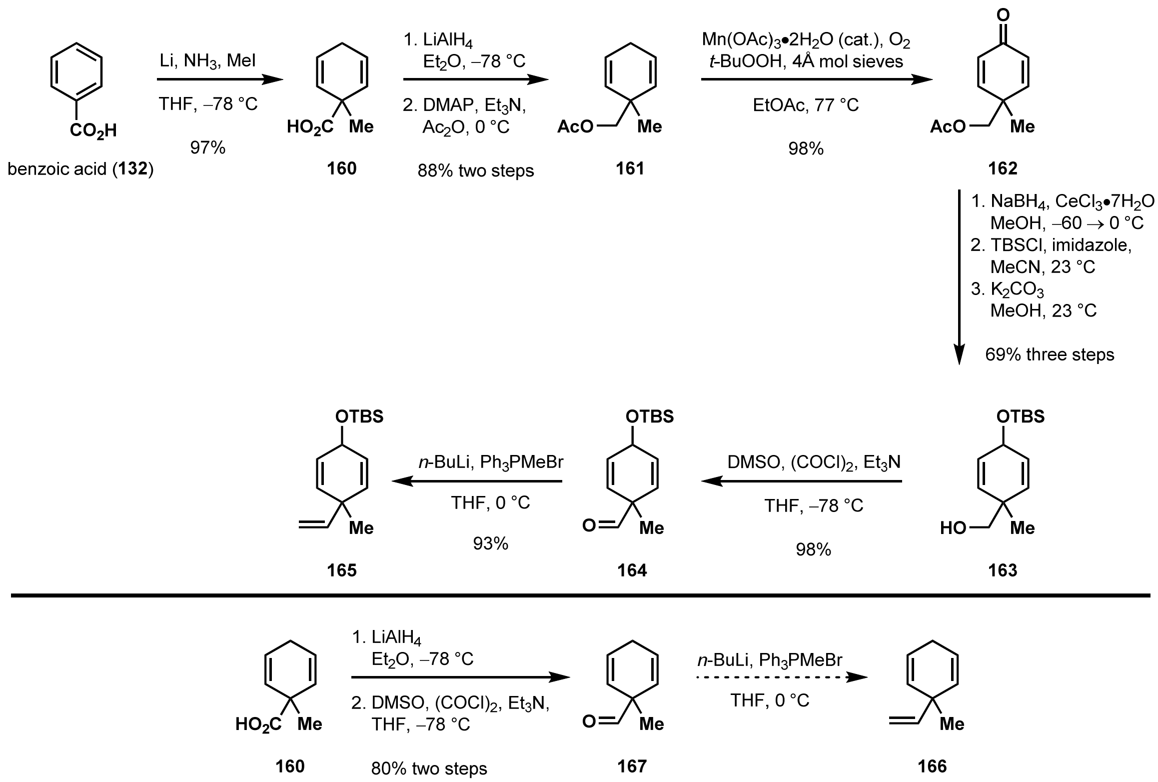


With access to **143** and proof of its excellent potential as a partner in cross-couplings, attention was directed towards constructing the alkyl boronate fragment **144** and examining its reactivity in B-alkyl Suzuki reactions. Birch reduction of benzoic acid using lithium metal in THF and liquid ammonia at −78 °C and then addition of iodomethane to the dark blue mixture to alkylate the resultant dianionic enolate afforded the cyclohexadiene **160** in 97% yield.[66-70] The acid was reduced with lithium aluminum hydride in ether at −78 °C to render the alcohol which was then immediately protected without purfication as the acetate using DMAP, triethylamine, and acetic anhydride to provide the acetate **161** in 88% over two steps. It was imperative to conduct the reduction at −78 °C due to the facile nature of isomerization to the conjugated diene. Also, the acetate was a vital protecting group because of its easy deprotection in later stages where other protecting groups facilitated decomposition during their removal.

Employing the protocol developed by Shing and co-workers, allylic oxidation mediated by manganese triacetate and *tert*-butylhydrogen peroxide in ethyl acetate heated to reflux under an aerobic atmosphere afforded the dienone **162** in near quantitative yield.[71] This material was extremely sensitive to acidic and basic conditions primarily decomposing through a 1,4-phenolic rearrangement pathway. It was therefore subjected to a Luche reduction using sodium borohydride and cerium trichloride heptahydrate in methanol at −60 °C to deliver the alcohol.[89] The temperature of this reaction was critical because significant 1,4-reduction was observed without proper cooling of the reaction. The allylic alcohol was then protected as the silyl ether with *tert*-butyldimethyl chlorosilane and imidazole in acetonitrile which was subjected to methanolysis to generate the alcohol **163** in 69% yield over three steps.

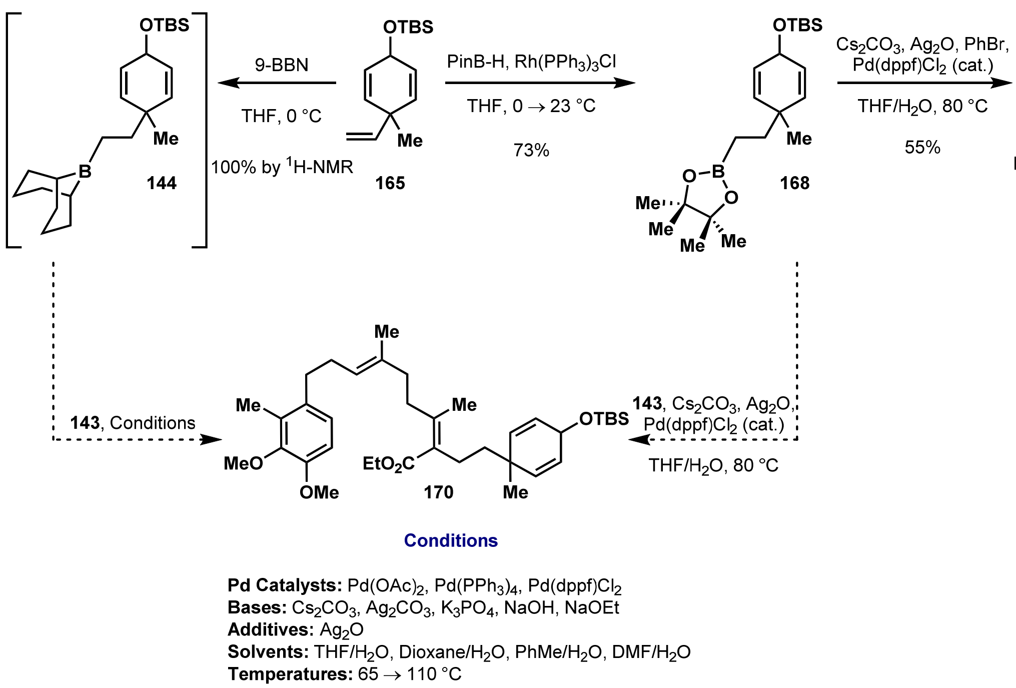
The use of Dess-Martin periodinane to oxidize the alcohol was problematic because the aldehyde rapidly decomposed under these conditions despite buffering the reaction. However, a modified Swern oxidation successfully generated the aldehyde **164** in near quantitative yield.[74] Lastly, Wittig olefination of the aldehyde with the freshly prepared methyl triphenylphosphorane ylide in THF at 0 °C delivered the triene **165** in 93% yield.[77] Despite undesired oxidation and protecting group manipulation steps, this route worked successfully on multigram scale to provide the triene. Attempts to minimize these unwanted steps were unsuccessful because of the volatility of triene **166**. Wittig olefination of the aldehyde **167** did work, but **166** could not be purified. The triene forms a positive azeotrope with THF and distillation caused decomposition to a black tar substance even in the presence of BHT. Hydroborating the crude material directly also did not work thereby prompting the lengthy oxidation strategy.

Scheme 2.6. Synthesis of triene fragment.



Employing the protocol developed by Evans, the triene **165** was selectively hydroborated using Wilkinson's catalyst and pinacolborane in deoxygenated THF to provide the desired alkylboronic ester **168** in 73% yield (Scheme 2.7). This moiety was initially reluctant to couple to simple aryl halides through a B-alkyl Suzuki coupling, but eventually I discovered that using a mixture of stoichiometric silver (I) oxide, catalytic palladium(dppf) dichloride, and cesium carbonate in hot THF/water, the alkyl boronic ester couples to simple aryl halides such as bromobenzene in modest yield. The silver (I) oxide is critical as no coupling occurs in its absence; only unreacted starting material is returned. Unfortunately, treating the mixture of boronate **168** and iodide **143** to these same conditions caused decomposition of the starting materials with no observation of the coupled product. At this stage, due to the difficulty of coupling the pinacolate to even simple substrates, boronate **144** was envisioned to be a better coupling partner due to the enhanced reactivity of these entities in cross-couplings.[81,82] Boronate **144** was accessed by selectively hydroborating the triene **165** with crystalline 9-BBN in THF at 0 °C. After examination of the key coupling reaction, however, the two fragments did not couple using this strategy thereby warranting a different approach to the polyene.

Scheme 2.7. Failed B-alkyl Suzuki-Miyaura to couple fragments.



Constructing the tetrasubstituted alkene remained elusive, so installing the olefin at the beginning became the focus. Originally, I sought to construct the alkene using a protocol developed by Maercker entailing the stereoselective reduction of an internal alkyne which generates a vicinal dimetallated olefin. Alkylation of the dianion with iodomethane would then deliver the desired alkene.[100-103] Unfortunately, this procedure failed. It was foreseen that the desired olefin could be synthesized in the initial step through a bromination of 2,3-dimethyl butadiene to afford the bromide **123**.[104,53] This provides a synthon to access the symmetrical diketone **171** which installs the functionality required to obtain the alcohol **172**. Coupling this moiety to the aryl fragment through a tin-lithium exchange mediated alkylation sequence would deliver the triene **173**. A selective oxidation and annulation installs the cyclohexenone fragment ultimately to afford the desired polyene **174**. This new strategy maximizes C-C bond formation and eliminates undesired oxidation and protecting group manipulation steps.

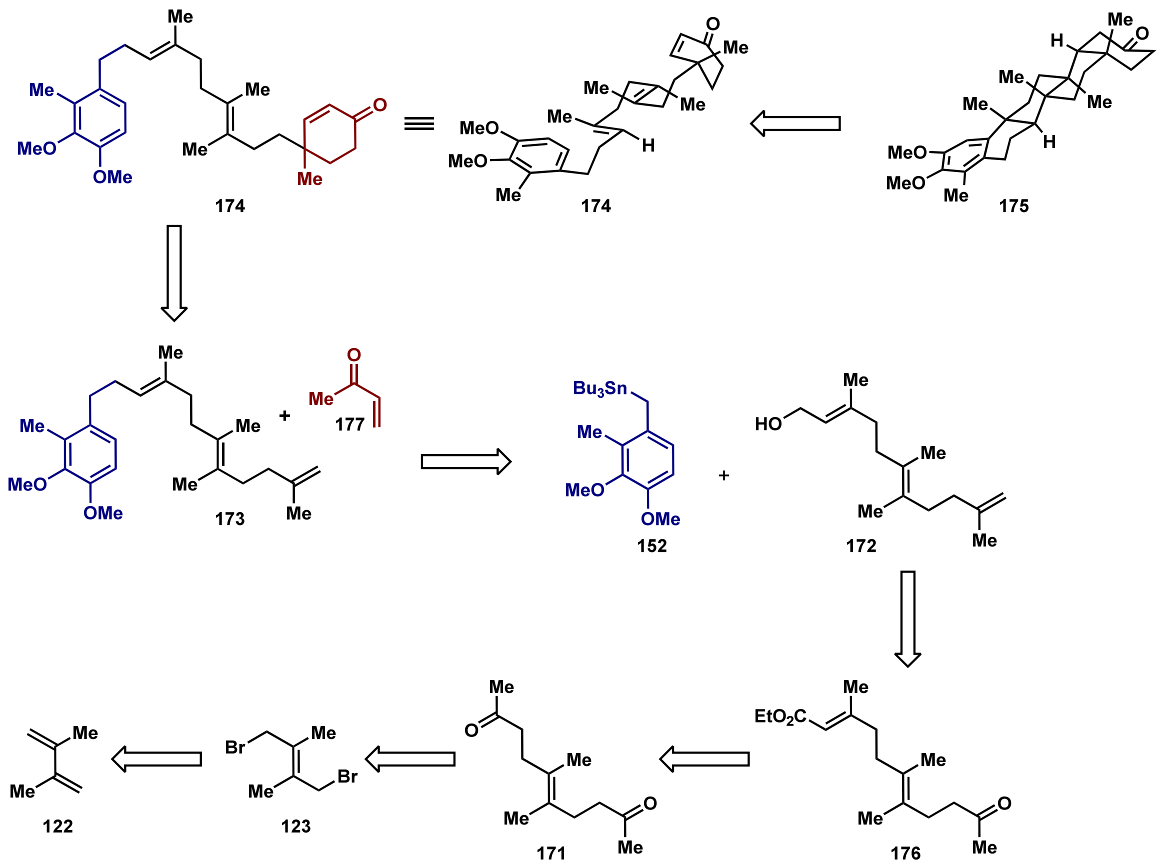
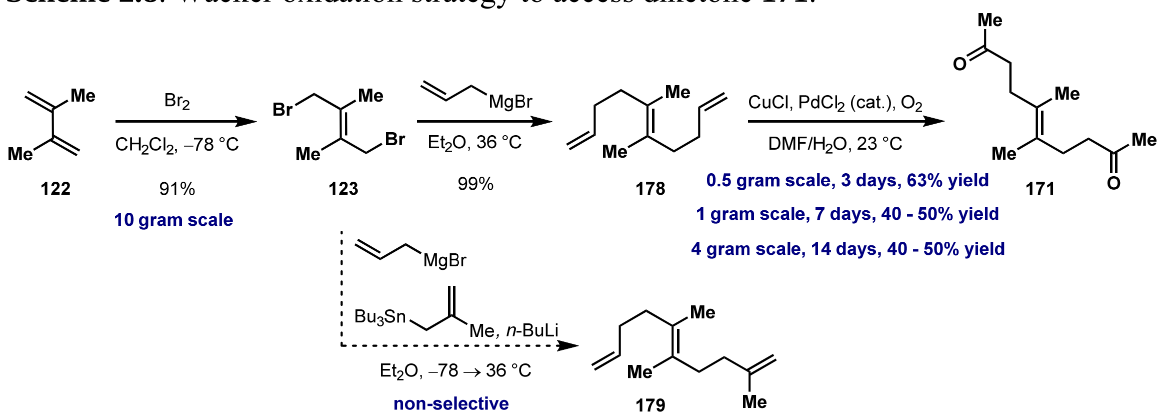


Figure 2.3. New strategy for the synthesis of the polyene **174**.

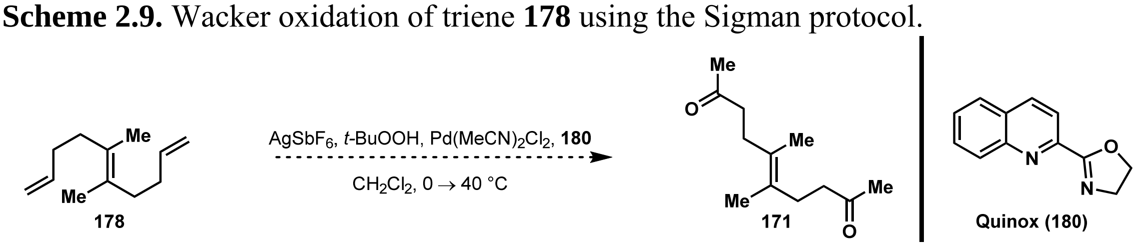
Slow addition of one equivalent of bromine to 2,3-dimethyl butadiene in methylene chloride at −78 °C afforded the dibromide **123** as a crystalline, lacrimating solid.[104] Desymmetrization proved unsuccessful using one equivalent of allylmagnesium bromide and methylallyl lithium (Scheme 2.8). However, allylation of the bromide with two equivalents of allylmagnesium bromide in ether heated to reflux provided the triene **178** in quantitative yield. Double Wacker oxidation using the Tsuji protocol produced the diketone, albeit in modest yields with moderate scalability.[105]

Scheme 2.8. Wacker oxidation strategy to access diketone **171**.



The long reaction times and low yields on appreciable scales warranted investigation into a more efficient process. The Wacker protocol developed by Sigman and co-workers was then employed using the quinox ligand **180**, catalytic palladium, TBHP, and silver hexafluoroantimonate in methylene chloride (Scheme 2.9).[106,107] These conditions induced rapid decomposition only to afford the desired diketone in low yields.

Scheme 2.9. Wacker oxidation of triene **178** using the Sigman protocol.

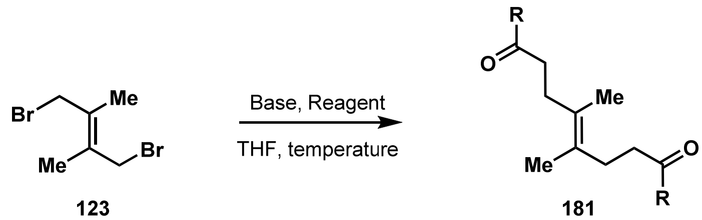


Heavy focus was now placed on alkylating enolates with the dibromide to install the desired carbonyl functionality. This was not a trivial task due to the formation of undesired cyclopropanated products (Table 2.2). Using the enolate of dimethylacetamide, however, the formation of these undesired adducts was minimized.

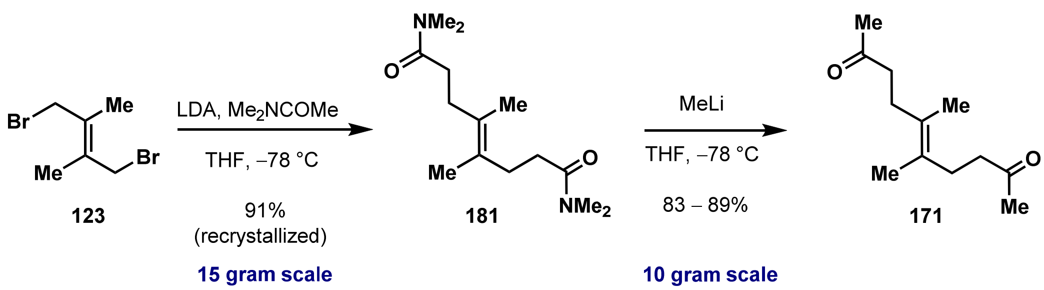
The steric bulk and the difficult nature of deprotonating the α-carbon of amides compared to esters, malonates, and β–keto esters facilitated the alkylation to generate the diamide **181** in high yield forestalling intramolecular cyclopropanation. Slow addition of dimethylacetamide to a freshly prepared solution of LDA in THF at −78 °C followed by the slow dropwise addition of bromide **123** as a solution in THF generated the diamide as a white crystalline solid in 91% yield after recrystallization. This reaction was successfully repeated on 15 gram scale to provide appreciable quantities of **181**.

Subjecting the amide to methylmagnesium bromide either alone or in combination with anhydrous cerium trichloride as well as BF_3-OEt_2 at various temperatures returned the unreacted starting material. Using methyl lithium at different temperatures in THF was unselective, but combined with freshly dried zinc bromide in ether at −10 °C afforded the desired ketone, albeit in variable yields with moderate scalability.[108,109] However, after examining the solubility of the diamide in ethereal solvents I discovered that prolonged cooling in THF at −78 °C produced a white heterogeneous mixture, and slow addition of methyl lithium to the mixture facilitated the synthesis of the diketone selectively in high yields reliably on multigram scales. The selective delivery of one equivalent of an alkyl lithium or a lithium acetylide into amides to generate ketones in a single operation has also been observed by Trost.[110,111] At −78 °C the tetrahedral intermediate, formed after the initial nucleophilic addition, is persistent which causes a selective addition to occur as long as the temperature remains at −78 °C. This was confirmed by Trost and Phan when they attempted to add a lithium acetylide into an amide.[110] Upon neutralization of the reaction media with water the starting amide was returned. However, when BF_3-OEt_2 was added at −78 °C the propargyl ketone was afforded in high yield after neutralization. Alkyl lithium reagents, however, do not require the use of Lewis acids prior to neutralization. This predicates the minimal selectivity originally observed at reaction temperatures warmer than −78 °C when using methyl lithium. However, upon properly cooling the reaction mixture to −78 °C through equilibration over one hour and maintaining this temperature through a controlled dropwise addition of methyl lithium, the diketone could be synthesized in high yield. Recrystallization from hexane produced a white crystalline solid which X-ray diffraction unambiguously confirmed as the diketone **171** (see Experimental Section).

Table 2.2. Alkylation of different enolates using bromide **123** ultimately providing diketone **171**.

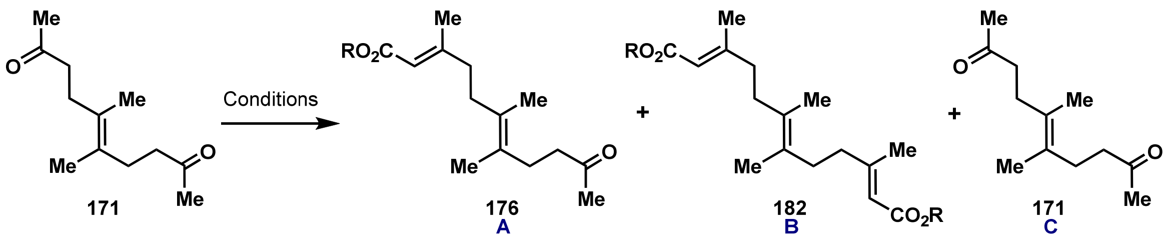


Base	Reagent	Temperature (°C)	Isolated Yield of Product (%)
NaH	EtO_2CCH_2COMe	0 → 23	trace, R = CH_2CO_2Et
LiHMDS	EtO_2CCH_2COMe	0 → 23	trace, R = CH_2CO_2Et
LDA	$MeCO_2Me$	–78	34, R = OMe
LDA	$MeCO_2Et$	–78	35, R = OEt
LDA	MeCON(OMe)Me	–78	0, R = N(OMe)Me
LDA	$MeCONMe_2$	–78	85, R = NMe_2



A Horner-Wadsworth-Emmons olefination was employed to desymmetrize the ketone (Table 2.3).[112] After varying the phosphonates, bases, solvents, and temperatures I discovered the ideal conditions, in regards to yield and E/Z selectivity, were triethyl acetophosphonate and sodium bis(trimethylsilyl) amide in warm toluene. The enoate **176** was provided in a 60% isolated yield with a 6:1 E/Z selectivity using this protocol. The remaining material consisted of the undesired dienoate **182** isolated in 26% yield and recovered starting material isolated in 14%. This yield varies from the expected statistical outcome possibly due to the slow elimination of the insipient alkoxy phosphonate after the initial nucleophilic addition. This produces an intermediate which is reluctant to form the high energy dianion generated through a second addition of the remaining acetophosphonate.

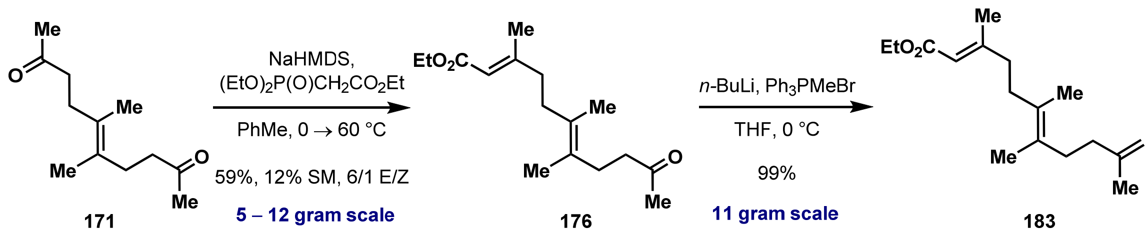
Table 2.3. Differentiation of symmetrical ketone **171** via HWE olefination.

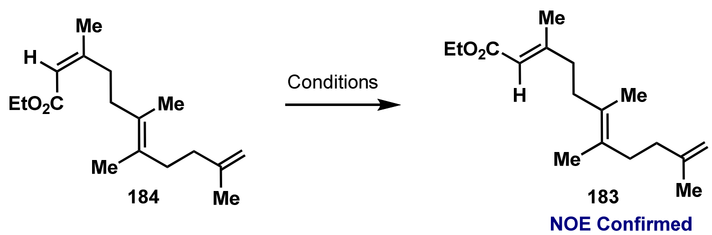


Solvent	Phosphonate	Base	Temp. (°C)	% Yield (A / B / C)	E : Z Ratio
THF	*t*-$BuO_2CCH_2PO(OMe)_2$	LiHMDS	0 → 23	24 / 40 / 36	4 : 1
THF	*t*-$BuO_2CCH_2PO(OMe)_2$	NaHMDS	0 → 23	33 / 30 / 36	3 : 1
THF	*t*-$BuO_2CCH_2PO(OEt)_2$	NaHMDS	0 → 23	37 / 30 / 33	6 : 1
THF	$EtO_2CCH_2PO(OEt)_2$	NaHMDS	0 → 23	60 / 18 / 21	4 : 1
PhMe	$EtO_2CCH_2PO(OEt)_2$	NaHMDS	0 → 23	37 / 20 / 43	6 : 1
PhMe	$EtO_2CCH_2PO(OEt)_2$	NaHMDS	0 → 60	60 / 26 / 14	6 : 1

The fidelity of this transformation was preserved on multigram scale with minimal loss in yield, but at this stage the olefin isomers were inseparable. Subjecting the ketone **176** to a Wittig olefination using the freshly prepared methyl triphenylphosphorane ylide in THF at 0 °C, the triene **183** was generated in quantitative yield (Scheme 2.10). After examination of different solvent conditions, the E/Z isomers could be separated chromatographically using benzene as the eluent, and the correct isomer was confirmed through NOE spectroscopy (see Experimental Section). In order to maximize material pushed to the forefront, the isomerization of the *cis*-isomer **184** was investigated. Usually iodine or transition metal catalysis is employed to isomerize these types of olefins, but these conditions are detrimental. So, different nucleophiles which add in a conjugate fashion to facilitate formation of the thermodynamic *trans*-isomer were examined. However, phosphine, thiol, and nitrogen nucleophiles were recalcitrant to reacting with this moiety. Focus was then placed on using bases to promote extended enolization. Subjecting the *cis*-enoate **184** to freshly prepared sodium ethoxide in ethanol at 23 °C generated the desired product in 51% isolated yield. The remaining recovered material was the *cis*-isomer.

Scheme 2.10. Synthesis of trienoate **183**.



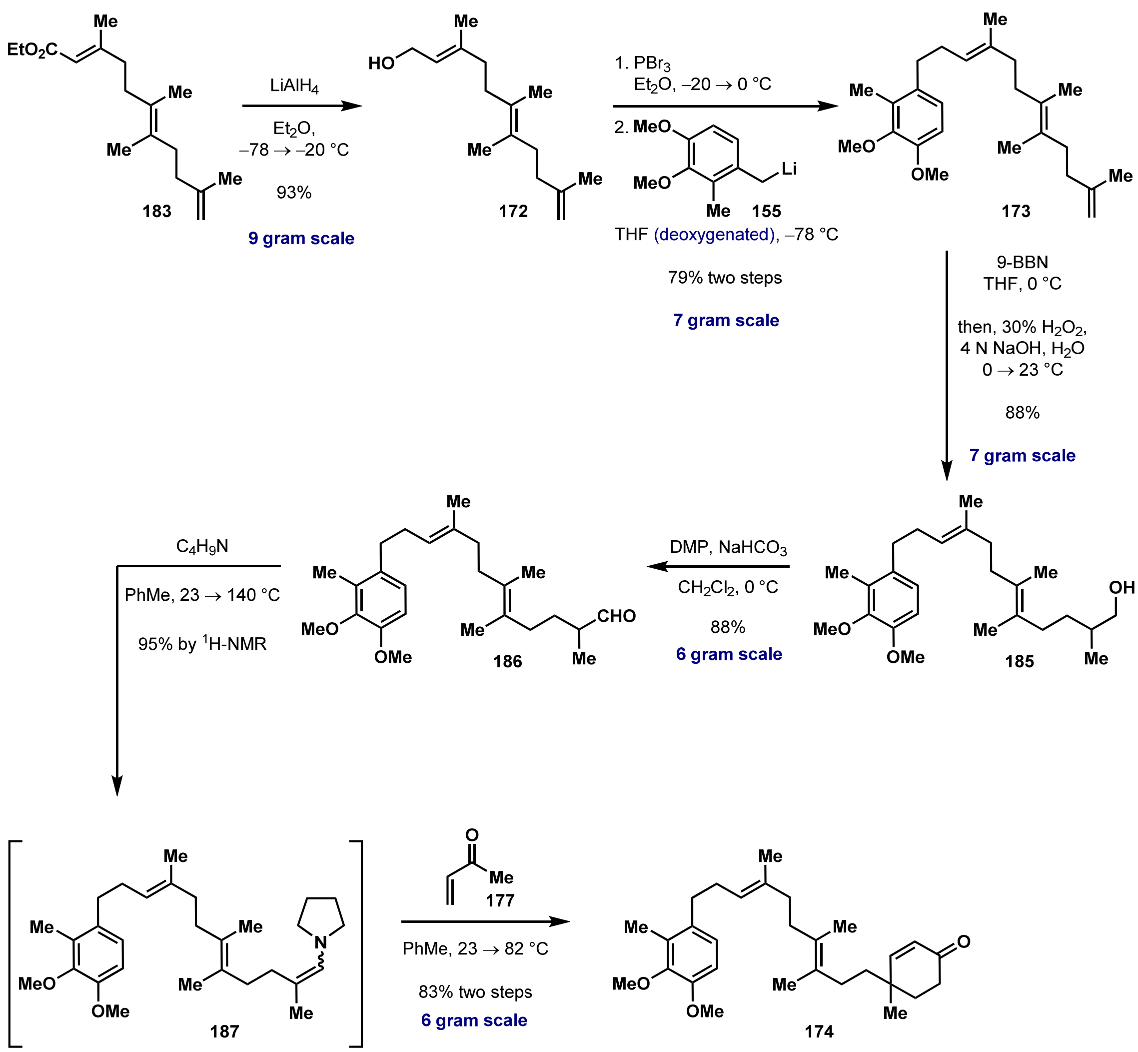


Solvent	Reagent	Temperature (°C)	Result (*trans*/*cis* %)
$EtOH/CHCl_3$	DABCO	0 → 80	No isomerization
$EtOH/CHCl_3$	PPh_3	0 → 80	No isomerization
$EtOH/CHCl_3$	PhSH/NaH	0 → 80	No isomerization
$EtOH/CHCl_3$	L-cysteine	0 → 80	No isomerization
$EtOH/CHCl_3$	L-cysteine•HCl	0 → 80	No isomerization
EtOH	NaOEt	0	<5% *trans*, 95% *cis*
EtOH	NaOEt	23	51% *trans*, 48% *cis*
EtOH	NaOEt	23 → 80	Decomposition

Addition of lithium aluminum hydride to an ethereal solution of the ester, and allowing the pale yellow homogeneous solution to warm gradually from −78 to −20 °C over five hours provided the alcohol **172** in 93% yield (Scheme 2.11). Careful analysis of the reaction progress by TLC proved necessary because significant 1,4-reduction was observed when the temperature rose above −10 °C. Halogenation of the alcohol using phosphorus tribromide in ether provided the allylic bromide.[112] After aqueous work-up, the crude bromide was used directly in the alkylation step without purification. Addition of *n*-butyllithium to a solution of the benzyl stannane **152** in deoxygenated THF at −78 °C generated a red-orange solution of the benzyl lithium species **155**. This was then alkylated by the bromide to couple the two fragments together, generating the aryl triene **173** in 79% yield starting from the alcohol. Selective hydroboration of the 1,1-disubstituted olefin with crystalline 9-BBN dimer in THF at 0 °C proceeded smoothly.[88] NMR analysis of an aliquot from the crude reaction solution determined complete conversion after four hours upon which a solution of 4 N NaOH with 30% H_2O_2 in water was added. The biphasic mixture was stirred vigorously for 60 hours to produce the desired alcohol **185** in 88% yield. Oxidation using Dess-Martin periodinane with solid sodium bicarbonate in methylene chloride at 0 °C afforded the aldehyde **186** in 88% yield.[113] Treatment with pyrrolidine in toluene and heating the solution to 140 °C for 24 hours generated the enamine **187**. After concentrating the reaction solution, analysis of the crude orange viscous oil by ^{1}H-NMR in C_6D_6 revealed the enamine was approximately 95% pure with 4% of the starting aldehyde remaining. Treatment with two equivalents of methyl vinyl ketone in toluene at 82 °C afforded the resultant annulated β-pyrrolidine adduct which was hydrolyzed with an acetic acid/sodium acetate buffer to deliver the desired enone **174** in 83% yield from the starting aldehyde.[64,115]

Commencing from 2,3-dimethyl butadiene, the polyene **174** was synthesized in 11 steps in an overall 21% yield. It is a highly scalable strategy capable of reliably providing the enone in quantities greater than five grams representing one of the most efficient, highest yielding syntheses of a polyene precursor to date.

Scheme 2.11. Synthesis of the polyene enone **174**.



Significant examination of the polyolefin cyclization ensued (Table 2.4). As a new type of initiator, this transformation is highly desirable not only to rapidly construct the carbocyclic core in a diastereoselective fashion, but also to deliver the pentacycle at the correct oxidation state. Heating the enone to various temperatures in methylene chloride, dichloroethane or even chlorobenzene under pressure promoted no reactivity.

The use of BF_3-OEt_2 or titanium tetrachloride at a range of temperatures only promoted decomposition of the starting material with no observation of the cyclized product. Titanium *iso*-propoxide induced no conversion of starting material despite heating the reaction mixture to reflux in methylene chloride.

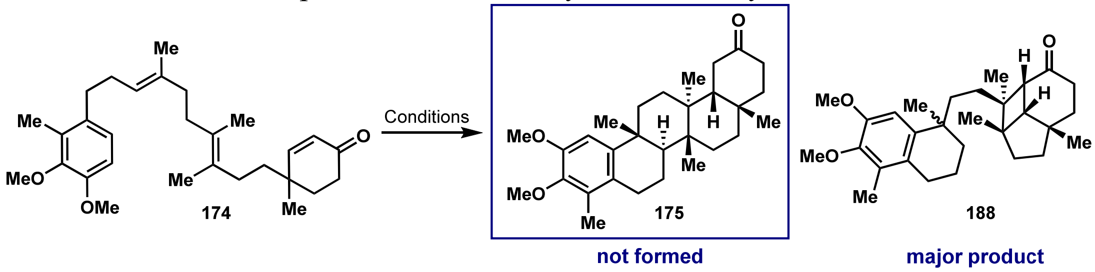
Treating the enone with *tert*-butyldimethylsilyl trifluoromethane sulfonate in a dilute solution of methylene chloride at 0 °C afforded **what was initially believed** to be the cyclized product **175** in an isolated 5% yield. No increase in yield was attained despite conducting the reaction at lower temperatures in a more dilute solution. Throughout the course of the reaction the silyl enol ether was never observed dictating that it was either being hydrolyzed or trifluoromethane sulfonic acid was actually promoting the cyclization. To confirm the latter, two control experiments were conducted. First, the enone was treated with the silyl triflate in the presence of freshly distilled Hunig's base. No cyclization was observed, only unreacted starting material was returned. Second, the enone was treated with catalytic and stoichiometric quantities of trifluoromethane sulfonic acid. Stoichiometric amounts of the acid prompted swift decomposition of the polyene, but the cyclized adduct was attained in 5% yield by treating the enone with 10 mol% of the acid. The remainder of the material consisted of products which were beyond structural assignment.

The use of milder Brønsted acids such as pyridinium *p*-toluenesulfonate, diphenyl phosphoric acid, or *p*-toluenesulfonic acid did not induce any reaction. Switching to concentrated hydrochloric acid in methylene chloride at 23 °C generated the product in a 35% yield as a 2:1 mixture of diastereomers. This result was somewhat surprising as in theory the cyclization should occur in a stereospecific manner. The diastereomers are formed as the aryl ring engages the trisubstituted olefin, which was determined by subjecting the isomerically impure starting material (6:1, trisubstituted alkene) to the identical reaction conditions. The product was isolated in the exact same yield and d.r. as when isomerically pure material was used. This was also unambiguously confirmed by 2D-NMR spectroscopy.

The lower yields and diastereoselectivity warranted further probing of milder Lewis acids to improve the yield. Despite literature precedence on promoting ene-type reactions with enones, aluminum reagents showed modest improvements in yield or diastereoselectivity.[115] Sen and co-workers showcased the use of anhydrous ferric chloride as well as its hexahydrate to promote polyene cyclizations with epoxides which prompted exploration of these reagents in the cyclization of enone **174**.[116] Treating a highly dilute solution of the enone in deoxygenated methylene chloride with 1.5 equivalents of anhydrous ferric chloride promoted the cyclization to afford the product in an isolated 77% yield on 20 milligram scale.

At this stage only ^{1}H-NMR analysis in a variety of deuterated solvents as well as IR spectroscopy and mass spectrometry were used to assign the structure because the mixture of diastereomers severely complicated the ^{13}C-NMR spectra. Therefore, the tentative structural assignment remained invalidated. After an exhaustive investigation, I discovered that using an isochratic solution of dioxane in hexane the diastereomers could be separated by silica gel chromatography. X-ray diffraction could not be used to confirm the structure because the ketone was an amorphous foam. Reducing the ketone and protecting the alcohol as the tosylate, conversion to the tosyl hydrazone, or protecting the catechol as either the *m*-dinitro or *p*-bromo benzoates only produced foams unworthy of X-ray diffraction. However, the fidelity of the cyclization translated excellently above the milligram scale. On one gram scale, the cyclized adduct was provided in 65% yield as a 3:1 mixture of diastereomers. The scalability of the reaction provided a surplus of material and the ability to separate the diastereomers allowed the structure to be elucidated by 2D-NMR: COSY, DEPT, NOESY, HSQC, HMBC, and ^{13}C-INADEQUATE. The results of these experiments clearly indicated that the cyclohexanone **188** was the actual product of these cyclizations, not the desired pentacycle **175**. This molecule was produced through a cationic [2+2] pathway to generate the 4,5,6-tricycle which then undergoes a second annulation between the arene and the trisubstituted olefin, ultimately generating the diastereomers of the reaction.[117-119] This heartbreaking result nearly thwarted future endeavors.

Table 2.4. Selected examples of the cationic cyclization of cyclohexenone **174**.



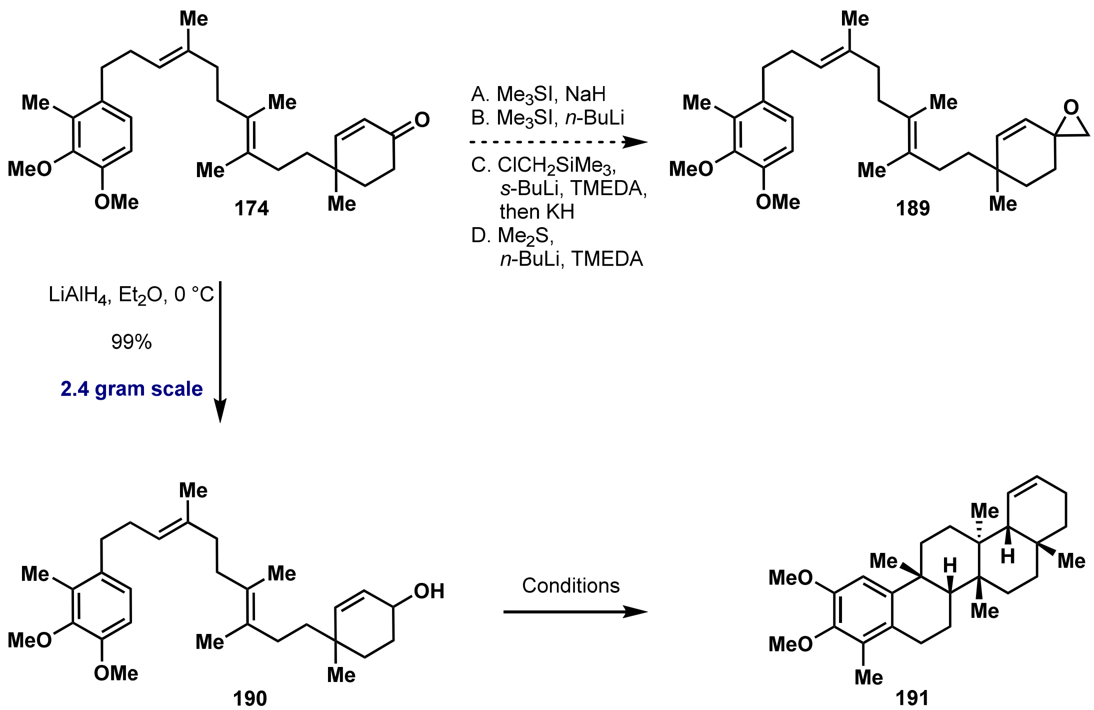
Reagent	Mol %	Solvent	Concentration (mM)	Temperature (°C)	Result (% Yield, D.R.)
----------	----------	CH_2Cl_2, DCE, or PhCl	100	40 → 165	No Reaction
PPTS	110	CH_2Cl_2	2	0 → 40	No Reaction
$(PhO)_2PO_2H$	110	CH_2Cl_2	2	0 → 40	No Reaction
TsOH – H_2O	110	CH_2Cl_2	2	0 → 40	No Reaction
HCl	110	CH_2Cl_2	2	0 → 23	**188** (35%, 2:1)
TfOH	150	CH_2Cl_2	3	–78 → 0	Decomposition
TfOH	10	CH_2Cl_2	3	–78 → 0	**188** (5%, 2:1)
Tf_2O	110	CH_2Cl_2	1	–78 → 0	No Reaction
Tf_2O	110	CH_2Cl_2	1	0 → 23	Decomposition
Tf_2O / K_2CO_3	110 / 300	CH_2Cl_2	1	–78 → 23	Decomposition
TBSOTf	150	CH_2Cl_2	3	–78 → 0	**188** (5%, 2:1)
TBSOTf / *i*-Pr_2NEt	150	CH_2Cl_2	3	–78 → 0	No Reaction
BF_3-OEt_2	150	CH_2Cl_2	3	–78 → 23	Decomposition
$TiCl_4$	150	CH_2Cl_2	3	–78 → 23	Decomposition
Ti(O*i*-Pr)$_4$	150	CH_2Cl_2	3	–78 → 40	No Reaction
Me_2AlCl	150	CH_2Cl_2	3	0 → 23	Decomposition
$AlMe_3$	150	CH_2Cl_2	3	0 → 23	Decomposition
$EtAlCl_2$	150	CH_2Cl_2	3	0 → 23	**188** (14%, 4:1)
$EtAlCl_2$	150	CH_2Cl_2	2	0 → 23	**188** (34%, 4:1)
$EtAlCl_2$	150	PhH	2	5 → 23	**188** (<5%)
$EtAlCl_2$	150	PhMe	2	–78 → 23	**188** (<5%)
$FeCl_3$	**110**	**CH_2Cl_2**	**2**	**0**	**188 (60%, 3:1)**
$FeCl_3$	**150**	**CH_2Cl_2**	**1**	**0**	**188 (77%, 3:1)**
$FeCl_3$	10	CH_2Cl_2	2	0	trace conversion of **174**
$FeCl_3(H_2O)_6$	110	CH_2Cl_2	2	0	**188** (55%, 3:1)

Inability to emulate the friedelin biosynthesis combined with the synthetic difficulties observed by Ireland and co-workers inspired the examination of new initiators for cationic polyolefin cyclizations which provide products at the desired oxidation state. The result of the cationic [2+2] prompted the use of an allylic epoxide as the initiator. However, this strategy was unsuccessful because the linear enone **174** could not be converted into the epoxide **189** (Table 2.5). Steric encumberance of the 4,4-disubstituted cyclohexenone prevents proper orbital alignment for addition of various nucleophiles thereby promoting enolization of the readily accessible □-protons as the sole pathway. Due to the presence of multiple alkenes I did not foresee selective epoxidation to occur though another manifold so this strategy was abandoned.

Ireland's work on polyene cascades using allylic alcohols coupled with the observations I had made attempting this reaction on the enone **174** led me to hypothesize that this transformation using the allylic alcohol would be viable. The use of strong protic acids as well as Lewis acids that strongly promote discrete cation formation (i.e. boron, aluminum, and tin) proved deleterious to the polyene causing degradation of the alkenes. However, iron induced the cyclization, albeit through the wrong pathway, in mild manner which did not decompose the olefins. High dilution also proved to be critical. Ireland's protocol used a concentration of 25 mM in methylene chloride. The enone **174** underwent massive degradation at this concentration, but this decomposition was not observed at 1 mM inspiring deeper experimentation.

Enone **174** was reduced using lithium aluminum hydride in ether at 0 °C to provide the allylic alcohol **190** in quantitative yield (Table 2.5). Under the identical conditions used by Ireland, the alcohol was treated with 1.5 equivalents of stannic chloride in a 25 mM solution of methylene chloride at −78 °C to afford the desired pentacyclic product **191** in a 15% isolated yield. Diluting the reaction concentration to 1 mM generated the cyclized product in 26% yield. Switching to ferric chloride and increasing the temperature to 0 °C, the pentacycle **191** was obtained in 33% yield. Increasing the amount of ferric chloride and allowing the temperature to warm from −78 to −30 °C provided the product in 38% yield, and finally, diluting the reaction to 500 μM with careful monitoring by TLC as the reaction warmed to −30 °C the pentacycle was afforded in a hard earned yield of 51%. The remainder of the material consisted of interrupted cyclized adducts as well as a small amount of polymerized products. It is important to note that the reaction occurred stereospecifically to provide a single diastereomer as initially postulated. When the isomerically impure material (6:1 at the trisubstituted olefin) was subjected to the reaction conditions, the pentacycle was generated as a diastereomeric mixture matching that of the starting material.

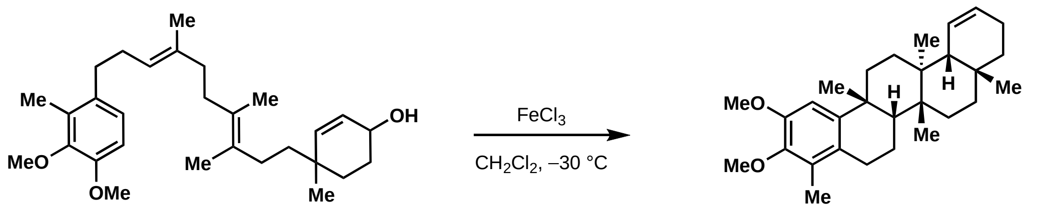
Table 2.5. Polyene cyclization of the allylic alcohol **190**.



Reagent	Mol %	Solvent	Concentration	Temperature (°C)	Isolated Yield (%)
$SnCl_4$	120	CH_2Cl_2	25 mM	–78 → 0	15
$SnCl_4$	120	CH_2Cl_2	1 mM	–78 → 0	26
$FeCl_3$	120	CH_2Cl_2	1 mM	0	33
$FeCl_3$	150	CH_2Cl_2	1 mM	–78 → –30	38
$FeCl_3$	150	CH_2Cl_2	500 μM	–78 → –30	51

Fortunately, the polyene cyclization proceeded smoothly on scales up to 1 gram with minimal loss in yield (Scheme 2.12). In regard to my knowledge of the literature this is the largest scale a polyolefin cascade has been conducted to generate either a tetracyclic or pentacyclic triterpenoid. Reactions larger than 1 gram scale were not conducted due to the lack of a flask large enough to accommodate the amount of solvent needed for the reaction at the optimal concentration. For instance, on 1 gram scale **4.7 L of methylene chloride** is needed in order to produce the pentacycle **191** in a 38% yield. This warranted further improvement in order to decrease the amount of solvent required to perform the cyclization successfully on larger scale in good yield while still maintaining the effective molarity of the substrate. Utilizing the concept of effective molarity, a protocol employing the syringe pump addition of a dilute solution of the substrate in a slow dropwise manner to a dilute solution of $FeCl_3$ in methylene chloride was investigated. While maintaining the reaction temperature at −30 °C the concentration of the substrate, addition rate, and concentration of ferric chloride were variables that were systematically examined, and they all proved to be critical. After optimization, the cyclization proceeded well on 100 mg scale to afford the cyclized product in 51% yield (Table 2.6). This proof of concept warranted further probing of the protocol's scalability. On 1 gram scale the starting alcohol was added as a dilute solution in methylene chloride over 6 hrs using a syringe pump to a solution of ferric chloride maintained at −30 °C, however, this only produced the pentacycle **191** in 26% yield. Although successful the yield is much lower on gram scale as compared to the original method to conduct the cyclization using very high dilution and a gradual warming of the temperature from −78 °C. It is important to note that using this strategy only **1.2 L of methylene chloride** was required to perform the cyclization which represents a 4-fold decrease in the amount of solvent used for this reaction.

Table 2.6. Slow addition protocol for the polyolefin cascade of allylic alcohol **190**.



190 **191**

Scale	Substrate Solution	Addition Rate	$FeCl_3$ Solution	Concentration	Isolated Yield (%)
100 mg	2.5 mL	0.8 mL / hr	225 mL	1 mM	48
100 mg	2.5 mL	2.5 mL / hr	225 mL	1 mM	43
100 mg	2.5 mL	2.5 mL / hr	110 mL	2 mM	41
100 mg	5 mL	10 mL / hr	110 mL	2 mM	47
100 mg	5 mL	5 mL / hr	55 mL	4 mM	42
100 mg	5 mL	10 mL / hr	55 mL	4 mM	35
100 mg	**10 mL**	**20 mL / hr**	**110 mL**	**2 mM**	**51**
100 mg	20 mL	40 mL / hr	110 mL	2 mM	48
300 mg	30 mL	20 mL / hr	330 mL	2 mM	42
1 gram	**100 mL**	**20 mL / hr**	**1.1 L**	**2 mM**	**26**

With adequate access to the pentacycle **191**, a bifurcated retrosynthetic analysis to install the remaining carbons and stereocenter was devised (Figure 2.4). Hydroboration of the alkene followed by oxidation would generate a carbonyl at C-20 which could provide the desired quaternary center (path A). However, the installation of a ketone at C-21 through an allylic oxidation could also provide a functional handle to install the remaining carbons. The latter was ideal as reduction and alkylation of an enolate was foreseen to generate the quaternary center at C-20 more selectively and in higher yield. The resultant molecule would be stable to a Wolff-Kishner reduction due to the saturated hydrocarbon backbone and literature precedence in regard to these moieties in these reductions.

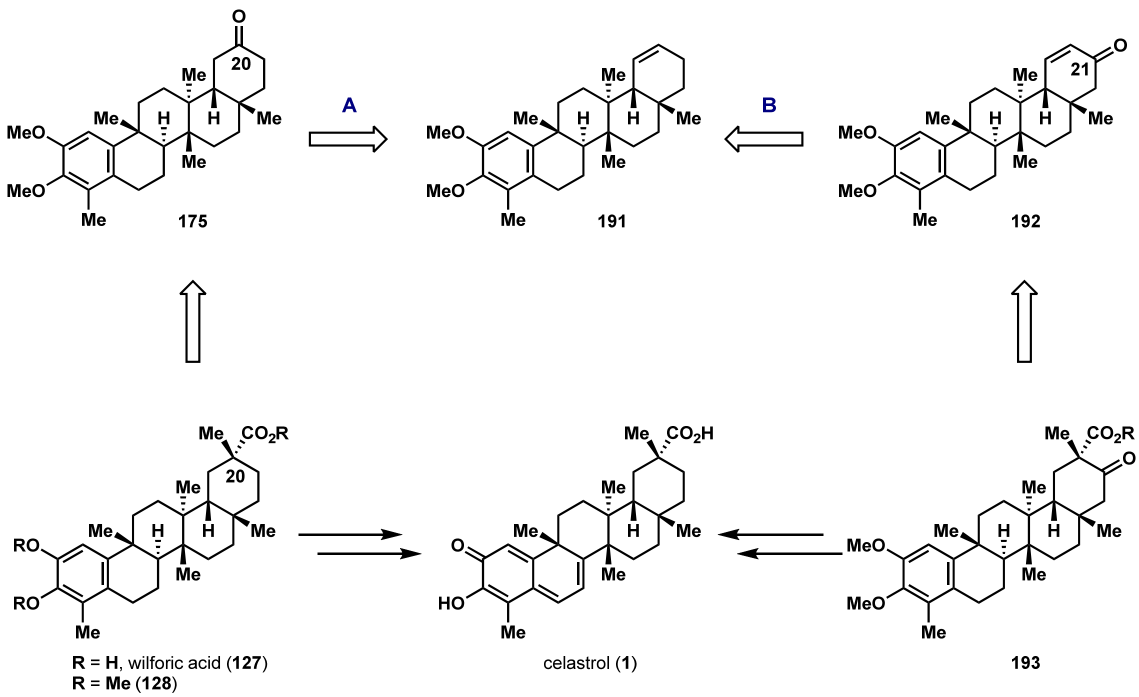
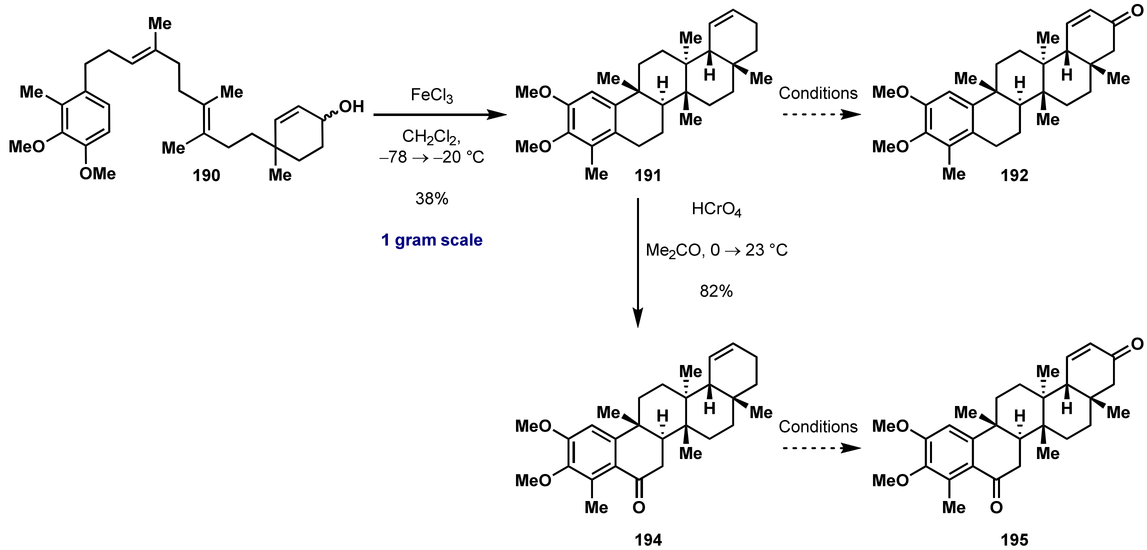


Figure 2.4. New retrosynthetic analysis through a bifurcated strategy from the alkene **191**.

Subjecting this material to a myriad of conditions to facilitate allylic oxidation failed because of selective benzylic oxidation. Treating **191** with 1.1 equivalents of Jones reagent in acetone at 0 °C and allowing the mixture to gradually warm generated the benzyl ketone **194** in 82% yield. Unfortunately, treating **191** with other oxidants or re-subjecting **194** to oxidizing conditions did not deliver the desired α,β-unsaturated ketones **192** or **195**. Only returned starting benzyl ketone or decomposed material was obtained.

Attempts to protect the benzyl ketone as a ketal or thio-ketal failed, and due to the observed adverse reactivity this strategy was abandoned.

Scheme 2.12. Attempted allylic oxidations of pentacycle **191** or benzyl ketone **194**.

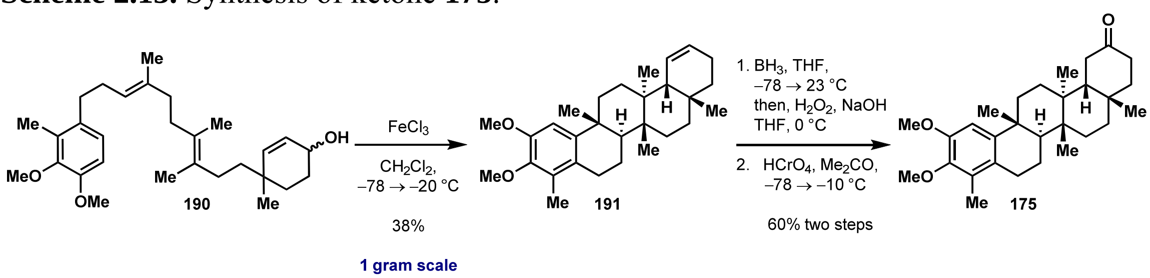


Starting Material	Reagent	Additive	Solvent	Temperature (°C)	Result
191	$HCrO_4$	----------	Me_2CO	0 → 23	Benzylic Oxidation
191 and **194**	$HCrO_4$	----------	Me_2CO	23 → 56	Decomposition
191	$Mn(OAc)_3{\bullet}2H_2O$	TBHP	EtOAc	77	Benzylic Oxidation
194	$Mn(OAc)_3{\bullet}2H_2O$	TBHP	EtOAc	77	Decomposition
191	CrO_3	3,5-dimethyl pyrazole	CH_2Cl_2	–20 → 0	Benzylic Oxidation
191 and **194**	CrO_3	3,5-dimethyl pyrazole	CH_2Cl_2	–20 → 23	Decomposition
191	SeO_2	H_2O	1,4-Dioxane	23 → 101	Diene
191	SeO_2	HCO_2H	1,4-Dioxane	23 → 101	Decomposition

Hydroboration of the pentacycle **191** proceeded with moderate selectivity using borane in THF while allowing the reaction to gradually warm to 23 °C from −78 °C. Steric compression of the E-ring prevented the use of larger hydroborating agents such as

9-BBN, which after heating to reflux in THF over 24 hours only returned unreacted starting material. After oxidative work-up the crude alcohol was oxidized with Jones reagent in acetone to afford the desired ketone **175** as a white solid in 60% yield over two steps (Scheme 2.13). The temperature of the reaction was critical due to competing benzylic oxidation, but this pathway was minimized by allowing the reaction to warm gradually from −78 °C to −10 °C with careful monitoring of the reaction's progress by TLC.

Scheme 2.13. Synthesis of ketone **175**.



Initially, the structure of the ketone was assigned using 2D-NMR (COSY, NOESY, HSQC, HMBC, and DEPT, see Experimental Section) as well as through subsequent reactions and full characterization of those products (see Scheme 2.14). Later, I fortuitously discovered that dissolving the white solid in hot methanol and patiently allowing the clear colorless solution to cool to 23 °C, a crystalline solid slowly formed. These colorless crystals were suitable for X-ray diffraction which unambiguously confirmed the structure as the ketone **175** (Figure 2.5). Analysis of the crystal structure clearly shows the sterical arrangement of the carbocyclic core and the twisting of the B, C, and D rings out of traditional chair conformity, preventing clashes between the angular methyls. Also observed is the half-chair conformation in which the

E-ring resides thereby forestalling the backside angular methyl at the C-D ring juncture from colliding with C-19 and C-21, their hydrogens, as well as C-20. This dictates that nucleophilic addition should occur diastereoselectively from the top face and electrophiles appended in a similar fashion.

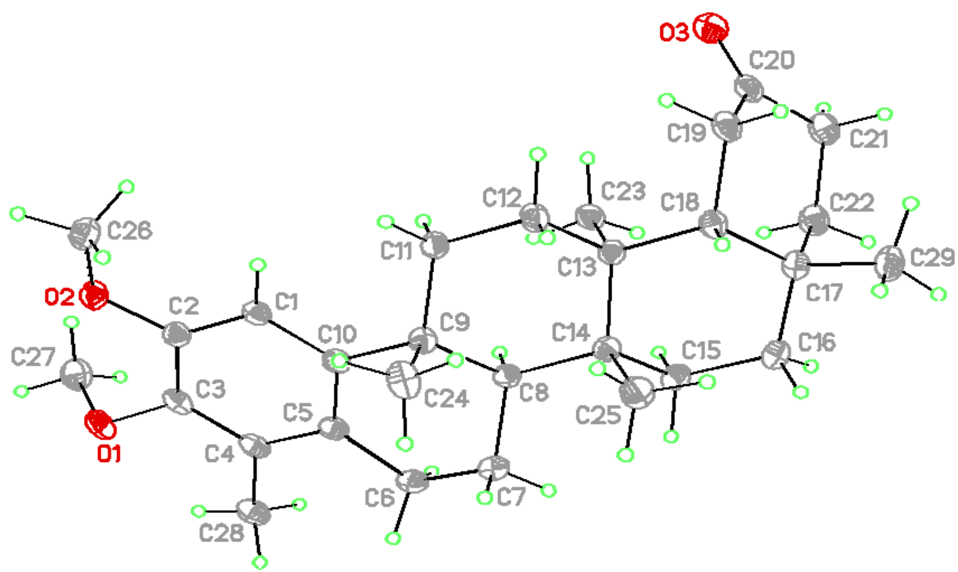


Figure 2.5. View of cyclized ketone **175**. Displacement ellipsoids are scaled to the 50% probability level.

At this stage the remainder of the synthesis entailed installation of the carbonyl and the methyl poised at C-20 as well as oxidation of wilforic acid (**127**) to afford celastrol (**1**) (Figure 2.6). Stereochemical analysis of the crystal structure delineated that the last methyl would be difficult to install because of sterics. A retrosynthetic analysis was conceived based on the literature precedence regarding installing methyls in crowded environments using cyclopropanation strategies.[47,51,53,59-61,120] A substrate guided cyclopropanation of methyl enol ether **196** provides **197**, which an acid mediated ring opening and oxidation sequence affords the acid **128**. Deprotection of the methyl ethers then generates wilforic acid. This strategy introduces the remaining carbons in a stereoselective fashion from **197**, which is accessed through a Wittig olefination of ketone **175**. If sterics precluded this transformation then a Peterson olefination of the methoxymethyl trimethylsilyl alcohol **198** could also provide access to the enol ether. Literature precedent established by Magnus and co-workers to access methyl enol ethers from sterically demanding ketones not amenable to Wittig olefinations further corroborated the viability of this approach.[121-123] Alternatively, the ketone **175** could be used in a carbonylation sequence to access **199** which provides a synthon to install the remaining methyl through an enolate alkylation strategy delivering **128**.

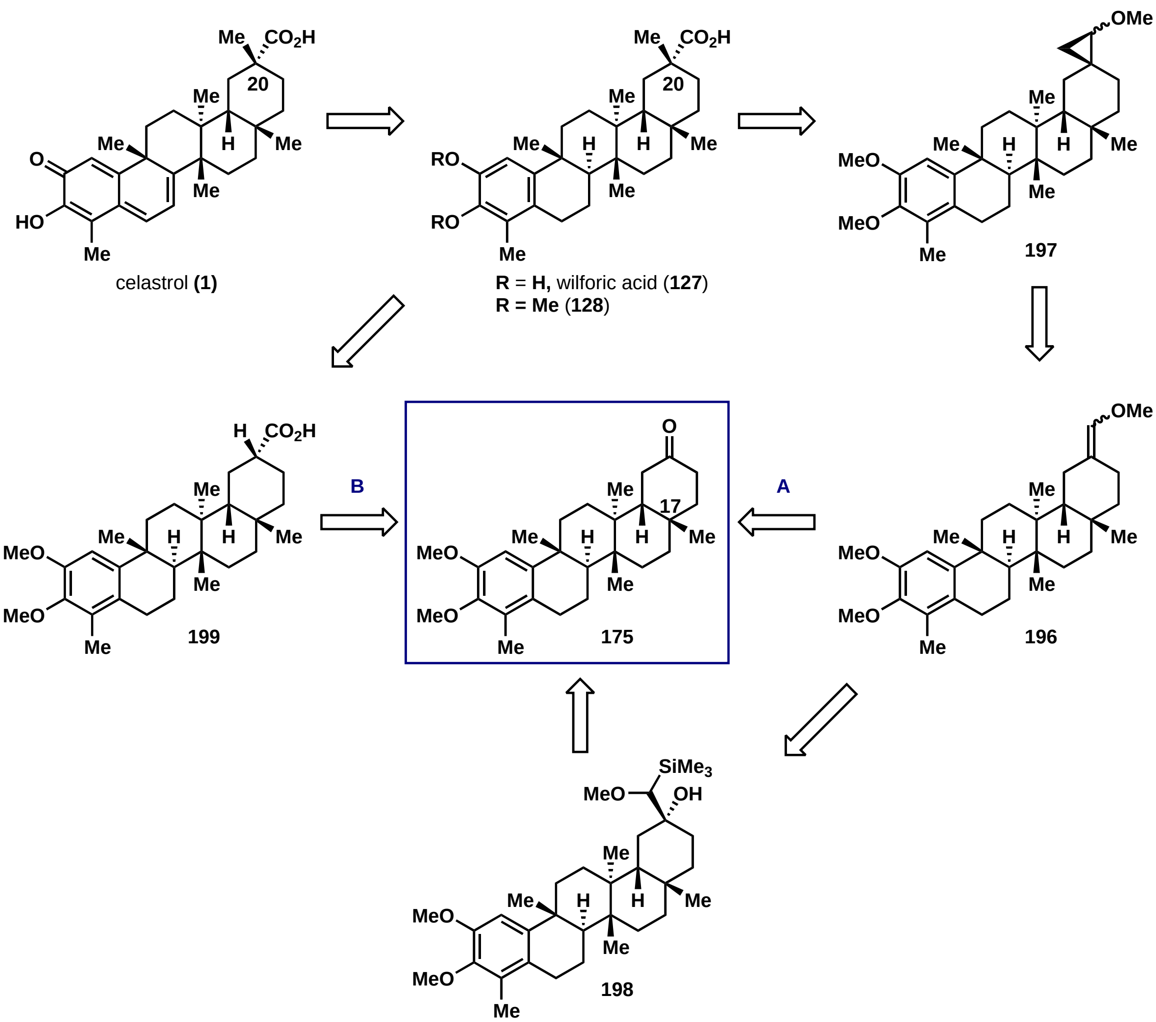
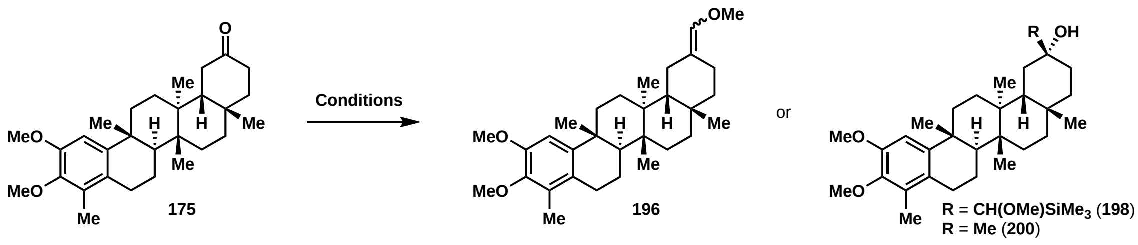


Figure 2.6. Retrosynthesis to access wilforic acid (**127**) and celastrol (**1**) from ketone **175**.

The ability of ketone **175** to undergo nucleophilic addition was examined with a variety of nucleophiles. The methyl positioned at C-17 posed a significant problem as it blocked the necessary trajectory for nucleophilic addition. To further complicate this issue, the ketone is flanked by two α-carbons bearing protons susceptible to enolization. Large reagents such as the ylides methoxymethyl triphenylphosphorane and methyl triphenylphosphorane did not react with the ketone in a productive manner despite using various equilibrating or non-equilibrating bases as well as different solvents and reaction temperatures. This also proved to be the case for the anions of methoxymethyl trimethylsilane, chloromethyl trimethylsilane, trimethyl sulfonium iodide, and trimethyl sulfoxonium iodide.[121-124] However, treating the ketone with methyl lithium at 23 °C generated the carbinol **200** in 72% yield as a single diastereomer, with the remaining material consisting of the starting ketone **175**. This enlightening result illustrates that small nucleophiles react diastereoselectively as initially postulated showcasing the potential of the enolate alkylation strategy.

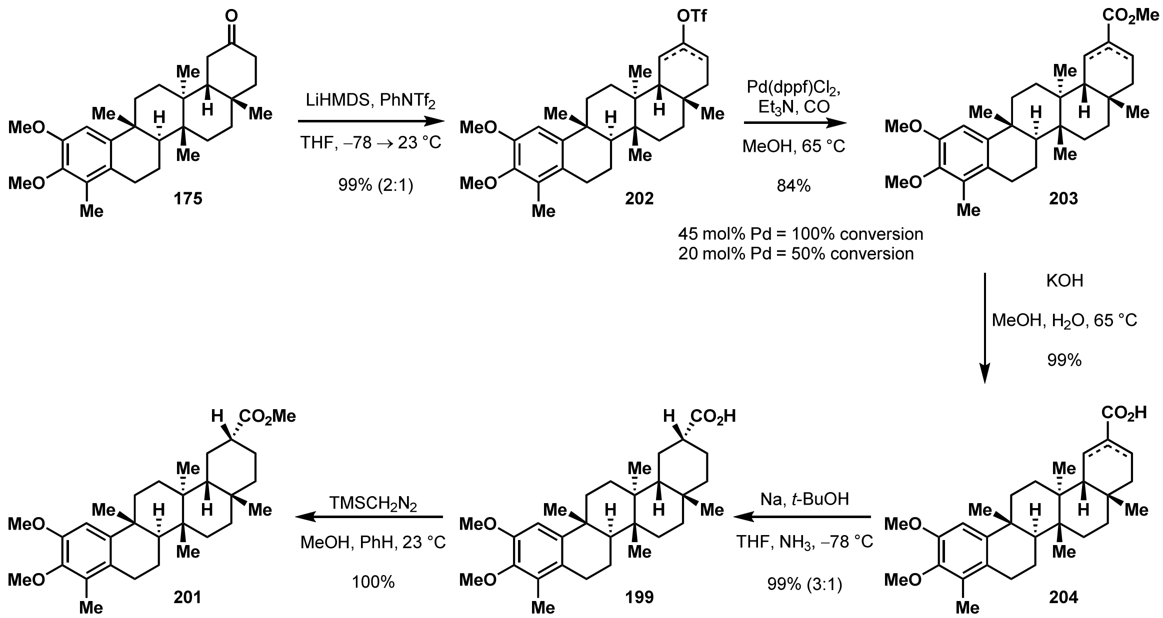
Table 2.7. Selected attempts to access methyl enol ether **196** or alcohols **198** and **200**.



Reagent	Base	Solvent	Temperature (°C)	Result
Ph_3PCH_2OMeCl	LiHMDS	THF	23	No Reaction
Ph_3PCH_2OMeCl	PhLi	THF/Bu_2O	23	trace
Ph_3PCH_2OMeCl	NaHMDS	THF	23	No Reaction
Ph_3PCH_2OMeCl	*t*-BuOK	THF/*t*-BuOH	23	No Reaction
Ph_3PCH_2OMeCl	$KOC(Me)_2CH_2Me$	PhMe	0 → 23	No Reaction
Ph_3PCH_2OMeCl	$KOC(Me)_2CH_2Me$	PhMe	23	trace
Ph_3PMeBr	$KOC(Me)_2CH_2Me$	PhMe	23 → 110	trace
$MeOCH_2SiMe_3$	*s*-BuLi	THF	−78 → 0	trace
$MeOCH_2SiMe_3$	*s*-BuLi	THF	0	Decomposition
$ClCH_2SiMe_3$	*s*-BuLi	THF/TMEDA	−55 → 0	trace
MeLi	----------	THF	23	**72% Product (200), 28% SM**
MeMgBr	----------	THF	23	trace
Me_3SI	*n*-BuLi	THF	23	No Reaction
Me_3SI	NaH	DMSO/THF	23	No Reaction
Me_3SOI	NaH	DMSO/THF	23 → 60	trace
Me_3SOI	*n*-BuLi	THF	23 → 60	trace

To examine the enolate alkylation strategy the syntheses of acid **199** and ester **201** were required. After the azeotropic removal of water with toluene, the ketone was deprotonated with a 1 M solution of LiHMDS in THF at −78 °C. After 1 hour the resultant enolate was trapped with N-phenyl-bis(trifluromethanesulfonimide) to afford the enol triflate **202** in 99% yield as a 2:1 mixture of olefinic isomers (Scheme 2.14). The isomeric mixture was carried forward because the olefin would ultimately be reduced. The carbonylation proceeded smoothly using palladium(dppf) dichloride and triethylamine in methanol heated to reflux under an atmosphere of carbon monoxide to provide the α,β-unsaturated ester **203** in an 84% yield. To facilitate maximum conversion of the starting material, 45 mol% of palladium(dppf) dichloride was needed. This is because only approximately 50% conversion was observed when lower amounts of the catalyst were used whereas other palladium catalysts rendered minimal success. Unfortunately, sterics made this material resistant to reduction using hydrogenation with platinum, palladium on carbon, or Pearlman's catalyst. Nickel boride, Stryker's reagent, and Lipshutz's modified Stryker's reagent likewise did not afford the reduced product, only unreacted starting material was returned.[125-127] A dissolving metal reduction in liquid ammonia reduced the enoate **203**, but amidation of the ester was observed. So, the ester was saponified, and as a solution in THF the acid **204** was added to a dark blue solution of sodium in liquid ammonia at −78 °C which generated the reduced product **199** as a 3:1 mixture of diastereomers in 98% yield over two steps. Presuming the dianionic enolate alkylation would be difficult, the acid was treated with trimethylsilyl diazomethane in a 1:1 mixture of methanol/benzene at 23 °C to afford the ester **201** as a white amorphous solid in quantitative yield.[128]

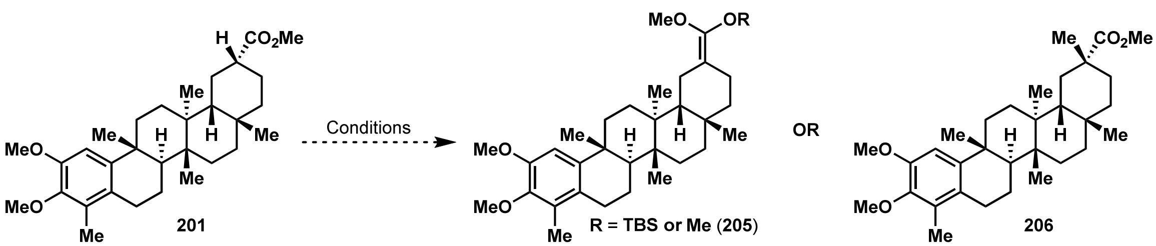
Scheme 2.14. Synthesis of the saturated acid **199** and ester **201**.



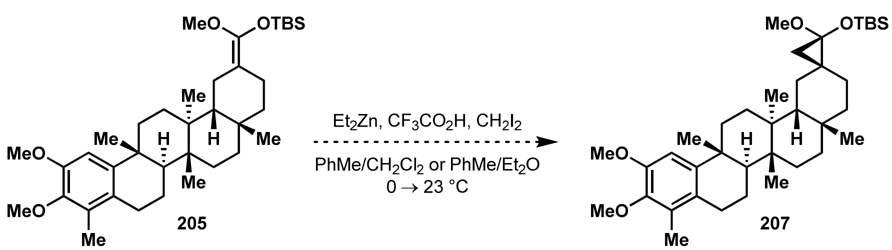
The original plan centered on converting the ester to its silyl or methyl ketene acetal (**205**) followed by cyclopropanation. Acid mediated hydrolysis would reveal the alkylated ester **206** or acid **128** as a single diastereomer. Initially, the ester proved reluctant to silyl ketene acetal formation using soft as well as hard enolization techniques (Table 2.8). LDA was too bulky of a base to promote full enolization, however, treating the ester with *tert*-butyldimethylsilyl trifluoromethane sulfonate in THF at 23 °C for one minute and then adding a freshly prepared solution of LDA in THF generated the desired silyl ketene acetal in ~75% yield. The other 25% of the material was the minor diastereomer of unreacted starting material which did not react with LDA as proven by treating this compound with freshly prepared LDA in THF at 23 °C for one hour, and then neutralizing this reaction at different temperatures. After an aqueous work-up, ^{1}H-NMR analysis showed pure starting material, revealing no enolization had occurred.

The silyl ketene acetal **205** was unfortunately resistant to cyclopropanation. Focus was then placed on generating the dimethyl variant as I hypothesized that this compound might be a more competent participant in the subsequent cyclopropanation. Despite using dimethyl sulfate, which prefers O-alkylation over C-alkylation, as well as using distilled HMPA as a co-solvent, the ketene acetal was not observed and only a trace amount of the alkylated adduct **206** was produced.[129] Subjecting the ester to a freshly prepared solution of lithium diethyl amide in THF at 23 °C for five minutes followed by the addition of iodomethane generated the alkylated product as a single diastereomer in 25% yield. The low yield is attributed to amidation of the starting ester. To circumvent this issue the reaction was cooled to −78 °C and then treated with freshly prepared lithium diethyl amide in order to promote enolization. The mixture was gradually warmed to 23 °C and iodomethane was added to the golden brown solution, however, this afforded the amidated product in a greater yield of approximately 90%.

Table 2.8. Alkylation of ester **201** and attempted formation of ketene acetals **205** and ester **206**.



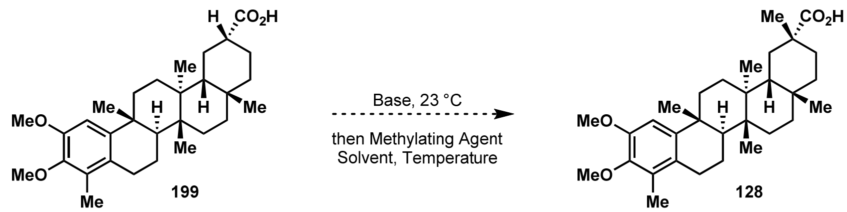
Base	Reagent	Solvent	Temperature (°C)	Result
LDA	TMSOTf	THF	–78 → 23	No Product
LDA	TBSOTf	THF	–78 → 23	No Product
Et_3N	TMSOTf	CH_2Cl_2	–78 → 40	No Reaction
LDA	TBSOTf	THF	23	Silyl Ketene Acetal **205** (~75%)
LDA	Me_2SO_4	THF	23	Trace Alkylation, No Ketene Acetal
LDA	Me_2SO_4	THF/HMPA	23	Trace Alkylation, No Ketene Acetal
Et_2NLi	MeI	THF	23	25% Alkylation, ~75% Amidation
Et_2NLi	MeI	THF	–78 → 23	10% Alkylation, ~90% Amidation



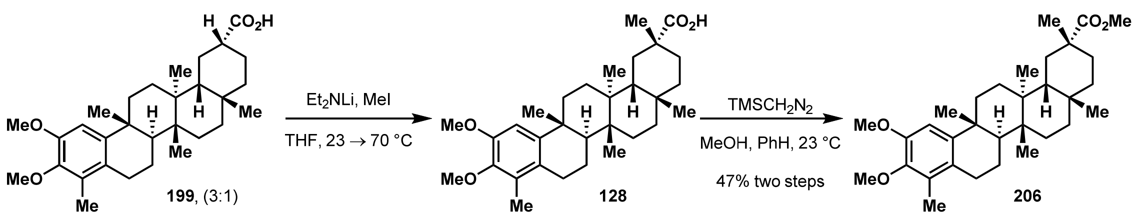
Compelled by the successful diastereoselective alkylation of the ester, heavy focus was centered on synthesizing the acid **128**. After azeotropic removal of water with toluene, the solid acid **199** was dissolved in THF, and this clear colorless solution was treated with an excess of freshly prepared LDA at 23 °C for 1 hour to provide a dark golden yellow solution of the dianionic enolate. Addition of iodomethane induced an exothermic reaction alkylating the enolate to afford **128** in 25% yield (Table 2.9). The residual material consisted of ~25% of the undesired diastereomer of **128** and ~50% of the starting material as an approximate 1:1.5 mixture of diastereomers. The recovery of starting material was surprising as 20 equivalents of LDA were used. Based on work conducted by Tamm, Seebach, and Meyers on the behavior of lithium enolates in solution, excess amide base should promote full alkylation.[129,130] Even more surprising was that the alkylation proceeded with no observed diasteroselectivity.

In order to solve the first issue, freshly prepared lithium diethyl amide was used to promote the full enolization of **199**. Despite using lithium diethyl amide in combination with *n*-butyllithium to deprotonate the two equivalents of diethyl amine generated in producing the dianion, enolized starting material was always recovered. The use of distilled HMPA as a co-solvent to break lithium aggregates or using stronger methylating agents only promoted O-alkylation to afford the ester **201**.[129] Neither the product **128** nor dimethyl ketene acetal **205** were observed. To insure **205** was not being hydrolyzed, a basic work-up as well as freshly base-washed glassware were used and the crude material was then analyzed by ^{1}H-NMR using C_6D_6. In an effort to enhance the diastereoselectively, the alkylation step was conducted at −78 °C and allowed to warm gradually to 23 °C. This however only afforded trace amounts of the desired product. Interestingly, when the reaction mixture was placed in a 23 °C water bath and the dianion was treated with iodomethane, only a trace amount of the desired product was observed; enolized starting material was returned in both cases. The exothermicity of the alkylation when the reaction was initially conducted at 23 °C without the water bath proved to be a highly critical observation. So, the starting acid was treated with an excess of a freshly prepared solution of lithium diethyl amide in THF at 23 °C for 30 minutes, and the resulting dark golden yellow solution was placed in an oil bath heated to 70 °C for 30 minutes. Iodomethane was then added, producing a heterogeneous mixture which was kept at 70 °C for 30 minutes which afforded the alkylated product in high yields, but with minimal diastereoselectivity. The alkylated acid was then dissolved in a 1:1 mixture of methanol/benzene and treated with a 2 M solution of trimethylsilyl diazomethane in ether. The ester was then purified by silica gel chromatography to afford the alkylated adduct **206** in an isolated yield of 47% over the two steps. The undesired diastereomer was also isolated in 36% yield. The esterification was conducted to aid the isolation and chromatographical separation of the diastereomers. The structure of the major product **206** was assigned using 2D-NMR spectroscopy (see Experimental Section).

Table 2.9. Synthesis of acid **128** through the dianionic alkylation of **199**.

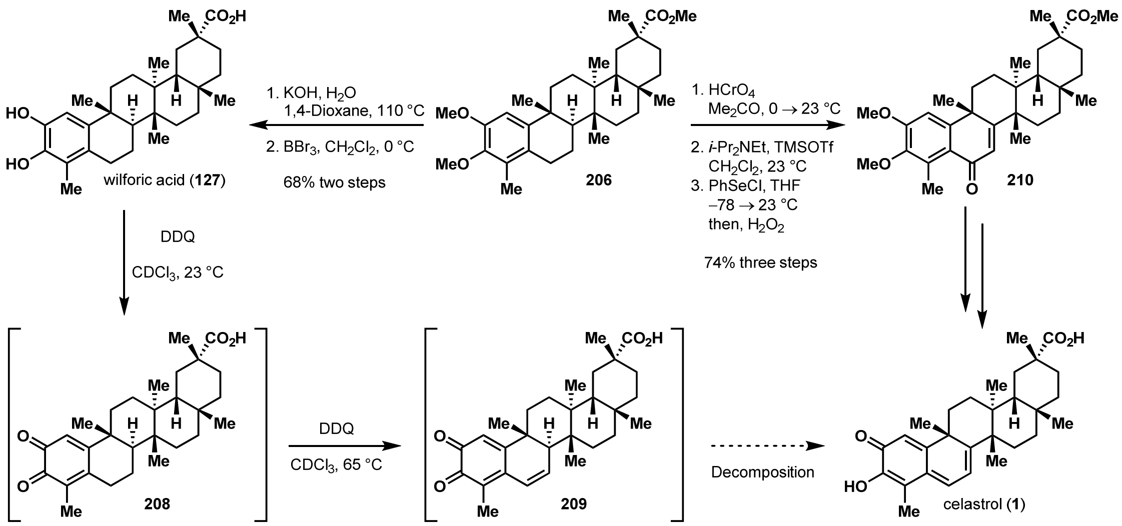


Base	Methylating Agent	Solvent	Temperature (°C)	Result (% Yield, D.R.)
LDA	MeI	THF	23	**128** (50%, 1:1), **199** (50%, 1:1.5)
LDA	MeI	THF/HMPA	23	Non-Alkylated Ester **201** (80%, 1:1.5)
LDA	Me_2SO_4	THF	23	Non-Alkylated Ester **201**, No Ketene Acetal
LDA	Me_2SO_4	THF/HMPA	23	Non-Alkylated Ester **201**, No Ketene Acetal
Et_2NLi, then *n*-BuLi	MeI	THF	23	**128** (50%, 1:1), **199** (48%, 1:1)
Et_2NLi, then *n*-BuLi	MeI	THF	23 °C water bath	Trace Alkylation, Enolized SM (**199**)
Et_2NLi, then *n*-BuLi	MeI	THF	−78 → 23	Trace Alkylation, Enolized SM (**199**)
Et_2NLi	MeI	THF	70	**128** (83%, 1.3:1), **SM** (16%)



The ester **206** was saponified using potassium hydroxide in dioxane/water heated to reflux (Scheme 2.15). Treating the acid **128** with boron tribromide in methylene chloride at 0 °C for five minutes afforded wilforic acid (**127**) as a white amorphous solid in 68% yield over two steps after recrystallization. ^{1}H-NMR analysis of this material in deuterated pyridine matched the reported chemical shifts for wilforic acid (see Experimental Section) representing the first total synthesis of wilforic acid.[131] The catechol was then oxidized instantaneously in $CDCl_3$ with two equivalents of DDQ to provide the *ortho*-quinone **208** as observed by ^{1}H-NMR. After placing the NMR tube in an oil bath heated to 65 °C for two hours the unsaturated quinone **209** was produced from the oxidation of **208**. Unfortunately, prolonged heating or the use of acids did not promote tautomerization to afford celastrol (**1**), only decomposition of the material was observed. Alternatively, ester **206** was oxidized to the benzyl ketone using Jones reagent which was then further oxidized to the enone **210** in a 74% yield over three steps using a selenoxide elimination. This is where the project currently lies. The final strategy is to reduce the enone to the benzyl alcohol using a Luche reduction, and the activated alcohol is foreseen to rapidly eliminate *in situ* during the deprotection of the methyl ethers to ultimately provide celastrol in a single step.

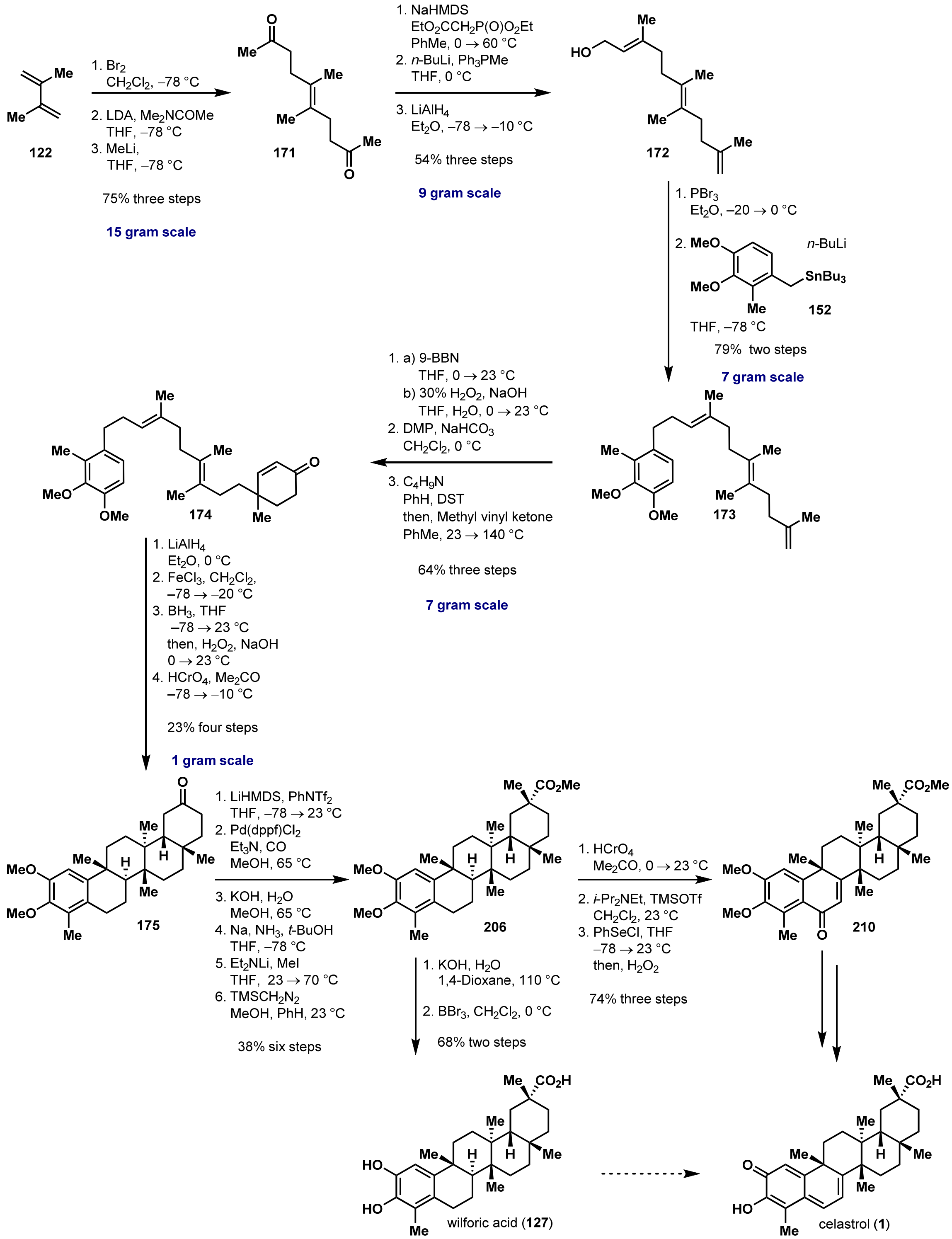
Scheme 2.15. Synthesis of wilforic acid (**127**), enone **210**, and the final strategy.



Conclusion

The total synthesis of celastrol (**1**) remains a work in progress. The arduous process of developing a strategy to access the natural product ultimately culminated in one of the fastest, highest yielding syntheses of a polyene to date. More importantly, a polyene cyclization that constructs the friedelin pentacyclic core in a diastereoselective fashion on one gram scale was developed providing rapid access to these complex frameworks. This is the highest scale a polyolefin cascade has been conducted to access a tetracyclic or pentacyclic terpenoid to date. Commencing from 2,3-dimethyl butadiene, the polyene **174** is accessed routinely in 5 gram quantities in 11 steps with an overall 21% yield (Scheme 2.16). Using ferric chloride and a slow addition protocol, the pentacycle **191** is generated in a single operation on 1 gram scale in a 38% yield improving the strategy originally exploited by Ireland. The alkene is then used to install the remaining functionality with the proper stereoselectivity highlighted by a carbonylation and a dianionic enolate alkylation. This strategy successfully completed the first total synthesis of wilforic acid (**127**); which unfortunately could not be oxidized to celastrol (**1**). A new strategy to synthesize celastrol from enone **210** that invokes an *in situ* deprotection and elimination is under development.

Scheme 2.16. Overall synthetic strategy to access wilforic acid (**127**) and enone **210**.



Experimental Section

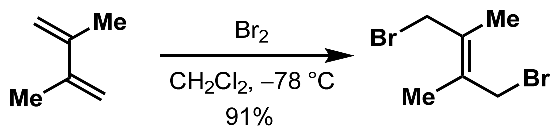
Studies Toward the Synthesis of Celastrol

Table of Contents

1. General Information

All reactions were performed in flame-dried round-bottomed or modified Schlenk flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Solvents (methylene chloride, ether, tetrahydrofuran, benzene, and toluene) were purified using a Pure-Solv MD-5 Solvent Purification System (Innovative Technology). Where necessary, solvents were deoxygenated by sparging with nitrogen for at least 1 hour unless otherwise noted. All other reagents were used directly from the supplier without further purification unless otherwise noted. Organic solutions were concentrated by rotary evaporation at ~25 mbar in a water bath heated to 40 °C unless otherwise noted. The molarity of n-butyllithium and methyllithium were determined by titration against diphenylacetic acid. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial glass-coated silica gel plates (silica gel 60, F254, EMD chemical). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or exposure to an acidic solution of ceric ammonium molybdate or a basic solution of potassium permanganate followed by heating on a hot plate. Infrared spectra were recorded on a Nicolet 380 FTIR using neat thin film technique. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+Na]^+$, $[M+H]^+$, $[M-H]^-$, $[M-AcOH]^-$, [M], or $[M+2H]^{2+}$. Nuclear magnetic resonance spectra (^{1}H-NMR and ^{13}C-NMR) were recorded with a Varian Gemini (400 MHz, ^{1}H at 400 MHz, ^{13}C at 100 MHz, 500 MHz, ^{1}H at 500 MHz, ^{13}C at 125 MHz, or 600 MHz, ^{1}H at 600 MHz, ^{13}C at 150 MHz). For $CDCl_3$ and C_6D_6 solution, chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvent; $CHCl_3$ δ 7.26 ppm, $CDCl_3$ δ 77.0 ppm, C_6D_5H δ 7.15 ppm, C_6D_6 δ 128.0 δ ppm, C_5D_4HN δ 7.19 ppm, C_5D_5N δ 135.9 ppm, and CD_2HCN δ 1.93 ppm. Coupling constants are reported in Hertz (Hz). Data for ^{1}H-NMR spectra are reported as follows: chemical shift (ppm, referenced to protium; (bs = broad singlet, s = singlet, br d = broad doublet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet, integration, and coupling constants (Hz)).

2. Synthesis of Wilforic Acid (127) and the Enone 210

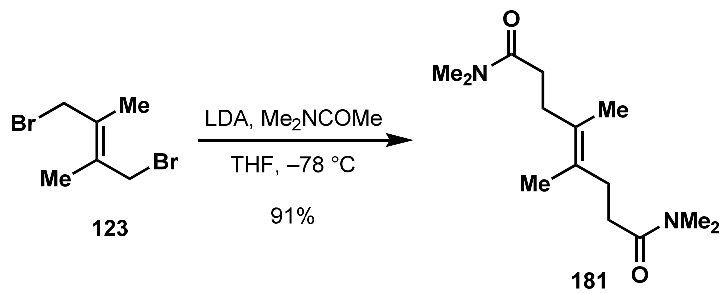


A solution of 2,3-dimethylbutadiene (10.1 g, 13.9 mL, 124 mmol, 1.00 eq.) in CH_2Cl_2 (88 mL) was placed in a bath cooled to −78 °C and allowed to stir vigorously (600 rpm) for 30 minutes. A solution of bromine (19.8 g, 6.3 mL, 124 mmol, 1.00 eq.) in CH_2Cl_2 (36 mL) was added dropwise via addition funnel over 4 hours. The heterogeneous and pale yellow colored mixture was allowed to stir for 2 hours after the complete addition of bromine at −78 °C upon which the golden yellow mixture was removed from the cooling bath and concentrated via rotary evaporation. (**Note**: The product readily sublimes and is a lachrymator. The pressure of the rotary evaporator was reduced to no lower than 100 mbar and the flask was submerged into an ice water bath). After complete evacuation of CH_2Cl_2, the golden yellow solution was allowed to stand at 23 °C in the dark upon which the colorless solid crystallized out of solution. Cooling in a freezer chilled to −20 °C aids full recovery of the crystalline solid. Removal of the mother liquor afforded the dibromide **123** as a colorless crystalline solid (27.5 g, 113 mmol, 91% yield). The spectral data matches that of the reported compound (Farkas, F.; Wellauer, T.; Esser, T.; and Sequin, U. *Helvetica Chimica Acta* **1991**, 74, 1511).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.00 (s, 4H), 1.88 (s, 6H)

^{13}C-NMR (100MHz, $CDCl_3$): δ 131.90, 35.00, 17.20

M.P.: 45 – 46 °C



A solution of diisoproplyamine (12.9 g, 17.8 mL, 127 mmol, 2.05 eq.) in THF (300 mL) was placed in a bath cooled to −78 °C for 30 minutes. *n*-Butyllitium (55.7 mL, 2.28 M in hexanes, 127 mmol, 2.05 eq.) was added dropwise over 5 minutes. After 5 minutes the colorless solution was placed in an ice water bath cooled to 0 °C for 20 minutes, and placed back into the bath cooled to −78 °C for 30 minutes. A solution of *N,N*-dimethylacetamide (11.1 g, 11.8 mL, 127 mmol, 2.05 eq.) in THF (100 mL) was placed in a bath cooled to −78 °C for 30 minutes and then added to the pale yellow solution of freshly prepared LDA by cannula over 1 hr. The residual *N,N*-dimethylacetamide in the reaction vessel was dissolved THF (10 mL) and transferred via cannula to the solution of LDA. This was repeated once more and the pale yellow solution was stirred for 30 minutes to provide a freshly prepared solution of lithium dimethyl acetamide.

A pale yellow solution of the dibromide **123** (15.0 g, 62.0 mmol, 1.00 eq.) in THF (270 mL) was placed in a bath cooled to −78 °C for 30 minutes and then added to the solution of lithium dimethyl acetamide dropwise under nitrogen via cannula over 90 minutes. Residual dibromide was dissolved in THF (10 mL) and transferred via cannula to the reaction solution. This process was repeated once more. After 20 minutes the excess enolate was quenched with brine (200 mL), the reaction vessel was quickly removed from the cooling bath, and the white mixture was allowed to stir vigorously (1000 rpm) at 23 °C for 1 hr. EtOAc (500 mL) was added to the biphasic mixture which was poured into a separatory funnel, partitioned, and the residual organics were extracted from the aqueous layer using EtOAc (4 x 100 mL). (**Note:** The product is soluble in water, so brine (50 mL) is added during each extraction). The combined organic extracts were washed with brine (2 x 50 mL), dried over solid Na_2SO_4, decanted, and concentrated. Recrystallization of the yellow solid from hexane-ethyl ether (3:2, 50 mL) afforded the diamide **181** as colorless crystalline solid (14.4 g, 56.5 mmol, 91%).

R_f = 0.35 (5% MeOH in CH_2Cl_2)

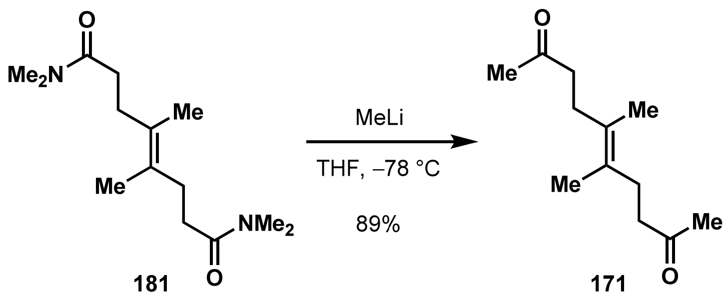
^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.00 (s, 6H), 2.94 (s, 6H), 2.33 (s, 8H), 1.67 (s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.06, 128.36, 37.48, 35.55, 31.98, 30.44, 18.11

IR (neat film, cm^{-1}): 3479, 2929, 1637, 1398

HRMS (EC-CI): calcd. for $C_{14}H_{27}N_2O_2$ $[M+H]^+$ 255.2073, found 255.2074.

M.P.: 69 – 71 °C.



A solution of diamide **181** (8.5 g, 33.4 mmol, 1.00 eq.) in deoxygenated THF (334 mL) was placed into a bath cooled to −78 °C for 1 hour upon which the clear colorless solution became a white heterogeneous mixture. While stirring vigorously (700 rpm) methyllithium (50.0 mL, 73.5 mmol, 1.47 M in ethyl ether, 2.20 eq.) was added dropwise over 15 minutes. 5 minutes after the complete addition of methyllithium the heterogeneous mixture had changed to a yellow homogeneous solution. After 15 minutes the yellow solution had changed to a white heterogeneous mixture upon which excess methyllithium was quenched with an aqueous phosphate buffer (100 mL, pH = 7, 0.2 M). The reaction vessel was removed from the cooling bath and allowed to warm to 23 °C over 30 minutes. The biphasic mixture was poured into a separatory funnel, partitioned, and the organics were extracted from the aqueous layer with ethyl ether (3 x 50 mL). Combined organics were washed with brine (1 x 50 mL), dried over solid Na_2SO_4, decanted, and concentrated under vacuum. The resulting yellow solid was purified by silica gel chromatography; 10 → 30% EtOAc in hexane to afford **171** as a white crystalline solid (5.9 g, 29.9 mmol, 89%). Crystals suitable for X-ray diffraction were grown from hexane by slow cold evaporation under a stream of nitrogen.

$\mathbf{R_f}$ = 0.43 (30% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.49 (dd, 4H, J = 7.2, 8.6 Hz), 2.26 (dd, 4H, J = 7.2, 8.6 Hz), 2.14 (s, 6H), 1.62 (s, 6H)

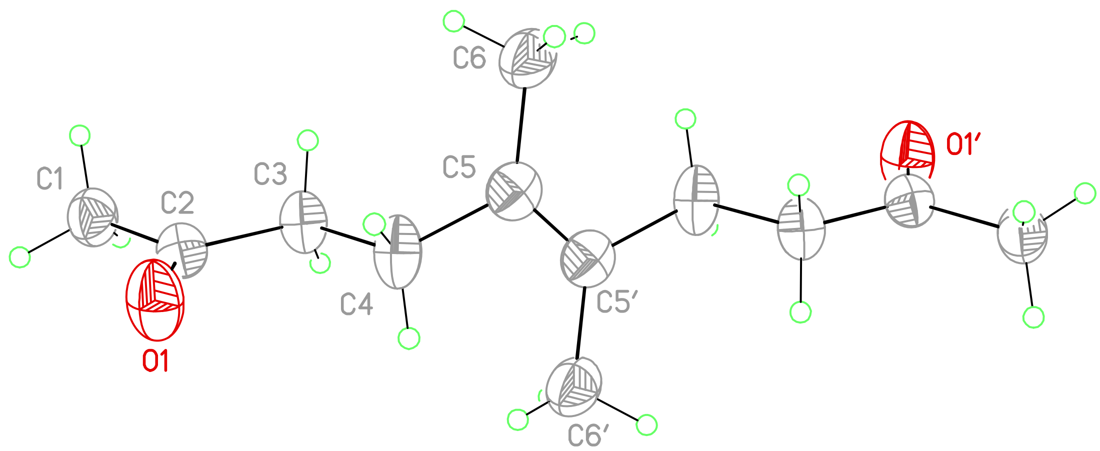
^{13}C-NMR (100 MHz, $CDCl_3$): δ 208.96, 127.92, 42.19, 30.04, 28.94, 17.93

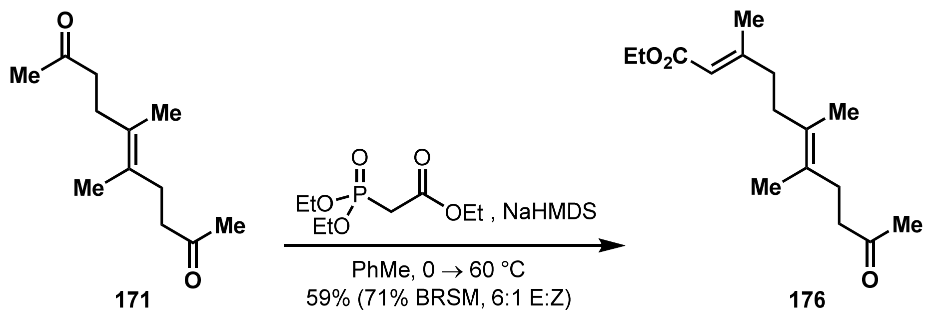
IR (neat film, cm^{-1}) 2360, 2340, 1708, 1364

HRMS (EC-CI): calcd. for $C_{12}H_{21}O_2$ $[M+H]^+$ 197.1542, found 197.1544.

M.P.: 55 – 57 °C

Crystal Structure of Diketone 171:





A solution of triethylacetophosphonate (5.6 g, 5.0 mL, 25 mmol, 1.35 eq.) in toluene (90 mL) was cooled to 0 °C in an ice bath. After stirring for 20 minutes NaHMDS (12.5 mL, 2.0 M in THF, 25 mmol, 1.35 eq.) was added dropwise over 3 minutes. After 30 minutes a solution of the diketone **171** (3.63 g, 18.5 mmol, 1.0 eq.) in toluene (74 mL) was cooled to 0 °C in an ice bath, stirred for 20 minutes, and to this clear solution was transferred the phosphonate via cannula over 15 minutes. Remaining phosphonate in the vessel was dissolved in toluene (7.0 mL) and transferred via cannula to the reaction solution. This process was repeated twice more. The golden-yellow solution was allowed to gradually warm to 23 °C over 60 minutes, stirred vigorously (1000 rpm) for 60 minutes at 23 °C, and the golden yellow solution was placed in an oil bath heated to 60 °C. After 22 hours the heterogeneous golden-orange mixture was removed from the oil bath and excess phosphonate was quenched with an aqueous phosphate buffer (10 mL, pH = 7, 0.2 M). The biphasic mixture was stirred vigorously (1000 rpm) for 10 minutes followed by which solid Na_2SO_4 was added and stirred for 10 minutes. The solid Na_2SO_4 was suction filtered over a pad of solid Na_2SO_4 and the golden-yellow filtrate solution was concentrated under vacuum. The resulting brown oil was purified by silica gel chromatography; hexane→20% Et_2O in hexane to afford the enoate **176** as a clear yellow oil as a 6:1 mixture of *trans* : *cis* isomers (2.9 g, 10.9 mmol, 59%). Further elution with 20% EtOAc in hexane affords the starting diketone **171** (0.4 g, 2.2 mmol, 12%).

Mixture of Isomers: (*) denotes *cis* isomer

$\mathbf{R_f}$ = 0.21 (15% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.63 (s, 1H), 4.13 (q, 2H, *J* = 2.4 Hz), 4.12* (q, 2H, *J* = 2.4 Hz) 2.44 (dd, 2H, *J* = 7.5, 8.6 Hz), 2.27 (dd, 2H, *J* = 7.2, 8.6 Hz), 2.16* (d, 3H, *J* = 1.4 Hz), 2.14 (s, 2H), 2.13 (s, 4H), 1.88* (d, 3H, *J* = 1.4 Hz), 1.68* (s, 3H), 1.66* (s, 3H), 1.63 (s, 3H), 1.60 (s, 3H), 1.26 (t, 3H, *J* = 7.0 Hz), 1.25 (t, 3H, *J* = 7.0 Hz)

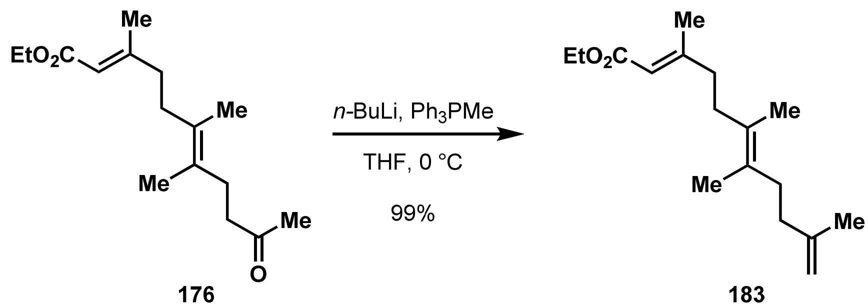
^{1}H-NMR (400 MHz, C_6D_6): δ 5.77 (s, 1H), 5.71* (s, 1H), 4.02 (q, 2H, *J* = 7.0 Hz), 3.90* (q, 2H, *J* = 7.1 Hz), 2.22* (s, 2H), 2.20* (s, 3H), 2.18 (s, 3H), 2.01 (dd, 2H, *J* = 7.2, 8.6

Hz), 1.96 – 1.84 (m, 4H), 1.69* (s, 3H), 1.64* (s, 3H), 1.63 (s, 3H), 1.51* (s, 3H), 1.43 (s, 3H), 1.39 (s, 3H), 0.98 (t, 3H, J = 6.9 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 208.95, 166.90 (166.37*), (160.23*) 159.60, (129.01*) 128.29, 127.98 (127.59*), (116.30*) 115.78, 59.59, 42.28, 39.45, (33.49*) 33.07, (32.13*) 30.06, (29.05*) 28.97, (25.56*), 19.05, 18.17 (18.13*), 17.98, 14.51

IR (neat film, cm^{-1}): 2980, 2930, 1717, 1647, 1446, 1366, 1224, 1145

HRMS (EC-CI): calcd. for $C_{16}H_{27}O_3$ $[M+H]^+$ 267.1960, found 267.1961.



A white suspension of methyl triphenylphosphonium bromide (18.1 g, 50.7 mmol, 1.25 eq.) in THF (205 mL) was placed in an ice water bath cooled to 0 °C and stirred vigorously (600 rpm) for 20 minutes. *n*-butyllithium (22.3 mL, 2.07 M in hexane, 46.2 mmol, 1.14 eq.) was added dropwise over 5 minutes and the resulting orange heterogeneous mixture was stirred for 30 minutes. The cooling bath was removed and the mixture was stirred for 10 minutes at 23 °C, and placed back into the ice water bath. After 10 minutes a solution of **176** (10.8 g, 40.5 mmol, 1.00 eq.) in THF (170 mL) was added dropwise via cannula over 15 minutes. Residual enoate **176** was dissolved THF (10 mL) and transferred via cannula to the now pale yellow reaction mixture. This process was repeated twice more. After 45 minutes excess ylide was quenched with an aqueous phosphate buffer (3 mL, pH = 7, 0.2 M) followed by the addition of pentane (100 mL). The biphasic mixture was stirred vigorously (600 rpm) for 10 minutes followed by which solid Na_2SO_4 was added. Vigorous stirring was continued for 10 minutes, and the solid Na_2SO_4, residual methyl triphenylphosphonium bromide, and triphenylphosphonium oxide were suction filtered over a pad of celite using pentane as the eluent. The resulting yellow solution was concentrated under vacuum to approximately 20 mL. Residual triphenylphosphonium oxide was triturated with pentane (100 mL). The resulting yellow mixture was suction filtered over a pad of celite using pentane and concentrated. The crude yellow oil was purified by silica gel chromatography; hexane → 2% EtOAc in hexane to afford the triene **183** as a clear yellow oil as a mixture of *trans* : *cis* isomers (10.7 g, 40.1 mmol, 99%). The isomers were then separated by silica gel chromatography; benzene.

***Trans* Isomer 183:**

$\mathbf{R_f}$ = 0.49 (15% EtOAc in hexane) and 0.45 (benzene):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.66 (s, 1H), 4.69 (s, 1H), 4.67 (s, 1H), 4.15 (q, 2H, *J* = 7.2 Hz), 2.18 (d, 3H, *J* = 1.1 Hz), 2.16 (s, 4H), 2.14 – 2.11 (m, 2H), 2.04 – 2.00 (m, 2H), 1.74 (s, 3H), 1.64 (s, 6H), 1.27 (t, 3H, *J* = 7.2 Hz)

^{1}**H-NMR** (400 MHz, C_6D_6): δ 5.79 (s, 1H), 4.77 (s, 2H), 4.01 (q, 2H, *J* = 7.2 Hz), 2.20 (d, 3H, *J* = 1.0 Hz), 2.11 – 2.07 (m, 2H), 2.01 (m, 4H), 1.93 – 1.89 (m, 2H), 1.64 (s, 3H), 1.48 (s, 6H), 0.98 (t, 3H, *J* = 7.2 Hz)
^{13}**C-NMR** (100 MHz, $CDCl_3$): δ 167.08, 160.30, 146.36, 129.44, 127.37, 115.74, 109.83, 59.65, 39.67, 36.44, 33.44, 33.19, 22.74, 19.13, 18.24, 18.18, 14.55

IR (neat film, cm^{-1}): 2979, 2934, 2867, 1717, 1649, 1446, 1373, 1223, 1144

HRMS (EC-CI): calcd. for $C_{17}H_{28}O_2$ $[M+H]^+$ 264.2089, found 264.2089.

***Cis* Isomer 184:**

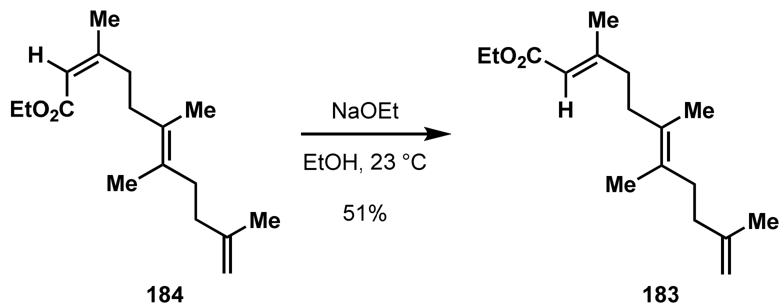
$\mathbf{R_f}$ = 0.49 (15% EtOAc in hexane) and 0.51 (benzene)

^{1}**H-NMR** (400 MHz, $CDCl_3$): δ 5.64 (s, 1H), 4.69 (s, 1H), 4.68 (s, 1H), 4.14 (q, 2H, *J* = 7.2 Hz), 2.64 (dd, 2H, *J* = 7.9, 8.6 Hz), 2.16 (m, 4H), 2.04 – 2.00 (m, 2H), 1.90 (s, 3H), 1.74 (s, 3H), 1.70 (s, 3H), 1.69 (s, 3H), 1.27 (t, 3H, *J* = 7.2 Hz)

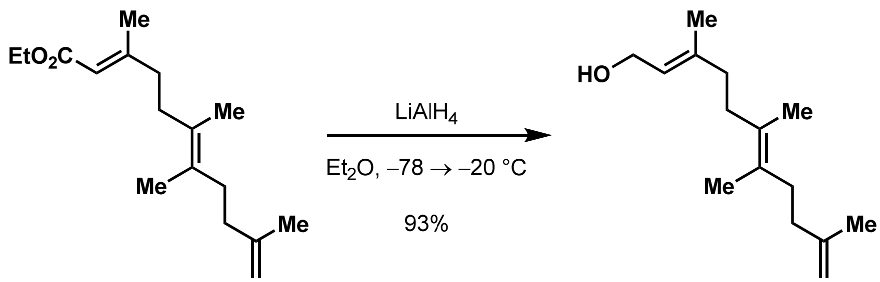
^{1}**H-NMR** (400 MHz, C_6D_6): δ 5.72 (s, 1H), 4.78 (s, 1H), 4.77 (s, 1H), 4.00 (q, 2H, *J* = 7.2 Hz), 2.77 (dd, 2H, *J* = 7.9, 8.6 Hz), 2.23 (d, 1H, *J* = 8.2 Hz), 2.21 (d, 1H, *J* = 8.2 Hz), 2.18 – 2.13 (m, 2H), 2.05 – 2.00 (m, 2H), 1.74 (s, 3H), 1.73 (s, 3H), 1.64 (s, 3H), 1.53 (d, 3H, *J* = 1.4 Hz), 0.96 (t, 3H, *J* = 7.2 Hz)

IR (neat film, cm^{-1}) 2979, 2934, 2867, 1717, 1649, 1446, 1373, 1223, 1144

HRMS (EC-CI): calcd. for $C_{17}H_{28}O_2$ $[M+H]^+$ 264.2089, found 264.2089.



To a clear colorless solution of freshly prepared sodium ethoxide (prepared from sodium metal (1.65 g, 72.2 mmol, 10.0 eq.) and anhydrous ethanol (52 mL)) was added the *cis*-isomer **184** (1.91 g, 7.22 mmol, 1.0 eq.) as a solution in ethanol (20 mL) via cannula. After 24 hours the solution had changed to a golden orange color and excess sodium ethoxide was quenched with an aqueous phosphate buffer (100 mL, pH = 7, 0.2 M). The ethanol was removed via rotary evaporation, and the resultant yellow mixture was diluted with ethyl ether (100 mL) and water (50 mL), poured into a separatory funnel, partitioned, and the organics were washed with water (1 x 50 mL). Residual organics were back extracted from the aqueous layer with ethyl ether (2 x 50 mL), washed with brine (1 x 25 mL), dried over sodium sulfate, decanted, concentrated and the resulting golden yellow oil was purified via silica gel chromatography; benzene to afford triene **183** (0.97 g, 3.68 mmol, 51%) as a clear golden yellow oil and the starting *cis*-isomer **184** (0.92 g, 3.47 mmol, 48%) as a clear golden yellow oil.



183 **172**

A yellow solution of the triene **183** (9.18 g, 34.7 mmol, 1.00 eq.) in ethyl ether (346 mL) was cooled to -78 °C and allowed to stir for 60 minutes. Lithium Aluminum Hydride (17.3 mL, 4 M in ethyl ether, 69.4 mmol, 2.00 eq.) was added dropwise over 5 minutes. The yellow solution was allowed to warm to −20 °C over 5 hours upon which the slightly white heterogeneous mixture was diluted with 300 mL of ethyl ether and excess lithium aluminum hydride was quenched by the sequential dropwise addition of water (5 mL), aqueous 15% NaOH solution (5 mL), and water (10 mL). The mixture was placed in an ice water bath cooled to 0 °C, stirred for 5 minutes, and an aqueous phosphate buffer (10 mL, pH = 7, 0.2 M) was added to the white heterogeneous mixture. The mixture was stirred vigorously (900 rpm) for 15 minutes and the cold bath was removed. Solid Na_2SO_4 was added and the heterogeneous mixture was stirred vigorously (1000 rpm) for 5 minutes, suction filtered over a pad of solid Na_2SO_4, and concentrated to reveal the alcohol **172** as a clear colorless oil (7.16 g, 32.2 mmol, 93%) which is submitted into the next reaction without further purification. An analytical sample was attained by purification via silica gel chromatography; 10% dioxane in hexane.

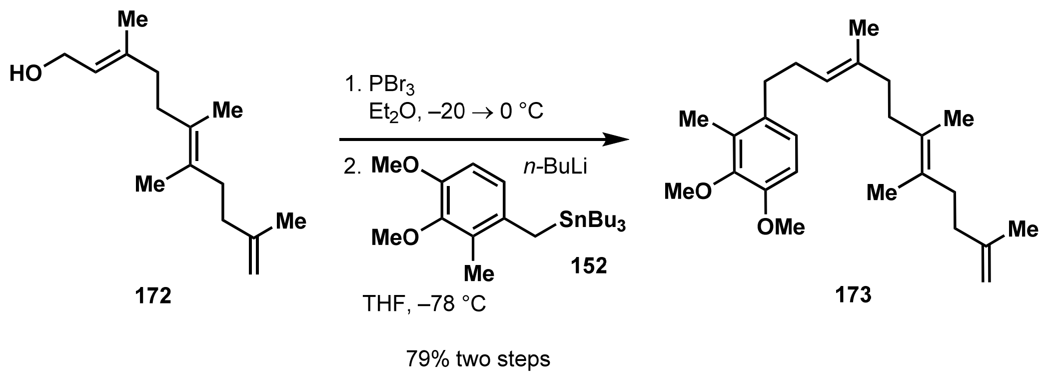
R_f = 0.56 (25% dioxane in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.41 (dt, 1H, *J* = 7.2, 6.6 Hz), 4.68 (s, 1H), 4.67 (s, 1H), 4.14 (d, 2H, *J* = 6.6 Hz), 2.14 – 2.09 (m, 4H), 2.05 – 1.99 (m, 4H), 1.73 (s, 3H), 1.69 (s, 3H), 1.64 (s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 146.3, 140.2, 128.4, 128.0, 123.1, 109.5, 59.4, 38.0, 36.3, 33.3, 33.2, 22.5, 18.01, 17.98, 16.37

IR (neat film, cm^{-1}): 3325, 2930, 2863, 1652, 1648, 1456, 1373, 1002, 885

HRMS (EC-CI): calcd. for $C_{15}H_{28}O$ $[M+2H]^{2+}$ 224.2140, found 224.2140.



A solution of the alcohol **172** (6.95 g, 31.3 mmol, 1.00 eq.) in ethyl ether (104 mL) was placed in a bath cooled to −20 °C and stirred for 20 minutes. PBr_3 (1.65 mL, 16.4 mmol, 0.51 eq.) was added dropwise over 2 minutes and the resulting pale yellow solution was stirred for 2 hours gradually warming to 0 °C. The solution was diluted with hexane (100 mL) and then the HBr was slowly neutralized with a saturated aqueous mixture of $NaHCO_3$ (20 mL). The biphasic mixture was poured into a separatory funnel and partitioned. (NOTE: The separatory funnel was swirled, not shaken, to avoid emulsion. If emulsion occurs, wash with copious amounts of water). The organic layer was washed with water (3 x 50 mL), and the residual organics were extracted from the aqueous layer using hexane (2 x 50 mL). The combined organics were washed with brine (2 x 30 mL), dried over solid Na_2SO_4, decanted, and concentrated under vacuum. The resulting clear pale yellow oil (8.90 g, 31.2 mmol, 100%) was used directly in the next reaction without further purification.

A solution of stannane **152** (13.0 g, 28.6 mmol, 1.20 eq.) in deoxygenated THF (177 mL) was placed in a bath cooled to −78 °C and stirred for 1 hour. *n*-Butyllithium (14.6 mL, 1.96 M in hexane, 28.6 mmol, 1.20 eq.) was added dropwise over 15 minutes and the color of the resulting solution changed to golden orange. After stirring for 30 minutes, a solution of the triene allylic bromide (6.8 g, 23.9 mmol, 1.00 eq.) in deoxygenated THF (40 mL) was added dropwise over 1 hour to the golden orange soltuion. Residual bromide was dissolved in deoxygenated THF (10 mL) and transferred to the now golden yellow reaction solution. This process was repeated once more. After stirring for 1 hour the excess benzyl anion was quenched with water (200 mL) and allowed to warm to room temperature while stirring for 30 minutes. The biphasic solution was poured into a separatory funnel containing water (200 mL) and hexane (300 mL). (NOTE: If emulsion occurs, add copious amounts of water and swirl the mixture, do not shake). The organics were washed with water (2 x 100 mL). Residual organics were extracted from the aqueous layer using hexane (2 x 100 mL), washed with brine (1 x 100 mL), dried over solid Na_2SO_4, decanted, and concentrated under vacuum. The resulting clear colorless oil was purified by silica gel chromatography; hexane (1 L) and then 2% benzene in toluene. Impure product is purified again by silica gel chromatography; 2% benzene in toluene to afford the triene **173** as a clear colorless oil (7.0 g, 19.0 mmol, 79%).

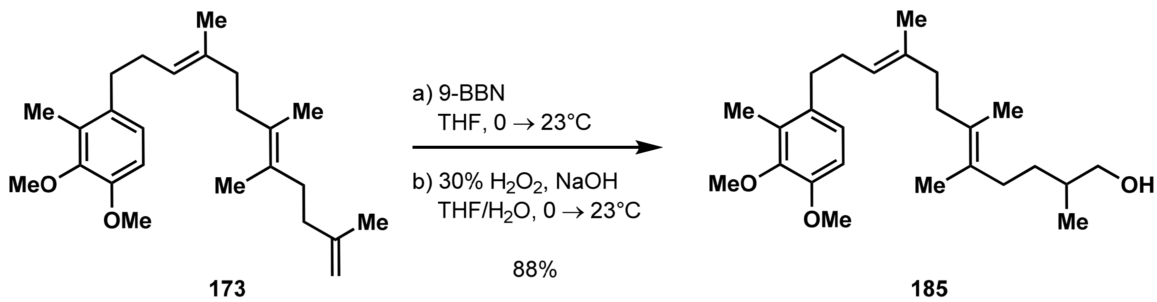
R_f = 0.36 (2% benzene in toluene)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.85 (d, 1H, *J* = 8.2 Hz), 6.70 (d, 1H, *J* = 8.2), 5.20 (dd, 1H, *J* = 7.2, 6.5 Hz), 4.69 (s, 1H), 4.68 (s, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 2.55 (dd, 2H, *J* = 7.5, 5.8 Hz), 2.24 (s, 3H), 2.24 – 2.18 (m, 2H), 2.15 – 2.07 (m, 4H), 2.05 – 1.97 (m, 4H), 1.75 (s, 3H), 1.65 (s, 6H), 1.59 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 151.02, 147.47, 146.62, 136.24, 134.13, 130.47, 128.62, 128.34, 124.29, 123.80, 109.76, 109.52, 60.42, 55.92, 38.41, 36.57, 33.89, 33.52, 33.50, 29.33, 22.83, 18.31, 18.25, 16.32, 11.97

IR (neat film, cm^{-1}): 1490, 1453, 1271, 1086

HRMS (EC-CI): calcd. for $C_{25}H_{38}O_2$ [M] 370.2872, found 370.2871.



A solution of the triene **173** (7.0 g, 18.9 mmol, 1.00 eq.) in THF (73 mL) was placed in an ice water bath cooled to 0 °C and stirred vigorously (500 rpm) for 20 minutes. Crystalline 9-BBN dimer (2.4 g, 9.8 mmol, 0.52 eq.) was added under a stream of nitrogen and the heterogeneous mixture was stirred (500 rpm) for 4 hours upon which the cooling bath had warmed to 23 °C. The clear solution was placed in an ice bath cooled to 0 °C and stirred for 20 minutes. Excess 9-BBN was quenched with water (31 mL) followed by the addition of an aqueous solution of H_2O_2 (30% w/v in water, 9.7 mL, 94.0 mmol, 5.00 eq.) and NaOH (4 N, 23.6 mL, 94.0 mmol, 5.00 eq.). The biphasic mixture was stirred vigorously (800 rpm) and allowed to gradually warm to 23°C. After 60 hours, excess H_2O_2 was quenched with a saturated aqueous mixture of $Na_2S_2O_3$ (100 mL). After stirring for 10 minutes excess hydroxide was quenched with an aqueous phosphate buffer (50 mL, pH = 7, 0.2 M). The biphasic mixture was poured into a separatory funnel, partitioned, and residual organics were extracted from the aqueous layer using ethyl acetate (4 x 50 mL). The combined organics were washed with brine (1 x 100 mL), dried over Na_2SO_4, decanted, and concentrated under vacuum. The resulting clear colorless oil was purified by silica gel chromatography; 1 → 12% EtOAc in hexane to afford the alcohol **185** as a clear colorless oil (6.48 g, 16.6 mmol, 88%) and the starting triene **173** as a clear colorless oil (0.70 g, 1.9 mmol, 10%).

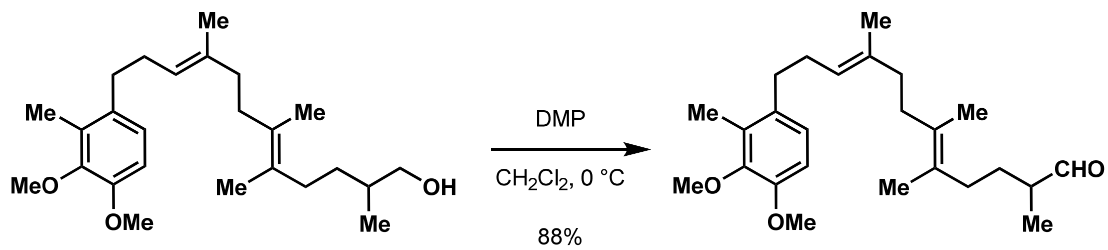
R$_f$ = 0.50 (50% EtOAc in hexane):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.85 (d, 1H, *J* = 8.2 Hz), 6.70 (d, 1H, *J* = 8.2), 5.20 (dd, 1H, *J* = 7.2, 6.8 Hz), 3.83 (s, 3H), 3.78 (s, 3H), 3.52 (dd, 1H, *J* = 5.8 Hz), 3.43 (dd, 1H, *J* = 6.5, 6.8 Hz), 2.55 (dd, 2H, *J* = 7.5, 5.8 Hz), 2.24 (s, 3H), 2.24 – 2.18 (m, 2H), 2.10 – 1.94 (m, 6H), 1.64 (s, 6H), 1.59 (s, 3H), 1.51 (m, 2H), 1.31 (bs, 1H), 1.19 – 1.09 (m, 1H), 0.95 (d, 3H, *J* = 6.5 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 150.78, 147.29, 136.00, 133.91, 130.21, 128.38, 128.10, 124.04, 123.55, 109.38, 68.35, 60.16, 55.71, 38.15, 35.88, 36.65, 33.23, 32.04, 31.55, 29.07, 18.06, 17.96, 16.60, 16.05, 11.70

IR (neat film, cm^{-1}): 3391, 1490, 1453, 1270, 1085

HRMS (EC-CI): calcd. for $C_{25}H_{40}O_3$ [M] 388.2977, found 388.2978.



185 **186**

A solution of the alcohol (6.48 g, 16.8 mmol, 1.00 eq.) in methylene chloride (162 mL) was placed in an ice bath cooled to 0 °C. After 20 minutes, solid $NaHCO_3$ (5.45 g, 64.9 mmol, 4.00 eq.), Dess-Martin periodinane (14.1 g, 33.6 mmol, 2.00 eq.), and water (2 drops) were added sequentially and the mixture was stirred vigorously (700 rpm). After 80 minutes residual acetic acid was neutralized with a saturated aqueous mixture of $NaHCO_3$ (100 mL) and excess Dess-Martin periodinane was quenched with a saturated aqueous mixture of $Na_2S_2O_3$ (200 mL). The biphasic mixture was removed from the cooling bath, stirred vigorously (1000 rpm) for 60 minutes at 23 °C, poured into a separatory funnel, and partitioned. The organic layer was washed with a saturated mixture of $Na_2S_2O_3$ and $NaHCO_3$ (2 x 50 mL, 1:1). Residual organics were extracted from the aqueous layer using methylene chloride (3 x 50 mL). The combined organics were washed with brine (1 x 25 mL), dried over solid Na_2SO_4, filtered, and concentrated under vacuum. The resulting clear pale yellow oil was purified by silica gel chromatography; hexane → 5% EtOAc in hexane to afford the aldehyde **186** as a clear colorless oil (5.73 g, 14.8 mmol, 88%).

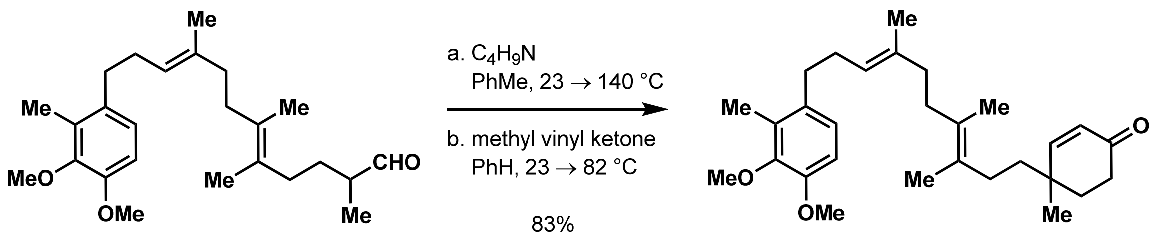
$\mathbf{R_f}$ = 0.65 (50% EtOAc in hexane):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.62 (d, 1H, J = 2.1 Hz), 6.85 (d, 1H, J = 8.2 Hz), 6.70 (d, 1H, J = 8.2), 5.20 (dd, 1H, J = 7.2, 6.8 Hz), 3.84 (s, 3H), 3.78 (s, 3H), 2.55 (dd, 2H, J = 7.9, 5.8 Hz), 2.31 (ddd, 1H, J = 1.7 Hz), 2.23 (s, 3H), 2.24 – 2.18 (m, 2H), 2.10 – 1.96 (m, 6H), 1.78 (m, 1H), 1.64 (s, 6H), 1.59 (s, 3H), 1.40 (m, 1H), 1.11 (d, 3H, J = 7.2 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 205.26, 151.02, 147.47, 136.10, 134.05, 130.42, 129.49, 127.56, 124.29, 123.88, 109.54, 60.38, 55.89, 46.37, 38.30, 33.86, 33.47, 32.12, 29.32, 29.17, 18.42, 18.14, 16.28, 13.72, 11.96

IR (neat film, cm^{-1}): 1724, 1490, 1454, 1271, 1085

HRMS (EC-CI): calcd. for $C_{25}H_{38}O_3$ [M] 386.2821, found 386.2822.



186 **174**

To a solution of the aldehyde **186** (5.73 g, 14.8 mmol, 1.00 eq.) in toluene (100 mL) in a reaction vessel equipped with a Dean-Stark trap was added pyrrolidine (15.2 mL, 185.0 mmol, 12.50 eq.). The yellow solution was stirred for 8 hours at 23 °C and then placed in an oil bath heated to 140 °C for 24 hours. The golden-yellow solution was removed from the oil bath, cooled to 23 °C, and concentrated under vacuum to remove excess pyrrolidine. The viscous orange oil was dissolved in toluene (100 mL) and then methyl vinyl ketone (2.4 mL, 29.6 mmol, 2.00 eq.) was added. The orange solution was stirred at 23 °C for 24 hours and then placed in an oil bath heated to 82 °C. After 48 hours, a solution of sodium acetate (4.0 g) and acetic acid (6.1 mL) in water (6.1 mL) was added to the dark red solution. The biphasic mixture was placed in an oil bath heated to 82 °C and stirred vigorously (700 rpm) for 6 hours. The reaction vessel was removed from the oil bath, cooled to 23 °C, and diluted with an aqueous phosphate buffer (50 mL, pH = 4, 0.2 M) and ethyl acetate (50 mL). The biphasic mixture was poured into a separatory funnel and partitioned. The organic layer was washed with an aqueous phosphate buffer (50 mL, pH = 4, 0.2 M) and then residual organics were extracted from the aqueous layer using ethyl acetate (3 x 50 mL). The combined organics were washed with brine (1 x 100 mL), dried over solid Na_2SO_4, decanted, and concentrated under vacuum. The resulting viscous red-brown oil was purified by silica gel chromatography; hexane → 10% EtOAc in hexane to afford the cyclohexenone **174** as a viscous clear amber oil (5.41 g, 12.3 mmol, 83%).

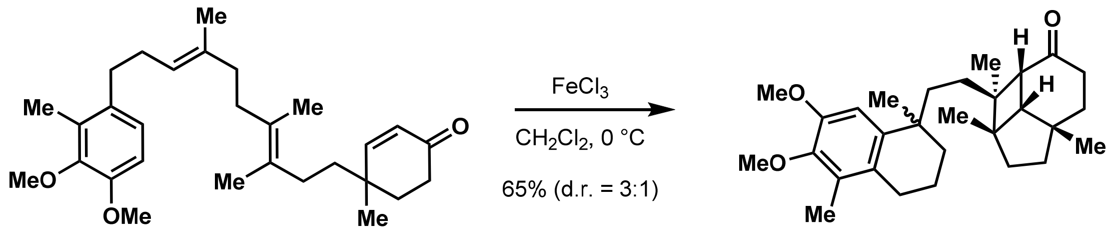
$\mathbf{R_f}$ = 0.37 (30% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.85 (d, 1H, J = 8.2 Hz), 6.70 (d, 1H, J = 7.9 Hz), 6.69 (d, 1H, J = 11.6 Hz), 5.90 (d, 1H, J = 10.3 Hz), 5.19 (t, 1H, J = 6.8 Hz), 3.83 (s, 3H), 3.78 (s, 3H), 2.55 (dd, 2H, J = 7.5, 5.8 Hz), 2.47 (dd, 1H, J = 2.4, 3.4 Hz), 2.45 (d, 1H, J = 6.2 Hz), 2.23 (s, 3H), 2.24 – 2.17 (m, 2H), 2.10 – 1.96 (m, 8H), 1.80 – 1.76 (m, 1H), 1.633 (s, 3H), 1.628 (s, 3H), 1.58 (s, 3H), 1.47 (m, 1H), 1.16 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.97, 159.51, 151.02, 147.47, 136.11, 134.07, 130.44, 128.84, 127.95, 127.60, 124.27, 123.87, 109.53, 60.42, 55.92, 39.29, 38.32, 35.88, 34.40, 33.83, 33.56, 33.47, 29.55, 29.33, 24.96, 18.37, 18.25, 16.31, 11.97

IR (neat film, cm^{-1}): 1683, 1490, 1454, 1271, 1084

HRMS (ESI): calcd. for $C_{29}H_{42}O_3$ $[M+Na]^+$ 461.3026, found 461.3027.



174 188

Anhydrous ferric chloride (1.12 g, 6.90 mmol, 3.00 eq.) was crushed under vacuum by stirring the solid vigorously (600 rpm) for 30 minutes. Deoxygenated CH_2Cl_2 (550 mL) was added and the suspension was vigorously stirred (600 rpm) at 23 °C for 20 minutes. Stirring was stopped and the residual powder was allowed to settle on the bottom of the reaction vessel and the yellow-green liquid was decanted by cannulation under nitrogen to a separate flask. The solubility of ferric chloride in deoxygenated CH_2Cl_2 was measured to be 1.1 mg / mL.

A solution of the enone **174** (1.00 g, 2.28 mmol, 1.00 eq.) in deoxygenated CH_2Cl_2 (2.3 L) was placed in an ice water bath cooled to 0 °C and stirred for 1 hour. The solution of $FeCl_3$ in CH_2Cl_2 was added dropwise over 70 minutes. The resulting yellow-orange solution was allowed to stir for 8 hours at 0 °C and then diluted with an aqueous phosphate buffer (400 mL, pH = 4, 0.2 M). The biphasic mixture was stirred vigorously (1000 rpm) for 60 minutes, poured into a separatory funnel, and the organic layer was removed. Residual organics were extracted from the aqueous layer using methylene chloride (3 x 100 mL). The combined organics were washed with brine, dried over solid Na_2SO_4, decanted, and concentrated. The resulting brown oil was purified by silica gel chromatography; hexane → 2% acetone in hexane to afford the ketone **188** as a colorless viscous foam (0.65 g, 1.50 mmol, 65%, d.r. = 3:1). The diastereomers were separated by silica gel chromatography several times; 3% 1,4-dioxane in hexane.

Major Diastereomer:

$\mathbf{R_f}$ = 0.43 (30% EtOAc in hexane) and 0.58 (10% 1,4-dioxane in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.70 (s, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 2.59 – 2.41 (m, 2H), 2.32 (dd, 2H, *J* = 9.2, 9.6 Hz), 2.23 (dt, 2H, *J* = 4.5, 4.8 Hz), 2.13 (s, 3H), 2.03 (d, 1H, *J* = 10.2 Hz), 1.89 – 1.70 (m, 8H), 1.53 – 1.35 (m, 5H), 1.26 (s, 3H), 1.06 (s, 3H), 1.02 (s, 3H), 0.83 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 213.86, 150.24, 144.83, 140.17, 129.51, 128.77, 107.95, 60.25, 55.65, 52.74, 50.84, 49.05, 44.50, 39.76, 37.72, 37.16, 36.47, 36.24, 36.03, 35.89, 34.63, 32.07, 30.97, 29.70, 27.59, 23.20, 19.44, 16.65, 11.90

IR (neat film, cm^{-1}): 1692, 1489, 1456, 1089

HRMS (EC-CI): calcd. for $C_{29}H_{42}O_3$ [M] 438.3134, found 438.3130.

Minor Diastereomer:

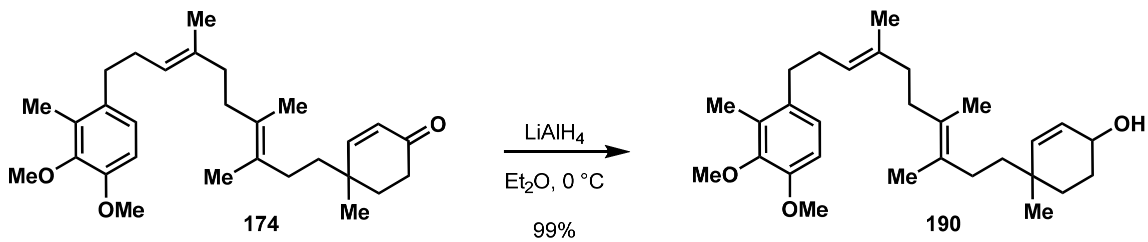
R_f = 0.43 (30% EtOAc in hexane) and 0.52 (10% 1,4-dioxane in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.68 (s, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 2.53 (dt, 1H, J = 5.5, 5.9 Hz), 2.48 – 2.44 (m, 1H), 2.41 (d, 1H, J = 10.4 Hz), 2.36 – 2.19 (m, 3H), 2.12 – 2.10 (m, 1H), 2.11 (s, 3H), 1.88 – 1.65 (m, 8H), 1.56 – 1.40 (m, 5H), 1.23 (s, 3H), 1.09 (s, 3H), 1.03 (s, 3H), 0.82 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 213.82, 150.27, 144.86, 140.66, 129.43, 128.21, 108.24, 60.27, 55.73, 52.97, 50.92, 49.02, 44.45, 39.77, 37.57, 36.68, 36.53, 36.28, 36.06, 35.81, 34.61, 32.11, 30.21, 29.77, 27.43, 23.45, 19.36, 16.87, 11.88

IR (neat film, cm^{-1}): 1694, 1489, 1456, 1088

HRMS (EC-CI): calcd. for $C_{29}H_{42}O_3$ [M] 438.3134, found 438.3130.



A yellow solution of the enone **174** (2.35 g, 5.36 mmol, 1.00 eq.) in ethyl ether (54 mL) was placed in an ice bath cooled to 0 °C and stirred for 20 minutes. $LiAlH_4$ (1.4 mL, 4 M in ethyl ether, 5.62 mmol, 1.05 eq.) was added dropwise over 2 minutes. After 5 minutes the clear colorless solution was diluted with ethyl ether (30 mL) and excess lithium aluminum hydride was quenched by the sequential dropwise addition of water (0.5 mL), aqueous NaOH (15%, 0.5 mL), and water (1.5 mL). After stirring for 5 minutes an aqueous phosphate buffer (1.5 mL, pH = 7, 0.2 M) was added to the white heterogeneous mixture and stirred vigorously (900 rpm) for 15 minutes. The cold bath was removed and the mixture was allowed to warm to 23 °C. Solid Na_2SO_4 was added and the heterogeneous mixture was stirred vigorously for 10 minutes, suction filtered over a pad of Na_2SO_4, and concentrated to reveal the alcohol **190** as a clear colorless oil (2.35 g, 5.33 mmol, 99%, d.r. = 1.4 : 1).

Major Diastereomer:

$\mathbf{R_f}$ = 0.24 (50% Et_2O in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.85 (d, 1H, *J* = 8.2 Hz), 6.70 (d, 1H, *J* = 8.2), 5.63 (dd, 1H, *J* = 2.3, 9.8 Hz), 5.52 (d, 1H, *J* = 10.2 Hz), 5.19 (t, 1H, *J* = 7.0 Hz), 4.14 (m, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 2.55 (m, 1H), 2.23 (s, 3H), 2.21 (m, 1H), 2.09 – 1.84 (m, 8H), 1.64 (s, 3H), 1.62 (s, 3H), 1.58 (s, 3H), 1.74 – 1.24 (m, 5H), 1.02 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 150.76, 139.98, 139.15, 135.96, 133.87, 128.64, 128.49, 127.85, 127.56, 124.05, 123.56, 109.30, 66.58, 60.18, 55.68, 40.37, 38.13, 34.70, 33.58, 33.25, 31.34, 29.27, 29.17, 29.10, 26.47, 18.13, 17.95, 16.08, 11.72

IR (neat film, cm^{-1}): 3370, 2931, 1490, 1454, 1270, 1084

HRMS (EC-CI): calcd. for $C_{29}H_{44}O_3$ [M] 440.3290, found 440.3288.

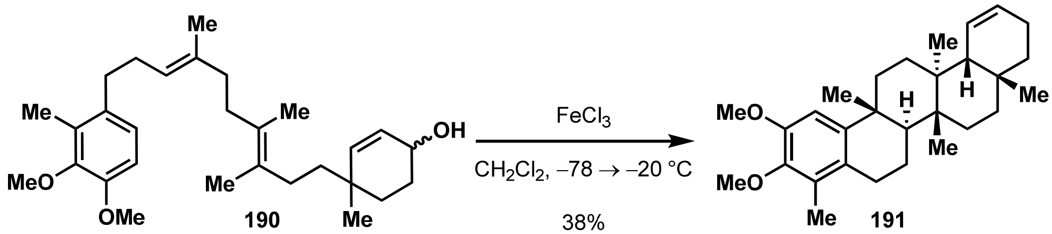
Minor Diastereomer:

$\mathbf{R_f}$ = 0.24 (50% Et_2O in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.85 (d, 1H, *J* = 8.2 Hz), 6.70 (d, 1H, *J* = 8.2), 5.67 (dd, 1H, *J* = 3.6, 10.2 Hz), 5.57 (d, 1H, *J* = 10.2 Hz), 5.19 (t, 1H, *J* = 7.0 Hz), 4.14 (m, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 2.55 (m, 1H), 2.23 (s, 3H), 2.21 (m, 1H), 2.09 – 1.84 (m, 8H), 1.64 (s, 3H), 1.62 (s, 3H), 1.58 (s, 3H), 1.74 – 1.24 (m, 5H), 0.96 (s, 3H)
^{13}C-NMR (100 MHz, $CDCl_3$): δ 147.22, 139.98, 139.15, 135.98, 130.20, 128.64, 128.47, 127.87, 127.56, 124.06, 123.56, 109.30, 65.32, 60.18, 55.68, 40.22, 38.13, 34.58, 33.58, 33.25, 30.39, 29.40, 29.10, 28.17, 26.00, 18.15, 16.08, 15.28, 11.72.

IR (neat film, cm^{-1}): 3370, 2931, 1490, 1454, 1270, 1084

HRMS (EC-CI): calcd. for $C_{29}H_{44}O_3$ [M] 440.3290, found 440.3288.



Ferric chloride (1.10 g, 6.81 mmol, 3.00 eq.) was added into a flame-dried round-bottomed flask in a glove box, removed, and crushed under vacuum by stirring the solid vigorously for 30 minutes. Freshly deoxygenated CH_2Cl_2 (550 mL) was added and the suspension was vigorously stirred (600 rpm) at 23 °C for 30 minutes. Stirring was stopped and the residual powder was allowed to congregate on the bottom of the reaction vessel. The yellow liquid was decanted by cannulation under nitrogen to a separate flame-dried flask.

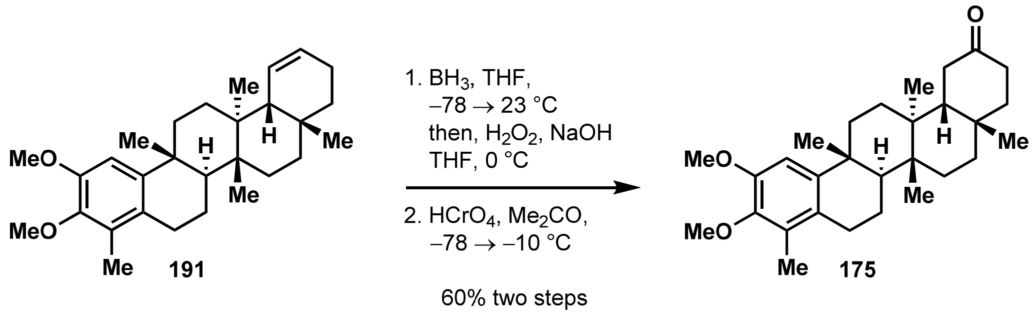
A solution of the alcohol **190** (1.00 g, 2.27 mmol, 1.00 eq.) in freshly deoxygenated CH_2Cl_2 (4.15 L) was placed in a bath cooled to −78 °C and stirred (500 rpm) for 1 hr. The solution of $FeCl_3$ in CH_2Cl_2 was added via cannula under nitrogen over 20 minutes. The golden yellow solution was stirred (500 rpm) for 6 hrs while gradually warming to −20 °C affording a purple-red solution. The excess $FeCl_3$ was quenched with an aqueous phosphate buffer (300 mL, pH = 7, 0.2 M), and the biphasic mixture was immediately removed from the cold bath, stirred vigorously (1000 rpm) for 60 minutes, poured into a separatory funnel, and the organic layer was removed. Residual organics were extracted from the aqueous layer using methylene chloride (2 x 100 mL), combined, dried over solid Na_2SO_4, decanted, and concentrated. The resulting golden yellow amorphous oil was purified by silica gel chromatography; benzene to afford the pentacycle **191** as a white solid which was ~65% pure determined by GC (300 °C) and ^{1}H-NMR (0.57 g, 0.86 mmol, 38%). Further purification using trituration, recrystallization, silica gel chromatography, or preparative TLC did not afford a more pure product. The impure compound was carried onto the next step without full structural characterization.

R_f = 0.64 (5% EtOAc in benzene)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.69 (s, 1H), 5.70 (m, 2H), 3.83 (s, 3H), 3.75 (s, 3H), 2.72 (dd, 1H, *J* = 4.8, 13.0 Hz), 2.54 (q, 1H, *J* = 8.5 Hz), 2.11 (s, 3H), 2.00 – 1.52 (m, 12H), 1.44 – 1.28 (m, 4H), 1.26 (s, 3H), 1.03 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H)

HRMS (ESI): calc'd. for $C_{29}H_{42}O_2Na$ $[M+Na]^+$ 445.3077, found 445.3082.

M.P.: 49 – 53 °C



A solution of the impure pentacycle **191** (0.25 g, 0.58 mmol, 1.00 eq.) in THF (5.8 mL) was placed in a bath cooled to −78 °C and stirred for 1 hour. A solution of borane in THF (1 M, 5.22 mL, 5.22 mmol, 9.00 eq.) was added to the pale yellow solution and stirred for 12 hrs. warming gradually to 23 °C. The clear solution was placed in an ice water bath cooled to 0 °C for 10 minutes and an aqueous solution of H_2O_2 (30% w/v, 7.0 mL) and NaOH (4 N, 7.0 mL) was added. The biphasic mixture was stirred for 8 hrs and excess peroxide was quenched with a saturated aqueous mixture of $Na_2S_2O_3$ (10 mL). An aqueous phosphate buffer (10 mL, pH = 7, 0.2 M) and EtOAc (10 mL) were added, the mixture was poured into a separatory funnel, partitioned, residual organics were extracted from the aqueous layer with EtOAc (2 x 15 mL), combined, washed with brine (1 x 10 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude alcohol was then submitted into the next reaction without purification or characterization.

A solution of the crude alcohol (0.26 g) in acetone (28.9 mL) was placed in a bath cooled to −78 °C and stirred for 30 minutes. Jones reagent (1.53 M, 0.40 mL, 0.61 mmol, 1.05 eq.) was added and the red-brown solution was allowed to warm gradually to −10 °C over 2 hrs. Excess chromic acid was quenched with 2-propanol (10 mL) and the green mixture was diluted with ethyl ether (30 mL) and an aqueous phosphate buffer (10 mL, pH = 7, 0.2 M). The biphasic mixture was poured into a separatory funnel, partitioned, and the organic layer was washed with a saturated aqueous mixture of $NaHCO_3$ (2 x 10 mL). The residual organics were extracted from the aqueous layer with ethyl ether (3 x 20 mL), combined, washed with brine (1 x 10 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude green mixture was purified by silica gel chromatography; 5% EtOAc in hexane to afford the pentacyclic ketone **175** as a white solid (0.152 g, 0.35 mmol, 60%).

$\mathbf{R_f}$ = 0.71 (40% EtOAc in hexane)

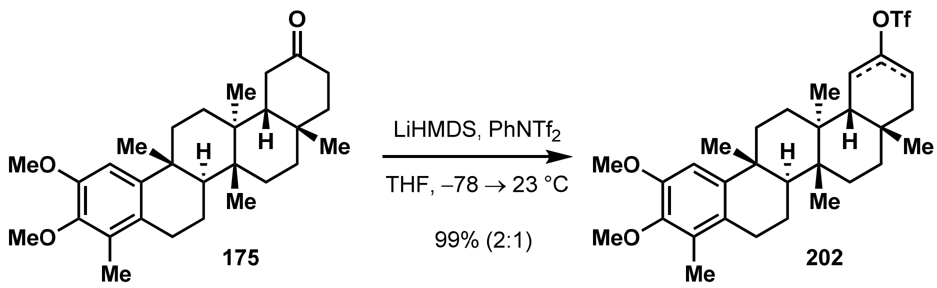
^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.66 (s, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 2.72 (dd, 1H, *J* = 6.5, 17.6 Hz), 2.56 (dd, 1H, *J* = 7.3, 17.6 Hz), 2.53 – 2.27 (m, 5H), 2.10 (s, 3H), 2.04 – 2.00 (m, 2H), 1.92 (ddd, 1H, *J* = 4.4, 13.7 Hz), 1.85 (m, 2H), 1.73 – 1.33 (m, 8H), 1.28 (s, 3H), 1.23 (s, 3H), 1.00 (s, 3H), 0.88 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 213.80, 150.44, 146.86, 144.93, 129.45, 126.33, 105.83, 60.29, 55.86, 47.98, 43.58, 40.10, 39.55, 37.72, 37.68, 37.56, 37.17, 35.06, 33.78, 31.50, 31.22, 29.42, 28.11, 27.88, 27.84, 18.13, 16.29, 15.02, 11.73

IR (neat film, cm^{-1}): 2935, 1709, 1487, 1091

HRMS (EC-CI): calcd. for $C_{29}H_{42}O_3$ [M] 438.3134, found 438.3129.

M.P.: 58 – 62 °C



The ketone was dried by the azeotropic removal of water using toluene (3 x 3 mL) prior to use. A solution of the ketone **175** (114 mg, 0.26 mmol, 1.00 eq.) in THF (3.7 mL) was placed in a bath cooled to −78 °C and stirred for 1 hr. A solution of LiHMDS (1 M, 1.00 mL, 1.04 mmol, 4.00 eq.) was added and the pale yellow solution was stirred for 1 hr. A solution of *N*-phenyl-bis(trifluoromethanesulfonimide) (371 mg, 1.04 mmol, 4.00 eq.) in THF (1.5 mL) was added to the enolate in a dropwise manner by cannula under nitrogen. The golden yellow solution was stirred for 20 minutes, the cold bath was removed, and the solution was allowed to gradually warm to 23 °C over 1 hr. An aqueous phosphate buffer (5 mL, pH = 10, 0.2 M) was added to neutralize excess LiHMDS and the biphasic mixture was poured into a separatory funnel containg Et_2O (10 mL). The organic layer was washed with a saturated aqueous mixture of $NaHCO_3$ (2 x 10 mL). Residual organics were extracted from the aqueous layer using Et_2O (2 x 10 mL), combined, dried over solid Na_2SO_4, decanted, and concentrated. The crude pale orange solid was purified by silica gel chromatography; 2% Et_2O in hexane to provide the enol triflate **202** as a white solid (0.146 g, 0.26 mmol, 99%, 2:1 mixture of olefin isomers).

Mixture of Isomers: (*) denotes minor isomer

$\mathbf{R_f}$ = 0.51 (15% Et_2O in hexane)

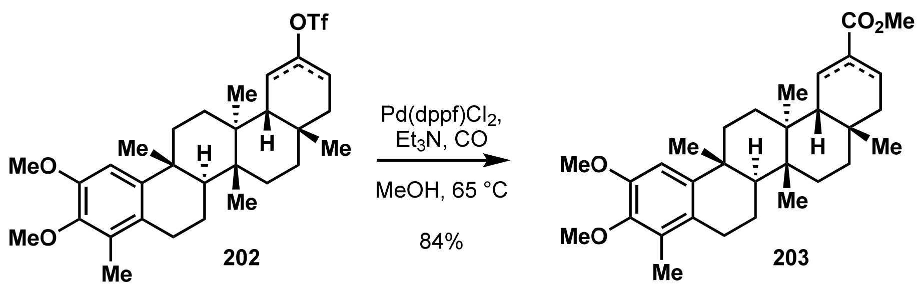
^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.67 (s, 1H), 5.77* (m, 1H), 5.64 (m, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 2.72 (dd, 1H, *J* = 6.5, 17.6 Hz), 2.66 – 2.20 (m, 8H), 2.10 (s, 3H), 2.05 – 1.40 (m, 8H), 1.25* (s, 3H), 1.23 (s, 3H), 1.05 (s, 3H), 1.03* (s, 3H), 1.01 (s, 3H), 1.00* (s, 3H), 0.93* (s, 3H), 0.92 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 150.43 (150.44*), 148.98 (148.89*), 146.94 (146.69*), 144.91 (144.87*), 129.45 (129.48*), 126.28 (126.32*), 119.09 (120.13*), 116.73, 105.70 (105.79*), 60.30, 55.78, (47.25*), (43.94*), 43.73, 43.39, (40.34*), 39.94, 39.84, (39.10*), (37.39*), 37.35, 37.11, 34.38 (34.52*), 34.08 (33.87*), 32.54, (31.12*), 30.55 (29.68*), 29.60 (29.45*), 28.31 (28.26*), 27.92, 27.82, 27.76, 24.44 (24.67*), 18.05 (18.21*), 16.91, 15.14 (15.09*), 13.83, 11.76

IR (neat film, cm^{-1}): 2924, 1413, 1207, 1143

HRMS (EC-CI): calcd. for $C_{30}H_{41}O_5F_3S$ $[M+H]^+$ 570.2627, found 570.2622.

M.P.: 54 – 56 °C



A mixture of the enol triflate **202** (109.0 mg, 0.19 mmol, 1.00 eq.) and Pd(dppf)Cl_2-CH_2Cl_2 (31.5 mg, 0.04 mmol, 0.20 eq.) was evacuated and then refilled with nitrogen. To the dry red mixture was added triethylamine (0.54 mL, 3.83 mmol, 20.0 eq.) and methanol (3 mL). The reaction vessel was stoppered with a plastic PTFE cap under a positive flow of carbon monoxide. The vessel was placed under an atmosphere of carbon monoxide (balloon), the dark red solution was placed in an oil bath heated to 65 and stirred (500 rpm) for 12 hrs. The black mixture was removed from the oil bath, cooled to 23 °C, and a second loading of Pd(dppf)Cl_2-CH_2Cl_2 (38.8 mg, 0.05 mmol, 0.25 eq.) was added. The black mixture was purged, placed under an atmosphere of carbon monoxide (balloon), and placed into the oil bath heated to 65 °C. After 24 hrs. the black mixture was removed from the oil bath, concentrated, and residual methanol was azeotropically removed with chloroform (3 x 3 mL). The black solid was dissolved in chloroform and hexane (2 mL, 3:1), loaded directly onto silica gel, and purified by silica gel chromatography; hexane → 10% EtOAc in hexane to afford the enoate **203** as a white solid (77.4 mg, 0.16 mmol, 84%).

Mixture of Isomers: (*) denotes minor isomer

$\mathbf{R_f}$ = 0.48 (35% Et_2O in hexane)

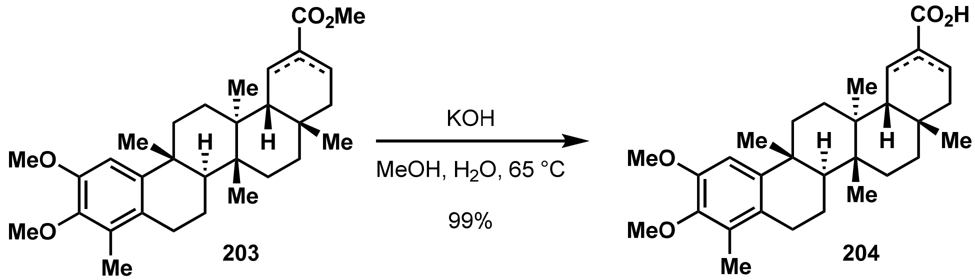
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.06* (d, 1H, J = 4.5 Hz), 6.89 (m, 1H), 6.67 (s, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H), 2.72 – 2.68 (m, 1H), 2.58 – 2.48 (m, 2H), 2.40 – 2.34* (m, 1H), 2.30 – 2.20 (m, 1H), 2.10 (s, 3H), 2.02 – 1.35 (m, 17H), 1.27* (s, 3H), 1.23 (s, 3H), 1.05* (s, 3H), 1.03 (s, 3H), 0.96 (s, 3H), 0.90* (s, 3H), 0.88* (s, 3H), 0.80 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ (167.97*) 167.86, (150.47*) 150.38, 147.19 (146.85*), (144.87*) 144.80, 140.97, 138.70, (129.54*), (129.47*), (129.41*) 129.39, (126.42*) 126.37, (105.82*) 105.75, 60.30, 55.79, 51.51, (48.10*), (43.91*) 43.40, 41.78, (40.75*) 40.04, 39.92, (39.35*) 38.74, (37.40*) 37.14, (35.24*) 34.97, 34.13 (33.96*), (33.47*) 33.02, (31.58*) 31.38, 30.27 (29.57*), 29.52 (29.50*), 28.41 (28.37*), (27.96*) 27.88, (22.66*), (21.45*) 20.91, (18.21*) 18.01, (17.64*), 15.30 (15.29*), (15.26*) 13.89, 11.75

IR (neat film, cm^{-1}): 3368, 2925, 1712, 1251, 1091

HRMS (EC-CI): calcd. for $C_{31}H_{44}O_4$ [M+H]+, 480.3240 found. 480.3241

M.P.: 83 – 87 °C



To a white mixture of the ester **203** (97.0 mg, 0.20 mmol, 1.00 eq.) in methanol (4.5 mL) and water (1.5 mL) was added KOH (227 mg, 4.04 mmol, 20.0 eq.). The reaction vessel was equipped with a plastic PTFE cap under a purging flow of nitrogen and placed in an oil bath heated to 65 °C. After stirring (500 rpm) for 2 hrs. the clear colorless solution was removed from the oil bath, allowed to cool to 23 °C, acidified to pH = 2 using 1 N HCl, diluted with EtOAc (5 mL), poured into a separatory funnel containing an aqueous phosphate buffer (10 mL, pH = 2, 0.2 M), and partitioned. The organic layer was washed with water (1 x 10 mL). The residual organics were extracted from the aqueous layer with EtOAc (2 x 10 mL), combined, dried over solid Na_2SO_4, decanted, and concentrated to afford the acid **204** as a white solid (92.2 mg, 0.20 mmol, 99%, 2:1). The product was carried onto the next step without further purification.

Mixture of Isomers: (*) denotes minor isomer

$\mathbf{R_f}$ = 0.31 (50% EtOAc in hexane)

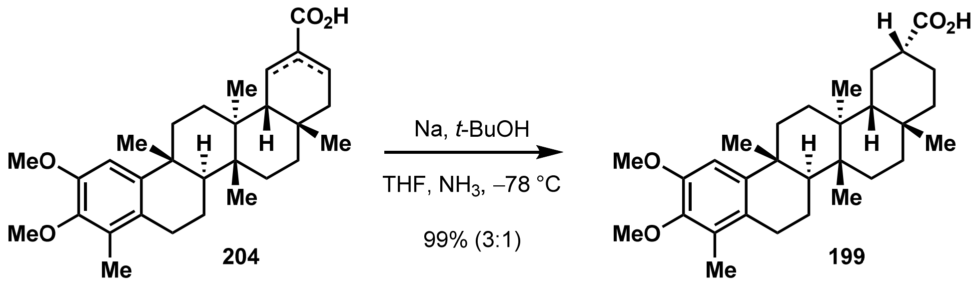
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.22* (s, 1H), 7.06 (s, 1H), 6.67 (s, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 2.71 (dd, 1H, J = 5.0, 16.1 Hz), 2.54 (m, 2H), 2.41 – 2.10 (m, 2H), 2.10 (s, 3H), 2.06 – 1.91 (m, 4H), 1.88 – 1.57 (m, 7H), 1.48 – 1.31 (m, 3H), 1.27* (s, 3H), 1.23 (s, 3H), 1.06* (s, 3H), 1.03 (s, 3H), 0.98 (s, 3H), 0.92* (s, 3H), 0.89* (s, 3H), 0.81 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ (172.80*) 172.71, (150.41*) 150.38, 147.18 (146.83*), (144.86*) 144.80, (143.85*) 141.53, (129.49*) 129.43, (129.08*) 128.91, (126.42*) 126.39, (105.84*) 105.77, 60.33, 55.81, (48.34*), (43.89*) 43.39, 41.70 (40.91*), 40.06, 39.92 (39.39*), (39.97*), (37.41*) 37.15, (35.18*) 34.94, 34.11 (33.94*), (33.41*), 33.06, (31.40*), 30.26, (29.71*), (29.61*) 29.54, 29.48, 28.41, (27.96*), 27.88, (21.07*) 20.49, (18.22*) 18.01, 17.74, 15.31 (15.28*), 13.94, 11.77

IR (neat film, cm^{-1}): 2946, 2636, 2527, 2250, 1683, 1486, 1278, 1092, 910, 732

HRMS (EC-CI): calcd. for $C_{30}H_{42}O_4$ $[M+H]^+$, 466.3083 found. 466.3075

M.P.: 159 – 162 °C



To a solution of liquid ammonia (5 mL) in a bath cooled to −78 °C was added sodium metal (46.0 mg, 2.00 mmol, 10.0 eq.) under a positive flow of nitrogen. The blue heterogeneous mixture was stirred (800 rpm) for 10 minutes upon which a solution of the acid **204** (92.2 mg, 0.20 mmol, 1.00 eq.) in THF (6 mL) was added over 1 minute via cannula under nitrogen. The blue heterogeneous mixture was stirred for 30 minutes and then *t*-BuOH (1.9 mL) was added to quench the excess sodium metal, sodium amide, and the enolate. After 30 minutes the mixture was slowly acidified to pH = 2 using concentrated HCl and then diluted with EtOAc (20 mL). The biphasic solution was removed from the cold bath, warmed to 23 °C, poured into a separatory funnel containing an aqueous phosphate buffer (10 mL, pH = 2, 0.2 M), and partitioned. The organics were extracted from the aqueous layer with EtOAc (2 x 20 mL), combined, washed with brine, dried over solid Na_2SO_4, decanted, and concentrated. The crude off-white solid was purified by silica gel chromatography; 2% EtOAc and 2% AcOH in hexane to afford the acid **199** as a white solid (91.7 mg, 0.20 mmol, 99%, d.r. = 3:1).

Mixture of Isomers: (*) denotes minor isomer

R_f = 0.66 (40% EtOAc and 2% AcOH in hexane)

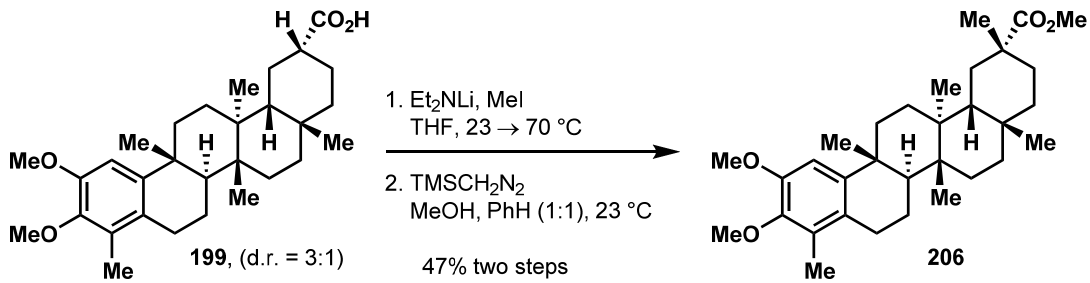
^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.69 (s, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 2.75 – 2.65 (m, 2H), 2.57 – 2.50 (m, 1H), 2.11 (s, 3H), 2.02 (d, 1H, *J* = 7.2 Hz), 1.90 – 1.46 (m, 16H), 1.38 – 1.32 (m, 2H), 1.26* (s, 3H), 1.23* (s, 3H), 1.19 (s, 6H), 1.11* (s, 3H), 1.10* (s, 3H), 1.07 (s, 3H), 0.98 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 183.59, 150.41, 146.52, 144.84, 129.54, 126.61 (126.52*), 106.10, 60.33, 55.85, 46.24, 44.94, 43.26, (40.10*), (39.68*), 39.40, 38.30, 37.42, 37.26, 36.43, 35.47, 34.27, 33.07, 32.17 (31.51*), 30.62, 30.27 (29.71*), 28.57 (28.07*), (27.83*), 26.50, 24.30, 21.10, (20.19*) 20.13, 16.96, (15.07*), 11.78

IR (neat film, cm^{-1}): 2932, 2871, 1699, 1486, 910, 734

HRMS (EC-CI): calcd. for $C_{30}H_{44}O_4$ [M], 468.3240 found. 468.3239

M.P.: 179 – 183 °C



A solution of diethylamine (0.25 mL, 2.42 mmol, 1.00 eq.) in THF (4.7 mL) was placed in a bath cooled to −78 °C and stirred (500 rpm) for 20 minutes. *n*-Butyllithium (1.26 mL, 2.42 mmol, 1.92 M in hexane, 1.00 eq.) was added, the pale yellow solution was stirred for 30 minutes at −78 °C, the cold bath was removed, and allowed to warm gradually to 23 °C over 20 minutes to provide a freshly prepared solution of lithium diethylamide (0.4 M).

Acid **199** was azeotroped with toluene (3 x 3 mL) and dried *in vacuo* prior to use. To a solution of the acid **199** (28.0 mg, 0.06 mmol, 1.00 eq.) in THF (1 mL) at 23 °C in a vessel equipped with a Claisen adapter and reflux condenser was added a freshly prepared solution of lithium diethylamide (3.00 mL, 1.19 mmol, 20.0 eq., 0.4 M in THF). The resultant golden yellow solution was stirred for 30 minutes and then placed in an oil bath heated to 70 °C. After 30 minutes iodomethane (0.17 mL, 2.68 mmol, 45.0 eq.) was added to the golden yellow solution. The now pale yellow mixture was stirred for 30 minutes, removed from the oil bath, cooled to 23 °C, and the mixture was acidified to a pH = 2 with an aqueous phosphate buffer (10 mL, pH = 2, 0.2 M). The biphasic mixture was diluted with EtOAc (10 mL), poured into a separatory funnel, partitioned, and the organic layer washed with an aqueous phosphate buffer (1 x 10 mL, pH = 2, 0.2 M). Residual organics were extracted from the aqueous layer with EtOAc (2 x 10 mL), combined, dried over solid Na_2SO_4, decanted, concentrated, and the crude golden yellow mixture was purified using silica gel chromatography; toluene (50 mL) and then 2% EtOAc and 2% AcOH in hexane (150 mL) to afford a mixture of the starting acid **199** and the methylated acid **128** (R_f = 0.75 (40% EtOAc and 2% AcOH in hexane)) as a white solid.

This mixture was azeotroped with toluene (3 x 3 mL), dried *in vacuo*, and subjected to the identical reaction conditions above. After aqueous work-up, the concentrated crude golden yellow mixture was purified by silica gel chromatography; toluene (50 mL) and then 2% EtOAc and 2% AcOH in hexane (150 mL) to afford the alkylated acid as a white solid which was dissolved in a solution of methanol-benzene (2 mL, 1 : 1). A solution of trimethylsilyl diazomethane (0.20 mL, 0.40 mmol, 6.67 eq., 2 M in Et_2O) was added. After 5 minutes the golden yellow solution was concentrated and purified by silica gel chromatography; 1% acetone in hexane to afford the ester **206** as a white amorphous foam (14.1 mg, 0.03 mmol, 47%).

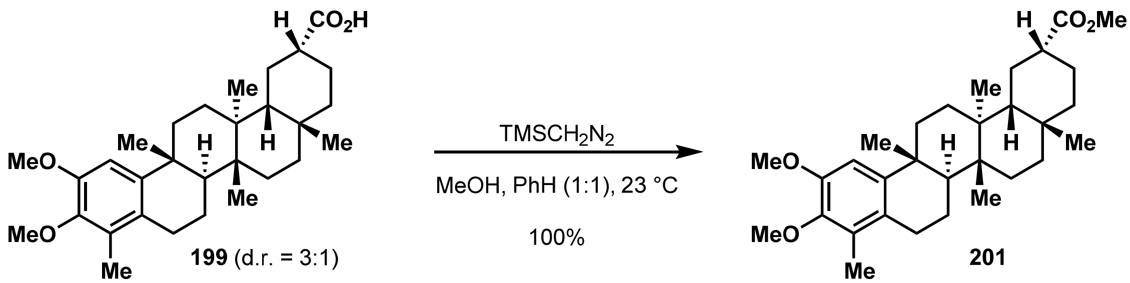
R_f = 0.54 (10% acetone in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.68 (s, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 3.60 (s, 3H), 2.72 (dd, 1H, *J* = 5.1, 17.1 Hz), 2.55 – 2.48 (m, 1H), 2.42 – 2.34 (m, 1H), 2.19 – 2.13 (m, 1H), 2.10 (s, 3H), 2.04 – 1.98 (m, 3H), 1.82 – 1.30 (m, 13H), 1.20 (s, 3H), 1.19 (s, 3H), 1.10 (s, 3H), 0.95 (s, 3H), 0.80 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 179.25, 150.35, 146.87, 144.81, 129.52, 126.61, 105.84, 60.31, 55.83, 51.52, 44.46, 43.98, 40.56, 39.47, 38.90, 37.24, 36.51, 36.24, 34.02, 32.01, 31.83, 30.60, 30.25, 30.17, 29.70, 28.90, 28.31, 27.33, 18.45, 17.35, 15.89, 11.75

IR (neat film, cm^{-1}): 2978, 2869, 1732, 1487, 1464, 1093

HRMS (EC-CI): calc'd. for $C_{32}H_{48}O_4$ [M], 496.3553 found. 496.3551



To a solution of the acid **199** (10.0 mg, 21.4 µmol, 1.00 eq.) in methanol and benzene (1 mL, 1:1) was added trimethylsilyl diazomethane (11.5 µL, 22.4 µmol, 1.05 eq., 2 M in Et_2O) at 23 °C. After 5 minutes the benzene and methanol were evaporated from the golden yellow solution by a continous flow of nitrogen and the resultant pale yellow residue was fully concentrated *in vacuo* to afford the ester **201** as a white amorphous foam (10.3 mg, 21.4 µmol, 100%).

Mixture of Isomers: (*) denotes minor isomer

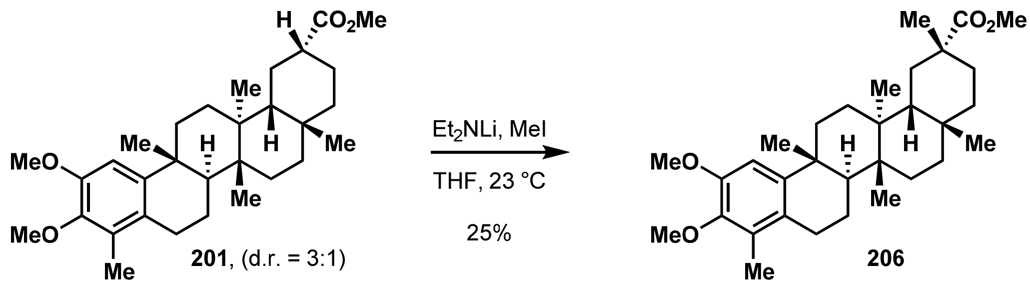
$\mathbf{R_f}$ = 0.55 (20% EtOAc in hexane)

^{1}H-NMR (400 MHz, C_6D_6): δ 6.73* (s, 1H), 6.72 (s, 1H), 3.72 (s, 3H), 3.71* (s, 3H), 3.54* (s, 3H), 3.49 (s, 3H), 3.40 (s, 3H), 3.39* (s, 3H), 2.62 – 2.52 (m, 2H), 2.48 – 2.34 (m, 1H), 2.14 (s, 3H), 2.13* (s, 3H), 2.10 – 2.05 (m, 1H), 1.98 – 1.57 (m, 10H), 1.50 – 1.24 (m, 7H), 1.21* (s, 3H), 1.20 (s, 3H), 1.00 (s, 3H), 0.99* (s, 3H), 0.92 (s, 3H), 0.89* (s, 3H), 0.80* (s, 3H), 0.77 (s, 3H)

^{13}C-NMR (100 MHz, C_6D_6): δ 176.62, 151.02, 146.12, 145.81, 129.29, 126.48, 106.75 (106.28*), 59.61, 55.35, 50.82 (50.68*), 46.30, 44.76, 43.35, (39.93*), (39.47*), 39.15, 38.11, (37.27*), 37.22, (37.04*), 36.48 (36.38*), 35.47, 34.33 (33.96*), 32.74, 32.05 (31.24*), 30.37, (30.12*) 30.04, 28.56 (28.03*), (27.66*) 26.39, (24.63*) 24.53, (23.68*) 21.29, 19.87 (19.75*), 18.47 (18.40*), 16.58 (14.85*), 11.69

IR (neat film, cm^{-1}): 2944, 1734, 1487, 1093

HRMS (EC-CI): calcd. for $C_{31}H_{46}O_4$ [M], 482.3396 found. 482.3391



A solution of diethylamine (0.25 mL, 2.42 mmol, 1.00 eq.) in THF (4.7 mL) was placed in a bath cooled to −78 °C and stirred (500 rpm) for 20 minutes. *n*-Butyllithium (1.26 mL, 2.42 mmol, 1.92 M in hexane, 1.00 eq.) was added, the pale yellow solution was stirred for 30 minutes at −78 °C, the cold bath was removed, and allowed to warm gradually to 23 °C over 20 minutes to provide a freshly prepared solution of lithium diethylamide (0.4 M).

Ester **201** was azeotroped with toluene (3 x 3 mL) and dried *in vacuo* prior to use. To a solution of the ester **201** (10.3 mg, 21.4 µmol, 1.00 eq.) in THF (1 mL) at 23 °C was added a freshly prepared solution of lithium diethylamide (27 µL, 107 µmol, 5.00 eq., 0.4 M in THF). The resultant golden yellow-brown solution was stirred for 5 minutes and then iodomethane (16 µL, 256 µmol, 12.0 eq.) was added to the golden brown solution. The now pale yellow mixture was stirred for 30 minutes and diluted with an aqueous phosphate buffer (5 mL, pH = 7, 0.2 M). The biphasic mixture was diluted with EtOAc (10 mL), poured into a separatory funnel, partitioned, and the organic layer washed with an aqueous phosphate buffer (2 x 10 mL, pH = 7, 0.2 M). Residual organics were extracted from the aqueous layer with EtOAc (2 x 10 mL), combined, dried over solid Na_2SO_4, decanted, concentrated, and the crude golden brown mixture was purified using silica gel chromatography; 1% acetone in hexane to afford the mixture of the ester **206** as a white amorphous film (2.7 mg, 5.4 µmol, 25%)

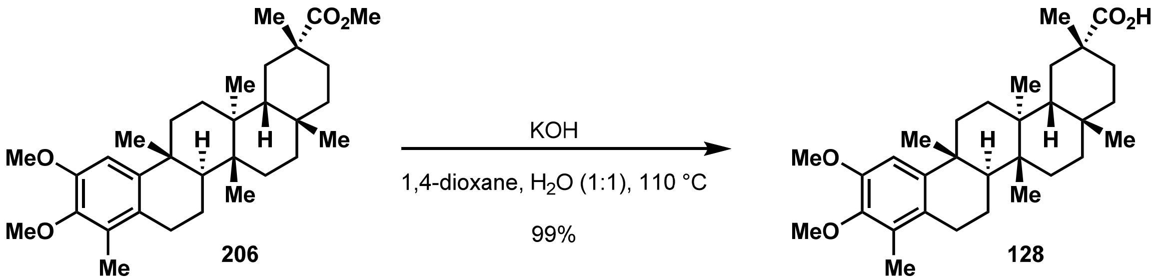
$\mathbf{R_f}$ = 0.54 (10% acetone in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.68 (s, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 3.60 (s, 3H), 2.72 (dd, 1H, *J* = 5.1, 17.1 Hz), 2.55 – 2.48 (m, 1H), 2.42 – 2.34 (m, 1H), 2.19 – 2.13 (m, 1H), 2.10 (s, 3H), 2.04 – 1.98 (m, 3H), 1.82 – 1.30 (m, 13H), 1.20 (s, 3H), 1.19 (s, 3H), 1.10 (s, 3H), 0.95 (s, 3H), 0.80 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 179.25, 150.35, 146.87, 144.81, 129.52, 126.61, 105.84, 60.31, 55.83, 51.52, 44.46, 43.98, 40.56, 39.47, 38.90, 37.24, 36.51, 36.24, 34.02, 32.01, 31.83, 30.60, 30.25, 30.17, 29.70, 28.90, 28.31, 27.33, 18.45, 17.35, 15.89, 11.75

IR (neat film, cm^{-1}): 2978, 2869, 1732, 1487, 1464, 1093

HRMS (EC-CI): calc'd. for $C_{32}H_{48}O_4$ [M], 496.3553 found. 496.3551



To a solution of the ester **206** (4.0 mg, 8.05 µmol, 1.00 eq.) in 1,4-dioxane and water (3 mL, 1:1) was added KOH (9.0 mg, 161 µmol, 20.0 eq.) under a positive flow of nitrogen and the reaction vessel was equipped with a plastic PTFE cap. The clear colorless solution was placed in an oil bath heated to 110 °C for 4 hrs., removed from the oil bath, and allowed to cool to 23 °C. The clear pale yellow solution was acidified to pH = 2 with an aqueous phosphate buffer (5 mL, pH = 2, 0.2 M) affording a white mixture which was diluted with EtOAc (10 mL), poured into a separatory funnel, and partitioned. The organic layer was washed with an aqueous phosphate buffer (1 x 5 mL, pH = 2, 0.2 M). The residual organics were extracted from the aqueous layer with EtOAc (2 x 10 mL), combined, dried over solid Na_2SO_4, decanted, and concentrated to afford the acid **128** as a crude white amorphous foam which was carried onto the next reaction without further purification (3.9 mg, 7.97 µmol, 99%).

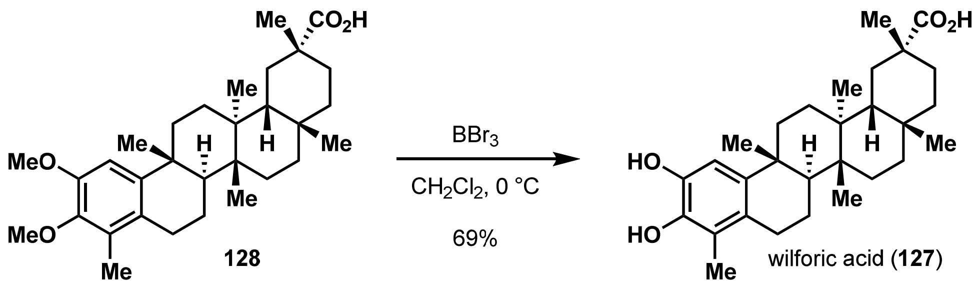
R_f = 0.75 (40% EtOAc and 2% AcOH in hexane)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.68 (s, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 2.72 (dd, 1H, *J* = 6.1, 17.1 Hz), 2.56 – 2.48 (m, 1H), 2.37 – 2.33 (m, 1H), 2.10 (s, 3H), 1.98 (br d, 2H, *J* = 12.9 Hz), 1.83 – 1.61 (m, 8H), 1.46 – 1.36 (m, 5H), 1.28 – 1.22 (m, 2H), 1.22 (s, 6H), 1.16 (s, 3H), 1.11 (s, 3H), 0.96 (s, 3H),

^{13}C-NMR (125 MHz, $CDCl_3$): δ 184.42, 150.36, 146.87, 144.81, 129.47, 126.55, 105.85, 60.29, 55.81, 44.21, 39.41, 39.00, 37.24, 36.57, 36.19, 34.05, 31.82, 31.50, 30.45, 30.29, 30.15, 29.69, 29.65, 29.58, 29.16, 28.28, 27.27, 18.47, 17.81, 16.29, 11.76

IR (neat film, cm^{-1}): 2929, 2870, 1697, 1487, 1463, 1270, 1093, 734

HRMS (EC-CI): calc'd. for $C_{31}H_{46}O_4$ [M], 482.3396 found. 482.3406

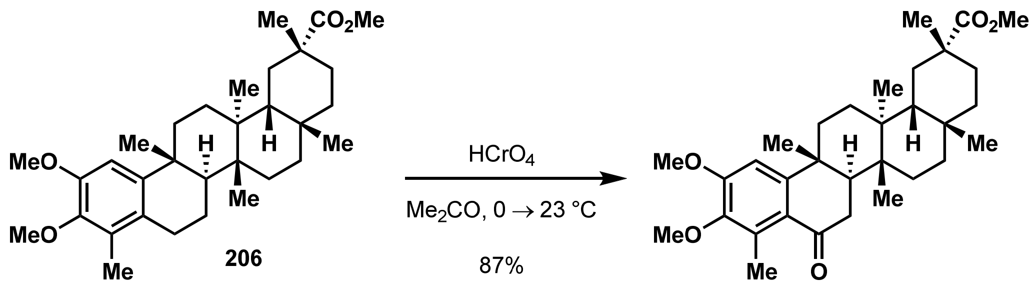


A solution of the crude acid **128** (3.9 mg, 7.97 μmol, 1.00 eq.) in methylene chloride (1 mL) was placed in an ice water bath cooled to 0 °C. After stirring for 20 minutes neat BBr_3 (3.0 μL, 24.0 μmol, 3.00 eq.) was added. The golden yellow-orange solution was stirred for 5 minutes, acidified with 1 N HCl (3 mL), and the cold bath was removed. The orange mixture was diluted with EtOAc (10 mL) and an aqueous phosphate buffer (5 mL, pH = 2, 0.2 M), stirred vigorously for 2 minutes, poured into a separatory funnel containing EtOAc (10 mL), and the organics were washed with an aqueous phosphate buffer (2 x 10 mL, pH = 2, 0.2 M). Residual organics were extracted from the aqueous layer with EtOAc (3 x 10 mL), washed with brine (1 x 10 mL), dried over solid Na_2SO_4, decanted, and concentrated. (**NOTE**: Throughout the work-up the catechol **127** remained under a positive flow of nitrogen to prevent oxidative degradation). The crude golden yellow mixture was dissolved in methylene chloride (0.5 mL), placed in an ice water bath cooled to 0 °C, and hexane (10 mL) was added to triturate the white solid product. After stirring for 2 minutes the mixture was concentrated by rotary evaporation to ~3 mL (100 mBar, no water bath) and hexane (10 mL) was added. The mixture was concentrated by rotary evaporation to ~3 mL (100 mBar, no water bath). This was repeated once more upon which hexane (5 mL) was added to the white mixture, and the suspension was placed in an ice water bath cooled to 0 °C for 20 minutes. The cold yellow liquid was decanted by syringe. The white solid was washed with hexane (2 x 3 mL) which was decanted by syringe to afford wilforic acid (**127**) as a white solid (2.5 mg, 5.50 μmol, 69%). The spectral data matches that of the reported compound (Li, K.; Duan, H.; Kawazoe, K.; and Takashi, Y. *Phytochemistry* **1997**, 45, 791.).[131]

^{1}H-NMR Shifts of Wilforic Acid in C_5D_5N:

Isolated	Synthesized	Deviation
7.07 (s, 1H)	7.07 (s, 1H)	0.00
2.78 (dd, 1H)	2.78 (dd, 1H)	0.00
2.66 (dd, 1H)	2.66 (dd, 1H)	0.00
2.59 (m, 1H)	2.57 (m, 1H)	− 0.02
2.52 (m, 1H)	2.52 (m, 1H)	0.00
2.39 (s, 3H)	2.38 (s, 3H)	− 0.01
2.31 (ddd, 1H)	2.30 (ddd, 1H)	− 0.01
1.98 (br d, 1H)	1.99 (br d, 1H)	+ 0.01
1.44 (s, 3H)	1.42 (s, 3H)	− 0.02
1.29 (s, 3H)	1.26 (s, 3H)	− 0.03
1.19 (s, 3H)	1.17 (s, 3H)	− 0.02
1.16 (s, 3H)	1.13 (s, 3H)	− 0.03
1.01 (s, 3H)	0.94 (s, 3H)	− 0.07

^{1}H-NMR (400 MHz, CD_3CN): δ 6.59 (s, 1H), 3.37 (bs, 2H), 2.67 (dd, 1H, *J* = 5.9, 6.8 Hz), 2.52 – 2.42 (m, 3H), 2.36 – 2.28 (m, 4H), 2.00 (s, 3H), 1.76 – 1.24 (m, 13H), 1.17 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H), 0.94 (s, 3H), 0.89 (s, 3H)



A clear colorless solution of the ester **206** (10.0 mg, 19.6 μmol, 1.00 eq.) in acetone (1.5 mL) was placed in an ice water bath cooled to 0 °C for 20 minutes. Jones reagent (27.0 μL, 41.1 μmol, 2.10 eq., 1.53 M) was added and after 2 minutes the red-brown mixture was removed from the cold bath. After 5 minutes the brown mixture was diluted with isopropanol (1 mL) to quench excess Jones reagent. The green mixture was diluted with Et_2O (10 mL) and an aqueous phosphate buffer (5 mL, pH = 7, 0.2 M), poured into a separatory funnel, partitioned, and the organic layer was washed with water (2 x 10 mL). Residual organics were extracted from the aqueous layer with Et_2O (2 x 10 mL), combined, dried over solid Na_2SO_4, decanted, and concentrated. The crude green mixture was purified by silica gel chromatography; hexane → 10% EtOAc in hexane to afford the benzyl ketone as a white amorphous foam (8.7 mg, 17.0 μmol, 87%).

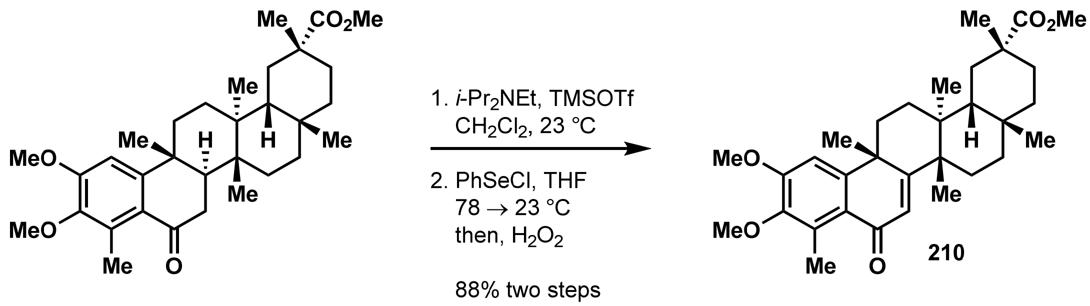
$\mathbf{R_f}$ = 0.51 (30% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.69 (s, 1H), 3.93 (s, 3H), 3.74 (s, 3H), 3.61 (s, 3H), 2.53 (d, 2H, *J* = 7.4 Hz), 2.51 (s, 3H), 2.42 – 2.38 (m, 1H), 2.30 (d, 1H, *J* = 7.4 Hz), 2.24 (dd, 1H, *J* = 5.9, 12.9 Hz), 2.16 (br d, 1H, *J* = 14.4 Hz), 2.05 – 1.93 (m, 4H), 1.72 – 1.28 (m, 8H), 1.19 (s, 3H), 1.16 (s, 3H), 1.09 (s, 3H), 1.02 (s, 3H), 0.81 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 200.42, 179.35, 155.94, 155.52, 134.77, 128.22, 124.48, 103.79, 60.24, 55.59, 51.62, 44.63, 42.38, 40.59, 39.41, 38.74, 37.66, 37.43, 36.15, 36.03, 33.24, 32.40, 31.71, 30.64, 30.26, 29.82, 29.76, 28.35, 25.53, 16.92, 15.35, 13.94

IR (neat film, cm^{-1}): 2924, 2852, 1734, 1669, 1585, 1484, 1287, 1099, 1020

HRMS (EC-CI): calc'd. for $C_{32}H_{46}O_5$ [M], 510.3345 found. 510.3346



To a solution of the ketone (8.7 mg, 17.0 µmol, 1.00 eq.) in methylene chloride (1 mL) was added freshly distilled Hunig's base (12.0 µL, 68.0 µmol, 4.00 eq.) and trimethylsilyl trifluoromethane sulfonate (16.0 µL, 85.0 µmol,, 5.00 eq.) sequentially. After 1 hr. the clear golden yellow solution was concentrated *in vacuo* to afford the crude silyl enol ether as a golden yellow solid mixture.

A solution of the crude silyl enol ether in THF (1 mL) was placed in a bath cooled to −78 °C for 30 minutes upon which a solution of PhSeCl (16.3 mg, 85.0 µmol, 5.00 eq.) in THF (1 mL) was added over 1 minute under nitrogen via cannula. After 30 minutes the yellow solution was removed from the cooling bath and allowed to gradually warm to 23 °C. After 1 hr the yellow solution was placed in an ice water bath for 20 minutes and then an aqueous solution of H_2O_2 (5.0 µL, 170.0 µmol, 10.0 eq., 30% w/v) was added. The pale yellow solution was stirred for 10 minutes, the cooling bath was removed, and after 10 minutes a saturated aqueous mixture of $Na_2S_2O_3$ (3 mL) was added followed by an aqueous phosphate buffer (3 mL, pH = 7, 0.2 M) and EtOAc (10 mL). The biphasic mixture was poured into a separatory funnel, partitioned, and the organic layer was washed with water (2 x 5 mL). The residual organics were extracted from the aqueous layer with EtOAc (2 x 10 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude yellow solid was purified by silica gel chromatography; hexane → 10% EtOAc in hexane to afford the enone **210** as a pale yellow amorphous foam (7.6 mg, 14.9 µmol, 88%).

R_f = 0.65 (35% EtOAc in hexane)

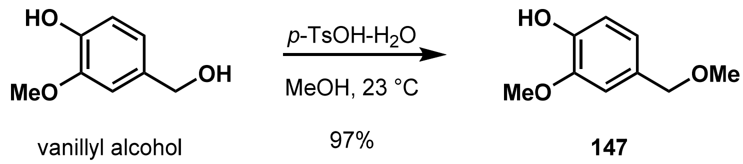
^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.82 (s, 1H), 6.23 (s, 1H), 3.91 (s, 3H), 3.75 (s, 3H), 3.52 (s, 3H), 2.63 (s, 3H), 2.42 (bd d, 1H, *J* = 15.7 Hz), 2.26 – 2.23 (m, 1H), 2.17 (br d, 1H, *J* = 14.4 Hz), 2.05 (dd, 1H, *J* = 4.1, 14.1 Hz), 2.01 (dd, 1H, *J* = 4.1, 8.0 Hz), 1.97 (dd, 1H, *J* = 5.0, 13.6 Hz), 1.86 (ddd, 1H, *J* = 6.2, 14.1 Hz), 1.82 (m, 1H), 1.72 – 1.56 (m, 4H), 1.54 (s, 3H), 1.49 (dd, 1H, *J* = 5.0, 16.0 Hz), 1.40 – 1.34 (m, 2H), 1.28 (s, 3H), 1.16 (s, 3H), 1.08 (s, 3H), 0.57 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 187.25, 178.97, 170.83, 155.63, 154.01, 145.93, 133.69, 126.29, 123.29, 105.41, 60.33, 55.61, 51.55, 44.68, 44.28, 40.49, 40.43, 38.94, 37.61, 36.68, 34.84, 34.23, 32.85, 31.60, 30.93, 30.53, 29.88, 29.76, 29.69, 28.53, 20.87, 18.35, 13.98

IR (neat film, cm^{-1}): 2924, 1734, 1653, 1457, 1294, 1093

HRMS (EC-CI): calc'd. for $C_{32}H_{45}O_5$ $[M+H]^+$, 509.3267 found. 510.3252

3. Preparation of the Benzyl Stannane 152



vanillyl alcohol **147**

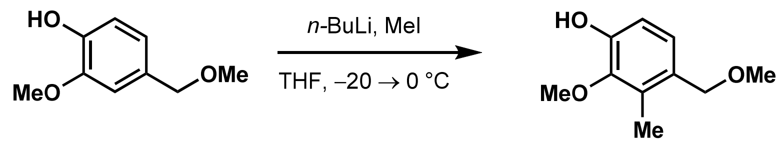
To a solution of vanillyl alcohol (56.0 g, 363 mmol, 1.00 eq.) in methanol (560 mL) at 23 °C was added *p*-toluenesulfonic acid monohydrate (3.5 g, 18.2 mmol, 0.05 eq.). After 6 hours the golden-yellow solution was diluted with an aqueous phosphate buffer (200 mL, pH = 4, 0.2 M) and brine (200 mL). Excess methanol was removed by rotary evaporation and the mixture was further diluted with EtOAc (400 mL). The biphasic mixture was poured into a separatory funnel, partitioned, and the organic layer was washed with water (1 x 100 mL). Residual organics were extracted from the aqueous layer using EtOAc (3 x 150 mL), combined, washed with brine (1 x 100 mL), dried over solid Na_2SO_4, filtered, and concentrated. The resulting golden-brown oil was dissolved in EtOAc (100 mL) and purified by elution through a short plug of silica gel using ethyl acetate (1.5 L) to afford the dimethyl ether **147** as a light yellow oil (59.3 g, 352 mmol, 97%). The spectral data matches that of the reported compound (Cook, S.P. and Danishefsky, S.J. *Organic Letters* **2006**, 8, 5693).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.86 (m, 3H), 5.76 (s, 1H), 4.38 (s, 2H), 3.88 (s, 3H), 3.37 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$) : δ 146.2, 144.8, 129.6, 120.3, 113.6, 110.0, 74.3, 57.3, 55.4;

IR (film, cm^{-1}): 3390, 2935, 1606, 1515, 1464, 1431, 1368, 1276, 1241, 1188, 1154, 1089.

HRMS (FAB): calcd. for $C_9H_{12}O_3$ $[M]^+$ 168.0786, found 168.0789



147

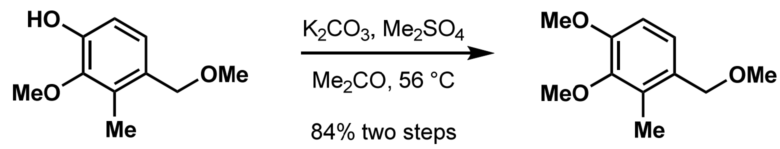
The phenol **147** (62.3 g, 0.37 mol, 1.00 eq.) was azeotroped with toluene (3 x 50 mL) and dissolved in THF (570 mL). The clear solution was placed in a bath cooled to −20 °C. After 30 minutes *n*-butyllithium (529 mL, 2.17 M in hexanes, 1.15 mol, 3.10 eq.) was added dropwise over 2.5 hours. The dark golden-yellow solution was placed in an ice bath cooled to 0 °C for 2.5 hours. The dark red-orange mixture was placed in a bath cooled to −20 °C for 30 minutes upon which iodomethane (92.0 mL, 1.48 mol, 4.00 eq.) was added dropwise over 30 minutes while stirring vigorously (800 rpm). The pale yellow solution was placed in a bath cooled to 0 °C for 30 minutes and then acidified to a pH = 7 with 1 N HCl (500 mL). The biphasic mixture was diluted with EtOAc (200 mL), poured into a separatory funnel and partitioned. Residual organics were extracted from the aqueous layer using ethyl acetate (4 x 200 mL). The combined organics were washed with brine (1 x 200 mL), dried over solid Na_2SO_4, decanted, and concentrated to afford the product as a crude brown oil (67.4 g) which was used directly in the next reaction without purification. The spectral data matches that of the reported compound (Cook, S.P. and Danishefsky, S.J. *Organic Letters* **2006**, 8, 5693).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.96 (d, 1H, J = 8.2 Hz), 6.77 (d, 1H, J = 8.2 Hz), 5.72 (bs, 1H), 4.36 (s, 2H), 3.77 (s, 3H), 3.37 (s, 3H), 2.29 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$) : δ 148.2, 145.2, 130.0, 128.5, 125.6, 111.8, 72.8, 60.4, 57.5, 11.2

IR (film, cm^{-1}): 3367, 2928, 1603, 1491, 1460, 1290, 1177, 1070.

HRMS (FAB): calcd. For $C_{10}H_{14}O_3$ [M] 182.0943, found 182.0947.



148

To a solution of the crude brown oil (67.4 g, 370 mmol, 1.00 eq) in acetone (1.2 L) was added potassium carbonate (102 g, 740 mmol, 2.00 eq.) and dimethyl sulfate (56.0 mL, 444 mmol, 1.49 eq) sequentially. The mixture was placed in an oil bath heated to 56 °C and stirred vigorously (800 rpm) for 48 hours. The heterogeneous mixture was removed from the oil bath, filtered over a pad of celite using acetone, and concentrated. The resulting brown oil was purified by silica gel chromatography; toluene → 4% EtOAc in toluene to afford the trimethyl ether **148** as a clear pale yellow oil (64.0 g, 294 mmol, 84% two steps).

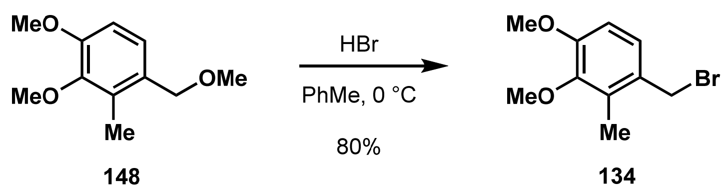
R_f = 0.43 (30% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.00 (d, 1H, J = 8.2 Hz), 6.72 (d, 1H, J = 8.2 Hz), 4.37 (s, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 3.37 (s, 3H), 2.27 (s, 3H)

^{13}C-NMR (100MHz, $CDCl_3$): δ 152.7, 147.6, 131.5, 129.6, 125.1, 109.1, 73.4, 60.4, 58.2, 55.9, 11.5

IR (neat film, cm^{-1}): 2932, 2821, 1604, 1492, 1456, 1380, 1271, 1223, 1083, 1007, 805

HRMS (EC-CI): calcd. for $C_{11}H_{16}O_3$ [M] 196.1099, found 196.1097.



A solution of the trimethyl ether **148** (9.8 g, 50.0 mmol, 1.00 eq.) in toluene (125 mL) was placed in an ice water bath cooled to 0 °C, stirred vigorously (1000 rpm) for 20 minutes, and then concentrated HBr (48% w/v, 29.4 mL, 260 mmol, 5.20 eq.) was added. The brown biphasic mixture was stirred for 2 hours upon which the excess acid was slowly quenched with a saturated aqueous mixture of $NaHCO_3$ (100 mL). The biphasic mixture was poured into a separatory funnel, partitioned, and residual organics were extracted from the aqueous layer using toluene (3 x 50 mL). The combined organics were washed with brine (1 x 50 mL), dried over solid Na_2SO_4, decanted, and concentrated. Recrystallization of the brown solid from hexane (30 mL) provided the bromide **134** as white needles (9.8 g, 40.0 mmol, 80%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.06 (d, 1H, J = 8.2 Hz), 6.72 (d, 1H, J = 8.2 Hz), 4.52 (s, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 2.33 (s, 3H)

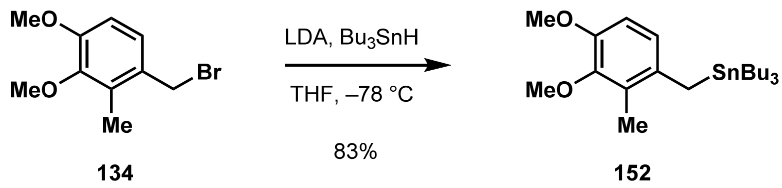
^{13}C-NMR (100 MHz, $CDCl_3$): δ 153.49, 147.82, 132.00, 129.12, 126.07, 109.67, 60.54, 55.89, 33.66, 11.67

IR (neat film, cm^{-1}): 1602, 1456, 1441, 1313, 1276, 1083, 1000, 807, 684, 661

HRMS (EC-CI): calcd. for $C_{10}H_{14}O_2Br$(79) $[M+H]^+$ 245.0177, found 245.0179

HRMS (EC-CI): calcd. for $C_{10}H_{14}O_2Br$(81) $[M+H]^+$ 247.0157, found 245.0154

M.P.: 66 – 68 °C.



A solution of diisoproplyamine (10.4 mL, 74.1 mmol, 1.10 eq.) in THF (340 mL) was placed in a bath cooled to −78 °C for 30 minutes. *n*-Butyllitium (37.8 mL, 74.1 mmol, 1.10 eq., 1.96 M in hexane) was added dropwise over 15 minutes. The clear colorless solution was stirred for 5 minutes, placed in an ice water cooling bath, and stirred for 30 minutes. Tri-*n*-butyltin hydride (19.9 mL, 74.1 mmol, 1.10 eq.) was added dropwise over 10 minutes to the clear pale yellow solution of LDA and stirred for 20 minutes. The olive green solution was placed in a bath cooled to −78 °C for 30 minutes upon which a solution of the bromide **134** (16.5 g, 67.4 mmol, 1.00 eq.) in THF (310 mL) was added under nitrogen via cannula to the olive green solution over 3 hrs. Residual bromide **152** in the vessel was dissolved in THF (10 mL) and transferred via cannula to the now pale yellow colored reaction solution. This process was repeated twice more. After 1 hr. the pale yellow solution was placed in an ice bath cooled to 0 °C, stirred for 10 minutes, and excess tri-*n*-butylstannyl lithium was quenched with an aqueous phosphate buffer (100 mL, pH = 7, 0.2 M). The biphasic mixture was poured into a separatory funnel, partitioned, and residual organics were extracted from the aqueous layer with ethyl ether (3 x 50 mL). The combined organics were washed with brine (1 x 100 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude pale yellow oil was purified using silica gel chromatography; hexane (1.5 L) and then toluene to provide the stannane **152** as a clear colorless oil (25.4 g, 55.9 mmol, 83%).

$\mathbf{R_f}$ = 0.69 (30% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.68 (d, 1H, *J* = 8.2 Hz), 6.63 (d, 1H, *J* = 8.2 Hz), 3.81 (s, 3H), 3.75 (s, 3H), 2.22 (s, 2H), 2.12 (s, 3H), 1.43 – 1.35 (m, 6H), 1.27 – 1.21 (q, 6H, *J* = 7.3 Hz), 0.85 (t, 9H, *J* = 7.3 Hz), 0.77 (dd, 6H, *J* = 8.2, 6.5 Hz)

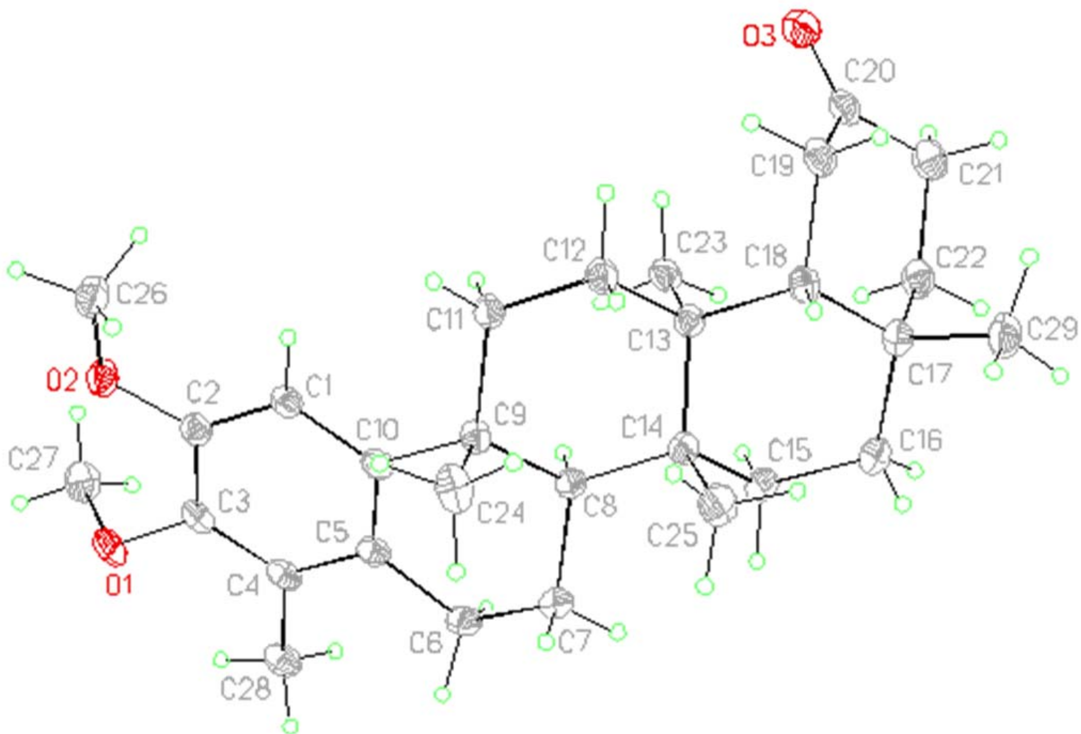
^{13}C-NMR (100 MHz, $CDCl_3$): δ 149.11, 147.66, 135.57, 127.93, 122.57, 110.15, 60.40, 56.11, 29.25, 27.60, 15.80, 13.91, 12.75, 9.90

IR (neat film, cm^{-1}): 2955, 2925, 1486, 1465, 1456, 1272, 1086, 1223, 1083, 1007, 805

HRMS (EC-CI): calcd. for $C_{22}H_{40}O_2Sn$ [M] 456.2050, found 456.2057.

4. Crystollagraphic Information for Pentacyclic Ketone 175

Crystal Structure of ketone 175. View of **175** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.



The crystals grew as large colorless prisms by slow evaporation from methanol. The data crystal was cut from a larger crystal and had approximate dimensions; 0.25 x 0.16 x 0.12 mm. The data were collected on a Rigaku AFC12 diffractometer with a Saturn 724+ CCD using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 1832 frames of data were collected using ω-scans with a scan range of 0.5° and a counting time of 36 seconds per frame. The data were collected at 100 K using a Rigaku XStream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using the Rigaku Americas Corporation's Crystal Clear version 1.40.[1] The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] Structure analysis was aided by use of the programs PLATON98[4] and WinGX.[5] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms).

The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0503*P)^2 + (0.8402*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_W(F^2)$ refined to 0.107, with R(F) equal to 0.0409 and a goodness of fit, S, = 1.04. Definitions used for calculating R(F), $R_W(F^2)$ and the goodness of fit, S, are given below.[6] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[7] All figures were generated using SHELXTL/PC.[8] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table 2.10. Crystal data and structure refinement for **175**.

Empirical formula	C29 H42 O3	
Formula weight	438.62	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 15.2493(6) Å	α= 90°.
	b = 7.6076(3) Å	β= 98.2440(10)°.
	c = 20.7445(8) Å	γ = 90°.
Volume	2381.71(16) $Å^3$	
Z	4	
Density (calculated)	1.223 Mg/m^3	
Absorption coefficient	0.077 mm^{-1}	
F(000)	960	
Crystal size	0.250 x 0.160 x 0.120 mm^3	
Theta range for data collection	2.999 to 27.485°.	
Index ranges	-19<=h<=19, -9<=k<=9, -26<=l<=26	
Reflections collected	41833	
Independent reflections	5445 [R(int) = 0.0534]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.810	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5445 / 0 / 296	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I)]	R1 = 0.0409, wR2 = 0.1029	
R indices (all data)	R1 = 0.0482, wR2 = 0.1070	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.298 and -0.172 e.$Å^{-3}$	

Table 2.11. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C1	2648(1)	5262(2)	3690(1)	17(1)
C2	3181(1)	6309(2)	3364(1)	17(1)
C3	4104(1)	6050(2)	3467(1)	18(1)
C4	4477(1)	4749(2)	3890(1)	18(1)
C5	3924(1)	3632(1)	4199(1)	16(1)
C6	4350(1)	2158(2)	4623(1)	19(1)
C7	3696(1)	831(2)	4832(1)	20(1)
C8	2878(1)	1785(1)	5009(1)	15(1)
C9	2368(1)	2642(2)	4380(1)	16(1)
C10	3007(1)	3902(1)	4103(1)	16(1)
C11	1547(1)	3625(2)	4552(1)	20(1)
C12	996(1)	2535(2)	4968(1)	21(1)
C13	1530(1)	1885(1)	5612(1)	16(1)
C14	2312(1)	707(1)	5438(1)	16(1)
C15	2871(1)	180(2)	6088(1)	21(1)
C16	2342(1)	-936(2)	6514(1)	24(1)
C17	1415(1)	-246(2)	6615(1)	20(1)
C18	935(1)	743(2)	6000(1)	17(1)
C19	110(1)	1726(2)	6173(1)	20(1)
C20	243(1)	2810(2)	6785(1)	20(1)
C21	705(1)	1873(2)	7374(1)	24(1)
C22	1539(1)	902(2)	7236(1)	23(1)
C23	1855(1)	3546(2)	6007(1)	19(1)
C24	2051(1)	1364(2)	3811(1)	24(1)

Table 2.11, continued.

C25	1990(1)	-1021(2)	5086(1)	24(1)
C26	1933(1)	7580(2)	2713(1)	24(1)
C27	4740(1)	8805(2)	3293(1)	26(1)
C28	5472(1)	4503(2)	4004(1)	22(1)
C29	853(1)	-1860(2)	6745(1)	27(1)
O1	4633(1)	7001(1)	3105(1)	23(1)
O2	2868(1)	7565(1)	2916(1)	21(1)
O3	-50(1)	4295(1)	6806(1)	29(1)

Table 2.12. Bond lengths [Å] and angles [°] for **175**.

C1-C2	1.3824(15)	C13-C18	1.5604(15)
C1-C10	1.4037(15)	C13-C14	1.5745(15)
C1-H1	0.95	C14-C15	1.5407(15)
C2-O2	1.3704(13)	C14-C25	1.5497(15)
C2-C3	1.4061(15)	C15-C16	1.5338(16)
C3-O1	1.3828(13)	C15-H15A	0.99
C3-C4	1.3896(16)	C15-H15B	0.99
C4-C5	1.4142(15)	C16-C17	1.5509(16)
C4-C28	1.5134(15)	C16-H16A	0.99
C5-C10	1.3985(15)	C16-H16B	0.99
C5-C6	1.5138(15)	C17-C29	1.5434(16)
C6-C7	1.5249(16)	C17-C22	1.5452(16)
C6-H6A	0.99	C17-C18	1.5681(15)
C6-H6B	0.99	C18-C19	1.5491(16)
C7-C8	1.5326(15)	C18-H18	1.00
C7-H7A	0.99	C19-C20	1.5038(16)
C7-H7B	0.99	C19-H19A	0.99
C8-C14	1.5595(15)	C19-H19B	0.99
C8-C9	1.5632(15)	C20-O3	1.2179(15)
C8-H8	1.00	C20-C21	1.5001(17)
C9-C10	1.5362(15)	C21-C22	1.5340(17)
C9-C11	1.5436(15)	C21-H21A	0.99
C9-C24	1.5507(15)	C21-H21B	0.99
C11-C12	1.5319(15)	C22-H22A	0.99
C11-H11A	0.99	C22-H22B	0.99
C11-H11B	0.99	C23-H23A	0.98
C12-C13	1.5430(15)	C23-H23B	0.98
C12-H12A	0.99	C23-H23C	0.98
C12-H12B	0.99	C24-H24A	0.98
C13-C23	1.5485(15)	C24-H24B	0.98

Table 2.12, continued.

C24-H24C	0.98	C27-H27A	0.98
C25-H25A	0.98	C27-H27B	0.98
C25-H25B	0.98	C27-H27C	0.98
C25-H25C	0.98	C28-H28A	0.98
C26-O2	1.4277(14)	C28-H28B	0.98
C26-H26A	0.98	C28-H28C	0.98
C26-H26B	0.98	C29-H29A	0.98
C26-H26C	0.98	C29-H29B	0.98
C27-O1	1.4301(15)	C29-H29C	0.98

C2-C1-C10	121.18(10)	C6-C7-H7A	109.6
C2-C1-H1	119.4	C8-C7-H7A	109.6
C10-C1-H1	119.4	C6-C7-H7B	109.6
O2-C2-C1	124.15(10)	C8-C7-H7B	109.6
O2-C2-C3	116.37(10)	H7A-C7-H7B	108.2
C1-C2-C3	119.42(10)	C7-C8-C14	115.08(9)
O1-C3-C4	119.83(10)	C7-C8-C9	108.81(9)
O1-C3-C2	119.54(10)	C14-C8-C9	116.49(9)
C4-C3-C2	120.42(10)	C7-C8-H8	105.1
C3-C4-C5	119.77(10)	C14-C8-H8	105.1
C3-C4-C28	119.87(10)	C9-C8-H8	105.1
C5-C4-C28	120.34(10)	C10-C9-C11	111.29(9)
C10-C5-C4	119.82(10)	C10-C9-C24	104.63(9)
C10-C5-C6	121.91(10)	C11-C9-C24	107.79(9)
C4-C5-C6	118.27(10)	C10-C9-C8	107.77(8)
C5-C6-C7	114.32(9)	C11-C9-C8	109.38(9)
C5-C6-H6A	108.7	C24-C9-C8	115.94(9)
C7-C6-H6A	108.7	C5-C10-C1	119.29(10)
C5-C6-H6B	108.7	C5-C10-C9	122.04(10)
C7-C6-H6B	108.7	C1-C10-C9	118.37(9)
H6A-C6-H6B	107.6	C12-C11-C9	113.38(9)
C6-C7-C8	110.05(9)	C12-C11-H11A	108.9

Table 2.12, continued

C9-C11-H11A	108.9	C17-C16-H16B	108.0
C12-C11-H11B	108.9	H16A-C16-H16B	107.3
C9-C11-H11B	108.9	C29-C17-C22	107.94(9)
H11A-C11-H11B	107.7	C29-C17-C16	107.16(10)
C11-C12-C13	113.38(9)	C22-C17-C16	107.39(10)
C11-C12-H12A	108.9	C29-C17-C18	108.56(9)
C13-C12-H12A	108.9	C22-C17-C18	113.18(9)
C11-C12-H12B	108.9	C16-C17-C18	112.36(9)
C13-C12-H12B	108.9	C19-C18-C13	113.68(9)
H12A-C12-H12B	107.7	C19-C18-C17	110.10(9)
C12-C13-C23	106.62(9)	C13-C18-C17	116.69(9)
C12-C13-C18	110.58(9)	C19-C18-H18	105.1
C23-C13-C18	110.29(9)	C13-C18-H18	105.1
C12-C13-C14	107.92(9)	C17-C18-H18	105.1
C23-C13-C14	112.96(9)	C20-C19-C18	116.40(9)
C18-C13-C14	108.45(9)	C20-C19-H19A	108.2
C15-C14-C25	106.88(9)	C18-C19-H19A	108.2
C15-C14-C8	110.77(9)	C20-C19-H19B	108.2
C25-C14-C8	109.90(9)	C18-C19-H19B	108.2
C15-C14-C13	106.85(9)	H19A-C19-H19B	107.3
C25-C14-C13	113.09(9)	O3-C20-C21	122.92(11)
C8-C14-C13	109.30(9)	O3-C20-C19	122.21(11)
C16-C15-C14	112.17(10)	C21-C20-C19	114.73(10)
C16-C15-H15A	109.2	C20-C21-C22	112.44(10)
C14-C15-H15A	109.2	C20-C21-H21A	109.1
C16-C15-H15B	109.2	C22-C21-H21A	109.1
C14-C15-H15B	109.2	C20-C21-H21B	109.1
H15A-C15-H15B	107.9	C22-C21-H21B	109.1
C15-C16-C17	117.05(9)	H21A-C21-H21B	107.8
C15-C16-H16A	108.0	C21-C22-C17	114.98(10)
C17-C16-H16A	108.0	C21-C22-H22A	108.5
C15-C16-H16B	108.0	C17-C22-H22A	108.5

Table 2.12, continued.

C21-C22-H22B	108.5	H26A-C26-H26B	109.5
C17-C22-H22B	108.5	O2-C26-H26C	109.5
H22A-C22-H22B	107.5	H26A-C26-H26C	109.5
C13-C23-H23A	109.5	H26B-C26-H26C	109.5
C13-C23-H23B	109.5	O1-C27-H27A	109.5
H23A-C23-H23B	109.5	O1-C27-H27B	109.5
C13-C23-H23C	109.5	H27A-C27-H27B	109.5
H23A-C23-H23C	109.5	O1-C27-H27C	109.5
H23B-C23-H23C	109.5	H27A-C27-H27C	109.5
C9-C24-H24A	109.5	H27B-C27-H27C	109.5
C9-C24-H24B	109.5	C4-C28-H28A	109.5
H24A-C24-H24B	109.5	C4-C28-H28B	109.5
C9-C24-H24C	109.5	H28A-C28-H28B	109.5
H24A-C24-H24C	109.5	C4-C28-H28C	109.5
H24B-C24-H24C	109.5	H28A-C28-H28C	109.5
C14-C25-H25A	109.5	H28B-C28-H28C	109.5
C14-C25-H25B	109.5	C17-C29-H29A	109.5
H25A-C25-H25B	109.5	C17-C29-H29B	109.5
C14-C25-H25C	109.5	H29A-C29-H29B	109.5
H25A-C25-H25C	109.5	C17-C29-H29C	109.5
H25B-C25-H25C	109.5	H29A-C29-H29C	109.5
O2-C26-H26A	109.5	H29B-C29-H29C	109.5
O2-C26-H26B	109.5	C3-O1-C27	113.96(9)
		C2-O2-C26	116.20(9)

Table 2.13. Anisotropic displacement parameters ($Å^2$x 10^3) for 1. The anisotropic displacement factor exponent takes the form: $-2\pi^2$[h^2 $a^{*2}U^{11}$ + ... + 2 h k a* b* U^{12}]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	14(1)	20(1)	17(1)	0(1)	4(1)	0(1)
C2	20(1)	17(1)	15(1)	-1(1)	4(1)	0(1)
C3	18(1)	20(1)	18(1)	-4(1)	8(1)	-4(1)
C4	15(1)	22(1)	17(1)	-6(1)	4(1)	-2(1)
C5	16(1)	18(1)	16(1)	-4(1)	3(1)	0(1)
C6	15(1)	22(1)	21(1)	-1(1)	3(1)	3(1)
C7	19(1)	19(1)	22(1)	0(1)	4(1)	4(1)
C8	15(1)	15(1)	16(1)	0(1)	2(1)	1(1)
C9	14(1)	18(1)	16(1)	1(1)	1(1)	-2(1)
C10	15(1)	17(1)	15(1)	-3(1)	3(1)	-1(1)
C11	14(1)	25(1)	20(1)	7(1)	3(1)	2(1)
C12	14(1)	28(1)	20(1)	7(1)	2(1)	0(1)
C13	15(1)	16(1)	16(1)	1(1)	2(1)	-1(1)
C14	17(1)	15(1)	17(1)	0(1)	2(1)	0(1)
C15	20(1)	22(1)	21(1)	4(1)	2(1)	4(1)
C16	26(1)	22(1)	24(1)	8(1)	5(1)	5(1)
C17	22(1)	18(1)	19(1)	3(1)	4(1)	-1(1)
C18	17(1)	18(1)	17(1)	0(1)	2(1)	-4(1)
C19	16(1)	25(1)	19(1)	3(1)	3(1)	-4(1)
C20	16(1)	22(1)	24(1)	1(1)	8(1)	-4(1)
C21	26(1)	28(1)	17(1)	-1(1)	4(1)	-3(1)
C22	24(1)	27(1)	16(1)	3(1)	1(1)	-1(1)
C23	19(1)	17(1)	23(1)	-1(1)	7(1)	-2(1)
C24	26(1)	28(1)	18(1)	-1(1)	2(1)	-10(1)
C25	29(1)	18(1)	26(1)	-3(1)	7(1)	-4(1)
C26	20(1)	27(1)	23(1)	8(1)	1(1)	-1(1)

Table 2.13, continued.

C27	26(1)	25(1)	29(1)	2(1)	6(1)	-7(1)
C28	16(1)	29(1)	23(1)	-4(1)	5(1)	-1(1)
C29	33(1)	20(1)	29(1)	5(1)	9(1)	-4(1)
O1	22(1)	26(1)	22(1)	-1(1)	11(1)	-6(1)
O2	19(1)	24(1)	22(1)	7(1)	4(1)	-2(1)
O3	31(1)	26(1)	33(1)	1(1)	13(1)	2(1)

Table 2.14. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **175**.

	x	y	z	U(eq)
H1	2027	5467	3634	20
H6A	4697	2675	5018	23
H6B	4770	1528	4382	23
H7A	3984	159	5213	24
H7B	3515	-8	4473	24
H8	3118	2796	5288	18
H11A	1744	4715	4790	24
H11B	1167	3968	4144	24
H12A	748	1505	4712	25
H12B	492	3256	5069	25
H15A	3395	-493	5997	25
H15B	3085	1256	6330	25
H16A	2703	-1067	6947	29
H16B	2267	-2124	6318	29
H18	694	-207	5692	20
H19A	-112	2510	5804	24
H19B	-358	848	6212	24
H21A	291	1018	7527	29
H21B	871	2738	7727	29
H22A	1751	143	7614	27
H22B	2008	1780	7197	27
H23A	2268	4198	5776	29
H23B	2156	3197	6437	29
H23C	1347	4295	6058	29
H24A	1849	2041	3416	36
H24B	1562	645	3924	36

Table 2.14, continued.

H24C	2543	599	3735	36
H25A	2497	-1637	4949	36
H25B	1558	-747	4702	36
H25C	1713	-1772	5383	36
H26A	1734	6397	2575	35
H26B	1791	8399	2349	35
H26C	1633	7956	3077	35
H27A	4156	9351	3283	39
H27B	5071	9421	2990	39
H27C	5066	8879	3735	39
H28A	5755	5452	3789	34
H28B	5623	3369	3825	34
H28C	5684	4530	4473	34
H29A	1177	-2568	7096	40
H29B	732	-2571	6349	40
H29C	291	-1465	6875	40

Table 2.15. Torsion angles [°] for **175**.

C10-C1-C2-O2	174.68(10)	C24-C9-C10-C5	-95.42(12)
C10-C1-C2-C3	-2.43(16)	C8-C9-C10-C5	28.53(14)
O2-C2-C3-O1	-2.30(15)	C11-C9-C10-C1	-37.93(13)
C1-C2-C3-O1	175.03(10)	C24-C9-C10-C1	78.21(12)
O2-C2-C3-C4	-177.01(10)	C8-C9-C10-C1	-157.85(9)
C1-C2-C3-C4	0.31(16)	C10-C9-C11-C12	-166.91(9)
O1-C3-C4-C5	-172.15(10)	C24-C9-C11-C12	78.90(12)
C2-C3-C4-C5	2.55(16)	C8-C9-C11-C12	-47.96(12)
O1-C3-C4-C28	6.26(16)	C9-C11-C12-C13	57.12(13)
C2-C3-C4-C28	-179.04(10)	C11-C12-C13-C23	61.70(12)
C3-C4-C5-C10	-3.34(16)	C11-C12-C13-C18	-178.39(9)
C28-C4-C5-C10	178.26(10)	C11-C12-C13-C14	-59.93(12)
C3-C4-C5-C6	176.21(10)	C7-C8-C14-C15	59.42(12)
C28-C4-C5-C6	-2.19(15)	C9-C8-C14-C15	-171.47(9)
C10-C5-C6-C7	10.20(15)	C7-C8-C14-C25	-58.46(12)
C4-C5-C6-C7	-169.35(10)	C9-C8-C14-C25	70.66(12)
C5-C6-C7-C8	-40.62(13)	C7-C8-C14-C13	176.88(9)
C6-C7-C8-C14	-160.82(9)	C9-C8-C14-C13	-54.00(12)
C6-C7-C8-C9	66.37(11)	C12-C13-C14-C15	176.24(9)
C7-C8-C9-C10	-58.27(11)	C23-C13-C14-C15	58.63(11)
C14-C8-C9-C10	169.67(9)	C18-C13-C14-C15	-63.94(11)
C7-C8-C9-C11	-179.38(9)	C12-C13-C14-C25	-66.45(11)
C14-C8-C9-C11	48.55(12)	C23-C13-C14-C25	175.94(9)
C7-C8-C9-C24	58.53(12)	C18-C13-C14-C25	53.38(12)
C14-C8-C9-C24	-73.53(12)	C12-C13-C14-C8	56.33(11)
C4-C5-C10-C1	1.28(16)	C23-C13-C14-C8	-61.28(11)
C6-C5-C10-C1	-178.26(10)	C18-C13-C14-C8	176.15(8)
C4-C5-C10-C9	174.84(10)	C25-C14-C15-C16	-58.41(12)
C6-C5-C10-C9	-4.70(16)	C8-C14-C15-C16	-178.11(9)
C2-C1-C10-C5	1.62(16)	C13-C14-C15-C16	62.93(12)
C2-C1-C10-C9	-172.18(10)	C14-C15-C16-C17	-48.94(14)
C11-C9-C10-C5	148.44(10)	C15-C16-C17-C29	152.96(11)

Table 2.15, continued.

C15-C16-C17-C22	-91.29(12)	C16-C17-C18-C13	-36.88(13)
C15-C16-C17-C18	33.80(14)	C13-C18-C19-C20	-85.46(12)
C12-C13-C18-C19	-58.99(12)	C17-C18-C19-C20	47.60(13)
C23-C13-C18-C19	58.69(12)	C18-C19-C20-O3	134.71(11)
C14-C13-C18-C19	-177.14(9)	C18-C19-C20-C21	-49.38(13)
C12-C13-C18-C17	171.19(9)	O3-C20-C21-C22	-136.65(12)
C23-C13-C18-C17	-71.14(12)	C19-C20-C21-C22	47.47(14)
C14-C13-C18-C17	53.04(12)	C20-C21-C22-C17	-48.16(14)
C29-C17-C18-C19	73.28(11)	C29-C17-C22-C21	-71.28(13)
C22-C17-C18-C19	-46.53(12)	C16-C17-C22-C21	173.48(10)
C16-C17-C18-C19	-168.38(9)	C18-C17-C22-C21	48.89(13)
C29-C17-C18-C13	-155.22(10)	C4-C3-O1-C27	-111.35(12)
C22-C17-C18-C13	84.97(12)	C2-C3-O1-C27	73.90(13)
		C1-C2-O2-C26	-9.63(16)
		C3-C2-O2-C26	167.55(10)

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6) $R_W(F^2) = \{\Sigma w(|F_O|^2 - |F_C|^2)^2/\Sigma w(|F_O|)^4\}^{1/2}$ where w is the weight given each reflection.
$R(F) = \Sigma(|F_O| - |F_C|)/\Sigma|F_O|\}$ for reflections with $F_O > 4(\sigma(F_O))$.
$S = [\Sigma w(|F_O|^2 - |F_C|^2)^2/(n - p)]^{1/2}$, where n is the number of reflections and p is the number of refined parameters.

7) International Tables for X-ray Crystallography (1992). Vol. C, Tables 4.2.6.8 and 6.1.1.4, A. J. C. Wilson, editor, Boston: Kluwer Academic Press.

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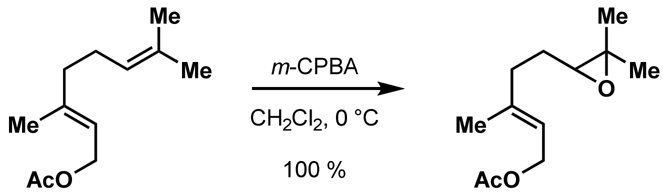
5. Experimental Procedures for the Synthesis of the Iodo-enoate 143



geraniol acetate (**137**)

A solution of geranyl acetate (5.20 g, 5.7 mL, 26.3 mmol, 1.00 eq.) in methylene chloride (176 mL) was placed in an ice water bath cooled to 0 °C for 20 minutes. *m*-CPBA (6.49 g, 26.3 mmol, 70% w/w, 1.00 eq.) was added in three separate portions over 15 minutes. After 45 minutes a saturated aqueous mixture of $NaHCO_3$ (25 mL) and a saturated aqueous mixture of $Na_2S_2O_3$ (25 mL) were added sequentially to the white heterogeneous reaction mixture. The biphasic mixture was poured into a separatory funnel, partitioned, and the organic layer was washed with a saturated aqueous mixture of $Na_2S_2O_3$ (1 x 20 mL) and a saturated aqueous mixture of $NaHCO_3$ (2 x 20 mL). Residual organics were extracted from the aqueous with methylene chloride (3 x 20 mL), dried over solid Na_2SO_4, decanted, and concentrated to afford the crude epoxide as a clear colorless oil (5.58 g) which was carried onto the next reaction without further purification.

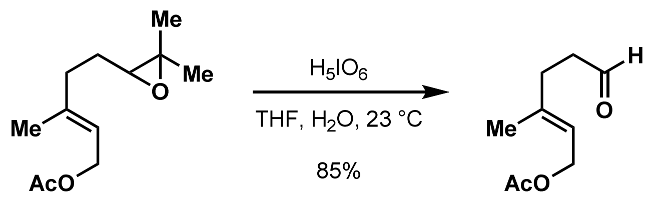
$\mathbf{R_f}$ = 0.30 (10% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.40 – 5.36 (m, 1H), 4.59 (d, 2H, *J* = 7.2 Hz), 2.70 (t, 1H, *J* = 6.1 Hz), 2.26 – 2.10 (m, 2H), 2.05 (s, 3H), 1.72 (s, 3H), 1.70 – 1.63 (m, 2H), 1.30 (s, 3H), 1.29 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.81, 141.04, 118.87, 63.72, 61.06, 58.18, 36.07, 26.94, 24.70, 20.86, 18.62, 16.32

IR (neat film, cm^{-1}): 1739, 1378, 1233, 1025

HRMS (EC-CI): calc'd. for $C_{10}H_{17}O$ $[M\text{-}AcOH]^-$, 153.1279 found. 153.1278



138

A biphasic solution of the crude epoxide (5.58 g, 26.3 mmol, 1.00 eq.) in THF-water (130 mL, 1:1) was placed in an ice water bath cooled to 0 °C for 20 minutes. Periodic acid (6.59 g, 28.9 mmol, 1.10 eq.) was added in four separate portions over 20 minutes. After 1 hr the excess acid was neutralized with a saturated aqueous mixture of $NaHCO_3$ (25 mL). The colorless biphasic solution was diluted with ethyl ether (50 mL), poured into a separatory funnel, and partitioned. The residual organics were extracted from the aqueous layer with ethyl ether (4 x 25 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude pale yellow oil was purified by silica gel chromatography; 15% EtOAc in hexane to afford the aldehyde **138** as a clear colorless oil (3.81 g, 22.4 mmol, 85%).

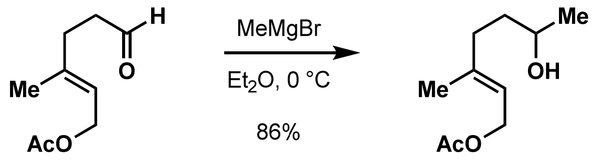
$\mathbf{R_f}$ = 0.37 (20% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.78 (t, 1H, *J* = 1.7 Hz), 5.36 (tq, 1H, *J* = 1.4 Hz), 4.57 (d, 2H, *J* = 7.2 Hz), 2.59 – 2.54 (m, 2H), 2.38 (t, 2H, *J* = 7.5 Hz), 2.05 (s, 3H), 1.72 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 201.91, 171.23, 140.20, 119.50, 61.29, 41.91, 31.62, 21.21, 16.80

IR (neat film, cm^{-1}): 1733, 1384, 1025

HRMS (EC-CI): calc'd. for $C_7H_{10}O$ [M-AcOH]$^-$, 110.0732 found. 110.0732



138

A solution of the aldehyde (76.0 mg, 0.45 mmol, 1.00 eq.) in ethyl ether (4.5 mL) was placed in an ice water bath cooled to 0 °C for 30 minutes. Methyl magnesiumbromide (0.21 mL, 0.63 mmol, 1.40 eq., 3 M in ethyl ether) was added via syringe. After 15 minutes an aqueous phosphate buffer (5 mL, pH = 7, 0.2 M) was added to the white heterogenous mixture to neutralize the excess Grignard and alkoxide. The biphasic mixture was poured into a separatory funnel, and partitioned. The residual organics were extracted from the aqueous layer with ethyl ether (3 x 10 mL), combined, dried over solid Na_2SO_4, decanted, and concentrated. The crude pale yellow oil was purified by silica gel chromatography; 15% EtOAc in hexane to afford the alcohol (71.4 mg, 0.38 mmol, 86%) as a clear colorless oil.

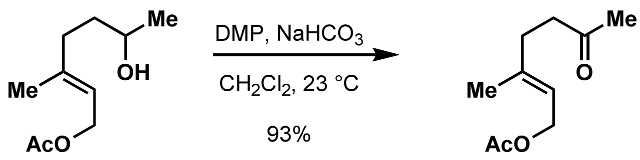
$\mathbf{R_f}$ = 0.19 (30% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.37 (dt, 1H, J = 1.0, 7.1 Hz), 4.58 (d, 2H, J = 7.1 Hz), 3.79 (q, 1H, J = 6.1 Hz), 2.21 – 2.06 (m, 2H), 2.05 (s, 3H), 1.71 (s, 3H), 1.62 – 1.54 (m, 2H), 1.39 (bs, 1H), 1.20 (d, 3H, J = 6.1 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.07, 142.06, 110.30, 67.60, 61.21, 36.86, 35.66, 23.41, 20.93, 16.33

IR (neat film, cm^{-1}): 3411, 2966, 2930, 1739, 1235

HRMS (EC-CI): calc'd. for $C_{10}H_{19}O_3$ $[M+H]^+$, 187.1334 found. 187.1331



135

To a mixture of the alcohol (0.30 g, 1.61 mmol, 1.00 eq.) and solid $NaHCO_3$ (0.54 g, 6.44 mmol, 4.00 eq.) in methylene chloride (16.0 mL) was added Dess-Martin periodinane (0.82 g, 1.93 mmol, 1.20 eq.). After two hours a saturated aqueous mixture of $NaHCO_3$ (20 mL) and a saturated aqueous mixture of $Na_2S_2O_3$ (20 mL) were added to the white heterogeneous reaction mixture to quench the residual acetic acid and Dess-Martin periodinane. The biphasic mixture was stirred vigorously (1000 rpm) for 30 minutes, poured into a separatory funnel, and partitioned. The organic layer was washed with a saturated aqueous mixture of $Na_2S_2O_3$ (2 x 20 mL) and a saturated aqueous mixture of $NaHCO_3$ (1 x 20 mL). The residual organics were extracted from the aqueous layer with methylene chloride (2 x 20 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude pale yellow mixture was purified by silica gel chromatography; 15% EtOAc in hexane to provide the ketone **135** as a clear colorless oil (0.28 g, 1.50 mmol, 93%).

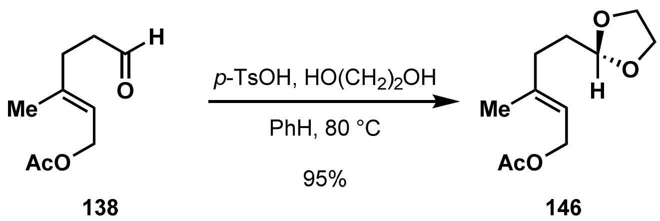
R_f = 0.51 (30% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.33 (dt, 1H, J = 1.3 Hz), 4.57 (d, 2H, J = 6.8 Hz), 2.57 (t, 2H, J = 7.2 Hz), 2.31 (t, 2H, J = 7.2 Hz), 2.16 (s, 3H), 2.05 (s, 3H), 1.70 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 207.95, 170.98, 140.64, 118.73, 61.11, 41.62, 33.00, 29.91, 20.97, 16.54

IR (neat film, cm^{-1}): 1738, 1718, 1367, 1234, 1024

HRMS (EC-CI): calc'd. for $C_8H_{13}O$ $[M\text{-}AcOH]^-$, 125.0966 found. 125.0963



A solution of the aldehyde **138** (3.47 g, 20.4 mmol, 1.00 eq.), ethylene glycol (12.7 g, 11.4 mL, 204 mmol, 10.0 eq.), and *p*-toluenesulfonic acid monohydrate (0.09 g, 0.41 mmol, 0.02 eq.) in benzene (68 mL) was placed in an oil bath heated to 80 °C. After 24 hrs the pale yellow solution was removed from oil bath, cooled to 23 °C, and an aqueous phosphate buffer (20 mL, pH = 7, 0.2 M) was added. The biphasic solution was poured into a separatory funnel, partitioned, and the organic layer was washed with water (2 x 20 mL). Residual organics were extracted from the aqueous layer with EtOAc (3 x 25 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude yellow oil was purified by silica gel chromatography; 10% EtOAc in hexane to afford the dioxolane **146** as a clear colorless oil (4.15 g, 19.4 mmol, 95%).

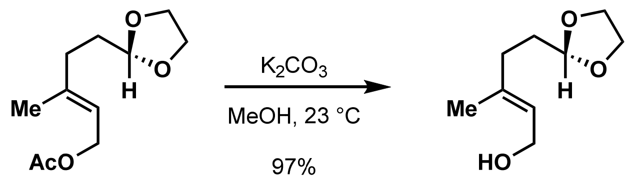
$\mathbf{R_f}$ = 0.53 (30% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.37 (tq, 1H, *J* = 1.4, 6.8 Hz), 4.86 (t, 1H, 4.8 Hz), 4.58 (d, 2H, *J* = 6.8 Hz), 3.97 – 3.83 (m, 4H), 2.16 (m, 2H), 2.05 (s, 3H), 1.79 (m, 2H), 1.71 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.93, 141.31, 118.33, 103.91, 64.77, 61.51, 33.46, 31.83, 20.91, 16.35

IR (neat film, cm^{-1}): 2955, 2885, 1738, 1234, 1141, 1027

HRMS (EC-CI): calc'd. for $C_9H_{15}O_2$ $[M\text{-}AcOH]^-$, 155.1072 found. 155.1068



146

To a solution of the acetate **146** (2.53 g, 11.81 mmol, 1.00 eq.) in methanol (40 mL) was added solid K_2CO_3 (3.25 g, 23.62 mmol, 2.00 eq.). After 15 minutes an aqueous phosphate buffer (20 mL, pH = 7, 0.2 M) and EtOAc (50 mL) was added to the white heterogenous mixture. The biphasic solution was poured into a separatory funnel, partitioned, and the organic layer was washed with water (2 x 30 mL). The residual organics were extracted from the aqueous layer with EtOAc (3 x 20 mL), combined, dried over solid Na_2SO_4, decanted, and concentrated. The crude colorless oil was purified by silica gel chromatography; 25% EtOAc in hexane to provide the alcohol product as a clear colorless oil (1.97 g, 11.44 mmol, 97%).

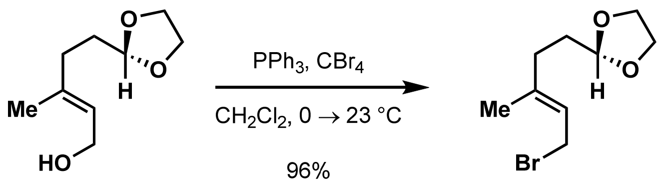
$\mathbf{R_f}$ = 0.42 (60% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.45 (dt, 1H, J = 1.0, 6.8 Hz), 4.86 (t, 1H, J = 4.8 Hz), 4.15 (d, 2H, J = 6.8 Hz), 3.99 – 3.84 (m, 4H), 2.15 (dd, 2H, J = 7.6, 8.5 Hz), 1.79 (m, 2H), 1.69 (s, 3H), 1.20 (bs, 1H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 130.10, 123.72, 104.07, 64.76, 58.92, 33.57, 31.90, 16.17

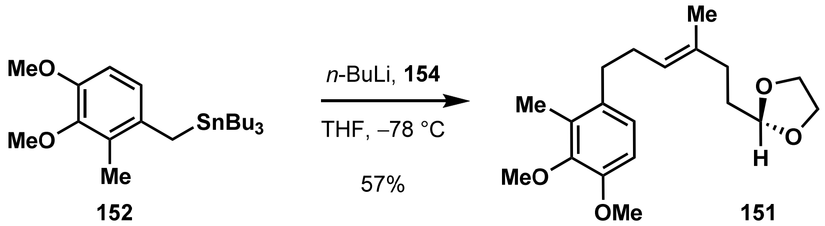
IR (neat film, cm^{-1}): 3401, 2955, 2920, 1403, 1140, 1030

HRMS (EC-CI): calc'd. for $C_9H_{15}O_3$ $[M+H]^+$, 171.1021 found. 171.1022



154

A solution of CBr_4 (4.17 g, 12.58 mmol, 1.10 eq.) in methylene chloride (10 mL) was placed in an ice water bath cooled to 0 °C for 20 minutes and then solid Ph_3P (3.30 g, 12.58 mmol, 1.10 eq.) was added under a positive flow of nitrogen. After 10 minutes a solution of the alcohol (1.97 g, 11.44 mmol, 1.00 eq.) was added via syringe to the golden yellow reaction solution. After 2 hrs the golden yellow solution was removed from the cold bath and allowed to stir for 30 minutes at 23 °C upon which pentane (50 mL) was added. The heterogeneous mixture was suction filtered through a pad of celite and concentrated to ~10 mL. Pentane (50 mL) was added and the mixture was placed in an ice water bath cooled to 0 °C for 10 minutes, suction filtered cold through a pad of celite, and concentrated to ~10 mL. This process was repeated once more to afford the bromide **154** as a pale yellow oil (2.58 g, 10.98 mmol, 96%). The bromide was carried onto the next reaction without characterization.



A solution of the benzyl stannane **152** (100.0 mg, 0.22 mmol, 1.00 eq.) in freshly deoxygenated THF (1.1 mL) was placed in a bath cooled to −78 °C. After 30 minutes *n*-butyllithium (0.11 mL, 0.24 mmol, 1.10 eq., 2.20 M in hexane) was added dropwise by syringe over 1 minute. After 1 hr the bromide **154** (72.3 mg, 0.31 mmol, 1.40 eq.) was added neat to the red-orange solution. After 1 hr the cold bath was removed and the golden yellow solution was warmed gradually to 23 °C. After 20 minutes the excess tolyl anion was neutralized with an aqueous phosphate buffer (10 mL, pH = 7, 0.2 M), the biphasic solution was poured into a separatory funnel, and partitioned. The residual organics were extracted from the aqueous layer with ethyl ether (3 x 10 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude pale yellow oil was purified by silica gel chromatography; hexane → 15% 1,4-dioxane in hexane to afford the arene **151** as a clear colorless oil (40.0 mg, 0.13 mmol, 57%).

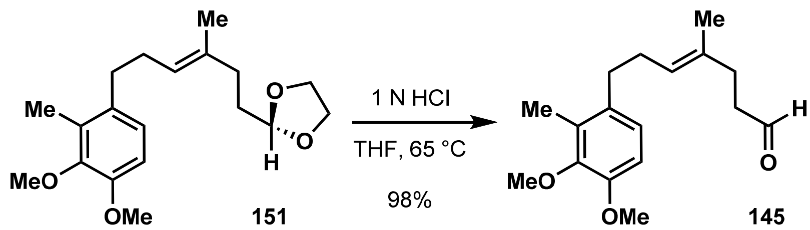
$\mathbf{R_f}$ = 0.55 (20% 1,4-dioxane in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.83 (d, 1H, *J* = 8.2 Hz), 6.69 (d, 1H, *J* = 8.2 Hz), 5.24 (m, 1H), 4.84 (t, 1H, *J* = 4.8 Hz), 3.99 – 3.84 (m, 4H), 3.83 (s, 3H), 3.77 (s, 3H), 2.55 (t, 2H, *J* = 8.5 Hz), 2.23 (s, 3H), 2.20 – 2.08 (m, 4H), 1.78 – 1.73 (m, 2H), 1.57 (s, 3H),

^{13}C-NMR (100 MHz, $CDCl_3$): δ 151.01, 147.45, 135.07, 133.97, 130.44, 124.32, 109.51, 104.56, 65.09, 60.40, 55.89, 34.11, 33.38, 32.63, 29.19, 16.20, 11.95

IR (neat film, cm^{-1}): 2930, 1490, 1453, 1270, 1084

HRMS (EC-CI): calc'd. for $C_{19}H_{28}O_4$ [M], 320.1988 found. 320.1985



A biphasic solution of the dioxolane **151** (1.09 g, 3.39 mmol, 1.00 eq.) in THF (17 mL) and 1 N HCl (17 mL) was placed in an oil bath heated to 65 °C. After 12 hrs the pale yellow biphasic solution was removed from the oil bath, neutralized to pH = 7 using an aqueous phosphate buffer (50 mL, pH = 7, 0.2 M), poured into a separatory funnel containing ethyl ether (30 mL), and partitioned. Residual organics were extracted from the aqueous layer with ethyl ether (4 x 10 mL), washed with brine (1 x 20 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude pale yellow oil was purified by silica gel chromatography; 10% EtOAc in hexane to afford the aldehyde **145** as a clear colorless oil (0.92 g, 3.33 mmol, 98%).

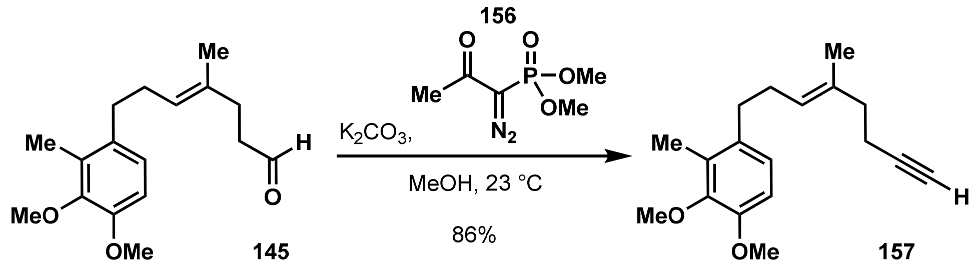
$\mathbf{R_f}$ = 0.55 (20% 1,4-dioxane in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.75 (t, 1H, *J* = 1.7 Hz), 6.82 (d, 1H, *J* = 8.6 Hz), 6.69 (d, 1H, *J* = 8.6 Hz), 5.25 – 5.20 (m, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 2.58 – 2.49 (m, 5H), 2.40 – 2.35 (m, 1H), 2.32 (t, 2H, *J* = 7.5 Hz), 2.28 (s, 3H), 1.56 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 202.85, 151.08, 147.50, 133.88, 133.73, 130.42, 124.34, 109.52, 60.42, 55.92, 42.33, 33.27, 32.03, 29.12, 16.26, 11.96

IR (neat film, cm^{-1}): 2933, 2835, 1723, 1489, 1455, 1418, 1270, 1224, 1083, 1005, 804

HRMS (EC-CI): calc'd. for $C_{17}H_{24}O_3$ [M], 276.1725 found. 276.1725



A mixture of the aldehyde **145** (0.93 g, 3.33 mmol, 1.00 eq.) and K_2CO_3 (1.62 g, 11.73 mmol, 3.50 eq.) in methanol (16.8 mL) was placed in an ice water bath cooled to 0 °C for 20 minutes and then the Bestman-Ohira reagent **156** (1.61 g, 8.38 mmol, 2.50 eq.) was added neat. The yellow heterogeneous mixture was rapidly stirred (800 rpm) for 12 hrs warming gradually to 23 °C, diluted with an aqueous phosphate buffer (20 mL, pH = 7, 0.2 M) and EtOAc (20 mL), poured into a separatory funnel, and partitioned. The organic layer was washed with water (1 x 20 mL). Residual organics were extracted from the aqueous layer with EtOAc (3 x 10 mL), washed with brine (1 x 10 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude pale yellow oil was purified by silica gel chromatography; benzene to afford the enyne **157** as a clear colorless oil (0.78 g, 2.88 mmol, 86%).

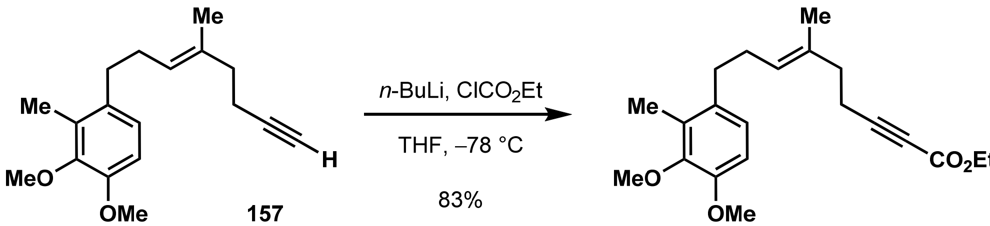
R_f = 0.43 (benzene)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.85 (d, 1H, *J* = 8.2 Hz), 6.70 (d, 1H, *J* = 8.2 Hz), 5.26 (t, 1H, *J* = 7.2 Hz), 3.84 (s, 3H), 3.77 (s, 3H), 2.60 – 2.54 (m, 2H), 2.30 – 2.23 (m, 2H), 2.23 (s, 3H), 2.23 – 2.18 (m, 4H), 1.96 (t, 1H, *J* = 2.8 Hz), 1.57 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 150.81, 147.24, 133.87, 133.65, 130.21, 125.04, 124.11, 109.28, 84.38, 68.39, 60.16, 55.68, 38.40, 33.11, 28.92, 17.55, 15.73, 11.73

IR (neat film, cm^{-1}): 2929, 1492, 1270, 1085

HRMS (EC-CI): calc'd. for $C_{18}H_{24}O_2$ [M], 272.1776 found. 272.1777



A clear colorless solution of the enyne **157** (0.44 g, 1.62 mmol, 1.00 eq.) in THF (16.2 mL) was placed in a bath cooled to −78 °C for 30 minutes. *n*-Butyllithium (1.00 mL, 2.26 mmol, 1.40 eq., 2.2 M in hexane) was added via syringe. After 1 hr ethyl chloroformate (0.35 g, 0.31 mL, 3.23 mmol, 2.00 eq.) was added neat to the clear colorless solution. After 30 minutes the solution was diluted with an aqueous phosphate buffer (10 mL, pH = 7, 0.2 M) and the mixture was removed from the cold bath, diluted with ethyl ether (20 mL), poured into a separatory funnel, and partitioned. Residual organics were extracted from the aqueous layer with ethyl ether (3 x 10 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude clear colorless oil was purified by silica gel chromatography; benzene to afford the ynoate product as a clear colorless oil (0.46 g, 1.34 mmol, 83%).

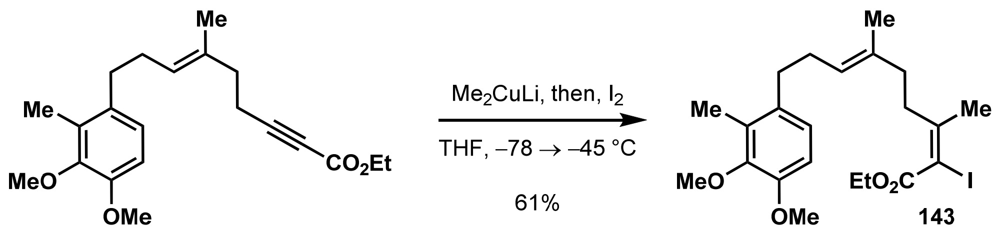
$\mathbf{R_f}$ = 0.33 (benzene)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.84 (d, 1H, *J* = 8.6 Hz), 6.70 (d, 1H, *J* = 8.6 Hz), 5.27 (t, 1H, *J* = 6.8 Hz), 4.21 (q, 2H, *J* = 7.2 Hz), 3.84 (s, 3H), 3.77 (s, 3H), 2.57 (t, 2H, *J* = 8.2 Hz), 2.41 (t, 7.9 Hz), 2.29 – 2.19 (m, 4H), 2.23 (s, 3H), 1.56 (s, 3H), 1.30 (t, 3H, *J* = 7.1 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 153.82, 150.83, 147.24, 133.52, 133.11, 130.15, 125.68, 124.13, 109.29, 88.99, 73.47, 61.75, 60.15, 55.66, 37.30, 33.03, 28.91, 17.82, 15.67, 14.04, 11.70

IR (neat film, cm^{-1}): 2933, 2234, 1711, 1492, 1250, 1082

HRMS (EC-CI): calc'd. for $C_{21}H_{28}O_4$ [M], 344.1988 found. 344.1985



A suspension of CuI (34.0 mg, 0.18 mmol, 2.05 eq.) in THF (0.46 mL) under nitrogen was placed in an ice water bath cooled to 0 °C. After 20 minutes methyl lithium (0.32 mL, 0.35 mmol, 4.00 eq., 1.10 M in Et_2O) was added. After 10 minutes the clear colorless solution was placed in a bath cooled to −78 °C. After 10 minutes a solution of the ynoate (30.0 mg, 0.09 mmol, 1.00 eq.) in THF (0.15 mL) was added by syringe in a dropwise fashion. After 1 hr a solution of iodine (66.3 mg, 0.26 mmol, 3.00 eq.) in THF (0.15 mL) was added under nitrogen via cannula in a dropwise fashion to the clear golden yellow solution. The purple solution was warmed to −45 °C and after 1 hr a saturated aqueous mixture of NH_4Cl (5 mL) was added. The blue mixture was removed from the cooling bath, diluted with Et_2O (5 mL), poured into a separatory funnel, partitioned, and the organic layer was washed with a saturated aqueous mixture of NH_4Cl (2 x 10 mL). Residual organics were extracted with Et_2O (2 x 10 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude brown amorphous oil was purified by silica gel chromatography; 2% benzene in toluene to afford the iodo-enoate **143** as a clear colorless oil (25.9 mg, 0.05 mmol, 61%).

R_f = 0.72 (10% Et_2O in benzene)

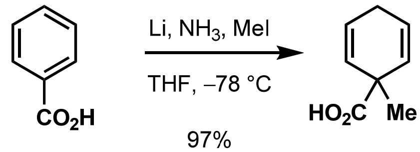
^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.84 (d, 1H, J = 8.6 Hz), 6.70 (d, 1H, J = 8.6 Hz), 5.21 (t, 1H, J = 6.5 Hz), 4.24 (q, 2H, J = 7.2 Hz), 3.83 (s, 3H), 3.77 (s, 3H), 2.57 – 2.53 (m, 3H), 2.23 (s, 3H), 2.23 – 2.12 (m, 5H), 2.06 (s, 3H), 1.56 (s, 3H), 1.31 (t, 3H, J = 7.2 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.89, 154.30, 151.05, 147.50, 134.71, 134.63, 130.45, 124.61, 109.54, 85.68, 62.11, 60.39, 55.90, 38.33, 35.80, 33.43, 29.93, 29.68, 29.19, 16.07, 14.30, 11.96

IR (neat film, cm^{-1}): 2919, 1706, 1489, 1270, 1237, 1085

HRMS (EC-CI): calc'd. for $C_{22}H_{31}O_4I$ [M], 486.1267 found. 486.1263

6. Experimental Procedures for Synthesis of Triene 165



benzoic acid (**132**) **160**

A solution of benzoic acid (5.23 g, 42.8 mmol, 1.00 eq.) in THF (210 mL) was placed in a bath cooled to −78 °C and liquid ammonia (500 mL) was condensed. Lithium wire (0.95 g, 137 mmol, 3.20 eq.) was added as small chunks over 1 minute. After two hours iodomethane (30.4 g, 13.3 mL, 214 mmol, 5.00 eq.) was added to the blue mixture. The resultant white heterogeneous mixture was removed from the cold bath and the ammonia was evaporated using a positive flow of nitrogen. The mixture was placed in an ice water bath cooled to 0 °C and water (150 mL) was added. The white mixture was acidified to pH = 3 using 1 N HCl, diluted with ethyl ether (100 mL), poured into a separatory funnel, and partitioned. Residual organics were extracted from the aqueous layer with ethyl ether (3 x 50 mL), washed with brine (1 x 50 mL), dried over solid Na_2SO_4, decanted, and concentrated. The pale yellow oil was then purified by distillation under vacuum to afford the acid **160** as a clear pale amber oil (5.74 g, 41.5 mmol, 97%, b.p. = 85 – 92 °C at 0.1 mmHg).

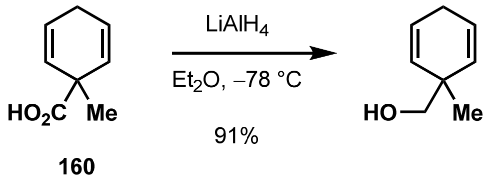
$\mathbf{R_f}$ = 0.46 (5% MeOH in CH_2Cl_2)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.75 (bs, 1H), 5.85 (dt, 2H, *J* = 3.1, 10.2 Hz), 5.77 (dt, 2H, *J* = 1.7, 10.2 Hz), 2.66 (m, 2H), 1.36 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 181.67, 128.08, 124.90, 43.65, 27.22, 25.85

IR (neat film, cm^{-1}): 3035 - 2817, 1699, 1415, 1294, 1260, 1126, 942, 702

HRMS (EC-CI): calc'd. for $C_8H_{11}O_2$ $[M+H]^+$, 139.0759 found. 139.0759



A solution of the acid **160** (5.92 g, 42.8 mmol, 1.00 eq.) in ethyl ether (214 mL) was placed in a bath cooled to −78 °C for 30 minutes. Lithium aluminum hydride (24.0 mL, 96.0 mmol, 2.24 eq., 4.0 M in ethyl ether) was added dropwise by syringe over 5 minutes. After 10 minutes the colorless solution was diluted with ethyl ether (200 mL), placed in an ice water bath cooled to 0 °C, and residual $LiAlH_4$ was quenched by the cautious, slow sequential addition of water (5 mL), NaOH (5 mL, 15% in water), and water (15 mL). After 5 minutes an aqueous phosphate buffer (10 mL, pH = 7, 0.2 M) was added. After 2 minutes solid Na_2SO_4 was added and the solid mixture was stirred vigorously (1000 rpm). After 20 minutes the white mixture was suction filtered through a pad of solid Na_2SO_4 and concentrated to afford the pure alcohol as a clear colorless oil (4.84 g, 38.95 mmol, 91%). **NOTE**: The product is slightly volatile under reduced pressure.

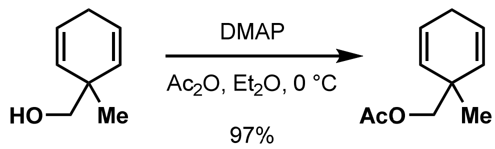
R_f = 0.36 (50% Et_2O in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.87 (dt, 2H, *J* = 3.4, 10.6 Hz), 5.43 (dt, 2H, *J* = 2.1, 10.6 Hz), 3.29 (d, 2H, *J* = 5.4 Hz), 2.63 (m, 2H), 1.60 (t, 1H, *J* = 5.4 Hz), 0.98 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 131.34, 126.24, 71.08, 39.25, 26.65, 25.01

IR (neat film, cm^{-1}): 3363, 3015, 2958, 2924, 2865, 2818, 1421, 1376, 1040, 711

HRMS (EC-CI): calc'd. for $C_8H_{13}O$ $[M+H]^+$, 125.0966 found. 125.0967



161

A solution of the alcohol (4.84 g, 39.0 mmol, 1.00 eq.) and *N*,*N*-dimethylamino pyridine (10.47 g, 86.0 mmol, 2.21 eq.) in ethyl ether (430 mL) was placed in an ice water bath cooled to 0 °C for 30 minutes upon which acetic anhydride (12.0 mL, 129 mmol, 4.46 eq.) was added by syringe over 2 minutes. After 20 minutes the golden yellow solution was removed from the cold bath, warmed gradually to 23 °C over 20 minutes, and an aqueous phosphate buffer (100 mL, pH = 4, 0.2 M) was added. The biphasic solution was poured into a separatory funnel, partitioned, and the organic layer was washed with an aqueous phosphate buffer (2 x 50 mL, pH = 4, 0.2 M). Residual organics were extracted from the aqueous with ethyl ether (2 x 25 mL), combined, and washed with a saturated aqueous mixture of $NaHCO_3$ (2 x 50 mL). Residual organics were extracted from the aqueous $NaHCO_3$ layer with ethyl ether (1 x 25 mL), washed with brine (1 x 100 mL), dried over solid Na_2SO_4, decanted, and concentrated to afford the acetate **161** as a pure clear colorless oil (6.28 g, 37.8 mmol, 97%).

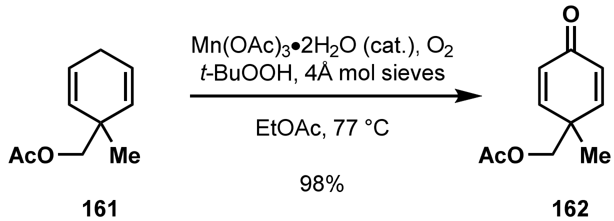
$\mathbf{R_f}$ = 0.67 (50% Et_2O in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.75 (dt, 2H, *J* = 3.1, 10.2 Hz), 5.48 (dt, 2H, *J* = 2.1, 10.2 Hz), 3.85 (s, 2H), 2.60 (m, 2H), 2.02 (s, 3H), 1.04 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.27, 130.93, 124.98, 71.74, 36.90, 26.55, 25.46, 21.12

IR (neat film, cm^{-1}): 3018, 2964, 2872, 1743, 1382, 1235, 1038

HRMS (EC-CI): calc'd. for C_8H_{11} [M-AcOH]$^-$, 107.0861 found. 107.0858



To a mixture of the acetate **161** (2.00 g, 12.03 mmol, 1.00 eq.), activated crushed mol sieves (1.0 g), and *t*-BuOOH (7.75 g, 8.3 mL, 60.2 mmol, 5.00 eq., 70% w/v) in EtOAc (80 mL) was added manganese triacetate dihydrate (0.32 g, 1.20 mmol, 0.10 eq.). The reaction vessel was equipped with a plastic PTFE cap and placed under an atmosphere of oxygen (balloon). The brown mixture was placed in an oil bath heated to 77 °C and stirred vigorously (800 rpm). After 12 hrs. the brown mixture was removed from the oil bath, cooled to 23 °C, suction filtered, concentrated, and purified by silica gel chromatography; 10% EtOAc in hexane → 30% EtOAc in hexane to afford the dienone **162** as a clear yellow oil (2.12 g, 11.8 mmol, 98%).

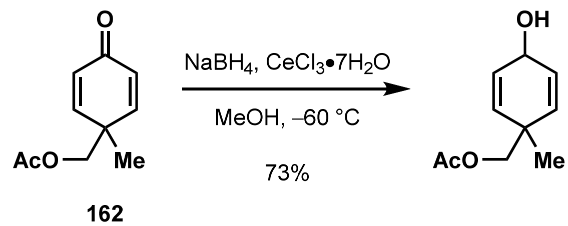
$\mathbf{R_f}$ = 0.41 (40% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.78 (d, 2H, *J* = 10.5 Hz), 6.26 (d, 2H, *J* = 10.5 Hz), 4.08 (s, 2H), 1.97 (s, 3H), 1.23 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 185.69, 170.52, 151.94, 129.80, 68.31, 41.92, 21.70, 20.65

IR (neat film, cm^{-1}): 1743, 1668, 1628, 1403, 1378, 1248, 1042, 862

HRMS (ESI): calc'd. for $C_{10}H_{12}O_3Na$ $[M+Na]^+$, 203.0679 found. 203.6810



A solution of the dienone **162** (99.0 mg, 0.55 mmol, 1.00 eq.) in methanol (5.5 mL) was placed in a bath cooled to −60 °C for 30 minutes. Cerium trichloride heptahydrate (614 mg, 1.65 mmol, 3.00 eq.) was added and the mixture was stirred vigorously (800 rpm) for 30 minutes upon which the reaction mixture had become a clear pale yellow homogeneous solution and then solid $NaBH_4$ (22.9 mg, 0.60 mmol, 1.10 eq.) was added. After 30 minutes excess $NaBH_4$ and the alkoxide were quenched with an aqueous phosphate buffer (10 mL, pH = 7, 0.2 M). The mixture was removed from the cold bath, diluted with EtOAc (20 mL), poured into a separatory funnel, partitioned, and the organic layer was washed with an aqueous phosphate buffer (2 x 10 mL). Residual organics were extracted from the aqueous layer with EtOAc (3 x 15 mL), washed with brine (1 x 10 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude pale yellow oil was purified by silica gel chromatography; 20% EtOAc in hexane to afford the alcohol as a clear pale yellow oil (73.0 mg, 0.40 mmol, 73%, d.r. = 1.5:1). **Note**: The crude alcohol can be carried on to the next step without purification.

Mixture of Isomers: (*) denotes minor isomer

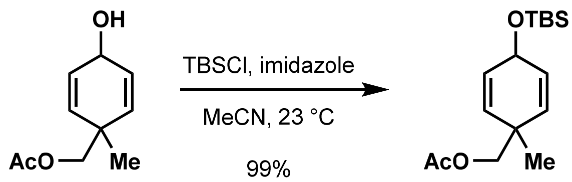
$\mathbf{R_f}$ = 0.39 (40% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.94 (m, 2H), 5.71 (t, 2H, J = 10.2 Hz), 5.49 (br d, 1H, J = 12.6 Hz), 3.92* (s, 2H), 3.87 (s, 2H), 2.05* (s, 3H), 2.02 (s, 3H), 1.58 (bs, 1H), 1.12* (s, 3H), 1.07 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.94 (170.90*), 133.67, 133.20, 128.46, 128.14, (70.59*) 70.04, (62.22*) 62.06, (37.68*) 37.55, 24.27, 23.68, (20.90*) 20.85

IR (neat film, cm^{-1}): 3399, 2966, 1741, 1254, 1037

HRMS (ESI): calc'd. for $C_{10}H_{14}O_3Na$ $[M+Na]^+$, 205.0835 found. 205.0840



A solution of the alcohol (60.0 mg, 0.33 mmol, 1.00 eq.) in acetonitrile (3.3 mL) was placed in an ice water bath cooled to 0 °C for 10 minutes upon which a mixture of TBSCl (54.6 mg, 0.36 mmol, 1.10 eq.) and imidazole (29.0 mg, 0.43 mmol, 1.30 eq.) was added together. After 2 minutes the white mixture was removed from the cold bath and allowed to stir (500 rpm) at 23 °C. After 2 hrs the heterogeneous mixture was diluted with an aqueous phosphate buffer (10 mL, pH = 7, 0.2 M) and EtOAc (10 mL), poured into a separatory funnel, partitioned, and the organic layer was washed with an aqueous phosphate buffer (1 x 10 mL, pH = 7, 0.2 M). Residual organics were extracted with EtOAc (2 x 10 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude pale yellow mixture was purified by silica gel chromatography; 2% EtOAc in hexane to afford the silyl ether product as a clear pale yellow oil (97.0 mg, 0.33 mmol, 99%).

Mixture of Isomers: (*) denotes minor isomer

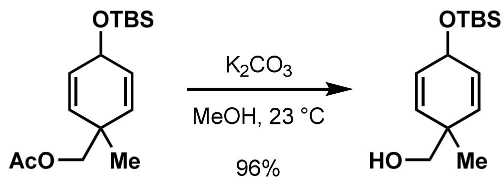
R_f = 0.75 (10% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.80 (ddd, 2H, *J* = 2.8, 10.2 Hz), 5.66* (dd, 2H, *J* = 1.7, 10.2 Hz), 5.61 (dd, 2H, *J* = 2.1, 10.2 Hz), 4.61 (m, 1H), 3.93* (s, 2H), 3.85 (s, 2H), 2.04* (s, 3H), 2.02 (s, 3H), 1.13 (s, 3H), 1.03* (s, 3H), 0.91 (s, 9H), 0.90* (s, 9H), 0.11* (s, 6H), 0.98 (s, 3H), 0.97 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ (171.07*) 170.88, 132.23, 131.87, 129.43, 128.79, 70.92 (70.04*), 63.20 (63.07*), (37.56*) 37.43, 25.93 (25.90*), 25.65, 24.42, 23.33, 20.94 (20.86*), (18.35*) 18.24

IR (neat film, cm^{-1}): 2957, 2930, 2857, 1747, 1253, 1056, 873, 837

HRMS (ESI): calc'd. for $C_{16}H_{28}O_3SiNa$ $[M+Na]^+$, 319.1700 found. 319.1750



163

To a solution of the silyl ether (1.07 g, 3.61 mmol, 1.00 eq.) in methanol (36 mL) was added K_2CO_3 (0.55 g, 3.97 mmol, 1.10 eq.) and the mixture was rapidly stirred (800 rpm) at 23 °C. After 1 hr. the heterogeneous mixture was diluted with an aqueous phosphate buffer (20 mL, pH = 7, 0.2 M) and EtOAc (20 mL), poured into a separatory funnel, partitioned, and the organic layer was washed with water (2 x 10 mL). Residual organics were extracted from the aqueous layer with EtOAc (2 x 20 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude yellow oil was purified by silica gel chromatography; 5% EtOAc in hexane to afford the alcohol **163** as a clear pale yellow oil (0.88 g, 3.46 mmol, 96%).

Mixture of Isomers: (*) denotes minor isomer

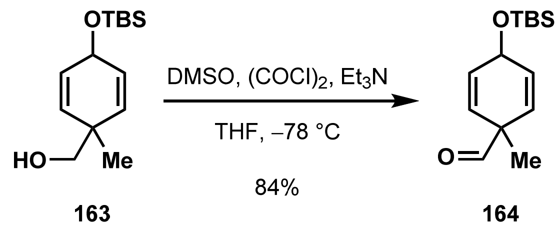
R_f = 0.33 (10% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.89 (m, 2H), 5.65* (dd, 2H, J = 1.2, 10.0 Hz), 5.61 (dd, 2H, J = 2.0, 10.1 Hz), 4.65 (m, 1H), 4.60* (m, 1H), 3.38 (s, 2H), 3.34* (s, 2H), 1.80 (bs, 1H), 1.07 (s, 3H), 1.01* (s, 3H), 0.91 (s, 9H), 0.89* (s, 9H), 0.11 (s, 6H), 0.10* (s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 133.79, 132.30, 130.31, 129.71, (70.30*) 69.03, 63.12 (62.58*), 40.04 (39.88*), 25.96 (25.90*), (23.88*) 22.92, 18.37 (18.24*), −4.34 (−4.43*)

IR (neat film, cm^{-1}): 3401, 2956, 2929, 2857, 1256, 1056, 872, 836, 776

HRMS (EC-CI): calc'd. for $C_{14}H_{27}O_2Si$ $[M+H]^+$, 255.1780 found. 255.1780



A solution of oxalyl chloride (1.76 g, 1.2 mL, 13.8 mmol, 4.00 eq.) in THF (5 mL) was placed in a bath cooled to −78 °C for 30 minutes upon which dimethyl sulfoxide (2.16 g, 2.0 mL, 27.7 mmol, 8.00 eq.) was added dropwise by syringe over 2 minutes. After 10 minutes a solution of the alcohol **163** (0.88 g, 3.46 mmol, 1.00 eq.) in THF (12 mL) was added by syringe over 5 minutes to the slightly heterogeneous mixture. After 1 hr triethylamine (7.00 g, 9.7 mL, 69.2 mmol, 20.0 eq.) was added by syringe to the pale yellow mixture. After 1 hr the yellow solution was removed from the cold bath and allowed to stir (500 rpm) at 23 °C. After 1 hr the golden yellow solution was diluted with an aqueous phosphate buffer (20 mL, pH = 7, 0.2 M) and ethyl ether (20 mL), poured into a separatory funnel, partitioned, and the organic layer was washed with water (2 x 10 mL). Residual organics were extracted from the aqueous layer with ethyl ether (3 x 15 mL), washed with brine (1 x 10 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude pale yellow oil was purified by silica gel chromatography; hexane → 2% EtOAc in hexane to afford the aldehyde **164** as a pale yellow oil (0.73 g, 2.91 mmol, 84%).

Mixture of Isomers: (*) denotes minor isomer

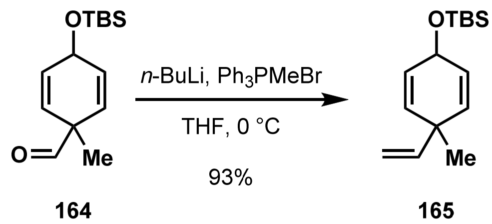
R_f = 0.53 (5% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.26* (s, 1H), 9.01 (s, 1H), 6.01 (m, 2H), 5.65* (d, 2H, *J* = 9.9 Hz), 5.52 (dd, 2H, *J* = 2.0, 10.2 Hz), 4.72 – 4.70 (m, 1H), 4.69 – 4.67* (m, 1H), 1.30 (s, 3H), 1.19* (s, 3H), 0.92 (s, 9H), 0.91* (s, 9H), 0.13 (s, 6H), 0.12* (s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ (198.81*), 197.19, 131.64, 131.33, 128.30, 126.27, (62.57*) 62.54, 51.64 (50.55*), 25.87, (20.97*) 19.33, 18.31 (18.24*), (−4.33*) −4.47

IR (neat film, cm^{-1}): 2966, 2929, 2857, 1728, 1069, 868, 836, 776

HRMS (EC-CI): calcd. for $C_{14}H_{25}O_2Si$ $[M+H]^+$, 253.1624 found. 253.1624



A mixture of Ph_3PMeBr (1.36 g, 3.81 mmol, 1.00 eq.) in THF (15 mL) was placed in a bath cooled to −78 °C for 20 minutes upon which *n*-butyllithium (1.97 mL, 3.36 mmol, 1.10 eq., 1.70 M in hexane) was added. After 20 minutes the orange heterogeneous mixture was removed from the cold bath and allowed to warm to 23 °C. After 20 minutes the orange mixture was placed in an ice water bath cooled to 0 °C for 30 minutes upon which a solution of the aldehyde **164** (0.77 g, 3.05 mmol, 1.00 eq.) in THF (15 mL) was added dropwise by syringe over 2 minutes. After 1 hr the pale yellow mixture was removed from the cold bath. After 30 minutes at 23 °C an aqueous phosphate buffer (20 mL, pH = 7, 0.2 M) was added to the pale yellow mixture to quench the excess ylide. The mixture was diluted with ethyl ether (20 mL), poured into a separatory funnel, and partitioned. Residual organics were extracted from the aqueous with ethyl ether (2 x 20 mL), dried over solid Na_2SO_4, suction filtered over a pad of celite, and concentrated. The crude pale yellow mixture was purified by silica gel chromatography; hexane → 2% EtOAc in hexane to afford the triene **165** as a pale yellow oil (0.71 g, 2.83 mmol, 93%).

Mixture of Isomers: (*) denotes minor isomer

$\mathbf{R_f}$ = 0.84 (5% EtOAc in hexane)

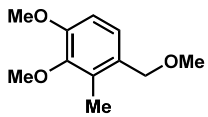
^{1}**H-NMR** (400 MHz, $CDCl_3$): δ 5.83 – 5.62 (m, 5H), 5.06 – 4.91 (m, 2H), 4.63 – 4.61 (m, 1H), 1.20 (s, 3H), 1.12* (s, 3H), 0.92 (s, 9H), 0.91* (s, 9H), 0.11 (s, 6H), 0.10* (s, 6H)

^{13}**C-NMR** (100 MHz, $CDCl_3$): δ 144.73 (144.09*), (134.21*) 133.76, 126.90 (126.69*), (112.44*) 111.75, 63.22 (63.05*), 40.07 (39.53*), 26.95, 25.99, 18.37 (18.36*), (−4.23*) −4.33

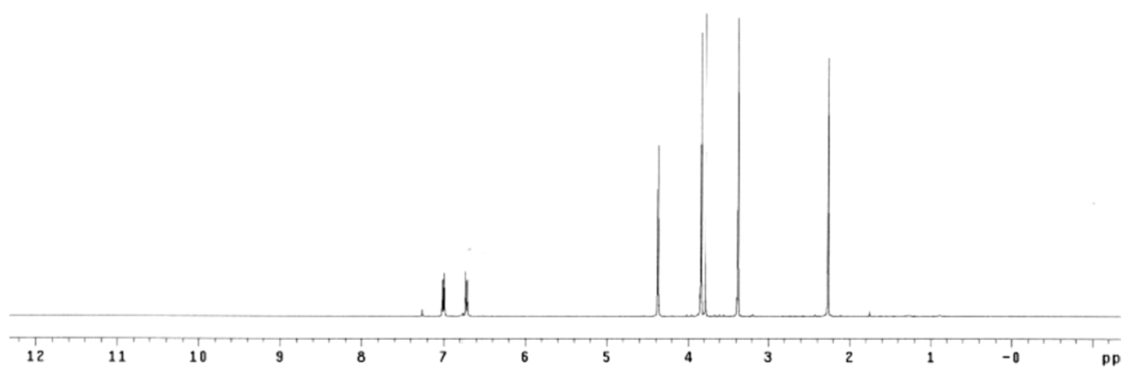
IR (neat film, cm^{-1}): 2958, 2928, 2857, 1253, 1063, 873, 836, 775

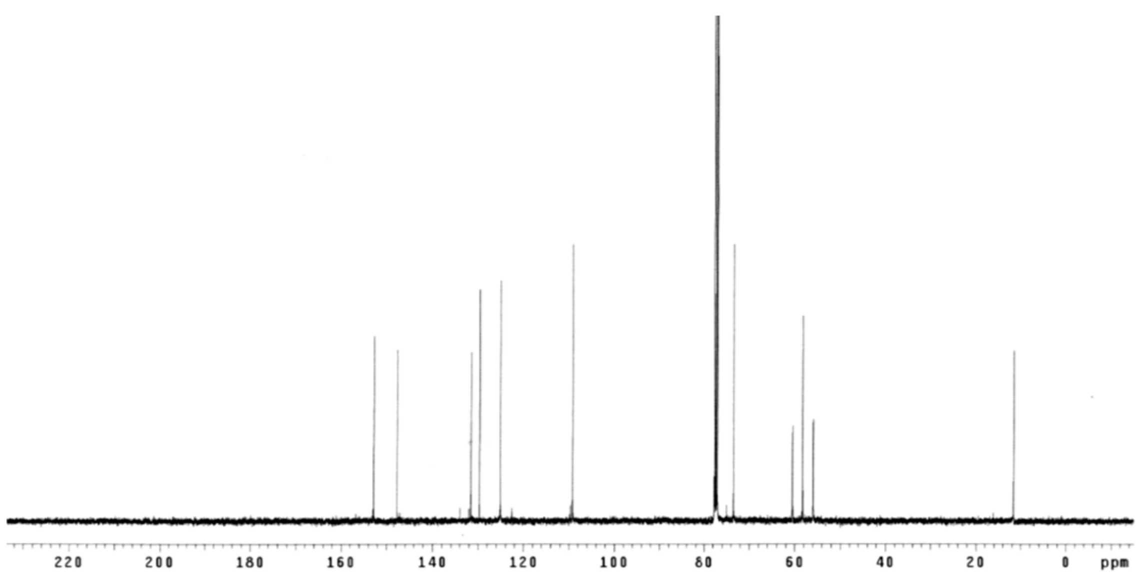
HRMS (EC-CI): calc'd. for $C_{15}H_{27}OSi$ $[M+H]^+$, 251.1831 found. 251.1823

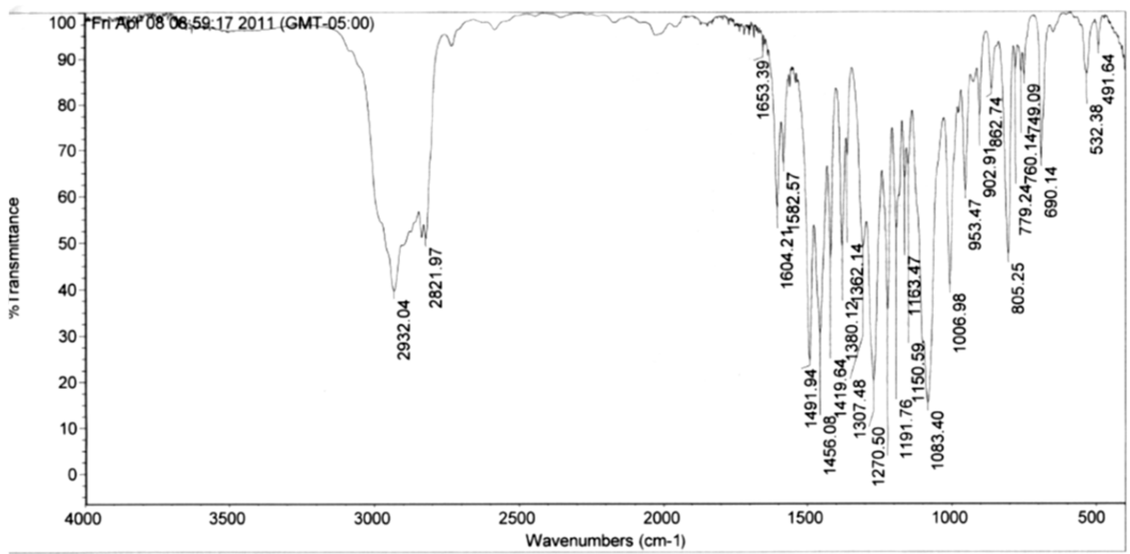
7. Catalog of Spectra



148



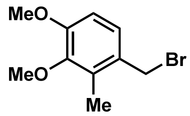




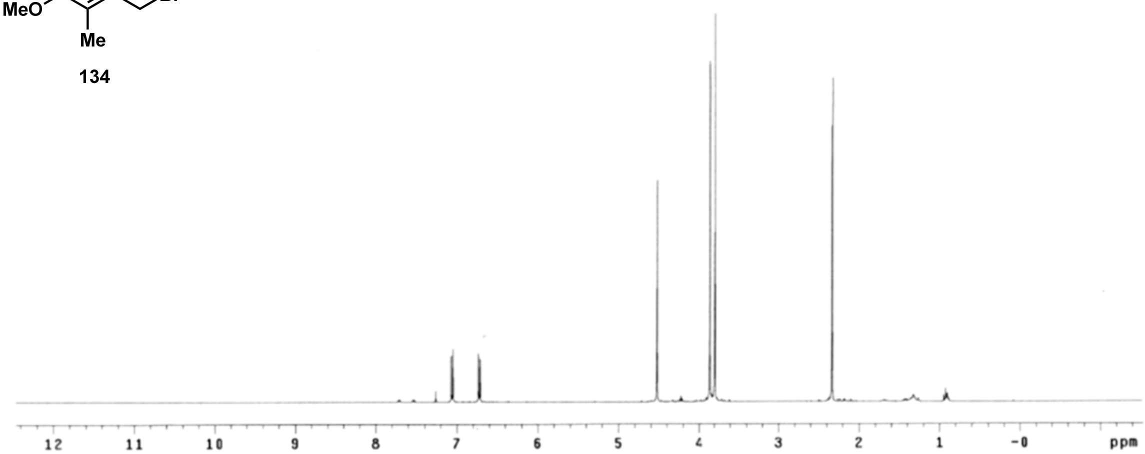
Fri Apr 08 09:01:42 2011 (GMT-05:00)
FIND PEAKS:

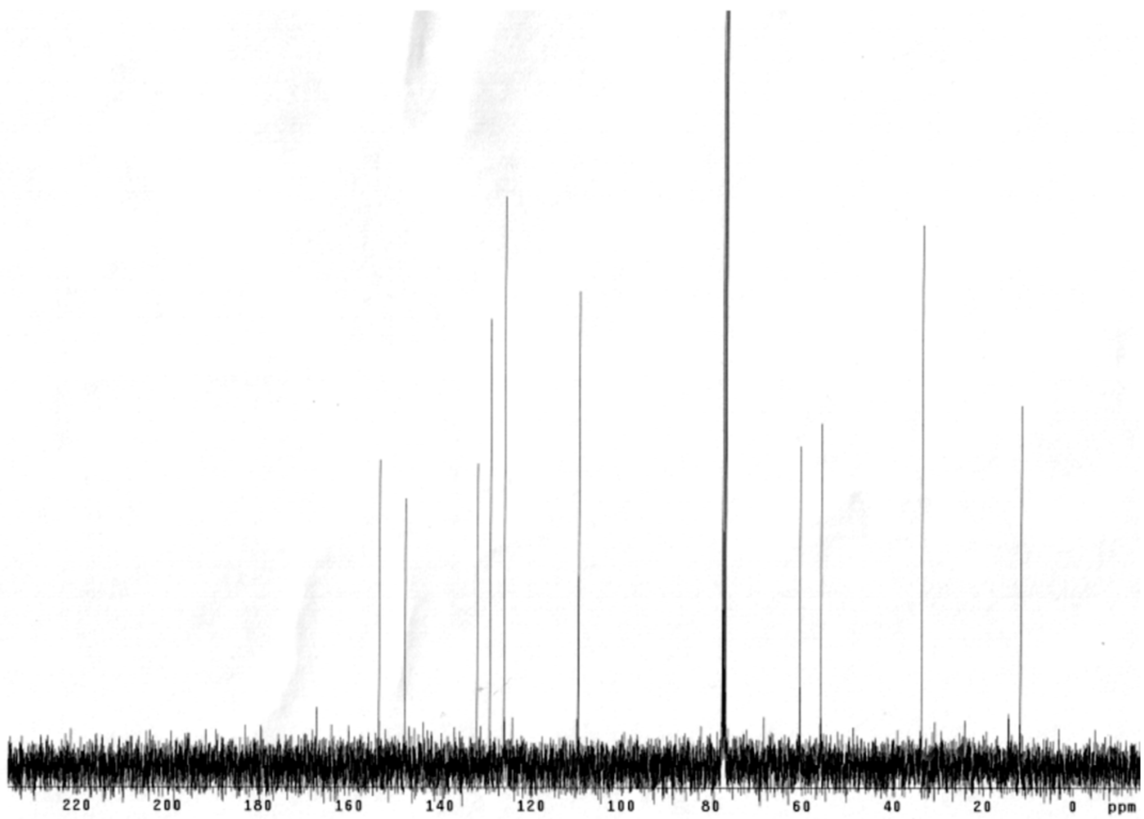
Spectrum: *Fri Apr 08 08:59:17 2011 (GMT-05:00)
Region: 4000.00 400.00
Absolute threshold: 94.127
Sensitivity: 50
Peak list:

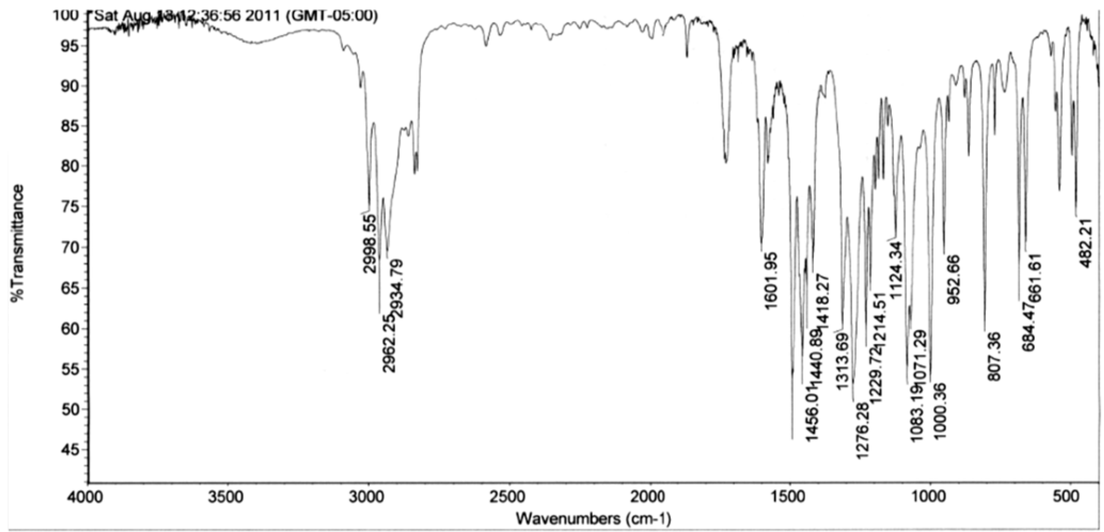
Position:	491.64	Intensity:	92.845
Position:	532.38	Intensity:	86.788
Position:	690.14	Intensity:	68.079
Position:	749.09	Intensity:	86.347
Position:	760.14	Intensity:	87.167
Position:	779.24	Intensity:	87.809
Position:	805.25	Intensity:	47.490
Position:	862.74	Intensity:	83.450


MeO
MeO
Me
Br

134


12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

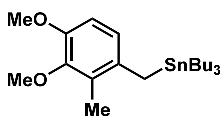

220 200 180 160 140 120 100 80 60 40 20 0 ppm



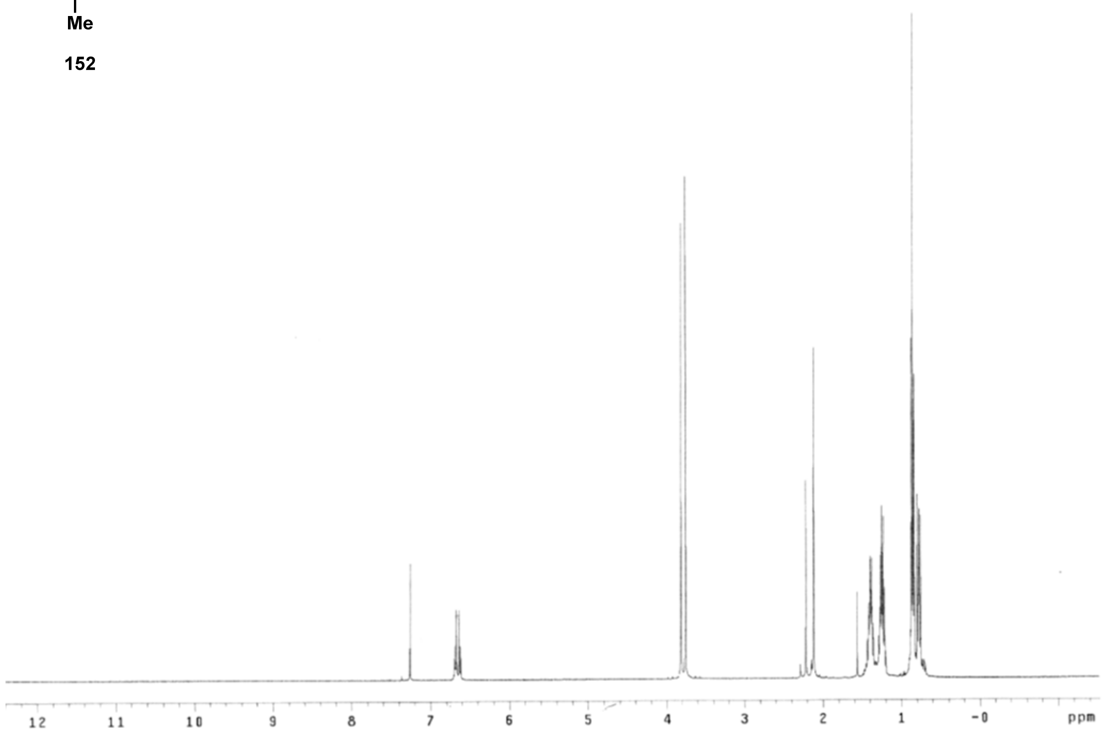
Sat Aug 13 12:43:52 2011 (GMT-05:00)
FIND PEAKS:

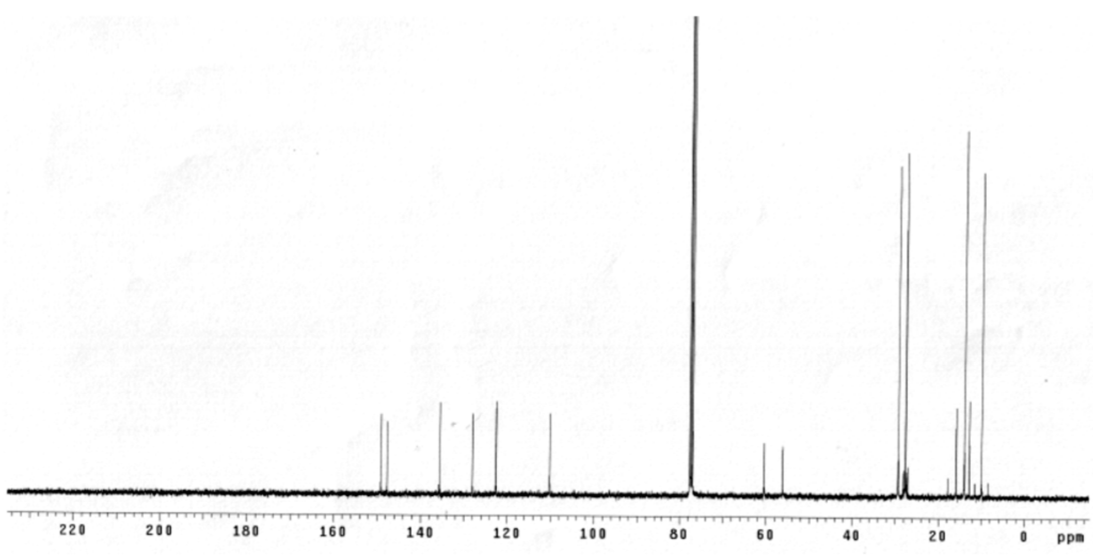
Spectrum: *Sat Aug 13 12:36:56 2011 (GMT-05:00)
Region: 4000.00 400.00
Absolute threshold: 75.362
Sensitivity: 50
Peak list:

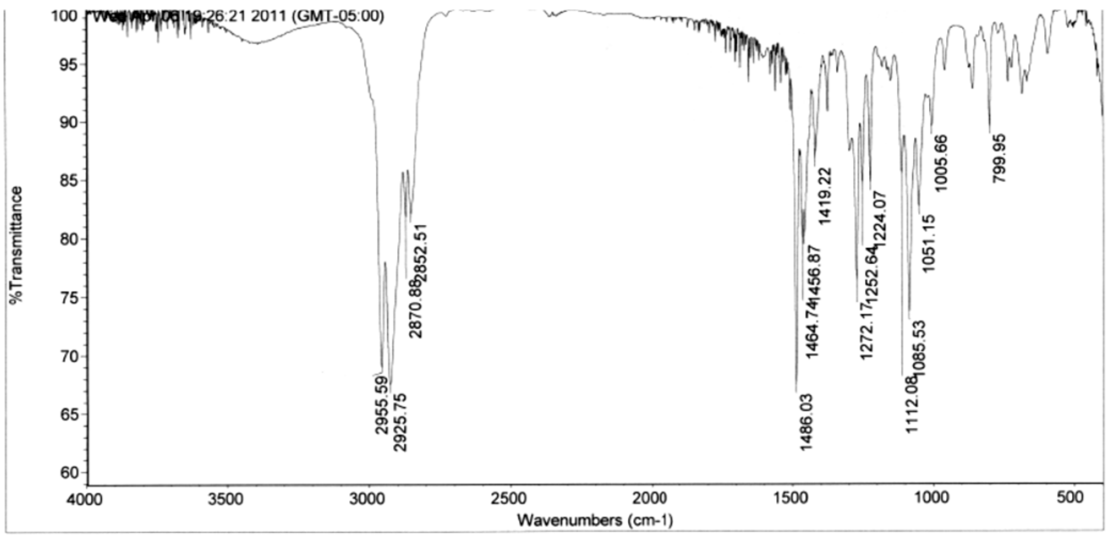
Position:	482.21	Intensity:	74.631
Position:	661.61	Intensity:	70.333
Position:	684.47	Intensity:	67.741
Position:	807.36	Intensity:	60.487
Position:	952.66	Intensity:	70.047
Position:	1000.36	Intensity:	54.115
Position:	1071.29	Intensity:	60.863
Position:	1083.19	Intensity:	55.201


MeO
MeO
SnBu3
Me

152

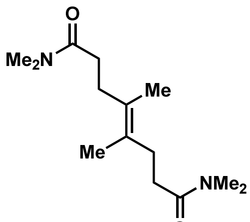

12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm


220 200 180 160 140 120 100 80 60 40 20 0 ppm

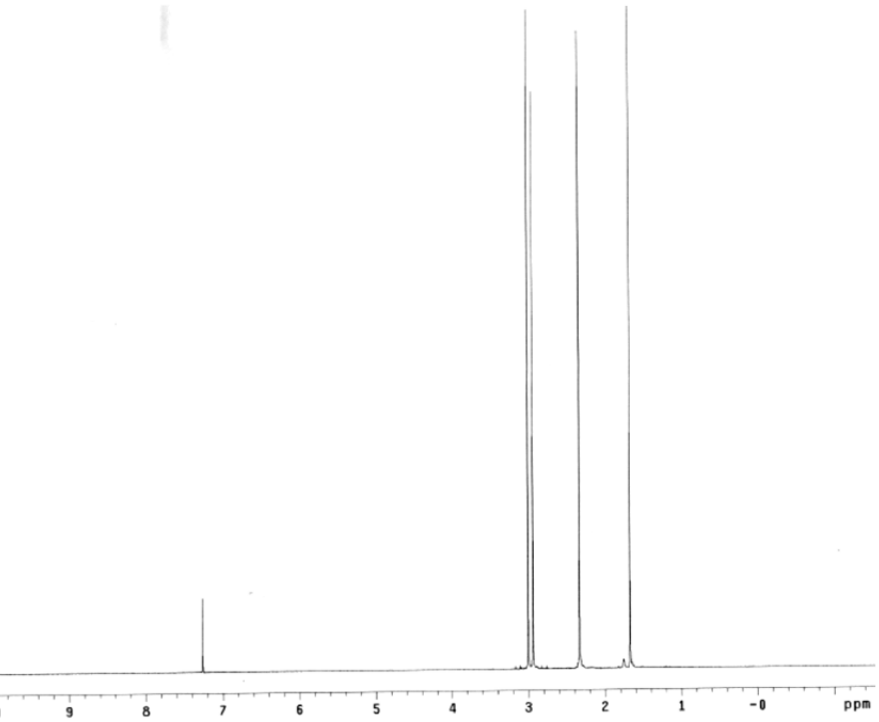


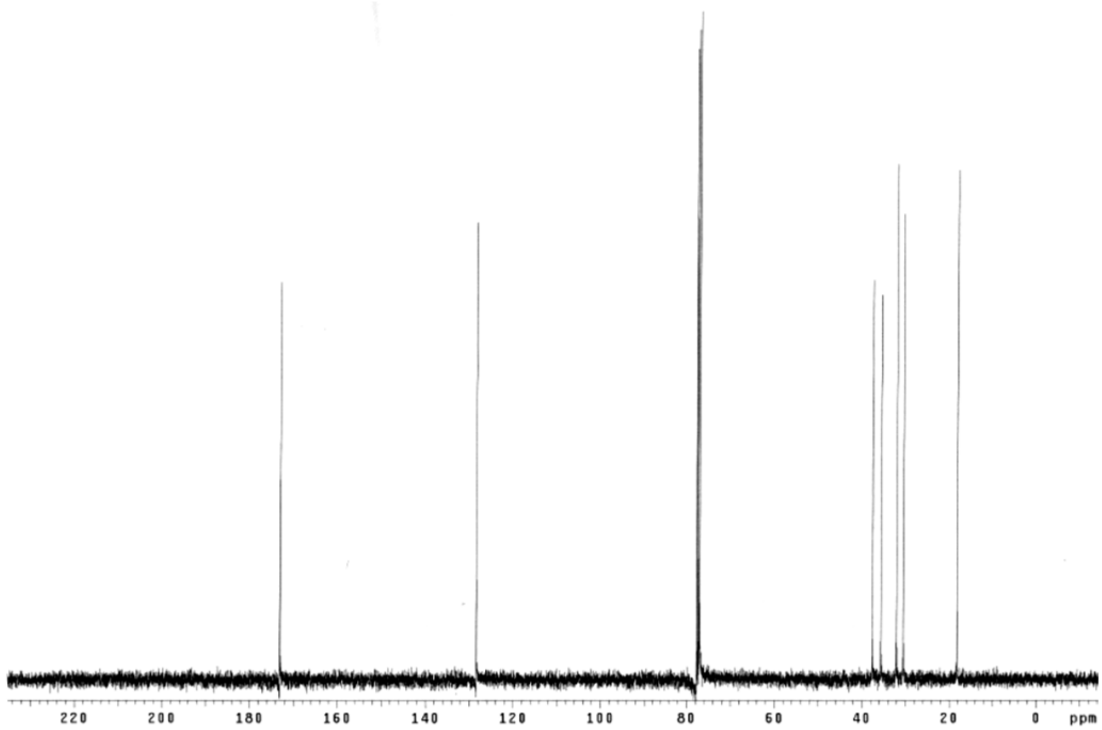
Wed Apr 06 19:32:53 2011 (GMT-05:00)
FIND PEAKS:

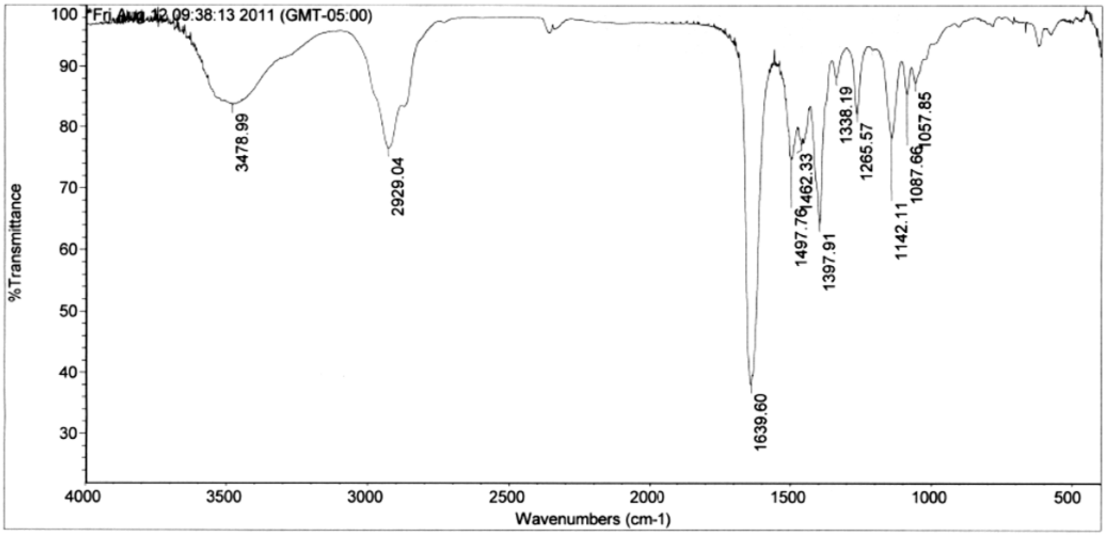
Spectrum:	*Wed Apr 06 19:26:21 2011 (GMT-05:00)			
Region:	4000.00	400.00		
Absolute threshold:	89.660			
Sensitivity:	50			
Peak list:				
	Position:	799.95	Intensity:	89.441
	Position:	1005.66	Intensity:	89.464
	Position:	1051.15	Intensity:	82.644
	Position:	1085.53	Intensity:	73.635
	Position:	1112.08	Intensity:	85.469
	Position:	1224.07	Intensity:	84.627
	Position:	1252.64	Intensity:	84.606
	Position:	1272.17	Intensity:	76.383


Me2N
Me
Me
NMe2

181

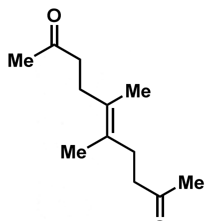

12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm


220 200 180 160 140 120 100 80 60 40 20 0 ppm

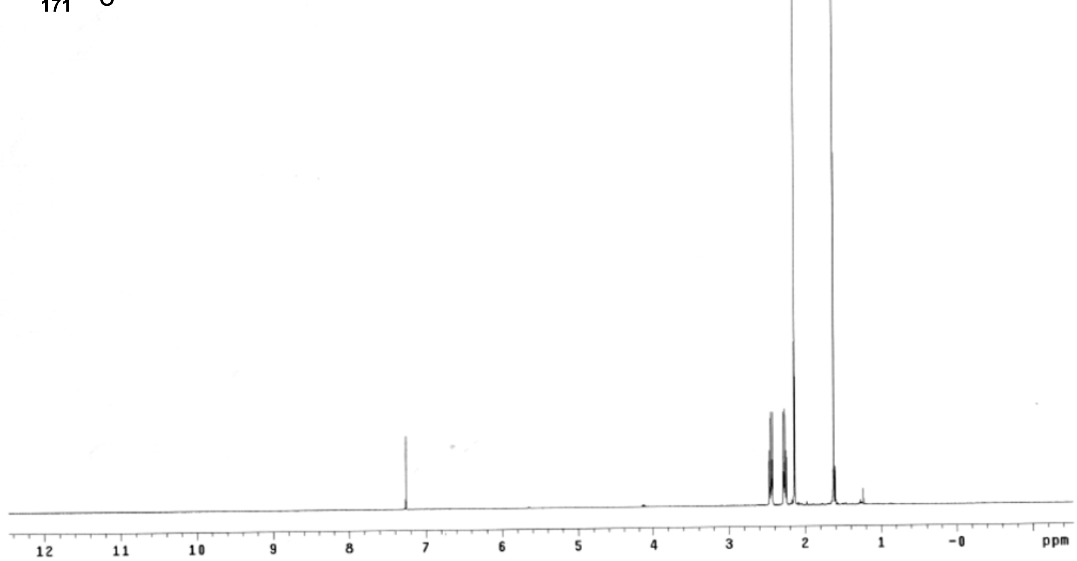


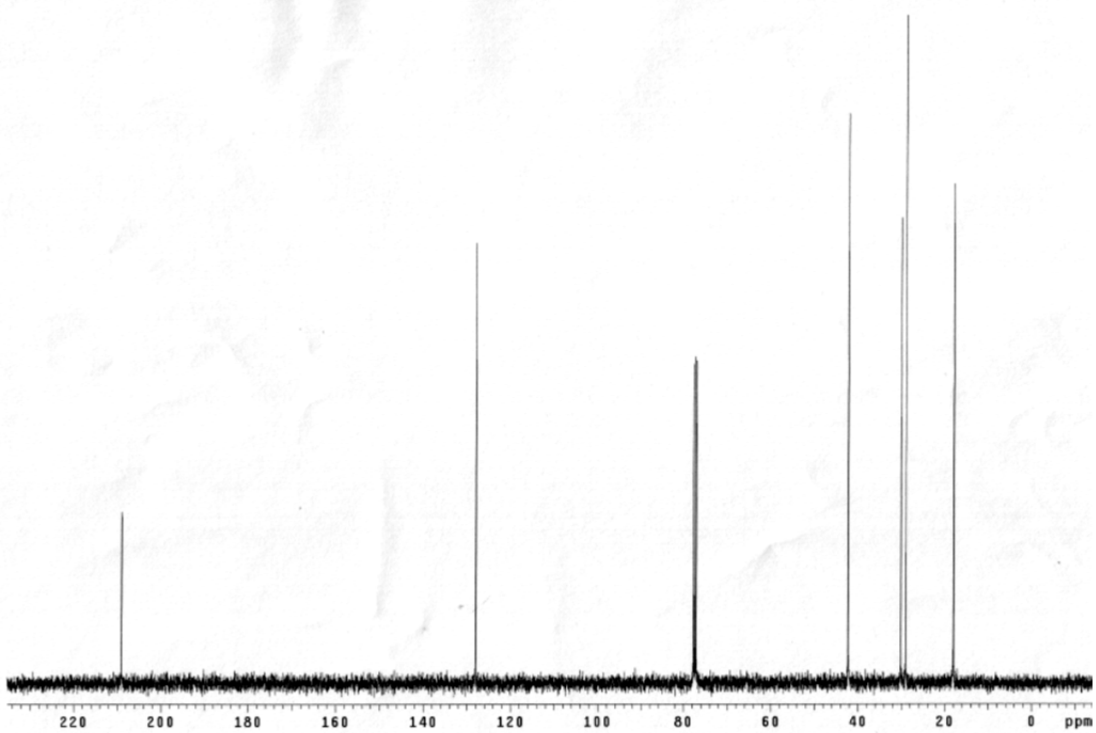
Fri Aug 12 09:40:48 2011 (GMT-05:00)
FIND PEAKS:
Spectrum: *Fri Aug 12 09:38:13 2011 (GMT-05:00)
Region: 4000.00 400.00
Absolute threshold: 92.267
Sensitivity: 50
Peak list:

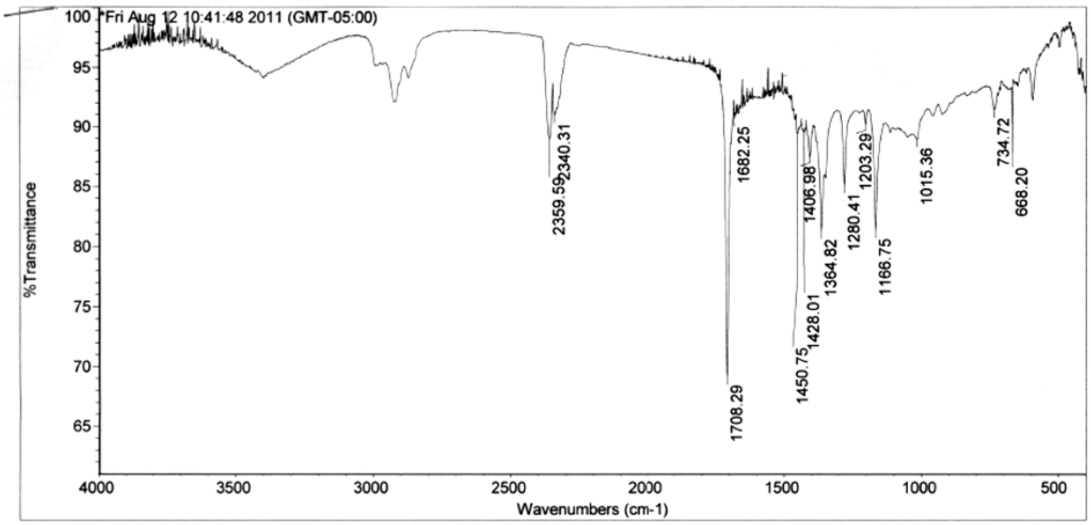
Position:	1057.85	Intensity:	87.345
Position:	1087.66	Intensity:	85.477
Position:	1142.11	Intensity:	78.215
Position:	1265.57	Intensity:	82.225
Position:	1338.19	Intensity:	88.261
Position:	1397.91	Intensity:	64.214
Position:	1462.33	Intensity:	77.139
Position:	1497.76	Intensity:	74.692


O
Me
Me
Me
O
Me

171

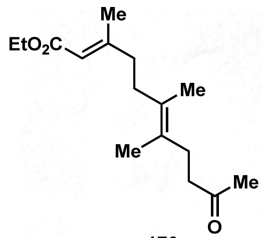

12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm


220 200 180 160 140 120 100 80 60 40 20 0 ppm

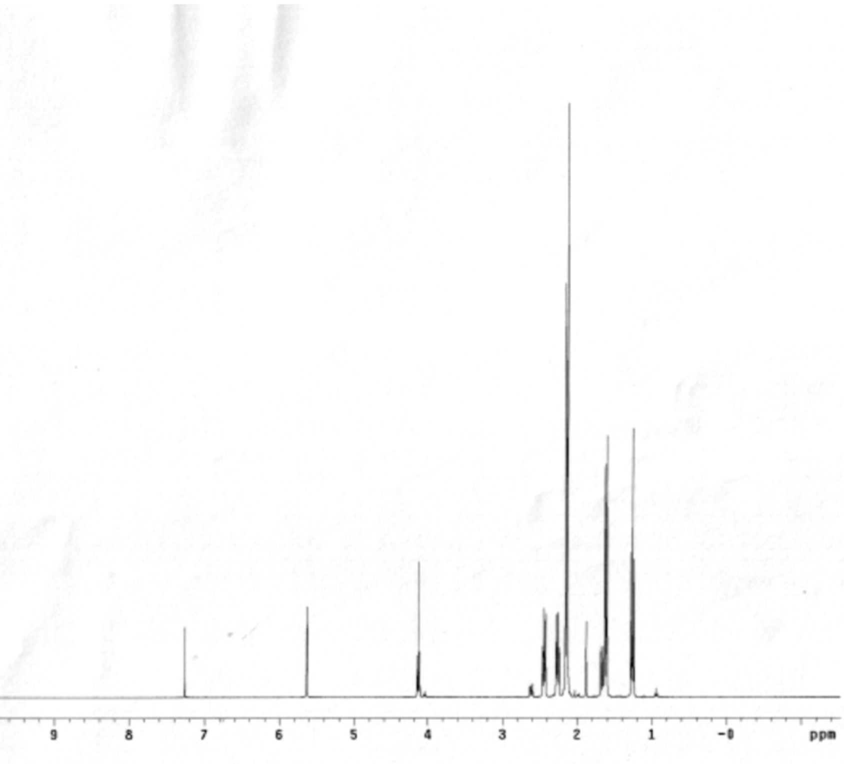


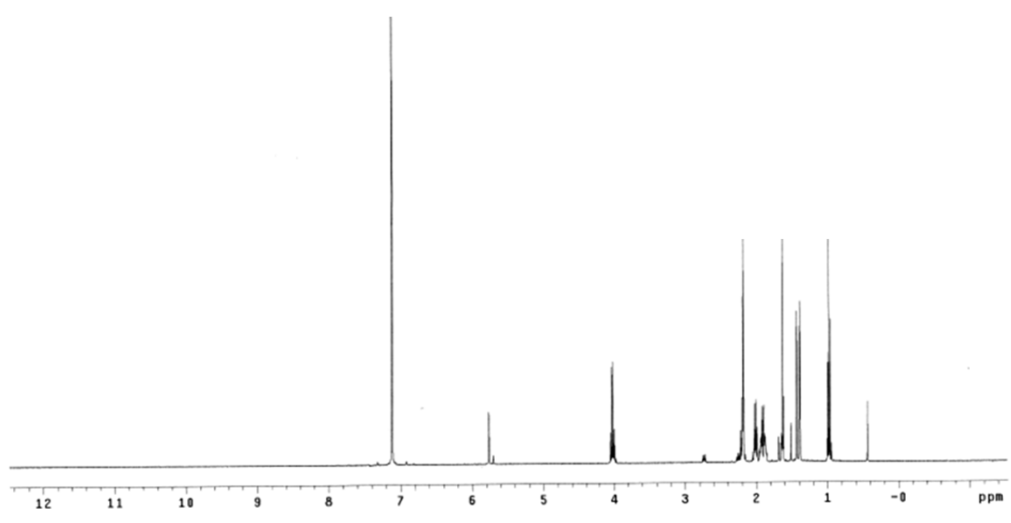
Fri Aug 12 10:45:43 2011 (GMT-05:00)
FIND PEAKS:
Spectrum: *Fri Aug 12 10:41:48 2011 (GMT-05:00)
Region: 4000.00 400.00
Absolute threshold: 91.536
Sensitivity: 50
Peak list:

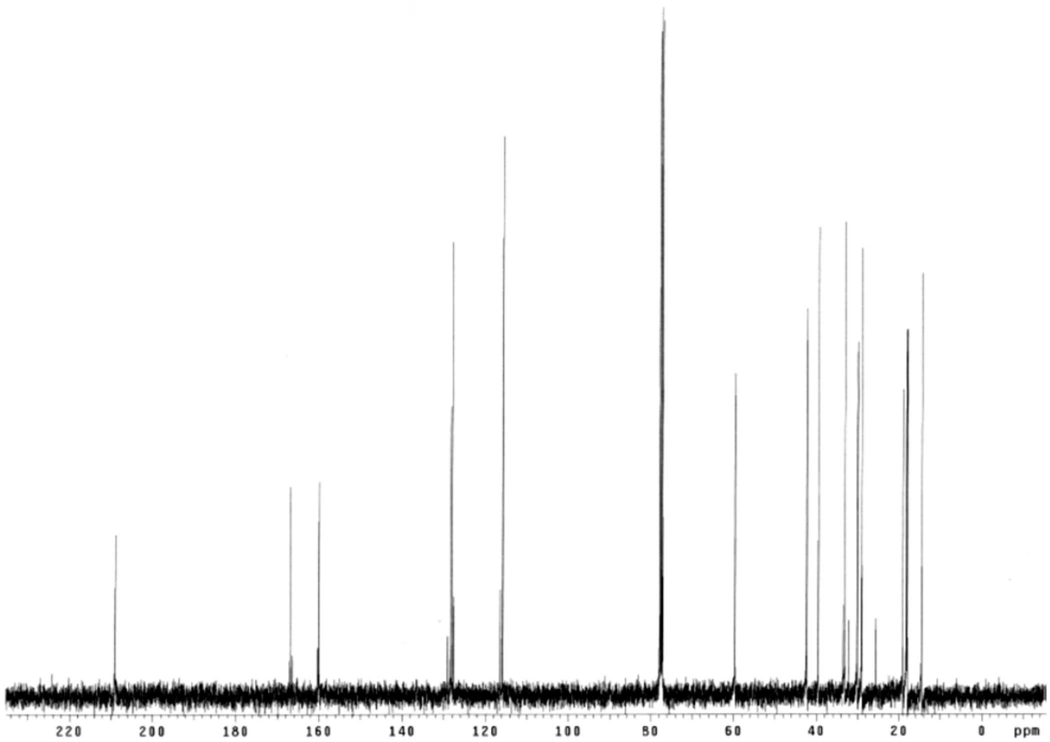
Position:	668.20	Intensity:	87.249
Position:	734.72	Intensity:	91.428
Position:	1015.36	Intensity:	88.904
Position:	1166.75	Intensity:	81.348
Position:	1203.29	Intensity:	90.144
Position:	1280.41	Intensity:	85.077
Position:	1364.82	Intensity:	81.263
Position:	1406.98	Intensity:	87.349

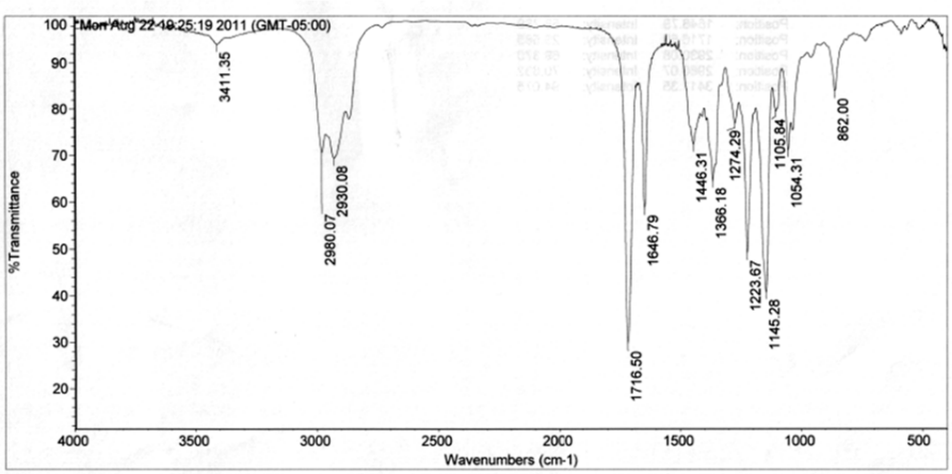

Me
EtO2C
Me
Me
Me
O

176


12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

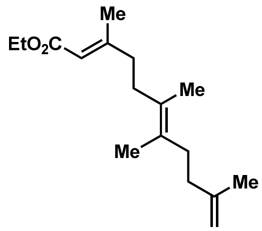

12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm



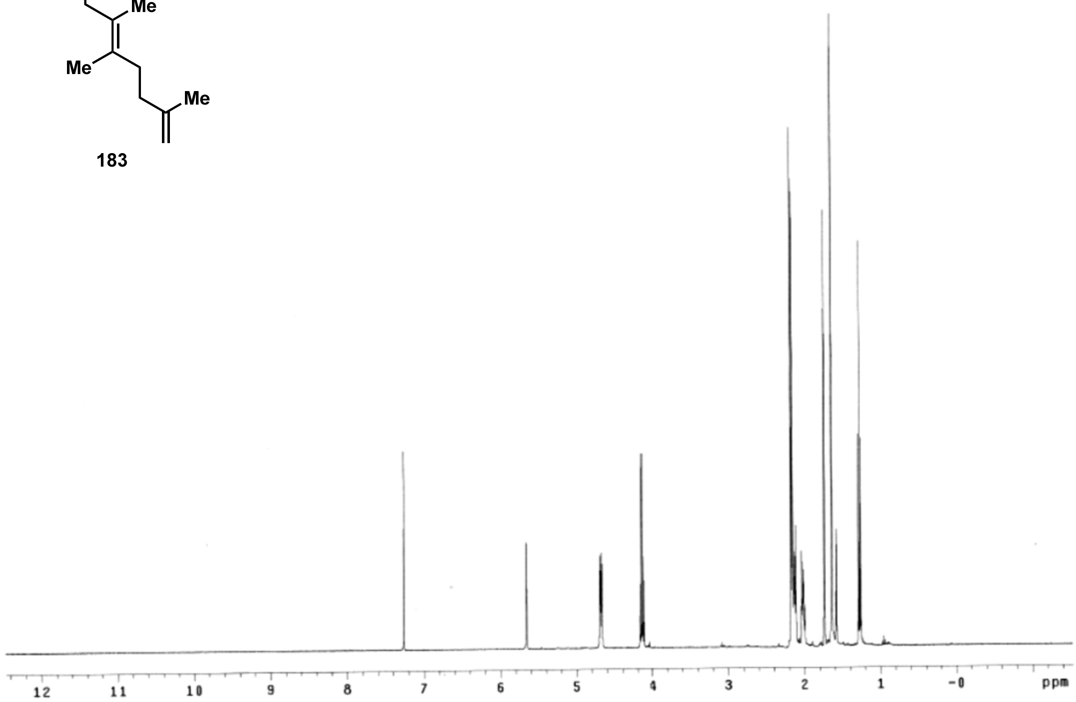


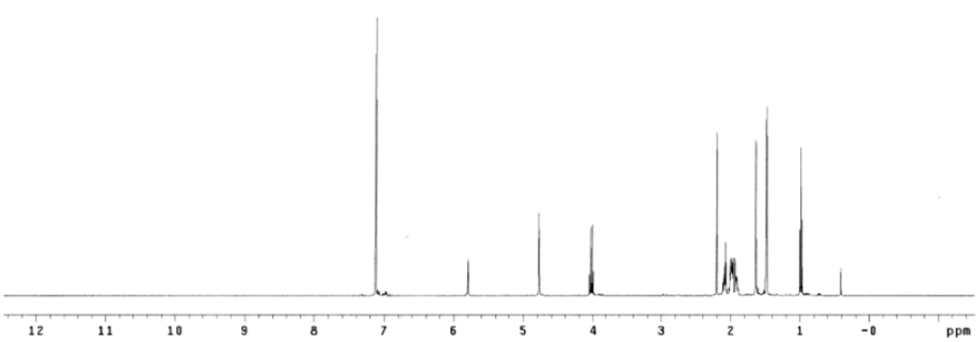
Mon Aug 22 19:28:01 2011 (GMT-05:00)
FIND PEAKS:
Spectrum: *Mon Aug 22 19:25:19 2011 (GMT-05:00)
Region: 4000.00 400.00
Absolute threshold: 94.146
Sensitivity: 50
Peak list:

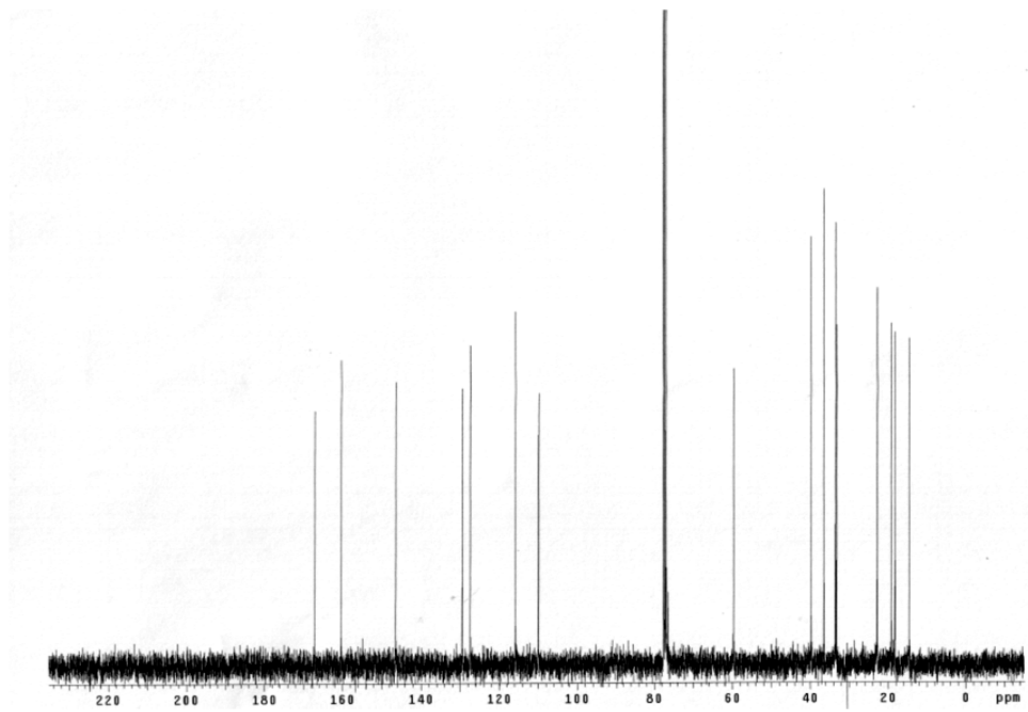
Position:	862.00	Intensity:	83.939
Position:	1054.31	Intensity:	71.139
Position:	1105.84	Intensity:	79.445
Position:	1145.28	Intensity:	40.744
Position:	1223.67	Intensity:	49.168
Position:	1274.29	Intensity:	76.862
Position:	1366.18	Intensity:	64.563
Position:	1446.31	Intensity:	72.290

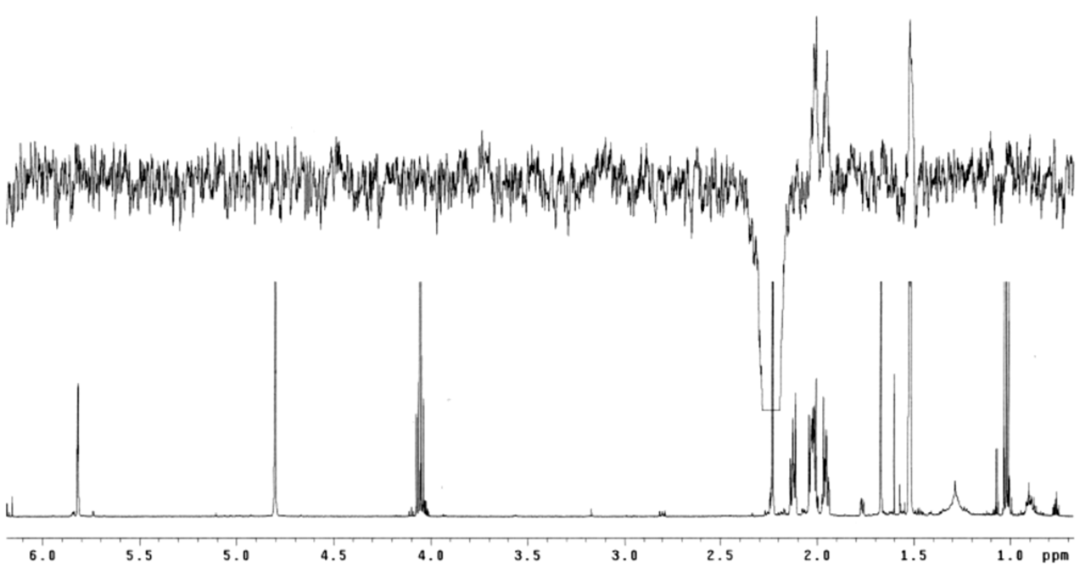

EtO2C
Me
Me
Me
Me

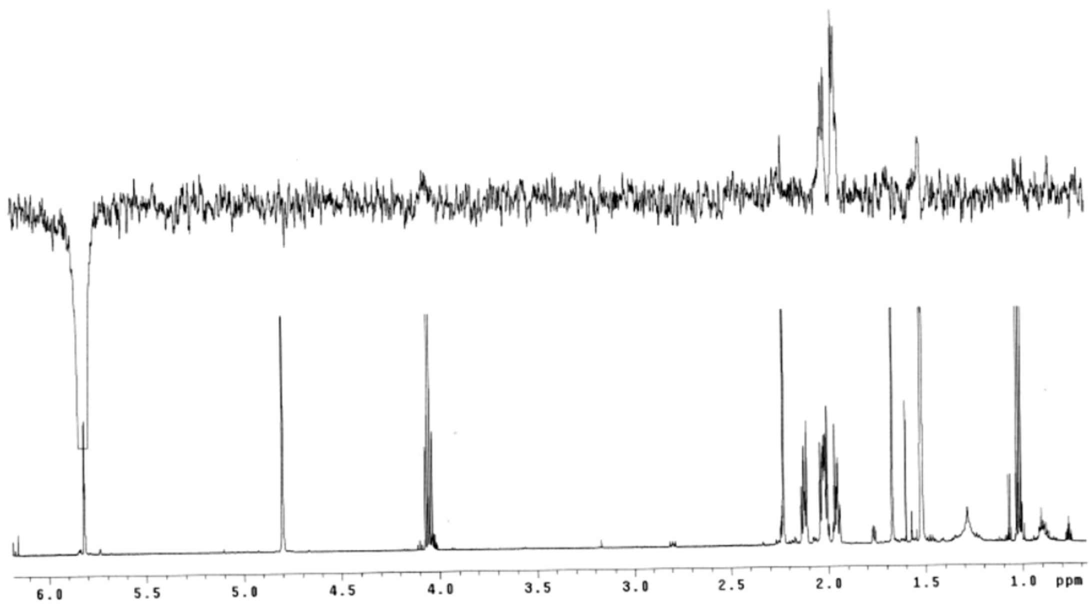
183

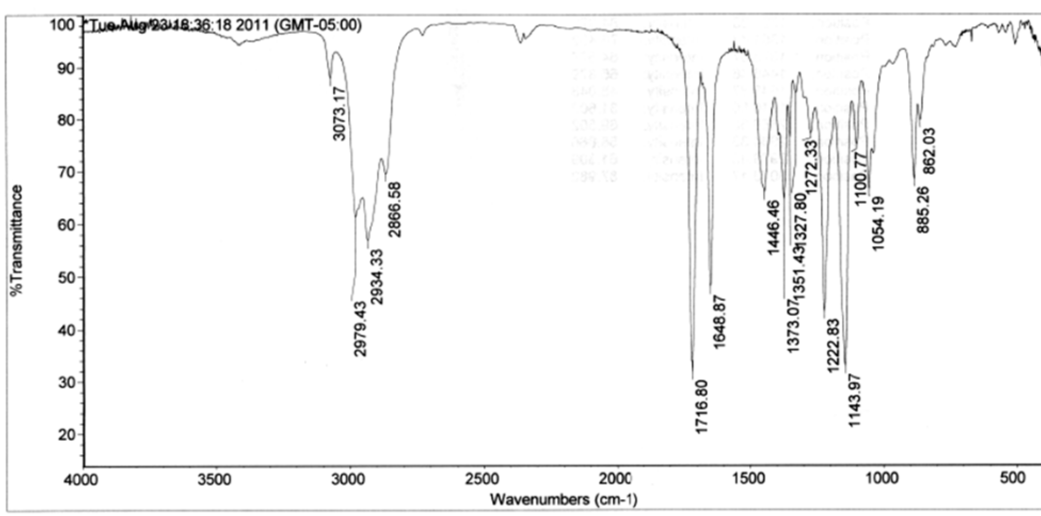

12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm


12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm


220 200 180 160 140 120 100 80 60 40 20 0 ppm

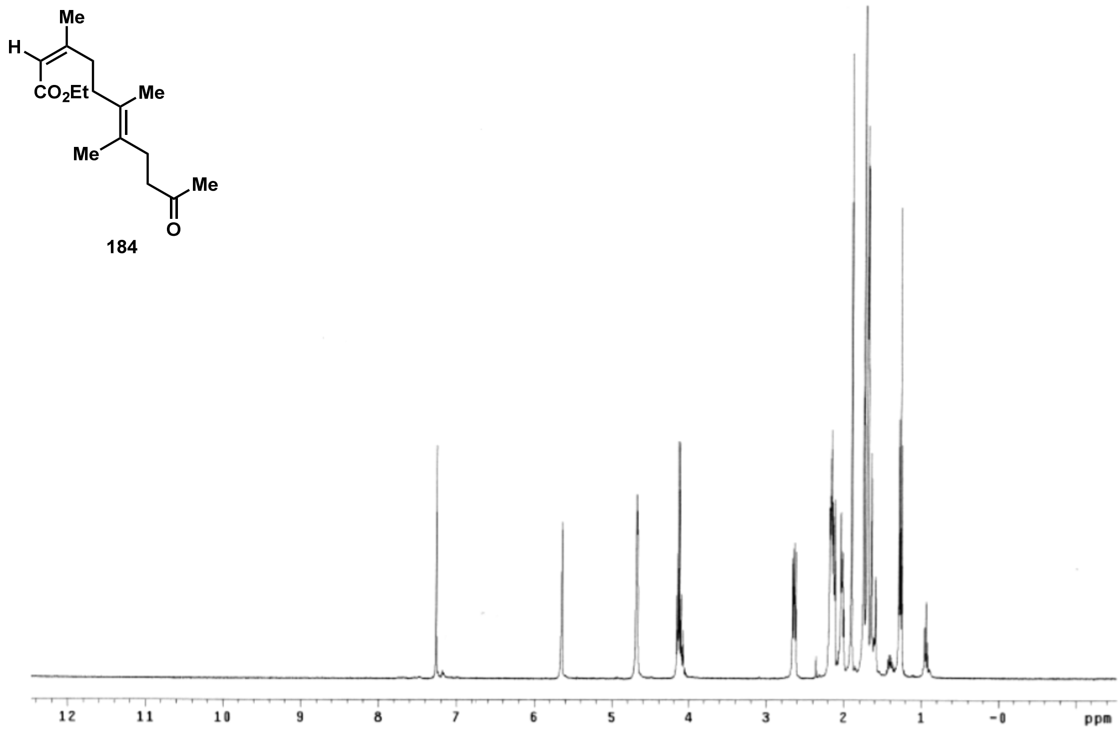

6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm





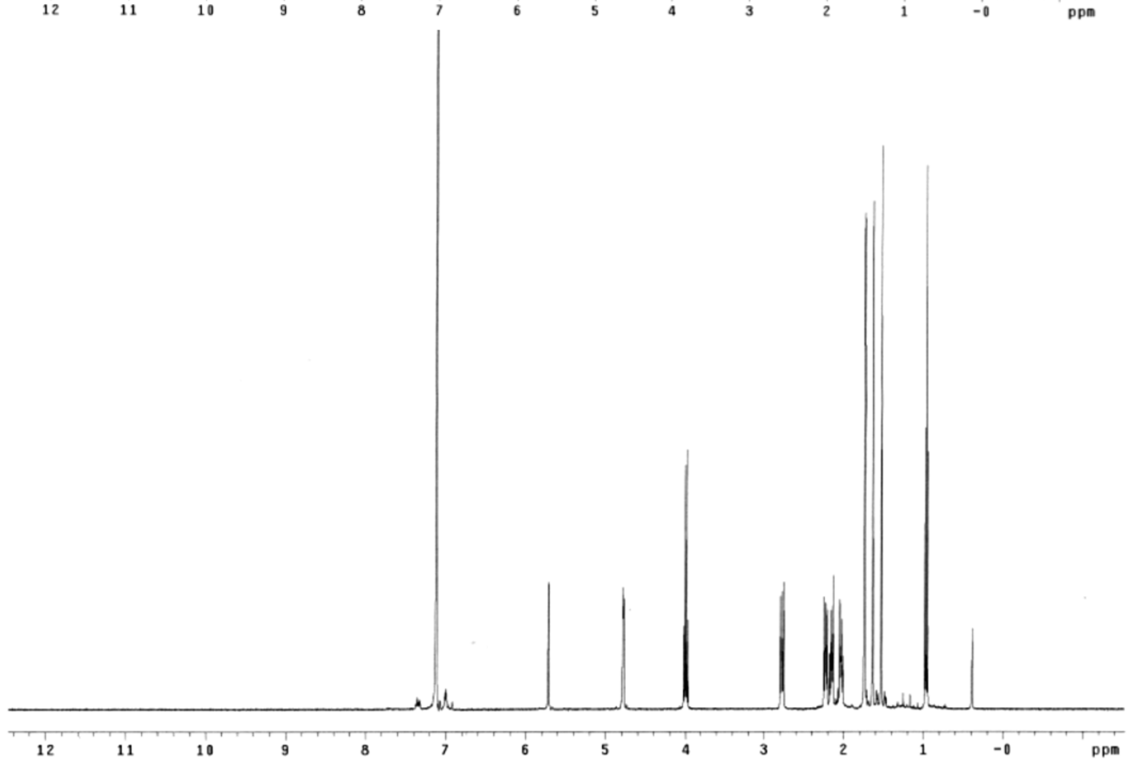
Tue Aug 23 18:38:45 2011 (GMT-05:00)
FIND PEAKS:
Spectrum: *Tue Aug 23 18:36:18 2011 (GMT-05:00)
Region: 4000.00 400.00
Absolute threshold: 92.825
Sensitivity: 50
Peak list:

Position:	404.08	Intensity:	91.470
Position:	862.03	Intensity:	79.738
Position:	885.26	Intensity:	68.475
Position:	1054.19	Intensity:	66.543
Position:	1100.77	Intensity:	75.087
Position:	1143.97	Intensity:	32.920
Position:	1222.83	Intensity:	43.352
Position:	1272.33	Intensity:	77.254

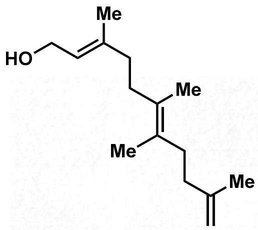


Me
H
CO2Et
Me
Me
Me
O
12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

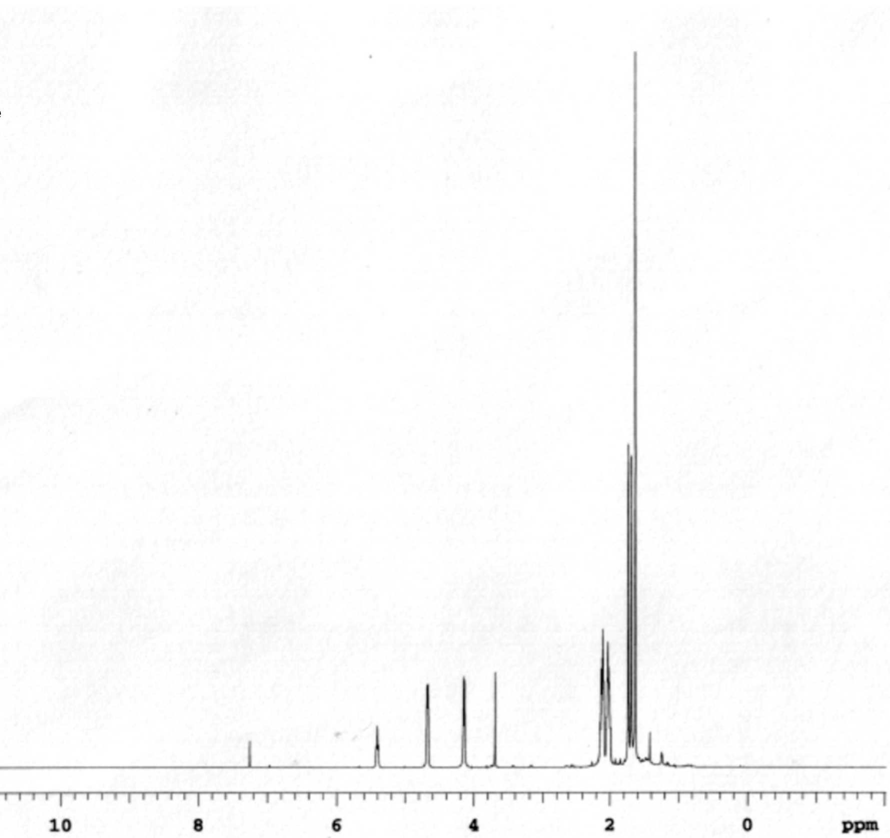
184

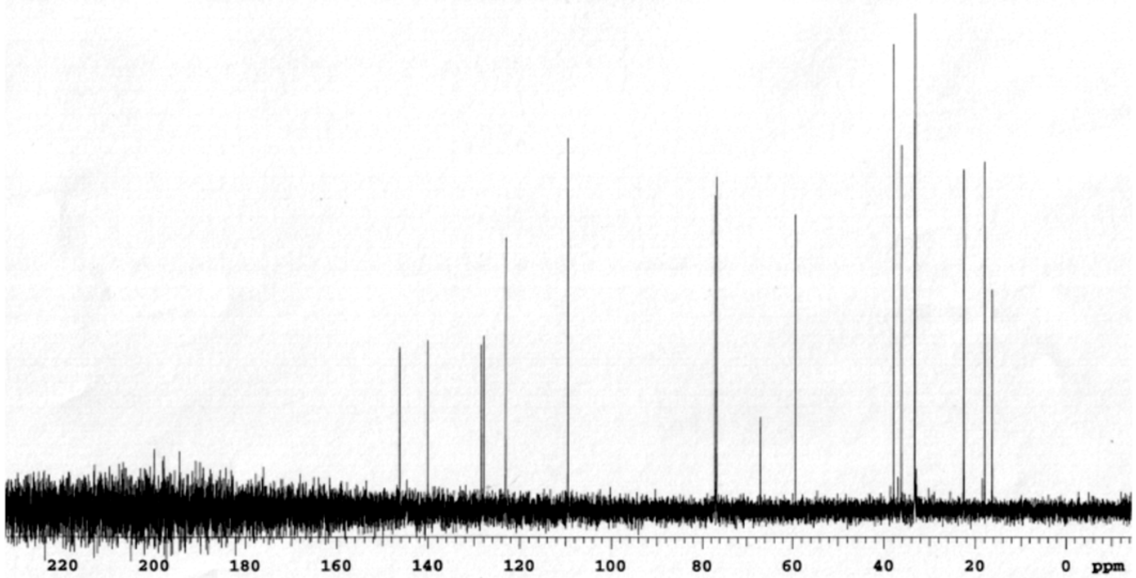


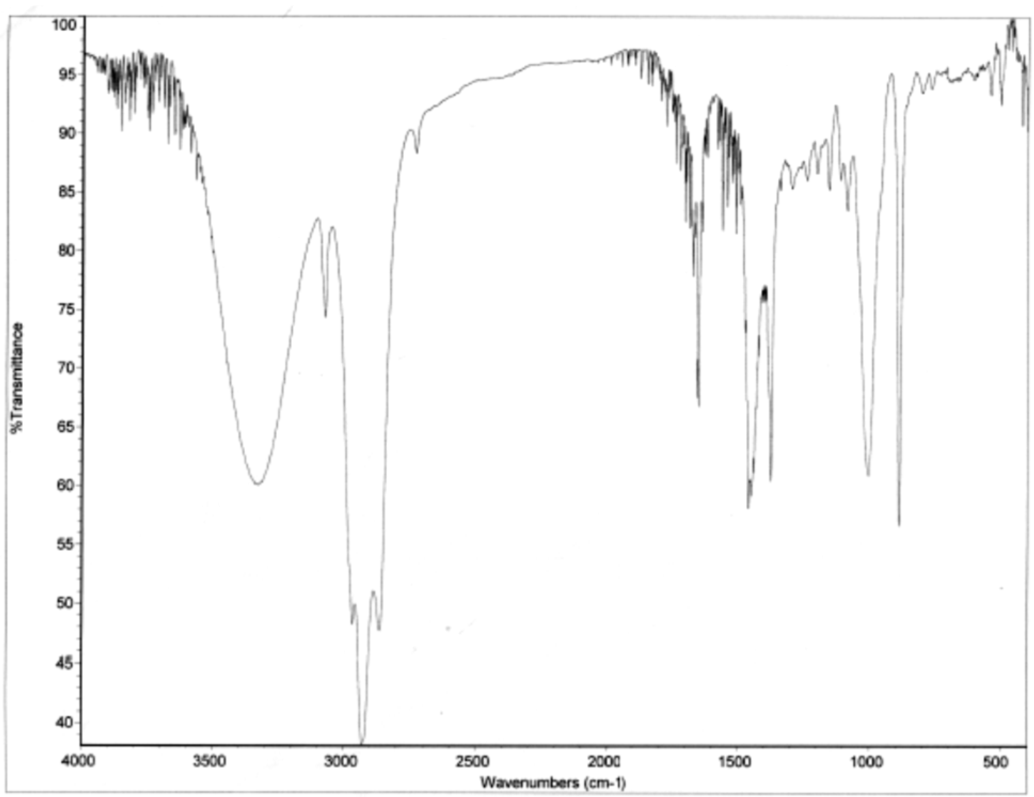
12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

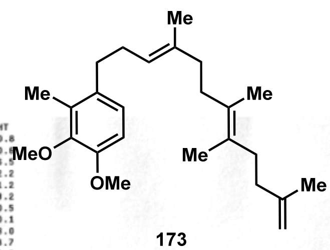

Me
HO
Me
Me
Me

172


12
10
8
6
4
2
0
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm


100
95
90
85
80
75
70
65
60
55
50
45
40
%Transmittance
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

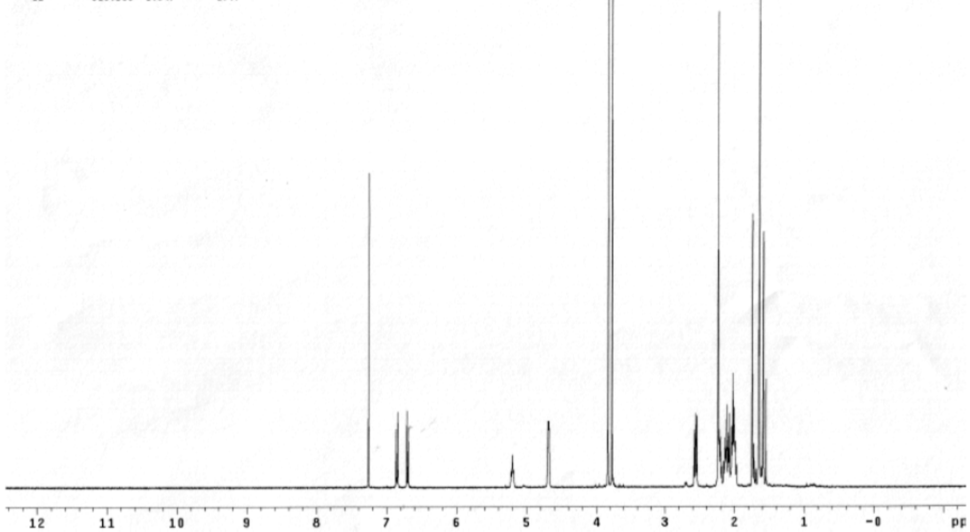


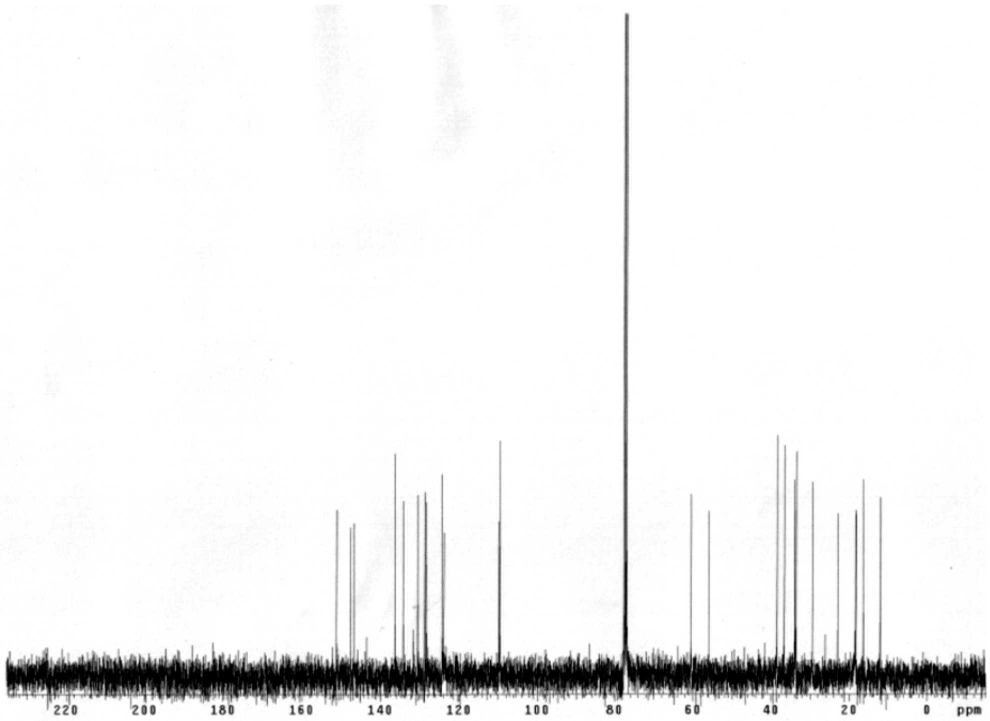
173

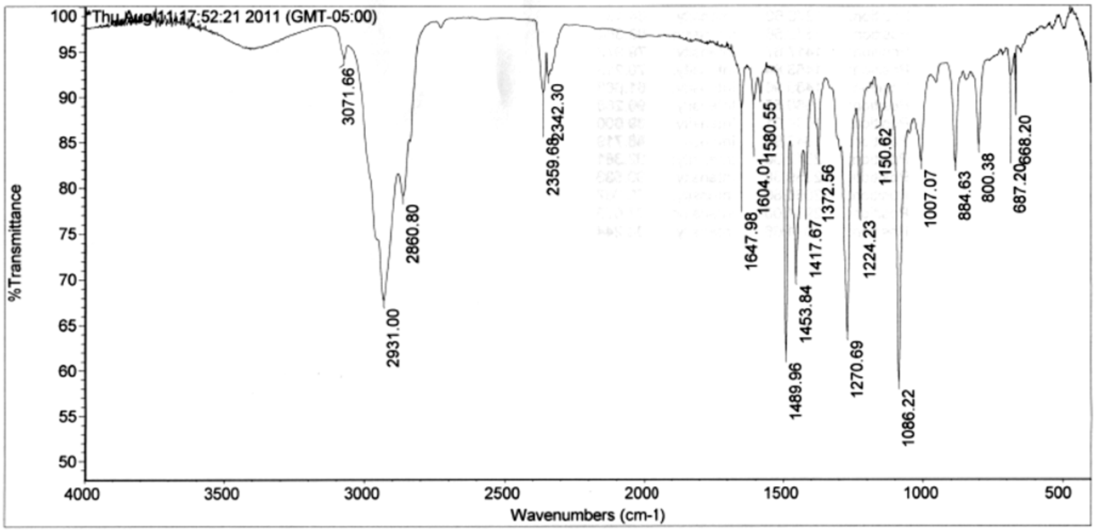
STANDARD 1H OBSERVE

Pulse Sequence: s2pul

INDEX	FREQUENCY	PPM	HEIGHT
1	2905.468	7.259	80.8
2	[illegible]	3.835	160.6
3	1512.088	3.778	156.5
4	895.582	2.237	122.2
5	846.344	2.114	21.2
6	810.099	2.024	29.2
7	804.286	2.009	20.5
8	698.970	1.746	70.1
9	662.041	1.654	53.0
10	659.306	1.647	218.7
11	636.054	1.589	65.6
12	619.300	1.547	27.7

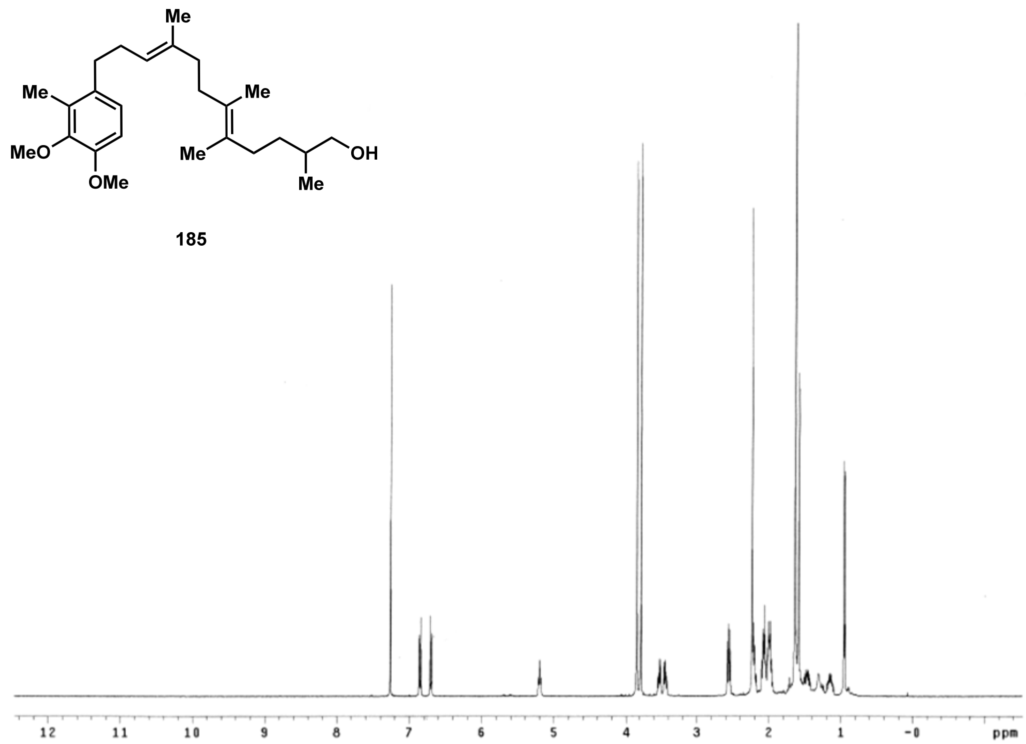


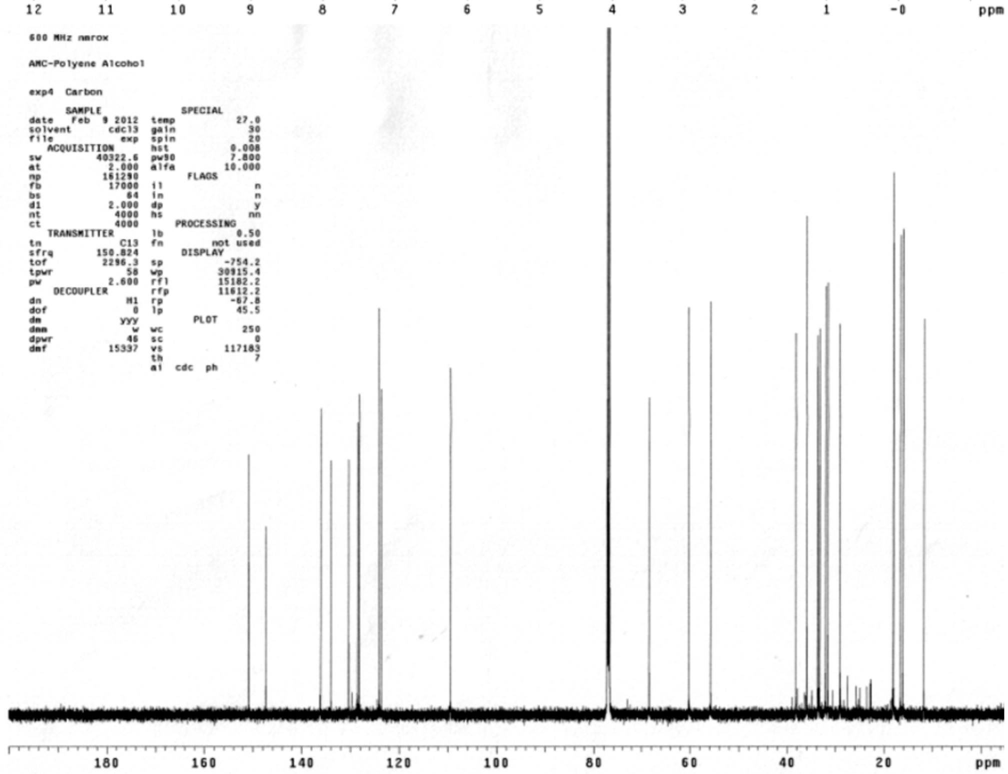


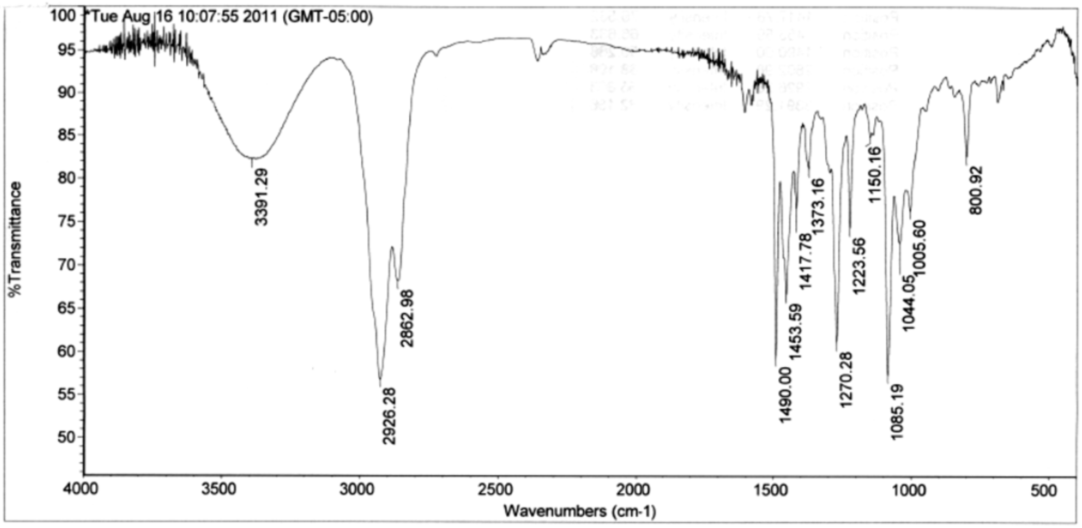


Thu Aug 11 17:57:34 2011 (GMT-05:00)
FIND PEAKS:
Spectrum: *Thu Aug 11 17:52:21 2011 (GMT-05:00)
Region: 4000.00 400.00
Absolute threshold: 94.763
Sensitivity: 50
Peak list:

Position:	668.20	Intensity:	88.789
Position:	687.20	Intensity:	92.369
Position:	800.38	Intensity:	84.656
Position:	884.63	Intensity:	82.641
Position:	1007.07	Intensity:	82.815
Position:	1086.22	Intensity:	58.662
Position:	1150.62	Intensity:	87.394
Position:	1224.23	Intensity:	77.202


Me
Me
Me
MeO
OMe
Me
OH
Me
Me
185
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm

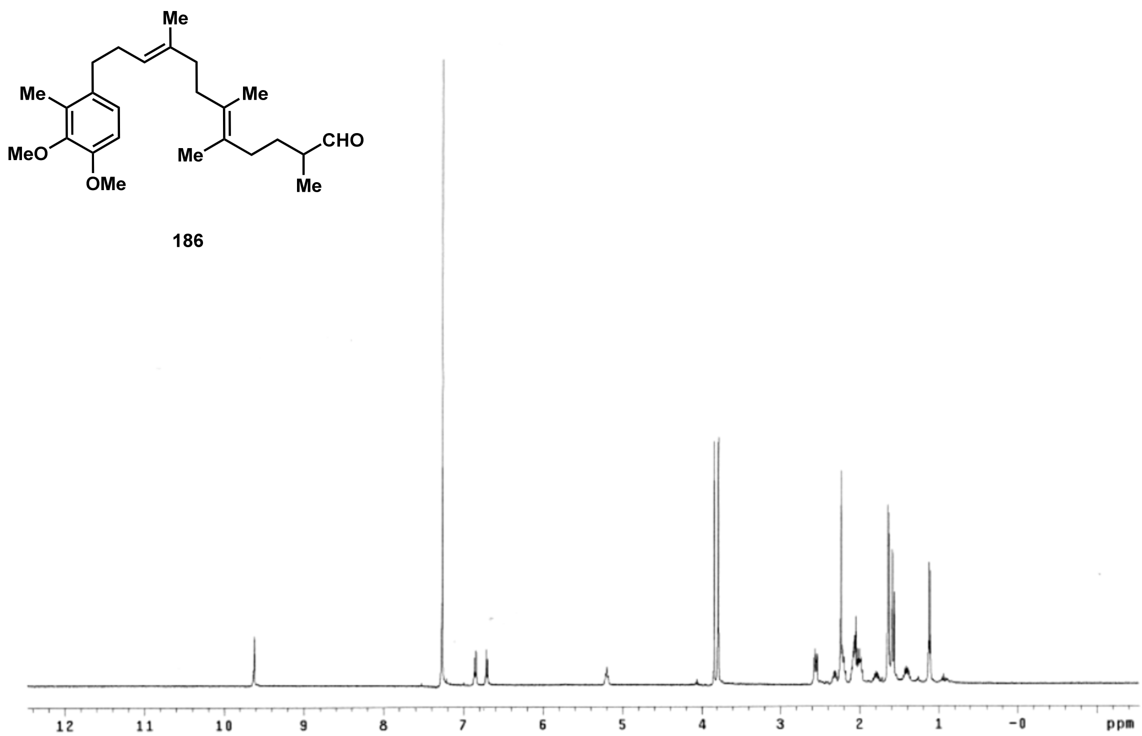

600 MHz nmrox
AMC-Polyene Alcohol
exp4 Carbon
SAMPLE
date Feb 9 2012
solvent cdcl3
file exp
ACQUISITION
sw 40322.6
at 2.000
np 161290
fb 17000
bs 64
d1 2.000
nt 4000
ct 4000
TRANSMITTER
tn C13
sfrq 150.824
tof 2296.3
tpwr 58
pw 2.600
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 46
dmf 15337
SPECIAL
temp 27.0
gain 30
spin 20
hst 0.008
pw90 7.800
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
fn not used
DISPLAY
sp -754.2
wp 30915.4
rfl 15182.2
rfp 11612.2
rp -67.8
lp 45.5
PLOT
wc 250
sc 0
vs 117183
th 7
ai cdc ph
180
160
140
120
100
80
60
40
20
ppm



Tue Aug 16 10:16:14 2011 (GMT-05:00)
FIND PEAKS:

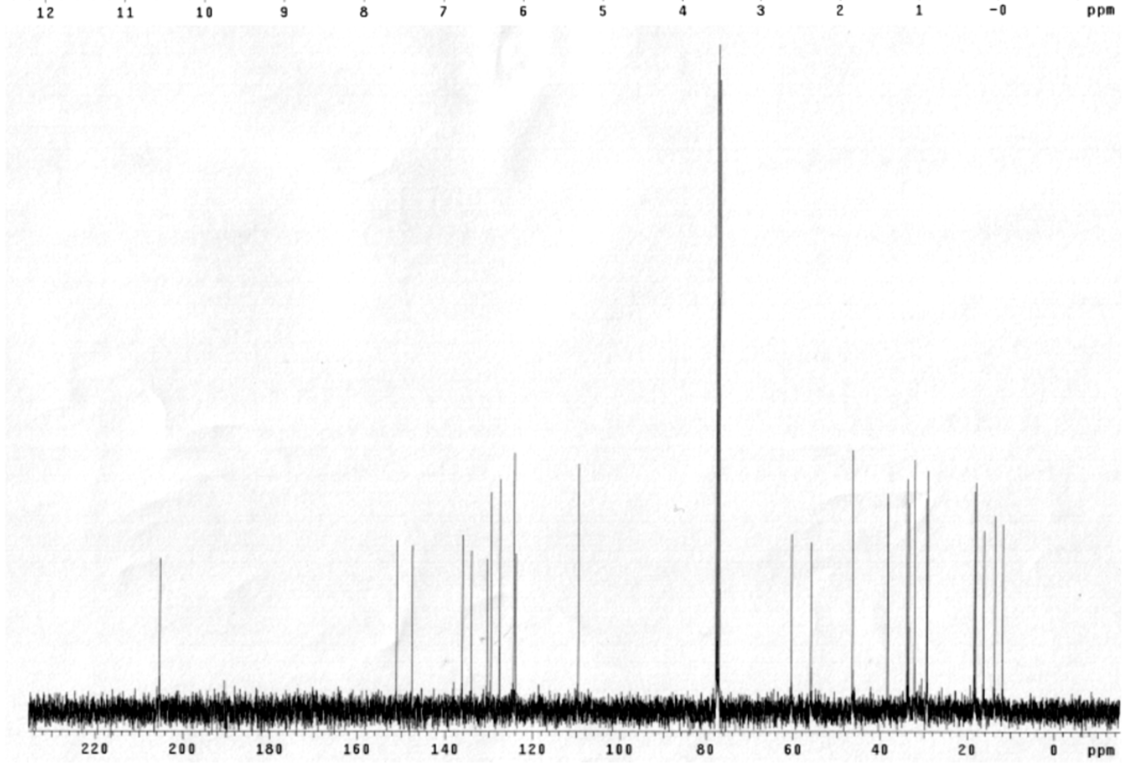
Spectrum: *Tue Aug 16 10:07:55 2011 (GMT-05:00)
Region: 4000.00 400.00
Absolute threshold: 85.023
Sensitivity: 50
Peak list:

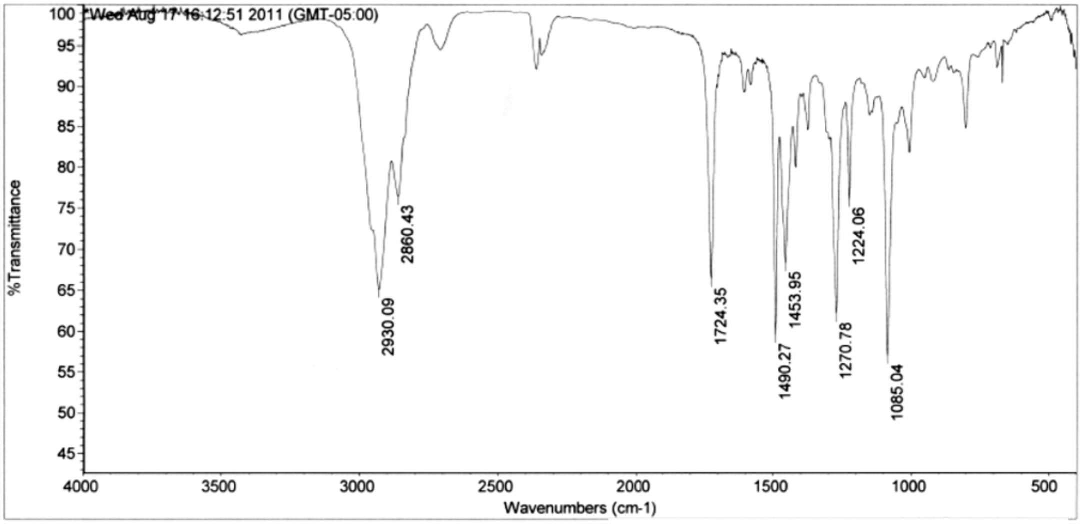
Position:	800.92	Intensity:	82.569
Position:	1005.60	Intensity:	76.289
Position:	1044.05	Intensity:	72.614
Position:	1085.19	Intensity:	57.244
Position:	1150.16	Intensity:	84.823
Position:	1223.56	Intensity:	74.238
Position:	1270.28	Intensity:	61.054
Position:	1373.16	Intensity:	81.159


Me
Me
Me
MeO
OMe
CHO
Me
Me

186

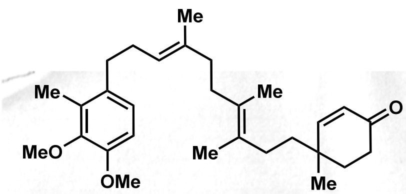
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm

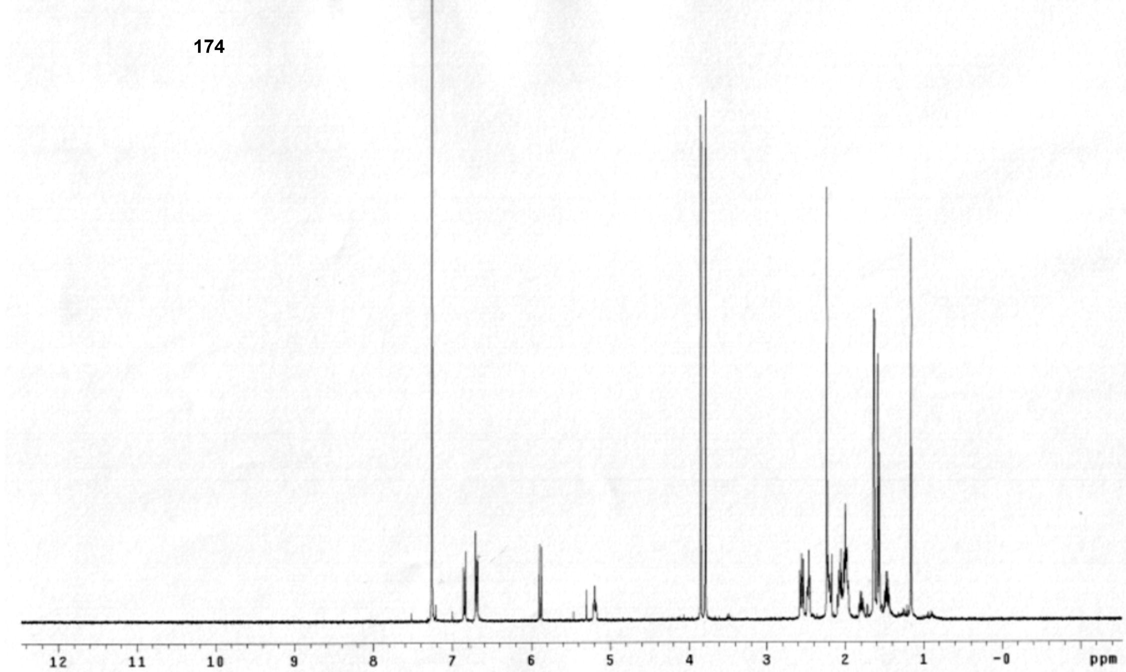


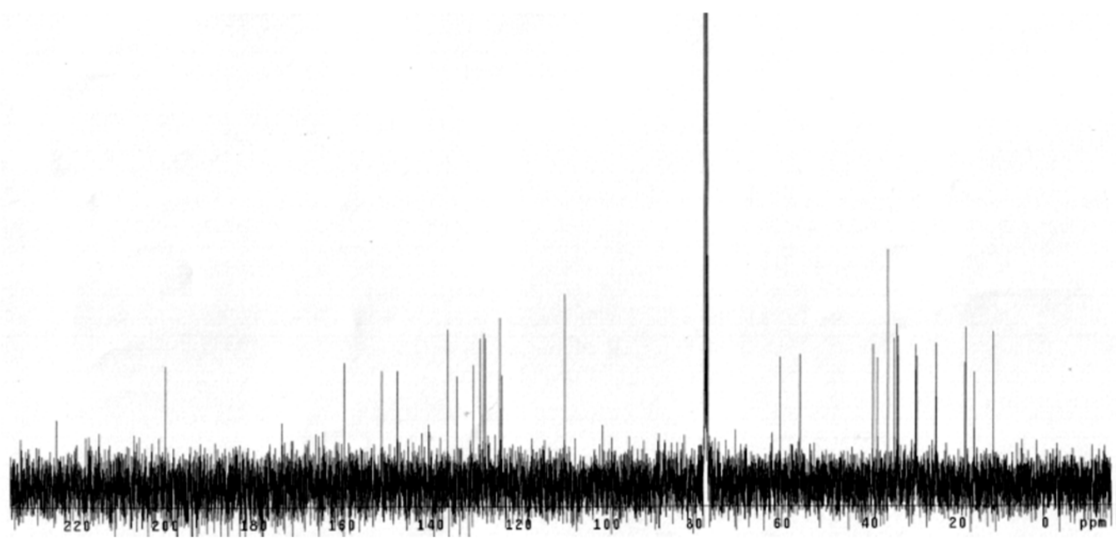
Wed Aug 17 16:15:06 2011 (GMT-05:00)
FIND PEAKS:

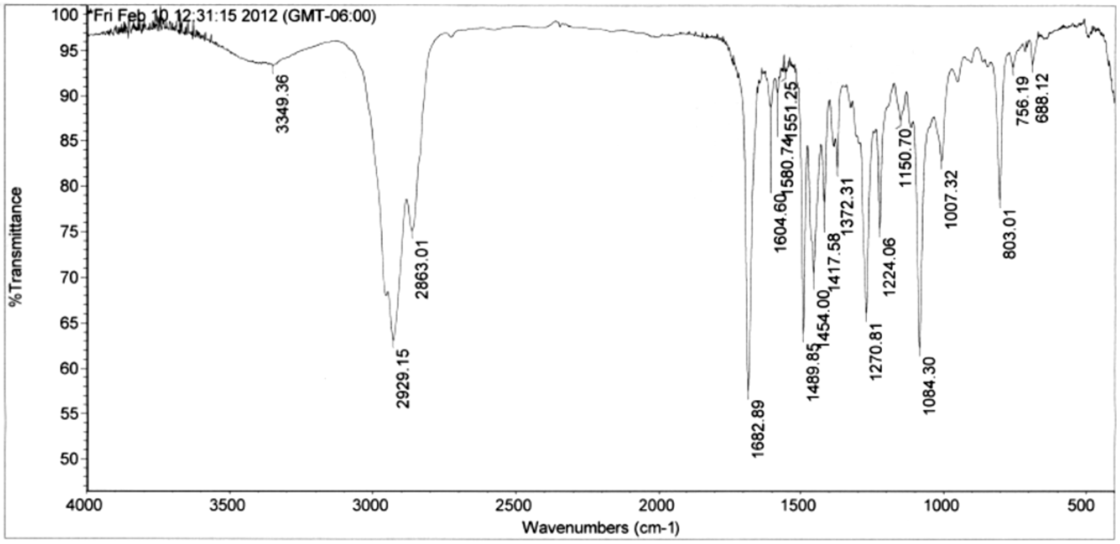
Spectrum:	*Wed Aug 17 16:12:51 2011 (GMT-05:00)			
Region:	4000.00	400.00		
Absolute threshold:	78.477			
Sensitivity:	50			
Peak list:				
	Position:	1085.04	Intensity:	56.939
	Position:	1224.06	Intensity:	76.009
	Position:	1270.78	Intensity:	62.123
	Position:	1453.95	Intensity:	68.346
	Position:	1490.27	Intensity:	59.436
	Position:	1724.35	Intensity:	66.350
	Position:	2860.43	Intensity:	76.412
	Position:	2930.09	Intensity:	65.065


Me
Me
Me
MeO
Me
OMe
Me
O

174


12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

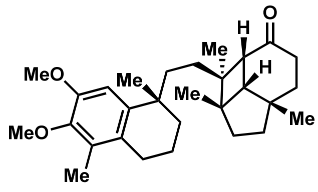

220 200 180 160 140 120 100 80 60 40 20 0 ppm



Fri Feb 10 12:33:26 2012 (GMT-06:00)
FIND PEAKS:

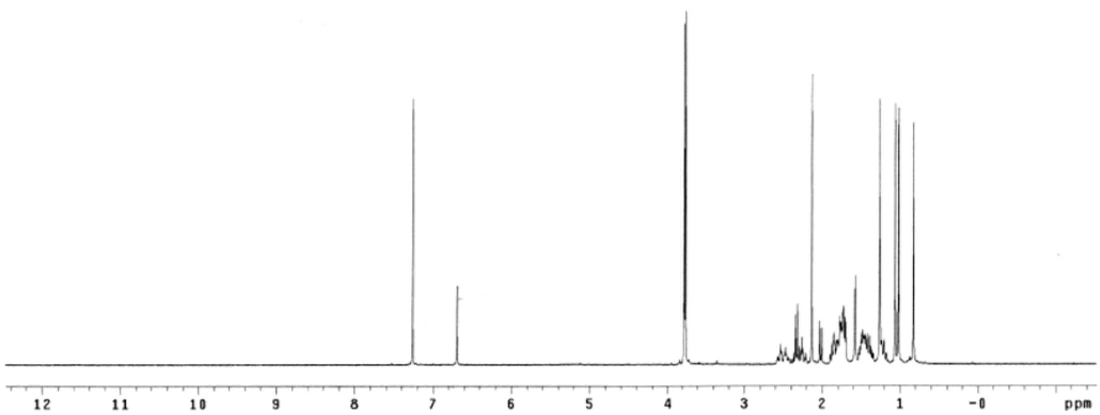
Spectrum: *Fri Feb 10 12:31:15 2012 (GMT-06:00)
Region: 4000.00 400.00
Absolute threshold: 94.445
Sensitivity: 50
Peak list:

Position:	688.12	Intensity:	93.513
Position:	756.19	Intensity:	93.218
Position:	803.01	Intensity:	78.503
Position:	1007.32	Intensity:	82.770
Position:	1084.30	Intensity:	62.223
Position:	1150.70	Intensity:	87.323
Position:	1224.06	Intensity:	75.312
Position:	1270.81	Intensity:	66.045

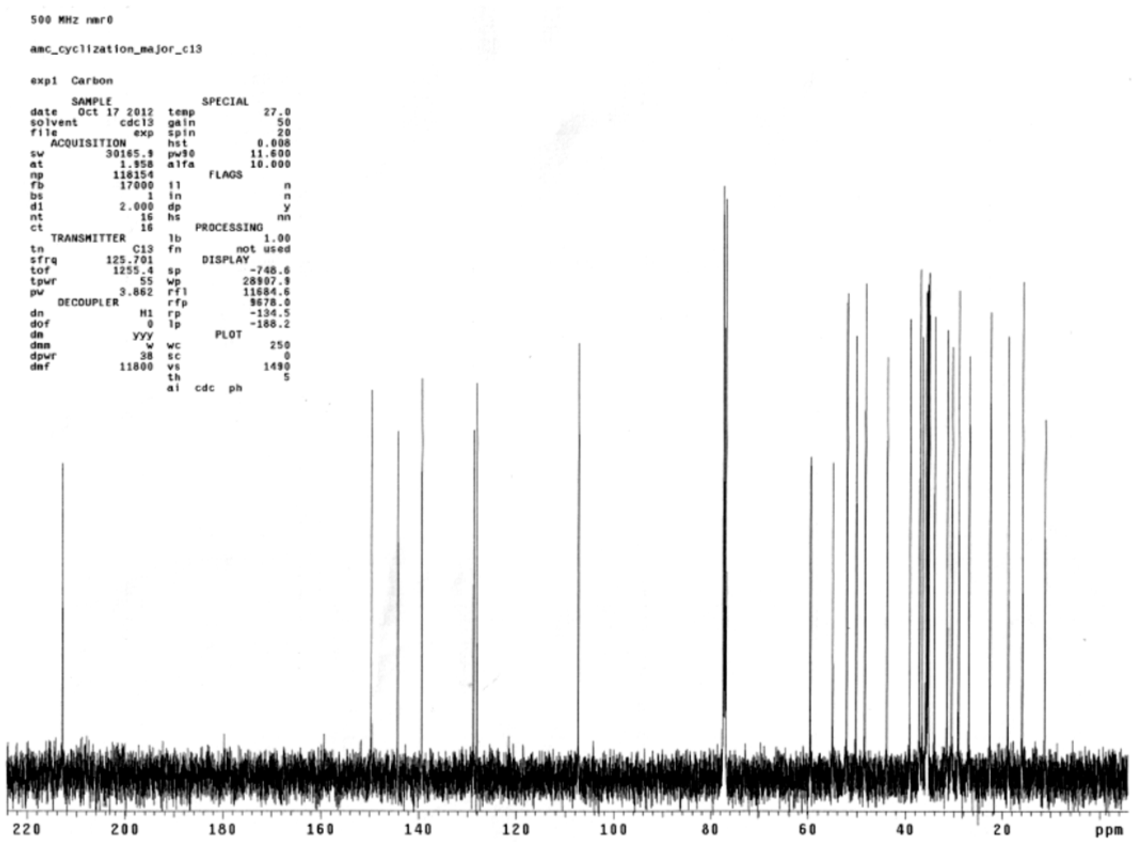


MeO
MeO
Me
Me
Me
H
O
H
Me
Me

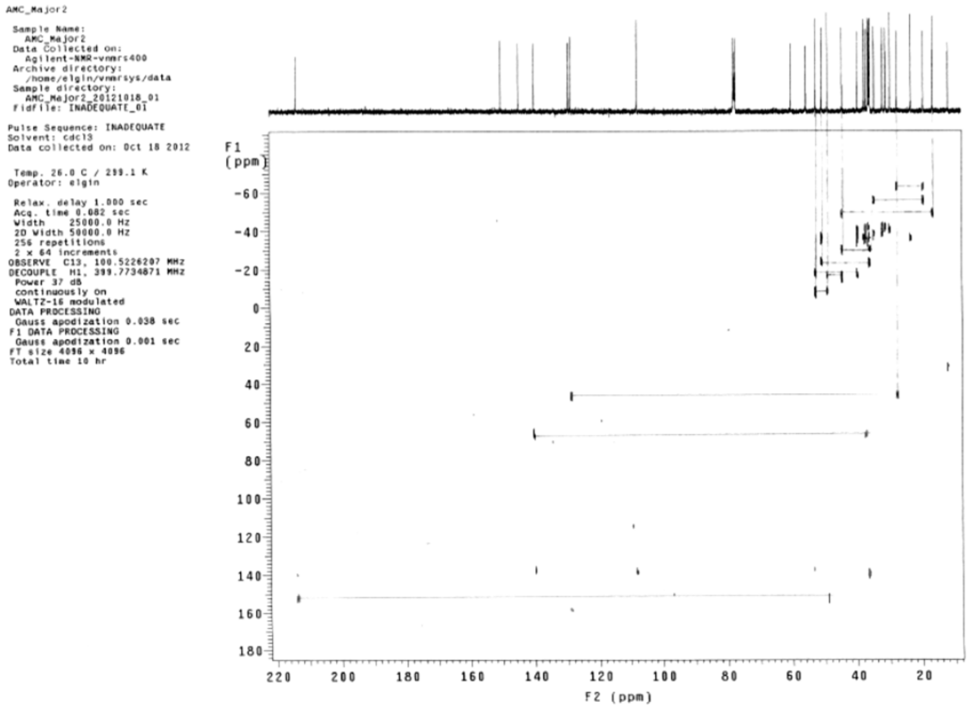
188 (Major)

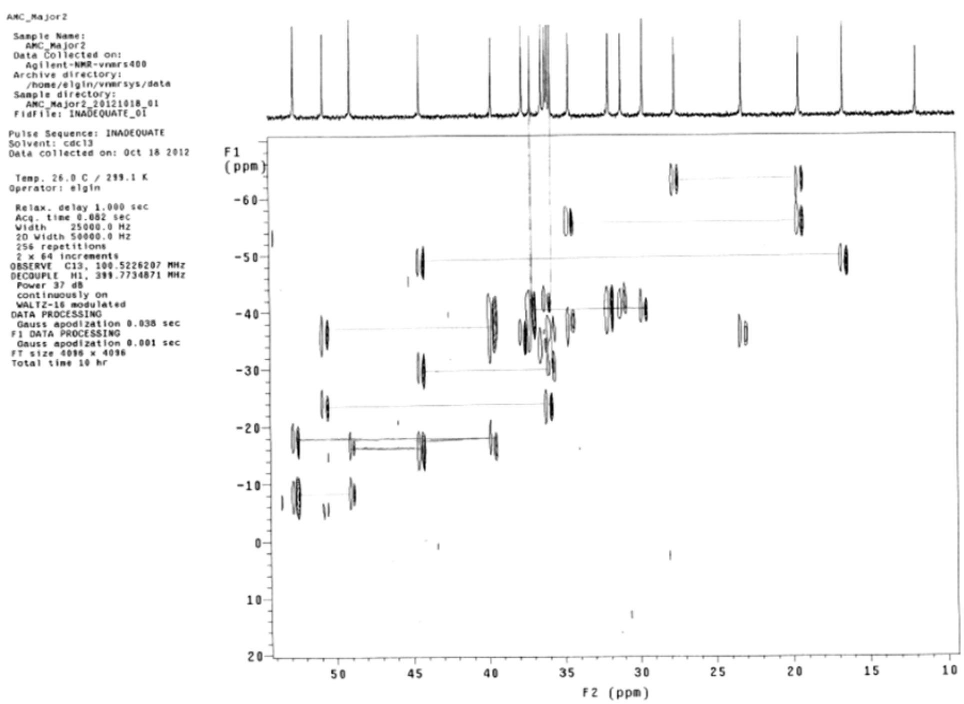


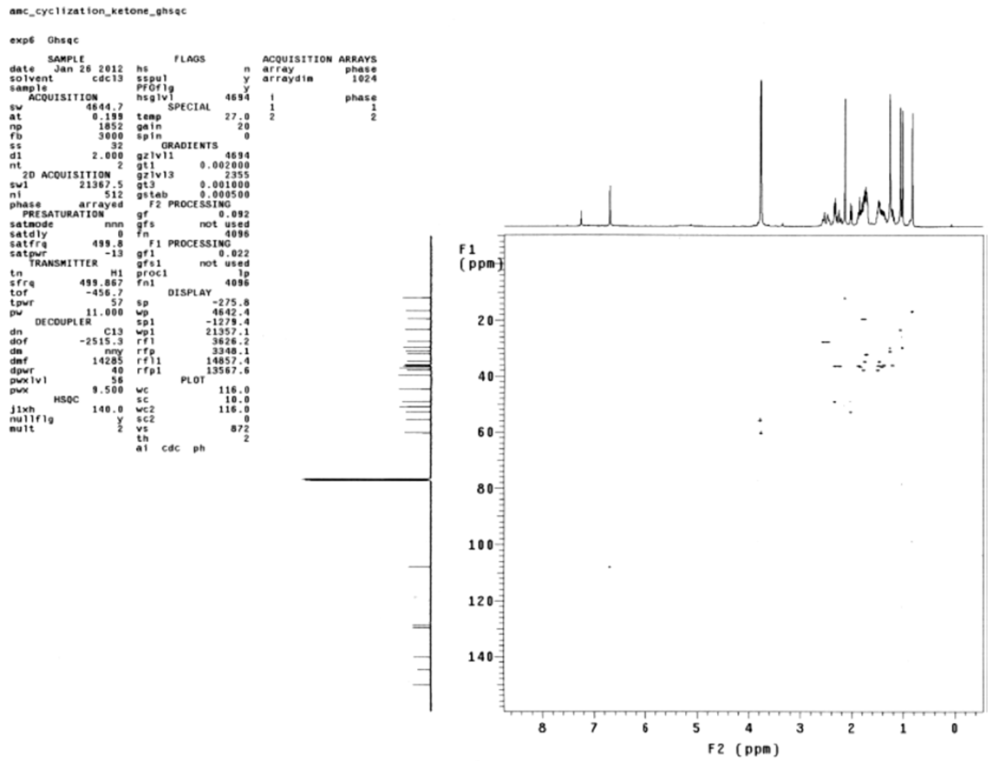
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm

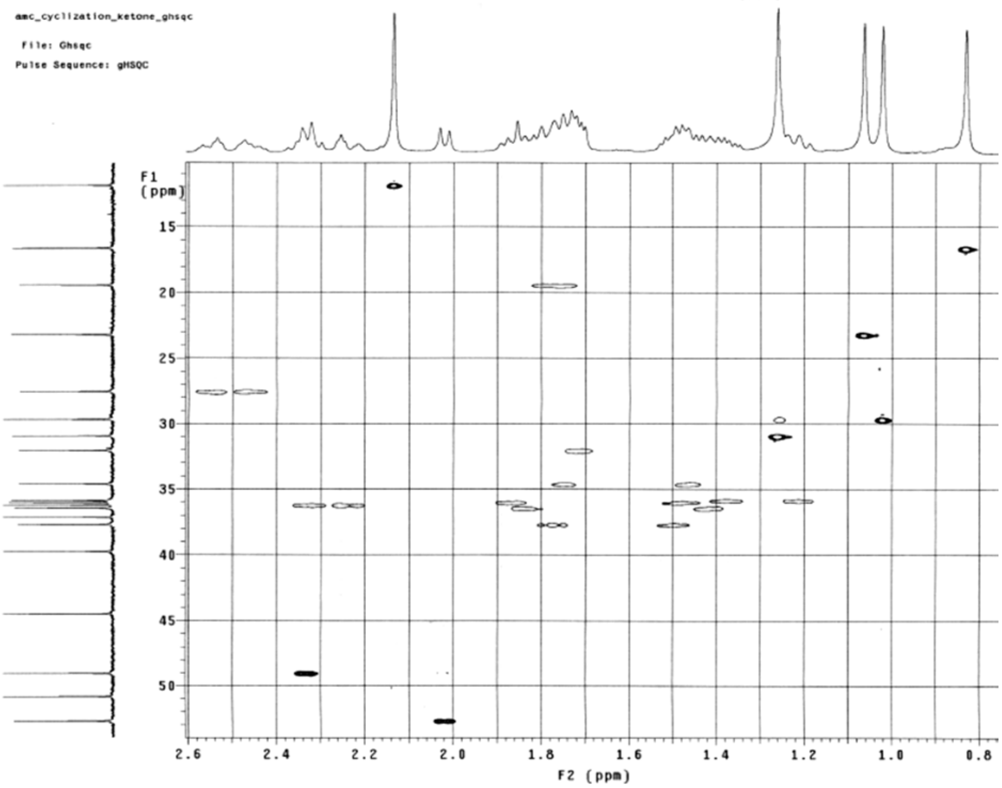


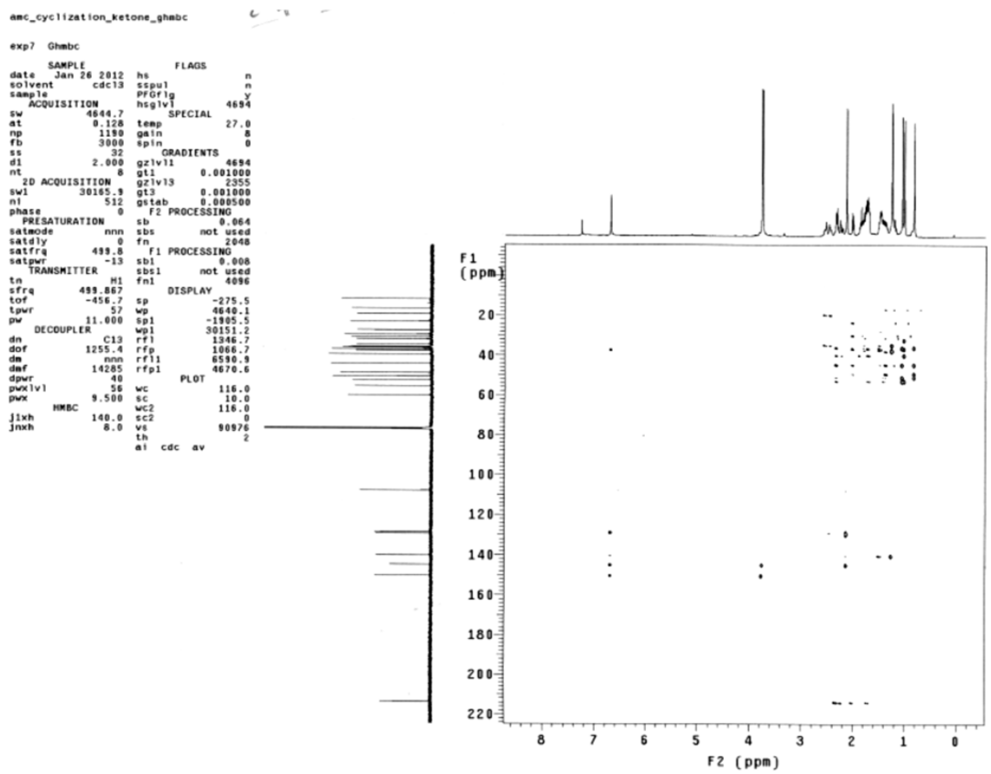
500 MHz nmr0
amc_cyclization_major_c13
exp1 Carbon
SAMPLE
date Oct 17 2012
solvent cdcl3
file exp
ACQUISITION
sw 30165.9
at 1.958
np 118154
fb 17000
bs 1
d1 2.000
nt 16
ct 16
TRANSMITTER
tn C13
sfrq 125.701
tof 1255.4
tpwr 55
pw 3.862
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 38
dmf 11800
SPECIAL
temp 27.0
gain 50
spin 20
hst 0.008
pw90 11.600
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -748.6
wp 28907.9
rfl 11684.6
rfp 9678.0
rp -134.5
lp -188.2
PLOT
wc 250
sc 0
vs 1490
th 5
ai cdc ph
220
200
180
160
140
120
100
80
60
40
20
ppm

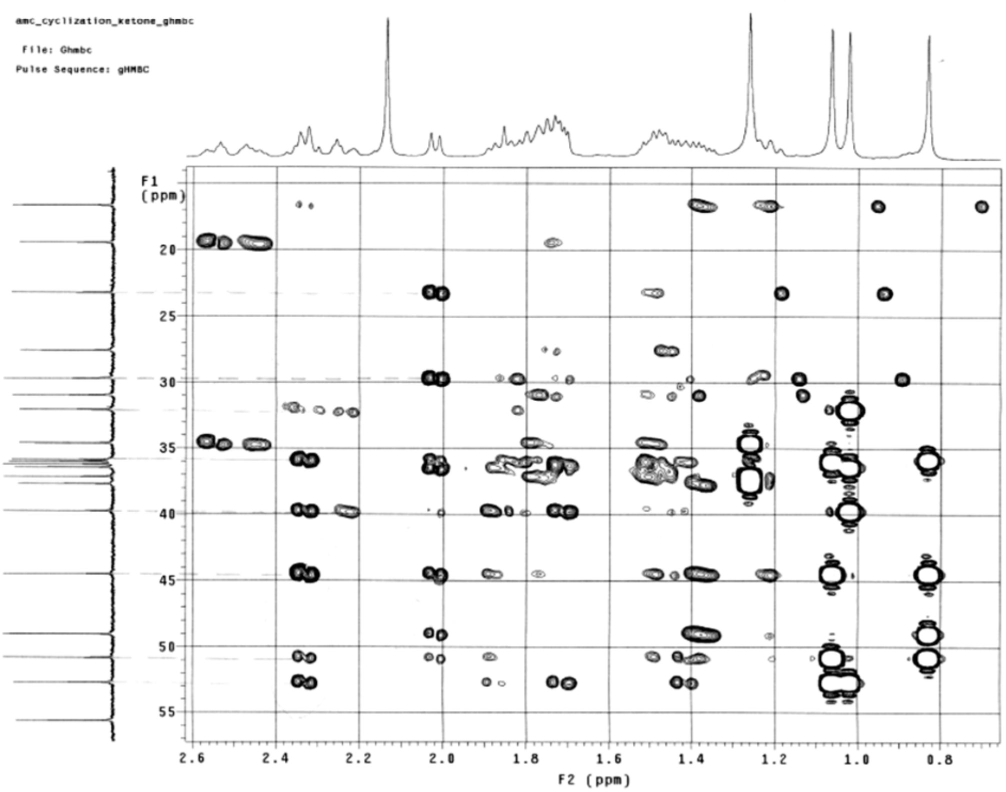

AMC_Major2
Sample Name:
AMC_Major2
Data Collected on:
Agilent-NMR-vnmrs400
Archive directory:
/home/elgin/vnmrsys/data
Sample directory:
AMC_Major2_20121018_01
Fidfile: INADEQUATE_01
Pulse Sequence: INADEQUATE
Solvent: cdcl3
Data collected on: Oct 18 2012
Temp. 26.0 C / 299.1 K
Operator: elgin
Relax. delay 1.000 sec
Acq. time 0.082 sec
Width 25000.0 Hz
2D Width 50000.0 Hz
256 repetitions
2 x 64 increments
OBSERVE C13, 100.5226207 MHz
DECOUPLE H1, 399.7734871 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Gauss apodization 0.038 sec
F1 DATA PROCESSING
Gauss apodization 0.001 sec
FT size 4096 x 4096
Total time 10 hr
F1 (ppm)
F2 (ppm)

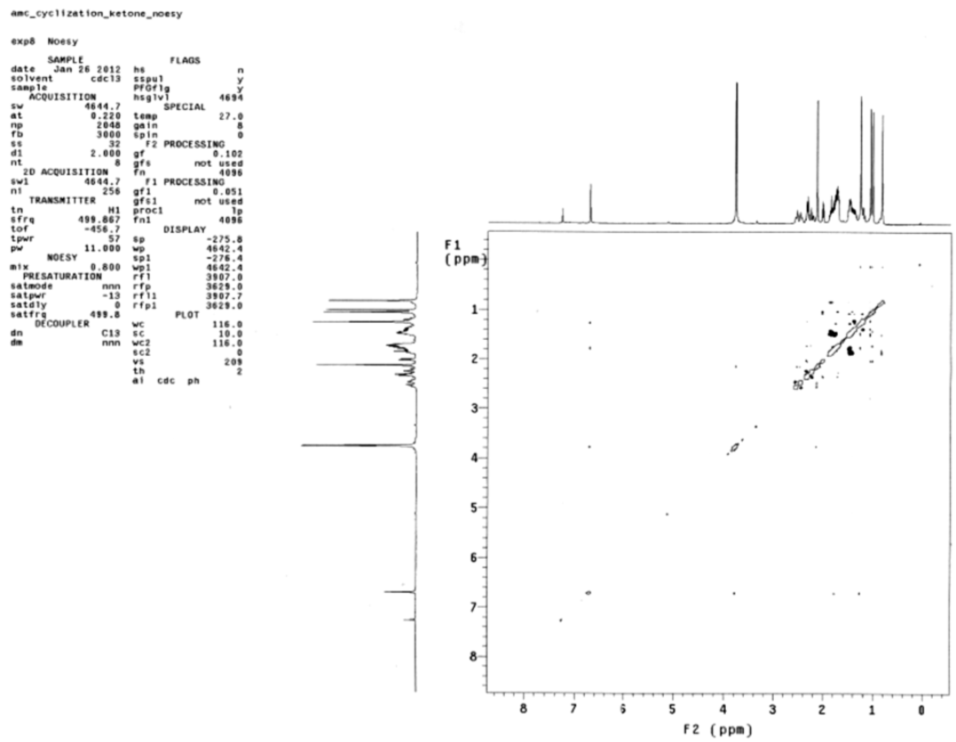

AMC_Major2
Sample Name:
AMC_Major2
Data Collected on:
Agilent-NMR-vnmrs400
Archive directory:
/home/elgin/vnmrsys/data
Sample directory:
AMC_Major2_20121018_01
Fidfile: INADEQUATE_01
Pulse Sequence: INADEQUATE
Solvent: cdcl3
Data collected on: Oct 18 2012
Temp. 26.0 C / 299.1 K
Operator: elgin
Relax. delay 1.000 sec
Acq. time 0.082 sec
Width 25000.0 Hz
2D Width 50000.0 Hz
256 repetitions
2 x 64 increments
OBSERVE C13, 100.5226207 MHz
DECOUPLE H1, 399.7734871 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Gauss apodization 0.038 sec
F1 DATA PROCESSING
Gauss apodization 0.001 sec
FT size 4096 x 4096
Total time 10 hr
F1 (ppm)
F2 (ppm)

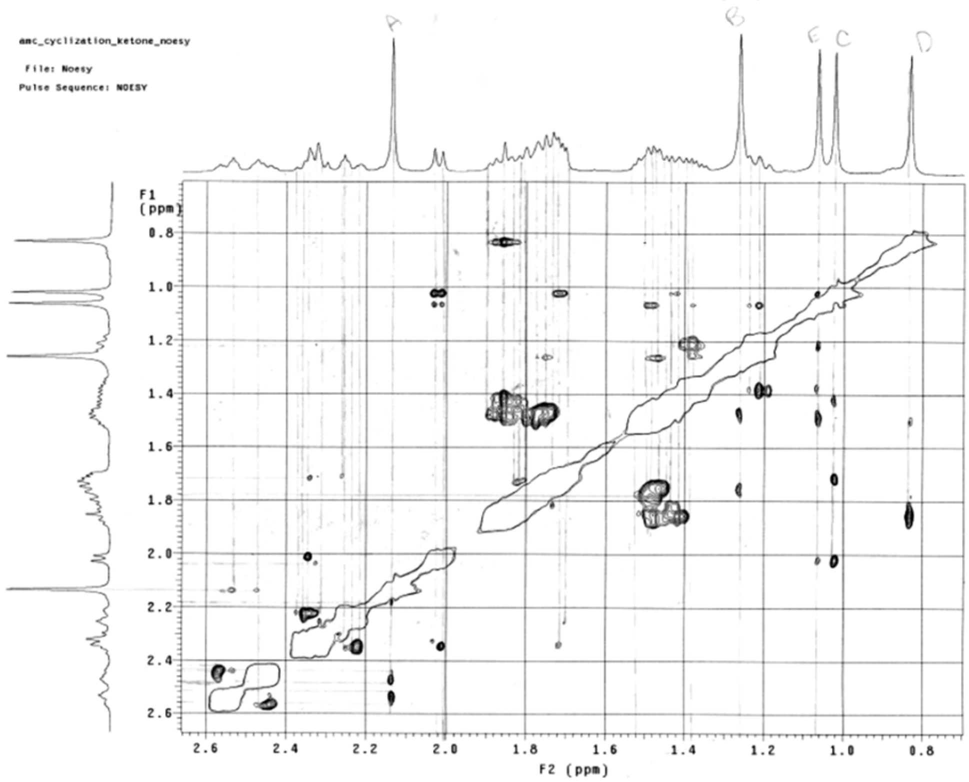

amc_cyclization_ketone_ghsqc
exp6 Ghsqc
SAMPLE
date Jan 26 2012
solvent cdcl3
sample
ACQUISITION
sw 4644.7
at 0.199
np 1852
fb 3000
ss 32
d1 2.000
nt 2
2D ACQUISITION
sw1 21367.5
ni 512
phase arrayed
PRESATURATION
satmode nnn
satdly 0
satfrq 499.8
satpwr -13
TRANSMITTER
tn H1
sfrq 499.867
tof -456.7
tpwr 57
pw 11.000
DECOUPLER
dn C13
dof -2515.3
dm nny
dmf 14285
dpwr 40
pwxlvl 56
pwx 9.500
HSQC
j1xh 140.0
nullflg y
mult 2
FLAGS
hs n
sspul y
PFGflg y
hsglvl 4694
SPECIAL
temp 27.0
gain 20
spin 0
GRADIENTS
gzlvl1 4694
gt1 0.002000
gzlvl3 2355
gt3 0.001000
gstab 0.000500
F2 PROCESSING
gf 0.092
gfs not used
fn 4096
F1 PROCESSING
gf1 0.022
gfs1 not used
proc1 lp
fn1 4096
DISPLAY
sp -275.8
wp 4642.4
sp1 -1279.4
wp1 21357.1
rfl 3626.2
rfp 3348.1
rfl1 14857.4
rfp1 13567.6
PLOT
wc 116.0
sc 10.0
wc2 116.0
sc2 0
vs 872
th 2
ai cdc ph
ACQUISITION ARRAYS
array phase
arraydim 1024
i phase
1 1
2 2
F1 (ppm)
F2 (ppm)

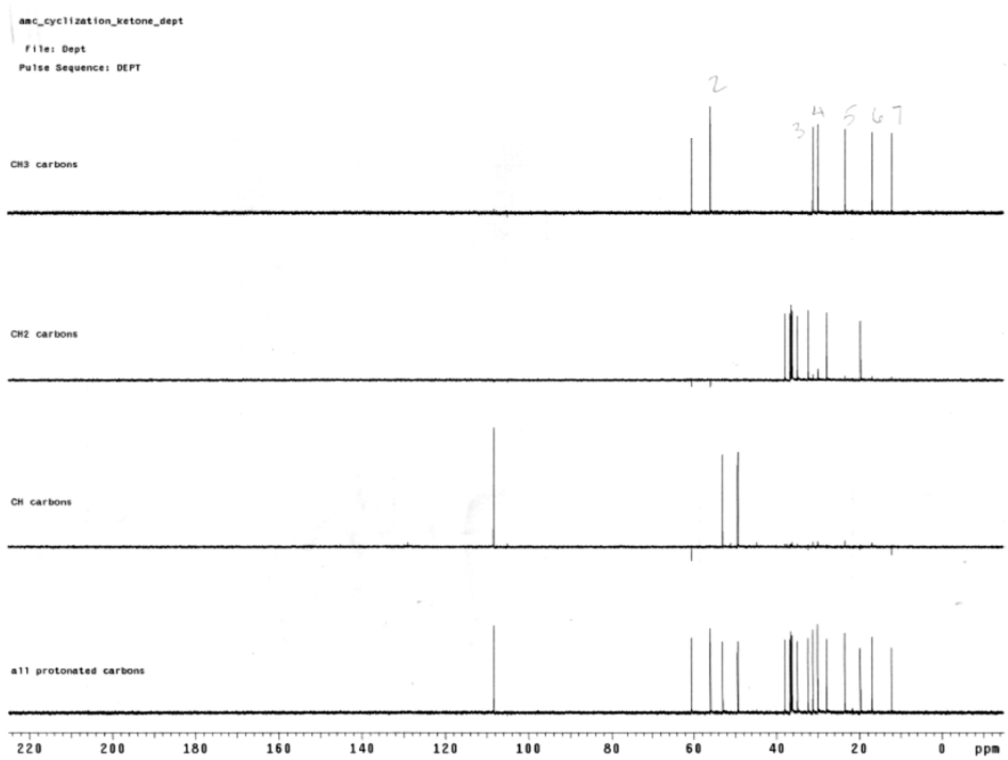

amc_cyclization_ketone_ghsqc
File: Ghsqc
Pulse Sequence: gHSQC
F1 (ppm)
F2 (ppm)

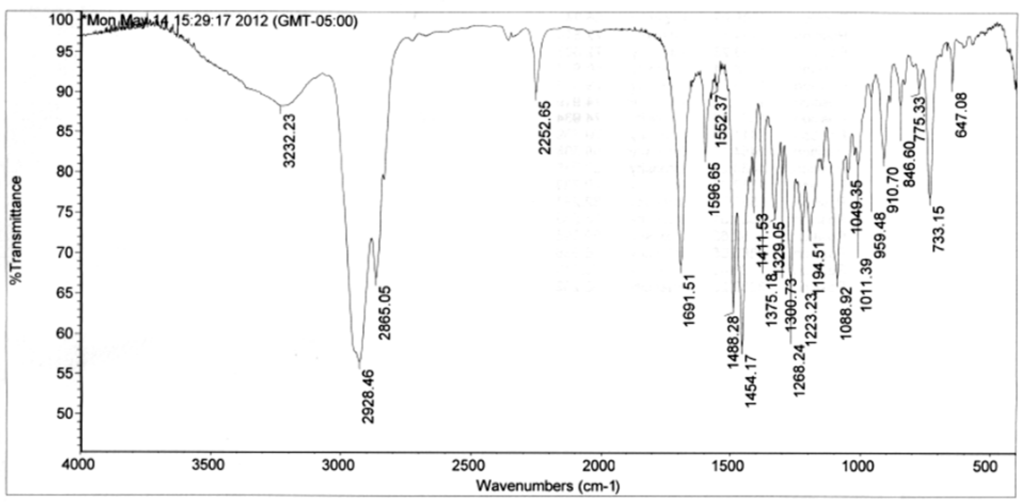

amc_cyclization_ketone_ghmbc
exp7 Ghmbc
F1 (ppm)
F2 (ppm)


amc_cyclization_ketone_ghmbc
File: Ghmbc
Pulse Sequence: gHMBC
F1 (ppm)
F2 (ppm)


amc_cyclization_ketone_noesy
exp8 Noesy
SAMPLE
date Jan 26 2012
solvent cdcl3
sample
ACQUISITION
sw 4644.7
at 0.220
np 2048
fb 3000
ss 32
d1 2.000
nt 8
2D ACQUISITION
sw1 4644.7
ni 256
TRANSMITTER
tn H1
sfrq 499.867
tof -456.7
tpwr 57
pw 11.000
NOESY
mix 0.800
PRESATURATION
satmode nnn
satpwr -13
satdly 0
satfrq 499.8
DECOUPLER
dn C13
dm nnn
FLAGS
hs n
sspul y
PFGflg y
hsglvl 4694
SPECIAL
temp 27.0
gain 8
spin 0
F2 PROCESSING
gf 0.102
gfs not used
fn 4096
F1 PROCESSING
gf1 0.051
gfs1 not used
proc1 lp
fn1 4096
DISPLAY
sp -275.8
wp 4642.4
sp1 -276.4
wp1 4642.4
rfl 3907.0
rfp 3629.0
rfl1 3907.7
rfp1 3629.0
PLOT
wc 116.0
sc 10.0
wc2 116.0
sc2 0
vs 209
th 2
ai cdc ph
F1 (ppm)
F2 (ppm)

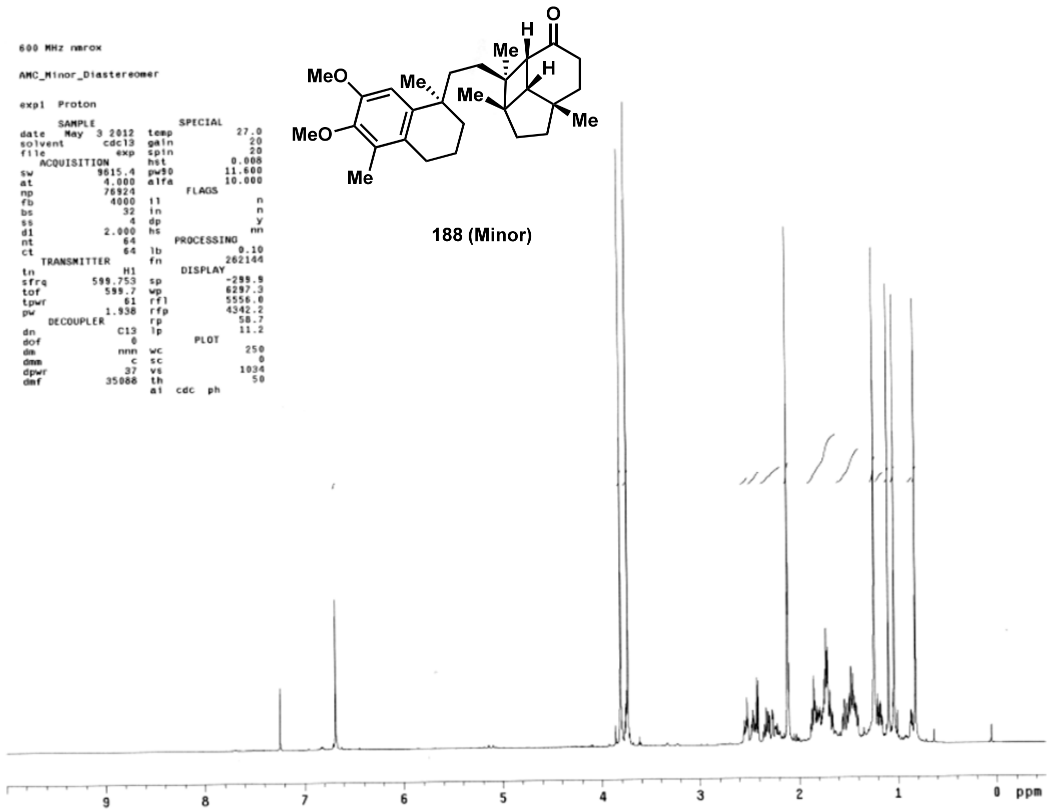

amc_cyclization_ketone_noesy
File: Noesy
Pulse Sequence: NOESY
A
B
E
C
D
F1 (ppm)
F2 (ppm)

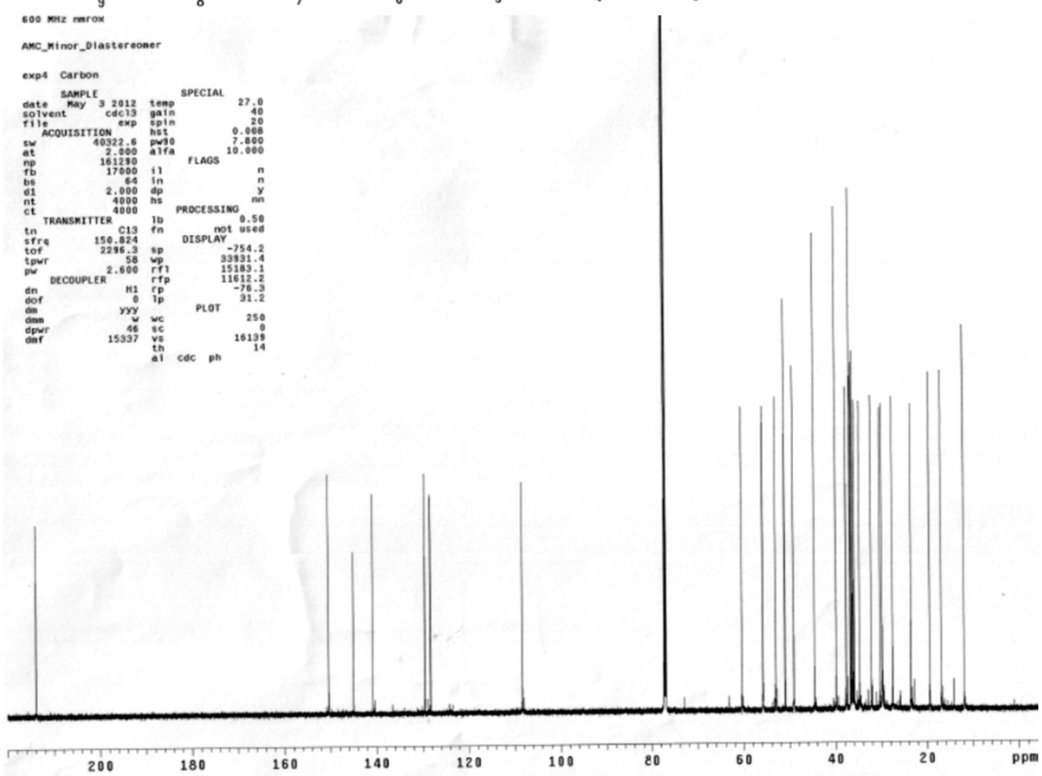


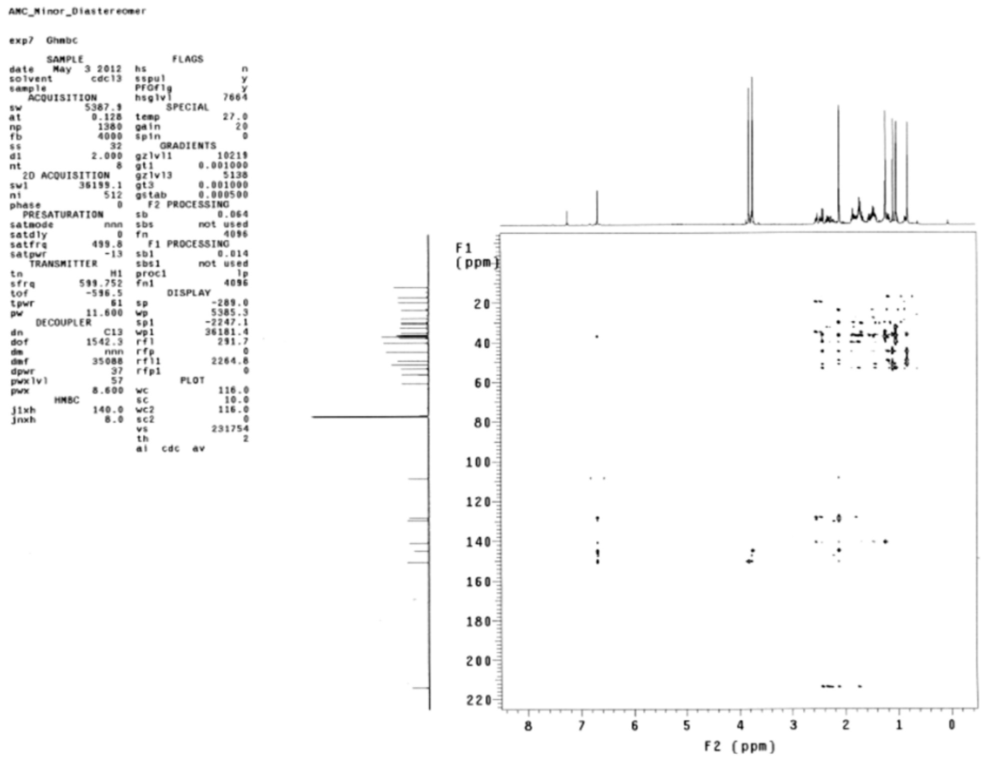


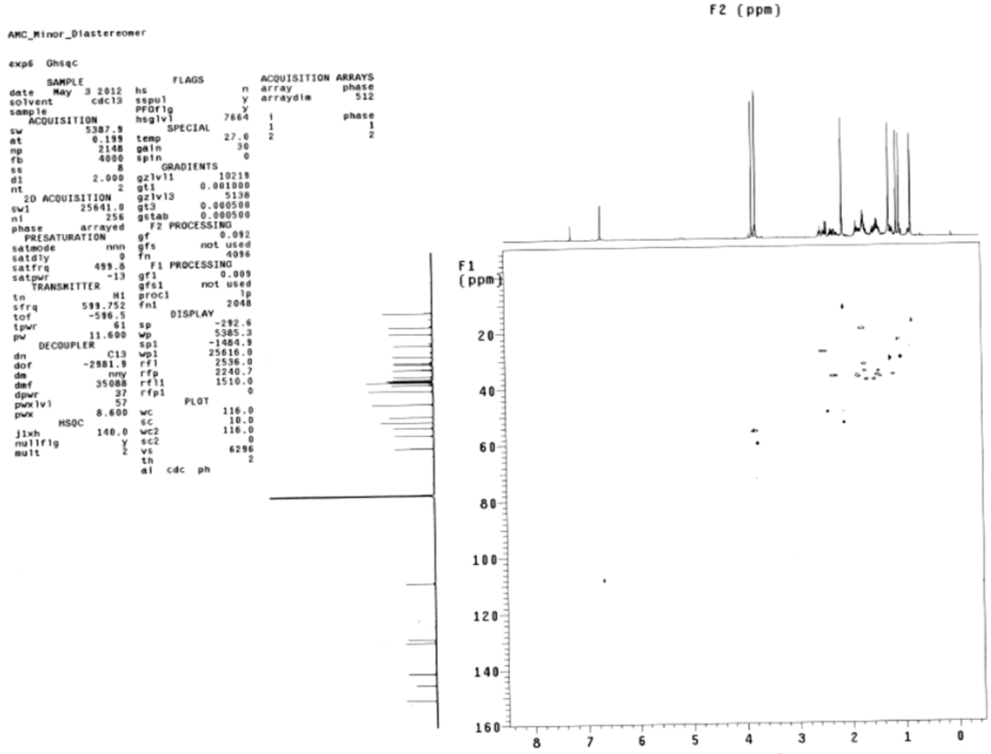
Mon May 14 15:32:57 2012 (GMT-05:00)
FIND PEAKS:

Spectrum:	*Mon May 14 15:29:17 2012 (GMT-05:00)			
Region:	4000.00	400.00		
Absolute threshold:	92.042			
Sensitivity:	50			
Peak list:				
	Position:	647.08	Intensity:	91.157
	Position:	733.15	Intensity:	76.911
	Position:	775.33	Intensity:	90.534
	Position:	846.60	Intensity:	88.466
	Position:	910.70	Intensity:	81.757
	Position:	959.48	Intensity:	89.534
	Position:	1011.39	Intensity:	81.037
	Position:	1049.35	Intensity:	80.098


MeO
MeO
Me
Me
Me
H
H
O
Me
Me
188 (Minor)
600 MHz nmrox
AMC_Minor_Diastereomer
exp1 Proton
SAMPLE
date May 3 2012
solvent cdcl3
file exp
ACQUISITION
sw 9615.4
at 4.000
np 76924
fb 4000
bs 32
ss 4
d1 2.000
nt 64
ct 64
TRANSMITTER
tn H1
sfrq 599.753
tof 599.7
tpwr 61
pw 1.938
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 37
dmf 35088
SPECIAL
temp 27.0
gain 20
spin 20
hst 0.008
pw90 11.600
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.10
fn 262144
DISPLAY
sp -299.9
wp 6297.3
rfl 5556.0
rfp 4342.2
rp 58.7
lp 11.2
PLOT
wc 250
sc 0
vs 1034
th 50
ai cdc ph
9
8
7
6
5
4
3
2
1
0
ppm


600 MHz nmrox
AMC_Minor_Diastereomer
exp4 Carbon
SAMPLE
date May 3 2012
solvent cdcl3
file exp
ACQUISITION
sw 40322.6
at 2.000
np 161290
fb 17000
bs 64
d1 2.000
nt 4000
ct 4000
TRANSMITTER
tn C13
sfrq 150.824
tof 2296.3
tpwr 58
pw 2.600
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 46
dmf 15337
SPECIAL
temp 27.0
gain 40
spin 20
hst 0.008
pw90 7.800
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
fn not used
DISPLAY
sp -754.2
wp 33931.4
rfl 15183.1
rfp 11612.2
rp -76.3
lp 31.2
PLOT
wc 250
sc 0
vs 16139
th 14
ai cdc ph
200
180
160
140
120
100
80
60
40
20
ppm

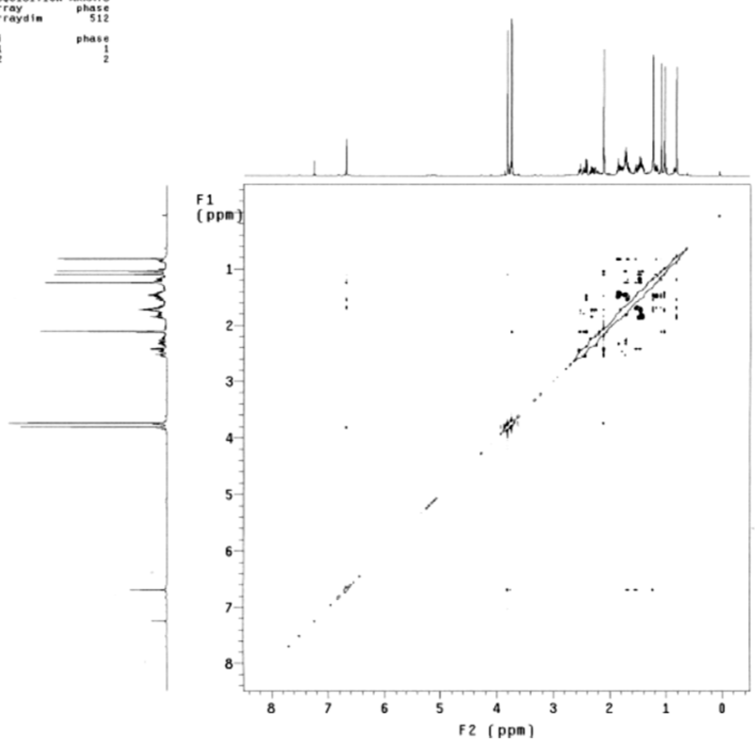

AMC_Minor_Diastereomer
exp7 Ghmbc
SAMPLE
date May 3 2012
solvent cdcl3
sample
ACQUISITION
sw 5387.9
at 0.128
np 1380
fb 4000
ss 32
d1 2.000
nt 8
2D ACQUISITION
sw1 36199.1
ni 512
phase 0
PRESATURATION
satmode nnn
satdly 0
satfrq 499.8
satpwr -13
TRANSMITTER
tn H1
sfrq 599.752
tof -596.5
tpwr 61
pw 11.600
DECOUPLER
dn C13
dof 1542.3
dm nnn
dmf 35088
dpwr 37
pwxlvl 57
pwx 8.600
HMBC
j1xh 140.0
jnxh 8.0
FLAGS
hs n
sspul y
PFGflg y
hsglvl 7664
SPECIAL
temp 27.0
gain 20
spin 0
GRADIENTS
gzlvl1 10219
gt1 0.001000
gzlvl3 5138
gt3 0.001000
gstab 0.000500
F2 PROCESSING
sb 0.064
sbs not used
fn 4096
F1 PROCESSING
sb1 0.014
sbs1 not used
proc1 lp
fn1 4096
DISPLAY
sp -289.0
wp 5385.3
sp1 -2247.1
wp1 36181.4
rfl 291.7
rfp 0
rfl1 2264.8
rfp1 0
PLOT
wc 116.0
sc 10.0
wc2 116.0
sc2 0
vs 231754
th 2
ai cdc av
F1 (ppm)
F2 (ppm)


AMC_Minor_Diastereomer
exp6 Ghsqc
SAMPLE
date May 3 2012
solvent cdcl3
sample
ACQUISITION
sw 5387.9
at 0.199
np 2148
fb 4000
ss 8
d1 2.000
nt 2
2D ACQUISITION
sw1 25641.0
ni 256
phase arrayed
PRESATURATION
satmode nnn
satdly 0
satfrq 499.8
satpwr -13
TRANSMITTER
tn H1
sfrq 599.752
tof -596.5
tpwr 61
pw 11.600
DECOUPLER
dn C13
dof -2981.9
dm nny
dmf 35088
dpwr 37
pwxlvl 57
pwx 8.600
HSQC
j1xh 140.0
nullflg y
mult 2
FLAGS
hs n
sspul y
PFGflg y
hsglvl 7664
SPECIAL
temp 27.0
gain 30
spin 0
GRADIENTS
gzlvl1 10219
gt1 0.001000
gzlvl3 5138
gt3 0.000500
gstab 0.000500
F2 PROCESSING
gf 0.092
gfs not used
fn 4096
F1 PROCESSING
gf1 0.009
gfs1 not used
proc1 lp
fn1 2048
DISPLAY
sp -292.6
wp 5385.3
sp1 -1484.9
wp1 25616.0
rfl 2536.0
rfp 2240.7
rfl1 1510.0
rfp1 0
PLOT
wc 116.0
sc 10.0
wc2 116.0
sc2 0
vs 6296
th 2
ai cdc ph
ACQUISITION ARRAYS
array phase
arraydim 512
i phase
1 1
2 2
F1 (ppm)
F2 (ppm)

AMC_Minor_Diastereomer

exp8 Noesy

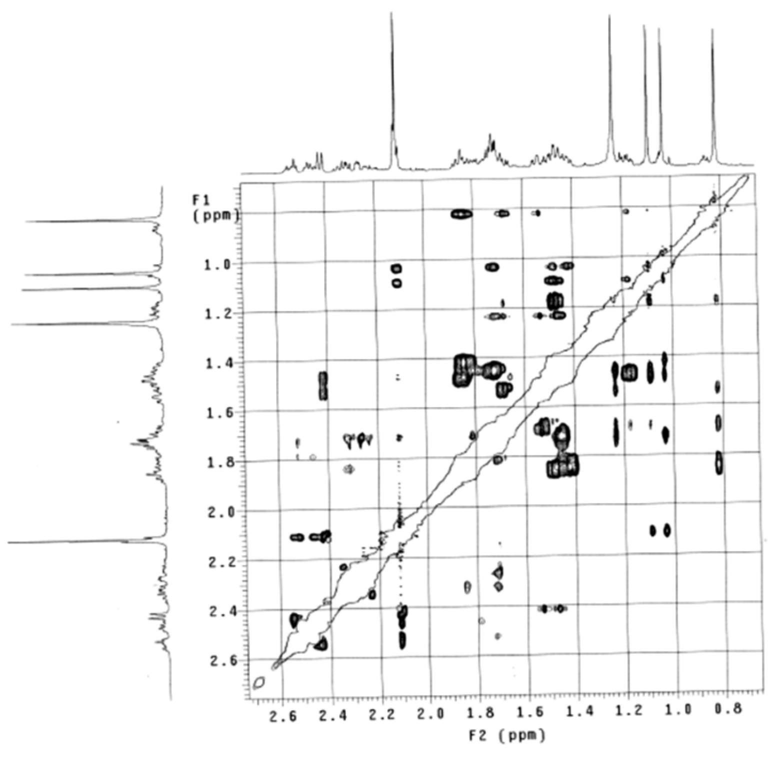
```
      SAMPLE              2D DISPLAY        ACQUISITION ARRAYS
date    May  3 2012  sp1           -291.5  array          phase
solvent      cdcl3   wp1           5382.7  arraydim         512
file           exp   sc2                0
   ACQUISITION       wc2              116   I             phase
sfrq       599.752   rfl1          4638.9   1                 1
tn              H1   rfp1          4342.2   2                 2
at           0.190         DEC. & VT
np            2048   dfrq         150.821
sw          5387.9   dn               C13
fb            4000   dpwr              31
bs              32   dof                0
ss              16   dm                 n
tpwr            61   dmm                c
pw            11.6   dmf            29412
compH       1.0639   dseq
d1           2.000   dres             9.0
mix          0.800   homo               n
tof         -596.5   temp            27.0
nt               8           DEC2
ct               8   dfrq2              0
gain            20   dn2
sspul            y   dpwr2              1
gt1         0.0025   dof2               0
gzlvl1        8175   dm2                n
hsgt        0.0020   dmm2               c
hsglvl        6131   dmf2           29412
satmode        nnn   dseq2
satpwr         -13   dres2            1.0
satdly           0   homo2              n
scuba            n           DEC3
zqflg            y   dfrq3              0
alt_grd          n   dn3
      FLAGS          dpwr3              1
il               n   dof3               0
in               n   dm3                n
dp               y   dmm3               c
hs              nn   dmf3           29412
sspul            y   dseq3
  2D ACQUISITION     dres3            1.0
sw1         5387.9   homo3              n
ni             256        PROCESSING
phase      arrayed   gf             0.088
     DISPLAY         gfs         not used
sp          -291.4   wtfile
wp          5382.7   proc              ft
vs           12991   fn              2048
sc              10   math               f
wc             116   ssfilter    not used
hzmm         46.40   ssorder            3
is         5325.63   ssntaps            3
rfl         4638.8     2D PROCESSING
rfp         4342.2   gf1            0.055
th               2   gfs1        not used
ins        100.000   wtfile1
ai  cdc  ph          proc1             lp
                     fn1             2048
```

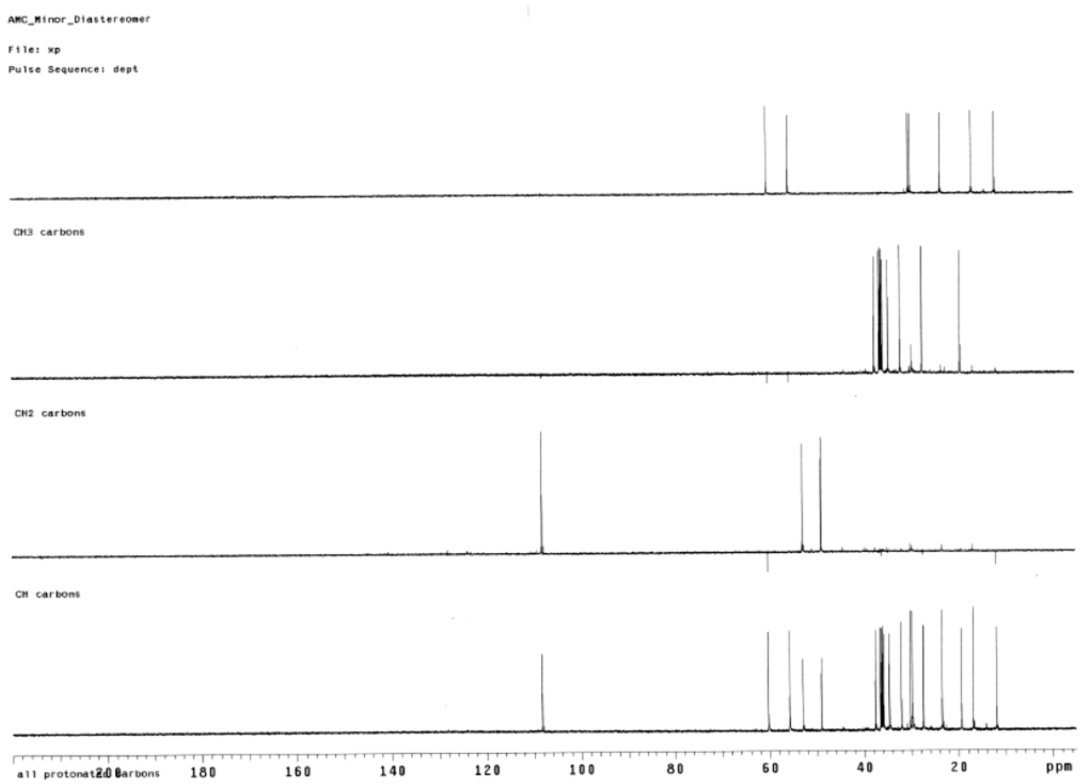


AMC_Minor_Diastereomer

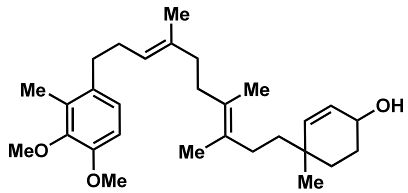
File: xp

Pulse Sequence: NOESY

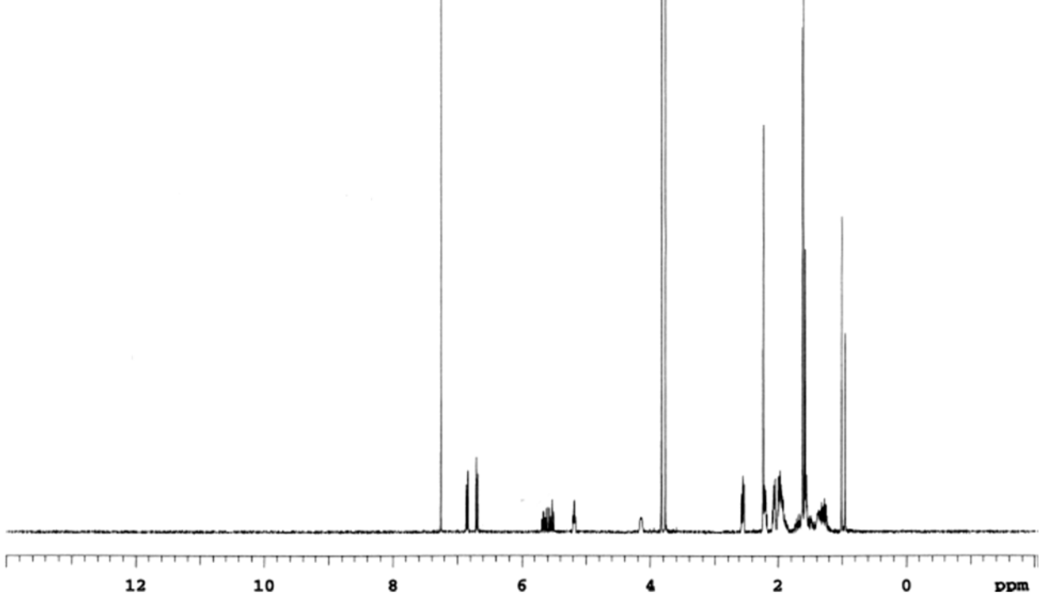


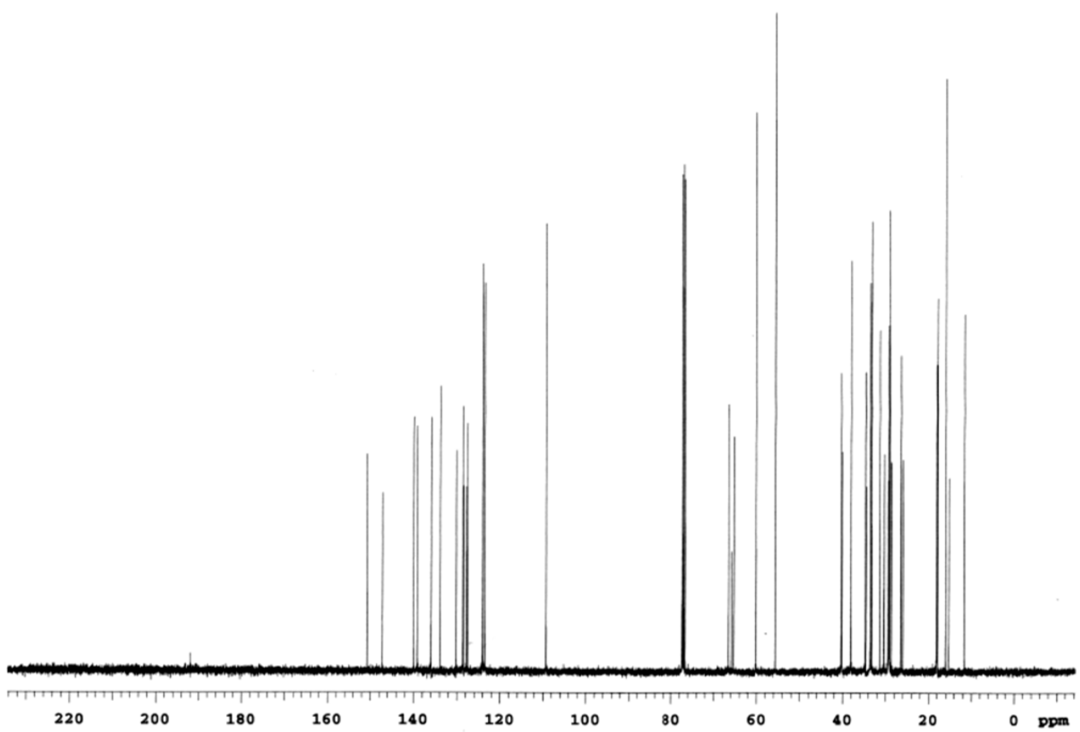


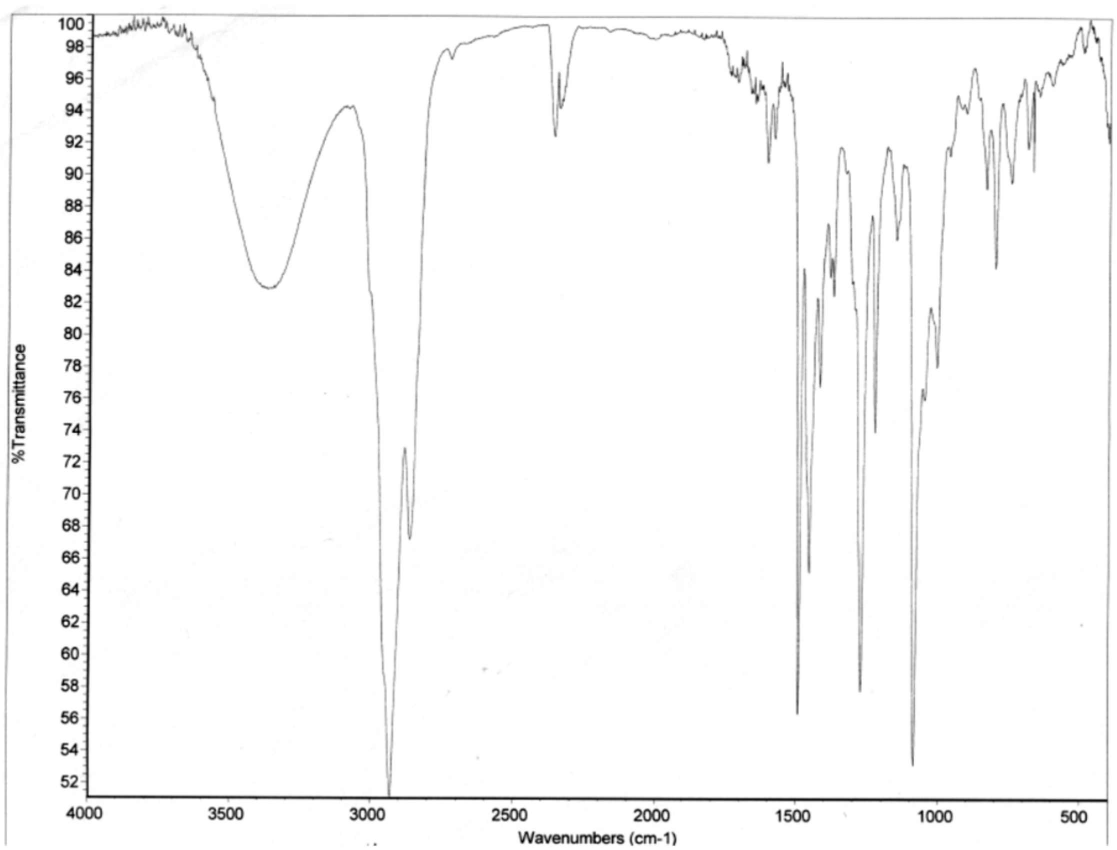
AMC_Minor_Diastereomer
File: xp
Pulse Sequence: dept
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
ppm

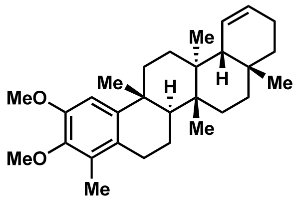

Me
Me
MeO
OMe
Me
Me
OH
Me

190 (d.r. = 1.5:1)

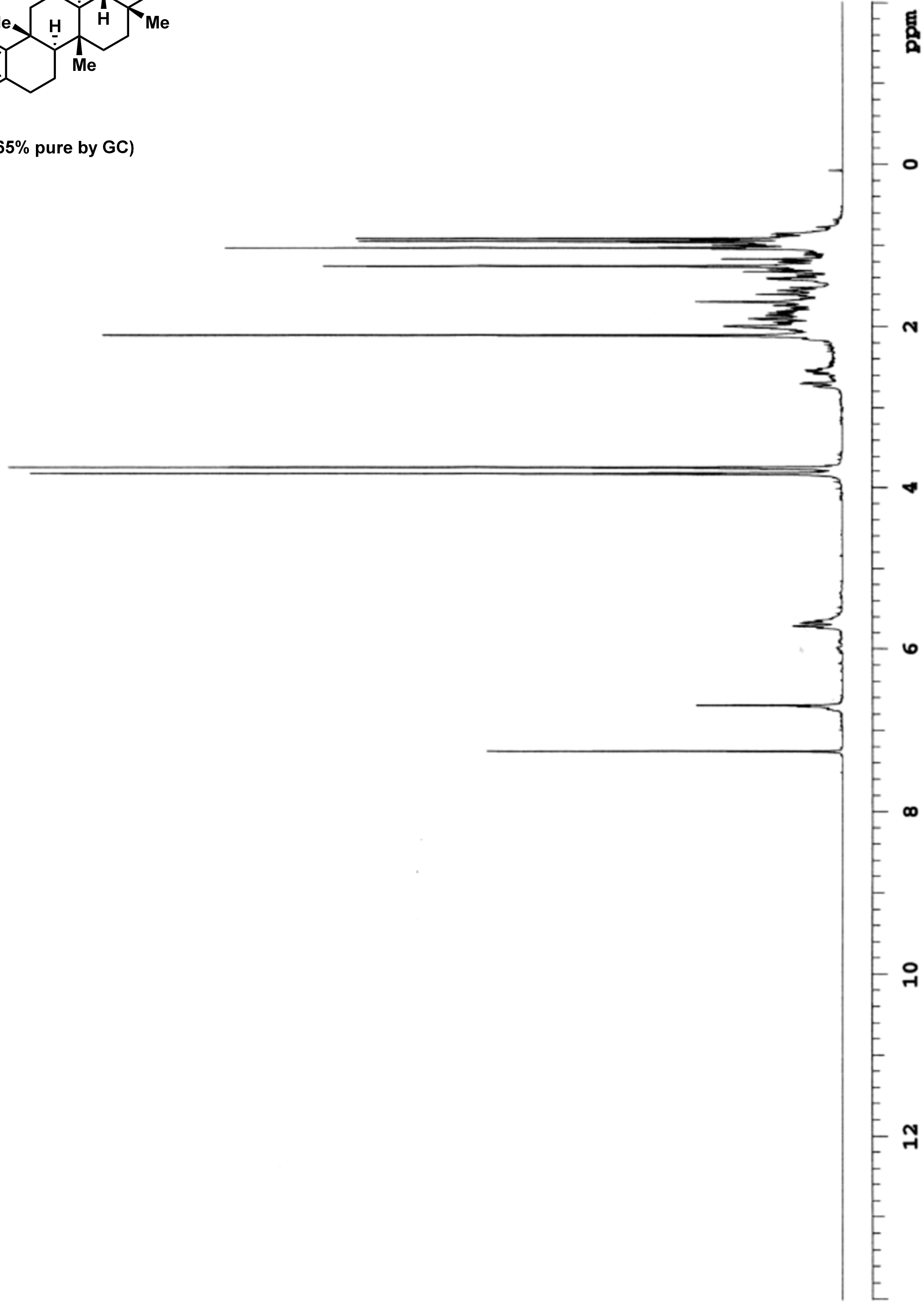

12
10
8
6
4
2
0
ppm

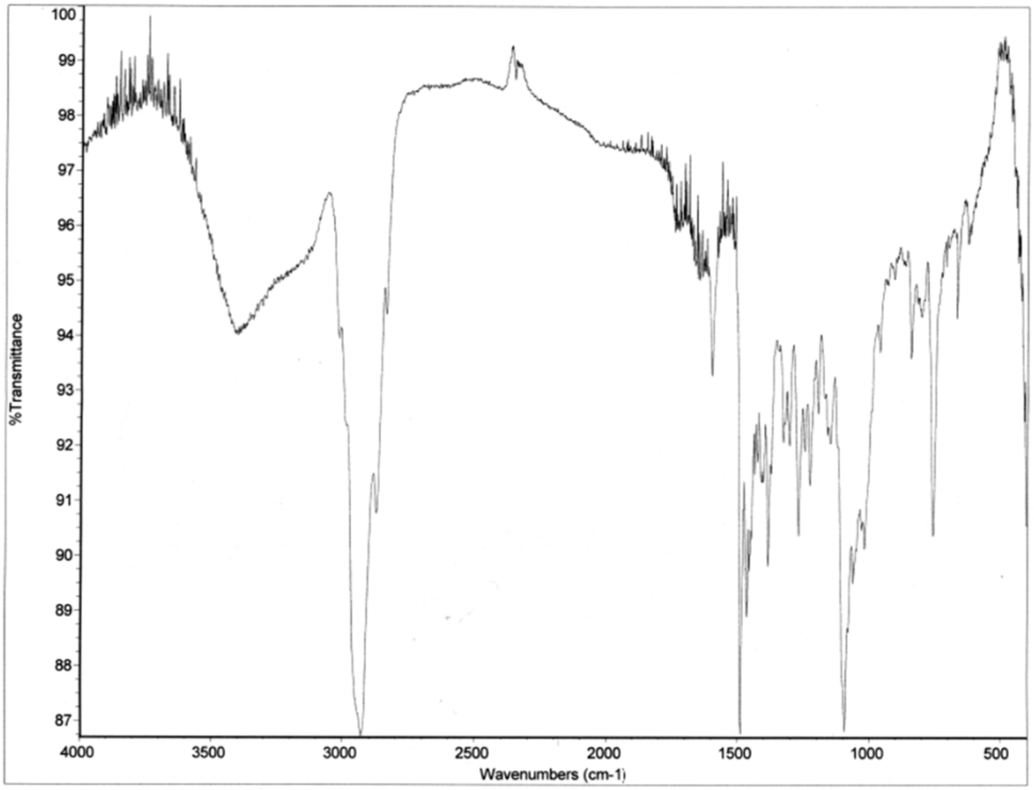

220
200
180
160
140
120
100
80
60
40
20
0
ppm

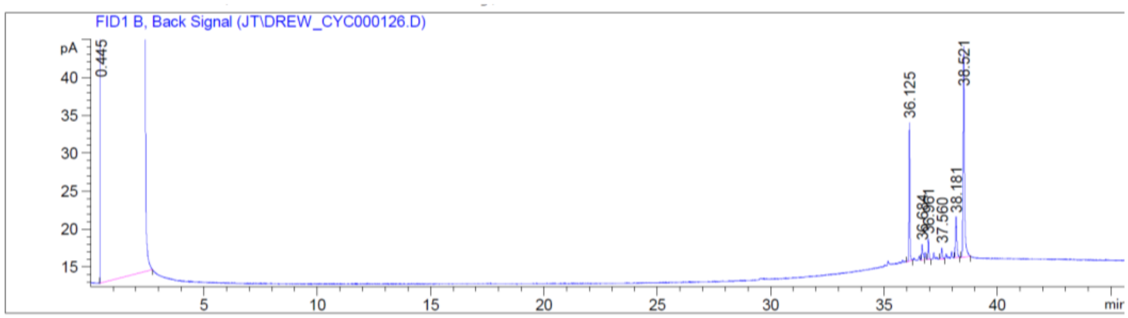

%Transmittance
Wavenumbers (cm-1)

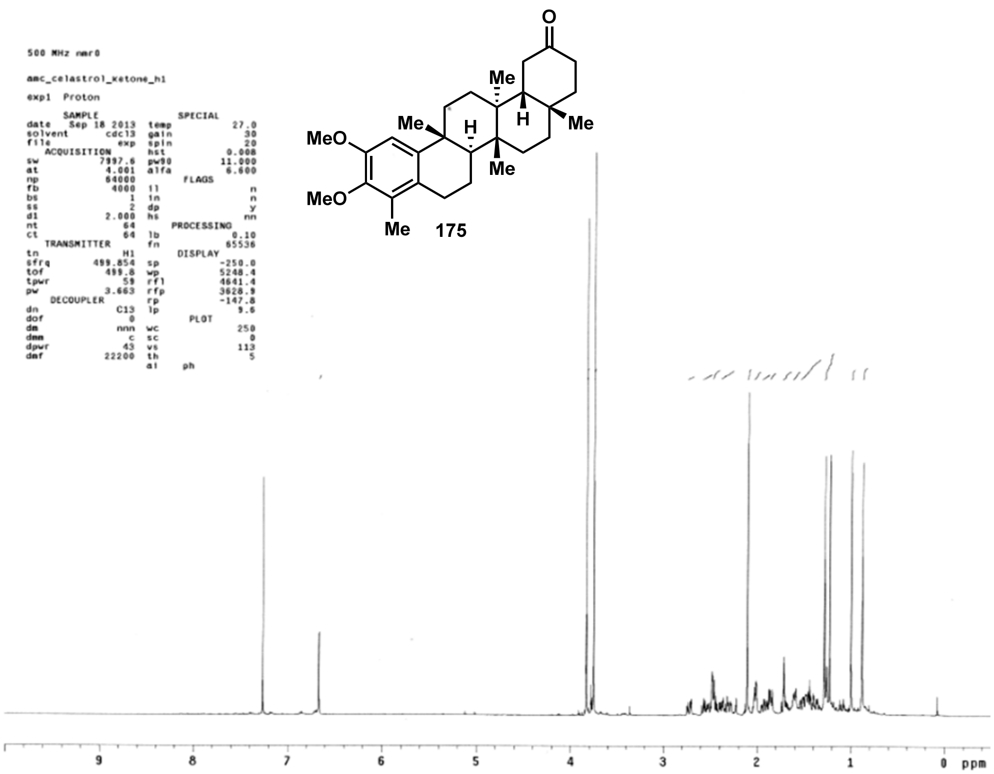


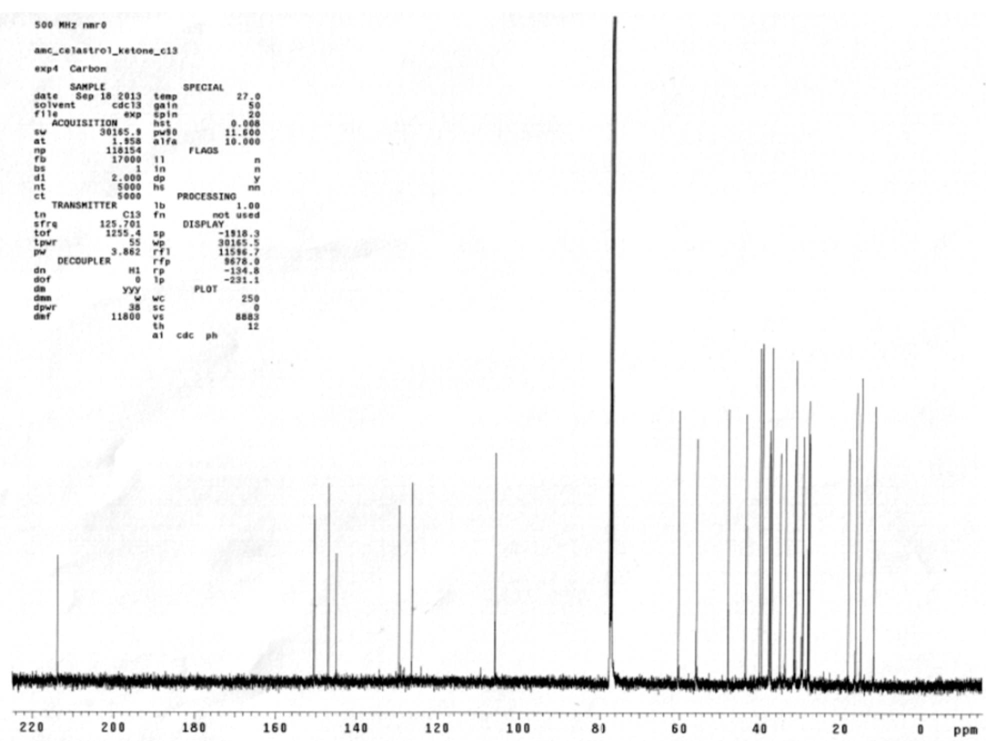
191 (~65% pure by GC)

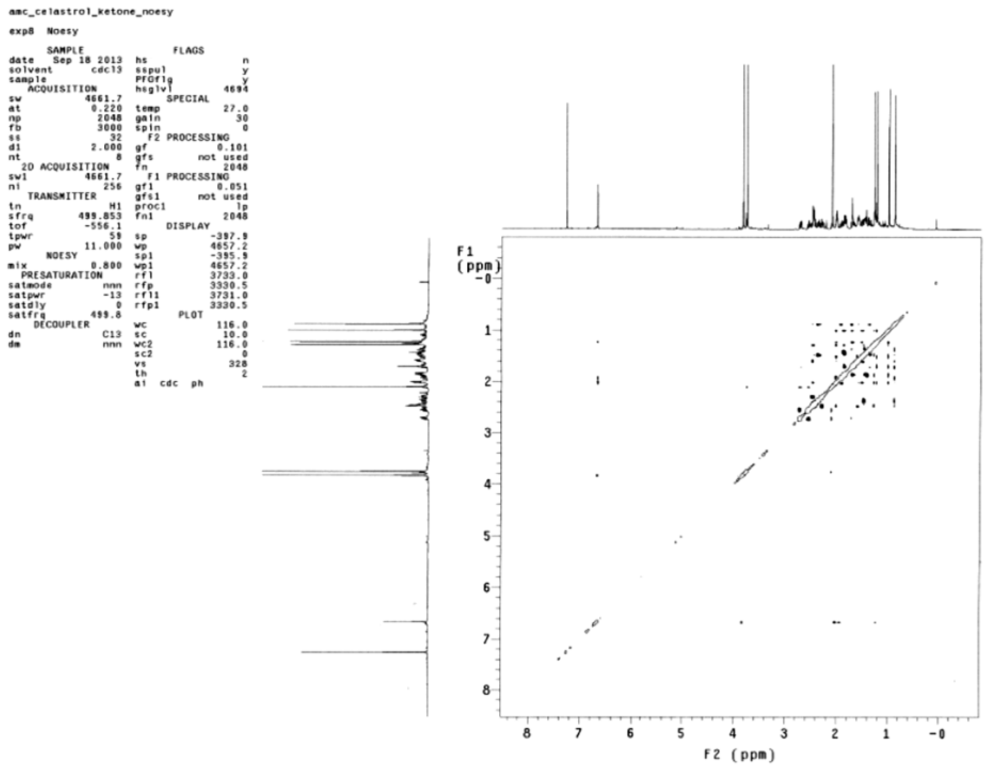


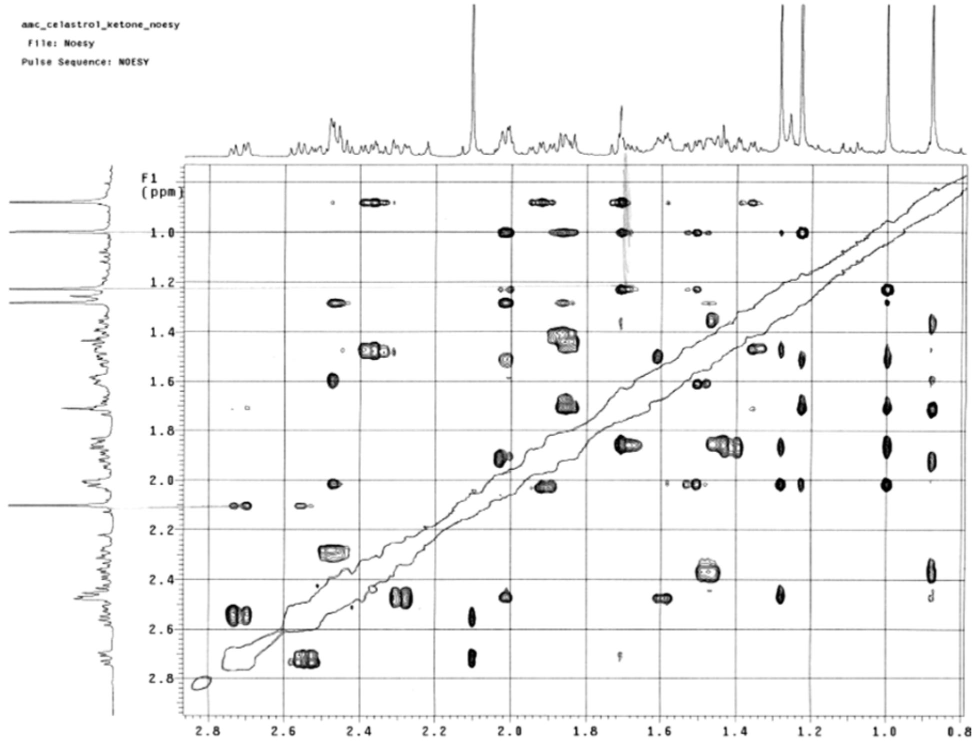

%Transmittance
Wavenumbers (cm-1)

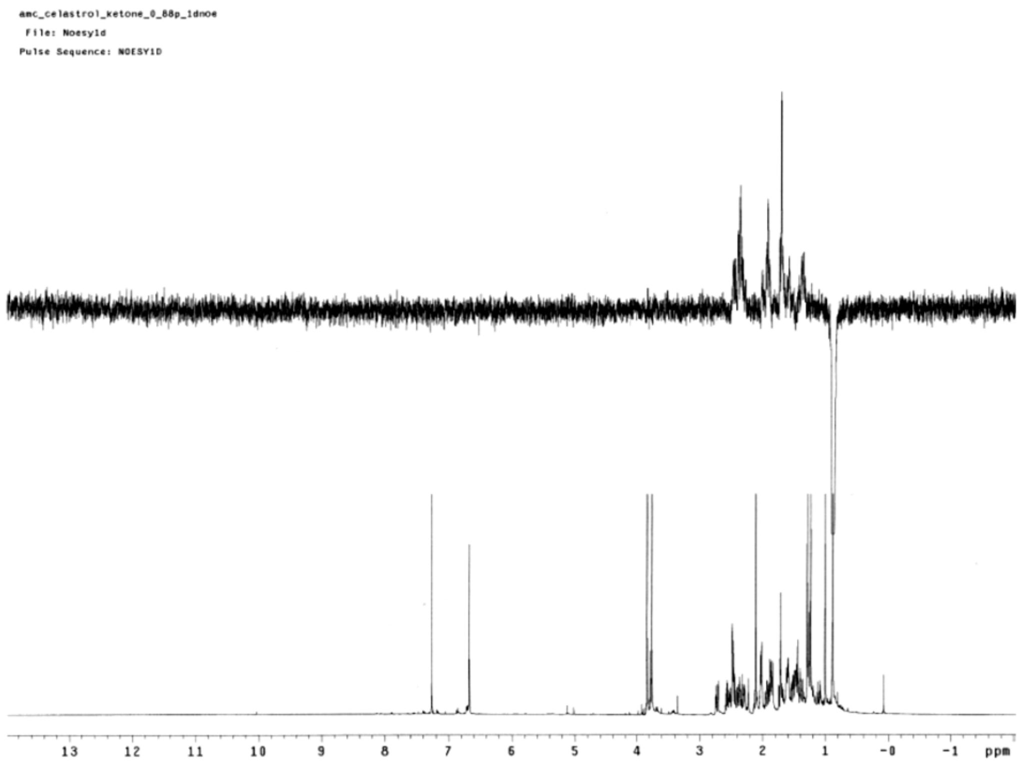

FID1 B, Back Signal (JT\DREW_CYC000126.D)
pA
0.445
36.125
36.684
36.961
37.560
38.181
38.521
min

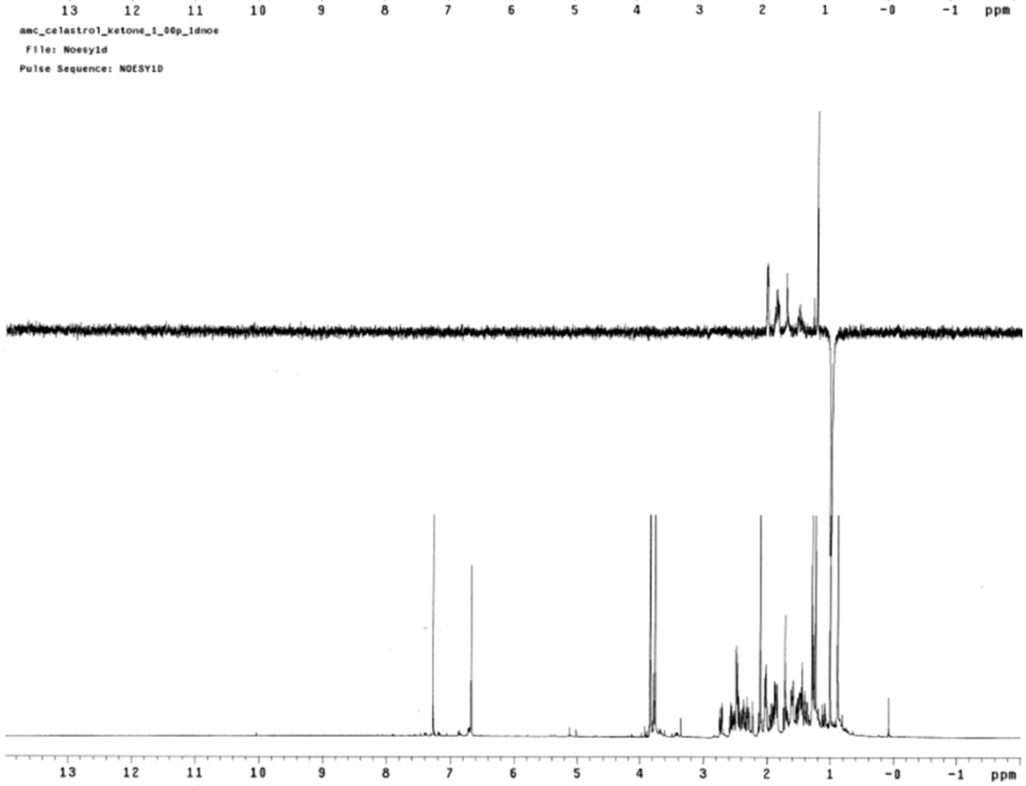

500 MHz nmr0
amc_celastrol_ketone_h1
exp1 Proton
MeO
MeO
Me
Me
Me
Me
Me
H
H
O
175
ppm

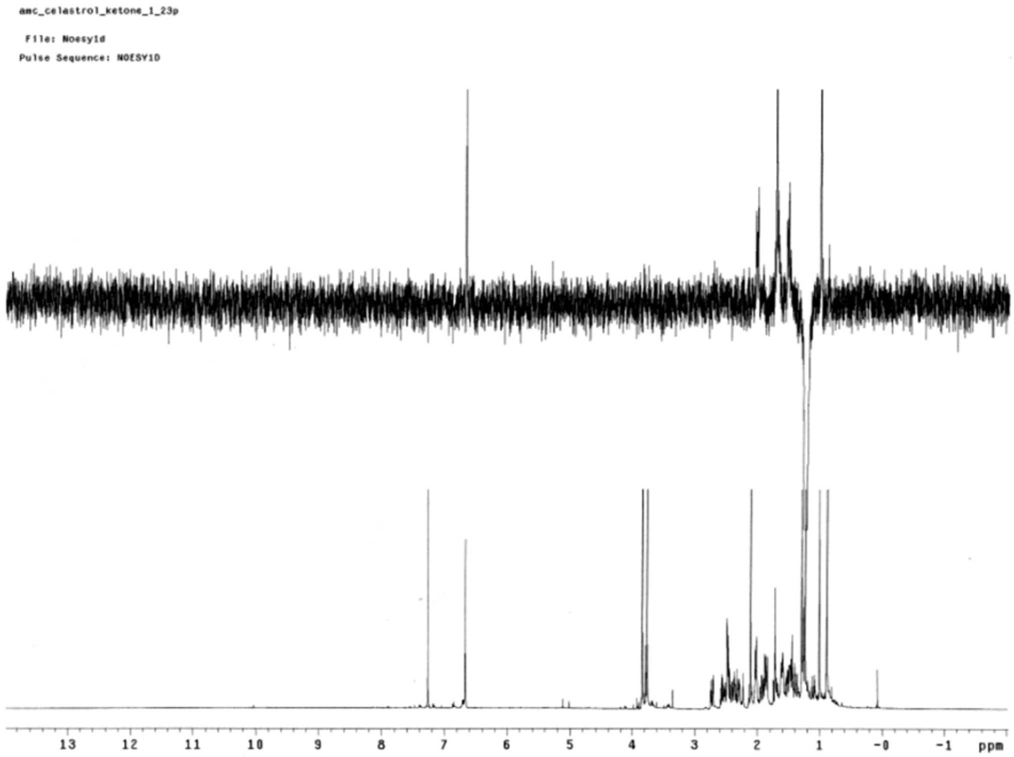

500 MHz nmr0
amc_celastrol_ketone_c13
exp4 Carbon
ppm

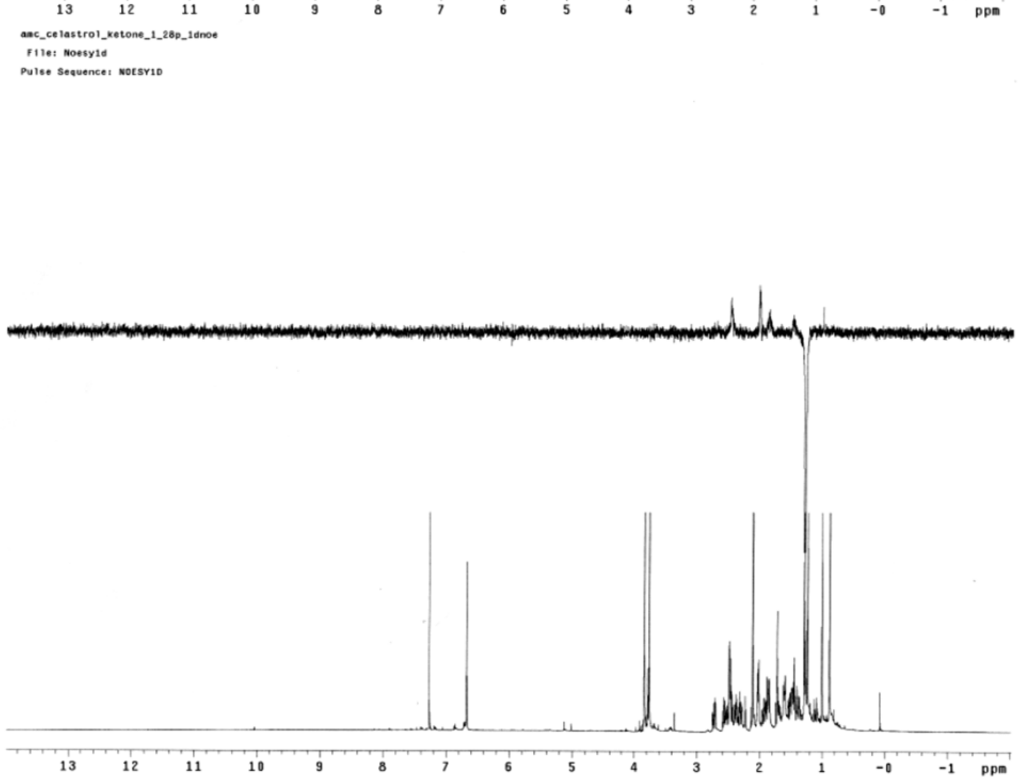

amc_celastrol_ketone_noesy
exp8 Noesy
SAMPLE
date Sep 18 2013
solvent cdcl3
sample
ACQUISITION
sw 4661.7
at 0.220
np 2048
fb 3000
ss 32
d1 2.000
nt 8
2D ACQUISITION
sw1 4661.7
ni 256
TRANSMITTER
tn H1
sfrq 499.853
tof -556.1
tpwr 59
pw 11.000
NOESY
mix 0.800
PRESATURATION
satmode nnn
satpwr -13
satdly 0
satfrq 499.8
DECOUPLER
dn C13
dm nnn
FLAGS
hs n
sspul y
PFGflg y
hsglvl 4694
SPECIAL
temp 27.0
gain 30
spin 0
F2 PROCESSING
gf 0.101
gfs not used
fn 2048
F1 PROCESSING
gf1 0.051
gfs1 not used
proc1 lp
fn1 2048
DISPLAY
sp -397.9
wp 4657.2
sp1 -395.9
wp1 4657.2
rfl 3733.0
rfp 3330.5
rfl1 3731.0
rfp1 3330.5
PLOT
wc 116.0
sc 10.0
wc2 116.0
sc2 0
vs 328
th 2
ai cdc ph
F1 (ppm)
F2 (ppm)

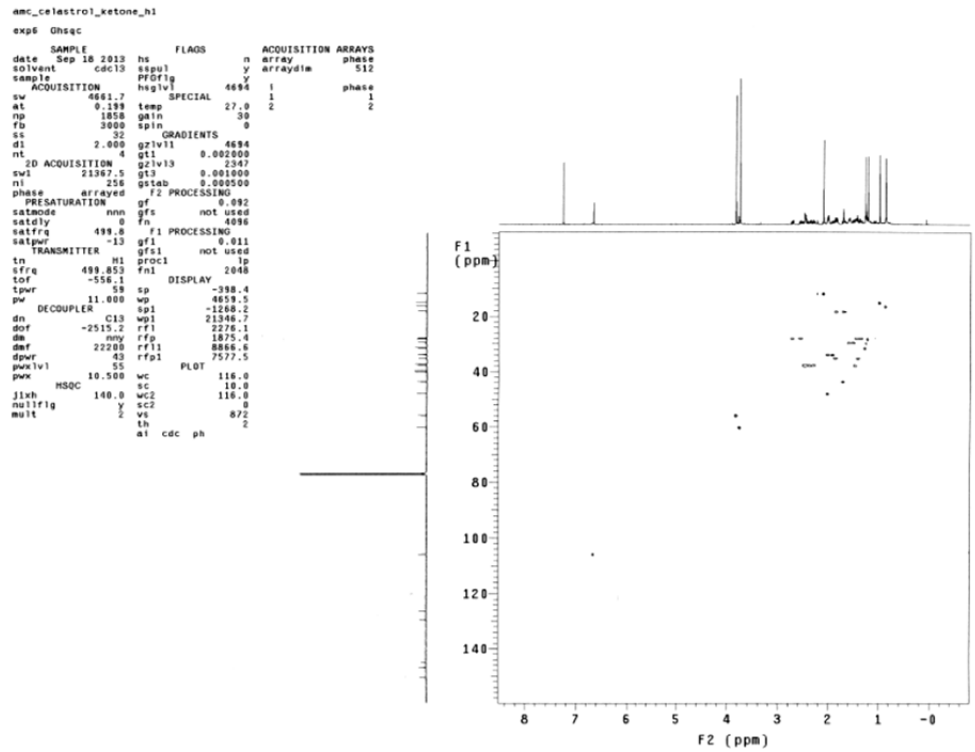

amc_celastrol_ketone_noesy
File: Noesy
Pulse Sequence: NOESY
F1 (ppm)
F2 (ppm)

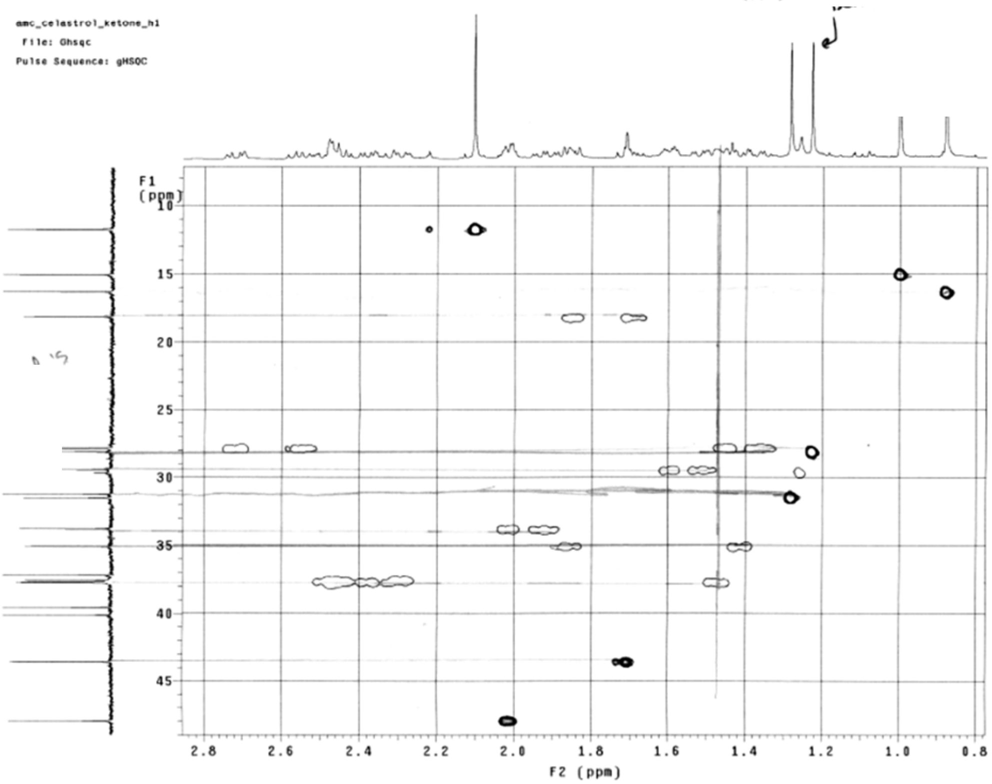

amc_celastrol_ketone_0_88p_1dnoe
File: Noesy1d
Pulse Sequence: NOESY1D
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm

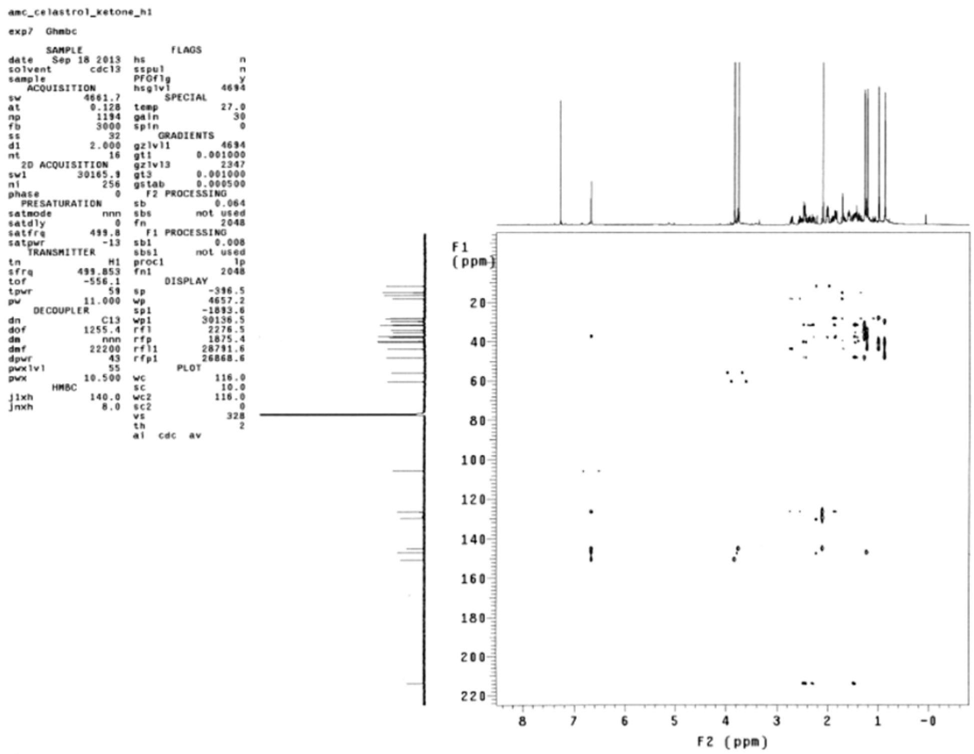

amc_celastrol_ketone_1_00p_1dnoe
File: Noesy1d
Pulse Sequence: NOESY1D
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm

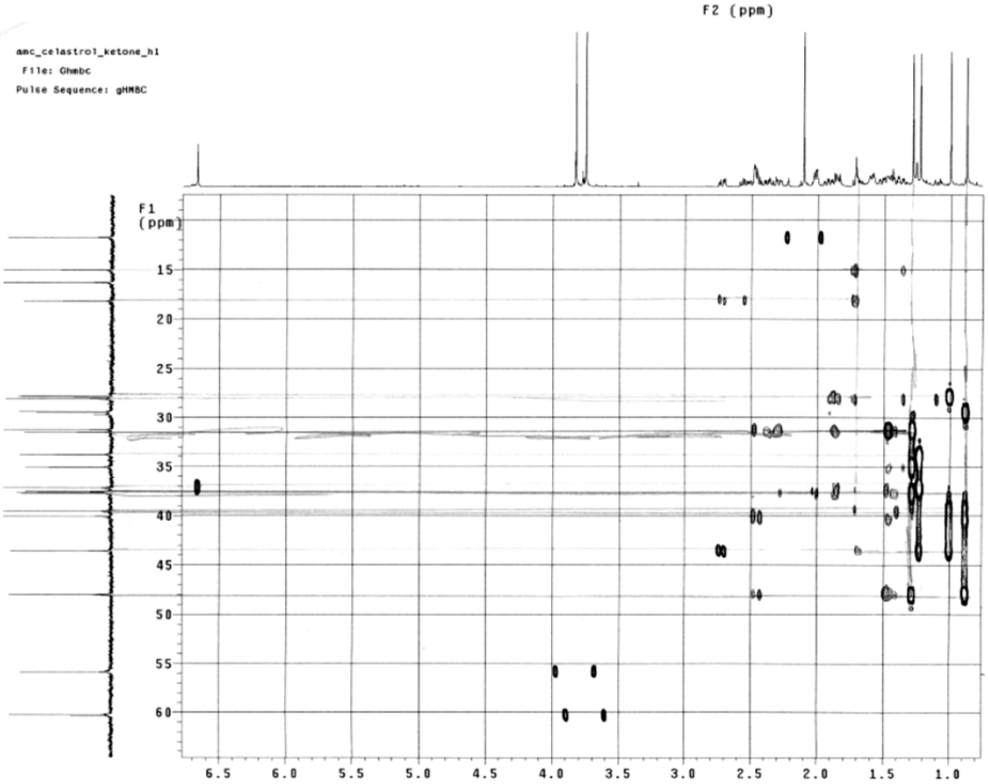

amc_celastrol_ketone_1_23p
File: Noesy1d
Pulse Sequence: NOESY1D
13 12 11 10 9 8 7 6 5 4 3 2 1 -0 -1 ppm

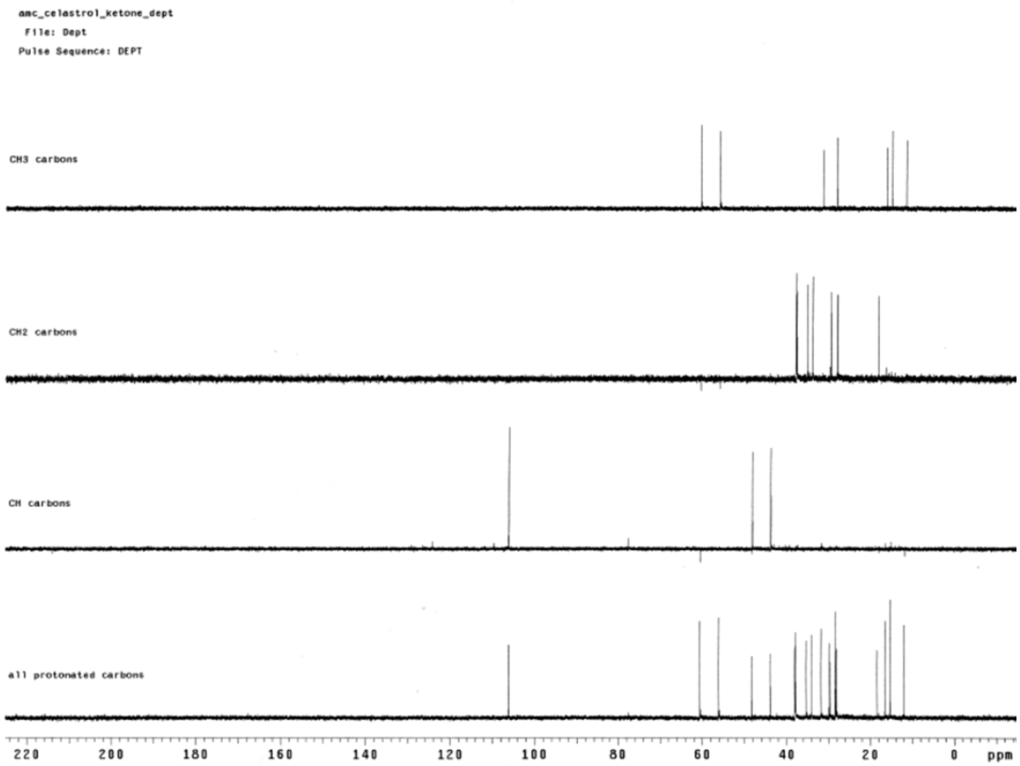

amc_celastrol_ketone_1_28p_1dnoe
File: Noesy1d
Pulse Sequence: NOESY1D
13 12 11 10 9 8 7 6 5 4 3 2 1 -0 -1 ppm

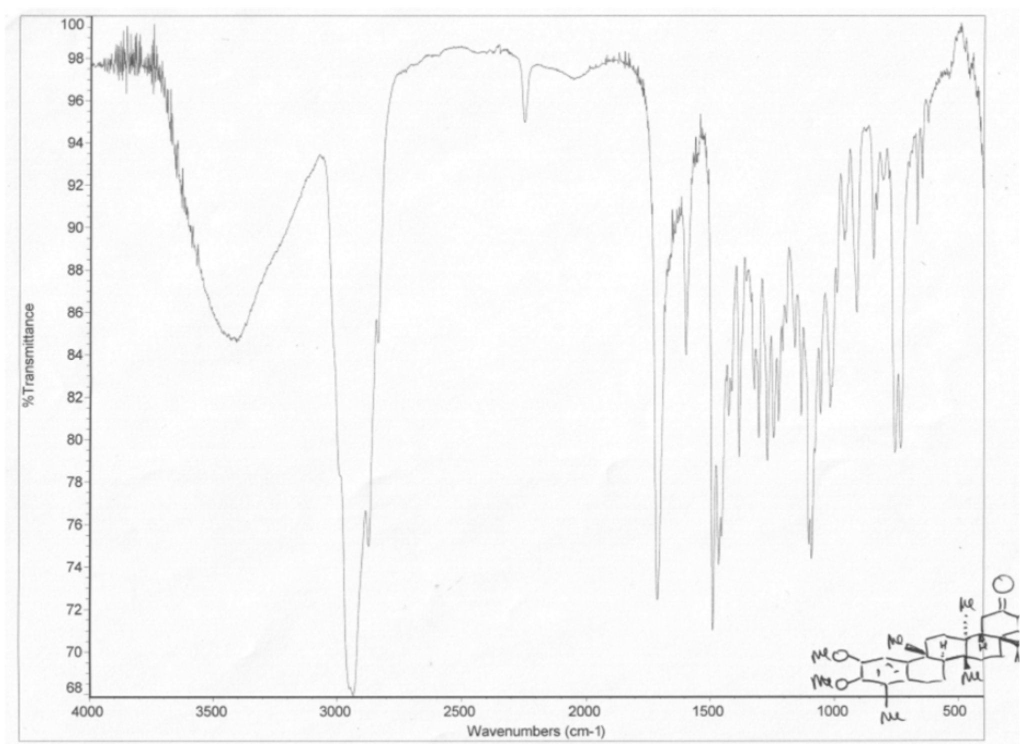

amc_celastrol_ketone_h1
exp6 Ghsqc
SAMPLE
date Sep 18 2013
solvent cdcl3
sample
ACQUISITION
sw 4661.7
at 0.199
np 1858
fb 3000
ss 32
d1 2.000
nt 4
2D ACQUISITION
sw1 21367.5
ni 256
phase arrayed
PRESATURATION
satmode nnn
satdly 0
satfrq 499.8
satpwr -13
TRANSMITTER
tn H1
sfrq 499.853
tof -556.1
tpwr 59
pw 11.000
DECOUPLER
dn C13
dof -2515.2
dm nny
dmf 22200
dpwr 43
pwxlvl 55
pwx 10.500
HSQC
j1xh 140.0
nullflg y
mult 2
FLAGS
hs n
sspul y
PFGflg y
hsglvl 4694
SPECIAL
temp 27.0
gain 30
spin 0
GRADIENTS
gzlvl1 4694
gt1 0.002000
gzlvl3 2347
gt3 0.001000
gstab 0.000500
F2 PROCESSING
gf 0.092
gfs not used
fn 4096
F1 PROCESSING
gf1 0.011
gfs1 not used
proc1 lp
fn1 2048
DISPLAY
sp -398.4
wp 4659.5
sp1 -1268.2
wp1 21346.7
rfl 2276.1
rfp 1875.4
rfl1 8866.6
rfp1 7577.5
PLOT
wc 116.0
sc 10.0
wc2 116.0
sc2 0
vs 872
th 2
ai cdc ph
ACQUISITION ARRAYS
array phase
arraydim 512
I phase
1 1
2 2
F1 (ppm)
F2 (ppm)

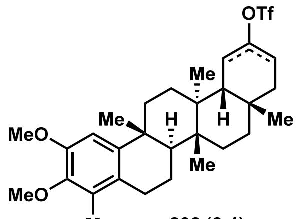

amc_celastrol_ketone_h1
File: Ghsqc
Pulse Sequence: gHSQC
F1 (ppm)
F2 (ppm)


amc_celastrol_ketone_h1
exp7 Ghmbc
F2 (ppm)
F1 (ppm)

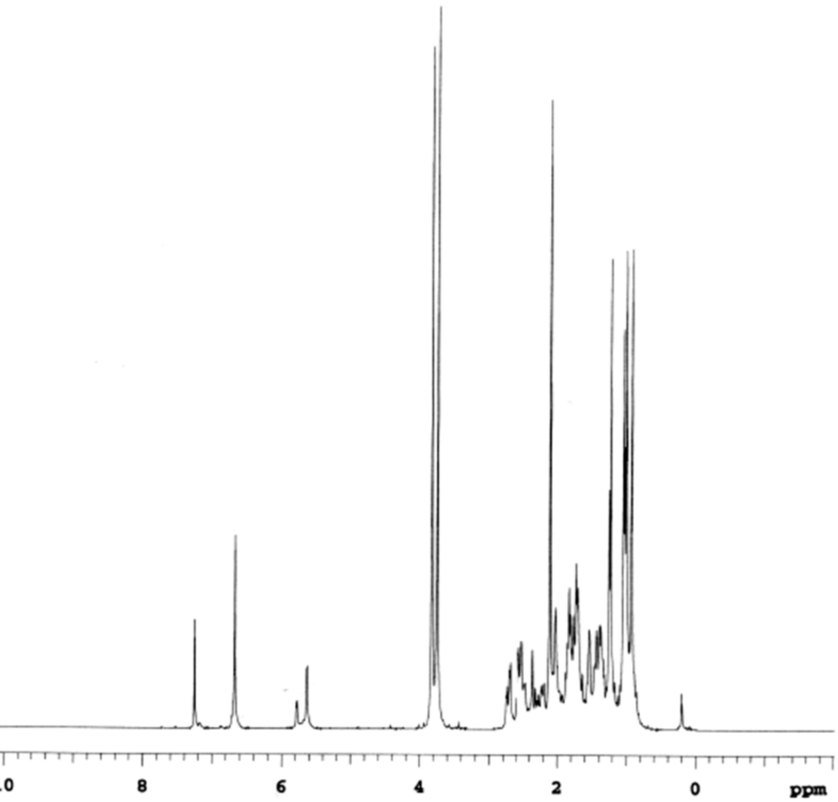

amc_celastrol_ketone_h1
File: Ghmbc
Pulse Sequence: gHMBC
F2 (ppm)
F1 (ppm)

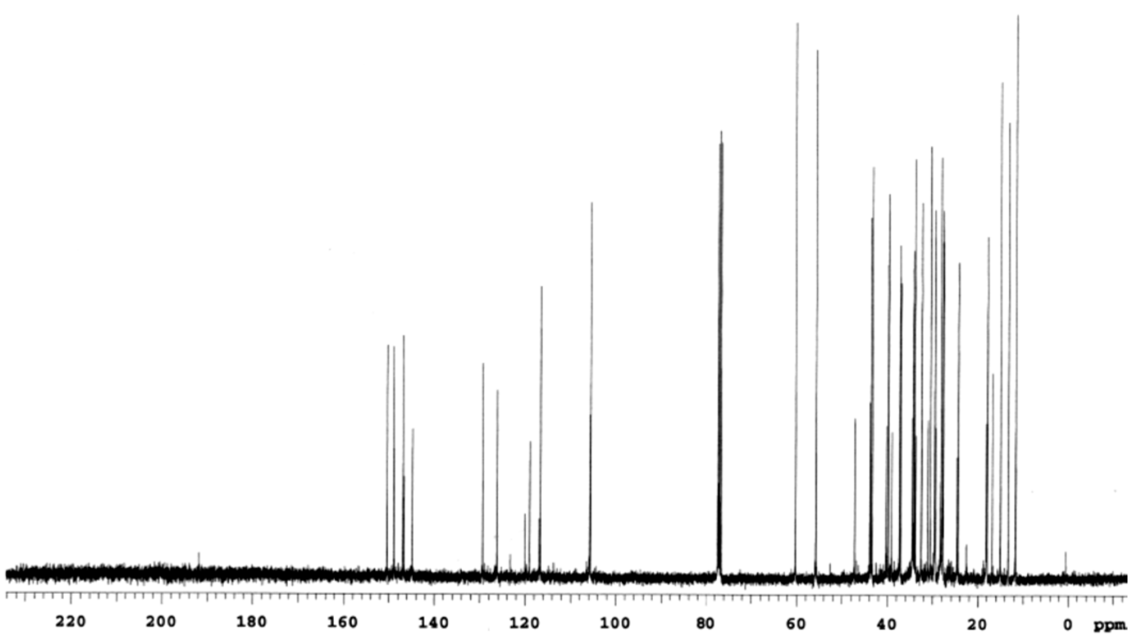

amc_celastrol_ketone_dept
File: Dept
Pulse Sequence: DEPT
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
220 200 180 160 140 120 100 80 60 40 20 0 ppm

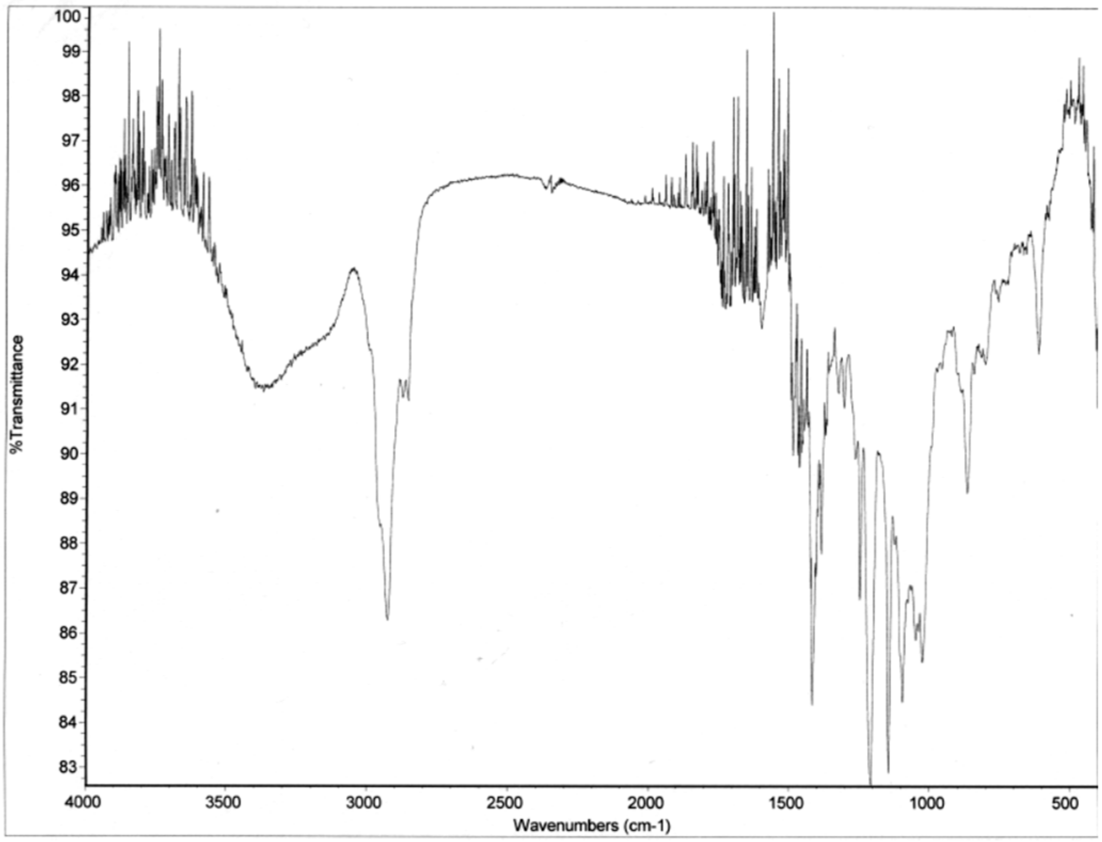

%Transmittance
Wavenumbers (cm-1)

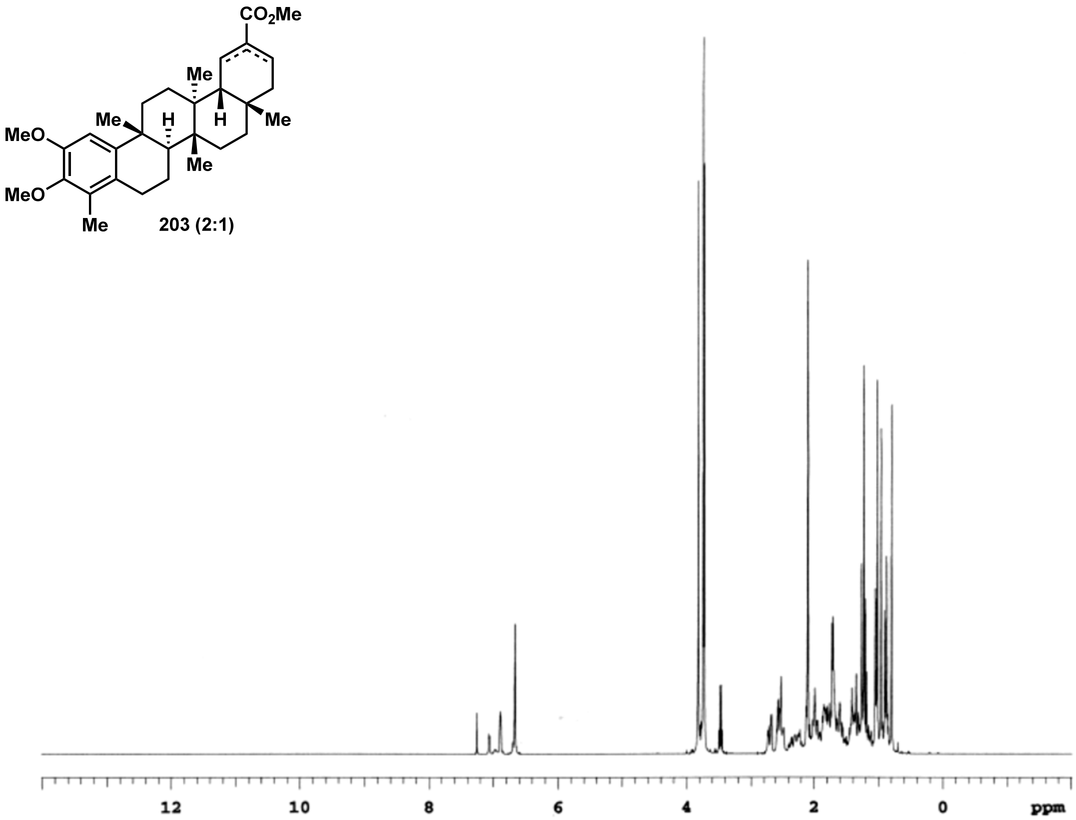

OTf
Me
MeO
Me
H
H
Me
MeO
Me
Me

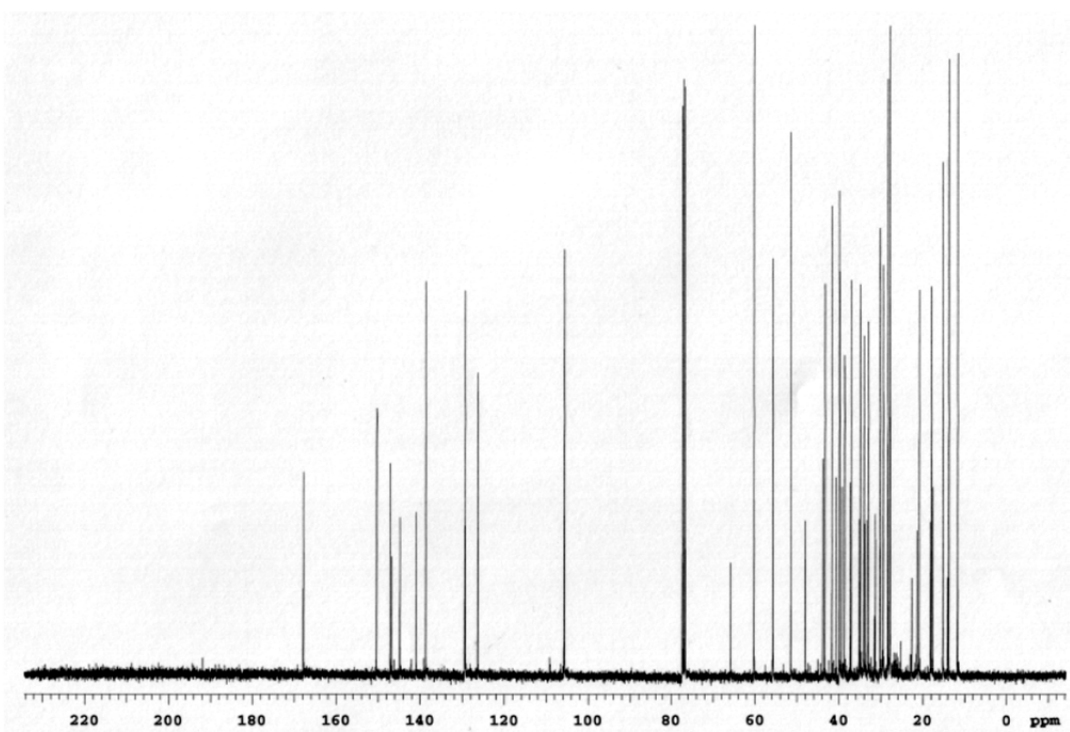
202 (2:1)

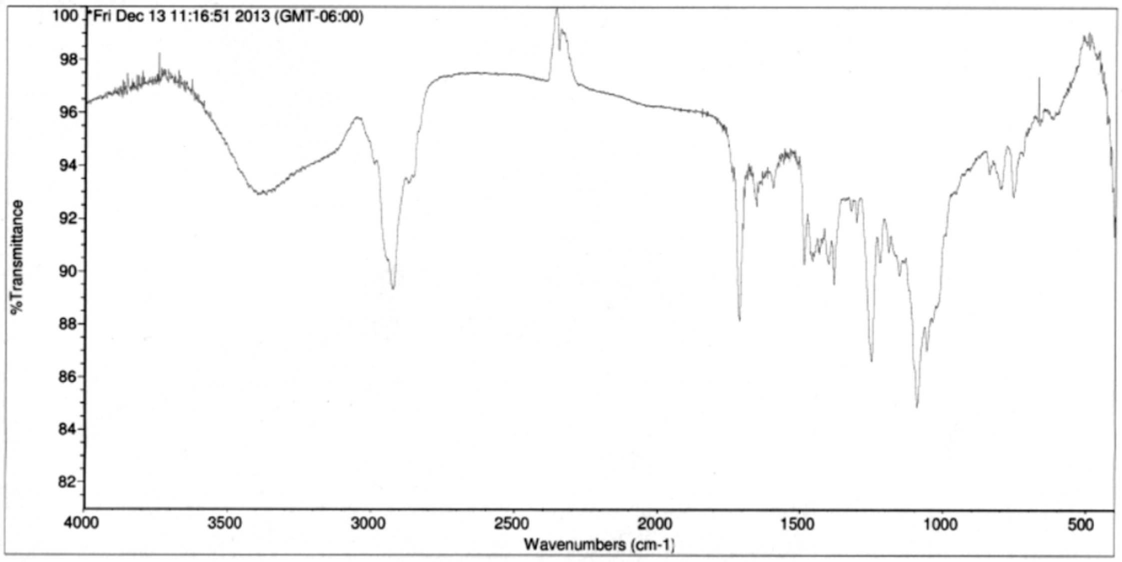

12
10
8
6
4
2
0
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm

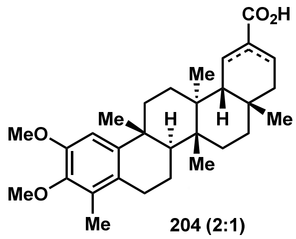

%Transmittance
Wavenumbers (cm-1)
100
99
98
97
96
95
94
93
92
91
90
89
88
87
86
85
84
83
4000
3500
3000
2500
2000
1500
1000
500


CO2Me
Me
H
H
Me
Me
MeO
MeO
Me
Me
203 (2:1)
12
10
8
6
4
2
0
ppm

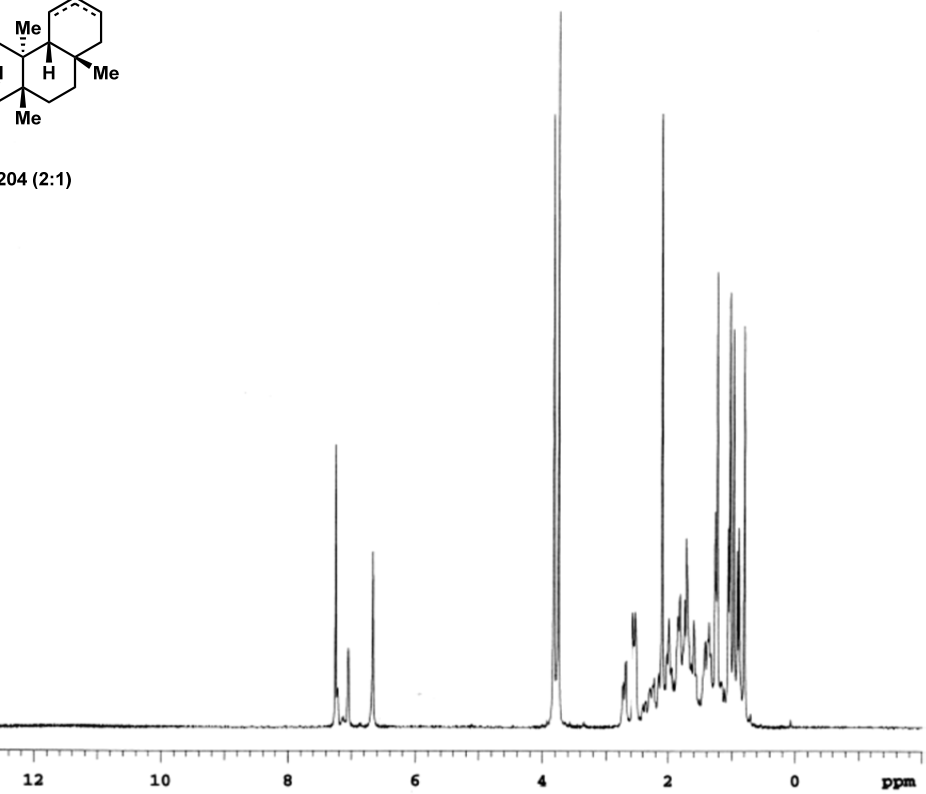

220
200
180
160
140
120
100
80
60
40
20
0
ppm

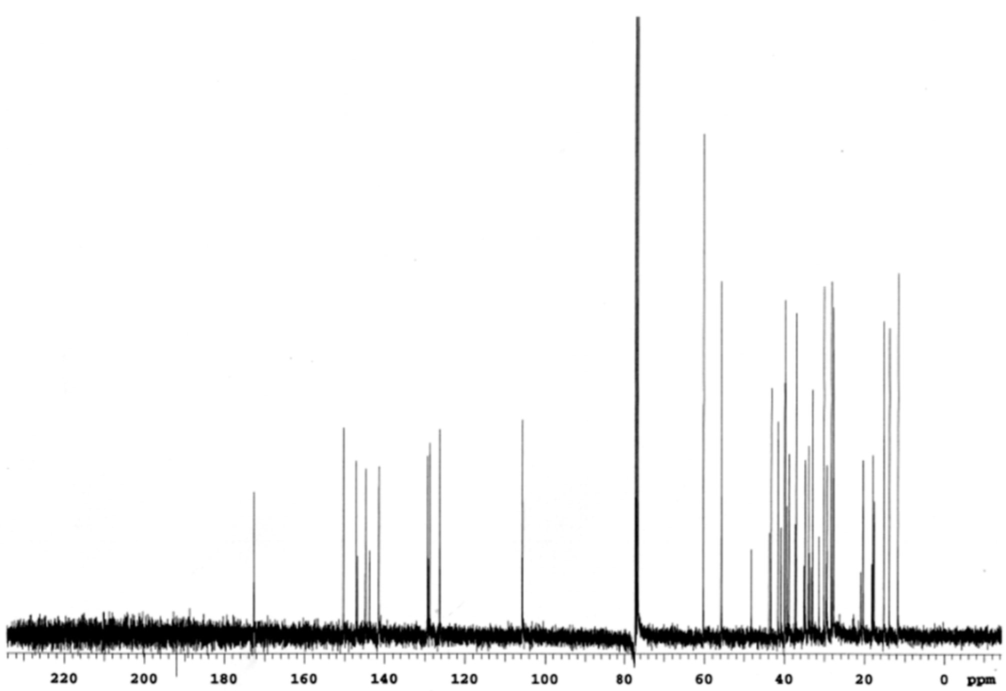


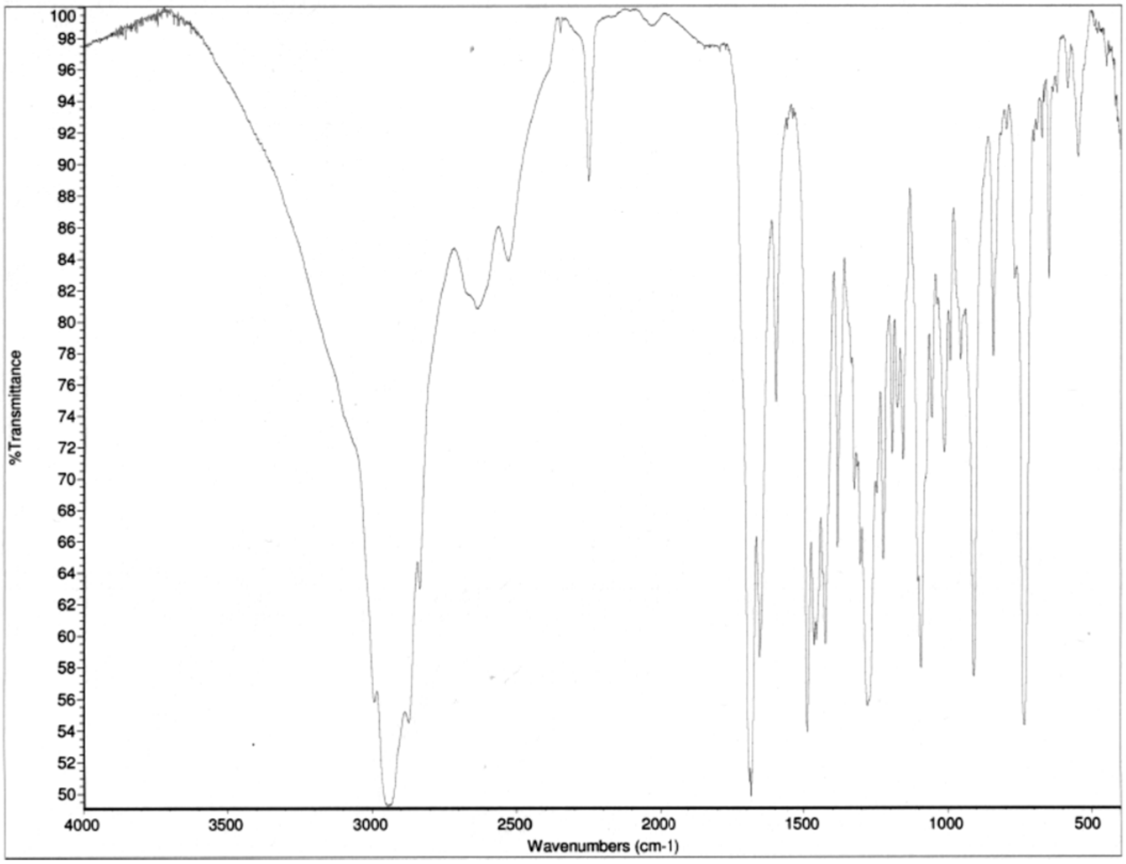
Fri Dec 13 11:26:16 2013 (GMT-06:00)
FIND PEAKS:
Spectrum: *Fri Dec 13 11:16:51 2013 (GMT-06:00)
Region: 4000.00 400.00
Absolute threshold: 82.305
Sensitivity: 50
Peak list:

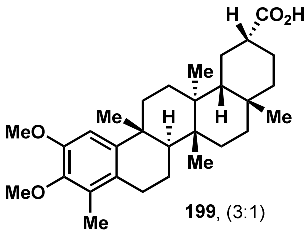

CO2H
Me
H
H
Me
Me
Me
MeO
MeO
Me

204 (2:1)


12
10
8
6
4
2
0
ppm

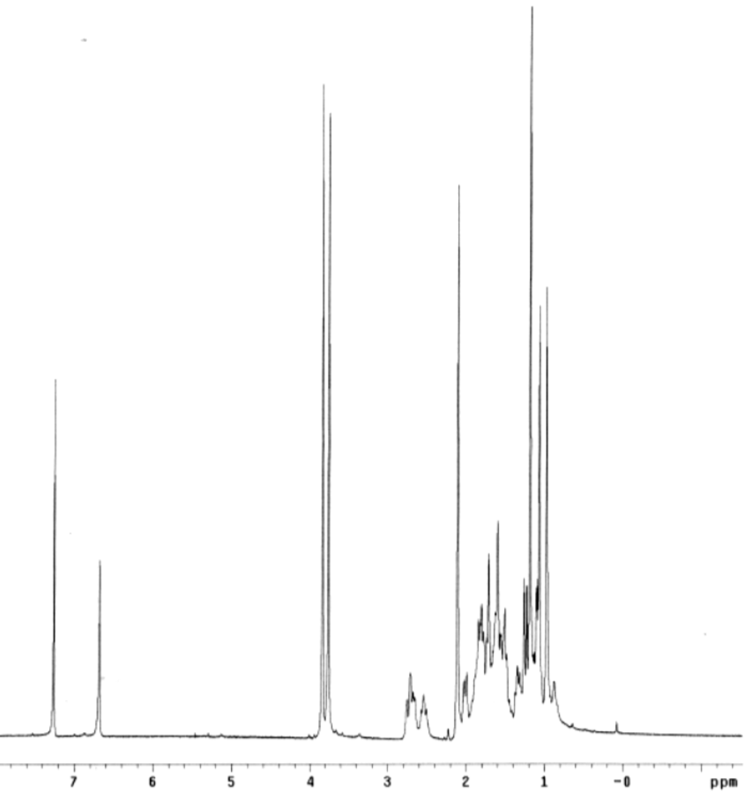

220
200
180
160
140
120
100
80
60
40
20
0
ppm


%Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
52
50
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

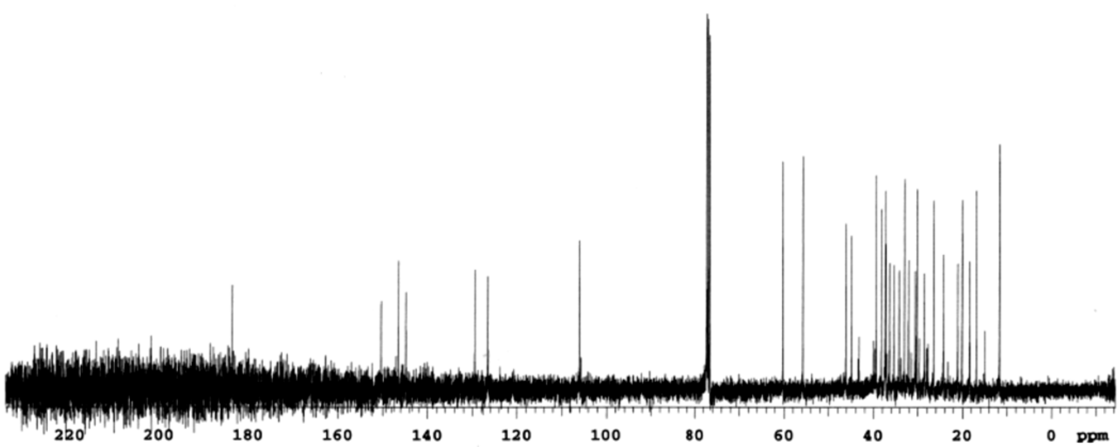


H
CO2H
Me
Me
H
H
Me
MeO
MeO
Me
Me

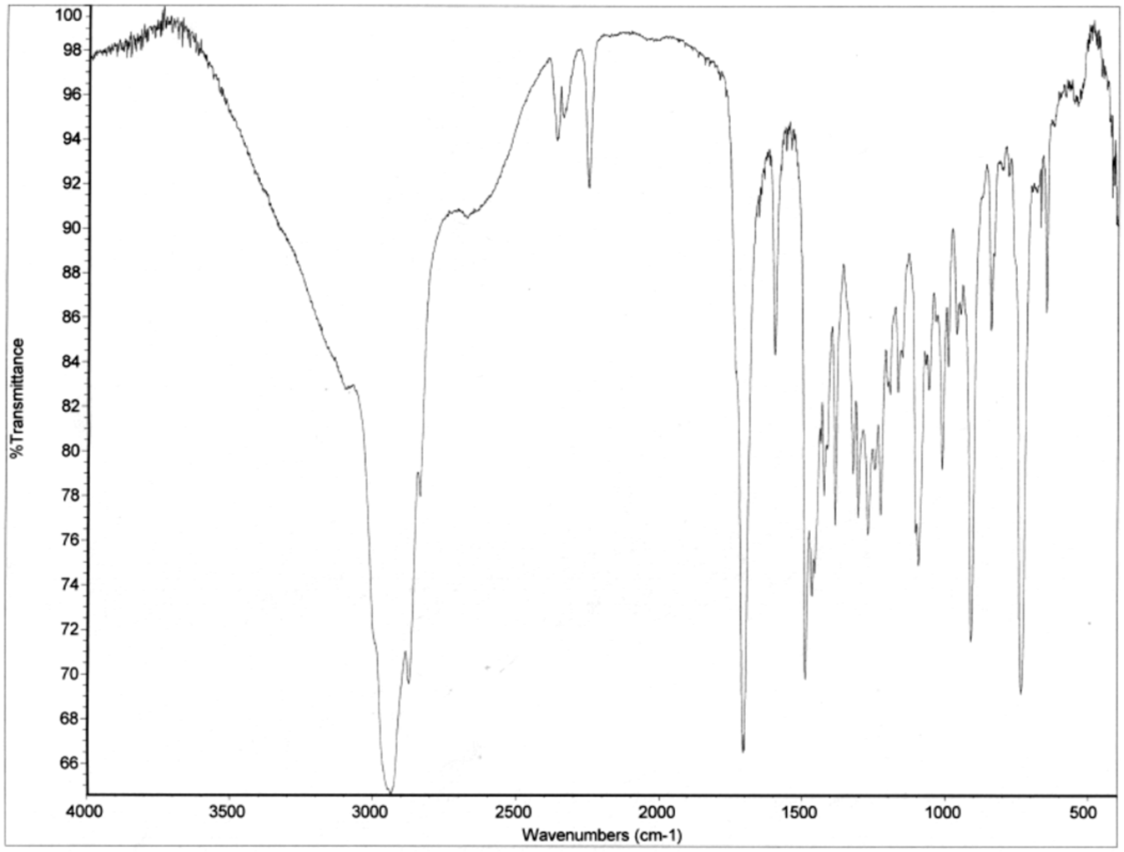
199, (3:1)



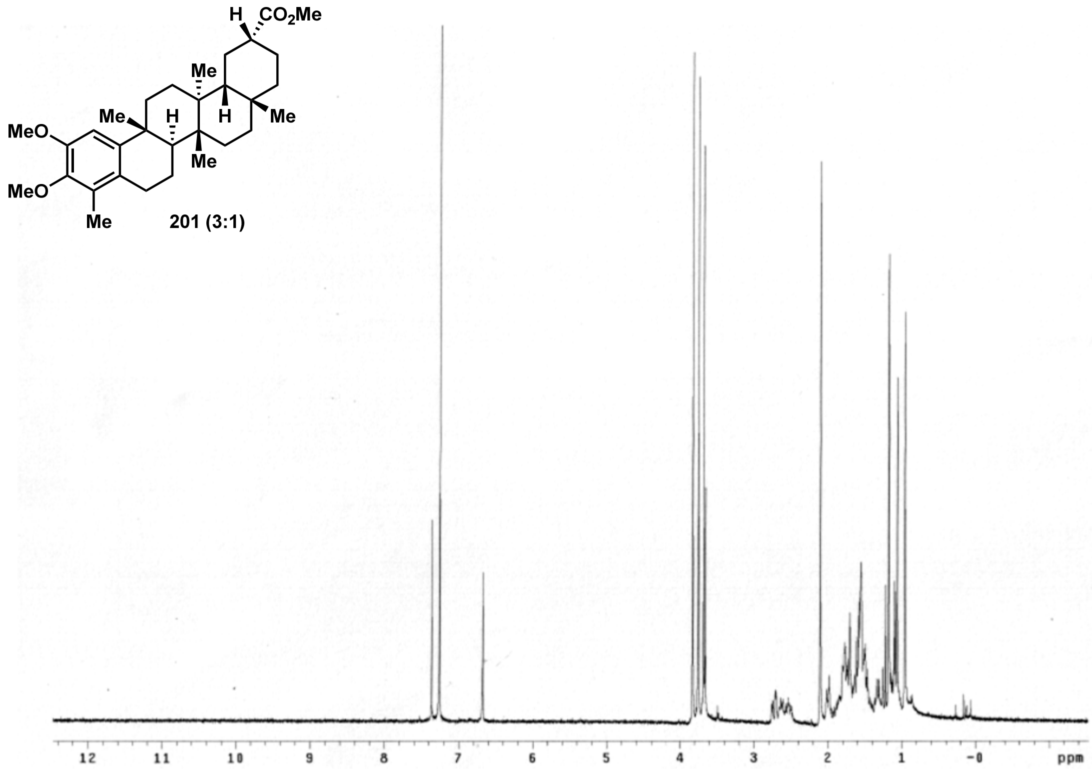
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm

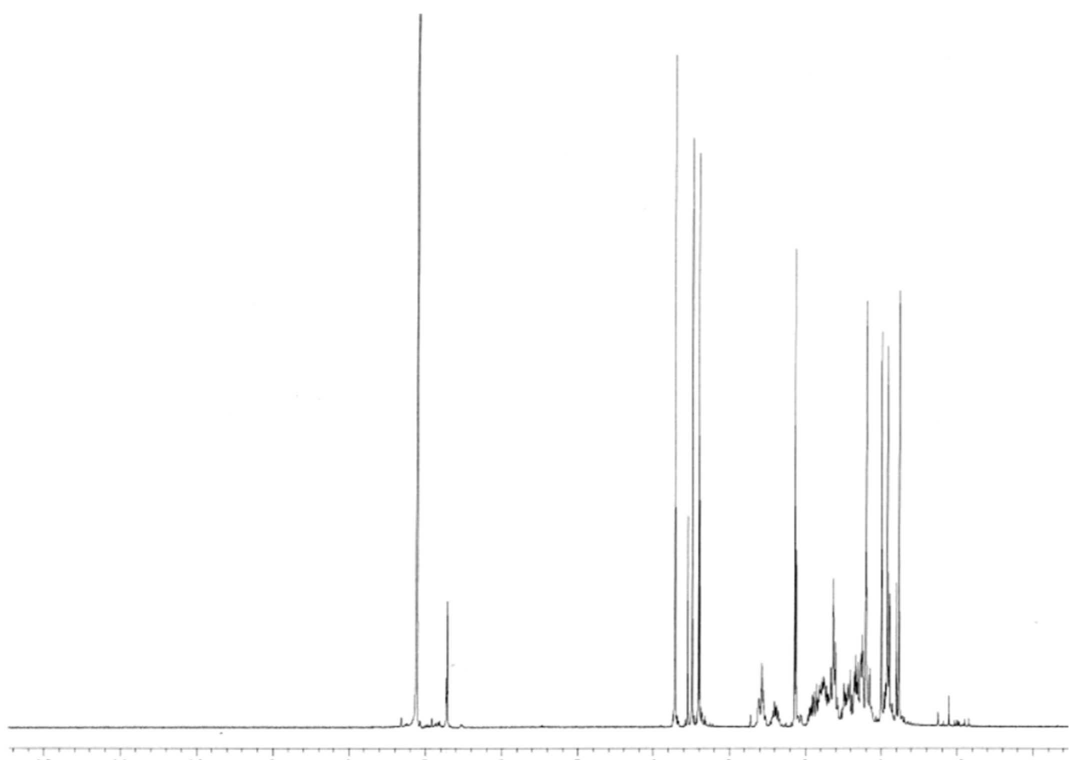


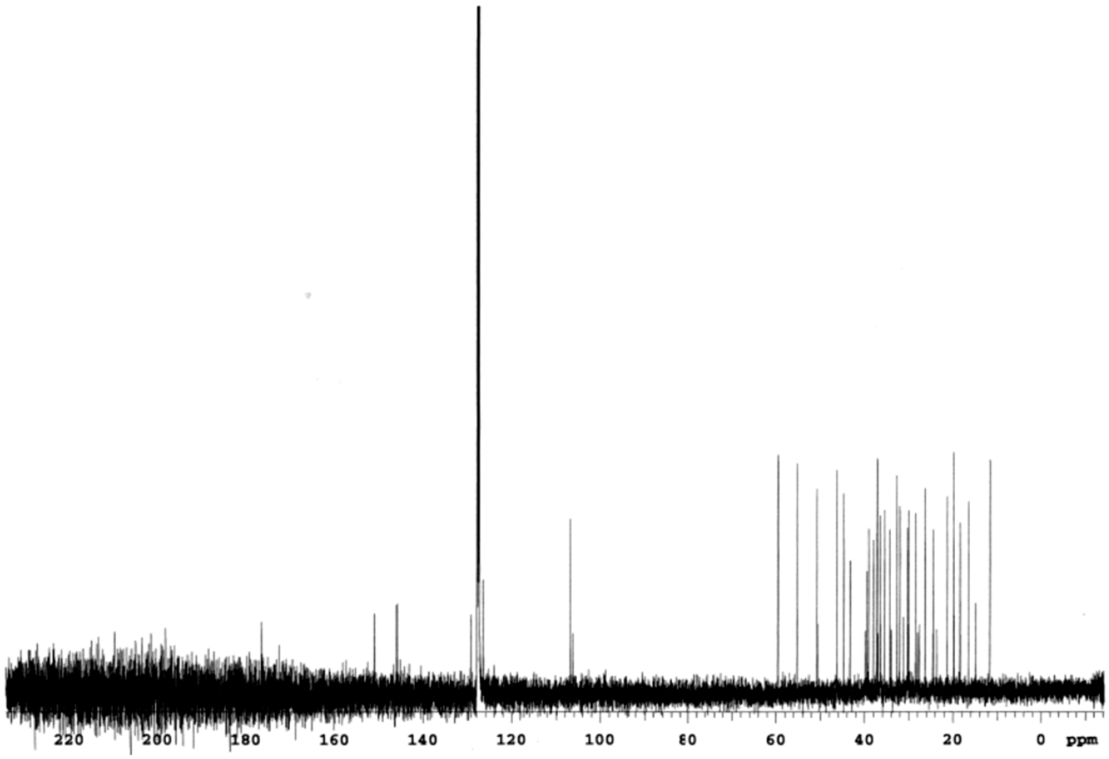
220
200
180
160
140
120
100
80
60
40
20
0
ppm

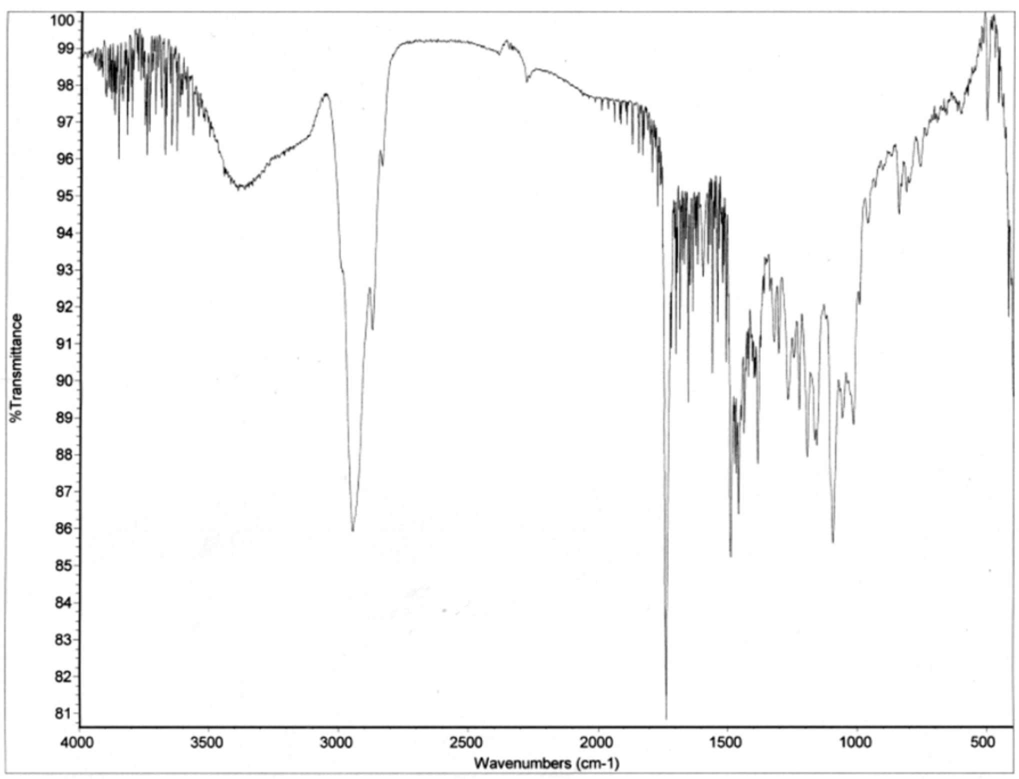


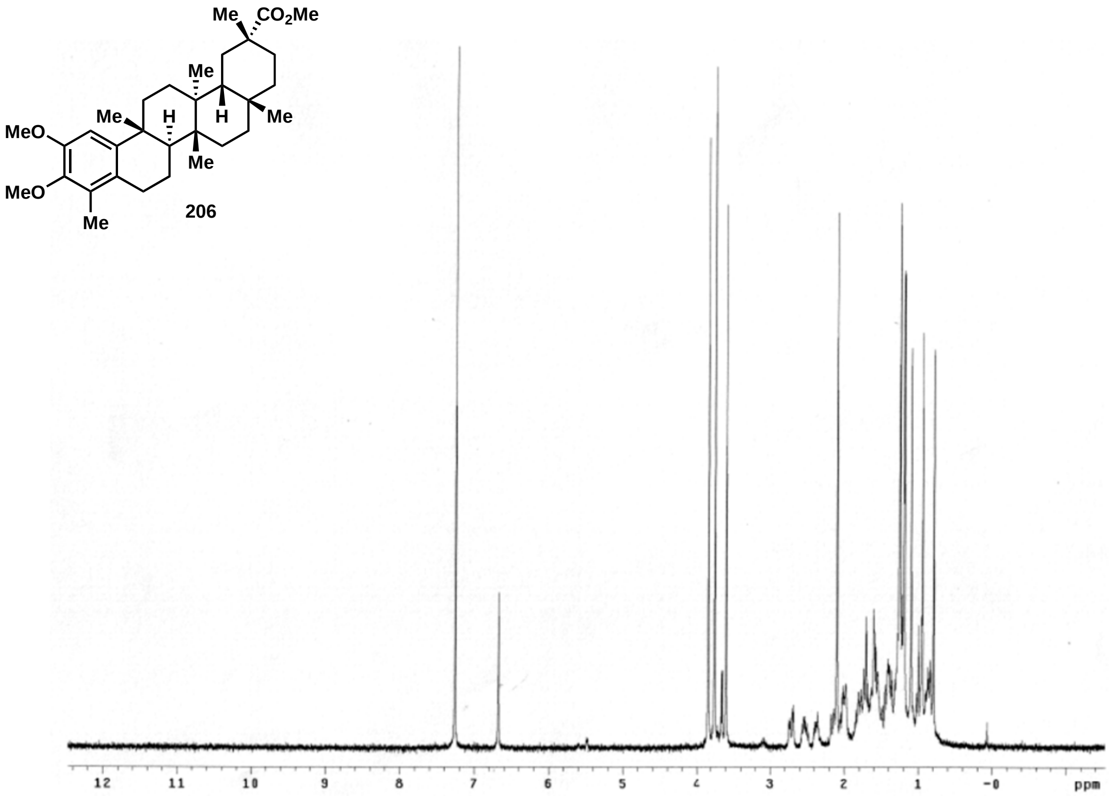
%Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

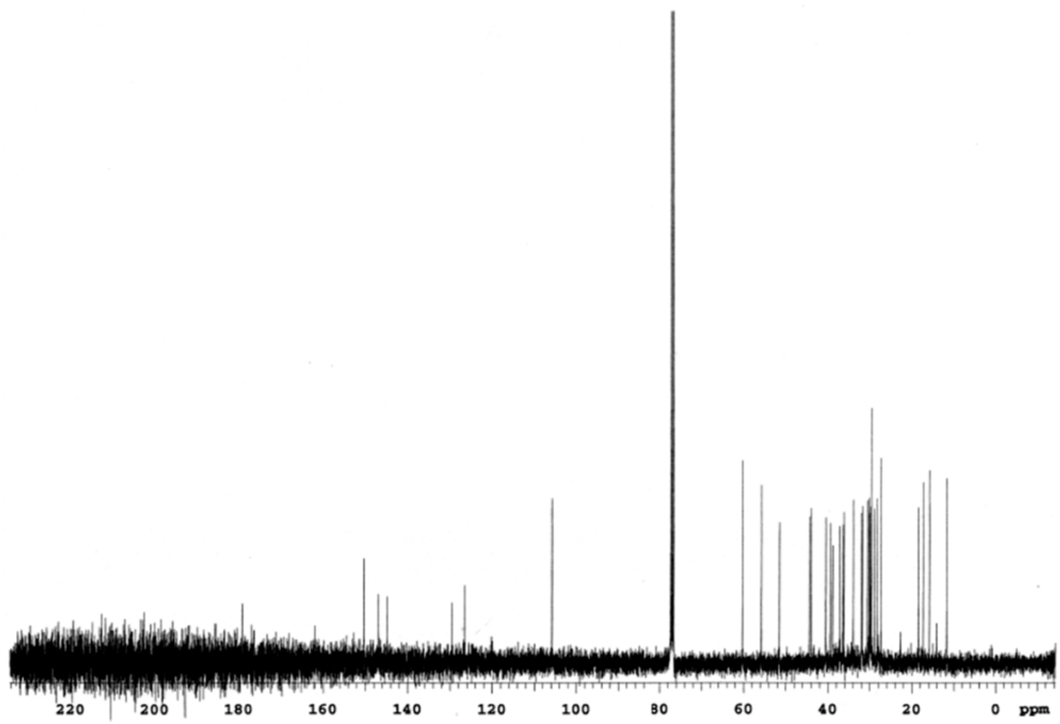

H
CO2Me
Me
Me
H
H
Me
MeO
MeO
Me
Me
201 (3:1)
12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

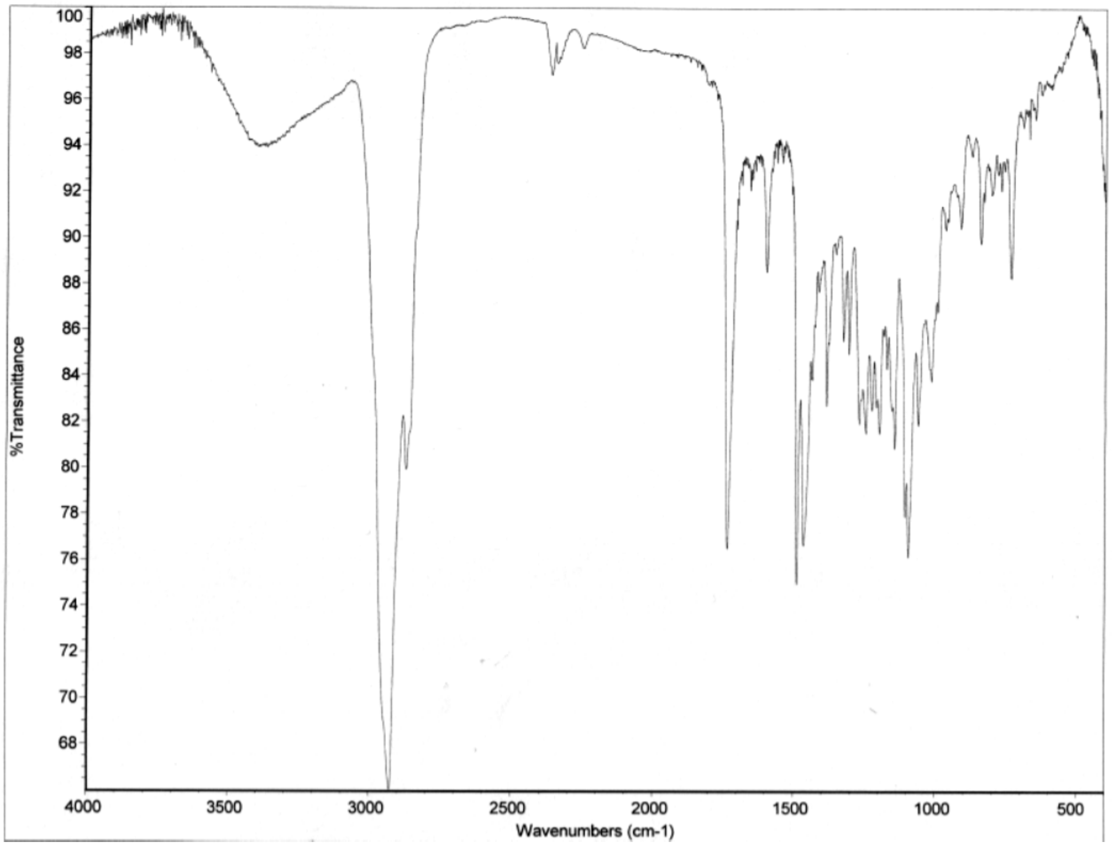

12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm

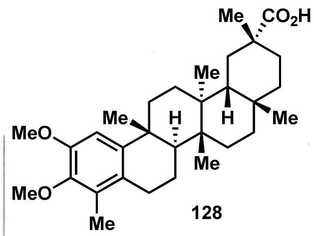

%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
100
99
98
97
96
95
94
93
92
91
90
89
88
87
86
85
84
83
82
81


Me
CO2Me
Me
Me
H
H
Me
MeO
MeO
Me
Me
206
12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

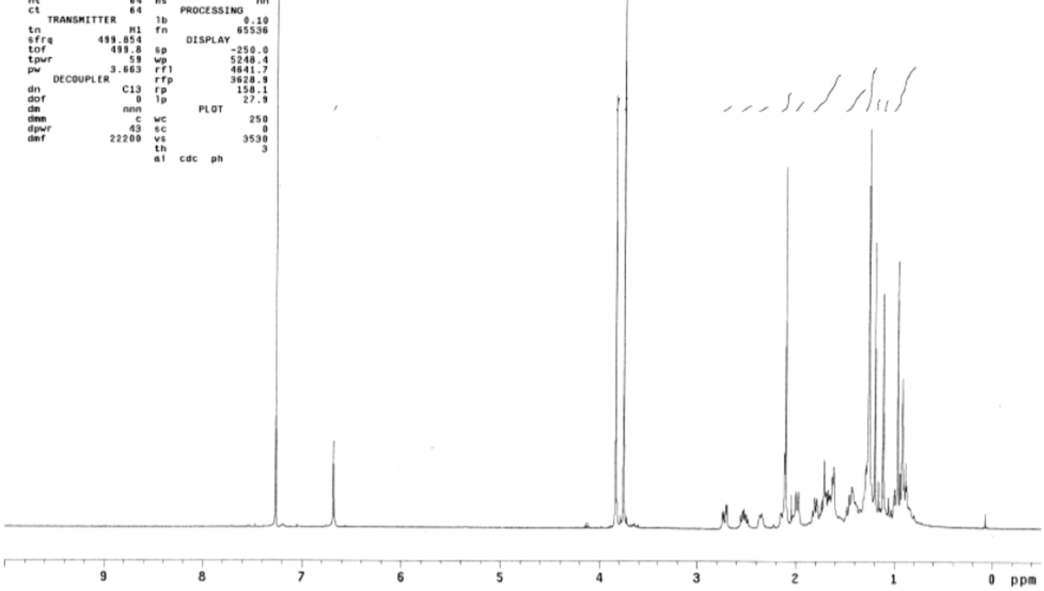

220 200 180 160 140 120 100 80 60 40 20 0 ppm

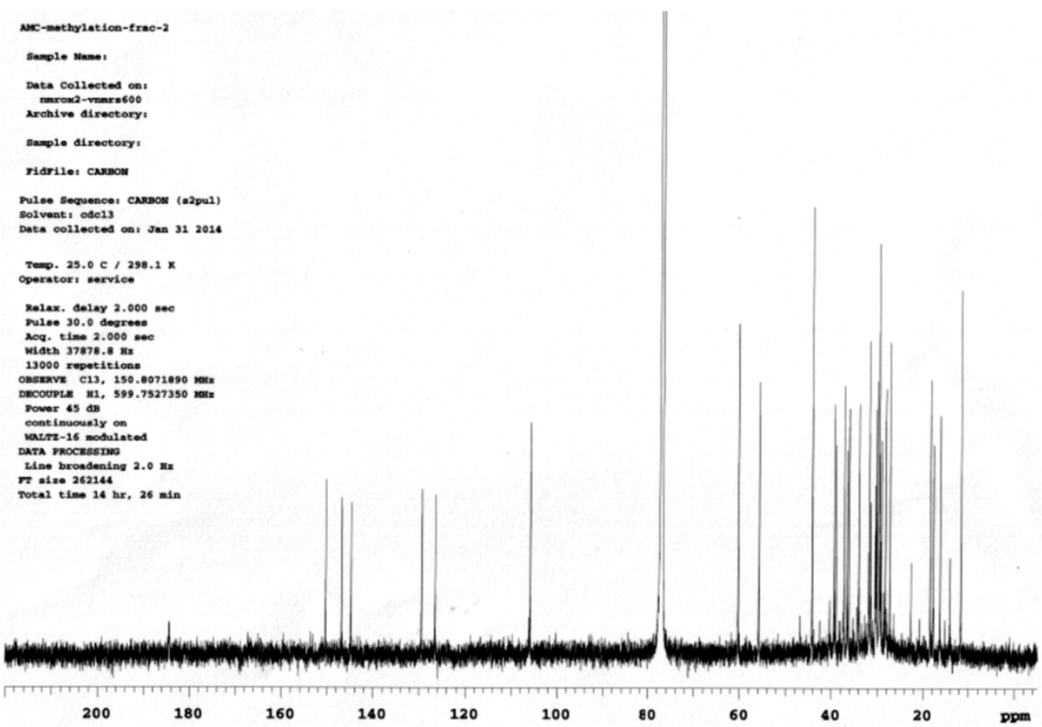


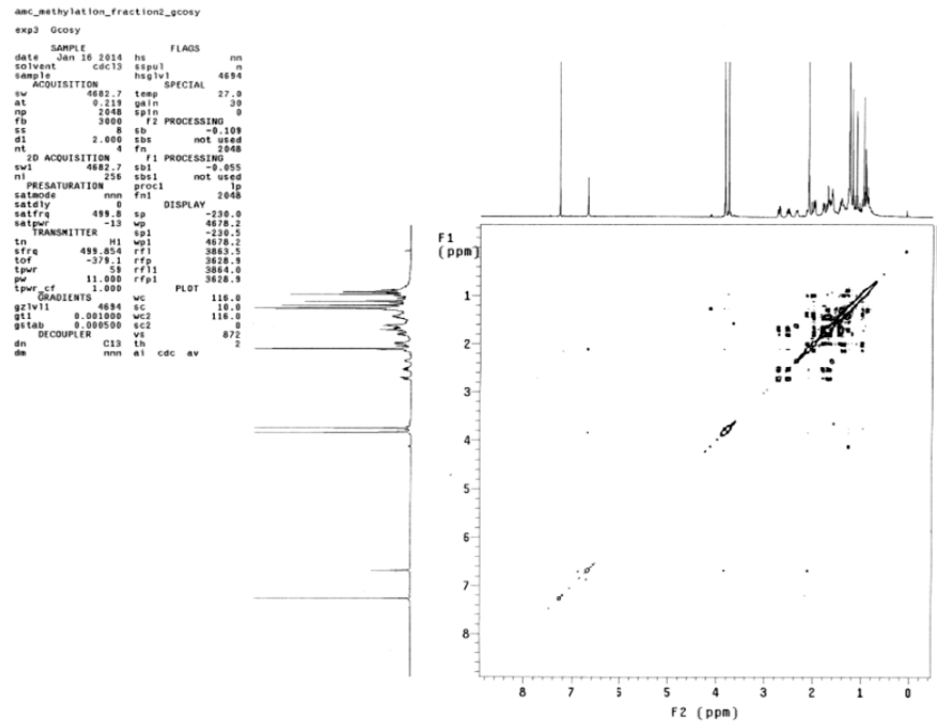
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
%Transmittance
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

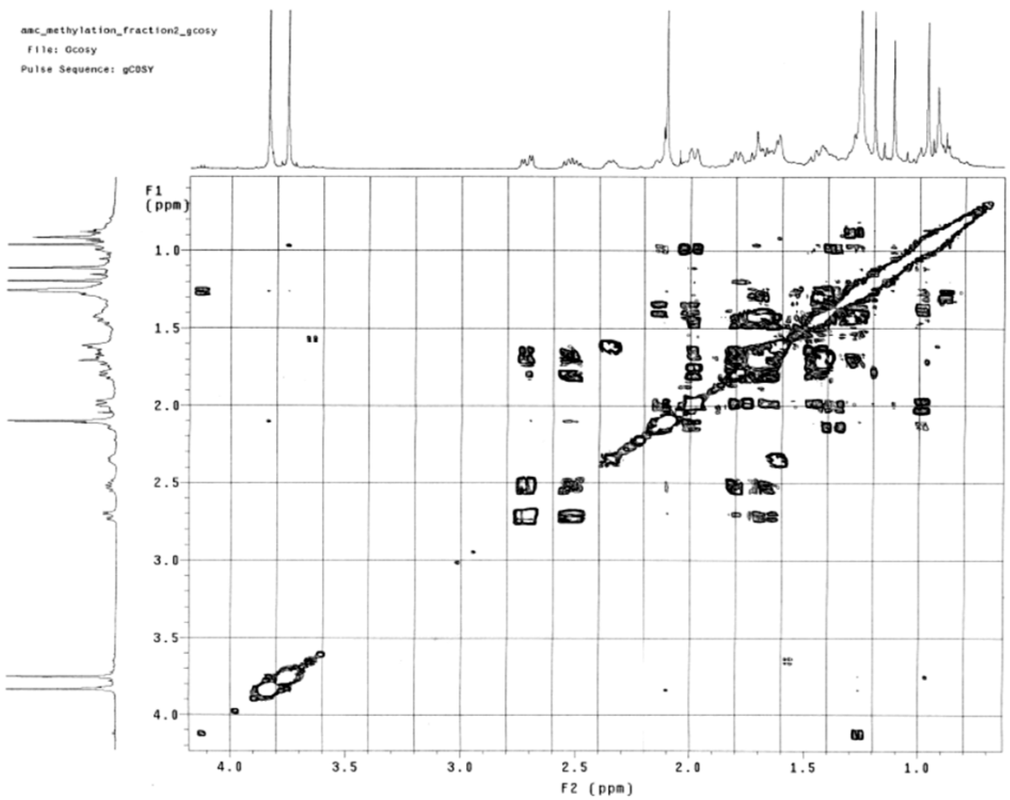

Me
CO2H
Me
Me
H
H
Me
MeO
MeO
Me
Me

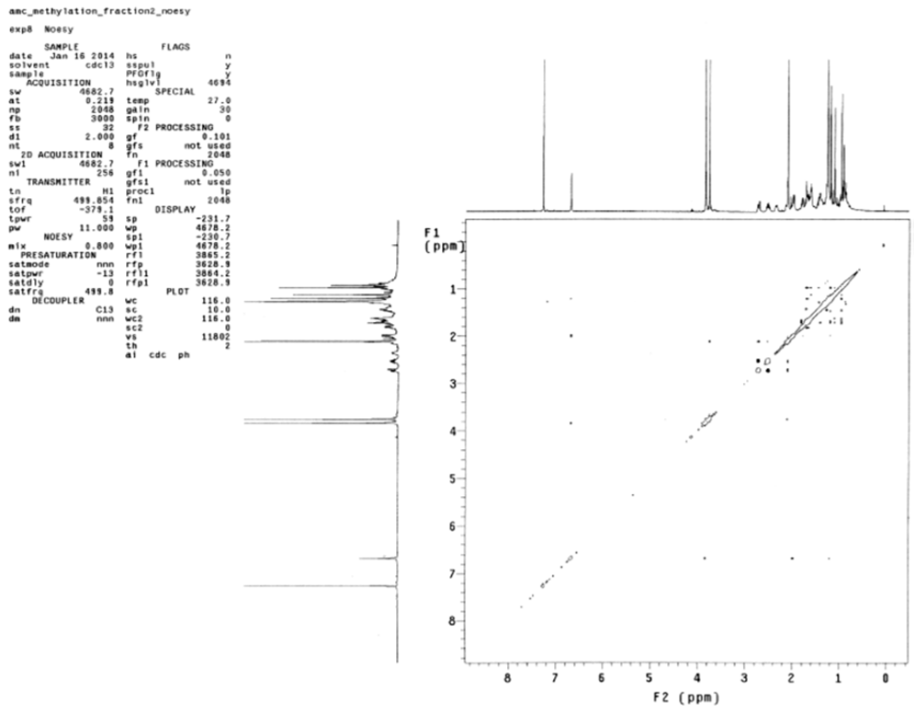
128

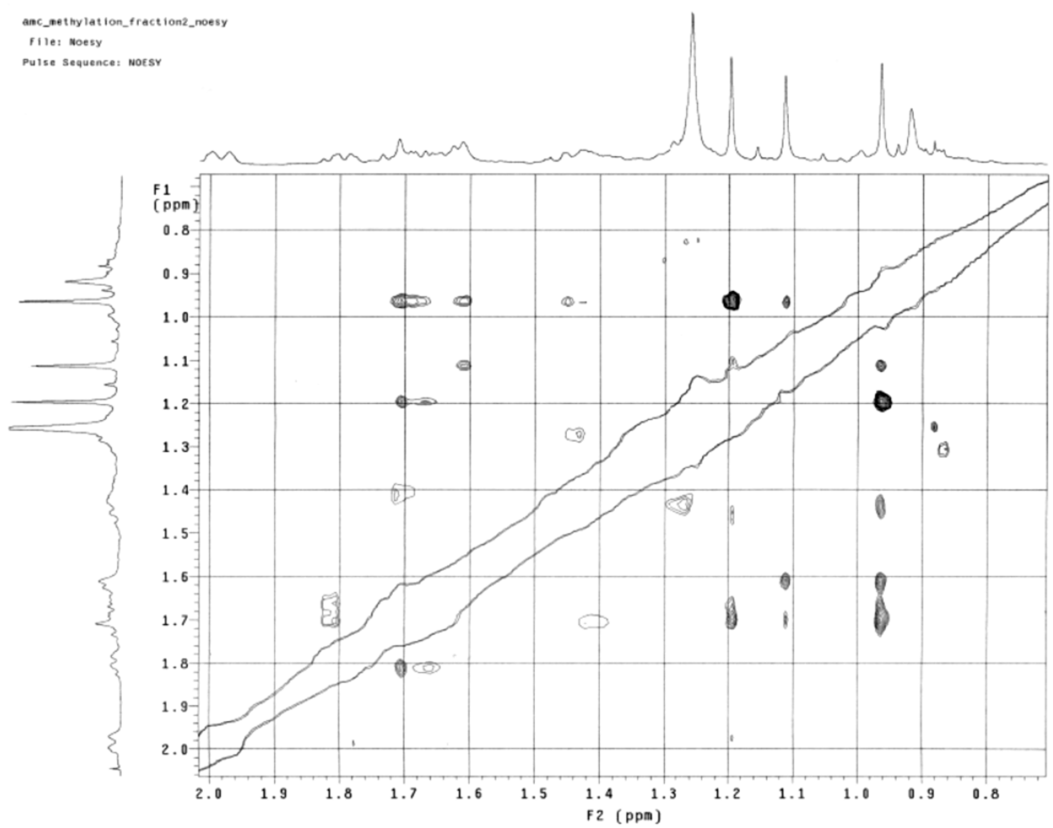

500 MHz nmr0
amc_methylation_fraction2_h1
exp1 Proton
9
8
7
6
5
4
3
2
1
0 ppm

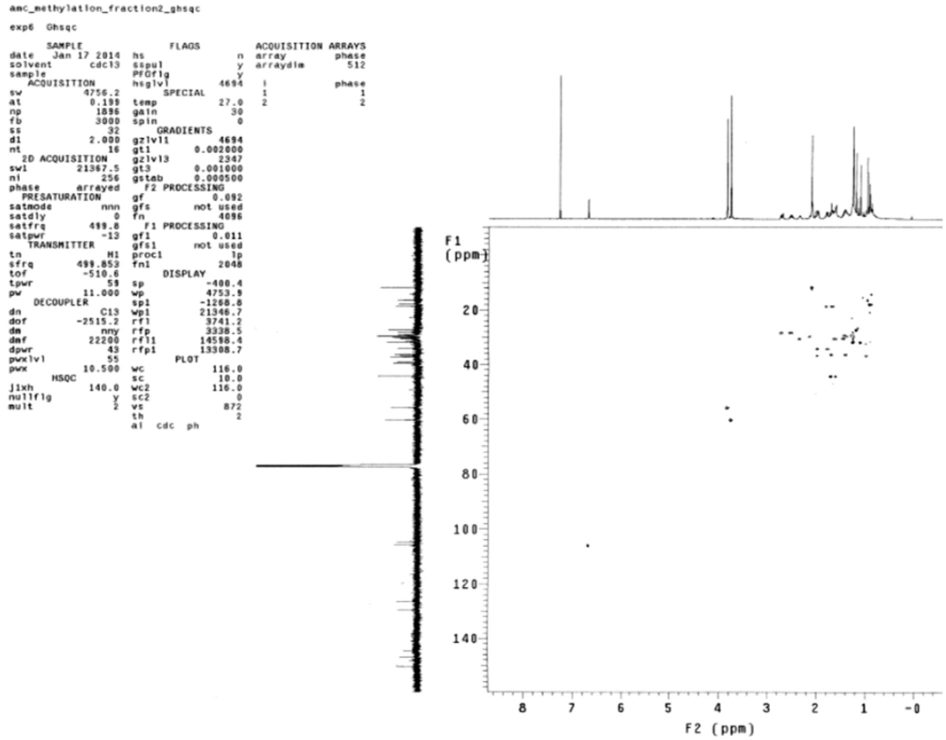

AMC-methylation-frac-2
Sample Name:
Data Collected on:
nmrox2-vnmrs600
Archive directory:
Sample directory:
FidFile: CARBON
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 31 2014
Temp. 25.0 C / 298.1 K
Operator: service
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 2.000 sec
Width 37878.8 Hz
13000 repetitions
OBSERVE C13, 150.8071890 MHz
DECOUPLE H1, 599.7527350 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 262144
Total time 14 hr, 26 min
200
180
160
140
120
100
80
60
40
20
ppm

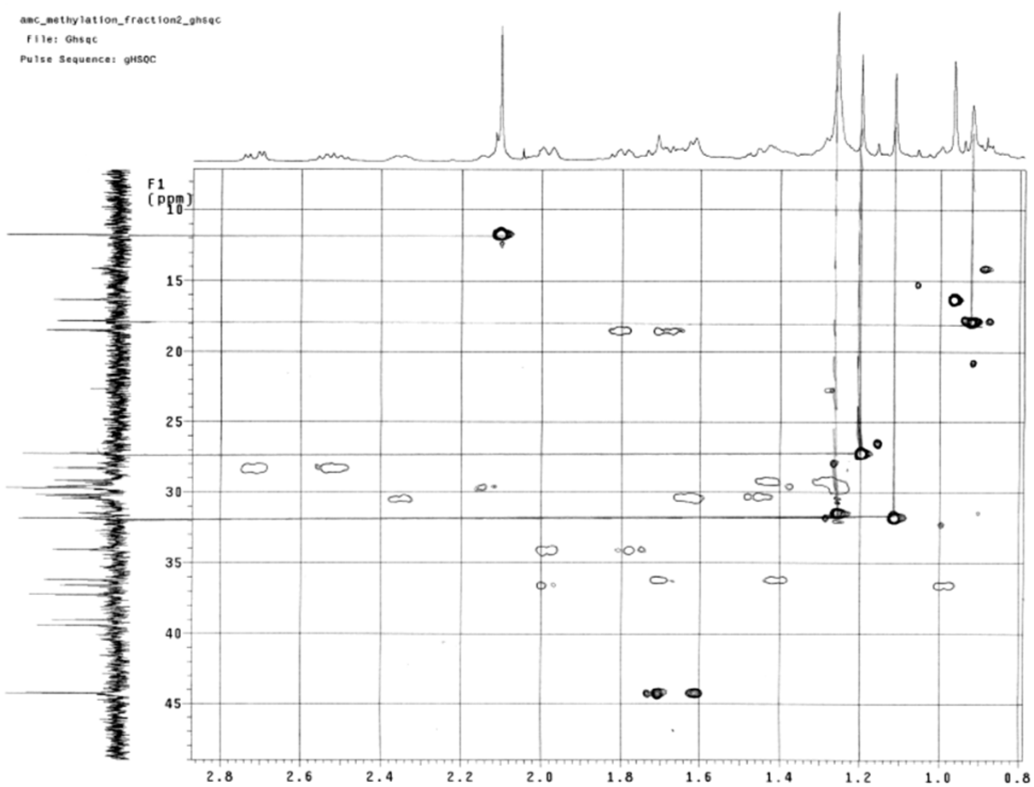

amc_methylation_fraction2_gcosy
exp3 Gcosy
SAMPLE
date Jan 16 2014
solvent cdcl3
sample
ACQUISITION
sw 4682.7
at 0.219
np 2048
fb 3000
ss 8
d1 2.000
nt 4
2D ACQUISITION
sw1 4682.7
ni 256
PRESATURATION
satmode nnn
satdly 0
satfrq 499.8
satpwr -13
TRANSMITTER
tn H1
sfrq 499.854
tof -379.1
tpwr 59
pw 11.000
tpwr_cf 1.000
GRADIENTS
gzlvl1 4694
gt1 0.001000
gstab 0.000500
DECOUPLER
dn C13
dm nnn
FLAGS
hs nn
sspul n
hsglvl 4694
SPECIAL
temp 27.0
gain 30
spin 0
F2 PROCESSING
sb -0.109
sbs not used
fn 2048
F1 PROCESSING
sb1 -0.055
sbs1 not used
proc1 lp
fn1 2048
DISPLAY
sp -230.0
wp 4678.2
sp1 -230.5
wp1 4678.2
rfl 3863.5
rfp 3628.9
rfl1 3864.0
rfp1 3628.9
PLOT
wc 116.0
sc 10.0
wc2 116.0
sc2 0
vs 872
th 2
ai cdc av
F1 (ppm)
F2 (ppm)

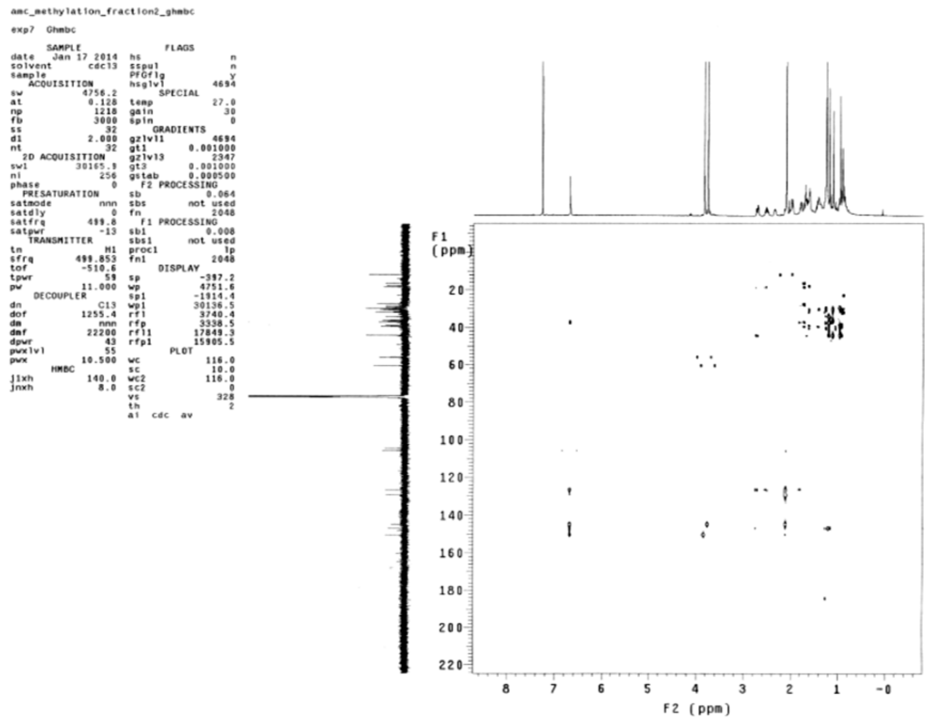

amc_methylation_fraction2_gcosy
File: Gcosy
Pulse Sequence: gCOSY
F1 (ppm)
F2 (ppm)

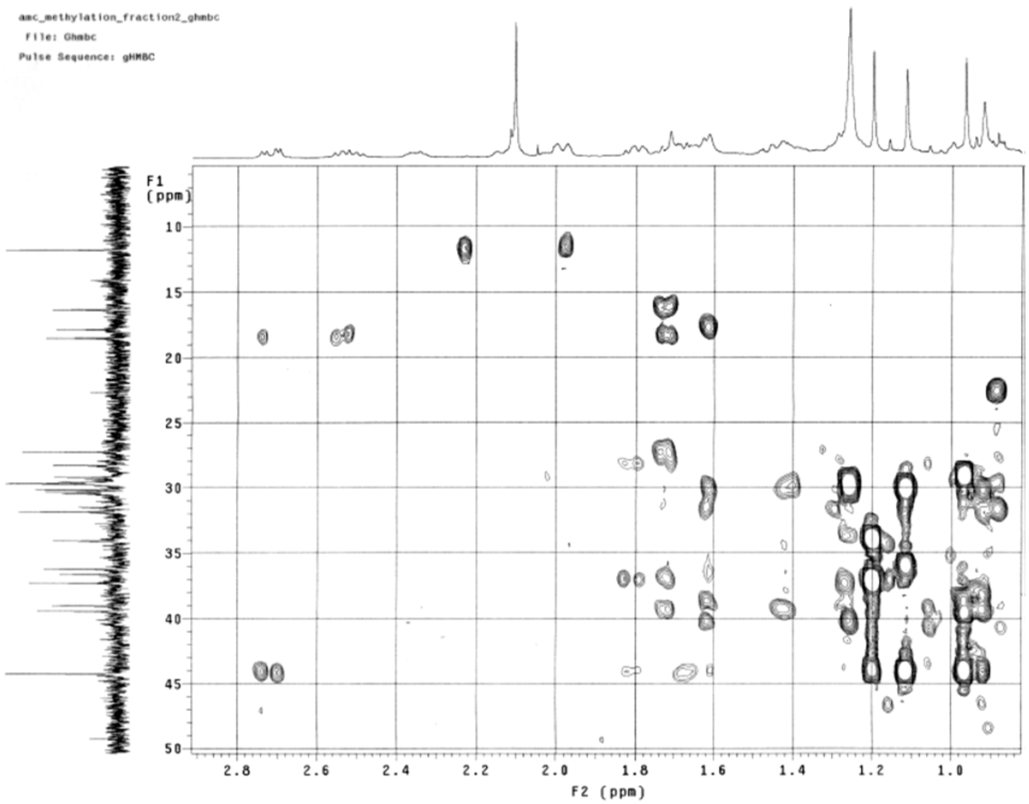

amc_methylation_fraction2_noesy
exp8 Noesy
SAMPLE
date Jan 16 2014
solvent cdcl3
sample
ACQUISITION
sw 4682.7
at 0.219
np 2048
fb 3000
ss 32
d1 2.000
nt 8
2D ACQUISITION
sw1 4682.7
ni 256
TRANSMITTER
tn H1
sfrq 499.854
tof -379.1
tpwr 59
pw 11.000
NOESY
mix 0.800
PRESATURATION
satmode nnn
satpwr -13
satdly 0
satfrq 499.8
DECOUPLER
dn C13
dm nnn
FLAGS
hs n
sspul y
PFGflg y
hsglvl 4694
SPECIAL
temp 27.0
gain 30
spin 0
F2 PROCESSING
gf 0.101
gfs not used
fn 2048
F1 PROCESSING
gf1 0.050
gfs1 not used
proc1 lp
fn1 2048
DISPLAY
sp -231.7
wp 4678.2
sp1 -230.7
wp1 4678.2
rfl 3865.2
rfp 3628.9
rfl1 3864.2
rfp1 3628.9
PLOT
wc 116.0
sc 10.0
wc2 116.0
sc2 0
vs 11802
th 2
ai cdc ph
F1 (ppm)
F2 (ppm)

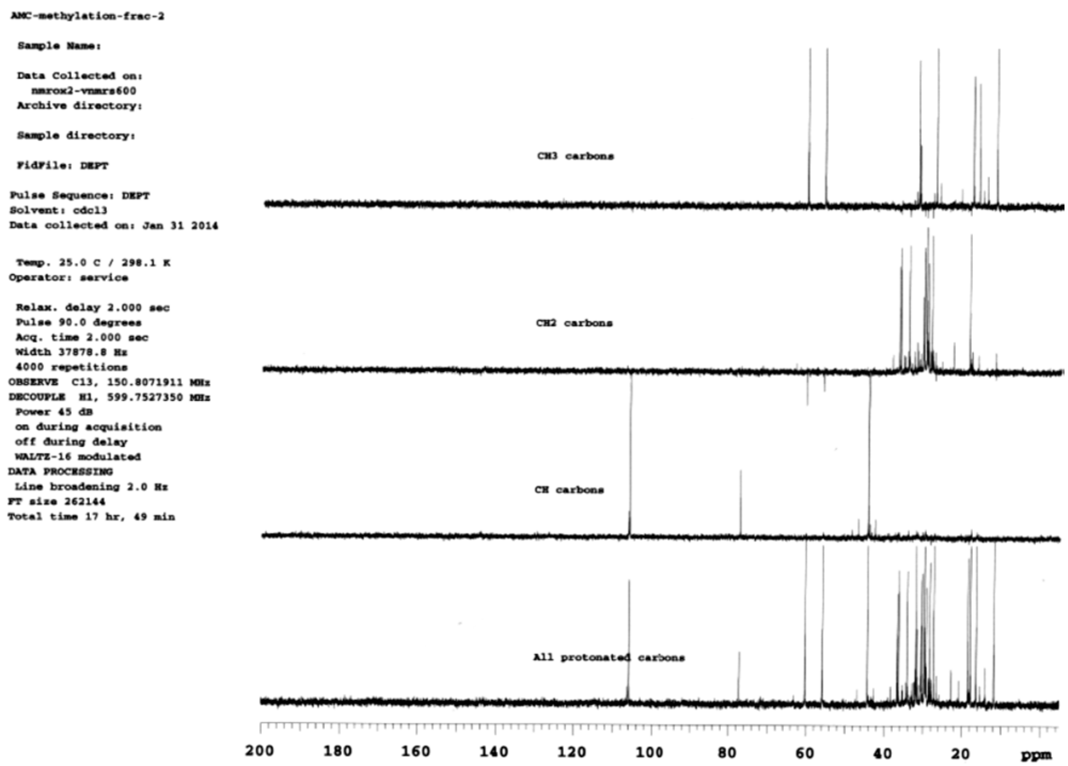

amc_methylation_fraction2_noesy
File: Noesy
Pulse Sequence: NOESY
F1 (ppm)
F2 (ppm)

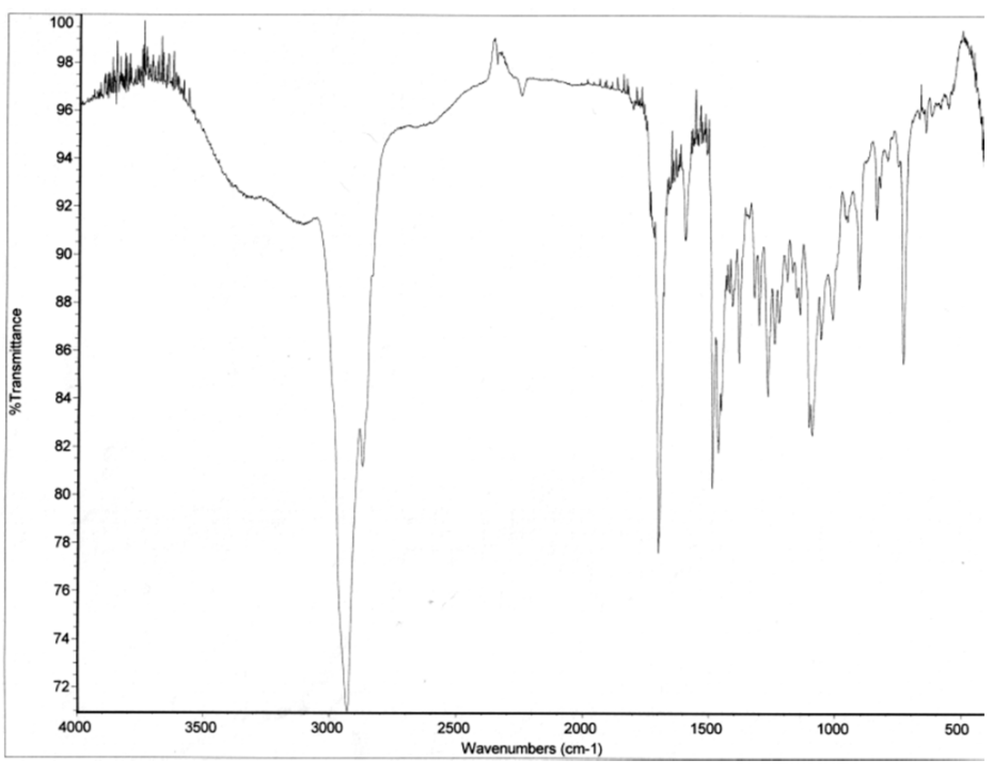

amc_methylation_fraction2_ghsqc
exp6 Ghsqc
SAMPLE
date Jan 17 2014
solvent cdcl3
sample
ACQUISITION
sw 4756.2
at 0.199
np 1896
fb 3000
ss 32
d1 2.000
nt 16
2D ACQUISITION
sw1 21367.5
ni 256
phase arrayed
PRESATURATION
satmode nnn
satdly 0
satfrq 499.8
satpwr -13
TRANSMITTER
tn H1
sfrq 499.853
tof -510.6
tpwr 59
pw 11.000
DECOUPLER
dn C13
dof -2515.2
dm nny
dmf 22200
dpwr 43
pwxlvl 55
pwx 10.500
HSQC
j1xh 140.0
nullflg y
mult 2
FLAGS
hs n
sspul y
PFGflg y
hsglvl 4694
SPECIAL
temp 27.0
gain 30
spin 0
GRADIENTS
gzlvl1 4694
gt1 0.002000
gzlvl3 2347
gt3 0.001000
gstab 0.000500
F2 PROCESSING
gf 0.092
gfs not used
fn 4096
F1 PROCESSING
gf1 0.011
gfs1 not used
proc1 lp
fn1 2048
DISPLAY
sp -400.4
wp 4753.9
sp1 -1268.8
wp1 21346.7
rfl 3741.2
rfp 3338.5
rfl1 14598.4
rfp1 13308.7
PLOT
wc 116.0
sc 10.0
wc2 116.0
sc2 0
vs 872
th 2
ai cdc ph
ACQUISITION ARRAYS
array phase
arraydim 512
i phase
1 1
2 2
F1 (ppm)
F2 (ppm)

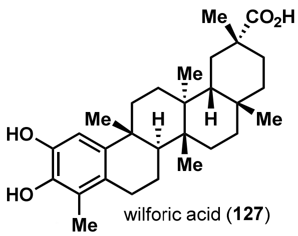

amc_methylation_fraction2_ghsqc
File: Ghsqc
Pulse Sequence: gHSQC
F1 (ppm)
F2 (ppm)


amc_methylation_fraction2_ghmbc
exp7 Ghmbc
SAMPLE
date Jan 17 2014
solvent cdcl3
sample
ACQUISITION
sw 4756.2
at 0.128
np 1218
fb 3000
ss 32
d1 2.000
nt 32
2D ACQUISITION
sw1 30165.9
ni 256
phase 0
PRESATURATION
satmode nnn
satdly 0
satfrq 499.8
satpwr -13
TRANSMITTER
tn H1
sfrq 499.853
tof -510.6
tpwr 59
pw 11.000
DECOUPLER
dn C13
dof 1255.4
dm nnn
dmf 22200
dpwr 43
pwxlvl 55
pwx 10.500
HMBC
j1xh 140.0
jnxh 8.0
FLAGS
hs n
sspul n
PFGflg y
hsglvl 4694
SPECIAL
temp 27.0
gain 30
spin 0
GRADIENTS
gzlvl1 4694
gt1 0.001000
gzlvl3 2347
gt3 0.001000
gstab 0.000500
F2 PROCESSING
sb 0.064
sbs not used
fn 2048
F1 PROCESSING
sb1 0.008
sbs1 not used
proc1 lp
fn1 2048
DISPLAY
sp -397.2
wp 4751.6
sp1 -1914.4
wp1 30136.5
rfl 3740.4
rfp 3338.5
rfl1 17849.3
rfp1 15905.5
PLOT
wc 116.0
sc 10.0
wc2 116.0
sc2 0
vs 328
th 2
ai cdc av
F1 (ppm)
F2 (ppm)

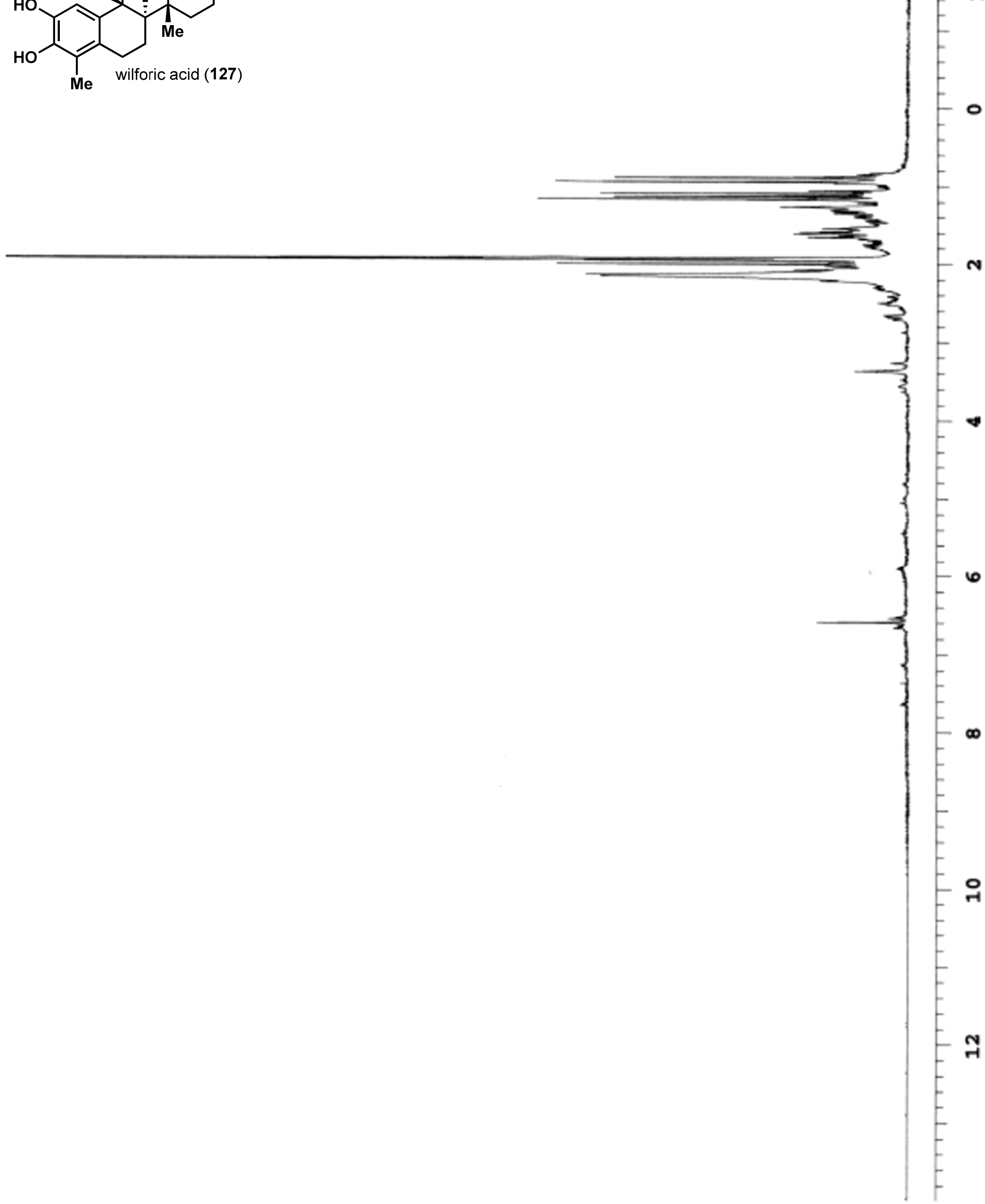

amc_methylation_fraction2_ghmbc
File: Ghmbc
Pulse Sequence: gHMBC
F1 (ppm)
F2 (ppm)

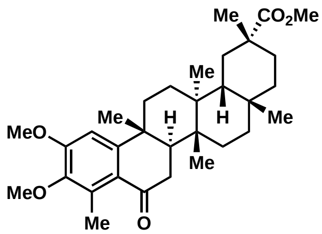

AMC-methylation-frac-2
Sample Name:
Data Collected on:
nmrox2-vnmrs600
Archive directory:
Sample directory:
FidFile: DEPT
Pulse Sequence: DEPT
Solvent: cdcl3
Data collected on: Jan 31 2014
Temp. 25.0 C / 298.1 K
Operator: service
Relax. delay 2.000 sec
Pulse 90.0 degrees
Acq. time 2.000 sec
Width 37878.8 Hz
4000 repetitions
OBSERVE C13, 150.8071911 MHz
DECOUPLE H1, 599.7527350 MHz
Power 45 dB
on during acquisition
off during delay
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 262144
Total time 17 hr, 49 min
CH3 carbons
CH2 carbons
CH carbons
All protonated carbons
200 180 160 140 120 100 80 60 40 20 ppm

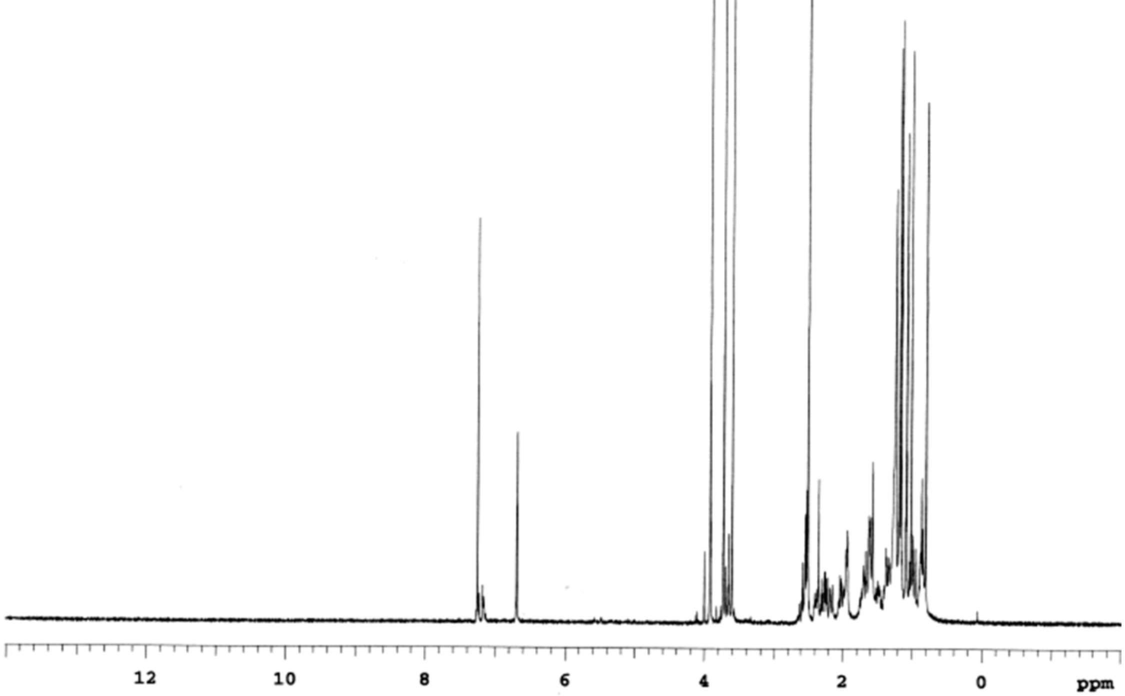

%Transmittance
100 98 96 94 92 90 88 86 84 82 80 78 76 74 72
4000 3500 3000 2500 2000 1500 1000 500
Wavenumbers (cm-1)

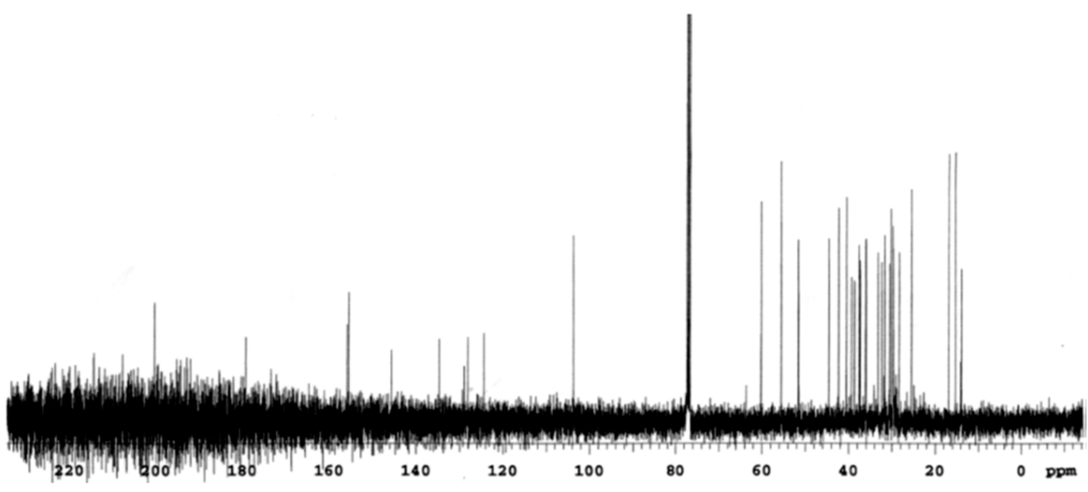


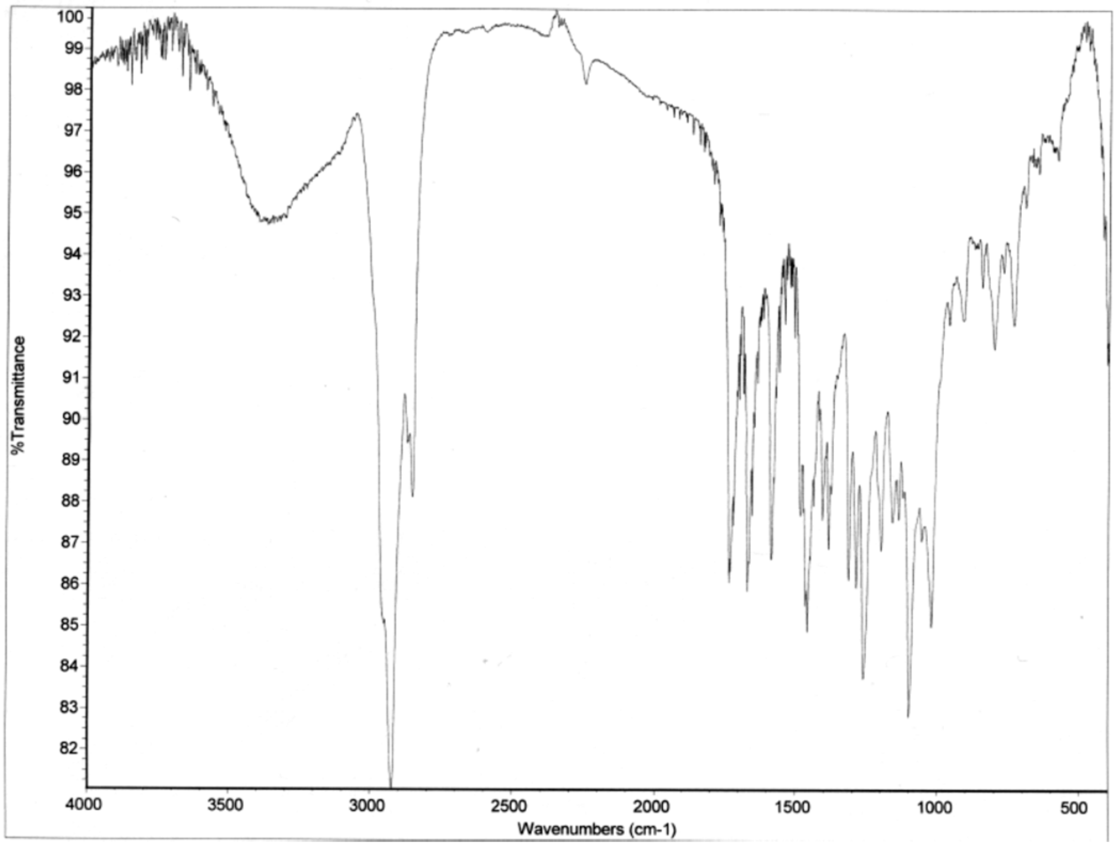
wilforic acid (**127**)

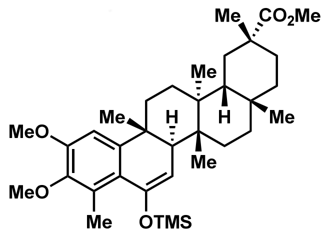



Me
CO_2Me
Me
Me
H
H
Me
MeO
Me
MeO
Me
O

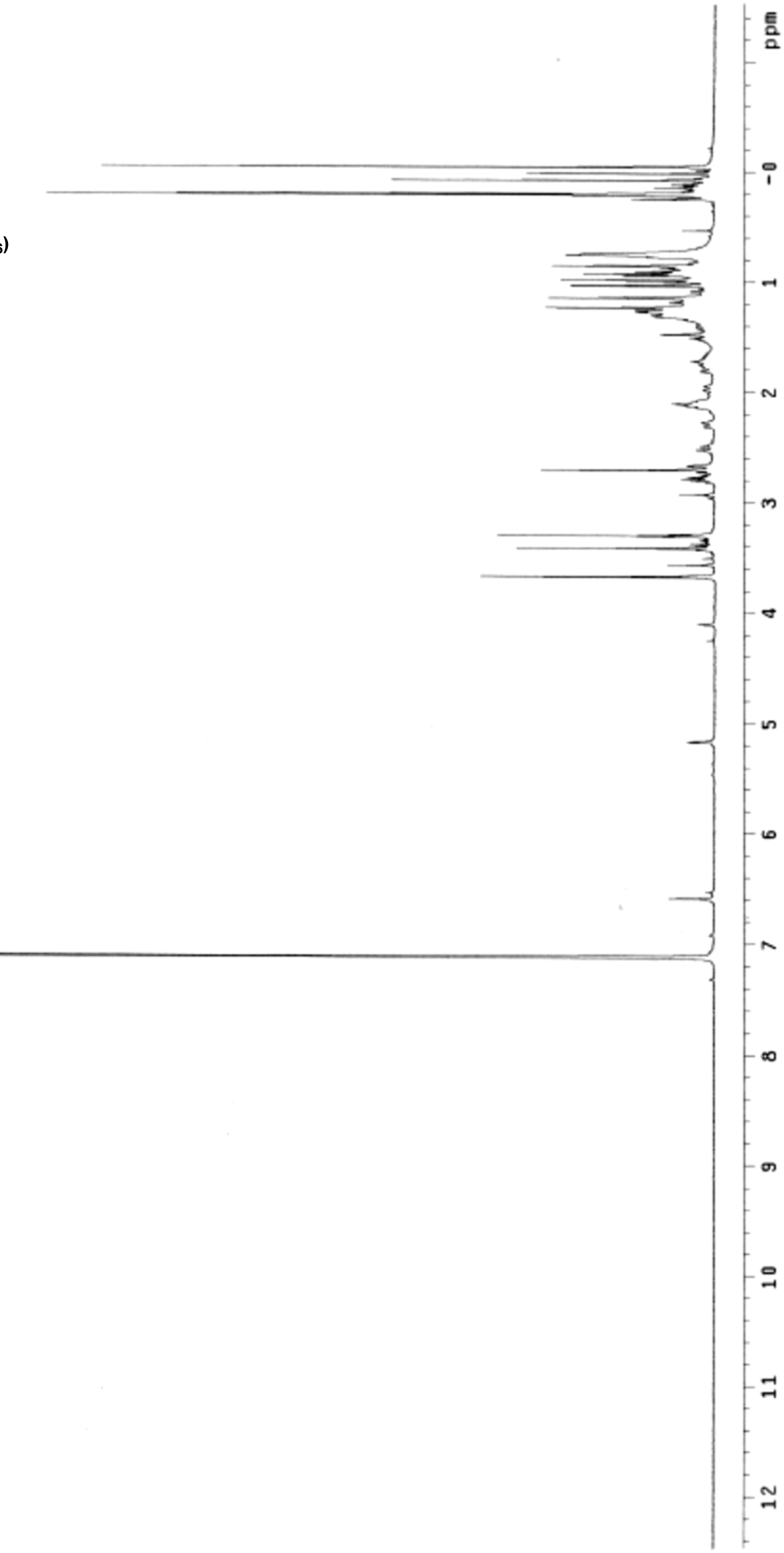

12
10
8
6
4
2
0
ppm

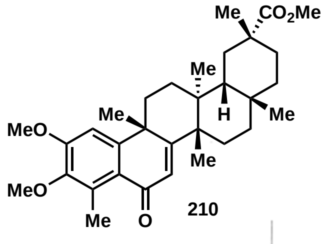

220
200
180
160
140
120
100
80
60
40
20
0
ppm


%Transmittance
100
99
98
97
96
95
94
93
92
91
90
89
88
87
86
85
84
83
82
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

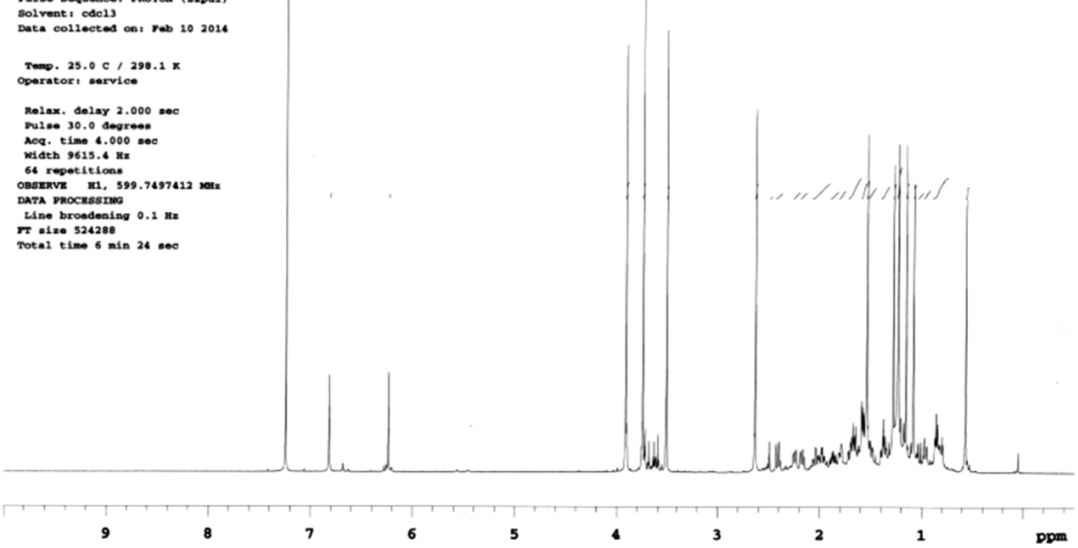


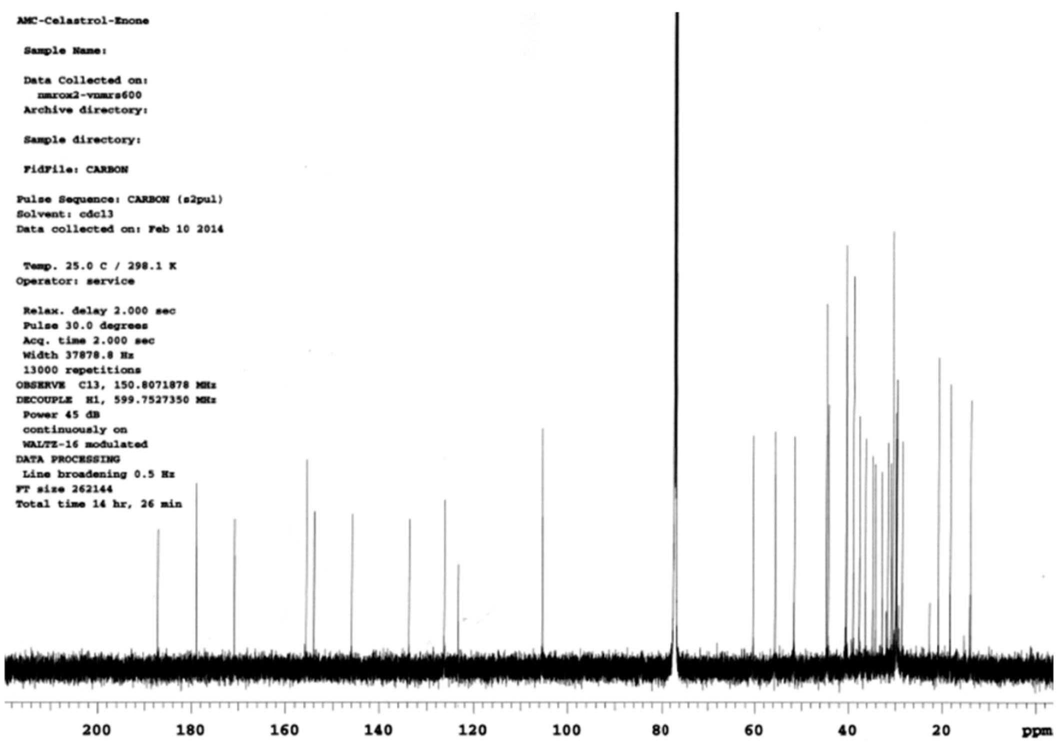
Crude Silyl Enol Ether (^{1}H-NMR in C_6D_6)
Prior to PhSeCl Addition




Me
CO2Me
Me
H
Me
Me
MeO
MeO
Me
Me
O

210


AMC-Celastrol-Enone
Sample Name:
Data Collected on:
nmrox2-vnmrs600
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 10 2014
Temp. 25.0 C / 298.1 K
Operator: service
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 9615.4 Hz
64 repetitions
OBSERVE H1, 599.7497412 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 524288
Total time 6 min 24 sec
9
8
7
6
5
4
3
2
1
ppm


AMC-Celastrol-Enone
Sample Name:
Data Collected on:
nmrox2-vnmrs600
Archive directory:
Sample directory:
FidFile: CARBON
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 10 2014
Temp. 25.0 C / 298.1 K
Operator: service
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 2.000 sec
Width 37878.8 Hz
13000 repetitions
OBSERVE C13, 150.8071878 MHz
DECOUPLE H1, 599.7527350 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 262144
Total time 14 hr, 26 min
200
180
160
140
120
100
80
60
40
20
ppm

AMC-Celastrol-Enone

Sample Name:

Data Collected on:
nmrox2-vnmrs600
Archive directory:

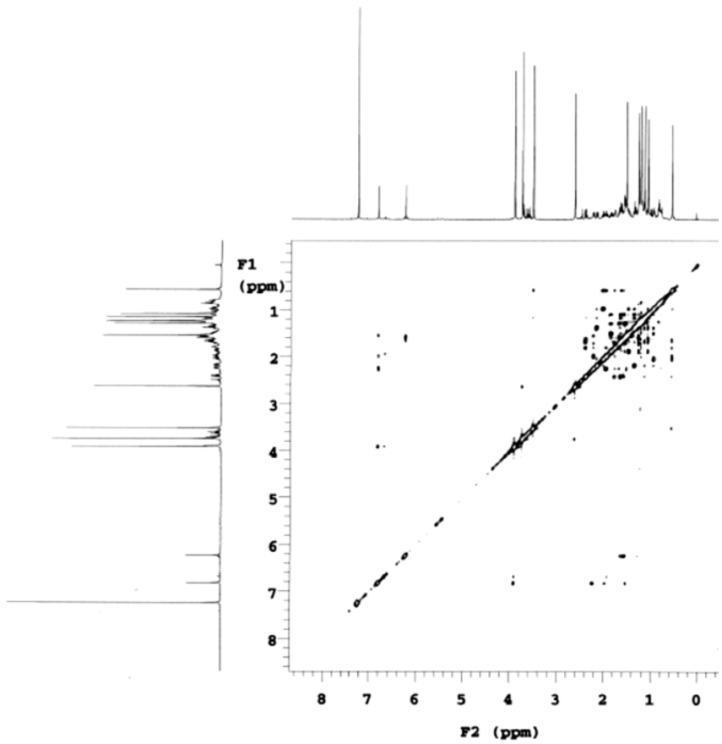
Sample directory:

FidFile: NOESY

Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Feb 10 2014

Temp. 25.0 C / 298.1 K
Operator: service

Relax. delay 2.000 sec
Acq. time 0.150 sec
Width 5506.6 Hz
2D Width 5506.6 Hz
8 repetitions
2 x 256 increments
OBSERVE H1, 599.7497412 MHz
DATA PROCESSING
Gauss apodization 0.049 sec
F1 DATA PROCESSING
Gauss apodization 0.024 sec
FT size 2048 x 2048
Total time 3 hr, 24 min



AMC-Celastrol-Enone

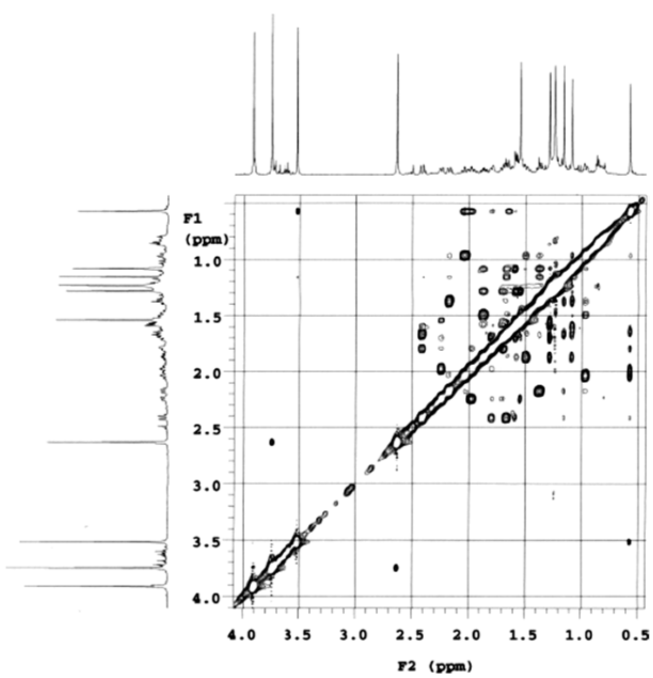
Sample Name:

Data Collected on:
nmrox2-vnmrs600
Archive directory:

Sample directory:

FidFile: NOESY

Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Feb 10 2014



AMC-Celastrol-Enone

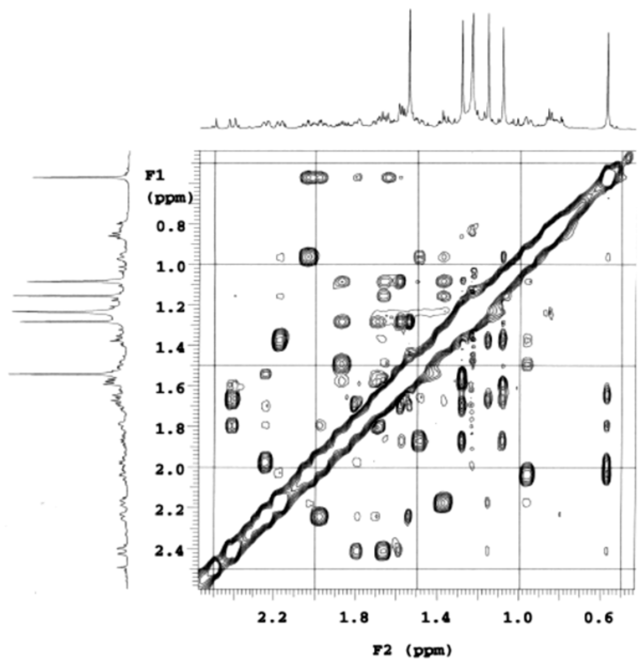
Sample Name:

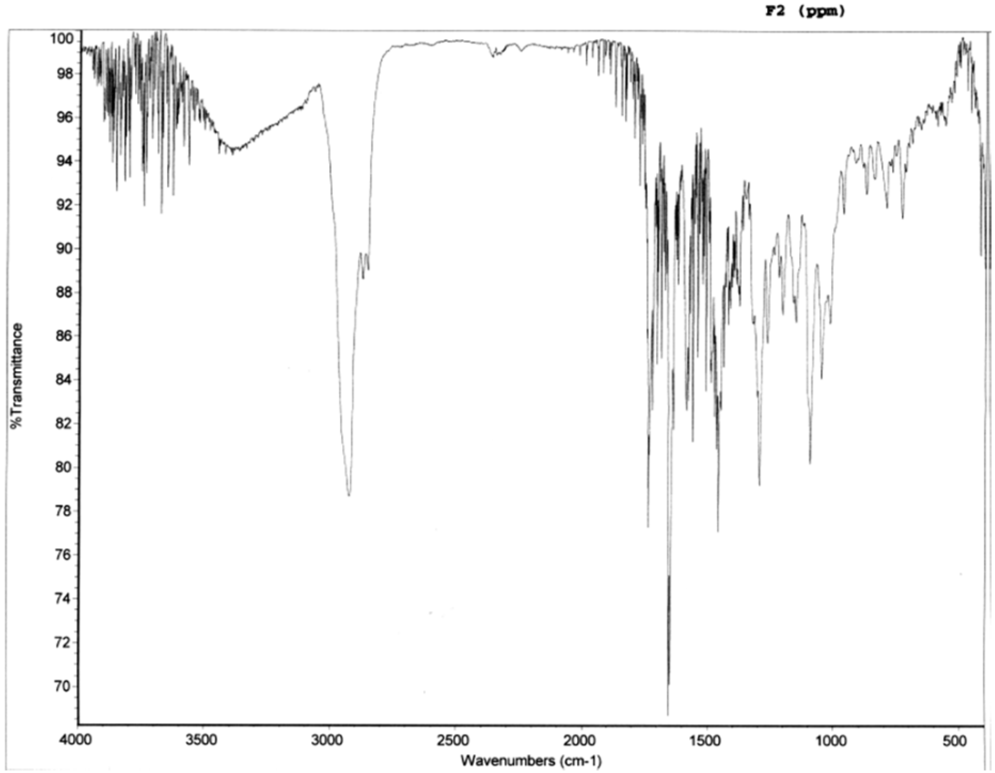
Data Collected on:
nmrox2-vnmrs600
Archive directory:

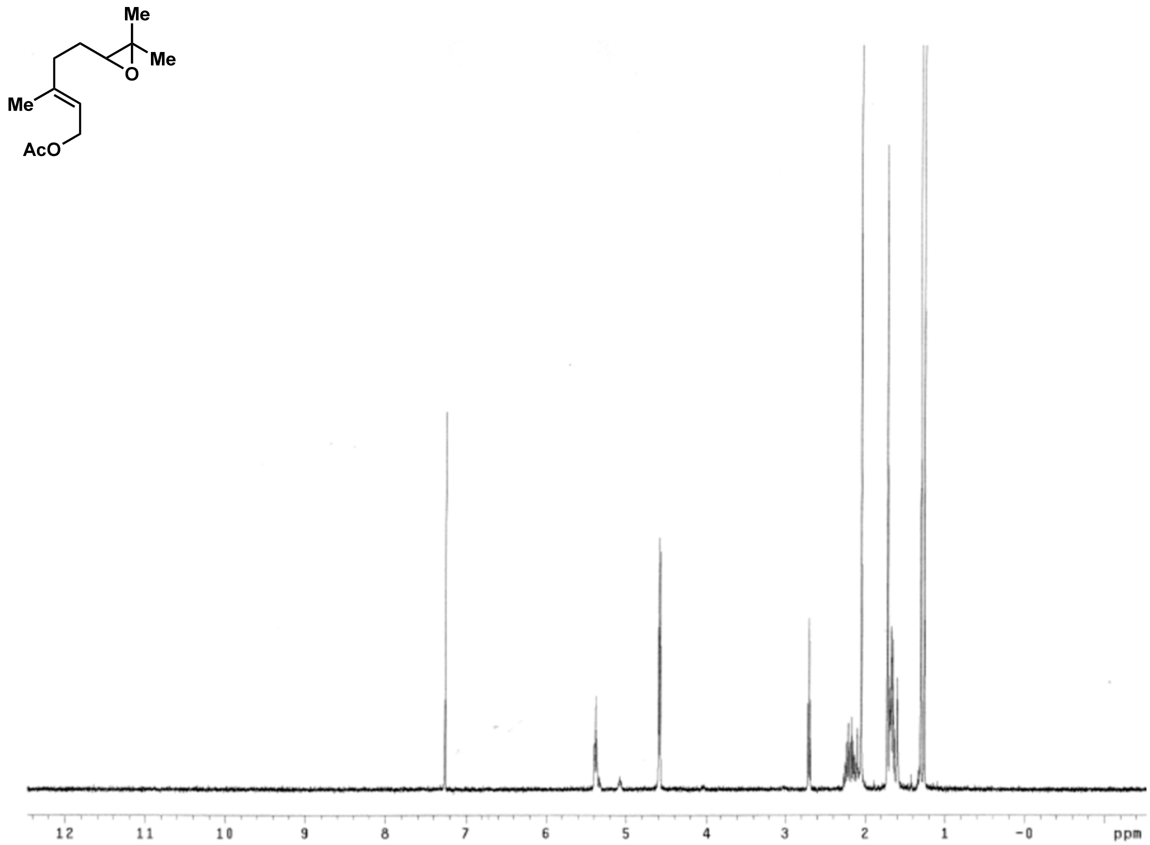
Sample directory:

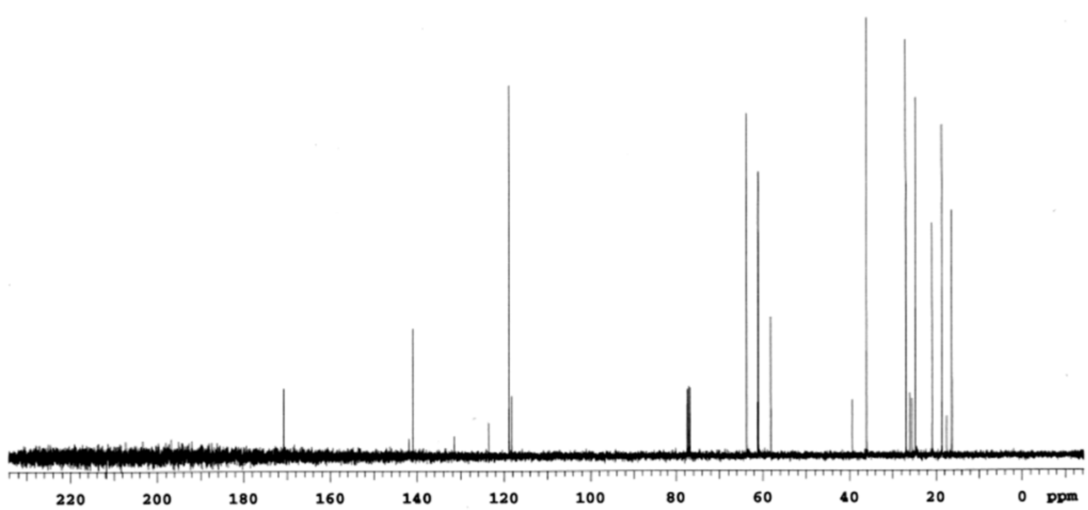
FidFile: NOESY

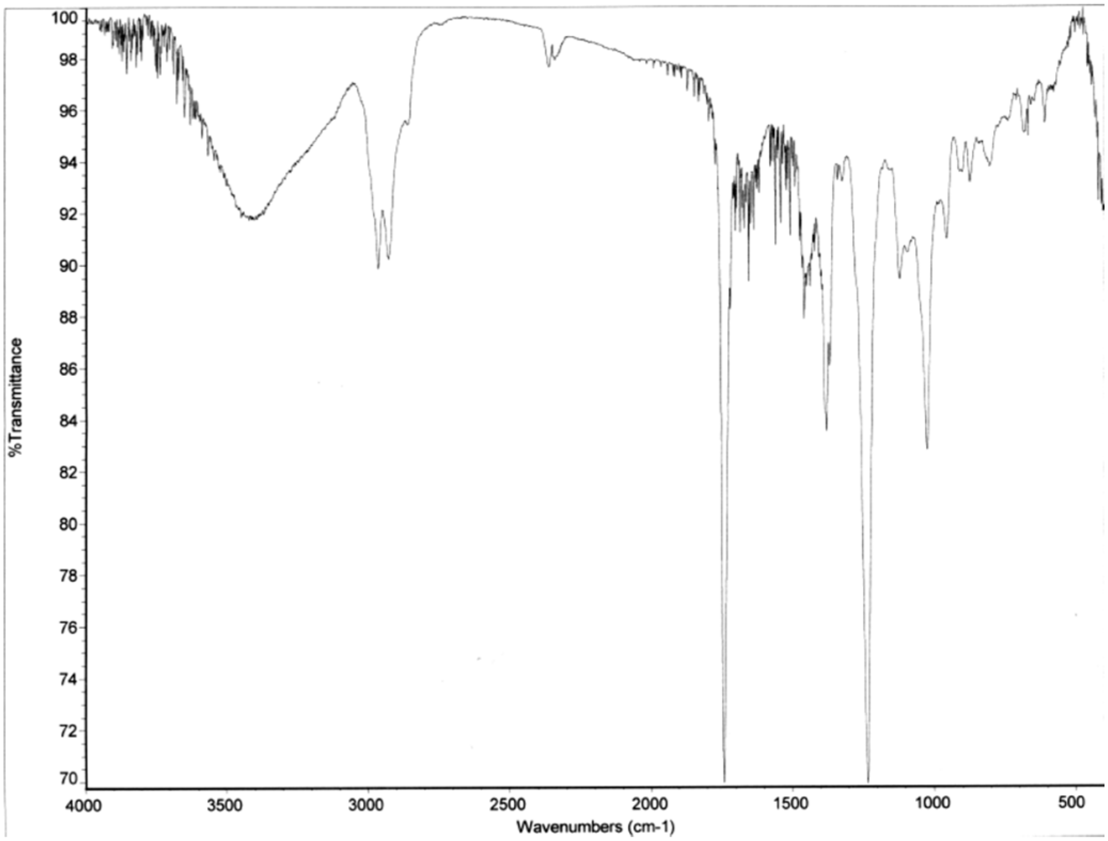
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Feb 10 2014

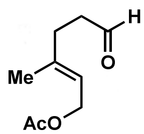




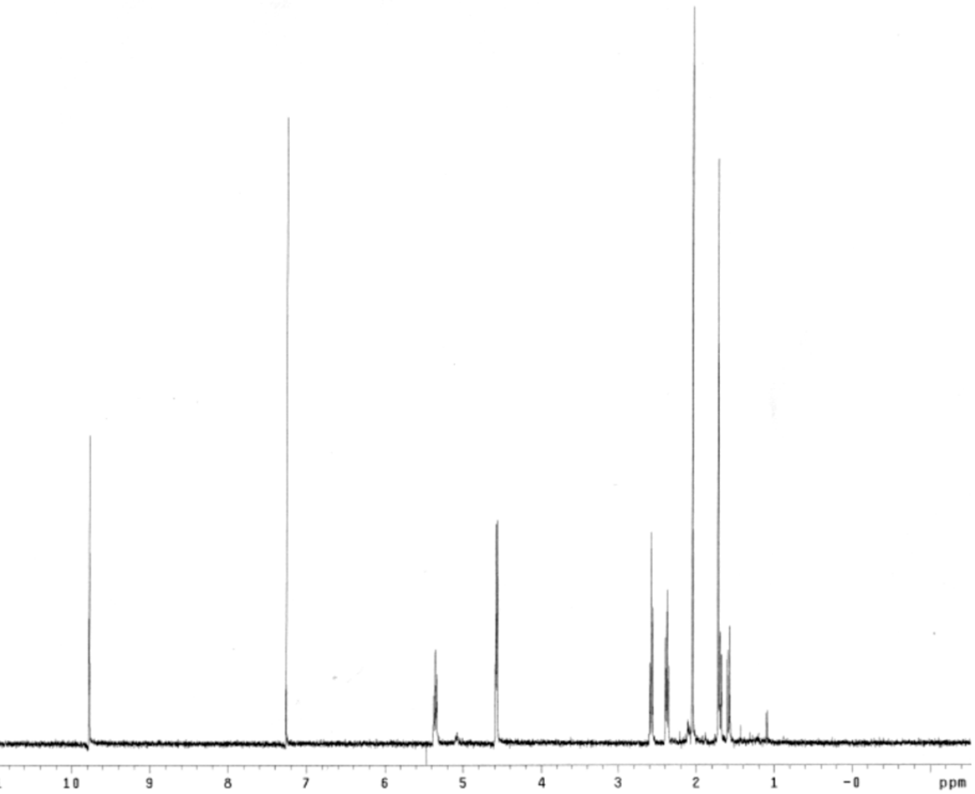

Me
Me
O
Me
AcO
12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

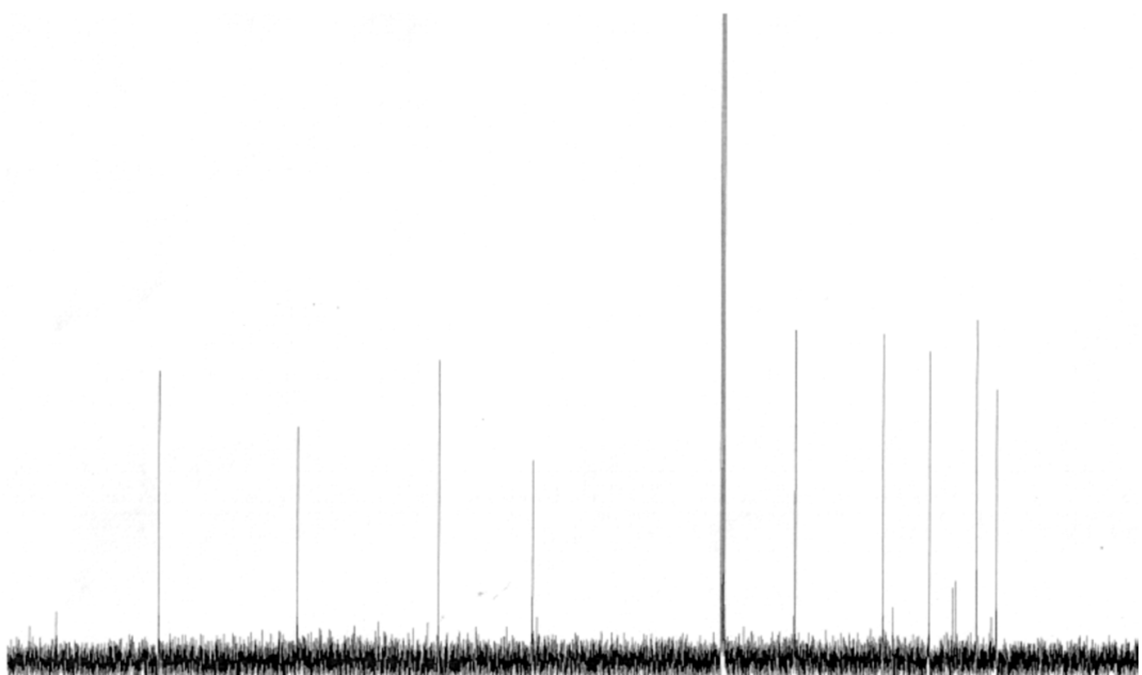

220 200 180 160 140 120 100 80 60 40 20 0 ppm

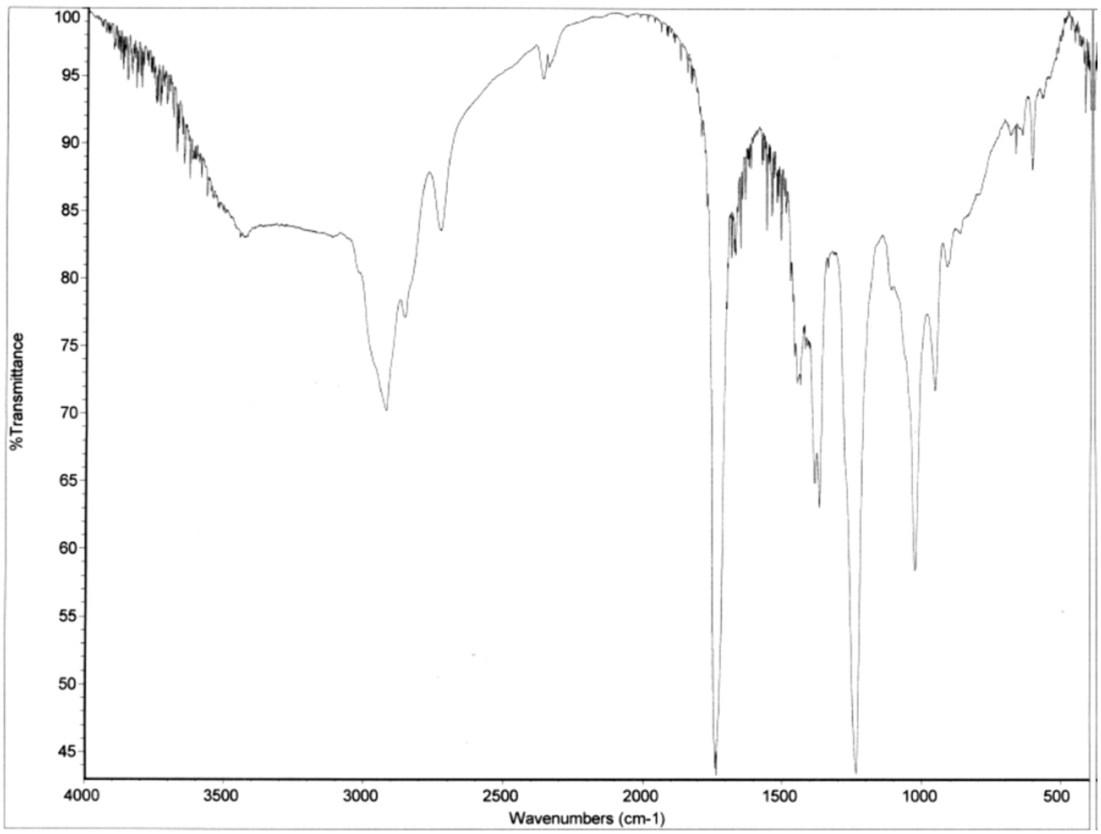

100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
%Transmittance
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

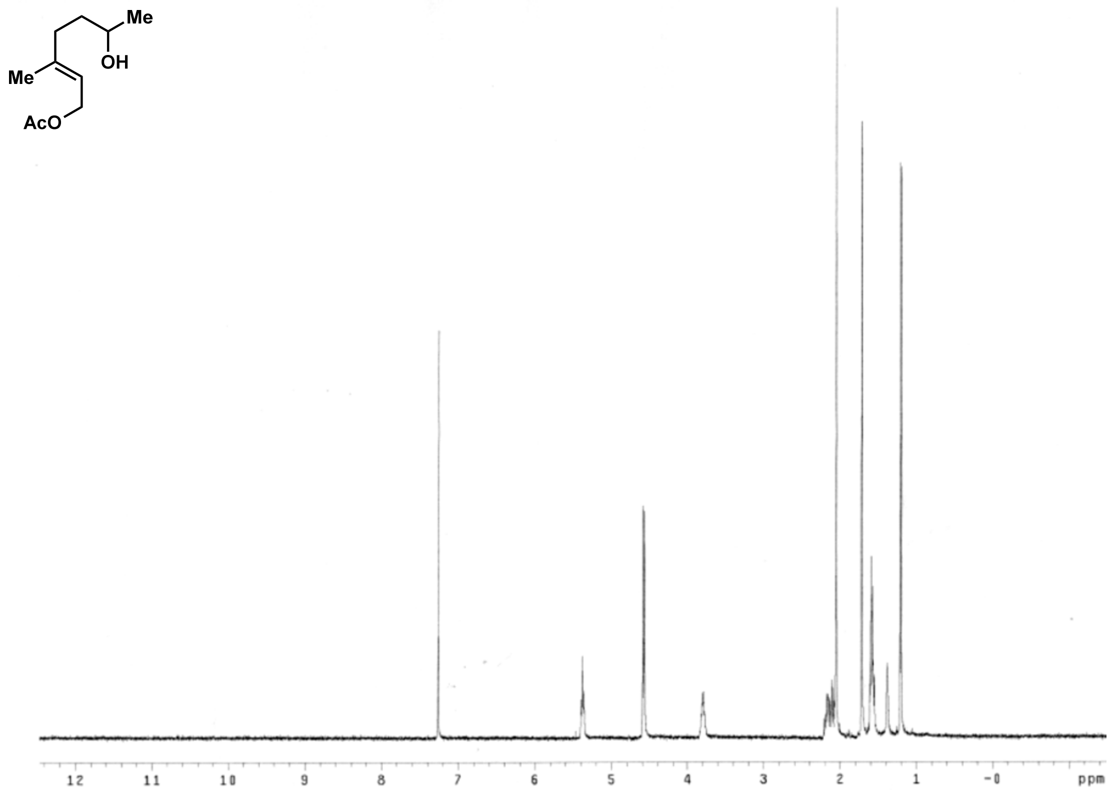

H
O
Me
AcO

138

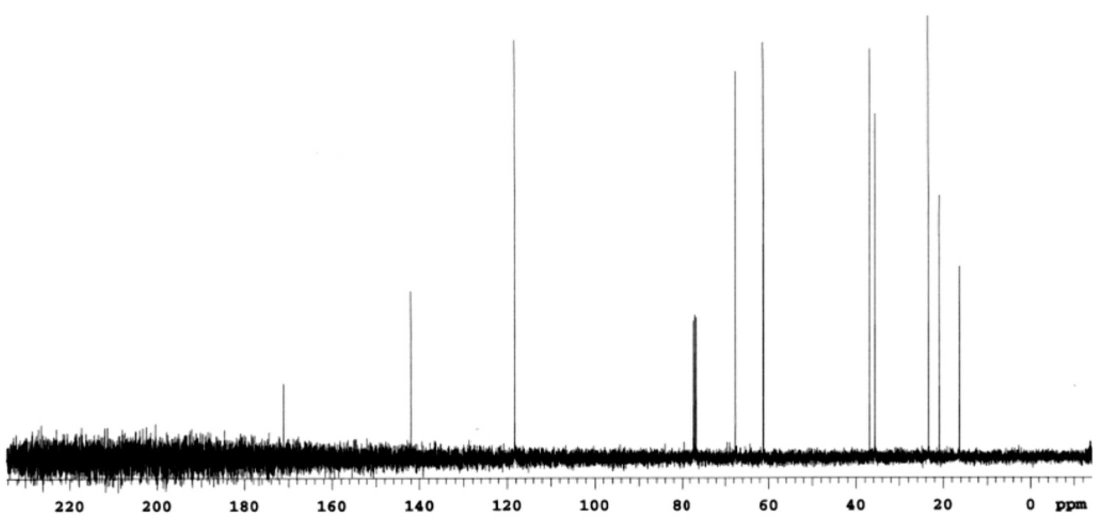

12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

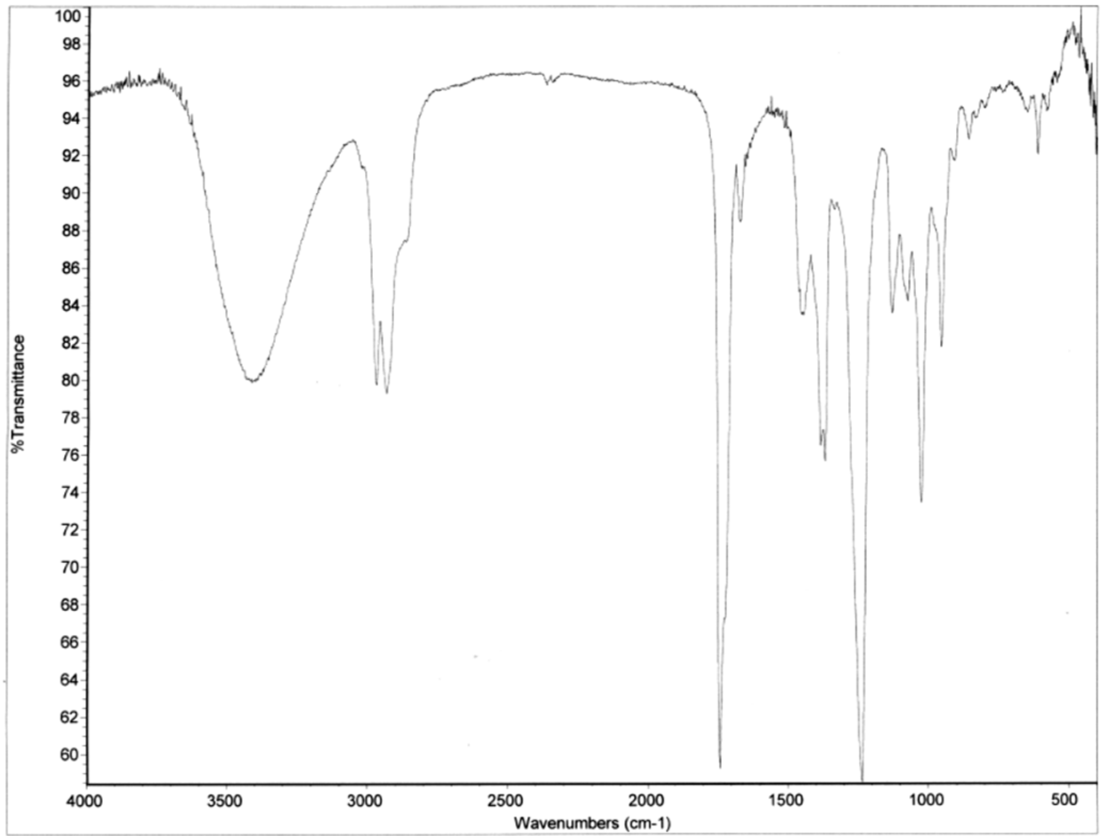

220 200 180 160 140 120 100 80 60 40 20 0 ppm

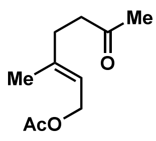

%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)



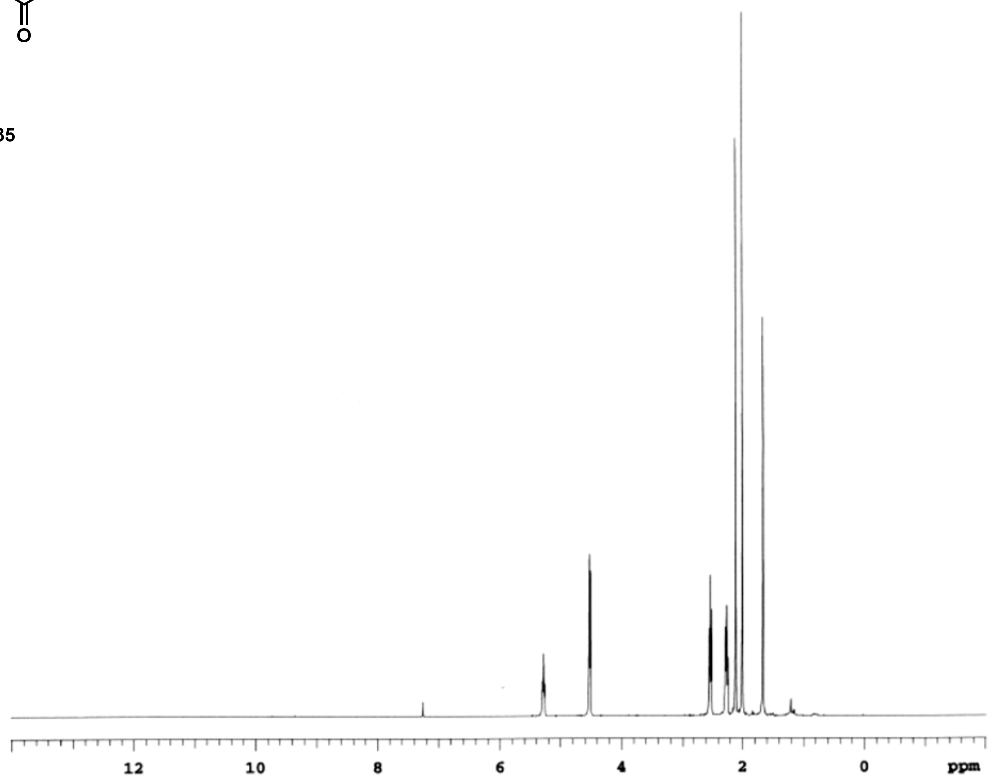
INDEX	FREQUENCY	PPM	HEIGHT
1	17210.1	171.072	17.2
2	14291.9	142.064	38.1
3	11901.6	118.304	95.8
4	7774.8	77.283	31.3
5	7742.8	76.965	32.7
6	7710.8	76.646	32.1
7	6800.6	67.599	88.6
8	6158.2	61.213	95.2
9	3708.4	36.862	93.7
10	3587.8	35.664	78.8
11	2354.9	23.408	101.2
12	2105.4	20.928	60.0
13	1643.1	16.333	43.6

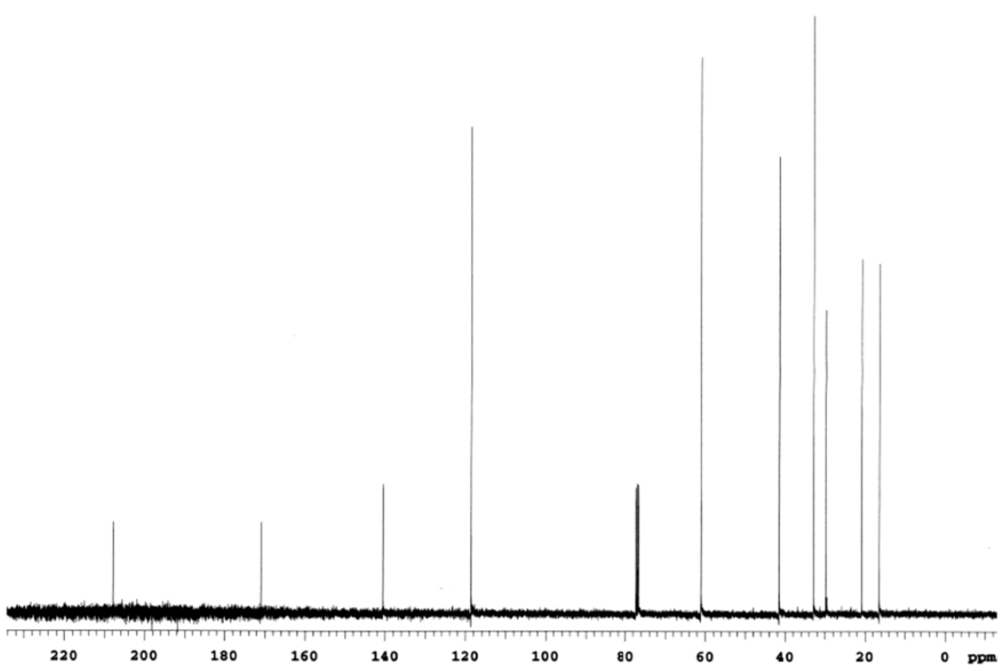


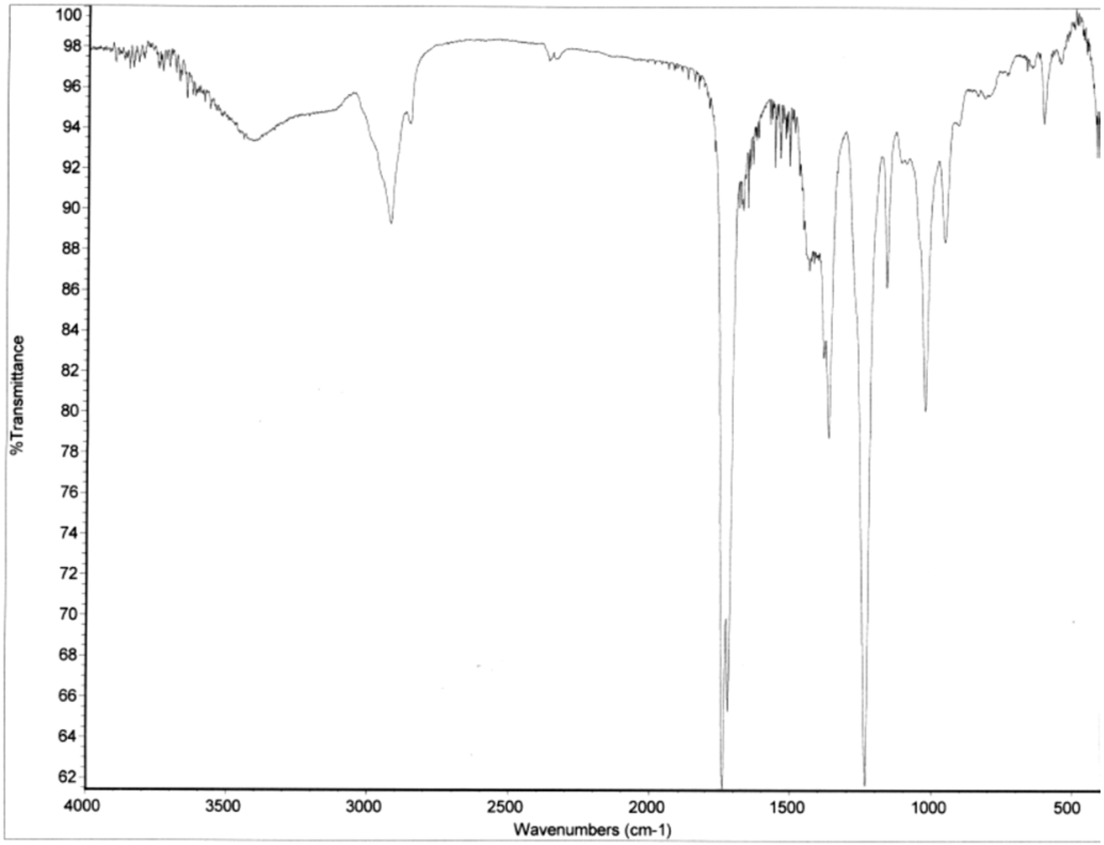

%Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

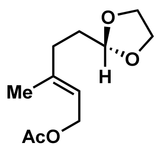

Me
O
Me
AcO

135

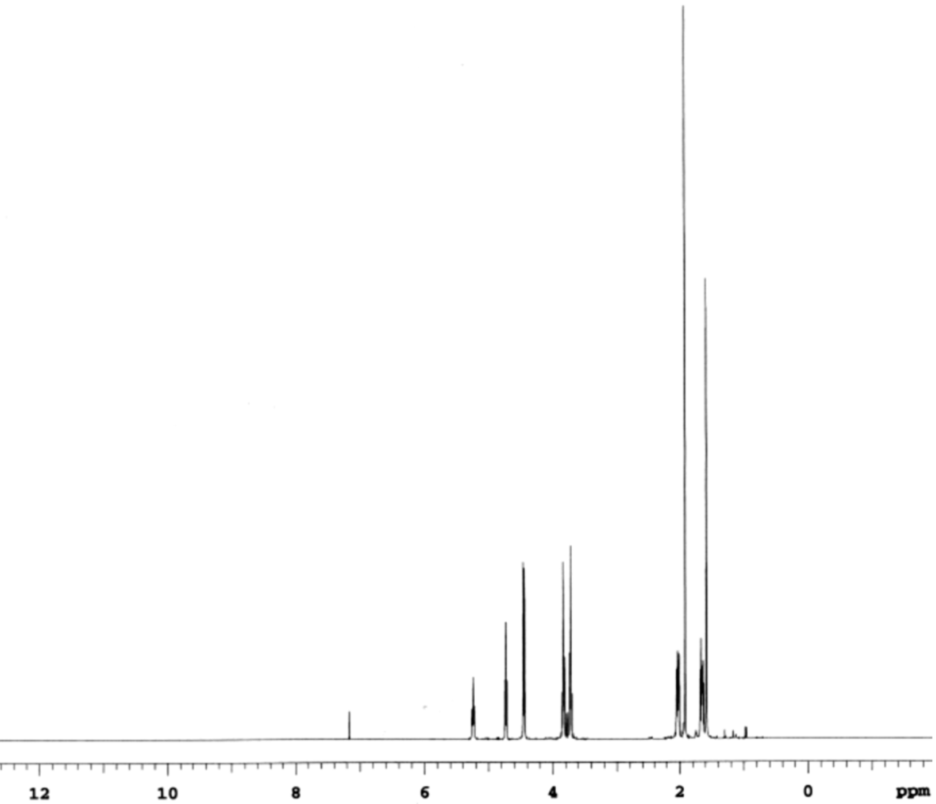

12
10
8
6
4
2
0
ppm

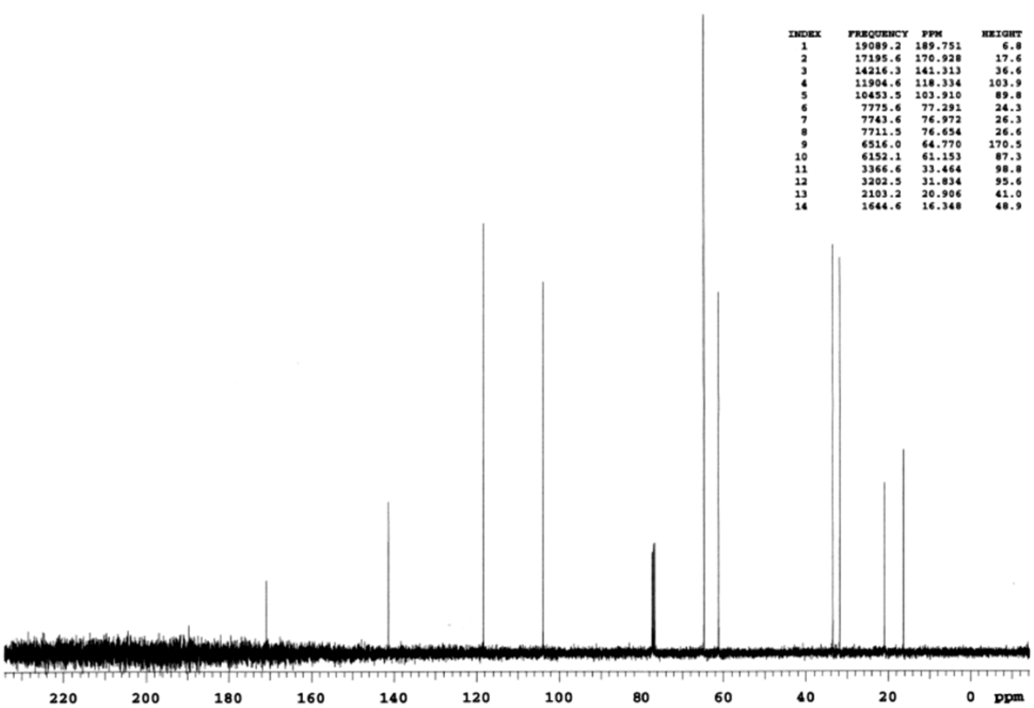

220
200
180
160
140
120
100
80
60
40
20
0
ppm


%Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

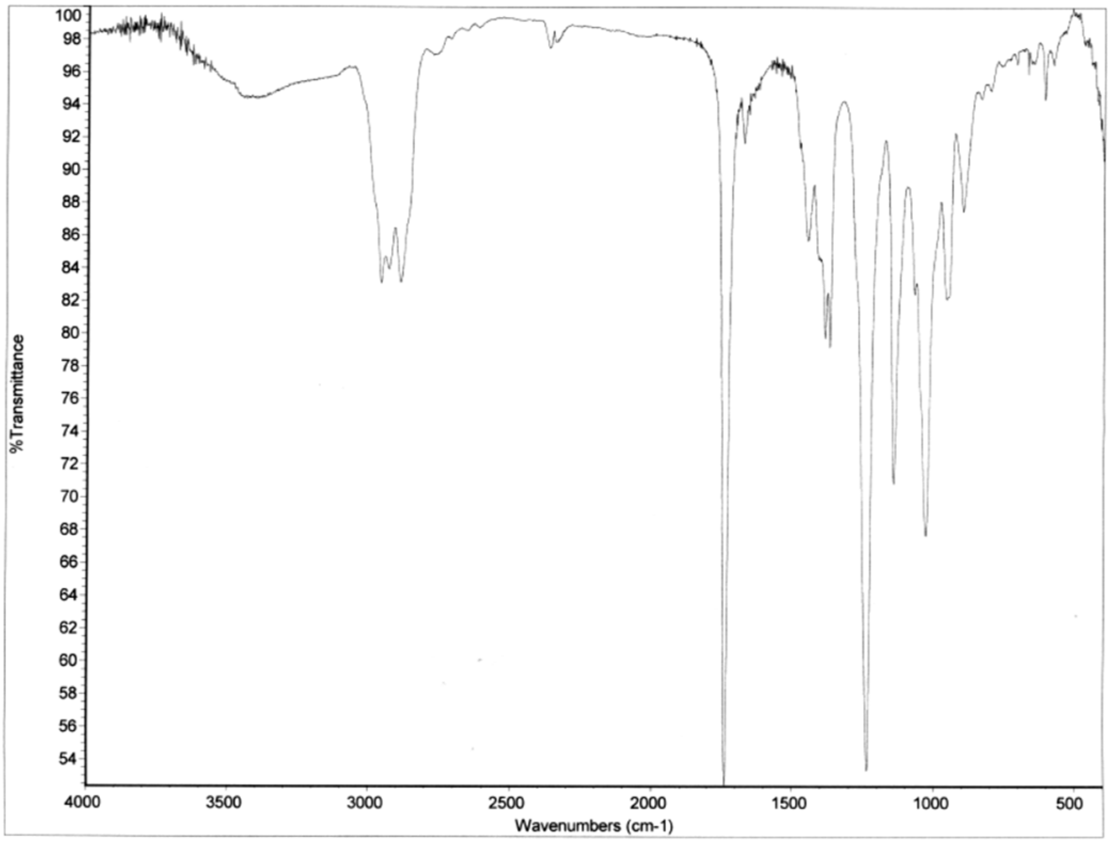


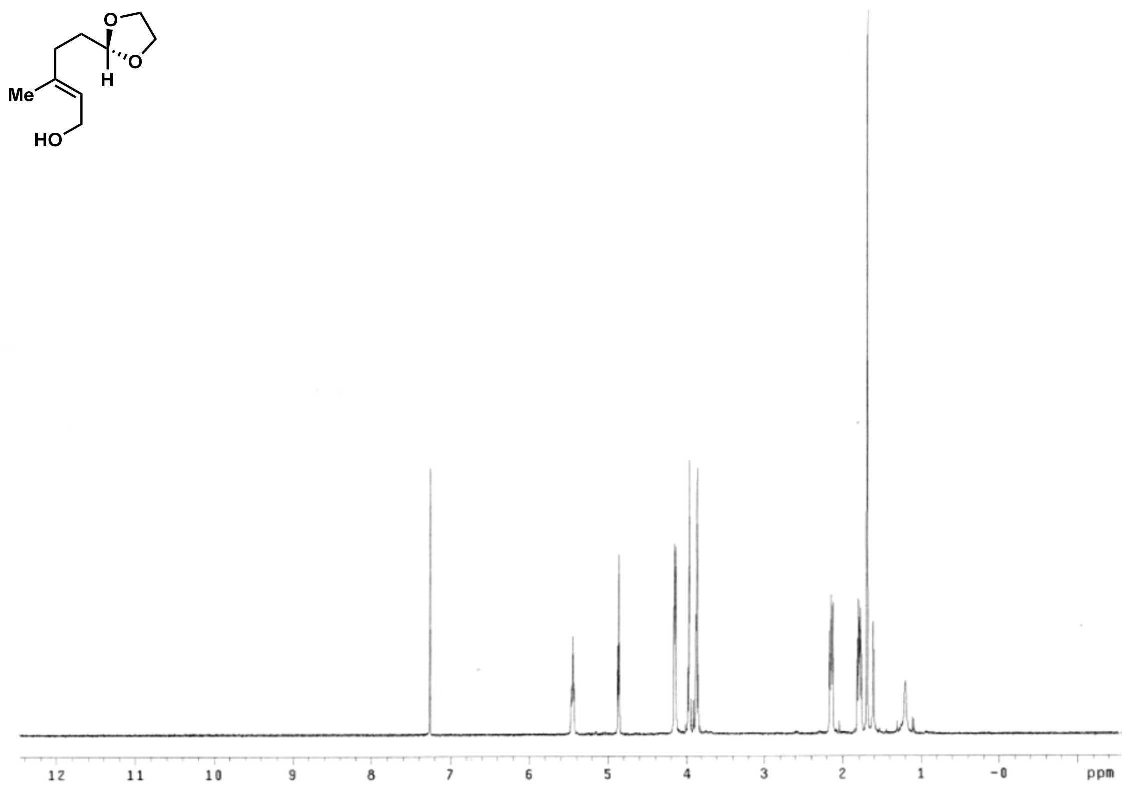
146

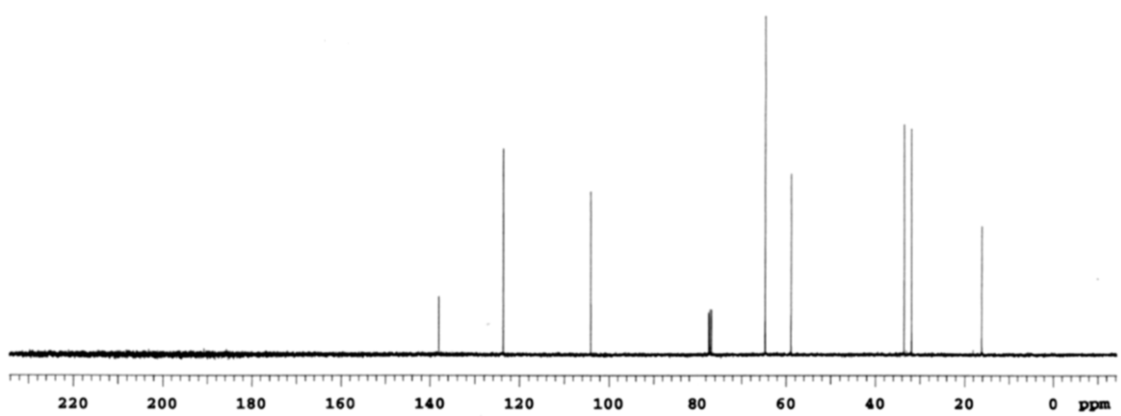


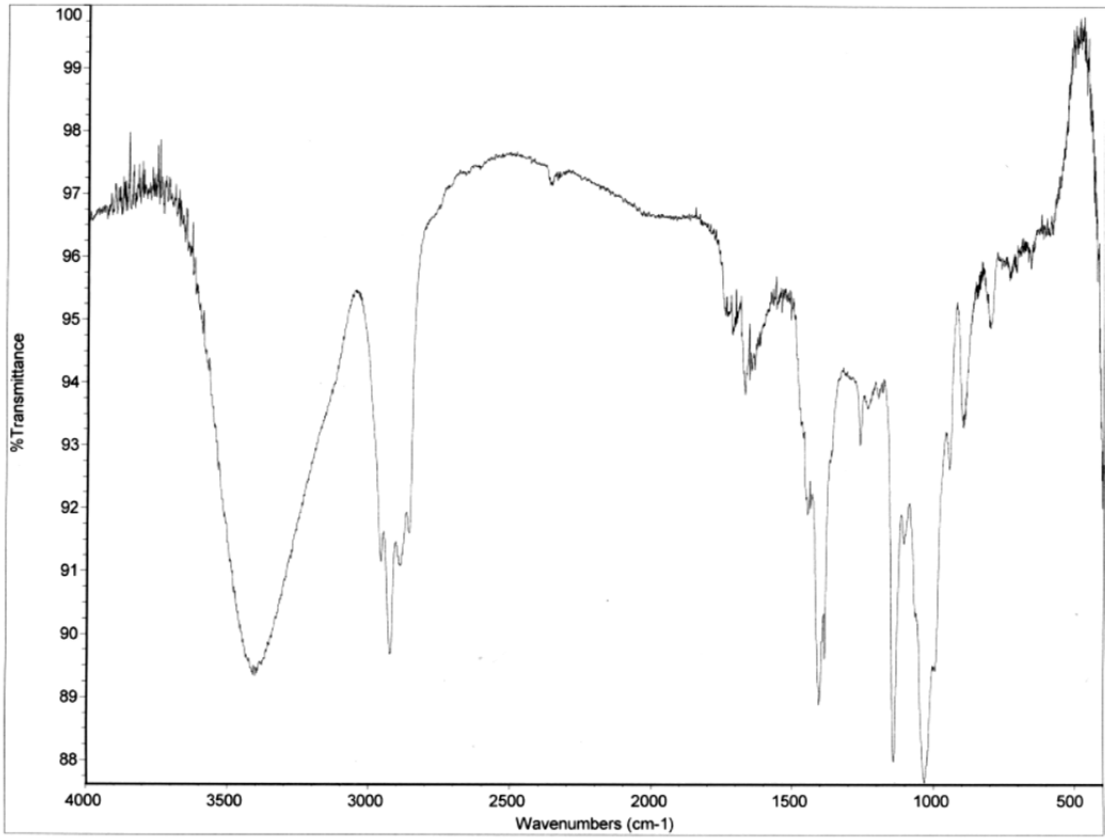


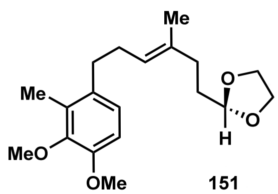
INDEX	FREQUENCY	PPM	HEIGHT
1	19089.2	189.751	6.8
2	17195.6	170.928	17.6
3	14216.3	141.313	36.6
4	11904.6	118.334	103.9
5	10453.5	103.910	89.8
6	7775.6	77.291	24.3
7	7743.6	76.972	26.3
8	7711.5	76.654	26.6
9	6516.0	64.770	170.5
10	6152.1	61.153	87.3
11	3366.6	33.464	98.8
12	3202.5	31.834	95.6
13	2103.2	20.906	41.0
14	1644.6	16.348	48.9


%Transmittance
Wavenumbers (cm-1)
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
4000
3500
3000
2500
2000
1500
1000
500

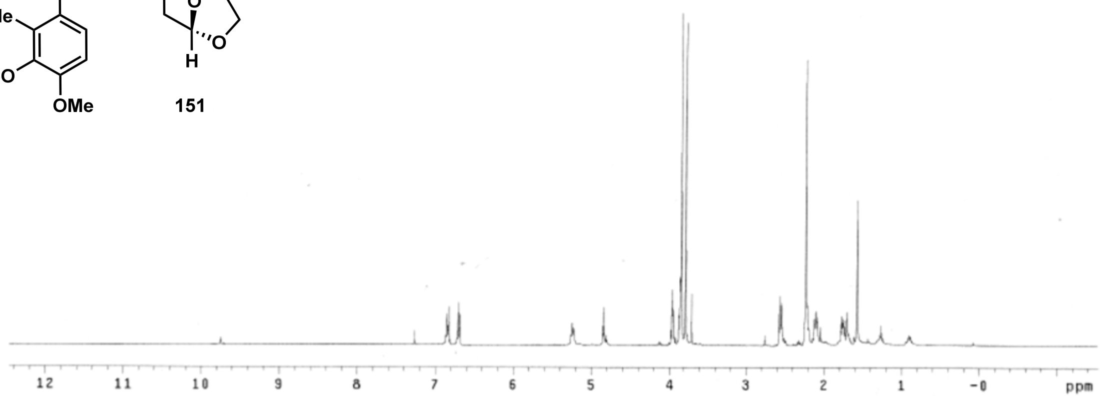

O
O
H
Me
HO
12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

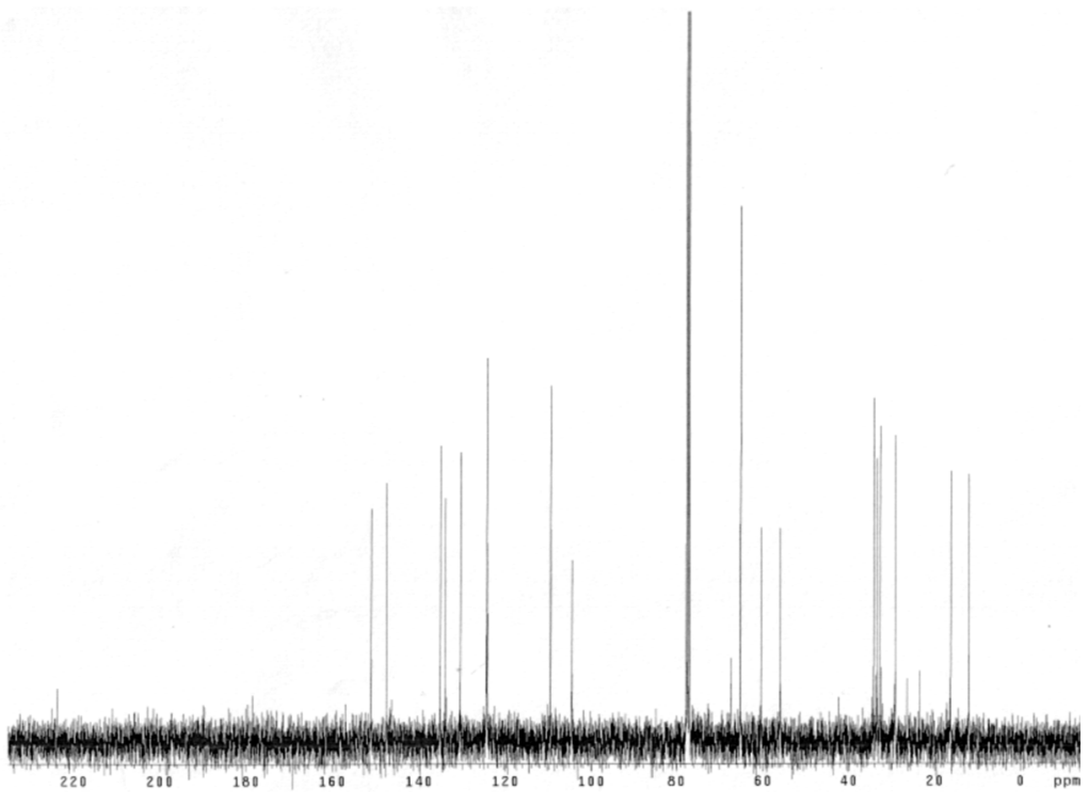

220 200 180 160 140 120 100 80 60 40 20 0 ppm

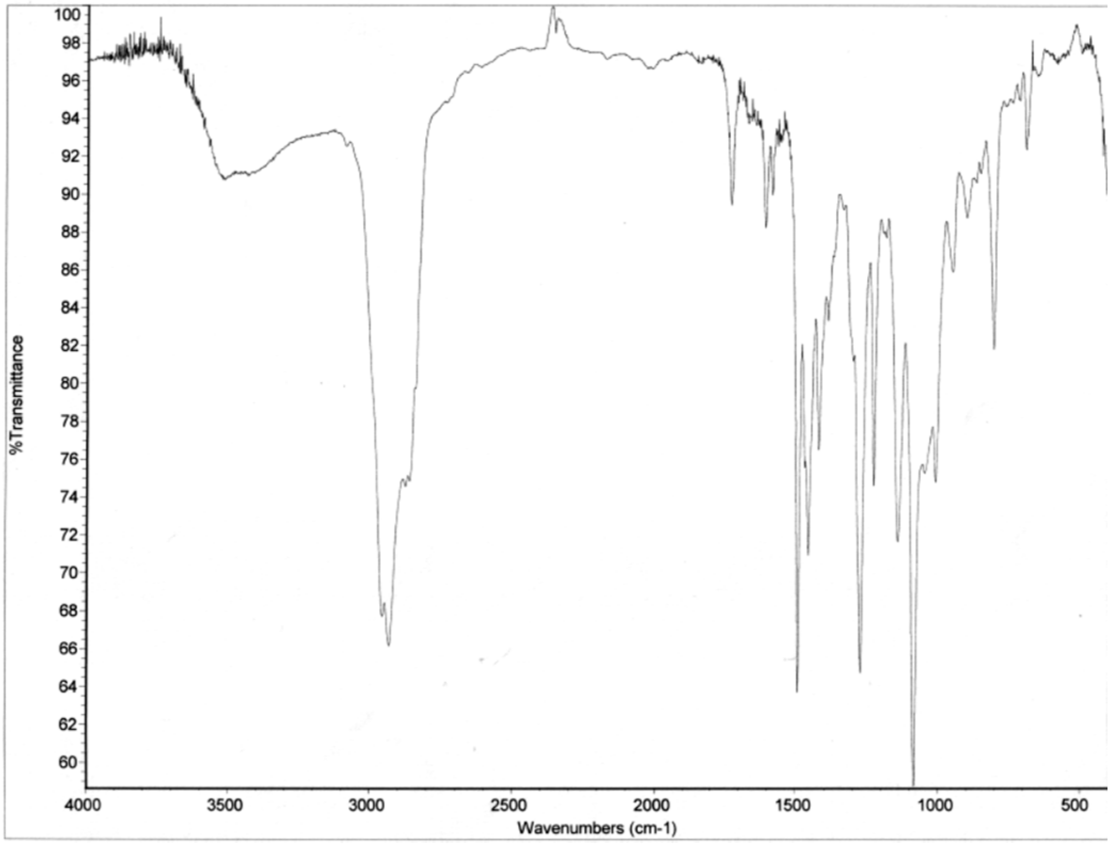

%Transmittance
100
99
98
97
96
95
94
93
92
91
90
89
88
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)


Me
Me
MeO
OMe
O
O
H

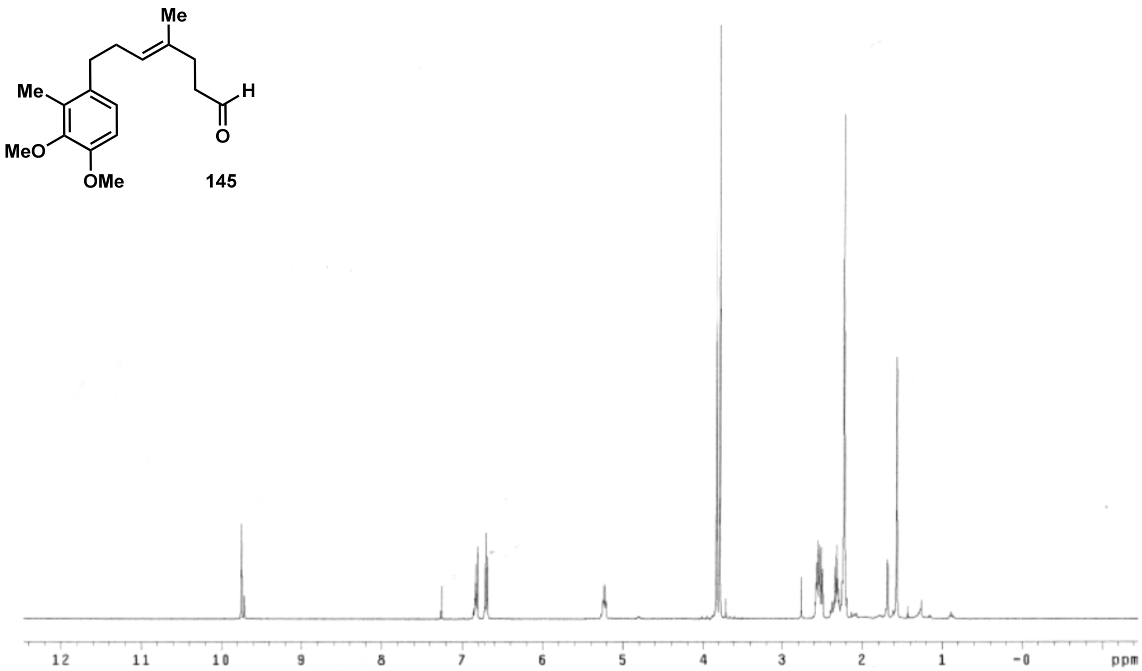
151

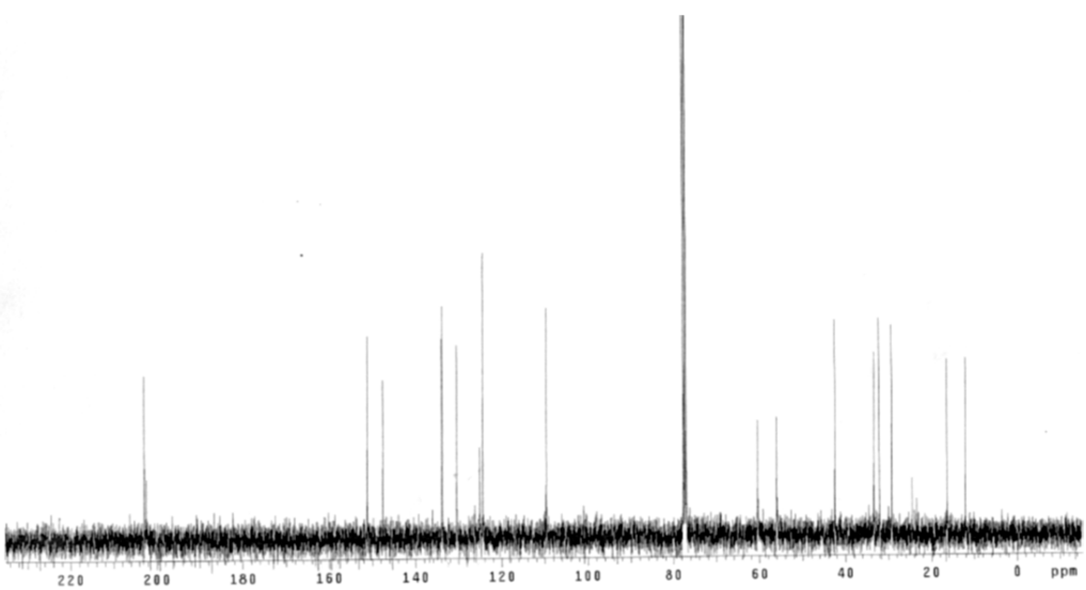

12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

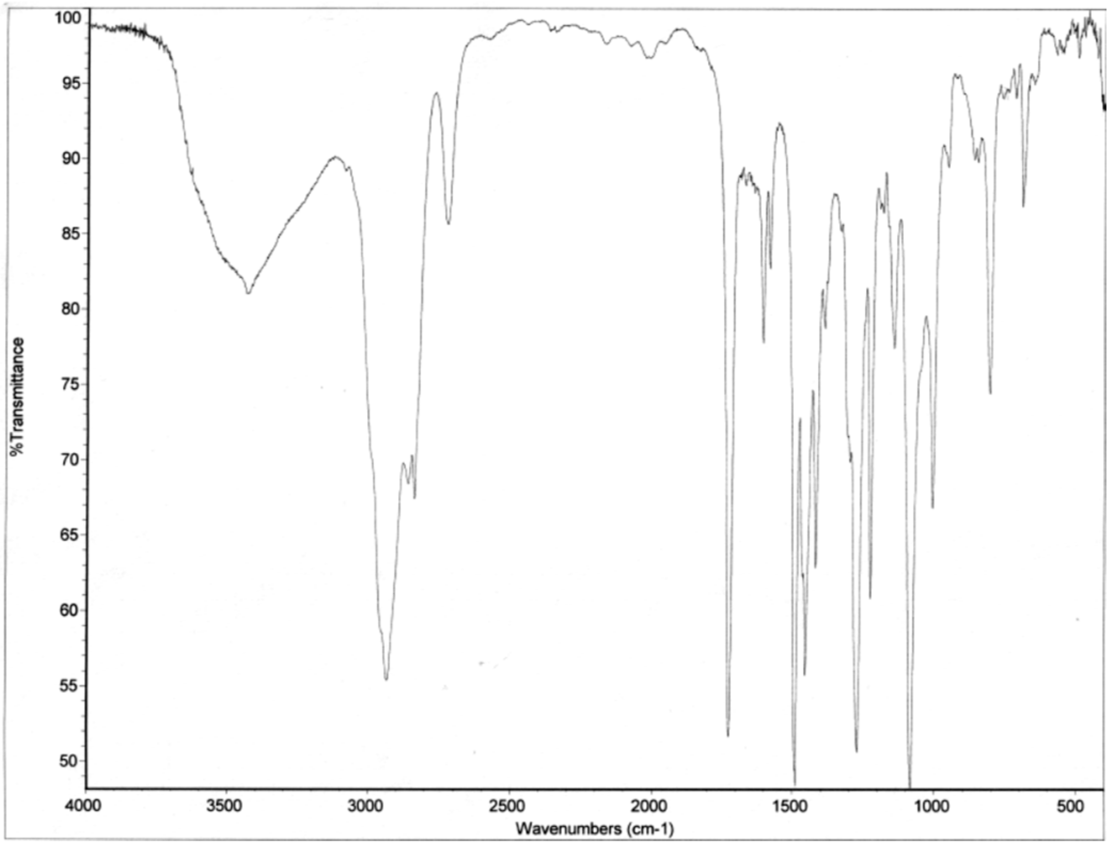

220 200 180 160 140 120 100 80 60 40 20 0 ppm



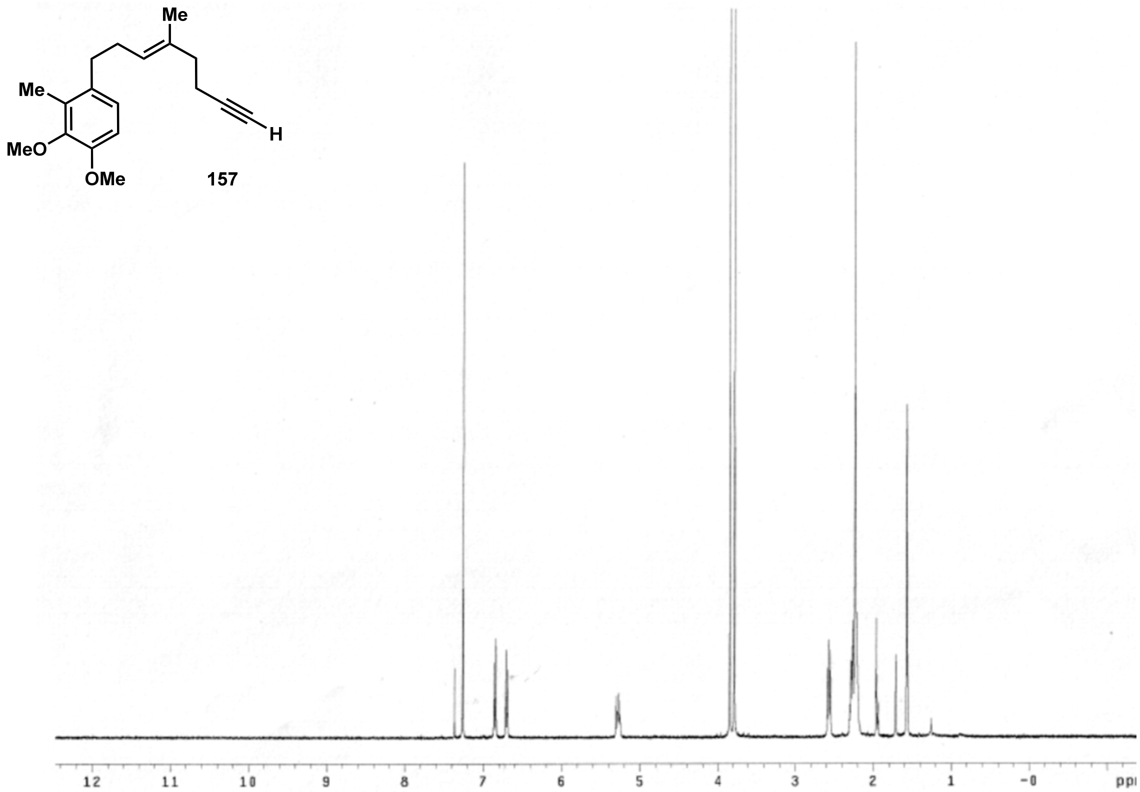
%Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

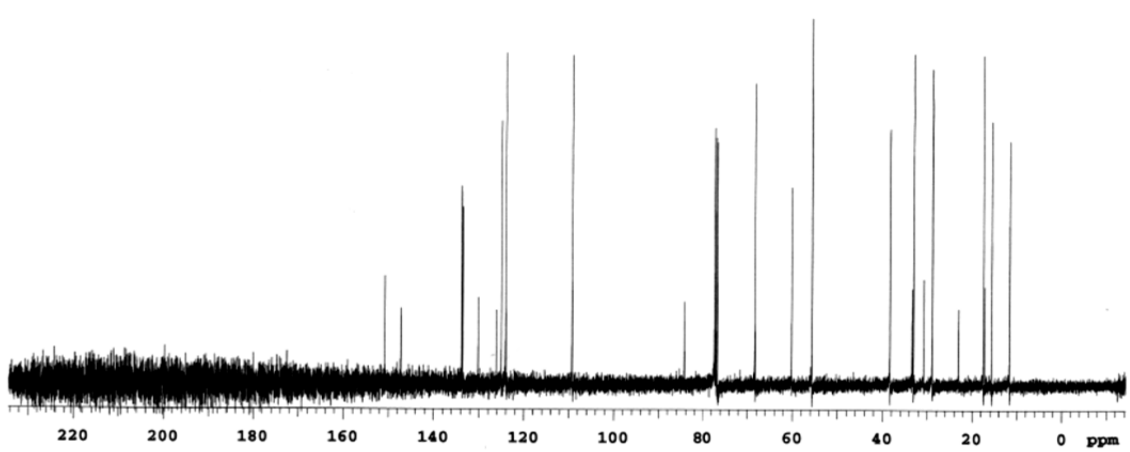

Me
Me
MeO
OMe
H
O
145
12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

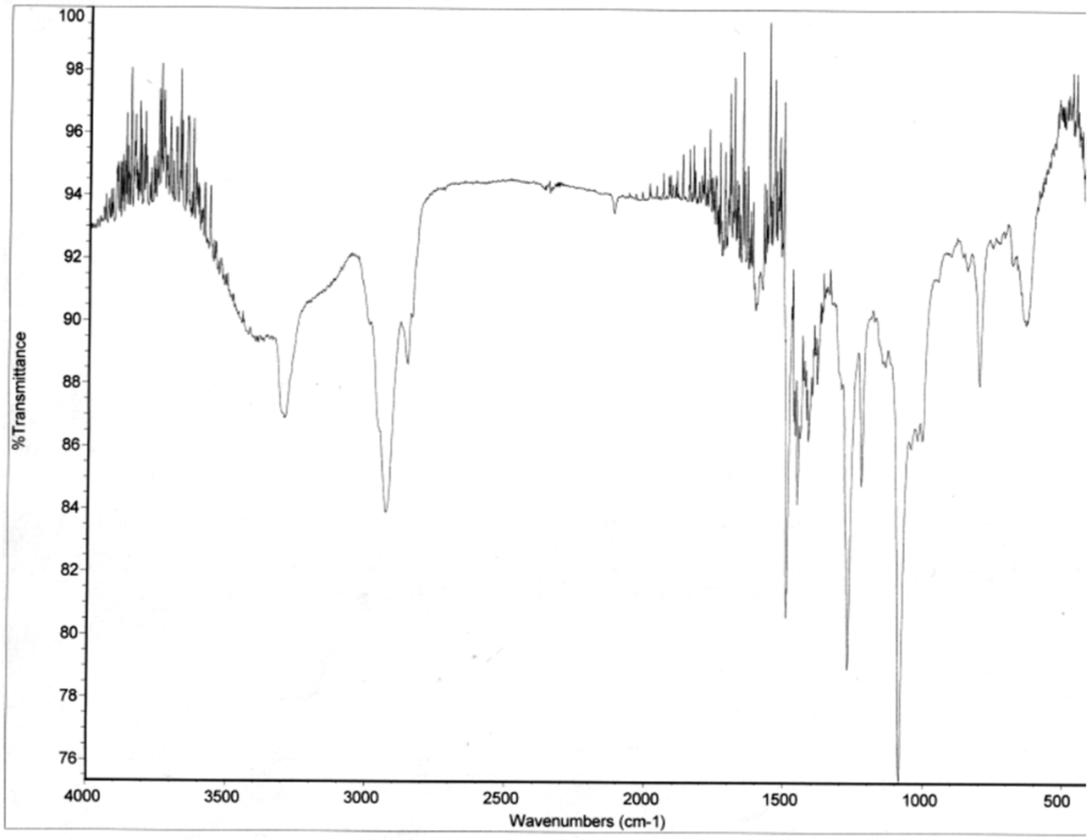

220 200 180 160 140 120 100 80 60 40 20 0 ppm



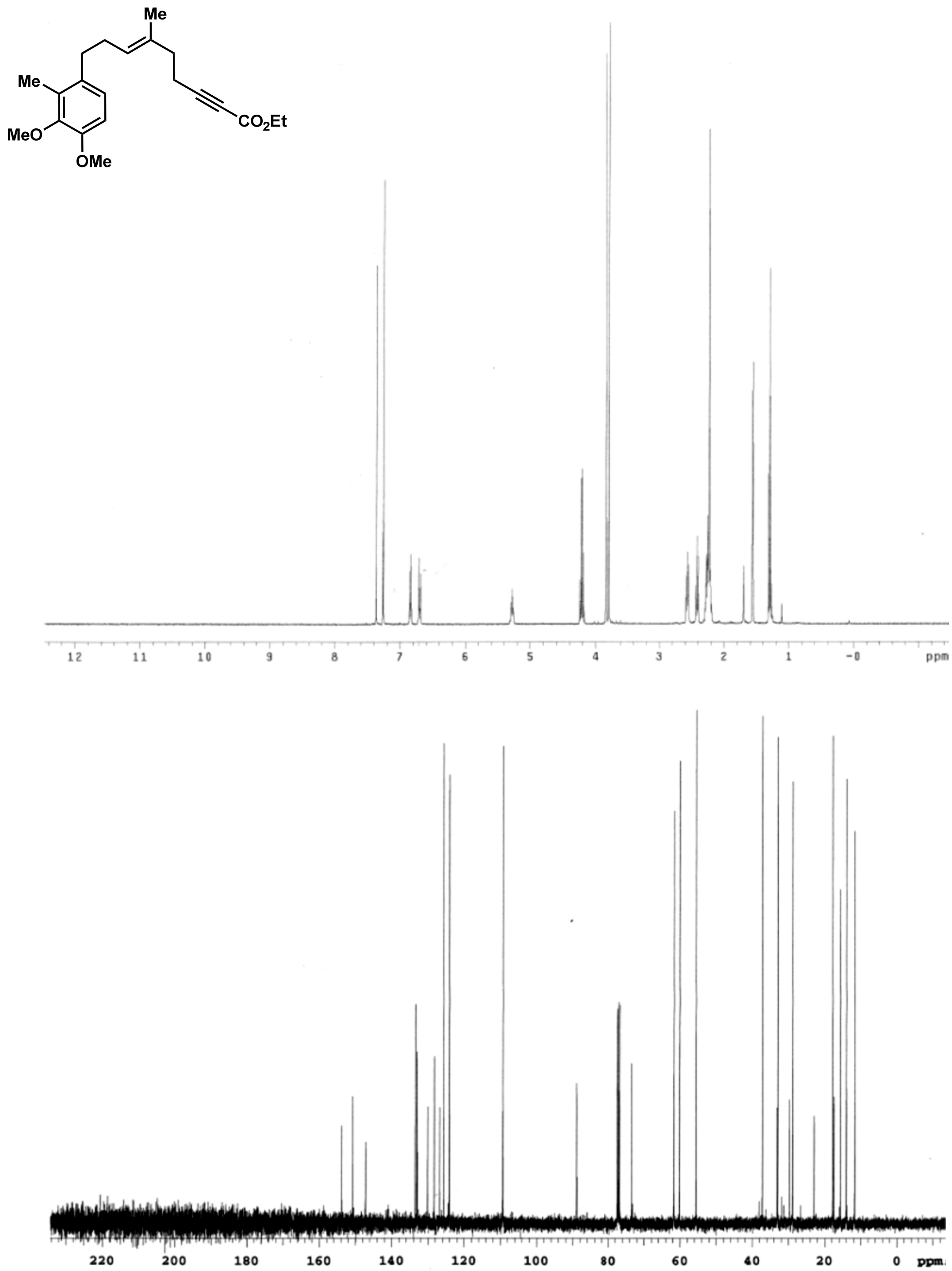
100
95
90
85
80
75
70
65
60
55
50
%Transmittance
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

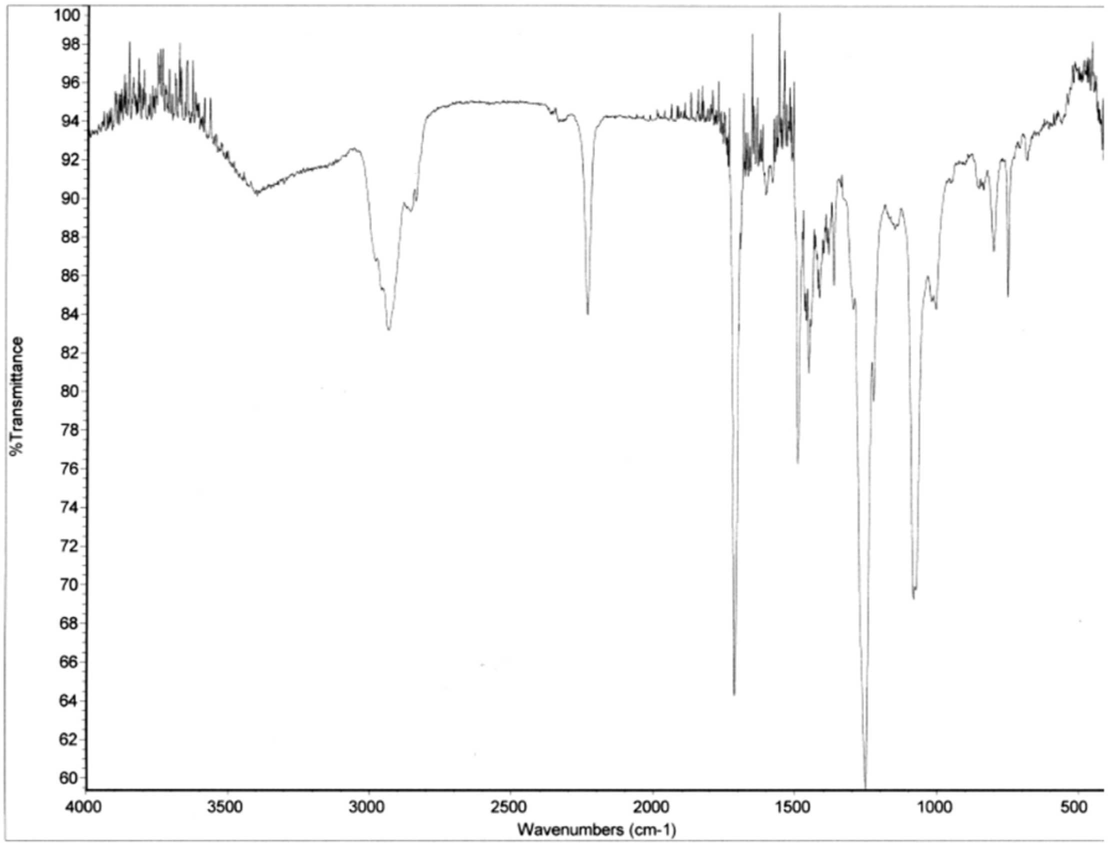

Me
Me
MeO
OMe
H
157
12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm


220 200 180 160 140 120 100 80 60 40 20 0 ppm

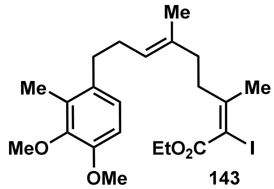


100
98
96
94
92
90
88
86
84
82
80
78
76
%Transmittance
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

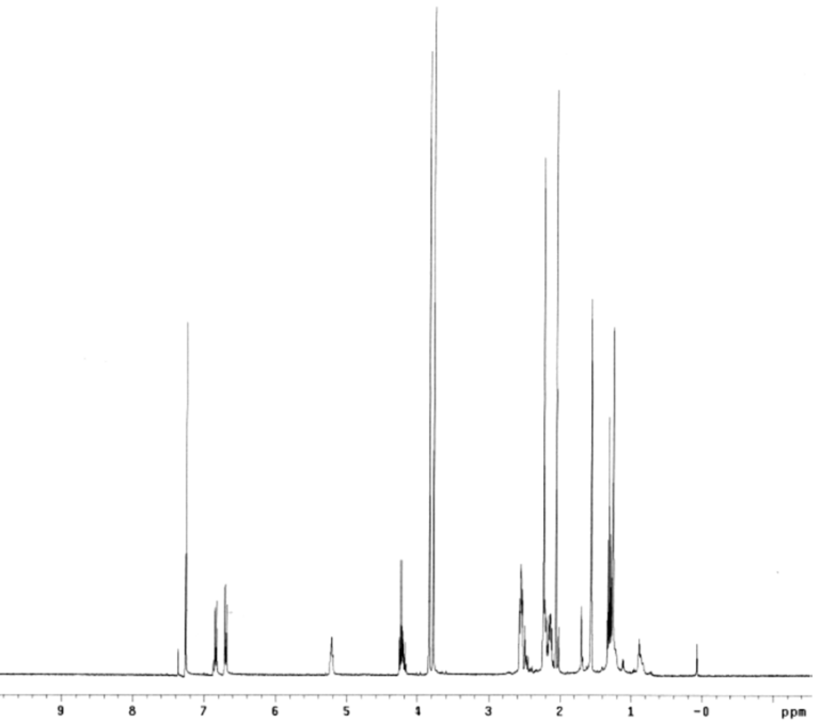

Me
Me
MeO
OMe
CO2Et
12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm
220 200 180 160 140 120 100 80 60 40 20 0 ppm

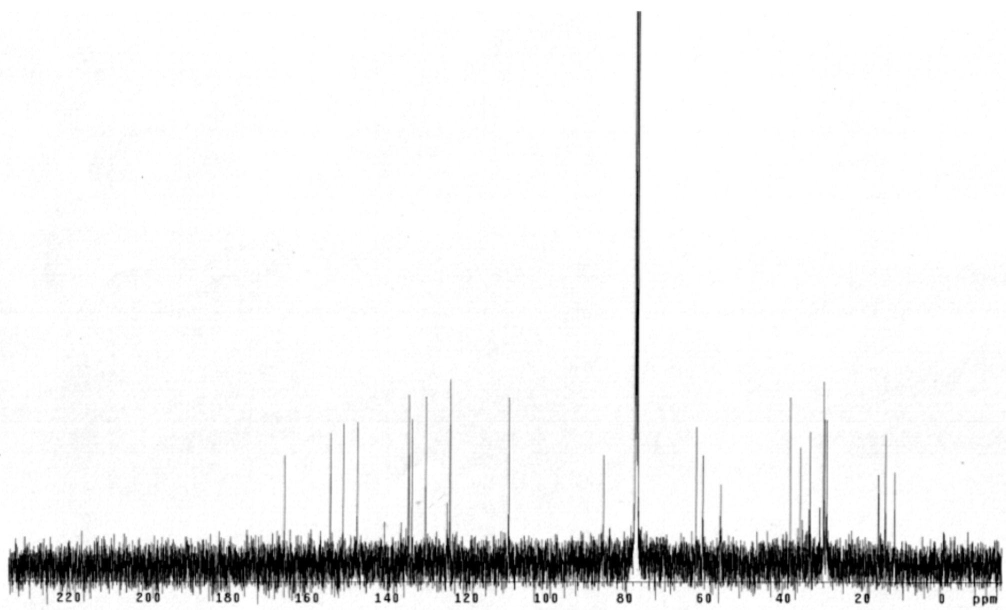


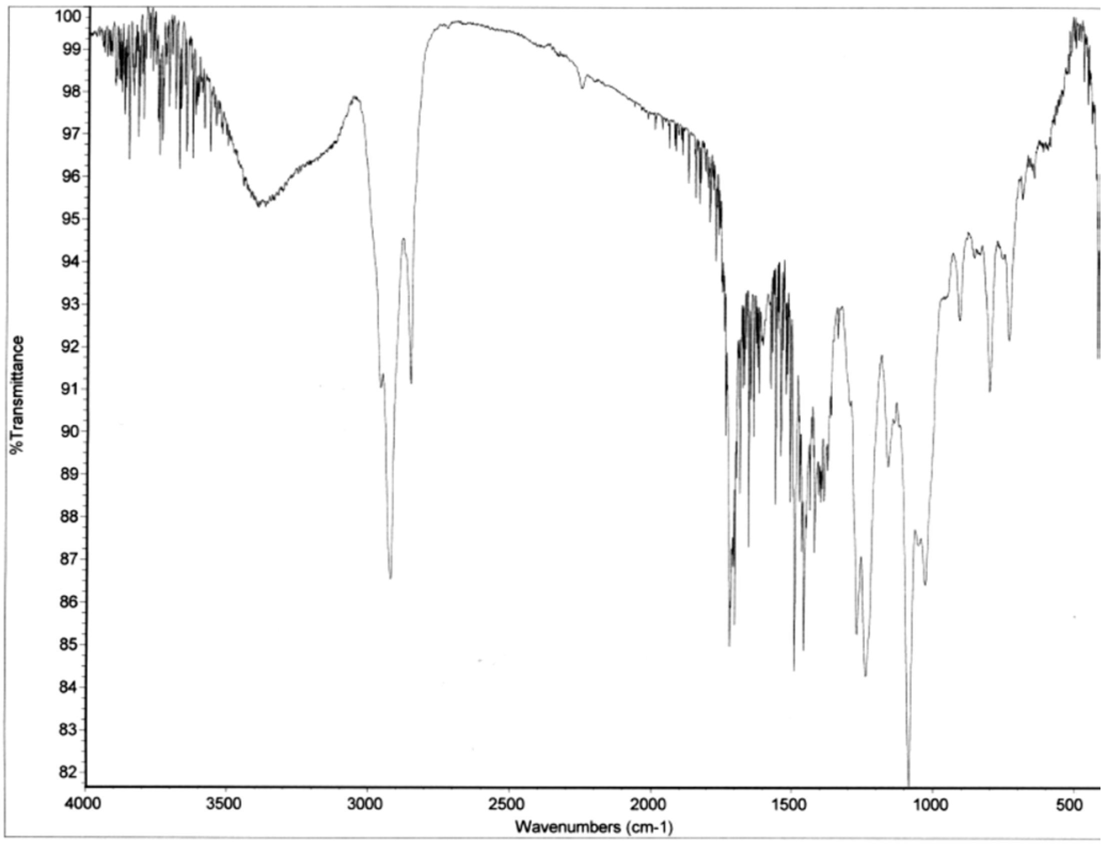
%Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

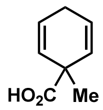

Me
Me
Me
MeO
OMe
EtO2C
I

143

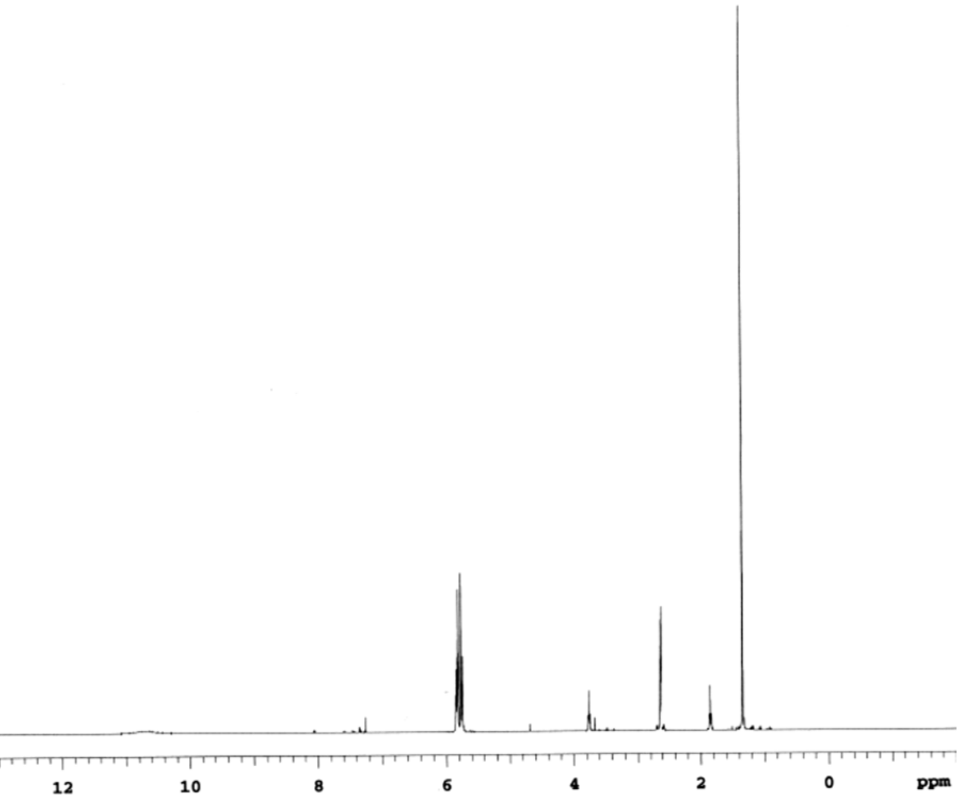

12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

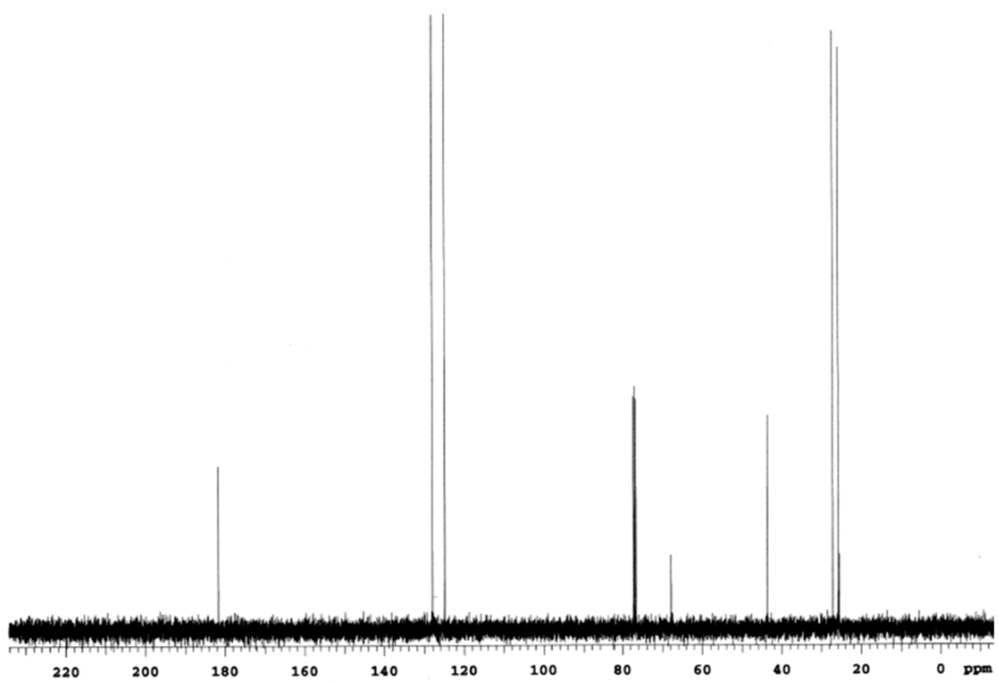

220 200 180 160 140 120 100 80 60 40 20 0 ppm

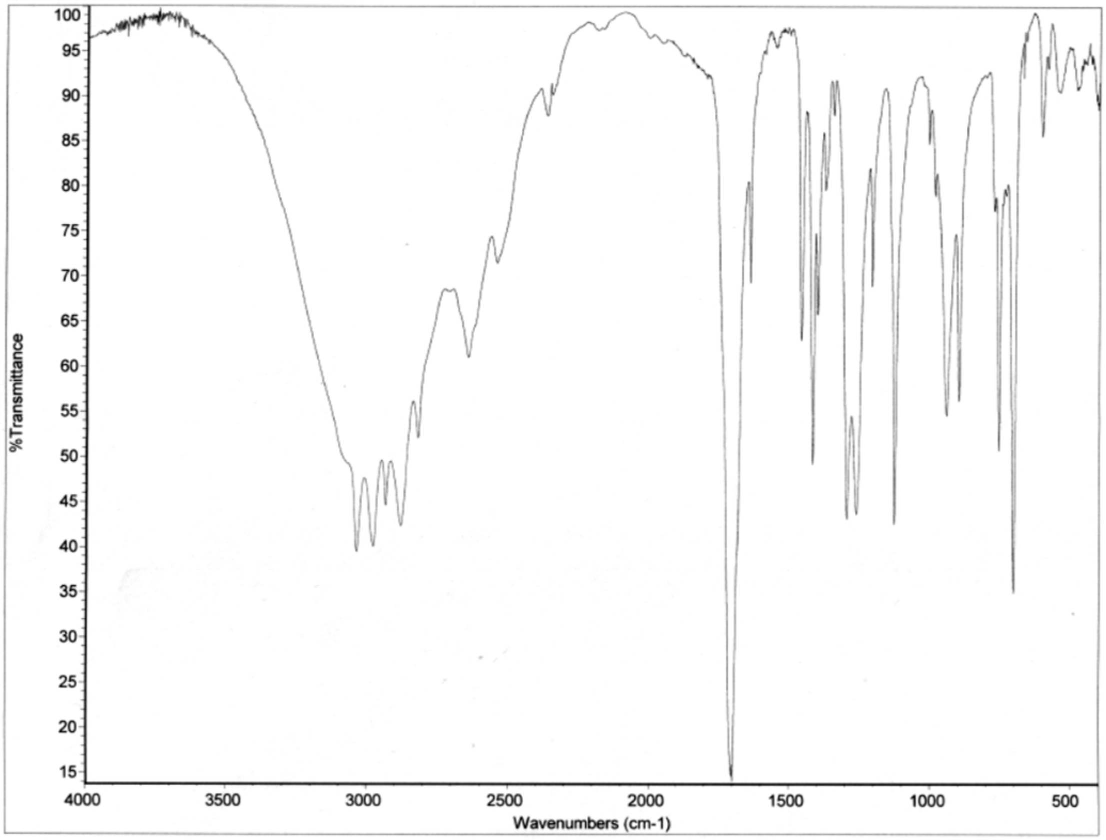

%Transmittance
100
99
98
97
96
95
94
93
92
91
90
89
88
87
86
85
84
83
82
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

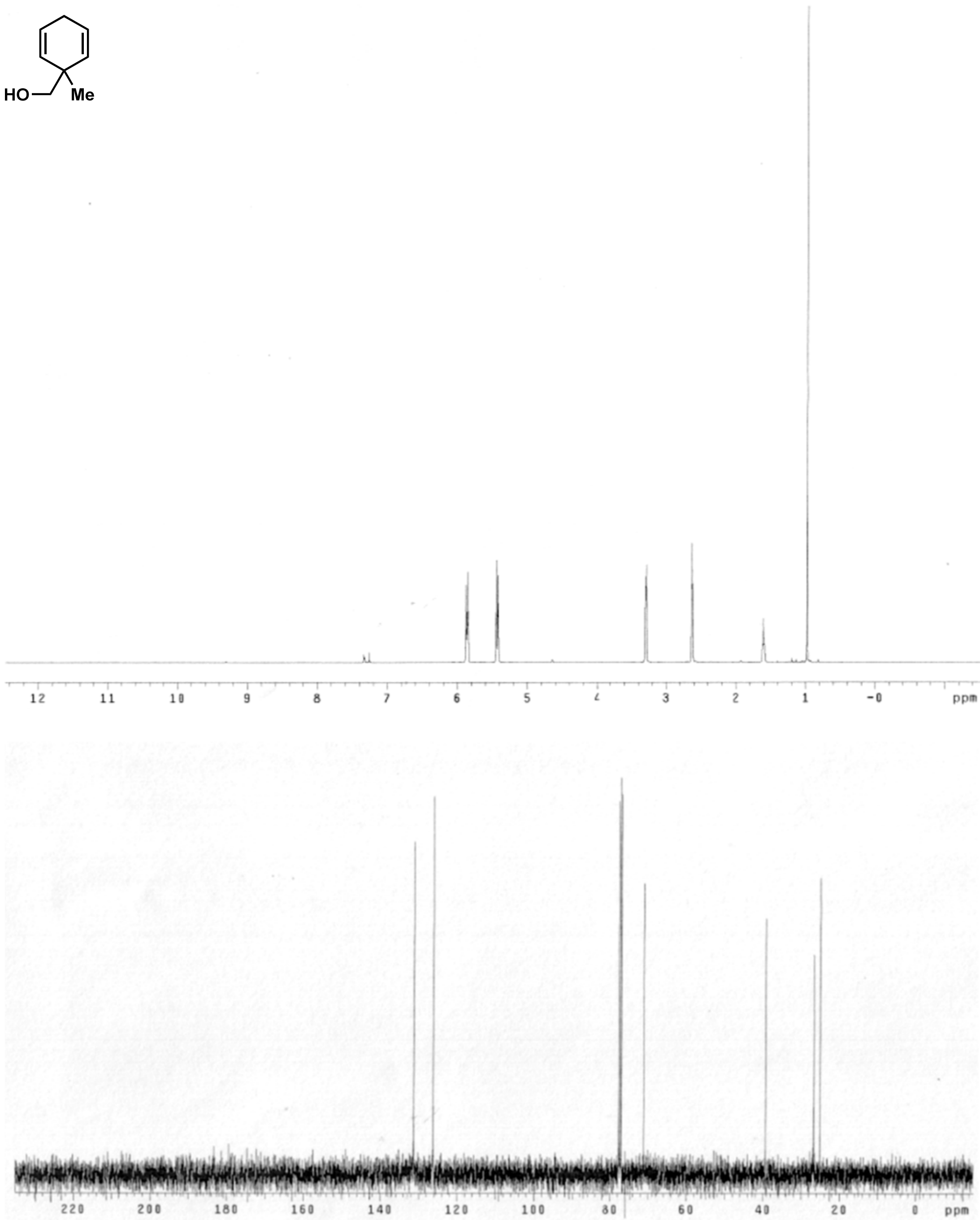

HO2C
Me

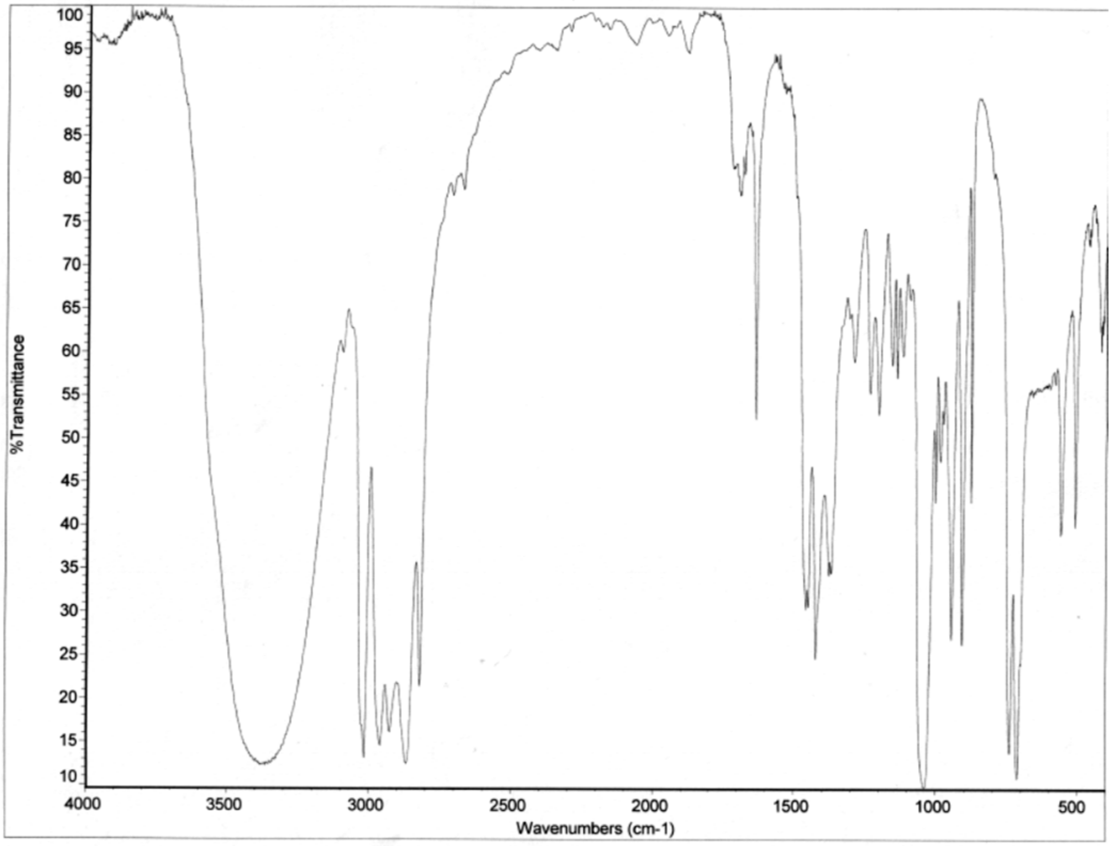
160

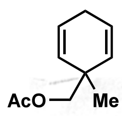

12
10
8
6
4
2
0
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm

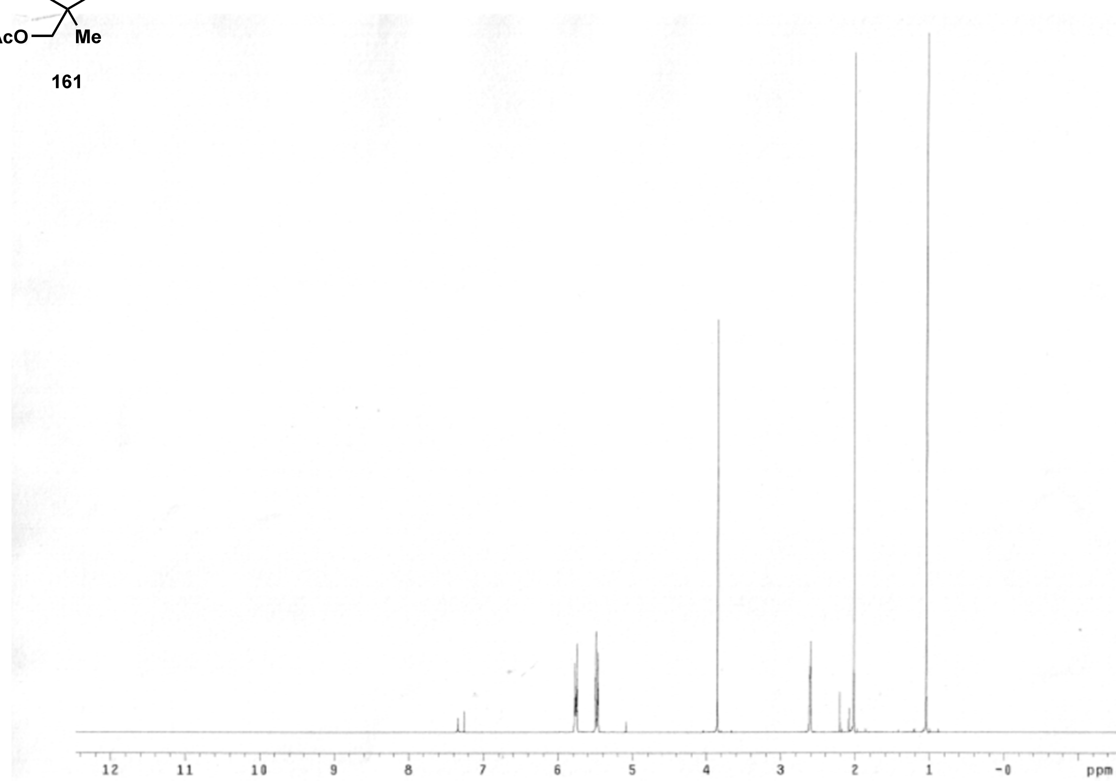

%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

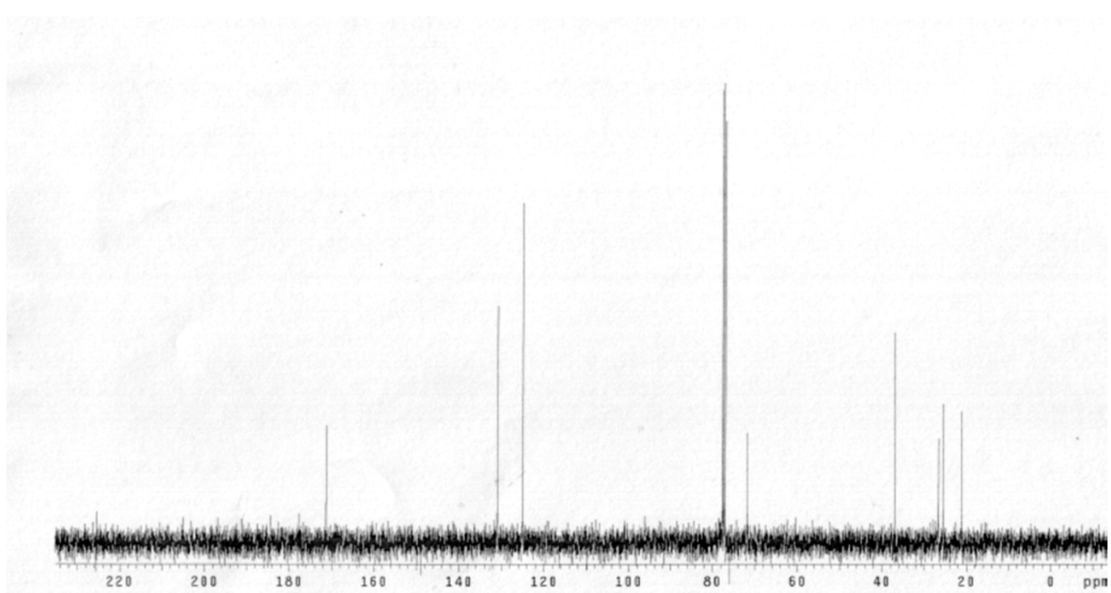

HO
Me
12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm
220 200 180 160 140 120 100 80 60 40 20 0 ppm

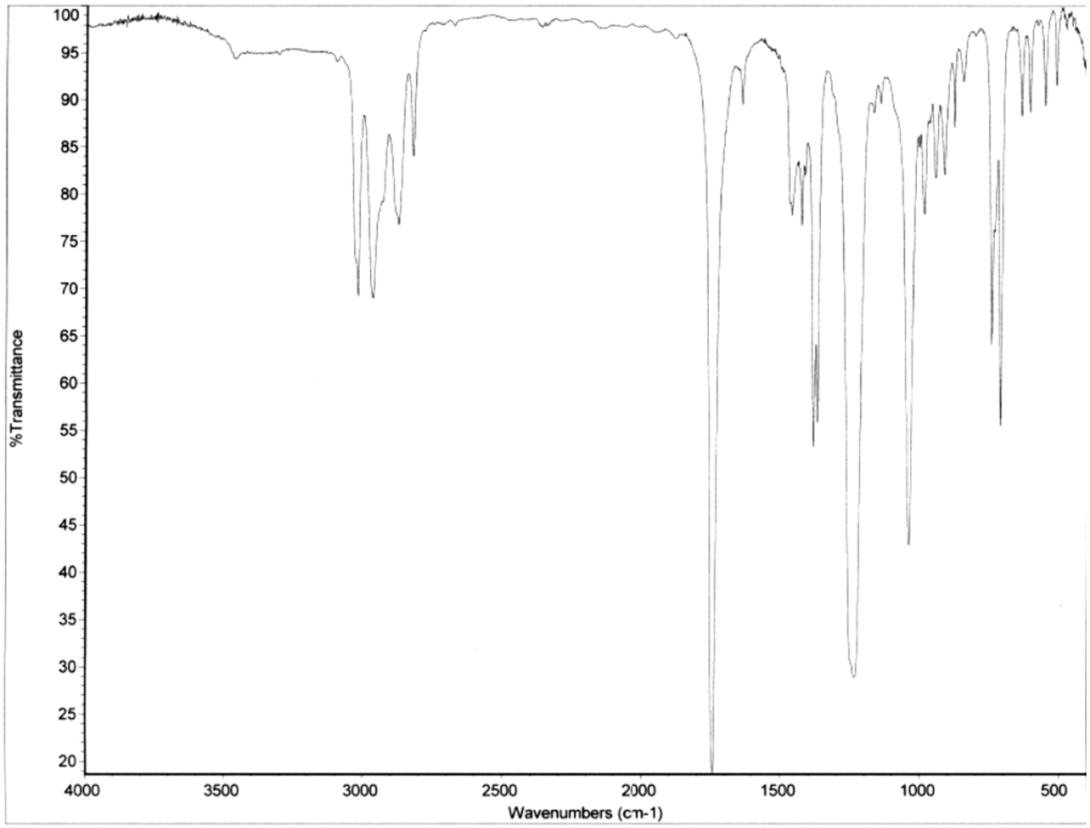

%Transmittance
Wavenumbers (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
4000
3500
3000
2500
2000
1500
1000
500


AcO
Me

161


12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm


%Transmittance
Wavenumbers (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
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30
25
20
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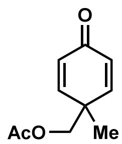
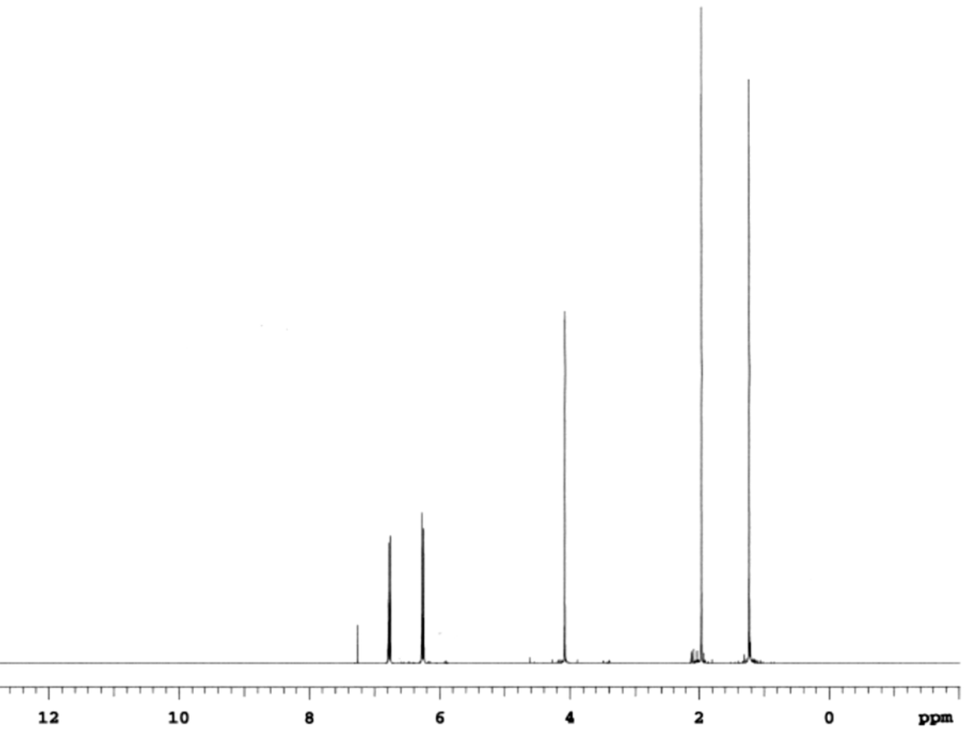
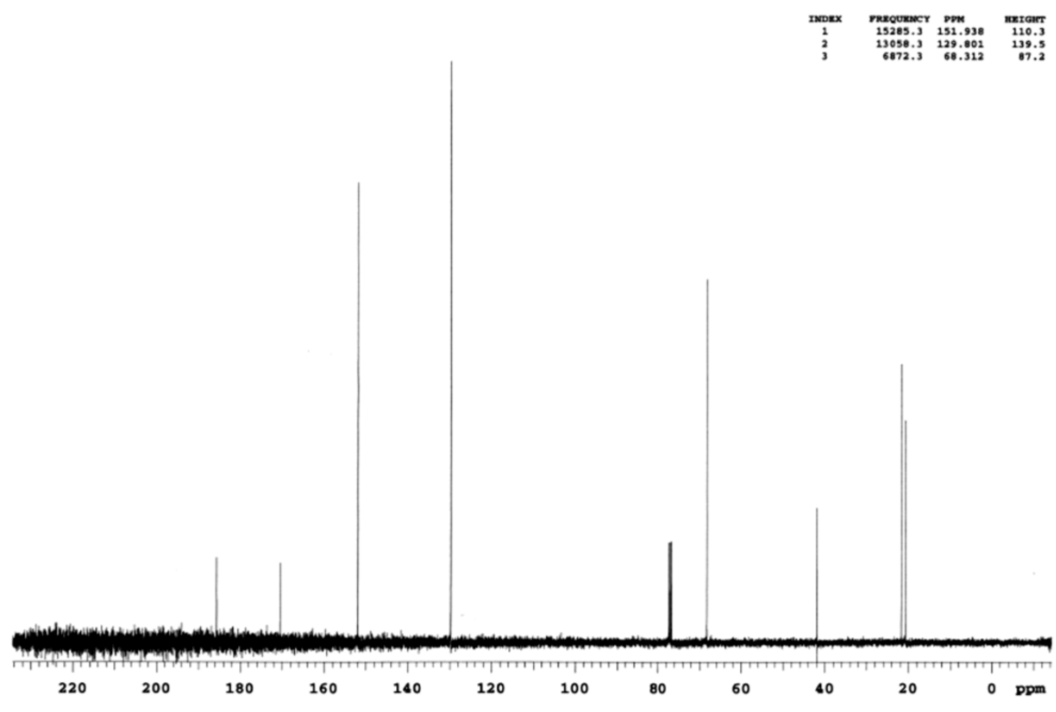
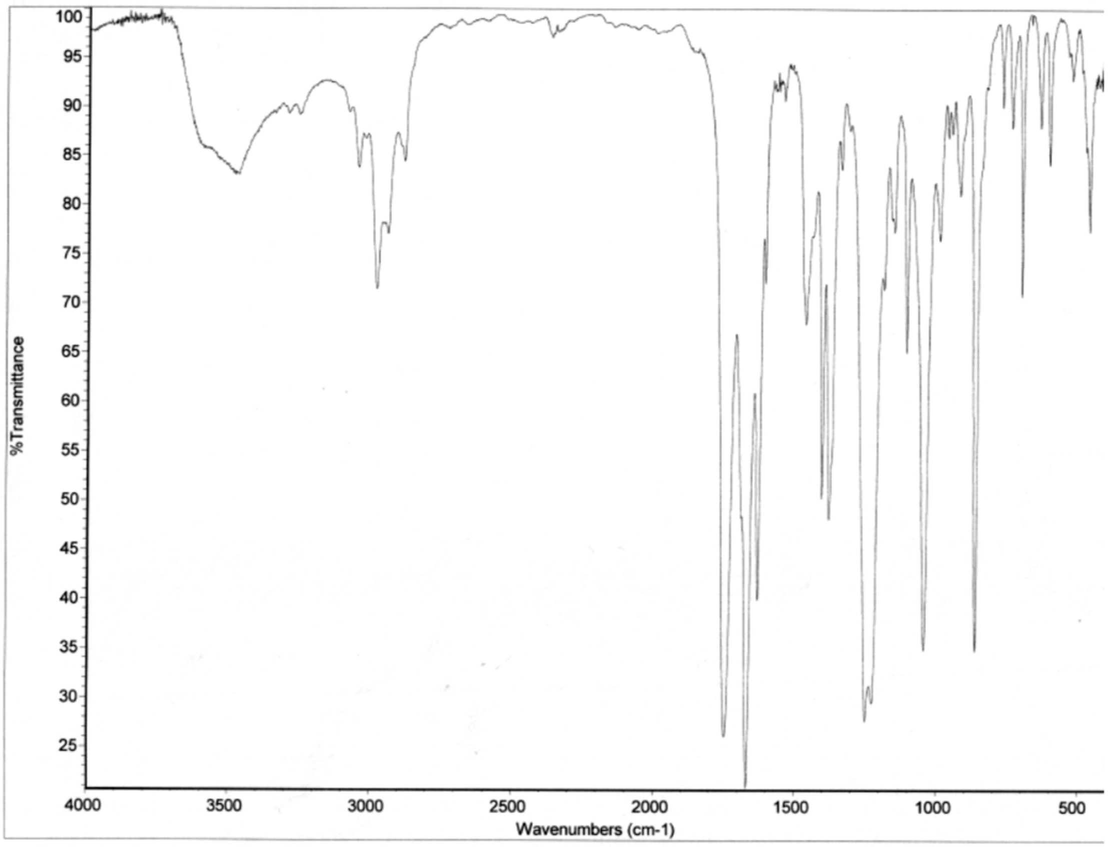
2500
2000
1500
1000
500

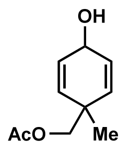

O
AcO
Me

162

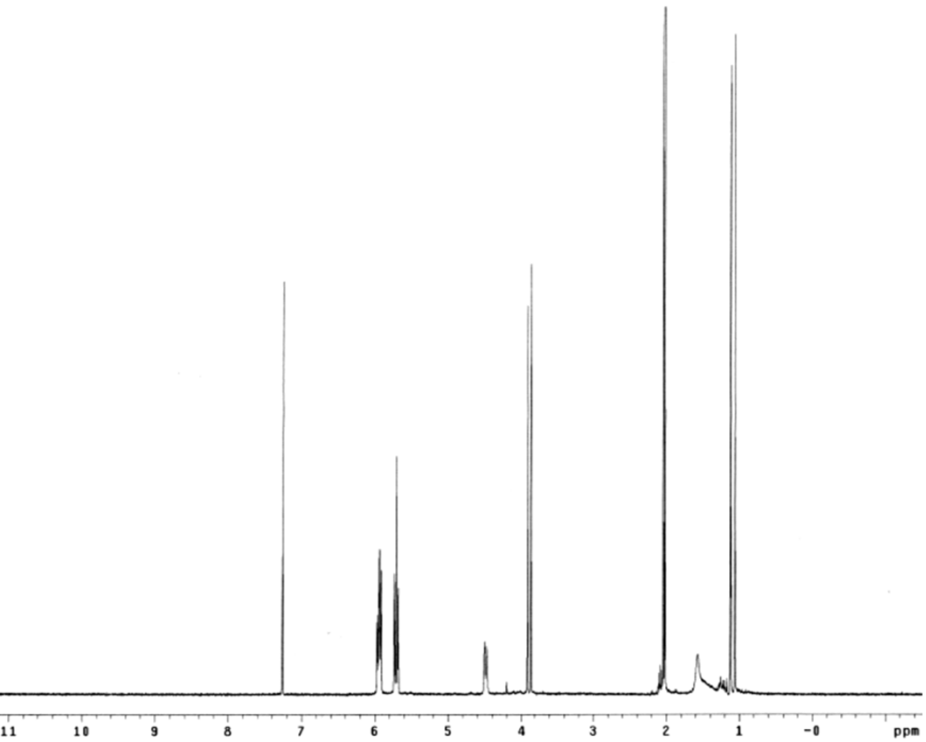

12
10
8
6
4
2
0
ppm

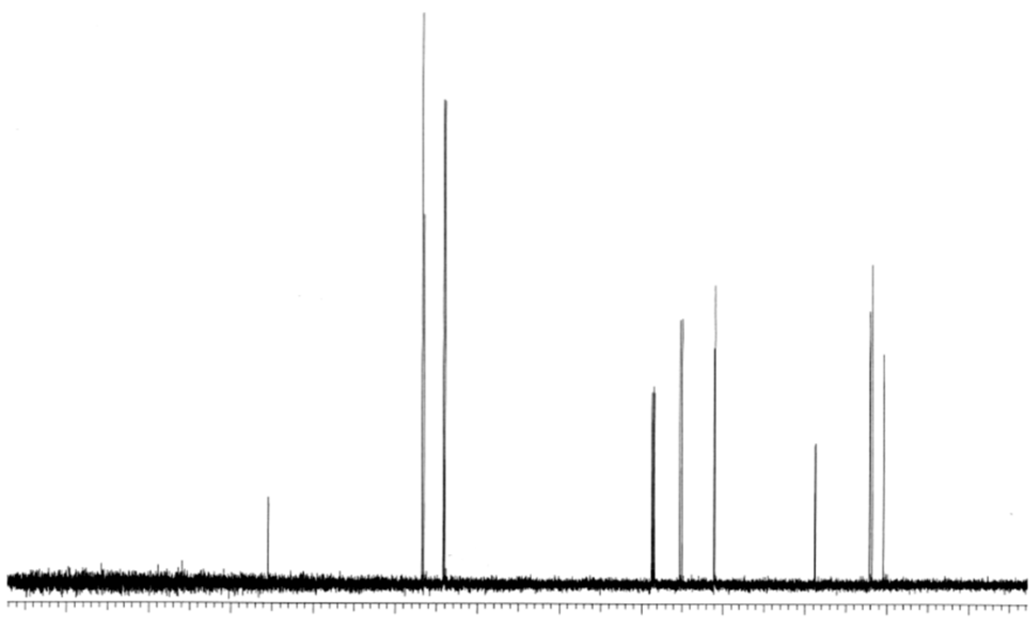

INDEX FREQUENCY PPM HEIGHT
1 15285.3 151.938 110.3
2 13058.3 129.801 139.5
3 6872.3 68.312 87.2
220
200
180
160
140
120
100
80
60
40
20
0
ppm

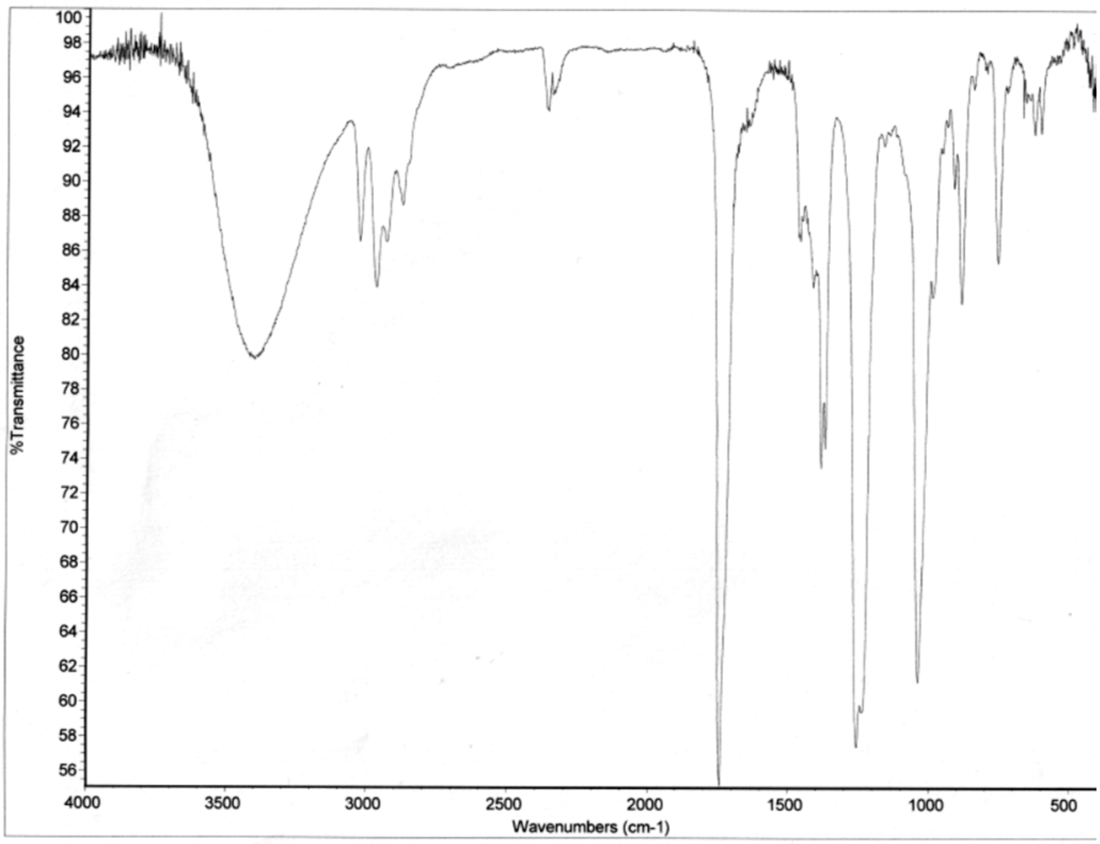

%Transmittance
Wavenumbers (cm-1)

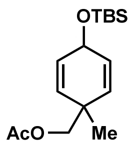

OH
AcO
Me

d.r. = 1.5:1

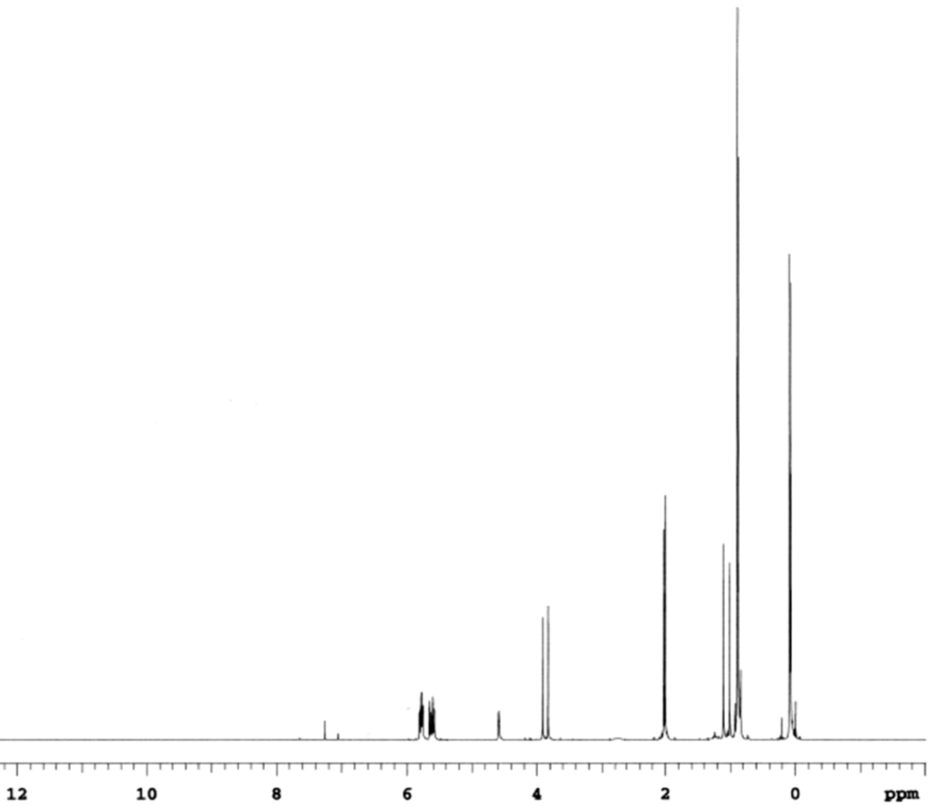

12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

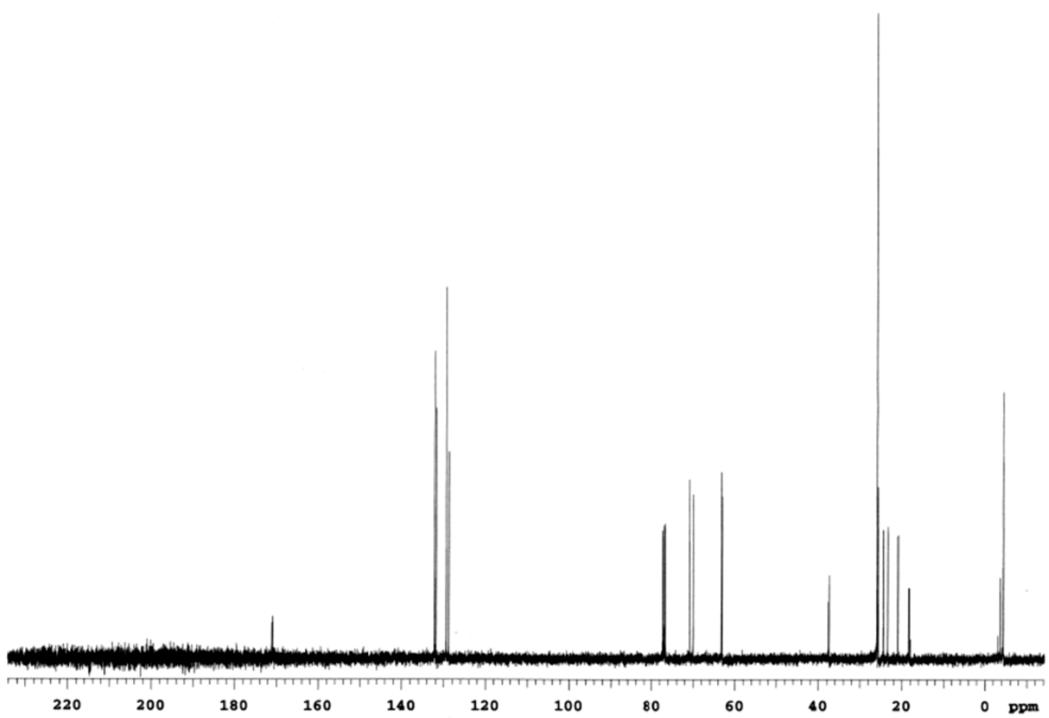

220 200 180 160 140 120 100 80 60 40 20 0 ppm

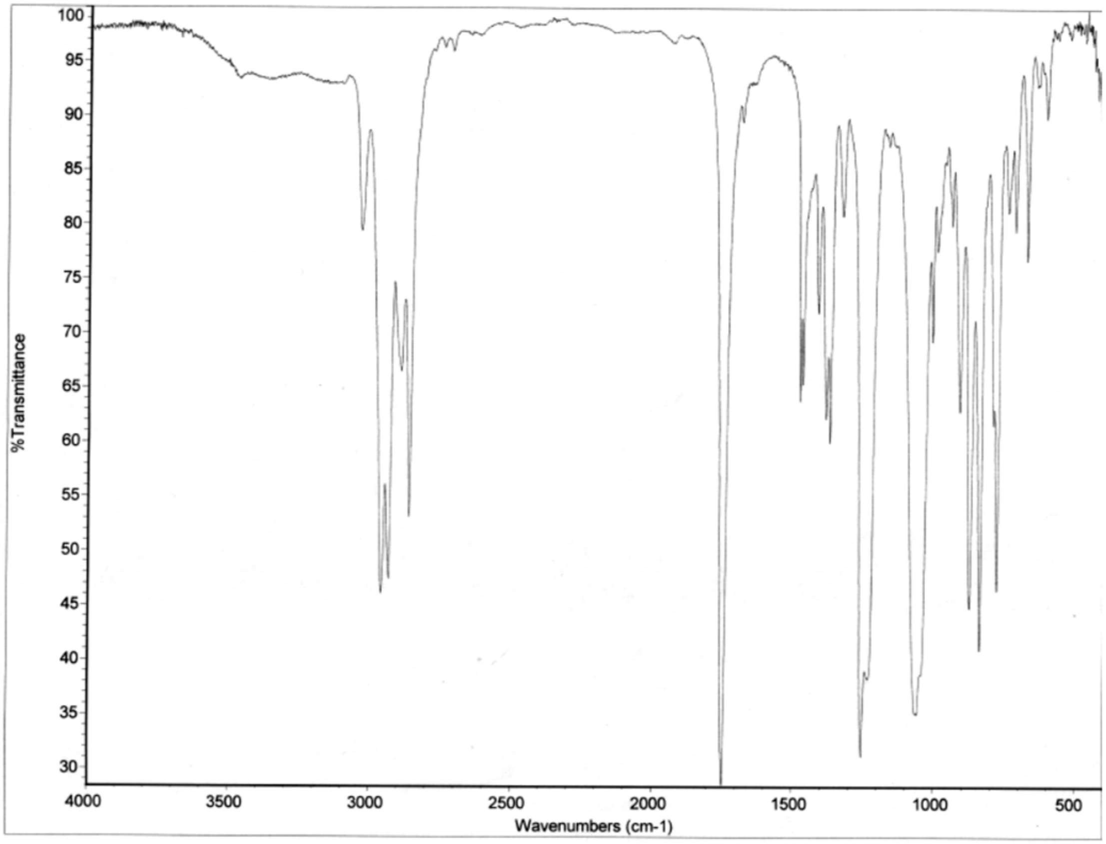

%Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

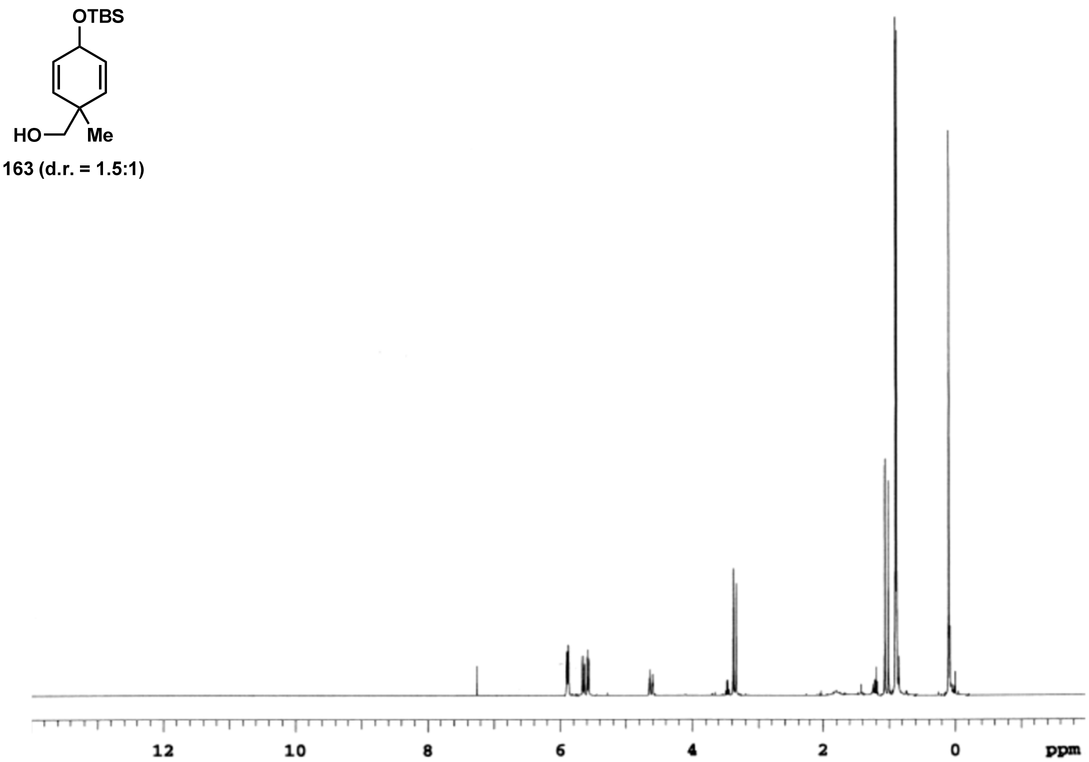

OTBS
AcO
Me

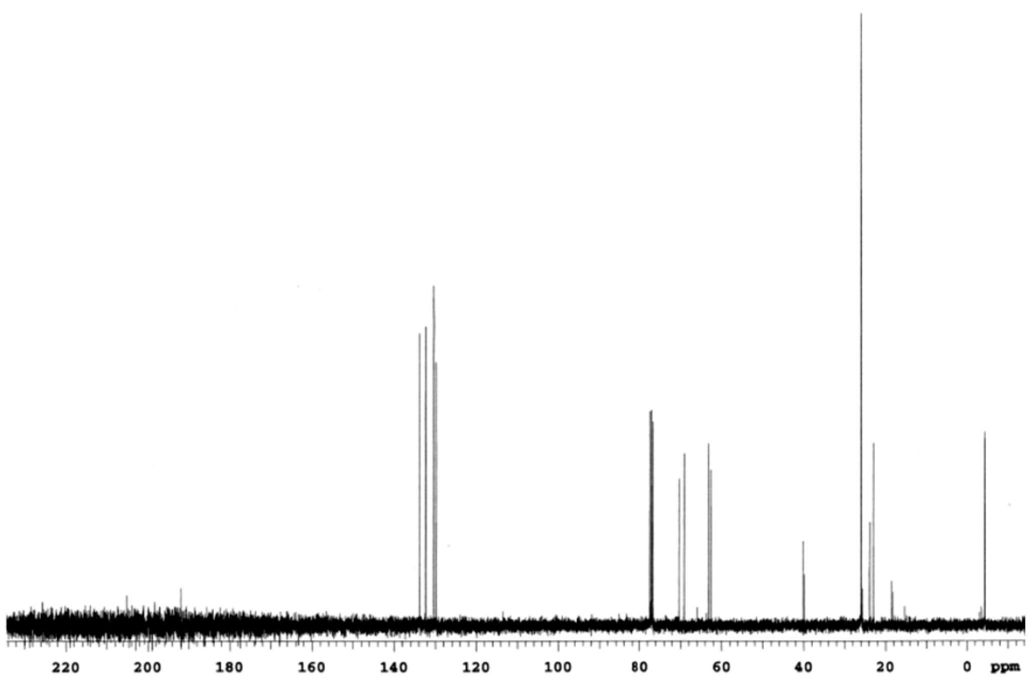
d.r. = 1.5:1

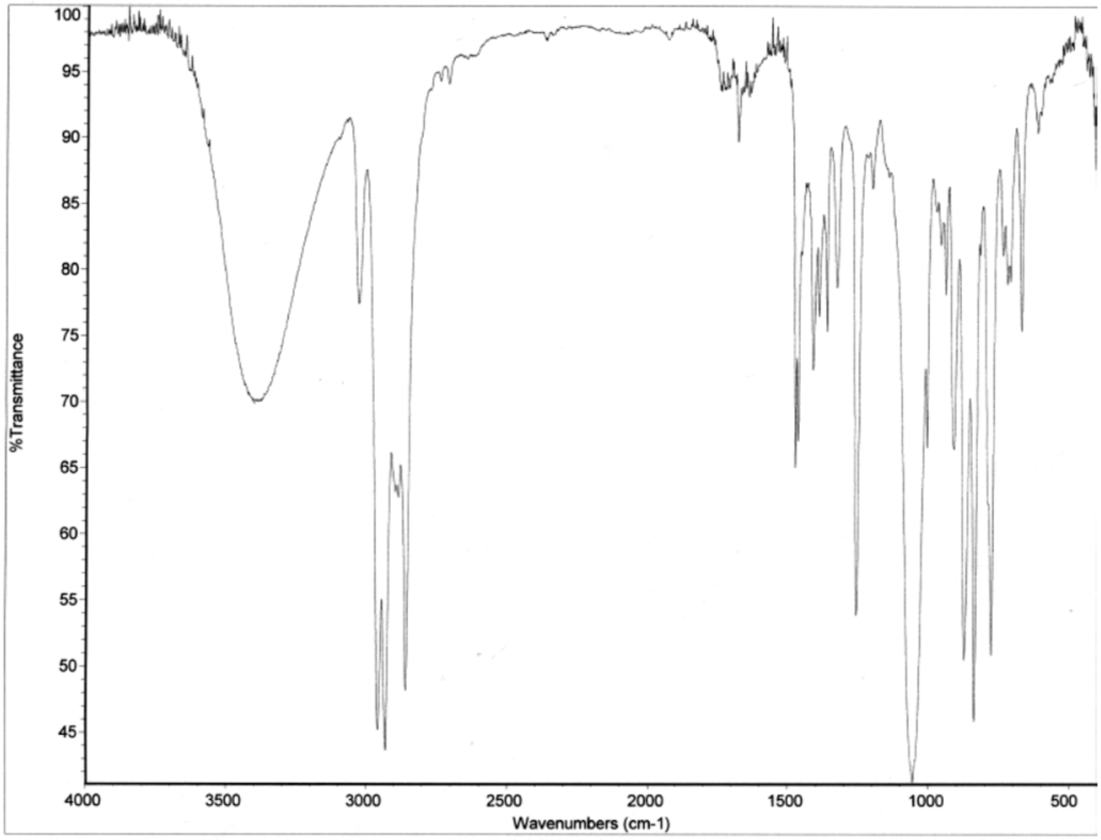

12
10
8
6
4
2
0
ppm

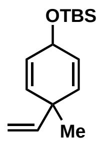

220
200
180
160
140
120
100
80
60
40
20
0
ppm


%Transmittance
Wavenumbers (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
4000
3500
3000
2500
2000
1500
1000
500

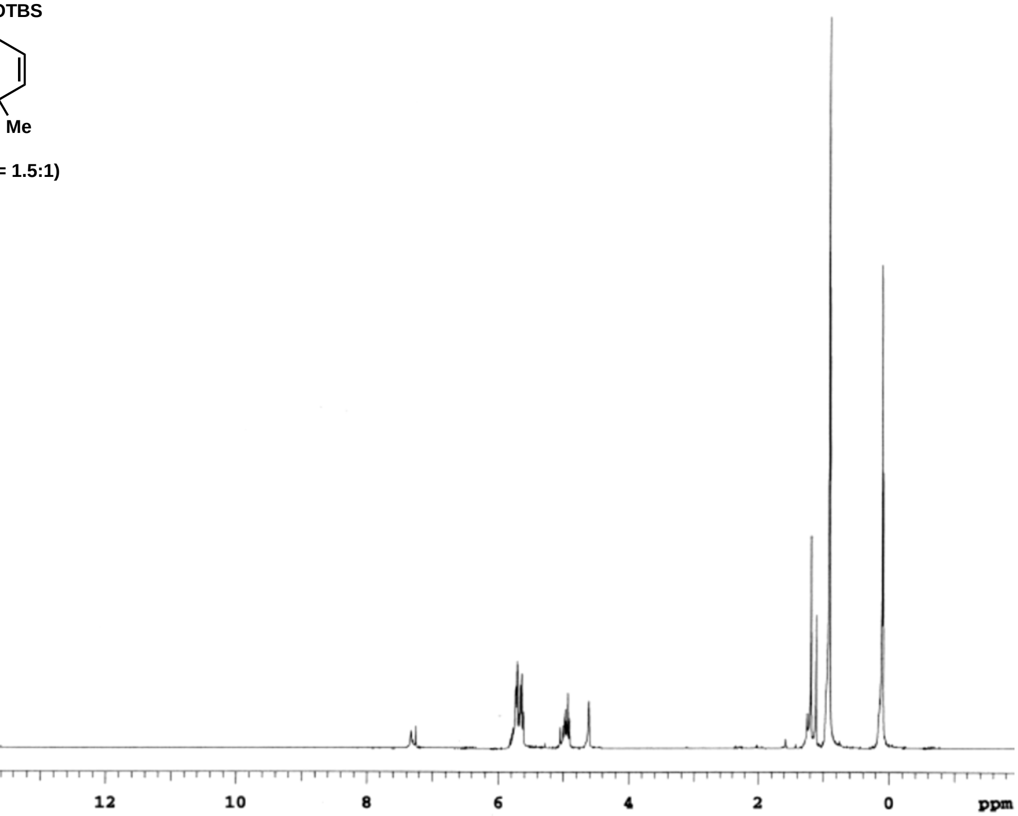

OTBS
HO
Me
163 (d.r. = 1.5:1)
12
10
8
6
4
2
0
ppm

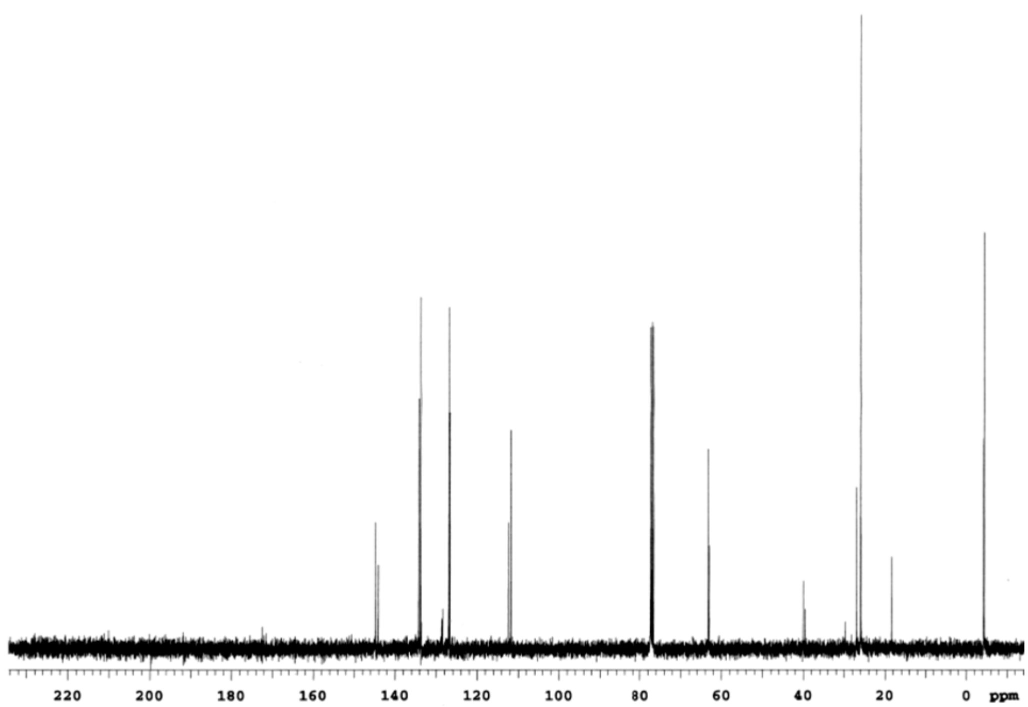

220
200
180
160
140
120
100
80
60
40
20
0
ppm

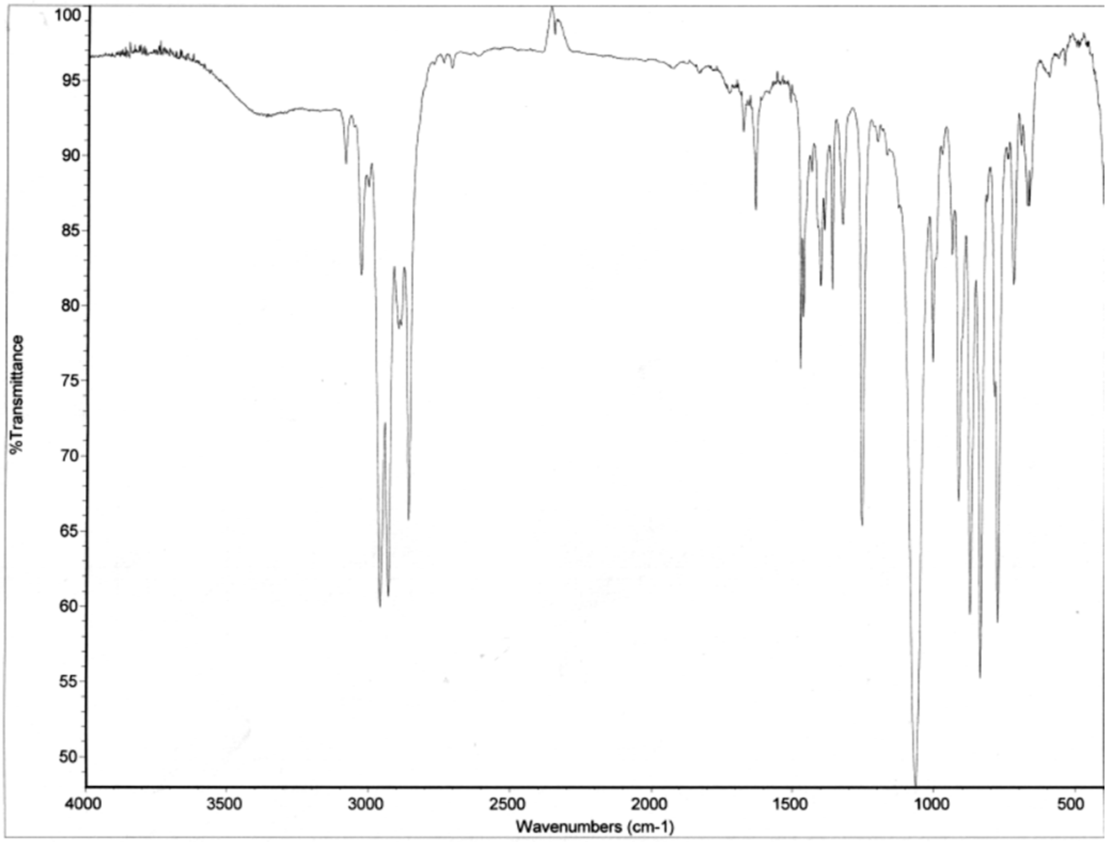

100
95
90
85
80
75
70
65
60
55
50
45
%Transmittance
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)


OTBS
Me

165 (d.r. = 1.5:1)


12 10 8 6 4 2 0 ppm


220 200 180 160 140 120 100 80 60 40 20 0 ppm



100
95
90
85
80
75
70
65
60
55
50
%Transmittance
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

Chapter 3 – Aryl Hydroxylation Mediated by 4,5-Dichlorophthaloyl Peroxide

Phenols are fundamentally important molecules which possess broad utility and perform a suite of applications in the pharmaceutical, agricultural, and commodity chemical industries.[132] Phenols are pharmacologically ubiquitous in drugs which serve a wide range of biological purposes.[133] During metabolism various aromatic compounds are also oxidized to phenols to increase their excretion from the body. The FDA mandates that metabolites generated in higher than 10% must be examined to elucidate their potential toxicity or side effects.[134] An effective synthetic protocol capable of accessing phenolic derivatives and potential metabolites of native pharmaceutical agents in an efficient, economical fashion would be an essential chemical and biological tool. Despite their vast importance, a procedure for the general, straightforward conversion of arenes to phenols does not exist. A protocol emulating cytochrome P450 which directly oxidizes aryl C-H bonds to C-OH bonds in a mild, selective manner is most ideal, but this rather rudimentary transformation poses many synthetic challenges.[135,136] The major problem in developing hydroxylation reactions is that the phenolic products are more reactive than the starting materials which leads to over-oxidation. A protocol that is also tolerant to a multitude of functional groups also remains elusive.[137]

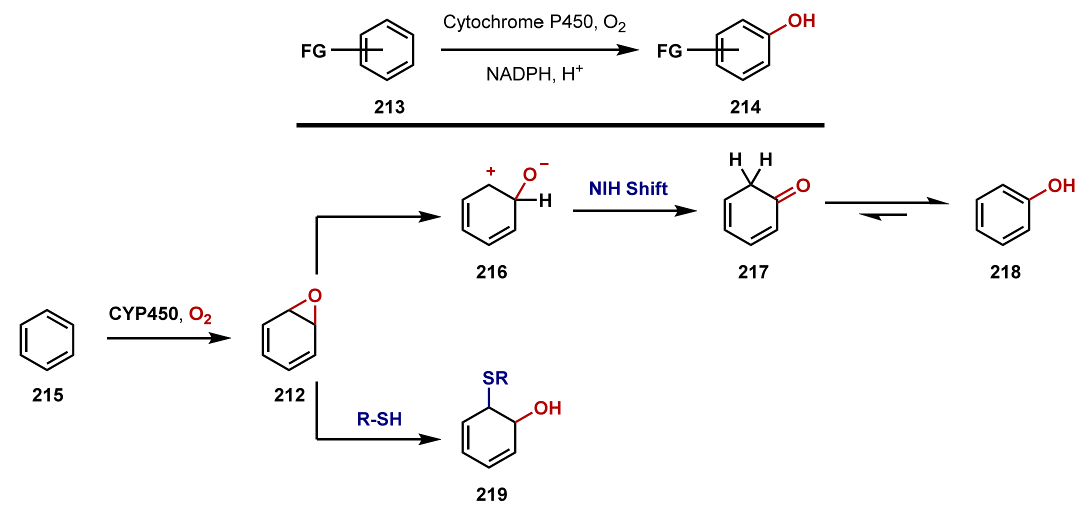
Early hydroxylation reactions employed peroxides, but had limited success in generating mono-hydroxylated products, and when successful they had a limited scope.[138-145] Methods to circumvent this problem using super acids to both activate the peroxides and subsequently deactivate the arenes were investigated.[146-149] These approaches lack generality because many functional groups cannot tolerate these exceptionally strong acids. Transition metal catalyzed oxidations of aromatics have improved upon the early acid-mediated processes which utilize peroxides, but these strategies are not ideal since they require precious metals and usually invoke directing groups to promote reactivity.[150-161] The use of directing groups inherently minimizes the substrate scope and the types of substituted phenols that can be accessed. The directing groups that are employed often need to be installed as well as removed creating an overall inefficient process with regard to step economy. Strategies that oxidize aryl silanes and aryl boronic acids or esters are also utilized to deliver phenols.[162-166] Although potentially high yielding, these strategies require multiple steps starting from halogenated arenes and predominantly use transition metal catalysis to install the silane or boronate. Late-stage halogenations and the subsequent oxidation of the silanes or boronates on highly functionalized molecules can pose significant problems often rendering these strategies inferior to the widely used Friedel-Crafts/Baeyer-Villiger sequences for the installation of oxygen into arenes. Although effective, this multi-step process utilizes reagents that may not be suitable to latent functionality in the later stages of a synthetic strategy.[167-169]

Phthaloyl peroxide (**211**), a reagent studied in detail by Greene in the 1950's, was recently shown to mono-hydroxylate arenes with a high degree of functional group tolerance.[170,171] A major limitation to this protocol, however, is that electronically rich arenes are needed. Interestingly, computational analysis dictates that the reaction proceeds through a novel diradical reverse-rebound mechanism, not the expected electrophilic aromatic substitution (EAS) pathway. This is perplexing and several mechanistic questions remain since there is no experimental evidence to substantiate these findings. Mechanistic evaluation and probing of different peroxide reagents could enhance this protocol thereby expanding the generality of the substrate scope to provide a more applicable strategy with higher utility.

Synthetic Protocols to Access Phenols

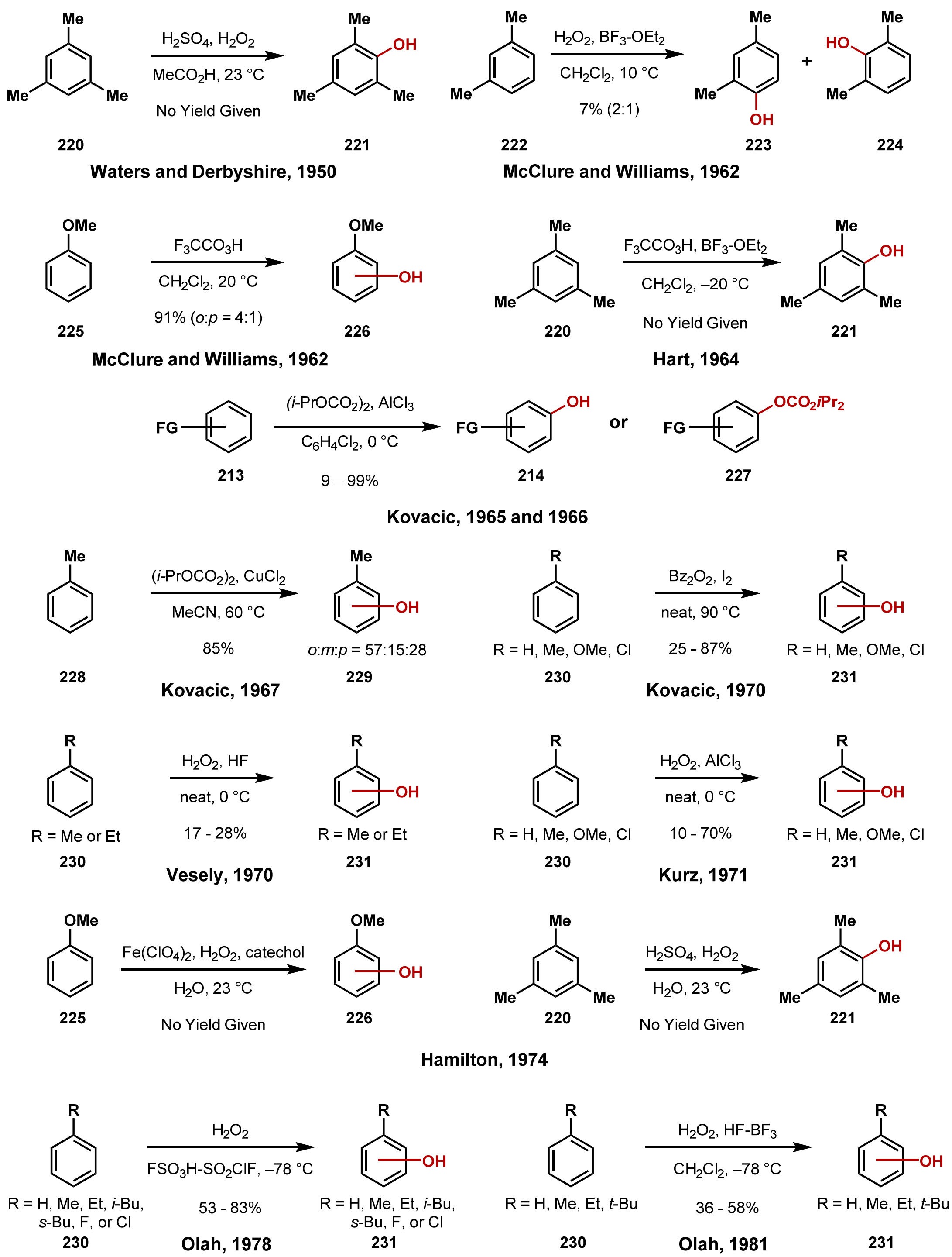
The monooxygenase super family of proteins that encompasses the cytochrome P450 catalyzes the oxidation of small molecules. These enzymes play an integral role in the biosynthesis of important compounds such as steroids and lipids, but they also metabolize drugs and foreign organic molecules to facilitate their excretion and clearance from the body.[135,136] They are responsible for the oxidation of arenes like benzene and various poly-aromatic hydrocarbons (PAHs) through the direct conversion of the arene to an epoxide which undergoes an NIH shift to afford the phenolic metabolites (Scheme 3.1). The oxirane intermediate **212** can undergo another pathway involving covalent modification via nucleophilic addition of cysteine residues ultimately leading to the carcinogenic properties of these aromatics. Despite the deleterious toxicity, the overall transformation is fascinating from a synthetic perspective. An iron-oxygen complex containing an iron (V) core effects this overall transformation inside the active site of the enzyme which directly oxidizes the arene.

Scheme 3.1. CYP450 mediated hydroxylation of arenes.[135,136]



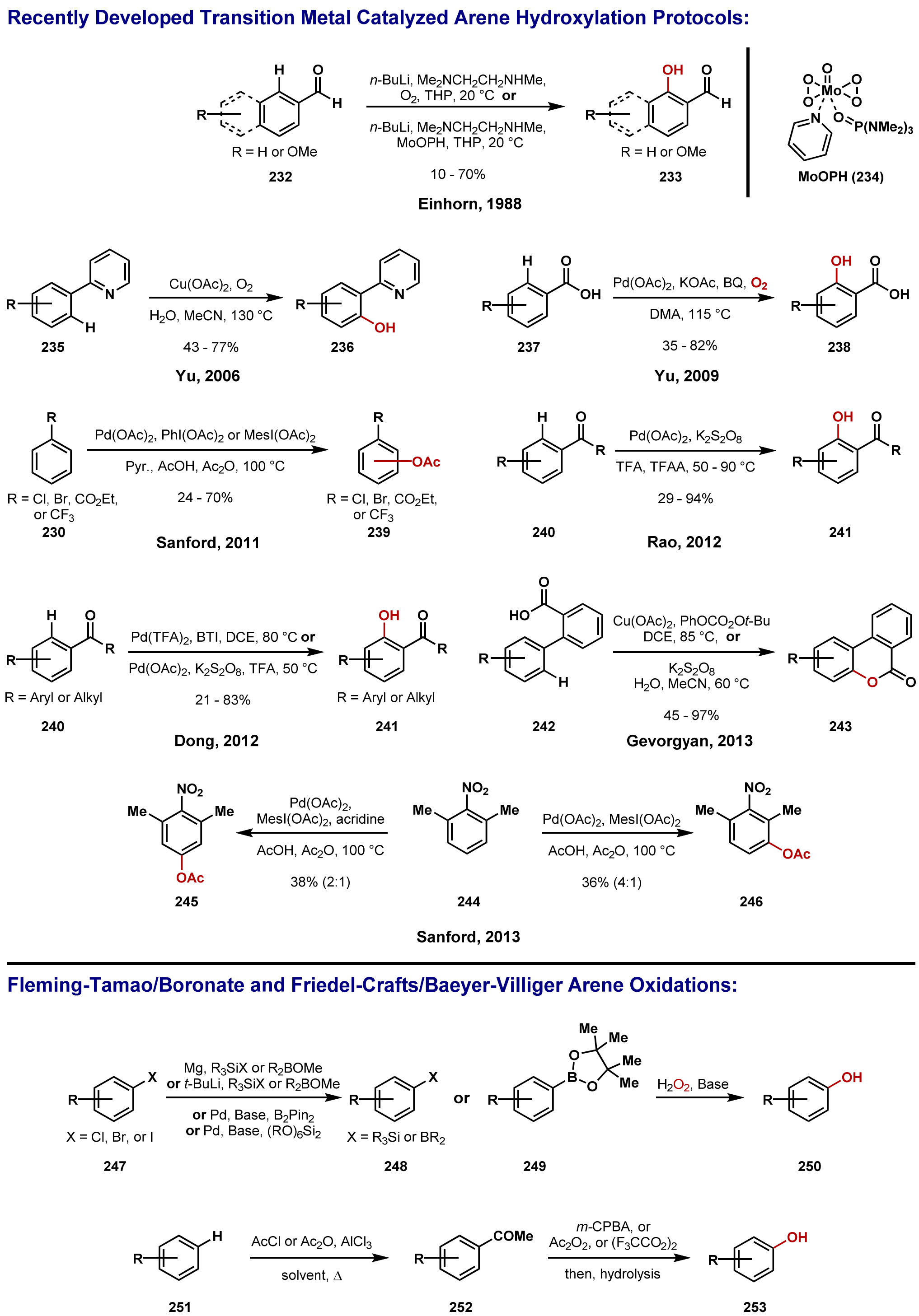
Emulating this transformation chemically has proven to be quite difficult. Fenton's reagent affects this transformation but acts as an indiscriminate oxidant. It has limited utility because the arene is used in excess and the oxidant is the limiting reagent. Since the phenolic products are more reactive to further oxidation. Over-oxidation coupled with functional group liability severely limits this protocol. Its indiscriminate oxidation potential, however, has warranted its use in water purification to remove PAHs as well as other toxic organic molecules like tri- and tetrachloroethylene.[138] The use of strong acids, Lewis or Brønsted, in combination with peroxides has also affected this transformation, but again functional group liability severely limits these processes (Scheme 3.2).[139-149] Additionally, these protocols typically use simple arenes in excess or as the solvent, further limiting the widespread synthetic utility of these approaches. Despite the major limitations these early developments laid significant groundwork in arene hydroxylation reactions.

Scheme 3.2. Early peroxide mediated hydroxylation of arenes.[138-149]



Remarkable achievements in the syntheses of phenols have recently been made using transition metal catalysis by researchers such as Crabtree, Sanford, Yu, Ritter, Gevorgyan, Dong, and Rao (Scheme 3.3).[150-161] These protocols can be effective, but tend to lack broad application due to the use of directing groups or contrived systems. The oxidation of aryl silanes or boronates is commonly implemented to provide phenols. Aryl silanes and boronic acids or esters, which essentially are masked phenols, are derived from the aryl halides through a cross-coupling approach such as the Miyauri boration or through anion mediated nucleophilic addition reactions.[167] Fleming-Tamao and boronate oxidation ultimately unmasks the phenols.[162-166] These strategies can be highly effective early in a synthetic strategy, but unselective aryl halogenation and peroxide mediated oxidations can be deleterious to common functional groups in the later stages of a synthetic strategy. This causes undesirable protecting group steps or alternative approaches. The universal protocol to synthesize a phenol is the Friedel-Crafts/Baeyer Villiger sequence.[168,169] Although effective, this strategy usually requires protecting group manipulations and compatible functional groups which often limit its generality.

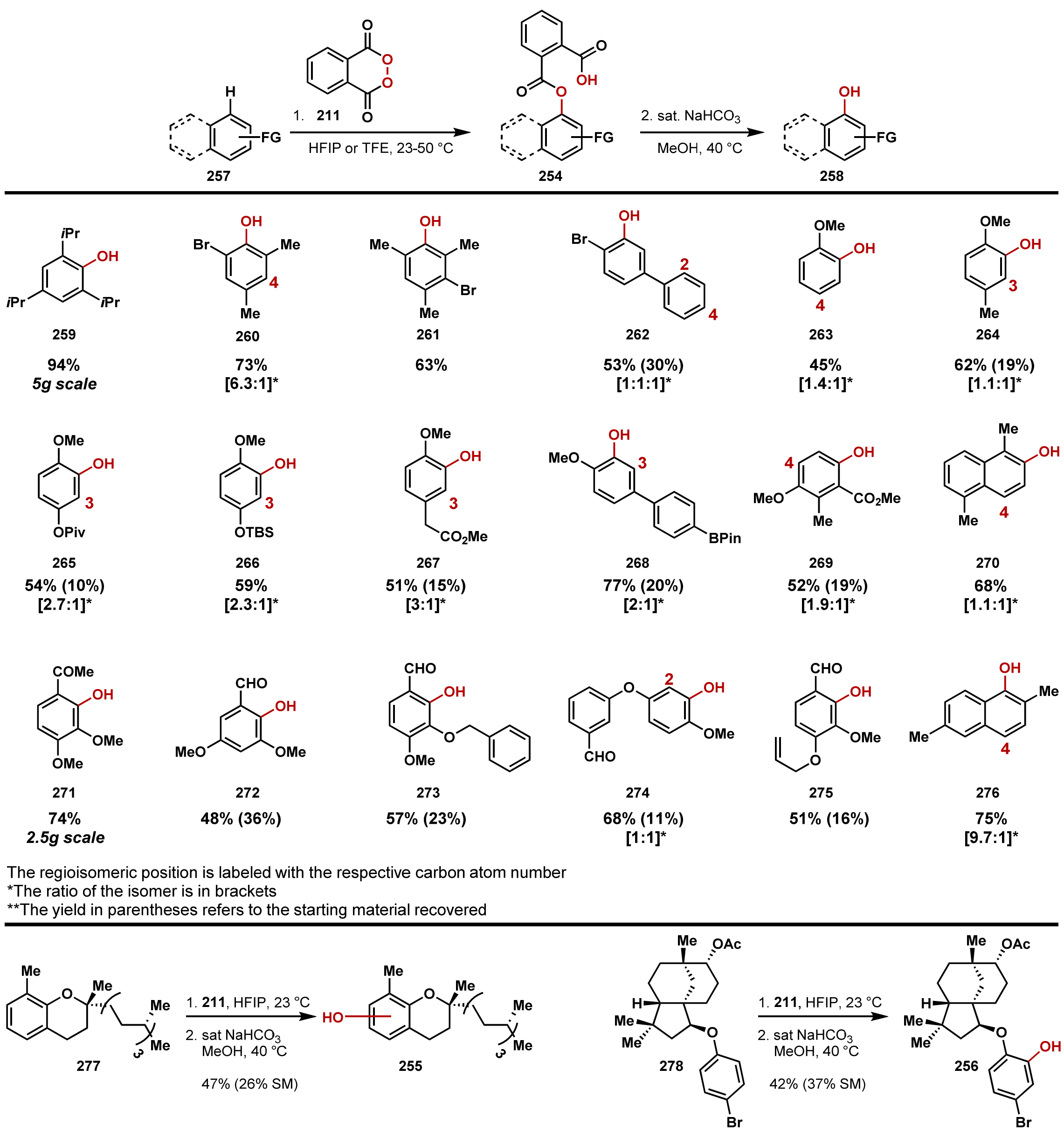
Scheme 3.3. Transition metal catalyzed and Friedel-Crafts/Baeyer Villiger syntheses of phenols.



Phthaloyl Peroxide Mediated Hydroxylation

Phthaloyl peroxide (**211**), originally studied in detail by Greene in the 1950's, has recently been exploited by our laboratory to oxidize arenes to phenols, converting C-H bonds to C-OH bonds (Table 3.1).[170,171] The reaction is predictable, occurring in a similar fashion to the Friedel-Crafts reaction to afford the phenol in a two step sequence with minimal over-oxidation. The reaction is controlled by the formation of mixed phthaloyl ester-acid **254** which is reluctant to another oxidation by a second equivalent of phthaloyl peroxide. The mixed phthalate is then hydrolyzed using aqueous sodium bicarbonate in warm, deoxygenated methanol in the second step to provide the phenol. Remarkably, the peroxide and the overall protocol possess excellent functional group tolerance. Aldehydes, ketones, esters, alkenes, boronic esters, nitriles, allenes, alkynes, cyclopropanes, and cyclobutanes are all tolerated under these conditions. This protocol is also applicable to the late-stage oxidation of complex molecules and natural products including phenolic derivatives of tocopherol **255** as well as the advanced clovanemagnolol intermediate **256**. The major limitations to this protocol are that the reaction only works on electronically moderate to rich arenes and the *ortho*/*para* selectivity is low.

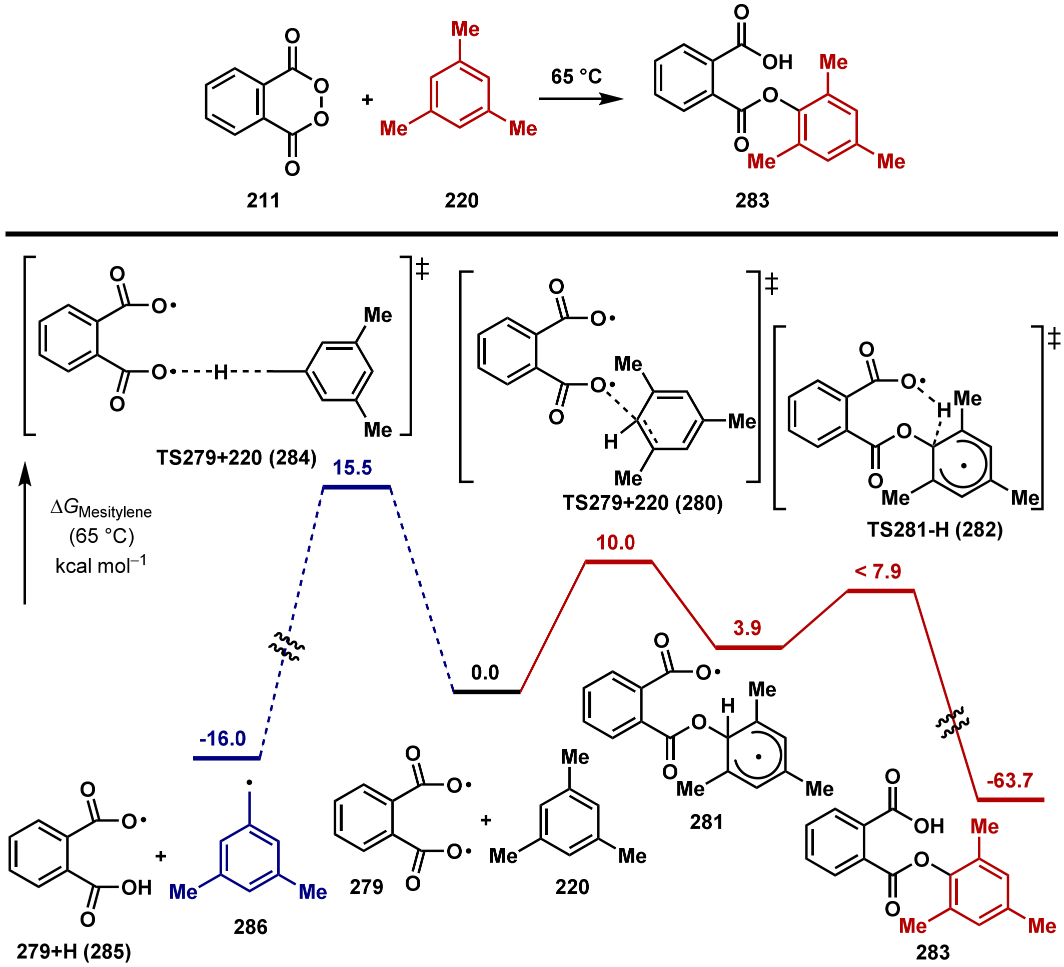
Table 3.1. Scope of arenes hydroxylated by phthaloyl peroxide.[171]



It was initially hypothesized that the reaction proceeded through an ionic pathway. This was substantiated by the selective oxidation of the arene over the alkyl substituents possessing benzylic hydrogens. In fact, no benzylic oxidation was observed throughout the hydroxylation reaction in the cases of substrates **259-261, 264, 270, 276**, or **277**. However, an ionic pathway contradicts the fact that no over-oxidation products were observed. The mixed phthaloyl ester-acid intermediate **254** would be more prone to oxidation than the starting arene through an EAS mechanism.[172] These contradicting results prompted computational analysis to determine the most plausible mechanistic pathway. There are potentially four major reaction pathways: ionic, direct hydrogen abstraction, single electron transfer (SET), or a diradical reverse-rebound addition. Density functional theory (DFT) and *ab initio* calculations dictate that the lowest energetic reaction pathway is the diradical reverse-rebound. The energy required for this mechanism is 30.5 kcal/mol, which is approximately 5.2 kcal/mol lower than the ionic pathway.[171]

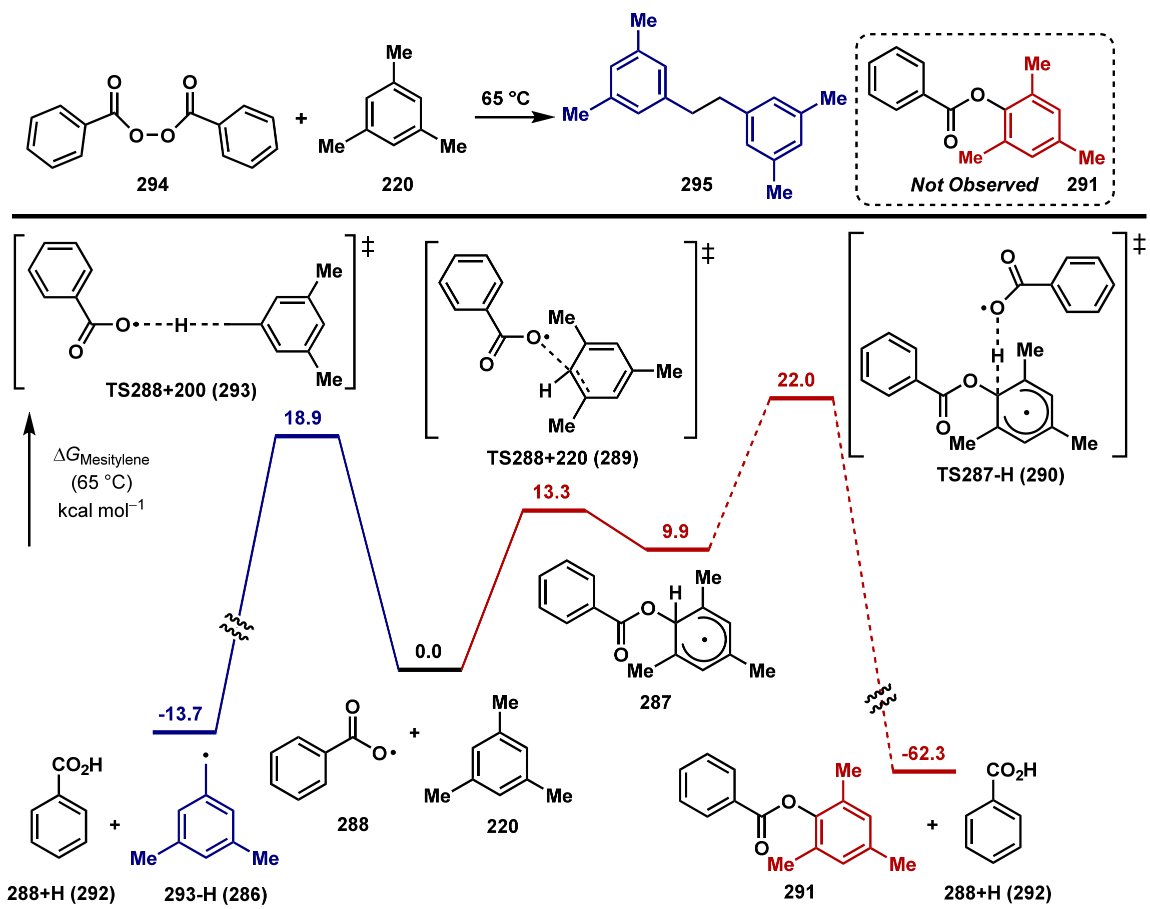
The reaction's selectivity for oxidizing the arene over the benzylic C-H bonds is rather surprising if a diradical process is actually occurring. Further DFT analysis using mesitylene (**220**) illustrated that benzylic oxidation via hydrogen abstraction is approximately 5.5 kcal/mol higher than aryl C-H oxidation (~10 kcal/mol), accounting for the arene selectivity (Scheme 3.4). The cyclohexadienyl diradical **281** then undergoes rearomatization via hydrogen abstraction which is expedited by the adjacent benzoyloxy radical to afford the mixed phthaloyl ester acid **283** as the sole product.

Scheme 3.4. CPCM-(U)B3LYP/6-31+G(d) computed free energy surfaces for aryl and benzylic functionalization of mesitylene using phthaloyl peroxide.



Phthaloyl peroxide is a special reagent in this process because peroxides such as benzoyl peroxide promote benzylic oxidation, not aryl oxidation (Scheme 3.5). Experimental observations confirm this result as no arene oxidation is observed when benzoyl peroxide is reacted with mesitylene. DFT and *ab initio* calculations on this process indicate that the aryl oxidation pathway for a mono-radical peroxide is lower in energy compared to the hydrogen abstraction pathway which forms the mesityl benzyl radical (13.3 kcal/mol versus 18.9 kcal/mol).[171] However, the energy associated with the rearomatization (25.8 kcal/mol) creates a barrier that is much higher compared to benzylic oxidation. Abstraction of the hydrogen from the cyclohexadienyl radical **287** requires a second benzoyloxy radical (**288**). This is entropically disfavored and causes the high energy penalty. Traversing this entropy barrier is nearly impossible under the reaction conditions so the only experimentally observed product is benzylic oxidation. Benzoyl peroxide is therefore a great oxidant in radical halogenations such as the Wohl-Ziegler reaction.[173] This entropic penalty does not exist when phthaloyl peroxide is used because the hydrogen abstraction is intramolecular.

Scheme 3.5. CPCM-(U)B3LYP/6-31+G(d) computed free energy surfaces for aryl and benzylic functionalization of mesitylene using benzoyl peroxide.



Development of an Arene Hydroxylation Protocol using 4,5-Dichlorophthaloyl Peroxide

Phthaloyl peroxide is a special oxidant which our laboratory has exploited to perform dihydroxylations of styrenes and, most notably, to oxidize arenes to phenols directly from the aryl C-H bond.[171,174] The latter is of specific interest because it provides access to phenols in a functional group tolerant fashion amenable to late-stage hydroxylation reactions. This protocol can rapidly deliver small molecules that are potential metabolites as well as oxidized analogs of drugs and pharmaceutical agents. The restricted scope of the reaction warrants further development of peroxides with the capability to access new arenes. There is also minimal experimental evidence to substantiate the DFT and *ab initio* calculations that dictate the most energetically favorable mechanistic pathway is a diradical reverse-rebound addition. A stronger peroxide reagent could also help provide this experimental evidence that remains elusive.

In the pursuit of new phthaloyl peroxide reagents, computational analysis and prior research regarding the dihydroxylation of styrenes illustrated that symmetrically halogenated phthaloyl peroxides possessed the highest potential for effecting the arene hydroxylation.[174] In 2011, our laboratory had shown that 4,5-dichlorophthaloyl peroxide (**296**) dihydroxylated styrenes as well as non-styrenyl alkenes, a reaction not observed using other types of phthaloyl peroxides. Computational analysis using DFT and *ab initio* calculations conducted in collaboration with Yong Liang and Ken Houk dictated that this reagent could potentially be a more powerful oxidant than phthaloyl peroxide in the arene hydroxylation as well (Figure 3.1). Through comparing their reactivities with three separate arenes: mesitylene, benzene, and 1,3,5-trichlorobenzene, the calculations delineated that the electron-rich arene is more reactive than the electron-deficient arene. This is predicated on the HOMO-SOMO interaction in the transition state illustrated by frontier molecular orbital (FMO) analysis. The energetic barrier for the transition state is lowered by enhancing the favorability of this interaction in elevating the HOMO energy of the arene. The barriers for the reactions are lowered by ~1-2 kcal/mol using 4,5-dichlorophthaloyl peroxide. The chlorides decrease the SOMO energy by approximately 0.2 eV as indicated by FMO analysis. This decrease in energy results in an increasingly favorable HOMO-SOMO interaction in the transition state. Overall, this suggests that 4,5-dichlorophthaloyl peroxide could react with benzene, an arene previously inaccessible in our hydroxylation reaction using phthaloyl peroxide.

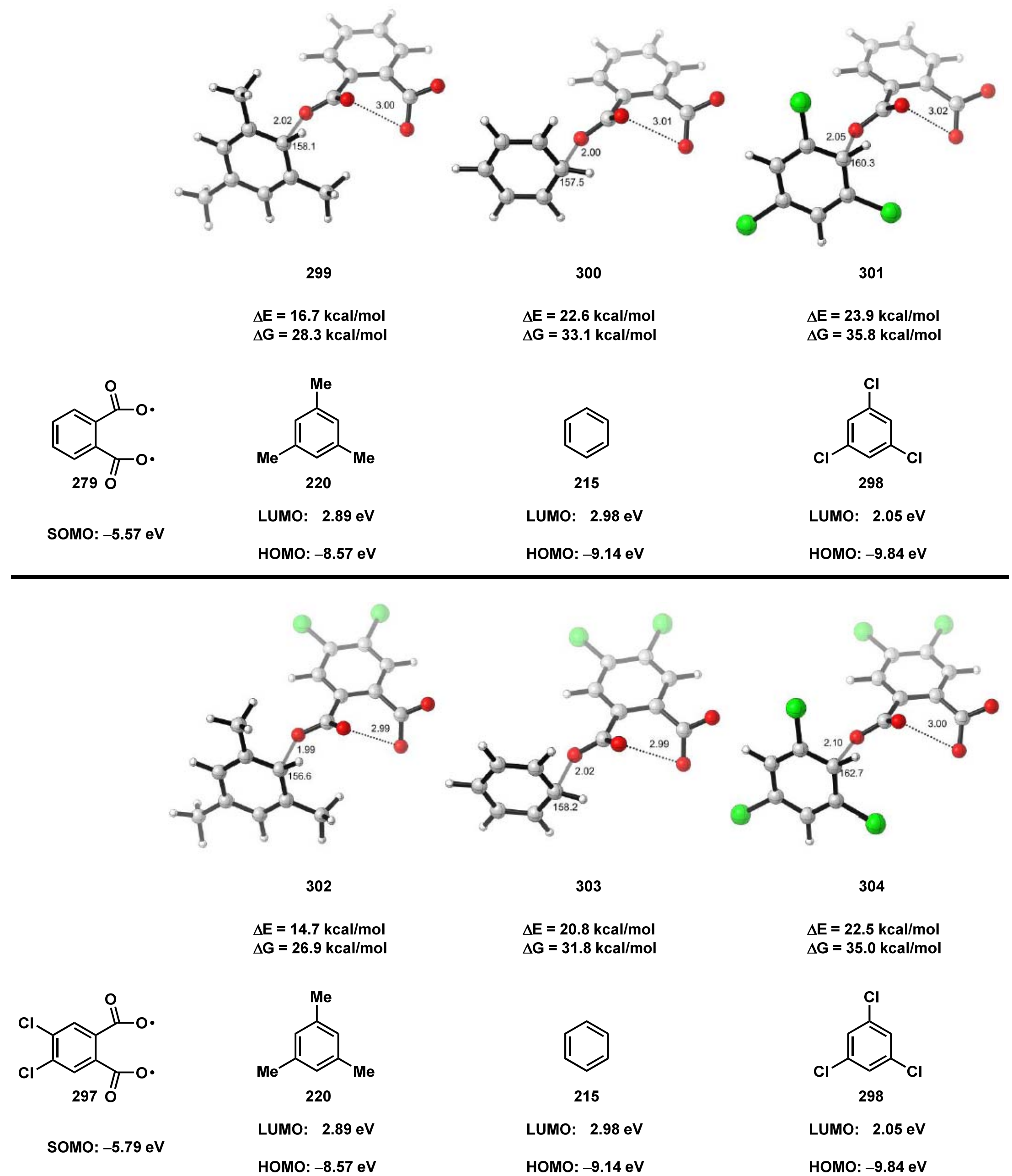


Figure 3.1. Arene reactivity difference between 4,5-dichloro- and phthaloyl peroxide via diradical addition.

Further computational investigation deciphered that 3,6-dichlorophthaloyl peroxide (**305**) would be a viable candidate for arene oxidation as well. Based on calculations conducted by Liang, the energetic barrier is only 16.7 kcal/mol for the oxidation of 1,3,5-trichlorobenzene using this reagent whereas the oxidation is 22.5 kcal/mol using 4,5-dichlorophthaloyl peroxide (Figure 3.2).

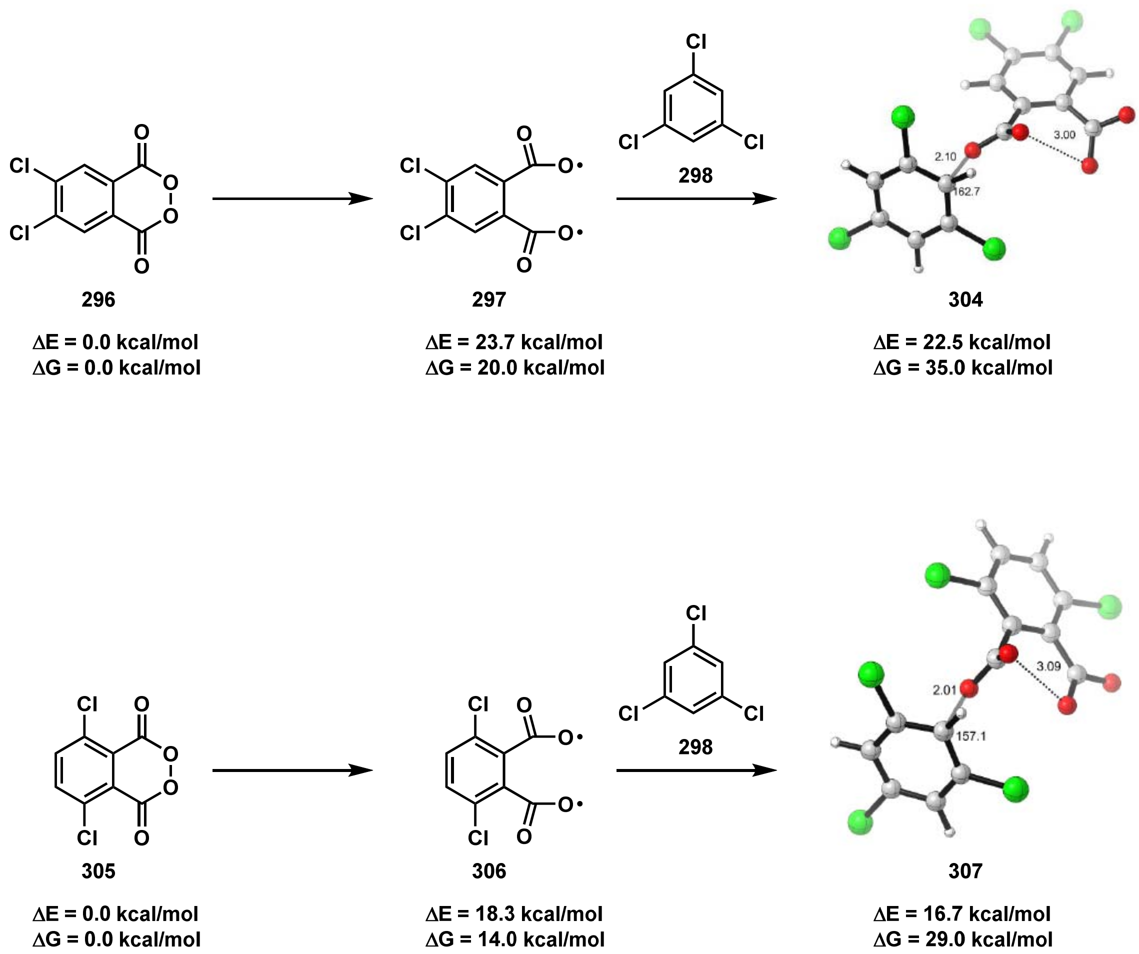


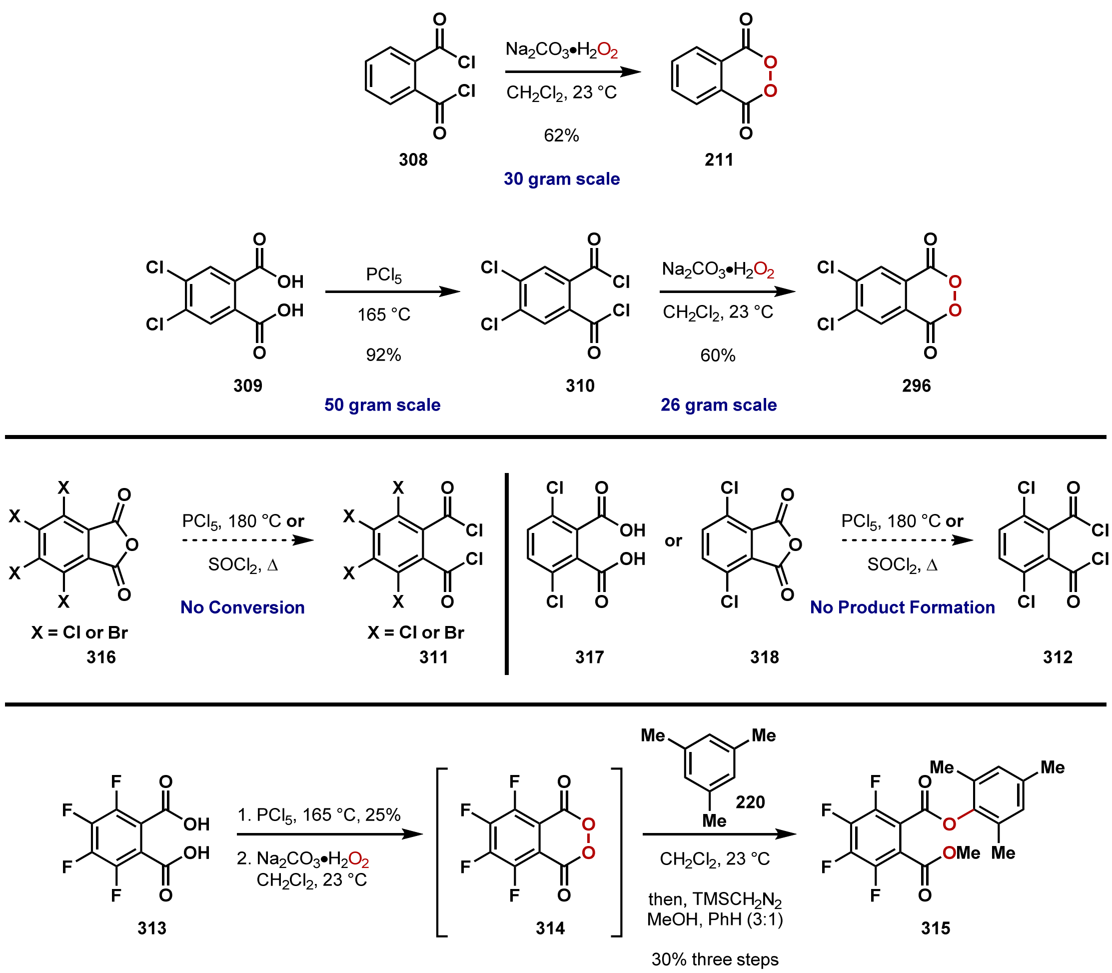
Figure 3.2. 4,5- and 3,6-dichlorophthaloyl peroxide oxidation of 1,3,5-trichlorobenzene.

The computational results combined with the previously observed reactivity mitigated by the dihydroxylation of alkenes provided plausibility for the synthesis of various halogenated peroxides. Phthaloyl peroxide is synthesized in one step from the cheap, commercially available phthaloyl chloride (**308**) using solid sodium percarbonate in wet methylene chloride (Scheme 3.6). This can be achieved on 30 gram scale to deliver the peroxide in 62% yield as a white, fluffy solid. This protocol has proven safe in repeatedly providing mass quantities of the peroxide without the occurrence of an explosion. 4,5-Dichlorophthaloyl peroxide was synthesized in a similar manner, but starting from the cheap, commercially available 4,5-dichlorophthalic acid (**309**). The diacid is first converted to the dichloride **310** by heating the solid acid to 165 °C in neat phosphorus pentachloride. After a three stage distillation the dichloride is afforded in 92% yield on 50 gram scale as a white, lacrimating solid. The dichloride was treated with solid sodium percarbonate in wet methylene chloride to afford the peroxide **296** in 60% yield as a white, flaky solid after recrsytallization from benzene and pentane. It is important to note that both peroxides (**211** and **296**) can be stored under nitrogen in a freezer cooled to −20 °C for prolonged periods of time (months up to one year) without degradation or loss of reactivity.

The tetrachloro-, tetrabromo-, and 3,6-dichlorophthaloyl chlorides (**311** and **312**) could not be synthesized due to instability of the diacyl chlorides.[175] Therefore, the corresponding peroxides could not be synthesized. However, the tetrafluorophthaloyl dichloride was afforded by heating the diacid **313** to 165 °C in neat phosphorus pentachloride. After distillation, the product was accessed in 25% yield. Due to instability and resultant decomposition, the reaction forming the peroxide needed to be closely monitored by ^{13}C-NMR. The tetrafluorophthaloyl peroxide (**314**) could not be purified or isolated due to degradation thereby the peroxide was treated *in situ* with mesitylene in methylene chloride at 23 °C. After five hours the solvent was removed and the resulting viscous orange oil was dissolved in a solution of benzene/methanol (3:1) and treated with excess trimethylsilyl diazomethane to afford the crude mixed phthaloyl ester **315**. The golden yellow oil was purified by silica gel chromatography to provide the mixed ester in 30% yield over the three steps. The low yield is attributed to the decomposition of the tetrafluorophthaloyl peroxide in the peroxide formation reaction.

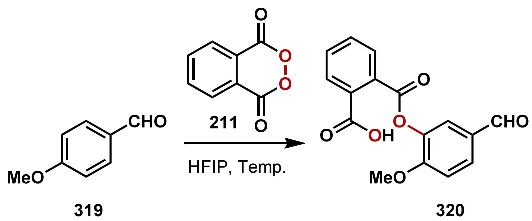
Despite the low yield, this was a good result because this type of reactivity was never observed using the parent phthaloyl peroxide or in non-fluorinated solvents. Fluorinated solvents such as HFIP and TFE at elevated temperatures are required when using phthaloyl peroxide to effect the arene hydroxylation in appreciable yields.

Scheme 3.6. Syntheses of different phthaloyl peroxides.

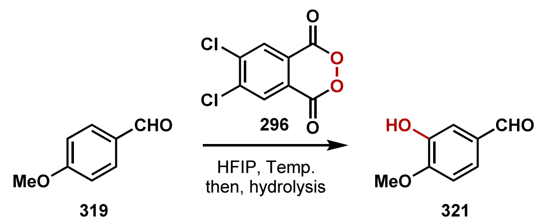


With multigram quantities of 4,5-dichlorophthaloyl peroxide available, its potential to hydroxylate arenes was initially examined using *p*-anisaldehyde (**319**). In comparison studies, the aldehyde was treated with four equivalents of phthaloyl peroxide in HFIP at 75 °C, however, this only promoted 6% conversion after 36 hours. Under identical conditions, but using the dichloroperoxide, *p*-anisaldehyde was oxidized with 80% conversion. After hydrolyzing the intermediate phthaloyl ester-acid, *iso*vanillin (**321**) was isolated in a 69% yield (Table 3.2).

Table 3.2. Reactivity comparison between peroxides **211** and **296** using *p*-anisaldehyde.



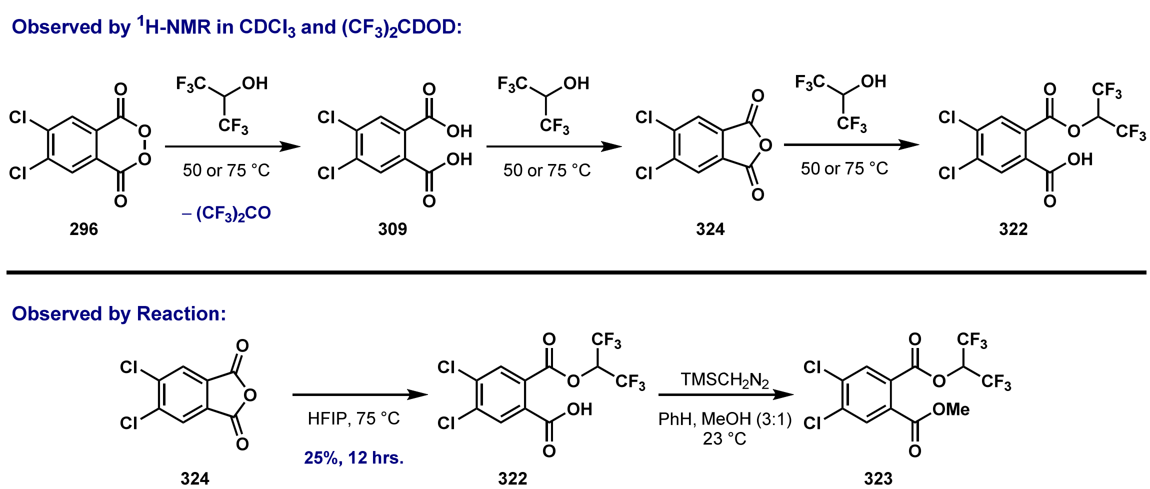
Temperature (°C)	Peroxide equiv.	Conversion (%)
50	1.3	0
50	2.5	0
75	2.5	2
75	4.0	6



Temperature (°C)	Peroxide equiv.	Conversion (%)
50	1.3	10
50	2.5	32
75	2.5	28
75	4.0	80 (69% yield)

The use of four equivalents of the peroxide was surprising, but necessary as using less equivalents resulted in lower conversion of the starting material. The high temperature proved necessary because the reaction was sluggish at temperatures below 75 °C, but this temperature also warranted the use of excess peroxide due to a higher degree of peroxide decomposition. ^{1}H-NMR experiments were then conducted to analyze the cause of decomposition and the rate at which it was occurring. First, the peroxide was heated in deuterated HFIP at 50 and 75 °C. This showed that 15-20% and 35-40% decomposition of the peroxide occurred in deuterated HFIP at 50 and 75 °C respectively over 48 hours. By conducting the same experiment in HFIP and then analyzing the crude reaction material by ^{1}H-NMR, it was found that the peroxide had converted to the mixed phthaloyl ester acid **322** (Scheme 3.7). In order to confirm this result, the crude acid was esterified using trimethylsilyl diazomethane to provide the diester **323** which was purified and then fully characterized (see Experimental Section). Also observed in both NMR experiments was the formation of 4,5-dichlorophthaloyl anhydride at the expense of the peroxide. The current hypothesis is that the peroxide oxidizes the solvent, leading to the diacid which is observed in both NMR experiments, and this material is then slowly converted to the anhydride (**324**) by the acidic reaction media. HFIP then reacts with the anhydride to form the ester **322**, and this was also confirmed by heating the anhydride in HFIP to 75 °C in a separate experiment. After 12 hours the solvent was removed and ^{1}H-NMR of the resultant crude yellow solid showed ~25% of the ester **322** and ~75% of the starting anhydride.

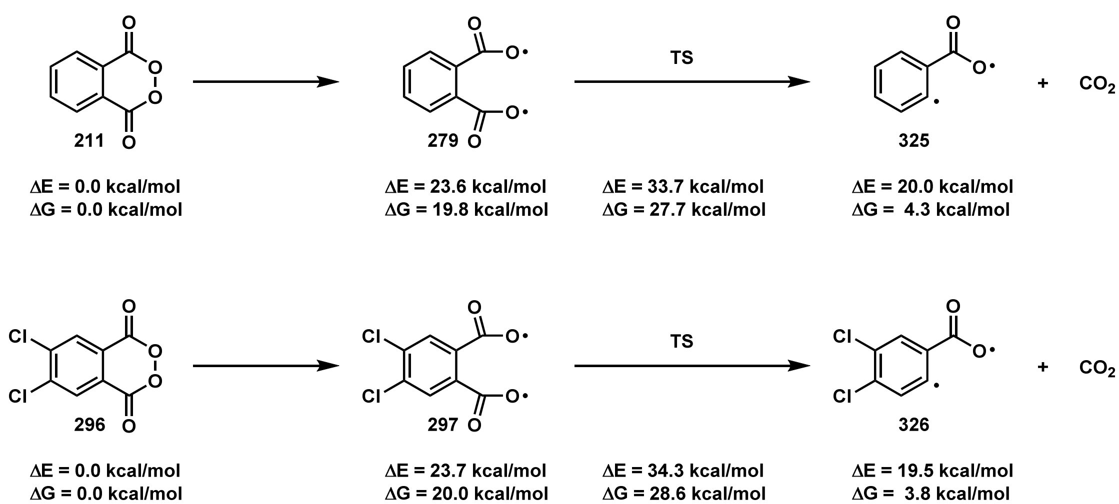
Scheme 3.7. Decomposition pathway of 4,5-dichlorophthaloyl peroxide in HFIP.



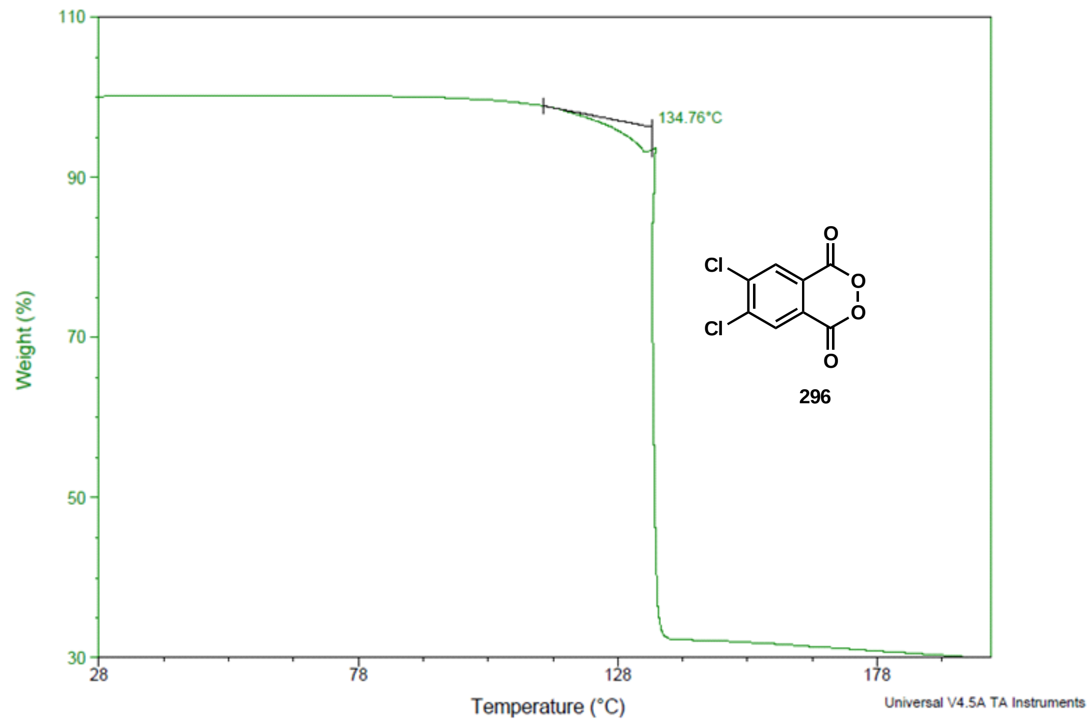
This decomposition was not observed in the original oxidation protocol developed by Changxia Yuan dictating that phthaloyl peroxide is more stable in fluorinated solvents. To understand the potential risks and dangers associated with using the new peroxide, DFT calculations were conducted to compare the thermal stabilities between the two oxidants (Scheme 3.8). Surprisingly, despite the enhanced reactivity, 4,5-

dichlorophthaloyl peroxide possesses slightly more thermal stability than phthaloyl peroxide, however, these computational experiments show another pathway for the peroxide decomposition. It is important to note that this type of decomposition was not observed in the original experiments examining the degradation, however, this internal decomposition has been observed during hydroxylation reactions on a small number of substrates using 4,5-dichlorophthaloyl peroxide.

Scheme 3.8. Thermal stability of 4,5-dichlorophthaloyl peroxide and phthaloyl peroxide.



The thermal stability of 4,5-dichlorophthaloyl peroxide was also investigated using thermogravimetric analysis (Figure 3.3). The TGA data indicates that the peroxide has a point of decomposition at 135 °C confirming that it is slightly more stable than phthaloyl peroxide which decomposes at 130 °C. These oxidants have remarkable thermal stability compared to benzoyl peroxide, which begins to gradually decompose at 105 °C. Unfortunately, both phthaloyl peroxides show a sharp decrease in mass at these respective temperatures indicating that when they are heated above these points a potential explosion could occur. In light of this, all experiments were conducted at or below 75 °C.



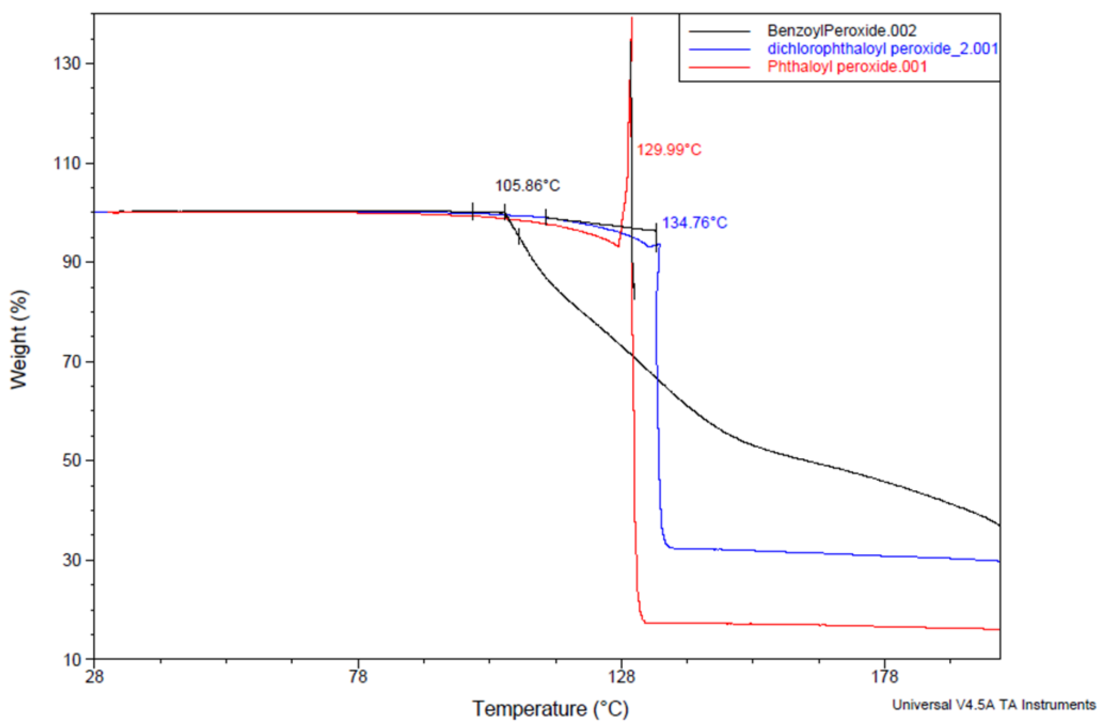


Figure 3.3. TGA data for 4,5-dichlorophthaloyl peroxide.

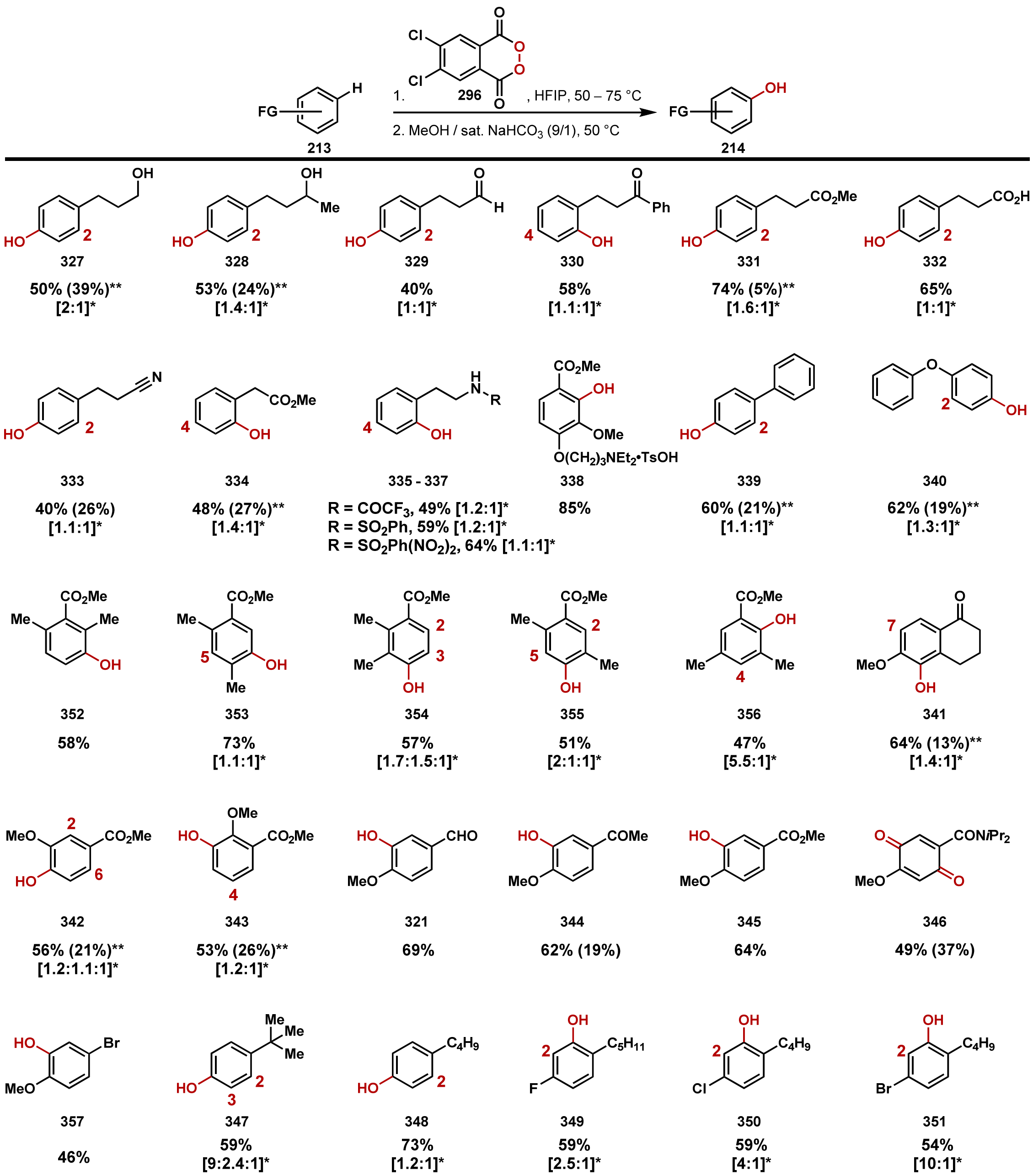
A full understanding of 4,5-dichlorophthaloyl peroxide's decomposition in HFIP, its thermal explosive potential, and the enhanced reactivity predicated on the oxidation of anisaldehyde, the hydroxylation reaction was next examined on previously inaccessible substrates. Two general sets of reaction conditions were developed. The oxidations were carried out using either 1.3 equivalents of 4,5-dichlorophthaloyl peroxide at 50 °C or 2.5 equivalents heated to 75 °C in HFIP. Operationally the reaction proceeds without the need for special exclusion of air or moisture and the use of commercial grade HFIP is sufficient. Karl Fisher titration on the HFIP routinely used in these reactions contained 924 ppm of water. Using purified HFIP rendered no difference in reactivity.

The products in Table 3.3 demonstrate the range of substituted arenes that can be successfully hydroxylated and the functional groups that are tolerated, adding to those already known.[171] Primary and secondary alcohols are tolerated providing phenols **327** and **328**. Substrates possessing tertiary alcohols can be hydroxylated, but the yields are low due to ionization of the alcohols in these arenes. A series of hydrocinnamyl derivatives with higher degrees of oxidation participated well in the reaction to afford the phenols of the aldehyde **329**, ketone **330**, ester **331**, acid **332**, and nitrile **333**. Removal of one methylene led to a diminished yield of 48% for the oxidation to generate the ester **334**.

After examining different nitrogen protecting groups, the trifluoroacetamide **335**, sulfonamide **336**, and dinitrosulfonamide **337** were all produced in moderate to good yield representing some of the first substrates containing nitrogens successfully hydroxylated under this manifold. After testing additives it was found that amines (in their ammonium form) are also tolerated. The addition of *p*-toluenesulfonic acid monohydrate (1.0 equivalent) prior to that of 4,5-dichlorophthaloyl peroxide leads to successful hydroxylation providing the aminophenol **338** in 85% yield. Hydroxylation of biphenyl (**339**), diphenyl ether (**340**), 6-methoxy tetralone (**341**) as well as methyl *m*-anisate (**342**) and methyl *o*-anisate (**343**) occurred in moderate to good yields, but provided mixtures of isomeric products. Single regioisomers were obtained in the hydroxylation of acetanisole (**344**), *p*-anisaldehyde (**319**), and methyl *p*-anisate (**345**) driven by synergistic regiochemical directing effects of the methyl ether and carbonyls. However, upon conducting the reaction using *p*-methoxy aryl amides, double hydroxylation of the arene occurred to afford the quinone **346**. Attempts to minimize this reaction to affect only mono-hydroxylation unfortunately were ineffective. Interchanging the methoxy group with a methyl or alkyl substituent rendered an unreactive arene and only returned the starting amide.

The oxidation of *tert*-butyl benzene delivered the *ortho*, *meta*, and *para* phenols **347** with the *para* isomer being the major product. This represented the first time a *meta* product was generated in the reaction and it potentially arose through rearrangement before aromatization to relieve steric strain of the *o*-phthalate intermediate. Butyl benzene (**348**) was converted in higher efficiency using 4,5-dichlorophthaloyl peroxide in 73% yield compared to 49% conversion using phthaloyl peroxide. A series of halogenated alkyl benzene derivatives (**349-351**) were oxidized to demonstrate the regioselectivities possible within these systems. As expected, the halogens were not as strong of a directing group as the alkyl substituents, and within these substrates fluorine is a stronger director than chlorine which in turn is more effective than bromine. Interestingly, the *ipso* products were formed in 2-5% yield replacing the halogen with a phenol.

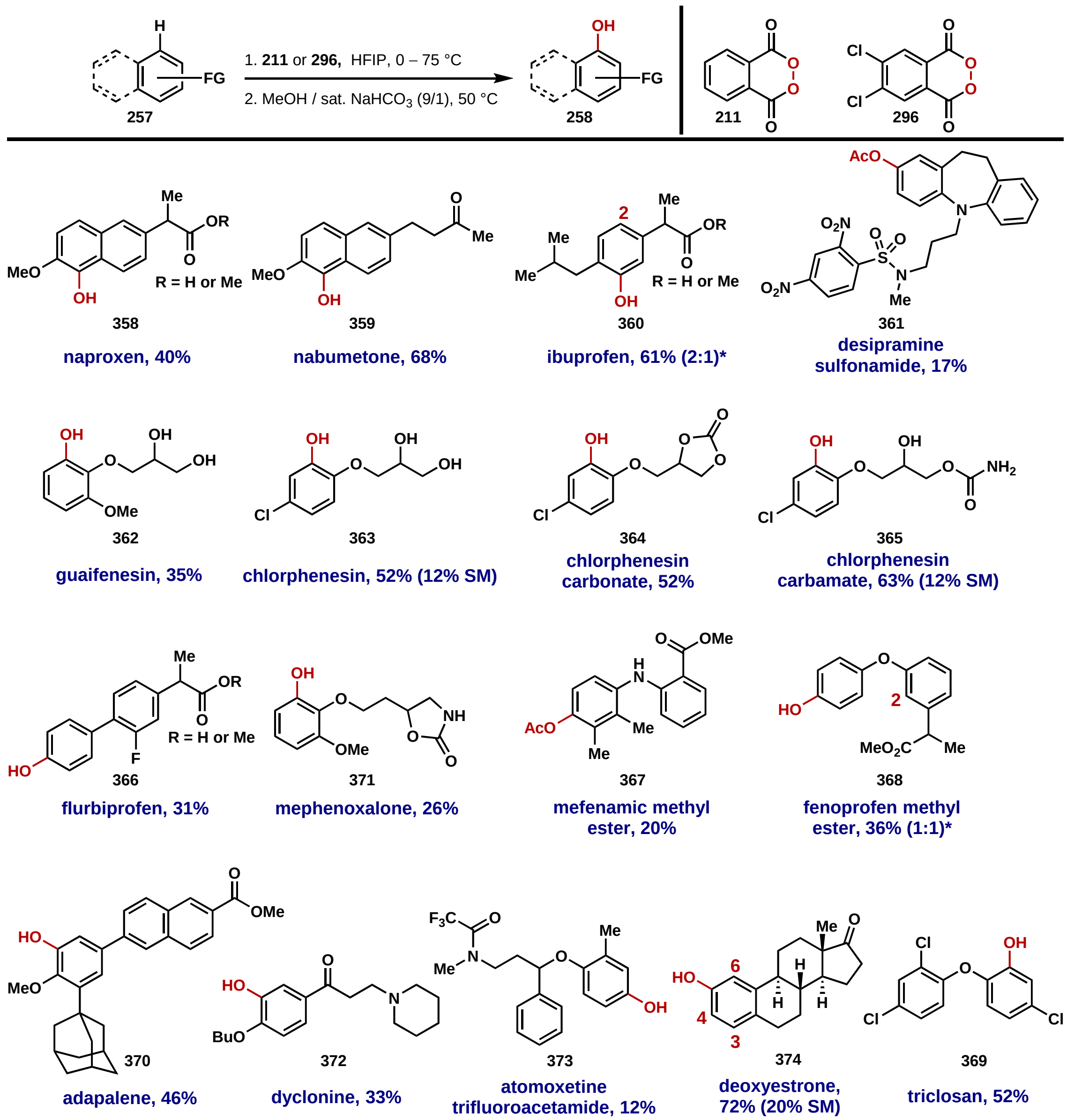
Table 3.3. Hydroxylation of arenes mediated by 4,5-dichlorophthaloyl peroxide.



The regioisomeric position is labeled with the respective carbon atom number
*The ratio of the isomer is in brackets
**The yield in parentheses refers to the starting material recovered

Since the oxidation proved highly tolerant to several functional groups, the protocol was applied to the syntheses of the phenolic derivatives of drugs as well as biocides in their native state (Table 3.4). Hydroxylation of the free acid as well as the esters of naproxen, nabumetone, and ibuprofen was achieved to generate the phenols **358,** **359,** and **360** in modest yield. Air oxidation of the electron rich naphthol led to the lower yields for the phenol **358**. Protection of the amine as the dinitrosulfonamide followed by oxidation provided the acetate derivative of desipramine (**361**) in 17% yield over three steps. The insipient phenol was protected as the acetate in order to separate the isomer from other minor isomers and to attain an accurate yield due to slight decomposition of the phenol during purification. Anilines do not participate well in the oxidation often leading to low selectivity as well as over-oxidized adducts and decomposition. As free alcohols were tolerated, guaifenesin and chlorphenesin glycol were hydroxylated to provide the phenols **362** and **363** in 35% and 52% yield respectively. The related carbonate and carbamate were similarly reacted to provide the corresponding phenols **364** and **365** in 52% and 63% yield. The NSAID flurbiprofen was also hydroxylated in 31% yield to provide the *para* phenol **366**. This phenol is a metabolite of flurbiprofen and has previously been synthesized through a Friedel-Crafts/Baeyer-Villiger sequence in an overall six steps and 20% yield, further substantiating the efficiency of our developed hydroxylation protocol.[176,177] Treating the ester of mefenamic acid with 2 equivalents of the peroxide delivered the *para* phenol which was immediately protected to afford the acetate **367** in 20% yield over the three steps. The phenol was protected as the acetate in order to attain an accurate yield which had been difficult due to decomposition of the phenol during purification. Minimal conversion of the starting material was observed if only one equivalent was used. The hydroxylation strategy also provided an alternative approach to access one of the metabolites of the NSAID fenoprofen **368** as well as the widely used household antibacterial and antifungal agent triclosan (**369**).[178,179] Hydroxylation of 2,4,4'-trichlorodiphenylether was achieved regioselectively to synthesize triclosan in 52% yield. Adapalene, an effective drug for treating acne, was hydroxylated to afford the phenolic derivative **370** in 46% yield without any observation of adamantyl hydrogen abstraction or decomposition.[180] The residual material consisted of phenolic isomers as well as those associated with *ipso* substitution, replacing the adamantyl substituent with a phenol.

Table 3.4. Hydroxylation of drugs to provide phenolic derivatives and metabolites using phthaloyl and 4,5-dichlorophthaloyl peroxide.

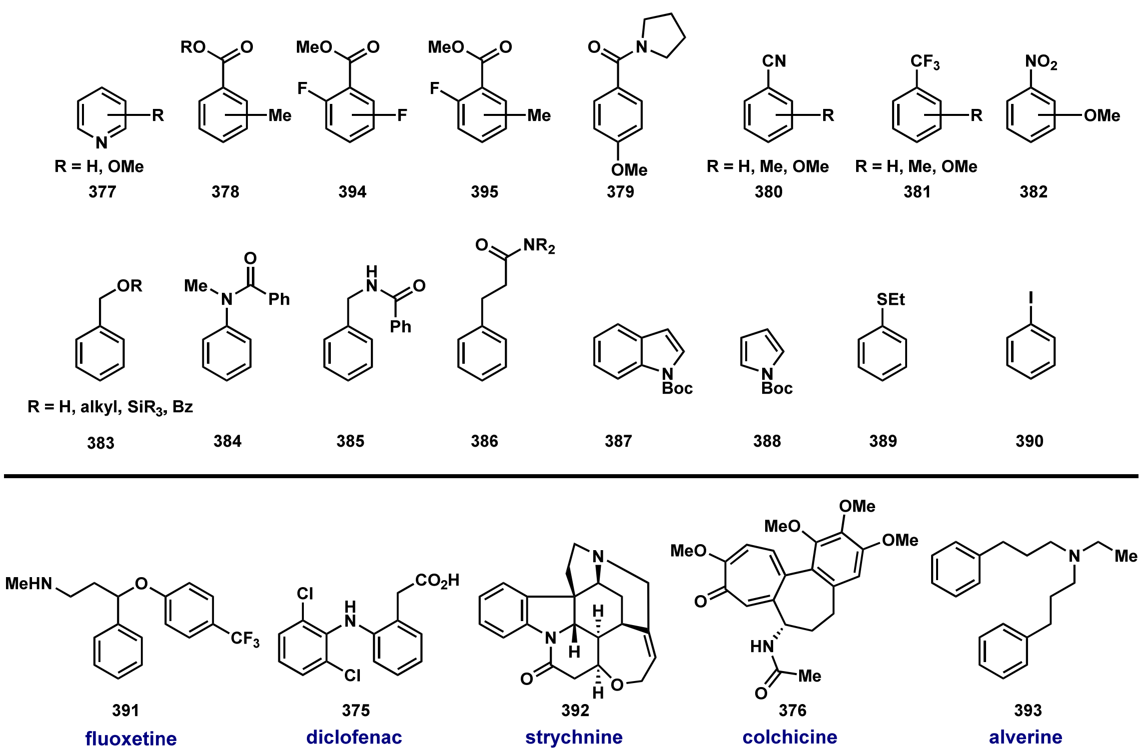


The regioisomeric position is labeled with the respective carbon atom number
*The ratio of the isomers are in parentheses

Although the hydroxylation proceeds well in a broadly functional group tolerant manner, incompatible functionality does exist (Table 3.5). Pyridines, thioethers, and aryl iodides are oxidized at the heteroatom. Pyridines are oxidized quantitatively to the N-oxides, which are in turn reluctant to react further with the peroxides. Aryl thioethers are selectively oxidized to the sulfoxide using 1 equivalent of the peroxide, whereas 2 equivalents provide the sulfone quantitatively. Unfortunately, arenes containing aryl, benzyl, or alkyl amides do not react with the peroxide in a productive manner; only unreacted starting material is returned. The peroxide is fully consumed throughout the course of the reaction, but as to why no product is attained remains an unsolved problem. NMR experiments conducted in deuterated HFIP provided no evidence as to what was occurring or how the peroxide was decomposing. The use of different additives, either Brønsted or Lewis acids, did not aid this process.

Aryl nitriles, benzyl ethers, and arenes containing trifluoromethyl or nitro groups are extremely sluggish in the reaction. Alternatively, pyrroles and indoles react violently with the peroxide to afford no desirable product, only black tar. Lastly, extremely electron rich arenes such as diclofenac (**375**) and colchicine (**376**) were destroyed beyond structural assignment under the reaction conditions.

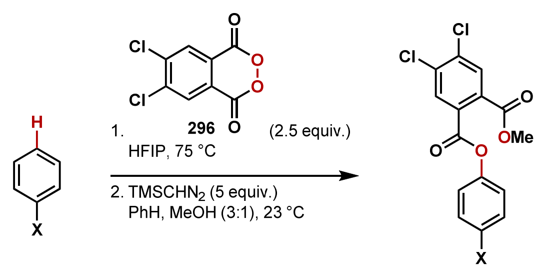
Table 3.5. Incompatible functional groups and arenes that are not oxidized using 4,5-dichlorophthaloyl peroxide.



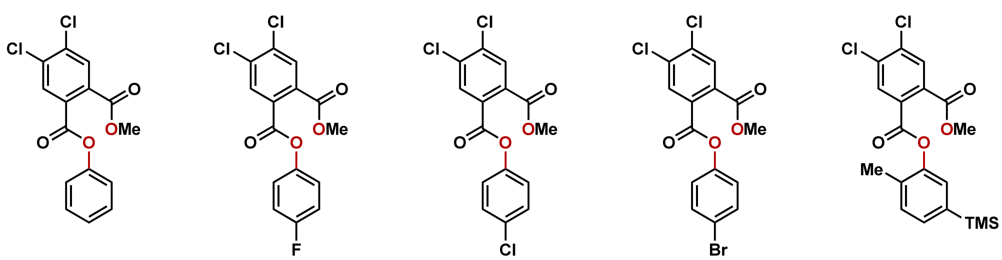
The majority of previous arene oxidation procedures have focused on the hydroxylation of simple aromatics such as benzene, which is typically used as solvent and substrate. To showcase the unique reactivity of 4,5-dichlorophthaloyl peroxide, benzene, fluorobenzene, chlorobenzene, and bromobenzene were reacted with 2.5 equivalents of the peroxide in HFIP at 75 °C. *p*-Trimethylsilyl toluene was also reacted with the peroxide, but TFE was used instead because HFIP promoted desilylation (Table 3.6). As the phenolic products were volatile, the intermediate mixed phthaloyl ester-acids were esterified using trimethylsilyl diazomethane to generate the mixed phthalate esters **396** – **400**. After purifying these adducts via silica gel chromatography, they were then fully characterized. While the yields were modest, the reactivity of 4,5-

dichlorophthaloyl peroxide with these less reactive arenes is noteworthy as secondary oxidation of the products was not found to be competitive. Also, *p*-trimethylsilyl toluene was oxidized to afford the ester **400** as the major product. The minor product was the adduct containing the phthalate ester *ortho* to the silyl group which was isolated in 12% yield. The residual material is unreacted starting silane. No *ipso* substitution product was observed, which is interesting as aryl silanes tend to react through an EAS pathway with electrophiles to provide products of *ipso* substitution.[181]

Table 3.6. Oxidation of halobenzenes and *p*-trimethylsilyl toluene using 4,5-dichlorophthaloyl peroxide.



401 402

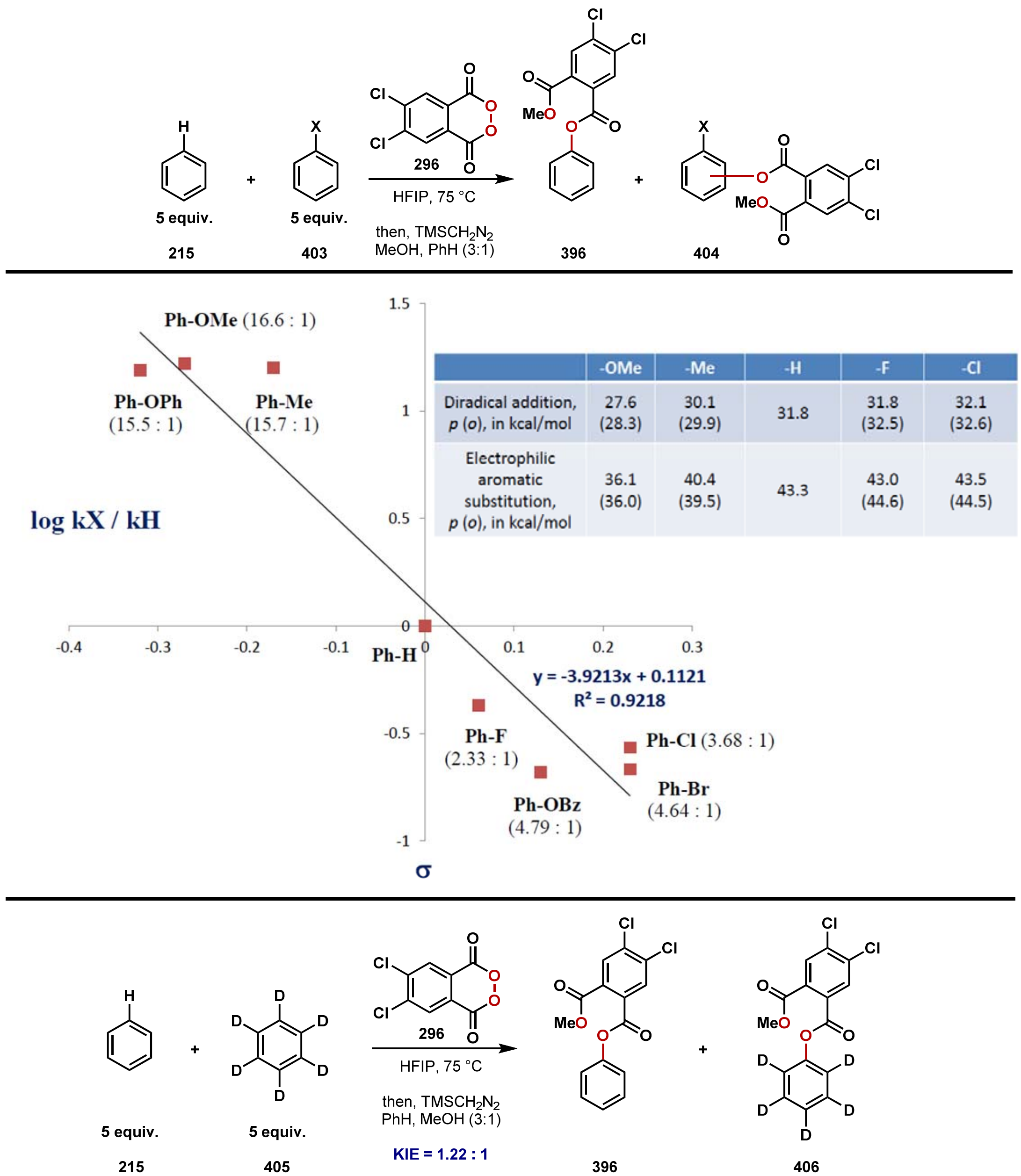


396	397	398	399	400
36%	**45%**	**33%**	**13%**	**36%** (using TFE)

Early computational analysis indicated that the phthaloyl peroxide mediated arene oxidation proceeded through a diradical reverse-rebound reaction pathway.[171] The 4,5-dichlorophthaloyl peroxide oxidation was initially hypothesized to proceed through an ionic or EAS pathway. However, the reactions producing the phenols of the dimethyl-methylbenzoates **354**-**356** (Table 3.3) and the phthalate ester of trimethylsilyl toluene contradict this theory. In light of these results and to fully elucidate the mechanism of this unique reaction, linear free energy relationships were examined to probe the transition state. Using the observed reactivity of benzene and the halobenzenes **397**-**399**, these relationships were assessed by reacting 5 equivalents of the corresponding arene and 5 equivalents of benzene with 1 equivalent of 4,5-dichlorophthaloyl peroxide in HFIP at 75 °C for 36 hours. The reaction mixture was then concentrated, re-dissolved in a mixture of benzene/methanol (3:1), and esterified using an excess of trimethylsilyl diazomethane. After concentration, the ratios of the crude phthalate esters were determined using ^{1}H-NMR. These experiments were conducted in duplicate to insure accuracy.

Examination of the reaction using the linear free energy relationships with σ vs. σ^{+} values established a linear trend with a low negative *rho* value (−3.92), corresponding best using σ values which supports a single electron process (Figure 3.4). This is in juxtaposition to EAS which best fits to σ^{+} values with large observed *rho* values (e.g. bromination, *rho* = −13).[182]

DFT and *ab initio* calculations on the barriers for diradical addition and electrophilic aromatic substitution show a similar reactivity trend to that depicted in the Hammett plot. The calculations show that the EAS pathway is sensitive for electron-rich arenes. The activation free energy difference is approximately 7 kcal/mol for the reactions using anisole and benzene, whereas the activation energy difference is only about 4 kcal/mol for the diradical addition. This further substantiates that the slope obtained from the Hammett plot is closer to that for the diradical addition. Further analysis of the transition state using kinetic isotope experiments (KIE) delineated that rearomatization via hydrogen abstraction is not the rate determining step extrapolated by the low KIE of 1.22.

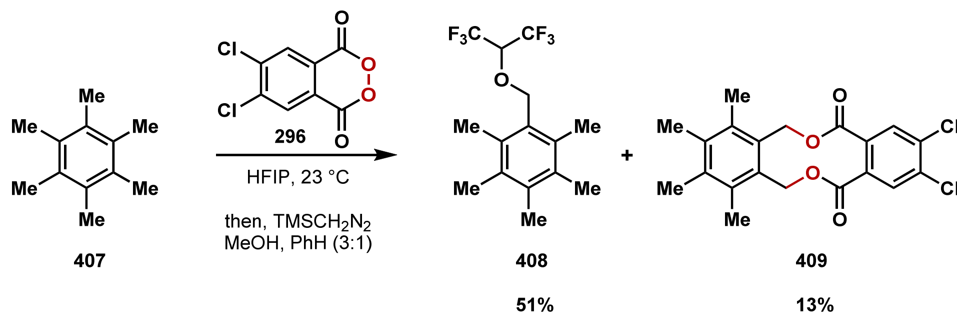


	-OMe	-Me	-H	-F	-Cl
Diradical addition, *p* (*o*), in kcal/mol	27.6 (28.3)	30.1 (29.9)	31.8	31.8 (32.5)	32.1 (32.6)
Electrophilic aromatic substitution, *p* (*o*), in kcal/mol	36.1 (36.0)	40.4 (39.5)	43.3	43.0 (44.6)	43.5 (44.5)

Figure 3.4. Linear free energy σ plot for the 4,5-dichlorophthaloyl peroxide mediated arene oxidation, computational analysis for the EAS and diradical addition pathways and KIE experiments depicting the major mechanistic pathway.

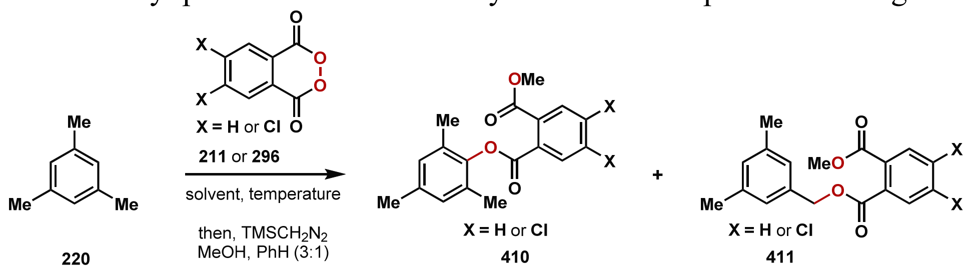
Hexamethylbenzene (**407**) was treated with 4,5-dichlorophthaloyl peroxide in HFIP at 23 °C to further indicate a diradical mechanism (Scheme 3.9). After concentration, the crude solid mixture was dissolved in a solution of benzene/methanol and esterified using trimethylsilyl diazomethane. The mixture was purified chromatographically to afford the ether **408** and the dibenzylester **409** which were then fully characterized. No products of *ipso* substitution or arene oxidation were observed.

Scheme 3.9. Reaction between hexamethylbenzene and 4,5-dichlorophthaloyl peroxide.



A surplus of evidence supports the major mechanistic pathway is the reverse-rebound diradical addition. To further confirm the presence of radicals, a series of benzylic oxidation experiments were conducted using mesitylene and both peroxides in different solvents at different temperatures. The hydroxylation reaction works optimally in the fluorinated solvents HFIP and TFE as the highest degree of oxidation is observed when using HFIP. These polar solvents can stabilize ionic intermediates and therefore can promote ionic reaction pathways. However, the experiments used to probe the transition state depict that the major reaction pathway is not ionic, but it is through a diradical addition process. HFIP and TFE can also stabilize radical intermediates through hydrogen bonding effects which cause a remarkable increase in their persistence.[183,184] This stabilization effect could in turn enhance the reaction's selectivity for arene oxidation over benzylic oxidation, whereas other solvents would not provide this stabilization (Schemes 3.4 and 3.5 depict the energetic barriers to effect these transformations). The hypothesis for these experiments is that if non-fluorinated solvents are used then significant amounts of benzylic oxidation should be observed compared to the use of HFIP and TFE. The use of non-protic halogenated solvents could potentially switch the mechanism to an ionic pathway, but if this were to occur then minimal benzylic oxidation should be observed, if any. This hypothesis proved to be correct as depicted in Table 3.7. When an excess of mesitylene was reacted with either peroxide in fluorinated or non-fluorinated solvents at different temperatures, a range of ratios for aryl versus benzylic oxidation was obtained. These ratios were assessed by ^{1}H-NMR analysis of the crude mixture and then confirmed by isolating the pure mixed phthalate esters after esterification. In HFIP at 23, 50 or 65 °C, this ratio was 99:1. The use of DCE at 65 °C promoted greater benzylic oxidation as observed by the ratio of 9:1. Using either cylcohexane or CCl_4 promoted more benzylic oxidation. Lastly, switching the solvent to benzene or conducting the reaction in neat mesitylene also increased the amount of benzylic oxidation.

Table 3.7. Phthaloyl peroxide mediated benzylic oxidation experiments using mesitylene.

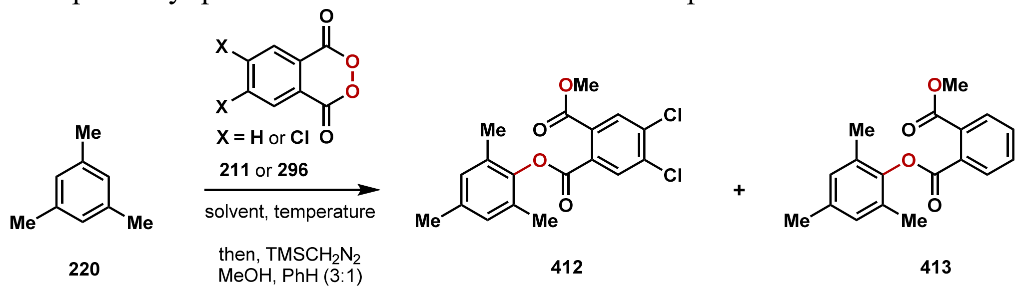


Peroxide	Solvent	Temperature	Ratio (410:411)	Isolated Yield
PPO (211)	HFIP	23 °C	>99:1	----------
PPO (211)	HFIP	50 °C	99:1	1.0% (411)
PPO (211)	HFIP	65 °C	99:1	1.3% (411)
DCPP (296)	HFIP	23 °C	>99:1	----------
DCPP (296)	HFIP	50 °C	99:1	1.0% (411)
PPO (211)	**$(CF_3)_2CH_3COH$**	**65 °C**	**19:1**	**4.2% (411)**
DCPP (296)	**$(CF_3)_2CH_3COH$**	**65 °C**	**49:1**	**1.5% (411)**
PPO (211)	TFE	23 °C	>99:1	----------
DCPP (296)	TFE	23 °C	>99:1	----------
DCPP (296)	DCE	65 °C	9:1	85%
DCPP (296)	PhH	65 °C	2.5:1	72%
PPO (211)	**PhH**	**65 °C**	**1.9:1**	**66%**
DCPP (296)	cyclohexane	65 °C	2.3:1	----------
DCPP (296)	CCl_4	65 °C	2:1	----------
PPO (211)	**Neat**	**50 °C**	**3:1**	**99%**
DCPP (296)	Neat	23 °C	2.8:1	93%
DCPP (296)	**Neat**	**50 °C**	**2.6:1**	**83%**

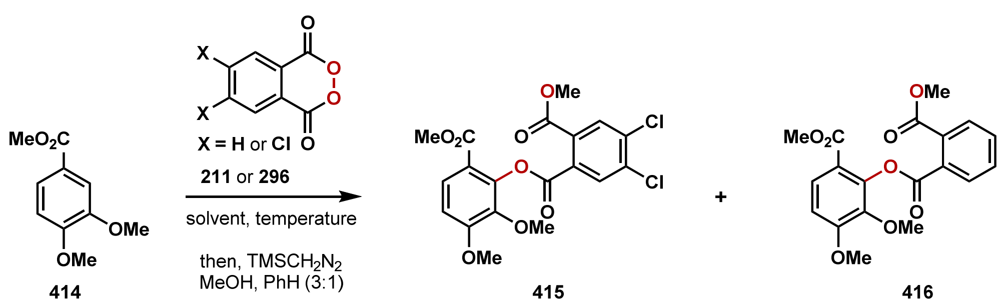
If the major reaction pathway was ionic then 4,5-dichlorophthaloyl peroxide should react much faster than phthaloyl peroxide, precluding the latter's reaction with a substrate especially in an ionizing solvent such as HFIP or TFE. However, this does not occur when a competition reaction is conducted using both peroxides (Table 3.8). Mesitylene was treated with 1 equivalent of phthaloyl peroxide and 1 equivalent of 4,5-dichlorophthaloyl peroxide in the same reaction vessel in different solvents at 23 or 65

°C. After concentration and esterification, the ratios of the phthalate adducts were determined by ^{1}H-NMR of the crude reaction mixture. As the solvent was changed from DCE to benzene, cyclohexane, and CCl_4 the ratio of phthalate adducts diminished drastically from 99:1 to 2:1. Also, when the reaction was conducted in HFIP or TFE at 23 °C the ratios were only 4.1:1 and 3.5:1 respectively. The experiments were also conducted using dimethoxy methylvanillate (**414**) at 23 and 65 °C as well. The same trend is observed thereby providing further evidence that the predominant pathway for the arene hydroxylation reaction using either peroxide is a diradical reverse-rebound addition. This does not exclude the possibility of an ionic mechanism, but this pathway is minor if it does occur.

Table 3.8. Competition experiments using mesitylene and dimethoxy methylvanillate comparing the rates of reactivity between 4,5-dichlorophthaloyl peroxide and phthaloyl peroxide in different solvents and temperatures.



Peroxide	Solvent	Temperature	Ratio (412:413)	Isolated Yield
PPO and DCPP	HFIP	23 °C	4.1:1	----------
PPO and DCPP	TFE	23 °C	3.5:1	----------
PPO and DCPP	DCE	65 °C	>99:1	85%
PPO and DCPP	PhH	65 °C	4.8:1	----------
PPO and DCPP	**cyclohexane**	**65 °C**	**2:1**	**----------**
PPO and DCPP	**CCl_4**	**65 °C**	**2:1**	**----------**



Peroxide	Solvent	Temperature	Ratio (415:416)	Isolated Yield
PPO and DCPP	HFIP	23 °C	23.5:1	----------
PPO and DCPP	TFE	23 °C	4.3:1	----------
PPO and DCPP	DCE	23 °C	4.2:1 **(20 mg Scale)**	----------
PPO and DCPP	DCE	23 °C	4.5:1 **(50 mg Scale)**	----------
PPO and DCPP	DCE	65 °C	8.9:1	----------
PPO and DCPP	PhH	23 °C	2.9:1	----------
PPO and DCPP	**cyclohexane**	**23 °C**	**1:1**	**----------**
PPO and DCPP	CCl_4	23 °C	3.7:1	----------

Conclusion

A new protocol utilizing 4,5-dichlorophthaloyl peroxide has been developed to provide a novel, selective, and reliable strategy that oxidizes arenes to phenols. With enhanced reactivity relative to the parent phthaloyl peroxide, this reagent can hydroxylate a wide range of substrates. In addition, a variety of functional groups including alcohols, diols, amines, nitriles, carbamates, esters, aldehydes, ketones, and carboxylic acids are compatible, consistent with the hydroxylation reaction having broad applicability in synthesis. This enhanced protocol is amenable for rapidly accessing various phenolic derivatives of drugs constituting that the strategy efficiently generates oxygenated analogs and metabolites.

Computational analysis conducted by Houk and Liang depicted that the major reaction pathway is a diradical reverse-rebound addition. Experiments probing the transition state were conducted using linear free energy relationships. The resultant Hammett plot supported the diradical addition mechanism as the major pathway as predicted by DFT and *ab initio* calculations. This was further corroborated using a series of benzylic oxidation and competition experiments that provided substantial evidence of the diradical intermediate. These mechanistic insights provide valuable information regarding a novel protocol that achieves selective C-H functionalization thereby creating a platform for the discovery of new chemical transformations using diradicals.

Experimental Section

Arene Hydroxylation Mediated by 4,5-Dichlorophthaloyl Peroxide

Table of Contents

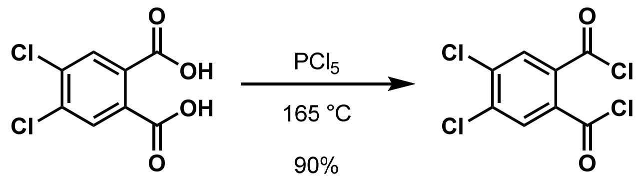
1. Safety Information

All peroxides can be dangerous when not handled correctly. The following procedures should be carried out by knowledgeable laboratory practitioners of organic synthesis. While we have not had a reaction using 4,5-dichlorophthaloyl peroxide detonate it is recommended that all reactions should be conducted with appropriate shielding as a precaution. Thermogravimetric analysis (TGA) data showed that 4,5-dichlorophthaloyl peroxide is stable below 115 ºC, however, there is a rapid loss in mass at ~135 °C indicating a potential exothermic decomposition. Earlier work with 4,5-dichlorophthaloyl peroxide also describes the stability and proper handling of this compound.[1]

2. General

Commercial reagents were purchased at the highest purity available and used without further purification. Trimethylsilyl diazomethane ($TMSCHN_2$) was purchased from Sigma-Aldrich as a 2.0 M solution in Et_2O. Reactions with 4,5-dichlorophthaloyl peroxide were performed without exclusion of air, other reactions were conducted under an atmosphere of N_2 unless otherwise indicated. Solvents (CH_2Cl_2 and Et_2O) were purified using a Pure-Solv MD-5 Solvent Purification System (Innovative Technology). 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) and 2,2,2-trifluoroethanol (TFE) were purchased from Oakwood Products and used without purification. Deoxygenated solvents were deoxygenated by sparging with nitrogen for at least 1 hour while stirring vigorously at a rate of 1000 rpm unless otherwise noted. HFIP, TFE, and methanol were removed by evaporation by positive flow of nitrogen. Other organic solutions were concentrated by evaporation using Buchi or Heidolph rotary evaporators. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial glass-coated silica gel plates (silica gel 60, F254, EMD chemical). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or exposure to iodine powder, an acidic solution of ceric ammonium molybdate, or a basic solution of potassium permanganate followed by heating on a hot plate. The chromatographic purification of products was achieved using silica gel chromatography with positive N_2 pressure as described by Still.[2] Infrared spectral data were recorded on a Nicolet 380 FTIR using neat thin film technique. High-resolution mass spectral data (HRMS) were obtained on a Karatos MS9 and reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+Na]^+$, $[M+H]^+$, $[M+2H]^{2+}$, [M], or $[M-H]^-$. Nuclear magnetic resonance spectral data (^1H NMR and ^{13}C NMR) were recorded with a Varian Gemini (400 MHz, ^1H at 400 MHz, ^{13}C at 100 MHz, 500 MHz, ^1H at 500 MHz, ^{13}C at 125 MHz, or 600 MHz, ^1H at 600 MHz, ^{13}C at 150 MHz). For $CDCl_3$, C_6D_6, CD_3OD, and C_3D_6O solutions, chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvent; $CHCl_3$ δ 7.26 ppm, $CDCl_3$ δ 77.00 ppm, C_6D_5H δ 7.15 ppm, C_6D_6 δ 128.00 ppm, CD_2HOH δ 4.85 ppm, CD_3OD δ 47.60 ppm, C_3D_5HO δ 2.05 ppm, and C_3D_6O δ 29.00 ppm. Coupling constants are reported in Hertz (Hz). Data for ^{1}H-NMR spectral data are reported as follows: chemical shift (ppm, referenced to protium); bs = broad singlet, s = singlet, br d = broad doublet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, m = multiplet, integration, and coupling constant (Hz). Melting points were measured on a MEL-TEMP device with calibration using Benzoic Acid (M.P. = 122 °C) as the standard. Thermogravimetric analysis (TGA) was obtained from a TGA Q500 V20.13 analyzer.

3. Experimental Procedure for 4,5-dichlorophthaloyl peroxide



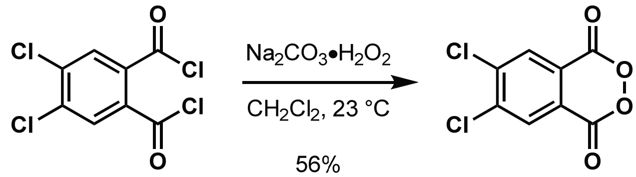
309 310

Solid 4,5-dichlorophthalic acid (**309**) (50.0 g, 213 mmol, 1.00 eq.) and solid phosphorus pentachloride (89.0 g, 427 mmol, 2.00 eq.) were added to a reaction vessel equipped under a continuous flow of nitrogen equipped with a reflux condenser and an outport leading to a saturated aqueous mixture of $NaHCO_3$. The solid mixture was placed in an oil bath heated to 180 °C and stirred vigorously (600 rpm). **Caution: HCl Gas Evolution.** After 12 hrs the reaction vessel was removed from the oil bath, cooled to 23 °C, equipped with a fractional distillation apparatus and the dark grey-black liquid was purified by fractional distillation *in vacuo* to afford the dichloride **310** (55.1 g, 192 mmol, 90%, b.p. = 155 – 160 °C at 0.1 mmHg) as a clear colorless oil which solidified upon cooling to 23 °C. The spectral data and physical properties match that for 4,5-dichlorophthaloyl chloride.[3]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 2H)

M.P. = 34 °C

B.P. = 155 – 160 °C (0.1 mmHg).



310 **296**

A mixture of solid 4,5-dichlorophthaloyl chloride **310** (25.5 g, 94 mmol, 1.00 eq.) and sodium percarbonate (16.2 g, 103 mmol, 1.10 eq.) were diluted with unpurified CH_2Cl_2 (469 mL). The white heterogeneous mixture was placed under an atmosphere of N_2 and stirred vigorously (1000 rpm). After 24 hrs the mixture was filtered over a pad of celite and carefully concentrated by rotary evaporation (water bath set to 23 °C) to afford a pale yellow solid. The solid was dissolved in benzene (110 mL) and then pentane (220 mL) was slowly added to the stirring solution inducing a slow precipitation of a white solid. The mixture was placed in an ice water bath cooled to 0 °C for 1 hr and filtered cold to afford the peroxide **296** as a white flakey solid (9.3 g, 40 mmol, 43%, 86% pure with 14% 4,5-dichlorophthaloyl anhydride). A second precipitation of the filtrate solution after concentration provided the peroxide **296** (2.7 g, 12 mmol, 13%, 86% pure with 14% 4,5-dichlorophthaloyl anhydride). Concentration of the filtrate solution after the second crop provided the starting 4,5-dichlorophthaloyl dichloride (5.7 g, 21 mmol, 22%). The spectral data data of **296** matches that for 4,5-dichlorophthaloyl peroxide.[4]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 142.4, 131.8, 122.6

IR (neat film, cm^{-1}) 1748, 906 cm^{-1}

4. Experimental Procedures

General Procedure A:

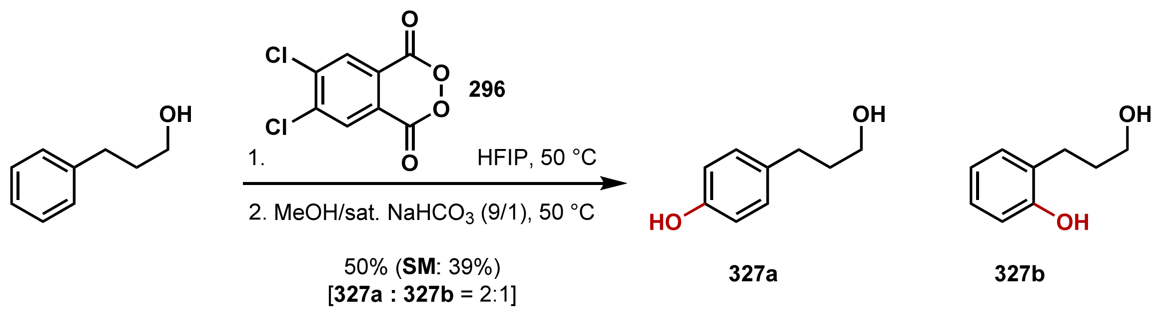
To a flame-dried borosilicate flask equipped with a magnetic stir bar was added the corresponding arene as a solid or neat followed by the syringe addition of HFIP to provide a clear homogeneous solution with a substrate concentration of 0.1 M. In some cases, when noted, $CHCl_3$ was added to aid homogeneity. Solid 4,5-dichlorophthaloyl peroxide **296** was then added in one portion unless otherwise noted. After stirring at a rate of 500 rpm at 23 °C for 1 minute to provide full dissolution of the peroxide, the reaction vessel was capped with a polyethylene stopper, clamped, placed in an oil bath heated to 50 °C, and stirred at a rate of 500 rpm. After 24 or 48 hrs the reaction was removed from the oil bath and allowed to cool to 23 °C, the stopper was removed carefully, and the HFIP was evaporated by a continous flow of N_2 to reveal a yellow, orange, or deep red solid mixture. The crude solid mixture was then placed under an atmosphere of N_2, and a deoxygenated mixture of MeOH and saturated aqueous $NaHCO_3$ (9:1) was added by syringe under N_2 to provide an overall reaction concentration of 0.1 M. The heterogeneous mixture was placed in an oil bath heated to 50 °C and stirred at a rate of 500 rpm. After 1 hr the methanol was removed by a continuous flow of N_2, and to the mixture was added Et_2O or EtOAc (10 mL) and an aqueous phosphate buffer (10 mL, 0.2 M, pH = 7). The mixture was vigorously stirred (800 rpm) at 23 °C for 2 minutes to provide a biphasic solution which was poured into a separatory funnel and partitioned. The organic layer was washed with an aqueous phosphate buffer (4 x 30 mL, 0.2 M, pH = 7) or with the combination of an aqueous saturated mixture of $NaHCO_3$ and brine (3 x 30 mL, 1:1). The residual organics were extracted from the aqueous layer with Et_2O (3 x 25 mL) or EtOAc (3 x 25 mL), dried over solid Na_2SO_4, decanted, and concentrated carefully (**NOTE**: Some of phenolic products are volatile). The crude material was then purified by silica gel chromatography using the noted solvent mixture to afford the phenolic products.

General Procedure B:

To a flame-dried borosilicate flask equipped with a magnetic stir bar was added the corresponding arene as a solid or neat followed by the syringe addition of HFIP to provide a clear homogeneous solution with a substrate concentration of 0.1 M. In some cases, when noted, $CHCl_3$ was added to aid homogeneity. Solid 4,5-dichlorophthaloyl peroxide **296** was then added in one portion. After stirring at a rate of 500 rpm at 23 °C for 1 minute to provide full dissolution of the peroxide, the reaction vessel was capped with a polyethylene stopper, clamped, placed in an oil bath heated to 75 °C, and stirred at a rate of 500 rpm. After 36 or 48 hours the reaction was removed from the oil bath and allowed to cool to 23 °C, the stopper was removed carefully, and the HFIP was evaporated by a continous flow of N_2 to reveal a yellow, orange, or deep red solid mixture. The crude solid mixture was then placed under an atmosphere of N_2, and a deoxygenated mixture of MeOH and saturated aqueous $NaHCO_3$ (9:1) was added by syringe under N_2 to provide an overall reaction concentration of 0.1 M. The heterogeneous mixture was then placed in an oil bath heated to 50 °C and stirred at a rate of 500 rpm. After 1 hr the methanol was removed by a continuous flow of N_2, and the mixture was diluted with Et_2O or EtOAc (10 mL) and an aqueous phosphate buffer (10 mL, 0.2 M, pH = 7). The mixture was vigorously stirred (800 rpm) at 23 °C for 2 minutes to provide a biphasic solution which was poured into a separatory funnel and partitioned. The organic layer was washed with an aqueous phosphate buffer (4 x 30 mL, 0.2 M, pH = 7) or with the combination of an aqueous saturated mixture of $NaHCO_3$ and brine (3 x 30 mL, 1:1). The residual organics were extracted from the aqueous layer with Et_2O (3 x 25 mL) or EtOAc (3 x 25 mL), dried over solid Na_2SO_4, decanted, and concentrated carefully (**NOTE**: Some of the phenolic products are volatile). The crude material was then purified by silica gel chromatography using the noted solvent mixture to provide the phenolic products.

General Procedure C:

To a flame-dried borosilicate flask equipped with a magnetic stir bar was added the corresponding arene as a solid or neat followed by the syringe addition of HFIP to provide a clear homogeneous solution with a substrate concentration of 0.1 M. Solid 4,5-dichlorophthaloyl peroxide was then added in one portion. After stirring at a rate of 500 rpm at 23 °C for 1 minute to provide full dissolution of the peroxide, the reaction vessel was capped with a polyethylene stopper, clamped, placed in an oil bath heated to 75 °C, and stirred at a rate of 500 rpm. After 36 hours the reaction was removed from the oil bath and allowed to cool to 23 °C. The stopper was removed carefully and the HFIP was evaporated to dryness by a continous flow of N_2 to reveal a yellow solid mixture. The crude mixture was then dissolved in a benzene/methanol solution (3:1) providing an overall substrate concentration of 0.1 M and the clear yellow homogeneous solution was stirred at a rate of 500 rpm. $TMSCHN_2$ (5.00 eq., 0.2 M in Et_2O) was added in a slow dropwise fashion over 1 minute. **Caution: Rapid N_2 gas evolution**. After 30 minutes the deep yellow–orange solution was evaporated by a continuous flow of N_2 to provide a yellow–orange foam which was purified by silica gel chromatography using the noted solvent mixture to provide the mixed phthalate ester products.



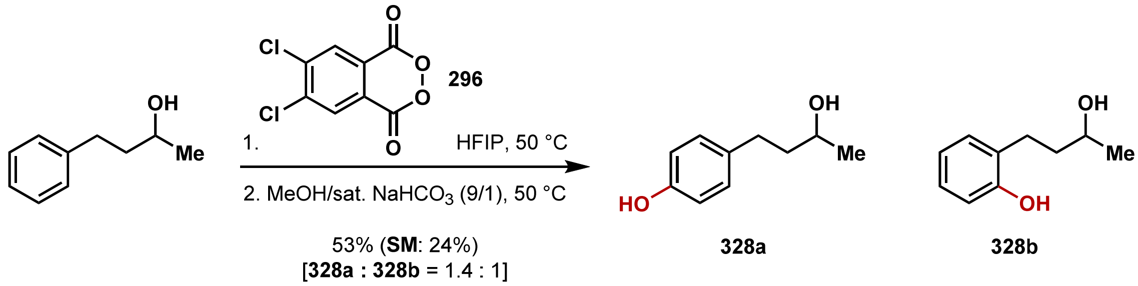
Diol 327a and **327b:** Prepared following General Procedure A using hydrocinnamyl alcohol (100.0 mg, 0.73 mmol, 1.00 eq), 4,5-dichlorophthaloyl peroxide (256.0 mg, 0.96 mmol, 1.30 eq., 86%), and HFIP (7.3 mL) at 50 °C for 48 hrs. The crude brown foam was purified by silica gel chromatography; 2 – 30% EtOAc in CH_2Cl_2 and hexane (1:1) to provide the title compounds **327a** and **327b** (56.0 mg, 0.37 mmol, 50%, **327a : 327b** = 2 : 1) as an orange foam and the starting alcohol (39.2 mg, 0.29 mmol, 39%) as a clear colorless oil. The spectral data of the title compounds match that for **327a** and **327b**.[5-8]

Major Isomer (327a):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.07 (d, 1H, J = 8.6 Hz), 6.76 (d, 1H, J = 8.6 Hz), 3.67 (t, 2H, J = 6.5 Hz), 2.64 (t, 2H, J = 7.9 Hz), 1.92 – 1.82 (m, 2H).[5-7]

Minor Isomer (327b):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.10 (d, 2H, J = 7.5 Hz), 6.88 (d, 1H, J = 7.5 Hz), 6.85 (d, 1H, J = 7.5 Hz), 3.66 (t, 2H, J = 5.8 Hz), 2.78 (dd, 2H, J = 6.5, 7.2 Hz), 1.92 – 1.82 (m, 2H).[8]



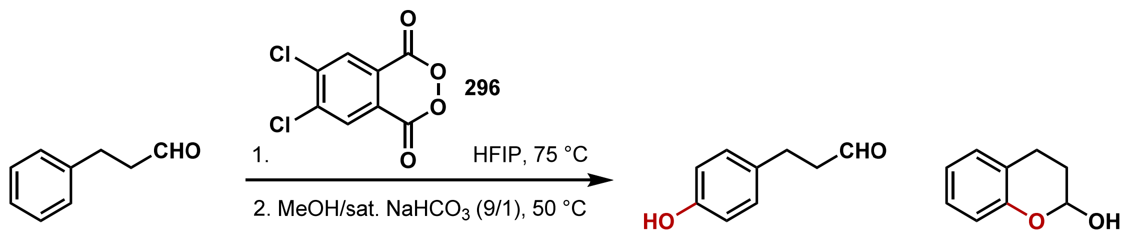
Diols 328a and 328b: Prepared following General Procedure A using methyl hydrocinnamyl alcohol (100.0 mg, 0.67 mmol, 1.00 eq), 4,5-dichlorophthaloyl peroxide (232.0 mg, 0.96 mmol, 1.30 eq., 87%), and HFIP (6.7 mL) at 50 °C for 48 hrs. The crude brown foam was purified by silica gel chromatography; 2 – 30% EtOAc in CH_2Cl_2 and hexane (1:1) to provide the title compounds **328a** and **328b** (59.0 mg, 0.36 mmol, 53%, **328a : 328b** = 1.4 : 1) as an orange foam and the starting alcohol (24.0 mg, 0.16 mmol, 24%) as a clear colorless oil. The spectral data of the title compounds match that for **328a** and **328b**.[9-10]

Major Isomer (328a):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.07 (d, 2H, *J* = 8.6 Hz), 6.75 (d, 2H, *J* = 8.6 Hz), 3.82 (m, 1H), 2.89 (m, 2H), 2.72 – 2.57 (m, 2H), 1.22 (d, 3H, *J* = 6.1 Hz).[9]

Minor Isomer (328b):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.09 (m, 2H), 6.88 (m, 2H), 3.76 (m, 1H), 2.89 (m, 2H), 2.72 – 2.57 (m, 2H), 1.22 (d, 3H, *J* = 6.1 Hz).[10]



40%
[**329a** : **329b** = 1 : 1]

329a **329b**

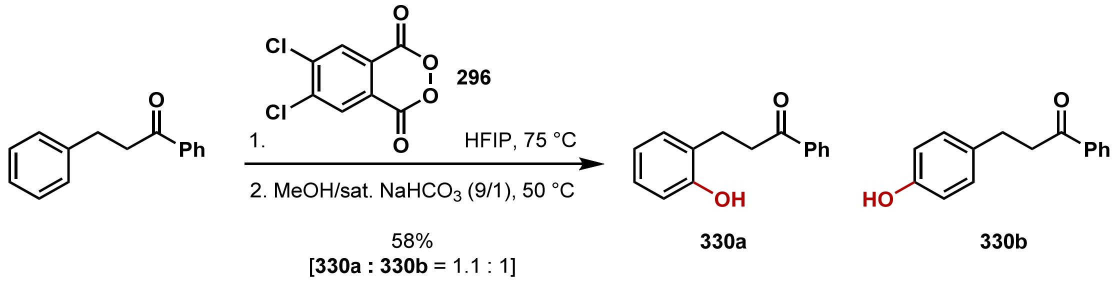
Aldehyde 329a and Lactol 329b: Prepared following General Procedure B using the hydrocinnamyl aldehyde (100.0 mg, 0.71 mmol, 1.00 eq., 95% pure), 4,5-dichlorophthaloyl peroxide (480.0 mg, 1.77 mmol, 2.50 eq., 86%), and HFIP (7.1 mL) at 75 °C for 36 hrs. The crude brown foam was purified by silica gel chromatography; 1 – 5% Et_2O in CH_2Cl_2 / hexane (1:1) to provide the aldehyde **329a** (21.0 mg, 0.14 mmol, 20%) and the lactol **329b** (21.0 mg, 0.14 mmol, 20%) as yellow foams. The spectral data of the title compounds match that for **329a** and **329b**.[11-12]

Aldehyde 329a:

^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.81 (t, 1H, *J* = 1.7 Hz), 7.06 (d, 2H, *J* = 8.6 Hz), 6.76 (d, 2H, *J* = 8.6 Hz), 4.59 (bs, 1H), 2.89 (t, 2H, *J* = 7.5 Hz), 2.74 (dd, 2H, *J* = 1.7, 7.5 Hz).[11]

Lactol 329b:

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.12 (t, 1H, *J* = 7.9 Hz), 7.07 (d, 1H, *J* = 7.2 Hz), 6.89 (t, 1H, *J* = 7.2 Hz), 6.82 (d, 1H, *J* = 7.9 Hz), 5.62 (m, 1H), 3.03 (bs, 1H,), 2.99 (m, 1H), 2.71 (dt, 1H, *J* = 5.1, 5.5 Hz), 2.06 – 1.99 (m, 2H).[12]



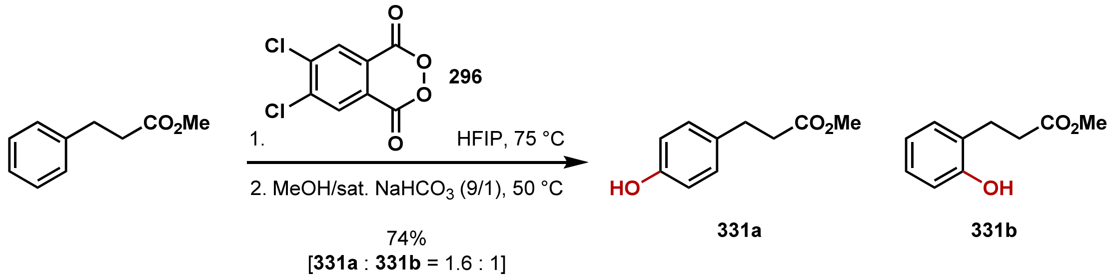
Ketones 330a and 330b: Prepared following General Procedure B using the hydrocinnamyl aryl ketone (100.0 mg, 0.48 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (322.0 mg, 1.19 mmol, 2.50 eq., 86%), and HFIP (4.8 mL) at 75 °C for 36 hours. The crude brown foam was purified by silica gel chromatography; 1 – 10% Et_2O in CH_2Cl_2 / hexane (1:1) to provide the ketone **330a** (32.3 mg, 0.14 mmol, 30%) and the ketone **330b** (30.0 mg, 0.13 mmol, 28%) as orange foams. The spectral data of the title compounds match that for **330a** and **330b**.[13-14]

Major Isomer (330a):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.98 (d, 2H, *J* = 7.2 Hz), 7.88 (bs, 1H), 7.58 (t, 1H, *J* = 7.2 Hz), 7.45 (t, 2H, *J* = 7.5 Hz), 7.11 (dd, 2H, *J* = 7.2, 7.5 Hz), 6.91 (d, 1H, *J* = 7.9 Hz), 6.85 (t, 1H, *J* = 7.5 Hz), 3.46 (dd, 2H, *J* = 5.8, 6.2 Hz), 3.04 (dd, 2H, *J* = 5.8, 6.2 Hz).[13]

Minor Isomer (330b):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.95 (d, 2H, *J* = 6.8 Hz), 7.56 (t, 1H, *J* = 7.5 Hz), 7.45 (t, 2H, *J* = 7.5 Hz), 7.12 (d, 2H, *J* = 8.6 Hz), 6.77 (d, 2H, *J* = 8.6 Hz), 4.58 (bs, 1H), 3.26 (t, 2H, *J* = 7.7 Hz), 3.00 (dd, 2H, *J* = 7.7 Hz).[14]



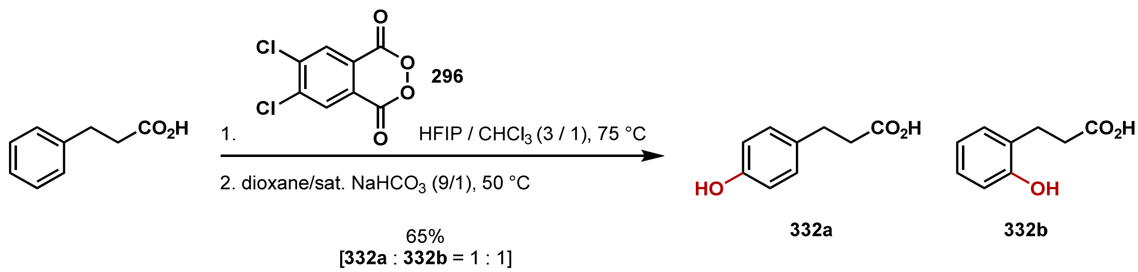
Esters 331a and 331b: Prepared following General Procedure B using the hydrocinnamyl methyl ester (100.0 mg, 0.61 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (399.0 mg, 1.52 mmol, 2.50 eq., 89%), and HFIP (6.1 mL) at 75 °C for 36 hrs. The crude brown foam was purified by silica gel chromatography; 1 – 5% Et_2O in CH_2Cl_2 / hexane (1:1) to provide the esters **331a** and **331b** (81.3 mg, 0.55 mmol, 74%, **331a** : **331b =** 1.6 : 1) as a pale yellow foam and the starting ester (5.1 mg, 0.03 mmol, 5%) as a clear colorless oil. The spectral data of the title compounds match that for **331a** and **331b**.[15-16]

Major Isomer (331a):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26 (bs, 1H), 7.06 (d, 2H, *J* = 8.6 Hz), 6.88 (d, 2H, *J* = 8.6 Hz), 3.69 (s, 3H), 2.91 (t, 2H, *J* = 6.8 Hz), 2.73 (t, 2H, *J* = 6.8 Hz).[15]

Minor Isomer (331b):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.11 (m, 2H), 6.75 (d, 2H, *J* = 8.6 Hz), 3.66 (s, 3H), 2.88 (t, 2H, *J* = 7.9 Hz), 2.59 (t, 2H, *J* = 7.9 Hz).[16]



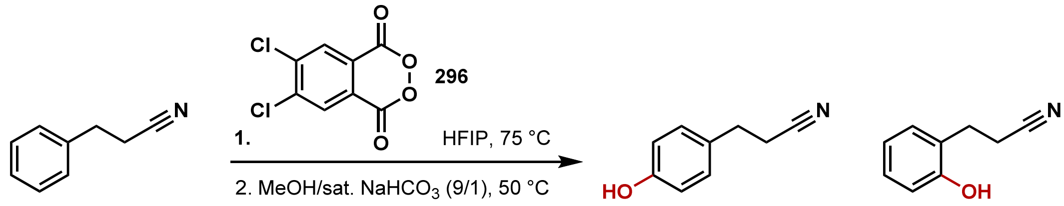
Acids 332a and 332b: Prepared following General Procedure B using hydrocinnamic acid (100.0 mg, 0.67 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (451.0 mg, 1.67 mmol, 2.50 eq., 86%), $CHCl_3$ (1.7 mL), and HFIP (5.0 mL) at 75 °C for 48 hrs. After removal of the HFIP and $CHCl_3$ by continuous positive flow of nitrogen, the mixed phthalate diacid was placed under an atmosphere of N_2, suspended in 1,4-dioxane (6.0 mL) added via syringe, and then a saturated aqueous mixture of $NaHCO_3$ (0.7 mL) was added via a syringe. The red-orange suspension was placed in an oil bath heated to 50 °C and stirred vigorously (700 rpm). After 1 hour the red solution was removed from the oil bath, acidified to a pH = 2 using 1 N HCl (3 mL), diluted with EtOAc (20 mL), poured into a separatory funnel containing brine (20 mL), and the layers were partioned. The organics were washed with an aqueous phosphate buffer (2 x 20 mL, 0.2 M, pH = 4) and the residual organics were extracted from the aqueous layer with a mixture of EtOAc and brine (4 x 30 mL, 1:1). The combined organics were dried over solid Na_2SO_4, decanted, and concentrated to reveal an orange solid. The orange solid was suspended in CH_2Cl_2 (30 mL), heated for 5 minutes with a heat gun, and sonicated for 1 minute. The residual orange mixture was filtered to remove the insoluble white solid 4,5-dichlorophthalic acid. The orange filtrate solution was concentrated to reveal an orange solid which was purified by silica gel chromatography; 1% CH_3OH and 1% AcOH in CH_2Cl_2 to provide the acids **332a** and **332b** (71.8 mg, 0.43 mmol, 65%, **332a** : **332b =** 1 : 1) as an orange solid mixture and the starting acid (12.0 mg, 0.08 mmol, 12%) as a white solid. The spectral data of the title compounds match that for **332a** and **332b**.[17,18]

Acid 332a:

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.08 (d, 2H, J = 8.6 Hz), 6.76 (d, 2H, J = 8.6 Hz), 2.90 (t, 2 H, J = 7.5 Hz), 2.65 (t, 2 H, J = 7.5 Hz).[17]

Acid 332b:

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.11 (d, 2H, J = 8.6 Hz), 6.82 – 6.89 (m, 2H, J = 8.6 Hz), 2.92 (t, 2 H, J = 6.5 Hz), 2.78 (t, 2 H, J = 6.5 Hz).[18]



40% (**SM**: 26%)
[**333a** : **333b** = 1.1:1]

333a **333b**

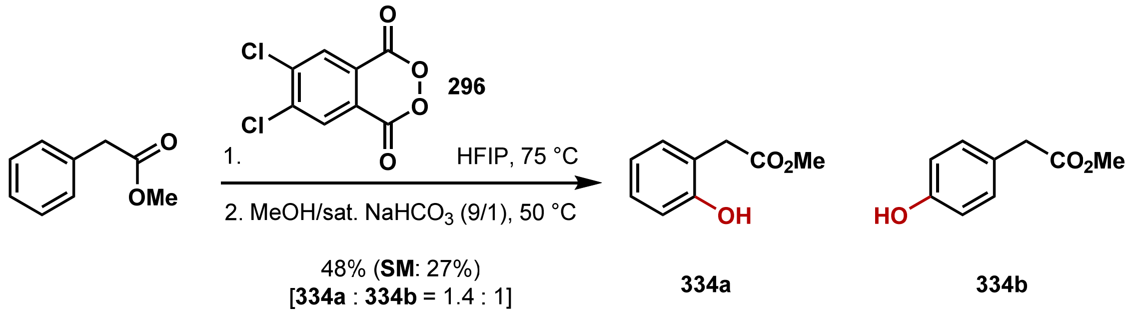
Nitriles 333a and 333b: Prepared following <u>General Procedure B</u> using the hydrocinnamyl nitrile (100.0 mg, 0.76 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (516.0 mg, 1.91 mmol, 2.50 eq., 86%), and HFIP (7.6 mL) at 75 °C for 36 hrs. The crude brown foam was purified by silica gel chromatography; 1 – 10% Et_2O in CH_2Cl_2 / hexane (1:1) to provide the nitriles **333a** (23.1 mg, 0.16 mmol, 21%) and **333b** (21.0 mg, 0.14 mmol, 19%) as pale yellow foams and the starting nitrile (25.8 mg, 0.20 mmol, 26%) as a clear colorless oil. The spectral data of the title compounds match that for **333a** and **333b**.[19,20]

Nitrile 333a:

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.11 (d, 2H, J = 8.6 Hz), 6.80 (d, 2H, J = 8.6 Hz), 4.67 (bs, 1H), 2.89 (t, 2H, J = 7.5 Hz), 2.58 (t, 2H, J = 7.5 Hz).[19]

Nitrile 333b:

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.17 (dd, 1H, J = 1.7, 7.2 Hz), 7.13 (dd, 1H, J = 1.7, 7.9 Hz), 6.91 (dt, 1H, J = 1.7, 7.2 Hz), 6.73 (d, 1H, J = 7.9 Hz), 4.85 (bs, 1H), 2.98 (t, 2H, J = 7.5 Hz), 2.67 (t, 2H, 7.5 Hz).[20]



334a

334b

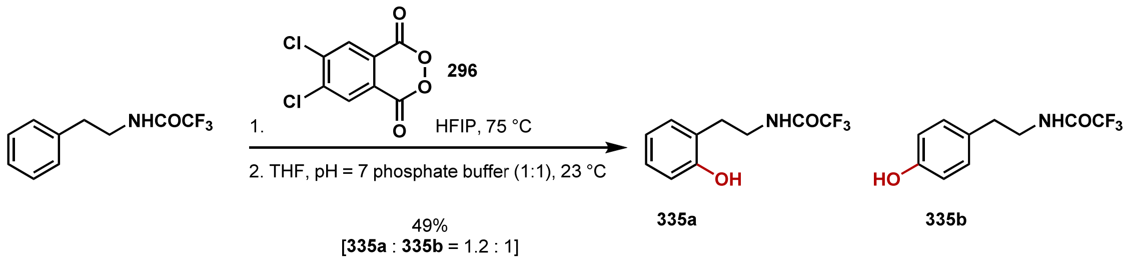
Esters 334a and 334b: Prepared following General Procedure B using the starting methyl ester (100.0 mg, 0.67 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (436.0 mg, 1.67 mmol, 2.50 eq., 89%), and HFIP (6.7 mL) at 75 °C for 36 hrs. The crude orange foam was purified by silica gel chromatography; 1 – 10% Et_2O in CH_2Cl_2 / hexane (1:1) to provide the esters **334a** and **334b** (52.4 mg, 0.32 mmol, 48%, **334a : 334b** = 1.4 : 1) as a pale yellow foam and the starting ester (27.1 mg, 0.18 mmol, 27%) as a clear colorless oil. The spectral data of the title compounds match that for **334a** and **334b**.[21-22]

Major Isomer (334a):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.33 (bs, 1H), 7.20 (m, 1H), 7.10 (dd, 1H, *J* = 1.6, 7.4 Hz), 6.94 (d, 1H, *J* = 8.2 Hz), 6.89 (dt, 1H, *J* = 1.2, 7.4 Hz), 3.75 (s, 3H), 3.68 (s, 2H).[21]

Minor Isomer (334b):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.15 (d, 2H, *J* = 8.2 Hz), 6.78 (d, 2H, *J* = 8.2 Hz), 3.72 (s, 3 H), 3.58 (s, 2 H).[22]



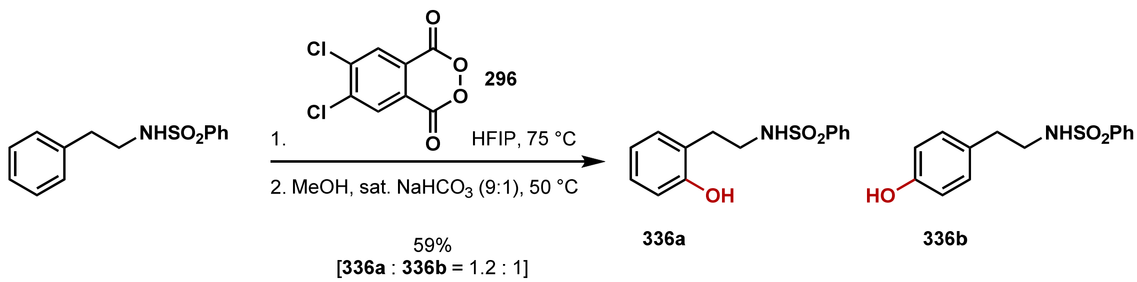
Amides 335a and **335b**: Prepared following General Procedure B using the starting trifluoroacetamide (100.0 mg, 0.46 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (523.0 mg, 1.84 mmol, 4.00 eq., 82%), and HFIP (4.6 mL) at 75 °C for 72 hrs. After removal of the HFIP by continuous positive flow of nitrogen, the mixed phthalate ester-acid was placed under an atmosphere of N_2, THF (2.3 mL) was added via syringe, and an aqueous phosphate buffer (2.3 mL, pH = 7, 0.2 M) was added via syringe. The yellow biphasic solution was stirred vigorously (1000 rpm) at 23 °C. After 24 hrs the solution was diluted with EtOAc (20 mL), poured into a separatory funnel containing an aqueous phosphate buffer (10 mL, pH = 7, 0.2 M), and the layers were partioned. The organics were washed with an aqueous phosphate buffer (4 x 20 mL, 0.2 M, pH = 7) and the residual organics were extracted from the aqueous layer with EtOAc (4 x 30 mL). The combined organics were dried over solid Na_2SO_4, decanted, and concentrated. The crude brown foam was purified by silica gel chromatography; hexane → 25% acetone in hexane to provide the amides **335a** (28.8 mg, 0.12 mmol, 27%) and **335b** (23.6 mg, 0.10 mmol, 22%) as pale yellow foams.[23]

Amide 335a:

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.17 – 7.10 (m, 2H), 7.05 (bs, 1H), 6.91 (dt, 1H, J = 1.0, 7.5 Hz), 6.80 (d, 1H, 8.2 Hz), 3.60 (q, 2H, J = 6.5 Hz), 2.93 (t, 2H, J = 6.5 Hz)

Amide 335b:

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.05 (d, 2H, J = 8.2 Hz), 6.80 (d, 2H, J = 8.2 Hz), 6.25 (bs, 1H), 3.58 (q, 2H, J = 6.5 Hz), 2.81 (t, 2H, J = 6.5 Hz).



Sulfonamides 336a and **336b**: Prepared following General Procedure B using the sulfonamide (100.0 mg, 0.38 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (265.0 mg, 0.96 mmol, 2.50 eq., 84%), and HFIP (3.8 mL) at 75 °C for 72 hrs. The crude orange foam was purified by silica gel chromatography; hexane – 25% acetone in hexane to provide the sulfonamide **336a** (34.8 mg, 0.13 mmol, 33%) as a yellow amorphous foam and **336b** (27.8 mg, 0.10 mmol, 26%) as a white solid.

Sulfonamide 336a:

$\mathbf{R_f}$ = 0.40 (35% acetone in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.78 (d, 2H, J = 7.2 Hz), 7.53 (d, 1H, J = 7.9 Hz), 7.45 (dt, 2H, J = 7.2, 7.9 Hz), 7.08 (t, 1H, 7.9 Hz), 6.97 (dd, 1H, J = 1.4, 7.5 Hz), 6.81 (t, 1H, J = 7.5 Hz), 6.75 (d, 1H, J = 7.9 Hz), 5.62 (bs, 1H), 4.99 (bs, 1H), 3.23 (m, 2H), 2.79 (t, 2H, J = 6.5 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 153.86, 139.46, 132.80, 132.60, 130.92, 129.07, 128.21, 127.00, 126.38, 124.40, 120.94, 115.60, 43.58, 30.39

IR (neat film, cm^{-1}): 3274, 1457, 1447, 1322, 1157, 1093, 755

HRMS (EC-CI): calcd. for $C_{14}H_{15}NO_3S$ [M] 277.0773, found 277.0779.

Sulfonamide 336b:

$\mathbf{R_f}$ = 0.33 (35% acetone in hexane)

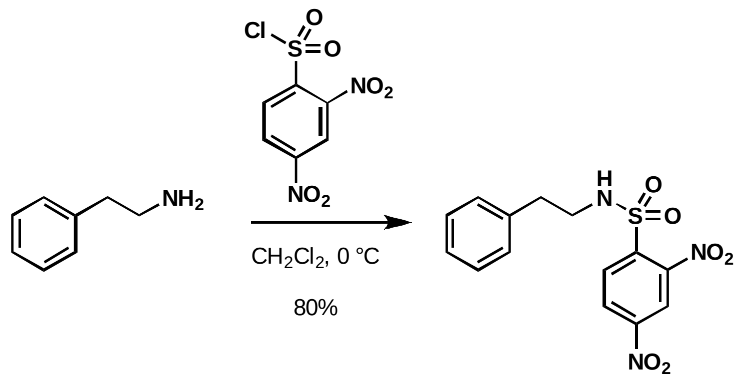
^{1}H-NMR (400 MHz, C_3D_6O): δ 8.14 (bs, 1H), 7.85 (m, 2H), 7.60 (m, 3H), 6.97 (d, 2H, J = 8.6 Hz), 6.71 (d, 2H, J = 8.6 Hz), 6.45 (bs, 1H), 3.09 (m, 2H), 2.67 (t, 2H, J = 7.2 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 156.73, 142.01, 133.06, 130.51, 130.21, 129.88, 127.71, 115.99, 45.70, 35.86

IR (neat film, cm^{-1}): 3391, 3019, 2924, 1215, 757

HRMS (EC-CI): calcd. for $C_{14}H_{15}NO_3S$ [M] 277.0773, found 277.0776.

M.P.: 116 – 121 °C



A solution of phenethylamine (0.29 g, 0.30 mL, 2.36 mmol, 2.10 eq.) in methylene chloride (11 mL) was placed in an ice water bath cooled to 0 °C for 20 minutes upon which solid dinitrobenzene sulfonyl chloride (0.30 g, 1.13 mmol, 1.00 eq.) was added under a positive flow of nitrogen. After 2 hrs the golden yellow-orange solution was diluted with an aqueous phosphate buffer (20 mL, pH = 7, 0.2 M), poured into a separatory funnel, partitioned, and the organic layer was washed with an aqueous phosphate buffer (2 x 10 mL, pH = 7, 0.2 M). Residual organics were extracted from the aqueous layer with methylene chloride (2 x 10 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude yellow-orange solid mixture was purified by silica gel chromatography; 10% acetone in hexane to afford the dinitrobenzene sulfonamide product as a yellow solid (0.32 g, 0.90 mmol, 80%).

$\mathbf{R_f}$ = 0.61 (50% acetone in hexane)

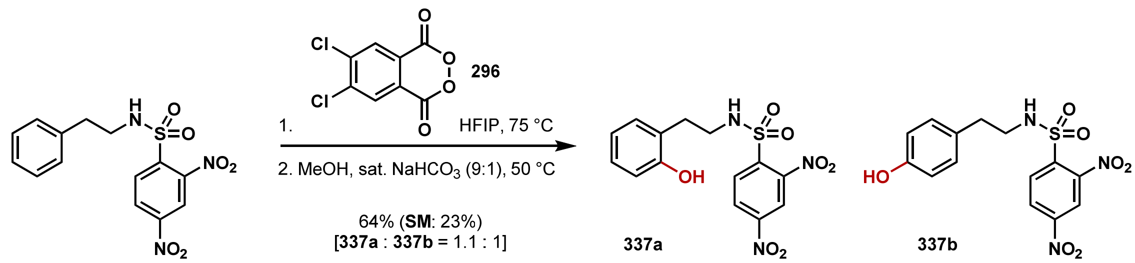
^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.59 (d, 1H, J = 2.0 Hz), 8.45 (dd, 1H, J = 2.4, 8.6 Hz), 8.19 (d, 1H, J = 8.6 Hz), 7.21 – 7.13 (m, 3H), 7.08 – 7.06 (m, 2H), 5.36 (t, 1H, J = 5.8 Hz), 3.50 (q, 2H, J = 6.5 Hz), 2.85 (t, 2H, J = 6.5 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 149.58, 147.80, 139.30, 137.15, 132.26, 128.76, 128.71, 127.13, 127.02, 120.73, 45.38, 36.01

IR (neat film, cm^{-1}): 1549, 1537, 1349, 1167, 747

HRMS (EC-CI): calcd. for $C_{14}H_{13}N_3O_6S$ [M] 352.0603, found 352.0602.

M.P.: 117 – 120 °C



Sulfonamides 337a and **337b**: Prepared following General Procedure B using the starting dinitrosulfonamide (100.0 mg, 0.29 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (197.0 mg, 0.71 mmol, 2.50 eq., 84%), and HFIP (2.9 mL) at 75 °C for 72 hrs. The crude orange foam was purified by silica gel chromatography; hexane – 25% acetone in hexane to provide the dinitrosulfonamides **337a** (34.1 mg, 0.09 mmol, 33%) and **337b** (33.2 mg, 0.09 mmol, 32%) as yellow solids and the starting dinitrosulfonamide as a yellow solid (22.7 mg, 0.07 mmol, 23%).

Sulfonamide 337a:

$\mathbf{R_f}$ = 0.56 (50% acetone in hexane)

^{1}H-NMR (400 MHz, C_3D_6O): δ 8.70 (d, 1H, J = 2.4 Hz), 8.59 (dd, 1H, J = 2.4, 8.9 Hz), 8.27 (d, 1H, J = 8.9 Hz), 7.04 (dd, 1H, 1.7, 7.5 Hz), 6.95 (dt, 1H, J = 1.7, 7.5 Hz), 6.71 (dd, 1H, J = 1.0, 7.5 Hz), 6.63 (dt, 1H, J = 1.0, 7.5 Hz), 3.49 (t, 2H, J = 7.1 Hz), 2.85 (t, 2H, J = 7.1 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.13, 149.58, 147.80, 138.80, 132.04, 130.92, 127.75, 127.14, 124.44, 120.31, 119.55, 114.80, 43.58, 30.60

IR (neat film, cm^{-1}): 3349, 1538, 1350, 1167, 748

HRMS (EC-CI): calcd. for $C_{14}H_{13}N_3O_7S$ [M] 367.0474, found 367.0471.

M.P.: 128 – 130 °C

Sulfonamide 336b:

$\mathbf{R_f}$ = 0.53 (50% acetone in hexane)

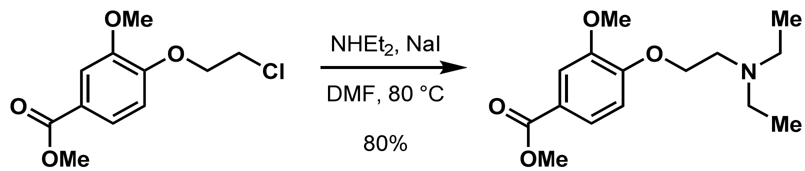
^{1}H-NMR (400 MHz, C_3D_6O): δ 8.70 (d, 1H, *J* = 1.2 Hz), 8.57 (m, 1H), 8.16 (dd, 1H, *J* = 1.6, 8.6 Hz), 6.97 (d, 2H, *J* = 8.2 Hz), 6.58 (d, 2H, *J* = 8.2 Hz), 3.46 (t, 2H, *J* = 7.1 Hz), 2.77 (t, 2H, *J* = 7.1 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 139.02, 132.01, 129.89, 128.93, 127.25, 120.22, 115.03, 45.62, 34.82

IR (neat film, cm^{-1}): 3391, 1538, 1350, 1165, 747

HRMS (EC-CI): calcd. for $C_{14}H_{13}N_3O_7S$ [M] 367.0474, found 367.0470.

M.P.: 134 – 136 °C



To a solution of methyl 4-(3-chloropropoxy)-3-methoxybenzoate (1.37 g, 5.30 mmol, 1.00 eq.) in dimethylformamide (28.5 mL) was added NaI (1.59 g, 10.59 mmol, 2.00 eq.) and diethylamine (1.64 mL, 15.89 mmol, 3.00 eq.). The flask was purged with N_2 and placed in an oil bath heated to 80 °C. After 24 hrs the solution was removed from the oil bath and allowed to cool to 23 °C, poured into a separatory funnel containing 3 N LiCl (150 mL), partitioned, and the organics were extracted from the aqueous layer with EtOAc (4 x 50 mL). The combined organics were washed with 3 N LiCl (1 x 50 mL) to remove residual DMF, washed with brine (1 x 50 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude mixture was purified by silica gel chromatography; 1% CH_3OH and 1% Et_3N in CH_2Cl_2 to provide the amine as an amber oil (1.25 g, 4.24 mmol, 80%).

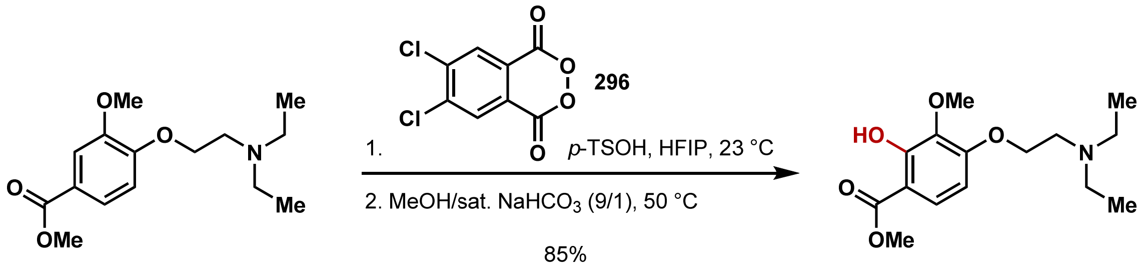
R_f = 0.40 (2% CH_3OH and 2% Et_3N in CH_2Cl_2)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.64 (dd, 1H, *J* = 2.0, 8.6 Hz), 7.53 (d, 1H, *J* =2.0 Hz), 6.90 (d, 1H, *J* = 8.2 Hz), 4.12 (t, 2H, *J* = 6.6 Hz), 3.90 (s, 3H), 3.89 (s, 3H), 2.61 (t, 2H, *J* = 7.1 Hz), 2.54 (q, 4H, *J* = 7.4 Hz), 1.99 (m, 2H), 1.01 (t, 6H, *J* = 7.4 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.92, 152.53, 148.81, 123.49, 122.4, 112.28, 111.52, 67.39, 56.01, 51.93, 49.07, 46.92, 26.61, 11.70

IR (neat film, cm^{-1}): 2967, 2809, 1717, 1293

HRMS (EC-CI): [M+Na]+ calc'd for $C_{16}H_{25}NO_4$: 318.16758. Found: 318.16729.



338

To a stirred solution of the starting amine (75.0 mg, 0.254 mmol, 1.00 eq.) in HFIP (2.5 mL) at 23 °C was added *p*-toluenesulfonic acid (43.7 mg, 0.254 mmol, 1.00 eq.). After 2 minutes 4,5-dichlorophthaloyl peroxide (89.0 mg, 0.33 mmol, 1.30 eq., 86%) was added. After 4 hrs the solvent was removed by a continuous flow of N_2 providing the mixed phthalate acid as a red solid. The crude solid was placed under an atmosphere of N_2, suspended in a deoxygenated mixture of methanol and saturated aqueous $NaHCO_3$ (9:1, 2.5 mL), and placed in an oil bath heated to 50 °C for 1 hr. The mixture was removed from the oil bath, cooled to 23 °C and an aqueous phosphate buffer (5 mL, 0.2 M, pH = 10) was added. The biphasic mixture was poured into a separatory funnel, partitioned, and the residual organics were extracted from the aqueous layer with EtOAc (3 x 5 mL). The combined organics were washed with an aqueous phosphate buffer (1 x 5 mL, 0.2 M, pH = 10), brine (1 x 5 mL), dried over solid Na_2SO_4, and concentrated. The crude mixture was purified by silica gel chromatography; 1% methanol and 1% triethylamine in CH_2Cl_2 to afford the phenol **338** as a clear colorless oil (67.7 mg, 0.22 mmol, 85%).

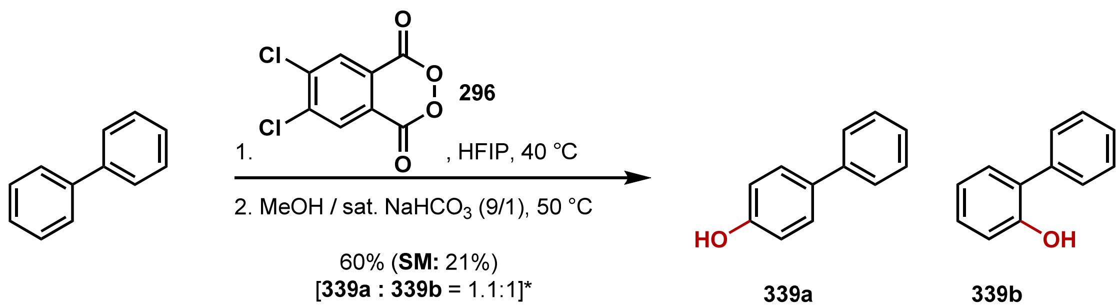
$\mathbf{R_f}$ = 0.40 (2% methanol and 2% triethylamine in CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.79 (s, 1 H), 7.55 (d, 1H, *J* = 9.0 Hz), 6.48 (d, 1H, *J* = 9.0 Hz), 4.12 (m, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 2.65 (t, 2H, *J* = 7.0 Hz), 2.57 (q, 4H, *J* = 7.0 Hz), 1.99 (t, 2H, *J* = 7.0 Hz), 1.04 (t, 6H, *J* = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.14, 157.28, 155.71, 136.35, 125.27, 106.52, 103.90, 66.84, 60.31, 51.76, 48.86, 46.66, 26.37, 11.21

IR (neat film, cm $^{-1}$): 3369, 2966, 2917, 1720, 1240

HRMS (EC-CI): [M+H]+ calc'd for $C_{16}H_{26}NO_5$: 312.1806; found: 312.1800.



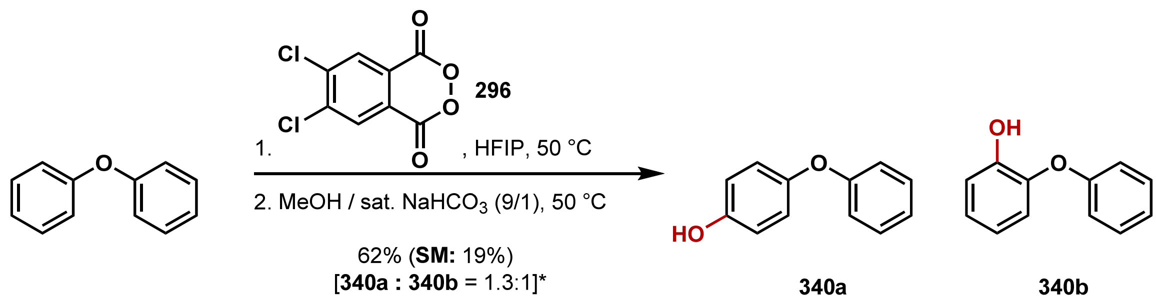
Phenols 339a and **339b**: Prepared following General Procedure A using biphenyl (100.0 mg, 0.65 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (226.0 mg, 0.84 mmol, 1.30 eq., 87%), and HFIP (6.5 mL) at 40 °C for 24 hrs. The crude orange foam was purified by silica gel chromatography; 1 – 10% Et_2O in CH_2Cl_2 / hexane (1:1) to afford the phenols **339a** (35.0 mg, 0.21 mmol, 32%) and **339b** (31.0 mg, 0.18 mmol, 28%) as pale yellow solids and the starting biphenyl as a white solid (21.1 mg, 0.13 mmol, 21%). The spectral data of the title compounds match that of the phenols **339a** and **339b**.[5]

Phenol 339a:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (m, 2H), 7.48 (d, 2H, *J* = 8.6 Hz), 7.41 (t, 2H, *J* =7.9 Hz), 7.30 (t, 1H, *J* = 7.9 Hz), 7.25 (m, 1H), 6.91 (d, 2H, *J* = 8.6 Hz), 4.70 (bs, 1H)

Phenol 339b:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (m, 4H), 7.40 (m, 1H), 7.26 (m, 2H), 7.00 (dt, 1H, *J* = 1.3, 6.1 Hz), 6.99 (d, 1H, *J* = 7.8 Hz), 5.18 (bs, 1H)



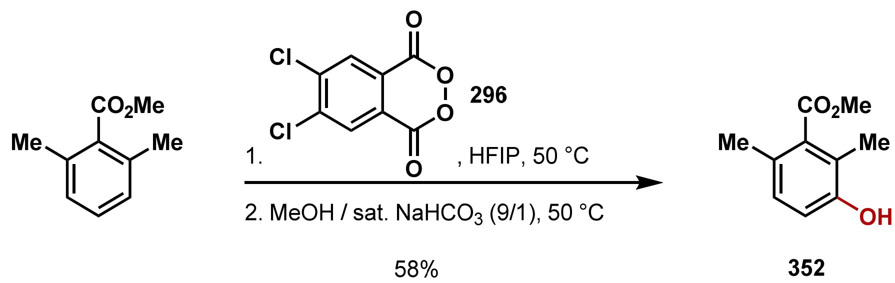
Phenols 340a and **340b**: Prepared following General Procedure A using diphenyl ether (100.0 mg, 0.59 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (207.0 mg, 0.76 mmol, 1.30 eq., 86%), and HFIP (6.5 mL) at 50 °C for 24 hrs. The crude orange foam was purified by silica gel chromatography; 1 – 10% Et_2O in CH_2Cl_2 / hexane (1:1) to afford the phenols **340a** (37.6 mg, 0.20 mmol, 35%) and **340b** (29.0 mg, 0.16 mmol, 27%) as pale yellow amorphous oils and the starting diphenyl ether as a clear colorless oil (18.6 mg, 0.11 mmol, 19%). The spectral data of the title compounds match that of the phenols **340a** and **340b**.[5]

Phenol 340a:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 2H), 7.04 (t, 1H, J = 7.5 Hz), 6.93 (m, 4H, J =7.9 Hz), 6.81 (d, 1H, J = 9.2 Hz) 4.56 (bs, 1H)

Phenol 340b:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (dd, 2H, J = 7.5, 8.5 Hz), 7.12 (t, 1H, J = 7.5 Hz), 7.04 (m, 4H), 6.90 – 6.84 (m, 2H), 5.55 (bs, 1H)



Phenol 352: Prepared following General Procedure B using 2,6-dimethyl methylbenzoate (100.0 mg, 0.61 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (422.0 mg, 1.52 mmol, 2.50 eq., 84%), and HFIP (6.1 mL) at 75 °C for 48 hrs. The crude orange foam was purified by silica gel chromatography; pentane and then hexane → 15% acetone in hexane to afford the phenol **352** as a pale yellow amorphous oil (63.0 mg, 0.35 mmol, 58%).

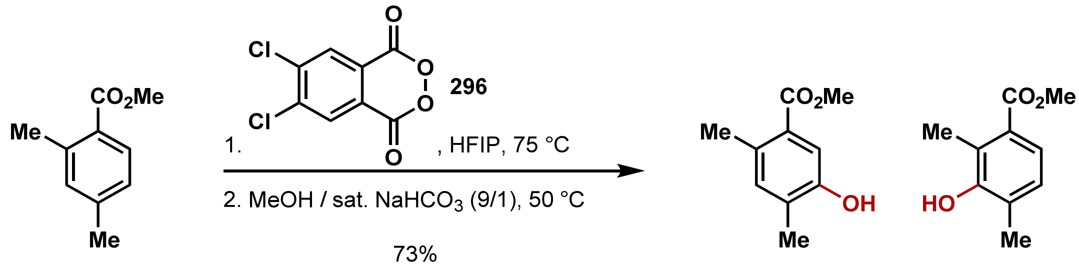
R_f = 0.46 (50% Et_2O in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (d, 1H, *J* = 8.2 Hz), 6.72 (d, 1H, *J* = 8.2 Hz), 4.64 (bs, 1H), 3.91 (s, 3H), 2.22 (s, 3H), 2.18 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.77, 151.81, 135.07, 128.30, 126.50, 121.10, 116.06, 52.14, 18.87, 12.85

IR (neat film, cm $^{-1}$): 3399, 2360, 2341, 1706, 1293, 1047

HRMS (EC-CI): calcd. for $C_{10}H_{12}O_3$ [M] 180.0786, found 180.0787.



73%
[**353a** : **353b** = 1.1:1]

353a **353b**

Phenols 353a and **353b**: Prepared following General Procedure B using 2,4-dimethyl methylbenzoate (150.0 mg, 0.91 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (649.0 mg, 2.28 mmol, 2.50 eq., 82%), and HFIP (9.1 mL) at 75 °C for 48 hrs. The crude orange foam was purified by silica gel chromatography; pentane and then hexane → 30% EtOAc in hexane to afford the phenol **353a** as a pale yellow amorphous oil (63.2 mg, 0.35 mmol, 38%) and phenol **353b** as a pale yellow oil (57.4 mg, 0.22 mmol, 35%). The spectral data for the title compound matches that of phenol **353a**.[24]

Phenol 353a:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 1H), 6.99 (s, 1H), 3.86 (s, 3H), 2.48 (s, 3H), 2.25 (s, 3H)

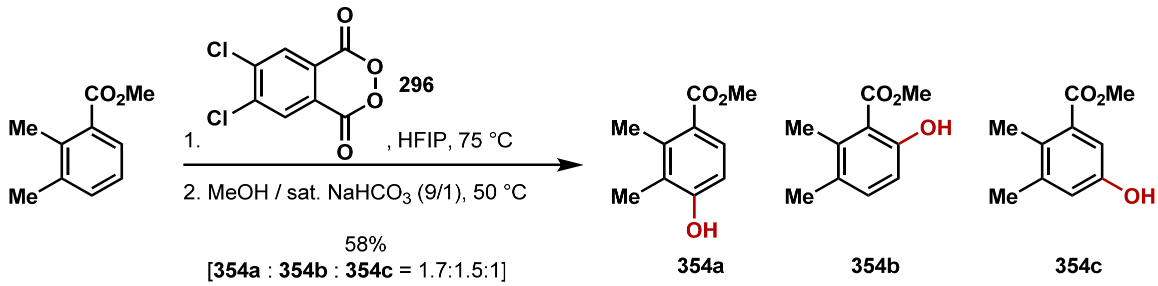
Phenol 353b:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, 1H, J = 7.8 Hz), 7.00 (d, 1H, J = 7.8 Hz), 4.91 (bs, 1H), 3.87 (s, 3H), 2.48 (s, 3H), 2.28 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.41, 152.57, 132.98, 129.10, 127.63, 124.65, 122.46, 51.87, 16.44, 12.63

IR (neat film, cm $^{-1}$): 3477, 2952, 1702, 1435, 1273, 1054

HRMS (EC-CI): calcd. for $C_{10}H_{13}O_3$ $[M+H]^+$ 181.0865, found 181.0865.



Phenols 354a, 354b, and **354c**: Prepared following General Procedure B using 2,3-dimethyl methylbenzoate (100.0 mg, 0.61 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (422.0 mg, 1.52 mmol, 2.50 eq., 84%), and HFIP (6.1 mL) at 75 °C for 48 hrs. The crude orange foam was purified by silica gel chromatography; 1 – 5% Et_2O in hexane / CH_2Cl_2 (1:1) to afford the phenols **354a** as a pale yellow amorphous oil (25.9 mg, 0.14 mmol, 24%), **354b** as a pale yellow amorphous oil (21.8 mg, 0.12 mmol, 20%), and **354c** as a pale yellow foam (14.9 mg, 0.08 mmol, 14%). The spectral data for the title compounds matches that for phenols **354a** and **354b**.[25, 26]

Phenol 354a:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, *J* = 8.2 Hz), 6.63 (d, 1H, *J* = 8.2 Hz), 3.85 (s, 3H), 2.51 (s, 3H), 2.20 (s, 3H)

Phenol 354b:

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.58 (bs, 1H), 7.28 (d, 1H, *J* = 7.8 Hz), 7.13 (d, 1H, *J* = 7.8 Hz), 3.88 (s, 3H), 2.45 (s, 3H), 2.32 (s, 3H)

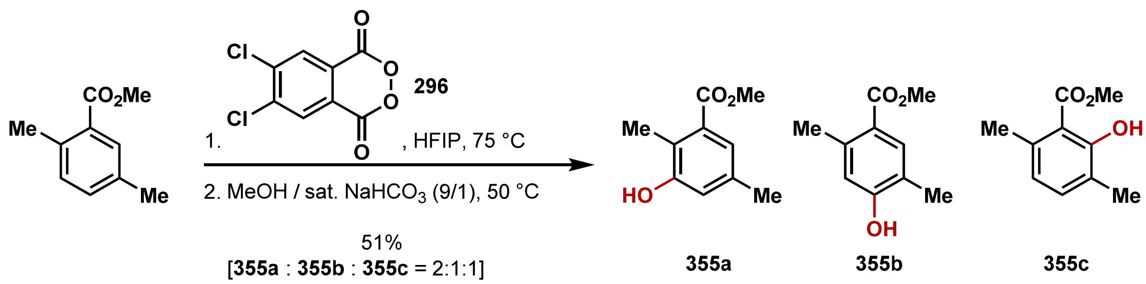
Phenol 354c:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, 1H, *J* = 2.7 Hz), 6.80 (d, 1H, *J* = 2.7 Hz), 5.25 (bs, 1H), 3.87 (s, 3H), 2.35 (s, 3H), 2.26 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.74, 152.61, 139.69, 131.72, 129.79, 120.41, 114.08, 51.99, 20.69, 15.80

IR (neat film, cm^{-1}): 3398, 1718, 1436, 1225

HRMS (EC-CI): calcd. for $C_{10}H_{13}O_3$ [M] 180.0786, found 180.0785.



Phenols 355a, 355b, and **355c**: Prepared following General Procedure B using 2,5-dimethyl methylbenzoate (100.0 mg, 0.61 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (422.0 mg, 1.52 mmol, 2.50 eq., 84%), and HFIP (6.1 mL) at 75 °C for 48 hrs. The crude orange foam was purified by silica gel chromatography; pentane and then hexane → 15% acetone in hexane to afford the phenols **355a** (27.7 mg, 0.15 mmol, 25%) and **355b** (14.5 mg, 0.08 mmol, 13%) as pale yellow foams, and **355c** as a pale yellow solid (13.9 mg, 0.08 mmol, 13%). The spectral data for the title compounds matches that for phenols **355a**, **355b**, and **355c**.[27, 28]

Phenol 355a:

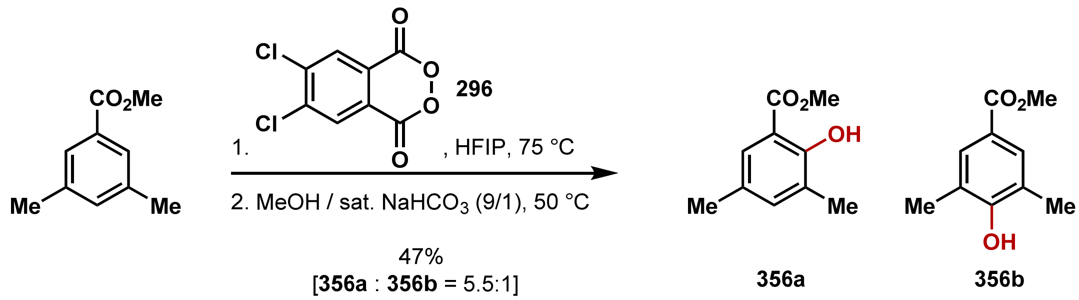
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (s, 1H), 6.77 (s, 1H), 5.22 (bs, 1H), 3.88 (s, 3H), 2.40 (s, 3H), 2.27 (s, 3H)

Phenol 355b:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H), 6.62 (s, 1H), 5.57 (bs, 1H), 3.85 (s, 3H), 2.52 (s, 3H), 2.22 (s, 3H)

Phenol 355c:

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.58 (bs, 1H), 7.15 (d, 1H, J = 7.5 Hz), 6.62 (d, 1H, J = 7.5 Hz), 3.95 (s, 3H), 2.50 (s, 3H), 2.22 (s, 3H)



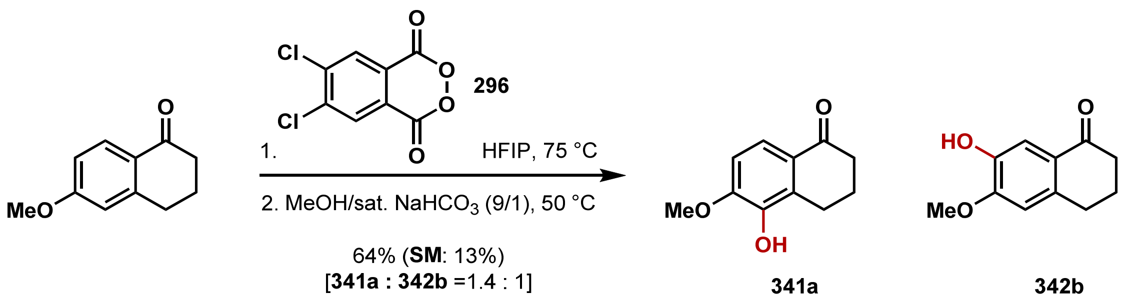
Phenols 356a and **356b**: Prepared following General Procedure B using 3,5-dimethyl methylbenzoate (100.0 mg, 0.61 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (422.0 mg, 1.52 mmol, 2.50 eq., 84%), and HFIP (6.1 mL) at 75 °C for 48 hrs. The crude orange foam was purified by silica gel chromatography; pentane and then hexane → 15% acetone in hexane to afford the phenol **356a** (44.0 mg, 0.24 mmol, 40%) as a white solid and the phenol **355b** (7.8 mg, 0.04 mmol, 7%) as a pale yellow foam. The spectral data for the title compounds matches that for phenols **356a** and **356b**.[26, 29]

Phenol 356a:

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.83 (bs, 1H) 7.48 (bs, 1H), 7.15 (bs, 1H), 3.93 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H)

Phenol 356b:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 2H), 5.34 (bs, 1H), 3.87 (s, 3H), 2.27 (s, 6H)



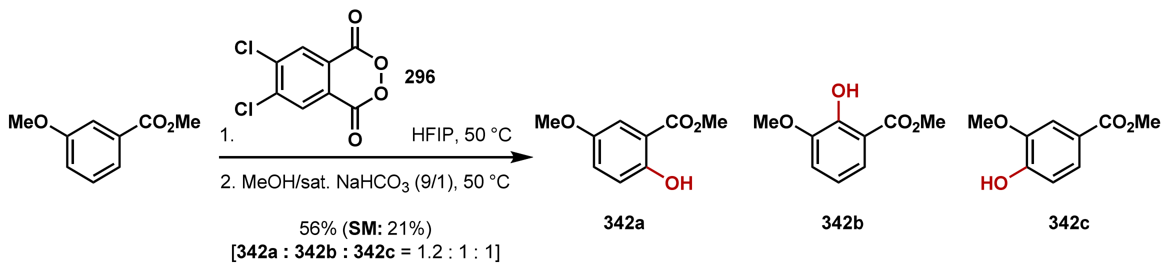
Tetralones 341a and 341b: Prepared following General Procedure B using 6-methoxy tetralone (100.0 mg, 0.57 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (367.0 mg, 1.42 mmol, 2.50 eq., 90%), and HFIP (5.7 mL) at 75 °C for 36 hrs. The crude brown foam was purified by silica gel chromatography; 1 – 20% EtOAc in CH_2Cl_2 / hexane (1:1) to afford the phenols **341a** (41.0 mg, 0.21 mmol, 38%) and **341b** (29.0 mg, 0.15 mmol, 48%) as yellow solids and the starting tetralone (13.0 mg, 0.07 mmol, 13%) as a pale yellow solid. The spectra of the title compounds match that for **341a** and **341b**.[30,31]

Major Isomer (341a):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.68 (d, 1H, J = 8.6 Hz), 6.84 (d, 1H, J = 8.6 Hz), 5.71 (bs, 1H), 3.96 (s, 3H), 2.93 (t, 2H, J = 6.2 Hz), 2.60 (t, 2H, J = 6.2 Hz), 2.11 (ddd, 2H, J = 6.2 Hz).[30]

Minor Isomer (341b):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.56 (s, 1H), 6.66 (s, 1H), 5.52 (bs, 1H), 3.95 (s, 3H), 2.88 (t, 2H, J = 6.5 Hz), 2.59 (t, 2H, J = 6.5 Hz), 2.10 (ddd, 2H, J = 6.5 Hz).[31]



Phenols 342a, 342b, and 342c: Prepared following General Procedure A using 3-methoxy methylbenzoate (100.0 mg, 0.60 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (212.0 mg, 0.78 mmol, 1.30 eq., 86%), and HFIP (6.0 mL) at 50 °C for 24 hrs. The crude brown foam was purified by silica gel chromatography; 1 – 20% Et_2O in CH_2Cl_2 / hexane (1:1) to provide the phenols **342a** (22.1 mg, 0.12 mmol, 20%), **342b** (19.7 mg, 0.11 mmol, 18%), **342c** (18.8 mg, 0.10 mmol, 17%) as pale yellow solids and the starting benzoate (20.9 mg, 0.13 mmol, 21%) as a clear colorless oil. The spectra of the title compounds match that for **342a**, **342b**, and **342c**.[5,6,32, 33]

Major Isomer (342a):

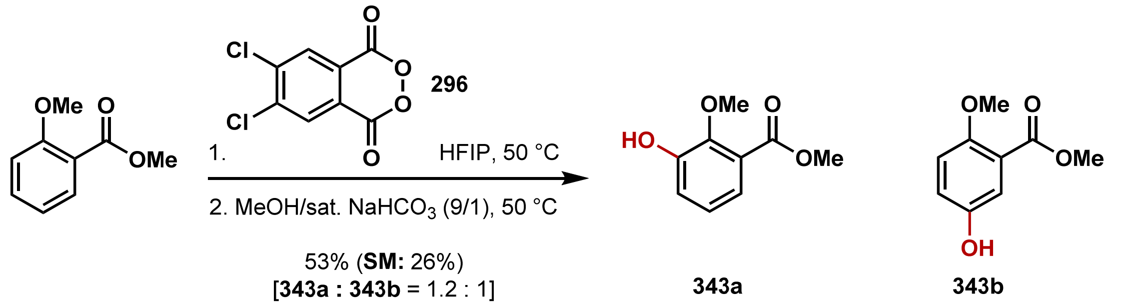
^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.37 (bs, 1H), 7.29 (d, 1H, J = 3.3 Hz), 7.08 (dd, 1H, J = 3.3, 8.9 Hz), 6.92 (d, 1H, J = 8.9 Hz), 3.95 (s, 3H), 3.78 (s, 3H).[32]

Minor Isomer (342b):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.00 (bs, 1H), 7.43 (dd, 1H, J = 1.5, 8.2 Hz), 7.04 (d, 1H, J = 8.2 Hz), 6.83 (t, 1H, J = 8.2 Hz), 3.95 (s, 3H), 3.91 (s, 3H).[5,6, 33]

Minor Isomer (342c):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.64 (d, 1H, J = 8.2 Hz), 7.55 (d, 1H, J = 2.1 Hz), 6.94 (d, 1H, J = 8.2 Hz), 5.97 (bs, 1H), 3.95 (s, 3H), 3.89 (s, 3H).[5, 6]



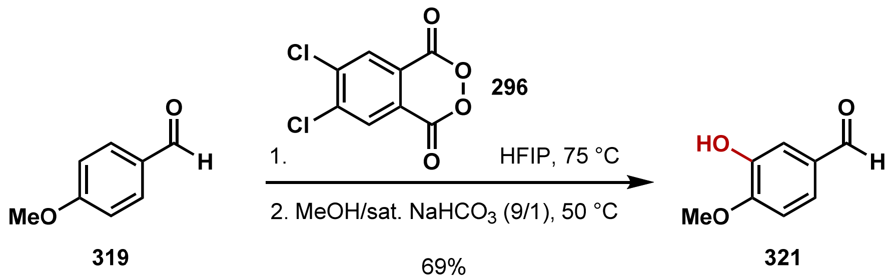
Phenols 343a and 343b: Prepared following General Procedure A using methyl salicylate (100.0 mg, 0.60 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (212.0 mg, 0.78 mmol, 1.30 eq., 86%), and HFIP (6.0 mL) at 50 °C for 24 hrs. The crude brown foam was purified by silica gel chromatography; 1 – 20% Et_2O in CH_2Cl_2 and hexane (1:1) to afford the phenols **343a** (31.0 mg, 0.17 mmol, 28%) and **343b** (27.2 mg, 0.15 mmol, 25%) as yellow solids and the starting salicylate (25.6 mg, 0.15 mmol, 26%) as a clear colorless oil. The spectra of the title compounds match that for **343a** and **343b**.[34, 35]

Major Isomer (343a):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, 1H, *J* = 1.7, 8.2 Hz), 7.15 (dd, 1H, *J* = 1.7, 8.2 Hz), 7.05 (t, 1H, *J* = 8.2 Hz), 5.91 (bs, 1H), 3.93 (s, 3H), 3.92 (s, 3H).[34]

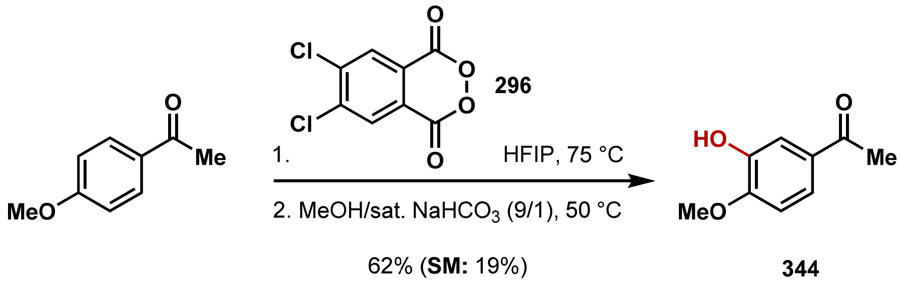
Minor Isomer (343b):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29 (d, 1H, *J* = 3.4 Hz), 6.97 (dd, 1H, *J* = 3.4, 8.9 Hz), 6.88 (d, 1H, *J* = 8.9 Hz), 4.52 (bs, 1H), 3.89 (s, 3H), 3.86 (s, 3H).[35]



***Iso*vanillin 321:** Prepared following General Procedure B using *p*-anisaldehyde (**319**) (30.0 mg, 0.22 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (239.0 mg, 0.88 mmol, 4.00 eq., 86%), and HFIP (2.2 mL) at 75 °C for 36 hrs. The crude golden orange foam was purified by silica gel chromatography; 1 – 10% Et_2O in CH_2Cl_2 and hexane (1:1) to afford *iso*vanillin (**321**) (23.0 mg, 0.15 mmol, 69%) as a yellow solid. The spectra of the title compound matches that for **321**.[5, 6]

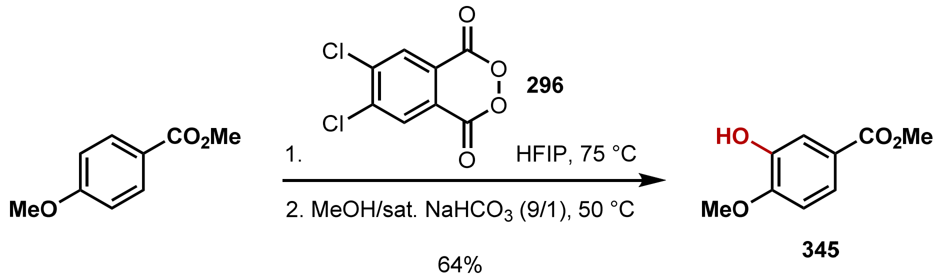
^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.85 (s, 1H), 7.45 (s, 1H), 7.44 (dd, 1H, *J* = 2.1, 6.5 Hz), 6.98 (d, 1H, *J* = 9.9 Hz), 6.72 (s, 1H), 3.99 (s, 3H).[5, 6]



344

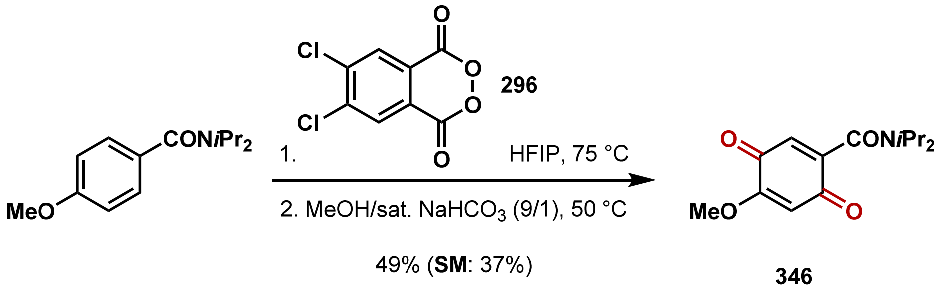
Ketone 344: Prepared following General Procedure B using 4-methoxy acetophenone (100.0 mg, 0.67 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (446.0 mg, 1.67 mmol, 2.50 eq., 86%), and HFIP (6.7 mL) at 75 °C for 36 hrs. The crude brown foam was purified by silica gel chromatography; 1 – 10% Et_2O in CH_2Cl_2 and hexane (1:1) to afford the ketone **344** (68.5 mg, 0.41 mmol, 62%) as a yellow solid and the starting acetophenone (18.8 mg, 0.13 mmol, 19%) as a white solid. The spectra of the title compound matches that for **344**.[36]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.54 (dd, 1H, J = 2.1, 10.6 Hz), 7.53 (s, 1H), 6.89 (d, 1H, J = 8.2 Hz), 5.64 (bs, 1H), 3.97 (s, 3H), 2.55 (s, 3H).[36]



Phenol 345: Prepared following General Procedure B using 4-methoxy methylbenzoate (100.0 mg, 0.60 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (408.0 mg, 1.50 mmol, 2.50 eq., 86%), and HFIP (6.0 mL) at 75 °C for 36 hrs. The crude brown foam was purified by silica gel chromatography; 1 – 20% Et_2O in CH_2Cl_2 and hexane (1:1) to afford the phenol **345** (70.0 mg, 0.39 mmol, 64%) as a yellow solid and the starting benzoate (5.0 mg, 0.03 mmol, 5%) as a white solid. The spectra of the title compound matches that for **345**.[37]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, 1H, *J* = 2.0, 8.6 Hz), 7.59 (d, 1H, *J* = 2.0 Hz), 6.87 (d, 1H, *J* = 8.6 Hz), 5.61 (s, 1H), 3.95 (s, 3H), 3.88 (s, 3H).[37]



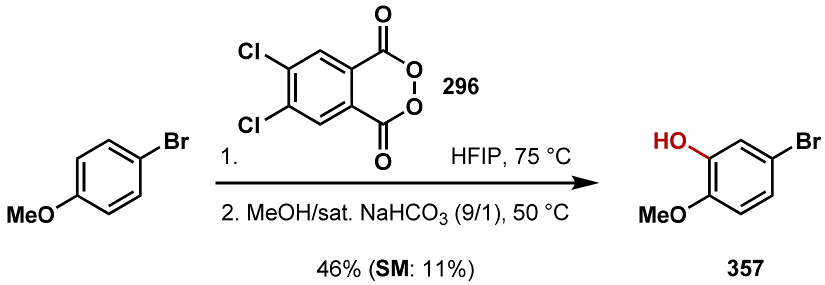
***p*-Quinone 346:** Prepared following General Procedure B using 4-methoxy diisopropylamide (90.0 mg, 0.35 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (259.0 mg, 0.96 mmol, 2.50 eq., 86%), and HFIP (3.8 mL) at 75 °C for 36 hrs. The crude brown foam was purified by silica gel chromatography; 1 – 30% EtOAc in CH_2Cl_2 and hexane (1:1) to afford the quinone **346** (50.0 mg, 0.19 mmol, 49%) as a dark yellow solid and the starting amide (33.7 mg, 0.14 mmol, 37%) as a viscous yellow oil.

^{1}H-NMR (500 MHz, C_3D_6O): δ 6.56 (s, 1H), 6.04 (s, 1H). 3.87 (s, 3H), 3.79 (ddd, 1H, *J* = 6.6 Hz), 3.56 (ddd, 1H, *J* = 6.9 Hz), 1.44 (bs, 6H), 1.14 (bs, 1H)

^{13}C-NMR (500 MHz, C_3D_6O): δ 186.09, 182.53, 163.92, 160.03, 145.74, 129.05, 107.78, 56.80, 51.68, 46.24, 20.71, 20.59, 20.45, 20.17

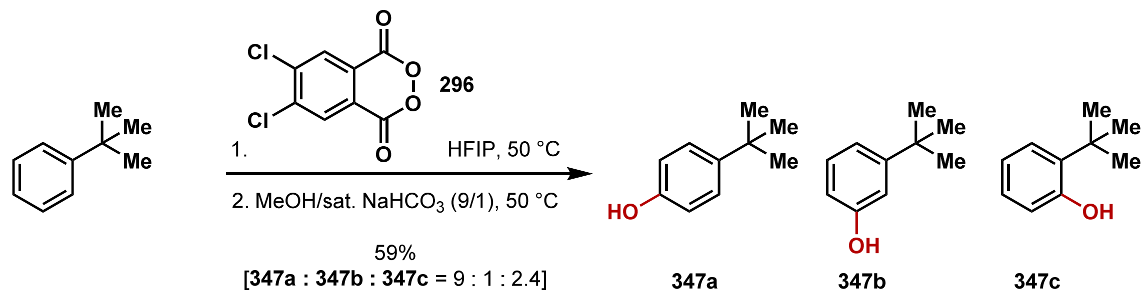
IR (neat film, cm^{-1}): 3419, 1637

HRMS (EC-CI): calcd. for $C_{14}H_{21}NO_4$ $[M+2H]^{2+}$ 267.1471, found 267.1474.



Phenol 357: Prepared following General Procedure A using 4-bromoanisole (100.0 mg, 0.54 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (186.0 mg, 0.70 mmol, 1.30 eq., 87%), and HFIP (5.4 mL) at 50 °C for 24 hrs. The crude brown foam was purified by silica gel chromatography; 1 – 10% Et_2O in CH_2Cl_2 and hexane (1:1) to afford the phenol **357** (50.0 mg, 0.25 mmol, 46%) as a pale yellow amorphous oil and the starting 4-bromoanisole (11.0 mg, 0.05 mmol, 11%) as a clear colorless oil. The spectra of the title compound matches that for **357**.[38]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.06 (d, 1H, J = 2.4 Hz), 6.96 (dd, 1H, J = 2.4, 8.6 Hz), 6.71 (d, 1H, J = 8.6 Hz), 5.63 (bs, 1H), 3.87 (s, 3H).[38]



Phenols 347a, 347b, and 347c: Prepared following General Procedure A using *tert*-butyl benzene (100.0 mg, 0.75 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (259.0 mg, 0.97 mmol, 1.30 eq., 87%), and HFIP (7.5 mL) at 50 °C for 24 hrs. The crude brown foam was purified by silica gel chromatography; 1 – 5% Et_2O in CH_2Cl_2 and hexane (1:1) to afford the phenols **347a** and **347b** (53.4 mg, 0.36 mmol, 48%, **347a : 347b** = 9 : 1) as an orange foam and **347c** (12.6 mg, 0.08 mmol, 11%) as a pale yellow foam. The spectra of the title compounds match that for **347a**, **347b**, and **347c**.[5-6]

Major Isomer (347a):

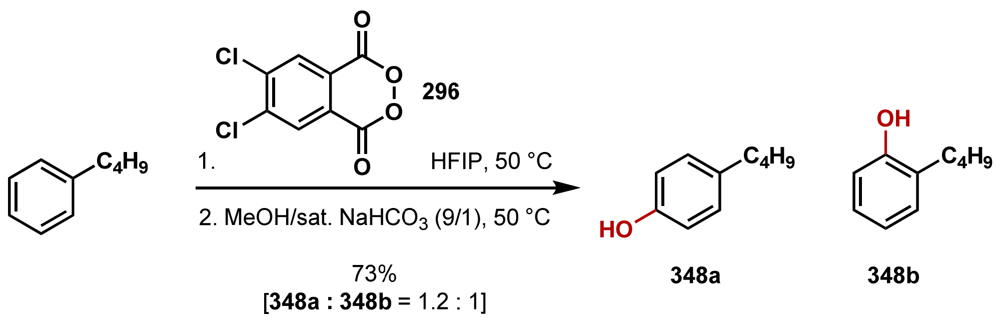
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26 (d, 2H, J = 8.9 Hz), 6.77 (d, 2H, J = 8.9 Hz), 4.54 (bs, 1H), 1.29 (s, 9H).[5]

Minor Isomer (347b):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.17 (t, 1H, J = 7.9 Hz), 6.97 (m, 1H), 6.87 (dd, 1H, J = 2.1, 2.4 Hz), 6.64 (m, 1H), 4.60 (bs, 1H), 1.30 (s, 9H).[5]

Minor Isomer (347c):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.27 (d, 1H, J = 8.6 Hz), 7.07 (t, 1H, J = 6.5 Hz), 6.88 (dd, 1H, J = 6.5, 8.6 Hz), 6.66 (d, 1H, J = 8.6 Hz), 4.71 (bs, 1H), 1.41 (s, 9H).[6]



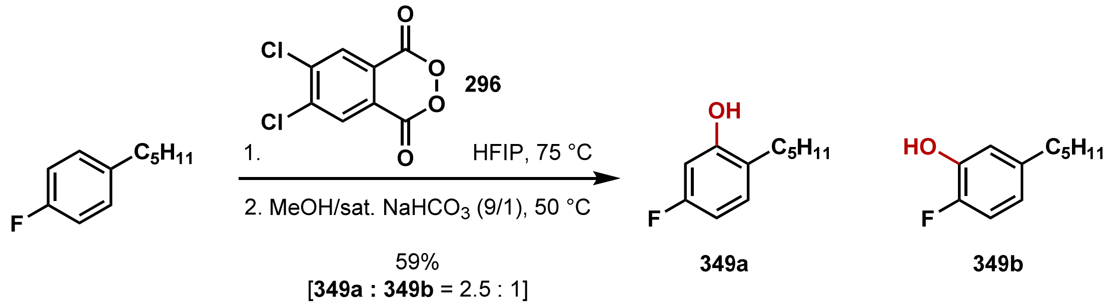
Phenols 348a and 348b: Prepared following General Procedure A using butyl benzene (100.0 mg, 0.75 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (262.0 mg, 0.97 mmol, 1.30 eq., 86%), and HFIP (7.5 mL) at 50 °C for 24 hrs. The crude orange foam was purified by silica gel chromatography; 1 – 5% Et_2O in CH_2Cl_2 and hexane (1:1) to afford the phenols **348a** and **348b** (81.1 mg, 0.54 mmol, 73%, **348a** : **348b** = 1.2 : 1) as a pale yellow foam. The spectra of the title compounds match that for **348a** and **348b**.[5, 6, 39]

Major Isomer (348a):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.04 (d, 2H, J = 8.6 Hz), 6.74 (d, 2H, J = 8.6 Hz), 4.56 (bs, 1H), 2.54 (t, 2H, J = 7.8 Hz), 1.64 – 1.52 (m, 2H), 1.44 – 1.31 (m, 2H), 0.92 (t, 3H, J = 7.1 Hz).[5, 6, 39]

Minor Isomer (348b):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.13 – 7.05 (m, 2H), 6.87 (dt, 1H, J = 1.1, 7.4 Hz), 6.77 – 6.74 (m, 1H), 4.64 (bs, 1H), 2.61 (t, 2H, J = 7.9 Hz), 1.64 – 1.52 (m, 2H), 1.44 – 1.31 (m, 2H), 0.94 (t, 3H, J = 7.5 Hz).[6, 39]



Fluorophenols **349a and 349b:** Prepared following General Procedure B using 4-pentyl fluorobenzene (100.0 mg, 0.60 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (403.0 mg, 1.50 mmol, 2.50 eq., 87%), and HFIP (6.0 mL) at 75 °C for 36 hrs. The crude brown foam was purified by silica gel chromatography; 1% Et_2O in CH_2Cl_2 and hexane (1:1) to afford the fluorophenols **349a** and **349b** (64.3 mg, 0.35 mmol, 59%, **349a : 349b** = 2.5 : 1) as a yellow oil. The spectra of the title compound matches that for **349b**.[40]

R_f = 0.57 (3% Et_2O in 49% hexane and 48% CH_2Cl_2);

Major Isomer (349a):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.03 (dd, 1H, J = 6.8, 8.6 Hz), 6.57 (dt, 1H, J = 5.8, 8.2 Hz), 6.52 (dd, 1H, J = 2.4, 9.9 Hz), 4.82 (bs, 1H), 2.53 (q, 2H, J = 8.2 Hz), 1.58 (m, 2H), 1.35 (m, 4H), 0.90 (m, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 161.43, 154.21, 130.66, 124.80, 107.50, 103.00, 31.59, 29.48, 29.29, 22.54, 14.02

IR (neat film, cm^{-1}): 3391, 2929, 1609, 1514, 1279, 1112

HRMS (EC-CI): calcd. for $C_{11}H_{15}OF$ $[M+H]^+$ 182.1107, found 182.1106.

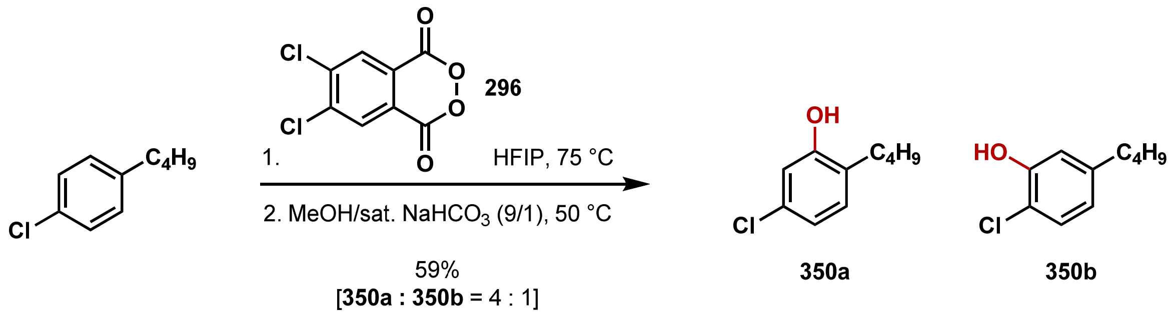
Minor Isomer (349b)[40]:

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.95 (dd, 1H, J = 8.2, 10.3 Hz), 6.84 (dd, 1H, J = 2.1, 8.2 Hz), 6.66 - 6.63 (m, 1H), 5.01 (bs, 1H), 2.53 (q, 2H, J = 8.2 Hz), 1.58 (m, 2H), 1.35 (m, 4H), 0.90 (m, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 149.28, 142.97, 139.89, 130.92, 120.52, 116.97, 114.97, 35.26, 31.35, 31.08, 22.51, 14.02

IR (neat film, cm^{-1}): 3391, 2929, 1609, 1514, 1279, 1112

HRMS (EC-CI): calcd. for $C_{11}H_{15}OF$ $[M+H]^+$ 182.1107, found 182.1106



Chlorophenols 350a and 350b: Prepared following General Procedure B using 4-butyl chlorobenzene (100.0 mg, 0.59 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (406.0 mg, 1.48 mmol, 2.50 eq., 85%), and HFIP (5.9 mL) at 75 °C for 36 hrs. The crude brown foam was purified by silica gel chromatography; 1% Et_2O in CH_2Cl_2 and hexane (1:1) to afford the chlorophenols **350a** and **350b** (64.4 mg, 0.35 mmol, 59%, **350a : 350b** = 4 : 1) as a yellow oil.

$\mathbf{R_f}$ = 0.57 (3% Et_2O in 49% hexane and 48% CH_2Cl_2);

Major Isomer (350a):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.02 (d, 1H, J = 8.2 Hz), 6.5 (dd, 1H, J = 2.1, 8.2 Hz), 6.78 (d, 1H, J = 2.1 Hz), 4.69 (bs, 1H), 2.56 (t, 2H, J = 7.5 Hz), 1.57 (ddd, 2H, J = 7.5 Hz), 1.37 (dddd, 2H, J = 7.5 Hz), 0.94 (t, 3H, J = 7.5 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.20, 132.00, 131.18, 127.44, 121.10, 115.76, 31.98, 29.38, 22.70, 14.16

IR (neat film, cm^{-1}): 3412, 2957, 2930, 1603, 1588, 1413

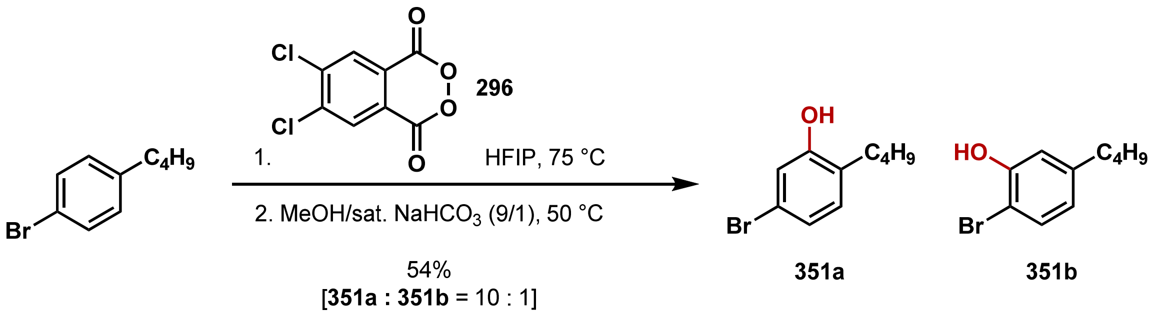
HRMS (EC-CI): calcd. for $C_{10}H_{13}OCl$ $[M+H]^+$ 184.0655, found 184.0653.

Minor Regioisomer (350b):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.19 (d, 1H, J = 8.2 Hz), 6.86 – 6.83 (m, 1H), 6.69 (dd, 1H, J = 2.05, 8.2 Hz), 5.43 (bs, 1H), 2.54 (t, 2H, J = 7.5 Hz), 1.57 (ddd, 2H, J = 7.5 Hz), 1.37 (dddd, 2H, J = 7.5 Hz), 0.92 (t, 3H, J = 7.5 Hz)

IR (neat film, cm^{-1}): 3412, 2957, 2930, 1603, 1588, 1413

HRMS (EC-CI): calcd. for $C_{10}H_{13}OCl$ $[M+H]^+$ 184.0655, found 184.0653.



Bromophenols 351a and 351b: Prepared following General Procedure B using 4-butyl bromobenzene (100.0 mg, 0.47 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (321.0 mg, 1.17 mmol, 2.50 eq., 85%), and HFIP (4.7 mL) at 75 °C for 36 hrs. The crude brown foam was purified by silica gel chromatography; 1% Et_2O in CH_2Cl_2 and hexane (1:1) to afford the bromophenols **351a** and **351b** (58.3 mg, 0.25 mmol, 54%, **351a : 351b** = 10 : 1) as a dark yellow oil.

$\mathbf{R_f}$ = 0.57 (3% Et_2O in 49% hexane and 48% CH_2Cl_2)

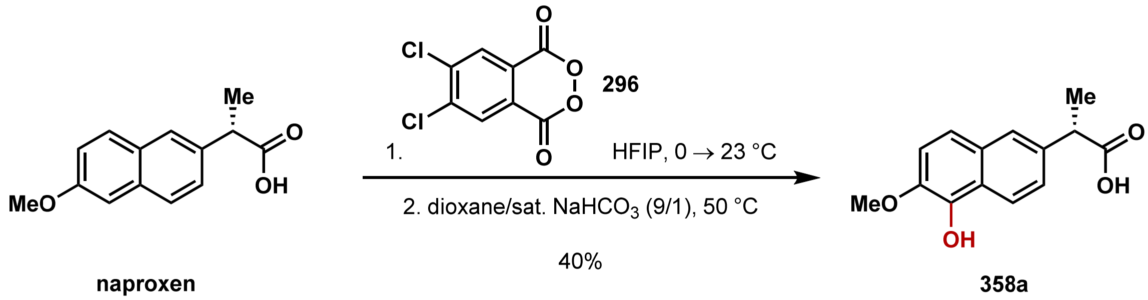
^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.98 (d, 1H, J = 1.7 Hz), 6.97 (bs, 1H), 6.93 (d, 1H, J = 1.7 Hz), 4.72 (bs, 1H), 2.55 (t, 2H, J = 7.5 Hz), 1.60 – 1.53 (m, 2H), 1.42 – 1.33 (dddd, 2H, J = 7.5 Hz), 0.93 (t, 3H, J = 7.5 Hz)

^{1}H-NMR (400 MHz, C_6D_6): δ 6.88 (dd, 1H, J = 2.1, 8.2 Hz), 6.58 (d, 1H, J = 8.2 Hz), 6.29 (bs, 1H), 3.90 (bs, 1H), 2.36 (t, 2H, J = 7.9 Hz), 1.40 (ddd, 2H, J = 7.9 Hz), 1.17 (dddd, 2H, J = 7.5 Hz), 0.80 (t, 3H, J = 7.5 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.45, 131.56, 128.04, 123.99, 119.63, 118.59, 31.91, 29.45, 22.70, 14.17

IR (neat film, cm^{-1}): 3390, 2957, 2928, 1408, 1123

HRMS (EC-CI): calcd. for $C_{10}H_{12}OBr$ $[M+H]^+$ 228.0150, found 228.0149.



Acid 358a: Prepared following General Procedure A using naproxen (100 mg, 0.43 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (153.0 mg, 0.57 mmol, 1.30 eq.), and HFIP (4.3 mL) at 0 °C gradually warming to 23 °C over 24 hrs. After removal of the HFIP by continuous positive flow of nitrogen, the mixed phthalate diacid was placed under an atmosphere of argon. The crude brown solid was suspended in a deoxygenated mixture composed of dioxane and aqueous saturated $NaHCO_3$ (9:1, 2.1 mL) and placed in an oil heated to 50 °C. After 20 minutes the brown solution was poured into an aqueous phosphate buffer (20 mL, 0.2 M, pH = 2) and adjusted to pH = 4. EtOAc (20 mL) was added and the layers were partitioned. The residual organics were extracted from the aqueous layer with EtOAc (2 x 20 ml), combined, dried over solid Na_2SO_4, filtered, and concentrated. The crude brown foam was purified by silica gel chromatography; 40% Et_2O and 1% acetic acid in hexane to afford the phenol **358a** (43.0 mg, 0.18 mmol, 40%) as a colorless solid that decomposes in air.

$\mathbf{R_f}$ = 0.09 (40% Et_2O and 1% AcOH in hexane)

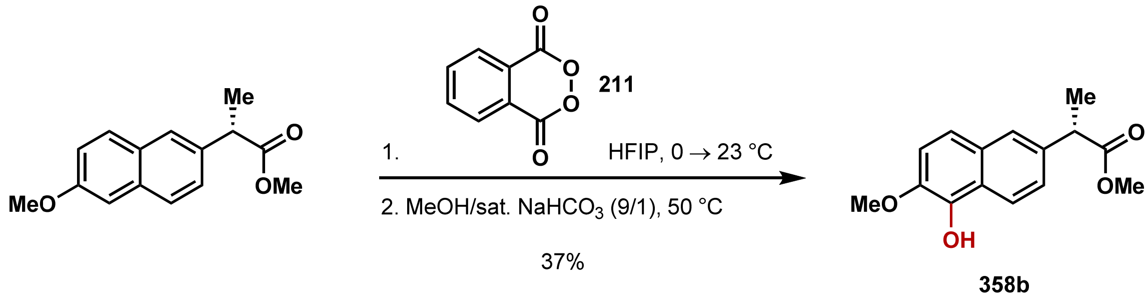
^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.11 (d, 1H, *J* = 8.9 Hz), 7.66 (d, 1H, *J* = 1.4 Hz), 7.41 (dd, 1H, *J* = 8.9, 1.7 Hz), 7.36 (d, 1H, *J* = 8.9 Hz), 7.24 (d, 1H, *J* = 8.9 Hz), 4.00 (s, 3H), 3.9 (q, 1H, J = 7.2 Hz), 1.59 (d, 3H, *J* = 7.2 Hz)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 179.5, 141.3, 139.7, 135.5, 129.5, 125.9, 125.2, 123.2, 121.9, 119.5, 113.6, 57.2, 45.2, 18.1

IR (neat film cm $^{-1}$): 3433, 2937, 1704, 1275

HRMS (EC-CI): calcd. for $C_{14}H_{14}O_4$: 246.0892, found 246.0894.

M.P. = 132 – 134 °C.



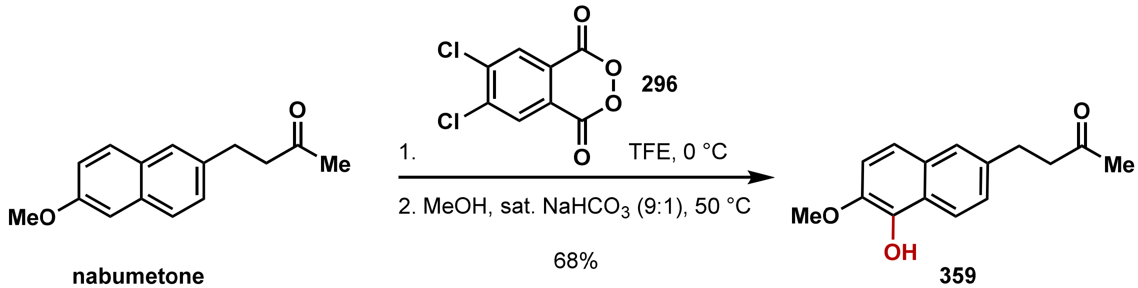
Ester 358b: Prepared following General Procedure A using the naproxen methyl ester (150.0 mg, 0.61 mmol, 1.00 eq.) which was dissolved in HFIP (6.1 mL), placed in an ice water bath cooled to 0 °C for 1 hr, and then phthaloyl peroxide (131.0 mg, 0.80 mmol, 1.30 eq.) was added over 15 minutes in six portions causing the solution to change to a dark turquoise color. After 20 minutes the HFIP was removed from the black mixture by continuous positive flow of nitrogen. The black mixture was placed under an atmosphere of nitrogen, a deoxygenated mixture of methanol and aqueous saturated $NaHCO_3$ (9:1, 6.1 mL) was added, and the black solution was placed in an oil bath heated to 50 °C. After 12 hrs the black solution was removed from the oil bath, cooled to 23 °C, diluted with an aqueous phosphate buffer (10 mL, pH = 7, 0.2 M) and EtOAc (10 mL), poured into a separatory funnel, partitioned, and the organic layer was washed with an aqueous phosphate buffer (3 x 20 mL, 0.2 M, pH = 7). Residual organics were extracted from the aqueous layer with EtOAc (3 x 20 ml), combined, dried over solid Na_2SO_4, filtered, and concentrated. The crude dark brown mixture was purified by silica gel chromatography; hexane – 10% EtOAc in hexane to afford the phenol **358b** (58.5 mg, 0.23 mmol, 37%) as an off white solid that decomposes in air.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.10 (d, 1H, *J* = 8.9 Hz), 7.63 (d, 1H, *J* = 1.7 Hz), 7.39 (dd, 1H, *J* = 1.7, 8.9 Hz), 7.36 (d, 1H, *J* = 8.9 Hz), 7.25 (d, 1H, *J* = 8.9 Hz), 5.98 (bs, 1H), 3.99 (s, 3H), 3.86 (q, 1H, *J* = 7.2 Hz), 3.66 (s, 3H), 1.57 (d, 3H, *J* = 7.2 Hz)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 175.11, 141.24, 139.71, 136.29, 129.56, 126.63, 125.24, 123.06, 121.78, 119.41, 113.54, 57.15, 52.07, 45.43, 18.50

IR (neat film cm $^{-1}$): 3434, 1731, 1594, 1475, 1263, 1072

M.P. = 78 – 79 °C.



Phenol 359: Prepared following General Procedure A: A clear colorless solution of nabumetone (250.0 mg, 1.10 mmol, 1.00 eq.) in TFE (11.0 mL) was placed in an ice water bath cooled to 0 °C for 1 hr. 4,5-dichlorophthaloyl peroxide (405.0 mg, 1.42 mmol, 1.30 eq.) was added in 8 portions over 10 minutes causing the solution to change to a dark brown mixture. After 1 hr the TFE was removed from the black mixture by continuous positive flow of nitrogen. The brown solid mixture containing the mixed phthalate ester-acid was placed under an atmosphere of nitrogen and a deoxygenated mixture composed of methanol and aqueous saturated $NaHCO_3$ (9:1, 11.0 mL) was added. The black solution was placed in an oil bath heated to 50 °C and after 2 hrs the black solution was removed from the oil bath, cooled to 23 °C, diluted with an aqueous phosphate buffer (10 mL, pH = 7, 0.2 M) and EtOAc (10 mL), poured into a separatory funnel, partitioned, and the organic layer was washed with an aqueous phosphate buffer (3 x 30 mL, pH = 7, 0.2 M). Residual organics were extracted from the aqueous layer with EtOAc (3 x 20 ml), combined, dried over solid Na_2SO_4, filtered, and concentrated. The crude dark brown foam was purified by silica gel chromatography; hexane – 30% EtOAc in hexane to afford the phenol **359** (183.0 mg, 0.75 mmol, 68%) as an off white amorphous foam that decomposes in air.

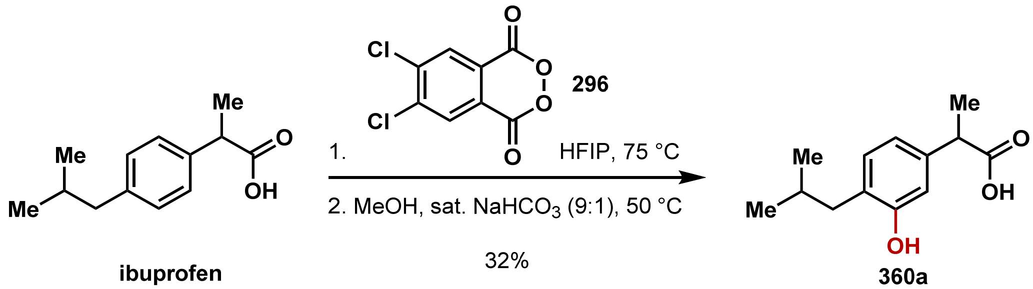
R_f = 0.14 (25% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.07 (d, 1H, J = 8.9 Hz), 7.52 (bs, 1H), 7.32 (d, 1H, J = 8.9 Hz,), 7.28 (dd, 1H, J = 8.9, 2.1 Hz), 7.23 (d, 1H, J = 8.9 Hz), 5.99 (bs, 1H), 3.99 (s, 3H), 3.03 (t, 2H, J = 7.9 Hz), 2.83 (t, 2H, J = 7.9 Hz), 2.15 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 208.1, 140.9, 139.7, 136.7, 129.7, 126.5, 125.9, 122.5, 121.5, 119.0, 113.5, 57.2, 45.1, 30.2, 29.8

IR (neat film, cm $^{-1}$): 3407, 2923, 1710, 1363, 1273

HRMS (EC-CI) calcd. for $C_{15}H_{16}O_3$: 244.1099. Found: 244.1100.



Phenol 360a: Prepared following General Procedure B using ibuprofen (50.0 mg, 0.24 mmol, 1 eq.), HFIP (0.5 mL), and 4,5-dichlorophthaloyl peroxide (164.0 mg, 0.61 mmol, 2.50 eq.) at 75 °C for 24 hrs. HFIP was removed *in vacuo* yielding a brown solid which was suspended in a deoxygenated mixture composed of methanol and aqueous saturated $NaHCO_3$ (9:1, 2.1 mL), placed in an oil bath heated to 50 °C, and after 1 hr the mixture was removed from the oil bath, cooled to 23 °C, diluted with an aqueous phosphate buffer (20 mL, pH = 2, 0.2 M) and adjusted to pH = 4. Ethyl ether (20mL) was added and the layers were partitioned. Residual organics were extracted from the aqueous layer with ether (2 x 20 mL), combined, dried over solid $MgSO_4$, and concentrated. The crude brown foam was purified by silica gel chromatography; 40% Et_2O and 1% AcOH in hexane to afford the phenol **360a** as an amorphous yellow oil (17.2 mg, 0.08 mmol, 32%).

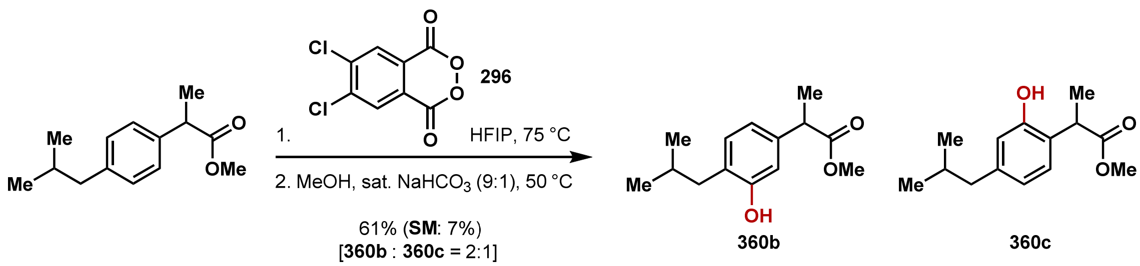
$\mathbf{R_f}$ = 0.26 (40% Et_2O and 1% AcOH in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.02 (d, 1H, J = 7.9 Hz), 6.80 (dd, 1H, J = 7.5, 1.7 Hz), 6.74 (d, 1H, J = 1.7 Hz), 3.66 (q, 1H, J = 7.2 Hz), 2.44 (d, 2H, J = 7.5 Hz), 1.91 (dddd, 1H, J = 6.8 Hz), 1.48 (d, 3H, J = 7.2 Hz), 0.92 (d, 6H, J = 6.8 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 179.9, 153.7, 138.7, 131.4, 126.7, 119.8, 114.3, 44.7, 39.0, 28.8, 22.5, 18.0

IR (neat film, cm^{-1}): 3399, 2955, 1707

HRMS (EC-CI): calcd. For $C_{13}H_{18}O_3$: 222.1256. Found: 222.1255.



Phenols 360b and 360c: Prepared following General Procedure B using ibuprofen methyl ester (300.0 mg, 1.36 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (747.0 mg, 2.72 mmol, 2.50 eq., 85%), and HFIP (13.6 mL) at 75 °C for 24 hrs. The crude brown tar was purified by silica gel chromatography; hexane – 4% EtOAc in hexane to provide the starting ester (22.3 mg, 0.10 mmol, 7%) as a clear colorless oil and the phenols as a mixture which were then further purified by silica gel chromatography; 1 - 2 % Et_2O in CH_2Cl_2 and hexane (1:1) to afford the phenol **360b** (130.0 mg, 0.55 mmol, 40%) and **360c** (66.0 mg, 0.28 mmol, 21%) as pale yellow amorphous oils.

Major Isomer (360b):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.01 (d, 1H, *J* = 7.7 Hz), 6.78 (dd, 1H, *J* = 1.6, 7.7 Hz), 6.75 (d, 1H, *J* = 1.6 Hz), 5.22 (bs, 1H), 3.67 (s, 1H), 3.65 (q, 1H, *J* = 7.2 Hz), 2.45 (d, 2H, *J* = 7.2 Hz), 1.92 (dddd, 1H, *J* = 6.7 Hz), 1.47 (d, 3H, *J* = 7.2 Hz), 0.92 (d, 6H, *J* = 6.7 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.46, 153.96, 139.35, 131.30, 126.57, 119.56, 114.04, 52.13, 45.00, 38.99, 28.75, 22.53, 18.51

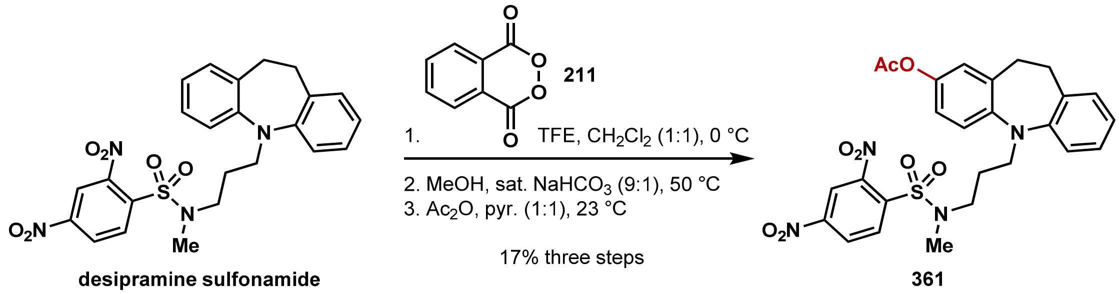
IR (neat film, cm^{-1}): 3401, 2953, 2360, 2342, 1715

Minor Isomer (361b):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.43 (bs, 1H), 6.98 (d, 1H, *J* = 7.9 Hz), 6.71 (d, 1H, *J* = 1.7 Hz), 6.67 (dd, 1H, *J* = 1.7, 7.9 Hz), 3.84 (q, 1H, *J* = 7.2 Hz) 3.73 (s, 1H), 2.39 (d, 2H, *J* = 7.2 Hz), 1.84 (dddd, 1H, *J* = 6.8 Hz), 1.54 (d, 3H, *J* = 7.2 Hz), 0.89 (d, 6H, *J* = 6.8 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 177.57, 154.30, 142.84, 128.48, 122.92, 121.66, 118.33, 52.65, 44.95, 42.03, 30.01, 22.42, 16.57

IR (neat film, cm^{-1}): 3401, 2953, 2360, 2342, 1734



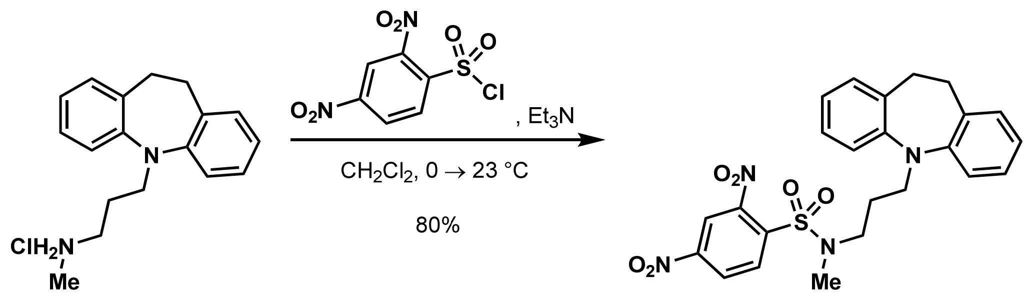
Acetate 361: Prepared following General Procedure A: A clear yellow solution of the desipramine dinitrosulfonamide (95.0 mg, 0.19 mmol, 1.00 eq.) in TFE and CH_2Cl_2 (4.0 mL, 1:1) was placed in an ice water bath cooled to 0 °C for 1 hr. Phthaloyl peroxide (40.0 mg, 0.25 mmol, 1.30 eq.) was added in 5 portions over 5 minutes causing the solution to change to a dark black mixture. After 1 hr the TFE and CH_2Cl_2 were removed from the black mixture by continuous positive flow of nitrogen. The black solid tar containing the mixed phthalate ester-acid was placed under an atmosphere of nitrogen and a deoxygenated mixture composed of methanol and aqueous saturated $NaHCO_3$ (9:1, 4.0 mL) was added. The black solution was placed in an oil bath heated to 50 °C. After 12 hrs the black solution was removed from the oil bath, cooled to 23 °C, diluted with an aqueous phosphate buffer (10 mL, pH = 7, 0.2 M) and EtOAc (10 mL), poured into a separatory funnel, partitioned, and the organic layer was washed with an aqueous phosphate buffer (3 x 30 mL, pH = 7, 0.2 M). Residual organics were extracted from the aqueous layer with EtOAc (3 x 20 ml), combined, dried over solid Na_2SO_4, filtered, and concentrated. The crude black tar was dissolved in CH_2Cl_2 (3.0 mL), pyridine (0.5 mL) and acetic anhydride (0.5 mL) were added sequentially, and the brown solution was allowed to stir at 23 °C. After 24 hrs the dark brown solution was diluted with an aqueous phosphate buffer (10 mL, pH = 4, 0.2 M) and EtOAc (10 mL), poured into a separatory funnel, partitioned, and the organic layer was washed with an aqueous phosphate buffer (2 x 10 mL, pH = 7, 0.2 M). Residual organics were extracted from the aqueous layer with EtOAc (2 x 10 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude dark brown foam was purified by silica gel chromatography; hexane – 20% EtOAc in hexane to afford the acetate **361** (18.2 mg, 0.03 mmol, 17%) as a golden yellow amorphous foam.

$\mathbf{R_f}$ = 0.66 (50% EtOAc in hexane)

^{1}**H-NMR** (400 MHz, $CDCl_3$): δ 8.38 (d, 1H, J = 2.4 Hz), 8.34 (dd, 1H, J = 2.4 Hz, 8.6 Hz), 8.03 (d, 1H, J = 8.6 Hz), 7.11 – 7.05 (m, 3H), 6.98 (t, 2H, J = 7.4 Hz), 6.90 (dd, 1H, J = 2.3 Hz, 7.4 Hz), 6.84 (dt, 1H, J = 1.1 Hz, 7.4 Hz), 3.88 – 3.82 (m, 1H), 3.60 – 3.48 (m, 2H), 3.35 – 3.24 (m, 3H), 2.93 – 2.87 (m, 1H), 2.85 (s, 3H), 2.76 (dt, 1H, J = 4.0 Hz, 12.9 Hz), 2.33 (s, 3H), 1.74 (ddd, 2H, J = 7.3 Hz)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.98, 149.49, 148.00, 146.33, 145.11, 142.04, 139.56, 138.12, 132.41, 131.54, 130.38, 126.42, 126.00, 125.67, 125.57, 121.77, 121.36, 119.93, 119.61, 49.21, 48.46, 34.48, 33.53, 31.05, 26.08, 21.21
IR (neat film, cm^{-1}): 1765, 1553, 1537, 1475, 1367, 1351, 1200, 1165, 750, 736

HRMS (EC-CI): calc'd. for $C_{26}H_{27}N_4O_8S$ $[M+H]^+$: 555.1550. Found: 555.1542.



desipramine hydrochloride **desipramine sulfonamide**

A solution of desipramine hydrochloride (200.0 mg, 0.69 mmol, 1.00 eq.) in CH_2Cl_2 (6.9 mL) was placed in an ice water bath cooled to 0 °C for 20 minutes. Freshly distilled triethylamine (0.15 g, 0.2 mL, 1.52 mmol, 2.20 eq.) was added followed by solid dinitrosulfonyl chloride (185.0 mg, 0.69 mmol, 1.00 eq.) under a positive flow of nitrogen. The golden yellow solution was warmed gradually to 23 °C over 12 hrs, diluted with an aqueous phosphate buffer (10 mL, pH = 4, 0.2 M) and EtOAc (20 mL), poured into a separatory funnel, partitioned, and the aqueous layer was washed with an aqueous phosphate buffer (2 x 10 mL, pH = 4, 0.2 M). Residual organics were extracted from the aqueous layer with EtOAc (2 x 10 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude orange mixture was purified by silica gel chromatography; 10% EtOAc in hexane to afford the desipramine sulfonamide as a dark yellow-orange solid (267.0 mg, 0.55 mmol, 80%).

$\mathbf{R_f}$ = 0.66 (50% EtOAc in hexane)

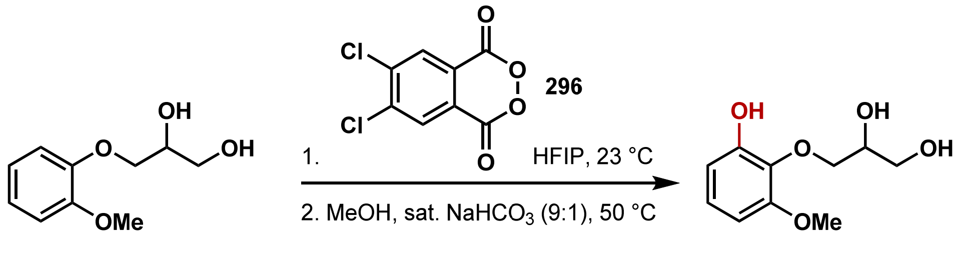
^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.34 (d, 1H, *J* = 2.0 Hz), 8.26 (dd, 1H, *J* = 2.0 Hz, 8.9 Hz), 8.0 (d, 1H, *J* = 8.9 Hz), 7.09 (d, 3H, *J* = 7.5 Hz), 6.98 (d, 2H, *J* = 7.5 Hz), 6.90 (t, 1H, *J* = 7.5 Hz), 3.71 (t, 2H, *J* = 6.1 Hz), 3.34 (t, 2H, *J* = 6.7 Hz), 3.14 (s, 4H), 2.87 (s, 3H), 1.80 (m, 2H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 149.49, 147.70, 138.14, 134.18, 132.30, 130.03, 126.53, 126.03, 122.97, 119.62, 119.56, 48.19, 46.87, 34.56, 32.04, 25.43

IR (neat film, cm^{-1}): 1603, 1573, 1351, 1163, 751

HRMS (EC-CI): calc'd. for $C_{24}H_{25}N_4O_6S$ $[M+H]^+$: 497.1495. Found: 497.1490.

M.P.: 52 – 56 °C



Phenol 362: Prepared following General Procedure A using (±)-guaifenesin (75.0 mg, 0.38 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (133.0 mg, 0.49 mmol, 1.30 eq.) in HFIP (3.8 mL) at 23 °C for 24 hrs. The crude dark brown foam was purified by silica gel chromatography; 50% EtOAc in hexane to afford the phenol **362** as an opaque colorless oil (27.9 mg, 0.13 mmol, 35%).

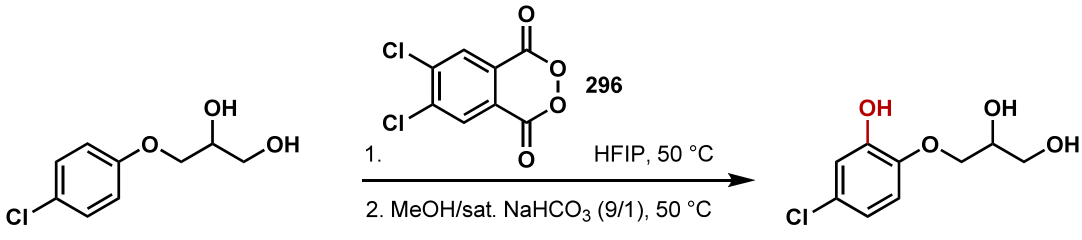
$\mathbf{R_f}$ = 0.55 (100% EtOAc)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.94 (t, 1H, *J* = 8.3 Hz), 6.59 (dd, 1H, *J* = 1.2, 8.3 Hz), 6.45 (dd, 1H, *J* = 1.2, 8.3 Hz), 4.16 (dd, 1H, *J* = 2.7, 10.3 Hz), 4.04 (m, 1H), 4.01 (t, 1H, *J* = 4.2 Hz), 3.85 (s, 3H), 3.82 (d, 1H, *J* = 3.7 Hz), 3.77 (m, 1H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 152.92, 150.38, 135.14, 124.62, 109.22, 103.45, 74.89, 70.76, 63.69, 55.83.

IR (neat film, cm^{-1}): 3371, 1236, 1201.

HRMS (EC-CI): calc'd for $C_{10}H_{14}O_5Na$ $[M+Na]^+$: 237.07334. Found: 237.07352.



Triol 363: Prepared following General Procedure A using chlorphenesin (95.0 mg, 0.47 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (165.0 mg, 0.61 mmol, 1.30 eq., 86%), and HFIP (4.7 mL) at 50 °C for 24 hrs. The crude brown solid was purified by silica gel chromatography; 5 - 50% acetone in hexane to provide the triol **363** (53.0 mg, 0.24 mmol, 52%) as a pale yellow foam and chlorphenesin (11.0 mg, 0.05 mmol, 12%) as a white solid.

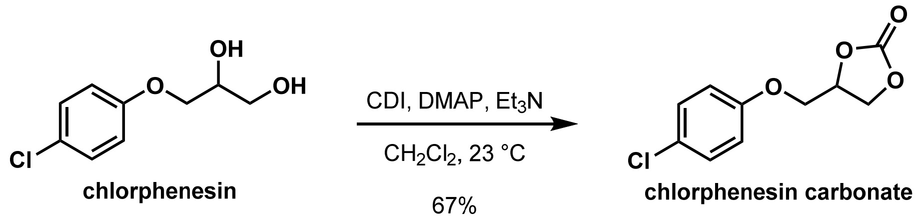
$\mathbf{R_f}$ = 0.47 (50% acetone in hexane)

^{1}H-NMR (400 MHz, C_3D_6O): δ 8.21 (bs, 1H), 6.98 (d, 1H, *J* = 8.6 Hz), 6.85 (d, 1H, *J* = 2.4 Hz), 6.79 (dd, 1H, *J* = 2.4, 8.6 Hz), 4.39 (bs, 1H), 4.14 (d, 1H, *J* = 5.8 Hz), 4.01 (m, 2H), 3.84 (t, 1H, *J* = 5.4 Hz), 3.67 (t, 2H, *J* = 5.4 Hz)

^{13}C-NMR (125 MHz, C_3D_6O): δ 148.14, 145.93, 125.81, 119.06, 115.47, 114.63, 71.43, 70.44, 62.88

IR (neat film, cm^{-1}): 3410, 2935, 1634, 1592, 1504, 1268, 1215

HRMS (EC-ESI): calc'd. for $C_9H_{11}ClNaO_4$ $[M+Na]^+$ 241.0238, found 241.0234.



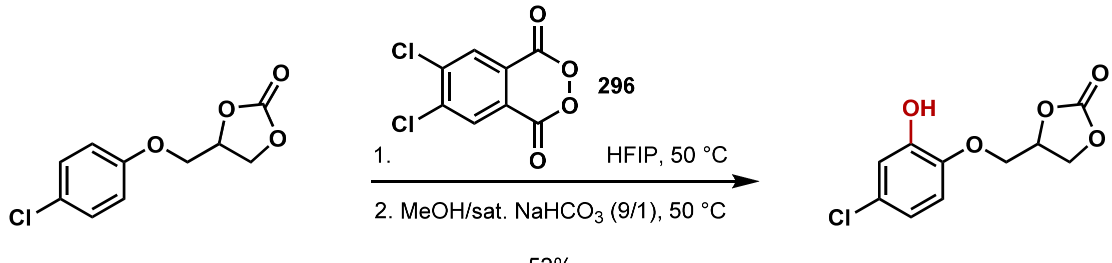
Chlorphenesin carbonate: To a white solid mixture of chlorphenesin (0.40 g, 1.97 mmol, 1.00 eq.), 1,1'-carbonyldiimidazole (0.48 g, 3.00 mmol, 1.50 eq.), and 4-*N,N'*-dimethylaminopyridine (0.01 g, 0.10 mmol, 0.05 eq.) in CH_2Cl_2 (19.7 mL) was added freshly distilled Et_3N (1.00 g, 1.4 mL, 9.87 mmol, 5.00 eq.). After 18 hrs at 23 °C the pale yellow homogeneous solution was diluted with Et_2O (30 mL) and residual CDI, DMAP, and Et_3N were quenched with an aqueous phosphate buffer (50 mL, pH = 7, 0.2 M), poured into a separatory funnel, and partitioned. The residual organics were extracted from the aqueous layer with Et_2O (4 x 20 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude off white solid was purified by silica gel chromatography; 5 – 25% acetone in hexane to afford the chlorphenesin carbonate as a white solid (0.30 g, 1.31 mmol, 67%). The spectra of the title compound matches that for carbonate.[41]

$\mathbf{R_f}$ = (40% acetone in hexane)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.27 (d, 2H, J = 8.9 Hz), 6.85 (d, 2H, J = 8.9 Hz), 5.02 (m, 1H), 4.62 (t, 1H, J = 8.6 Hz), 4.52 (dd, 1H, J = 5.8, 8.6 Hz), 4.22 (dd, 1H, J = 4.1, 10.6 Hz), 4.12 (dd, 1H, J = 3.4, 10.6 Hz)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 156.32, 154.49, 129.60, 127.04, 115.92, 73.90, 67.25, 66.08

IR (neat film, cm^{-1}) 1790, 1492, 1243, 1169



Phenol 364: Prepared following General Procedure A using chlorphenesin carbonate (50.0 mg, 0.22 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (138.0 mg, 0.51 mmol, 2.50 eq., 86%), and HFIP (2.0 mL) at 50 °C for 24 hrs. The crude brown foam was purified by silica gel chromatography; 5 - 30% acetone in hexane to provide the phenol **364** (28.0 mg, 0.11 mmol, 52%) as an off white solid.

$\mathbf{R_f}$ = 0.46 (40% acetone in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.98 (d, 1H, *J* = 2.4 Hz), 6.84 (dd, 1H, *J* = 2.4, 8.6 Hz), 6.78 (d, 1H, *J* = 8.6 Hz), 5.48 (bs, 1H), 5.07 (m, 1H), 4.66 (dd, 1H, *J* = 7.8, 8.9 Hz), 4.47 (dd, 1H, *J* = 5.8, 8.9 Hz), 4.30 (dd, 1H, *J* = 3.4, 10.9 Hz), 4.20 (dd, 1H, *J* = 4.4, 10.9 Hz)

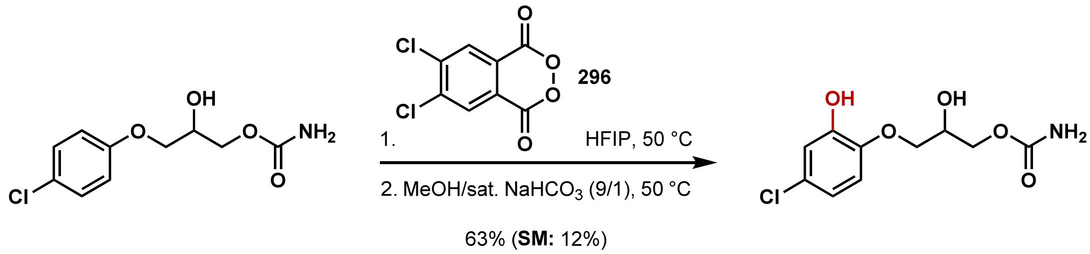
^{1}H-NMR (400 MHz, C_3D_6O): δ 8.39 (bs, 1H), 7.01 (d, 1H, *J* = 8.7 Hz), 6.88 (d, 1H, *J* = 2.6 Hz), 6.80 (dd, 1H, *J* = 2.6, 8.7 Hz), 5.20 (m, 1H), 4.71 (t, 1H, *J* = 8.4 Hz), 4.56 (dd, 1H, *J* = 6.9, 8.5 Hz), 4.39 (dd, 1H, *J* = 3.4, 11.2 Hz), 4.33 (dd, 1H, *J* = 4.7, 11.2 Hz)

^{13}C-NMR (100 MHz, C_3D_6O): δ 155.48, 148.85, 146.29, 127.20, 120.04, 116.79, 115.78, 75.67, 69.51, 66.69

IR (neat film, cm^{-1}): 3400, 2922, 1783, 1634

HRMS (EC-CI): calcd. for $C_{10}H_9ClO_5$ [M], 244.0139, found 244.0141

M.P. = 122 - 125°C.



chlorphenesin carbamate **365**

Carbamate 365: Prepared following General Procedure A using chlorphenesin carbamate (85.0 mg, 0.35 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (122.0 mg, 0.45 mmol, 1.30 eq., 86%), and HFIP (3.5 mL) at 50 °C for 24 hrs. The crude brown solid mixture was purified by silica gel chromatography; 5 - 35% acetone in hexane to afford the carbamate **365** (57.0 mg, 0.22 mmol, 63%) as an off-white solid and the starting chlorphenesin carbamate (10.2 mg, 0.04 mmol, 12%).

$\mathbf{R_f}$ = 0.45 (50% acetone in hexane)

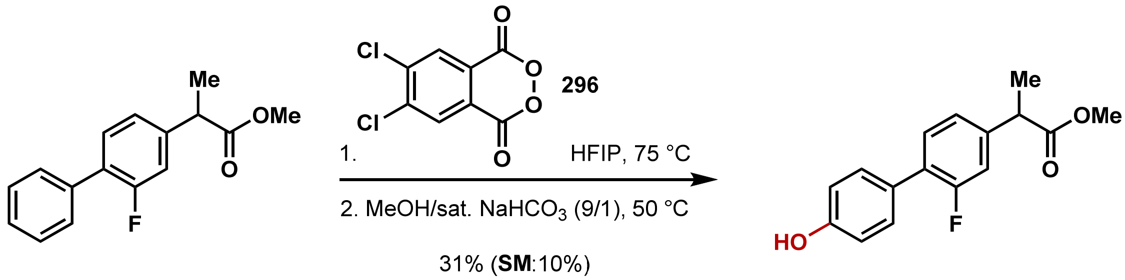
^{1}H-NMR (400 MHz, CD_3OD): δ 6.88 (d, 1H, *J* = 8.6 Hz), 6.80 (d, 1H, *J* = 2.7 Hz), 6.74 (dd, 1H, *J* = 2.7, 8.6 Hz), 4.16 (m, 3H), 4.06 (m, 1H), 3.98 (m, 1H)

^{13}C-NMR (100 MHz, C_3D_6O): δ 158.25, 147.58, 145.60, 125.98, 118.86, 115.51, 113.82, 70.04, 68.05, 64.92

IR (neat film, cm^{-1}): 3369, 1706, 1501

HRMS (EC-ESI): calc'd. for $C_{10}H_{12}ClNNaO_5$ $[M+Na]^+$ 284.0296, found 284.0293

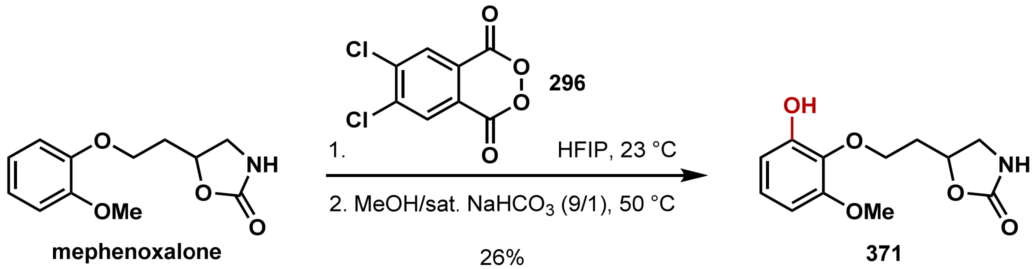
M.P. = 124 - 127°C.



flurbiprofen methyl ester **366**

Phenol 366: Prepared following General Procedure B using flurbiprofen methyl ester (210.0 mg, 0.81 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (446.0 mg, 1.63 mmol, 2.00 eq., 85%), and HFIP (8.1 mL) at 75 °C for 24 hrs. The crude dark yellow solid mixture was purified by silica gel chromatography; 1% 1,4-dioxane in benzene to afford the phenol **366** (69.0 mg, 0.25 mmol, 31%) as a pale yellow foam and the starting flurbiprofen (20.9 mg, 0.08 mmol, 10%). The spectral data of the title compound matches that for the phenol **366**.[42,43]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.42 (dd, 2H, J = 1.5, 7.1 Hz), 7.34 (t, 1H, J = 7.4 Hz), 7.11 (m, 2H), 6.89 (d, 2H, J = 8.6 Hz), 4.99 (bs, 1H), 3.75 (q, 2H, J = 7.0 Hz), 3.70 (s, 3H), 1.53 (d, 3H, J = 7.0 Hz)[42,43]



Phenol 371: Prepared following General Procedure B using (±)-mephenoxalone (50.0 mg, 0.22 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (67.8 mg, 0.29 mmol, 1.30 eq.), and HFIP (2.2 mL). The crude dark brown foam was purified by silica gel chromatography; 50% EtOAc in hexane to afford phenol **371** as an opaque pale yellow oil (13.9 mg, 0.06 mmol, 26%).

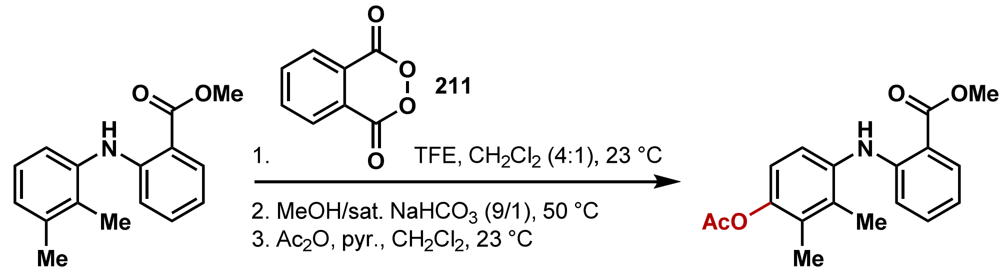
R_f = 0.47 (100% EtOAc)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.95 (t, 1H, *J* = 8.2 Hz), 6.61 (dd, 1H, *J* = 1.6, 8.2 Hz), 6.46 (dd,1H, *J* = 1.2, 8.2 Hz), 6.02 (s, 1H), 5.45 (s, 1H), 4.93 (m, 1H), 4.29 (dd, 1H, *J* = 3.5, 11.0 Hz), 4.14 (dd, 1H *J* = 5.9, 11.0 Hz), 3.84 (s, 3H), 3.74 (t, 1H, *J* = 8.6 Hz), 3.58 (t, 1H, *J* = 6.6 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 158.94, 152.40, 149.72, 133.87, 124.73, 108.77, 103.77, 74.76, 73.13, 55.81, 41.90

IR (neat film, cm^{-1}): 3346, 1733, 1253, 1198

HRMS (EC-CI): calc'd for $C_{11}H_{13}NO_5Na$ $[M+Na]^+$: 262.06859. Found: 262.06826.



Acetate 367: Prepared using General Procedure A: A clear colorless solution of mefenamic methyl ester (50.0 mg, 0.20 mmol, 1.00 eq.) in TFE and CH_2Cl_2 (4.0 mL, 4:1) was placed in an ice water bath cooled to 0 °C for 30 minutes. Phthaloyl peroxide (71.0 mg, 0.43 mmol, 2.20 eq.) was added in 5 portions over 5 minutes causing the solution to change to a dark black mixture. The mixture was allowed to warm gradually to 23 °C over 12 hrs following which the TFE and CH_2Cl_2 were removed from the black mixture by continuous positive flow of nitrogen. The black solid tar was placed under an atmosphere of nitrogen and a deoxygenated mixture composed of methanol and aqueous saturated $NaHCO_3$ (9:1, 4.0 mL) was added. The black solution was placed in an oil bath heated to 50 °C. After 12 hrs the black solution was removed from the oil bath, cooled to 23 °C, diluted with an aqueous phosphate buffer (10 mL, pH = 7, 0.2 M) and EtOAc (10 mL), poured into a separatory funnel, partitioned, and the organic layer was washed with an aqueous phosphate buffer (3 x 30 mL, pH = 7, 0.2 M). Residual organics were extracted from the aqueous layer with EtOAc (3 x 20 mL), combined, dried over solid Na_2SO_4, decanted, and concentrated. The crude black tar was dissolved in CH_2Cl_2 (4.0 mL) upon which pyridine (155.0 mg, 0.2 mL, 1.96 mmol, 10.0 eq.) and acetic anhydride (60.0 mg, 0.1 mL, 0.59 mmol, 3.00 eq.) were added sequentially. After 24 hrs at 23 °C the dark brown solution was diluted with an aqueous phosphate buffer (10 mL, pH = 4, 0.2 M) and EtOAc (10 mL), poured into a separatory funnel, partitioned, and the organic layer was washed with an aqueous phosphate buffer (2 x 10 mL, pH = 7, 0.2 M). Residual organics were extracted from the aqueous layer with EtOAc (2 x 10 mL), dried over solid Na_2SO_4, decanted, and concentrated. The crude dark brown foam was purified by silica gel chromatography; hexane – 2% EtOAc in hexane to afford the acetate **367** (12.3 mg, 0.04 mmol, 20%) as a golden yellow amorphous foam.

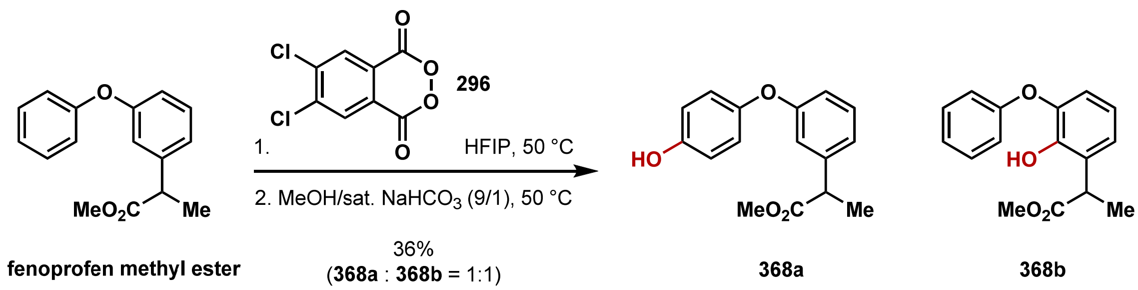
$\mathbf{R_f}$ = 0.59 (40% EtOAc in hexane)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.19 (bs, 1H), 7.95 (dd, 1H, *J* = 1.4, 7.1 Hz), 7.24 (m, 1H), 7.16 (d, 1H, *J* = 8.3 Hz), 6.88 (d, 1H, *J* = 8.3 Hz), 6.71 (dd, 1H, *J* = 1.1, 8.3 Hz), 6.66 (dt, 1H, *J* = 1.2, 5.9 Hz), 3.91 (s, 3H), 2.34 (s, 3H), 2.20 (s, 3H), 2.13 (s, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.56, 169.11, 149.44, 146.53, 136.61, 134.60, 134.21, 134.46, 130.05, 123.90, 119.75, 116.19, 113.67, 110.81, 51.69, 20.86, 14.63, 13.30

IR (neat film, cm^{-1}): 2918, 2360, 2340, 1760, 1703, 1252, 1195, 1090

HRMS (EC-CI): calcd. for $C_{17}H_{16}NO_3$ $[M+H]^+$ 282.1130, found 282.1131.



Phenols 368a and **368b**: Prepared following General Procedure A using fenoprofen methyl ester (128.0 mg, 0.50 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (181.0 mg, 0.65 mmol, 1.30 eq.), and HFIP (5.0 mL) at 50 °C for 24 hrs. The crude orange foam was purified by silica gel chromatography; hexane – 12% EtOAc in hexane to afford the phenol **368a** as a white solid (24.0 mg, 0.09 mmol, 18%) and phenol **368b** as a pale yellow foam (24.2 mg, 0.09 mmol, 18%).

Phenol 368a:

$\mathbf{R_f}$ = 0.56 (30% EtOAc in hexane)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.25 (m, 3H), 6.97 (d, 1H, *J* = 7.2 Hz), 6.92 (d, 2H, *J* = 8.8 Hz), 6.91 (bs, 1H), 6.81 (d, 2H, *J* = 8.8 Hz), 3.67 (q, 1H, *J* = 7.2 Hz), 1.47 (d, 3H, *J* = 7.2 Hz)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 175.05, 158.70, 152.03, 149.75, 142.22, 129.74, 121.47, 121.07, 116.83, 116.33, 115.97, 52.20, 45.30, 18.43

IR (neat film, cm^{-1}): 3411, 2922, 1732, 1587, 1471, 1266, 1215

HRMS (EC-CI): calcd. for $C_{16}H_{16}O_4$ [M] 272.1049, found 272.1049.

M.P. = 102 – 105 °C

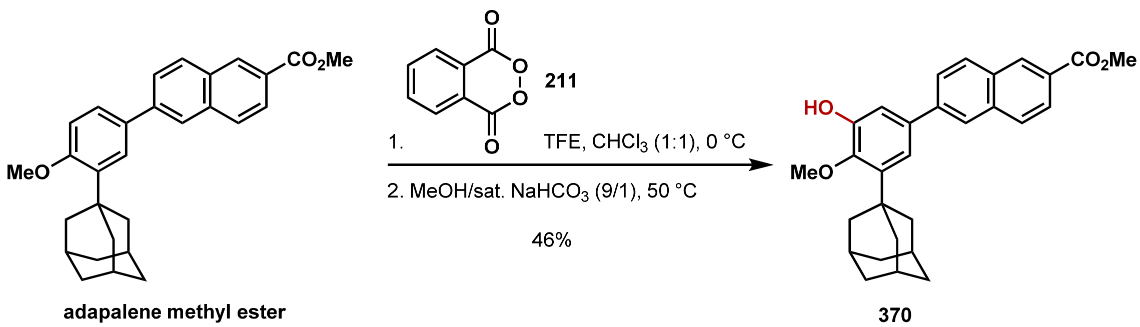
Phenol 368b:

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.35 (dd, 2H, *J* = 1.2, 7.2 Hz), 7.13 (dt, 1H, *J* = 1.0, 7.2 Hz), 7.04 (m, 2H), 6.99 (dd, 1H, *J* = 2.0, 7.2 Hz), 6.83 – 6.79 (m, 2H), 5.99 (bs, 1H), 4.12 (q, 1H, *J* = 7.1 Hz), 3.71 (s, 3H), 1.53 (d, 3H, *J* = 7.1 Hz)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 175.36, 156.57, 145.01, 143.86, 129.87, 128.21, 123.74, 123.12, 120.13, 118.32, 117.07, 52.14, 39.32, 17.24

IR (neat film, cm^{-1}): 3411, 2922, 1732, 1587, 1471, 1266, 1215

HRMS (EC-CI): calcd. for $C_{16}H_{16}O_4$ [M] 272.1049, found 272.1050.



Phenol 370: Prepared using General Procedure A: A clear colorless solution of adapalene methyl ester (100.0 mg, 0.23 mmol, 1.00 eq.) in TFE and $CHCl_3$ (9.4 mL, 1:1) was placed in an ice water bath cooled to 0 °C for 1 hr. Phthaloyl peroxide (46.0 mg, 0.28 mmol, 1.20 eq.) was added in 10 portions over 10 minutes changing the colorless solution to a dark brown mixture. After 2 hrs the TFE and $CHCl_3$ were removed from the brown mixture by continuous positive flow of nitrogen. The black solid containing the mixed phthalate ester-acid was placed under an atmosphere of nitrogen and a deoxygenated mixture composed of methanol and aqueous saturated $NaHCO_3$ (9:1, 4.0 mL) was added. The brown solution was placed in an oil bath heated to 50 °C. After 12 hrs the brown solution was removed from the oil bath, cooled to 23 °C, diluted with an aqueous phosphate buffer (10 mL, pH = 7, 0.2 M) and EtOAc (10 mL), poured into a separatory funnel, partitioned, and the organic layer was washed with an aqueous phosphate buffer (3 x 30 mL, pH = 7, 0.2 M). Residual organics were extracted from the aqueous layer with EtOAc (3 x 20 mL), combined, dried over solid Na_2SO_4, filtered, and concentrated. The crude dark brown foam was purified by silica gel chromatography; hexane – 20% EtOAc in hexane and then purified again by silica gel chromatography; 12% 1,4-dioxane in hexane to afford the phenol **370** as a white solid (48.0 mg, 0.11 mmol, 46%).

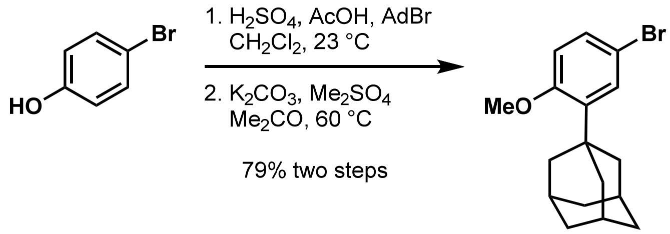
$\mathbf{R_f}$ = 0.78 (40% 1,4-dioxane in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.07 (d, 1H, J = 8.6 Hz), 8.00 (s, 1H), 7.98 (d, 1H, J = 8.6 Hz), 7.91 (d, 1H, J = 8.6 Hz), 7.76 (d, 1H, J = 8.6 Hz), 7.20 (d, 1H, 2.0 Hz), 5.41 (bs, 1H), 3.99 (s, 3H), 3.90 (s, 3H), 2.15 (bs, 7H), 2.12 (bs, 2H), 1.81 (bs, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.31, 149.96, 147.28, 143.88, 140.97, 136.45, 135.79, 131.50, 130.82, 129.73, 128.33, 127.16, 126.42, 125.25, 118.24, 113.35, 61.36, 52.25, 41.78, 37.65, 36.91, 29.70, 29.10

IR (neat film, cm^{-1}): 3445, 1656

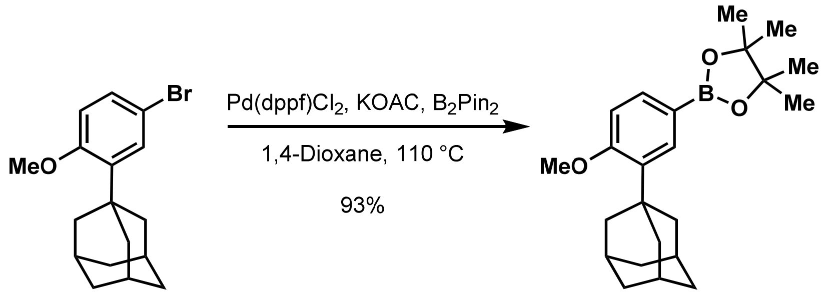
M.P. = 240 – 242 °C



To a solution of *p*-bromophenol (750.0 mg, 4.34 mmol, 1.00 eq.) in CH_2Cl_2 (2.2 mL) and AcOH (1.25 mL) was added sulfuric acid (0.3 mL, 4.69 mmol, 1.08 eq., 98%) and then 1-adamantyl alcohol (660.0 mg, 4.34 mmol, 1.00 eq.) at 23 °C. After 36 hrs the pale yellow solution was poured into a separatory funnel containing an aqueous phosphate buffer (30 mL, pH = 7, 0.2 M) and CH_2Cl_2 (20 mL), partitioned, and the organics were washed with a saturated aqueous mixture of $NaHCO_3$ (1 x 20 mL). Residual organics were extracted from the aqueous layer with CH_2Cl_2 (2 x 10 mL), combined, washed with brine (2 x 10 mL), dried over solid Na_2SO_4, decanted, and concentrated. The phenolic product was carried into the next reaction without further purification or characterization.

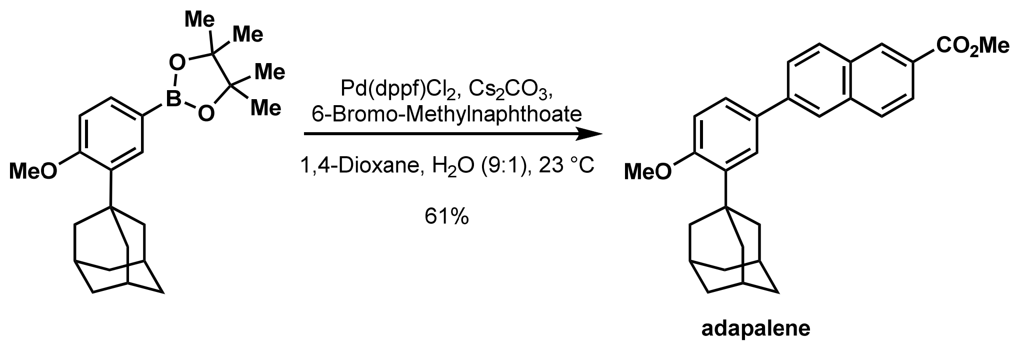
A mixture of the crude adamantyl *p*-bromophenol, K_2CO_3 (1.80 g, 13.0 mmol, 3.00 eq.), and Me_2SO_4 (0.41 mL, 4.34 mmol, 1.00 eq.) in acetone (44 mL) was purged with nitrogen and stoppered with a plastic PTFE cap. The mixture was placed in an oil bath heated to 60 °C and stirred vigorously (1000 rpm). After 24 hrs the white heterogeneous mixture was removed from the oil bath, cooled to 23 °C, suction filtered over a pad of celite, and concentrated. The pale yellow foam was dissolved in Et_2O (20 mL), poured into a separatory funnel, and washed with an aqueous NaOH solution (3 x 20 mL, 1 N) to remove the unreacted phenol. Residual organics were extracted from the aqueous layer with Et_2O (2 x 15 mL), combined, dried over solid Na_2SO_4, decanted, and fully concentrated *in vacuo* to remove any residual unreacted *p*-bromoanisole to afford the adamantyl *p*-bromoanisole as a pale yellow solid (1.10 g, 3.42 mmol, 79%, two steps). The spectral data of the title compound matches that of 3-adamantyl *p*-bromoanisole.[44]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.24 (m, 2H), 6.73 (d, 1H, *J* = 8.6 Hz), 3.81 (s, 3H), 2.05 bs, 9H), 1.75 (bs, 6H)



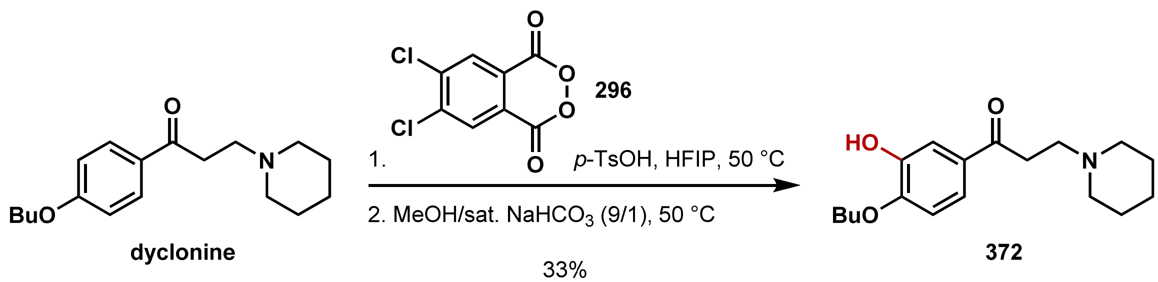
To a solution of 3-adamantyl *p*-bromoanisole (320.0 mg, 1.00 mmol, 1.00 eq.), KOAc (303.0 mg, 3.09 mmol, 3.10 eq.), and B_2Pin_2 (278.0 mg, 1.10 mmol, 1.10 eq.) in 1,4-dioxane (10 mL) was added Pd(dppf)Cl_2-CH_2Cl_2 (49.0 mg, 0.06 mmol, 0.06 eq.) under a positive flow of nitrogen. The red mixture was sparged with nitrogen, stoppered with a plastic PTFE cap, and placed into an oil bath heated to 110 °C. After 4 hrs the black mixture was removed from the oil bath, cooled to 23 °C, concentrated, and residual 1,4-dioxane was azeotropically removed with $CHCl_3$ (3 x 3 mL). The black mixture was dissolved in a solution of $CHCl_3$ and hexane (2 mL, 1:1), loaded directly onto silica gel, and purified by silica chromatography; hexane – 5% EtOAc in hexane to afford the boronic ester as a pale yellow foam which solidified upon standing at 23 °C (340.0 mg, 0.92 mmol, 93%). The boronic ester was carried onto to the next reaction without full characterization.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.66 – 7.64 (m, 2H), 6.86 (d, 1H, *J* = 7.8 Hz), 3.85 (s, 3H), 2.12 bs, 6H), 2.05 (bs, 3H), 1.76 (bs, 6H), 1.32 (s, 12H)



To a solution of the boronic ester (340.0 mg, 0.92 mmol, 1.00 eq.) in 1,4-dioxane and water (9.2 mL, 9:1) was added Pd(dppf)Cl_2-CH_2Cl_2 (75.0 mg, 0.09 mmol, 0.10 eq.) and Cs_2CO_3 (932.0 mg, 2.86 mmol, 3.10 eq.) under a positive flow of nitrogen. 6-bromo-methylnaphthoate (269.0 mg, 1.02 mmol, 1.10 eq.) was added under a positive flow of nitrogen to the now black mixture. After stirring rapidly (800 rpm) at 23 °C for 16 hrs the black mixture was poured into a separatory funnel containing CH_2Cl_2 (20 mL) and brine (10 mL), partitioned, and the residual organics were extracted from the aqueous layer with CH_2Cl_2 (1 x 10 mL), dried over solid Na_2SO_4, suction filtered over a pad of celite, and concentrated. The crude pale yellow mixture was purified by silica gel chromatography to afford the adapalene methyl ester as a white solid (241.0 mg, 0.57 mmol, 61%). The spectral data of the title compound matches that of the adapalene methyl ester.[44]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.61 (s, 1H), 8.07 (dd, 1H, *J* = 1.4, 8.9 Hz), 8.01 (d, 1H, *J* = 1.4 Hz), 7.98 (d, 1H, *J* = 8.6 Hz), 7.92 (d, 1H, *J* = 8.2 Hz), 7.79 (dd, 1H, *J* = 1.7, 8.6 Hz), 7.60 (d, 1H, *J* = 2.3 Hz), 7.54 (dd, 1H, *J* = 2.4, 8.6 Hz), 7.00 (d, 1H, *J* = 8.2 Hz), 3.99 (s, 3H), 3.91 (s, 3H), 2.18 (bs, 6H), 2.10 (bs, 3H), 1.80 (bs, 6H)



Phenol 372: Prepared following General Procedure A: To a solution of dyclonine (131.0 mg, 0.45 mmol, 1.00 eq.) in HFIP (4.5 mL) was added *p*-toluenesulfonic acid monohydrate (86.0 mg, 0.45 mmol, 1.00 eq.). The pale yellow solution was stirred for 2 minutes at 23 °C upon which 4,5-dichlorophthaloyl peroxide (514.0 mg, 1.81 mmol, 4.00 eq., 82%) was added. The pale yellow solution was stoppered with a plastic PTFE cap and placed in an oil bath heated to 50 °C. After 12 hrs the red solution was removed from the oil bath, cooled to 23 °C, and HFIP was removed by a continuous flow of nitrogen. The dark red mixture was placed under an atmosphere of nitrogen upon which a deoxygenated mixture of methanol and a saturated aqueous mixture of $NaHCO_3$ (4.5 mL, 9:1) was added. The dark red solution was placed in an oil bath heated to 50 °C. After 2 hrs the dark red solution was removed from the oil bath, cooled to 23 °C, diluted with a saturated aqueous mixture of $NaHCO_3$ (10 mL) and EtOAc (10 mL), poured into a separatory funnel, partitioned, and the aqueous layer was washed with a saturated aqueous mixture of $NaHCO_3$ and brine (3 x 30 mL, 1:1). Residual organics were extracted from the aqueous layer with a combination of EtOAc and brine (3 x 30 mL, 2:1), combined, dried over solid Na_2SO_4, decanted, and concentrated. The crude black foam was purified by silica gel chromatography; 1 – 5% MeOH in CH_2Cl_2, then 1% MeOH and 1% Et_3N in CH_2Cl_2 to afford the aminophenol **372** as a red solid (50.6 mg, 0.15 mmol, 33%, 90% pure by ^{1}H-NMR).

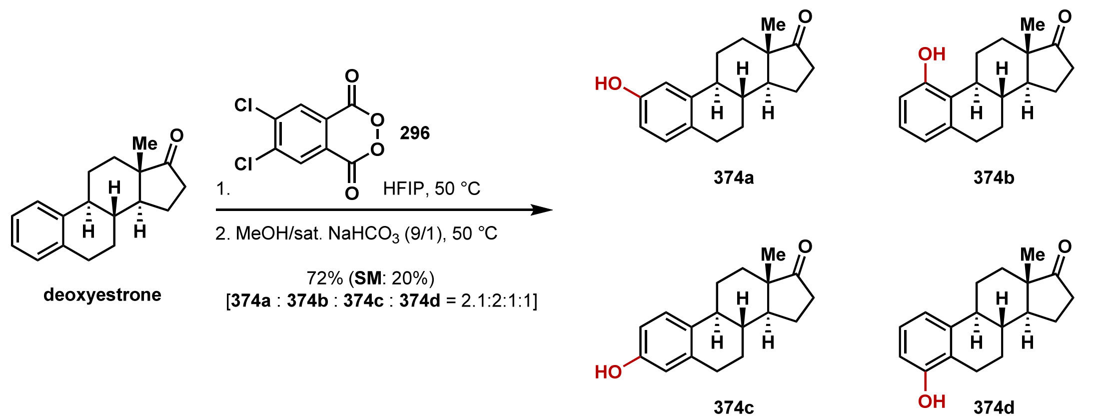
$\mathbf{R_f}$ = 0.50 (5% MeOH in CH_2Cl_2)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.58 (dd, 1H, *J* = 2.0, 8.2 Hz), 7.56 (d, 1H, 2.0 Hz), 6.86 (d, 1H, *J* = 8.2 Hz), 4.12 (t, 2H, *J* = 6.8 Hz), 3.64 (t, 2H, *J* = 6.8 Hz), 3.36 (t, 2H, *J* = 6.8 Hz), 3.03 (bs, 4H), 1.97 (bs, 4H), 1.83 (ddd, 2H, *J* = 7.8 Hz), 1.63 (bs, 2H), 1.51 (ddd, 2H, *J* = 7.8 Hz), 1.00 (t, 3H, *J* = 7.8 Hz)

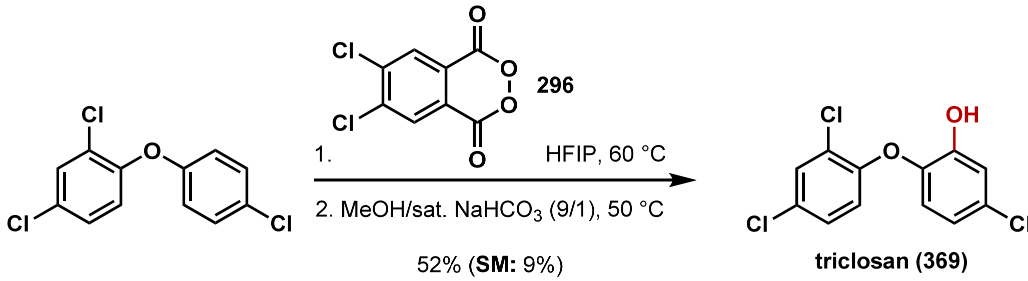
^{13}C-NMR (100 MHz, $CDCl_3$): δ 195.14, 151.12, 145.90, 129.10, 122.04, 114.15, 110.83, 68.83, 53.73, 52.27, 33.07, 30.97, 22.92, 22.18, 19.12, 13.78

IR (neat film, cm^{-1}): 3401, 2957, 2873, 1673, 1604, 1435, 1276,

M.P. = 140 – 144 °C

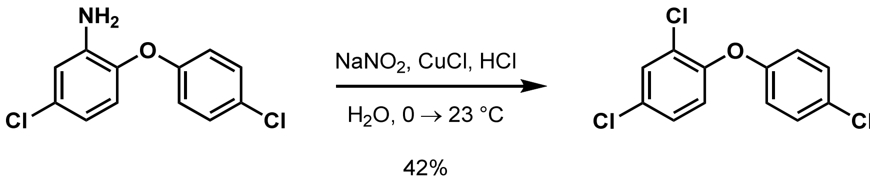


Phenols 374a – 374d: Prepared following General Procedure A using deoxyestrone (100.0 mg, 0.39 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (142.0 mg, 0.51 mmol, 1.30 eq., 84%), and HFIP (3.9 mL) at 50 °C for 24 hrs. The crude pale yellow solid was purified by silica gel chromatography; 5 - 20% EtOAc in CH_2Cl_2 and hexane (1:1) to afford the mixture of estrone phenols **374a**, **374b**, **374c**, and **374d** (76.4 mg, 0.28 mmol, 72%, **374a : 374b : 374c : 374d** = 2.1:2:1:1) as a white solid and the starting deoxyestrone as a white solid (19.5 mg, 0.08 mmol, 20%). The spectra of the title compounds match that for **374a**, **374b**, **374c**, and **374d**.[45,46]



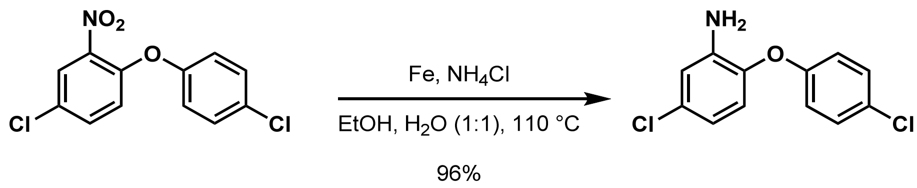
Triclosan (369): Prepared following General Procedure B using 2,4,4'-trichlorophenylether (95.0 mg, 0.35 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (188.0 mg, 0.70 mmol, 2.00 eq., 86%), and HFIP (3.5 mL) at 60 °C for 24 hrs. The crude brown foam was purified by silica gel chromatography; 1 – 10% Et_2O in pentane to provide triclosan (**369**) (52.0 mg, 0.18 mmol, 52%) as a pale yellow foam and the starting trichloride (8.4 mg, 0.03 mmol, 9%). The spectra of the title compound matches that of triclosan (**369**).[47]

^{1}H-NMR (400 MHz, $CDCl_3$)[47]: δ 7.48 (d, 1H, J = 2.2 Hz), 7.22 (dd, 1H, J = 2.2, 8.5 Hz), 7.07 (d, 1H, J = 2.2 Hz), 6.95 (d, 1H, J = 8.5 Hz), 6.81 (dd, 1H, J = 2.2, 8.5 Hz), 6.66 (d, 1H, J = 8.5 Hz), 5.63 (bs, 1H)



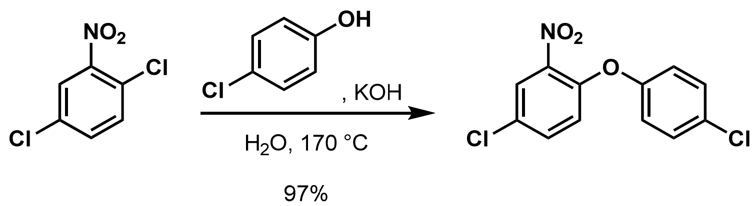
The aniline (2.96 g, 11.7 mmol, 1.00 eq.) was suspended in water (9 mL) and concentrated HCl (7 mL, 87.0 mmol, 7.45 eq., 38%, 12.4 M). The orange solid mixture was placed in an ice water bath cooled to 0 °C and stirred vigorously (400 rpm). After 5 minutes $NaNO_2$ (0.88 g, 12.8 mmol, 1.10 eq.) was added all at once and the mixture immediately changed to a deep red-orange color. After 25 minutes, CuCl (1.73 g, 17.5 mmol, 1.50 eq.) was added all at once followed by concentrated HCl (1.5 mL, 18.0 mmol, 1.55 eq., 38%, 12.4 M). The dark red-orange solution was removed from the cooling bath and stirred vigorously (400 rpm) at 23 °C. After 30 minutes the dark orange biphasic mixture was diluted with Et_2O (20 mL), poured into a separatory funnel, partitioned, and the organic layer was washed with 1 N HCl (3 x 25 mL). Residual organics were extracted from the aqueous layer with Et_2O (3 x 25 mL), combined, dried over solid Na_2SO_4, decanted, and concentrated. The crude dark yellow solid was purified by silica gel chromatography; hexane to provide the known 2,4,4'-trichlorophenylether (1.34 g, 4.90 mmol, 42%) as a white crystalline solid.[48] The spectra of the title compound matches that of the trichloride**.**[48]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.47 (d, 1H, J = 2.7 Hz), 7.29 (d, 2H, J = 8.9 Hz), 7.21 (dd, 1H, J = 2.7, 8.9 Hz), 6.92 (d, 1H, J = 8.9 Hz), 6.88 (d, 2H, J = 8.9 Hz)



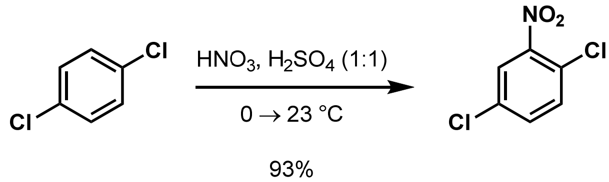
To a suspension of 2-nitro-4,4'-dichlorophenyl ether (3.43 g, 12.1 mmol, 1.00 eq.) in ethanol (48.3 mL) and water (48.3 mL) was added iron powder (1.82 g, 32.6 mmol, 2.70 eq.) and solid NH_4Cl (2.91 g, 54.3 mmol, 4.50 eq.). The reaction vessel was equipped with a reflux condenser, purged with N_2, and the black mixture was placed in an oil bath heated to 110 °C stirring vigorously (800 rpm). After 12 hrs the black mixture was suction filtered over celite to remove the iron and the filtrate solution was concentrated to remove the EtOH. The resultant yellow solid mixture was diluted with CH_2Cl_2 (50 mL) and an aqueous phosphate buffer (50 mL, 0.2 M, pH = 10), poured into a separatory funnel, partitioned, and the organics were washed with an aqueous phosphate buffer (1 x 25 mL, 0.2 M, pH = 10). Residual organics were extracted from the aqueous with CH_2Cl_2 (2 x 30 mL), combined, dried over solid Na_2SO_4, decanted, and concentrated to provide the known aniline (2.96 g, 11.7 mmol, 96%) pure as a yellow solid.[48]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26 (d, 2H, J = 5.5 Hz), 6.89 (d, 2H, J = 9.2 Hz), 6.80 (d, 1H, J = 2.4 Hz), 6.76 (d, 1H, J = 8.6 Hz), 6.67 (dd, 1H, J = 2.4, 8.6 Hz), 3.86 (bs, 2H).



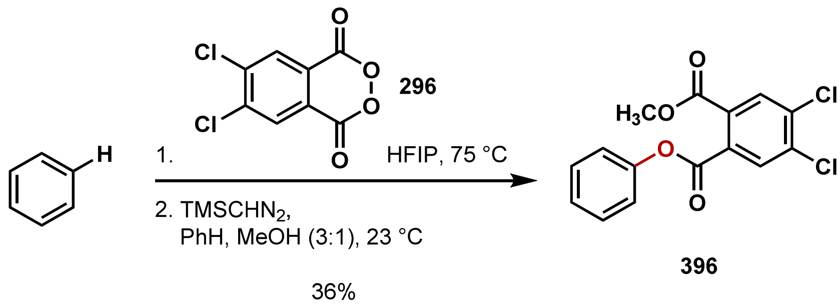
The solid mixture of 1,4,-dichloro-2-nitrobenzene (2.40 g, 12.50 mmol, 1.00 eq.), KOH (0.74 g, 13.13 mmol, 1.05 eq.), and 4-chlorophenol (1.77 g, 13.75 mmol, 1.10 eq.) was suspended in water (1 mL), placed in an oil bath heated to 170 °C, and stirred rapidly (400 rpm). After 2.5 hrs the reddish-brown liquid was removed from the oil bath, cooled to 23 °C, diluted with Et_2O (20 mL), and residual 4-chlorophenol was quenched with 4 N NaOH (20 mL). The biphasic mixture was then poured into a separatory funnel. 4 N NaOH (20 mL) and Et_2O (20 mL) was added to the reaction vessel to dissolve residual solids with the aid of sonication, and this yellow-orange mixture was added to the separatory funnel. The layers were partitioned and the organic layer was washed with 4 N NaOH (3 x 20 mL) to remove the excess 4-chlorophenol. The residual organics were extracted from the aqueous layer with Et_2O (3 x 20 mL), combined, dried over solid Na_2SO_4, decanted, and concentrated to reveal the known 2-nitro-4,4'-dichlorophenyl ether (3.43 g, 12.07 mmol, 97%) pure as a dark yellow solid.[48]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.95 (d, 1H, *J* = 2.4 Hz), 7.48 (dd, 1H, *J* = 2.4, 8.9 Hz), 7.35 (d, 2H, *J* = 8.9 Hz), 6.97 (d, 3H, *J* = 8.9 Hz).



Concentrated H_2SO_4 (6.7 mL, 18 M, 98%) was slowly added to fuming HNO_3 (6.7 mL, 90%) in an ice water bath cooled to 0 °C. After 5 minutes *p*-dichlorobenzene (2.00 g, 13.61 mmol, 1.00 eq.) was added all at once. After 2 minutes the cold bath was removed and the yellow heterogeneous mixture was stirred vigorously (500 rpm) at 23 °C. After 15 minutes the yellow homogeneous solution was poured into ice water (250 mL), and the resultant yellow solid was filtered. The yellow solid was then dried *in vacuo* with heating (100 °C) for 30 minutes to remove excess H_2O to afford the known 2-nitro-4-dichlorobenzene (2.43 g, 12.66 mmol, 93%) pure as a yellow solid which solidified upon cooling to 23 °C.[48]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.89 (bs, 1H), 7.50 (d, 2H, J = 1.0 Hz).



Phthalate Ester 396: Prepared following General Procedure C using benzene (10.0 mg, 0.13 mmol, 1.00 eq), 4,5-dichlorophthaloyl peroxide (87.0 mg, 0.32 mmol, 2.50 eq., 86%), HFIP (1.3 mL), and $TMSCHN_2$ (0.3 mL, 0.64 mmol, 5.00 eq., 2.0 M). The crude yellow foam was purified by silica gel chromatography; benzene to provide the phthalate ester **396** (15.1 mg, 0.05 mmol, 36%) as a clear amorphous solid.

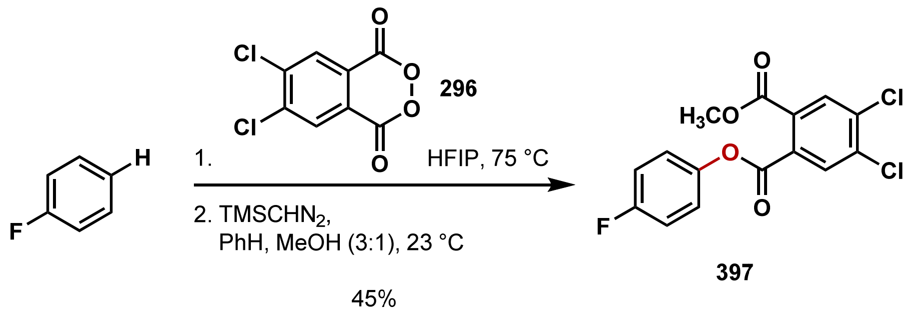
$\mathbf{R_f}$ = 0.56 (benzene)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.91 (s, 1H), 7.44 (t, 2H, *J* = 7.9 Hz), 7.29 (t, 1H, *J* = 7.9), 7.25 (d, 2H, *J* = 7.9), 3.93 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.93, 164.47, 150.79, 136.44, 136.37, 131.53, 131.45, 131.40, 129.86, 128.55, 126.60, 121.47, 53.42

IR (neat film, cm^{-1}): 2955, 1733, 1436, 1288, 1069

HRMS (EC-CI): calcd. for $C_{15}H_{10}O_4Cl_2$ $[M+H]^+$ 325.0034, found 325.0028.



Phthalate Ester 397: Prepared following General Procedure C using fluorobenzene (10.0 mg, 0.10 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (69.0 mg, 0.26 mmol, 2.50 eq., 88%), HFIP (1.0 mL), and $TMSCHN_2$ (0.3 ml, 0.52 mmol, 5.00 eq., 2.0 M). The crude yellow foam was purified by silica gel chromatography; benzene to provide the phthalate ester **397** (16.0 mg, 0.05 mmol, 45%) as a white solid.

$\mathbf{R_f}$ = 0.63 (benzene)

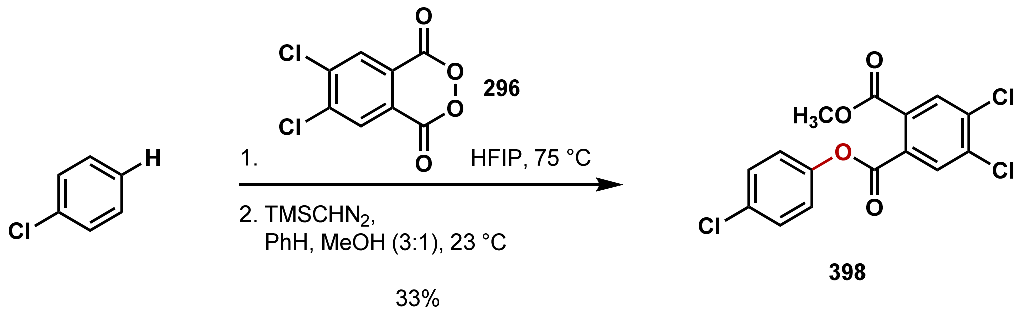
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.93 (s, 1H), 7.24 – 7.21 (m, 2H,), 7.12 (dd, 2H, J = 8.2, 8.9), 3.93 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.76, 164.62, 161.98, 146.60, 136.52, 136.48, 131.54, 131.36, 131.31, 131.28, 123.00, 116.23, 53.42

IR (neat film, cm^{-1}): 2924, 2356, 1733, 1503, 1291, 1116

HRMS (EC-CI): calcd. for $C_{15}H_9O_4Cl_2F$ $[M+H]^+$ 342.9940, found 342.9934.

M.P. = 96 – 99 °C.



398

Phthalate Ester 398: Prepared following General Procedure C using chlorobenzene (10.0 mg, 0.09 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (60.0 mg, 0.22 mmol, 2.50 eq., 86%), HFIP (0.88 mL), and $TMSCHN_2$ (0.2 mL, 0.44 mmol, 5.00 eq., 2.0 M). The crude yellow foam was purified by silica gel chromatography; benzene to provide the phthalate ester **398** (10.3 mg, 0.03 mmol, 33%) as a clear foam.

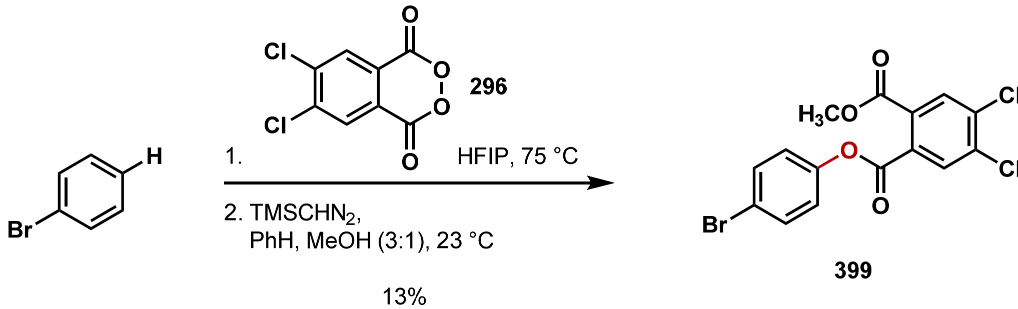
$\mathbf{R_f}$ = 0.69 (benzene)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 2H), 7.40 (d, 2H, *J* = 8.9 Hz), 7.21 (d, 2H, *J* = 8.9 Hz), 3.92 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.48, 164.16, 149.00, 136.33, 136.30, 131.80, 131.33, 131.08, 131.03, 130.99, 129.70, 122.66, 53.22

IR (neat film, cm^{-1}): 2955, 2924, 1733, 1503, 1487, 1288

HRMS (EC-CI) calcd. for $C_{15}H_9O_4Cl_3$ $[M+H]^+$ 358.9645, found 358.9636.



Phthalate Ester 399: Prepared following General Procedure C using bromobenzene (10.0 mg, 0.06 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (43.0 mg, 0.16 mmol, 2.50 eq., 86%), HFIP (0.6 mL), and $TMSCHN_2$ (0.2 ml, 0.32 mmol, 5.00 eq., 2.0 M). The crude yellow foam was purified by silica gel chromatography; hexane – 3% EtOAc in hexane to afford the phthalate **399** (3.2 mg, 0.01 mmol, 13%) as a colorless foam.

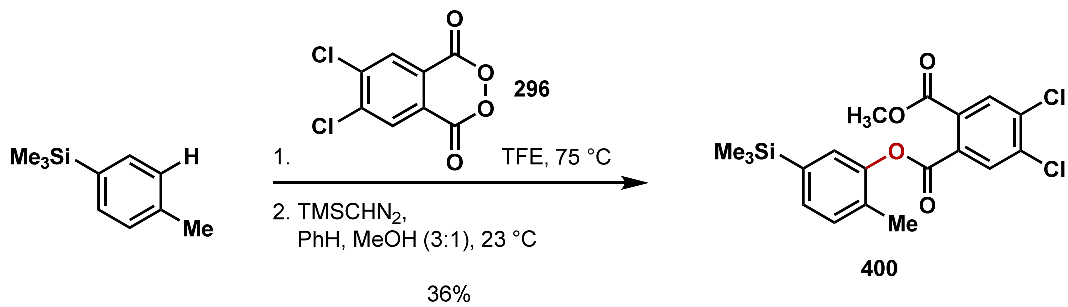
$\mathbf{R_f}$ = 0.40 (10% EtOAc in hexane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 2H), 7.55 (d, 2H, *J* = 8.9 Hz), 7.15 (d, 2H, *J* = 8.9 Hz), 3.92 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.48, 164.08, 149.55, 136.32, 132.68, 131.33, 131.08, 131.02, 131.00, 123.08, 119.53, 53.22

IR (neat film, cm^{-1}) 2952, 1731, 1513, 1286

HRMS (EC-ESI): calcd. for $C_{15}H_9O_4Cl_2Br$ $[M+Na]^+$ 426.8931, found 426.8923.



Phthalate Ester 400: Prepared following General Procedure C using *p*-trimethylsilyl toluene (30.0 mg, 0.18 mmol, 1.00 eq.), 4,5-dichlorophthaloyl peroxide (124.0 mg, 0.46 mmol, 2.50 eq., 86%), TFE (1.8 mL), and $TMSCHN_2$ (0.5 ml, 0.91 mmol, 5.00 eq., 2.0 M). The crude yellow foam was purified by silica gel chromatography; benzene to afford the phthalate **400** (27.1 mg, 0.07 mmol, 36%) as a colorless foam.

$\mathbf{R_f}$ = 0.70 (benzene)

^{1}H-NMR (400 MHz, C_6D_6): δ 7.74 (s, 1H), 7.59 (s, 1H), 7.42 (s, 1H), 7.25 (d, 1H, *J* = 6.6 Hz), 7.08 (d, 1H, *J* = 6.6 Hz), 3.42 (s, 3H), 2.13 (s, 3H), 0.20 (s, 9H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.64, 163.48, 149.87, 139.95, 136.25, 135.79, 132.60, 131.63, 131.37, 131.35, 131.24, 131.23, 131.20, 126.60, 52.47, 16.22, 1.19

IR (neat film, cm^{-1}) 1738, 1287, 1249

5. References

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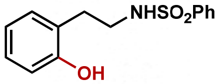
6. Catalog of Spectra



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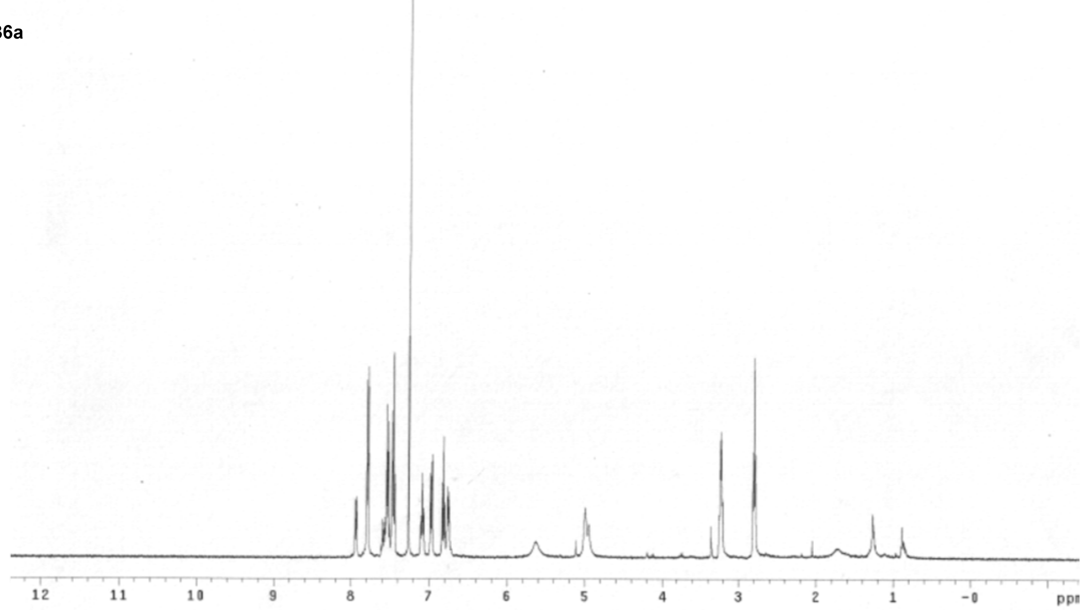

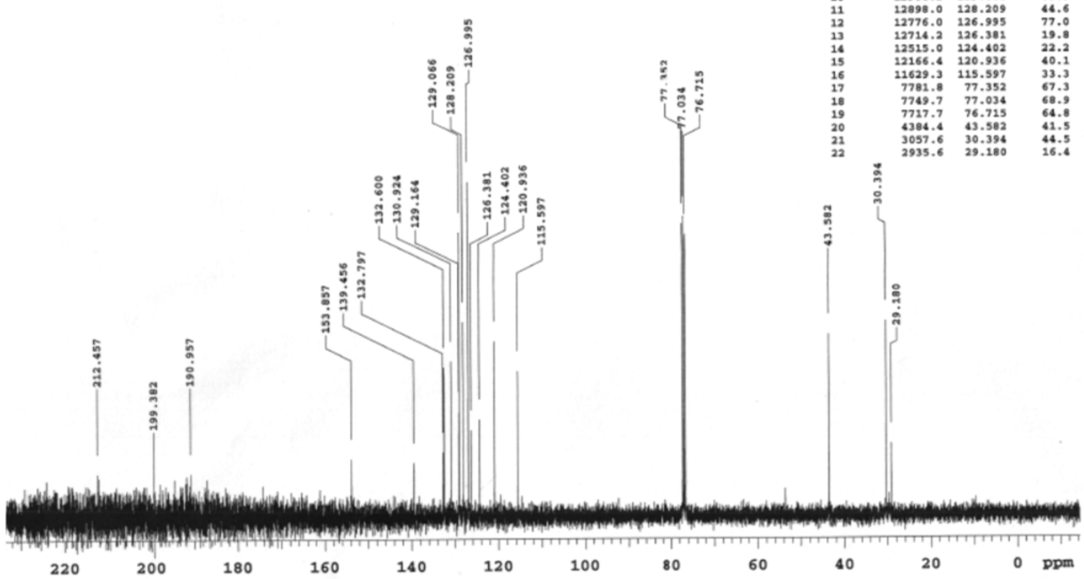

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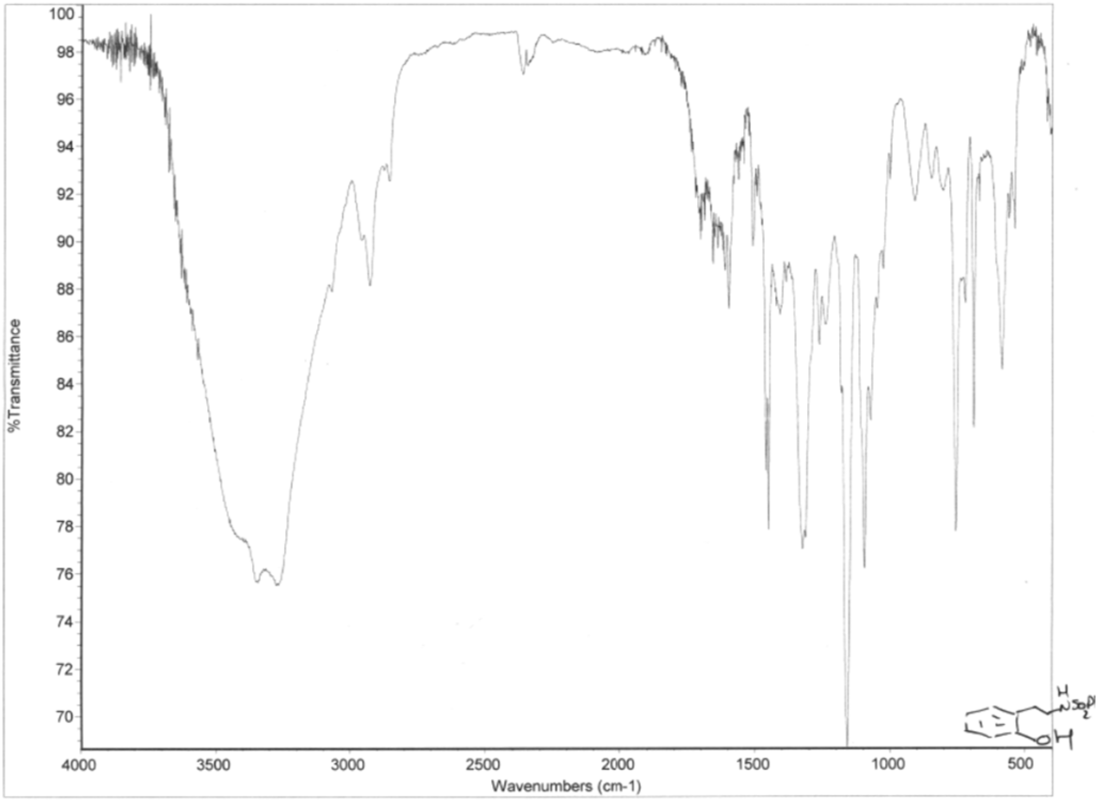
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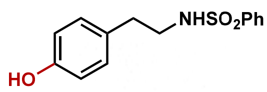
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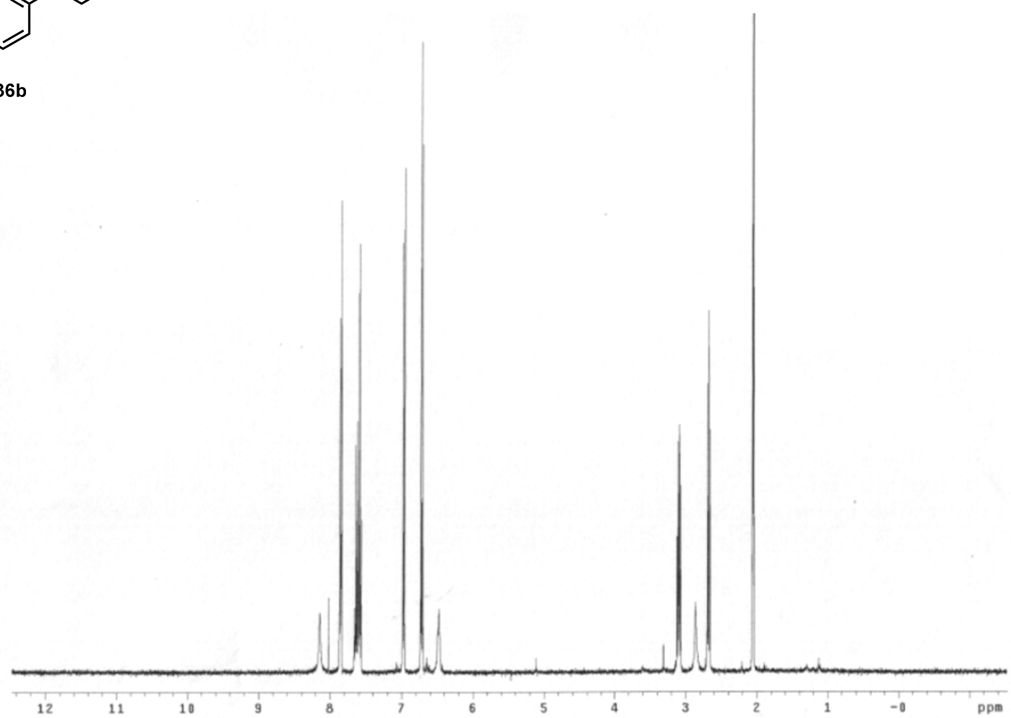
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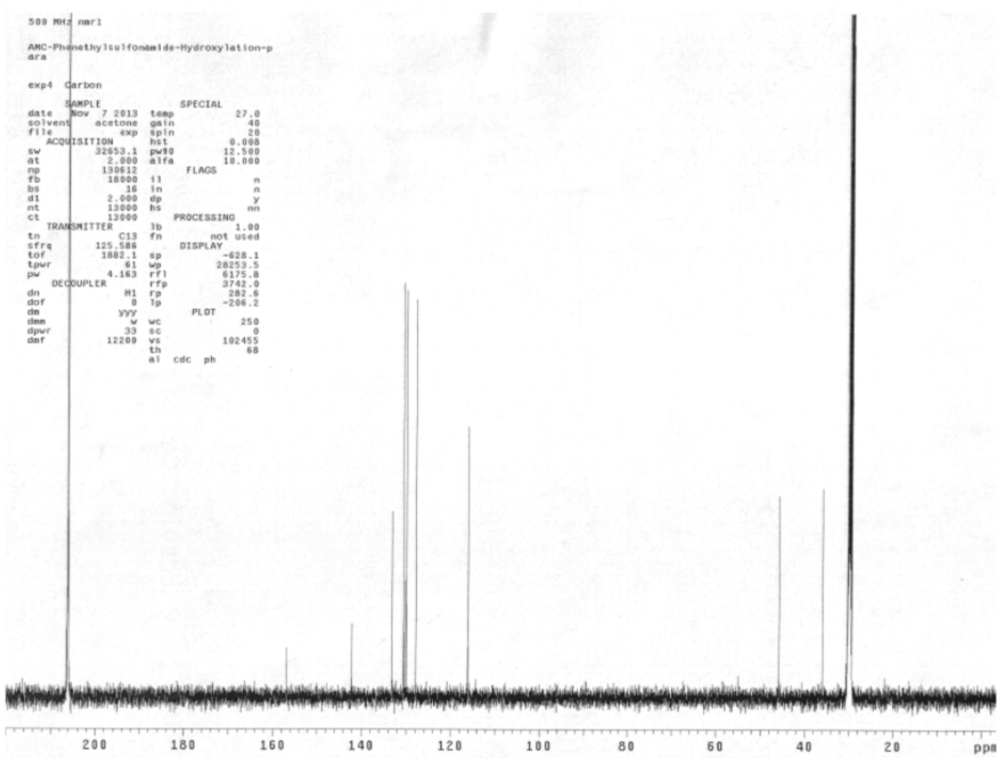
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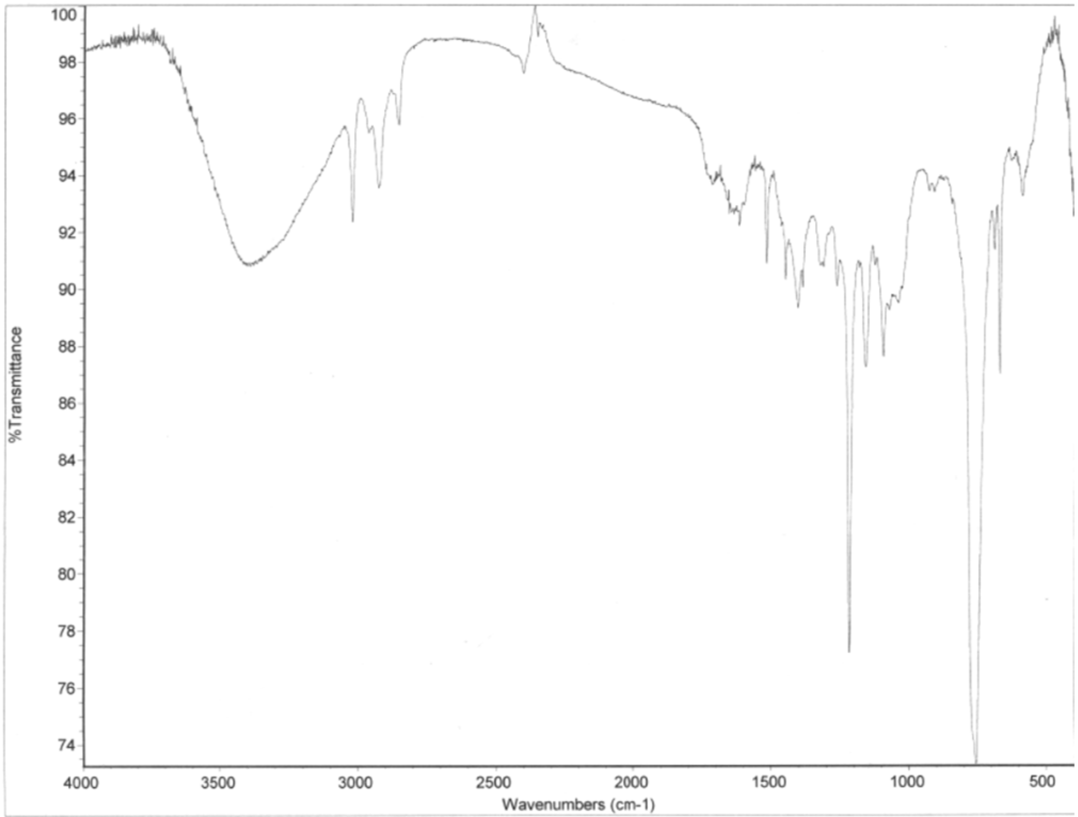

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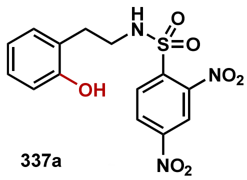
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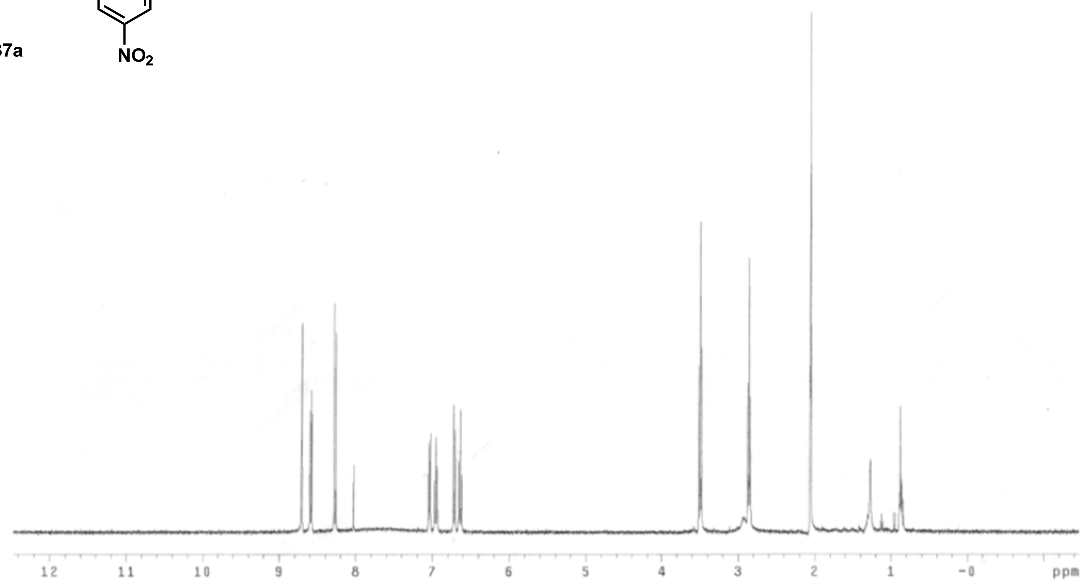
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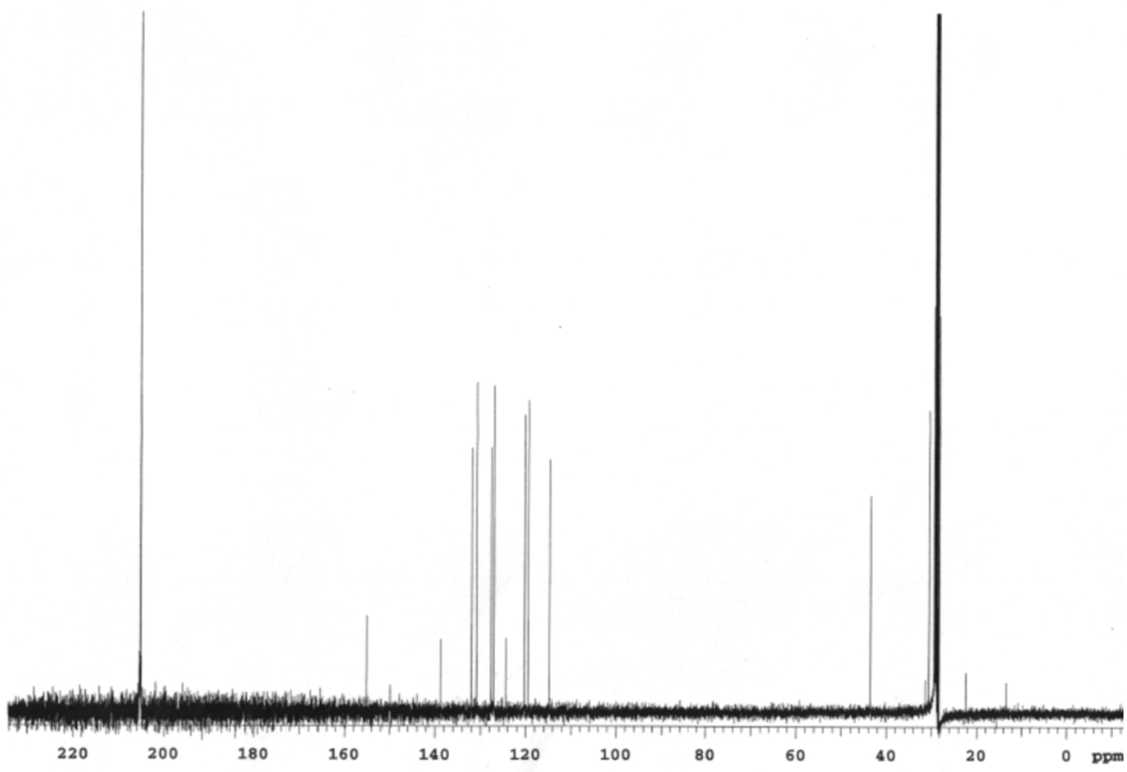
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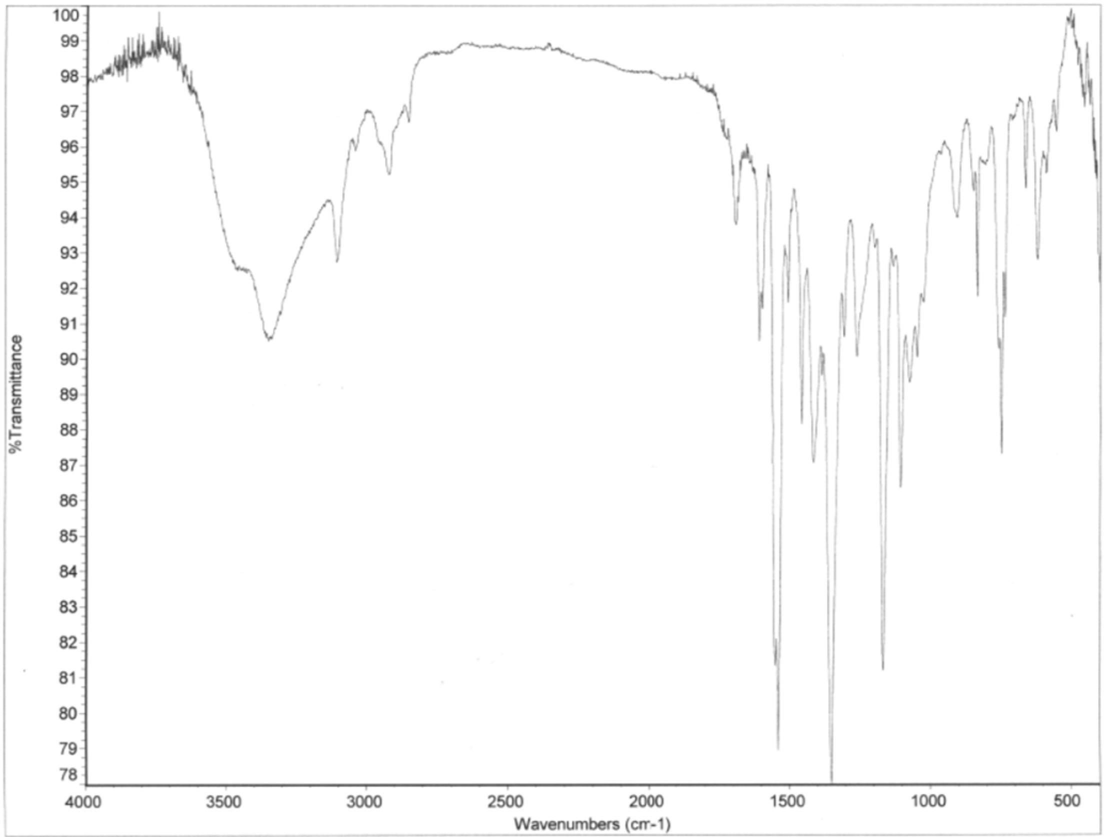
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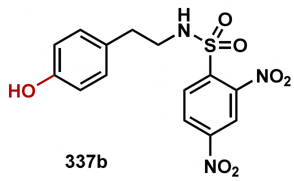
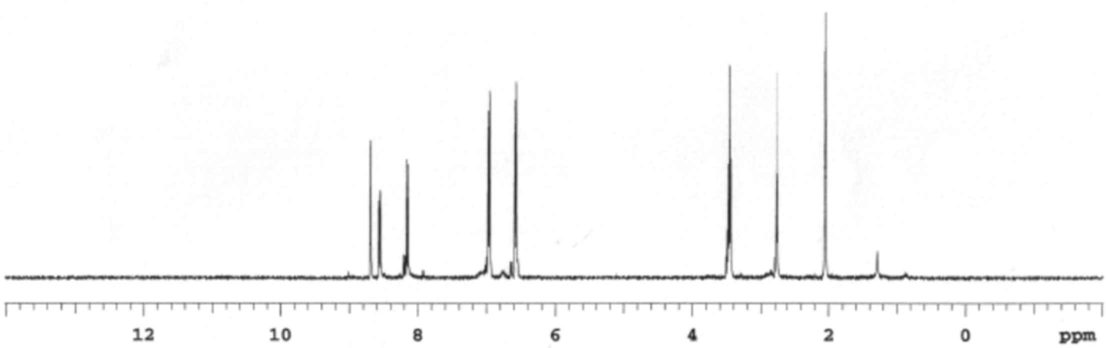
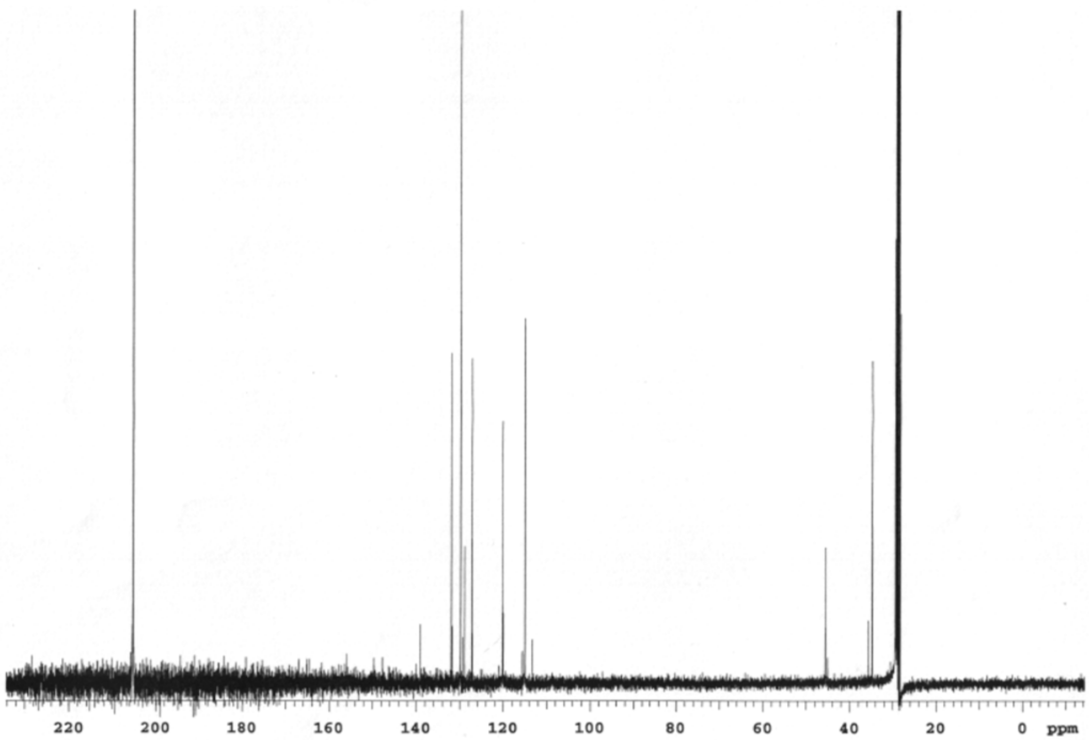
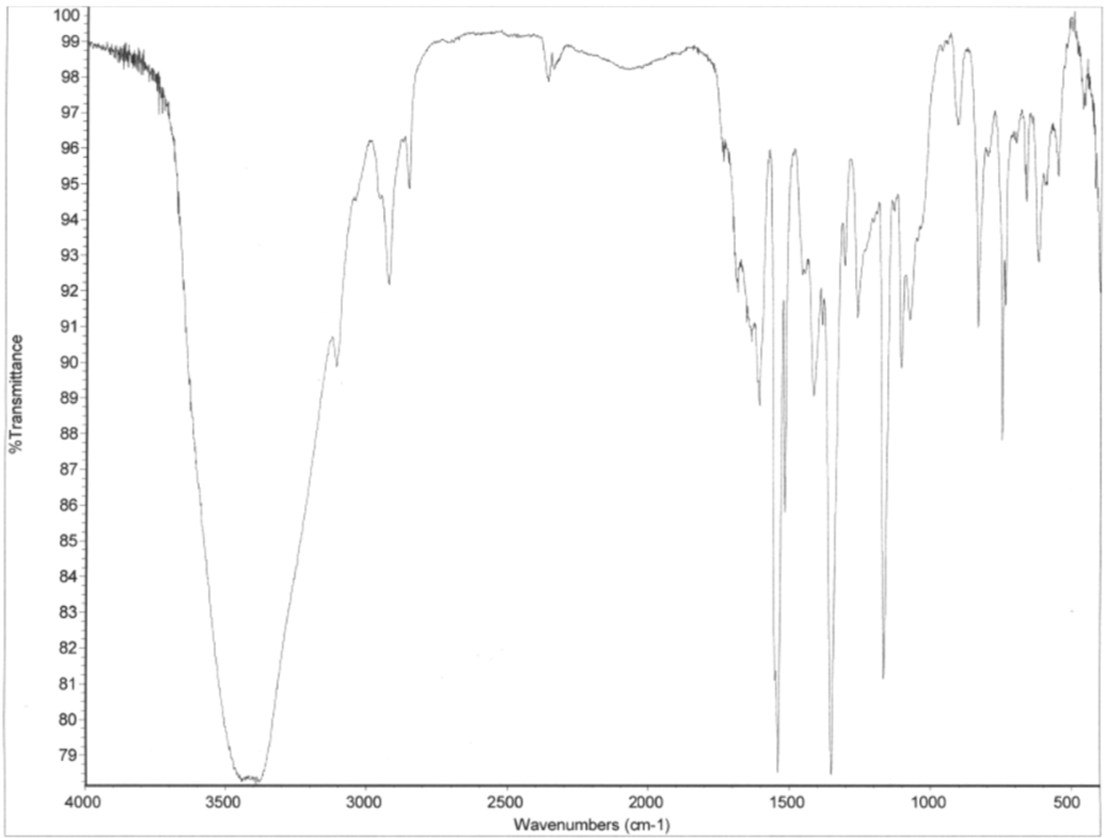
1000
500
Wavenumbers (cm-1)


HO
N
H
S
O
O
NO2
NO2

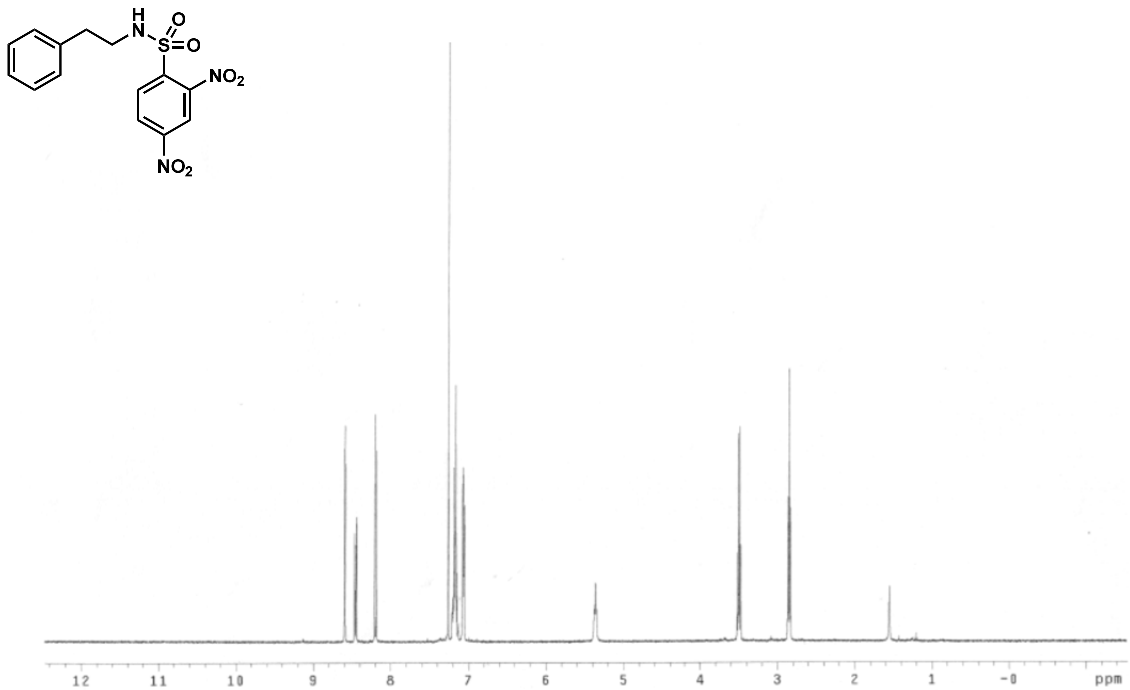
337b

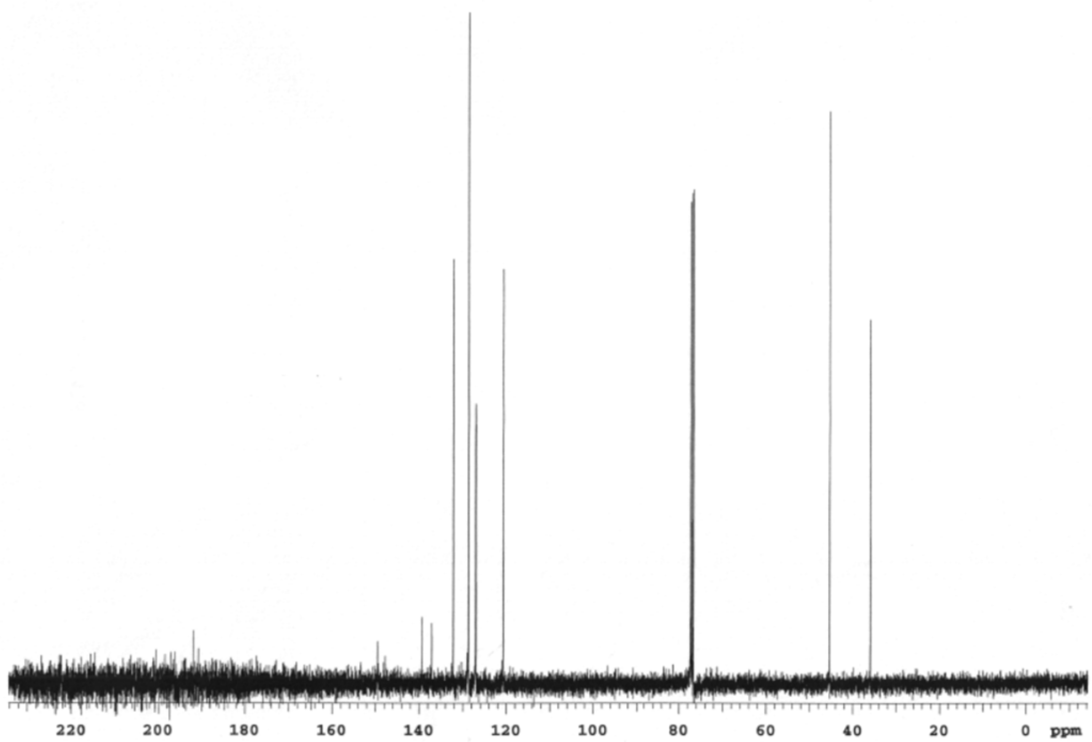

12
10
8
6
4
2
0
ppm

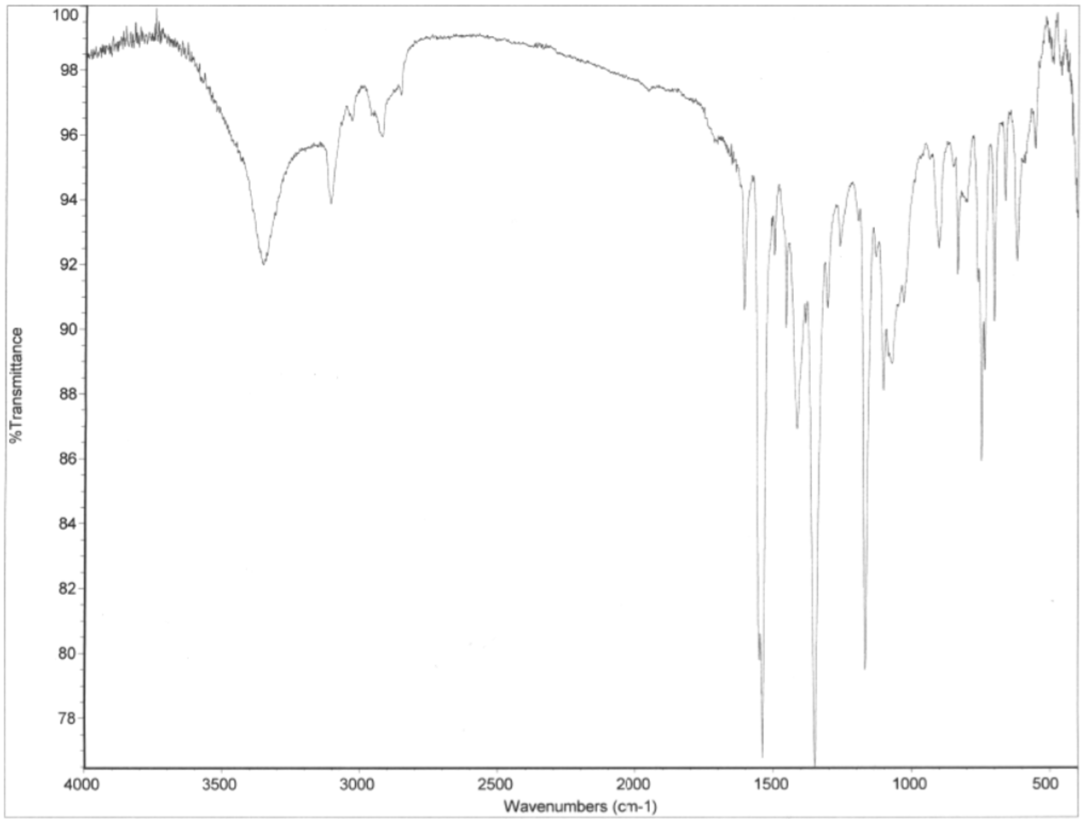

220
200
180
160
140
120
100
80
60
40
20
0
ppm

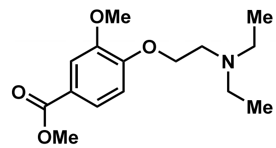


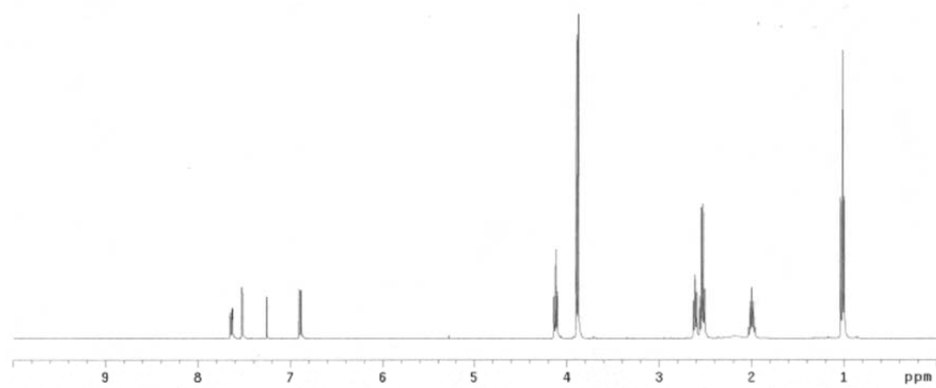
%Transmittance
100
99
98
97
96
95
94
93
92
91
90
89
88
87
86
85
84
83
82
81
80
79
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

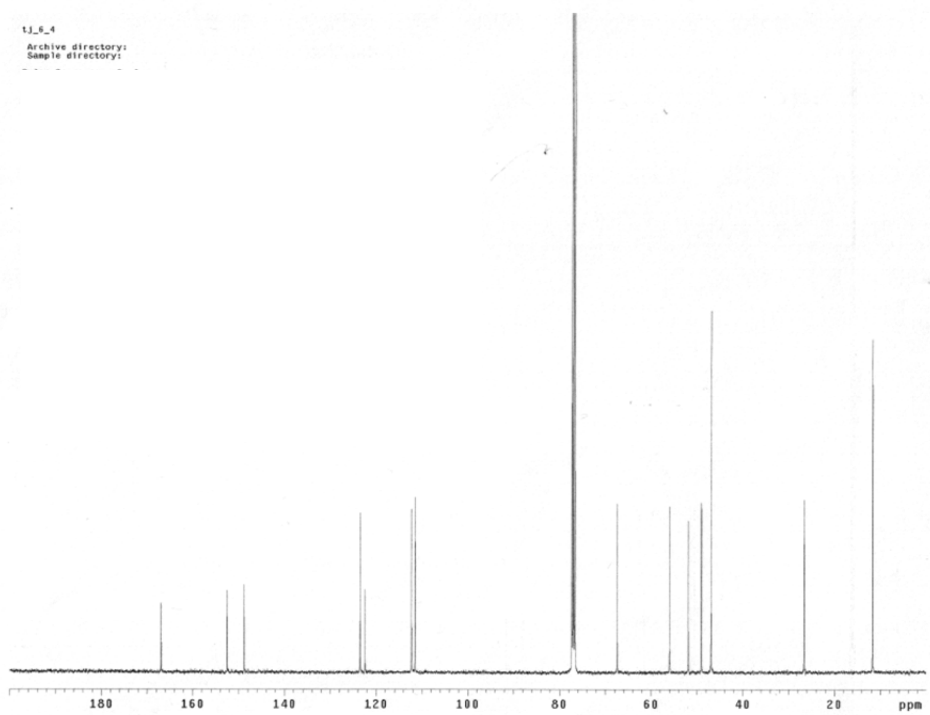

H
N
S
O
O
NO2
NO2
12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

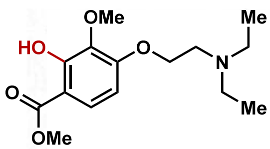

220 200 180 160 140 120 100 80 60 40 20 0 ppm


100
98
96
94
92
90
88
86
84
82
80
78
%Transmittance
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

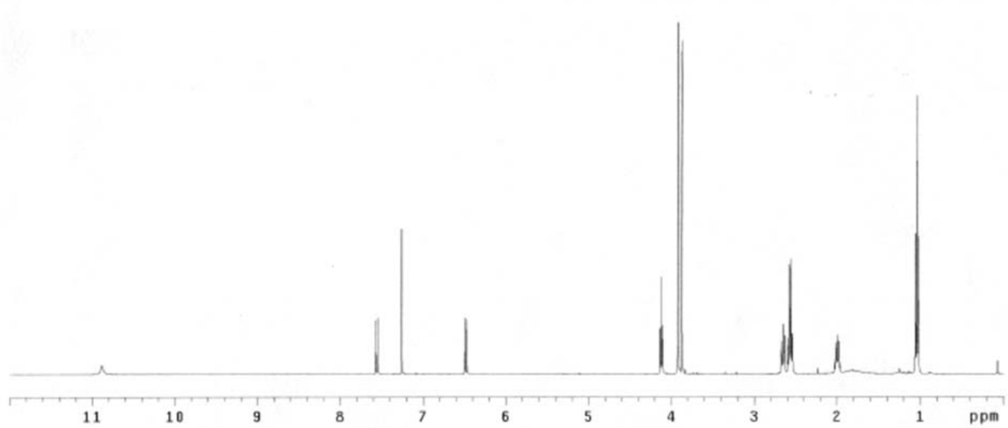

OMe
O
N
Me
Me
O
OMe

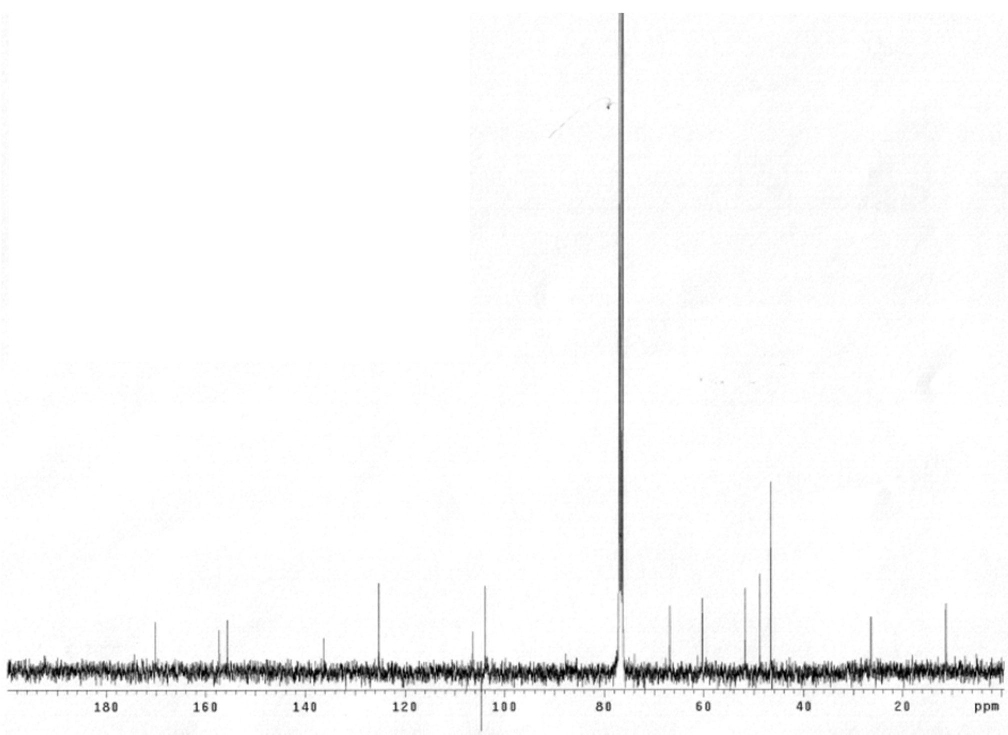

9
8
7
6
5
4
3
2
1
ppm


tj_6_4
Archive directory:
Sample directory:
180
160
140
120
100
80
60
40
20
ppm

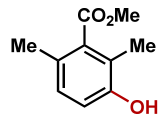

OMe
HO
O
N
Me
Me
O
OMe

338

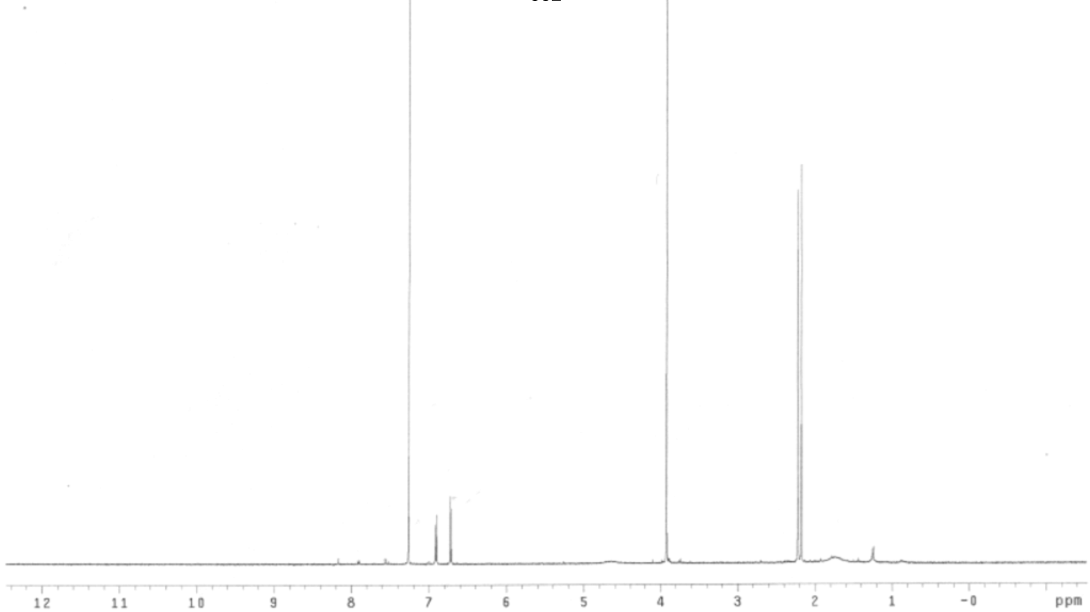

11
10
9
8
7
6
5
4
3
2
1
ppm


180
160
140
120
100
80
60
40
20
ppm

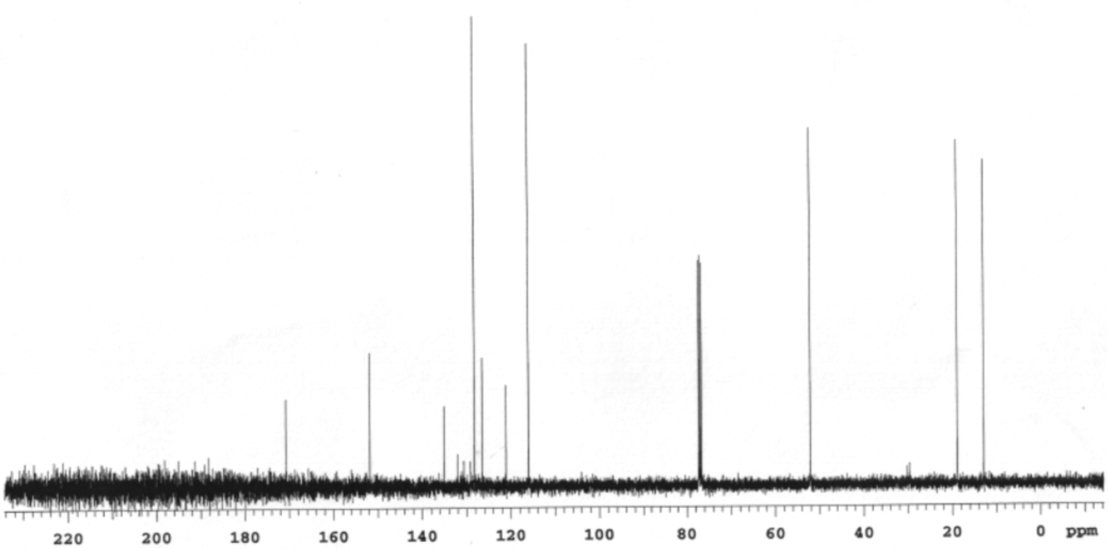
INDEX	FREQUENCY	PPM	HEIGHT
1	2905.468	7.259	141.8
2	1566.456	3.914	151.2
3	888.401	2.220	86.3
4	870.621	2.175	92.1

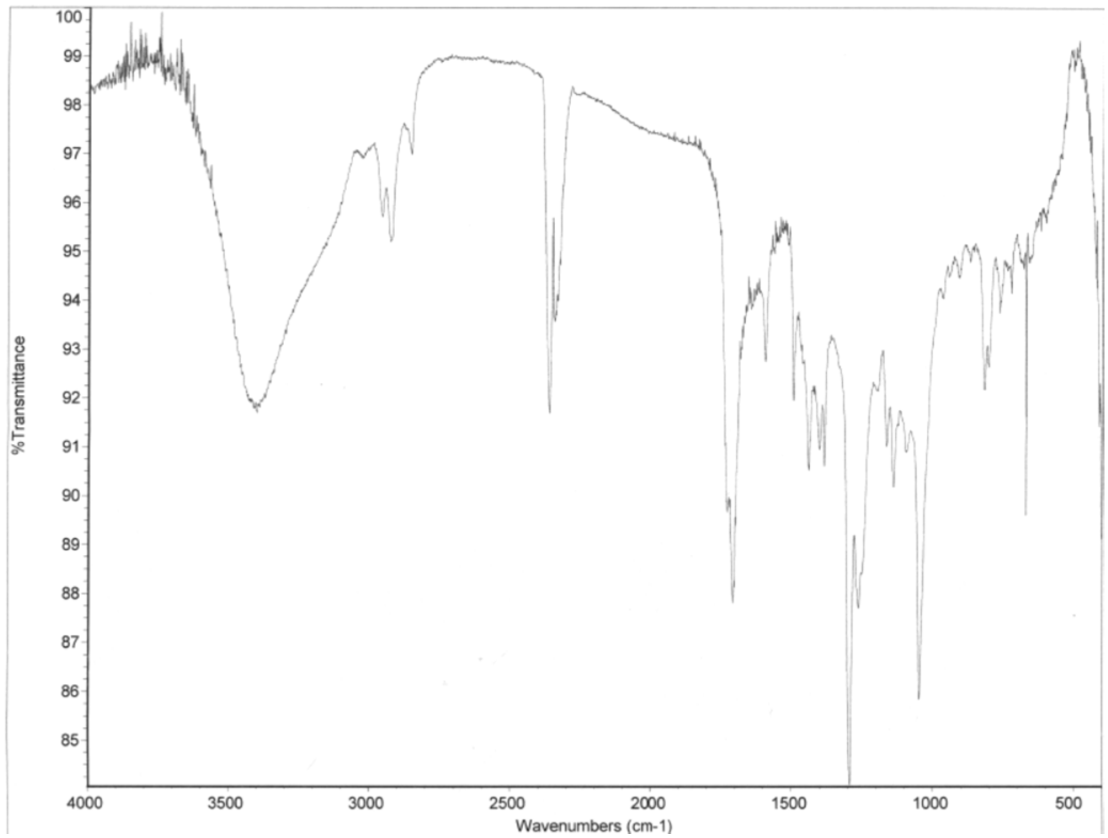


352

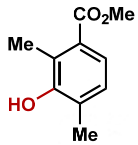


INDEX	FREQUENCY	PPM	HEIGHT
1	17179.7	170.769	19.9
2	15272.3	151.810	30.2
3	13588.5	135.072	18.2
4	12907.2	128.300	106.2
5	12726.4	126.503	28.9
6	12182.4	121.095	22.8
7	11675.8	116.060	100.0
8	7782.5	77.360	50.6
9	7750.5	77.041	51.7
10	7718.4	76.723	50.0
11	5245.0	52.136	80.6
12	1898.7	18.874	77.6
13	1293.0	12.852	73.1

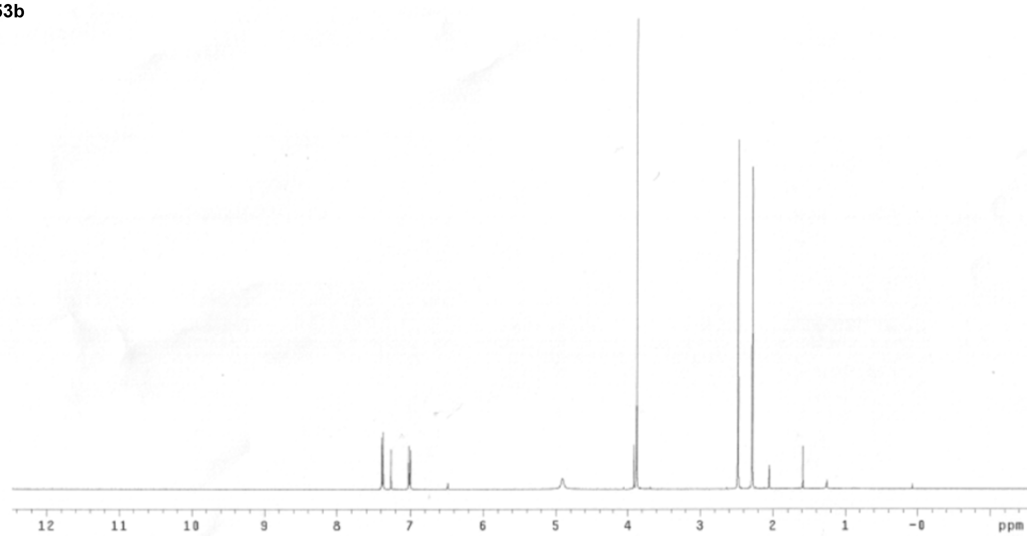




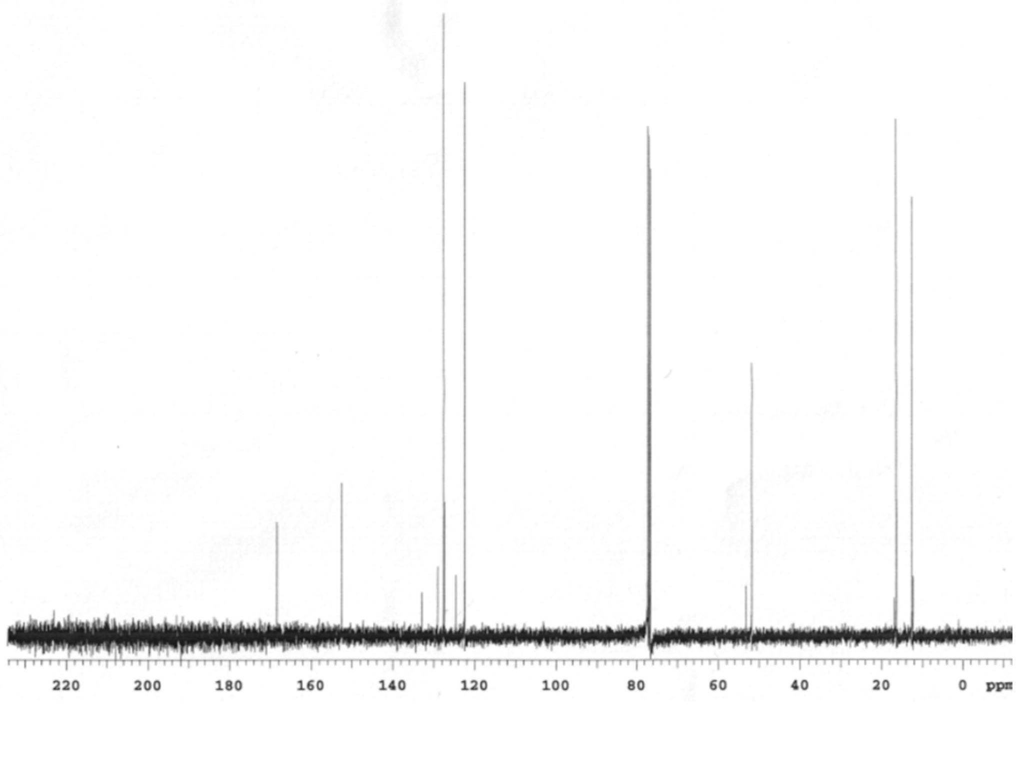
100
99
98
97
96
95
94
93
92
91
90
89
88
87
86
85
%Transmittance
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)



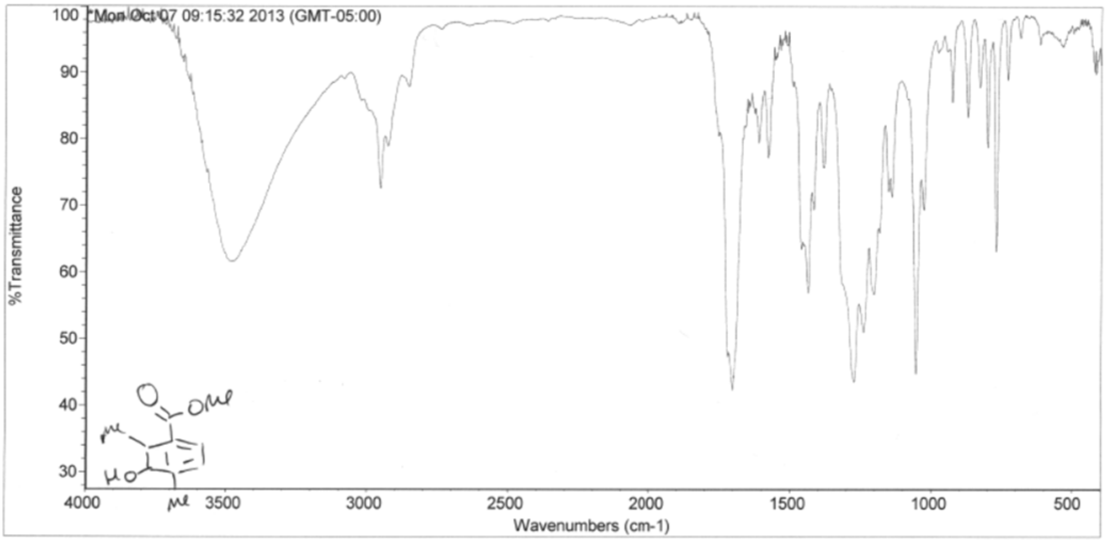
353b

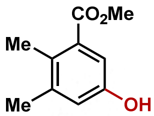


12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm

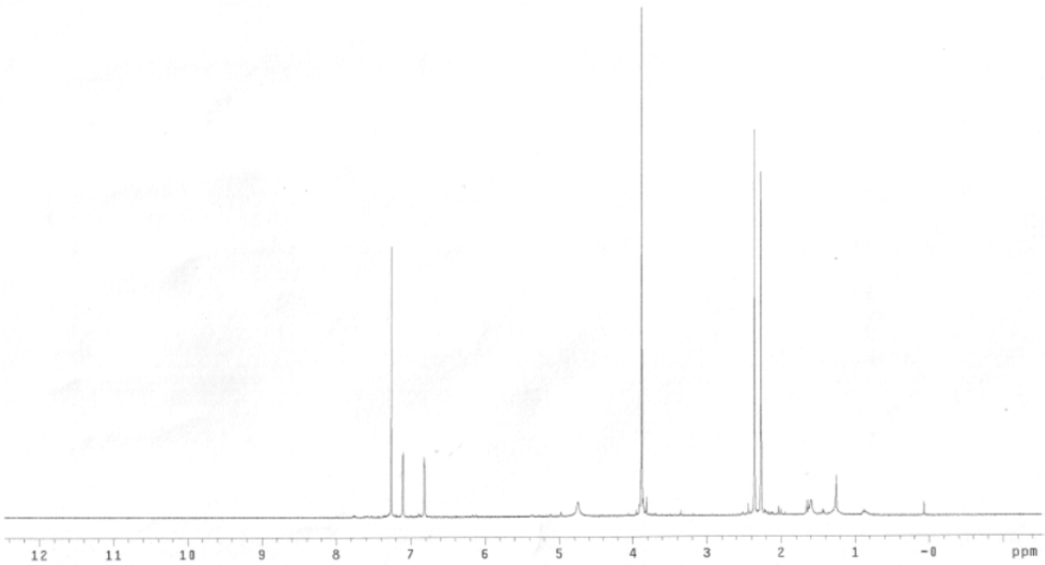


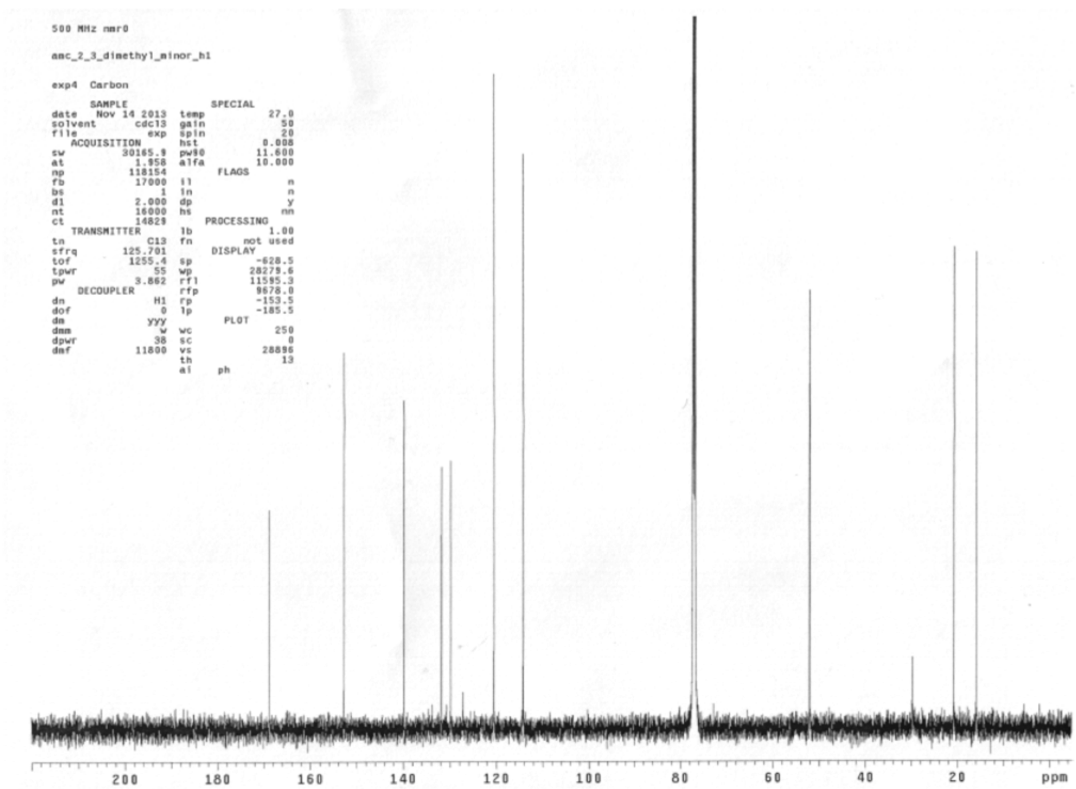
220
200
180
160
140
120
100
80
60
40
20
0
ppm

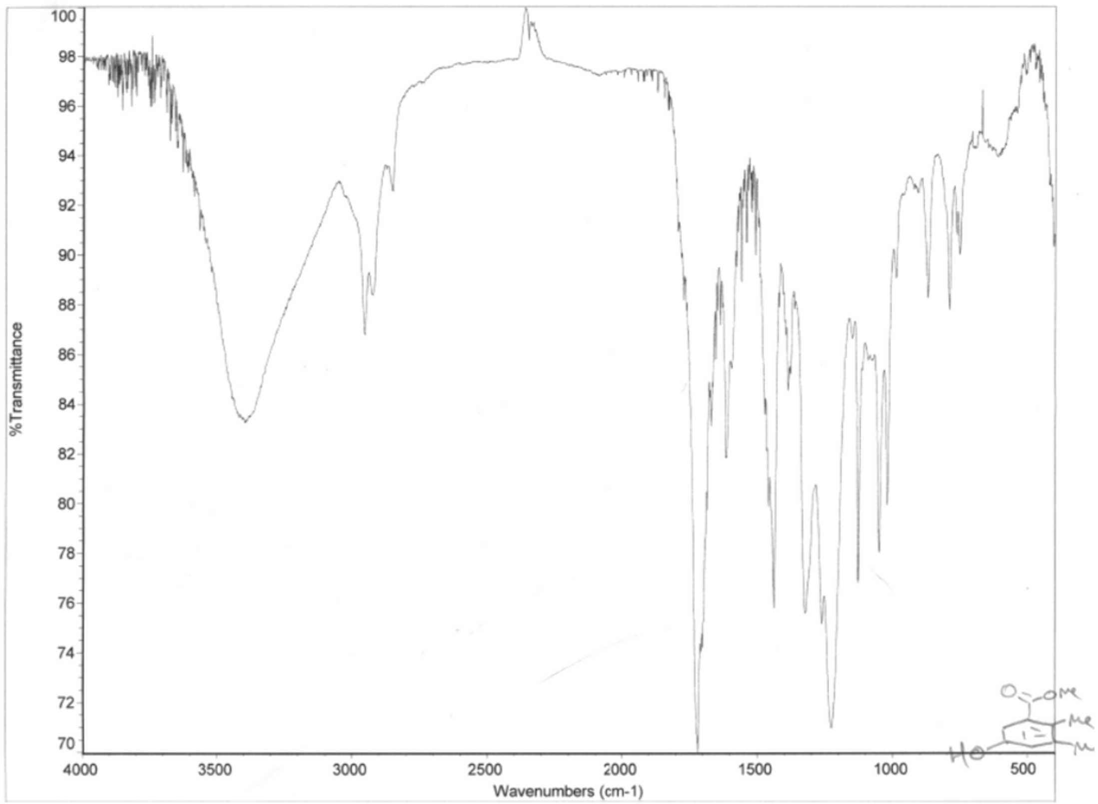

Mon Oct 07 09:15:32 2013 (GMT-05:00)
%Transmittance
Wavenumbers (cm-1)
100
90
80
70
60
50
40
30
4000
3500
3000
2500
2000
1500
1000
500

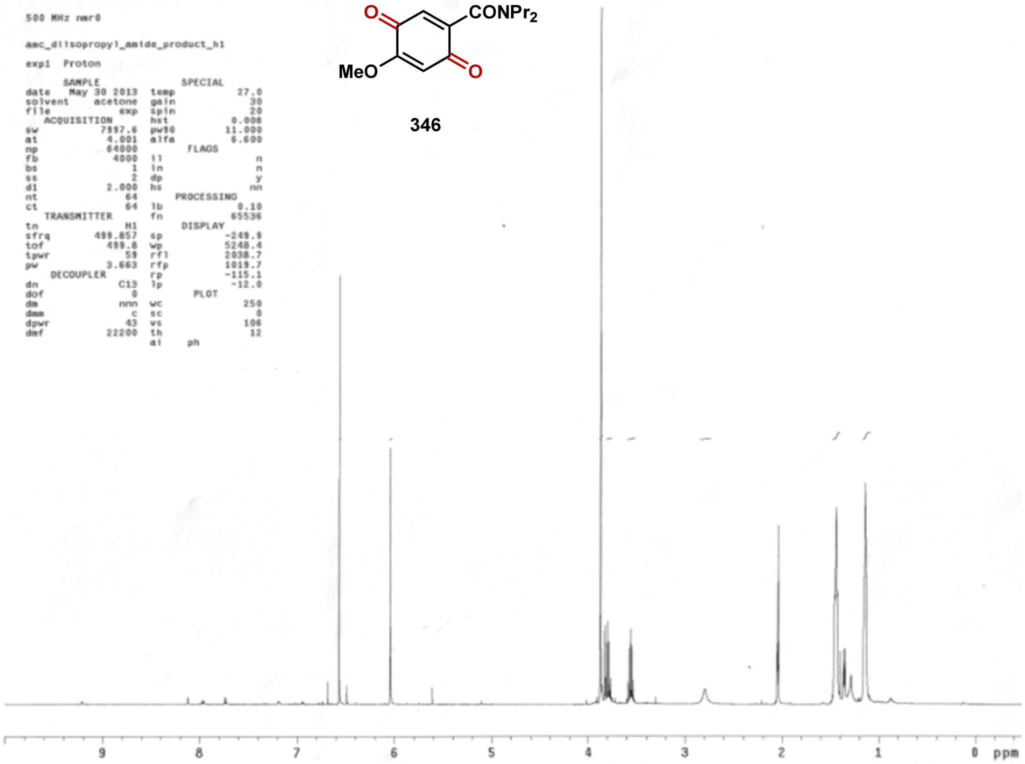

CO2Me
Me
Me
OH

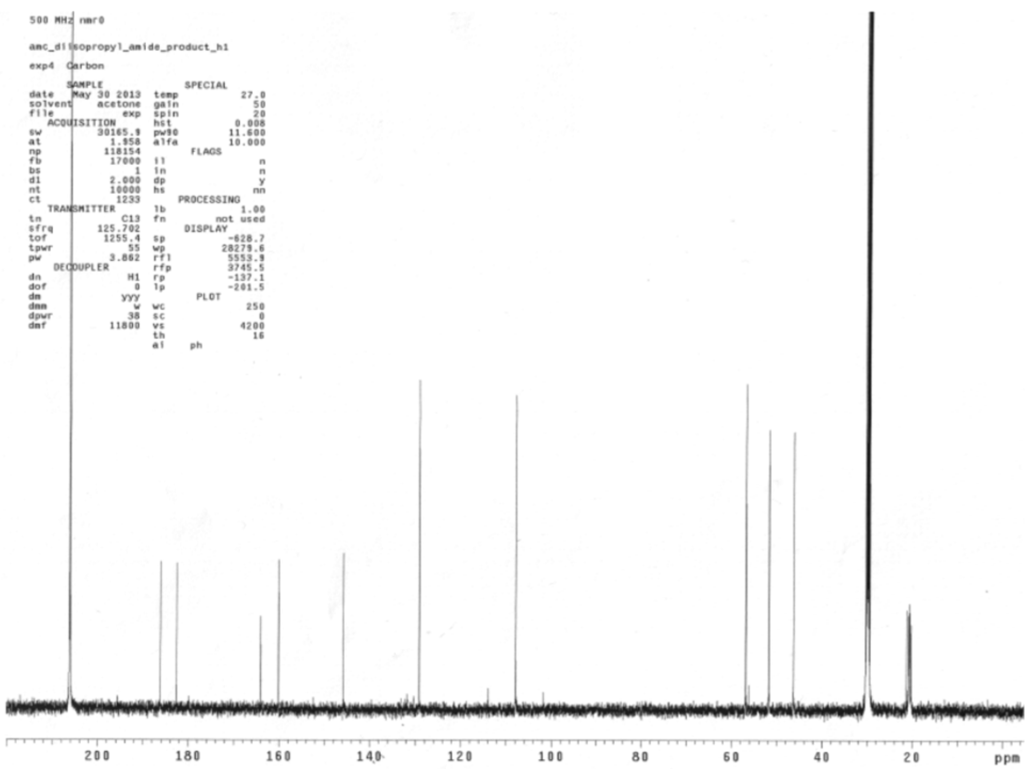
354c

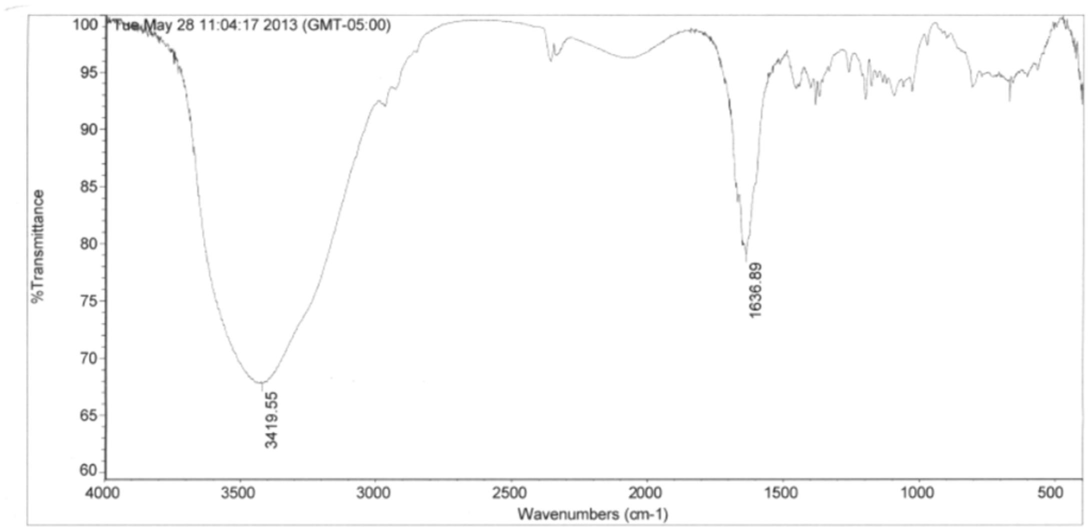

12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm


500 MHz nmr0
amc_2_3_dimethyl_minor_h1
exp4 Carbon
SAMPLE
date Nov 14 2013
solvent cdcl3
file exp
ACQUISITION
sw 30165.9
at 1.958
np 118154
fb 17000
bs 1
d1 2.000
nt 16000
ct 14829
TRANSMITTER
tn C13
sfrq 125.701
tof 1255.4
tpwr 55
pw 3.862
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 38
dmf 11800
SPECIAL
temp 27.0
gain 50
spin 20
hst 0.008
pw90 11.600
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -628.5
wp 28279.6
rfl 11595.3
rfp 9678.0
rp -153.5
lp -185.5
PLOT
wc 250
sc 0
vs 28896
th 13
ai ph
200 180 160 140 120 100 80 60 40 20 ppm


%Transmittance
Wavenumbers (cm-1)
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
4000
3500
3000
2500
2000
1500
1000
500
HO
Me
OMe

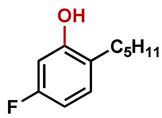

O
CONPr2
MeO
O
346
500 MHz nmr0
amc_diisopropyl_amide_product_h1
exp1 Proton
SAMPLE
date May 30 2013
solvent acetone
file exp
ACQUISITION
sw 7997.6
at 4.001
np 64000
fb 4000
bs 1
ss 2
d1 2.000
nt 64
ct 64
TRANSMITTER
tn H1
sfrq 499.857
tof 499.8
tpwr 59
pw 3.663
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 43
dmf 22200
SPECIAL
temp 27.0
gain 30
spin 20
hst 0.008
pw90 11.000
alfa 6.600
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.10
fn 65536
DISPLAY
sp -249.9
wp 5248.4
rfl 2038.7
rfp 1019.7
rp -115.1
lp -12.0
PLOT
wc 250
sc 0
vs 106
th 12
ai ph
9
8
7
6
5
4
3
2
1
0
ppm


500 MHz nmr0
amc_diisopropyl_amide_product_h1
exp4 Carbon
SAMPLE
date May 30 2013
solvent acetone
file exp
ACQUISITION
sw 30165.9
at 1.958
np 118154
fb 17000
bs 1
d1 2.000
nt 10000
ct 1233
TRANSMITTER
tn C13
sfrq 125.702
tof 1255.4
tpwr 55
pw 3.882
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 38
dmf 11800
SPECIAL
temp 27.0
gain 50
spin 20
hst 0.008
pw90 11.600
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -628.7
wp 28279.6
rfl 5553.9
rfp 3745.5
rp -137.1
lp -201.5
PLOT
wc 250
sc 0
vs 4200
th 16
ai ph
200
180
160
140
120
100
80
60
40
20
ppm

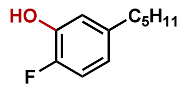


Tue May 28 11:06:08 2013 (GMT-05:00)
FIND PEAKS:

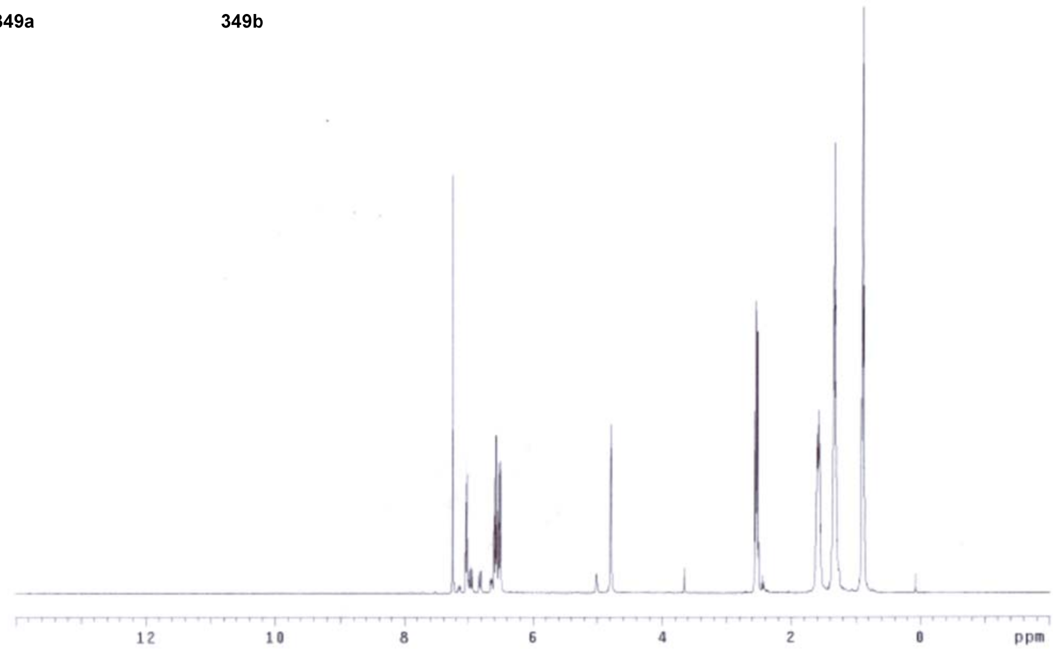
Spectrum:	*Tue May 28 11:04:17 2013 (GMT-05:00)			
Region:	4000.00	400.00		
Absolute threshold:	93.557			
Sensitivity:	15			
Peak list:				
	Position:	1636.89	Intensity:	79.079
	Position:	3419.55	Intensity:	67.770

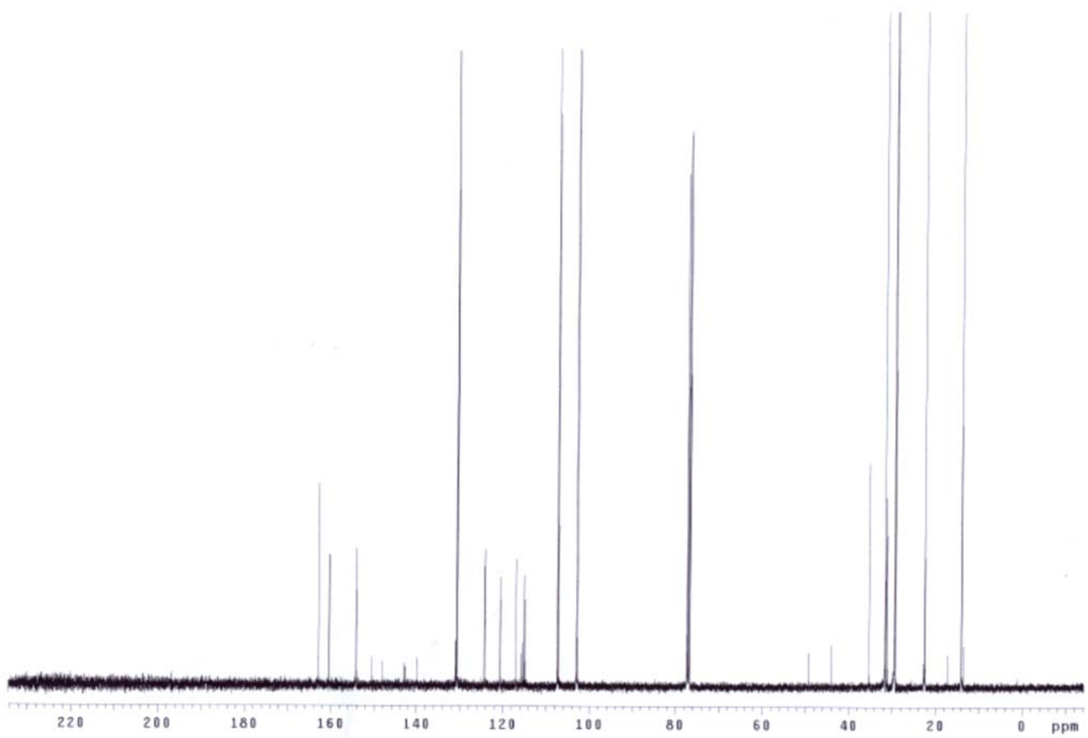

OH
C5H11
F

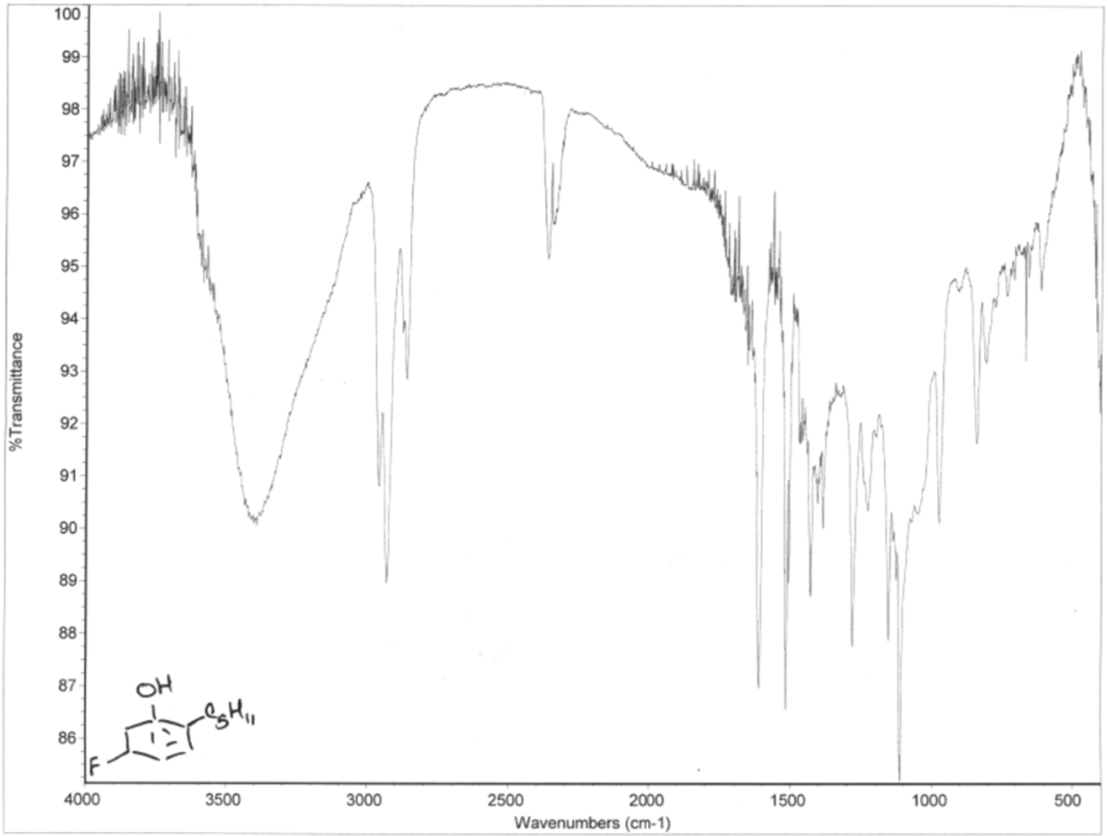
349a


HO
C5H11
F

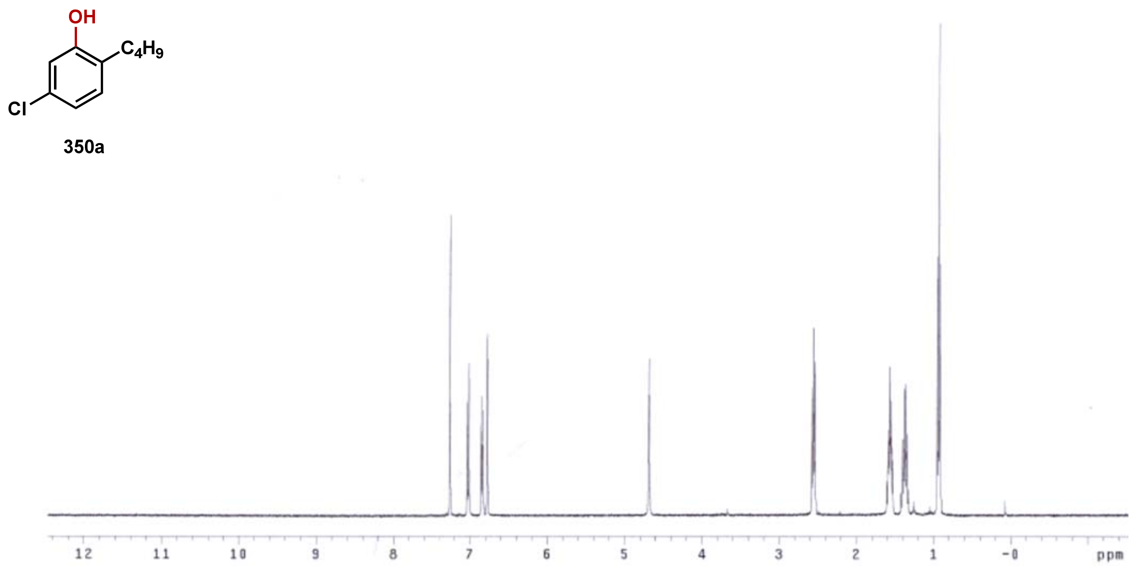
349b


12
10
8
6
4
2
0
ppm

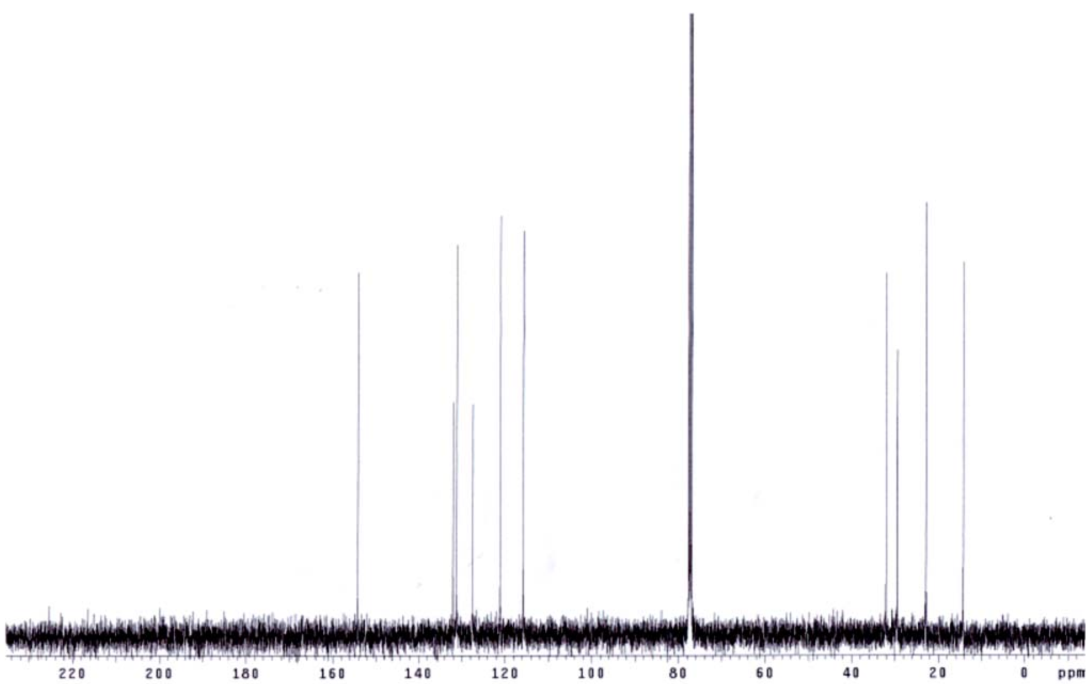

220
200
180
160
140
120
100
80
60
40
20
0
ppm

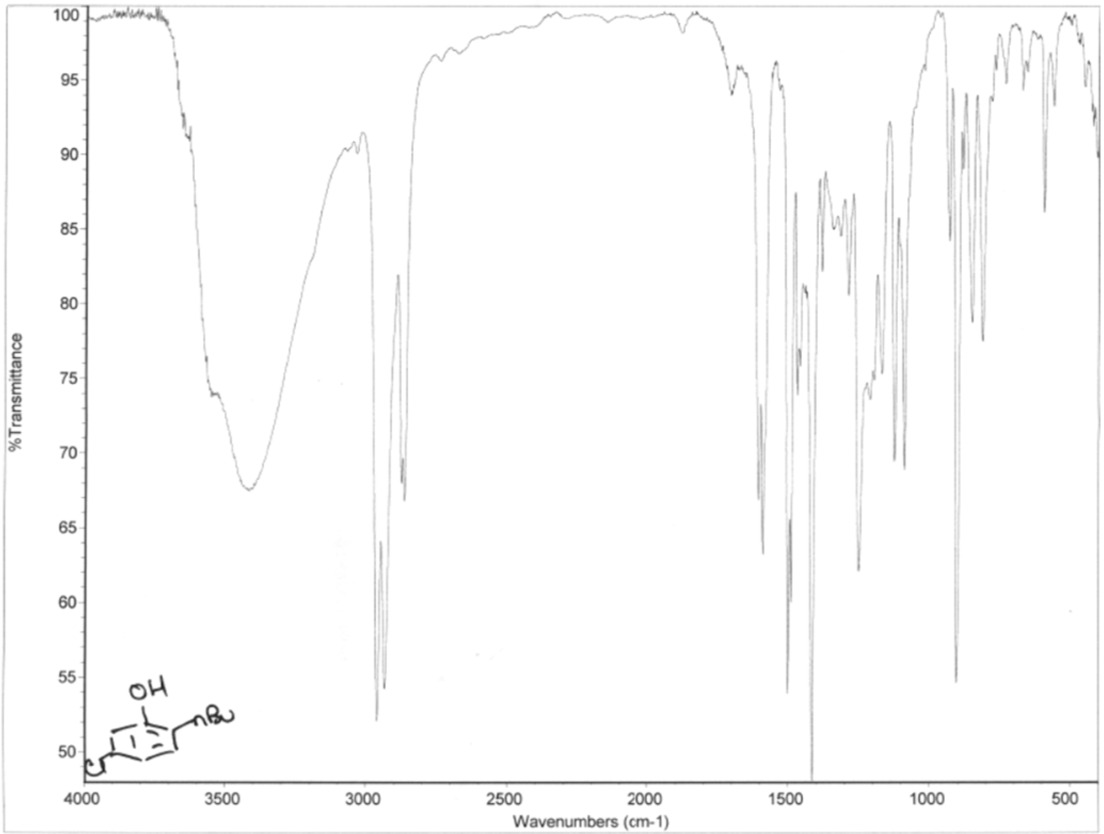


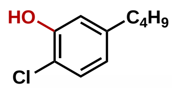
%Transmittance
100
99
98
97
96
95
94
93
92
91
90
89
88
87
86
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)
OH
F



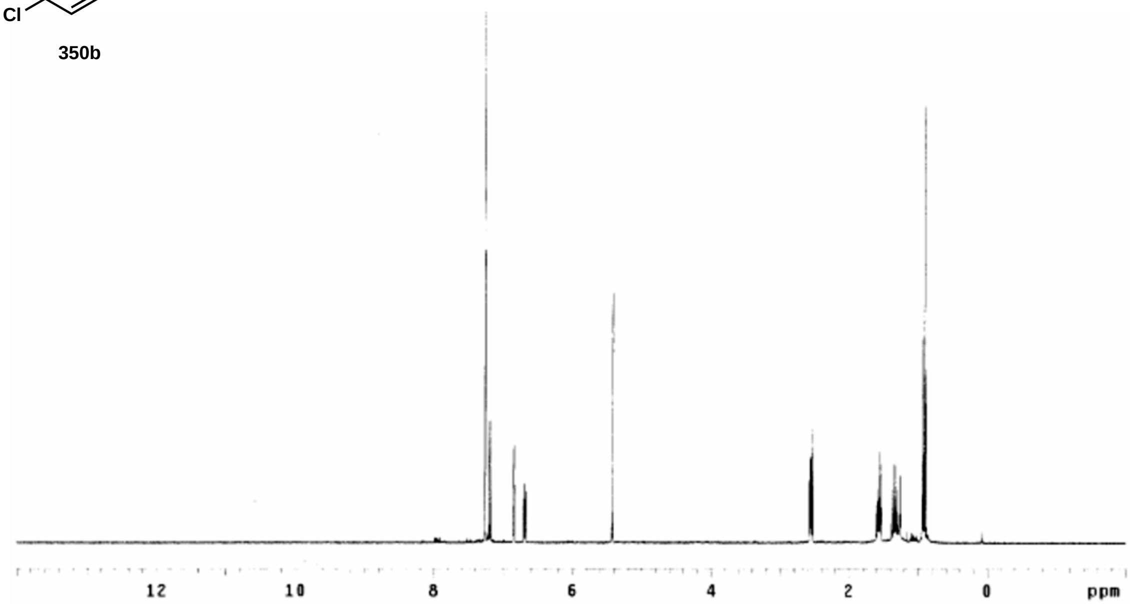
350a

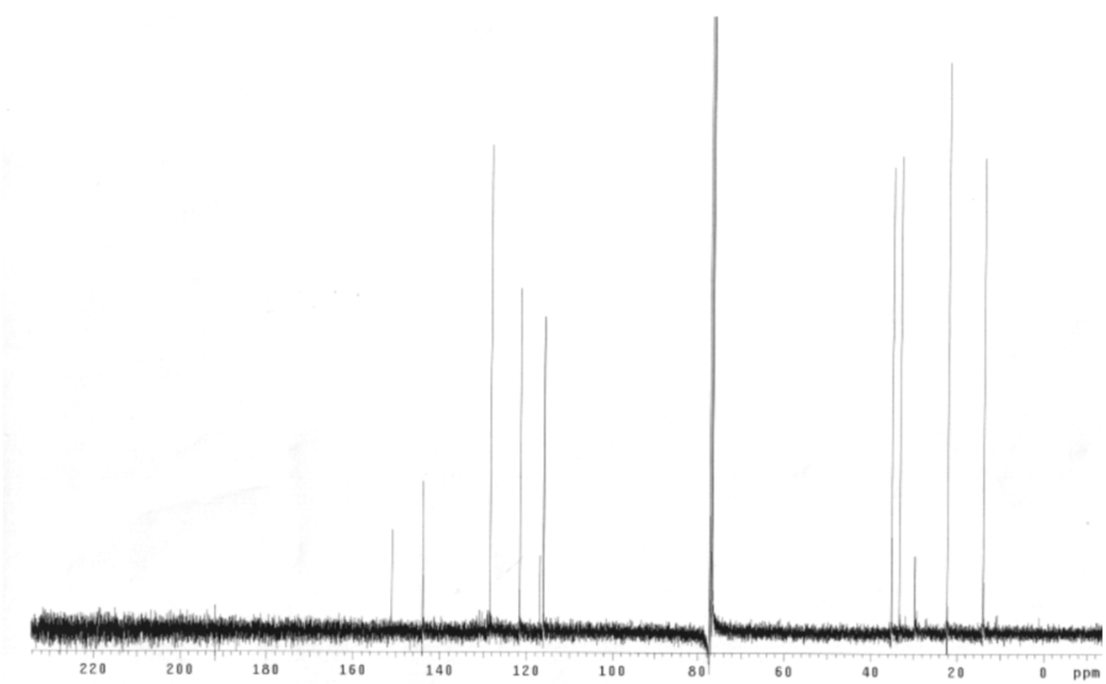


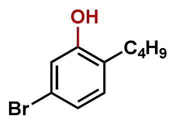

%Transmittance
Wavenumbers (cm-1)
100
95
90
85
80
75
70
65
60
55
50
4000
3500
3000
2500
2000
1500
1000
500
OH
nBu
Cl


HO
C4H9
Cl

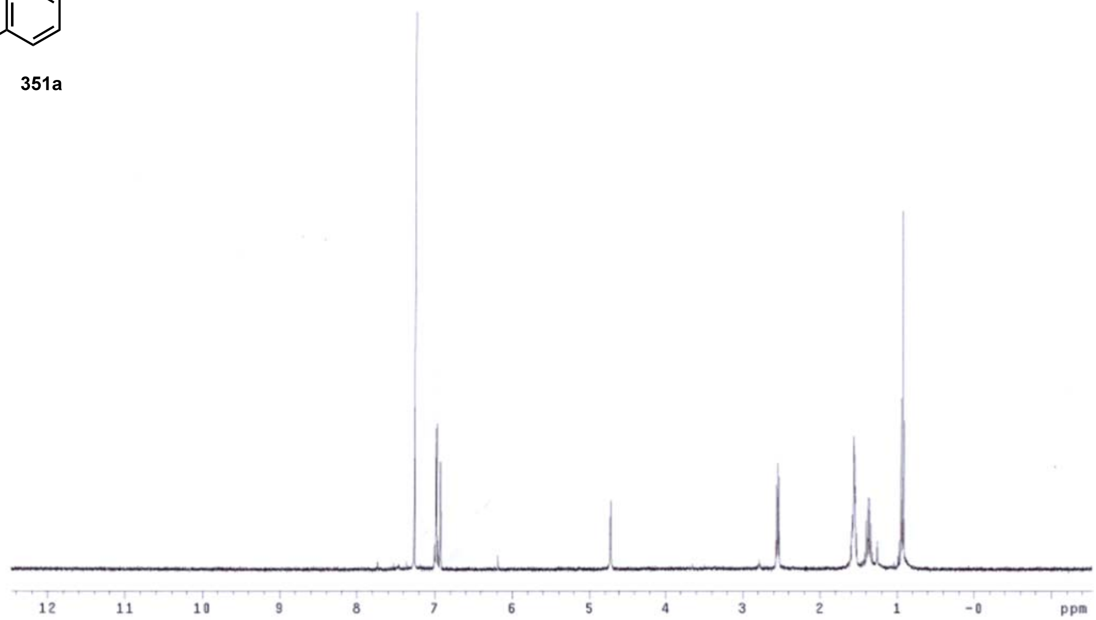
350b

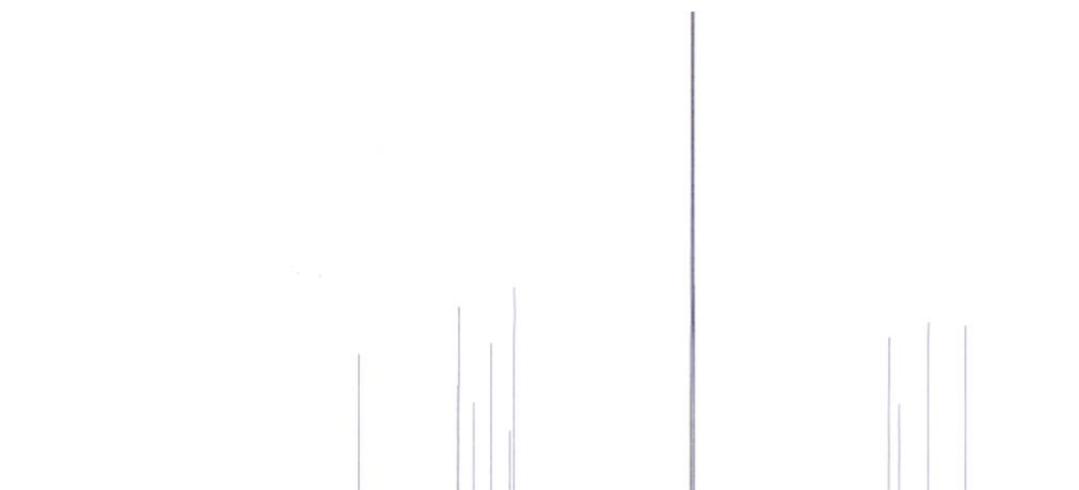

12
10
8
6
4
2
0
ppm

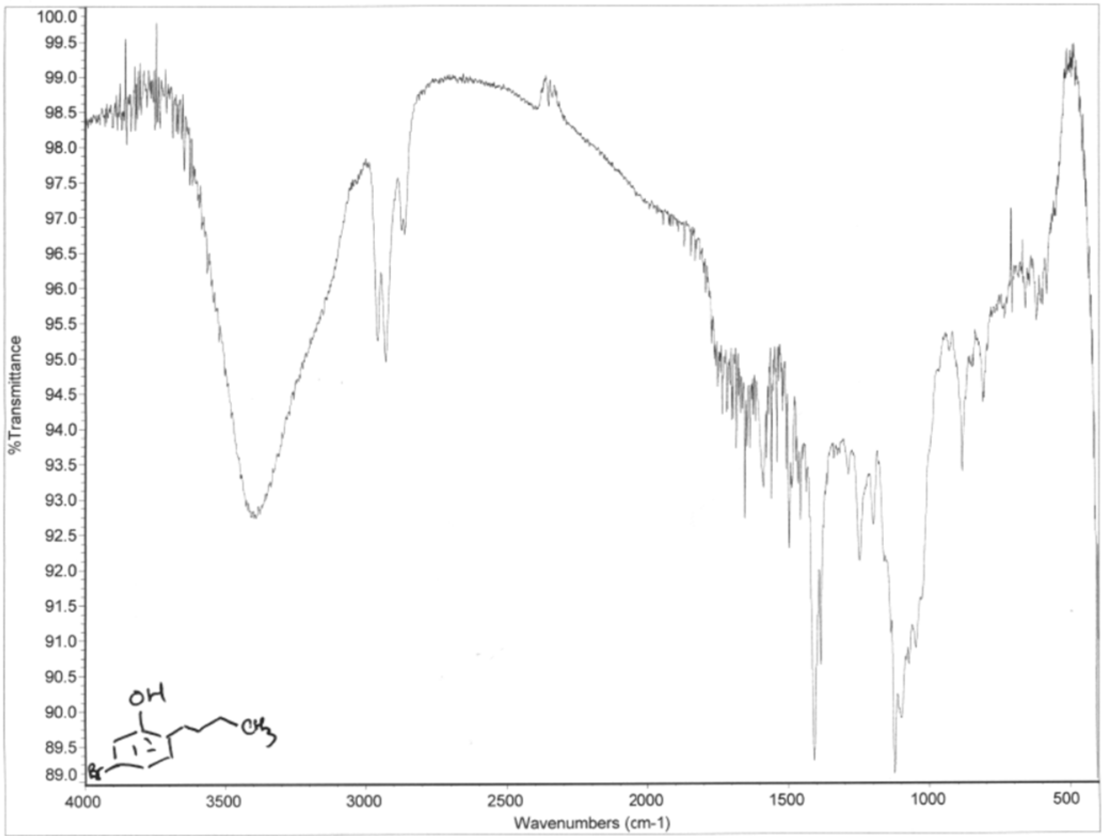

220
200
180
160
140
120
100
80
60
40
20
0
ppm


OH
C4H9
Br

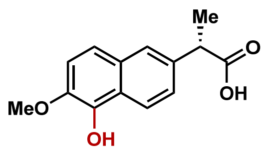
351a


12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

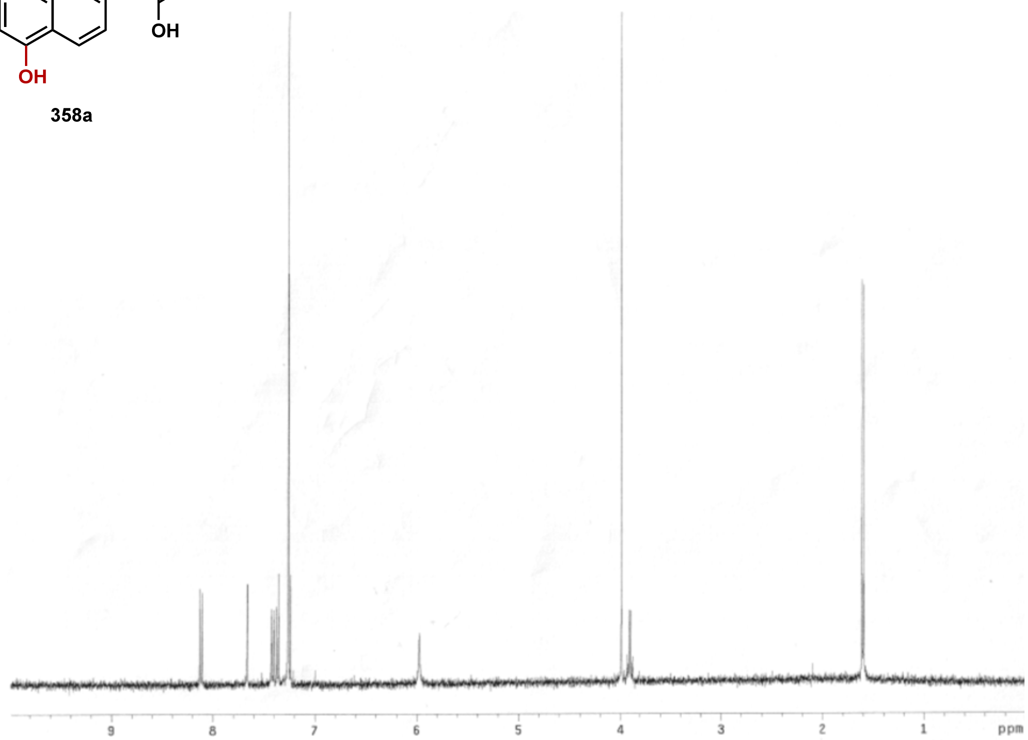

220 200 180 160 140 120 100 80 60 40 20 0 ppm

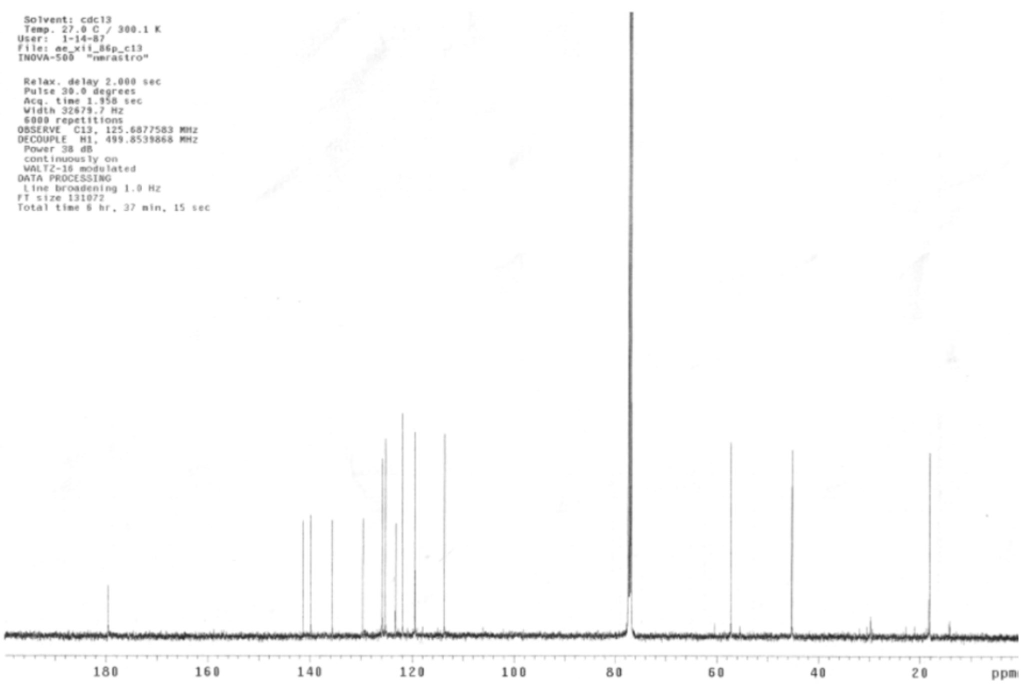


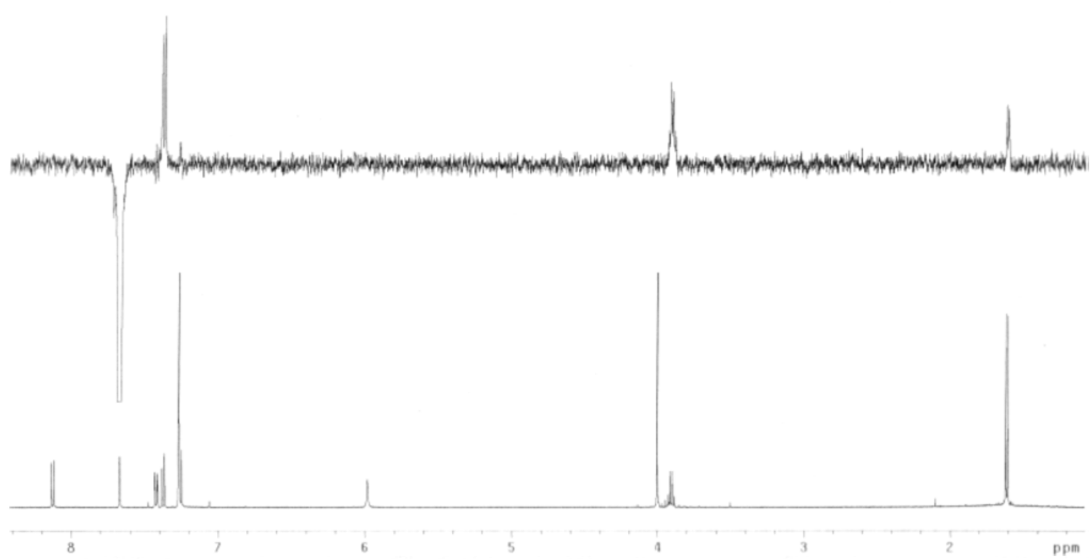
100.0
99.5
99.0
98.5
98.0
97.5
97.0
96.5
96.0
95.5
95.0
94.5
94.0
93.5
93.0
92.5
92.0
91.5
91.0
90.5
90.0
89.5
89.0
%Transmittance
OH
CH3
Br
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

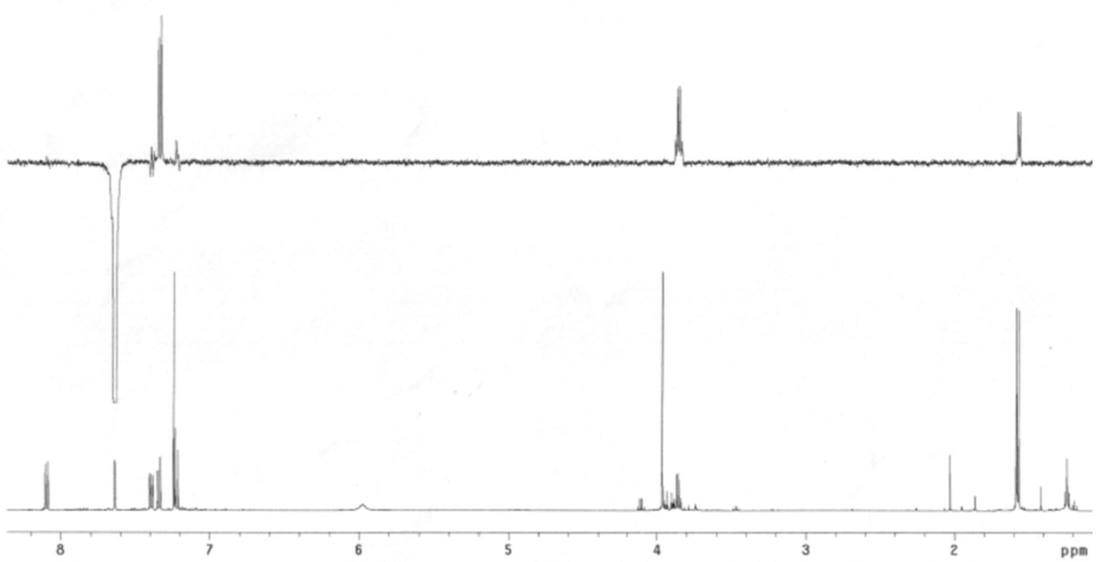

Me
O
OH
MeO
OH

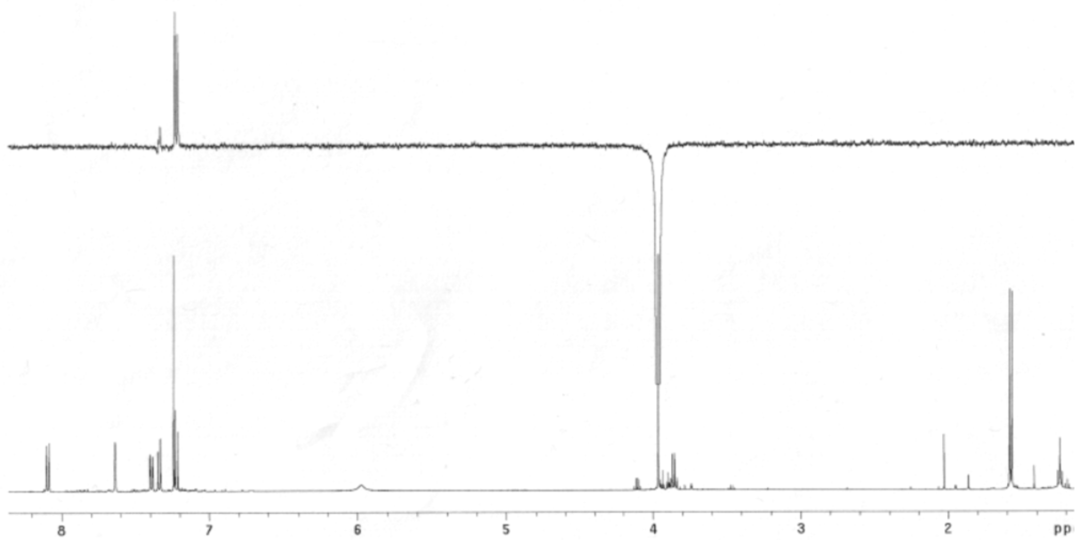
358a

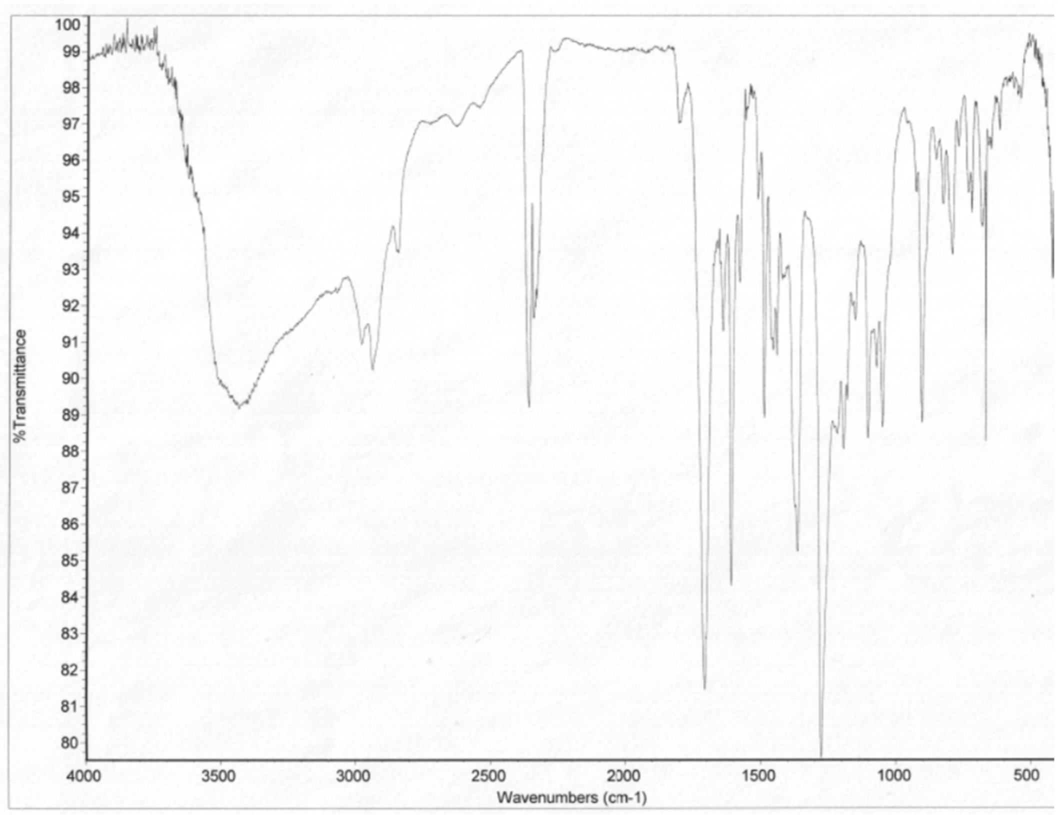

9
8
7
6
5
4
3
2
1
ppm

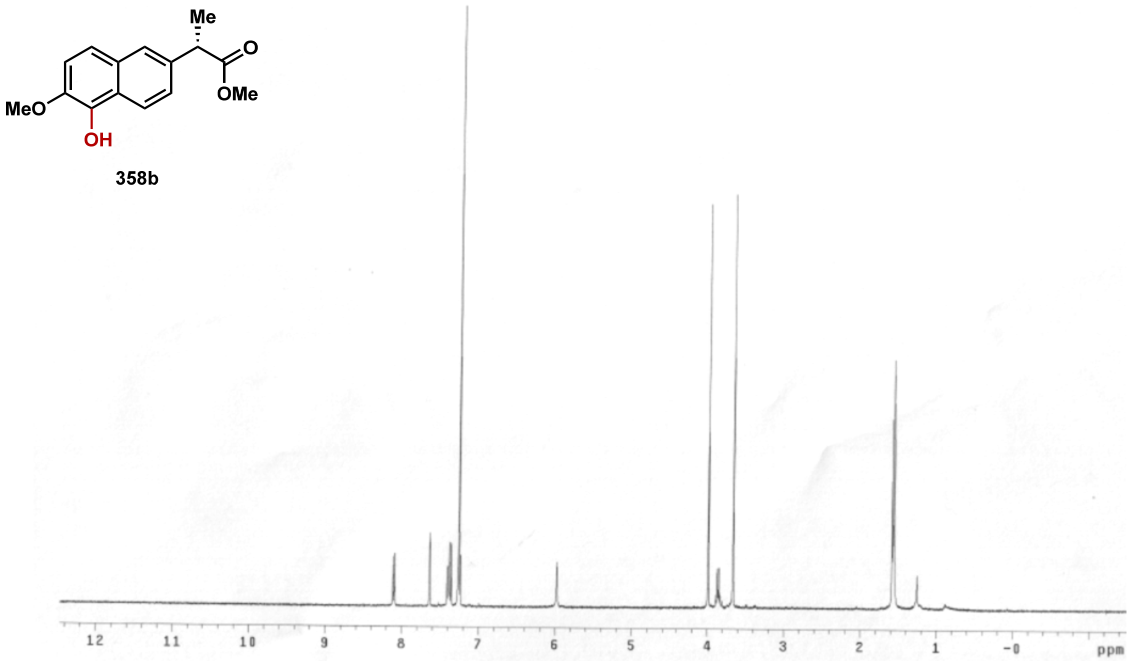

Solvent: cdcl3
Temp. 27.0 C / 300.1 K
User: 1-14-87
File: ae_xii_86p_c13
INOVA-500 "nmrastro"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.958 sec
Width 32679.7 Hz
6000 repetitions
OBSERVE C13, 125.6877583 MHz
DECOUPLE H1, 499.8539868 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 6 hr, 37 min, 15 sec
180
160
140
120
100
80
60
40
20
ppm


8
7
6
5
4
3
2
ppm

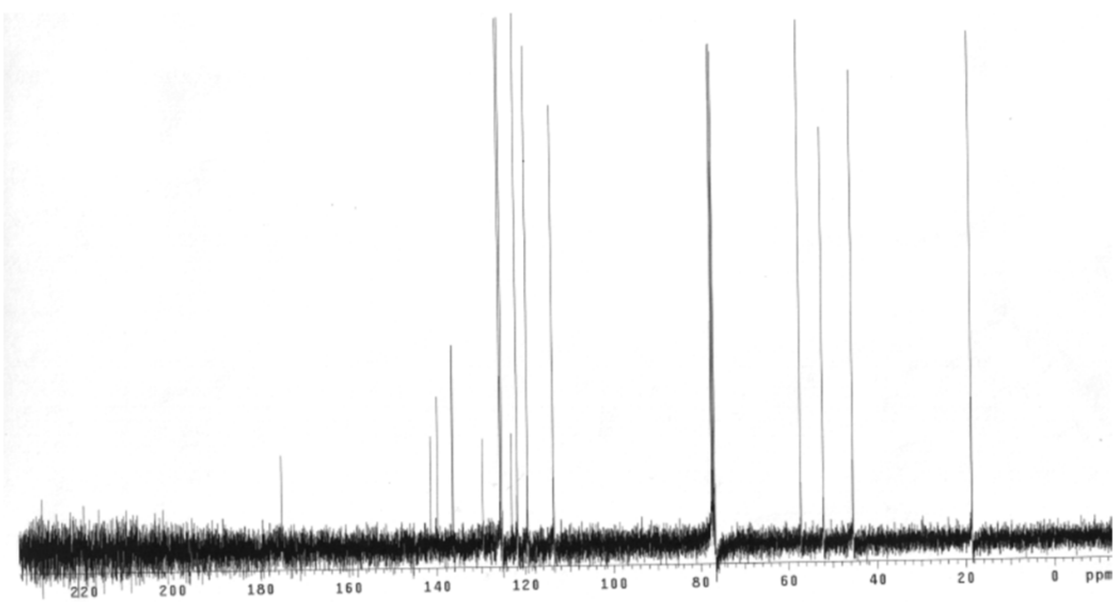

8
7
6
5
4
3
2
ppm

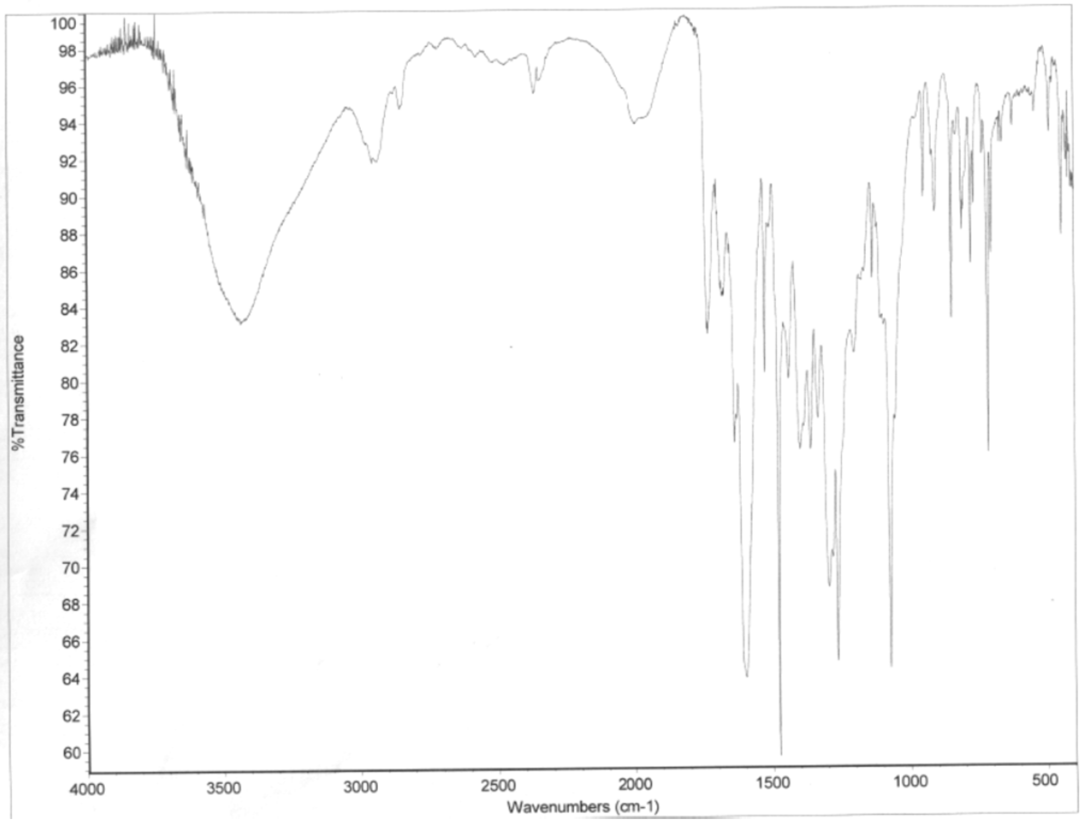

8
7
6
5
4
3
2
ppm

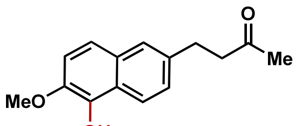

%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500



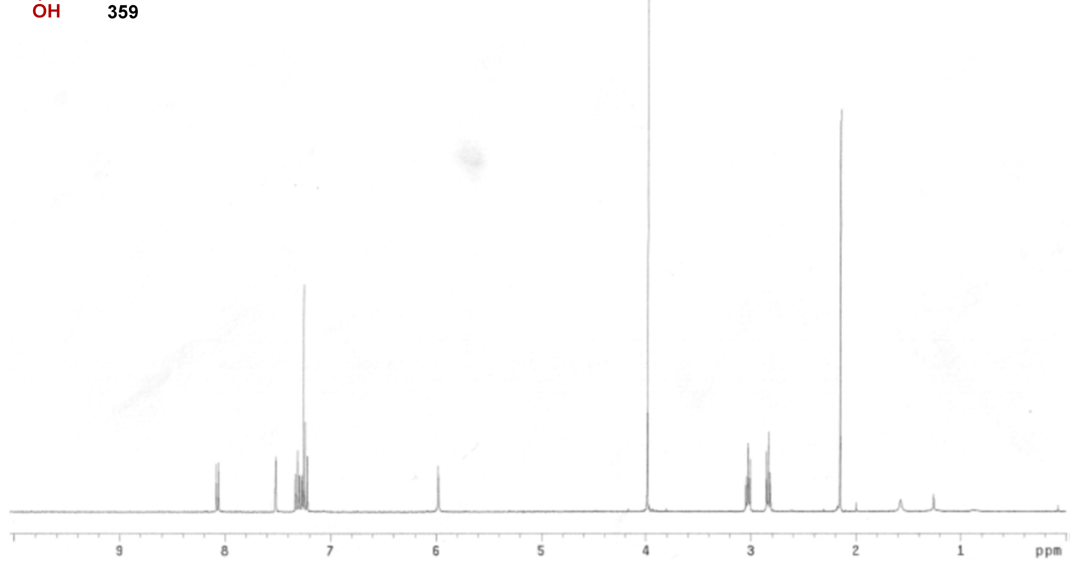
358b

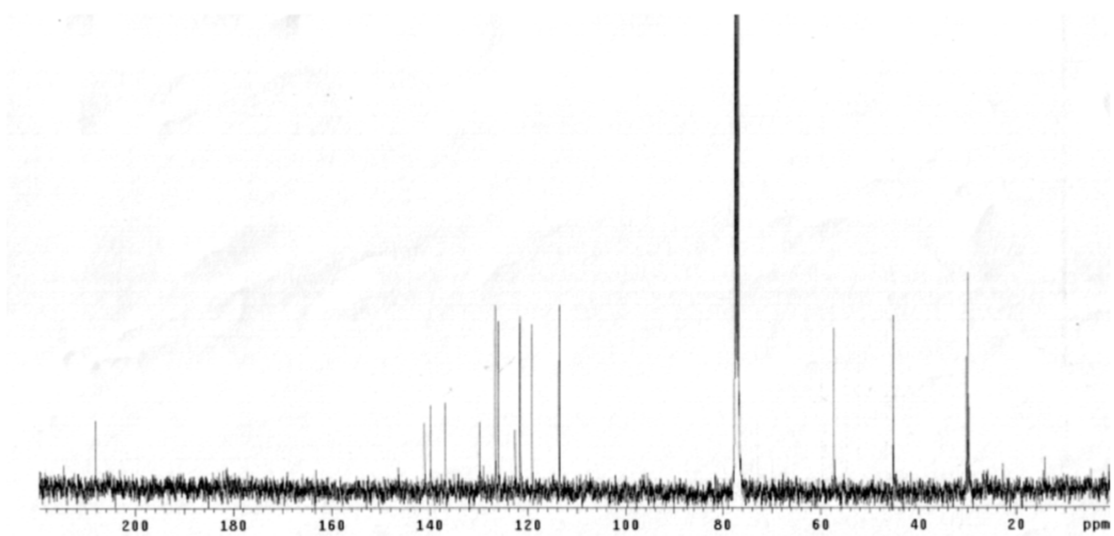


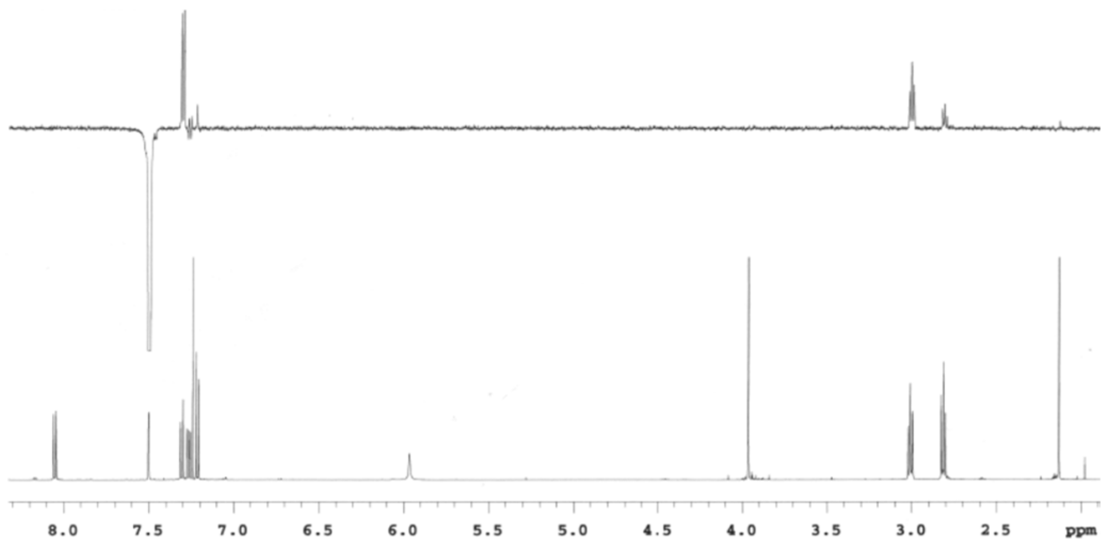

%Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

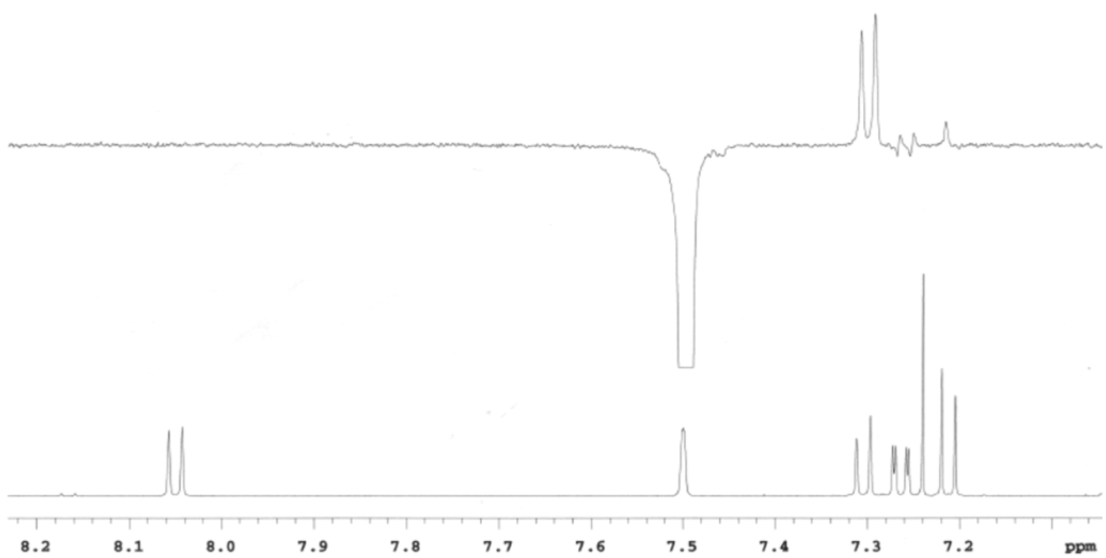


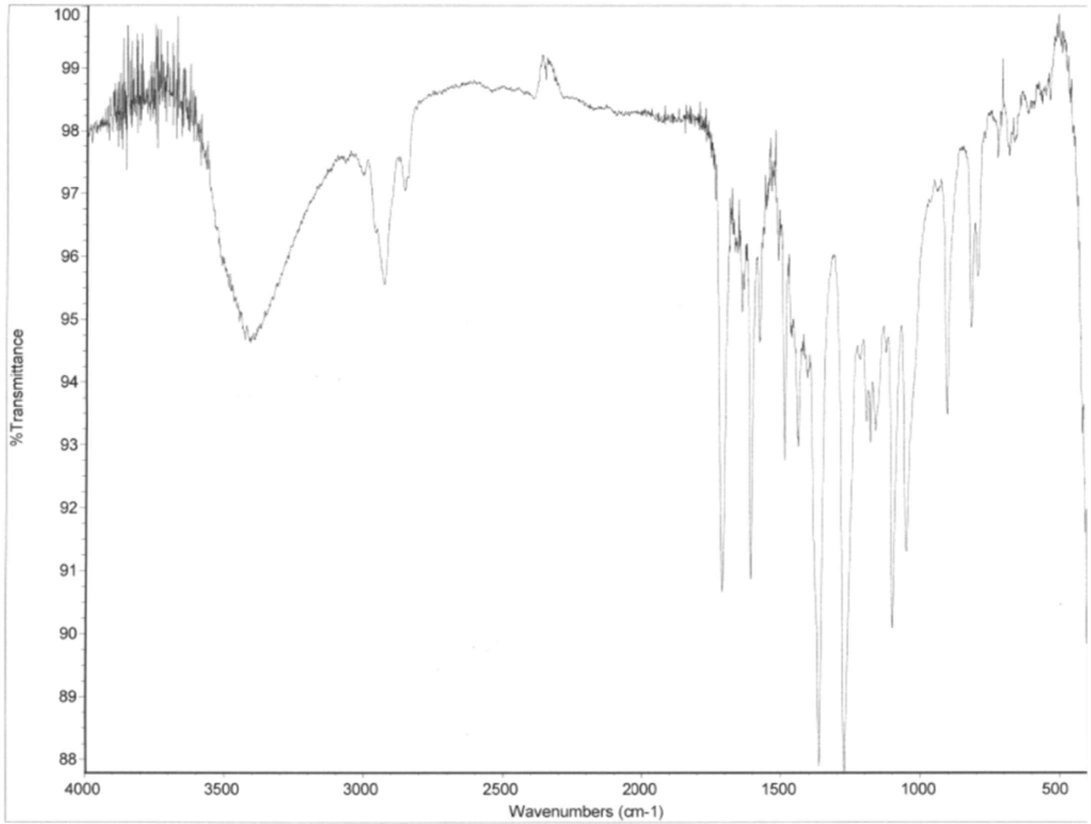
359

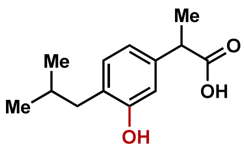




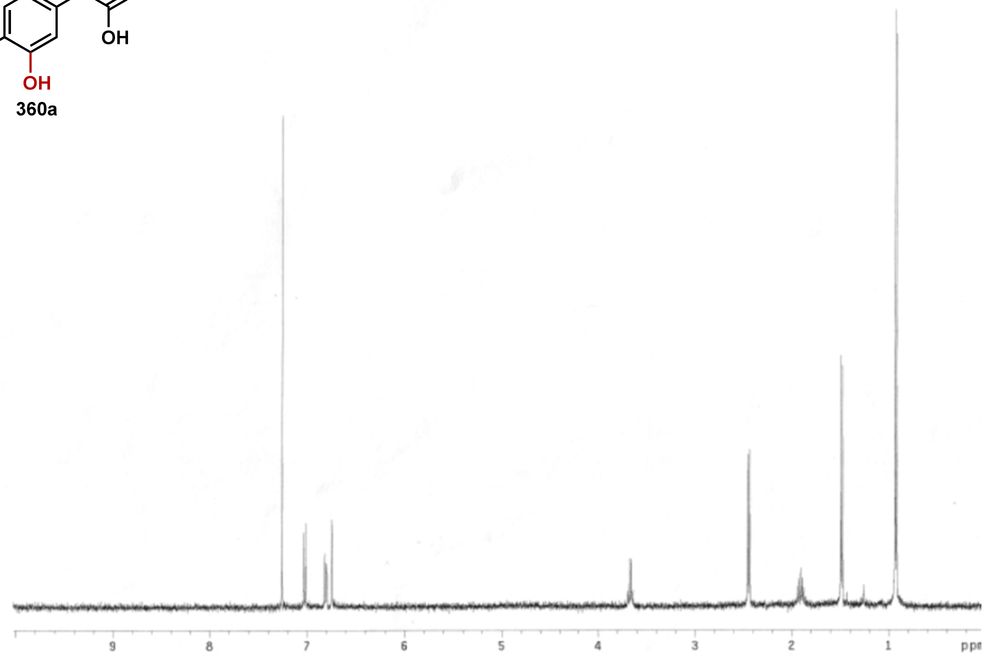

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm

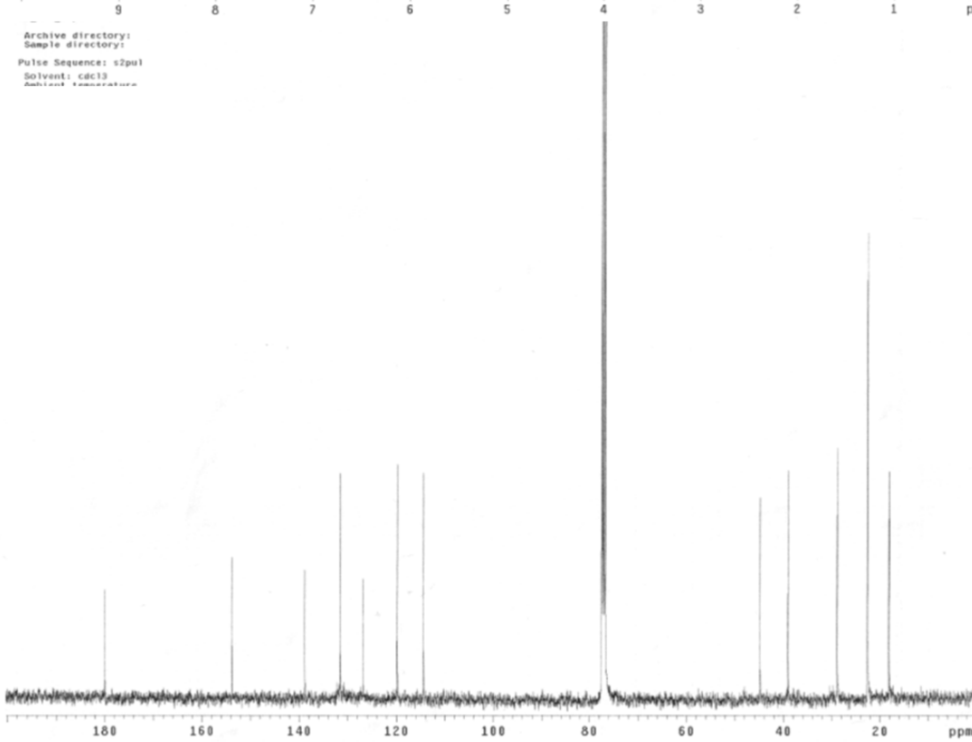

8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
ppm

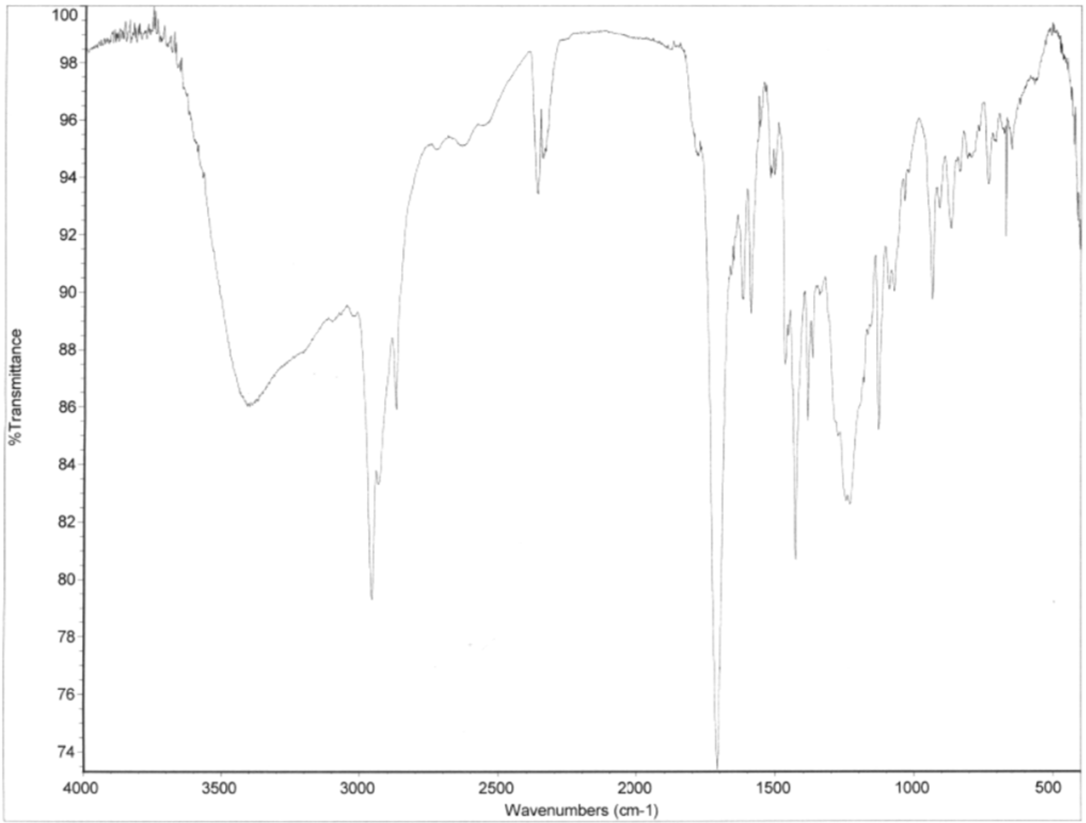

%Transmittance
Wavenumbers (cm-1)
100
99
98
97
96
95
94
93
92
91
90
89
88
4000
3500
3000
2500
2000
1500
1000
500

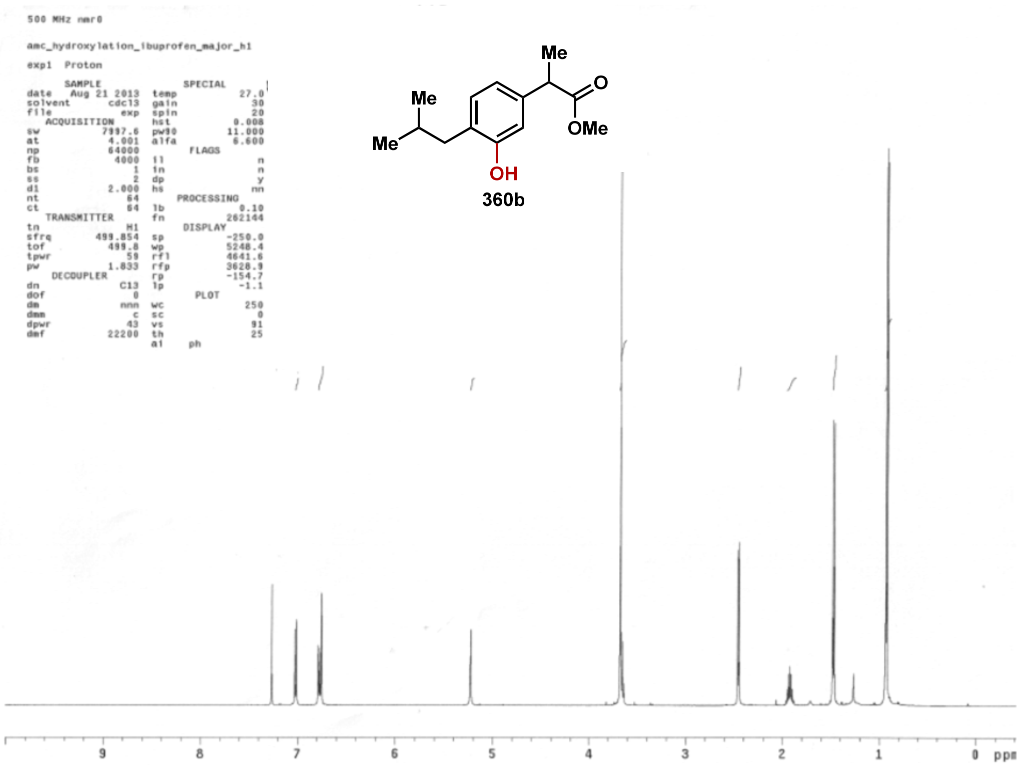

Me
Me
Me
OH
O
OH

360a

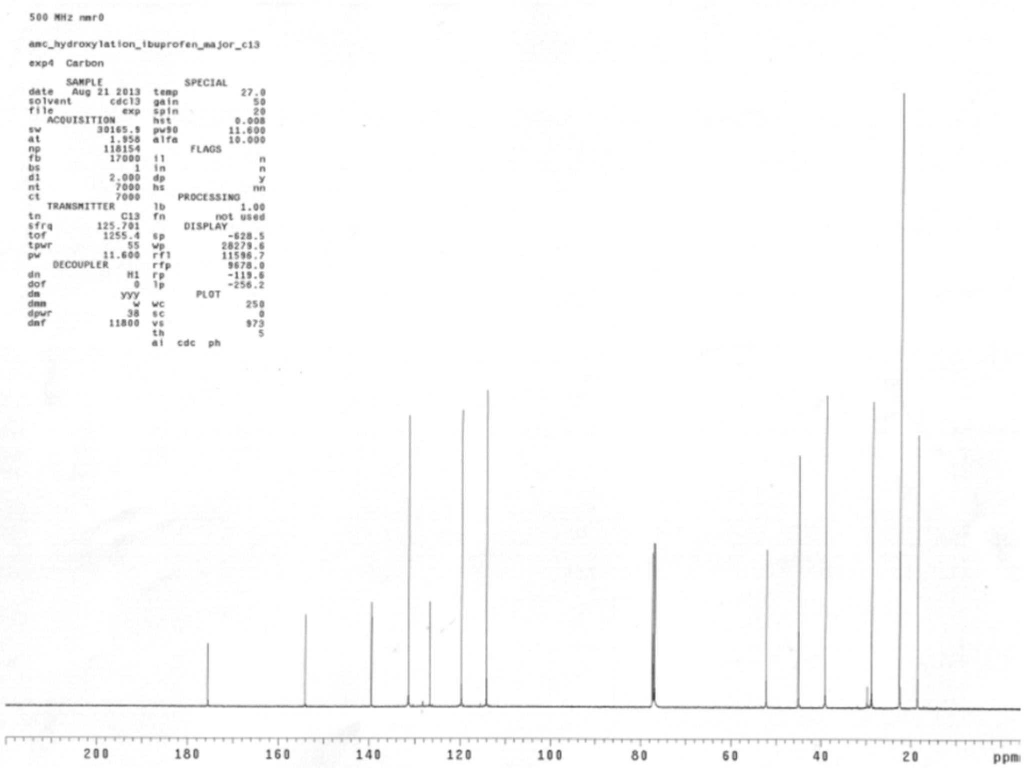

9
8
7
6
5
4
3
2
1
ppm


Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
180
160
140
120
100
80
60
40
20
ppm

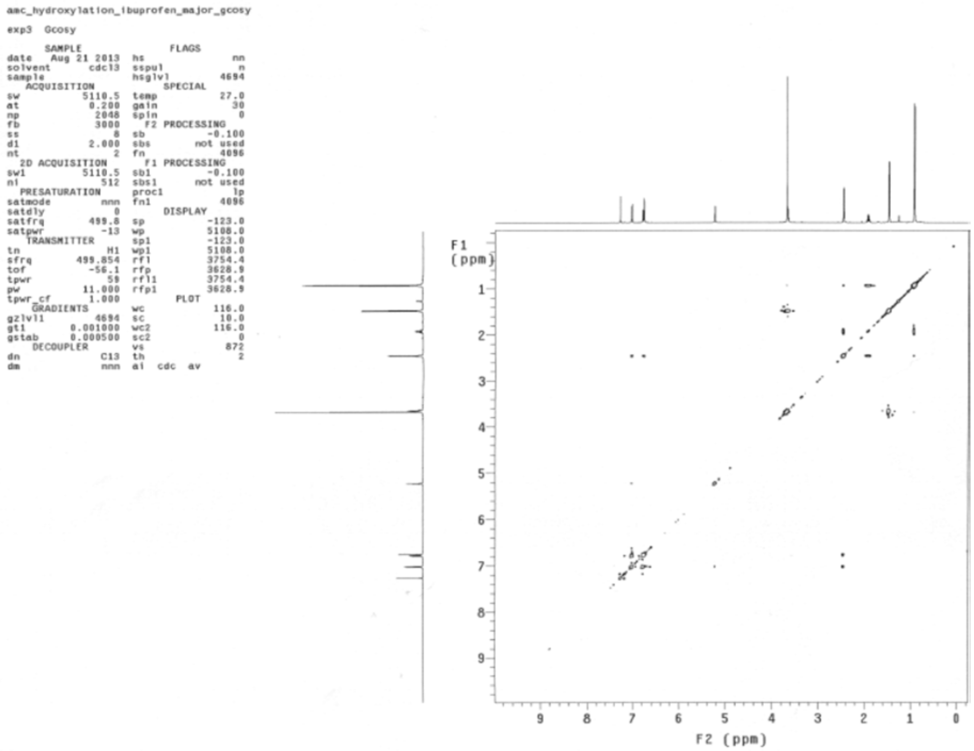

%Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
76
74
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

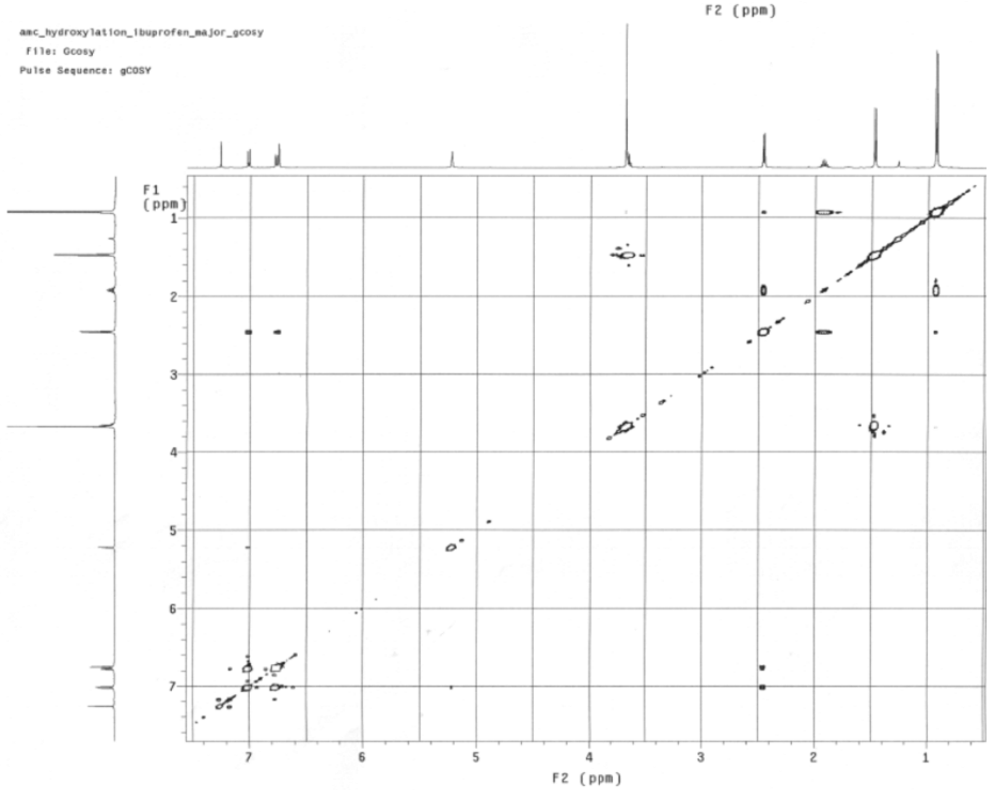


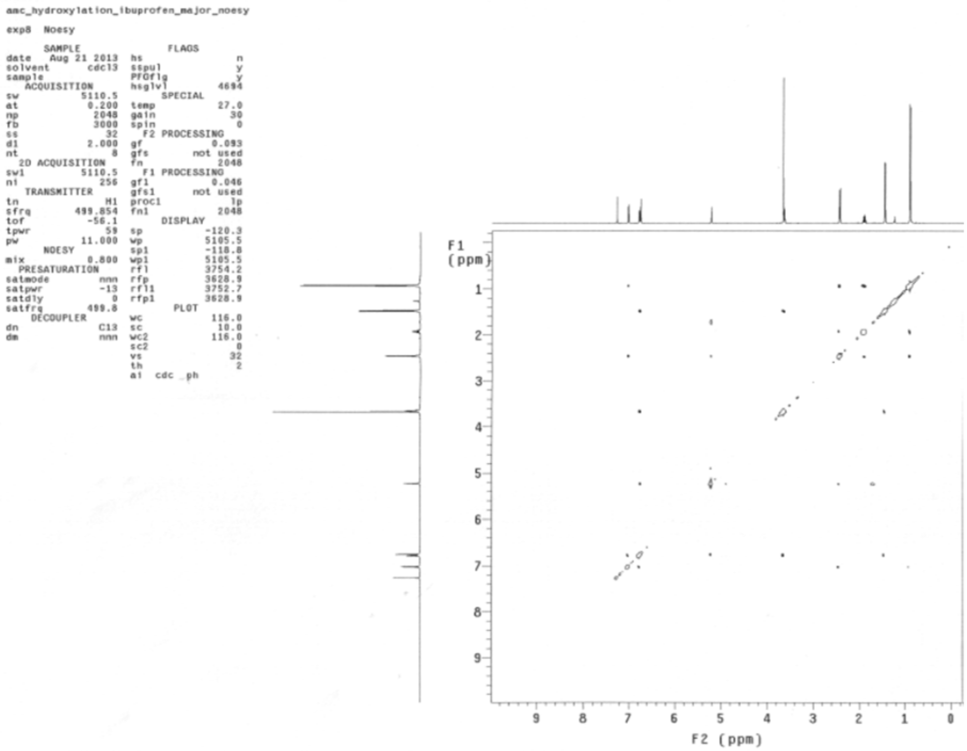
500 MHz nmr0
amc_hydroxylation_ibuprofen_major_h1
exp1 Proton
Me
Me
Me
O
OMe
OH
360b
9
8
7
6
5
4
3
2
1
0
ppm

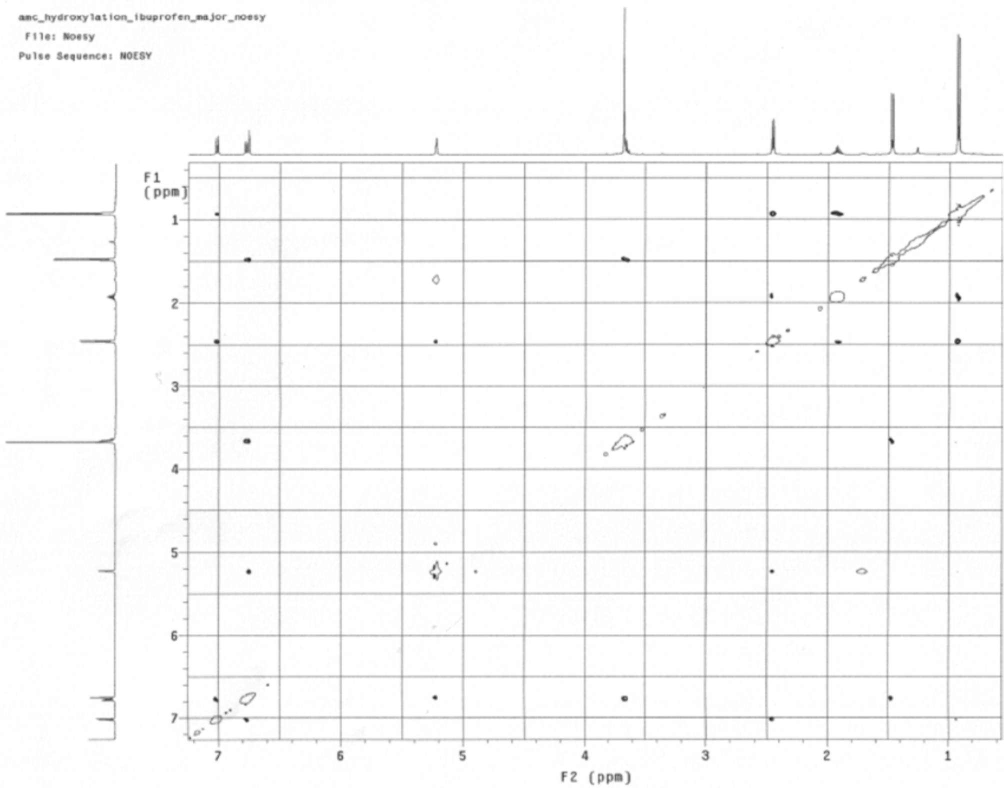


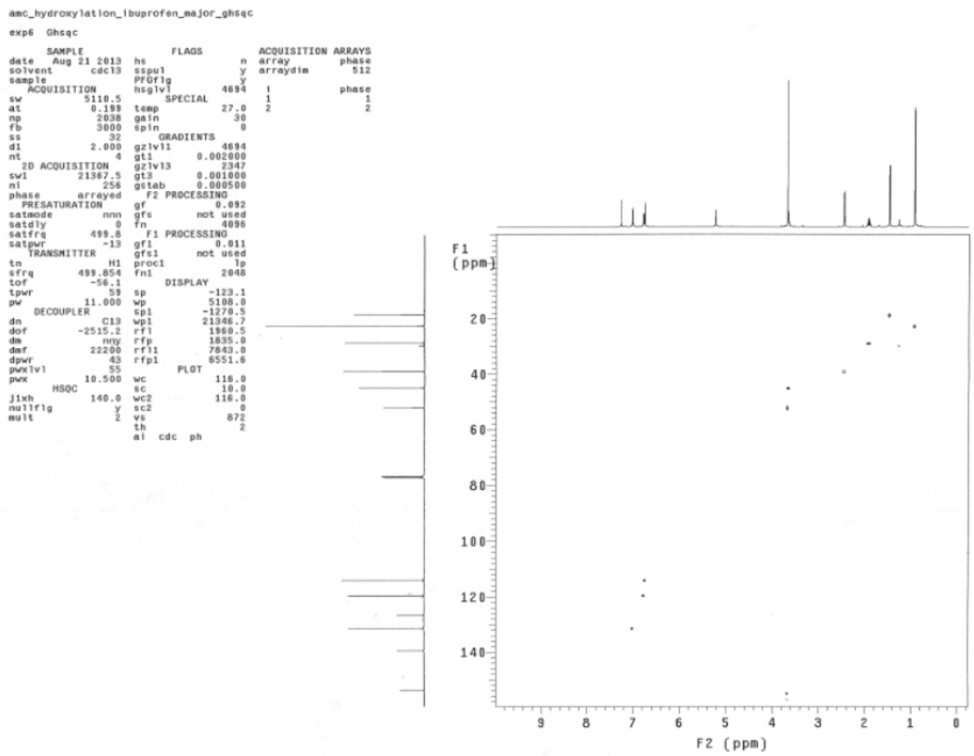
500 MHz nmr0
amc_hydroxylation_ibuprofen_major_c13
exp4 Carbon
200
180
160
140
120
100
80
60
40
20
ppm

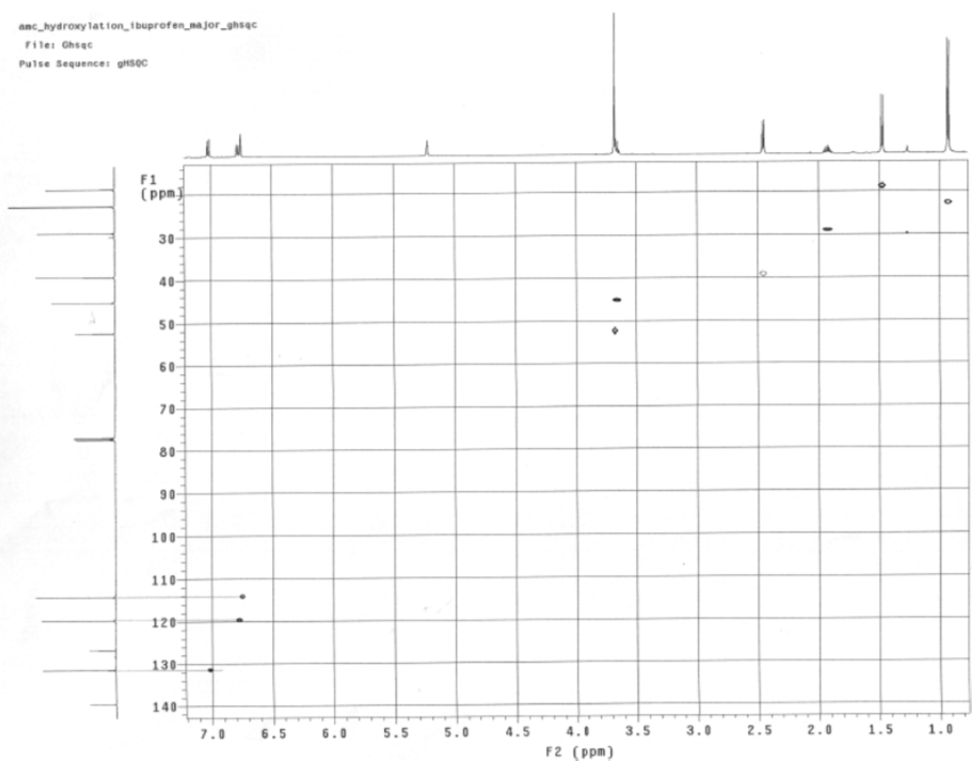

amc_hydroxylation_ibuprofen_major_gcosy
exp3 Gcosy
SAMPLE
date Aug 21 2013
solvent cdcl3
sample
ACQUISITION
sw 5110.5
at 0.200
np 2048
fb 3000
ss 8
d1 2.000
nt 2
2D ACQUISITION
sw1 5110.5
ni 512
PRESATURATION
satmode nnn
satdly 0
satfrq 499.8
satpwr -13
TRANSMITTER
tn H1
sfrq 499.854
tof -56.1
tpwr 59
pw 11.000
tpwr_cf 1.000
GRADIENTS
gzlvl1 4694
gt1 0.001000
gstab 0.000500
DECOUPLER
dn C13
dm nnn
FLAGS
hs nn
sspul n
hsglvl 4694
SPECIAL
temp 27.0
gain 30
spin 0
F2 PROCESSING
sb -0.100
sbs not used
fn 4096
F1 PROCESSING
sb1 -0.100
sbs1 not used
proc1 lp
fn1 4096
DISPLAY
sp -123.0
wp 5108.0
sp1 -123.0
wp1 5108.0
rfl 3754.4
rfp 3628.9
rfl1 3754.4
rfp1 3628.9
PLOT
wc 116.0
sc 10.0
wc2 116.0
sc2 0
vs 872
th 2
ai cdc av
F1 (ppm)
F2 (ppm)


amc_hydroxylation_ibuprofen_major_gcosy
File: Gcosy
Pulse Sequence: gCOSY
F1 (ppm)
F2 (ppm)


amc_hydroxylation_ibuprofen_major_noesy
exp8 Noesy
SAMPLE
date Aug 21 2013
solvent cdcl3
sample
ACQUISITION
sw 5110.5
at 0.200
np 2048
fb 3000
ss 32
d1 2.000
nt 8
2D ACQUISITION
sw1 5110.5
ni 256
TRANSMITTER
tn H1
sfrq 499.854
tof -56.1
tpwr 59
pw 11.000
NOESY
mix 0.800
PRESATURATION
satmode nnn
satpwr -13
satdly 0
satfrq 499.8
DECOUPLER
dn C13
dm nnn
FLAGS
hs n
sspul y
PFGflg y
hsglvl 4694
SPECIAL
temp 27.0
gain 30
spin 0
F2 PROCESSING
gf 0.093
gfs not used
fn 2048
F1 PROCESSING
gf1 0.046
gfs1 not used
proc1 lp
fn1 2048
DISPLAY
sp -120.3
wp 5105.5
sp1 -118.8
wp1 5105.5
rfl 3754.2
rfp 3628.9
rfl1 3752.7
rfp1 3628.9
PLOT
wc 116.0
sc 10.0
wc2 116.0
sc2 0
vs 32
th 2
ai cdc ph
F1 (ppm)
F2 (ppm)


amc_hydroxylation_ibuprofen_major_noesy
File: Noesy
Pulse Sequence: NOESY
F1 (ppm)
F2 (ppm)

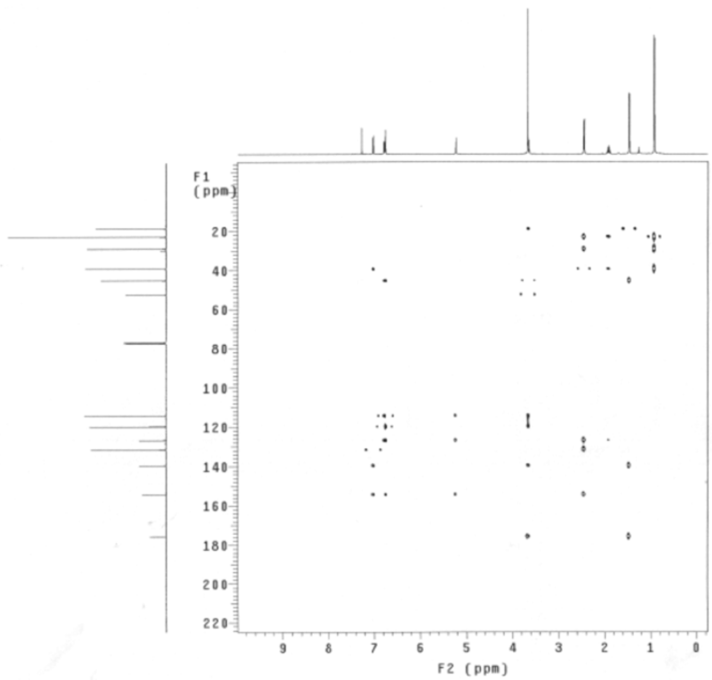

amc_hydroxylation_ibuprofen_major_ghsqc
exp6 Ghsqc
SAMPLE
date Aug 21 2013
solvent cdcl3
sample
ACQUISITION
sw 5110.5
at 0.199
np 2038
fb 3000
ss 32
d1 2.000
nt 4
2D ACQUISITION
sw1 21367.5
ni 256
phase arrayed
PRESATURATION
satmode nnn
satdly 0
satfrq 499.8
satpwr -13
TRANSMITTER
tn H1
sfrq 499.854
tof -56.1
tpwr 59
pw 11.000
DECOUPLER
dn C13
dof -2515.2
dm nny
dmf 22200
dpwr 43
pwxlvl 55
pwx 10.500
HSQC
j1xh 140.0
nullflg y
mult 2
FLAGS
hs n
sspul y
PFGflg y
hsglvl 4694
SPECIAL
temp 27.0
gain 30
spin 0
GRADIENTS
gzlvl1 4694
gt1 0.002000
gzlvl3 2347
gt3 0.001000
gstab 0.000500
F2 PROCESSING
gf 0.092
gfs not used
fn 4096
F1 PROCESSING
gf1 0.011
gfs1 not used
proc1 lp
fn1 2048
DISPLAY
sp -123.1
wp 5108.0
sp1 -1270.5
wp1 21346.7
rfl 1960.5
rfp 1835.0
rfl1 7843.0
rfp1 6551.6
PLOT
wc 116.0
sc 10.0
wc2 116.0
sc2 0
vs 872
th 2
ai cdc ph
ACQUISITION ARRAYS
array phase
arraydim 512
1 phase
1 1
2 2
F1 (ppm)
F2 (ppm)


amc_hydroxylation_ibuprofen_major_ghsqc
File: Ghsqc
Pulse Sequence: gHSQC
F1 (ppm)
F2 (ppm)

amc_hydroxylation_ibuprofen_major_ghmbc

exp7 Ghmbc

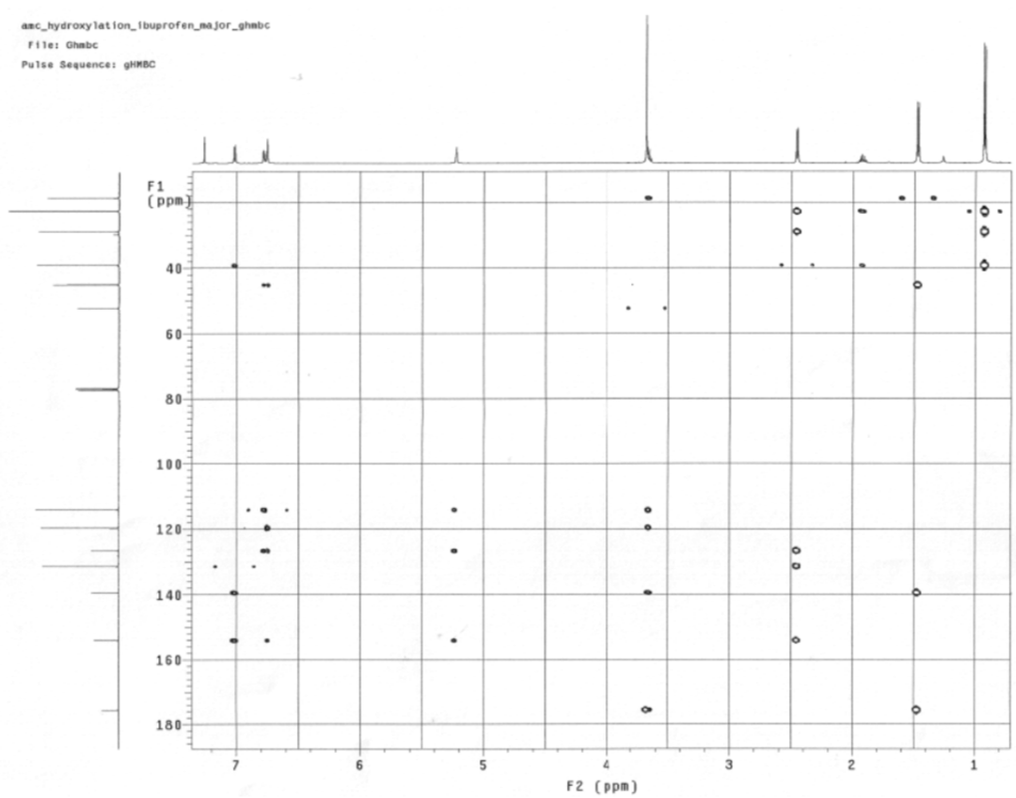
SAMPLE		FLAGS	
date	Aug 21 2013	hs	n
solvent	cdcl3	sspul	n
sample		PFGflg	y
ACQUISITION		hsglvl	4694
sw	5110.5	SPECIAL	
at	0.128	temp	27.0
np	1308	gain	30
fb	3000	spin	0
ss	32	GRADIENTS	
d1	2.000	gzlvl1	4694
nt	16	gt1	0.001000
2D ACQUISITION		gzlvl3	2347
sw1	30165.9	gt3	0.001000
ni	256	gstab	0.000500
phase	0	F2 PROCESSING	
PRESATURATION		sb	0.064
satmode	nnn	sbs	not used
satdly	0	fn	2048
satfrq	499.8	F1 PROCESSING	
satpwr	-13	sb1	0.008
TRANSMITTER		sbs1	not used
tn	H1	proc1	lp
sfrq	499.854	fn1	2048
tof	-56.1	DISPLAY	
tpwr	59	sp	-120.3
pw	11.000	wp	5105.5
DECOUPLER		sp1	-1882.9
dn	C13	wp1	30136.5
dof	1255.4	rfl	860.1
dm	nnn	rfp	734.8
dmf	22200	rfl1	23963.5
dpwr	43	rfp1	22051.1
pwxlvl	55	PLOT	
pwx	10.500	wc	116.0
HMBC		sc	10.0
j1xh	140.0	wc2	116.0
jnxh	8.0	sc2	0
		vs	328
		th	2
		al cdc av	



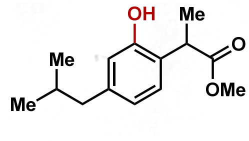
amc_hydroxylation_ibuprofen_major_ghmbc

File: Ghmbc

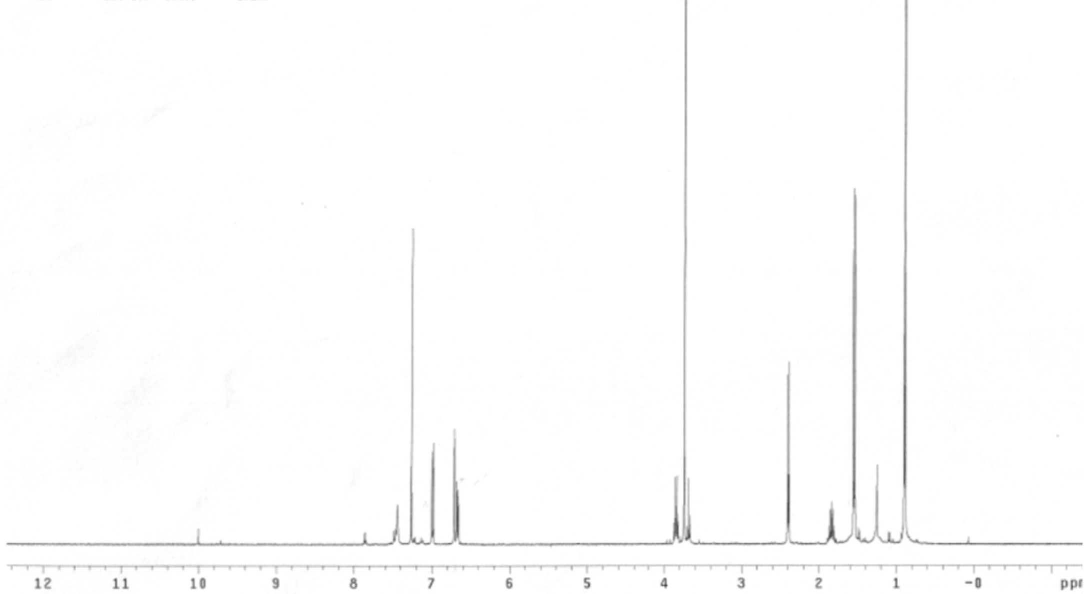
Pulse Sequence: gHMBC

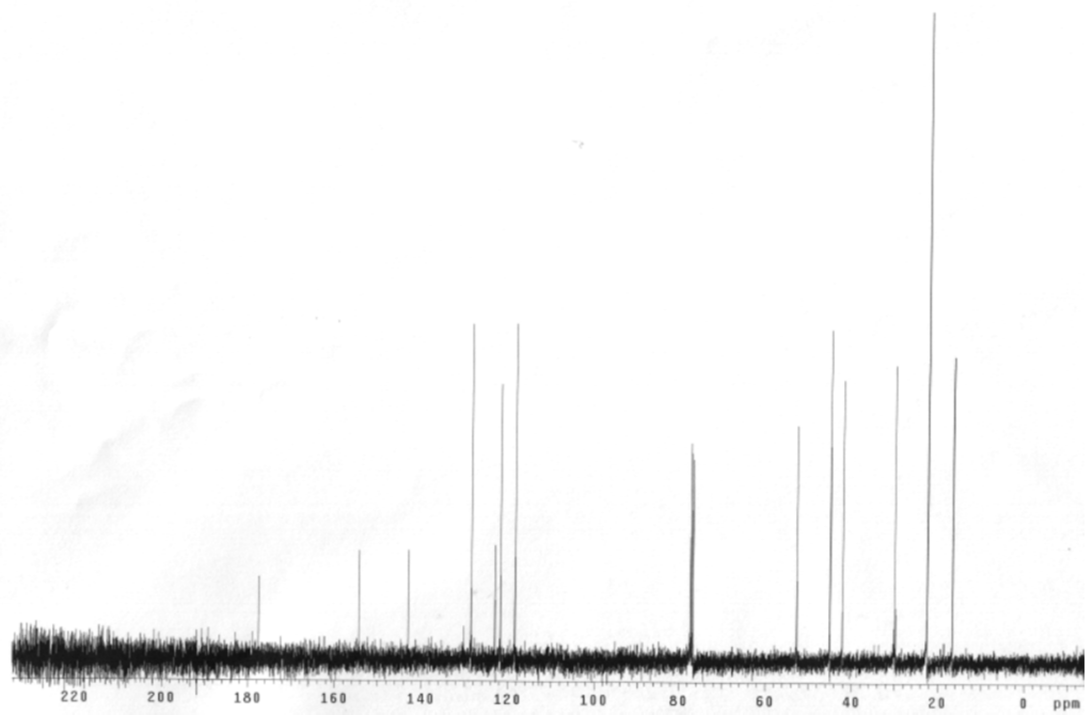


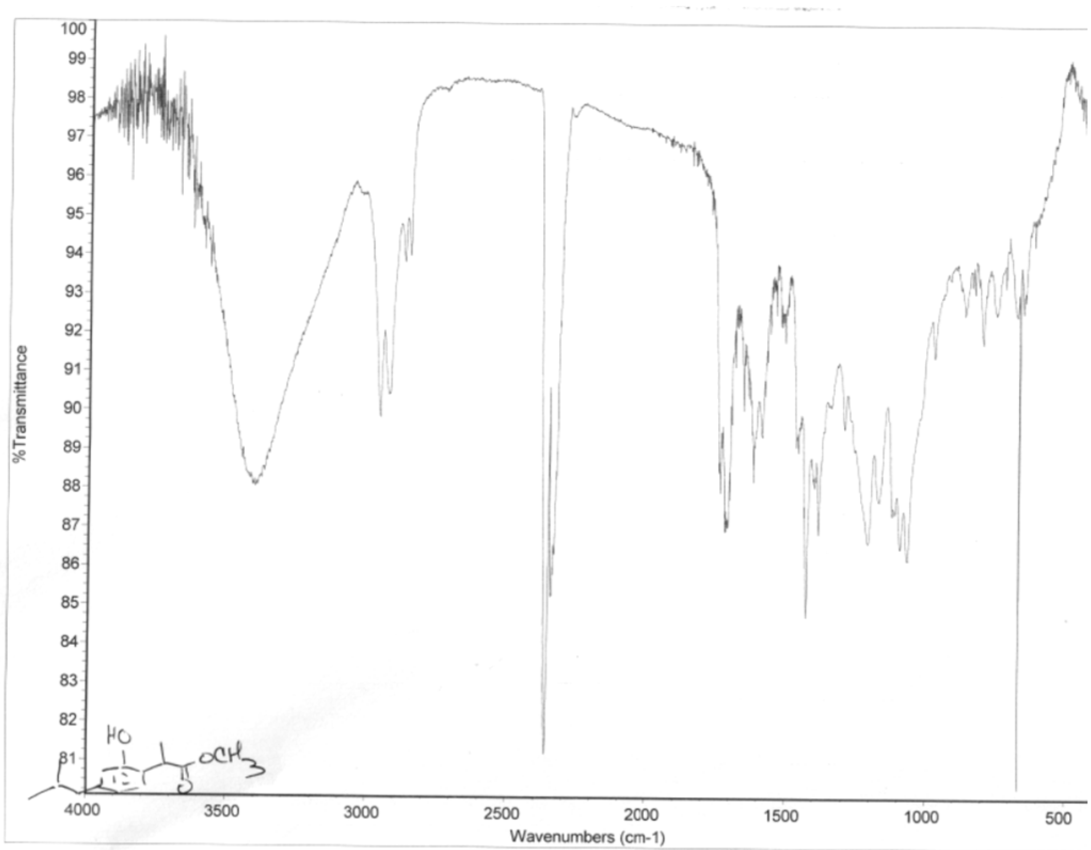
INDEX	FREQUENCY	PPM	HEIGHT
1	2905.468	7.259	72.6
2	2801.520	6.999	21.4
3	2793.656	6.979	23.3
4	2687.656	6.715	22.2
5	2685.947	6.710	26.6
6	1494.308	3.733	199.7
7	961.575	2.402	38.9
8	954.395	2.384	41.9
9	622.377	1.555	81.9
10	615.196	1.537	80.4
11	359.772	0.899	156.4
12	353.275	0.883	161.7

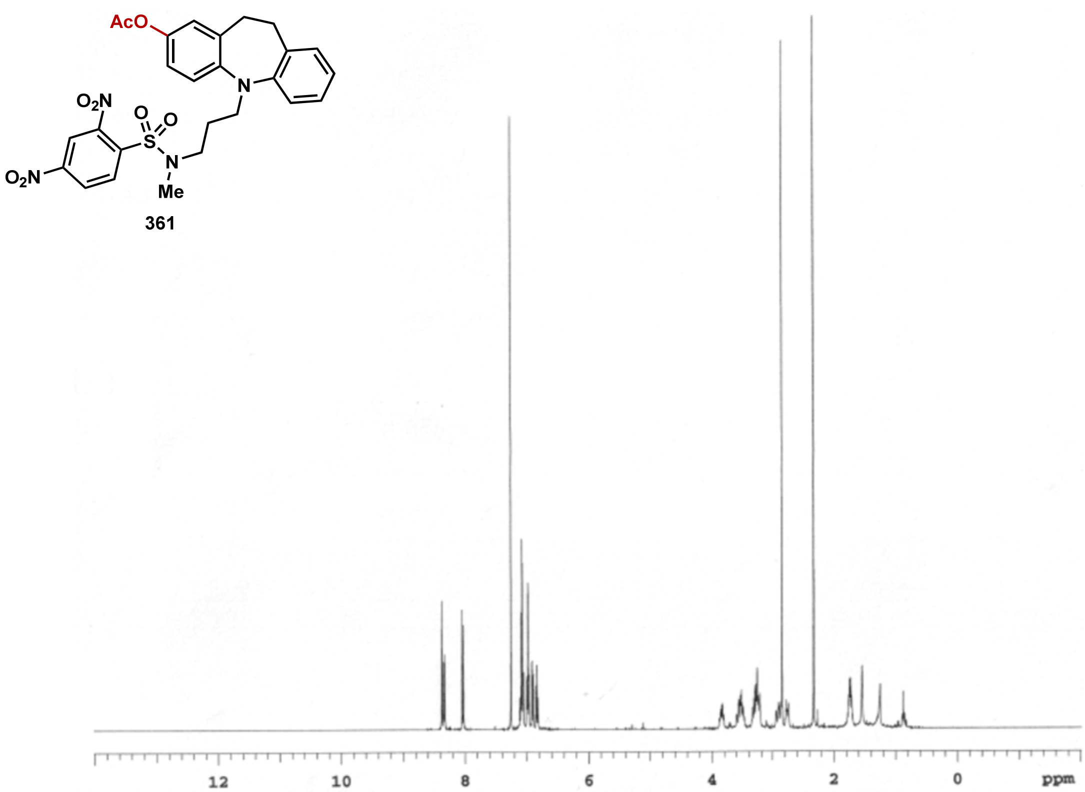


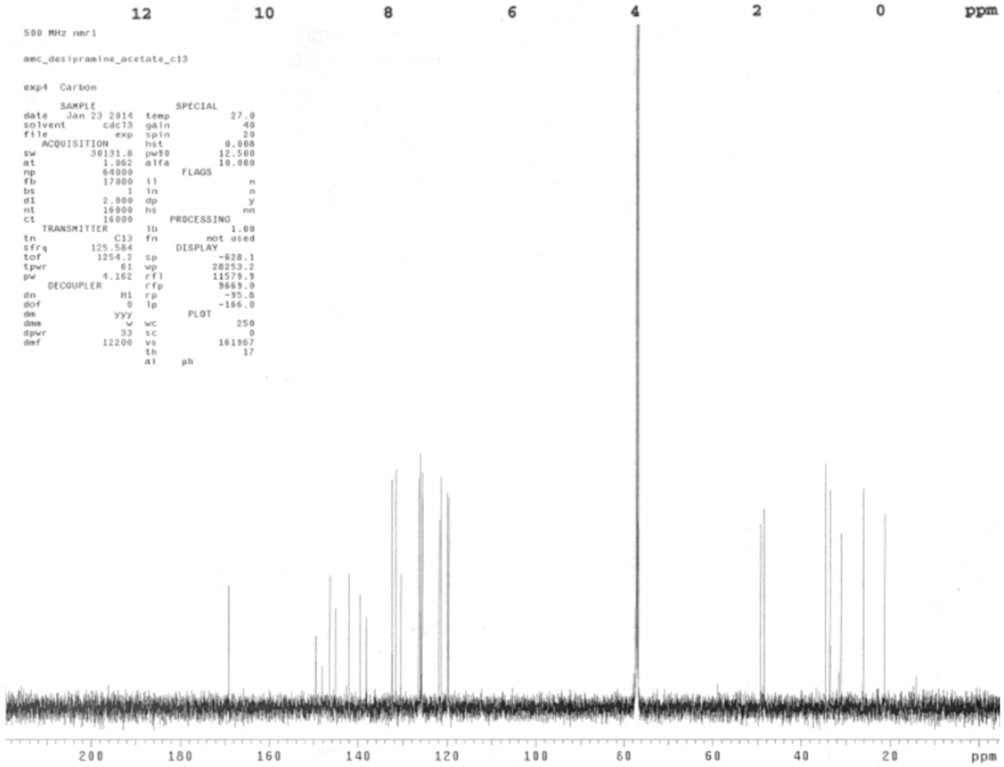
360c

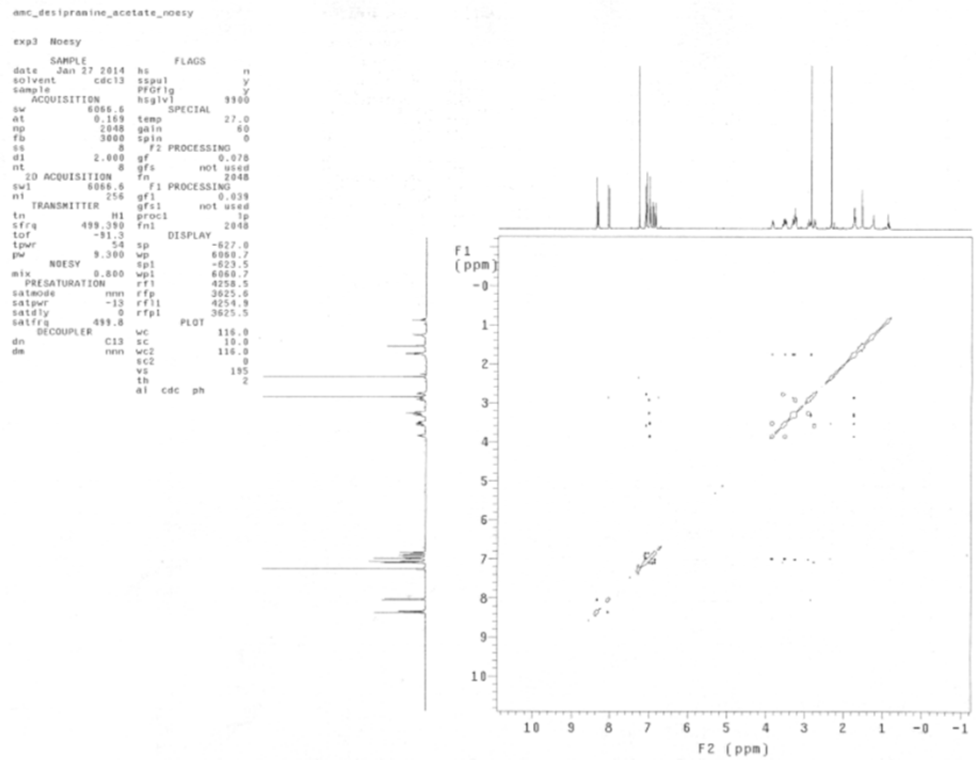


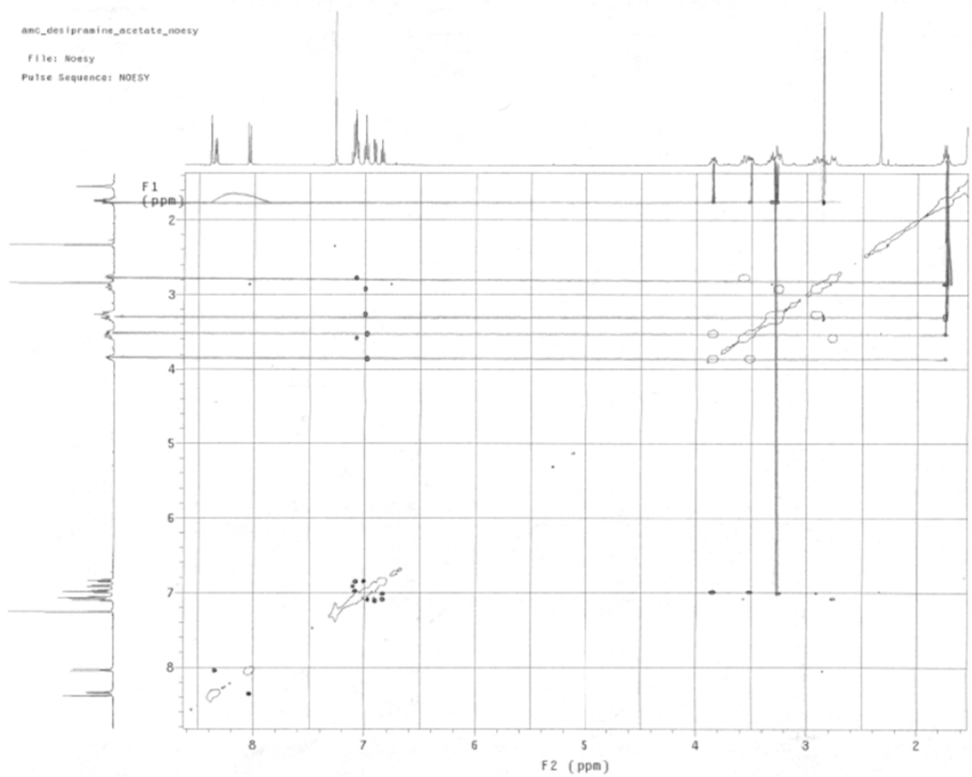


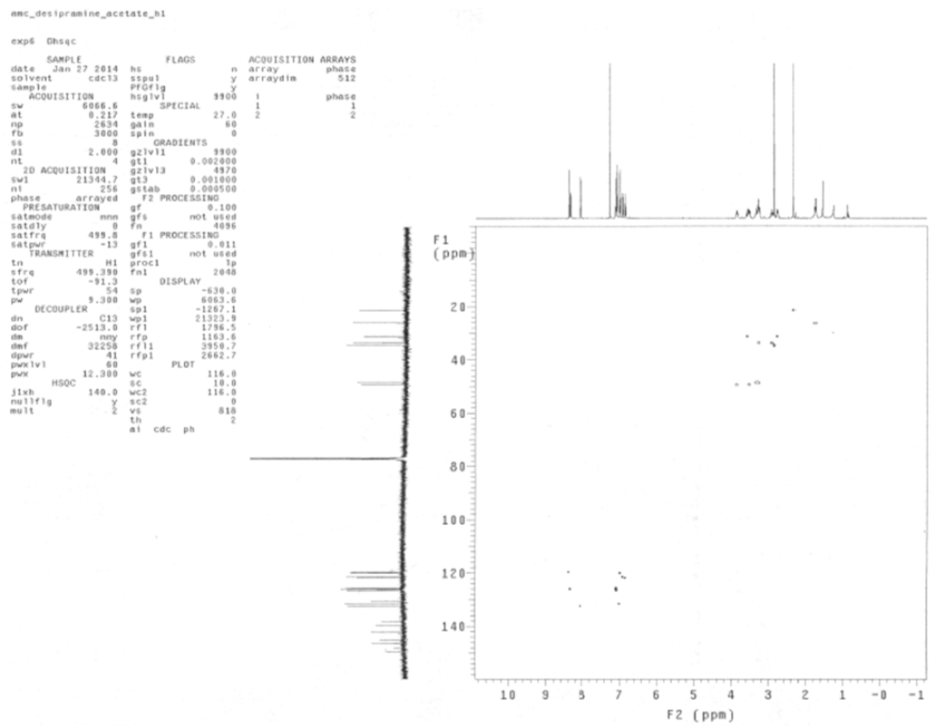

%Transmittance
Wavenumbers (cm-1)
HO
OCH3

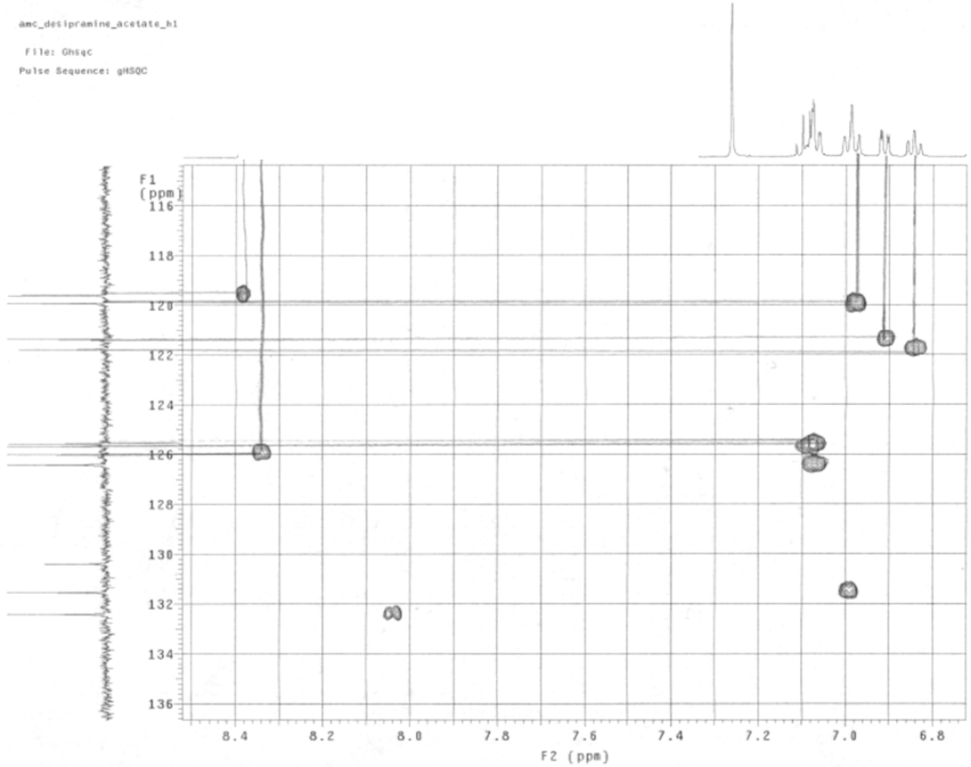

AcO
O2N
O
O
S
N
N
Me
O2N
361
12
10
8
6
4
2
0
ppm

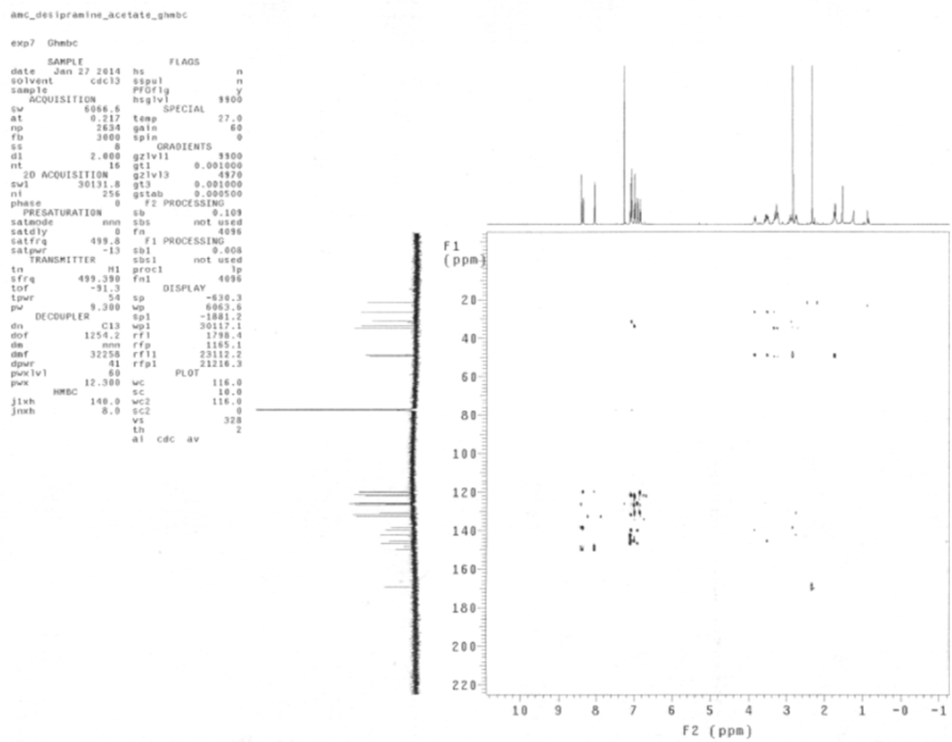

500 MHz nmr1
amc_desipramine_acetate_c13
exp4 Carbon
SAMPLE
date Jan 23 2014
solvent cdcl3
file exp
ACQUISITION
sw 30131.8
at 1.062
np 64000
fb 17000
bs 1
d1 2.000
nt 16000
ct 16000
TRANSMITTER
tn C13
sfrq 125.584
tof 1254.2
tpwr 61
pw 4.162
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 33
dmf 12200
SPECIAL
temp 27.0
gain 40
spin 20
hst 0.008
pw90 12.500
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -628.1
wp 28253.2
rfl 11579.9
rfp 9669.0
rp -95.8
lp -166.0
PLOT
wc 250
sc 0
vs 161967
th 17
ai ph
200
180
160
140
120
100
80
60
40
20
ppm

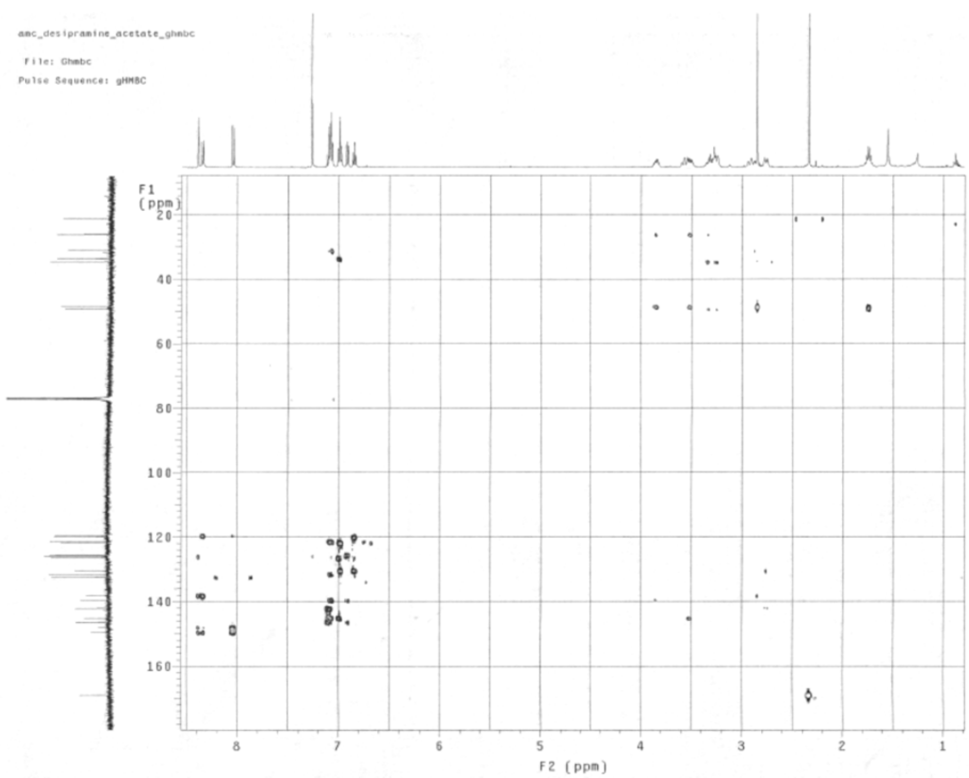

amc_desipramine_acetate_noesy
exp3 Noesy
F1 (ppm)
F2 (ppm)

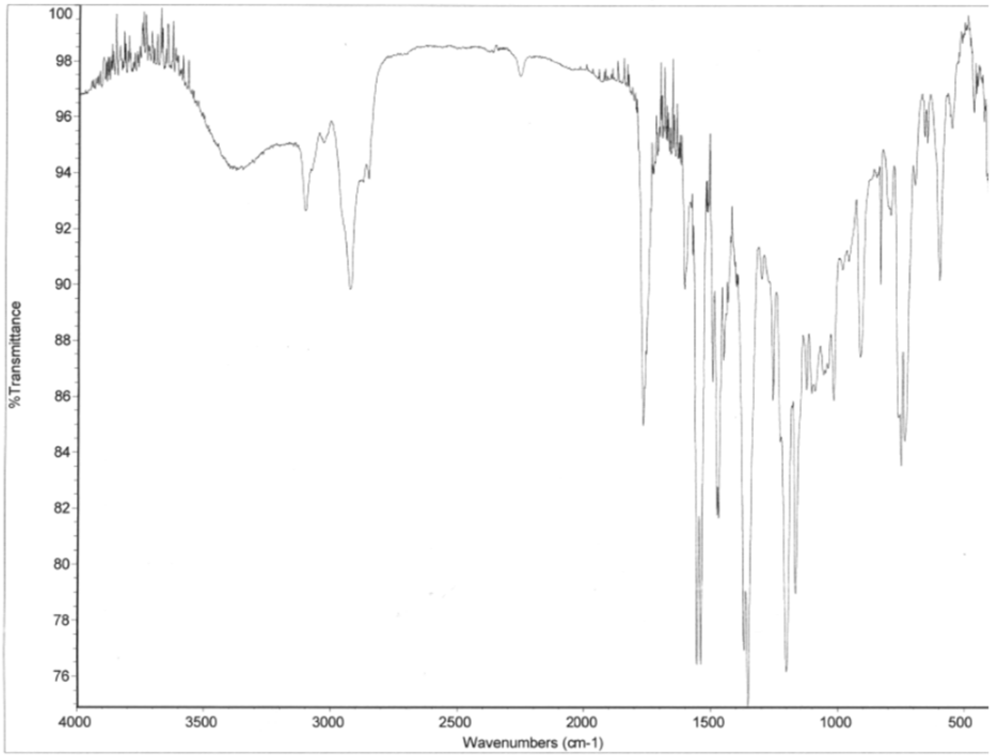

amc_desipramine_acetate_noesy
File: Noesy
Pulse Sequence: NOESY
F1 (ppm)
F2 (ppm)

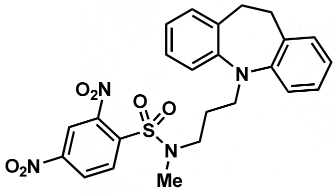

amc_desipramine_acetate_h1
exp6 Ghsqc
SAMPLE
date Jan 27 2014
solvent cdcl3
sample
ACQUISITION
sw 6066.6
at 0.217
np 2634
fb 3000
ss 8
d1 2.000
nt 4
2D ACQUISITION
sw1 21344.7
ni 256
phase arrayed
PRESATURATION
satmode nnn
satdly 0
satfrq 499.8
satpwr -13
TRANSMITTER
tn H1
sfrq 499.390
tof -91.3
tpwr 54
pw 9.300
DECOUPLER
dn C13
dof -2513.0
dm nny
dmf 32258
dpwr 41
pwxlvl 60
pwx 12.300
HSQC
j1xh 140.0
nullflg y
mult 2
FLAGS
hs n
sspul y
PFGflg y
hsglvl 9900
SPECIAL
temp 27.0
gain 60
spin 0
GRADIENTS
gzlvl1 9900
gt1 0.002000
gzlvl3 4970
gt3 0.001000
gstab 0.000500
F2 PROCESSING
gf 0.100
gfs not used
fn 4096
F1 PROCESSING
gf1 0.011
gfs1 not used
proc1 lp
fn1 2048
DISPLAY
sp -630.0
wp 6063.6
sp1 -1267.1
wp1 21323.9
rfl 1796.5
rfp 1163.6
rfl1 3950.7
rfp1 2662.7
PLOT
wc 116.0
sc 10.0
wc2 116.0
sc2 0
vs 818
th 2
ai cdc ph
ACQUISITION ARRAYS
array phase
arraydim 512
I phase
1 1
2 2
F1 (ppm)
F2 (ppm)


amc_desipramine_acetate_h1
File: Ghsqc
Pulse Sequence: gHSQC
F1 (ppm)
F2 (ppm)

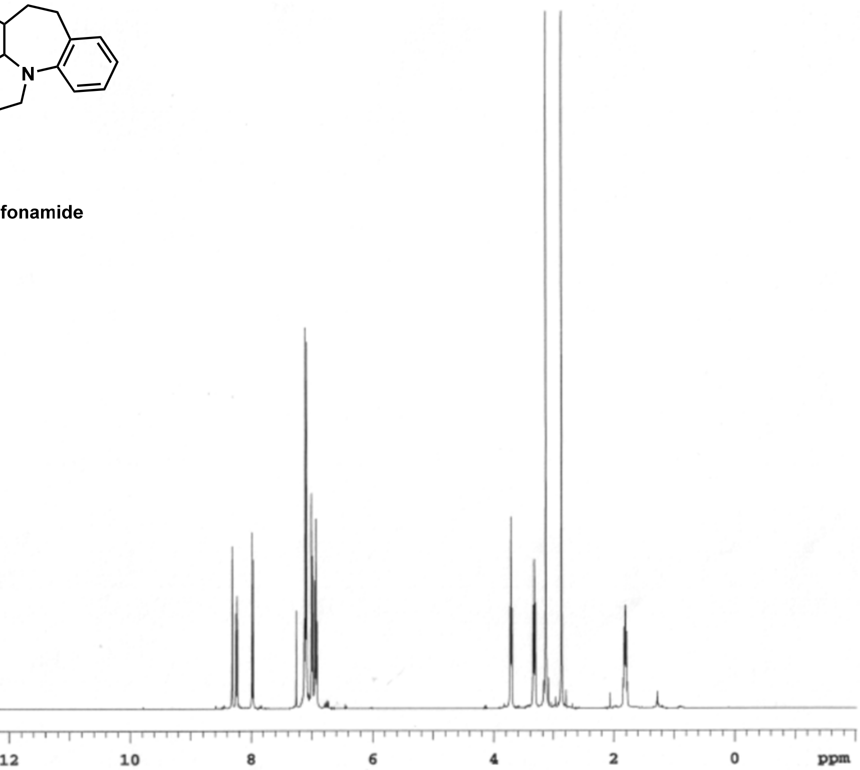


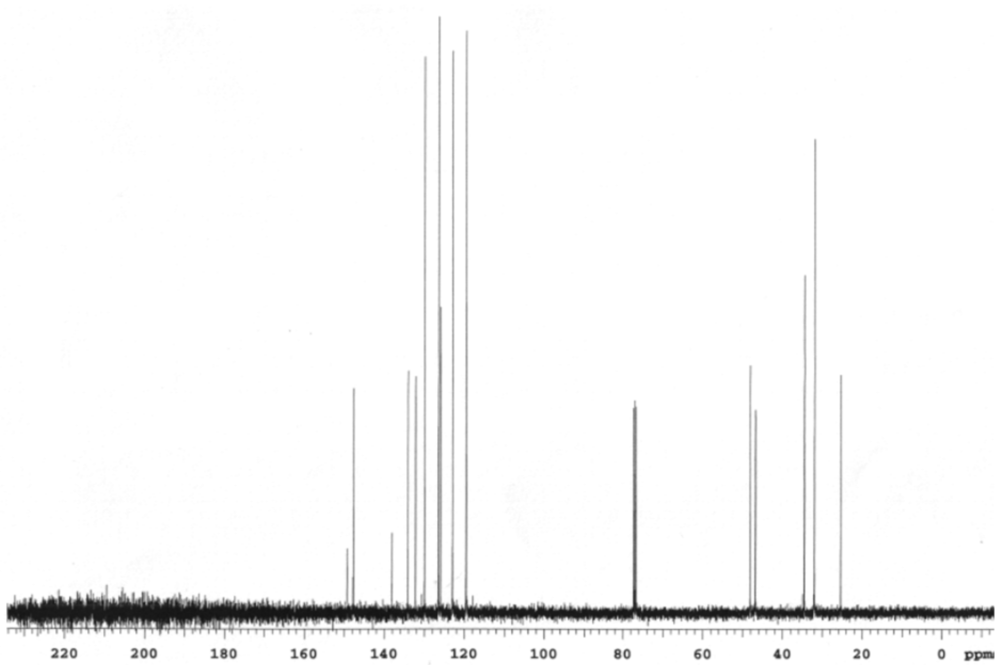


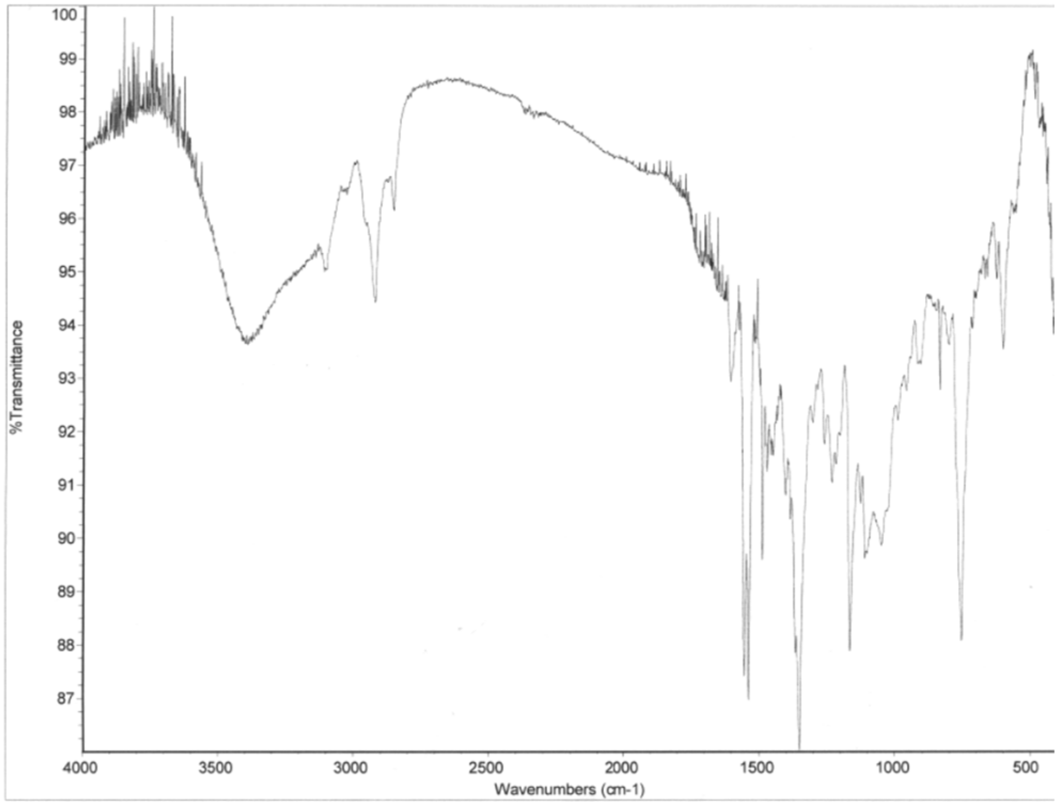

%Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
76
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)



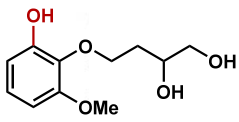
desipiramine sulfonamide



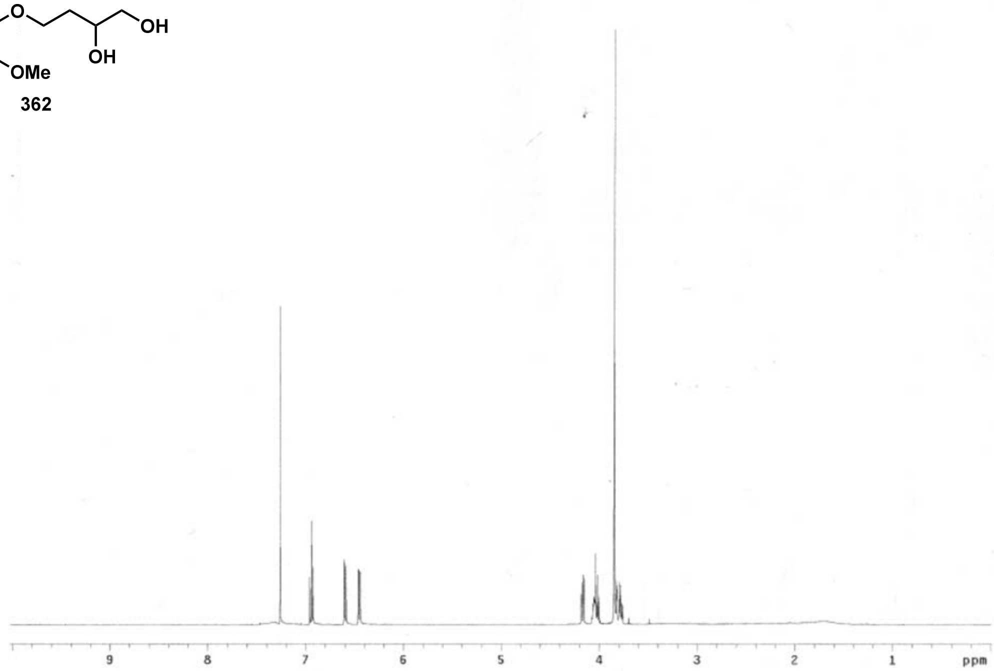


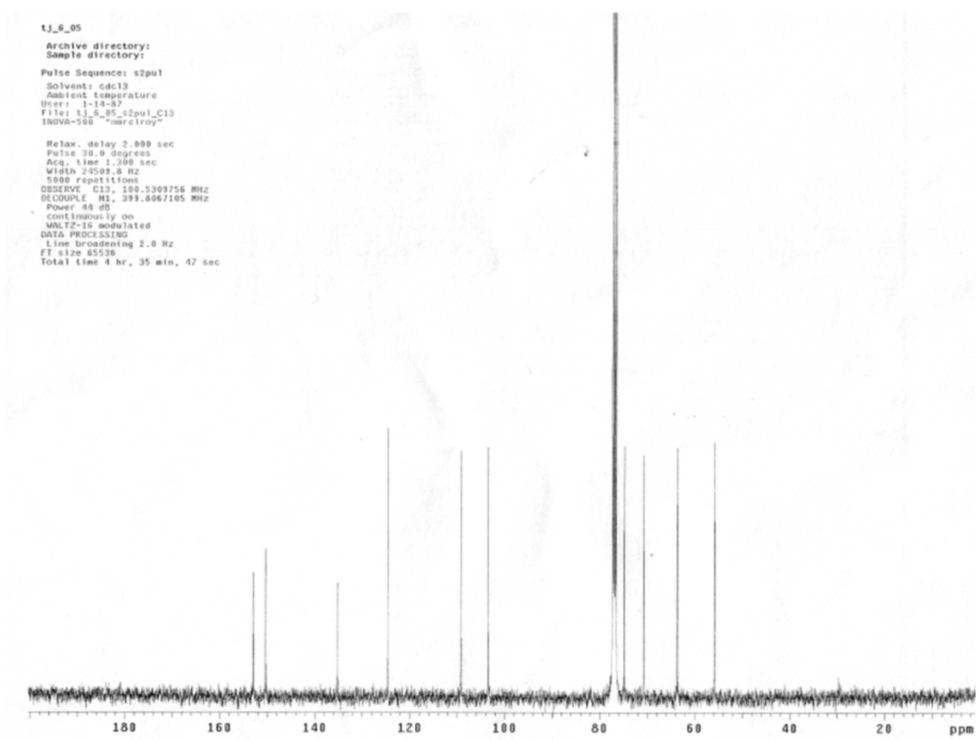


%Transmittance
100
99
98
97
96
95
94
93
92
91
90
89
88
87
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

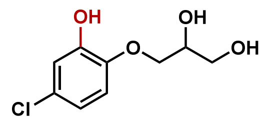

OH
O
OH
OH
OMe

362

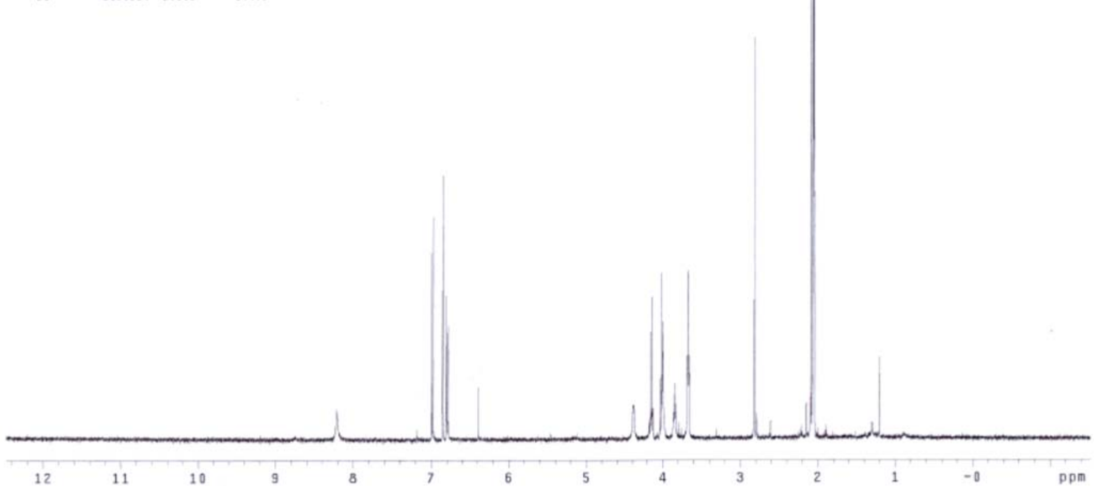

9
8
7
6
5
4
3
2
1
ppm

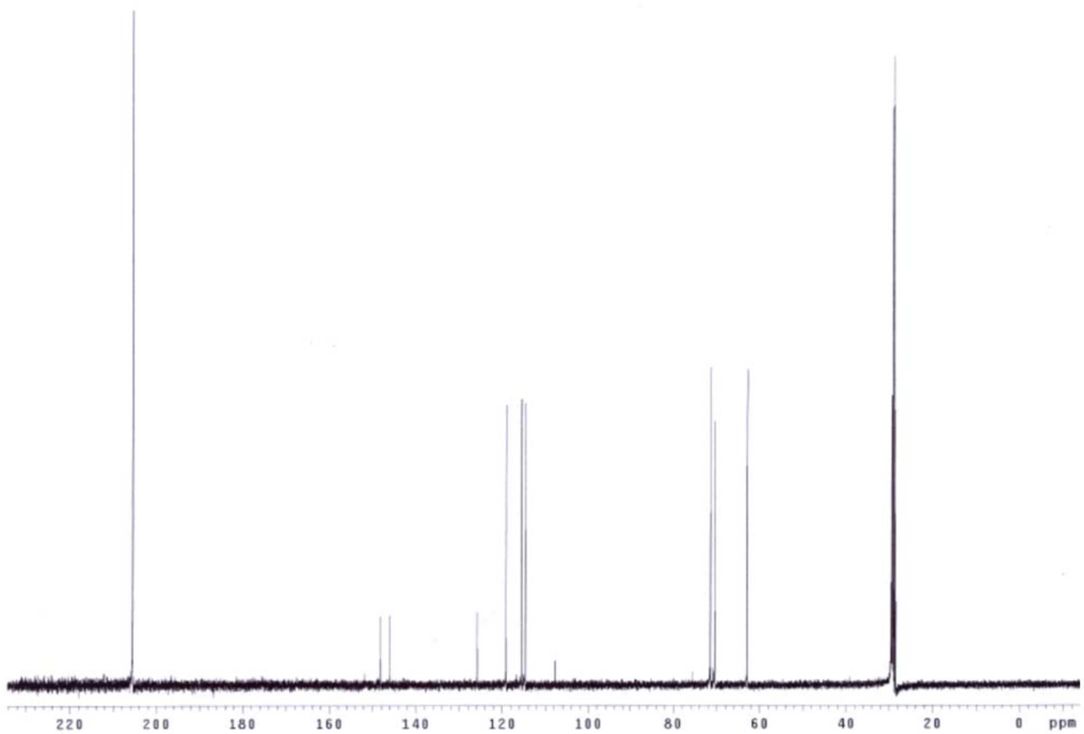

tj_6_05
Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
User: 1-14-87
File: tj_6_05_s2pul_C13
INOVA-500 "nmrclroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309756 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
180
160
140
120
100
80
60
40
20
ppm

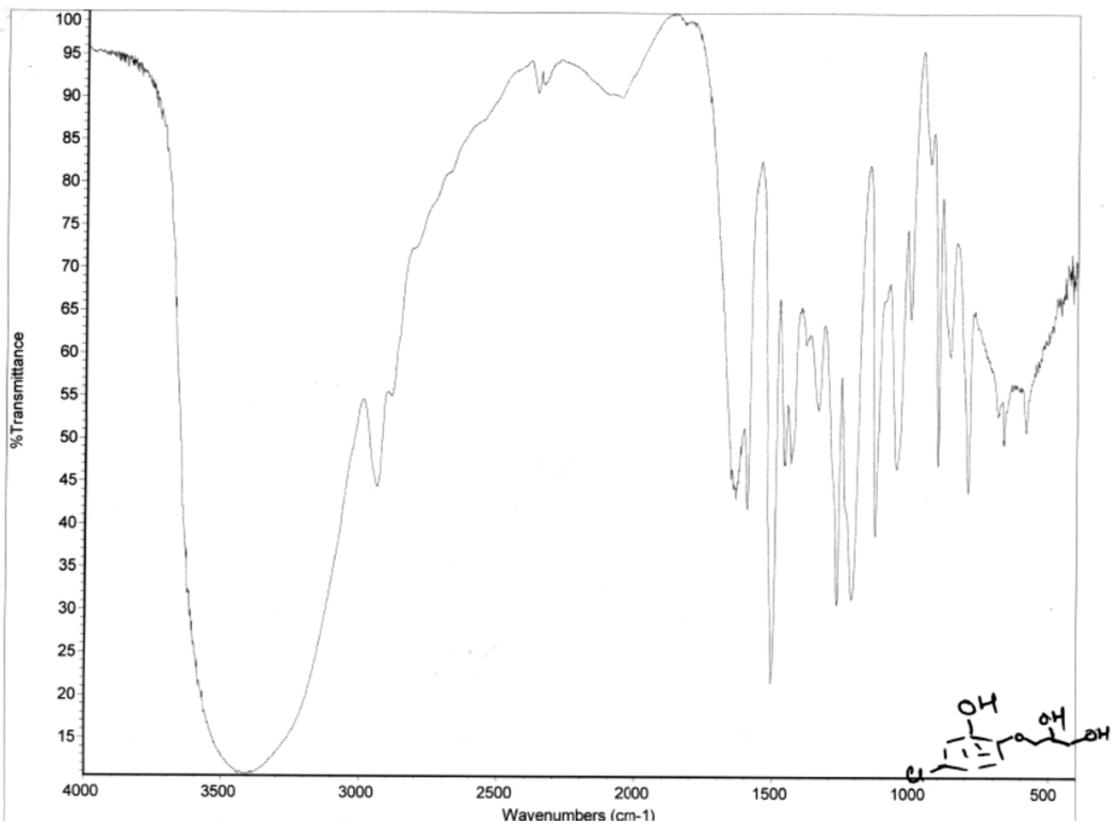
INDEX	FREQUENCY	PPM	HEIGHT
1	2799.145	6.993	42.7
2	2790.597	6.972	51.0
3	2742.726	6.852	49.0
4	2740.332	6.846	60.6
5	2724.262	6.806	32.9
6	2721.526	6.799	24.5
7	2715.713	6.785	26.0
8	2712.978	6.778	20.8
9	1661.190	4.150	24.6
10	1655.377	4.136	32.6
11	1605.455	4.011	38.1
12	1598.616	3.994	27.0
13	1468.339	3.668	38.7
14	1126.748	2.815	92.5
15	835.762	2.088	283.4
16	825.504	2.062	170.4
17	823.452	2.057	316.9
18	821.059	2.051	458.3
19	819.007	2.046	318.2
20	816.614	2.040	144.6

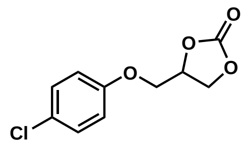


363

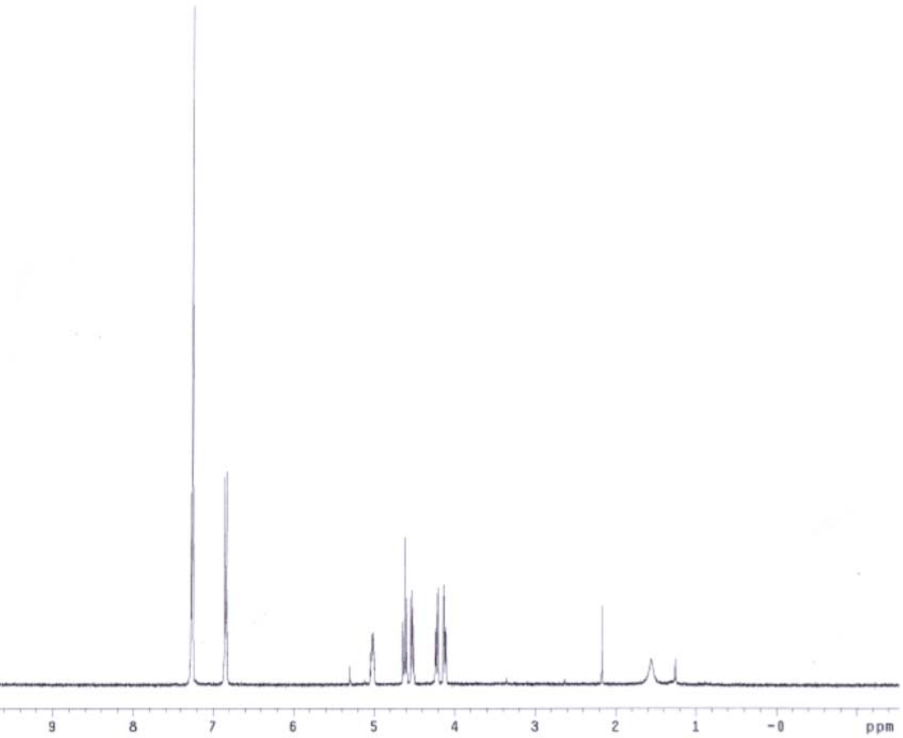


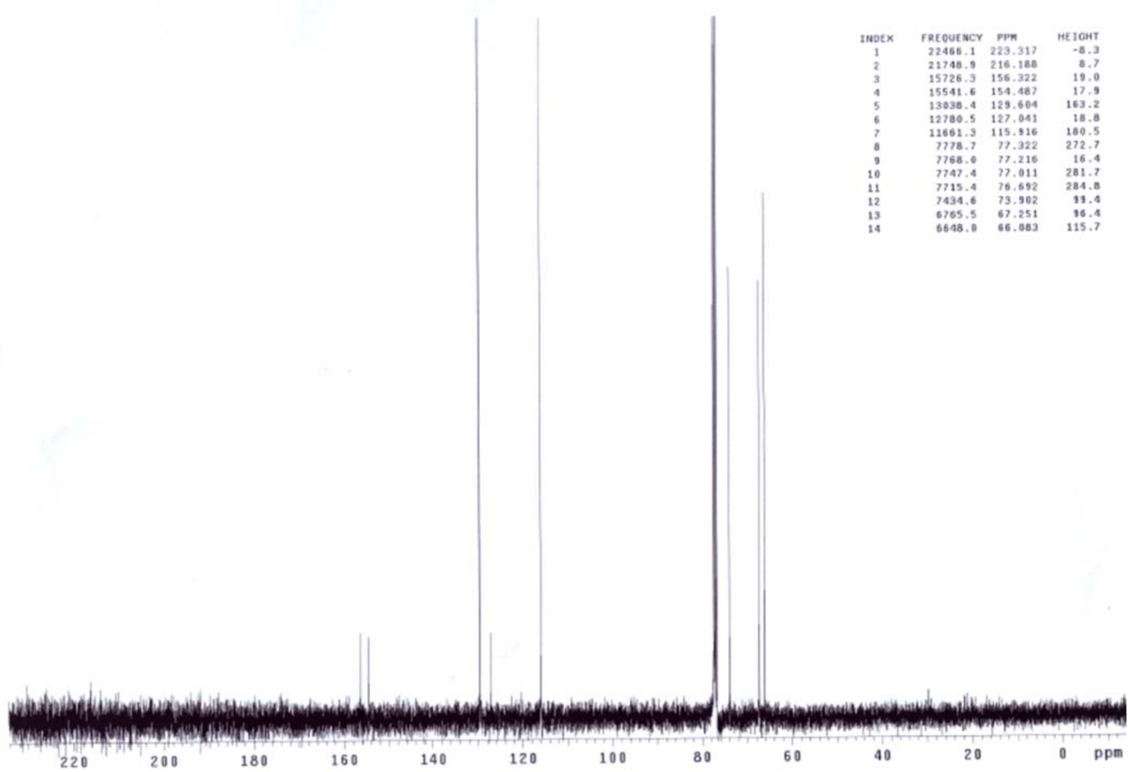



%Transmittance
Wavenumbers (cm-1)
OH
OH
OH
Cl

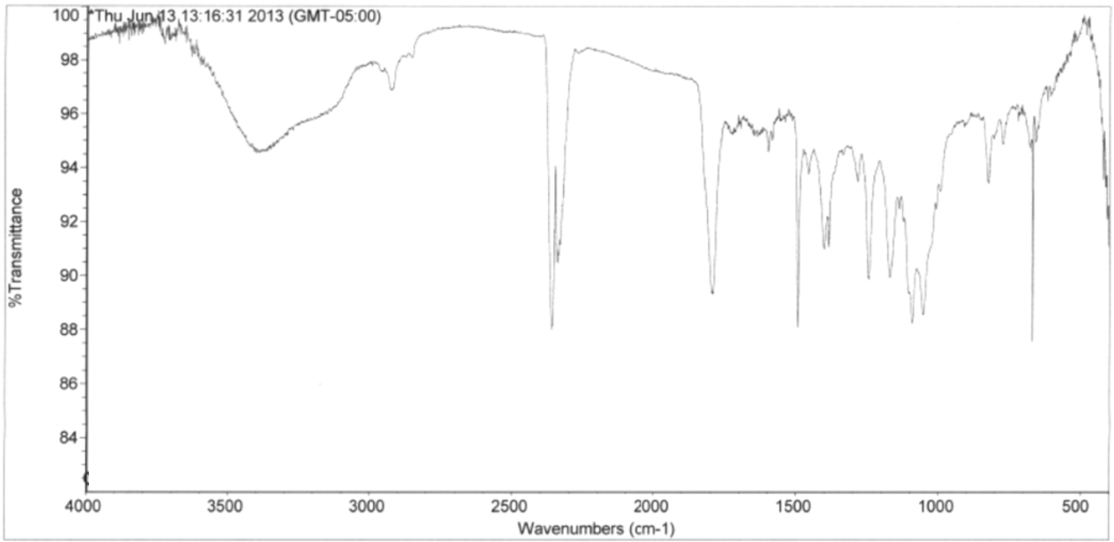


chlorophenesin carbonate



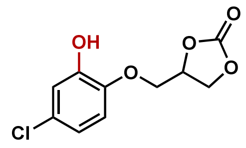


INDEX	FREQUENCY	PPM	HEIGHT
1	22466.1	223.317	-8.3
2	21748.9	216.188	8.7
3	15726.3	156.322	19.0
4	15541.6	154.487	17.9
5	13038.4	129.604	163.2
6	12780.5	127.041	18.8
7	11661.3	115.916	180.5
8	7778.7	77.322	272.7
9	7768.0	77.216	16.4
10	7747.4	77.011	281.7
11	7715.4	76.692	284.8
12	7434.6	73.902	99.4
13	6765.5	67.251	96.4
14	6648.0	66.083	115.7

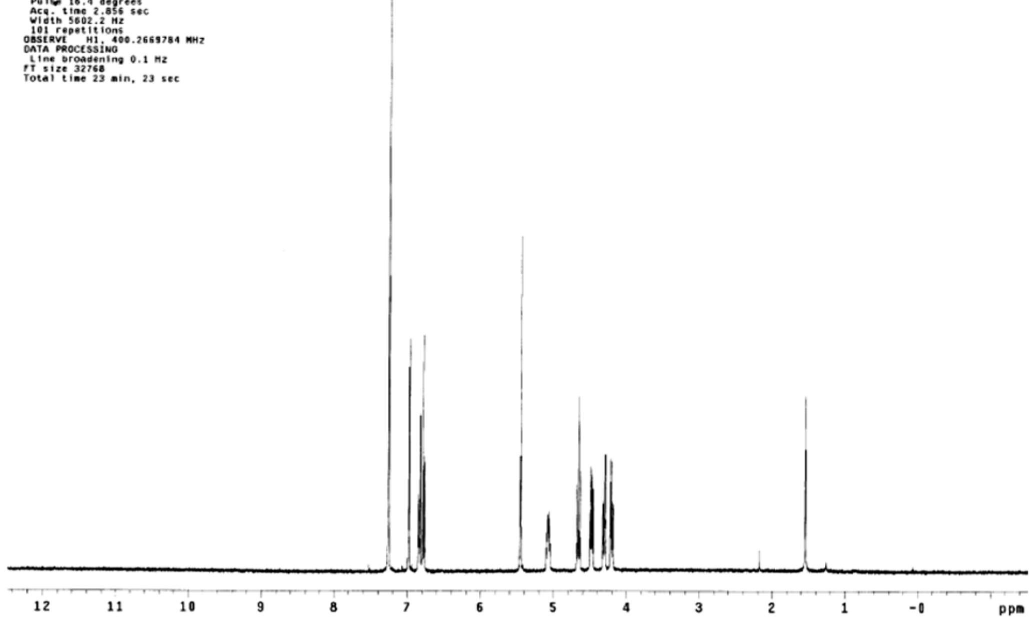


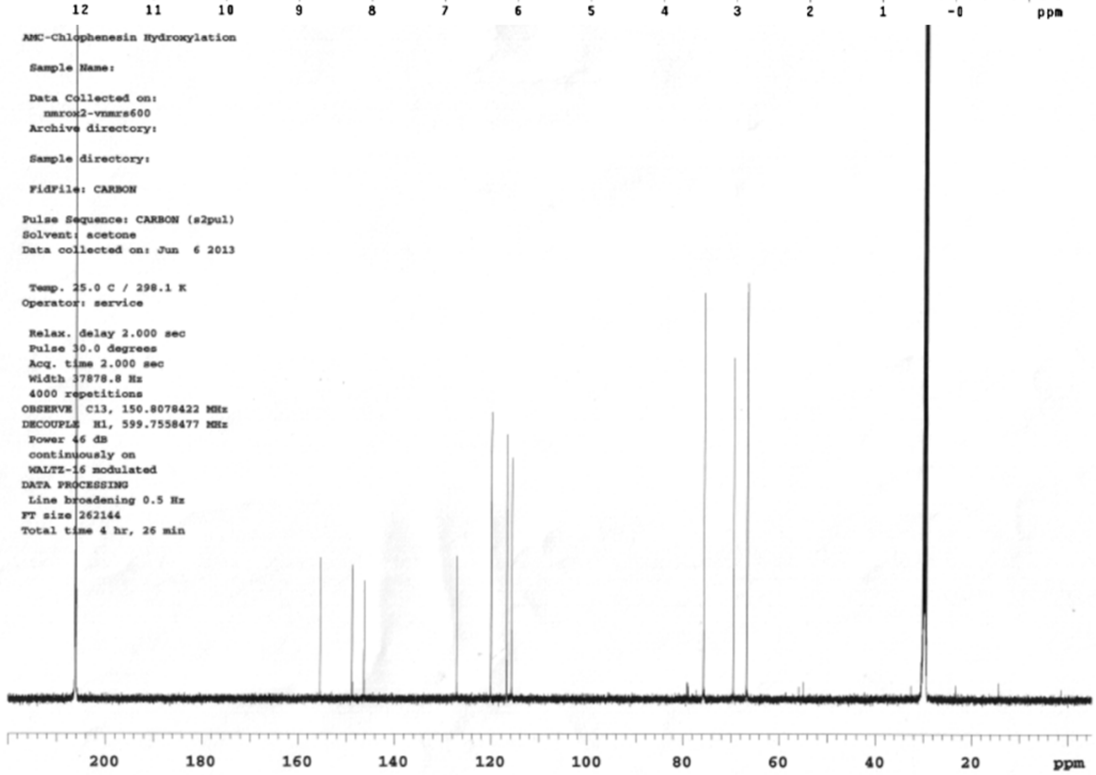
Thu Jun 13 13:18:23 2013 (GMT-05:00)
FIND PEAKS:

Spectrum:	*Thu Jun 13 13:16:31 2013 (GMT-05:00)	
Region:	4000.00	400.00
Absolute threshold:	82.188	
Sensitivity:	50	
Peak list:		


OH
O
O
O
O
Cl

364


STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "nmr6"
Relax. delay 2.000 sec
Pulse 16.4 degrees
Acq. time 2.856 sec
Width 5602.2 Hz
101 repetitions
OBSERVE H1, 400.2669784 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 23 min, 23 sec
12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm


AMC-Chlophenesin Hydroxylation
Sample Name:
Data Collected on:
nmrox2-vnmrs600
Archive directory:
Sample directory:
FidFile: CARBON
Pulse Sequence: CARBON (s2pul)
Solvent: acetone
Data collected on: Jun 6 2013
Temp. 25.0 C / 298.1 K
Operator: service
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 2.000 sec
Width 37878.8 Hz
4000 repetitions
OBSERVE C13, 150.8078422 MHz
DECOUPLE H1, 599.7558477 MHz
Power 46 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 262144
Total time 4 hr, 26 min
200 180 160 140 120 100 80 60 40 20 ppm

AMC-Chlophenesin Hydroxylation

Sample Name:

Data Collected on:
nmrox2-vnmrs600
Archive directory:

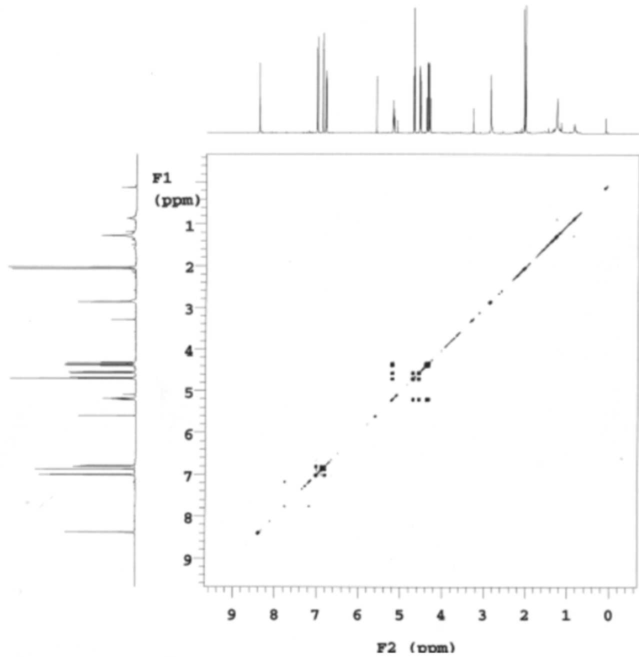
Sample directory:

FidFile: gCOSY

Pulse Sequence: gCOSY
Solvent: acetone
Data collected on: Jun 6 2013

Temp. 25.0 C / 298.1 K
Operator: service

Relax. delay 2.000 sec
Acq. time 0.150 sec
Width 6218.9 Hz
2D Width 6218.9 Hz
2 repetitions
512 increments
OBSERVE H1, 599.7528489 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.082 sec
FT size 4096 x 4096
Total time 39 min



AMC-Chlophenesin Hydroxylation

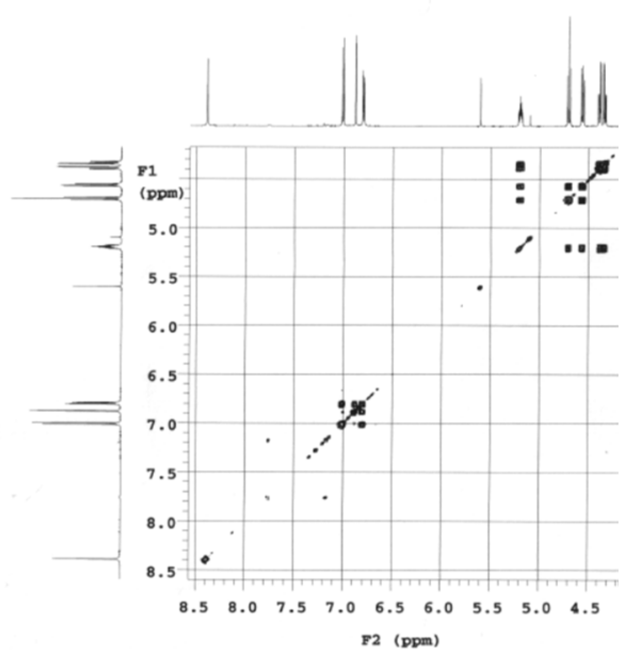
Sample Name:

Data Collected on:
nmrox2-vnmrs600
Archive directory:

Sample directory:

FidFile: gCOSY

Pulse Sequence: gCOSY
Solvent: acetone
Data collected on: Jun 6 2013



AMC-Chlophenesin Hydroxylation

Sample Name:

Data Collected on:
nmrox2-vnmrs600
Archive directory:

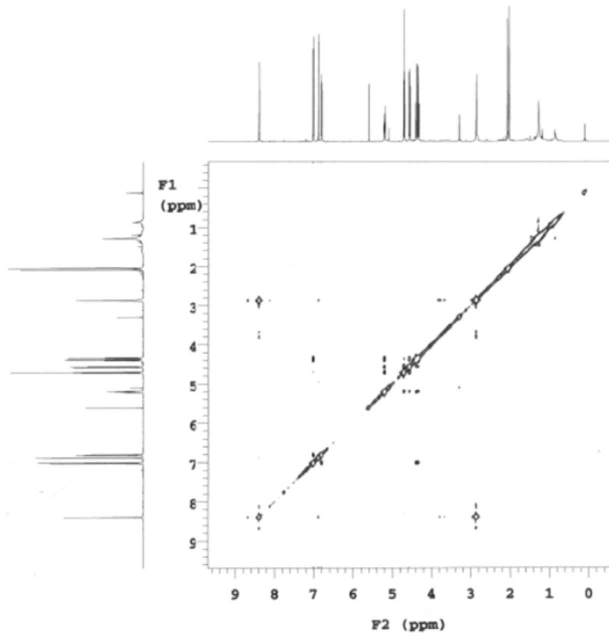
Sample directory:

FidFile: NOESY

Pulse Sequence: NOESY
Solvent: acetone
Data collected on: Jun 6 2013

Temp. 25.0 C / 298.1 K
Operator: service

Relax. delay 2.000 sec
Acq. time 0.150 sec
Width 6218.9 Hz
2D Width 6218.9 Hz
8 repetitions
2 x 256 increments
OBSERVE H1, 599.7528489 MHz
DATA PROCESSING
Gauss apodization 0.045 sec
F1 DATA PROCESSING
Gauss apodization 0.018 sec
FT size 2048 x 2048
Total time 3 hr, 24 min



AMC-Chlophenesin Hydroxylation

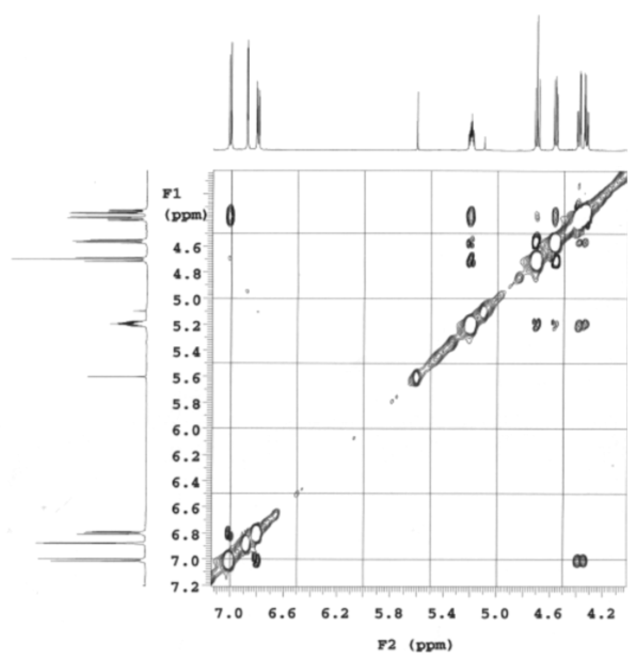
Sample Name:

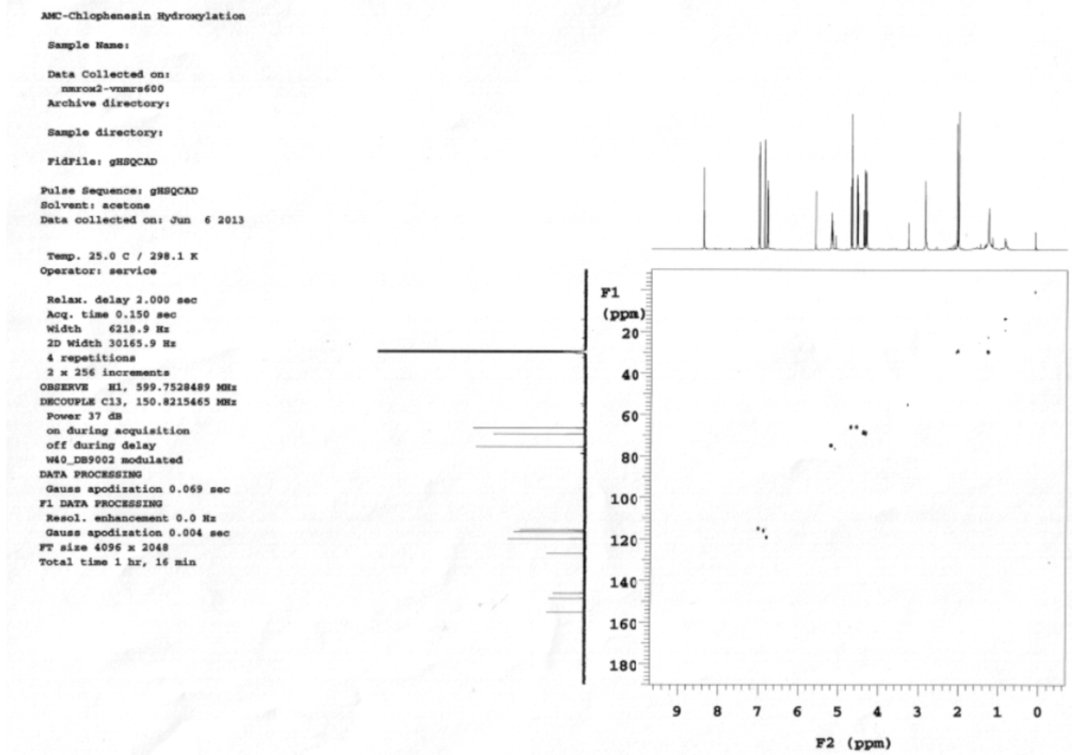
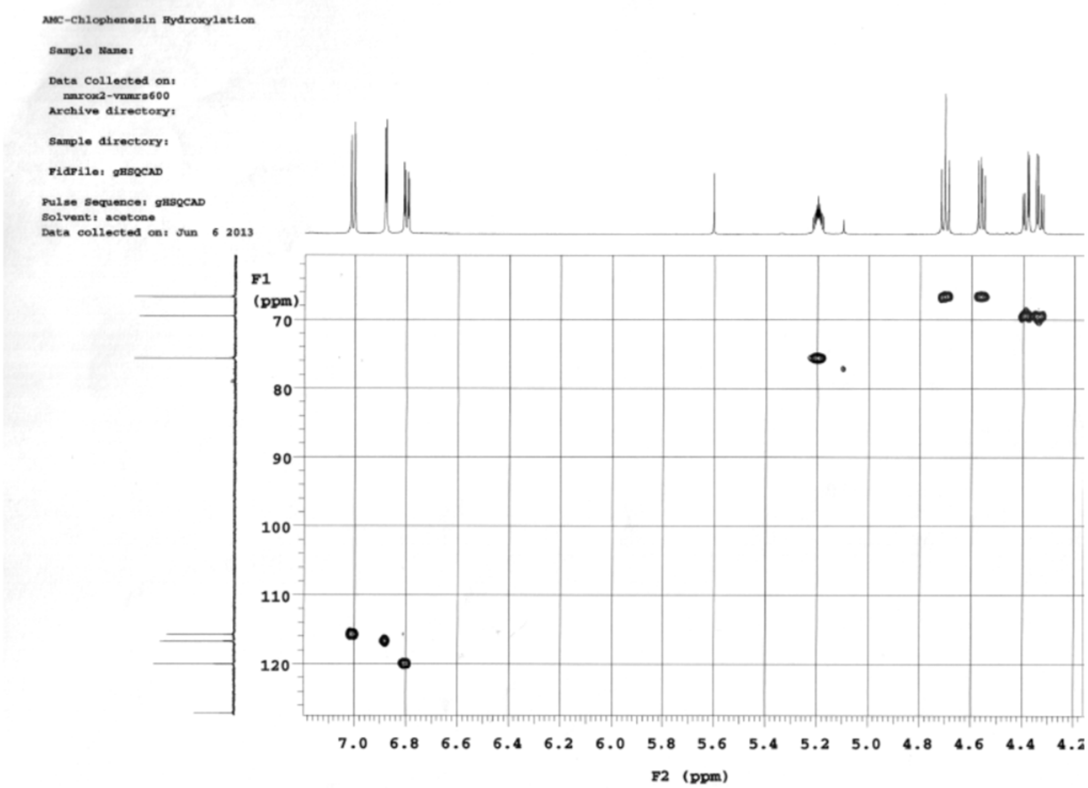
Data Collected on:
nmrox2-vnmrs600
Archive directory:

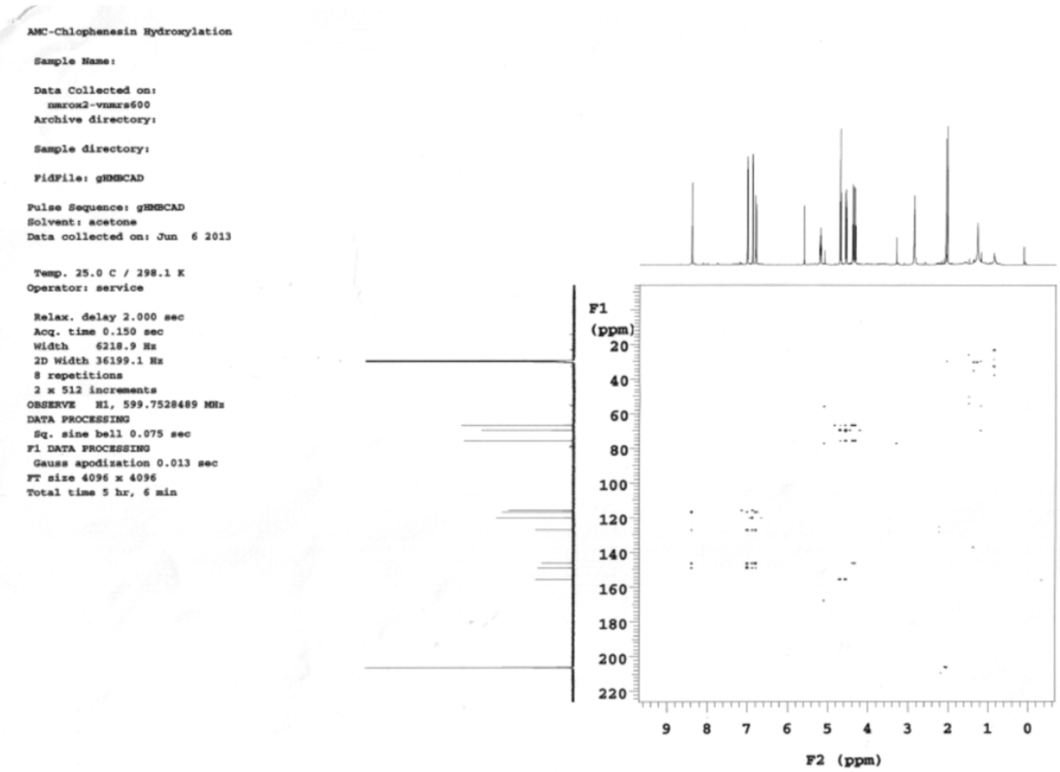
Sample directory:

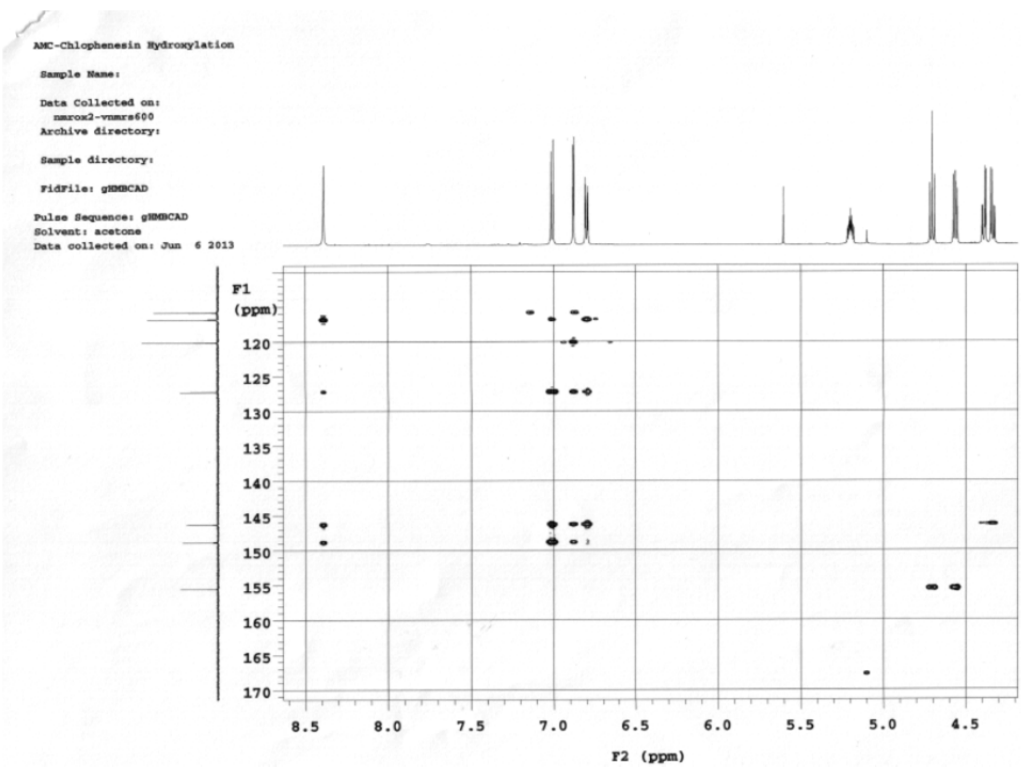
FidFile: NOESY

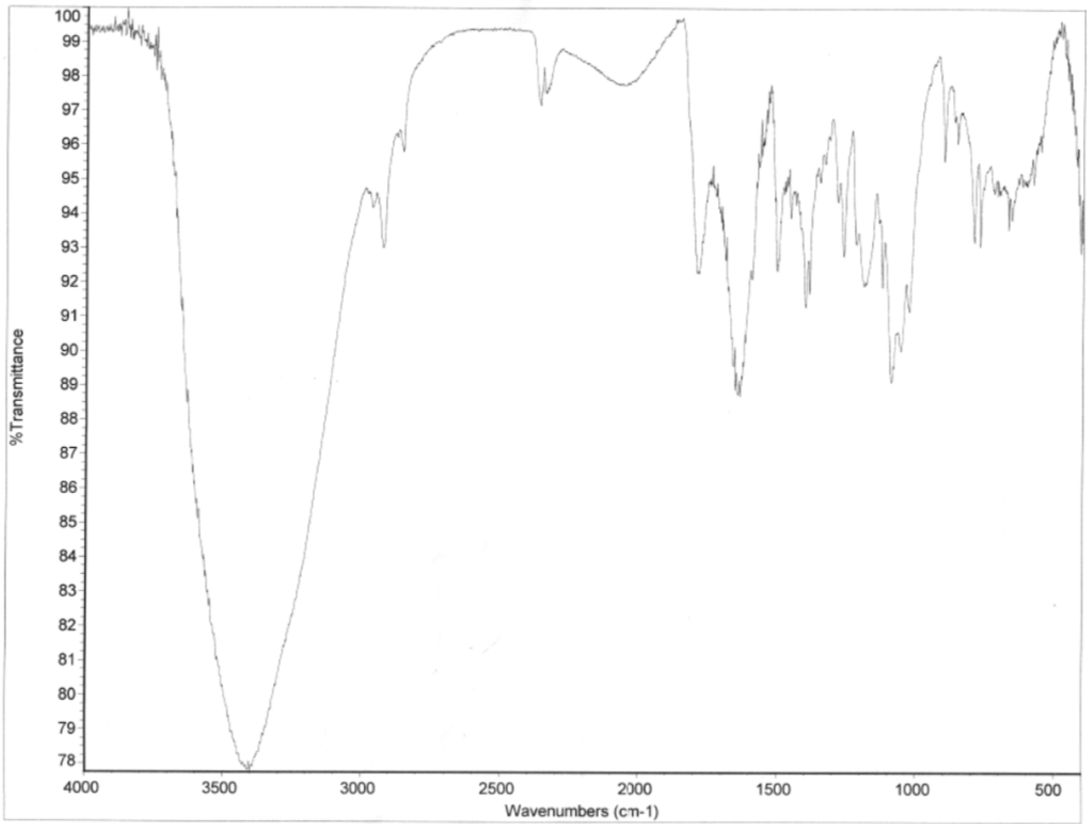
Pulse Sequence: NOESY
Solvent: acetone
Data collected on: Jun 6 2013



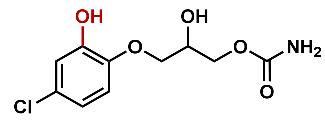

AMC-Chlophenesin Hydroxylation
Sample Name:
Data Collected on:
nmrox2-vnmrs600
Archive directory:
Sample directory:
FidFile: gHSQCAD
Pulse Sequence: gHSQCAD
Solvent: acetone
Data collected on: Jun 6 2013
Temp. 25.0 C / 298.1 K
Operator: service
Relax. delay 2.000 sec
Acq. time 0.150 sec
Width 6218.9 Hz
2D Width 30165.9 Hz
4 repetitions
2 x 256 increments
OBSERVE H1, 599.7528489 MHz
DECOUPLE C13, 150.8215465 MHz
Power 37 dB
on during acquisition
off during delay
W40_DB9002 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Resol. enhancement 0.0 Hz
Gauss apodization 0.004 sec
FT size 4096 x 2048
Total time 1 hr, 16 min
F1 (ppm)
20
40
60
80
100
120
140
160
180
9 8 7 6 5 4 3 2 1 0
F2 (ppm)

AMC-Chlophenesin Hydroxylation
Sample Name:
Data Collected on:
nmrox2-vnmrs600
Archive directory:
Sample directory:
FidFile: gHSQCAD
Pulse Sequence: gHSQCAD
Solvent: acetone
Data collected on: Jun 6 2013
F1 (ppm)
70
80
90
100
110
120
7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2
F2 (ppm)


AMC-Chlophenesin Hydroxylation
Sample Name:
Data Collected on:
nmrox2-vnmrs600
Archive directory:
Sample directory:
FidFile: gHMBCAD
Pulse Sequence: gHMBCAD
Solvent: acetone
Data collected on: Jun 6 2013
Temp. 25.0 C / 298.1 K
Operator: service
Relax. delay 2.000 sec
Acq. time 0.150 sec
Width 6218.9 Hz
2D Width 36199.1 Hz
8 repetitions
2 x 512 increments
OBSERVE H1, 599.7528489 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Gauss apodization 0.013 sec
FT size 4096 x 4096
Total time 5 hr, 6 min
F1 (ppm)
F2 (ppm)

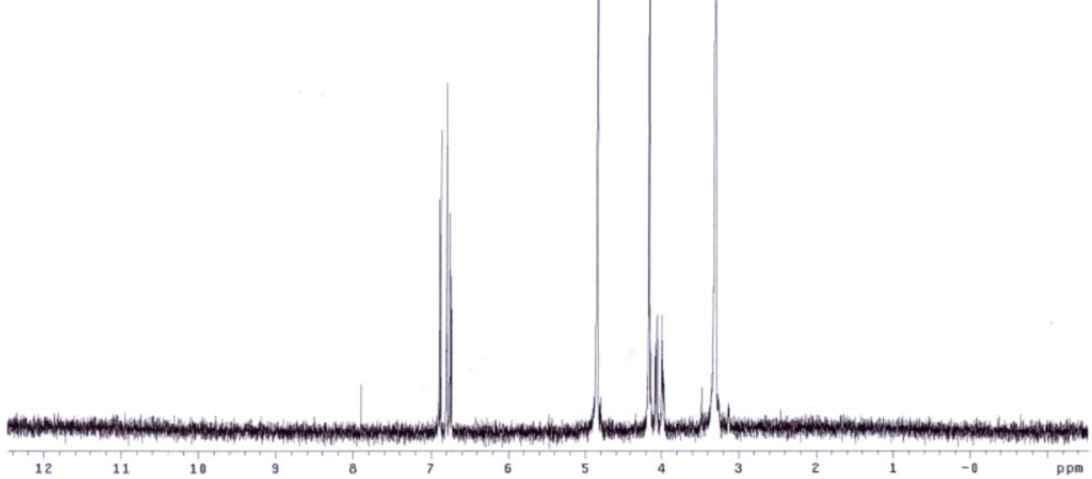

AMC-Chlophenesin Hydroxylation
Sample Name:
Data Collected on:
nmrox2-vnmrs600
Archive directory:
Sample directory:
FidFile: gHMBCAD
Pulse Sequence: gHMBCAD
Solvent: acetone
Data collected on: Jun 6 2013
F1 (ppm)
F2 (ppm)



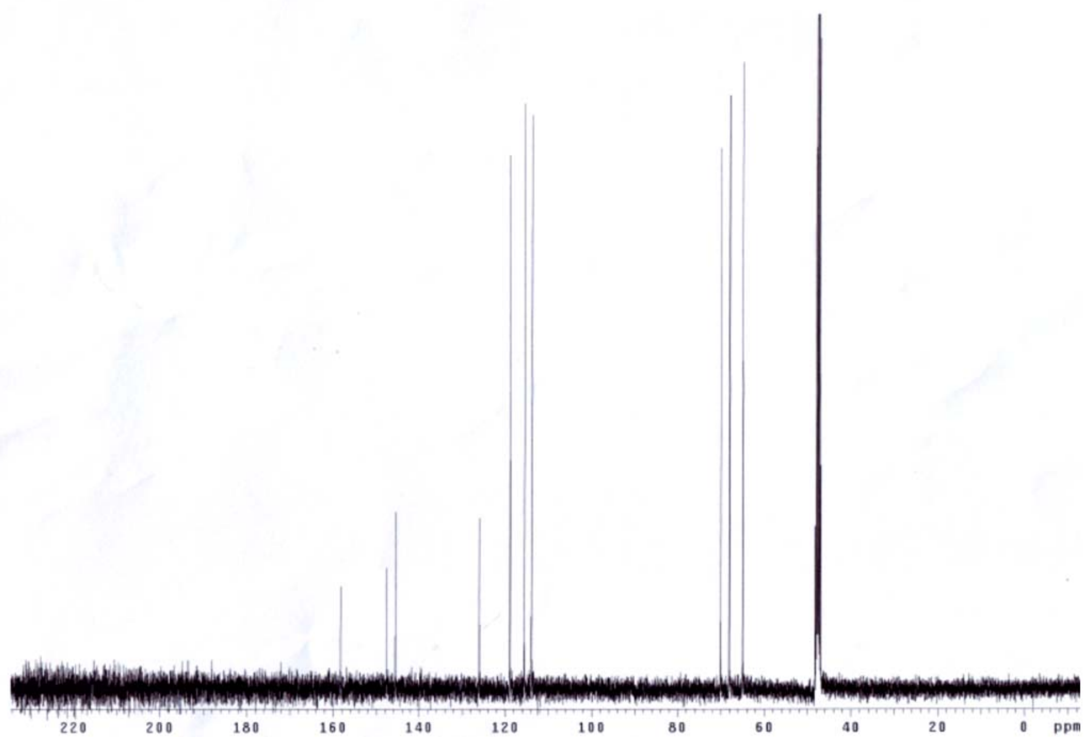
%Transmittance
100
99
98
97
96
95
94
93
92
91
90
89
88
87
86
85
84
83
82
81
80
79
78
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

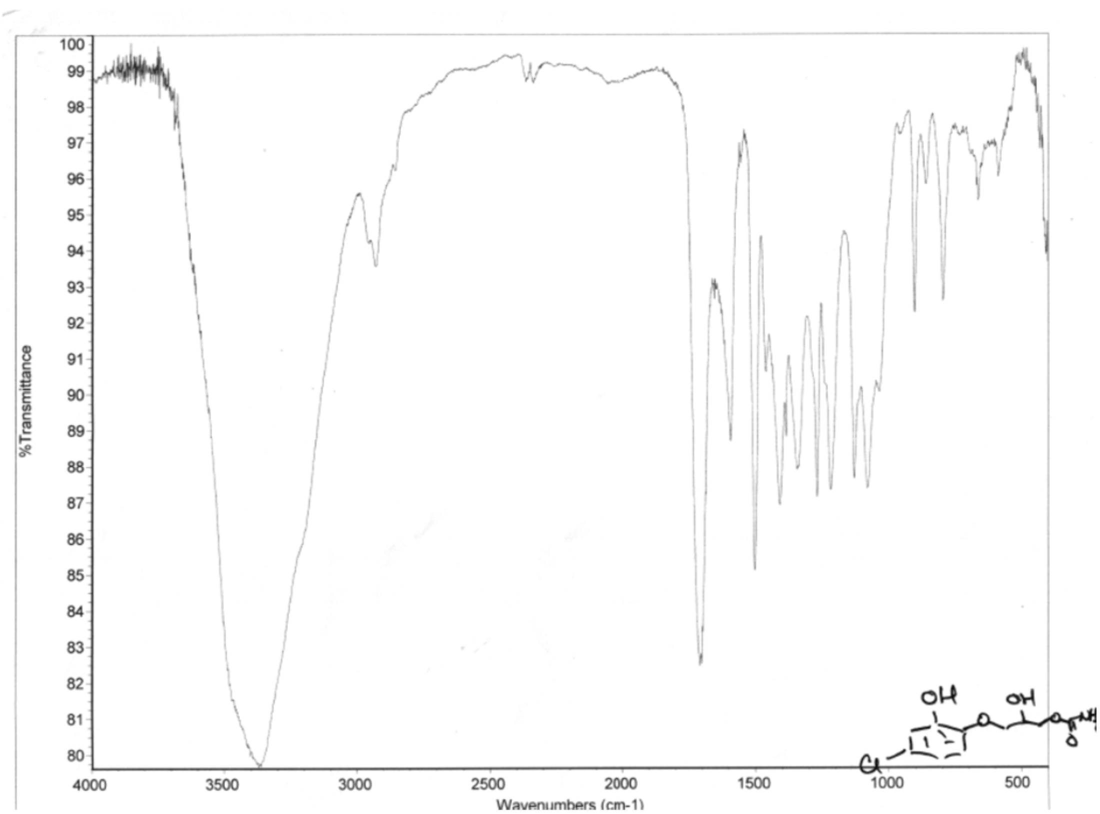


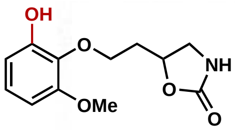
365



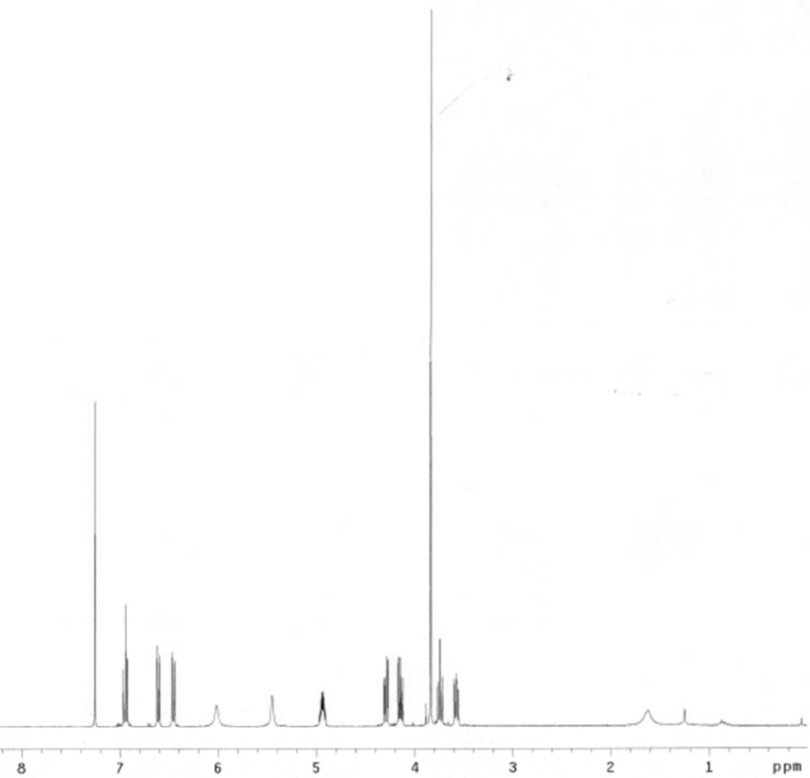
INDEX	FREQUENCY	PPM	HEIGHT
1	2760.506	6.897	53.0
2	2751.958	6.875	69.0
3	2723.236	6.804	65.3
4	2720.500	6.797	80.0
5	2705.797	6.760	49.8
6	2703.404	6.754	36.6
7	2697.249	6.739	35.2
8	2694.855	6.733	27.8
9	1939.524	4.846	2162.2
10	1663.925	4.157	130.6
11	1660.848	4.149	28.5
12	1633.151	4.080	20.1
13	1621.867	4.052	26.6
14	1600.326	3.998	26.4
15	1594.171	3.983	20.6
16	1325.753	3.312	668.7
17	1324.043	3.308	1274.3
18	1322.334	3.304	1733.3
19	1320.966	3.300	1157.7
20	1319.256	3.296	606.7

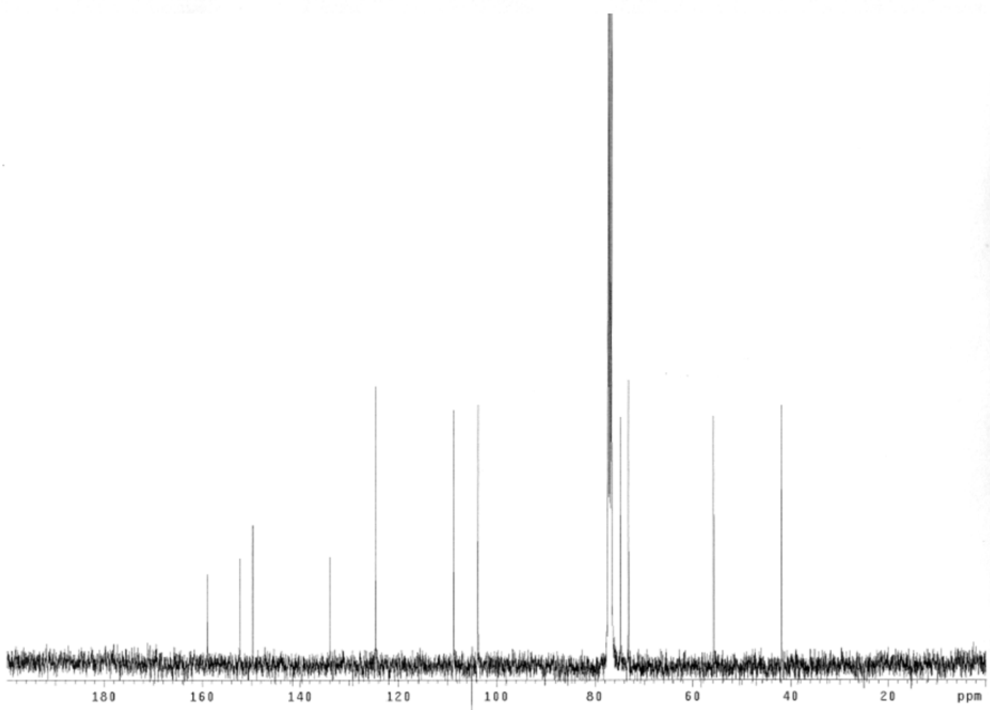


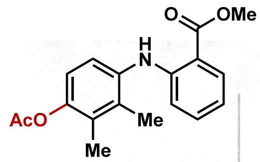

%Transmittance
Wavenumbers (cm-1)
OH
OH
Cl



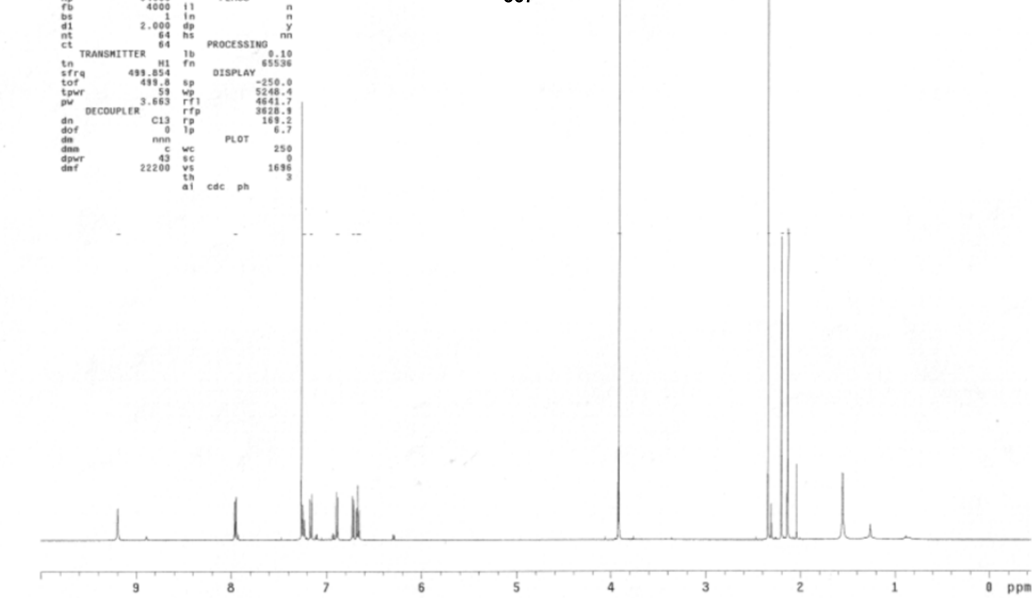
371

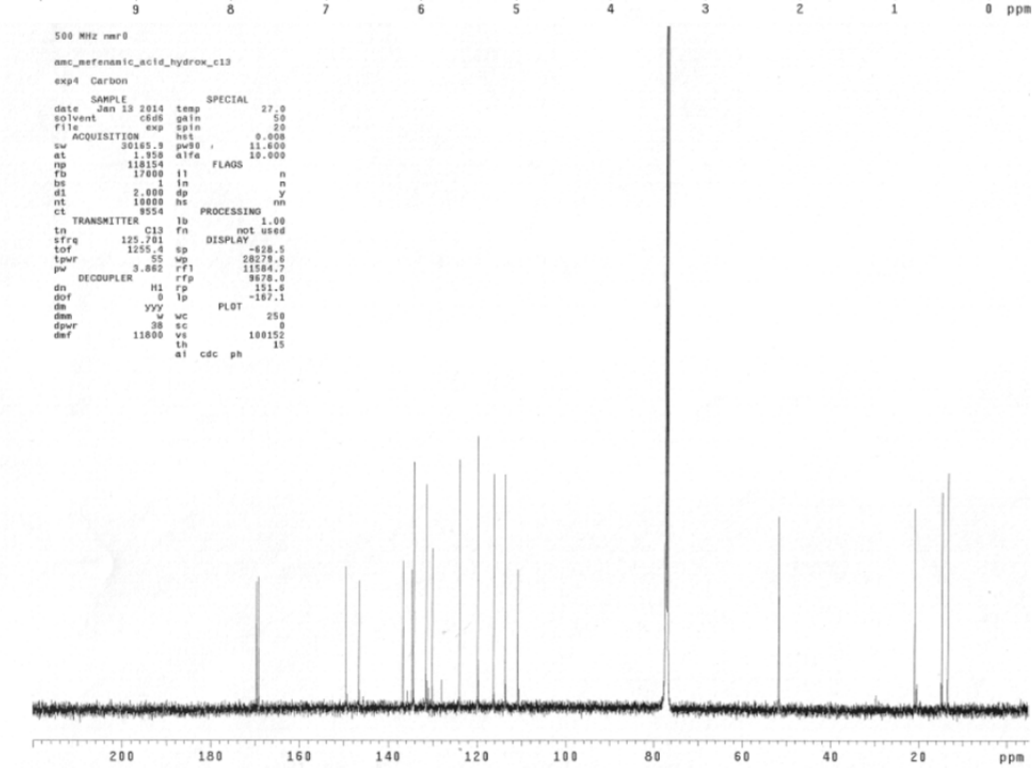


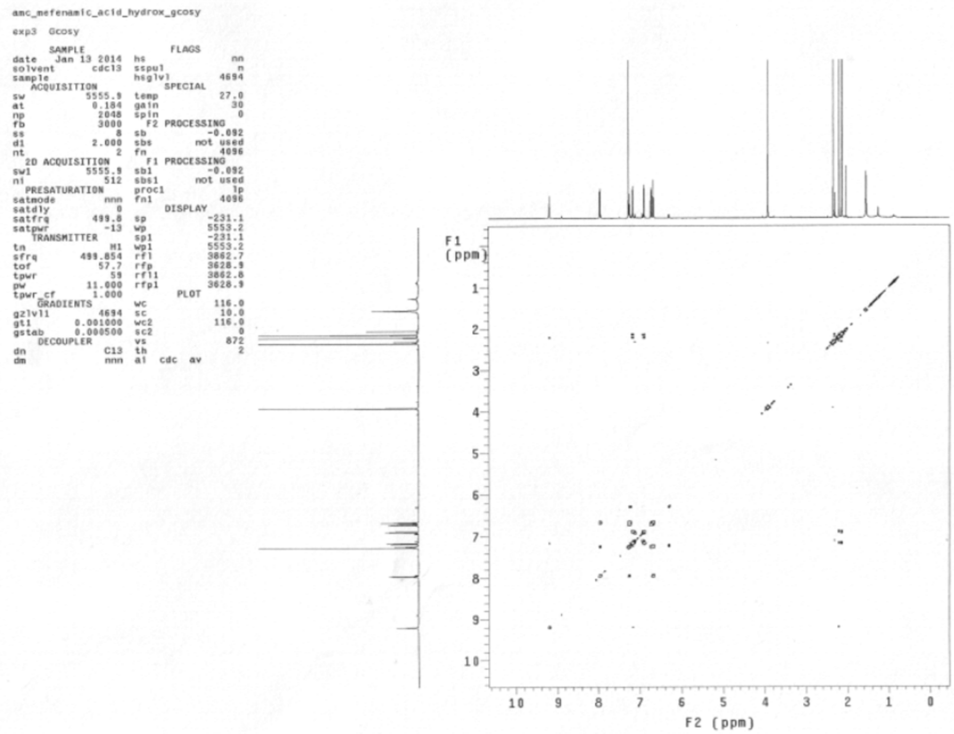


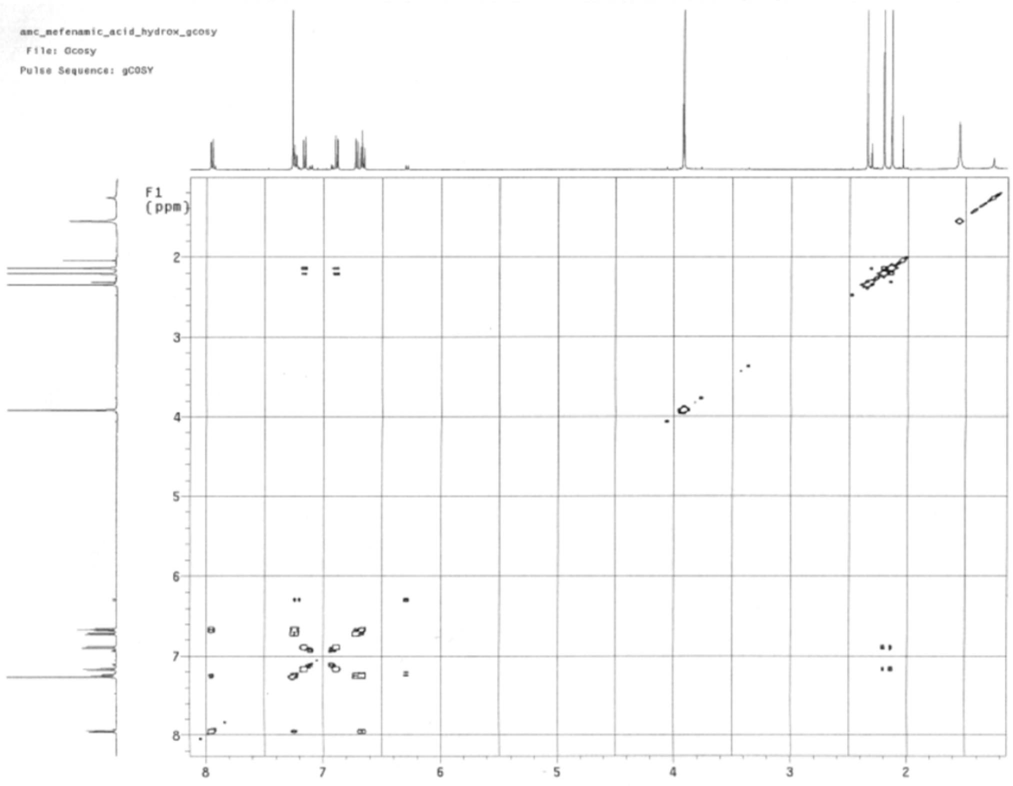

O
OMe
H
N
AcO
Me
Me

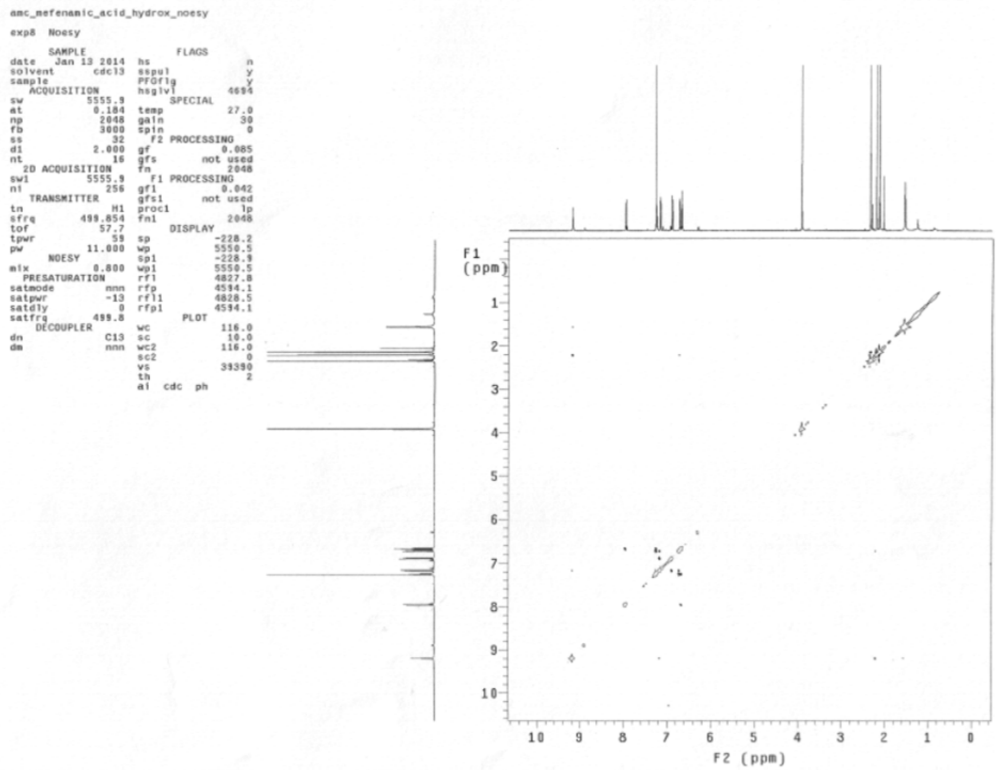
367

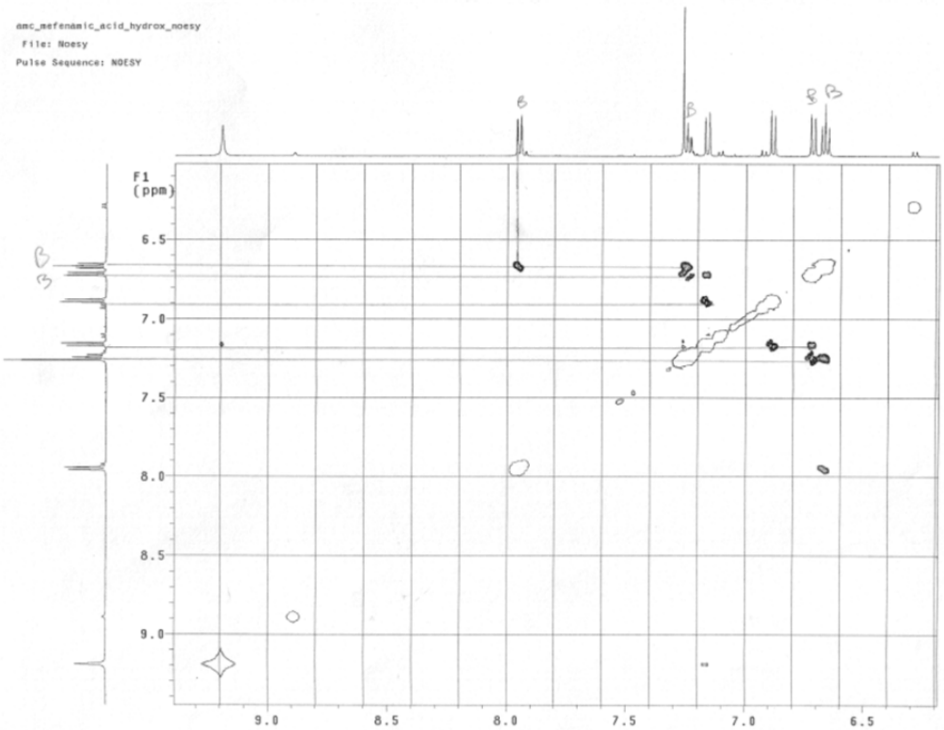

500 MHz nmr0
amc_mefenamic_acid_hydrox_h1
exp1 Proton
9
8
7
6
5
4
3
2
1
0 ppm

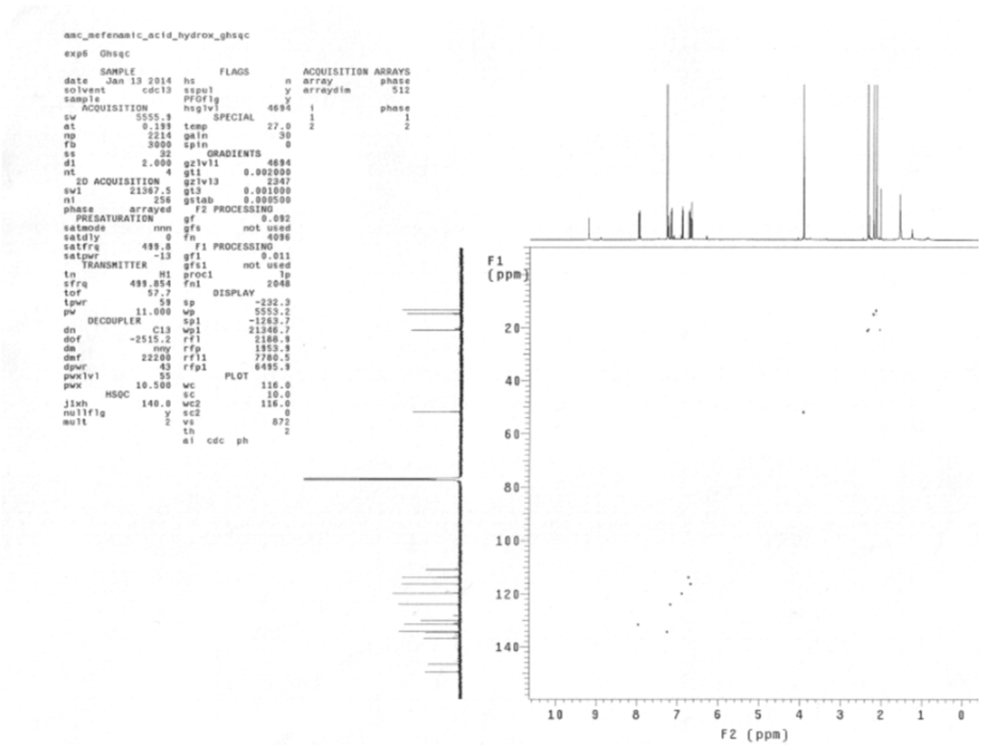

500 MHz nmr0
amc_mefenamic_acid_hydrox_c13
exp4 Carbon
200
180
160
140
120
100
80
60
40
20
ppm

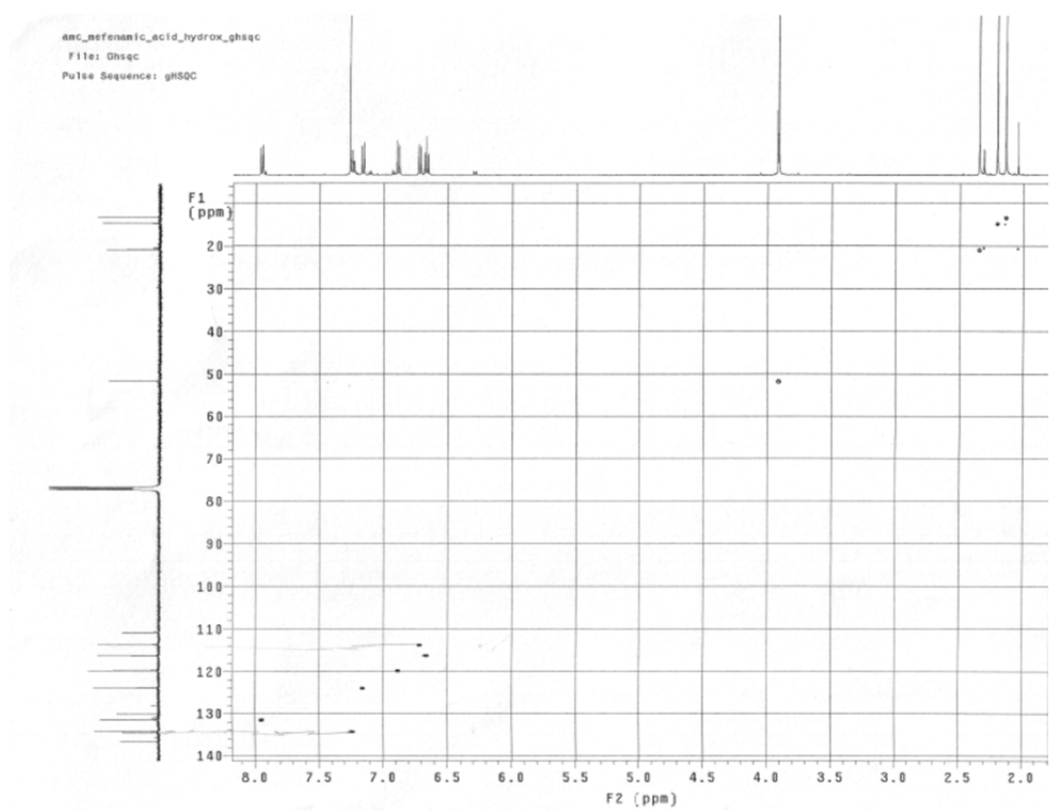

amc_mefenamic_acid_hydrox_gcosy
exp3 Gcosy
SAMPLE
date Jan 13 2014
solvent cdcl3
sample
ACQUISITION
sw 5555.9
at 0.184
np 2048
fb 3000
ss 8
d1 2.000
nt 2
2D ACQUISITION
sw1 5555.9
ni 512
PRESATURATION
satmode nnn
satdly 0
satfrq 499.8
satpwr -13
TRANSMITTER
tn H1
sfrq 499.854
tof 57.7
tpwr 59
pw 11.000
tpwr_cf 1.000
GRADIENTS
gzlvl1 4694
gt1 0.001000
gstab 0.000500
DECOUPLER
dn C13
dm nnn
FLAGS
hs nn
sspul n
hsglvl 4694
SPECIAL
temp 27.0
gain 30
spin 0
F2 PROCESSING
sb -0.092
sbs not used
fn 4096
F1 PROCESSING
sb1 -0.092
sbs1 not used
proc1 lp
fn1 4096
DISPLAY
sp -231.1
wp 5553.2
sp1 -231.1
wp1 5553.2
rfl 3862.7
rfp 3628.9
rfl1 3862.8
rfp1 3628.9
PLOT
wc 116.0
sc 10.0
wc2 116.0
sc2 0
vs 872
th 2
ai cdc av
F1 (ppm)
F2 (ppm)

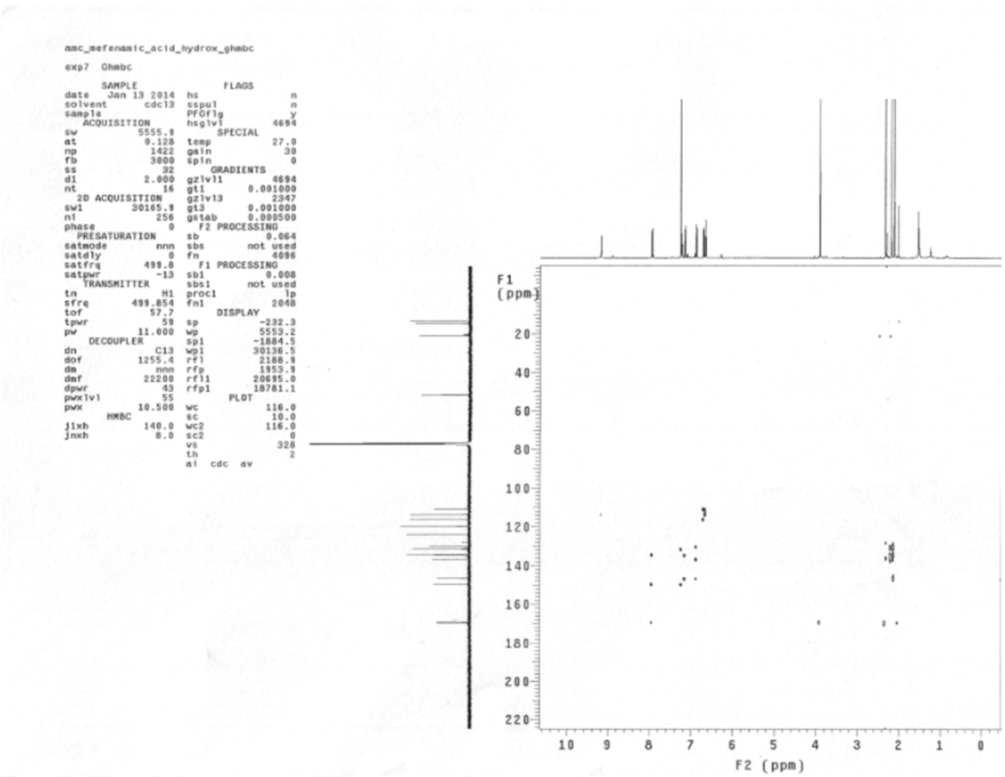

amc_mefenamic_acid_hydrox_gcosy
File: Gcosy
Pulse Sequence: gCOSY
F1 (ppm)
F2 (ppm)

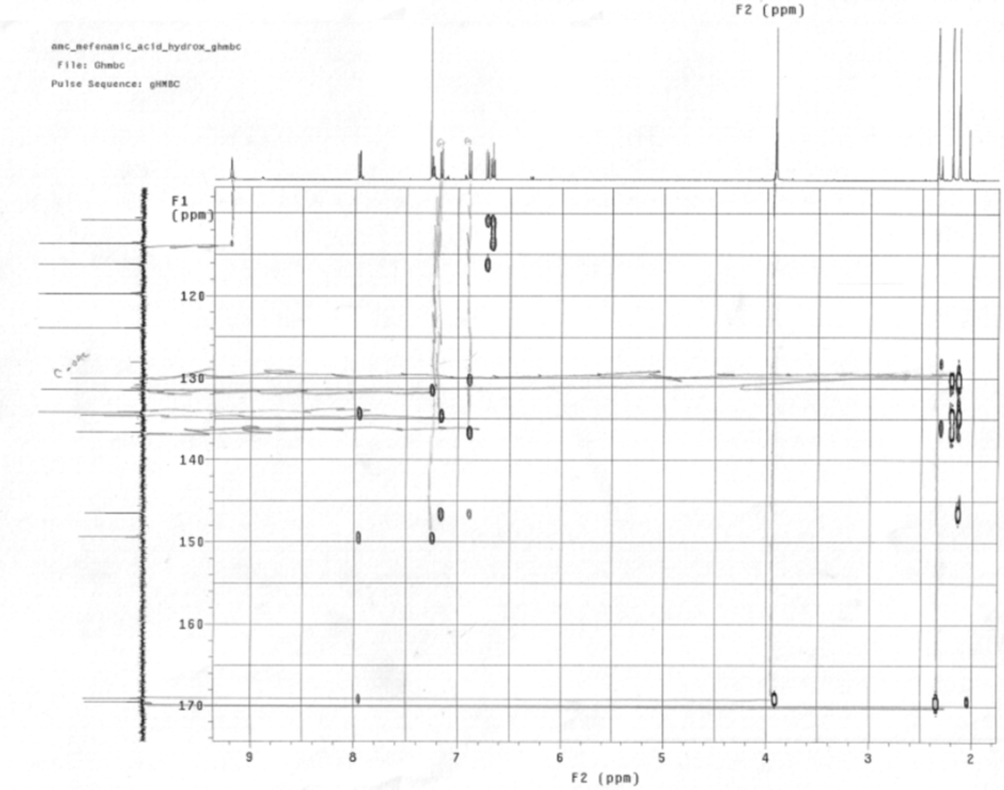

amc_mefenamic_acid_hydrox_noesy
exp8 Noesy
SAMPLE
date Jan 13 2014
solvent cdcl3
sample
ACQUISITION
sw 5555.9
at 0.184
np 2048
fb 3000
ss 32
d1 2.000
nt 16
2D ACQUISITION
sw1 5555.9
ni 256
TRANSMITTER
tn H1
sfrq 499.854
tof 57.7
tpwr 59
pw 11.000
NOESY
mix 0.800
PRESATURATION
satmode nnn
satpwr -13
satdly 0
satfrq 499.8
DECOUPLER
dn C13
dm nnn
FLAGS
hs n
sspul y
PFGflg y
hsglvl 4694
SPECIAL
temp 27.0
gain 30
spin 0
F2 PROCESSING
gf 0.085
gfs not used
fn 2048
F1 PROCESSING
gf1 0.042
gfs1 not used
proc1 lp
fn1 2048
DISPLAY
sp -228.2
wp 5550.5
sp1 -228.9
wp1 5550.5
rfl 4827.8
rfp 4594.1
rfl1 4828.5
rfp1 4594.1
PLOT
wc 116.0
sc 10.0
wc2 116.0
sc2 0
vs 39390
th 2
ai cdc ph
F1 (ppm)
F2 (ppm)

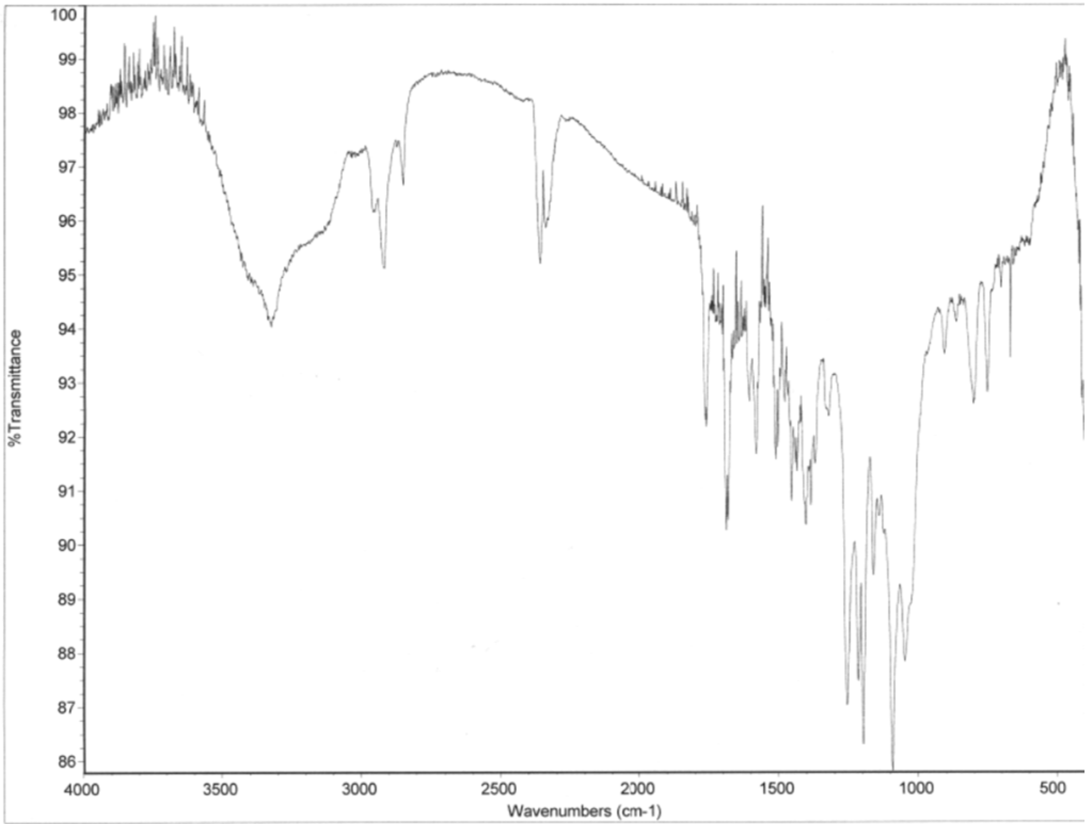

amc_mefenamic_acid_hydrox_noesy
File: Noesy
Pulse Sequence: NOESY
F1 (ppm)
F2 (ppm)


amc_mefenamic_acid_hydrox_ghsqc
exp6 Ghsqc
SAMPLE
date Jan 13 2014
solvent cdcl3
sample
ACQUISITION
sw 5555.9
at 0.199
np 2214
fb 3000
ss 32
d1 2.000
nt 4
2D ACQUISITION
sw1 21367.5
ni 256
phase arrayed
PRESATURATION
satmode nnn
satdly 0
satfrq 499.8
satpwr -13
TRANSMITTER
tn H1
sfrq 499.854
tof 57.7
tpwr 59
pw 11.000
DECOUPLER
dn C13
dof -2515.2
dm nny
dmf 22200
dpwr 43
pwxlvl 55
pwx 10.500
HSQC
j1xh 140.0
nullflg y
mult 2
FLAGS
hs n
sspul y
PFGflg y
hsglvl 4694
SPECIAL
temp 27.0
gain 30
spin 0
GRADIENTS
gzlvl1 4694
gt1 0.002000
gzlvl3 2347
gt3 0.001000
gstab 0.000500
F2 PROCESSING
gf 0.092
gfs not used
fn 4096
F1 PROCESSING
gf1 0.011
gfs1 not used
proc1 lp
fn1 2048
DISPLAY
sp -232.3
wp 5553.2
sp1 -1263.7
wp1 21346.7
rfl 2188.9
rfp 1953.9
rfl1 7780.5
rfp1 6495.9
PLOT
wc 116.0
sc 10.0
wc2 116.0
sc2 0
vs 872
th 2
ai cdc ph
ACQUISITION ARRAYS
array phase
arraydim 512
i phase
1 1
2 2
F1 (ppm)
20
40
60
80
100
120
140
10 9 8 7 6 5 4 3 2 1 0
F2 (ppm)

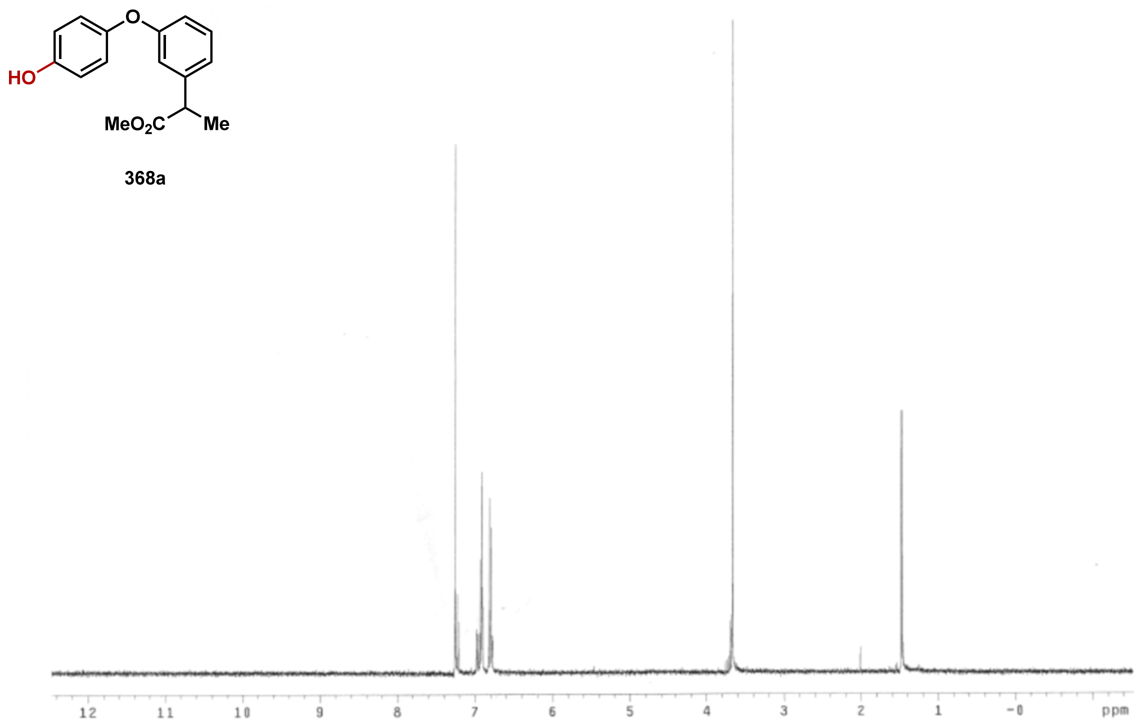

amc_mefenamic_acid_hydrox_ghsqc
File: Ghsqc
Pulse Sequence: gHSQC
F1 (ppm)
20
30
40
50
60
70
80
90
100
110
120
130
140
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0
F2 (ppm)


amc_mefenamic_acid_hydrox_ghmbc
exp7 Ghmbc
SAMPLE
date Jan 13 2014
solvent cdcl3
sample
ACQUISITION
sw 5555.9
at 0.128
np 1422
fb 3000
ss 32
d1 2.000
nt 16
2D ACQUISITION
sw1 30165.9
ni 256
phase 0
PRESATURATION
satmode nnn
satdly 0
satfrq 499.8
satpwr -13
TRANSMITTER
tn H1
sfrq 499.854
tof 57.7
tpwr 59
pw 11.000
DECOUPLER
dn C13
dof 1255.4
dm nnn
dmf 22200
dpwr 43
pwxlvl 55
pwx 10.500
HMBC
j1xh 140.0
jnxh 8.0
FLAGS
hs n
sspul n
PFGflg y
hsglvl 4694
SPECIAL
temp 27.0
gain 30
spin 0
GRADIENTS
gzlvl1 4694
gt1 0.001000
gzlvl3 2347
gt3 0.001000
gstab 0.000500
F2 PROCESSING
sb 0.064
sbs not used
fn 4096
F1 PROCESSING
sb1 0.008
sbs1 not used
proc1 lp
fn1 2048
DISPLAY
sp -232.3
wp 5553.2
sp1 -1884.5
wp1 30136.5
rfl 2188.9
rfp 1953.9
rfl1 20695.0
rfp1 18781.1
PLOT
wc 116.0
sc 10.0
wc2 116.0
sc2 0
vs 328
th 2
ai cdc av
F1 (ppm)
F2 (ppm)

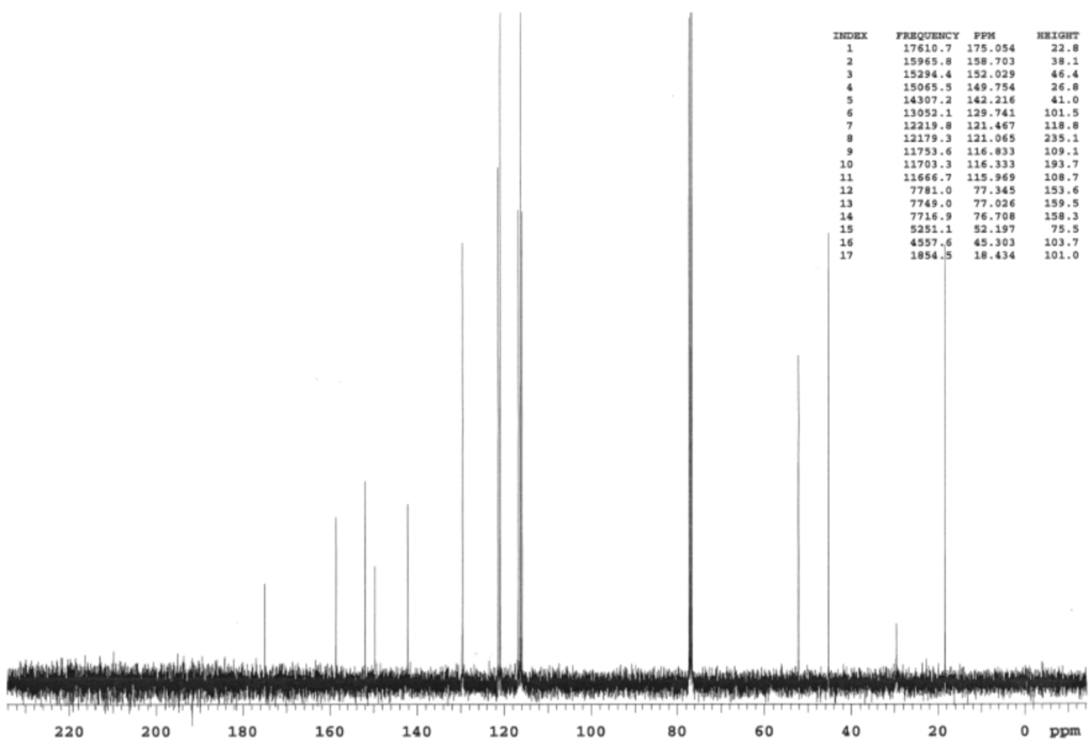

amc_mefenamic_acid_hydrox_ghmbc
File: Ghmbc
Pulse Sequence: gHMBC
F1 (ppm)
F2 (ppm)



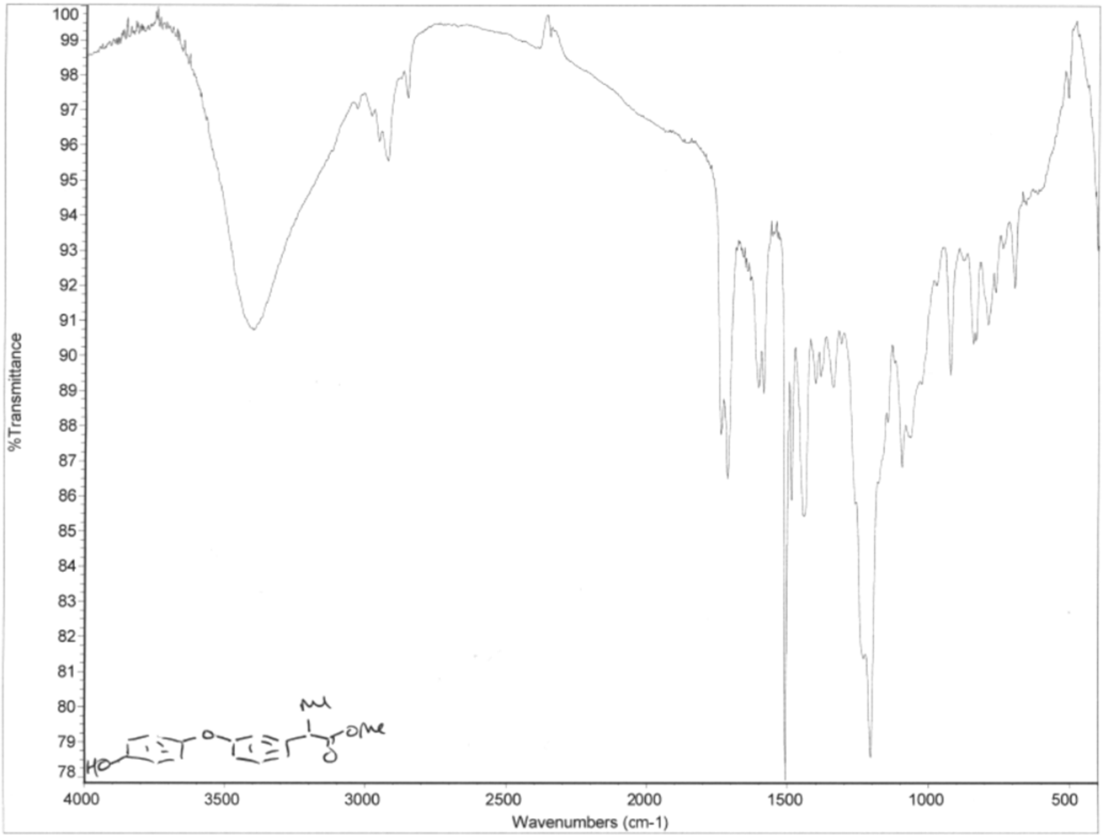
100
99
98
97
96
95
94
93
92
91
90
89
88
87
86
%Transmittance
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

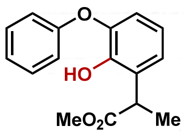


368a

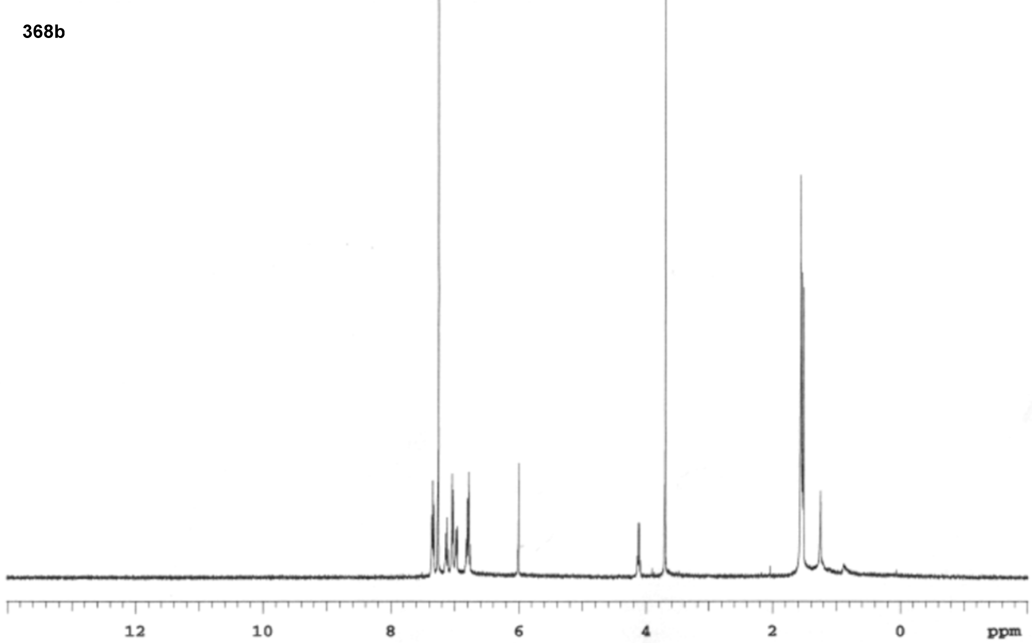


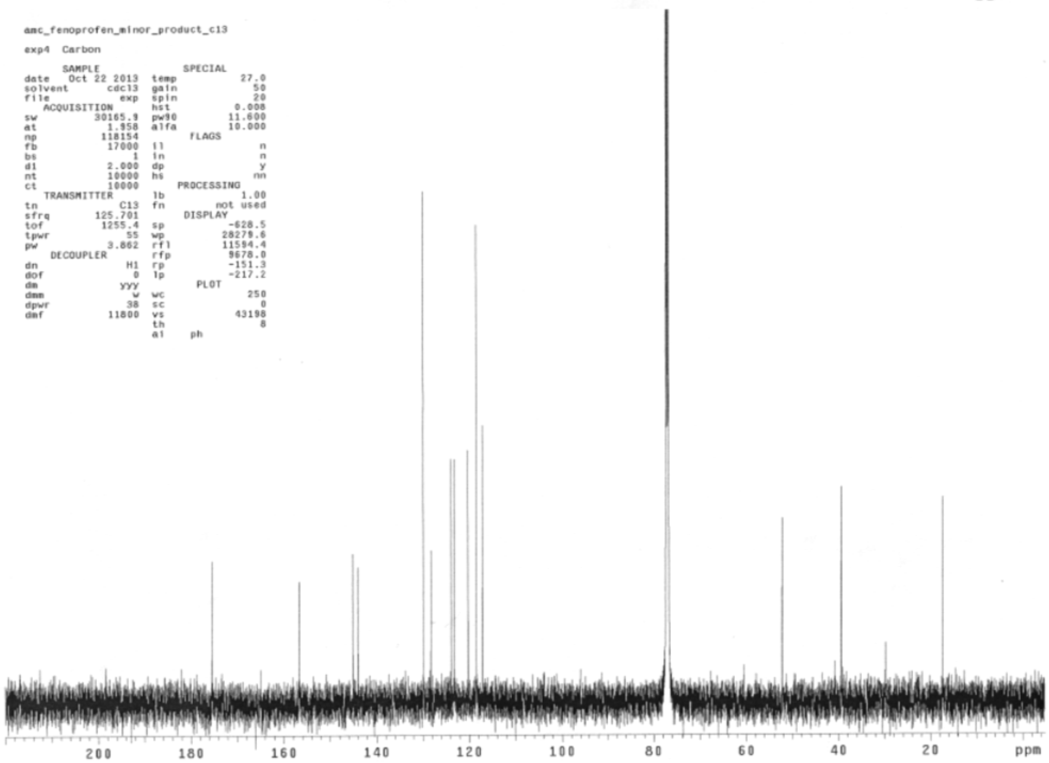
INDEX	FREQUENCY	PPM	HEIGHT
1	17610.7	175.054	22.8
2	15965.8	158.703	38.1
3	15294.4	152.029	46.4
4	15065.5	149.754	26.8
5	14307.2	142.216	41.0
6	13052.1	129.741	101.5
7	12219.8	121.467	118.8
8	12179.3	121.065	235.1
9	11753.6	116.833	109.1
10	11703.3	116.333	193.7
11	11666.7	115.969	108.7
12	7781.0	77.345	153.6
13	7749.0	77.026	159.5
14	7716.9	76.708	158.3
15	5251.1	52.197	75.5
16	4557.6	45.303	103.7
17	1854.5	18.434	101.0

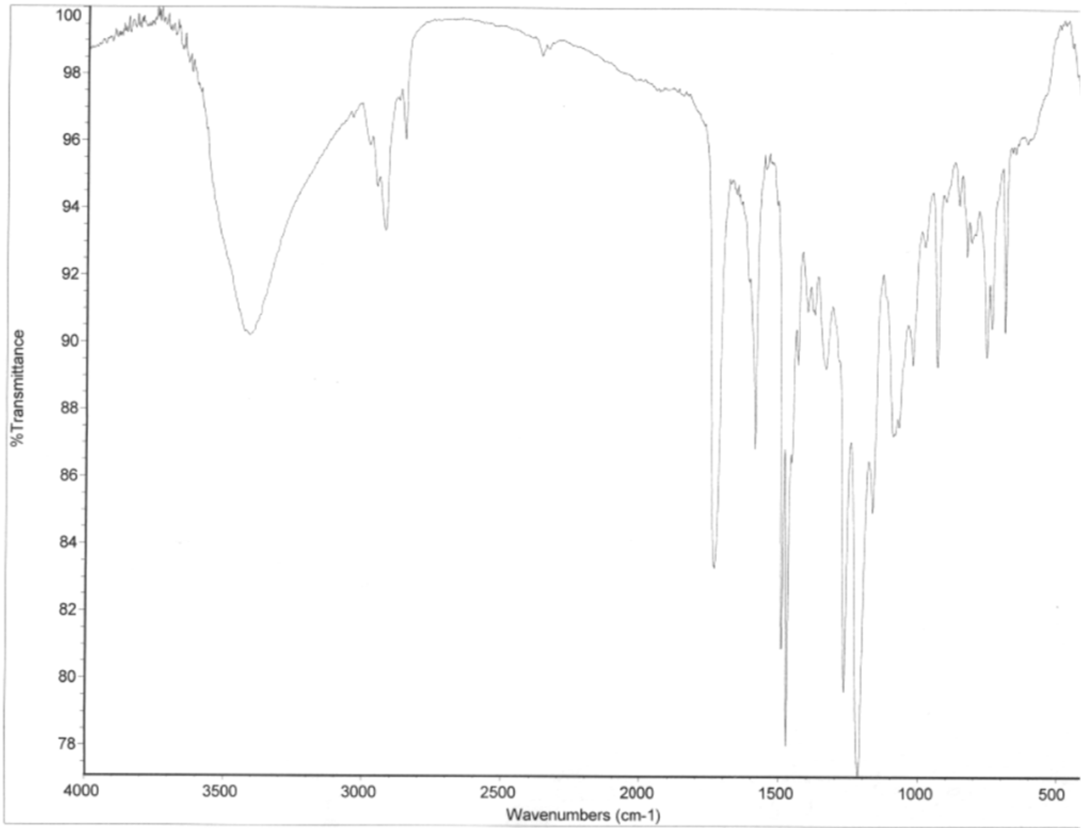

%Transmittance
Wavenumbers (cm-1)
100
99
98
97
96
95
94
93
92
91
90
89
88
87
86
85
84
83
82
81
80
79
78
4000
3500
3000
2500
2000
1500
1000
500


O
HO
MeO2C
Me

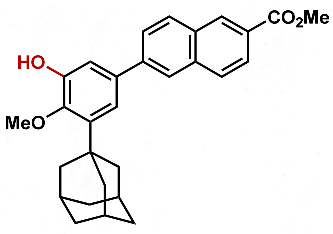
368b


12
10
8
6
4
2
0
ppm


amc_fenoprofen_minor_product_c13
exp4 Carbon
SAMPLE
date Oct 22 2013
solvent cdcl3
file exp
ACQUISITION
sw 30165.9
at 1.958
np 118154
fb 17000
bs 1
d1 2.000
nt 10000
ct 10000
TRANSMITTER
tn C13
sfrq 125.701
tof 1255.4
tpwr 55
pw 3.862
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 38
dmf 11800
SPECIAL
temp 27.0
gain 50
spin 20
hst 0.008
pw90 11.600
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -628.5
wp 28279.6
rfl 11594.4
rfp 9678.0
rp -151.3
lp -217.2
PLOT
wc 250
sc 0
vs 43198
th 8
ai ph
200
180
160
140
120
100
80
60
40
20
ppm

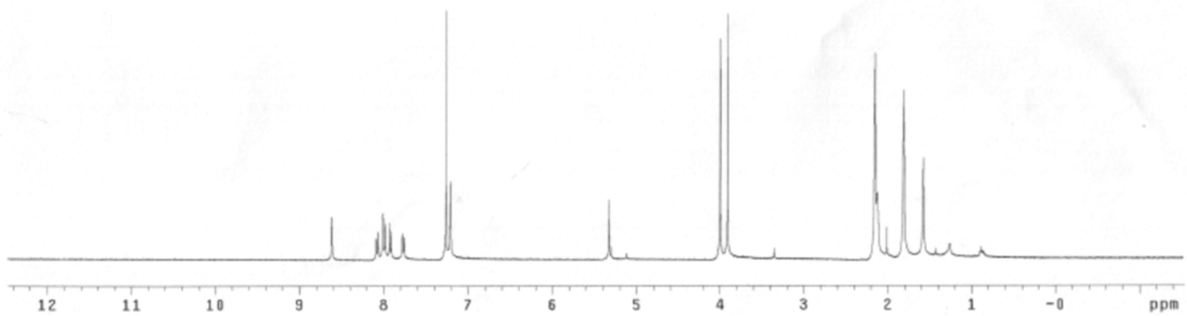


%Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

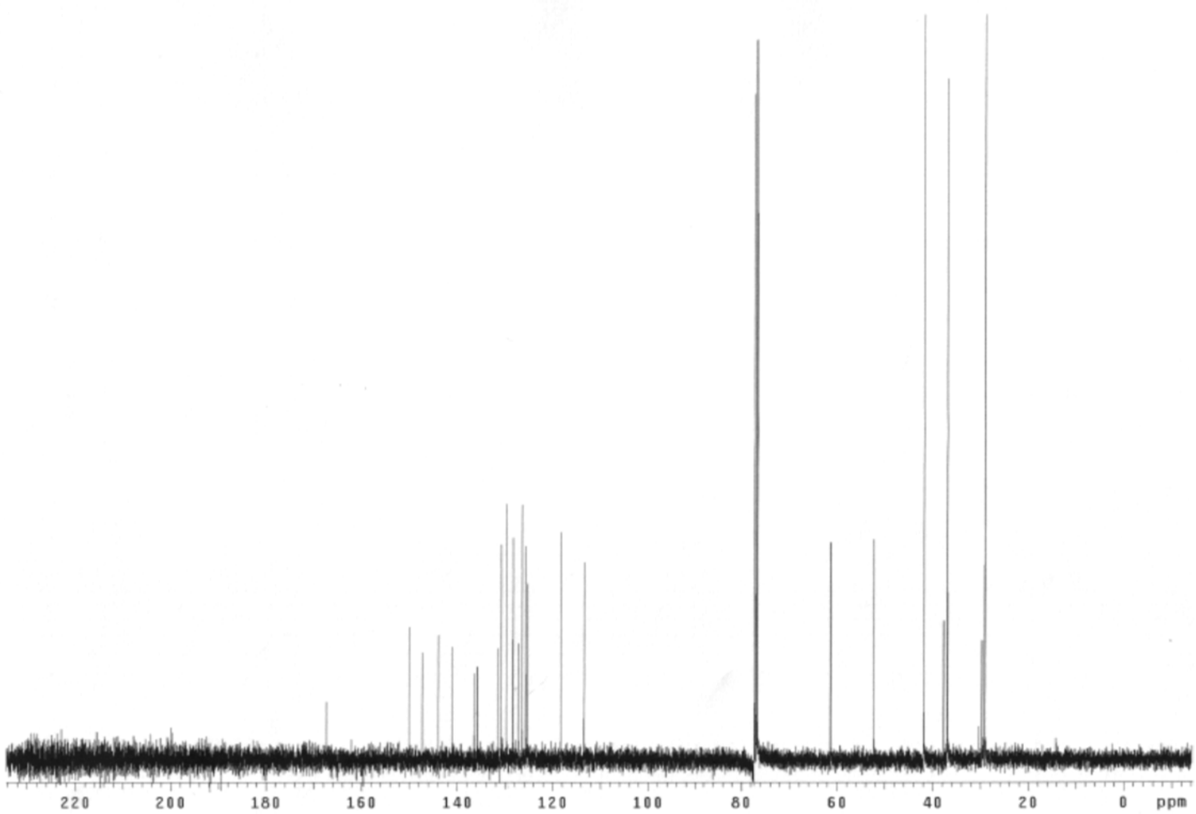


CO2Me
HO
MeO

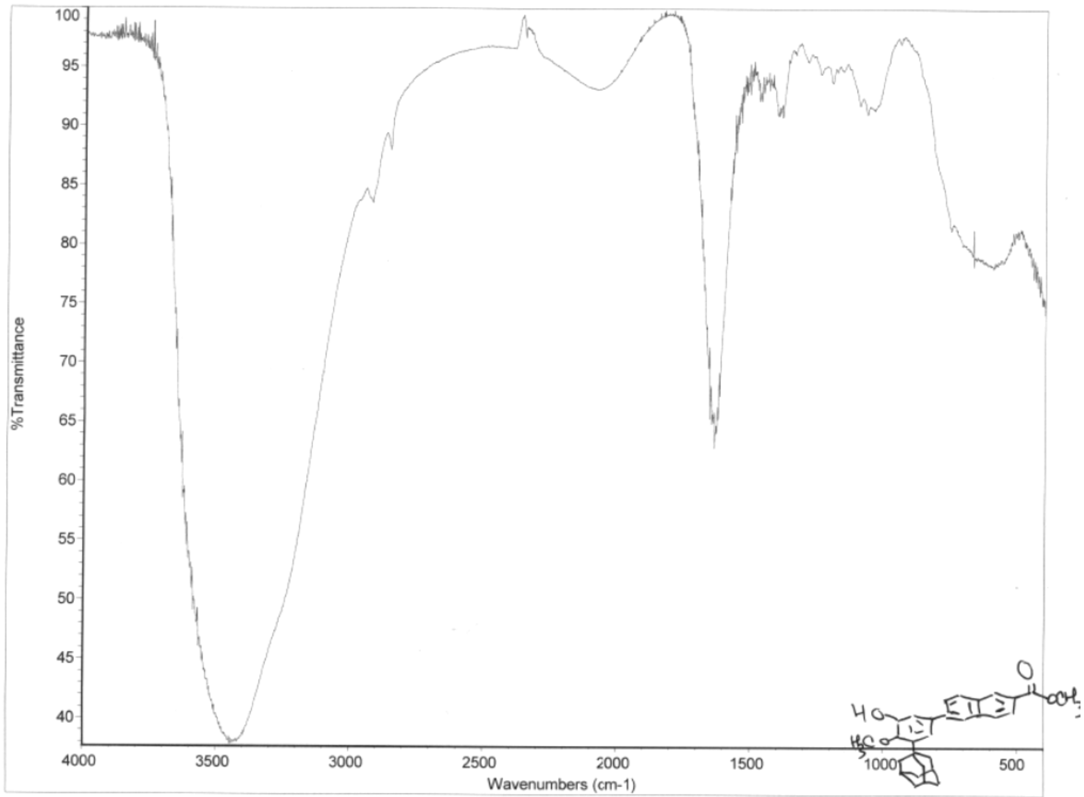
370

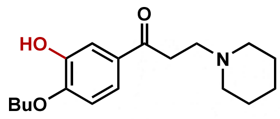


12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

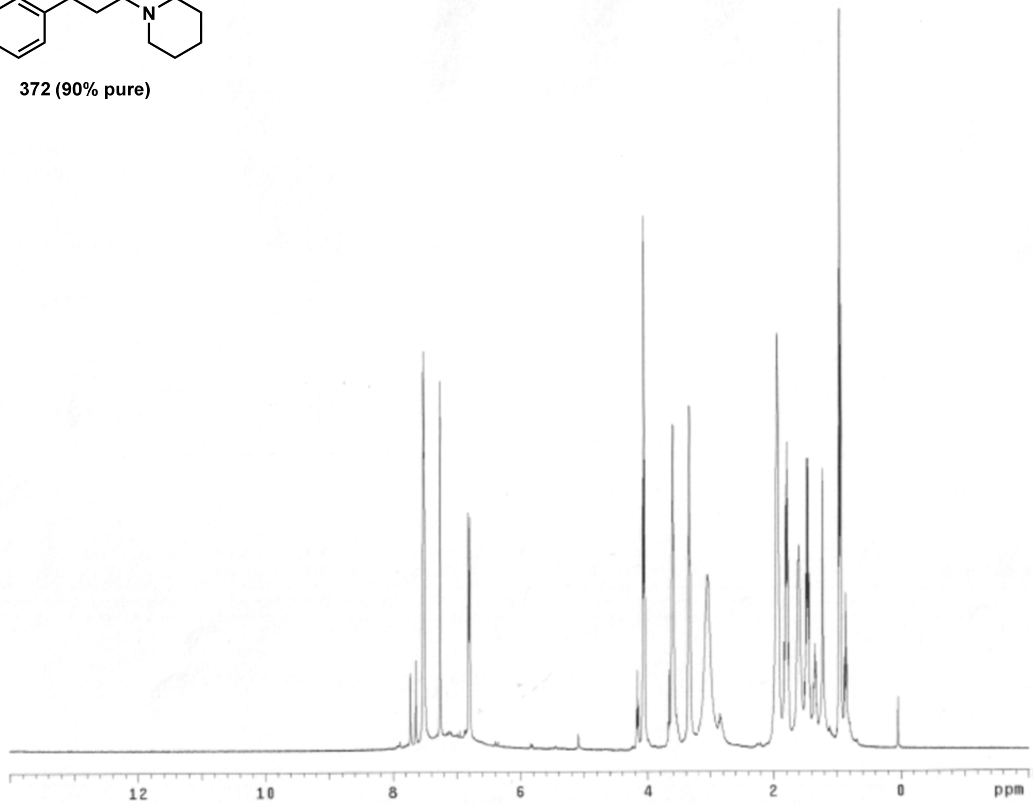


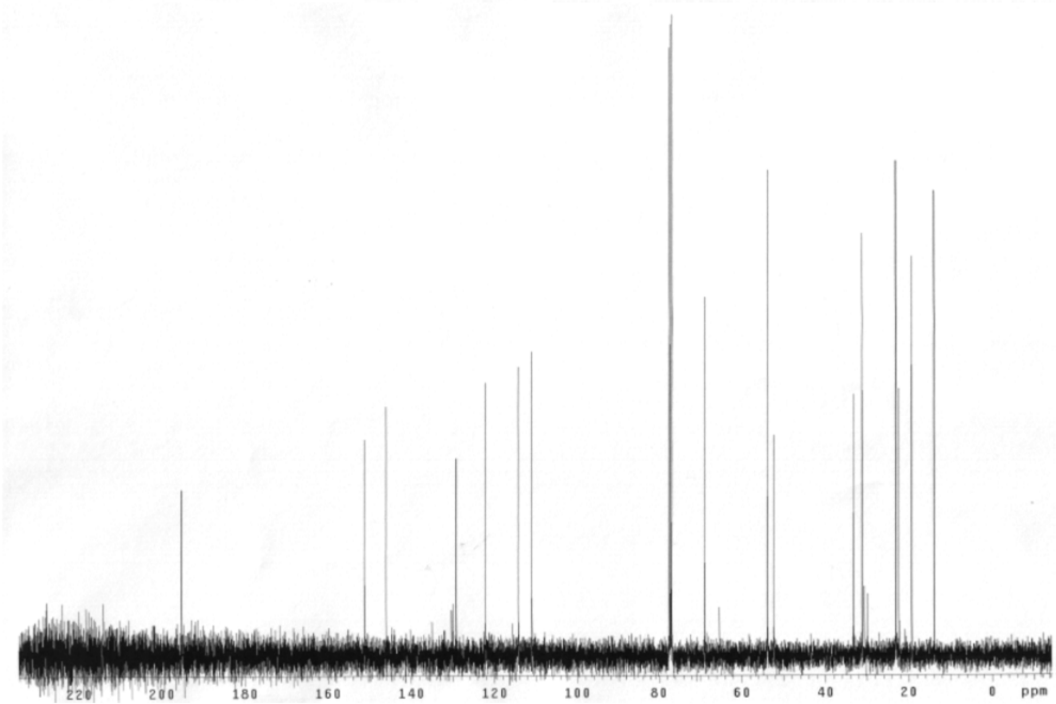
220 200 180 160 140 120 100 80 60 40 20 0 ppm

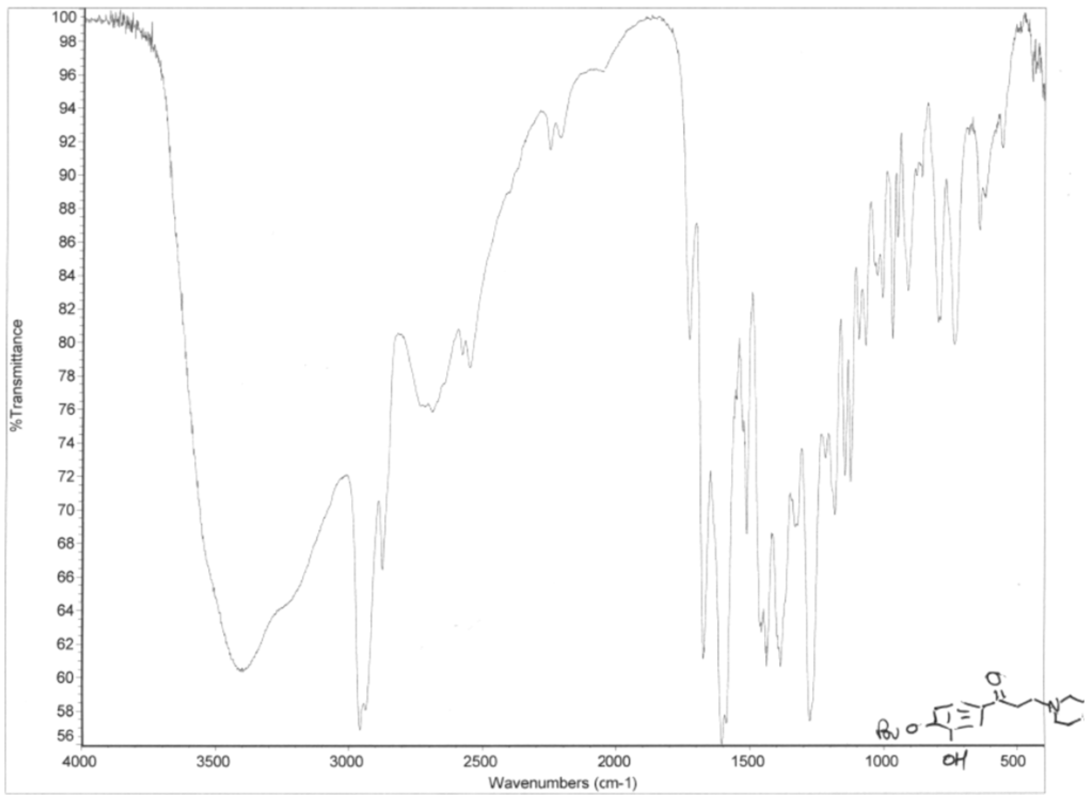

%Transmittance
Wavenumbers (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
4000
3500
3000
2500
2000
1500
1000
500


HO
O
N
BuO

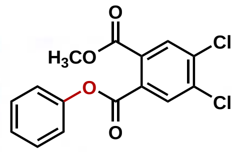
372 (90% pure)


12
10
8
6
4
2
0
ppm

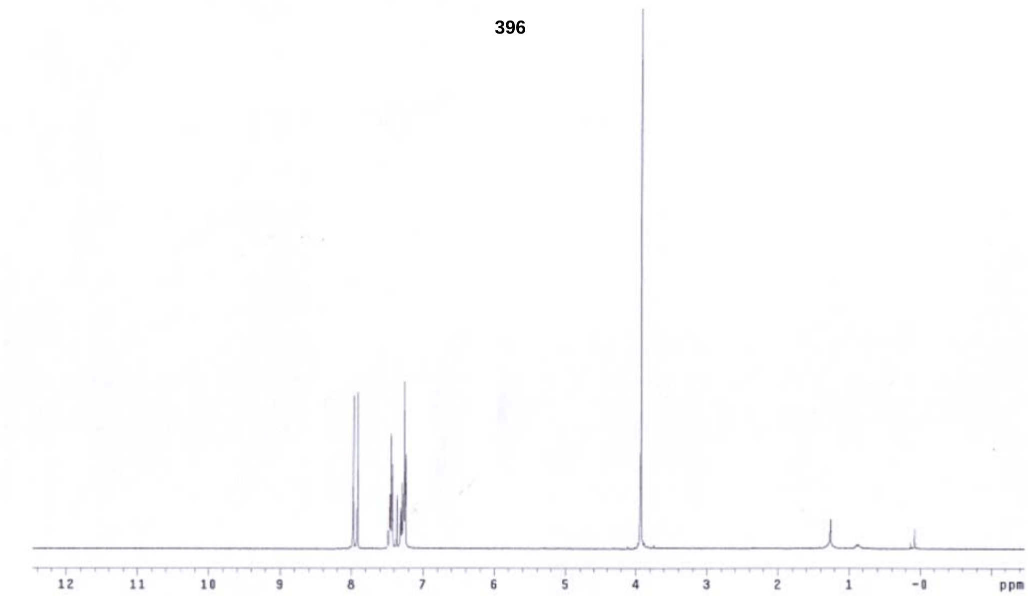

220
200
180
160
140
120
100
80
60
40
20
0
ppm

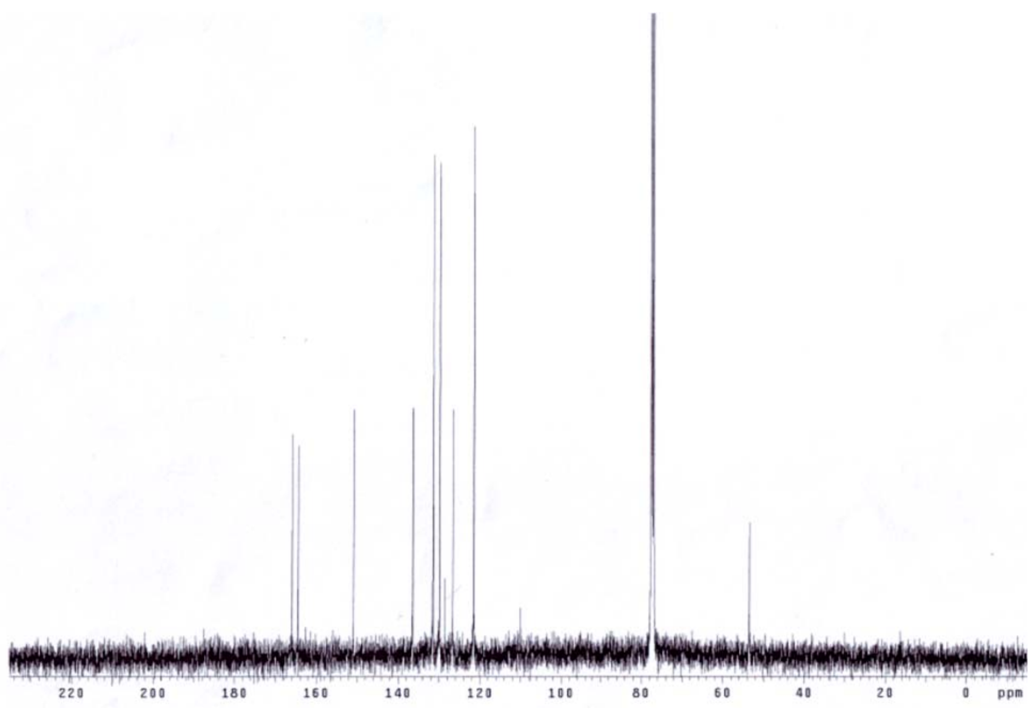

%Transmittance
Wavenumbers (cm-1)
OH

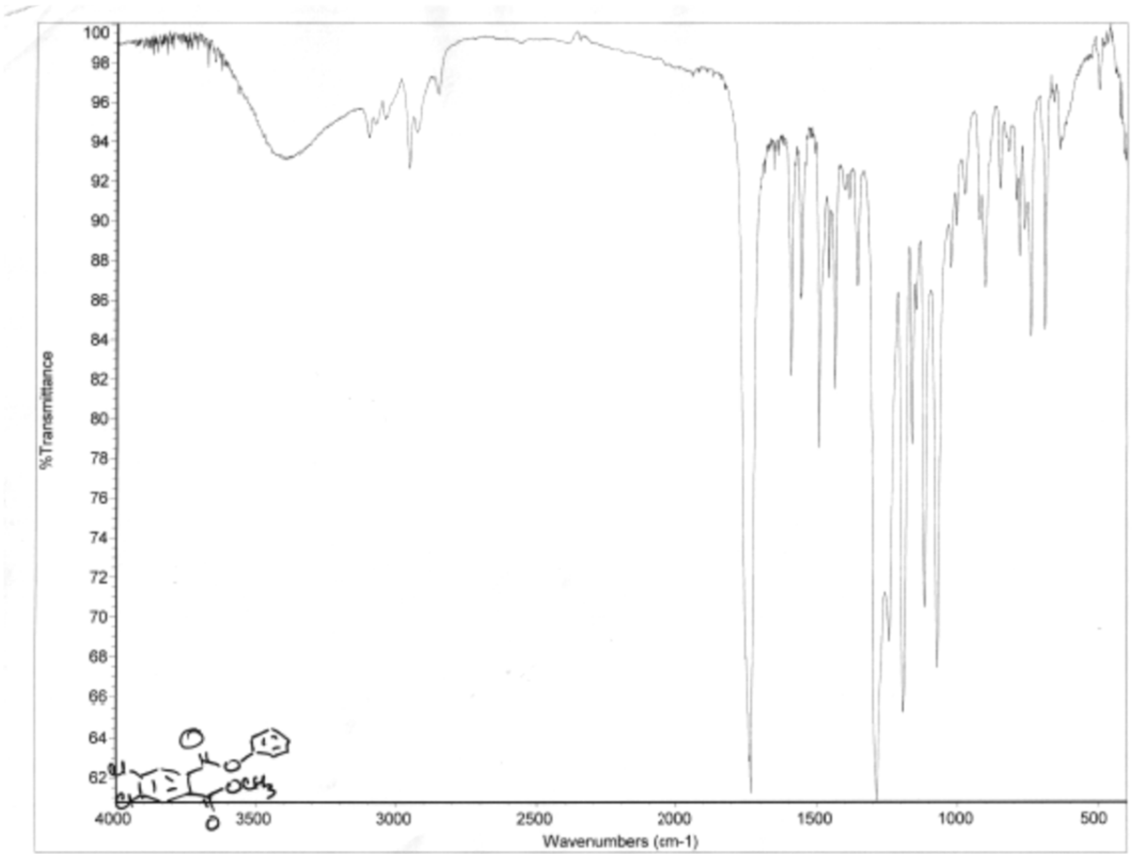
INDEX	FREQUENCY	PPM	HEIGHT
1	3190.641	7.971	38.1
2	3167.389	7.913	39.0
3	2978.300	7.441	28.7
4	2970.435	7.421	21.1
5	2905.468	7.259	41.7
6	2898.287	7.241	23.7
7	1570.901	3.925	135.2



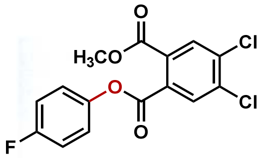
396



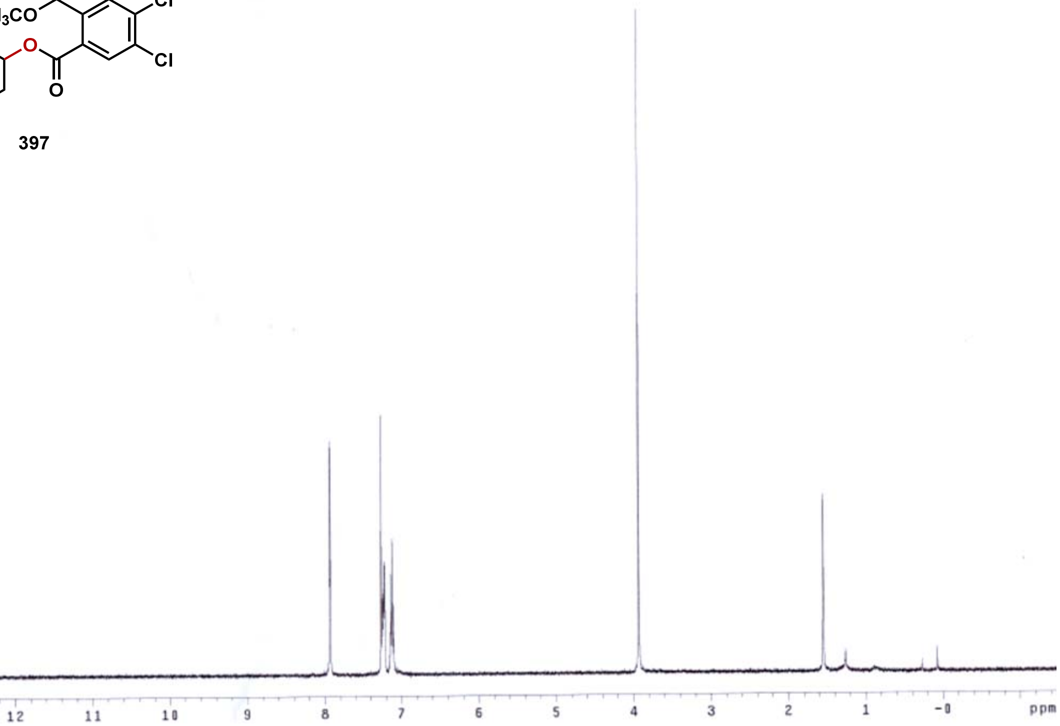


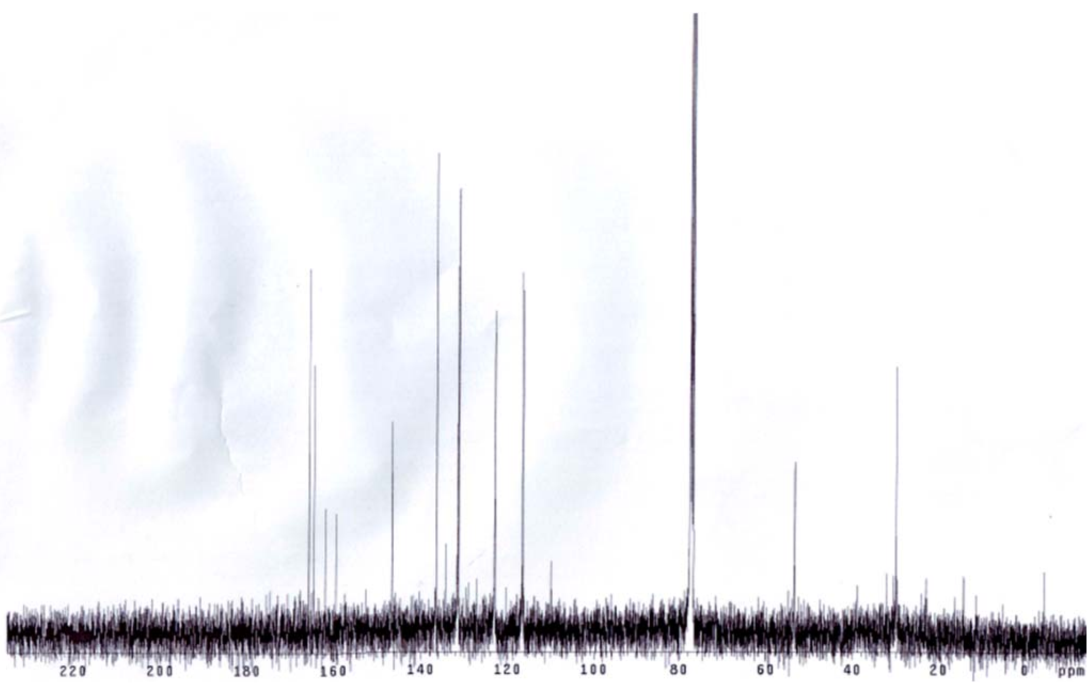


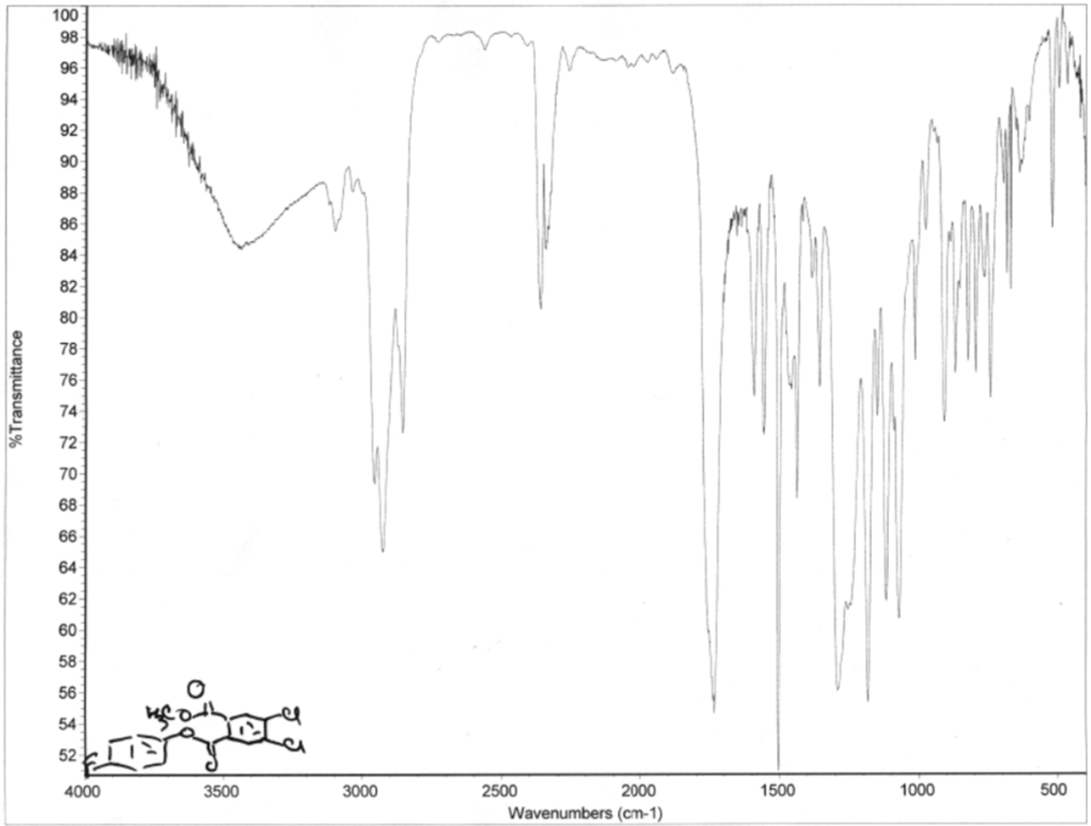
%Transmittance
Wavenumbers (cm-1)

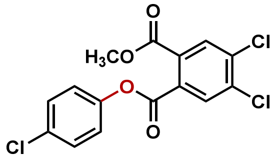

O
H3CO
Cl
O
Cl
F
O

397

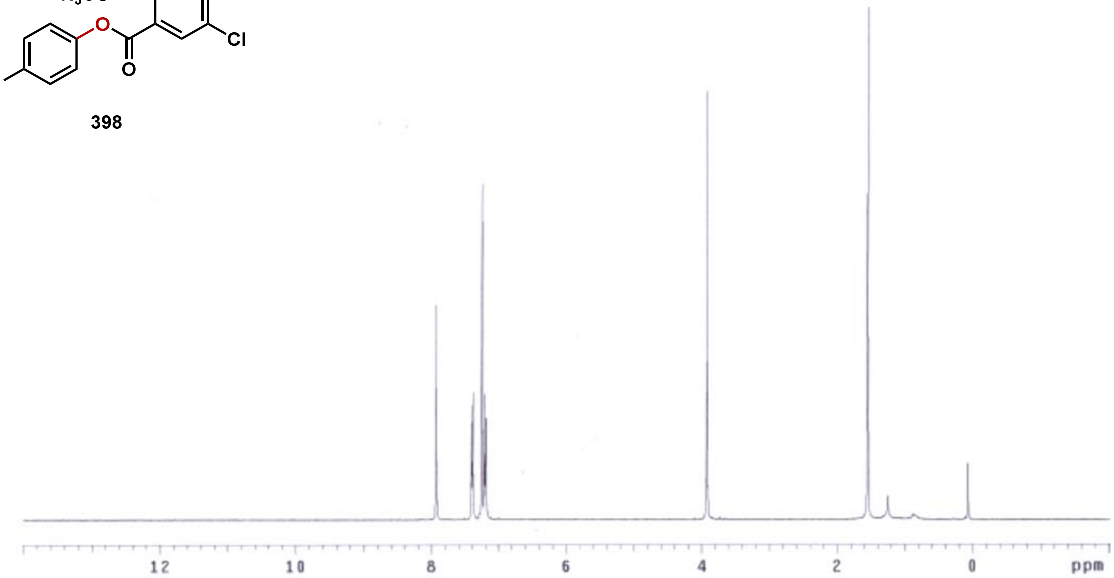

12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

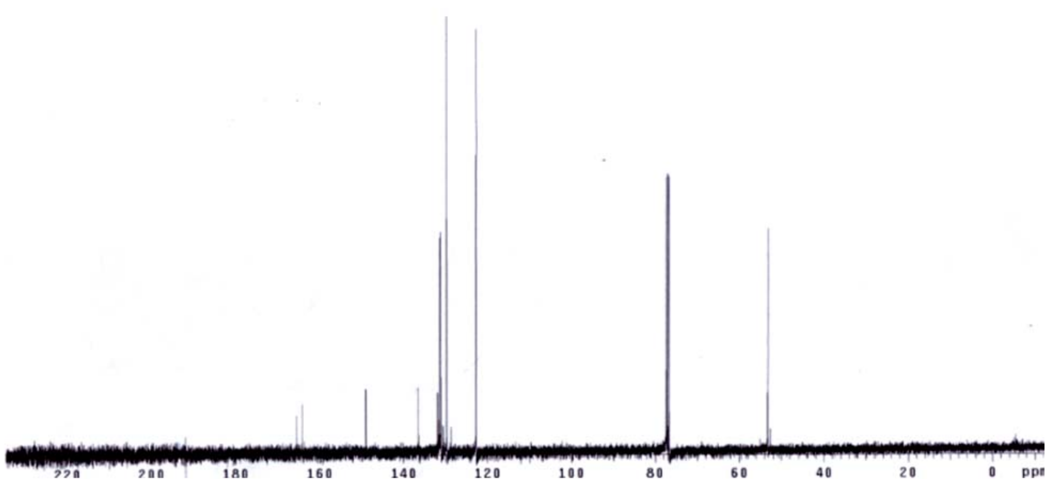

220 200 180 160 140 120 100 80 60 40 20 0 ppm

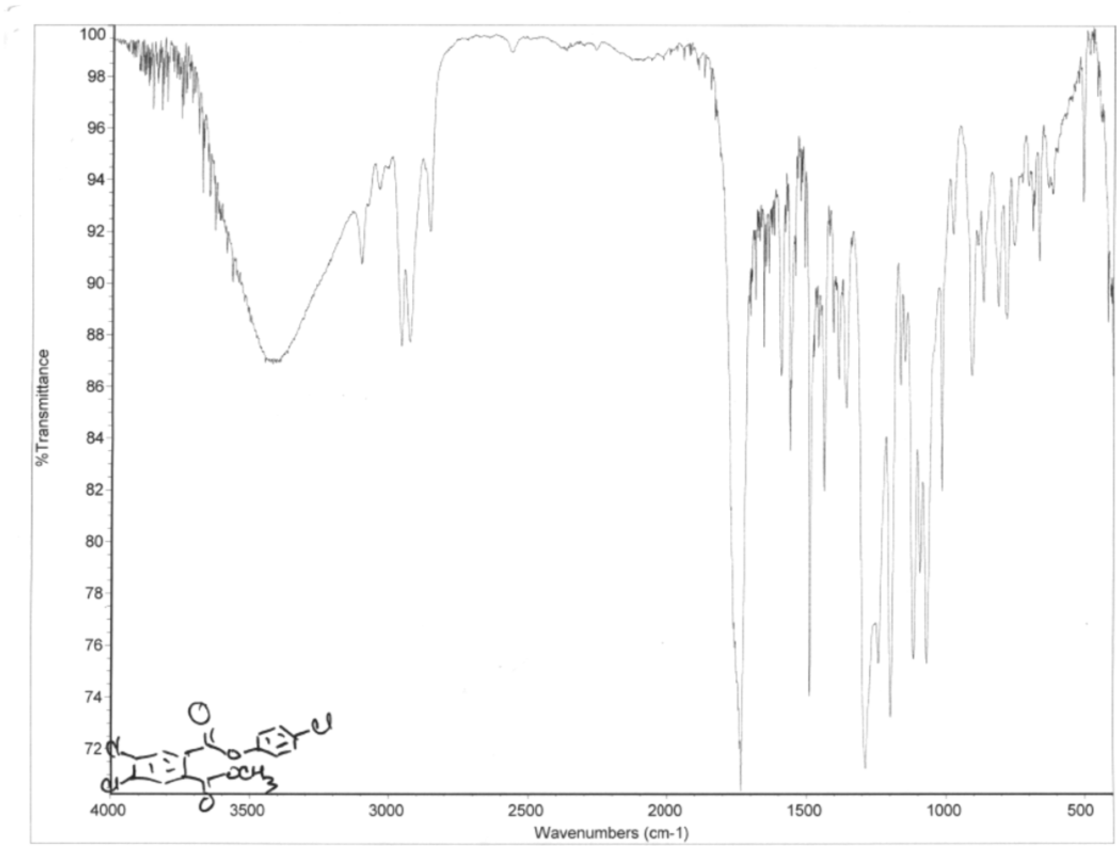

%Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
52
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

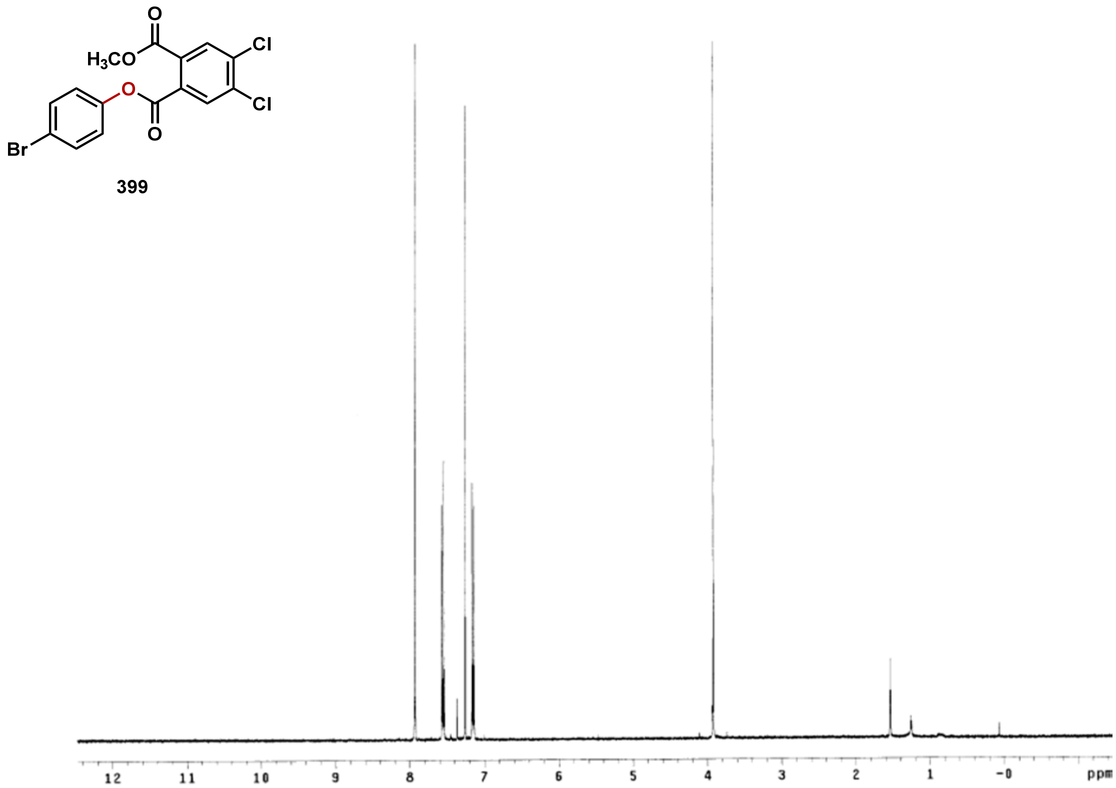

O
H3CO
Cl
O
Cl
O
Cl

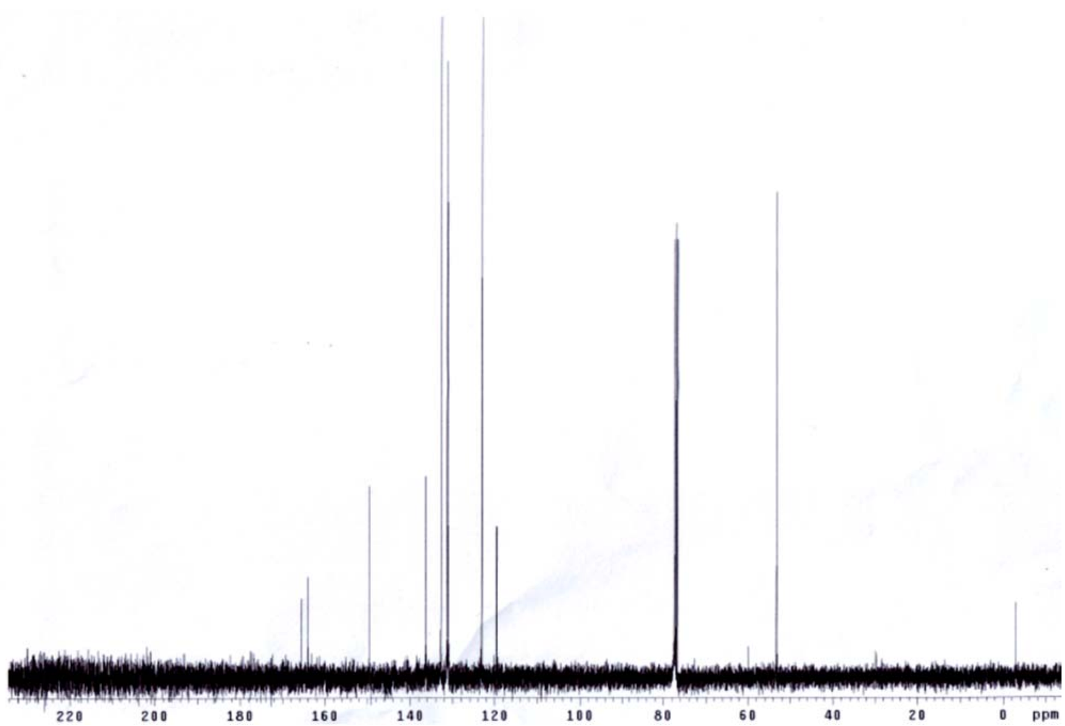
398

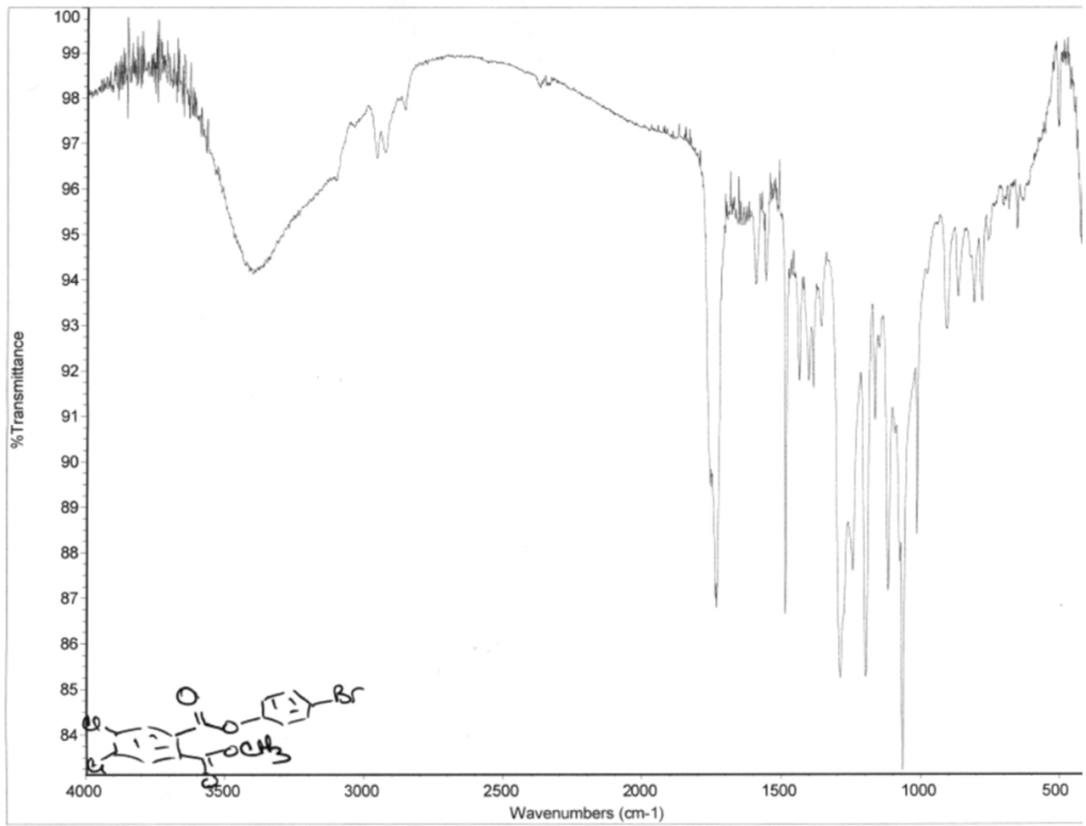

12
10
8
6
4
2
0
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm

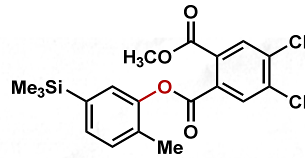

100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
%Transmittance
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)


O
H3CO
Cl
O
Cl
O
Br
399
12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm


220 200 180 160 140 120 100 80 60 40 20 0 ppm

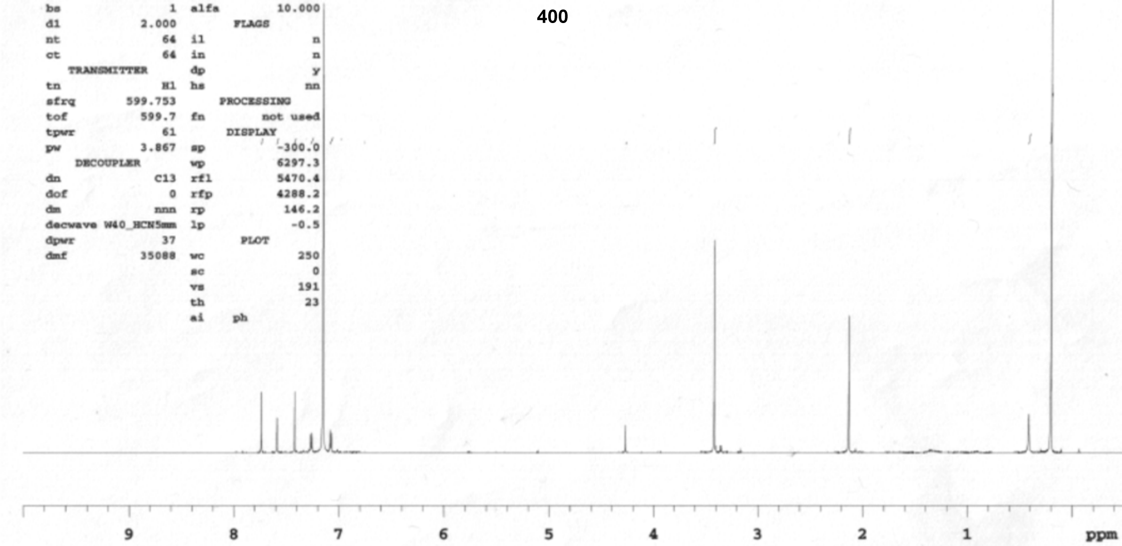


%Transmittance
100
99
98
97
96
95
94
93
92
91
90
89
88
87
86
85
84
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)
Br
OCH3

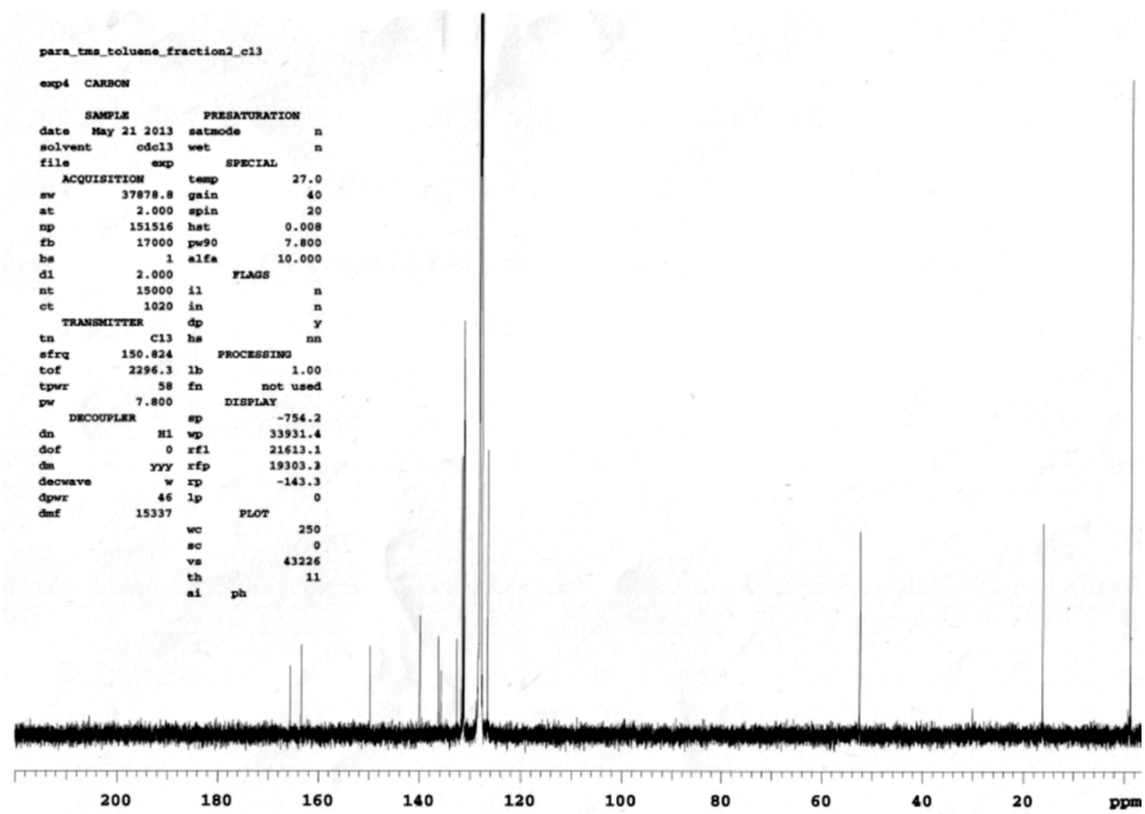


H3CO
O
O
O
Cl
Cl
Me3Si
Me

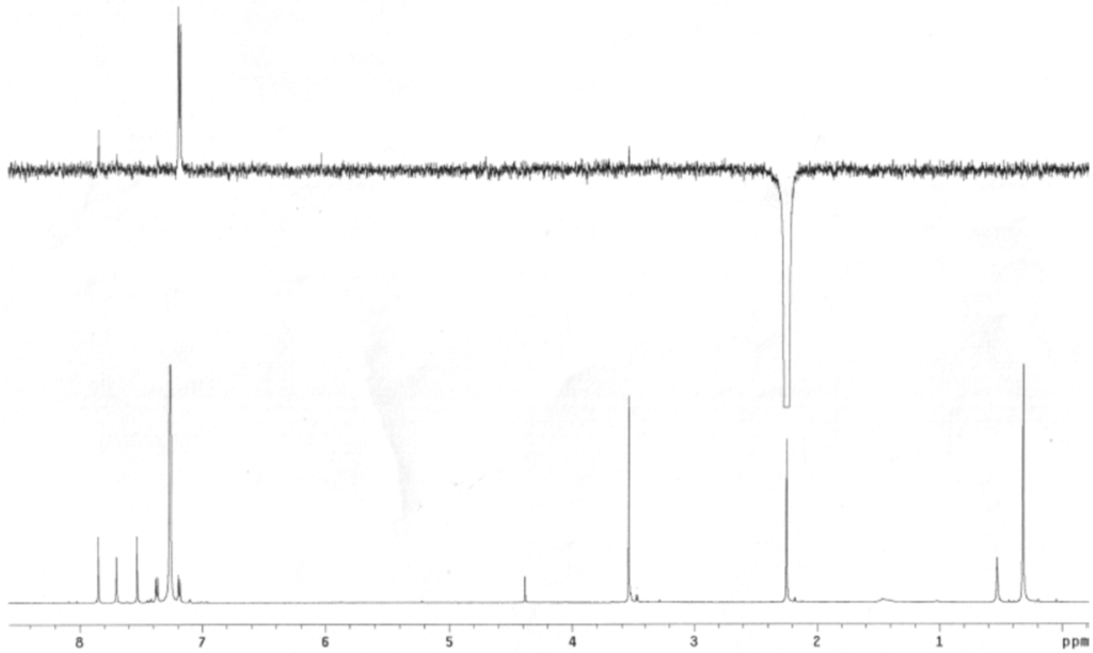
400

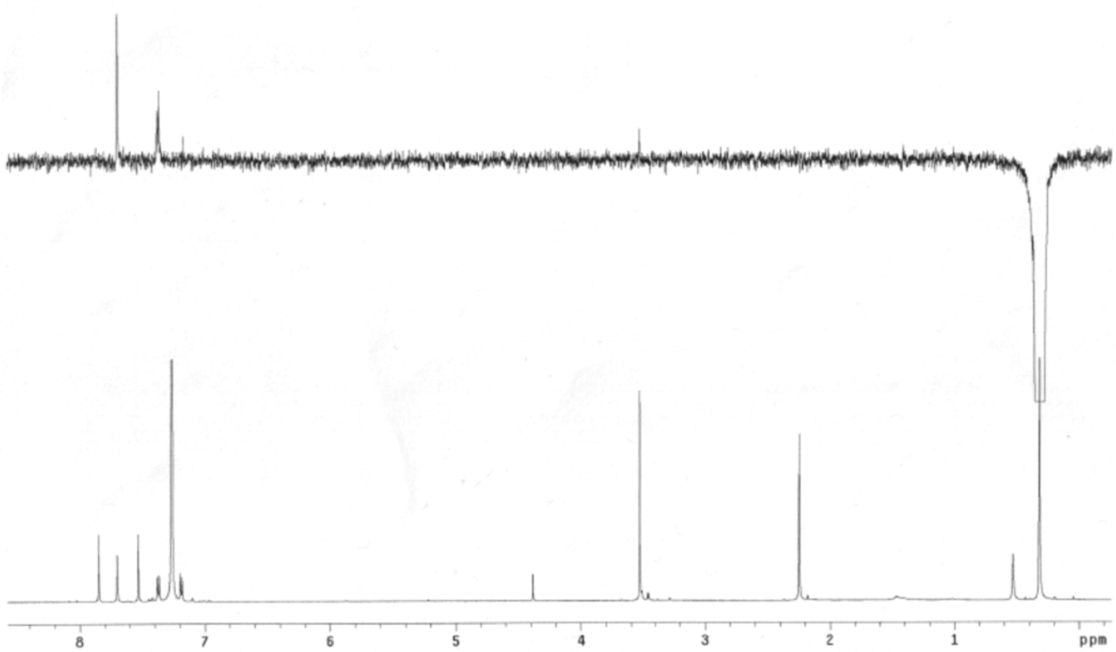


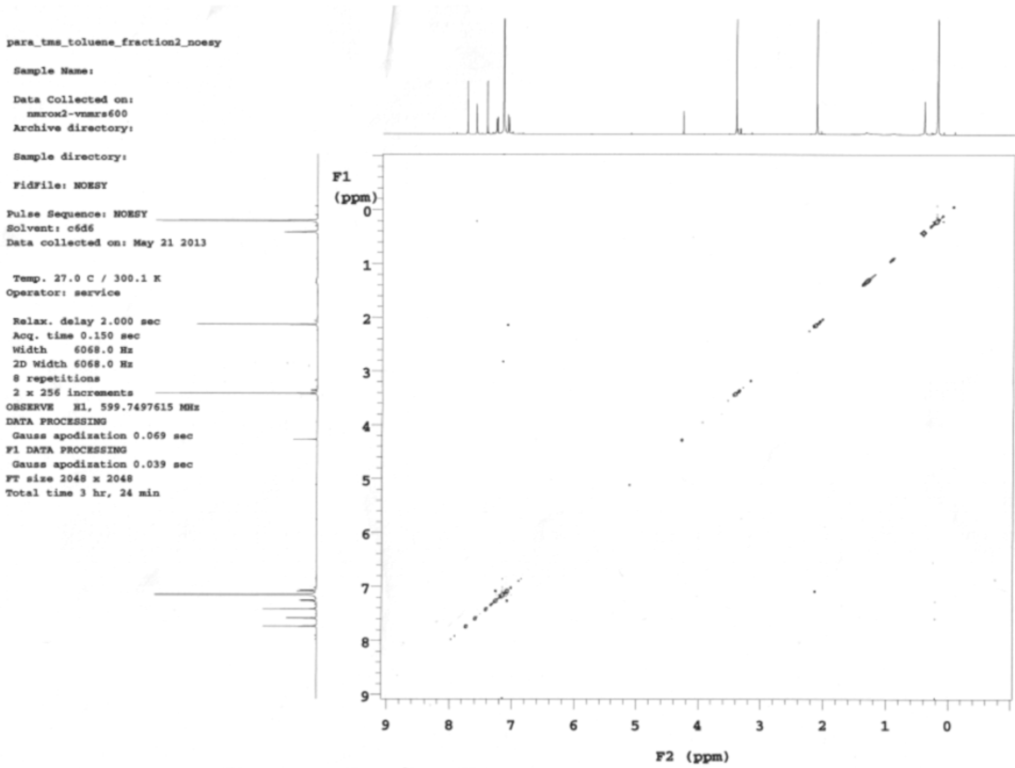
date May 21 2013
solvent c6d6
file exp
ACQUISITION
sw 9615.4
at 4.000
np 76924
fb 4000
bs 1
d1 2.000
nt 64
ct 64
TRANSMITTER
tn H1
sfrq 599.753
tof 599.7
tpwr 61
pw 3.867
DECOUPLER
dn C13
dof 0
dm nnn
decwave W40_HCN5mm
dpwr 37
dmf 35088
satmode n
wet n
SPECIAL
temp 27.0
gain 30
spin 20
hst 0.008
pw90 11.600
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp -300.0
wp 6297.3
rfl 5470.4
rfp 4288.2
rp 146.2
lp -0.5
PLOT
wc 250
sc 0
vs 191
th 23
ai ph
9 8 7 6 5 4 3 2 1 ppm

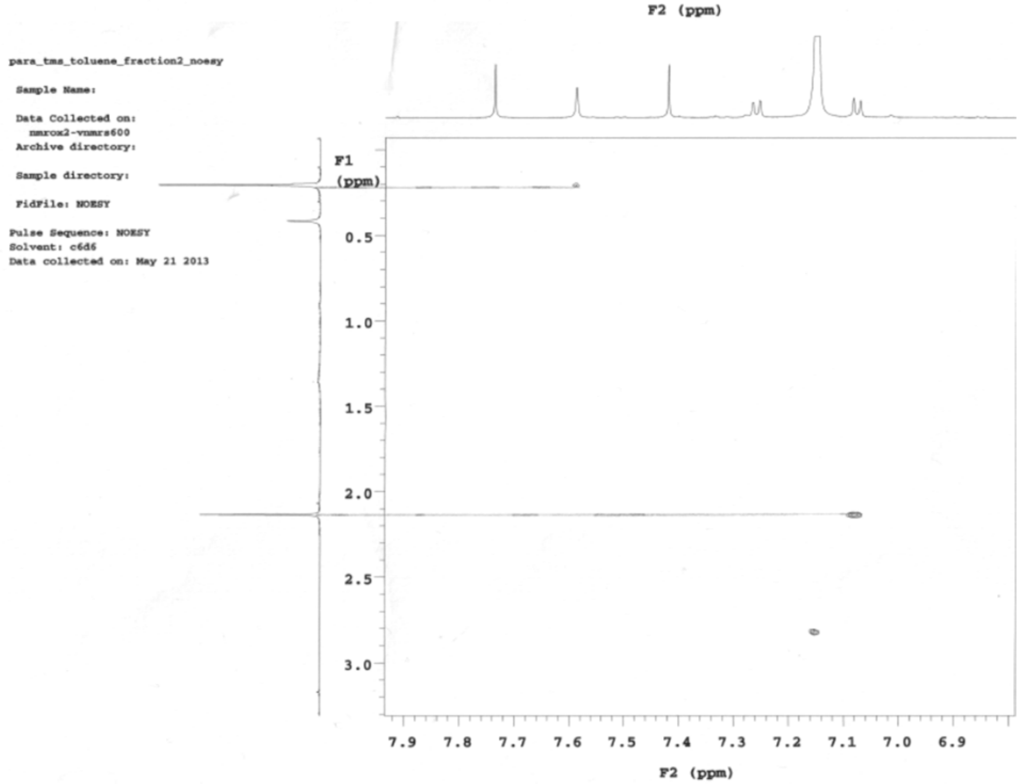


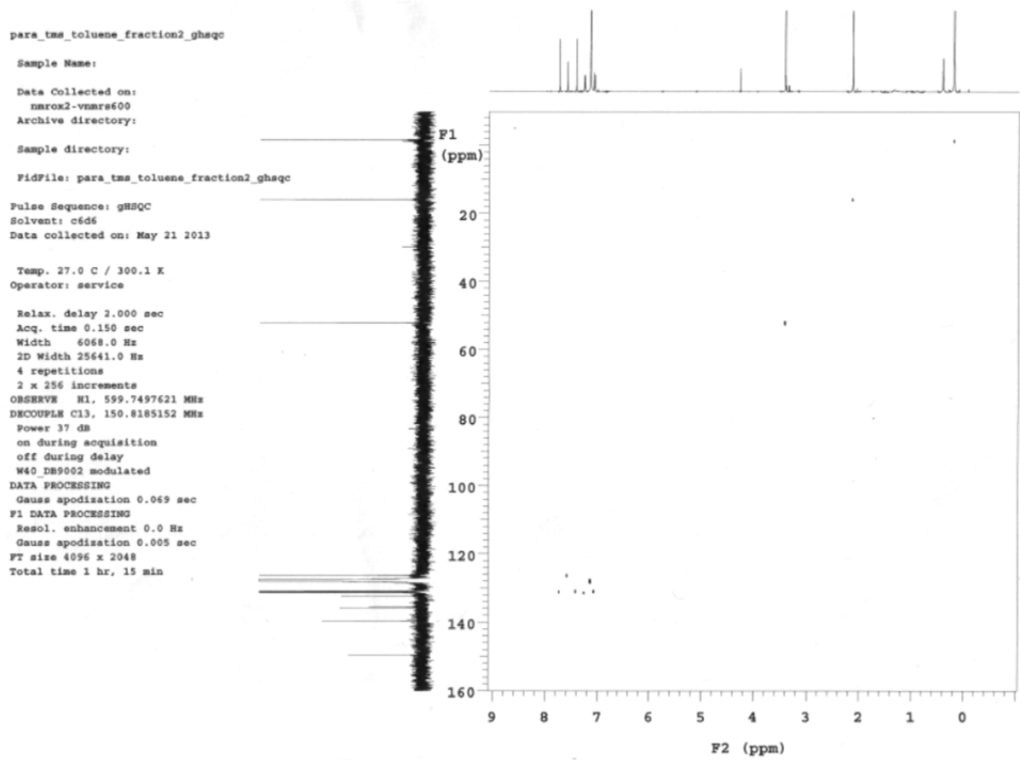
para_tms_toluene_fraction2_c13
exp4 CARBON
SAMPLE
date May 21 2013
solvent cdcl3
file exp
ACQUISITION
sw 37878.8
at 2.000
np 151516
fb 17000
bs 1
d1 2.000
nt 15000
ct 1020
TRANSMITTER
tn C13
sfrq 150.824
tof 2296.3
tpwr 58
pw 7.800
DECOUPLER
dn H1
dof 0
dm yyy
decwave w
dpwr 46
dmf 15337
PRESATURATION
satmode n
wet n
SPECIAL
temp 27.0
gain 40
spin 20
hst 0.008
pw90 7.800
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -754.2
wp 33931.4
rfl 21613.1
rfp 19303.3
rp -143.3
lp 0
PLOT
wc 250
sc 0
vs 43226
th 11
ai ph
200 180 160 140 120 100 80 60 40 20 ppm

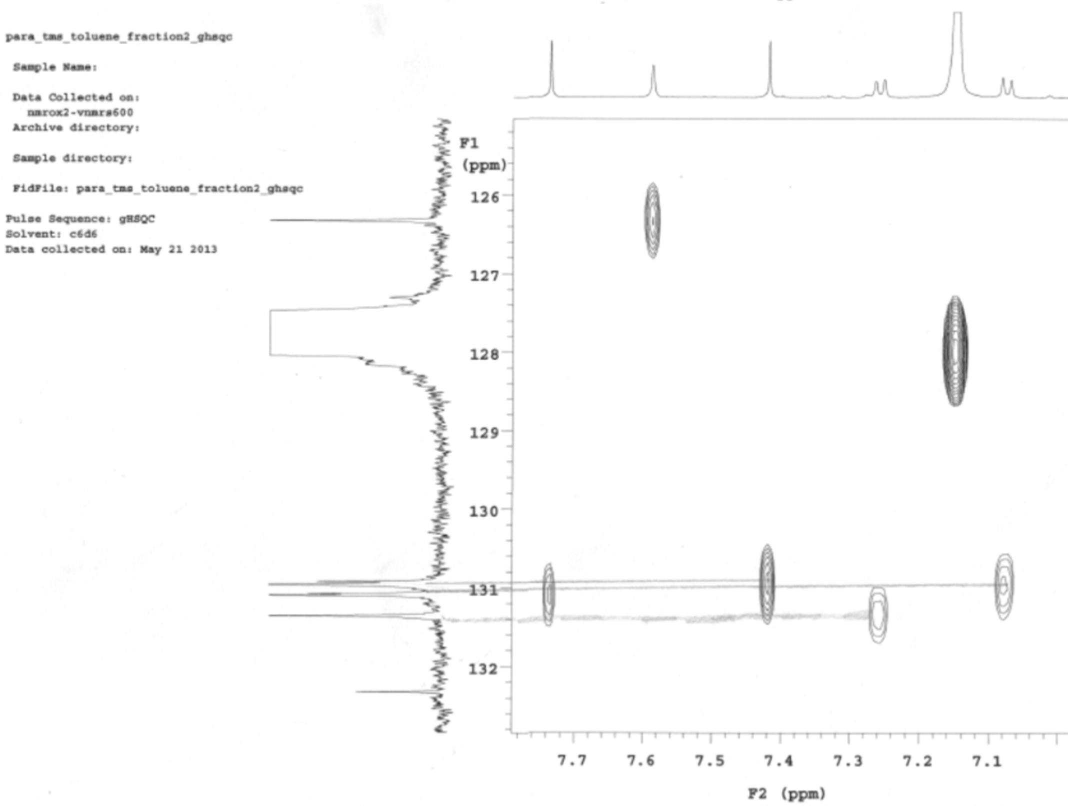

8
7
6
5
4
3
2
1
ppm

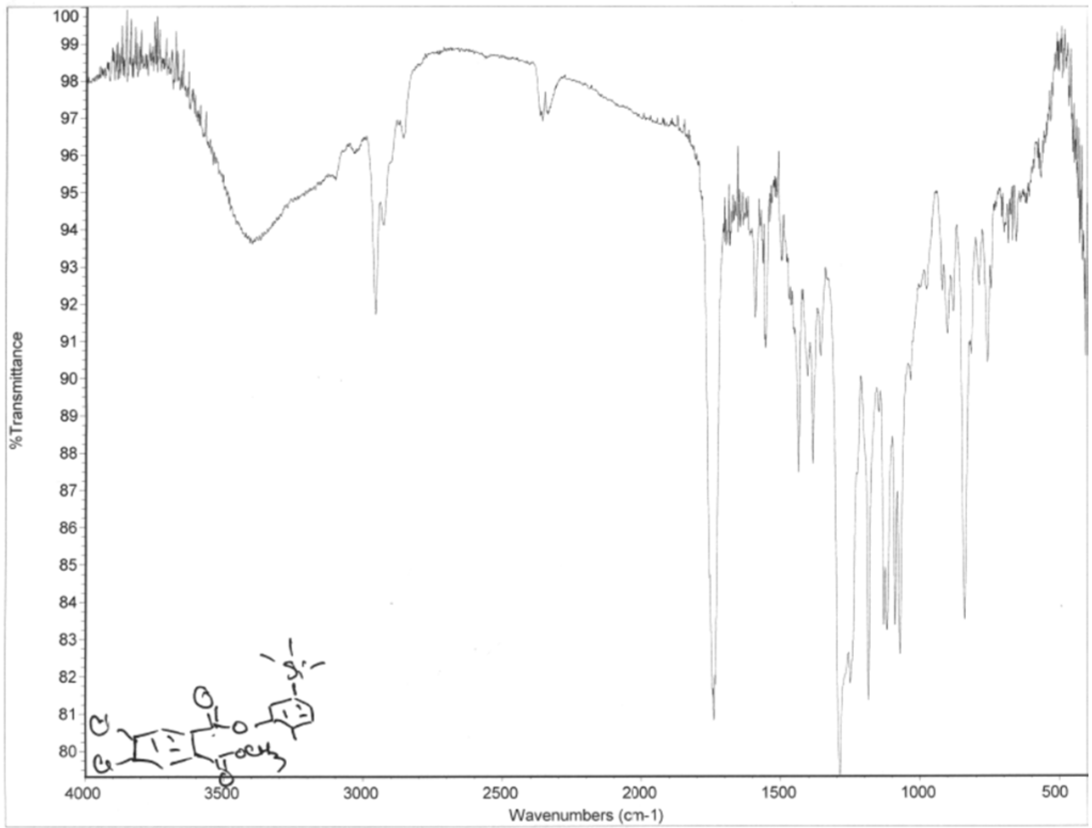

8
7
6
5
4
3
2
1
ppm


para_tms_toluene_fraction2_noesy
Sample Name:
Data Collected on:
nmrox2-vnmrs600
Archive directory:
Sample directory:
FidFile: NOESY
Pulse Sequence: NOESY
Solvent: c6d6
Data collected on: May 21 2013
Temp. 27.0 C / 300.1 K
Operator: service
Relax. delay 2.000 sec
Acq. time 0.150 sec
Width 6068.0 Hz
2D Width 6068.0 Hz
8 repetitions
2 x 256 increments
OBSERVE H1, 599.7497615 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.039 sec
FT size 2048 x 2048
Total time 3 hr, 24 min
F1 (ppm)
F2 (ppm)

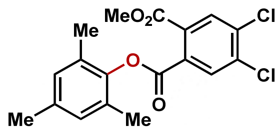

para_tms_toluene_fraction2_noesy
Sample Name:
Data Collected on:
nmrox2-vnmrs600
Archive directory:
Sample directory:
FidFile: NOESY
Pulse Sequence: NOESY
Solvent: c6d6
Data collected on: May 21 2013
F1 (ppm)
F2 (ppm)


para_tms_toluene_fraction2_ghsqc
Sample Name:
Data Collected on:
nmrox2-vnmrs600
Archive directory:
Sample directory:
FidFile: para_tms_toluene_fraction2_ghsqc
Pulse Sequence: gHSQC
Solvent: c6d6
Data collected on: May 21 2013
Temp. 27.0 C / 300.1 K
Operator: service
Relax. delay 2.000 sec
Acq. time 0.150 sec
Width 6068.0 Hz
2D Width 25641.0 Hz
4 repetitions
2 x 256 increments
OBSERVE H1, 599.7497621 MHz
DECOUPLE C13, 150.8185152 MHz
Power 37 dB
on during acquisition
off during delay
W40_DB9002 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Resol. enhancement 0.0 Hz
Gauss apodization 0.005 sec
FT size 4096 x 2048
Total time 1 hr, 15 min
F1 (ppm)
20
40
60
80
100
120
140
160
9
8
7
6
5
4
3
2
1
0
F2 (ppm)

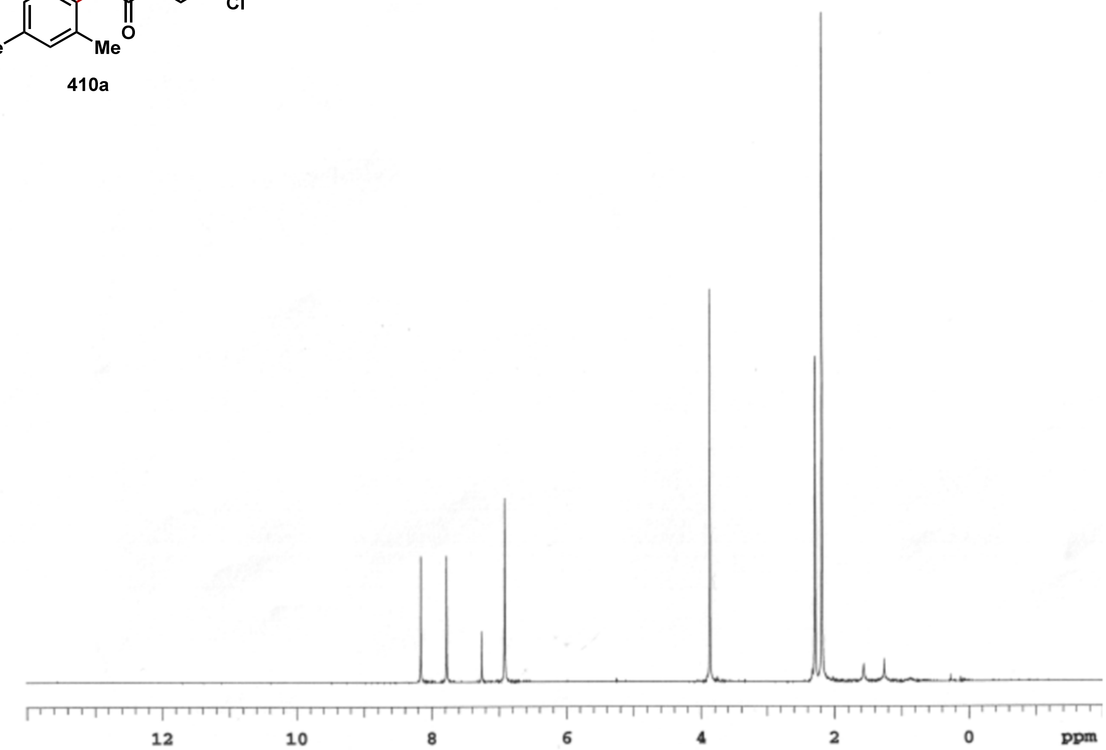

para_tms_toluene_fraction2_ghsqc
Sample Name:
Data Collected on:
nmrox2-vnmrs600
Archive directory:
Sample directory:
FidFile: para_tms_toluene_fraction2_ghsqc
Pulse Sequence: gHSQC
Solvent: c6d6
Data collected on: May 21 2013
F1 (ppm)
126
127
128
129
130
131
132
7.7
7.6
7.5
7.4
7.3
7.2
7.1
F2 (ppm)

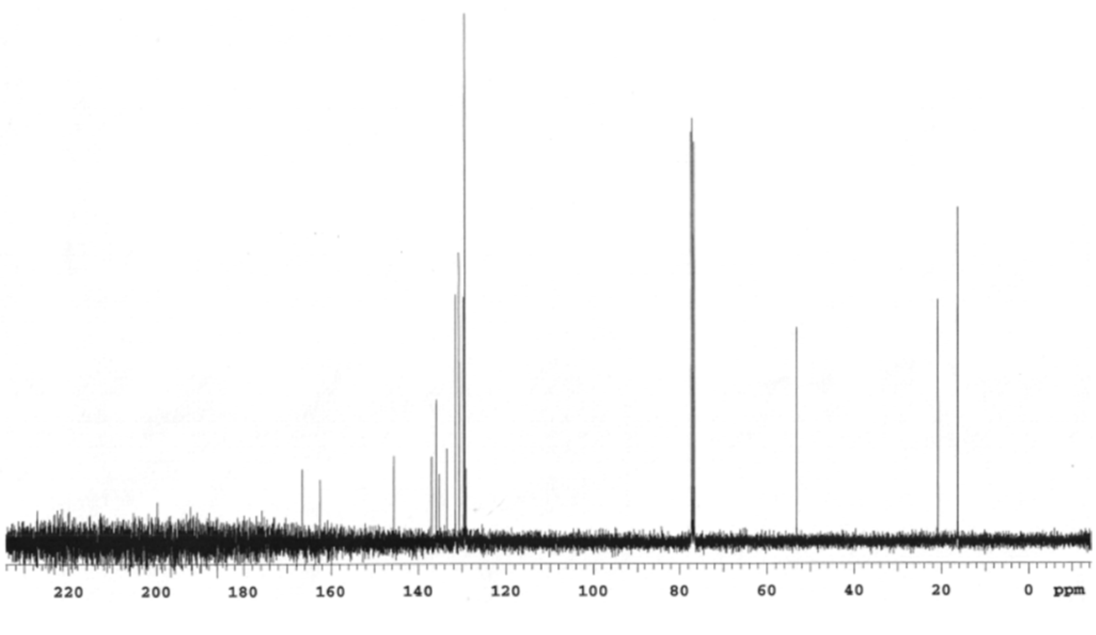


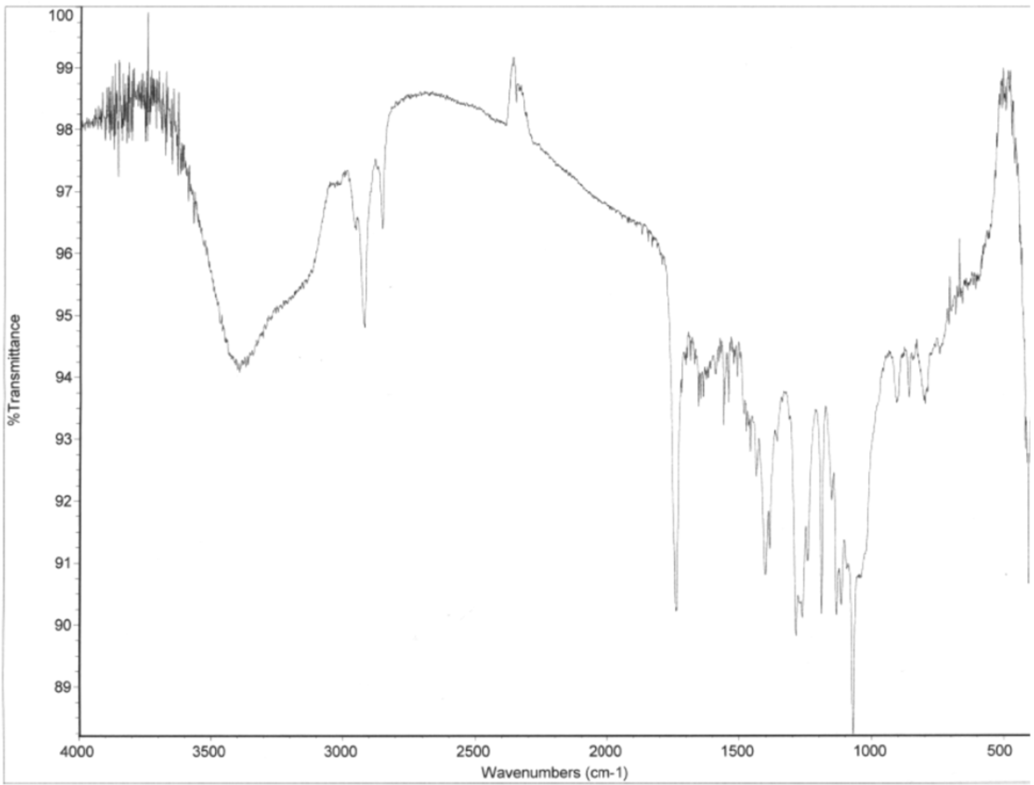
%Transmittance
Wavenumbers (cm-1)
100
99
98
97
96
95
94
93
92
91
90
89
88
87
86
85
84
83
82
81
80
4000
3500
3000
2500
2000
1500
1000
500


MeO2C
Cl
Me
O
Cl
O
Me
Me

410a


12
10
8
6
4
2
0
ppm

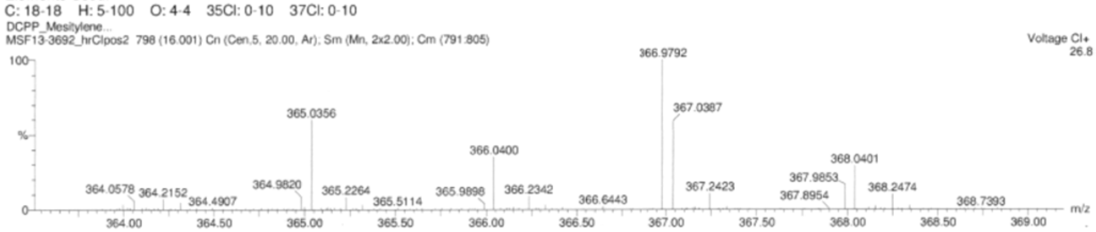

220
200
180
160
140
120
100
80
60
40
20
0
ppm



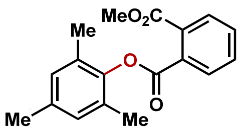
Elemental Composition Report **Page 1**

Single Mass Analysis (displaying only valid results)
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

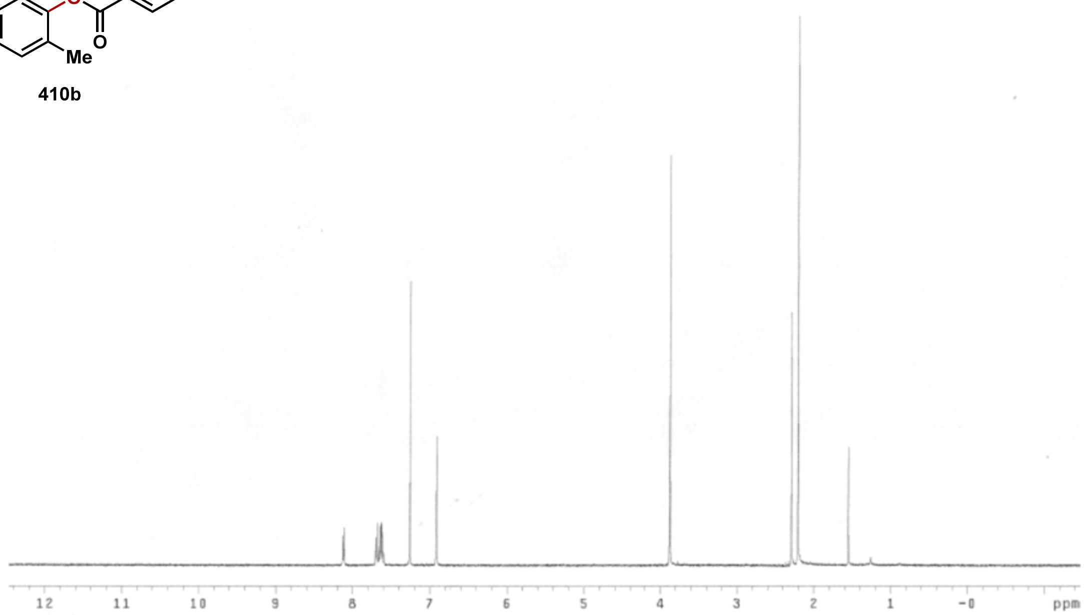
Monoisotopic Mass, Odd and Even Electron Ions
45 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 18-18 H: 5-100 O: 4-4 35Cl: 0-10 37Cl: 0-10

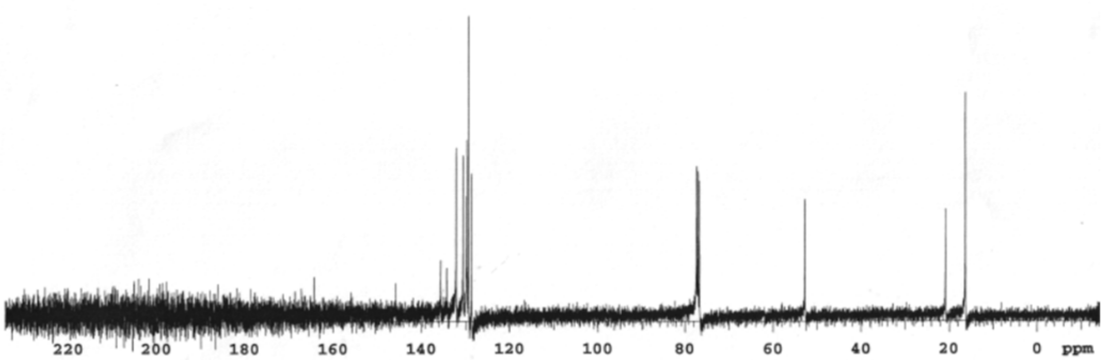


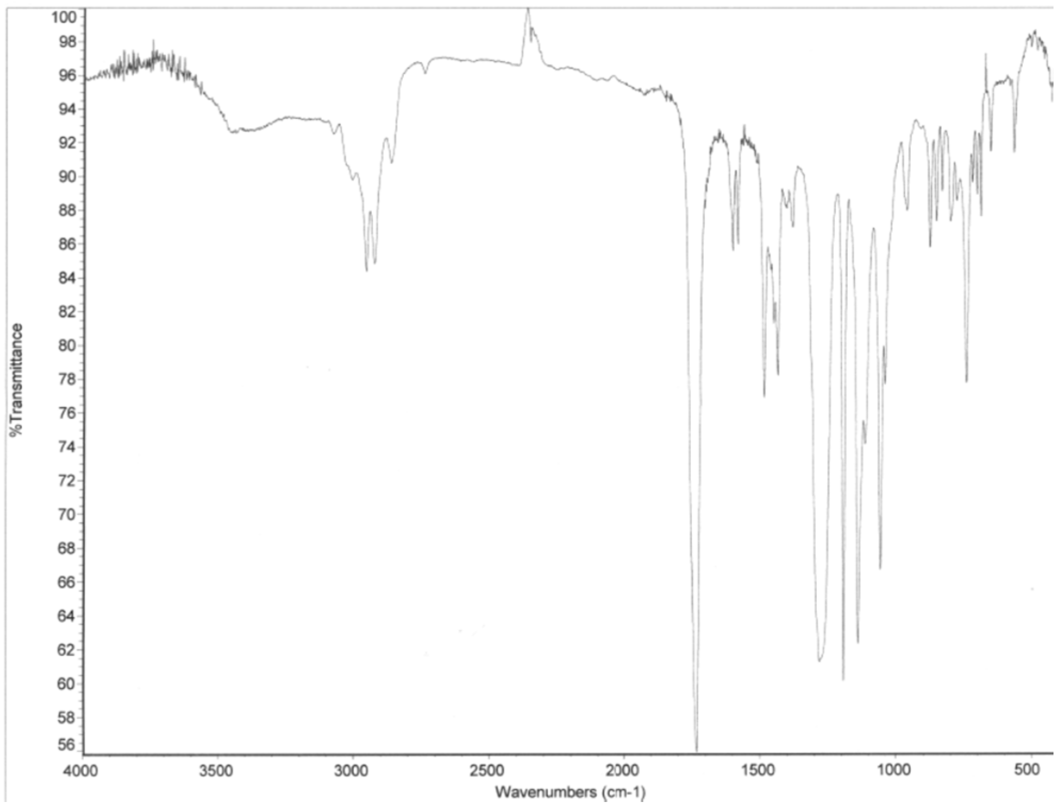
Minimum:				-1.5		
Maximum:		5.0	20.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
365.0356	365.0347	0.9	2.5	10.5	2.2	C18 H15 O4 35Cl2


MeO2C
Me
O
O
Me
Me

410b


12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm

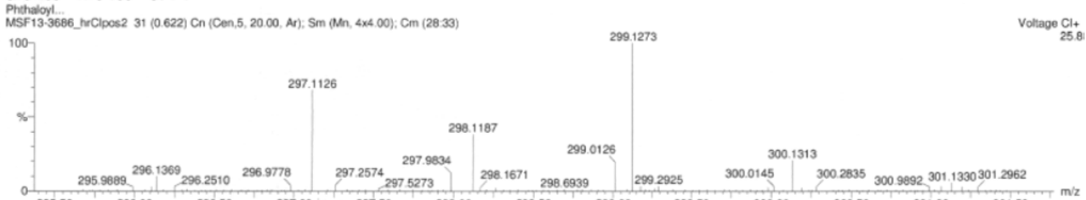

220
200
180
160
140
120
100
80
60
40
20
0
ppm



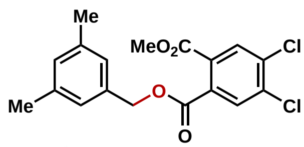
Elemental Composition Report **Page 1**

Multiple Mass Analysis: 6 mass(es) processed - displaying only valid results
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

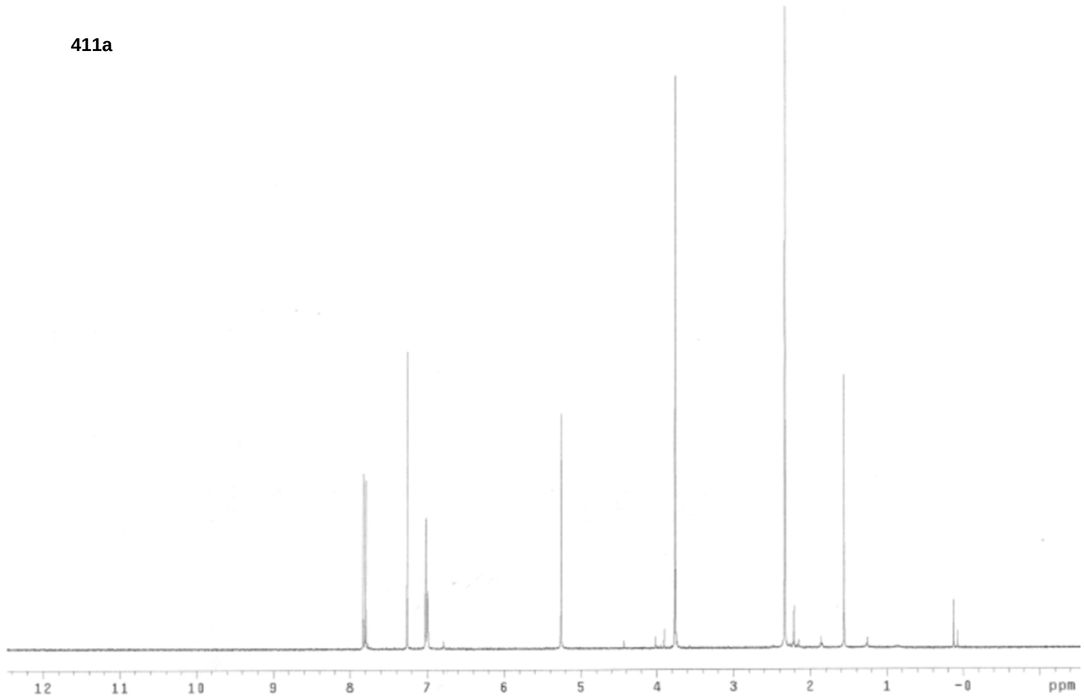
Monoisotopic Mass, Odd and Even Electron Ions
24 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 O: 4-4
Phthaloyl...
MSF13-3686_hrClpos2 31 (0.622) Cn (Cen,5, 20.00, Ar); Sm (Mn, 4x4.00); Cm (28:33)

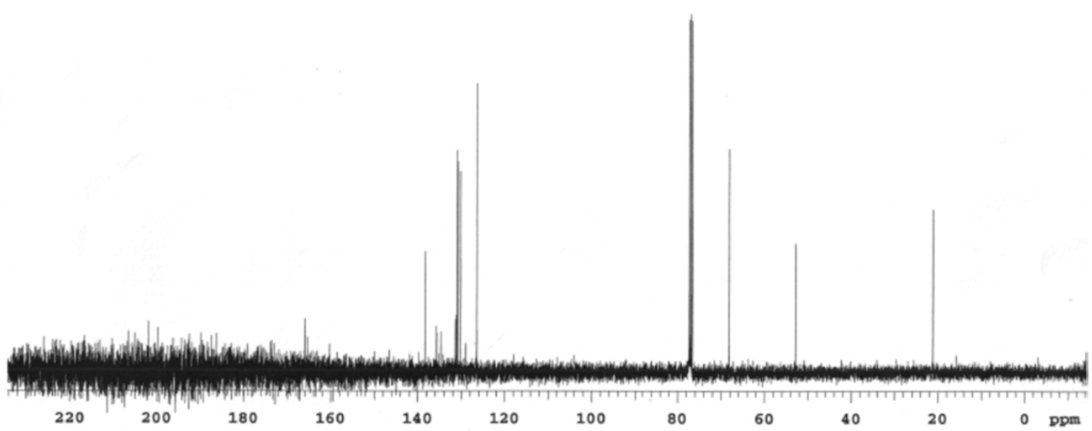


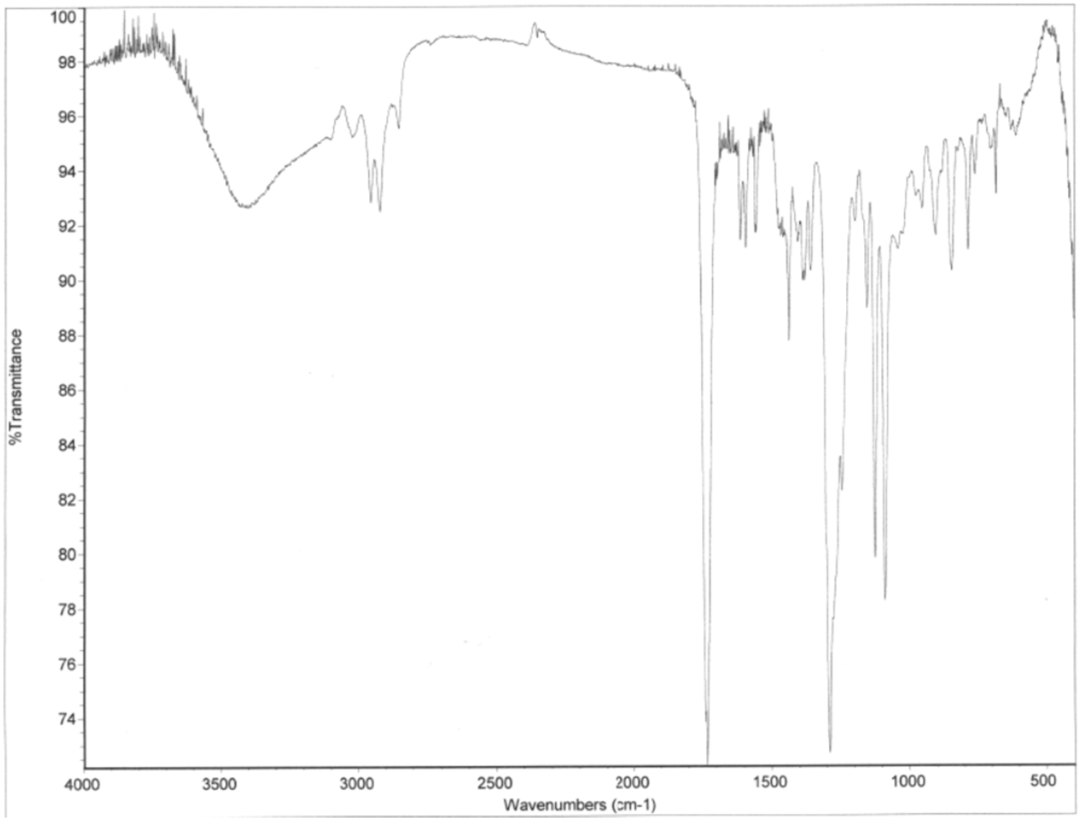
Minimum:	10.00				-1.5		
Maximum:	100.00		5.0	5.0	50.0		
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
297.1126	68.27	297.1127	-0.1	-0.3	10.5	14.3	C18 H17 O4
299.1273	100.00	299.1283	-1.0	-3.3	9.5	0.2	C18 H19 O4


Me
MeO2C
Cl
O
Me
Cl
O

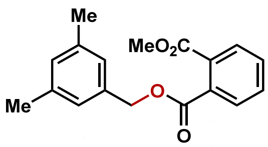
411a


12 11 10 9 8 7 6 5 4 3 2 1 -0 ppm

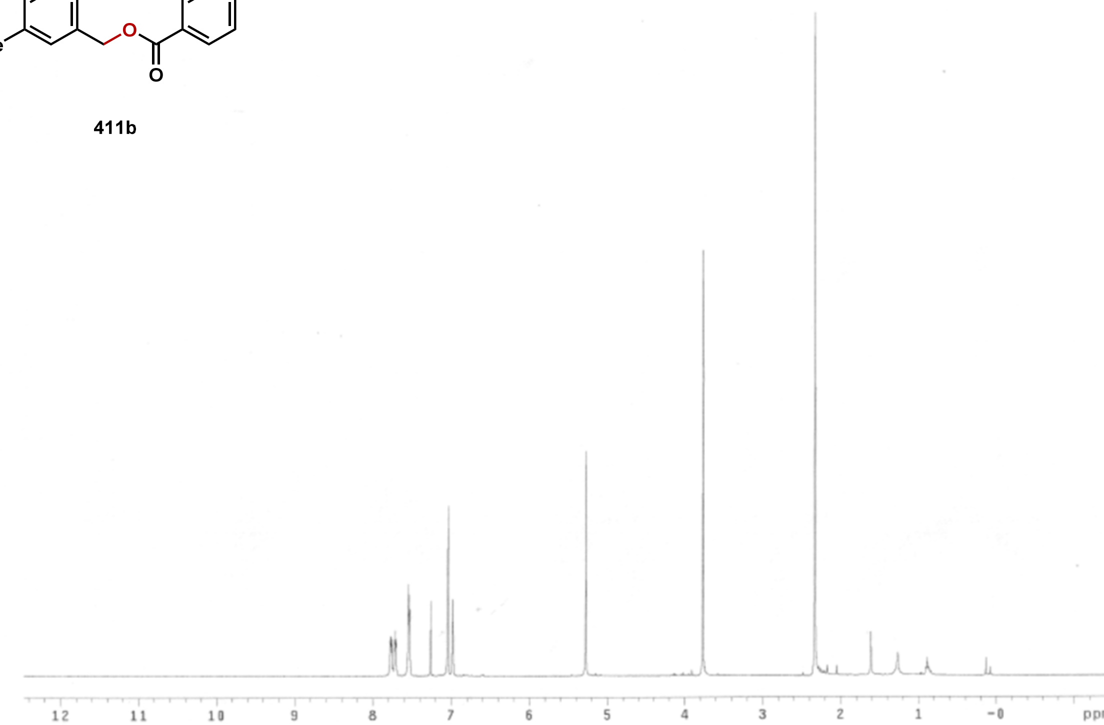

220 200 180 160 140 120 100 80 60 40 20 0 ppm

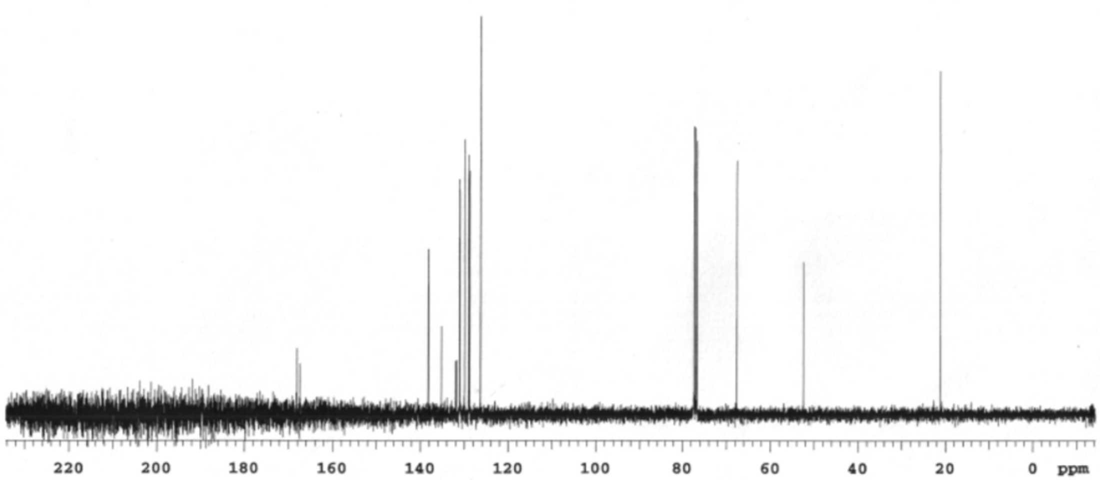


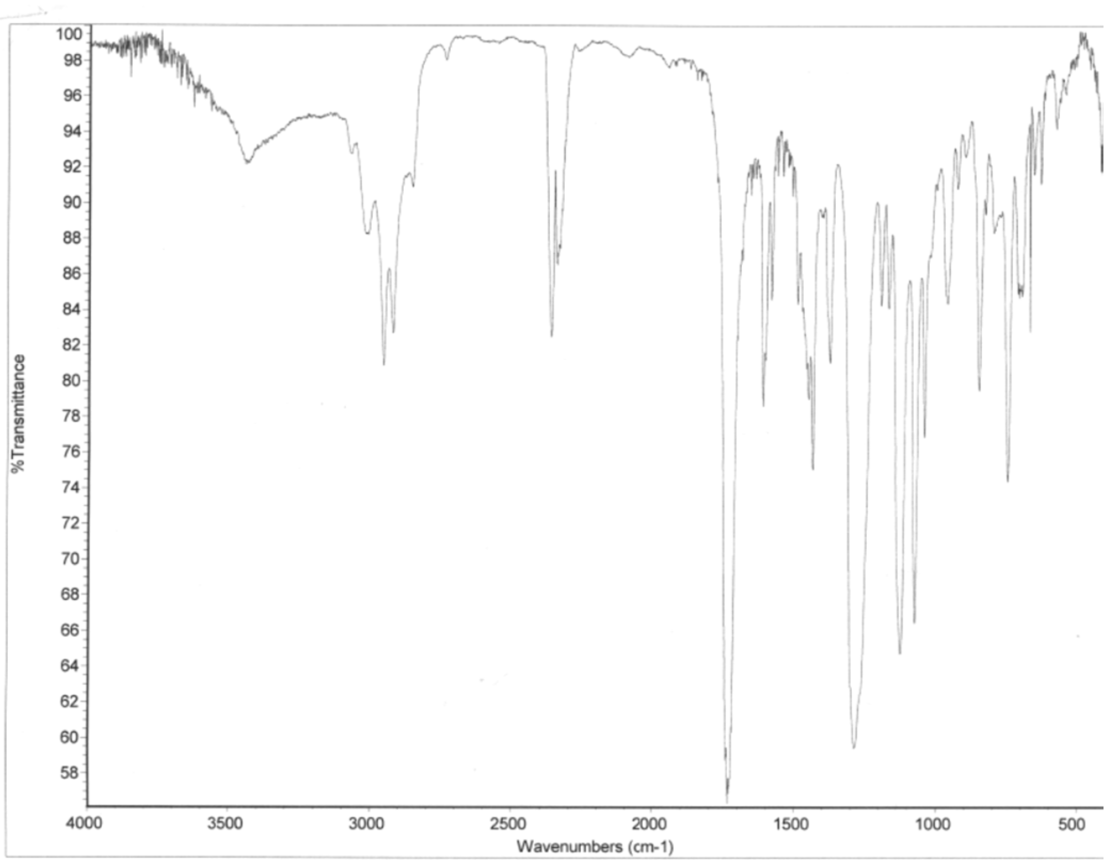
100
98
96
94
92
90
88
86
84
82
80
78
76
74
%Transmittance
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

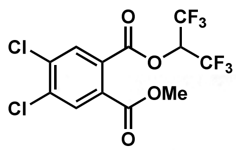

Me
MeO2C
Me
O
O

411b

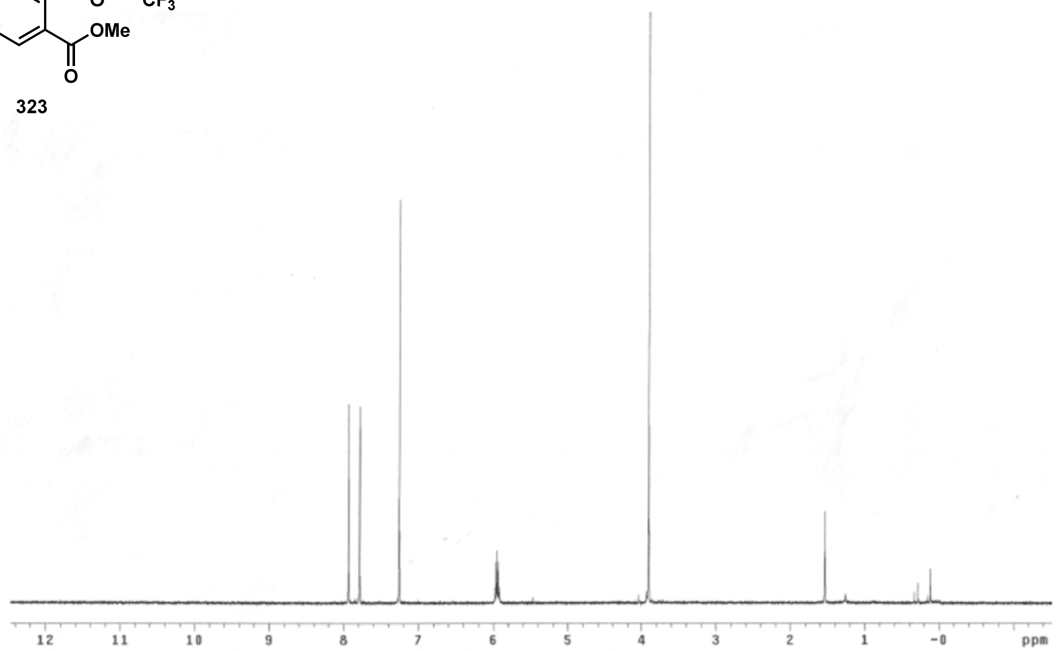

12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

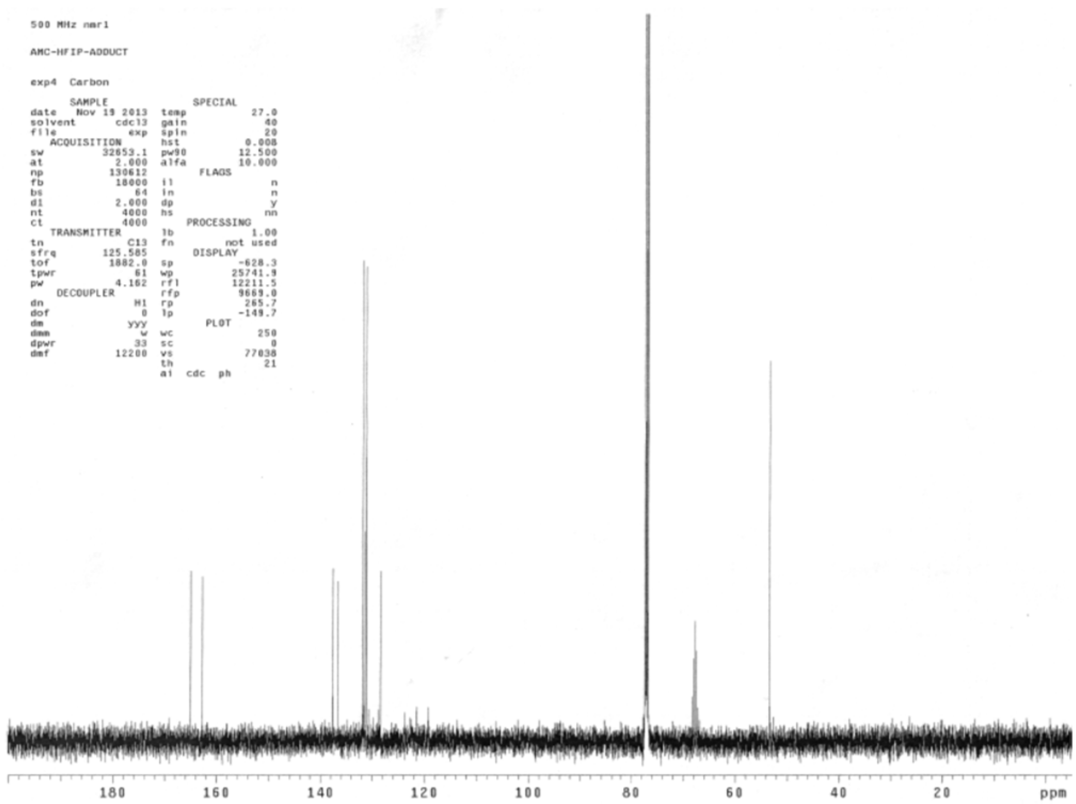

220
200
180
160
140
120
100
80
60
40
20
0
ppm

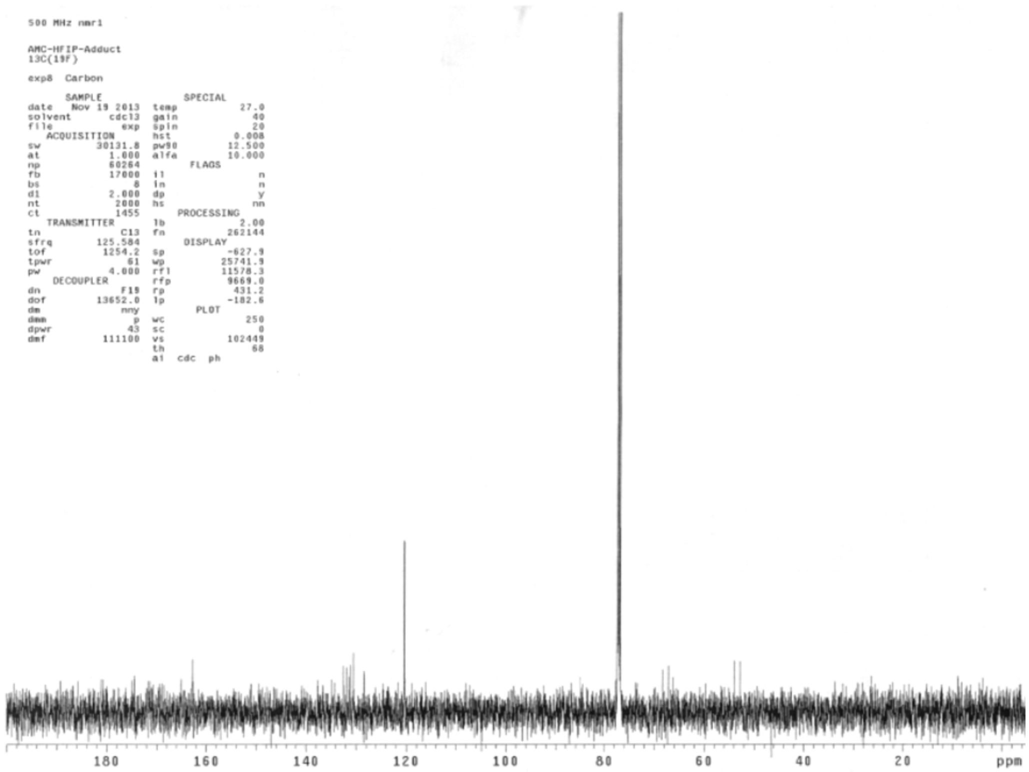

%Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

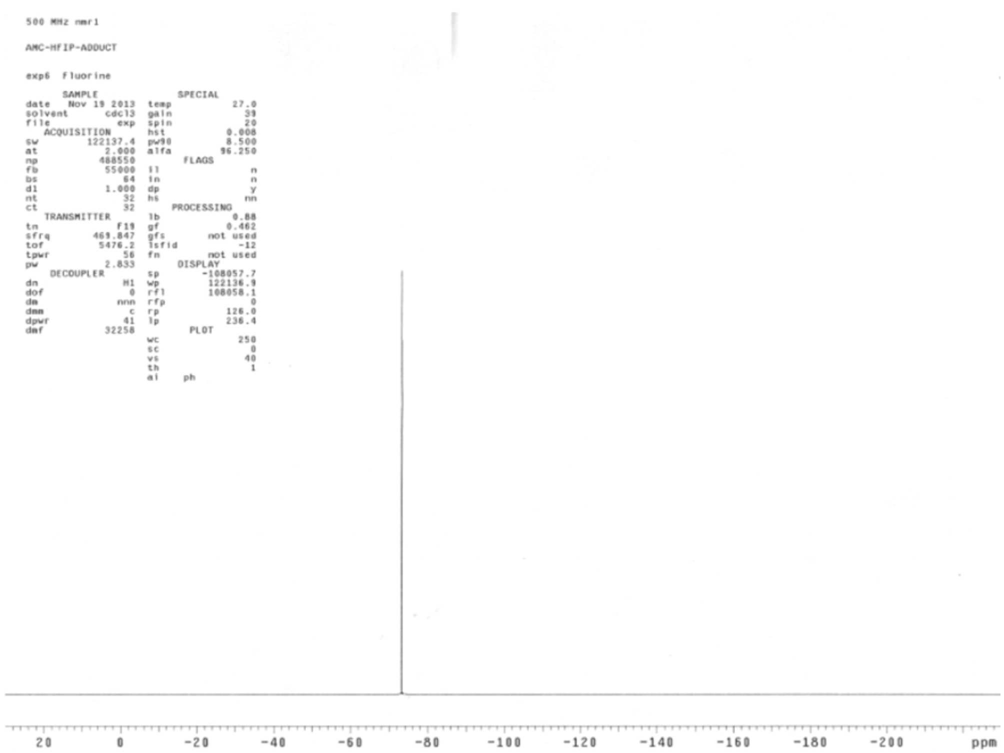

Cl
Cl
O
O
CF3
CF3
O
OMe

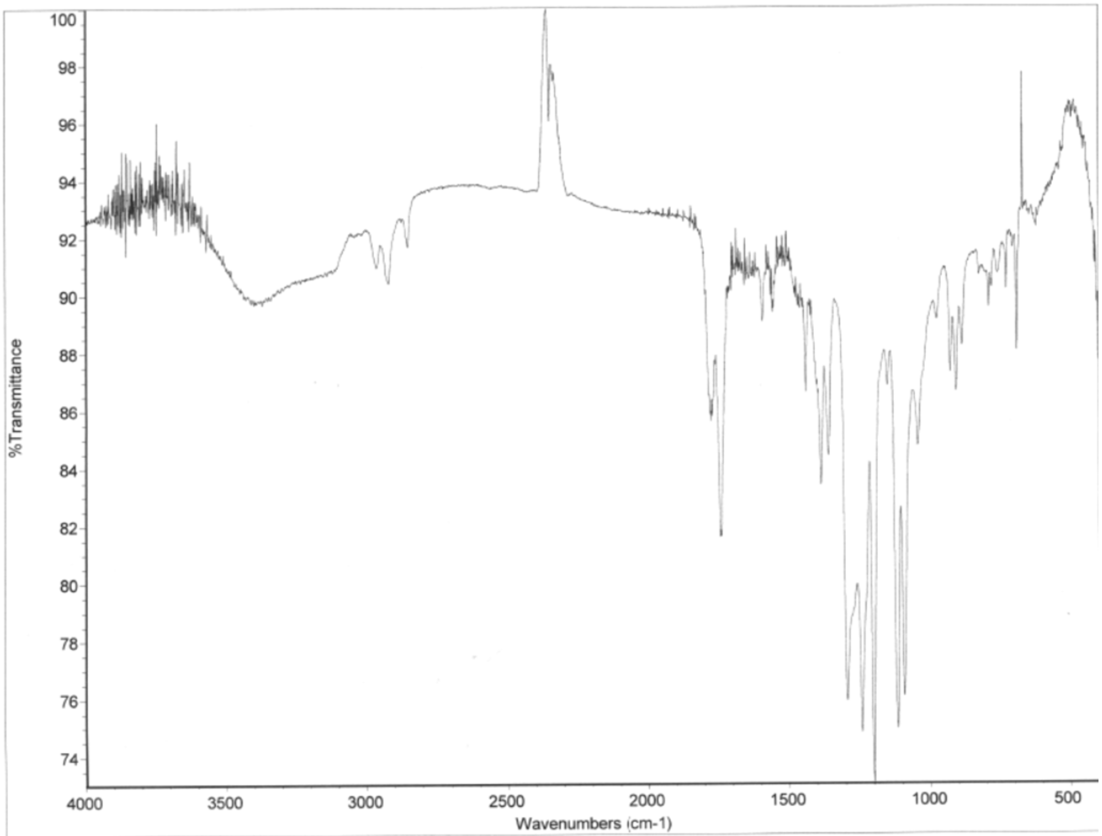
323


12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm


500 MHz nmr1
AMC-HFIP-ADDUCT
exp4 Carbon
SAMPLE
date Nov 19 2013
solvent cdcl3
file exp
ACQUISITION
sw 32653.1
at 2.000
np 130612
fb 18000
bs 64
d1 2.000
nt 4000
ct 4000
TRANSMITTER
tn C13
sfrq 125.585
tof 1882.0
tpwr 61
pw 4.162
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 33
dmf 12200
SPECIAL
temp 27.0
gain 40
spin 20
hst 0.008
pw90 12.500
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -628.3
wp 25741.9
rfl 12211.5
rfp 9669.0
rp 265.7
lp -149.7
PLOT
wc 250
sc 0
vs 77038
th 21
ai cdc ph
180
160
140
120
100
80
60
40
20
ppm


500 MHz nmr1
AMC-HFIP-Adduct
13C(19F)
exp8 Carbon
SAMPLE
date Nov 19 2013
solvent cdcl3
file exp
ACQUISITION
sw 30131.8
at 1.000
np 60264
fb 17000
bs 8
d1 2.000
nt 2000
ct 1455
TRANSMITTER
tn C13
sfrq 125.584
tof 1254.2
tpwr 61
pw 4.000
DECOUPLER
dn F19
dof 13652.0
dm nny
dmm p
dpwr 43
dmf 111100
SPECIAL
temp 27.0
gain 40
spin 20
hst 0.008
pw90 12.500
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 2.00
fn 262144
DISPLAY
sp -627.9
wp 25741.9
rfl 11578.3
rfp 9669.0
rp 431.2
lp -182.6
PLOT
wc 250
sc 0
vs 102449
th 68
ai cdc ph
180
160
140
120
100
80
60
40
20
ppm

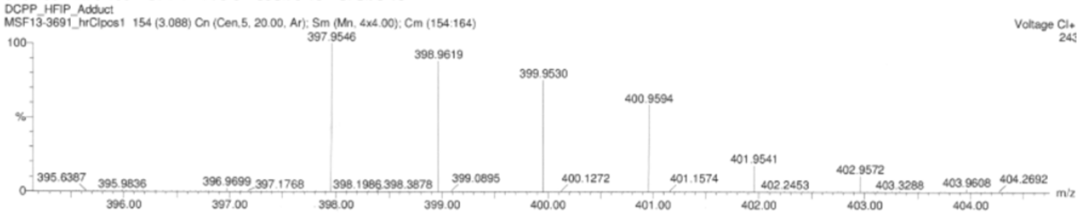

500 MHz nmr1
AMC-HFIP-ADDUCT
exp6 Fluorine
SAMPLE
date Nov 19 2013
solvent cdcl3
file exp
ACQUISITION
sw 122137.4
at 2.000
np 488550
fb 55000
bs 64
d1 1.000
nt 32
ct 32
TRANSMITTER
tn F19
sfrq 469.847
tof 5476.2
tpwr 56
pw 2.833
DECOUPLER
dn H1
dof 0
dm nnn
dmm c
dpwr 41
dmf 32258
SPECIAL
temp 27.0
gain 39
spin 20
hst 0.008
pw90 8.500
alfa 96.250
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.88
gf 0.462
gfs not used
lsfid -12
fn not used
DISPLAY
sp -108057.7
wp 122136.9
rfl 108058.1
rfp 0
rp 126.0
lp 236.4
PLOT
wc 250
sc 0
vs 40
th 1
ai ph
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm



Elemental Composition Report **Page 1**

Multiple Mass Analysis: 4 mass(es) processed - displaying only valid results
Tolerance = 4.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Odd and Even Electron Ions
167 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 O: 4-4 F: 6-6 35Cl: 0-10 37Cl: 0-10
DCPP_HFIP_Adduct
MSF13-3691_hrClpos1 154 (3.088) Cn (Cen,5, 20.00, Ar); Sm (Mn, 4x4.00); Cm (154:164)



Minimum:	20.00				-1.5		
Maximum:	100.00		5.0	4.0	50.0		

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
397.9546	100.00	397.9547	-0.1	-0.3	6.0	75.3	C12 H6 O4 F6 35Cl2
398.9619	88.17	398.9626	-0.7	-1.8	5.5	64.5	C12 H7 O4 F6 35Cl2
399.9530	75.43	399.9518	1.2	3.0	6.0	48.4	C12 H6 O4 F6 35Cl 37Cl
400.9594	58.67	400.9596	-0.2	-0.5	5.5	6.2	C12 H7 O4 F6 35Cl 37Cl

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