University of Alberta

Seven- and Eight-Membered Ether Formation via Sulfonium Ylide Rearrangement Processes and Application in an Approach to (+)-Laurencin

by

Liya Cao

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry

Spring, 2010
Edmonton, Alberta

Examining Committee

Frederick G. West, Department of Chemistry

Dennis Hall, Organic Chemistry

Liang Li, Analytical Chemistry

Christopher W. Cairo, Organic Chemistry

John M. Seubert, Pharmaceutical Sciences

Jon D. Rainier, Organic Chemistry, University of Utah

In Loving Memory of

Changqing Cao

08/24/1953 to 09/23/2009

Abstract

Given the large number of biologically active natural products containing medium-sized ether motifs, many organic chemists have shown great interest for developing new methodologies to access these structures. In particular, numerous synthetic methodologies for the construction of seven-membered and eight-membered ethers have been developed by research groups around the world.

Recent advances in the synthesis of seven-membered and eight-membered ethers will be reviewed in chapter one. This chapter will cover some of the more notable publications from the last five years (from 2005 to 2009).

In chapter two, the development of ring expansion reactions via [1,2]-shift rearrangements of thioacetal-derived sulfonium ylides will be described. A variety of functionalized diazoketones and diazoketoesters were made from commercially available starting materials. Sulfur-bridged seven-membered and eight-membered ethers were constructed upon treatment of these diazo precursors with suitable metal catalysts. It was found that $Rh_2(OAc)_4$ was a better catalyst for diazoketones, while $Cu(hfacac)_2$ proved to be more effective for diazoketoesters. This methodology provides a convenient route to the seven- and eight-membered ethers in relatively few steps.

In chapter three, the methodology for construction of sulfur-bridged ethers was employed as the key step in the attempted formal synthesis of (+)-laurencin. In this approach, the relative and absolute stereochemistry was established by a

highly enantioselective and diastereoselective allylboration, a facially selective Michael addition, and a thermodynamically controlled acetal formation. The eight-membered sulfur-bridged ether was efficiently constructed using our [1,2]-shift reaction of a sulfonium ylide in toluene at 100 ^{o}C in the presence of Cu(hfacac)$_2$. The following desulfurization and decarboxylation was effective at affording an advanced intermediate in this synthesis. The chemistry demonstrated in this chapter outlines a promising strategy for the formal synthesis of (+)-laurencin.

Acknowledgements

I am heartily thankful to my supervisor, Dr. F. G. West, who has supported me during my graduate studies with his guidance, patience and encouragement. In particular, I appreciate the great understanding and patience he showed to me during this year.

I would also like to thank all members of the West group. They helped me a lot not only inside the lab but also outside the lab. I especially thank Tina Grant and Craig Stewart for the friendly environment in W5-50 during these years. I thank Tina Bott and Shaon Joy for their careful review of my thesis.

I would also like to thank the supporting members of the Chemistry department, especially the staff of the spectral services, glass shop, machine shop and chemical store.

Also many thanks go to Lianpeng for his tolerance when I'm preparing this thesis.

Last but not the least, I want to thank my whole family for their understanding and support. Especially my mum's encouragement gave me great courage during this tough year.

TABLE OF CONTENTS

List of Tables

Chapter 1

Chapter 2

Chapter 3

List of Figures

Chapter 1

Chapter 2

Chapter 3

List of Schemes

Chapter 1

Chapter 2

Chapter 3

Standard List of Abbreviations

Ac	acetyl
acac	acetylacetone
AIBN	2,2-azobisisobutyronitrile
Ar	aryl
app	apparent (spectral)
aq	aqueous
9-BBN	9-borabicyclo[3,3,1]nonane
Bn	benzyl
br	broad (spectral)
^{n}Bu	butyl
^{t}Bu	*tert*-butyl
^{o}C	degrees Celsius
CAN	ceric ammonium nitrate
calcd	calculated
Cb	*N*,*N*-diisopropylcabamate
COSY	homonuclear correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphor-10-sulfonic acid
Cy	cyclohexyl
d	day(s); doublet (spectral)

DABCO	1,4-diazabicyclo[2,2,2]octane
dba	dibenzylideneacetone
dd	doublet-of-doublet (spectral)
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DIBALH	diisobutylaluminum hydride
DMAC	dimethylacetamide
DMAP	4-*N*,*N*-dimethylaminopyridine
DME	dimethyl ether
DMF	*N*,*N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
DVS	1,3-divinyl-1,1,3,3-tetramethyldisiloxane
ee	enantiomeric excess
EI	electron impact (mass spectrometry)

eq	equivalents
ESI	electrospray ionization (mass spectrometry)
EtOAc	ethyl acetate
g	gram(s)
hfacac	hexafluoroacetylacetonate
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HMBC	heteronuclear multiple bond coherence
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum choherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
Hz	hertz
IBX	*o*-iodoxybenzoic acid
ipc	isopinocampheyl
J	coupling constant (in NMR)
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
M	moles per liter
m	multiplet (spectral)
Me	methyl

MHz	megahertz
min.	minute(s)
MP	*p*-methoxyphenyl
m.p.	melting point
Ms	mesyl; methanesulfonyl
MS	molecular sieves
m/z	mass to charge ratio (mass spectrometry)
NaHMDS	sodium hexamethyldisilazide
NMO	*N*-methylmopholine-*N*-oxide
NMR	nuclear magnetic resonance
NMQ	*N*-methylquinolinium
Oct_3P	trioctylphosphine
PBB	*p*-bromobenzyl
Ph	phenyl
piv	pivaloyl
PMB	*p*-methoxybenzyl
PPA	polyphosphoric acid
ppm	parts per million (spectral)
PPTS	Pyridinium *p*-toluenesulfonate
Pr	propyl
Pv	pivaloyl

q	quartet (spectral)
RaNi	Raney nickel
R*f*	retention factor (in chromatography)
rt	room temperature
s	singlet (spectral); second(s)
t	triplet (spectral)
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
tfacac	trifluoroacetylacetonate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
tpa	triphenylacetyl
TPAP	tetrapropylammonium perruthenate
Ts	tosyl; *p*-toluenesulfonyl

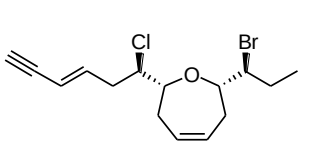
p-TsOH	*p*-toluenesulfonic acid

Chapter 1

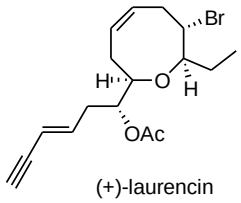
Synthesis of Seven- and Eight-Membered Ethers

1.1. Introduction

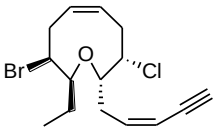
Given the large number of natural products having medium-sized ethers as the core structures, the interest for synthesis of medium-sized oxacycles has increased steadily in recent years. Examples of their occurrence in nature include isolaurepinnacin, [1] laurencin, [2] obtusenyne, [3,4] brevetoxin,[5] and many others (Figure 1.1). Though they are regarded difficult structures to access because of entropic and enthalpic reasons,[6] various synthetic methodologies have been developed by numerous research groups around the world. Several excellent reviews about the medium-sized ether syntheses have been published already.[7-16] The purpose of this review is to cover approaches to medium-sized ethers, especially seven-membered and eight-membered ethers that have been published in the last five years (from 2005 to 2009).



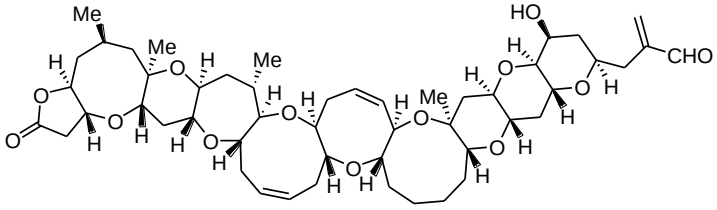
isolaurepinnacin



(+)-laurencin



(+)-obtusenyne



brevetoxin A

Figure 1.1: Examples of medium-sized ethers.

Similar to Hoberg's classification,[9] the construction of medium-sized ethers can be classified into five basic categories (Figure 1.2). The first one is through carbon-carbon single bond formation. The second one involves the formation of carbon-oxygen single bond. The third category discusses the carbon-carbon double bond formation. This section is focused on the olefination reaction through the ring closing metathesis (RCM), which provides highly efficient ways for medium-sized ether formation. The fourth strategy involves ring-expansion reactions of different size rings. In the end, in the last section, the conversion of lactones into ethers will be discussed.

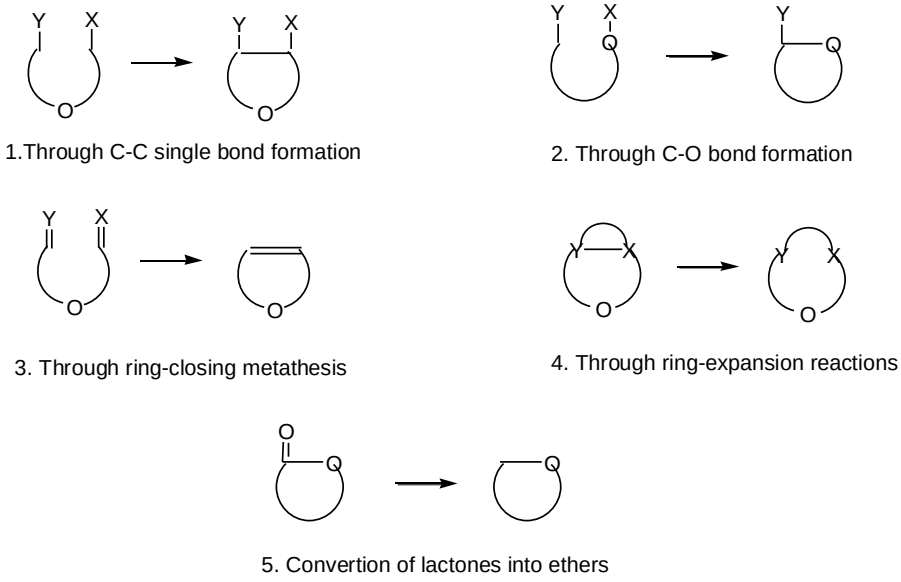


Figure 1.2: Five categories for medium-sized ether formation.

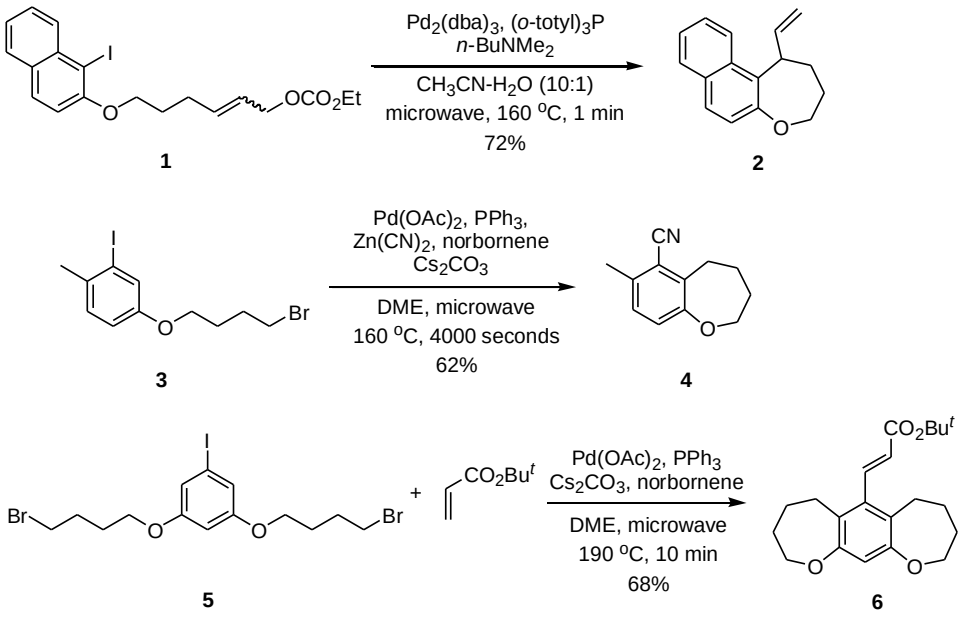
1.2. Cyclization through carbon-carbon single bond formation

This strategy has been widely utilized for the formation of medium-sized ethers. This section is focused on the metal catalyzed cyclization, free radical cyclization and the allylation reactions.

1.2.1. Palladium catalyzed cyclizations

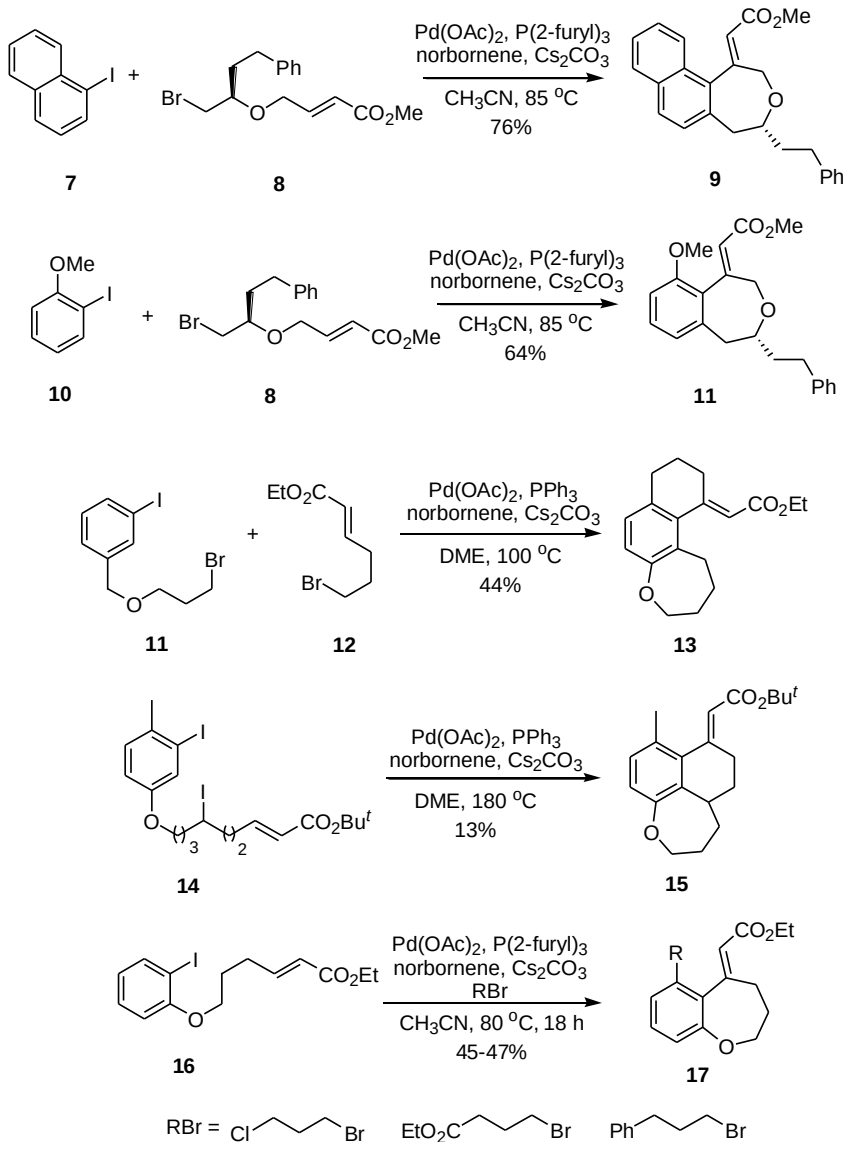
Palladium catalyzed cyclization involves the process of addition of the carbon-palladium bond to another carbon based center. Provided with easily accessible starting materials and mild reaction conditions, carbopalladation has been viewed as one of the most important methods for organic synthesis.[17]

Lautens reported a series of palladium-catalyzed coupling reactions between aryl iodides and allyl moieties under microwave-assisted conditions (Scheme 1.1).[18-21] The iodide precursor **1** cyclized efficiently to provide seven-membered ether **2** in good yield.[18a] The compound **3** underwent a palladium-catalyzed intramolecular alkylation/intermolecular cyanation reaction to form the nitrile product **4**.[18b,19] Also, the tricyclic heterocycle **6** was made from **5** and *tert*-butyl methacrylate via a tandem aryl alkylation/Heck coupling sequence.[20,21]



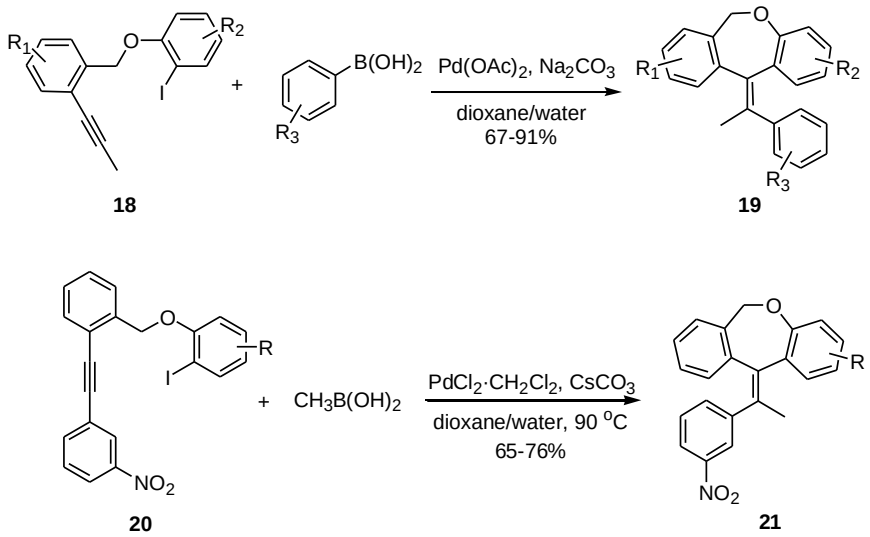
Scheme 1.1: Lautens' palladium-catalyzed cyclizations under microwave conditions.

Lautens also reported the palladium-catalyzed cyclization reactions under thermal-assisted conditions (Scheme 1.2).[22-25] The iodide precursors **7** and **10** reacted with the substituted oxygenated bromoenoate **8** to afford the seven-membered ethers **9** and **11** via sequential alkylation-alkenylation reactions.[22] Compounds **11** and **12** could couple together to form the tricyclic product **13**.[23] Compound **14** could undergo a domino aryl alkylation reaction to provide compound **15** in one step, though the yield was low.[24] Compound **16** underwent ortho-alkylation followed by intramolecular Heck reaction to afford the ether **17**.[25]



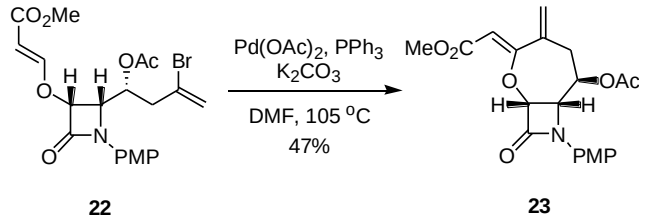
Scheme 1.2: Lautens' palladium-catalyzed cyclization under thermal conditions.

Yu and co-workers reported cyclocarbopalladation reaction of alkynes (Scheme 1.3).[26,27] The alkyne **18** and aryl boronic acids were treated with palladium catalyst to afford the product **19** in good yields.[26] Also the alkyne **20** reacted with methylboronic acid to provide **21** efficiently.[27]



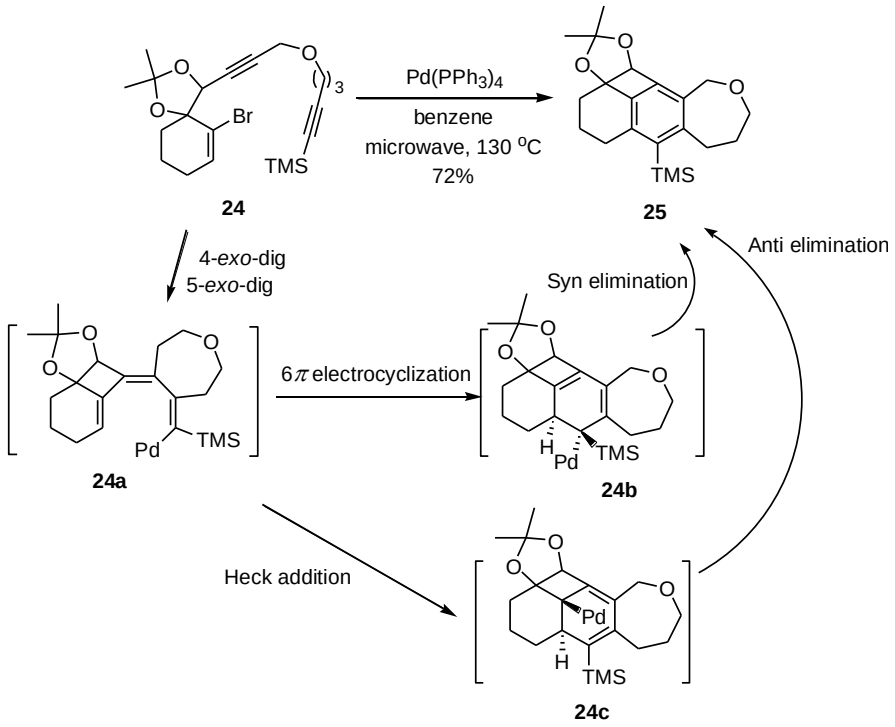
Scheme 1.3: Yu's alkyne cyclocarbopalladation reaction.

Alcaida and Almendros utilized the Heck reaction to access the bicyclic systems.[28] As shown in Scheme 1.4, compound **22** was treated with palladium catalyst to provide the desired product **23** with moderate yield.



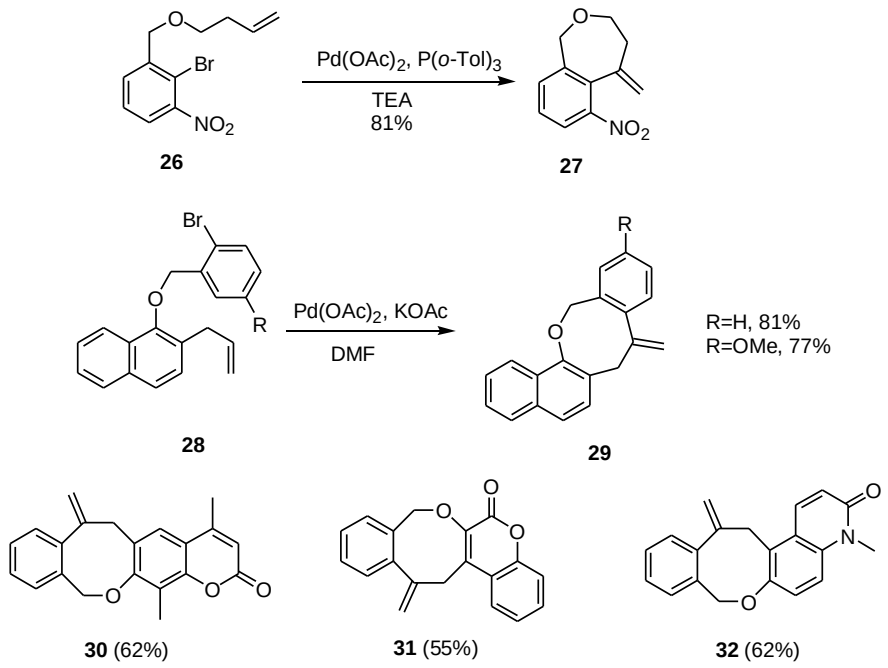
Scheme 1.4: Alcaida and Almendros' Heck reaction to make bicyclic compounds.

Suffert reported a palladium catalyzed cascade reaction to convert bromodienynes into strained aromatic polycycles in one step.[29] As shown in Scheme 1.5, upon treatment of **24** with palladium catalyst, an initial 4-*exo*-dig followed by a 5-*exo*-dig cyclocarbopalladation led to the palladated triene intermediate **24a**, which then underwent a 6π electrocyclization to afford **24b** or a Heck addition to afford **24c**. A syn dehydropalladation elimination of **24b** or an anti dehydropalladation elimination of **24c** provided the final product **25**.



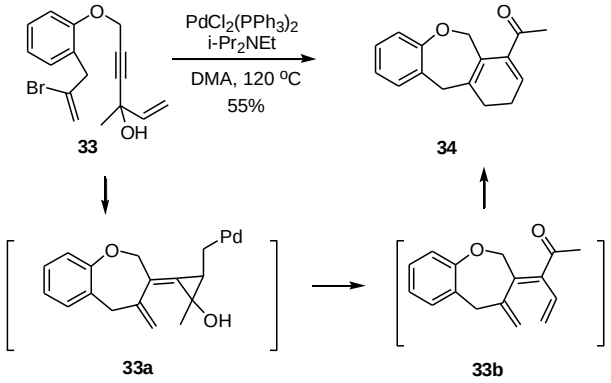
Scheme 1.5: Suffert's palladium catalyzed cascade reation.

Söderberg[30], Majumdar[31] and Chattopadhyay[32] also reported the synthesis of medium sized oxa-heterocycles by palladium-catalyzed intramolecular Heck reaction. As shown in Scheme 1.6, seven- and eight-membered ethers **27** and **29** were obtained from the corresponding aryl bromide precursors **26** and **28** in good yields. Similar reactions were also reported by Chattopadhyay and co-workers to access the 8-membered ethers **30**, **31** and **32** in moderate yields.[32]



Scheme 1.6: Söderberg's, Majumdar's and Chattopadhyay's intramolecular Heck reaction.

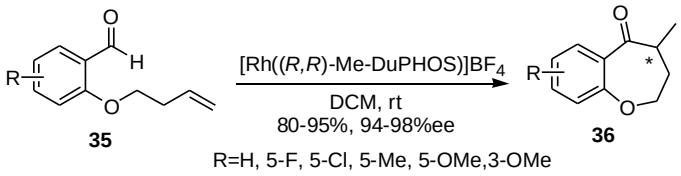
Sarpong[33] reported a tandem anomalous Heck/6π electrocyclization cascade reaction. As shown in Scheme 1.7, the dieynol **33** was converted into the tricyclic cycohexadiene **34** in 55% overall yield through a process believed to involve intermediate **33a** and **33b**.



Scheme 1.7: Sarpong's Heck/6π electrocyclization cascade reaction.

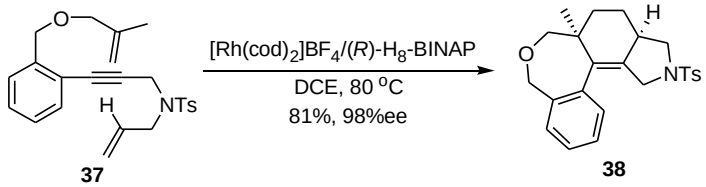
1.2.2. Rhodium catalyzed cyclizations

Dong reported a highly asymmetric rhodium catalyzed synthesis of 7-membered ethers.[34] As shown in Scheme 1.8, the alkenals **35** underwent oxygen-assisted intramolecular olefin hydroacylation process to provide the products **36** in excellent yields and with excellent enantiomeric excesses.



Scheme 1.8: Dong's olefin hydroacylation reaction to make 7-membered ethers.

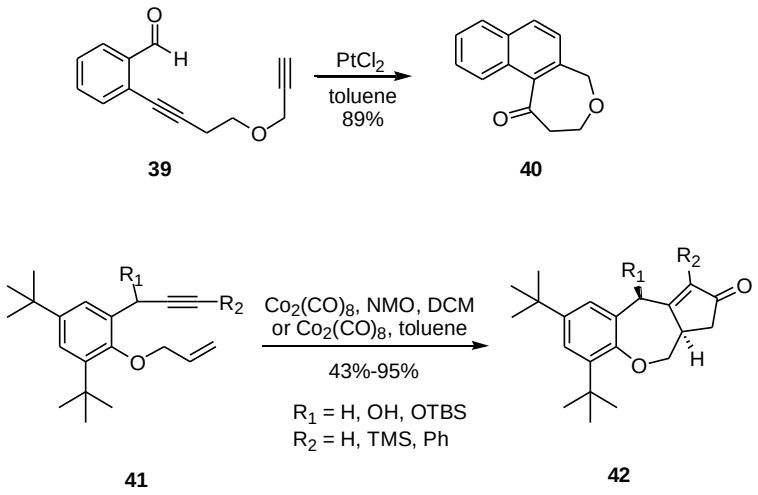
Tanaka published a rhodium catalyzed enantio- and diastereoselective intramolecular [2+2+2] cycloaddition of unsymmetrical dienynes (Scheme 1.9).[35] The dienyne **37** was treated with rhodium catalyst to afford the tetracyclic product **38** in good yield and excellent enantiomeric excess.



Scheme 1.9: Tanaka's rhodium catalyzed cyclization.

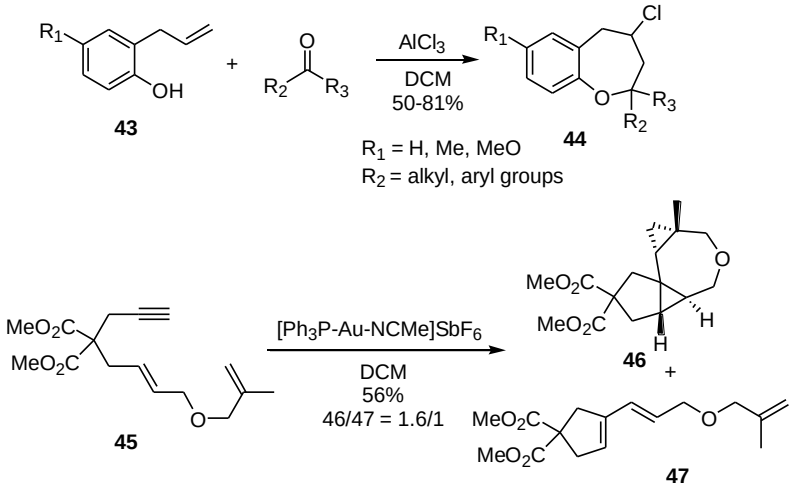
1.2.3. Cyclization using other metal catalysts

Other metals could also catalyze the formation of 7- and 8-membered ethers (Scheme 1.10). Under the platinum catalyzed reaction conditions, the dialkyne **39** underwent an intramolecular domino reaction to afford the product **40**.[36] After the cobalt catalyzed intramolecular Pauson-Khand reactions, the 1,8-enynes **41** were converted into the 7-membered ether products **42**.[37]



Scheme 1.10: Platinum and cobalt catalyzed cyclization reactions.

Aluminum and gold complexes can also be utilized for medium-sized ether synthesis.[38,39] As shown in Scheme 1.11,[38] aluminum chloride catalyzed the cross coupling between 2-allylphenols **43** and ketones to yield a wide range of benzoxepin derivatives **44** via Prins type cyclization. Upon treatment with a gold (I) complex, dienyne **45** underwent bis(cyclopropanation) to provide the complex tetracyclic product **46**.[39]

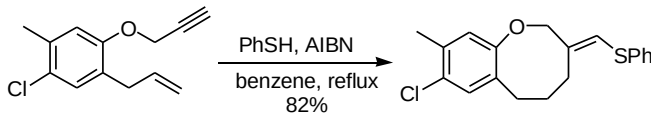


Scheme 1.11: Aluminum and gold catalyzed cyclization reactions.

1.2.4. Free radical cyclization

Free radical cyclization reactions are important synthetic tools due to mild reaction conditions along with high levels of chemoselectivity and stereoselectivity. Recent advances in radical chemistry have led to the development of new methodologies to construct medium-sized ethers efficiently.

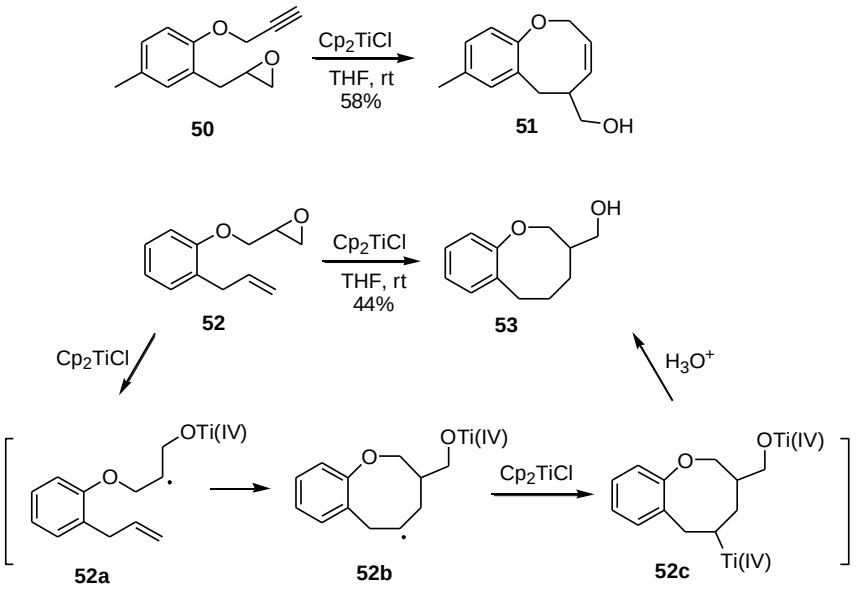
Majumdar[40] reported the thiophenol-mediated radical cyclization reactions to form the benzoxocine derivatives. As shown in Scheme 1.12, the eight-membered ether **49** was formed from the enyne **48** via sulfanyl radical addition-cyclization process.



48 **49**

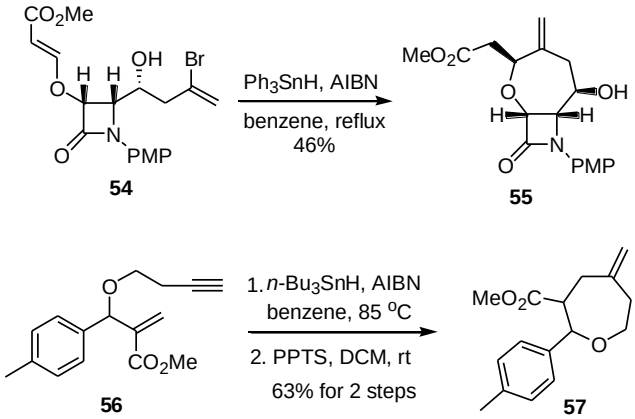
Scheme 1.12: Majumdar's thiophenol-mediated radical cyclization.

Roy[41,42] developed novel titanocene chloride mediated 8-*endo* radical cyclizations (Scheme 1.13). Through radical cyclization of epoxides **50** and **52**, the eight-membered ethers **51** and **53** were formed. The mechanism for the formation of **53** from **52** was also shown in Scheme 1.12. Ti(III) reacted as a single electron reductant to open the epoxide motif in **52** to form **52a**, which then underwent a 8-*endo* radical cyclization to form **52b**. Radical intermediate **52b** was reduced by a second equivalent of Ti(III) to form **52c**, which underwent protonation to furnish **53**.



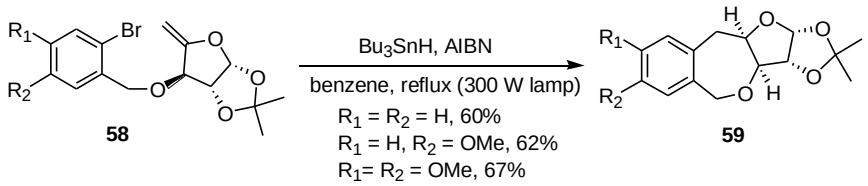
Scheme 1.13: Roy's radical cyclization reactions.

Since their introduction in 1982,[43] vinyl radical cyclizations received intensive interest in organic synthesis. As shown in Scheme 1.14, the tin-promoted radical reaction of bromodienic alcohol **54** provided the product **55** in moderate yield.[44] Tin-initiated radical cyclization of compound **56** followed by protiodestannylation afforded the 7-membered ether **57** in good yields for two steps.[45]



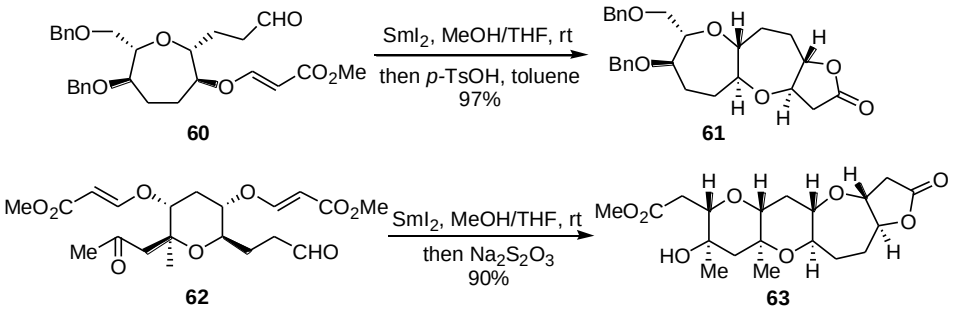
Scheme 1.14: Alcaide's and Shanmugam's vinyl cyclization reactions.

The Chattopadhyay group published a report describing aryl radical cyclization reactions to form the medium sized ethers (Scheme 1.15).[46] Tin-promoted radical cyclization of the *exo*-methylene precursors **58** yielded the tricyclic ethers **59** efficiently as the only product. The regiochemical preference was the result of geometric factors.[43] The stereochemical outcome results from preferential delivery of hydrogen to the bridgehead radical formed after cyclization from the more accessible convex face.



Scheme 1.15: Chattopadhyay's aryl radical cyclization.

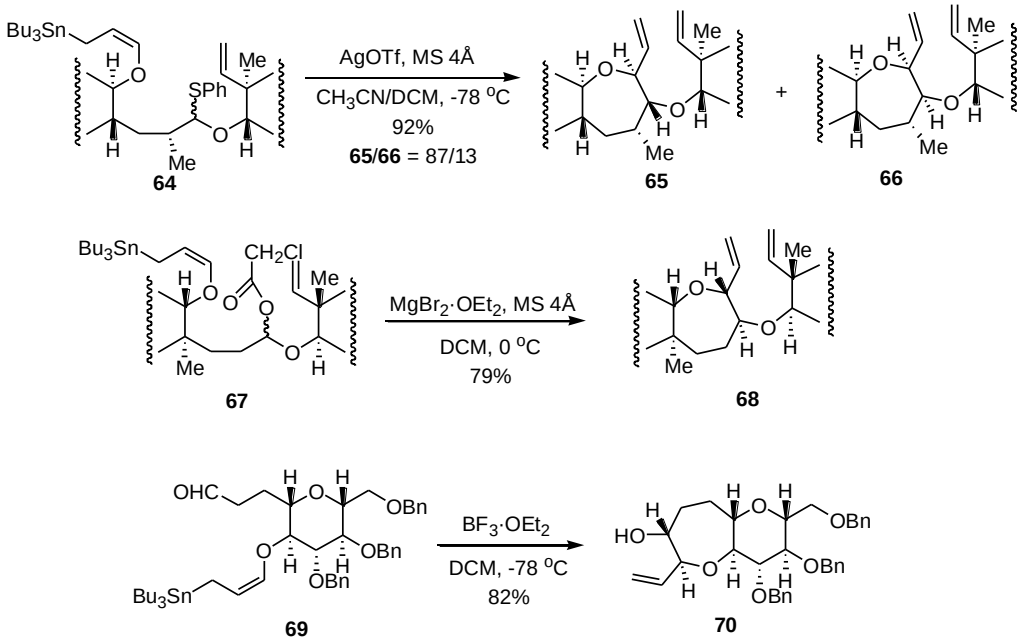
Samarium diiodide is also an efficient reagent for radical cyclization reactions using precursors with readily reducible carbonyl moieties. As shown in Scheme 1.16, when treated with SmI_2, the aldehyde **60** was converted into product **61** in almost quantitative yield.[47] The ketone aldehyde **62** underwent double cyclization reaction to give the tricyclic ether **63** in excellent yield.[48]



Scheme 1.16: SmI_2 catalyzed radical cyclization.

1.2.5. Intramolecular allylation using allylic stannanes

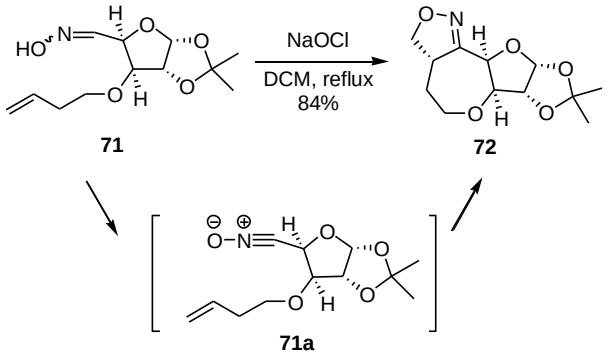
Intramolecular attack of allylic stannanes on aldehydes or acetals is a widely used strategy for medium-sized ether formation, especially in the case of marine polyether ladder toxin synthesis. As shown in Scheme 1.17, Kadota and co-workers published the construction of the seven-membered ether motif through an intramolecular allylation reaction on the *O,S*-mixed acetal **64** during the synthesis of brevetoxin B.[49,50] With silver triflate as the catalyst, the diastereomeric products **65** and **66** were formed in high yields with **65** as the major product. The same group also published the total synthesis of hemibrevetoxin B[51] and the synthesis of the AB ring segment of ciguatoxin[52] by utilizing the same strategy to construct the 7-membered ether motifs. The acylated *O,O*-acetal allylic stannane **67** was treated with magnesium bromide to yield the product **68** in good yield.[51] The aldehyde **69** was converted into **70** with excellent yield through a direct allylation reaction on the aldehyde.[52]



Scheme 1.17: Intramolecular allylation of allylic stannanes.

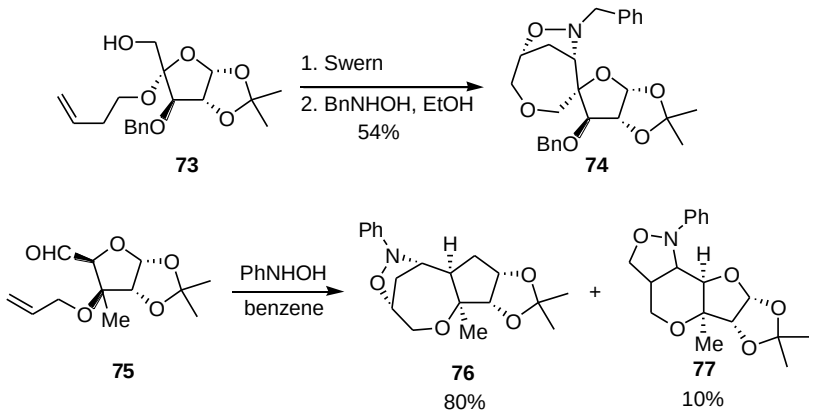
1.2.6. Intramolecular nitrile oxide-alkene cycloaddition strategy

Shing reported the synthesis of medium-sized ethers from carbohydrates via intramolecular 1,3-dipolar cycloaddtions of nitrile oxides and alkenes.[53] As shown in Scheme 1.18, on treatment with NaOCl, the oxime **71** was converted into the corresponding 7-membered ether **72** in excellent yield via the nitrile oxide intermediate **71a**.



Scheme 1.18: Shing's intramolecular nitrile oxide-alkene cycloaddition.

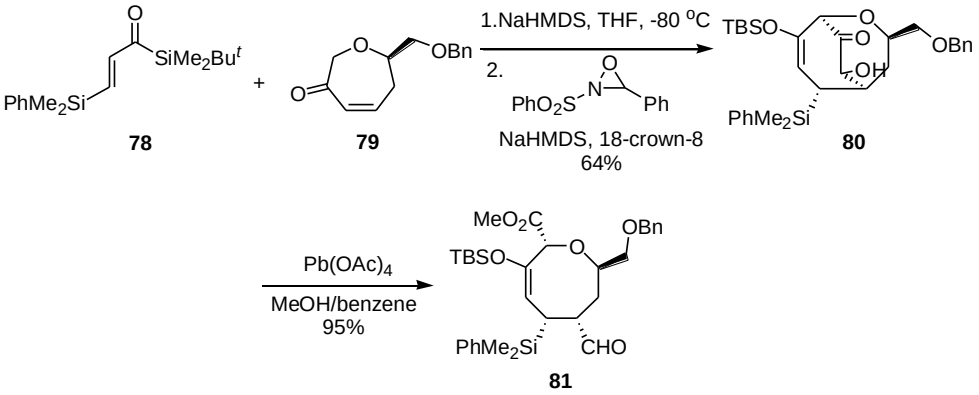
Mandal reported formation of 7-membered ethers via intramolecular *N*-benzyl nitrone alkene cycloaddition reactions.[54] As shown in Scheme 1.19, the alcohol **73** underwent Swern oxidation reaction followed by condensation with N-benzyl hydroxylamine and 1,3-dipolar addition to afford the product **74** in good yield for two steps. Bhattacharjya and co-workers used a similar strategy to make the 7-membered ethers from *N*-phenyl nitrones.[55] The aldehyde **75** was treated with PhNHOH in benzene to provide the desired product **76** in good yield.



Scheme 1.19: Mandal and Bhattacharjya's intramolecular nitrile oxide-alkene cycloaddition.

1.2.7. Diastereoselective Brook rearrangement-mediated [3+4] annulations

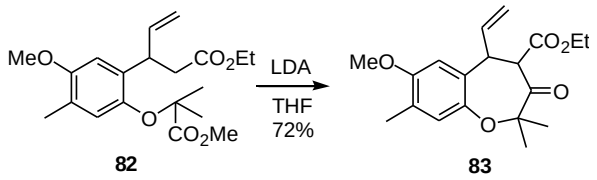
Takeda reported the formal synthesis of (+)-laurallene via Brook rearrangement-mediated [3+4] annulation reaction.[56] As shown in Scheme 1.20, the acryloysilane **78** and unsaturated 7-membered ketone **79** were converted into **80** via a one-pot [3+4] annulation/oxidation process. Bicyclic intermediate **80** was then treated with lead tetraacetate to reveal the eight-membered ether **81**.



Scheme 1.20: Takeda's one-pot [3+4] annulation/oxidation reaction.

1.2.8. Cyclization catalyzed by base or acid

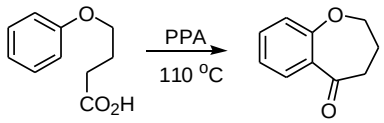
Venkataswaran and co-workers reported the formation of medium-sized ethers via base catalyzed Dieckman condensation reactions.[57,58] As shown in Scheme 1.21, ester **82** was treated with LDA in THF to provide the desired ketoester **83** in good yield.



82 **83**

Scheme 1.21: Venkataswaran's base catalyzed acyloin condensation reaction.

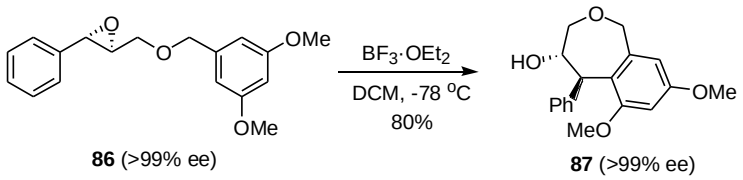
Meegan reported the construction of a seven-membered ether by an acid promoted cyclization.[59] As shown in Scheme 1.22, the acid **84** was treated with PPA to form the product **85** via an intramolecular Friedel-Crafts acylation.



84 **85**

Scheme 1.22: Meegan's acid promoted cyclization reaction.

Pericàs reported the Lewis acid catalyzed cyclization reaction to make seven-membered ethers.[60] As shown in Scheme 1.23, the 7-membered ether **87** was constructed via a $BF_3 \cdot OEt_2$ promoted stereospecificly rearrangement cyclization reaction of the epoxide **86** with excellent yield.



86 (>99% ee) **87** (>99% ee)

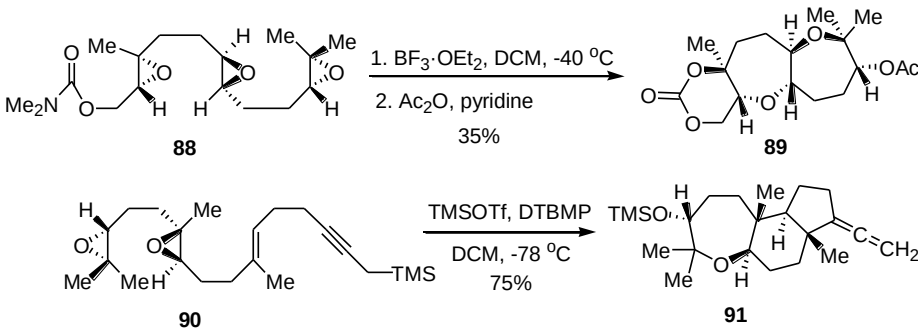
Scheme 1.23: Pericàs' Lewis acid promoted cyclization

1.3. Cyclization through carbon-oxygen single bond formation

Carbon-oxygen single bond formation is widely used for the synthesis of oxygen containing compounds, especially for cyclic ethers. During the past few years, many methodologies have been reported in this field. This section is focused on the intramolecular cyclization of epoxides, hydroxyl carbonyls, alkynyl alcohols, diols, dienes and so on.

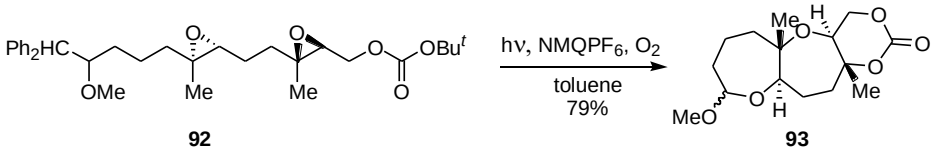
1.3.1. Intramolecular cyclization of epoxides

Intramolecular cyclization of epoxides has provided an efficient way to construct the medium-sized motifs during total synthesis of many natural products. In particular, via the Lewis acid-initiated oxacyclization of polyepoxides, multiple carbon-oxygen bonds could form in one step, offering a different route to obtain polyethers. McDonald reported the biomimetic synthesis of 7-membered polyoxepanes by using this strategy.[61] As shown in Scheme 1.24, the polyepoxide **88** on treatment with Lewis acid followed by protection step afforded the product **89** in one step. The same group then published the synthesis of abudinol B by using this strategy.[62,63] Upon treatment with TMSOTf, the enyne diepoxide **90** was converted into the tricyclic allene **91** in good yields. The polyepoxides **88** and **90** were easily made via asymmetric epoxidation of corresponding triene or diene.



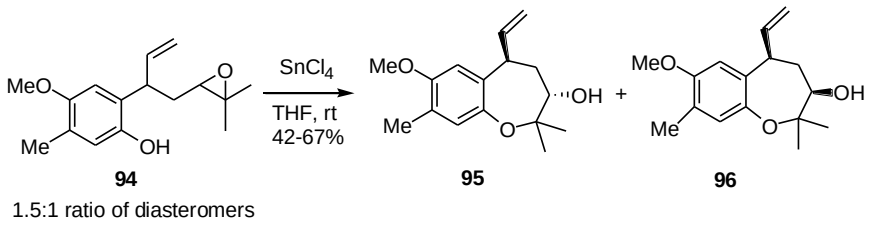
Scheme 1.24: McDonald's intramolecular cyclization of polyepoxides.

Houk, Floreancig reported the formation of cyclic ethers via the attack of oxocarbenium ions by the pendent epoxides.[64] As shown in Scheme 1.25, upon treatment of diepoxide **92** under oxidative conditions, the *endo*-cyclization product **93** was formed in good yield. *N*-methylquinolinium hexafluorophosphate ($NMQPF_6$) was an effective single-electron oxidant in a photoinitiated carbon-carbon σ-bond activation process. Conveniently, O_2 (from air) served as the terminal oxidant to regenerate the $NMQPF_6$ catalyst.



Scheme 1.25: Houk and Floreancig's cyclization of diepoxide.

Vyvyan[65] reported the total synthesis of heliannuol E with 7-*endo* phenol epoxide cyclization as the key step. As shown in Scheme 1.26, treatment of epoxide **94** with tin(IV) chloride resulted in benzoxepanes **95** and **96**.



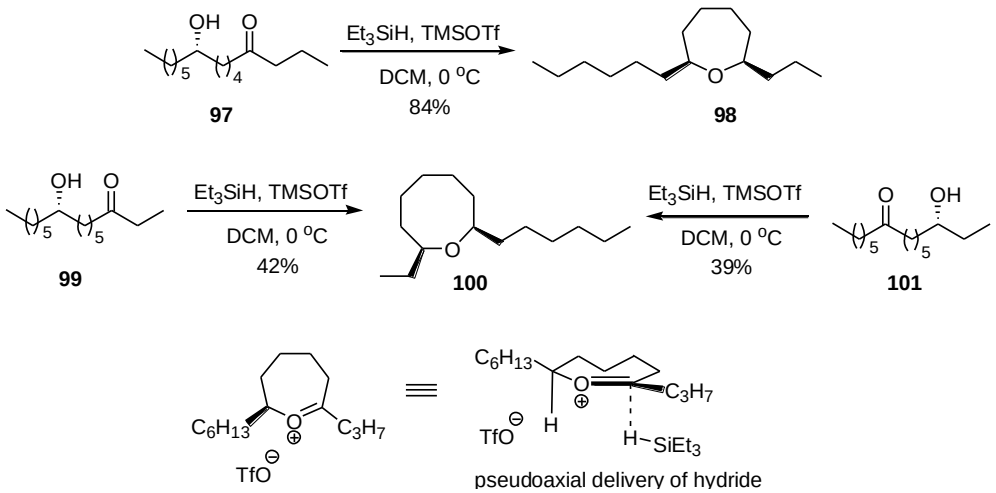
94 **95** **96**

1.5:1 ratio of diasteromers

Scheme 1.26: Vyvyan's cyclization of phenol epoxide.

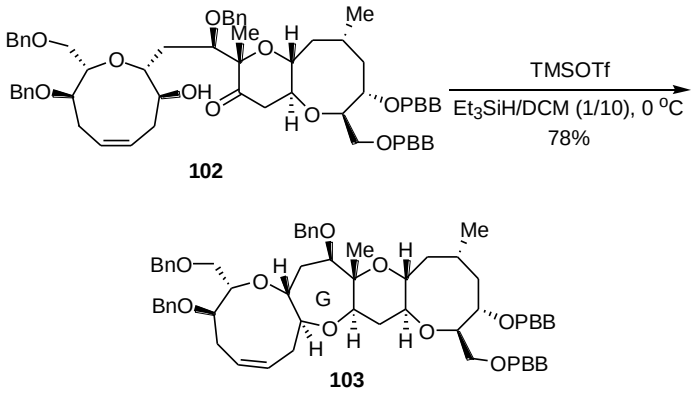
1.3.2. Intramolecular cyclization of hydroxyl carbonyls

Reductive cyclization of hydroxyl carbonyls has been used frequently during the total synthesis of natural products with medium-sized ether moieties. Kumar reported a short approach to (+)-isolaurepan by using this strategy.[66] As shown in Scheme 1.27, treatment of hydroxyl ketone **97** with Et_3SiH and TMSOTf resulted in exclusively the *cis* disubstituted cyclic 7-membered ether **98** in excellent yield. This strategy had also been utilized for the total synthesis of (-)-*cis*-lauthisan,[67] which is an 8-membered ether. Under the same reaction conditions, the hydroxyketone **99** was converted into the desired product **100** in moderate yield. Carreño also reported the total synthesis of (-)- and (+)-cis-lauthisan via the same strategy.[68] The similar precursor **101** underwent reductive cyclization to afford the same product **100** also in moderate yield. It seemed the formation of 7-membered ether was much easier compared with 8-membered ether by using this strategy. The formation of *cis* diatereomers was due to the pseudoaxial delivery of hydride to the oxocarbenium ion intermediate. A similar mechanism could also apply to the formation of the *cis* isomer in the case of eight-membered cyclic ethers.



Scheme 1.27: Kumar's and Carreño's reductive cyclization of hydroxyketones

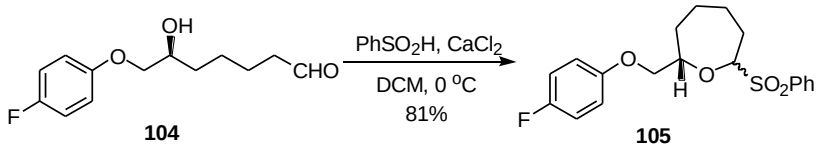
Fujiwara and co-workers utilized reductive cyclization of hydroxyketones to form the G-ring part of ciguatoxin.[69] As shown in Scheme 1.28, when treated with excess Et_3SiH in the presence of TMSOTf at 0 °C, the precursor **102** was converted stereoselectively into the desired product **103** with excellent yield.



Scheme 1.28: Fujiwara's reductive cyclization of hydroxyketones.

Chorghade reported a short synthesis of 7-membered oxepane derivatives via an acid catalyzed hydroxyaldehyde cyclization reaction.[70] As shown in Scheme 1.29, the precursor **104** was treated with benzenesulfinic acid and calcium chloride to form 2-benzenesulfonyloxepane **105** in excellent yield. The formation

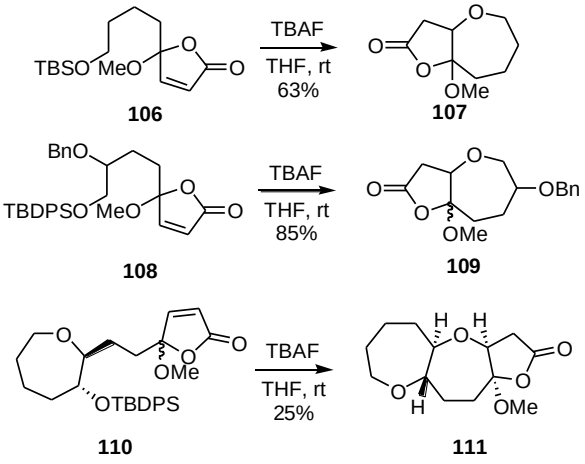
of the stable sulfone by trapping the intermediate oxocarbenium ion might help the reaction by preventing secondary acid-catalysed decomposition processes.



Scheme 1.29: Chorghade's hydroxyaldehyde cyclization.

1.3.3. Intramolecular Michael addition cyclization

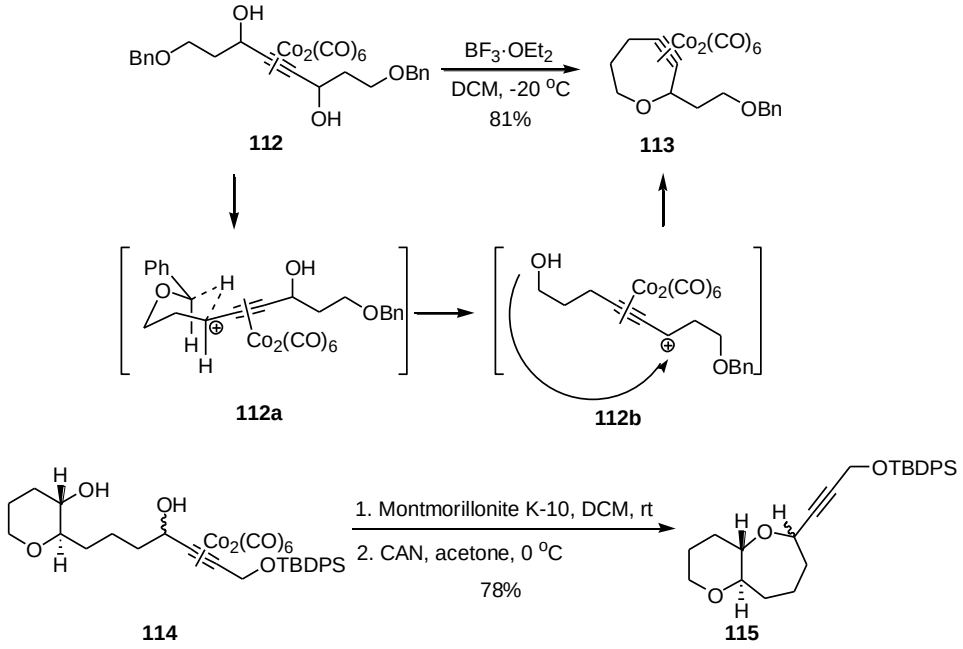
Fall and co-workers reported the formation of 7-membered ether motifs via an intramolecular Michael addition reaction.[71-73] As shown in Scheme 1.30, removal of the TBS group of **106** resulted in the cyclization product **107**.[71] The same group utilized this strategy to make fused polyoxepanes and zoapatanol. Treatment of the similar starting compound **108** with TBAF led to product **109** in good yield. [72] The butenolide **110** was also converted into the tricyclic product **111** under the same conditions.[73]



Scheme 1.30: Fall's intramolecular Michael addition.

1.3.4. Cyclization of alkynyl alcohols

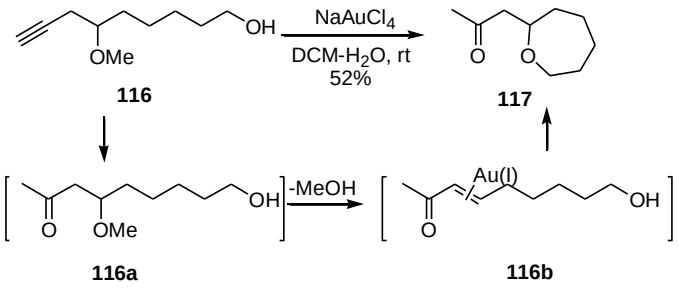
Martín reported the formation of 7-membered ethers via Nicholas reactions by acid treatment of $Co_2(CO)_6$-complexed secondary propargylic alcohols.[74,75] As shown in Scheme 1.31, with Lewis acid catalyzed conditions, the $Co_2(CO)_6$-complexed propargylic alcohol **112** was converted into 7-membered ether **113** in excellent yield through a processes believed to involve intermediates **112a** and **112b**.[74] Montmorillonite K-10 could also catalyze this reaction. $Co_2(CO)_6$-complexed precursor **113** was treated with Montomorillonite K-10 followed by alkyne decomplexation with CAN to afford the product **115** efficiently.[75]



Scheme 1.31: Martín's cyclization via Nicholas reaction.

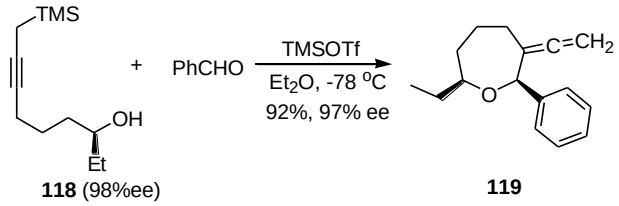
Floreancig and co-workers reported the formation of 7-membered ethers via cyclization reaction of homopropargylic ethers.[76,77] As shown in Scheme 1.32, with gold as the catalyst, the homopropargylic ether **116** with pendent hydroxyl group was converted into the 7-membered ether **117** in moderate yield. Gold-mediated hydration of the alkyne afforded ketone intermediate **116a**, which

underwent methanol elimination to provide enone **116b**. Enone **116b** was then converted into the cyclization product **117** via metal-promoted conjugate addition.



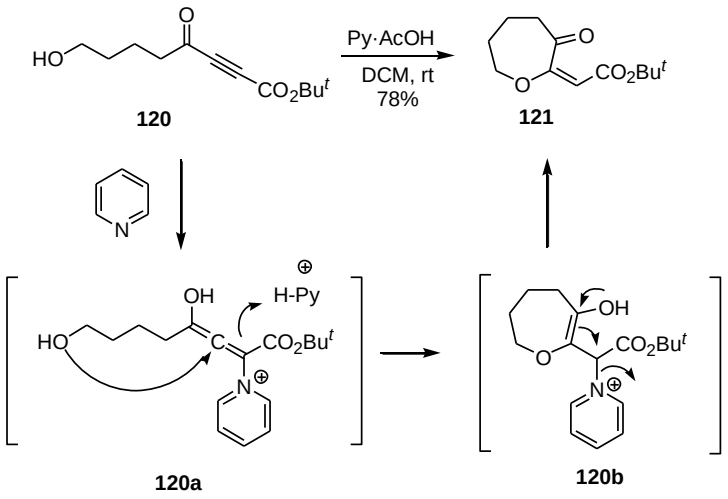
Scheme 1.32: Floreancig's cyclization of homopropargylic ether.

Furman reported the formation of 3-vinylidine oxepanes via silyl-Prins cyclization of propargylsilanes (Scheme 1.33).[78] Catalyzed by TMSOTf, the propargylisilane **118** reacted with aldehyde to provide exclusively *cis*-configuration product **119** in excellent yield and high stereoselectivity.



Scheme 1.33: Furman's silyl-Prins cyclization of propargylsilanes.

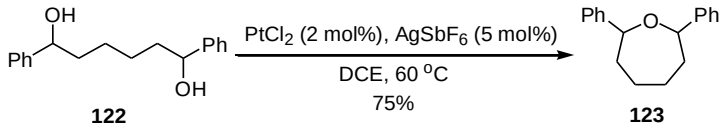
West reported the formation of seven-membered cyclic ethers in the presence of pyridinium acetate.[79] As shown in Scheme 1.34, compound **120** underwent clean conversion to oxepane **121** with the treatment of pyridinium acetate in DCM. The mechanism was proposed to include nucleophilic activation of the ynone to give allenol intermediate **120a**, which then underwent intramolecular Michael addition followed by release of pyridine.



Scheme 1.34: West's pyridinium acetate catalyzed cyclization.

1.3.5. Intramolecular etherification of diols and dienes

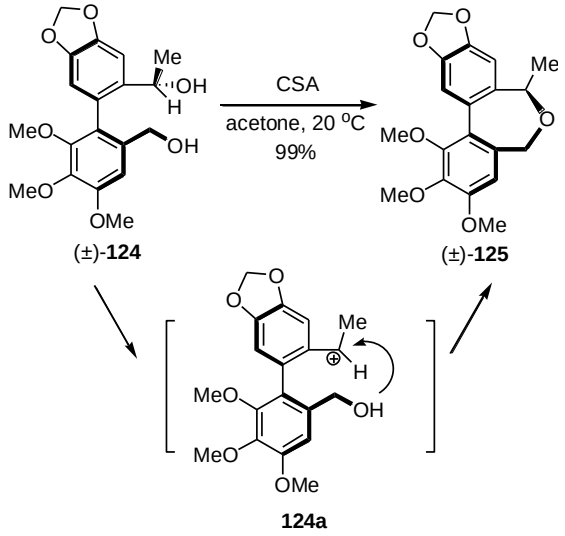
Dehydration of alcohols provides a direct way for ether formation. Protic acids and Lewis acids are common catalysts for this reaction. Shibata reported the cationic platinum catalyzed intramolecular etherification to make the cyclic ethers. As shown in Scheme 1.35, the benzylic diol **122** was treated with platinum catalyst to provide the intramolecular dehydration product **123** in good yield.[80]



Scheme 1.35: Shibata's etherification of diols.

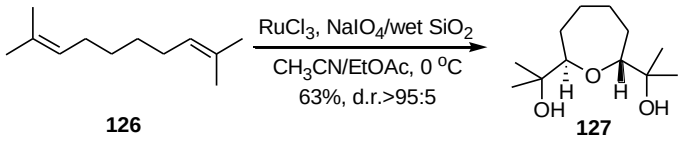
Baudoin and co-workers published the formation of dibenzoxepine products through an intramolecular dehydration process catalyzed by acid (Scheme 1.36).[81] The biphenyl diol **124** was treated with camphorsulfonic acid to afford the etherification product **125** in almost quantitative yield via intermediate **124a** through an intramolecular S_N1 process. The biaryl stereogenic axis provided

asymmetry relay for the benzylic stereocenter, which was temporarily destroyed as shown in intermediate **124a**.



Scheme 1.36: Baudoin's etherification of biphenyl diol.

Piccialli reported the ruthenium-catalyzed oxidative cyclization of 1,7-dienes.[82] As shown in Scheme 1.37, when treated with $RuCl_3$ and $NaIO_4$, diene **126** furnished the seven-membered oxacycle **127** in one step via an intramolecular cyclization process. The d.r. for this reaction was greater than 95:5.

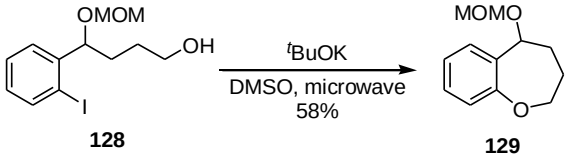


Scheme 1.37: Piccialli's oxidative cyclization of diene.

1.3.6. Cyclization via intramolecular coupling of halides and alcohols

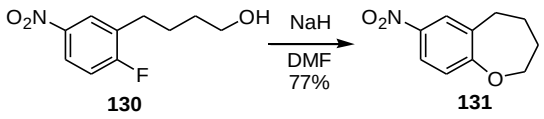
Li and co-workers published the preparation of benzo-fused ethers via a microwave-assisted intramolecular coupling reaction (Scheme 1.38).[83] The alcohol **128** was subjected to microwave heating in the presence of strong base to

afford the seven-membered ether **129** in moderate yield via the coupling reaction between the hydroxyl and aryl iodide.



Scheme 1.38: Li's cyclization via coupling reaction between hydroxyl and iodide.

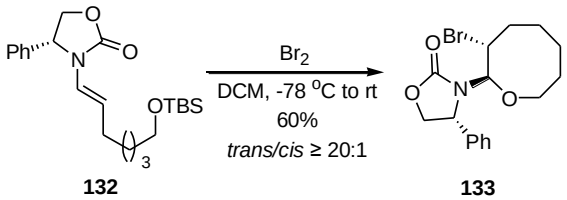
Bunce reported the formation of benzo-fused heterocyclic compounds through intramolecular S_NAr displacement of an activated *ortho* fluoro group by a side-chain alkoxide.[84] As shown in Scheme 1.39, treatment of **130** with sodium hydride afforded benzoxepin product **131** in 77% yield.



Scheme 1.39: Bunce's intramolecular cyclization of hydroxyl and fluoride.

1.3.7. Halo-etherification of enamides

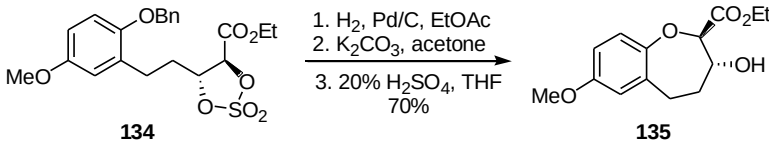
Hsung reported a stereoselective halo-etherification of chiral enamides to make halogen-containing cyclic ethers.[85] As shown in Scheme 1.40, treatment of chiral enamide **132** with Br_2 furnished the eight-membered ether **133** in good yield with the *trans* product as the major diastereomer.



Scheme 1.40: Hsung's halo-etherification of enamides.

1.3.8. Cyclization of cyclic sulfates

Das reported an asymmetric synthesis of 2,3-disubstituted 1-benzoxepines via phenoxide ion mediated intramolecular cyclization of cyclic sulfates.[86] As shown in Scheme 1.41, the cyclic sulfate **134** was debenzylated first to provide the phenol which was then treated with K_2CO_3 followed by H_2SO_4 cleavage of the resulting sulfate to afford the cyclic product **135**.



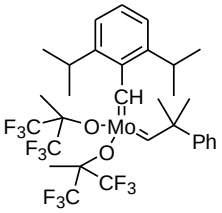
134 **135**

Scheme 1.41: Das' cyclization of cyclic sulphates.

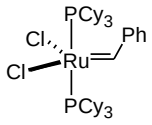
1.4. Cyclization through ring-closing metathesis

Ring-closing metathesis (RCM) of dienes is one of the most important reactions to construct cyclic compounds and has frequently been utilized to make the medium-sized ethers.[87] Several reviews have been published in this area in recent years.[87] The most common catalysts for this reaction include Schrock's molybdenum complex, Grubbs' ruthenium complex (first and second generation), and the Hoveyda-Grubbs ruthenium complex (Figue 1.3). Schrock's complex is highly reactive but has low functional group tolerance and stability. Grubbs' 1st generation catalyst is less reactive but has high functional group tolerance and stability. Grubbs' 2nd generation complex is very reactive and thermally stable. Likewise, the Hoveyda-Grubbs catalyst is very reactive and is a stable catalyst. Dichloromethane, dichloroethane, benzene and toluene are frequently used as solvents. The reaction temperatures vary from room temperature to 110 ^{o}C. Such reaction conditions are quite mild and compatible with many sensitive functional groups including esters, amides, ketones, ethers, acetals and others. The ring sizes available from the RCM are mainly limited to five-, six-, seven-membered rings and macrocycles, while three-, four-, and eight- to eleven-membered rings are

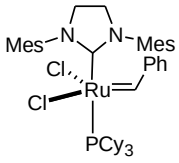
always difficult to construct.[88] Recent publications concerning the formation of seven- and eight-membered ethers via ring-closing metathesis are summarized in Table 1.1. In most cases, RCM is applied directly to construct the medium-sized ethers. However, when substrate alkenes were either sterically hindered or electronically deactivated, relay ring-closing metathesis (RRCM) was utilized as shown in entries 20, 23 and 24.



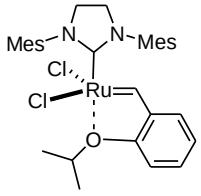
136
Schrock's catalyst



137
Grubbs' first gerenation catalyst



138
Grubbs' second gereration catalyst



139
Hoveyda-Grubbs ruthenium catalyst

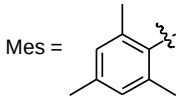


Figure 1.3: Common RCM catalysts.

Table 1.1: RCM for construction of seven- and eight-membered ethers.

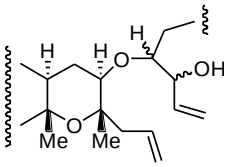
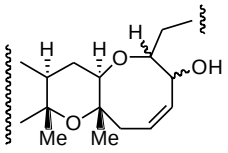
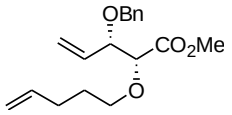
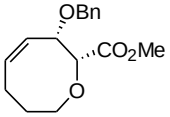
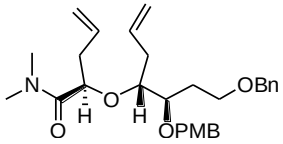
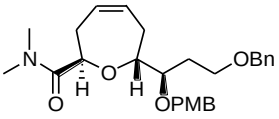
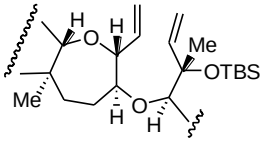
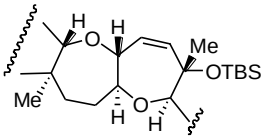
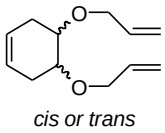
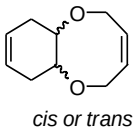
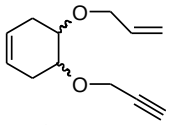
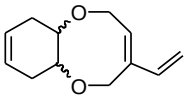
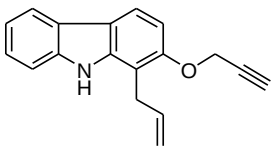
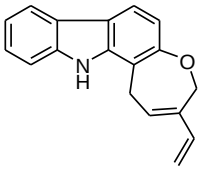
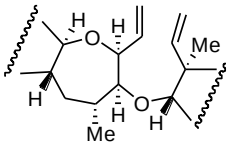
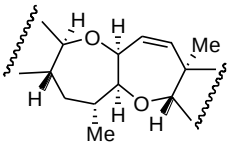
Entry	Precursor	Product	Cat.	Yield	Ref.
1			**138**	58%	89

Table 1.1 (continued)

Entry	Precursor	Product	Cat.	Yield	Ref.
2			**137**	87%	90
3			**137**	65%	91
4			**138**	76%	51
5	 *cis or trans*	 *cis or trans*	**138**	71% (*cis*) 97% (*trans*)	92
6	 *cis or trans*	 *cis or trans*	**137**	58% (*cis*) 78% (*trans*)	92
7			**137**	67%	93
8			**138**	100%	49

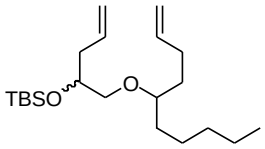
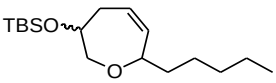
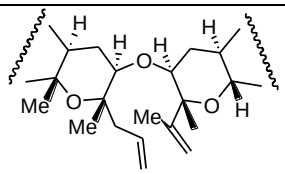
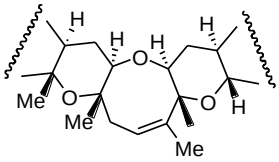
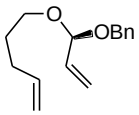
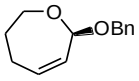
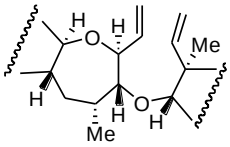
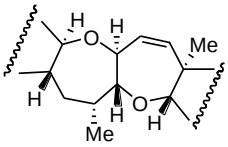
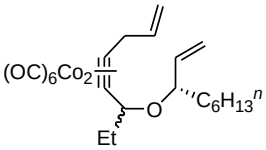
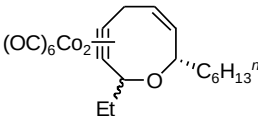
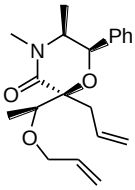
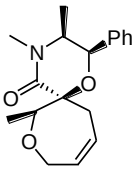
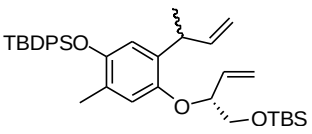
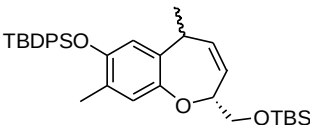
9			**137, 138, 139**	65%	94

Table 1.1 (continued)

Entry	Precursor	Product	Cat.	Yield	Ref.
10			**138**	52%	95
11			**137**	71%	96
12			**137**	84%	50
13			**138**	83%	97
14			**137**	70%	98
15			**138**	92%	99

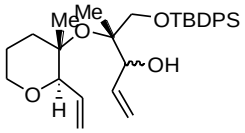
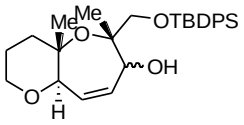
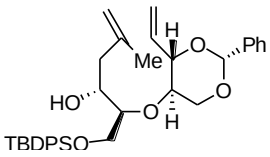
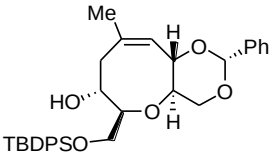
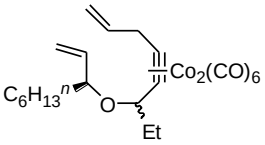
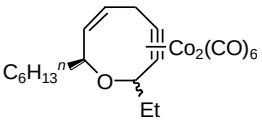
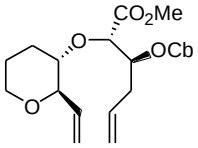
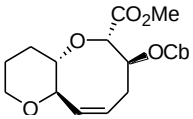
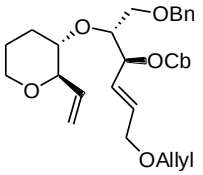
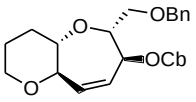
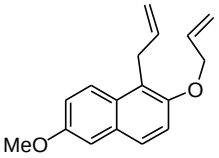
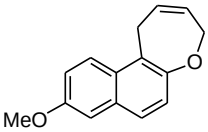
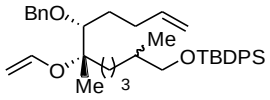
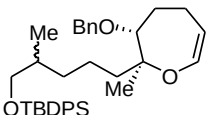
16			**137**	84%	100
17			**138**	82%	101

Table 1.1 (continued)

Entry	Precursor	Product	Cat.	Yield	Ref.
18			**138**	83%	102
19			**138**	80%	103
20			**138**	96%	103
21			**137**	96%	104
22			**137**	70%	105

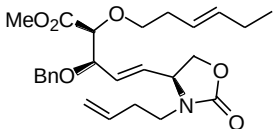
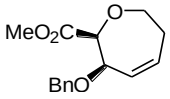
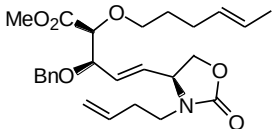
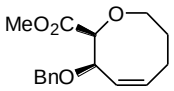
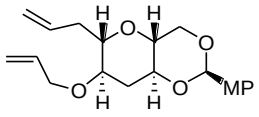
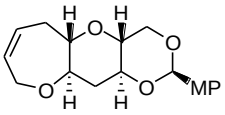
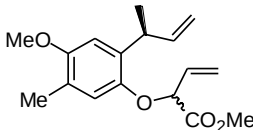
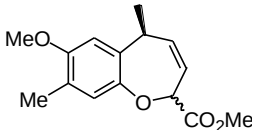
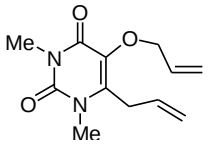
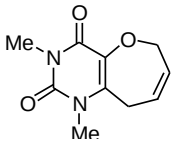
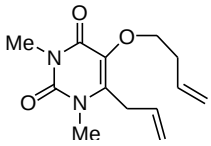
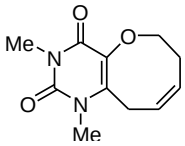
23			**138**	57%	106
24			**138**	58%	106
25			**137**	96%	107

Table 1.1 (continued)

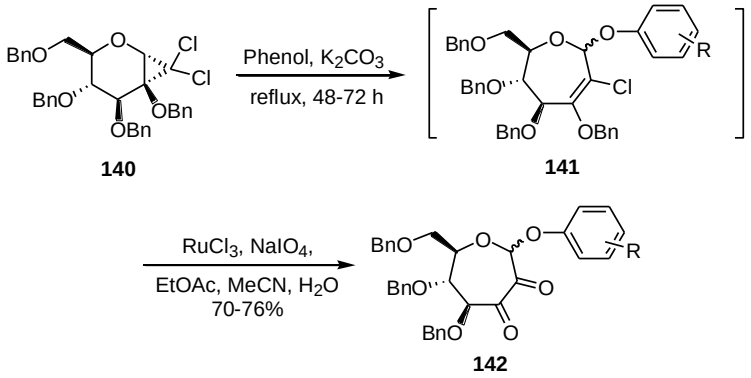
Entry	Precursor	Product	Cat.	Yield	Ref.
26			**138**	85%	108
27			**137**	77%	109
28			**137**	76%	109

1.5. Formation of seven- and eight-membered ethers via ring-expansion reactions

Ring expansion reactions allow the transformation of more readily available small rings into less common medium-sized ethers, which provide chemists an alternative way to construct the medium-sized ethers as compared to direct ways. This section is focused on the ring-expansion reactions of cyclopropane, furan and pyran.

1.5.1. Ring-expansion reactions of cyclopropanes

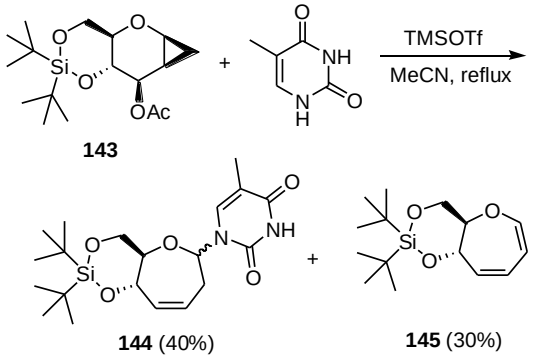
Jayaraman reported the formation of septanoside derivatives via the ring-expansion reactions of cyclopropane precursors (Scheme 1.42).[110,111] The dichlorocyclopropane **140**, derived from the corresponding glycal precursor, was treated with K_2CO_3 and phenol to afford the chloro-oxepines **141**, which were not stable and were oxidized to the diketones with in-situ-generated RuO_4 to provide the seven-membered ethers **142** with excellent yields.



Scheme 1.42: Jayaraman's ring-expansion reactions of cyclopropanated precursors.

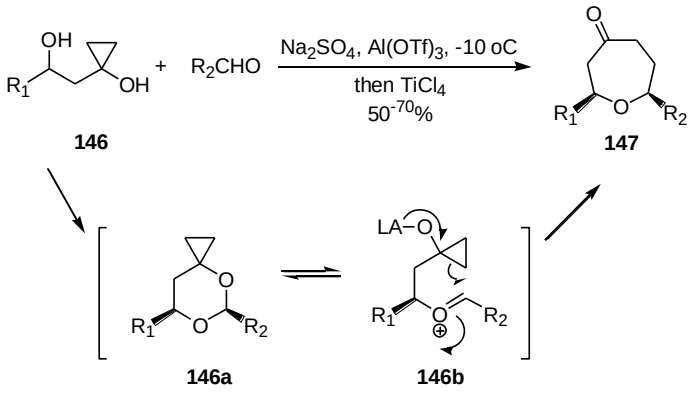
Damha and co-workers also reported the formation of seven-membered ethers via ring-expansion reactions of cyclopropanes.[112] As shown in Scheme 1.43, the precursor **143** underwent Vorbrüggen type glycosylation reaction with

concomitant cleavage of the cyclopropane to afford the oxepine **144** and the diene **145**.



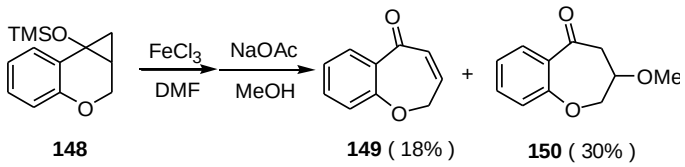
Scheme 1.43: Damha's ring-expansion reactions of cyclopropanes.

Minbiole reported the formation of oxepanes via the cyclopropane fragmentation reaction.[113] As shown in Scheme 1.44, the cyclopropyl diol **146** and an aldehyde were treated with $Al(OTf)_3$ followed by addition of $TiCl_4$ to provide the *cis* product **147** in good yield through intermediate **146a** and **146b**.



Scheme 1.44: Minbiole's cyclopropane fragmentation reaction.

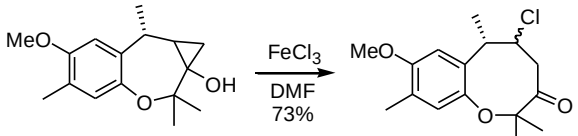
Hasegawa reported $FeCl_3$-promoted regioselective ring-expansion reactions to construct the seven-membered ethers (Scheme 1.45).[114] The cyclopropyl trimethylsilyl ether **148** underwent ring-opening reactions to afford the enone **149** and MeO-adduct **150**.



148 **149** (18%) **150** (30%)

Scheme 1.45: Hasegawa's ring-expansion reactions.

Ollivier and co-workers also reported $FeCl_3$-promoted ring-expansion reactions to form the eight-membered ethers.[115] As shown in Scheme 1.46, the cyclopropyl alcohol **151** was treated with $FeCl_3$ to provide the chlorinated eight-membered ether **152** in good yield.

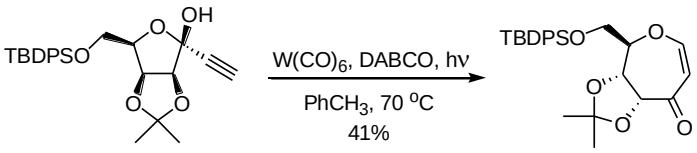


151 **152**

Scheme 1.46: Ollivier's ring-expansion reactions.

1.5.2. Ring-expansion reactions of five-membered ethers

Peczuh and co-workers reported the formation of oxepinones via ring-expansion reactions of tetrahydrofuran (Scheme 1.47).[116] The hemiketal **153** was treated with $W(CO)_6$ and radiation to provide the oxepinone product **154** in moderate yield.

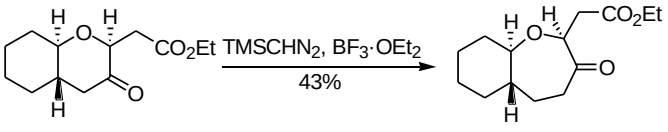


153 **154**

Scheme 1.47: Peczuh's ring-expansion reactions.

1.5.3. Ring-expansion reactions of six-membered rings

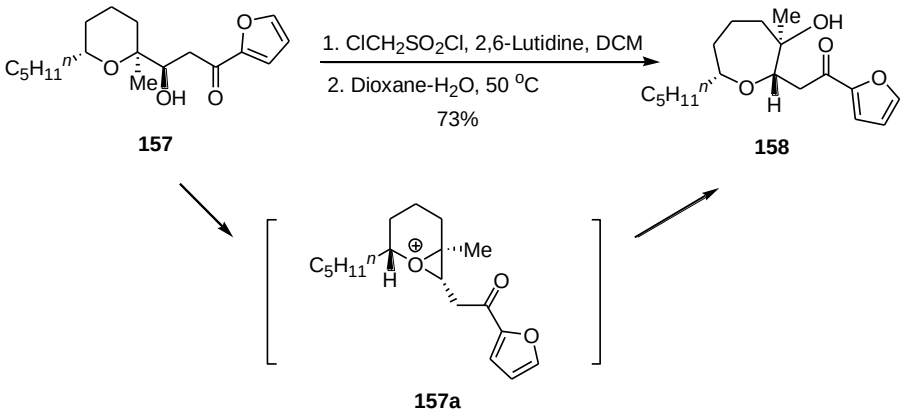
McErlean reported the ring-expansion reaction of pyran to construct an oxapanone (Scheme 1.48).[117] After the treatment of trimethylsilyldiazomethane and Lewis acid, the pyran **155** was converted into oxapanone **156** via a Demjanov-Tiffeneau type ring-expansion reaction.



155 **156**

Scheme 1.48: McErlean's ring-expansion reactions of pyran.

Nelson and co-workers reported the ring-expansion reaction to construct the C ring of hemibrevetoxin B.[118] As shown in Scheme 1.49, treatment of the tetrahydropyranyl alcohol **157** with chloromethanesulfonyl chloride followed by heating to 50 ^{o}C in dioxane-water resulted in the ring-expansion product **158** in good yield via the intermediate **157a**.

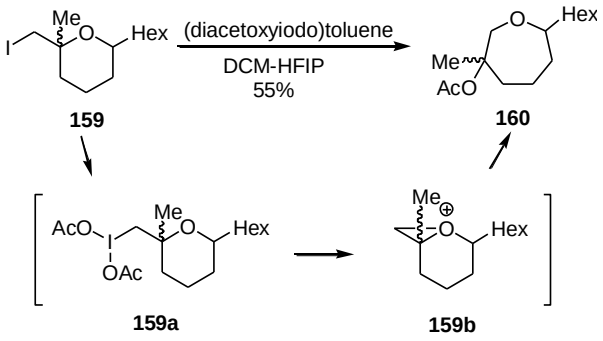


157 **158**

157a

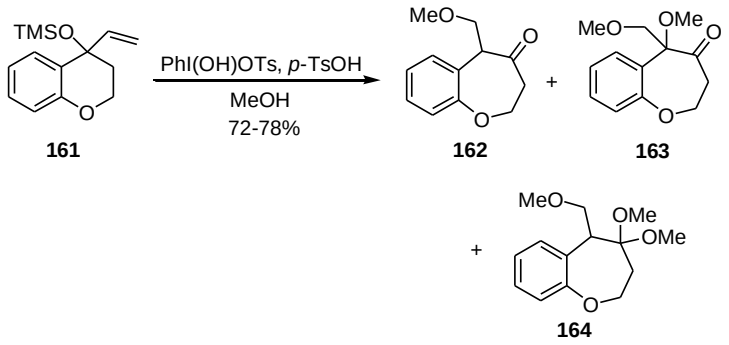
Scheme 1.49: Nelson's ring-expansion reaction of pyran.

Hara reported the synthesis of seven-membered ethers via deiodonative ring-enlargement reaction.[119] As shown in Scheme 1.50, when treated with hypervalent iodine reagent, the iodopyran **159** was converted into oxepane product **160** with moderate yield via intermediates **159a** and **159b**.



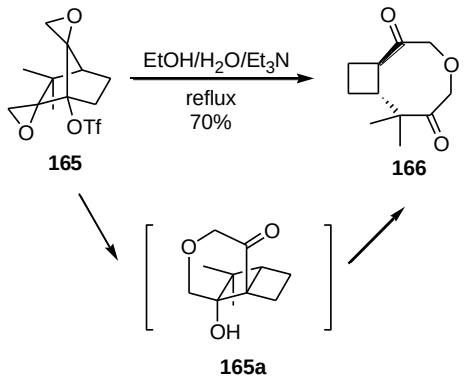
Scheme 1.50: Hara's ring-expansion reactions of pyran.

Silva and co-workers developed hypervalent iodine-promoted ring-expansion reactions of 1-vinyl cycloalkanol derivatives to construct seven-membered rings (Scheme 1.51).[120] The pyran **161** was treated with Koser's reagent to provide an inseparable mixture of oxepanes **162**, **163** and **164**.



Scheme 1.51: Silva's ring-expansion reations.

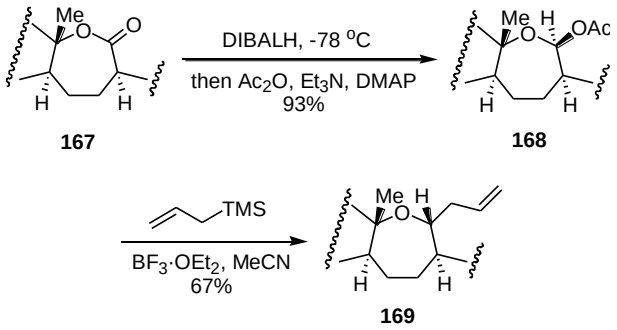
Martínez and co-workers reported the ring-expansion reactions of camphor to form eight-membered ethers.[121] As shown in Scheme 1.52, the diepoxide precursor **165** was heated at reflux in aqueous ethanol buffered with triethylamine to provide the cyclobutane-fused eight-membered ether **166** via the ring-expansion reactions of intermediate **165a**.



Scheme 1.52: Martínez and Cerero's ring-expansion reactions.

1.6. Conversion of lactones into ethers

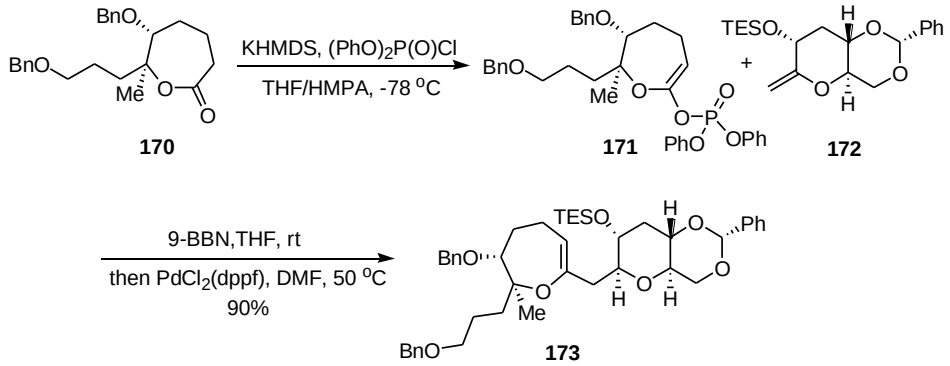
The conversion of lactones into seven- and eight-membered ethers is also a widely used strategy for medium-sized ether formation. Sasaki reported the conversion of a seven-membered lactone into a seven-membered ether (E ring) during the synthesis of gambieric acids.[122,123] As shown in Scheme 1.53, reduction of lactone **167** followed by acetylation resulted in the acetal **168**, which could then be allylated to provide the product **169** in good yield.



167 168 169

Scheme 1.53: Sasaki's conversion of seven-membered lactone.

The functionalization of lactones via their enolate derivatives has been intensively investigated in recent years. Current methodology includes the processes via cyclic ketene acetal triflates and phosphates. In comparing these two together, cyclic ketene acetal phosphates typically give better results due to their greater stability as compared to the highly labile triflates.[124,125] Sasaki reported the conversion reactions of lactones during the total synthesis of Gymnocin A (Scheme 1.54).[126] Following the procedure of Nicolaou, the lactone **170** was converted into enol phosphate **171**, which then underwent cross-coupling reaction with hydroborated **172** in the presence of palladium catalyst to provide the enol ether **173** in excellent yield.

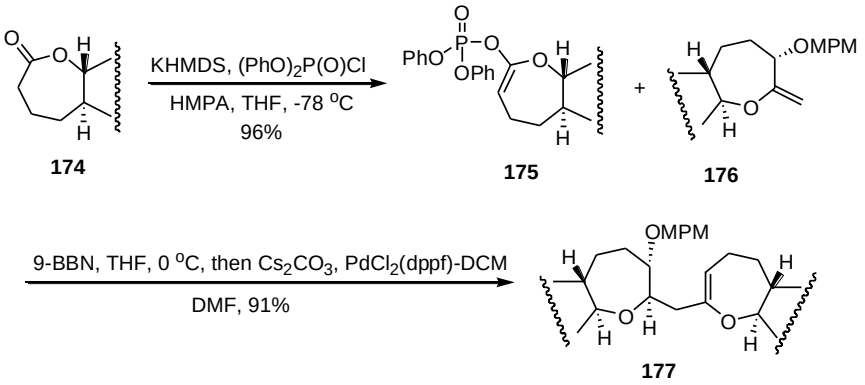


170 171 172 173

Scheme 1.54: Sasaki's convertion reaction via enol phosphate.

Tachibana also utilized the conversion of lactones via enol phosphate during the formation of polycyclic ethers.[127] As shown in Scheme 1.55, the

treatment of lactone **174** with KHMDS, HMPA and $(PhO)_2P(O)Cl$ resulted in the enol phosphate **175**, which then coupled with hydroborated **176** to yield the product **177** in excellent yield.



Scheme 1.55: Tschibana's conversion of lactones via enol phosphate.

1.7. Conclusions and thesis objectives

The results presented herein have highlighted some recent publications about the formation of seven- and eight-membered ethers. Due to the large number of natural products containing medium-sized ether motifs, more methodologies are likely to be developed to access these structures. In Chapter 2, our efforts toward the seven- and eight-membered ether will be presented. The key step for our strategy is the Stevens rearrangement of sulfonium ylides to construct the sulfur-bridged medium-sized ethers. With copper or rhodium complexes as the catalysts, these reactions have proved to work efficiently and afford the desired ethers in relatively few steps and good yields. In Chapter 3, this methodology will be applied towards the formal synthesis of the marine natural product laurencin, which contains an eight-membered ether motif as the core structure.

1.8. References

1. Fukuzawa, A.; Masamune, T. *Tetrahedron Lett*. **1981**, *22*, 4081.

2. Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron Lett.* **1965**, 1091.
3. King, T. J.; Imre, S.; Oztune, A.; Thomson, R. H. *Tetrahedron Lett.* **1979**, *20*, 1453.
4. Howard, B. M.; Schulte, G. R.; Fenical, W.; Solheim, B.; Clardy, J. *Tetrahedron* **1980**, *36*, 1747.
5. Shimizu, Y,; Chou, H. N.; Bando, H.; Van Duyne, G.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514.
6. Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.
7. Raveto, J. L.; Regueiro, A.; Marine, J. D. *Tetrahedron Lett*. **1992**, *33*, 3389.
8. Roxburgh, C. J. *Tetrahedron* **1993**, *49*, 10749.
9. Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631.
10. Yet. L. *Chem. Rev.* **2000**, *100*, 2863.
11. Elliott, M. C. Williams, E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2303
12. Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301.
13. Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.
14. Inoue, M. *Chem. Rev.* **2005**, *105*, 4379.
15. Rousseau, G. *Tetrahedron* **1995**, *51*, 2777.
16. Shiina, I. *Chem. Rev.* **2007**, *107*, 239.
17. Cardenas, D. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 384.
18. (a) Lautens, M.; Tayama, E.; Herse, C. *J. Am. Chem. Soc*. **2005**, *127*, 72. (b) Mariampillai, B.; Alberico, D.; Bidao, V.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 14436.
19. Mariampillai, B.; Alliot, J.; Li, M.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 15372.
20. Alberico, D.; Lautens, M. *Synlett* **2006**, 2969.
21. Alberico, D.; Rudolph, A.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 775.
22. Alberico, D.; Paquin, J.-F.; Lautens, M. *Tetrahedron*, **2005**, *61*, 6283.
23. Jafarpour, F.; Lautens, M. *Org. Lett.* **2006**, *8*, 3601.
24. Rudolph, A.; Rackelmann, N. Turcotte-Savard, M.-O.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 289.

25. Martins, A.; Marquardt, U.; Kasravi,N.; Alberica, D.; Lautens, M. *J. Org. Chem.* **2006**, *71*, 4937.
26. Yu, H.; Richey, R. N.; Carson, M. W.; Coghlan, M. J. *Org. Lett.* **2006**, *8*, 1685.
27. Yu, H.; Richey, R. N.; Mendiola, J.; Adeva, M.; Somoza, C.; May, S. A.; Carson, M. W.; Coghlan, M. J. *Tetrahedron Lett.* **2008**, *49*, 1915.
28. Alcaide, B.; Almendros, P.; Rodríguez-Acebes, R. *J. Org. Chem.* **2005**, *70*, 2713.
29. Blond, G.; Bour, C.; Salem, B.; Suffert, J. *Org. Lett.* **2008**, *10*, 1075.
30. Söderberg, B. C.; Hubbard, J. W.; Rector, S. R.; O'Neil S. N. *Tetrahedron*, **2005**, *61*, 3637.
31. Majumdar, K. C.; Chattopadhyay, B.; Ray. K. *Tetrahedron Lett.* **2007**, *48*, 7633.
32. Chattopadhyay, S.K.; Neogi, K.; Singha, S. K.; Dey, R. *Synlett* **2008**, 1137.
33. Ndungu, J. M.; Larson, K. K.; Spargone, R.; *Org. Lett.* **2005**, *7*, 5845.
34. Coulter, M. M.; Dornan, P. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 6932.
35. Sagae, H.; Noguchi, K.; Hirano, M.; Tanaka, K. *Chem. Commun*. **2008**, 3804.
36. Hildebrandt, D.; Hüggenberg, W.; Kanthak, M.;Plöger, T.; Müller, I. M. Dyker, G. *Chem. Commun.* **2006**, 2260.
37. Madu, C. E.; Lovely, C. J. *Synlett.* **2007**, 2011.
38. Yadav, J. S.; Reddy, B. V. S.; Yadav, N. N.; Satheesh, G. *Synthesis* **2008**, 2733.
39. Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez-Núñez, E.; Buñuel. E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1694.
40. Majumdar, K. C.; Ray, K.; Debnath, P.; Maji, P. K.; Kundu, N. *Tetrahedron Lett.* **2008**, *49*, 5597.
41. Mandal, S. K.; Roy, S. C. *Tetrahedron Lett.* **2006**, *47*, 1599.

42. (a) Mandal, S. K.; Roy, S. C. *Tetradedron* **2007**, *63*, 11341. (b) Mandal, P. K.; Maiti, G.; Roy, S. C. *J. Org. Chem.* **1998**, *63*, 2829.
43. Stork, G.; Baine, N. H.; *J. Am. Chem. Soc.* **1982**, *104*, 2321.
44. Alcaide, B.; Almendros, R.; Rodriguez-Acebes, R. *Synthesis* **2005**, 2335.
45. Shanmugam, P.; Rajasingh, P. *Tetrahedron Lett.* **2005**, *46*, 3369.
46. Neogi, A.; Majhi, T. P.; Ghoshal, N.; Chattopadhyay, P. *Tetrahedron* **2005**, *61*, 9368.
47. Fuwa, H.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 9648.
48. Saito, T.; Nakata, T. *Org. Lett.* **2009**, *11*, 113.
49. Kadota, I.; Takamura, H.; Nishii, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9246.
50. Kadota, I.; Nishii, H.; Ishioka, H.; Takamura, H.; Yamamoto, Y.; *J. Org. Chem.* **2006**, *71*, 4183.
51. Kadota, I.; Abe, T.; Ishitsuka, Y.; Touchy, A. S.; Nagata, R.; Yamamoto, Y. *Tetrahedron Lett.* **2007**, *48*, 219.
52. Kadota, I.; Abe, T.; Uni, M.; Takamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2008**, *49*, 3643.
53. Shing, T. K. M.; Zhong, Y.-L. *Synlett* **2006**, 1205.
54. Tripathi, S.; Roy, B. G.; Drew, M. G. B.; Achari, B.; Mandal, S. B. *J. Org. Chem.* **2007**, *72*, 7427.
55. Datta, S.; Nath, M.; Chowdhury, S.; Bhattacharjya, A. *Tetrahedron Lett.* **2008**, *49*, 2935.
56. Sasaki, M.; Hashimoto, A.; Tanaka, K.; Kawahata, M.; Yamaguchi, K.; Takeda, K. *Org. Lett*. **2008**, *10*, 1803.
57. Biswas, B.; Sen, P. K.; Venkateswaran, R. V. *Tetrahedron Lett.* **2006**, *47*, 4019.
58. Biswas, B.; Sen, P. K.; Venkateswaran, R. V. *Tetrahedron* **2007**, *63*, 12026.
59. Barrett, I.; Meegan, M. J.; Hughes, R. B.; Carr, M.; Knox, A. J. S.; Artemenko, N.; Golfis, G.; Zisterer, D. M.; Lioyd, D. G. *Bioorg. Med. Chem.* **2008**, 9554.

60. Islas-González, G.; Benet-Buchholz, J.; Maestro, M. A.; Riera, A.; Pericàs. M. A. *J. Org. Chem.* **2006**, *71*, 1537.
61. Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586.
62. Tong, R.; Valentine, J. C.; McDonald, F. E.; Cao, R.; Fang, X.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2007**, *129*, 1050.
63. Tong, R.; McDonald, F. E. *Angew. Chem. Int. Ed.* **2008**, *47*, 4377.
64. Wan, S.; Gunaydin, H.; Houk, K. N.; Floreancig, P. E. *J. Am. Chem. Soc*. **2007**, *129*, 7915.
65. Vyvyan, J. R.; Oaksmith, J. M.; Parks, B. W.; Peterson, E. M. *Tetrahedron Lett.* **2005**, *46*, 2457.
66. Tripathi, D.; Kumar, P. *Tetrahedron Lett.* **2008**, *49*, 7012.
67. Tripathi, D.; Pandey, S. K.; Kumar, P. *Tetrahedron* **2009**, *65*, 2226.
68. Carreño, M. C.; Des Mazery, R.; Urbano, A.; Colobert, F.; Solladié, G. *Org. Lett.* **2005**, *7*, 2039.
69. Takizawa, A.; Fujiwara, K.; Doi, E.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron* **2006**, *62*, 7408.
70. Gurjar, M. K.; Rao, B. V.; Krishina, L. M.; Chorghade, M. S.; Ley, S. V. *Tetrahdedron: Asymmetry* **2005**, *16*, 935.
71. Pérez, M.; Canoa, P.; Gómez, G.; Teijeira, M.; Fall. Y. *Synthesis* **2005**, 411.
72. García, I.; Pérez, M.; Besada, P.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* **2008**, *49*, 1344.
73. Canoa, P.; Pérez, M.; Covelo, B.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* **2007**, *48*, 3441.
74. Díaz, D. D.; Ramírez, M. A.; Martín, V. S. *Chem. Eur. J.* **2006**, *12*, 2593.
75. Crisóstomo, F. R. P.; Carrillo, R.; Martín, R.; Martín, V. S. *Tetrahedron Lett.* **2005**, *46*, 2829.
76. Jung, H. H.; Floreancig, P. E. *Org. Lett.* **2006**, 8, 1949.
77. Jung, H. H.; Floreancig, P. E. *J. Org. Chem.* **2007**, *72*, 7359.
78. Furman, B.; Dziedzic, M.; Justyniak, I. *Tetrahedron* **2008**, *64*, 3103.

79. Grant, T. N.; Benson, C. L.; West, F. G. *Org. Lett*. **2008**, *10*, 3985.

80. Shibata, T.; Fujiwara, R.; Ueno, Y. *Synlett* **2005**, 152.

81. Joncour, A.; Dcor, A.; Thoret, S.; Chiaroni, A.; Baudoin, O. *Angew. Chem. Int. Ed.* **2006**, *45*, 4149.

82. Piccialli, V.; Borbone, N.; Oliviero, G. *Tetrahedron Lett.* **2007**, *48*, 5131

83. Xu, B.; Xue, J.; Zhu, J.; Li, Y. *Chem. Lett.* **2008**, *37*, 202.

84. Bunce, R. A.; Nago, T.; Sonobe, N.; Slaughter, L. M. *J. Heterocyclic Chem.* **2008**, *45*, 551.

85. Ko, C.; Hsung, R. P.; Al-Rashid, Z. F.; Feltenberger, J. B.; Lu, T.; Yang, J.-H.; Wei, Y.; Zificsak, C. A. *Org. Lett.* **2007**, *9*, 4459.

86. Das, S. K.; Dinda, S. K.; Panda, G. *Eur. J. Org. Chem.* **2009**, 204.

87. (a) Schrock, R. R. *Chem. Rev.* **2009**, *109*, 3211. (b) Samojiowicz, C.; Bieniek, G. K.; Grela, K. *Chem. Rev*. **2009**, *109*, 3708. (c) Monsaert, S.; Vial, A. L.; Drozdzak, R.; Der Voort, P. V.; Verpoort, F. *Chem. Soc. Rev.* **2009**, *38*, 3360. (d) Hoveyda, A. H.; Zhugralin, A. R. *Nature*, **2007**, *450*, 243. (e) Drozdzak, R.; Verpoort, F. *Coord. Chem. Rev.* **2005**, *249*, 3055. (e) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592.

88. (a) Fürstner, A.; Langemann, K. *Synthesis*, **1997**, 792. (b) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc*. **1997**, *119*, 9130.

89. Watanabe, K.; Suzuki, M.; Murata, M.; Oishi, T. *Tetrahedron Lett*. **2005**, *46*, 3991.

90. Fujiwara, K.; Goto, A.; Sato, D.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 3465.

91. Lee, H.; Kim, H.; Yoon, T.; Kim, B.; Kim, S.; Kim, H.-D.; Kim, D. *J. Org. Chem.* **2005**, *70*, 8723.

92. Groaz, E.; Banti, D.; North, M. *Eur. J. Org. Chem*. **2007**, 3727.

93. Chattopadhyay, S. K.; Roy, S. P.; Ghosh, D.; Biswas, G.; *Tetrahedron Lett.* **2006**, *47*, 6895.

94. Basu, S.; Waldmann, H. *J. Org. Chem.* **2006**, *71*, 3977.

95. Kadota, I.; Ueno, H.; Sato, Y.; Yamamoto, Y. *Tetrahedron Lett*. **2006**, *47*, 89.

96. Yu, X. M.; Han, H. Blagg, B. S. J. *J. Org. Chem.* **2005**, *70*, 5599.
97. Ortega, N.; Martín, T.; Martín, V. S. *Org. Lett.* **2006**, *8*, 871.
98. Pansare, S. V.; Adsool, V. A. *Org. Lett.* **2006**, *8*, 5897.
99. Zhang, J.; Wang, X.; Wang, W.; Quan, W.; She, X.; Pan, X. *Tetrahedron* **2007**, *63*, 6990.
100. Tsukano, C.; Sasaki, M. *Tetrahedron Lett.* **2005**, *46*, 4617.
101. Domon, D.; Fujiwara, K.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 8285.
102. Ortega, N.; Martn, T.; Martn, V. S. *Eur. J. Org. Chem.* **2009**, 554.
103. Fujiwara, K.; Kawamura, N.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2009**, *50,* 1236.
104. Kotha, S.; Mandal. K.; Tiwari, A.; Mobin, S. M. *Chem. Eur. J.* **2006**, *12*, 8024.
105. Taillier, C.; Gille, B.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2005**, *70*, 2097.
106. Sato, D.; Fujiwara, K.; Kawai, H.; Suzuki, T. *Tetrahedron Lett*. **2008**, *49*, 1514.
107. Inoue, M.; Saito, F.; Iwatsu, M.; Ishihara, Y.; Hirama, M. *Tetrahedron Lett*. **2007**, *48*, 2171.
108. Roy, A.; Biswas, B.; Sen, P. K.; Venkateswaran, R. V. *Tetrahedron Lett*. **2007**, *48*, 6933.
109. Majumdar, K. C.; Maji, P. K.; Rahaman, H.; Roy, B. *Letters in Organic Chemistry* **2006**, *3*, 845.
110. Ganesh, N. V.; Jayaraman, N. *J. Org. Chem*. **2009**, *74*, 739.
111. Ganesh, N. V.; Jayaraman, N. J. Org. Chem. **2007**, *72*, 5500.
112. Sabation, D.; Damha, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 8259.
113. O'Neil, K. E.; Kingree, S. V.; Minbiole, K. P. C. *Org. Lett.* **2005**, *7*, 515.
114. Hasegawa, E.; Tsuchida, H.; Tamura, M. *Chem. Lett*. **2005**, *34*, 1688.
115. Lecornué, F.; Paugan, R.; Ollivier, J. *Eur. J. Org. Chem*. **2005**, 2589.
116. Castro, S.; Johnson, C. S. Surana, B.; Peczuh, M. W. *Tetrahedron* **2009**, *65*, 7921.
117. McErlean, C. S. P.; Willis, A. C. *Synlett* **2009**, 233.

118. Crawford, C.; Nelson, A.; Patel, I. *Org. Lett.* **2006**, *8*, 4231.
119. Abo, T.; Sawaguchi, M.; Senboku, H.; Hara, S. *Molecules* **2005**, *10*, 183.
120. Silva, Jr. L. F.; Vasconcelos, R. S.; Nogueira, M. A. *Org. Lett*. **2008**, *10*, 1017.
121. Martínez, A. G.; Vilar, E. T.; Fraile, A. G.; Cerero, S. M.; Morillo, C. D. *Tetrahedron Lett.* **2007**, *48*, 5185.
122. Sato, K.; Sasaki, M. *Org. Lett*. **2005**, *7*, 2441.
123. Sato, K.; Sasaki, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 2518.
124. Nicolaou, K. C.; Shi, G. –Q.; Gunzner, J. L.; Gärtner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 5467.
125. Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett.* **1999**, *1*, 1075.
126. Tsukano, C.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc*. **2005**, *127*, 4326.
127. Sasaki, M.; Tachibana, K. *Tetrahdron Lett.* **2007**, *48,* 3181.

Chapter 2

Seven- and Eight-Membered Ether Formation via the Stevens Rearrangement of Sulfonium Ylides

2.1. Introduction

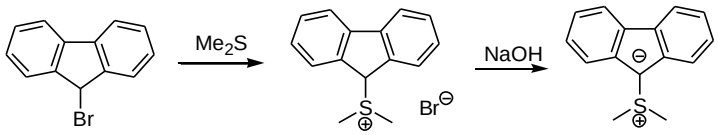
An ylide can be viewed as a neutral dipolar molecule with positive and negative charges on adjacent atoms. In 1953, Wittig and co-workers first proposed the existence of this kind of compound.[1] Since then, there has been a rapidly increasing interest in ylide chemistry. Basically, there are three types[2] of ylide reactions: olefination, formation of a three-membered ring and rearrangement reactions (Sommelet-Hauser rearrangement or Stevens rearrangement). The most common ylides are phosphonium ylides, used in the Wittig reaction for olefination. Other common ylides include sulfonium ylides, sulfoxonium ylides, ammonium ylides and oxonium ylides. This chapter is concerned mainly about the chemistry of sulfonium ylides.

2.2. Background

The preparation of sulfonium ylides is generally easier than that of ammonium or oxonium ylides due to the their greater stability.[3,4,5] Participation in back-bonding by empty d-obitals on the sulfur atom has been postulated as a reason for this additional stability. It has been shown that sulfur can stabilize the adjacent negative charge via the usage of vacant low energy 3d-obitals. In some cases, it is even possible to isolate them and perform reactions in separate steps. There are four common ways to generate sulfonium ylides.[4]

2.2.1. Deprotonation of sulfonium salts

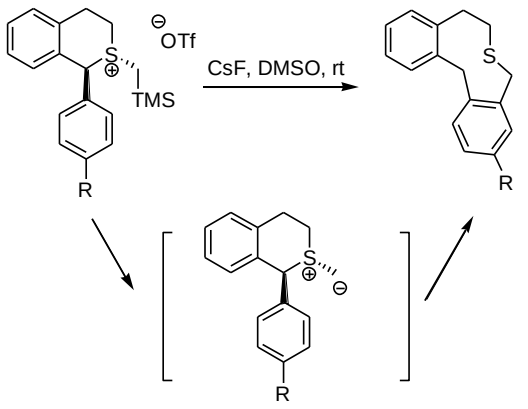
Sulfonium ylides can be prepared by deprotonation of chloride, bromide, iodide, perchlorate, tetrafluoroborate or triflate sulfonium salts with base (Scheme 2.1).[4,6,7,8,9] This method is especially useful when the resulting ylide can be stabilized by neighbouring groups. As shown in Scheme 2.1, 9-bromofluorene reacted with dimethyl sulfide to form the dimethyl-9-fluorenylsulfonium bromide, which was then deprotonated with sodium hydroxide to get the 9-dimethylsulfonium fluorenylide. The conjugation from the aromatic system along with the aromatic fluorenyl anion stabilize the ylide allowing it to be easily made, and even isolated.



Scheme 2.1: Preparation of a sulfonium ylide by deprotonation of a sulfonium salt.

2.2.2. Desilylation of α–silyl sulfonium salts

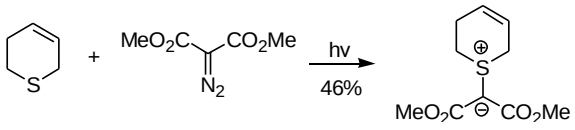
Fluoride ion-induced desilylation of α–silyl sulfonium salts is also widely used to generate sulfonium ylides, which can be obtained from the reaction of sulfide and trimethylsilylmethyl triflate.[4,10-12] This method is useful when there are base-sensitive functional groups present in the substrates. As shown in Scheme 2.2,[10,11] treatment of an *α*–silyl sulfonium triflate salt with cesium fluoride afforded the ylide intermediate which then underwent a [2,3]-sigmatropic rearrangement to give the observed product.



Scheme 2.2: Preparation of a sulfonium ylide by desilylation of an α–silyl sulfonium salt.

2.2.3. Addition of thermally or photochemically generated carbenes to sulfide

Sulfonium ylides can also be prepared thermally or photochemically from carbenes. Although this method generally suffers from low yields and multiple by-products, it still works well in some cases. As shown in Scheme 2.3,[4,13,14] photolysis of dimethyl diazomalonate in the presence of 5,6-dihydrothiopyran gave the isolable sulfonium ylide in moderate yield (46 %).

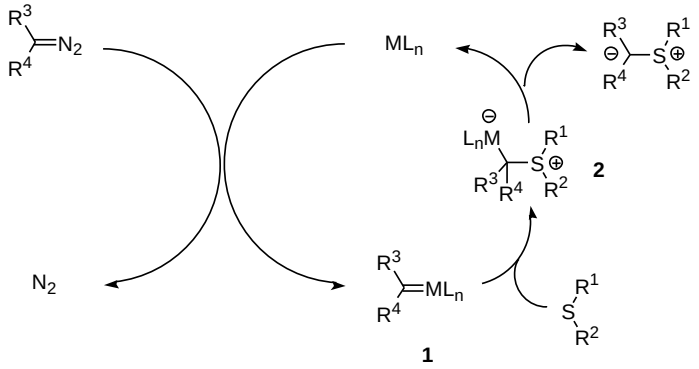


Scheme 2.3: Preparation of a sulfonium ylide from dihydrothiopyran via a photochemically generated carbene.

2.2.4. Addition of catalytically generated metallocarbenes to sulfides

The decomposition of diazo compounds with rhodium or copper catalysts generates metal-stabilized carbenes. Sulfonium ylides can then be generated using mild reaction conditions by nucleophilic attack of a sulfide on electrophilic metallocarbene.[4,15,16] The mechanism of metal-catalyzed generation of sulfonium

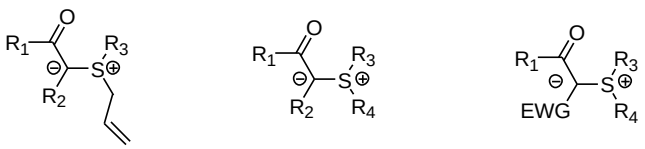
ylides from a diazo compound and a sulfide is shown in Scheme 2.4.[16] The diazo compound reacts with the metal to form a metallocarbene **1**, which is then attacked by the sulfide to form intermediate **2**. Dissociation of the metal regenerates the catalysts and releases the sulfonium ylide.



Scheme 2.4: The mechanism of sulfur ylide formation from a metal carbene.

2.2.5. The reactions of sulfonium ylides

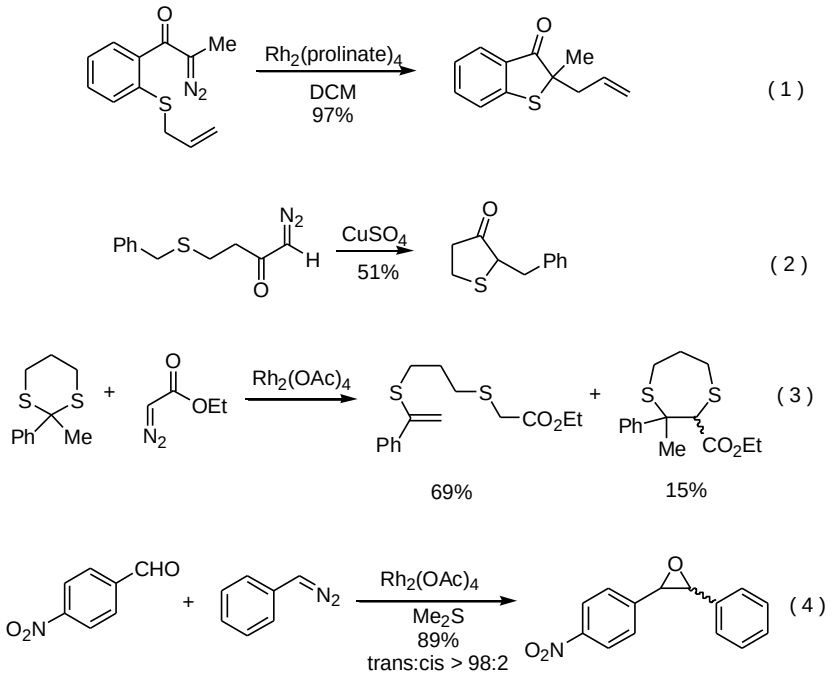
The stability and reactivity of ylides are determined by their structures.[16] Ylides in which the negative charge is stabilized by a single electron-withdrawing group will typically undergo rearrangement processes under mild conditions. For example, ylides such as **3** possessing an S-allyl substituent will undergo facile [2,3]-sigmatropic rearrangement (Figure 2.1). Ylides such as **4** lacking an allyl group may still rearrange, but typically via a stepwise [1,2]-shift (Stevens rearrangement) that may require higher temperatures than the [2,3]-shift. More highly stabilized ylides such as **5** are typically isolable, and require harsh conditions before any rearrangement is seen.



3 **4** **5**

Figure 2.1: Sulfonium ylides generated from metal carbenes.

In the case of ylides generated in situ from metallocarbenes, there are several common pathways (Scheme 2.5).[15,17-20] Intramolecular addition to an S-allyl sulfide results in a high yield of the [2,3]-sigmatropic shift product (eq.1). On the other hand, an S-benzyl sulfide provides the [1,2]-shift product in moderate yield (eq. 2). Intermolecular addition of ethyl diazoacetate to a dithiane leads to minor amounts of a ring-expanded [1,2]-shift product, but the major product results from a competing *α',β*–elimination process (eq. 3). *p*-Nitrobenzaldehyde and phenyldiazomethane undergo epoxidation reaction via sulfur ylide intermediate, which is catalyzed by rhodium acetate (eq. 4).



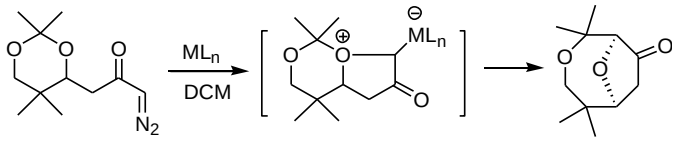
Scheme 2.5: Common reactions of sulfonium ylides.

This chapter will concern the generation and [1,2]-shift reactions of sulfonium ylides derived from monothioacetals, and the application of this process to the construction of medium-sized cyclic ethers.

2.3. Results and discussion

2.3.1. The initial investigations

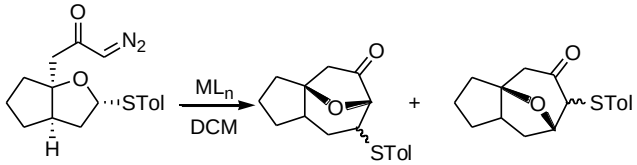
Past work in our group by Dr. R. W. Tester[21] and Dr. G. K. Murphy[22] inspired this project. Cyclic acetals and ketals with pendant diazoketones were treated with $Rh_2(OAc)_4$ or $Cu(hfacac)_2$ to provide O-bridged medium-sized ethers via [1,2]-shift reactions of fused bicyclic oxonium ylides (Scheme 2.6).



$Rh_2(OAc)_4$ (3 mol%), r.t.	61%
$Cu(hfacac)_2$ (15 mol%), reflux	88%

Scheme 2.6: Preliminary work by Dr. R. W. Tester.

When diazo compound **6** was treated with a copper or rhodium catalyst, a mixture of compounds **7** and **8** was observed (Scheme 2.7). The ratio of these two products was different when the catalyst was changed.

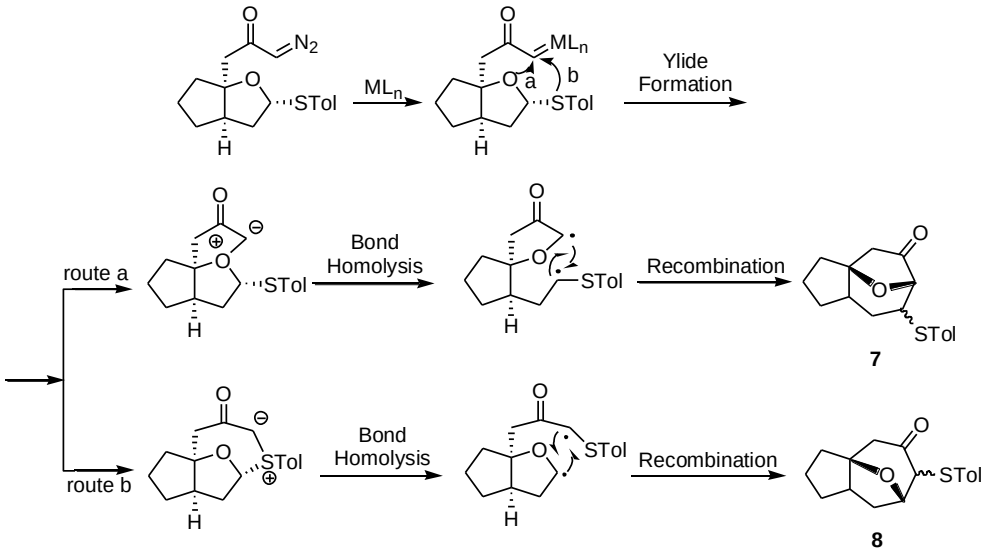


6 **7** **8**

$Rh_2(OAc)_4$ (3 mol%), r.t.	1	:	1.3
$Rh_2(tpa)_4$ (3 mol%), r.t.	1	:	1
$Cu(tfacac)_2$ (10 mol%), reflux	1	:	3
$Cu(hfacac)_2$ (10 mol%), reflux	4.2	:	1

Scheme 2.7: Preliminary work by Dr. G. K. Murphy.

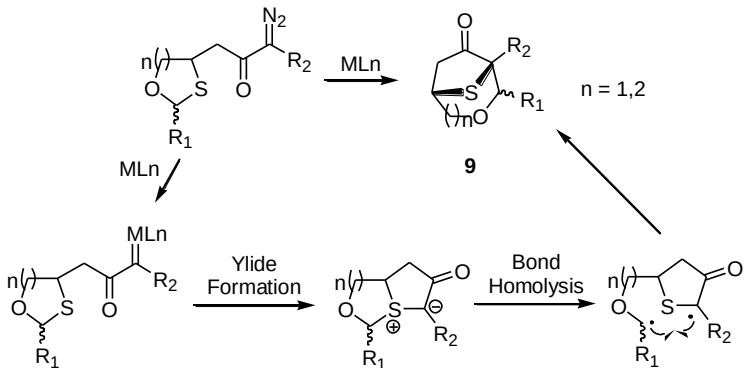
Product **7** was the result of an oxonium ylide rearrangement, while product **8** came from a competing sulfonium ylide rearrangement (Scheme 2.7).[22] The more stable sulfur ylide was competitive in this case because of the geometry of the bicyclic system. The mechanism is shown in Scheme 2.8. The metal reacts with the diazo compound to form the metallocarbene, which then undergoes ylide formation by one of two ways shown as routes a and b. In route a the oxonium ylide is formed, followed by bond homolysis to generate the biradical in which the migrating center is stabilized by an adjacent STol group, which then recombines to form the desired product **7**. On the other hand, a sulfonium ylide can also be formed as shown in route b. Through similar bond homolysis to give an ether-stabilized biradical and biradical recombination, the product **8** is formed. There is considerable evidence for a stepwise mechanism for the Stevens [1,2]-shift.[22] While it is depicted here as proceeding through a biradical intermediate, we cannot rule out an alternative heterolytic mechanism involving charged intermediates.



Scheme 2.8: Mechanism for the formation of two different ylide-derived products.

2.3.2. The proposal

This result clearly demonstrated that the anomeric carbon of a monothioacetal-derived sulfonium ylide could undergo an effective [1,2]-shift. We envisioned an alternative substitution pattern in which both heteroatoms were contained within a ring, in analogy to the earlier cyclic acetal studies by Tester (Scheme 2.9). In this case, treatment of a cyclic mixed monothioacetal bearing a pendent diazoketone with metal catalyst would form a fused bicyclic sulfonium ylide, and [1,2]-shift by the usual pathway would then provide a sulfur-bridged cyclic ether **9**. If such a process could be developed, optimized, and generalized, it could serve as an effective strategy for the formation of marine-derived cyclic ethers such as those described in Chapter 1.



Scheme 2.9: Our proposed strategy: sulfur-bridged ethers via Stevens [1,2]-shift.

2.3.3. The retrosynthesis

A retrosynthetic plan for making 7- and 8-member ethers via a Stevens [1,2]-shift of sulfonium ylides is shown in Figure 2.2. The target **10** would result from the sulfur bridged ether **11** by desulfurization using Raney nickel. Ether **11** would come from the diazoketone mixed acetal **12** through the Stevens rearrangement of the sulfonium ylide. Intermediate **12** would arise from the mixed acetal **13**, which could be derived from monothioglycol **14**. Compound **14**

would be formed from lactone **15** via treatment with Weinreb amine. Lactone **15** could be obtained from readily available α,β–unsaturated lactone **16** through a Michael addition reaction.

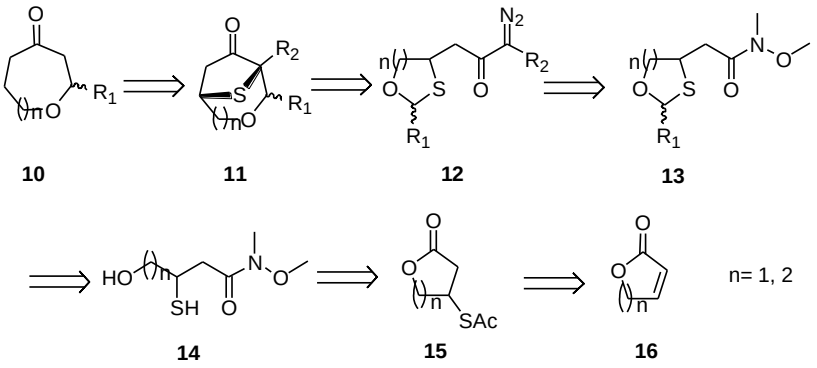
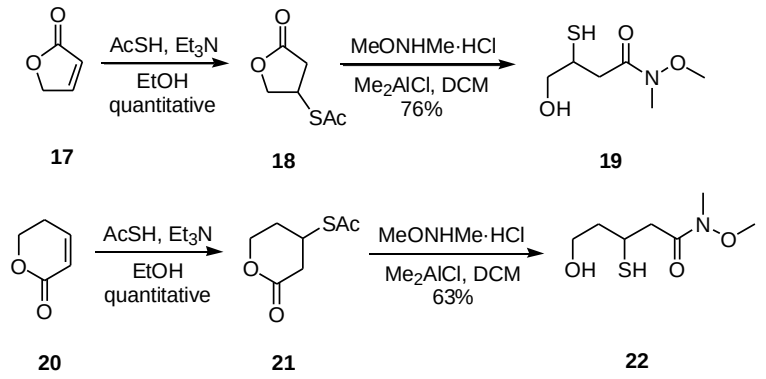


Figure 2.2: Retrosynthetic analysis for 7- and 8- member ethers.

2.3.4. Preparation of the monothioglycols

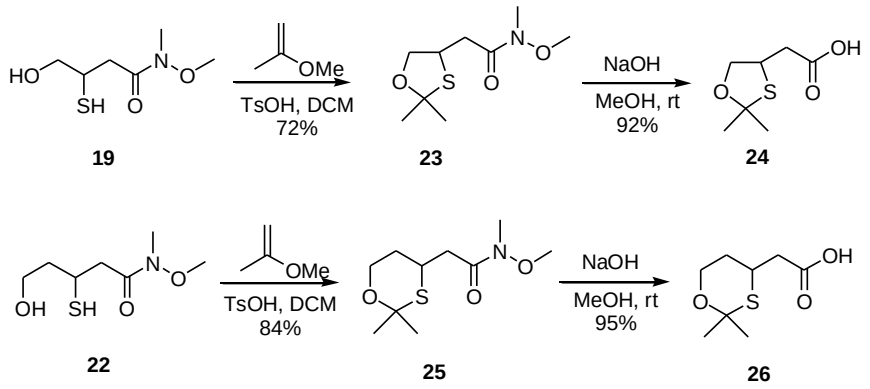
Our synthesis began with commercially available α,β–unsaturated lactones **17** and **20** (Scheme 2.10). Treatment of **17** or **20** with thioacetic acid and catalytic triethylamine afforded the corresponding Michael adducts (**18** and **21**). Literature procedures[23] called for using DCM as the solvent; however, the reaction was slow under these conditions. Changing the solvent to ethanol sped up the reaction and gave quantitative yields for both cases. To convert the lactones to the monothioglycols, we first tried to saponify them under basic conditions. Unfortunately, standard conditions (aq. NaOH, LiOH or K_2CO_3) decomposed both of the lactones. Next we tried treating them with Weinreb amine in the presence of dimethylaluminum chloride,[24] and monothioglycols **19** and **22** were obtained in good yields.



Scheme 2.10: Preparation of the monothioglycols.

2.3.5. Making the mixed acetal acids

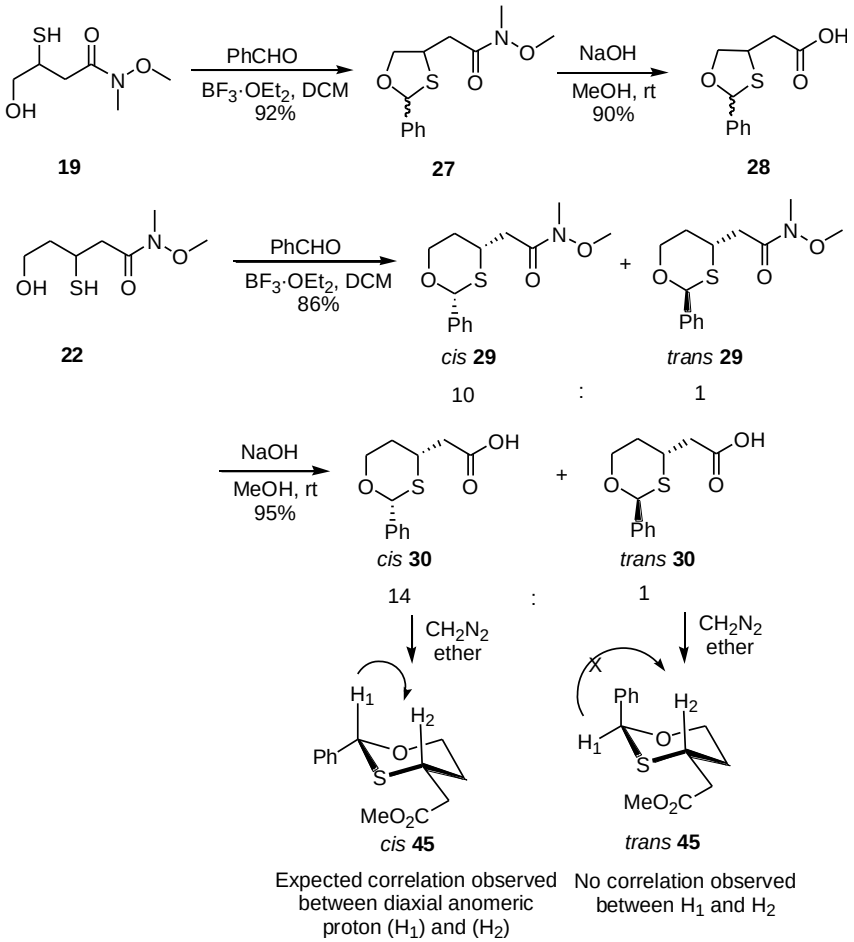
The dimethyl mixed acetals were easily made by treating monothioglycols **19** and **22** with 2-methoxypropene in the presence of catalytic *p*-toluenesulfonic acid. This afforded mixed acetals **23** and **25** in excellent yields (Scheme 2.11). Saponification of Weinreb amides **23** and **25** with sodium hydroxide allowed for conversion to acids **24** and **26** in almost quantitative yields.



Scheme 2.11: Preparation of the dimethyl mixed acetal acids.

Treatment of mercaptoalcohols **19** and **22** with benzaldehyde in the presence of $BF_3{\cdot}OEt_2$ generated mixed acetals **27** and **29** in excellent yields (Scheme 2.12). For mixed acetal **27**, the ratio of the inseparable *cis* and *trans* isomers was about 2.4:1 which was determined by ^1H NMR integration of the

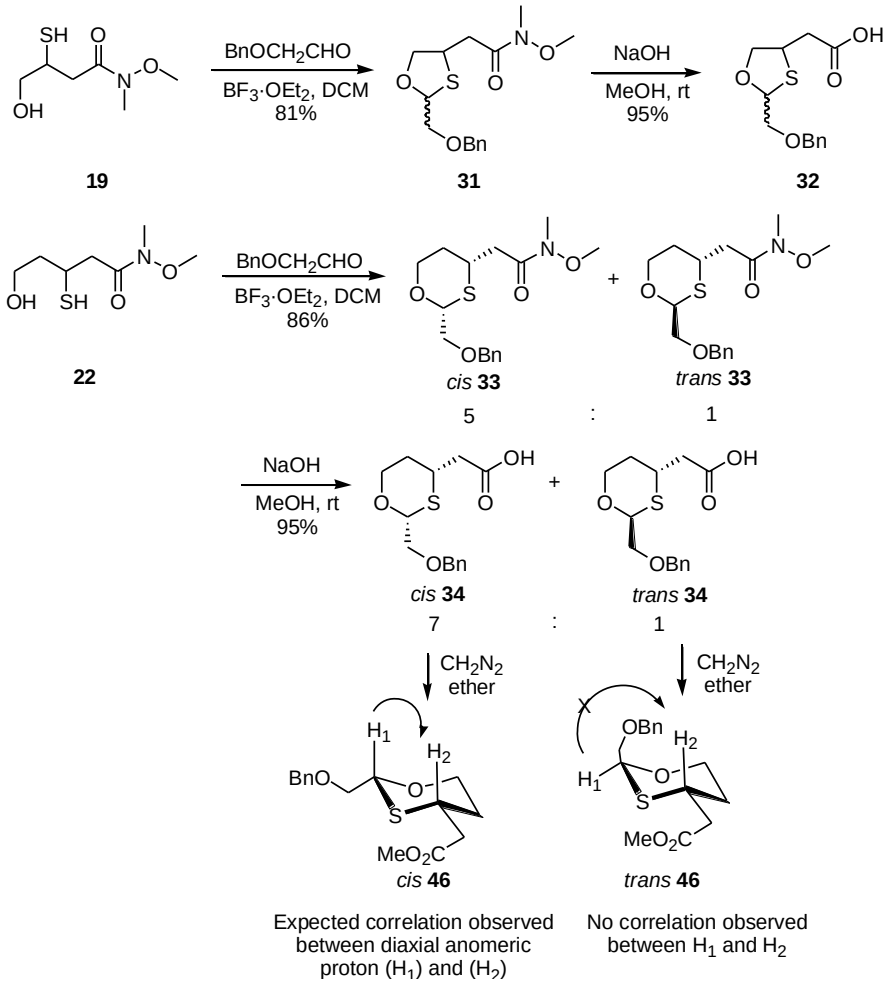
acetal proton. Unfortunately, it was not possible to tell which isomer was *cis* and which was *trans*. For mixed acetal **29**, it was not possible to identify the major isomer due to extensive spectral overlap in the ^{1}H NMR spectrum. However, later conversion to the methyl ester (see Scheme 2.15) furnished a compound (**45**) whose TROESY spectrum showed diagnostic correlations consistent with the *cis* isomer. The minor isomer was then presumed to be the epimeric *trans* isomer. Predominant formation of the *cis* isomer in this case is not surprising, given the diequatorial disposition of the two large groups.



Scheme 2.12: Preparation of the benzylidene mixed acetal acids.

A similar procedure shown in Scheme 2.13 was used in the synthesis of benzyloxymethyl mixed acetal acids **32** and **34** in excellent yields. The

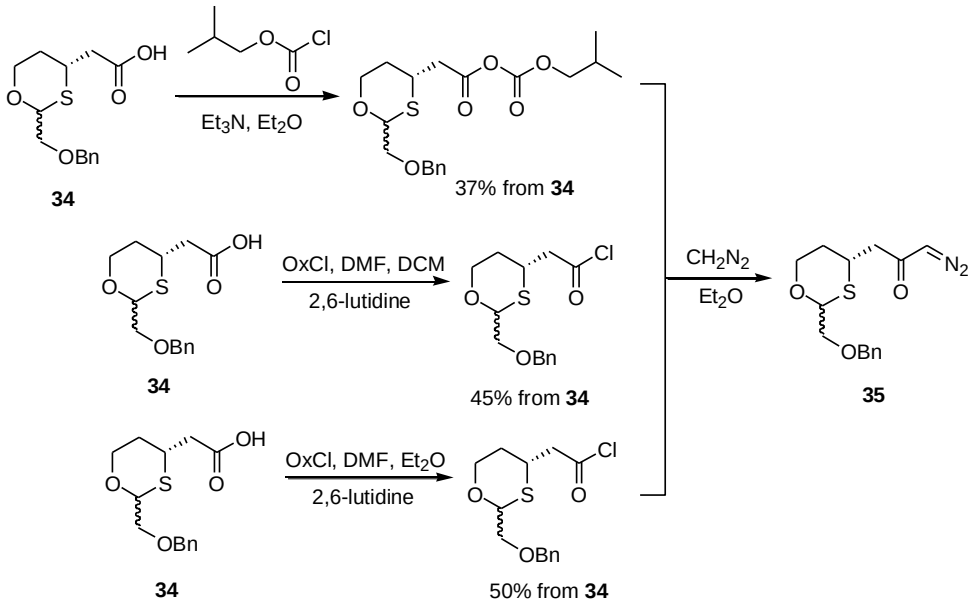
inseparable *cis* and *trans* ratio for mixed acetal **31** was approximately 1:1.1 determined by ^{1}H NMR integration of the acetal protons. However it was not possible to determine which isomer was *cis* or which was *trans.* Again, for mixed acetal **33**, it was impossible to tell which one was the major isomer directly from the NMR data due to spectral overlap. However, when acid **34** was converted into ester **46** (Scheme 2.15), the TROESY spectrum once again provided evidence consistent with a *cis* relationship for the major isomer, with the minor product presumed to be the *trans* isomer.



Scheme 2.13: Preparation of the benzyloxymethyl mixed acetal acids.

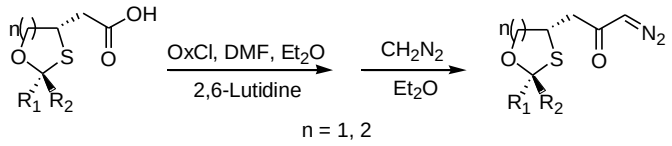
2.3.6. Preparation of the diazoketone substrates

Inseparable *cis* and *trans* **34** were used to investigate the conditions needed for diazoketone formation (Scheme 2.14). Due to the acid sensitivity of the mixed acetals, we were not able to use the standard conditions for forming a diazoketone since HCl was generated during the reaction. To remedy this problem, we tried the mild mixed anhydride procedure by treating acid **34** with isobutyl chloroformate and triethylamine. The resulting mixed anhydride was then reacted with diazomethane in ether to provide diazoketone **35** in 37 % yield over two steps. Not being satisfied with the yield of the reaction we decided to try a modified acid chloride procedure developed in our lab using 2,6-lutidine instead of triethylamine. The 2,6-lutidine base had been shown to sequester HCl and worked well for acid sensitive acetal groups.[22] Following this procedure, acid **34** was treated with oxalyl chloride, DMF and 2,6-lutidine in DCM to generate the acid chloride, which was purified by removal of the solvent followed by redissolving the residue in ether, filtration and finally concentration under vacuum. The acid chloride was then treated with ethereal diazomethane to afford the diazo ketone **35** in 45 % yield over two steps. Due to the sensitivity of the acid chloride to water, it's thought that maybe the yield was low because of exposure to moisture in the atmosphere during the purification process. Changing the solvent from DCM to ether followed by filtration of the acid chloride solution directly into the ethereal diazomethane increased the yield to 59 % over two steps. Products *cis* **35** and *trans* **35** could be separated carefully by chromatography.



Scheme 2.14: Optimization of the procedure for making diazoketone **35**.

Using the improved procedure, it was able to generate different diazo ketones from a variety of different acids summarized in Table 2.1 in good to excellent yields over two steps (from 59 % to 79 %).

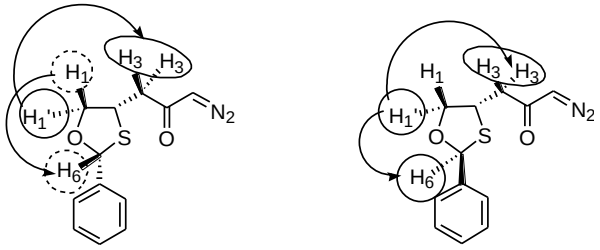


	R^1	R^2	Product	Yield over two steps (%)
n = 1	Me	Me	**36**	73
	Ph, H		*cis* **37**+ *trans* **37**	73 (1.3:1) (separable)
	CH_2OBn, H		*cis* **38**+ *trans* **38**	64 (1:1) (separable)
n = 2	Me	Me	**39**	75
	Ph, H		*cis* **40**+ *trans* **40**	79 (5.6:1) (separable)
	CH_2OBn, H		*cis* **35**+ *trans* **35**	59 (2.7:1) (separable)

Table 2.1: Preparation of diazo ketones from the corresponding acids.

2.3.7. Determination of the configuration of the diazoketone substrates

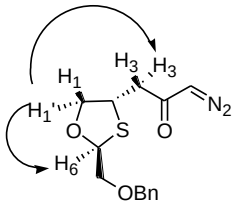
To determine the configuration of diazoketones **37** and **38**, the ^{1}H NMR, COSY and TROESY data were utilized. Analysis of ^{1}H NMR and COSY spectra led to the assignment of H_1-H_6, while TROESY spectra were used to determine the relative stereochemistry. As shown in Figure 2.3, for *cis* **37**, H_1 should correlate with H_6 and H_1' should correlate with H_3. For *trans* **37**, H_1' should correlate with both H_6 and H_3. Both TROESY spectra were consistent with this analysis.



cis **37** *trans* **37**

Figure 2.3: Expected TROESY correlations for *cis* **37** and *trans* **37**.

Using a similar approach, the configuration of *cis* **38** and *trans* **38** were also determined (Figure 2.4). The TROESY spectrum of *trans* **38** showed that H_1' correlated with both H_6 and H_3 protons, which indicated a *trans* configuration. The other isomer was then inferred to be of *cis* configuration.



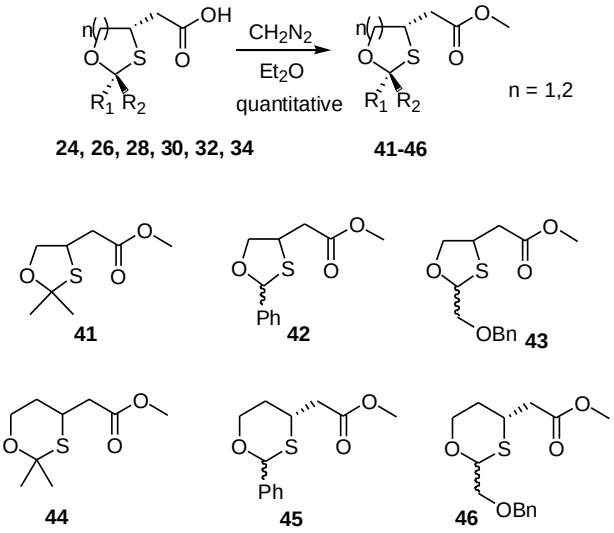
trans **38**

Figure 2.4: Expected TROESY analysis of *trans* **38**.

For *cis* **35**, *trans* **35** and *cis* **40**, *trans* **40**, the relative configuration was assigned based on the TROESY data for the closely related methyl esters, as well as due to the presumed strong preference for formation of the more stable all-equatorial *cis* isomer under the thermodynamically controlled acetal-forming conditions.

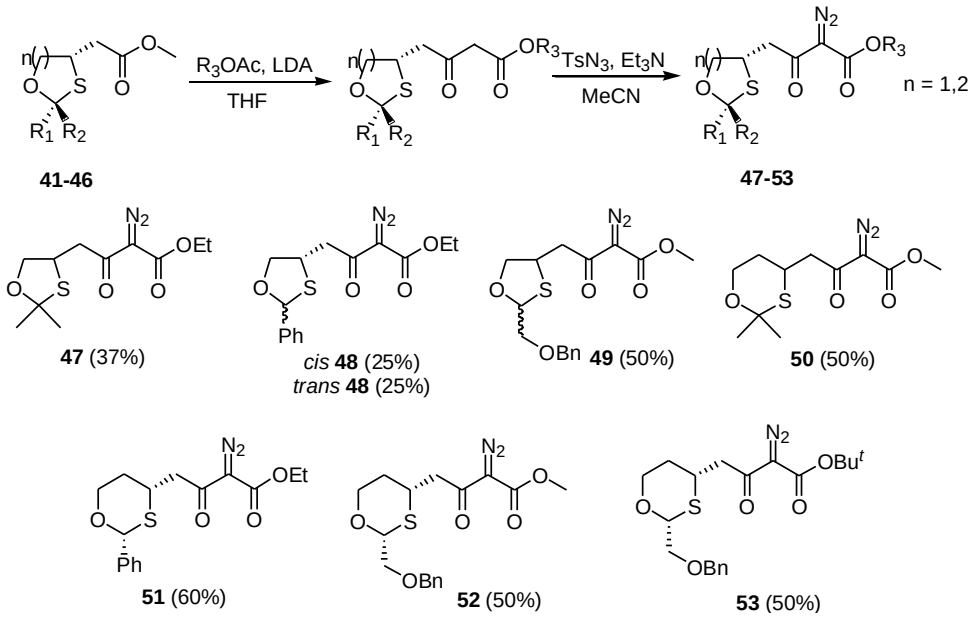
2.3.8. Preparation of diazoketoesters from acids

The preparation of diazoketoesters (**47** to **53**) began with acids **24**, **26**, **28**, **30**, **32** and **34**. Treatment of the acids with diazomethane in ether afforded esters **41** to **46** in quantitative yields (Scheme 2.15).



Scheme 2.15: Preparation of ester from acids.

As shown in Scheme 2.16, the esters were then condensed with ethyl acetate or *tert*-butyl acetate to give the ketoesters, which were converted to diazoketoesters **47** to **53** using tosyl azide in the presence of triethylamine in 37% to 60% yield for two steps.

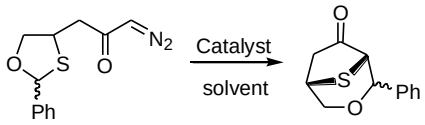


Scheme 2.16: Preparation of diazoketoesters from corresponding esters.

2.3.9. Sulfur ylide ring expansion of diazoketones

We chose diazoketone **37** as the substrate for investigating the best reaction conditions for ring expansion. The results are summarized in Table 2.2. Previously, Dr. G. K. Murphy had developed a procedure by which the ylide formation and subsequent ring expansion occurred in refluxing DCM with $Cu(hfacac)_2$ as the catalyst. Excellent yields were reported using these conditions, so we began our investigation by following his procedure. Unfortunately, it was only able to obtain a trace amount of the desired product **54** (Entry 1). Changing the catalyst to $Rh_2(OAc)_4$ only gave an 8 % yield (Entry 2), while $Rh_2(tfa)_4$ gave a complex mixture (Entry 3). Trace amounts of the desired product were obtained with $Rh_2(Piv)_4$ and $Rh_2(TPA)_4$ (Entries 4 and 5). Changing the solvent to toluene and heating to 100 ^oC with $Rh_2(OAc)_4$ as the catalyst improved the yield to 60 % (Entry 6). We then rescreened the catalysts at this temperature to determine which would be the most efficient for the reaction. As shown in Entries 7 and 8, both $Rh_2(Piv)_4$ and $Rh_2(TPA)_4$ gave much lower yield (15 % and 31 %) compared to $Rh_2(OAc)_4$. Copper catalysts such as $Cu(hfacac)_2$, $Cu(tfacac)_2$, $Cu(acac)_2$ and

Cu(0), also gave lower yields (Entries 9 to 12). With $Pd(OAc)_2$, the reaction was very messy, giving a complex mixture (Entry 13). As seen from the results in Table 2.2, the best reaction conditions were found to be with 5 mol% $Rh_2(OAc)_4$ in toluene at 100 ^oC. Higher temperature was needed for this reaction probably because of greater stability of sulfur ylides, necessitating more energy to effect the [1,2]-shift process. While at low temperature, this kind of stability gave the ylides more chances to undergo random side reactions. Under all of these conditions, the diazoketone could never be recovered. Following its consumption, it either rapidly formed the desired product, or decomposed to polar, uncharacterizable side products. It's obvious that the catalyst affected the reaction a lot, but we can not come up with a good explanation for that.



37 **54**

Entry[a]	Conditions[b]	Yield[c](%)
1	$Cu(hfacac)_2$, DCM, reflux	Trace
2	$Rh_2(OAc)_4$, DCM, reflux	8
3	$Rh_2(tfa)_4$, DCM, reflux	Complex mixture
4	$Rh_2(Piv)_4$, DCM, reflux	Trace
5	$Rh_2(TPA)_4$, DCM, reflux	Trace
6	$Rh_2(OAc)_4$, toluene, 100 ^oC	60
7	$Rh_2(Piv)_4$, toluene, 100 ^oC	15
8	$Rh_2(TPA)_4$, toluene, 100 ^oC	31
9	$Cu(hfacac)_2$, toluene, 100 ^oC	20

10	$Cu(tfacac)_2$, toluene, 100 ^oC	28
11	$Cu(acac)_2$, toluene, 100 ^oC	25
12	Cu(0), toluene, 100 ^oC	19
13	$Pd(OAc)_2$, toluene, 100 ^oC	Complex mixture

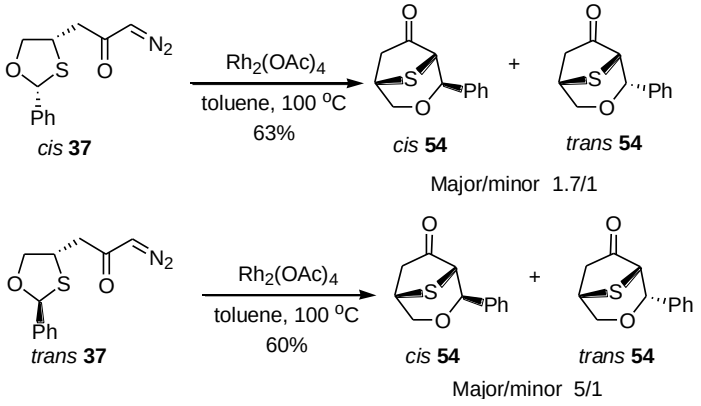
a: The starting material was a mixture of *cis* **37** and *trans* **37** (1:1).

b: Catalyst loading for rhodium catalysts was 5 mol%; for copper and platinum catalysts it was 10 mol%.

c: Total yields contain a mixture of *cis* and *trans* isomers (ratios not determined).

Table 2.2: Optimization of the ring expansion of diazoketone **37**.

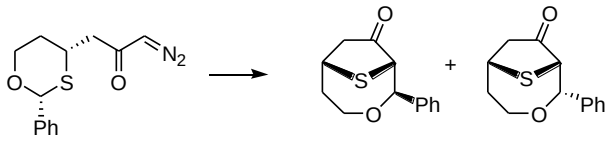
The ring expansion reaction was then performed on different diazoketones under the optimized reaction conditions. As shown in Scheme 2.17, *cis* **37** yielded 63 % of the desired product with a 1.7:1 ratio of major and minor isomers. The other isomer *trans* **37** yielded 60 % of the ring expansion product with a 5:1 ratio of major and minor isomers, with the same isomer predominating as in the case of *cis* **37**.



Scheme 2.17: Ring expansion of *cis* **37** and *trans* **37**.

For diazo ketone **40**, we decided to try both $Rh_2(OAc)_4$ and $Cu(hfacac)_2$ catalysts in toluene at 100 ^oC. For $Rh_2(OAc)_4$, the result shown in Scheme 2.18

was a total yield of 70 % for the two diastereomers with a 1:2.5 ratio of *cis* **55** to *trans* **55**. Using $Cu(hfacac)_2$, the total yield for the two diastereomers was 60 % with a 1:3.3 ratio of *cis* **55** to *trans* **55**. Thus, for **37** we found $Rh_2(OAc)_4$ to be the superior catalyst, although $Cu(hfacac)_2$ did result in slightly higher diastereoselectivity.

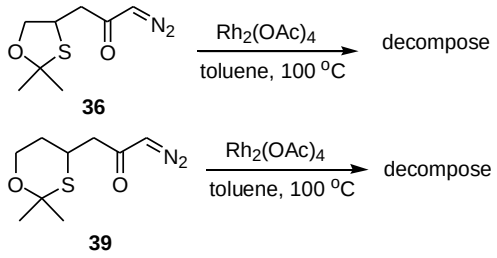


40 *cis* **55** *trans* **55**

$Rh_2(OAc)_4$: 70%	1	:	2.5
$Cu(hfacac)_2$: 60%	1	:	3.3

Scheme 2.18: Ring expansion of diazo ketone **40**.

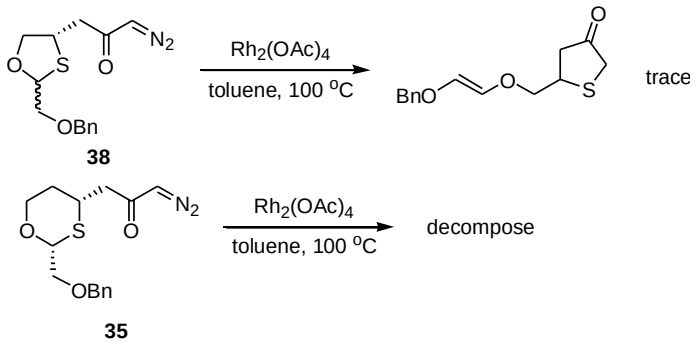
Next, acetonides **36** and **39** were evaluated under the optimized conditions (Scheme 2.19). The absence of any conjugating group on the migrating carbons raised concerns about their suitability in this process. In the event, while both **36** and **39** were quickly consumed, none of the desired ring expansion products were isolated. Crude proton NMR spectra indicated the formation of what appeared to be oligomeric products that could not be characterized.



Scheme 2.19: Attempted ring expansion of diazo ketones **36** and **39**.

Also, less hindered benzyloxymethyl mixed acetals **38** and **35** were tested under the optimized conditions (Scheme 2.20). The benzyloxylmethyl group cannot provide any conjugative stabilization for the migration carbons either. However, given the convenience of this functionalized side-chain for further

synthetic processing, the evaluation of **38** and **35** was thought to be worthwhile. In the event, under the optimized conditions, both **35** and **38** were rapidly consumed, providing uncharacterizable decomposition products, although trace amounts of a β-elimination product was isolated from the reaction of **38**.

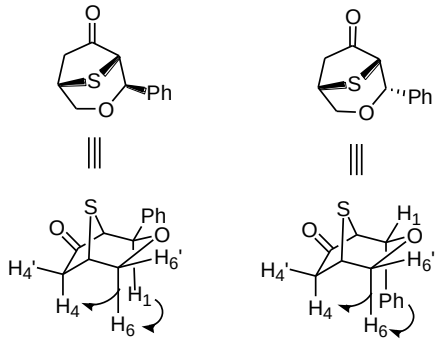


Scheme 2.20: Attempted ring expansion of diazo ketones **35** and **38**.

2.3.10. Determination of the relative configuration of the ring expansion products

For *cis* **54** and *trans* **54**, the ^{1}H NMR, COSY and TROESY data were not sufficient to determine the relative configurations. The expected TROESY correlations are shown in Figure 2.5. For *cis* **54**, H_1 was expected to correlate with H_4 and H_6. For *trans* **54**, *ortho* protons on the phenyl group should correlate with H_4 and H_6. But the actual TROESY spectra did not show any of these correlations. However, the product ratios offered some evidence regarding the relative configurations. For both substrates, *cis* **37** and *trans* **37**, the same major product was obtained. However, the ratio was much higher for *trans* **37** (5:1) than for *cis* **37** (1.7:1). This suggested that the major product might be the product of stereochemical retention from *trans* **37** (i.e., *cis* **54**). The product ratios of distabilized diazoketoester *cis* **48** and *trans* **48** also provided some evidence for this assumption (see Scheme 2.22). In both cases, the *cis* **56** was the major product while *trans* **48** offered a higher ratio (7.5:1) than *cis* **48** (3:1) because of

stereochemical retention from *trans* **48.** However, further evidence, such as X-ray crystallography analysis of a suitable derivative, is still necessary before a definitive assignment can be made.



cis **54** *trans* **54**

Figure 2.5: Expected TROESY correlations for *cis* **54** and *trans* **54**.

The ^{1}H NMR, COSY and TROESY data were sufficient to assign the relative configurations of *cis* **55** and *trans* **55** (Figure 2.6). ^{1}H NMR and COSY spectra enabled us to assign the protons and analysis of the TROESY spectrum provided us with enough information to determine the relative configurations. For the *cis* isomer, H_1 and H_4 were expected to correlate with one another, while for the *trans* isomer H_1 should not correlate with either H_4 or H_4'. In fact, for the minor product the TROESY spectrum showed a correlation between H_1 and H_4 as expected for the *cis* diastereomer. On the other hand, no correlations between H_1 and either H_4 or H_4' were seen for the major product, consistent with *trans* **55.**

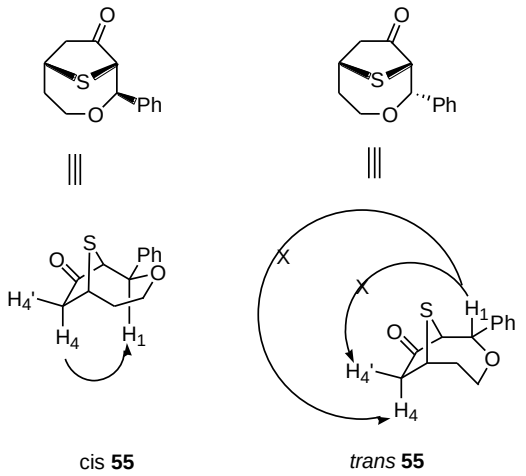
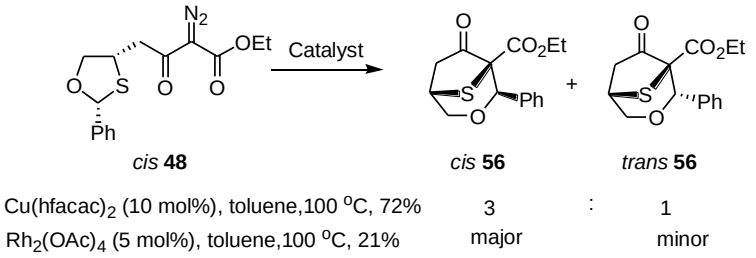


Figure 2.6: Expected TROESY correlations for *cis* **55** and *trans* **55**.

2.3.11. Sulfur ylide ring expansion of diazoketoesters

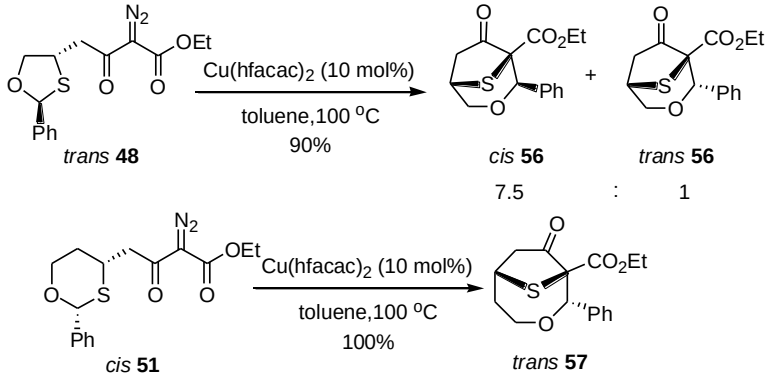
Diazoketoester *cis* **48** was used to investigate the conditions for the ring expansion reaction (Scheme 2.21). When $Cu(hfacac)_2$ was used as the catalyst the yield was 72 % with a 3:1 ratio of *cis* and *trans* isomers. Changing the catalyst to $Rh_2(OAc)_4$ decreased the yield to 21 % with the same major and minor products. Based on these results, $Cu(hfacac)_2$ was chosen as the preferred catalyst for rearrangement of diazoketoester substrates.



Scheme 2.21: Optimization of ring expansion conditions for *cis* **48**.

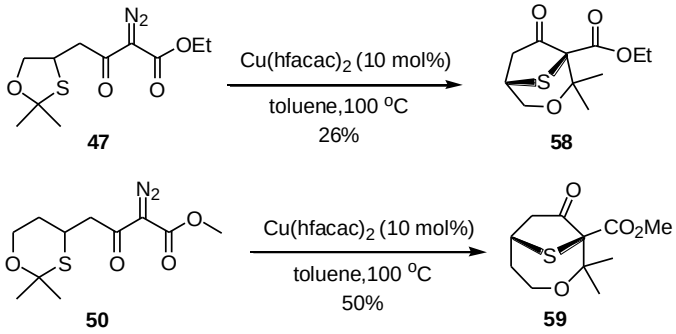
Different diazoketoesters were then treated with the optimized reaction conditions to give ring expansion products. As shown in Scheme 2.22, *trans* **48** provided the desired products in 90 % yield with a 7.5:1 ratio (*cis*:*trans*) of

diastereomers. Diazoketoester *cis* **51** also provided the ring expanded product *trans* **57** in quantitative yield with the *trans* diastereomer being the only product.



Scheme 2.22: Ring expansion reactions of diazoketoesters *trans* **48** and *cis* **51.**

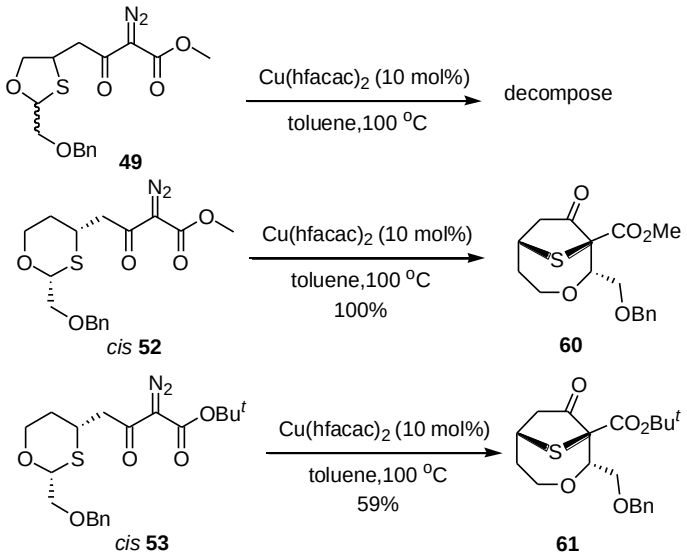
Then acetonide diazoketoesters **47** and **50** were tested under the same reaction conditions (Scheme 2.23). Compared with **36** and **39**, they had an additional stabilizing ester group for sulfonium ylide intermediates, but still no conjugating group for the migrating carbons. In the event, diazoketoesters **47** and **50** were consumed quickly, providing the desired products in reduced yields relative to **48** and **51**, along with uncharacterizable side-products. Diazoketoester **47** gave **58** in 26 % yield and **50** gave **59** in 50 % yield.



Scheme 2.23: Ring expansion reactions of diazoketoester **47** and **50**.

Benzyloxymethyl mixed acetals **49, 52** and **53** were also evaluated under the optimized conditions (Scheme 2.24). Diazoketoester **49** decomposed quickly

to give an uncharacterizable mixture. Surprisingly, diazoketoester *cis* **52** gave the ring expansion product **60** in almost quantitative yield with exclusive formation of the *trans* product. The more hindered diazoketoester *cis* **53** afforded the analogous *trans* product **61** in 59 % yield.



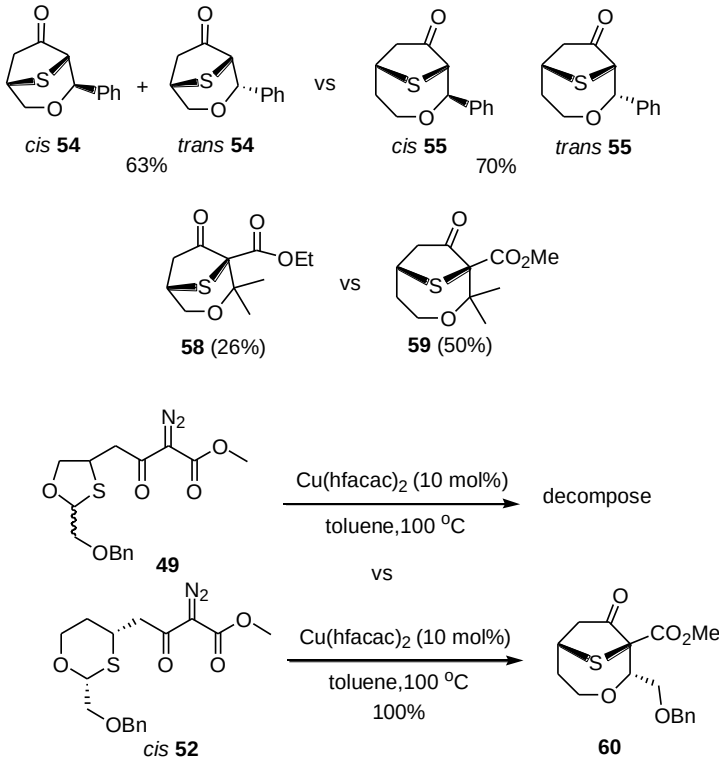
Scheme 2.24: Ring expansion reactions of diazoketoester **49**, **52** and **53**.

2.3.12. Factors affecting [1,2]-shift reactions of sulfonium ylides

There are several factors that affect the efficiency of the [1,2]-shift reactions of sulfonium ylides, including ring size, substitution on the anomeric center, stabilizing groups on the ylide carbons and steric factors.

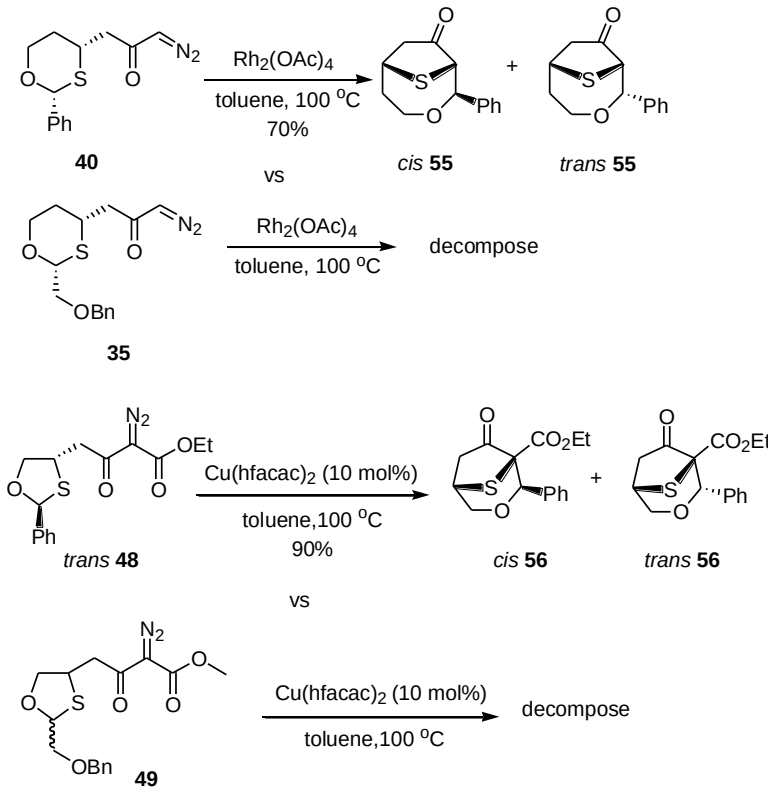
Generally speaking, the eight-membered ethers were always easier to form compared with seven-membered ethers under the same reaction conditions. As shown in Scheme 2.25, eight-membered products **55** and **59** were obtained with higher yields compared with seven-membered ethers **54** and **58**. The most impressive cases were the reactions of **49** and **52**. Diazoketoester **49** did not afford any desired seven-membered product, while **52** provided eight-membered

ether **60** in quantitative yield. While this effect appears to be significant, we do not have a plausible rationale for the superior outcomes for the 6→8 ring enlargement conversion. However, the higher yields and greater consistency in those cases provided a strong incentive for further synthetic work directed towards the 8-membered ether natural product laurencin (see Chapter 3).



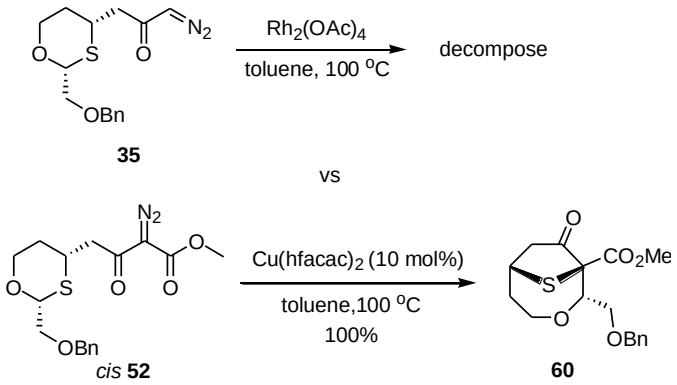
Scheme 2.25: Ring size factors affecting [1,2]-shift of sulfonium ylides.

Substitutions on the anomeric center also affected the reaction. Substrates with conjugating groups generally resulted in higher yields of the desired rearrangement products. As shown in Scheme 2.26, diazo compounds **40** and **48** provided the desired products with high yields, while **35** and **49** decomposed under the same reaction conditions. This substituent effect is consistent with the proposed mechanism, involving homolytic cleavage to a biradical. Greater stabilization of this intermediate through conjugation should be advantageous.



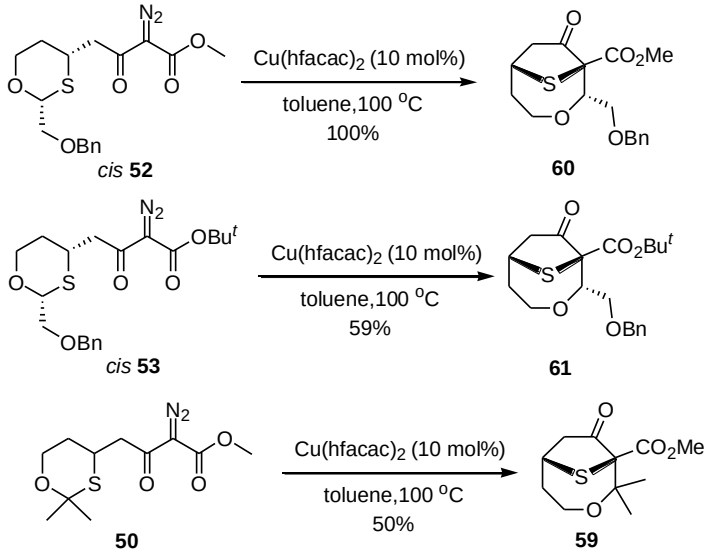
Scheme 2.26: Substitutions on the anomeric carbon affecting [1,2]-shift of sulfonium ylides.

Stabilization at the ylide carbon was also important for this reaction. Distabilized ylides always gave higher yields compared with monostabilized ylides. As shown in Scheme 2.27, diazoketone **35** decomposed quickly without forming any product, while distabilized **52** afforded **60** in quantitative yield. This disparity may result from the higher reactivity and decreased stability of the monostabilized ylides, which are thus able to undergo a variety of alternative reactions in competition with the desired Stevens rearrangement.



Scheme 2.27: Stabilization groups affecting [1,2]-shift of sulfonium ylides

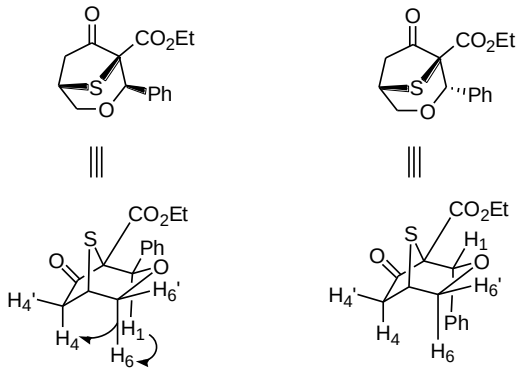
Steric factors also had an effect on this ring expansion reaction. More sterically hindered ylides provided the desired products in lower yields. As shown in Scheme 2.28, the more hindered *t*-butyl ester **53** gave a significantly lower yield of rearrangement product than the corresponding methyl ester **52**. Steric effects may also contribute to the lower yields seen with **50**, although direct comparison with **52** is dubious due to the difference in stabilization at the migrating center.



Scheme 2.28: Steric factors affecting [1,2]-shift of sulfonium ylides.

2.3.13. Determination of the relative configuration of the ring expansion products

The ^{1}H NMR, COSY and TROESY data were all utilized to determine the configurations of *cis* **56** and *trans* **56** (Figure 2.7). The ^{1}H NMR and COSY spectra enabled us to assign the protons and analysis of the TROESY data provided us with sufficient information to determine the relative configurations. For *cis* **56,** H_1 was expected to correlate with H_4 and H_6, while for trans **56**, H_1 would not be expected to show any significant correlations with these protons. Only the major product's H_1 showed correlation with H_4 and H_6, so the major product was assigned to be *cis* **56**. The minor product displayed no correlations to H_1, consistent with the *trans* diastereomer.



cis **56** *trans* **56**

Figure 2.7: Expected TROESY correlation for *cis* **56** and *trans* **56**.

Determination of the relative configuration of **57**, **60** and **61** also relied on ^{1}H NMR, COSY and TROESY data. The ^{1}H NMR and COSY spectra were used to assign the protons and the TROESY correlations enabled the determination of relative configuration. As shown in Figure 2.8, for *trans* configurations of all of these three compounds, H_4 was expected to correlate with H_7, while for cis isomers, H_1 was expected to correlate with H_4. The actual TROESY spectra only showed correlation between H_4 and H_7, which indicated these three compounds were most likely the *trans* isomer. In each of these cases, the product was formed

as a single diastereomer, thus precluding the comparison of its TROESY data to an epimeric compound.

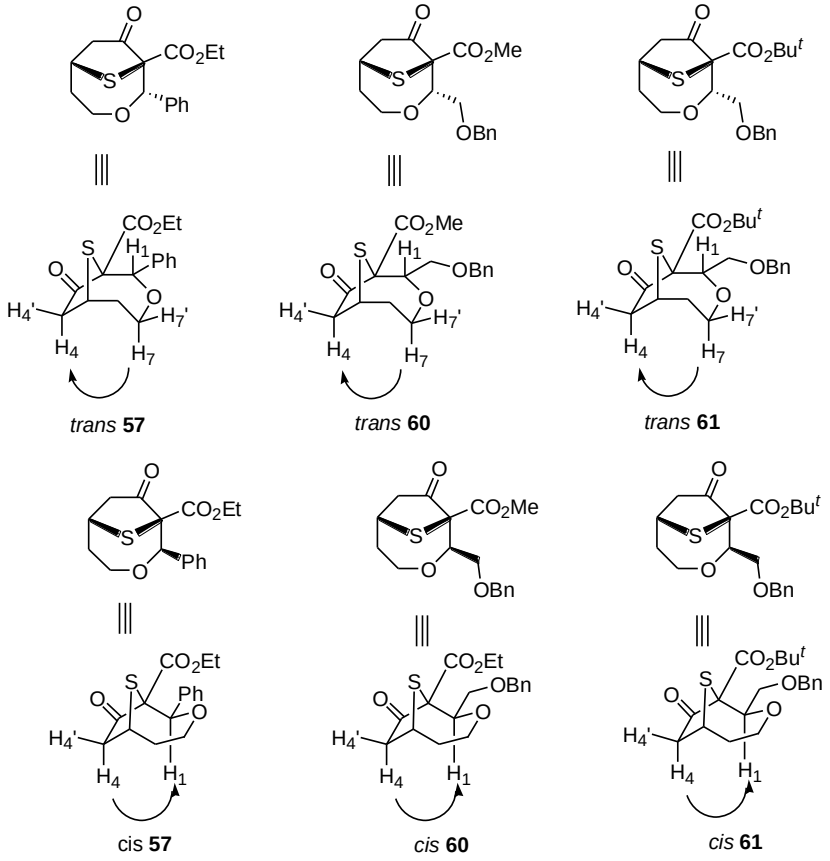
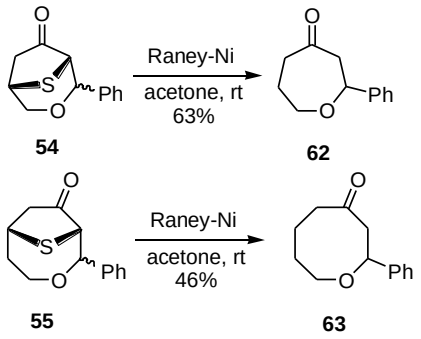


Figure 2.8: Expected TROESY correlations for *cis* **57**, *cis* **60**, *cis* **61** and *trans* **67**, *trans* **60**, *trans* **61**.

2.3.14. Desulfurization of the sulfur-bridged ether

To validate this chemistry as an effective route to medium-ring ethers, it was necessary to demonstrate the effective removal of the bridging sulfur. Typical desulfurization conditions included radical reduction by tin reagents or Raney nickel.[25] Raney nickel appeared to be a cleaner and more easily handled reagent, so we chose to try it first. In the event, treatment of **54** and **55** with Raney nickel in acetone provided ethers **62** and **63** in 63 % yield and 46 % yield respectively under the same reaction conditions (Scheme 2.29).



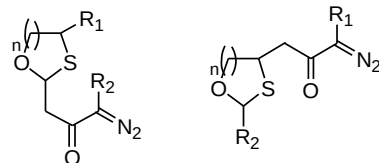
54 **62** **55** **63**

Scheme 2.29: Desulfurization of sulfur-bridged ethers **54** and **55**.

2.4. Conclusions and future work

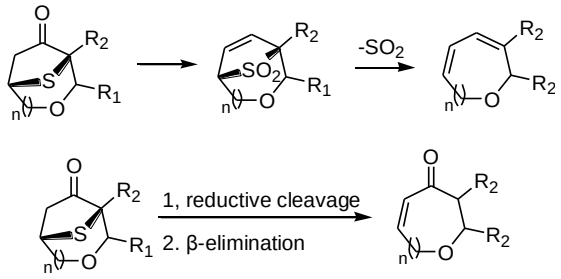
The methodology described herein provided a way to construct 7- and 8-membered ethers in relatively few steps from commercially available starting materials. The key step was the ring expansion of thioacetal-derived sulfonium ylides, which was performed in toluene at 100 ^{o}C in the presence of a suitable metal catalyst. Both the stabilization and steric factors of the biradical intermediate played an important role in the reaction. Diazoketoesters always provided higher yields compared with diazoketones. For monostabilized diazoketones, $Rh_2(OAc)_4$ was a more effective catalyst. In contrast for distabilized diazoketoesters, $Cu(hfacac)_2$ proved to be a more effective catalyst. Direct comparison of a methyl diazoketoester vs a *t*-butyl diazoketoester suggests that steric factors may diminish the efficiency of the process.

We have currently only investigated the ring expansion reactions with metal catalysts in refluxing solvents. Future work may include using other conditions such as microwave or irradiation. Also, determination of the relative configurations of the sulfur-bridged seven-membered ethers needs further investigation. To broaden the scope of this methodology, a more diverse range of substituents on the migrating center and on the ylide will be employed as shown in Scheme 2.30. The formation of nine- or ten-membered sulfur-bridged ethers via [1,2]-shift rearrangement of sulfonium ylides is also worthwhile to be investigated.



Scheme 2.30: Future plan for [1,2]-shift rearrangement of sulfonium ylides.

Considering the moderate yield under current desulfurization condition, the optimization of desulfurization is necessary. The possible strategies are shown in Scheme 2.31. Conversion of the ketone to an olefin and the sulfide to a sulfone followed by cheleotropic extrusion of SO_2 is supposed to afford a diene. Also, reductive cleavage of the C-S bond between the ketone and ester followed by β-elimination can provide an enone, which is a convenient handle for further functionalization.



Scheme 2.31: Future plan for functionalization of the sulfur-bridge.

Given the number of natural products that contain the 7- or 8-membered ether framework, we believe this methodology should be amenable towards the total synthesis of all these compounds. Efforts toward the formal synthesis of (+)-laurencin will be described in Chapter 3, with the ring expansion reaction of a sulfonium ylide as the key step.

2.5. Experimental

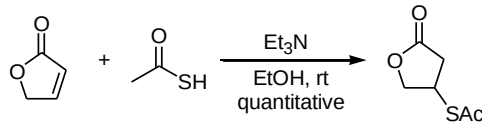
2.5.1. General

Reactions were conducted in oven-dried (120 ^{o}C) or flame-dried glassware under a positive argon atmosphere unless otherwise stated. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes or cannulation. Solvents were dried and distilled before use: dichloromethane over calcium hydride; toluene over sodium; diethyl ether and tetrahydrofuran over sodium benzophenone ketyl. Thin layer chromatography (T.L.C.) was performed on precoated silica plates with 0.25 mm Kiesegel 60 F_{254}. Flash chromatography columns were packed with 230-240 mesh silica gel. Where given, column dimensions reflect outer diameters.

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 500 MHz on Varian Inova 500 and Unity 500 spectrometers, and the chemical shifts are reported on the δ scale (ppm) downfield from tetramethysilane. Coupling constants (*J*) are reported in Hz. Second order splitting patterns are indicated. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets, dt, doublet of triplets, etc. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 125 MHz and are reported in ppm relative to the center line of a triplet at 77.23 ppm for deuterochloroform. Infrared (IR) spectra were measured with a Nicolet Magna 750 FT-IR infrared spectrophotometer. Mass spectra were determined on a Kratos Analytical MS-50 (EI) or Applied Biosystems Mariner Biospectrometry Workstation (ESI). Elemental analyses were obtained on a Carlo Erba CHNS-O EA 1108 Elemental Analyzer.

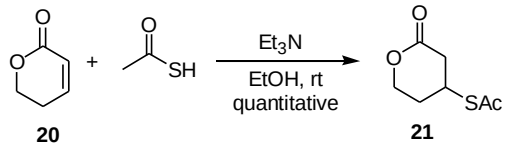
2.5.2. Substrate syntheses

2.5.2.1. Preparation of monothioglycol



17 **18**

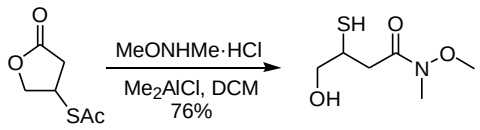
Lactone 18. To a solution of **17** (1.000 g, 11.91 mmol) in EtOH (15 mL) was added thioacetic acid (1.140 g, 1.07 mL, 15.00 mmol) and 10 drops of triethylamine at room temperature. After stirring at ambient temperature overnight, the reaction mixture was poured into a mixture of Na_2CO_3 (0.5 N, 30 mL) and DCM (30 mL). After the initial separation, the aqueous phase was extracted twice more with DCM (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes:EtOAc 2:1) provided **18** (1.900 g, quantitative) as a yellow oil: R_f 0.40 (hexanes:EtOAc 2:1); IR (thin film) 2976, 2914, 1784, 1693, 1414, 1357, 1167, 1127, 1062, 1017 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.70 (dd, J = 9.7, 6.8 Hz, 1H), 4.25-4.23 (m, 1H), 4.18 (dd, J = 9.7, 5.6 Hz, 1H), 2.98 (dd, J = 18.1, 8.8 Hz, 1H), 2.50 (dd, J = 18.1, 6.4 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4, 174.4, 72.9, 37.3, 33.9, 30.5; HRMS (ESI, $[M+Na]^+$) for $C_6H_8O_3SNa$ calcd 183.0086, found: m/z 183.0085.



20 **21**

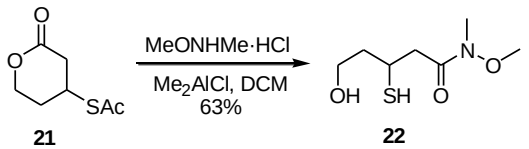
Lactone 21. The aforementioned method was also employed in the synthesis of **21** starting with **20** (1.000 g, 10.204 mmol) and thioacetic acid (1.14 g, 1.1 mL, 15.0 mmol). Column chromatography (silica gel, hexanes:EtOAc 2:1) provided 1.770 g (quantitative) of **21** as a yellow oil: R_f 0.40 (hexanes:EtOAc 2:1); IR (thin film) 2978, 2916, 1725, 1686, 1479, 1427, 1405, 1352, 1299, 1252, 1218, 1164, 1133, 1110, 1067 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.48 (ddd, J = 11.7,

5.6, 4.6 Hz, 1H), 4.36 (ddd, *J* = 11.7, 8.9, 3.9 Hz, 1H), 3.92 (dddd, *J* = 8.9, 8.9, 6.5, 4.9 Hz, 1H), 3.01 (ddd, *J* = 17.8, 6.5, 1.2 Hz, 1H), 2.59 (dd, *J* = 17.8, 8.9 Hz, 1H), 2.36 (s, 3H), 2.28-2.17 (m, 1H), 1.96-1.93 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.2, 168.5, 67.5, 36.2, 35.2, 30.9, 28.9; HRMS (ESI, $[M+Na]^+$) for $C_7H_{10}O_3SNa$ calcd 197.0243, found: m/z 197.0242.



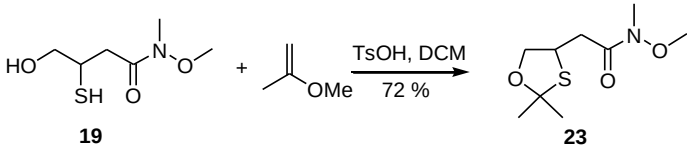
18 **19**

Monothioglycol 19. A solution of Me_2AlCl (9.0 mmol, 9.0 mL, 1.0 M in hexanes) was added dropwise to a stirred suspension of MeONHMe·HCl (0.780 g, 8.00 mmol) in DCM (20 mL) under argon at 0 ^oC. The resulting mixture was stirred at 0 ^oC for 0.5 hour followed by an additional 0.5 hour at room temperature. Subsequently, a solution of **18** (0.180 g, 1.01 mmol) in DCM (10 mL) was transferred via cannula. After stirring at room temperature for an additional 1 hour, 2 mL of HCl (3 M) was added. The whole mixture was then poured into 20 mL of aqueous HCl (1 M) solution. The aqueous phase was extracted with two portions of DCM (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, DCM:EtOAc 1:2) provided **19** (0.153 g, 76%) as a colorless oil: R_f 0.29 (DCM:EtOAc 1:2); IR (thin film) 3413, 2939, 2546, 1643, 1463, 1426, 1390, 1180, 1114, 1063, 998 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75-3.66 (m, 2H), 3.72 (s, 3H), 3.44-3.40 (m, 1H), 3.21 (s, 3H), 2.89-2.79 (m, 2H), 1.83 (d, *J* = 8.2 Hz, 1H) (OH proton not detected); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 67.5, 61.4, 38.1, 37.7, 32.2; HRMS (ESI, $[M+Na]^+$) for $C_6H_{13}NO_3SNa$ calcd 202.0508, found: m/z 202.0510.



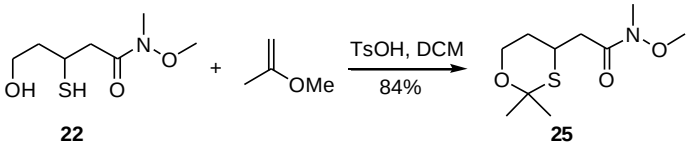
Monothioglycol 22. The aforementioned method was also employed in the synthesis of **22** starting with **21** (1.053 g, 6.05 mmol), MeONHMe·HCl (3.902 g, 40.00 mmol) and Me_2AlCl solution (40.0 mmol, 40.0 mL, 1.0 M in hexanes). Column chromatography (silica gel, DCM:EtOAc 1:2) provided **22** (0.739 g, 63%) as a colorless oil: R_f 0.21 (DCM:EtOAc 1:2); IR (thin film) 3419, 2938, 2546, 1650, 1464, 1429, 1389, 1179, 1114, 1051, 996 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.83-3.77 (m, 2H), 3.71 (s, 3H), 3.53-3.49 (m, 1H), 3.20 (s, 3H), 2.83-2.78 (m, 2H), 1.97-1.92 (m, 1H), 1.89 (d, J = 7.3 Hz, 1H), 1.85-1.80 (m, 1H) (OH proton not detected); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 61.6, 60.6, 42.0, 41.2, 33.2, 32.4; HRMS (ESI, $[M+Na]^+$) for $C_7H_{15}NO_3SNa$ calcd 216.0665, found: m/z 216.0665.

2.5.2.2. Preparation of mixed acetals



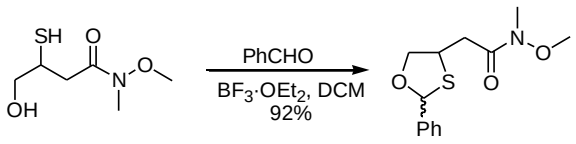
Mixed acetal 23. To a solution of **19** (0.254 g, 1.42 mmol) and 2-methoxypropene (0.205 g, 2.84 mmol) in DCM (20 mL) at room temperature was added 10 mg TsOH. After stirring for 1 hour, the resulting solution was poured into a mixture of saturated $KHCO_3$ (20 mL) and DCM (30 mL). The aqueous phase was extracted with DCM (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes:EtOAc 1:1) provided **23** (0.224 g, 72%) as a yellow oil: R_f 0.37 (hexanes:EtOAc 1:1); IR (thin film) 2972, 2929, 1664, 1417, 1385, 1366, 1209, 1180, 1126, 1060 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.23 (dd, J = 9.5, 4.9 Hz, 1H), 4.00 (dd, J = 9.5, 3.7 Hz, 1H), 3.99-3.96 (m, 1H), 3.68 (s, 3H), 3.16 (s, 3H), 2.81 (m, 2H), 1.67 (s, 3H), 1.60 (s,

3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 92.2, 74.4, 61.3, 46.3, 38.1, 32.1, 31.8, 30.9; HRMS (ESI, $[M+Na]^+$) for $C_9H_{17}NO_3SNa$ calcd 242.0821, found: m/z 242.0820.



22 25

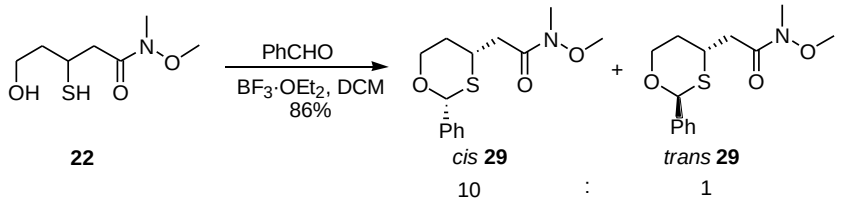
Mixed acetal 25. The aforementioned method was also employed in the synthesis of **25** starting with **22** (0.070 g, 0.39 mmol) and 2-methoxypropene (0.058 g, 0.07 mL, 0.80 mmol). Column chromatography (silica gel, hexanes:EtOAc 1:1) provided 0.072 g (84%) of **25** as a yellow oil: R_f 0.38 (hexanes:EtOAc 1:1); IR (thin film) 2974, 2937, 1664, 1460, 1420, 1384, 1365, 1322, 1216, 1170, 1135, 1085, 1058, 998 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90-3.88 (m, 2H), 3.64 (s, 3H), 3.65-3.61 (m, 1H), 3.15 (s, 3H), 2.50 (app d, J = 6.5, 2H), 1.89-1.86 (m, 1H), 1.67 (s, 3H), 1.55-1.48 (m, 1H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 80.5, 62.4, 61.3, 37.8, 34.5, 32.6, 32.1, 31.3, 26.6; HRMS (ESI, $[M+Na]^+$) for $C_{10}H_{19}NO_3SNa$ calcd 256.0978, found: m/z 256.0979; Anal. Calcd for for $C_{10}H_{19}NO_3S$: C, 51.48; H, 8.21; N, 6.00; S, 13.74. Found: C, 51.30; H, 8.10; N, 5.86; S, 13.47.



19 27

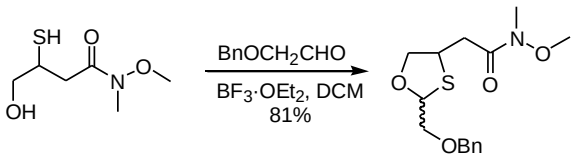
Mixed acetal 27. To a solution of benzaldehyde (0.637 g, 6.00 mmol) in DCM (30 mL) at 0 ^{o}C was added $BF_3{\cdot}OEt_2$ (6.0 mmol, 0.74 mL). After stirring at 0 ^{o}C for 5 minutes, a solution of **19** (0.536 g, 3.00 mmol) in DCM (10 mL) was added dropwise via cannula. The whole resulting solution was stirred for 0.5 h, then poured into a mixture of DCM (30 mL) and water (30 mL). The aqueous phase was extracted with DCM (2×40 mL). The combined organic layers were washed

with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes:EtOAc 2:1) provided **27** (0.739 g, 92 %) as an inseparable mixture of *cis* **27** and *trans* **27** isomers (1:2.4, ratio determined by ^{1}H NMR integration of acetal proton): R_f 0.19 (hexanes:EtOAc 2:1); IR (thin film) 3010, 2967, 2937, 2871, 1660, 1495, 1454, 1421, 1387, 1333, 1276, 1233, 1177, 1115, 1063, 1027, 996 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.47 (m, 2.8H), 7.38-7.30 (m, 4.3H), 6.16 (s, 0.4H), 6.07 (s, 1H), 4.62 (dd, *J* = 9.5, 6.9 Hz, 0.4H), 4.36 (d, *J* = 9.6 Hz, 1H), 4.18 (dddd, *J* = 6.9, 6.9, 6.9, 6.9 Hz, 0.4H), 4.10 (ddd, *J* = 5.7, 5.7, 5.7 Hz, 1H), 4.04 (dd, *J* = 9.6, 5.7 Hz, 1H), 3.74 (dd, J = 9.5, 6.9 Hz, 0.4H), 3.71 (s, 1.3H), 3.68 (s, 3H), 3.20 (s, 1.3H), 3.18 (s, 3H), 3.00-2.80 (m, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ Major: 172.1, 138.9, 128.7, 128.5, 126.7, 87.5, 76.5, 61.3, 45.9, 39.6, 32.1, Minor: 172.0, 139.2, 128.6, 128.4, 126.7, 86.9, 76.4, 61.3, 46.0, 37.4, 32.1; HRMS (ESI, $[M+Na]^+$) for $C_{13}H_{17}NO_3SNa$ calcd 290.0821, found: m/z 290.0824; Anal. Calcd for for $C_{13}H_{17}NO_3S$: C, 58.40; H, 6.41; N, 5.24; S, 11.99. Found: C, 58.50; H, 6.44; N, 5.18; S, 11.60.



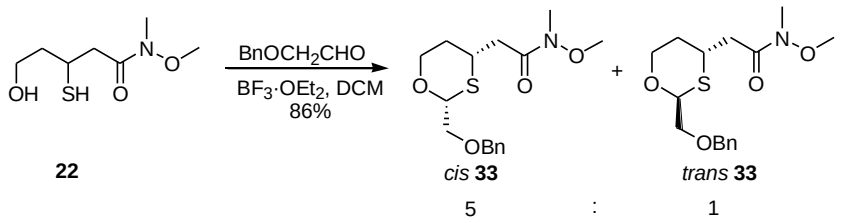
Mixed acetal 29. The aforementioned method was also employed in the synthesis of **29** starting with **22** (0.225 g, 1.17 mmol) and benzaldehyde (0.248 g, 2.34 mmol). Column chromatography (silica gel, hexanes:EtOAc 2:1) provided **29** (0.283 g, 86 %) as an inseparable mixture of *cis* **29** and *trans* **29** isomers (11:1, ratio determined by ^{1}H NMR integration of acetal proton): R_f 0.22 (hexanes:EtOAc 2:1); IR (thin film) 3062, 3031, 2966, 2938, 2858, 1717, 1659, 1452, 1422, 1386, 1239, 1176, 1082, 1018, 996 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ Major: 7.48-7.45 (m, 2H), 7.35-7.28 (m, 3H), 5.81 (s, 1H), 4.36 (ddd, *J* = 12.3, 4.0, 2.3 Hz, 1H), 3.80 (ddd, *J* = 12.3, 12.3, 2.0 Hz, 1H), 3.76-3.74 (m, 1H), 3.67 (s,

3H), 3.19 (s, 3H), 2.68-2.58 (m, 2H), 2.00-1.97 (m, 1H), 1.82-1.74 (m, 1H); Partial Minor: 5.97 (s, 0.1H), 3.22 (s, 0.3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ Major: 171.1, 138.9, 128.5, 128.4, 126.1, 84.7, 70.2, 61.4, 39.0, 37.8, 32.1, 29.3; Partial Minor: 133.3, 130.3, 79.8, 85.2, 35.2, 29.3; HRMS (ESI, $[M+Na]^+$) for $C_{14}H_{19}NO_3SNa$ calcd 304.0978, found: m/z 304.0978.



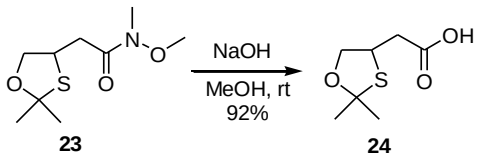
19 **31**

Mixed acetal 31. The aforementioned method was also employed in the synthesis of **31** starting with **19** (0.120 g, 0.67 mmol) and $BnOCH_2CHO$ (0.200 g, 1.34 mmol). Column chromatography (silica gel, hexanes:EtOAc 1:1) provided **31** (0.168 g, 81 %) as an inseparable mixture of *cis* **31** and *trans* **31** isomers (1:1.1 ratio determined by ^{1}H NMR integration of acetal proton): R_f 0.28 (hexanes:EtOAc 1:1); IR (thin film) 3088, 3063, 3030, 2937, 2866, 1660, 1496, 1454, 1420, 1387, 1332, 1270, 1199, 1177, 1095, 1029, 1001 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.30 (m, 7.6H), 7.29-7.26 (m, 1.9H), 5.41 (dd, *J* = 7.5, 4.1 Hz, 0.9H), 5.29 (dd, *J* = 7.0, 3.5 Hz, 1H), 4.66-4.56 (m, 3.8H), 4.29 (dd, *J* = 9.5, 5.3 Hz, 0.9H), 4.16 (dd, *J* = 9.4, 1.8 Hz, 1H), 3.97-3.94 (m, 1H), 3.93-3.89 (m, 1.9H), 3.78 (dd, *J* = 9.5, 5.3 Hz, 1H), 3.74-3.64 (m, 2H) overlapping with 3.69-3.66 (m, 0.9H), 3.68 (s, 3H), 3.63 (s, 2.7H), 3.50 (dd, *J* = 10.8, 3.5 Hz, 0.9H), 3.17 (s, 2.7H), 3.16 (s, 3H), 2.72-2.42 (m, 3.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ Major: 171.8, 138.1, 128.7, 128.1, 128.0, 85.2, 76.6, 73.8, 72.7, 61.6, 44.6, 39.2, 32.4, Minor: 171.8, 138.1, 128.1, 128.0, 127.9, 84.7, 75.7, 73.7, 73.3, 61.5, 44.5, 37.6, 32.4; HRMS (ESI, $[M+Na]^+$) for $C_{15}H_{21}NO_4SNa$ calcd 334.1084, found: m/z 334.1080.



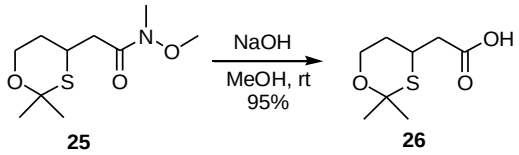
Mixed acetal 33. The aforementioned method was also employed in the synthesis of **33** starting with **22** (0.290 g, 1.50 mmol) and $BnOCH_2CHO$ (0.450 g, 3.00 mmol). Column chromatography (silica gel, DCM:EtOAc 5:1) provided **33** (0.420 g, 86 %) as an inseparable mixture of *cis* **33** and *trans* **33** isomers (5:1 ratio determined by ^{1}H NMR integration of acetal proton: R_f 0.38 (DCM:EtOAc 5:1); IR (thin film) 3062, 3030, 2937, 2902, 2861, 1661, 1496, 1454, 1422, 1385, 1323, 1282, 1178, 1105, 1029^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.30 (m, 4.8H), 7.30-7.27 (m, 1.2H), 5.16 (dd, *J* = 7.1, 3.8 Hz, 0.2H), 5.04 (dd, *J* = 6.1, 3.5 Hz, 1H), 4.64-4.57 (m, 2.4H), 4.25 (ddd, *J* = 12.0, 4.0, 2.2 Hz, 1H), 4.03 (ddd, *J* = 12.5, 4.0, 4.0 Hz, 0.2H), 3.90-3.83 (m, 0.2H), 3.75-3.72 (m, 0.2H), 3.72 (s, 0.6H), 3.70-3.66 (m, 1H), 3.69 (s, 3H), 3.66-3.64 (m, 0.2H), 3.64-3.59 (m, 1H), 3.60-3.58 (m, 1H), 3.56-3.52 (m, 0.2H), 3.20 (s, 0.6H), 3.19 (s, 3H), 3.16-3.02 (m, 0.2H), 2.95-2.90 (m, 0.2H), 2.66-2.56 (m, 2H), 2.30-2.22 (m, 0.2H), 1.94-1.90 (m, 1H), 1.69-1.66 (m, 1H), 1.66-1.64 (m, 0.2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ Major: 171.3, 138.0, 128.7, 128.1, 128.0, 82.8, 73.8, 72.2, 70.1, 61.6, 38.1, 33.9, 33.2, 32.4, Minor: 171.3, 138.0, 128.2, 128.1, 128.0, 82.8, 73.9, 72.3, 64.6, 61.6, 38.3, 36.3, 32.4, 29.9; HRMS (ESI, $[M+Na]^+$) for $C_{16}H_{23}NO_4SNa$ calcd 348.1240, found: m/z 348.1238; Anal. Calcd for for $C_{16}H_{23}NO_4S$: C, 59.05; H, 7.12; N, 4.30; S, 9.85. Found: C, 58.77; H, 7.18; N, 3.97; S, 9.50.

2.5.2.3. Preparation of carboxylic acid



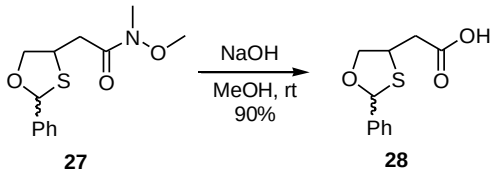
Carboxylic acid 24. A solution of NaOH (2.0 N, 2.0 mL, 2.0 mmol) was added into a solution of **23** (0.210 g, 1.00 mmol) in MeOH (3 mL) at room temperature.

After stirring at ambient temperature for overnight, 10 mL HCl (3 N) was added to quench the reaction, the whole mixture was poured into a mixture of HCl (30 mL, 1 N) and DCM (30 mL). The aqueous phase was extracted with DCM (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and filtered. After removing the solvent, **24** (0.156 g, 92%) was obtained as a colorless oil: IR (thin film) 3400-2700, 2974, 2927, 1710, 1405, 1367, 1301, 1208, 1180, 1125, 1062, 1008 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.21 (dd, J = 9.8, 5.0 Hz, 1H), 4.01 (dd, J = 9.8, 3.6 Hz, 1H), 3.92-3.88 (m, 1H), 2.78 (dd, J_{AB} = 16.9, J_{AX} = 7.6 Hz, 1H), 2.70 (dd, J_{AB} = 16.9, J_{AX} = 7.2 Hz, 1H), 1.69 (s, 3H), 1.61 (s, 3H) (COOH proton not detected); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 92.6, 74.0, 45.9, 40.1, 31.8, 30.8; HRMS (ESI, $[M+Na]^+$) for $C_7H_{12}O_3SNa$ calcd 199.0399, found: m/z 199.0400.



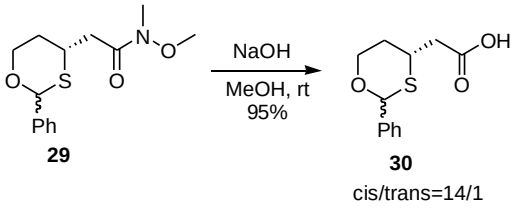
25 **26**

Carboxylic acid 26. The aforementioned method was also employed in the synthesis of **26** starting with **25** (0.072 g, 0.31 mmol). Removing the solvent provided **26** (0.056 g, 95%) as a white solid: m.p. 86-87 ^oC; IR (thin film) 3500-2300, 2981, 2742, 1695, 1475, 1460, 1428, 1402, 1383, 1369, 1214, 1281, 1271, 1238, 1215, 1190, 1168, 1137, 1101, 1061, 1013 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.96-3.89 (m, 2H), 3.55 (m, 1H), 2.49 (app d, J = 7.2 Hz, 2H), 1.91 (dddd, J = 13.5, 2.5, 2.5, 2.5 Hz, 1H), 1.70 (s, 3H), 1.62-1.55 (m, 1H), 1.54 (s, 3H) (COOH proton not detected); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 80.9, 62.5, 40.5, 34.6, 32.4, 31.4, 26.9; HRMS (ESI, $[M+Na]^+$) for $C_8H_{14}O_3SNa$ calcd 213.0556, found: m/z 213.0557.



27 **28**

Carboxylic acid 28. The aforementioned method was also employed in the synthesis of **28** starting with inseparable *cis* **27** and *trans* **27** isomers (0.673 g, 2.52 mmol). Removing the solvent provided **28** (0.511 g, 90 %) as an inseparable mixture of *cis* **28** and *trans* **28** isomers as a yellow oil (1:1.1, ratio determined by ^{1}H NMR integration of acetal proton): IR (thin film) 3500-2500, 3031, 2874, 1697, 1496, 1454, 1430, 1394, 1355, 1297, 1272, 1249, 1231, 1200, 1077, 1065, 1027, 1006 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.47 (m, 3.8 H), 7.40-7.32 (m, 5.6 H), 6.18 (s, 1H), 6.08 (s, 0.9H), 4.58 (dd, *J* = 9.0, 6.0 Hz, 1H), 4.36 (d, *J* = 7.9 Hz, 0.9H), 4.16-4.10 (m, 1H), 4.02-4.01 (m, 0.9H), 4.01-3.99 (m, 0.9H), 3.74 (dd, *J* = 9.0, 9.0 Hz, 1H), 3.00-2.91 (m, 0.9H), 2.90-2.82 (m, 2H), 2.83-2.80 (m, 0.9H) (COOH protons not detected); ^{13}C NMR (125 MHz, $CDCl_3$) δ Major: 179.0, 138.8, 128.8, 128.5, 126.7, 87.2, 76.0, 45.5, 39.1, Minor: 179.0, 138.4, 128.9, 128.5, 126.8, 87.8, 76.1, 45.6, 41.6; HRMS (ESI, $[M+Na]^+$) for $C_{11}H_{12}O_3SNa$ calcd 247.0399, found: m/z 247.0400.

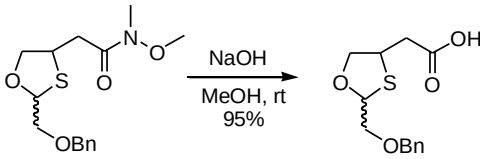


29 **30**

cis/trans=14/1

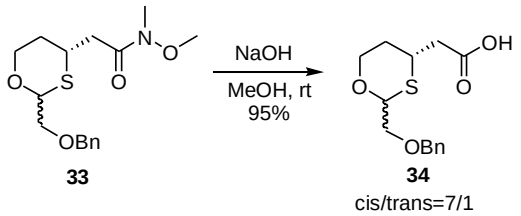
Carboxylic acid 30. The aforementioned method was also employed in the synthesis of **30** starting with **29** (0.283 g, 1.00 mmol). Removing the solvent provided **30** (0.226 g, 95 %) as an inseparable mixture of *cis* **30** and *trans* **30** isomers as a colorless oil (14:1, ratio determined by ^{1}H NMR integration of acetal proton): IR (thin film) 3500-2400, 3064, 3032, 2995, 2899, 1694, 1498, 1450, 1428, 1405, 1269, 1234, 1194, 1183, 1171, 1110, 1100, 1071, 1061, 1030, 1018 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ Major: 7.48-7.45 (m, 2H), 7.37-7.30 (m, 3H),

5.81 (s, 1H), 4.39 (ddd, J = 12.3, 4.0, 2.3 Hz, 1H), 3.79 (ddd, J = 12.3, 12.3, 2.3 Hz, 1H), 3.66 (m, 1H), 2.57 (app d, J = 7.2 Hz, 2H), 1.98 (dddd, J = 13.7, 2.3, 2.3, 2.3 Hz, 1H), 1.86-1.77 (m, 1H) (COOH protons not detected); Partial Minor: 5.95 (s, 0.07 H), 4.20-4.15 (m, 0.07H), 4.00-3.85 (m, 0.07H), 3.55-3.50 (m, 0.07H), 3.22-3.17 (m, 0.07H), 3.05-2.97 (m, 0.07H), 2.45-2.38 (m, 0.07H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 138.9, 129.0, 128.7, 126.4, 84.9, 70.3, 40.4, 39.0, 32.6; HRMS (ESI, $[M+Na]^+$) for $C_{12}H_{14}O_3SNa$ calcd 261.0556, found: m/z 261.0556.



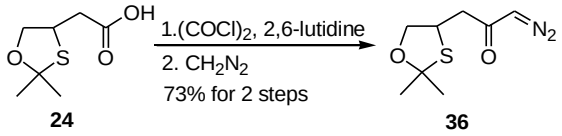
31 **32**

Carboxylic acid 32. The aforementioned method was also employed in the synthesis of **32** starting with **31** (0.031 g, 0.10 mmol). Removing the solvent provided **32** (0.025 g, 95 %) as an inseparable mixture of *cis* **32** and *trans* **32** isomers as a yellow oil (1:1.1, ratio determined by ^{1}H NMR integration of acetal proton): IR (thin film) 3400-2600, 3062, 3031, 2867, 1709, 1496, 1454, 1403, 1368, 1304, 1270, 1213, 1158, 1090, 1029 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.32 (m, 7.6H), 7.31-7.27 (m, 1.9H), 5.42 (dd, J = 7.3, 3.7 Hz, 1H), 5.30 (dd, J = 7.0, 3.7 Hz, 0.9H), 4.65 (d, J_{AB} = 12.0 Hz, 0.9H), 4.64 (d, J_{AB} = 12.1 Hz, 1H), 4.59 (d, J_{AB} = 12.0 Hz, 0.9 H), 4.58 (d, J_{AB} = 12.1 Hz, 1H), 4.27 (dd, J = 9.4, 5.2 Hz, 1H), 4.16 (dd, J = 9.7, 1.9 Hz, 0.9H), 3.93 (dd, J = 9.7, 4.9 Hz, 0.9H), 3.87-3.81 (m, 1.9H), 3.77 (dd, J = 9.4, 5.3 Hz, 1H), 3.74-3.64 (m, 2.8H), 3.51 (dd, J = 10.9, 3.7 Hz, 1H), 2.80-2.66 (m, 3.8H) (COOH protons not detected); ^{13}C NMR (125 MHz, $CDCl_3$) δ Major:176.6, 138.0, 128.7, 128.1, 128.1, 84.9, 75.4, 73.7, 72.5, 44.3, 39.3, Minor: 176.7, 138.0, 128.7, 128.1, 128.1, 85.4, 76.3, 73.9, 73.2, 44.1, 41.0; HRMS (ESI, $[M+Na]^+$) for $C_{13}H_{16}O_4SNa$ calcd 291.0662, found: m/z 291.0660.



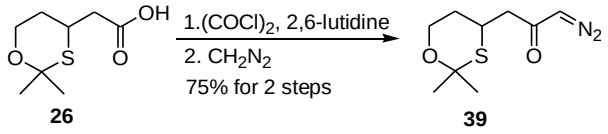
Carboxylic acid 34. The aforementioned method was also employed in the synthesis of **34** starting with **33** (0.690 g, 2.12 mmol). Removing the solvent provided **34** (0.570 g, 95 %) as an inseparable mixture of *cis* **34** and *trans* **34** isomers as a white solid (7:1, ratio determined by ^{1}H NMR integration of acetal proton): IR (thin film) 3400-2500, 3031, 2979, 2956, 2898, 2866, 2808, 1693, 1496, 1471, 1429, 1412, 1397, 1371, 1337, 1275, 1231, 1195, 1015 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ Major: 7.35-7.34 (m, 4H), 7.33-7.28 (m, 1H), 5.03 (dd, *J* = 6.1, 3.7 Hz, 1H), 4.64-4.58 (m, 2H), 4.26 (ddd, *J* = 12.1, 4.0, 2.2 Hz, 1H), 3.70-3.65 (m, 1H), 3.65-3.60 (m, 1H), 3.60-3.57 (m, 1H), 3.57-3.44 (m, 1H), 2.54 (app d, *J* = 6.8 Hz, 2H), 1.91-1.86 (m, 1H), 1.73-1.60 (m, 1H) (COOH proton not detected); Partial Minor: 5.12 (dd, *J* = 6.7, 3.5 Hz, 0.14H), 4.05-4.00 (m, 0.14H), 3.85-3.77 (m, 0.14H), 3.05-2.95 (m, 0.14H), 2.88-2.80 (m, 0.14H); ^{13}C NMR (125 MHz, $CDCl_3$) δ Major: 176.6, 137.9, 128.7, 128.1, 128.1, 82.8, 73.9, 72.2, 69.9, 40.7, 37.8, 32.7; Partial Minor: 64.4, 38.8, 32.7, 29.6; HRMS (ESI, $[M+Na]^+$) for $C_{14}H_{18}O_4SNa$ calcd 305.0818, found: m/z 305.0820.

2.5.2.4. Preparation of diazoketones



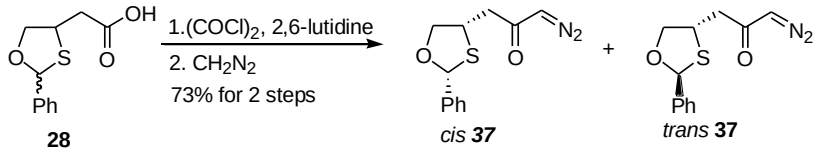
Diazoketone 36. To a solution of acid **24** (0.036 g, 0.21 mmol) in Et_2O (8 mL) at -15 ^{o}C was added 2,6-lutidine (80 μL, 0.70 mmol) followed by oxalyl chloride (27 μL, 0.30 mmol) and DMF (1 drop, ~5 μL), resulting in the evolution of gas and white precipitates. After stirring at -15 ^{o}C for 0.5 hour, the mixture was warmed to room temperature and stirred for additional 10 minutes. Through a fritted filter (D), the suspension was filtered directly into a solution of freshly prepared

diazomethane[26] (2 mmol) in Et_2O (5 mL) at -15 °C. The resulting mixture was stirred overnight as the cooling bath expired. A gentle stream of argon was applied to the system to allow evaporation of both excess diazomethane and solvent, and the resulting yellow oil was purified by column chromatography (silica gel, hexanes:EtOAc 2:1) directly to provide **36** (0.029 g, 73 % for 2 steps) as a yellow oil: R_f 0.33 (hexanes:EtOAc 2:1); IR (thin film) 3089, 2973, 2927, 2874, 2106, 1639, 1369, 1331, 1180, 1125, 1055 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.21 (br s, 1H), 4.23-4.18 (m, 1H), 3.98-3.95 (m, 1H), 3.96-3.95 (m, 1H), 2.76-2.0 (br m, 2H), 1.67 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 92.8, 74.5, 52.0, 46.6, 43.2, 32.1, 31.2; HRMS (ESI, $[M+Na]^+$) for $C_8H_{12}N_2O_2SNa$ calcd 223.0512, found: m/z 223.0513.



26 **39**

Diazoketone 39. The aforementioned method was also employed in the synthesis of **39** starting with **26** (0.025 g, 0.13 mmol) and diazomethane in Et_2O. Column chromatography (silica gel, hexanes:EtOAc 3:1) provided **39** (0.021 g, 75%) as a yellow oil: R_f 0.30 (hexanes:EtOAc 2:1); IR (thin film) 3082, 2976, 2928, 2904, 2877, 2105, 1736, 1638, 1424, 1366, 1324, 1276, 1250, 1170, 1132, 1082, 1036 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.30 (br s, 1H), 3.91 (app dd, J = 8.4, 2.2 Hz, 2H), 3.66-3.63 (m, 1H), 2.40 (br s, 2H), 1.85 (dd, J = 13.4, 2.2 Hz, 1H), 1.70 (s, 3H), 1.58-1.50 (m, 1H), 1.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.8, 80.9, 62.6, 55.9, 46.8, 35.2, 32.6, 31.5, 26.9; HRMS (ESI, $[M+Na]^+$) for $C_9H_{14}N_2O_2SNa$ calcd 237.0668, found: m/z 237.0668.



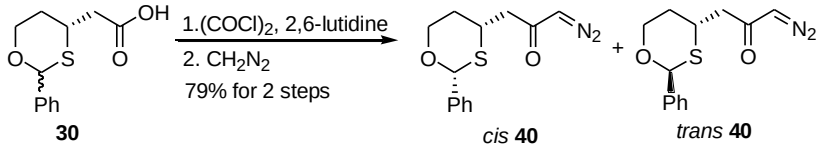
28 *cis* ***37*** *trans* **37**

Diazoketone 37. The aforementioned method was also employed in the synthesis of *cis* **37** and *trans* **37** starting with inseparable *cis* **28** and *trans* **28** isomers (66

mg, 0.3 mmol, 1:1.1). Column chromatography (silica gel, hexanes:EtOAc 1:1) provided *cis* **37** (0.030 g, 41%) and *trans* **37** (0.023 g, 32%) as colorless oils. The determination of the two isomers was based on the TROESY spectra.

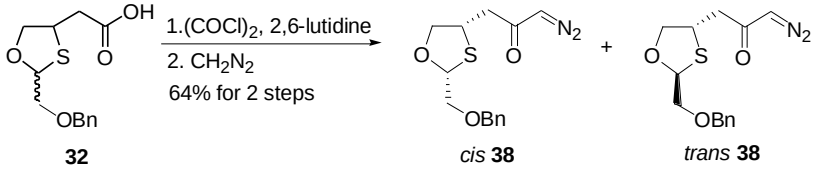
cis **37**: R_f 0.42 (hexanes:EtOAc 1:1); IR (thin film) 3093, 2935, 2872, 2106, 1720, 1638, 1496, 1454, 1376, 1332, 1272, 1246, 1125, 1059, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47-7.45 (m, 2H), 7.39-7.31 (m, 3H), 6.06 (s, 1H), 5.28 (br s, 1H), 4.32 (dd, *J* = 9.6, 1.5 Hz, 1H), 4.12-4.07 (m, 1H), 4.01 (dd, *J* = 9.6, 5.2 Hz, 1H), 2.90-2.80 (br m, 1H), 2.80-2.68 (br m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 138.6, 128.8, 128.5, 126.7, 87.7, 76.3, 55.2, 47.8, 45.9; HRMS (ESI, $[M+Na]^+$) for $C_{12}H_{12}N_2O_2SNa$ calcd 271.0512, found: m/z 271.0510.

trans **37**: R_f 0.33 (hexanes:EtOAc 1:1); IR (thin film) 3091, 3063, 3028, 2938, 2901, 2875, 2108, 1721, 1634, 1452, 1392, 1329, 1270, 1235, 1177, 1115, 1070, 1042, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.38-7.30 (m, 3H), 6.15 (s, 1H), 5.32 (br s, 1H), 4.57 (dd, *J* = 9.4, 7.1 Hz, 1H), 4.16 (dddd, *J* = 7.1, 7.1, 7.1, 7.1 Hz, 1H), 3.71 (dd, *J* = 9.4, 7.1 Hz, 1H), 2.76 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 139.3, 129.0, 128.7, 127.0, 87.4, 76.6, 55.4, 46.4, 45.6; HRMS (ESI, $[M+Na]^+$) for $C_{12}H_{12}N_2O_2SNa$ calcd 271.0512, found: m/z 271.0514; Anal. Calcd for for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28; S, 12.91. Found: C, 57.78; H, 4.99; N, 10.16; S, 12.67.



Diazoketone 40. The aforementioned method was also employed in the synthesis of **40** starting with inseparable *cis* **30** and *trans* **30** isomers (0.052 g, 0.22 mmol, 10:1). Column chromatography (silica gel, hexanes:EtOAc 2:1) provided *cis* **40** (0.038 g, 67%) and a 1:1 mixture of *cis* **40** and *trans* **40** (0.007 g, 12%) as colorless oils. *cis* **40** (major): R_f 0.28 (hexanes:EtOAc 2:1); IR (thin film) 3082, 2990, 2934, 2906, 2870, 2852, 2109, 1615, 1492, 1453, 1421, 1406, 1373, 1359,

1348, 1326, 1281, 1240, 1198, 1174, 1124, 1102, 1081, 1048, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46-7.44 (m, 2H), 7.36-7.28 (m, 3H), 5.80 (s, 1H), 5.29 (br s, 1H), 4.36 (ddd, *J* = 12.2, 4.0, 2.3 Hz, 1H), 3.78 (ddd, *J* = 12.2, 12.2, 2.0 Hz, 1H), 3.77-3.71 (m, 1H), 2.47 (br s, 2H), 1.95-1.91 (m, 1H), 1.82-1.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.2, 138.8, 128.6, 128.4, 126.1, 84.6, 70.1, 55.7, 46.4, 39.3, 32.6; HRMS (ESI, $[M+Na]^+$) for $C_{13}H_{14}N_2O_2SNa$ calcd 285.0668, found: m/z 285.0668.

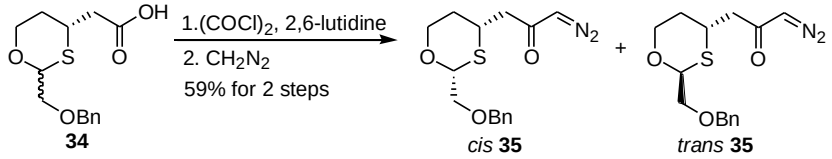


Diazoketone 38. The aforementioned method was also employed in the synthesis of **38** starting with **32** (0.080 g, 0.300 mmol, 1:1.1). Column chromatography (silica gel, hexanes:EtOAc 2:1) provided *cis* **38** (0.019 g, 22%), *trans* **38** (0.018 g, 21%), along with an unseparated mixture of *cis* **38** and *trans* **38** (0.018 g, 21%, 1:1 ratio), all as colorless oils.

cis **38**: R_f 0.25 (hexanes:EtOAc 2:1); IR (thin film) 3089, 3064, 3030, 2865, 2106, 1734, 1637, 1496, 1454, 1373, 1331, 1274, 1204, 1101 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.32 (m, 4H), 7.32-7.27 (m, 1H), 5.40 (dd, *J* = 7.3, 3.7 Hz, 1H), 5.27 (br s, 1H), 4.62 (d, J_{AB} = 12.1 Hz, 1H), 4.56 (d, J_{AB} = 12.1 Hz, 1H), 4.26 (dd, *J* = 9.5, 5.3 Hz, 1H), 3.92-3.89 (m, 1H), 3.75 (dd, *J* = 9.5, 5.4 Hz, 1H), 3.68 (dd, *J* = 10.8, 7.3 Hz, 1H), 3.50 (dd, *J* = 10.8, 3.7 Hz, 1H), 2.67 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.7, 137.8, 128.5, 128.4, 127.8, 84.7, 75.3, 73.5, 72.3, 55.2, 45.1, 44.4; HRMS (ESI, $[M+Na]^+$) for $C_{14}H_{16}N_2O_3SNa$ calcd 315.0774, found: m/z 315.0773.

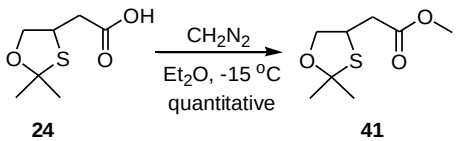
trans **38**: R_f 0.23 (hexanes:EtOAc 2:1); IR (thin film) 3089, 3064, 3030, 2865, 2106, 1734, 1637, 1496, 1454, 1373, 1331, 1274, 1204, 1101 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.31 (m, 4H), 7.31-7.27 (m, 1H), 5.29 (dd, *J* = 6.6, 3.6 Hz,

1H), 5.17 (br s, 1H), 4.63 (d, J_{AB} = 12.0 Hz, 1H), 4.58 (d, J_{AB} = 12.0 Hz, 1H), 4.14-4.11 (m, 1H), 3.94-3.92 (m, 1H), 3.92-3.90 (m, 1H), 3.69 (dd, J_{AB} = 10.8, J_{AX} = 6.6 Hz, 1H), 3.65 (dd, J_{AB} = 10.8, J_{BX} = 3.6 Hz, 1H), 2.70-2.60 (br m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 137.8, 128.4, 127.8, 127.8, 85.1, 76.3, 73.6, 72.8, 55.1, 46.9, 44.3; HRMS (ESI, $[M+Na]^+$) for $C_{14}H_{16}N_2O_3SNa$ calcd 315.0774, found: m/z 315.0773.

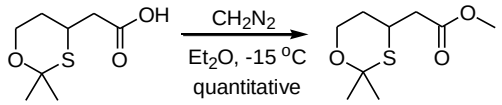


Diazoketone 35. The aforementioned method was also employed in the synthesis of **35** starting with inseparable *cis* **34** and *trans* **34** isomers (0.056 g, 0.20 mmol, 5:1). Column chromatography (silica gel, hexanes:EtOAc 2:1) provided *cis* **35** (0.026 g, 43%) and an unseparated mixture of *cis* **35** and *trans* **35** (0.010 mg, 16%, 1:1 ratio) as colorless oils. *cis* 35(major): R_f 0.20 (hexanes:EtOAc 2:1); IR (thin film) 3088, 3031, 2902, 2861, 2105, 1728, 1639, 1496, 1454, 1424, 1373, 1325, 1284, 1207, 1182, 1103, 1029 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.30 (m, 4H), 7.29-7.27 (m, 1H), 5.30 (br s, 1H), 5.01 (dd, J = 6.1, 3.7 Hz, 1H), 4.59 (d, J_{AB} = 12.3 Hz, 1H), 4.57 (d, J_{AB} = 12.3 Hz, 1H), 4.23 (ddd, J = 12.2, 4.1, 2.4 Hz, 1H), 3.65 (dd, J_{AB} = 10.7, J_{AX} = 6.1 Hz, 1H), 3.63-3.60 (m, 1H), 3.61-3.55 (m, 1H), 3.57 (dd, J_{AB} = 10.7, J_{BX} = 3.7 Hz, 1H), 2.46 (br s, 2H), 1.85 (br dd, J = 13.7, 2.1 Hz, 1H), 1.70-1.62 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.1, 137.7, 128.4, 127.8, 127.8, 82.6, 73.6, 71.9, 69.7, 55.7, 46.6, 38.1, 32.7; HRMS (ESI, $[M+Na]^+$) for $C_{15}H_{18}N_2O_3SNa$ calcd 329.0929, found: m/z 329.0930.

2.5.2.5. Preparation of mixed acetal esters

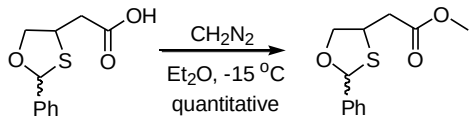


Ester 41. To a solution of freshly prepared diazomethane (4 mmol) in Et_2O (10 mL) at -15 ^oC was added acid **41** (0.120 g, 0.67 mmol). The resulting mixture was stirred overnight as the cooling bath expired. A gentle stream of argon was applied to the system to allow evaporation of both excess diazomethane and solvent to provide **47** (0.129 g, quantitative) as a colorless oil: R_f 0.32 (hexanes:EtOAc 10:1); IR (thin film) 2925, 2854, 1735, 1462, 1378, 1274, 1166, 1073 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.21 (dd, J = 9.8, 5.0 Hz, 1H), 3.99 (dd, J = 9.8, 3.7 Hz, 1H), 3.93-3.90 (m, 1H), 3.70 (s, 3H), 2.73 (dd, J_{AB} = 16.4, J_{AX} = 7.6 Hz, 1H), 2.67 (dd, J_{AB} = 16.4, J_{BX} = 7.0 Hz, 1H), 1.68 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 92.5, 74.1, 51.8, 46.3, 40.1, 31.8, 30.9; HRMS (ESI, $[M+Na]^+$) for $C_8H_{14}O_3SNa$ calcd 213.0556, found: m/z 213.0555.



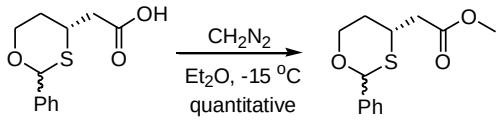
26 **44**

Ester 44. The aforementioned method was also employed in the synthesis of **44** starting with **26** (0.080 g, 0.42 mmol) and diazomethane in Et_2O. Column chromatography (silica gel, hexanes:EtOAc 3:1) provided **44** (0.085 g, quantitative) as a colorless oil: R_f 0.45 (hexanes:EtOAc 3:1); IR (thin film) 2976, 2952, 2930, 2875, 1740, 1437, 1364, 1352, 1308, 1258, 1209, 1168, 1134, 1095, 1065 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.93 (d, J = 2.4 Hz, 1H), 3.91 (dd, J = 3.6, 2.4 Hz, 1H), 3.69 (s, 3H), 3.56 (dddd, J = 14.0, 7.2, 7.2, 2.8 Hz, 1H), 2.43 (app d, J = 7.2 Hz, 2H), 1.86 (dddd, J = 14.0, 2.4, 2.4, 2.4 Hz, 1H), 1.70 (s, 3H), 1.59-1.52 (m, 2H), 1.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 80.8, 62.6, 52.1, 40.6, 35.0, 32.5, 31.5, 26.9; HRMS (ESI, $[M+Na]^+$) for $C_9H_{16}O_3SNa$ calcd 227.0712, found: m/z 227.0714; Anal. Calcd for for $C_9H_{16}O_3S$: C, 52.91; H, 7.89; S, 15.70. Found: C, 52.70; H, 7.63; S, 15.34.



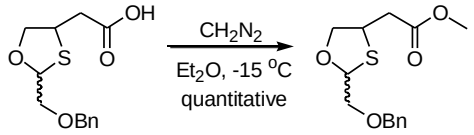
28 **42**

Ester 42. The aforementioned method was also employed in the synthesis of **42** starting with inseparable *cis* **28** and *trans* **28** isomers (0.123 g, 0.55 mmol, 1:0.9). Column chromatography (silica gel, hexanes:EtOAc 5:1) provided inseparable *cis* **42** and *trans* **42** isomers (0.130 g, quantitative, 1:0.9) as a colorless oil (ratio determined by ^{1}H NMR integration of acetal proton): R_f 0.32 (hexanes:EtOAc 5:1); IR (thin film) 3064, 3031, 2952, 2871, 1736, 1496, 1455, 1411, 1357, 1306, 1227, 1201, 1172, 1066, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.46 (m, 3.8 H), 7.38-7.30 (m, 5.7 H), 6.16 (s, 1H), 6.06 (s, 0.9H), 4.56 (dd, *J* = 9.4, 6.0 Hz, 1H), 4.32 (d, *J* = 8.4 Hz, 0.9H), 4.14-4.11 (m, 1H), 4.04-4.01 (m, 0.9H), 4.02-3.98 (m, 0.9H), 3.72-3.69 (m, 1H), 3.71 (s, 3H), 3.70 (s, 2.7H), 2.90-2.72 (m, 1.8H), 2.82-2.72 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ Major: 171.8, 139.2, 129.0, 128.7, 127.0, 87.4, 76.4, 52.2, 46.3, 39.4, Minor: 172.0, 138.9, 129.1, 128.8, 127.1, 88.0, 76.4, 52.1, 46.2, 41.9; HRMS (ESI, $[M+Na]^+$) for $C_{12}H_{14}O_3SNa$ calcd 261.0556, found: m/z 261.0555.



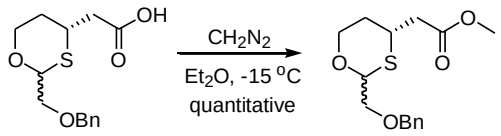
Ester 45. The aforementioned method was also employed in the synthesis of **45** starting with *cis* **30** and *trans* **30** isomers (0.010 g, 0.04 mmol, 14:1). Column chromatography (silica gel, hexanes:EtOAc 4:1) provided **45** (0.011 g, quantitative) as an inseparable mixture of *cis* **45** and *trans* **45** isomers (14:1, ratio determined by ^{1}H NMR integration of acetal proton). R_f 0.44 (hexanes:EtOAc 3:1); IR (thin film) 3063, 3031, 2952, 2904, 2857, 1738, 1495, 1453, 1436, 1355, 1306, 1247, 1219, 1161, 1102, 1069, 1024 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ Major: 7.47-7.45 (m, 2H), 7.37-7.31 (m, 3H), 5.80 (s, 1H), 4.38 (ddd, *J* = 12.2, 4.0, 2.3 Hz, 1H), 3.79 (ddd, *J* = 12.2, 12.2, 2.1 Hz, 1H), 3.71 (s, 3H), 3.70-3.63 (m, 1H), 2.52 (app d, *J* = 7.2 Hz, 2H), 1.96-1.93 (m, 1H), 1.83-1.78 (m, 1H); Partial Minor: 5.93 (s, 0.07H); 3.18-3.10 (m, 0.07H), 3.00-2.93 (m, 0.07H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 171.4, 139.0, 128.9, 128.7, 126.4, 84.9, 70.4, 52.2, 40.6, 39.3, 32.7; HRMS (ESI, $[M+Na]^+$) for $C_{13}H_{16}O_3SNa$ calcd 275.0712, found: m/z 275.0713.



32 **43**

Ester 43. The aforementioned method was also employed in the synthesis of **43** starting with *cis* **32** and *trans* **32** isomers (0.027 g, 0.10 mmol, 1.1:1). Column chromatography (silica gel, hexanes:EtOAc 3:1) provided inseparable *cis* **43** and *trans* **43** isomers (0.028 g, quantitative, 1.1:1) as colorless oils (ratio determined by ^{1}H NMR integration of acetal proton): R_f 0.37 (hexanes:EtOAc 3:1); IR (thin film) 3063, 3030, 2951, 2864, 1737, 1497, 1453, 1437, 1411, 1367, 1301, 1253, 1207, 1172, 1093, 1028, 1014, 986 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.33 (m, 7.6H), 7.30-7.28 (m, 1.9H), 5.41 (dd, J = 7.4, 3.7 Hz, 1H), 5.29 (dd, J = 7.0, 3.6 Hz, 0.9H), 4.62 (dd, J_{AB} = 12.0, J_{AX} = 5.8 Hz, 1.9H), 4.57 (dd, J_{AB} = 12.0, J_{BX} = 2.6 Hz, 1.9H), 4.27 (dd, J = 9.4, 5.3 Hz, 1H), 4.14 (dd, J = 9.7, 2.0 Hz, 0.9H), 3.93 (dd, J = 9.7, 4.9 Hz, 0.9H), 3.87-3.83 (m, 1.9H), 3.76 (dd, J = 9.4, 5.4 Hz, 1H), 3.75-3.63 (m, 2.8H) overlapping with 3.70 (s, 3H) and 3.69 (s, 2.7H), 3.51 (dd, J = 10.8, 3.7 Hz, 1H), 2.74-2.60 (m, 3.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ Major:172.0, 138.1, 128.7, 128.1, 128.0, 84.9, 75.5, 73.7, 72.5, 52.2, 44.6, 41.1, Minor: 171.8, 138.0, 128.7, 128.1, 128.0, 85.4, 76.4, 73.8, 73.3, 52.1, 44.5, 41.1; HRMS (ESI, $[M+Na]^+$) for $C_{14}H_{18}O_4SNa$ calcd 305.0818, found: m/z 305.0818.

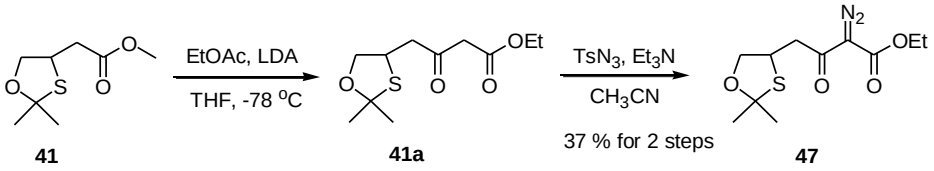


34 **46**

Ester 46. The aforementioned method was also employed in the synthesis of **46** starting with inseparable *cis* **34** and *trans* **34** isomers (0.070 g, 0.25 mmol, 7:1)

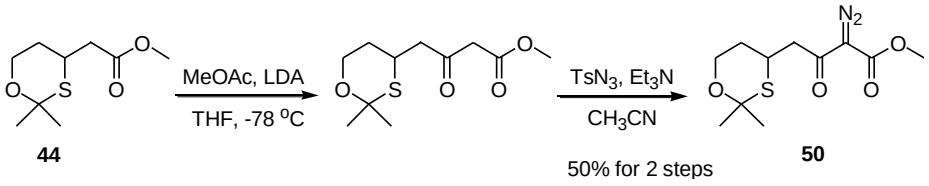
and diazomethane in Et_2O. Column chromatography (silica gel, hexanes:EtOAc 3:1) provided inseparable *cis* **46** and *trans* **46** isomers (0.072 g, quantitive, 7:1) as a colorless oil. Careful column chromatography (silica gel, hexanes:EtOAc 10:1) provided *cis* **46** for characterization: R_f 0.31 (hexanes:EtOAc 3:1); IR (thin film) 3063, 3030, 2951, 2903, 2860, 1738, 1454, 1437, 1369, 1352, 1248, 1218, 1190, 1162, 1112, 1061, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.30 (m, 4H), 7.30-7.28 (m, 1H), 5.02 (dd, J = 6.1, 3.6 Hz, 1H), 4.62 (d, J_{AB} = 12.2 Hz, 1H), 4.59 (d, J_{AB} = 12.2 Hz, 1H), 4.25 (ddd, J = 12.2, 4.0, 2.3 Hz, 1H), 3.71 (s, 3H), 3.69 (dd, J = 10.7, 6.1 Hz, 1H), 3.63 (ddd, J = 12.2, 12.2, 2.0 Hz, 1H), 3.59 (dd, J = 10.7, 3.7 Hz, 1H), 3.53-3.48 (m, 1H), 2.50 (app d, J = 7.3 Hz, 2H), 1.85 (dddd, J = 12.2, 2.3, 2.3, 2.3 Hz, 1H), 1.71-1.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 138.0, 128.7, 128.1, 128.0, 82.8, 73.9, 72.2, 70.0, 52.1, 40.8, 38.2, 32.8; HRMS (ESI, $[M+Na]^+$) for $C_{15}H_{20}O_4SNa$ calcd 319.0975, found: m/z 319.0974; Anal. Calcd for for $C_{15}H_{20}O_4S$: C, 60.79; H, 6.80; S, 10.82. Found: C, 60.53; H, 6.93; S, 10.74.

2.5.2.6. Preparation of diazoketoesters



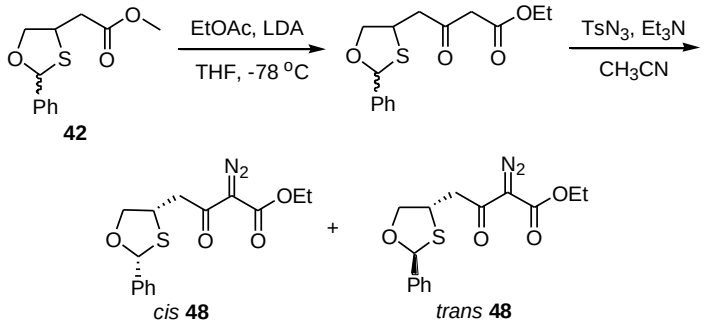
Diazoketoester 47. Into a stirring solution of diisopropyl amine (0.42 mL, 3.00 mmol) in THF (3 mL) at -78 °C was added ^{n}BuLi (2.00 mL, 1.42 M, 2.84 mmol) and the resulting mixture was stirred at -78 °C for 30 minutes. Then the mixture was warmed to 0 °C and stirred for another 30 minutes before being cooled again to -78 °C. Ethyl acetate (1.28 mL, 2.80 mmol) was added dropwise, and the resulting mixture was stirred for 1 hour. A solution of **41** (0.060 g, 0.31 mmol) in THF (2 mL) was added dropwise to the above mixture and the resulting mixture was stirred overnight, allowing cooling bath to expire. Then the whole mixture was poured into a mixture of HCl (20 mL, 0.5 N) and Et_2O (30 mL). The aqueous phase was extracted with Et_2O (2×30 mL). The combined organic layers were

washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes:EtOAc 10:1, 5:1) provided **41**a (0.060 g, 77%) as crude product, which was added into a solution of tosyl azide (0.100 g, 0.50 mmol) and triethylamine (70 μL, 0.50 mmol) in CH_3CN (5 mL). After stirring at room temperature for overnight, the solvent was removed to give yellow oil, which was purified by column chromatography (silica gel, hexanes:EtOAc 10:1 (+1 v% Et_3N)) to provide product **47** (0.032 g, 37 % for 2 steps) as yellow oil: R_f 0.24 (hexanes:EtOAc 10:1); IR (thin film) 2980, 2929, 2873, 2138, 1720, 1656, 1449, 1373, 1316, 1207, 1180, 1129, 1062, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.30 (q, J = 7.1 Hz, 2H), 4.23 (dd, J = 9.5, 5.0 Hz, 1H), 4.01-3.97 (m, 1H), 3.95 (dd, J = 9.5, 4.1 Hz, 1H), 3.26 (dd, J_{AB} = 17.9 Hz, J_{AX} = 7.4 Hz, 1H), 3.21 (dd, J_{AB} = 17.9 Hz, J_{BX} = 6.7 Hz, 1H), 1.66 (s, 3H), 1.58 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.8, 161.4, 92.5, 74.4, 61.8, 46.3, 45.9, 32.0, 31.2, 14.6 (diazo carbon not detected); HRMS (ESI, $[M+Na]^+$) for $C_{11}H_{16}N_2O_4SNa$ calcd 295.0723, found: m/z 295.0724.



Diazoketoester 50. The aforementioned method was also employed in the synthesis of **50** starting with **44** (0.062 g, 0.30 mmol), LDA and methyl acetate (1.28 mL, 3.00 mmol) followed by diazo exchange with triethylamine (70 μL, 0.50 mmol) and tosyl azide (0.100 g, 0.50 mmol). Column chromatography (silica gel, hexanes:EtOAc 3:1) provided 0.041 g (50%) of **50** as a colorless oil: R_f 0.43 (hexanes:EtOAc 3:1); IR (thin film) 2977, 2956, 2929, 2875, 2137, 1725, 1656, 1438, 1372, 1364, 1316, 1258, 1224, 1194, 1169, 1132, 1092, 1063, 1013 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.93 (dd, J = 3.6, 2.5 Hz, 1H), 3.91 (d, J = 2.5 Hz, 1H), 3.84 (s, 3H), 3.73-3.66 (m, 1H), 3.02 (dd, J_{AB} = 16.9, J_{AX} = 4.0 Hz, 1H), 2.95 (dd, J_{AB} = 16.9, J_{BX} = 2.9 Hz, 1H), 1.85 (ddd, J = 13.6, 2.5, 2.5, 2.5 Hz, 1H), 1.70 (s, 3H), 1.63-1.54 (m, 1H), 1.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

189.8, 161.8, 80.8, 62.7, 52.6, 45.9, 34.4, 32.7, 31.5, 26.9 (diazo carbon not detected); HRMS (ESI, $[M+Na]^+$) for $C_{11}H_{16}N_2O_4SNa$ calcd 295.0723, found: m/z 295.0722.

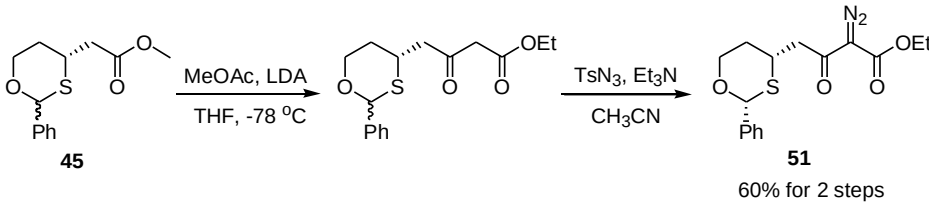


Diazoketoester 48. The aforementioned method was also employed in the synthesis of **48** starting with **42** (0.240 g, 1.00 mmol), LDA and ethyl acetate (3.00 mL, 6.56 mmol) followed by diazo exchange with triethylamine (210 μL, 1.50 mmol) and tosyl azide (0.300 g, 1.50 mmol). Column chromatography (silica gel, hexanes:EtOAc 4:1) provided *cis* **48** (0.080 g, 25 %) and *trans* **48** (0.080 g, 25%).

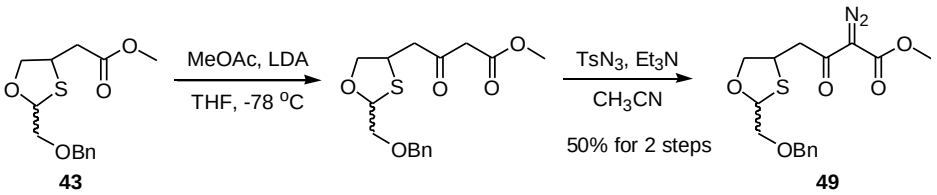
cis **48**: R_f 0.38 (hexanes:EtOAc 4:1); IR (thin film) 3064, 3032, 2982, 2936, 2871, 2137, 1714, 1651, 1495, 1454, 1373, 1296, 1224, 1174, 1133, 1065, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49-7.47 (m, 2H), 7.38-7.30 (m, 3H), 6.06 (s, 1H), 4.32 (q, J = 7.2 Hz, 2H), 4.30 (dd, J = 9.5, 1.6 Hz, 1H), 4.12-4.09 (m, 1H), 4.04 (dd, J = 9.5, 5.0 Hz, 1H), 3.43 (dd, J_{AB} = 18.1, J_{AX} = 7.1 Hz, 1H), 3.35 (dd, J_{AB} = 18.1, J_{BX} = 6.9 Hz, 1H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.8, 161.4, 138.9, 129.0, 128.7, 127.1, 87.9, 76.4, 61.8, 48.0, 45.6, 14.6 (diazo carbon not detected); HRMS (ESI, $[M+Na]^+$) for $C_{15}H_{16}N_2O_4SNa$ calcd 343.0723, found: m/z 343.0721.

trans **48**: R_f 0.42 (hexanes:EtOAc 4:1); IR (thin film) 3064, 3032, 2982, 2908, 2872, 2138, 1714, 1653, 1495, 1455, 1374, 1352, 1315, 1225, 1175, 1133, 1069, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48-7.46 (m, 2H), 7.37-7.30 (m, 3H),

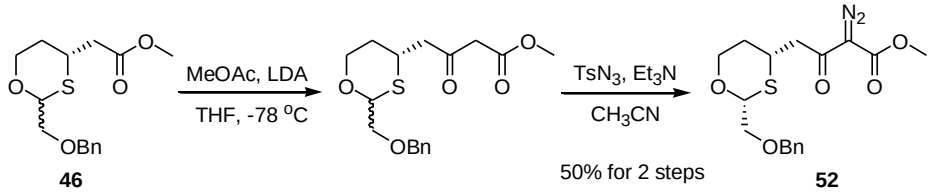
6.12 (s, 1H), 4.59 (dd, J = 9.4, 6.0 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 4.21-4.16 (m, 1H), 3.70 (dd, J = 9.4, 7.5 Hz, 1H), 3.35 (dd, J_{AB} = 17.9, J_{AX} = 7.7 Hz, 1H), 3.28 (dd, J_{AB} = 17.9, J_{BX} = 6.4 Hz, 1H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.1, 161.2, 139.0, 128.6, 128.4, 126.7, 87.0, 76.2, 61.6, 45.4, 45.3, 14.4 (diazo carbon not detected); HRMS (ESI, $[M+Na]^+$) for $C_{15}H_{16}N_2O_4SNa$ calcd 343.0723, found: m/z 343.0722.



Diazoketoester 45. The aforementioned method was also employed in the synthesis of **51** starting with inseparable *cis* **45** and *trans* **45** isomer (0.169 g, 0.67 mmol, 14:1), LDA and ethyl acetate (2.60 mL, 5.69 mmol) followed by diazo exchange with triethylamine (150 μL, 1.07 mmol) and tosyl azide (0.230 g, 1.07 mmol). Column chromatography (silica gel, *t*-BuOH:EtOAc 4:1) provided 0.134 g (60%) of **51** as a single diastereomer as a yellow oil: R_f 0.19 (*t*-BuOH:EtOAc 4:1); IR (thin film) 3050, 3010, 2980, 2900, 2890, 2870, 2137, 1715, 1652, 1452, 1374, 1309, 1221, 1189, 1174, 1098, 1066, 1024 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.45 (m, 2H), 7.36-7.28 (m, 3H), 5.81 (s, 1H), 4.36 (ddd, J = 12.3, 4.0, 2.4 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 3.83-3.80 (m, 1H), 3.81-3.77 (m, 1H), 3.08 (d, J_{AB} = 2.2 Hz, 1H), 3.07 (d, J_{AB} = 2.2 Hz, 1H), 1.95-1.91 (m, 1H), 1.87-1.80 (m, 1H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.5, 161.1, 138.9, 128.5, 128.4, 126.2, 84.7, 70.2, 61.6, 45.5, 38.6, 32.7, 14.3 (diazo carbon not detected); HRMS (ESI, $[M+Na]^+$) for $C_{16}H_{18}N_2O_4SNa$ calcd 357.0880, found: m/z 357.0878.

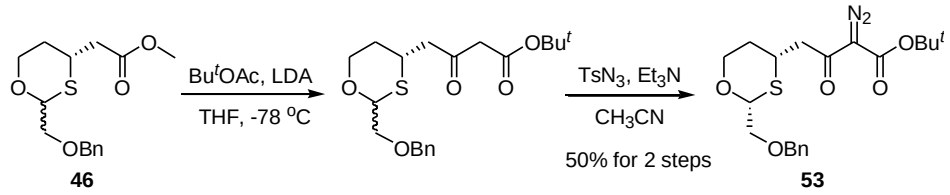


Diazoketoester 49. The aforementioned method was also employed in the synthesis of **49** starting with **43** (0.137 g, 0.49 mmol), LDA and methyl acetate (0.40 mL, 5.00 mmol) followed by diazo exchange with triethylamine (150 μL, 1.07 mmol) and tosyl azide (0.230 g, 1.07 mmol). Column chromatography (silica gel, hexanes:EtOAc 2:1) provided **49** (0.085 g, 50 %) as an inseparable mixture of *cis* **49** and *trans* **49** isomers (1:1.1, ratio determined by ^{1}H NMR integration of acetal proton): R_f 0.42 (hexanes:EtOAc 2:1); IR (thin film) 3030, 2954, 2863, 2137, 1722, 1653, 1437, 1370, 1319, 1224, 1133, 1093, 1028 cm^{1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.31 (m, 7.6H), 7.30-7.27 (m, 1.9H), 5.38 (dd, *J* = 7.4, 3.6 Hz, 1H), 5.29 (dd, *J* = 7.1, 3.5 Hz, 0.9H), 4.62 (dd, J_{AB} = 12.1 Hz, J_{AX} = 4.7 Hz, 1.9H), 4.56 (dd, J_{AB} = 12.1 Hz, J_{BX} = 1.0 Hz, 1.9H), 4.31 (dd, *J* = 9.5, 5.5 Hz, 1H), 4.11 (dd, *J* = 9.3, 2.1 Hz, 0.9H), 3.98-3.93 (m, 0.9H), 3.93-3.88 (m, 1.9H), 3.74-3.71 (m, 1H), 3.72-3.70 (m, 0.9H), 3.71-3.66 (m, 1H), 3.62 (dd, *J* = 10.8, 3.5 Hz, 0.9H), 3.53 (dd, J = 10.8, 3.6 Hz, 1H), 3.30-3.17 (m, 3.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.6,190.3, 161.8, 138.1, 128.7, 128.0, 128.0, 85.3, 84.8, 76.3, 75.7, 73.8, 73.7, 73.3, 72.7, 52.6, 52.5, 47.2, 45.5, 44.0, 43.8 (diazo carbon not detected); HRMS (ESI, $[M+Na]^{+}$) for $C_{16}H_{18}N_2O_5SNa$ calcd 373.0829, found: m/z 373.0827; Anal. Calcd for for $C_{16}H_{18}N_2O_5S$: C, 54.85; H, 5.18; N, 7.99; S, 9.15. Found: C, 54.77; H, 5.16; N, 7.67; S, 9.20.



Diazoketoester 52. The aforementioned method was also employed in the synthesis of **52** starting with inseparable *cis* **46** and *trans* **46** isomer (0.184 g, 0.62

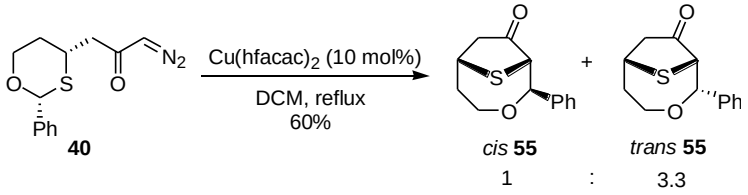
mmol, 7:1), LDA and methyl acetate (0.40 mL, 5.00 mmol) followed by diazo exchange with triethylamine (150 μL, 1.07 mmol) and tosyl azide (0.230 g, 1.07 mmol). Column chromatography (silica gel, hexanes:EtOAc 2:1) provided 0.114 g (50%) of *cis* **52** as a single isomer as a yellow oil: R_f 0.38 (hexanes:EtOAc 2:1); IR (thin film) 3063, 3030, 2954, 2903, 2860, 2138, 1721, 1656, 1497, 1453, 1437, 1372, 1316, 1222, 1196, 1133, 1105, 1061, 1009 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.33 (m, 4H), 7.29-7.27 (m, 1H), 5.02 (dd, J = 6.3, 3.5 Hz, 1H), 4.59 (d, J_{AB} = 12.2 Hz, 1H), 4.56 (d, J_{AB} = 12.2 Hz, 1H), 4.23 (ddd, J = 12.1, 4.0, 2.2 Hz, 1H), 3.84 (s, 3H), 3.67 (dd, J_{AB} = 10.9 Hz, J_{AX} = 6.3 Hz, 1H), 3.65-3.63 (m, 1H), 3.64-3.61 (m, 1H), 3.56 (dd, J_{AB} = 10.9 Hz, J_{BX} = 3.5 Hz, 1H), 3.05 (dd, J_{AB} = 16.7 Hz, J_{AX} = 7.1 Hz, 1H), 3.01 (dd, J_{AB} = 16.7 Hz, J_{BX} = 6.8 Hz, 1H), 1.88-1.82 (m, 1H), 1.77-1.63 (m, 1H)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.5, 161.8, 138.0, 128.7, 128.1, 128.0, 82.8, 73.8, 72.2, 70.0, 52.6, 46.0, 37.7, 33.0 (diazo carbon not detected); HRMS (ESI, $[M+Na]^+$) for $C_{17}H_{20}N_2O_5SNa$ calcd 387.0985, found: m/z 387.0987.



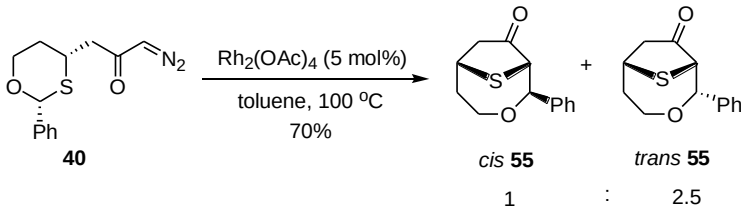
Diazoketoester 53. The aforementioned method was also employed in the synthesis of **53** starting with inseparable *cis* **46** and *trans* **46** isomer (0.073 g, 0.25 mmol), LDA and *tert*-butyl acetate (0.33 mL, 2.50 mmol) followed by diazo exchange with triethylamine (75 μL, 0.50 mmol) and tosyl azide (0.115 g, 0.54 mmol). Column chromatography (silica gel, hexanes:EtOAc 2:1) provided 0.050 g (50%) of **53** as a single isomer as a light yellow oil: R_f 0.31 (hexanes:EtOAc 3:1); IR (thin film) 3028, 2977, 2932, 2904, 2860, 2133, 1710, 1652, 1455, 1394, 1370, 1315, 1258, 1220, 1169, 1135, 1104, 1028, 999 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.33 (m, 4H), 7.29-7.28 (m, 1H), 5.03 (dd, J = 6.3, 3.5 Hz, 1H), 4.61 (d, J_{AB} = 12.2 Hz, 1H), 4.58 (d, J_{AB} = 12.2 Hz, 1H), 4.23 (ddd, J = 12.1, 4.0,

2.3 Hz, 1H), 3.67 (dd, J_{AB} = 10.7 Hz, J_{AX} = 6.3 Hz, 1H), 3.68-3.62 (m, 1H), 3.62-3.60 (m, 1H), 3.58 (dd, J_{AB} = 10.7 Hz, J_{BX} = 3.5 Hz, 1H), 3.02 (app dd, J = 7.0, 2.1 Hz, 2H), 1.88-1.83 (m, 1H), 1.80-1.74 (m, 1H), 1.53 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.0, 160.5, 138.0, 128.7, 128.1, 128.0, 83.8, 82.8, 73.8, 72.2, 70.0, 46.0, 37.7, 33.1, 28.6 (diazo carbon not detected); HRMS (ESI, $[M+Na]^+$) for $C_{20}H_{26}N_2O_5SNa$ calcd 429.1455, found: m/z 429.1455; Anal. Calcd for for $C_{20}H_{26}N_2O_5S$: C, 59.09; H, 6.45; N, 6.89; S, 7.89. Found: C, 59.14; H, 6.49; N, 6.89; S, 7.99.

2.5.2.7. Preparation of sulfur-bridged ethers from diazoketones



Sulfur-briged ether 55. To a refluxing solution of **40** (0.034 g, 0.13 mmol) in DCM (15 mL) was added $Cu(hfacac)_2$ (0.007 g, 0.01 mmol, 10 mol%). After refluxing for 0.5 hour, the starting material was completely consumed. The reaction mixture was cooled to room temperature and concentrated. Column chromatography (silica gel, hexanes:EtOAc 5:1) provided *cis* **55** (0.004 g, 13 %) and *trans* **55** (0.014 g, 47 %) as yellow oils.

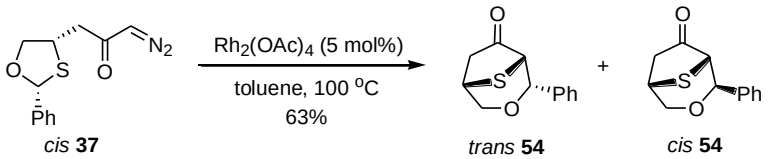


Sulfur-briged ether 55. To a solution of **40** (0.045 g, 0.17 mmol) in toluene (30 mL) at 100 °C was added $Rh_2(OAc)_4$ (0.004 g, 0.09 mmol, 5 mol%). After stirring at 100 °C for 0.5 hour, the starting material was completely consumed. The reaction mixture was cooled to room temperature and concentrated. Column

chromatography (silica gel, hexanes:EtOAc 5:1) provided *cis* **55** (0.008 g, 20 %) and *trans* **55** (0.020 g, 50 %) as yellow oils.

cis **55**: R_f 0.45 (hexanes:EtOAc 4:1); IR (thin film) 3062, 3029, 2945, 2873, 1729, 1469, 1453, 1359, 1279, 1257, 1185, 1148, 1135, 1095, 1077, 1068, 1053 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.47-7.45 (m, 2H), 7.13-7.09 (m, 2H), 7.05-7.01 (m, 1H), 4.98 (s, 1H), 3.67 (ddd, *J* = 14.1, 4.2, 4.2 Hz, 1H), 3.41 (s, 1H), 2.83 (dd, *J* = 7.2, 4.2 Hz, 1H), 2.80 (ddd, *J* = 14.1, 12.3, 1.7 Hz, 1H), 2.26 (dd, *J* = 17.7, 7.2 Hz, 1H), 1.94 (ddd, *J* = 14.6, 12.3, 4.2 Hz, 1H), 1.78 (d, *J* = 17.7 Hz, 1H), 0.98 (dddd, *J* = 14.6, 4.2, 4.2, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 214.5, 142.1, 128.5, 128.4, 126.7, 84.1, 65.4, 62.0, 45.6, 39.3, 38.8; HRMS (EI, $[M]^+$) for $C_{13}H_{14}O_2S$ calcd 234.0715, found: m/z 234.0714.

trans **55**: R_f 0.37 (hexanes:EtOAc 4:1); IR (thin film) 3061, 3029, 2937, 2875, 1731, 1496, 1451, 1352, 1276, 1260, 1195, 1134, 1101, 1071, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.33 (m, 2H), 7.29-7.27 (m, 1H), 7.25-7.24 (m, 2H), 4.86 (s, 1H), 4.46-4.36 (m, 2H), 3.90 (t, *J* = 8.7 Hz, 1H), 3.55 (s, 1H), 2.87 (dd, *J* = 18.6, 8.7 Hz, 1H), 2.58 (d, *J* = 18.6 Hz, 1H), 2.32 (ddd, *J* = 14.2,11.3, 6.5 Hz, 1H), 2.12 (ddd, *J* = 14.2, 8.7, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.8, 139.5, 128.2, 127.8, 125.6, 89.3, 71.1, 57.8, 48.3, 39.5, 39.1; HRMS (EI, $[M]^+$) for $C_{13}H_{14}O_2S$ calcd 234.0715, found: m/z 234.0715.

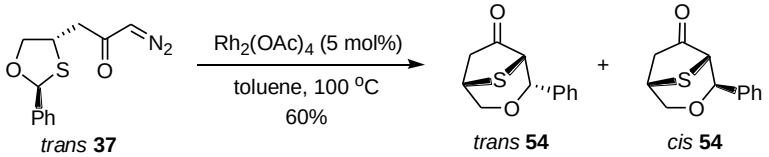


cis **37** → *trans* **54** + *cis* **54**

Major/minor 1.7/1

Sulfur-bridged ether 54. The aforementioned method was also employed in the reaction starting with *cis* **37** (0.021 g, 0.09 mmol) and $Rh_2(OAc)_4$ (0.002 g, 0.005 mmol, 5 mol%) in toluene (20 mL). The same workup procedure and column chromatography (silica gel, hexanes:EtOAc 5:1 (+1 v% Et_3N)) provided a mixture of two diastereomers (0.012 g, 63%) as a yellow oil. Further separation of the

two diastereomers could be employed using column chromatography (DCM:hexanes:EtOAc 10:10:1).



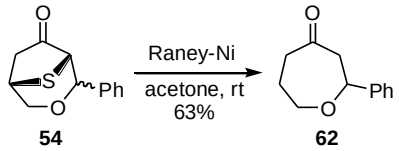
Sulfur-bridged ether 54. The aforementioned method was also employed in the reaction starting with *trans* **37** (0.023 g, 0.09 mmol) and $Rh_2(OAc)_4$ (0.002 g, 0.005 mmol, 5 mol%) in toluene (20 mL). The same workup procedure and column chromatography (silica gel, hexanes:EtOAc 5:1 (+1 v% Et_3N)) provided a mixture of two diastereomers (0.012 g, 60%) as a yellow oil. Further separation of the two diastereomers could be employed using column chromatography (DCM:hexanes:EtOAc 10:10:1).

Major isomer: R_f 0.42 (hexanes:EtOAc 4:1); IR (thin film) 3059, 3028, 2922, 2872, 1741, 1495, 1448, 1401, 1370, 1335, 1297, 1262, 1235, 1194, 1161, 1140, 1088, 1069, 1047, 1031, 1000 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44-7.41 (m, 2H), 7.35-7.32 (m, 3H), 5.35 (d, J = 3.0 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 3.88 (dd, J = 11.5, 2.9 Hz, 1H), 3.87-3.85 (m, 1H), 3.48-3.46 (m, 1H), 2.90 (dd, J_{AB} = 17.5, J_{AX} = 6.4 Hz, 1H), 2.84 (dd, J_{AB} = 17.5, J_{BX} = 0.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.8, 138.1, 128.9, 127.8, 126.7, 74.7, 67.9, 53.9, 43.4, 41.2; HRMS (ESI, $[M+Na]^+$) for $C_{12}H_{12}O_2SNa$ calcd 243.0450, found: m/z 243.0450.

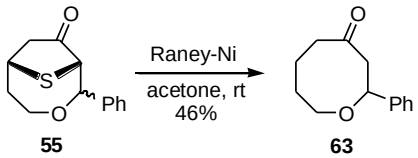
Minor isomer: R_f 0.42 (hexanes:EtOAc 4:1); IR (thin film) 3062, 3030, 2917, 2864, 1737, 1494, 1452, 1401, 1367, 1349, 1294, 1265, 1214, 1163, 1138, 1124, 1087, 1029, 1010, 976 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.33 (m, 2H), 7.32-7.27 (m, 3H), 5.06 (s, 1H), 4.47 (d, J = 11.7 Hz, 1H), 4.27 (dd, J = 11.7, 3.2 Hz, 1H), 3.64-3.62 (m, 1H), 3.4 (s, 1H), 2.83 (dd, J_{AB} = 17.4, J_{AX} = 6.5 Hz, 1H), 2.76 (dd, J_{AB} = 17.4, J_{BX} = 0.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.4,

139.4, 128.8, 128.6, 125.9, 83.8, 74.2, 54.8, 43.1, 40.3; HRMS (EI, $[M]^+$) for $C_{12}H_{12}O_2S$ calcd 220.0558, found: m/z 220.0556.

2.5.2.8. Desulfurization of sulfur-bridged ethers



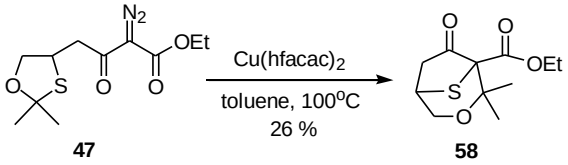
Ketone 62. To a suspension of Raney nickel 4200 (Aldrich; 100 g suspended in 100 mL water, ~2 g) in acetone (5 mL) was added the mixture of *cis* **54** and *trans* **54** isomers (0.022 g, 0.10 mmol, 5:1) at room temperature. This resulting mixture was stirred for 0.5 h until starting material was totally consumed and then filtered via quantitative filter paper (Waterman; #2). The Raney nickel was washed with acetone. The combined mixture was concentrated. The residue was redissolved with DCM (30 mL), washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes:EtOAc 3:1) gave **62** (0.012 g, 63%) as a colorless oil: R_f 0.34 (hexanes:EtOAc 3:1); IR (thin film) 3063, 3031, 2948, 2856, 1704, 1496, 1452, 1440, 1364, 1323, 1281, 1265, 1203, 1157, 1106, 1048, 1021 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.33 (m, 4H), 7.30-7.27 (m, 1H), 4.75 (dd, J = 10.7, 2.3 Hz, 1H), 4.34-4.30 (m, 1H), 3.74 (ddd, J = 13.0, 10.8, 2.3 Hz, 1H), 3.02 (dd, J = 16.6, 10.7 Hz, 1H), 2.86-2.84 (m, 1H), 2.84-2.79 (m, 1H), 2.74-2.69 (m, 1H), 2.10-2.00 (m, 1H), 1.98-1.89 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.8, 142.3, 128.9, 128.0, 125.8, 79.0, 72.4, 54.0, 43.2, 27.0; HRMS (EI, M^+) for $C_{12}H_{14}O_2$ calcd 190.0994, found: m/z 190.0997.



Ketone 63. The aforementioned method was also employed in the synthesis of **63** starting with **55** (0.015 g, 0.06 mmol) and Raney nickel 4200 (Aldrich; 100 g

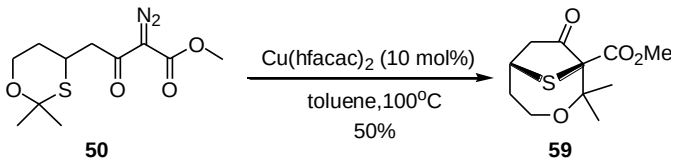
suspended in 100 mL water, ~2 g). Column chromatography (silica gel, hexanes:EtOAc 3:1) provided 0.006 g (46%) **63** as a colorless oil: R_f 0.37 (hexanes:EtOAc 3:1); IR (thin film) 3031, 2933, 2884, 1698, 1495, 1452, 1345, 1330, 1312, 1284, 1258, 1212, 1138, 1097, 1074, 1052, 1024 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.34 (m, 4H), 7.30-7.27 (m, 1H), 4.75 (dd, *J* = 11.2, 2.6 Hz, 1H), 4.07 (ddd, *J* = 13.1, 4.6, 4.6 Hz, 1H), 3.38 (ddd, *J* = 13.1, 10.0, 3.4 Hz, 1H), 3.18 (dd, *J* = 11.2, 11.2 Hz, 1H), 2.71 (ddd, *J* = 14.6, 7.6, 2.9 Hz, 1H), 2.55 (dd, *J* = 11.2, 2.6 Hz, 1H), 2.43 (ddd, J = 14.6, 11.3, 3.1 Hz, 1H), 2.36-2.26 (m, 1H), 2.00-1.89 (m, 2H), 1.66-1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.9, 142.3, 128.8, 128.0, 125.9, 82.0, 69.4, 51.4, 43.9, 29.7, 22.0; HRMS (EI, M^+) for $C_{13}H_{16}O_2$ calcd 204.1150, found: m/z 204.1146.

2.5.2.9. Preparation of sulfur-bridged ethers from diazoketoesters



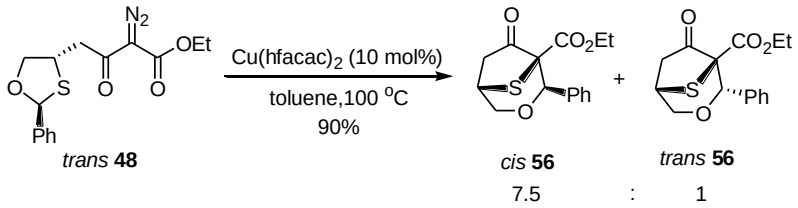
47 **58**

Sulfur-bridged ether 58. To a solution of **47** (0.014 g, 0.05 mmol) in toluene (10 mL) at 100 °C was added $Cu(hfacac)_2$ powder (0.003 g, 0.005 mmol, 10 mol%). After stirring at 100 °C for 50 minutes, the starting material was completely consumed. The reaction mixture was cooled to room temperature and concentrated. Column chromatography (silica gel, hexanes:EtOAc 5:1) provided **58** (0.003 g, 26%) as a yellow oil: R_f 0.32 (hexanes:EtOAc 4:1); IR (thin film) 3281, 3209, 3145, 3100, 3056, 1667, 1637, 1609, 1555, 1498, 1443, 1408, 1332, 1255, 1204, 1067 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.31 (d, *J* = 11.8 Hz, 1H), 4.22-4.16 (m, 2H), 3.75 (dd, *J* =11.8, 3.0 Hz, 1H), 3.45 (dd, *J* = 6.2, 3.0, 1H), 2.91 (dd, *J* = 17.4, 6.2 Hz, 1H), 2.70 (d, *J* = 17.4 Hz, 1H), 1.63 (s, 3H), 1.49 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0, 166.3, 77.5, 68.7, 67.3, 62.2, 43.4, 39.6, 25.6, 20.3, 14.2; HRMS (ESI, $[M+Na]^+$) for $C_{11}H_{16}O_4SNa$ calcd 267.0662, found: m/z 267.0661.



50 **59**

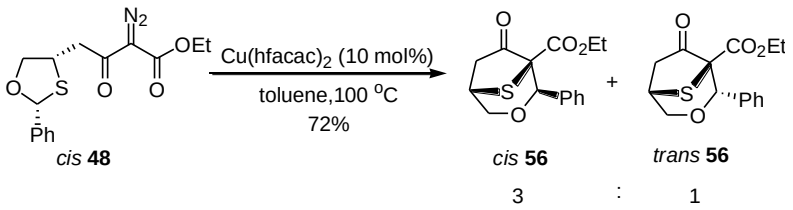
Sulfur-bridged ether 59. The aforementioned method was also employed in the reaction starting with **50** (0.016 g, 0.06 mmol) and $Cu(hfacac)_2$ (0.003 g, 0.006 mmol, 10 mol%) in toluene (10 mL). The same workup procedure and column chromatography (silica gel, hexanes:EtOAc 3:1 (+1 v% Et_3N)) provided **59** (0.007 g, 50%) as a yellow oil. R_f 0.43 (hexanes:EtOAc 3:1); IR (thin film) 3014, 3000, 2950, 2936, 2896, 2861, 1732, 1694, 1477, 1452, 1433, 1387, 1379, 1366, 1345, 1315, 1296, 1267, 1229, 1202, 1187, 1131, 1094, 1048, 1029, 1011 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.21 (ddd, *J* = 13.5, 8.7, 4.4 Hz, 1H), 3.72 (s, 3H), 3.68-3.64 (m, 1H), 3.62 (ddd, *J* = 13.5, 4.8, 4.8 Hz, 1H), 3.08 (dd, *J* = 18.2, 8.4 Hz, 1H), 2.62 (d, *J* = 18.2 Hz, 1H), 2.11-2.07 (m, 1H), 1.99-1.96 (m, 1H), 1.52 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.6, 167.5, 81.3, 73.6, 61.7, 53.3, 49.3, 38.4, 37.3, 24.6, 24.0; HRMS (ESI, $[M+Na]^+$) for $C_{11}H_{16}O_4SNa$ calcd 267.0662, found: m/z 267.0663.



trans **48** *cis* **56** : *trans* **56**

7.5 : 1

Sulfur-bridged ether 56. The aforementioned method was also employed in the reaction starting with *trans* **48** (0.021 g, 0.07 mmol) and $Cu(hfacac)_2$ (0.003 mg, 0.007 mmol, 10 mol%) in toluene (10 mL). The same workup procedure and column chromatography (silica gel, hexanes:EtOAc 5:1 (+1 v% Et_3N)) provided *trans* **56** (0.002 g, 11%) and *cis* **56** (0.015 g, 79%) as yellow oils.



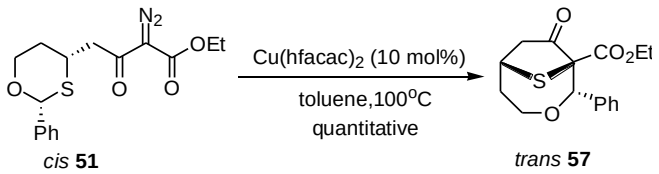
cis **48** *cis* **56** : *trans* **56**

3 : 1

Sulfur-bridged ethers 56. The aforementioned method was also employed in the reaction starting with *cis* **48** (0.038 g, 0.12 mmol) and $Cu(hfacac)_2$ (0.006 g, 0.012 mmol, 10 mol%) in toluene (10 mL). The same workup procedure and column chromatography (silica gel, hexanes:EtOAc 5:1 (+1 v% Et_3N)) provided *trans* **56** (6 mg, 17%) and *cis* **56** (19 mg, 55%) as yellow oils.

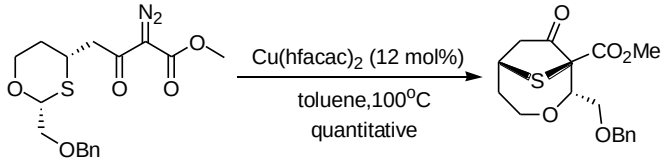
trans **56**: R_f 0.44 (hexanes:EtOAc 5:1); IR (thin film) 3062, 2988, 2954, 2937, 2916, 2877, 1741, 1717, 1602, 1585, 1497, 1466, 1447, 1403, 1386, 1365, 1290, 1261, 1244, 1187, 1140, 1098, 1019, 1004 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.32 (m, 5H), 5.71 (s, 1H), 4.35-4.28 (m, 2H), 4.04 (dd, *J* = 11.7, 0.6 Hz, 1H), 3.73 (dd, *J* = 11.7, 3.0 Hz, 1H), 3.51 (ddd, *J* = 6.0, 3.0, 0.6 Hz, 1H), 3.05 (dd, *J* = 17.4, 6.0 Hz, 1H), 2.88 (dd, *J* = 17.4, 0.6 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2, 166.3, 135.9, 128.3, 128.0, 127.9, 76.2, 66.5, 65.6, 62.8, 43.3, 39.4, 13.9; HRMS (ESI, $[M+Na]^+$) for $C_{15}H_{16}O_4SNa$ calcd 315.0662, found: m/z 315.0665.

cis **56**: R_f 0.35 (hexanes:EtOAc 5:1); IR (thin film) 3033, 2982, 2921,2869, 1766, 1720, 1700, 1495, 1454, 1400, 1368, 1294, 1252, 1142, 1086, 1077, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.27 (m, 5H), 5.28 (s, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 4.24 (dd, *J* = 11.6, 2.9 Hz, 1H), 4.04-3.94 (m, 2H), 3.62 (dd, *J* = 6.3, 2.9 Hz, 1H), 3.07 (dd, *J* = 17.5, 6.3 Hz, 1H), 2.92 (d, *J* = 17.5 Hz, 1H), 1.05 (t, *J* = 14.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.7, 165.1, 137.3, 128.9, 128.1, 127.5, 87.3, 73.8, 63.3, 61.8, 45.0, 38.5, 13.7; HRMS (ESI, $[M+Na]^+$) for $C_{15}H_{16}O_4SNa$ calcd 315.0662, found: m/z 315.0663.



cis **51** *trans* **57**

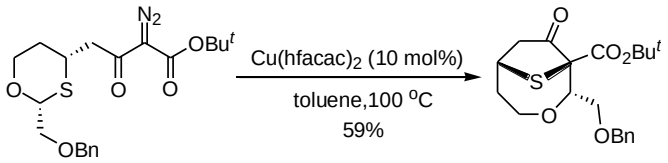
Sulfur-bridged ether 57. To a solution of *cis* **51** (0.053 g, 0.16 mmol) in toluene (15 mL) at 100 °C was added powder $Cu(hfacac)_2$ (0.007 g, 0.02 mmol, 10 mol%). After stirring at 100 °C for 1 hour, the starting material was completely consumed. The reaction mixture was cooled to room temperature and concentrated. Column chromatography (silica gel, hexanes:EtOAc 4:1) provided *trans* **57** (0.048 g, 100 %) as a yellow oil: R_f 0.22 (hexanes:EtOAc 4:1); IR (thin film) 3062, 3033, 2981, 2950, 2881, 1753, 1727, 1658, 1494, 1470, 1455, 1398, 1365, 1299, 1277,1230, 1174, 1133, 1101, 1076, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2H), 7.32-7.27 (m, 3H), 5.21 (s, 1H), 4.15 (app dt, *J* = 13.7, 4.0 Hz, 1H), 3.82-3.76 (m, 2H), 3.66 (ddd, *J* = 7.2, 3.5, 3.5 Hz, 1H), 3.37 (ddd, *J* = 13.7, 10.9, 1.9 Hz, 1H), 3.14 (dd, *J* = 17.4, 7.2 Hz, 1H), 2.64 (d, *J* = 17.4 Hz, 1H), 2.44-2.41 (m, 1H), 1.91 (br d, *J* = 13.2 Hz, 1H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.4, 164.9, 137.9, 128.7, 128.0, 127.9, 87.0, 74.1, 65.7, 62.4, 47.3, 38.6, 35.9, 13.5; HRMS (ESI, $[M+Na]^+$) for $C_{16}H_{18}O_4SNa$ calcd 329.0818, found: m/z 329.0816.



52 **60**

Sulfur-bridged ether 60. The aforementioned method was also employed in the synthesis of **60** starting with **52** (0.017 g, 0.05 mmol) and $Cu(hfacac)_2$ (0.003 g, 0.006 mmol, 12 mol%). Column chromatography (silica gel, hexanes:EtOAc 2:1) provided 0.016 g (100%) of **60** as a yellow oil: R_f 0.32 (hexanes:EtOAc 2:1); IR (thin film) 3063, 3030, 2951, 1750, 1729, 1533, 1497, 1454, 1435, 1398, 1366, 1240, 1189, 1111, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.31 (m, 4H),

7.29-7.27 (m, 1H), 4.64 (dd, J = 6.5, 4.8 Hz, 1H), 4.52 (d, J_{AB} = 12.0 Hz, 1H), 4.48 (d, J_{AB} = 12.0 Hz, 1H), 4.19 (ddd, J = 11.3, 6.8, 4.4 Hz, 1H), 3.83 (dd, J = 10.6, 6.5 Hz, 1H), 3.65 (ddd, J = 7.8, 5.6, 1.8 Hz, 1H), 3.61 (dd, J = 10.6, 4.8 Hz, 1H), 3.59 (s, 3H), 3.50 (ddd, J = 13.7, 6.8, 3.8 Hz, 1H), 3.07 (dd, J = 17.7, 7.8 Hz, 1H), 2.60 (d, J = 17.7 Hz, 1H), 2.23-2.15 (m, 1H), 1.93-1.87 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.2, 166.0, 138.0, 128.6, 128.1, 128.0, 81.7, 73.5, 71.0, 68.9, 63.8, 53.5, 48.3, 38.6, 36.8; HRMS (ESI, $[M+Na]^+$) for $C_{17}H_{20}O_5SNa$ calcd 359.0924, found: m/z 359.0923.



53 **61**

Sulfur-bridged ether 61. The aforementioned method was also employed in the synthesis of **61** starting with **53** (0.037 g, 0.09 mmol) and $Cu(hfacac)_2$ (0.005 g, 0.01 mmol, 10 mol%). Column chromatography (silica gel, hexanes:EtOAc 3:1) provided 0.020 g (59%) of **61** as a colorless oil: R_f 0.31 (hexanes:EtOAc 3:1); IR (thin film) 3063, 3030, 2978, 2935, 2880, 1747, 1724, 1497, 1474, 1455, 1394, 1369, 1250, 1155, 1102, 1037 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.33 (m, 4H), 7.30-7.27 (m, 1H), 4.63 (dd, J = 7.5, 3.2 Hz, 1H), 4.59 (d, J_{AB} = 12.0 Hz, 1H), 4.53 (d, J_{AB} = 12.0 Hz, 1H), 4.23 (ddd, J = 13.7, 7.5, 4.4 Hz, 1H), 3.85 (dd, J = 10.8, 7.5 Hz, 1H), 3.64 (ddd, J = 7.8, 5.7, 1.8 Hz, 1H), 3.56 (dd, J = 10.8, 3.2 Hz, 1H), 3.51 (ddd, J = 13.7, 6.4, 4.1 Hz, 1H), 3.04 (dd, J = 17.7, 7.8 Hz, 1H), 2.57 (d, J = 17.7 Hz, 1H), 2.20-2.14 (m, 1H), 1.95-1.89 (m, 1H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.2, 164.4, 138.2, 128.7, 128.0, 128.0, 83.9, 81.3, 73.3, 71.6, 68.3, 63.3, 48.2, 38.7, 36.8, 27.9; HRMS (ESI, $[M+Na]^+$) for $C_{20}H_{26}O_5SNa$ calcd 401.1393, found: m/z 401.1393.

2.6. References

1. Wittig, G.; Geissler, G. *Justus Liebigs Ann. Chem.* **1953**, *580*, 44.

2. Li, A. H.; Dai, L. X.; *Chem. Rev.* **1997**, *97*, 2341.
3. Johnson, A. W. *Ylide Chemistry;* Academic Press: New York, **1966**, p 306.
4. Clark, J. K. In *Nitrogen, Oxygen and Sulfur Ylide Chemistry*; Clark, J. K., Ed.; Oxford University Press: New York, **2002**; p 1-113.
5. Craig, D. P.; Magnusson, E. A. *ibid.* **1956**, 4895.
6. Ingold, C. K.; Jessop, J. A. *J. Chem. Soc.* **1930**, 713.
7. Johnson, A. W.; LaCount, R. B. *J. Am. Chem. Soc*. **1961**, *83*, 417.
8. Li, A.; Dai, L.; Hou, X.; Huang, Y.; Li, F. *J. Org. Chem.* **1996**, *61*, 489.
9. Trost, B. M.; Hammen, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 962.
10. Padwa, A.; Gasdaska, J. R. *J. Org. Chem.* **1986**, *51*, 2857.
11. Padwa, A.; Gasdaska, J. R. *Tetrahedron* **1988**, *44*, 4147.
12. Cohen, T.; Kosarych, G. R.; Suzuki, K.; Yu, L. *J. Org. Chem.* **1985**, *50*, 2965.
13. Ando, W.; Kondo. S.; Nakayama, K.; Ichibori, K.; Kohoda, H.; Yamato, H.; Imai, I.; Nakaido, S.; Migita, T. *J. Am. Chem. Soc.* **1972**, *94*, 3870.
14. Ando, W.; Yagihara, T.; Tozune, S.; Imai, I.; Suzuki, J.; Toyama, T.; Nakaido, S.; Migita, T. *J. Org. Chem.* **1972**, *37*, 1721.
15. Doyle, M. P.; McKervey. M. A.; Ye, T. *Mordern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, **1997**, p 356.
16. Sato, Y.; Davies, H. M. L.; Ando, W.; Matsuyama, H. In *Nitrogen, Oxygen and Sulfur Ylide Chemistry;* Clark, J. K., Ed.; Oxford University Press: New York, **2002**, p 153-179.
17. Ye, T.; García, C. F., McKervey, M. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1373.
18. Kondo, K.; Ojima, I. *J. Chem. Soc., Chem. Commun.* **1972**, 860.
19. Doyle, M. P.; Griffin, J. H.; Chinn, M. S.; van Leusen, D. *J. Org. Chem.* **1984**, *49*, 1917.
20. Aggarwal, V. K.; Abdel-Rahman, H.; Fan, L.; Jones, R. V. H.; Standen, M. C. H. *Chem. Eur. J.* **1996**, *2*, 1024.
21. Tester, R. W.; West, F. G. *Tetrahedron Lett.* **1998**, *39*, 4631.

22. Murphy, G. K. *Oxonium Ylides in the Synthesis of Fused, Medium-Sized Rings. PhD Thesis The University of Alberta*, Alberta, 2007
23. Busqué, F.; de March, P.; Figueredo, M.; Font, J.; González, L. *Eur. J. Org. Chem.* **2004**, 1492.
24. Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron*, **1997**, *38*, 2685.
25. Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1993**, *115*, 30.
26. Sigmaaldrich Technical Bulletin AL-180 available at *www.**sigmaaldrich**.com*.

Chapter 3

An Approach to the Formal Synthesis of (+)-Laurencin

3.1. Introduction

The marine natural product (+)-laurencin is an eight-membered halogenated ether isolated from *Laurencia glandilifera* by Irie and Masamune.[1,2] It can be classified as a C_{15} bromoether (Figure 3.1), and is an example of a C_{15} nonterpenoid.[3] The structure was determined on the basis of chemical degradation, spectroscopic analysis and X-ray crystallography.[4,5] Though this molecule possesses little to no known biological activity, it has attracted the attention of many organic chemists around the world because of the notable challenge in assembling medium ring ethers. Masamune and co-workers finished the first racemic synthesis of this natural product,[6-8] and the Murai group finished the first asymmetric synthesis in 1992.[9] To date, it remains an attractive target for organic syntheses. A total of ten research groups have published total syntheses or formal syntheses of this molecule, employing ring-expansion, cyclization, ring-closing metathesis and alkylation. We have also investigated the formal synthesis of (+)-laurencin by utilizing the methodology presented in Chapter 2, entailing the Stevens [1,2]-shift of sulfur ylides derived from mixed monothioacetals, and these studies will be discussed in this chapter.

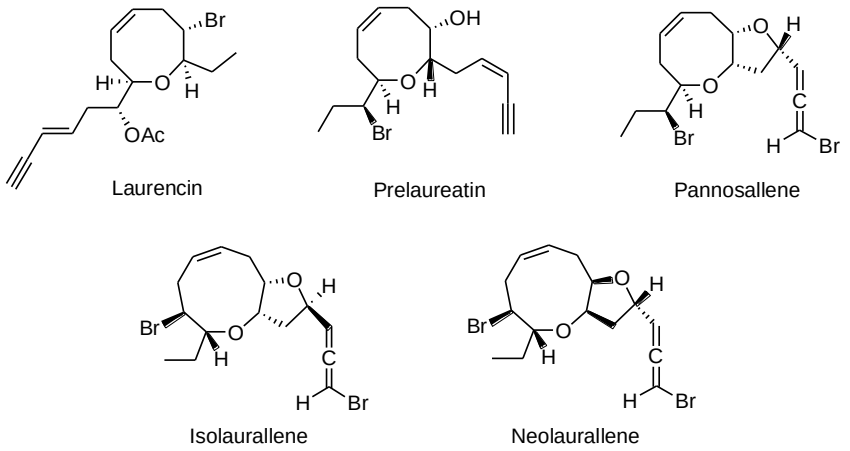
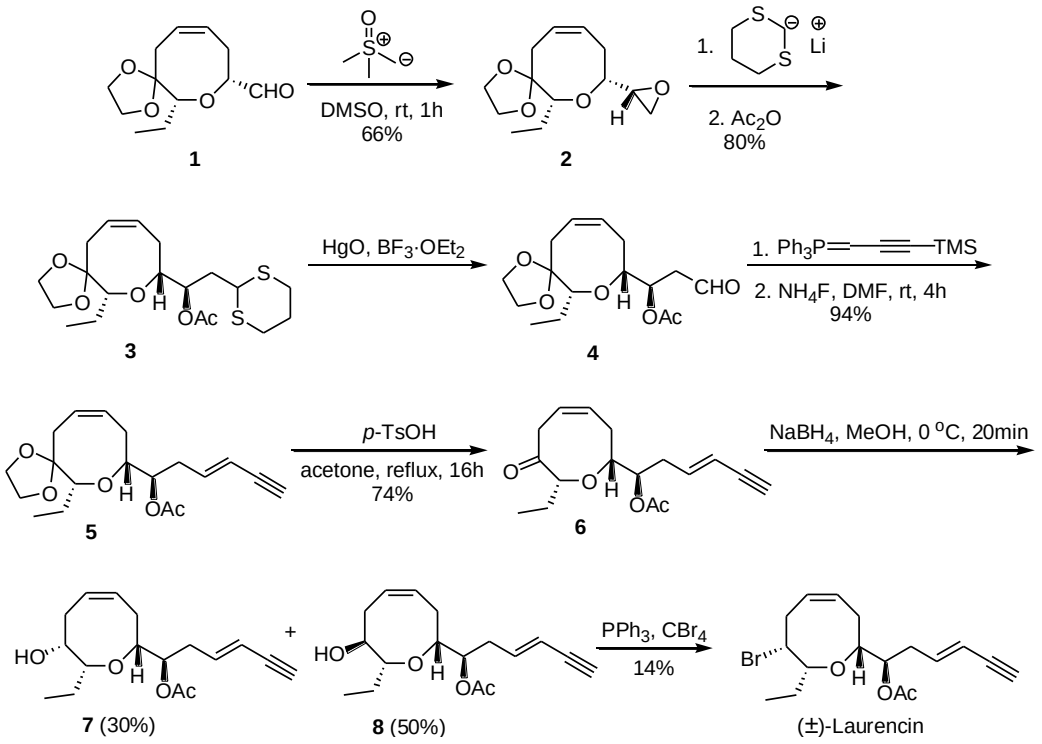


Figure 3.1: Examples of C_{15} bromoethers.

3.2. Background

3.2.1. The Masamune racemic synthesis of (±)-laurencin

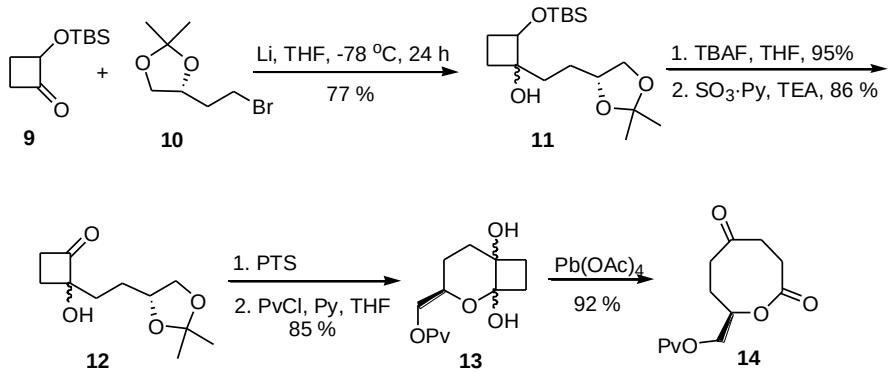
The original racemic synthesis of (±)-laurencin was completed by Masamune and coworkers in 1977 (Scheme 3.1).[6] The synthesis started with compound **1**, which was made by the same group in 1975.[10] When treated with dimethyloxosulfonium methylide, the compound was converted into epoxide **2** in 66% yield. Treatment with 2-lithio-1,3-dithiane yielded 2-(2-hydroxyalkyl)-1,3-dithiane **3**, which was protected as the acetate. Deprotection of the 1,3-dithiane group afforded the aldehyde **4**, which then underwent Wittig reaction followed by removal of the terminal TMS group with fluoride to afford the desired enyne **5** in 94% yield. Acetal hydrolysis under acid conditions gave ketone **6** in 74% yield, which underwent hydride reduction to afford a mixture of diastereomers **7** and **8** in 50% and 30% yields. Bromination of alcohol **8** using triphenylphosphine and carbon tetrabromide provided the final product (±)-laurencin in 14% yield.



Scheme 3.1: The Masamune racemic synthesis of (±)-laurencin.

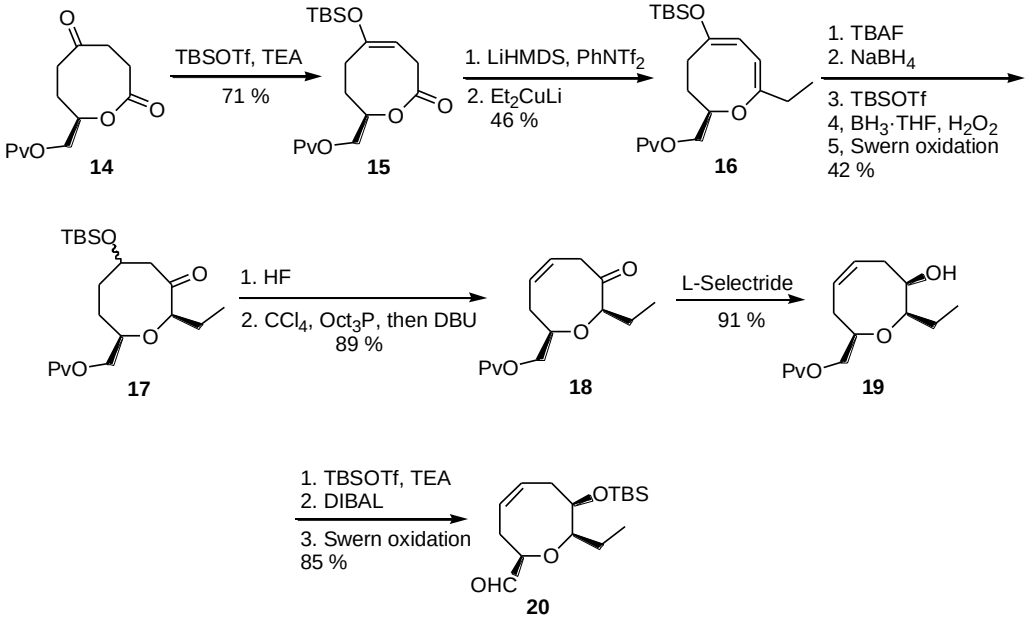
3.2.2. The Murai synthesis of (+)-laurencin

The first asymmetric total synthesis of (+)-laurencin to appear in the literature was from Murai and co-workers.[9] To construct the eight-membered ether, they utilized a novel ring-expansion reaction of a four-membered ring fused to a tetrahydropyran. As shown in Scheme 3.2, treatment of **9** and **10** in the presence of Li in THF at -78°C provided **11** in 77 % yield. Deprotection and oxidation of **11** afforded **12** in 82 % yield. Acid treatment of **12** followed by the selective protection of the primary alcohol gave **13** in 85 % yield. Oxidation of **13** with $Pb(OAc)_4$ provided the desired eight-membered lactone **14** in 92 % yield.



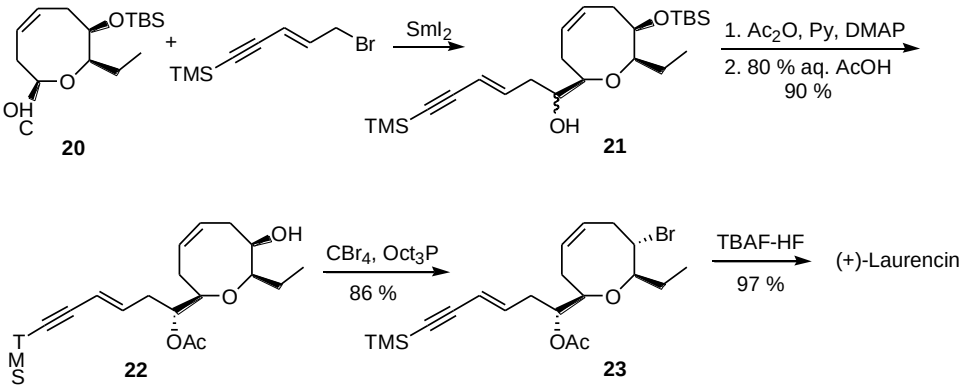
Scheme 3.2: The Murai total synthesis of (+)-laurencin, part 1.

Treatment of **14** with TBSOTf and Et_3N afforded **15** (Scheme 3.3). Lactone **15** was treated with LiHMDS and $PhNTf_2$ to give the corresponding dienol triflate, which was coupled with Et_2CuLi to provide ethyl derivative **16**. Dienol ether **16** underwent a 5-step sequence to give compound **17**. Deprotection and elimination reaction afforded compound **18**, which was then reduced to give the compound **19**. The secondary alcohol of **19** was protected, then the primary pivalate was deprotected and oxidized to provide aldehyde **20**.



Scheme 3.3: The Murai total synthesis of (+)-laurencin, part 2.

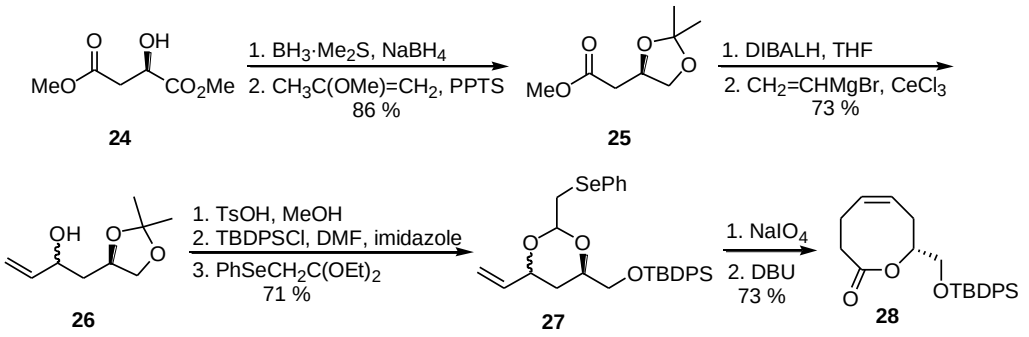
Upon treatment with (3E)-5-bromo-3-penten-1-ynyltrimethylsilane and SmI_2, compound **20** was transformed into a 55:45 separable mixture of *α*–**21** and *β*–**21** (Scheme 3.4). The undesired *β*–**21** could be oxidized and reduced to give additional *α*–**21**. Acetylation of *α*–**21** and desilylation afforded alcohol **22** which was then treated with CBr_4 in the presence of Oct_3P to give bromide **23**. Removal of the terminal silyl group then gave (+)-laurencin.



Scheme 3.4: The Murai total synthesis of (+)-laurencin, part 3.

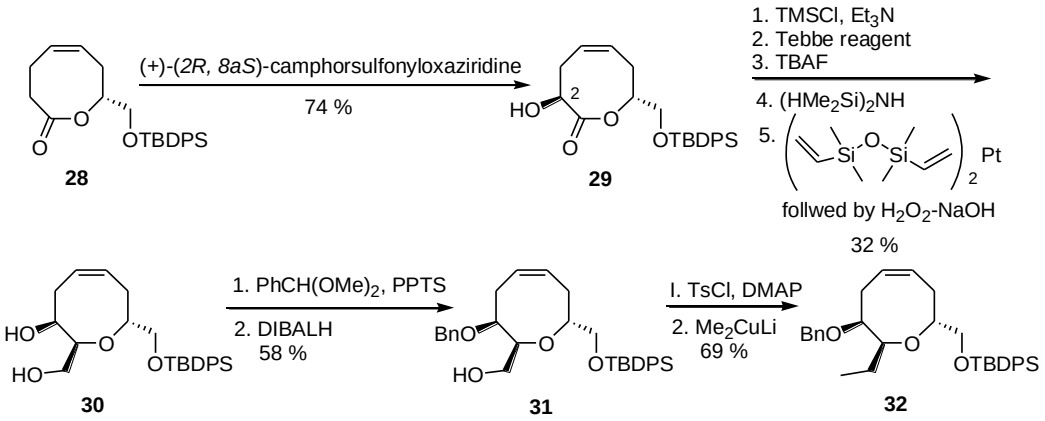
3.2.3. The Holmes synthesis of (+)-laurencin

In 1993, Holmes and co-workers published the total synthesis of (+)-laurencin.[11,12] They utilized the Claisen rearrangement to construct the eight-membered ether motif. Selective reduction of malic diester **24** gave a diol compound, which was then protected as acetonide **25** (Scheme 3.5). Half reduction of the ester to the aldehyde, followed by addition of vinylmagnesium bromide in the presence of cerium(III) chloride provided allylic alcohol **26** as a 1: 1 mixture of diastereoisomers. Acetonide removal followed by selective protection of the primary alcohol gave a monoprotected triol, which was then treated with phenylselenoacetaldehyde diethyl acetal to afford the dioxan **27** as a mixture of diastereoisomers. Acetal **27** was then oxidized to give the selenoxide, which was then treated with DBU in reflux xylene to provide the Claisen rearrangement product **28** in 73 % yield.



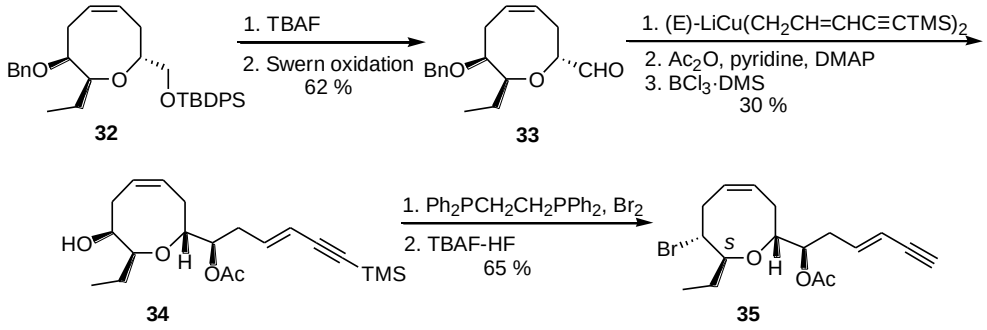
Scheme 3.5: The Holmes total synthesis of (+)-laurencin, part 1.

The synthesis for (+)-laurencin needed a *R* configuration at C_2. Unfortunately, hydroxylation of the potassium enolate of **28** with (*2R, 8aS*)-camphorsulfonyloxaziridine afforded **29** with *S* configuration in 74 % yield (Scheme 3.6). (*2S, 8aR*)-Camphorsulfonyloxaziridine provided *R* alcohol in 7.5 % yield and *S* alcohol in 1.5 % yield. Later in 1997, they improved the yield of the desired alcohol to 26 % but not as the exclusive product.[13] Alcohol **29** was silylated and subjected to Tebbe methylenation. The TMS group was replaced with Me_2SiH, followed by Pt-catalyzed intramolecular hydrosilylation and oxidation to give **30** and its *2β*-hydroxymethyl epimer in a 3.5: 1 ratio. Then the diol was transformed to corresponding benzylidene acetal, which was treated with DIBALH to give the product **31**. Intermediate **31** underwent tosylation and coupling reaction to afford compound **32**.



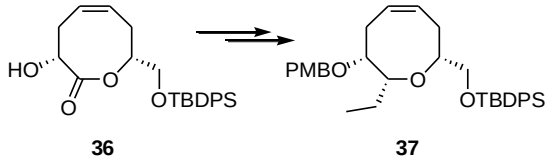
Scheme 3.6: The Holmes total synthesis of (+)-laurencin, part 2.

Deprotection of the silyl ether **32** and Swern oxidation gave the aldehyde **33** (Scheme 3.7). Upon treatment with (*E*)-LiCu(CH_2CH=CHC≡$CSiMe_3$), **33** was converted into a 55:45 separable mixture of diastereoisomers. The minor isomer could be recycled to the required isomer by an oxidation-reduction sequence. The desired isomer was then acetylated followed by debenzylation to provide compound **34**. After bromination and desilylation reaction, **34** was transformed into compound **35**, whose C_1 position existed in the unnatural S configuration rather than the R configuration found in (+)-laurencin.



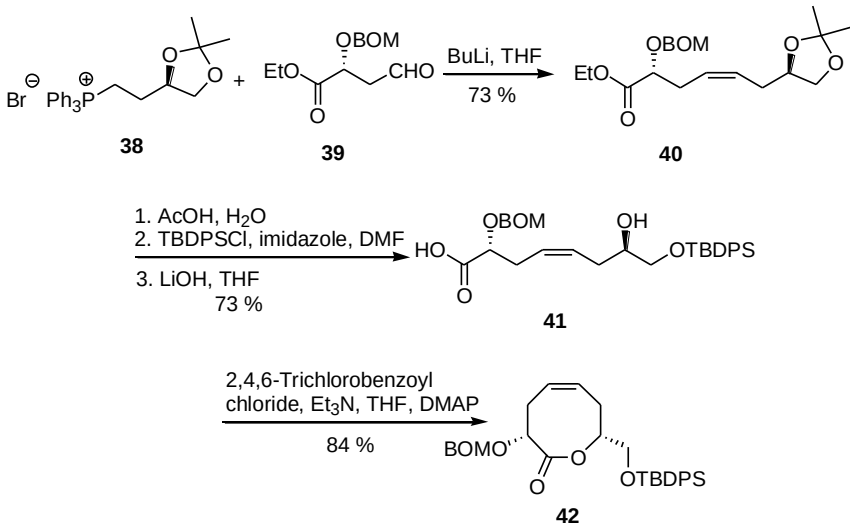
Scheme 3.7: The Holmes total synthesis of (+)-laurencin, part 3.

The required (*R)*-alcohol **36** could be obtained through the same hydroxylation procedure described previously, utilizing utilizing (*2S, 8aR*)-camphorsulfonyloxaziridine instead of (*2R, 8aS*)-camphorsulfonyloxaziridine. Hydroxylactone **36** could be coverted into oxocane **37** (Scheme 3.8), which is identical (except the oxygen protecting groups) to an advanced intermediate used by Murai in the synthesis of (+)-laurencin.



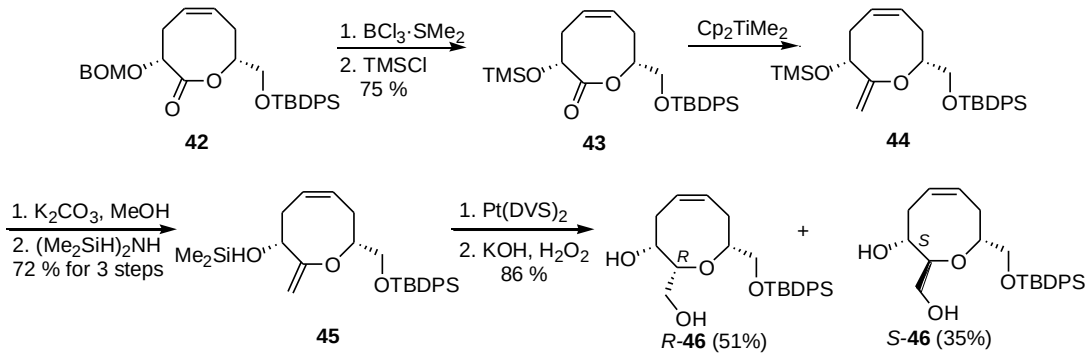
Scheme 3.8: The Holmes total synthesis of (+)-laurencin, part 4.

In 1997, the Holmes group reported an alternative route to the elusive (*R*)-alcohol.[13] Compound **40** was made from Wittig reaction of phosphonium salt **38** and aldehyde **39** (Scheme 3.9), both available from (*R*)-malic acid. Acetonide removal followed by the selective protection of the primary alcohol and saponification gave the compound **41**, which was then treated under the Yamaguchi lactonization conditions to afford the required lactone **42**.



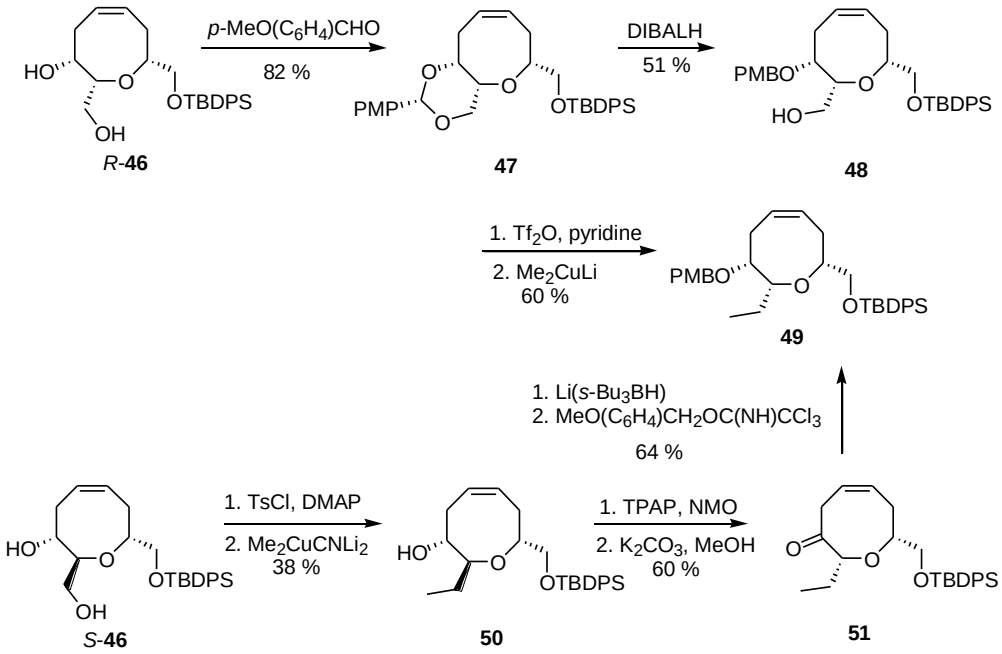
Scheme 3.9: The Holmes alternative route to total synthesis of (+)-laurencin, part 1.

Deprotection of the BOM ether followed by the trimethylsilylation of the hydroxylactones afforded compound **43** (Scheme 3.10), which was then methylenated using the Petasis reagent[14,15] to provide the enol ether **44**. Compound **44** was converted into silane **45**, which was then hydrosilylated and oxidized to provide the diols *R*-**46** and *S*-**46** as a 58:42 mixture. Both isomers could be utilized to finish the total synthesis of (+)-laurencin.



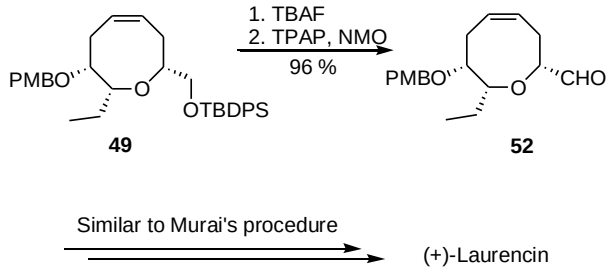
Scheme 3.10: The Holmes alternative route to total synthesis of (+)-laurencin, part 2.

Conversion of the diol *R*-**46** into the corresponding *p*-methoxybenzylidene acetal **47** followed by DIBALH reduction afforded the primary alcohol **48** (Scheme 3.11). Compound **48** was then converted into the corresponding triflate, which was treated with Me_2CuLi to give **49** in 60 % yield. On the other hand, the diol *S*-**46** was monotosylated and coupled with methyl group to afford compound **50**. Oxidation and epimerization provided ketone **51**, which was then reduced with L-Selectride and protected with PMB group to yield **49**.



Scheme 3.11: The Holmes alternative route to total synthesis of (+)-laurencin, part 3.

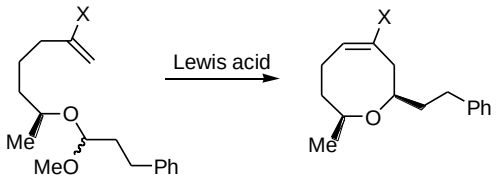
The primary silyl ether of **49** was deprotected and oxidized to give the aldehyde **52** (Scheme 3.12). Then by using the similar procedure as Murai's,[9] the pentenynyl side chain and the bromide were introduced to finish the total synthesis of (+)-laurencin.



Scheme 3.12: The Holmes alternative route to total synthesis of (+)-laurencin, part 4.

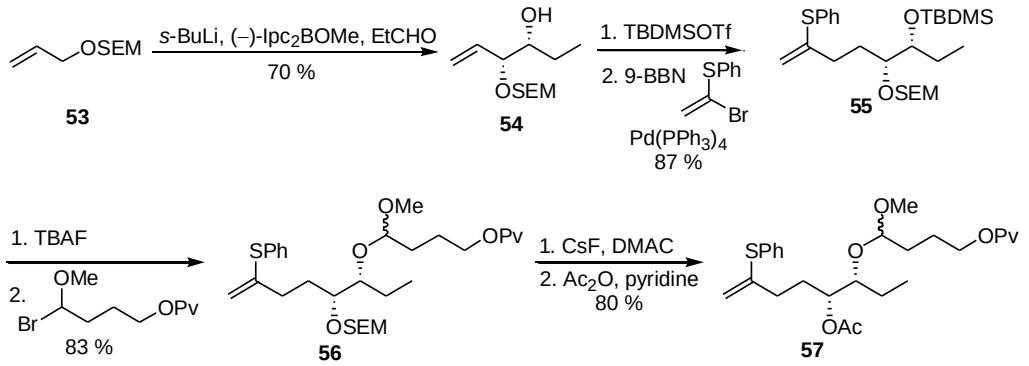
3.2.4. Overman synthesis of (+)-laurencin

In 1995, Overman and co-workers published the total synthesis of (+)-laurencin by utilizing direct acetal-vinyl sulfide cyclization to construct the oxocene ring.[16] Their synthesis was stimulated by the investigation of the reaction showed in Scheme 3.13.[17] When the 5-substituent was changed from Me_3Si to PhS, the yield of cyclization increased dramatically.



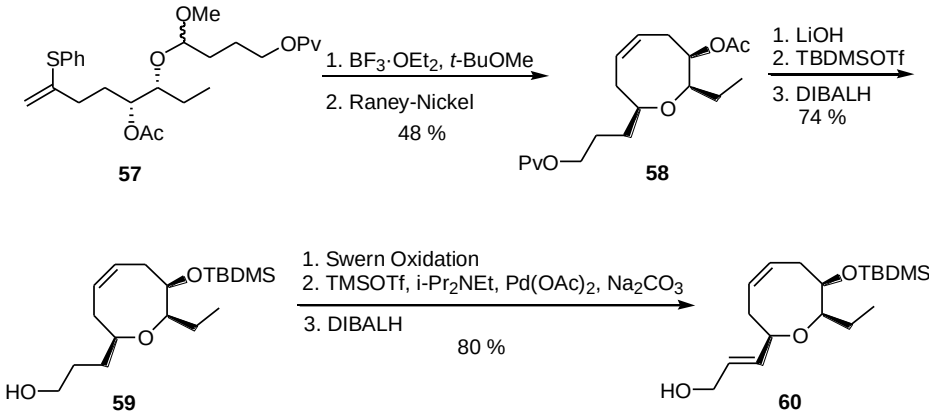
Scheme 3.13: The Overman total synthesis of (+)-laurencin, part 1.

Asymmetric allylboration of propanal using SEM-protected allyl alcohol **53** provided **54** in 70 % yield and 95 % ee (Scheme 3.14). Silyl protection, hydroboration, and a (*B*)-alkyl Suzuki coupling reaction gave vinyl sulfide **55**. Compound **55** was deprotected with TBAF to afford the monoprotected diol, which was then treated with a functionalized α–bromoether to yield the mixed acetal **56**. Removing the SEM group and protecting with acetyl group gave **57**, which was ready for cyclization.



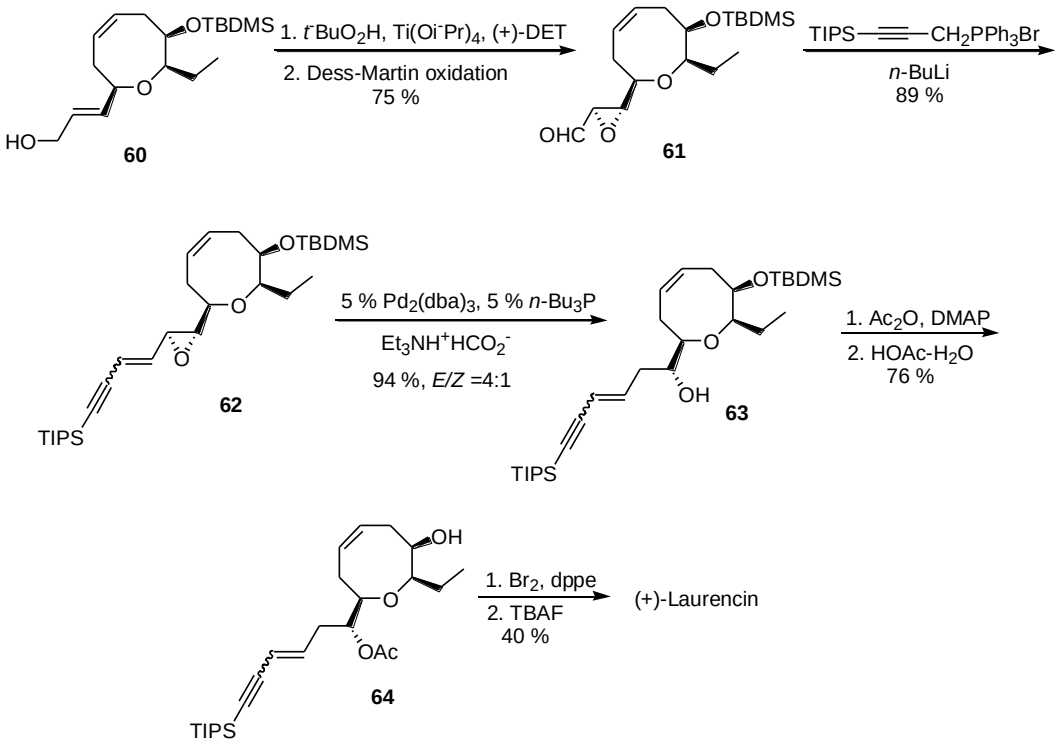
Scheme 3.14: The Overman total synthesis of (+)-laurencin, part 2.

Cyclization promoted by $BF_3{\cdot}OEt_2$ in *t*-BuOMe afforded the oxocene, which was then desulfurized using Raney nickel to provide **58** (Scheme 3.15). Changing the hydroxyl protecting group at C_4 to TBDMS and cleaving the pivaloyl group afforded the primary alcohol **59**. Swern oxidation followed by Saegusa-Ito oxidation provided the (*E*)-enal, which was then reduced by DIBALH to afford allylic alcohol **60**.



Scheme 3.15: The Overman total synthesis of (+)-laurencin, part 3.

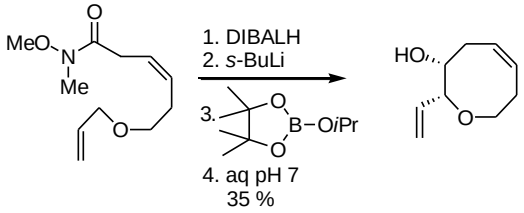
As shown in Scheme 3.16, compound **60** underwent Sharpless epoxidation and Dess-Martin oxidation reaction to provide aldehyde **61**, which was then treated with the Wittig reagent to afford enyne **62** as a 3:1 mixture of *E* and *Z* stereoisomers. Both double bond isomers were converted to **63** with similar stereoselectivity (*E:Z* = 4:1) in a Pd-catalyzed reductive opening of the vinyl epoxide. Acetylation of **63** followed by cleavage of the TBDMS group yielded alcohol **64**, which underwent bromination reaction and cleavage of the TIPS group to afford the final product (+)-laurencin.



Scheme 3.16: The Overman total synthesis of (+)-laurencin, part 4.

3.2.5. Hoffmann formal synthesis of (+)-laurencin

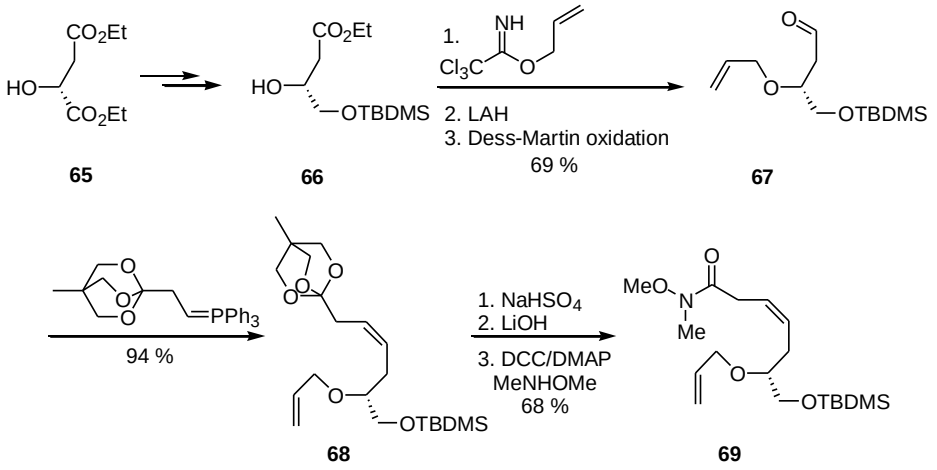
In 1997, Hoffmann published the formal synthesis of (+)-laurencin using an intramolecular aldehyde-allylboration reaction to construct the oxocene ring (Scheme 3.17).[18] Though the overall yield for the reaction is moderate, the entry into the oxocene ring system is remarkably direct.



Scheme 3.17: The Hoffmann formal synthesis of (+)-laurencin, part 1.

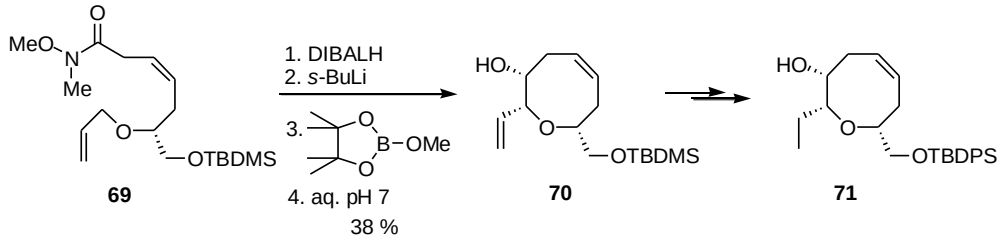
The starting material for their synthesis was the monoprotected diol **66** (Scheme 3.18), which can be made from the ethyl ester of malic acid **65**.[19]

Allylation of **66** followed by reduction and oxidation reaction provided aldehyde **67**, which then underwent a Wittig reaction to afford compound **68**. The side-chain OBO ester was then transformed into Weinreb amide **69**.



Scheme 3.18: The Hoffmann formal synthesis of (+)-laurencin, part 2.

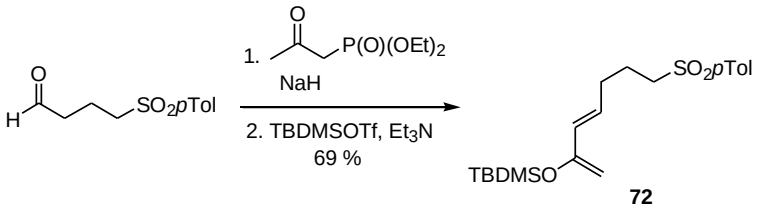
DIBAL reduction of Weinreb amide **69**, *in situ* lithiation, transmetallation to the allylboronate, and liberation of the aldehyde set the stage for intramolecular allylboration to give cyclized product **70** (Scheme 3.19). Selective hydrogenation of the terminal double bond and changing the TBDMS protecting group to TBDPS group afforded the intermediate **71** which was identical to the intermediate reported by Holmes and co-workers.[11,12]



Scheme 3.19: The Hoffmann formal synthesis of (+)-laurencin, part 3.

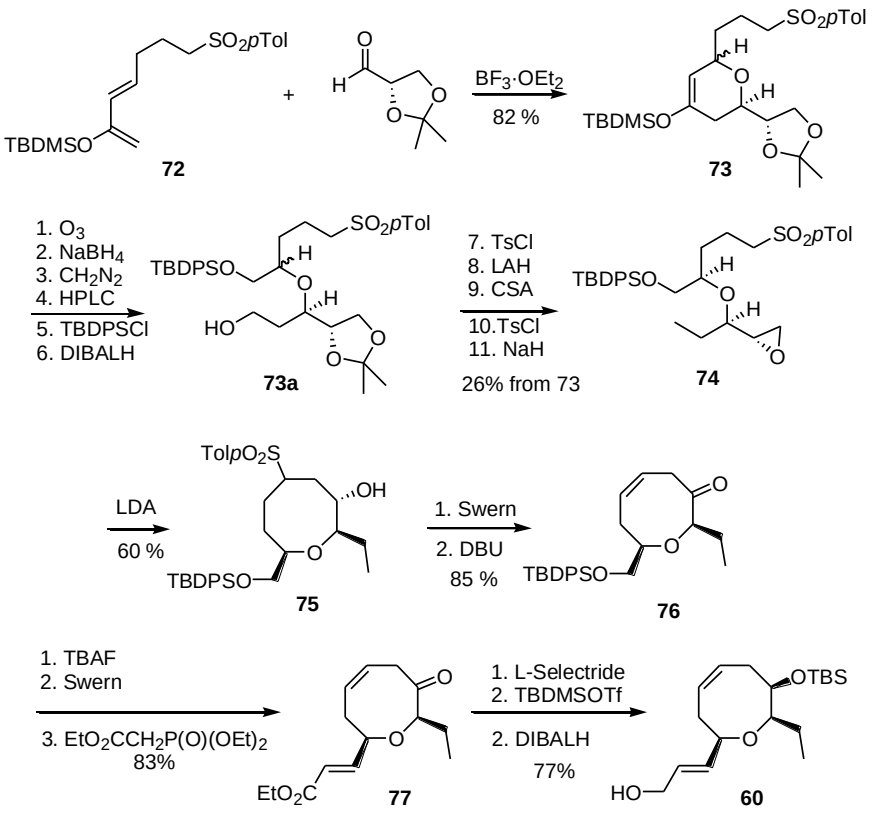
3.2.6. Palenzuela formal synthesis of (+)-laurencin

In 1998, Palenzuela and co-workers published the formal synthesis of (+)-laurencin.[20] Their strategy was based on the regioselective intramolecular alkylation and a hetero Diels-Alder reaction to establish the chiral centers adjacent to the oxygen atom. The diene partner **72** for the [4+2]-cycloaddition was prepared from the corresponding aldehyde by HWE olefination (Scheme 3.20).



Scheme 3.20: The Palenzuela formal synthesis of (+)-laurencin, part 1.

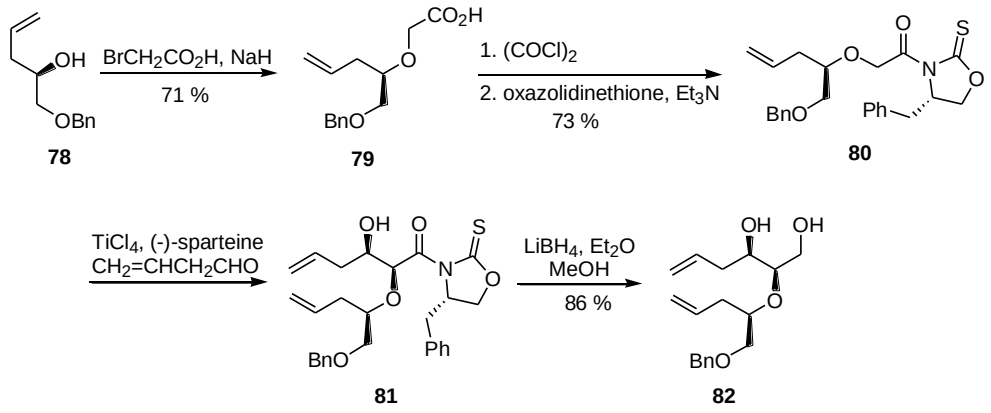
The hetero Diels-Alder reaction of (L)-glyceraldehyde acetonide and diene **72** using boron trifluoride etherate as a Lewis acid catalyst afforded **73** with a 7:1 ratio of *cis:trans* isomers (Scheme 3.21). Dihydropyran **73** underwent a series of reactions to afford **74**, which was treated with LDA to give the alcohol **75**. Oxocane **75** underwent Swern oxidation and DBU mediated elimination to yield *β,γ*-enone **76**. Deprotection of **76** followed by Swern oxidation gave the corresponding aldehyde, which was converted into ester **77** via a Wittig-Horner reaction. L-Selectride reduction of **77** followed by protection of the hydroxyl group and DIBALH reduction of the ester afforded compound **60**, which was an advanced intermediate in Overman's total synthesis.[16]



Scheme 3.21: The Palenzuela formal synthesis of (+)-laurencin, part 2.

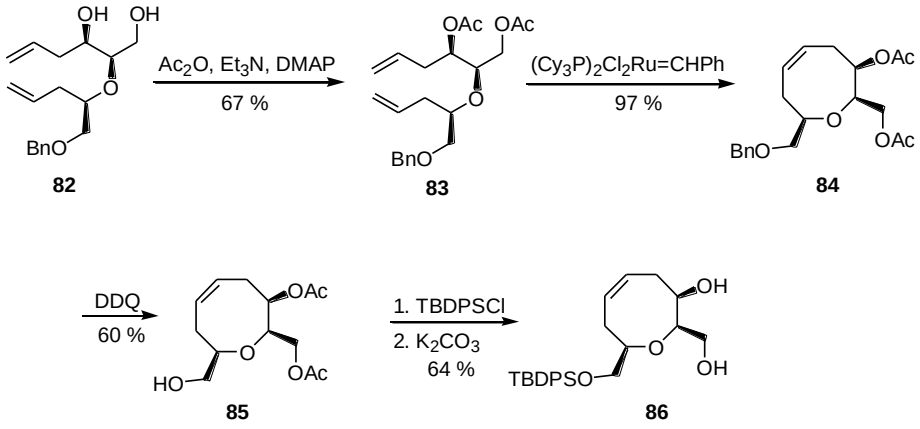
3.2.7. Crimmins formal and total synthesis of (+)-laurencin

In 1999, Crimmins and co-workers published a new general strategy for the asymmetric synthesis of unsaturated medium-ring ethers.[21] There were two key reactions for this strategy: the auxiliary-mediated asymmetric aldol addition and ring-closing metathesis to construct the oxocene ring. As shown in Scheme 3.22, treatment of the secondary alcohol **78** and bromoacetic acid with sodium hydride provided the required alkoxy acetic acid **79**, which was then converted into the acyloxazolidinethione **80**. Compound **80** underwent aldol reaction with 3-buten-1-al to afford **81**, which was then reduced to give diol **82**.



Scheme 3.22: The Crimmins formal synthesis of (+)-laurencin, part 1.

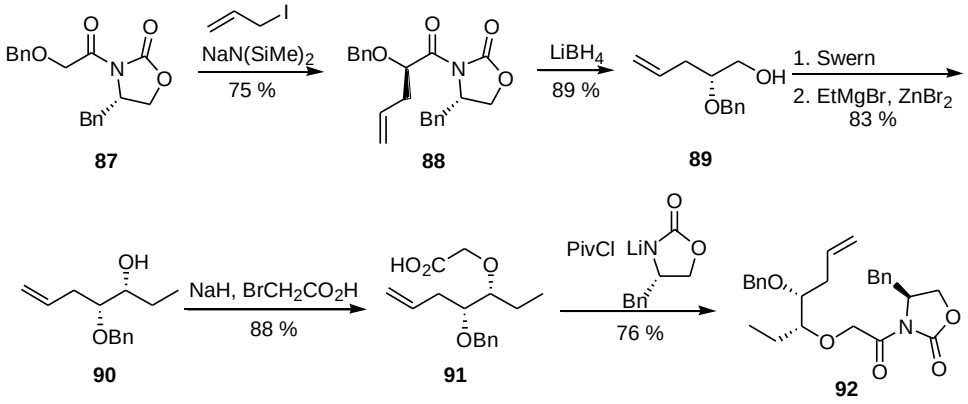
Acetylation of the diol gave the diacetate **83** (Scheme 3.23), which then underwent the ring-closing metathesis reaction to provide the oxocene **84**. The benzyl group was cleaved using DDQ to yield **85**, which underwent protection reaction and deprotection reaction to afford the Holmes intermediate diol **86**.[11-13]



Scheme 3.23: The Crimmins formal synthesis of (+)-laurencin, part 2.

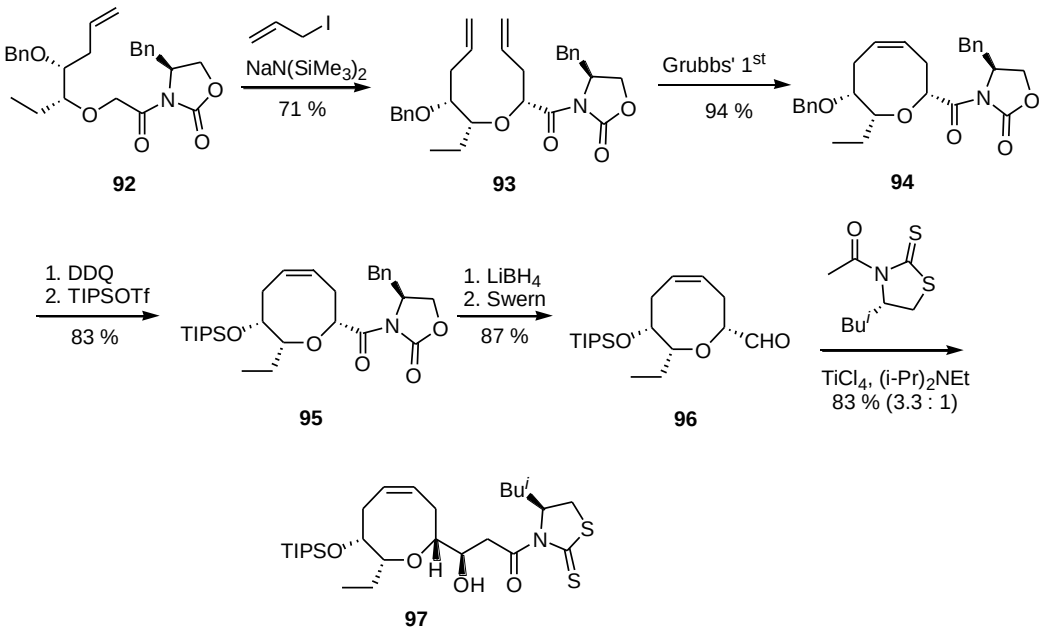
In the same year, Crimmins and co-workers also published the total synthesis of (+)-laurencin using a similar strategy.[22] Alkylation of the starting material **87** provided the acyl oxazolidinone **88** (Scheme 3.24), which was then reduced to give the chiral alcohol **89**. Swern oxidation followed by chelation-controlled addition of ethylmagnesium bromide provided the desired alcohol **90**.

Treatment with sodium hydride and bromoacetic acid afforded compound **91**, which was then converted into acyl oxazolidinone **92**.



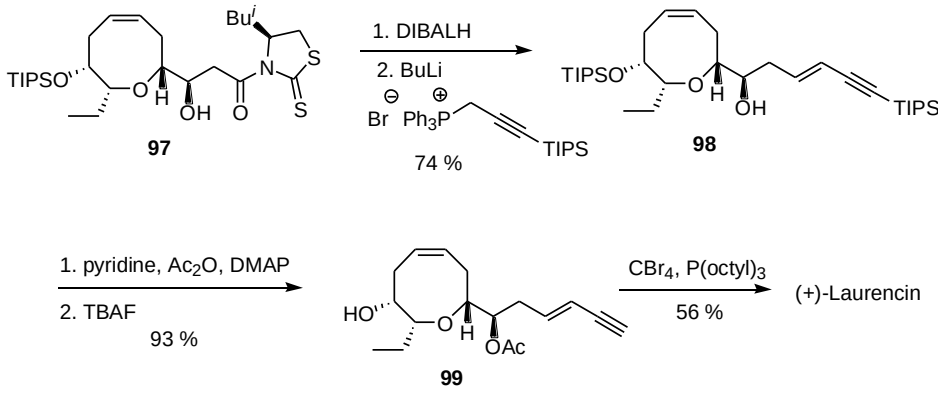
Scheme 3.24: The Crimmins total synthesis of (+)-laurencin, part 1.

Stereoselective alkylation of compound **92** afforded diene **93** (Scheme 3.25), which then underwent ring-closing metathesis reaction to give oxocene **94**. Converting the benzyl ether to the TIPS ether provided compound **95**, which was then reduced and oxidized to yield aldehyde **96**. Asymmetric aldol addition to **96** provided an 83% yield of **97** as a 3.3:1 mixture of diastereomers.



Scheme 3.25: The Crimmins total synthesis of (+)-laurencin, part 2.

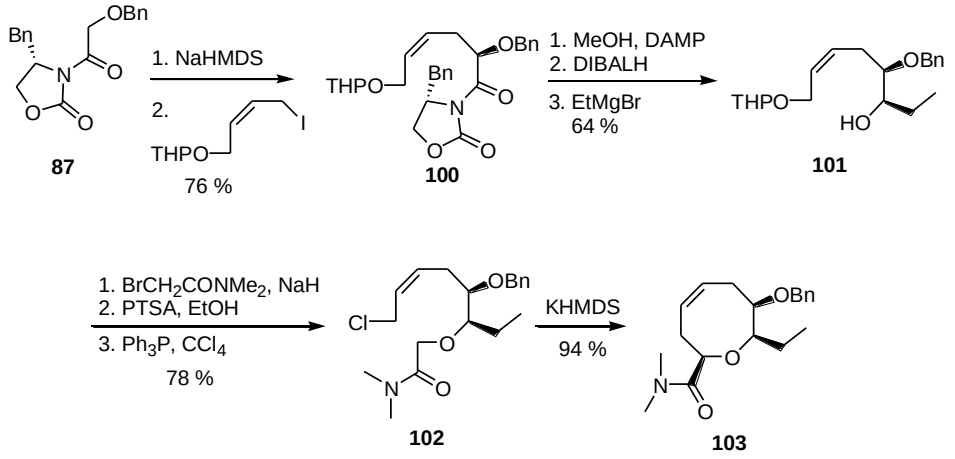
Half reduction of the N-acyloxazolidinethione followed by Wittig reaction afforded compound **98** (Scheme 3.26). Acetate formation and cleavage of the TIPS group gave **99**, which was brominated to afford (+)-laurencin as the final product.



Scheme 3.26: The Crimmins total synthesis of (+)-laurencin, part 3.

3.2.8. Kim total synthesis of (+)-laurencin

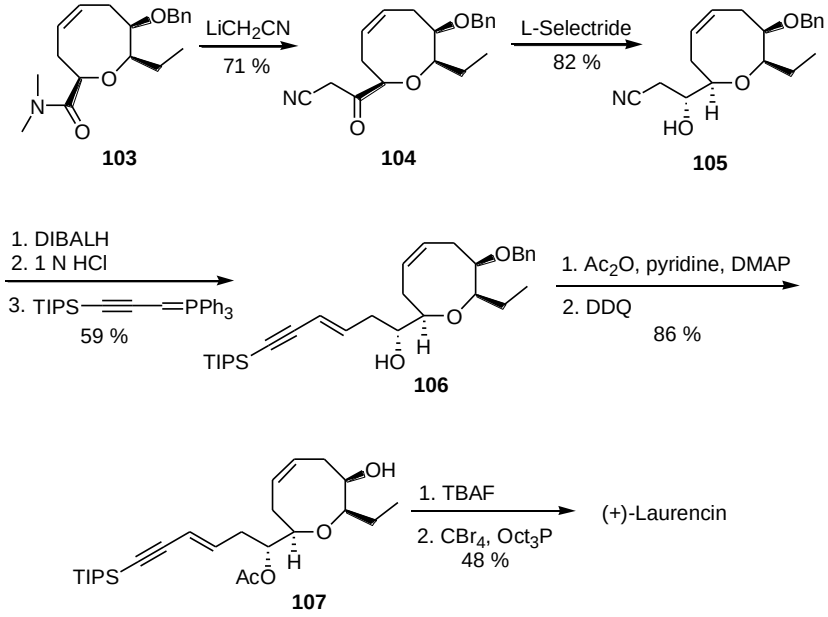
In 2005, Kim and co-workers published the total synthesis of (+)-laurencin.[23] Their strategy was based on olefin geometry-dependent internal alkylation to construct the oxocene ring. Alkylation of the *N*-acyloxazolidinone **87** with the allylic iodide reagent yielded compound **100** (Scheme 3.27). Methanolysis of **100** followed by reduction and chelation-controlled nucleophilic addition provided **101**. *O*-Alkylation with *N*,*N*-dimethyl bromoacetamide, removal of the THP group and chlorination gave the amide **102**, which was then treated with KHMDS to afford the desired oxocene **103** via "olefin geometry-dependent' internal alkylation. The regiochemical behaviour (S_N2 vs S_N2') was probably because the geometrically restricted cis configuration decreased the entropic and enthalpic barriers associated with formation of the eight-membered ring.[23b]



Scheme 3.27: The Kim total synthesis of (+)-laurencin, part 1.

The addition of the lithium anion of acetonitrile to amide **103** afforded compound **104** (Scheme 3.28), which was then reduced stereoselectively with L-selectride to give **105**. Hydroxynitrile **105** was reduced with DIBALH to provide the aldehyde, which then underwent Wittig reaction to yield **106**. Acetylation of secondary alcohol and removal of the benzyl protecting group afforded **107**.

Removing the TIPS group and bromination afforded the final product (+)-laurencin.

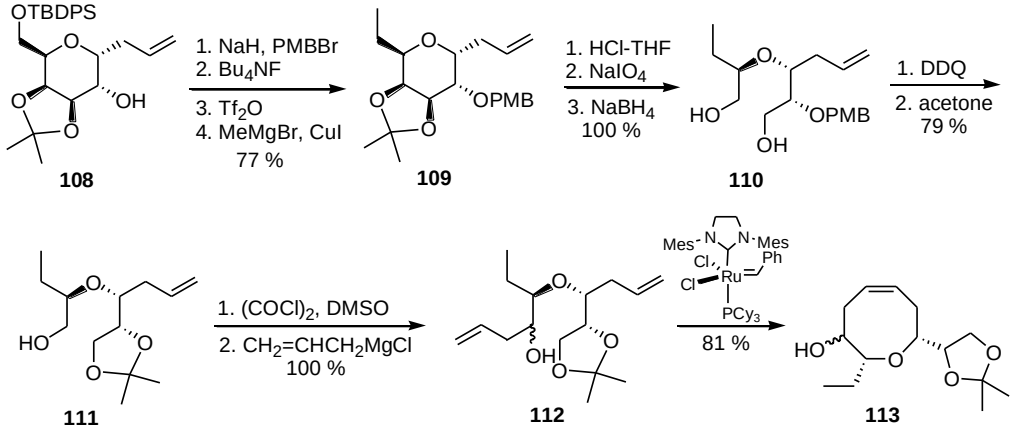


Scheme 3.28: The Kim total synthesis of (+)-laurencin, part 2.

3.2.9. Fujiwara total synthesis of (+)-laurencin

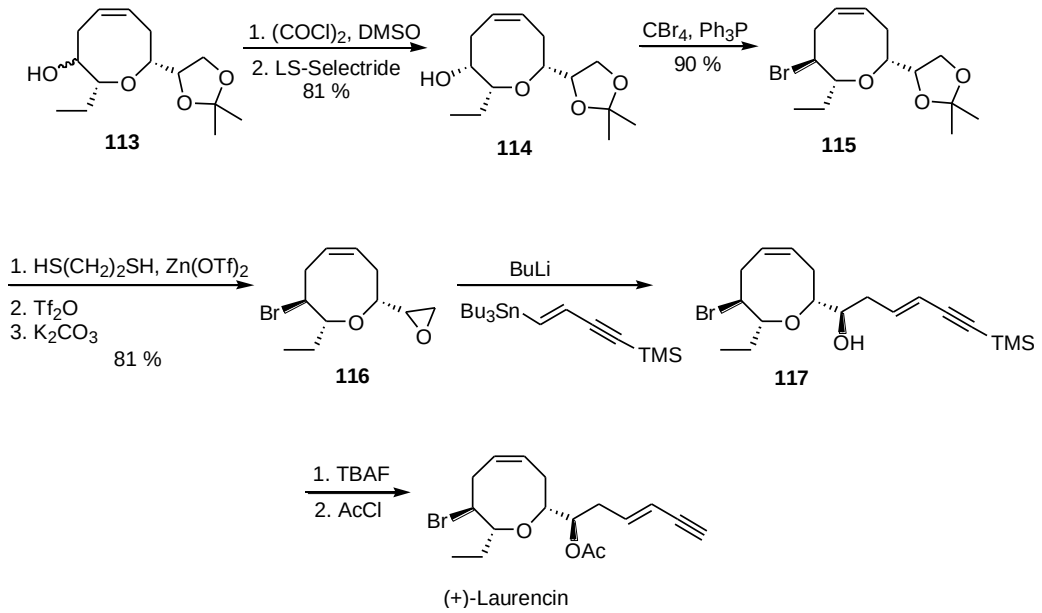
In 2005, Fujiwara and co-workers published the total synthesis of (+)-laurencin by ring expansion of the tetrahydropyran ring of a C-glycoside substrate to construct the oxocene ring through a common ring-cleavage/ring-closing olefin metathesis process.[24] The starting material **108** was made from a known procedure (Scheme 3.29).[24b] After a series of protection and deprotection steps, **108** was converted into triflate, which then underwent the Kotsuki procedure to afford **109**.[25,26] The acetonide protecting group was then hydrolyzed and the resulting diol underwent oxidative cleavage to the acyclic dialdehyde, which was immediately reduced to diol **110**. Treatment with DDQ resulted in formation of the 5-membered benzylidene acetal, which was exchanged to the acetonide to give **111**. After a one-pot procedure of Swern oxidation and addition of allyl magnesium chloride, the diene **112** was obtained as a 1:1 mixture of

diastereomers. The diene was then cyclized to yield oxocene **113** in good yield (81 %).



Scheme 3.29: The Fujiwara total synthesis of (+)-laurencin, part 1.

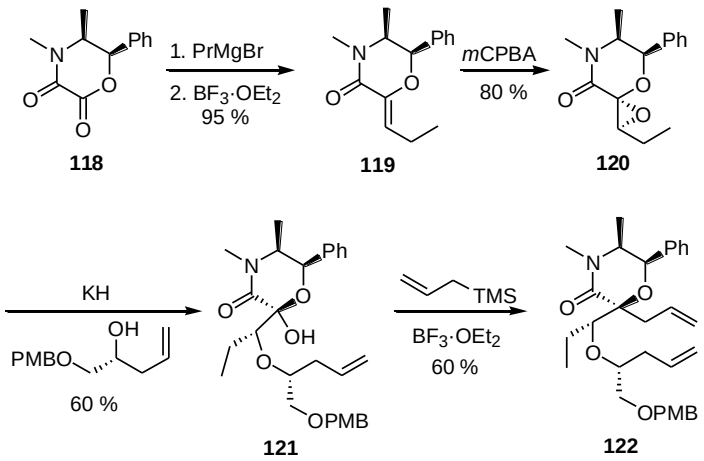
Swern oxidation of **113** followed by reduction with LS-Selectride provided the alcohol **114** (Scheme 3.30), which was then brominated to provide intermediate **115**. Deprotection of **115** followed by regioselective formation of the primary triflate and treatment with base afforded the epoxide **116**, which underwent epoxide opening to provide **117**. After desilylation and acetylation process, (+)-laurencin was formed.



Scheme 3.30: The Fujiwara total synthesis of (+)-laurencin, part 2.

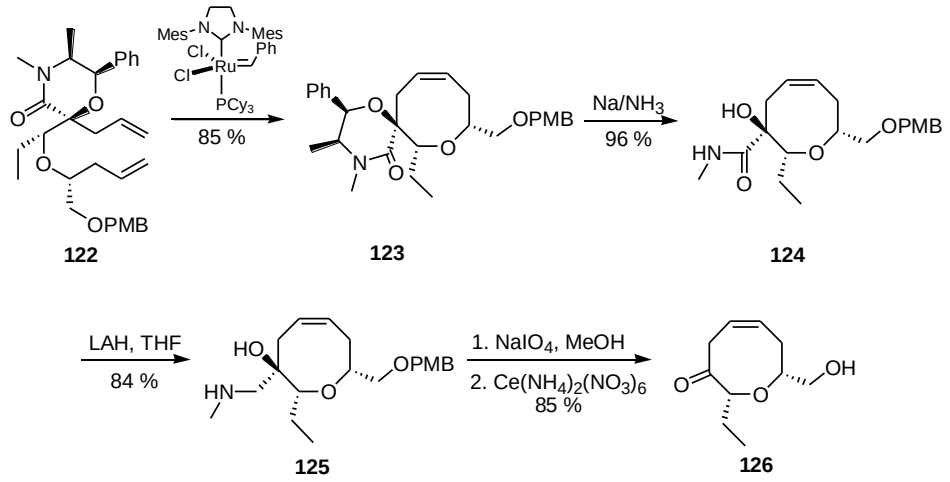
3.2.10. Pansare formal synthesis of (+)-laurencin

The latest formal synthesis of (+)-laurencin to appear in the literature was from Pansare and co-workers.[27] Their strategy relied on the opening of a chiral epoxide, followed by ring closing metathesis to construct the oxocene ring. Optically pure morpholinedione **118** was treated with propylmagnesium bromide, followed by dehydration of the resulting hemiacetal to furnish olefin **119** (Scheme 3.31). This compound underwent facially selective epoxidation with m-CPBA to afford **120**, which was then subjected to regioselective epoxide opening to give hemiacetal **121**. Finaly, allylation under Lewis acid conditions provided diene **121** with complete diastereoselectivity resulting from allyl delivery from the less hindered face of the oxocarbenium ion intermediate.



Scheme 3.31: The Pansare formal synthesis of (+)-laurencin, part 1.

Diene **122** underwent ring-closing metathesis reaction to afford oxocene **123** (Scheme 3.32). Removal of the ephedrine portion in morpholinone gave compound **124**, which was then reduced by LAH to provide **125**. Treatment with $NaIO_4$ followed by removal of the *p*-methoxyphenyl protecting group afforded the intermediate **126**, which was an advanced intermediate in an earlier approach to Laurencin.[20]



Scheme 3.32: The Pansare formal synthesis of (+)-laurencin, part 2.

3.3.11. Summary of the formal and total syntheses of (+)-laurencin

The previous formal and total syntheses of (+)-laurencin can be summarized in Table 3.1. These syntheses clearly reveal that stereocontrolled formation of the oxocene ring is the single most important challenge in the synthesis of laurencin, and a number of diverse strategies have been successfully applied. These include oxidative ring expansion, Claisen rearrangement, Yamaguchi lactonization, actal-vinyl sulfide cyclization, intramolecular allylboration, regioselective intramolecular alkylation, and ring closing metathesis. As a result of these synthetic efforts, the repertoire of available methods for the synthesis of medium-sized ethers has been greatly enriched. Among these syntheses, it seems apparent that those form the Crimmins and Kim groups were the most effective with respect to step count, overall yield, and availability of starting materials, though each one has its strengths. However, there is still room for the development of alternative, complementary methods for the formation of eight-membered cyclic ethers, especially when it is associated with the study of novel reaction processes.

Group,Year	Type	Brief summary
Masamune 1977	Racemic synthesis	9 steps, 3 % yield Starting material prepared via Robinson-Schöpf condesation
Murai 1992	Total synthesis	27 steps, 2 % yield Oxidative ring expansion reaction as the key step
Holmes 1993, 1997	Total synthesis	24 steps, 1 % yield [3,3]-sigmatropic rearrangement as the key step
Overman 1995	Total synthesis	24 steps, 2 % yield Acetal-vinyl sulfide cyclization as the key step
Hoffmann 1997	Formal synthesis	15 steps, 11 % yield Intramolecular allylboration as the key step
Palenzuela 1998	Formal synthesis	14 steps, 5 % yield Regioselective intramolecular alkylation and a hetero Diels-Alder reaction as key steps
Crimmins 1999	Formal synthesis	10 steps, 11 % yield Stereoselective alkylation, ring closing metathesis as key steps
	Total synthesis	18 steps, 4 % yield Stereoselective alkylation, ring closing metathesis as key step
Kim 2005	Total synthesis	15 steps, 5 % yield Internal alkylation to form oxocene as key step
Fujiwara 2005	Total synthesis	21 steps, 16 % yield Ring closing metathesis as key step
Pansare 2008	Formal synthesis	10 steps, 11 % yield Facially-selective additions to chiral morpholine, ring closing metathesis as key steps

Table 3.1: Brief summary of total and formal syntheses of (+)-laurencin

3.3. Results and discussion

3.3.1. Preliminary considerations

The methodology developed in our research group described in Chapter 2 provided a new strategy to construct the medium-sized ethers through ring expansion reaction via the Stevens [1,2]-shift of sulfonium ylides. We showed that the sulfur-bridged eight-membered ethers were made in relatively few steps and the Stevens [1,2]-shift reaction proceeded cleanly under relatively simple conditions providing high yields. Also the sulfur bridge was easily cleaved using Raney nickel. Based on these results, we can provide a strategy for the formal synthesis of (+)-laurencin by utilizing a Stevens [1,2]-shift of the sulfonium ylide as the key step. We believed that the generation of the metallocarbene using copper catalyst should result in the formation of the sulfur-bridged oxecane ring, which can be further converted into (+)-laurencin. Our efforts toward the target will be presented in the following sections.

3.3.2. The retrosynthesis

On the way to the formal synthesis of (+)-laurencin, we encountered some unexpected difficulties approaching to the ring expansion precursor. Basically, our effort can be divided into four strategies. A retrosynthetic analysis of our first intended sequence is depicted in Figure 3.2. Our target **49** is an advanced intermediate of Holmes' total synthesis of (+)-laurencin,[13] which is shown in Scheme 3.11. Target **49** would result from the sulfur-bridged ether **127** via an olefination, decarboxylation and desulfurization reaction. The ether **127** was expected to come from the diazoketoester **128** through the Stevens rearrangement of the sulfur ylide. Based on the closely related example in chapter 2, it is obvious that the diazoketoester is a better precursor compared with diazoketone, though it seemed to be more straightforward. The intermediate **128** is envisioned

to arise from the mercaptoalcohol **129** via the formation of the mixed acetal and the diazoketoester. The mercaptoalcohol **129** can be made by opening the cyclic dithiocarbonate of the intermediate **130**, which could be derived from the diol **131** by treatment with sodium hydride and carbon disulfide. The diol **131** was expected to arise from the aldehyde **132** via a Wittig reaction and a Sharpless AD reaction.

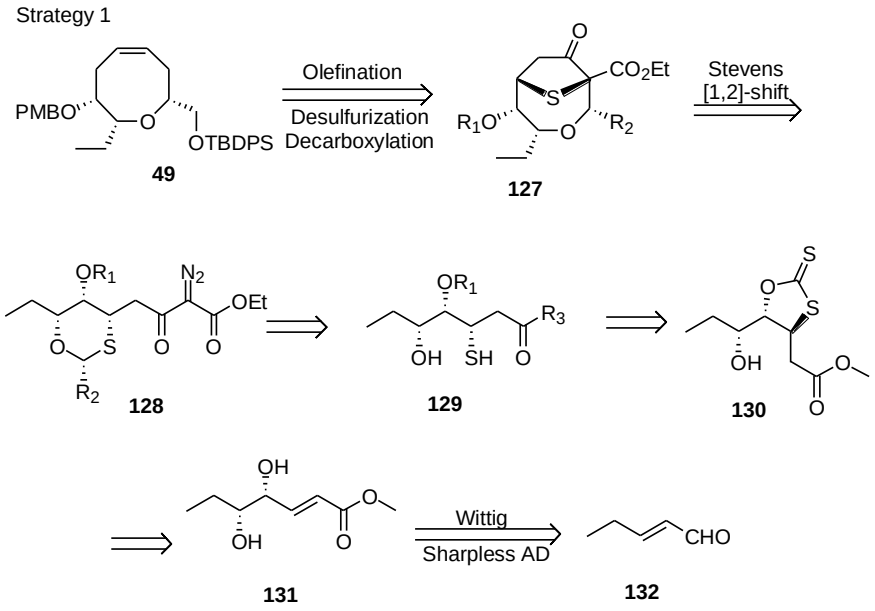


Figure 3.2: The retrosynthetic strategy 1 for laurencin intermediate **49**.

To obtain the mercaptoalcohol **129**, another two strategies are also proposed, which are shown in Figure 3.3. In the second strategy, the mercaptoalcohol **129** was envisioned to arise from the lactone **133** through the treatment with Weinreb amine. The lactone **133** could be obtained from the alcohol **134**, which was expected to arise from aldehyde **132** via aldol addition. For the third strategy, the mercaptoalcohol **129** would come from the lactone **135**, which in turn would be formed from the diene **136** through the ring closing metathesis reaction followed by the Michael addition reaction. The diene **136** can be made from the aldehyde **137** and the ether **138**.

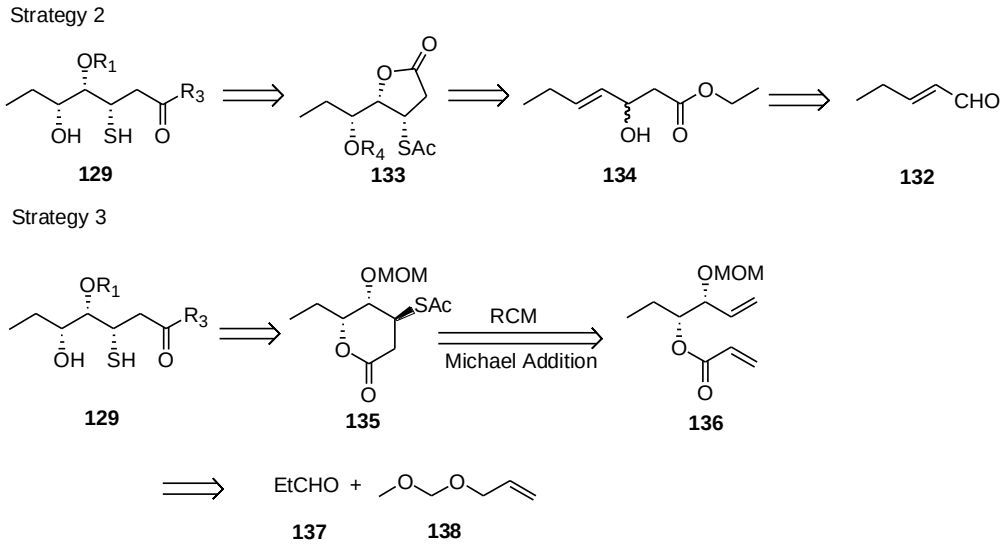


Figure 3.3: Alternative retrosynthetic strategies 2 and 3 for laurencin intermediate **49**.

Finally, in light of difficulties encountered with each of these approaches, a fourth route was also envisioned (Figure 3.4). In this approach, target **49** was envisioned to arise from sulfur-bridged ether **139** through olefin formation, desulfurization and decarboxylation. Compound **139** is the expected product from diazoketoester **140**, via stereoselective Stevens [1,2]-shift of the intermediate sulfur ylide. Diazoketoester **140** was projected to come from aldehyde **141**, which would be formed from bicyclic lactone **142**. This intermediate could be formed from lactone **143**, the product of ring closing metathesis and stereoselective Michael addition from diene **136**. As noted previously, this acyclic precursor could arise from the two simple building blocks **137** and **138**.

In this approach, the eight-membered ether would be formed through the Stevens [1,2]-shift of a sulfur ylide formed from a relatively simple six-membered monothioacetal. The absolute stereochemistry would be set through an asymmetric allylboration reaction, followed by facially selective Michael addition to a rigid six-membered unsaturated lactone. The final stereocenter would arise from thermodynamically controlled formation of the monothioacetal, with the

one-carbon CH_2OBn side-chain at the anomeric centre occupying the more stable equatorial position. It was hoped that this anomeric center would retain its configuration during the [1,2]-shift.

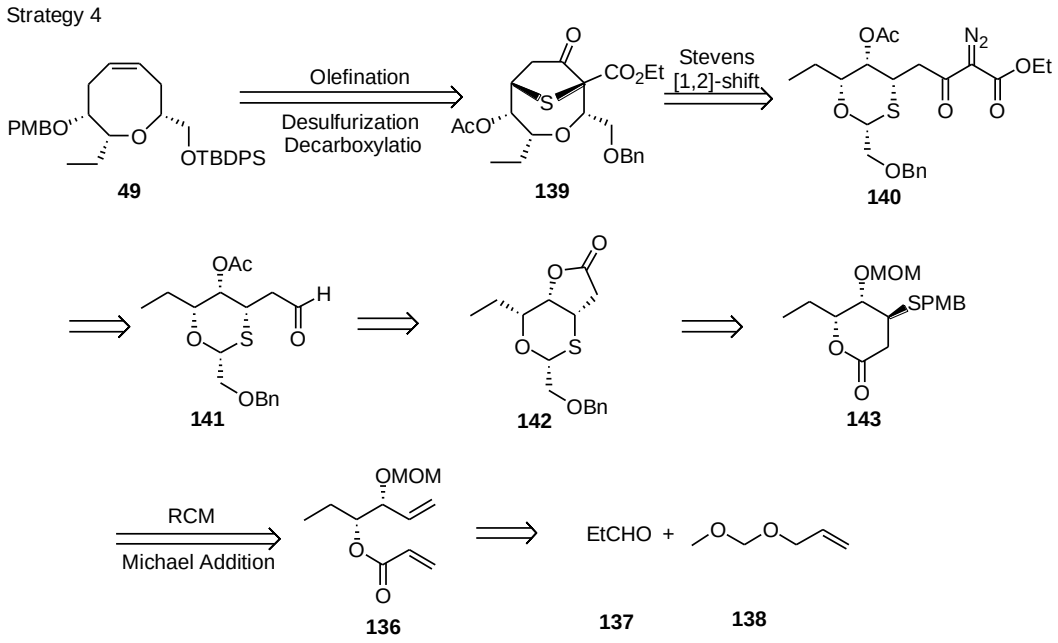
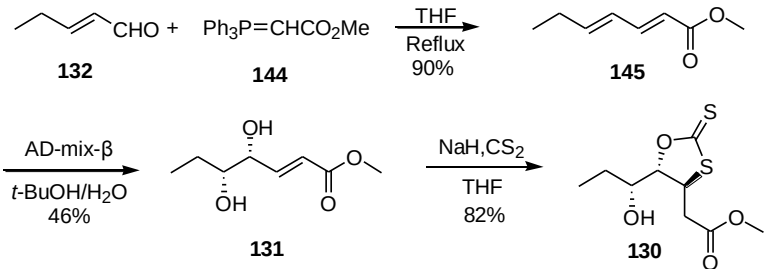


Figure 3.4: The fourth retrosynthetic strategy for laurencin intermediate **49**.

3.3.3. The first strategy approach to formal synthesis of (+)-laurencin

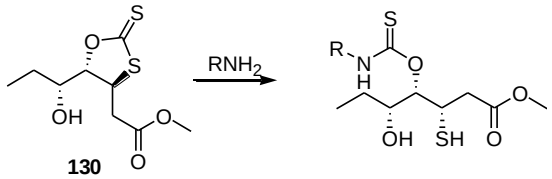
Our initial efforts in this synthetic study began with aldehyde **132** and Wittig reagent **144** (Scheme 3.33). Treatment of **132** with **144** together in refluxing THF afforded diene ester **145** in 90 % yield. Ester **145** was then treated with AD-mix-β in $^{t}BuOH/H_2O$ (1/1) at room temperature for 3 days to provide the diol **131** in 46 % yield. According to the literature,[28] the Sharpless AD reaction of the conjugated diene ester should be performed at 0 ^{o}C to obtain higher enantiomeric excesses, however, we found the reaction was too slow at that temperature. Raising the reaction temperature to room temperature increased the yield to 46 %. The enantioselectivity obtained in this asymmetric dihydroxylation reaction was not determined, due to problems encountered in a later step (see below). Treatment of **131** with sodium hydride and carbon disulfide in THF at

room temperature provided a cyclic monothiocarbonate **130** in 82 % yield with the desired diastereomer.[29a]



Scheme 3.33: Towards the formal synthesis of (+)-laurencin, strategy 1, part 1.

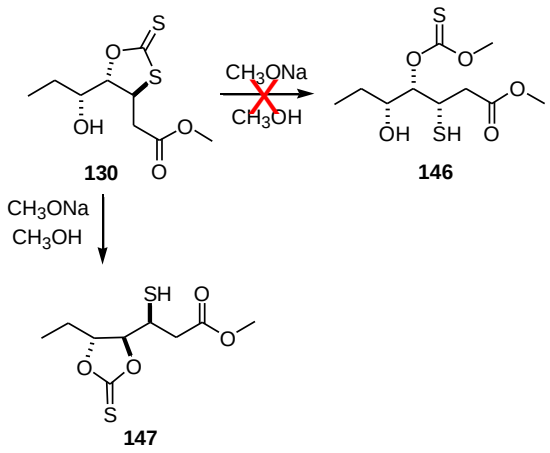
The next step was to open the cyclic monothiocarbonate ring in compound **130**. According to the literature, the typical procedure to open the ring was to use amine.[29] Unfortunately, treatment of **130** with different amines resulted in either no reaction or complete decomposition. Only benzylamine afforded any of the desired ring-opened thionocarbamate, but the yield was poor and purification was difficult. The results are summarized in Scheme 3.34.



Pyrolidine	Decomposition
Morpholine	Decomposition
$PhNH_2$	No reaction
$NH_2CH_2CH_2NH_2$	Decomposition
Liquid NH_3	Decomposition
$EtNH_2$	Decomposition
$PhCH_2NH_2$	Poor yield

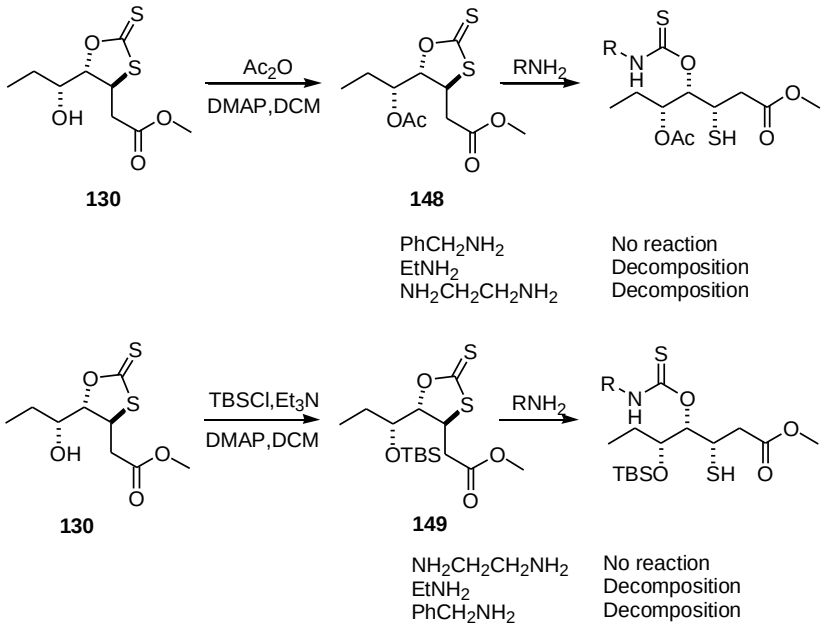
Scheme 3.34: Attempted opening of cyclic monothiocarbonate **130**.

Sodium methoxide was also examined to open the cyclic monothiocarbonate ring (Scheme 3.35). Unfortunately, what we obtained was the product **147** instead of the desired product **146**.



Scheme 3.35: Attempted ring opening using sodium methoxide.

Then we thought the hydroxyl group in compound **130** may have caused trouble for the ring opening step. Protection of **130** with acetyl and TBS group provided **148** and **149** in quantitative yield (Scheme **3.36**). Unfortunately, treatment of **148** or **149** with different amines did not afford the desired products. The starting material decomposed or remained unreacted.

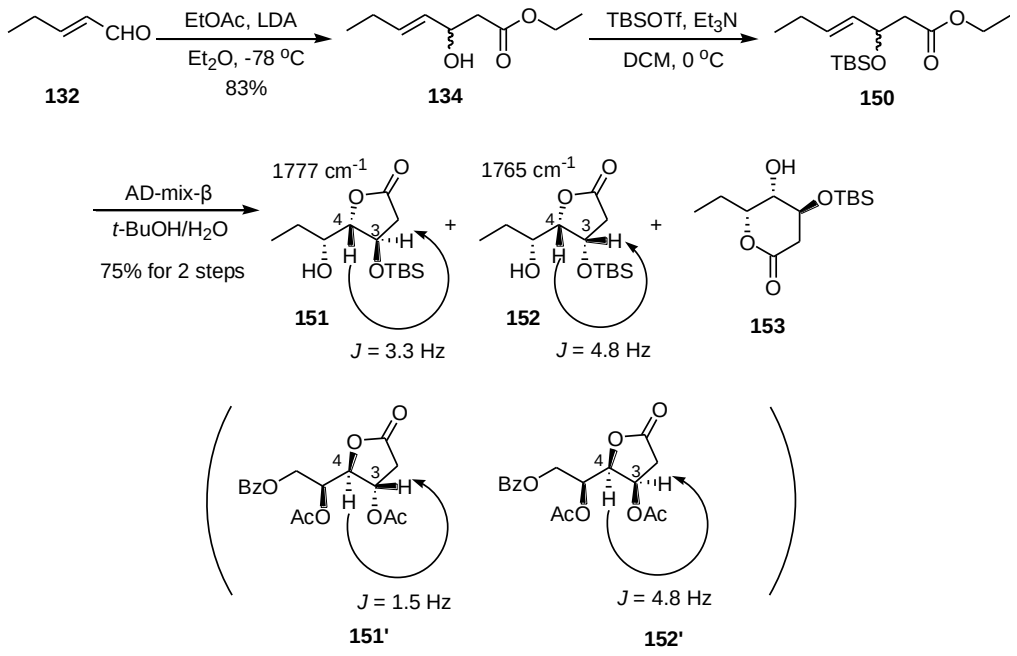


Scheme 3.36: Attempted opening of protected cyclic monothiocarbonate **130**.

Lacking an effective method to elaborate the cyclic dithiocarbonate **130** and its derivatives, we chose to explore one of the alternative strategies discussed above.

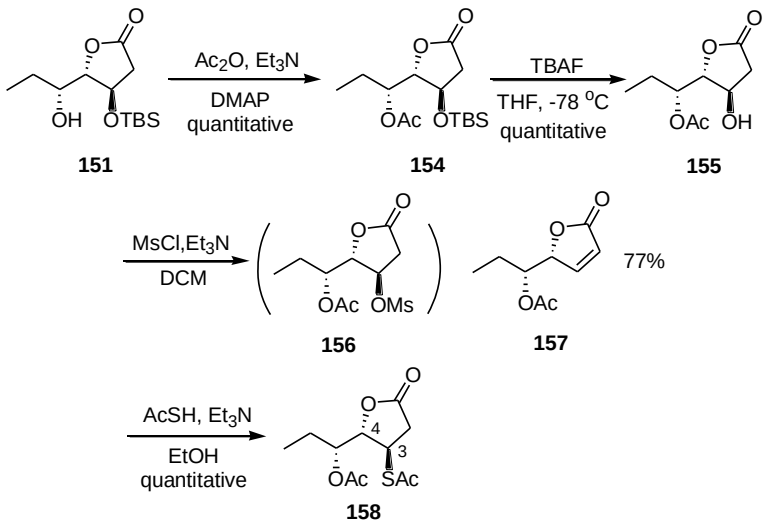
3.3.4. Attempted application of the second strategy to formal synthesis of (+)-laurencin

The second strategy also began with the aldehyde **132** (Scheme 3.37), which was treated with ethyl acetate and LDA in ether at -78 ^{o}C to yield the racemic alcohol **134** in excellent yield. Treatment of **134** with TBSOTf provided product **150**, which then underwent the Sharpless asymmetric dihydroxylation reaction to afford three separable lactones **151**, **152** and **153** in 75 % total yield. These three lactones were characterized by IR and NMR. Lactone **151** had strong absorption at 1777 cm^{-1} and **152** at 1765 cm^{-1}, which indicated that these two are five membered lactones. We assumed that these two compounds differed in their relative configurations at C_4 (i.e., OTBS ether *cis* or *trans* to the hydrogen at C_5). Precedent in the literature suggests that isomers possessing a *trans* relationship between the hydrogens at these positions will display small vicinal coupling constants. For example, the similar compounds **151'** and **152'** were prepared to have H_4-H_5 coupling constants of 1.5 Hz and 4.8 Hz, respectively. In the case of **151** and **152**, a similar trend was seen (3.3 Hz and 4.8 Hz). Thus we tentatively assigned **151** as the *trans* diastereomer and **152** as the *cis* diastereomer, as shown. We did not determine the enantiomeric points of these intermediates, due to subsequent difficulties in the route. Also, trace amount of a third lactone product, possibly structure **153**, was obtained. However, this material was not fully characterized due to insufficient quantities.



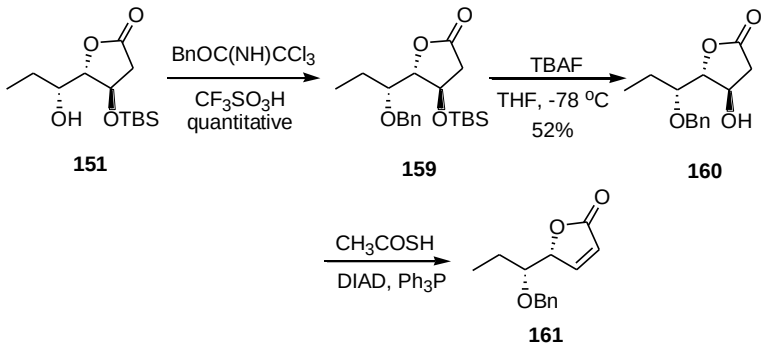
Scheme 3.37: Making the desired lactones starting with the 2-pentenal.

The desired lactone **151** was then treated with acetic anhydride to give compound **154** in quantitative yield (Scheme 3.38). Treatment of **154** with TBAF at low temperature (-78 ^{o}C) provided the deprotection product **155** in quantitative yield. To make compound **156**, lactone **155** was treated with MsCl and Et_3N in DCM. But unfortunately, the elimination product **157** was formed instead of **156** in 77 % yield. Lactone **157** then underwent Michael addition reaction by treatment with thioacetic acid to afford product **158** in quantitative yield. We assumed the product was a *trans* lactone because the nucleophile was likely to attack from the opposite direction of the neighbouring group at C_4. Unfortunately, this predicted configuration for C_3 is the opposite to what is required for our proposed route to (+)-laurencin.



Scheme 3.38: Making the thiosubstituted lactone.

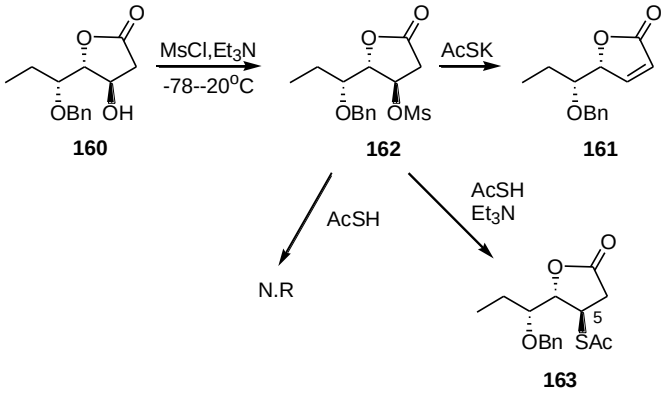
To make the thiosubstituted lactone with correct stereo configuration, the Mitsunobu reaction was also tried. We hoped that under neutral condition, the elimination process could be minimized. Protection of the hydroxyl group in lactone **151** afforded product **159** (Scheme 3.39), which was then deprotected with TBAF to give the alcohol **160**. Alcohol **160** was treated with thioacetic acid under the typical Mitsunobu conditions. Unfortunately, the elimination occurred again to yield **161**.



Scheme 3.39: Approach to the thiosubstituted lactone by Mitsunobu reaction

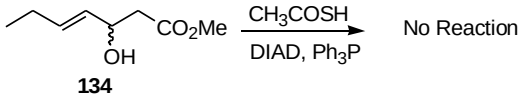
When compound **160** was treated with MsCl at low temperature and worked up carefully, the product **162** was formed in low yield (Scheme 3.40).

Treatment of **162** with AcSK once again resulted in elimination. When treated with thioacetic acid only, no reaction occurred. Upon treatment with thioacetic acid and triethylamine, compound **163** was formed with the undesired configuration at C_5 through the Michael addition of thioacetic acid to unsaturated lactone.



Scheme 3.40: Approach to the thiosubstituted lactone by S_N2 reaction.

Then we decided to try the Mitsunobu reaction in an earlier liner stage (Scheme 3.41) instead of at five-membered lactone stage. We hoped elimination could be avoided by that way. However, under Mitsunobu conditions, alcohol **134** remained unreacted.

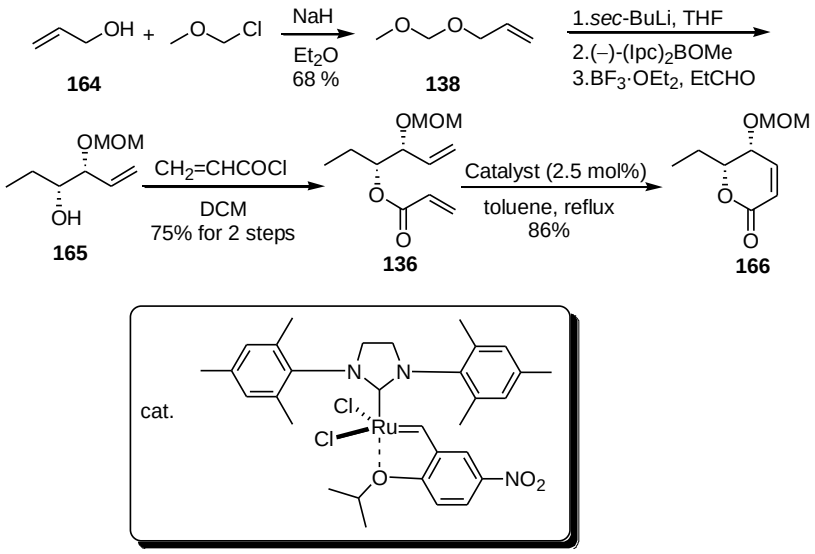


Scheme 3.41: The Mitsunobu reaction of linear compound **134**.

Given the difficulties experienced in establishing the correct absolute configuration at the sulfur-substituted carbon, we next examined the third approach outlined above.

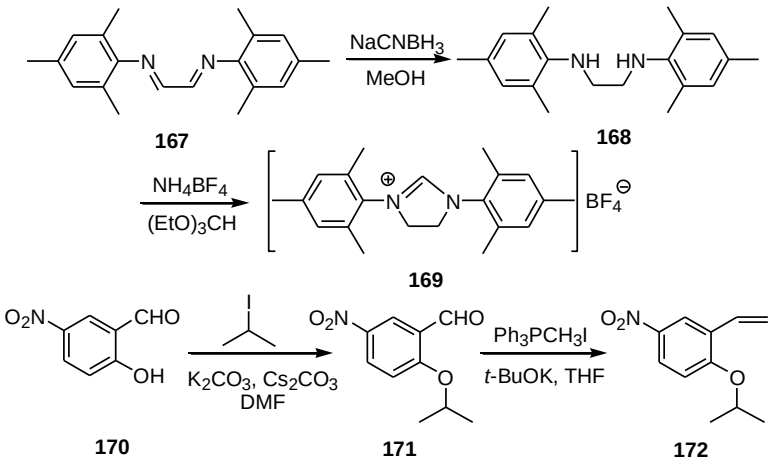
3.3.5. Attempted application of the third strategy approach to formal synthesis of (+)-laurencin

This approach began with the methoxymethyl ether of allyl alcohol **164**, prepared via Yamamoto's procedure.[30] Then following Brown's procedure,[31] the resulting ether **138** was treated sequentially with *sec*-butyllithium and (−)-B-methoxydiisopinocampheylboran and boron trifluoride etherate to generate an allylborane bearing chiral pinene units. Direct reaction with propionaldehyde then furnished alcohol **165** with 61% ee, which is determined by ^{1}H NMR intergration of its Mosher's ester derivative. Compound **165** was then esterified using acryloyl chloride, and the resulting diene **136** was subjected to ring closing metathesis to provide the α,β–unsaturated lactone **166**. Notably, the first generation Grubbs catalyst was completely ineffective for this reaction, but the second generation catalyst provided **166** in 77% yield on a small scale. The best results were obtained using a nitro-substituted Grubbs-Hoveyda catalyst, affording **166** in 86% yield with only 2.5 mol% catalyst loading. Though Grubbs' 2nd catalyst was commercially available and worked well, we used the nitro-substituted Grubbs-Hoveyda catalyst because of economical consideration.



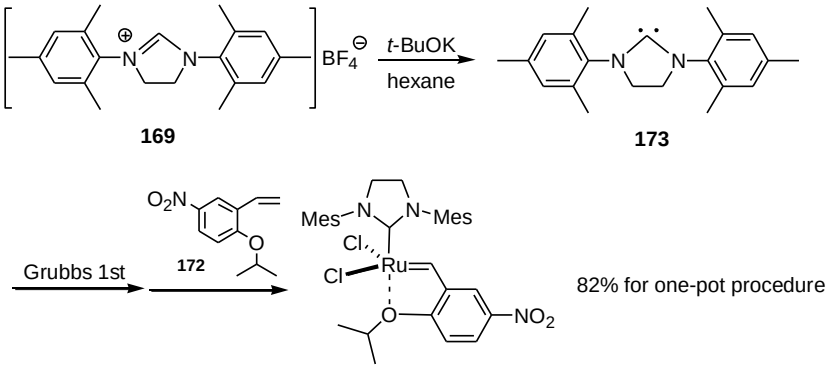
Scheme 3.42: Lactone formation through ring closing metathesis.

The nitro substituted Hoveyda-Grubbs ruthenium catalyst was made easily from the Grubbs first generation catalyst through a one-pot procedure.[32] As shown in Scheme 3.43, the two ligands needed were easily accessible from simple starting materials. The Schiff base **167** was reduced by $NaCNBH_3$ to afford the diamine **168**,[33] which was then treated with ammonium tetrafluoroborate and triethylorthoformate to yield white crystalline compound **169**.[33] The other ligand was made from the nitro aldehyde **170**, which was treated with 2-iodopropane and base in DMF to provide compound **171**. Aldehyde **171** then underwent Wittig olefination to afford the ligand **172**.[32]



Scheme 3.43: Ligand formation for the nitro substituted Hoveyda-Grubbs catalyst.

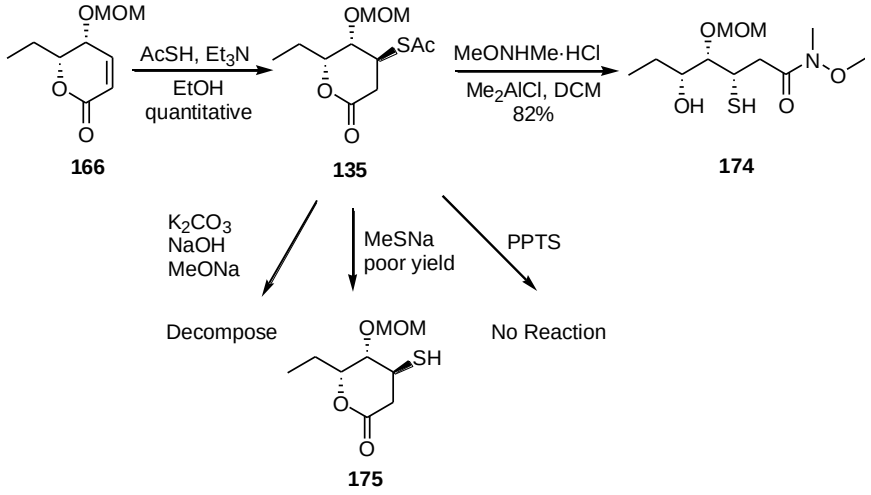
The nitro substituted Hoveyda-Grubbs ruthenium catalyst was made by Grela's one-pot procedure (Scheme 3.44).[32] Treated with base, compound **169** was converted into carbene **173**, which was then reacted with Grubbs' first generation catalyst followed by reaction with the other ligand **172** to afford the nitro substituted Hoveyda-Grubbs catalyst in 82 % yield. This catalyst was stable in the air and could be purified by chromatography.



Scheme 3.44: Preparation of the nitro substituted Hoveyda-Grubbs ruthenium catalyst.

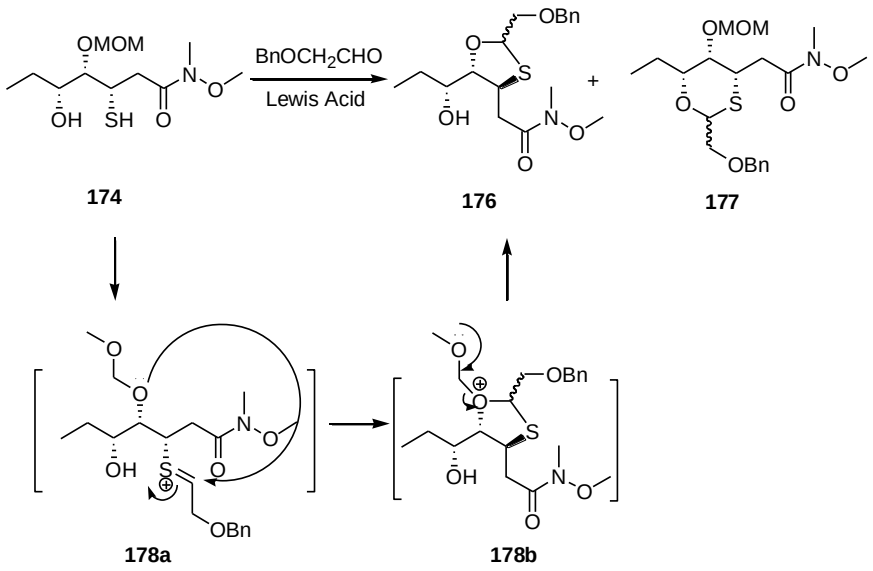
Treatment of compound **166** with thioacetic acid and triethylamine afforded the lactone **135** in quantitative yield (Scheme 3.45).[34] Lactone **135** was then treated with Weinreb amine to effect both opening of the lactone and

deacetylation of the sulfur, providing mercaptoalcohol **174**.[35] Other basic conditions (aq. K_2CO_3, NaOH or MeONa) decomposed the lactone with no discernable saponification. Conditions employing PPTS[34] or sodium thiomethoxide[36] were also examined as a possible way to selectively deacylate the sulfur while leaving the lactone intact. Unfortunately, no reaction was seen with PPTS, while thiomethoxide furnished **175** in only low yields.



Scheme 3.45: Preparation of the mercaptoalcohol.

The mercaptoalcohol **174** was then treated with aldehyde and different Lewis acids (Scheme 3.46). The desired product was the mixed monothioacetal **177**. Unfortunately, in most cases the five-membered monothioacetal **176** was the major or only product formed. Only one set of conditions ($InCl_3$ in Et_2O) gave six-membered acetal **177** as the principal product, but in this case the yield was quite low. The results are summarized in Table 3.2. We believe that formation of the undesired oxathiolane **176** results from participation of the MOM ether during reaction of the thiol with aldehyde to form thiocarbenium ion **178a**. Attack by the proximal oxygen atom can proceed through a kinetically favourable 5-membered transition state to give **178b**, with subsequent fragmentation of the MOM group to afford the neutral oxathiolane **176**.

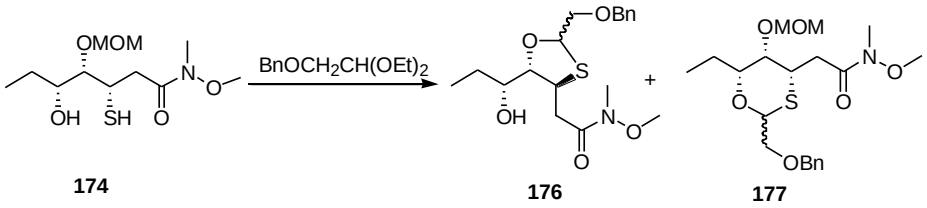


Scheme 3.46: Approach to the mixed monothioacetal **177** and the mechanism to form **176**.

	DCM	Et_2O
$BF_3{\cdot}OEt_2$	**176**	**176**+**177**
Me_2AlCl		-
$AlCl_3$	**176** (messy)	-
$TiCl_4$	Complex mixture	-
$CeCl_3$	NR	-
$FeCl_3$	**176**	**176**
$RuCl_3$	NR	-
$InCl_3$	**176**	**177** (trace)
$NbCl_5$	**176**+unknown	-

Table 3.2: Results for making mixed monothioacetals **176** and **177**.

The diethoxy acetal was also examined for making the mixed monothioacetal (Table 3.3). However, once again the result was not satisfactory. $InCl_3$ in DCM gave **177** as the only product at first, but slowly it converted into the undesired product **176**. In ether, the starting material remained unreacted. $BF_3{\cdot}OEt_2$ gave complex mixtures in both DCM and Et_2O.

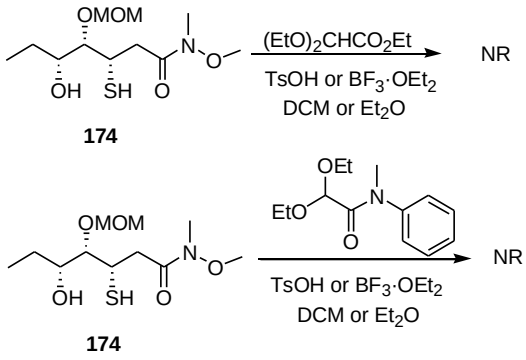


174 **176** **177**

	DCM	Et_2O
$BF_3{\cdot}OEt_2$	Complex mixture	Complex mixture
$InCl_3$	**177 →176**	NR

Table 3.3: Approach to mixed monothioacetal by using diethoxy acetal.

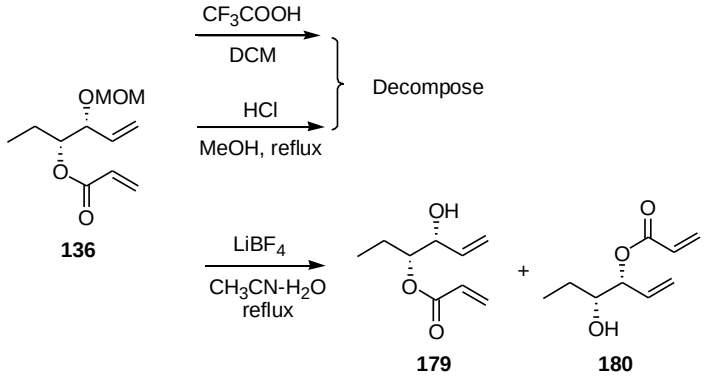
Formation of a six-membered mixed monothioacetal with other reagents bearing carbonyl functionality (either ester or amide) was also examined (Scheme 3.47). However, once again no reaction was seen using either Brønsted or Lewis acid catalysis.



174 **174**

Scheme 3.47: Approach to six-membered mixed monothioacetal by using diethoxy ester and amide

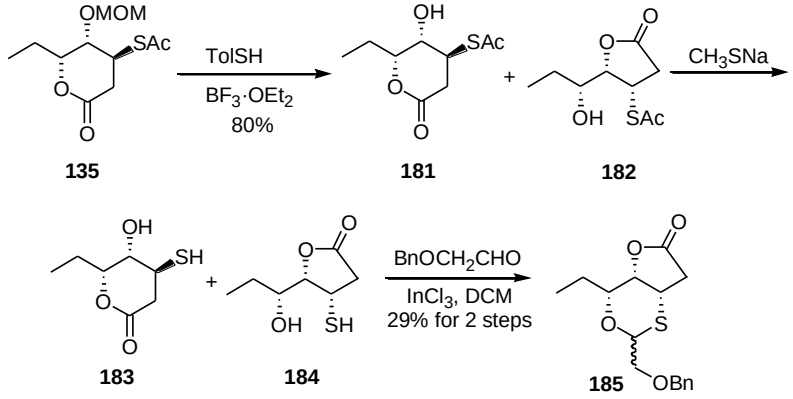
Given the apparent involvement of the MOM ether in the undesired processes described above, we decided to attempt to introduce a different protecting group prior to formation of the mixed monothioacetal. Unfortunately, the MOM group was considered essential for the initial allylboration step, so the first viable intermediate with which to explore protecting group exchange was acrylate **136**. Acidic conditions caused extensive decomposition of **136** (Scheme 3.48). Milder conditions employing $LiBF_4$[37] in aqueous acetonitrile did effectively remove the MOM group, but partial migration of the acrylate occurred, giving an inseparable mixture of isomers **179** and **180**.



Scheme 3.48: Deprotection of the MOM group.

These difficulties suggested that it would be desirable to exchange protecting groups at a later stage of the synthetic route. With this in mind, lactone **135** was treated with BF_3•OEt_2 in the presence of thiocresol to remove the MOM group[38] (Scheme 3.49). However, an inseparable mixture was obtained, consisting of the six-membered lactone **181** and the five-membered translactone isomer **182**. This mixture was then treated with sodium thiomethoxide[36] to deacetylate the thiol, resulting in isomeric mercaptoalcohols **183** and **184**. As seen earlier (Scheme 3.46), the yield for the deacylation process was low, and the overall yield of **185** over two steps was only 29%. As a result, this approach was

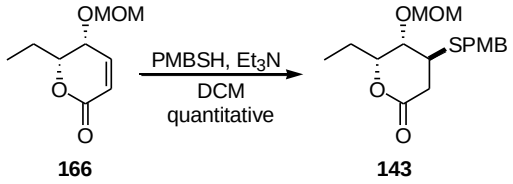
deemed unsuitable for a multistep synthesis, and we once again revisited the overall strategy.



Scheme 3.49: Preparation of the six-membered mixed acetal through the mercaptoalcohol.

3.3.6. Attempted application of the fourth strategy to formal synthesis of (+)-laurencin

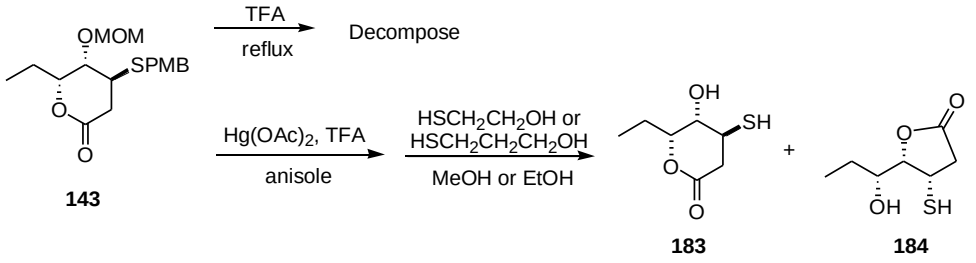
The fourth strategy began with the α,β–unsaturated lactone **166** made in Scheme 3.45. As shown in Scheme 3.50, treated with PMBSH and triethylamine in DCM, lactone **166** underwent a Michael addition reaction to provide compound **143** in quantitative yield.



Scheme 3.50: Preparation of the desired lactone **143** via Michael addition reaction.

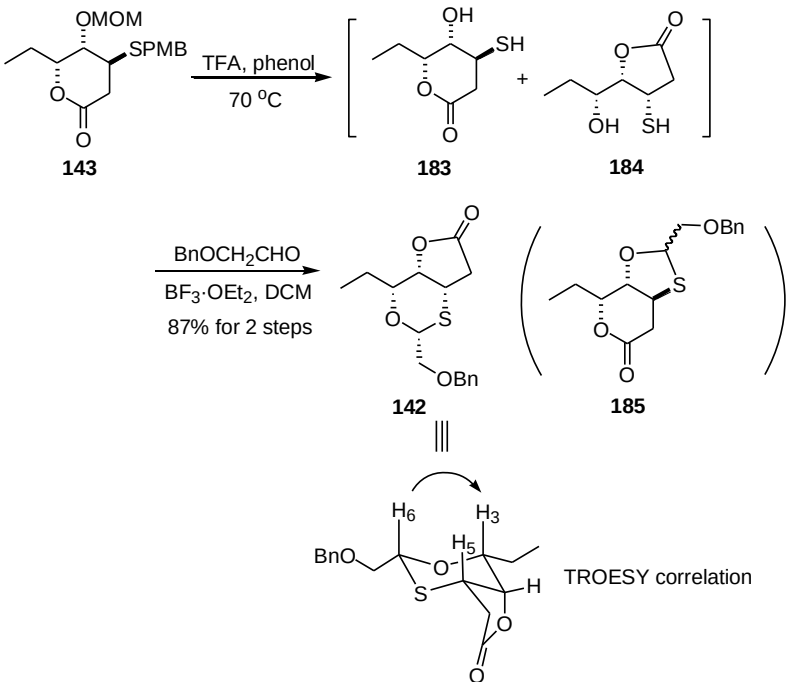
It was hoped that the MOM group and the PMB group could be cleaved together in one step. As in the initial investigation, use of conditions employing trifluoroacetic acid were tried. However, when refluxed in trifluoroacetic acid,

the starting material **143** decomposed quickly (Scheme 3.51). Then an alternative approach was employed by treatment of **143** with mercury(II) acetate and TFA followed by addition of mercaptoalcohol.[39] These conditions resulted in an inseparable mixture of lactones **183** and **184**, in less than 30 % yield.



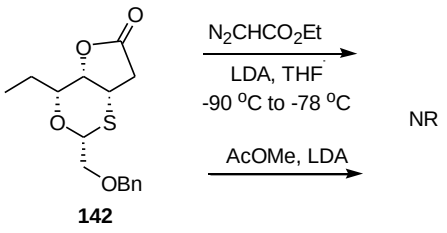
Scheme 3.51: Approach to the mecaptoalcohols in one step.

On the other hand, treatment of lactone **143** with trifluoroacetic acid and phenol at 70 °C led to the efficient formation of lactones **183** and **184** (Scheme 3.52). After a quick chromatographic purification, this mixture was subjected to benzyloxyacetaldehyde and BF_3•OEt_2 to give the desired bicyclic mixed monothioacetal **142** as a single diastereomer in 87% over two steps. The isomeric product **185** was not isolated. One possible reason for this is the necessary *trans* ring fusion found in that bicyclo[4.3.0]nonane skeleton, as compared with the *cis* ring-fusion of **142**, which may entail less ring strain. Formation of **142** as a single diastereomer indicates complete control over the anomeric configuration, consistent with an equatorial disposition in the presumed chair conformation of the six-membered ring. The TROESY spectra of **142** showed obvious correlation between H_3 and H_6, which indicated **142** had to be the *cis* configuration.



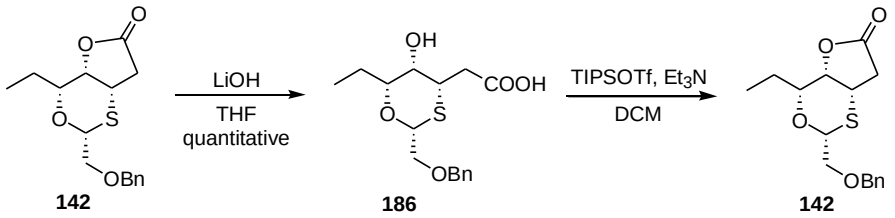
Scheme 3.52: Preparation of the mixed thioacetal.

According to Hodgson's procedure,[40] the five-membered lactone could be opened directly by ethyl diazo acetate under strong base conditions at low temperature. However, treatment of **142** under the same condition did not provide the desired diazoketoester. The starting material remained unreacted (Scheme 3.53). Compound **142** was also supposed to react with methyl acetate to form ketoester in the presence of LDA. However, in our hands **142** was completely unaffected by these conditions, returning only starting material.



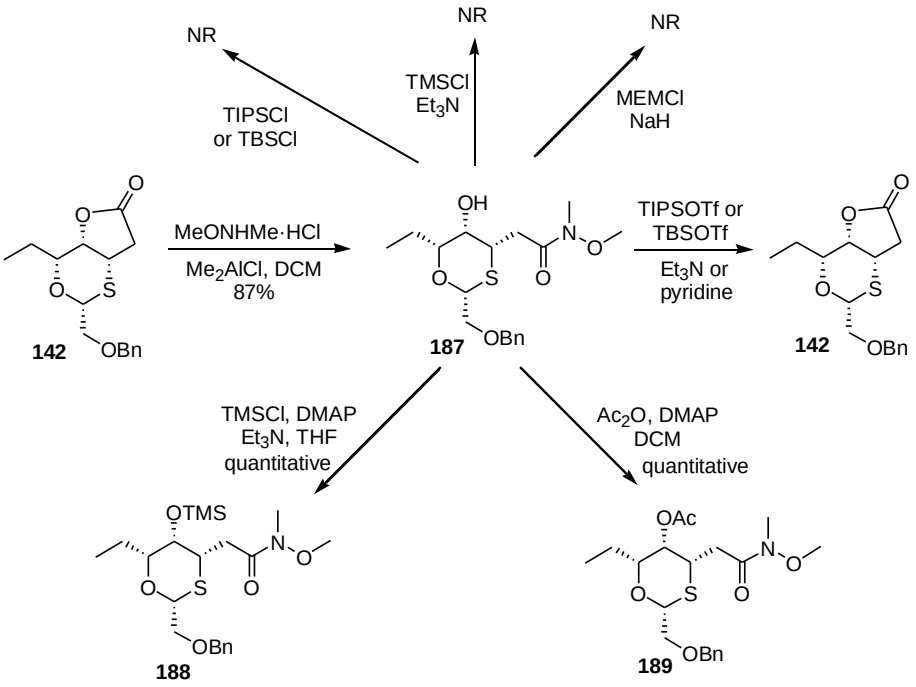
Scheme 3.53: Approach to the diazoketoester and ketoester.

It was possible to open the lactone ring of **142** using LiOH in THF, furnishing acid **186** in quantitative yield (Scheme 3.54). However, attempts to protect the secondary alcohol using TIPSOTf and triethylamine resulted in complete conversion back to lactone **142**.



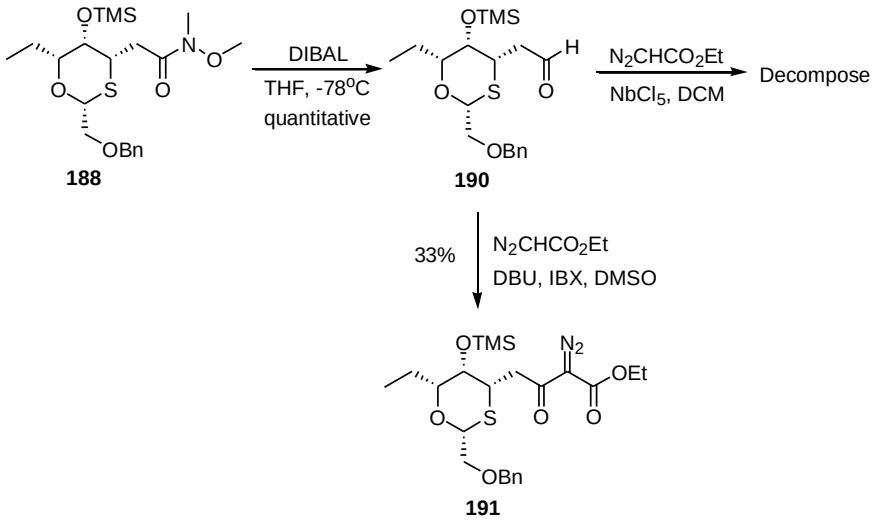
Scheme 3.54: Saponification reaction of lactone **142**.

Treatment of **142** with Weinreb amine provided the amide **187** in 87 % yield without affecting the mixed acetal (Scheme 3.55).[35] However when **187** was treated with TIPSOTf or TBSOTf under a variety of conditions, the lactone **142** was reformed again. For TIPSCl, TBSCl or MEMCl, the Weinreb amide **187** remained unreacted. The difficulties encountered while trying to introduce MEM or trialkylsilyl protecting groups may derive from the axial disposition of this alcohol, which may render it less accessible and create unfavourable steric interactions in the transition state. If this was the case, we imagined that a smaller group might be more easily accommodated. In the event, both trimethylsilyl and acetate groups could be installed. Treatment of **187** with TMSCl/DMAP afforded silyl ether **188** in quantitative yield, while Ac_2O/DMAP gave acetate **189**, also in quantitative yield.



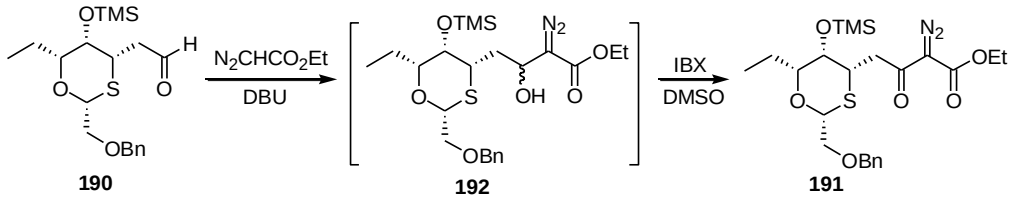
Scheme 3.55: Preparation of the Weinreb amide and protection of the axial hydroxyl group.

Treatment of **188** with DIBALH at -78 ^{o}C afforded the aldehyde **190** (Scheme 3.56). This compound was targeted as a precursor of the desired diazoketoester via Roskamp's method.[41] However, **190** was rapidly destroyed under these conditions, possibly due to the lability of the silyl ether in the presence of Lewis acid. Fortunately, when **190** was treated directly with ethyl diazoacetate in the presence of DBU and IBX in DMSO,[42] the diazoketoester **191** was formed in one step in low yield (33%).



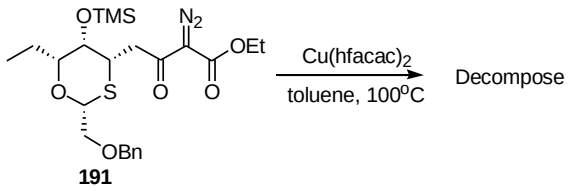
Scheme 3.56: Preparation of the diazoketoester.

The one-pot procedure is presumed to involve initial addition of the ethyl diazoester to the aldehyde to furnish transient hydroxy diazoester **192** (Scheme 3.57). This intermediate is then rapidly oxidized by IBX to furnish the desired diazoketoester.



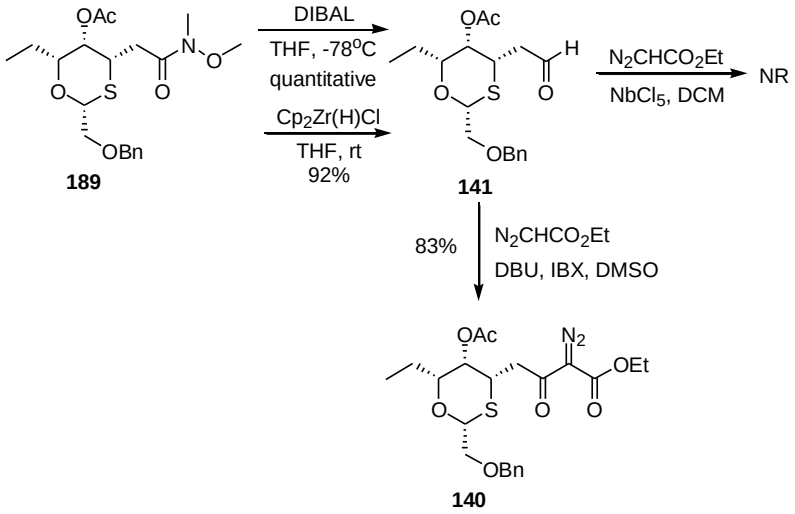
Scheme 3.57: Possible intermediate for the one-pot procedure.

Unfortunately, diazoketoester **191** failed to provide the desired Stevens [1,2]-shift product when treated under the optimized conditions from Chapter 2 (Scheme 3.58). Instead, only decomposition to an uncharacterizable mixture of products was seen. Bearing in mind the possible lability of the TMS group to these reaction conditions, we chose to examine the corresponding acetate.



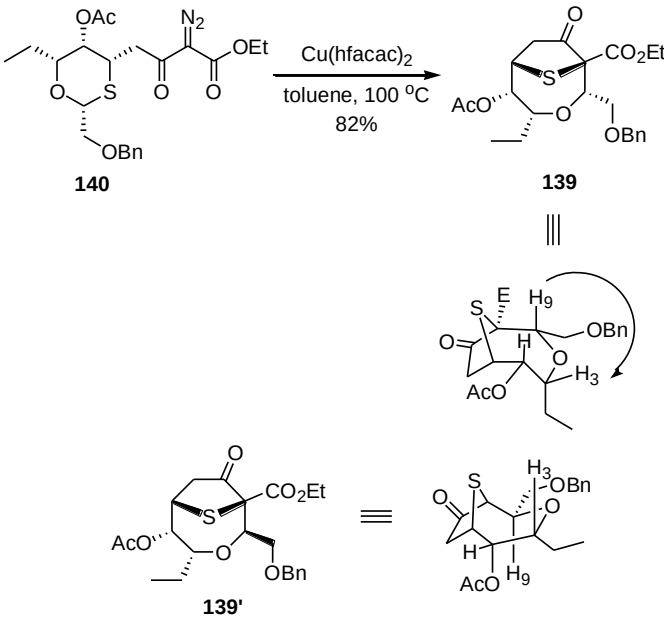
Scheme 3.58: Treatment of the diazoketoester **194** under Stevens [1,2]-shift conditions.

As shown in Scheme 3.59, treatment of the Weinreb amide **189** with DIBALH at -78 ^{o}C afforded the aldehyde **141** without affecting the ester group. Preferential addition to the Weinreb amide may once again be due to the axial disposition of the acetate group, which may hinder approach of the relatively bulky DIBALH reagent. Steric factors should be much less significant for the Weinreb amide, since the side-chain should be readily accessible. However when the reaction was scaled up, this DIBALH reduction process gave inseparable complex mixtures in low yield, necessitating the development of an alternative approach. Fortunately, Schwartz's reagent reduced the Weinreb amide to aldehyde **141** chemoselectively in the presence of the ester with excellent yield even in large scale.[43] The Roskamp procedure was ineffective with **141**, with no apparent reaction. On the other hand, the one-pot procedure with ethyl diazoacetate, DBU and IBX in DMSO provided the desired diazoketoester **140** in excellent yield for a small scale reaction.



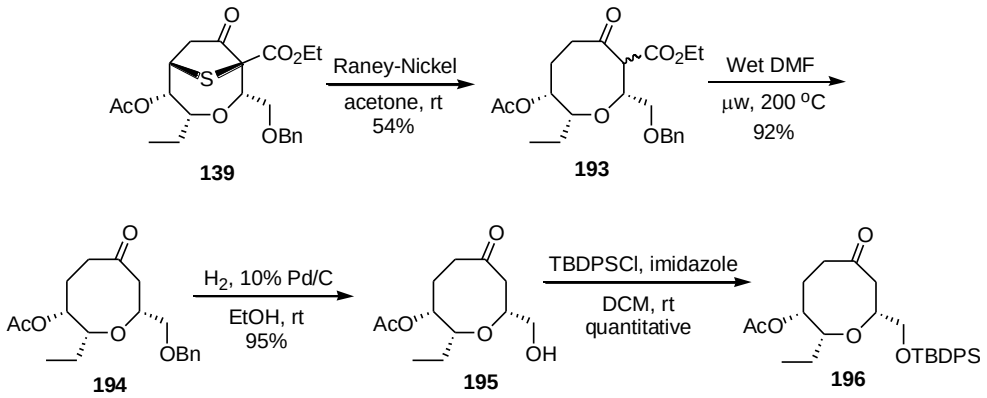
Scheme 3.59: Preparation of the diazo keto ester by one pot procedure.

With diazoketoester **140** in hand, we treated this substrate with $Cu(hfacac)_2$ in toluene at 100 ^oC, and to our delight we obtained the sulfur-bridged ether **139** in 82 % yield (Scheme 3.60). Three of the four stereocenters in this product were not expected to be affected by the rearrangement, but the anomeric center could migrate either with retention or inversion. Prior studies in related systems provided strong precedent for migration with retention, but it was critical to obtain objective evidence for the relative configuration. The 2D TROESY spectrum of this product displayed a key correlation between H_3 and H_9 (see arrow), which should only be present in the diastereomer **139**, the product of retention. In the case of the alternative isomer **139'**, the distance between the two protons would be too great to permit any detectable enhancement in the TROESY experiment.



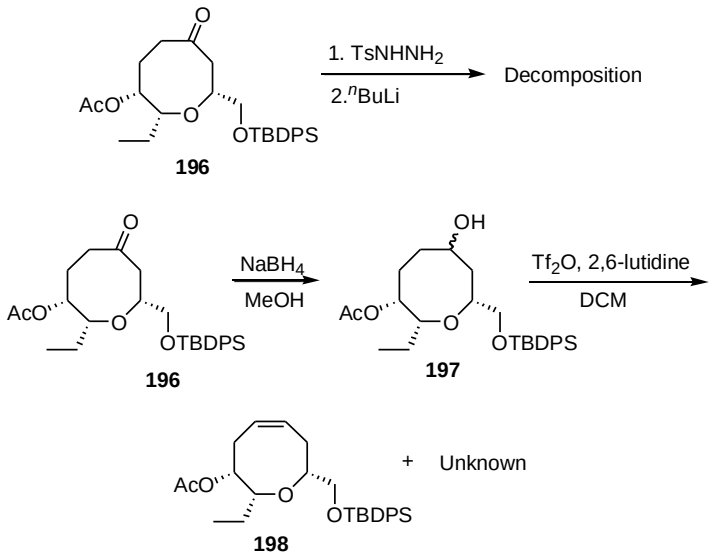
Scheme 3.60: Rearrangement of diazoketoester **140** and the TROESY analysis of product **139** (arrow indicates the correlation).

Having successfully formed the advanced intermediate **139**, it was now necessary to carry out several key transformations: removal of the bridging sulfide, decarboxylation of the carboethoxy group, and installation of the oxocene C=C bond, using the ketone or a suitable derivative as a synthetic handle. Initial efforts to remove the ester via Barton radical conditions were not promising, so we chose to focus on desulfurization first, before returning to the decarboxylation. In the event, treatment of **139** with Raney nickel under the conditions[44] used in Chapter 2 afforded ketoester **193** in 54% yield (Scheme 3.61). This monocyclic keto ester could be decarboxylated under Krapcho-type conditions. The optimal procedure uitilized wet DMF with microwave heating, providing ketone **194** in excellent yield.[45] Removal of the benzyl protecting group under the typical hydrogenation conditions provided compound **195** in 95 % yield. The hydroxyl group in **195** was then protected as *tert*-butyldiphenylsilyl ether **196** in quantitative yield.



Scheme 3.61: Desulfurization, decarboxylation and changing the protecting group towards the target.

To olefinate ketone **196**, the Shapiro reaction was investigated. However, treatment of **196** with tosylhydrazide followed by addition with *n*-butyllithium failed to provide the desired oxocene product (Scheme 3.62). The crude H^1 NMR spectrum indicated the formation of uncharacterizable decomposition products. Then an alternative method was tried via elimination of the corresponding triflate. Reduction of ketone **196** afforded alcohol **197** in quantitative yield, which was then treated with Tf_2O and 2,6-lutidine. However, the desired product **198** was obtained only in trace amount. The major product was an unknown compound without TBDPS group and double bond. Determination of its structure was still under investigation.



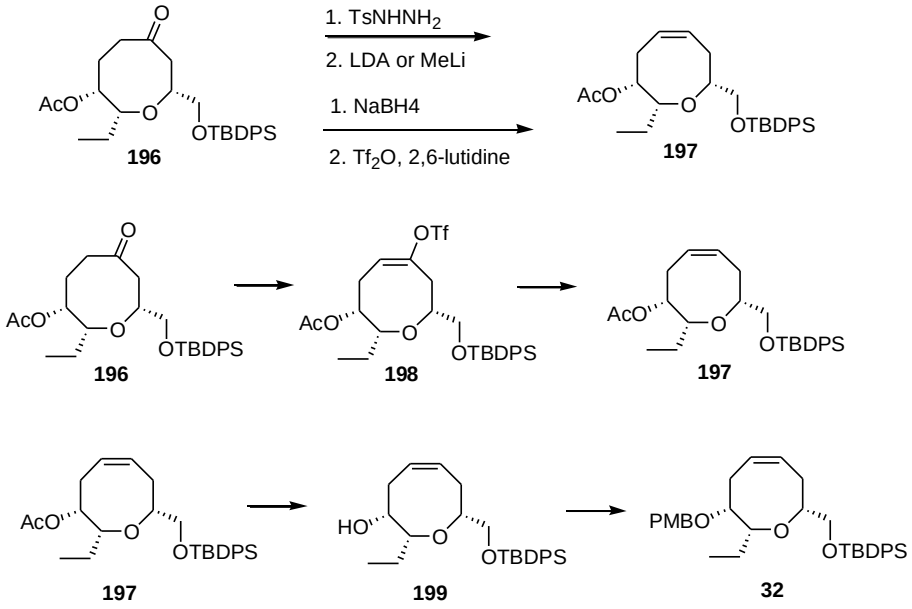
Scheme 3.62: Approach to the oxocene **198**.

3.4. Conclusions and future work

Our efforts toward the formal synthesis of (+)-laurencin have been presented. The key step was the ring expansion of a monothioacetal-derived sulfur ylide, a methodology which has been discussed in detail in Chapter 2. The relative and absolute stereochemistry was established by a highly selective allylboration, a facially selective Michael addition, and thermodynamically controlled acetal formation, and the desired mixed acetal was formed regioselectively via the more favourable *cis* bicyclo[4,3,0]nonane skeleton over *trans* bicycle[4,3,0]nonane skeleton. Then we showed that the eight-membered sulfur-bridged ether could be formed efficiently via the [1,2]-shift reaction of a sulfonium ylide in toluene at 100 ^{o}C catalyzed by Cu(hfacac)$_2$. We further demonstrated that the sulfur-bridge could be easily removed with Raney nickel, and the ester group could be easily removed via decarboxylation under microwave heating.

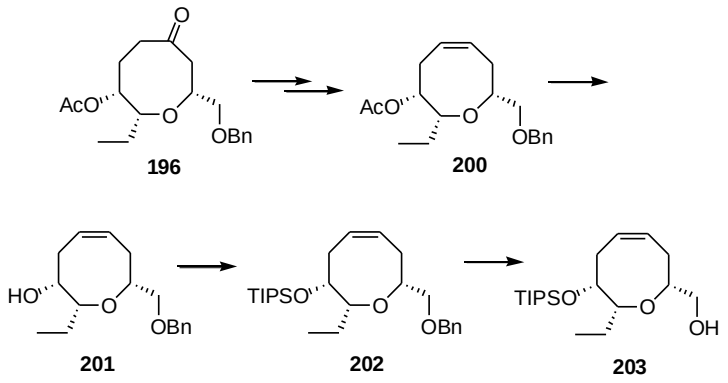
Future work will be focused on the conversion of ketone **196** into alkene **198** (Scheme 3.63). The Shapiro reaction will be evaluated again by changing the base to LDA or MeLi. Also the elimination of triflate strategy will be examined

by lowering the temperature to -78 ^{o}C or 0 ^{o}C. An alternative strategy is also proposed in case the previous two strategies do not work. Treatment of ketone **196** with a suitable base and triflating reagent should furnish enol triflate **198**. Upon treatment of **198** with palladium and reducing reagent, oxocene **197** is expected to be obtained. Then oxocene **197** will be deacylated and protected as a PMB ether to afford the target **32**.



Scheme 3.63: Future plans to obtain target **32**.

We also plan to make Crimmins' intermediate **203**, which seemed to be a better intermediate for the total synthesis of (+)-laurencin considering the later chemistry.[22] As shown in Scheme 3.64, ketone **196** will be converted into compound **200**, which will be deacylated and protected as TIPS ether **202**. Removal of the benzyl group will result in the target **203**. Successful execution of one or more of these projected routes will allow us the option of completing the synthesis of laurencin, or attaining a formal synthesis through preparation of Crimmins' or Holmes' intermediate.



Scheme 3.64: Another plan to access Crimmins' intermediate **203**.

3.5. Experimental

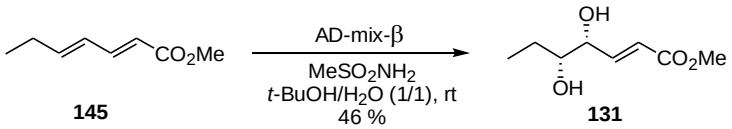
3.5.1. General

Reactions were conducted in oven-dried (120 ^{o}C) or flame-dried glassware under a positive argon atmosphere unless otherwise stated. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes or via cannula. Solvents were dried and distilled before use: dichloromethane over calcium hydride; toluene over sodium; diethyl ether and tetrahydrofuran over sodium benzophenone ketyl. Thin layer chromatography (T.L.C.) was performed on precoated silica plates with 0.25 mm Kiesegel 60 F_{254}. Flash chromatography columns were packed with 230-240 mesh silica gel. Where given, column dimensions reflect outer diameters. Microwave heating was carried out in a Biotage Initiator microwave reactor. Reaction temperature was determined through measurement of the vial surface temperature using an infrared sensor, then correction for internal temperature by the unit's processor using a proprietary algorithm.

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 500 MHz on Varian Inova 500 and Unity 500 spectrometers, and the chemical shifts are reported on the δ scale (ppm) downfield from tetramethysilane. Coupling constants (*J*) are reported in Hz. Second order splitting patterns are

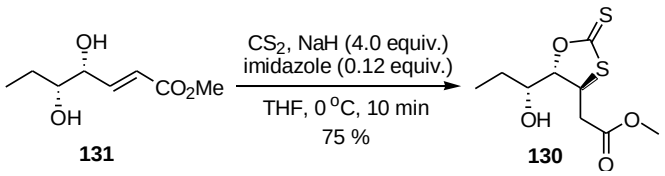
indicated. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets, dt, doublet of triplets, etc. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 125 MHz and are reported in ppm relative to the center line of a triplet at 77.23 ppm for deuterochloroform. Infrared (IR) spectra were measured with a Nicolet Magna 750 FT-IR infrared spectrophotometer. Mass spectra were determined on a Kratos Analytical MS-50 (EI) or Applied Biosystems Mariner Biospectrometry Workstation (ESI). Elemental analyses were obtained on a Carlo Erba CHNS-O EA 1108 Elemental Analyzer.

3.5.2. Substrate syntheses

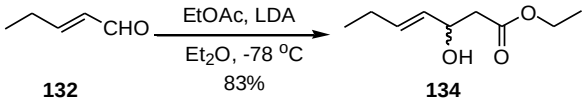


145 **131**

Diol 131. To a well stirred mixture of AD-mix-β (2.44 g) in 10 mL of t-BuOH/H_2O (1/1 v/v) was added methansulfonamide (0.160 g, 1.60 mmol) at room temperature under argon. Then unsaturated ester **145** (0.220 g, 1.60 mmol) was added into the yellow mixture. After stirring vigorously at room temperature for 48 h, 2.500 g of solid Na_2SO_3 was added to quench the reaction. The mixture was stirred for 50 min, extracted with 3×20 mL of CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes:EtOAc 1:1) provided the diol **131** (0.130 g, 46%) as a colorless oil: R_f 0.41 (hexanes:EtOAc 1:1); IR (thin film) 3421, 2965, 2880, 1710, 1660, 1439, 1401, 1313, 1285, 1197, 1174, 1132, 1067, 1037 cm^{-1}; 1H NMR (500 MHz, $CDCl_3$) δ 6.96 (dd, *J* = 15.7, 5.0 Hz, 1H), 6.16 (dd, *J* = 15.7, 1.5 Hz, 1H), 4.16 (dddd, *J* = 5.2, 5.2, 5.2, 1.5 Hz, 1H), 3.76 (s, 3H), 3.50 (app ddt, *J* = 9.8, 5.2, 4.6 Hz, 1H), 2.54 (d, *J* = 5.2 Hz, 1H), 2.18 (d, *J* = 4.6 Hz, 1H), 1.65-1.62 (m, 1H), 1.56-1.50 (m, 1H), 1.01 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 147.1, 122.0, 75.4, 73.7, 51.7, 26.1, 9.9; HRMS (ESI, $[M+Na]^+$) for $C_8H_{14}O_4Na$ calcd 197.0784, found: m/z 197.0784.

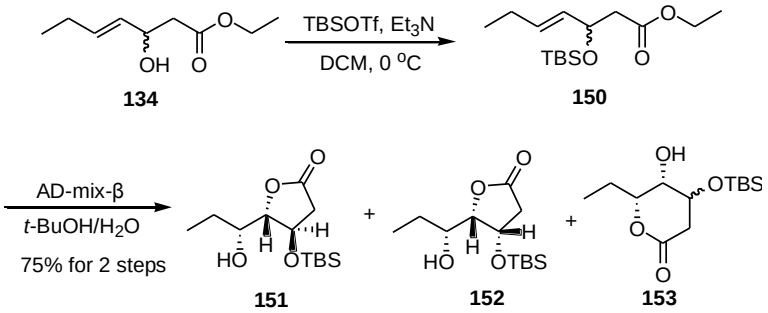


Monothiocarbonate 130. Imidazole (0.036 g, 0.48 mmol) was added to a solution of the ester **131** (0.700 g, 4.00 mmol) in THF (15 mL) under argon and the resulting solution cooled to 0 °C using ice-water bath. Sodium hydride (60% dispersion in mineral oil, 0.640 g, 16.00 mmol) was added to the reaction mixture and the resulting mixture stirred at 0 °C for 10 min followed by the dropwise addition of carbon disulfide (15 mL). After 10 min, the ice bath was removed and the mixture stirred at room temperature for 20 min then carefully poured into a mixture of saturated NH_4Cl (100 mL) and EtOAc (50 mL) with rapid stirring. The aqueous phase was extracted with EtOAc (3×30 mL). The combined organic organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes:EtOAc 2:1) provided the cyclic xanthate **130** (0.750 g, 75%) as a yellow oil: R_f 0.55 (hexanes:EtOAc 1:1); IR (thin film) 3443, 2966, 2879, 1730, 1438, 1350, 1193, 1057 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.76 (dd, *J* = 6.2, 3.5 Hz, 1H), 4.45 (dt, *J* = 8.6, 6.2 Hz, 1H), 3.74 (br s, 4H), 2.92 (dd, *J* = 17.1, 6.2 Hz, 1H), 2.81 (dd, *J* = 17.1, 8.6 Hz, 1H), 1.70-1.76 (m, 2H), 1.06 (t, *J* = 7.4 Hz, 3H) (OH proton not detected); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.3, 170.4, 96.2, 72.5, 52.5, 47.3, 38.7, 26.6, 10.1; HRMS (EI, M^+) for $C_9H_{14}O_4S_2$ calcd 250.0334, found: m/z 250.0337.



Alcohol 134. To a solution of LDA (11.2 mL, 1.8 M in THF, 20.0 mmol) in ether (16 mL) was added ethyl acetate (1.76 g, 20.0 mmol) dropwise at -78 °C, and the resulting mixture was stirred for 1 h. A solution of **132** (1.80 g, 21.4 mmol) in ether (4 mL) was added dropwise to the above mixture and the resulting mixture was stirred overnight, allowing cooling bath to expire. Then the whole mixture

was poured into a mixture of saturated NH_4Cl solution (30 mL) and Et_2O (50 mL). The aqueous phase was extracted with Et_2O (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes:EtOAc 4:1) provided **134** (2.80 g, 83%) as a colorless oil.

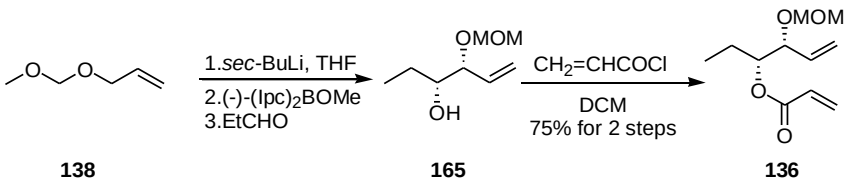


Lactones 151-153. To a solution of **134** (2.800 g, 16.30 mmol) in DCM (50 mL) was added TBSOTf (5.300 g, 20.00 mmol) and triethylamine (2.020 g, 2.80 mL, 20.00 mmol) at 0 °C. After stirring for 0.5 h at 0 °C, the whole mixture was poured into a saturated $NaHCO_3$ solution (40 mL). The aqueous phase was extracted with DCM (2×50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to provide crude **150** (4.580 g, quantitative) as a yellow oil, which was used directly for the next step without purification. Crude **150** and methansulfonamide (2.080 g, 20.80 mmol) were added directly into a well stirred mixture of AD-mix-β (33g) in 130 mL of t-BuOH/H_2O (1/1 v/v) at room temperature under argon. After stirring vigorously at room temperature for one day, 30g of solid Na_2SO_3 was added to quench the reaction. The mixture was stirred for 50 min, extracted with 3×80 mL of DCM, dried over Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes:EtOAc 3:1, 2:1, 1:1) provided **151** (2.210 g, 50%), **152** (0.642 g, 15%) and a mixture of **152** and **153** (0.446 g, 10%, 20:1) for two steps) as colorless oils.

151: R_f 0.60 (hexanes:EtOAc 2:1); IR (thin film) 3453, 2957, 2932, 2885, 2859, 1777, 1472, 1464, 1364, 1259, 1191, 1127, 1060, 1040, 1005 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$) δ 4.53 (ddd, *J* = 7.1, 4.2, 3.3 Hz, 1H), 4.21 (dd, *J* = 3.3, 2.4 Hz, 1H), 3.60 (ddd, *J* = 8.0, 6.2, 2.4 Hz, 1H), 2.88 (dd, *J* = 17.7, 7.1 Hz, 1H), 2.43 (dd, *J* = 17.7, 4.2 Hz, 1H), 1.70-1.60 (m, 2H), 1.02 (t, *J* = 9.5 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 6H) (OH proton not detected); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 89.1, 72.6, 69.9, 38.8, 27.0, 25.6, 17.9, 10.0, -4.7, -4.8.

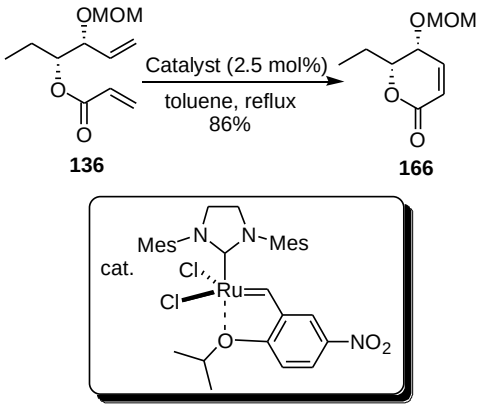
152: R_f 0.35 (hexanes:EtOAc 2:1); IR (thin film) 3470, 2977, 2953, 2937, 2903, 2858, 1765, 1474, 1462, 1443, 1400, 1361, 1343, 1300, 1255, 1218, 1174, 1142, 1097, 1049, 1026, 1007 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.65 (ddd, *J* = 6.5, 4.8, 3.3 Hz, 1H), 4.28 (app t, *J* = 4.8, 4.8 Hz, 1H), 3.92 (ddd, *J* = 10.5, 5.7, 4.8 Hz, 1H), 2.75 (dd, J_{AB} = 17.5, J_{AX} = 6.5 Hz, 1H), 2.56 (dd, J_{AB} = 17.5, J_{BX} = 3.3 Hz, 1H), 1.64-1.56 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 6H) (OH proton not detected); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 85.2, 71.3, 69.6, 39.3, 25.6, 25.1, 17.8, 9.9, -4.5, -5.2.



138 **165** **136**

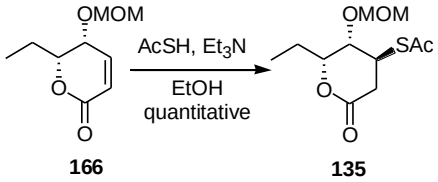
Diene 136. To a well stirred solution of **138** (2.000 g, 20.00 mmol) in THF was added sec-BuLi (27.00 mL, 38.00 mmol, 1.4 M in hexanes) at -78 °C over 0.5 h. After stirring at -78 °C for an additional 0.5 h, (-)-*B*-methoxydiisopinocampheylborane in THF (20.0 mL, 20.0 mmol, 1.0 M) was added dropwise. The mixture was stirred at -78 °C for 1 h, and boron trifluoride etherate (5.0 mL, 40.0 mmol) was added. Immediately afterwards, propionaldehyde (2.0 mL, 30.0 mmol) was added. After stirring at -78 °C for 3 hours, the mixture was slowly warmed up to room temperature. The solvent was removed and the residue was dissolved in ether (50 mL) and oxidized with alkaline hydrogen peroxide for overnight. The aqueous phase was extracted with ether (2×50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Bulb to bulb distillation

at 100 °C (20 mm) provided crude product **165** (3.270 g, TLC indicated some isopinocampheyl alcohol) as a colorless oil, which was then dissolved in DCM (40 mL). To the solution was added triethylamine (4 mL) at 0 °C, followed by addition of acryloyl chloride (2.24 g, 25.00 mmol, 2 mL). After stirring for 0.5 hour, the whole mixture was poured into a saturated $NaHCO_3$ solution (40 mL). The aqueous phase was extracted with DCM (2×40 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes:EtOAc 10:1) provided **136** (3 g, 75 % for 2 steps) as a colorless oil: R_f 0.35 (hexanes:EtOAc 10:1); $[\alpha]^{25}_D$ = -61.79 (c 0.9, $CHCl_3$); IR (thin film) 3050, 2972, 2888, 2824, 1727, 1406, 1296, 1270, 1149, 1095, 1039 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.44 (dd, *J* = 17.3, 1.5 Hz, 1H), 6.17 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.84 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.70 (ddd, *J* = 17.9, 10.3, 6.6 Hz, 1H), 5.36-5.32 (m, 1H), 5.30-5.28 (m, 1H), 5.02 (ddd, *J* = 10.1, 6.6, 4.4 Hz, 1H), 4.69 (d, *J* = 6.8 Hz, 1H), 4.56 (d, *J* = 6.8 Hz, 1H), 4.15 (dd, *J* = 6.6, 6.6 Hz, 1H), 3.36 (s, 3H), 1.75-1.71 (m, 1H), 1.67-1.57 (m, 1H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 134.0, 130.8, 128.5, 119.6, 93.8, 77.5, 76.3, 55.6, 23.4, 9.6; HRMS (ESI, $[M+Na]^+$) for $C_{11}H_{18}O_4Na$ calcd 237.1097, found: m/z 237.1098.



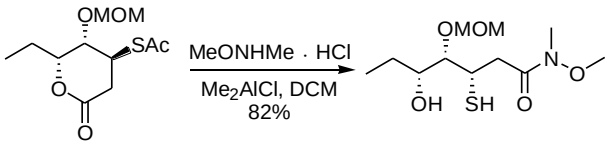
Unsaturated lactone 166. Acrylate **136** (0.230 g, 1.10 mmol) was heated in toluene (25 mL) at 100 °C for 120 min. The nitro substituted Hoveyda-Grubbs catalyst (0.020 g, 0.03 mmol, 2.5 mol%) was added in two portions, 5 h apart. After heating at 100 °C for 1 day, the solvent was removed and the crude product

was purified by column chromatography (silica gel, hexanes:EtOAc 1:1) to provide **166** (0.172 g, 86 %) as a colorless oil: R_f 0.36 (hexanes:EtOAc 1:1); $[\alpha]^{25}_D$ = -221.77 (c 1.4, $CHCl_3$); IR (thin film) 3040, 2973, 2941, 2891, 2827, 1725, 1631, 1465, 1382, 1300, 1258, 1214, 1152, 1114, 1093, 1064, 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.00 (dd, J = 9.8, 5.6 Hz, 1H), 6.12 (dd, J = 9.8 Hz, 1H), 4.70 (d, J_{AB} = 7.0 Hz, 1H), 4.65 (d, J_{AB} = 7.0 Hz, 1H), 4.26 (ddd, J = 8.4, 6.0, 2.8 Hz, 1H), 4.00 (dd, J = 5.5, 2.8 Hz, 1H), 3.34 (s, 3H), 1.97-1.91 (m, 1H), 1.82-1.76 (m, 1H), 1.04 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 143.6, 123.3, 96.2, 81.6, 66.7, 55.8, 23.2, 9.6; HRMS (ESI, $[M+Na]^+$) for $C_9H_{14}O_4Na$ calcd 209.0784, found: m/z 209.0783.



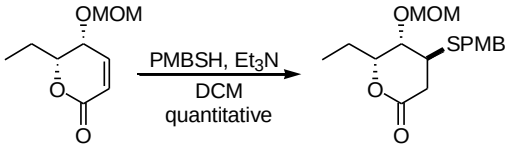
166 **135**

Lactone 135. To a solution of **166** (0.186 g, 1.00 mmol) in EtOH (10 mL) was added thioacetic acid (0.090 g, 1.18 mmol) and 10 drops of triethylamine at room temperature. After stirring at ambient temperature for overnight, the mixture was poured into a mixture of saturated $NaHCO_3$ solution (20 mL) and DCM (20 mL). The aqueous phase was extracted with DCM (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes:EtOAc 2:1) provided Michael adduct **135** (0.280 g, quantitative) as a yellow oil: R_f 0.43 (hexanes:EtOAc 2:1); IR (thin film) 2972, 2827, 1742, 1698, 1464, 1358, 1326, 1247, 1208, 1153, 1120, 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.91 (d, J_{AB} = 7.0 Hz, 1H), 4.69 (d, J_{AB} = 7.0 Hz, 1H), 4.37 (ddd, J = 7.8, 5.8, 1.8 Hz, 1H), 4.03 (ddd, J = 7.3, 3.5, 3.5 Hz, 1H), 3.77 (dd, J = 3.5, 1.8 Hz, 1H), 3.43 (s, 3H), 3.15 (dd, J = 18.1, 7.5 Hz, 1H), 2.58 (dd, J = 18.1, 3.5 Hz, 1H), 2.37 (s, 3H), 1.94-1.88 (m, 1H), 1.74-1.68 (m, 1H), 1.03 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.4, 168.6, 95.7, 80.9, 72.7, 56.4, 38.6, 31.7, 30.7, 24.3, 9.6; HRMS (EI, M^+) for $C_{11}H_{18}O_5S$ calcd 262.0875, found: m/z 262.0867.

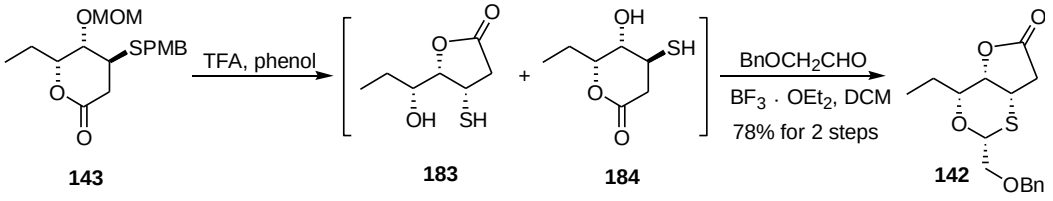


135 **174**

Weinreb Amide 174. A solution of Me_2AlCl (0.50 mL, 1.0 M in hexanes, 0.50 mmol) was added dropwise to a stirred suspension of MeONHMe·HCl (0.049 g, 0.500 mmol) in DCM (2 mL) under argon at 0 ^oC. The resulting mixture was stirred at 0 ^oC for 0.5 hour followed by an additional 0.5 hour at room temperature. Subsequently, a solution of **135** (0.016 g, 0.06 mmol) in DCM (2 mL) was transferred via cannula. After stirring at room temperature for an additional 1 hour, 0.5 mL of HCl (3.0 M) was added. The whole mixture was then poured into 10 mL of aqueous HCl (1 M) solution. The aqueous phase was extracted with two portions of DCM (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, DCM:EtOAc 1:2) provided **174** (0.014 g, 82%) as a yellow oil: R_f 0.38 (DCM:EtOAc 1:2); IR (thin film) 3459, 2938, 2824, 2563, 1657, 1464, 1389, 1326, 1151, 1100, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.79 (d, J_{AB} = 6.7 Hz, 1H), 4.73 (d, J_{AB} = 6.7 Hz, 1H), 3.81-3.78 (m, 1H), 3.78 (s, 2.3H), 3.68 (s, 0.7H), 3.51-3.49 (m, 2H), 3.48 (s, 3H), 3.19 (s, 2.3H), 3.17 (s, 0.7H), 2.91-2.86 (m, 2H), 2.12 (s, 1H), 1.85 (d, J = 9.3 Hz, 1H), 1.66-1.61 (m, 1H), 1.49-1.44 (m, 1H), 1.01 (t, J = 7.3 Hz, 3H) (An unequal mixture (3:1) of amide rotamers was observed, with distinct pairs of singlets for the N-Me and O-Me groups); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 98.4, 85.6, 73.0, 61.3, 56.2, 39.0, 37.3, 26.2, 21.0, 9.6; HRMS (ESI, $[M+Na]^+$) for $C_{11}H_{23}NO_5SNa$ calcd 304.1189, found: m/z 304.1187.

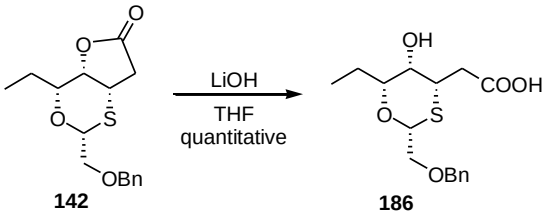


Lactone 143. To a solution of **166** (0.186 g, 1.00 mmol) in DCM (10 mL) was added *p*-methoxybenzylthiol (0.170 g, 1.10 mmol) and 5 drops of triethylamine at room temperature. After stirring at ambient temperature for overnight, the solvent was removed under vacuum. Column chromatography (silica gel, hexanes:EtOAc 2:1) provided **143** (0.339 g, quantitative) as a yellow oil: R_f 0.37 (hexanes:EtOAc 2:1); $[\alpha]^{25}_D$ = -4.2 (c 1.3, $CHCl_3$); IR (thin film) 3010, 2968, 2937, 2837, 1737, 1610, 1584, 1513, 1464, 1442, 1386, 1367, 1319, 1303, 1250, 1206, 1176, 1151, 1109, 1094, 1023 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.24 (m, 2H), 6.88-6.85 (m, 2H), 4.61 (d, J_{AB} = 7.1 Hz, 1H), 4.54 (d, J_{AB} = 7.1 Hz, 1H), 4.53 (ddd, *J* = 7.7, 5.9, 1.8 Hz, 1H), 3.81 (s, 3H), 3.78 (d, J_{AB} = 13.9 Hz, 1H), 3.74 (d, J_{AB} = 13.9 Hz, 1H), 3.70 (dd, *J* = 2.8, 1.8 Hz, 1H), 3.36 (s, 3H), 3.18-3.15 (m, 1H), 3.01 (dd, *J* = 17.7, 7.2 Hz, 1H), 2.46 (dd, *J* = 17.7, 3.9 Hz, 1H), 1.91-1.85 (m, 1H), 1.69-1.64 (m, 1H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 159.3, 130.2, 129.3, 114.4, 95.9, 80.0, 73.2, 56.4, 55.6, 39.2, 35.7, 33.1, 24.4, 9.9; HRMS (EI, M^+) for $C_{17}H_{24}O_5S$ calcd 340.1345, found: m/z 340.1348; Anal. Calcd. for $C_{17}H_{24}O_5S$: C, 59.98; H, 7.11; S, 9.42. Found: C, 59.77; H, 6.96; S, 9.36.



Mixed acetal 142. To a solution of **143** (0.250 g, 0.82 mmol) in trifluoroacetic acid (4.00 mL) was added phenol (0.155 g, 1.64 mmol). After stirring at 70 ^oC for 1h, the solvent was removed under vacuum. The residue was dissolved in DCM (60 mL), washed with saturated $NaHCO_3$ solution (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. A quick column

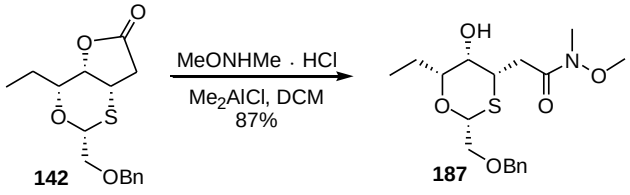
chromatography (hexanes:EtOAc 1:1) provided crude products as a mixture of two isomeric mercaptoalcohols **183** and **184**, which was utilized directly for the next step. To a solution of benzyloxyacetaldehyde (0.300 g, 1.53 mmol) in DCM (10 mL) at 0°C was added $BF_3 \cdot OEt_2$ (0.40 mL, 3.20 mmol). After stirring at 0°C for 5 minutes, a solution of **183** and **184** (crude from previous step without further purification) in DCM (5 mL) was transferred dropwise into the reaction mixture via cannula. The whole resulting solution was stirred for 0.5 h, then was poured into a mixture of DCM (20 mL) and water (30 mL). The aqueous phase was extracted with DCM (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes:EtOAc 1:1) provided solid **142** (0.194 g, 87 % for 2 steps) as a single diastereomer: m.p. 102-106 °C; R_f 0.38 (hexanes:EtOAc 1:1); $[\alpha]^{25}_D$ = -140.87 (c 0.2, $CHCl_3$); IR (thin film) 3088, 3035, 3010, 2982, 2970, 2943, 2932, 2911, 2880, 1792, 1765, 1496, 1456, 1414, 1401, 1390, 1377, 1370, 1359, 1341, 1316, 1272, 1256, 1229, 1200, 1155, 1118, 1078, 1065, 1045, 1028, 1007 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.33 (m, 4H), 7.31-7.27 (m, 1H), 5.01 (dd, *J* = 6.1, 4.6 Hz, 1H), 4.63 (d, J_{AB} = 12.0 Hz, 1H), 4.60 (d, J_{AB} = 12.0 Hz, 1H), 4.20 (dd, *J* = 3.9, 1.7 Hz, 1H), 3.98 (dd, *J* = 5.9, 3.9 Hz, 1H), 3.78 (dd, *J* = 10.8, 6.1 Hz, 1H), 3.61 (dd, *J* = 10.8, 4.6 Hz, 1H), 3.52 (ddd, *J* = 7.9, 5.9, 1.7 Hz, 1H), 2.96 (dd, *J* = 17.3, 5.9 Hz, 1H), 2.44, (d, *J* = 17.3 Hz, 1H), 1.94-1.87 (m, 1H), 1.78-1.72 (m, 1H), 1.04 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 137.9, 128.7, 128.1, 128.1, 81.3, 79.8, 74.0, 73.0, 71.9, 38.7, 38.4, 25.6, 10.2; HRMS (EI, M^+) for $C_{16}H_{20}O_4S$ calcd 308.1083, found: m/z 308.1084; Anal. Calcd. for $C_{16}H_{20}O_4S$: C, 62.31; H, 6.54; S, 10.40. Found: C, 61.96; H, 6.55; S, 10.23.



142 **186**

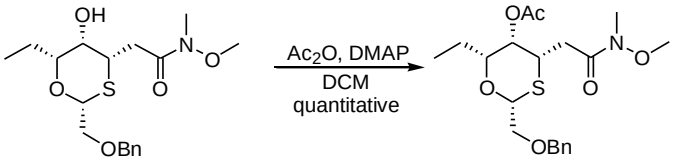
Acid 186. A solution of LiOH (2.0 N, 0.5 mL, 1.0 mmol) was added into a solution of **142** (0.031 g, 0.10 mmol) in THF (2 mL) at room temperature. After

stirring at ambient temperature for overnight, the whole mixture was poured into a mixture of HCl (10 mL, 1 N) and DCM (15 mL). The aqueous phase was extracted with DCM (2×15 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and filtered. After removing the solvent, **186** (0.032 g, quantitative) was obtained as a colorless oil: IR (thin film) 3500-2877, 3064, 3031, 2968, 2935, 2876, 1729, 1497, 1454, 1390, 1250, 1215, 1155, 1083, 1052, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.33 (m, 4H), 7.33-7.28 (m, 1H), 5.05 (dd, J = 5.8, 4.5 Hz, 1H), 4.63 (d, J_{AB} = 12.2 Hz, 1H), 4.60 (d, J_{AB} = 12.2 Hz, 1H), 3.72 (dd, J = 10.8, 5.8 Hz, 1H), 3.61 (dd, J = 10.8, 4.5 Hz, 1H), 3.64-3.60 (m, 1H), 3.55-3.53 (m, 1H), 3.32 (dd, J = 7.3, 6.0 Hz, 1H), 2.85 (dd, J = 17.0, 8.2 Hz, 1H), 2.59 (dd, J = 17.0, 6.0 Hz, 1H), 1.80-1.66 (m, 1H), 1.64-1.58 (m, 1H), 0.94 (t, J = 7.4 Hz, 3H) (OH, COOH protons not detected); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 137.9, 128.7, 128.1, 128.0, 84.4, 83.3, 73.9, 71.7, 64.6, 44.4, 36.4, 25.4, 10.0; HRMS (ESI, $[M-H]^-$) for $C_{16}H_{21}O_5S$ calcd 325.1115, found: m/z 325.1117.



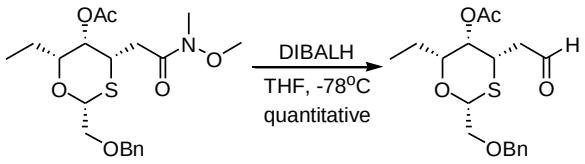
Weinreb Amide 187. 4.00 mL Me_2AlCl solution (1.0 M in hexanes, 4.00 mmol) was added dropwise to a stirred suspension of MeONHMe·HCl (0.390 g, 4.00 mmol) in DCM (25 mL) under argon at 0 ^oC. The resulting mixture was stirred at 0 ^oC for 0.5 h and at room temperature for 0.5 hour. Then a solution of **142** (0.243 g, 1.130 mmol) in DCM (10 mL) added in via cannula. After stirring at room temperature for 1 hour, 2 mL HCl (3 M) was added. Then the whole mixture was poured into 20 mL HCl (1 M) solution. The aqueous phase was extracted with DCM (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, DCM:EtOAc 2:1) provided **187** (0.360 g, 87%) as a colorless oil: R_f

0.45 (DCM:EtOAc 2:1); $[\alpha]^{25}_{D}$ = 80.65 (c 0.3, $CHCl_3$); IR (thin film) 3070, 3063, 3031, 2967, 2937, 2875, 1659, 1496, 1454, 1418, 1388, 1272, 1199, 1179, 1123, 1097, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.32 (m, 4H), 7.30-7.27 (m, 1H), 5.06 (dd, *J* = 6.0, 4.3 Hz, 1H), 4.61 (d, J_{AB} = 12.2 Hz, 1H), 4.57 (d, J_{AB} = 12.2 Hz, 1H), 3.76 (ddd, *J* = 8.6, 5.4, 1.4 Hz, 1H), 3.72 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.68 (s, 3H), 3.60 (dd, *J* = 10.8, 4.3 Hz, 1H), 3.50 (br s, 1H), 3.34 (ddd, *J* = 7.8, 5.8, 0.6 Hz, 1H), 3.18 (s, 3H), 2.93-2.86 (m, 1H), 2.53-2.46 (m, 1H), 1.75-1.69 (m, 1H), 1.61-1.56 (m, 1H), 0.94 (t, *J* = 7.5 Hz, 3H) (OH proton not detected); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 138.1, 128.7, 128.0, 128.0, 84.4, 83.3, 73.8, 71.9, 64.9, 61.7, 44.6, 34.1, 32.4, 25.4, 10.0; HRMS (ESI, $[M+Na]^+$) for $C_{18}H_{27}NO_5SNa$ calcd 392.1502, found: m/z 392.1501.



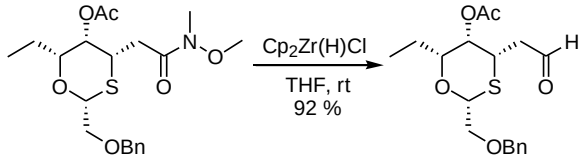
Weinreb Amide 189. To a solution of **187** (0.067 g, 0.18 mmol) in DCM (5 mL) was added acetic anhydride (0.050 g, 0.50 mmol) and DMAP (0.045 g, 0.37 mmol). After stirring at room temperature for overnight, the mixture was poured into a saturated $NaHCO_3$ solution (20 mL). The aqueous phase was extracted with DCM (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, Hexanes:EtOAc 1:1) provided **189** (0.074 g, quantitative yield) as a colorless oil: R_f 0.43 (Hexanes:EtOAc 1:1); $[\alpha]^{25}_{D}$ = -11.13 (c 1.2, $CHCl_3$); IR (thin film) 3029, 2968, 2940, 2863, 1737, 1662, 1497, 1454, 1422, 1386, 1369, 1322, 1234, 1122, 1085, 1040, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.34 (m, 4H), 7.30-7.27 (m, 1H), 5.16 (dd, *J* = 6.2, 4.4 Hz, 1H); 5.09 (dd, *J* = 1.7, 1.7 Hz, 1H), 4.62 (d, J_{AB} = 12.1 Hz, 1H), 4.58 (d, J_{AB} = 12.1 Hz, 1H), 3.93-3.89 (m, 1H), 3.79 (dd, *J* = 10.8, 6.2 Hz, 1H), 3.63 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.63 (s, 3H), 3.47 (ddd, *J* = 8.2, 5.2, 1.3 Hz, 1H), 3.18 (s, 3H), 2.70-2.65 (m, 1H), 2.42-

2.38 (m, 1H), 2.19 (s, 3H), 1.60-1.55 (m, 1H), 1.46-1.43 (m, 1H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 170.8, 138.1, 128.7, 128.0, 128.0, 83.5, 82.9, 73.8, 72.0, 66.0, 61.5, 41.6, 33.8, 32.5, 25.4, 21.1, 10.1; HRMS (ESI, $[M+Na]^+$) for $C_{20}H_{29}NO_6SNa$ calcd 434.1608, found: m/z 434.1601.



189 **141**

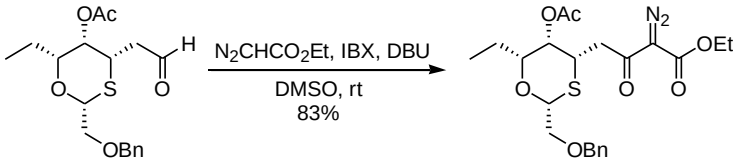
Aldehyde 141 (DIBALH Reduction). To a solution of **189** (0.021 g, 0.050 mmol) in THF at -78 °C was added DIBALH solution (60 μL, 1.0 M in DCM, 0.06 mmol). After stirring at -78 °C for 1 h, 50 mg $Na_2SO_4 \cdot 10H_2O$ was added and the reaction mixture was warmed to room temperature. The whole mixture was stirred for 2 h and filtered through a short pad consisting of a 1:1 mixture of $MgSO_4$ and Celite. The filtrate was concentrated and column chromatography (silica gel, hexanes:EtOAc 2:1) provided **141** (0.018 g, quantitative yield) as a colorless oil. Spectral data for **141** are given at the end of the next procedure.



189 **141**

Aldehyde 141 ($Cp_2Zr(H)Cl$ Reduction). To a suspension of $Cp_2Zr(H)Cl$ (0.320 g, 1.24 mmol) in THF (10 mL) was added **189** (0.340 g, 0.83 mmol) in THF (3 mL) at room temperature under argon. The mixture was stirred until the suspension turned clear and then poured into a mixture of water (30 mL) and ether (30 mL). The aqueous phase was extracted with ether (2×30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes:EtOAc 2:1) provided **141** (0.270 g, 92 %) as a colorless oil: R_f 0.45 (hexanes:EtOAc 2:1);

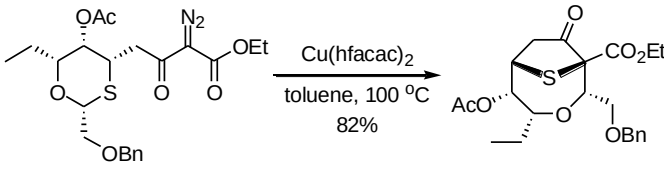
$[\alpha]^{25}_D$ = -12.30 (c 0.2, $CHCl_3$); IR (thin film) 3063, 3031, 2968, 2938, 2877, 1737, 1497, 1454, 1374, 1234, 1124, 1093, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.36-7.33 (m, 4H), 7.31-7.28 (m, 1H), 5.16 (dd, *J* = 6.0, 4.7 Hz, 1H), 5.02-4.93 (m, 1H), 4.62 (d, J_{AB} = 12.0 Hz, 1H), 4.59 (d, J_{AB} = 12.0 Hz, 1H), 3.89 (ddd, *J* = 7.7, 6.4, 1.9 Hz, 1H), 3.80 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.64 (dd, *J* = 10.8, 4.7 Hz, 1H), 3.47 (ddd, *J* = 8.1, 5.4, 1.3 Hz, 1H), 2.70 (ddd, *J* = 18.2, 7.7, 0.7 Hz, 1H), 2.45 (ddd, *J* = 18.2, 6.4, 1.3 Hz, 1H), 2.17 (s, 3H), 1.62-1.57 (m, 1H), 1.46-1.40 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 171.4, 138.0, 128.7, 128.1, 83.6, 82.8, 73.9, 71.8, 65.8, 45.6, 39.6, 25.3, 21.0, 10.0 (one of phenyl carbons not detected due to spectral overlap); HRMS (ESI, $[M+Na]^+$) for $C_{18}H_{24}O_5SNa$ calcd 375.1237, found: m/z 375.1233; Anal. Calcd for $C_{18}H_{24}O_5S$: C, 61.34; H, 6.86; S, 9.10. Found: C, 61.46; H, 6.83; S, 9.07.



141 **140**

Diazoketoester 140. To a solution of ethyl diazoacetate (7.0 μL, 0.05 mmol) in DMSO (1 mL) at room temperature was added DBU (1.0 μL, 0.006 mmol), compound **141** (0.018 g, 0.05 mmol) and IBX (0.030 mg, 0.10 mmol). After **141** was totally consumed, the whole solution was poured into the mixture of $Na_2S_2O_3$ solution (10 %, 10 mL) and ether (15 mL). The aqueous phase was extracted with ether (2×10 mL). The combined ether layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes:EtOAc 3:1) provided **140** (0.019 g, 83 %) as a colorless oil: R_f 0.38 (hexanes:EtOAc 3:1); $[\alpha]^{25}_D$ = 20.50 (c 1.1, $CHCl_3$); IR (thin film) 3064, 3030, 2974, 2938, 2862, 2138, 1737, 1716, 1655, 1497, 1454, 1375, 1302, 1235, 1180, 1126, 1093, 1055, 1027, 991 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.32 (m, 4H), 7.32-7.27 (m, 1H), 5.15 (dd, *J* = 6.1, 4.5 Hz, 1H), 5.04-4.92 (m, 1H), 4.63 (d, J_{AB} = 12.1 Hz, 1H), 4.60 (d, J_{AB} = 12.1 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H),

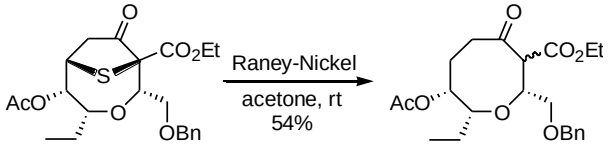
3.97 (ddd, *J* = 8.5, 5.6, 1.2 Hz, 1H), 3.80 (dd, *J* = 10.7, 6.1 Hz, 1H), 3.64 (dd, *J* = 10.7, 4.53 Hz, 1H), 3.46 (ddd, *J* = 8.0, 5.2, 0.9 Hz, 1H), 3.27 (dd, J = 17.6, 8.6 Hz, 1H), 2.71 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.16 (s, 3H), 1.64-1.55 (m, 1H), 1.46-1.38 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.3, 171.5, 161.3, 138.1, 128.7, 128.1, 128.0, 83.6, 82.8, 73.9, 72.0, 65.7, 61.8, 41.3, 41.1, 25.4, 21.0, 14.6, 10.1 (diazo carbon not detected); HRMS (ESI, $[M+Na]^+$) for $C_{22}H_{28}N_2O_7SNa$ calcd 487.1509, found: m/z 487.1507.



140 **139**

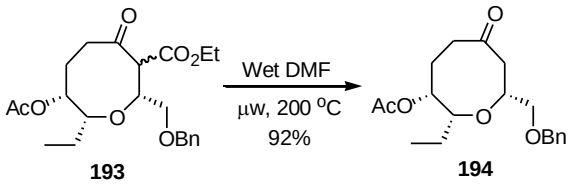
Compound 139. To a solution of **140** (0.019 g, 0.04 mmol) in toluene (8 mL) at 100 °C was added powder $Cu(hfacac)_2$ (0.003 g, 0.004 mmol, 10 mol%). After stirring at 100 °C for 1 hour, the starting material was completely consumed. The reaction mixture was cooled to room temperature and diluted with ether (30 mL). The resulting mixture was washed with water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes:EtOAc 3:1) provided **139** (0.014 g, 82%) as a yellow oil: R_f 0.39 (hexanes:EtOAc 3:1); $[\alpha]^{25}_D$ = 66.02 (c 0.64, $CHCl_3$); IR (thin film) 3064, 3031, 2969, 2936, 2877, 1765, 1741, 1497, 1454, 1372, 1326, 1232, 1173, 1150, 1099, 1067, 1026 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.30 (m, 4H), 7.28-7.26 (m, 1H), 5.19 (dd, *J* =7.2, 3.4 Hz, 1H), 4.60 (ddd, *J* = 9.4, 3.7, 3.7 Hz, 1H), 4.53 (d, J_{AB} = 10.8 Hz, 1H), 4.48 (d, J_{AB} = 10.8 Hz, 1H), 4.31 (dd, *J* = 7.1, 4.5 Hz, 1H), 4.13-4.02 (m, 2H), 3.87 (dd, *J* = 8.2, 7.3 Hz, 1H), 3.71 (dd, *J* = 10.6, 4.5 Hz, 1H), 3.61 (dd, *J* = 10.6, 7.1 Hz, 1H), 3.05 (dd, *J* = 19.0, 0.9 Hz, 1H), 2.70 (dd, *J* = 19.0, 9.2 Hz, 1H), 2.11 (s, 3H), 1.60-1.56 (m, 1H), 1.42-1.37 (m, 1H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6, 170.3, 165.7, 138.2, 128.5, 128.0, 127.9, 88.7, 85.1, 77.0, 73.7, 70.4, 64.6, 62.3, 41.9,

19.0, 25.3, 21.0, 14.1, 10.6; HRMS (ESI, $[M+Na]^+$) for $C_{22}H_{28}O_7SNa$ calcd 459.1448, found: m/z 459.1453.



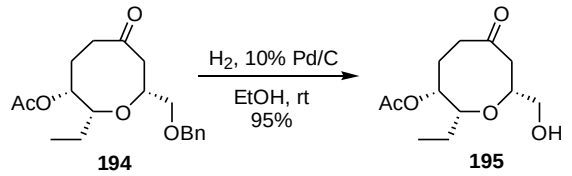
139 **193**

Ketoester 193. To a suspension of Raney nickel 4200 (Aldrich; 100 g suspended in 100 mL water, ~5 g) in acetone (10 mL) was added compound **139** (0.140 g, 0.32 mmol) at room temperature. This resulting mixture was stirred for 0.5 h until starting material was totally consumed and then the reaction mixture was filtered through qualitative filter paper (Whatman; #2). The residue on the filter paper was washed with acetone (3×5 mL). The combined filtrates were concentrated. The residue was redissolved with DCM (50 mL), washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes:EtOAc 3:1) gave a mixture of two inseparable diastereomers **193** (0.070 g, 54%, ~20:1) as a yellow oil: R_f 0.39 (hexanes:EtOAc 3:1); IR (thin film) 3050, 2967, 2937, 2876, 1738, 1706, 1497, 1454, 1371, 1340, 1303, 1240, 1181, 1153, 1096, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ Major: 7.37-7.27 (m, 5H), 4.90 (ddd, J = 8.5, 3.7, 2.3 Hz, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.20-4.17 (m, 2H), 4.17-4.05 (m, 2H), 3.74 (dd, J_{AB} = 10.7, J_{AX} = 4.0 Hz, 1H), 3.67 (dd, J_{AB} = 10.7, J_{BX} = 2.3 Hz, 1H), 3.23 (ddd, J = 7.9, 4.9, 2.4 Hz, 1H), 2.86 (ddd, J = 14.3, 8.7, 2.5 Hz, 1H), 2.49 (ddd, J = 14.0, 11.3, 2.7 Hz, 1H), 2.40-2.35 (m, 1H), 2.09 (s, 3H), 2.10-2.03 (m, 1H), 1.63-1.55 (m, 1H), 1.45-1.40 (m, 1H), 1.20 (t, J = 7.4 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.8, 170.7, 167.8, 138.3, 128.6, 127.9, 127.9, 82.3, 81.7, 73.7, 73.3, 72.5, 61.5, 60.1, 40.3, 27.0, 25.5, 21.3, 14.2, 10.5; HRMS (ESI, $[M+Na]^+$) for $C_{22}H_{30}O_7Na$ calcd 429.1884, found: m/z 429.1888.



193 194

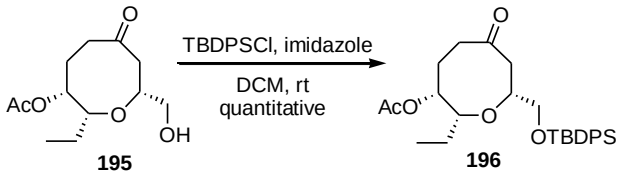
Ketone 194. To a solution of **193** (0.030 g, 0.07 mmol) in DMF (1.5 mL) in a 5 mL Biotage microwave vial was added 1 drop of water. The vial was sealed and the resulting mixture was subjected to microwave irradiation (200 ^{o}C) in a Biotage Initiator microwave reactor for 0.5 h. (See the general information for description of temperature monitoring in microwave reactions.) The reaction mixture was cooled down and diluted with ether (30 mL), washed with water (15 mL), brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes:EtOAc 2:1) gave **194** (0.023 g, 92%) as a yellow oil: R_f 0.26 (hexanes:EtOAc 2:1); $[\alpha]^{25}_{D} = 26.04^{o}$ (c 0.40, $CHCl_3$); IR (thin film) 3063, 3031, 2966, 2937, 2877, 1734, 1699, 1497, 1454, 1375, 1341, 1317, 1241, 1167, 1117, 1082, 1027 1027 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.31 (m, 4H), 7.31-7.27 (m, 1H), 4.81 (ddd, *J* = 10.4, 4.7, 2.5 Hz, 1H), 4.59 (d, J_{AB} = 12.1 Hz, 1H), 4.57 (d, J_{AB} = 12.1 Hz, 1H), 3.83 (dddd, *J* = 10.8, 5.5, 5.5, 2.1 Hz, 1H), 3.65 (dd, *J* = 10.0, 5.5 Hz, 1H), 3.51 (dd, *J* = 10.0, 5.5 Hz, 1H), 3.07 (ddd, *J* = 9.1, 4.3, 2.5 Hz, 1H), 3.01 (app t, *J* = 10.8, 10.8 Hz, 1H), 2.61-2.56 (m, 1H), 2.56-2.48 (m, 1H), 2.46-2.43 (m, 1H), 2.43-2.37 (m, 1H), 2.08 (s, 3H), 2.02-2.00 (m, 1H), 1.63-1.57 (m, 1H), 1.40-1.37 (m, 1H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.8, 170.7, 138.3, 128.6, 127.9, 127.9, 81.4, 81.4, 74.8, 73.6, 73.0, 45.7, 41.3, 25.8, 25.8, 21.3, 10.5; HRMS (ESI, $[M+Na]^{+}$) for $C_{19}H_{26}O_5Na$ calcd 357.1672, found: m/z 357.1678.



194 195

Ketone 195. To a solution of **194** (0.023 g, 0.07 mmol) in EtOH (5 mL) was added 10% w/w Pd/C (0.005 g). The whole mixture was shaken under 55 psi H_2

atmosphere using a Parr shaker for overnight and then filtered. The filtrate was concentrated to yield **195** (0.016 g, 95%) as a colorless oil: R_f 0.33 (DCM:EtOAc 1:1); $[\alpha]^{25}_D = 21.26^o$ (c 0.19, $CHCl_3$); IR (thin film) 3458, 2967, 2938, 2879, 1735, 1700, 1457, 1413, 1376, 1327, 1243, 1163, 1141, 1123, 1071, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.82 (ddd, *J* = 10.3, 4.4, 2.3, 1H), 3.76 (dddd, *J* = 11.0, 7.0, 3.7, 2.2 Hz, 1H), 3.71-3.62 (m, 2H), 3.11 (ddd, *J* = 10.9, 4.5, 2.3 Hz, 1H), 3.04 (app t, *J* = 11.0, 11.0 Hz, 1H), 2.61-2.56 (m, 1H), 2.55-2.47 (m, 1H), 2.47-2.39 (m, 1H), 2.27 (dd, *J* = 11.0, 2.1 Hz, 1H), 2.10 (s, 3H), 2.06-2.00 (m, 1H), 1.66-1.57 (m, 1H), 1.46-1.38 (m, 1H), 0.93 (t, *J* = 7.4 Hz, 3H) (OH proton not detected); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.1, 170.6, 82.4, 81.1, 74.7, 66.2, 44.8, 41.3, 25.8, 25.6, 21.3, 10.5; HRMS (ESI, $[M+Na]^+$) for $C_{12}H_{20}O_5Na$ calcd 267.1203, found: m/z 267.1204.



Ketone 196. To a solution of **195** (0.016 g, 0.07 mmol) in DCM (5 mL) was added TBDPSCl (0.066 g, 0.24 mmol) and imidazole (0.016 g, 0.24 mmol) at room temperature. After **195** was totally consumed, the whole solution was poured into the mixture of HCl solution (1M, 10 mL) and DCM (15 mL). The aqueous phase was extracted with DCM (2×10 mL). The combined organic layers were washed with saturated $NaHCO_3$ (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, hexanes:EtOAc 4:1) provided **196** (31 mg, quantitative) as a colorless oil: R_f 0.27 (hexanes:EtOAc 4:1); $[\alpha]^{25}_D = 29.56$ (c 0.97, $CHCl_3$); IR (thin film) 3072, 3049, 3016, 2963, 2932, 2879, 2858, 1736, 1701, 1473, 1463, 1428, 1390, 1375, 1362, 1341, 1242, 1167, 1082, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70-7.68 (m, 4H), 7.45-7.37 (m, 6H), 4.79 (ddd, *J* = 10.3, 4.6, 2.3 Hz, 1H), 3.82 (dd, *J* = 10.1, 4.9 Hz, 1H), 3.75-3.70 (m, 1H), 3.63 (dd, *J* = 10.1, 6.3 Hz, 1H), 3.04 (ddd, *J* = 9.0, 4.2, 2.3 Hz, 1H), 2.98 (app t, *J* = 10.8, 10.8 Hz, 1H), 2.59 (ddd, *J* = 15.9, 6.6, 2.1

Hz, 1H), 2.55 (dd, J = 10.8, 2.1 Hz, 1H), 2.55-2.47 (m, 1H), 2.44-2.37 (m, 1H), 2.08 (s, 3H), 2.02-1.96 (m, 1H), 1.56-1.48 (m, 1H), 1.37-1.29 (m, 1H), 1.07 (s, 9H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2, 170.7, 136.0, 135.9, 133.6, 133.5, 130.0, 128.0, 127.9, 82.8, 81.0, 74.9, 66.9, 45.8, 41.4, 27.1, 25.8, 25.8, 21.3, 19.5, 10.4 (one of phenyl carbons not detected due to spectral overlap); HRMS (ESI, $[M+Na]^+$) for $C_{28}H_{38}O_5SiNa$ calcd 505.2381, found: m/z 505.2389.

3.6. References

1. Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron Lett.* **1965**, 1091.
2. Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron* **1968**, *24*, 4193.
3. Masuda, M.; Abe, T.; Sato, S. *J. Phycol*. **1997**, *33*, 196.
4. Cameron, A. F.; Cheung, K. K.; Ferguson, G.; Robertson, J. M. *J. Chem. Soc., Chem. Commun*. **1965**, 638.
5. Cameron, A. F.; Cheung, K. K.; Ferguson, G.; Robertson, J. M. *J. Chem. Soc. B* **1969**, 559.
6. Murai, A.; Murase, H.; Matsue, H.; Masamune, T. *Tetrahedron Lett.* **1977**, *18*, 2507.
7. Masamune, T.; Matsue, H.; Murase, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 127.
8. Masamune, T.; Murase, H.; Matsue, H.; Murai, A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 135.
9. Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345.
10. Masamune, T.; Matsue, H. *Chem. Lett.* **1975**, *4*, 895.
11. Robinson, R. A.; Clark, J. S.; Holmes, A. B. *J. Am. Chem. Soc*. **1993**, *115*, 10400.
12. Burton, J. W.; Clark, J. S.; Bendall, J.; Derrer, S.; Stork, T.; Holmes, A. B. *J. Am. Chem. Soc.* **1996**, *118*, 6808.
13. Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483.

14. Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
15. Petasis, N. A.; Lu, S. P.; Bzowej, E. I.; Staszewski, J. P.; Akritopoulou-Zanze, I.; Pantane, M. A.; Hu, Y. H. *Pure Appl. Chem.* **1996**, *68*, 667.
16. Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958.
17. Blumenkopf, T. A.; Bratz, M.; Castañeda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc*. **1990**, *112*, 4386.
18. Krüger, J.; Hoffmann, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7499.
19. Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067.
20. Mujica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *J. Org. Chem*. **1998**, *63*, 9728.
21. Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653.
22. Crimmins, M. T.; Emmitte, K. A. *Org. Lett*. **1999**, *1*, 2029.
23. Baek, S.; Jo, H.; Kim, H.; Kim, H.; Kim, S.; Kim, D. *Org. Lett*. **2005**, *7*, 75.
24. (a) Fujiwara, K.; Yoshimoto, S.; Takizawa, A.; Souma, S-i.; Mishima, H.; Murai, A.; Kawa, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 6819. (b) Fujiwara, K.; Souma, S.; Mishima, H.; Murai, A. *Synlett* **2002**, *1493*.
25. Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett*. **1989**, *30*, 1281.
26. Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett*. **1989**, *30*. 3999.
27. Adsool, V. A.; Pansare, S. V. *Org. Biomol. Chem.* **2008**, *6*, 2011.
28. Sunazuka, T.; Hirose, T.; Chikaraishi, N.; Harigaya, Y.; Hayashi, M.; Komiyama, K.; Sprengeler, P. A.; Smith, A. B.; Ōmura, S. *Tetrahedron* **2005**, *61*, 3789.
29. (a) Weinstein, D. S.; Nicolaou, K. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 545. (b) Pakulski, Z.; Zamojski, A. *Tetrahedron* **1995**, *51*, 871.
30. Yamamoto, Y.; Yatagai, H.; Saito, Y.; Maruyama, K. *J. Org. Chem*. **1984**, *49*, 1096.
31. Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc*. **1988**, *110*, 1535.

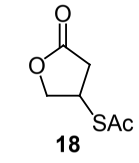
32. Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318.
33. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
34. Busqué, F.; de March, P.; Figueredo, M.; Font, J.; González, L. *Eur. J. Org. Chem.* **2004**, 1492.
35. Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron* **1997**, *38*, 2685.
36. Wallace, O. B.; Springer, D. M. *Tetrahedron Lett.* **1998**, *39*, 2693.
37. Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635.
38. Kieczykowski, G. R.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 1938.
39. Holler, T. P.; Spaltenstein, E.; Turner, E.; Klevit, R. E.; Shapiro, B. M.; Hopkins, P. B. *J. Org. Chem.* **1987**, *52*, 4420.
40. Hodgson, D. M.; Bailey, J. M.; Villalonga-Barber, C.; Drew, M. G. B.; Harrison, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3432.
41. Yadav, J. S.; Reddy, B. V. S.; Eeshwaraiah, B.; Reddy, P. N. *Tetrahedron* **2005**, *61*, 875.
42. Erhunmwunse, M. O.; Steel, P. G. *J. Org. Chem.* **2008**, *73*, 8675.
43. Spletstoser, J. T.; White, J. M.; Tunoori, A. R.; Georg. G. I. *J. Am. Chem. Soc.* **2007**, *129*, 3408.
44. Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1993**, *115*, 30.
45. Curran, D. P.; Zhang, Q. *Adv. Synth. Catal.* **2003**, 329.

Appedix I: Selected NMR Spectra

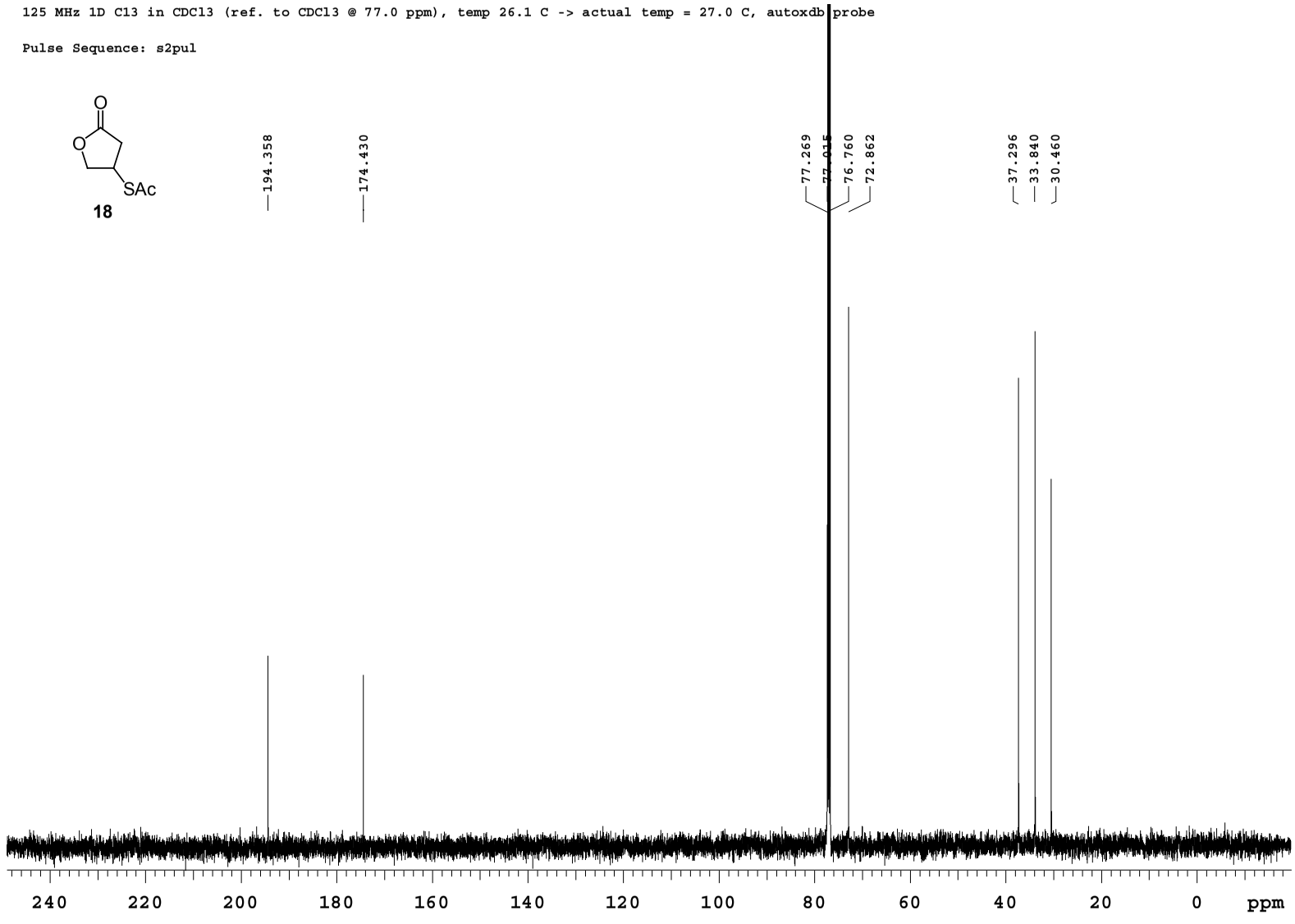
(Chapter 2)

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul

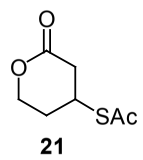


18

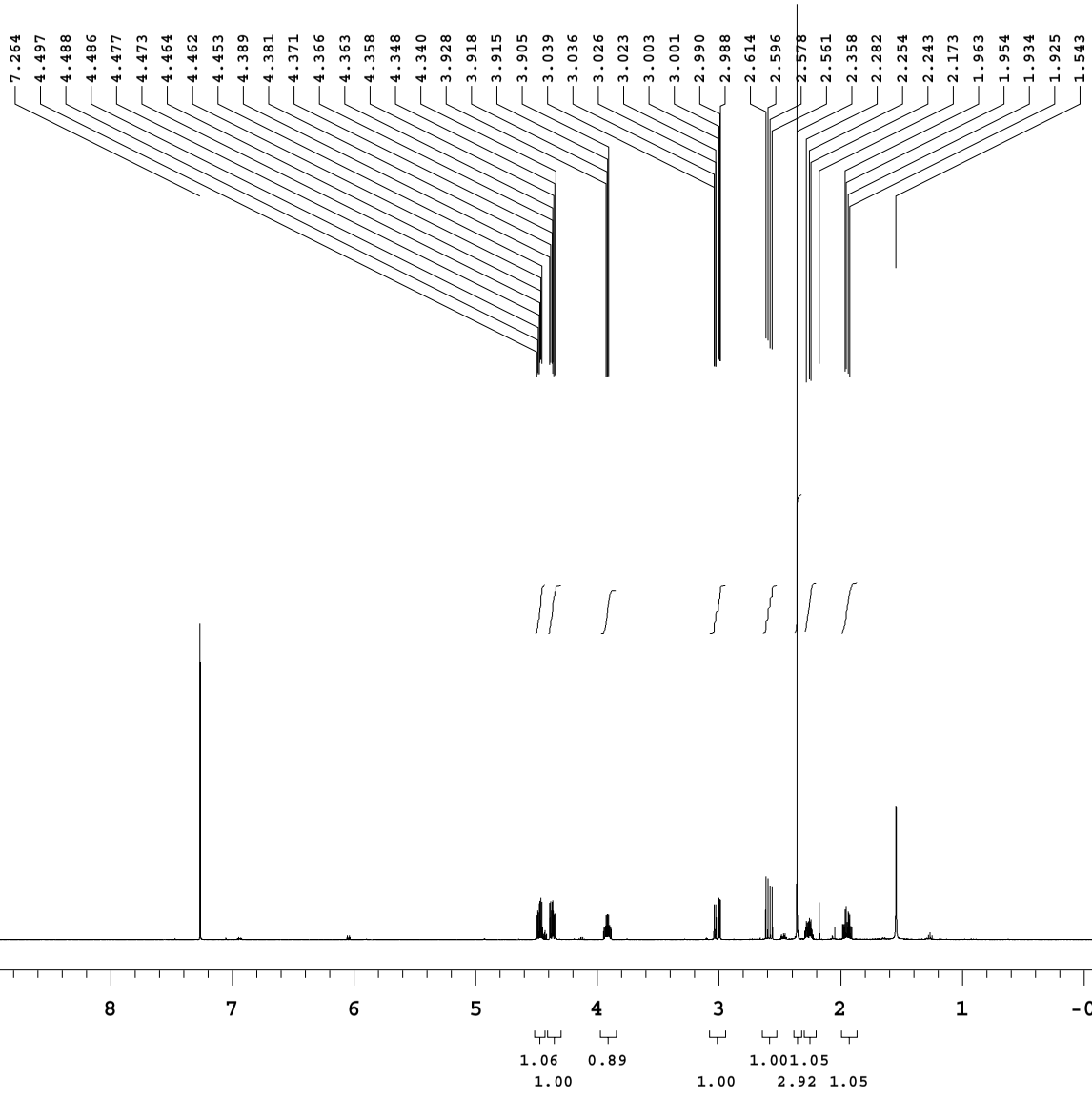

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
O
O
SAc
18
194.358
174.430
77.269
77.015
76.760
72.862
37.296
33.840
30.460
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

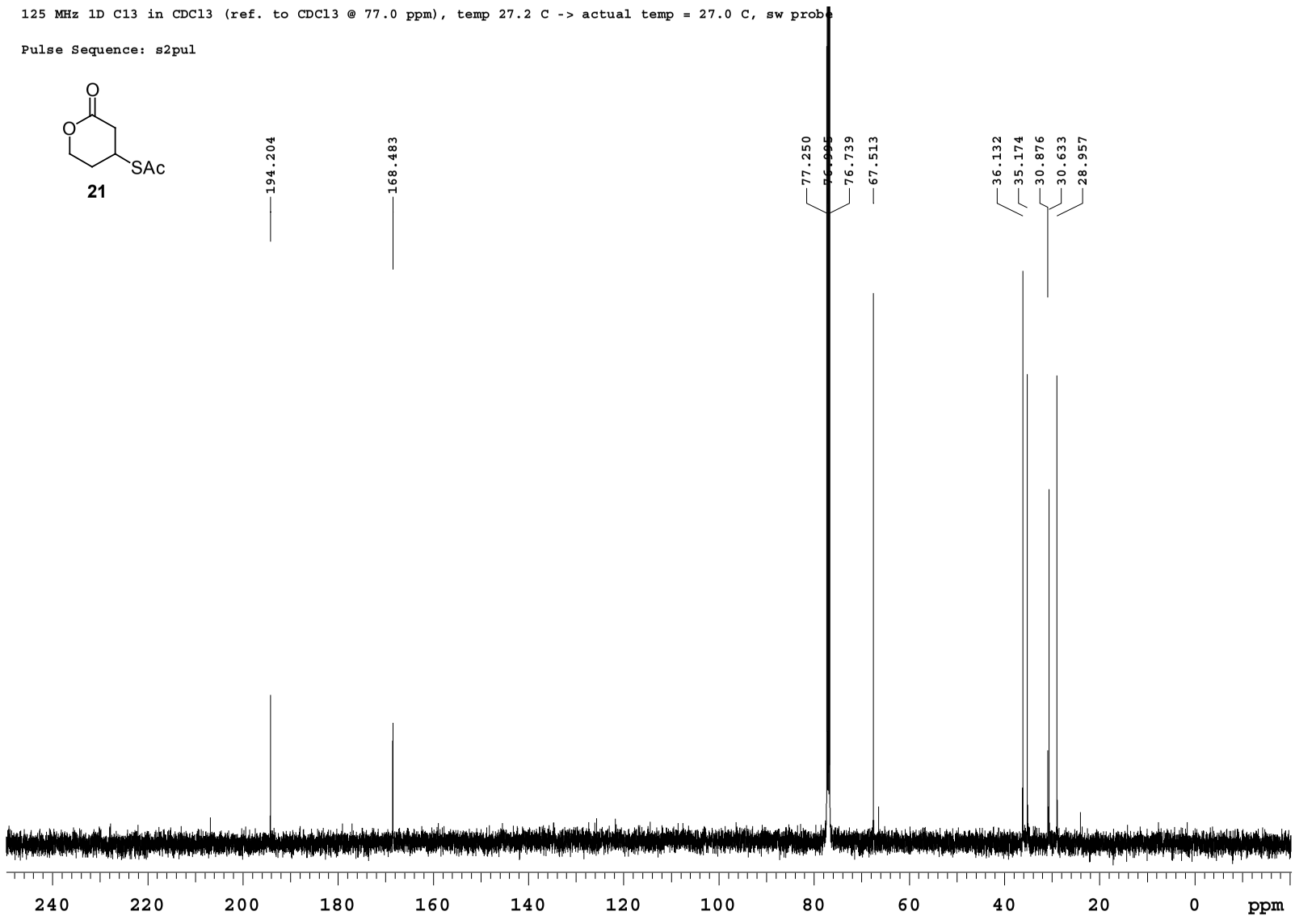
500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe

Pulse Sequence: s2pul



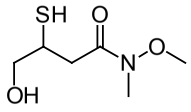
21




125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
Pulse Sequence: s2pul
O
O
SAc
21
194.204
168.483
77.250
76.739
67.513
36.132
35.174
30.876
30.633
28.957
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe

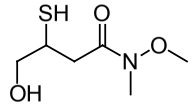
Pulse Sequence: s2pul



19

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe

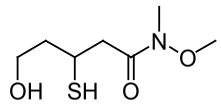
Pulse Sequence: s2pul



19

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe

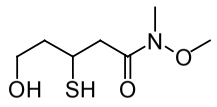
Pulse Sequence: s2pul



22

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe

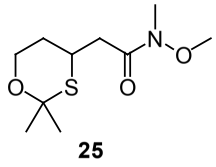
Pulse Sequence: s2pul



22

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe

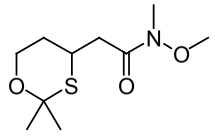
Pulse Sequence: s2pul



25

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe

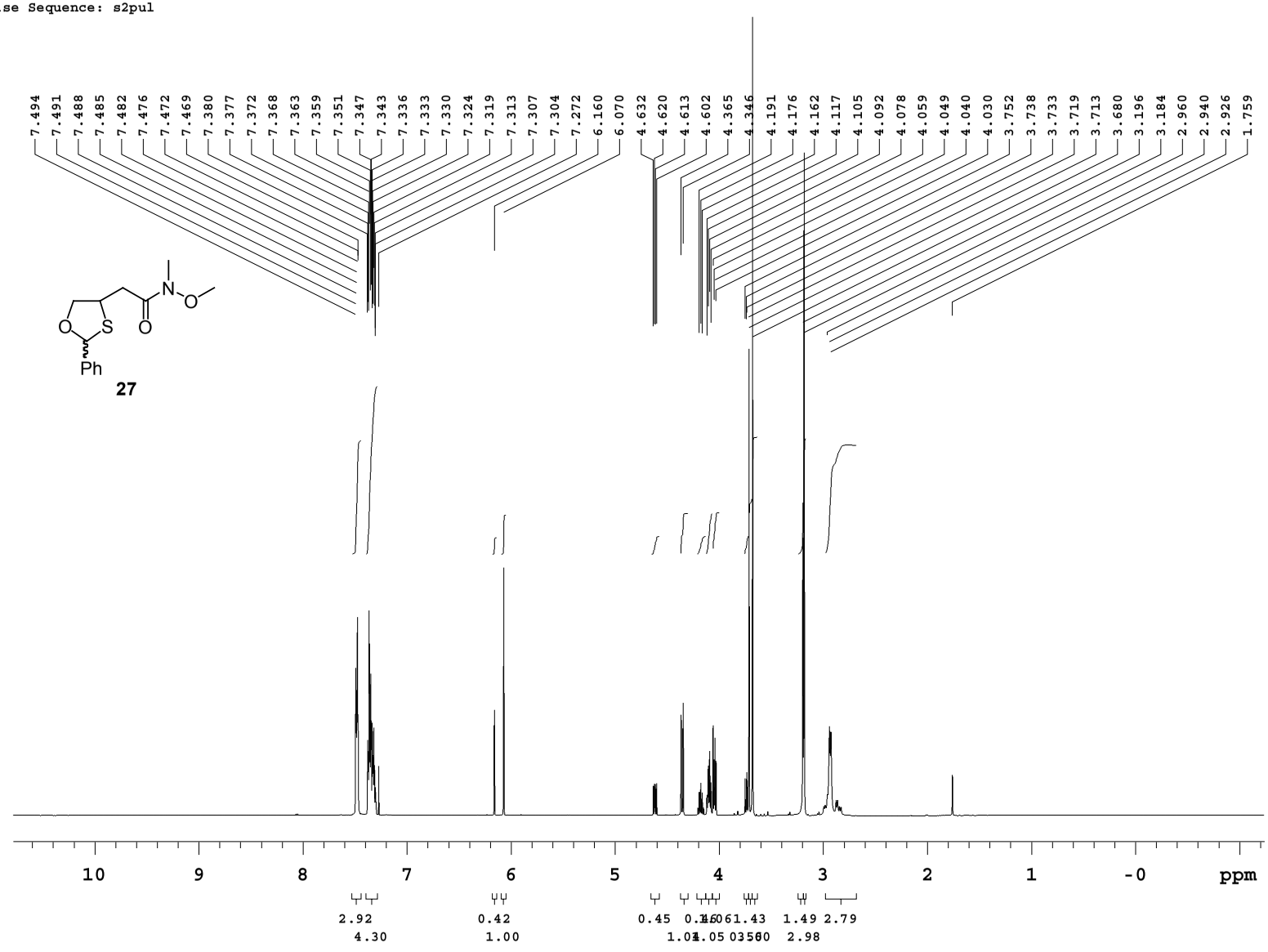
Pulse Sequence: s2pul



25

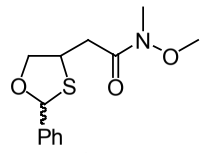
500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul



125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

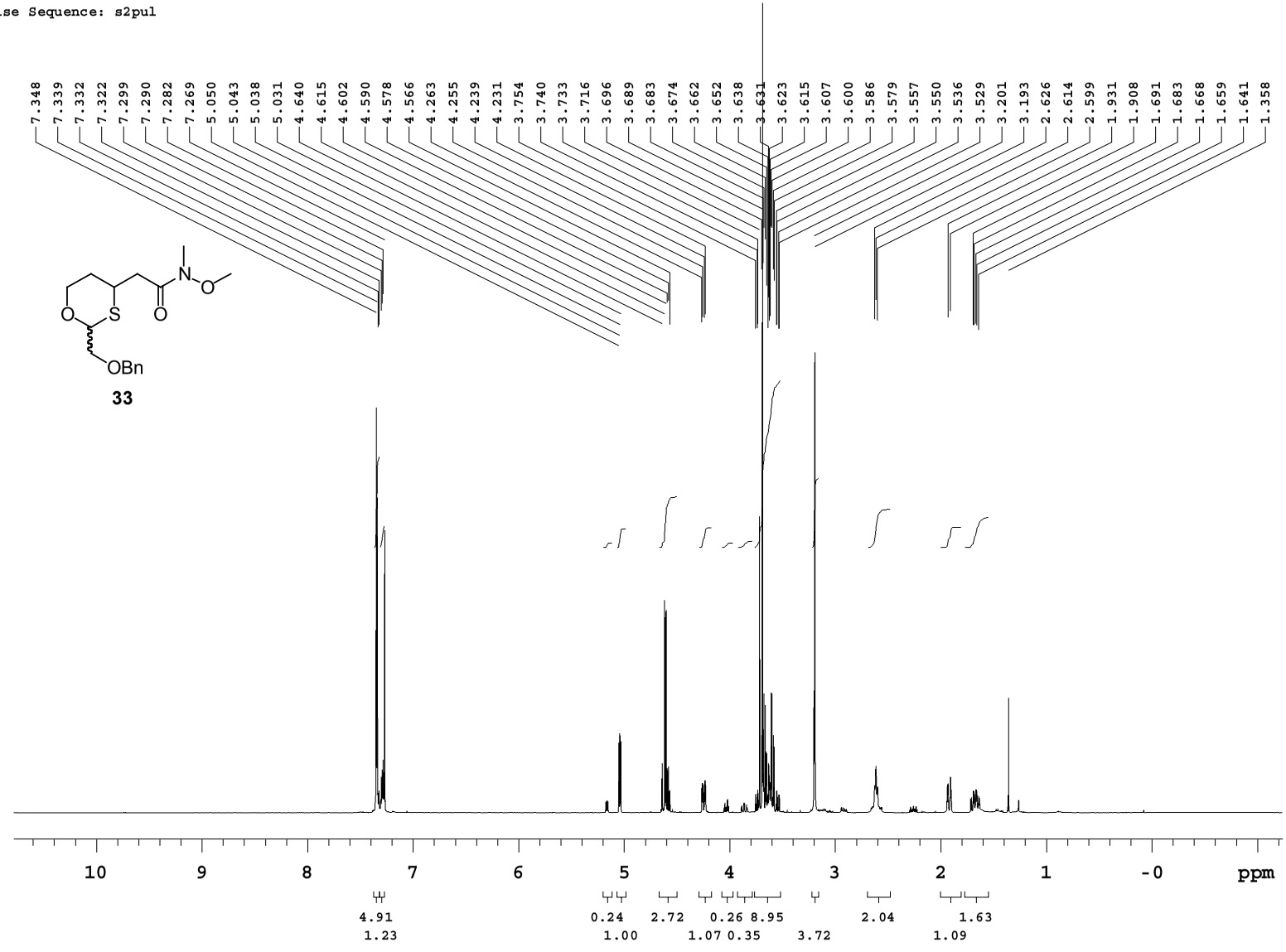
Pulse Sequence: s2pul

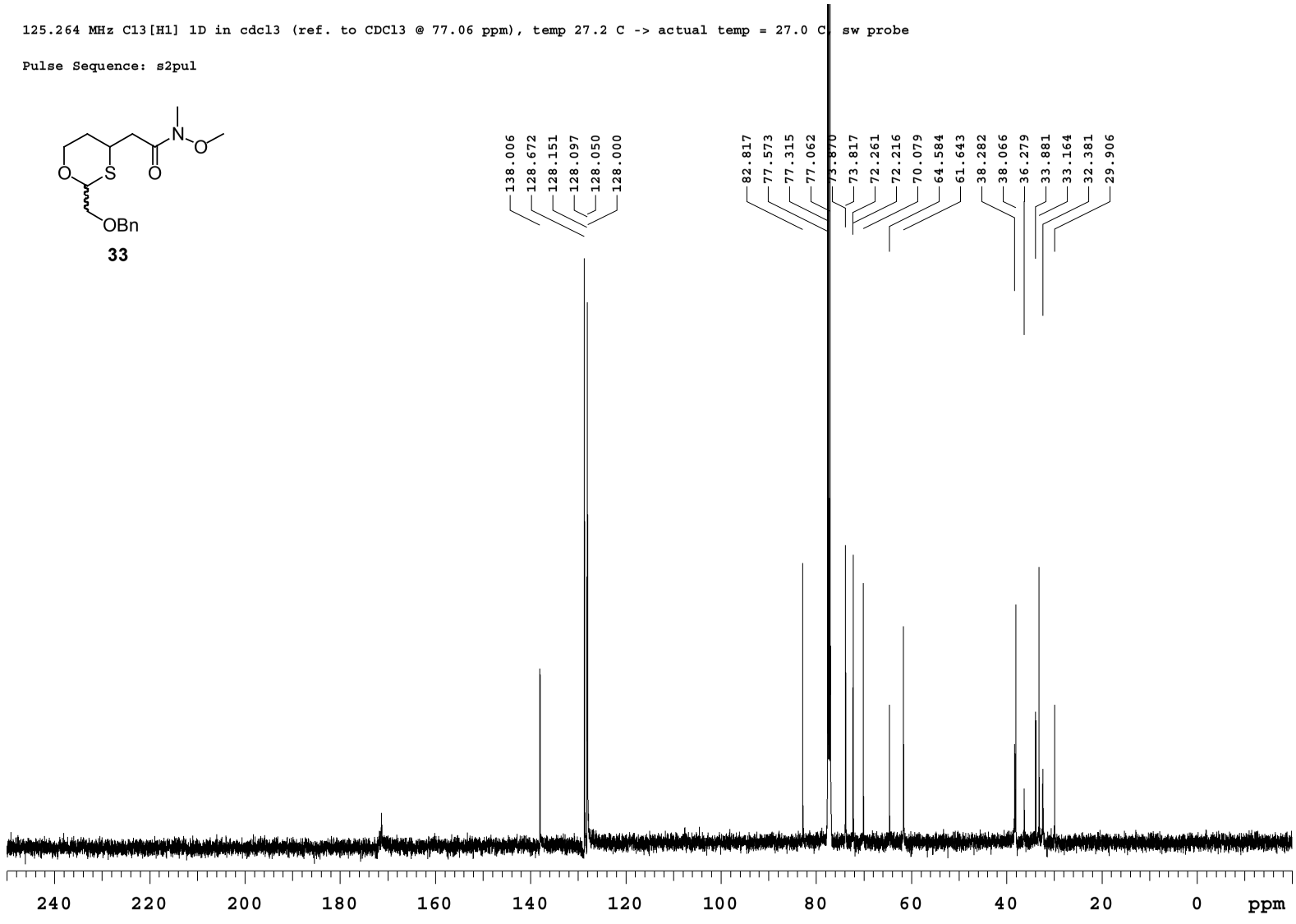


27

499.821 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

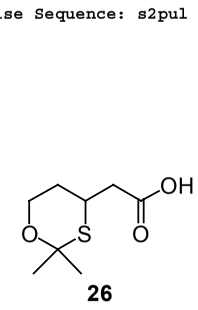
Pulse Sequence: s2pul



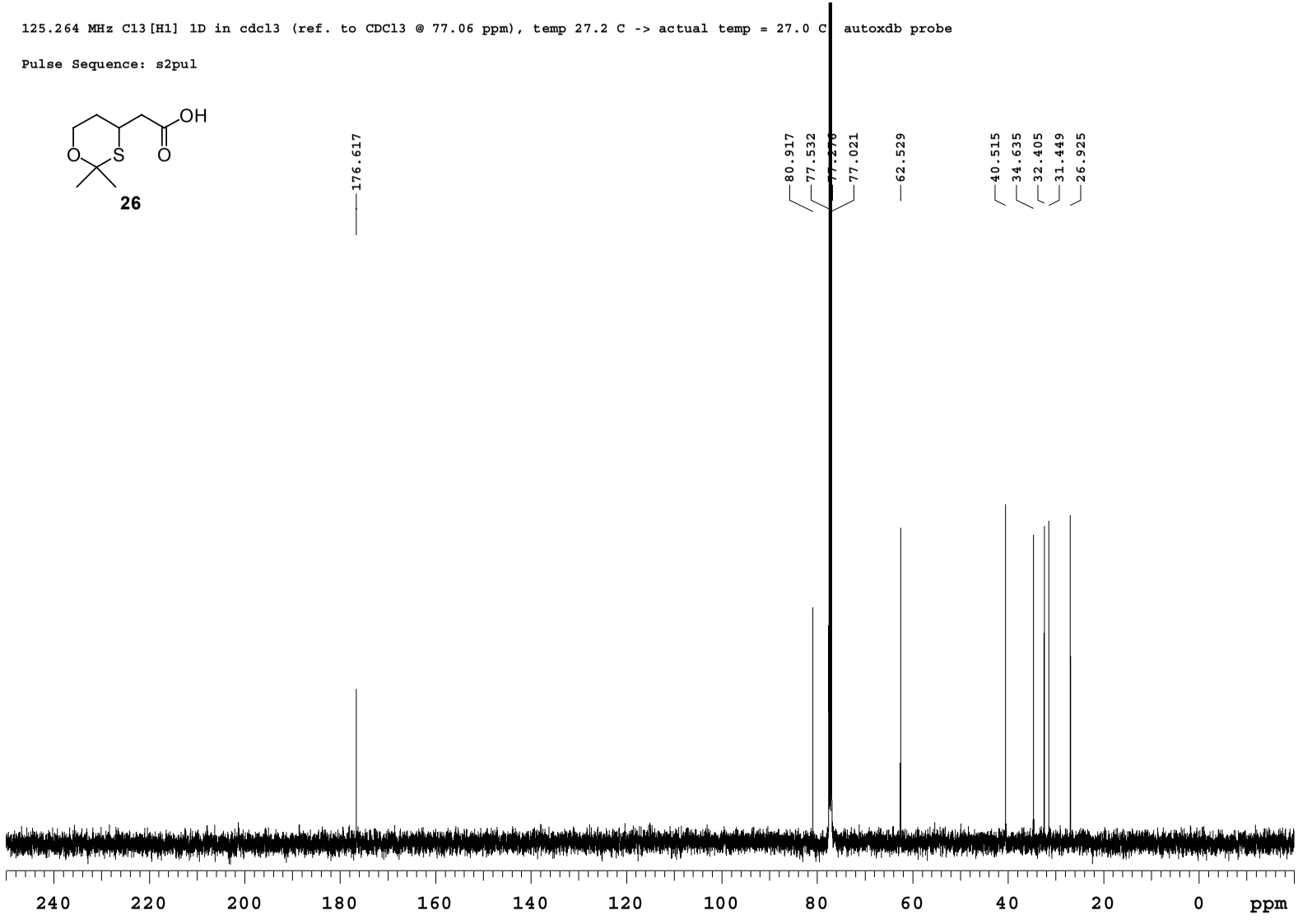

125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C sw probe
Pulse Sequence: s2pul
O
S
O
N
O
OBn
33
138.006
128.672
128.151
128.097
128.050
128.000
82.817
77.573
77.315
77.062
73.870
73.817
72.261
72.216
70.079
64.584
61.643
38.282
38.066
36.279
33.881
33.164
32.381
29.906
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul

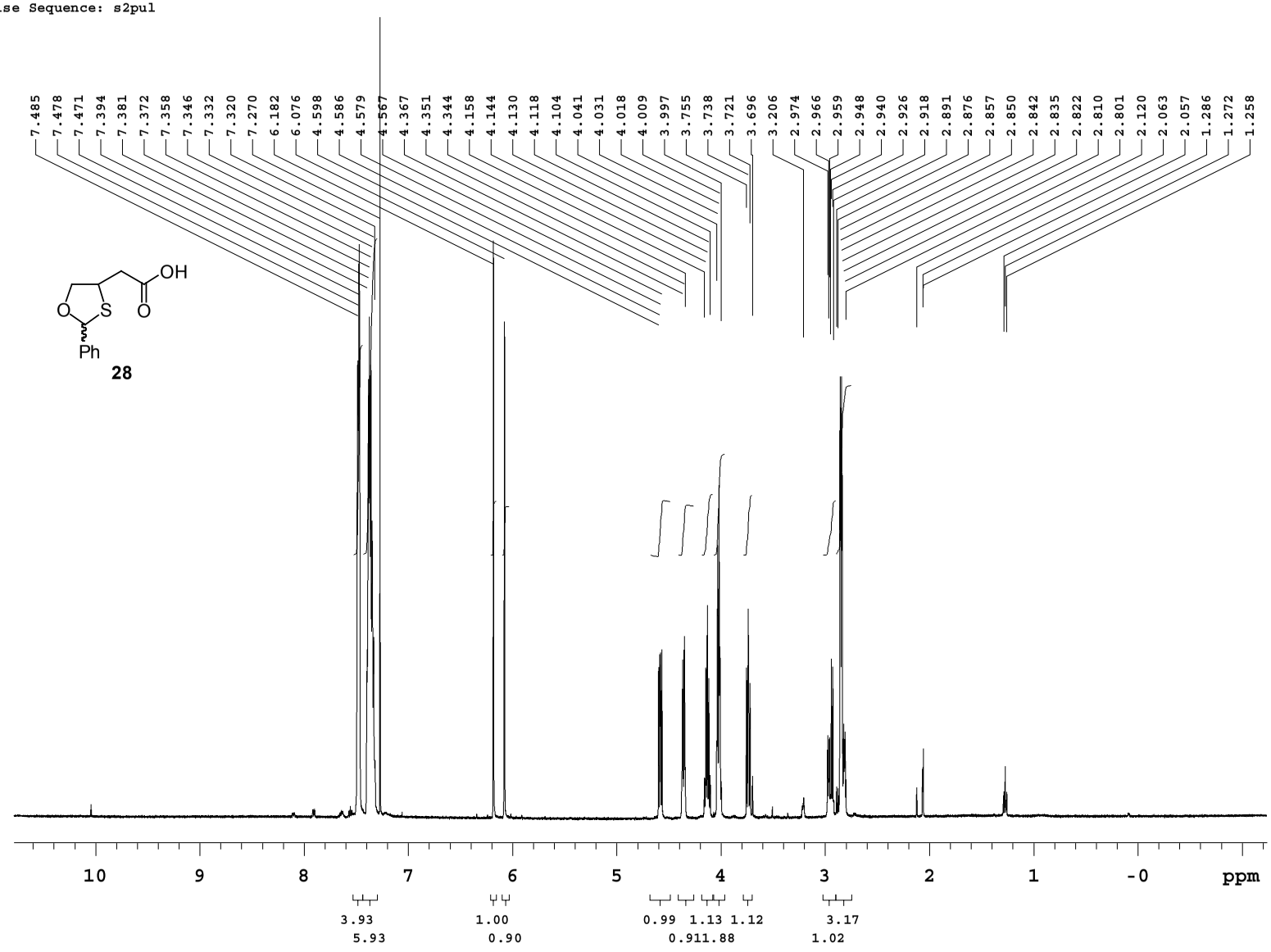


26


125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C autoxdb probe
Pulse Sequence: s2pul
OH
O
S
O
26
176.617
80.917
77.532
77.276
77.021
62.529
40.515
34.635
32.405
31.449
26.925
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

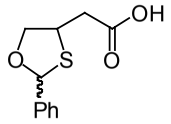
500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul



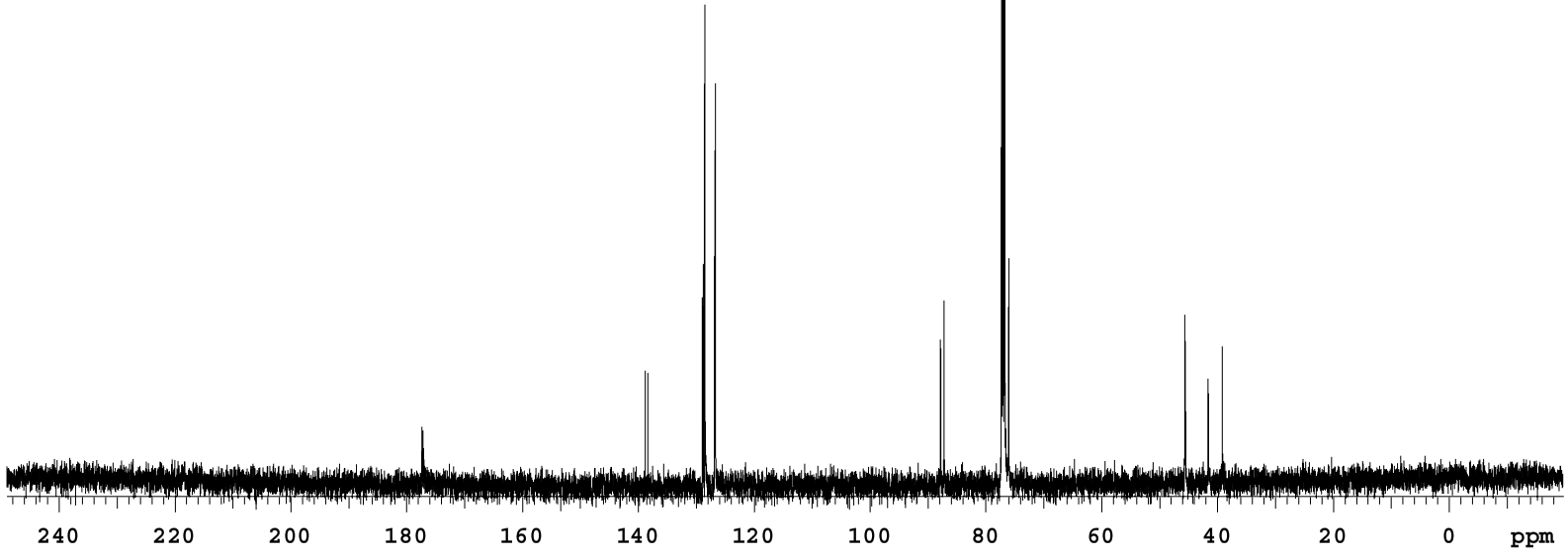
125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul



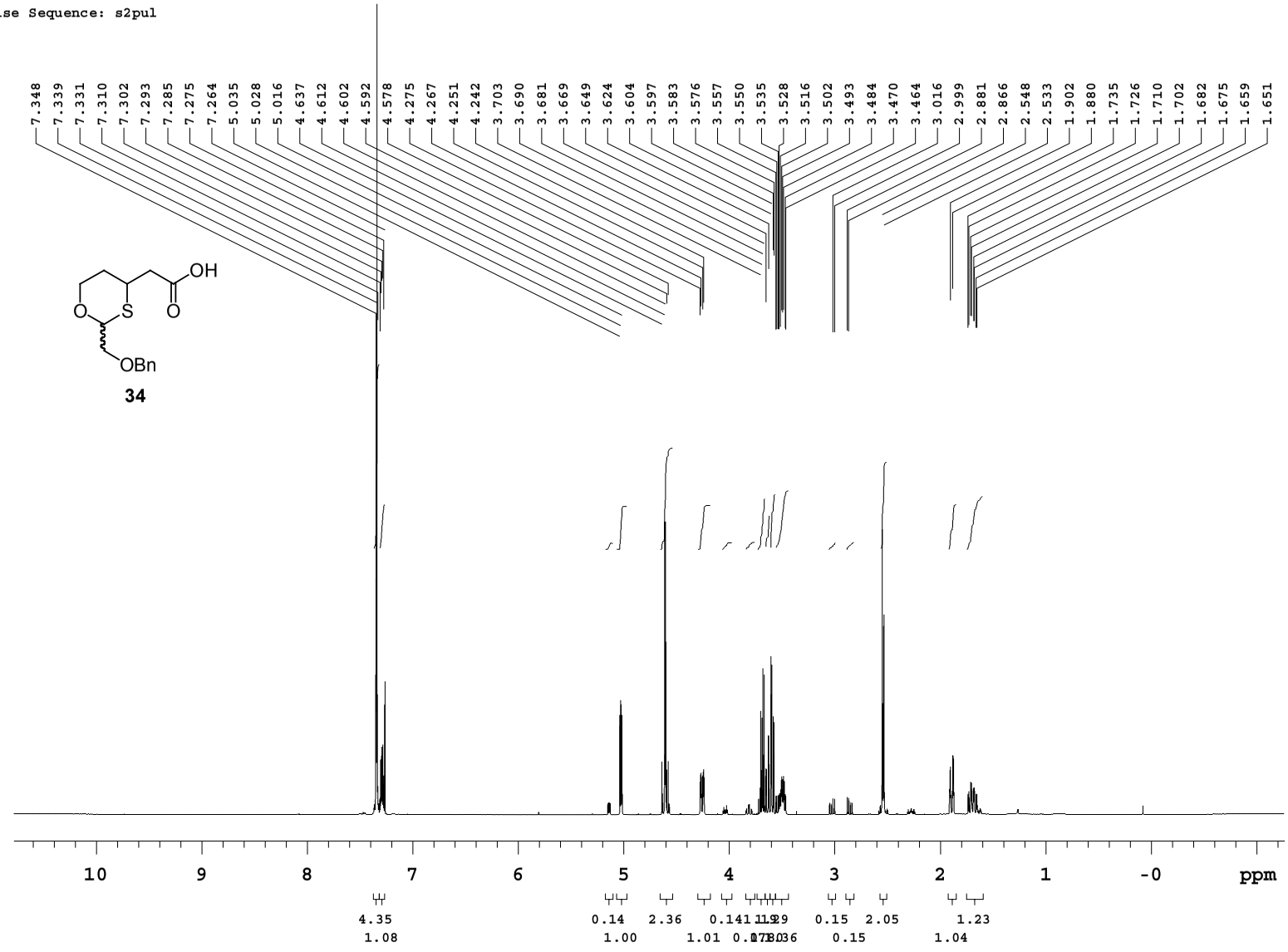
28

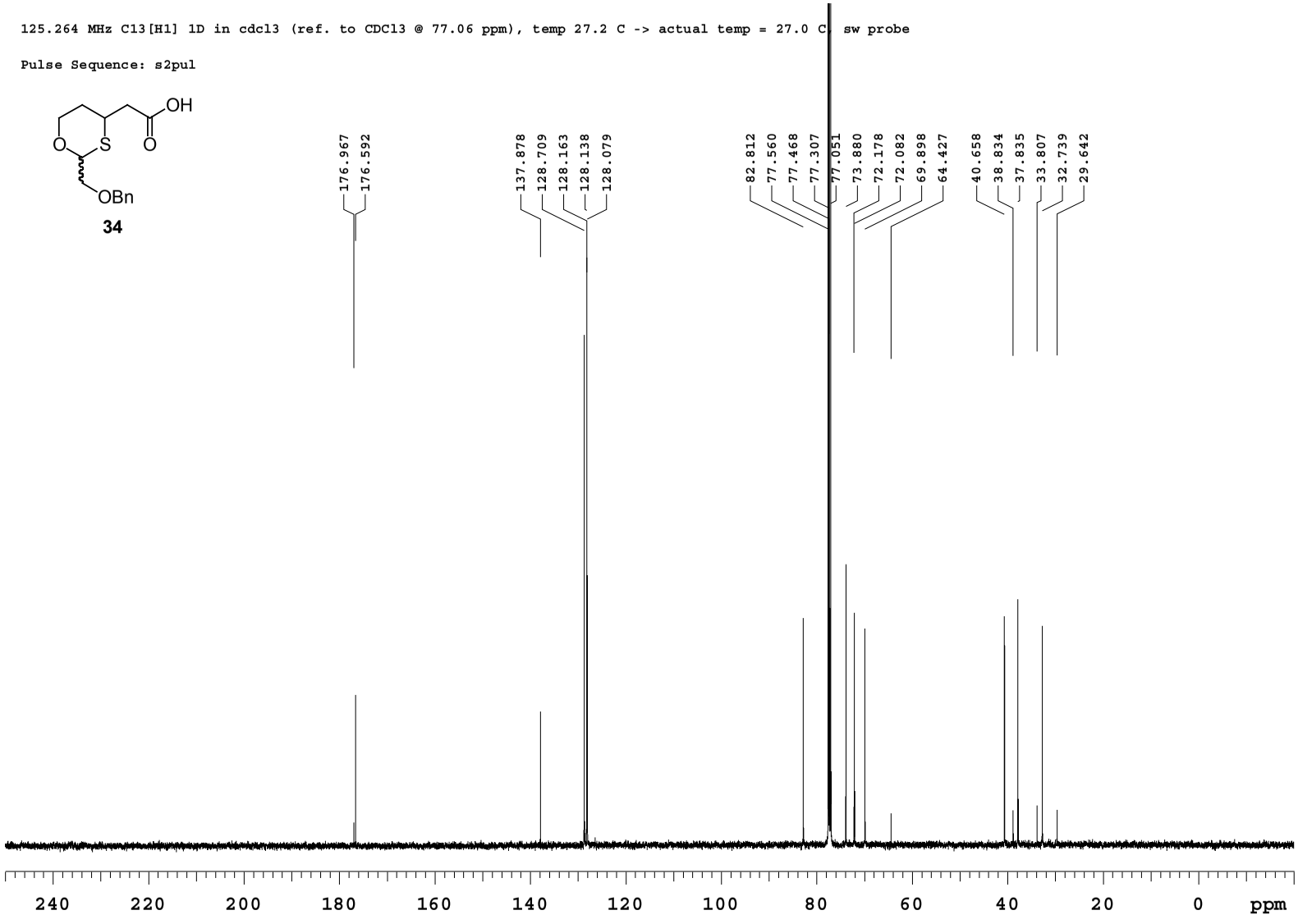
138.785
138.358
128.896
128.779
128.541
128.479
126.794
126.687
87.787
87.200
77.278
77.249
77.026
76.995
76.771
76.741
76.070
76.009
45.603
45.500
41.575
39.130



498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe

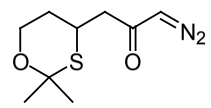
Pulse Sequence: s2pul



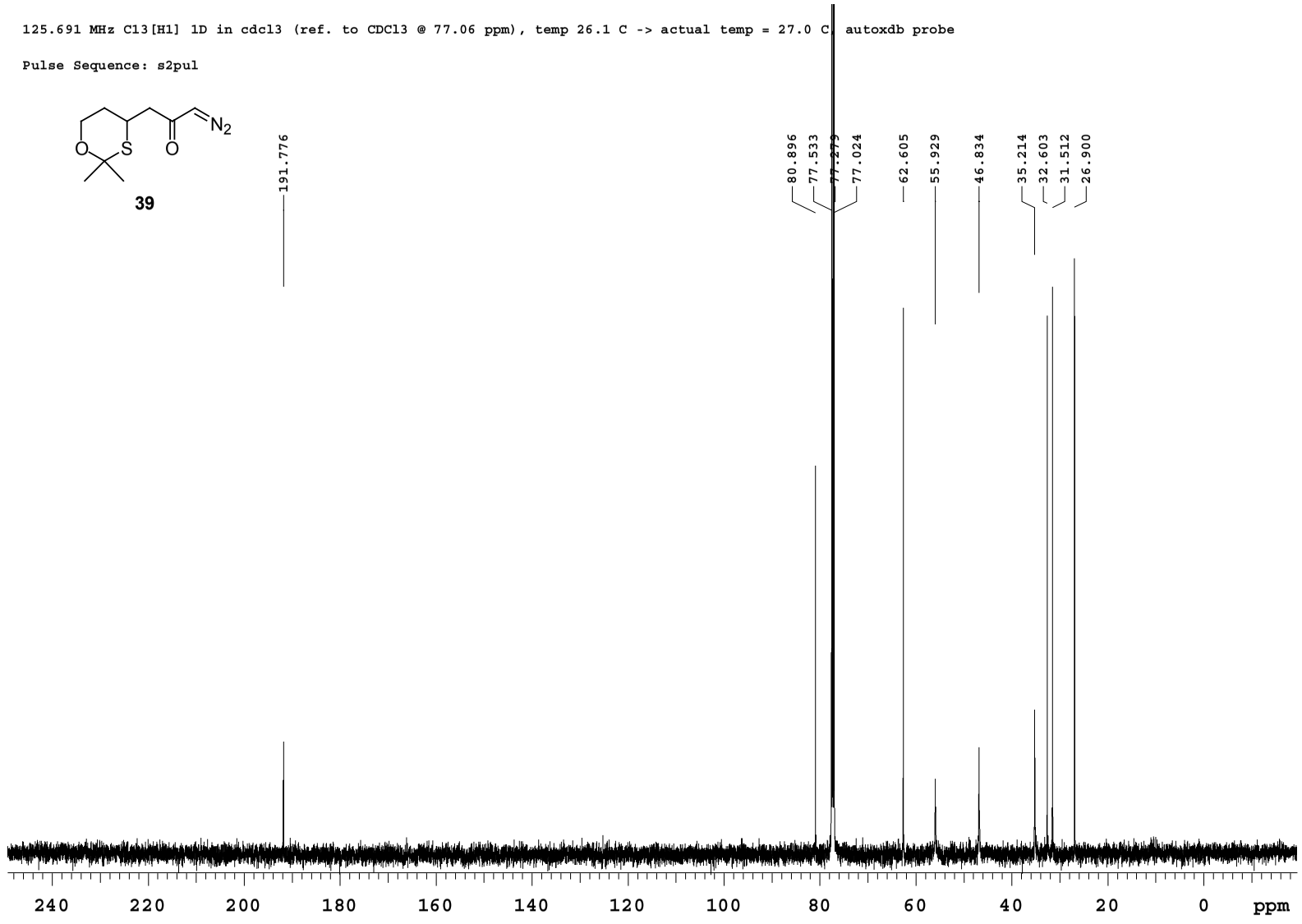

125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
Pulse Sequence: s2pul
OH
O
S
O
OBn
34
176.967
176.592
137.878
128.709
128.163
128.138
128.079
82.812
77.560
77.468
77.307
77.051
73.880
72.178
72.082
69.898
64.427
40.658
38.834
37.835
33.807
32.739
29.642
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

499.821 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul

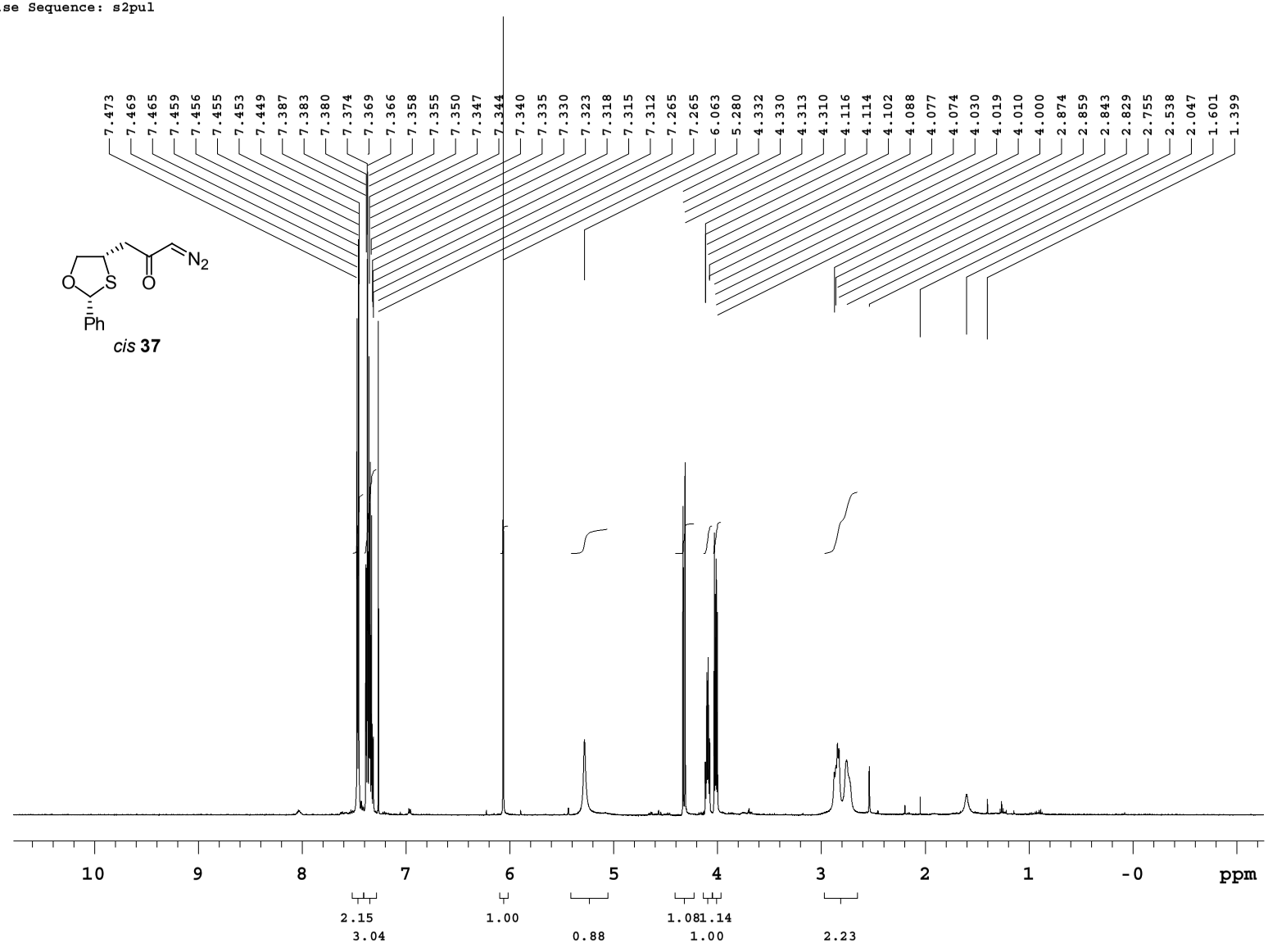


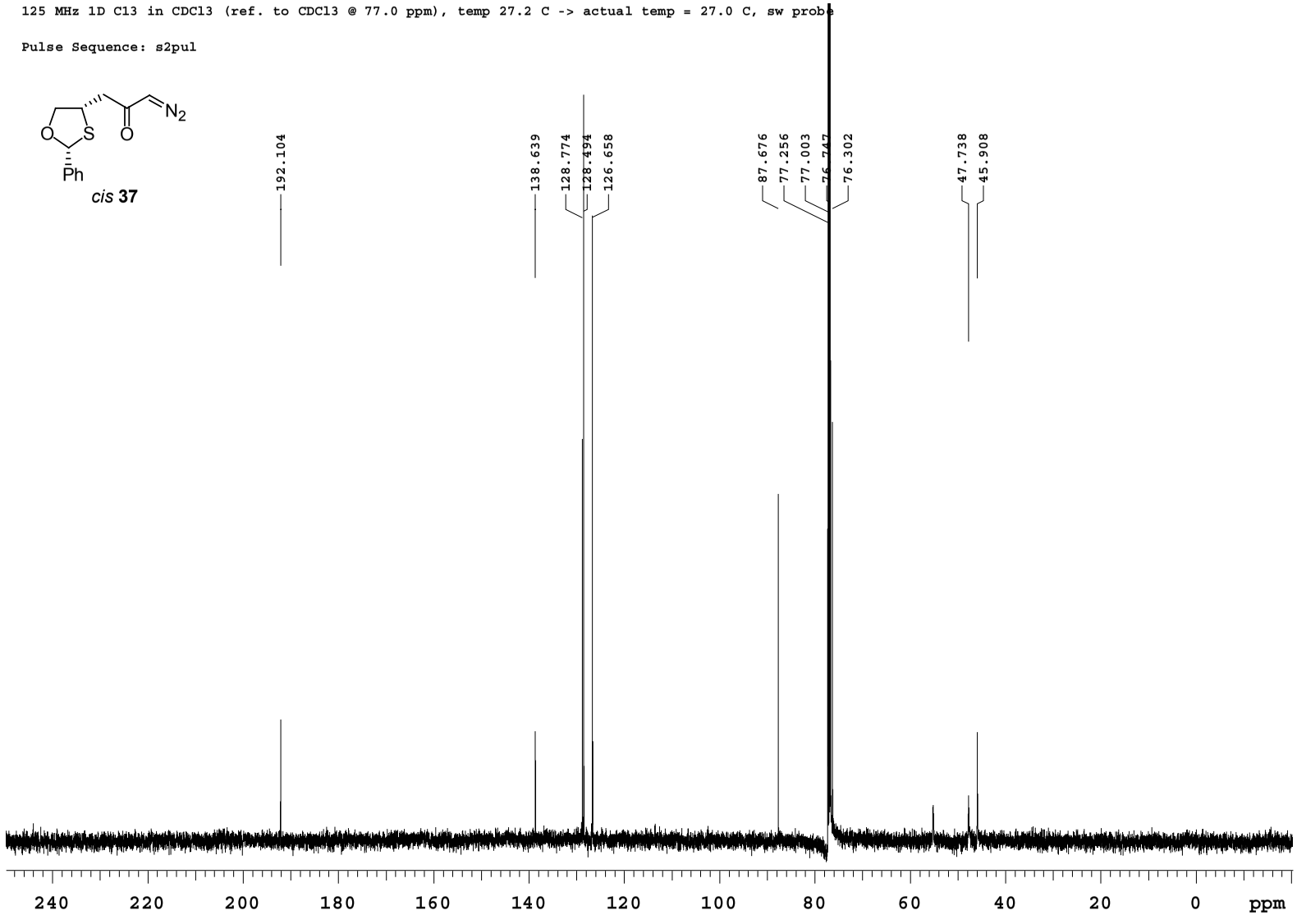
39

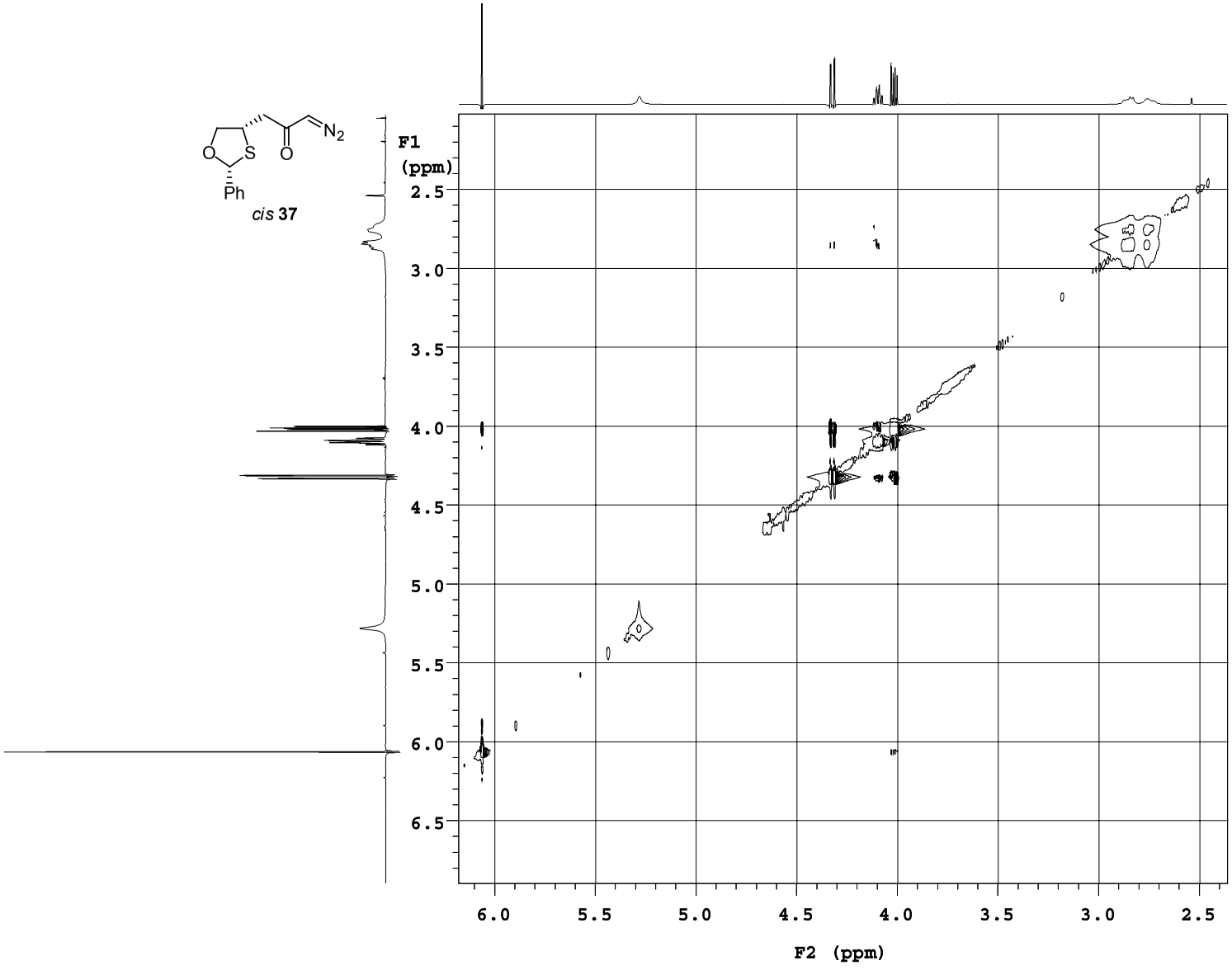

125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.1 C -> actual temp = 27.0 C. autoxdb probe
Pulse Sequence: s2pul
39
191.776
80.896
77.533
77.279
77.024
62.605
55.929
46.834
35.214
32.603
31.512
26.900
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

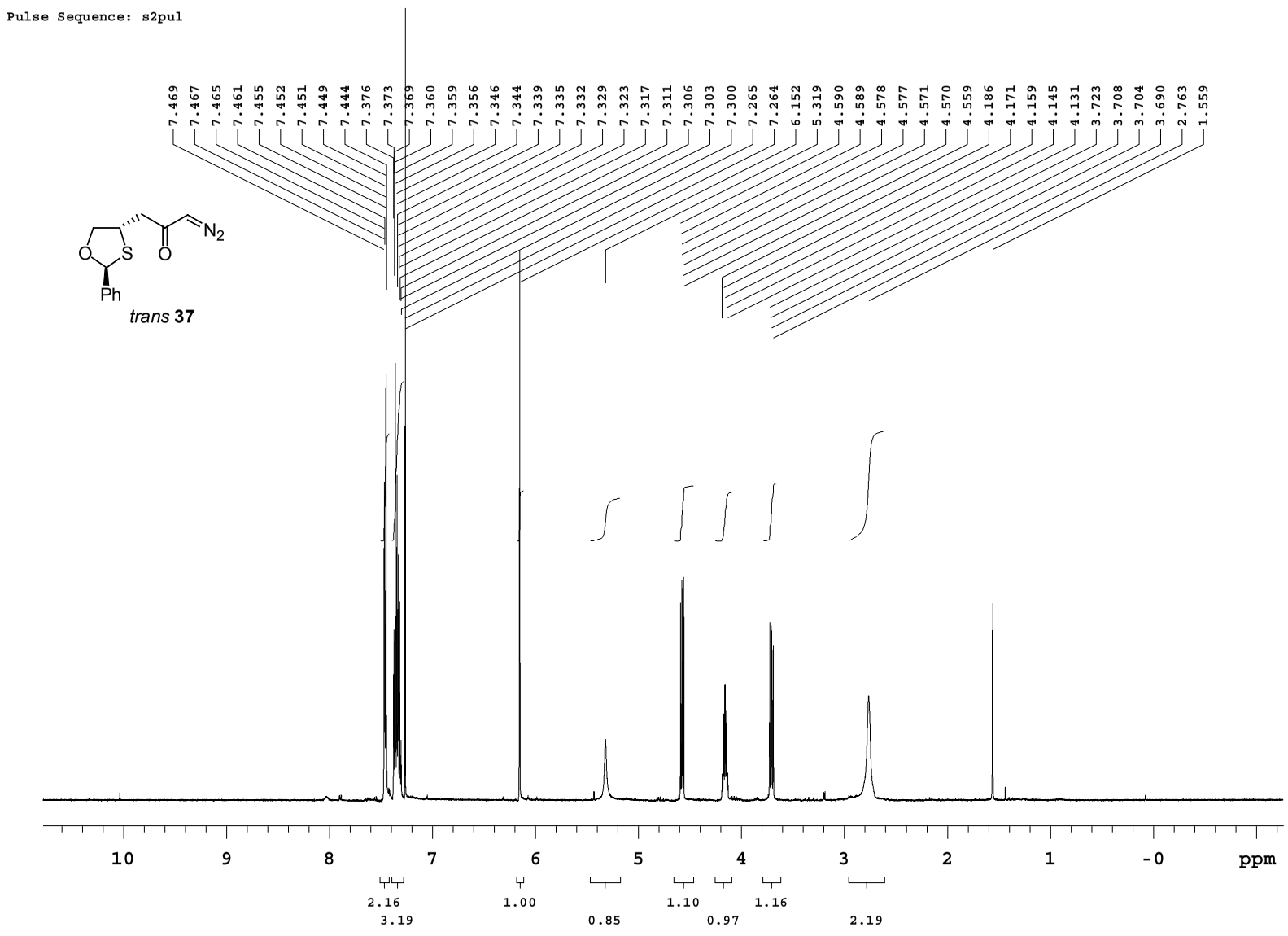
500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe

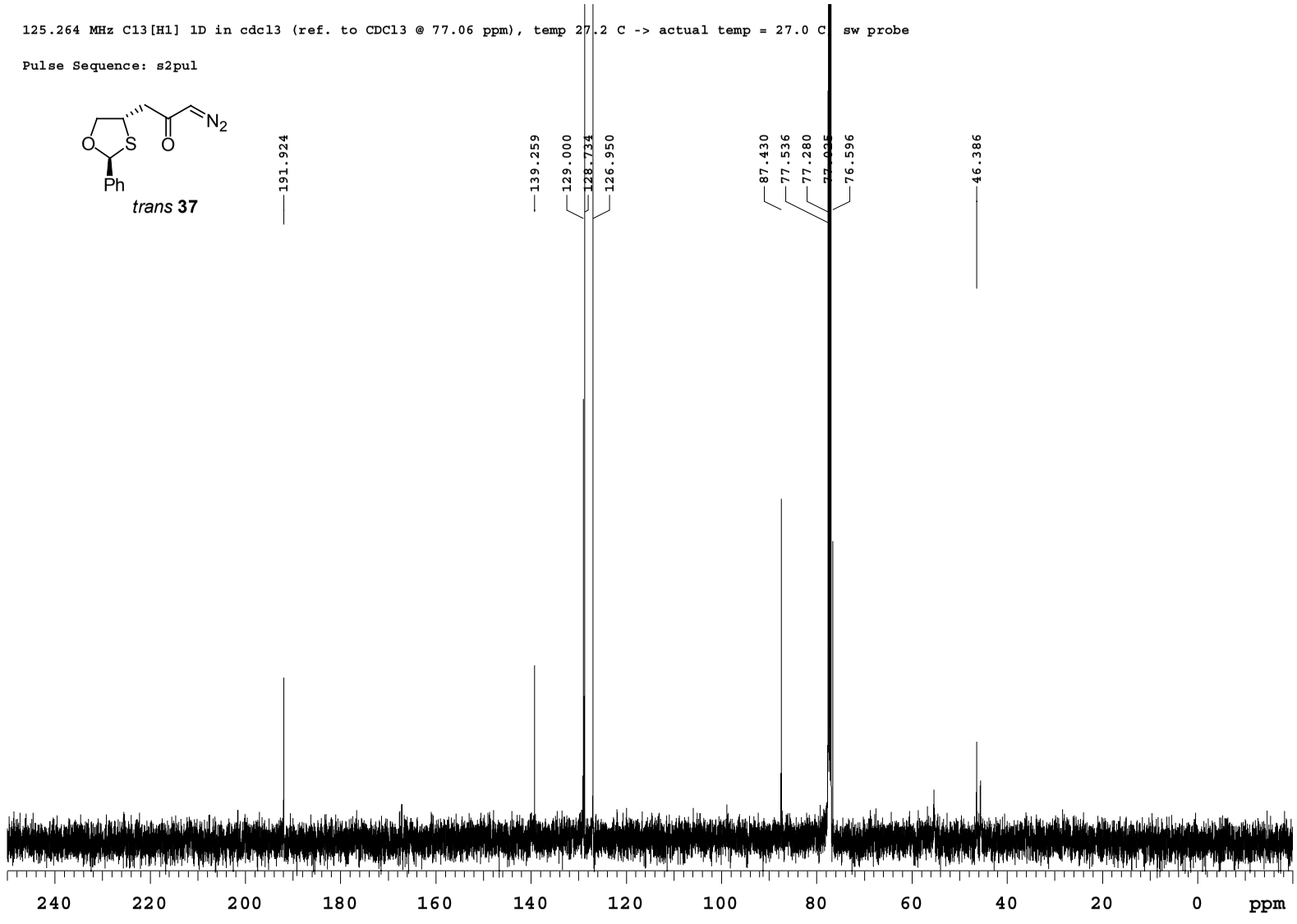
Pulse Sequence: s2pul

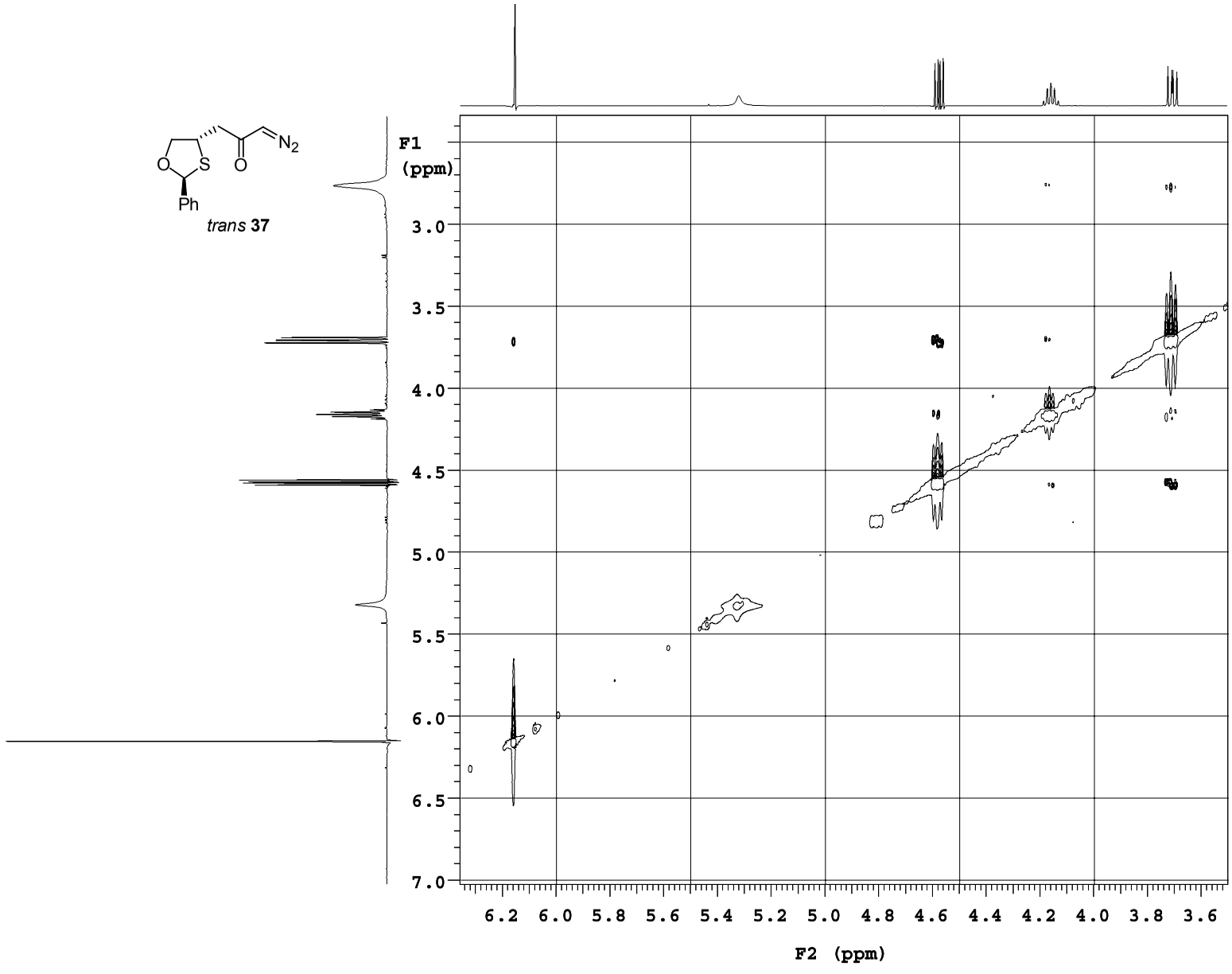



125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
Pulse Sequence: s2pul
cis 37
192.104
138.639
128.774
128.494
126.658
87.676
77.256
77.003
76.747
76.302
47.738
45.908
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


cis 37
F1 (ppm)
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
F2 (ppm)

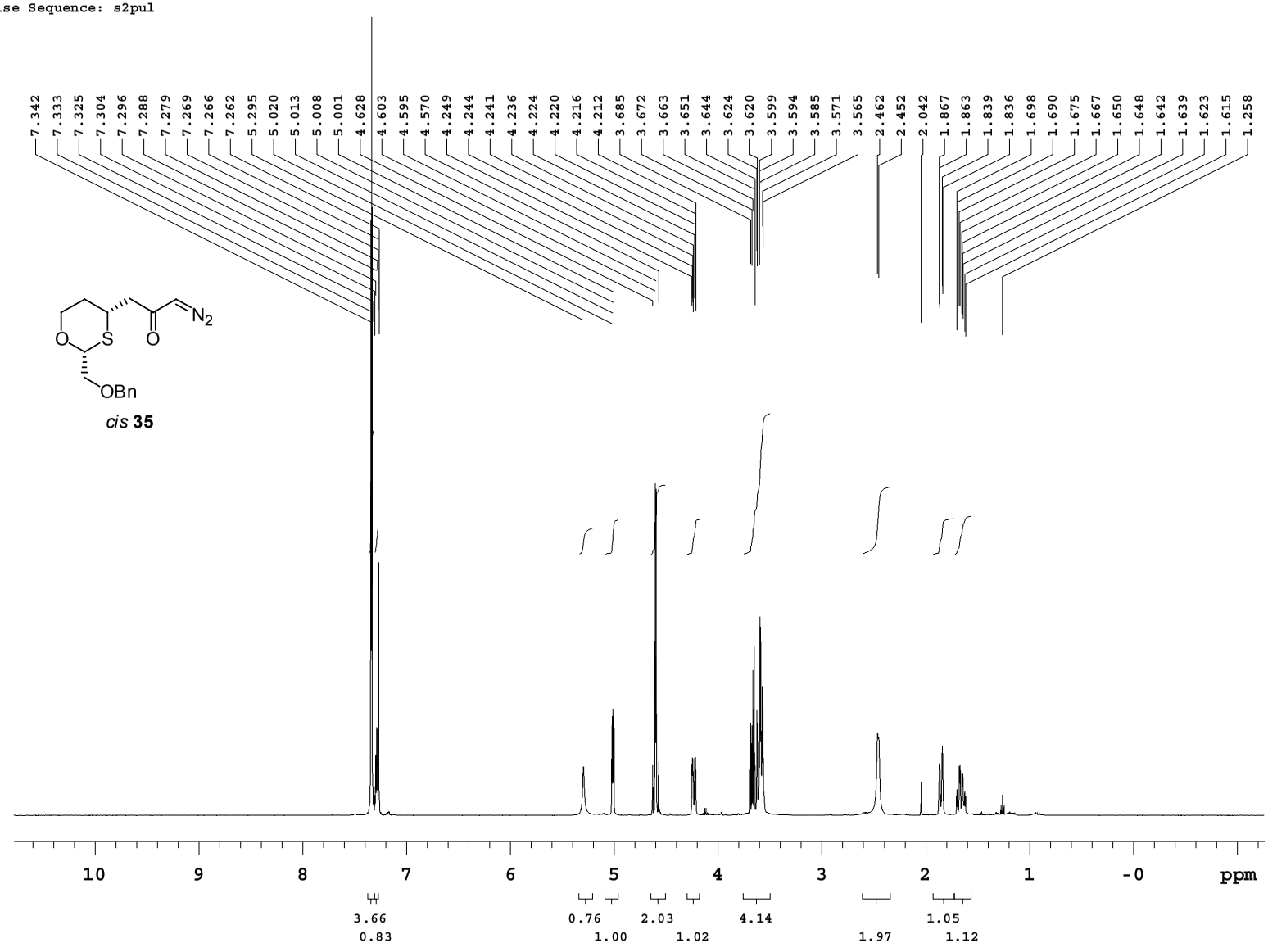

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
Pulse Sequence: s2pul
7.469
7.467
7.465
7.461
7.455
7.452
7.451
7.449
7.444
7.376
7.373
7.369
7.360
7.359
7.356
7.346
7.344
7.339
7.335
7.332
7.329
7.323
7.317
7.311
7.306
7.303
7.300
7.265
7.264
6.152
5.319
4.590
4.589
4.578
4.577
4.571
4.570
4.559
4.186
4.171
4.159
4.145
4.131
3.723
3.708
3.704
3.690
2.763
1.559
O
S
O
N2
Ph
trans 37
10
9
8
7
6
5
4
3
2
1
-0
ppm
2.16
3.19
1.00
0.85
1.10
0.97
1.16
2.19


125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C sw probe
Pulse Sequence: s2pul
trans 37
191.924
139.259
129.000
128.734
126.950
87.430
77.536
77.280
76.596
46.386
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


trans 37
F1 (ppm)
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6
F2 (ppm)

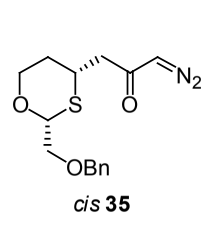
500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe

Pulse Sequence: s2pul



125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe

Pulse Sequence: s2pul



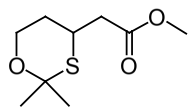
cis **35**

191.144
137.679
128.415
127.828
127.764
82.576
77.291
77.036
76.780
73.581
71.874
69.713
55.667
46.574
38.145
32.668

240 220 200 180 160 140 120 100 80 60 40 20 0 ppm

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

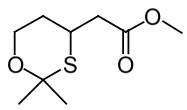
Pulse Sequence: s2pul



44

125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C autoxdb probe

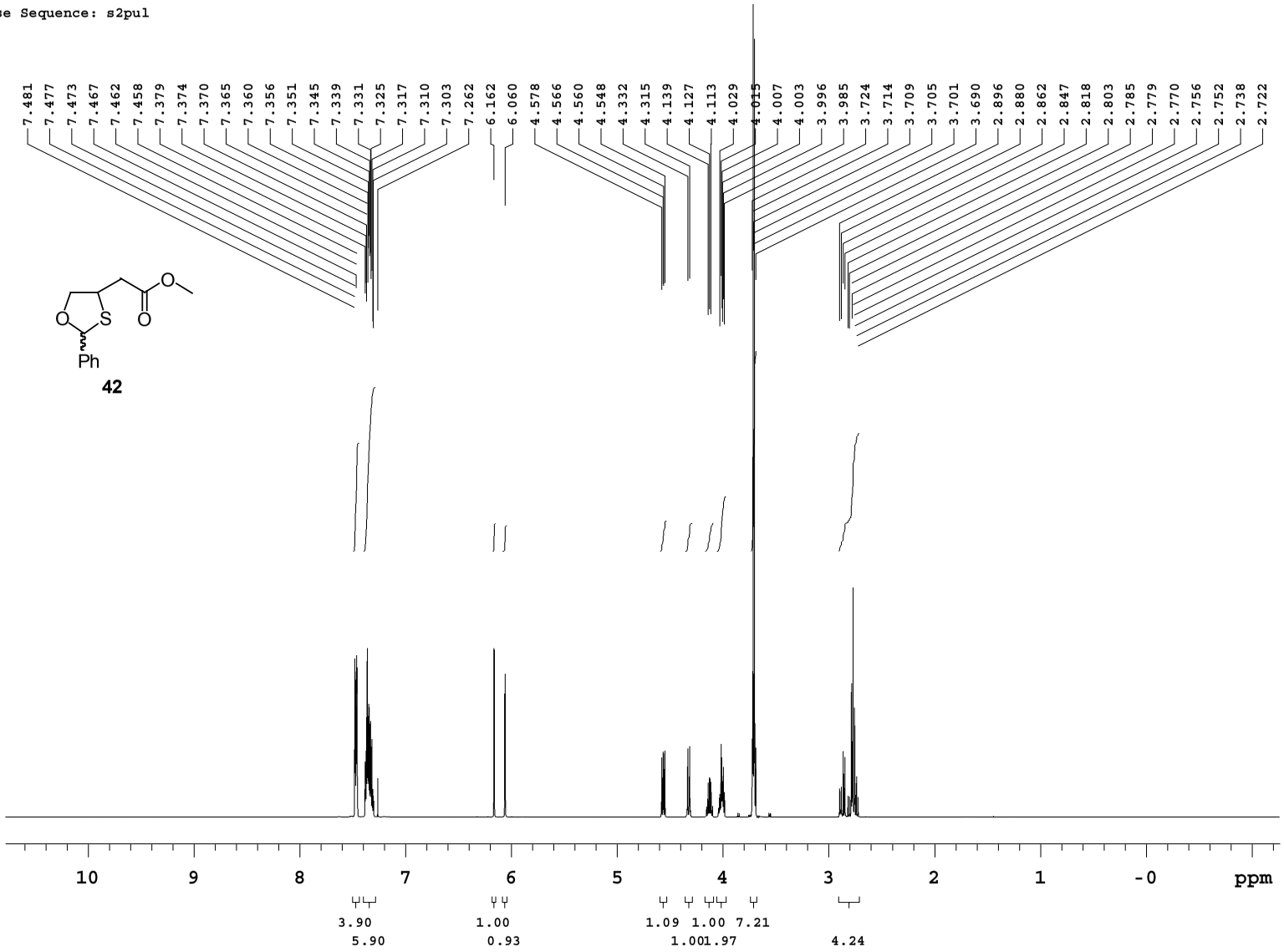
Pulse Sequence: s2pul



44

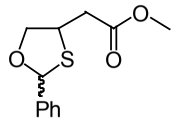
498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul



125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

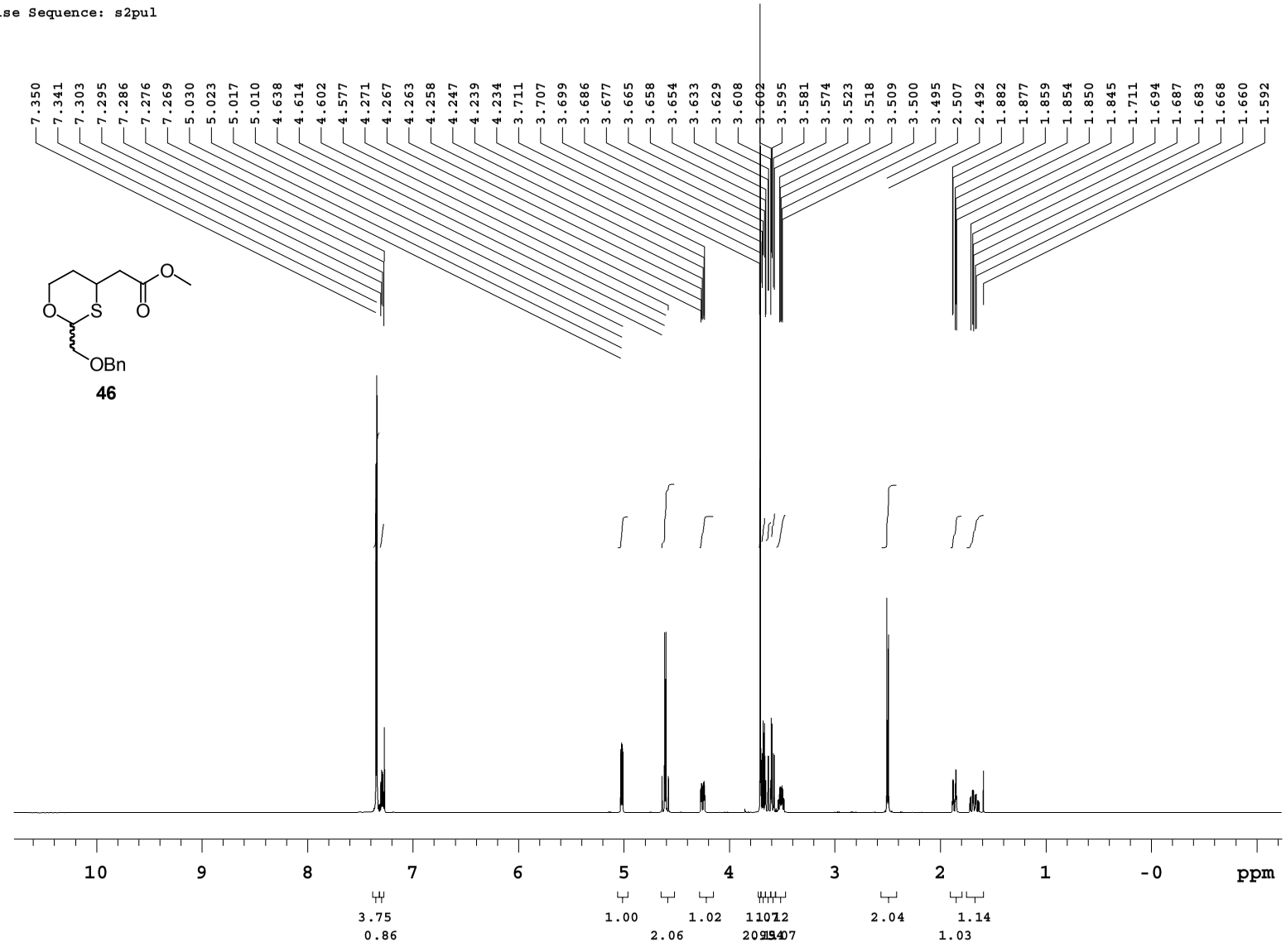
Pulse Sequence: s2pul

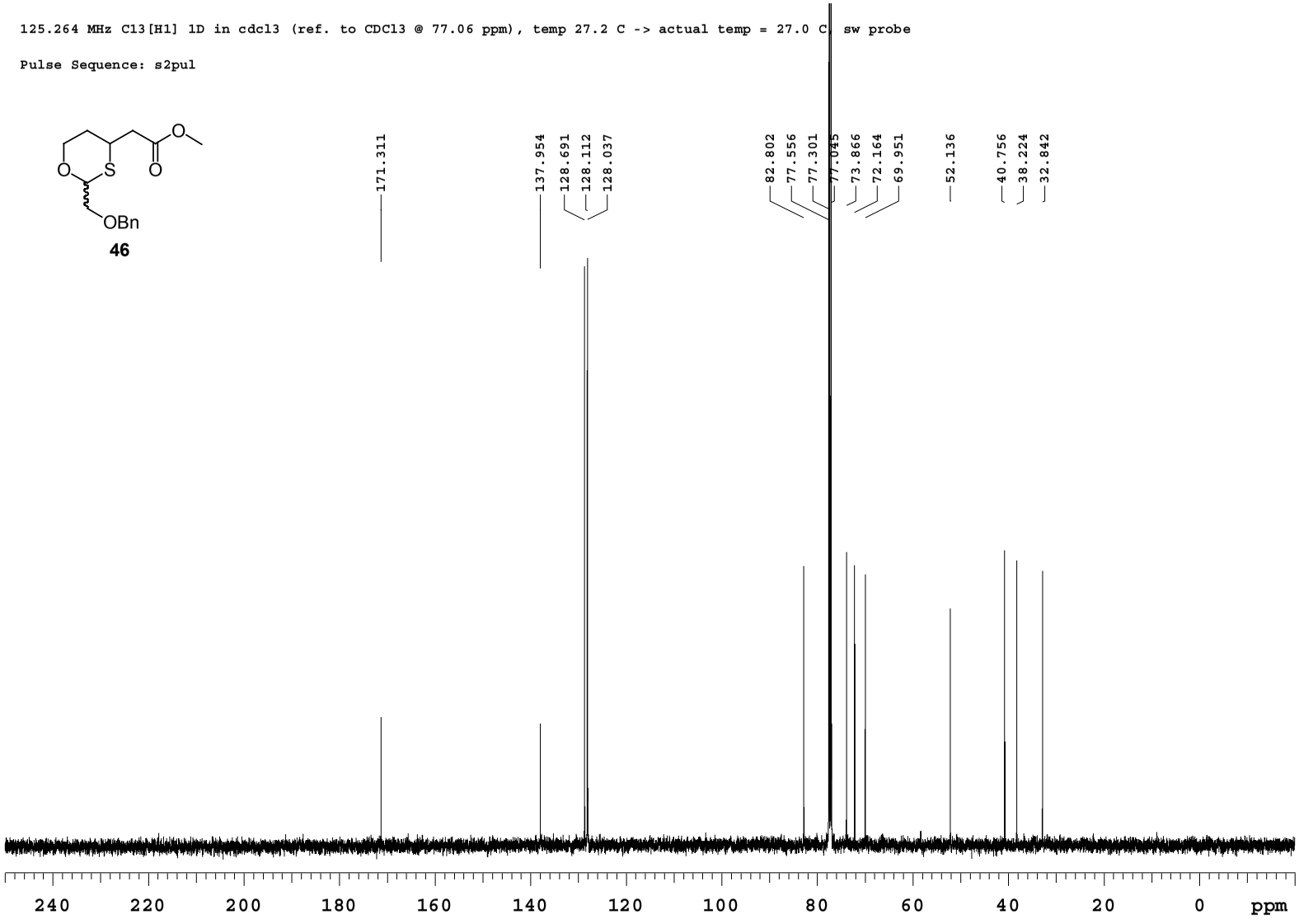


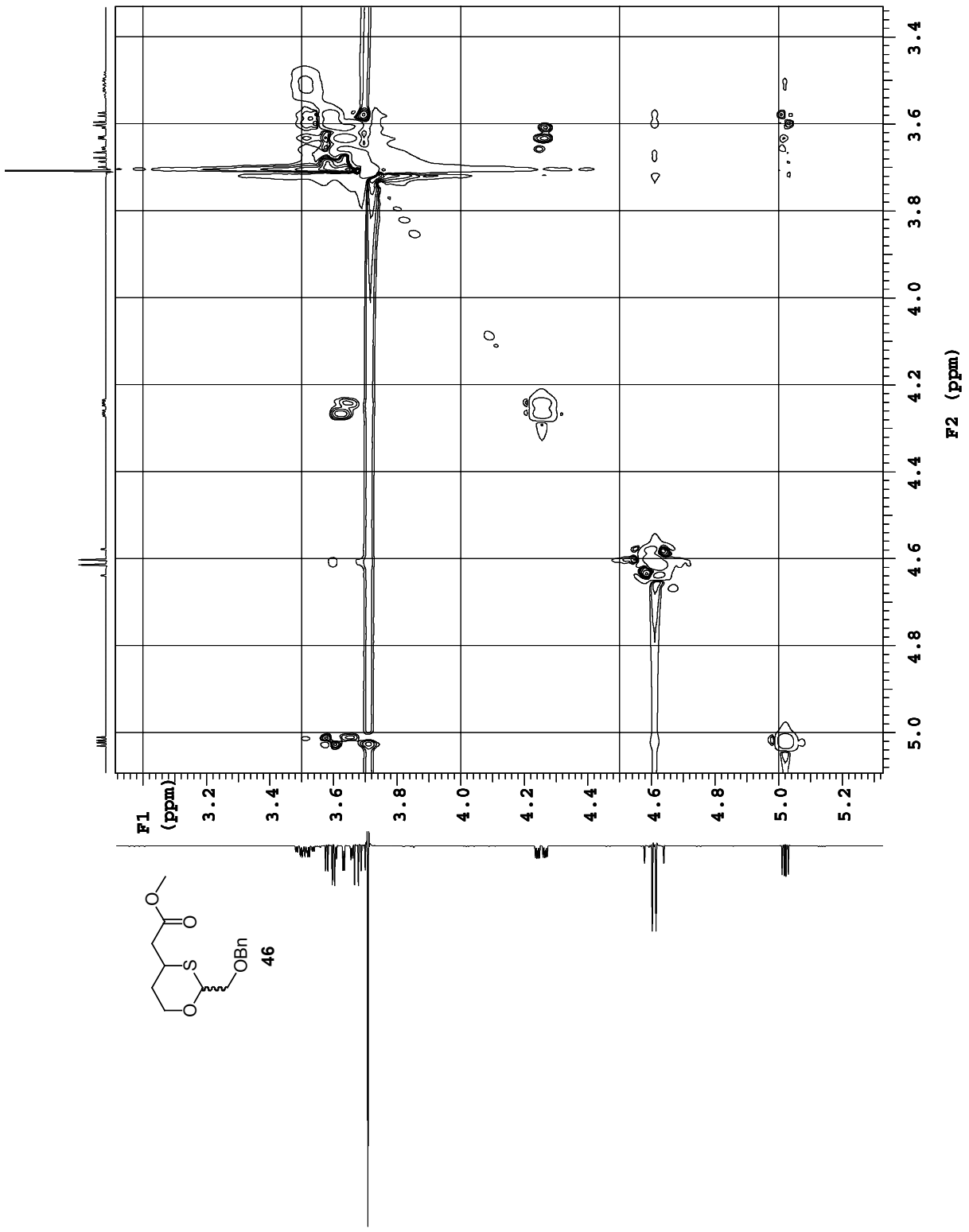
42

499.821 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul

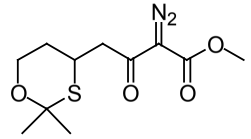



125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
Pulse Sequence: s2pul
O
O
O
S
OBn
46
171.311
137.954
128.691
128.112
128.037
82.802
77.556
77.301
77.045
73.866
72.164
69.951
52.136
40.756
38.224
32.842
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

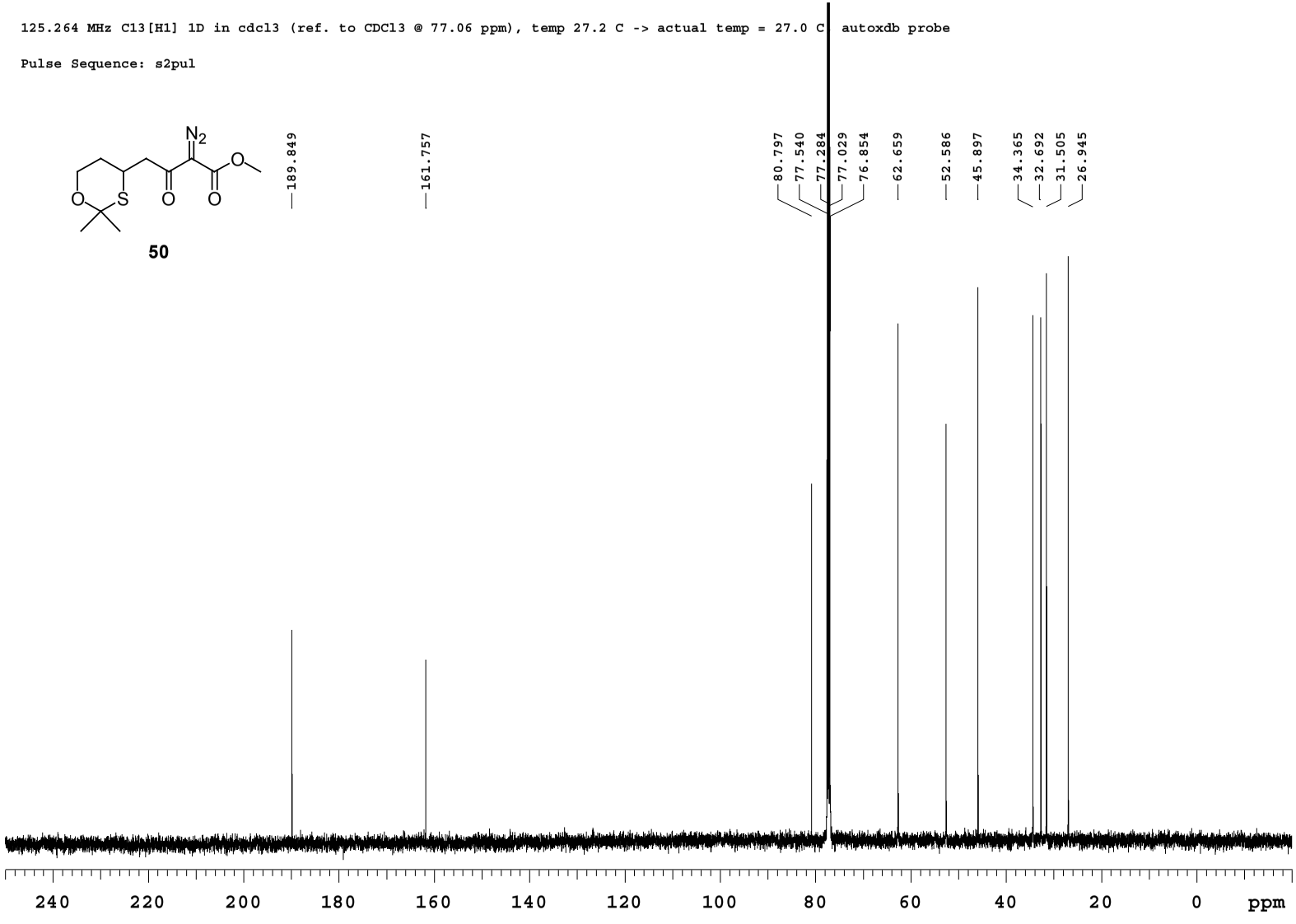

F1 (ppm)
3.2
3.4
3.6
3.8
4.0
4.2
4.4
4.6
4.8
5.0
5.2
F2 (ppm)
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
O
O
S
OBn
O
46

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul

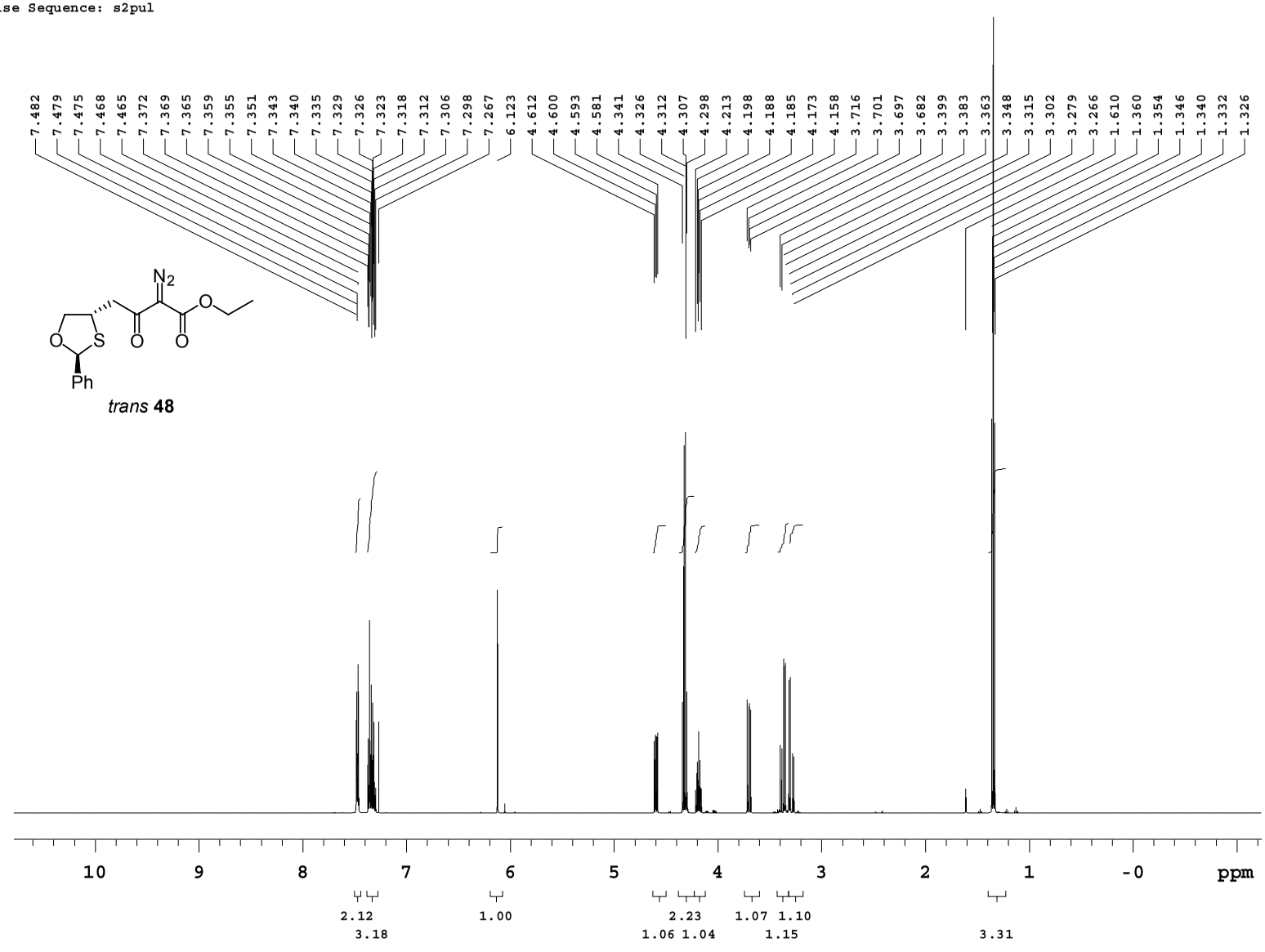


50


125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C autoxdb probe
Pulse Sequence: s2pul
N2
O
S
O
O
O
50
189.849
161.757
80.797
77.540
77.284
77.029
76.854
62.659
52.586
45.897
34.365
32.692
31.505
26.945
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

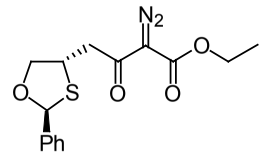
500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul



125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe

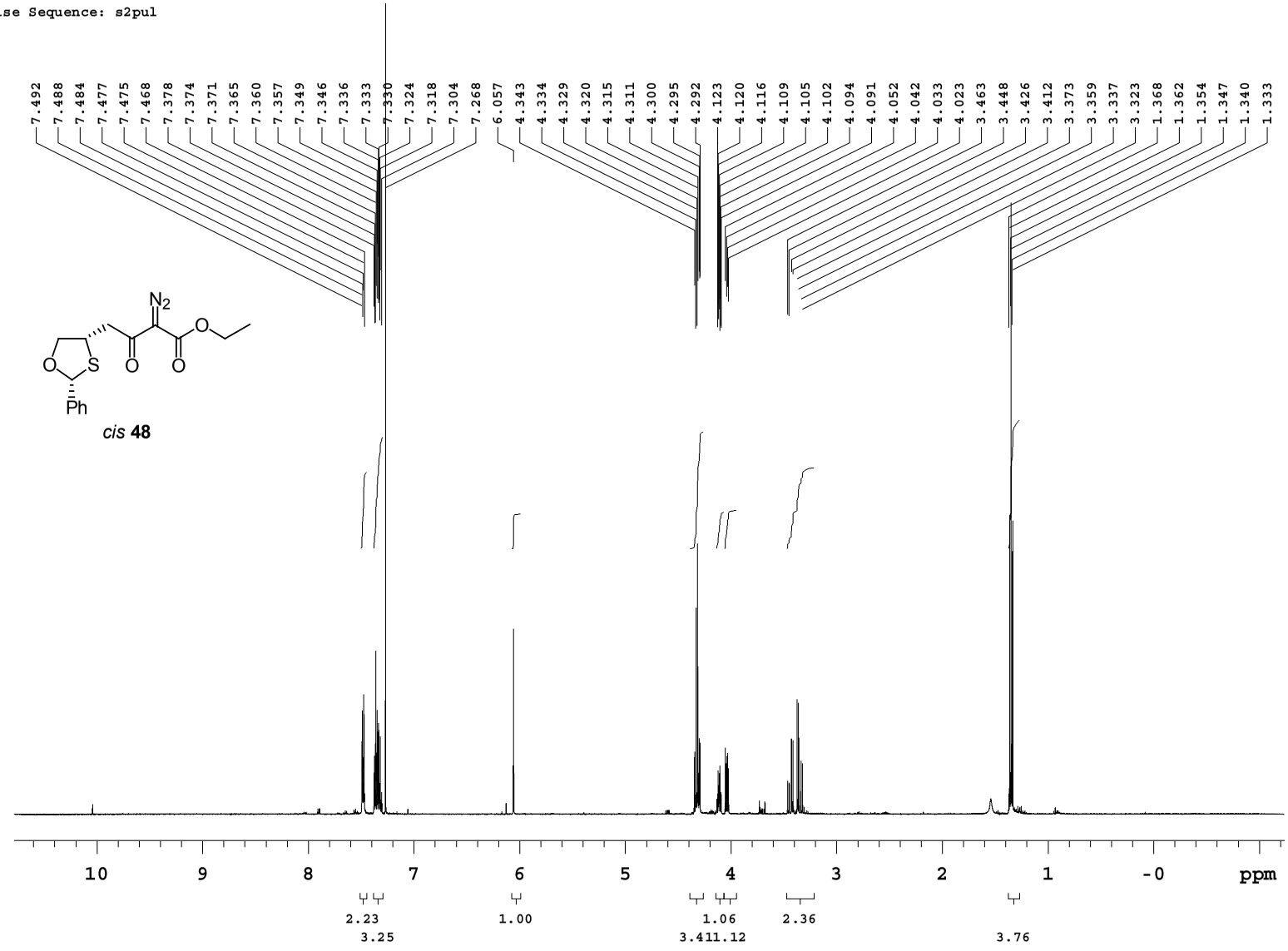
Pulse Sequence: s2pul

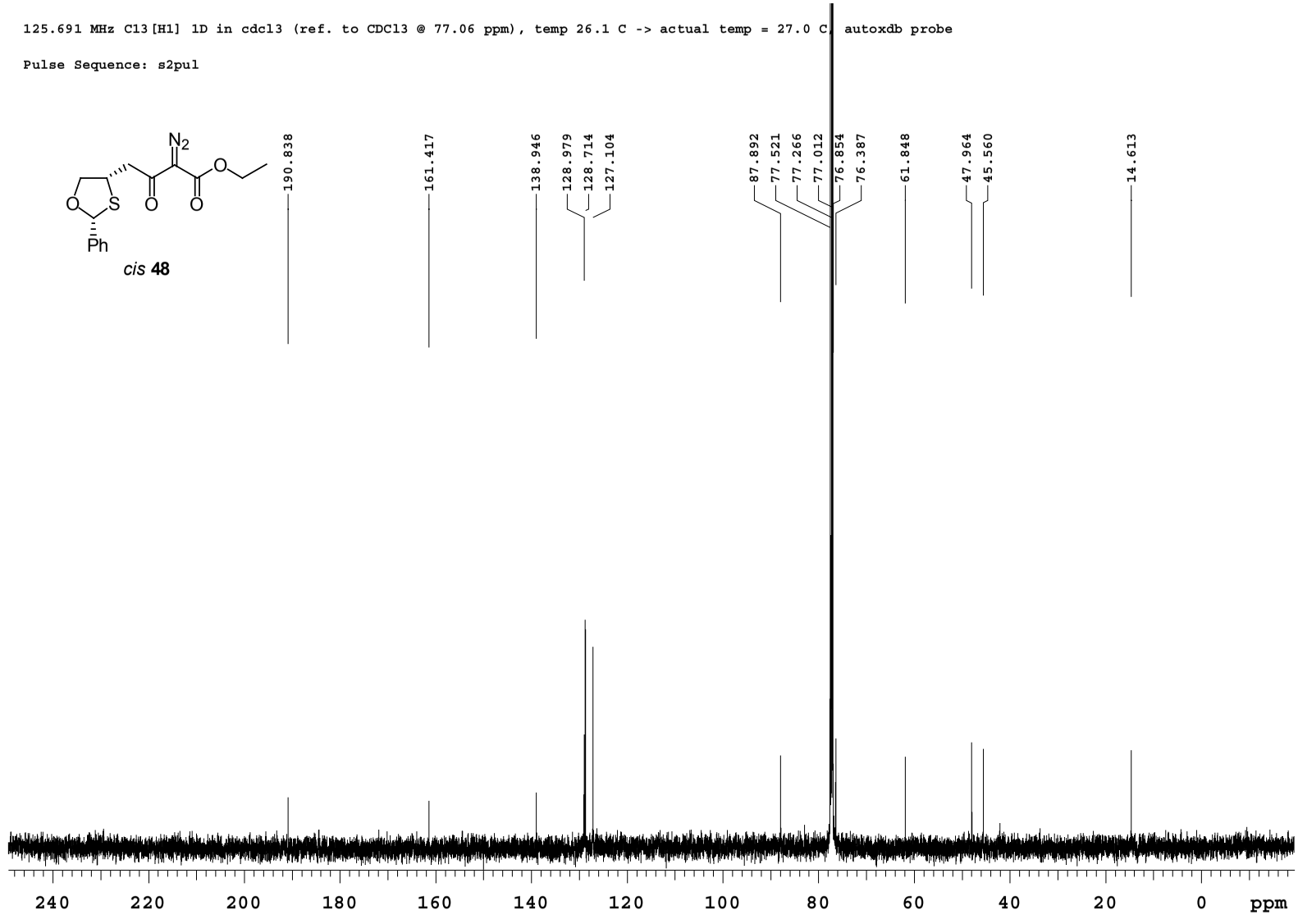


trans **48**

499.821 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

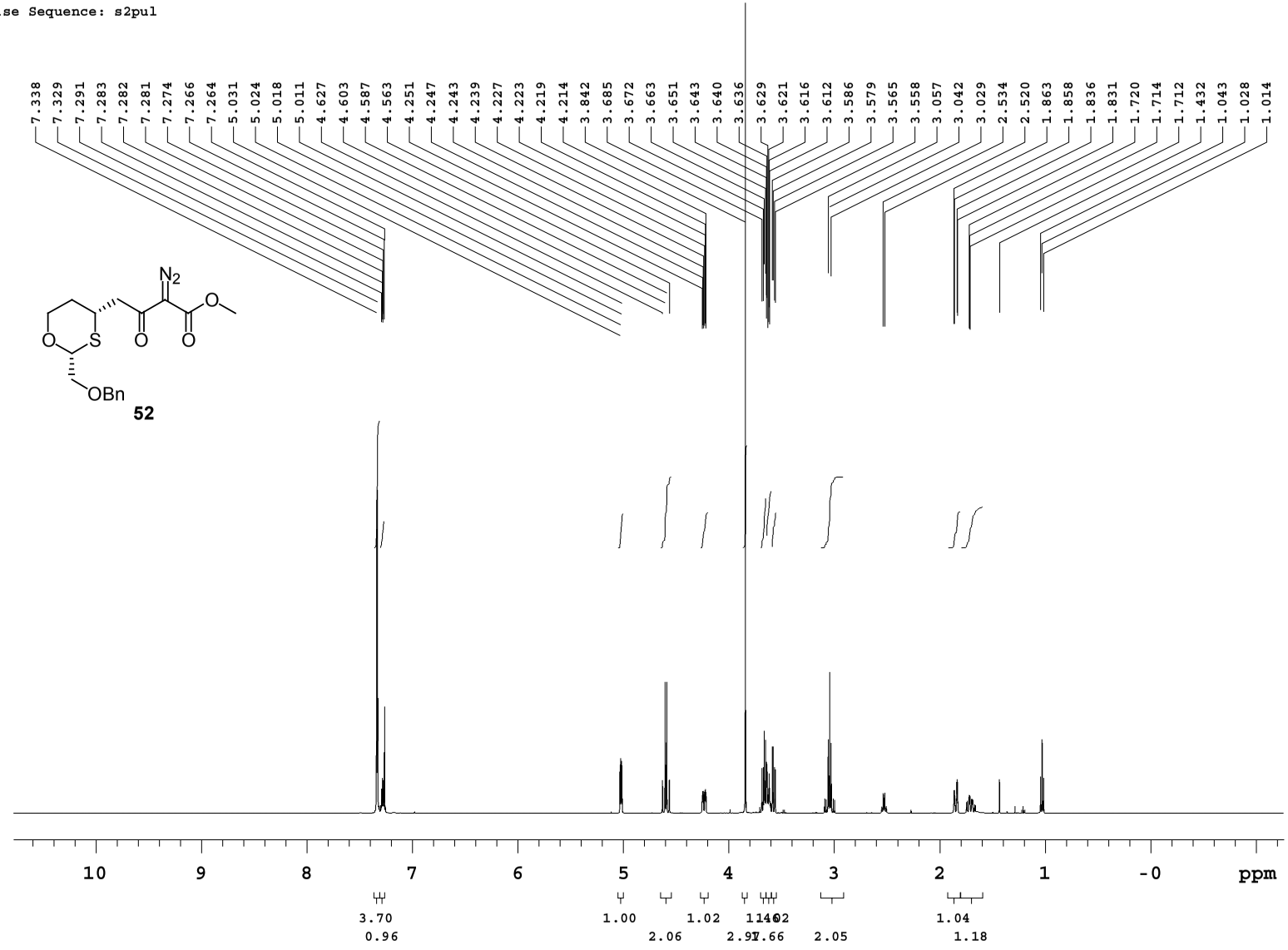
Pulse Sequence: s2pul

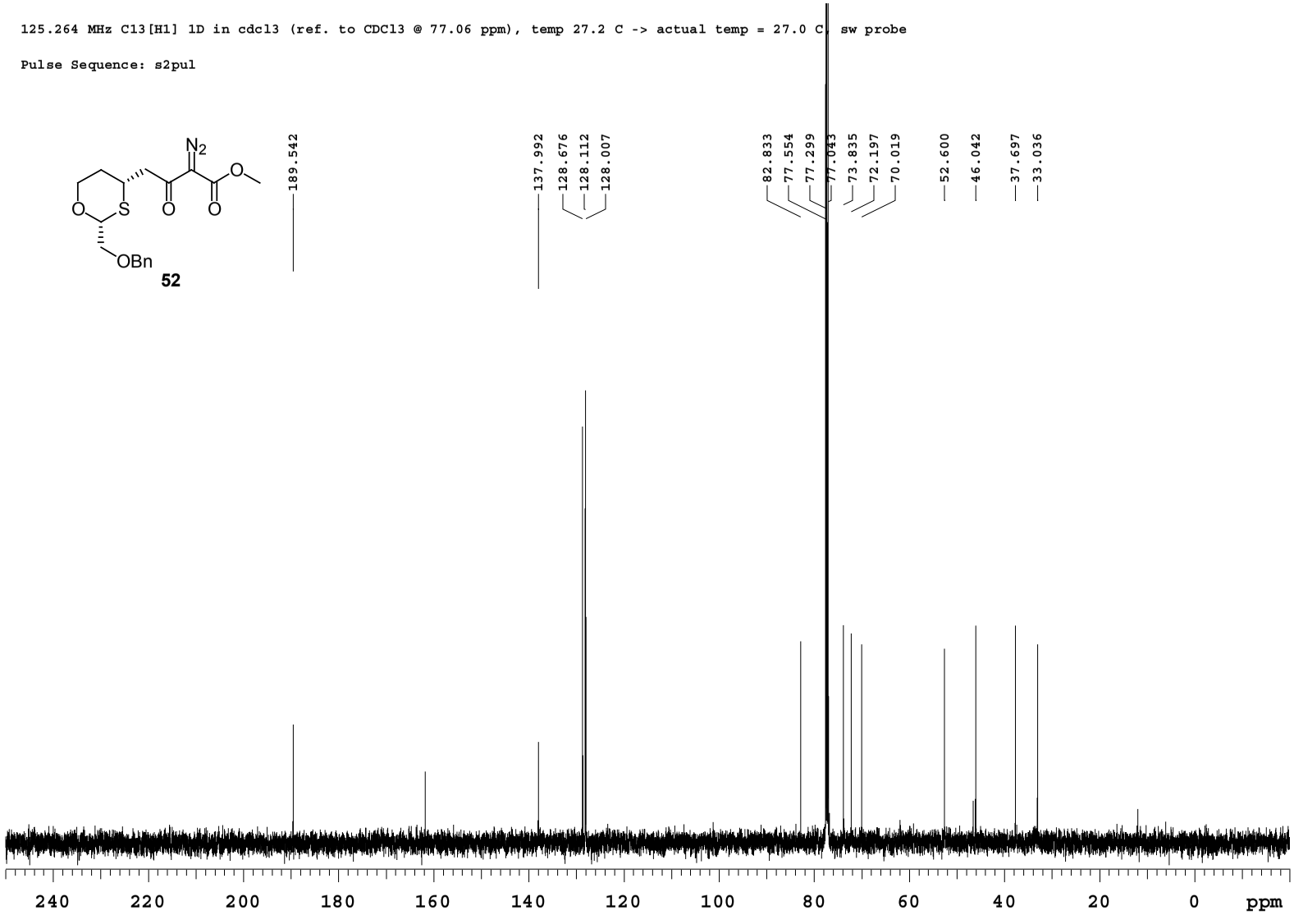



125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
N2
O
S
O
O
O
Ph
cis 48
190.838
161.417
138.946
128.979
128.714
127.104
87.892
77.521
77.266
77.012
76.854
76.387
61.848
47.964
45.560
14.613
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe

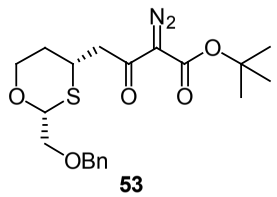
Pulse Sequence: s2pul



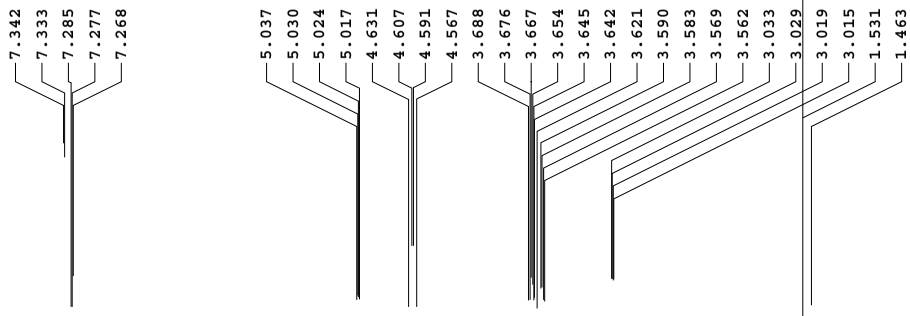

125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
Pulse Sequence: s2pul
N2
O
O
O
O
S
OBn
52
189.542
137.992
128.676
128.112
128.007
82.833
77.554
77.299
77.043
73.835
72.197
70.019
52.600
46.042
37.697
33.036
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

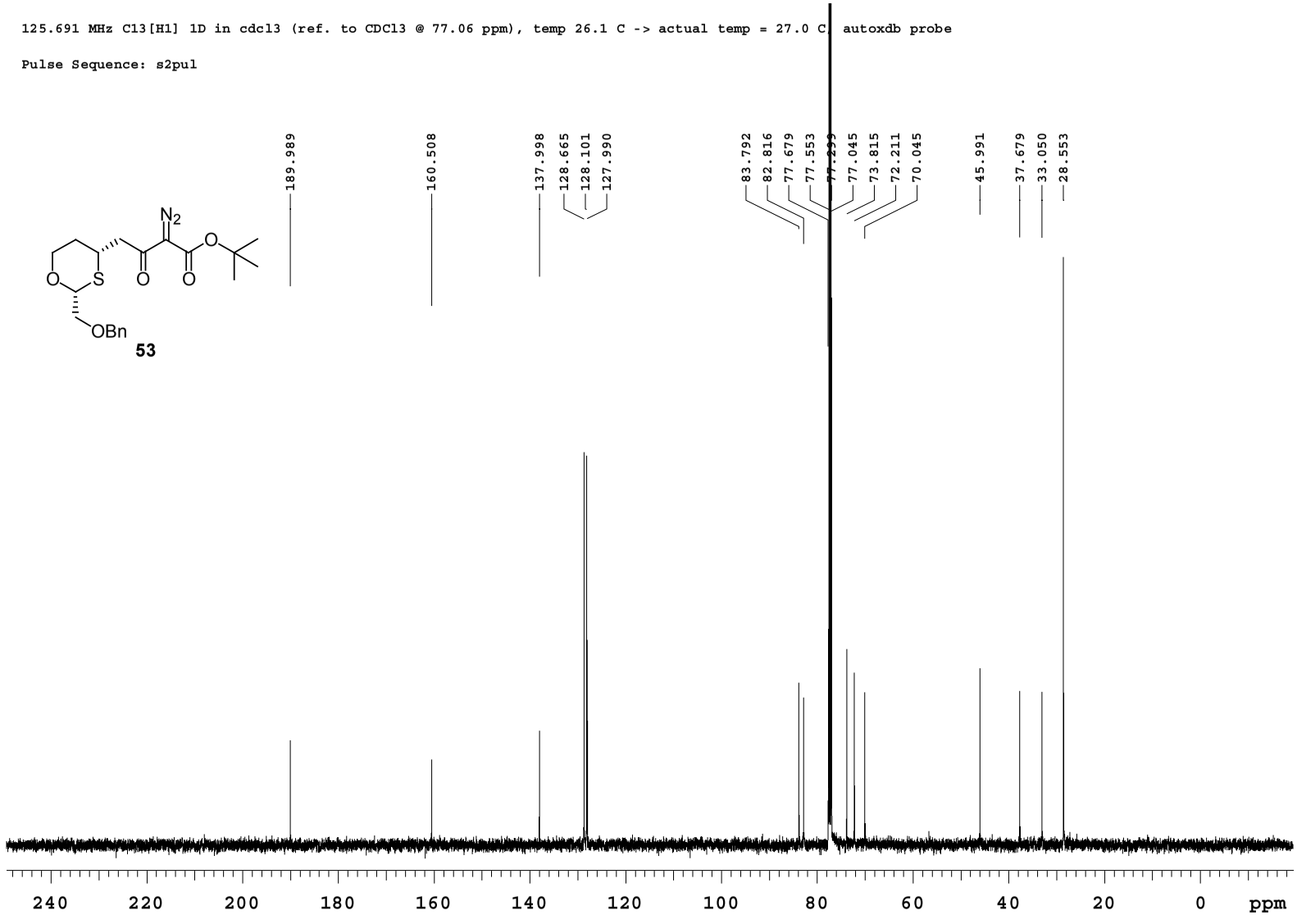
499.821 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul



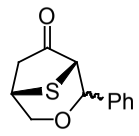
53



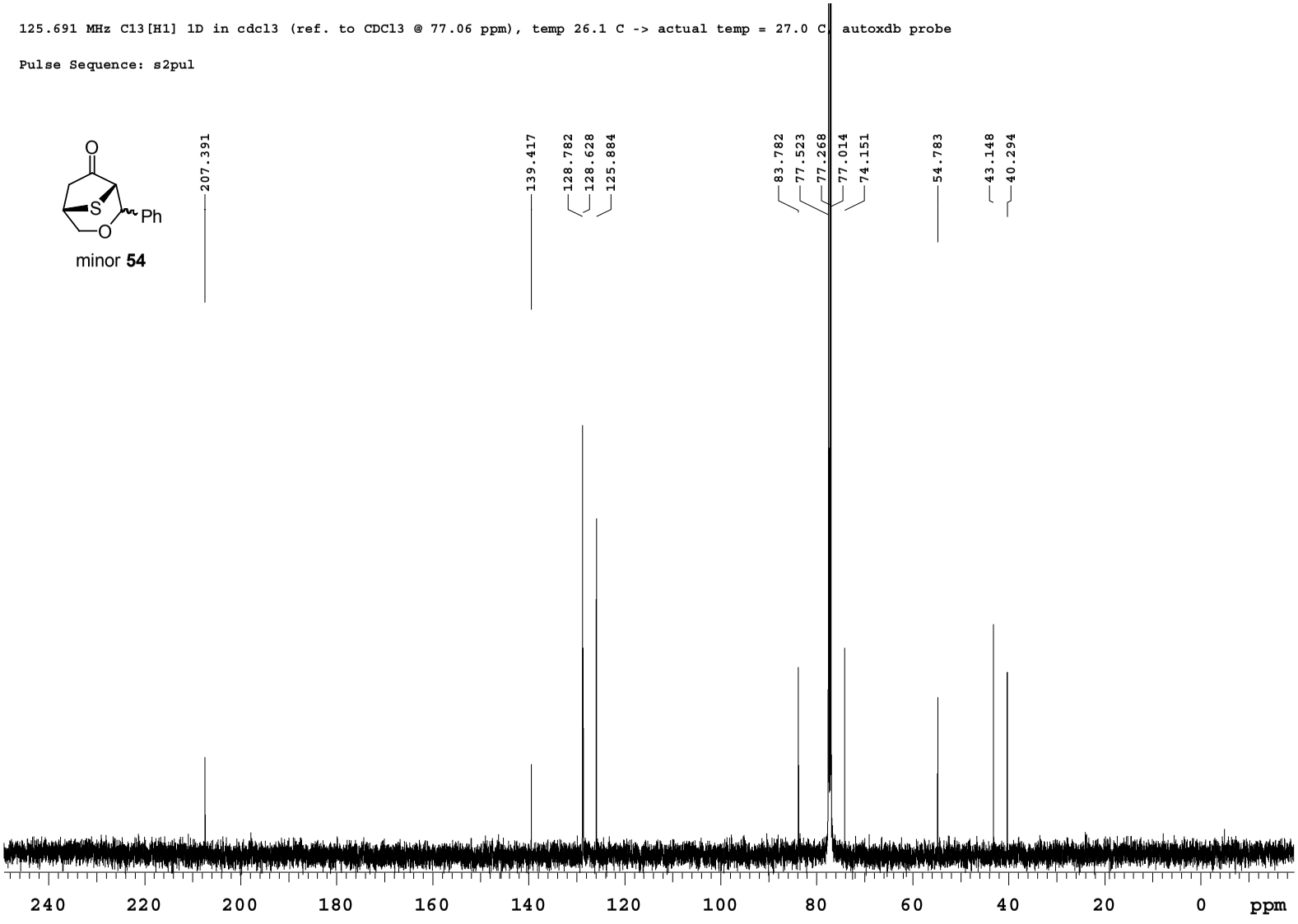

125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.1 C -> actual temp = 27.0 C autoxdb probe
Pulse Sequence: s2pul
189.989
160.508
137.998
128.665
128.101
127.990
83.792
82.816
77.679
77.553
77.299
77.045
73.815
72.211
70.045
45.991
37.679
33.050
28.553
N2
O
S
O
O
O
OBn
53
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

499.821 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul

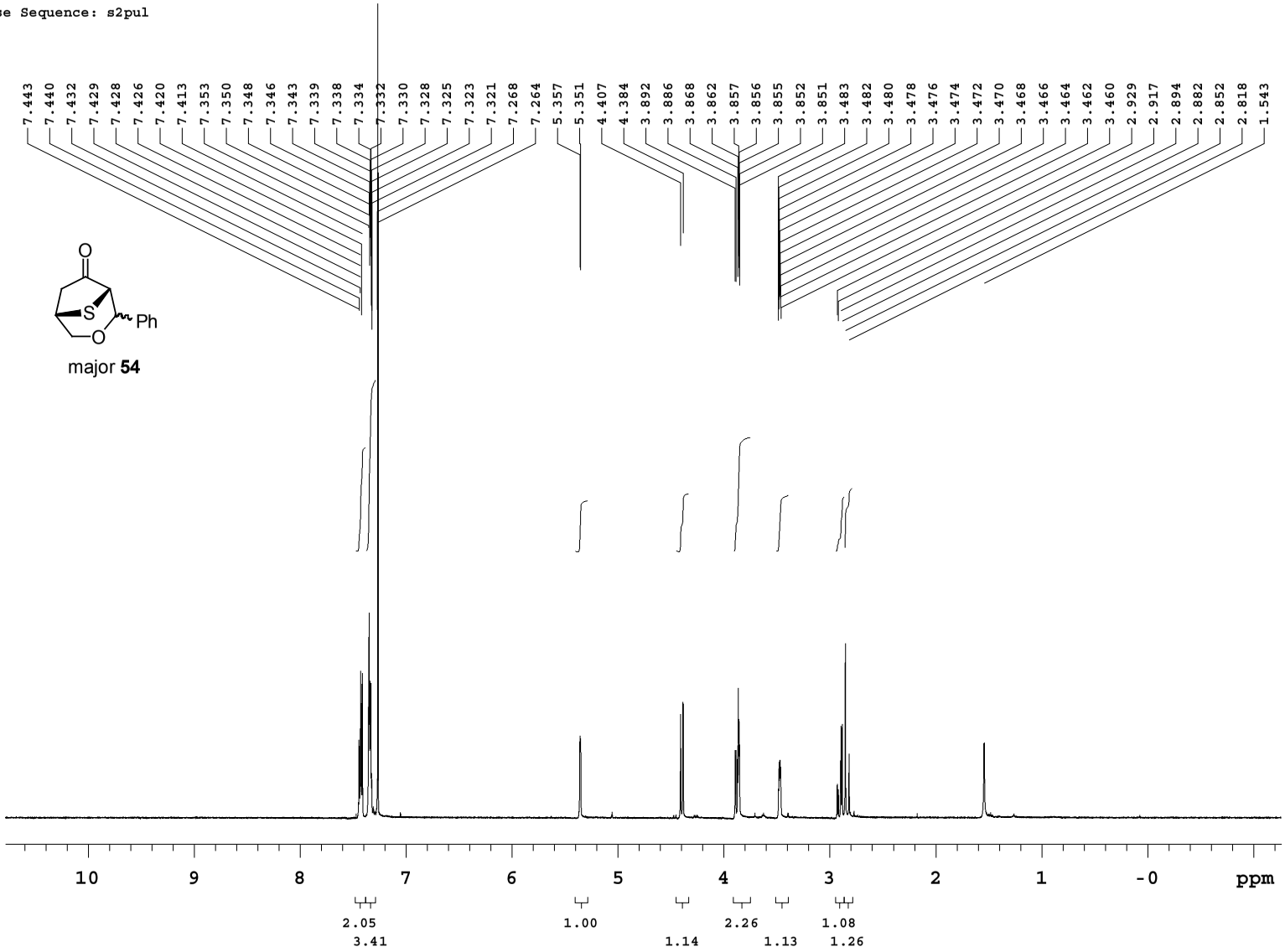


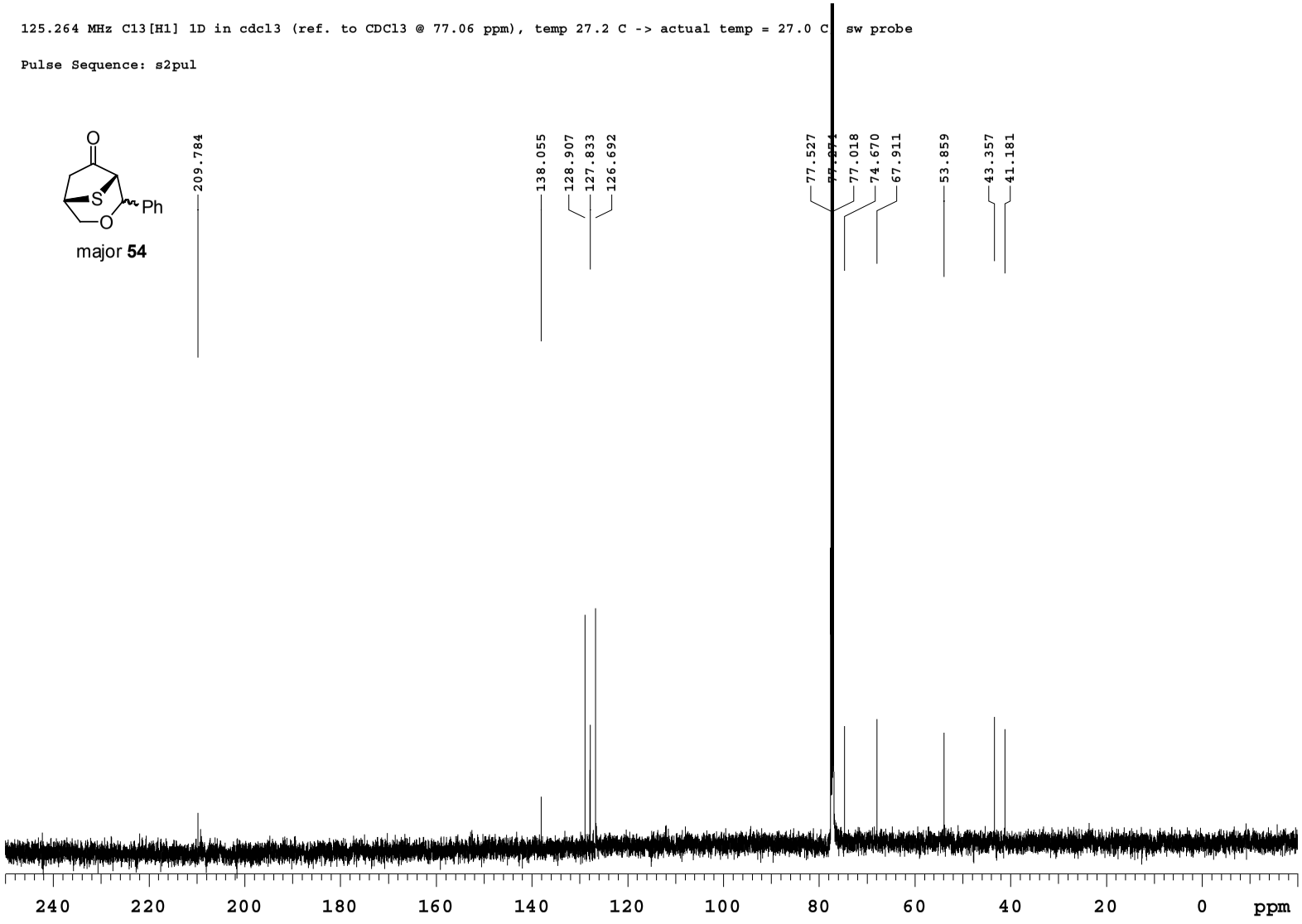
minor **54**


125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
O
S
O
Ph
minor 54
207.391
139.417
128.782
128.628
125.884
83.782
77.523
77.268
77.014
74.151
54.783
43.148
40.294
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe

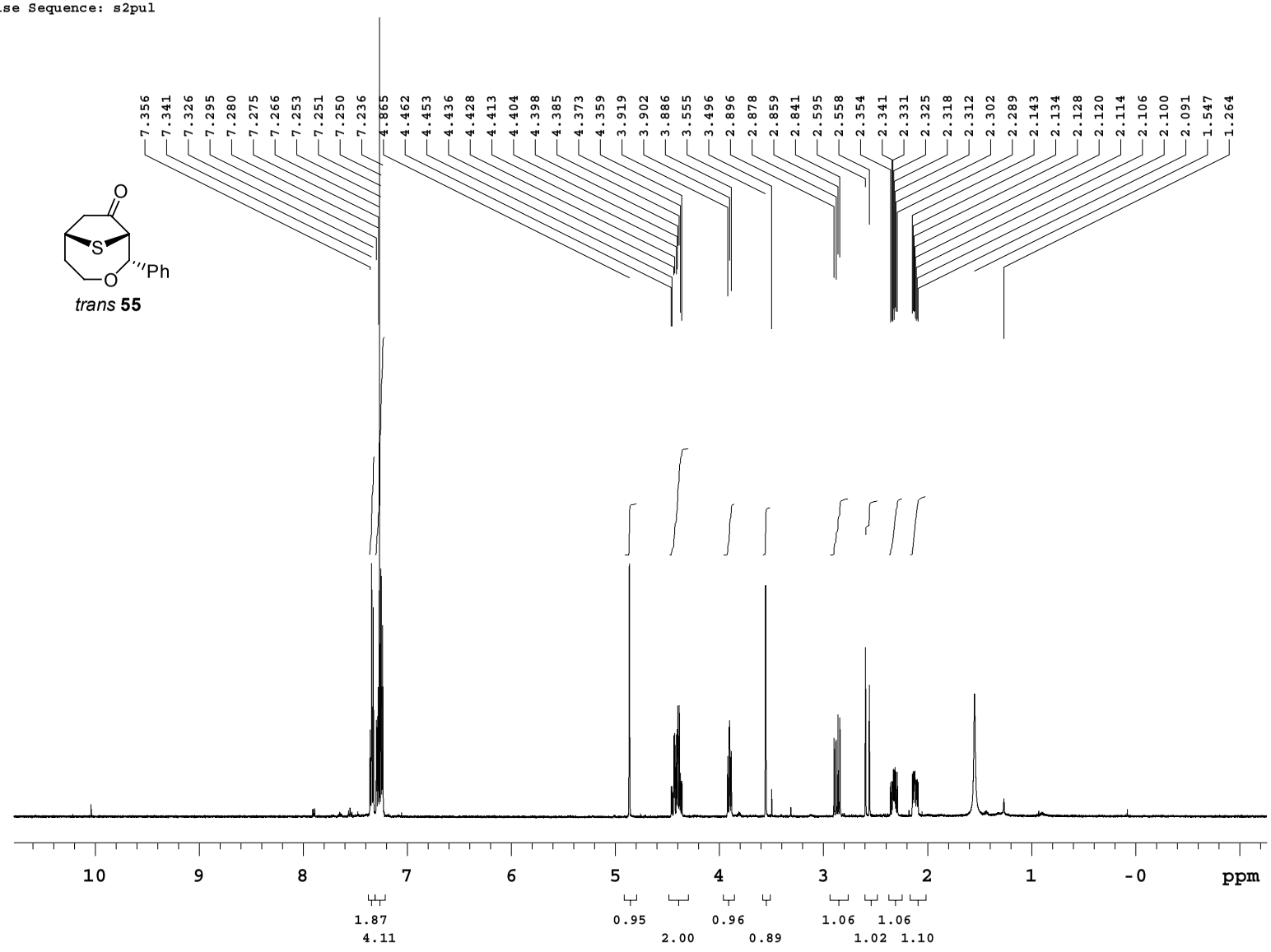
Pulse Sequence: s2pul

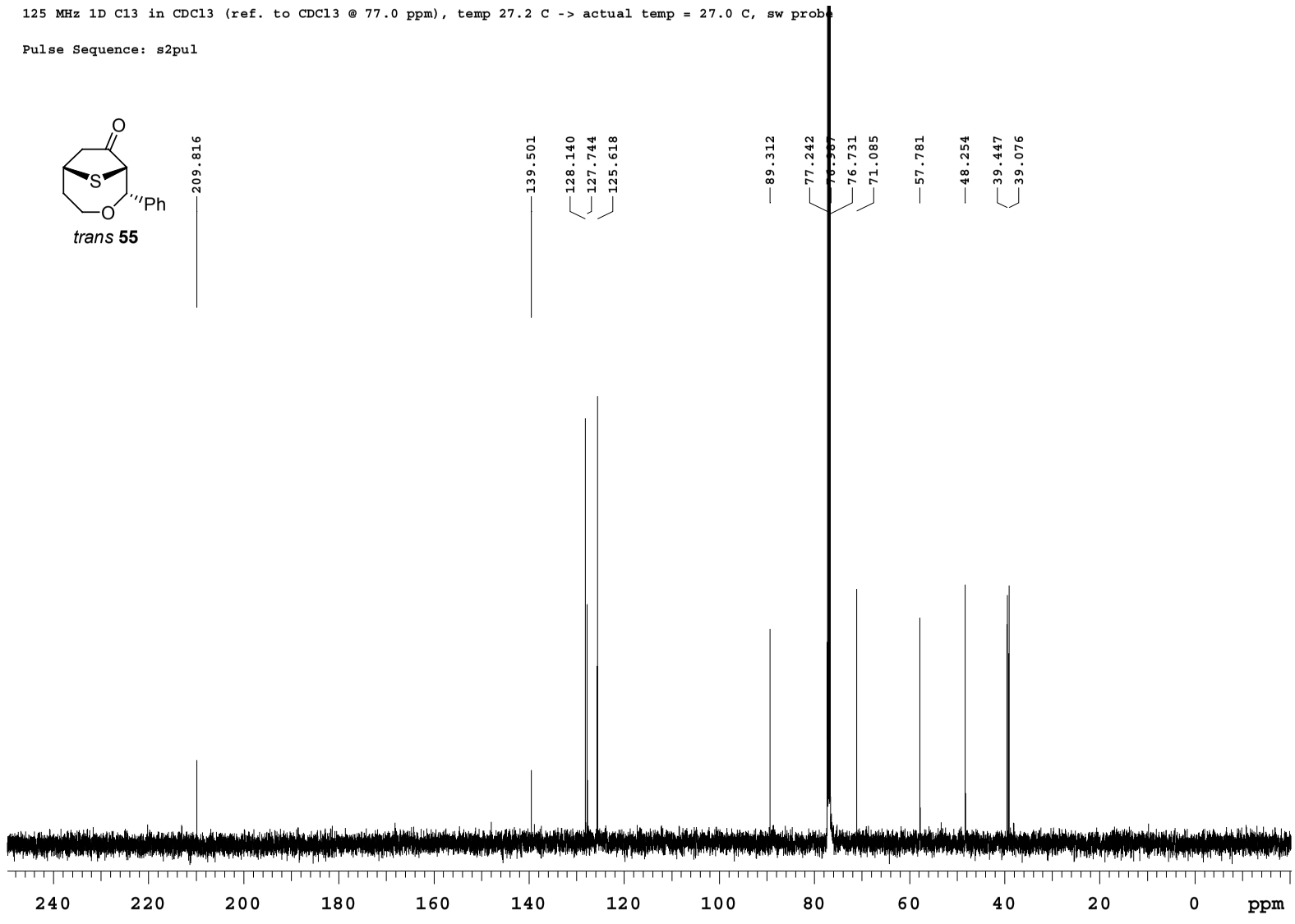



125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C sw probe
Pulse Sequence: s2pul
major 54
209.784
138.055
128.907
127.833
126.692
77.527
77.271
77.018
74.670
67.911
53.859
43.357
41.181
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe

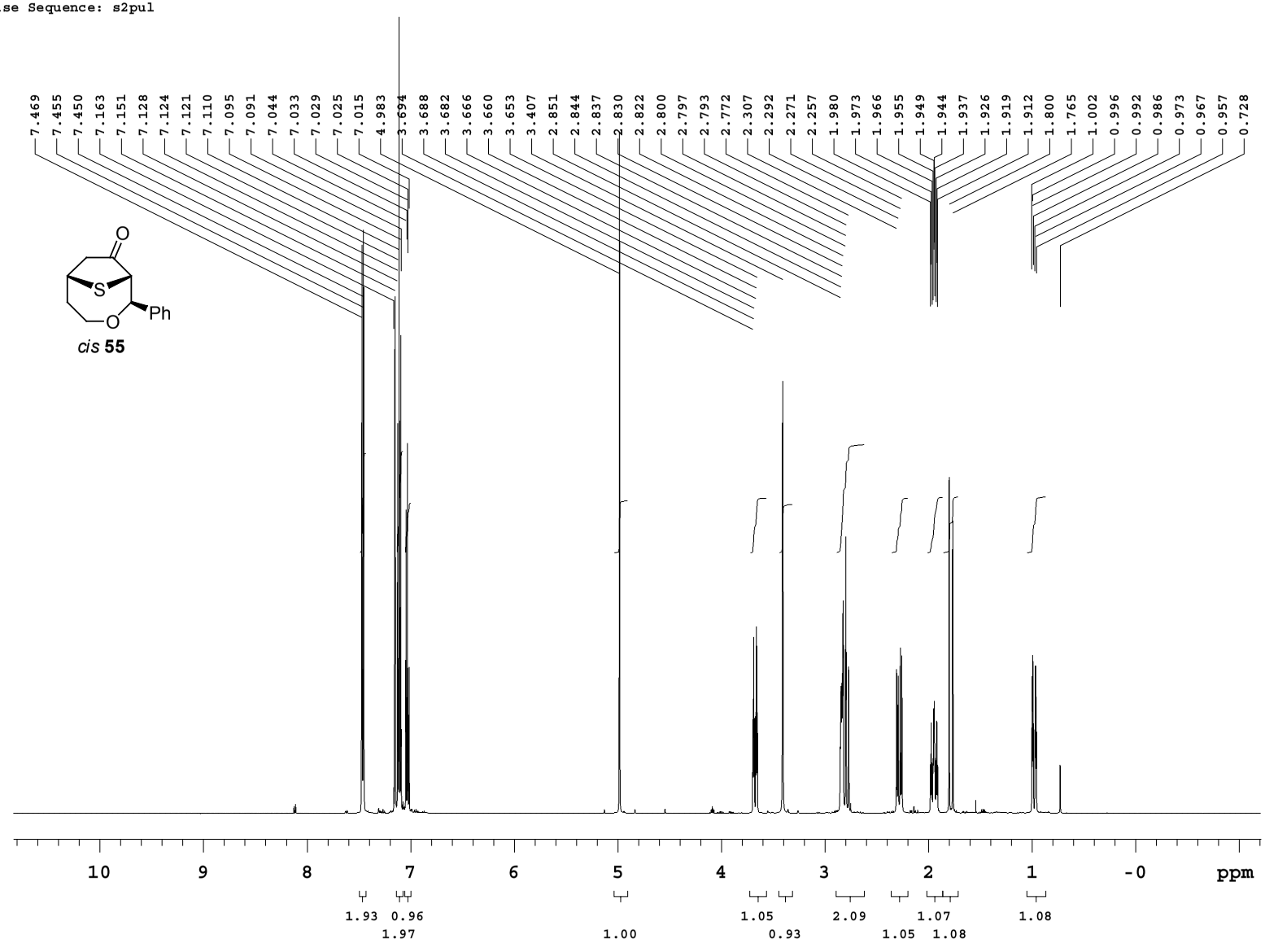
Pulse Sequence: s2pul




125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
Pulse Sequence: s2pul
O
S
O
Ph
trans 55
209.816
139.501
128.140
127.744
125.618
89.312
77.242
76.731
71.085
57.781
48.254
39.447
39.076
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

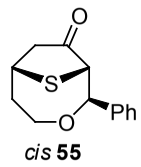
500 MHz 1D in C6D6 (ref. to C6D6 @ 7.15 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe

Pulse Sequence: s2pul



125 MHz 1D C13 in C6D6 (ref. to C6D6 @ 128.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe

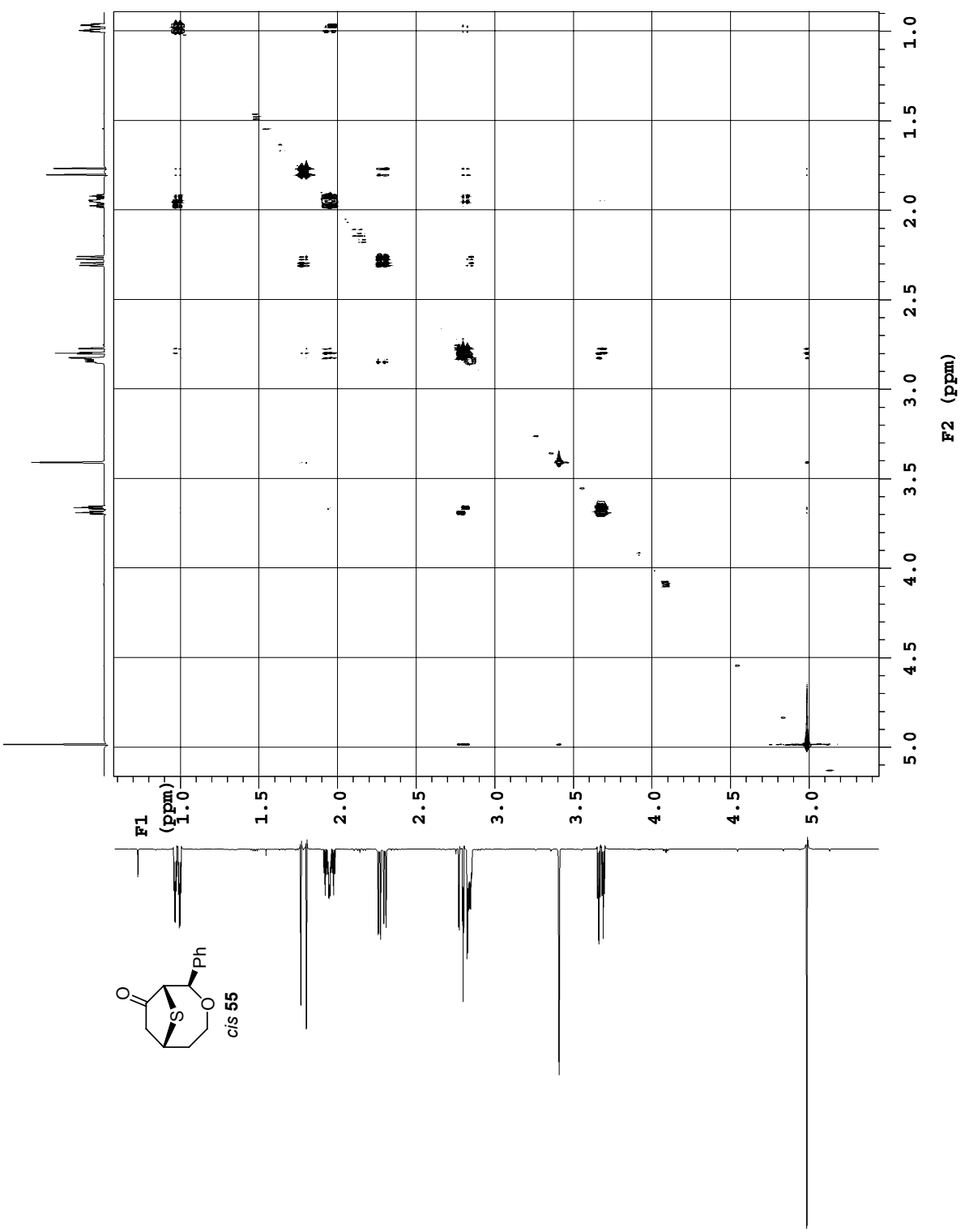
Pulse Sequence: s2pul



cis **55**

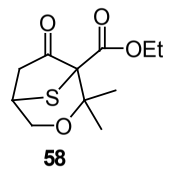
214.472
142.070
128.524
128.341
128.242
128.048
127.958
127.894
127.855
126.558
84.037
65.406
61.957
45.560
39.278
38.771

240 220 200 180 160 140 120 100 80 60 40 20 0 ppm


F1 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
F2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
O
S
O
Ph
cis 55

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe

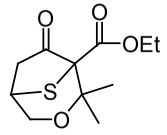
Pulse Sequence: s2pul



58

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe

Pulse Sequence: s2pul



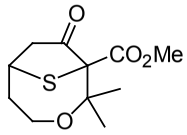
58

204.042
166.327
77.521
77.268
77.010
68.740
67.328
62.229
43.408
39.596
25.627
20.344
14.181

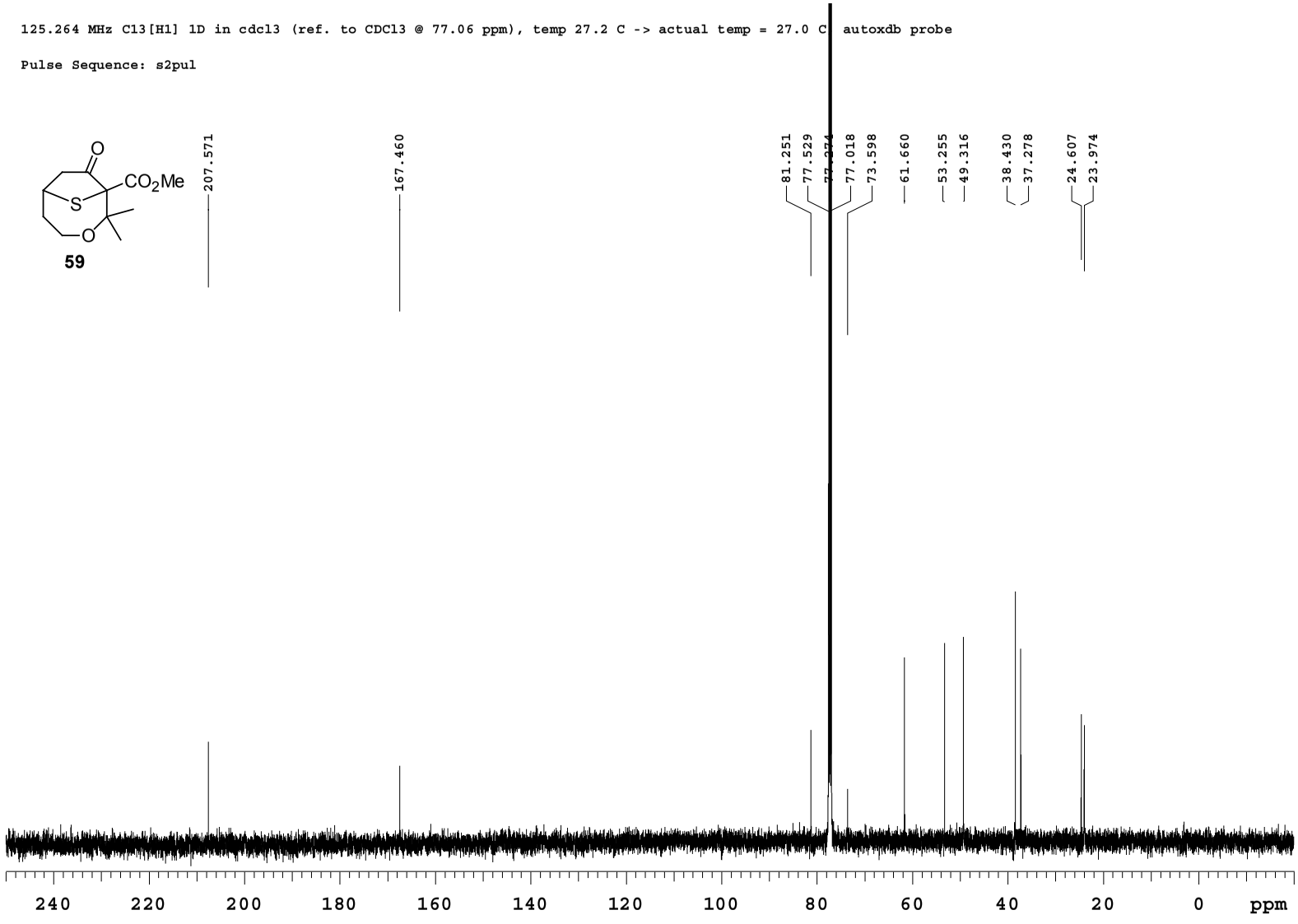
240 220 200 180 160 140 120 100 80 60 40 20 0 ppm

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul

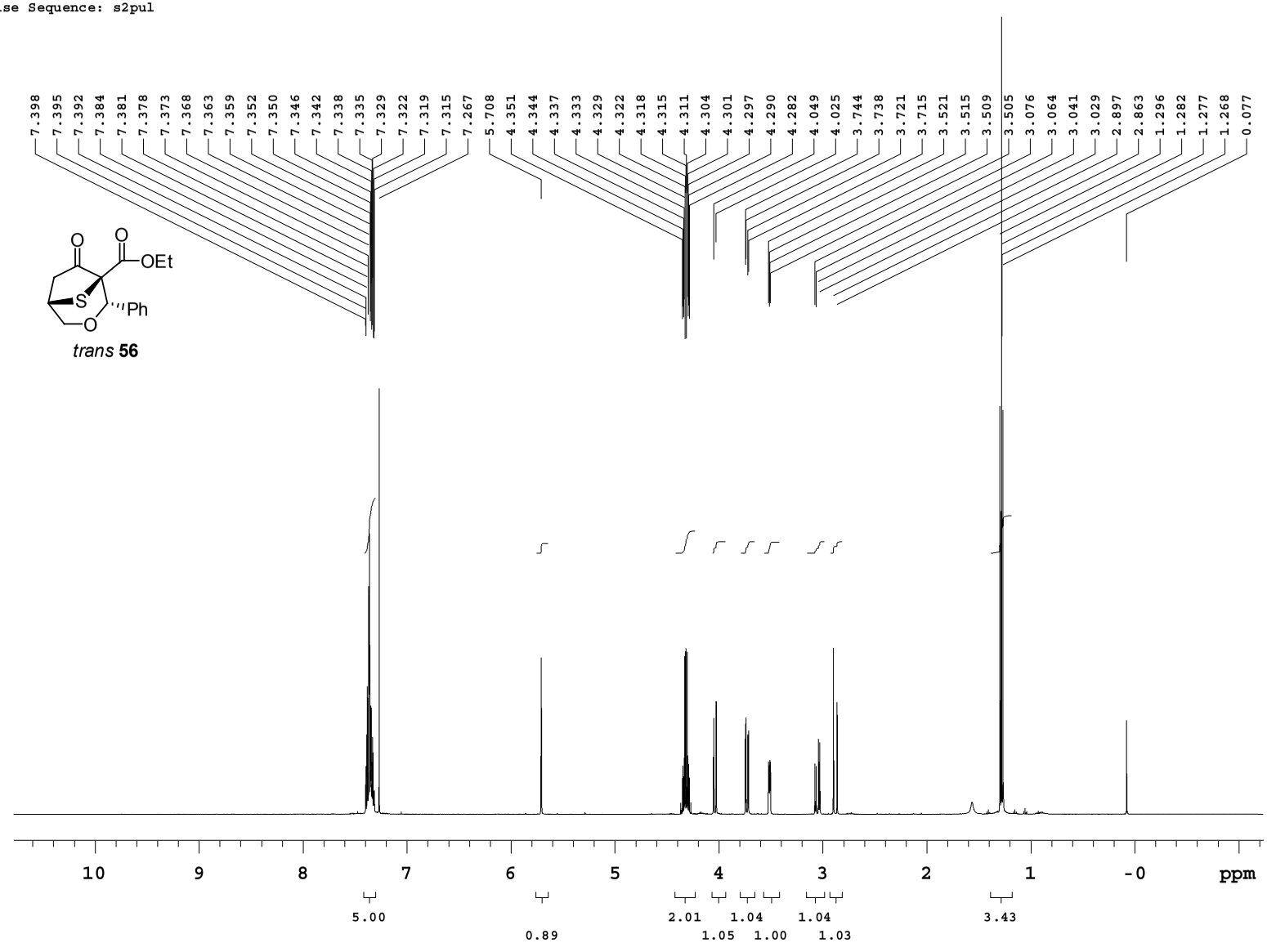


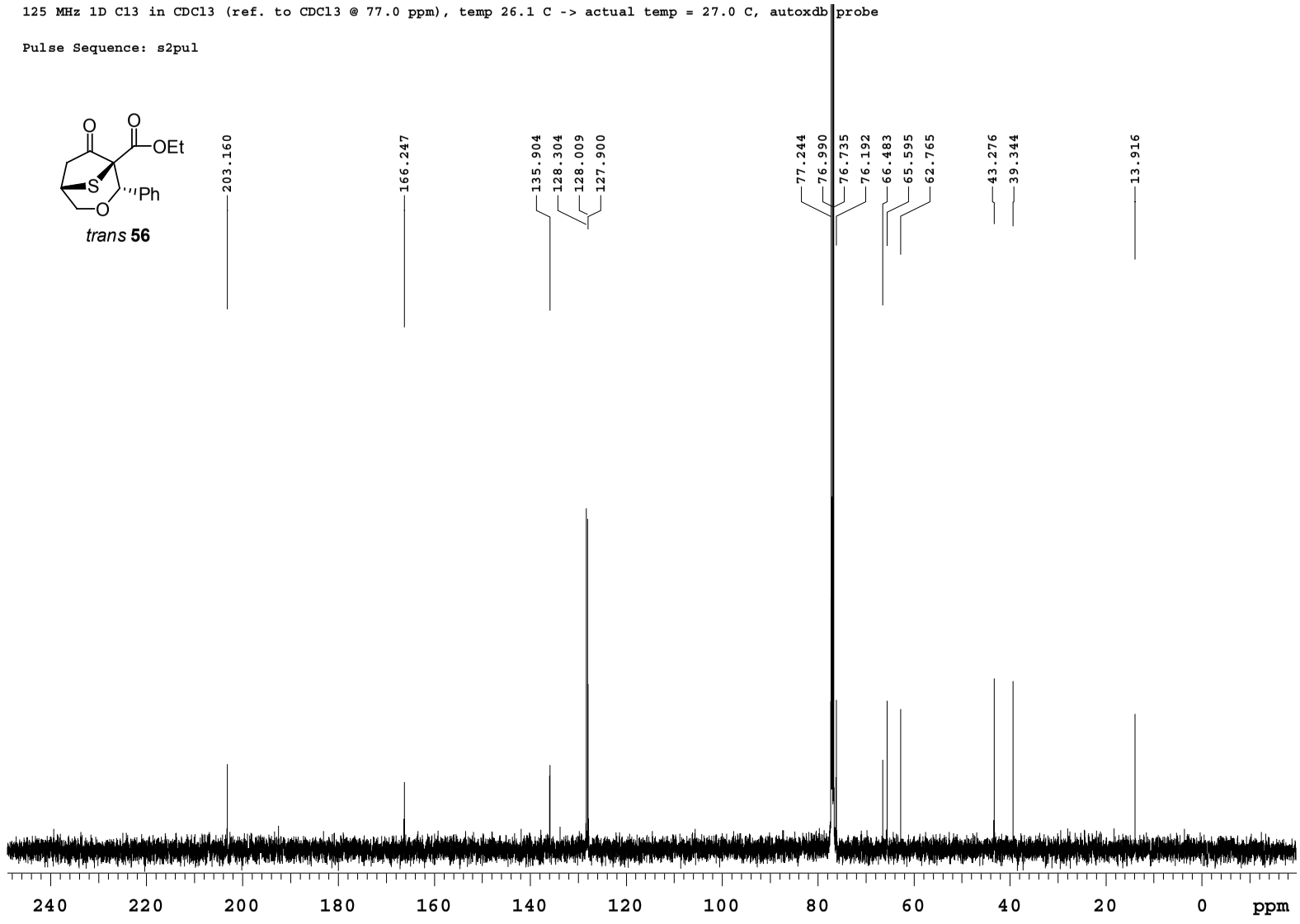
59

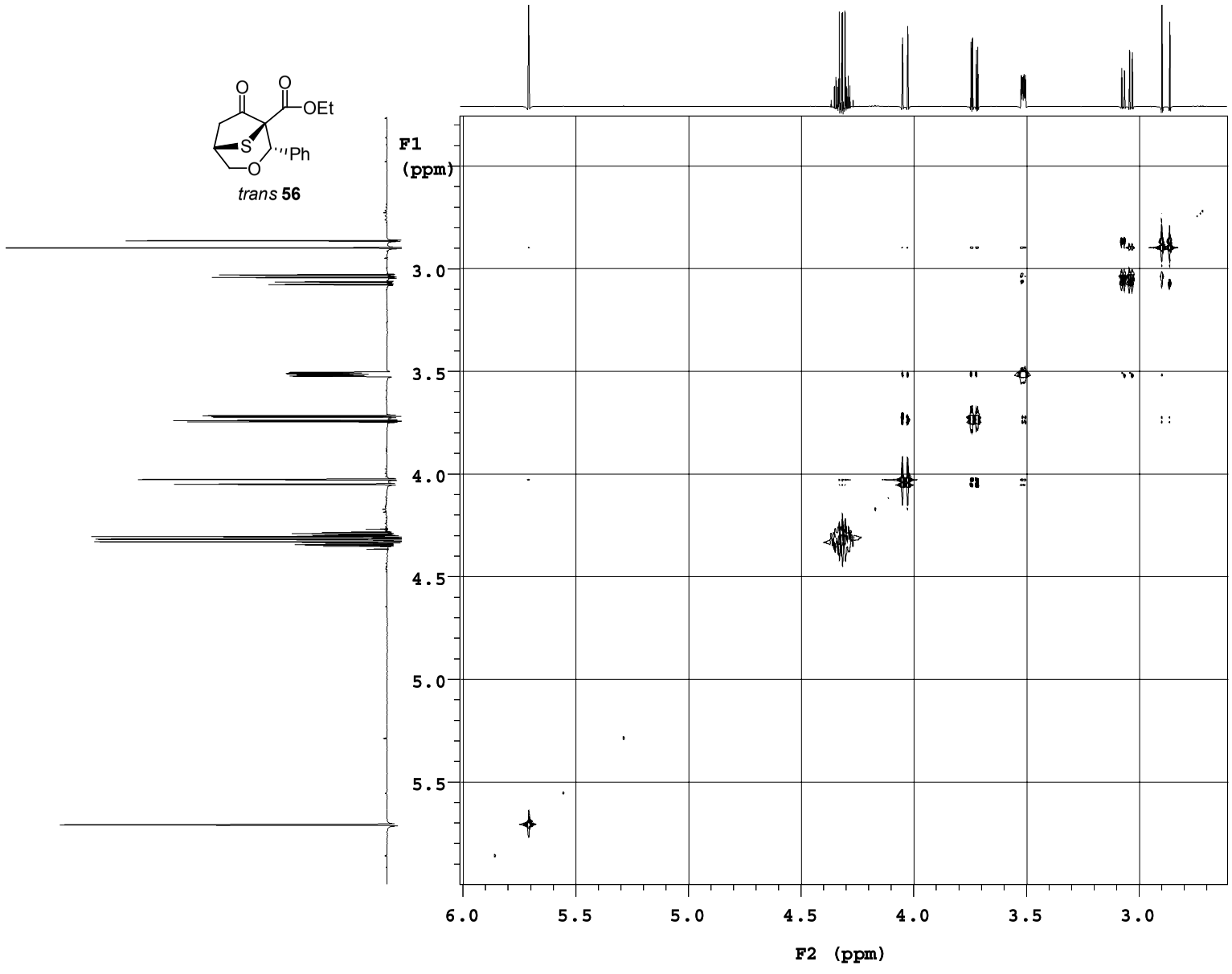

125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C autoxdb probe
Pulse Sequence: s2pul
O
CO2Me
S
O
59
207.571
167.460
81.251
77.529
77.274
77.018
73.598
61.660
53.255
49.316
38.430
37.278
24.607
23.974
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul

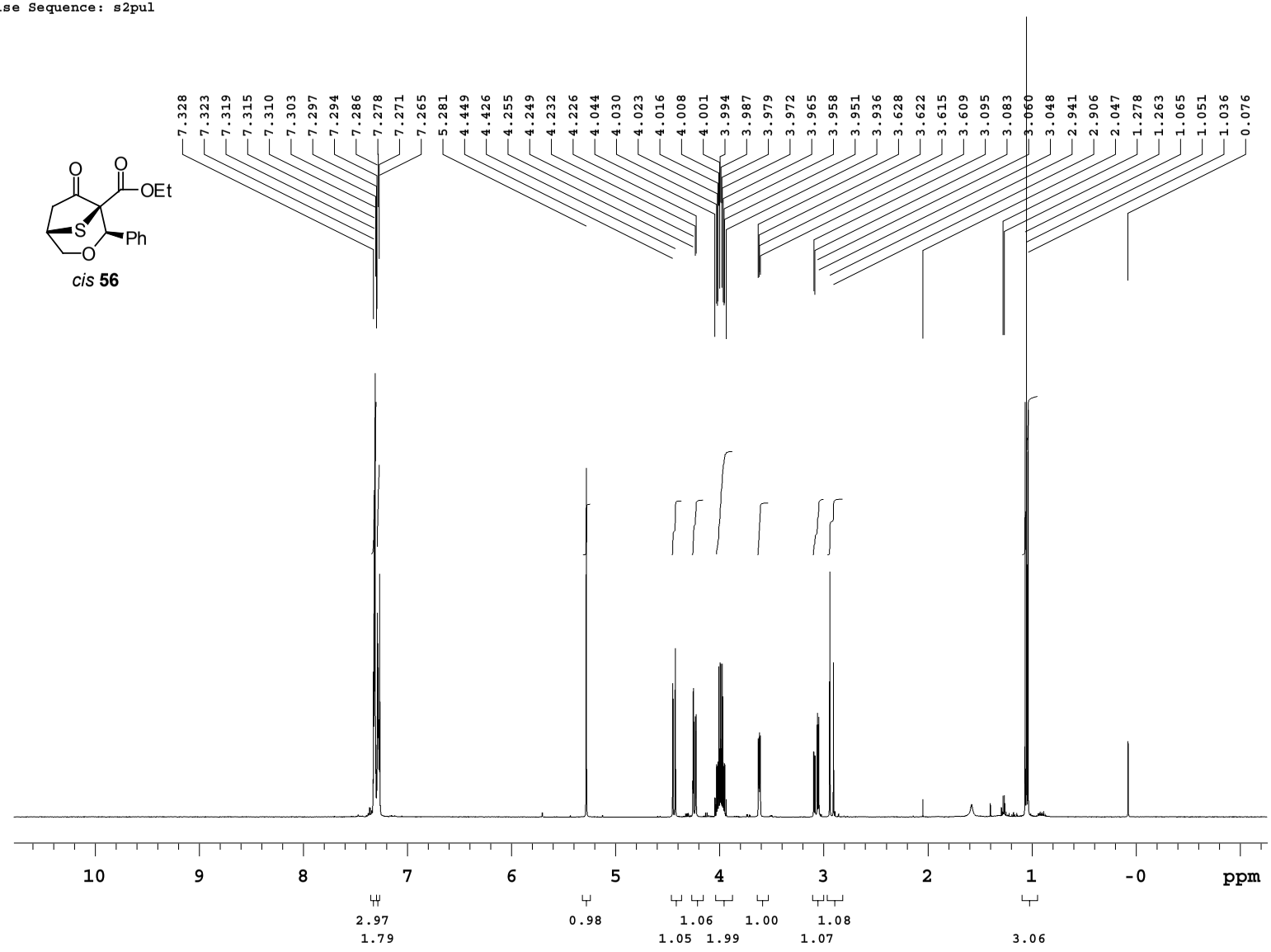


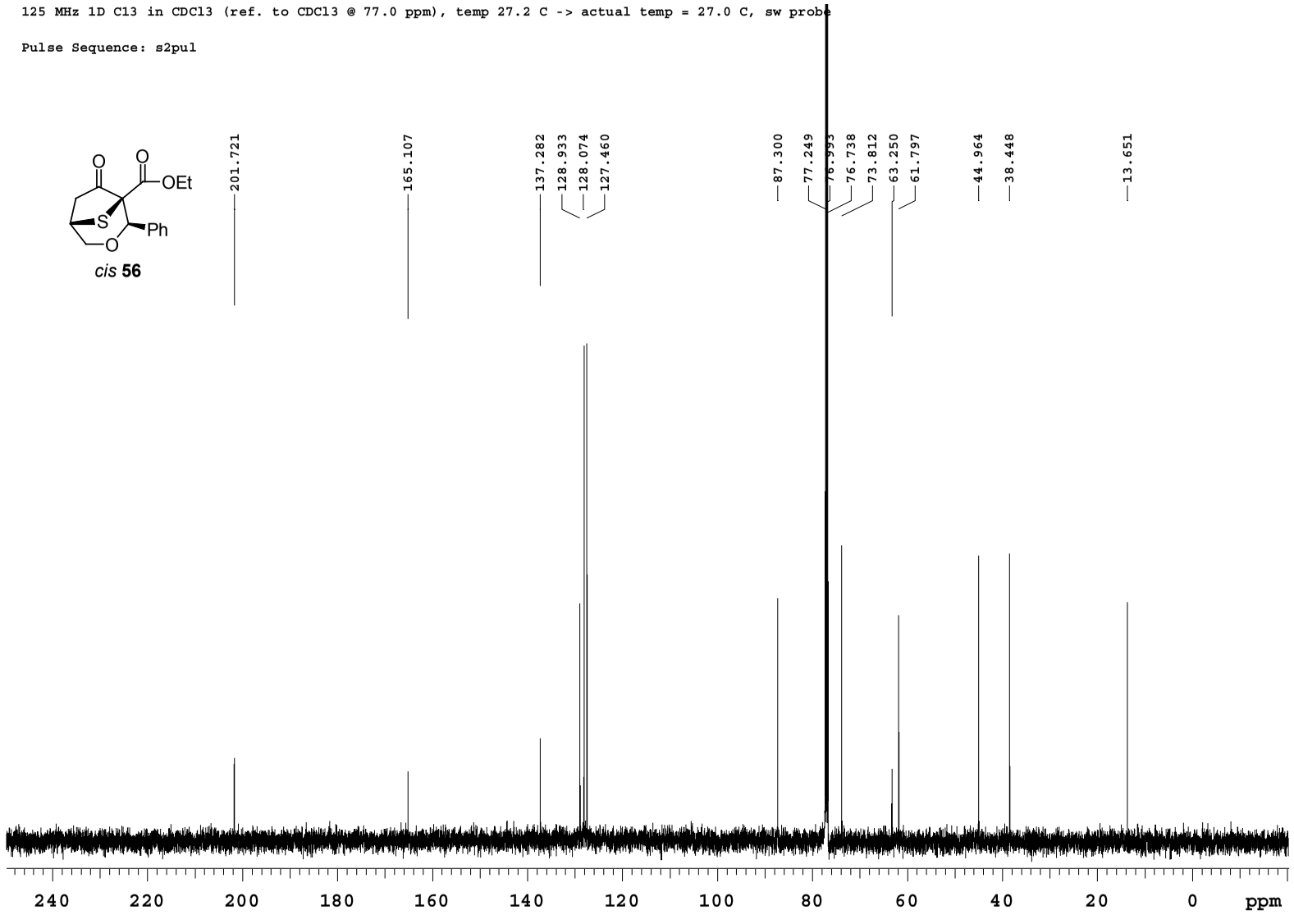

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
O
O
OEt
S
Ph
O
trans 56
203.160
166.247
135.904
128.304
128.009
127.900
77.244
76.990
76.735
76.192
66.483
65.595
62.765
43.276
39.344
13.916
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

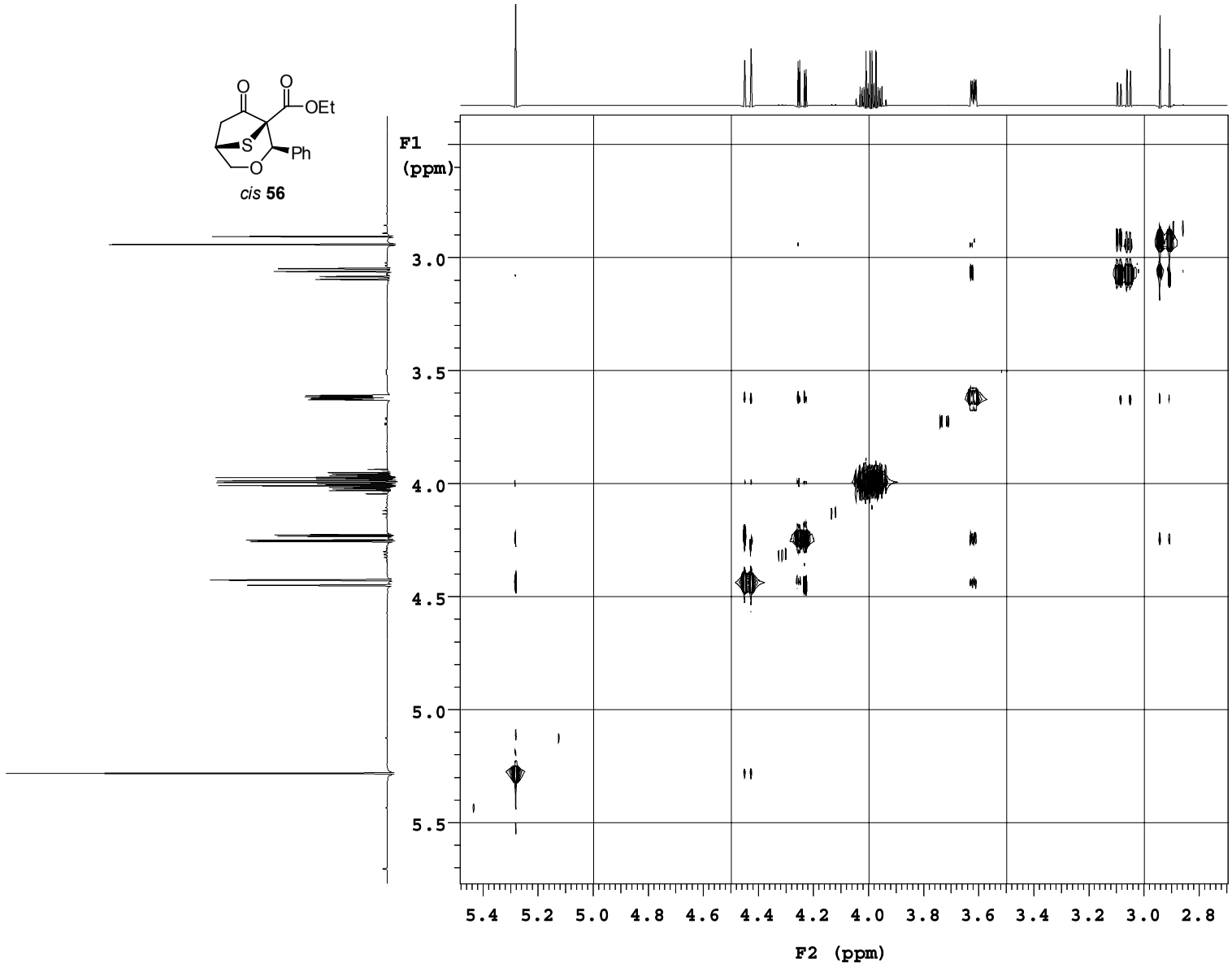

O
O
OEt
S
Ph
O
trans 56
F1
(ppm)
3.0
3.5
4.0
4.5
5.0
5.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
F2 (ppm)

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe

Pulse Sequence: s2pul

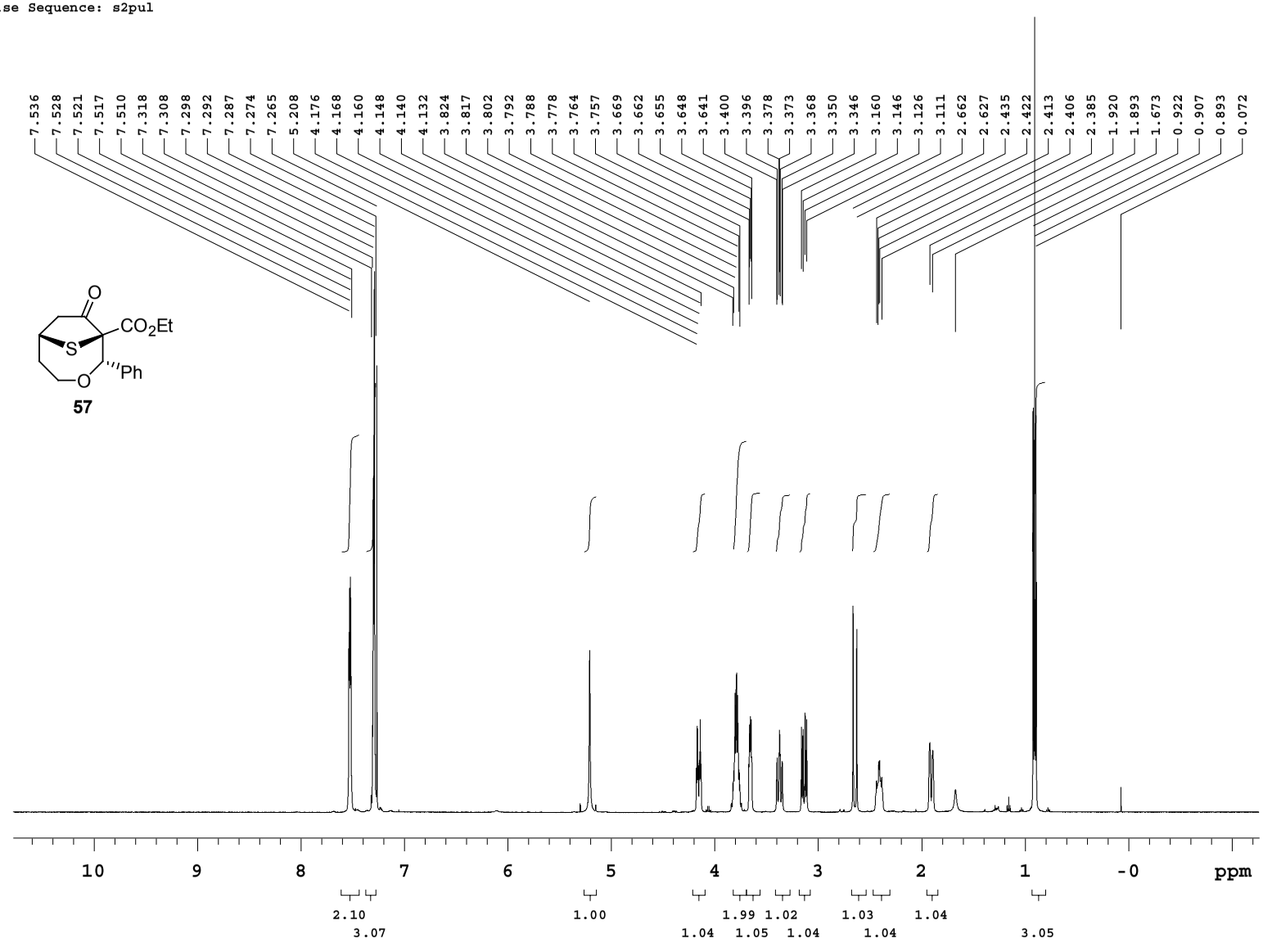


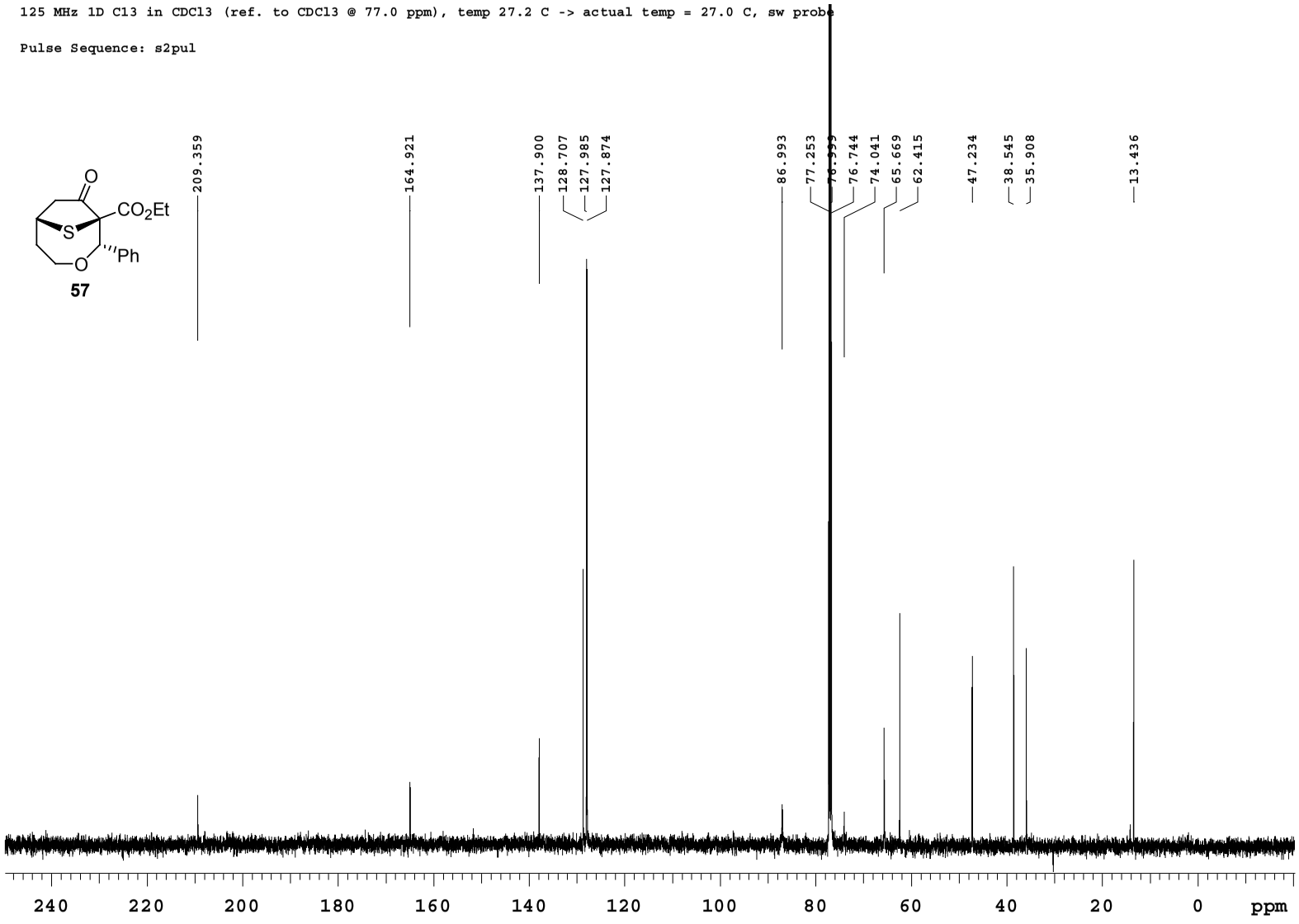

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
Pulse Sequence: s2pul
O
O
OEt
S
Ph
O
cis 56
201.721
165.107
137.282
128.933
128.074
127.460
87.300
77.249
76.993
76.738
73.812
63.250
61.797
44.964
38.448
13.651
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
O
OEt
S
Ph
O
cis 56
F1
(ppm)
3.0
3.5
4.0
4.5
5.0
5.5
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
F2 (ppm)

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe

Pulse Sequence: s2pul

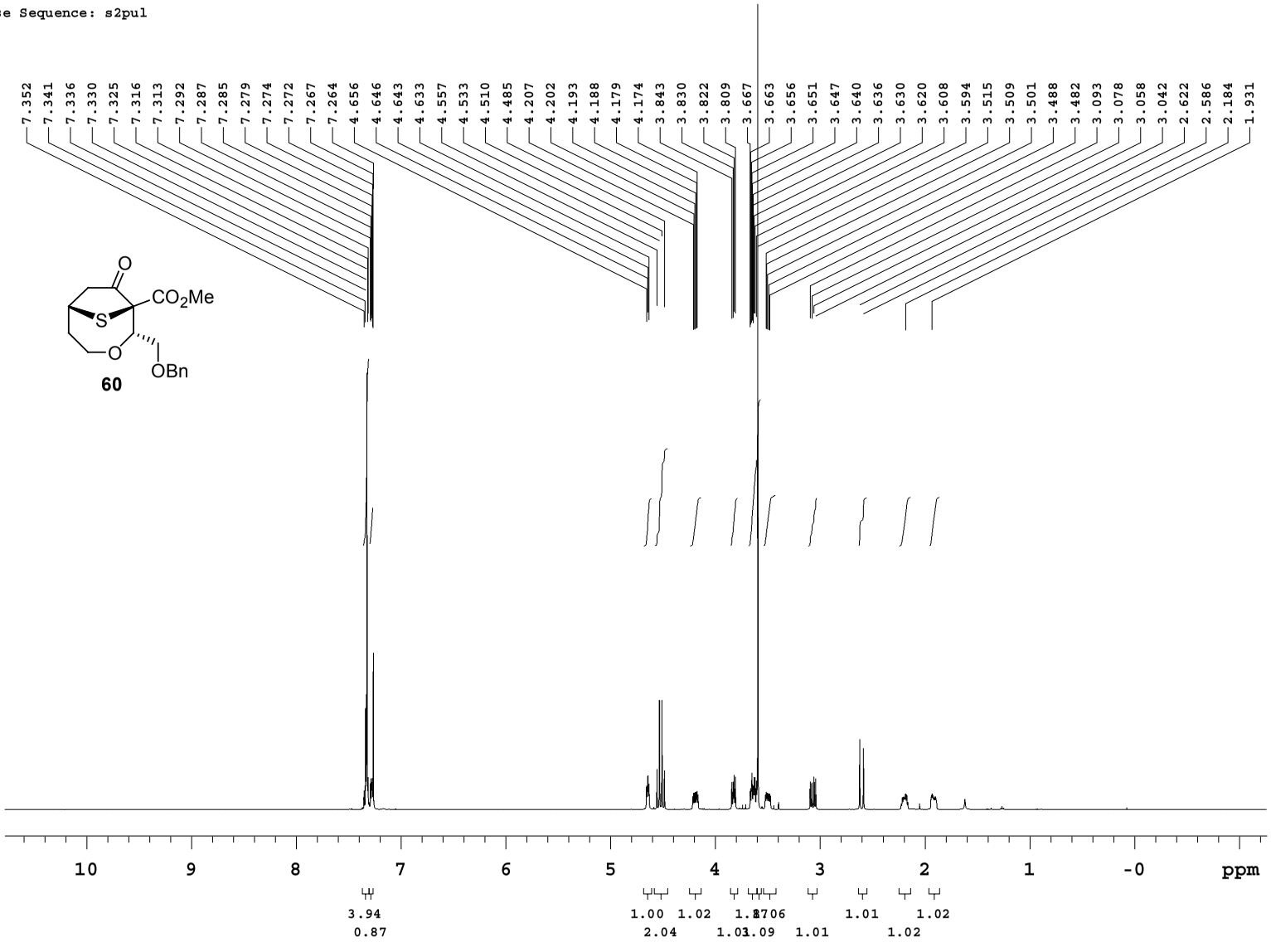


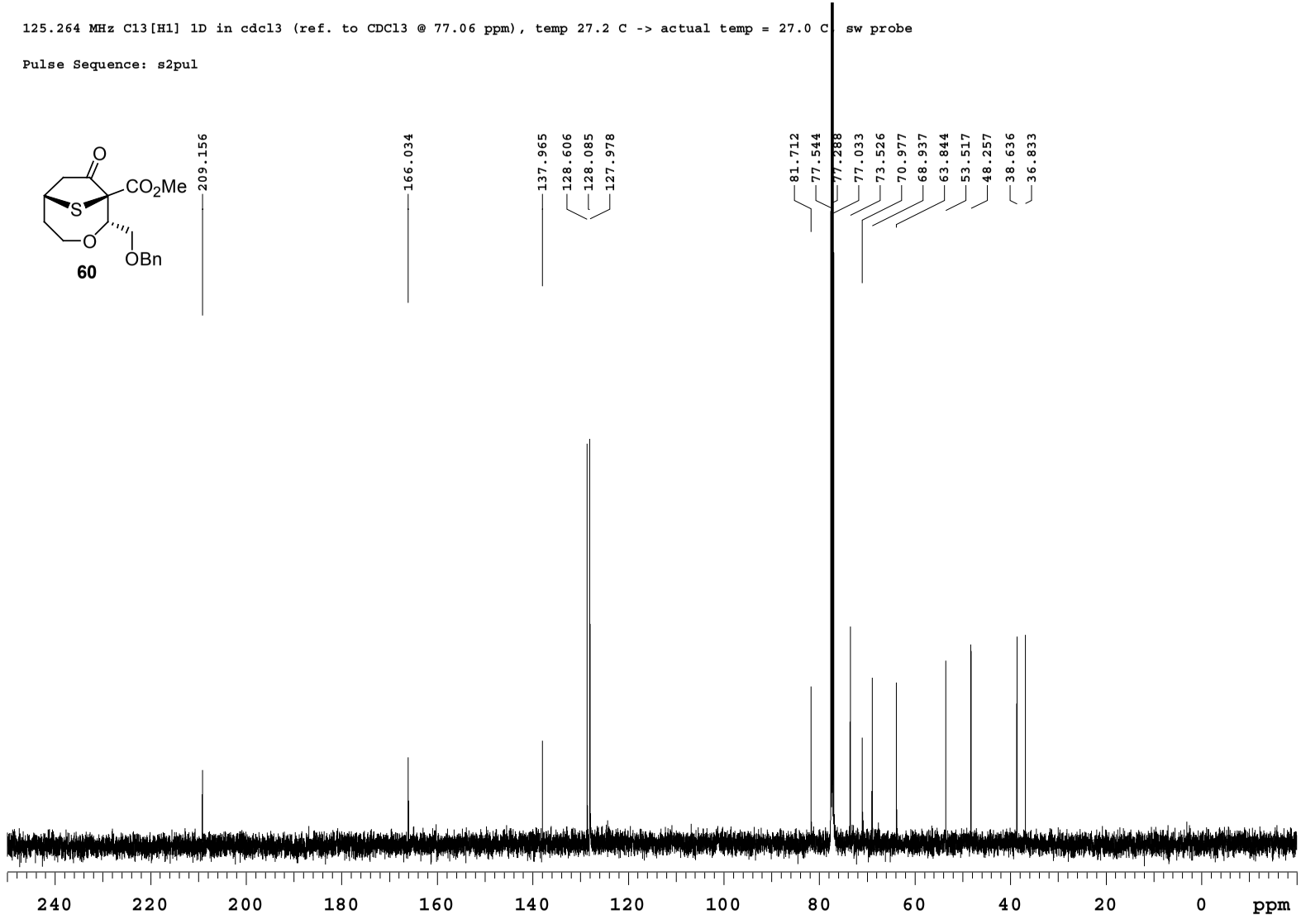

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
Pulse Sequence: s2pul
209.359
164.921
137.900
128.707
127.985
127.874
86.993
77.253
76.333
76.744
74.041
65.669
62.415
47.234
38.545
35.908
13.436
O
CO2Et
S
O
Ph
57
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

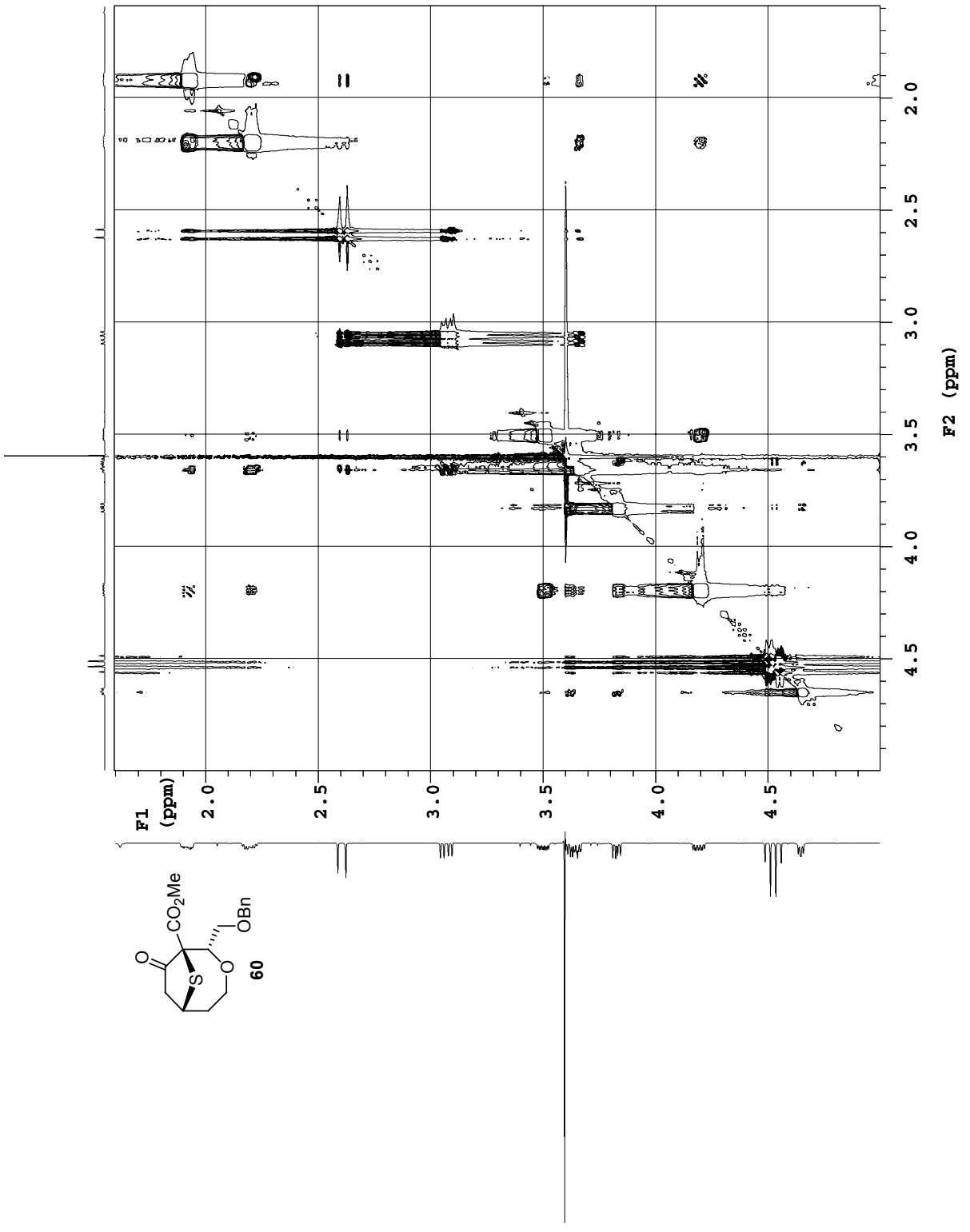
F1 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
F2 (ppm)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
CO2Et
Ph
O
S
O
57

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe

Pulse Sequence: s2pul

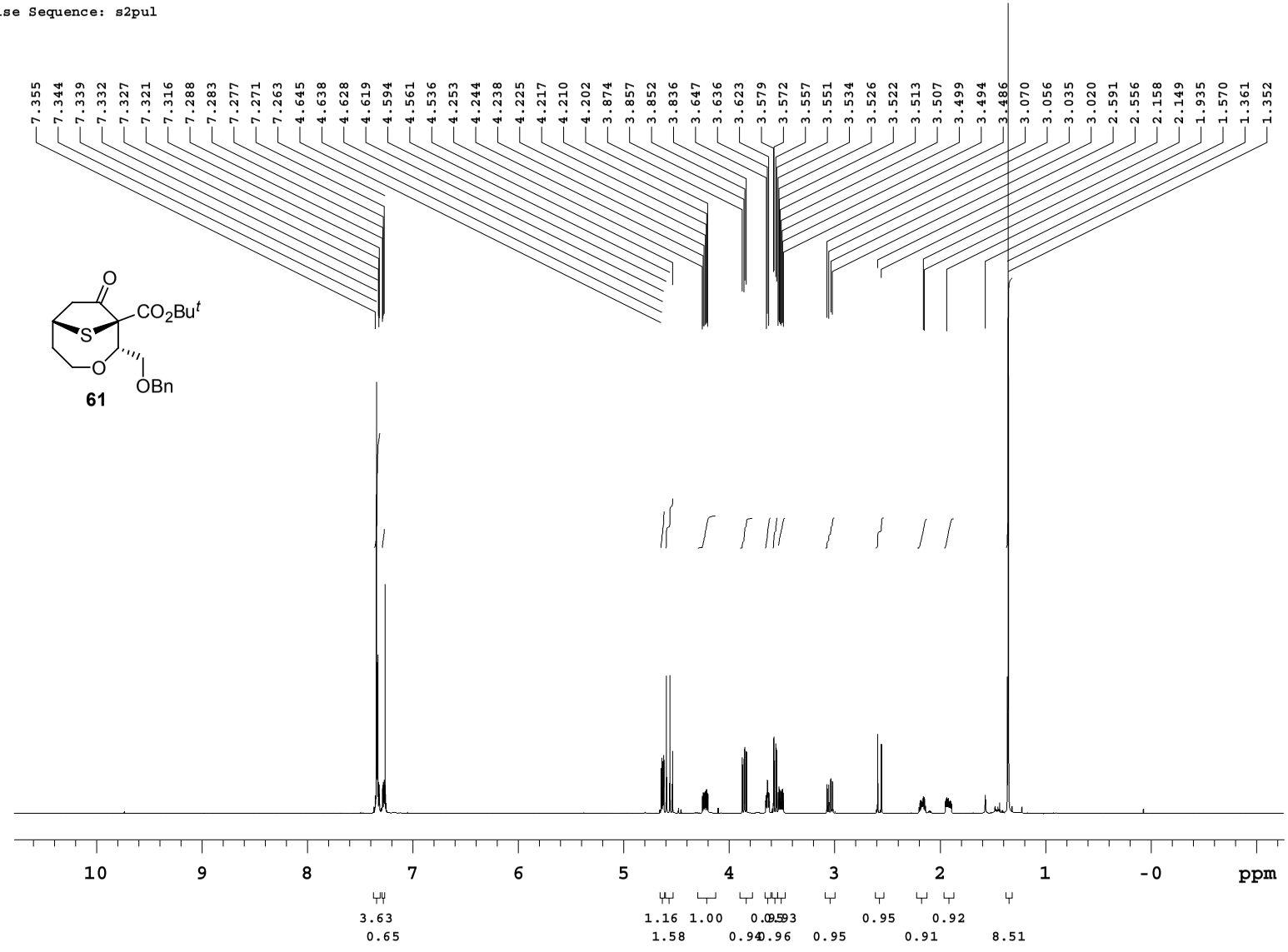


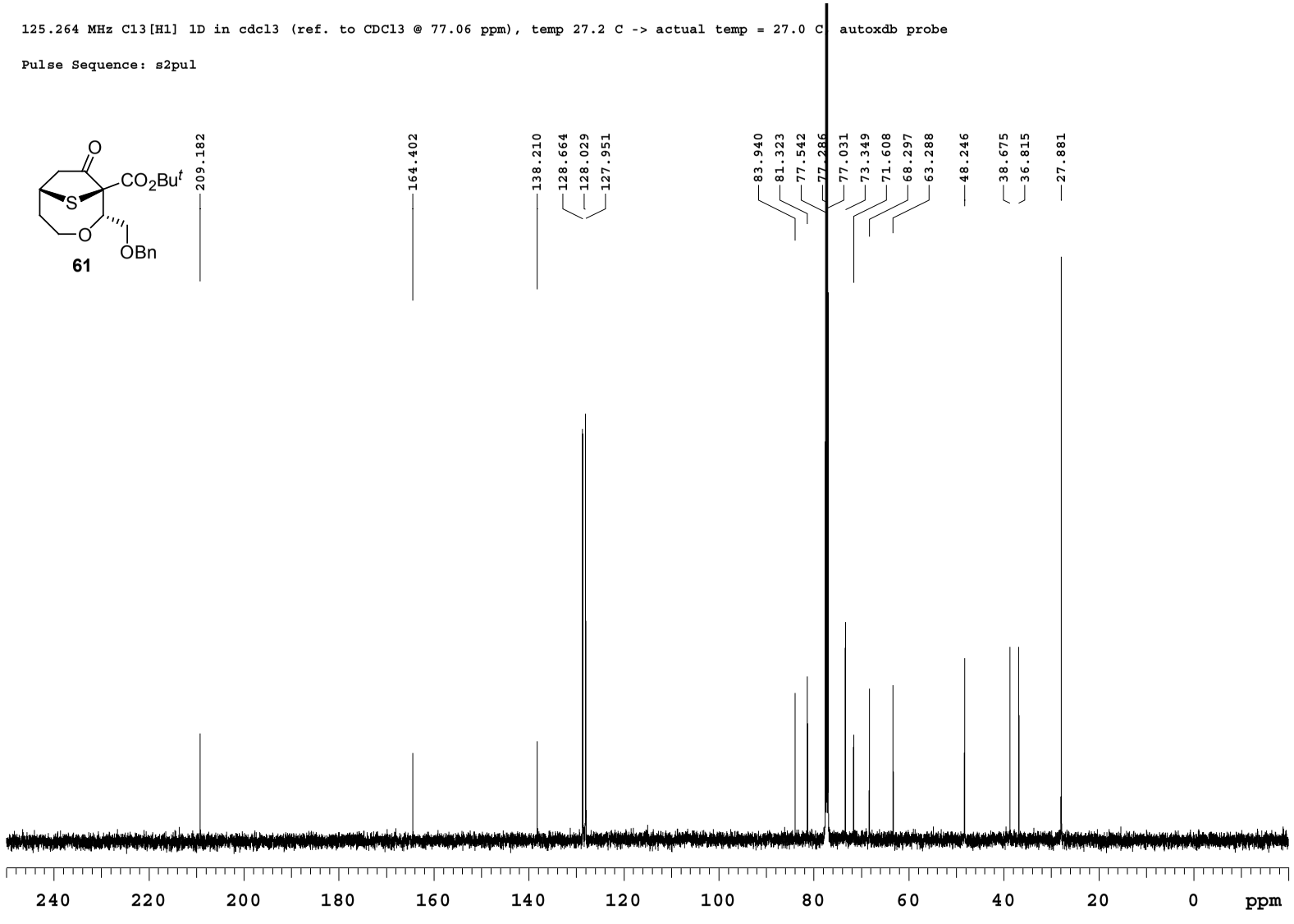

125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C sw probe
Pulse Sequence: s2pul
O
CO2Me
S
O
OBn
60
209.156
166.034
137.965
128.606
128.085
127.978
81.712
77.544
77.288
77.033
73.526
70.977
68.937
63.844
53.517
48.257
38.636
36.833
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


F1 (ppm)
2.0
2.5
3.0
3.5
4.0
4.5
F2 (ppm)
CO2Me
OBn
O
S
O
60

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul

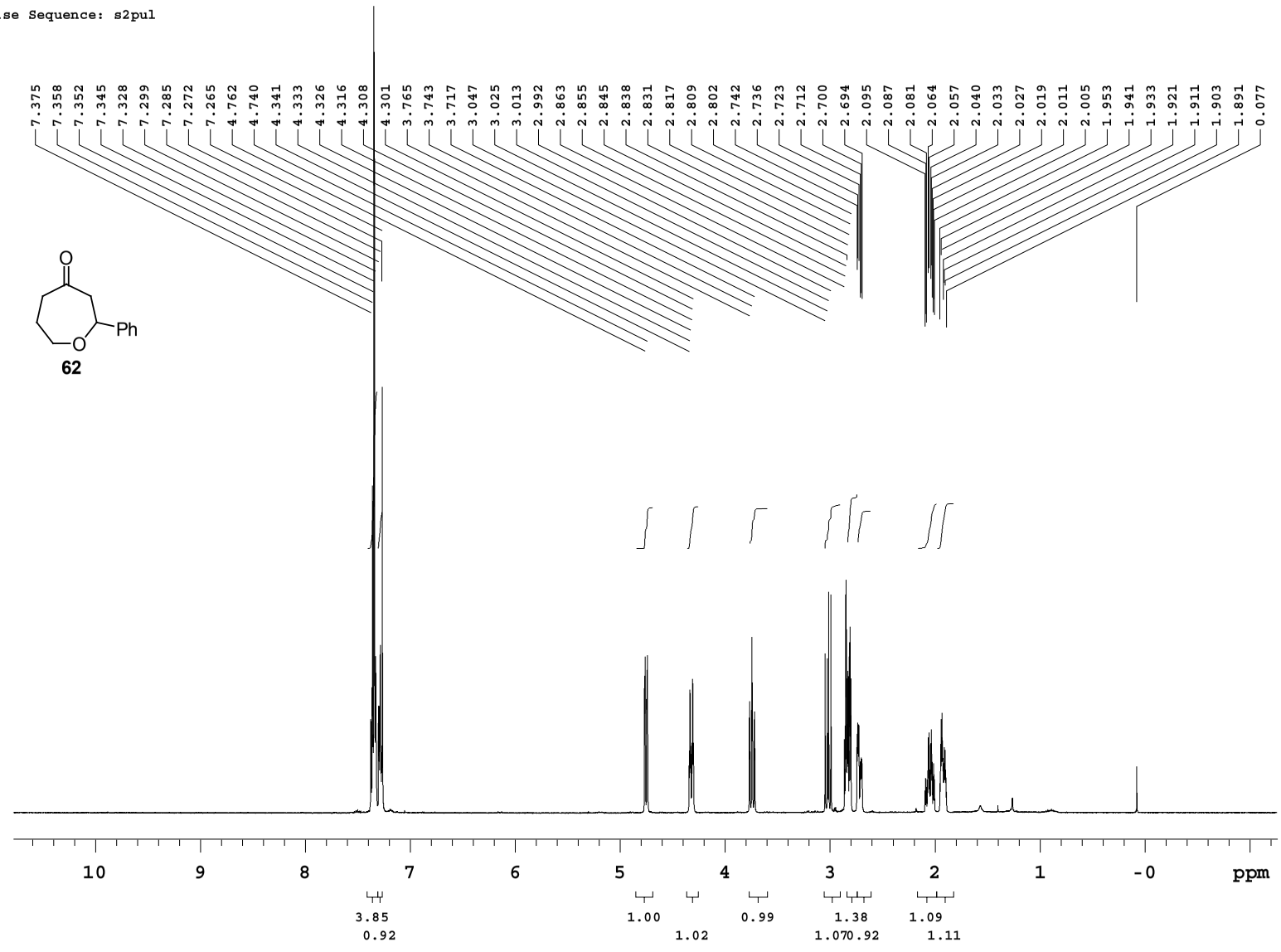


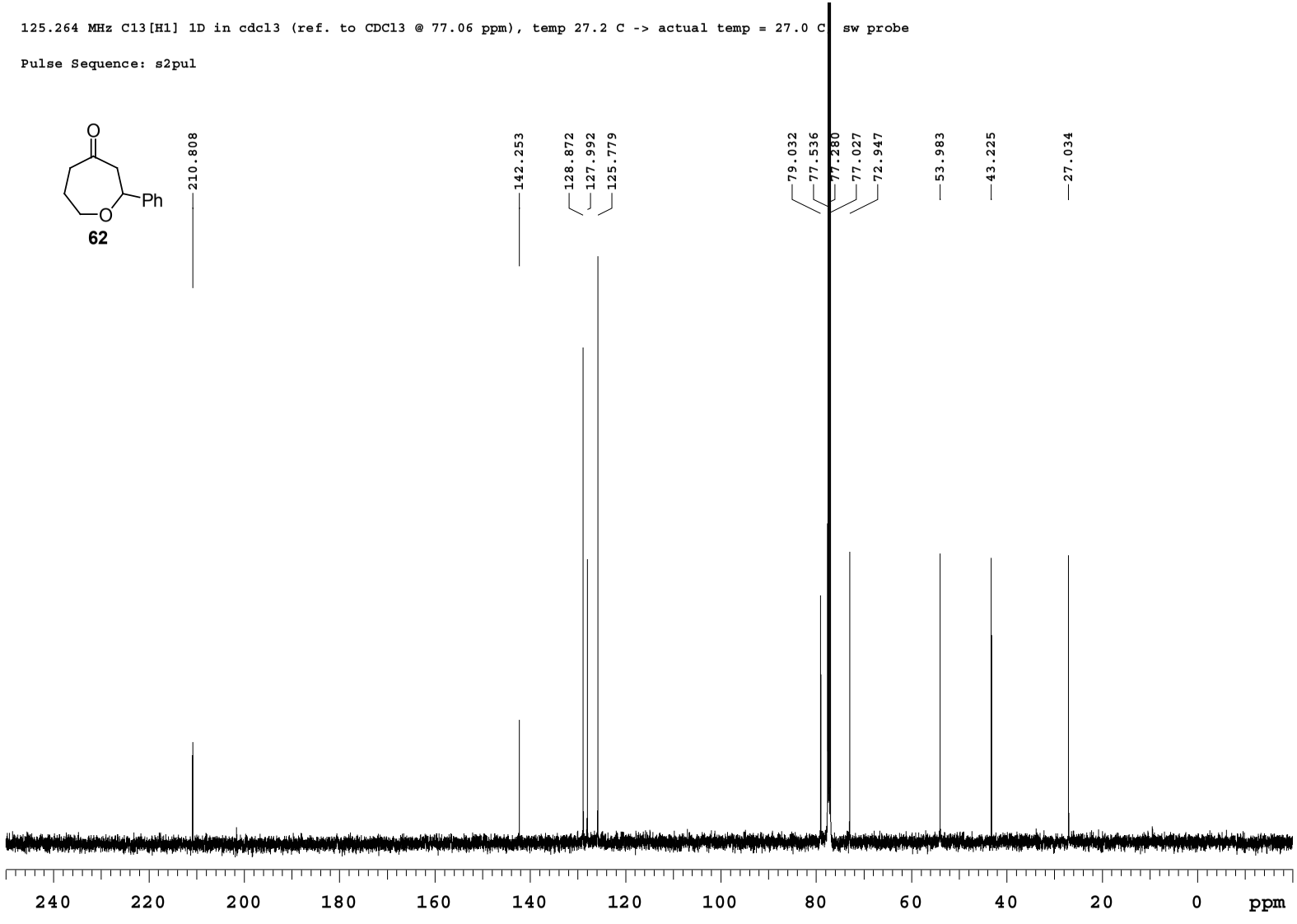

125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C autoxdb probe
Pulse Sequence: s2pul
O
CO2But
S
O
OBn
61
209.182
164.402
138.210
128.664
128.029
127.951
83.940
81.323
77.542
77.286
77.031
73.349
71.608
68.297
63.288
48.246
38.675
36.815
27.881
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

F1 (ppm)
2.0
2.5
3.0
3.5
4.0
4.5
F2 (ppm)
4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8
CO2But
OBn
O
S
O
61

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe

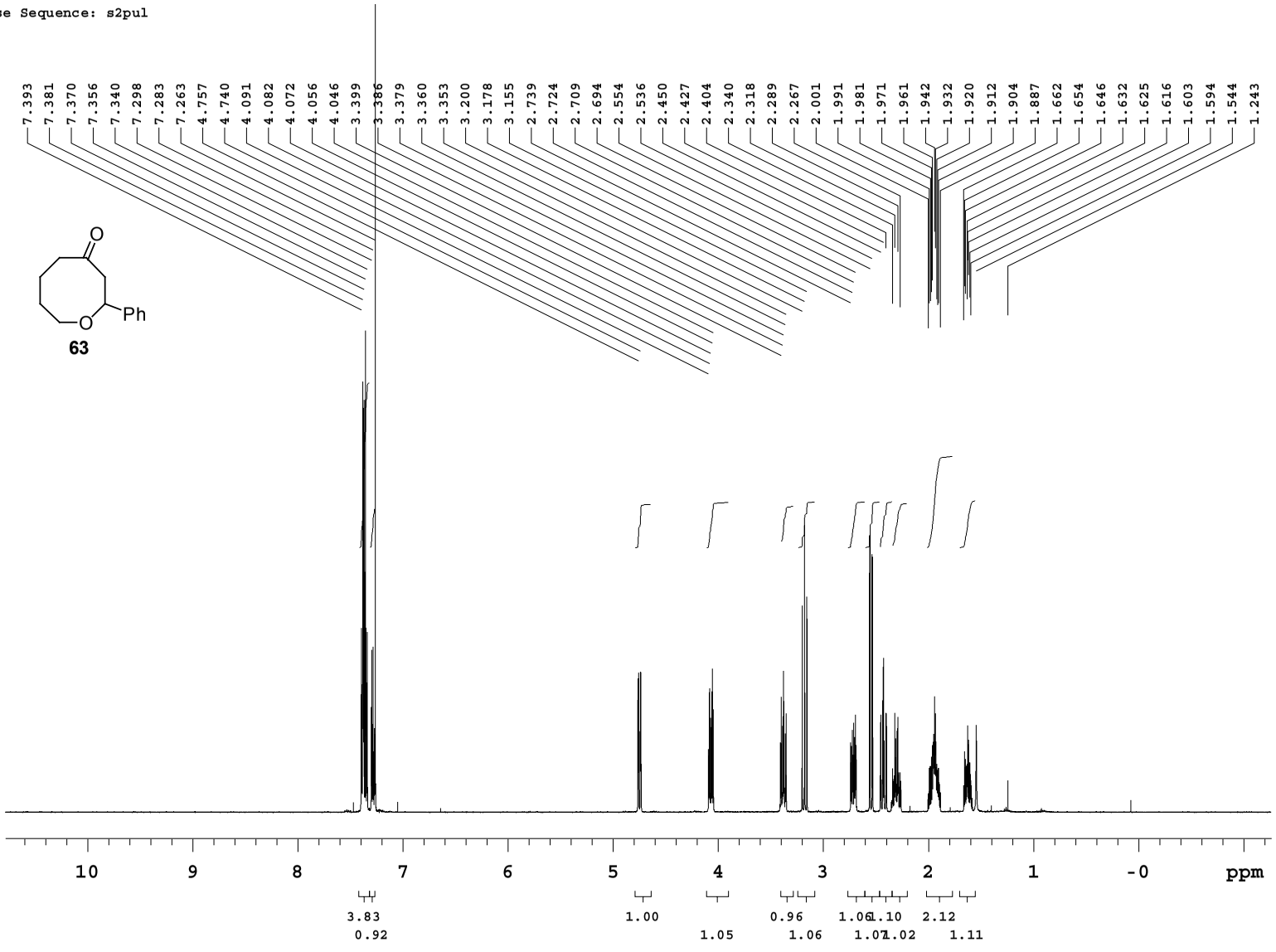
Pulse Sequence: s2pul

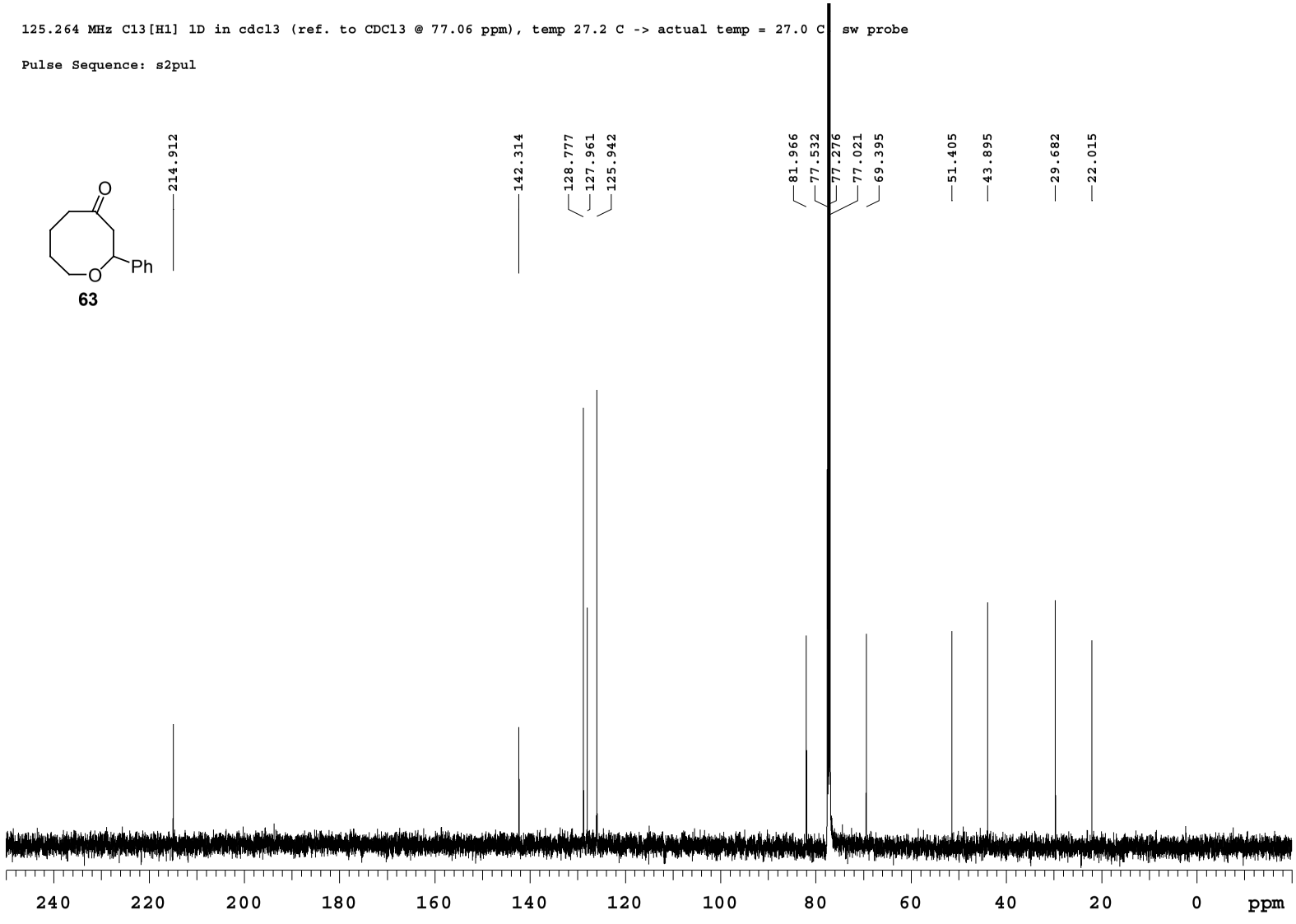



125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C sw probe
Pulse Sequence: s2pul
O
Ph
O
62
210.808
142.253
128.872
127.992
125.779
79.032
77.536
77.280
77.027
72.947
53.983
43.225
27.034
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul



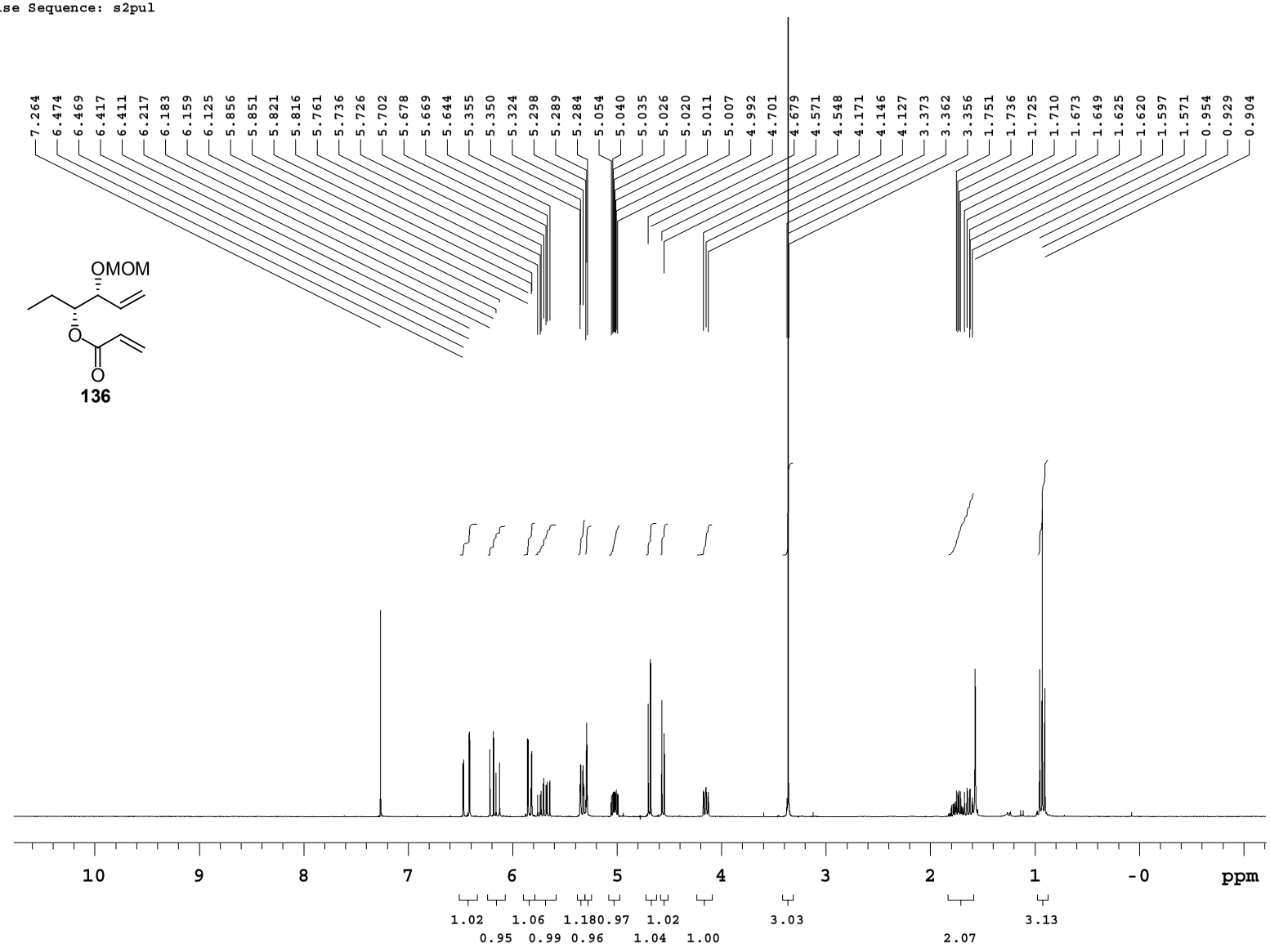

125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C sw probe
Pulse Sequence: s2pul
214.912
142.314
128.777
127.961
125.942
81.966
77.532
77.276
77.021
69.395
51.405
43.895
29.682
22.015
O
Ph
O
63
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

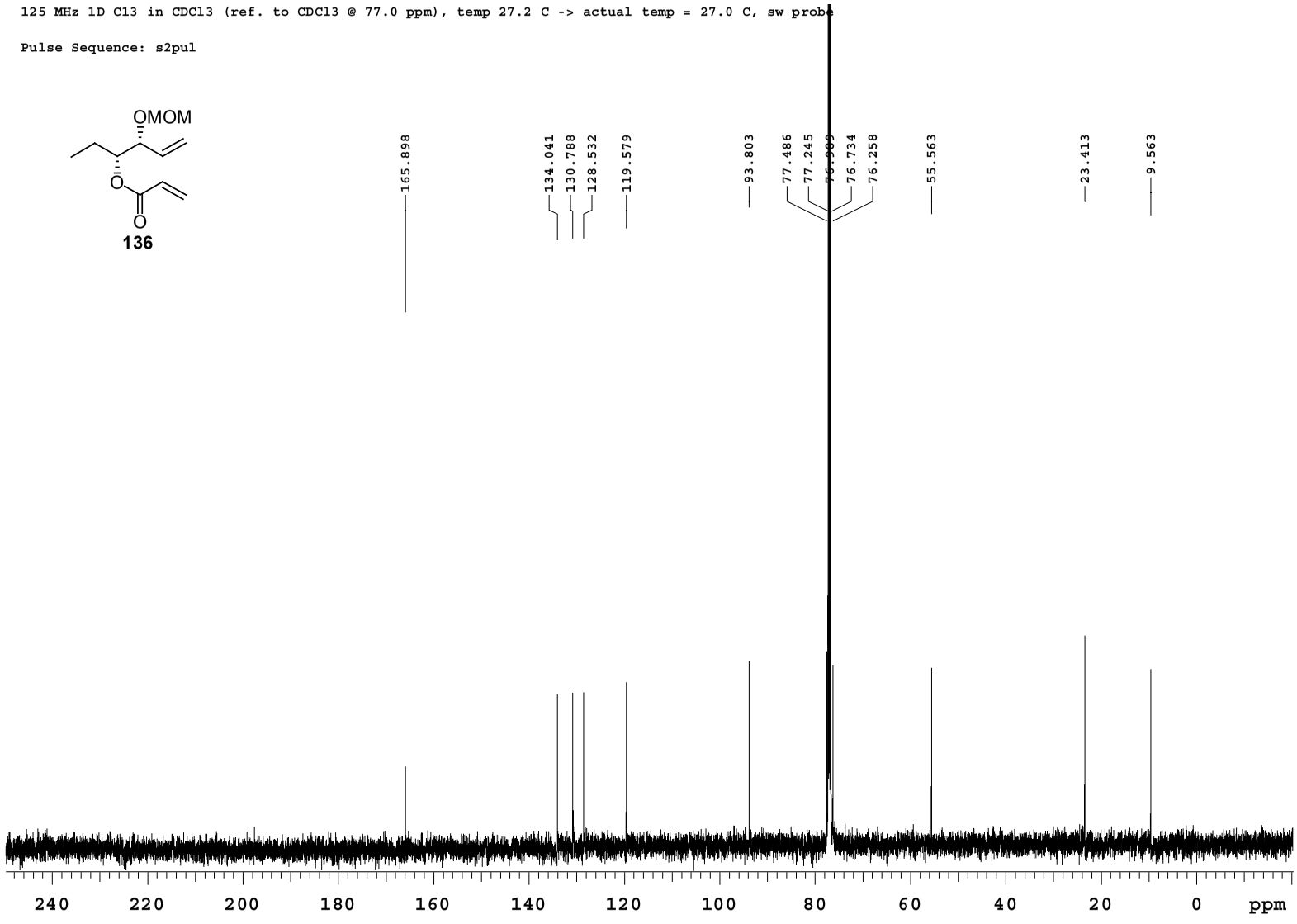
Appedix II: Selected NMR Spectra

(Chapter 3)

300 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.5 C -> actual temp = 27.0 C, id probe

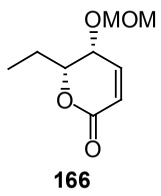
Pulse Sequence: s2pul



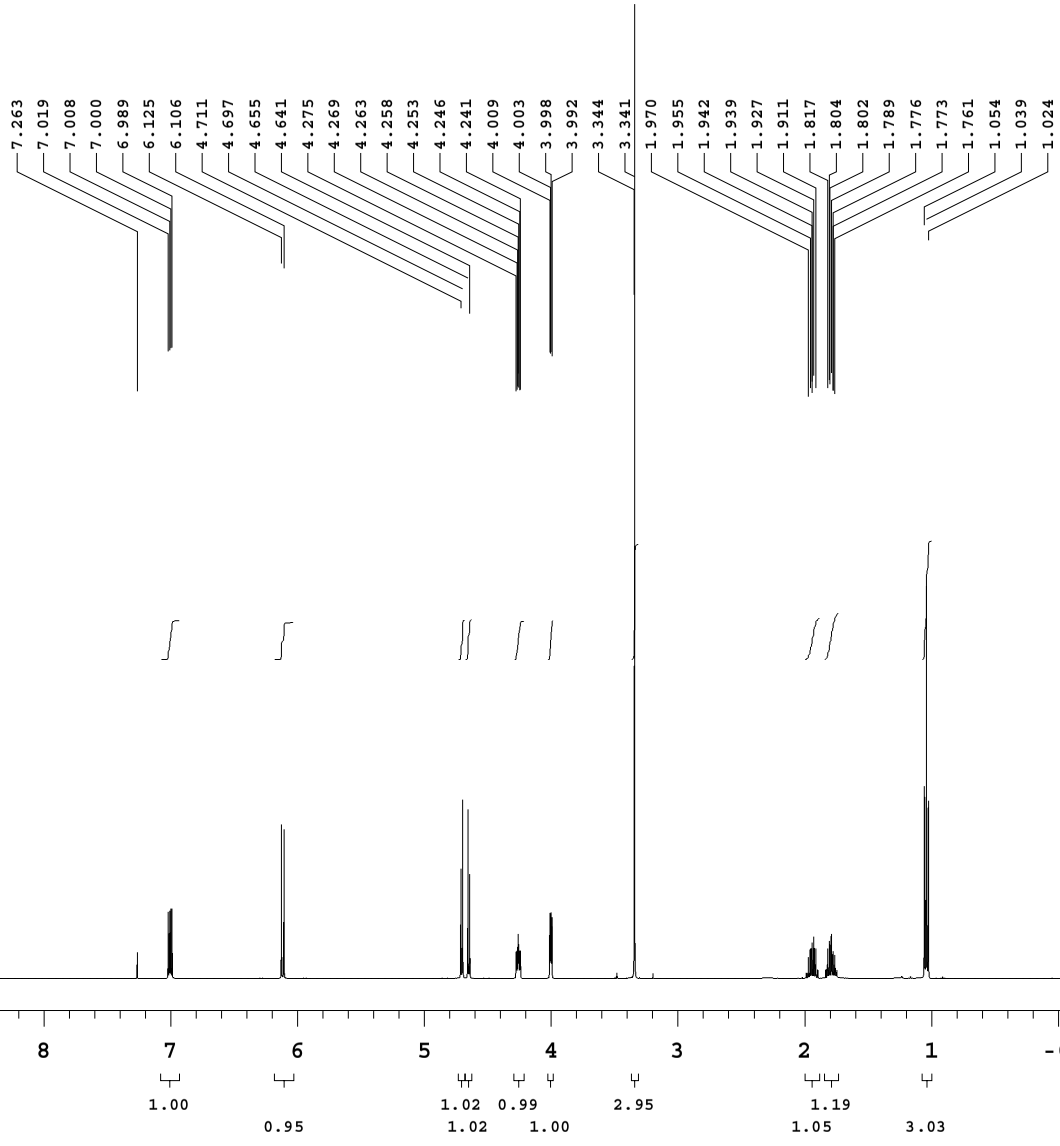

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
Pulse Sequence: s2pul
OMOM
O
O
136
165.898
134.041
130.788
128.532
119.579
93.803
77.486
77.245
76.734
76.258
55.563
23.413
9.563
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe

Pulse Sequence: s2pul

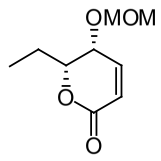


166



125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe

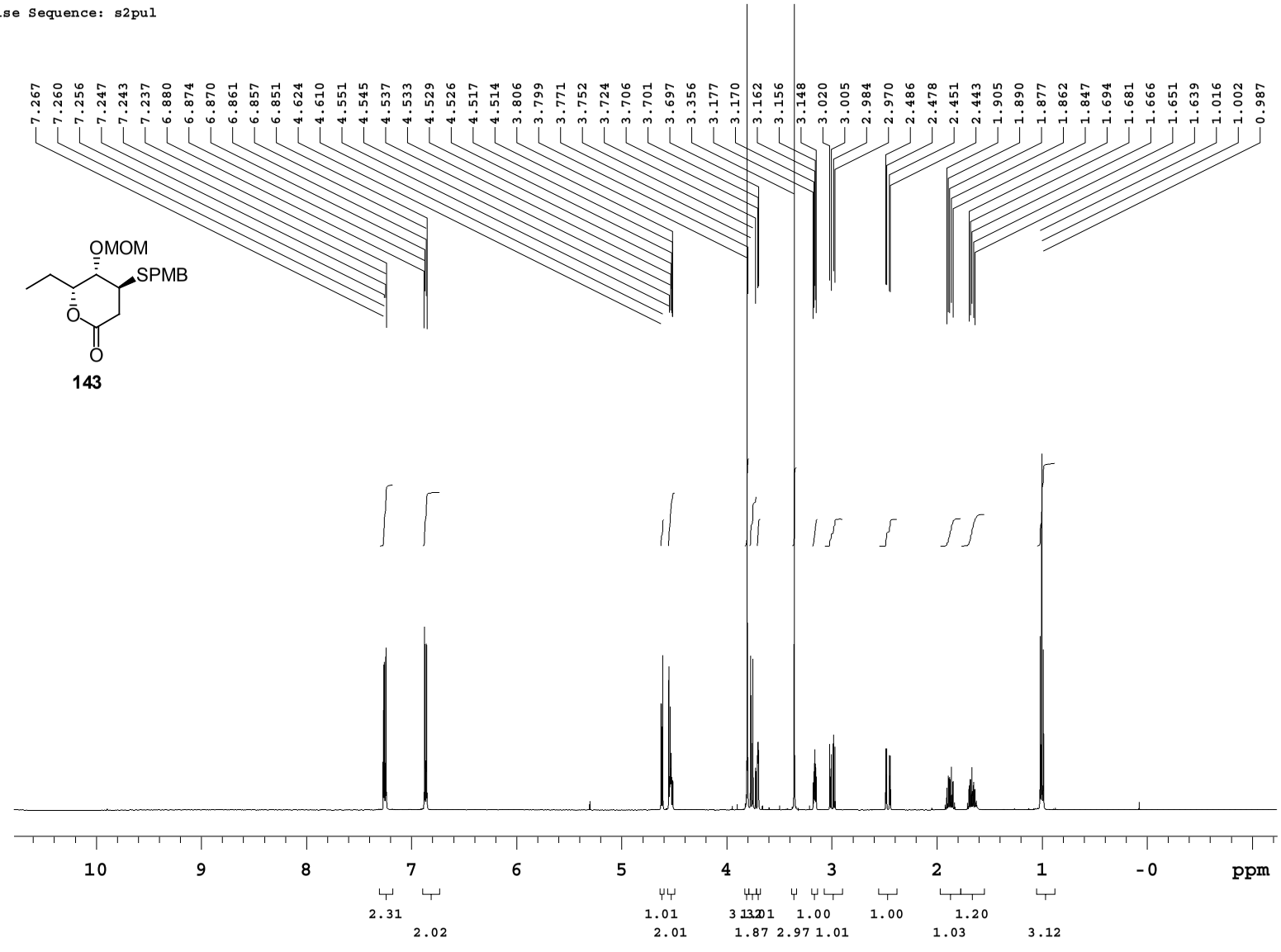
Pulse Sequence: s2pul



166

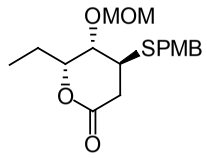
499.821 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul



125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

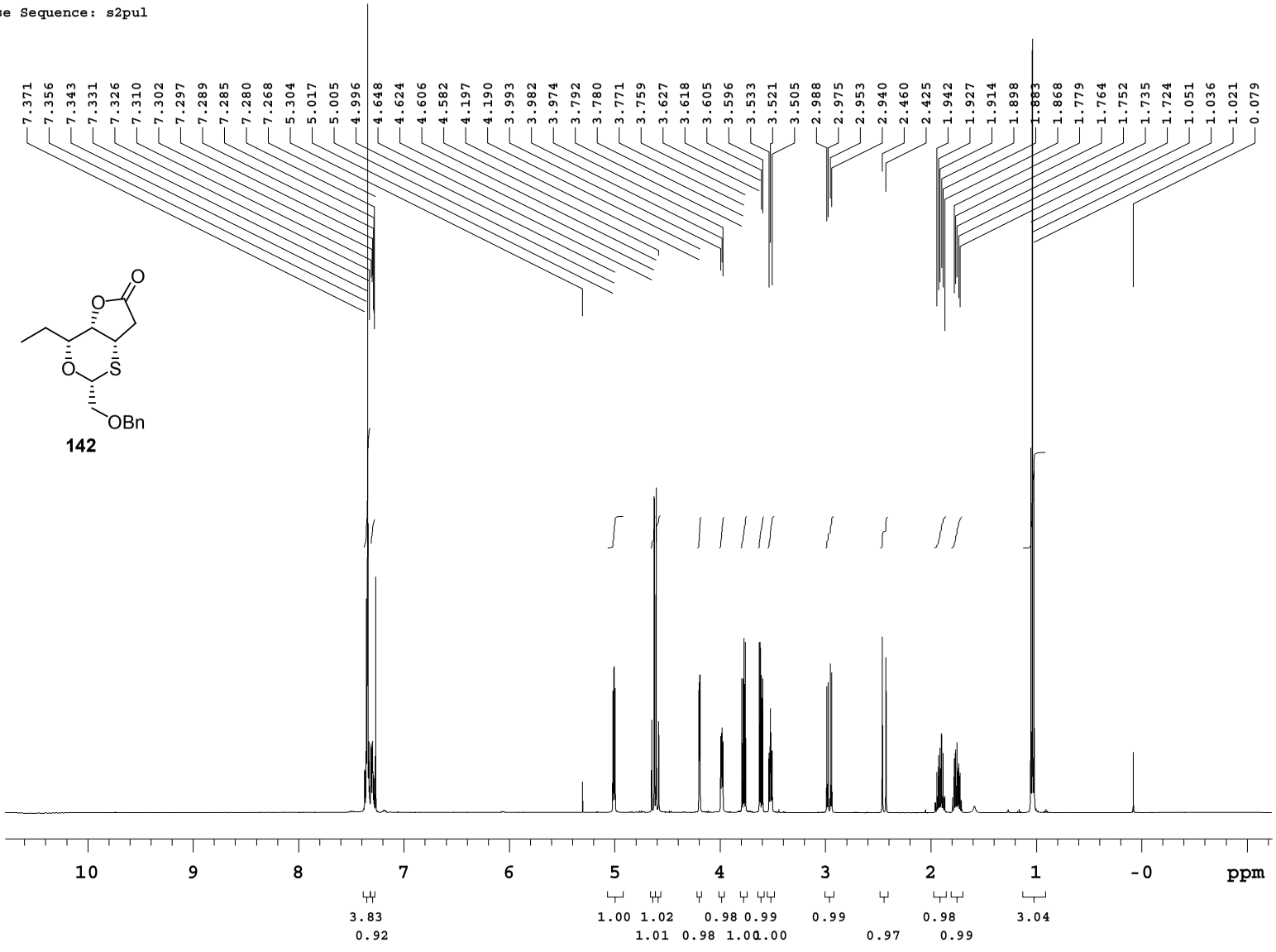
Pulse Sequence: s2pul

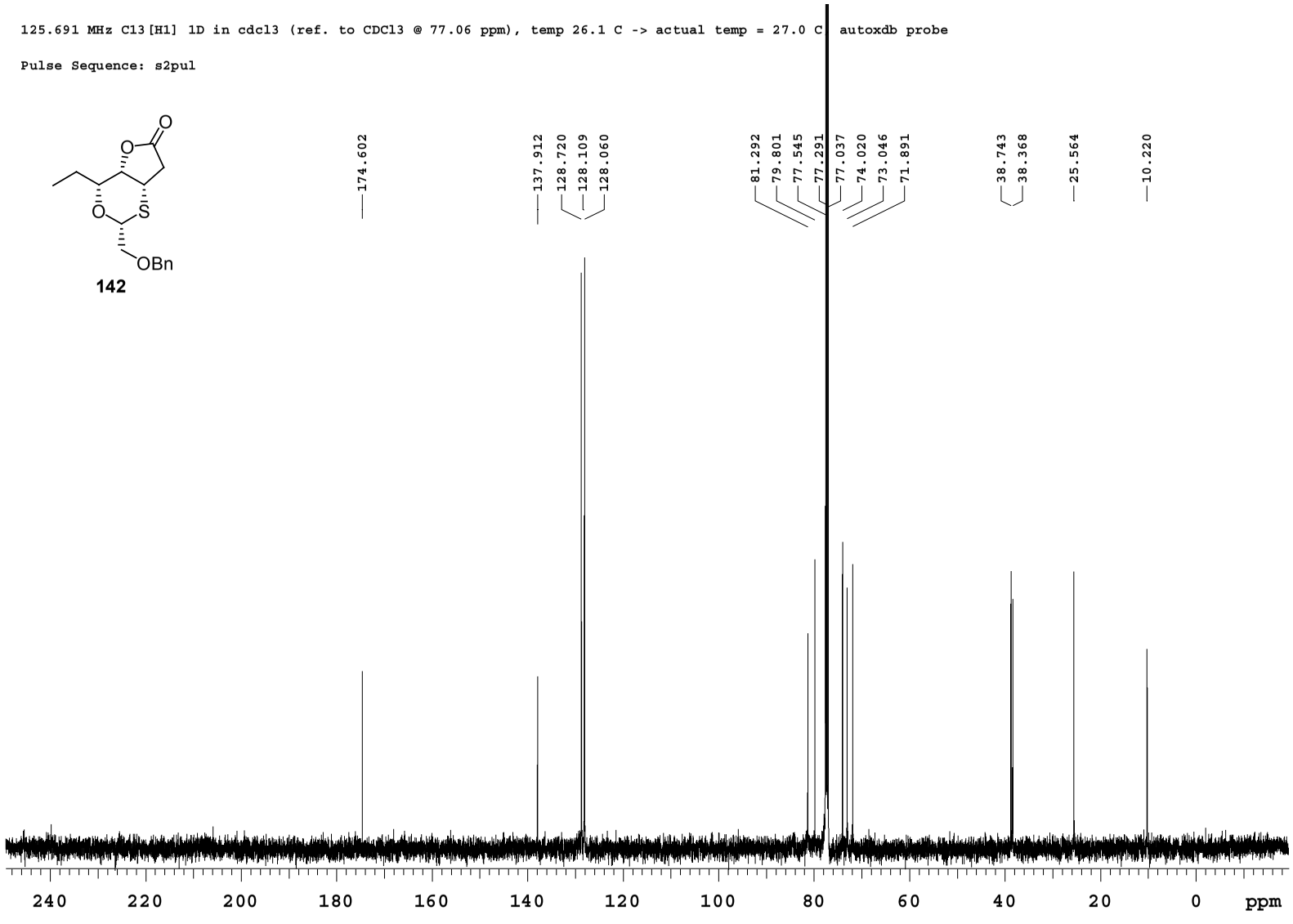


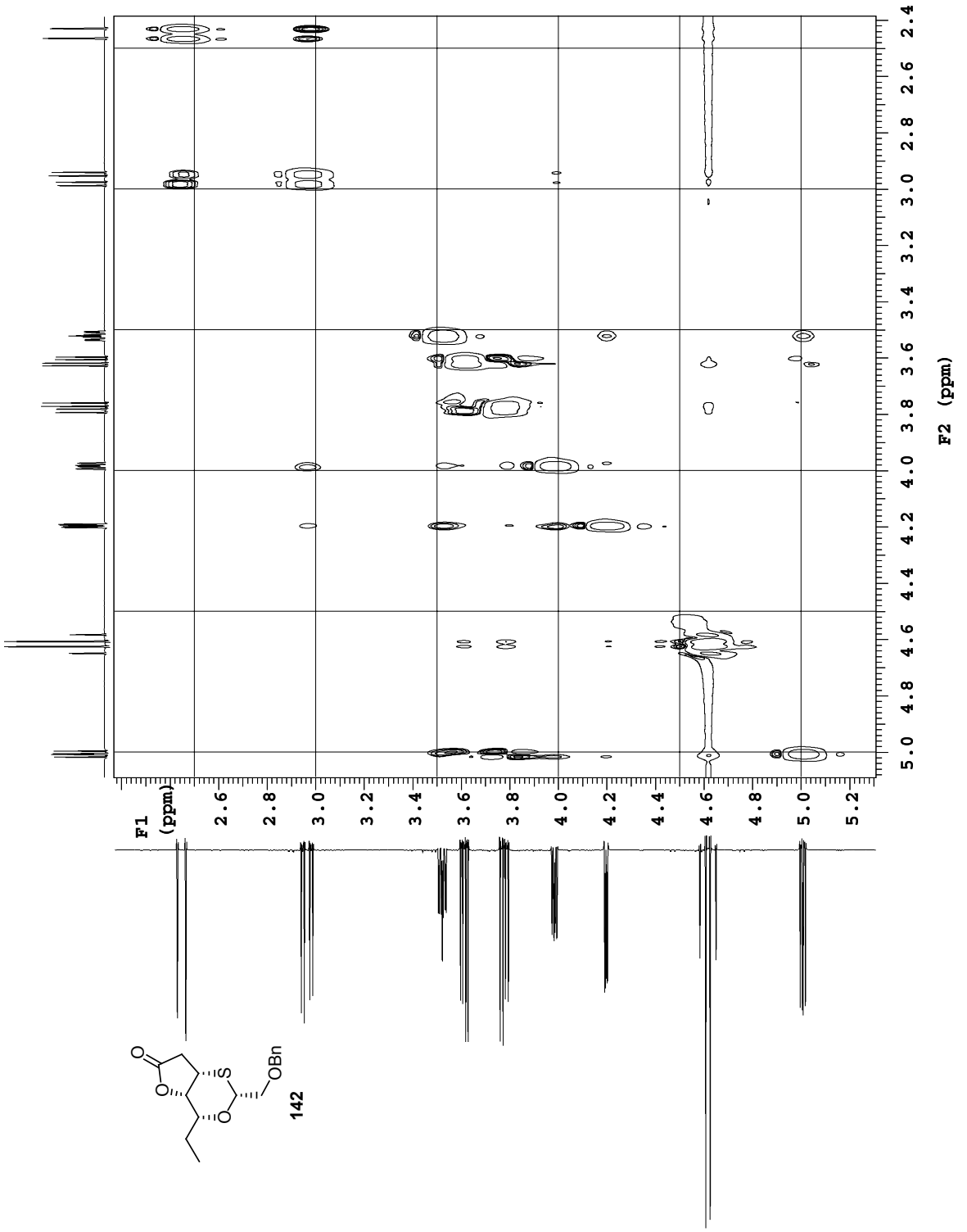
143

499.821 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul

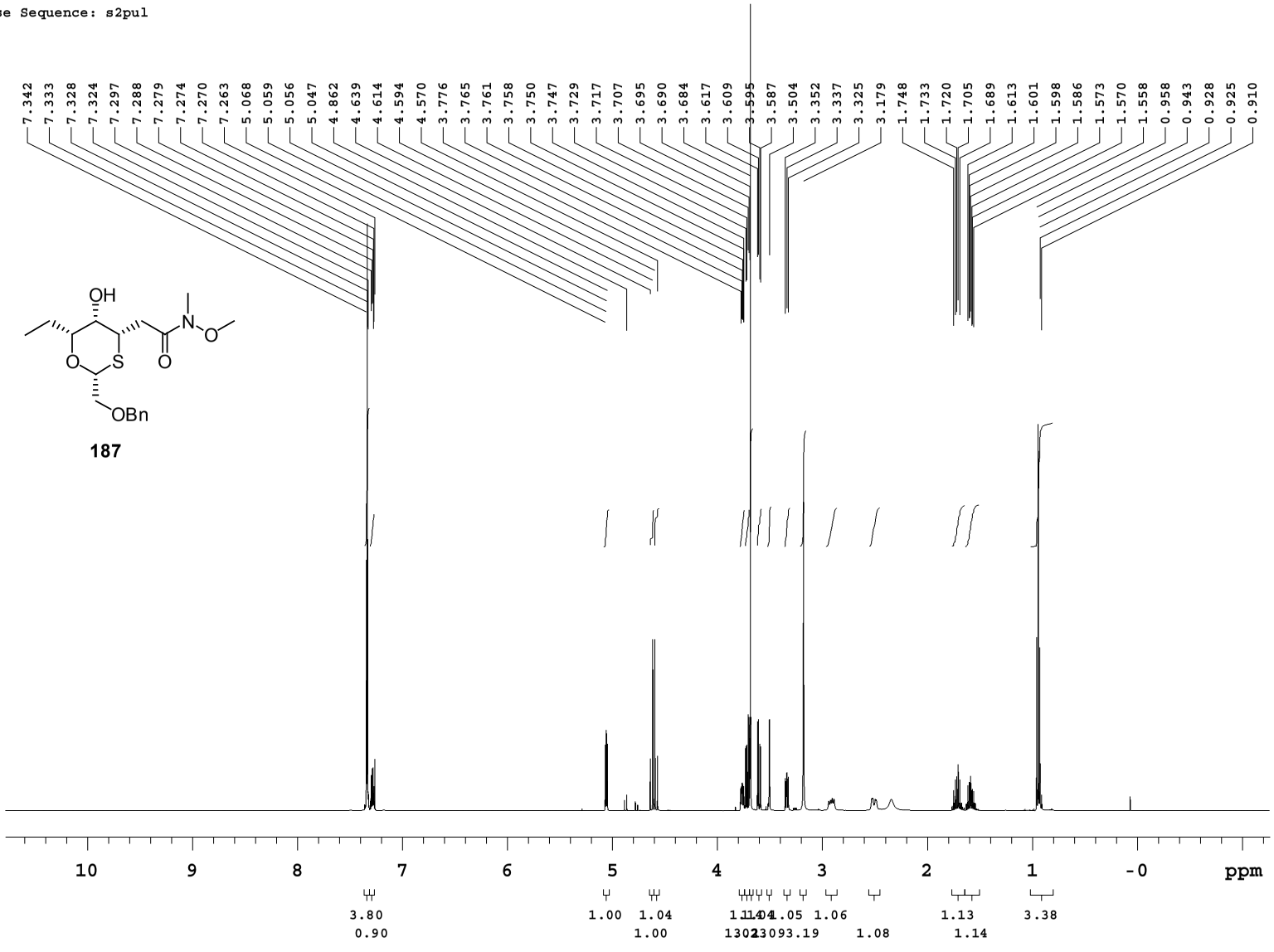


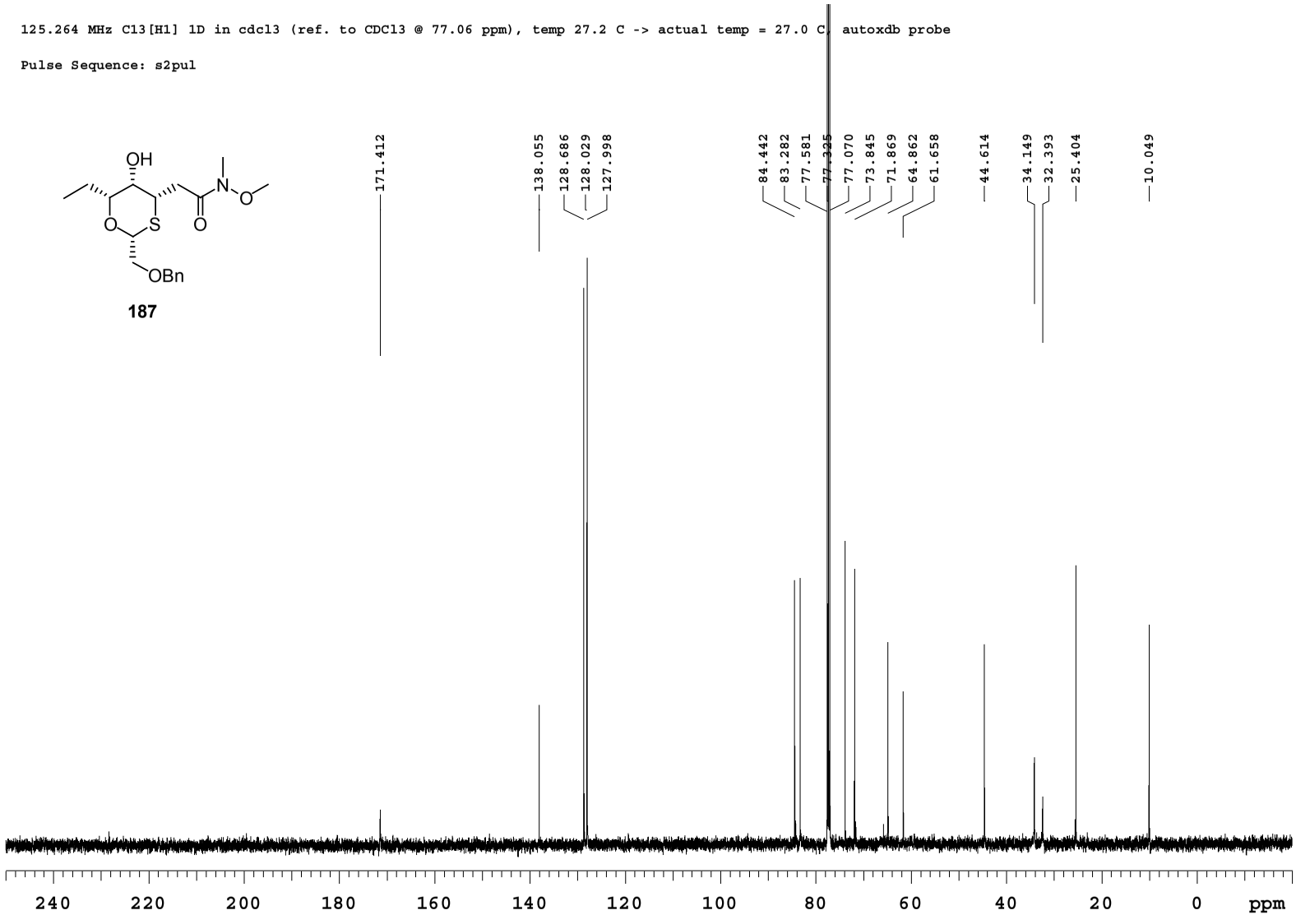

125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.1 C -> actual temp = 27.0 C autoxdb probe
Pulse Sequence: s2pul
O
O
O
S
OBn
142
174.602
137.912
128.720
128.109
128.060
81.292
79.801
77.545
77.291
77.037
74.020
73.046
71.891
38.743
38.368
25.564
10.220
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


F1 (ppm)
F2 (ppm)
OBn
142

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

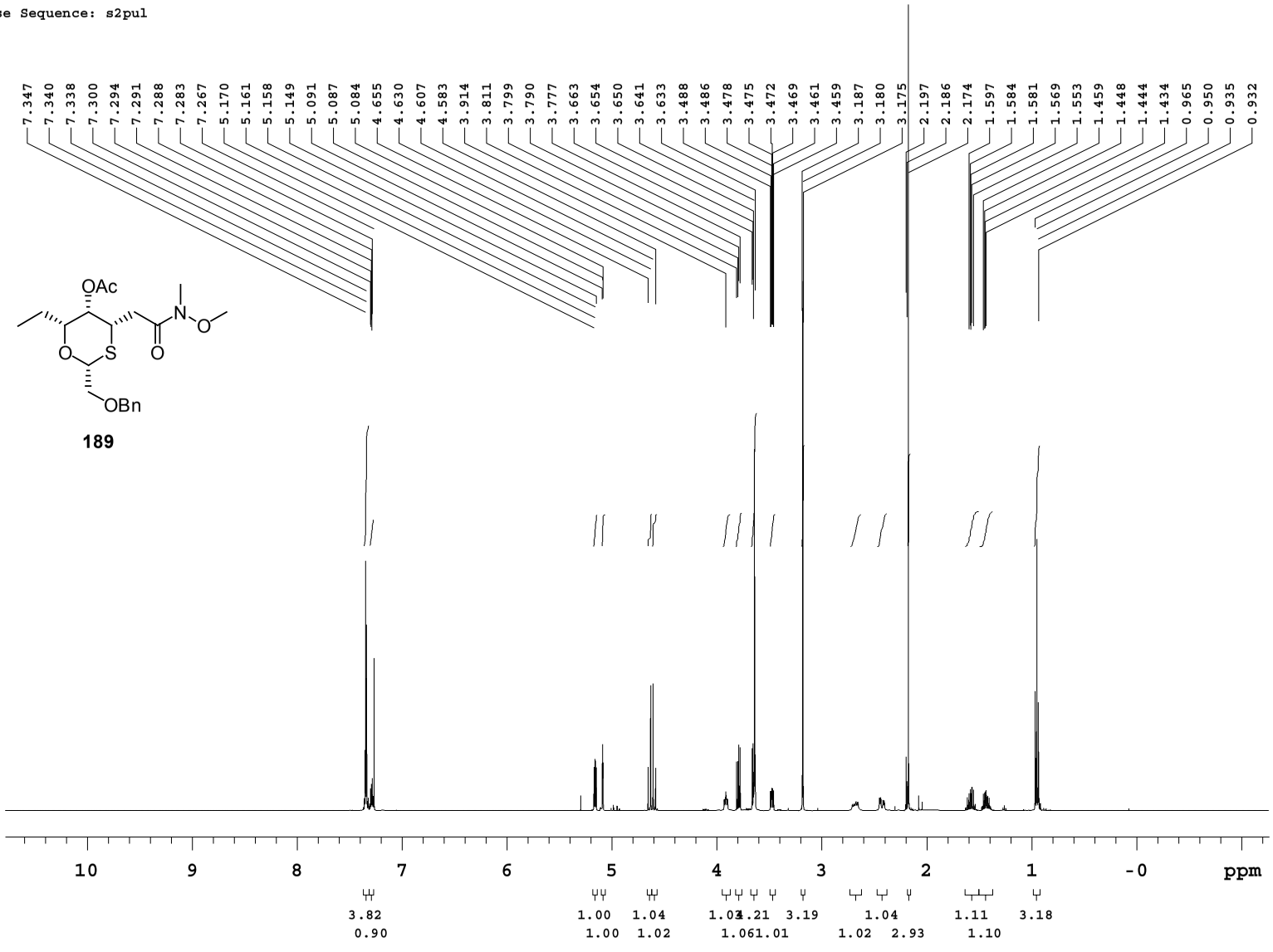
Pulse Sequence: s2pul

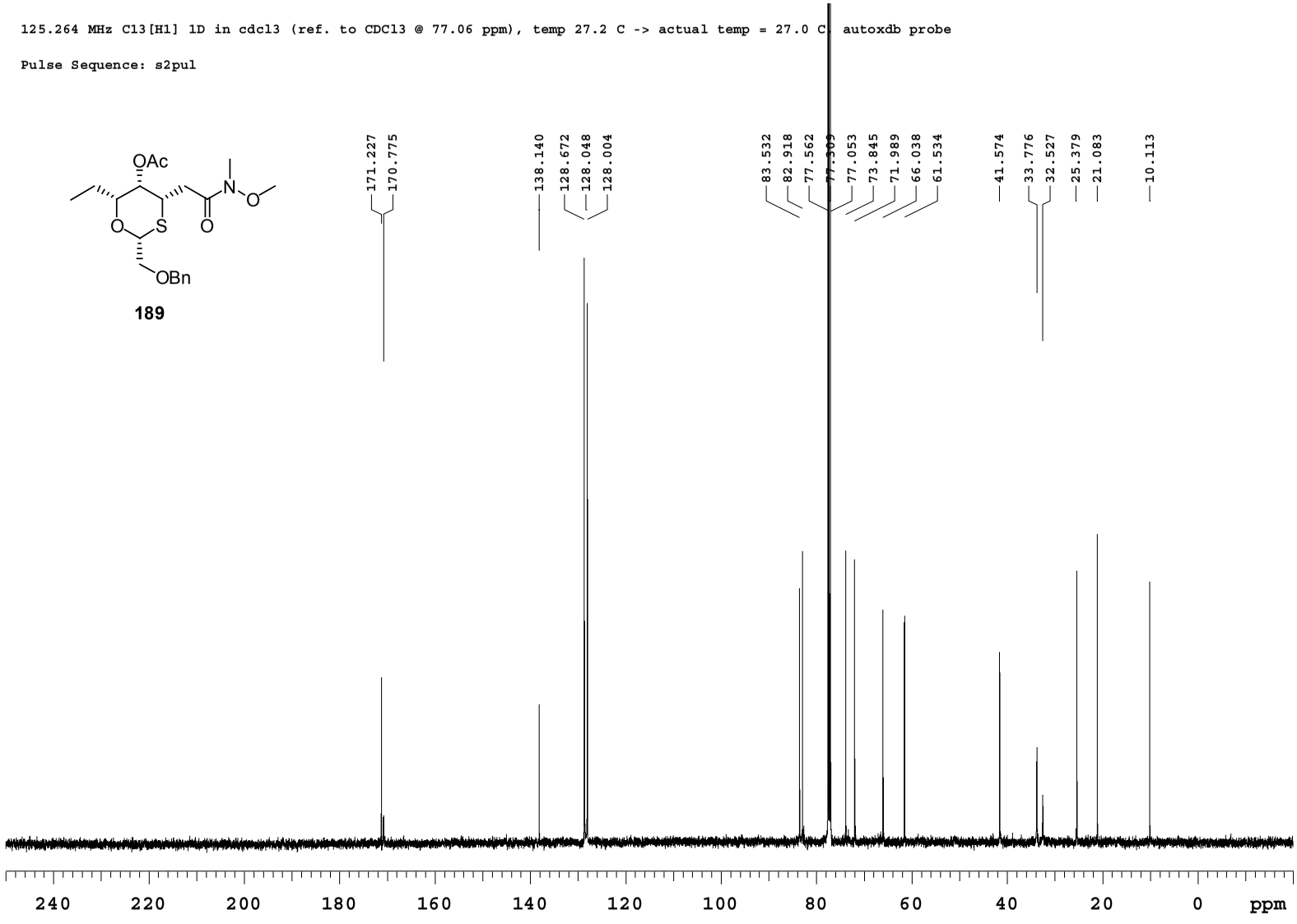



125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
OH
N
O
O
S
O
OBn
187
171.412
138.055
128.686
128.029
127.998
84.442
83.282
77.581
77.325
77.070
73.845
71.869
64.862
61.658
44.614
34.149
32.393
25.404
10.049
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

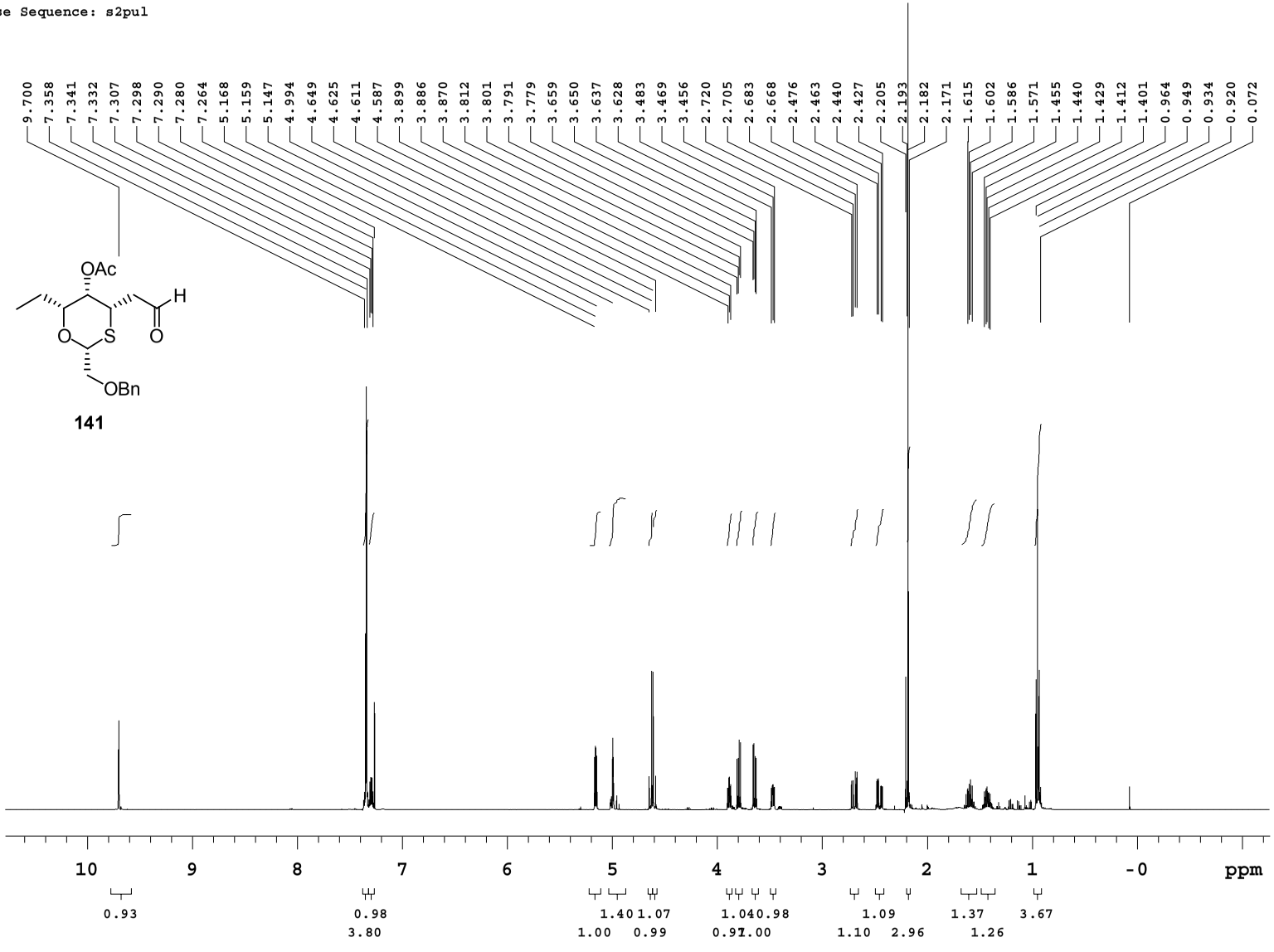
Pulse Sequence: s2pul

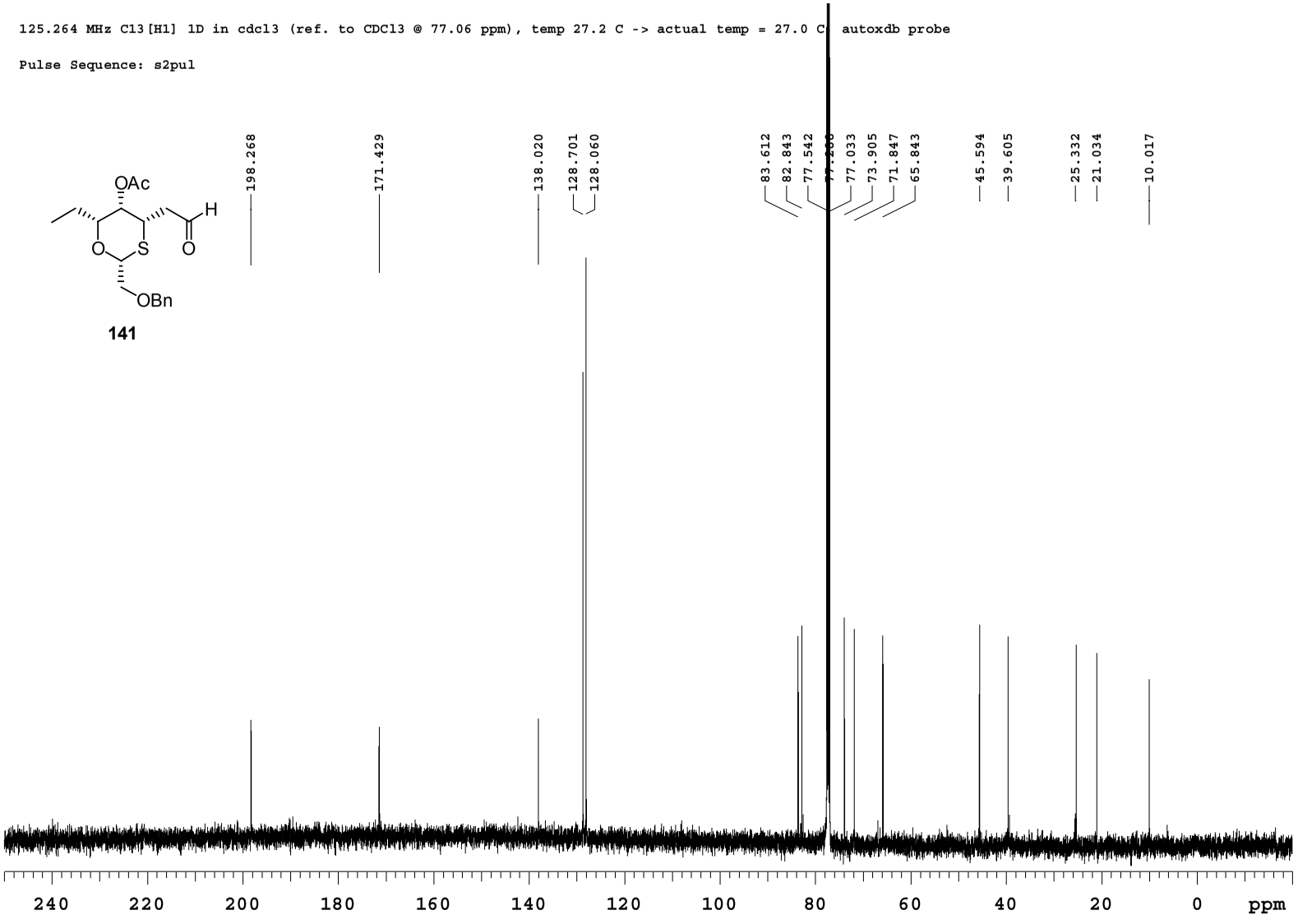



125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C autoxdb probe
Pulse Sequence: s2pul
OAc
N
O
O
S
O
OBn
189
171.227
170.775
138.140
128.672
128.048
128.004
83.532
82.918
77.562
77.309
77.053
73.845
71.989
66.038
61.534
41.574
33.776
32.527
25.379
21.083
10.113
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

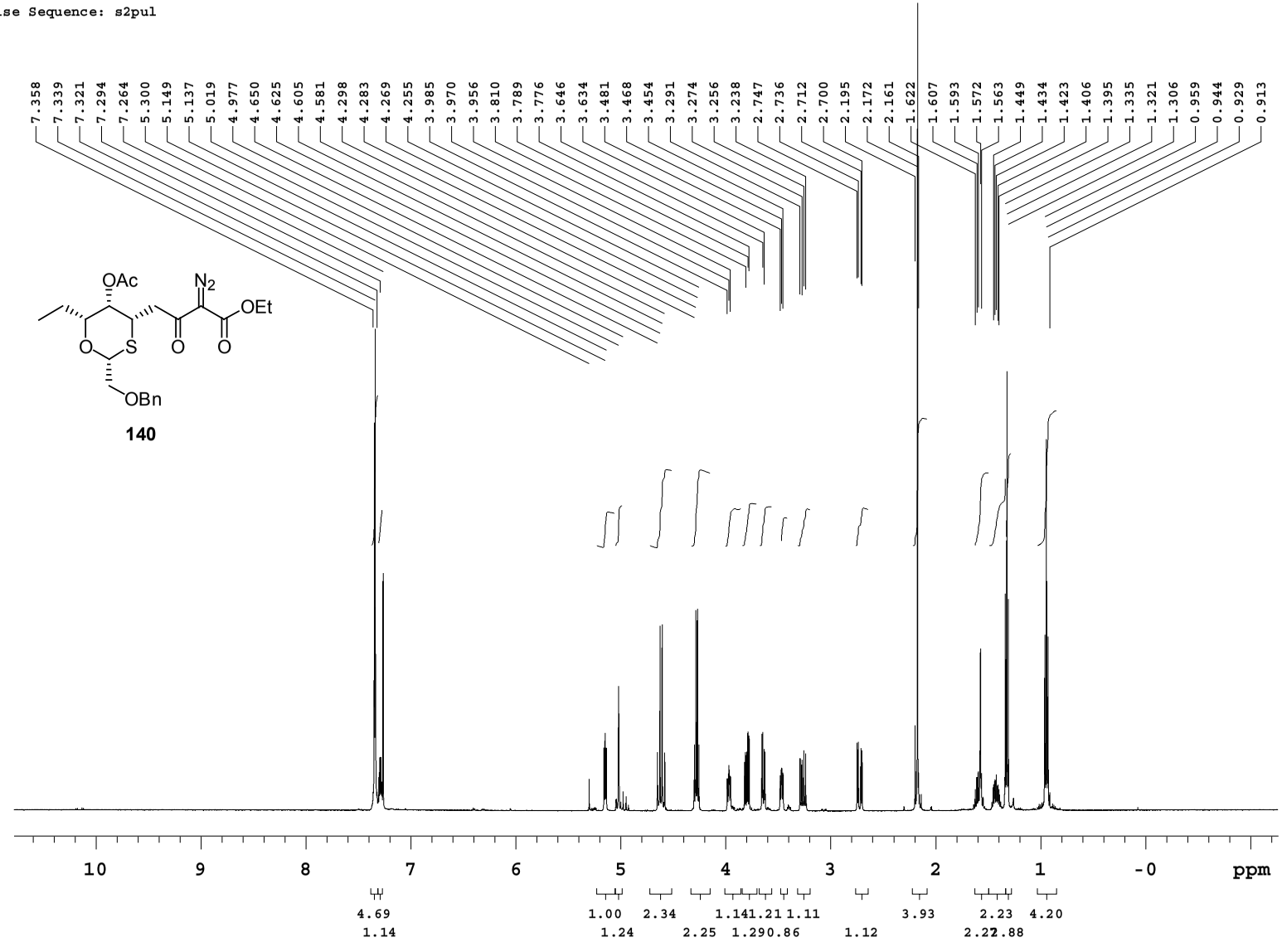
Pulse Sequence: s2pul

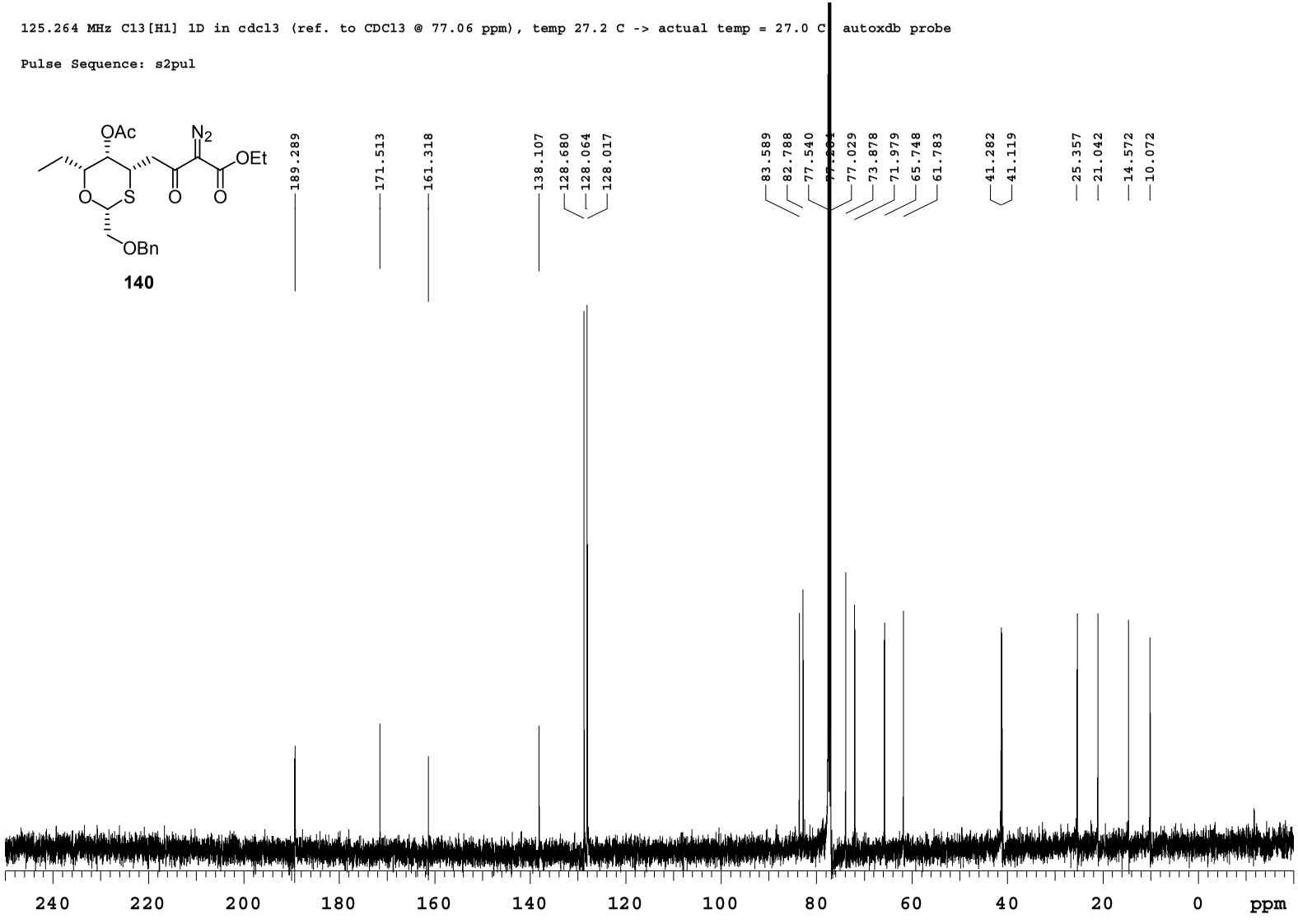



125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C autoxdb probe
Pulse Sequence: s2pul
198.268
171.429
138.020
128.701
128.060
83.612
82.843
77.542
77.033
73.905
71.847
65.843
45.594
39.605
25.332
21.034
10.017
OAc
H
O
S
O
OBn
141
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

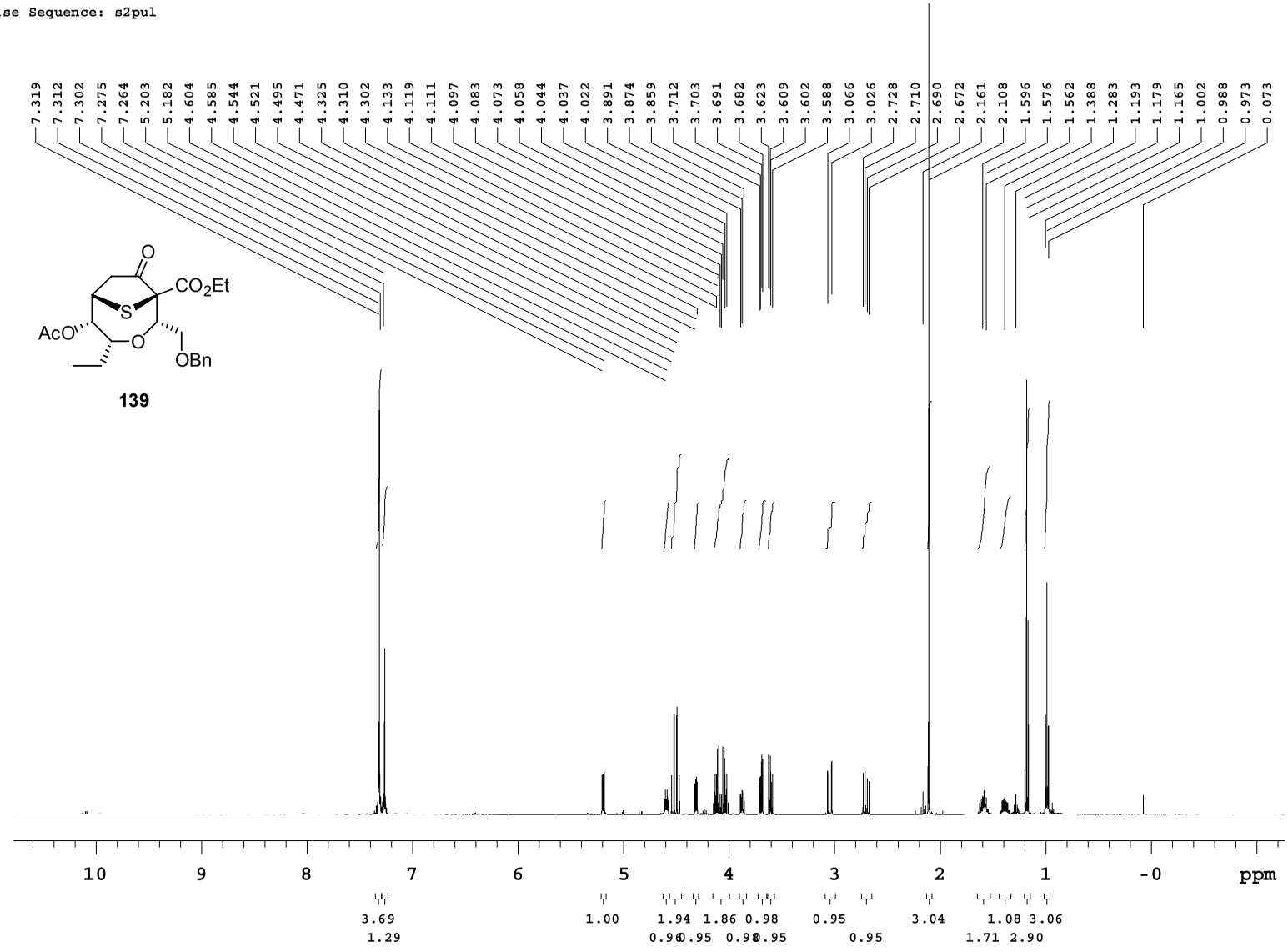
Pulse Sequence: s2pul

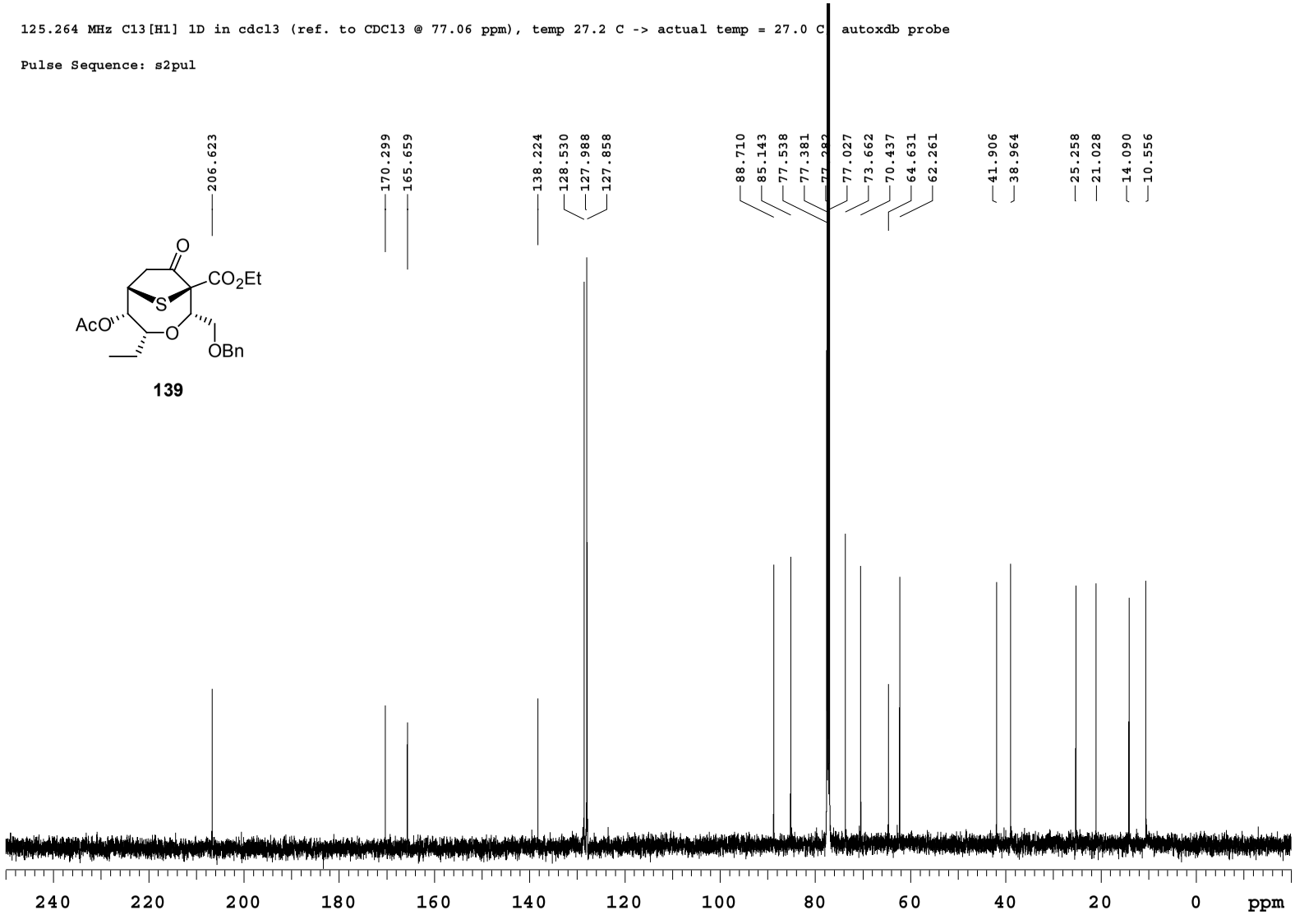


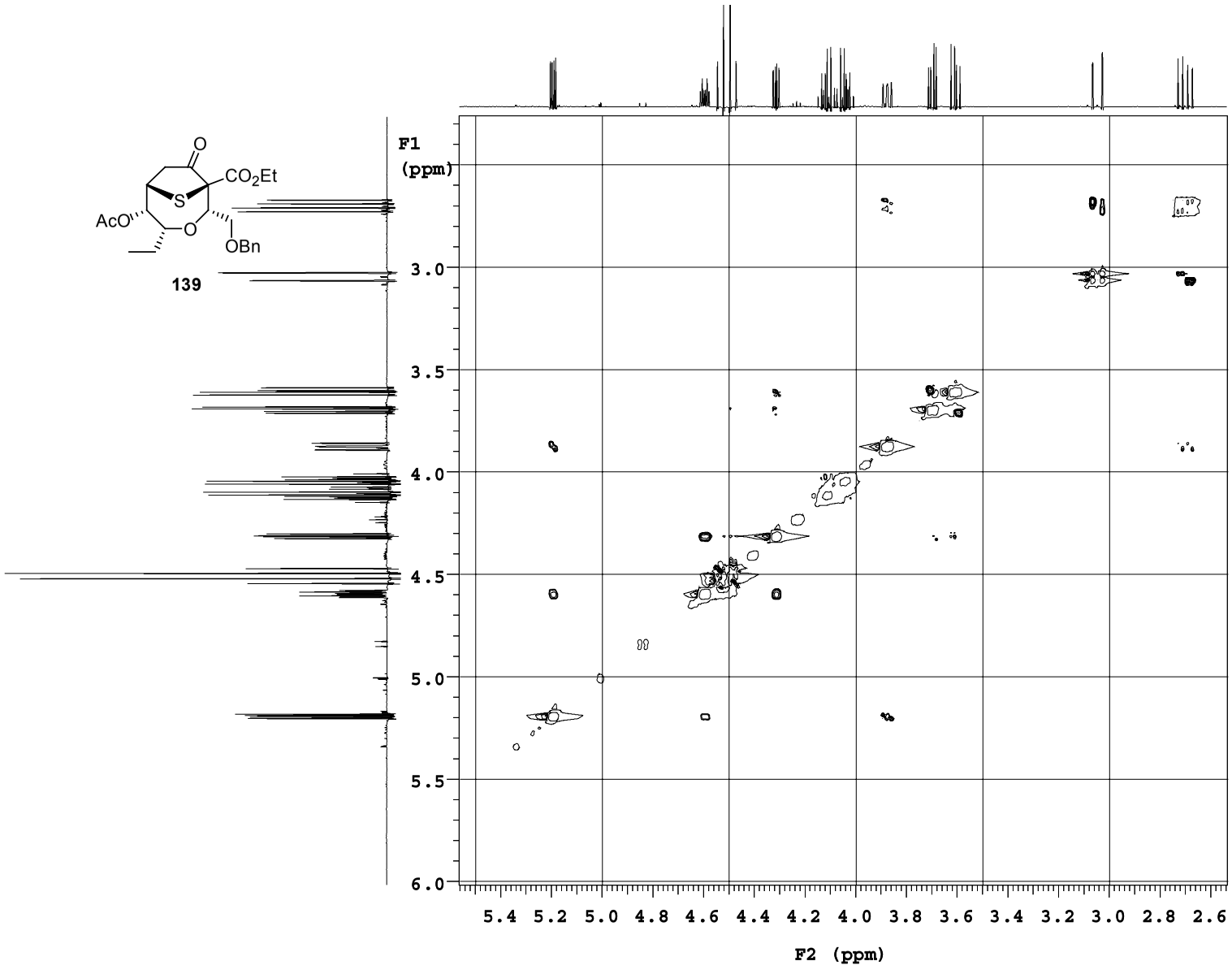

125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C autoxdb probe
Pulse Sequence: s2pul
OAc
N2
OEt
O
S
O
O
OBn
140
189.289
171.513
161.318
138.107
128.680
128.064
128.017
83.589
82.788
77.540
77.284
77.029
73.878
71.979
65.748
61.783
41.282
41.119
25.357
21.042
14.572
10.072
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul

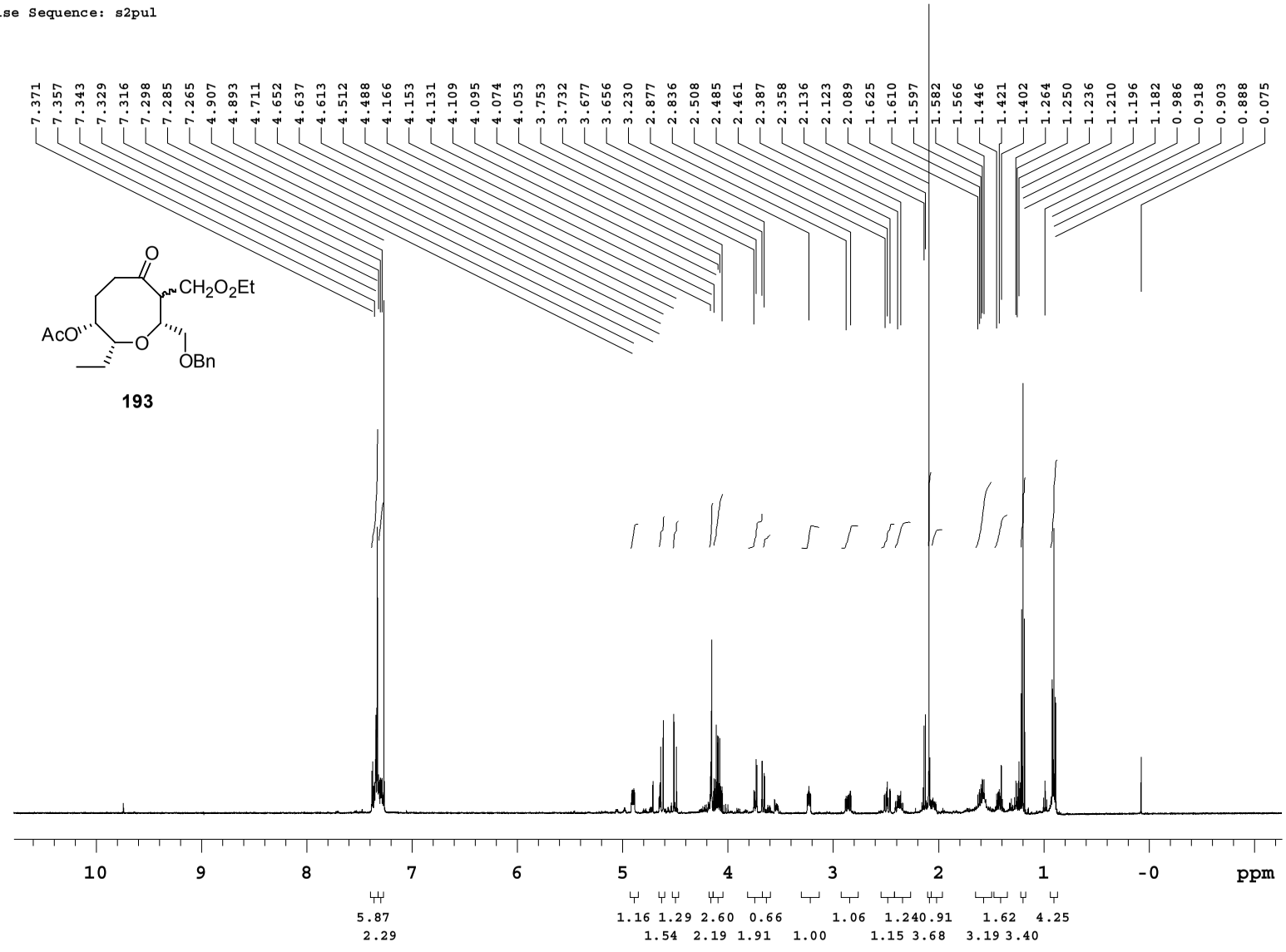


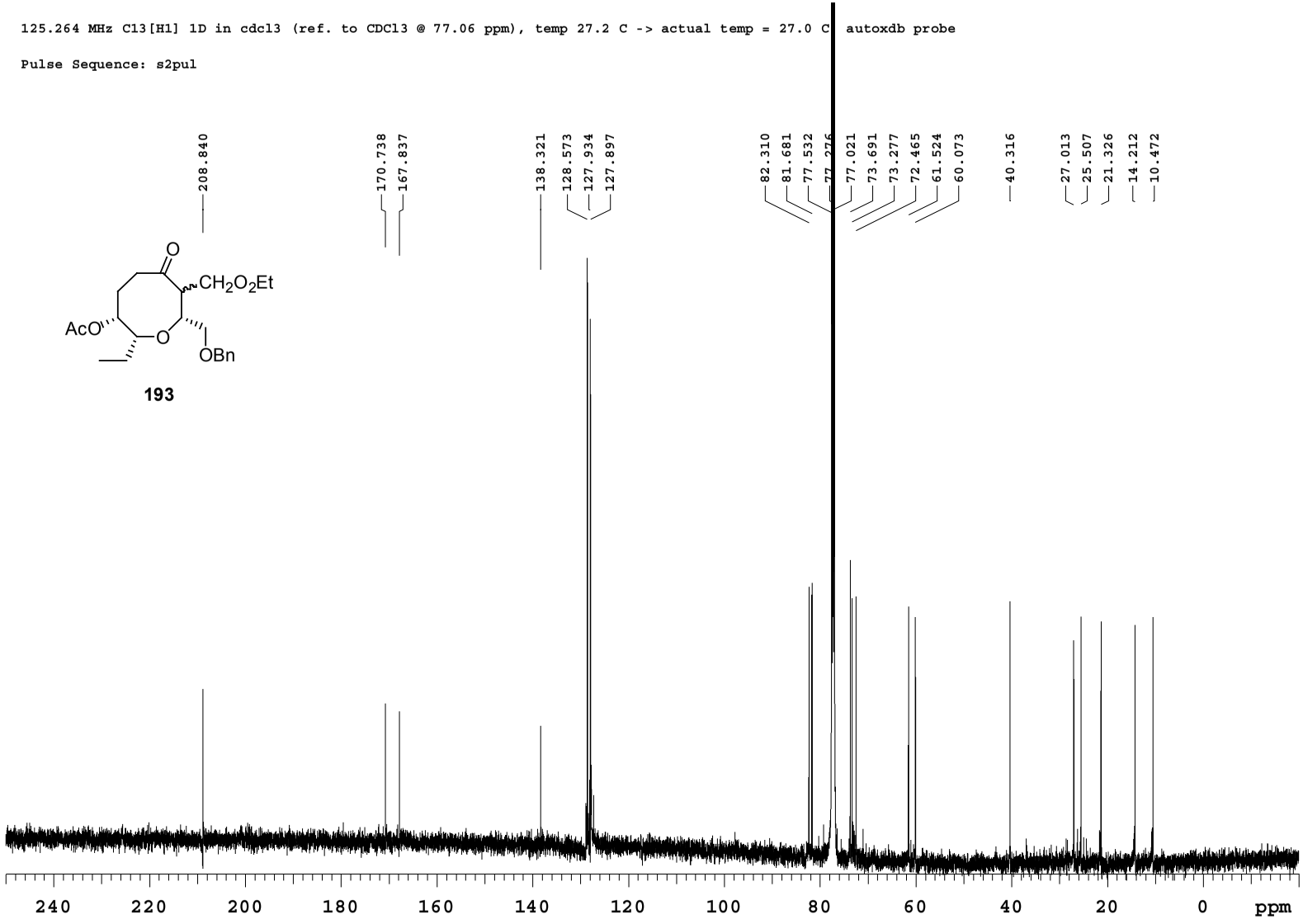

125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C autoxdb probe
Pulse Sequence: s2pul
206.623
170.299
165.659
138.224
128.530
127.988
127.858
88.710
85.143
77.538
77.381
77.282
77.027
73.662
70.437
64.631
62.261
41.906
38.964
25.258
21.028
14.090
10.556
O
CO2Et
S
AcO
O
OBn
139
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
CO2Et
S
AcO
O
OBn
139
F1
(ppm)
3.0
3.5
4.0
4.5
5.0
5.5
6.0
5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6
F2 (ppm)

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

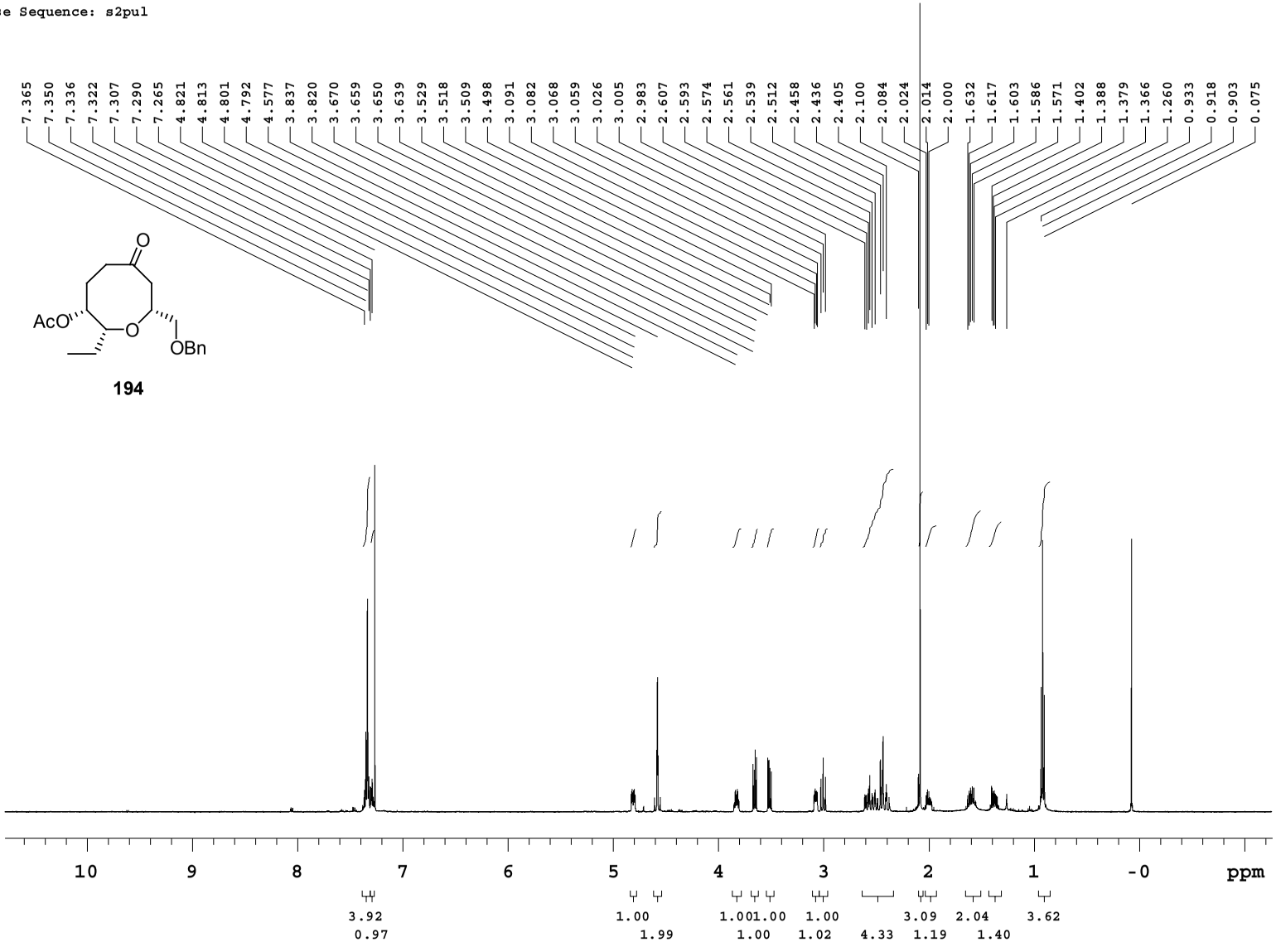
Pulse Sequence: s2pul

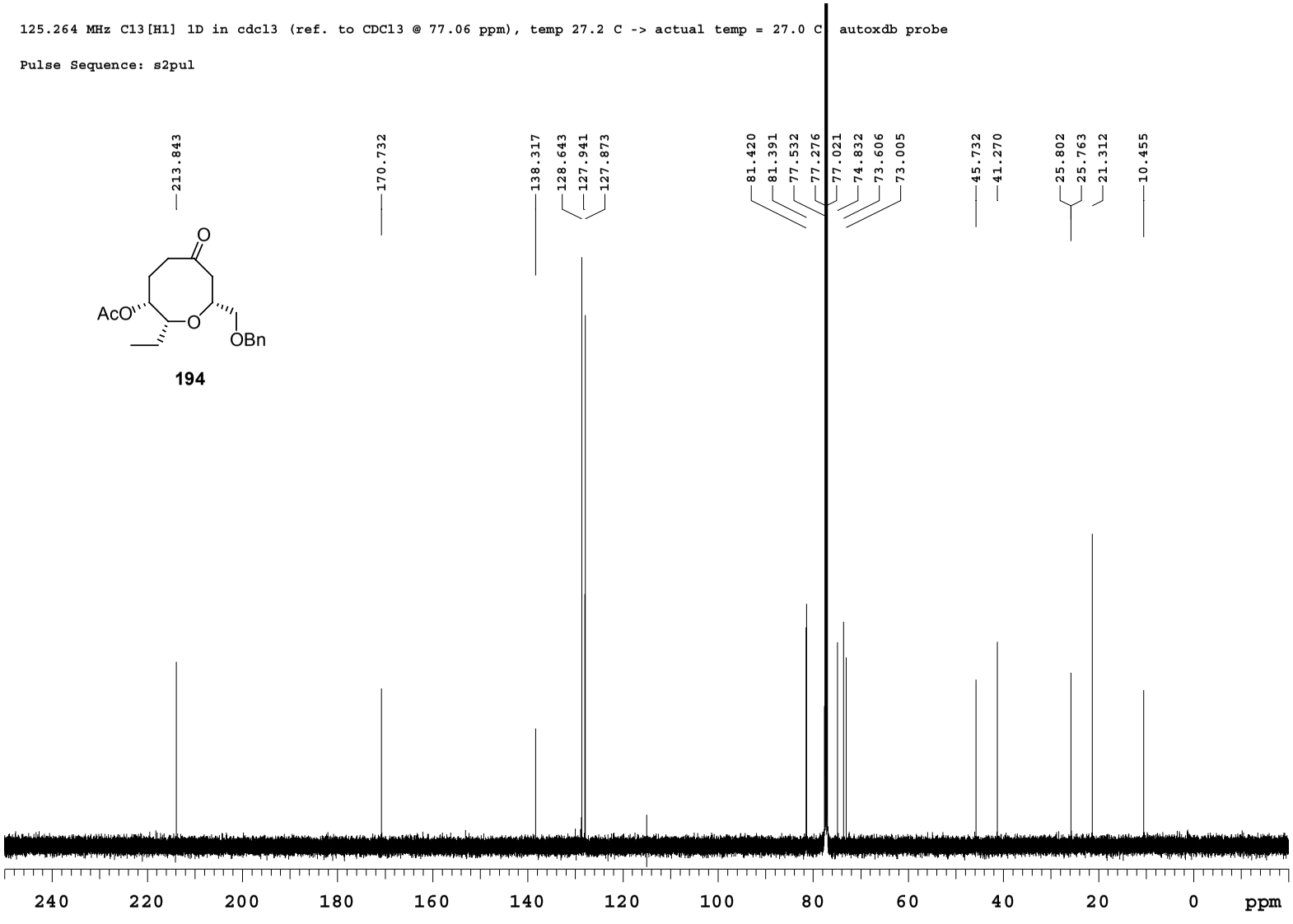



125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C autoxdb probe
Pulse Sequence: s2pul
208.840
170.738
167.837
138.321
128.573
127.934
127.897
82.310
81.681
77.532
77.276
77.021
73.691
73.277
72.465
61.524
60.073
40.316
27.013
25.507
21.326
14.212
10.472
O
CH2O2Et
AcO
O
OBn
193
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

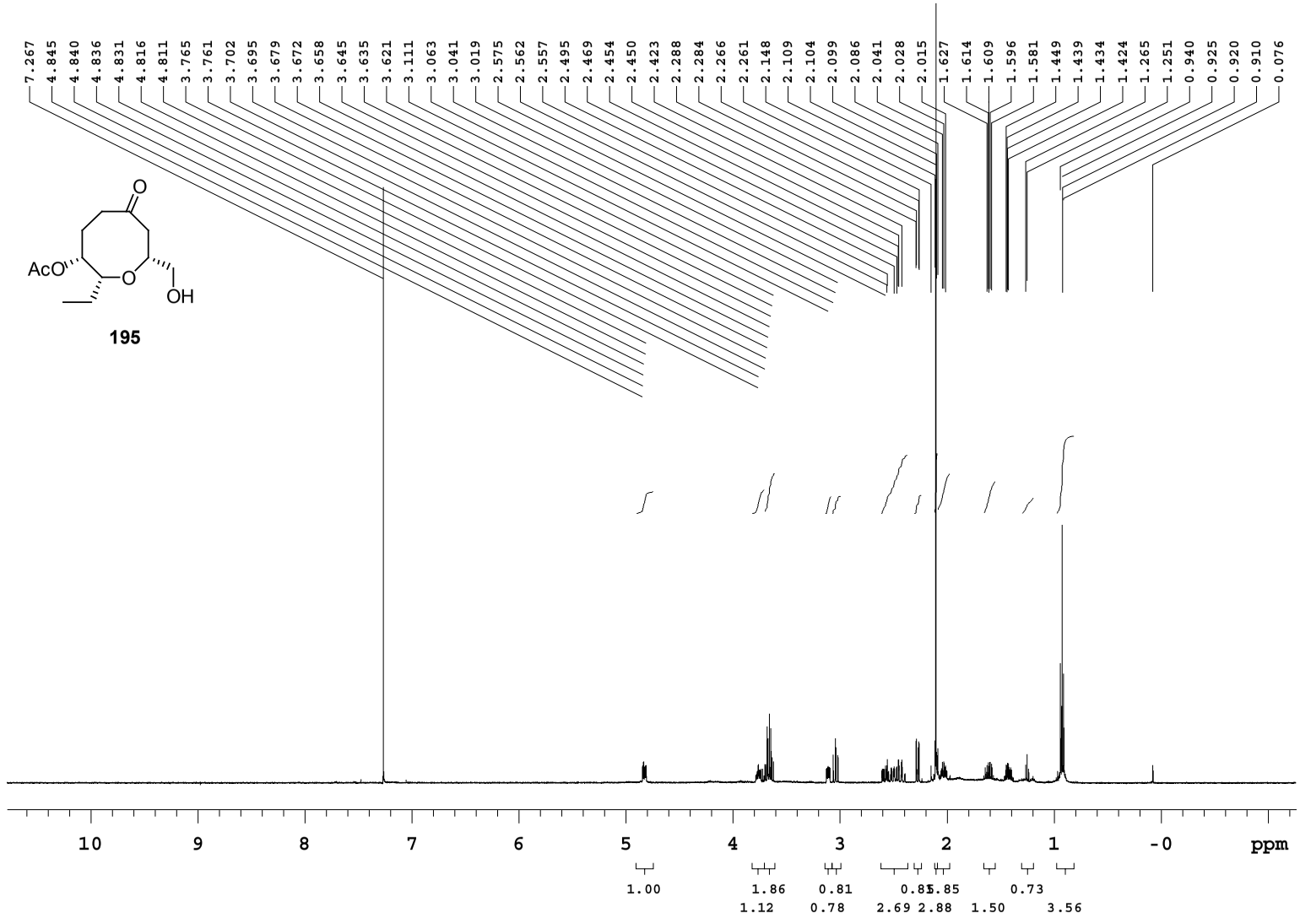
Pulse Sequence: s2pul

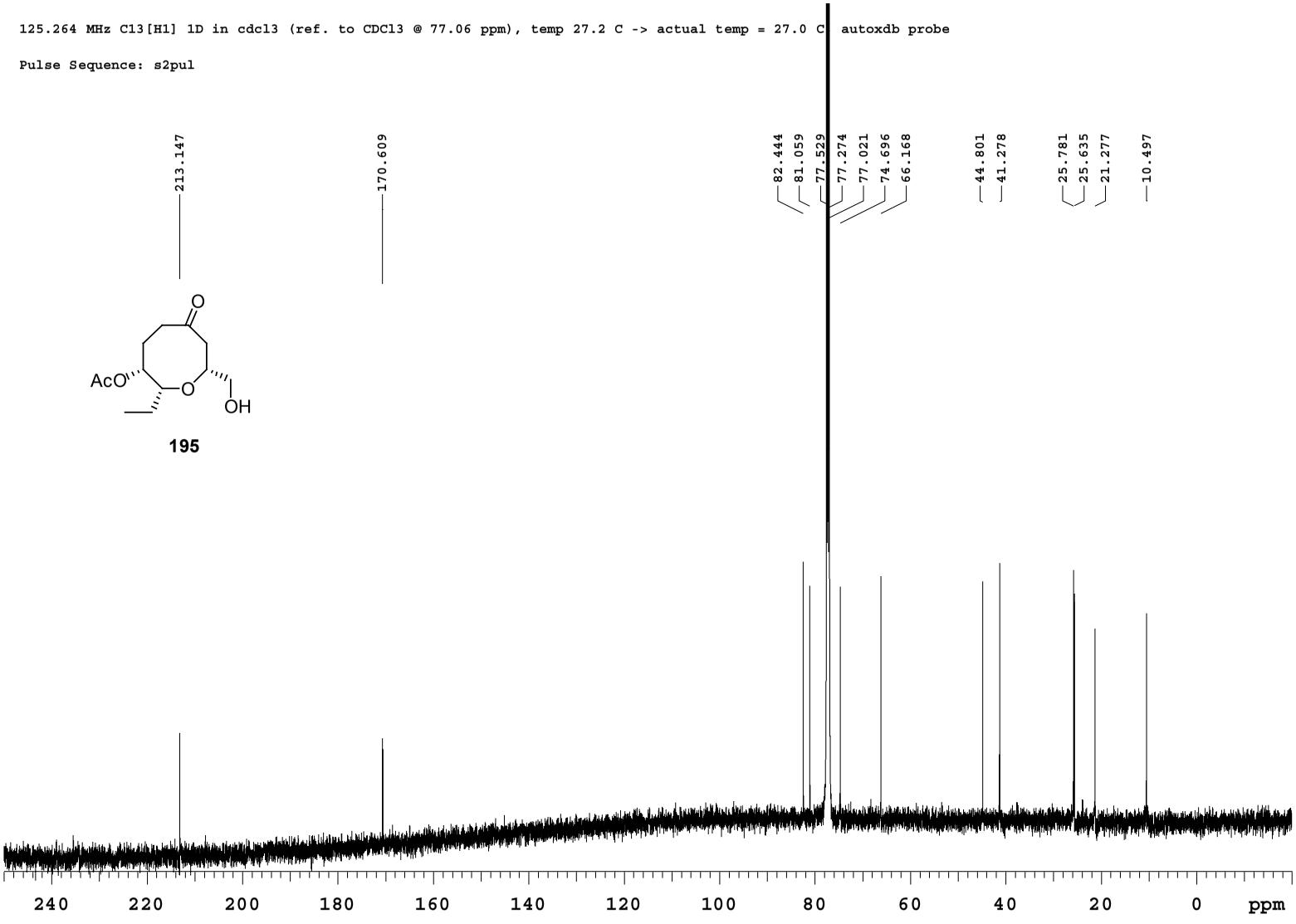



125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C autoxdb probe
Pulse Sequence: s2pul
213.843
170.732
138.317
128.643
127.941
127.873
81.420
81.391
77.532
77.276
77.021
74.832
73.606
73.005
45.732
41.270
25.802
25.763
21.312
10.455
AcO
O
OBn
194
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

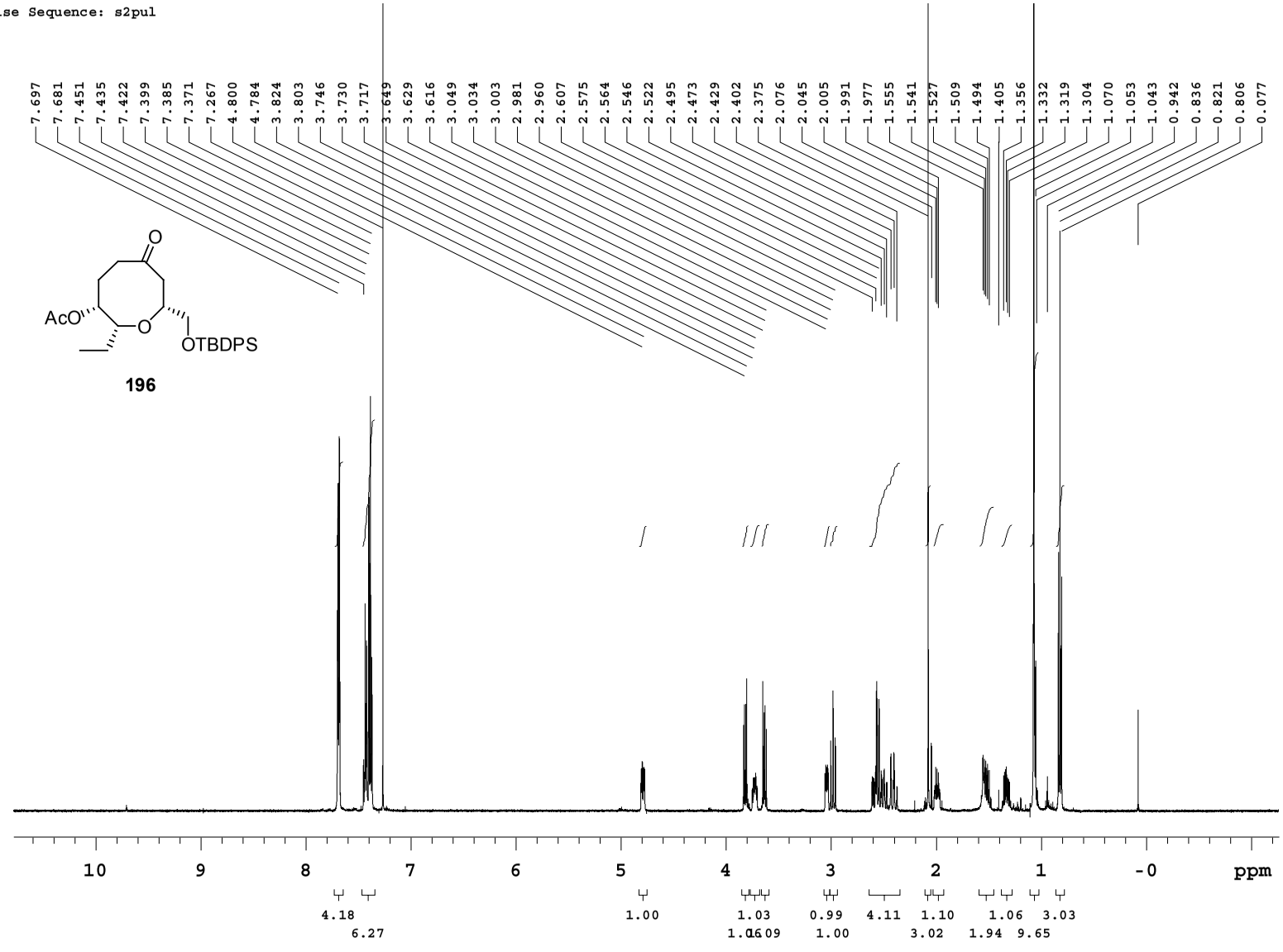
Pulse Sequence: s2pul

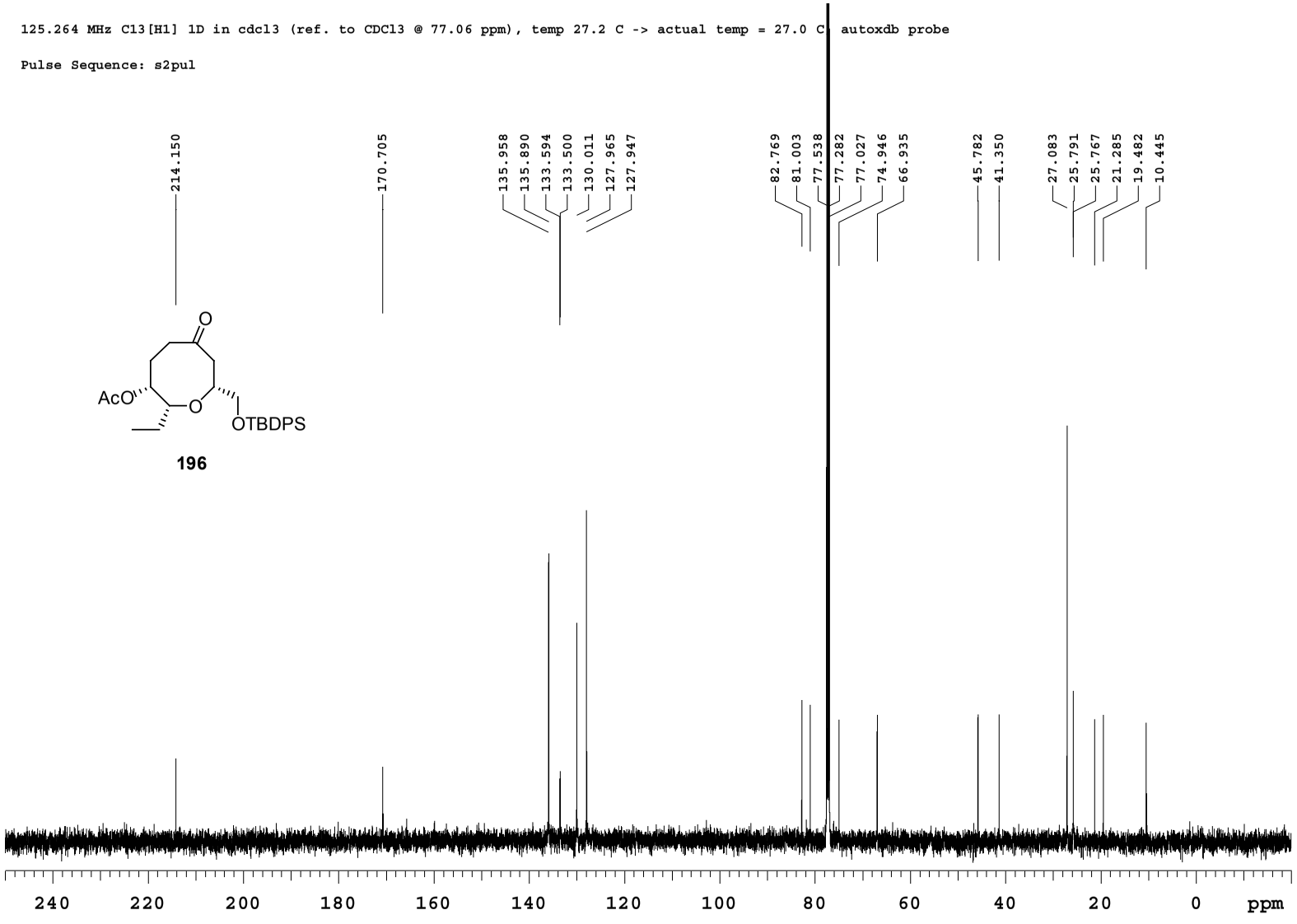



125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C autoxdb probe
Pulse Sequence: s2pul
213.147
170.609
82.444
81.059
77.529
77.274
77.021
74.696
66.168
44.801
41.278
25.781
25.635
21.277
10.497
AcO
O
OH
195
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul




125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
214.150
170.705
135.958
135.890
133.594
133.500
130.011
127.965
127.947
82.769
81.003
77.538
77.282
77.027
74.946
66.935
45.782
41.350
27.083
25.791
25.767
21.285
19.482
10.445
O
AcO
O
OTBDPS
196
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm