Title

Michael–Heck Approach Towards the Synthesis of Highly Functionalized Polyalkyl Furans and Application of the Vinylogous Michael–Heck Reaction Towards the Total Synthesis of Furanosesquiterpenes and Furanoeremophilanes

Author

Chen, Violet

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A dissertation submitted in partial satisfaction of the requirements for the degree of Doctor of Philosophy in Chemistry

by

Yi-Jang Chen

2021

ABSTRACT OF THE DISSERTATION

Michael–Heck Approach Towards the Synthesis of Highly Functionalized Polyalkyl Furans

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Application of the Vinylogous Michael–Heck Reaction Towards the Total Synthesis of Furanosesquiterpenes and Furanoeremophilanes

by

Violet Yijang Chen

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2021

Professor Ohyun Kwon, Chair

Chapter 1 presents an overview and classification of furan-containing natural products based on skeletal structures, characteristic functional group or by the number of carbons. It also contains a summary of traditional as well as frequently encountered modern synthetic methodologies developed for the preparation of the furan nucleus.

Chapter 2 presents the development and applications of the Michael–Heck methodology for the synthesis of polyalkyl furans and polyalkyl furan-containing natural products, including furanoterpenes, furan fatty acids (F-acids) and their derivatives. Mechanistic investigations are also discussed in this chapter.

Chapter 3 presents attempts to apply the vinylogous Michael–Heck reaction to the total synthesis of furanosesquiterpenes agassizin, pallescensin G and F as well as various furanoeremophilanes using both intramolecular and intermolecular routes.

The dissertation of Yi-Jang Chen is approved.

Patrick G. Harran

Kendall N. Houk

Yves F. Rubin

Ohyun Kwon, Committee Chair

University of California, Los Angeles

2021

To my loving parents, Diana Wanmei Tsai and Thomas Honchi Chen

Also, to my baby sister, Belinda Yiwoei Chen and our furry, adorable pug Lion

TABLE OF CONTENTS

LIST OF FIGURES

Chapter 1

Chapter 2

Chapter 3

LIST OF SCHEMES

Chapter 1

Chapter 2

Chapter 3

LIST OF TABLES

Chapter 2

Chapter 3

LIST OF ABBREVIATIONS

DMSO	dimethyl sulfoxide
DMS	dimethyl sulfide
TMSCl	trimethylsilyl chloride
HCl	hydrochloric acid
MeOH	methanol
S_N2	bimolecular nucleophilic substitution
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
LAH	lithium aluminum hydride
FCC	flash column chromatography
DMF	dimethyl formamide
THF	tetrahydrofuran
PCC	pyridinium chlorochromate
DMP	Dess Martin periodinane
DHP	dihydropyran
TBDPS	tri-*t*-butyldiphenylsilyl
DCM	dichloromethane
NaI	sodium iodide
AcOH	acetic acid
CF_3	trifluoromethyl
MeCN	acetonitrile
equiv	equivalents
min	minutes

NMR	nuclear Magnetic Resonance
Ar	argon
TBAC	tetrabutylammonium chloride
LiTMP	lithium tetramethylpiperidide
DABCO	1,4-diazabicyclo2.2.2octane
NOE	nuclear Overhauser effect
DIBAL	diisobutylaluminum hydride
Et_2O	diethyl ether
*n*BuLi	*n*-butyllithium
TEA	triethylamine
TLC	thin layer chromatography
rt	room temperature
cat.	catalytic
M	molar
t	triplet
d	doublet
s	singlet
bs	broad singlet
dd	double doublet
q	quartet
EtOAc	ethyl acetate
TMEDA	tetramethylethylenediamine
LiHMDS	lithium hexamethyldisilazide

Dppe	1,2-Bis(diphenylphosphino)ethane
TBHP	*tert*-butylhydroperoxide
PDC	pyridinium dichromate
PPTS	pyridinium *p*-toluenesulfonate
TBAF	tetrabutylammonium fluoride
TPAP	tetrapropylammonium perruthenate
NMO	N-methylmorpholine N-oxide
LDA	lithium diisopropyl amide
NBS	N-bromosuccinimide
iPrOH	isopropanol
NaOBn	sodium benzylate
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
TCDI	thiocarbonyldiimidazole
18-c-6.	18-crown-6
PhH	benzene
DMA	dimethylacetamide
mCPBA	*m*-chloroperoxybenzoic acid
HMPA	hexamethylphosphoramide
DIPEA	diisopropylethylamine
MOMBr	bromomethyl methyl ether
TMSI	trimethylsilyl iodide
BOMBr	benzyl bromomethyl ether

BOMI	benzyl iodomethyl ether
AcBr	acetyl bromide
AOMCl	allyloxymethyl chloride
quant	quantitative
d.r	diastereoselectivity ratio
TMS	trimethylsilyl
CAN	ceric ammonium nitrate
R_f	reflux
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
4 Å MS	4 Angstrom molecular sieves
IR	infrared radiation
NaOMe	sodium methoxide
ESI	electrospray ionization
b.p	boiling point
R_f	retention factor
quint	quintet
dt	double triplet
m	multiplet
m.p.	melting point

VITA

Education

2016–2021 **University of California–Los Angeles**, PhD. Chemistry (expected June 2021)
2015–2016 **National Taiwan University/Academia Sinica**, lab intern
2012–2015 **National Taiwan University**, B.S Chemistry
2010–2012 **National Taiwan University**, Biochemistry and Biotechnology

Research Experience

Fall 2013–Fall 2015 National Taiwan University, Taipei, Taiwan
Research Advisor: Dr. Shiuh–Tzung Liu
Synthesis of 2,4,6-trisubstituted pyrimidines
Synthesis of octahydroacrine derivatives
Synthesis of bimetallic naphthyridine complexes
C-H activation using N-nitroso directing groups

Fall 2015–Summer 2016 Academia Sinica, Taipei, Taiwan
Research Advisor: Rong-Jie Chein
Preparation of furanonaphthoquinone derivatives
Total synthesis of anti-Candida cassane-type diterpenoids from the root bark of Swartzia simplex

Fall 2016–present University of California–Los Angeles, Los Angeles, California
Michael–Heck approach for the synthesis of highly substituted polyalkyl furans
Vinylogous Michael–Heck reaction for the total synthesis of furanosesquiterpenes and furanoeremophilanes

Awards

Outstanding Research Poster Award, Spring 2015
Dr. Myung Ki Hong Dissertation Award, Spring 2021

Publications

1. **Chen**, **Y**.; M. Ramanathan.; S. T. Liu. Intramolecular Aza-Diels–Alder Cyclization of a Dimerized Citral with Anilines Catalyzed by $InCl_3$. *J. Chin. Chem. Soc.* **2015**, *62*, 761–765.
2. **Chen, V. Y**; Kwon, O. Unified Approach to Furan Natural Products via Phosphine–Palladium Catalysis.
Angew. Chem., Int. Ed. **2021**, *60*, 8874–8881.

CHAPTER ONE

Occurrence, Classification and Synthesis of Furans

1.1 Abstract

This chapter describes the occurrence and classification of furan natural products according to skeletal structure or backbone, defining functional group, and number of carbons. Traditional methods for preparing furans as well as an overview of the most frequently encountered modern synthetic methodologies for preparing furans are also presented.

1. Occurrence, Classification and Synthesis of Furans

1.2 Furan-Containing Natural Products

The furan ring is present in a multitude of bioactive and structurally diverse natural products such as terpenes, complex alkaloids and is also a prominent component of pharmaceuticals,[1] agrochemicals,[2] essential oils,[3] cosmetics[4] and fragrances.[5] In addition to their biologically important roles in nature, this useful and versatile heterocycle is also a valuable intermediate in organic synthesis as it contains masked enol ether, diene and 1,4-dicarbonyl functionalities.[6] While an official classification of furan natural products does not seem to be available, a literature survey of >10000 furan natural products reveals that they can be categorized by their skeletal structures, by defining functional group, or by the number of carbons (Figure 1.1).

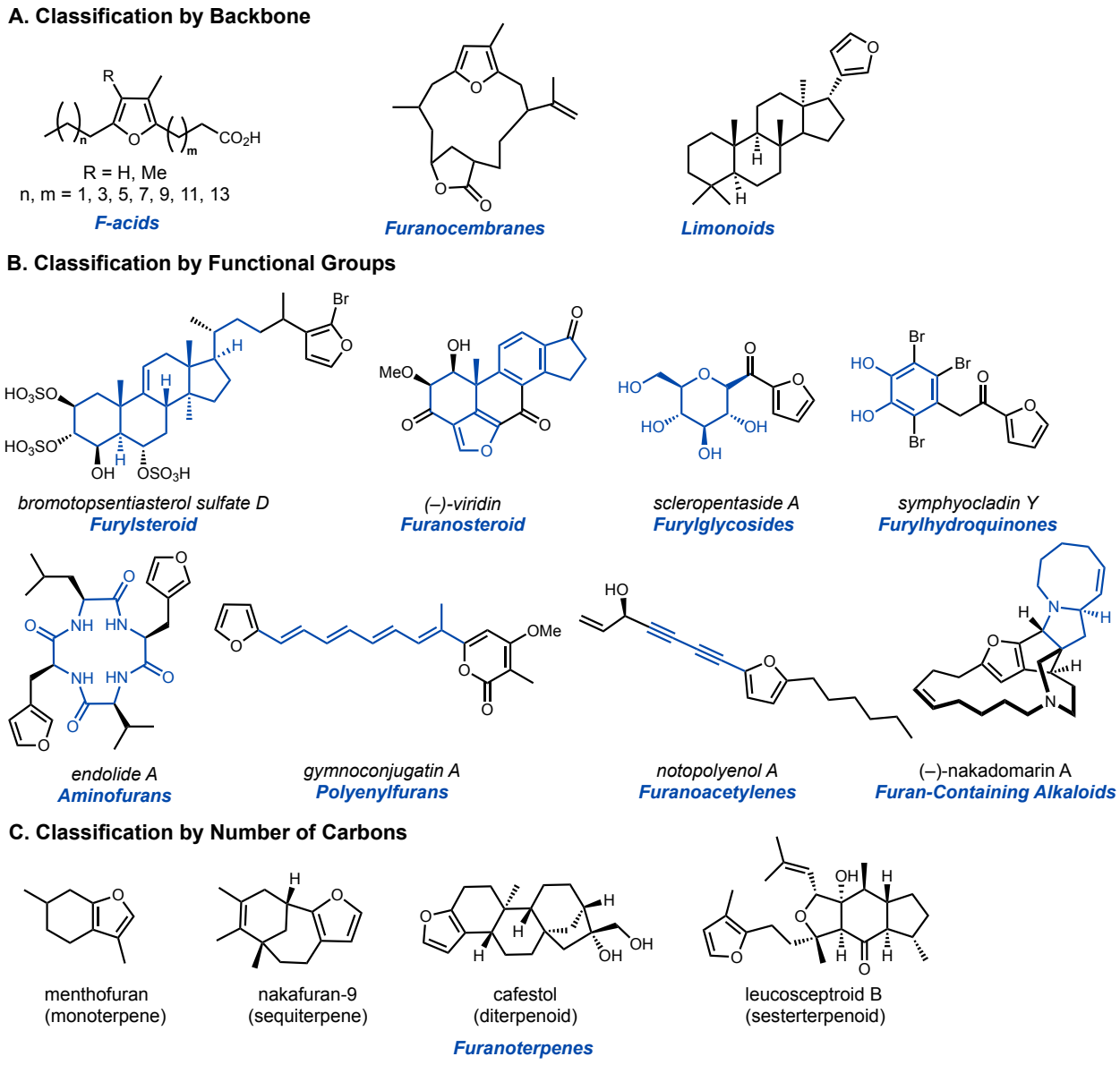


Figure 1.1. Categories of furan natural products

1.2.1 Classification by Backbone or Skeletal Structure

Furan natural products that have well-defined backbones include furan fatty acids[7] (F-acids), furanocembranes[8] and limonoids.[9] F-acids are an important class of naturally occurring heterocyclic fatty acids characterized by either a tri- or tetrasubstituted furan nucleus with an odd-numbered C2-carboxyalkyl group, C3-methyl, C4-methyl or hydrogen and an odd-numbered C5-alkyl group (Figure 1.1A). Found in a myriad of both marine and terrestrial sources, F-acids serve

to protect polyunsaturated fatty acids from lipid peroxidation by acting as potent anti-inflammatory agents and radical scavengers.[7a,c] While F-acids are found almost everywhere in nature, marine sources such as fish are the richest sources of naturally occurring F-acids. Examples of F-acids and their derivatives are shown below (Figure 1.2). 11D5, also known as F_6, is found in fish and has also been identified as one of the anti-inflammatory components of the lipid extract of the New Zealand green-lipped mussel that was found to be more effective against the inhibition of adjuvant-induced arthritis than eicosapentaenoic acid (EPA).[7b] Compound (1) is one of the polyunsaturated F-acid derivatives found in marine sponge *D. incisa* that shows anti-inflammatory activity.[10] Glanvillic acid A[11] and plakorsin C[12] are also found in the *Plakortis* marine sponges *P. halichondrioides* and *P. simplex*, respectively. Mumiamicin,[13] on the other hand, is an antibiotic isolated from the rare actinomycete strain *Mumia* sp. YSP-2-79, which also has antioxidative activity.

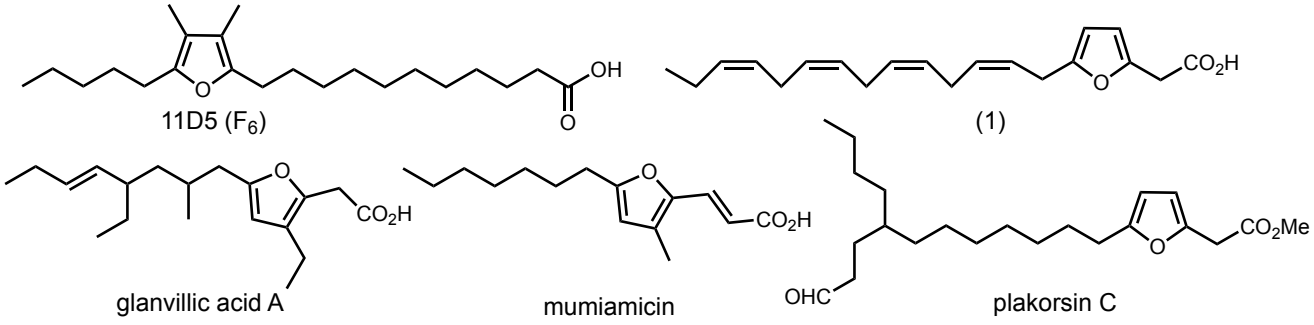


Figure 1.2. Examples of F-acids and F-acid derivatives

Another class of furan natural products with marine origins are the furanocembranes. Found in octocorals such as blue corals, soft corals, sea fans, and sea whips, these diterpenoid macrocyclic compounds are characterized by a 14-membered carbocyclic skeleton that features a furan ring at C3–C6 and a butanolide at C10–C12. Furanocembranes are structurally related to the pseudopterane and gersolane natural products, which are presumed to be biosynthesized from

furanocembranes through photochemical or enzymatic transformations.[14,15] Examples of these include providencin,[16] a cytotoxic diterpene isolated from the Caribbean gorgonian coral, which also shows modest anticancer activity against human breast (MCF7), lung (NCI-H460), and CNS (SF-268) cancer cell lines (Figure 1.3). Another furanocembrane is lophotoxin[17], a neurotoxin isolated from the Caribbean gorgonian coral *L. peruana*. While efforts towards the preparation of these two furanocembranes have been made, they have yet to succumb to total synthesis. Kallolide A,[18] on the other hand, belongs to the rare ring-contracted pseudopterolide family and exhibits anti-inflammatory activity on par with indomethacin, a non-steroidal anti-inflammatory drug (NSAID) commonly used to treat pain, swelling and joint stiffness caused by arthritis, gout, bursitis and tendonitis.

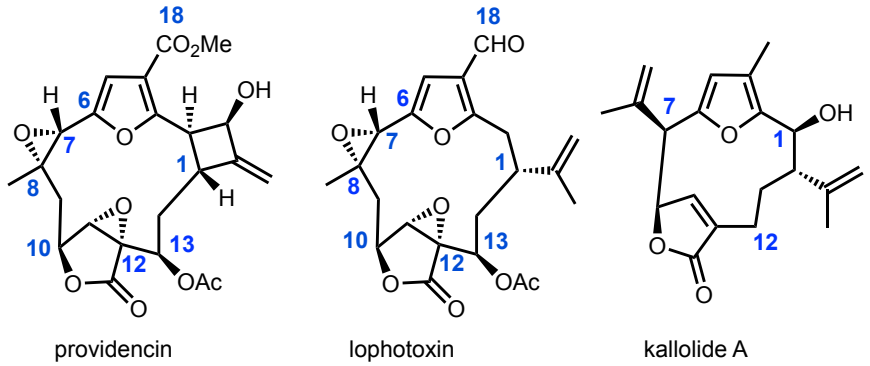


Figure 1.3. Examples of furanocembranes

Perhaps the largest class of furan-containing natural products are the limonoids, which are a group of highly oxidized triterpenoids found in the *Rutaceae* and *Meliaceae* plant families. This class of natural products derives its name from limonin,[19] a triterpene that accounts for the bitter taste of citrus fruits. These compounds also exhibit a wide spectrum of interesting bioactivities, including insecticidal, antifeedant, antimalarial, antioxidant, cytotoxic and antiviral activities. Although the basic limonoid backbone consists of a 4,4,8-trimethyl-17-furyl steroidal backbone, a wide array of structural variation is often seen in the polycylic portion. While all limonoids have a 3-furyl group

and many feature a furanolactone motif, skeletal rearrangement and differing oxidation patterns leads to a dizzying array of variation in the polycyclic portion. This is evidenced by swietenolide,[20] a limonoid isolated from the seeds of *S. macrophylla* (mahogany), which shows antifeedant activity. Further examples include cipatrijugin[21], a trijugin-type limonoid isolated from the leaves of *C. cinarescens* and cedmiline[22], an unusual limonoid derivative isolated from the *C. grevei,* a Madagascan medicinal plant whose bark is used to relieve muscle fatigue when soaked in bath water (Figure 1.4).

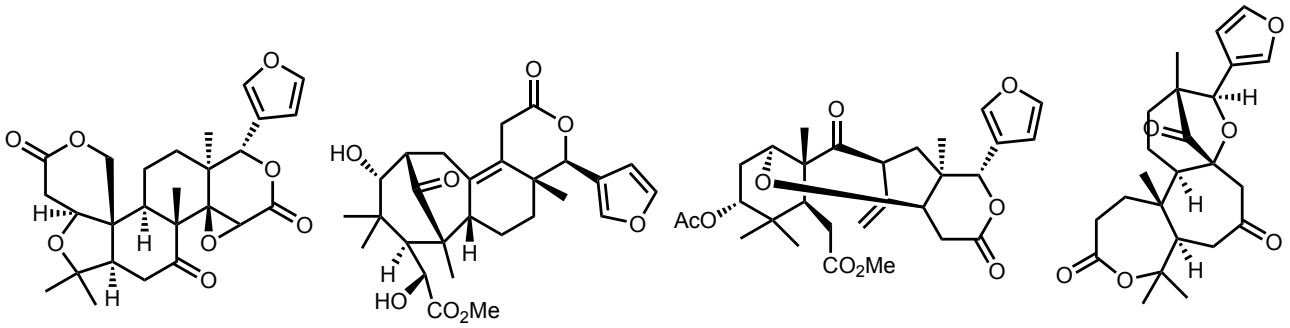


Figure 1.4. Examples of limonoids

1.2.2 Classification by Defining Functional Group

While F-acids, furanocembranes and limonoids have a characteristic backbone that allows them to be easily recognized, the bewildering structural diversity exhibited by other furan-containing natural products means that they can only be classed by their defining functional group (Figure 1.1B) or number of carbons using the isoprene rule (Figure 1.1C). These functional groups include steroids, glycosides, hydroquinones, amides, polyenes and polyacetylenes. Steroid-containing furans include furylsteroids and furanosteroids, the latter of which have a fused furan at the positions 4 and 6 of the steroid skeleton instead of an attached furyl group. Notable examples include furanosteroids (–)-viridin[23] and wortmannin,[24] potent inhibitors of phosphoinoside 3-

kinases (PI3Ks), whose overactivity in many cancers is associated with enhanced survival and growth of tumor cells (Figure 1.5).

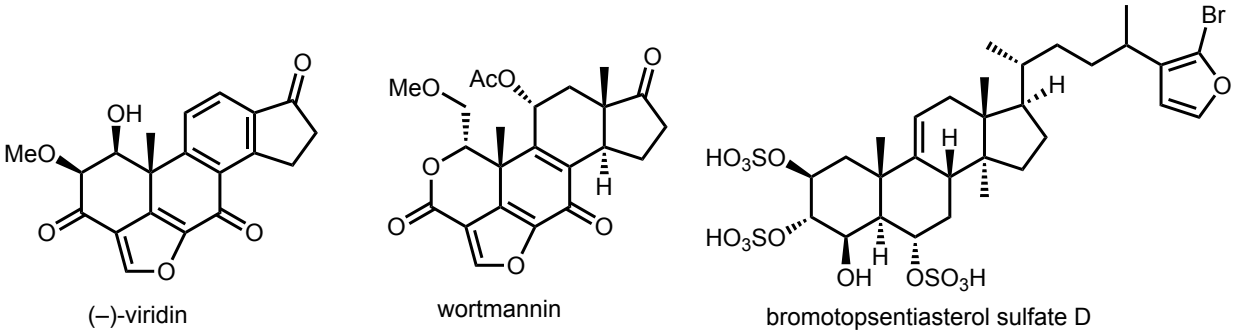


Figure 1.5. Examples of furanosteroids and furylsteroids

The steroid motif is also found in furylsteroids such as bromotopsentiasterol sulfate D,[25] an unusual polysulfated steroid isolated from marine sponge *H. vansoesti*. Furyl glycoside natural products can be either 2- or 3-substituted and include both C- and O-glycosidic linkages. Examples include scleropentaside A,[26] a furan-2-carbonyl monosaccharide from *S. pentantrum*, which has radical scavenging and cytoprotective properties. More complex furylglycosides include sublanceoside E1,[27] a pregnane glycoside isolated from the roots of *C. atratum*, a plant used in traditional Chinese medicine for its antifebrile, diuretic, anti-inflammatory, cytotoxic and anti-acetylcholinesterase activities, as well as seguinoside A,[28] a phenolic glycoside isolated from the perennial tree *M. seguinii* (Figure 1.6).

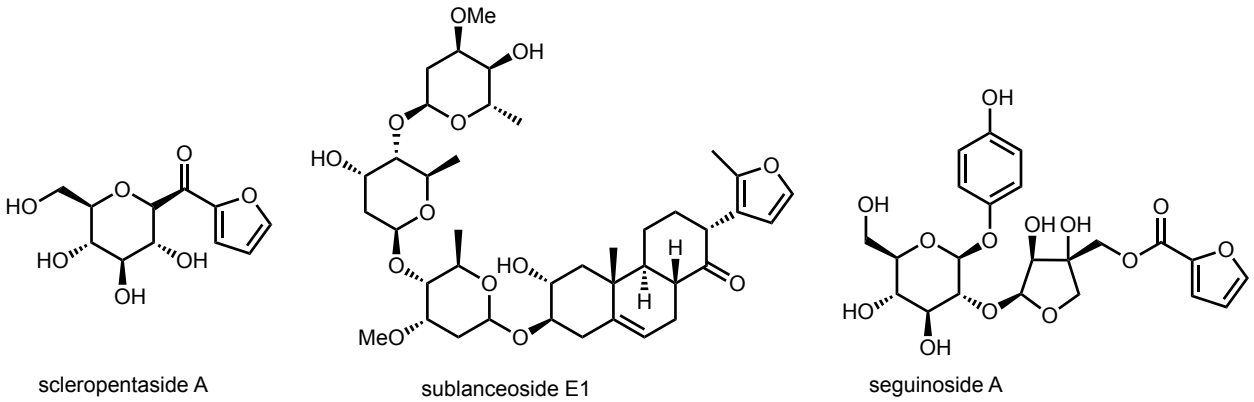


Figure 1.6. Examples of furylglycosides

Hydroquinones, phenols, catechols and lignans are also found in some furan-containing natural products. Cristatic acid[29] is isolated from *A. cristatus* mushrooms and exhibits a range of desirable bioactivities such as antibiotic activity against gram-positive bacteria, hemolytic activity and inhibitory properties against cells of the ascites form of Ehrlich carcinoma. Diethylfuroguaiacidin[30] is one of the three rare furan-containing lignans isolated from the heartwood of *G. officinale.* Symphyocladin F[31] is a polybromocatechol isolated from marine red algae *S. latiuscula* and shikonofuran E[32] is a phenolic compound isolated from the roots of *O. paniculatum* with potent anti-inflammatory, antioxidant and enzyme inhibitory activities (Figure 1.7).

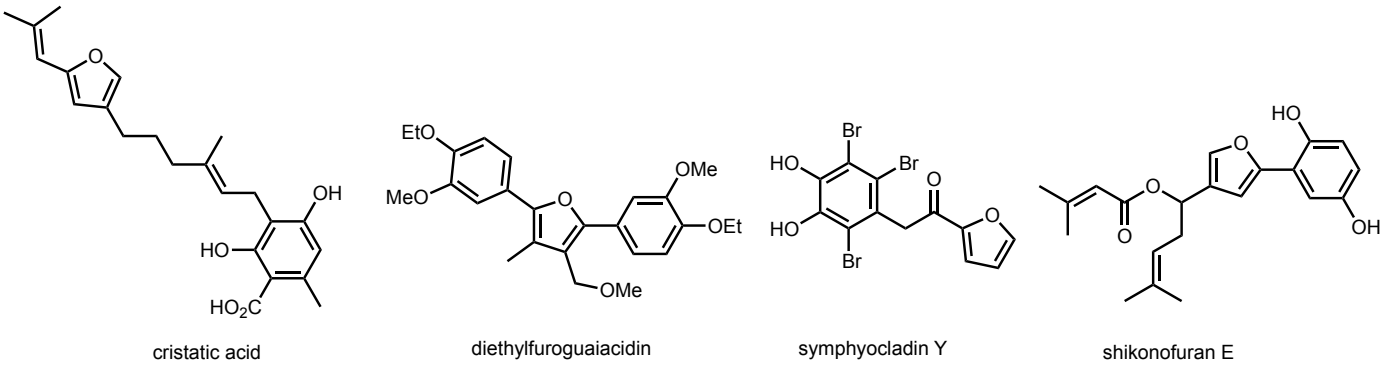


Figure 1.7. Examples of furylhydroquinones, lignans and catechols

Compared to the previous two classes of functional groups in furans, amides and polyunsaturated moieties such as polyenes and polyacetylenes are much less common. Aminofurans are rare in nature and mostly exist in the form of peptides. Examples include proximicin F,[33] an aminofuran isolated from the rare actinomycete strain *Verrucosispora* sp. SCSIO 40062, and endolide A,[34] a highly unusual tetrapeptide containing the highly unusual 3-(3-furyl)-alanine that is isolated from marine fungus *Stachylidium* sp., which shows affinity to the vasopressin receptor 1A (Figure 1.8).

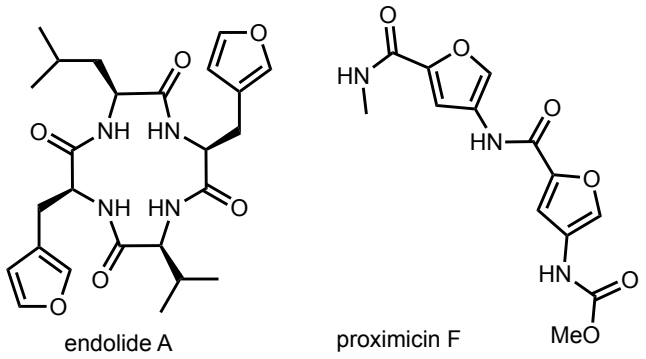


Figure 1.8. Examples of aminofurans

Polyenylfurans and furanoacetylenes, which feature either 2- or 2, 5-disubstituted furans, are also scarce in nature. Examples include gymnoconjugatins A and B,[35] polyenylfurans isolated from soil ascomycete *G. reessii*; atractylodinol,[36] a potent inhibitor of PRRSV (porcine reproductive and respiratory syndrome) isolated from the rhizomes of *A. lancea*; wyerone acid,[37] an antifungal phytoalexin (secondary metabolite with antimicrobial activities), and notopolyenol A,[38] a cytotoxic polyacetylene that exhibits significant cytotoxicity against MCF-7, H1299 and HepG2 cancer cells (Figure 1.9).

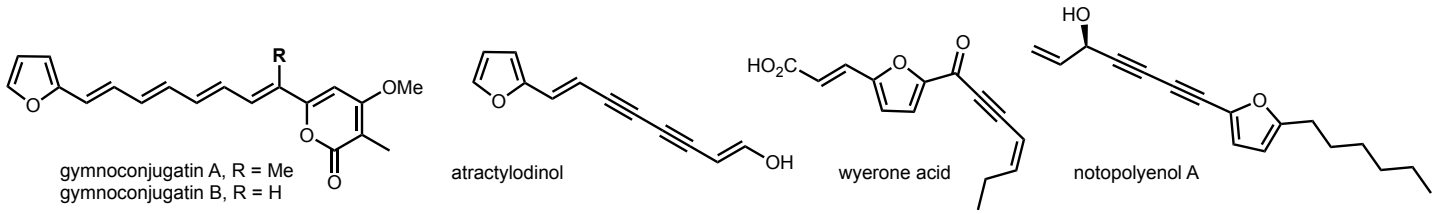


Figure 1.9. Examples of polyenylfurans and furanoacetylenes

Unlike the previous categories of furan natural products, furan-containing alkaloids are pervasive in nature and often feature intricate and highly variable carbocyclic skeletons. Interesting examples include huperphlegmine A,[39] a novel *Lycopodium* alkaloid from *H. phlegmaria* with acetylcholinesterase inhibitory activities; nupharpumilamine D,[40] a thiaspirane sulfoxide *Nuphar* alkaloid isolated from the rhizomes of *N. pumilum*, commonly known as small yellow pond-lily; (–)-nakadomarin A,[41] an unique manzamine alkaloid featuring a fused furan ring isolated from the

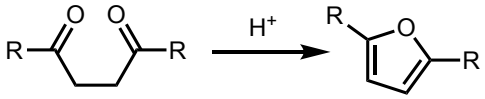
Okinawan sponge *Amphimedon* sp., and roseophilin,[42] a novel antibiotic isolated from *S. griseoviridis* with a strained macrocyclic framework and an *ansa*-bridged pyrrole, also shows promising cytotoxicity against K562 human erythroid leukemia and KB human epidermoid carcinoma cell lines (Figure 1.1B).

1.2.3 Classification by Number of Carbons

A wide range of structural variation also exists within the furanoterpene family of natural products. Examples of these include menthofuran,[43] a highly toxic monoterpene found in a variety of essential oils; nakafuran-9,[44] a sesquiterpene isolated from the chromodorid nudibranch *H. infucata* with antifeedant properties; cafestol,[45] a diterpene responsible for the pharmacological effects of coffee, and leucosceptroid B,[46] a sesterterpenoid with potent antifeedant and antifungal activities isolated from the glandular trichomes of *L. canum* (Figure 1.1C).

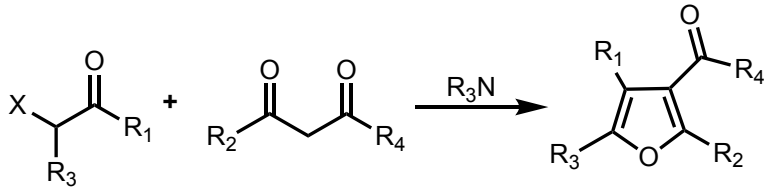
1.3 Traditional Methods for the Preparation of Furans

The two main classical methods used for the preparation of furans are the Paal–Knorr reaction[47] and the Feist–Benary reaction.[48] In the Paal–Knorr reaction, a 1,4-diketone is treated with an acid catalyst that protonates one of the carbonyls, which is then attacked by the enol of the other carbonyl. Dehydration of the resulting hemiacetal then forms the furan (Scheme 1.1). By addition of an amine or a sulfurizing agent, the Paal–Knorr reaction can also be used to prepare pyrroles and thiophenes. While the Paal–Knorr reaction is quite versatile and is able to convert almost all dicarbonyls to their corresponding furan, it is limited in scope by the availability of 1,4-diketone precursor as well as by harsh reaction conditions that involve prolonged heating in acid, which may not be tolerated by more sensitive functionalities.



Scheme 1.1. Paal–Knorr reaction

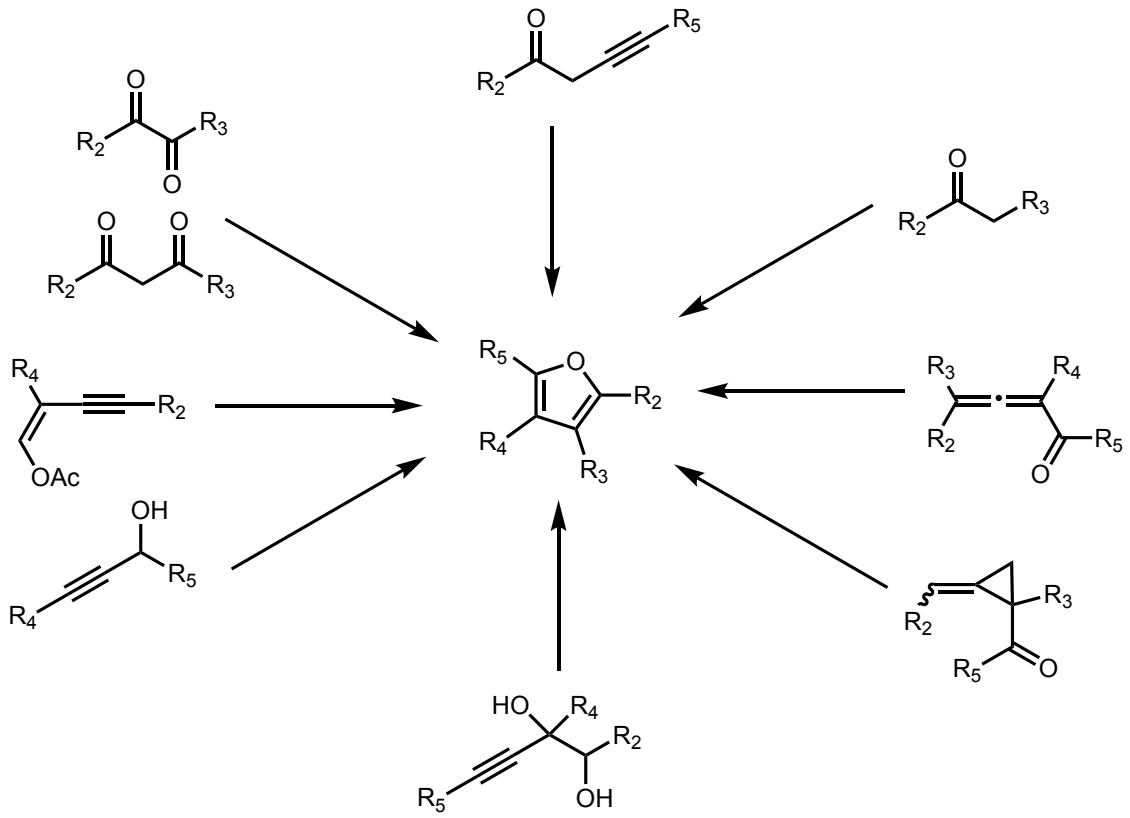
In the Feist–Benary reaction, α-halo ketones and β-dicarbonyls undergo base-mediated condensation followed by nucleophilic displacement of the halogen by the enolate to form a dihydrofuran intermediate, which undergoes dehydration to form C3-carbonyl furans (Scheme 1.2).



Scheme 1.2. Feist–Benary reaction

1.4 Modern Methods for the Preparation of Furans

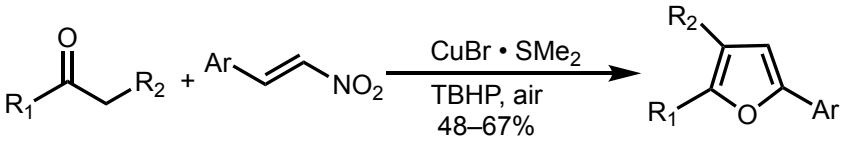
Over the years, an innumerable number of synthetic methodologies have been developed towards the milder, more versatile and efficient synthesis of furans. Both transition-metal and Lewis acid-catalyzed or -mediated approaches have been reported, and various substrates can be used. Some typical precursors used include ketones, dicarbonyls, enyne acetates, propargyl alcohols, alkyne-1,2-diols, alkylidene cyclopropanes and allenones (Scheme 1.3).



Scheme 1.3. Commonly used substrates in modern furan synthetic methodologies

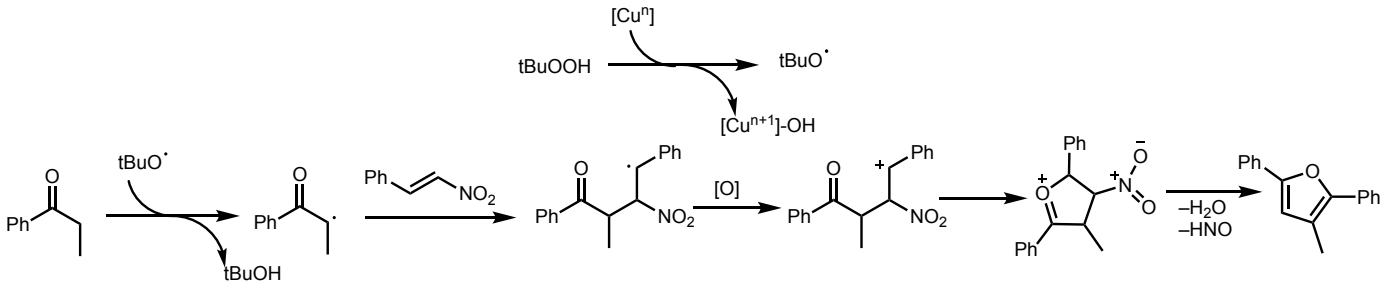
1.4.1. Syntheses using Ketones

Ketones are frequently used in furan synthesis. Hajra and coworkers reported a copper-mediated intermolecular annulation of ketones with β-nitrostyrenes to yield 2,3,5-trisubstituted furans in moderate yields (Scheme 1.4).[49a]



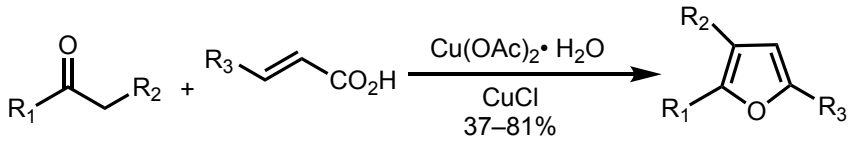
Scheme 1.4. Cu(I)-mediated intermolecular annulation of ketones with β-nitrostyrenes

In the presence of Cu(I), the *tert*-butylhydroperoxide radical is formed and reacts with propiophenone to generate a carbon-based radical, which then undergoes addition to β-nitrostyrene. The resulting radical intermediate is then oxidized to a benzylic carbocation, which undergoes cyclization followed by dehydration to give the desired furan product (Scheme 1.5).



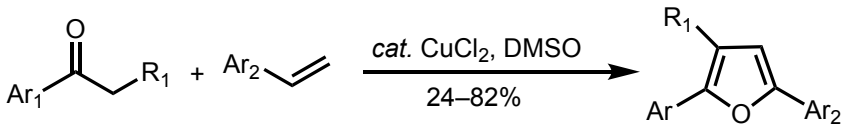
Scheme 1.5. Mechanism of the Cu(I)-mediated furan formation from ketones and β-nitrostyrenes

A similar copper-mediated furan synthesis using ketones is also reported by Zhang and coworkers, wherein ketones are annulated with various α, β-unsaturated carboxylic acids to form 2,3,5-trisubstituted furans (Scheme 1.6).[49b]



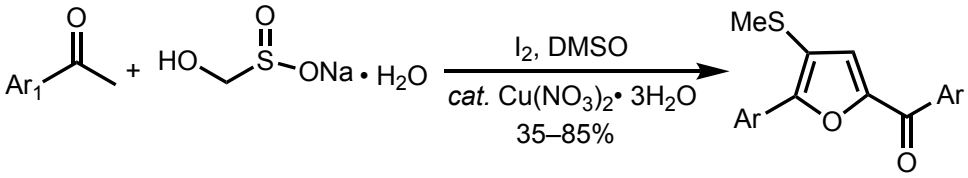
Scheme 1.6. Cu(I)-mediated annulation of ketones with α, β-unsaturated carboxylic acids

Lei and coworkers demonstrated the catalytic version of this transformation by using DMSO as both solvent and oxidant in the intermolecular annulation of aromatic ketones and styrene derivatives (Scheme 1.7).[49c] This reaction, as well as the previous one, follows a mechanism very similar to that in Scheme 1.5.



Scheme 1.7. Catalytic annulation of aromatic ketones with styrene derivatives

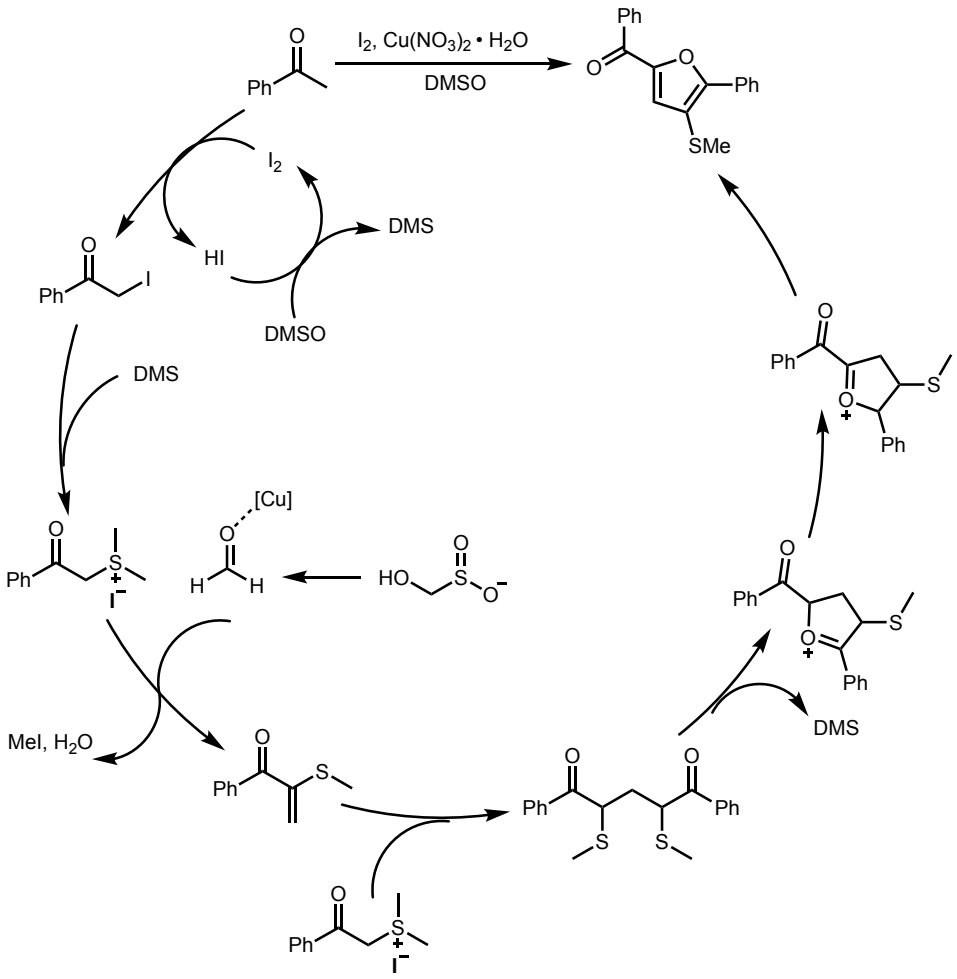
Wu and coworkers developed a I_2/Cu(II)-mediated functionalization reaction for the synthesis of 2,4,5-trisubstituted furans from aromatic ketones and rongalite, which acts as a C1 unit.[49d] Mechanistic studies indicate that the reaction proceeds via an *in situ* generated dimethyl(phenacyl)-sulfonium iodine derived from reduced DMSO and an α-iodoacetophenone intermediate (Scheme 1.8).



Scheme 1.8. I_2/Cu(II) mediated annulation of aromatic ketones with rongalite

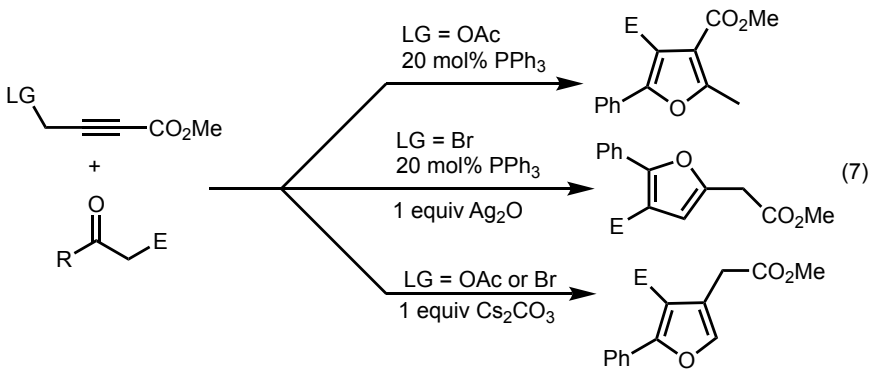
In this reaction, acetophenone is oxidized by molecular iodine to form α-iodoacetophenone, which then reacts with DMS (generated from the reduction of DMSO) to form a sulfonium iodide

intermediate. Formaldehyde, which is generated from the decomposition of rongalite, is captured by the sulfonium intermediate to form an enone intermediate. This enone then dimerizes and undergoes an intramolecular addition to form an oxonium intermediate, which undergoes isomerization, deprotonation and aromatization to give the furan product.



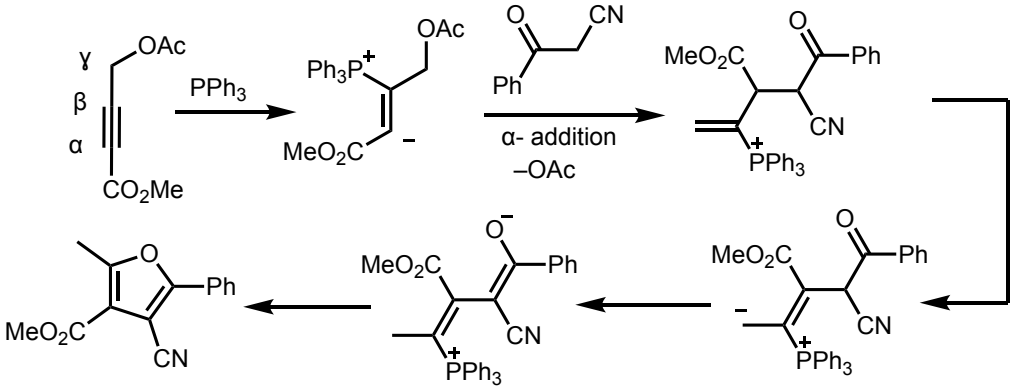
Scheme 1.9. Mechanism of the I_2/Cu(II) mediated annulation of aromatic ketones with rongalite

Finally, a novel and selective phosphine catalyzed [3+2] annulation between γ-substituted butynoates and ketones was developed by Tong and coworkers. Depending on the conditions used, three different types of furans can be prepared according to whether α, β or γ-addition occurred (Scheme 1.10).[49e]



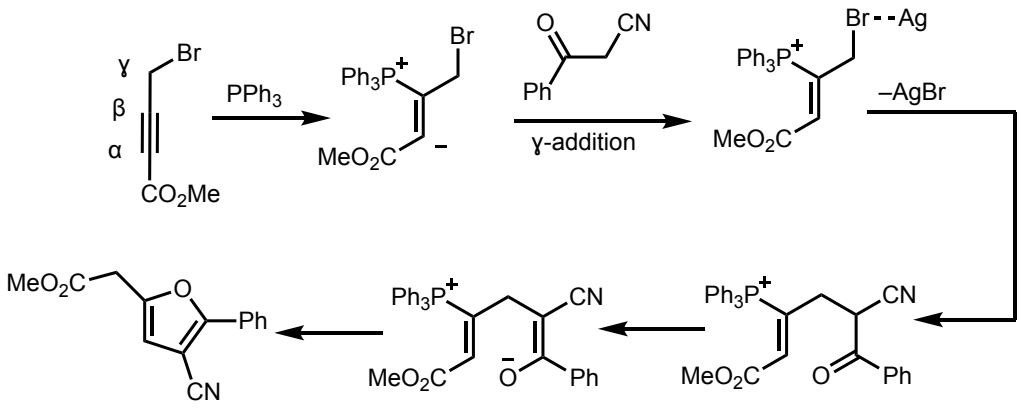
Scheme 1.10. Phosphine-catalyzed [3+2] annulation of ketones with γ-substituted butynoates

In the α-addition mode, deprotonation of the acidic proton alpha to the nitrile by the phosphonium zwitterion produces an enolate, which then adds onto the α-position of the butynoate to produce another phosphonium intermediate, which undergoes a series of proton transfer/isomerization steps to form a dienolate intermediate, which undergoes cyclization, elimination and aromatization to give the tetrasubstituted furan product (Scheme 1.11).



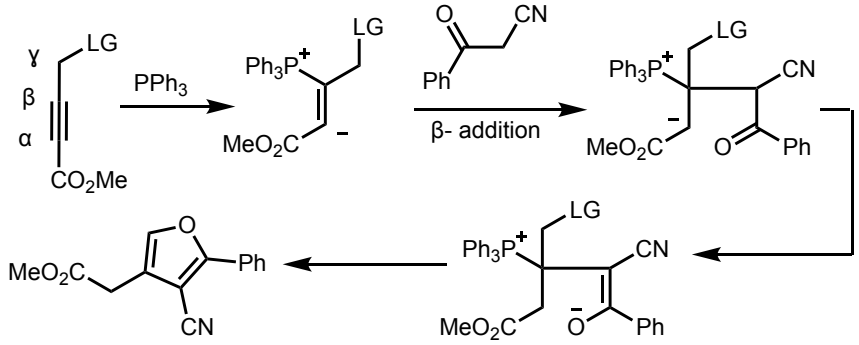
Scheme 1.11. α-addition mode to form tetrasubstituted furans

In the γ-addition mode, the same enolate attacks the allylic bromide (which is activated by Ag^+). Enolization, intramolecular cyclization followed by elimination and aromatization then delivers the 2,3,5-trisubstituted furan product (Scheme 1.12).



Scheme 1.12. γ-addition mode to form 2,3,5-trisubstituted furans

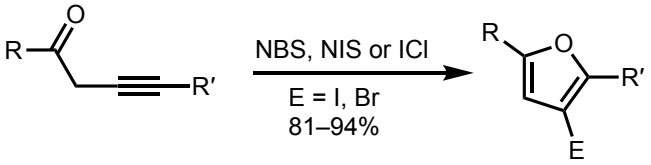
In the β-addition mode, the enolate undergoes β-addition, proton transfer, alkylation, elimination and aromatization to furnish the 2,3,4-trisubstituted furan product (Scheme 1.13).



Scheme 1.13. β-addition mode to form 2,3,4-trisubstituted furans

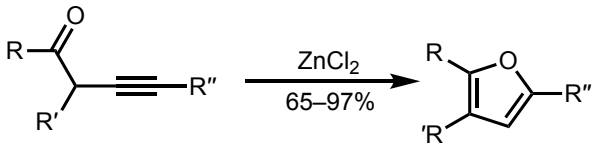
1.4.2. Syntheses Using Homopropargyl Ketones

While simple aromatic or aliphatic ketones are usually used in intermolecular annulations, homopropargyl ketones can be used in transition metal or Lewis acid-catalyzed intramolecular cycloisomerizations to furnish furans. An example of this is Dembinski and coworkers' report on the highly efficient 5-*endo-dig* electrophilic cyclization of homopropargyl ketones to form aromatic 2,5-disubstituted 3-bromo- or iodofurans (Scheme 1.14).[49f]



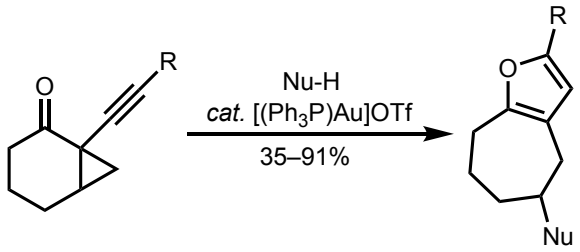
Scheme 1.14. Halocyclization of homopropargyl ketones to form trisubstituted halofurans

The same transformation can also be achieved with Lewis acid catalysis under very mild conditions, as seen in Dembinski's subsequent report (Scheme 1.15).[49g]



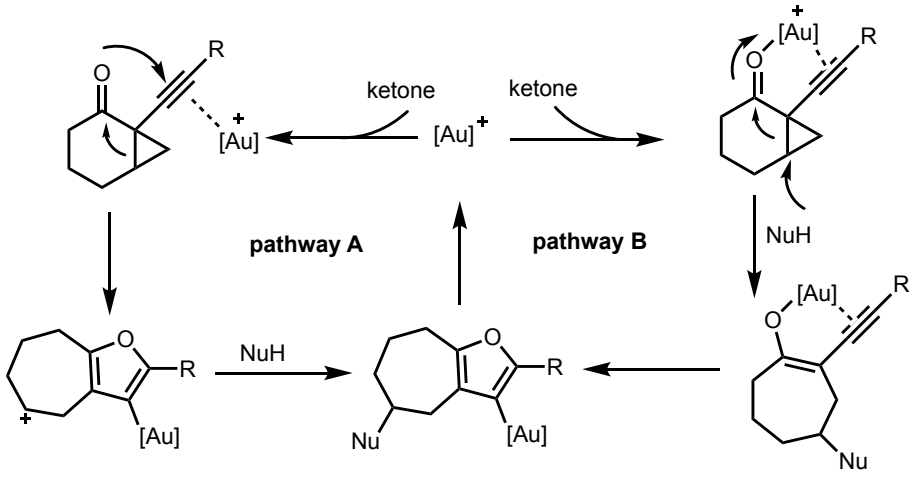
Scheme 1.15. Zn(II)-catalyzed cyclization of homopropargyl ketones to form trisubstituted furans

Schmalz and coworkers reported an Au(I)-catalyzed reaction of alkynyl cyclopropyl ketones with nucleophiles to yield various structurally interesting cycloalkyl-fused trisubstituted furans (Scheme 1.16).[49h]



Scheme 1.16. Au(I)-catalzyzed reaction of alkynyl cyclopropyl ketones with nucleophiles

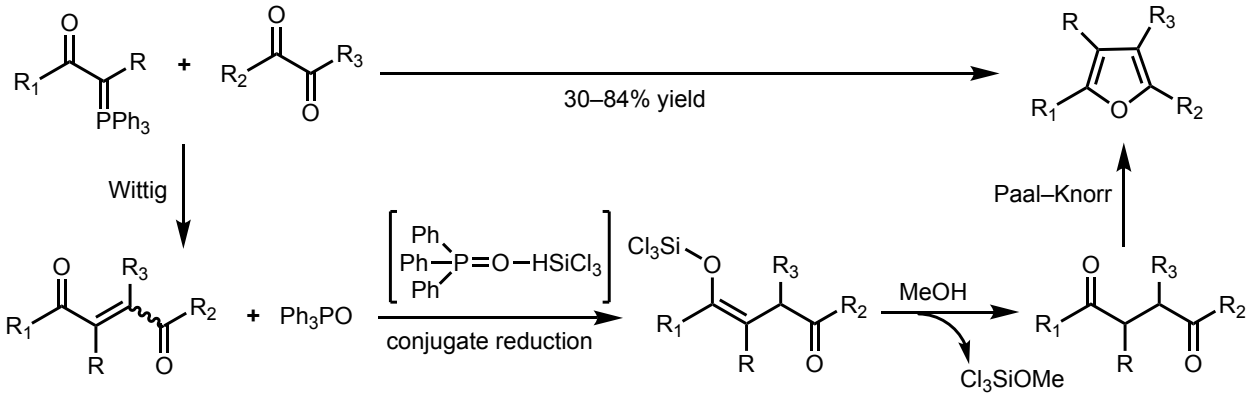
Two plausible pathways have been proposed for this transformation. In cycle A, coordination of Au(I) to the triple bond induces ring-opening of the fused cyclopropane to produce furan-fused cycloheptyl carbocation, which then undergoes nucleophilic trapping and protodeauration to deliver the product. In cycle B, Au(I) forms a chelated intermediate that undergoes homo-Michael type addition to yield a gold enolate intermediate, which then undergoes cycloisomerization followed by protodeauration to give the product (Scheme 1.17).



Scheme 1.17. Mechanistic proposal for synthesis of cycloalkyl-fused furans

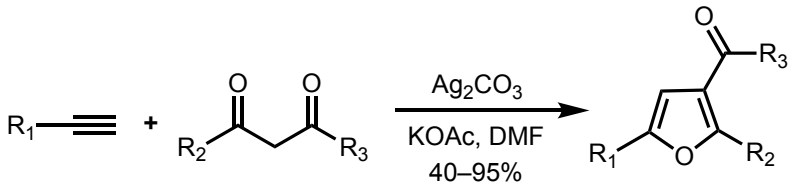
1.4.3. Syntheses Using Dicarbonyl Compounds

Dicarbonyl compounds were among one of the most important precursors to be employed in the classical preparation of furans, as seen by the use of 1,4-diketones in the Paal-Knorr reaction. The use of 1,2-diketones in the preparation of polysubstituted furans is demonstrated by Zhou's ingenious report on the use of a one-pot Wittig/1,4-reduction/Paal–Knorr sequence between 1,2-diketones and α-keto phosphoranes (Scheme 1.18).[50a] In this case, the triphenylphosphine oxide waste generated in the first Wittig step reduces the enone intermediate formed along with TMSCl, generating a silyl enol ether that undergoes methanolysis to produce a 1,4-diketone, which undergoes a Paal–Knorr reaction catalyzed by the HCl generated in the previous step.



Scheme 1.18. Reaction design of the one-pot Wittig/1,4-reduction/Paal–Knorr sequence between 1,2-diketones and α-keto phosphoranes

An example of the use of 1,3-dicarbonyls in the synthesis of polysubstituted furans is seen in Lei's report, where a silver-mediated oxidative C–H functionalization reaction of aryl acetylenes and 1,3-dicarbonyls is used to prepare various trisubstituted furans (Scheme 1.19).[50b]

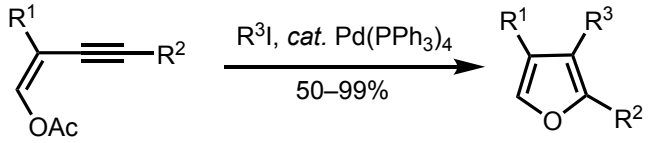


Scheme 1.19. Ag(I)-mediated oxidative C–H functionalization of aryl acetylenes and 1,3-dicarbonyl compounds

Preliminary mechanistic investigations indicate that silver acetylides could be involved as reaction intermediates, with Ag_2CO_3 acting as the additional oxidant required for this oxidative coupling.

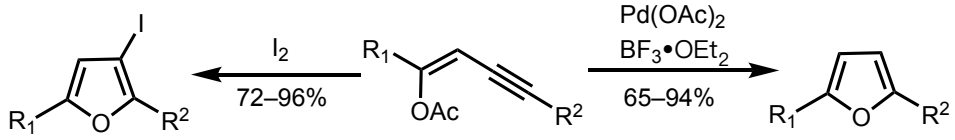
1.4.4. Syntheses Using Enyne Acetates

Li and coworkers reported a palladium-catalyzed cascade reaction of enyne acetates and aromatic iodides for the synthesis of 2,3,4-trisubstituted furans (Scheme 1.20).[51a]



Scheme 1.20. Pd(0)-catalyzed annulation of enyne acetates and aromatic iodides

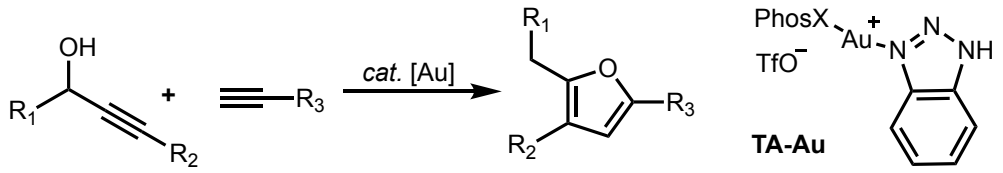
Enyne acetates can also undergo electrophilic iodocyclization to generate 2,5-disubstituted 3-iodofurans as well as undergo Lewis acid and palladium (II)-catalyzed cyclization to form 2,5-disubstituted furans (Scheme 1.21).[51b,c]



Scheme 1.21. Cyclization of enyne acetates to form trisubstituted iodofurans or disubstituted furans

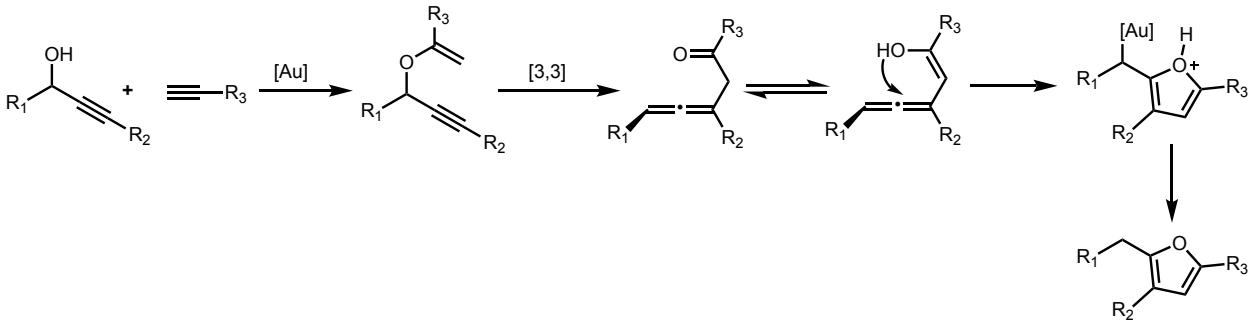
1.4.5. Syntheses Using Alkynols

Among the substrates commonly employed for furan syntheses, alkynols and their derivatives are perhaps the most frequently used. The presence of the triple bond in these precursors allows them to be easily applied in gold-catalyzed transformations. An example of this is seen in Shi's report, where 2,3,5-trisubstituted furans are obtained via the gold-catalyzed reaction between alkynols and alkynes (Scheme 1.22).[52a]



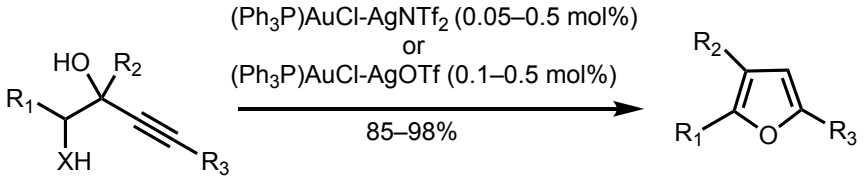
Scheme 1.22. Au(I)-catalyzed annulation of alkynols with alkynes

In this reaction, the alcohol first undergoes addition to the acetylene to form a propargyl vinyl ether, which then undergoes Saucy–Marbet rearrangement to give an allenyl ketone intermediate. This then tautomerizes to an allenyl enol, which undergoes *5-exo-trig* cyclization followed by protodeauration to give the furan product. Interestingly, *6-endo-trig* cyclization occurred exclusively to give the pyran in the presence of protic solvent such as MeOH, while *5-exo-trig* cyclization occurred exclusively when toluene was used as solvent (Scheme 1.23).



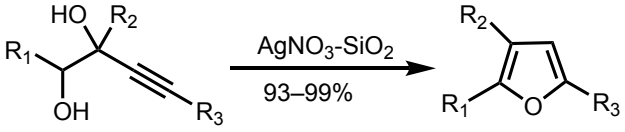
Scheme 1.23. Mechanism of the Au(I)-catalyzed annulation of alkynols and alkynes

Multiple examples of gold-catalyzed intramolecular cyclizations of alkyne-1,2-diols have been reported. One of these is Akai's report on the use of cationic Au(I) complexes for the intramolecular cyclization of alkyne-1,2-diols and their derivatives for the preparation of trisubstituted furans and pyrroles (Scheme 1.24).[52b]



Scheme 1.24. Au(I)-catalyzed intramolecular cyclization of alkyne-1,2-diols

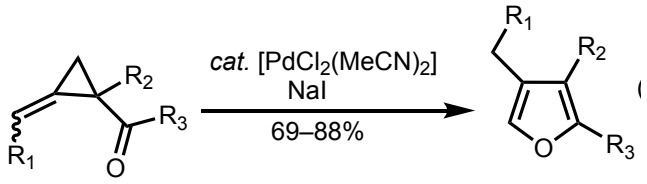
Tan and coworkers have also developed a Lewis-acid catalyzed 5-*endo-dig* cyclization of alkyne-1,2-diols to yield trisubstituted furans in excellent yields (Scheme 1.25).[52c]



Scheme 1.25. Ag(I)-catalyzed cyclization of alkyne-1,2-diols

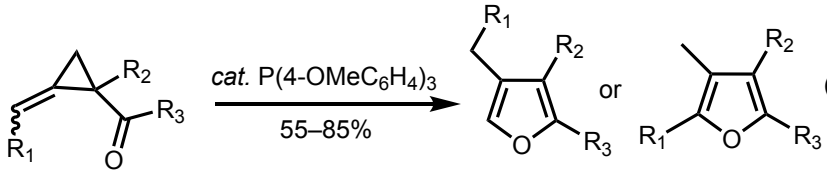
1.4.6. Syntheses Using Cyclopropanes

Zhang and coworkers reported on a Pd(II)-catalyzed ring opening/cycloisomerization of alkylidene cyclopropyl ketones to yield 2,3,4-trisubstituted furans (Scheme 1.26).[53a]



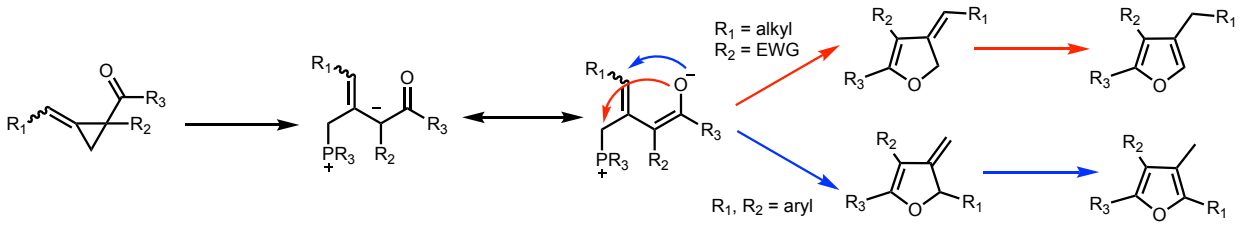
Scheme 1.26. Pd(II)-catalyzed ring opening/cycloisomerization of alkylidene cyclopropyl ketones

Li and coworkers also reported on the phosphine-catalyzed ring opening of electron-deficient alkylidene cyclopropanes to form allylic phosphonium zwitterions that then undergo cyclization to form tri- or tetrasubstituted furans (Scheme 1.27).[53b]



Scheme 1.27. Phosphine-catalyzed ring opening of electron-deficient alkylidene cyclopropanes

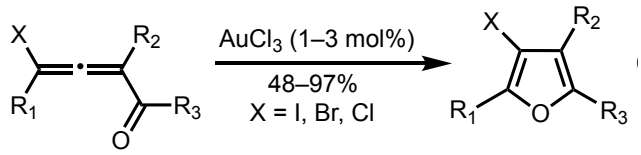
In this reaction, nucleophilic attack of the phosphine on the cyclopropane gives an allylic phosphonium intermediate, which can form either a tri- or tetrasubstituted furan depending on the nature of the R_2 substituent. When R_2 is an electron-withdrawing group, direct S_N2 displacement of the phosphine by the enolate generates a dihydrofuran intermediate that isomerizes to trisubstituted furan product. Replacement of the R_2 electron-withdrawing group by an aryl group enhances the basicity of the dienolate and intramolecular S_N2 ′occurs to form a dihydrofuran that isomerizes to the fully-substituted furan (Scheme 1.28).



Scheme 1.28. Mechanism for the formation of tri- or tetrasubstituted furans from electron-deficient alkylidene cyclopropanes

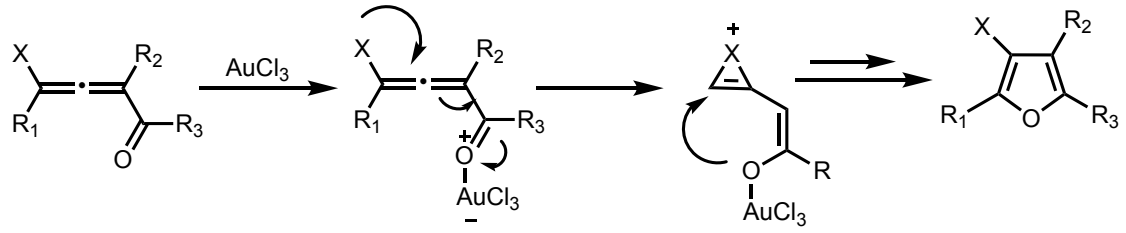
1.4.7. Syntheses Using Allenones

Gevorgyan and coworkers reported a selective Au-catalyzed 1,2-migration of halides for the formation of 3-halofurans (Scheme 1.29).[54a]



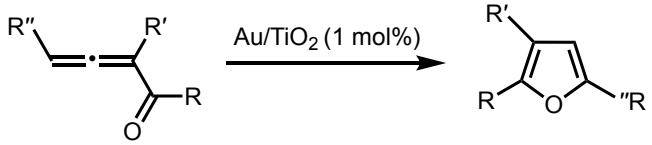
Scheme 1.29. Au(III)-catalyzed 1,2-migration of halides to form 3-halofurans

In this reaction, the oxophilic Au(III) coordinates to the ketone oxygen and triggers an intramolecular Michael addition of Br onto the enone to produce a haloirenium intermediate, which undergoes addition–elimination to furnish 3-halofurans (Scheme 1.30).



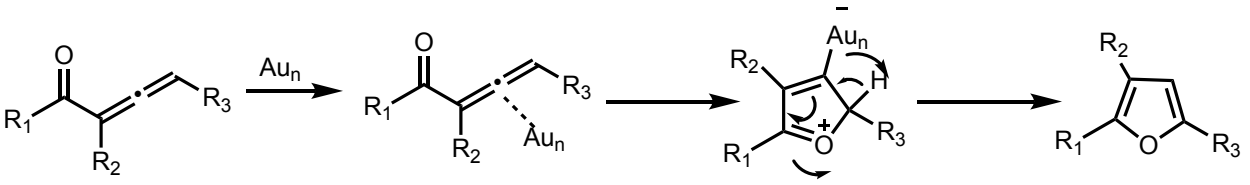
Scheme 1.30. Mechanism for the Au(III)-catalyzed formation of 3-halofurans from allenones

A similar transformation is also reported by Stratakis and coworkers, where catalytic amounts of Au nanoparticles supported on TiO_2 are used to promote the quantitative cycloisomerization of conjugated allenones to trisubstituted furans under very mild conditions (Scheme 1.31).[54b]



Scheme 1.31. Au/TiO_2-catalyzed cycloisomerization of allenones to form 2,3,5-trisubstituted furans

In this reaction, π-philic Au coordinates to the allene moiety and activates it towards attack by the ketone oxygen to form a cyclic intermediate that then undergoes protodeauration to give the furan product (Scheme 1.32).



Scheme 1.32. Proposed formation of trisubstituted furans from allenones

1.5 References

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CHAPTER TWO

Michael–Heck Approach to the Synthesis of Polyalkyl Furans

Adapted from: Chen, V. Y; Kwon, O. *Angew. Chem., Int. Ed.* **2021**, *60*, 8874–8881.

2.1. Abstract

This chapter describes the development of a sequential phosphine/palladium catalyzed Michael–Heck reaction for the synthesis of highly substituted polyalkyl furans, including starting material preparation, reaction optimization, substrate scope and mechanistic studies. The application of to the total synthesis of *P. simplex* polyketides plakorsin A, B, D; furanoterpenes rosefuran, sesquirosefuran, mikanifuran, and furan fatty acids (F-acids) 3D5 and hydromumiamicin are also presented.

2.2. Development of the Michael–Heck Reaction for Furan Synthesis

The furan ring frequently encountered in a variety of bioactive natural products,[1] pharmaceuticals,[2] and useful intermediates in organic synthesis.[3] Polyalkyl furans, in particular, feature prominently in biologically-active natural products (Figure 2.1), including the galerucella pheromone;[4] calicogorgins A–C;[1d] furan fatty acids (F-acids),[5] potent antioxidants and radical scavengers that protect polyunsaturated fatty acids from lipid peroxidation; rosefuran,[6] the fragrant component of highly prized rose oil; and plakorsins D[7] and B,[8] cytotoxic F-acid derivatives isolated from the marine sponge *P. simplex*.

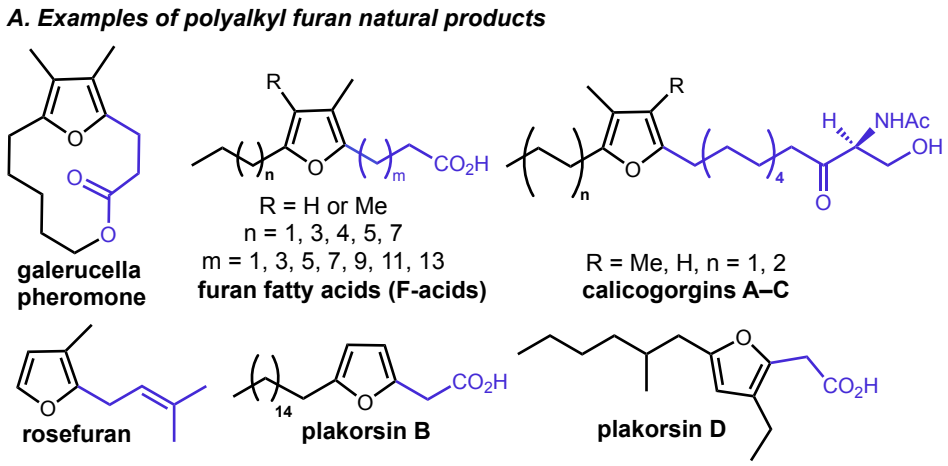
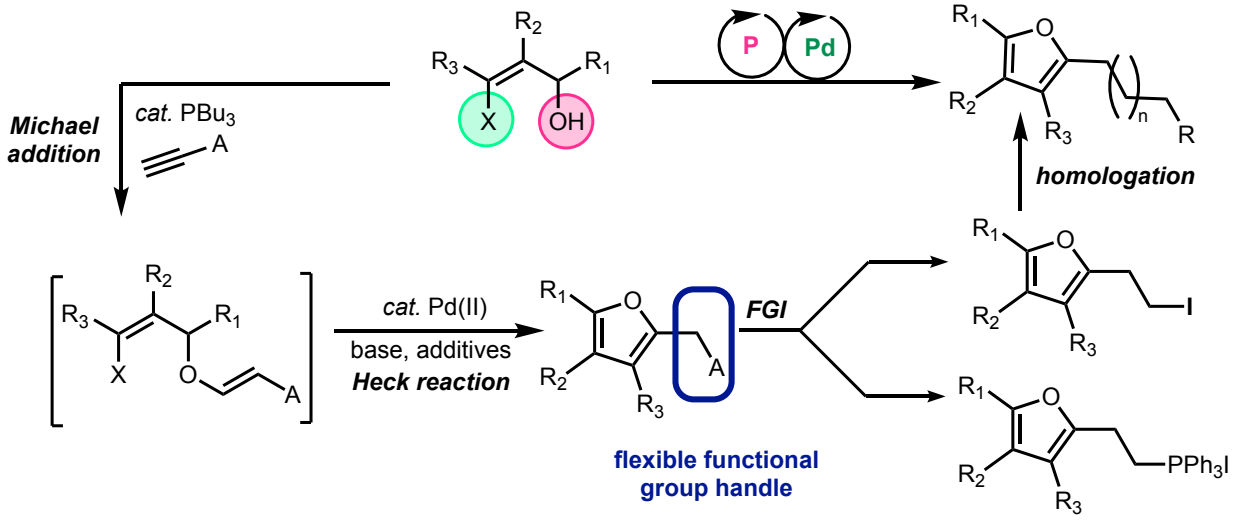


Figure 2.1. Examples of polyalkyl furan natural products

While C2/C5-functionalization of furans can be achieved quite readily through metalation or electrophilic aromatic substitution,[9] the regioselective construction of highly functionalized furans is a nontrivial task. Among the plethora of methods available for the construction of tetrasubstituted furans, the overwhelming majority provide carbonyl-,[10] thioalkyl-,[11] halo-,[12] and amino- and aryl-substituted[13] furans, but very few enable direct access to the tetraalkyl furans[14] that feature prominently in biologically important compounds (e.g., the F-acids). Notably, none of the three known syntheses of tetraalkyl furans[14] have, to the best of knowledge, ever provided furans with four non-identical alkyl substituents. Given the prevalence and desirable bioactivities of polyalkyl furans and the relative paucity of aryl substituents in

furan-containing natural products,[15] the ability to prepare polyalkyl furans efficiently would be extremely useful.

Tertiary phosphines are useful reagents that are able to serve as efficient organocatalysts as well as ligands for cross coupling reactions. In this chapter, we employ the dual reactivity of phosphines in a Michael–Heck reaction for the synthesis of highly functionalized furans by using the sequential reaction between (*Z*)-β-haloallylic alcohols and activated acetylenes. In this reaction, the alcohol group initially undergoes phosphine-catalyzed (*E*)-selective Michael addition to activated alkynes to give vinyl ether intermediates,[16] which then undergo sequential Heck cyclization and spontaneous aromatization to give highly substituted furans (Scheme 2.1). The phosphine organocatalyst for the Michael addition also acts as a ligand in the Heck reaction. The resulting (alkoxycarbonyl)alkyl side chain can then be transformed into other functional groups and homologated.[17–19] Using appropriately substituted (*Z*)-*β*-haloallylic alcohols, this approach provides a general and versatile method for the synthesis of various bioactive polyalkyl furans from readily accessible precursors.

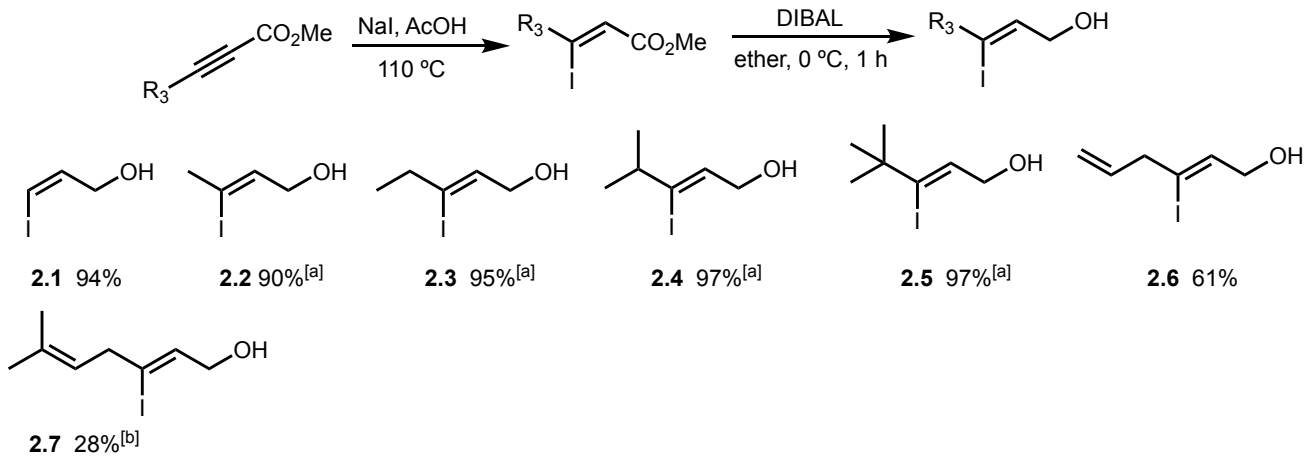


Scheme 2.1. Reaction design of the Michael–Heck reaction for furan synthesis

2.3 Preparation of the Michael–Heck Precursors

(*Z*)-3-halo-2-propen-1-ols are versatile substrates that can be rapidly and stereoselectively prepared from readily available propargyl alcohols and alkynoates through hydro/carbometalation–iodinolysis and hydroiodination–reduction sequences, respectively.[20] Having both hydroxyl and vinyl halide functionalities, they integrate seamlessly into sequential phosphine–palladium catalysis. Our synthesis of these precursors follow well-established methods in the chemical literature and can be subdivided into six main categories: hydroiodination/reduction of alkynoates,[21] hydroalumination of propargyl alcohols,[22] Cu(I)-catalyzed carbocupration of propargyl alcohols,[23] Vilsmeier–Haack reaction of cycloalkanones,[24] partial reduction/Grignard addition[25] and oxidation/Grignard addition.[26]

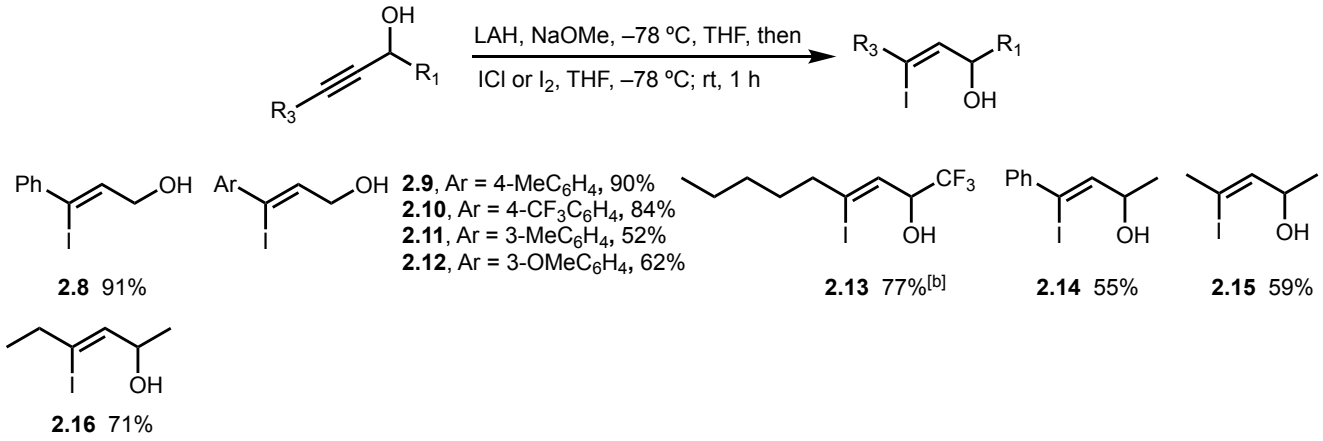
Table 2.1. Preparation of substrates via hydroiodination/reduction



Yields represent isolated yields obtained after FCC. [a] Can also be prepared via hydroalumination/iodination. [b] Unstable, used directly without purification.

The hydroiodination/reduction reaction was used to prepare **2.1**–**2.7** (Table 2.1). Substrates **2.1–2.5** can also be prepared from the corresponding propargyl alcohols using the hydroalumination/iodination reaction with either Red-Al or LAH and NaOMe in a 1:2 ratio. Unlike **2.2–2.5**, attempts to prepare **2.6** and **2.7** via hydroalumination/iodination resulted in rapid decomposition. Substrate **2.8** can also be prepared using this method.

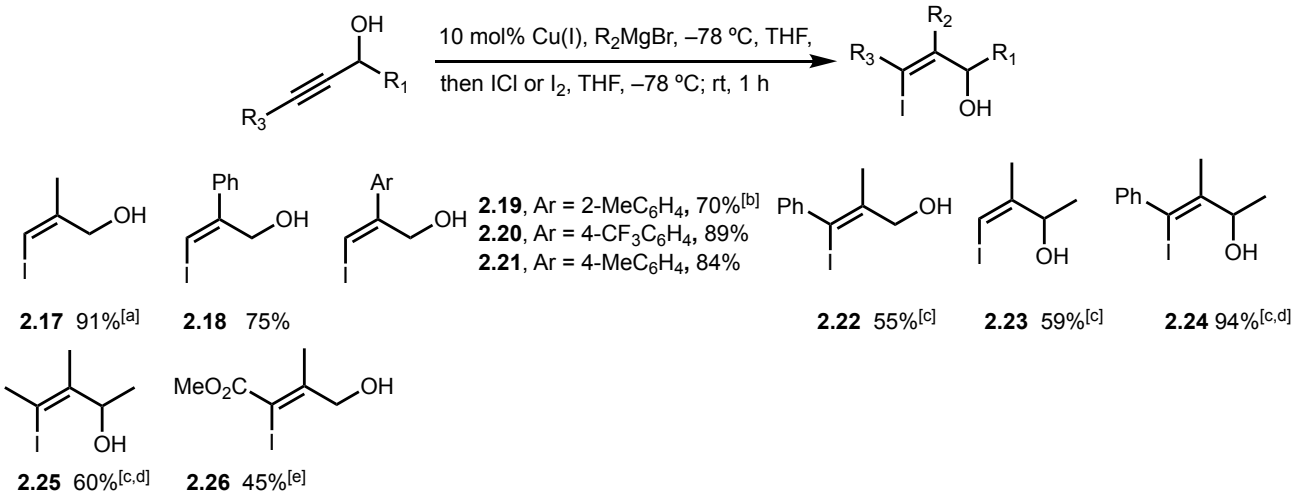
Table 2.2. Preparation of substrates via hydroalumination/iodination



Yields represent isolated yields obtained after FCC.[a] Red-Al can also be used in place of the LAH/NaOMe combination. [b] contains ~24% of linear regioisomer.

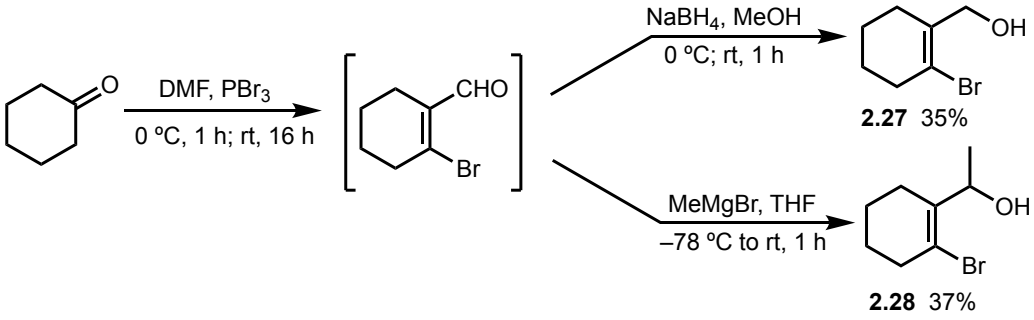
The hydroalumination/iodination reaction was used to prepare **2.8–2.16** (Table 2.2). In the case of **2.13**, small amounts of linear regioisomer that doesn't affect the Michael–Heck reaction is formed. While this type of reaction is typically done using Red-Al (Sodium bis(2-methoxyethoxy)aluminium hydride), similar results were obtained using LAH and NaOMe in a 1:2 ratio.

Table 2.3. Preparation of substrates via carbocupration/iodination



Yields represent isolated yields obtained after FCC. [a] 35 mol% CuBr used. [b] contains ~5% of linear isomer. [c] 50 mol% CuI used. [d] carbocupration done for 24 h. [e] 1.5 equiv CuI used.

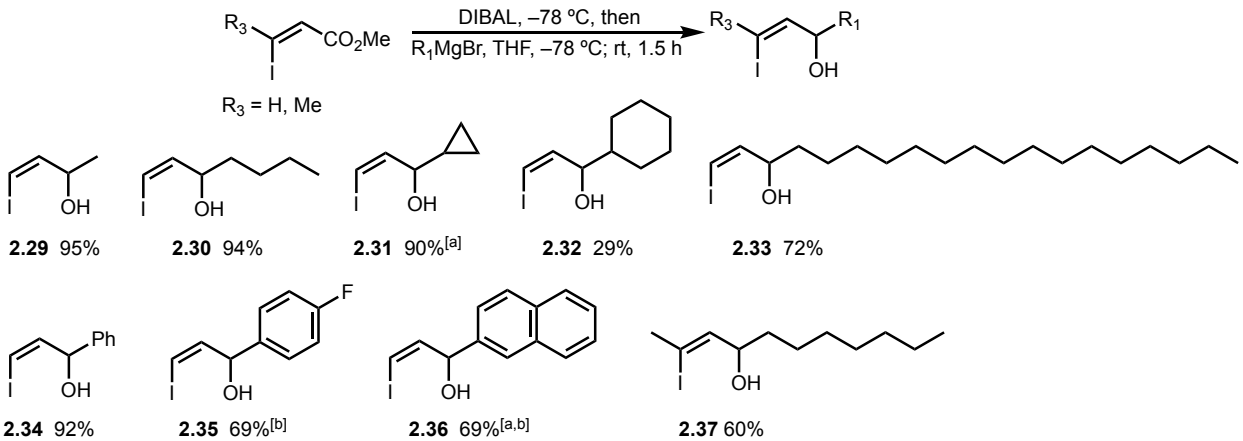
The Cu(I)-catalyzed carbocupration/iodination was used to prepare **2.17–2.26** (Table 2.1).While catalytic or substoichiometric amounts of either CuI or CuBr were able to promote this reaction, in the case of substrate **2.26**, a 2:1 ratio between MeMgBr and CuI was needed to suppress the competitive addition of MeMgBr to the ester carbonyl.[27] Carbometalation of bulkier substrates, such as secondary or tertiary propargylic alcohols, is known to produce small amounts of linear isomers as side products. In the case of **2.19**, the small amounts of linear regioisomer[28] formed did not affect the subsequent Michael–Heck reaction.



Scheme 2.2. Preparation of substrates via Vilsmeier–Haack reaction

For the cyclic β-bromoallylic alcohol substrates, Vilsmeier–Haack reaction of cyclohexanone was used to prepare substrates **2.27** and **2.28** (Scheme 2.2).

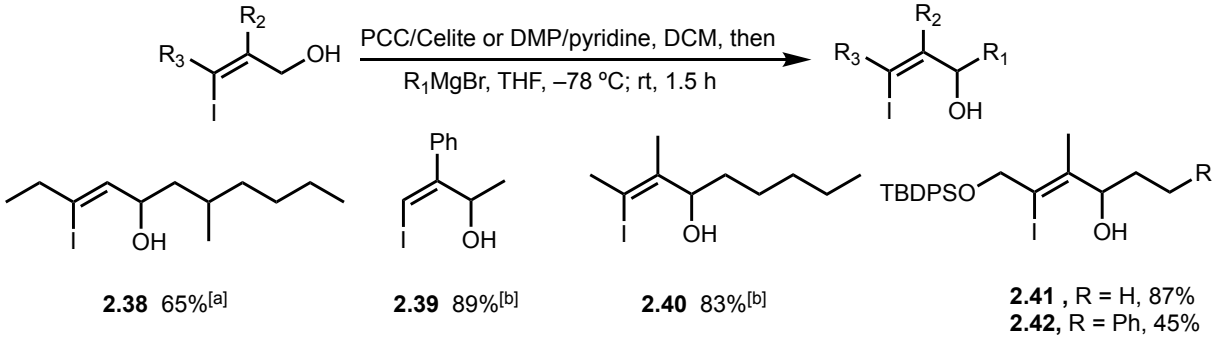
Table 2.4. Preparation of substrates via partial reduction/Grignard addition



Yields represent isolated yields obtained after FCC.[a] 2–2.5 equiv Grignard reagent used. [b] Decomposition observed after ~2 weeks under refrigeration.

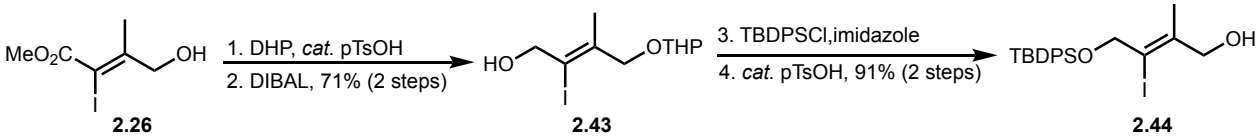
The partial reduction/Grignard addition reaction was used to prepare substrates **2.29–2.37** (Table 2.4). Substrates **2.35** and **2.36** were found to be unstable even when stored at –20 ºC. While **2.29** can also be prepared using the hydroalumination/iodination reaction, the other substrates are not compatible due to the presence of non-methyl substituents at C1 of the corresponding propargyl alcohol. For substrates with R_3 other than H or Me, the partial reduction/Grignard addition protocol is complicated by significant amounts of overreduction side product, thus necessitating the use of the oxidation/Grignard addition method below.

Table 2.5. Preparation of substrates via oxidation/Grignard addition



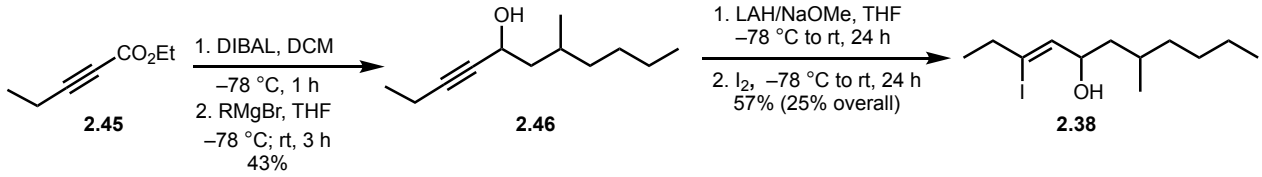
Yields represent isolated yields obtained after FCC. [a] with DMP and pyridine. [b] with PCC and Celite.

The oxidation/Grignard addition was used to prepare substrates **2.38–2.42** (Table 2.5). The use of Celite is necessary to facilitate isolation of the unstable intermediate β-iodoallylic aldehyde while the use of pyridine is crucial due to the acid sensitivity of the aldehyde. In the case of **2.41** and **2.42**, the starting alcohol was derived from **2.26** following a sequence of DHP protection, ester reduction, TBDPS protection and DHP deprotection.



Scheme 2.3. Preparation of **2.44** from **2.26**

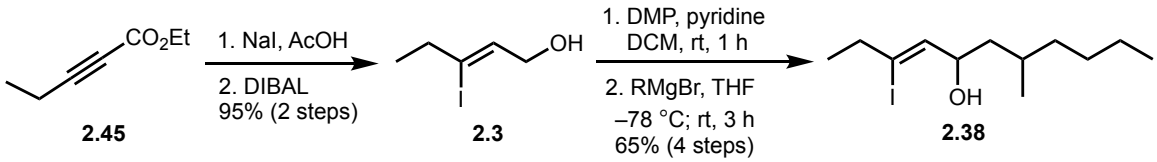
While the oxidation/Grignard addition sequence provided satisfactory yields for **2.39** and **2.40**, in the case of **2.38**, poor yields (< 34%) were obtained using this protocol. Initially, we envisioned preparing **2.38** from ethyl 2-pentynoate through a sequence of partial reduction/Grignard addition followed by hydroalumination/I_2 quenching (Scheme 2.4). Over-reduction of ethyl-2-pentynoate was, however, difficult to control and significant amounts of 2-pentyn-1-ol formed, despite careful control of the addition rate, temperature, and use of nonpolar solvents, resulting in a low yield of **2.46**. In addition, the steric effect of the long alkyl substituent at the C1 position of **2.46** resulted in the hydroalumination sometimes not reaching completion. Because **2.46** and **2.38** have the same value of R_f and would both have been reactive toward Michael addition, the inseparability of **2.43** and **2.35** presented a problem. Therefore, we devised an alternative approach.



2.45 **2.46** **2.38**

Scheme 2.4. Initial approach for the preparation of **2.38**

In this approach, we envisioned preparing **2.38** through hydroiodination/reduction of ethyl 2-pentynoate followed by oxidation/Grignard addition (Scheme 2.3). In contrast to our previous approach, the presence of the long alkyl chain in **2.46** would allow straightforward chromatographic separation from any unreacted **2.45**. A quick screen of common oxidants and bases revealed that the use of DMP and pyridine effected the desired oxidation/Grignard addition sequence in 68% overall yield.

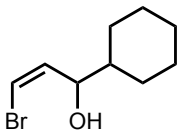
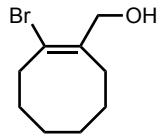
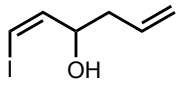
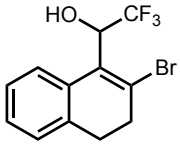
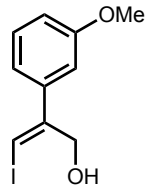
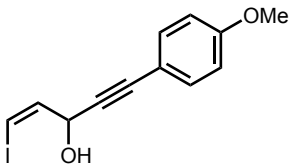
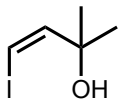
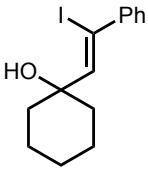


2.45 **2.3** **2.38**

Scheme 2.5. Alternative approach for the preparation of **2.38**

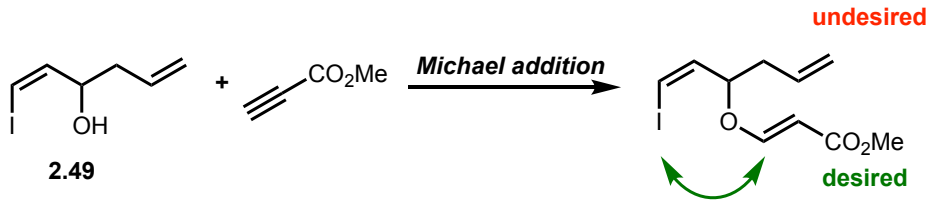
Substrates that were also prepared using one of the following methods above but were either unstable or incompatible with the Michael–Heck reaction are also listed in the table below.

Table 2.6. Incompatible haloalcohol substrates

No Heck reaction:	 **2.47** conditions A	 **2.48** conditions B, C	 **2.49** conditions A	 **2.50** conditions B, C
No Michael addition[a] or unstable Michael adduct:	 **2.51** conditions A	 **2.52** conditions A	 **2.53** conditions A	 **2.54** conditions A

[a] Tertiary alcohols do not usually undergo phosphine-catalyzed Michael addition to propiolates.

In the case of the allyl-substituted substrate, it is hypothesized that the presence of more than one reactive position for the Heck cyclization resulted in decomposition (Scheme 2.6):



2.49

Scheme 2.6. Rationalization for the incompatibility of **2.49**

On the other hand, given that the CF_3 group in **2.13** and the fused cycloalkyl groups in **2.27** and **2.28** were compatible with the reaction, it is not clear why substrate **2.50** is incompatible. While the 3-anisyl group was compatible at the C3 position of the (*Z*)-3-iodo-β-allylic alcohol (as in **2.12**), it remains unclear why substitution of 3-anisyl at the C2 position of the alcohol would result in no Michael addition, even when the more reactive 3-butyn-2-one was used as Michael acceptor. In the case of **2.52**, Michael addition formed an unstable Michael adduct that underwent rapid decomposition in the presence of base. Having demonstrated that both primary and secondary (*Z*)-3-haloallylic alcohols were suitable substrates for the Michael–Heck reaction, we wondered whether corresponding tertiary alcohols could be used to obtain furanylidene derivatives. Unfortunately, neither **2.53** nor **2.54** underwent Michael addition, consistent

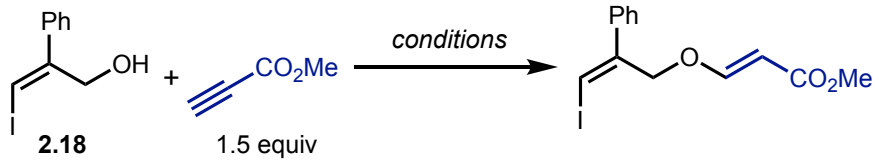
with the fact that literature precedents for phosphine-catalyzed Michael additions of tertiary alcohols with propiolates are rare or nonexistent.[29]

2.4 Optimization of the Michael–Heck Reaction

To separate the effects of each reaction parameter on the Michael and Heck reactions, these reactions were examined individually (Table 2.7). To facilitate reaction monitoring, a UV-active known compound that could be prepared in one step from cheap and commercially available chemicals was chosen. In addition, we suspected a substituent at the C2 position of the (*Z*)-3-iodo-2-propen-1-ol precursor would exert less of a steric effect on the Heck cyclization than would a substituent at either the C1 or C3 position. Because of its slight volatility, 1.5 equivalents of methyl propiolate (b.p. = 104 °C) were used.

Initially, we chose the air-stable solid catalyst PPh_3, but a long reaction time was required (entry 1). Given that the resulting vinyl ether intermediates were not particularly stable (light-sensitive), we sought reaction conditions that would expedite product formation. Taking inspiration from Inanaga's trialkylphosphine-catalyzed Michael addition of alcohols onto propiolates,[30] we selected tributylphosphine instead. To our delight, the reaction was complete within 15 min and the Michael adduct was obtained in excellent yield (entry 2). Although the reaction failed to reach completion in THF (entry 3), toluene proved to be a good solvent for the Michael addition (entry 4). To examine the possibility of performing a one-pot tandem Michael–Heck reaction, we examined solvents of higher boiling point (MeCN and toluene). Although the reaction failed to reach completion after 15 min at rt (entry 5), heating under reflux in MeCN furnished the Michael adduct in excellent yield (entry 6). The use of toluene as the solvent provided similar results (entry 7). Therefore, we considered the parameters in entry 2 to be the optimal conditions.

Table 2.7. Optimization of the Michael addition between **2.18** and methyl propiolate[a,b]



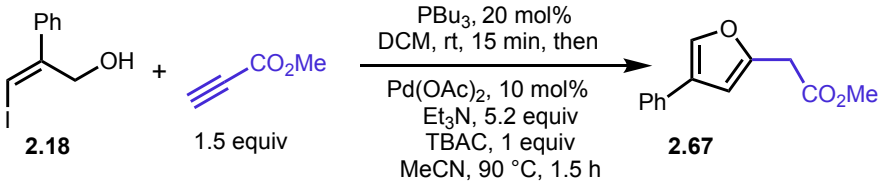
Entry	Temp. (°C)	Time	Phosphine (20 mol%)	Solvent	Results (%)[c,d]
1	rt	16 h	PPh_3	CH_2Cl_2	71
2	rt	15 min	PBu_3	CH_2Cl_2	96
3	rt	16 h	PBu_3	THF	product: **1m** = 1: 0.3
4	rt	15 min	PBu_3	toluene	72
5	rt	15 min	PBu_3	MeCN	product: **1m** = 1:1.4
6	90 °C	15 min	PBu_3	MeCN	95
7	90 °C	15 min	PBu_3	toluene	90

[a] Unless otherwise indicated, the reactions were conducted with anhydrous solvents under an Ar atmosphere. [b] Reactions were performed on 0.1 mmol scale. [c] Yields refer to isolated yields after passing through a silica plug. [d] Product:**1m** ratios were determined from ^{1}H NMR spectra.

Having determined the optimal conditions for the Michael addition of **2.18** onto methyl propiolate, these conditions were used to examine the Michael–Heck reaction (Table 2.8). Entries 2–4 indicate that organic bases were preferred over inorganic ones, with triethylamine (entry 1) outperforming Hünig's base (entry 2). While 2 equivalents of triethylamine were sufficient to promote the reaction (entry 4), 2 equivalents of K_2CO_3 produced the furan **2.67** in low yield (entry 4) and 5.2 equivalents resulted in complete decomposition. Therefore, we used 5.2 equivalents of anhydrous triethylamine to examine the effects of solvents. Entries 5–7 reveal that although toluene (entry 5) significantly outperformed dioxane and THF (entries 6,7), the yield obtained was slightly lower than that in MeCN. Entries 8–13 reveal the effects of additives. In general, tetrabutylammonium halides (entries 8 and 9) were more effective than simple alkali metal salts (entries 10–12), with TBAI (entry 9) being almost as effective as TBAC. The complete absence of an additive was detrimental to the reaction (entry 13). Finally, we examined the effects of the palladium source. While $Pd(PPh_3)_4$ failed to promote the Heck reaction

(entry 15), $Pd_2(dba)_3$ furnished the furan **2.67** in modest yield (entry 14). $PdCl_2$ (entry 16) was less effective than $Pd(OAc)_2$, presumably because of its poor solubility in the reaction medium. While variations of the solvent, base, additive, and palladium source were not successful at pushing the yield to greater than 90%, we found that the use of non-anhydrous triethylamine furnished the furan **2.67** in excellent yield (entry 17).

Table 2.8. Optimization of the Michael–Heck reaction[a,b]



Entry	Deviation from standard conditions	Yield (%)[c]
1	none	90
2	*i*Pr_2NEt_2	71
3	2 equiv[d] K_2CO_3	42
4	2 equiv NEt_3	75
5	toluene instead of MeCN	86
6	dioxane instead of MeCN	49
7	THF instead of MeCN	41
8	TBAB instead of TBAC	52
9	TBAI instead of TBAC	96
10	LiCl instead of TBAC	41
11	KOAc instead of TBAC	45
12	NaOAc instead of TBAC	48
13	no additive	38
14	5 mol % $Pd_2(dba)_3$ instead of 10 mol % $Pd(OAc)_2$	41
15	5 mol % $Pd(PPh_3)_4$ instead of 10 mol % $Pd(OAc)_2$	Michael adduct only
16	$PdCl_2$ instead of $Pd(OAc)_2$	62
17	non-anhydrous NEt_3	97

[a] Unless otherwise indicated, all reactions were conducted with anhydrous solvents under an Ar atmosphere. [b] Reactions were performed on 0.1 mmol scale. [c] All yields refer to isolated yields. [d] Decomposition observed when 5.2 equiv K_2CO_3 was used.

Table 2.9 revealed that the use of anhydrous triethylamine led to the formation of **2.67** in 90% yield (entry 1), whereas the use of non-anhydrous triethylamine produced it in 97% yield (entry 17). To determine the amount of water that would optimize the reaction, we added water to anhydrous triethylamine and observed its effects on the Heck reaction (Table 2.9). Entries 1–3 reveal that triethylamine containing 1% water produced the best results, suggesting that the non-anhydrous triethylamine used had a water content of approximately 1%.

Table 2.9. Effect of water on the Michael–Heck reaction

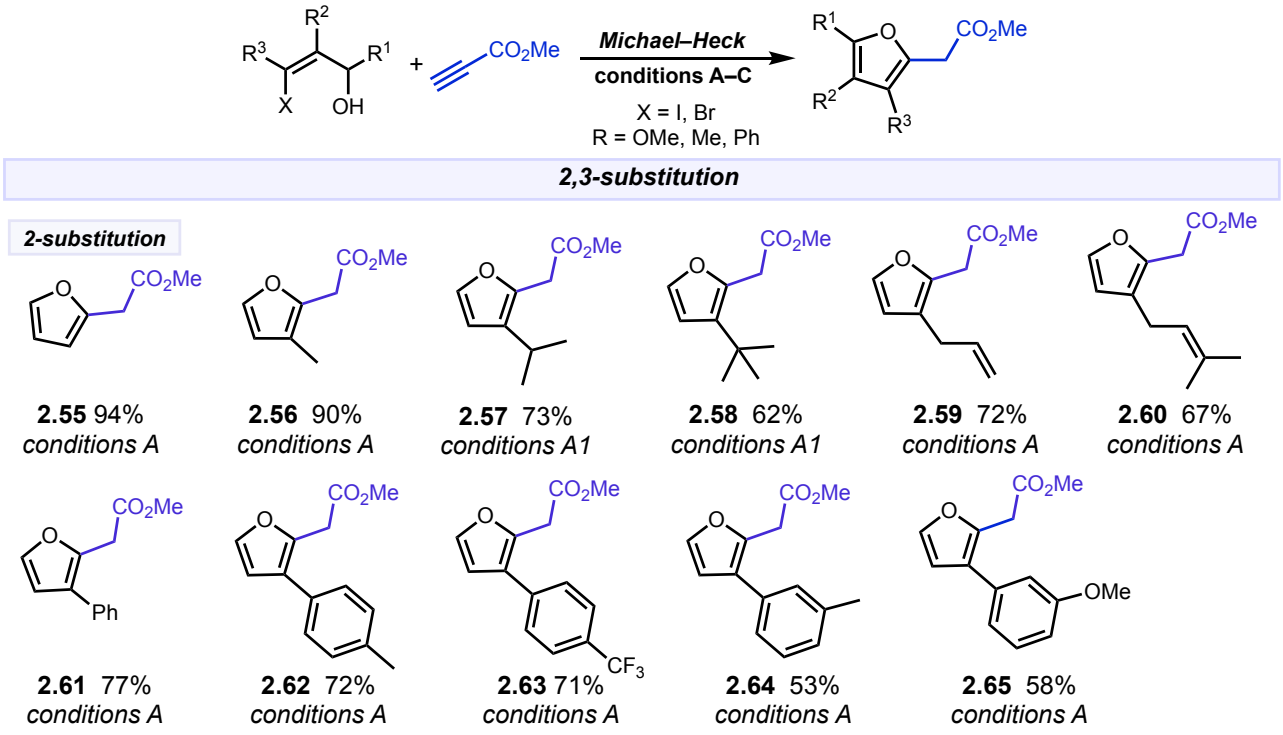
Entry	Amount of water added (%)[a]	Yield (%)
1	0.5	85
2	1	97
3	2	92

[a] The percentage of water added is the volume relative to the total volume of triethylamine.

2.5 Substrate Scope of the Michael–Heck Reaction

Having established the ideal reaction conditions, the substrate scope of the Michael–Heck reaction was examined (Table 2.10). Using conditions A, 2-substituted furan **2.55** was obtained in 94% yield. These conditions were also compatible with both C3-alkyl and -aryl groups, delivering the 2,3-disubstituted furans **2.56–2.65** in good yields (53–90%). Elevated temperatures were required in the cases of the bulky 3-isopropyl– and 3-*tert*-butyl–substituted furans **2.57** and **2.58** (conditions A1). Notably, potentially reactive allyl and prenyl groups were inert to the Heck conditions, delivering **2.59** and **2.60**, respectively, in good yields. While both electron-donating and -withdrawing substituents on the C3-phenyl ring were tolerated, the reaction was sensitive to steric effects, with *meta* substituents (**2.64**, **2.65**) giving substantially lower yields than *para* (**2.62**, **2.63**) ones.

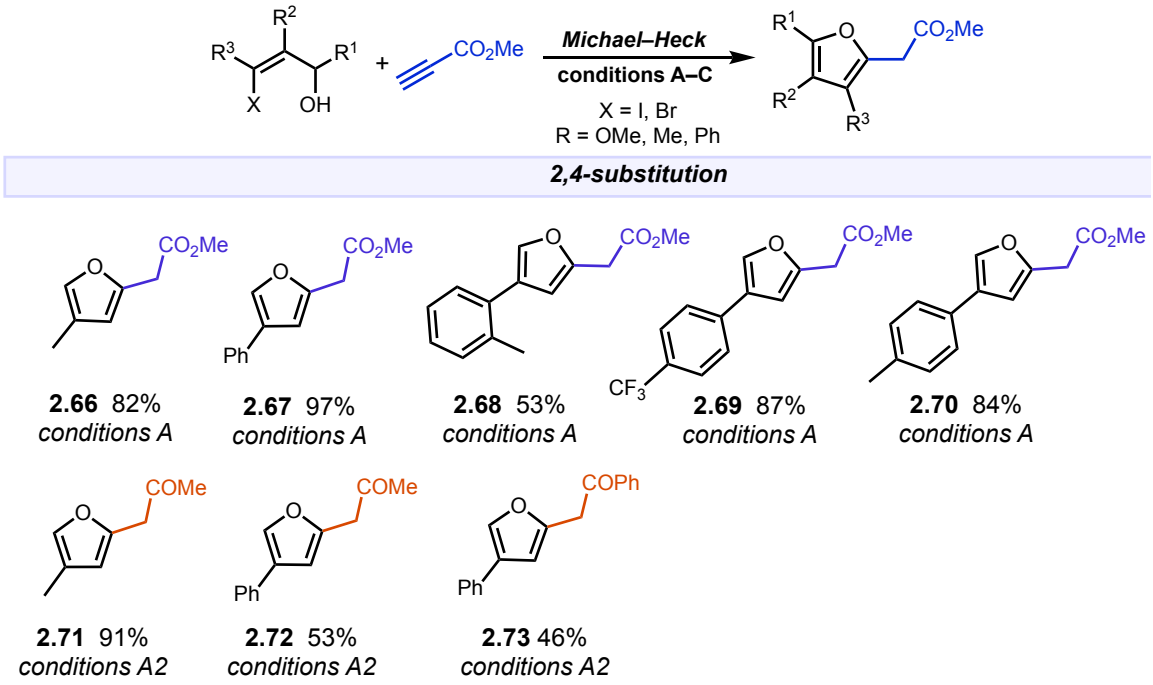
Table 2.10. Substrate scope for 2,3-disubstituted furans



A similar trend occurred among the 2,4-disubstituted furans, where C2-aryl substrates containing *para* electron-withdrawing (**2.69**) and -donating (**2.70**) groups outperformed an *ortho*-substituted one (**2.68**). While both C4-alkyl (**2.66**) and -aryl (**2.67**) groups were compatible, the use of 3-butyn-2-one (**2.71**, **2.72**)

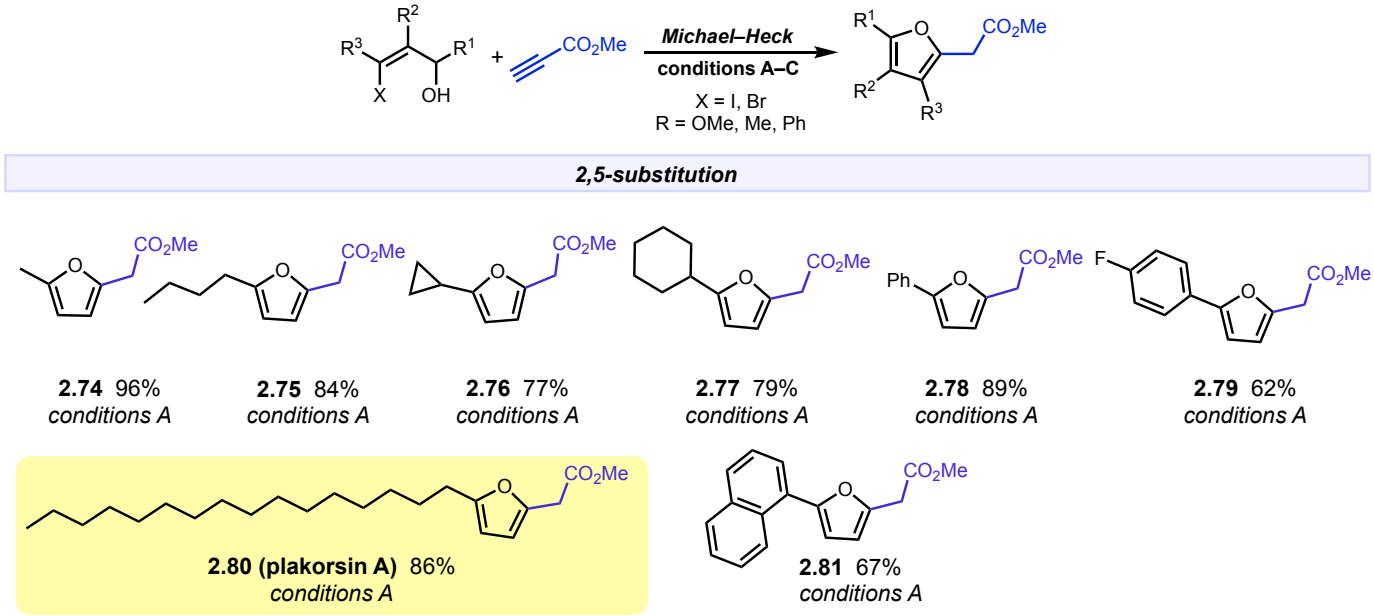
and ethynyl phenyl ketone (**2.73**) in place of methyl propiolate required slow addition of the alkyne (conditions A2) to prevent rapid polymerization of the Michael acceptor under phosphine catalysis. The ease with which the starting (*Z*)-3-halo-2-propen-1-ol could be functionalized enabled facile access to both 2,3- and 2,4-functionalized furans, which are difficult to obtain regioselectively when using conventional methods.[31]

Table 2.11. Substrate scope for 2,4-disubstituted furans

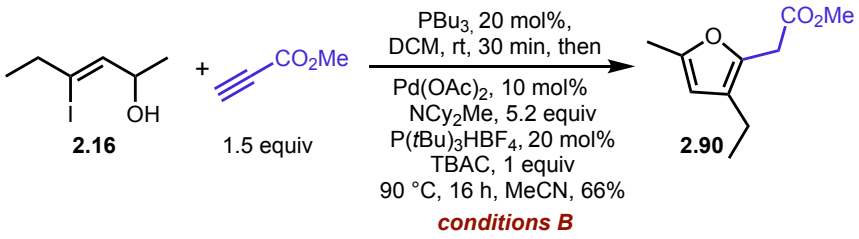


Conditions A were also applicable for the synthesis of 2,5-disubstituted furans, where C5-alkyl (**2.74**, **2.75**), -cycloalkyl (**2.76**, **2.77**), and -aryl (**2.78**, **2.79**, **2.81**) groups were all compatible (Table 2.11). No ring-opening of the cyclopropyl ring (**2.76**) was observed, and both bulky cyclohexyl (**2.77**) and 1-naphthyl (**2.81**) groups were compatible (Table 2.12). Plakorsin A,[8a] an F-acid derivative from the marine sponge *P. simplex,* was also obtained in 86% yield.

Table 2.12. Substrate scope for 2,5-disubstituted furans



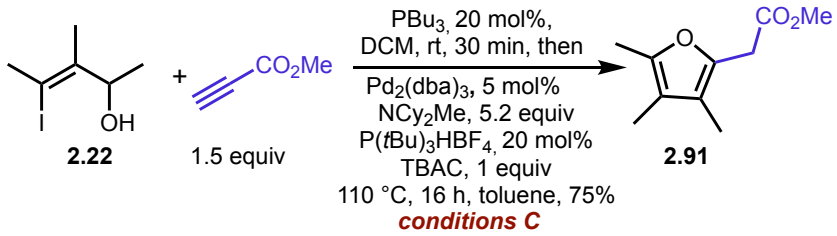
We turned our attention to the preparation of tri- and tetrasubstituted furans (Table 2.13). While conditions A1 delivered the aryl-containing trisubstituted furans **2.82**, **2.84**, and **2.87** in good yields, they failed for di- or trialkyl-substituted substrates. Because conditions A worked well for the preparation of furans containing at least one electron-withdrawing group, we attempted to make the Michael acceptor more electron-deficient, but detected no product and obtained copious amounts of polymerized Michael acceptor.[17c] Intrigued by Fu's report on the use of air-stable trialkylphosphonium salts for various cross-couplings of deactivated aryl chlorides and bromides,[32] we adapted those conditions for our Michael–Heck reaction (Scheme 2.7).



Scheme 2.7. Use of conditions B for the synthesis of trialkyl furans

Using P(*t*-Bu)$_3$HBF$_4$ along with Cy$_2$NMe as the base, trialkyl furans with fused cycloalkyl (**2.83**) and linear alkyl (**2.85, 2.88**–**2.90**) substituents could be prepared in moderate to good yields. Plakorsin D methyl ester,[7] a polyketide isolated from the marine sponge *P. simplex*, was obtained in 64% yield.

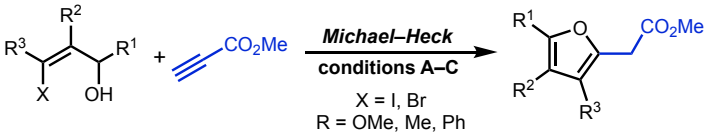
Significantly, the medicinally relevant CF_3 group was compatible, furnishing the furan **2.86** in good yield.[33,34] While these conditions failed for the synthesis of tetraalkyl furans, a slight increase in the reaction temperature to 110 °C (from 90 °C for conditions B) and the use of $Pd_2(dba)_3$ as a catalyst enabled the preparation of tetraalkyl furans in good yields (Scheme 2.8)

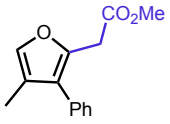
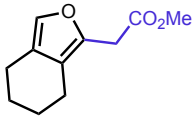
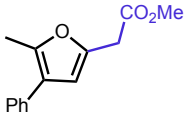
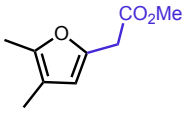
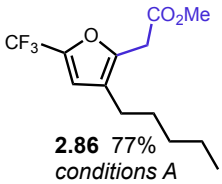
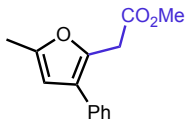


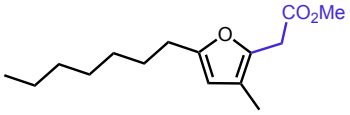
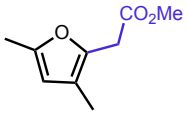
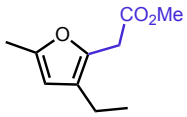
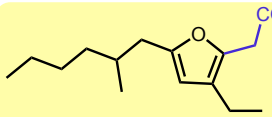
Scheme 2.8. Use of conditions C for the synthesis of tetraalkyl furans

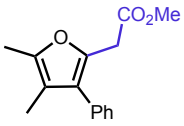
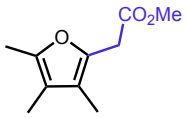
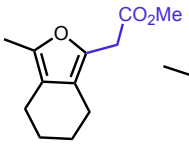
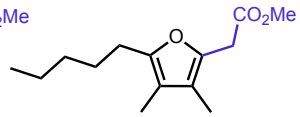
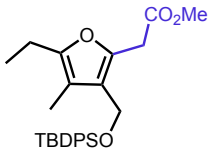
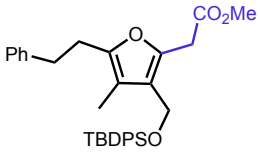
While the presence of a C3-aryl group led to a slightly diminished yield (**2.91**), tetraalkyl furans with either fused cycloalkyl (**2.93**) or linear alkyl (**2.92**, **2.94**) groups were prepared in good yields. In the cases of **2.83** and **2.93**, we used a 3-bromoallylic alcohol substrate, further highlighting the versatility of this method. Finally, furans substituted with four different alkyl groups (**2.95** and **2.96**) could be prepared in good yields. To the best of your knowledge, this is the first report of a methodology that results in the synthesis asymmetrically-substituted tetraalkyl furans. Among the >90 reports on the synthesis of tetrasubstituted furans, only three were amenable to the preparation of tetraalkyl furans,[14] none of which were applicable to the synthesis of furans of four different alkyl substituents. The compatibility of the silyl ether groups is also significant, indicating potential application of this method towards total synthesis of complex furan natural products.

Table 2.13. Substrate Scope for tri- and tetrasubstituted furans



2,3,4-substitution		*2,4,5-substitution*		*2,3,5-substitution*	
					
2.82 75% *conditions A1*	**2.83** 96%[c] *conditions B*	**2.84** 79% *conditions A1*	**2.85** 93% *conditions B*	**2.86** 77% *conditions A*	**2.87** 78% *conditions A1*

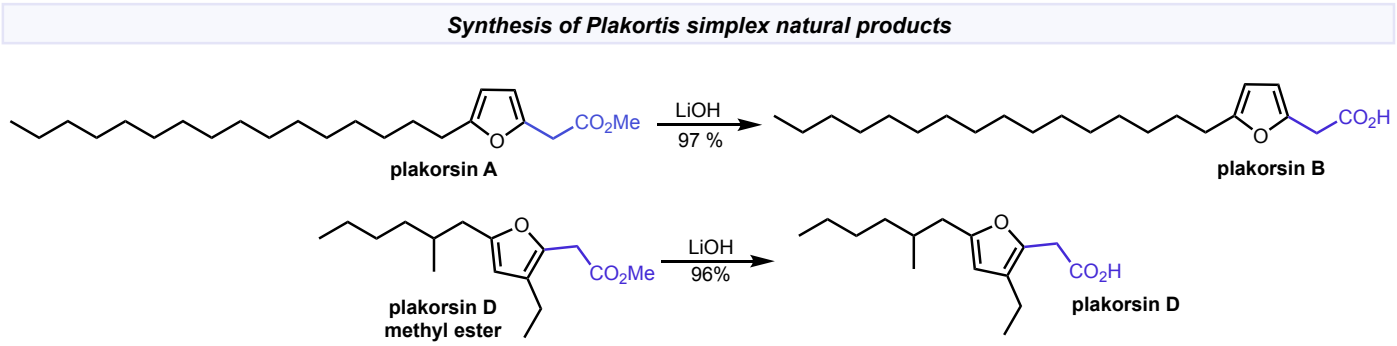
2,3,5-substitution			
			
2.88 70% *conditions B*	**2.89** 81% *conditions B*	**2.90** 66% *conditions B*	**2.91 (plakorsin D methyl ester)** 64% *conditions B*

2,3,4,5-substitution					
					
2.91 54% *conditions B*	**2.92** 75% *conditions C*	**2.93** 69%[c] *conditions C*	**2.94** 89% *conditions C*	**2.95** 86% *conditions C*	**2.96** 70% *conditions C*

[a] All reactions were performed under Ar using anhydrous solvents. [b] Isolated yields after flash-column chromatography. [c] X = Br

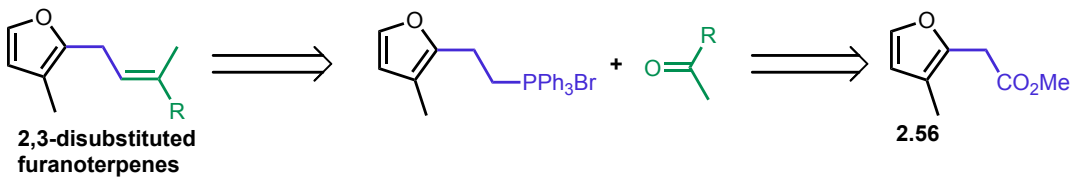
2.6 Applications of the Michael–Heck Reaction

Having demonstrated the wide substrate scope of the Michael–Heck reaction, we explored its applications in the total syntheses of bioactive furans (Scheme 2.9). Hydrolysis of plakorsin A produced plakorsin B, known to exhibit strong cytotoxicity against colon carcinoma (COLO-250) cells and weak activity against nasopharyngeal carcinoma (KB-16) cells.[8a] Previous approaches to plakorsins A and B have included Lewis acid–mediated 5-*endo*-dig cyclization of 3-alkyne-1,2-diols,[35] sequential functionalization of furan through lithiation/alkylation,[36] and electrophilic aromatic substitution of methyl 2-furylacetate[37] and 2-cyanomethylfuran,[37,38] the latter of which suffered from highly variable yields (23–92%). On the other hand, our Michael–Heck approach reliably furnished plakorsin A from methyl propiolate in 62% yield over three steps. Basic hydrolysis of the ester in plakorsin D methyl ester then furnished plakorsin D—its first total synthesis.[39]



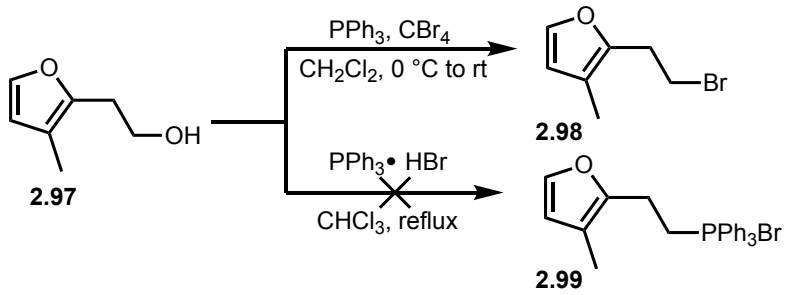
Scheme 2.9. Synthesis of *P. simplex* natural products

Next, we moved on to the synthesis of 2,3-disubstituted furanoterpenes. We envisioned that these could be derived from an *E*-selective Wittig olefination between phosphonium bromide elaborated from furan **2.56** and a ketone derivative (Scheme 2.10).



Scheme 2.10. Retrosynthetic analysis for the 2,3-disubstituted furanoterpenes

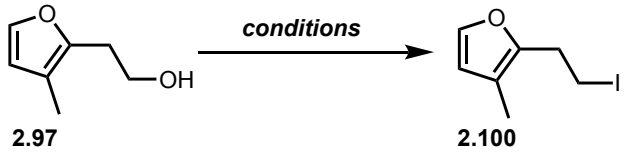
Therefore, following literature procedures, reduction of the ester group of the furan **2.56** produced an alcohol intermediate,[40] which we transformed to a halide. Surprisingly, the bromide was unstable,[41] decomposing to a black tarry solid within ten minutes at room temperature. To avoid having to isolate the unstable bromide, we used $PPh_3 \cdot HBr$[42] to convert the alcohol directly to phosphonium bromide **2.99** through protonation, *in situ* formation of the bromide, and displacement by PPh_3. Disappointingly, rapid decomposition occurred, so we sought alternative leaving groups (Scheme 2.11).



Scheme 2.11. Attempts to prepare bromide **2.98** and phosphonium bromide **2.99**

Intrigued by a literature report regarding the relative stabilities of 2-furfuryl halides, we attempted to prepare the corresponding iodide derivative through an Appel reaction. In stark contrast to the instability of the bromide, the corresponding iodide was stable. A quick screen of various solvents indicated that THF was the ideal solvent for this transformation, furnishing the desired iodide efficiently in excellent yield (Table 2.14). With a robust and high-yielding route to the iodide in hand, we optimized the preparation of the corresponding phosphonium iodide.

Table 2.14. Optimization of the preparation of iodide **2.100**



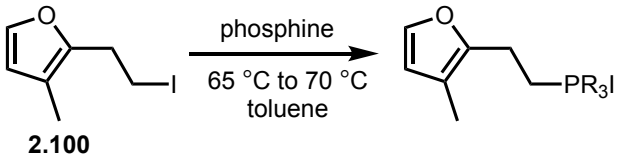
2.97 **2.100**

Entry	Conditions	X	Yield (%)
1	PPh_3, CBr_4, DCM, 0 °C, 1 h	Br	83[d]
2	PPh_3, I_2, imidazole, DCM, rt, 1 h	I	54
3	PPh_3, I_2, imidazole, MeCN, rt, 1 h	I	56
4	PPh_3, I_2, imidazole, Et_2O, rt, 1 h	I	57
5	PPh_3, I_2, imidazole, MeCN/Et_2O, rt, 1 h	I	56
6	PPh_3, I_2, imidazole, THF, rt, 15 min	I	98

[a] Unless otherwise indicated, all reactions were conducted with anhydrous solvents under argon atmosphere. [b] The reactions were all carried out on 1 mmol scale. [c] All yields refer to isolated yields. [d] Complete decomposition within 10 minutes at room temperature.

A screen of common phosphines [PPh_3, PPh_2Et, PPh_2Me, $PPhMe_2$, PBu_3, P(*p*-tol)$_3$] indicated that the reaction efficiency increased upon increasing the electron density at phosphorus, with the fastest reaction occurring with PBu_3 (4 h, 99%) and the slowest with PPh_3 (5 days, 58%). Unfortunately, while allylic tributylphosphonium halides are known to act as Wittig reagents,[43] their alkyl analogs are not. Therefore, phosphines with at least one aryl group were used. Of the phosphines investigated, PPh_2Me gave the best results (1 h, 84%). However, the presence of P-alkyl groups would allow ylide formation to occur at more than one site, so we returned to triarylphosphines. To make up for the decreased nucleophilicity of triarylphosphines, we performed the reactions at a slightly higher temperature (80–85 °C instead of 65–70 °C). Although P(*p*-tol)$_3$ gave a better yield (87%, 1 h) of the phosphonium salt than did PPh_3 (53%, 1 h), the resulting product was sticky and difficult to handle. Because PPh_3 melts at 80 °C,[44] performing the reaction at temperatures greater than 80 °C allowed it to be used as the solvent. Therefore, with 2.5 equivalents of PPh_3 at 80–85 °C for 1 h, we obtained the phosphonium iodide in 76% yield (Table 2.15).

Table 2.15. Optimization of the preparation of phosphonium iodide **2.101**



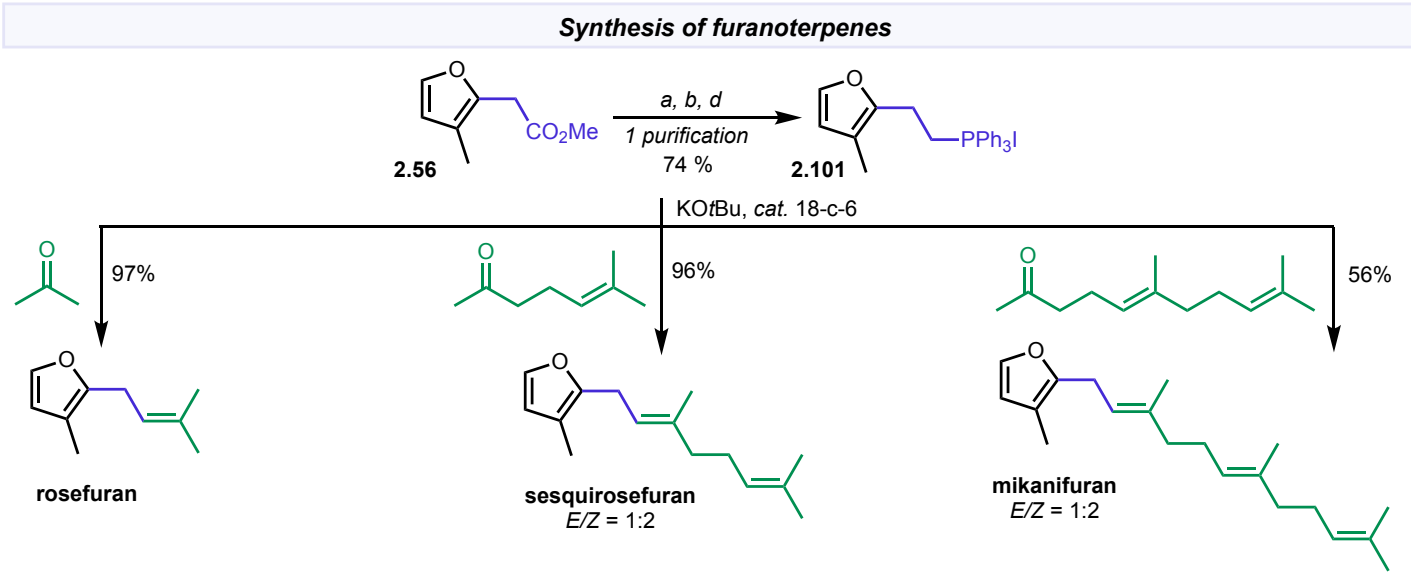
2.100

Entry	Phosphine[d]	Time	Yield (%)
1	PPh_3	5 days	58
2	PPh_3, neat	5 days	57
3	PPh_2Et	5 days	33
4	PPh_2Et, neat	5 days	93
5	$PPhMe_2$	16 h	46
6	PBu_3	4 h	99
7	PPh_2Et, neat	1 h	81
8	$PPhMe_2$, neat	1 h	84
9	PPh_2Me, neat	1 h	96
10[e]	P(*p*-tol)$_3$, neat	1 h	87
11[e]	PPh_3, neat	1 h	53
12[e,f]	PPh_3, neat	1 h	76

[a] All reactions were done in 4 mL sample vials. [b] The reactions were all carried out on 0.4–1 mmol scale. [c] 0.6 mL toluene used in entries 1, 3, 5, 6. [d] 1 equivalent phosphine used in entries 1–11. [e] Done with 80–85 °C. [f] with 2.5 equiv PPh_3.

With a high yielding route to the prerequisite phosphonium iodide in hand, we were set to carry out the homologation reaction (Scheme 2.11). Therefore, Wittig reaction under Boden's conditions[45] furnished rosefuran in 97% yield. To prevent complications resulting from lithiation of the free C5 position of **2.101**, we chose KO*t*Bu as the base. We used the same approach for the syntheses of sesquirosefuran[46] and mikanifuran.[47] In these cases, excess ketone and high reaction concentrations were necessary to prevent the formation of 3-methyl-2-vinylfuran as a side product (presumably resulting from E2 elimination of **2.101**).[48] Under these conditions, we obtained sesquirosefuran in 96% as a mixture of *E*/*Z* isomers. Despite efforts to selectively obtain the *E*-isomer,[49] the inherent *Z*-selectivity of Wittig reactions with unstabilized ylides resulted in a mixture of isomers.[50] We also used these conditions to prepare

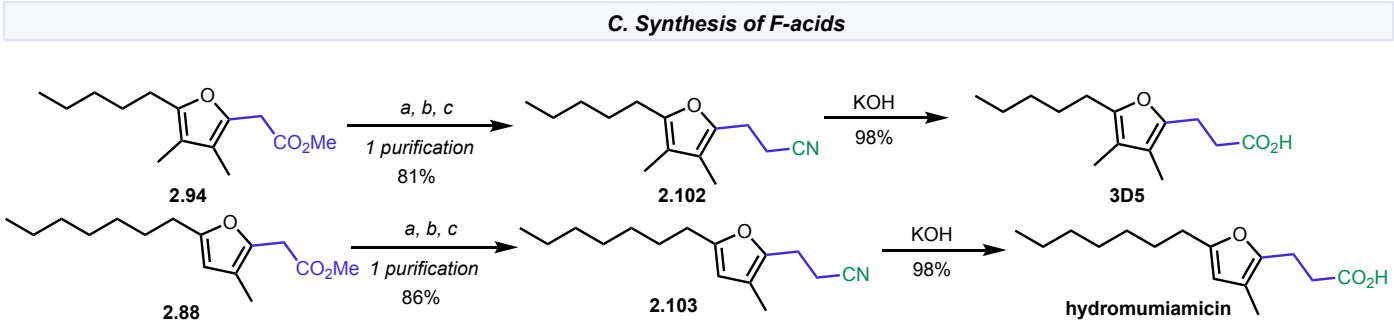
mikanifuran in 56% yield as a mixture of *E*/*Z* isomers. In addition to being used in fragrances and spices, rosefuran is also a female sex pheromone in the acarid mite, *Caloglyphus* sp., capable of triggering sexual excitation at less than 100 ng.[6a,b] While mikanifuran has no known biological activity, sesquirosefuran displays significant cytotoxicity against HeLa cells *in vivo*.[38] The commercial importance and biological activity of rosefuran has inspired several ingenious syntheses of it and related furanoterpenes. These strategies can be classified into alkylation, transition metal–catalyzed methods, functionalization of cyclic precursors, and cyclization of linear precursors.[51]



Scheme 2.12. Synthesis of 2,3-disubstituted furanoterpenes

For the total synthesis of **3D5**, a unique F-acid found in the soft corals *S. glaucum* and *S. gemmatun* (Scheme 2.8), we employed a sequence of reduction, Appel reaction, and cyanation of the furan **2.94** to produce the nitrile **2.102**, which underwent hydrolysis in 98% yield to give the F-acid.[52] Similarly, the furan **2.88** was converted into the nitrile **2.103**, which was hydrolyzed in 98% yield to produce hydromumiamicin,[53] an F-acid derivative in the actinomycete strain *Mumia sp*. YSP-2-79 with antimicrobial and antioxidant activity. While several syntheses have been reported of F-acids featuring long carboxyalkyl chains, these total syntheses are the first for F-acids having a three-carbon carboxyalkyl chain.[54] While many efficient methods are available for the syntheses of 2,3-disubstituted furanoterpenes,

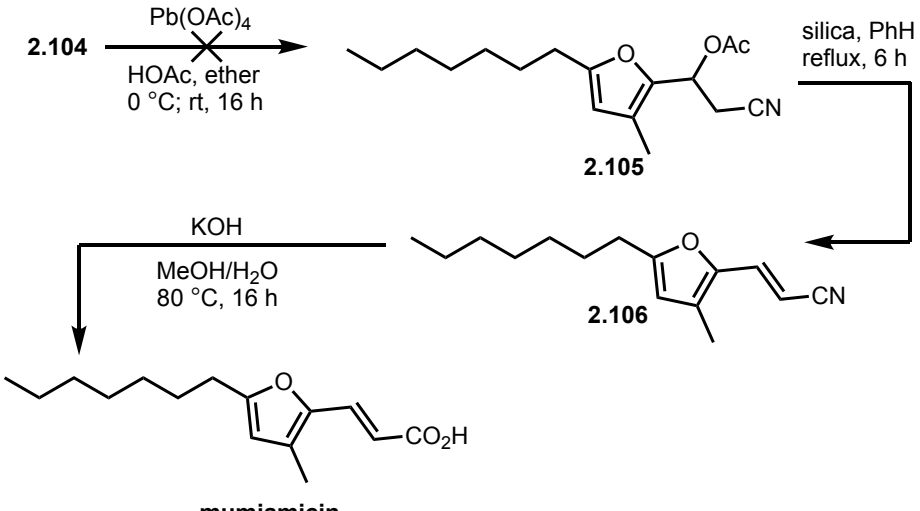
F-acids, and their derivatives, only this present approach is applicable to the preparation of all three types of natural products.



Reaction conditions: a) $LiAlH_4$, Et_2O, 0 °C, 15 min. b) PPh_3, I_2, imidazole, THF, rt, 15 min. c) KCN, acetone/water, reflux, 16 h. d) PPh_3, neat, 1 h, 80–85 °C

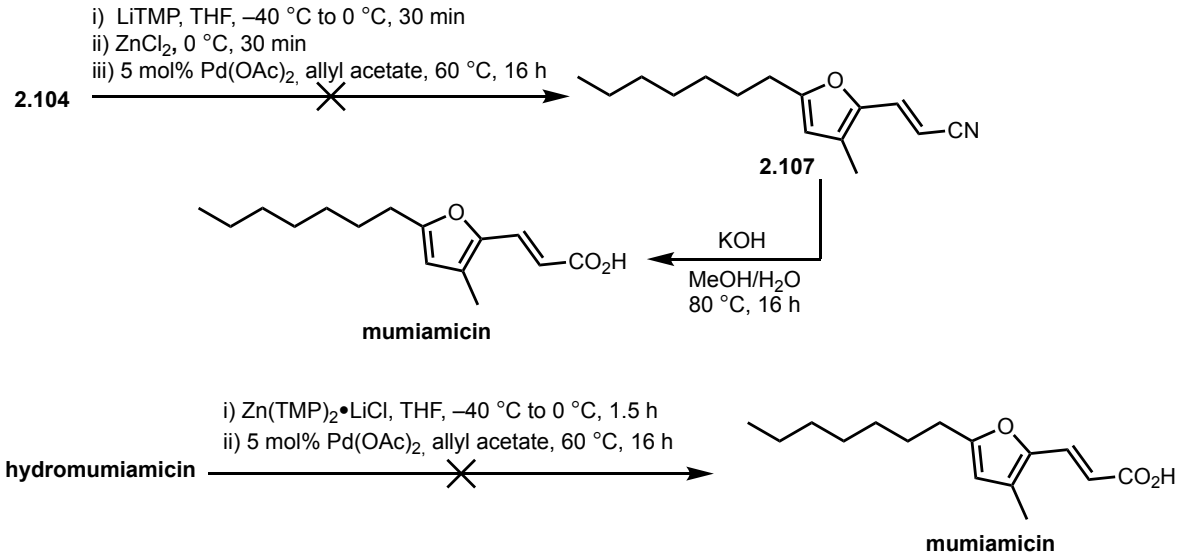
Scheme 2.13. Synthesis of Furan Fatty Acids

Attempts were also made towards the preparation of mumiamicin, an unique F-acid derivative with an unsaturated carboxylic acid side chain. In Tsukasa's synthesis of α-clausenan,[55] benzylic acetoxylation of the methyl 2-carboxypropyl side chain of a 2,3-disubstituted furan followed by elimination with SiO_2 furnished a α, β-unsaturated ester that was transformed to α-clausenan after two steps. We attempted to carry out the same transformation on **2.104**, hoping that it would deliver the corresponding α, β-unsaturated cyanide, which would produce mumiamicin after basic hydrolysis (Scheme 2.14). However, the benzylic acetoxylation occurred at the more electron-rich heptyl side chain instead of at the cyanopropyl side chain.



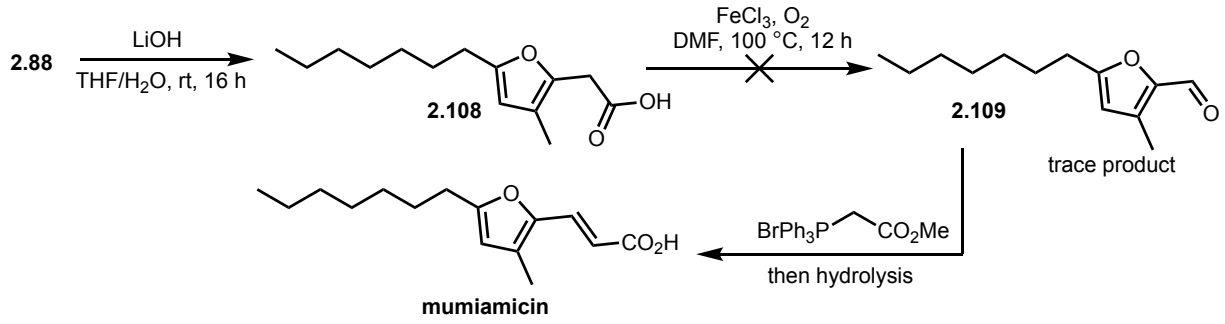
Scheme 2.14. Attempts to prepare mumiamicin via benzylic oxidation/elimination

In Newhouse's reports on the palladium-catalyzed α,β-dehydrogenation of carbonyl compounds,[56] various unsaturated nitriles and carboxylic acids were prepared in good yields. We attempted to apply this to the preparation of mumiamicin (Scheme 2.15). Unfortunately, application of the conditions for α, β-dehydrogenation of **2.104** failed to furnish the corresponding unsaturated nitrile and rapid decomposition was observed upon addition of LiTMP. Suspecting that strong alkyllithium bases might not be compatible with **2.104**, we attempted to carry out the dehydrogenation with hydromumiamicin using a milder base. In this case, however, no reaction occurred and hydromumiamicin was recovered.



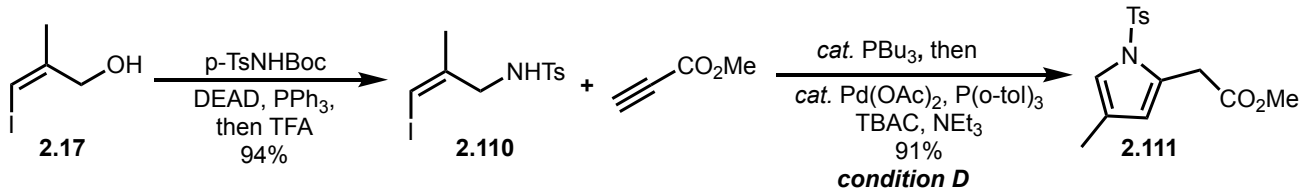
Scheme 2.15. Attempts to prepare mumiamicin via Pd-catalyzed α, β-dehydrogenation

Here, we attempted to carry out the 1-carbon dehomologation of the carboxylic acid derivative of **2.88** using iron-catalyzed oxidative decarboxylation[57] to obtain the corresponding furfural derivative. Unfortunately, extensive decomposition (presumably due to oxidation of the furan ring or the heptyl side chain) was observed and only trace amounts of the desired aldehyde was detected (Scheme 2.16).



Scheme 2.16. Attempts to prepare mumiamicin via oxidative decarboxylation/Wittig homologation

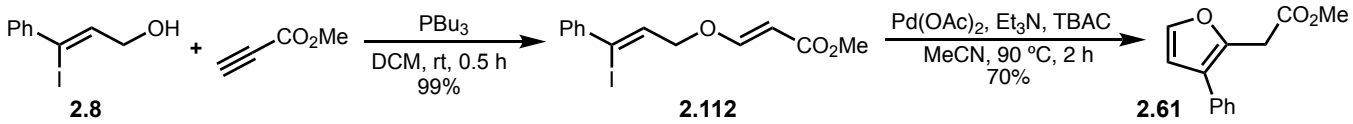
Finally, we also demonstrated that our methodology could also be applied to the synthesis of polysubsituted pyrroles by replacing the oxygen heteroarom with nitrogen via the Mitsunobu reaction. Following known literature procedures,[58] **2.17** was thus converted to its N-tolylsulfonamide analog **2.110** and subjected to Michael–Heck conditions. While condition A failed to produce the desired pyrrole product, replacement of PBu_3 with P(*o*-tol)$_3$ furnished pyrrole **2.111** in 91% yield (Scheme 2.17).



Scheme 2.17. Application of the Michael–Heck reaction to pyrrole synthesis

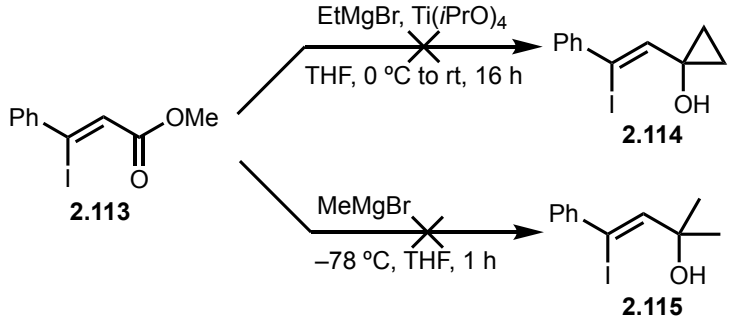
2.7 Mechanistic Studies

To verify the reaction mechanism, the putative Michael adduct (*E*)-alkoxyacrylate[59] intermediate **2.112** was isolated and subjected to the optimized Heck conditions to obtain furan **2.61**, albeit in slightly diminished yield compared with the one-pot procedure (Scheme 2.18).



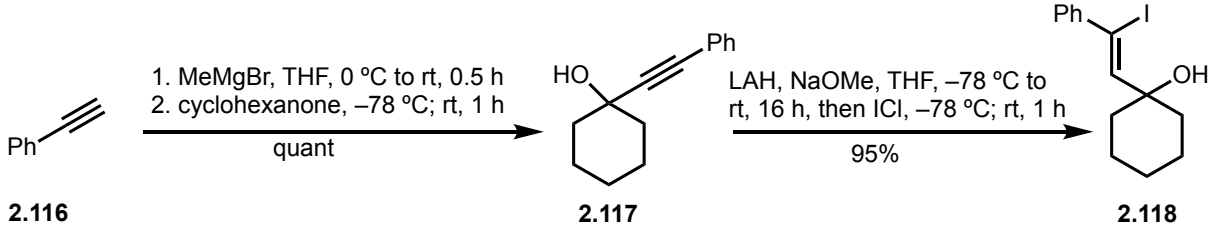
Scheme 2.18. Isolation and proof of the intermediacy of **2.112**

To confirm our hypothesis that the final furan product is formed by spontaneous aromatization of the intermediate dihydrofuran intermediate, we attempted to do the Michael–Heck reaction with tertiary alcohols, which would form *gem*-disubstituted dihydrofurans that cannot undergo aromatization. Initial attempts to prepare the tertiary β-iodoallylic alcohol involved Kulinkovich cyclopropanation or double Grignard addition (Scheme 2.19) to iodoester **2.113**.[60] However, neither of these reactions were successful.



Scheme 2.19. Attempted preparation of geminally-substituted tertiary alcohol

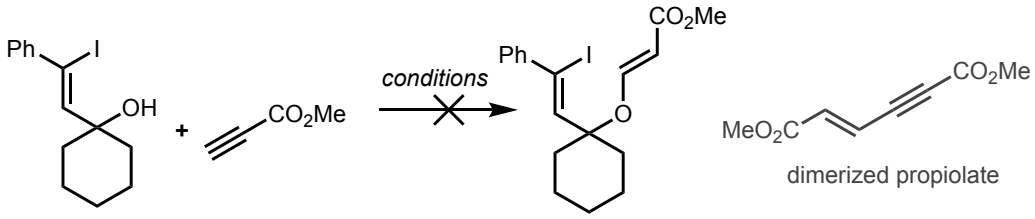
Efforts were then made to prepare the spirocyclic alcohol **2.118** using hydroalumination/iodination reaction (Scheme 2.20).



Scheme 2.20. Preparation of spirocyclic alcohol **2.118**

While the phosphine- catalyzed Michael addition of primary and secondary alcohols onto alkyl propiolates is well established, examples involving tertiary alcohols are extremely rare and often involve the use of more reactive PMe_3.[61] We found, however, that employing PMe_3 resulted in the rapid polymerization of methyl propiolate. Use of amine bases such as DABCO or Et_3N, on the other hand, lead to dimerization of methyl propiolate (Table 2.16).

Table 2.16. Attempted Michael addition of alcohol **2.118**

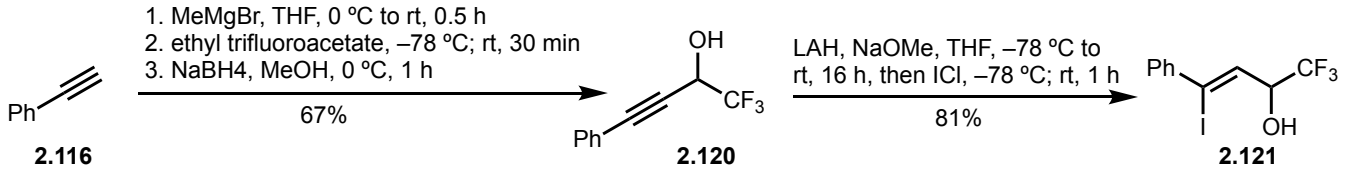


2.118 **2.119**

Entry	Conditions	Result
1	50 mol% PMe_3, 4 equiv propiolate	SM + polymerized propiolate
2	5 equiv PMe_3, 3 equiv propiolate	SM + polymerized propiolate
3	2 equiv Et_3N, 3 equiv propiolate	SM + dimerized propiolate
4	50 mol% DABCO, 4 equiv propiolate	SM + dimerized propiolate

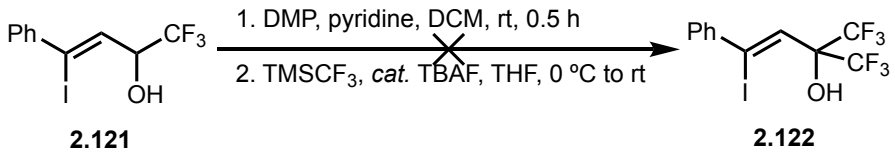
Tejedor's insightful report on Lewis base–catalyzed addition of primary, secondary, and tertiary alcohols onto alkyl propiolates suggested that the increased basicity of a tertiary alcohol, as well as the decreased nucleophilicity of the corresponding tertiary alkoxide, made it unable to compete with the dimerization or polymerization of alkyl propiolates in the presence of amines or phosphine catalysts.[17c] In their paper, they reported that replacement of one of the methyl groups in *t*-butyl alcohol with an ethynyl group produced a drop in pKa from 17 to 15, while replacement with a vinyl group or a phenyl group resulted in a decrease of 0.82 and 0.89 pKa units, respectively. While previous studies have already indicated the incompatibility of the Michael–Heck reaction with acetylenic substituents (4-fluorophenylacetylene and 4-methoxyacetylene), the CF_3 group was compatible. Given the fact that replacement of one of the methyl groups in *t*-butyl alcohol with a CF_3 group lowers the pKa from 17 to 12.6, the trifluoromethyl group should have a more potent pKa-lowering effect than ethynyl, vinyl or phenyl. Therefore, we prepared a

tertiary β-iodoallylic alcohol containing CF_3 groups at the C1 position. Known alcohol **2.120**[62] was subjected to hydroalumination/iodination to provide alcohol **2.121** in 81% yield (Scheme 2.21).



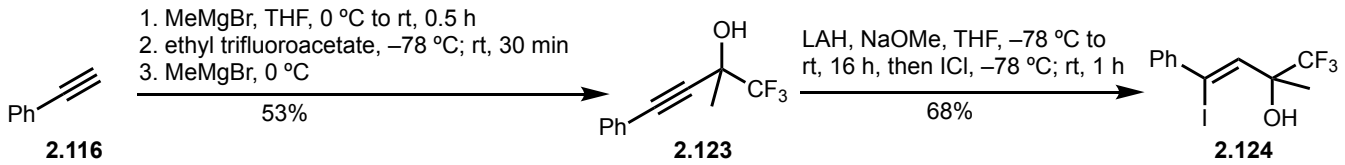
Scheme 2.21. Preparation of alcohol **2.121**

However, attempts to append another CF_3 group at the C1 position by treating the intermediate trifluoromethylketone from oxidation of **2.121** with the Ruppert–Prakash reagent in the presence of TBAF[61] were unsuccessful (Scheme 2.22).



Scheme 2.22. Attempted preparation of alcohol **2.122**

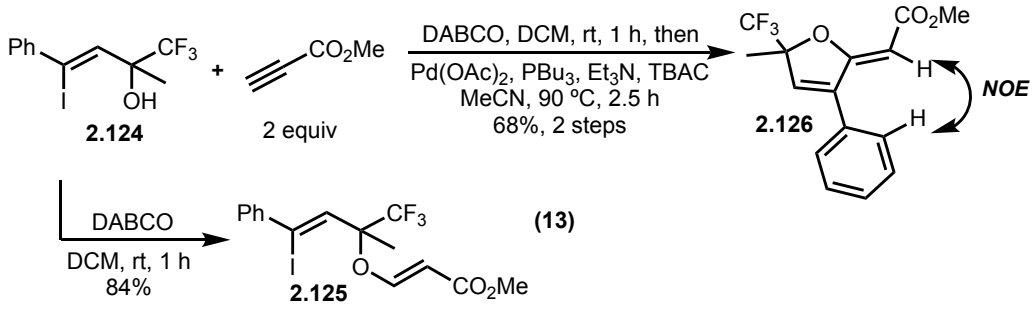
Therefore, a monotrifluoromethyl-substituted tertiary alcohol was prepared from known tertiary trifluoromethyl propargyl alcohol[63] using hydroalumination/iodination to give **2.124** in 68% yield (Scheme 2.23).



Scheme 2.23. Preparation of tertiary alcohol **2.118**

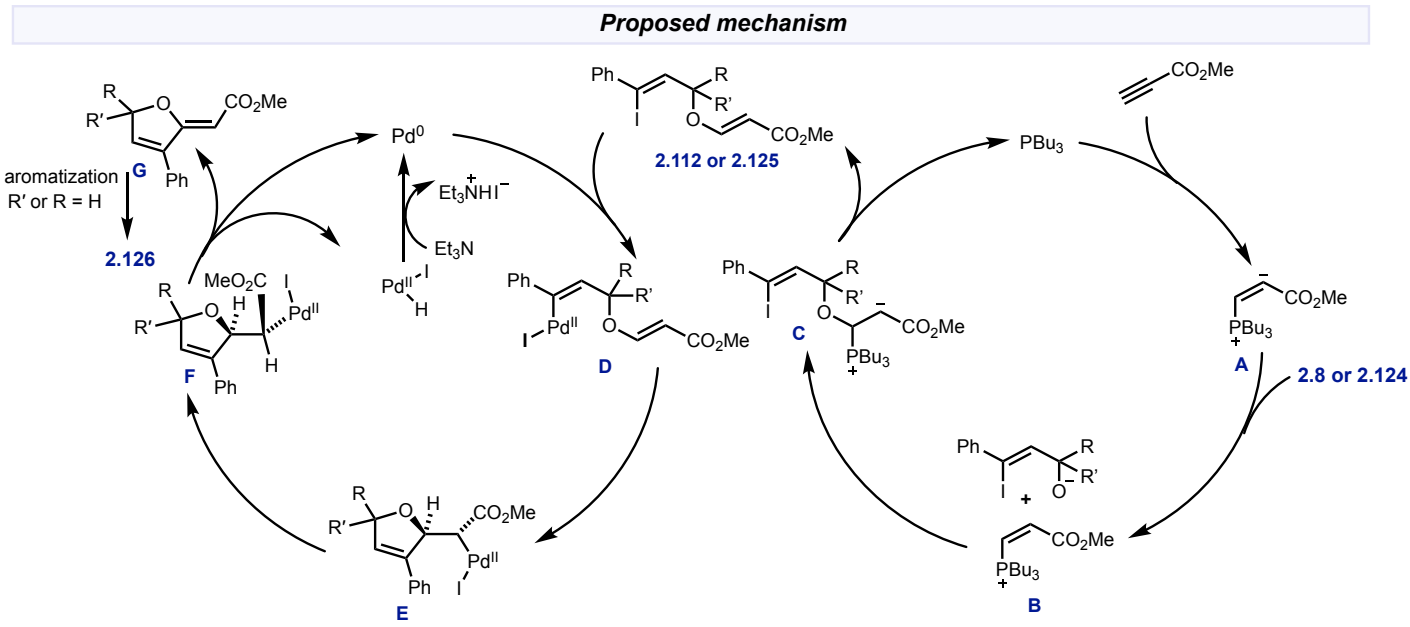
To our delight, we obtained the Michael adduct **2.125** from **2.124** in 84% yield using Tejedor's conditions (equation 13). Having verified the feasibility of the DABCO-catalyzed Michael addition of acidic tertiary alcohols onto methyl propiolate, we then subjected **2.124** to the Heck conditions. Gratifyingly, the small

amount of methyl propiolate dimer[64] formed did not interfere with the Heck reaction, and the (*Z*)-2-[furan-2(5*H*)-ylidene]acetate **2.126** was isolated in 68% yield (Scheme 2.24). Notably, only (Z)-2-[furan-2(5*H*)-ylidene]acetate **2.126** was isolated in 68% yield, supporting the stereospecific syn-insertion and syn-elimination during the Heck process. NOE correlations between the electron-deficient vinyl proton and the *ortho* phenyl protons confirmed the (*Z*)-geometry of **2.126**.



Scheme 2.24. Proving the existence of intermediates **2.125** and **G**

The observations described above underpin the following mechanism for our Michael–Heck reaction (Scheme 2.12). Initially, tributylphosphine adds onto the electron-deficient acetylene to produce zwitterion **A**, which deprotonates alcohol **1** to form the corresponding phosphonium alkoxide ion pair **B**. The alkoxide ion then adds onto the β-phosphonium enoate to produce the zwitterion **C**, which eliminates tributylphosphine to furnish Michael adduct **D**. Subsequent oxidative addition of palladium(0) complex leads to **E**, which undergoes *syn*-carbopalladation to produce dihydrofuran intermediate **F**. After C–C single bond rotation, the resulting intermediate **G** undergoes stereospecific *syn*-β-hydride elimination to generate (*Z*)-2-[furan-2(5*H*)-ylidene]acetate, which spontaneously undergoes aromatization to give the desired furan products when one of the C5 substituent is hydrogen.



Scheme 2.25. Proposed mechanism for the Michael–Heck reaction

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37. a) Ref. 8a. b) Ref 8d. c) Ref 8e

38. Ref 8c

39. a) Although plakorsin D methyl ester has not been prepared de novo, it, along with another furanylidene P. simplex natural product, has been demonstrated to arise from the $FeCl_3$-mediated rearrangement of the cyclic endoperoxide analogue of plakodiepoxide derived from *P. simplex* sponges; see Ref. 7b. b) Lee, R. J.; Lindley, M. R.; Pritchard, G. J.; Kimber, M. C. *Chem. Commun*. **2017**, *53*, 6327 – 6330.

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44. Performing the reaction at the melting point of PPh_3 allows it to be used as a solvent: „Triphenylphosphine“: Cobb, J. E.; Cribbs, C. M.; Henke, B. R.; Uehling, D. E. *e-EROS Encyclopedia of Reagents for Organic Synthesis*, Wiley, Hoboken, 2005 ; https :// doi.org/10.1002/047084289X.rt366.

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48. A similar E2-elimination has been observed in the basic decomposition of β-phenethylphosphonium bromides : Alunni, S.; Giulietti, G. *Z. Naturforsch. B.* **2014**, *38*, 115 – 116.

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51. Examples include alkylations of (3-furylmethyl)indate[41] and 2,2’-di-3-methylfurylmercury with prenyl,[42a] geranyl,[42b,c] and farnesyl[42d] bromides; Au^{I}-,[43a] Ir^{I}-,[43b] and Pd^{II}[43c,d]-catalyzed cycloisomerizations of (*Z*)-2-en-4-yn-1-ols; reductions of prenyl-[44a] and geranyl[44b-d]-substituted furanones; and cyclizations of α-allenic alcohols.[45] In the case of mikanifuran, alkylation of geranyl p-tolyl sulfone with the allylic chloride derivative[46] prepared from rosefuran has also been reported. See the Supporting Information for a full list of previous syntheses.

52. a) Jie, L. K.; Marcel, S. F. *Methods Enzymol*. **1981**, *72*, 443 – 471. b) Groweiss, Y.; Kashman, A. *Cell. Mol. Life Sci*. **1978**, *34*, 299. c) Imbs, A. B. *Russ. J. Mar. Biol.* **2013**, *39*, 153 – 168.

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54. In addition to the strategies used for the preparation of plakorsin natural products and 2,3-disubstituted furanoterpenes, rearrangements of cyclic endoperoxides (Ref. 31b) and catalytic iso merization of cyclic epoxyalkynols have also been reported for the synthesis of 11M5 and its methyl ester. Other syntheses include lithiation/alkylation of 3-iodofurans; Sonogashira and Negishi couplings of methyl 4,5-dibromofurano-2-carboxylate; electrophilic aromatic substitution of methyl 3-methyl-2-furoate; and reduction/iodination/reduction of 3-ethoxycarbonylfurans. See the Supporting Information for a list of previous syntheses.

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59. The coupling constants (J) for the vinyl protons of methyl (*Z*)- β- alkoxyacrylates range from 6.7 to 7.2 Hz, in contrast to values of approximately 12 Hz for corresponding *E* isomers. For examples, see: a) Singh, S. P.; O'Donnell, J. S.; Schwan, A. L. *Org. Biomol. Chem*. **2010**, *8*, 1712 – 1717. b) Sarrafi, Y.; Sadatshahabi, M.; Alimohammadi, K.; Tajbakhsh, M. *Green Chem*. **2011**, *13*, 2851 – 2858; c) Bergbreiter, D. E.; Yang, Y-.C.; Hobbs, C. E. *J. Org. Chem*. **2011**, *76*, 6912 – 6917.

60. a) Dieter, R. K; Lu, K. *J. Org. Chem.* **2002**, *67*, 847–855. b) Luo, F.-T.; Hsieh, L.-C. *J. Chin. Chem. Soc.* **1994**, *41*, 871–873.

61. Examples of PMe_3-catalyzed addition of tertiary alcohols onto methyl propiolate: a) Sato, K.; Sasaki, M. *Org. Lett*. **2005**, *7*, 2441 – 2444. b) Sato, K.; Sasaki, M. *Tetrahedron* **2007**, *63*, 5977 – 6003. c) Davy, J. A.; Mason, J. W.; Moreau, B.; Wulff, J. E. *J. Org. Chem*. **2012**, *77*, 6332 – 6339. d) Kunitake, M.; Oshima, T.; Konoki, K.; Ebine, M.; Torikai, K.; Murata, M.; Oishi, T. *J. Org. Chem*. **2014**, *79*, 4948 – 4962.

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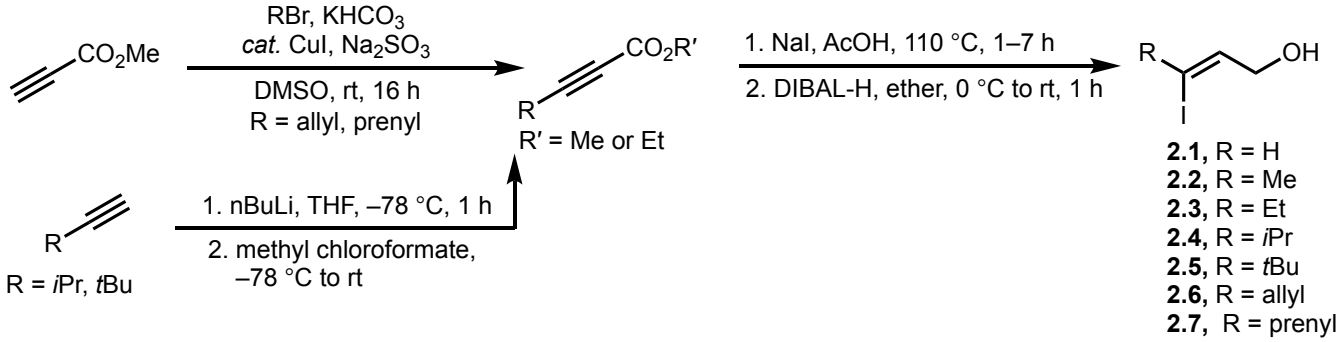
64. DABCO is known to quantitatively dimerize methyl propiolate to (*E*)-hex-2-en-4-ynedioic acid dimethyl ester: a) Matsuya,Y.; Hayashi, K.; Nemoto, H. *J. Am. Chem. Soc*. **2003**, *125*, 646 – 647. b) Zhou, L.-H.; Yu, X.-Q.; Pu, L. *Tetrahedron Lett.* **2010**, *51*, 425 – 427. c) Pünner, F.; Hilt, G. *Chem. Commun*. **2012**, *48*, 3617 – 3619. d) Choi, J.-H.; Park, C.-M. *Adv. Synth. Catal*. **2018**, *360*, 3553 – 3562.

2.9. Experimental

2.9.1. Starting Material Preparation

Procedure 1: Hydroiodination–Reduction (2.1–2.7)



Modified from literature procedures for the synthesis of the known compounds **2.1**–**2.4**.[1–4] NaI (1.6 equiv) and acetic acid (2.7 M) were placed in an oven-dried round-bottom flask. The alkynoate (1 equiv) was added at rt and the mixture was heated under reflux at 110 °C for 1 to 7 h. Upon completion of the reaction (TLC), the crude mixture was poured onto ice and solid $NaHCO_3$ was added *slowly* until no more fizzing occurred. (*Note:* Pouring onto ice reduced the amount of fizzing that occurred.) The aqueous mixture was extracted with Et_2O; the combined organic phases were washed with aqueous $Na_2S_2O_3$ and then with brine. The organic phase was dried (anhydrous Na_2SO_4) and concentrated *in vacuo*. The crude iodoester was dissolved in dry Et_2O (1 M) and cooled to 0 °C. DIBAL-H (1 M in hexanes) was added slowly and then the mixture was stirred at the same temperature for 1 h. Upon completion of the reaction (TLC), the mixture was diluted with Et_2O and the reaction quenched carefully through the addition of water, 1 M NaOH, water, and anhydrous Na_2SO_4 (Fieser workup). The mixture was filtered and concentrated *in vacuo*. The residue was purified through FCC to obtain the desired product.

Note 1: For substrates **2.1**, **2.6**, and **2.7**, commercially available methyl propiolate was used.

Note 2: For substrates **2.2** and **2.3**, commercially available ethyl 2-butynoate and ethyl 2-pentynoate were used, respectively.

Note 3: For substrates **2.4** and **2.5**, commercially available 3-methyl-1-butyne and 3,3-dimethyl-1-butyne were used, respectively.

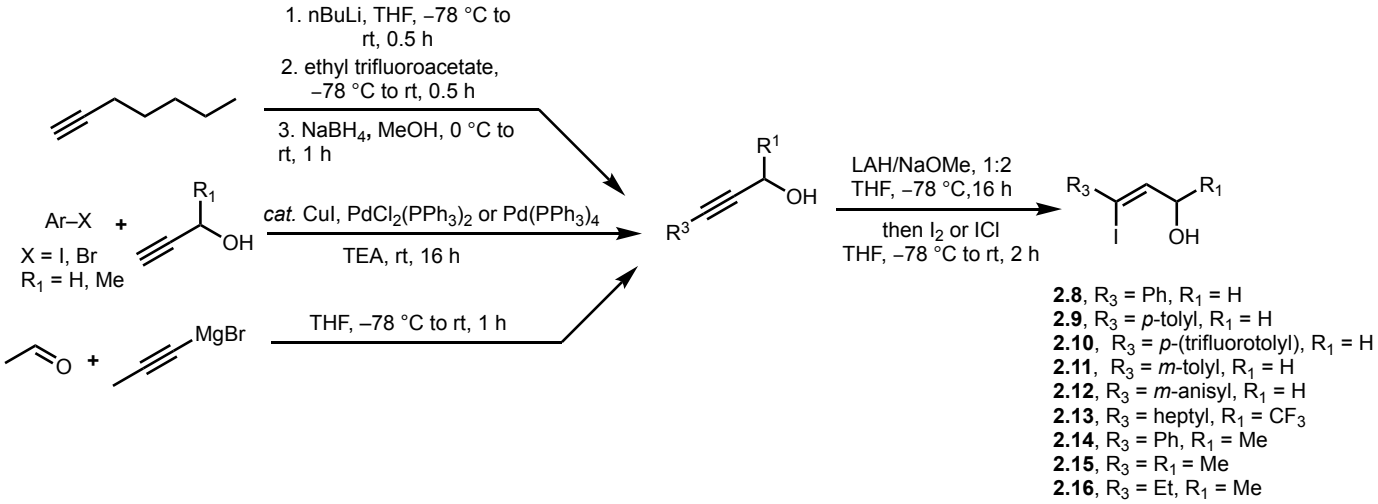
Note 4: For the hydroiodination step, a reaction time of 7 h was required for **2.5** and 2.5–3 h for **2.6** and **2.7**.

Note 5: Known compounds **2.1**,[1] **2.2**,[2] **2.4**,[3] and **2.3**[4] were prepared according to literature procedures.

Note 6: The alkynoate precursor for **2.5** is a known compound. It was prepared through lithiation/methoxycarbonylation of 3,3-dimethyl-1-butyne, according to literature procedures,[5] and used directly for the next step without purification.

Note 7: The alkynoate precursors for **2.6** and **2.7** are known compounds. They were prepared through Cu(I)-catalyzed allylation or prenylation of methyl propiolate, according to literature procedures,[6] and used directly for the next step without purification.

Procedure 2: Hydroalumination–Iodinolysis (2.8–2.16)



Modified from literature procedures for the synthesis of the known compounds **2.8**,[7] **2.14**,[8] **2.15**,[9] and **2.16**.[10] Lithium aluminum hydride (LAH, 1.6 equiv) and NaOMe (3.2 equiv) were placed in an oven-dried round-bottom flask. (*Note*: dry NaOMe was weighed from the glove box.) After cooling to –78 °C, dry THF (0.2 M) was added, followed by the *dropwise* addition of the alkynol starting material (1 equiv). (*Note:* vigorous fizzing occurred.) The mixture was warmed to rt over 16 h. After re-cooling to –78 °C, a solution of I_2 (2 equiv, 0.7 M in THF) or ICl (2 equiv, 1 M in DCM) was added slowly. After 5 min at –78 °C, the cooling bath was removed and the mixture was stirred at rt for 1–2 h. Upon completion (TLC), the reaction was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with EtOAc and the combined extracts were dried (anhydrous Na_2SO_4). After evaporating the solvent, the residue was purified through FCC to give the desired product.

Note 1: The alkynol starting materials for **2.8**, **2.9**,[11] **2.10**,[12] **2.11**,[13] **2.12**,[14] and **2.14**[15] were prepared through Sonogashira coupling of corresponding commercially available aryl halides and either propargyl alcohol or 3-butyn-2-ol, following literature procedures. For **2.8–2.11**, and **2.14**, the corresponding aryl iodide and $PdCl_2(PPh_3)_2$ were used; for **2.12**; the aryl bromide and $Pd(PPh_3)_4$ were used.

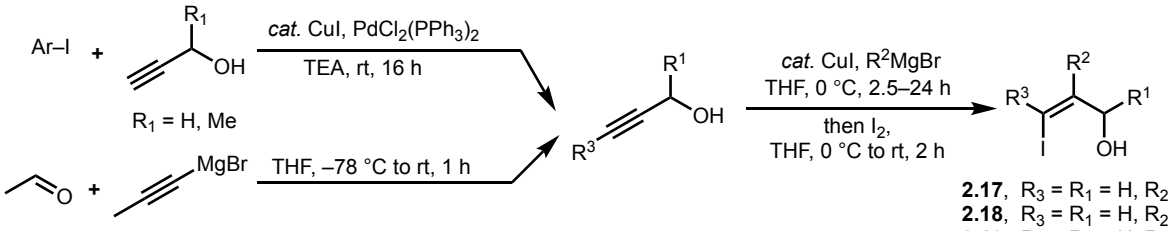
Note 2: 1,1,1-Trifluoronon-3-yn-2-ol (the alkynol precursor of **2.13**) was prepared according to the literature procedures for the preparation of 1,1,1-trifluorodec-3-yn-2-ol,[16] using commercially available 1-heptyne.

Note 3: The alkynol starting material for **2.15**[17] was prepared through Grignard addition, according to literature procedures.

Note 4: Commercially available 3-hexyn-2-ol was used for the preparation of **2.16**.

Note 5: The known compounds **2.8**,[7] **2.14**,[8] **2.15**,[9] and **2.16**[10] were prepared according to literature procedures.

Procedure 3: Carbocupration–Iodinolysis



2.17, $R_3 = R_1 = H$, $R_2 = Me$
2.18, $R_3 = R_1 = H$, $R_2 = Ph$
2.19, $R_3 = R_1 = H$, $R_2 = o$-tolyl
2.20, $R_3 = R_1 = H$, $R_2 = p$-(trifluorotolyl)
2.21, $R_3 = R_1 = H$, $R_2 = p$-tolyl
2.22, $R_3 = Ph$, $R_2 = Me$, $R_1 = H$
2.23, $R_3 = H$, $R_1 = R_2 = Me$
2.24, $R_3 = Ph$, $R_1 = R_2 = Me$
2.25, $R_3 = R_1 = R_2 = Me$

Modified from literature procedures for the synthesis of the known compounds **2.17**,[18] **2.18**,[19] **2.22**,[20] and **2.23**.[21] CuI (0.1 equiv) and dry THF (0.67 M) were placed in an oven-dried round-bottom flask. Propargyl alcohol (1 equiv) and a freshly prepared solution of RMgBr in THF (3.5 equiv) were added at 0 °C. The resulting mixture was stirred at the same temperature for 2.5–24 h. I_2 (0.7 M in THF, 2 equiv) or ICl (2 equiv, 1 M in DCM) was then added at 0 °C. The reaction was gradually warmed to rt over 2 h. Upon completion of the reaction (TLC), the crude solution was transferred to an extraction funnel and washed with saturated NH_4Cl until the aqueous layer was no longer blue. The organic phase was washed with saturated $Na_2S_2O_3$ and brine, dried (anhydrous Na_2SO_4), and concentrated *in vacuo*. The residue was purified through FCC.

Note 1: Carbocupration required a reaction time of 24 h to obtain satisfactory yields of **2.24** and **2.25**. For **2.22**, **2.23**, **2.24**, and **2.25**, 0.5 equiv of CuI in 0.12 M THF was used instead of 0.1 equiv of CuI in 0.67 M THF.

Note 2: For substrates **2.17–2.21**, commercially available propargyl alcohol was used.

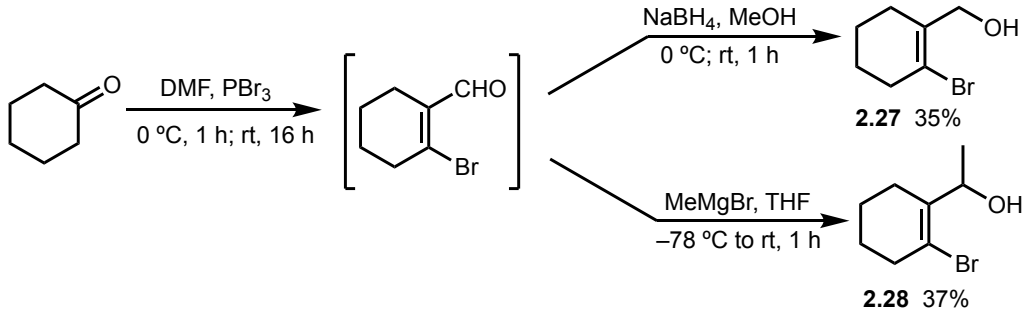
Note 3: The alkynol precursor for substrate **2.22**[22] was prepared through Sonogashira coupling of commercially available iodobenzene and propargyl alcohol, following literature procedures.

Note 4: For substrate **2.23**, commercially available 3-butyn-2-ol was used.

Note 5: The alkynol precursor for substrate **2.24**[15] was prepared through Sonogashira coupling of commercially available iodobenzene and 3-butyn-2-ol, following literature procedures.

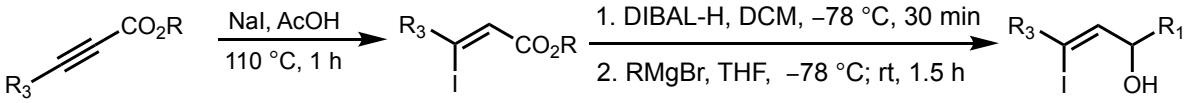
Note 6: The alkynol precursor for substrate **2.25**[17] was prepared through Grignard addition, according to literature procedures.

Procedure 4: Vilsmeier–Haack and Reduction or Grignard Addition



2.27 and **2.28** were prepared according to literature procedures.[23,24] Spectroscopic data matched those reported previously.

Procedure 5: Partial Reduction and Grignard Addition



R_3 = H, Me
R = Me or Et

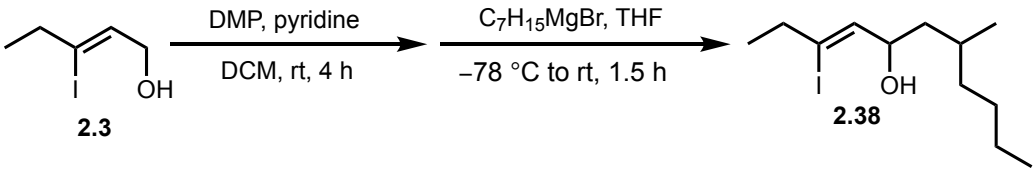
2.29, R_1 = Me, R_3 = H
2.30, R_1 = *n*Bu, R_3 = H
2.31, R_1 = cyclopropyl, R_3 = H
2.32, R_1 = cyclohexyl, R_3 = H
2.33, R_1 = hexadecyl, R_3 = H
2.34, R_1 = Ph, R_3 = H
2.35, R_1= *p*-fluorophenyl, R_3 = H
2.36, R_1 = 1-naphthyl, R_3 = H
2.37, R_1 = *n*-heptyl, R_3 = Me

Modified from literature procedures for the preparation of the known compounds **2.29**,[25] **2.30**,[26] and **2.34**.[26] DIBAL-H (1 equiv) was added slowly to a solution of (*Z*)-methyl-3-iodoacrylate or (*Z*)-ethyl-3-iodoacrylate (1 equiv) in dry DCM (0.44 M) at –78 °C. The mixture was then stirred at the same temperature for 30 min. A solution of freshly prepared RMgBr (1.5 equiv) was then added slowly at the same temperature. The resulting solution was warmed to rt and stirred for 1.5 h. Upon completion (TLC), the reaction was quenched with 1 M HCl at 0 °C. The aqueous phase was extracted with EtOAc; the combined extracts were dried (anhydrous Na_2SO_4) and concentrated *in vacuo*. The residue was purified through silica gel chromatography.

Note: For **2.31**, **2.32**, **2.35**, **2.36**, and **2.33**, the partial reduction step was performed for 10 min in dry toluene. For **2.31**, 2.5 equivalents of cyclopropylmagnesium bromide were used. For **2.36**, 2 equivalents of 1-naphthylmagnesium bromide were used.

Procedure 6: Oxidation and Grignard addition (2.38, 1gg, 1ll)

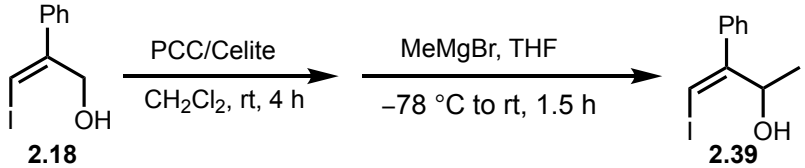
Preparation of **1ff**



Dess–Martin periodinane (DMP) (1.10 g, 2.59 mmol, 1.1 equiv), pyridine (760 µL, 9.43 mmol, 4 equiv), and DCM (6 mL, 0.4 M) were placed in an oven-dried round-bottom flask. A solution of (*Z*)-3-iodopent-2-en-1-ol (**2.3**, 500 mg, 2.36 mmol, 1 equiv) in DCM (6 mL, 0.4 M) was added slowly and then the mixture was stirred at rt for 1 h *in the dark*. Upon completion of the reaction (TLC), the mixture was concentrated to a minimal volume, diluted with dry Et_2O, and passed quickly through a silica plug directly into another oven-dried round-bottom flask. This solution of the crude aldehyde was immediately cooled to –78 °C and a solution of freshly prepared Grignard reagent (3.54 mmol, 1.5 equiv) was added slowly. The mixture was warmed to rt over 1.5 h. Upon completion of the reaction (TLC), the mixture was re-cooled to 0 °C and the reaction quenched with 1 M HCl (50 mL). The aqueous phase was extracted with EtOAc (3 × 60 mL) and the combined extracts were dried (anhydrous Na_2SO_4). After evaporating the solvent, the residue was purified through FCC to give (*Z*)-3-iodo-7-methylundec-3-en-5-ol (**2.38**) as a pale-yellow oil (497 mg, 65% from ethyl-2-pentynoate, mixture of diastereoisomers).

Note: The prerequisite 2-bromomethylhexane[27] was prepared in 52% over three steps (alkylation, reduction, and Appel reaction) from commercially available methyl hexanoate, following known literature procedures.

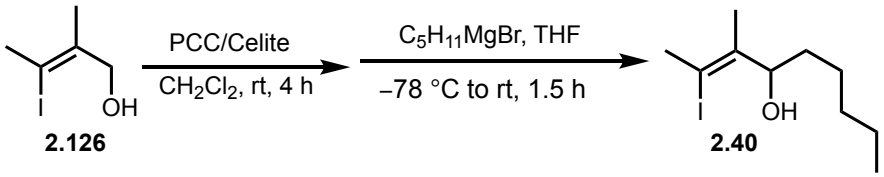
Preparation of **2.39**



Prepared following modified literature procedures.[28] PCC (918 mg, 4.26 mmol, 2 equiv), Celite (1.00 g), and DCM (8.5 mL, 0.5 M) were placed in an oven-dried round-bottom flask. A solution of (*Z*)-3-iodo-2-phenylprop-2-en-1-ol (**1m**, 554 mg, 2.13 mmol, 1 equiv) in DCM (4.2 mL, 0.5 M) was added slowly. The mixture was then stirred for 4 h at rt *in the dark*. Upon completion of the reaction (TLC), the mixture was

filtered quickly through a short plug of silica into another oven-dried round-bottom flask. (*Note*: The aldehyde intermediate is very light-sensitive.) This solution was immediately cooled to –78 °C and then a solution of methylmagnesium bromide (1.10 mL, 3.20 mmol, 1.5 equiv) was added slowly. The mixture was warmed to rt over 1.5 h. After re-cooling to 0 °C, the reaction was quenched with 1 M HCl (20 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL) and the combined extracts dried (anhydrous Na_2SO_4). After evaporating the solvent, the residue was purified through FCC to give (*Z*)-4-iodo-3-phenylbut-3-en-2-ol (**2.39**) as a white solid (520 mg, 89% from **2.18**).

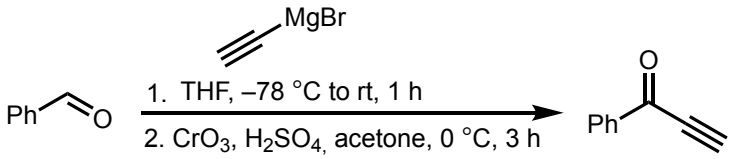
Preparation of **2.40**



2.126 **2.40**

(*Z*)-3-Iodo-2-methylbut-2-en-1-ol[29] (**2.126**) was prepared according to literature procedures in 80% yield; its spectral data matched those previously reported. PCC (4.00 g, 18.9 mmol, 2 equiv), Celite (4.00 g), and DCM (24 mL, 0.8 M) were placed in an oven-dried round-bottom flask. A solution of **2.126** (2.00 g, 9.43 mmol, 1 equiv) in DCM (12 mL, 0.8 M) was added slowly. The mixture was stirred for 4 h at rt *in the dark*. Upon completion of the reaction (TLC), the mixture was filtered quickly through a short plug of silica into another oven-dried round-bottom flask. (*Note*: The aldehyde intermediate is very light-sensitive.) The solution was immediately cooled to –78 °C and then a solution of freshly prepared *n*-pentylmagnesium bromide (14.1 mmol, 1.5 equiv) was added slowly. The mixture was warmed to rt over 1.5 h. After re-cooling to 0 °C, the reaction was quenched with 1 M HCl (20 mL). The aqueous phase was extracted with EtOAc (3 × 70 mL) and the combined extracts were dried (anhydrous Na_2SO_4). After evaporating the solvent, the residue was purified through FCC (0–8% EtOAc/hexanes) to give (*Z*)-2-iodo-3-methylnon-2-en-4-ol (**2.40**) as a pale-yellow oil (2.2 g, 83% from **2.126**).

2.9.2. Preparation of Acetylenic Electrophiles

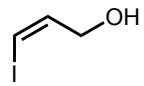


1-Phenyl-2-propyn-1-one

Prepared according to literature procedures[30] (170 mg, 69% over two steps from commercially available benzaldehyde). Spectroscopic data matched those previously reported.[30]

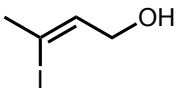
Note: Methyl propiolate and 3-butyn-2-one were purchased and used as received.

2.9.3. Characterization Data for Michael–Heck Substrates



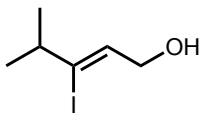
(Z)-3-Iodoprop-2-en-1-ol (2.1)

Prepared (818 mg, 94%) from commercially available methyl propiolate (376 µL, 4.73 mmol) according to literature procedures.[1] Spectroscopic data matched those reported.[1]



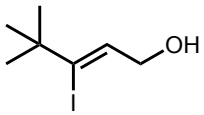
(Z)-3-Iodobut-2-en-1-ol (2.2)

Prepared (2.70 g, 90%) from commercially available ethyl-2-butynoate (1.77 mL, 15.2 mmol) according to literature procedures.[2] Spectroscopic data matched those reported.[2]



(Z)-3-Iodo-4-methylpent-2-en-1-ol (2.4)

Prepared (424 mg, 97%) from commercially available 3-methyl-1-butyne (200 µL, 1.93 mmol) according to literature procedures.[3] Spectroscopic data matched those reported.[3]



(*Z*)-3-Iodo-4,4-dimethylpent-2-en-1-ol (2..5)

Prepared according to procedure 1 (1.66 g, 97% over three steps) from commercially available 3,3-dimethyl-1-butyne.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86 (t, J = 5.3 Hz, 1H), 4.21 (t, J = 5.3 Hz, 2H), 1.61 (t, J = 5 Hz, 1H) 1.19 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 130.8, 126.4, 68.5, 40.3, 30.3.

IR (neat): 3299, 2962, 2904, 2871, 1628, 1457, 1310, 1262, 1034, 980, 713 cm^{-1}.

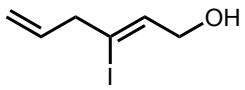
HRMS (ESI): calc'd for $C_7H_{13}IO$ $[M + H]^+$, *m/z* 240.0006; found 240.0000.

R_f = 0.35 (10% EtOAc/hexanes).

Appearance: light-yellow oil.

Reaction scale: 7.12 mmol.

Purification: FCC on SiO_2, 0–13% EtOAc/hexanes.



(*Z*)-3-iodohexa-2,5-dien-1-ol (2.6)

Prepared (2.3 g, 61% over three steps) was prepared according to procedure 1 from commercially available methyl propiolate.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.90–5.93 (m, 1H), 5.76–5.84 (m, 1H), 5.15–5.20 (m, 2H), 4.20–4.21 (m, 2H), 3.30 (dd, J = 5.7, 0.95 Hz, 2H), 1.68 (bs, 1H).

^{13}C NMR (125 MHz, CDCl3): δ 134.9, 134.4, 118.0, 106.9, 67.3, 49.5.

IR (neat): 3324, 2976, 2875, 1636, 1418, 1273, 1112, 1074, 1017 cm^{-1}.

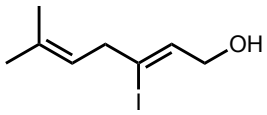
HRMS (ESI): calc'd for C_6H_9IO $[M + H]^+$ *m/z* 223.9693**; found** 223.9685

R_f = 0.51 with 25% EtOAc/hexanes).

Appearance: clear oil

Reaction scale: 16.885 mmol.

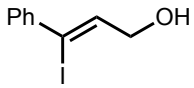
Purification: FCC on SiO_2, 0–13% EtOAc/hexanes.



(*Z*)-3-Iodo-6-methylhepta-2,5-dien-1-ol (2.7)

Prepared as a clear oil, according to procedure 1 (473 mg, 28% over three steps) from commercially available methyl propiolate. Unstable and used directly for the Michael–Heck reaction without characterization.

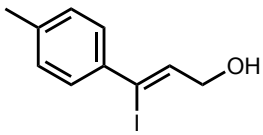
Reaction scale: 6.71 mmol.



(*Z*)-3-Iodo-3-phenylprop-2-en-1-ol (2.8)

Prepared from propargyl alcohol (1.76 g, 91% over two steps) following literature procedures.[7]

Spectroscopic data matched those found in the literature.



(*Z*)-3-Iodo-3-(*p*-tolyl)prop-2-en-1-ol (2.9)

Prepared (354 mg, 90% over two steps) according to procedure 2 from commercially available propargyl alcohol and 4-iodotoluene.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 6.21 (t, J = 5.7 Hz, 1H), 4.38 (t, J = 5.8 Hz, 2H), 2.36 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 139.4, 138.7, 136.0, 128.9, 128.3, 105.5, 68.3, 21.1.

IR (neat): 3334, 3092, 2923, 1902, 1801, 1642, 1512, 1442, 1309, 1211, 1066, 742 cm^{-1}.

HRMS (ESI): calc'd for $C_{10}H_{11}IO$ $[M + H]^+$, *m/z* 273.9849; found 273.9843.

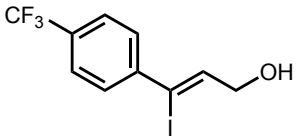
M.p. = 52–53 °C.

R_f = 0.25 (10% EtOAc/hexanes).

Appearance: pale-yellow solid.

Reaction scale: 1.44 mmol.

Purification: FCC on SiO_2, 0–15% EtOAc/hexanes.



(*Z*)-3-Iodo-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (2.10)

Prepared (382 mg, 84% over two steps) according to procedure 2 from commercially available propargyl alcohol and 4-iodobenzotrifluoride.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (s, 4H), 6.34 (t, J = 5.5 Hz, 1H), 4.4 (d, J = 5.5 Hz, 2H), 2.41 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): 145.5, 139.0, 130.6 (q, $^2J_{C–F}$ = 32.4 Hz), 128.8, 125.3 (q, $^3J_{C–F}$ = 3.7 Hz), 123.8 (q, $^1J_{C–F}$ = 270.5 Hz), 102.2, 68.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.6.

IR (neat): 3363, 2954, 1624, 1403, 1308, 1255, 1153, 1063, 846, 738 cm^{-1}.

HRMS (ESI): calc'd for $C_{10}H_8F_3IO$ $[M + H]^+$, *m/z* 327.9566; found 327.9552.

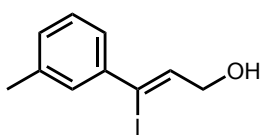
M.p. = 40–42 °C.

***R*$_f$** = 0.29 (10% EtOAc/hexanes).

Appearance: light-orange solid.

Reaction scale: 1.38 mmol.

Purification: FCC on SiO_2, 0–15% EtOAc/hexanes.



(*Z*)-3-Iodo-3-(*m*-tolyl)prop-2-en-1-ol (2.11)

Prepared (513 mg, 52% over two steps from propargyl alcohol) according to procedure 2 from commercially available propargyl alcohol and 3-iodotoluene.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, J = 8.6 Hz, 2H), 7.19 (t, J = 7.5 Hz, 1H), 7.09 (d, J = 7.4 Hz, 1H), 6.23 (t, J = 5.6 Hz, 1H), 4.38 (d, J = 5.6 Hz, 2H), 2.35 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.1, 137.9, 136.7, 129.4, 129.0, 128.1, 125.6, 105.2, 68.2, 21.3.

IR (neat): 3321, 2976, 2869, 2242, 1603, 1479, 1452, 1233, 1162, 1098, 912, 777, 766, 693 cm^{-1}.

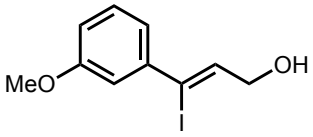
HRMS (ESI): calc'd for $C_{10}H_{11}IO$ $[M + H]^+$, *m/z* 273.9849; found 273.9840.

R_f = 0.31 (10% EtOAc/hexanes).

Appearance: light-brown oil.

Reaction scale: 3.60 mmol.

Purification: FCC on SiO_2, 0–15% EtOAc/hexanes.



(*Z*)-3-Iodo-3-(3-methoxyphenyl)prop-2-en-1-ol (2.12)

Prepared (810 mg, 62% over two steps from propargyl alcohol) according to procedure 2 from commercially available propargyl alcohol and 3-bromoanisole.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (t, J = 8.0 Hz, 1H), 7.06 (dd, J = 7.6, 0.65 Hz, 1H), 7.01 (t, J = 2.1 Hz, 1H), 6.83 (dd, J = 8.2, 2.5 Hz, 1H), 6.27 (t, J = 5.6 Hz, 1H), 4.39 (d, J = 5.5 Hz, 2H), 3.83 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 143.6, 137.1, 129.2, 120.8, 114.3, 114.2, 104.7, 68.2, 55.4.

IR (neat): 3333, 2974, 2933, 2868, 2836, 1597, 1575, 1480, 1461, 1425, 1316, 1286, 1254, 1193, 1171, 1156, 1088, 1074, 1041 cm^{-1}.

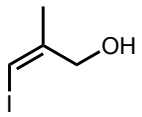
HRMS (ESI): calc'd for $C_{10}H_{11}IO_2$ $[M + H]^+$, *m/z* 289.9798; found 289.9790.

***R*$_f$** = 0.31 (25% EtOAc/hexanes).

Appearance: pale-yellow oil.

Reaction scale: 4.50 mmol.

Purification: FCC on SiO_2, 0–17% EtOAc/hexanes.



(*Z*)-3-Iodo-2-methylprop-2-en-1-ol (2.17)

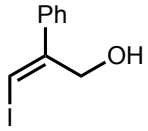
Prepared (3.28 g, 91%) according to procedure 3 using 35 mol% CuBr in 0.12 M THF instead of 10 mol% CuI in 0.67 M THF. Spectral data matched those found in the literature.[18]

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.98 (s, 1H), 4.25 (s, 2H), 1.98 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 74.8, 68.0, 21.6.

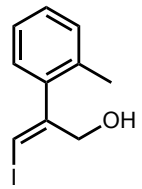
Reaction scale: 18.24 mmol.

Purification: FCC on SiO_2, 0–13% EtOAc/hexanes.



(*Z*)-3-Iodo-2-phenylprop-2-en-1-ol (2.18)

Prepared (1.25 g, 75%) following literature procedures.[19] Spectral data matched those found in the literature.



(*Z*)-3-Iodo-2-(*o*-tolyl)prop-2-en-1-ol (2.19)

Prepared (663 mg, 70%) according to procedure 3 from commercially available propargyl alcohol and 2-bromotoluene; obtained as an inseparable mixture of regioisomers.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09–7.25 (m, 4H), 6.25 (s, 1H), 4.49 (s, 2H), 2.28 (s, 3H), 1.73 (bs, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 150.9, 139.0, 135.6, 130.3, 128.8, 128.1, 125.7, 80.0, 67.7, 19.9.

IR (neat): 3367, 3060, 2958, 1599, 1490, 1450, 1298, 1038, 750 cm^{-1}.

HRMS (ESI): calc'd for $C_{10}H_{11}IO$ $[M + H]^+$, *m/z* 273.9849; found 273.9840.

R_f = 0.35 (10% EtOAc/hexanes).

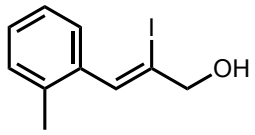
Appearance: yellow oil.

Reaction scale: 3.46 mmol.

Regioisomeric ratio: **2.19**:**2.128** = 1:0.05.

Purification: FCC on SiO_2, 0–15% EtOAc/hexanes.

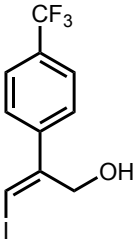
Note: The regioisomer **2.128**[31] was inseparable from **2.19**, but it did not affect the Michael–Heck reaction.



(*Z*)-2-Iodo-3-(*o*-tolyl)prop-2-en-1-ol (2.128)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09–7.25 (m, 0.22H), 6.19 (s, 0.05H), 4.54 (s, 0.11H), 2.30 (s, 0.15H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 145.4, 137.9, 136.0, 130.3, 129.1, 128.2, 125.7, 106.6, 63.5, 14.1.



(*Z*)-3-Iodo-2-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (2.20)

Prepared (593 mg, 89%) according to procedure 3 using commercially available propargyl alcohol and 4-bromobenzotrifluoride.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 6.78 (s, 1H), 4.71 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 142.5, 130.2 (q, $^2J_{C–F}$ = 32.5 Hz), 126.9, 125.6 (q, $^3J_{C–F}$ = 3.8 Hz), 124.0 (q, $^1J_{C–F}$ = 270.5 Hz), 83.4, 66.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ –62.7.

IR (neat): 3307, 3065, 2949, 2900, 1619, 1615, 1402, 1325, 1173, 1067, 955, 850, 697 cm^{-1}.

HRMS (ESI): calc'd for $C_{10}H_8F_3IO$ $[M + H]^+$, *m/z* 327.9566; found 327.9555.

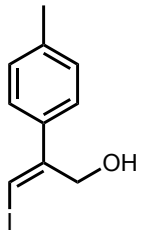
M.p. = 74–75 °C.

R_f = 0.32 (10% EtOAc/hexanes).

Appearance: light-orange solid.

Reaction scale: 2.03 mmol.

Purification: FCC on SiO_2, 0–15% EtOAc/hexanes.



(*Z*)-3-Iodo-2-(*p*-tolyl)prop-2-en-1-ol (2.21)

Prepared (1.75 g, 84%) according to procedure 3 from commercially available propargyl alcohol and 4-bromotoluene.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 6.58 (s, 1H), 4.68 (d, J = 6.3 Hz, 2H), 2.35 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 149.6, 138.2, 136.0, 129.4, 126.4, 80.2, 66.9, 21.2.

IR (neat): 3393, 3060, 2920, 1609, 1590, 1511, 1454, 1378, 1298, 1201,1039, 959, 828, 796 cm^{-1}.

HRMS (ESI): calc'd for $C_{10}H_{11}IO$ $[M + H]^+$, *m/z* 273.9849; found 273.9838.

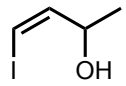
M.p. : 50–51 °C.

R_f = 0.29 (10% EtOAc/hexanes).

Appearance: pale-yellow solid.

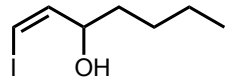
Reaction scale: 7.60 mmol.

Purification: FCC on SiO_2, 0–15% EtOAc/hexanes.



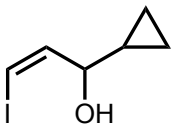
(*Z*)-4-Iodobut-3-en-2-ol (2.29)

Prepared (450 mg, 95% over two steps from methyl propiolate) following literature procedures.[25] Spectral data matched those found in the literature.



(*Z*)-1-Iodohept-1-en-3-ol (2.30)

Prepared (860 mg, 94% over two steps from methyl propiolate) following literature procedures.[26] Spectral data matched those found in the literature.



(*Z*)-1-Cyclopropyl-3-iodoprop-2-en-1-ol (2.31)

Prepared (1 g, 90% over two steps) according to procedure 5 from commercially available methyl propiolate and cyclopropyl bromide.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.35 (d, J = 7.6 Hz, 1H), 6.32 (d, J = 7.7 Hz, 1H), 3.89 (t, J = 7.6 Hz, 1H), 1.85 (bs, 1H), 1.08–1.11 (m, 1H), 0.41–0.57 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.0, 82.4, 77.6, 16.6, 2.7, 1.6.

IR (neat): 3316, 3074, 3001, 2973, 2869, 1721, 1614, 1430, 1263, 1126, 1027 cm^{-1}.

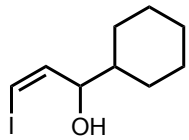
HRMS (EI): calc'd for C_6H_9O $[M - I]^+$, *m/z* 97.0653; found 97.0650.

R_f = 0.61 (10% EtOAc/hexanes).

Appearance: pale-yellow oil.

Reaction scale: 4.96 mmol.

Purification: FCC on SiO_2, 0–12% EtOAc/hexanes.



(*Z*)-1-Cyclohexyl-3-iodoprop-2-en-1-ol (2.32)

Prepared (252 mg, 29% over two steps) according to procedure 5 from commercially available methyl propiolate and cyclohexyl bromide.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.40 (d, J = 7.7 Hz, 1H), 6.24 (t, J = 7.9 Hz, 1H), 4.16 (td, J = 9.1, 3.6 Hz, 1H), 1.91–1.94 (m, 1H), 1.74–1.78 (m, 1H), 1.66–1.68 (m, 2H), 1.50–1.56 (m, 2H), 1.01–1.27 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.1, 83.4, 78.2, 43.1, 28.4, 26.4, 26.0, 25.9.

IR (neat): 3349, 3067, 2921, 2856, 1611, 1449, 1382, 1318, 1269, 1175, 1096, 1081, 1013, 953, 911, 893, 723, 641, 562, 531 cm^{-1}.

HRMS (EI): calc'd for $C_9H_{15}O$ $[M - I]^+$, *m/z* 139.1117; found 139.1119.

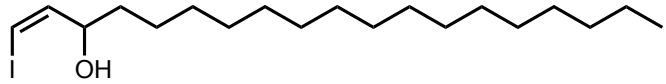
M.p. : = 39–40 °C.

R_f = 0.45 (10% EtOAc/hexanes).

Appearance: viscous white solid.

Reaction scale: 3.28 mmol.

Purification: FCC on SiO_2, 0–11% EtOAc/hexanes.



(*Z*)-1-Iodononadec-1-en-3-ol (2.33)

Prepared (463 mg, 72% over two steps) according to procedure 5 from commercially available methyl propiolate and *n*-hexadecyl bromide.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.33 (d, J = 7.6 Hz, 1H), 6.24 (t, J = 7.7 Hz, 1H), 4.37–4.42 (m, 1H), 1.71 (bs, 1H), 1.42–1.64 (m, 4H), 1.25 (bs, 26H), 0.88 (t, J = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 143.4, 82.3, 74.4, 35.9, 31.9, 29.7, 29.7, 29.6, 29.5, 29.5, 29.4, 25.0, 22.7, 14.1.

IR (neat): 3342, 2921, 2856, 2852, 1716, 1611, 1465, 1265, 1062, 1013, 739, 719 cm^{-1}.

HRMS (ESI): calc'd for $C_{19}H_{37}IO$ $[M + H]^+$, *m/z* 408.1884; found 408.1870.

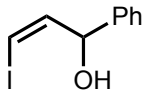
M.p. : = 50–51 °C.

R_f = 0.49 (10% EtOAc/hexanes).

Appearance: white solid.

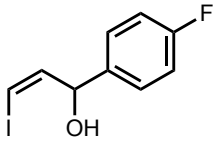
Reaction scale: 1.55 mmol.

Purification: FCC on SiO_2, 0–12% EtOAc/hexanes.



(*Z*)-3-Iodo-1-phenylprop-2-en-1-ol (2.34)

Prepared (725 mg, 92% over two steps) following literature procedures.[27a] Spectral data matched that found in the literature.[26]



(*Z*)-1-(4-Fluorophenyl)-3-iodoprop-2-en-1-ol (2.35)

Prepared (1.26 g, 69% over two steps) according to procedure 5 from commercially available methyl propiolate and 1-bromo-4-fluorobenzene.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42–7.44 (m, 2H), 7.05 (t, J = 8.7 Hz, 2H), 6.42–6.47 (m, 2H), 5.51 (t, J = 4.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.4 (d, J = 244.8 Hz), 142.4, 137.2 (d, J = 3.1 Hz), 127.8 (d, J = 8.1 Hz), 115.6 (d, J = 21.4 Hz), 83.3, 75.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ –114.1.

IR (neat): 3281, 3063, 2976, 2879, 1604, 1507, 1264, 1223, 1156, 1094, 1039 cm^{-1}.

HRMS (EI): calc'd for C_9H_8FO $[M - I]^+$, *m/z* 151.0554; found 151.0555.

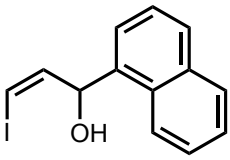
R_f = 0.65 (25% EtOAc/hexanes).

Appearance: yellow oil.

Reaction scale: 6.57 mmol.

Purification: FCC on SiO_2, 0–15% EtOAc/hexanes.

***Note*:** Refrigerate immediately after use. Gradually turns black and decomposes completely within 2 weeks under refrigeration.



(*Z*)-3-Iodo-1-(naphth-1-yl)prop-2-en-1-ol (2.36)

Prepared (1.4 g, 69% over two steps) according to procedure 5 from commercially available methyl propiolate and 1-bromonaphthalene.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.5 Hz, 1H), 7.89 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.74 (d, *J* = 7.1 Hz, 1H), 7.47–7.57 (m, 3H), 6.69 (t, *J* = 7.8 Hz, 1H), 6.55 (dd, *J* = 7.7, 0.95 Hz, 1H), 6.11 (d, *J* = 7.9 Hz, 1H), 2.25 (bs, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.4, 137.0, 133.9, 130.6, 128.9, 128.7, 126.3, 125.8, 125.4, 124.1, 124.0, 84.6, 74.4.

IR (neat) = 3310, 3056, 2974, 2875, 2359, 1711, 1595, 1510, 1390, 1359, 1274, 1256, 1169, 1107, 1047 cm^{-1}.

HRMS (EI): calc'd for $C_{13}H_{11}O$ $[M - I]^+$, *m/z* 183.0804; found 183.0806.

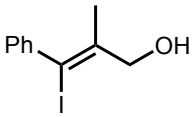
R_f = 0.56 (25% EtOAc/hexanes).

Appearance: orange oil.

Reaction scale: 6.54 mmol.

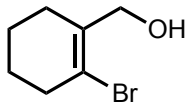
Purification: FCC on SiO_2, 0–17% EtOAc/hexanes.

***Note*:** Refrigerate immediately after use. Gradually turns black and decomposes completely within 2 weeks under refrigeration.



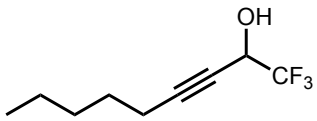
(*Z*)-3-Iodo-2-methyl-3-phenylprop-2-en-1-ol (2.22)

Prepared (396 mg, 55%) following literature procedures.[20] Spectral data matched those found in the literature.[20]



(2-Bromocyclohex-1-en-1-yl)methanol (2.27)

Prepared (629 mg, 35% over two steps) following literature procedures[23]. Spectral data matched those found in the literature.[23]



1,1,1-Trifluoronon-3-yn-2-ol (2.129)

Prepared according to the literature procedures for the preparation of 1,1,1-trifluorodec-3-yn-2-ol[16] using commercially available 1-heptyne.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.62–4.67 (m, 1H), 2.32 (d, J = 6.8 Hz, 1H), 2.24 (td, J = 7.0, 1.9 Hz, 2H), 1.54 (quint, J = 7.1 Hz, 2H), 1.28–1.39 (m, 4H), 0.90 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 122.8 (q, $^{1}J_{C–F}$ = 280 Hz), 89.7, 72.1 (q, $^{3}J_{C–F}$ = 2.3 Hz), 62.6 (q, $^{2}J_{C–F}$ = 36 Hz), 30.9, 27.7, 22.1, 18.5, 13.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ –79.9.

IR (neat): 3328, 2960, 2930, 2862, 1707, 1463, 1431, 1377, 1352, 1272, 1179, 1156, 1134, 1052 cm^{-1}.

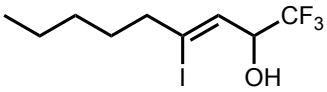
HRMS (ESI): calc'd for $C_9H_{13}F_3O$ $[M + H]^+$, *m/z* 194.0913; found 194.0910.

R_f = 0.56 (10% EtOAc/hexanes).

Appearance: clear oil.

Reaction scale: 15.85 mmol.

Purification: FCC on SiO_2, 0–13% EtOAc/hexanes.



(*Z*)-1,1,1-Trifluoro-4-iodonon-3-en-2-ol (2.13)

Prepared (1 g, 77% over two steps from 1-heptyne) according to procedure 2 from **S2**, as an inseparable mixture of regioisomers.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.72 (d, J = 8.3 Hz, 1H), 4.70–4.73 (m, 1H), 2.56 (t, J = 7.3 Hz, 2H), 2.22 (bs, 1H), 1.53–1.59 (m, 2H), 1.26–1.35 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 144.3, 124.3 (q, $^1J_{C–F}$ = 280 Hz), 118.5, 75.5 (q, $^2J_{C–F}$ = 32 Hz), 45.8, 30.2, 28.7, 22.3, 13.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ –78.4.

IR (neat): 2958, 2932, 2870, 2860, 1701, 1646, 1460, 1433, 1370, 1355, 1265, 1175, 1128, 1096, 1046 $cm^{–1}$.

HRMS (EI): calc'd for $C_8H_{15}IO$ $[M–CF_3]^+$, *m/z* 254.0162; found 254.0172.

R_f = 0.58 (10% EtOAc/hexanes).

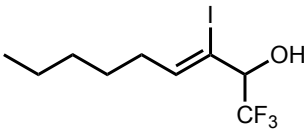
Appearance: clear oil.

Reaction scale: 4.03 mmol.

Regioisomeric ratio: **1aa**:**S3** = 1:0.24.

Purification: FCC on SiO_2, 0–8% EtOAc/hexanes.

Note: Regioisomer **S3**[31] was inseparable from **1aa**, but did not interfere with the Michael–Heck reaction.

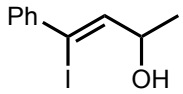


(*Z*)-1,1,1-Trifluoro-4-iodonon-3-en-2-ol (2.130)

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.20 (t, J = 6.8 Hz, 0.24H), 4.26 (quint, J = 6.7 Hz, 0.25H), 2.56 (t, J = 7.3 Hz, 0.33H), 1.53–1.59 (m, 1.83H), 1.46 (quint, J = 7.1 Hz, 0.65H), 1.26–1.35 (m, 1.60H), 0.90 (t, J = 7.2 Hz, 1H),

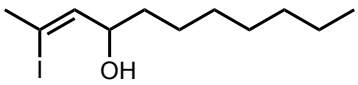
^{13}C NMR (125 MHz, $CDCl_3$): δ 127.1, 123.5 (q, $^1J_{C–F}$ = 282 Hz), 99.3, 75.6 (q, $^2J_{C–F}$ = 32 Hz), 36.0, 31.2, 27.4, 22.4, 13.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ –76.2.



(*Z*)-4-Iodo-4-phenylbut-3-en-2-ol (2.14)

Prepared (1.61 g, 55% over two steps) according to literature procedures.[8] Spectroscopic data matched those reported in the literature.[8]



(*Z*)-2-Iodoundec-2-en-4-ol (2.37)

Prepared (1.6 g, 60% over two steps) according to procedure 5 from commercially available methyl propiolate.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.50 (dd, J = 7.7, 1.4 Hz, 1H), 4.23 (q, J = 6.0 Hz, 1H), 2.52 (d, J = 1.4 Hz, 3H), 1.72–1.74 (m, 1H), 1.50–1.61 (m, 2H), 1.37–1.42 (m, 1H), 1.27–1.35 (m, 8H), 0.88 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.0, 101.6, 76.7, 36.2, 33.8, 31.8, 29.5, 29.2, 25.1, 22.6, 14.1.

IR (neat) = 3303, 2923, 2853, 1653, 1645, 1453, 1425, 1375, 1304, 1242, 1175, 1120, 1101, 1068, 1047 cm^{-1}.

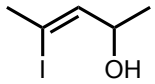
HRMS (EI): calc'd for $C_{11}H_{21}O$ $[M – I]^+$, *m/z* 169.1590; found 169.1592.

R_f = 0.63 (20% EtOAc/hexanes).

Appearance: light-yellow oil.

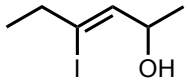
Reaction scale: 9 mmol.

Purification: FCC on SiO_2, 0–12% EtOAc/hexanes.



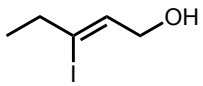
(*Z*)-4-Iodopent-3-en-2-ol (2.15)

Prepared (746 mg, 59% over two steps) according to literature procedures.[9] Spectroscopic data matched those reported in the literature.[9]



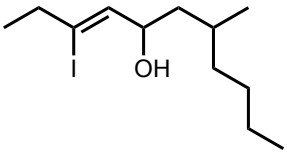
(*Z*)-4-Iodohex-3-en-2-ol (2.16)

Prepared (440 mg, 71%) according to literature procedures.[10] Spectroscopic data matched those reported in the literature.[10]



(Z)-3-Iodopent-2-en-1-ol (2.3)

Prepared (1.3 g, 95%) according to literature procedures.[4] Spectroscopic data matched those reported in the literature.[4]



(*Z*)-3-Iodo-7-methylundec-3-en-5-ol (2.38)

Prepared (65% over three steps) according to procedure 6 from ethyl 2-pentynoate.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.57 (dd, J = 7.5 Hz, J = 7.7 Hz, 1H), 4.38–4.39 (m, 1H), 2.49–2.52 (m, 2H), 1.72–1.74 (m, 1H), 1.57–1.65 (m, 1H), 1.40–1.52 (m, 1H), 1.21–1.29 (m, 6H), 1.13–1.19 (m, 1H), 1.08 (dd, J = 7.3, 1.6 Hz, 3H), 0.89–0.96 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 136.5, 136.4, 111.9, 111.2, 75.0, 74.7, 43.6, 43.4, 39.1, 39.0, 37.2, 36.4, 36.2, 31.8, 29.2, 29.2, 29.1, 29.0, 28.9, 25.1, 23.0, 22.9, 22.6, 20.5, 19.4, 14.7, 14.7.

IR (neat): 3309, 2954, 2923, 2871, 2857, 1644, 1455, 1428, 1377, 1227, 1055 cm^{-1}.

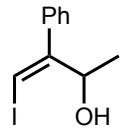
HRMS (EI): calc'd for $C_{10}H_{18}IO$ [M – C_2H_5]$^+$, *m/z* 281.0402; found 281.0397.

R_f = 0.47 (10% EtOAc/hexanes).

Appearance: pale-yellow oil.

Reaction scale: 2.36 mmol

Purification: FCC on SiO_2, 0–7% EtOAc/hexanes.



(*Z*)-4-Iodo-3-phenylbut-3-en-2-ol (2.39)

Prepared according to procedure 6 from **2.18** (89%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31–7.35 (m, 5H), 6.33 (s, 1H), 5.03 (quint, J = 6.1 Hz, 1H), 1.33 (d, J = 6.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.7, 138.5, 128.2, 128.2, 128.0, 79.8, 72.6, 21.3.

IR (neat): 3281, 3048, 2966, 2848, 1600, 1586, 1572, 1453, 1362, 1278, 1189, 1109, 1074 cm^{-1}.

HRMS (ESI): calc'd for $C_{10}H_{11}IO$ [M + H]$^+$, *m/z* 273.9849; found 273.9846.

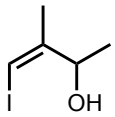
M.p. = 67–68 °C.

***R*$_f$** = 0.36 (10% EtOAc/hexanes).

Appearance: white solid.

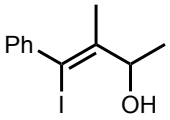
Reaction scale: 2.13 mmol.

Purification: FCC on SiO_2, 0–15% EtOAc/hexanes.



(*Z*)-4-Iodo-3-methylbut-3-en-2-ol (2.23)

Prepared (639 mg, 59%) following literature procedures.[21] Spectral data matched those found in the literature.[21]



(*Z*)-4-Iodo-3-methyl-4-phenylbut-3-en-2-ol (2.24)

Prepared (1.04 g, 94% over two steps from 3-butyn-2-ol) according to procedure 3 from commercially available iodobenzene and 3-butyn-2-ol.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (t, J = 7.6 Hz, 2H), 7.20–7.24 (m, 3H), 4.95 (q, J = 6.5 Hz, 1H), 1.77 (bs, 1H), 1.71 (s, 3H), 1.35 (d, J = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 144.8, 144.2, 128.6, 128.2, 127.6, 94.1, 76.8, 20.3, 13.9.

IR (neat): 3326, 2972, 2925, 1484, 1440, 1375, 1285, 1229, 1098, 1071, 1008, 972, 908, 845, 753, 734, 689, 650, 599 cm^{-1}.

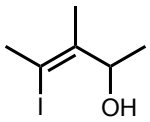
HRMS (ESI): calc'd for $C_{11}H_{13}IO$ $[M + H]^+$, *m/z* 288.0006; found 287.9996.

R_f = 0.38 (10% EtOAc/hexanes).

Appearance: yellow oil.

Reaction scale: 3.84 mmol.

Purification: FCC on SiO_2, 0–15% EtOAc/hexanes



(*Z*)-4-Iodo-3-methylpent-3-en-2-ol (2.25)

Prepared (767 mg, 60% over two steps) according to procedure 3 from commercially available propynylmagnesium bromide and acetaldehyde.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.76 (q, J = 6.2 Hz, 1H), 2.51 (s, 3H), 1.78 (s, 3H), 1.20 (d, J = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 141.2, 92.9, 77.3, 30.5, 20.1, 11.9.

IR (neat): 3311, 2969, 2917, 1633, 1442, 1433, 1379, 1366, 1327, 1283, 1167, 1055, 1013 cm^{-1}.

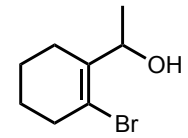
HRMS (ESI): calc'd for $C_6H_{11}IO$ $[M + H]^+$, *m/z* 225.9849; found 225.9842.

R_f = 0.32 (10% EtOAc/hexanes).

Appearance: clear oil.

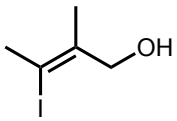
Reaction scale: 5.65 mmol.

Purification: FCC on SiO_2, 0–12% EtOAc/hexanes.



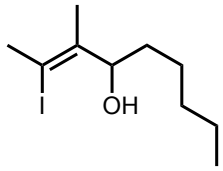
1-(2-Bromocyclohex-1-en-1-yl)ethanol (2.28)

Prepared (698 mg, 37% over two steps) following literature procedures.[24] Spectroscopic data matched those previously reported.[24]



(*Z*)-3-Iodo-2-methylbut-2-en-1-ol (2.127)

Prepared following literature procedures.[29] Spectroscopic data matched those previously reported.[29]



(*Z*)-2-Iodo-3-methylnon-2-en-4-ol (2.40)

Prepared according to procedure 6 from **2.126** (83%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.56 (t, J = 5.2 Hz, 1H), 2.52 (s, 3H), 1.75 (s, 3H), 1.40–1.55 (m, 4H), 1.24–1.33 (m, 4H), 0.89 (t, J = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 140.5, 94.0, 81.1, 34.4, 31.7, 30.6, 25.2, 22.6, 14.0, 12.2.

IR (neat): 3353, 2947, 2931, 2860, 1633, 1457, 1443, 1378, 1295, 1216, 1115, 1047, 1010, 911, 908, 731, 630 cm^{-1}.

HRMS (ESI): calc'd for $C_{10}H_{19}IO$ $[M + H]^+$, *m/z* 282.0475; found 282.0471.

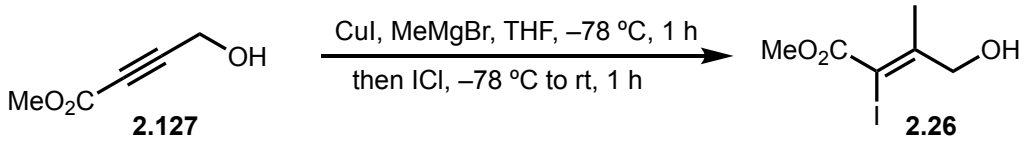
R_f = 0.45 (10% EtOAc/hexanes).

Appearance: clear oil.

Reaction scale: 9.43 mmol.

Purification: FCC on SiO_2, 0–9% EtOAc/hexanes.

Preparation of 2.26



2.127 **2.26**

CuI (8.70 g, 45.8 mmol, 1.5 equiv), THF (57 mL, 0.8 M), and a solution of the propargyl alcohol **2.127**[30] (3.48 g, 30.5 mmol, 1 equiv) in THF (30.5 mL, 1 M) were placed in an oven-dried round-bottom flask. After cooling to –78 °C, a solution of MeMgBr in THF (30.5 mL, 3 M, 91.5 mmol, 3 equiv) was added slowly and then the mixture was stirred at the same temperature for 1 h. A solution of ICl (45.8 mL, 1 M in CH_2Cl_2 45.77 mmol, 1.5 equiv) was added slowly at the same temperature. The cooling bath was removed when the addition was complete and the solution was stirred for another 1 h. The resulting solution was diluted with EtOAc and washed with saturated NH_4Cl until the aqueous layer was no longer blue. The organic phase was washed with brine, dried (anhydrous Na_2SO_4), and concentrated. The residue was purified through FCC (25–30% EtOAc//hexanes) to yield **2.26** as a bright-yellow oil (3.5g, 45%).

Note: The propargyl alcohol **2.127** is a known compound that was prepared according to literature procedures.[30] Spectral data matched those found in the literature.[30]

Methyl (*Z*)-4-hydroxy-2-iodo-3-methylbut-2-enoate (2.26)

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.32 (s, 2H), 3.81 (s, 3H), 2.15 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6, 152.4, 82.9, 71.9, 53.0, 18.8.

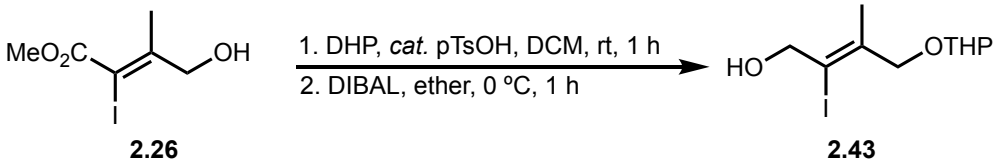
IR (neat): 3050, 2952, 1709, 1434, 1268, 1223, 1081, 1024 cm^{-1}.

HRMS (ESI): calc'd for $C_6H_9IO_3$ $[M + H]^+$, *m*/*z* 255.9591; found 255.9588.

R_f = 0.38 (25% EtOAc/hexanes)

Appearance: bright-yellow oil.

Reaction scale: 30.51 mmol



2.26 **2.43**

(*Z*)-2-Iodo-3-methyl-4-((tetrahydro-2*H*-pyran-2-yl)oxy)but-2-en-1-ol (2.43)

2.26 (5.00 g, 19.5 mmol, 1 equiv), DCM (19.5 mL, 1 M), and *p*TsOH (37.0 mg, 0.195 mmol, 10 mol%) were placed in an oven-dried round-bottom flask. The mixture was stirred at room temperature for 1 h. Upon completion of the reaction (TLC), the mixture was poured onto saturated $NaHCO_3$. The aqueous phase was extracted three times with DCM and then washed with brine. The organic phase was dried (anhydrous Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in dry Et_2O and transferred directly to another oven-dried round-bottom flask for the next step. After cooling to 0 °C, DIBAL (40.7 mL, 1.2 M, 2.5 equiv) was added slowly and then the mixture was stirred at the same temperature for 1 h. Upon completion of the reaction (TLC), the mixture was diluted with the same volume of Et_2O and slowly quenched through the addition of saturated Rochelle's salt, followed by anhydrous Na_2SO_4. The resulting gelatinous slurry was filtered through a Celite plug and concentrated *in vacuo*. The residue was purified through FCC (15–18% EtOAc/hexanes) to obtain the title compound as a clear oil (4.3 g, 71% over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.62 (t, J = 3.0 Hz, 1H), 4.38 (d, J = 5.8 Hz, 2H), 4.32 (d, J = 12.2 Hz, 1H), 4.17 (d, J = 12.2 Hz, 1H), 3.88 (t, J = 11.2 Hz, 1H), 3.53–3.55 (m, 1H), 2.19 (br s, 1H), 1.97 (s, 3H), 1.52–1.82 (m, 6H).

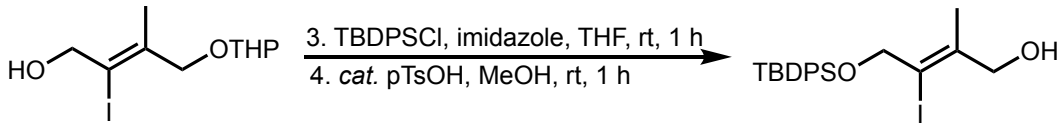
^{13}C NMR (125 MHz, $CDCl_3$): δ 140.2, 103.8, 98.3, 76.8, 67.5, 62.3, 30.5, 25.3, 19.3, 16.7.

IR (neat): 3396, 2928, 2857, 1706, 1632, 1462, 1434, 1322, 1278, 1228, 1199, 1117, 1052, 1016 cm^{-1}.

HRMS (ESI): calc'd for $C_{10}H_{17}O_3$ $[M - I]^+$, m/z 185.1172; found 185.1176.

R_f = 0.66 (25% EtOAc/hexanes).

Reaction scale: 19.53 mmol.



2.43 **2.44**

(*Z*)-4-((*tert*-Butyldiphenylsilyl)oxy)-3-iodo-2-methylbut-2-en-1-ol (2.44)

2.43 (4.30 g, 13.9 mmol, 1 equiv), imidazole (1.90 g, 27.7 mmol, 2 equiv), and THF (28 mL, 0.5 M) were placed in an oven-dried round-bottom flask. TBDPSCl (3.80 mL, 14.6 mmol, 1.05 equiv) was added and then the mixture was stirred at room temperature for 1 h. Upon completion of the reaction (TLC), the crude mixture was poured onto saturated NH_4Cl and extracted three times with EtOAc. The organic phase was washed with brine, dried (anhydrous Na_2SO_4), and concentrated *in vacuo*. The residue was dissolved in MeOH (0.5 M) and transferred to another round-bottom flask. *p*TsOH (528 mg, 2.77 mmol, 20 mol%) was added and then the mixture was stirred at room temperature for 1 h. Upon completion of the reaction (TLC), the solution was concentrated *in vacuo*. The residue was purified through FCC (15–20% EtOAc/hexanes) to obtain the title product as a clear oil (5.89 g, 91%, 2 steps).

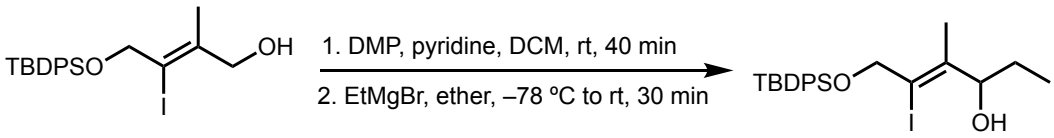
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (dd, J = 7.9 Hz, 4H), 7.38–7.46 (m, 6H), 4.38 (s, 2H), 4.22 (d, J = 6.1 Hz, 2H), 1.68 (s, 3H), 1.57 (br s, 1H), 1.09 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 140.5, 135.7, 134.8, 133.3, 129.8, 127.7, 103.5, 73.1, 67.3, 26.8, 19.3, 16.8.

IR (neat): 3320, 3070, 2927, 2856, 1589, 1472, 1463, 1425, 1389, 1362, 1262, 1190, 1019, 1006 cm^{-1}.

HRMS (ESI): calc'd for $C_{17}H_{19}IO_2Si$ $[M - C_4H_9]^+$, m/z 409.0115; found 409.0112.

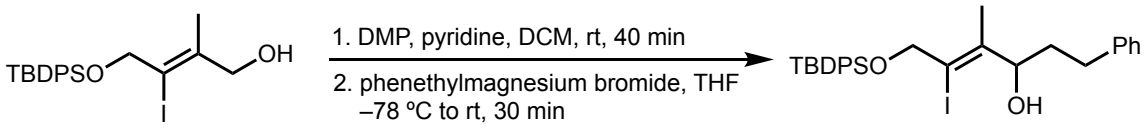
R_f = 0.57 (25% EtOAc/hexanes).



2.44 **2.41**

DMP (1.30 g, 3.07 mmol, 1.1 equiv), pyridine (1.00 mL, 12.3 mmol, 4.4 equiv), and DCM (28 mL, 0.1 M) were placed in an oven-dried round-bottom flask. A solution of **2.44** (1.30 g, 2.79 mmol, 1 equiv) in DCM (2.8 mL, 1 M) was added slowly and then the mixture was stirred at room temperature for 40 min. The resulting mixture was filtered through a silica plug into another oven-dried round-bottom flask and cooled to –78 °C. EtMgBr (5.00 mL, 15.0 mmol, 3 M in ether, 5 equiv) was added slowly. The mixture was gradually warmed to room temperature over 30 min. Upon completion of the reaction (TLC), the mixture was cooled to 0 °C and quenched with 1 M HCl. The aqueous phase was extracted three times

with EtOAc and washed with brine. The organic phase was then dried (anhydrous Na_2SO_4) and concentrated *in vacuo*. The residue was purified through FCC (12–15% EtOAc/hexanes) to give the product as a pale-yellow oil (1.2 g, 87%, 2 steps).

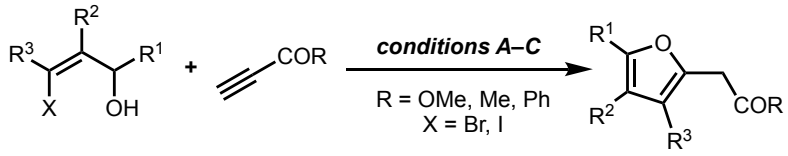


2.44 **2.42**

DMP (600 mg, 1.42 mmol, 1.1 equiv), pyridine (460 μL, 5.66 mmol, 4.4 equiv), and DCM (13 mL, 0.1 M) were placed in an oven-dried round-bottom flask. A solution of **2.44** (600 mg, 1.29 mmol, 1 equiv) in DCM (1.3 mL, 1 M) was added slowly and then the mixture was stirred at room temperature for 40 min. The resulting mixture was filtered through a silica plug into another oven-dried round-bottom flask and cooled to –78 °C. A solution of freshly prepared phenethylmagnesium bromide (prepared from 3.6 equiv Mg and 3.6 equiv phenethyl bromide in THF) was added slowly. The mixture was gradually warmed to room temperature over 30 min. Upon completion of the reaction (TLC), the mixture was cooled to 0 °C and quenched with 1 M HCl. The aqueous phase was extracted three times with EtOAc and washed with brine. The organic phase was dried (anhydrous Na_2SO_4) and concentrated *in vacuo*. The residue was purified through FCC (12–15% EtOAc/hexanes) to give the product as a clear oil (327 mg, 45%, 2 steps).

2.9.4. Michael–Heck Reactions

General Procedures for the Michael–Heck Reactions



The Michael–Heck reactions using conditions A were performed under the optimized conditions in Tables 2.7 and 2.8. Although the conditions in entry 6 of Table 2.7 would allow a one-pot reaction, the use of the conditions in entry 2 gave better results for substrates featuring secondary alcohols. In addition, because PBu_3 is a stronger ligand for palladium than tri-*tert*-butylphosphine, the removal of PBu_3 after the initial Michael addition step would be necessary under conditions B and C, and the use of MeCN

would complicate its removal. Therefore, for consistency, we used the Michael conditions in entry 2 of Table S1 for all five conditions A–C with only the Heck reaction conditions varying.

Conditions A: Synthesis of 2.55, 2.56, 2.59–2.70, 2.74–2.81, 2.86

(*Z*)-3-Iodo-2-propen-1-ol (1 equiv) and DCM (0.1 M) were placed in an oven-dried round-bottom flask under Ar. PBu_3 (0.2 equiv) was added, followed by the dropwise addition of methyl propiolate (1.5 equiv) at rt (flask A). This mixture was stirred at rt for 15–30 min. $Pd(OAc)_2$ (10 mol%) and TBAC (1 equiv) were placed in another oven-dried round-bottom flask under Ar (flask B). Upon formation of the Michael adduct (TLC), the mixture in flask A was concentrated to a minimal volume, re-dissolved in MeCN (0.1 M), and transferred to flask B. Triethylamine (5.2 equiv) was added to flask B and the solution was heated under reflux at 90 °C for 1–3 h. Upon completion of the reaction (TLC), the mixture was concentrated *in vacuo* and the residue purified through FCC to give the desired products.

Conditions A1: Synthesis of 2.57, 2.58, 2.82, 2.84, 2.87

(*Z*)-3-Iodo-2-propen-1-ol (1 equiv) and DCM (0.1 M) were placed in an oven-dried round-bottom flask. PBu_3 (0.2 equiv) was added, followed by dropwise addition of methyl propiolate (1.5 equiv) at rt (flask A). The mixture was stirred at rt for 15–30 min. $Pd(OAc)_2$ (0.1 equiv) and TBAC (1 equiv) were placed in an oven-dried sealed tube (flask B). Upon formation of the Michael adduct (TLC), the mixture in flask A was concentrated to a minimal volume, re-dissolved in MeCN (0.1 M), and transferred to flask B. Triethylamine (5.2 equiv) was added to flask B and the solution was heated under reflux at 110 °C for 1–2 h. Upon completion of the reaction (TLC), the mixture was concentrated *in vacuo* and the residue purified through FCC to give the desired products.

Conditions A2: Synthesis of 2.71–2.73

(*Z*)-3-Iodo-2-propen-1-ol (1 equiv), PBu_3 (0.2 equiv), and DCM (0.1 M) were placed in an oven-dried round-bottom flask. A solution of 3-butyn-2-one or 1-phenylprop-2-yn-1-one (1.5 equiv) in DCM (0.5 M) was added over 1 h using a syringe pump. $Pd(OAc)_2$ (0.1 equiv) and TBAC (1 equiv) were placed in another oven-dried round-bottom flask under Ar (flask B). Upon formation of the Michael adduct (TLC),

the mixture in flask A was concentrated to a minimal volume, re-dissolved in MeCN (0.1 M), and transferred to flask B. Triethylamine (5.2 equiv) was added to flask B and then the solution was heated under reflux at 90 °C for 1–3 h. Upon completion of the reaction (TLC), the mixture was concentrated *in vacuo* and the residue purified through FCC to give the desired products.

Conditions B: Synthesis of 2.83, 2.85, 2.88–2.91 (plakorsin D methyl ester), 2.91

(*Z*)-3-Iodo-2-propen-1-ol (1 equiv) and DCM (0.1 M) were placed in an oven-dried round-bottom flask. PBu_3 (0.2 equiv) was added, followed by dropwise addition of methyl propiolate (1.5 equiv) at rt (flask A). The mixture was stirred at rt for 15–30 min. $Pd(OAc)_2$ (0.1 equiv), tri *tert*-butylphosphonium tetrafluoroborate (0.2 equiv), and TBAC (1 equiv) were placed in another oven-dried round-bottom flask (flask B). Upon formation of the Michael adduct (TLC), the mixture in flask A was passed through a short pad of silica and concentrated to a minimal volume. (*Note:* Filtration of the crude Michael adduct through silica was necessary to remove PBu_3.) The crude Michael adduct was then re-dissolved in dry MeCN (0.1 M) and transferred to flask B. *N*,*N*-Dicyclohexylamine (5.2 equiv) was added and the mixture was stirred for 12–16 h at 90 °C. The mixture was concentrated *in vacuo* and the residue purified through FCC to give the desired products.

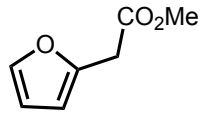
Note 1: Conditions C could also be used, but conditions B gave slightly better results.

Conditions C: Synthesis of 2.92–2.96

(*Z*)-3-Iodo-2-propen-1-ol (1 equiv) and DCM (0.1 M) were placed in an oven-dried round-bottom flask. PBu_3 (0.2 equiv) was added, followed by the dropwise addition of methyl propiolate (1.5 equiv) at rt (flask A). The mixture was stirred at rt for 15–30 min. $Pd_2(dba)_3$ complex (5 mol%), tri-*tert*-butylphosphonium tetrafluoroborate (0.2 equiv), and TBAC (1 equiv) were placed in another oven-dried round-bottom flask (flask B). Upon formation of the Michael adduct (TLC), the mixture in flask A was passed through a short pad of silica and concentrated to a minimal volume. (*Note:* Filtration of the crude Michael adduct through silica was necessary to remove PBu_3.) The crude Michael adduct was re-dissolved in dry MeCN (0.1 M) and transferred to flask B. *N*,*N*-Dicyclohexylamine (5.2 equiv) was added and the mixture was stirred for 12–16 h at 110 °C. The mixture was diluted with MeOH (same volume as the

volume of toluene used) and concentrated *in vacuo*. The residue was purified through FCC (0–4% EtOAc/hexanes) to give the desired products.

2.9.5. Characterization Data for Furan Products



Methyl 2-(fur-2-yl)acetate (2.55)

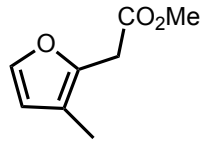
Prepared (222 mg, 94%) under conditions A. Spectral data matched those in the literature.[34]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, J = 0.95 Hz, 1H), 6.33 (dd, J = 3.2, 0.9 Hz, 1H), 6.22 (d, J = 3.1 Hz, 1H), 3.71 (s, 3H), 3.69 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 147.5, 142.0, 110.5, 108.0, 52.2, 33.8.

Reaction scale: 1.68 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



Methyl 2-(3-methylfur-2-yl)acetate (2.56)

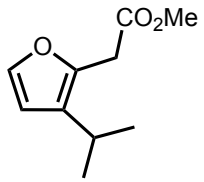
Prepared (773 mg, 90%) under conditions A. Spectral data matched those in the literature.[35]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, J = 1.6 Hz, 1H), 6.20 (d, J = 1.53 Hz, 1H), 3.70 (s, 3H), 3.61 (s, 2H), 1.98 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 143.1, 141.0, 116.9, 113.0, 52.1, 32.0, 9.7.

Reaction scale: 5.57 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



Methyl 2-(3-isopropylfur-2-yl)acetate (2.57)

Prepared (417 mg, 73%) under conditions A1.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, J = 1.9 Hz, 1H), 6.29 (d, J = 1.9 Hz, 1H), 3.70 (s, 3H), 3.64 (s, 2H), 2.78 (sept, J = 6.9 Hz, 1H), 1.15 (d, J = 6.9 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 141.5, 141.3, 128.5, 109.1, 52.2, 32.2, 24.5, 23.5.

IR (neat): 3115, 2954, 2868, 1740, 1624, 1512, 1465, 1449, 1439, 1380 1222, 1161, 1068, 995, 901, 823, 732, 624 cm^{-1}.

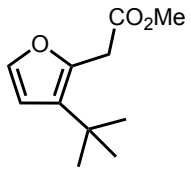
HRMS (ESI): calc'd for $C_{10}H_{14}O_3$ $[M + H]^+$, *m/z* 182.0937; found 182.0940.

R_f = 0.53 (10% EtOAc/hexanes).

Appearance: orange oil.

Reaction scale: 3.14 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



Methyl 2-(3-(*tert*-butyl)fur-2-yl)acetate (2.58)

Prepared (184 mg, 62%) under conditions A1.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, J = 1.9 Hz, 1H), 6.30 (d, J = 1.9 Hz, 1H), 3.78 (s, 2H), 3.71 (s, 3H), 1.26 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 141.4, 140.3, 130.8, 110.8, 52.1, 34.2, 31.1, 30.1.

IR (neat): 2954, 2904, 1740, 1682, 1523, 1478, 1436, 1407, 1389, 1338, 1277, 1172, 1110, 886, 785, 697 cm^{-1}.

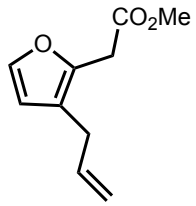
HRMS (ESI): calc'd for $C_{11}H_{16}O_3$ $[M + H]^+$, *m/z* 196.1094; found 196.1095.

R_f = 0.54 (10% EtOAc/hexanes).

Appearance: orange oil.

Reaction scale: 1.52 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



Methyl 2-(3-allylfur-2-yl)acetate (2.59)

Prepared (318 mg, 72%) under conditions A.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, J = 1.9 Hz, 1H), 6.24 (d, J = 1.8 Hz, 1H), 5.84–5.91 (m, 1H), 5.02–5.07 (m, 2H), 3.70 (s, 3H), 3.63 (s, 2H), 3.14 (dt, J = 6.3, 1.5 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 143.4, 141.3, 136.2, 119.5, 115.5, 112.1, 52.2, 32.1, 29.1.

IR (neat): 2974, 2956, 1741, 1636, 1623, 1510, 1437, 1340, 1234, 1203, 1164, 1068, 1011 cm^{-1}.

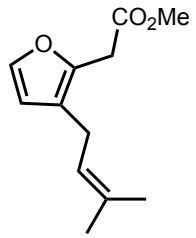
HRMS (ESI): calc'd for $C_{10}H_{12}O_3$ $[M + H]^+$, *m/z* 180.0781; found 180.0779.

R_f = 0.56 (10% EtOAc/hexanes).

Appearance: orange oil.

Reaction scale: 2.45 mmol.

Purification: FCC on SiO_2, 0–4% EtOAc/hexanes.



Methyl 2-(3-(3-methylbut-2-en-1-yl)fur-2-yl)acetate (2.60)

Prepared (220 mg, 67%) under conditions A.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, J = 1.9 Hz, 1H), 6.22 (d, J = 1.9 Hz, 1H), 5.20 (tq, J = 7.2, 1.4 Hz, 1H), 3.71 (s, 3H), 3.63 (s, 2H), 3.07 (d, J = 7.2 Hz, 2H), 1.72 (s, 3H), 1.69 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 142.7, 141.2, 132.5, 122.1, 121.3, 112.0, 52.2, 32.2, 25.6, 23.6, 17.7.

IR (neat): 2954, 2920, 2852, 1741, 1509, 1437, 1376, 1338, 1267, 1208, 1166, 1071, 1011 cm^{-1}.

HRMS (ESI): calc'd for $C_{12}H_{16}O_3$ $[M + H]^+$, *m/z* 208.1094; found 208.1091.

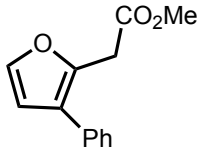
R_f = 0.56 (10% EtOAc/hexanes).

Appearance: dark-orange oil.

Reaction scale: 1.58 mmol.

Purification: FCC on SiO_2, 0–4% EtOAc/hexanes.

Note: Limited stability; must be refrigerated immediately.



Methyl 2-(3-phenylfur-2-yl)acetate (2.61)

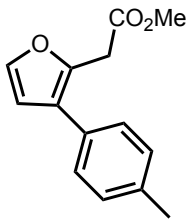
Prepared (278 mg, 56%) under conditions A. Spectral data matched those in the literature.[36]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40–7.44 (m, 5H), 7.30–7.33 (m, 1H), 6.56 (d, J = 1.9 Hz, 1H), 3.81 (s, 2H), 3.76 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 143.2, 141.8, 133.2, 128.7, 127.7, 127.0, 124.0, 111.5, 52.3, 32.9.

Reaction scale: 2.30 mmol.

Purification: FCC on SiO_2, 0–6% EtOAc/hexanes.



Methyl 2-(3-(*p*-tolyl)fur-2-yl)acetate (2.62)

Prepared (60 mg, 72%) under conditions A.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, J = 1.9 Hz, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 6.53 (d, J = 1.9 Hz, 1H), 3.79 (s, 2H), 3.75 (s, 3H), 2.38 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 143.0, 141.7, 136.7, 130.3, 129.4, 127.6, 123.9, 111.6, 52.3, 33.0, 21.1.

IR (neat): 3154, 2923, 2850, 2734, 1740, 1613, 1519, 1436, 1338, 1306, 1255, 1178, 1013, 973, 821, 719, 600 cm^{-1}.

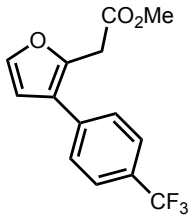
HRMS (ESI): calc'd for $C_{14}H_{14}O_3$ $[M + H]^+$, *m/z* 230.0937; found 230.0939.

R_f = 0.51 (10% EtOAc/hexanes).

Appearance: light-brown oil.

Reaction scale: 0.36 mmol.

Purification: FCC on SiO_2, 0–6% EtOAc/hexanes.



Methyl 2-(3-(4-(trifluoromethyl)phenyl)fur-2-yl)acetate (2.63)

Prepared (176 mg, 71%) under conditions A.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 2.0 Hz, 1H), 6.56 (d, J = 1.9 Hz, 1H), 3.79 (s, 2H), 3.76 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 144.1, 142.2, 129.1 (q, $^2J_{C–F}$ = 32.4 Hz), 128.8 (q, $^3J_{C–F}$ = 12.5 Hz), 128.0, 125.7 (q, $^4J_{C–F}$ = 3.8 Hz), 124.2 (q, $^1J_{C–F}$ = 270.3 Hz), 123.0, 111.3, 52.5, 33.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.6.

IR (neat): 2954, 2859, 1743, 1620, 1526, 1504, 1440, 1392, 1324, 1255, 1066, 973, 847, 793, 753, 686, 607 cm^{-1}.

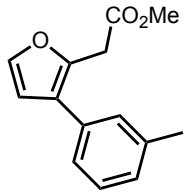
HRMS (ESI): calc'd for $C_{14}H_{11}F_3O_3$ $[M + H]^+$, *m/z* 284.0655; found 284.0660.

R_f = 0.5 (10% EtOAc/hexanes).

Appearance: orange oil.

Reaction scale: 0.75 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



Methyl 2-(3-(*m*-tolyl)fur-2-yl)acetate (2.64)

Prepared (147 mg, 53%) under conditions A.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, J = 1.95 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 8.9 Hz, 2H), 7.13 (d, J = 7.5 Hz, 1H), 6.54 (d, J = 1.9 Hz, 1H), 3.80 (s, 2H), 3.76 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 143.2, 141.7, 138.3, 133.1, 128.6, 128.5, 127.8, 124.8, 124.0, 111.5, 52.3, 33.0, 21.4.

IR (neat): 3026, 2951, 2925, 2860, 1732, 1611, 1585, 1510, 1491, 1439, 1336, 1261, 1160, 1062, 911, 893, 784, 701 cm^{-1}.

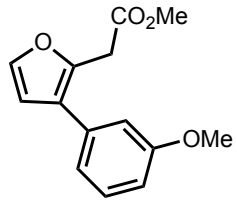
HRMS (ESI): calc'd for $C_{14}H_{14}O_3$ $[M + H]^+$ *m/z* 230.0937**; found** 230.0939.

R_f = 0.56 (10% EtOAc/hexanes).

Appearance: yellow oil.

Reaction scale: 1.21 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



Methyl 2-(3-(3-methoxyphenyl)fur-2-yl)acetate (2.65)

Prepared (271 mg, 78%) under conditions A.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, J = 1.9 Hz, 1H), 7.32 (t, J = 7.7 Hz, 1H), 6.97–6.99 (m, 2H), 6.86 (dq, J = 8.3, 0.85 Hz, 1H), 6.54 (d, J = 1.9 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 2H), 3.75 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 159.8, 143.4, 141.8, 134.6, 129.7, 124.0, 120.2, 113.4, 112.6, 111.5, 55.2, 52.4, 33.1.

IR (neat): 2949, 2836, 1736, 1603, 1579, 1515, 1486, 1459, 1434, 1334, 1317, 1304, 1286, 1260, 1225, 1168, 1140, 1046, 1010 cm^{-1}.

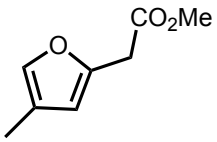
HRMS (ESI): calc'd for $C_{14}H_{14}O_4$ $[M + H]^+$, *m/z* 246.0887; found 246.0885.

***R*$_f$** = 0.37 (10% EtOAc/hexanes).

Appearance: reddish-orange oil.

Reaction scale: 1.41 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



Methyl 2-(4-methylfur-2-yl)acetate (2.66)

Prepared (224 mg, 82%) under conditions A.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (s, 1H), 6.08 (s, 1H), 3.71 (s, 3H), 3.63 (s, 2H), 1.99 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 147.5, 138.7, 120.8, 110.7, 52.2, 34.0, 9.7.

IR (neat): 2958, 1750, 1686, 1653, 1555, 1454, 1370, 1345, 1306, 1204, 1143, 1089, 951, 810, 723, 633 cm^{-1}.

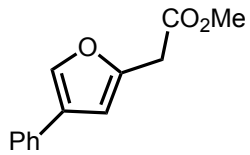
HRMS (ESI): calc'd for $C_8H_{10}O_3$ $[M + H]^+$, *m/z* 154.0624; found 154.0627.

***R*$_f$** = 0.54 (10% EtOAc/hexanes).

Appearance: yellow oil.

Reaction scale: 1.77 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



Methyl 2-(4-phenylfur-2-yl)acetate (2.67)

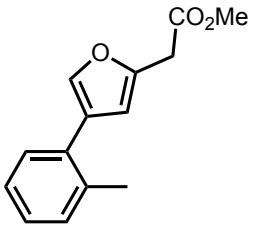
Prepared (176 mg, 97%) under conditions A. Spectral data matched those in the literature.[36]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.46 (d, J = 7.4 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.25 (t, J = 7.3 Hz, 1H), 6.56 (s, 1H), 3.75 (s, 3H), 3.73 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 148.7, 137.9, 132.3, 128.7, 127.4, 127.0, 125.7, 107.4, 52.3, 34.0.

Reaction scale: 0.84 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



Methyl 2-(4-(*o*-tolyl)fur-2-yl)acetate (2.68)

Prepared (114 mg, 53%) under conditions A.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, J = 2.0 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 8.9 Hz, 2H), 7.13 (d, J = 7.5 Hz, 1H), 6.54 (d, J = 1.9 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 2H), 2.40 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 147.5, 139.3, 135.6, 132.0, 130.6, 129.0, 127.1, 126.5, 125.8, 109.9, 52.2, 33.9, 21.1.

IR (neat): 3060, 3016, 2948, 2846, 1739, 1642, 1602, 1548, 1483, 1461, 1436, 1375, 1335, 1258, 1139, 1038, 903, 828, 759 cm^{-1}.

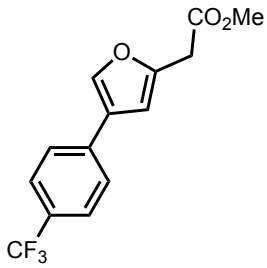
HRMS (ESI): calc'd for $C_{14}H_{14}O_3$ $[M + H]^+$, *m/z* 230.0937; found 230.0940.

$\boldsymbol{R_f}$ = 0.57 (10% EtOAc/hexanes).

Appearance: pale-yellow oil.

Reaction scale: 0.94 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



Methyl 2-(4-(4-(trifluoromethyl)phenyl)fur-2-yl)acetate (2.69)

Prepared (143 mg, 87%) under conditions A.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (s, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 6.58 (d, J = 0.7 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5, 149.3, 138.8, 135.9 (q, $^4J_{C–F}$ = 1.2 Hz), 128.9 (q, $^2J_{C–F}$ = 32.4 Hz), 126.3, 125.8, 125.7 (q, $^3J_{C–F}$ = 3.8 Hz), 124.2 (q, $^1J_{C–F}$ = 270.2 Hz), 107.2, 52.4, 33.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.7.

IR (neat): 2973, 2868, 1725, 1613, 1515, 1486, 1450, 1425, 1324, 1161, 911, 821, 730, 651 cm^{-1}.

HRMS (ESI): calc'd for $C_{14}H_{11}F_3O_3$ $[M + H]^+$, *m/z* 284.0655; found 284.0658.

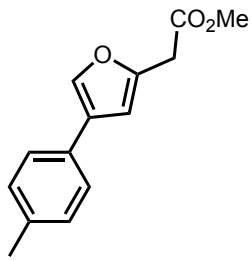
M.p. = 74–75 °C.

R_f = 0.43 (10% EtOAc/hexanes).

Appearance: white solid.

Reaction scale: 0.57 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



Methyl 2-(4-(*p*-tolyl)fur-2-yl)acetate (2.70)

Prepared (494 mg, 84%) under conditions A.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.35 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 6.54 (s, 1H), 3.75 (s, 3H), 3.73 (s, 2H), 2.36 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 148.5, 137.5, 136.7, 129.4, 127.3, 125.8, 125.6, 107.5, 52.3, 34.1, 21.1.

IR (neat): 3136, 3024, 2919, 2861, 1740, 1696, 1653, 1620, 1562, 1504, 1436, 1378, 1341, 1201, 1135, 1042, 907, 810, 773, 701, 650 cm^{-1}.

HRMS (ESI): calc'd for $C_{14}H_{14}O_3$ $[M + H]^+$, *m/z* 230.0937; found 230.0940.

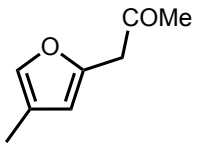
M.p. = 50–51 °C.

R_f = 0.54 (10% EtOAc/hexanes).

Appearance: pale-yellow solid.

Reaction scale: 2.56 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



1-(4-Methylfur-2-yl)propan-2-one (2.71)

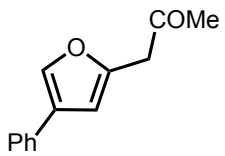
Prepared (710 mg, 91%) under conditions A2. Spectral data matched those in the literature.[37]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (s, 1H), 6.04 (s, 1H), 3.63 (s, 2H), 2.14 (s, 3H), 1.98 (d, J = 1.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 204.3, 148.1, 138.7, 120.9, 110.9, 43.3, 29.1, 9.6.

Reaction scale: 5.65 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



1-(4-Phenylfur-2-yl)propan-2-one (2.72)

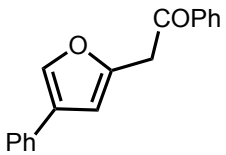
Prepared (92 mg, 53%) under conditions A2. Spectral data matched those in the literature.[38]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.46 (dd, J = 8.3, 1.3 Hz, 2H), 7.36 (t, J = 7.5 Hz, 2H), 7.24–7.27 (m, 1H), 6.53 (s, 1H), 3.74 (s, 2H), 2.21 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 204.0, 149.3, 138.0, 132.2, 128.8, 127.5, 127.1, 125.7, 107.6, 43.3, 29.3.

Reaction scale:1 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



1-Phenyl-2-(4-phenylfur-2-yl)ethanone (2.73)

Prepared (161 mg, 46%) under conditions A2.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, J = 7.6 Hz, 2H), 7.67 (s, 1H), 7.59 (t, J = 7.4 Hz, 1H), 7.45–7.51 (m, 4H), 7.35 (t, J = 7.7 Hz, 2H), 7.23–7.26 (m, 1H), 6.58 (s, 1H), 4.35 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.9, 149.4, 137.9, 136.2, 133.5, 132.4, 128.7, 128.7 128.6, 127.5, 126.9, 125.8, 107.7, 38.5.

IR (neat): 2977, 2876, 1761, 1721, 1686, 1602, 1573, 1552, 1479, 1446, 1396, 1338, 1302, 1204, 1070, 911, 839, 727, 690 cm^{-1}.

HRMS (ESI): calc'd for $C_{18}H_{14}O_2$ $[M + H]^+$, *m/z* 262.0988; found 262.0992.

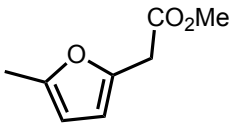
M.p. = 120–121 °C.

$\boldsymbol{R_f}$ = 0.42 (10% EtOAc/hexanes).

Appearance: light-orange solid.

Reaction scale: 1.33 mmol.

Purification: FCC on SiO_2, 0–8% EtOAc/hexanes.



Methyl 2-(5-methylfur-2-yl)acetate (2.74)

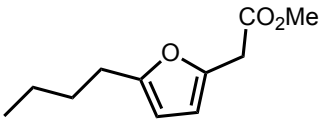
Prepared (154 mg, 96%) under conditions A. Spectral data matched those in the literature.[39]

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.08 (d, J = 2.9 Hz, 1H), 5.89 (d, J = 2.1 Hz, 1H), 3.71 (s, 3H), 3.62 (s, 2H), 2.26 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 151.6, 145.6, 108.7, 106.3, 52.1, 33.9, 13.4.

Reaction scale: 1.04 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



Methyl 2-(5-butylfur-2-yl)acetate (2.75)

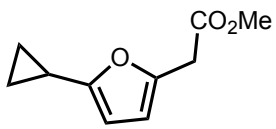
Prepared (164 mg, 84%) under conditions A. Spectral data matched those in the literature.[40]

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.09 (d, J = 2.9 Hz, 1H), 5.90 (d, J = 2.9 Hz, 1H), 3.71 (s, 3H), 3.63 (s, 2H), 2.58 (t, J = 7.6 Hz, 2H), 1.60 (quint, J = 7.4 Hz, 2H), 1.36 (sext, J = 7.5 Hz, 2H), 0.92 (t, J = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 156.2, 145.4, 108.4, 105.4, 52.1, 34.0, 30.1, 27.7, 22.2, 13.8.

Reaction scale: 1 mmol.

Purification: FCC on SiO_2, 0–4% EtOAc/hexanes.



Methyl 2-(5-cyclopropylfur-2-yl)acetate (2.76)

Prepared (310 mg, 77%) under conditions A.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.07 (d, J = 3 Hz, 1H), 5.87 (d, J = 3 Hz, 1H), 3.71 (s, 3H), 3.62 (s, 2H), 1.82–1.87 (m, 1H), 0.82–0.86 (m, 2H), 0.71–0.74 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 157.0, 145.3, 108.6, 104.3, 52.2, 34.0, 8.7, 6.5.

IR (neat): 3003, 2949, 1740, 1615, 1568, 1434, 1433, 1338, 1271, 1227, 1200, 1168, 1148, 1066, 1052, 1013 cm^{-1}.

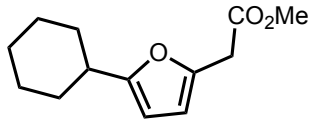
HRMS (ESI): calc'd for $C_{10}H_{12}O_3$ $[M + H]^+$, *m/z* 180.0781; found 180.0785.

R_f = 0.55 (10% EtOAc/hexanes).

Appearance: orange oil.

Reaction scale: 2.23 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



Methyl 2-(5-cyclohexylfur-2-yl)acetate (2.77)

Prepared (196 mg, 79%) under conditions A.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.09 (d, J = 2.9 Hz, 1H), 5.88 (d, J = 2.7 Hz, 1H), 3.72 (s, 3H), 3.64 (s, 2H), 2.56–2.58 (m, 1H), 1.99–2.01 (m, 2H), 1.77 (d, J = 4.5 Hz, 2H), 1.68–1.70 (m, 1H), 1.30–1.39 (m, 4H), 1.20–1.26 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 160.7, 145.2, 108.2, 103.5, 52.2, 37.2, 34.0, 31.5, 26.1, 25.9.

IR (neat): 2925, 2856, 1736, 1615, 1558, 1449, 1439, 1340, 1269, 1164, 1017, 968, 889, 851, 788, 743, 693, 581 cm^{-1}.

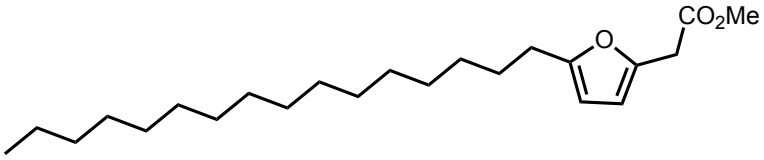
HRMS (ESI): calc'd for $C_{13}H_{18}O_3$ $[M + H]^+$, *m/z* 222.1250; found 222.1252.

R_f = 0.59 (10% EtOAc/hexanes).

Appearance: reddish-brown oil

Reaction scale: 1.11 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



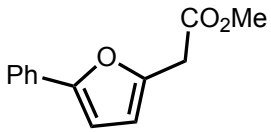
Plakorsin A (2.80)
Prepared (176 mg, 86%) under conditions A. Spectral data matched those in the literature.[41]

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.09 (d, J = 3.1 Hz, 1H), 5.90 (d, J = 3.0 Hz, 1H), 3.72 (s, 3H), 3.64 (s, 2H), 2.57 (t, J = 7.6 Hz, 2H), 1.61 (quint, J = 7.7 Hz, 2H), 1.26 (s, 26H), 0.88 (t, J = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 156.3, 145.5, 108.5, 105.4, 52.2, 34.0, 31.9, 29.7, 29.7, 29.7, 29.6, 29.6, 29.4, 29.2, 28.0, 28.0, 22.7, 14.1.

Reaction scale: 0.56 mmol.

Purification: FCC on SiO_2, 0–4% EtOAc/hexanes.



Methyl 2-(5-phenylfur-2-yl)acetate (2.78)

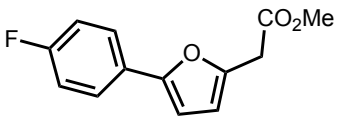
Prepared (52 mg, 89%) under conditions A. Spectral data matched those in the literature.[42]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (dd, J = 8.5, 1.4 Hz, 2H), 7.37 (t, J = 7.7 Hz, 2H), 7.25 (t, J = 7.4 Hz, 1H), 6.60 (d, J = 3.3 Hz, 1H), 6.32 (d, J = 3.3 Hz, 1H), 3.77 (s, 2H), 3.75 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 153.5, 147.2, 130.7, 128.6, 127.2, 123.6, 110.2, 105.9, 52.3, 34.1.

Reaction scale: 0.27 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



Methyl 2-(5-(4-fluorophenyl)fur-2-yl)acetate (2.79)

Prepared (314 mg, 62%) under conditions A.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59–7.62 (m, 2H), 7.06 (t, J = 8.7 Hz, 2H), 6.52 (d, J = 3.3 Hz, 1H), 6.30 (d, J = 3.3 Hz, 1H), 3.75 (s, 5H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 162.0 (d, J = 245 Hz), 152.7, 147.2, 127.1 (d, J = 3.2 Hz), 125.4 (d, J = 8.0 Hz), 115.6 (d, J = 21.8 Hz), 110.2, 105.6 (d, J = 1.3 Hz), 52.3, 34.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ –114.5.

IR (neat): 2954, 1739, 1614, 1595, 1551, 1496, 1437, 1409, 1379, 1336, 1262, 1227, 1156, 1142, 1096, 1058, 1047, 1017, 1007 cm^{-1}.

HRMS (ESI): calc'd for $C_{13}H_{11}FO_3$ $[M + H]^+$, *m/z* 234.0687; found 234.069.

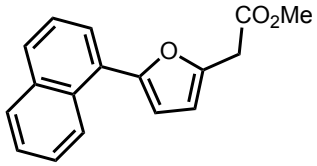
R_f = 0.51 (10% EtOAc/hexanes).

Appearance: orange oil.

Reaction scale: 2.16 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.

***Note*:** Small unassignable signals present at δ 7.4 (^{1}H NMR) and 51.7 and 148.8 (^{13}C NMR).



Methyl 2-(5-(naphth-1-yl)fur-2-yl)acetate (2.81)

Prepared (320 mg, 67%) under conditions A.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.72 (dd, J = 7.2, 0.95 Hz, 1H), 7.48–7.55 (m, 3H), 6.67 (d, J = 3.2 Hz, 1H), 6.43 (d, J = 3.2 Hz, 1H), 3.84 (s, 2H), 3.78 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 153.0, 147.6, 133.9, 130.3, 128.5, 128.5, 128.4, 126.5, 126.0, 125.9, 125.5, 125.3, 110.2, 109.9, 52.3, 34.2.

IR (neat): 2951, 1744, 1738, 1608, 1587, 1546, 1507, 1446, 1392, 1340, 1312, 1256, 1219, 1186, 1145, 1096, 1017 cm^{-1}.

HRMS (ESI): calc'd for $C_{17}H_{14}O_3$ $[M + H]^+$, *m/z* 266.0937; found 266.0939.

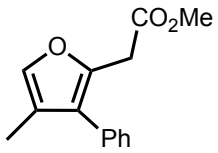
R_f = 0.34 (10% EtOAc/hexanes).

Appearance: orange oil.

Reaction scale: 1.79 mmol.

Purification: FCC on SiO_2, 0–7% EtOAc/hexanes.

***Note*:** Small unassignable signals present at δ 7.4 (^{1}H NMR) and 51.7 and 148.8 (^{13}C NMR).



Methyl 2-(4-methyl-3-phenylfur-2-yl)acetate (2.82)

Prepared (52 mg, 75%) under conditions A1.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.44 (m, 2H), 7.29–7.35 (m, 3H), 7.24 (q, *J* = 1.5 Hz, 1H), 3.72 (s, 3H), 3.65 (s, 2H), 1.99 (d, *J* = 1.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 144.0, 138.6, 132.7, 129.2, 128.4, 127.0, 125.0, 120.2, 52.2, 32.7, 8.9.

IR (neat): 3031, 2952, 2926, 1746, 1634, 1630, 1599, 1565, 1494, 1447, 1435, 1391, 1340, 1261, 1144, 1086, 905, 837, 769, 699 cm^{-1}.

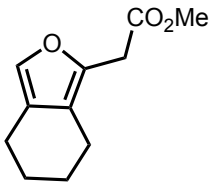
HRMS (ESI): calc'd for $C_{14}H_{14}O_3$ $[M + H]^+$, *m/z* 230.0937; found 230.0940.

R_f = 0.51 (10% EtOAc/hexanes).

Appearance: yellow oil.

Reaction scale: 0.36 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



Methyl 2-(4,5,6,7-tetrahydroisobenzofur-1-yl)acetate (2.83)

Prepared (194 mg, 96%) under conditions B.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (s, 1H), 3.70 (s, 3H), 3.57 (s, 2H), 2.51 (t, J = 6.1 Hz, 2H), 2.44 (t, J = 6.8 Hz, 2H), 1.65–1.72 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 141.0, 136.2, 122.3, 118.7, 52.1, 32.4, 23.1, 23.1, 20.1, 20.0.

IR (neat): 2931, 2856, 1740, 1637, 1558, 1443, 1408, 1326, 1261, 1247, 1168, 1006, 908, 844, 735, 644, 600, 566 cm^{-1}.

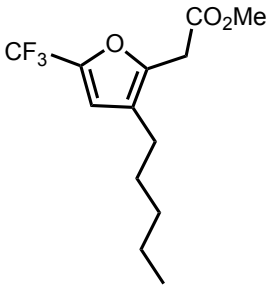
HRMS (ESI): calc'd for $C_{11}H_{14}O_3$ $[M + H]^+$, *m/z* 194.0937; found 194.0937.

R_f = 0.57 (10% EtOAc/hexanes).

Appearance: light-yellow oil.

Reaction scale: 1.03 mmol.

Purification: FCC on SiO_2, 0–4% EtOAc/hexanes.



Methyl 2-(3-pentyl-5-(trifluoromethyl)fur-2-yl)acetate (2.86)

Prepared (237 mg, 77%) under conditions A.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.64 (s, 1H), 3.72 (s, 3H), 3.66 (s, 2H), 2.35 (t, J = 7.7 Hz, 2H), 1.49–1.57 (m, 2H), 1.25–1.36 (m, 4H), 0.89 (t, J = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 145.9, 140.4 (q, J = 42 Hz), 123.5, 119.1 (q, J = 15 Hz), 113.5 (q, J = 2.6 Hz), 52.4, 32.1, 31.3, 29.6, 24.4, 22.4, 14.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ –64.0.

IR (neat): 2957, 2927, 2858, 1735, 1650, 1628, 1571, 1459, 1436, 1340, 1267, 1179, 1134, 1044, 1033, 1014 cm^{-1}.

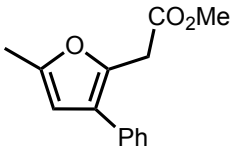
HRMS (ESI): calc'd for $C_{13}H_{17}F_3O_3$ $[M + H]^+$, *m/z* 278.1124; found 278.1123.

R_f = 0.67 (10% EtOAc/hexanes).

Appearance: orange oil.

Reaction scale: 1.10 mmol.

Purification: FCC on SiO_2, 0–3% EtOAc/hexanes.



Methyl 2-(5-methyl-3-phenylfur-2-yl)acetate (2.87)

Prepared (69 mg, 78%) under conditions A1.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.40 (m, 4H), 7.26–7.31 (m, 1H), 6.15 (d, J = 0.7 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 2H), 2.32 (d, J = 0.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 151.4, 141.3, 133.6, 128.6, 127.6, 126.8, 124.7, 107.5, 52.3, 33.0, 13.5.

IR (neat): 3031, 2949, 1736, 1642, 1602, 1577, 1532, 1498, 1441, 1380, 1309, 1228, 1134, 1011, 915, 806, 764, 698 cm^{-1}.

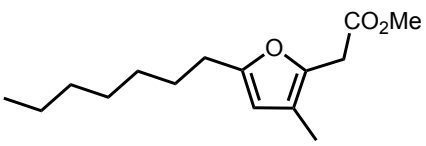
HRMS (ESI): calc'd for $C_{14}H_{14}O_3$ $[M + H]^+$, *m/z* 230.0937; found 230.0941.

R_f = 0.53 (10% EtOAc/hexanes).

Appearance: light-brown oil.

Reaction scale: 0.43 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



Methyl 2-(5-heptyl-3-methylfur-2-yl)acetate (2.88)

Prepared (480 mg, 70%) under conditions B.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.80 (s, 1H), 3.70 (s, 3H), 3.57 (s, 2H), 2.53 (t, J = 7.6 Hz, 2H), 1.93 (s, 3H), 1.59 (quint, J = 7.6 Hz, 2H), 1.25–1.34 (m, 8H), 0.88 (t, J = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 155.1, 140.9, 117.3, 108.1, 52.1, 32.0, 31.7, 29.1, 29.0, 28.0, 27.9, 22.6, 14.1, 9.8.

IR (neat): 2924, 2855, 1744, 1716, 1642, 1621, 1574, 1458, 1434, 1379, 1332, 1275, 1212, 1186, 1137, 1047, 1014 cm^{-1}.

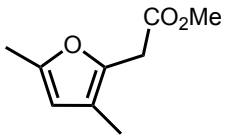
HRMS (ESI): calc'd for $C_{15}H_{24}O_3$ $[M + H]^+$, *m/z* 252.1720; found 252.1725.

R_f = 0.68 (10% EtOAc/hexanes).

Appearance: yellow oil.

Reaction scale: 2.71 mmol.

Purification: FCC on SiO_2, 0–4% EtOAc/hexanes.



Methyl 2-(3,5-dimethylfur-2-yl)acetate (2.89)

Prepared (160 mg, 81%) under conditions B.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.79 (s, 1H), 3.70 (s, 3H), 3.56 (s, 2H), 2.22 (s, 3H), 1.93 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 150.5, 141.0, 117.6, 109.1, 52.1, 32.0, 13.4, 9.8.

IR (neat): 2951, 2928, 1732, 1641, 1578, 1439, 1333, 1247, 1209, 1156, 1099, 1010, 968, 806, 739, 667, 588 cm^{-1}.

HRMS (ESI): calc'd for $C_9H_{12}O_3$ $[M + H]^+$, *m/z* 168.0781; found 168.0779.

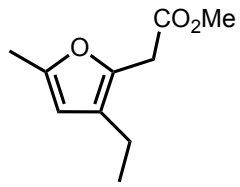
R_f = 0.53 (10% EtOAc/hexanes).

Appearance: pale-yellow oil.

Reaction scale: 1.17 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.

***Note*:** Product contained ca. 5% of an unidentified isomer.



Methyl 2-(3-ethyl-5-methylfur-2-yl)acetate (2.90)

Prepared (233 mg, 66%) under conditions B.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.85 (s, 1H), 3.69 (s, 3H), 3.56 (s, 2H), 2.32 (q, J = 7.6 Hz, 2H), 2.22 (s, 3H), 1.11 (t, J = 7.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 150.7, 140.3, 124.4, 107.4, 52.1, 32.1, 18.0, 14.8, 13.5.

IR (neat): 2949, 2928, 2865, 1741, 1713, 1642, 1575, 1436, 1336, 1273, 1134, 901, 805, 734, 662, 579 cm^{-1}.

HRMS (ESI): calc'd for $C_{10}H_{14}O_3$ $[M + H]^+$, *m/z* 182.0937; found 182.0943.

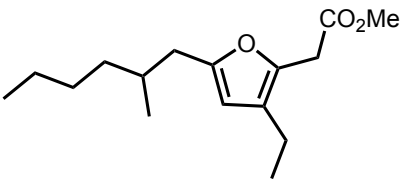
R_f = 0.54 (10% EtOAc/hexanes).

Appearance: yellow oil.

Reaction scale: 1.94 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.

***Note*:** Product contained ca. 5% of an unidentified isomer.



Plakorsin D methyl ester (2.91)

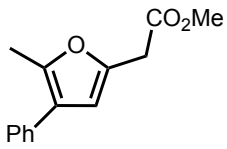
Prepared (201 mg, 64%) under conditions B. Spectral data matched those in the literature.[43]

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.85 (s, 1H), 3.68 (s, 3H), 3.57 (s, 2H), 2.53 (dd, J = 15.2, 6.1 Hz, 1H), 2.33 (quint, J = 7.7 Hz, 3H), 1.75 (sext, J = 6.4 Hz, 1H), 1.22–1.33 (m, 5H), 1.12 (t, J = 7.7 Hz, 4H), 0.88 (t, J = 6.3 Hz, 6H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 154.2, 140.2, 124.0, 107.5, 52.0, 36.3, 35.5, 32.5, 32.1, 29.2, 22.8, 19.5, 18.0, 14.8, 14.1.

Reaction scale: 1.17 mmol.

Purification: FCC on SiO_2, 0–3% EtOAc/hexanes.



Methyl 2-(5-methyl-4-phenylfur-2-yl)acetate (2.84)

Prepared (133 mg, 79%) under conditions A1.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.39 (m, 4H), 7.24–7.27 (m, 1H), 6.36 (s, 1H), 3.75 (s, 3H), 3.68 (s, 2H), 2.43 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 147.3, 145.2, 134.0, 128.5, 127.4, 126.2, 121.7, 109.6, 52.3, 33.9, 13.0.

IR (neat): 3037, 2853,1740, 1718, 1651, 1590, 1572, 1492, 1436, 1401, 1373, 1352, 1217, 1121, 1045, 960, 909, 832, 763, 697 cm^{-1}.

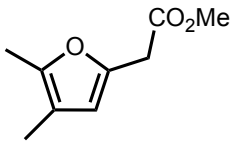
HRMS (ESI): calc'd for $C_{14}H_{14}O_3$ $[M + H]^+$, *m/z* 230.0937; found 230.0940.

R_f = 0.55 (10% EtOAc/hexanes).

Appearance: light-brown oil.

Reaction scale: 0.73 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



Methyl 2-(4,5-dimethylfur-2-yl)acetate (2.85)

Prepared (191 mg, 93%) under conditions B.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.98 (s, 1H), 3.71 (s, 3H), 3.59 (s, 2H), 2.16 (s, 3H), 1.90 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 146.8, 144.3, 114.7, 111.2, 52.1, 33.9, 11.2, 9.8.

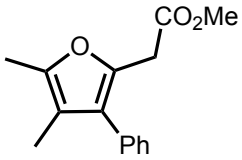
IR (neat): 2951, 2925, 2258, 1743, 1645, 1581, 1443, 1340, 1243, 1156, 1013, 964, 727, 656, 573 cm^{-1}.

HRMS (ESI): calc'd for $C_9H_{12}O_3$ $[M + H]^+$, *m/z* 168.0781; found 168.0785.

R_f = 0.55 (10% EtOAc/hexanes).

Appearance: yellow oil.

Reaction scale: 1.23 mmol.



Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.

Methyl 2-(4,5-dimethyl-3-phenylfur-2-yl)acetate (2.91)

Prepared (84 mg, 54%) under conditions B.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (t, J = 7.4 Hz, 2H), 7.29–7.32 (m, 3H), 3.72 (s, 3H), 3.61 (s, 2H), 2.25 (s, 3H), 1.91 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 146.8, 141.1, 133.3, 129.2, 128.4, 126.8, 125.6, 114.3, 52.2, 32.6, 11.6, 9.0.

IR (neat): 2951, 2925, 2856, 2258, 1740, 1611, 1581, 1495, 1449, 1390, 1340, 1265, 1160, 1073, 911, 832, 735, 693 cm^{-1}.

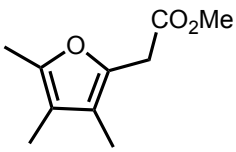
HRMS (ESI): calc'd for $C_{15}H_{16}O_3$ $[M + H]^+$, *m/z* 244.1094; found 244.1095.

R_f = 0.53 (10% EtOAc/hexanes).

Appearance: clear oil.

Reaction scale: 0.62 mmol.

Purification: FCC on SiO_2, 0–5% EtOAc/hexanes.



Methyl 2-(3,4,5-trimethylfur-2-yl)acetate (2.92)

Prepared (151 mg, 75%) under conditions C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.70 (s, 3H), 3.56 (s, 2H), 2.16 (s, 3H), 1.86 (s, 3H), 1.83 (d, J = 0.75 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 145.8, 139.9, 118.1, 115.3, 52.1, 32.2, 11.4, 8.4, 8.3.

IR (neat): 2953, 2925, 2865, 2250, 1738, 1638, 1599, 1440, 1340, 1285, 1166, 1004, 912, 833, 725, 654 cm^{-1}.

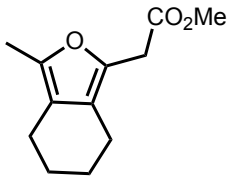
HRMS (ESI): calc'd for $C_{10}H_{14}O_3$ $[M + H]^+$, *m/z* 182.0937; found 182.0943.

R_f = 0.54 (10% EtOAc/hexanes).

Appearance: light-yellow oil.

Reaction scale: 1.11 mmol.

Purification: FCC on SiO_2, 0–4% EtOAc/hexanes.



Methyl 2-(3-methyl-4,5,6,7-tetrahydroisobenzofur-1-yl)acetate (2.93)

Prepared (227 mg, 69%) under conditions C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.70 (s, 3H), 3.54 (s, 2H), 2.38–2.41 (m, 4H), 2.14 (s, 3H), 1.66 (quint, J = 3.4 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 144.6, 138.5, 119.3, 116.6, 52.1, 32.4, 23.2, 23.1, 20.3, 20.2, 11.5.

IR (neat): 2921, 2856, 2842, 1736, 1641, 1600, 1435, 1352, 1322, 1281, 1156, 1089, 976, 946, 905, 844, 735, 689, 663 cm^{-1}.

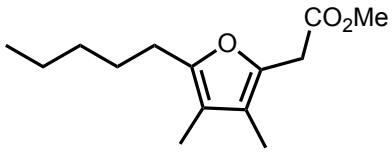
HRMS (ESI): calc'd for $C_{12}H_{16}O_3$ $[M + H]^+$, *m/z* 208.1094; found 208.1096.

R_f = 0.57 (10% EtOAc/hexanes).

Appearance: light-yellow oil.

Reaction scale: 1.58 mmol.

Purification: FCC on SiO_2, 0–4% EtOAc/hexanes.



Methyl 2-(3,4-dimethyl-5-pentylfur-2-yl)acetate (2.94)

Prepared (269 mg, 89%) under conditions C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.70 (s, 3H), 3.56 (s, 2H), 2.50 (t, J = 7.5 Hz, 2H), 1.87 (s, 3H), 1.84 (s, 3H), 1.56 (quint, J = 7.7 Hz, 2H), 1.26–1.34 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 150.1, 139.9, 117.9, 114.9, 52.0, 32.2, 31.3, 28.3, 26.0, 22.4, 14.0, 8.3, 8.3.

IR (neat): 2951, 2928, 2864, 1740, 1637, 1627, 1600, 1449, 1378, 1333, 1273, 1130, 1013, 915, 832, 735, 705 cm^{-1}.

HRMS (ESI): calc'd for $C_{14}H_{22}O_3$ $[M + H]^+$, *m/z* 238.1563; found 238.1566.

R_f = 0.57 (10% EtOAc/hexanes).

Appearance: pale-yellow oil.

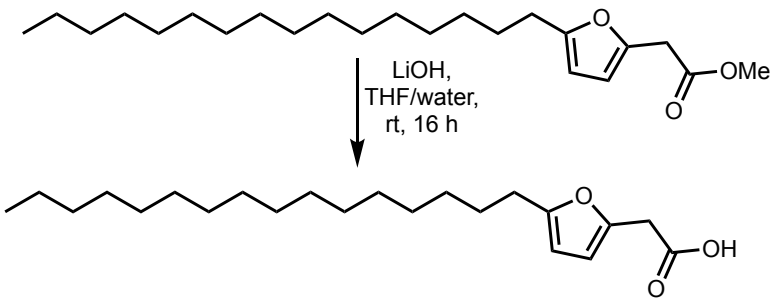
Reaction scale: 1.27 mmol.

Purification: FCC on SiO_2, 0–4% EtOAc/hexanes.

2.9.6. Applications

Synthesis of Plakorsins B and D

Synthesis of Plakorsin B



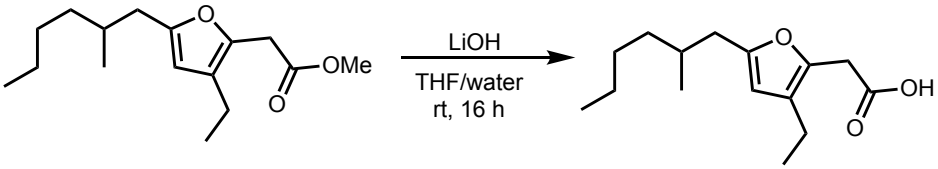
Plakorsin A (**2.80**, 43.0 mg, 0.118 mmol, 1 equiv), THF (1.7 mL), and water (0.7 mL) were placed in a round-bottom flask. LiOH monohydrate (15.0 mg, 0.354 mmol, 1 equiv) was added and the mixture was stirred at room temperature for overnight. The mixture was acidified to pH 2 using 1 M HCl (10 mL) and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined extracts were dried (anhydrous Na_2SO_4), concentrated *in vacuo*, and purified through FCC to yield plakorsin B as a white solid (40 mg, 97%; 83% from **2.33**). Spectral data matched those in the literature.[41]

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.12 (d, J = 2.8 Hz, 1H), 5.91 (d, J = 2.8 Hz, 1H), 3.68 (s, 2H), 2.57 (t, J = 7.6 Hz, 2H), 1.61 (quint, J = 7.6 Hz, 2H), 1.25 (s, 26H), 0.88 (t, J = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 174.2, 156.6, 144.7, 108.9, 105.5, 33.8, 33.7, 31.9, 29.7, 29.7, 29.6, 29.6, 29.4, 29.2, 28.0, 28.0, 22.7, 14.1.

Purification: FCC on SiO_2, 0–15% EtOAc/hexanes.

Synthesis of Plakorsin D



Plakorsin D methyl ester (**2.91**, 69.0 mg, 0.259 mmol, 1 equiv), THF (3.6 mL), and water (1.5 mL) were placed in a round-bottom flask. LiOH monohydrate (33.0 mg, 0.776 mmol, 3 equiv) was added and the mixture was stirred at room temperature overnight. The mixture was acidified to pH 2 using 1 M HCl (20 mL) and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined extracts were dried (anhydrous Na_2SO_4) and concentrated *in vacuo*. The residue was purified through FCC (10–15%

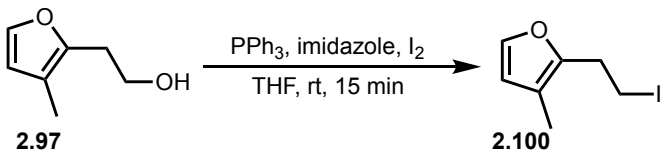
EtOAc/hexanes) to yield plakorsin D as a pale-yellow oil (62 mg, 95%; 61% from **2.38**). Spectral data matched those in the literature.[44]

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86 (s, 1H), 3.60 (s, 2H), 2.53 (dd, J = 15, Hz, 1H), 2.34 (quint, J = 7.5 Hz, 3H), 1.76 (sext, J = 6.5 Hz, 1H), 1.22–1.33 (m, 5H), 1.12 (t, J = 7.6 Hz, 4H), 0.88 (t, J = 5.5 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 175.8, 154.5, 139.6, 124.5, 107.6, 36.3, 35.6, 32.5, 32.0, 29.2, 22.9, 19.6, 18.0, 14.8, 14.1.

Purification: FCC on SiO_2, 0–15% EtOAc/hexanes.

Preparation of 2.100



2.97 **2.100**

The reduction of the furan **2.56** to the alcohol **2.97** was performed following literature procedures.[47] PPh_3 (4.10 g, 15.6 mmol, 2.4 equiv), imidazole (2.10 g, 31.1 mmol, 4.8 equiv), and THF (16 mL, 0.4 M) were placed in an oven-dried round-bottom flask at rt. Iodine (4.00 g, 15.6 mmol, 2.4 equiv) was added neat, followed by slow addition of **2.97** (818 mg, 6.49 mmol, 1 equiv) *in the dark*. The mixture was stirred at rt for 15 min. Upon completion of the reaction (TLC), the mixture was concentrated to a minimal volume, loaded onto a silica plug, and subjected to FCC to obtain 2-(2-iodoethyl)-3-methylfuran (**2.100**) as a yellow oil (1.33 g, 97%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (s, 1H), 6.18 (s, 1H), 3.33 (t, J = 7.6 Hz, 2H), 3.15 (t, J = 7.5 Hz, 2H), 1.98 (d, J = 2.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 149.2, 140.5, 115.6, 112.9, 30.5, 9.8, 2.8.

IR (neat): 2962, 2923, 2877, 1507, 1440, 1429, 1271, 1207, 1170, 1057, 892, 839, 730, 557 cm^{-1}.

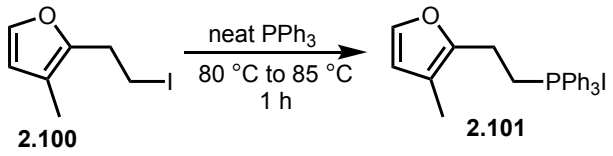
HRMS (ESI): calc'd for C_7H_9IO $[M + H]^+$, *m/z* 235.9693; found 235.9693.

R_f = 0.83 (10% EtOAc/hexanes).

Purification: silica plug, 10% EtOAc/hexanes.

***Note*:** Iodide **2.100** is indefinitely stable when stored in the dark under refrigeration

Preparation of 2.101



2.100 **2.101**

PPh_3 (1.91 mmol, 2.5 equiv) was added to a 4-mL sample vial and heated at 80–85 °C until completely molten. The iodide **2.100** (180 mg, 0.763 mmol, 1 equiv) was added neat and then the mixture was stirred at 80–85 °C for 1 h. After cooling to rt, Et_2O (1 mL) was added and the mixture was stirred for 1 min. The Et_2O layer was then decanted off. This process was repeated until PPh_3 could no longer be detected in the Et_2O washings (20 × 1 mL). The solid residue was then dried under high vacuum for 10 min to yield iodo(2-(3-methylfur-2-yl)ethyl)triphenylphosphorane (**2.101**) as a pale-yellow solid (289 mg, 76%), which was used directly without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67–7.77 (m, 15H), 6.97 (s, 1H), 5.99 (s, 1H), 3.98 (quint, J = 6.8 Hz, 2H), 3.14 (sext, J = 6.8 Hz, 2H), 1.76 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 145.5 (d, $J_{C–P}$ = 7.5 Hz), 140.6, 135.0 (d, $J_{C–P}$ = 3 Hz), 133.6 (d, $J_{C–P}$ = 10.1 Hz), 130.4 (d, $J_{C–P}$ = 12.6 Hz), 118.1, 117.5, 116.7, 113.3, 22.8 (d, $J_{C–P}$ = 50 Hz), 19.3 ($J_{C–P}$ = 4.2 Hz), 9.94.

^{31}P NMR (202 MHz, $CDCl_3$): δ 24.1.

IR (neat): 3099, 3048, 3009, 2841, 2777, 1584, 1512, 1485, 1439, 1428, 1338, 1226, 1145, 1107, 1073, 1035 cm^{-1}.

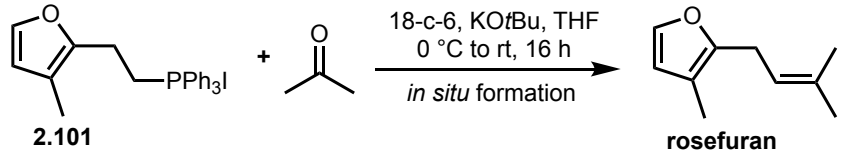
HRMS (EI): calc'd for C_7H_8O $[M – PPh_3I]^+$, *m/z* 108.0575; found 108.0570.

M.p. = 162–166 °C.

***R*$_f$** = 0.15 (10% MeOH/DCM).

Purification: none.

Synthesis of Rosefuran



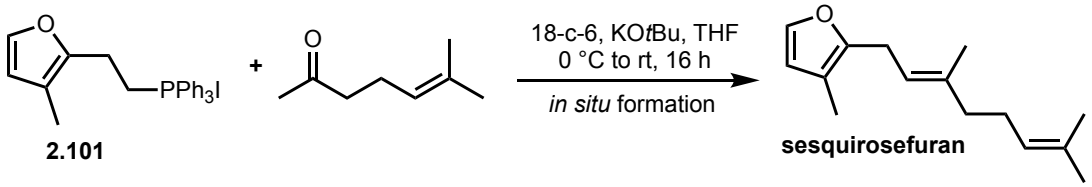
Performed using modified literature procedures.[49] The phosphonium salt **2.101** (660 mg, 1.32 mmol, 1 equiv), KO*t*Bu (149 mg, 1.32 mmol, 1 equiv), and [18]crown-6 (35.0 mg, 0.132 mmol, 10 mol%) were placed in an oven-dried round bottom flask *without stirring*. After cooling to 0 °C, dry acetone (782 μL, 5.30 mmol, 4 equiv) and THF (1.1 mL, 1.2 M) were added. The ice bath was removed and stirring was initiated. The mixture was then stirred overnight at rt. The mixture was diluted with hexanes (20 mL) and passed through a silica plug to give a solution that was concentrated *in vacuo*. The residue was purified through FCC to give 3-methyl-2-(3-methylbut-2-en-1-yl)furan (rosefuran) as a clear oil (193 mg, 1.28 mmol, 97%). The spectral data matched those found in the literature.[50]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, J = 1.6 Hz, 1H), 6.16 (d, J = 1.4 Hz, 1H), 5.27 (tq, J = 7.2, 1.25 Hz, 1H), 3.29 (d, J = 7.1 Hz, 2H), 1.98 (s, 3H), 1.73 (s, 3H), 1.73 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 150.1, 139.8, 133.0, 120.1, 113.3, 112.8, 25.6, 25.2, 17.7, 9.7.

Purification: silica plug, hexanes

Synthesis of Sesquirosefuran



Performed using modified literature procedures.[49] The phosphonium salt **2.101** (600 mg, 1.20 mmol, 1 equiv), KO*t*Bu (135 mg, 1.20 mmol, 1 equiv), and [18]crown-6 (32.0 mg, 0.120 mmol, 10 mol%) were placed in an oven-dried round-bottom flask *without stirring*. After cooling to 0 °C, sulcatone (533 μL, 3.61 mmol, 3 equiv) was added neat along with THF (1 mL, 1.2 M). (*Note:* The absence of stirring until everything had been added ensured that the ylide was generated in the presence of excess ketone, thereby preventing the formation of 3-methyl-2-vinylfuran as a side product.) The ice bath was removed and

stirring was initiated. The mixture was stirred overnight at rt. The mixture was diluted with hexanes (15 mL) and passed through a silica plug to give a solution that was concentrated *in vacuo*. The residue was purified through FCC to give (*E*)-2-(3,7-dimethylocta-2,6-dien-1-yl)-3-methylfuran (sesquirosefuran) as a clear oil (252 mg, 1.16 mmol, 96%; *E*/*Z* = 1:2). The spectral data matched those found in the literature.[53]

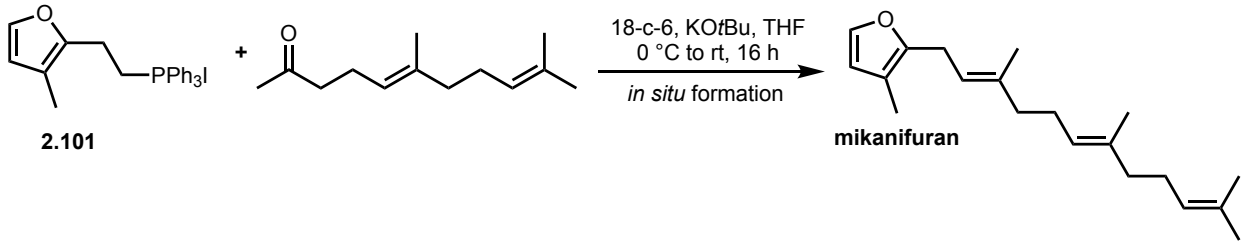
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, J = 1.1 Hz, 1H), 6.16 (d, J = 1.6 Hz, 1H), 5.27–5.30 (m, 1H), 5.09–5.18 (m, 1H), 3.29 (d, J = 7.1 Hz, 2H), 2.08–2.17 (m, 4H), 1.97 (s, 3H), 1.73 (s, 3H), 1.70 (s, 3H), 1.64 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 150.1, 150.0, 139.8, 139.8, 136.7, 136.5, 131.7, 131.4, 124.2, 124.1, 120.7, 119.9, 113.4, 113.3, 112.8, 112.8, 39.6, 32.0, 26.5, 26.5, 25.7, 25.7, 25.2, 24.9, 23.3, 17.6, 17.6, 16.1, 9.8, 9.8.

Purification: silica plug, hexanes.

Synthesis of Mikanifuran

To suppress the formation of the E2-elimination side product, which was difficult to separate from the desired product, we modified the original Boden conditions to use a higher concentration of **2.101** (1.2 M instead of 0.2 M), excess geranylacetone (three equivalents instead of one), and a lower temperature (from 0 °C to rt, instead of rt), furnishing mikanifuran in 56% as a mixture of *E*/*Z* isomers.



Performed using modified literature procedures.[49] The phosphonium salt **2.101** (500 mg, 1.00 mmol, 1 equiv), KO*t*Bu (113 mg, 1.00 mmol, 1 equiv), and [18]crown-6 (27 mg, 0.100 mmol, 10 mol %) were placed in an oven-dried round bottom flask *without stirring*. After cooling to 0 °C, the ketone (673 μL, 3.01 mmol, 3 equiv) was added neat along with THF (1.2 M, 0.8 mL). (*Note:* The absence of stirring until everything had been added ensured that the ylide was generated in the presence of excess ketone, thereby

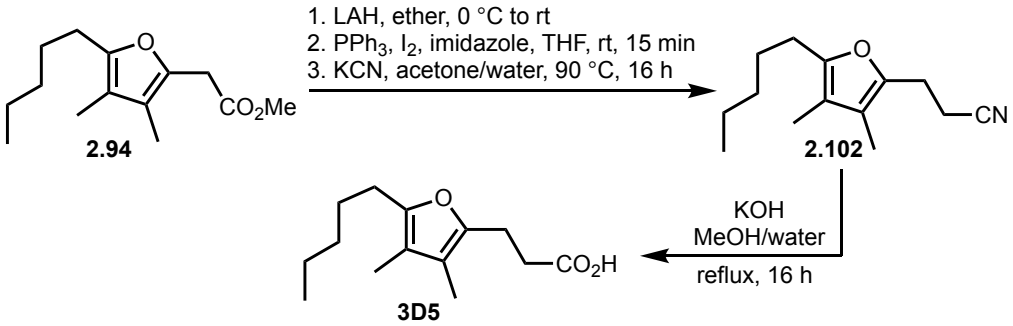
preventing the formation of 3-methyl-2-vinylfuran as a side product.) The ice bath was removed and stirring was initiated. The mixture was then stirred overnight at rt. The mixture was diluted with hexanes (15 mL) and passed through a silica plug to give a solution that was concentrated *in vacuo*. The residue was purified through FCC to give 3-methyl-2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)furan (mikanifuran) as a clear oil (161 mg, 0.562 mmol, 56%; *E*/*Z* = 1:2). The spectral data matched those found in the literature.[53]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, J = 1.7 Hz, 1H), 6.15 (s, 1H), 5.27 (t, J = 7.1 Hz, 1H), 5.17 (t, J = 6.6 Hz, 1H), 5.11 (t, J = 6.9 Hz, 1H), 3.29 (d, J = 7.1 Hz, 2H), 2.0–2.15 (m, 8H), 1.97 (s, 3H), 1.72 (s, 3H), 1.69 (s, 3H), 1.63 (s, 3H), 1.61 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 150.1, 150.0, 139.8, 139.8, 136.8, 136.5, 135.3, 135.1, 131.3, 131.2, 124.4, 124.3, 124.0, 124.0, 120.6, 119.9, 113.4, 113.3, 112.8, 112.8, 39.7, 39.7, 39.6, 31.9, 26.7, 26.7, 26.5, 26.4, 25.7, 25.1, 25.1, 24.9, 23.4, 17.7, 16.1, 16.0, 16.0, 9.8, 9.8.

Purification: silica plug, hexanes.

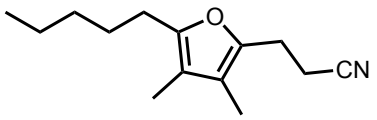
Synthesis of Furan Fatty Acid 3D5



LAH (60.0 mg, 1.57 mmol, 1.5 equiv) and dry Et_2O (3.1 mL, 0.5 M) were placed in an oven-dried round-bottom flask. After cooling to 0 °C, a solution of the furan **2.94** (250 mg, 1.05 mmol, 1 equiv) in dry Et_2O (1.6 mL, 0.67 M) was added slowly. (*Note:* Vigorous fizzing occurred.) The resulting solution was then stirred at rt for 20 min. Upon completion of the reaction (TLC), the mixture was re-cooled to 0 °C and a Fieser workup was used to obtain the alcohol product, which was used directly, without purification, in the next step.

PPh_3 (743 mg, 2.83 mmol, 2.4 equiv), imidazole (386 mg, 5.67 mmol, 4.8 equiv), and THF (2.6 mL, 0.4 M) were placed in an oven-dried 25-mL round-bottom flask under Ar at rt. Iodine (719 mg, 2.83 mmol, 2.4 equiv) was added, followed by slow addition of a solution of the alcohol intermediate in THF (2 mL) *in the dark*. The mixture was stirred at rt for 15 min. Upon completion of the reaction (TLC), the mixture was concentrated to a minimal volume and quickly filtered through a silica plug (10% EtOAc/hexanes) to obtain the iodide as an unstable light-sensitive yellow oil, which was used immediately in the next step. The iodide from the previous step was immediately dissolved in acetone (8 mL) and water (2 mL) and transferred to a sealed tube. KCN (273 mg, 4.30 mmol, 4 equiv) was added in one portion and then the resulting solution was heated overnight under reflux at 90 °C *in the dark*. Upon completion of the reaction (TLC), the mixture was concentrated *in vacuo* and purified through FCC (0–2.5% EtOAc/hexanes) to give the nitrile **2.102** (184 mg, 0.839 mmol, 80% from **2.94**) as a pale-yellow oil.

Nitrile **2.102** (1 equiv, 0.851 mmol) was added to a solution of KOH (4 equiv, 3.41 mmol, 191 mg) in water (300 μL) and MeOH (300 μL) at rt. The mixture was then heated under reflux for 5 h. The mixture was cooled to 0 °C, acidified to pH 1 using 1 M HCl, and extracted with DCM (3 × 20 mL). The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give **3D5** (200 mg, 0.839 mmol, 99%) as a pale-yellow oil. The spectral data matched those found in the literature.[54]



3-(3,4-Dimethyl-5-pentylfur-2-yl)propanenitrile (2.102)

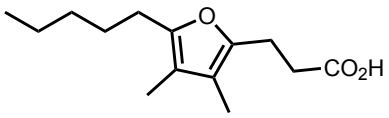
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.88 (t, J = 7.4 Hz, 2H), 2.59 (t, J = 7.4 Hz, 2H), 2.48 (t, J = 7.5 Hz, 2H), 1.88 (s, 3H), 1.83 (s, 3H), 1.55 (quint, J = 7.6 Hz, 2H), 1.24–1.35 (m, 4H), 0.89 (t, J = 7 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 149.9, 143.3, 119.2, 117.1, 114.9, 31.3, 28.2, 26.0, 22.5, 22.4, 16.8, 14.0, 8.3, 8.2.

IR (neat): 2951, 2928, 2864, 2247, 1596, 1443, 1382, 1257, 1126, 1085, 911, 731, 727, 709 cm^{-1}.

HRMS (ESI): calc'd for $C_{14}H_{21}NO$ $[M + H]^+$, *m/z* 219.1618; found 219.1618.

R_f = 0.68 (10% EtOAc/hexanes).

Purification: FCC on SiO_2, 0–4% EtOAc/hexanes.



3D5

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.85 (t, J = 7.4 Hz, 2H), 2.65 (t, J = 7.9 Hz, 2H), 2.48 (t, J = 7.5 Hz, 2H), 1.85 (s, 3H), 1.83 (s, 3H), 1.56 (quint, J = 7.7 Hz, 2H), 1.26–1.35 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 179.3, 149.2, 145.4, 115.6, 114.6, 33.0, 31.4, 28.3, 26.0, 22.4, 21.3, 14.0, 8.3, 8.2.

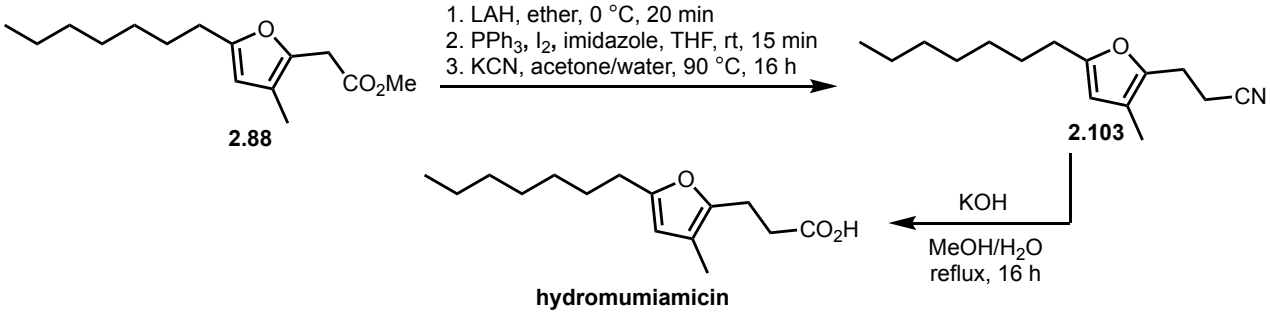
IR (neat): 2928, 2864, 1713, 1600, 1439, 1419, 1382, 1216, 1122, 911, 731, 709 cm^{-1}.

HRMS (ESI): calc'd for $C_{14}H_{22}O_3$ $[M + H]^+$, *m/z* 238.1563; found 238.1566.

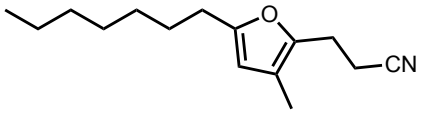
R_f = 0.38 (25% EtOAc/hexanes).

Purification: FCC on SiO_2, 0–15% EtOAc/hexanes.

Synthesis of Hydromumiamicin



Hydromumiamicin was prepared following the same protocol (reduction, iodination, cyanation, and hydrolysis) as that used in the preparation of **3D5** from the furan **2.88** (650 mg, 2.58 mmol, 1 equiv).



3-(5-Heptyl-3-methylfur-2-yl)propanenitrile (2.103)

Prepared (451 mg, 75% from **2.88**) following the same procedure as that described for **2.94**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.77 (s, 1H), 2.89 (t, J = 7.4 Hz, 2H), 2.60 (t, J = 7.4 Hz, 2H), 2.51 (t, J = 7.6 Hz, 2H), 1.95 (s, 3H), 1.55–1.61 (m, 2H), 1.27–1.32 (m, 8H), 0.88 (t, J = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.1, 144.3, 119.1, 116.6, 108.1, 31.7, 29.1, 29.0, 28.0, 27.9, 22.6, 22.3, 16.9, 14.1, 9.8.

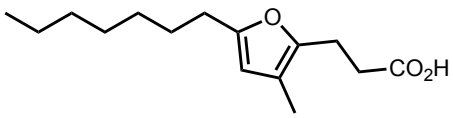
IR (neat): 2923, 2855, 2358, 1574, 1461, 1434, 1379, 1256, 1230, 1111 cm^{-1}.

HRMS (ESI): calc'd for $C_{15}H_{23}NO$ $[M + H]^+$, *m/z* 233.1774; found 233.1772.

R_f = 0.49 (10% EtOAc/hexanes).

Appearance: pale-yellow oil.

Purification: FCC on SiO_2, 0–4% EtOAc/hexanes.



Hydromumiamicin

Prepared (483 mg, 74% from **2.88**) following the same procedure as that described for **3D5**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.74 (s, 1H), 2.85 (t, J = 7.5 Hz, 2H), 2.65 (t, J = 7.9 Hz, 2H), 2.50 (t, J = 7.6 Hz, 2H), 1.91 (s, 3H), 1.58 (quint, J = 7.6 Hz, 2H), 1.27–1.32 (m, 8H), 0.88 (t, J = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 178.9, 154.3, 146.4, 115.0, 107.8, 32.9, 31.8, 29.2, 29.0, 28.0, 28.0, 22.6, 21.1, 14.1, 9.8.

IR (neat): 2923, 2855, 1710, 1579, 1430, 1414, 1286, 1217, 1104 cm^{-1}.

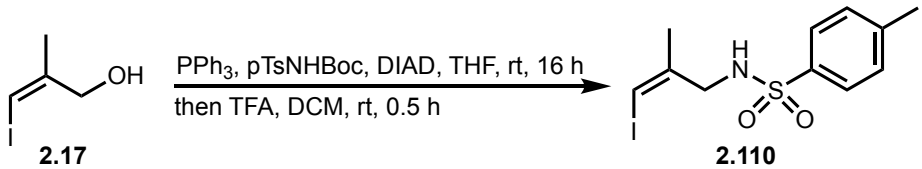
HRMS (ESI): calc'd for $C_{15}H_{24}O_3$ $[M + H]^+$, *m/z* 252.1720; found 252.1718.

R_f = 0.47 (25% EtOAc/hexanes).

Appearance: light-yellow oil.

Purification: FCC on SiO_2, 0–15% EtOAc/hexanes.

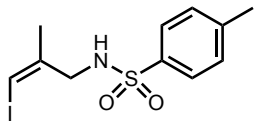
Mitsunobu Reaction of 2.17



2.17 **2.110**

Modified from literature procedures.[59] To an oven-dried round-bottomed flask containing a THF solution of PPh_3 (1.4 equiv, 4.5253 mmol, 1.2 g, 0.1M, 45 mL) and *p*TsNHBoc (1 equiv, 3.2323 mmol, 877 mg) at room temperature was slowly added a THF solution (0.1 M, 32 mL) of **2.17** (1 equiv, 3.2323 mmol, 640 mg). DIAD (1.3 equiv, 4.2020 mmol, 830 µL) was then slowly added to this mixture. This mixture was then stirred for 16 h. Upon completion as indicated by TLC, the crude mixture was concentrated *in vacuo*, diluted with 1:1 ether and hexane, filtered through a silica plug and concentrated. The resulting Boc-protected tosylamide was then re-dissolved in DCM (0.1 M, 32 mL) and TFA (30 equiv, 96.969 mmol, 7.4 mL) was added at rt. This was then stirred at room temperature for 30 minutes. Upon completion as indicated by TLC, water and then, solid $NaHCO_3$ was *slowly* added in small portions until no more gas evolution is observed. *Note*: vigorous fizzing occurs in this step. The organic layer was then separated out using a separatory funnel, dried with anhydrous sodium sulfate and concentrated *in vacuo*. The crude amine was then purified using column chromatography (15–20% ethyl acetate/hexanes) to obtain **2.110** as a white solid (94%, 1.08g).

Note: *p*TsNHBoc was prepared according to literature procedures.[60]



(*Z*)-*N*-(3-iodo-2-methylallyl)-4-methylbenzenesulfonamide (2.110)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, J = 8.3 Hz, 2 H), 7.32 (d, J = 8.3 Hz, 2 H), 6.02 (s, 1 H), 4.47 (s, 1 H), 3.67 (s, 2 H), 2.44 (s, 3 H), 1.89 (d, J = 1.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 143.7, 142.6, 136.6, 129.7, 127.2, 77.7, 50.2, 22.3, 21.5.

IR (neat): 3255, 2938, 1595, 1491, 1437, 1317, 1302, 1287, 1153, 1068, 1028, 1021 cm^{-1}.

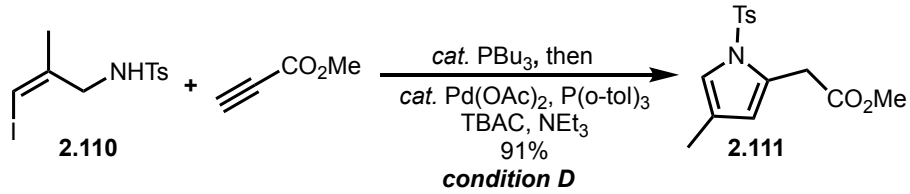
HRMS (ESI): calc'd for $C_{11}H_{14}INO_2S$ $[M + H]^+$ *m/z*, found.

m.p = 78–80 °C

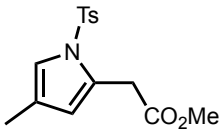
$\mathbf{R_f}$ = 0.42 in 25% ethyl acetate/hexanes.

Purification: FCC on SiO_2, 15 to 20% ethyl acetate/hexanes.

Michael–Heck Reaction of 2.110



To an oven-dried round bottomed flask was added (*Z*)-*N*-(3-iodo-2-methylallyl)-4-methylbenzenesulfonamide **2.110** (1 equiv, 1.4237 mmol, 500 mg) and DCM (0.1 M, 14 mL). After cooling to 0°C, PBu_3 (0.2 equiv, 0.2847 mmol, 70 µL) was added followed by dropwise addition of methyl propiolate (1.5 equiv, 2.1355 mmol, 190 µL) (flask A). This was then stirred for 30 minutes at the same temperature. To another oven-dried round-bottomed flask was added $Pd(OAc)_2$ (10 mol%, 0.1424 mmol, 32 mg), tris-(o-tolyl)phosphine (20 mol%, 0.2847 mmol, 43 mg) and TBAC (1 equiv, 1.4237 mmol, 396 mg) (flask B). Upon formation of the Michael adduct as indicated by TLC, the reaction in flask A was passed through a short pad of silica and concentrated to minimal volume. *Note:* Filtration of the crude Michael adduct through silica is necessary to remove PBu_3. The crude Michael adduct was then re-dissolved in dry toluene (0.1 M) and transferred to flask B. Triethylamine (5.2 equiv, 7.4032 mmol, 1 mL) was added and the reaction was stirred for 2 hours at 100 °C. The crude product was then concentrated *in vacuo* and purified using flash column chromatography (25–30% ethyl acetate/hexanes) to give the desired pyrrole **2.111** as a white solid (91%)



methyl 2-(4-methyl-1-tosyl-1*H*-pyrrol-2-yl)acetate (2.111)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, J = 8.3 Hz, 2 H), 7.29 (d, J = 8.1 Hz, 2 H), 7.00 (s, 1 H), 6.01 (s, 1 H), 3.76 (s, 2 H), 3.65 (s, 3 H), 2.40 (s, 3 H), 2.01 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 144.7, 136.4, 130.0, 127.0, 126.8, 122.4, 120.0, 117.8, 52.1, 33.2, 21.6, 11.8.

IR (neat): 2951, 2926, 1743, 1595, 1496, 1437, 1406, 1360, 1302, 1260, 1192, 1173, 1126, 1096, 1069 cm^{-1}.

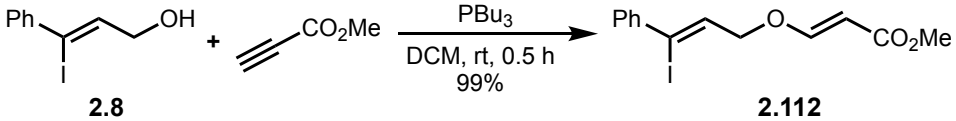
m.p = 82–84 °C

R_f = 0.42 in 25% ethyl acetate/hexanes.

Purification: FCC on SiO_2, 15 to 20% ethyl acetate/hexanes.

2.9.7. Mechanistic Investigations

Preparation of Michael Adducts 2.112 and 2.125



2.8 **2.112**

To an oven-dried round-bottomed flask was added **2.8** (300 mg, 1.15 mmol, 1 equiv), DCM (12 mL, 0.1 M) and PBu_3 (57 µL, 0.23 mmol, 20 mol%). Methyl propiolate (154 µL, 1.73 mmol, 1.5 equiv) was then slowly added. The resulting solution was stirred at room temperature for 30 minutes. Upon completion as indicated by TLC, the solution was concentrated *in vacuo* and purified using flash column chromatography (15–17% EtOAc/hexanes) on Et_3N-neutralized SiO_2 to give **2.112** as a bright yellow oil (396 mg, 99%).

Methyl (*E*)-3-(((*Z*)-3-iodo-3-phenylallyl)oxy)acrylate (2.112)

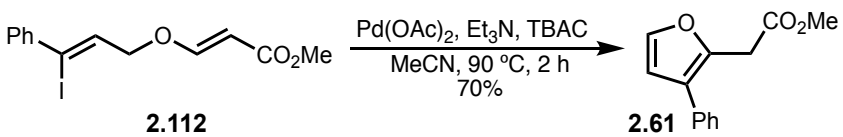
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 12.7 Hz, 1 H), 7.47 (dd, *J* = Hz, 2 H), 7.30–7.35 (m, 3 H), 6.25 (t, *J* = 5.4 Hz, 1 H), 5.30 (d, *J* = 12.7 Hz, 1 H), 4.61 (d, *J* = 5.4 Hz, 2 H), 3.72 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 167.9, 161.6, 141.6, 131.9, 129.1, 128.4, 128.3, 107.1, 97.3, 75.6, 51.2.

IR (neat): 2949, 1706, 1623, 1489, 1486, 1436, 1428, 1373, 1327, 1283, 1193, 1132, 1045, 1033 cm^{-1}.

HRMS (ESI): calc'd for $C_{13}H_{13}IO_3$ $[M - C_6H_5]^+$, *m/z* 266.9513; found 266.9518.

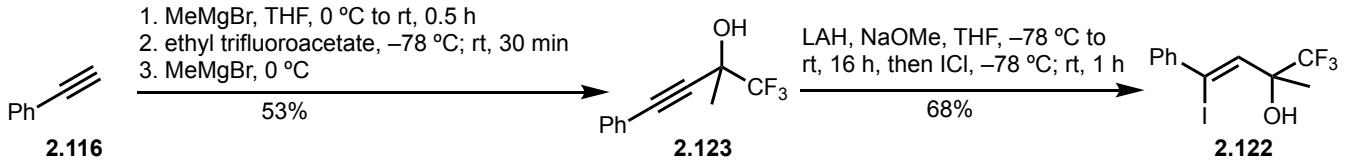
***R*$_f$** = 0.36 (10% EtOAc/hexanes).



2.112 **2.61**

To an oven-dried round-bottomed flask was added $Pd(OAc)_2$ (17 mg, 0.077 mol, 10 mol%) and TBAC (214 mg, 0.77 mmol, 1 equiv). A solution of **2.112** (265 mg, 0.77 mmol, 1 equiv) in MeCN (0.1 M) was then added, followed by Et_3N (560 µL, 4.00 mmol, 5.2 equiv). The resulting mixture was then refluxed for 2 hours. Upon completion as indicated by TLC, the solution was concentrated *in vacuo*, re-dissolved in 150mL 35% EtOAc/hexanes, filtered through a silica plug and concentrated *in vacuo.* The crude product was purified using flash column chromatography (8–10% EtOAc/hexanes) to obtain the title compound as an orange oil (117 mg, 70%). The spectral properties were identical to those of **2.61** prepared from **2.8** following conditions A.

Preparation of 2.122 and 2.126



To an oven-dried round-bottomed flask was added phenylacetylene (4 mL, 36.42 mmol, 1 equiv) and THF (36 mL, 1 M). After cooling to 0 ºC, a solution of MeMgBr (12 mL, 36.42 mmol, 3 M in ether, 1 equiv) was slowly added (*Note*: vigorous gas evolution occurs). The resulting solution was then stirred from 0 ºC to room temperature for 30 minutes. This freshly prepared Grignard solution was then cooled to –78 ºC and ethyl trifluoroacetate (4.8 mL, 40.07 mmol, 1.1 equiv) was slowly added. This solution was then moved to room temperature and stirred for 30 minutes. Upon formation of the trifluoromethyl ketone intermediate as indicated by TLC, the reaction was re-cooled to 0 ºC and MeMgBr (18 mL, 54.63 mmol, 3 M in ether, 1.5 equiv) was slowly added. This was then moved to room temperature and stirred for 1 hour. Upon completion as indicated by TLC, the reaction was poured onto saturated NH_4Cl and extracted three times with ethyl acetate. The organic layer was then washed with brine, dried over anhydrous sodium sulfate, concentrated *in vacuo* and purified using flash column chromatography (10–13% EtOAc/hexanes) to give the known compound **2.123** as a pale yellow oil (4.1g, 53% over 3 steps). Spectral data matches those found in the literature.[56]

To an oven-dried round-bottomed flask was added LAH (844 mg, 22.41 mmol, 4 equiv), NaOMe (2.4 g, 44.82 mmol, 8 equiv) and THF (22 mL, 1 M) (*Note*: NaOMe was weighed from the glovebox). After

cooling to –78 ºC, a solution of **2.123** (1.2 g, 5.60 mmol, 1 equiv) in THF (6 mL, 1 M) was slowly added (*Note*: vigorous gas evolution occurs). The resulting solution was allowed to warm naturally to room temperature overnight. The solution was then re-cooled to –78 ºC and a solution of ICl (16.5 mL, 16.5 mmol, 1 M in DCM, 2.5 equiv) was then slowly added. The cooling bath was then removed and the reaction was then stirred at room temperature for 1 hour. The resulting solution was then transferred to a separatory funnel and washed three times with saturated NH_4Cl. The organic layer was then washed with saturated $Na_2S_2O_3$ and then with brine. After drying with anhydrous sodium sulfate, the organic layer was concentrated *in vacuo* and purified using flash column chromatography (6–8% EtOAc/hexanes) to give **2.122** as a light orange oil (1.3 g, 68%).

(*Z*)-1,1,1-trifluoro-4-iodo-2-methyl-4-phenylbut-3-en-2-ol (2.122)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41–7.43 (m, 2 H), 7.31–7.36 (m, 3 H), 6.45 (s, 1 H), 3.03 (bs, 1 H), 1.67 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 143.9, 133.3, 129.1, 128.3, 128.2, 125.3 (q, $^1J_{C\text{-}F}$ = 285 Hz), 103.4, 74.3 (q, $^2J_{C\text{-}F}$ = 29 Hz), 20.9.

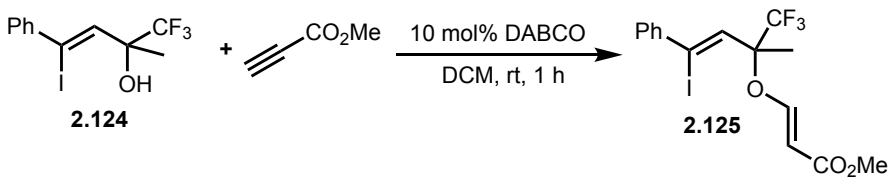
^{19}F NMR (376 MHz, $CDCl_3$): δ –83.1.

IR (neat): 3371, 1706, 1628, 1488, 1456, 1444, 1376, 1327, 1283, 1212, 1167, 1101 cm^{-1}.

HRMS (ESI): calc'd for $C_{11}H_{10}F_3IO$, *m/z* 342.9801 ; found 342.9806

R_f = 0.35 (10% EtOAc/hexanes).

Note: very light sensitive, gradually turns pink in solution.



These conditions were adapted from Tejedor's report[34] on the use of Lewis bases to catalyze the addition of alcohols onto alkyl propiolates. To a solution of **2.124** (300 mg, 0.88 mmol, 1 equiv) in DCM (1.8 mL, 0.5 M) was added DABCO (10 mg, 0.088 mmol, 10 mol%). Methyl propiolate (156 μL, 1.75 mmol, 2 equiv) was then added as 6 portions every 5 minutes. After complete addition, the solution was stirred for

an additional 30 minutes. The crude Michael adduct was then concentrated and purified using flash column chromatography on Et_3N-neutralized silica (0–3.5% EtOAc/hexanes) to give the title product as a pale yellow oil (314 mg, 84%).

Note: **2.125** partially overlaps with (*E*)-hex-2-en-4-ynedioic acid dimethyl ester[57] (dimerized methyl propiolate) and contains very small amounts of this dimer.

Methyl (*E*)-3-(((*Z*)-1,1,1-trifluoro-4-iodo-2-methyl-4-phenylbut-3-en-2-yl)oxy)acrylate (2.125)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (dd, *J* = 12.0, 1.44 Hz, 1 H), 7.44–7.46 (m, 2 H), 7.33–7.36 (m, 3 H), 6.51 (s, 1 H), 5.62 (d, *J* = 12.0 Hz, 1 H), 3.71 (s, 3 H), 1.86 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 167.6, 156.6, 143.7, 129.8, 129.6, 128.4, 128.2, 124.4 (q, $^1J_{C\text{-}F}$ = 285.6 Hz), 108.8, 102.3, 81.3 (q, $^2J_{C\text{-}F}$ = 28.1 Hz), 51.3, 18.8

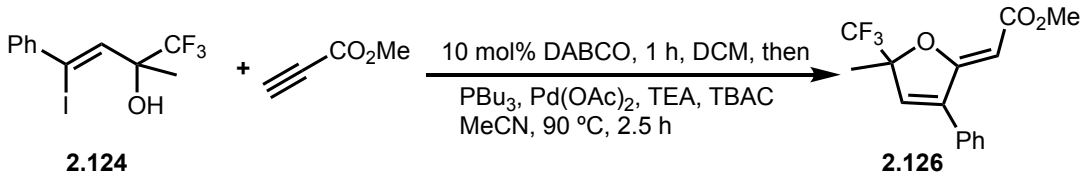
^{19}F NMR (376 MHz, $CDCl_3$): *δ* –80.3.

IR (neat): 2953, 1713, 1645, 1488, 1442, 1436, 1384, 1329, 1288, 1179, 1129, 1098, 1049 cm^{-1}

HRMS (ESI): calc'd for $C_{15}H_{14}F_3IO_3$, *m/z* 427.0021 ; found 427.0018

R_f = 0.41 (10% EtOAc/hexanes)

Preparation of 2.126



To a solution of **2.124** (1.3 g, 3.80 mmol, 1 equiv) in DCM (7.6 mL, 0.5 M) was added DABCO (43 mg, 0.38 mmol, 10 mol%). Methyl propiolate (676 µL, 7.6 mmol, 2 equiv) was then added as 6 portions every 5 minutes. After complete addition, the solution was stirred for an additional 30 minutes. The crude Michael adduct was then concentrated to minimal volume, re-dissolved in anhydrous MeCN (12 mL, 0.3 M) and added to another oven-dried round-bottomed flask containing $Pd(OAc)_2$ (85 mg, 0.38 mmol, 10 mol%) and TBAC (1.06g, 3.8 mmol, 1 equiv). PBu_3 (188 µL, 0.76 mmol, 20 mol%) and Et_3N (2.8 mL, 19.76 mmol, 5.2 equiv) was then added and the reaction was refluxed for 2.5 hours. The solution was

then concentrated *in vacuo*, dissolved in 300 mL 40% EtOAc/hexanes, filtered through a silica plug and concentrated *in vacuo*. The crude product was then purified using flash column chromatography (10–13% EtOAc/hexanes) to give the title product as a light orange solid (748 mg, 68%).

Methyl (*Z*)-2-(5-methyl-3-phenyl-5-(trifluoromethyl)furan-2(5*H*)-ylidene)acetate (2.126)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42–7.44 (m, 3 H), 7.35–7.37 (m, 2 H), 6.49 (s, 1 H), 5.17 (d, J = 0.65 Hz, 1 H), 3.71 (s, 3 H), 1.75 (d, J = 0.7 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 167.9, 165.7, 143.2, 133.6, 130.2, 129.6, 128.9, 128.3, 123.4 (q, $^{1}J_{C–F}$ = 282.8 Hz), 91.3, 91.0, 51.1, 18.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ –79.5.

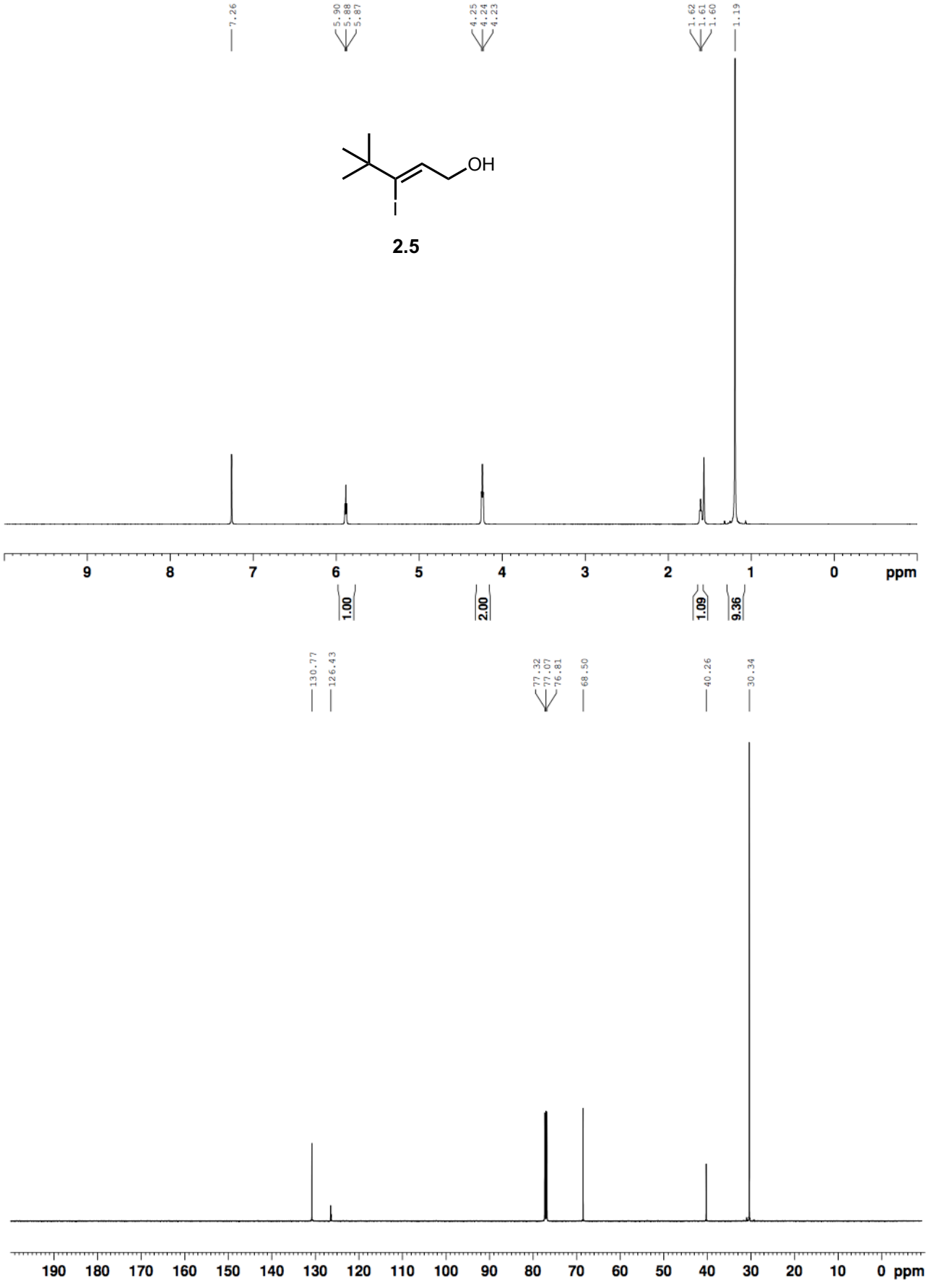
IR (neat): 1719, 1708, 1651, 1489, 1447, 1434, 1379, 1354, 1318, 1280, 1230, 1194, 1164, 1131, 1101, 1043 cm^{-1}.

HRMS (ESI): calc'd for $C_{15}H_{13}F_3O_3$, *m/z* 299.0890 ; found 299.0894

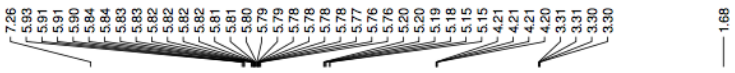
m.p = 60–63 ºC

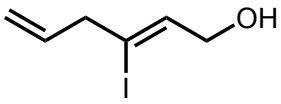
R_f = 0.65 (20% EtOAc/hexanes)

2.9.8. Copies of NMR Spectra

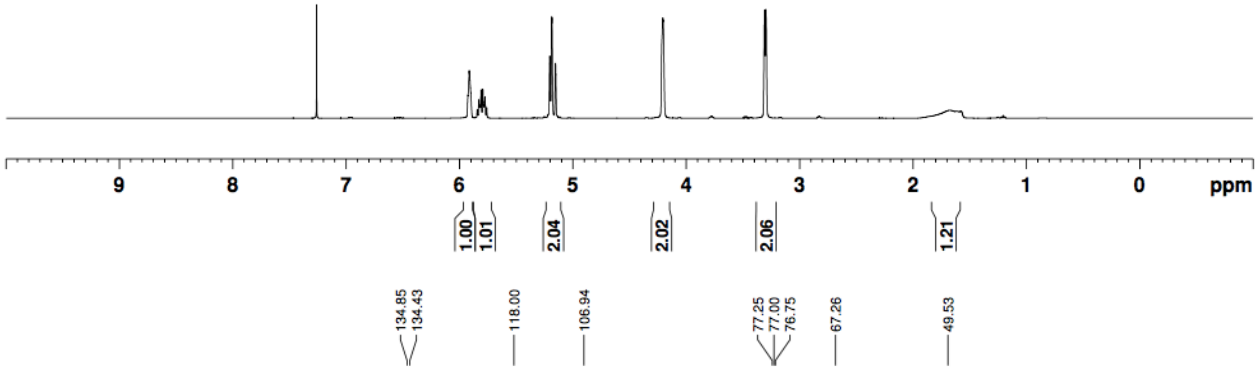


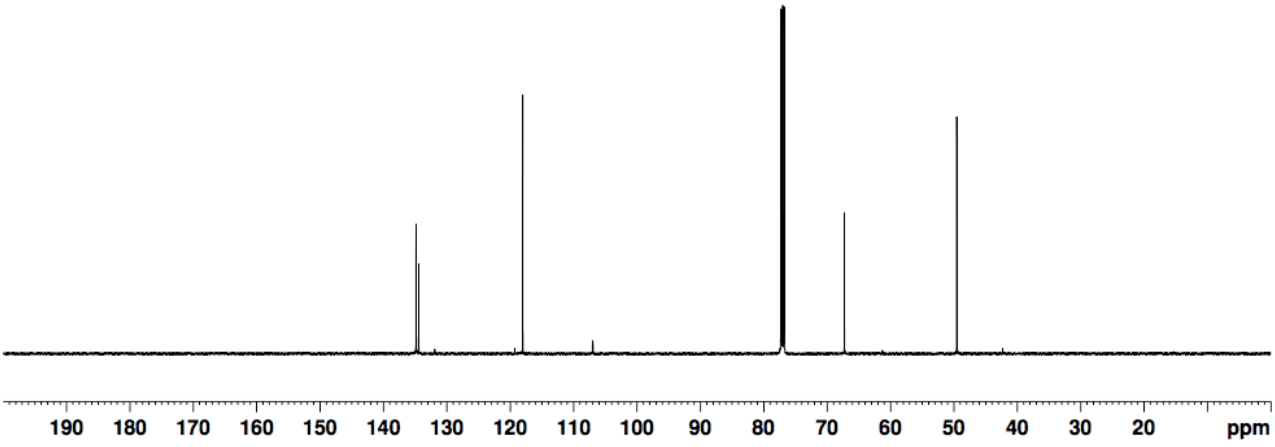
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.5**



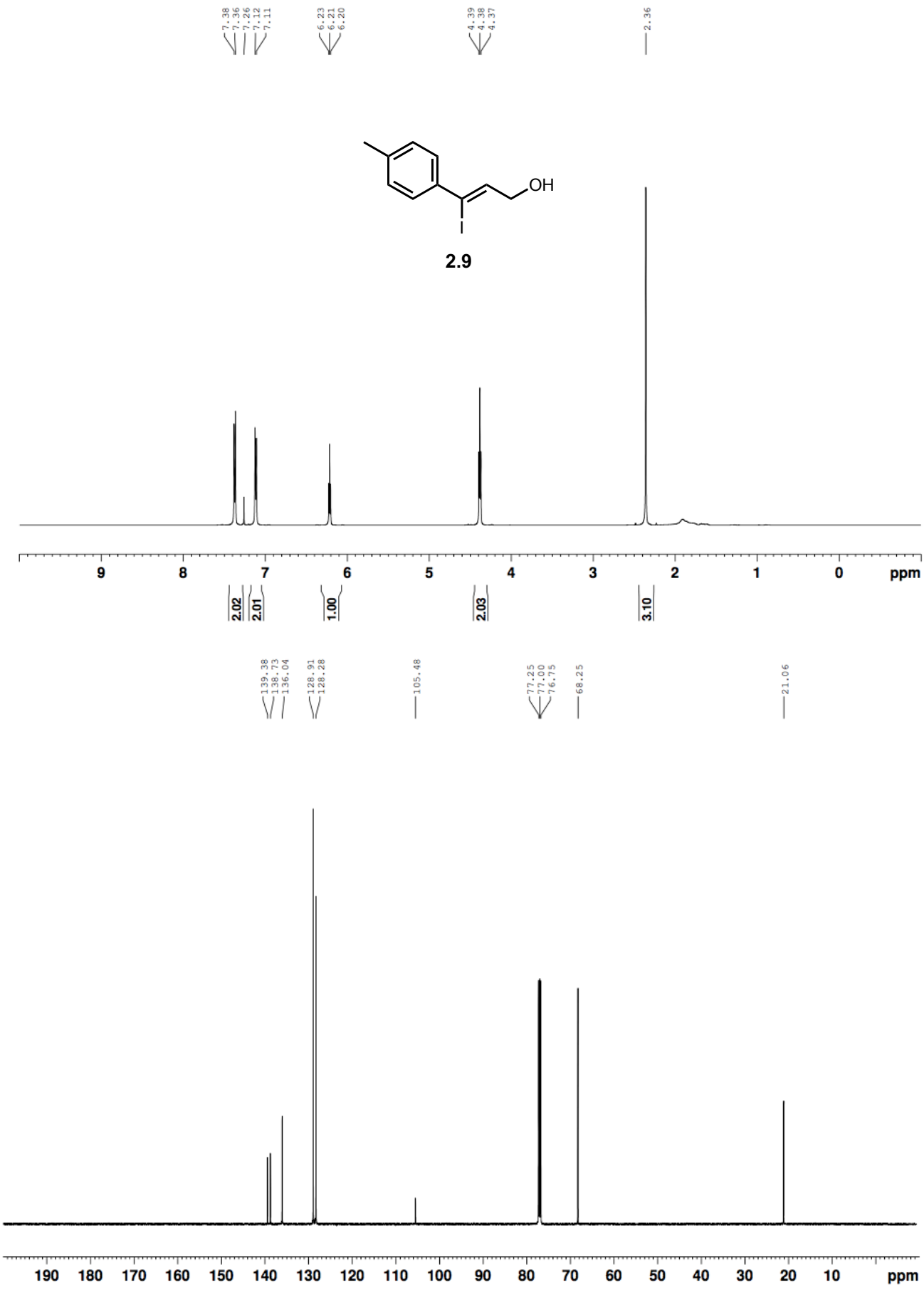


2.6

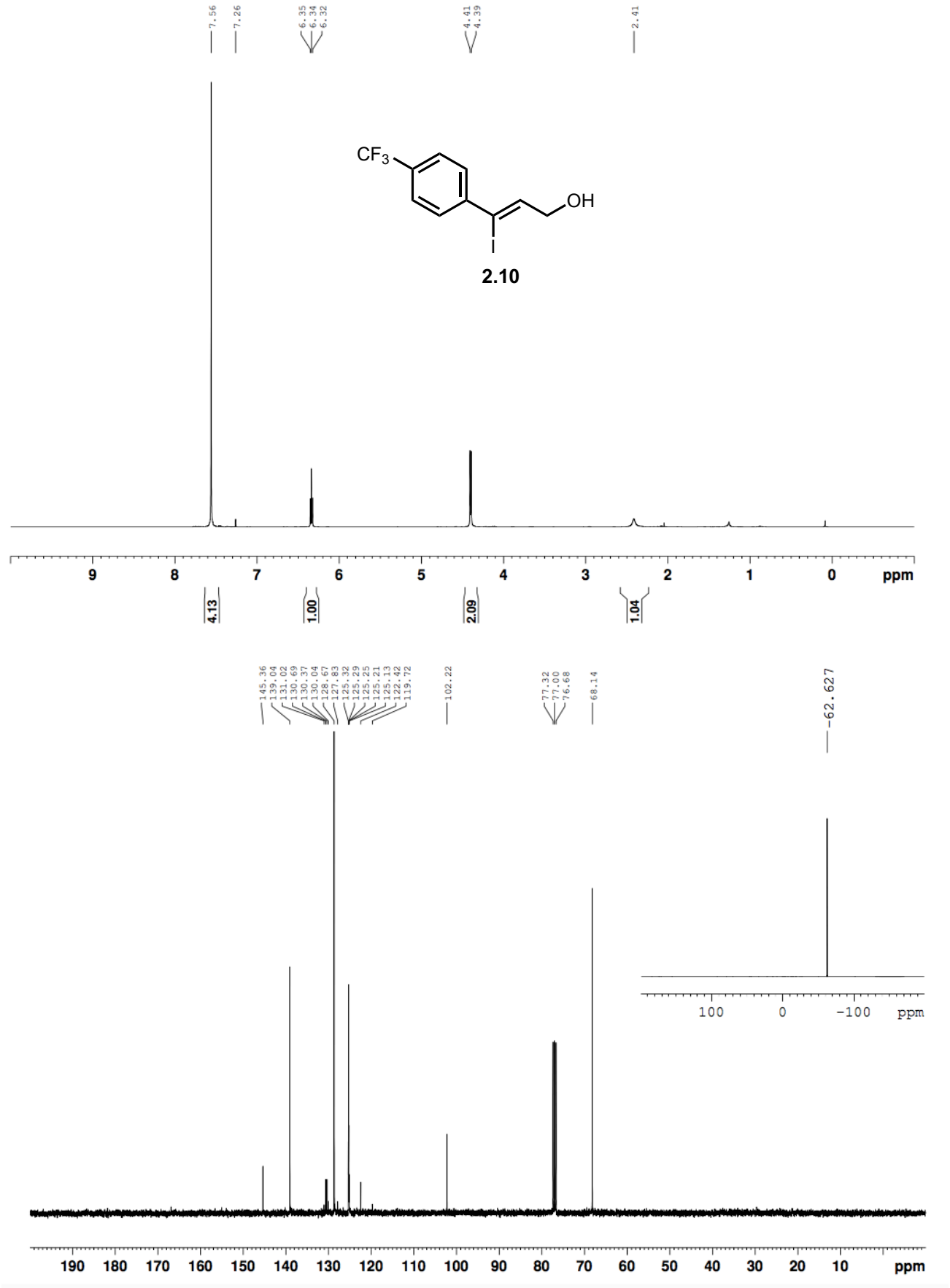




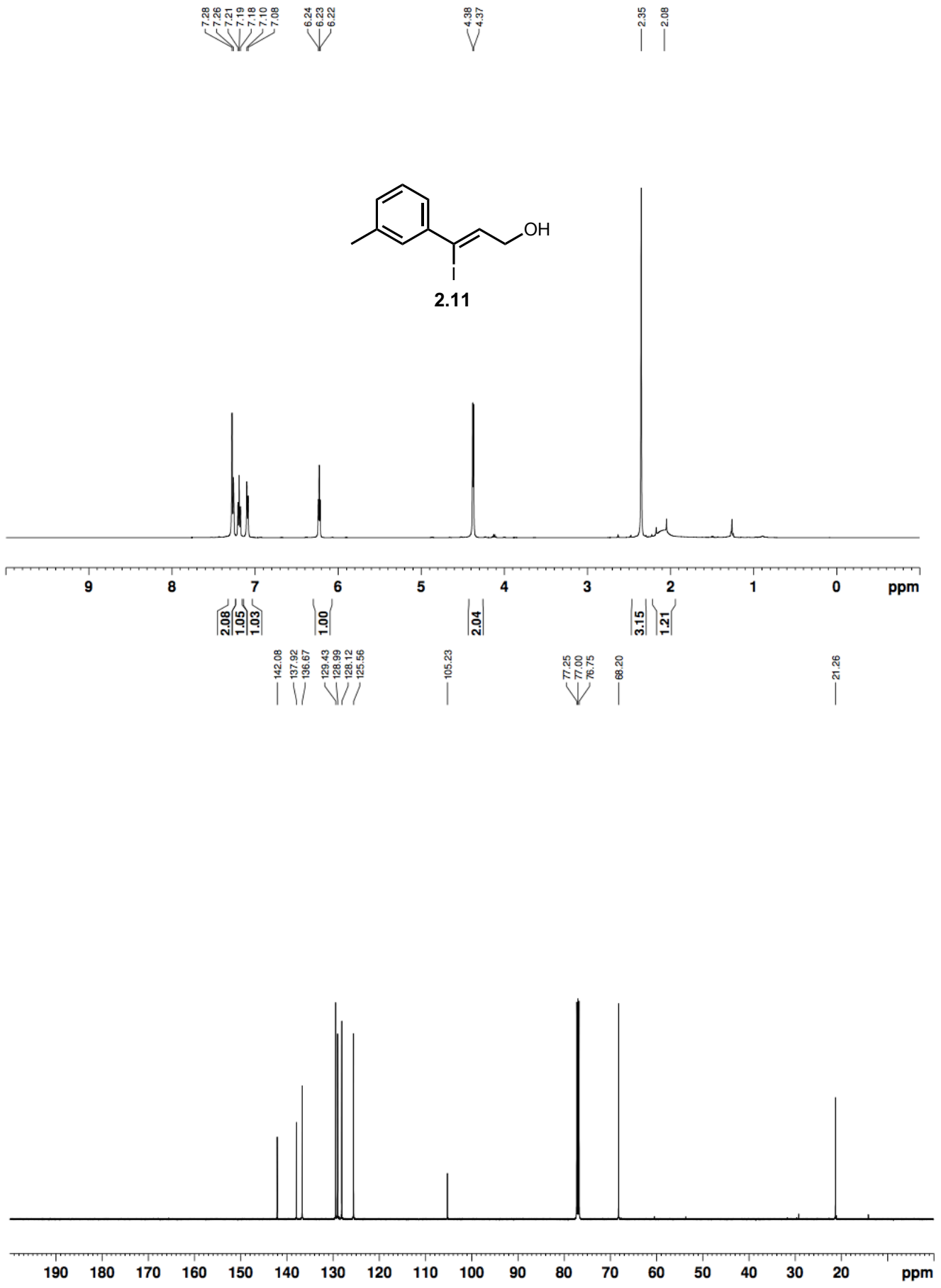
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.6**



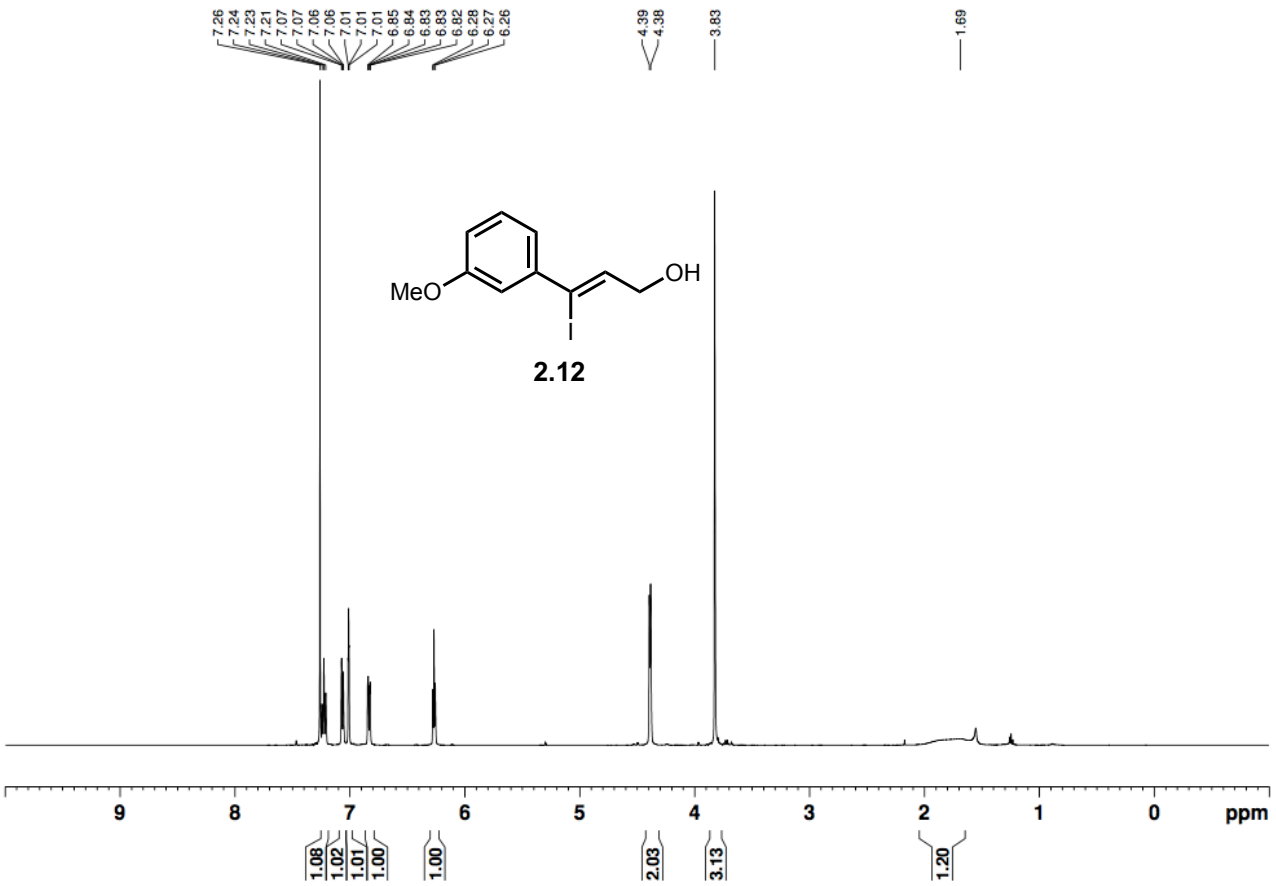
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.9**

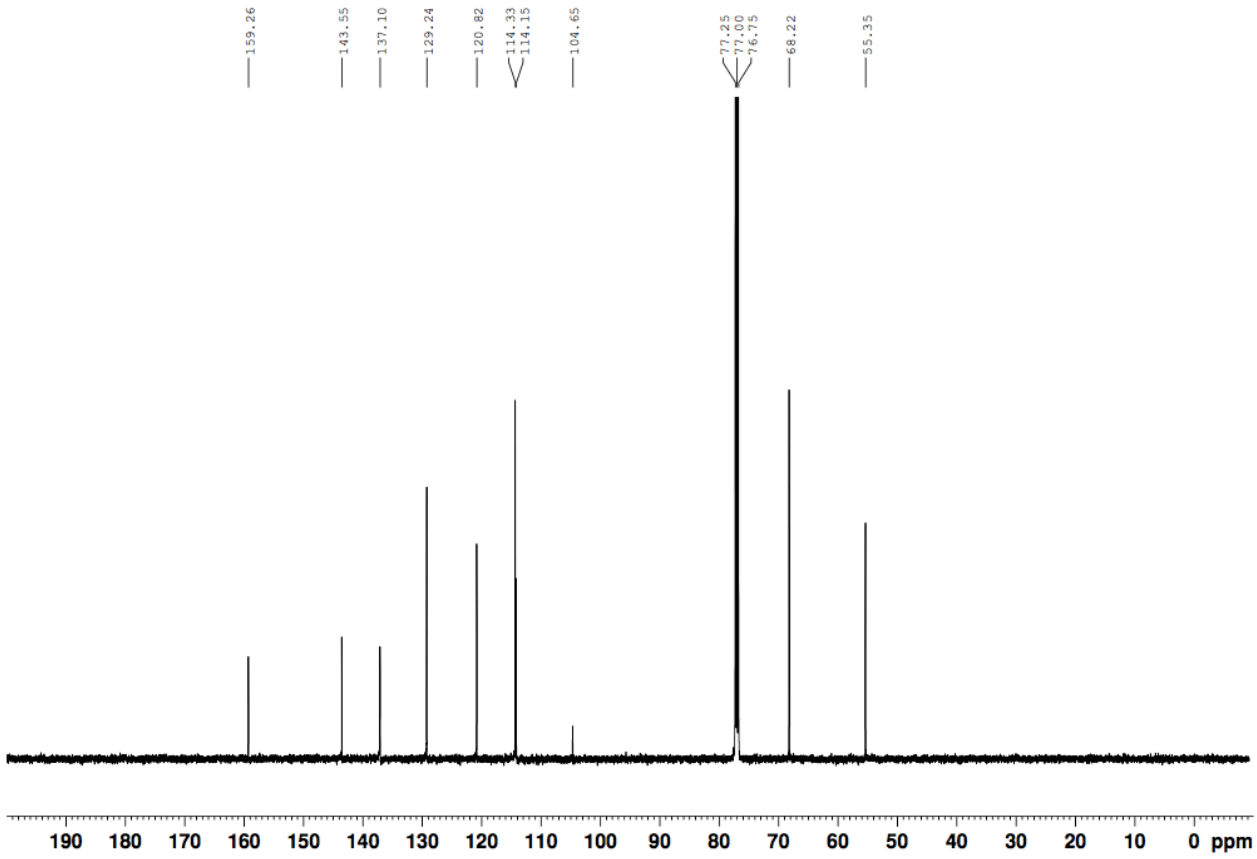


^{1}H (400 MHz, $CDCl_3$), ^{13}C (100 MHz, $CDCl_3$) and ^{19}F (376 MHz, $CDCl_3$) NMR Spectra of **2.10**

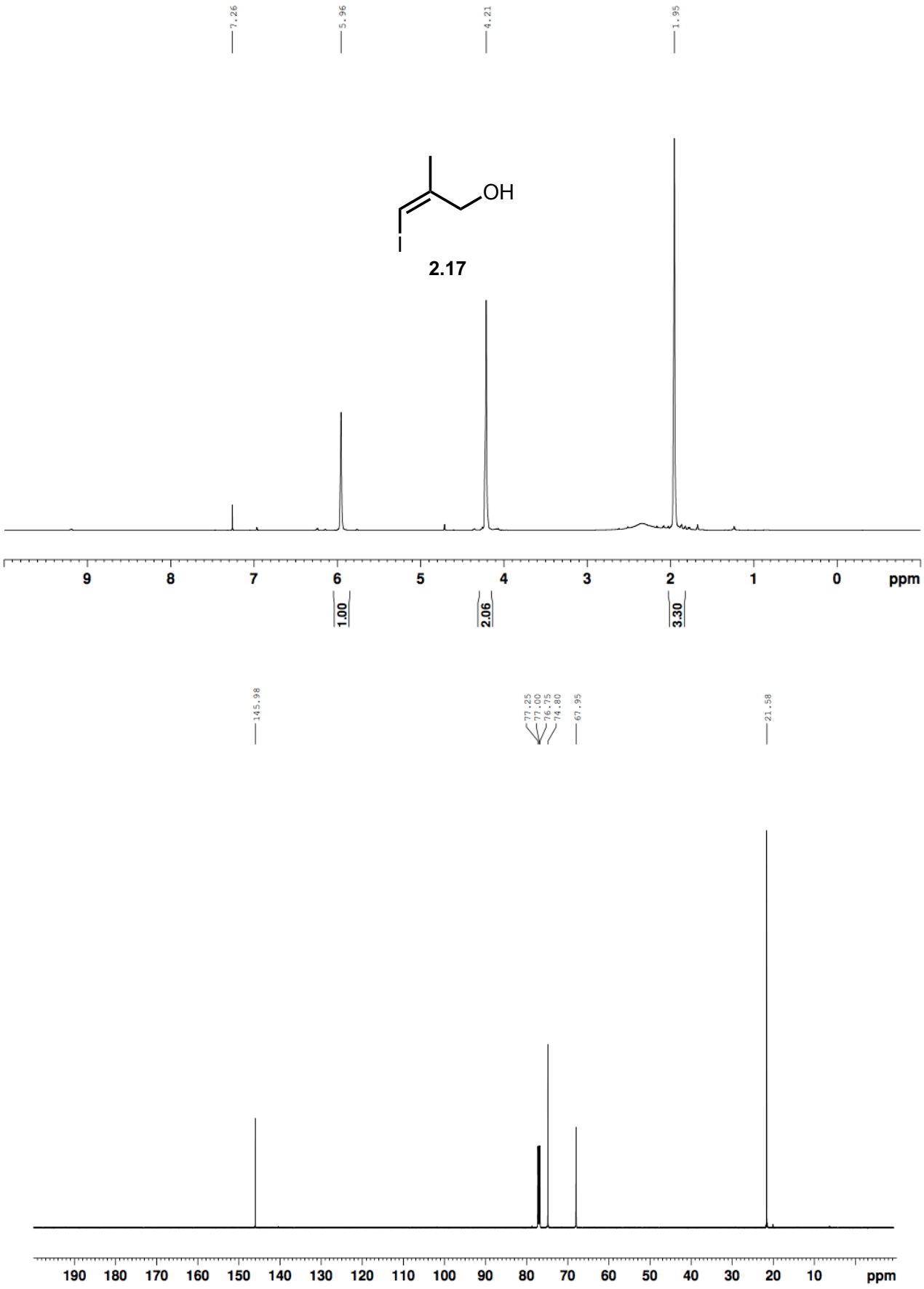


^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.11**

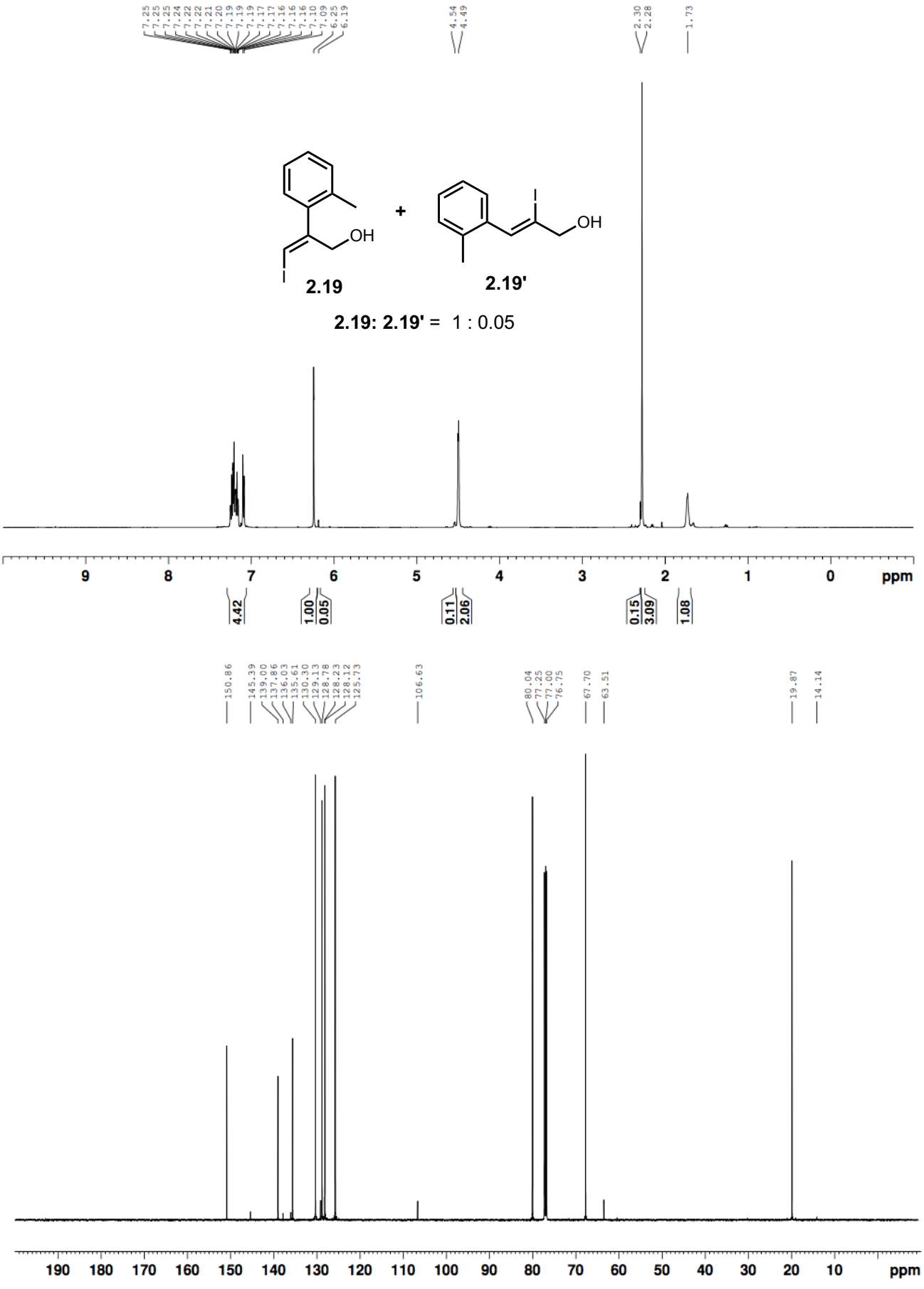




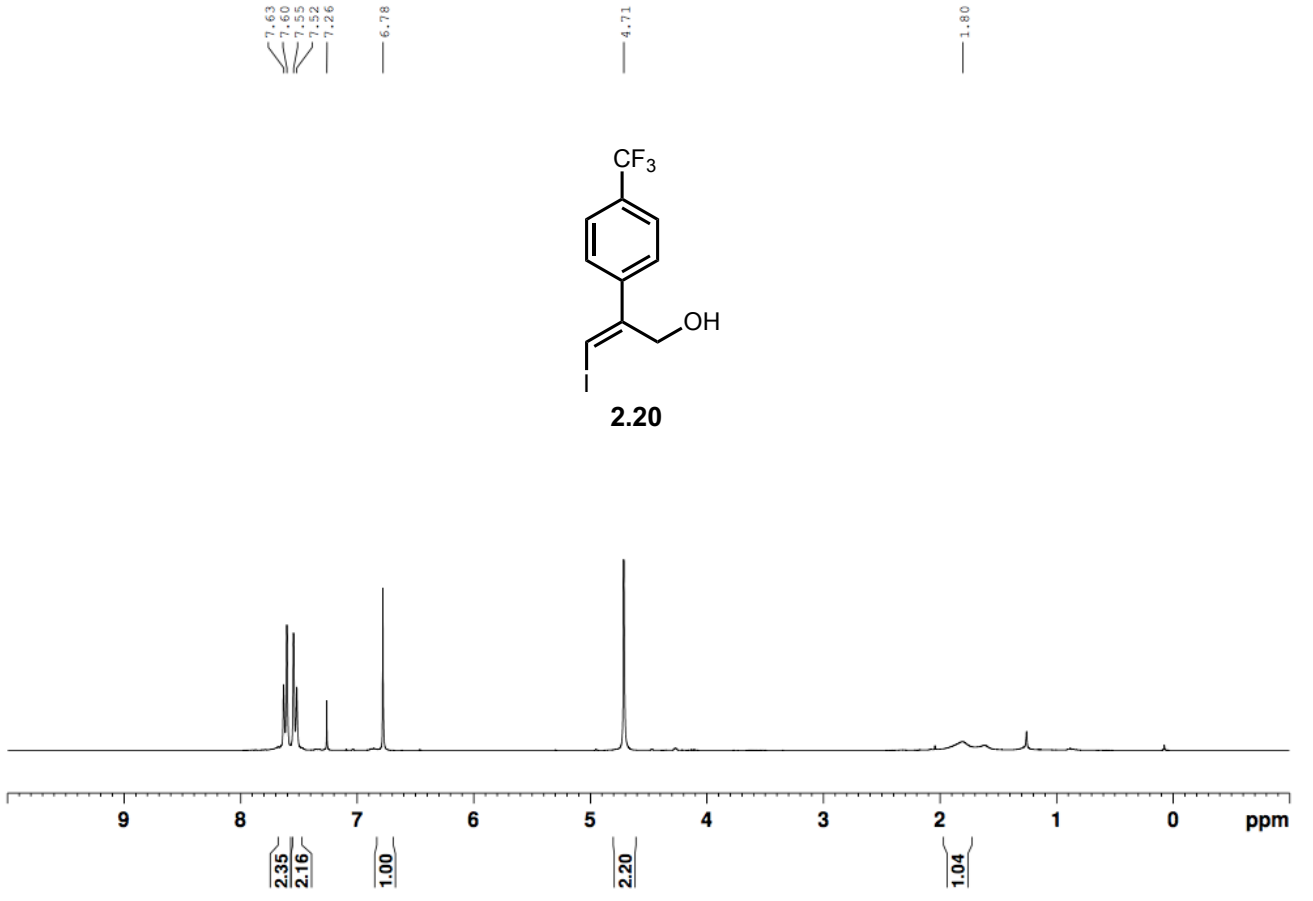
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.12**

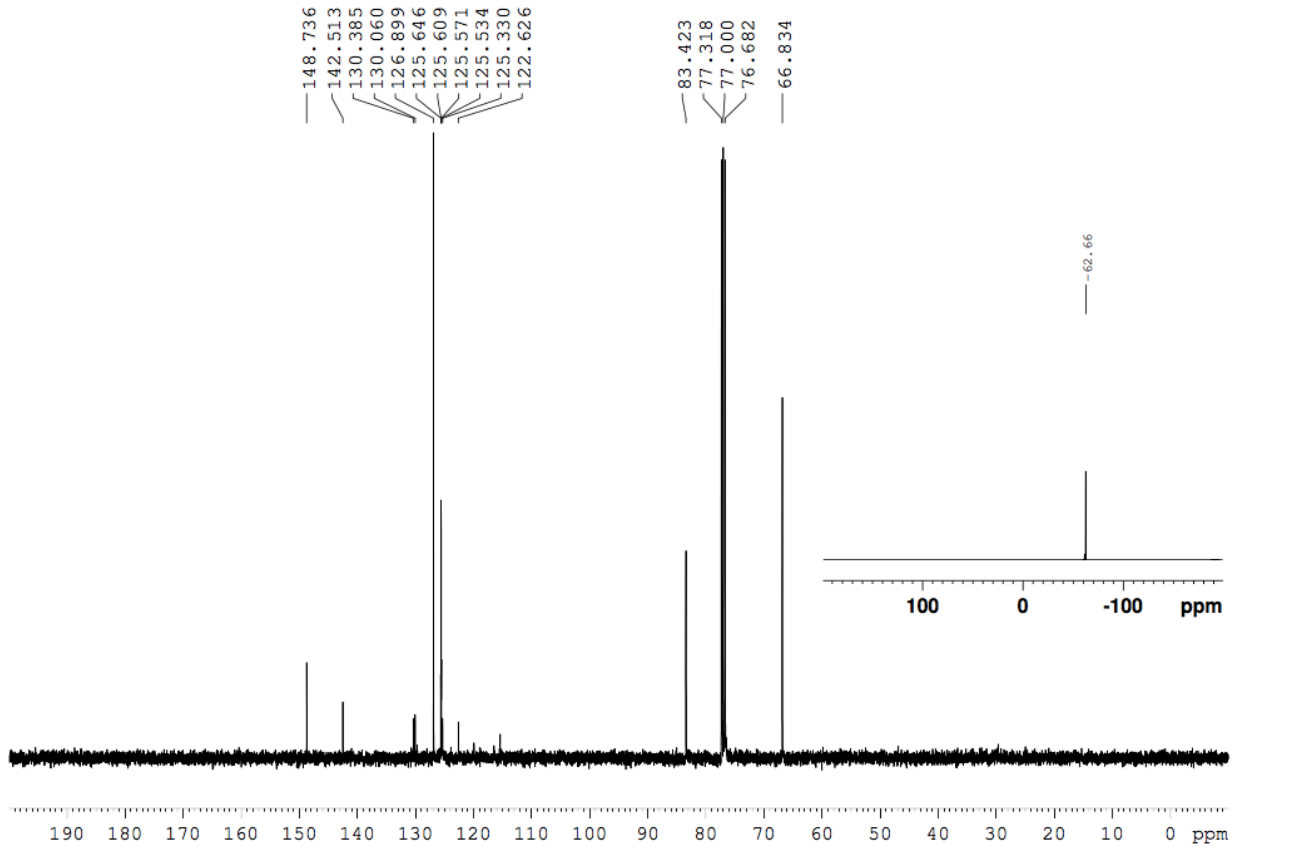


^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.17**

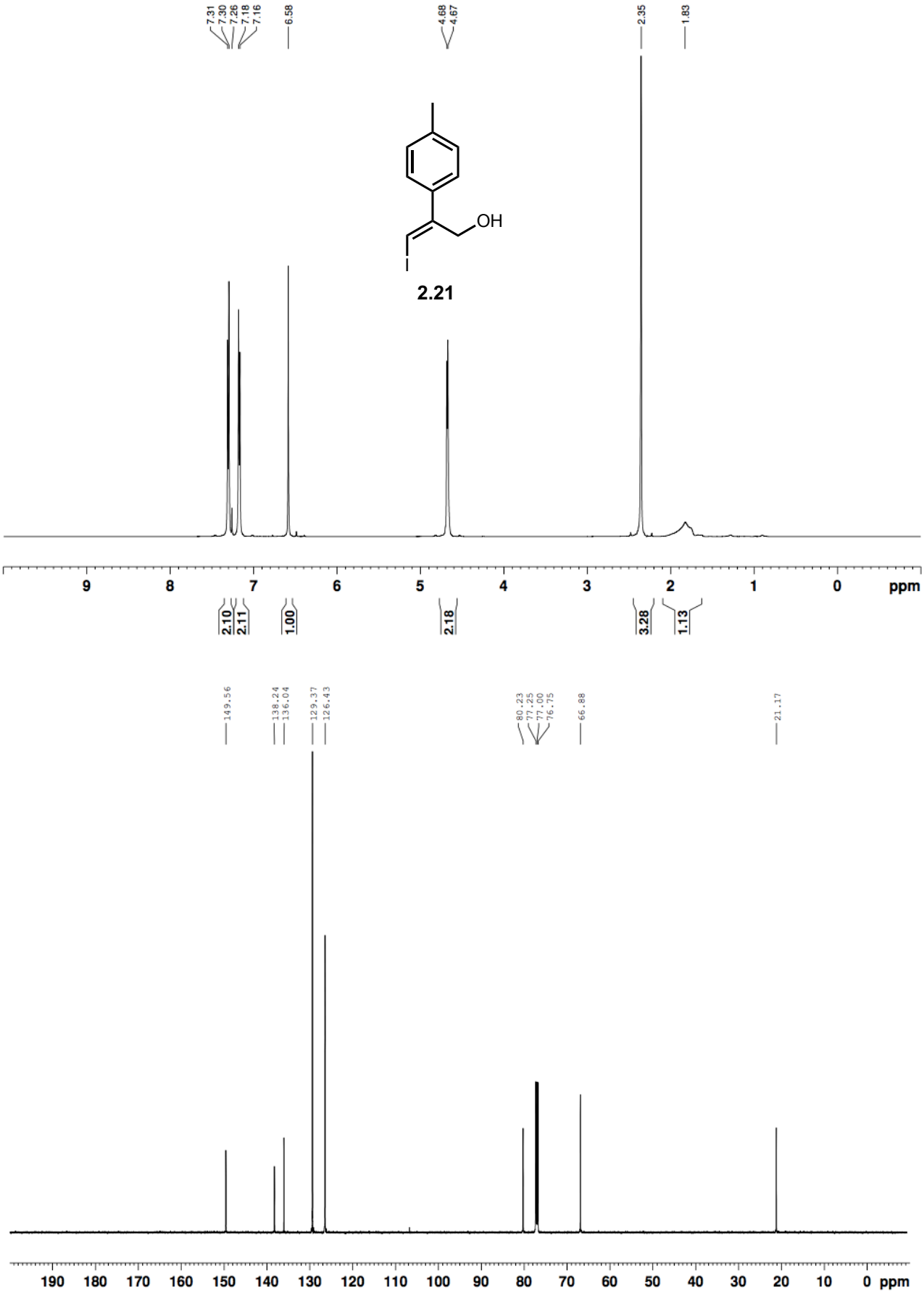


^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.19**

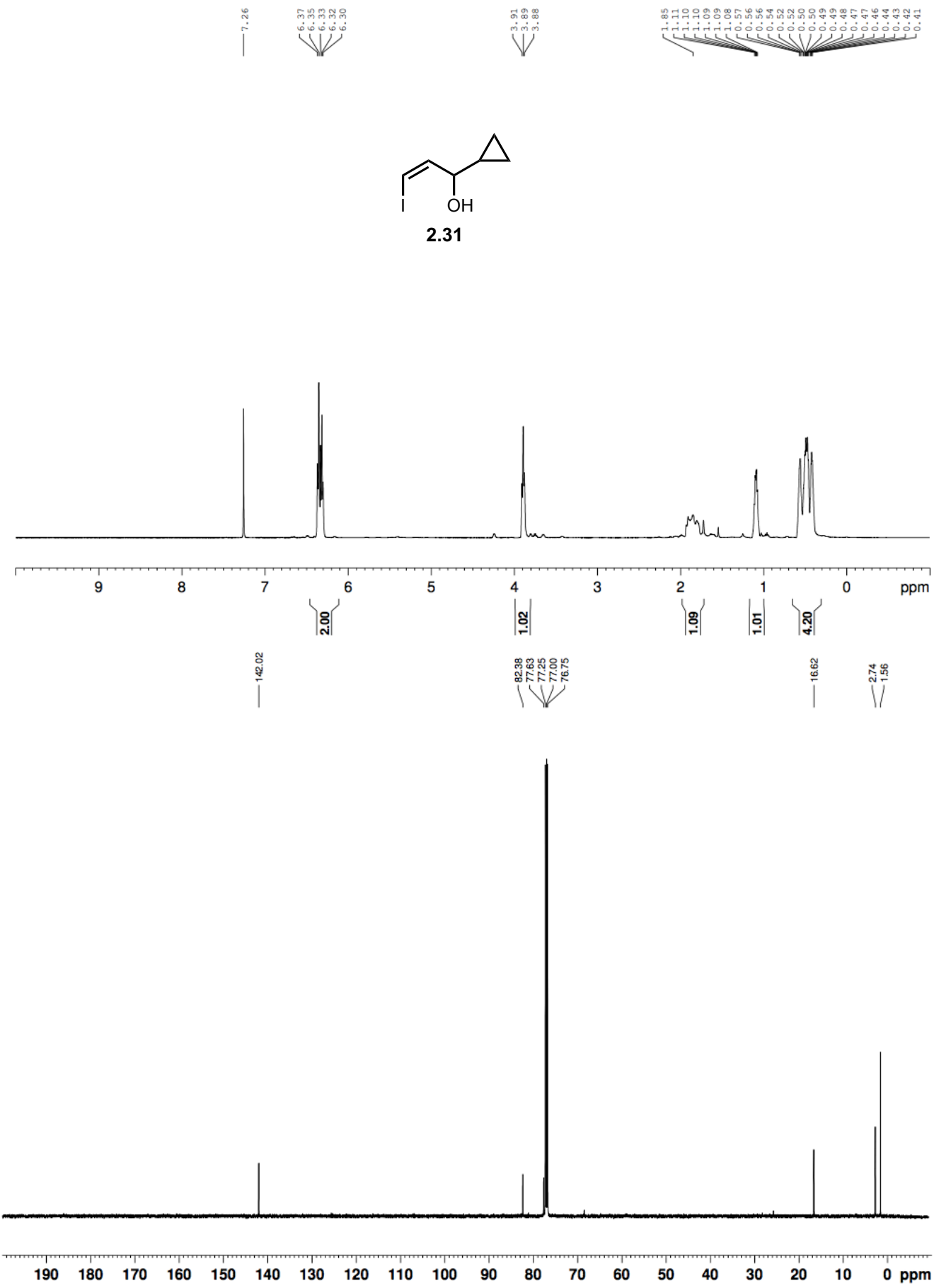




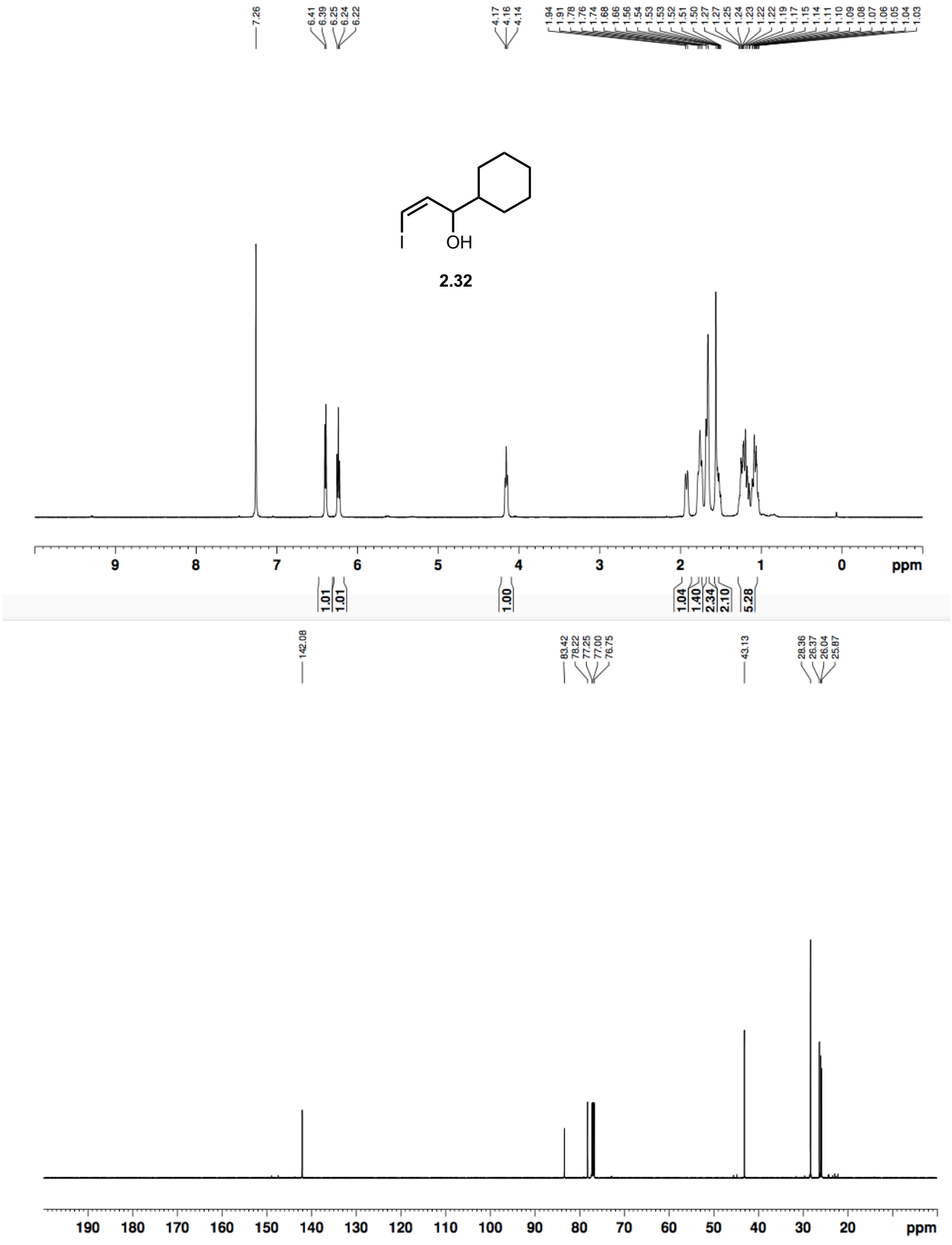
^{1}H (300 MHz, $CDCl_3$), ^{13}C (100 MHz, $CDCl_3$) and ^{19}F (376 MHz, $CDCl_3$) NMR Spectra of **2.20**



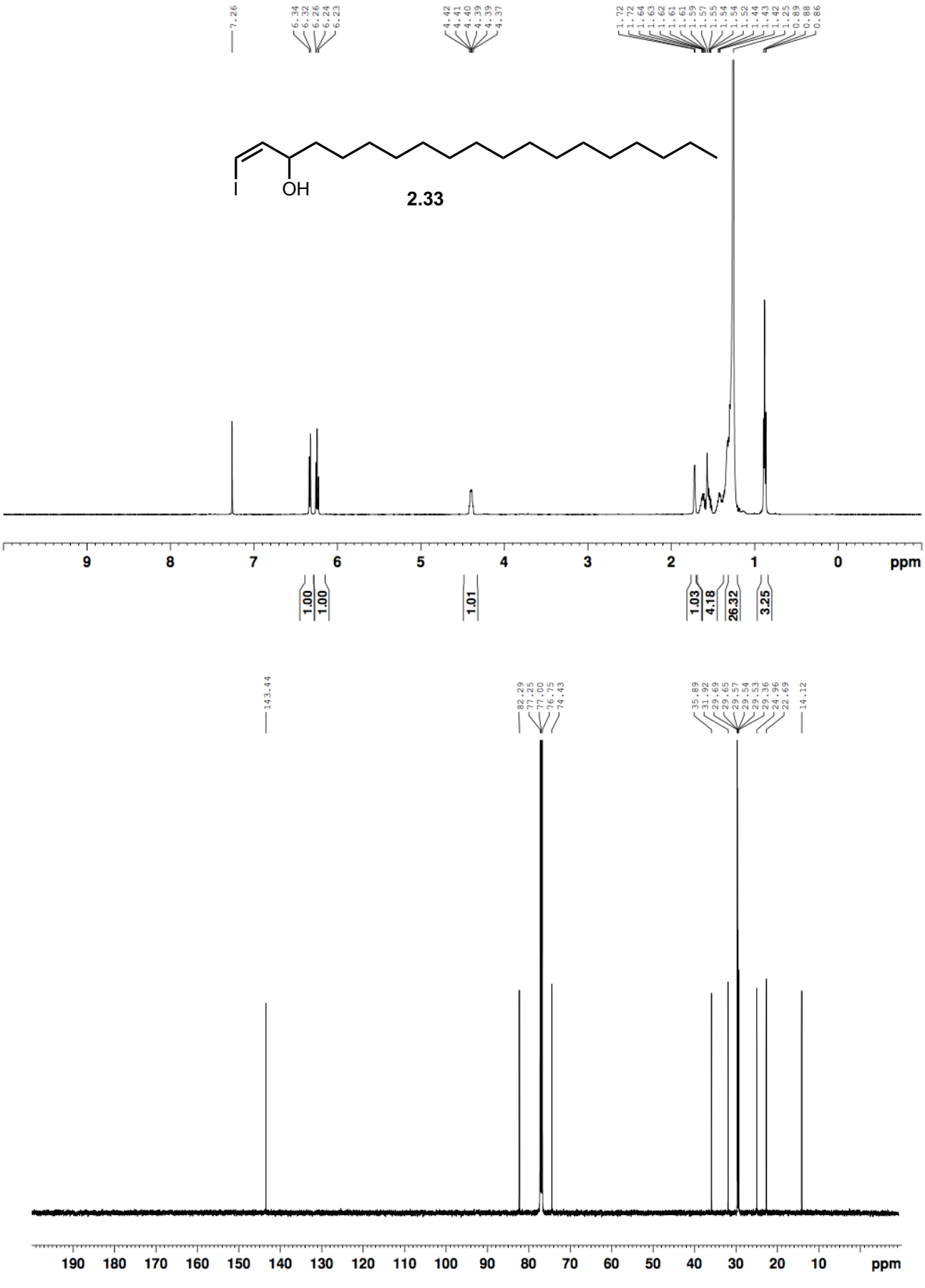
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.21**



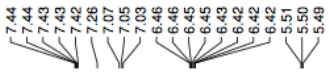
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.31**

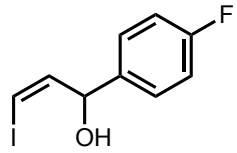


^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.32**

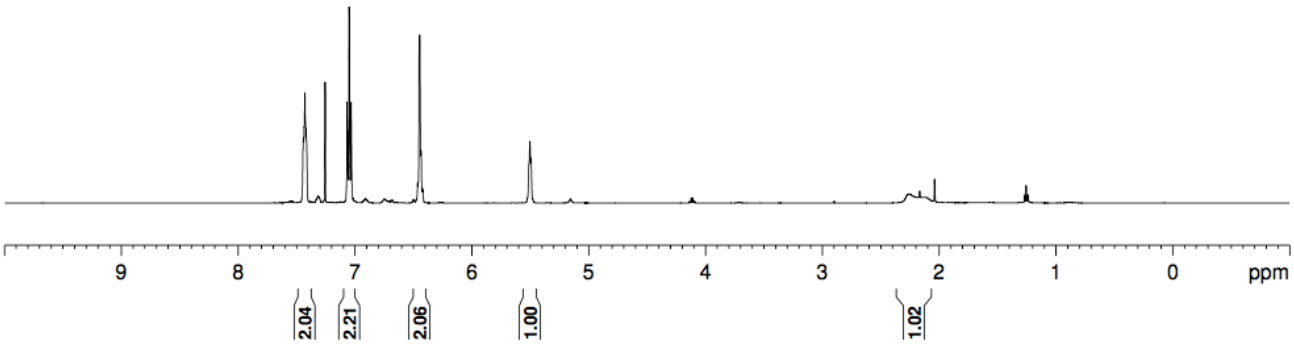


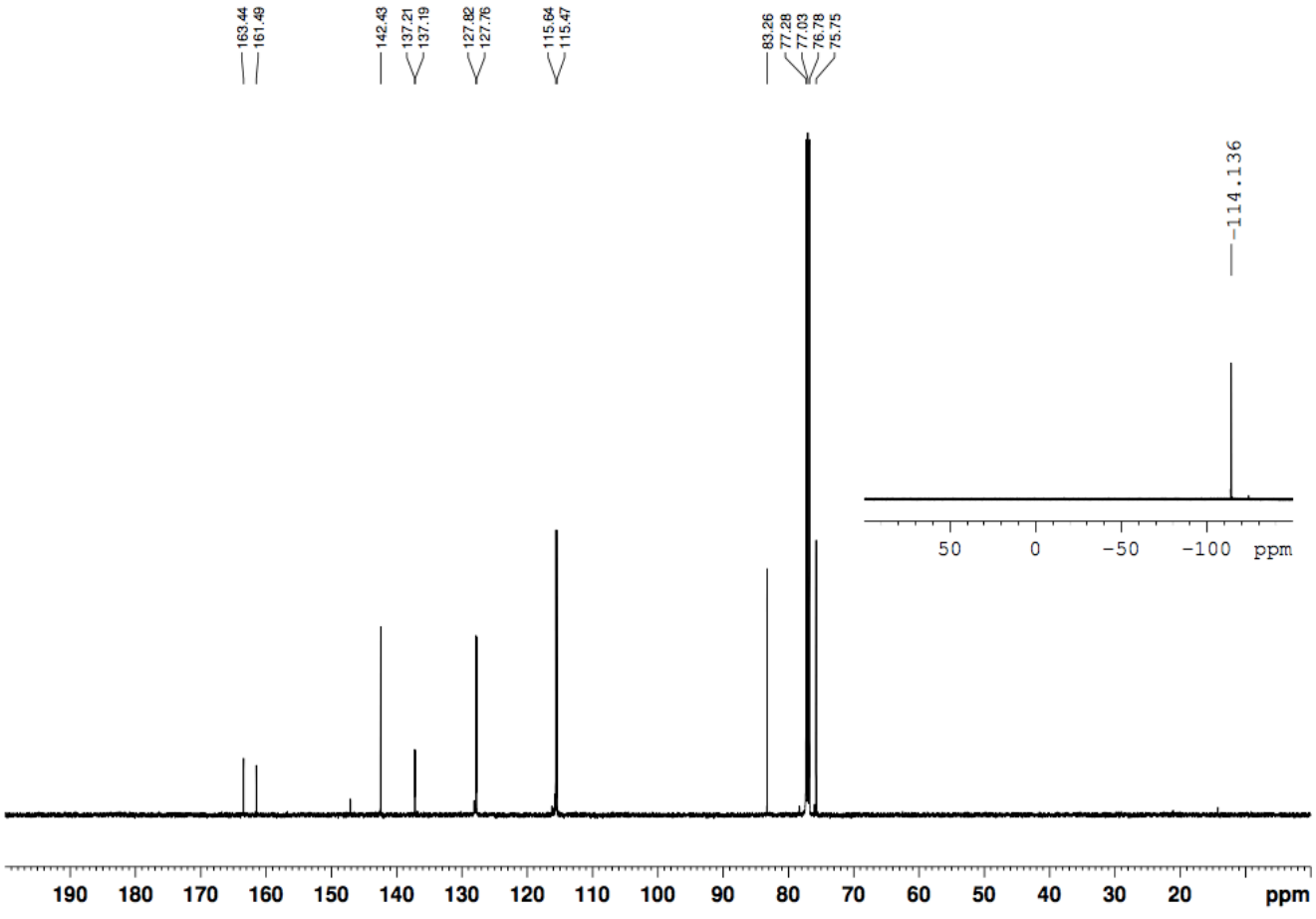
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.33**



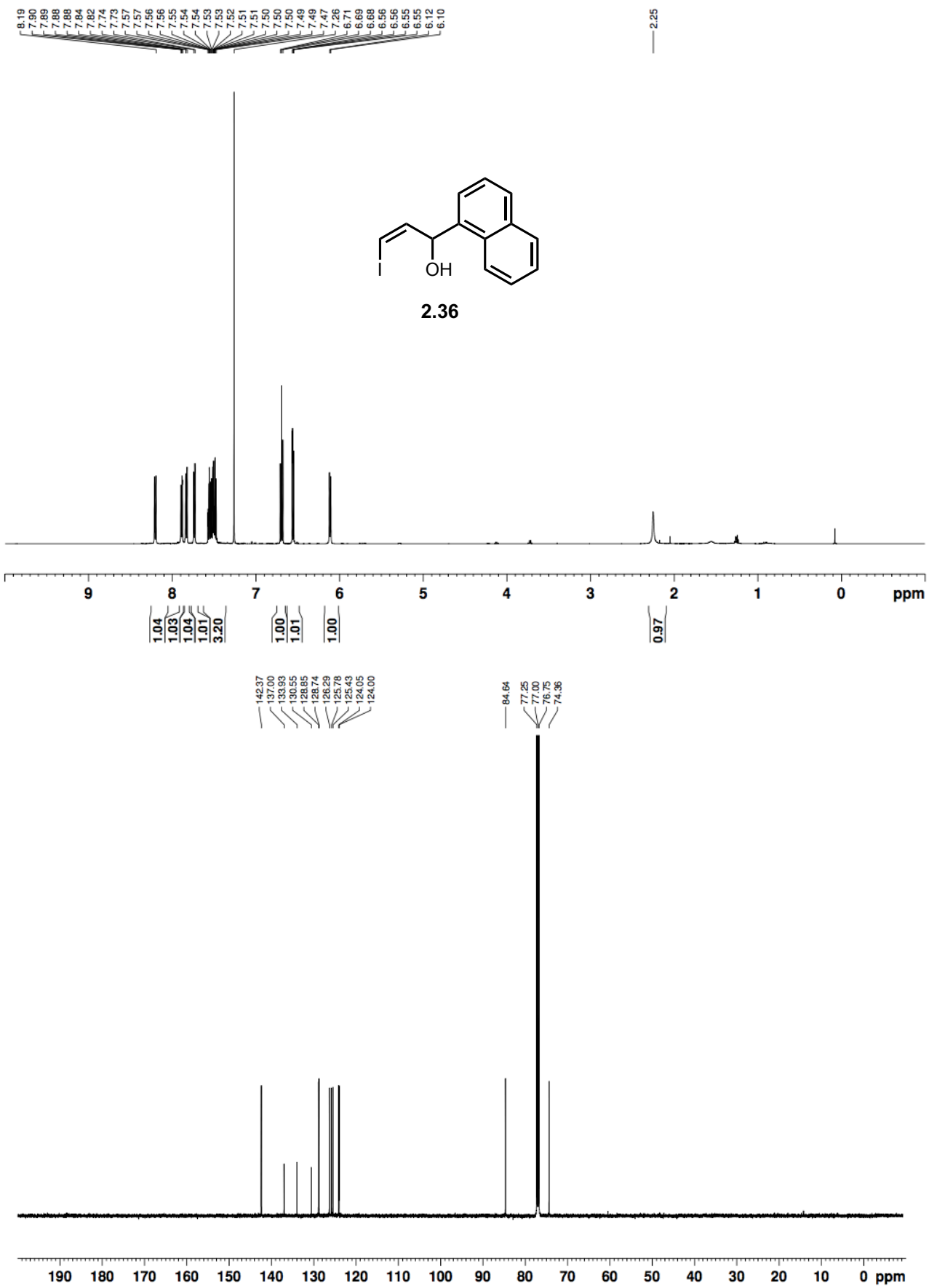


2.35

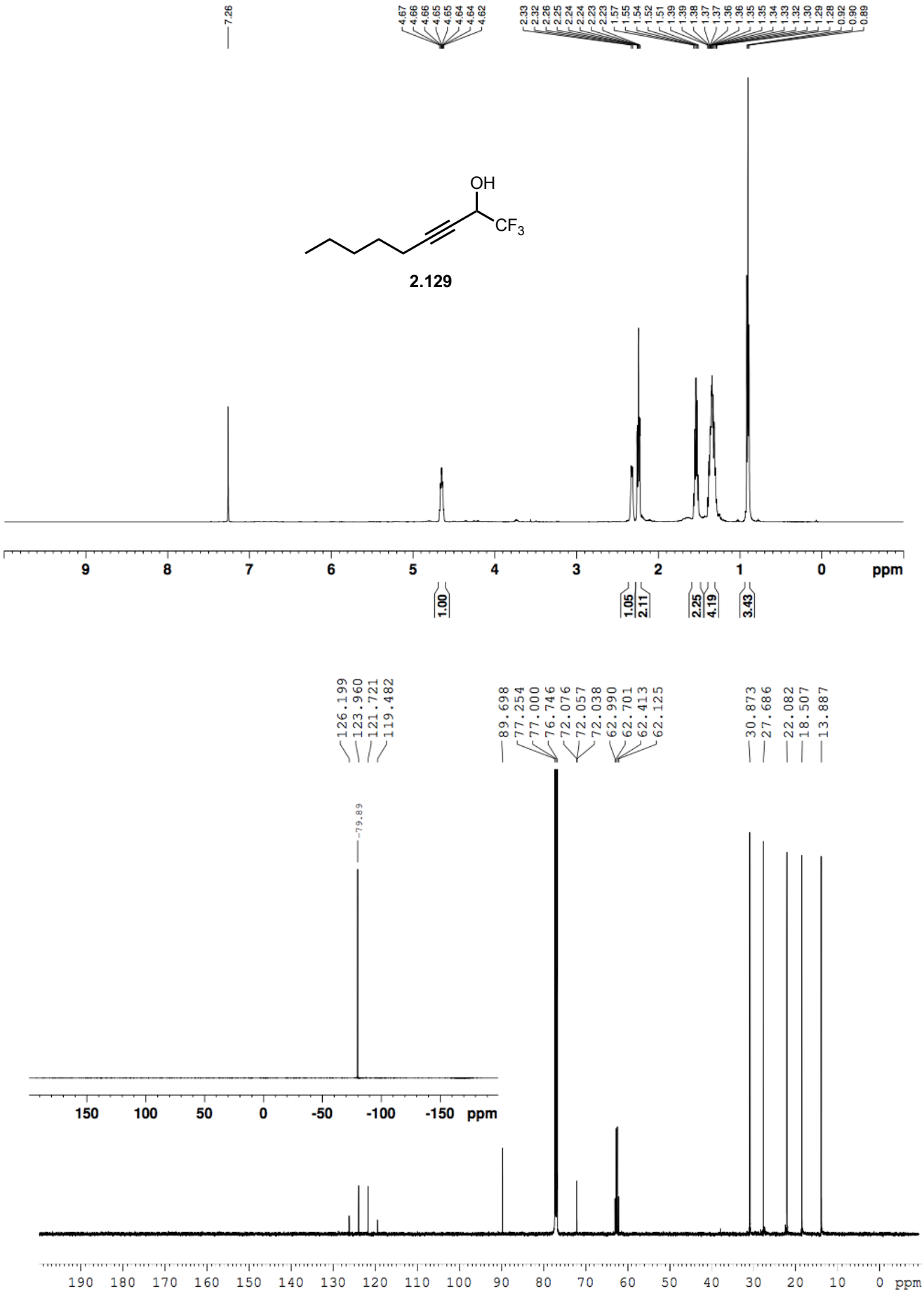




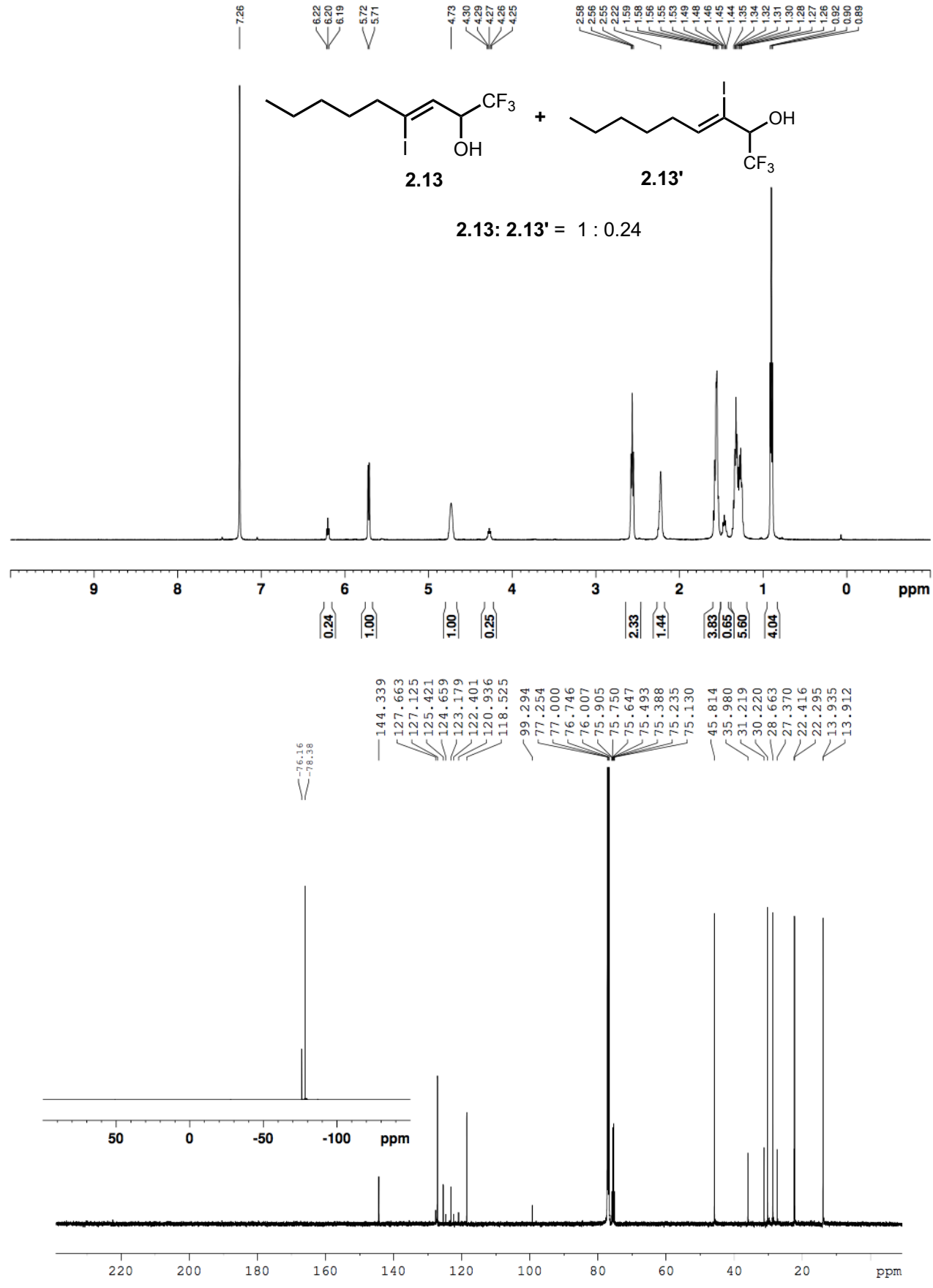
^{1}H (500 MHz, $CDCl_3$), ^{13}C (125 MHz, $CDCl_3$) and ^{19}F (376 MHz, $CDCl_3$) NMR Spectra of **2.35**



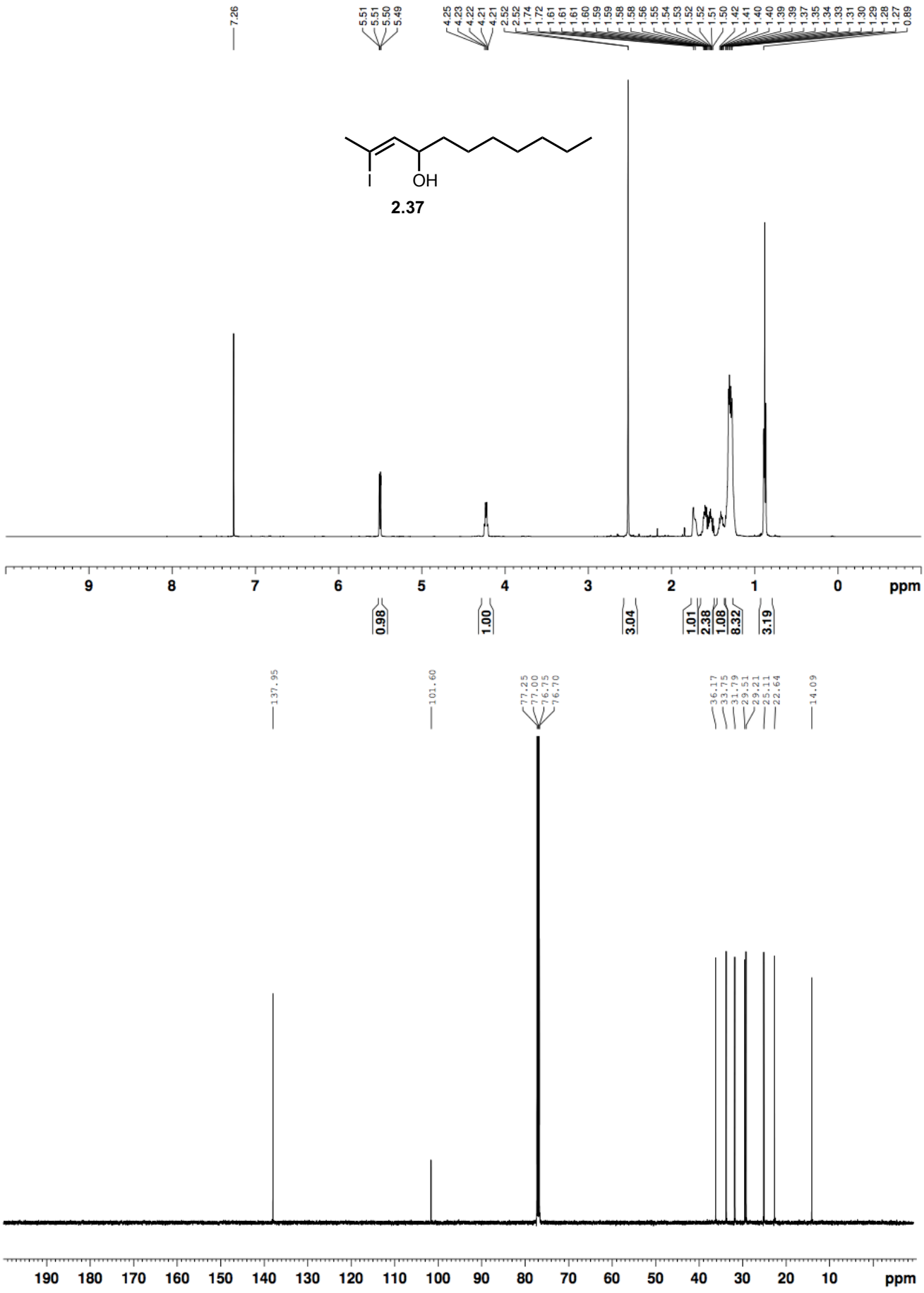
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.36**



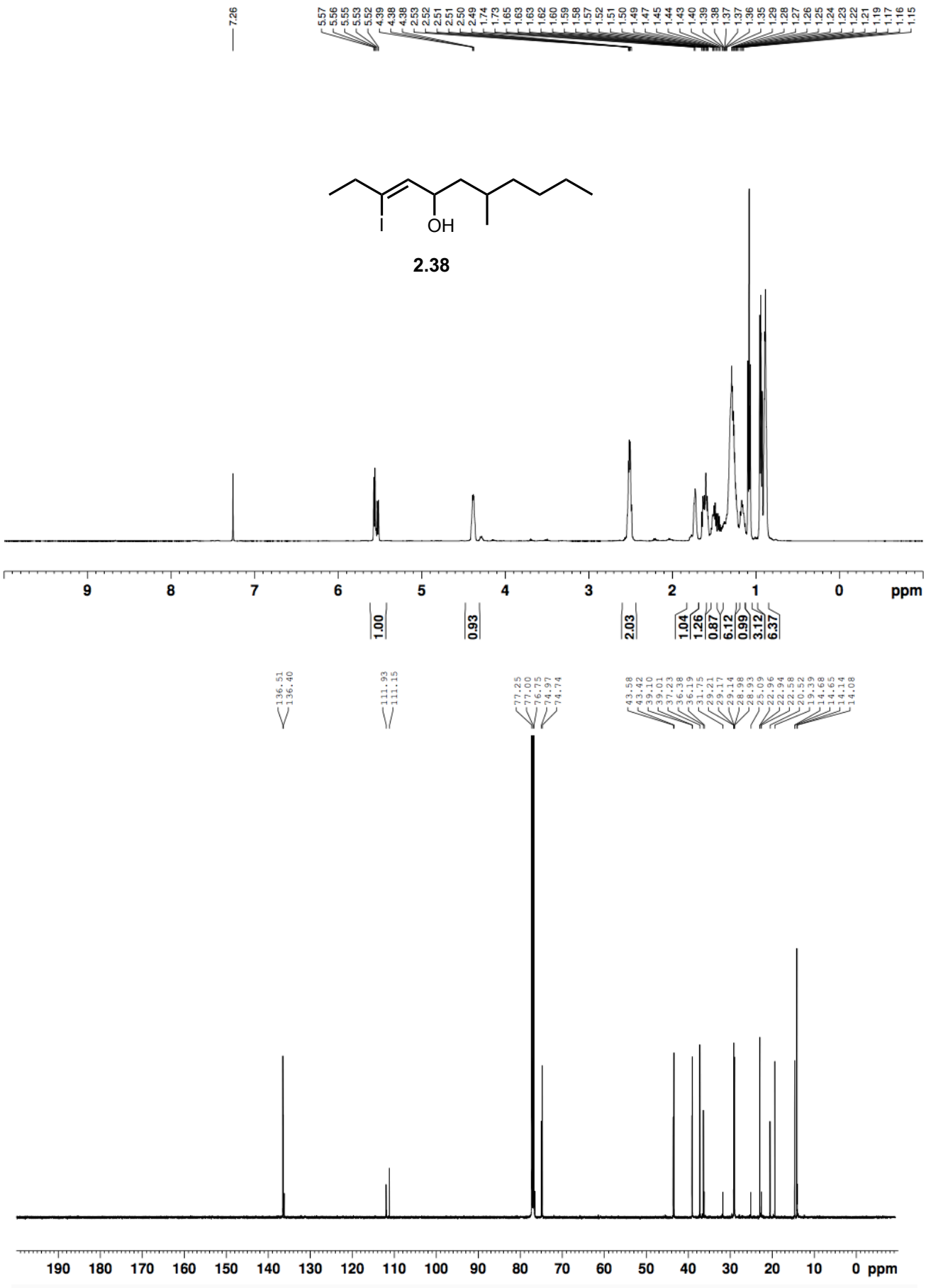
^{1}H (500 MHz, $CDCl_3$), ^{13}C (125 MHz, $CDCl_3$) and ^{19}F (376 MHz, $CDCl_3$) NMR Spectra of **2.129**



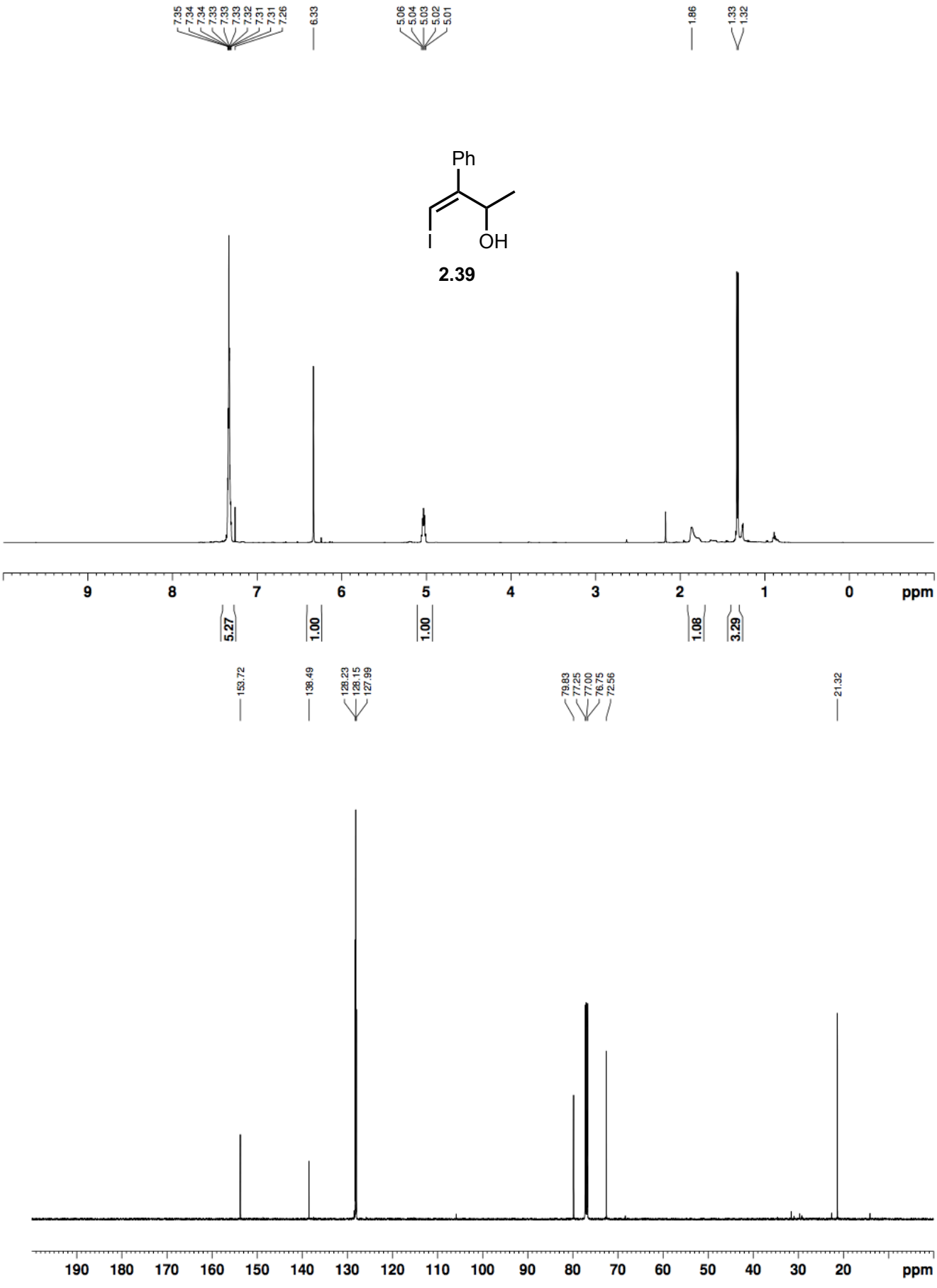
^{1}H (500 MHz, $CDCl_3$), ^{13}C (125 MHz, $CDCl_3$) and ^{19}F (376 MHz, $CDCl_3$) NMR Spectra of **2.13**



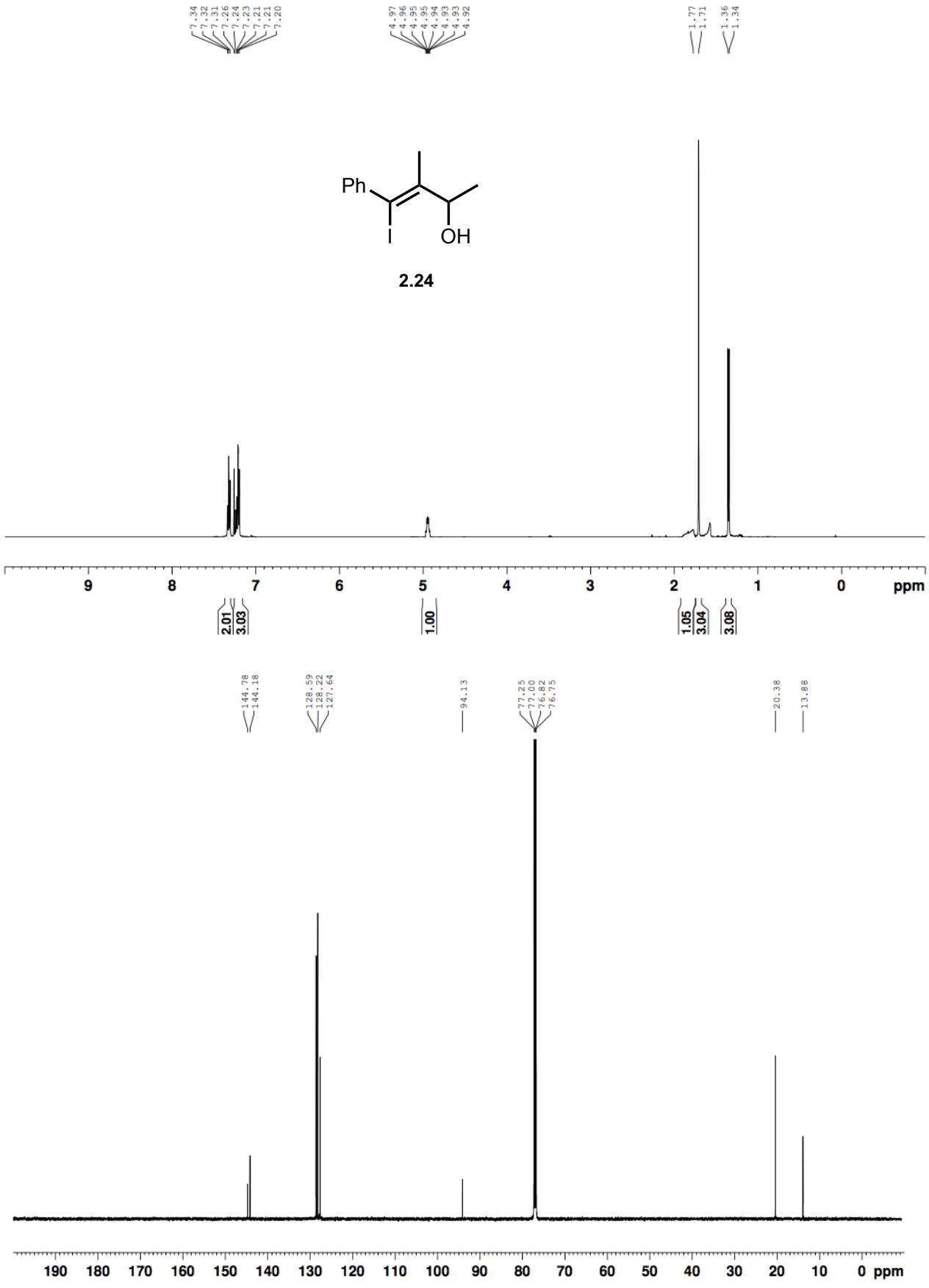
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.37**



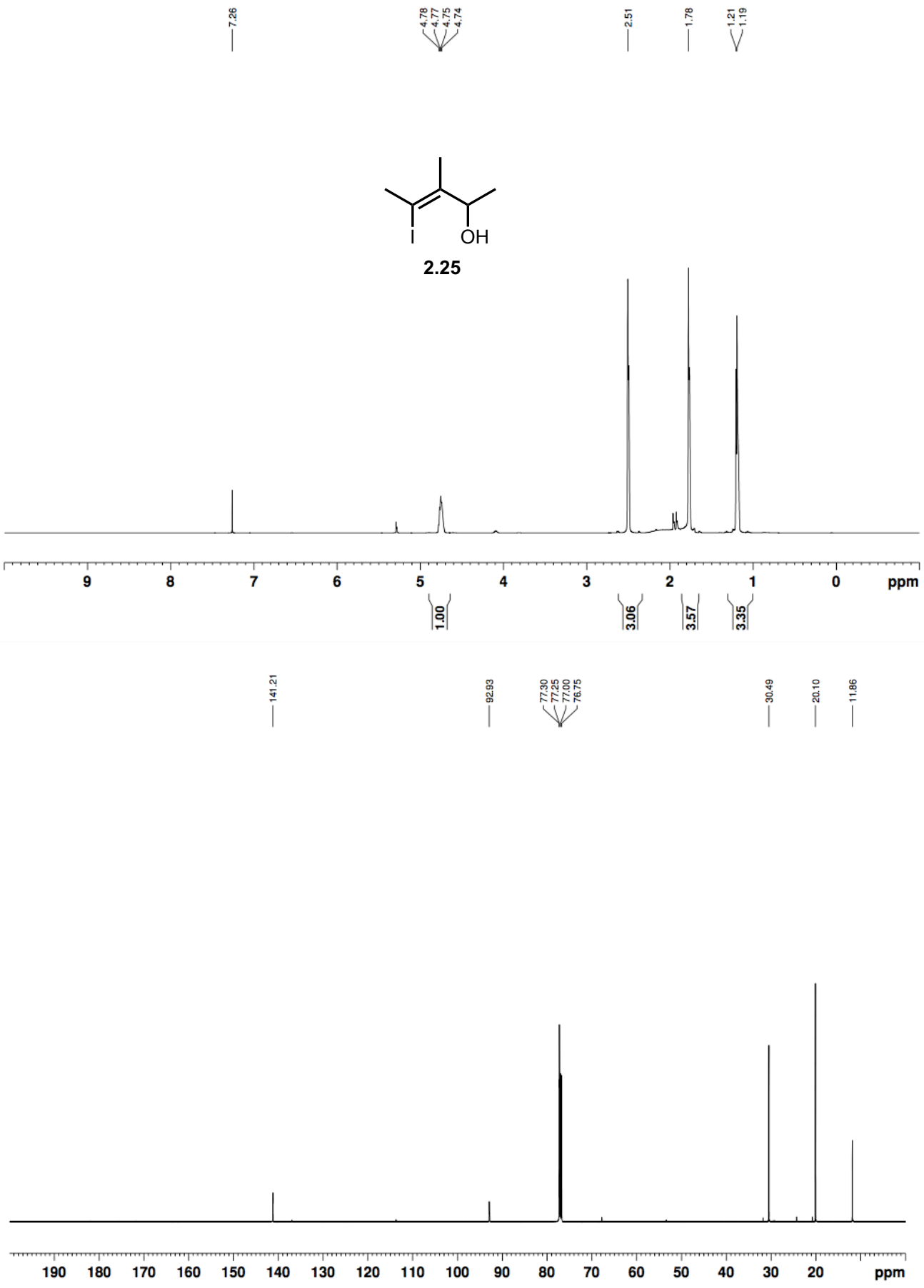
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.38**



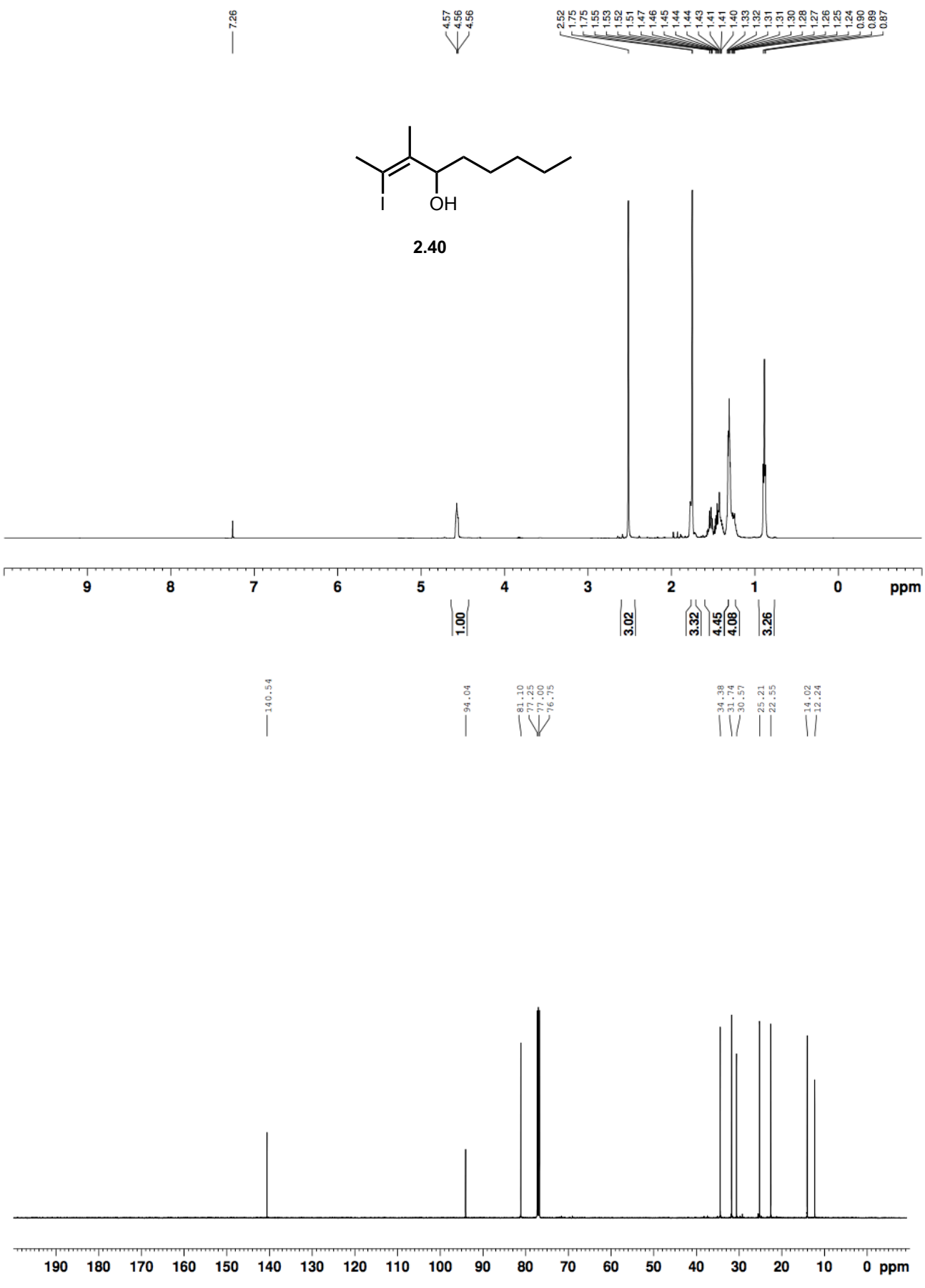
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.39**



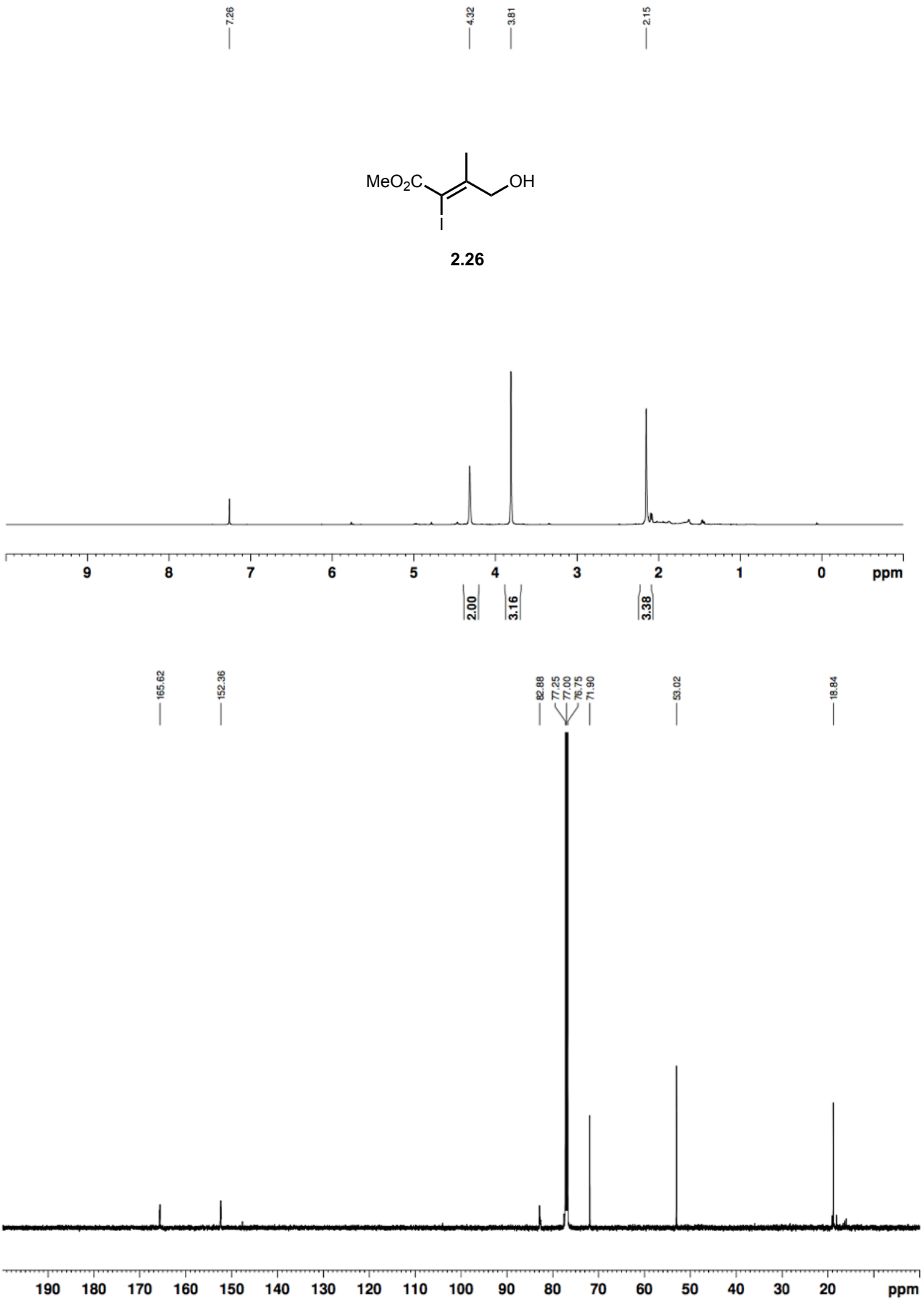
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.24**



^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.25**

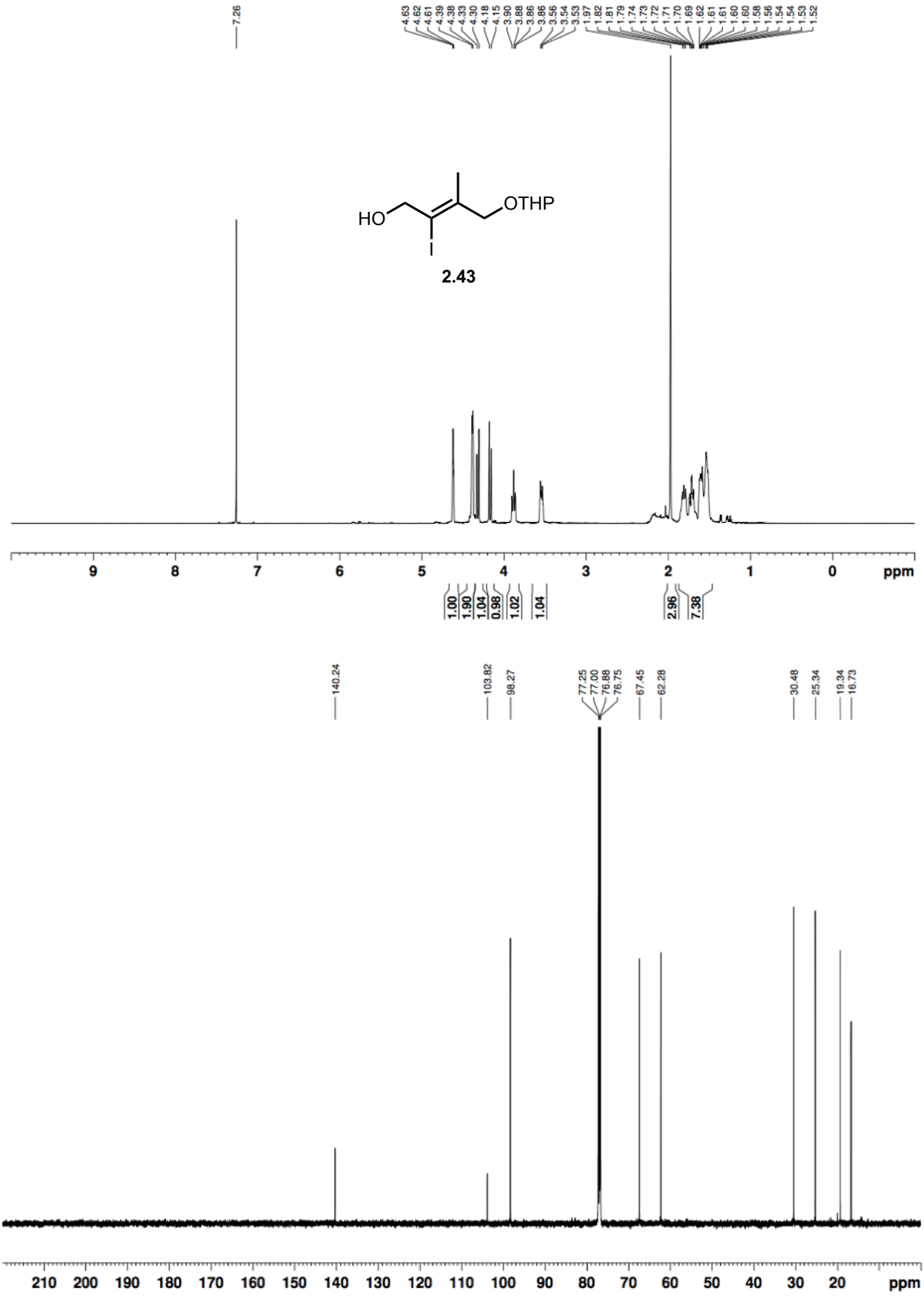


^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.40**

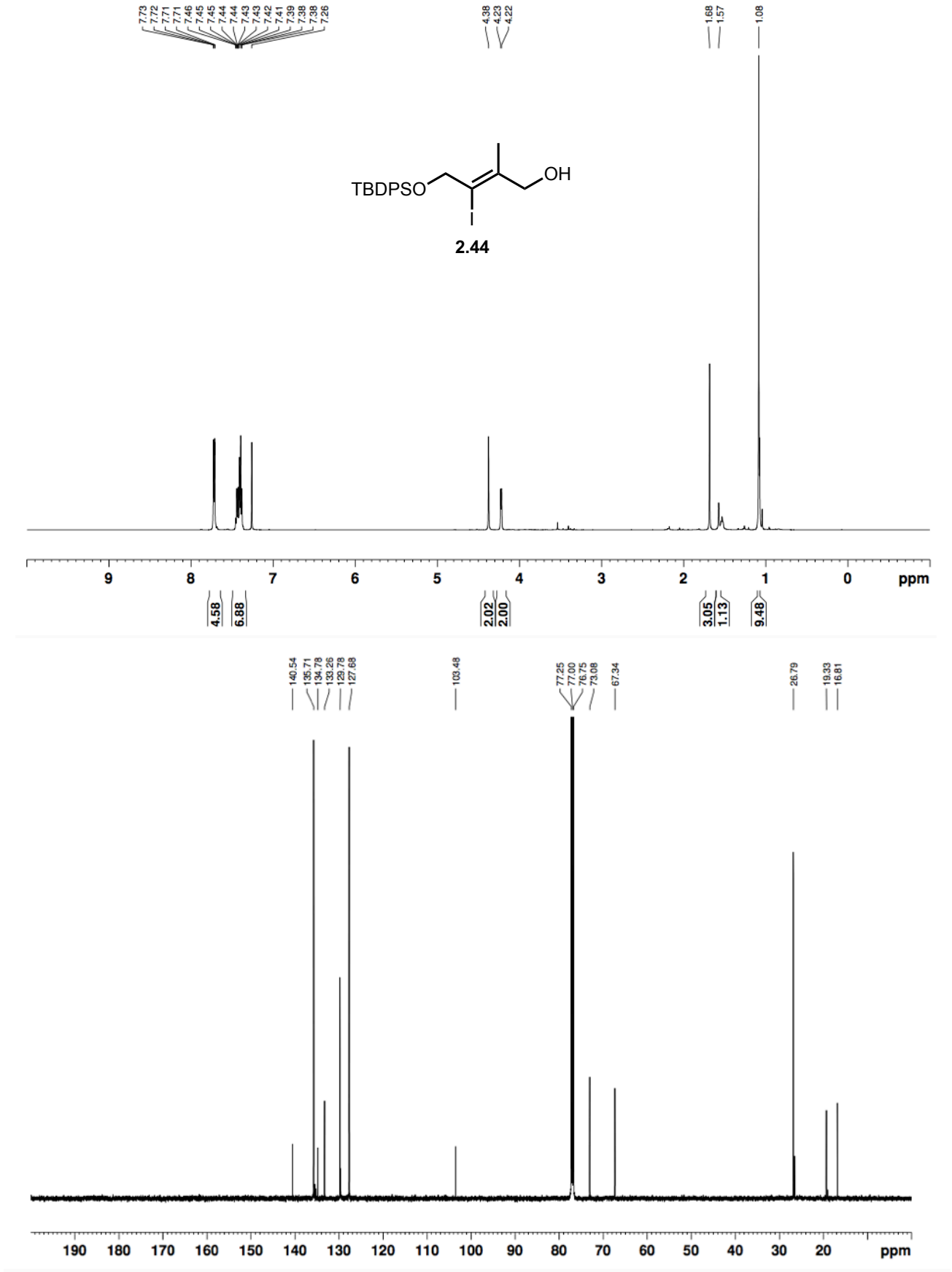


2.26

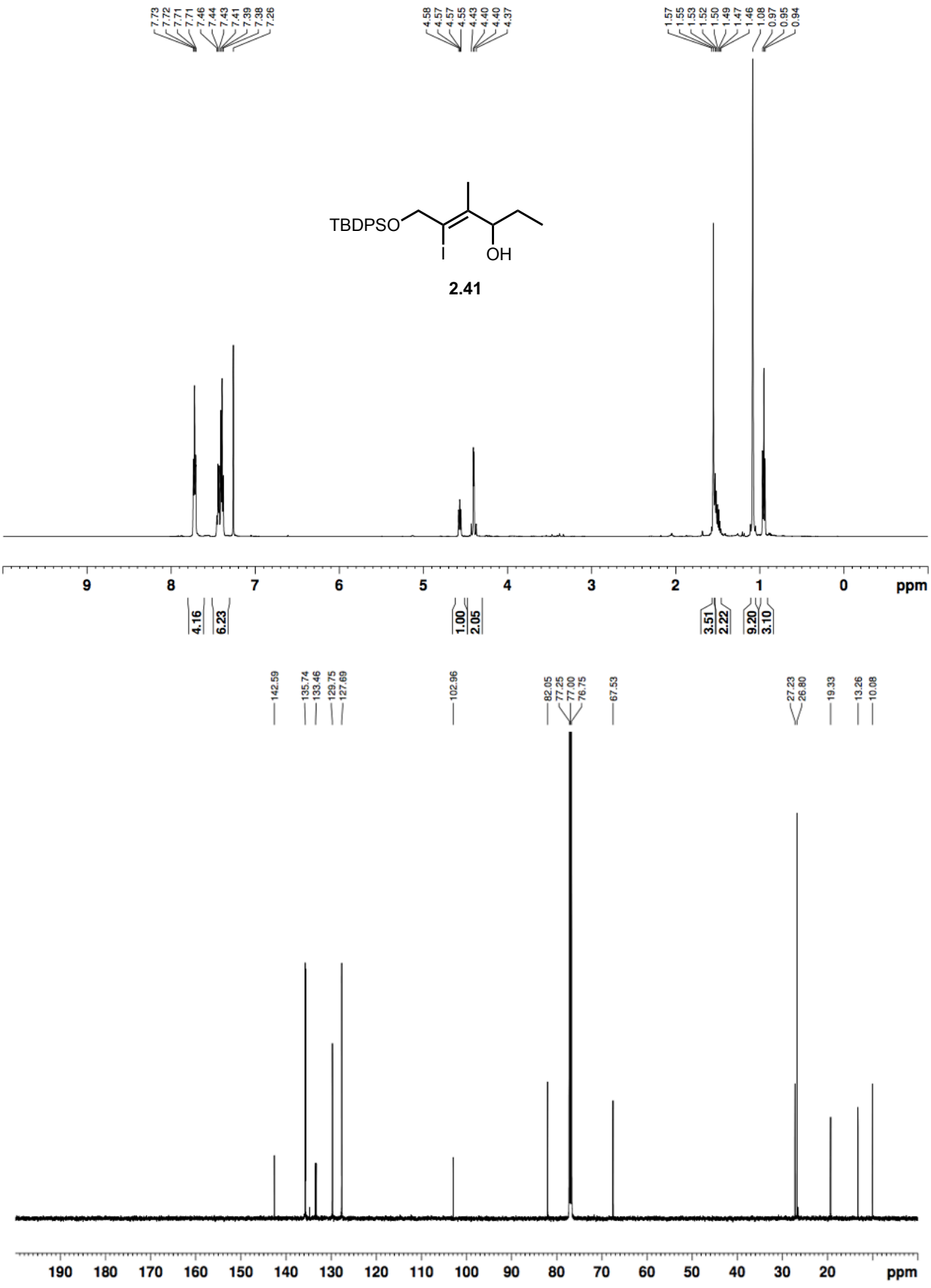
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.26**



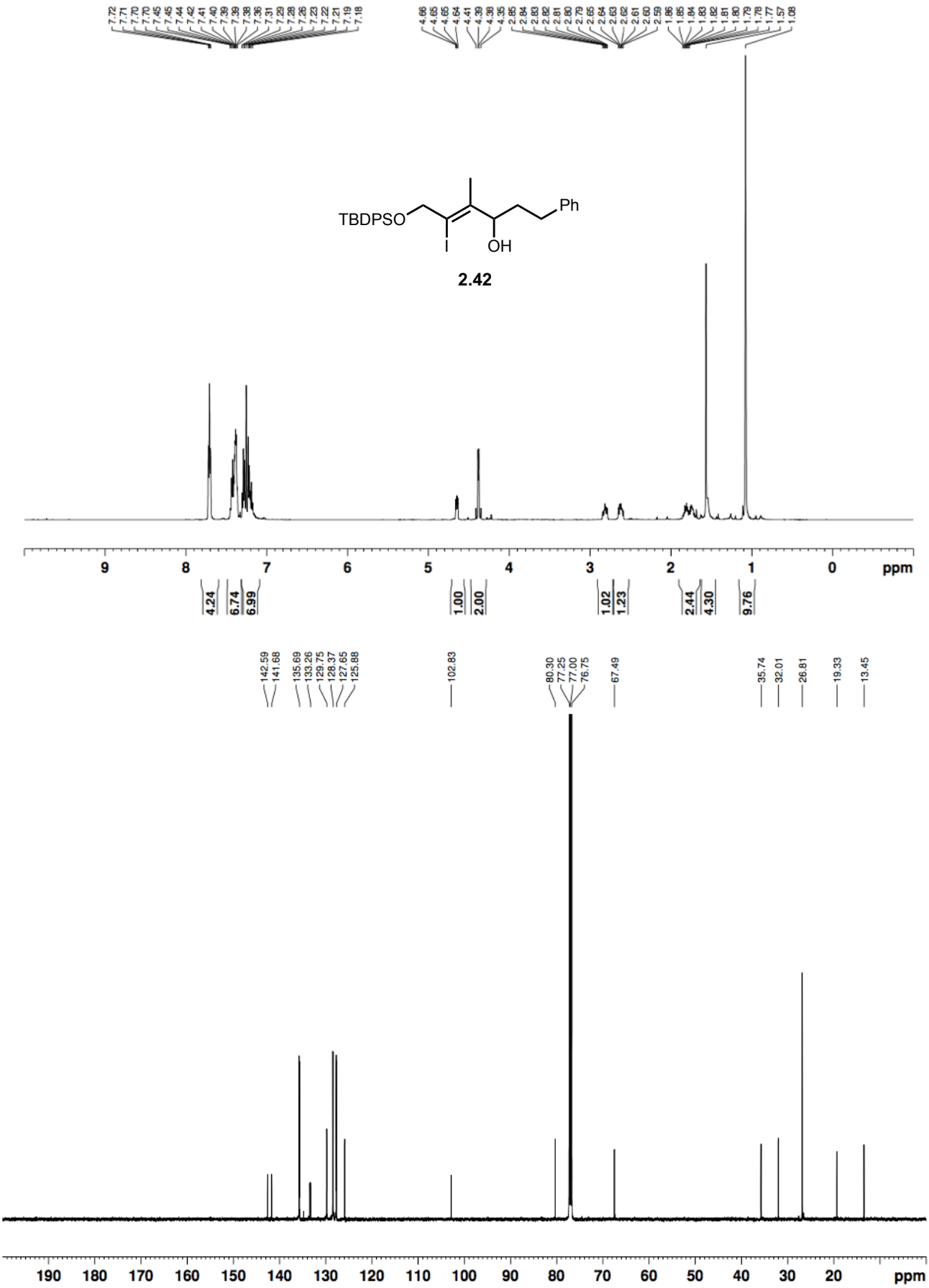
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.43**



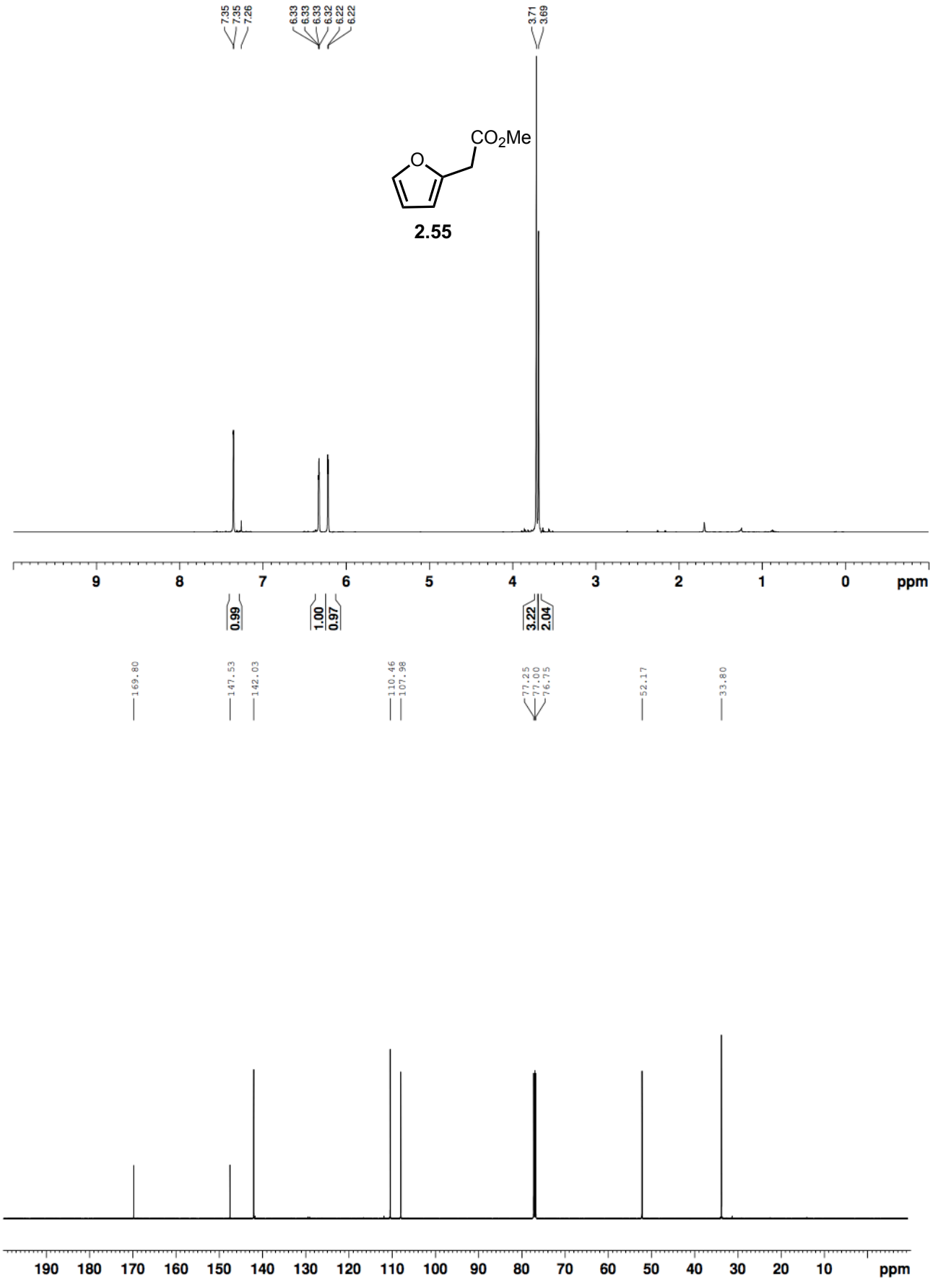
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.44**



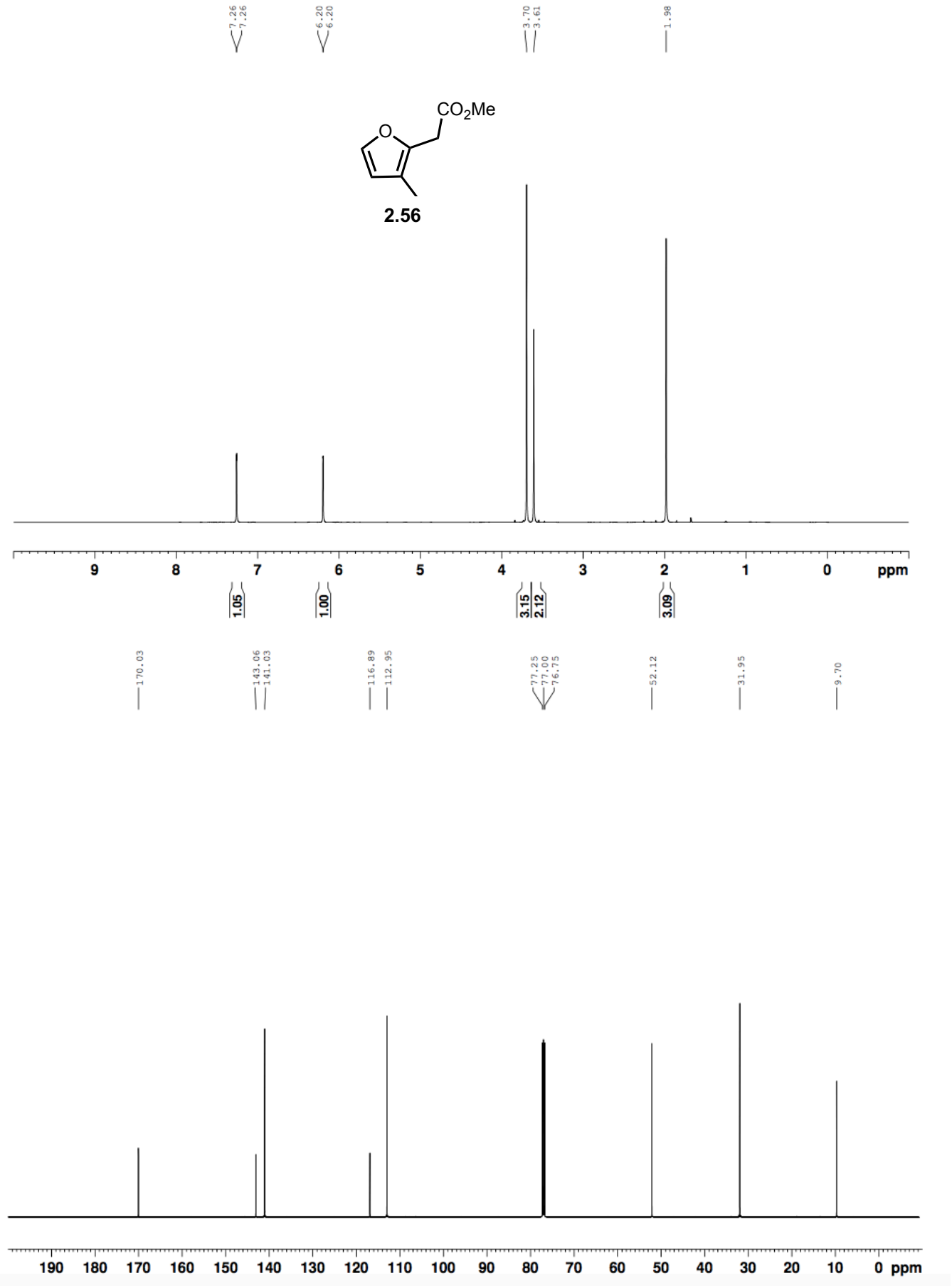
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.41**



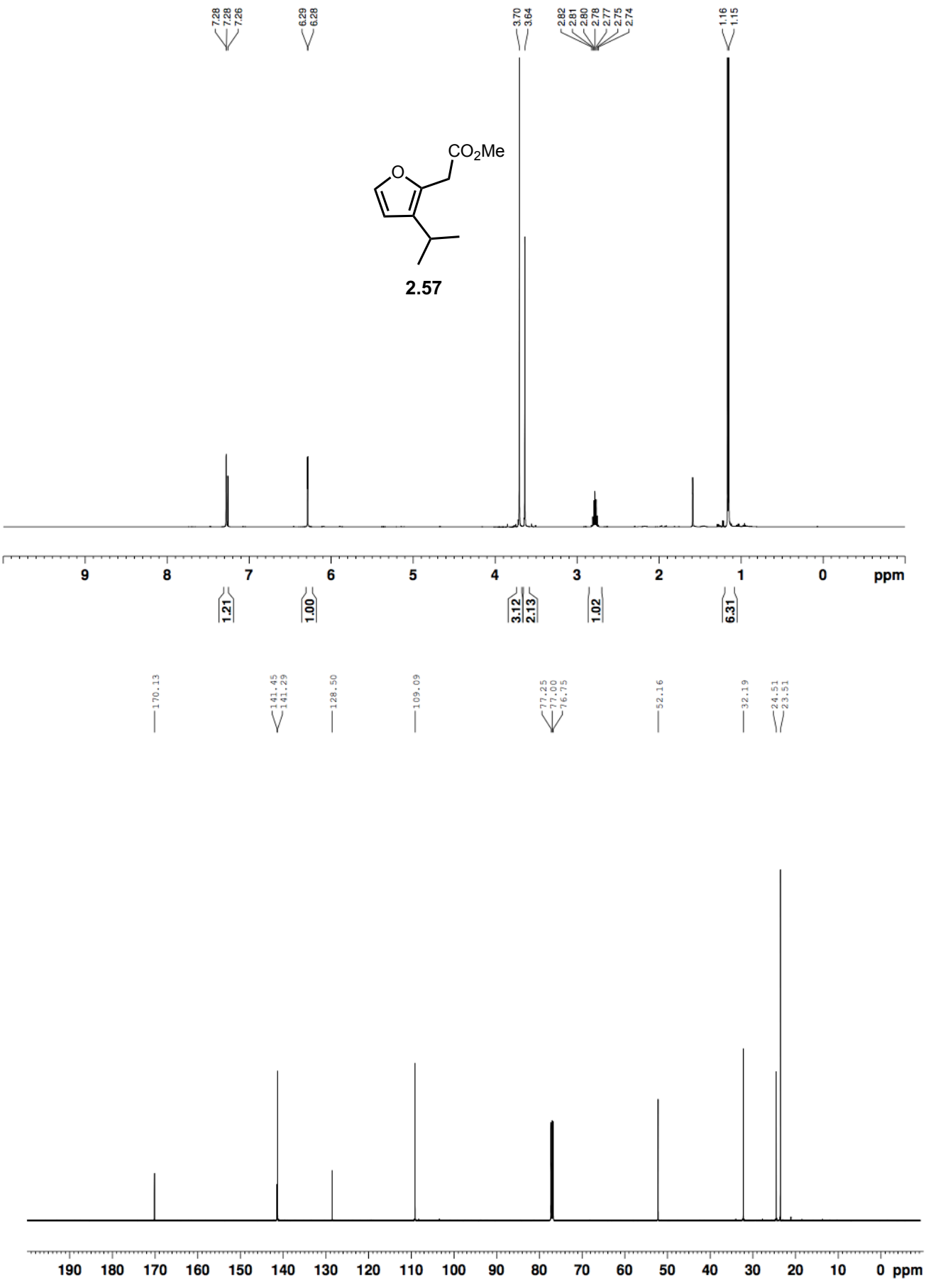
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.42**



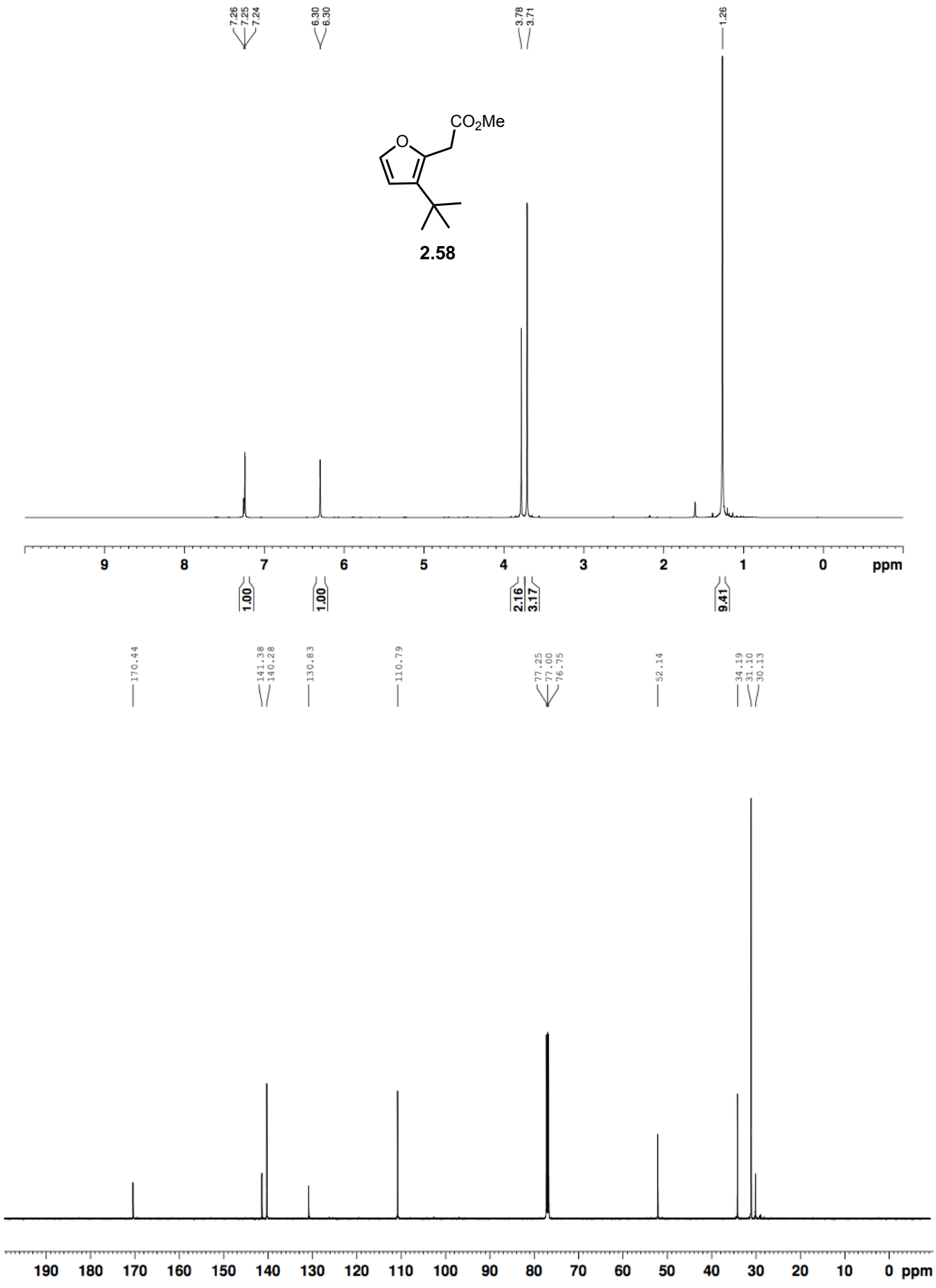
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.55**



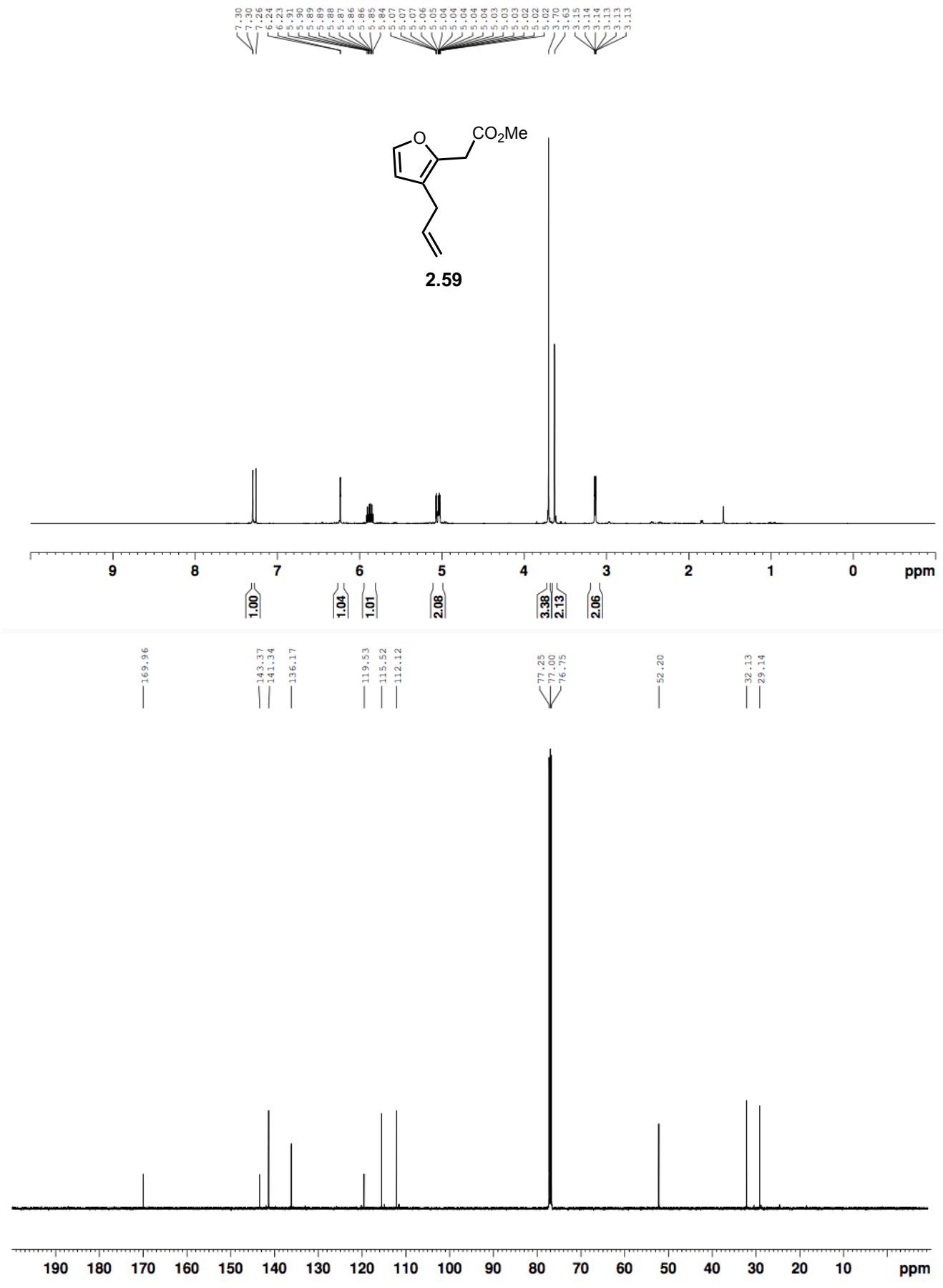
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.56**



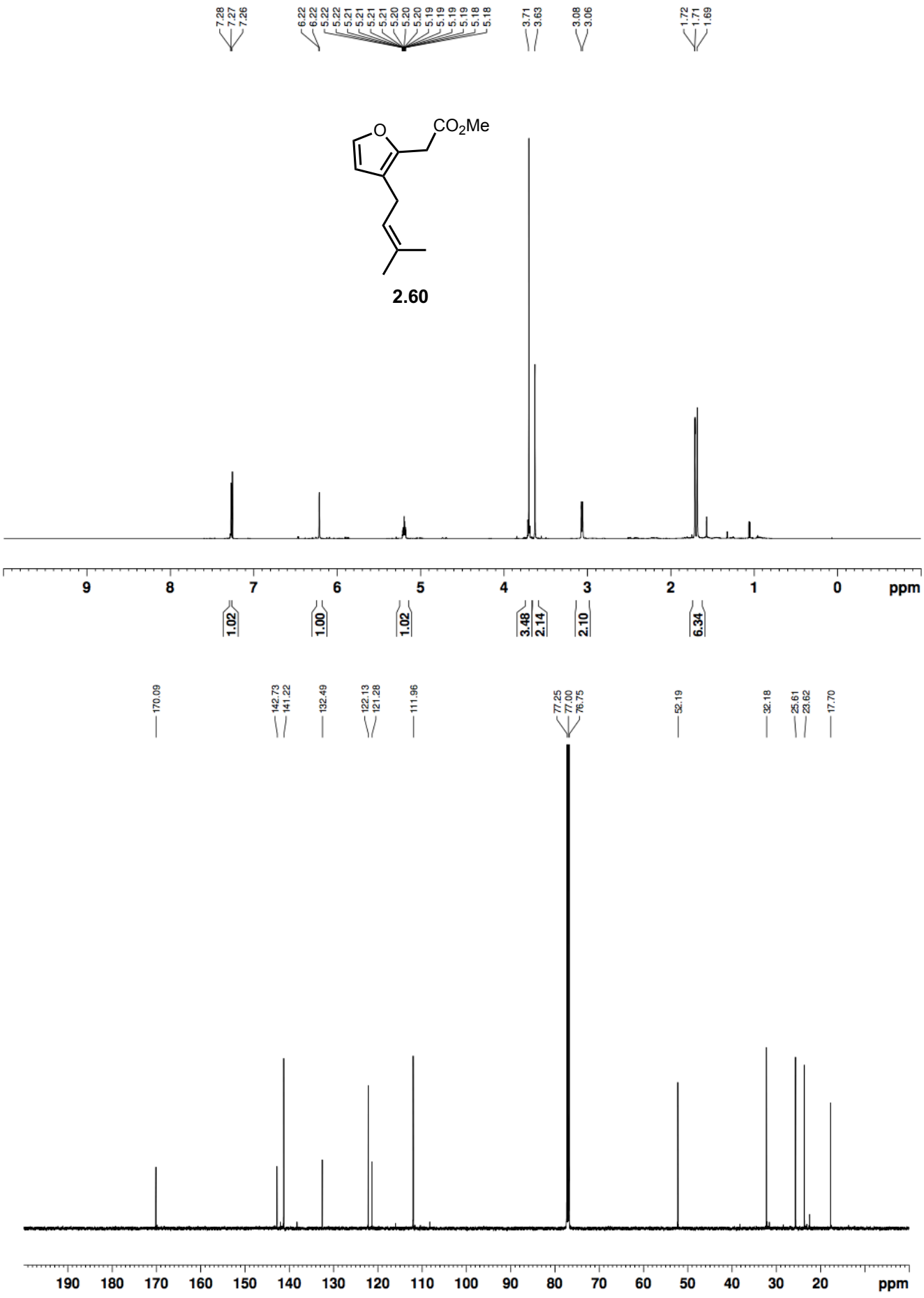
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.57**



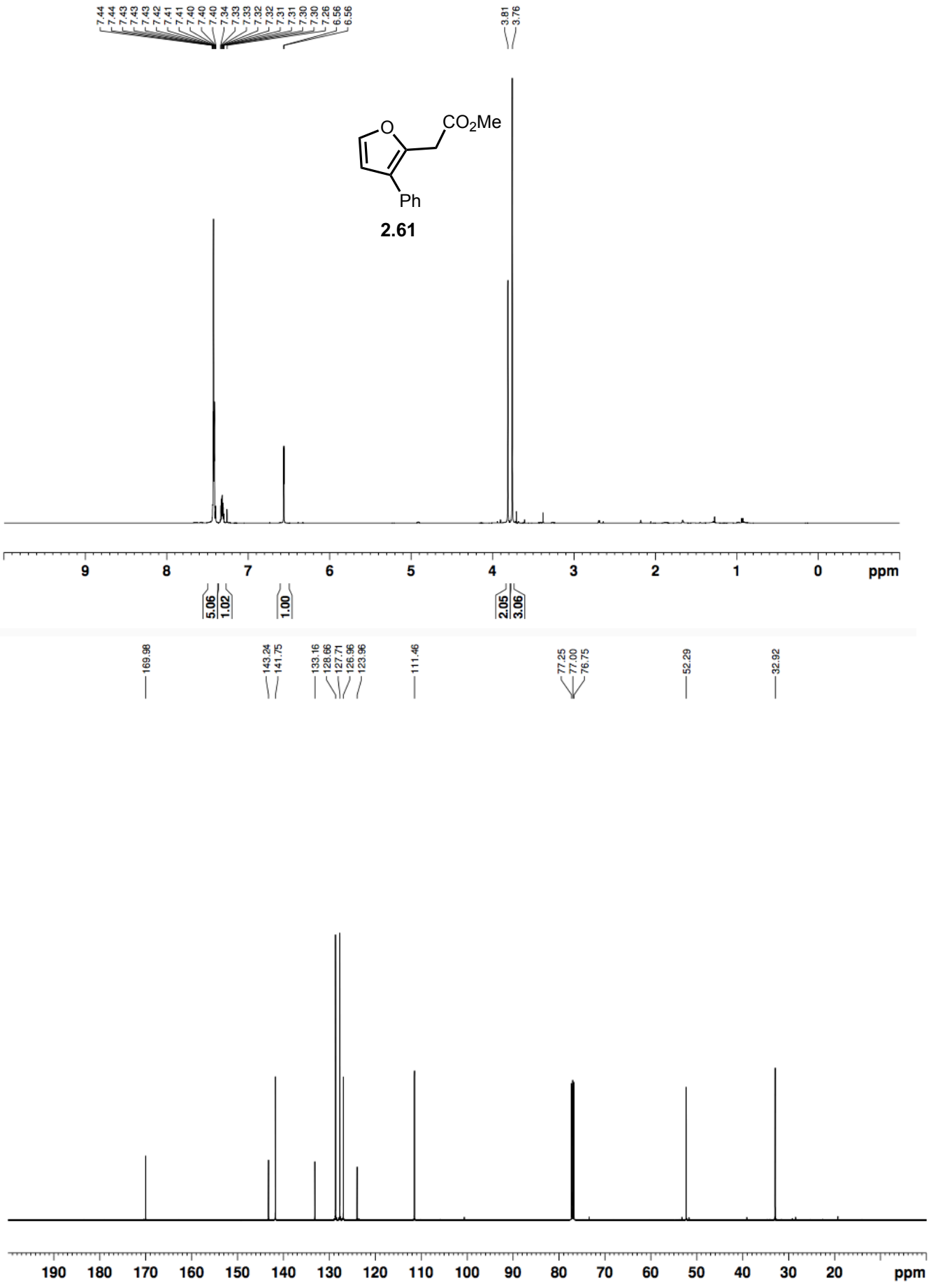
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.58**



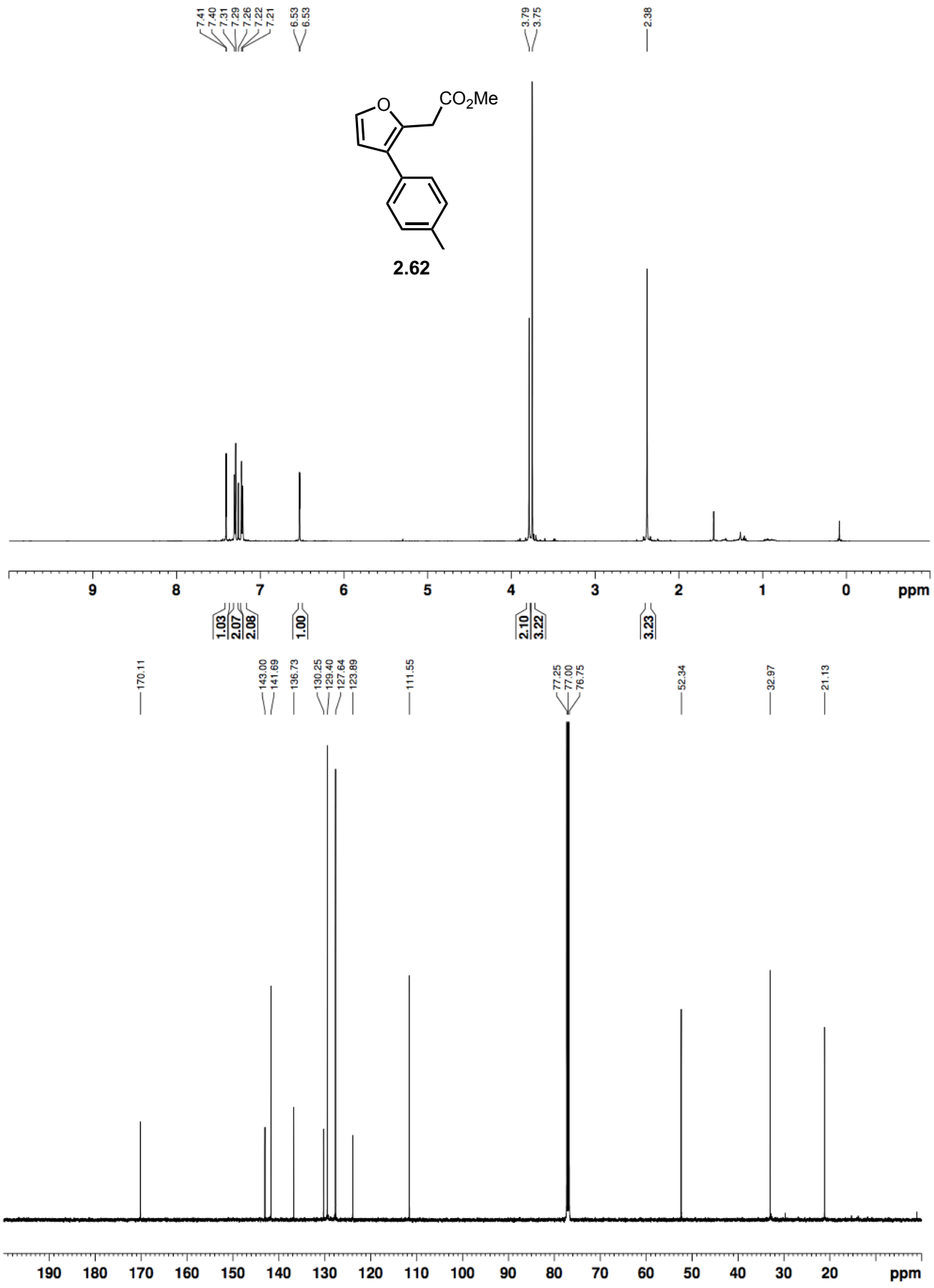
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.59**



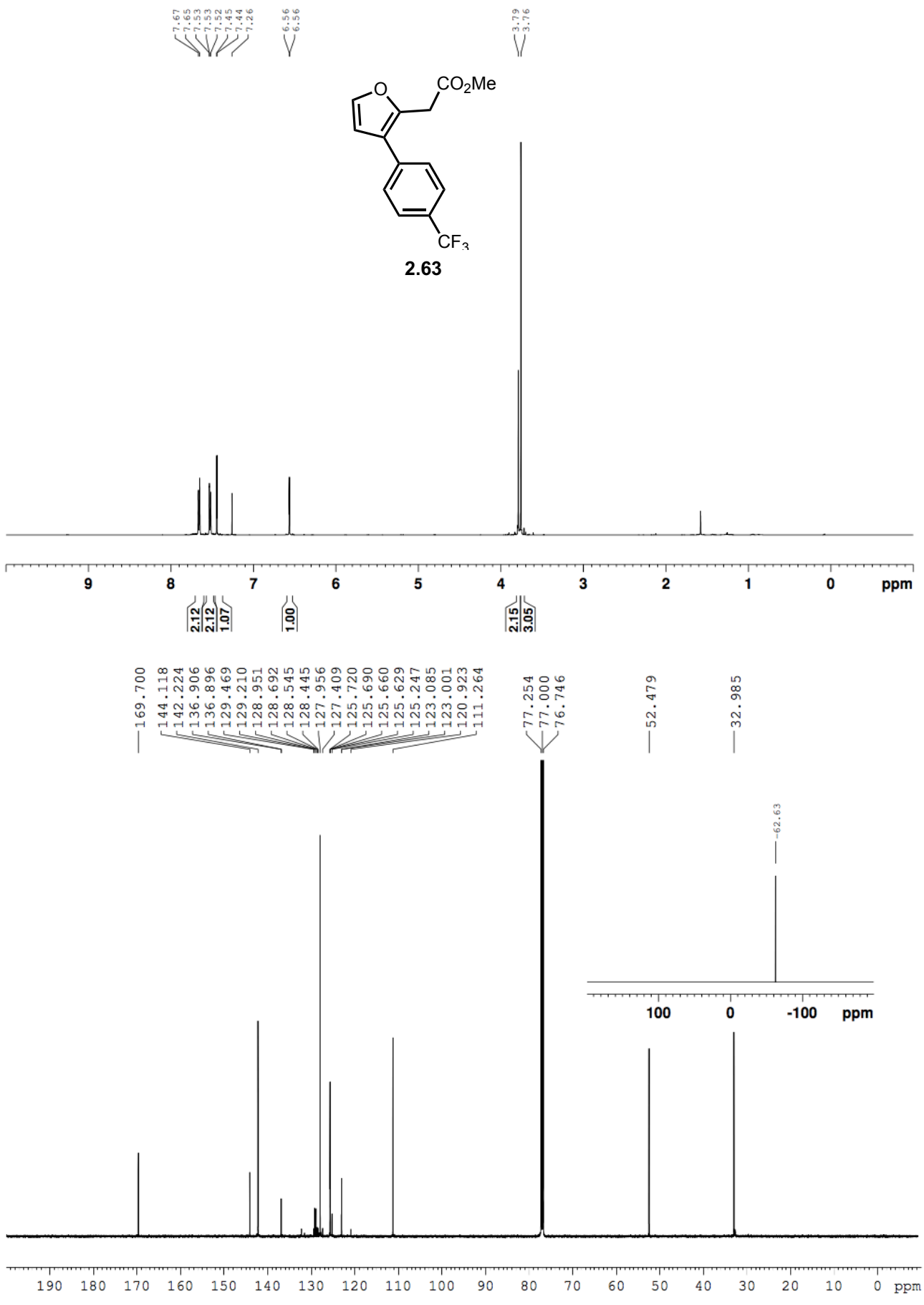
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.60**



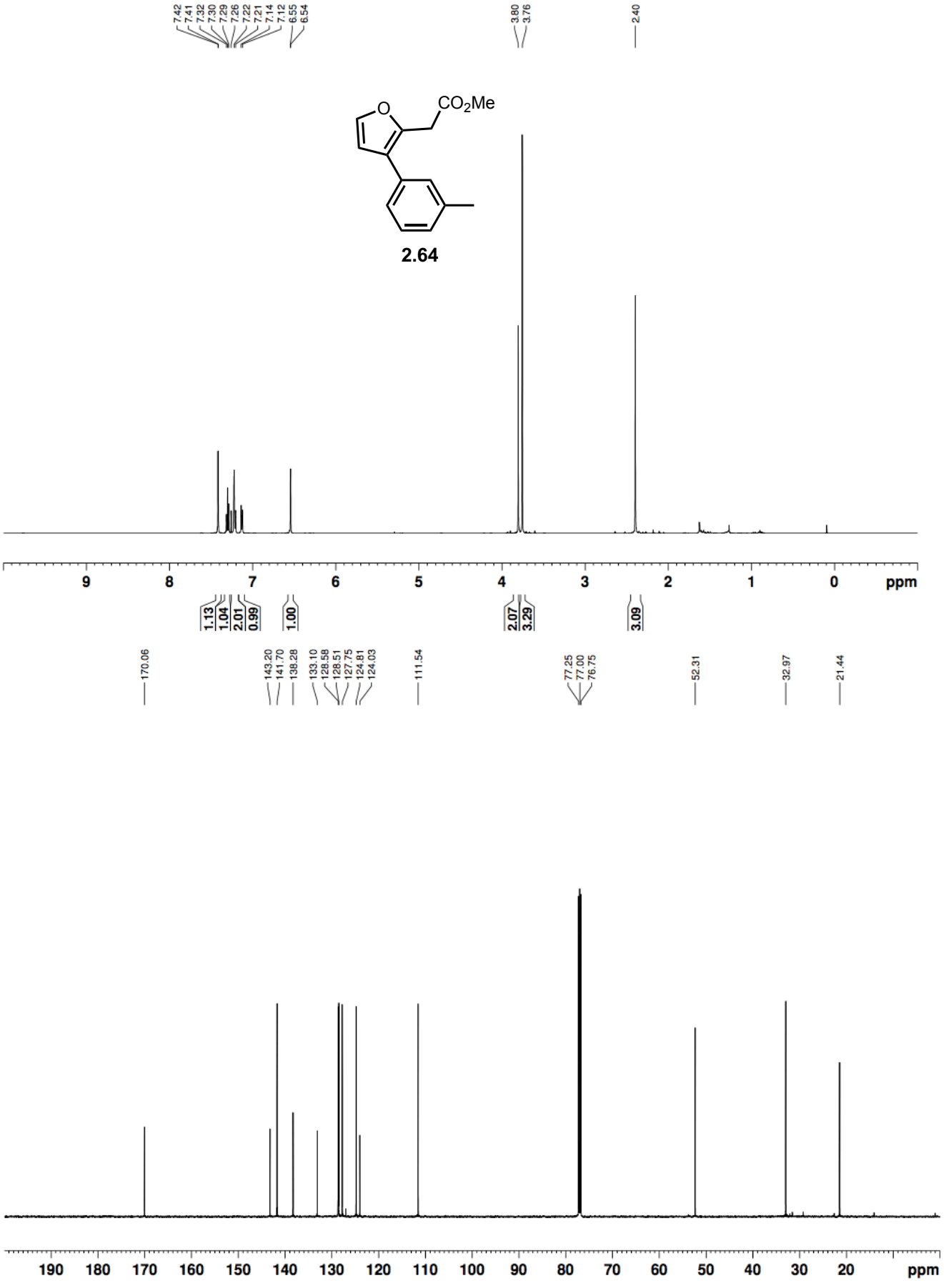
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.61**



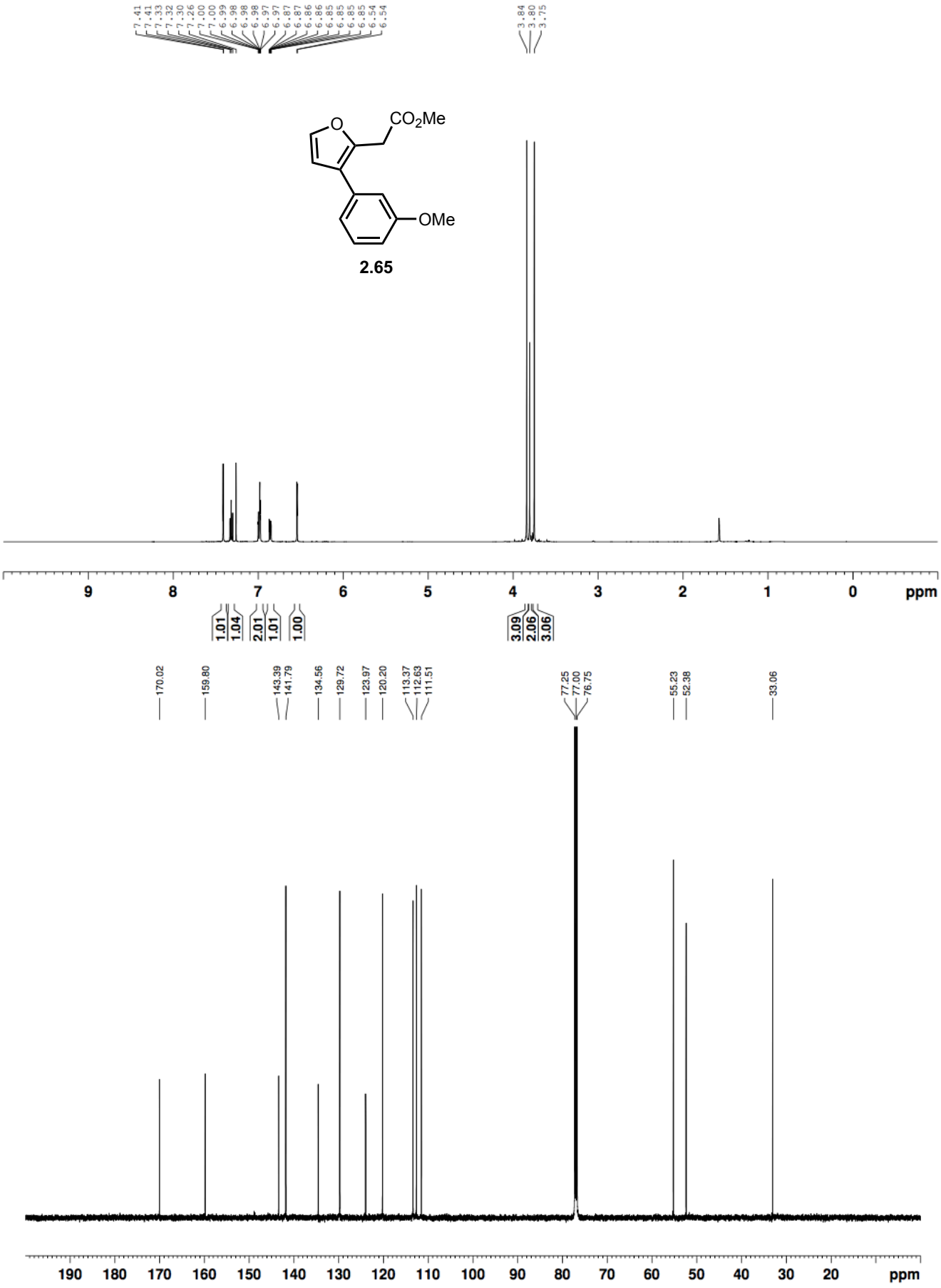
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.62**



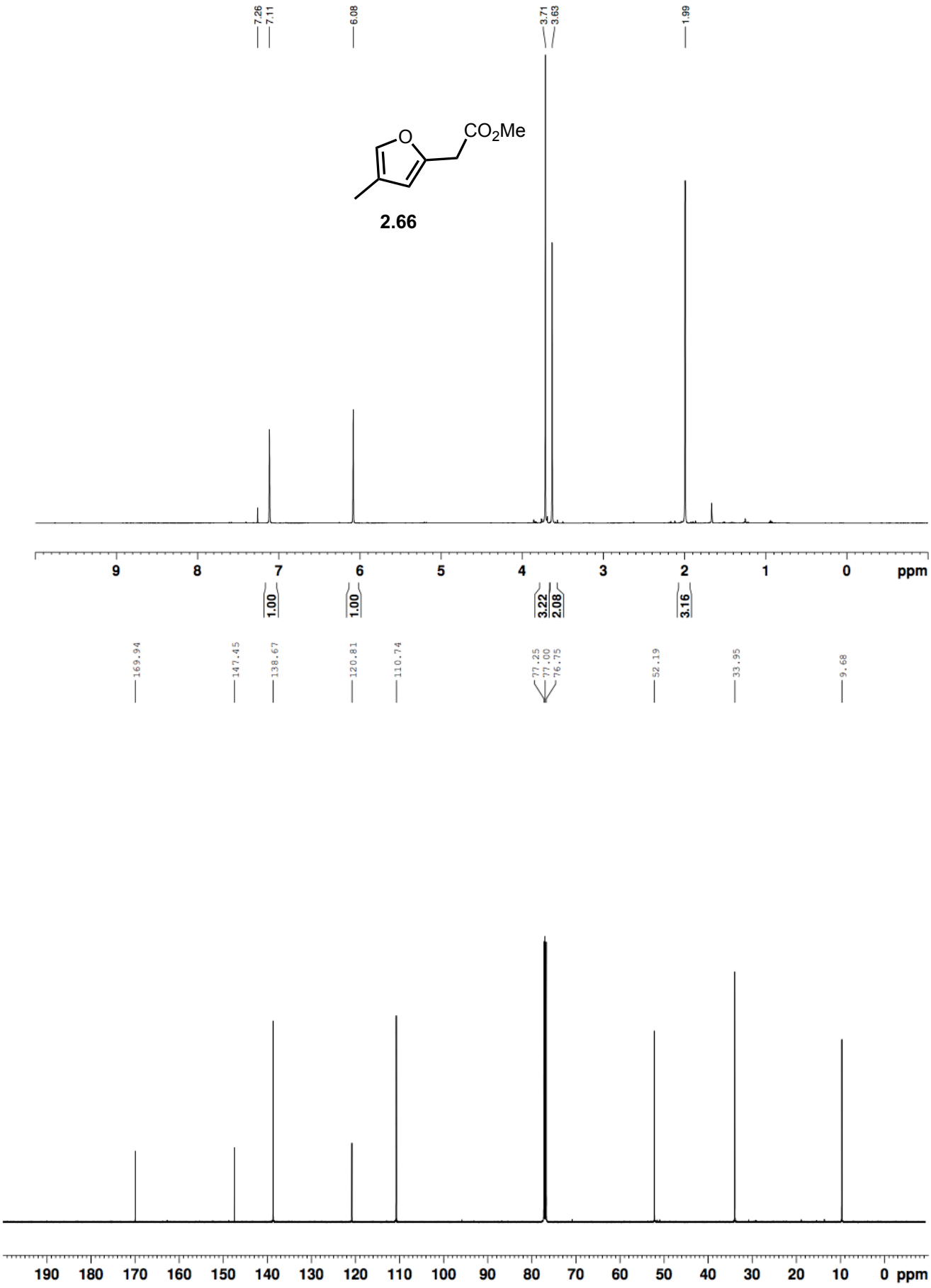
^{1}H (500 MHz, $CDCl_3$), ^{13}C (125 MHz, $CDCl_3$) and ^{19}F (376 MHz, $CDCl_3$) NMR Spectra of **2.63**



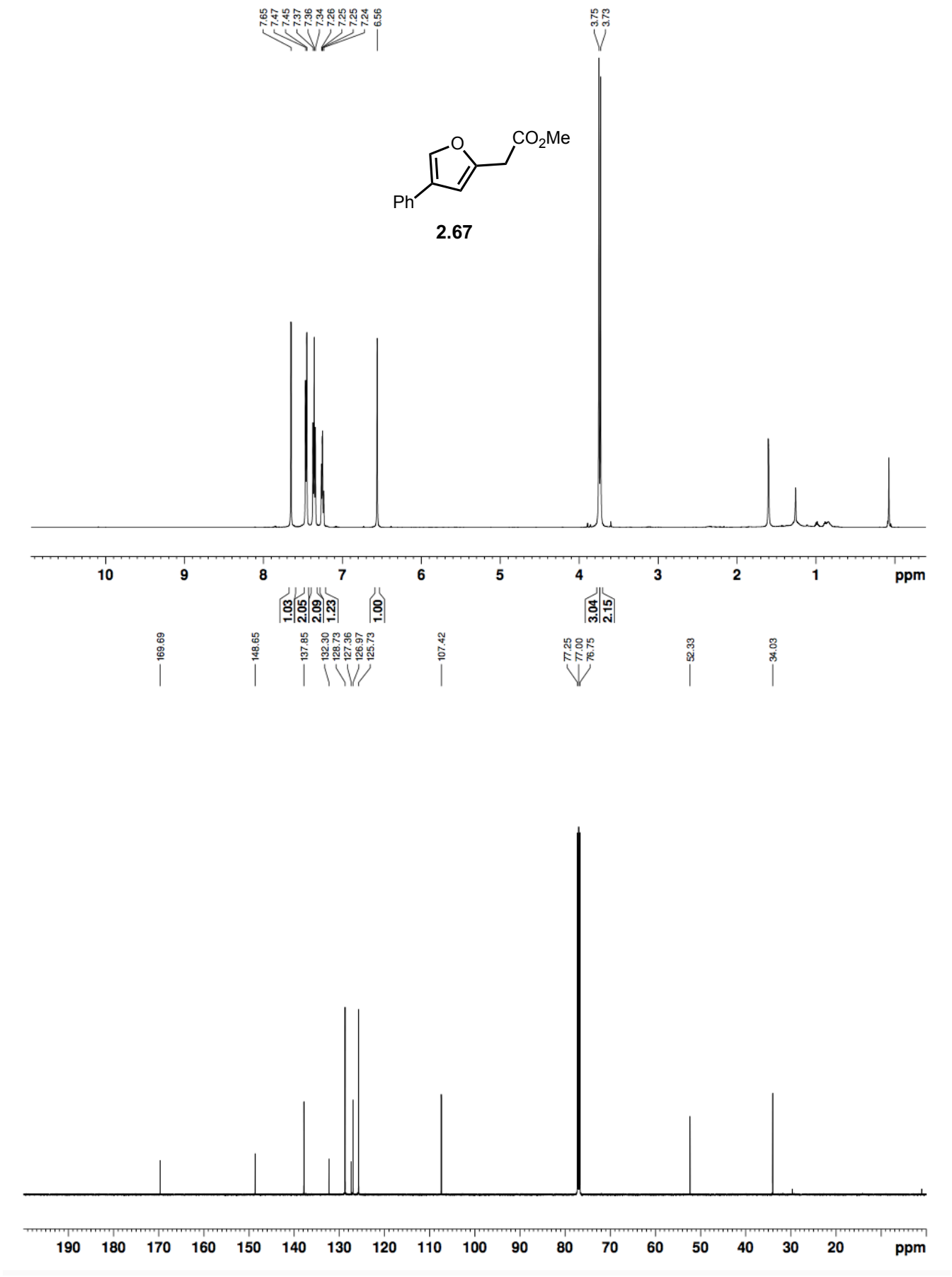
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.64**



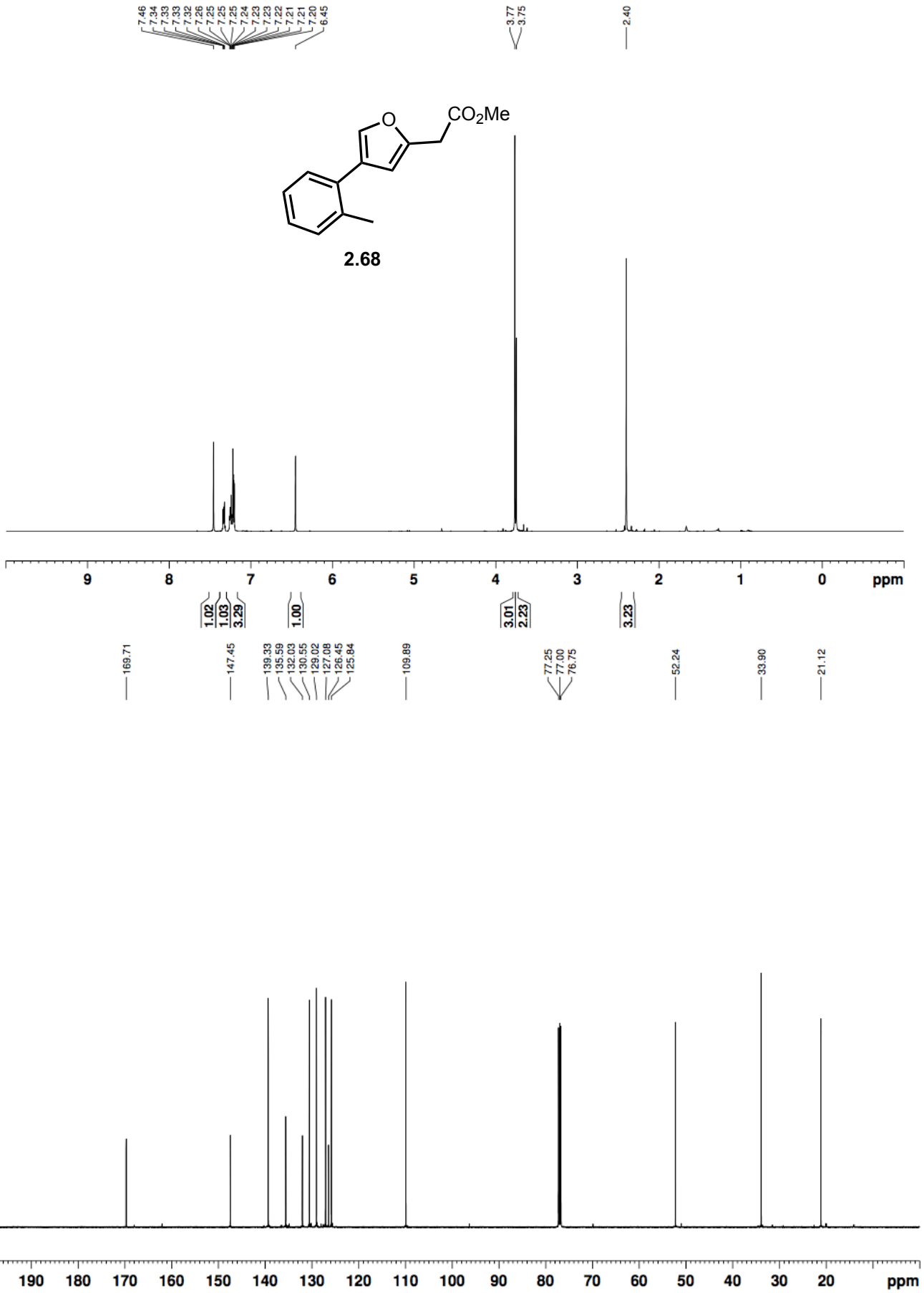
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.65**



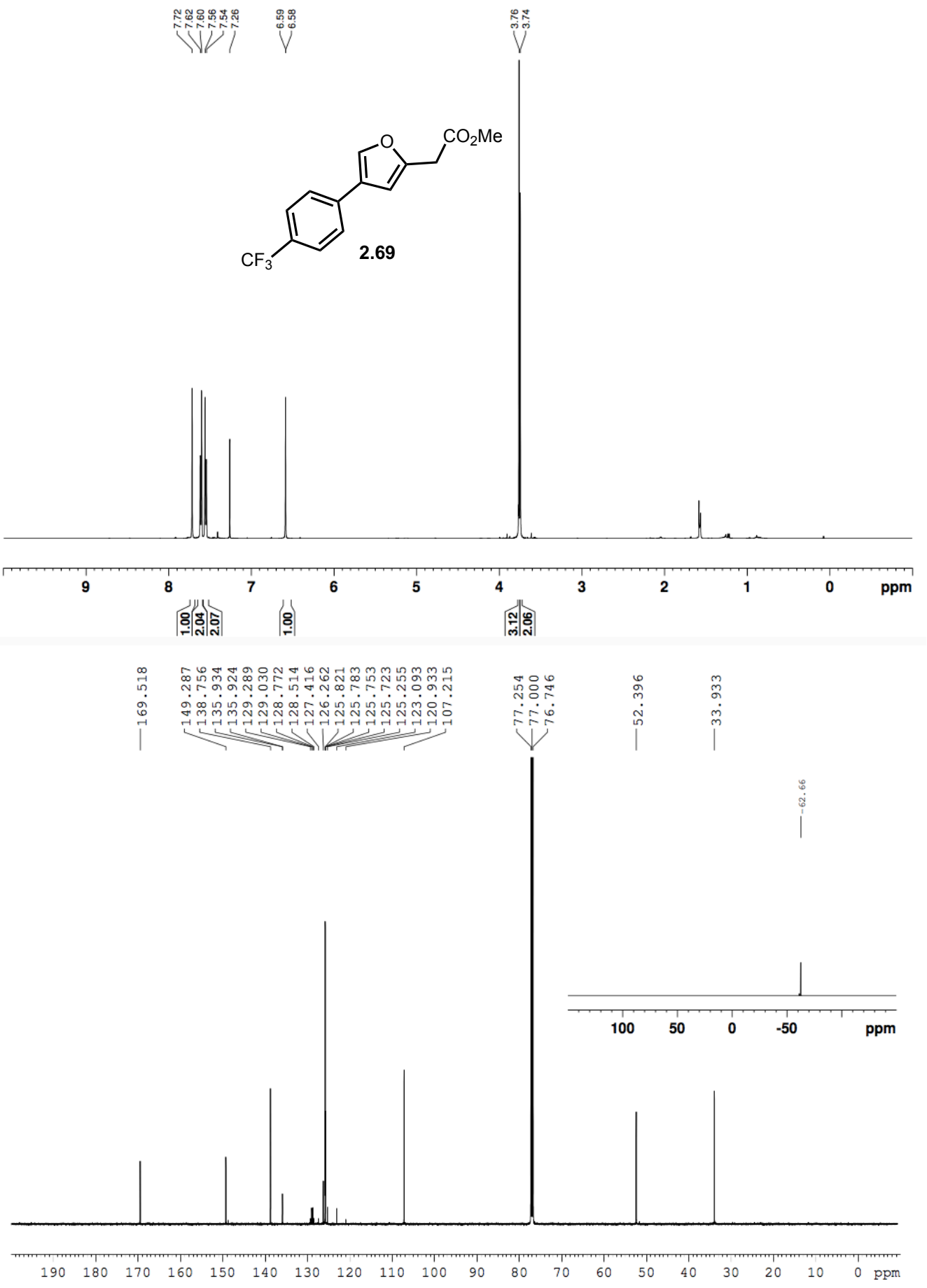
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.66**



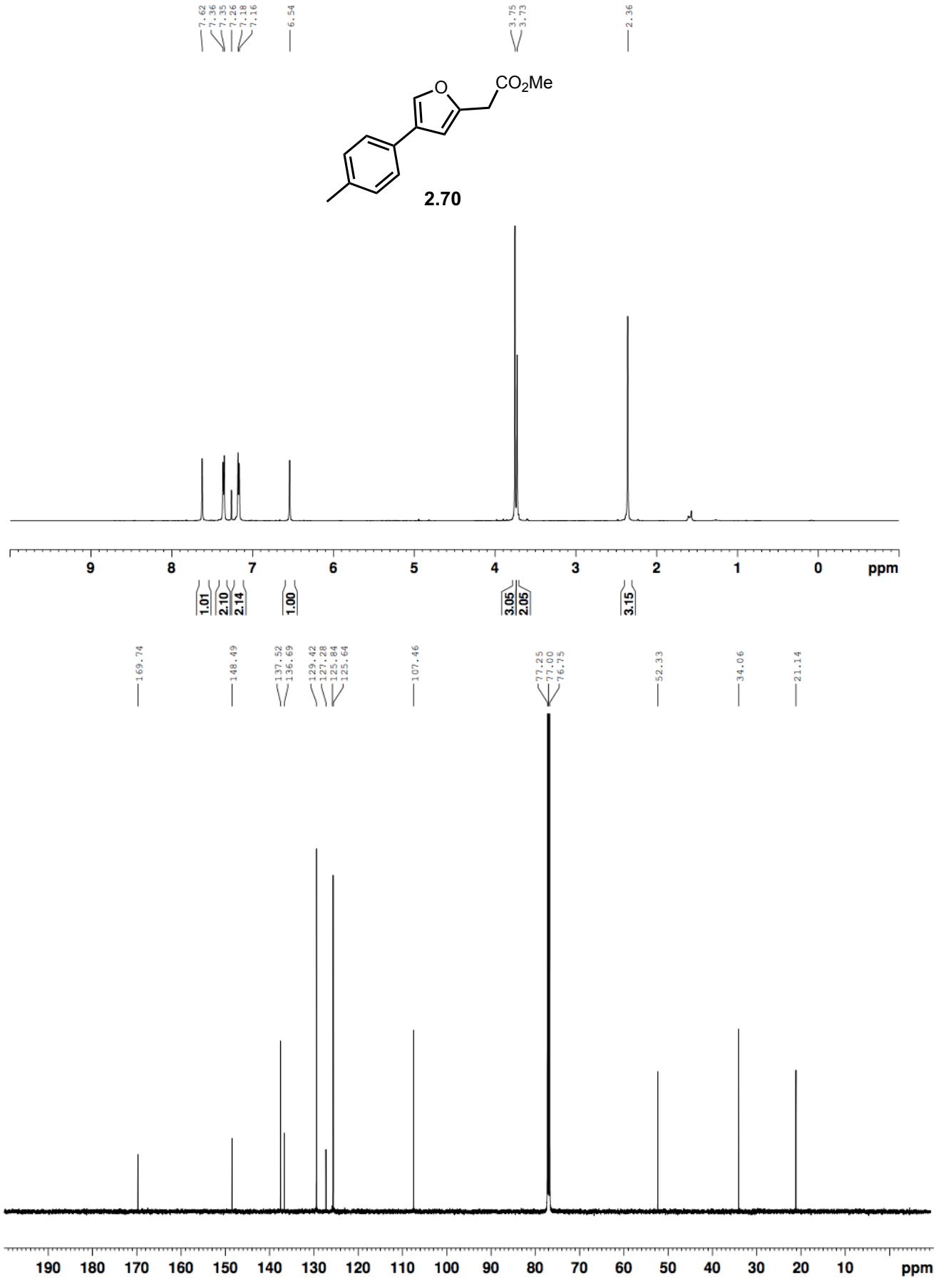
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.67**



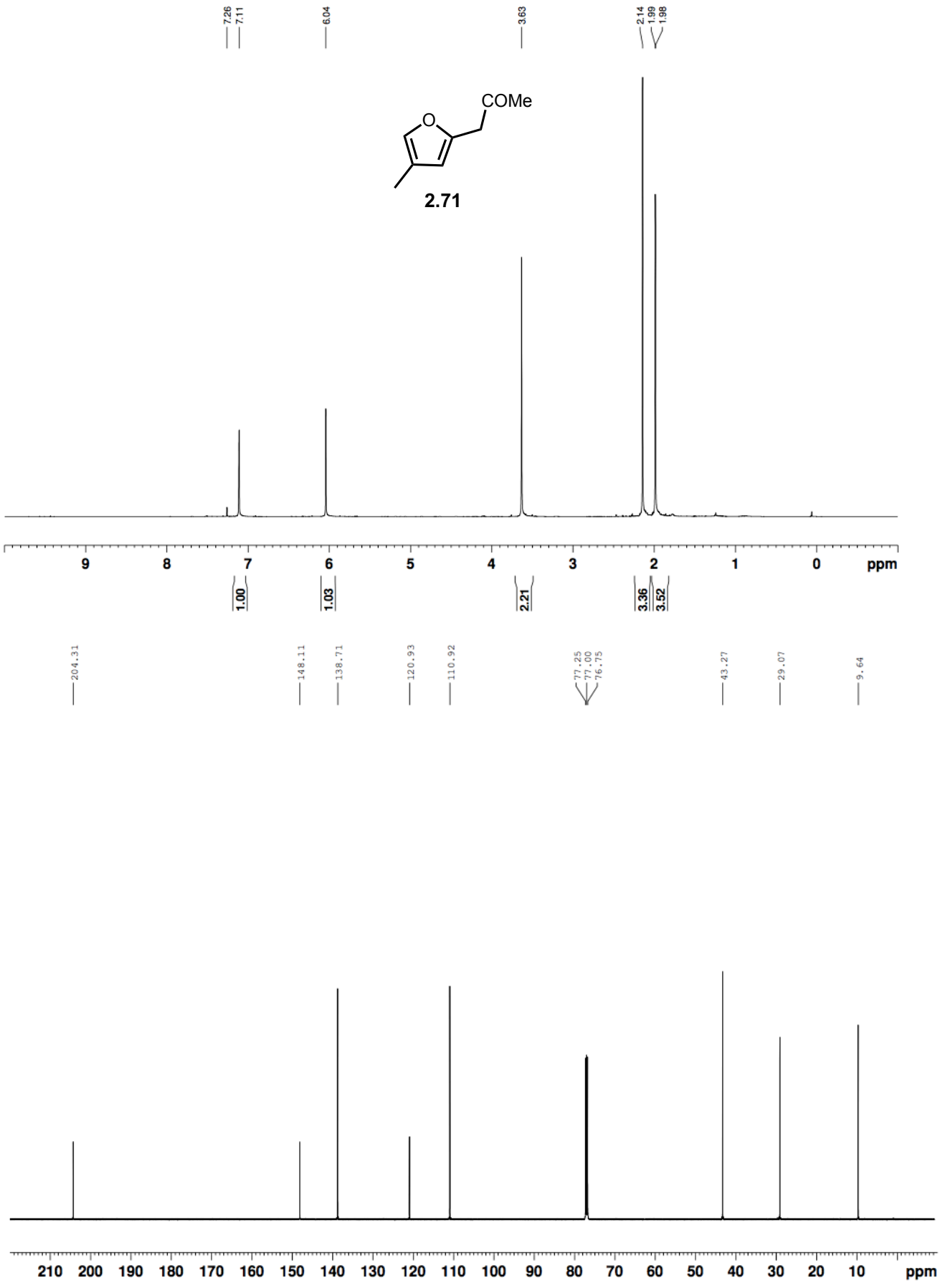
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.68**



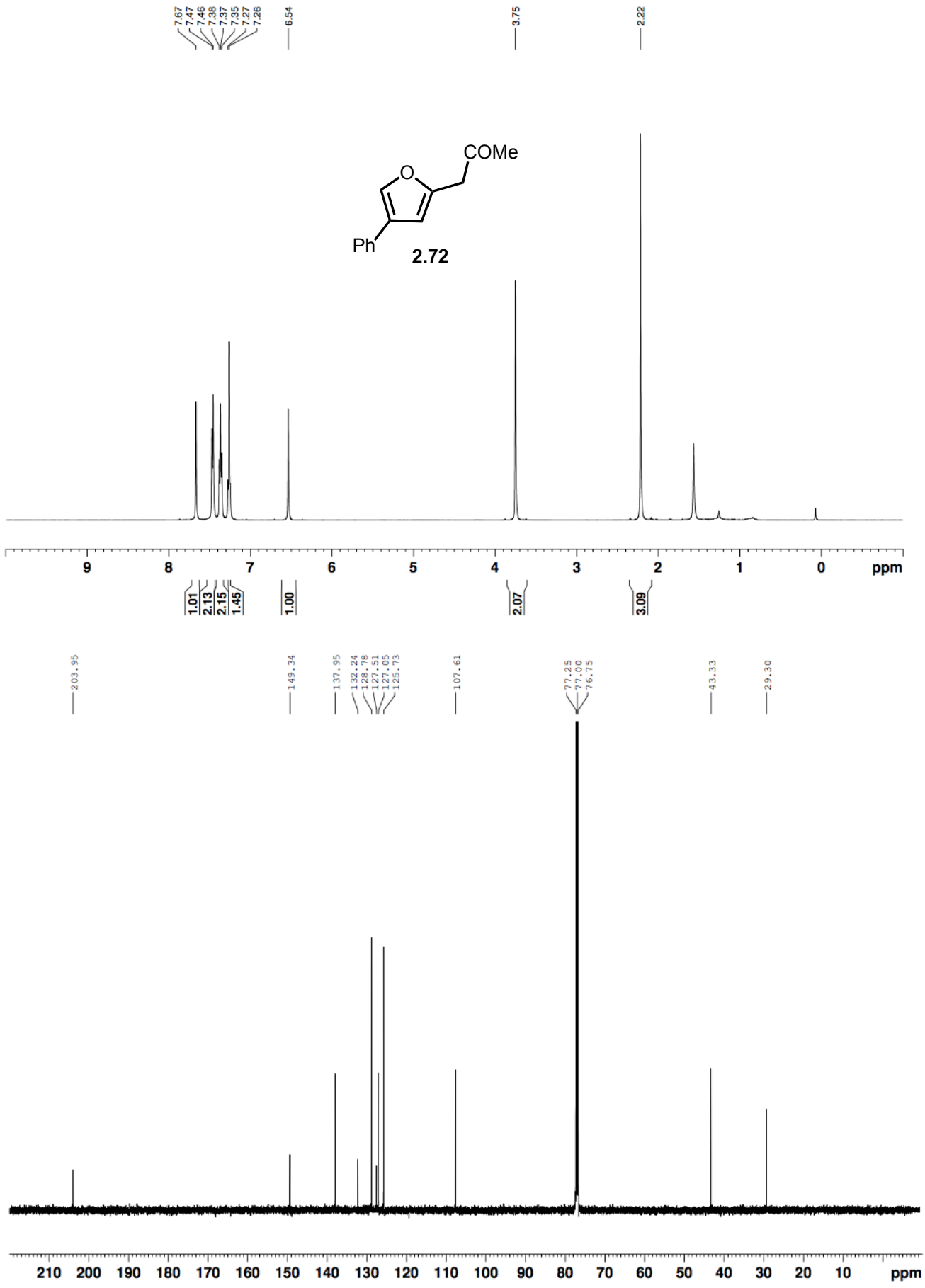
^{1}H (500 MHz, $CDCl_3$), ^{13}C (125 MHz, $CDCl_3$) and ^{19}F (376 MHz, $CDCl_3$) NMR Spectra of **2.69**



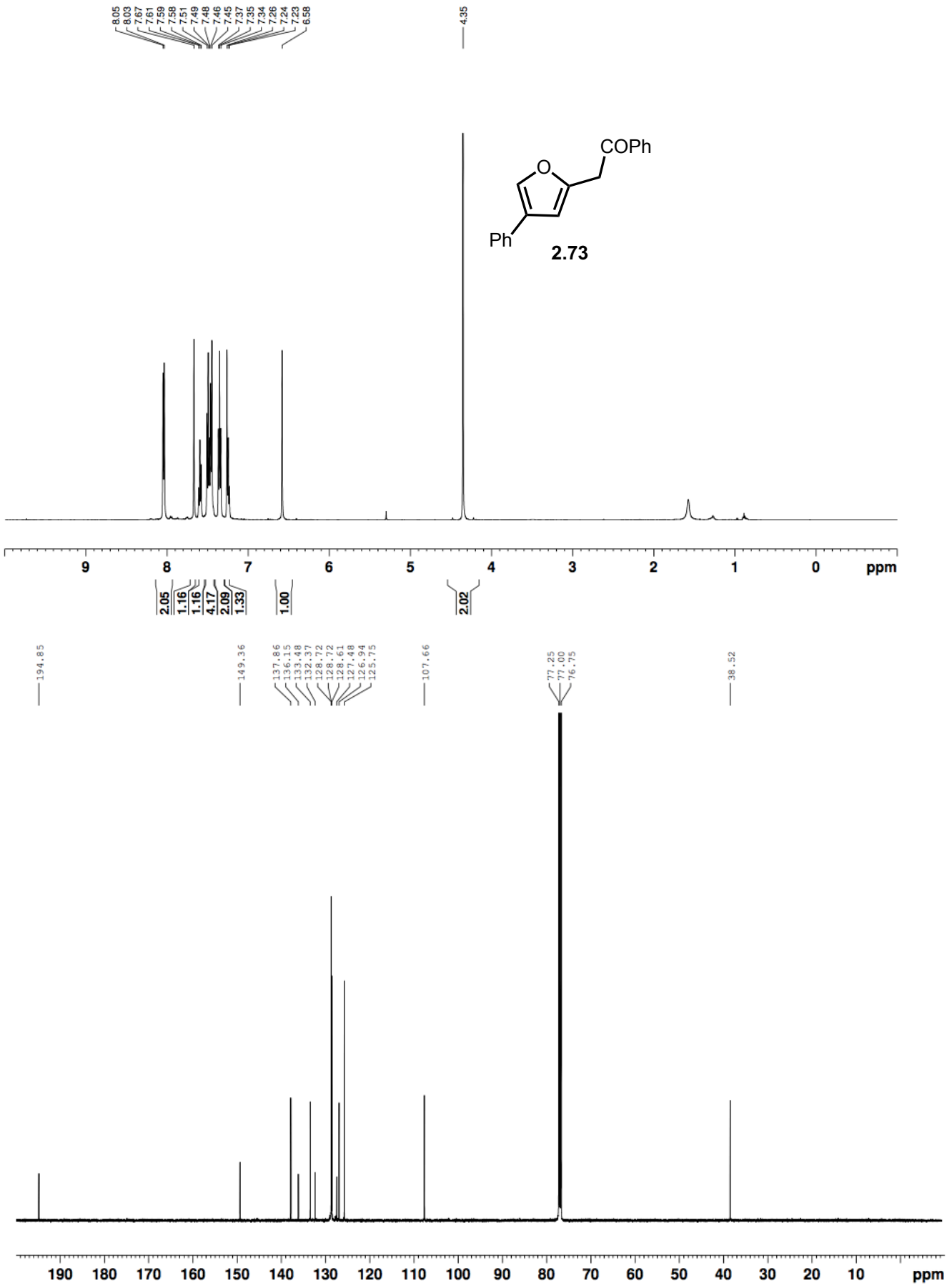
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.70**



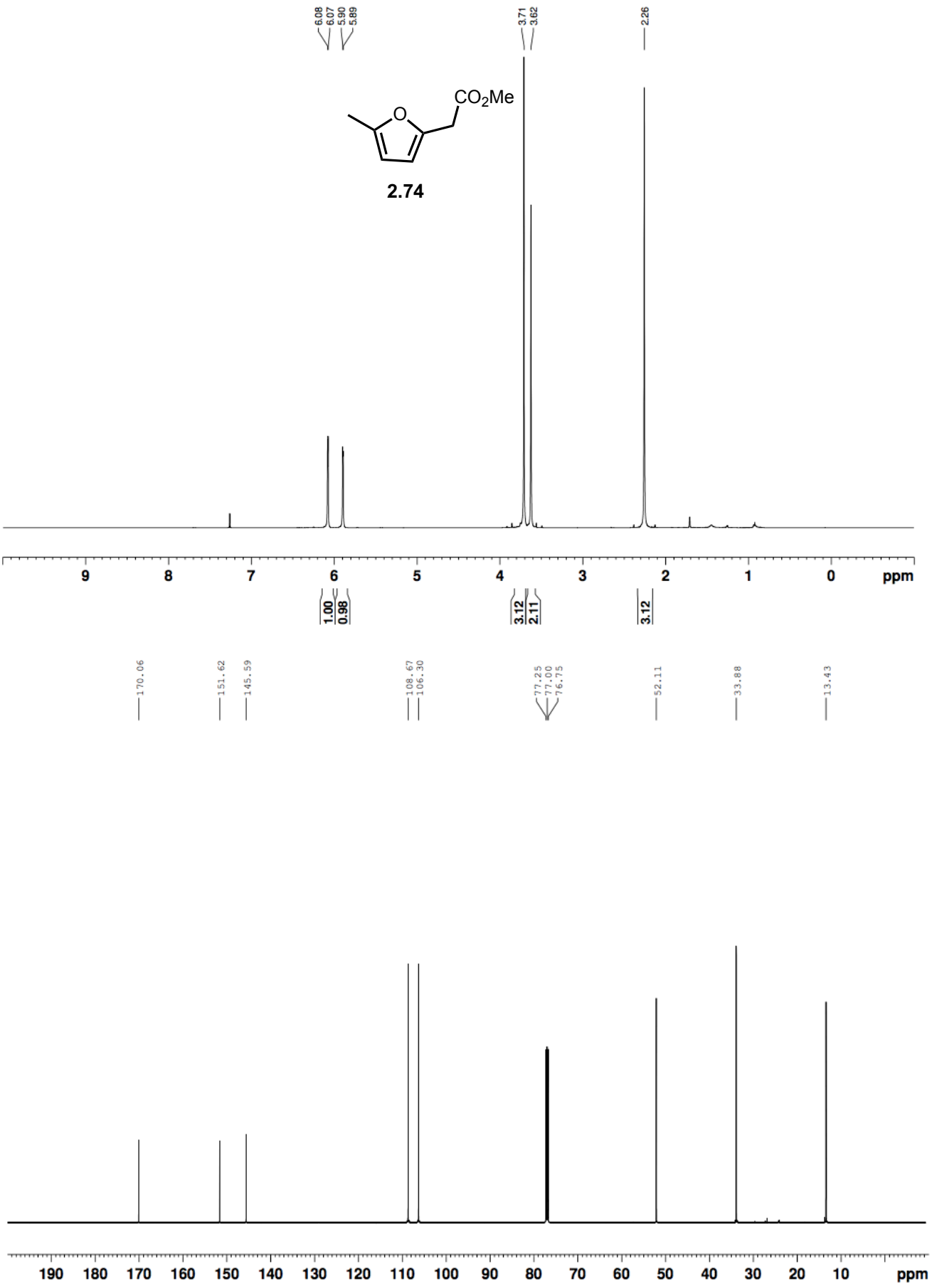
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.71**



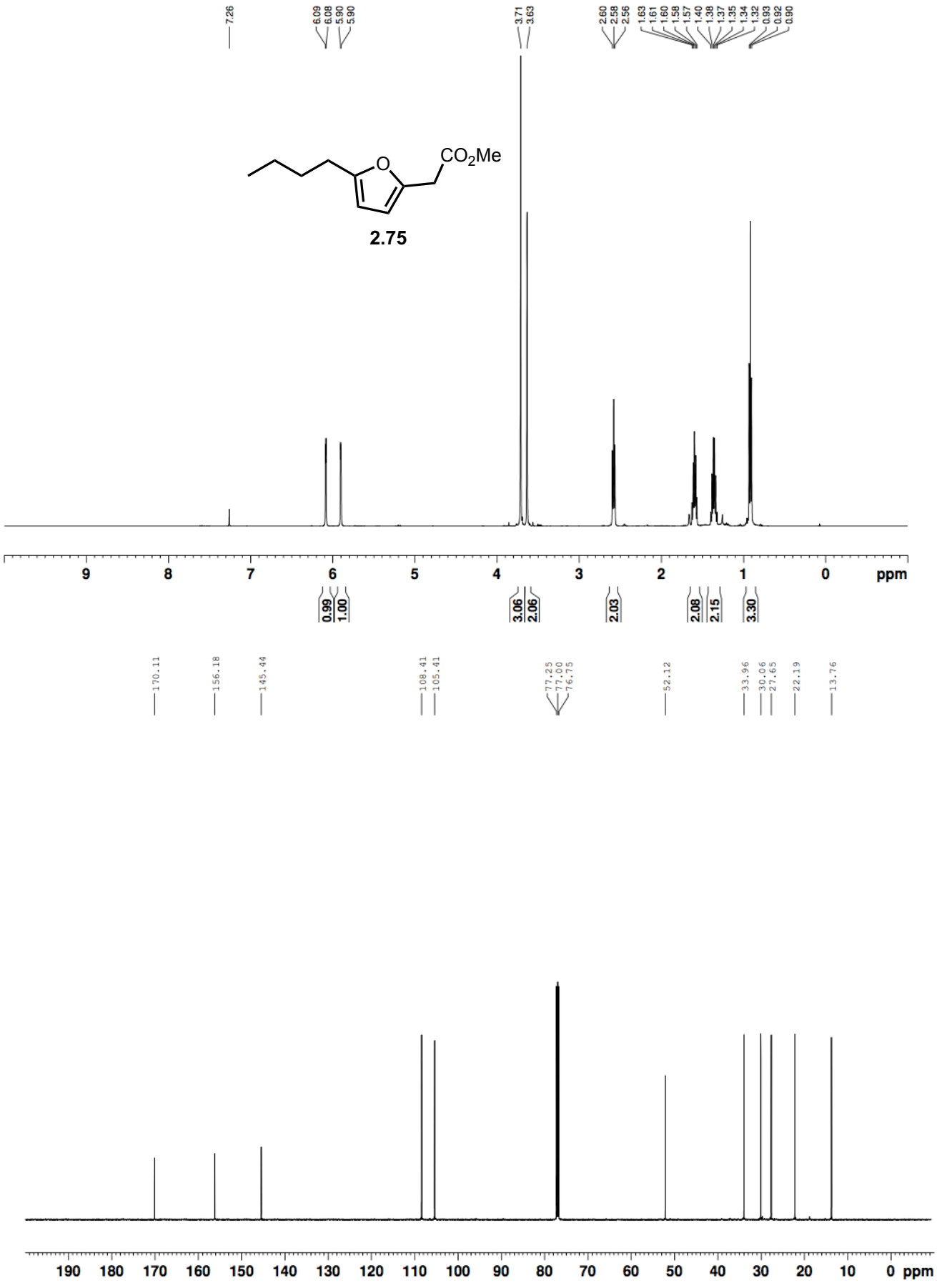
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.72**



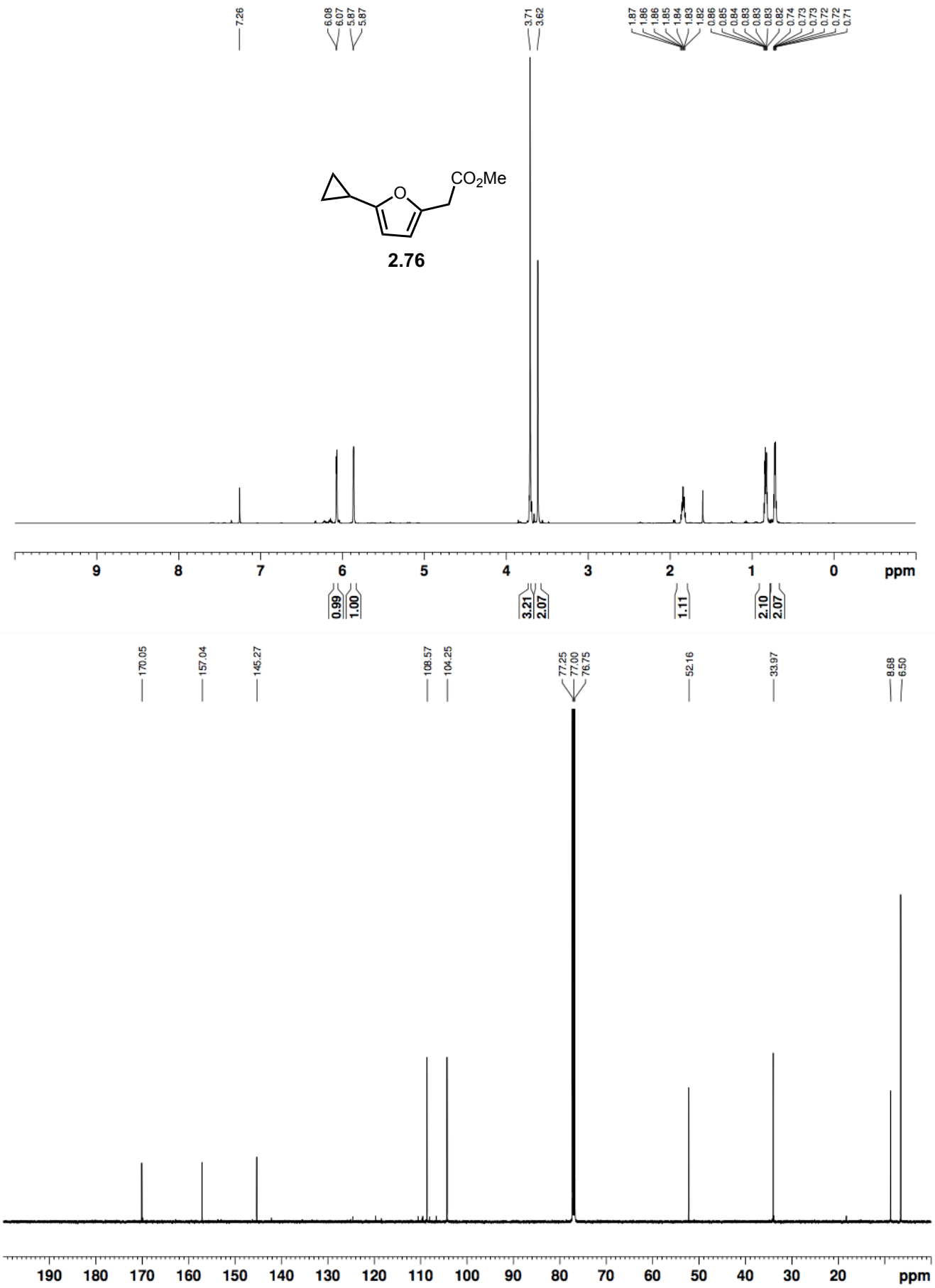
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.73**



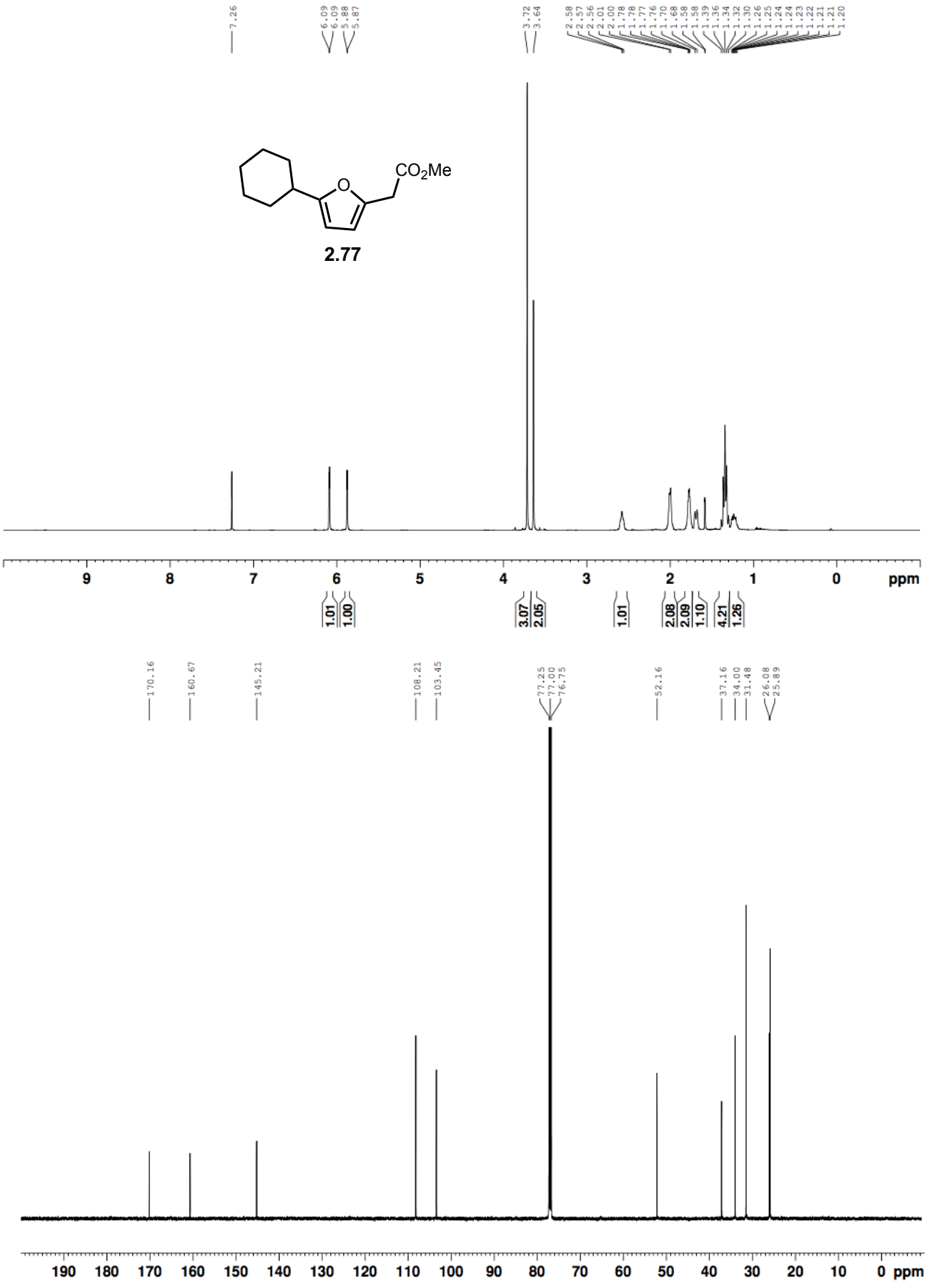
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.74**



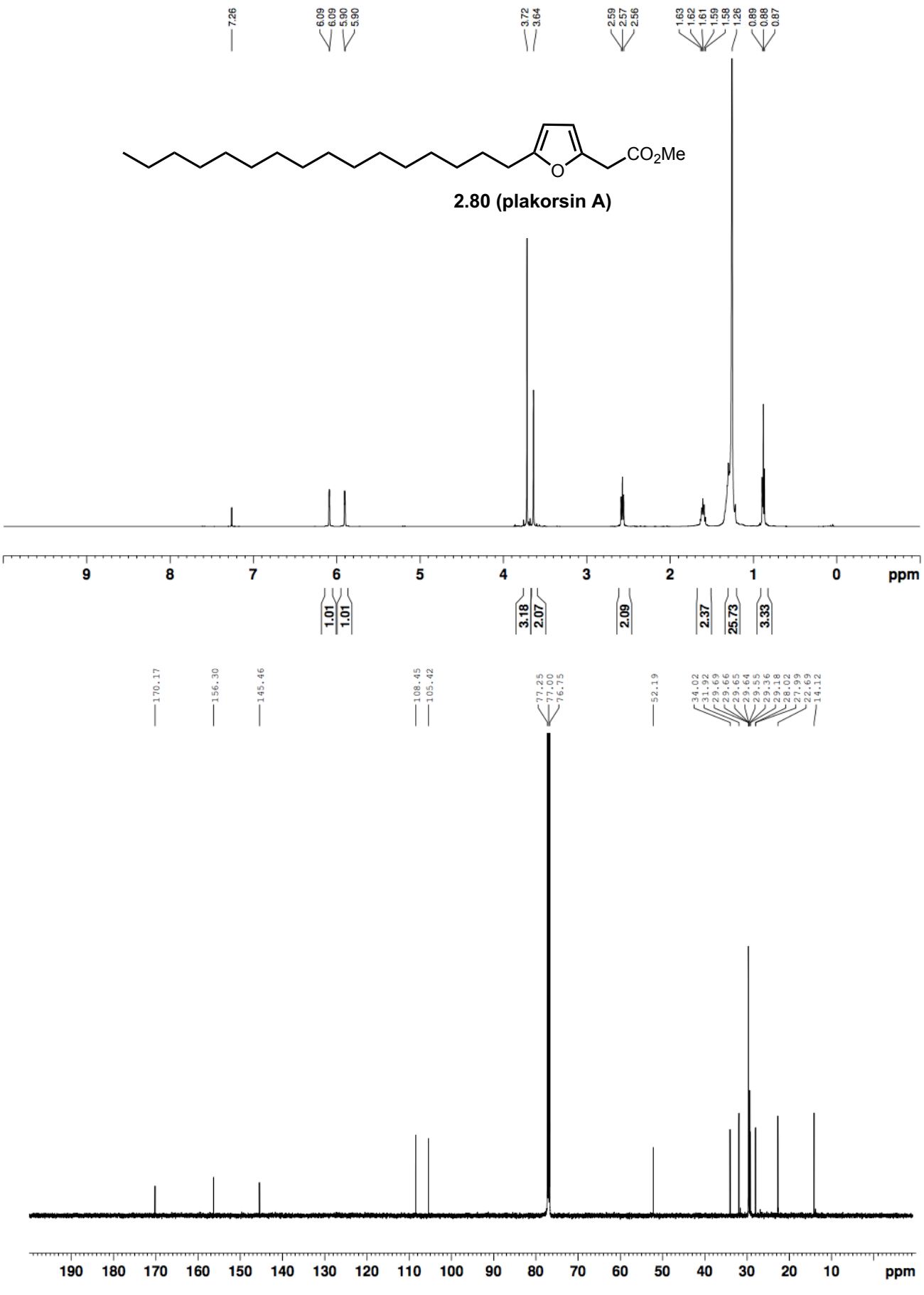
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.75**



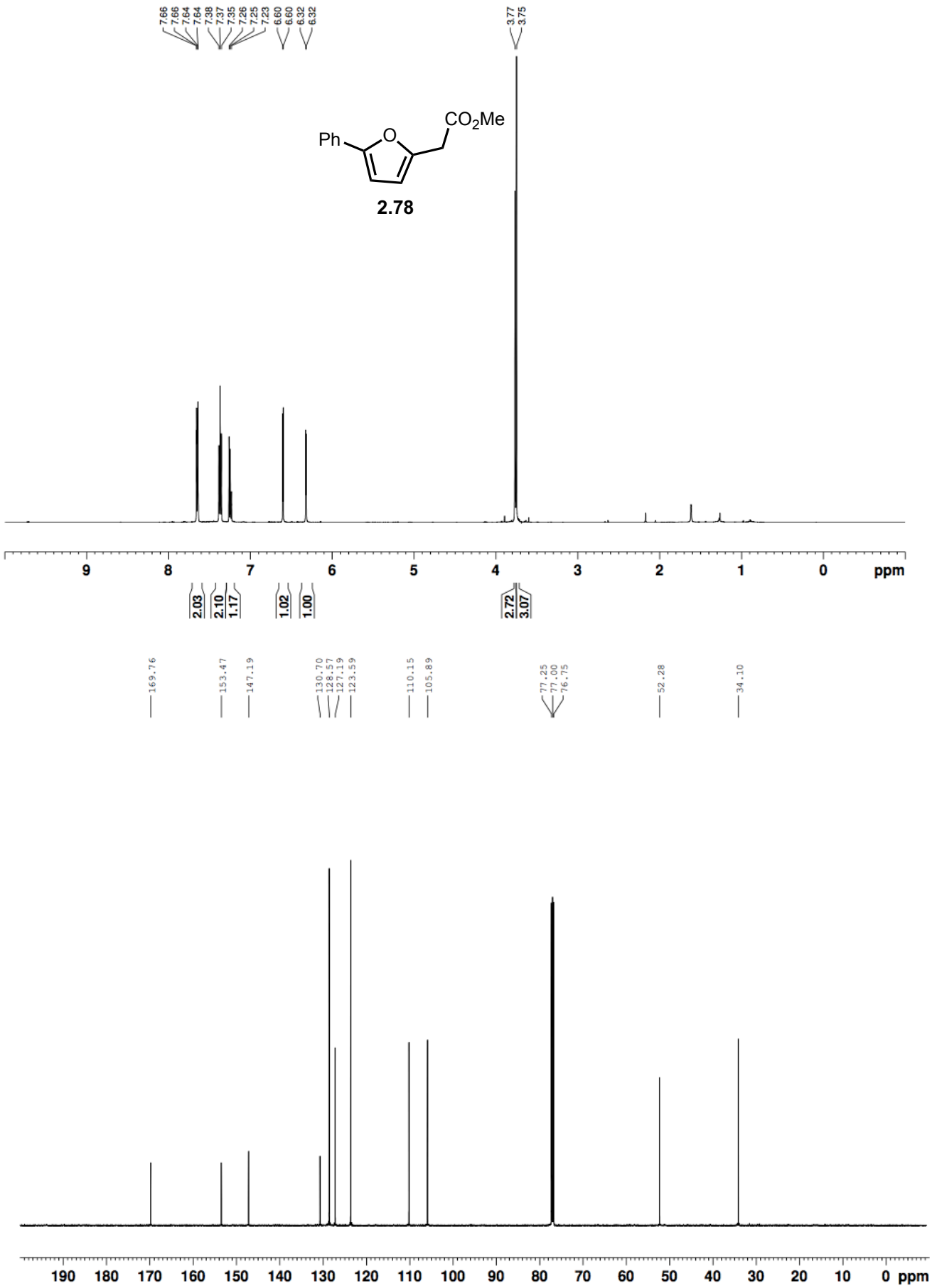
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.76**



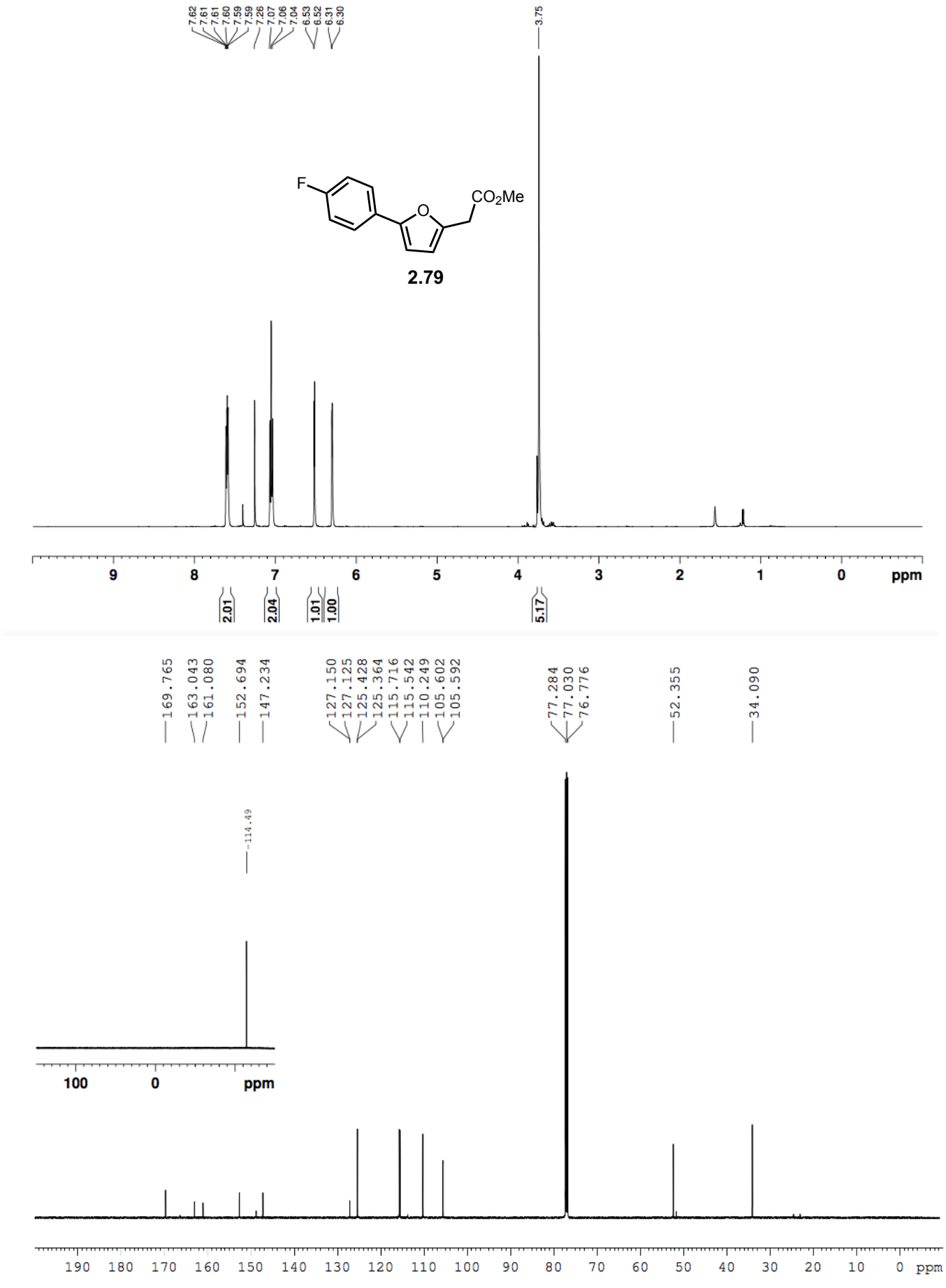
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.77**



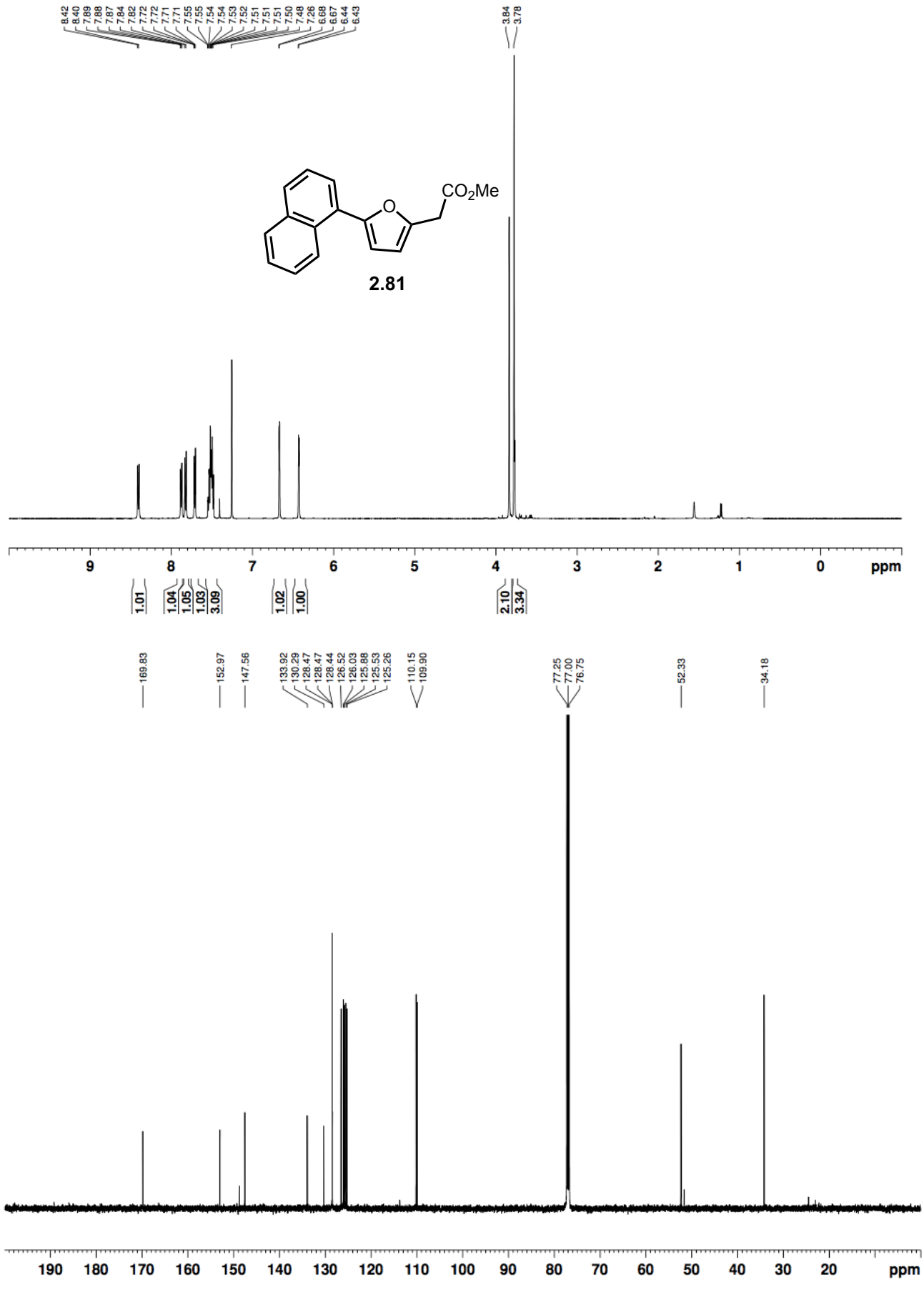
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.80 (plakorsin A)**



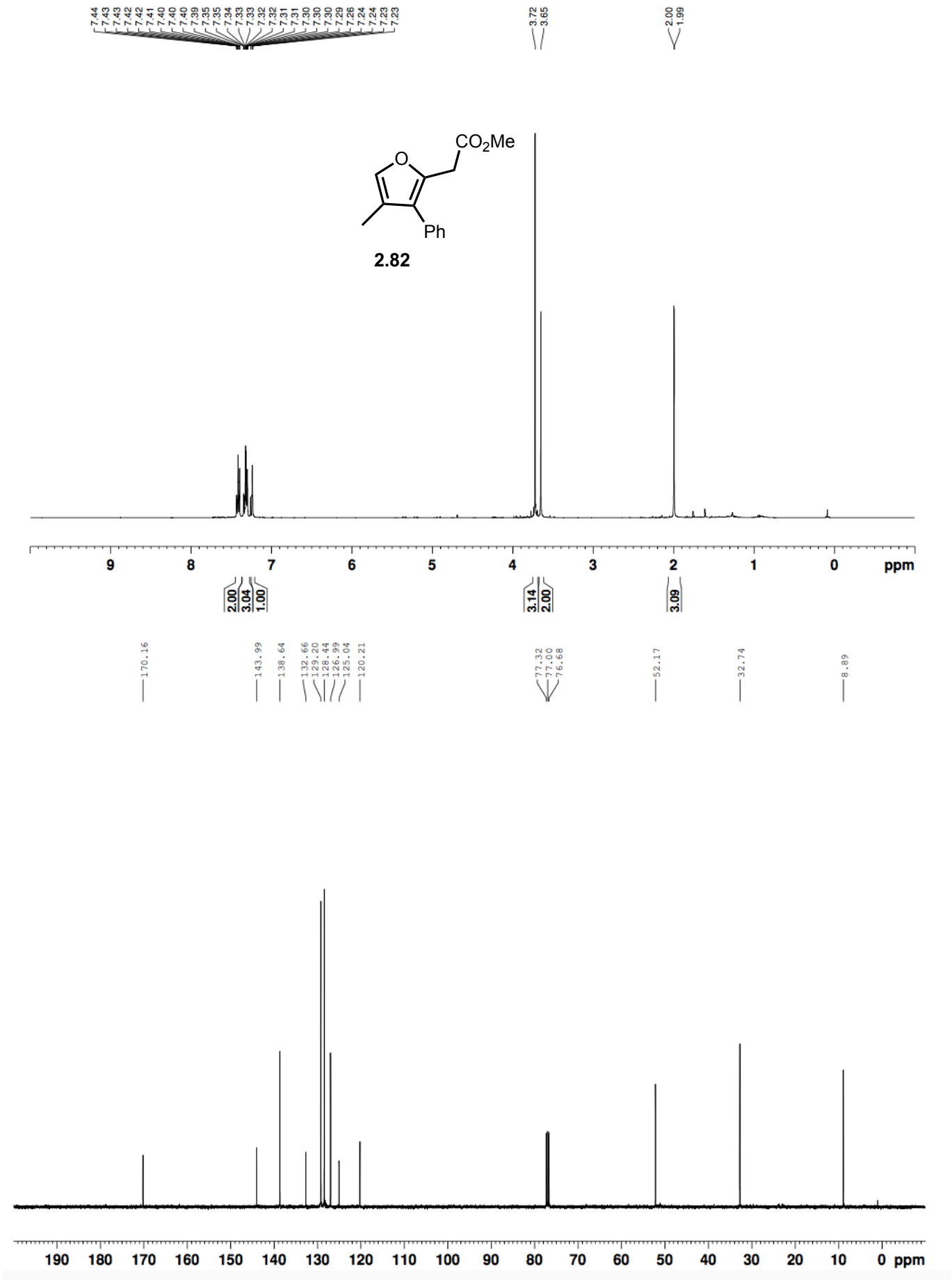
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.78**



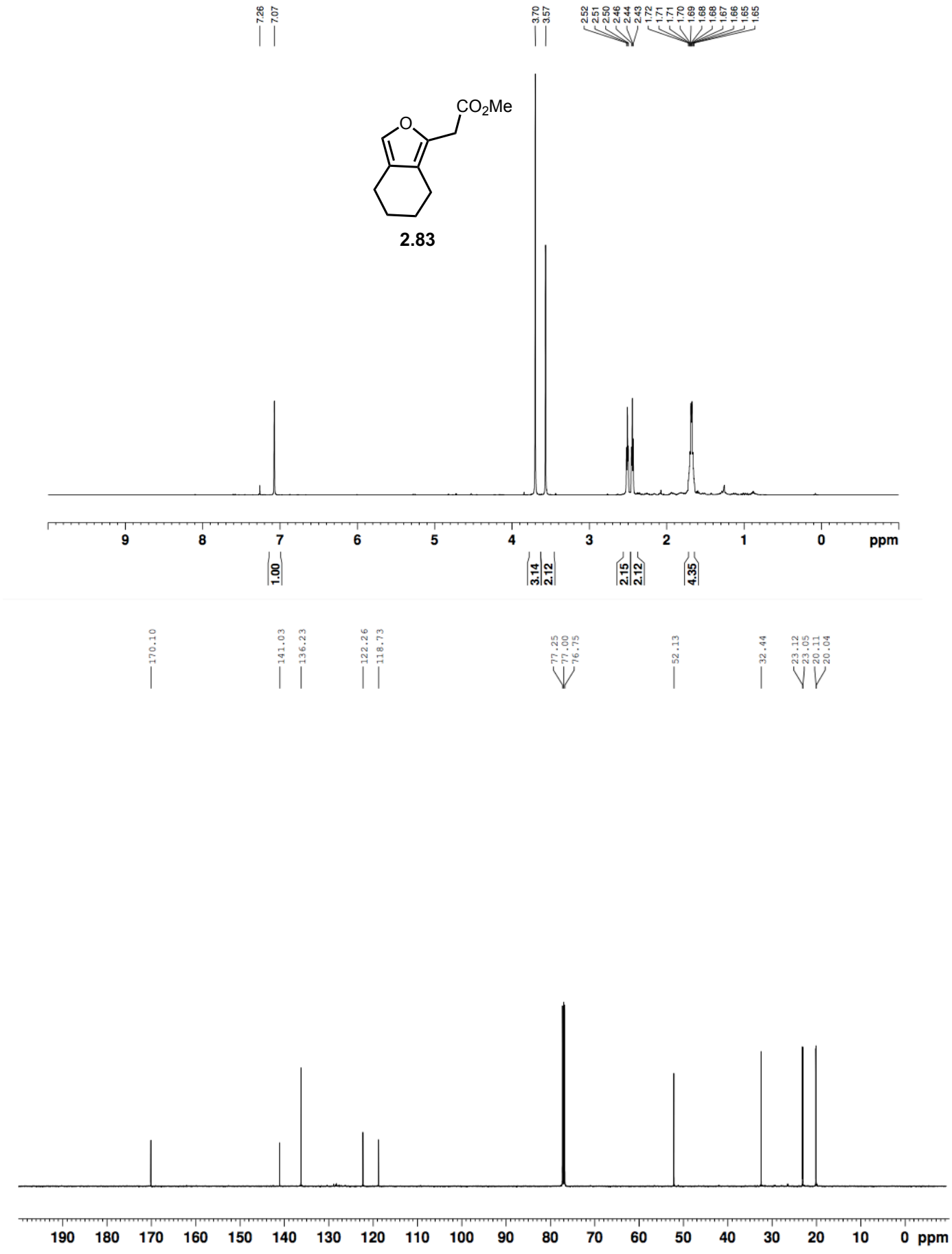
^{1}H (500 MHz, $CDCl_3$), ^{13}C (125 MHz, $CDCl_3$) and ^{19}F (376 MHz, $CDCl_3$) NMR Spectra of **2.79**



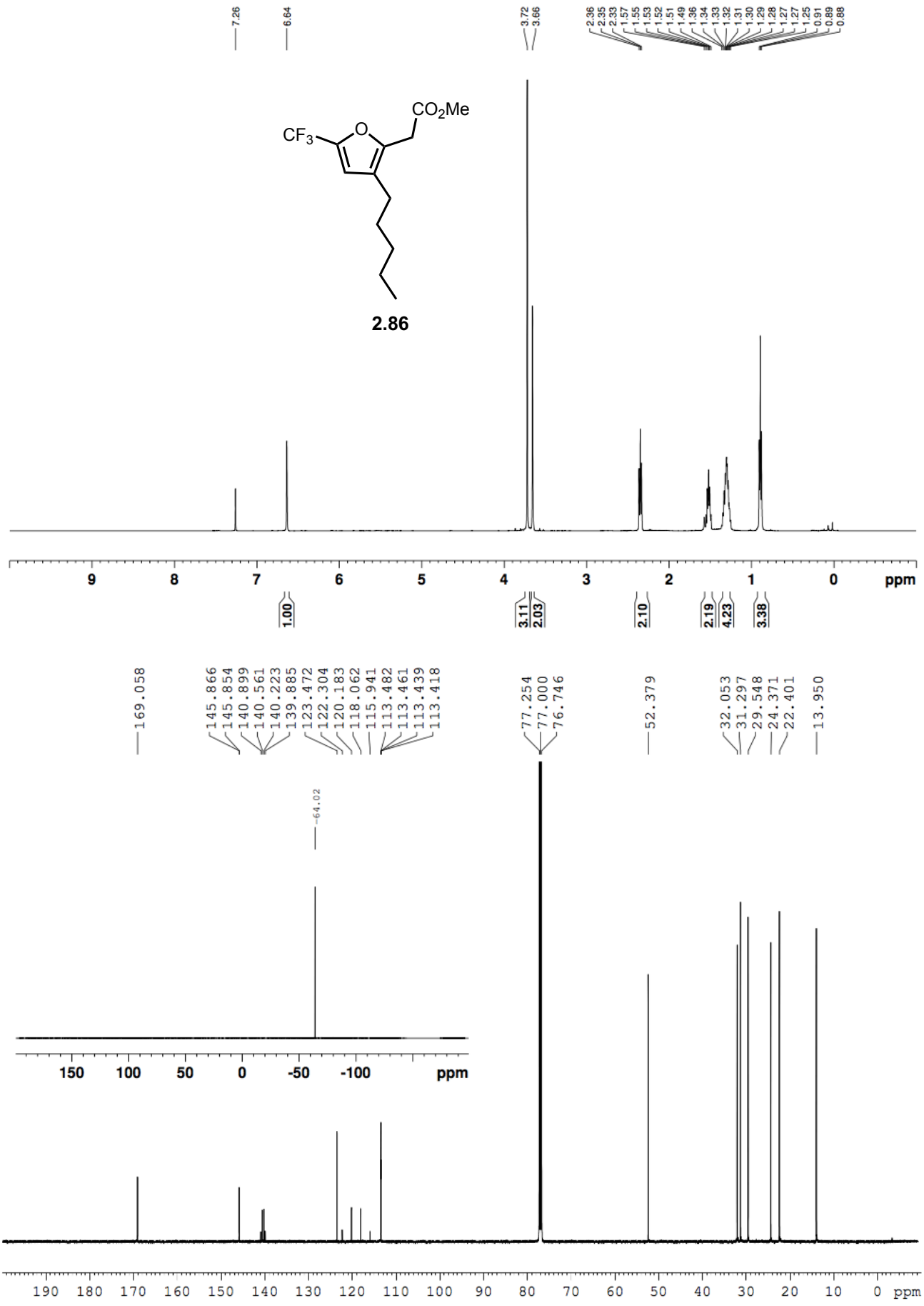
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.81**



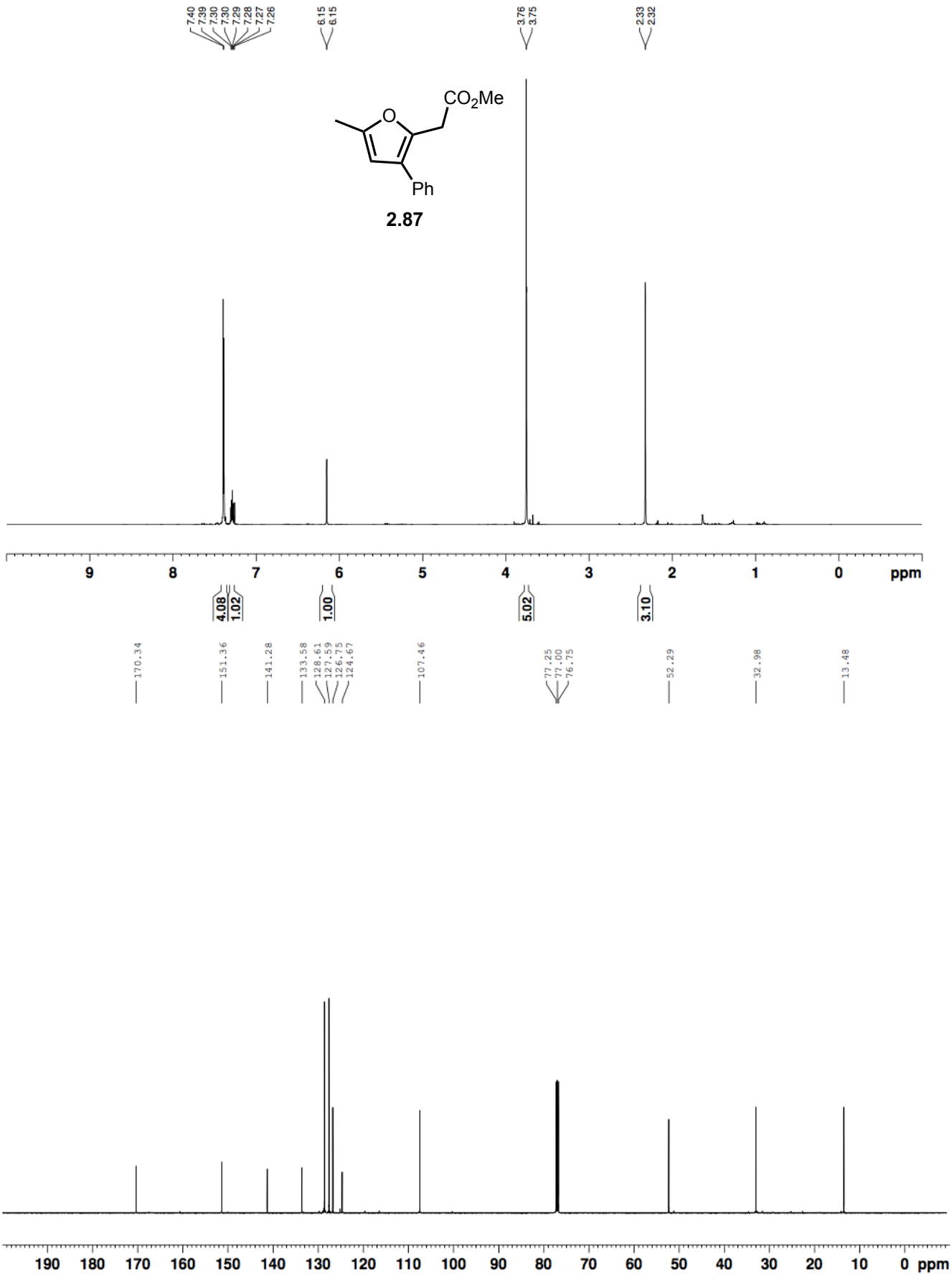
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.82**



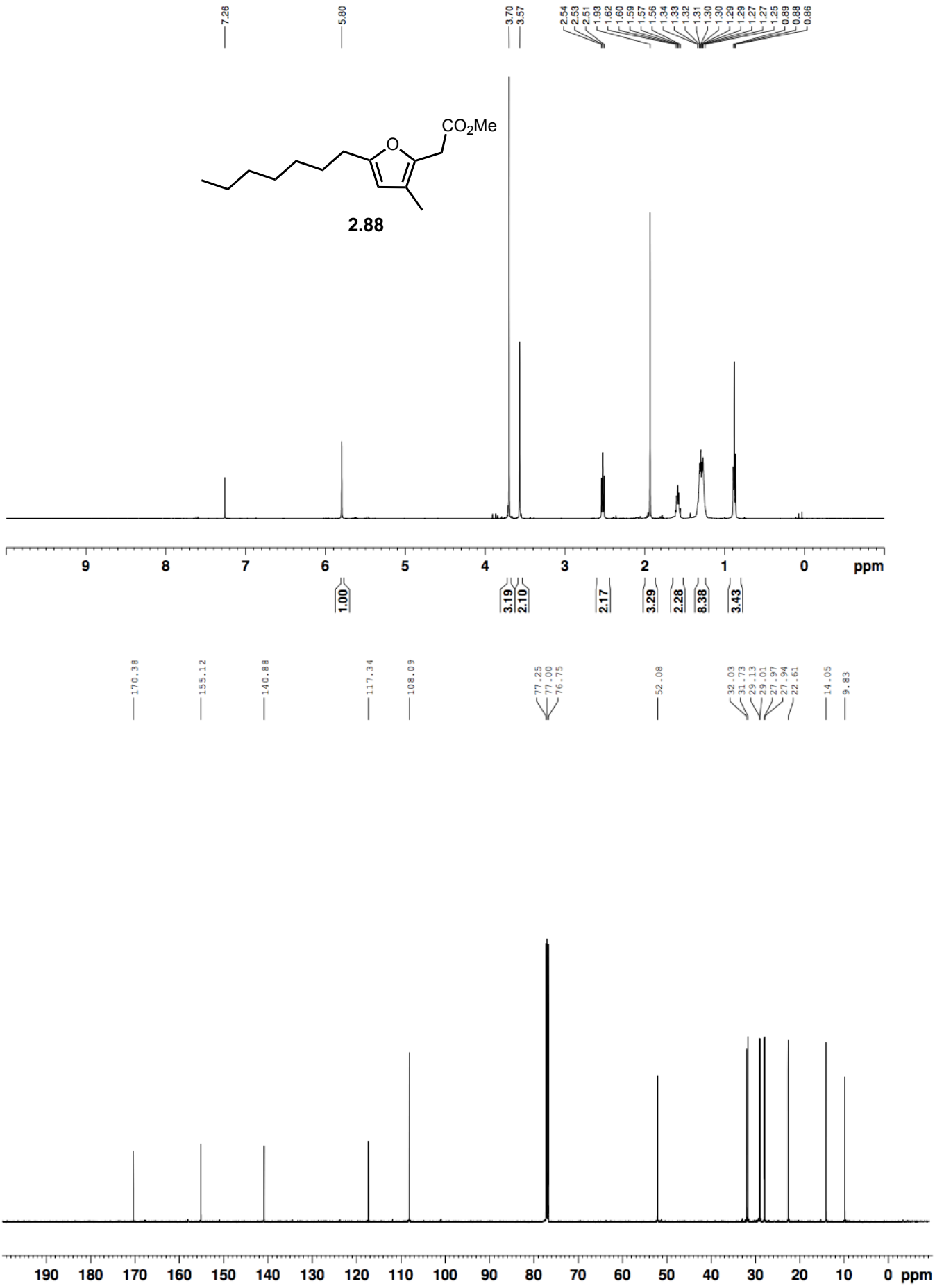
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.83**



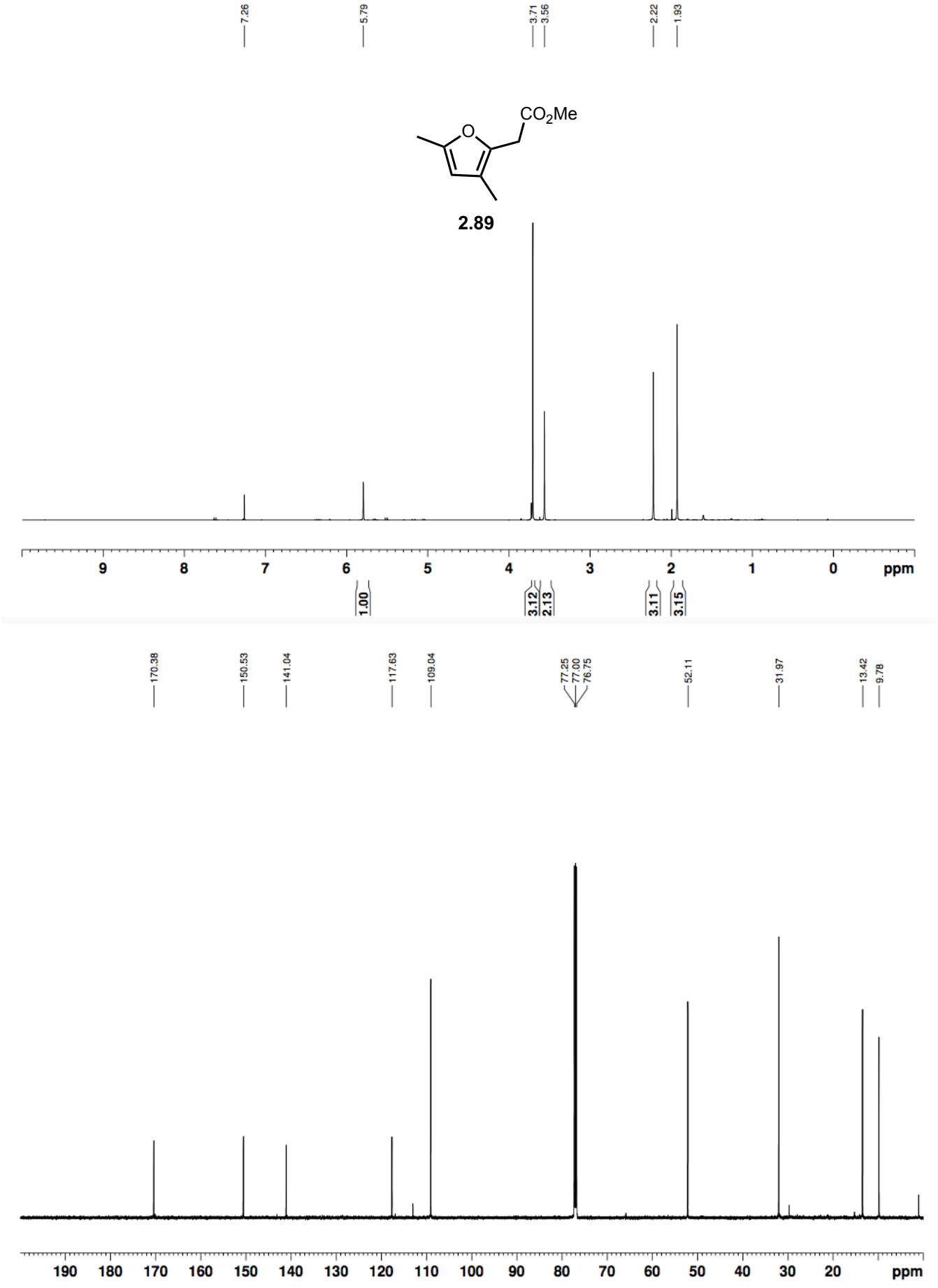
^{1}H (500 MHz, $CDCl_3$), ^{13}C (125 MHz, $CDCl_3$) and ^{19}F (376 MHz, $CDCl_3$) NMR Spectra of **2.86**



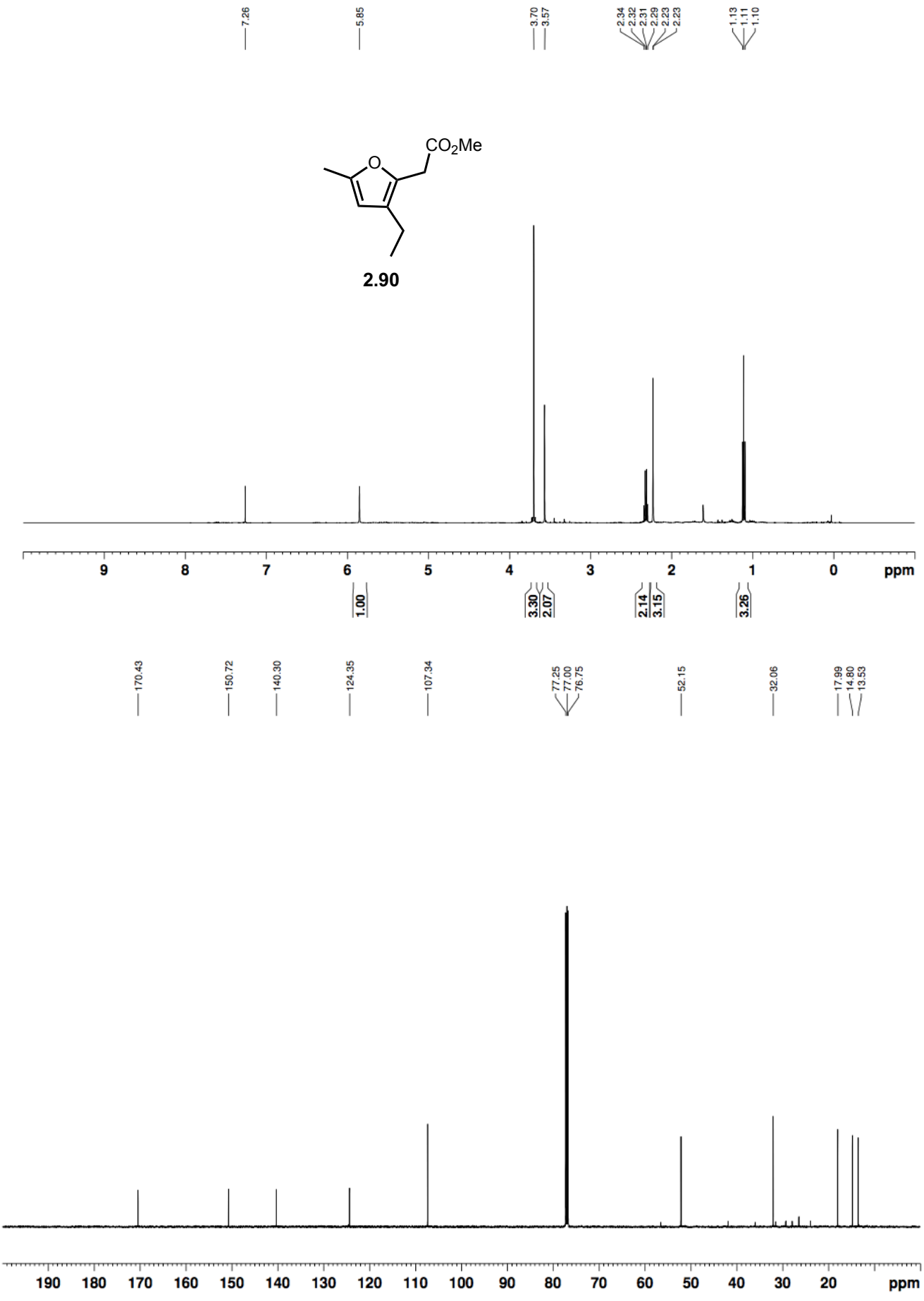
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.87**



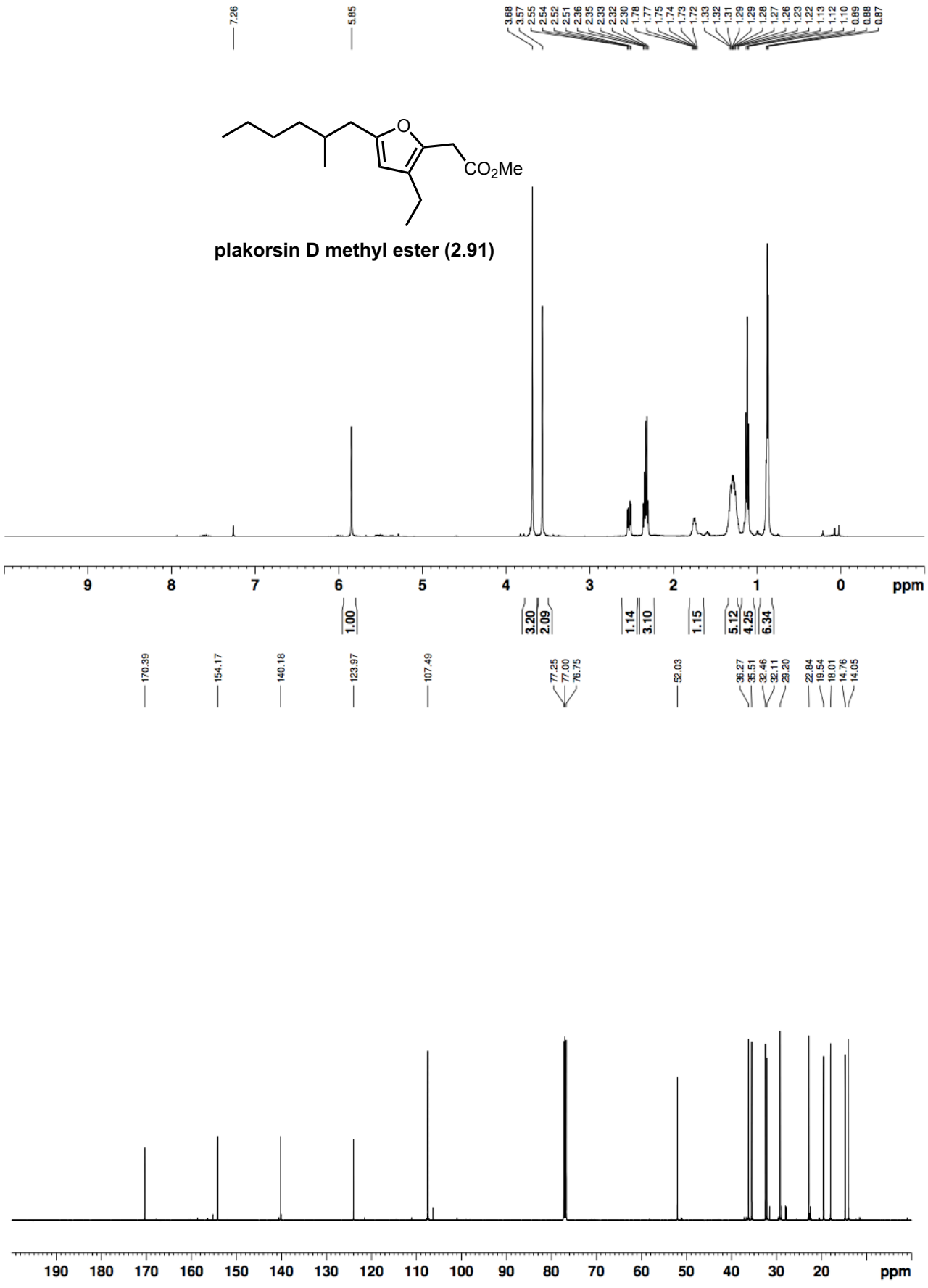
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.88**



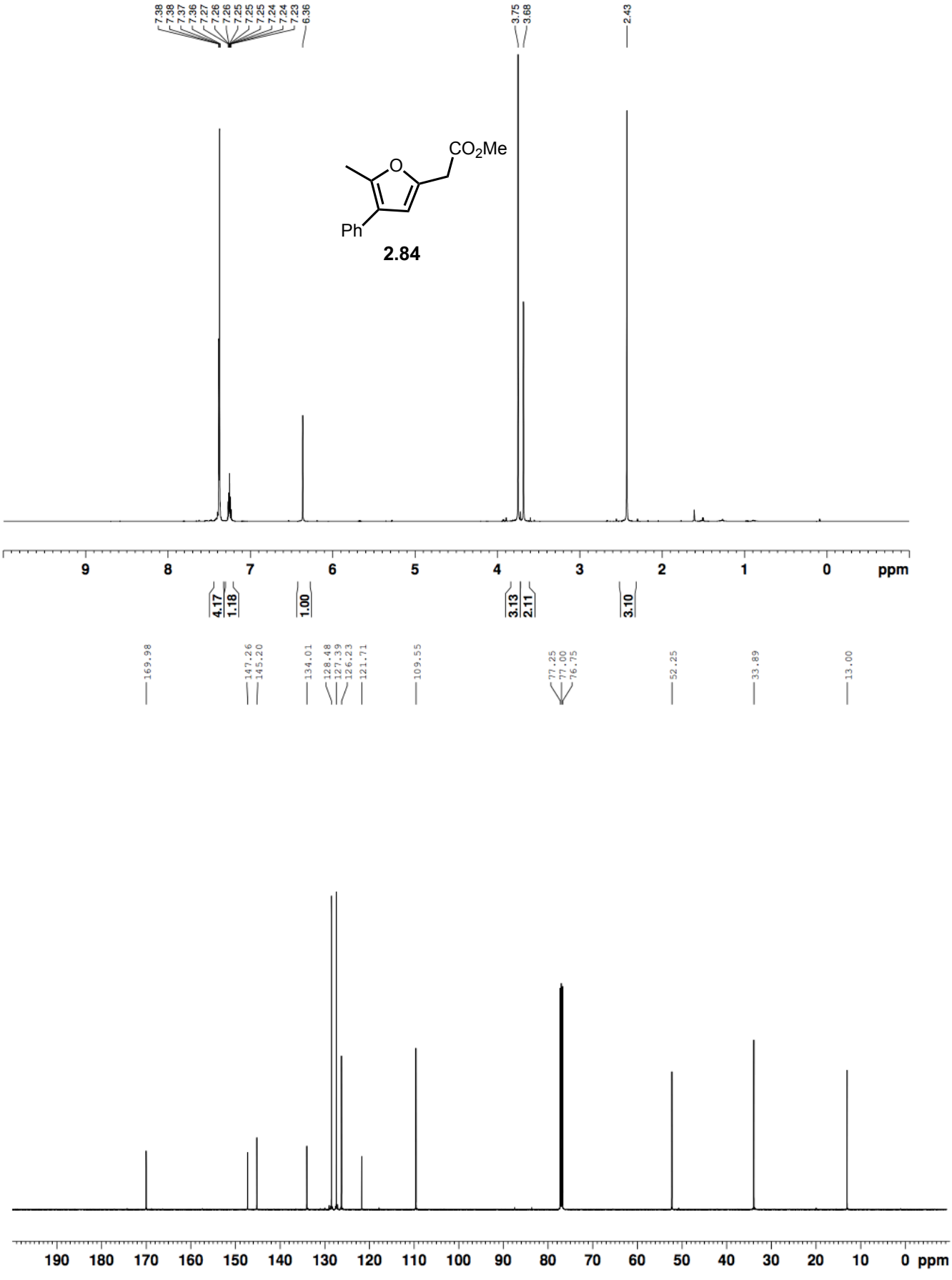
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.89**



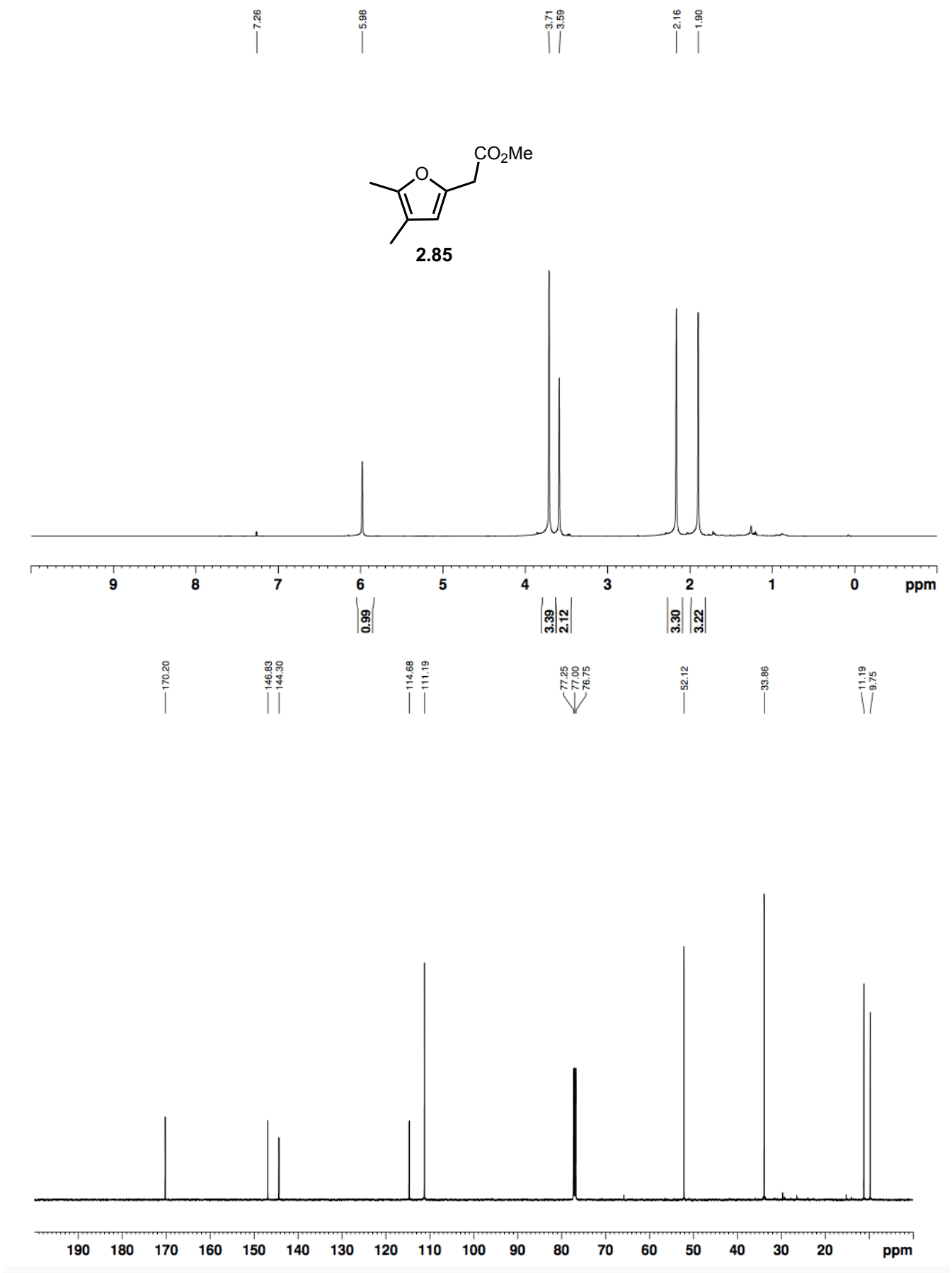
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.90**



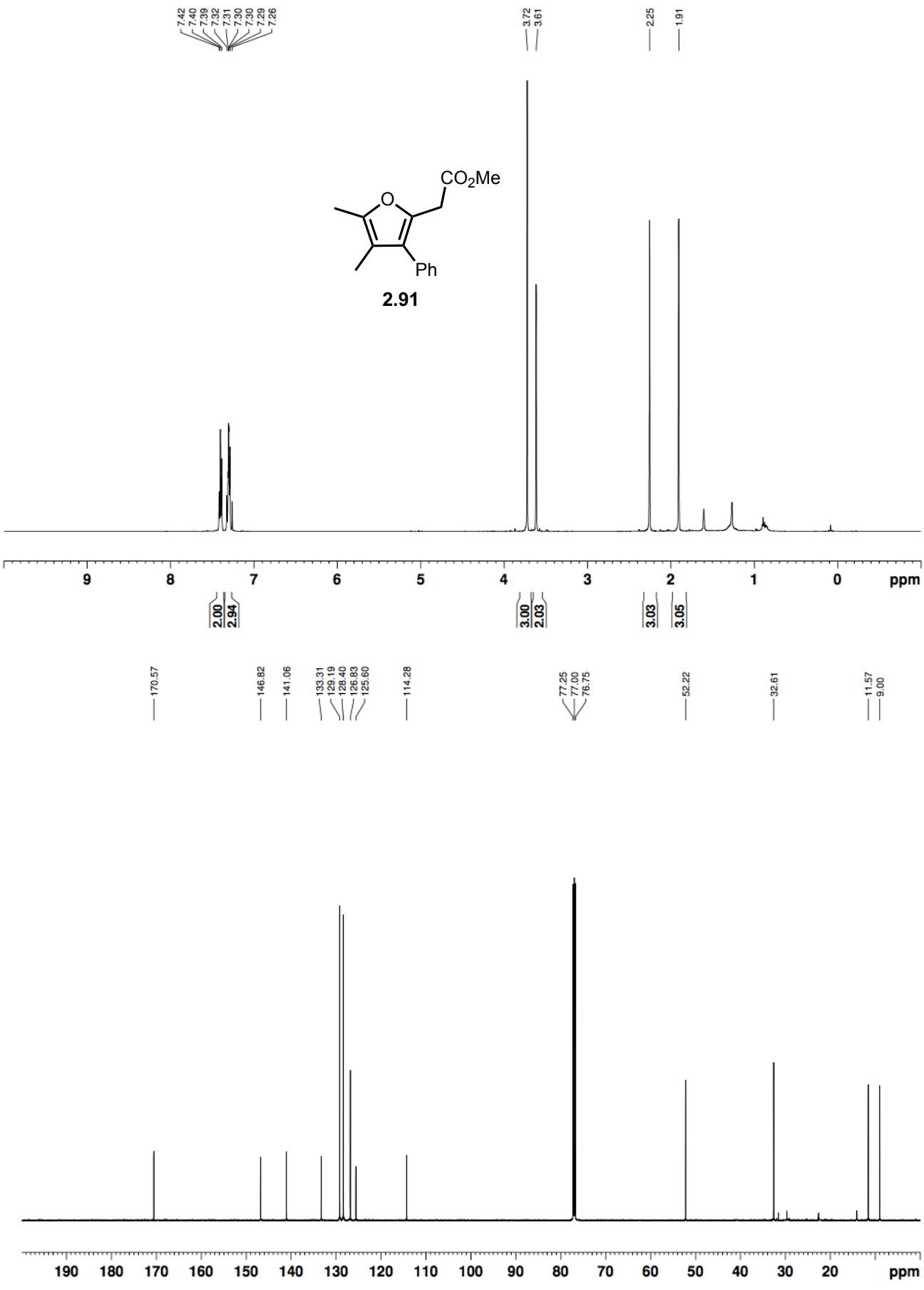
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.91 (plakorsin D methyl ester)**



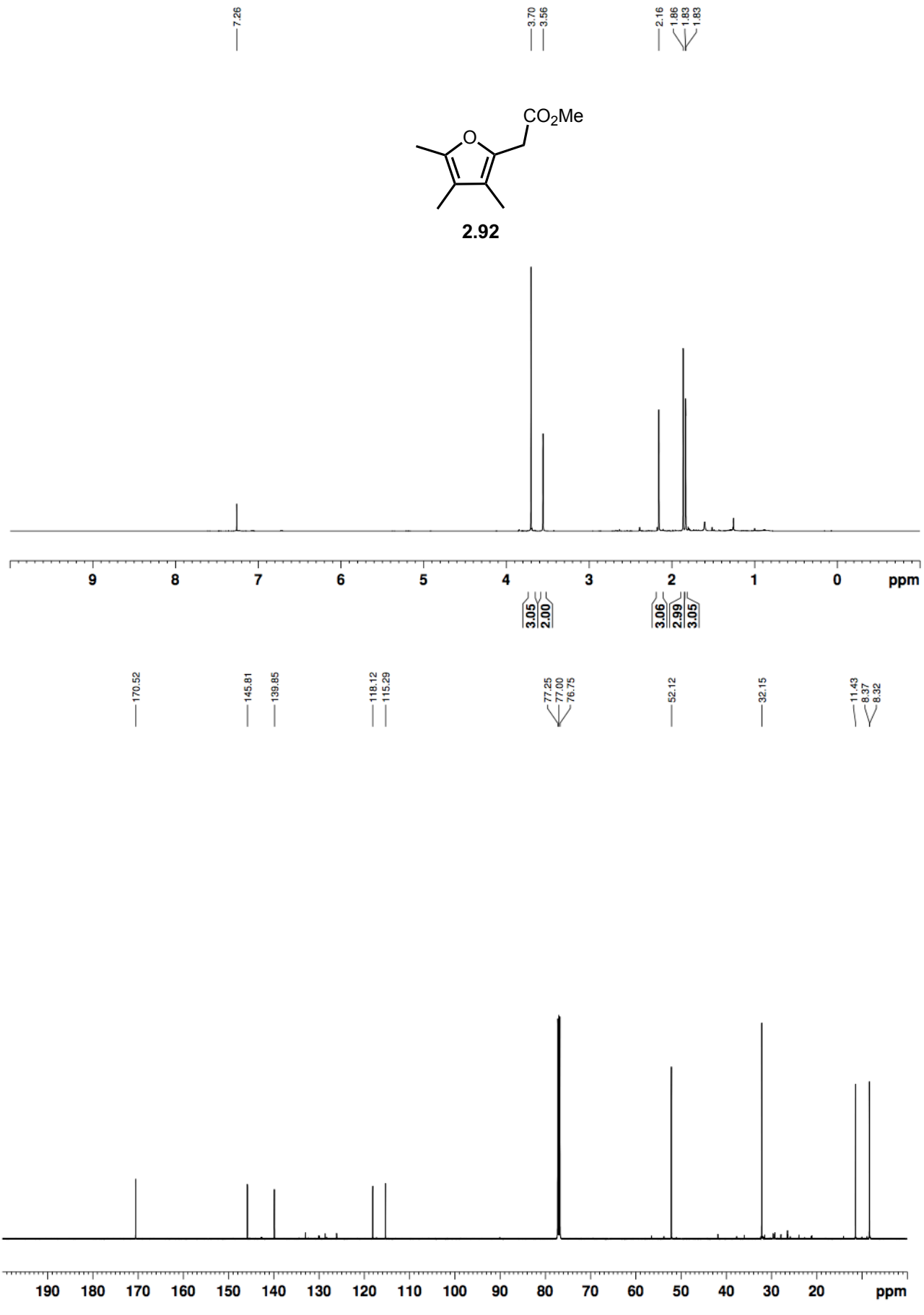
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.84**



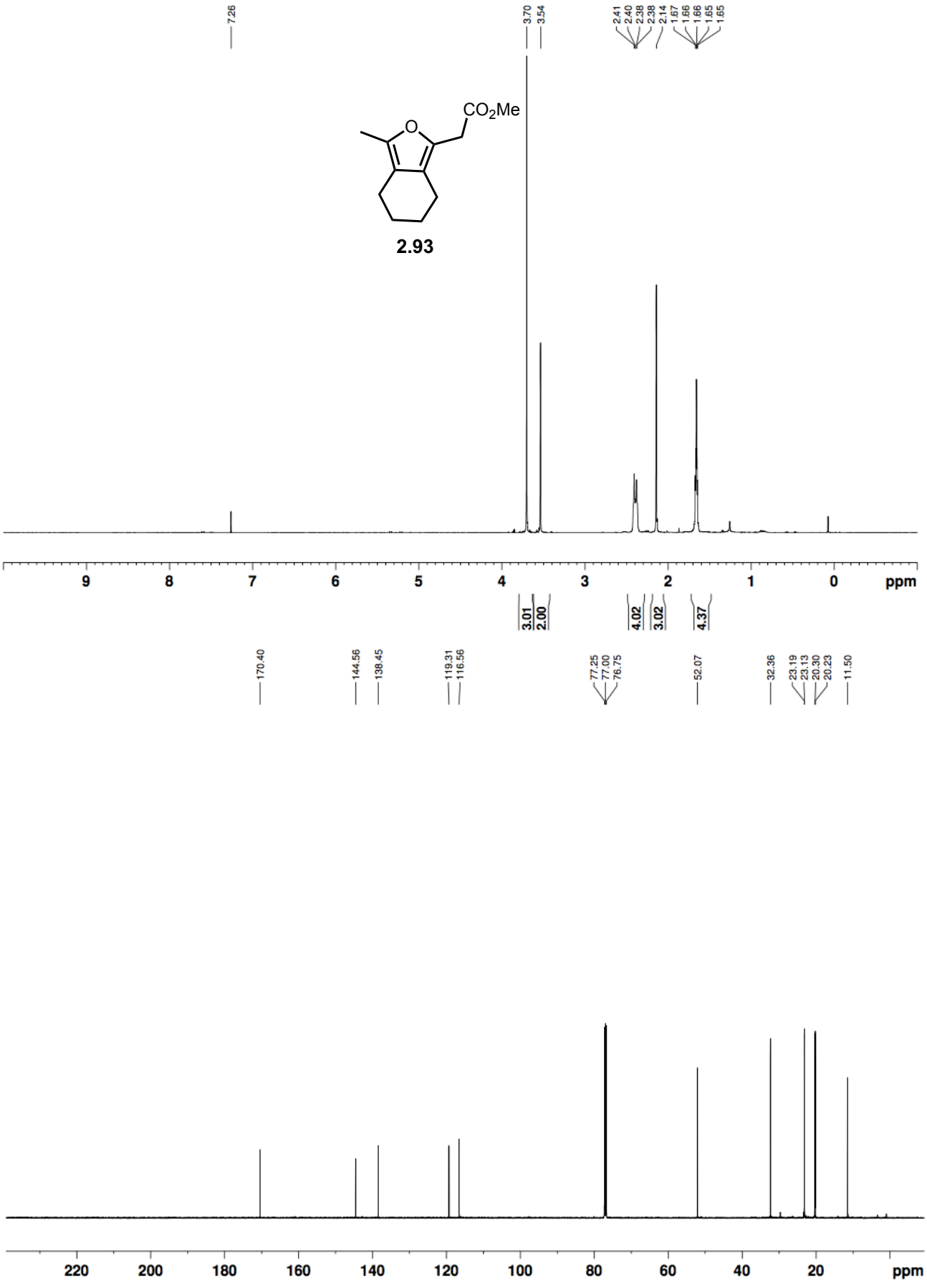
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.85**



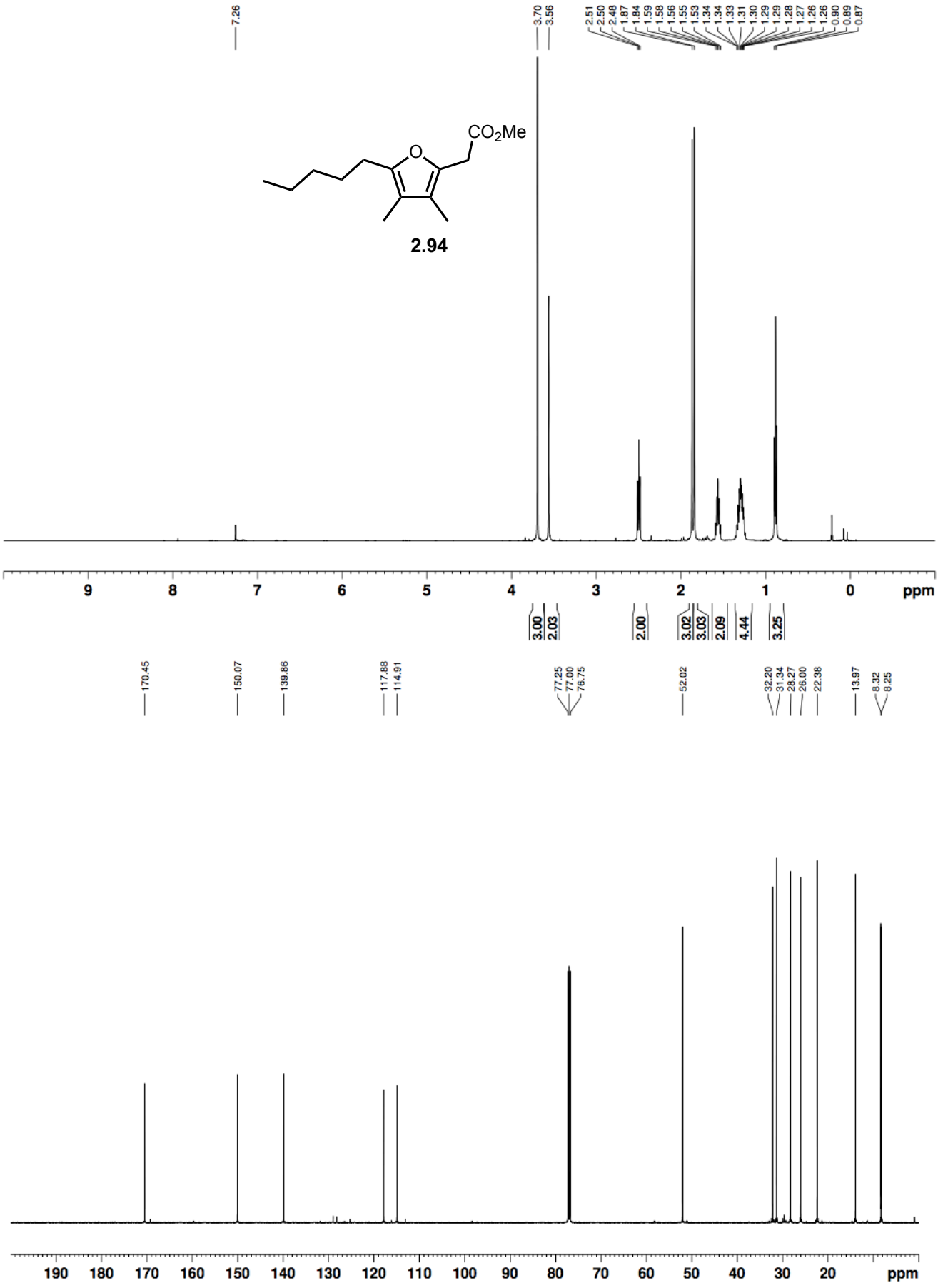
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.91**



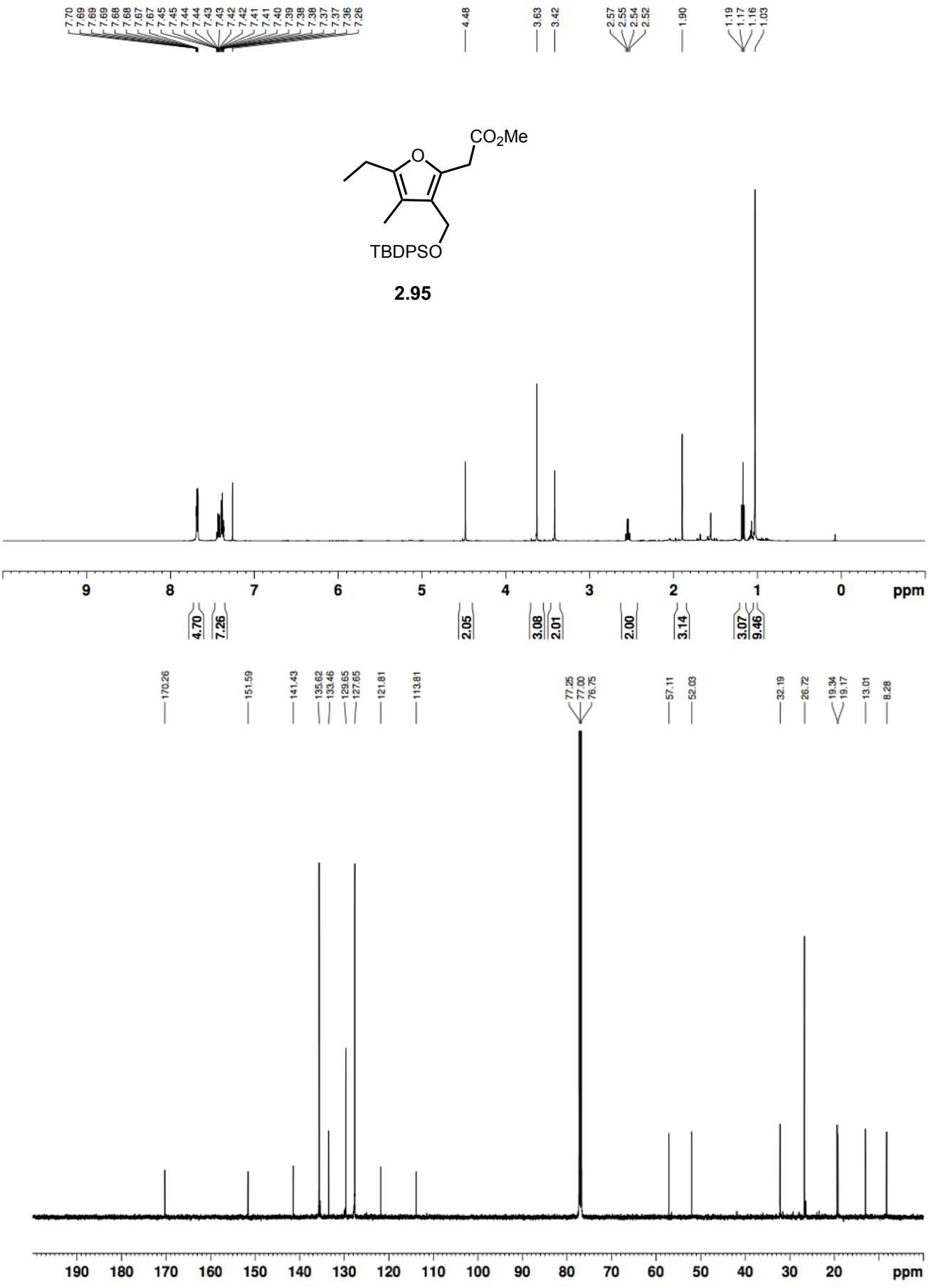
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.92**



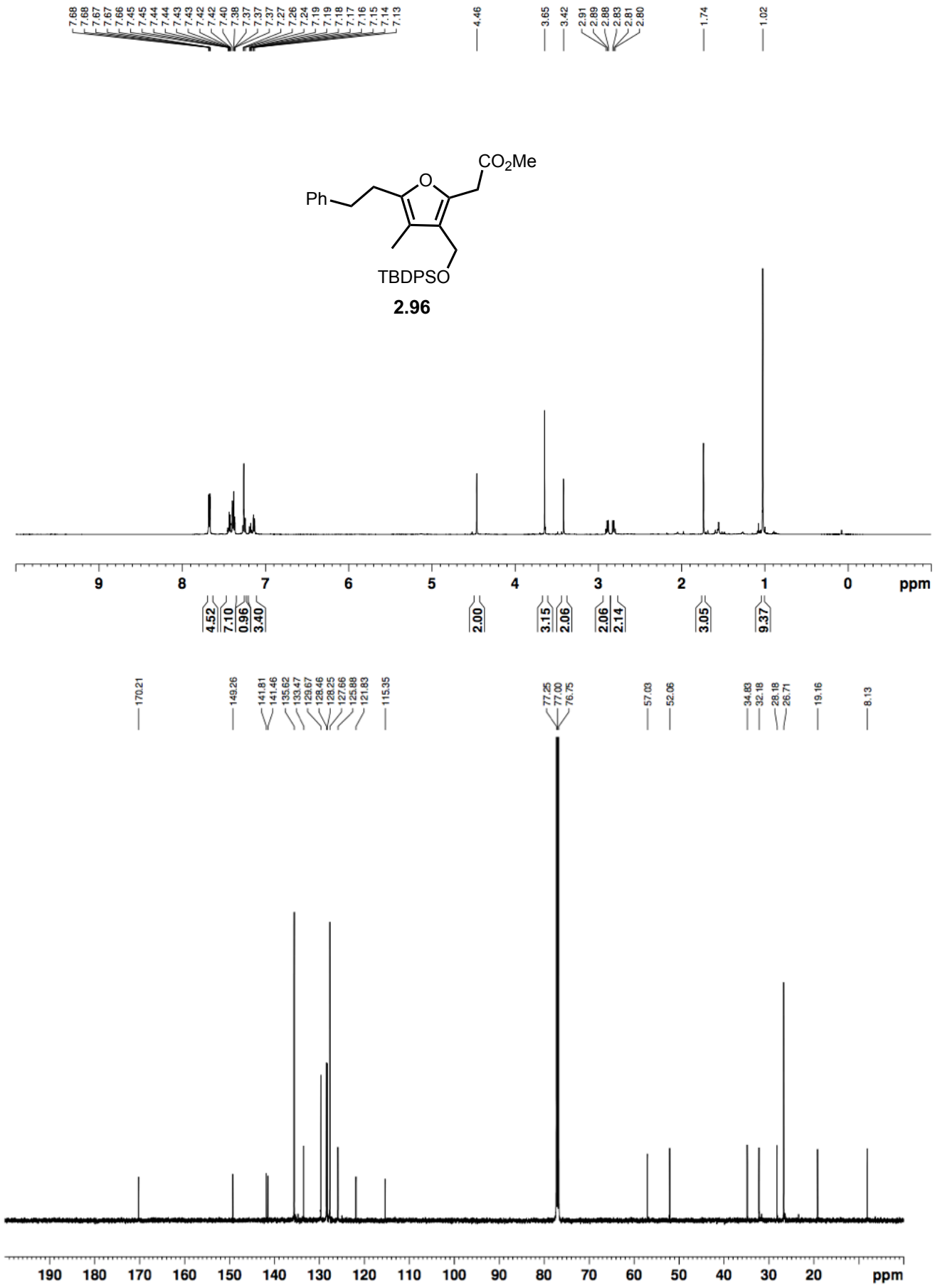
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.93**



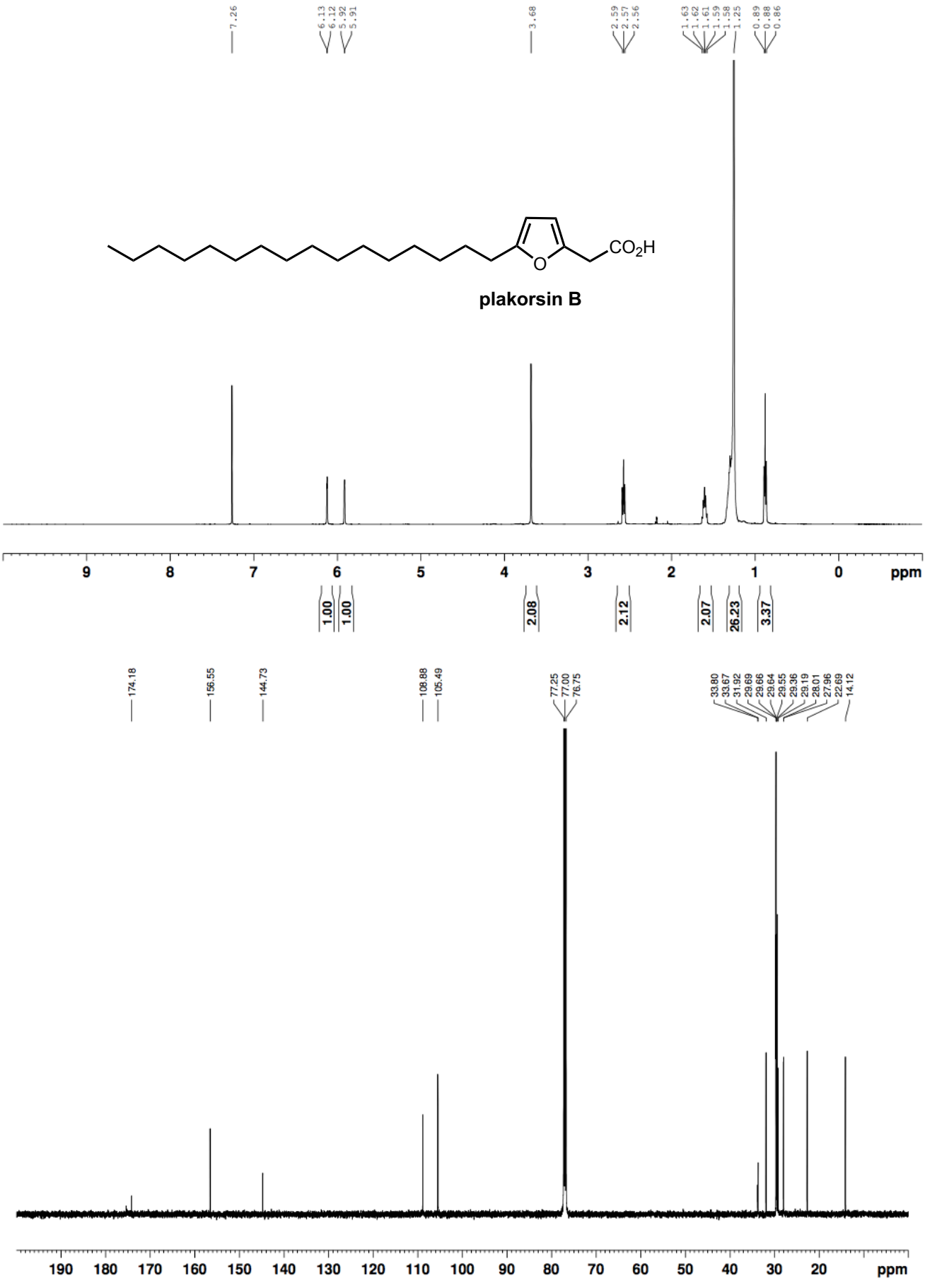
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.94**



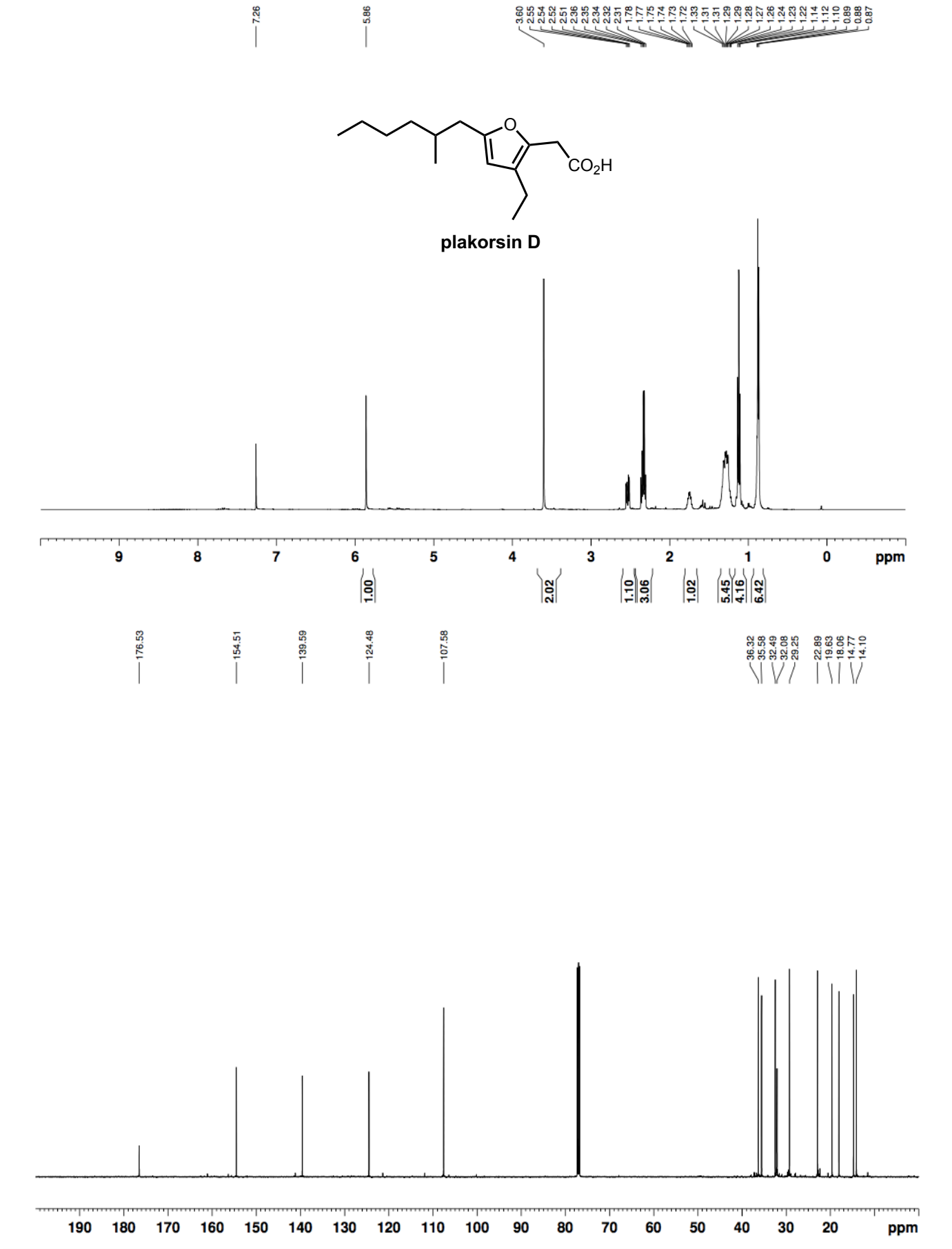
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) Spectra of **2.95**



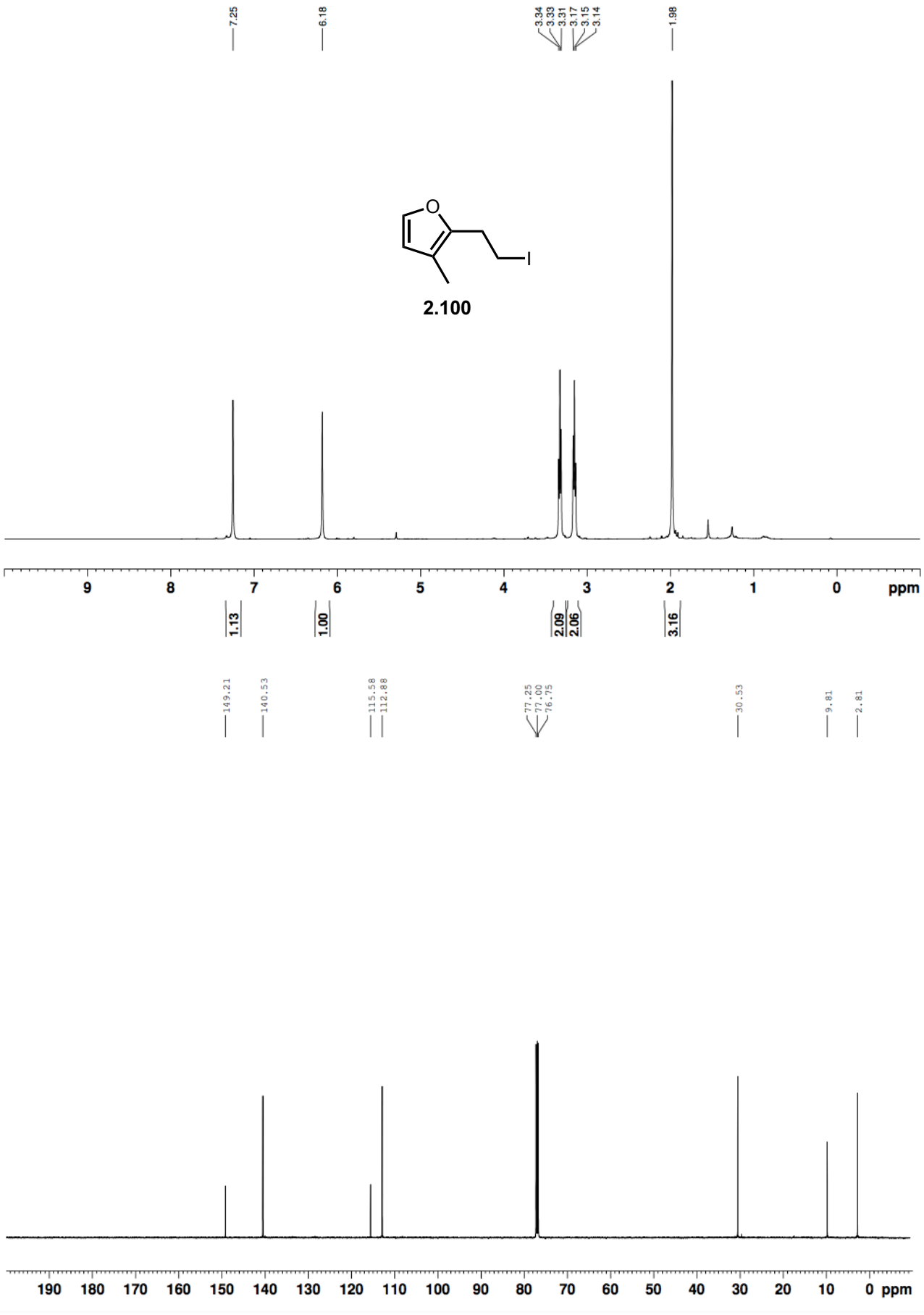
^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) Spectra of **2.96**



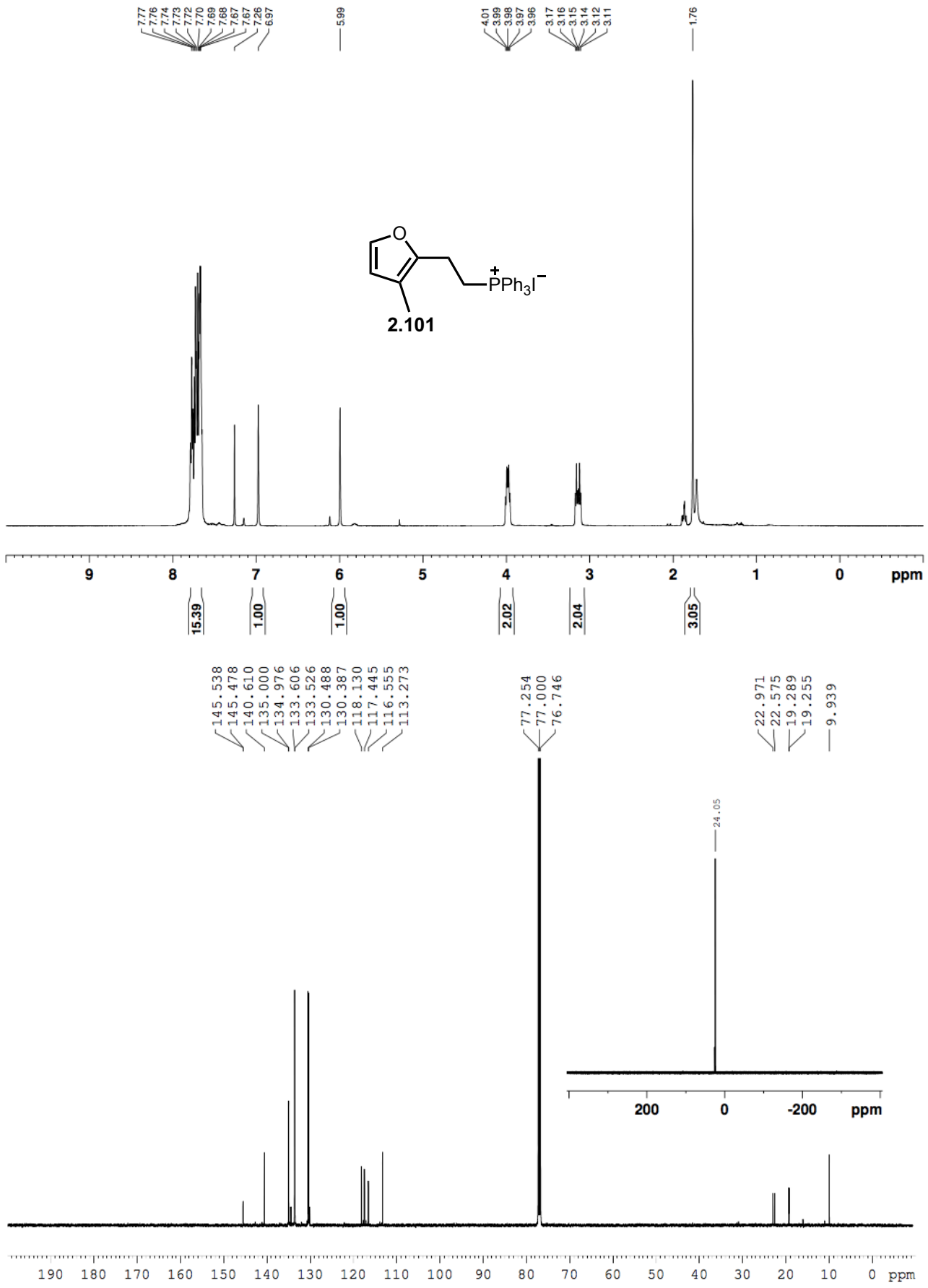
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **plakorsin B**



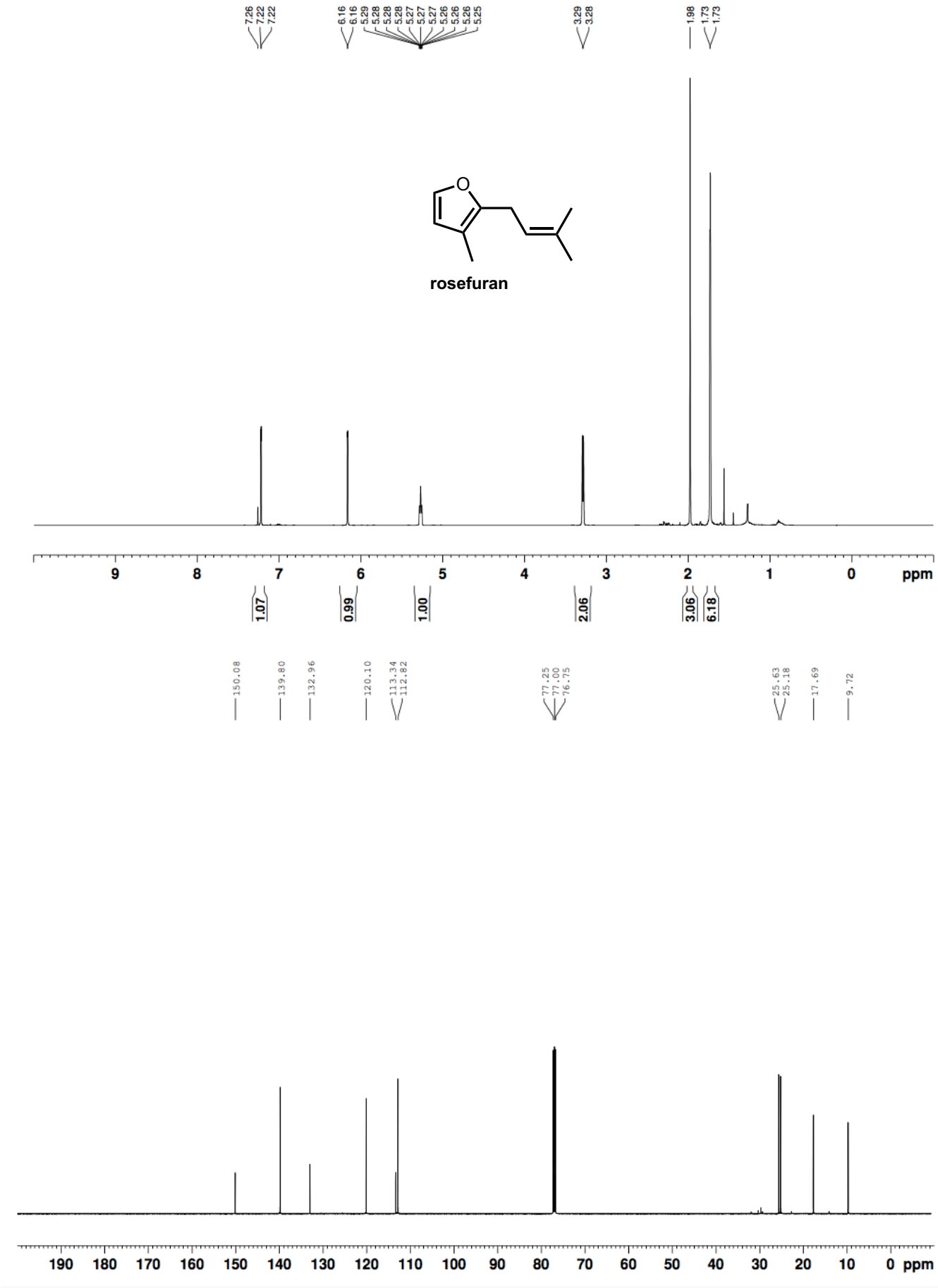
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **plakorsin D**



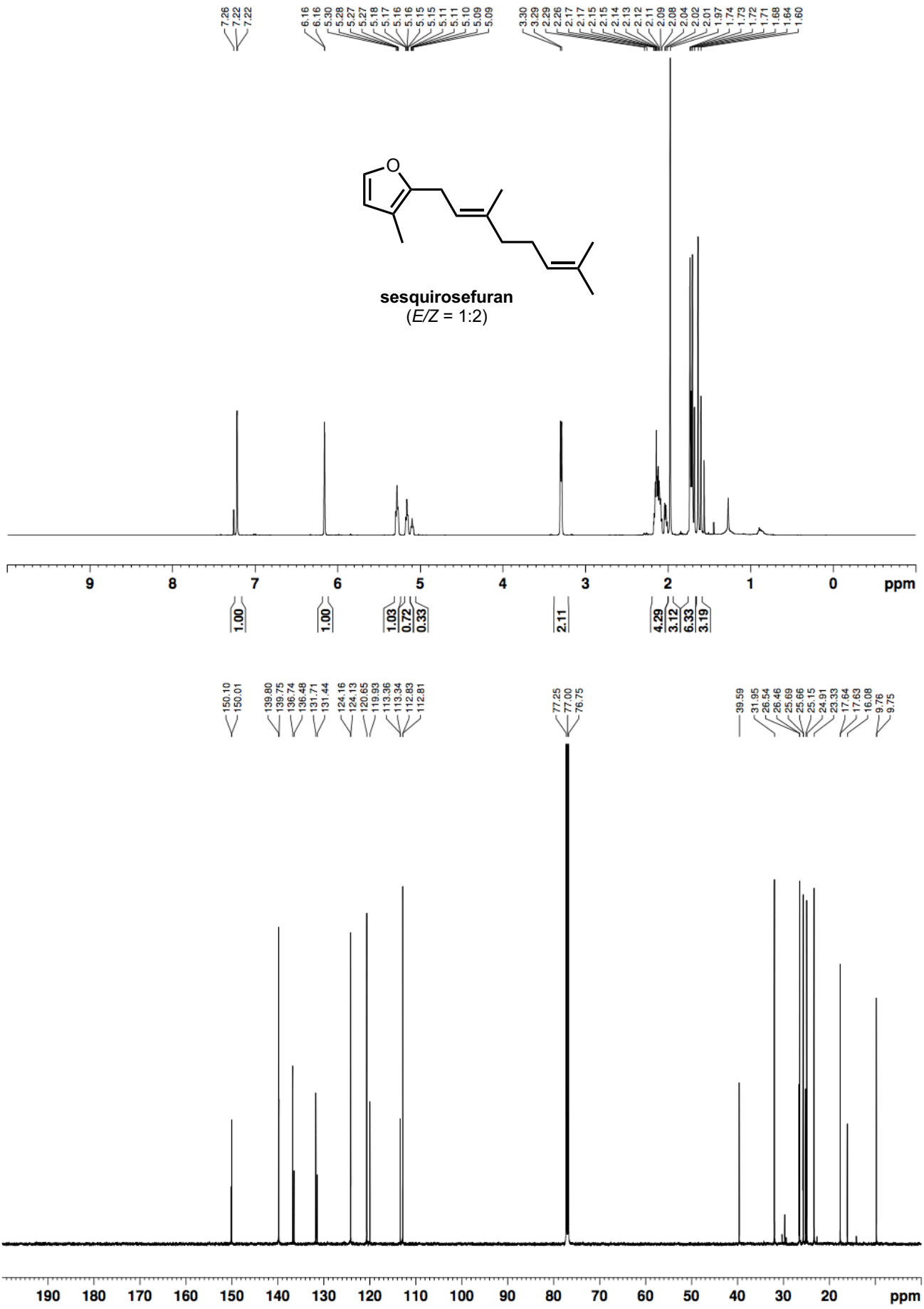
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.100**



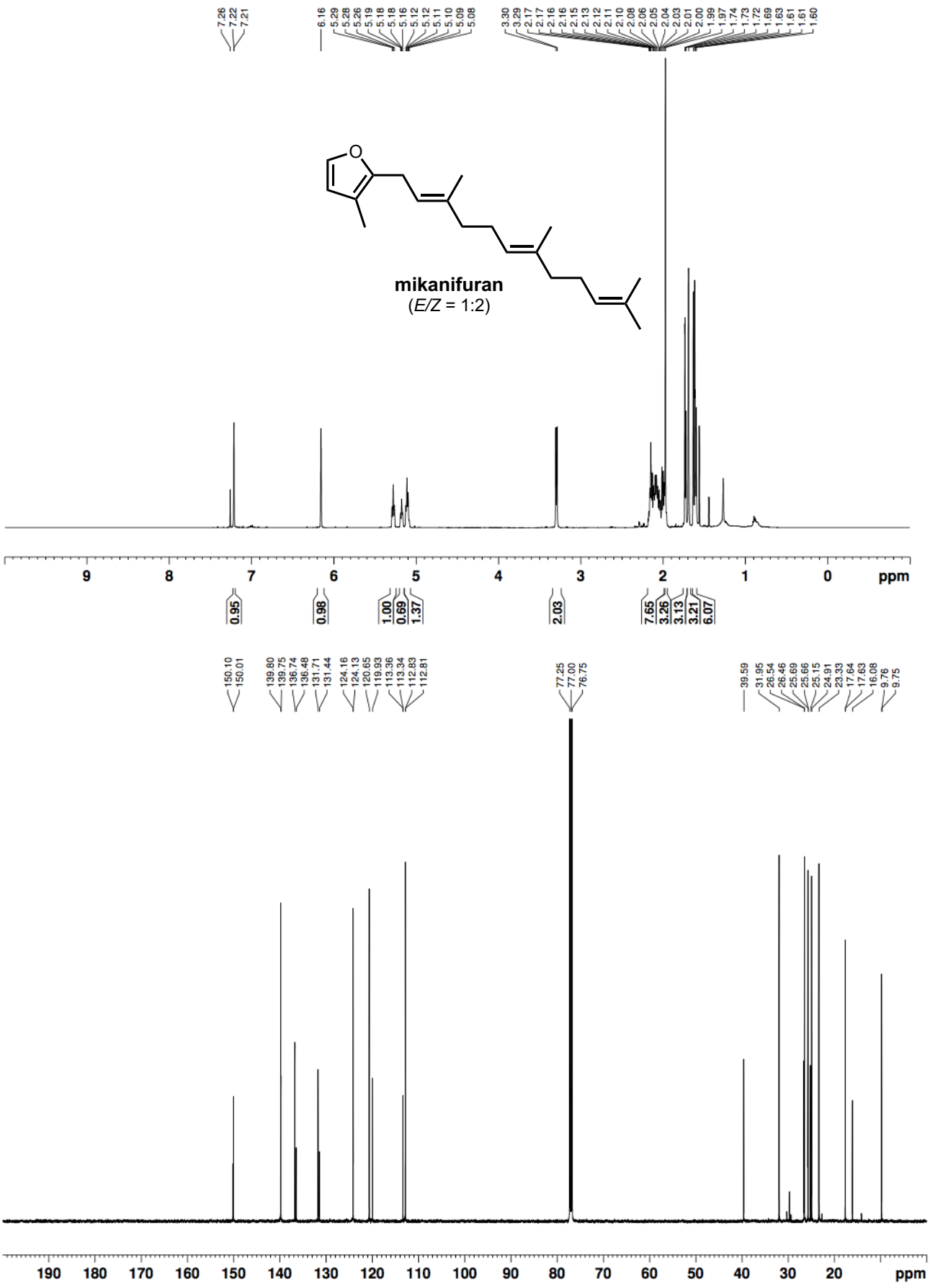
^{1}H (500 MHz, $CDCl_3$), ^{13}C (125 MHz, $CDCl_3$) and ^{31}P (162 MHz, $CDCl_3$) NMR Spectra of **2.101**



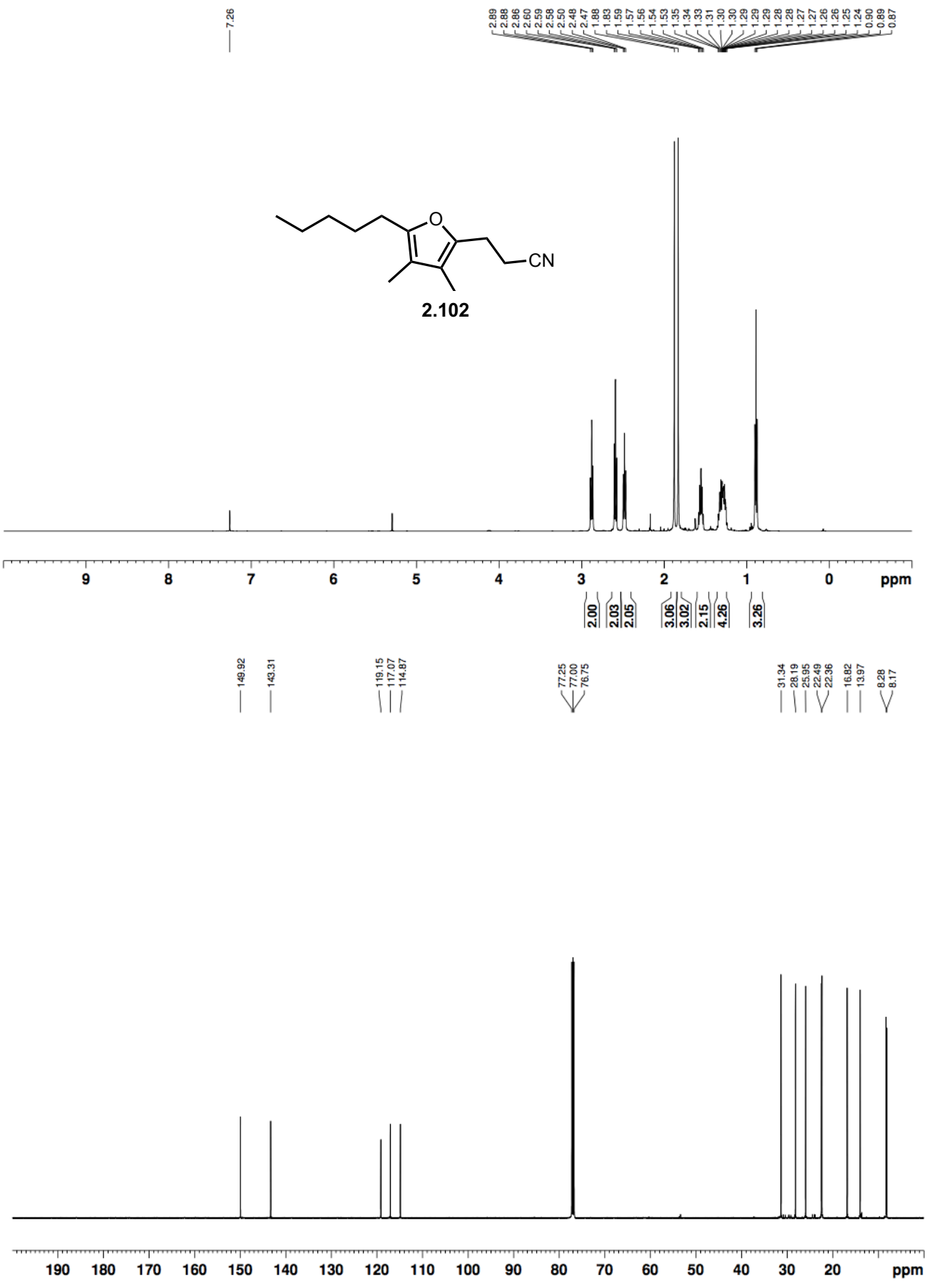
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **rosefuran**



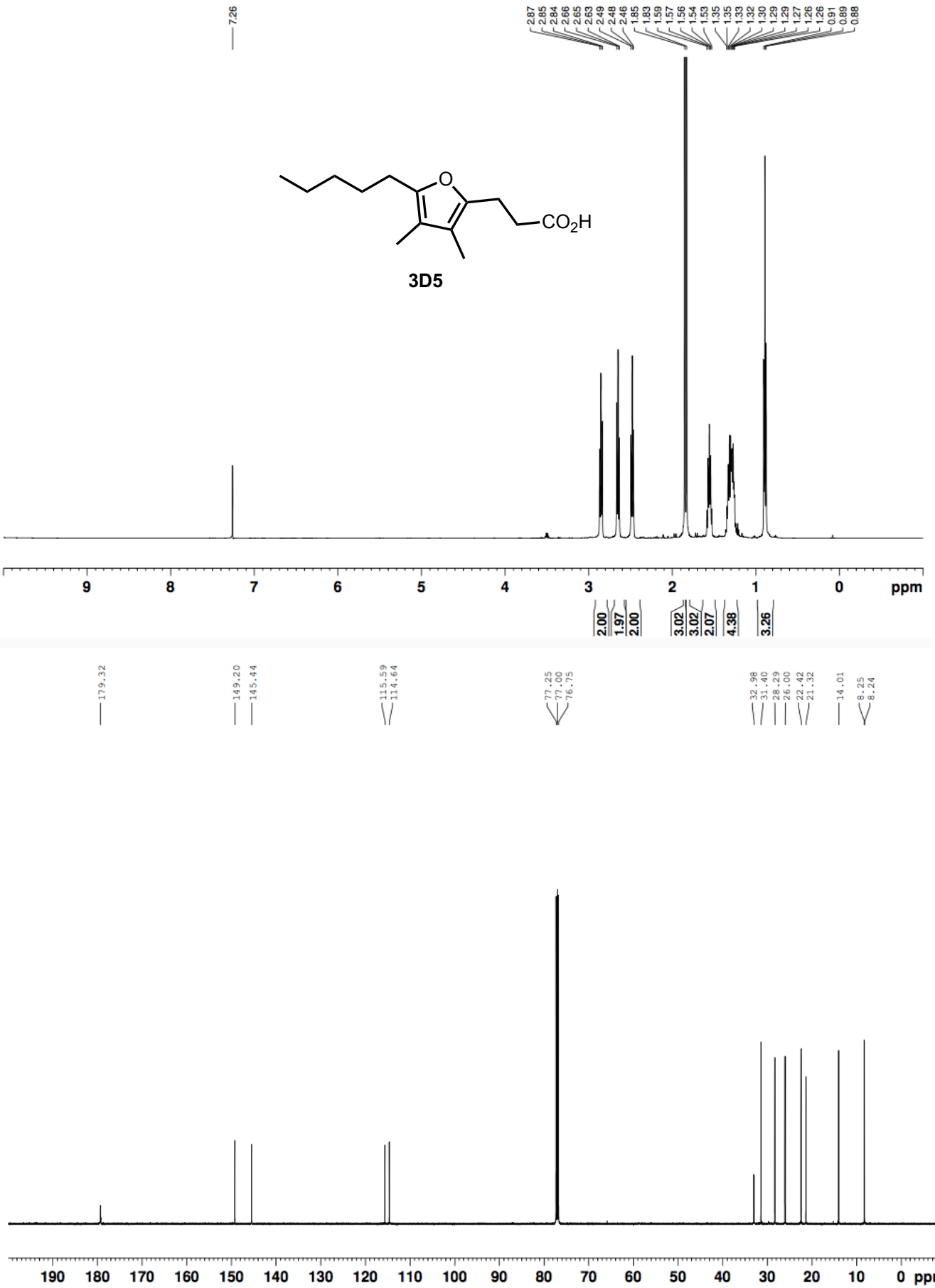
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **sesquirosefuran**



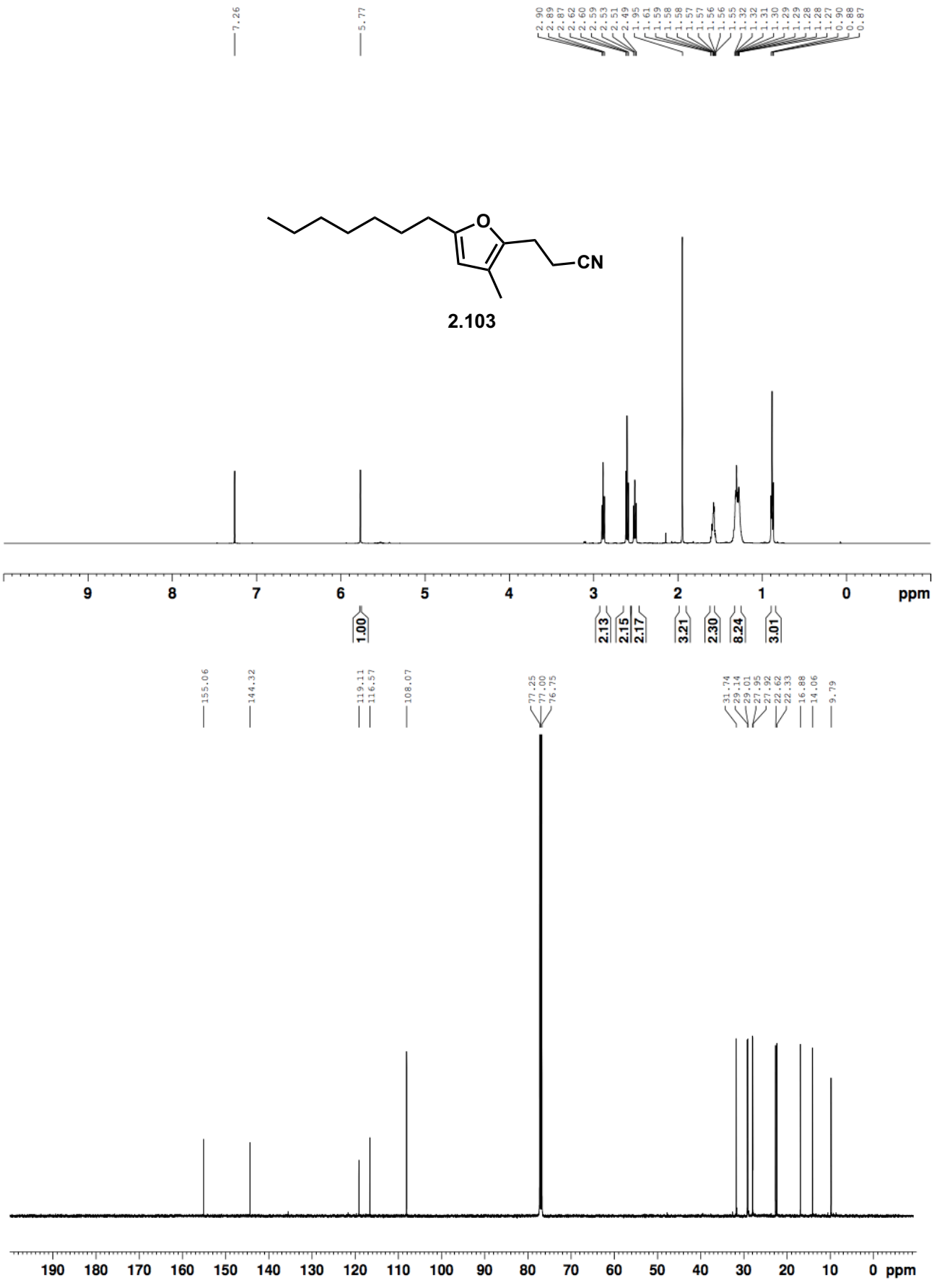
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **mikanifuran**



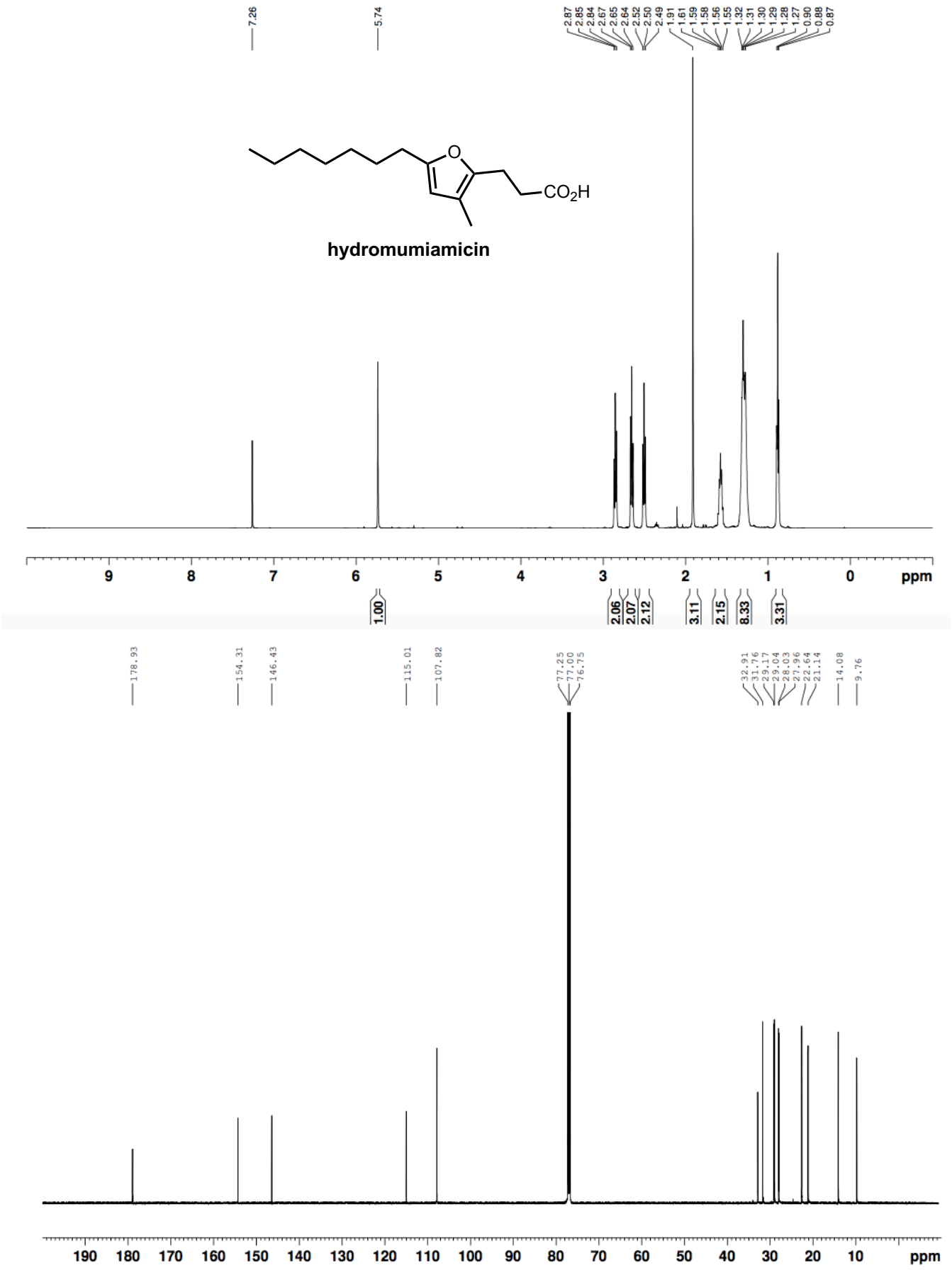
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.102**



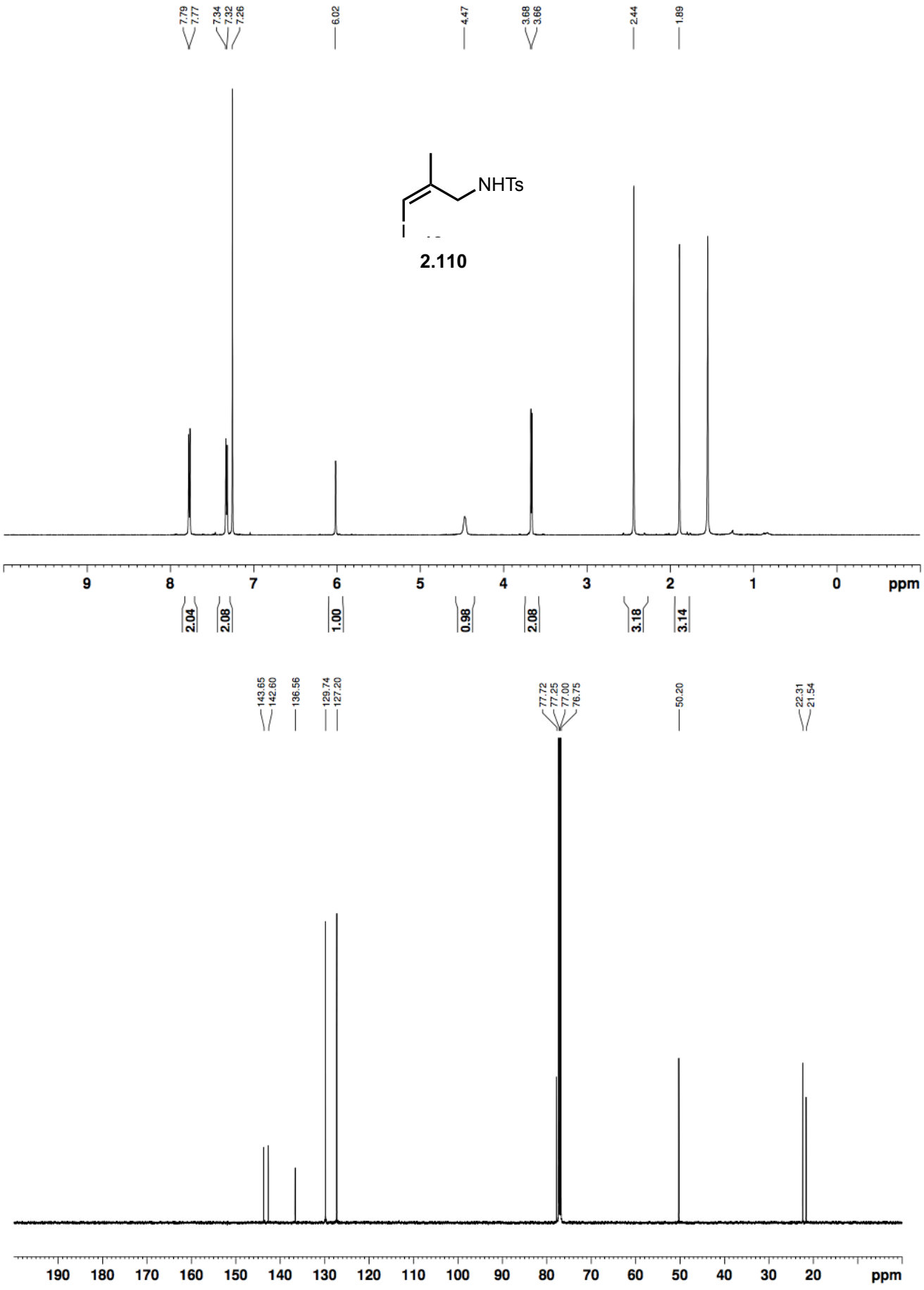
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3D5**



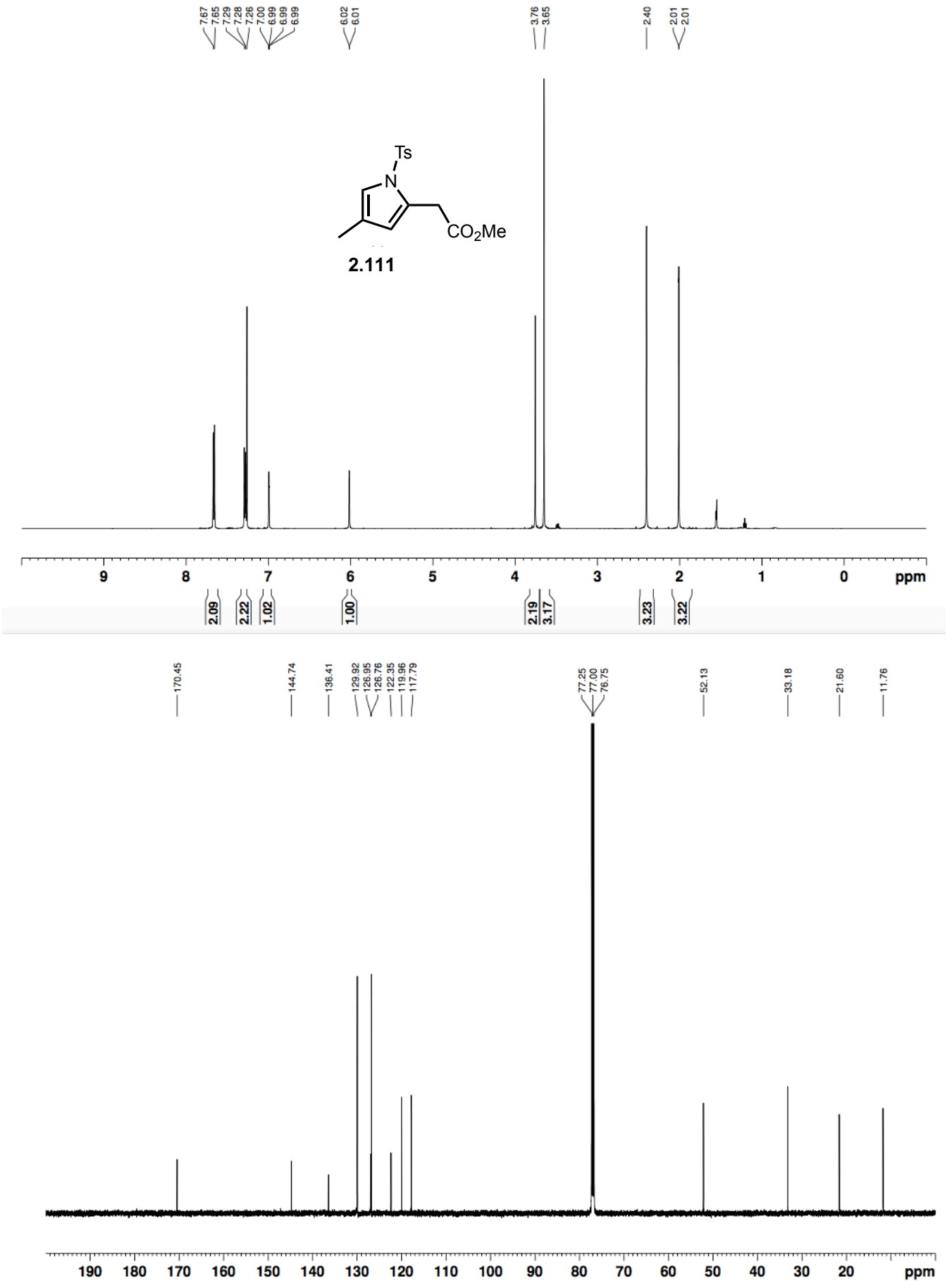
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.103**



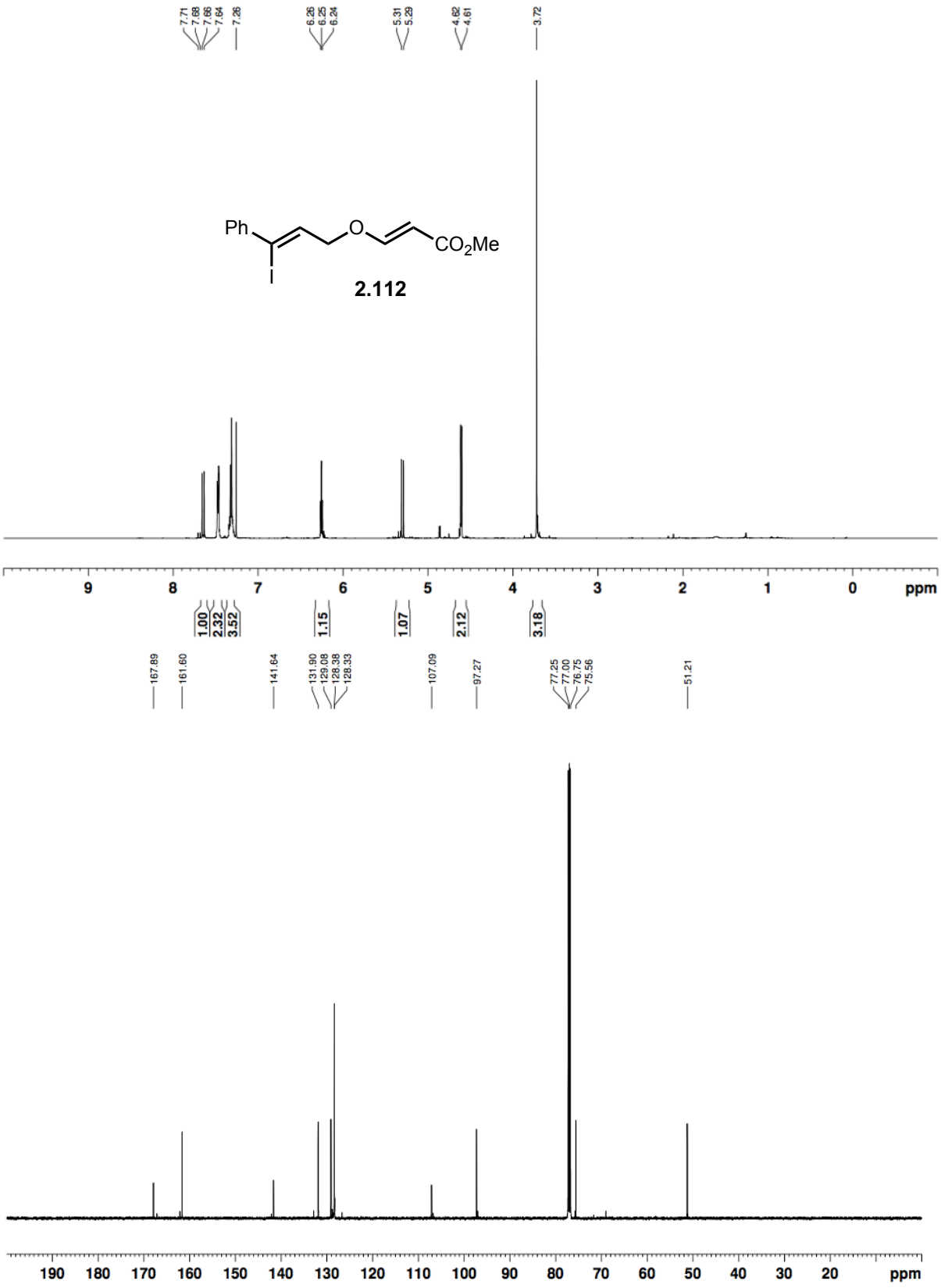
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **hydromumiamicin**



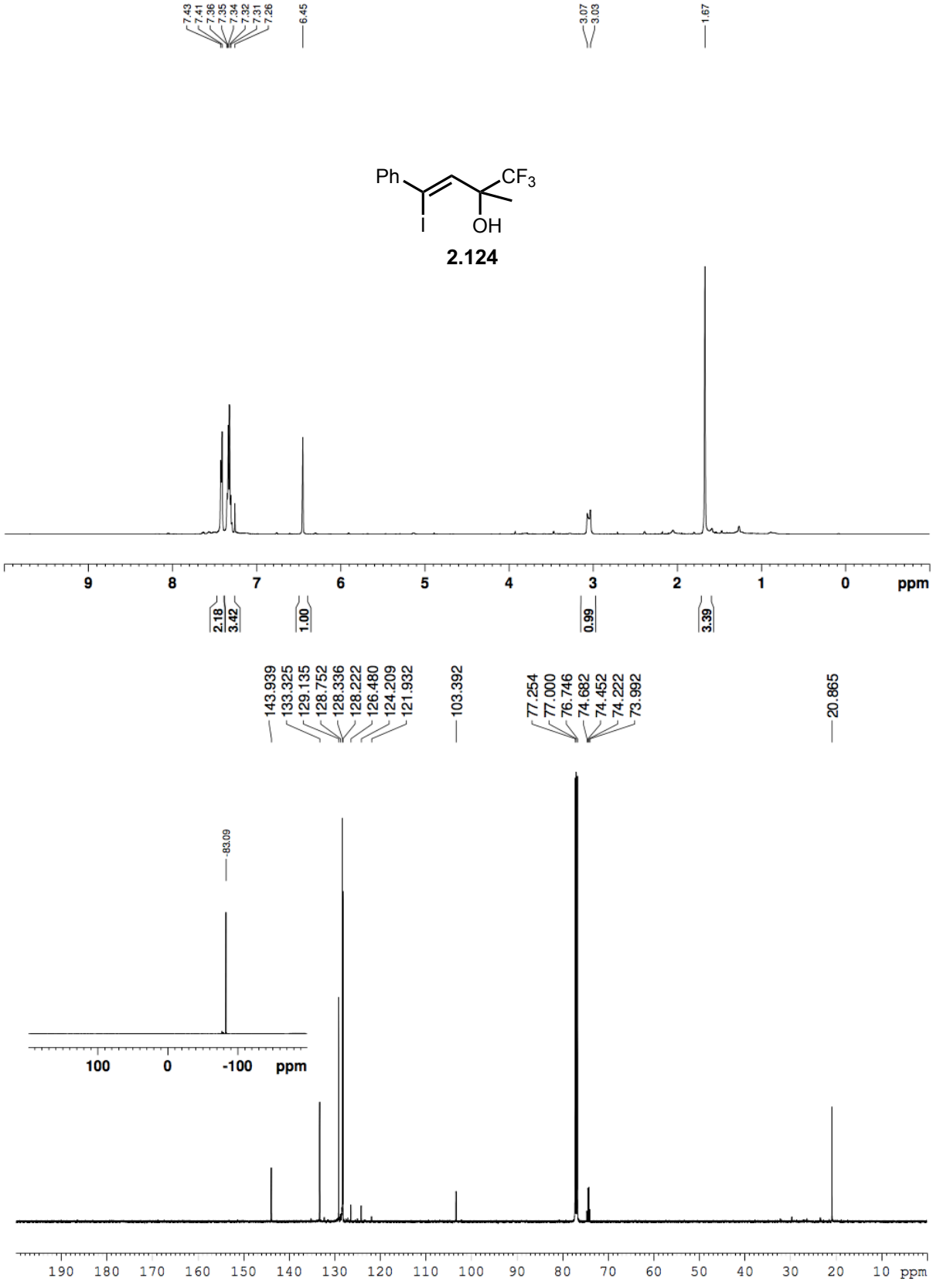
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.110**



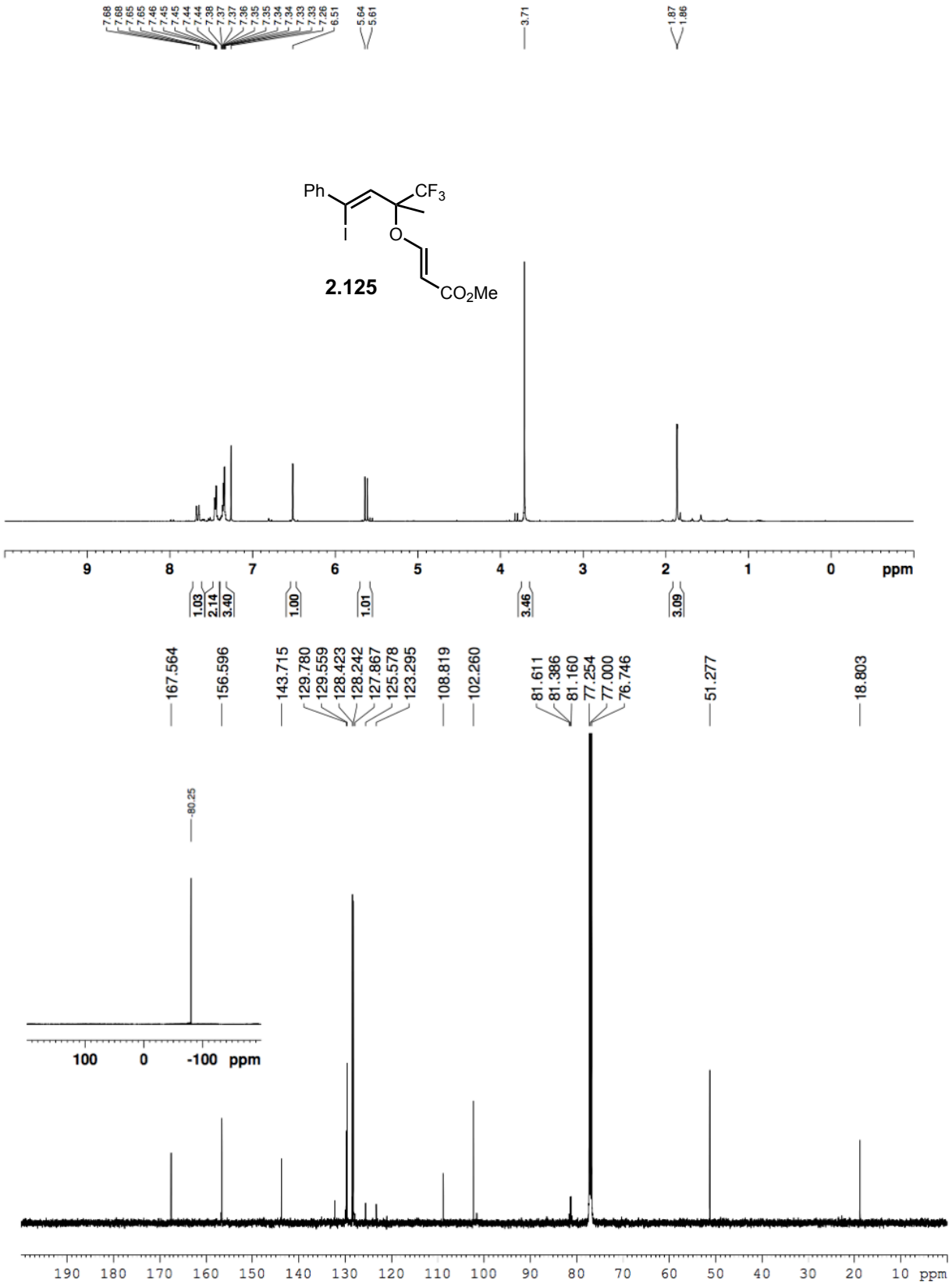
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.111**



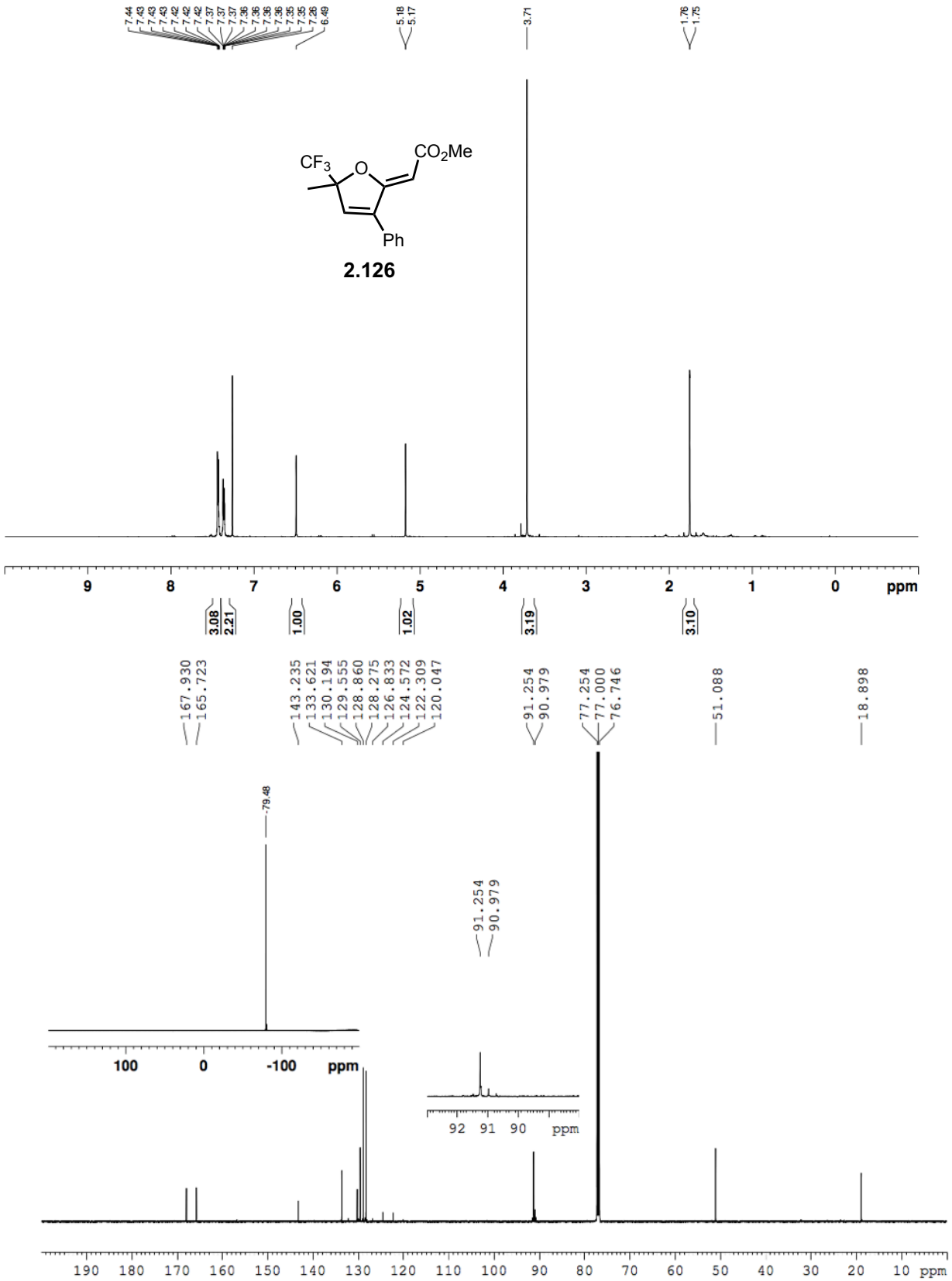
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.112**



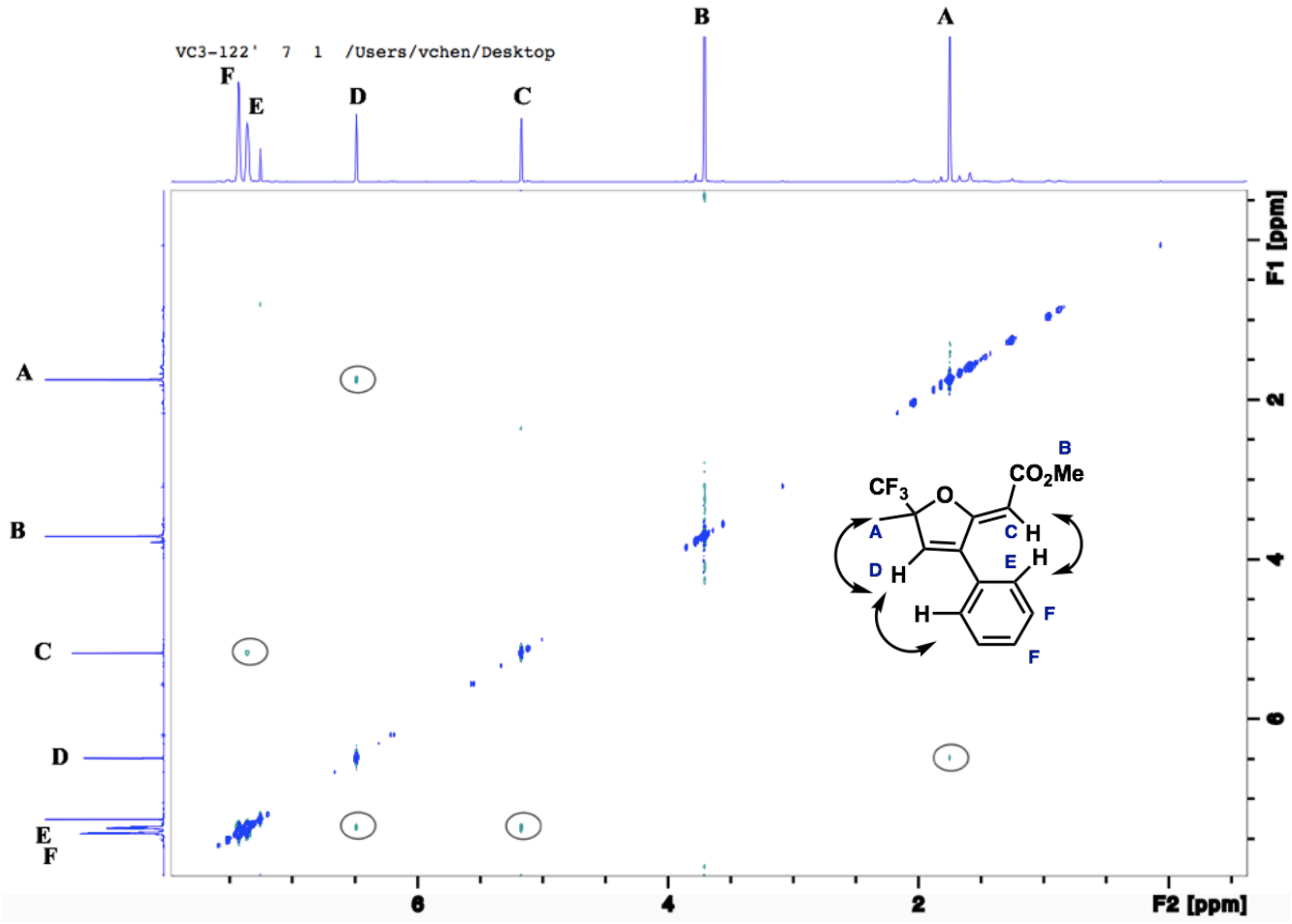
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **2.124**



^{1}H NMR (500 MHz, $CDCl_3$), ^{13}C (125 MHz, $CDCl_3$) and ^{19}F (376 MHz, $CDCl_3$) Spectra of **2.125**



^{1}H NMR (500 MHz, $CDCl_3$), ^{13}C (125 MHz, $CDCl_3$) and ^{19}F (376 MHz, $CDCl_3$) Spectra of **2.126**



NOESY NMR (500 MHz, $CDCl_3$) Spectra of Compound **2.126**

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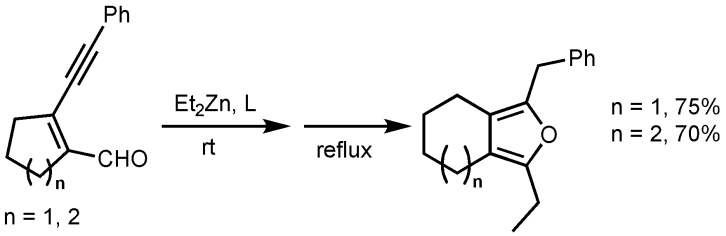

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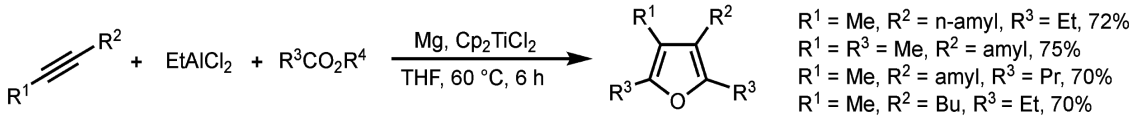

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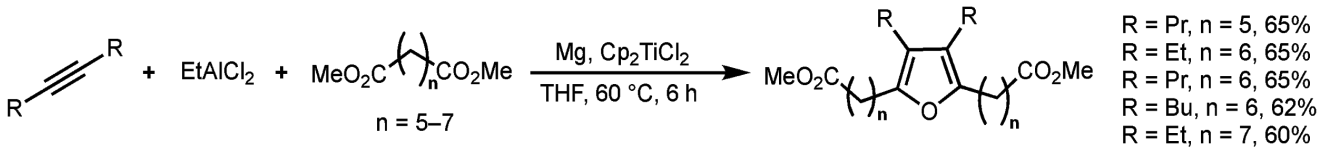

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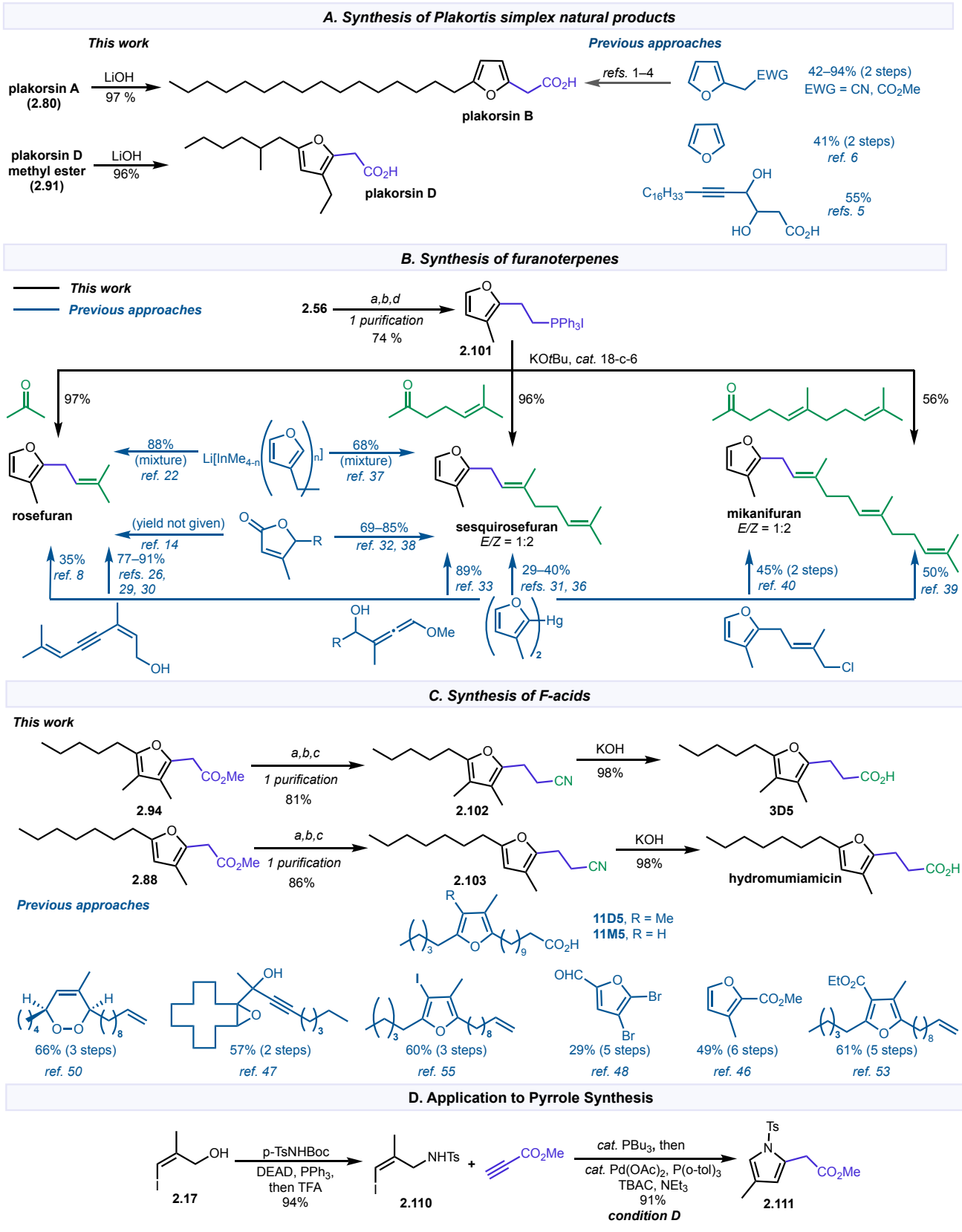
2.9.10. Previous Syntheses of the Furan Natural Products

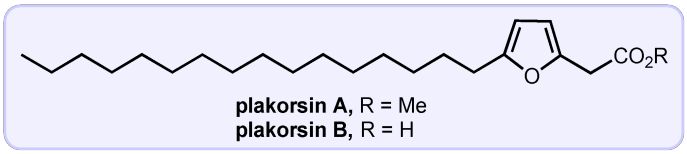
Application of the Michael–Heck Reaction to the Synthesis of Polyalkyl Furan Natural Products



Note: All references above refer to those in sections 13.1–3 below.

2.9.11. References for the Previous Syntheses

Plakorsins A, B, and D and Plakorsin D methyl ester



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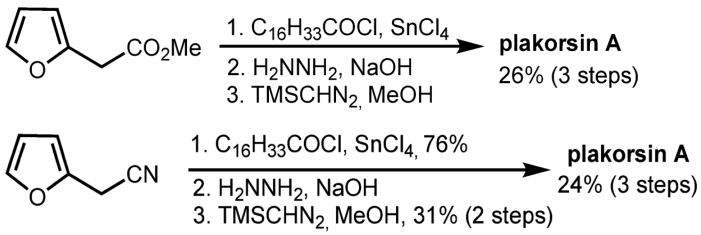

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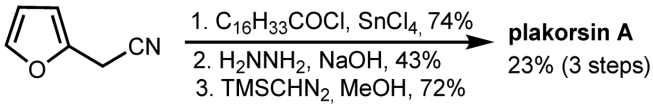

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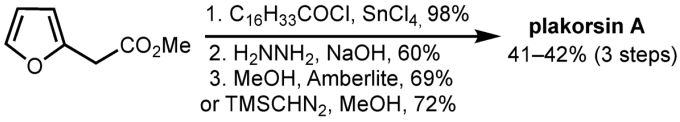

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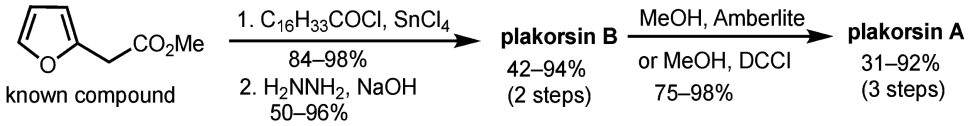

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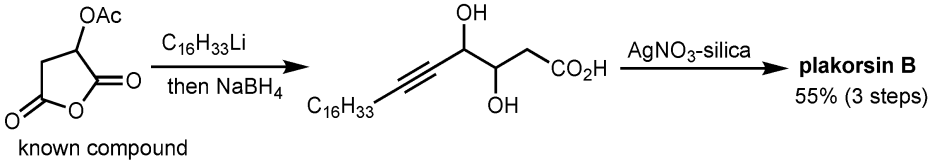

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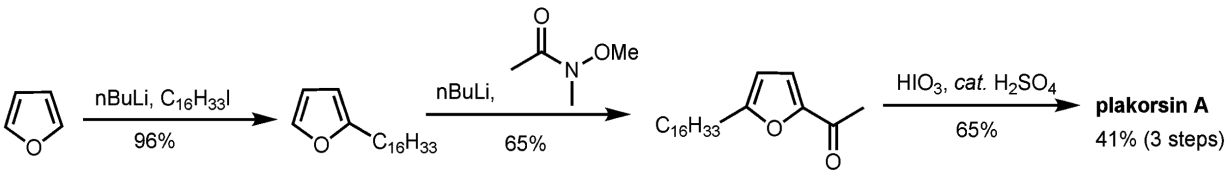

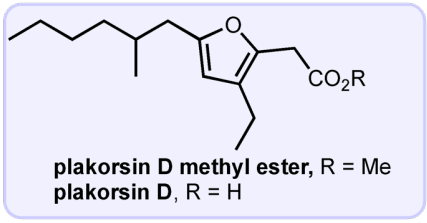

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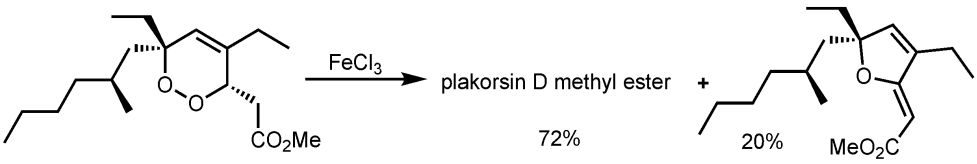
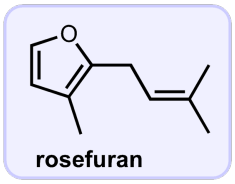


13.2. Rosefuran, Sesquirosefuran, and Mikanifuran



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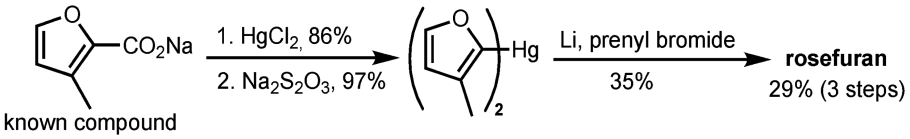

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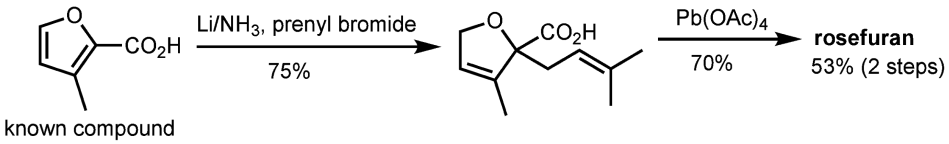

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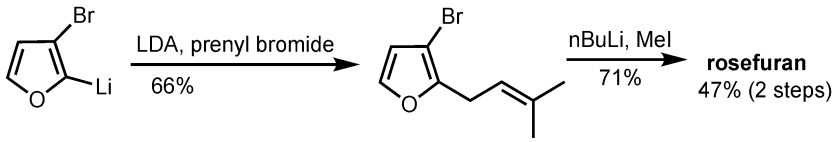

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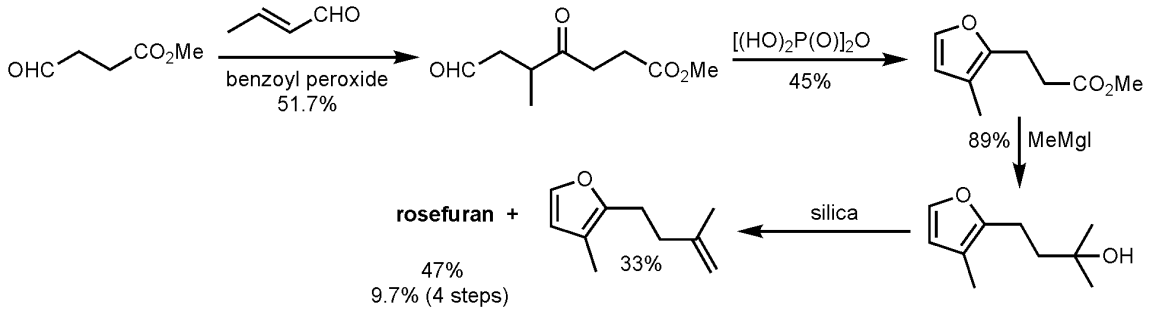

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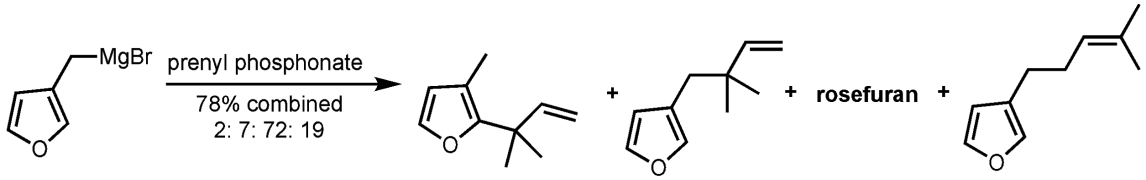

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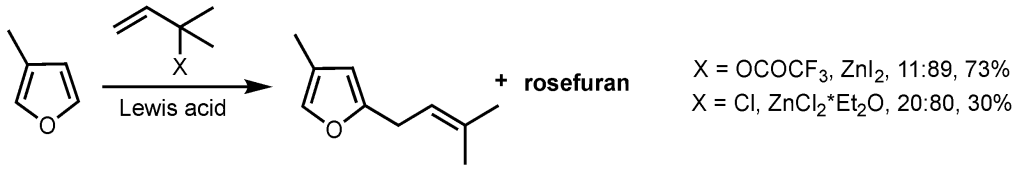

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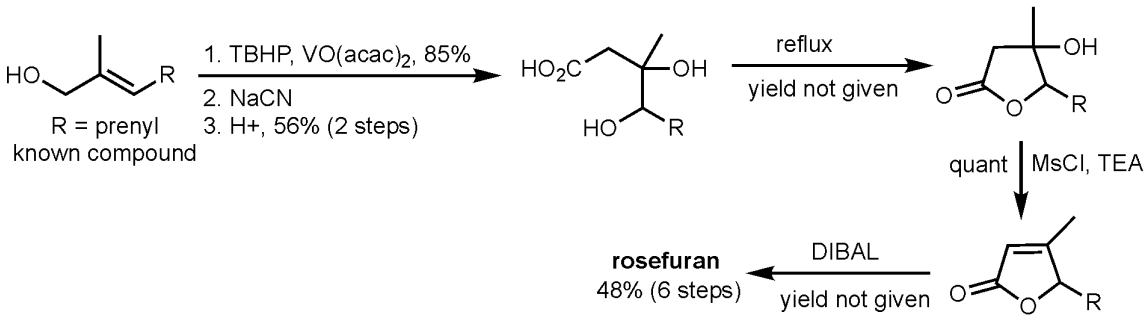

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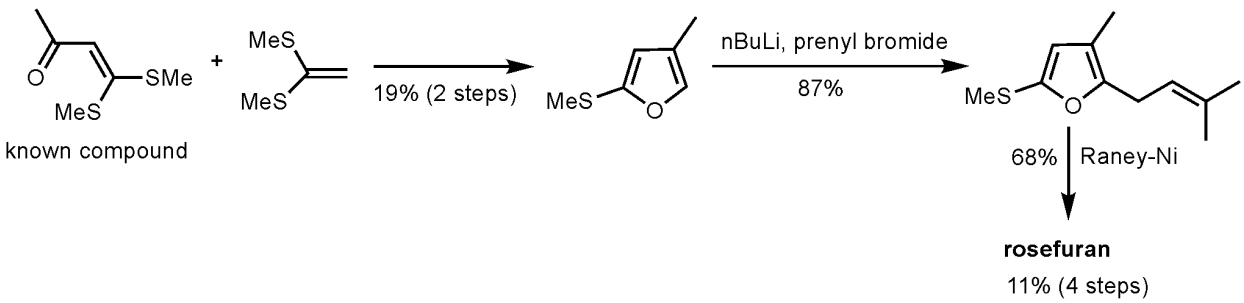

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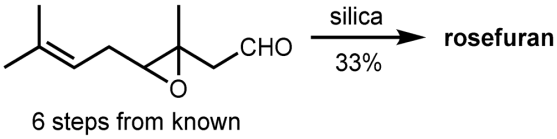

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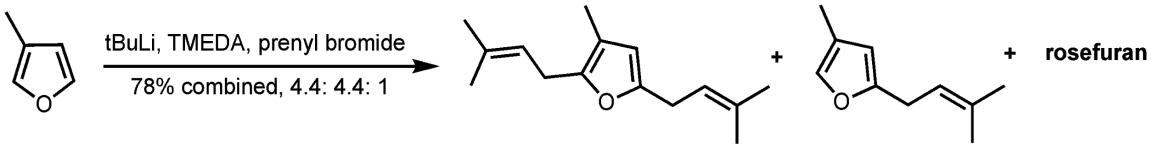

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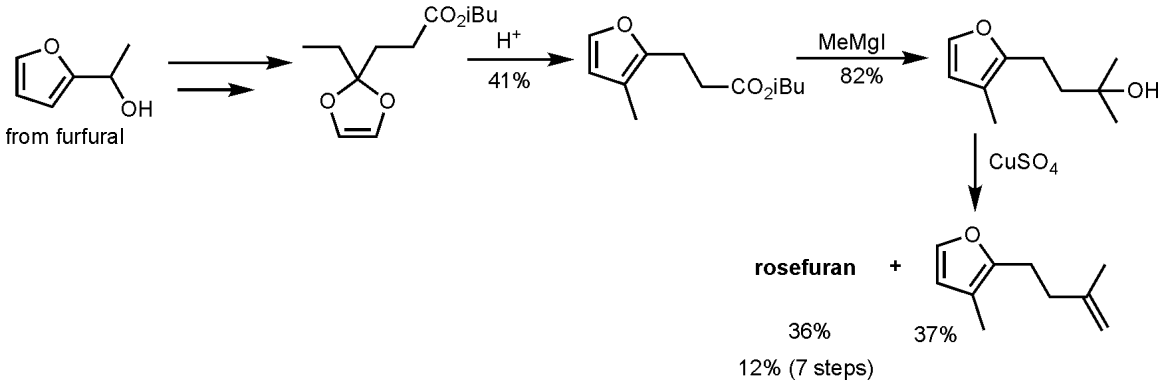

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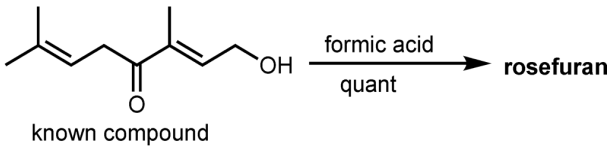

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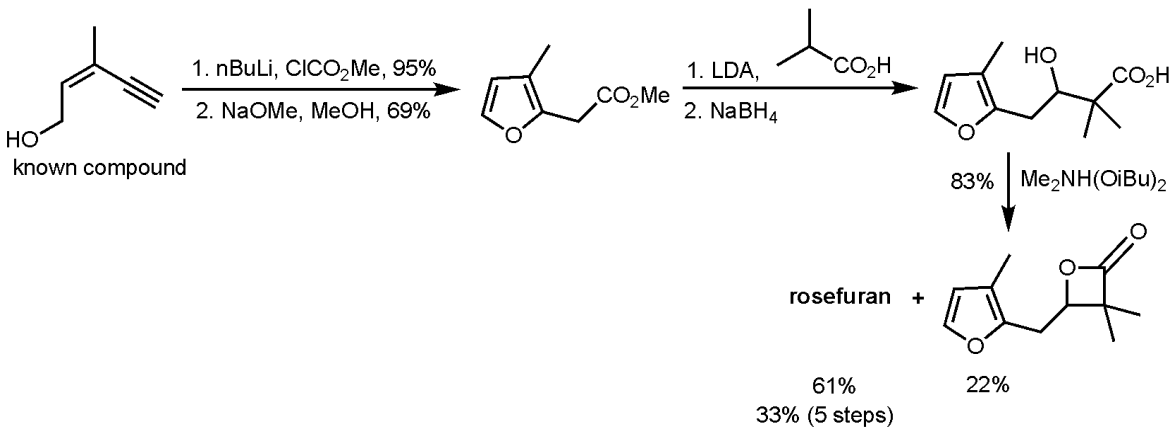

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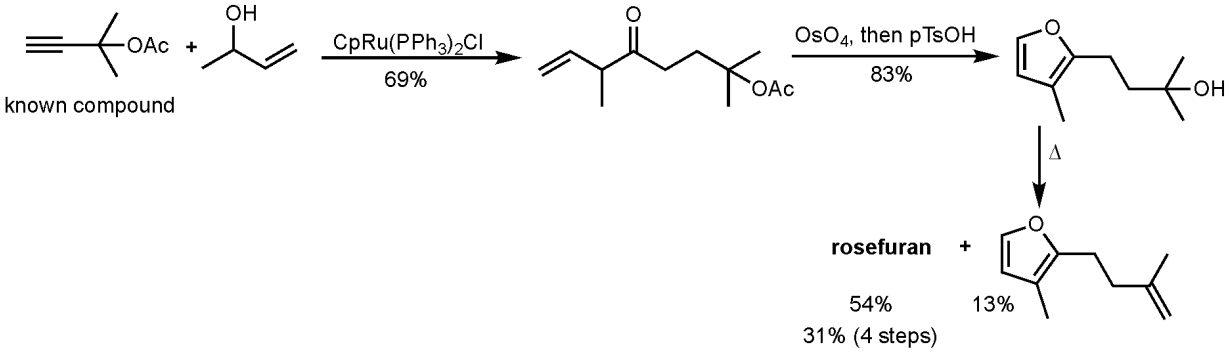

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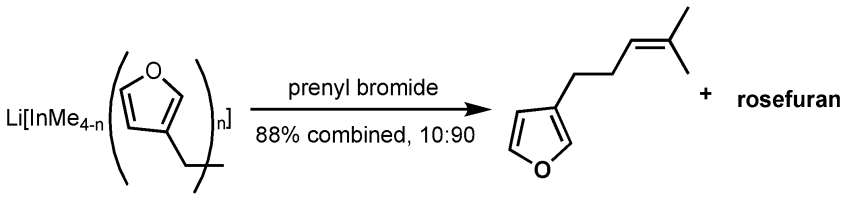

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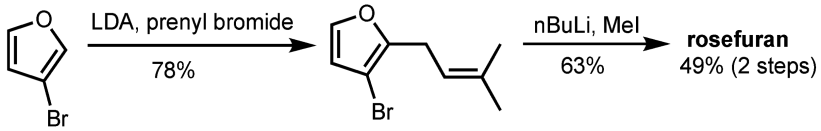

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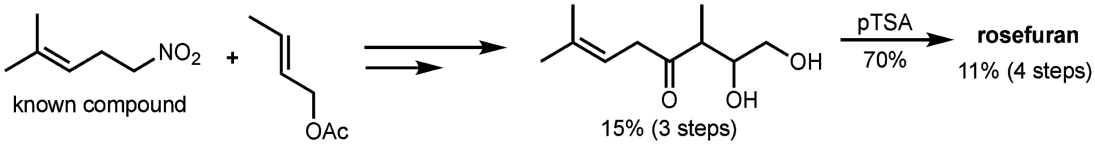

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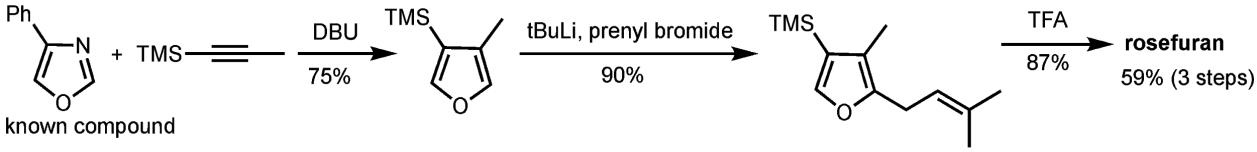

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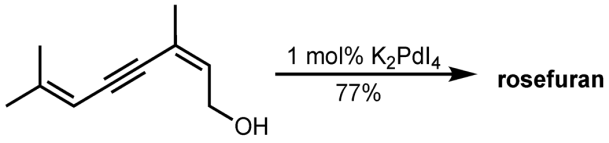

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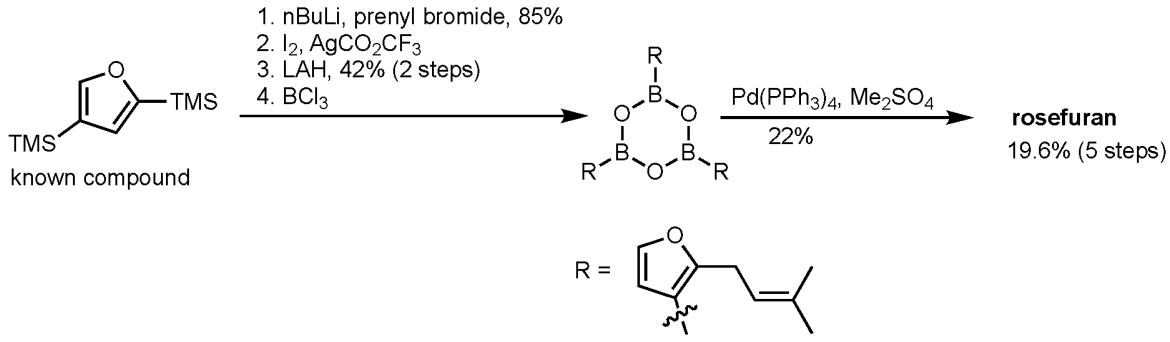

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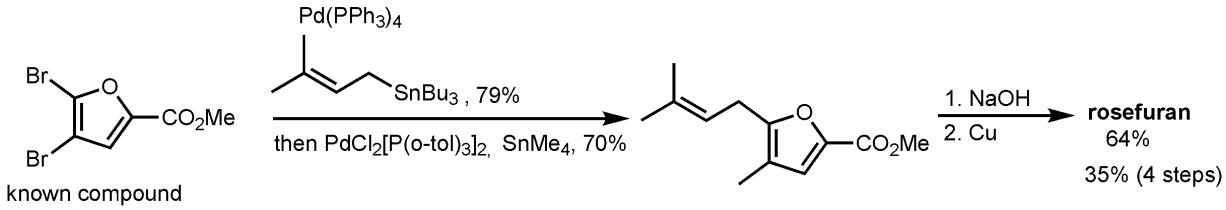

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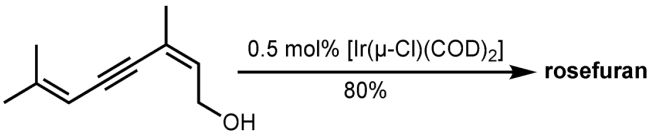

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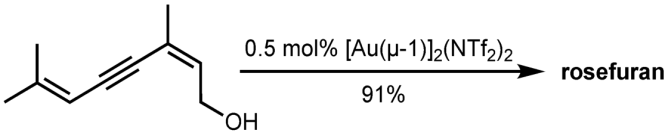

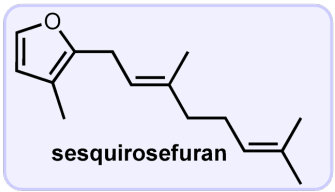

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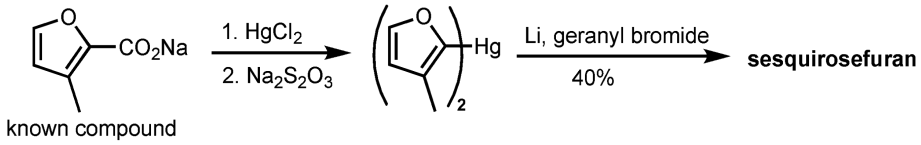

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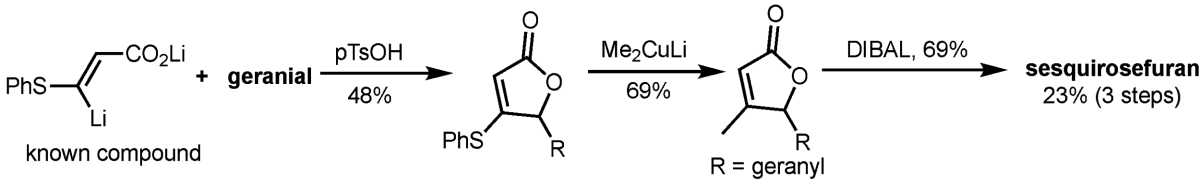

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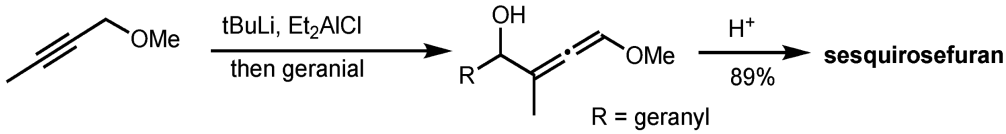

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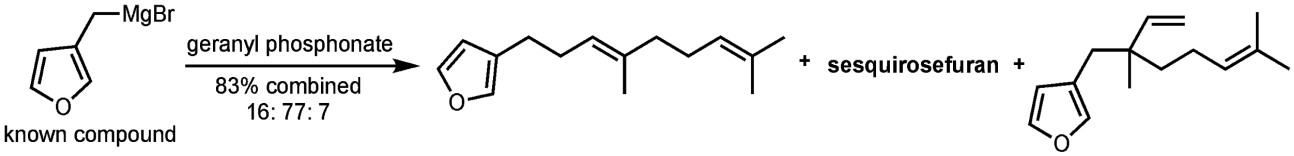

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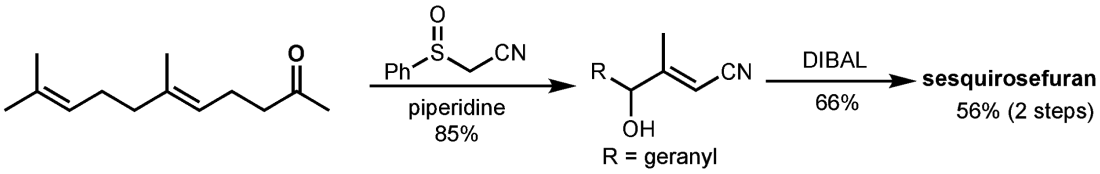

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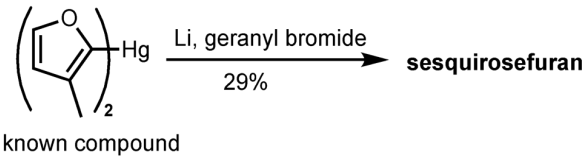

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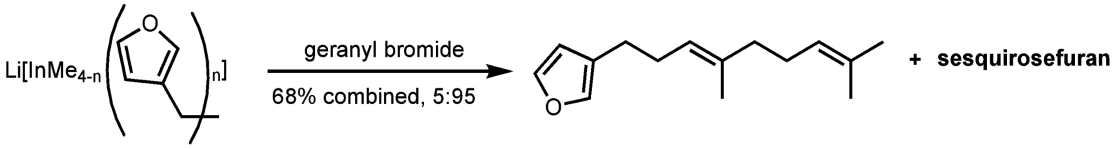

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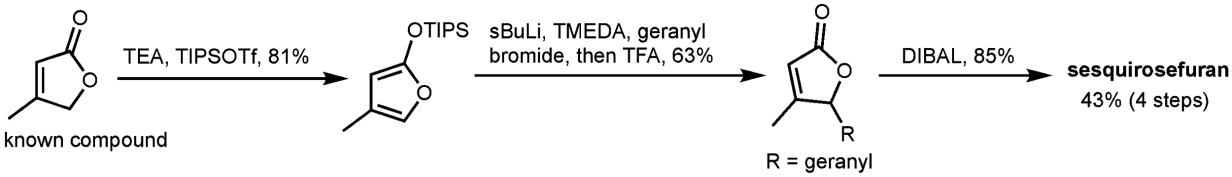

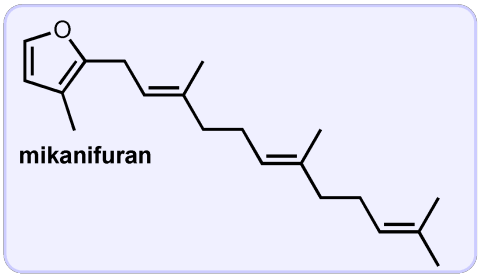

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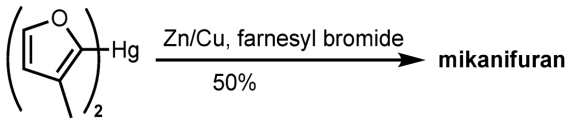

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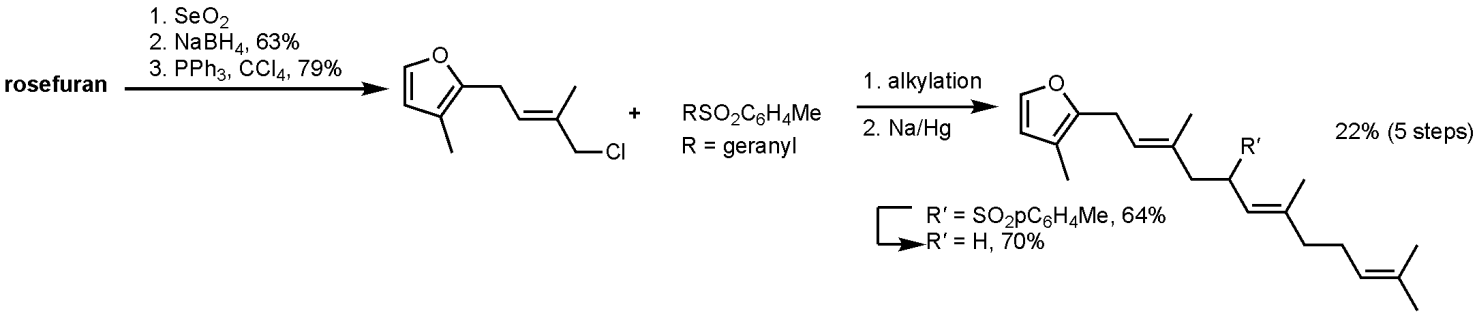
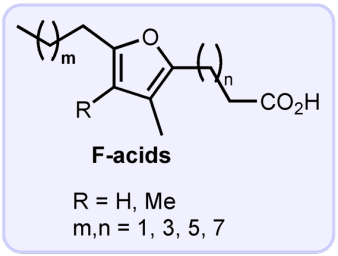
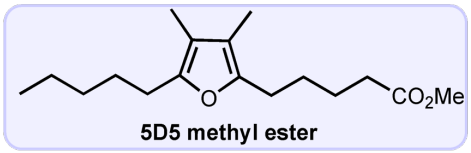


13.3. Furan Fatty Acids



No previous syntheses have been reported for the ***F-acids 3D5*** *and* ***hydromumiamicin****.*



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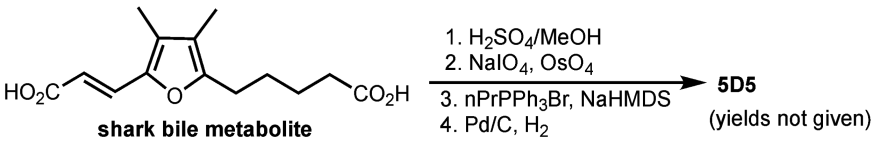

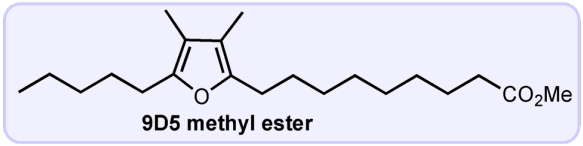

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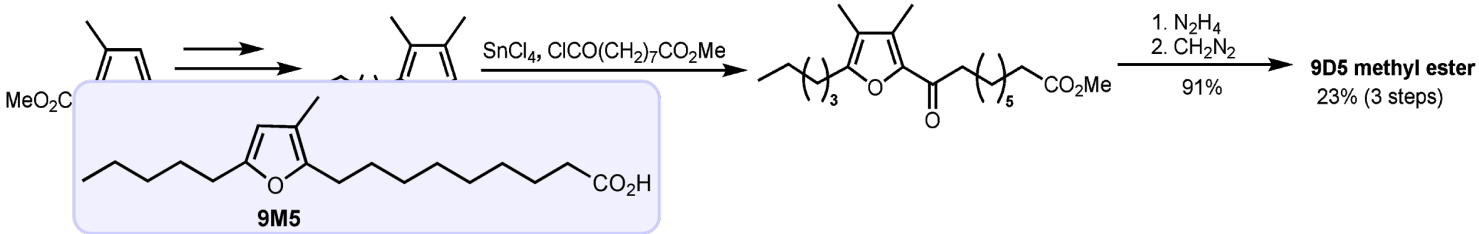

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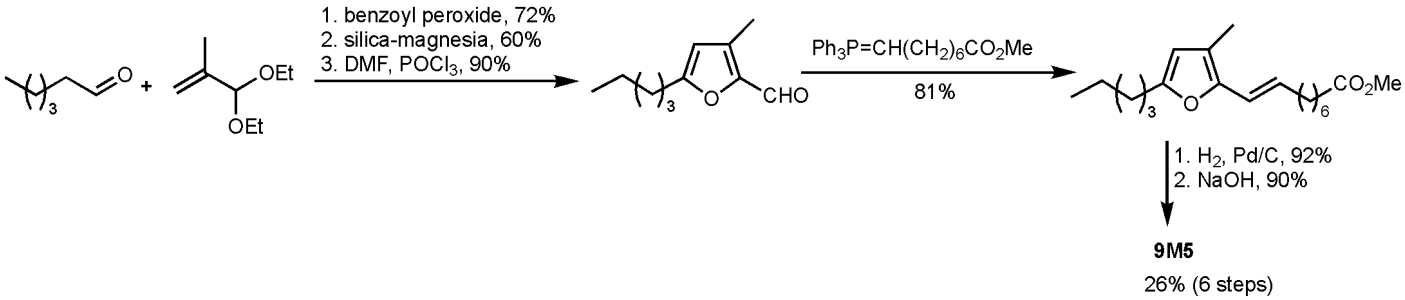

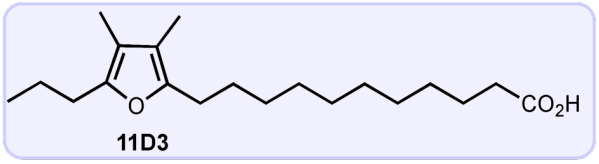

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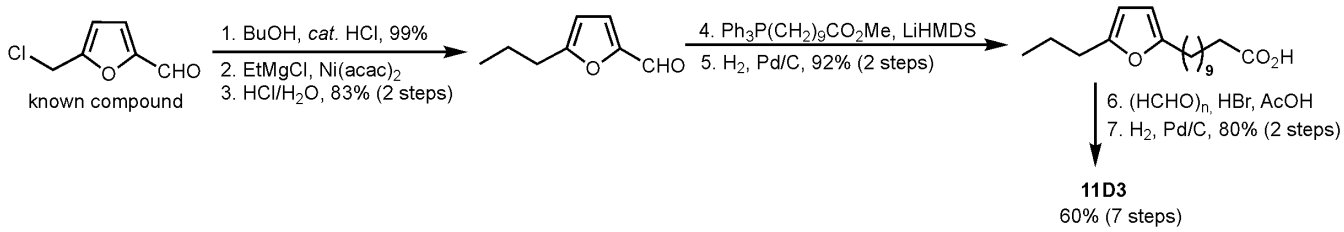

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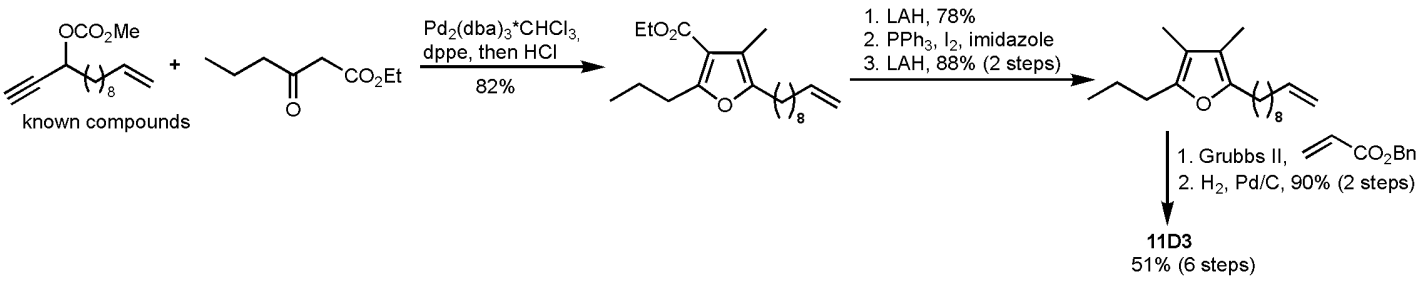
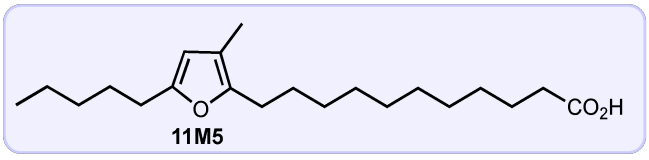
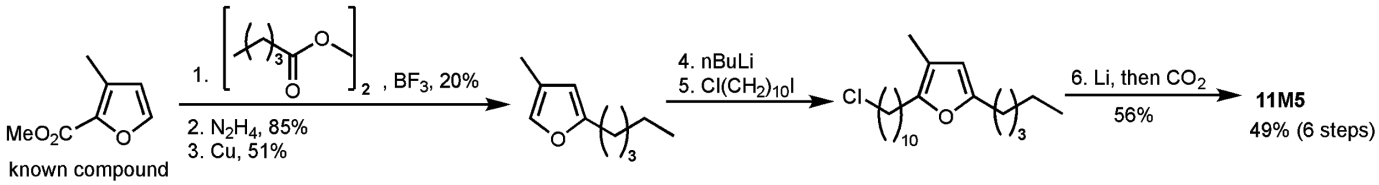
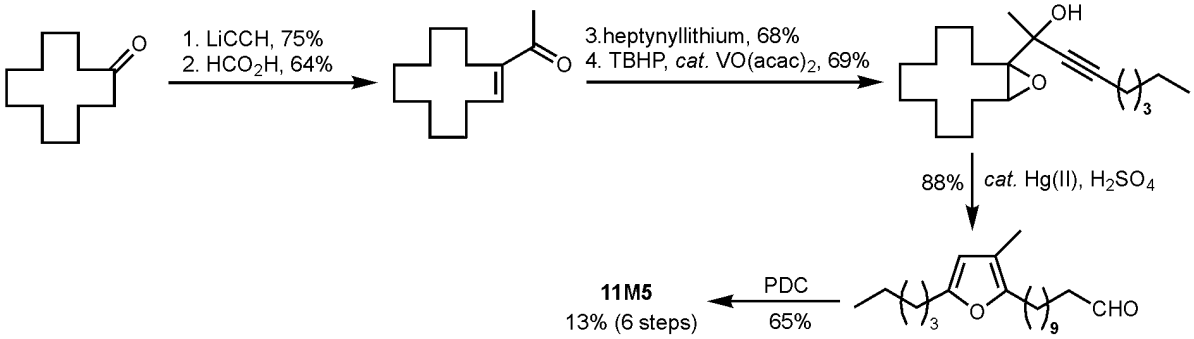




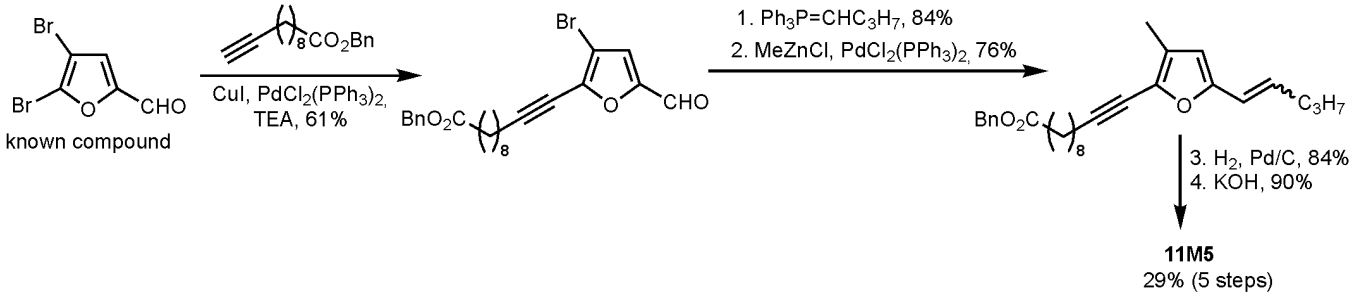
46. *J. Org. Chem.* **1979**, *44*, 3420–3424.



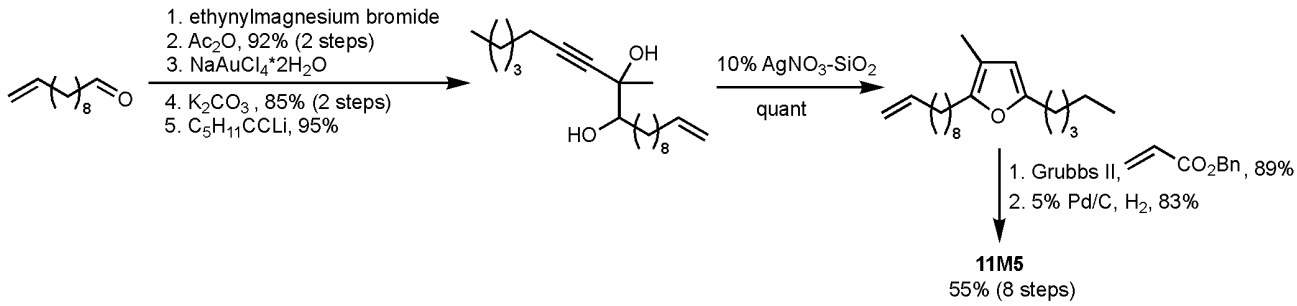
47. *Tetrahedron Lett.* **1998**, *39*, 333–334.



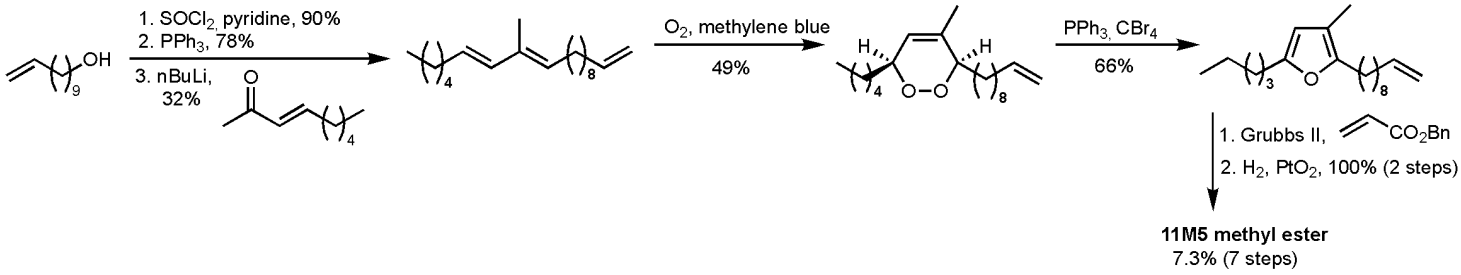
48. *Tetrahedron Lett.* **1998**, *39*, 1729–1732; *Eur. J. Org. Chem*. **1999**, 2045–2057.

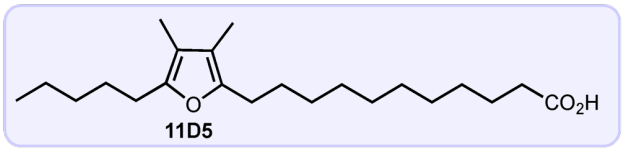


49. *Heterocycles* **2012**, *84*, 361–369; *Tetrahedron* **2015**, *71*, 7436–7444.

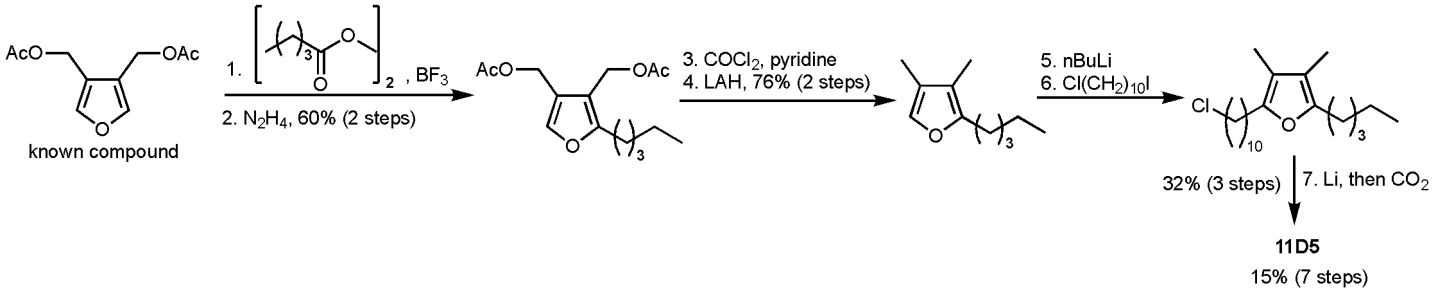


50. *Chem. Commun*. **2017**, *53*, 6327.

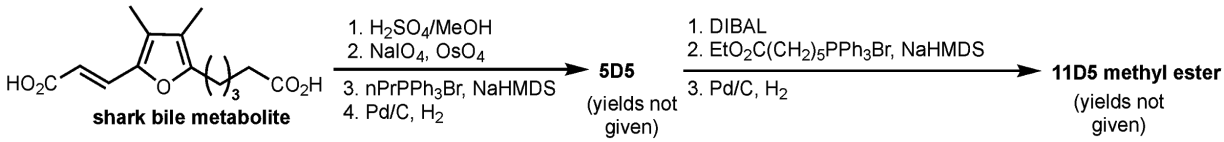




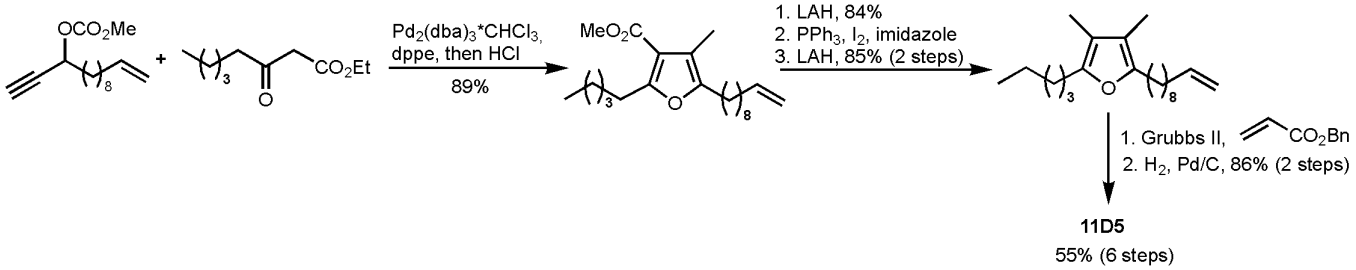
51. *J. Org. Chem.* **1979**, *44*, 3420–3424.



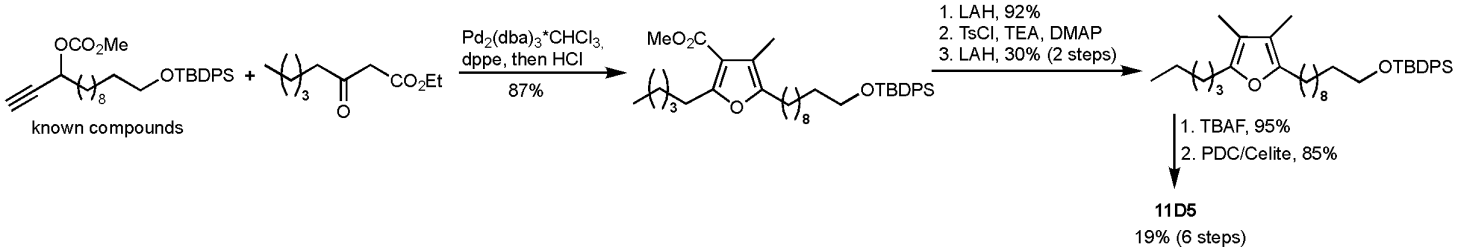
52. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 17533–17537.



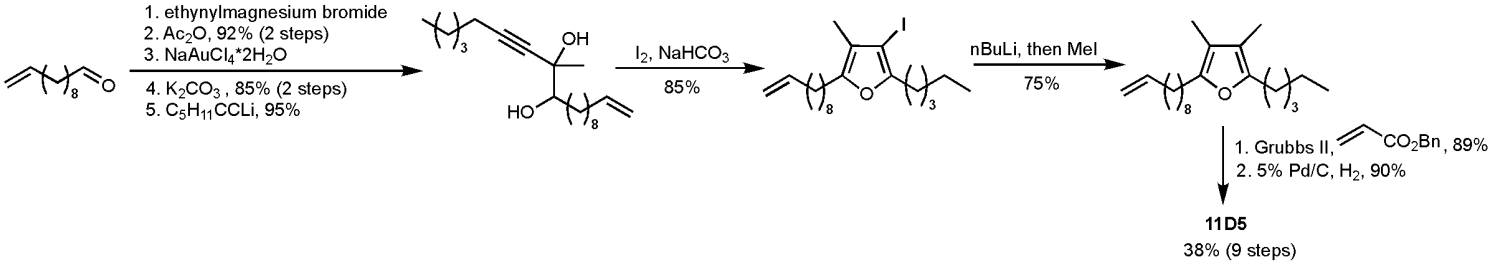
53. *Eur. J. Org. Chem.* **2020**, 2914–2922.

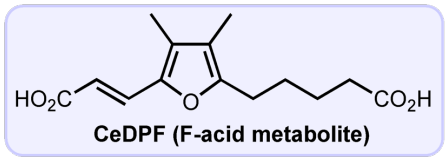


54. *Eur. J. Org. Chem.* **2020**, 2914–2922.



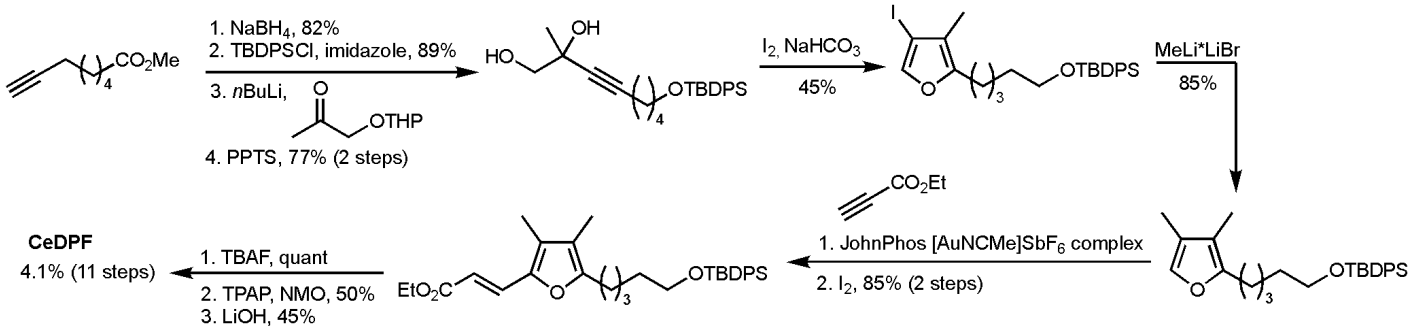
55. *Tetrahedron* **2015**, *71*, 7436–7444.





CeDPF (F-acid metabolite)

56. *Org. Lett.* **2019**, *21*, 4892–4895.



CHAPTER THREE

Application of the Vinylogous Michael–Heck Reaction to the Total Synthesis of Furanosesquiterpenes Agassizin, Pallescensins G and F, and Furanoeremophilanes

3.1. Abstract

This chapter describes the development of and application of the vinylogous Michael–Heck reaction for the total synthesis of furanosesquiterpenes, such as agassizin, pallescensins G and F, as well as furanoeremophilanes with varying oxidation patterns, including euryopsin, 6-oxoeuryopsin, 9-oxoeuryopsin, furanoeremophilane, furanoeremophilone, ligularone, and petasalbine.

Application of the Vinylogous Michael–Heck Reaction to the Total Synthesis of Polyalkyl Furan Natural Products

3.2. Intramolecular Approach to Agassizin via Enolate Alkylation

Furanoterpenes containing 2,3-fused six- or seven-membered rings occur frequently in nature. Some of these examples include menthofuran,[1] a toxin found in pennyroyal and a variety of essential oils; echinofuran,[2] and nakafuran-9,[3] furanosesquiterpenes with antibacterial and cytotoxic properties; cafestol,[4] the diterpenoid responsible for the pharmacological properties of coffee; tubipofuran[5] and agassizin,[6] furanosesquiterpenes with ichthyotoxic properties; atractylone,[7] a furanosesquiterpene exhibiting anti-inflammatory and acaricidal activity as well as cytotoxicity against various human cell lines; and 9-oxoeuryopsin,[8] a furanosesquiterpene with antiplasmodial activity (Figure 3.1).

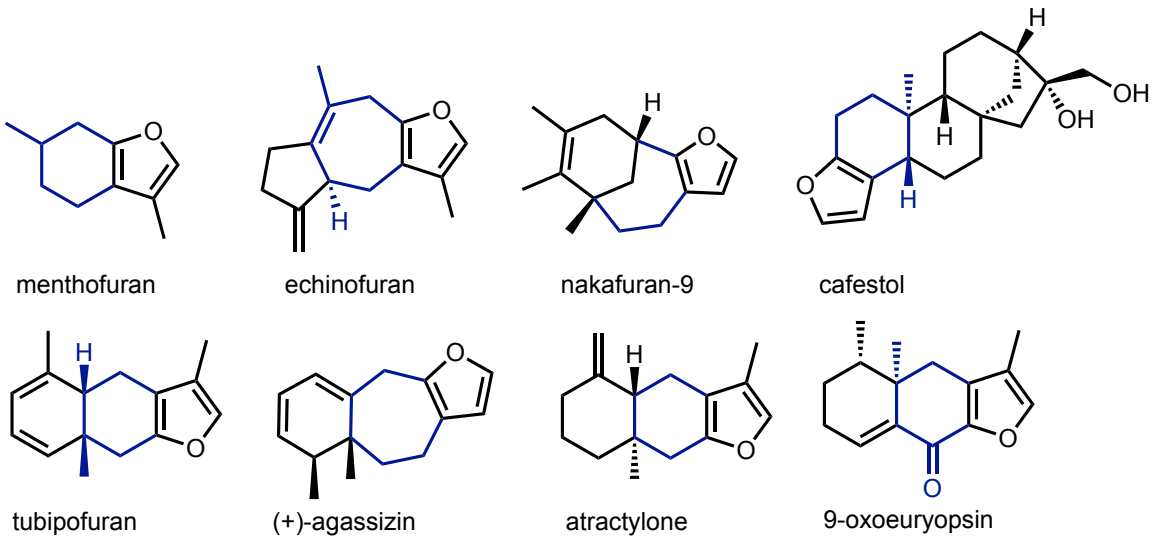
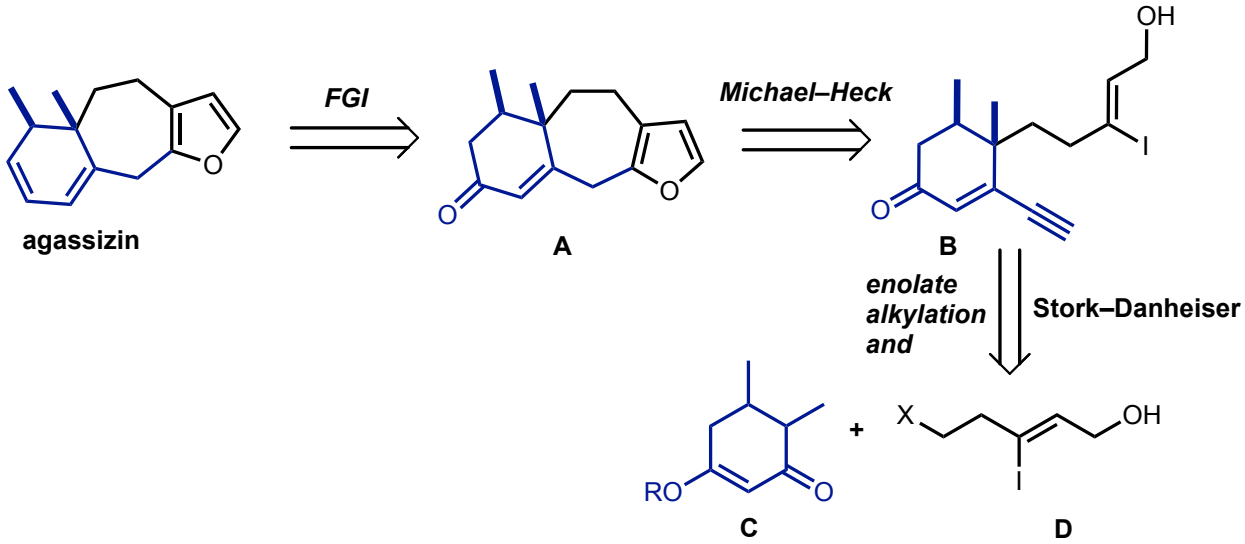


Figure 3.1. Examples of 2,3-ring fused polyalkyl furan natural products

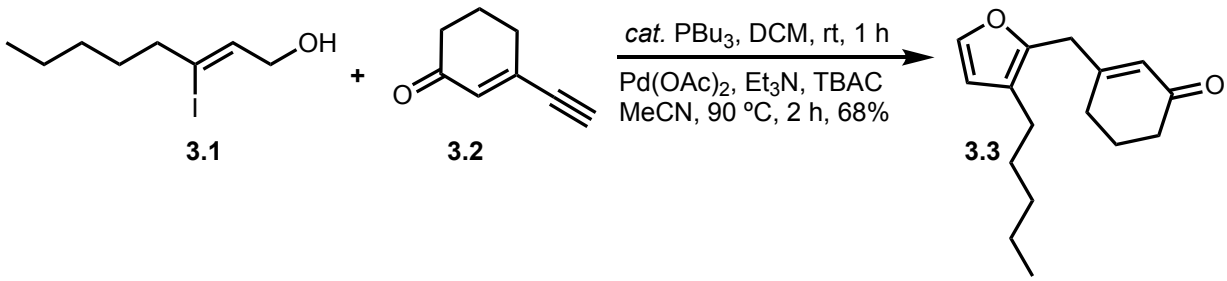
As part of our continuing interest in expanding the scope and applicability of our sequential phosphine–palladium Michael–Heck reaction for the synthesis of complex bioactive polyalkyl natural products, we sought to develop a vinylogous Michael–Heck reaction that would enable

access to furanosesquiterpenes, such as agassizin, a natural product that has never been synthesized before. Using this idea, we proposed the following retrosynthetic scheme for agassizin (Scheme 3.1). We envisioned that the cyclohexadiene ring in agassizin can be derived from the enone **A** via enol triflate formation followed by reduction, while **A** itself can be obtained via an intramolecular vinylogous Michael–Heck reaction of **B**, which is in turn prepared from vinylogous ester **C** and homoallylic halide **D**.



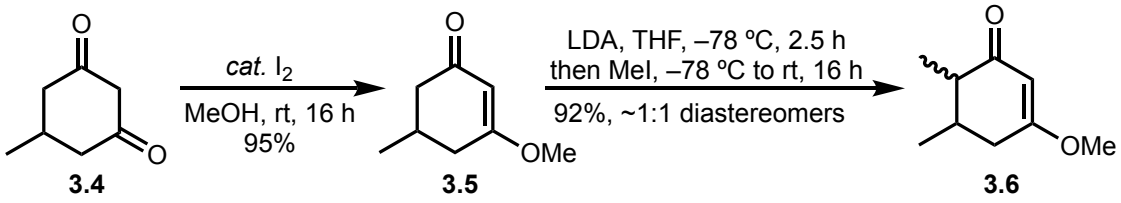
Scheme 3.1. Retrosynthetic analysis of agassizin via intramolecular Michael–Heck reaction

In order to verify the ability of cyclic enynones to undergo the key Michael–Heck reaction, a model reaction with known compounds **3.1**[9] and **3.2**[10] using the optimized Michael–Heck conditions developed previously was carried out (Scheme 3.2).



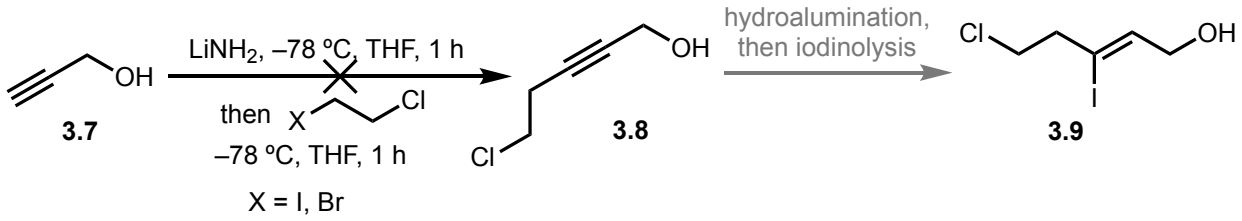
Scheme 3.2. Model vinylogous Michael–Heck reaction

To our delight, the vinylogous Michael–Heck reaction proceeded smoothly and delivered the desired furan product **3.3** in 68% isolated yield. Having established the competence of enynones such as **3.2** as Michael acceptors, we then proceeded to prepare the alkylation precursors **C** and **D**.



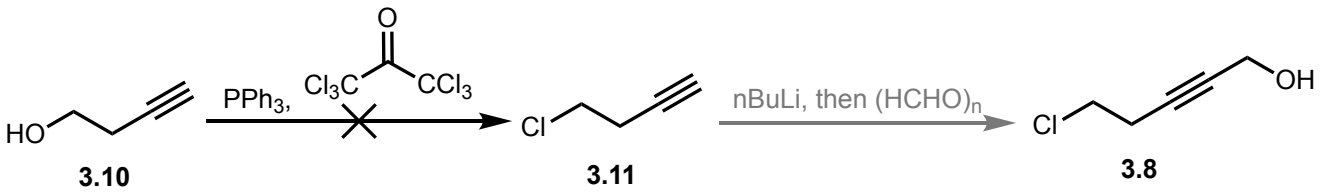
Scheme 3.3. Preparation of vinylogous ester **3.6**

Starting from commercially available **3.4**, iodine-catalyzed protection[11] of the 1,3-dione moiety as vinylogous ester **3.5** followed by methylation smoothly delivered the vinylogous ester **3.6** in 87% yield over two steps (Scheme 3.3). With plentiful amounts of vinylogous ester **3.6** in hand, we then turned our attention to the preparation of the homoallylic electrophile **D**. Initially, we envisioned that **3.9** could be accessed via hydroalumination/iodinolysis of known compound **3.8**,[12] which itself could be prepared from alkylation of propargyl alcohol **3.7**. However, alkylation of **3.7** with either 1,2-bromochloroethane or 1,2-chloroiodoethane using lithium amide were unsuccessful (Scheme 3.4).



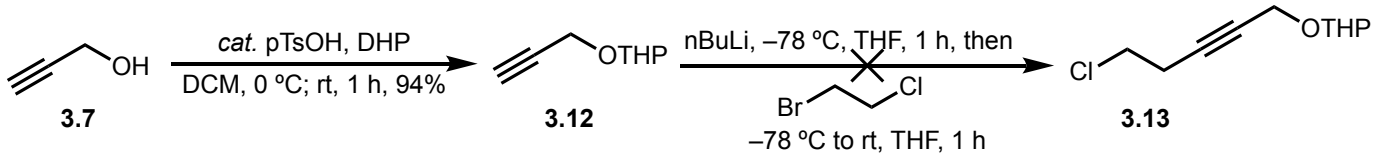
Scheme 3.4. Preparation of homoallylic chloride **3.9** via alkylation followed by hydroalumination/iodination

We then attempted to prepare **3.8** from **3.11** via hydroxymethylation (Scheme 3.5). However, attempted Appel reaction of **3.10** following literature conditions[13] for the preparation of **3.11** resulted in rapid decomposition.



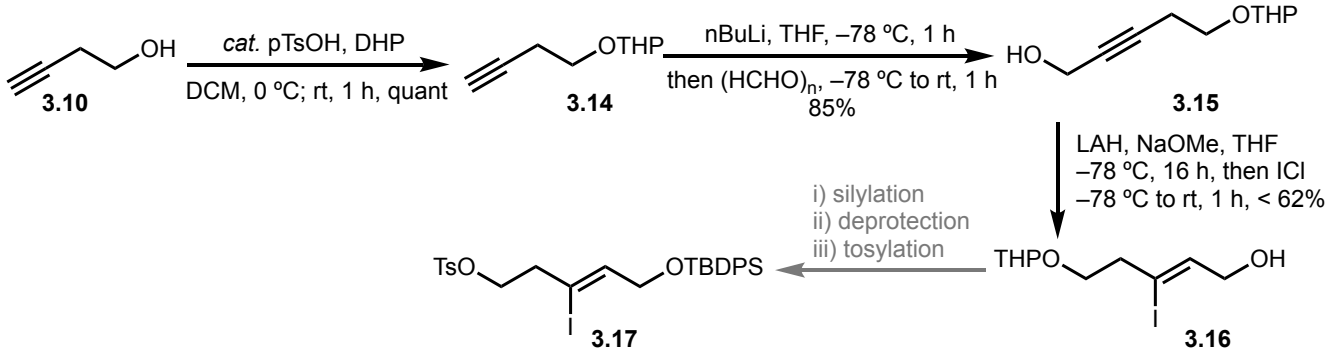
Scheme 3.5. Preparation of homopropargylic chloride **3.8** via Appel reaction followed by hydroxymethylation

Attempts to alkylate **3.12** with 1,2-bromochloroethane also proved unfruitful (Scheme 3.6).



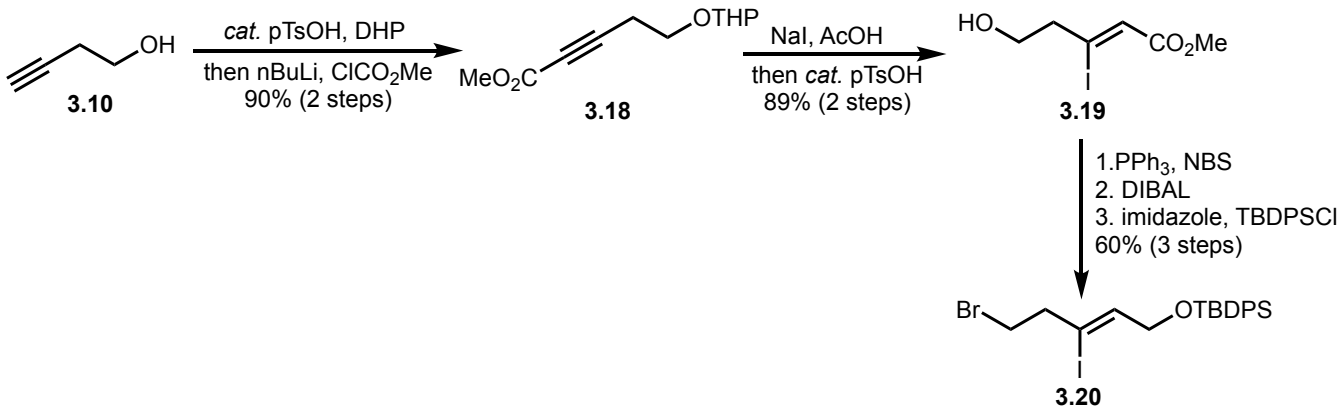
Scheme 3.6. Preparation of homopropargylic chloride **3.13** via alkylation

In an alternative approach, we attempted to directly carry out hydroalumination/iodinolysis on known compound **3.15**,[14] which could then be transformed to the corresponding homoallylic tosylate **3.17** via a sequence of silylation of the allylic alcohol, THP deprotection and tosylation of **3.16**.[15]



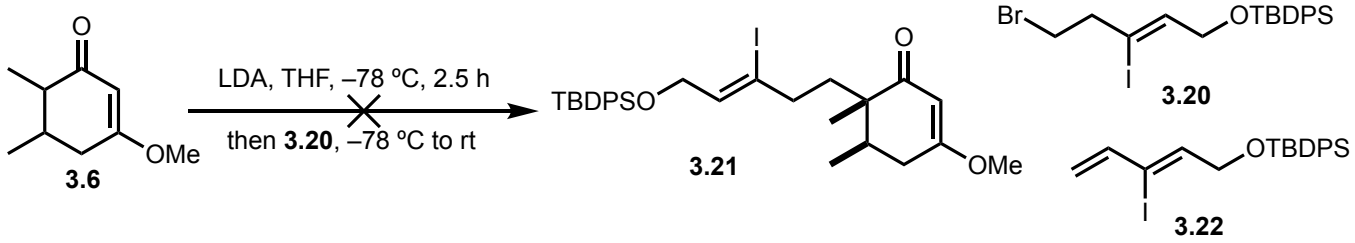
Scheme 3.7. Preparation of homoallylic alcohol **3.16** via hydroalumination/iodinolysis

Unfortunately, **3.16** proved very difficult to purify (Scheme 3.7). Therefore, we turned to a more reliable hydroiodination/reduction approach (Scheme 3.8).



Scheme 3.8. Preparation of homoallylic bromide **3.20** via hydroiodination/reduction/Appel reaction

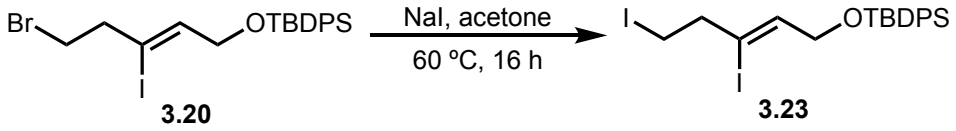
In this approach, hydroiodination of known compound **3.18**[16] followed by deprotection of the THP group smoothly furnished intermediate **3.19** in good yield. This was then transformed to the desired homoallylic bromide **3.20** in 60% over three steps using a sequence of Appel reaction, DIBAL reduction of the allylic ester followed by silylation of alcohol **3.19**. Having secured a robust route to the prerequisite alkylation precursor, we then proceeded to prepare **3.21** using enolate alkylation of **3.6** (Scheme 3.9).



Scheme 3.9. Enolate alkylation of vinylogous ester **3.6** by homoallylic bromide **3.20**

However, alkylation of **3.6** with homoallylic bromide **3.20** produced only the E2-elimination product **3.22**, a result that was unchanged by change in reaction time, temperature or amount of **3.20**. Suspecting that as an alkylating agent, the homoallylic bromide **3.20** might not be reactive

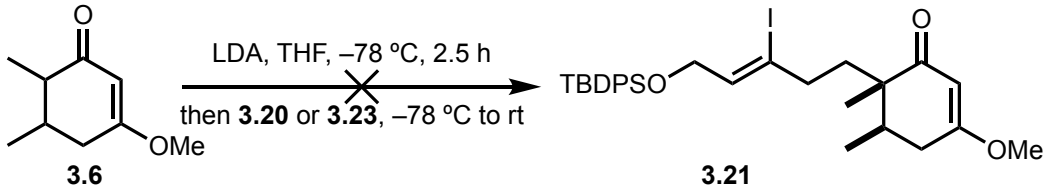
enough to outcompete E2-elimination to form **3.22**, we attempted to increase the reactivity of **3.20** by converting it to homoallylic iodide **3.23** using the Finkelstein reaction (Scheme 3.10).



3.20 **3.23**

Scheme 3.10. Preparation of homoallylic iodide **3.23** via Finkelstein reaction of **3.20**

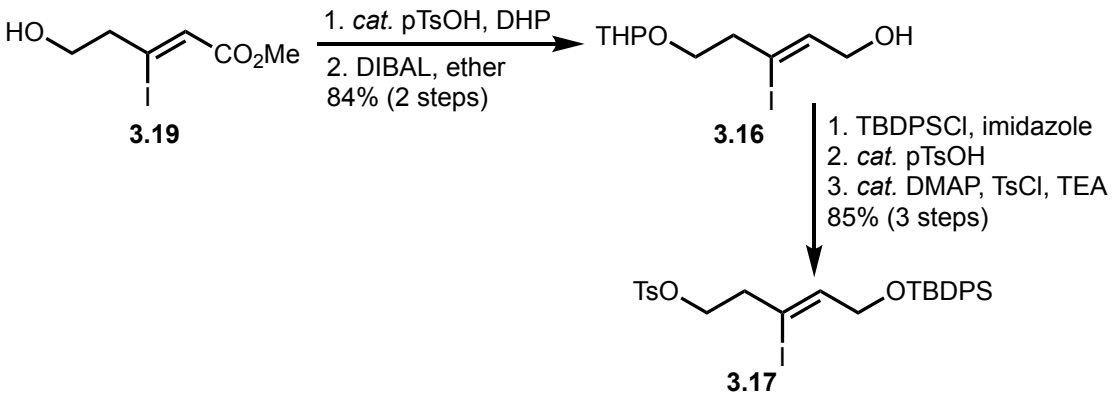
The homoallylic iodide thus formed was used directly in the alkylation of **3.6**. Disappointingly, E2-elimination of either **3.20** or **3.23** still prevailed over alkylation to form **3.21**; the same result was observed regardless of change in temperature, reaction time, concentration, use of other bases or use of additives such as HMPA (Scheme 3.11).



3.6 **3.21**

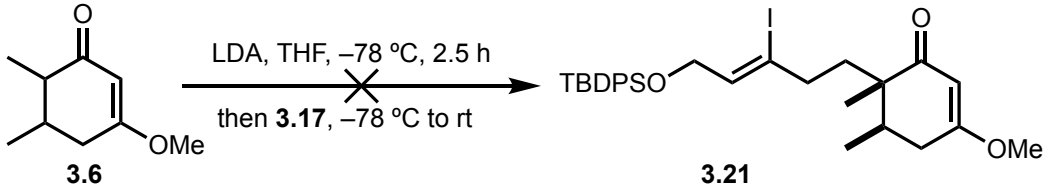
Scheme 3.11. Enolate alkylation of vinylogous ester **3.6** by homoallylic halides **3.20** and **3.23**

Further attempts to effect the enolate alkylation of vinylogous ester **3.6** by homoallylic electrophiles were also carried out with tosylate **3.17** (Scheme 3.12). Therefore, THP protection of **3.19** followed by DIBAL reduction produced known compound **3.16**,[15] which was then converted to homoallylic tosylate **3.17** using a sequence of TBDPS protection, THP deprotection and tosylation in 85% over three steps (Scheme 3.12)



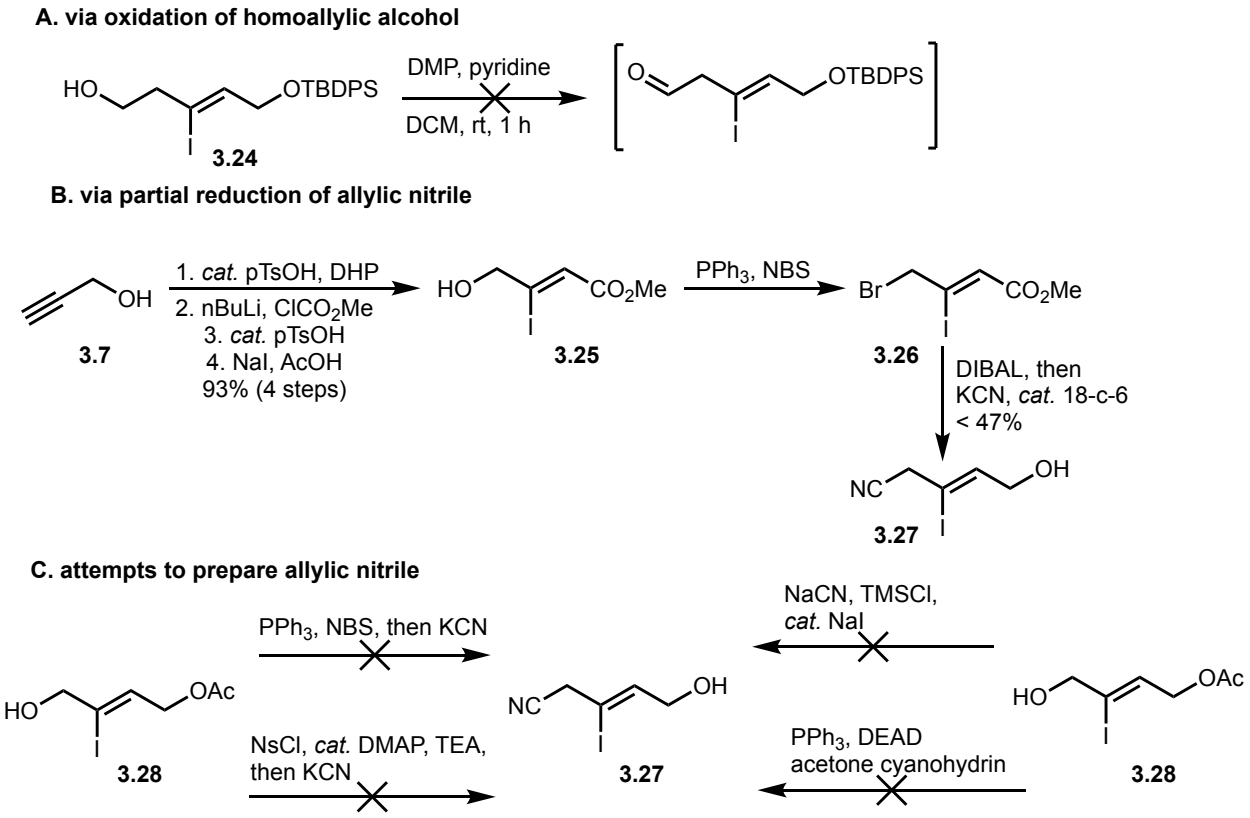
Scheme 3.12. Preparation of homoallylic tosylate **3.17**

Disappointingly, attempted alkylation of vinylogous ester **3.6** with **3.17** still yielded the E2-elimination product **3.22** as the sole product (Scheme 3.13).



Scheme 3.13. Enolate alkylation of vinylogous ester **3.6** by homoallylic tosylate **3.17**

Due to the strong propensity of the homoallylic electrophiles **3.20, 3.23** and **3.17** to undergo E2-elimination, we then attempted an aldol approach (Scheme 3.14A).



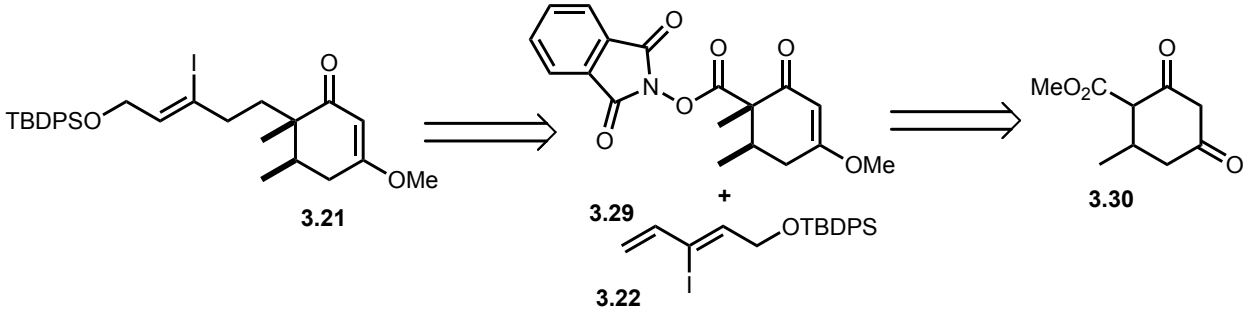
Scheme 3.14. Attempted preparation of allylic aldehyde or nitrile

However, attempts to prepare homoallylic aldehyde via oxidation of the homoallylic alcohol **3.24** was unsuccessful and resulted in rapid decomposition (Scheme 3.14A). We then attempted to prepare the aldehyde from the partial reduction of the allylic nitrile **3.27** (Scheme 3.14B). Therefore, known allylic alcohol **3.25**[17] was prepared in 93% over four steps using a sequence of THP protection, alkoxycarbonylation, deprotection and hydroiodination. This was then transformed to known allylic bromide **3.26**,[18] which was reduced and treated with KCN under phase-transfer conditions to produce **3.27**, which proved to be very difficult to purify. Therefore, we looked into different routes for preparing allylic nitrile **3.27**, including Appel reaction of allylic alcohol **3.28** or nosylate and direct conversion of the alcohol functionality to a nitrile group using NaCN/TMSCl/NaI[19] or PPh_3/DEAD/acetone cyanohydrin[20] (Scheme 3.14C). Unfortunately, none of these routes provided the desired allylic nitrile **3.27**. Having shown that neither the enolate

alkylation route nor the aldol route were viable approaches for the preparation of Michael–Heck precursor **3.21**, we looked into alternative ways for its preparation.

3.3. Intramolecular Approach to Agassizin via Radical Addition

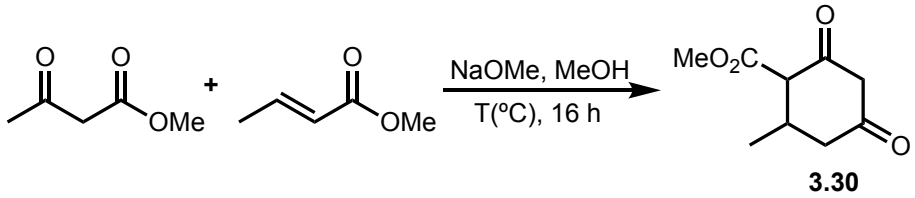
Since the propensity for the homoallylic electrophiles **3.17**, **3.20** and **3.23** to undergo E2-elimination to form diene **3.22** has rendered the enolate alkylation route impractical, a new approach to **3.21** that took advantage of this undesired reactivity was devised:



Scheme 3.15. Radical addition approach to vinylogous ester **3.21**

In this approach, we envisioned that the known dione **3.30**,[21] which can be prepared using a Michael–Claisen condensation between commercially available methyl crotonate and methyl acetatoacetate, could be transformed to N-hydroxymethylphthalimide **3.29**, which would then generate a carbon-centered radical that would add onto diene **3.22** to furnish **3.21**. To this end, we commenced with the preparation of dione **3.30** (Table 3.1):

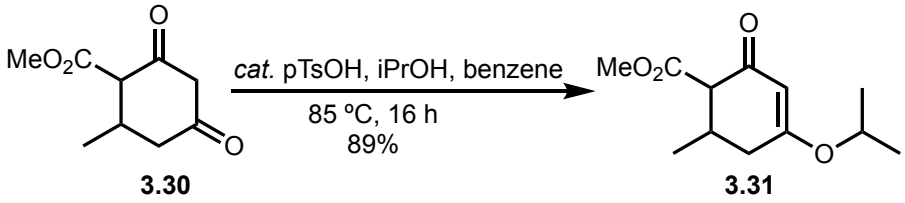
Table 3.1. Optimization of the Michael–Claisen condensation



3.30

Entry	T (ºC)	Concentration (M)	Yield (%)
1	70–75	0.67	19
2	70–75	1.3	74
3	70–75	2.	78
4	70–75	3.8	70
5	80–85	3.8	87

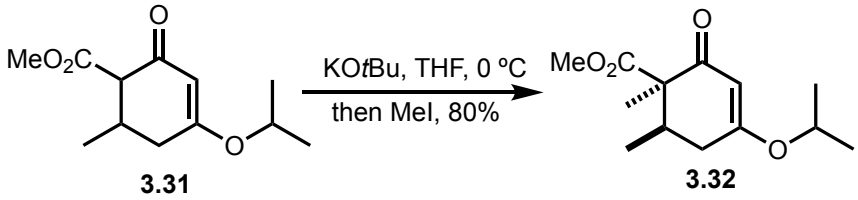
As can be seen from the table above, high concentrations are essential for satisfactory yield. Next, the dione moiety in **3.30** was protected as known vinylogous ester **3.31**.[22] In this case, isopropanol was used to ensure regioselective formation of the desired isomer (Scheme 3.16):



3.30 **3.31**

Scheme 3.16. Preparation of vinylogous ester **3.31**

Vinylogous ester **3.31** was then alkylated with MeI to furnish the precursor for the redox-active ester **3.29**.While the alkylation using K_2CO_3 under phase transfer conditions were unsuccessful, use of KO*t*Bu furnished the vinylogous ester **3.32** in good yield as a single *trans* diastereomer (Scheme 3.17).

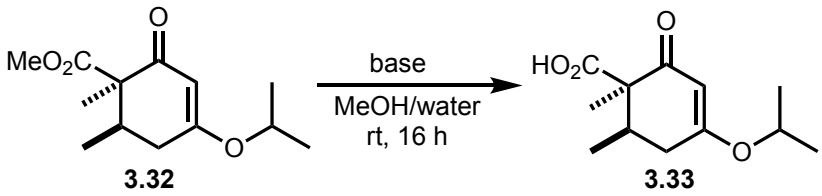


3.31 **3.32**

Scheme 3.17. Methylation of vinylogous ester **3.31**

With β-ketoester **3.32** in hand, all that remained was ester hydrolysis and conversion of the β-ketoacid to the redox-active ester **3.29**. To our surprise, attempted ester hydrolysis under basic conditions proved problematic, leading either to deprotection to form the corresponding dione or decomposition (Table 3.3). Attempts to hydrolyze the ester of the dione derived from **3.32** resulted in decomposition. Given the instability of this compound towards both acids and bases, we reasoned that use of a benzyl ester would provide a way of conversion to the corresponding acid undergo neutral conditions via hydrogenolysis.

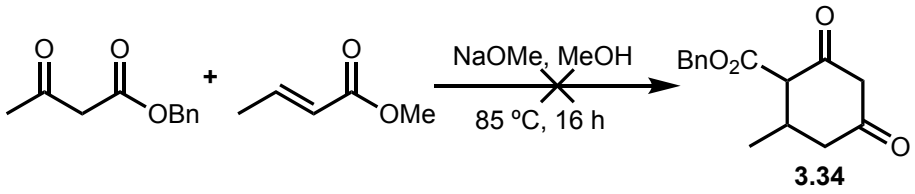
Table 3.2. Attempts to hydrolyze the β-ketoester **3.32**



3.32 **3.33**

Entry	Base	Result
1	KOH	SM only
2	LiOH	dione, 33%
3	K_2CO_3	SM after rt/16 h, dione after 50 ºC/16 h

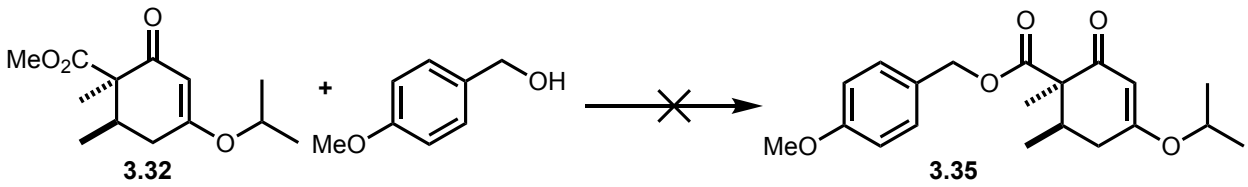
To this end, we attempted to prepare the corresponding benzyl ester analog by performing the Michael–Claisen condensation using benzyl acetotacetate. However, use of the optimized conditions established previously produced only the transesterification product (methyl ester) while use of NaOBn[23] produced a complex mixture (Scheme 3.18).



3.34

Scheme 3.18. Attempted preparation of dione **3.34**

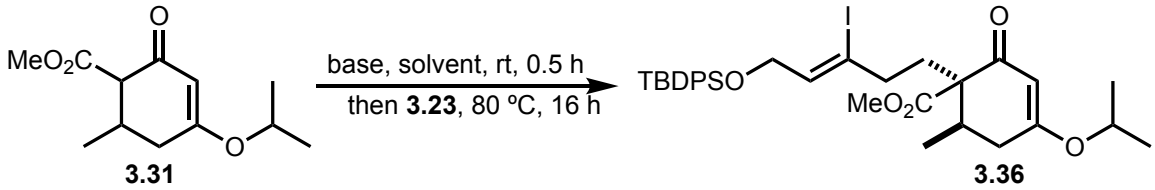
We then attempted to directly do transesterification on vinylogous ester **3.32** with 4-methoxybenzyl alcohol to obtain **3.35**. However, neither the use of neat conditions and refluxing temperature[24a] or the use catalytic amounts of DMAP[24b] were successful (Scheme 3.19):



Scheme 3.19. Attempted transesterification of **3.35**

We then hypothesized that since alkylation of β-ketoester **3.34** with **3.23** could be carried out with a weaker base, it might be possible to favor enolate alkylation over E2-elimination of **3.23** (Table 3.3):

Table 3.3. Enolate alkylation of β-ketoester **3.31** by Homoallylic Iodide **3.23**



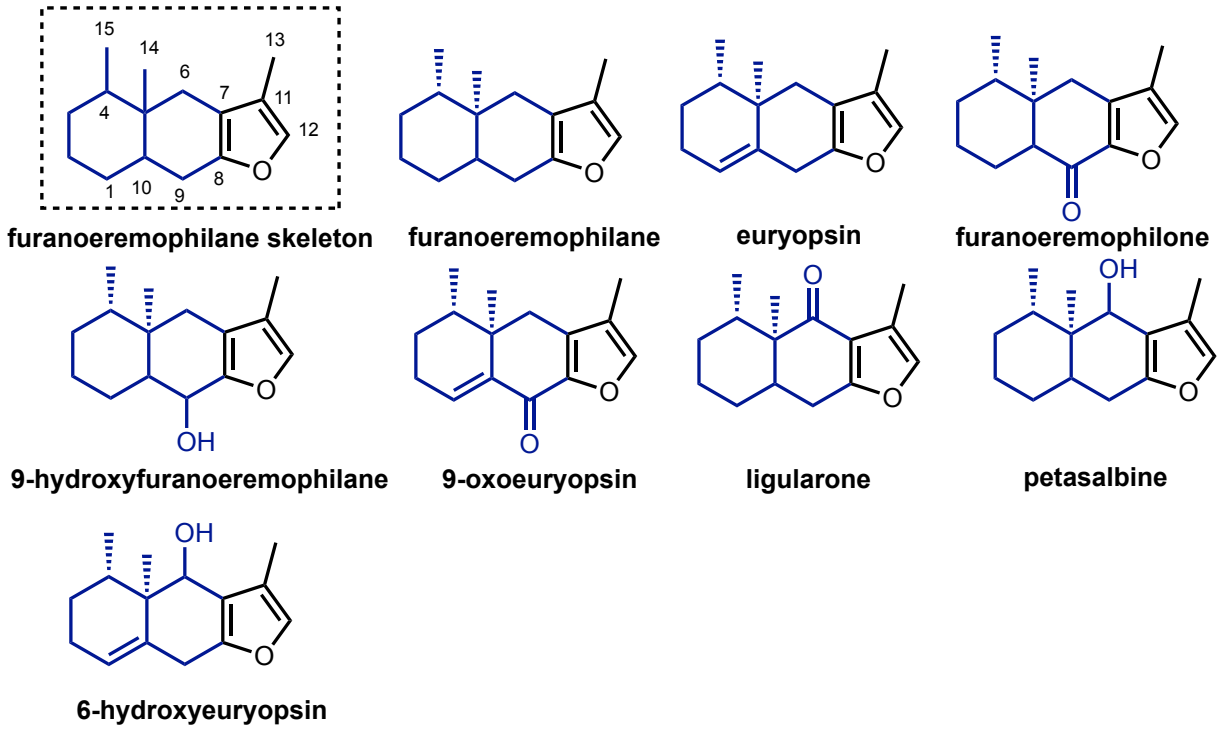
Entry	Base	Result
1	NaOMe, MeOH	E2 only
2	NaOMe, MeOH, rt, 16 h	SM only
3	K_2CO_3, DMF	E2 only
4	K_2CO_3, DMF, rt, 16 h	SM only

However, even the use of weak inorganic bases such as K_2CO_3 produced E2-elimination as the only product. Since it has become abundantly clear that **3.23** is not a viable substrate for enolate alkylation and that the redox-active ester **3.29** would not be trivial to prepare, we decided to prepare a different natural product target that uses an allylic rather than homoallylic alkylating agent in order to establish the feasibility of the key intramolecular vinylogous Michael–Heck reaction.

3.4. Intramolecular Approach to Furanoeremophilanes via Enolate Alkylation

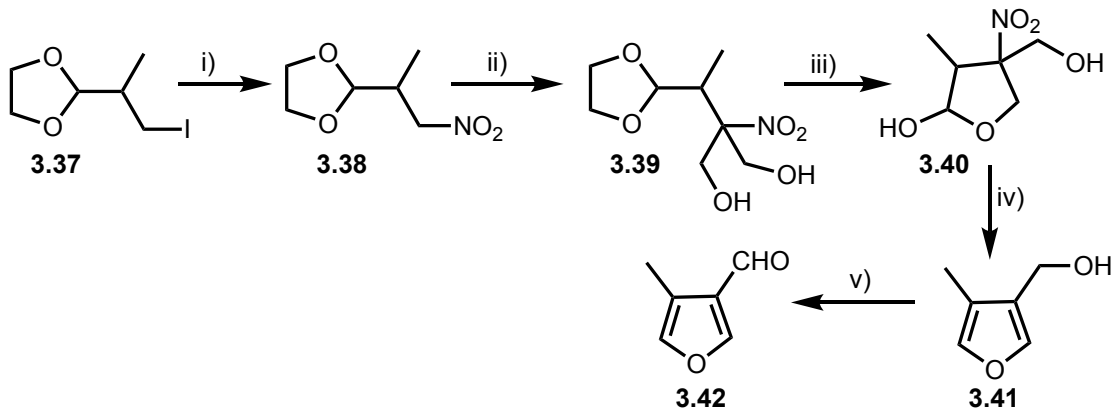
The furanoeremophilanes are a structurally diverse class of sesquiterpenes that are characterized by a linearly fused 6/6/4 tricyclic system with methyl groups at C4, C5 and C11 as well as various oxygenation patterns at C3, C6, and C9.[25] Derived from plants of the genus *Senecio*, *Euryops, Ligularia* and *Petasites*, these furanosesquiterpenes are reported to have a wide range of desirable biological properties such as cytotoxicity,[26a] antifungal,[26b] antifeedant,[26c] phytotoxic,[26d] anti-inflammatory,[26e] antibacterial,[26f] antihyperglycemic[26g] and hepatotoxic[26h,i] activities (Fig 3.2). While no previous syntheses have been reported for furanoeremophilane, furanoeremophilone, euryopsin and 9-hydroxyeuryopsin, total syntheses 9-oxoeuryopsin, ligularone, petasalbine and 6-hydroxyeuryopsin have been reported.

Figure 3.2. Examples of furanoeremophilanes



3.4.1. Silva's Synthesis of (+)-9-Oxoeuryopsin

In 2013, Silva and coworkers reported the first enantioselective synthesis[10c] of (+)-9-oxoeuryopsin using a key $Cu(OTf)_2$-catalyzed tandem asymmetric conjugate addition of $AlMe_3$ to 2-methyl-2-cyclohexen-1-one with the Feringa (*S, R, R*)-phosphoramidite binaphthol ligand, followed by aldol condensation of the resulting aluminum enolate with 4-methyl-3-furaldehyde. Functional group transformation, followed by Friedel–Crafts acylation then closed the central six-membered ring to deliver (+)-9-oxoeuryopsin. Their synthesis commenced with the preparation of the required furaldehyde precursor **3.42** from known iodoketal **3.37**, which was converted to the corresponding nitroketal **3.38**, which then undergoes double condensation with formalin to give diol **3.39**. Treatment of **3.39** with acidic conditions then induced an intramolecular cyclization to form tetrahydrofuran **3.40**, which then undergoes aromative elimination to form furanmethanol **3.41**, which is then oxidized to form the desired furaldehyde **3.42** (Scheme 3.20).

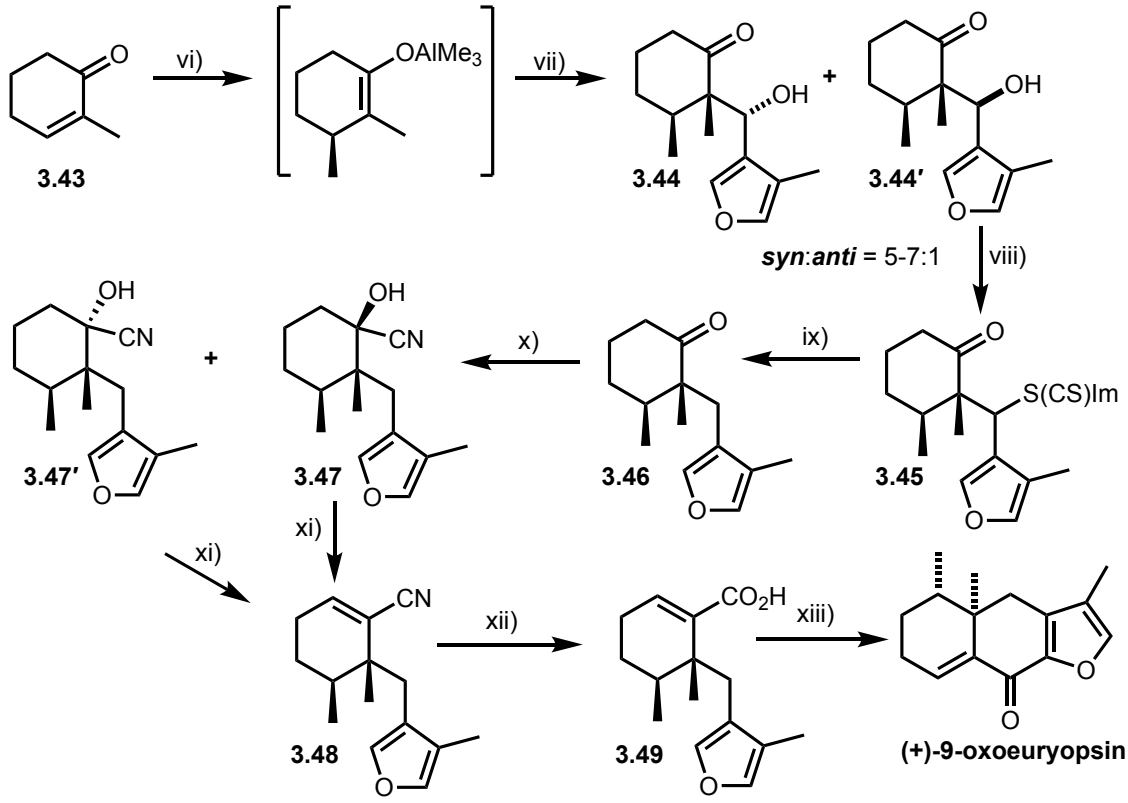


i) phloroglucinol, $NaNO_2$, DMSO, rt, 24 h, 82%. ii) formalin, $Ba(OH)_2$, rt, 2 h, 100%. iii) HCl, acetone, reflux, 27 h, 71%. iv) DABCO, DME, reflux, 24 h, 82%. v) MnO_2, DCM, rt, 24 h, 70–72%.

Scheme 3.20. Preparation of furan **3.42**

With the requisite furaldehyde **3.42** in hand, conjugate addition of $AlMe_3$ to enone **3.43** in the presence of $Cu(OTf)_2$ and the Feringa ligand followed by quenching with furaldehyde **3.42**

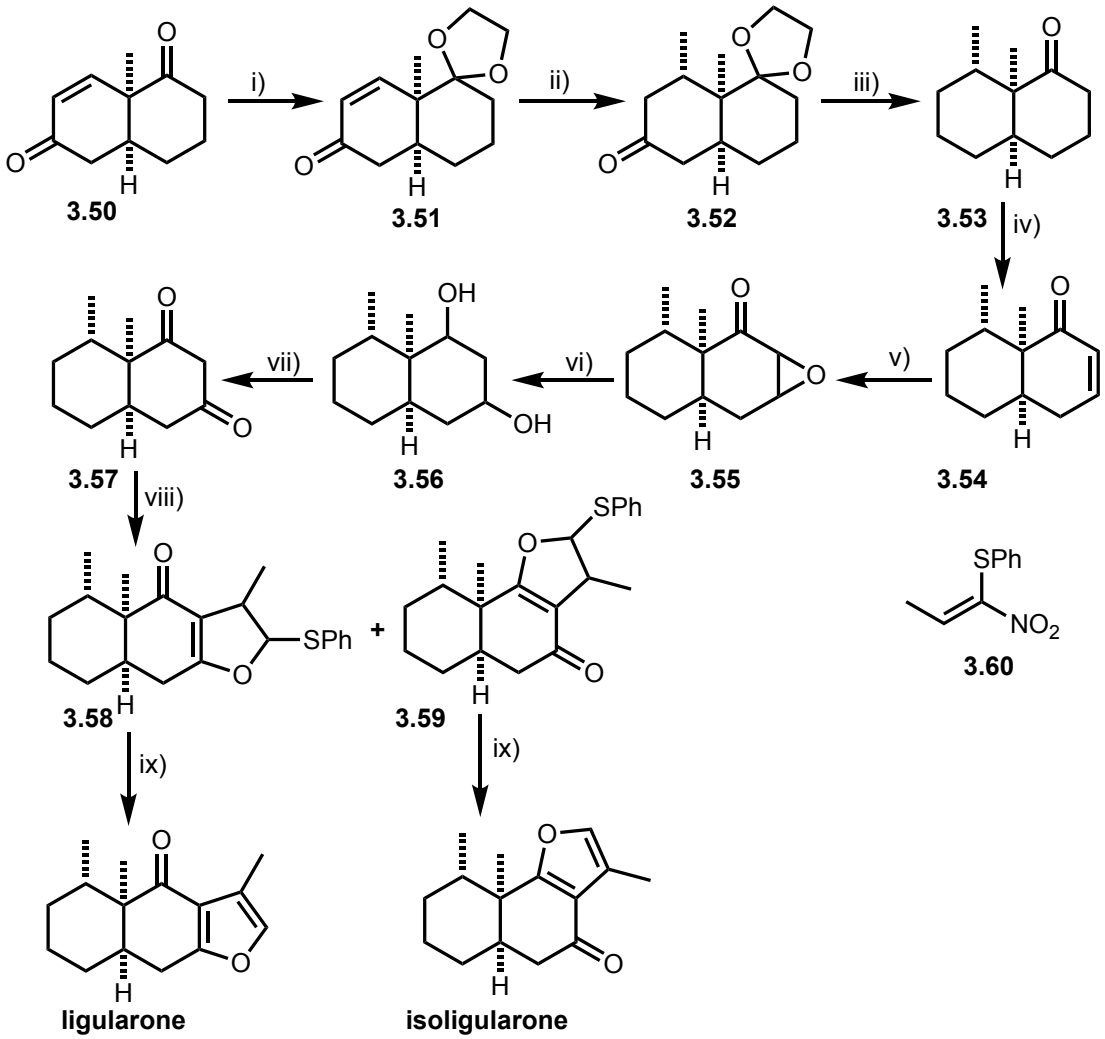
smoothly delivered the aldol products **3.44** and **3.44'** with *syn*/*anti* ratio of 5–7:1 (Scheme 3.21). This mixture was then converted to the corresponding thiocarbonates and deoxygenated using Barton-McCombie conditions to give **3.46**, which was converted to a 3:1 mixture of cyanohydrins **3.47** and **3.47'** using Greenlee and Hangauer's method. Both cyanohydrins were then dehydrated to give unsaturated nitrile **3.48**. Hydrolysis of nitrile **3.48** gave the corresponding carboxylic acid **3.49**, which was sequentially treated with PCl_5 and then $SnCl_4$ to furnish the desired natural product (+)-9-oxoeuryopsin after Friedel–Crafts acylation of the carboxylic acid chloride formed *in situ.*



vi, vii) AlMe3, (*S, R, R*)-Feringa ligand, $Cu(OTf)_2$, ether, –30 ºC, then **3.42**, –20 ºC to –5 ºC, 50–65%. viii) TCDI, rt. ix) nBu$_3$SnH, ACHN, toluene, 75 ºC, 53% from **3.44**, 36% from **3.44'**. x) TMSCN, KCN, 18-c-6, then HCl, 60% (**3.47**), 28% (**3.47'**). xi) POCl3, py, 70% (from **3.47**), 31% (from **3.47'**). xii) KOH, 180 ºC, 24 h, 70%. xiii) PCl_5, 5 ºC, 25 min, then rt, 1 h, then $SnCl_4$, 30 min, 59%.

Scheme 3.21. Completion of the total synthesis of (+)-9-oxoeuryopsin

3.4.2. Miyashita's Synthesis of Ligularone and Isoligularone



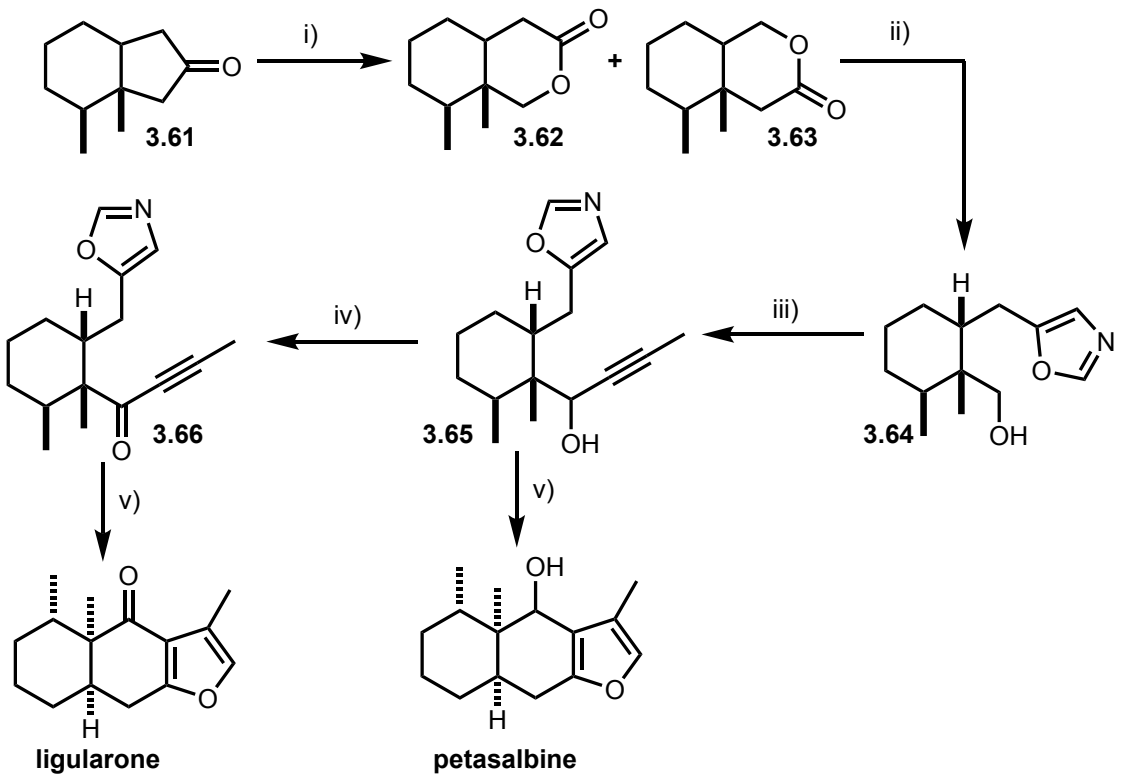
i) *p*TsOH, PhH, 95%. ii) $LiMe_2Cu$, ether, 87%. iii) NH_2NH_2, then AcOH, 80%. iv) $PhMe_3NBr_3$, then Li_2CO_3, DMA. v) H_2O_2. vi) Li, NH_3. 93%. vii) CrO_3, 72%. viii) KF, **3.60**, PhH, 62% (**3.58**: **3.59** = 1:2). ix) $NaIO_4$, MeOH, then pyridine, Al_2O_3.

Scheme 3.22. Miyashita's total synthesis of ligularone and isoligularone

In 1979, Miyashita and coworkers reported a total synthesis of racemic ligularone and isoligularone from known enedione **3.50** (Scheme 3.22).[60d] Selective monoacetalization of **3.50** produced **3.51**, which then underwent conjugate addition with lithium dimethylcuprate from the convex face to yield **3.52**. Huang-Minlon reduction of **3.52** followed by acetal deprotection then

produced decalone **3.53**, which underwent α, β-dehydrogenation to form **3.54** upon bromination with phenyltrimethylammonium tribromide and dehydrobromination under basic conditions. Epoxidation of **3.54** then gave a mixture of epoxides **3.55**, which were then treated without purification with Li/NH_3 to give diol **3.56** as a diastereomeric mixture. Jones oxidation then delivered dione **3.57**, which was then treated with KF and **3.60**[60e] to afford a 1:2 mixture of dihydrofurans **3.58** and **3.59**. Chromatographic separation of **3.58** and **3.59** followed by oxidation with $NaIO_4$ to the sulfoxide followed by elimination of benzenesulfenic acid then afforded ligularone in 47% yield. Using the same sequence of reactions, **3.59** was then transformed to isoligularone.

3.4.2. Jacobi's Synthesis of Ligularone and Petasalbine



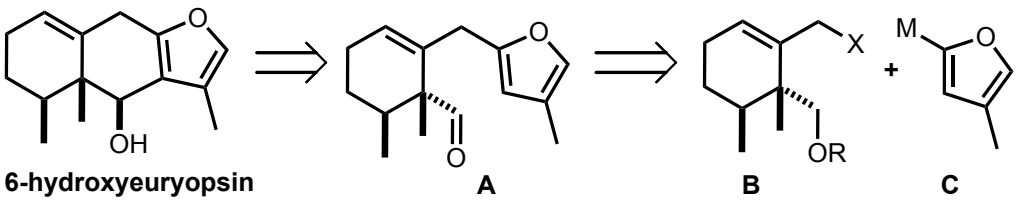
i) mCPBA, DCM, 77% (**3.62**), 23% (**3.63**). ii) $LiCH_2CN$, THF, DME, 51%. iii) DMSO, $(COCl)_2$, 99%, then propynyllithium, THF, 69%. iv) DMSO, $(COCl)_2$, 98%. v) ethylbenzene, reflux, 92% (**ligularone**), 84% (**petasalbine**).

Scheme 3.23. Jacobi's total synthesis of ligularone and petasalbine

Another total synthesis of ligularone was reported by Jacobi in 1981 using a key Diels–Alder reaction (Scheme 3.23).[60a,b] Baeyer–Villiger reaction of known perhydroindanone **3.61** produced a ~3:1 mixture of **3.62** and **3.63**. After chromatographic separation, **3.62** was smoothly converted to oxazole alcohol **3.64** through the use of a modified Schöllkopf reaction. Oxidation of **3.64** produced an aldehyde that was directly condensed with propynyllithium to give a 55:45 mixture of diastereomeric alcohols **3.65** that were quantitatively oxidized to give acetylenic ketone **3.66**. Diels–Alder reaction of **3.66** then produced ligularone, while the same reaction with **3.65** furnished petasalbine.

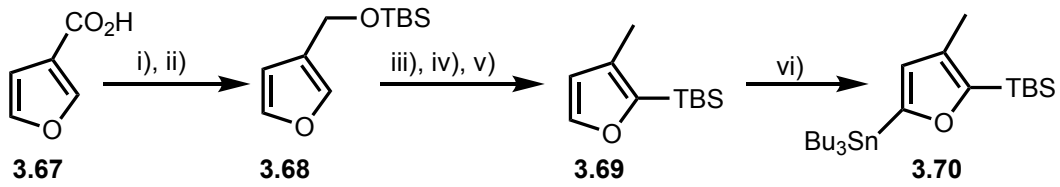
3.4.4. Mace's Synthesis of 6-Hydroxyeuryopsin

In 2005, Mace and coworkers reported a total synthesis of 6-hydroxyeuryopsin using a key Stille reaction between 2,4-disusbtituted furan **A** and allylic halide **B** and an intramolecular formylation of furan **C** using TMSOTf (Scheme 3.24).[59a]



Scheme 3.24. Mace's retrosynthetic analysis of 6-hydroxyeuryopsin

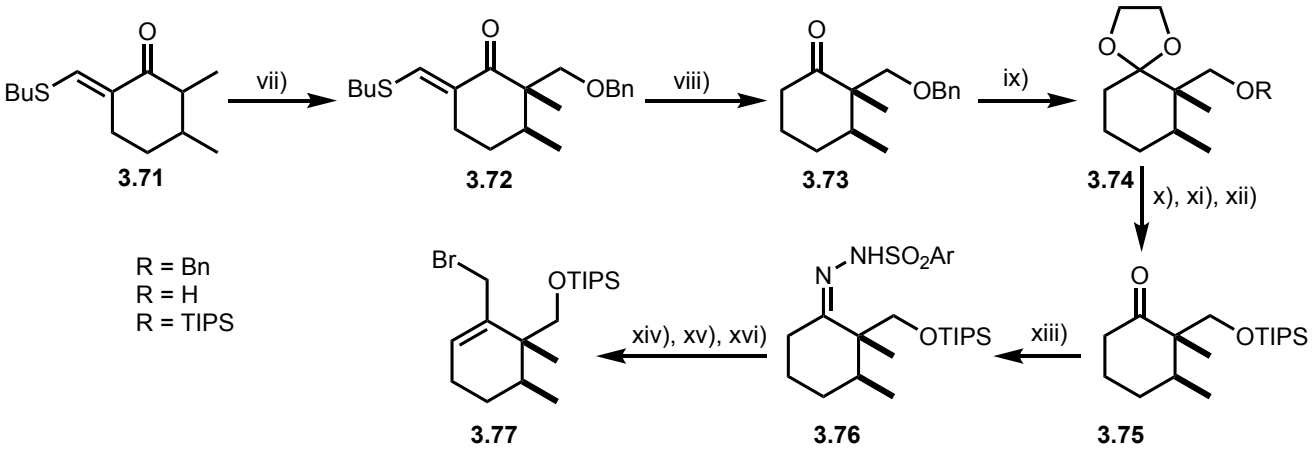
Their synthesis commenced with the preparation of furan **3.70** from commercially available 3-furoic acid **3.67** (Scheme 3.25). Reduction of the carboxylic acid group, followed by TBS-protection of the resulting primary alcohol produced **3.68**, which is then subjected to a 1,3-retro Brook rearrangement, mesylation, and reduction to install the C3-methyl group in **3.69**. Lithiation at C5, followed by quenching with $SnBu_3Cl$ then produced stannane **3.70**.



i) BH_3•DMS, THF, 0 ºC to rt, 24 h, 80%. ii) TBSCl, imidazole, DCM, 0 ºC, 10 min, then rt, 2 h, 100%. iii) nBuLi, HMPA, hexane, –78 ºC to rt, 6 h, then rt, 12 h, 79%. iv) Ms_2O, DIPEA, PhMe, 0 ºC. v) $LiBHEt_3$, THF, 0 ºC, 1 h, 93% (2 steps). vi) tBuLi, hexane-TMEDA, –78 ºC to rt, 6 h, then Bu_3SnCl, 95%.

Scheme 3.25. Preparation of furan **3.70**

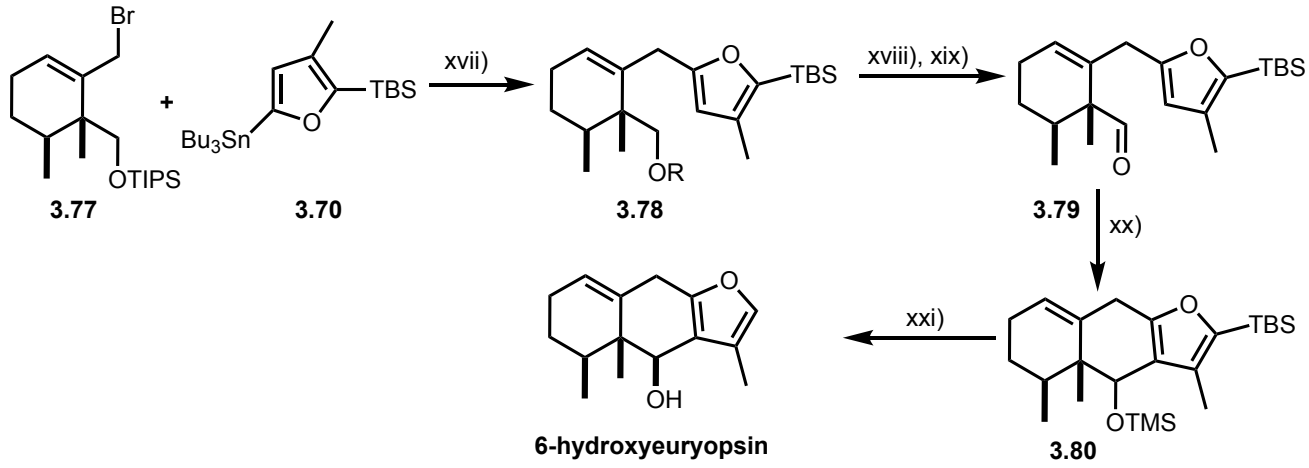
The preparation of allylic halide **3.77** commenced from known ketone **3.71** (Scheme 3.26). Benzyloxymethylation of **3.71**, followed by deprotection produced **3.73**. Ketalization of ketone **3.73**, benzyl deprotection, TIPS protection followed by ketal deprotection then yielded **3.75**. Shapiro reaction of **3.75**, aldehyde formation, reduction, mesylation and Finkelstein reaction then furnished allylic bromide **3.77**.



vii) LiHMDS, then BOMCl, 75%. viii) KOH, H_2O, reflux, 73%. ix) $(TMSOCH_2)_2$, TMSOTf, DCM, –78 ºC, 4 h, then rt, 14 h, 99%. x) Li, NH_3, THF, –78 ºC, 1 h, 96%. xi) TIPSOTf, 2,6-lutidine, DCM, –78 ºC to –20 ºC, 4 h, 100%. xii) PPTS, acetone/water, 65 ºC, 18 h, 93%. xiii) H_2NNHSO_2Ar, THF, rt, 14 h, 78%. xiv) tBuLi. then DMF, then DIBAL, 75% (2 steps). xvi) Ms_2O, TEA, DCM, then LiBr, THF, 92% (2 steps).

Scheme 3.26. Preparation of allylic bromide **3.77**

With both fragments of the key Stille reaction in hand, all that was left was coupling of furan **3.70** and allylic bromide **3.77** and closing of the central six-membered ring (Scheme 3.27). Therefore, Stille coupling between **3.77** and **3.70** under ligandless condition, selective TIPS protection in the presence of TBS group followed by Ley oxidation smoothly furnished furan **3.78**. Treatment of aldehyde **3.79** with TMSOTf then triggered an intramolecular cyclization to close the central cyclohexane ring to form **3.80** in good yield. Finally, global deprotection of the silyl protecting groups delivered 6-hydroxyeuryopsin.

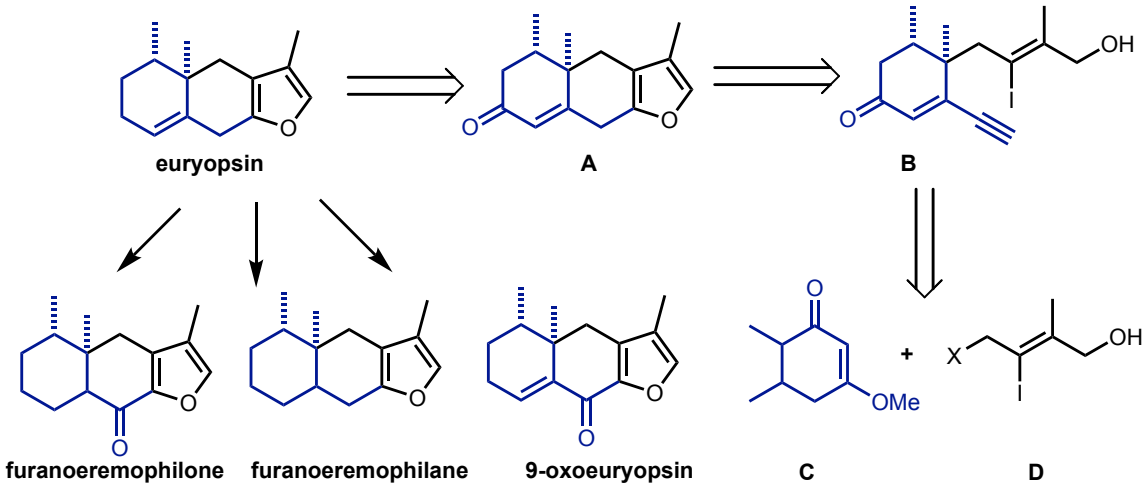


xvii) $Pd_2(dba)_3$, THF, rt, 36 h. xviii) TBAF, THF, rt, 5 h, 97% (2 steps). xix) TPAP, NMO, 4Å MS, DCM, rt, 1 h. xx) TMSOTf, 2,6,-lutidine, DCM, –78 ºC, 16 h, 93% (2 steps). xxi) TBAF, THF, 60 ºC, 24 h, 60%.

Scheme 3.27. Completion of the total synthesis of 6-hydroxyeuryopsin

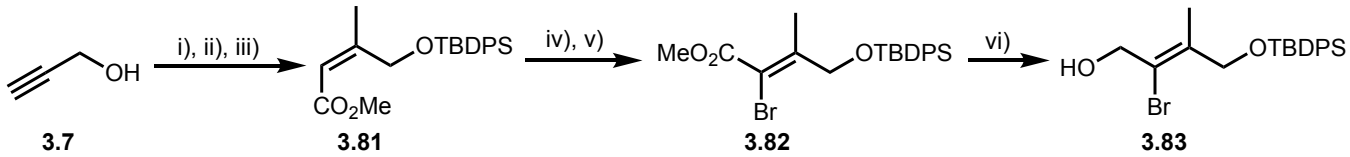
3.4.5. Intramolecular Approach to Euryopsin via Enolate Alkylation

Using the same retrosynthetic approach used for the total synthesis of the 5/7/6 tricyclic system of agassizin, pallescensin G and F,[27] we applied to the total synthesis of euryopsin,[28] which could also be transformed to furanoeremophilane, furanoeremophilone and 9-oxoeuryopsin via functional group transformations (Scheme 3.28). In this case, the Michael–Heck precursor **B** would be derived from enolate alkylation of **C** by allylic halide **D**, which is not only more reactive than the homoallylic iodide **3.23** but more importantly, cannot undergo E2-elimination.



Scheme 3.28. Retrosynthetic Analysis for Euryopsin, 9-Oxoeuryopsin, Furanoeremophilane and Furanoeremophilone via Intramolecular Michael–Heck

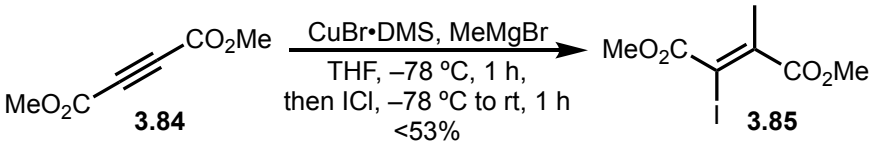
To this end, we commenced with the preparation of the allylic halide intermediate. Following literature procedures, we prepared the known vinyl bromide precursor from commercially available propargyl alcohol using a sequence of silylation, alkoxycarbonylation, carbocupration, bromination, dehydrobromination and ester reduction (Scheme 3.29).



i) TBDPSCl, imidazole, THF, rt, 0.5 h. ii) nBuLi, THF, –78 ºC, 1 h, then $ClCO_2Me$, –78 ºC; rt, 1 h. iii) MeLi, CuI, THF, 0 ºC 10 min, then –78 ºC, 40 min (quant, 3 steps). iv) Br_2, DIPEA, DCM, 0 ºC to rt, 3 days. v) KOtBu, MeOH, 0 ºC to rt, 0.5 h, 80% (2 steps). vi) DIBAL, ether, 0 ºC, 30 min, 61%.

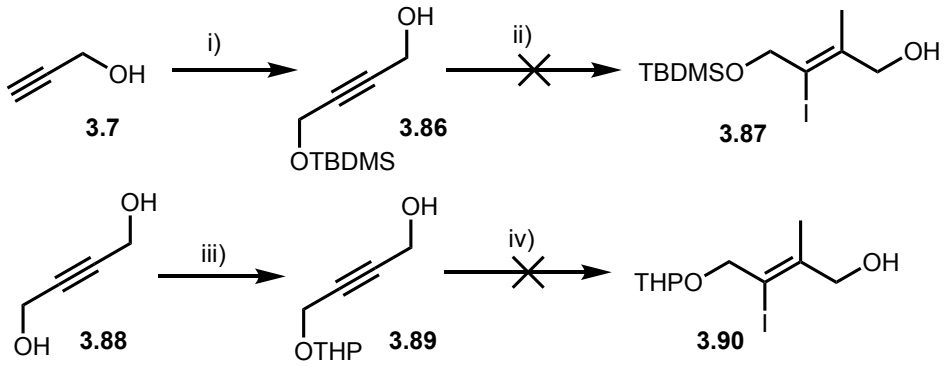
Scheme 3.29. Preparation of allylic bromide **3.83** via bromination/dehydrobromination

At first, attempts were made to prepare **3.83** from known compound **3.81**[29] using a three-step sequence of bromination, dehydrobromination and reduction. However, although the bromination/dehydrobromination[29b] step was reported to be (*Z*)-selective for **3.82**, the results were rather irreproducible and inconsistent in both yield and *E*/*Z* selectivity. Therefore, we turned to the carbocupration/iodination[30] route using dimethyl acetylenedicarboxylate and methylmagnesium bromide (Scheme 3.30).



Scheme 3.30. Preparation of iodoester **3.85** via carbocupration/iodination

However, the reaction was not very efficient so we then turned to the carbocupration of mono-protected 2-butyne-1,4-diols. Unfortunately, use of either the THP- and TBDMS-protected diols led to decomposition (Scheme 3.31).

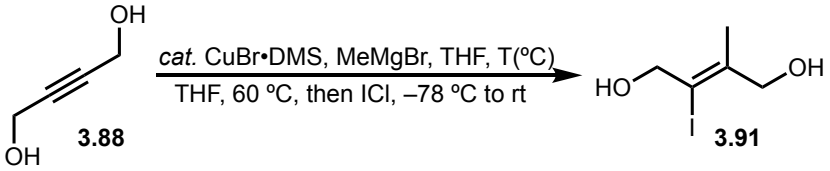


i) TBDMSCl, imidazole, rt, 30 min, then nBuLi, THF, –78 ºC, 1 h, then $(HCHO)_n$, –78 ºC to rt, 1 h, 70% (2 steps). ii) CuBr, MeMgBr, THF, 0 ºC to rt, 1 h then ICl, 0 ºC to rt, 1 h. iii) *cat.* pTsOH, DHP, DCM, rt, 2.5 h, 90%. iv) *cat.* CuI, MeMgBr, THF, 0 ºC to rt, 16 h.

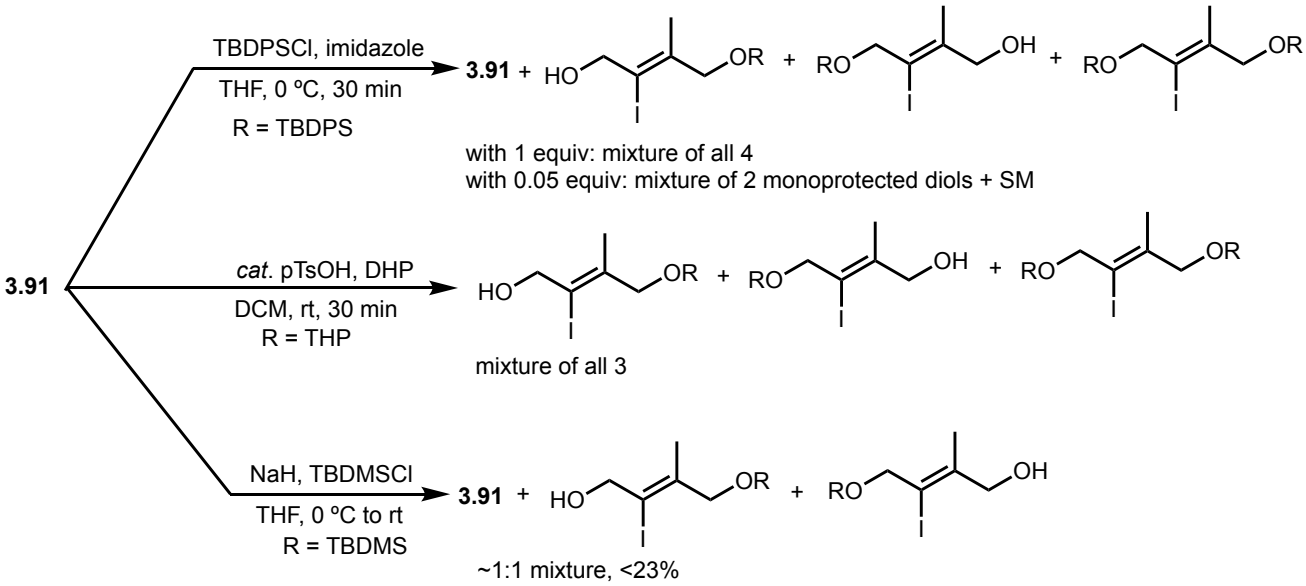
Scheme 3.31. Attempted carbocupration/iodination of mono-protected 2-butyne-1,4-diols

Surprisingly, unprotected 2-butyne-1,4-diol itself was found to be a competent substrate for the catalytic carbocupration with MeMgBr (Table 3.4). Following a modified procedure[31] used for the preparation of the analogous benzyl-substituted substrate, the desired diol could be prepared in 46% yield. With the diol in hand, we then sought after selective monoprotection (Scheme 3.32). Unfortunately, attempts at selective monoprotection using either stoichiometric or substoichiometric amounts of TBDPSCl gave a complex mixture. Similar results were observed using DHP and TBDMSCl (Scheme 3.32).

Table 3.4. Optimization of the carbocupration/iodination of diol **3.91**

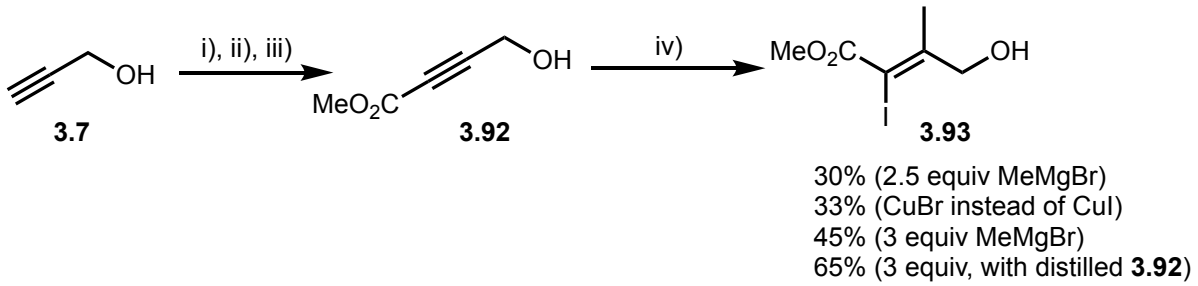


Entry	Cu(I) source (mol %)	MeMgBr (equiv)	T (ºC)/t (h)	Yield (%)
1	4 mol% CuBr•DMS	6 equiv	60 ºC/4 h	23%
2	10 mol% CuBr•DMS	4 equiv	50 ºC/1.5 h	43%
3	30 mol% CuBr•DMS	4 equiv	50 ºC/1 h	42%
4	10 mol% CuI	4 equiv	50 ºC/1 h	42%
5	30 mol% CuBr	4 equiv	50 ºC/1 h	46%
6	2 mol% CuBr•DMS	3 equiv	60 ºC/6 h	23%



Scheme 3.32. Attempts at selective monoprotection of diol **3.91**

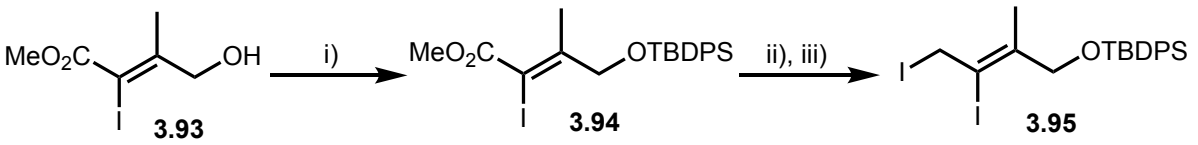
While carbocupration with unprotected or monoprotected butynediols required heating, we found that reaction with electron-withdrawing group containing propargyl alcohol **3.92**[32] proceeded rapidly at low temperatures to give the desired allylic alcohol **3.93** in 45% yield.



i) DHP, *cat.* pTsOH, DCM, rt, 0.5 h. ii) nBuLi, THF –78 ºC, then $ClCO_2Me$, –78 ºC to rt, 1 h. iii) *cat.* pTsOH, MeOH, rt, 0.5 h, 98%, 3 steps. iv) CuI, MeMgBr, 1:2, THF, –78º C, then ICl, –78 ºC to rt, 1 h.

Scheme 3.33. Optimization of the carbocupration/iodination of **3.93**

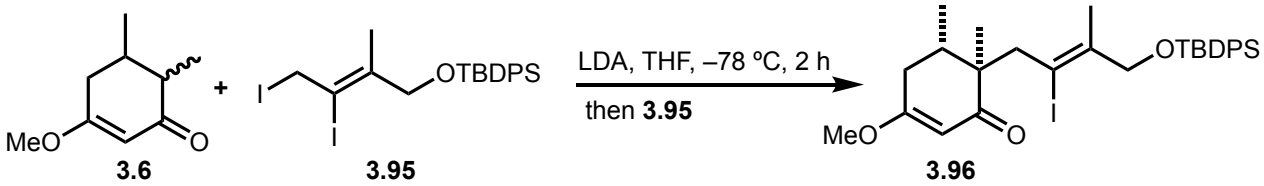
Although changing the amounts of MeMgBr and/or amount or type of Cu(I) source were unsuccessful in increasing the yield, it was found that use of distilled propargyl alcohol (clear oil instead of orange oil) was critical for obtaining satisfactory yield (Scheme 3.33). Having determined the ideal conditions for the carbocupration/iodinolysis sequence, allylic alcohol **3.93** was then further transformed to allylic iodide **3.95** via a sequence of silylation, reduction and Appel reaction (Scheme 3.34).



i) TBDPSCl, imidazole, THF, rt, 0.5 h. ii) DIBAL, ether, 0 ºC, 30 min, 85%. iii) PPh_3, imidazole, ICl, THF, 0 ºC, 20 min.

Scheme 3.34. Preparation of allylic iodide **3.95**

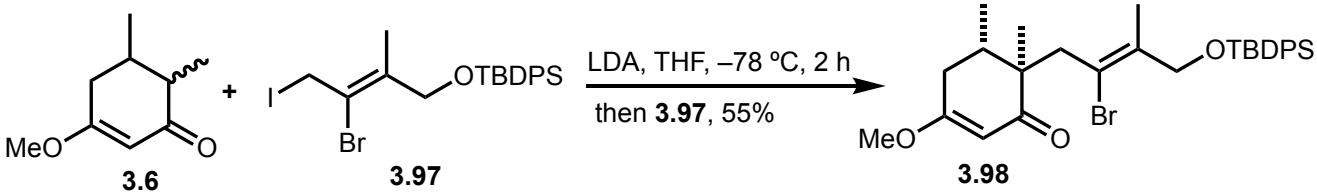
Table 3.5. Optimization of the enolate alkylation of vinylogous ester **3.6** by allylic iodide **3.95**



Entry	Iodide (equiv)	T (ºC), t (h)	Additives (equiv)	Yield (%)[a]
1	3 equiv	–78 ºC to rt, 16 h	HMPA (10 equiv)	44%
2	2 equiv	–78 ºC to 65 ºC, 4 h	HMPA (10 equiv)	48%
3	1 equiv	–78 ºC to rt, 1.5 h	HMPA (10 equiv)	20%

[a] **3.96** was obtained as a single diastereomer in all cases

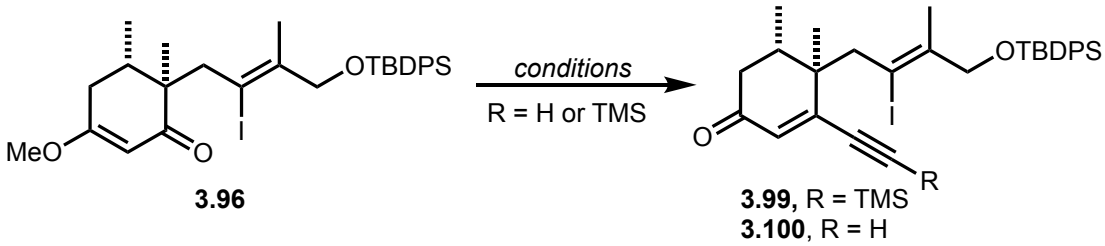
Due to the instability of the allylic iodide, it was used directly without purification for the subsequent enolate alkylation (Table 3.5). However, even with excess amounts of allylic iodide **3.95**, vinylogous ester **3.6** was never completely consumed (entries 1, 2). Use of 1 equivalent of iodide **3.95** and 2.5 equivalents vinylogous ester **3.6** resulted in even lower yields (entry 3). Interestingly, the analogous alkylation with vinyl bromide **3.97** afforded the product as a single diastereomer in higher yields, presumably due to the smaller size of the Br atom relative to the I atom (Scheme 3.35).



Scheme 3.35. Preparation of **3.98**

Nevertheless, to confirm the viability of the key intramolecular vinylogous Michael–Heck reaction, the synthesis was continued. Thus the alkylated vinylogous ester was subjected to Stork–Danheiser transposition to produce the Michael–Heck precursor (Table 3.6):

Table 3.6. Optimization of the Stork–Danheiser transposition of **3.96**

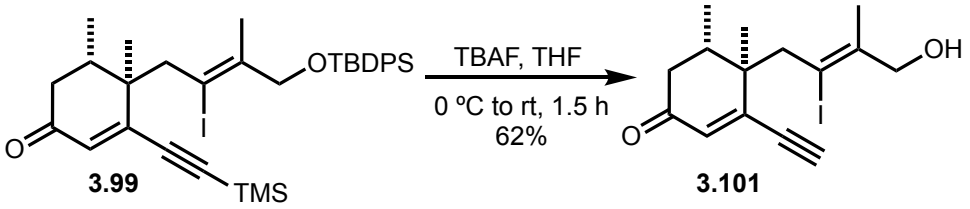


3.96

3.99, R = TMS
3.100, R = H

Entry	Conditions	Results
1	ethynylmagnesium bromide, 1.5 equiv, 0 ºC to rt, 16 h	SM only
2	TMS-acetylene, MeMgBr, 2.5 equiv, 0 ºC to rt, 16 h	SM only
3	TMS-acetylene, nBuLi, 2 equiv, –78 ºC to rt, 16 h	1: 0.23
4	TMS-acetylene, nBuLi, 2.5 equiv, –78 ºC to rt, 16 h	82%

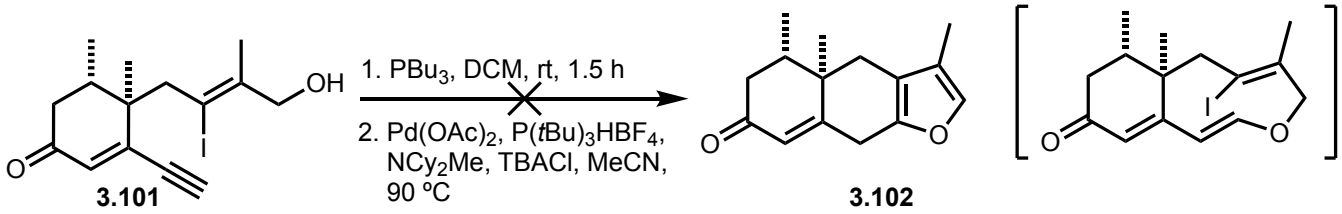
While the of ethynylmagnesium bromide was unsuccessful (entry 1), the use of 2.5 equivalents of the more nucleophilic lithium trimethylsilylacetylide smoothly delivered the enynone **3.99** in 82% yield (entry 4). Global deprotection of the silyl protecting groups then delivered enynone **3.101** in 62% yield (Scheme 3.36).



3.99 **3.101**

Scheme 3.36. Deprotection of **3.99**

The enynone was then subjected to the intramolecular vinylogous Michael–Heck conditions (Scheme 3.37). Disappointingly, the Michael addition did not proceed at all, presumably due to the intermediacy of a strained Michael adduct containing a trans nine-membered ring, a fact that clearly indicated the need for an intermolecular rather than an intramolecular vinylogous Michael–Heck reaction.

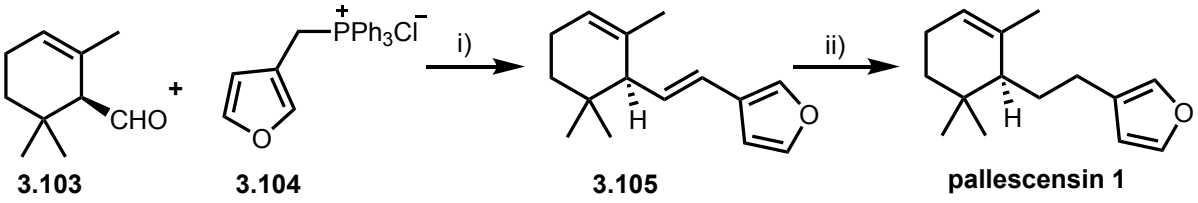


Scheme 3.37. Attempted Michael–Heck reaction of **3.101**

3.5. Intermolecular Approach to Furanoeremophilanes via Reductive Coupling

3.5.1 Matsumoto's Synthesis of Pallescensins 1, G, and F

While no previous total synthesis of agassizin has been reported, the first and only total synthesis of its isomers pallescensins G and F from pallescensin 1[27] was reported by Matsumoto in 1982. Pallescensin 1, a furanosesquiterpene isolated along with pallescensin-2, pallescensin-3 and pallescensin A from the maine sponge *D. pallescens* by Cimino in 1975, was rapidly prepared from commercially available (R)-(–)-α-cyclocitral **3.103** using a Wittig reaction followed by partial catalytic hydrogenation of **3.105** (Scheme 3.38):



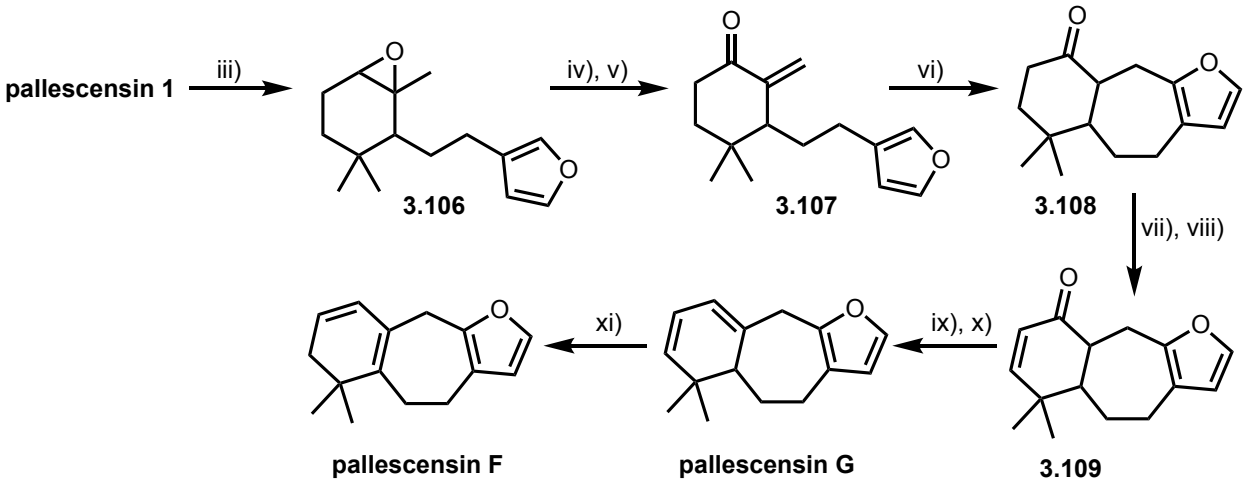
3.103 **3.104** **3.105** **pallescensin 1**

i) nBuLi, PhH, 3 h, reflux, 70%. ii) 5% Pd/C, rt, 40 min, 79%.

Scheme 3.38. Matsumoto's synthesis of pallescensin 1

Pallescensin 1 was then transformed to pallescensins G and F in 10–11 steps (Scheme 3.39). Thus, epoxidation of pallescensin 1 produced crude epoxide **3.106**, which was directly treated with lithium diethylamide to form an allylic alcohol intermediate that was then oxidized with PCC to produce enone **3.107** in 49% over two steps from pallescensin 1. Treatment of enone **3.107** with H_3PO_4 then triggered an intramolecular cyclization to form tricyclic intermediate **3.108** in 79% yield. Dehydrogenation of the ketone moiety in **3.108** was then carried out using a two-step sequence of phenylselenation with PhSeBr followed by selenoxide elimination to produce enone **3.109**. Subsequent reduction of the enone carbonyl followed by thermal elimination then furnished

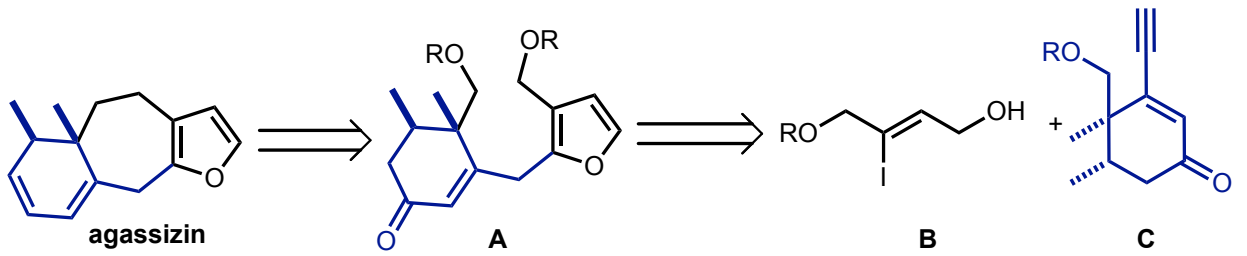
pallescensin G in 51% over two steps from enone **3.109**. Thermal isomerization of the diene moiety in pallescensin G in HMPA then delivered pallescensin F in 75%.



iii) mCPBA, DCM, 0–5 ºC, 1 h. iv) $LiNEt_2$, THF, rt, 30 min, then reflux, 3 h, 49% from pallescensin 1. v) PCC, DCM, rt, 3 h, 80%. vi) H_3PO_4, THF, rt, 10 h, 79%. vii) LDA, PhSeBr, THF –70 ºC, 10 min, 80%. viii) H_2O_2, THF, rt, 1.5 h, 69%. ix) LAH, ether, 0–5 ºC, 30 min. x) HMPA, 200–210 ºC, 1 h, 51% from **3.109**. xi) HMPA, reflux, 1 h, 75%.

Scheme 3.39. Matsumoto's synthesis of pallescensin G and F

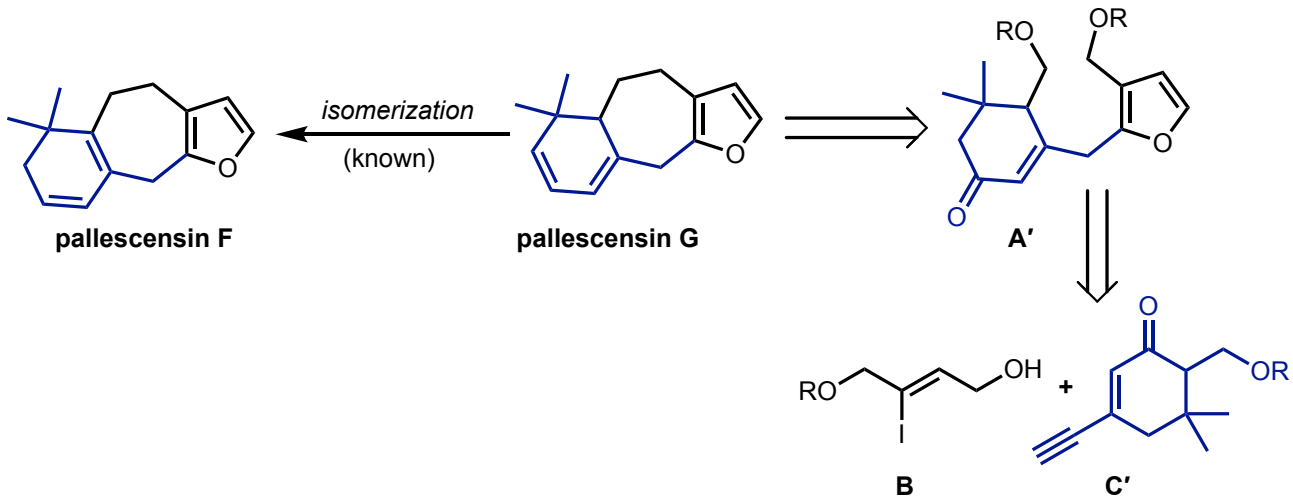
3.5.2. Intermolecular Approach to Agassizin, Pallescensin G and F via Reductive Coupling



Scheme 3.40. Retrosynthetic analysis of agassizin via intermolecular Michael–Heck reaction

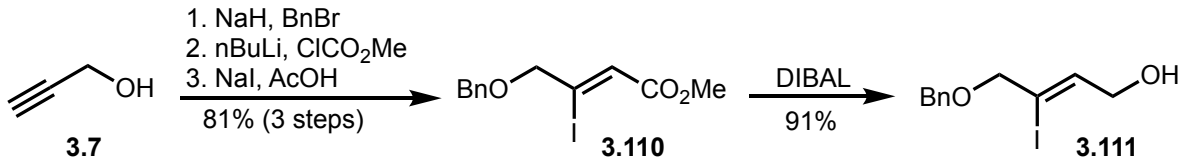
In this new approach, we envisioned that disconnection of the central seven-membered ring at the ethylene bridge would yield diol intermediate **A**, which can be transformed to a dihalide intermediate that can then undergo reductive coupling[33] to forge the central ring. The diol intermediate **A** can be accessed from an intermolecular vinylogous Michael–Heck reaction

between allylic alcohol **B** and enynone **C**, which themselves can be derived from commercially available propargyl alcohol and 5-methyl-1,3-cyclohexanedione (Scheme 3.40). Analogous retrosynthetic analyses can be devised for the isomeric pallescensins G and F:[32]



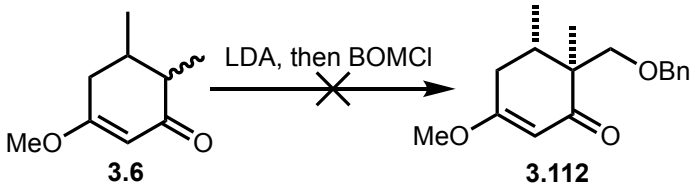
Scheme 3.41. Retrosynthetic analyses for pallescensin G and F via intermolecular Michael–Heck rection

Pallescensin F can be obtained from the known thermal isomerization of pallescensin G,[34] which itself is derived from the protected diol intermediate **A'** produced by the vinylogous intermolecular Michael–Heck reaction between allylic alcohol **B** and enynone **C'**, which themselves can be prepared from commercially available propargyl alcohol and dimedone (Scheme 3.41). To this end, we commenced with the preparation of the allylic alcohol and enynone. Following known literature procedures, **3.7** was smoothly converted to the known allylic alcohol **3.111**[35] following a sequence of benzylation, alkoxycarbonylation, hydroiodionation and ester reduction (Scheme 3.42).



Scheme 3.42. Preparation of allylic alcohol **3.111**

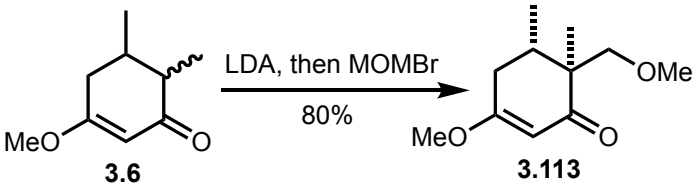
However, the preparation of the enynone precursor was not so straightforward. Attempted enolate alkylation of vinylogous ester **3.6** with BOMCl resulted in a messy reaction that was very difficult to purify, suggesting that the reactivity of BOMCl as an alkylating reagent might be insufficient (Scheme 3.43).



3.6 **3.112**

Scheme 3.43. Attempted benzyloxymethylation of vinylogous ester **3.6**

Inspired by Berliner's report on the simple and convenient preparation of bromomethyl ether via Zn(II)-catalyzed exchange reaction between dimethoxymethane and acetyl bromide,[36] we decided to use bromomethyl ether as a more reactive alkylating reagent for the installation of a protected hydroxymethyl group on the vinylogous ester. Delightfully, the desired alkylation product was obtained in 80% using MOMBr prepared *in situ* from the exchange reaction between dimethoxymethane, AcBr and catalytic $ZnBr_2$ (Scheme 3.44).



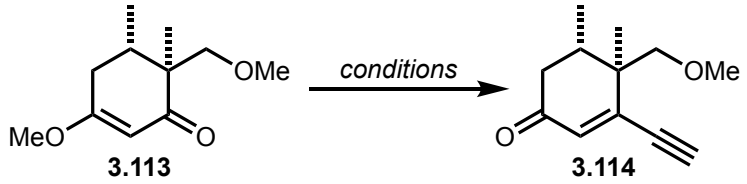
3.6 **3.113**

Scheme 3.44. Methyloxymethylation of vinylogous ester **3.6**

With the desired vinylogous ester **3.113** in hand, we then proceeded to investigate the Stork–Danheiser transposition (Table 3.7). While the Stork–Danheiser transposition of vinylogous ester **3.113** with lithium trimethylsilylacetylide led either to very low yields or decomposition (entries

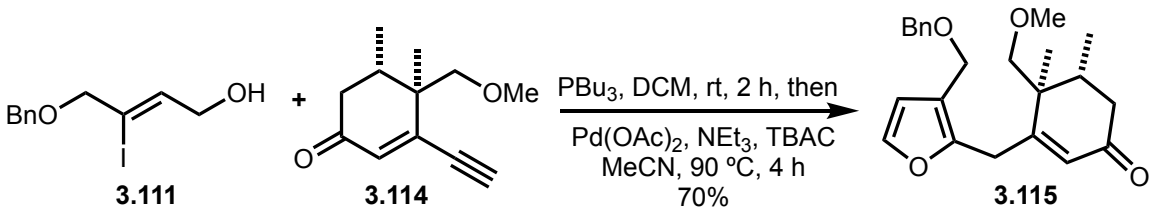
1, 2), use of excess ethynylmagnesium bromide provided the desired product in 80% yield (entry 3).

Table 3.7. Optimization of the Stork–Danheiser transposition of **3.113**



Entry	Conditions	Results
1	1.5 equiv lithium TMS-acetylide, then KF, $BnBu_4NCl$	24%
2	3 equiv lithium TMS-acetylide, then KF, $BnBu_4NCl$	decomposition
3	2.5 equiv ethynylmagnesium bromide	80%

With both the required enynone **3.114** and allylic alcohol **3.111** in hand, we then proceeded to the key intermolecular vinylogous Michael–Heck reaction. Using the previously established optimized Michael–Heck conditions, furan **3.115** was obtained in 70% yield (Scheme 3.45).

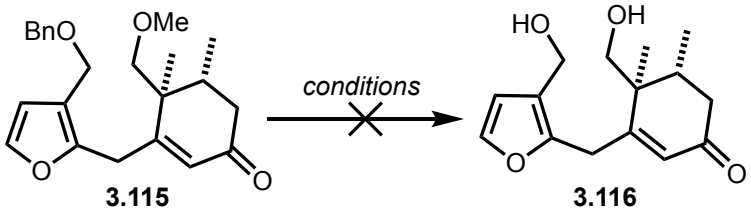


Scheme 3.45. Michael–Heck reaction of **3.111** and **3.114**

With the protected diol **3.115** in hand, all that remained for the investigation of the reductive coupling was deprotection and Appel reaction. However, deprotection using reagents commonly used to deprotect alkyl ethers was unsuccessful (Table 3.8). Use of Lewis acids such as TMSI (entry 1) and boron trihalides (entries 2,3) lead to rapid decomposition even at low temperatures. Attempts to perform hydrosilylation[37] of protected diols using catalytic $B(C_6F_5)_3$ also led to decomposition (entry 4). The chemical inertness combined with the lability of the furan system

towards Lewis acids indicated that the methyl ether group would not be a viable protecting group and that a protecting group that can be removed under neutral conditions must be used instead.

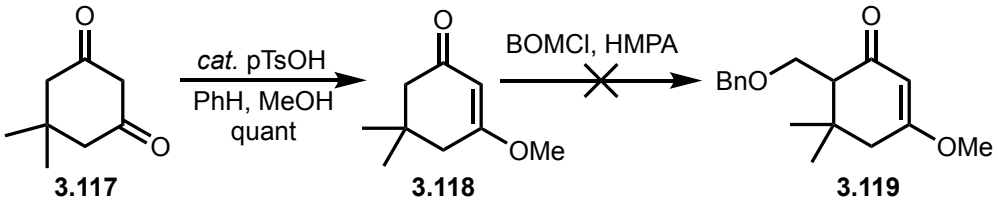
Table 3.8. Attempts to deprotect furan **3.115**



3.115 **3.116**

Entry	Conditions	Results
1	2 equiv NaI, TMSCl	decomposition
2	2 equiv BBr3•DMS	decomposition
3	2 equiv BCl_3	decomposition
4	*cat.* $B(C_6F_5)_3$, Et_3SiH	decomposition

Therefore, to address the previous problem encountered with the BOMCl alkylation, attempts to prepare the more reactive BOMBr or BOMI were made. Since dimedone is significantly cheaper than 5-methyl-1,3-cyclohexanedione, the optimization of the benzyloxymethylation of the vinylogous ester precursor was investigated using dimedone instead. First, dimedone was protected as the corresponding vinylogous ester following literature conditions.[38]

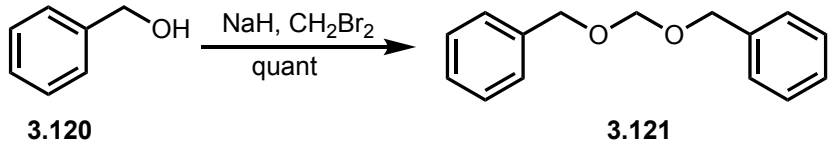


3.117 **3.118** **3.119**

Scheme 3.46. Attempted benzyloxymethylation of vinylogous ester **3.118**

However, direct alkylation of vinylogous ester **3.118** was unsuccessful, with the use of 1.2 equiv BOMCl and HMPA giving no reaction and larger excesses giving very dirty reaction mixtures (Scheme 3.46). Therefore, we attempted to prepare the more reactive BOMBr or BOMI using the

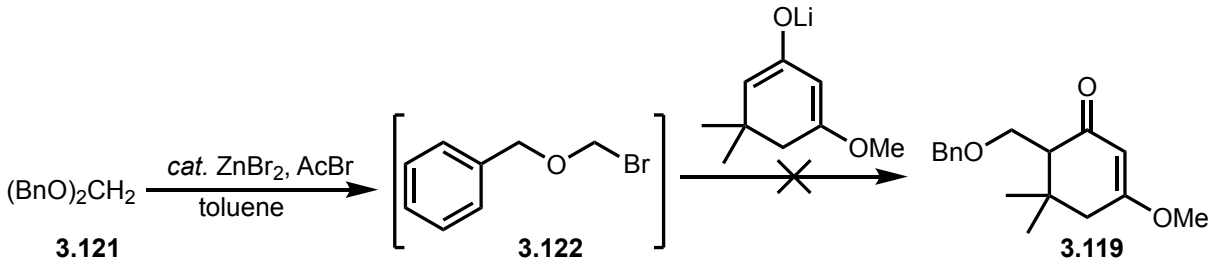
Zn(II)-catalyzed exchange conditions developed by Berliner. Therefore, using modified literature conditions,[39] dibenzyl formal **3.121** was prepared in quantitative yields (Scheme 3.47).



3.120 **3.121**

Scheme 3.47. Preparation of dibenzyl formal

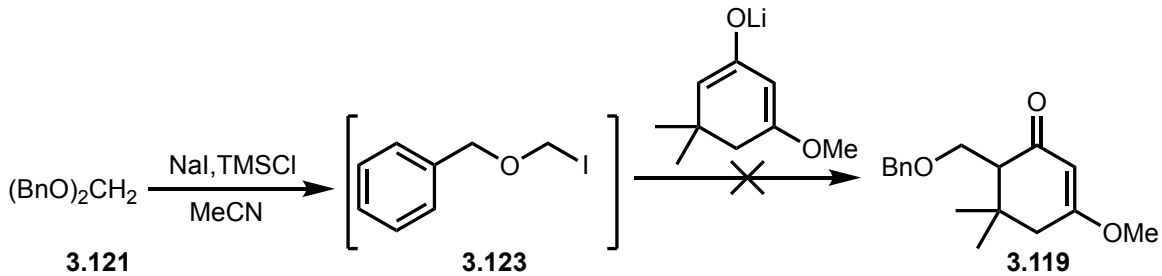
With dibenzyl formal in hand, we applied the same Zn(II)-catalyzed exchange conditions used to prepare bromomethyl ether from dimethoxymethane and AcBr to **3.121** (Scheme 3.48). However, regardless of the amount of $ZnBr_2$ used (1 or 10 mol%) used, no alkylation product was observed, indicating that BOMBr was not generated in this process.



3.121 **3.122** **3.119**

Scheme 3.48. Attempted generation of BOMBr from $(BnO)_2CH_2$ using Berliner's conditions

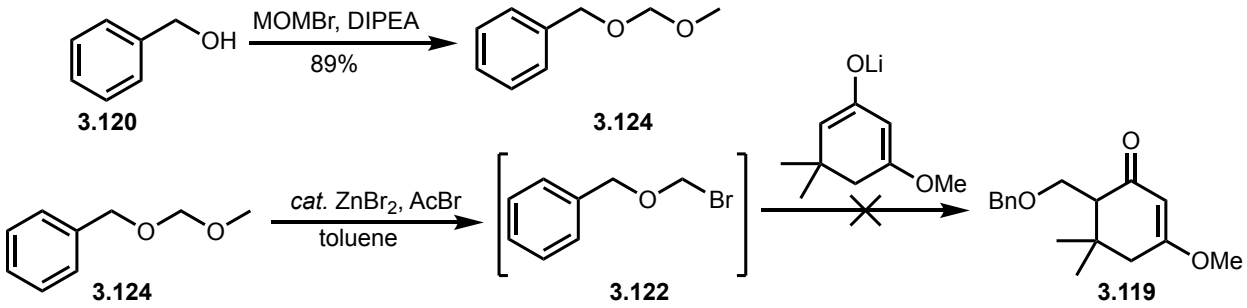
We also attempted to use TMSI, which was prepared *in situ* from NaI and TMSCl to prepare BOMI *in situ*[40] (Scheme 3.49):



3.121 **3.123** **3.119**

Scheme 3.49. Attempted generation of BOMI from $(BnO)_2CH_2$ using TMSI

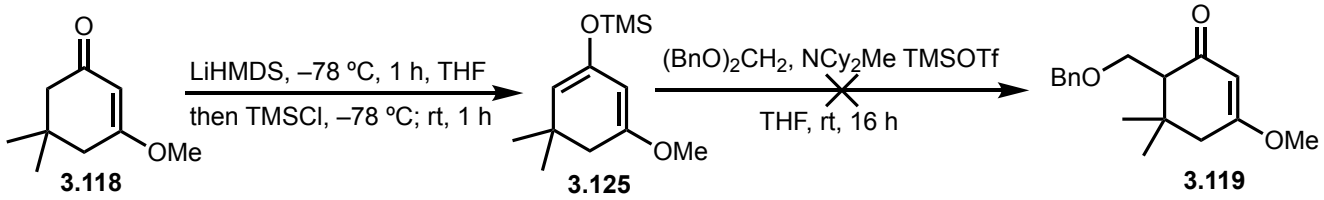
However, no alkylation product was observed either, indicating that BOMI was not generated. Suspecting that the Zn(II)-catalyzed exchange reaction might not be compatible with benzyl groups on **3.121**, we prepared (BnO)(OMe)CH_2[41] and subjected it to the exchange reaction. However, regardless of whether 2 or 3.5 equivalents of (BnO)(OMe)CH_2 and AcBr were used, only starting material was observed, indicating that BOMBr was not generated under these conditions (Scheme 3.50).



Scheme 3.50. Attempted generation of BOMBr from (BnO)(OMe)CH_2

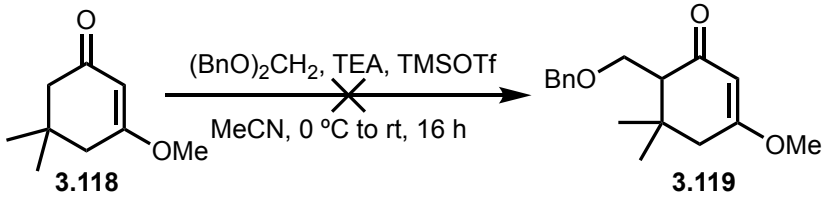
Catalytic TMSOTf and sterically hindered amine bases have been shown to convert bis(benzyloxy)methane to a carboxonium triflate, which can be trapped by a silyl enol ether.[42] Following this procedure, we attempted the benzyloxymethylation of the silyl enol ether generated from the vinylogous ester (Table 3.9). However, regardless of the amounts of TMSOTf and NCy_2Me used, none of the desired alkylation product was formed.

Table 3.9. Benzyloxymethylation of the silyl enol ether



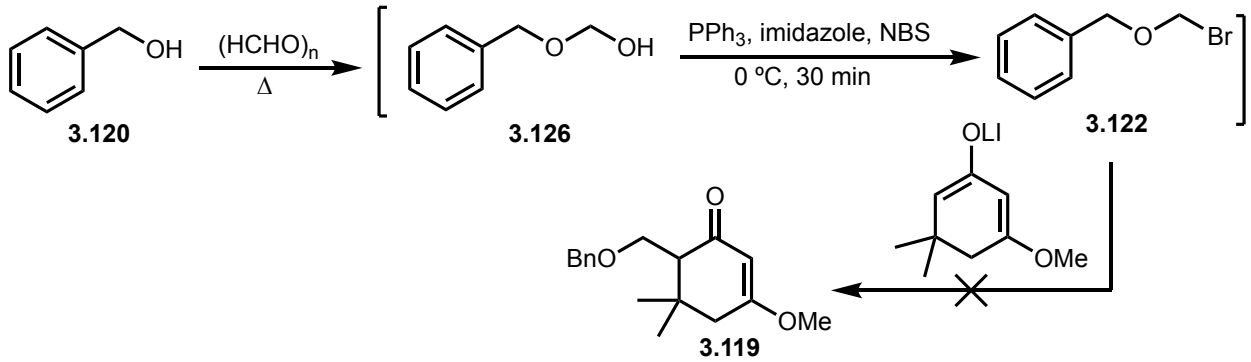
Entry	Conditions	Results
1	10 mol% NCy_2Me, TMSOTf	silyl enol ether only
2	30 mol% NCy_2Me, TMSOTf	silyl enol ether only
3	1 equiv NCy_2Me, TMSOTf	decomposition

However, directly treating the vinylogous ester with the carboxonium triflate formed by the reaction between $(BnO)_2CH_2$, TMSOTf and TEA[43] resulted in decomposition (Scheme 3.51).



Scheme 3.51. Attempted benzyloxymethylation of vinylogous ester **3.118**

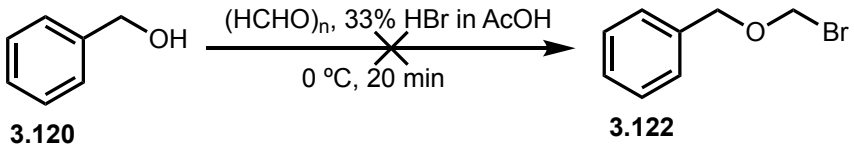
Attempts to prepare BOMBr using an Appel reaction were also unsuccessful (Scheme 3.52):



Scheme 3.52. Attempted generation of BOMBr from alcohol **3.126**

Since the standard procedure[44] for preparing BOMBr from benzyl alcohol requires the use of anhydrous HBr, we also tried using 33% HBr in AcOH as a source of anhydrous HBr. Following

the procedure used by Silva-Cuevas in their report on the bromomethylation of thiols,[45] we were delighted to observe clean and rapid formation of BOMBr (Scheme 3.53).

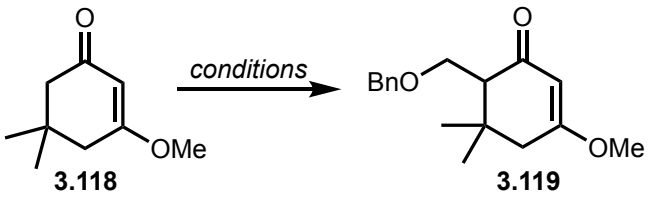


3.120 **3.122**

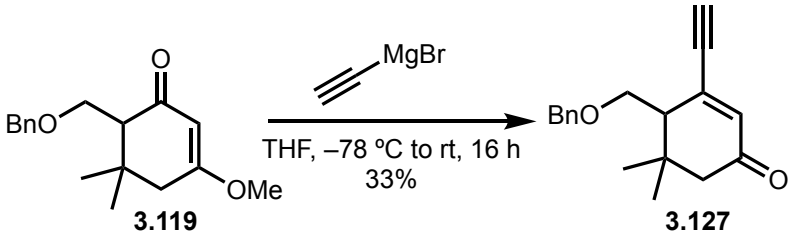
Scheme 3.53. Bromomethylation of benzyl alcohol

However, the small amounts of AcOH and water present in the final product were extremely difficult to remove completely, and attempts to distill the product were also unsuccessful due to the tendency of the product to hydrolyze under neat conditions. Due to the difficulties encountered in the preparation of BOMBr, we thought to increase the reactivity of BOMCl by doing a Finkelstein reaction to convert BOMCl to BOMI *in situ*.[46] A screen of various bromide or iodide salts including LiBr, NaI,[47] TBAI[48] and LiI revealed that LiI was extremely effective in the rapid conversion of BOMCl to BOMI *in situ,* presumably due to the high solubility of LiI in THF (Table 3.10). Unfortunately, we found that the quality and appearance of LiI varies significantly from bottle to bottle and the results in entries 5 and 6 were not reproducible with LiI from a bottle other than the one used for entries 1–6. Attempts to purify or to dry the commercially available samples were also unsuccessful. Nevertheless, we decided to move the synthesis forward with the material we have already obtained.

Table 3.10. Optimization of the benzyloxymethylation of vinylogous ester **3.118**

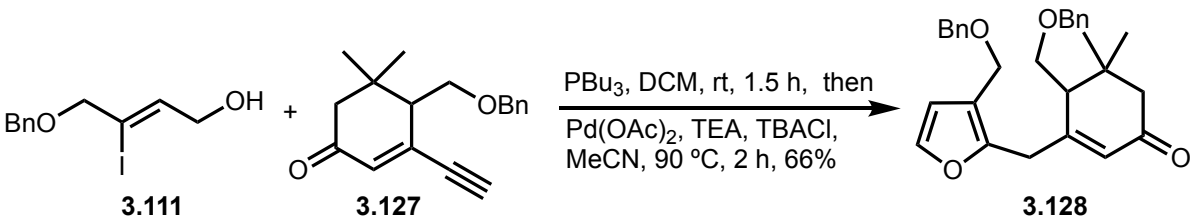


Entry	Conditions	Results
1	3 equiv BOMCl/LiBr, 4 h	unknown product
2	3 equiv BOMCl/NaI, 1 h	SM only
3	3 equiv BOMCl/TBAI,1 h	45%
3	1.5 equiv BOMCl/LiI, 1 h	55%
4	2.5 equiv BOMCl/LiI, 1 h	70%
5	3 equiv BOMCl/LiI, 1 h	quant
6	3.5 equiv BOMCl/LiI, 1 h	quant



Scheme 3.54. Stork–Danheiser Reaction of Vinylogous Ester **3.119**

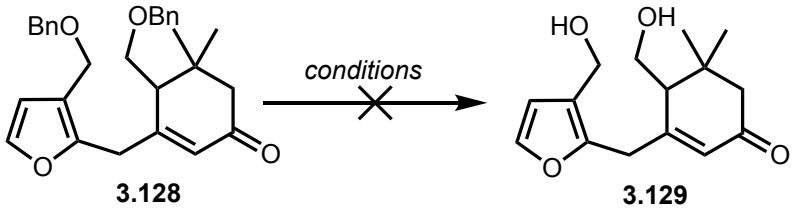
In this case, with the use of either 2.5 to 3 equiv ethynylmagnesium bromide, the desired enynone was only isolated in 33% yield (Scheme 3.54), presumably due to the presence of the acidic α-proton and the formation of significant amounts of deprotected product (1,3-dione). Subsequent Michael–Heck reaction of alcohol **3.111** and enynone **3.127** then yielded the bis(benzyloxymethyl) substituted furan **3.128** in 66% yield (Scheme 3.55).



Scheme 3.55. Michael–Heck reaction of alcohol **3.111** and enynone **3.127**

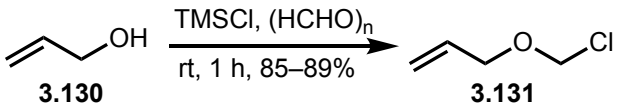
We then attempted to deprotect the benzyl groups using both transfer hydrogenation[49] and standard hydrogenation conditions. To our surprise, the benzyl ether groups proved to be very difficult to remove under the standard conditions used for their deprotection (Table 3.11). Due to the difficulty introducing the benzyloxymethyl group and deprotecting the benzyl ether, we decided to use a different protected hydroxymethyl group that can also be deprotected under neutral conditions .

Table 3.11. Attempts to deprotect furan **3.128**



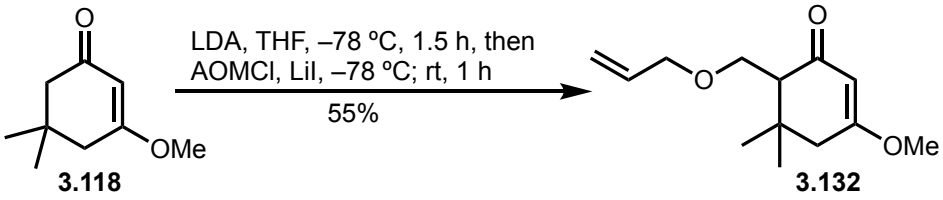
Entry	Conditions	Results
1	Pd/C, ammonium formate, MeOH, 50 ºC/3 h	SM only
2	Pd/C, triethylsilane, MeOH, rt, 16 h	SM only
3[50]	$Pd(OAc)_2$, NaH, DMA, 60 ºC, 0.5 h	decomposition
3	Pd/C, H_2, ethanol, rt, 4 h	SM only

Therefore, following literature conditions,[51] allyl chloromethyl ether was prepared from allyl alcohol and was isolated in 85–89% after careful isolation of the volatile product (Scheme 3.56)



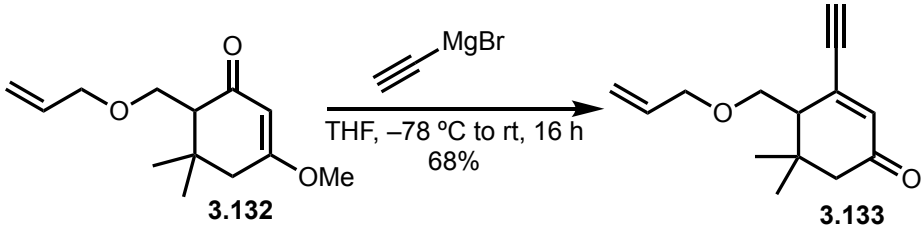
Scheme 3.56. Preparation of allyloxymethyl chloride **3.131**

The crude allyl chloromethyl ether was very clean and was used directly for the allyloxymethylation of vinylogous ester **3.118** to yield the corresponding product in 55% yield (Scheme 3.57).



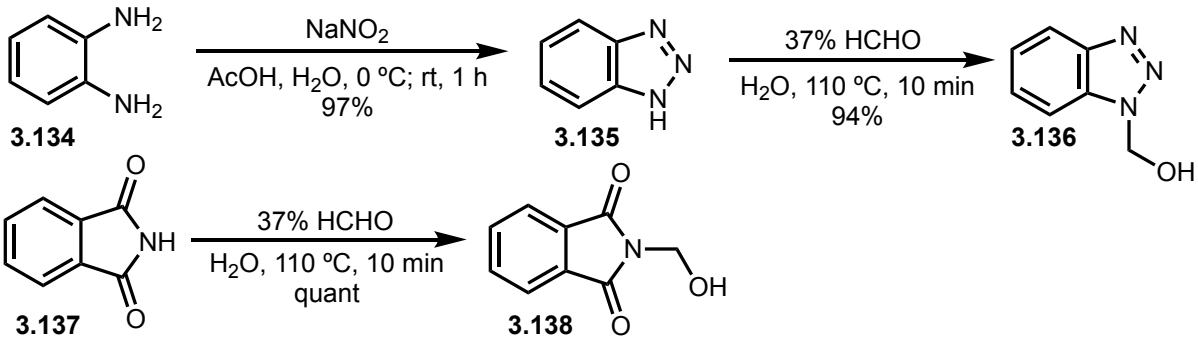
Scheme 3.57. Allyloxymethylation of vinylogous ester **3.118**

Stork–Danheiser transposition of the vinylogous ester **3.132** then furnished the desired enynone **3.133** in 68% yield (Scheme 3.58).



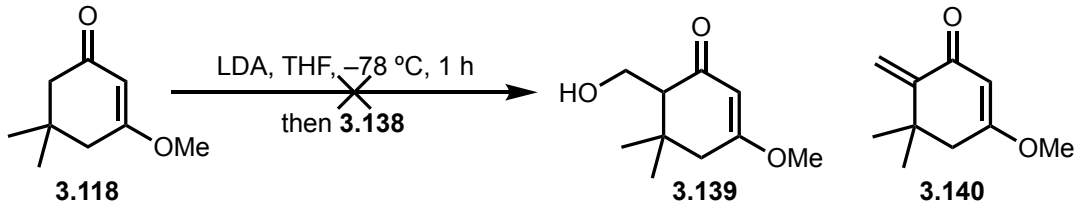
Scheme 3.58. Stork–Danheiser reaction of vinylogous ester **3.132**

Unfortunately, enynone **3.133** completely failed to undergo Michael addition. Being unable to install a protected hydroxymethyl group on the vinylogous ester in one step, we resorted to a two-step hydroxymethylation/protection approach. To avoid the hassle of generating toxic formaldehyde gas by the thermal cracking of paraformaldehyde, we looked into anhydrous sources of formaldehyde such as N-hydroxymethylphthalimide[50] and N-hydroxymethylbenzotriazole.[52]



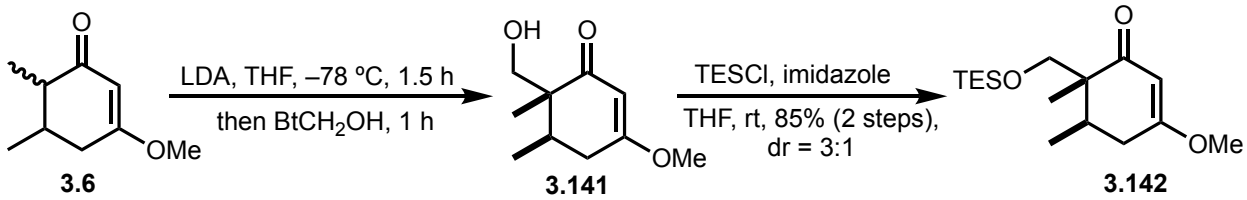
Scheme 3.59. Preparation of anhydrous sources of formaldehyde **3.136** and **3.138**

Following literature procedures,[53] known compounds **3.136** and **3.138** were easily prepared from commercially available materials in high yields (Scheme 3.59).While both of these reagents were reported to be effective sources of anhydrous formaldehyde, only N-hydroxymethylbenzotriazole **3.136** produced the hydroxymethylated product **3.139**. Unfortunately, despite careful workup, the product was found to be unstable with respect to elimination and enone **3.140** was the only product that was isolated (Scheme 3.60).



Scheme 3.60. Attempted hydroxymethylation of vinylogous ester **3.118**

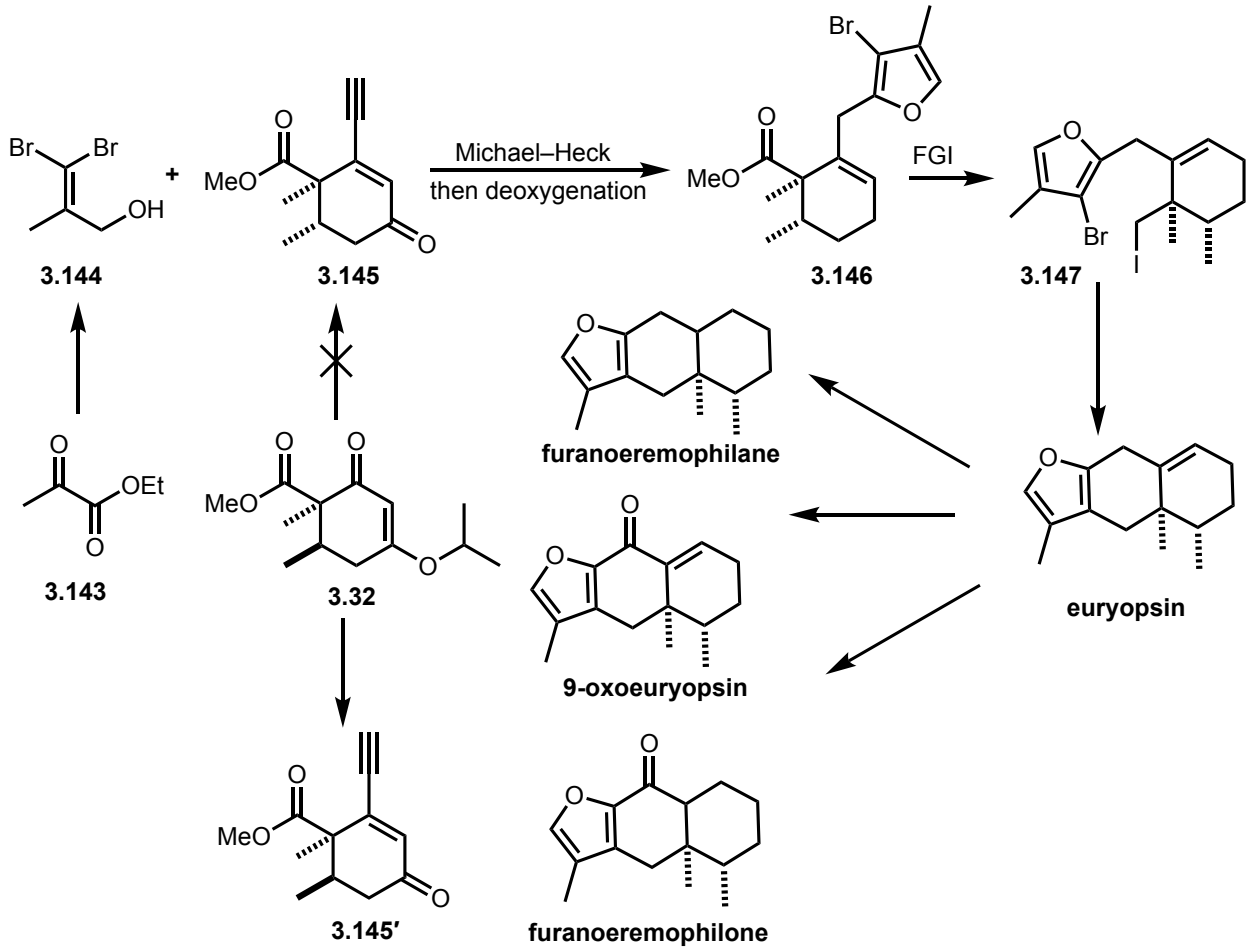
To avoid competitive elimination to form enone **3.140**, vinylogous ester **3.6** was used for the hydroxymethylation reaction with **3.136** instead. While the resulting vinylogous ester **3.141** is unable to undergo elimination to form the corresponding enone, it was still found to be unstable towards chromatographic purification on silica gel and had to be used directly after aqueous workup. However, in contrast to the alkylation with BOMCl/LiI or AOMCl/LiI, which both produced the desired product as a single diastereoisomer, the hydroxymethylation/silylation sequence gave a relatively low d.r of 3:1 for **3.142** (Scheme 3.61).



Scheme 3.61. Hydroxymethylation/silylation of vinylogous ester **3.6**

Given the difficulties encountered with this approach and the fact that there are more furan natural products with 6/6/5 tricyclic system than 6/7/5 system, two new routes for the total synthesis of furanoeremophilanes was devised.

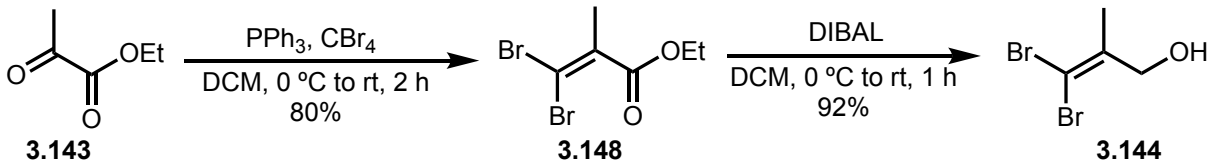
3.6. Intermolecular Approach to Furanoeremophilanes



Scheme 3.62. Retrosynthetic analysis for the preparation of furanoeremophilane natural products via intermolecular Michael–Heck reaction and C(sp^3)-C(sp^2) coupling

In this new approach, we envisioned that the key bromofuran intermediate can be accessed from the intermolecular vinylogous Michael–Heck reaction and deoxygenation of known *gem*-dibromo allylic alcohol **3.144**,[54] which can be prepared from ethyl pyruvate **3.143** using the Corey–Fuchs reaction and DIBAL reduction, and enynone **3.145**. The tertiary ester group in bromofuran **3.146** can then be converted to an iodomethyl group that can undergo a Pd-catalyzed alkylation[55] to forge the central six-membered ring in euryopsin, which then becomes the common intermediate for the divergent syntheses of other furanoeremophilane natural products (Scheme 3.62). In order to verify

the feasibility of this approach, a few concerns had to be addressed. Firstly, the compatibility of *gem*-dibromo allylic alcohol **3.144** with the Michael–Heck conditions needed to be established. Secondly, since carrying out Stork–Danheiser reaction on vinylogous ester **3.32** would produce **3.145'**, the *trans* isomer of **3.145**, a way to prepare the *cis* isomer of **3.32** would have to be figured out. In addition, conditions for the chemoselective addition of either ethynylmagnesium bromide or lithium TMS-acetylide to the ketone carbonyl of the β-ketoester **3.32** or its *cis* isomer had to be determined. In order to address the first concern, the *gem*-dibromo allylic alcohol **3.144** was prepared according to literature procedures[54] (Scheme 3.63):

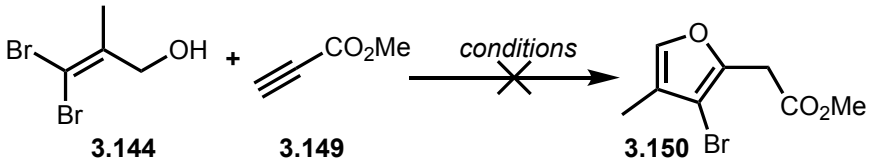


3.143 **3.148** **3.144**

Scheme 3.63. Preparation alcohol **3.144**

Next, it was subjected to the Michael–Heck conditions developed previously. Surprisingly, although the Michael addition step proceeded smoothly to deliver the (*E*)-β-alkoxyacrylate intermediate, the Heck reaction did not proceed at all under the conditions used (Table 3.12).

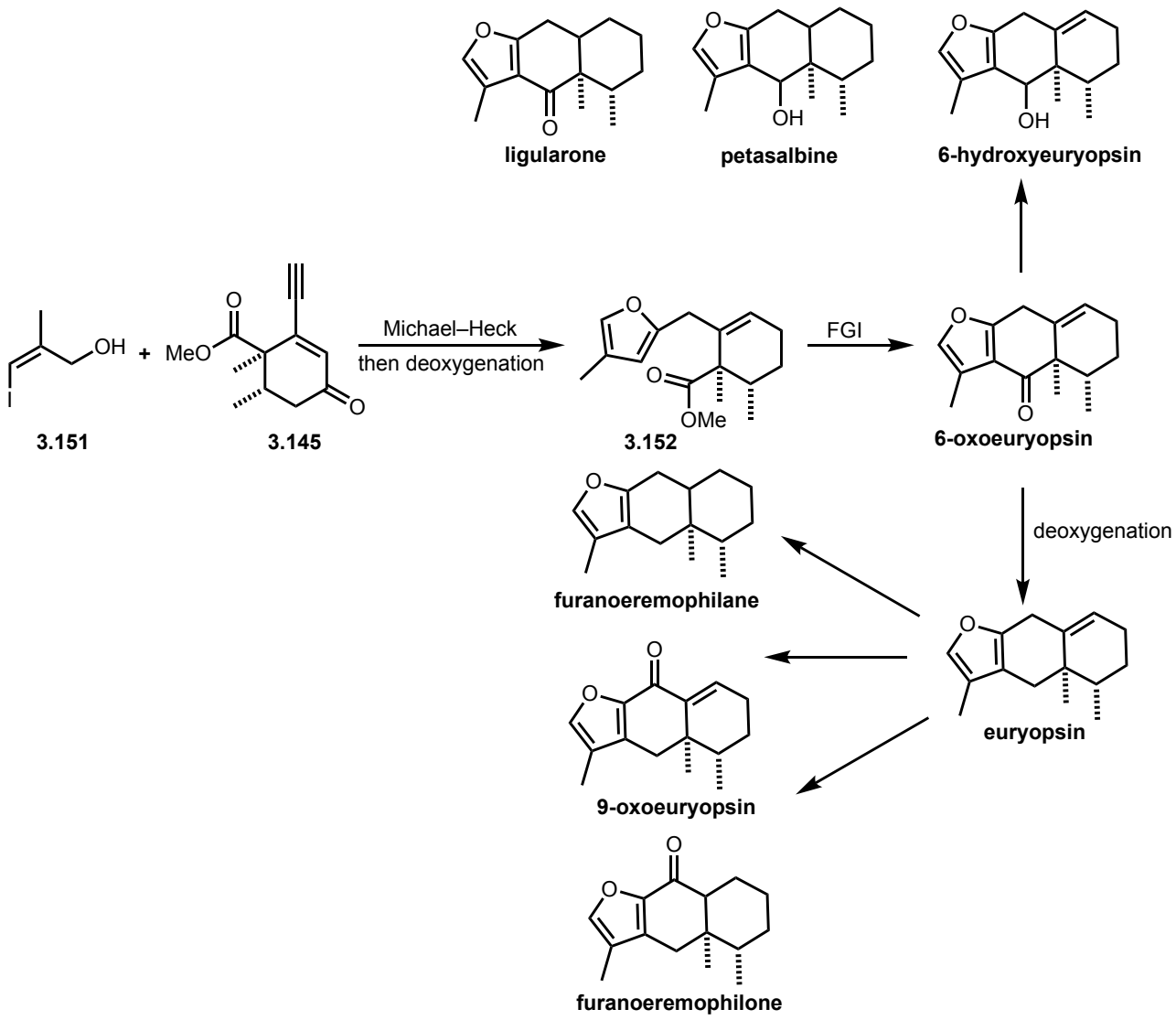
Table 3.12. Attempted Michael–Heck reaction of *gem* dibromo allylic alcohol **3.144**



3.144 **3.149** **3.150**

Entry	Conditions	Results
1	*cat.* PBu_3, then $Pd(OAc)_2$, TEA, TBAC	Michael adduct only
2	*cat.* PBu_3, then $Pd(OAc)_2$, $P(tBu)_3HBF_4$, NCy_2Me, TBAC	Michael adduct only

Having established that this starting material would not be compatible with the Michael–Heck conditions, a new synthetic plan was devised. In this approach, intermolecular vinylogous Michael–Heck addition between known allylic alcohol **3.151**[56] and enynone **3.145** followed by deoxygenation of the enone carbonyl would deliver the key 2,5-disubstituted furan **3.152**. The tertiary ester functional group handle can then be transformed to the corresponding acid chloride, which can then undergo intramolecular Friedel–Crafts acylation to close the central six-membered ring in 6-oxoeuryopsin. Deoxygenation of the benzylic ketone would then produce euryopsin, which can then be further used to diversified to access other furanoeremophilane natural products such as furanoeremophilane,[57] 9-oxoeuryopin[8] and furanoeremophilone[58]. 6-oxoeuryopsin itself can also serve as the common intermediate for the divergent syntheses of 6-hydroxyeuryopsin[59], petasalbine[60] and ligularone[60] (Scheme 3.64).

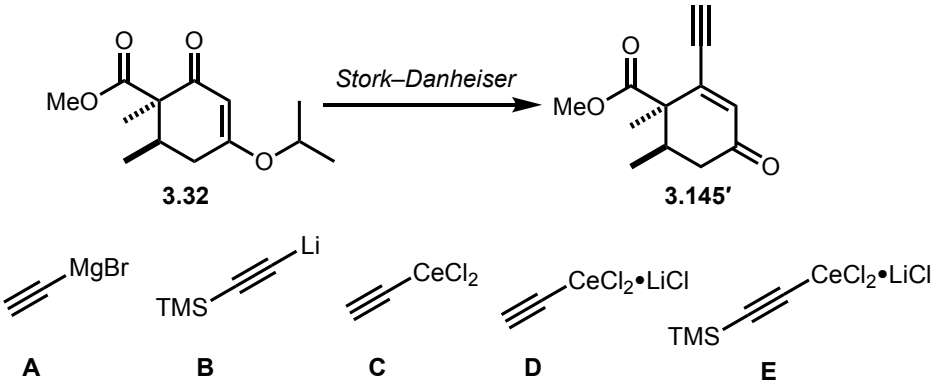


Scheme 3.64. Retrosynthetic analysis for the preparation of furanoeremophilane natural products via intermolecular/electrophilic aromatic substitution approach

With this new approach in mind, we commenced with the preparation of the key enynone **3.145**. The fact that large quantities of vinylogous ester **3.32** had already been prepared, we decided to test the feasibility of this synthetic plan by preparing **3.145'** from **3.32** and checking its compatibility with the Michael–Heck reaction. Therefore, **3.32** was subjected to the Stork–Danheiser reaction (Table 3.13). While ethynylmagnesium bromide failed to produce any detectable product (entries 1–4), the more nucleophilic lithium trimethylsilylacetylide followed by

deprotection with KF under phase transfer catalysis[61] produced small amounts of product, albeit in low yields (entries 5–7). Surmising that the strong basicity of the organolithium or Grignard reagents could be problematic for the rather base-sensitive β-ketoester precursor, we looked for non-basic sources of nucleophilic ethynyl group. Organocerium reagents[62] are known to be highly oxophilic but completely non-basic, compatible even with free alcohol or amine groups.

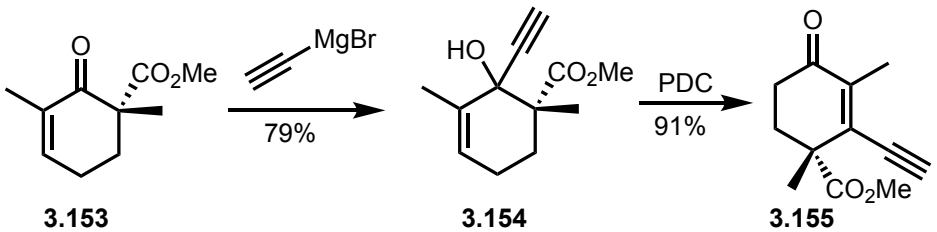
Table 3.13. Stork–Danheiser reaction of vinylogous ester **3.32**



Entry	Conditions	Result
1	1.6 equiv **A,** 0 ºC to rt, 16 h	SM only
2	1.6 equiv **A**, LiCl, 0 ºC to rt, 16 h	SM only
3	2.5 equiv **A**, 0 ºC to rt, 16 h	SM only
4	3 equiv **A**, 0 ºC to rt, 16 h	decomposition
5	2.5 equiv **B**, –78 ºC to rt, 1 h, then KF, *cat*. $BnBu_3NCl$	50% (yellow oil), < 20% (solid)
6	2 equiv **B**, –78 ºC to rt, 1 h, then KF, *cat*. $BnBu_3NCl$	15% (solid)
7	1.5 equiv **B**, –78 ºC to rt, 1 h, then KF, *cat*. $BnBu_3NCl$	~1: 0.33 product to SM
8	1.6 equiv **A**, $CeCl_3$, 0 ºC to rt, 16 h	SM only
9	1.1 equiv **A**, 1 equiv $LaCl_3$, 0 ºC to rt, 16 h	SM only
10[a]	1.6 equiv **A**, $CeCl_3$, 0 ºC to rt, 16 h	SM only
11	2 equiv **A**, $CeCl_3$•2LiCl, 0 ºC to rt, 16 h	SM only
12	2 equiv **A**, $LaCl_3$•2LiCl, 0 ºC to rt, 16 h	SM only
13[b]	1.6 equiv **C**, 0 ºC to rt, 16 h	SM only
14[b]	2 equiv **D**, –78 ºC to rt, 16 h	SM only
15[c]	2 equiv **E**, –78 ºC to rt, 1.5 h	~1:1 product to SM
16[c]	2.5 equiv **E**, –78 ºC to rt, 1.5 h	no SM, unknown
17[c]	3 equiv **E**, –78 ºC to rt, 1.5 h	no SM, unknown
18[c]	3.5 equiv **E**, –78 ºC to rt, 1.5 h	no SM, unknown

a) precomplexation of ketone with $CeCl_3$. b) transmetallated from **A**. c) transmetallated from **B**.

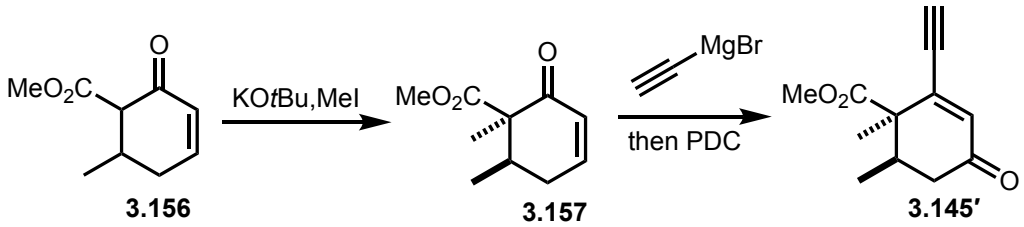
However, use of neither $CeCl_3$ nor $LaCl_3$ in the presence of ethynylmagnesium bromide[63] provided the desired product (entries 8, 9). Precomplexation[64] of the ketone with $CeCl_3$ prior to the addition of ethynylmagnesium bromide also proved futile (entry 10). Knochel and coworkers have reported on the use of soluble lanthanide salts to promote the addition of Grignard reagents to sterically hindered, enolizable ketones as well as α,β-unsaturated ketones and imines in excellent yields.[65] Disappointingly, neither the lanthanum or cerium (III) chloride lithium chloride complex[66] were successful in promoting the reaction (entries 11, 12). Suspecting that free ethynylmagnesium bromide might still be present, we decided to directly prepare the ethynylorganocerium species **C**, **D**, and **E**. Initially, the ethynylcerium(III) reagent **C** was prepared following Suzuki's method[67] (entry 13). However, no desired product could be detected, a situation also observed in the presence of LiCl[68] (entry 14). Suspecting that the transmetallation of $CeCl_3$ with ethynylmagnesium bromide could be inefficient, the lithium chloride complex of ethynylcerium (III) chloride **E** was prepared by transmetallation of $CeCl_3$ with **B**. In this case, the desired product was observed in ~1:1 ratio with the starting material (entry 15). Unfortunately, the reaction did not proceed to completion with neither prolonged reaction time nor larger amounts of **E** (entries 16–18). The results above suggested that Stork–Danheiser reaction of this vinylogous ester precursor would not be a viable way to prepare the desired enynone starting material. In Dubberke's total synthesis of trisporic acid B,[69] a Grignard addition/oxidative allylic transposition sequence was employed for the preparation of a key enynone intermediate **3.155** in good yield (Scheme 3.65):



3.153 **3.154** **3.155**

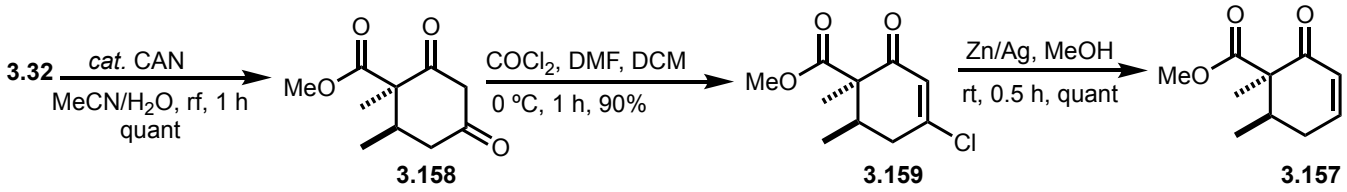
Scheme 3.65. Dubberke's preparation of enynone **3.155**

Therefore, we envisioned that the required enynone precursor **3.145'** could be prepared following the same logic. Methylation of the known β-ketoester **3.156**,[70] followed by Grignard addition and oxidative allylic transposition of **3.157** would furnish the desired enynone product **3.145'** (Scheme 3.66).



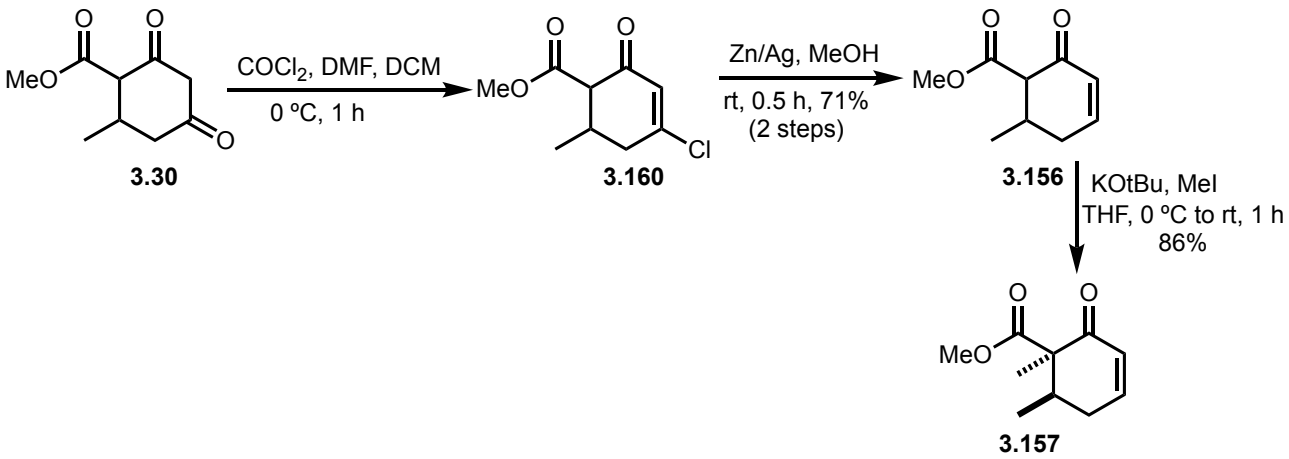
Scheme 3.66. Plan for the preparation of enynone **3.145'**

Given this precedent, we then decided to pursue the oxidative allylic transposition approach and converted the vinylogous β-ketoester **3.32** to the enone precursor **3.156** (Scheme 3.67):



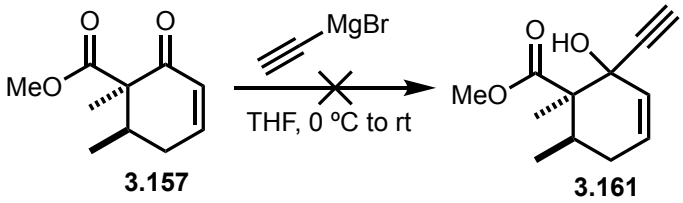
Scheme 3.67. Preparation of enone **3.156** from vinylogous ester **3.32**

Following Roy's method,[71] vinylogous ester **3.32** was quantitatively deprotected to form the corresponding dione **3.158** using catalytic amounts of ceric ammonium nitrate (CAN), which was then converted to chloroenone **3.159**, which was then efficiently reduced using a Zn/Ag couple following Clark's method to yield **3.157**.[72] Alternatively, enone **3.157** can be prepared in fewer steps from known dione **3.30** prepared by the previously used Michael–Claisen sequence[21] (Scheme 3.68):



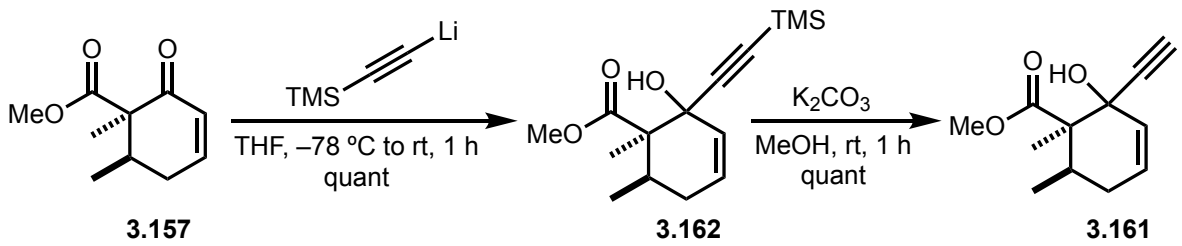
Scheme 3.68. Shorter route for preparation of **3.157**

Thus, treatment of known dione **3.30** with the Vilsmeier reagent generated *in situ* from oxalyl chloride and DMF[71] produced **3.160**, the methyl ester analog of known chloroenone,[74] which was then reduced using a Zn/Ag couple[72] to give known β-ketoester **3.156**[70] in 71% over two steps. Methylation then provided the desired β-ketoester **3.157** in 86% yield. With a robust route to the prerequisite enone **3.157**, we then investigated conditions for the addition of nucleophilic ethynyl group to the enone carbonyl (Scheme 3.69).



Scheme 3.69. Addition of ethynylmagnesium bromide to enone **3.157**

However, use of the conditions reported in Dubberke's paper failed to produce any detectable product even after 16 h. Fortunately, use of lithium trimethylsilylacetylide proceeded smoothly, affording both the TMS-protected **3.162** or deprotected **3.161** in quantitative yields (Scheme 3.70).

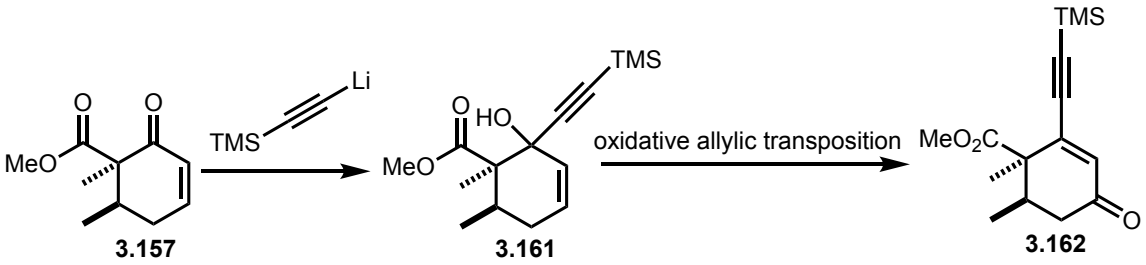


3.157 **3.162** **3.161**

Scheme 3.70. Preparation of alcohol **3.161**

With the propargyl alcohols in hand, we then set out to investigate the oxidative allylic transposition (Table 3.14). Since suprastoichiometric amounts of chromium (VI) oxidants such as pyridinium chlorochromate (PCC) or pyridinium dichromate (PDC) are typically used for oxidative allylic transpositions,[75] we started by using a combination of PCC and 4Å molecular sieves,[76] which are known to accelerate oxidation reactions with PCC (entry 1). However, neither **3.161** nor its free ethynyl analog were able to provide the desired enynone in synthetically useful yields.

Table 3.14. Oxidative allylic transposition of alcohol **3.161**

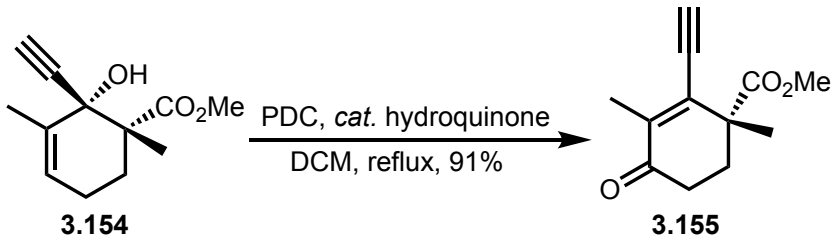


3.157 **3.161** **3.162**

Entry	Conditions	Result[a]
1	3 equiv PCC/4Å MS, rt, 16 h, then KF, *cat.* $BnBu_3NCl$	35%[c]
2	*cat.* TEMPO, 2 equiv $CuCl_2$, rt, 16 h	SM only
3	3 equiv $TEMPO^+BF_4^-$, rt, 16 h	SM only
4	3 equiv PDC, *cat.* hydroquinone, reflux, 24 h	SM only
5	3 equiv PDC, reflux, 24 h	1: 10 product to SM
6	3.5 equiv PCC/Celite, 0.7 equiv TEA, rt, 16 h	1:0.95 product to SM
7	3.5 equiv PCC/4A MS, NaOAc, rt, 22 h, then KF, *cat.* $BnBu_3NCl$, water/THF, 0.5 h	55%[b,c]
8	3.5 equiv PCC/4A MS, NaOAc, rt, 22 h, then KF, *cat.* $BnBu_3NCl$, water/THF, 0.5 h	65%[c]

[a] propargyl alcohol **3.161** was used directly. [b] with recovered SM. [c] 3-step yield.

Multiple methods involving the use of catalytic TEMPO and stoichiometric amounts of co-oxidant such as $CuCl_2$,[77a] $NaIO_4$/silica,[77b] PhIO,[77c], Oxone,[77d] etc, have also been reported. Unfortunately, in this case, neither the use of catalytic TEMPO in combination with excess $CuCl_2$ (entry 2) nor the direct use of excess cationic TEMPO[78] (entries 3) were able to provide any desired product. In Westermann's total synthesis of nagilactone A,[79] a highly efficient oxidative allylic transposition of **3.154** using PDC in the presence of catalytic amounts of hydroquinone (presumably as a polymerization inhibitor) was employed to prepare highly functionalized enynone **3.155** (Scheme 3.71). However, subjecting **3.161** to Westermann's conditions provided none of the desired product (entries 4). In the absence of hydroquinone, small amounts of product was observed for the **3.162** (entry 5) while none was detected for its free ethynyl analog, presumably due to the fact that the presence of the TMS-protecting group significantly slows down competitive polymerization.

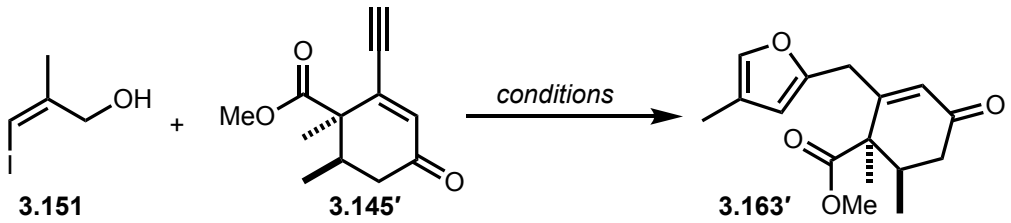


Scheme 3.71. Westermann's preparation of enynone **3.155**

Suspecting that the low yields of the PCC oxidation reactions might be due to the acid lability of the propargyl alcohol precursor, the reaction was then retried in the presence of triethylamine as a base. However, incomplete reaction was observed for **3.162** (entry 6) while no reaction was observed for its free ethynyl analog. To our delight, use of NaOAc in combination with PCC/4Å molecular sieves furnished the desired product in 55% yield (using starting material recycled from

the previous failed reactions, entry 7) and in 65% yield (using fresh starting material, entry 8) over three steps. With a robust route to the requisite enynone in hand, we then proceeded to the optimization of the key Michael–Heck reaction (Table 3.15). Subjecting **3.152** and **3.148'** to the previously developed Michael–Heck conditions (with DIPEA instead of Et_3N) produced the desired furan intermediate **3.163'** in 34% yield (entry 1). Extending the reaction time resulted in a much improved yield of 68% (entry 2). Use of PMe_3 as the organocatalyst for the Michael addition followed by use of PBu_3 (entry 3) or P(o-tol)$_3$ (entry 4) in the Heck reaction resulted in much lower yields.

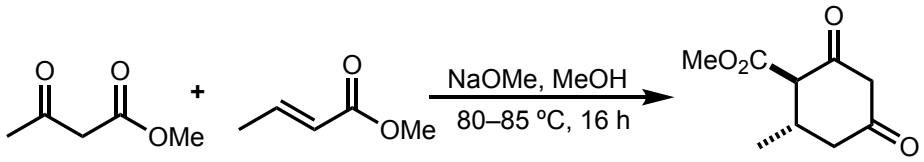
Table 3.15. Michael–Heck reaction of alcohol **3.151** and enynone **3.145'**



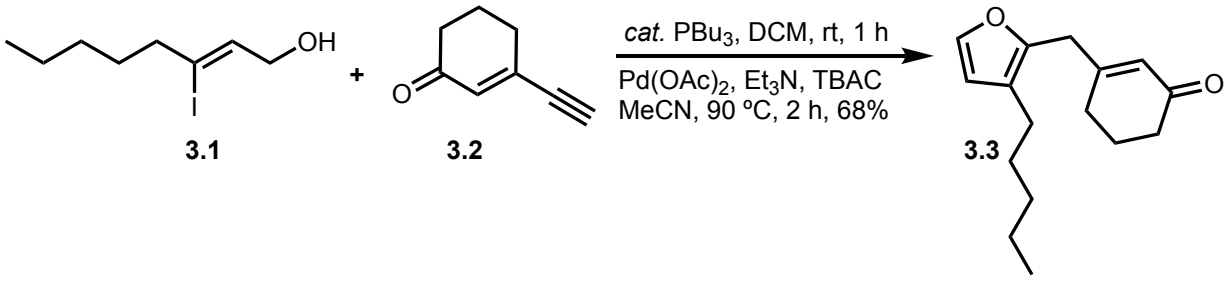
3.151 **3.145′** **3.163′**

Entry	*Conditions*	*Result*[a]
1	*cat.* PBu_3, then $Pd(OAc)_2$, DIPEA, TBAC, MeCN, 90 ºC, 4 h	34%
2	*cat.* PBu_3, then $Pd(OAc)_2$, DIPEA, TBAC, MeCN, 90 ºC, 14 h	68%
3	*cat.* PMe_3, then $Pd(OAc)_2$, PBu_3, DIPEA, TBAC, MeCN, 90 ºC,14 h	messy
4	*cat.* PMe_3, then $Pd(OAc)_2$, P(o-tol)$_3$, DIPEA, TBAC, MeCN, 90 ºC, 14 h	31%

3.7. Experimental



The known dione was prepared according to modified literature procedures. To a 250mL round-bottomed flask equipped with a magnetic stir bar and reflux condenser was added NaOMe (4.6 g, 84.6952 mmol, 1.3 equiv) and anhydrous MeOH (22 mL, 3.9 M) (*Caution*: very exothermic). Upon complete dissolution of the NaOMe, methyl acetoacetate (7 mL, 65.1501 mmol, 1 equiv) was slowly added neat under stirring. Methyl crotonate (8.3 mL, 78.1801 mmol, 1.2 equiv) was then added neat. Once heat evolution ceases, the flask was immersed in the oil bath and refluxed for overnight. After cooling the reaction mixture to room temperature, it was concentrated to dryness *in vacuo*. 1M HCl was then added to dissolve the crude orange solid and adjust its pH to 1. The orange solution was then extracted 3x with ethyl acetate until no more product could be detected in the aqueous layer. The organic layer was then washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude light orange solid thus obtained was then washed 3x with 50% ether/hexane until the ether/hexane layer was clear and the solid thus obtained was carefully air-dried and then dried under high vacuum to yield the title product as an ivory white solid (10.4 g, 87%). Spectroscopic data matches those found in the literature.



3.1 3.2 3.3

To an oven-dried round-bottomed flask A containing **3.1** (350 mg, 1.3774 mmol, 1 equiv), PBu_3 (68µL, 0.2755 mmol, 20 mol%) and anhydrous DCM (14 mL, 0.1 M) was slowly added a solution of enynone **3.2** (200mg, 1.6528 mmol, 1.2 equiv) in DCM (2 mL, 1 M). The resulting solution was then stirred at rt for 30 minutes. To a separate round-bottomed flask B was added $Pd(OAc)_2$ (31 mg, 0.1377 mmol, 10 mol%) and TBAC (383 mg, 1.3774 mmol, 1 equiv). Upon completion of the Michael addition as indicated by TLC, the solution was concentrated to minimal volume, re-dissolved in anhydrous MeCN (14 mL, 0.1 M) and added to flask B. Triethylamine (1 mL, 7.1623 mmol, 5.2 equiv) was then added and the resulting solution was then heated to reflux for 2 hours. Upon completion as indicated by TLC, the crude reaction was concentrated *in vacuo* , re-dissolved in 20% ethyl acetate/hexanes, filtered through a silica plug and concentrated *in vacuo.* The crude product was then purified using flash column chromatography (10–15% ethyl acetate/hexanes) to deliver furan **3.3** as a yellow oil (230 mg, 68%).

3-((3-Pentylfuran-2-yl)methyl)cyclohex-2-en-1-one (3.3)

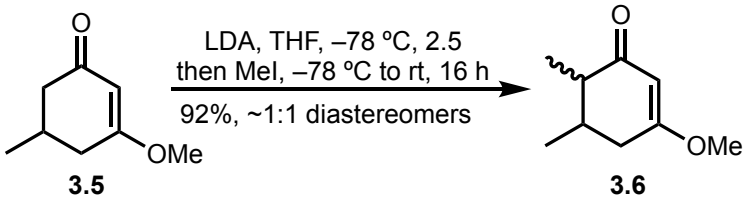
^{1}H NMR (500 MHz, $CDCl_3$):δ 7.25 (d, *J* = 1.9 Hz, 1 H), 6.22 (d, *J* = 1.8 Hz, 1 H), 5.80 (t, *J* = 1.4 Hz, 1 H), 3.47 (s, 2 H), 2.25–2.37 (m, 6 H), 1.98 (quintet, *J* = 6.3 Hz, 2 H), 1.49 (quintet, *J* = 7.6 Hz, 2 H), 1.22–1.53 (m, 4 H), 0.87 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 199.8, 162.4, 145.4, 141.0, 126.6, 121.8, 111.6, 37.2, 34.5, 31.5, 29.9, 29.2, 24.6, 22.5, 22.4, 14.0.

IR (neat): 2954, 2925, 2872, 2859, 1665, 1627, 1562, 1512, 1456, 1428, 1371, 1349, 1321, 1251, 1193, 1147, 1133, 1093, 1052, 1010 cm^{-1}.

HRMS (ESI): calc'd for $C_{16}H_{22}O_2$ $[M + H]^+$, *m/z* 246.1614; found 246.1614.

R_f = 0.32 (10% EtOAc/hexanes).



To an oven-dried round-bottomed flask was added diisopropylamine (3.7 mL, 26.7513 mmol, 1.25 equiv) and anhydrous THF (27 mL, 1 M). After cooling to 0 ºC, nBuLi (9.9 mL, 26.7513 mmol, 1.25 equiv, 2.7 M in hexanes) was then slowly added and the reaction was continued for another 30 minutes. The reaction was then cooled to –78 ºC and a solution of vinylogous ester **3.5** (3 g, 21.4011 mmol, 1 equiv) in THF (15 mL, 1.4 M) was then slowly added and the reaction was continued for another 3 h at the same temperature. MeI (2.2 mL, 34.8837 mmol, 1.6 equiv) was then slowly added and the reaction was moved to rt. The reaction was then allowed to continue at rt and stirred for overnight. The reaction was then quenched with 1 M HCl and extracted with ethyl acetate. The crude organic layer was washed with brine, dried with anhydrous Na_2SO_4, concentrated *in vacuo* and purified using flash column chromatography (15–18% ethyl acetate/hexanes) to give **3.6** as a light orange oil (3.04 g, 92%)

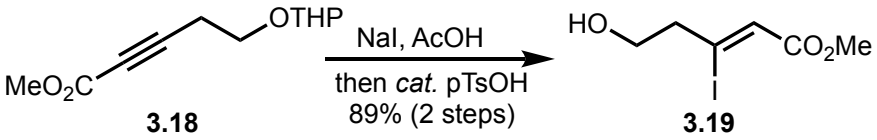
3-Methoxy-5,6-dimethylcyclohex-2-en-1-one (3.6)

^{1}H NMR (500 MHz, $CDCl_3$):δ 5.31 (s, 1 H), 5.26 (s, 1 H), 3.64 (s, 3 H), 2.25–2.43 (m, 4 H), 2.14–2.22 (m, 2 H), 1.80–1.95 (m, 2 H), 1.12 (dd, *J* = 6.6, 1.4 Hz, 3 H), 1.06 (dd, *J* = 6.6, 1.3 Hz, 3 H), 1.02 (dd, *J* =7.1, 1.4 Hz, 3 H), 0.94 (dd, *J* = 7.0, 1.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 202.9, 201.5, 176.5, 176.4, 101.2, 100.7, 55.5, 55.5, 47.1, 44.9, 36.5, 34.8, 34.4, 31.9, 19.7, 15.7, 12.8, 11.0.

IR (neat): 3053, 2971, 1717, 1646, 1610, 1453, 1379, 1265, 1220, 1193, 1167 cm^{-1}.

***R*$_f$** = 0.66 (25% EtOAc/hexanes).



To an oven-dried round-bottomed flask was added **3.18** (4.4533 g, 20.98 mmol, 1 equiv), NaI (5.08 g, 33.8915 mmol, 1.6 equiv) and AcOH (8 mL). The resulting mixture was then refluxed for 30 minutes at 115 ºC. Upon completion as indicated by TLC, the reaction was cooled to rt and slowly added to a solution of saturated $NaHCO_3$ (*Note*: vigorous fizzing occurs). After no more fizzing occurs, the mixture was extracted three times with ethyl acetate. The organic layer was then washed with brine, dried with anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was then passed through a silica plug (45% ethyl acetate) to remove baseline impurities and concentrated *in vacuo*. The crude product was then dissolved in MeOH (40 mL, 0.5 M) and pTsOH• H_2O (807 mg, 4.2403 mmol, 20 mol%) was added and the reaction was continued at room temperature for 1 h. Upon completion as indicated by TLC, the reaction was concentrated *in vacuo* and purified using flash column chromatography (20–35% ethyl acetate/hexanes) to give **3.19** as a yellow oil (4.6974 g, 89%).

Methyl (*Z*)-5-hydroxy-3-iodopent-2-enoate (3.19)

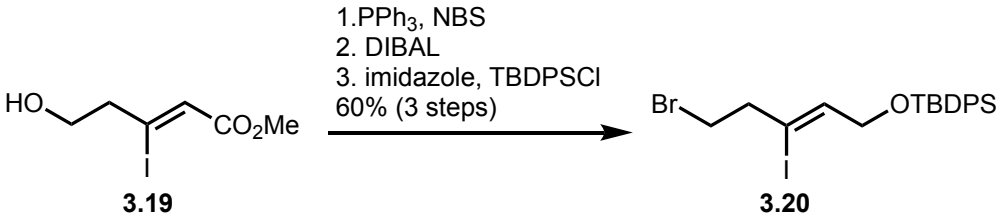
^{1}H NMR (500 MHz, $CDCl_3$):δ 6.48 (s, 1 H), 3.85 (t, *J* = 5.8 Hz, 2 H), 3.76 (s, 3 H), 2.94 (td, *J* = 5.9, 1.1 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 164.8, 126.9, 116.8, 60.8, 51.7, 50.4.

IR (neat): 3367, 2946, 1720, 1622, 1434, 1328, 1311, 1201, 1171, 1047 cm^{-1}.

***R*$_f$** = 0.25 (25% EtOAc/hexanes).

HRMS (ESI): calc'd for $C_6H_9IO_3$ $[M + H]^+$, *m/z* 255.9591; found 255.9586.



To an oven-dried round-bottomed flask was added NBS (4.7 g, 26.2459 mmol, 1.6 equiv), **3.19** (4.2 g, 16.4037 mmol, 1 equiv) and anhydrous THF (32 mL, 0.5 M). After cooling to 0 ºC, a solution of PPh_3 (6.5 g, 24.6055 mmol, 1.5 equiv) in THF (50 mL, 0.5 M) was then slowly added. After the addition was complete, the cooling bath was removed and the resulting solution was then stirred in the dark for 20 minutes at rt. Upon completion as indicated by TLC, the crude reaction was concentrated *in vacuo* to minimal volume, re-dissolved in 50% ether/hexane, filtered through a silica plug and concentrated *in vacuo.* The crude bromide was then re-dissolved in dry ether and added to another oven-dried round bottomed flask. After cooling to 0 ºC, DIBAL (41 mL, 41.0092 mmol, 1 M in hexane, 2.5 equiv) was slowly added and the reaction was continued at the same temperature for 1 h. Upon completion as indicated by TLC, the reaction was slowly quenched following Fieser's work-up protocol. The crude bromoalcohol was concentrated *in vacuo*, re-dissolved in anhydrous THF (32 mL, 0.5 M) and transferred to another oven-dried round-bottomed flask containing imidazole (2.2 g, 32.8074 mmol, 2 equiv). TBDPSCl (4.5 mL, 17.2239 mmol,

1.05 equiv) was then slowly added under stirring and the reaction was continued at rt for 30 minutes. Upon completion as indicated by TLC, the reaction was quenched by saturated NH_4Cl, extracted three times with ethyl acetate and washed with brine. The organic layer was then dried with anhydrous Na_2SO_4, concentrated *in vacuo* and purified using flash column chromatography (0–6% ethyl acetate/hexanes) to give **3.20** as white solid (5.12 g, 60%).

(*Z*)-((5-Bromo-3-iodopent-2-en-1-yl)oxy)(*tert*-butyl)diphenylsilane (3.20)

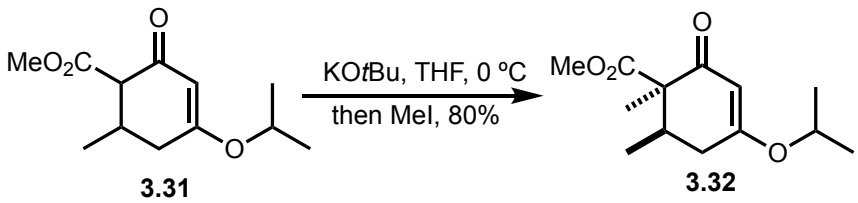
^{1}H NMR (500 MHz, $CDCl_3$):δ 7.67–7.69 (m, 4 H), 7.38–7.46 (m, 6 H), 6.02 (t, *J* = 5.1 Hz, 1 H), 4.26 (d, *J* = 5.1 Hz, 2 H), 3.45 (t, *J* = 6.9 Hz, 2 H), 2.95 (t, *J* = 6.9 Hz, 2 H), 1.06 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 138.2, 135.6, 134.8, 133.4, 129.7, 127.8, 101.5, 68.8, 47.5, 31.3, 26.8, 19.2.

IR (neat): 3074, 3048, 2956, 2931, 2894, 2858, 1474, 1463, 1425, 1390, 1264, 1182, 1107, 1071 cm^{-1}.

***R*$_f$** = 0.66 (10% EtOAc/hexanes).

HRMS (ESI): calc'd for $C17H17BrIOSi$ $[M - C4H9]^+$, *m/z* 470.9271; found 470.9270, 471.9297.



3.31 **3.32**

To an oven-dried round-bottomed flask containing **3.31** (6 g, 26.5270 mmol, 1 equiv) and anhydrous THF (38 mL, 0.7 M) at 0 ºC was slowly added a solution of KO*t*Bu (3.57 g, 31.8204 mmol, 1.2 equiv) in THF (32 mL, 1 M). The resulting enolate solution was stirred at the same temperature for 20 minutes and MeI (5 mL, 79.581 mmol, 3 equiv) was slowly added. The ice bath was then removed and the reaction was continued for another 1 h. Upon completion as indicated by TLC, the reaction as quenched with 1 M HCl and extracted three times with ethyl acetate. The

organic layer was then washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified using flash column chromatography (20–22% ethyl acetate) to give **3.32** as a light yellow oil (4.97 g, 78%, *trans* diastereomer)

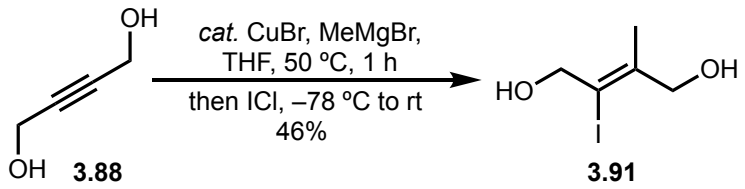
Methyl 4-isopropoxy-1,6-dimethyl-2-oxocyclohex-3-ene-1-carboxylate (3.32)

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.39 (s, 1 H), 4.46 (septet, *J* = 6.1 Hz, 1 H), 3.66 (s, 3 H), 2.57 (dd, *J* = 17.4, 1.1 Hz, 1 H), 2.23 (dd, *J* = 17.4, 4.8 Hz, 1 H), 2.07–2.14 (m, 1 H), 1.42 (s, 3 H), 1.30 (dd, *J* = 6, 1.7 Hz, 6 H), 1.07 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 197.0, 175.9, 171.5, 101.8, 71.1, 56.2, 52.0, 37.2, 35.3, 21.5, 21.5, 19.4, 16.5.

IR (neat): 2982, 2878, 1730, 1651, 1601, 1455, 1382, 1324, 1266, 1217, 1139, 1109 cm^{-1}.

***R*$_f$** = 0.48 (25% EtOAc/hexanes).



To an oven-dried two-necked round-bottomed flask was added 2-butyne-1,4-diol **3.88** (945 mg, 10.9769 mmol, 1 equiv) and THF (21 mL, 0.5 M). After cooling to 0 ºC, MeMgBr (14.6 mL, 4. equiv, 3 M in ether) was slowly added. The reaction was then moved to rt and stirred for five minutes before CuBr (472 mg, 3.2931 mmol, 30 mol%) was added. The reaction was then moved to a pre-heated oil bath and heated to 50 ºC for 1 h. The reaction was then moved to –78 ºC and ICl (16.5 mL, 16.4654 mmol, 1.5 equiv, 1 M in DCM) was then slowly added and the reaction was continued at –78 ºC to rt for 1 h. Upon completion as indicated by TLC, the reaction was quenched saturated NH_4Cl and extracted three times with ethyl acetate. The organic layer was then washed

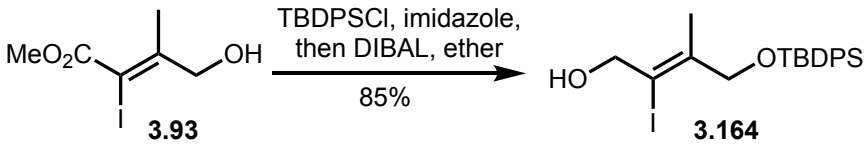
with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo,* and purified using flash column chromatography (50–70% ethyl acetate/hexanes) to give diol **3.91** as a white solid (1.1588g, 46%).

(*Z*)-2-Iodo-3-methylbut-2-ene-1,4-diol (3.91)

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.38 (s, 2 H), 4.27 (s, 2 H), 2.01 (s, 3 H), 1.93 (bs, 1 H), 1.69 (bs, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 142.0, 103.3, 73.0, 67.4, 16.7.

***R*$_f$** = 0.47 (50% EtOAc/hexanes).



To an oven-dried round-bottomed flask containing **3.93** (2.6 g, 10.1547 mmol, 1 equiv), imidazole (1.4 g, 20.3093 mmol, 2 equiv) and anhydrous THF (20 mL, 0.5 M) was added TBDPSCl (2.6 mL, 10.1547 mmol, 1.05 equiv) at rt. After 30 minutes at the same temperature, the reaction was quenched with saturated NH_4Cl and extracted three times with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give the crude TBDPS ether, which was re-dissolved in dry ether and transferred to another oven-dried round-bottomed flask. After cooling to 0ºC, DIBAL (25 mL, 25.3868 mmol, 2.5 equiv, 1 M in hexanes) was slowly added and the reaction was continued at the same temperature for 1 h. Upon completion as indicated by TLC, the reaction was worked up using Fieser's workup protocol and the crude reaction was concentrated *in vacuo*. Purification with flash column chromatography (10–16% ethyl acetate/hexanes) then furnished **3.164** as a clear oil (4g, 85%, 2 steps).

(*Z*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-iodo-3-methylbut-2-en-1-ol (3.164)

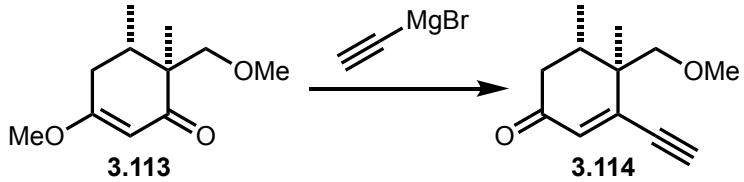
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (dd, *J* = 8.0, 1.6 Hz, 4 H), 7.38–7.46 (m, 6 H), 4.36 (s, 2 H), 4.32 (s, 2 H), 1.08 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 142.3, 135.6, 133.2, 129.7, 127.7, 100.7, 73.7, 67.5, 26.8, 19.3, 16.3.

IR (neat): 3296, 3069, 3048, 2956, 2927, 2890, 2853, 1474, 1459, 1426, 1425, 1263, 1110, 1074 cm^{-1}.

***R*$_f$** = 0.68 (25% EtOAc/hexanes).

HRMS (ESI): calc'd for $C_{17}H_{18}IO_2Si$ $[M - C_4H_9]^+$, *m/z* 409.0115; found 409.0111.

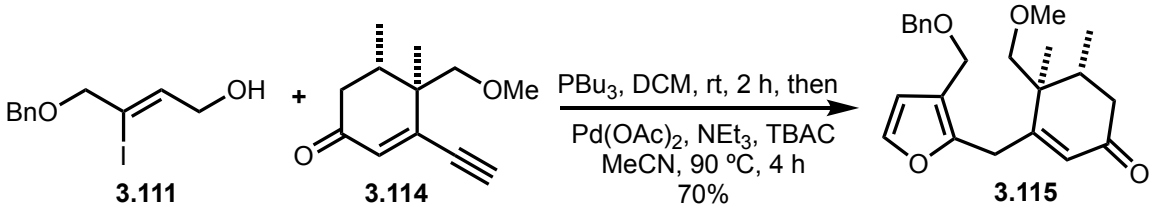


To an oven-dried round-bottomed flask was added **3.113** (740 mg, 3.7325 mmol, 1 equiv) and anhydrous THF (7.5 mL, 0.5 M). After cooling to 0 ºC, ethynylmagnesium bromide (18.7 mL, 9.3312 mmol, 2.5 equiv, 0.5 M in ether) was added slowly. After addition was complete, the reaction was moved to rt and the reaction was stirred for overnight. The reaction was then quenched 1 M HCl and extracted three times with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified using flash column chromatography (10–15% ethyl acetate/hexanes to give **3.114** as a light yellow oil (574 mg, 80%, *cis* diastereoisomer).

3-Ethynyl-4-(methoxymethyl)-4,5-dimethylcyclohex-2-en-1-one (3.114)

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.29 (s, 1 H), 3.64 (d, *J* = 9.4 Hz, 1 H), 3.51 (s, 1 H), 3.37 (d, *J* = 9.5 Hz, 1 H), 3.35 (s, 3 H), 2.53–2.60 (m, 1 H), 2.40 (dd, *J* = 16.9, 4.3 Hz, 1 H), 2.25–2.31 (m, 1 H), 1.00 (s, 3 H), 0.98 (d, *J* = 6.9 Hz, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 198.1, 149.2, 134.9, 87.4, 80.7, 75.7, 59.2, 43.2, 41.7, 31.5, 15.7, 15.6.

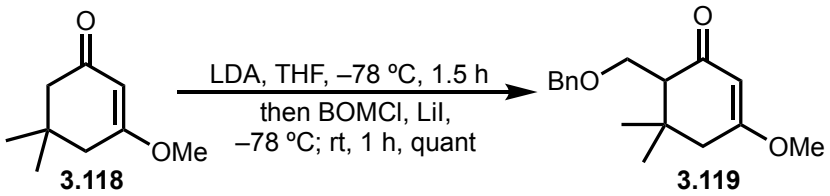


To an oven-dried round-bottomed flask A containing **3.111** (600 mg, 1.9728 mmol, 1 equiv), PBu_3 (97 µL, 0.3946 mmol, 20 mol%) and anhydrous DCM (20 mL DCM, 0.1 M). A solution of **3.114** (455 mg, 2.3674 mmol, 1.2 equiv) in DCM (2.4 mL, 1 M) was then slowly added at rt. The resulting solution was then stirred at rt for 2 h. To another round-bottomed flask B was added $Pd(OAc)_2$ (44 mg, 0.1973 mmol, 10 mol%) and TBAC (548 mg, 1.9728 mmol, 1 equiv). Upon completion of the Michael reaction, the reaction was concentrated to minimal volume, re-dissolved in anhydrous MeCN (20 mL, 0.1 M) and added to flask B. Triethylamine (1.4 mL, 10.2588 mmol, 5.2 equiv) was then added and the reaction was refluxed for 4 h. Upon completion as indicated by TLC, the reaction was concentrated *in vacuo*, re-dissolved in 35% ethyl acetate/hexane, filtered through a silica plug and concentrated *in vacuo*. Purification with flash column chromatography (10–15% ethyl acetate/hexane) then furnished **3.115** as a light orange oil (508 mg, 70%).

3-((3-((Benzyloxy)methyl)furan-2-yl)methyl)-4-(methoxymethyl)-4,5-dimethylcyclohex-2-en-1-one (3.115)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27–7.37 (m, 6 H), 6.39 (d, *J* = 1.6 Hz, 1 H), 5.53 (s, 1 H), 4.50 (s, 2 H), 4.32 (dd, *J* = 17.0, 11.9 Hz, 2 H), 3.58 (q, *J* = 17.9 Hz, 2 H), 3.44 (d, *J* = 9.8 Hz, 1 H), 3.35 (d, *J* = 9.8 Hz, 1 H), 3.30 (s, 3 H), 2.46–2.54 (m, 1 H), 2.36 (dd, *J* = 17.5, 4.5 Hz, 1 H), 2.17–2.26 (m, 1 H), 0.96 (d, *J* = 6.9 Hz, 3 H), 0.90 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 198.8, 167.0, 148.7,141.7, 138.1, 128.4, 127.8, 127.7, 127.7, 118.8, 111.6, 71.9, 63.1, 59.1, 43.3, 41.8, 33.1, 29.4, 15.5, 15.2.



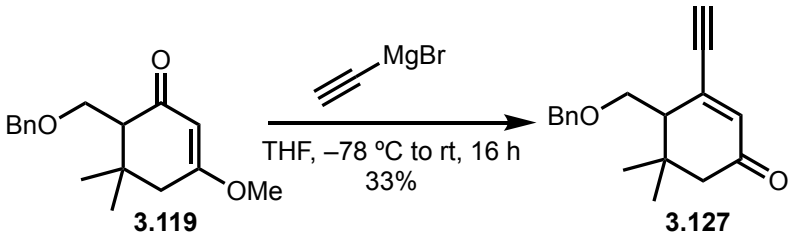
3.118 **3.119**

To an oven-dried round-bottomed flask was added diisopropylamine (341 µL, 2.4318 mmol, 1.5 equiv) and anhydrous THF (2.5 mL, 1 M). After cooling to 0 ºC, nBuLi (1 mL, 2.4318 mmol, 1.5 equiv, 2.5 M in hexanes) was then slowly added and the reaction was continued for another 30 minutes. The reaction was then cooled to –78 ºC and a solution of **3.118** (250 mg, 1.6212 mmol, 1 equiv) in anhydrous THF (2 mL, 0.8 M) was slowly added. After stirring for 1.5 h at the same temperature, LiI (651 mg, 4.8636 mmol, 3 equiv) in THF (6 mL, 0.8 M) was then added, followed by BOMCl (676 µL, 4.8636 mmol, 3 equiv). The reaction was then moved to rt and the reaction was continued at the same temperature for 1 h. Upon completion as indicated by TLC, the reaction was quenched with 1 M HCl and extracted three times with ethyl acetate. The organic layer was then washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified using flask column chromatography (10–13% ethyl acetate/hexanes) to furnish **3.119** as a light yellow oil (445 mg, quant, single diastereomer).

6-((Benzyloxy)methyl)-3-methoxy-5,5-dimethylcyclohex-2-en-1-one (3.119)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.37 (m, 5 H), 5.39 (s, 1 H), 4.49 (s, 2 H), 3.87 (dd, *J* = 12.2, 5.5 Hz, 1 H), 3.67 (dd, *J* = 12.2, 5.5 Hz, 1 H), 3.67 (s, 3 H), 2.48 (d, *J* = 17.4 Hz, 1 H), 2.27 (t, *J* = 5.7 Hz, 1 H), 2.20 (d, *J* = 17.4 Hz, 1 H), 1.12 (s, 3 H), 1.02 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 200.2, 176.4, 138.4, 128.2, 127.4, 127.4, 101.2, 73.2, 68.4, 56.8, 55.6, 42.6, 34.4, 29.4, 24.7.



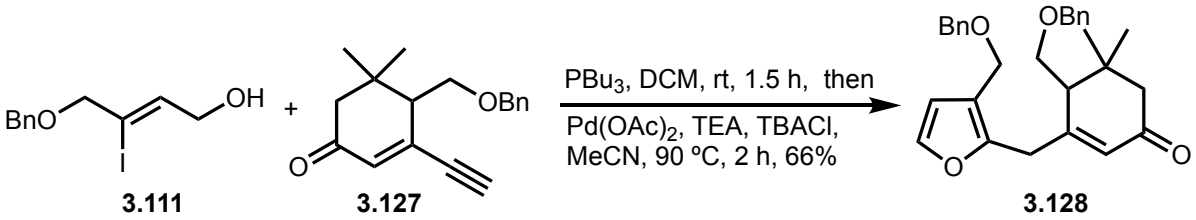
3.119 **3.127**

To an oven-dried round-bottomed flask containing **3.119** (558 mg, 2.0338 mmol, 1 equiv) and anhydrous THF (2 mL, 1 M) was added ethynylmagnesium bromide (12.2 mL, 6.1016 mmol, 3 equiv, 0.5 M in ether) at 0 ºC. After addition was complete, the reaction was moved to rt and stirred for overnight at rt. The reaction was then quenched with 1 M HCl and extracted three times with ethyl acetate. The organic layer was then washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified using flash column chromatography (10–15% ethyl acetate/hexanes) to give **3.127** (178 mg, 33%, single diastereomer).

4-((Benzyloxy)methyl)-3-ethynyl-5,5-dimethylcyclohex-2-en-1-one (3.127)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.33 (m, 5 H), 6.35 (s, 1 H), 4.49 (dd, *J* = 17.2, 12.2 Hz, 2 H), 3.81 (qd, *J* = 16.4, 3.2 Hz, 2 H), 3.45 (s, 1 H), 2.78 (d, *J* = 16.6 Hz, 1 H), 2.24 (t, *J* = 3.3 Hz, 1 H), 2.10 (d, *J* = 16.7 Hz, 1 H), 1.10 (s, 3 H), 1.07 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 199.2, 141.3, 137.9, 134.3, 128.3, 127.6, 127.4, 86.5, 82.6, 73.4, 68.9, 50.8, 49.4, 35.1, 29.1, 26.6.

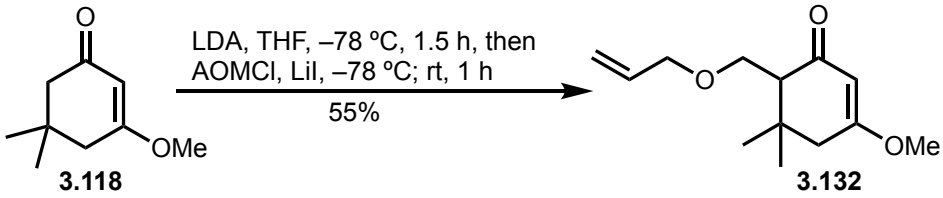


To an oven-dried round-bottomed flask A containing **3.111** (244 mg, 0.8012 mmol, 1 equiv), PBu_3 (40 µL, 0.1602 mmol, 20 mol%) and anhydrous DCM (8 mL DCM, 0.1 M). A solution of **3.127** (258 mg, 0.9614 mmol, 1.2 equiv) in DCM (1 mL, 1 M) was then slowly added at rt. The resulting solution was then stirred at rt for 1.5 h. To another round-bottomed flask B was added $Pd(OAc)_2$ (18 mg, 0.08012 mmol, 10 mol%) and TBAC (223 mg, 0.8012 mmol, 1 equiv). Upon completion of the Michael reaction, the reaction was concentrated to minimal volume, re-dissolved in anhydrous MeCN (8 mL, 0.1 M) and added to flask B. Triethylamine (581 µL, 4.1661 mmol, 5.2 equiv) was then added and the reaction was refluxed for 2 h. Upon completion as indicated by TLC, the reaction was concentrated *in vacuo*, re-dissolved in 35% ethyl acetate/hexane, filtered through a silica plug and concentrated *in vacuo*. Purification with flash column chromatography (10–15% ethyl acetate/hexane) then furnished **3.128** as a light orange oil (233 mg, 66%).

4-((Benzyloxy)methyl)-3-((3-((benzyloxy)methyl)furan-2-yl)methyl)-5,5-dimethylcyclohex-2-en-1-one (3.128)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.36 (m, 11 H), 6.38 (d, *J* = 1.8 Hz, 1 H), 5.84 (s, 1 H), 4.45 (s, 2 H), 4.42 (s, 2 H), 4.30 (dd, *J* = 15.8, 11.8 Hz, 2 H), 3.60–3.63 (m, 4 H), 2.60 (d, *J* = 17.1 Hz, 1 H), 2.00–2.09 (m, 2 H), 1.02 (s, 3 H), 0.88 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 199.7, 161.2, 148.3, 141.6, 138.0, 137.9, 128.4, 127.7, 127.7, 127.5, 127.0, 118.8, 111.6, 73.3, 72.0, 69.4, 63.2, 49.3, 48.3, 35.3, 34.1, 28.6, 27.2.



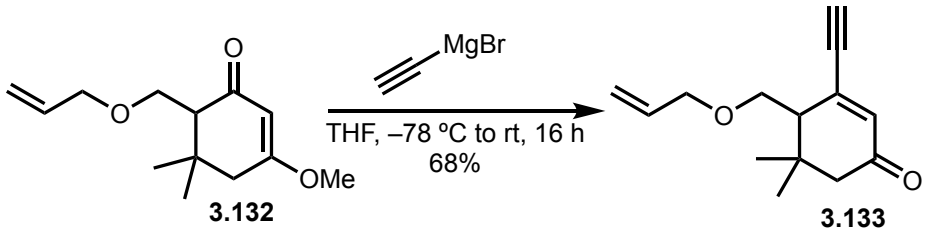
3.118 3.132

To an oven-dried round-bottomed flask was added diisopropylamine (340 µL, 2.4318 mmol, 1.5 equiv) and anhydrous THF (2.5 mL, 1 M). After cooling to 0 ºC, nBuLi (1 mL, 2.4318 mmol, 1.5 equiv, 2.5 M in hexanes) was then slowly added and the reaction was continued for another 30 minutes. The reaction was then cooled to –78 ºC and a solution of **3.118** (250 mg, 1.6212 mmol, 1 equiv) in THF (2 mL, 0.8 M) was added and the reaction was continued at the same temperature for 1.5 h. LiI (868 mg, 6.4848 mmol, 4 equiv) in THF (8.1 mL, 0.8 M) was then added, followed by allyloxymethyl chloride (691 mg, 6.4848 mmol, 4 equiv). The reaction was then moved to rt and stirred for 1 h. Upon completion as indicated by TLC, the reaction was quenched with 1 M HCl and extracted three times with ethyl acetate. The organic layer was then washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified using flask column chromatography (10–16% ethyl acetate/hexanes) to furnish **3.132** as a light yellow oil (200 mg, 55%, single diastereomer).

6-((Allyloxy)methyl)-3-methoxy-5,5-dimethylcyclohex-2-en-1-one (3.132)

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82–5.90 (m, 1 H), 5.37 (s, 1 H), 5.22 (dd, *J* = 17, 1.4 Hz, 1 H), 5.13 (dd, *J* = 10.5, 1.3 Hz, 1 H), 3.93 (dd, *J* = 5.5, 1.2 Hz, 2 H), 3.81 (dd, *J* = 9.9, 4.4 Hz, 1 H), 3.68 (s, 3 H), 3.63 (dd, *J* = 9.9, 4.4 Hz, 1 H), 2.47 (d, *J* = 17.4 Hz, 1 H), 2.18–2.22 (m, 2 H), 1.12 (s, 3 H), 1.04 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 200.2, 176.3, 134.8, 116.5, 101.2, 72.0, 68.2, 56.8, 55.6, 42.6, 34.4, 29.4, 24.6.

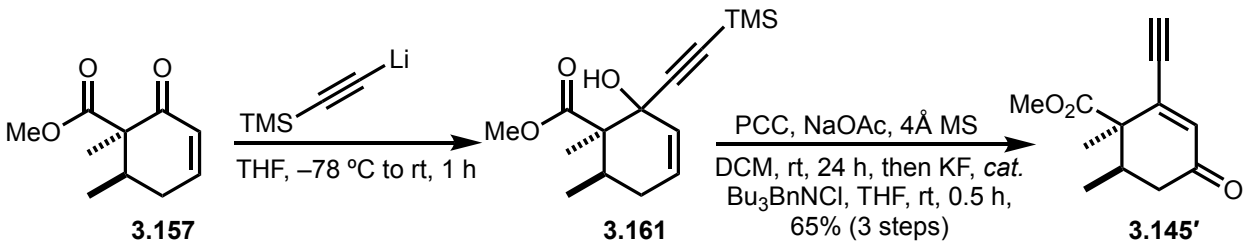


To an oven-dried round-bottomed flask containing **3.132** (300 mg, 1.3375 mmol, 1 equiv) and anhydrous THF (1 mL, 1 M) was added ethynylmagnesium bromide (8 mL, 4.0125 mmol, 3 equiv, 0.5 M in ether) at 0 ºC. After addition was complete, the reaction was moved to rt and stirred for overnight at rt. The reaction was then quenched with 1 M HCl and extracted three times with ethyl acetate. The organic layer was then washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified using flash column chromatography (10–15% ethyl acetate/hexanes) to give **3.133** (198 mg, 68%, single diastereomer).

4-((Allyloxy)methyl)-3-ethynyl-5,5-dimethylcyclohex-2-en-1-one (3.133)

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.33 (s, 1 H), 5.80–5.88 (m, 1 H), 5.22 (dd, *J* = 17.3, 1.5 Hz, 1 H), 5.15 (d, *J* = 10.5 Hz, 1 H), 3.94 (d, *J* = 5.4 Hz, 2 H), 3.81 (dd, *J* = 10, 3.3 Hz, 1 H), 3.74 (dd, *J* = 10, 3.3 Hz, 1 H), 3.48 (s, 1 H), 2.75 (d, *J* = 16.7 Hz, 1 H), 2.22 (s, 1 H), 2.10 (d, *J* = 16.7 Hz, 1 H), 1.12 (s, 3 H), 1.08 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 199.2, 141.3, 134.4, 134.3, 116.8, 86.5, 82.7, 72.2, 68.8, 50.8, 49.3, 35.1, 29.1, 26.7.



A round-bottomed flask containing trimethylsilylacetylene (2.6 mL, 19.0558 mmol, 1.6 equiv) and anhydrous THF (19 mL, 1 M) was cooled to –78 ºC and nBuLi (7.6 mL, 19.0558 mmol, 1.6 equiv, 2.5 M in hexanes) was slowly added. The resulting solution was then stirred at the same temperature for 1 h. To another round-bottomed flask was added **3.157** (2.17g, 11.9099 mmol, 1 equiv) and anhydrous THF (12 mL, 1 M). After cooling to –78 ºC, the solution of freshly prepared lithium trimethylsilylacetylide was slowly added. After addition was complete, the cooling bath was removed and the reaction was stirred at rt for 1 h. Upon completion as indicated by TLC, the reaction was quenched with saturated NH_4Cl and extracted three times with ethyl acetate. The organic layer was then washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo.* The resulting crude **3.161** was quickly re-dissolved in anhydrous DCM (60 mL, 0.2 M) and slowly added to another round-bottomed flask containing PCC (9 g, 41.6847 mmol, 3.5 equiv), 4Å molecular sieves (9 g), NaOAc (5.1g, 62.5271 mmol, 5.25 equiv) and anhydrous DCM (60 mL, 0.2 M). The resulting solution was then stirred at rt for 24 h. The reaction was then filtered through a silica plug and concentrated *in vacuo*. The crude TMS-protected enynone was then re-dissolved in THF (12 mL, 1 M) and added to a round-bottomed flask containing Bu_3BnNCl (372 mg, 1.1910 mmol, 10 mol%) and THF (12 mL, 1 M). KF (1.04g, 17.8649 mmol, 1.5 equiv) in water (9 mL, 2 M) was then added at rt under stirring. The resulting reaction was then stirred at the same temperature for 15 min. Upon completion as indicated by TLC, the reaction was quenched with saturated NH_4Cl and extracted three times with ethyl acetate. The organic layer was then washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification using flash

column chromatography (10–15% ethyl acetate) then delivered enynone **3.145'** as a pale yellow solid (1.6g, 65%, *trans* diastereomer).

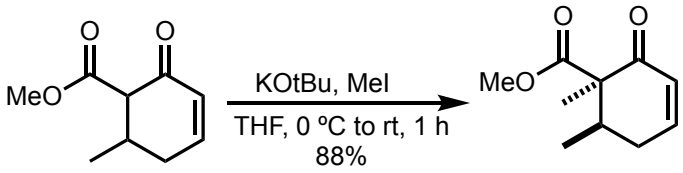
Methyl 2-ethynyl-1,6-dimethyl-4-oxocyclohex-2-ene-1-carboxylate (3.145')

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.35 (s, 1 H), 3.74 (s, 3 H), 3.51 (s, 1 H), 2.55–2.61 (m, 1 H), 2.36 (dd, *J* = 17.2, 3.3 Hz, 1 H), 2.15–2.20 (m, 1 H), 1.56 (s, 3 H), 1.03 (dd, *J* = 6.9, 1.1 Hz, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 197.9, 171.5, 143.2, 134.8, 88.3, 80.4, 52.5, 50.7, 42.2, 38.3, 22.3, 17.1.

IR (neat): 3276, 3252, 3039, 2996, 2950, 2091, 1728, 1663, 1581, 1452, 1433, 1411, 1384, 1340, 1317, 1268, 1112, 1095, 1047, 1014 cm^{-1}.

m.p = 42–44 ºC



3.156 **3.157**

An oven-dried round-bottomed flask was added **3.156** (2.3 g, 13.675 mmol, 1 equiv) and THF (14 mL, 1 M) was cooled to 0 ºC. A solution of KO*t*Bu (1.5 g, 13.6750 mmol, 1 equiv) in THF (16 mL, 0.88 M) was then slowly added and the resulting solution was then stirred at the same temperature for 30 minutes. MeI (2.1 mL, 34.1875 mmol, 2.5 equiv) was then added at 0 ºC and the resulting solution was stirred at rt for 1 h. Upon completion as indicated by TLC, the reaction was quenched by 1 M HCl and extracted three times with ethyl acetate. The organic layer was then washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* The crude product was then purified using flash column chromatography (10–15% ethyl acetate/hexanes) to give **3.157** as a white solid (*trans* diastereomer, 2.2 g, 88%).

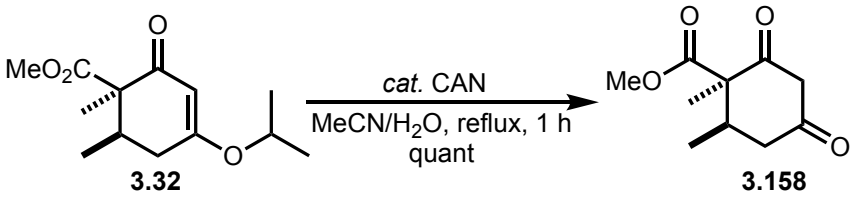
Methyl 1,6-dimethyl-2-oxocyclohex-3-ene-1-carboxylate (3.157)

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.94–7.00 (m, 1 H), 6.07 (dt, *J* = 10.1, 1.1 Hz, 1 H), 3.65 (s, 3 H), 2.28–2.43 (m, 2 H), 2.06–2.13 (m, 1 H), 1.42 (d, *J* = Hz, 3 H), 1.12 (d, *J* = 6.9 Hz, 3 H).

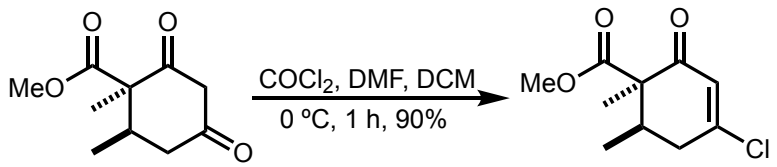
^{13}C NMR (125 MHz, $CDCl_3$): *δ* 196.9, 171.3, 149.7, 128.7, 57.2, 52.0, 38.8, 32.4, 18.5, 16.5.

IR (neat): 2993, 2957, 2909, 1733, 1649, 1449, 1437, 1392, 1370, 1354, 1341, 1264, 1235, 1194, 1115, 1104, 1025 cm^{-1}.

m.p = 36–38 ºC



To a round-bottomed flask was added **3.32** (1.5 g, 6.2422 mmol, 1 equiv), ceric ammonium nitrate (856 mg, 1.5605 mmol, 25 mol%), MeCN (24 mL, 0.26 M) and water (24 mL, 0.26 M). The resulting solution was then refluxed for 1 h. Upon completion as indicated by TLC, the reaction was poured onto brine and extracted three times with ethyl acetate. The organic layer was dried with anhydrous Na_2SO_4 and concentrated *in vacuo* to give **3.158** as a white solid that was used directly without further purification (1.24 g, quant).



3.158 **3.159**

To a round-bottomed flask containing **3.158** (3.75 g, 18.9184 mmol, 1 equiv), DMF (1.9 mL, 24.5396 mmol, 1.3 equiv) and DCM (38 mL, 0.5 M) was added oxalyl chloride (1.9 mL, 22.4533 mmol, 1.2 equiv) at 0 ºC (*Note*: vigorous gas evolution occurs, add very slowly). The resulting solution was then stirred at the same temperature for 1 h. Upon completion, the reaction was poured onto brine and extracted three times with ethyl acetate. The organic layer was then dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified using flash column chromatography (10–15% ethyl acetate/hexanes) to give **3.159** as a white solid (*trans* diastereomer, 3.7 g, 90%).

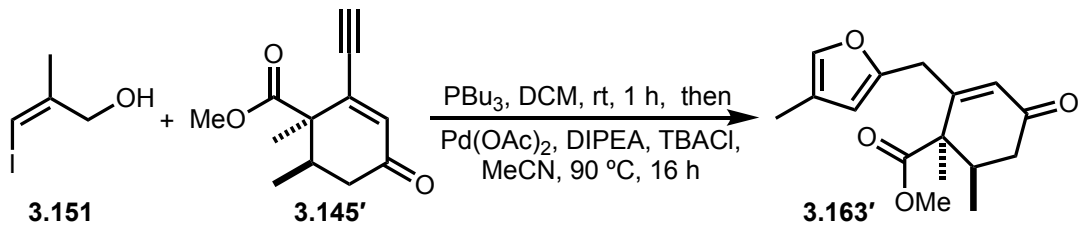
Methyl 4-chloro-1,6-dimethyl-2-oxocyclohex-3-ene-1-carboxylate (3.159)

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.26 (d, *J* = 2.3 Hz, 1 H), 3.6 (s, 3 H), 2.80 (ddd, *J* = 18.8, 11.3, 2.4 Hz, 1 H), 2.56 (dd, *J* = 18.8, 4.9 Hz, 1 H), 2.16–2.21 (m, 1 H), 1.41 (s, 3 H), 1.13 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 194.4, 170.5, 157.7, 127.1, 56.1, 52.3, 40.1, 38.7, 18.4, 16.1.

IR (neat): 3073, 2984, 2947, 2887, 1725, 1663, 1613, 1447, 1429, 1387, 1373, 1355, 1305, 1278, 1260, 1232, 1182, 1131, 1111, 1017 cm^{-1}.

m.p = 68–70 ºC



To an oven-dried round-bottomed flask A containing **3.151** (1.22 g, 6.1711 mmol, 1 equiv), PBu_3 (250 µL, 1.2342 mmol, 20 mol%) and anhydrous DCM (62 mL DCM, 0.1 M). A solution of **3.145'** (1.4 g, 6.7882 mmol, 1.2 equiv) in DCM (7 mL, 1 M) was then slowly added at rt. The resulting solution was then stirred at rt for 1.5 h. To another round-bottomed flask B was added $Pd(OAc)_2$ (139 mg, 0.6171 mmol, 10 mol%) and TBAC (1.7 g, 6.1711 mmol, 1 equiv). Upon completion of the Michael reaction, the reaction was concentrated to minimal volume, re-dissolved in anhydrous MeCN (62 mL, 0.1 M) and added to flask B. DIPEA (5.6 mL, 32.0897 mmol, 5.2 equiv) was then added and the reaction was refluxed for 16 h. Upon completion as indicated by TLC, the reaction was concentrated *in vacuo*, re-dissolved in 45% ethyl acetate/hexane, filtered through a silica plug and concentrated *in vacuo*. Purification with flash column chromatography (10–15% ethyl acetate/hexane) then furnished **3.163'** as a light orange oil (1.17 g, 68%).

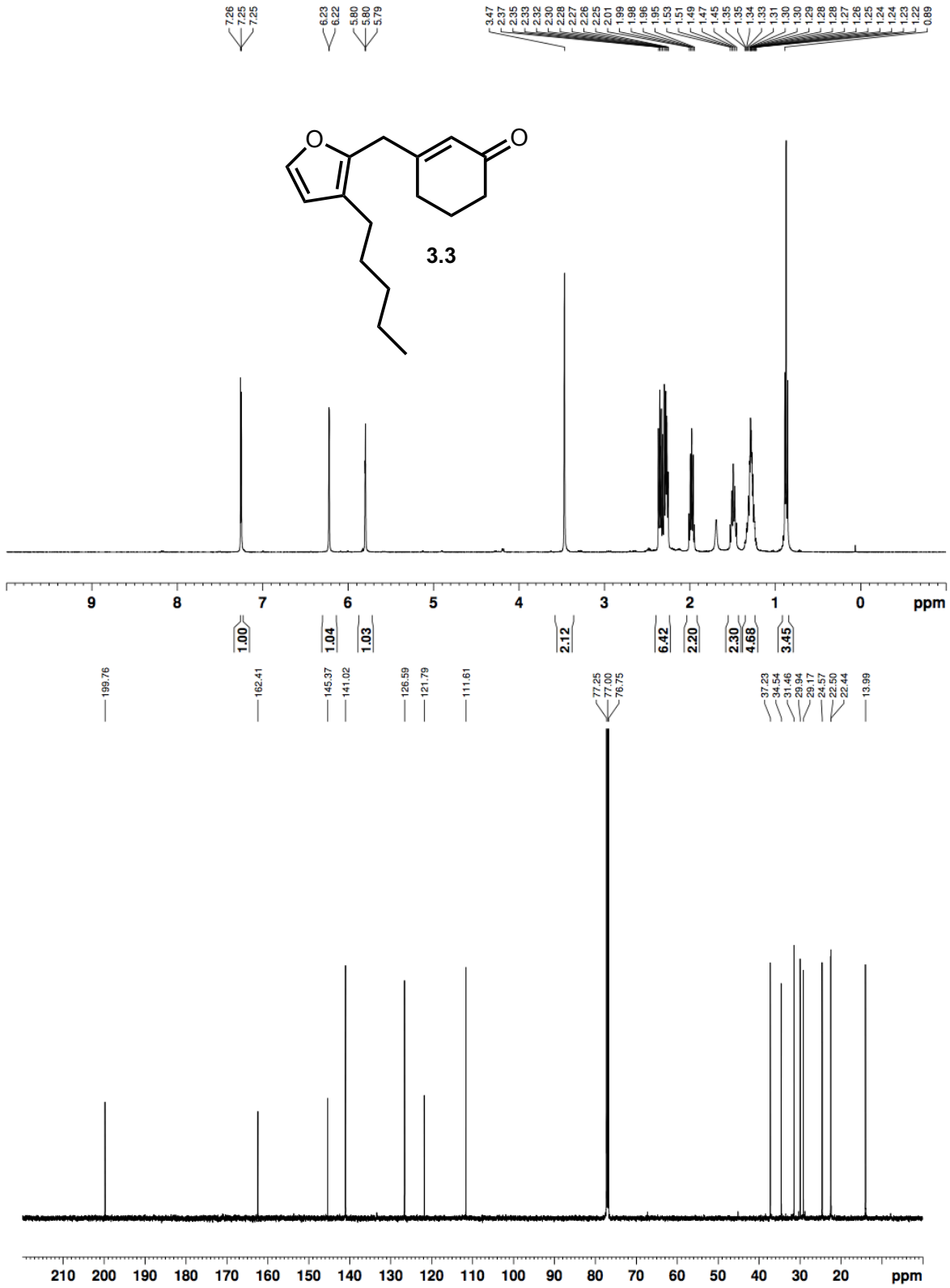
Methyl 1,6-dimethyl-2-((4-methylfuran-2-yl)methyl)-4-oxocyclohex-2-ene-1-carboxylate (3.163')

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 (s, 1 H), 5.96 (s, 1 H), 5.88 (s, 1 H), 3.65 (s, 3 H), 3.43–3.51 (m, 2 H), 2.53–2.59 (m, 1 H), 2.34 (dd, *J* = 17.5, 4.4 Hz, 1 H), 2.15–2.21 (m, 1H), 1.98 (s, 3 H), 1.48 (s, 3 H)

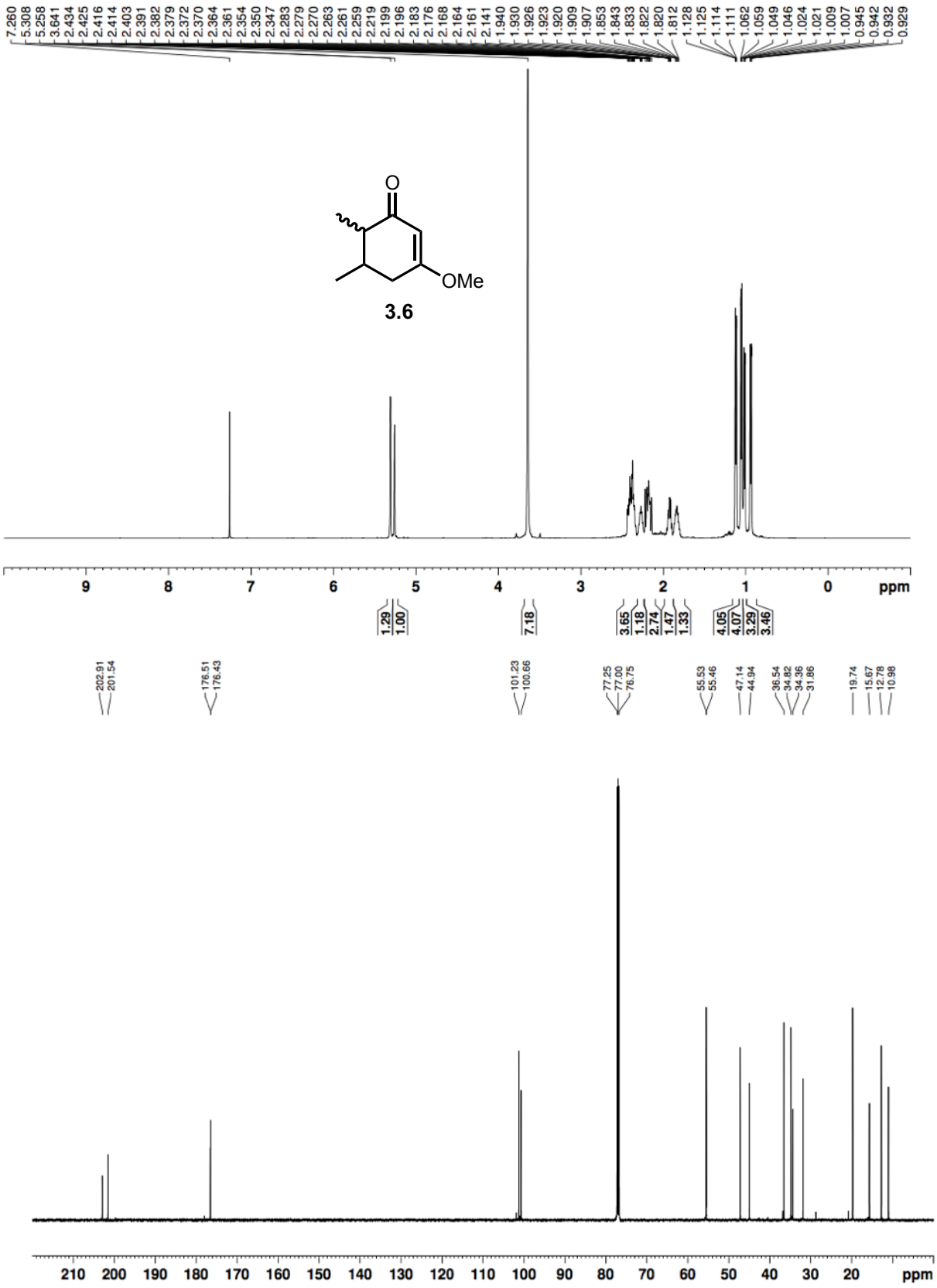
^{13}C NMR (125 MHz, $CDCl_3$): *δ* 198.8, 172.2, 160.3, 150.2, 138.7, 128.7, 120.8, 111.0, 52.2, 51.1, 42.1, 38.7, 32.8, 21.3, 16.9, 9.7.

m.p: 70–72 ºC

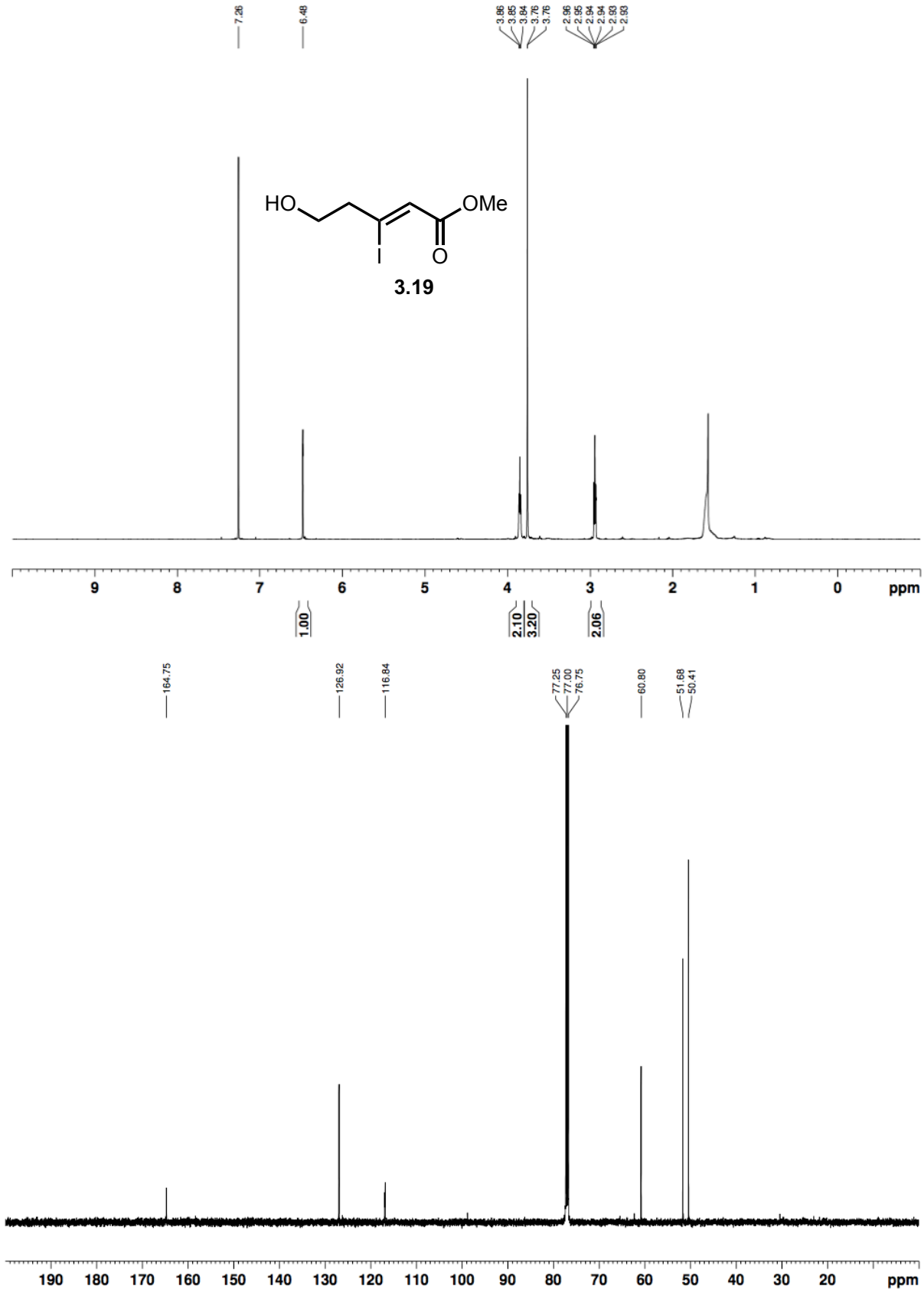
3.8 Copies of NMR Spectra



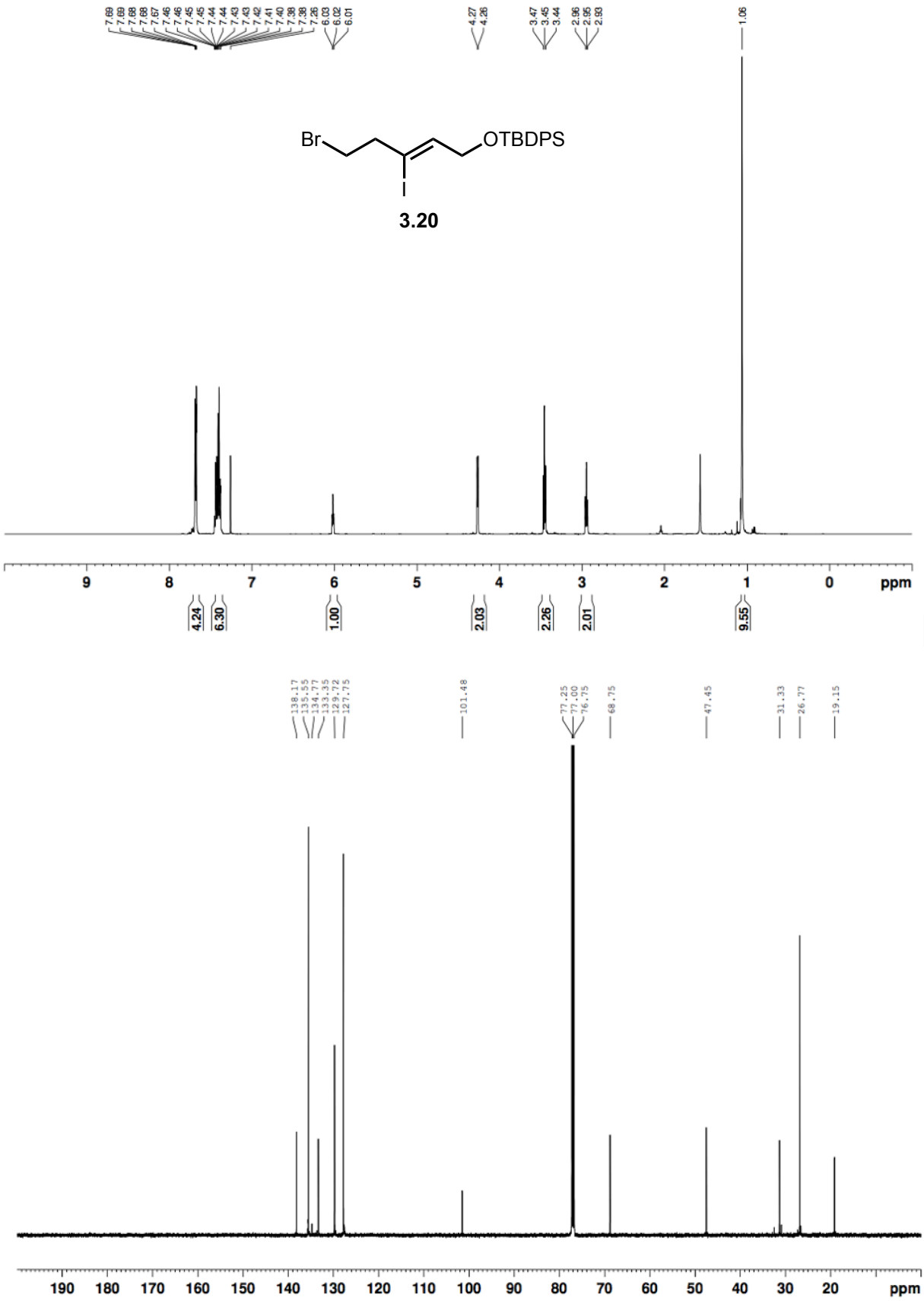
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.3**



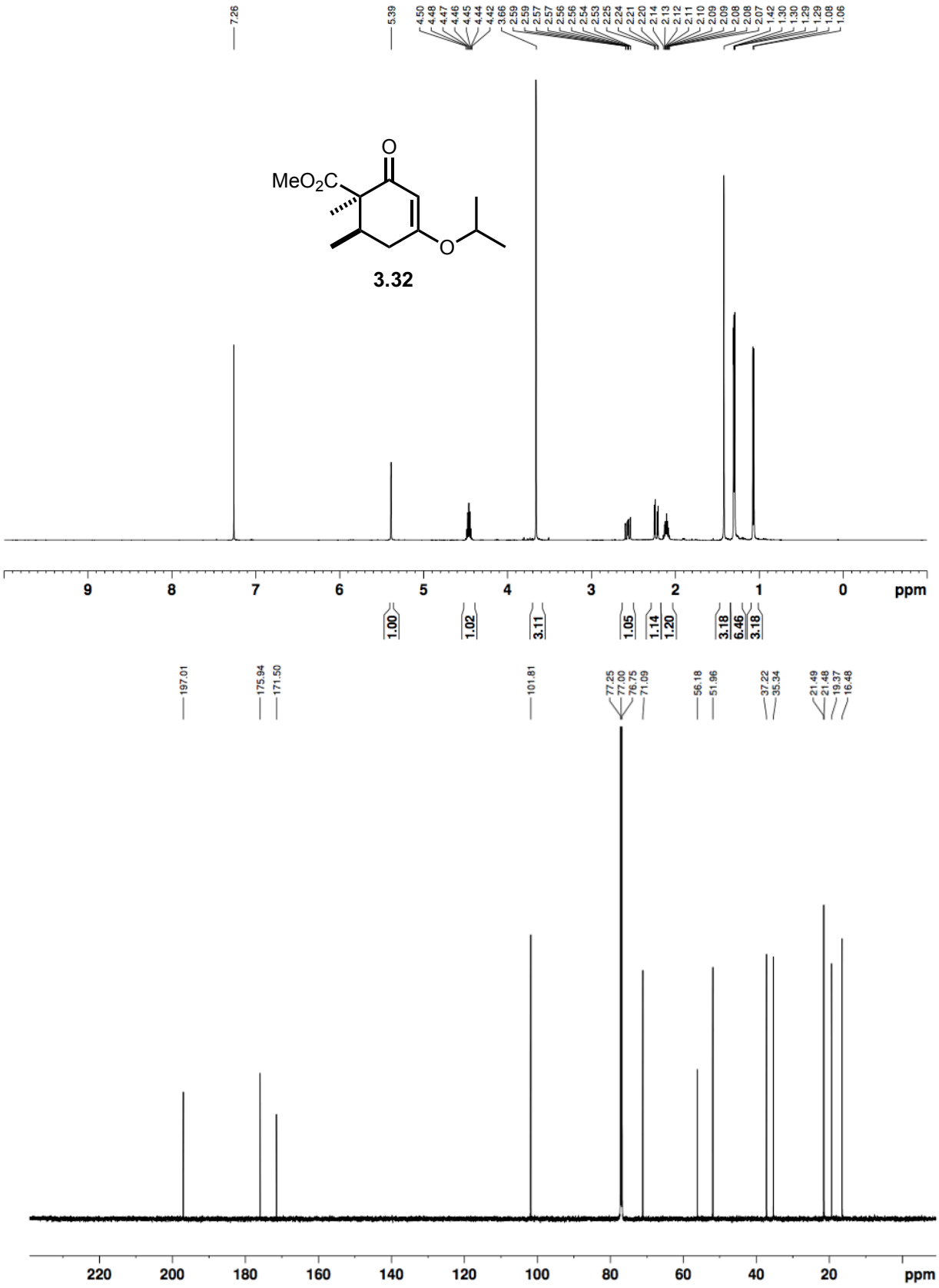
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.6**



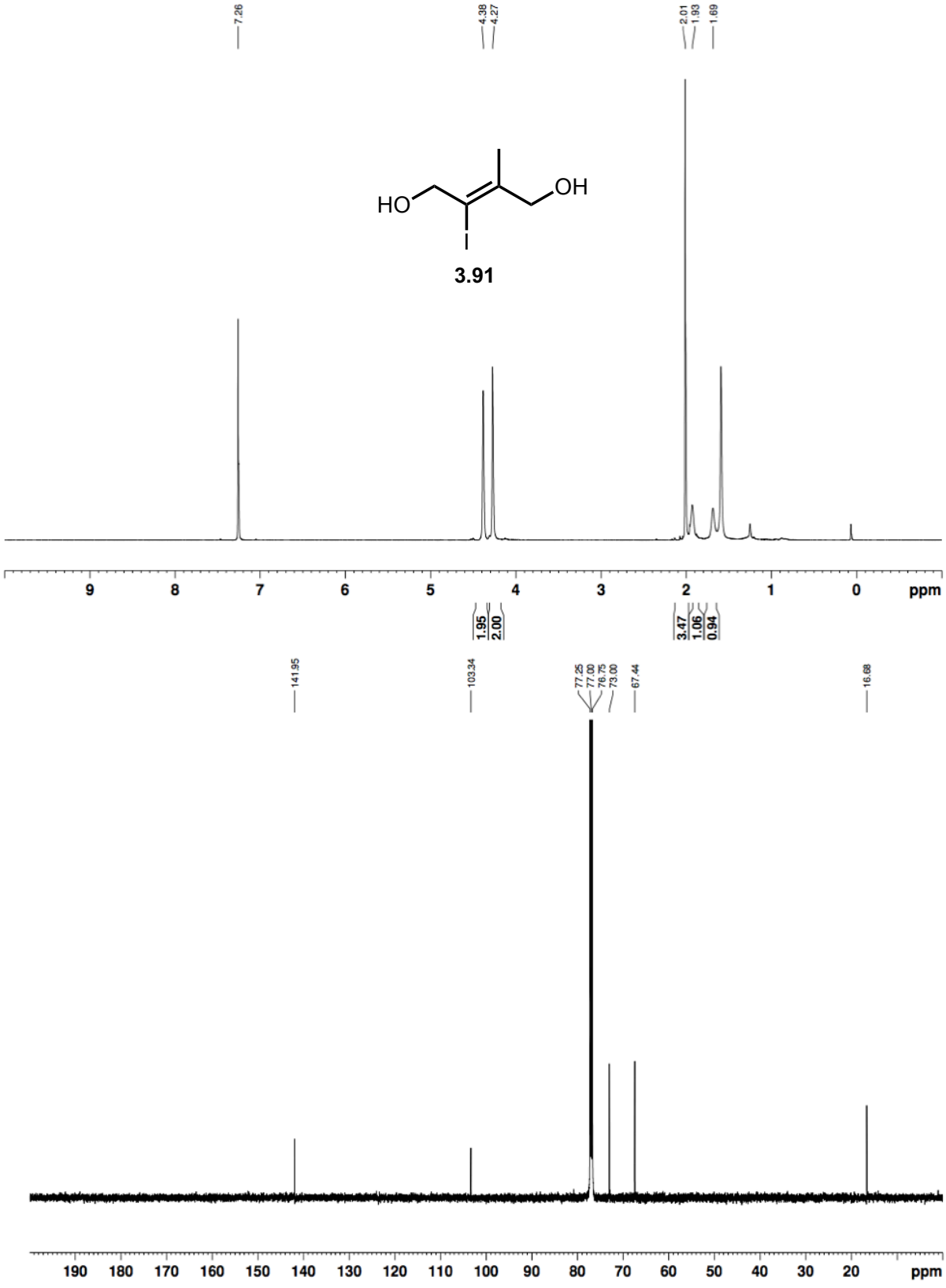
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.19**



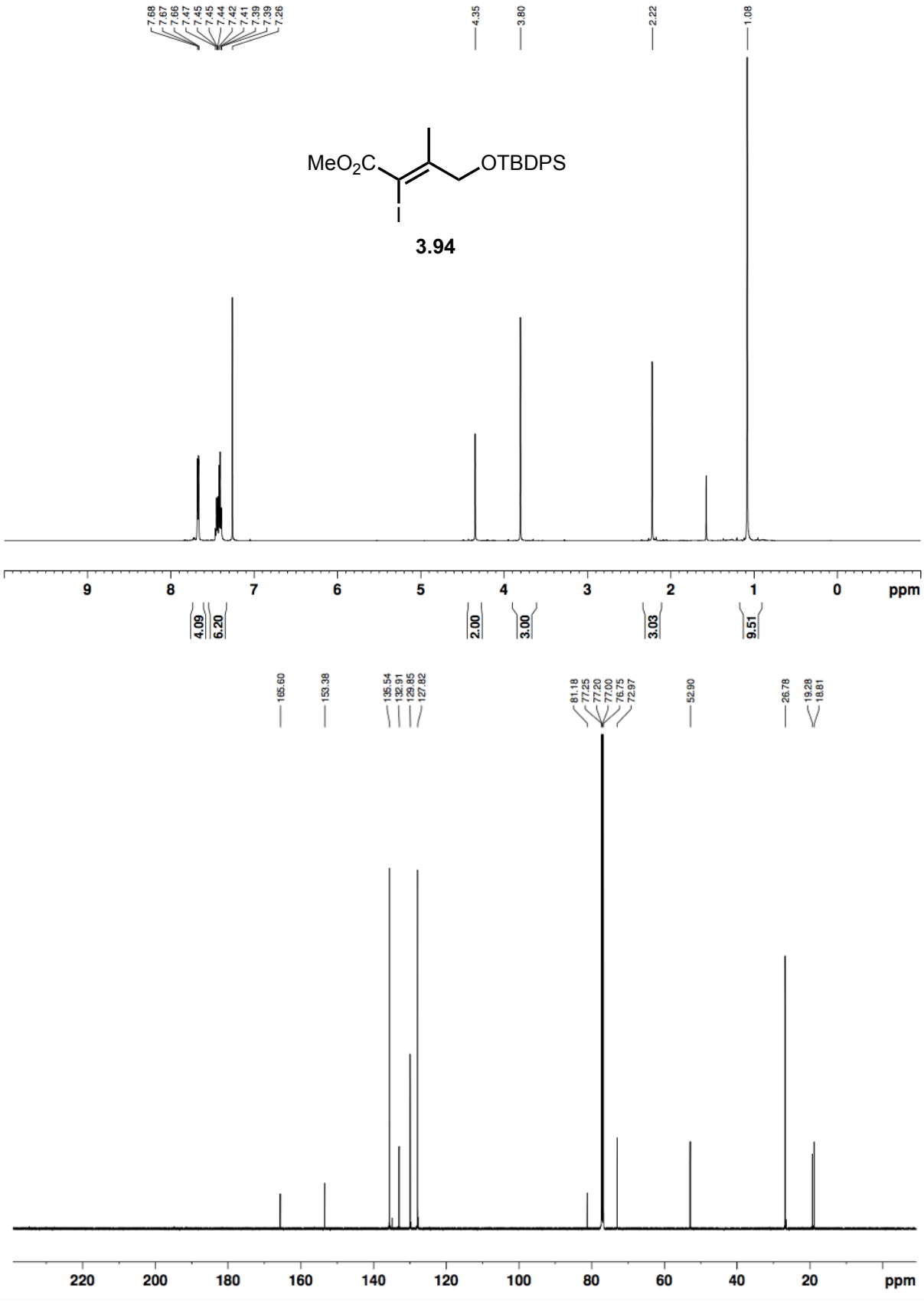
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.20**



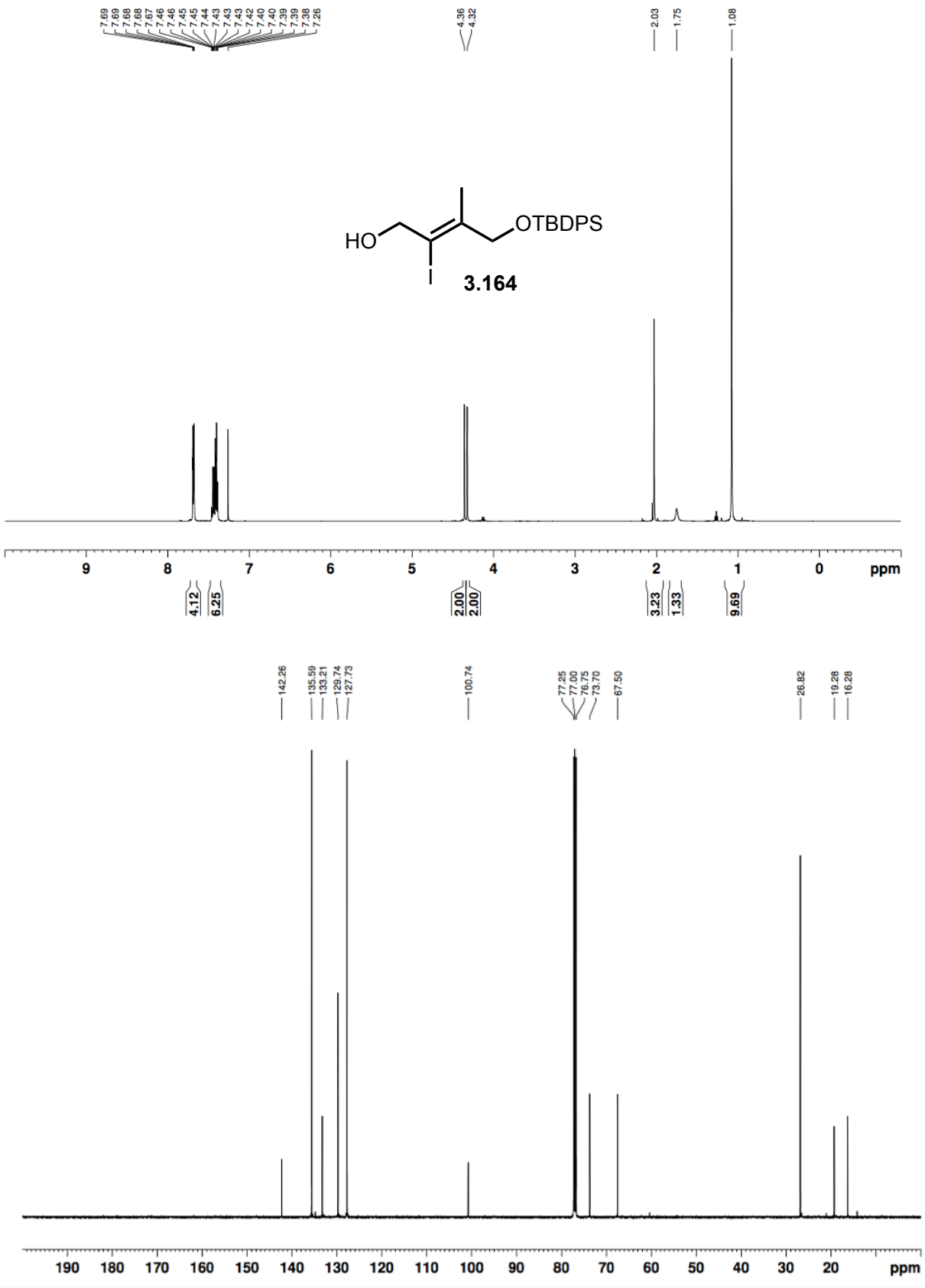
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.32**



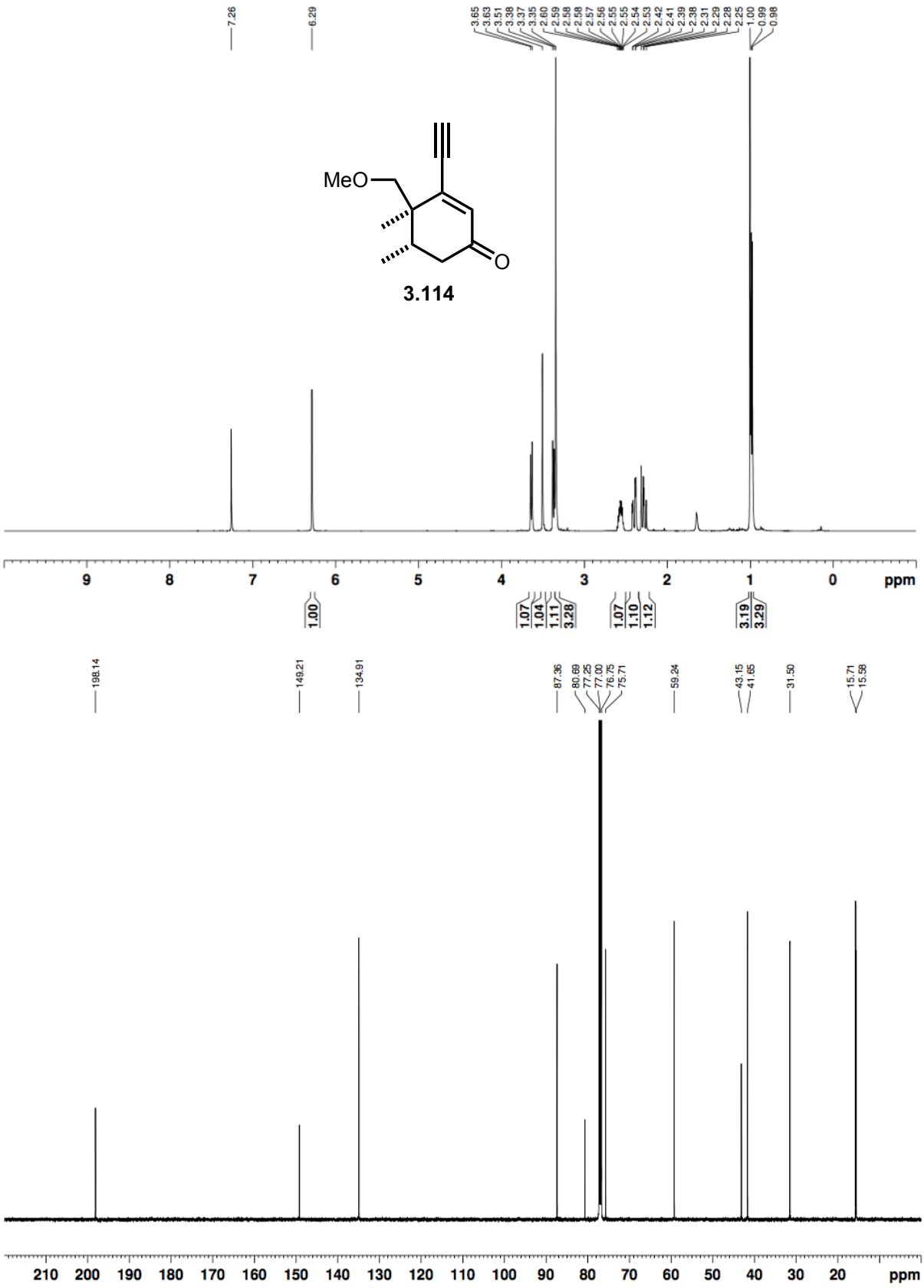
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.91**



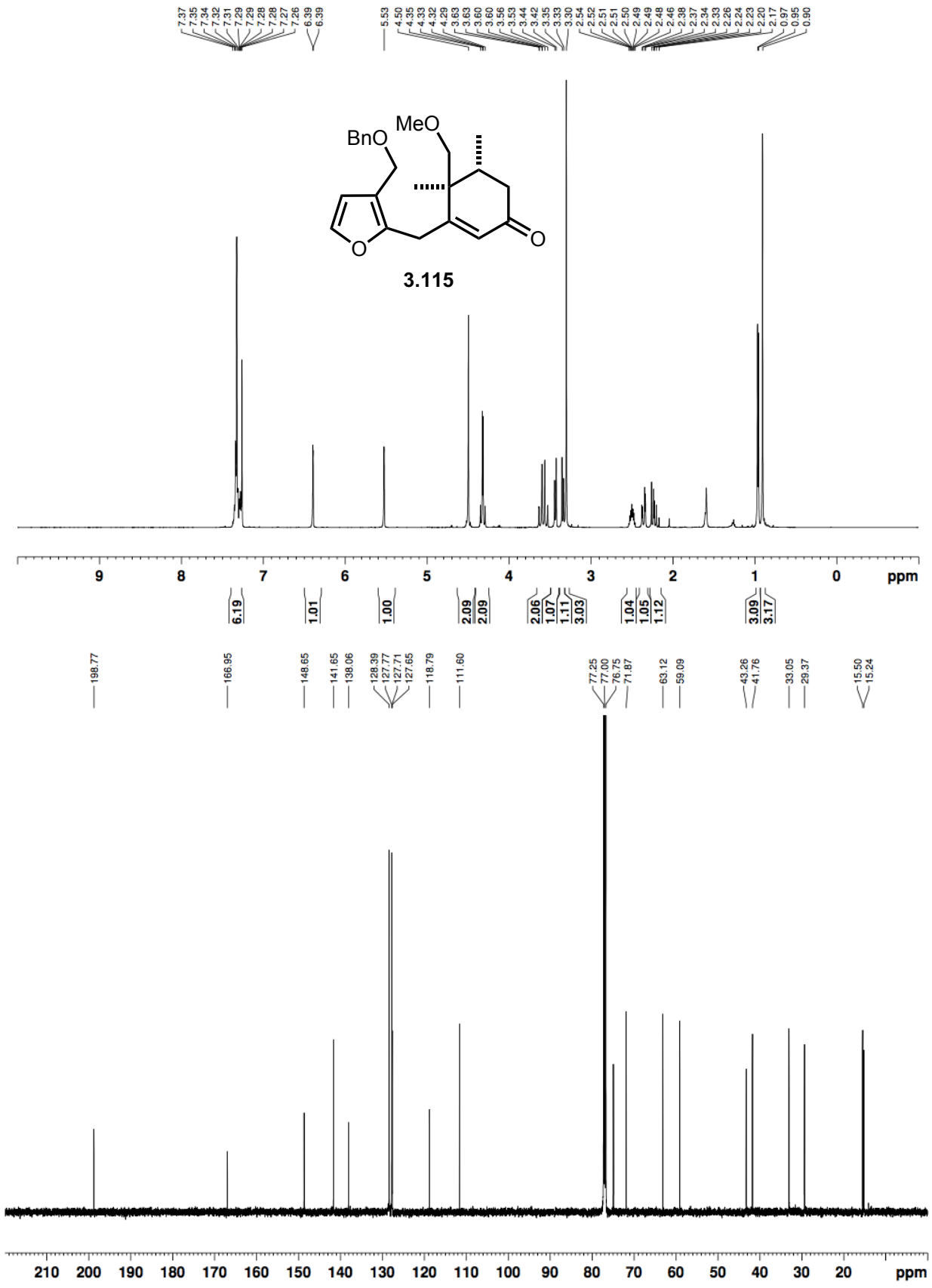
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.94**



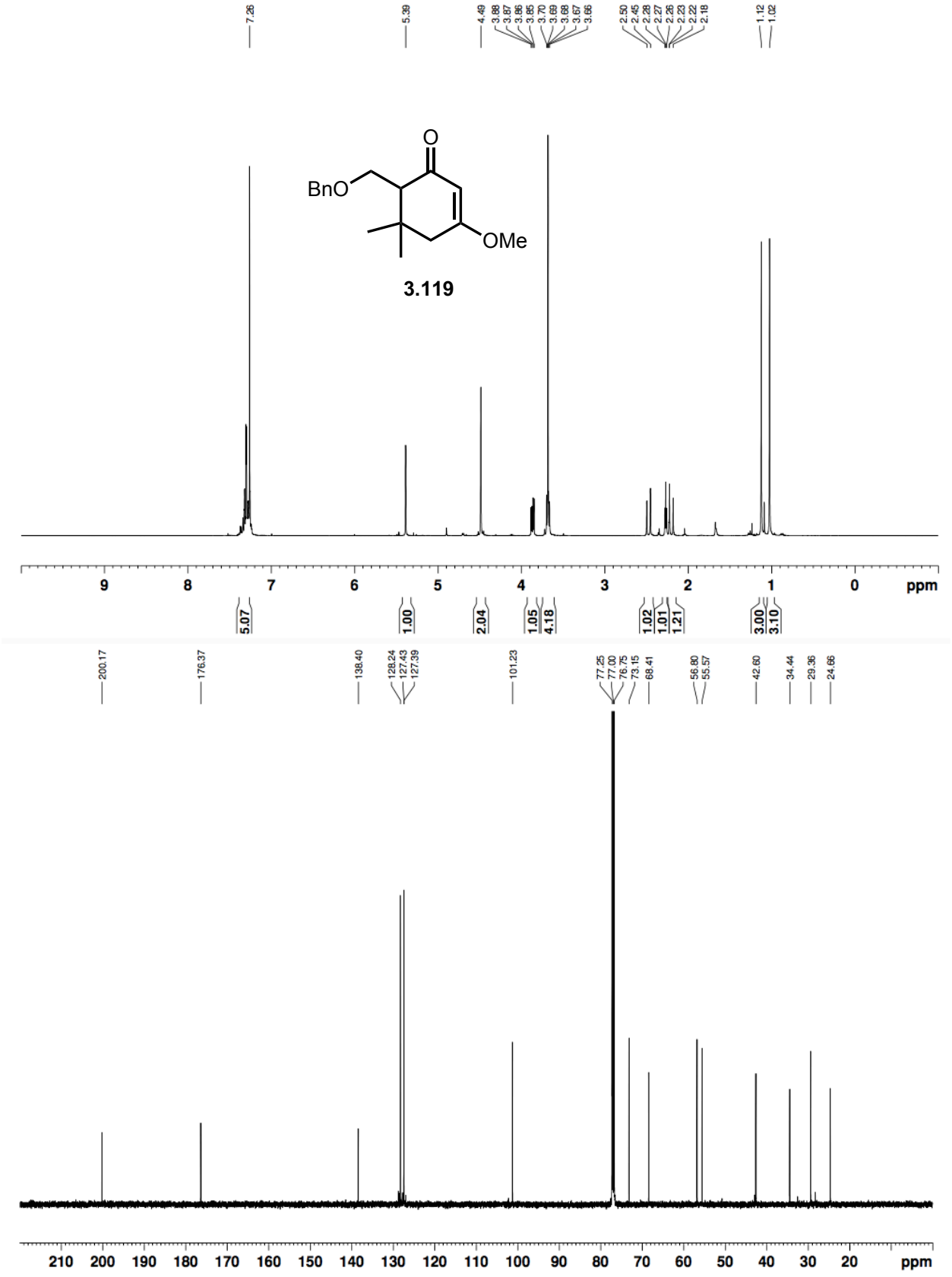
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.164**



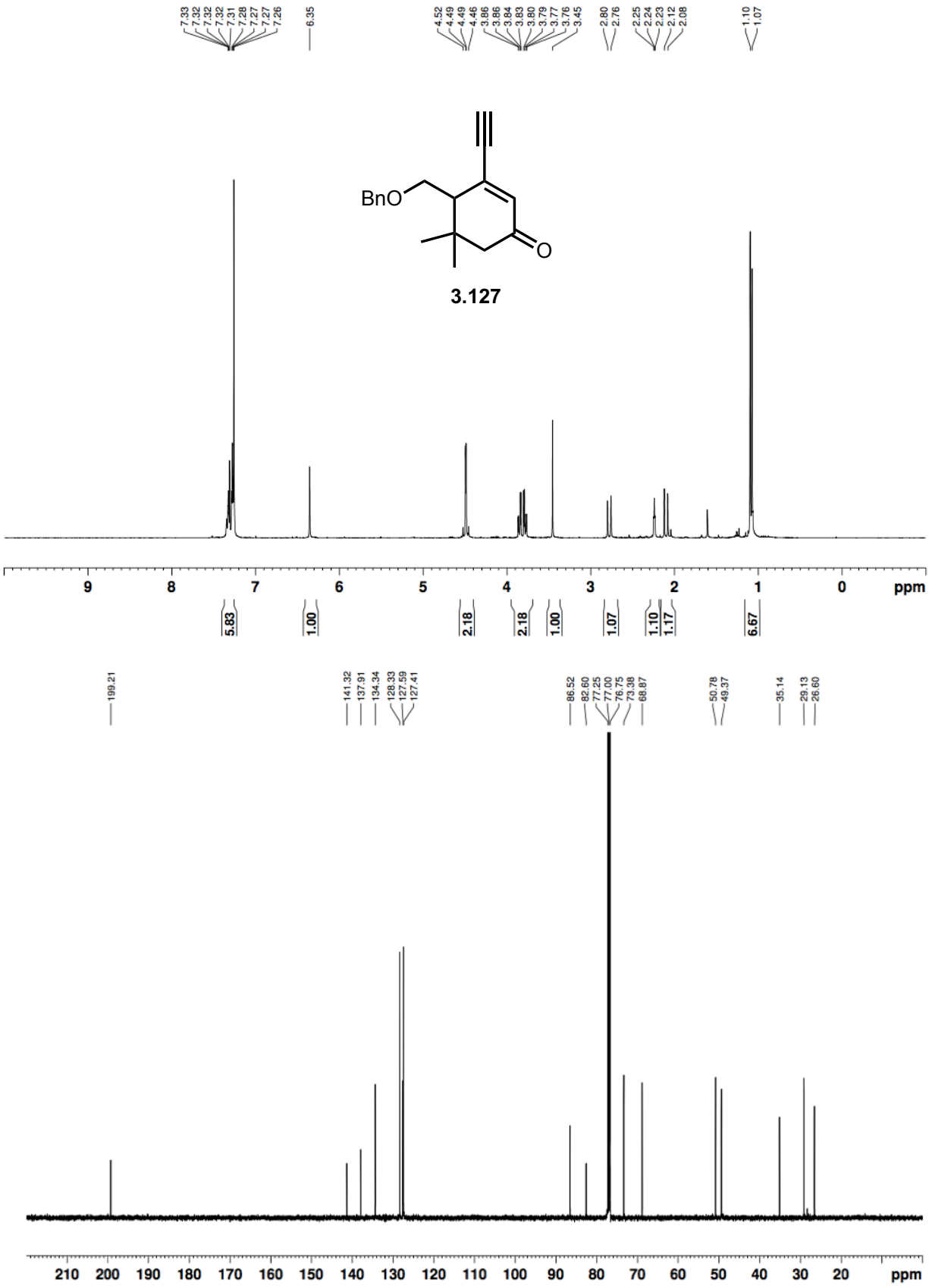
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.114**



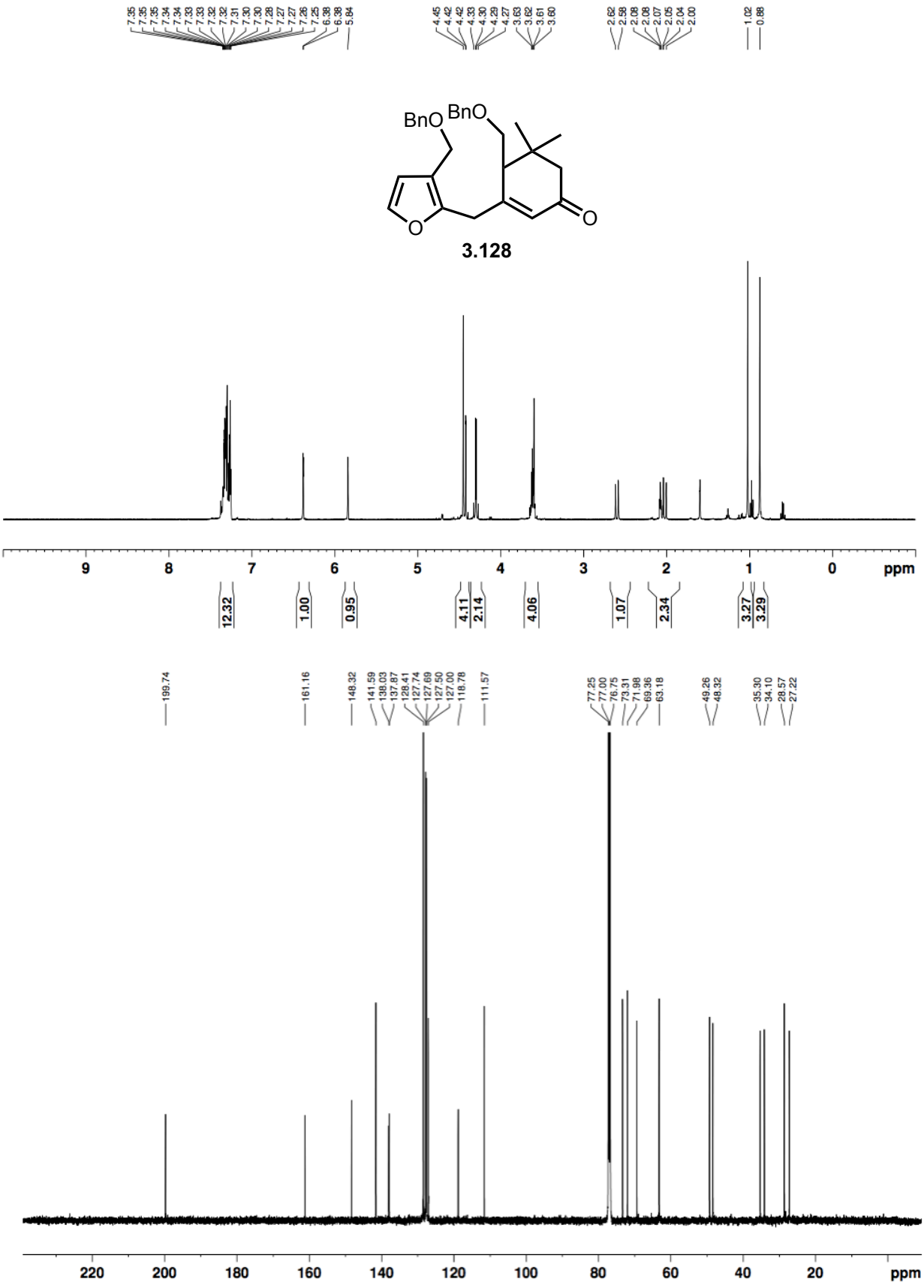
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.115**



^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.119**

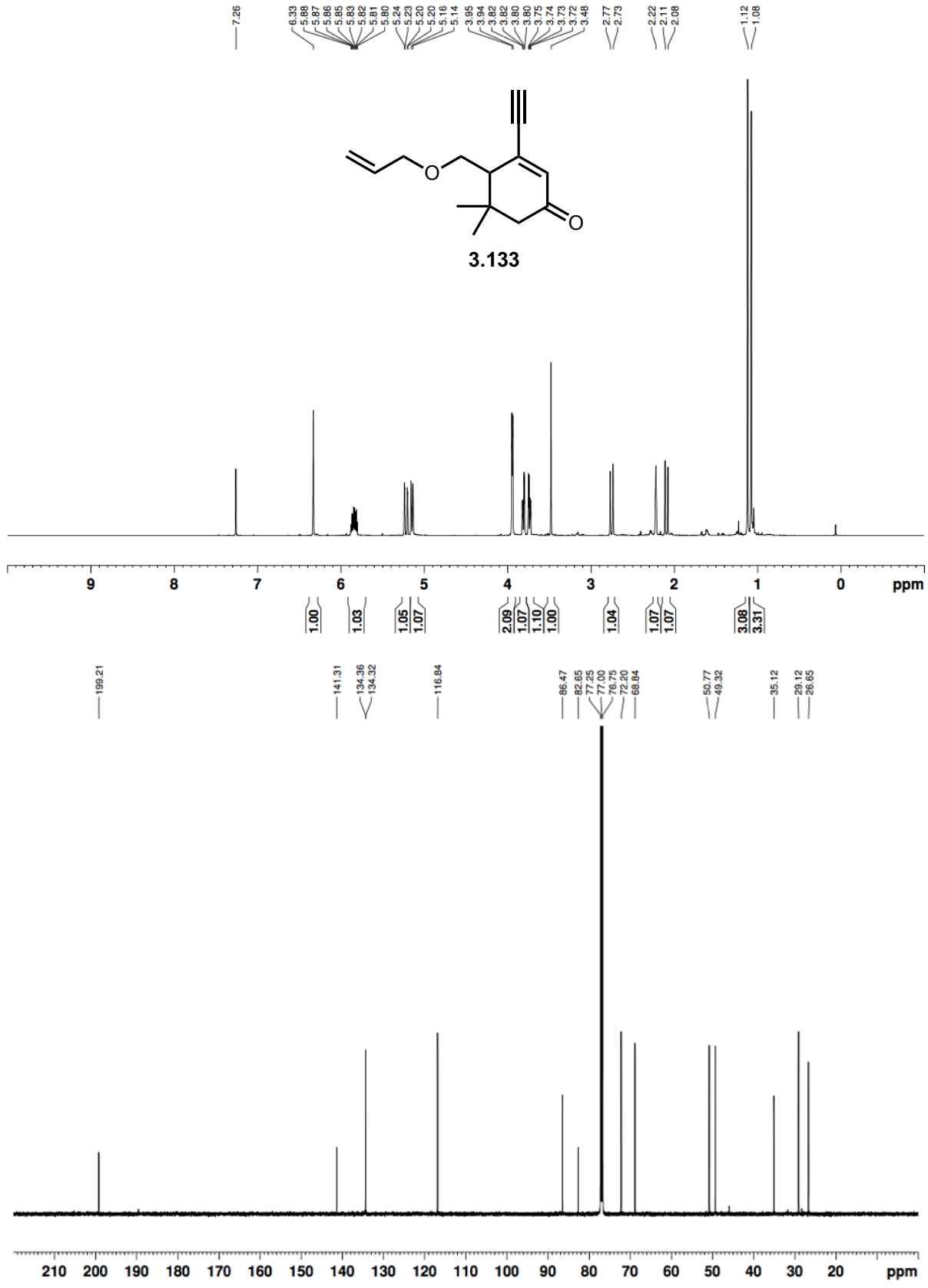


^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.127**

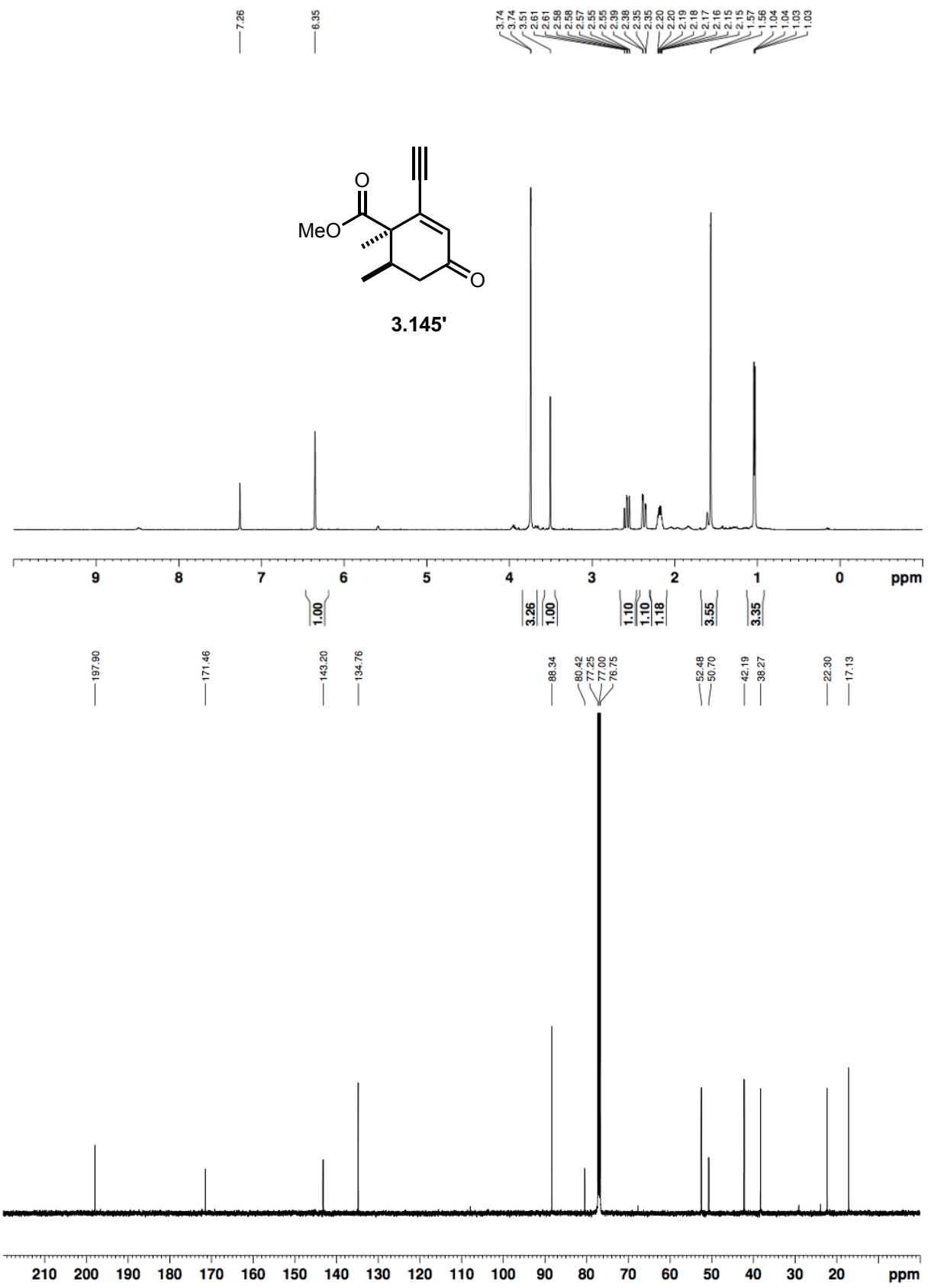


^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.128**

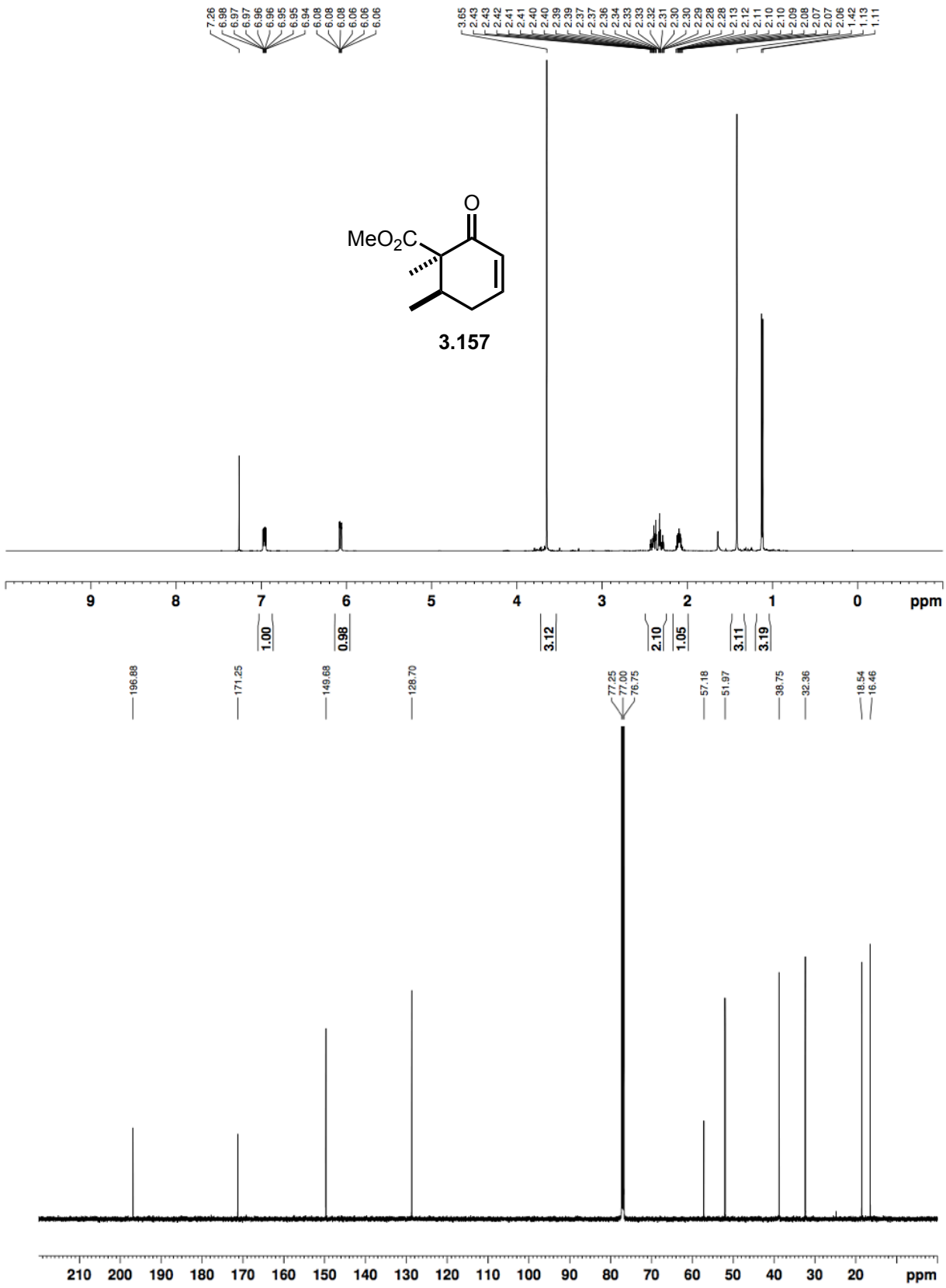
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.132**



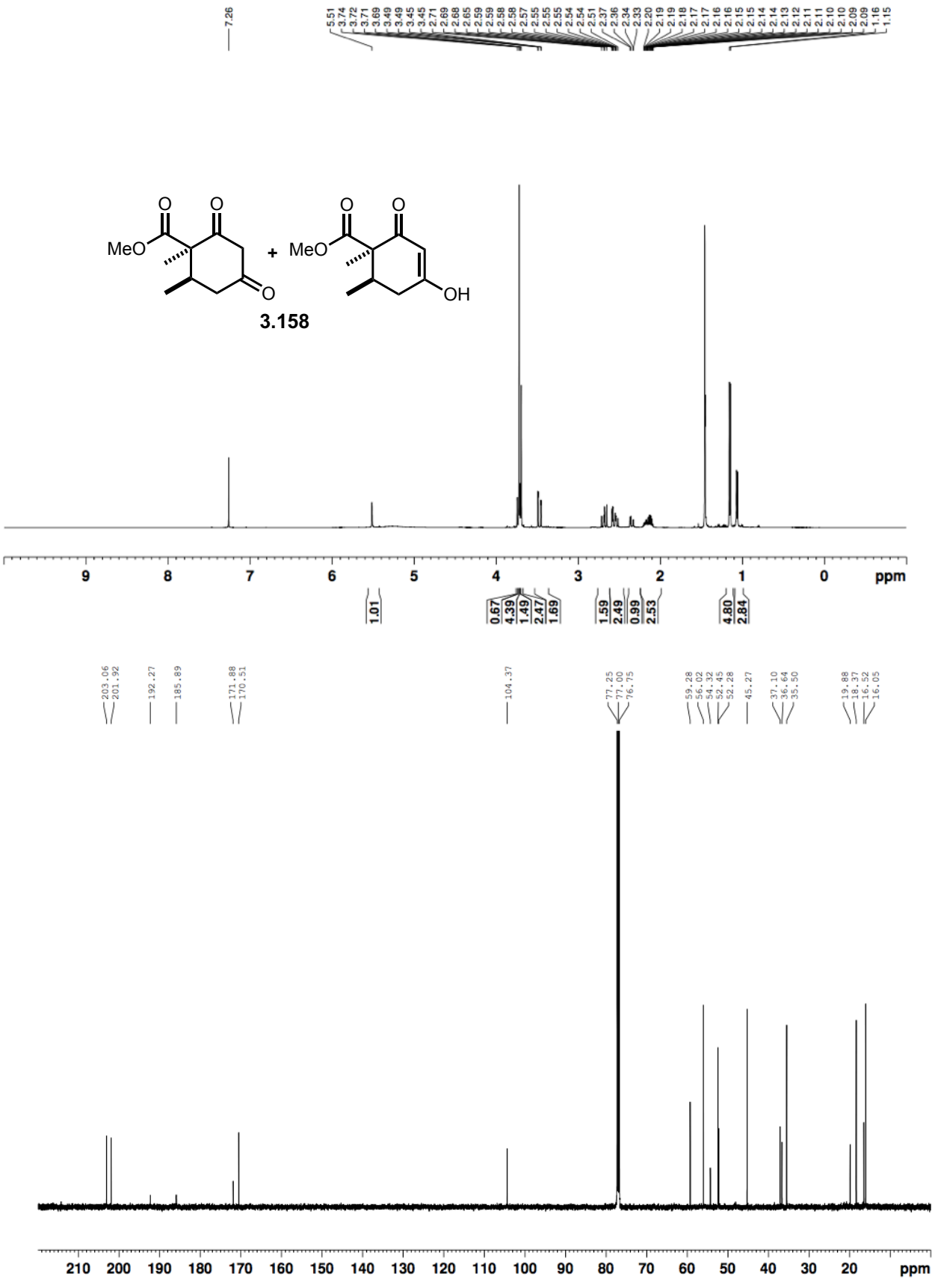
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.133**



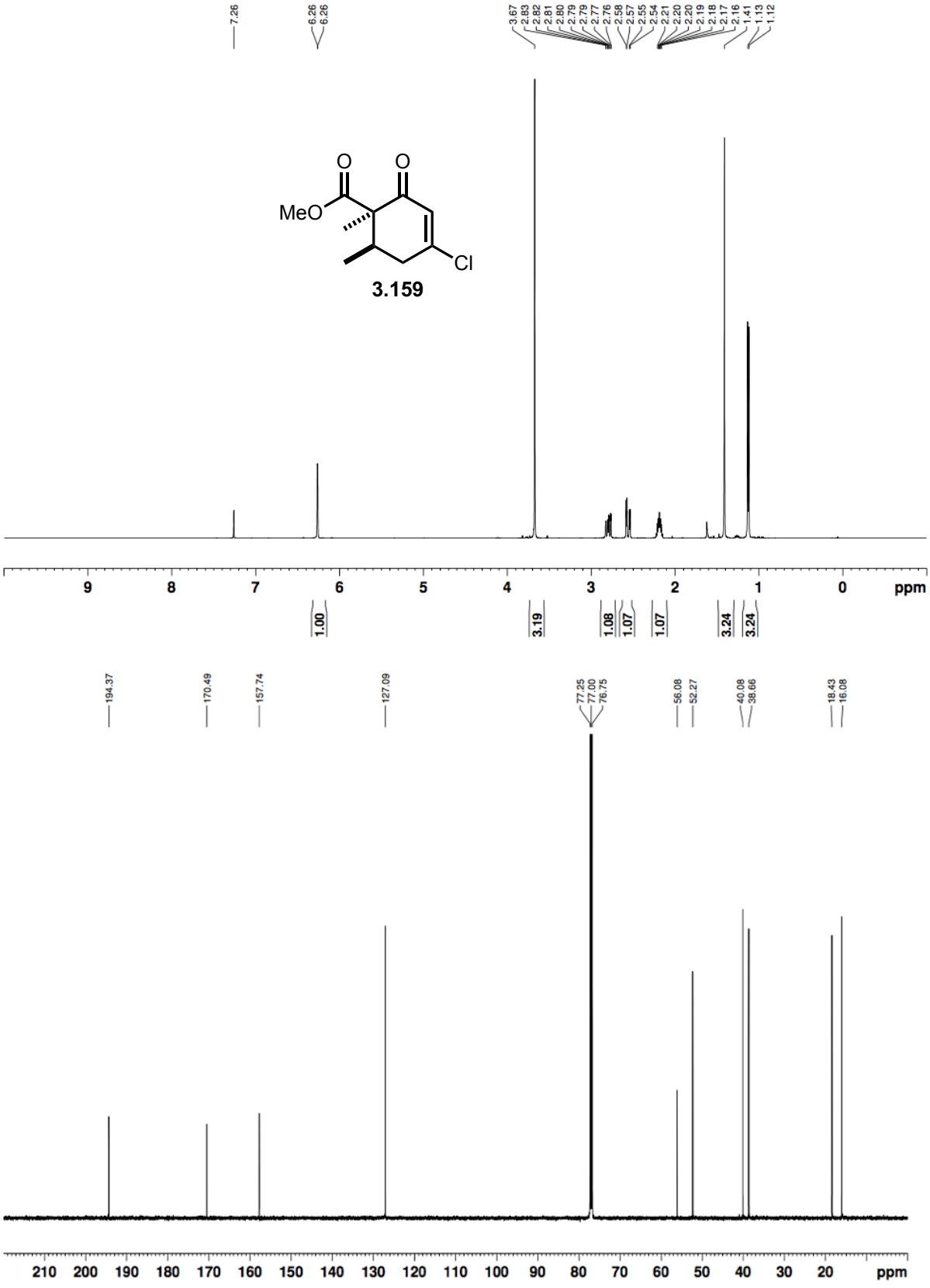
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.145'**



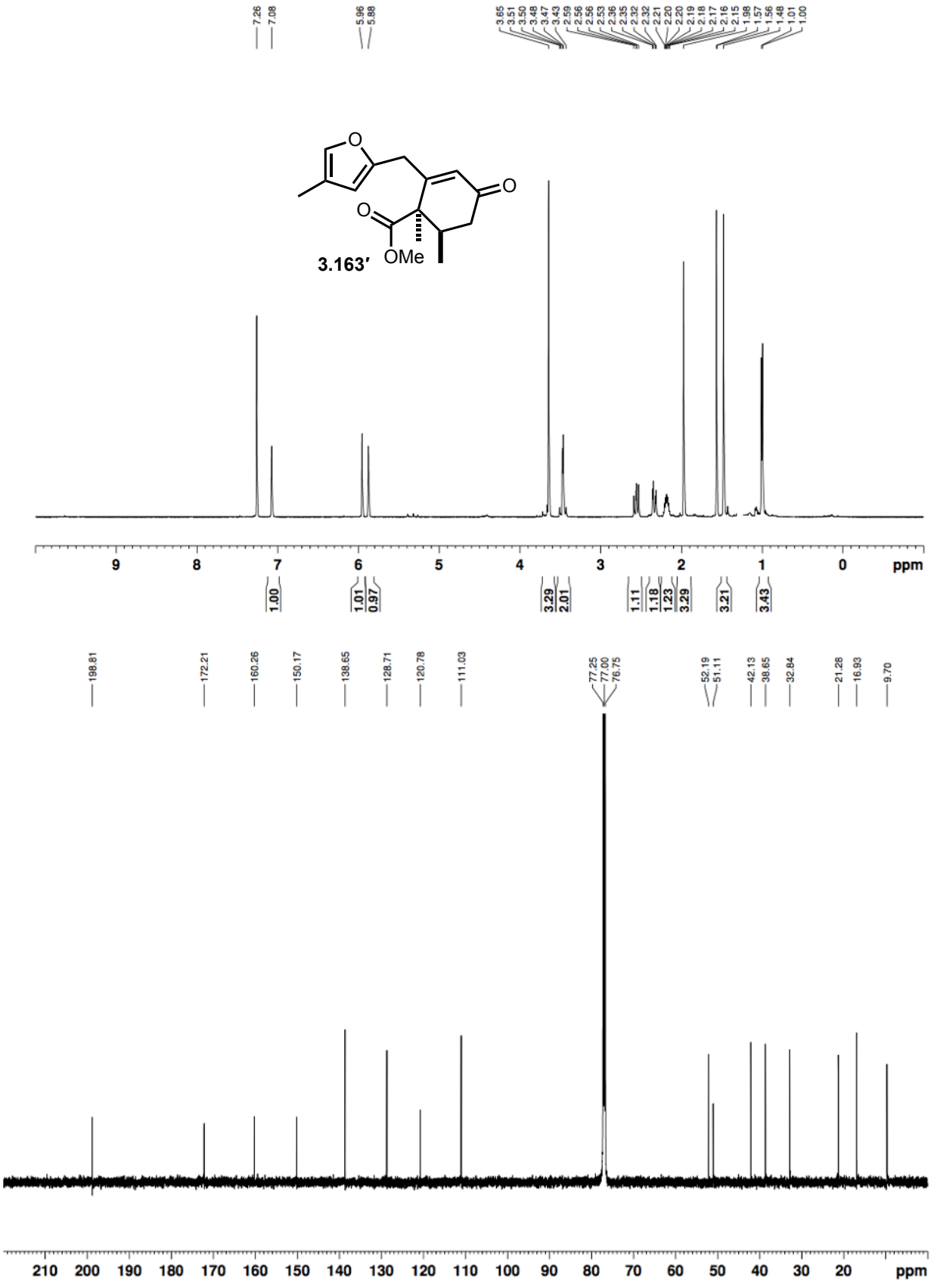
^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.157**



^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.158**



^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.159**



^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR Spectra of **3.163'**

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