University of Alberta

Oxonium Ylide Rearrangements: A Novel Approach Towards the Synthesis of the Phorbol Skeleton

by

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"Keep away from people who try to belittle your ambitions. Small people always do that, but the really great make you feel that you, too, can become great."

Mark Twain

"Two things are infinite: the universe and human stupidity; and I'm not sure about the universe."

Albert Einstein

"Beer. Now there's a temporary solution."

Homer Simpson

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For Mom and Dad

Abstract

Oxonium ylides are highly reactive intermediates that can be used for the synthesis of heterocyclic and carbocyclic frameworks. These putative intermediates are almost exclusively formed from diazocarbonyl derived metallocarbenes, by attack of a pendent oxygen atom. Oxonium ylides have been shown to furnish products derived from the [1,2]-shift (Stevens rearrangement) or the [2,3]-shift in an efficient manner. Chapter 1 is a review of oxonium ylides in synthesis focusing on factors that influence the reactivity of these intermediates.

Previous work has shown that the sulfur-directed Stevens rearrangement is an efficient reaction for the generation of seven and eight-membered oxa-bridged carbocycles fused to five-membered rings. Chapter 2 describes an extension of this chemistry where six-seven and six-eight membered oxa-bridged carbocyclic products were furnished in good yields. The chemo- and diastereoselectivity of these rearrangements was dependent on the configuration of the acetal stereocentre present in the diazoketone precursor.

A novel approach towards the synthesis of the tigliane and daphnane diterpenes is described in Chapter 3. The tricyclic framework was generated from a highly stereoselective oxygen-directed Stevens rearrangement of an oxonium ylide. This methodology provides a straightforward route to the construction of the five-seven-six ring system found in these classes of natural products.

Finally, the sulfur-directed Stevens [1,2]-shift was employed in an attempted total synthesis of the natural product (+)-phorbol in Chapter 4. Several

variations of the original synthetic scheme were examined, in an effort to construct the core 6-7 ring structure. The Stevens rearrangement was found to provide the 6-7 ring system of phorbol in excellent yield. The chemo- and diastereoselectivity of this rearrangement was dependent on the configuration of the acetal centre as well as the conformation of the six-membered ring in the starting material. In the future, this advanced intermediate could be used to achieve the total synthesis of (+)-phorbol.

Acknowledgements

When I moved to Edmonton from Oshawa I had no idea what to expect. However, I think I made two excellent decisions: doing my graduate training at the University of Alberta and joining Dr. Frederick G. West's research group.

Boss, it has been five years since I joined your group and it has been a pleasure working for you. Your patience, guidance and support throughout my graduate studies will never be forgotten. I value our discussions about research as well as chemistry in general. Not only have you been a great boss, you have been a good friend too. I have enjoyed our weekly squash games – they were a good break from the lab. I appreciate your sense of humour and have enjoyed our talks about music, movies and everything else. I look forward to getting group updates in years to come.

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I would finally like to thank Evelyn McClure, my best friend. I will never be able to tell you how much your support has meant to me. I always remember teaching Chem 101 in the lab next to you and how much fun we had doing that together. Thank you for putting up with the long hours and weekends that I have spent in the lab. Your patience and understanding over the last 4 years will never be forgotten. I promise that I will make it up to you soon. Thanks for always being able to make me laugh.

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Standard List of Abbreviations

Ac	acetyl
acac	acetylacetonate
Ar	aryl
app	apparent (spectral)
aq	aqueous
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Br	broad (spectral)
*n*Bu	butyl
*t*Bu	*tert*-butyl
ºC	degrees Celcius
calcd	calculated
COSY	homonuclear correlation spectroscopy
d	day(s); doublet (spectral)
dd	doublet-of-doublets
DBU	1,8-diazabicyclo[5.4.0.]undec-7-ene
DIBALH	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMS	dimethyl sulfide
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact (mass spectrometry)
ESI	electrospray ionization (mass spectrometry)
EtOAc	ethyl acetate
g	gram(s)

h	hour(s)
hfacac	hexafluoroacetylacetonate
HMBC	heteronuclear multiple bond coherence
HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectrum
Hz	hertz
J	coupling constant (in NMR)
L	litre(s)
LiDBB	lithium 4,4'-di-*tert*-butylbiphenylide
M	moles per litre
m	multiplet (spectral)
*m*CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
m.p.	melting point
Ms	mesyl; methanesulfonyl
MS	molecular sieves
m/z	mass to charge ratio (mass spectrometry)
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
Nu	nucleophile
PCC	pyridinium chloroformate
Ph	phenyl
Piv	pivaloyl
PMB	*p*-methoxybenzyl
ppm	parts per million (spectral)
pyr	pyridine
q	quartet (spectral)
R_f	retention factor (chromatography)

rt	room temperature
s	singlet (spectral); second (s)
t	triplet (spectral)
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethyl silyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	tri-*iso*-propyl silyl
TLC	thin layer chromatography
TMS	trimethyl silyl
Tol	tolyl
TPAP	tetra-*n*-propylammonium perruthenate
Ts	tosyl; *p*-toluenesulfonyl

Chapter 1

Oxonium Ylide Rearrangements Generated from Diazocarbonyl Compounds

1.1 Introduction

Diazocarbonyl compounds are known to be versatile building blocks in synthesis. The earliest example of using diazoketones in synthesis was reported in 1902 by Wolff, who demonstrated that treatment of diazoacetophenone with silver oxide and water resulted in rearrangement to give phenylacetic acid.[1] A few years later Wolff found that heating or irradiating diazoketones generated ketenes or products derived from ketenes (Figure 1.1). This was believed to proceed through a carbene intermediate and this transformation is now widely known as the Wolff rearrangement.[2]

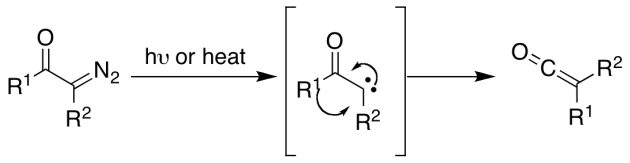


Figure 1.1 Wolff rearrangement.

Since Wolff's initial findings, diazocarbonyl compounds have been used in a variety of chemical reactions including cyclopropanation, C-H insertion, dimerization and ylide formation. These reactions are usually initiated by the formation of a carbene species either via photolysis/thermolysis conditions or, alternatively, by reacting the diazo compound with a metal catalyst, forming a transient metallocarbene species by the expulsion of dinitrogen gas (Figure 1.2).[3] The carbene/carbenoid species can then react with a variety of functionalities

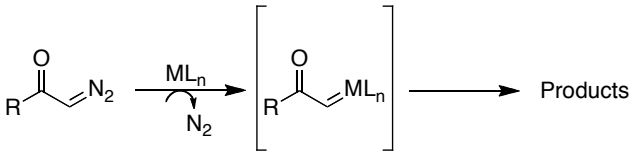


Figure 1.2 Metallocarbene formation.

including double bonds, C-H bonds and heteroatoms. Selectivity in this competing carbene/carbenoid pathway can be controlled by intelligent substrate design and/or choosing the appropriate metal catalyst. This chapter will focus on the generation and rearrangement of oxonium ylides derived from the decomposition of diazoketones.

Ylide formation occurs when the lone pair of electrons from a Lewis base attacks an electrophilic carbene or metallocarbene species (Figure 1.3). Depending on the type of ylide and the nature of the substituents, these reactive intermediates may undergo a variety of chemical processes as depicted below. Nitrogen, sulfur and phosphorus ylides have been extensively studied over the last century. Ylides resulting from attack by oxygen have received considerably less

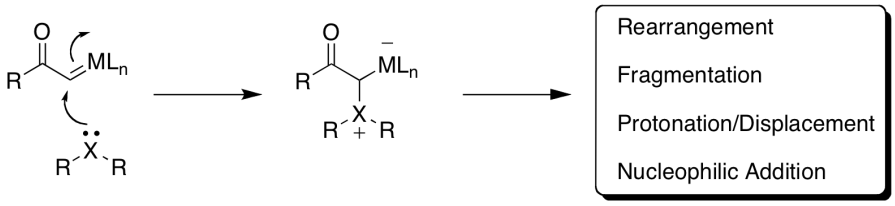


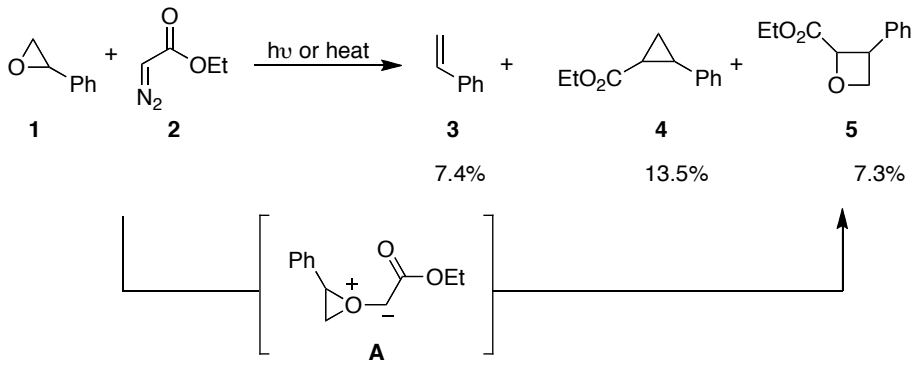
Figure 1.3 Ylide formation.

attention in the literature; only in the past two decades has there been an explosion of activity in the development of oxonium ylide reactions. Oxonium ylides are known for their instability and high reactivity, therefore the existence of these chemical species has not been proven by spectroscopic means.[4,5] The only proof supporting the existence of these intermediates has resulted from the isolation and analysis of products expected from rearrangement, fragmentation, or

protonation/displacement processes. Onium ylides of nitrogen, sulfur and phosphorus, can be generated from deprotonation next to the positively charged heteroatom and have found success as viable intermediates in synthesis. Unfortunately oxonium ylides derived from deprotonation do not undergo selective ylide reactions.[6] Due to the instability of these intermediates, oxonium ylides are usually generated either from photolysis/thermolysis or catalytic decomposition of a diazo compound.

1.2 Early Investigations: Oxonium Ylide Generation and Rearrangement

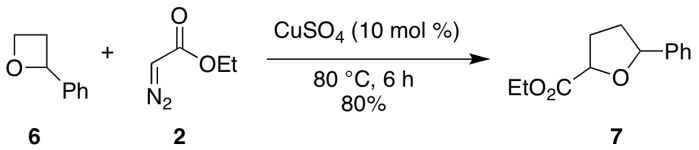
Oxonium ylides can be formed by first converting a diazo compound to a free or metal associated carbene followed by attack of this electrophilic intermediate with the lone pair of an oxygen atom. One of the earliest reports of a free carbene reacting with the lone pair of an oxygen atom was reported by Nozaki[7] in 1965. Irradiation or thermolysis of ethyl diazoacetate **2** provided the free carbene



Scheme 1.1 Free carbene reaction.

intermediate, which was found to react with styrene oxide **1** resulting in a variety of different products (Scheme 1.1). It was proposed that the carbene was attacked by the lone pair of the oxygen atom of the epoxide **1** to form an oxonium ylide intermediate **A**. This highly reactive intermediate yielded styrene (**3**) from an elimination pathway, ethyl 2-phenylcyclopropanecarboxylate (**4**) from

cyclopropanation of styrene by the carbene, and finally 2-carbethoxy-3-phenyloxetane **5** from a [1,2]-shift of the oxonium ylide. The mechanism of this rearrangement will be discussed in detail in section 1.3. This example shows how the stoichiometric generation of a free carbene is not selective and yields a variety of different products. One year later, Nozaki[8] found this reaction was more selective when a catalytic amount of copper(II) sulfate was added to a solution of ethyl diazoacetate **2** and 2-phenyloxetane **6**. This cleanly afforded 2-carbethoxy-3-phenyltetrahydrofuran **7** as the sole product, which was proposed to arise from the [1,2]-shift of an oxonium ylide intermediate (Scheme 1.2).



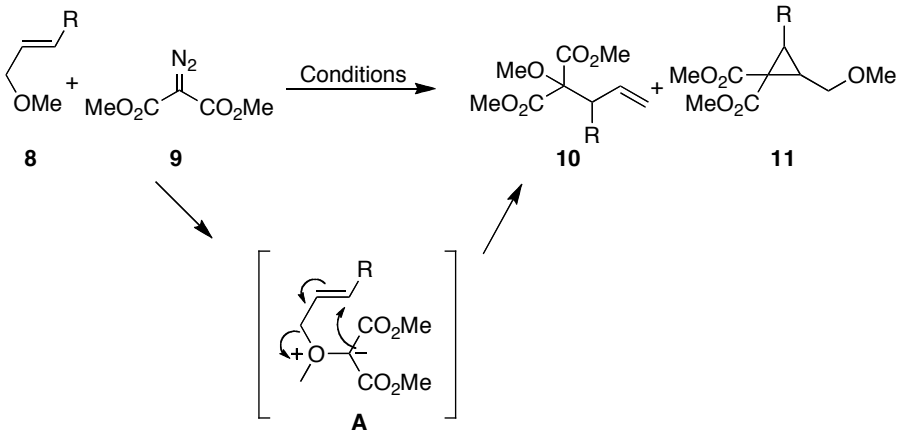
6 **2** **7**

Scheme 1.2 Copper catalyzed [1,2]-shift of 2-phenyloxetane **6**.

Ando[9] reported similar findings when irradiating dimethyl diazomalonate in the presence of allyl compounds containing a heteroatom. When dimethyl diazomalonate **9** was irradiated in the presence of allyl ether **8**, two major products were formed (Table 1.1). The major product **10** was a result of oxonium ylide formation followed by a concerted [2,3]-shift **A** to while the minor product **11** was formed by cyclopropanation of the allyl group with free carbene generated from irradiation. The addition of a photosensitizer to these reactions produced only addition products **11,** confirming that a singlet carbene was necessary for oxonium ylide formation to occur. Ando found that with catalytic copper conditions the addition product **11** could be suppressed with an increased yield of the desired insertion product **10**. The work conducted by Nozaki and Ando showed that oxonium ylides could be formed thermally, photochemically, or catalytically and were able to undergo subsequent rearrangements. These results

suggest that using a metal catalyst is a mild and more selective way to induce oxonium ylide formation and subsequent rearrangement.

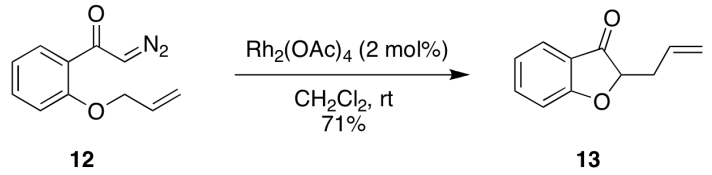
In 1986 Pirrung[10] and Johnson[11] published pioneering work utilizing transition metal mediated oxonium ylide formation. These reports allowed for the development of mild and selective ways of generating and subsequently rearranging oxonium ylides. Pirrung showed that catalytic decomposition of a variety of diazocarbonyl compounds using $Rh_2(OAc)_4$ would result in oxonium



R	Conditions	Insertion **10** (%)	Addition **11** (%)
H	Photolysis	31	20
H	$CuSO_4$, heat	60	20
Me	Photolysis	37	17
Me	$CuSO_4$, heat	75	trace

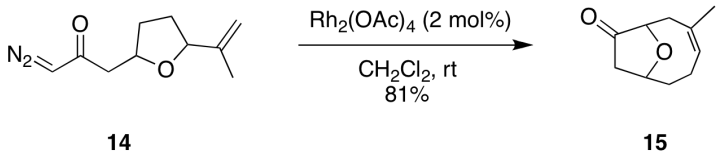
Table 1.1 [2,3]-rearrangement of oxonium ylide.

ylide formation followed by [2,3]-rearrangement. This report showed that 3-furanones could be prepared in good to excellent yield using mild reaction conditions (Scheme 1.3). 3-Furanone **13** was obtained from the [2,3]-rearrangement of an oxonium ylide generated by the reaction of diazoketone **12** with a catalytic amount of $Rh_2(OAc)_4$. It was also demonstrated that an eight-



Scheme 1.3 Synthesis of 3-furanone **13** by a [2,3]-rearrangement of an oxonium ylide.

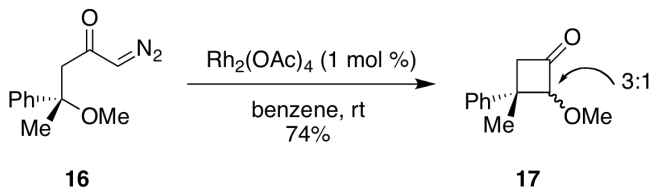
membered ether bridged compound **15** could be formed through a 3-carbon ring expansion by subjecting diazoketone **14** to identical reaction conditions (Scheme 1.4). Johnson observed similar results, which could be explained by [2,3]-rearrangements or [1,2]-shifts of a catalytically generated oxonium ylide derived from the reactions of an appropriate diazoketone with $Rh_2(OAc)_4$. A variety of heterocycles as well as carbocycles were prepared in good yield from simple,



Scheme 1.4 Ring enlargement of diazoketone **14**.

readily available starting materials. The products arising from a [1,2]-shift were formed with retention of stereochemistry and this was confirmed by the synthesis and rearrangement of optically active **16** (Scheme 1.5). The absolute configuration at the new quaternary center was formed with retention when diazoketone **16** furnished cyclobutanone **17** in good yield and the relative stereochemistry was confirmed by X-ray crystallography. The mechanism of this rearrangement was postulated to occur through generation of a metal-associated oxonium ylide followed by a metal-assisted [1,2]-shift. A concerted suprafacial [1,2]-shift of the free ylide is forbidden by Woodward-Hoffmann rules and this

would also require inversion of stereochemistry at the migrating carbon. This mechanism will be



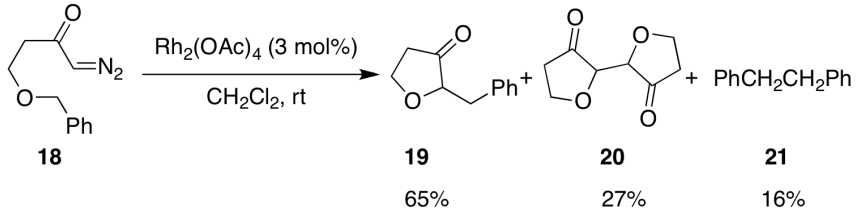
Scheme 1.5 [1,2]-Shift with retention of stereochemistry at the quaternary center.

discussed in more detail in the next section.

The findings described in this section inspired many chemists to investigate the chemistry of oxonium ylides and their potential use in the synthesis of interesting molecular scaffolds found in biologically important molecules.

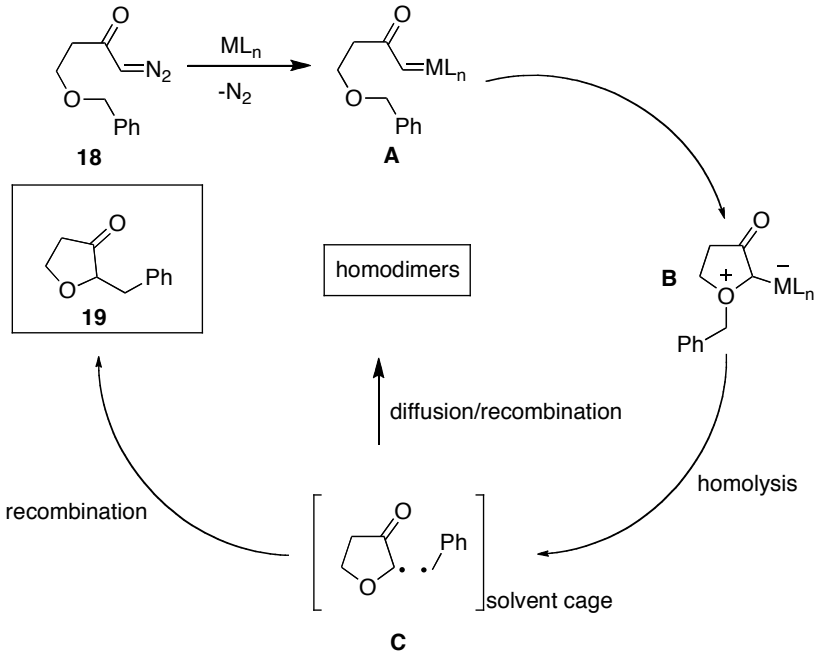
1.3 Mechanism of the Stevens Rearrangement

The [1,2]-shift of an oxonium ylide could proceed through one of three possible mechanisms: a concerted [1,2]-sigmatropic rearrangement with retention of stereochemistry, initial homolysis to give a radical pair, or heterolysis to give an ion pair followed by rapid recombination. The first process is symmetry forbidden by Woodward-Hoffmann rules, so this mechanism is unlikely.



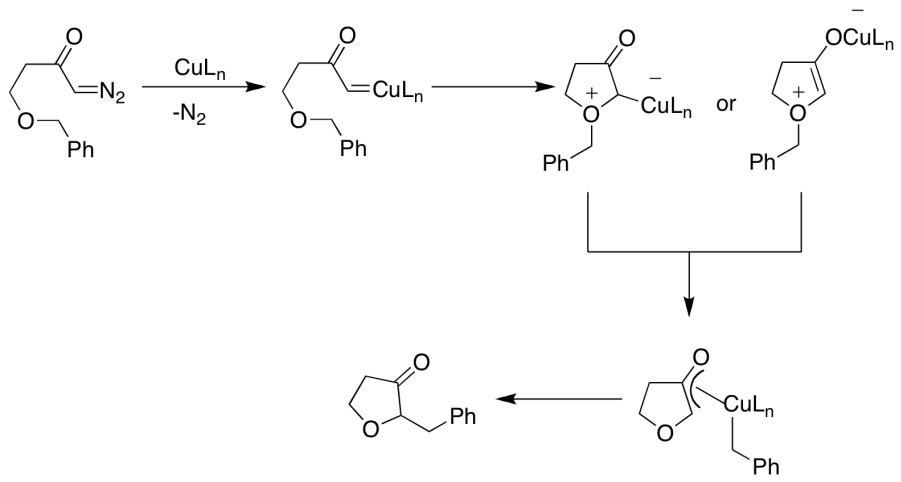
Scheme 1.6 Formation of homodimers in the Stevens rearrangement.

Oxonium ylides are usually generated by catalytic decomposition of a diazocarbonyl compound so there is also the possibility of a metal bound/associated mechanism. West[12] proposed evidence for the radical pair mechanism during an investigation into the synthesis of 3-furanones resulting from a Stevens [1,2]-shift of an oxonium ylide. When diazoketone **18** was reacted with catalytic $Rh_2(OAc)_4$ 3-furanone **19** was isolated as the major product along with homodimers **20** and **21** (Scheme 1.6). The isolation of homodimers is the signature of a radical pair mechanism, so West proposed the mechanism illustrated in Scheme 1.7. The metal-catalyzed Stevens rearrangement operates first by coordination of the diazoketone to the metal catalyst followed by expulsion of dinitrogen gas to form the transient metallocarbene intermediate **A**. The lone pair of the oxygen atom attacks the electrophilic carbenoid to form the ylide **B**. Since homodimers are evidence for radical intermediates, subsequent homolysis of the ylide is proposed to provide radical pair **C**. If radical recombination is fast, no homodimers should be seen, but if the radicals were able to diffuse from the solvent cage, dimerization products would be observed.



Scheme 1.7 Proposed radical pair mechanism.

Interestingly, West[13] found that when the catalyst was changed from $Rh_2(OAc)_4$ to $Cu(hfacac)_2$, no homodimers were isolated, which implicates the metal in the bond forming process. Therefore, an alternative metal-assisted mechanism must also be considered (Scheme 1.8), as was previously proposed by Johnson.[11] This proposed mechanism suggests transfer of the migrating group to the metal followed by reductive elimination to afford the [1,2]-shift product.

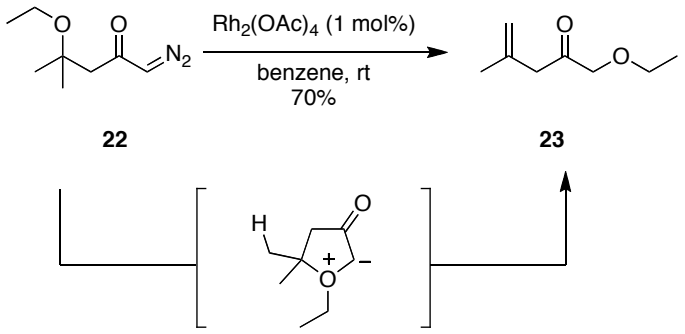


Scheme 1.8 Proposed metal-assisted mechanism.

The mechanism is still unclear, but a few conclusions can be drawn from the previously described observations. The isolation of homodimers suggests that the Stevens rearrangement proceeds through a radical pair intermediate followed by recombination. The high degree of retention of stereochemistry can be attributed to fast carbon-carbon bond formation before randomization can occur. Secondly, the metal catalyst is an important factor in these rearrangements as seen in the suppression of homodimers by copper catalysis. Despite uncertainties regarding the actual mechanism, the development of the oxonium ylide Stevens [1,2]-shift has not been hindered and will be further highlighted in Section 1.4.

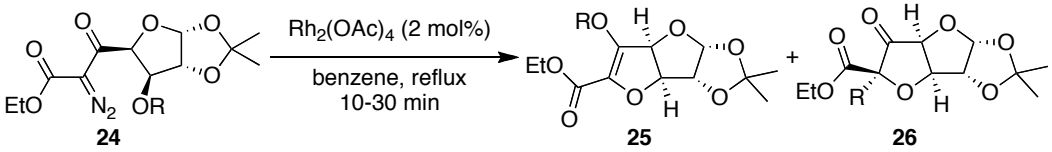
1.3.1 Importance of the Migrating Group

The success of the Stevens [1,2]-shift of an oxonium ylide is dependent on the nature of substituents on the migrating carbon. If indeed this rearrangement is proceeding through radicals, then adequate stabilization of the radical intermediate is needed for the reaction to be successful. Johnson showed that the key to the [1,2]-shift was stabilization of the electron deficient carbon by either oxygen, vinyl or aryl substituents.[11] Simple tertiary center stabilization did not appear to be effective since diazoketone **22** failed to yield the [1,2]-shift product and instead furnished the α,β'-fragmentation product **23** in a 70% yield (Scheme 1.9).[11]



Scheme 1.9 Formation of α,β'-fragmentation product.

In 2001 Dhavale[14] showed that varying the electronics of benzyl migrating groups in the $Rh_2(OAc)_4$ catalyzed decomposition of diazo compounds **24** resulted in [1,4] or [1,2] migration products formed in good yield and excellent regioselectivity (Scheme 1.7). [1,4]-Migration products were formed exclusively over [1,2]-migration products when the migrating group was electron rich as in substrates **24b-d**. When the migrating group was electron deficient, product **26** was formed preferentially over product **25**, as seen in substrates **24e,f**. Dhavale proposed a mechanism to rationalize his findings in this report (Table 1.2). Dhavale suggested that after initial metallocarbene formation **A**, oxygen ylide

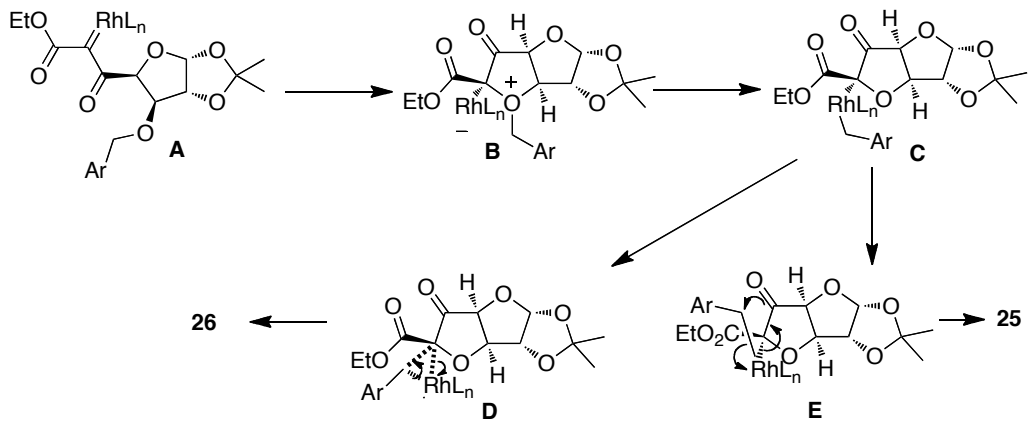


a benzyl
b 4'-methoxy benzyl
c 3',4'-methylenedioxy benzyl
d 3',4'-dimethoxy benzyl
e 4'-carbmethoxy benzyl
f 4'-nitro benzyl

Diazo compound	Time (min)	Ratio **25:26** ([1,4]:[1,2])	Combined yield (%)
24a	10	62:38	77
24b	30	100:0	75
24c	30	100:0	75
24d	30	100:0	76
24e	10	38:62	81
24f	10	32:68	82

Table 1.2 [1,4] vs [1,2]-migration of compounds **24**.

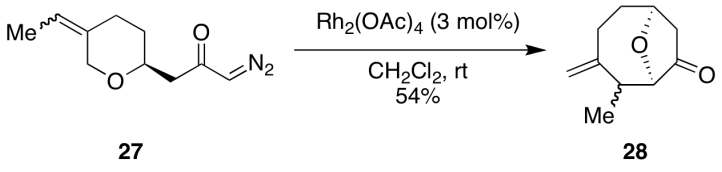
formation occurs giving intermediate **B**, which is proposed to transfer the migrating group through a four-centered oxabicyclo-[3.2.0]heptane transition state to produce intermediate **C** (Scheme 1.10). In the cases where the migrating groups are electron-rich there is stronger back-bonding to the metal, the electrophilicity of Rh decreases and the metal carbon bond becomes weaker as compared to the Rh-CH_2Ar bond. Free rotation of intermediate **C** brings the migrating group close to the carbonyl allowing for a concerted transfer of the benzylic group to oxygen (**E**) affording [1,4] product **25**. In the case of electron-poor aryl groups, the electrophilicity of the Rh complex is increased and the metal carbenoid bond becomes stronger than the Rh-CH_2Ar bond. Therefore initial cleavage of the weaker Rh-CH_2Ar bond followed by formation of the new C-C bond via a three-membered transition state **D** yields [1,2] product **26**.



Scheme 1.10 Proposed mechanism for [1,4] and [1,2]-migration.

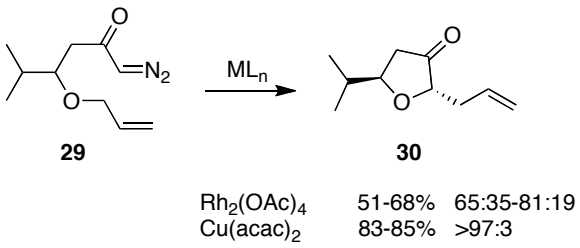
1.3.2 Mechanism of the [2,3]-sigmatropic shift.

Unlike the [1,2]-shift the [2,3]-rearrangement is believed to occur through a concerted sigmatropic process. The [2,3] product could arise from a stepwise process with allylic inversion, though one would normally expect a mixture of regioisomers. An early example supporting the concerted mechanism was reported by West[15] in 1993 when diazoketone **27** was subjected to $Rh_2(OAc)_4$ catalysis and furnished the ring expanded product **28** in good yield and with complete allylic inversion (Scheme 1.11). Although this example supports a concerted mechanism it does not account for the role of the catalyst nor whether



Scheme 1.11 Ring expansion of **27** by a concerted [2,3]-shift.

it is present at the time of bond formation or if this process is occurring through the free ylide.[16] Clark[17] observed interesting catalyst effects in his diastereoselective synthesis of tetrahydrofuran-3-ones. When diazoketone **29** was



Scheme 1.12 Catalyst effects in the [2,3]-rearrangement.

subjected to rhodium catalysis, **30** was furnished in fair yield with modest preference for the *trans*-tetrahydrofuran-3-one **30** (Scheme 1.12). An improvement was seen when $Cu(acac)_2$ was used in place of $Rh_2(OAc)_4$ resulting in excellent yields and almost complete diastereoselectivity being observed. Clark suggested that the rearrangement occurred through a metal-bound ylide-enolate species, such as **A** or **B**, rather than free ylide intermediate **C**. If the rearrangement occurred through the free ylide, the diastereoselectivity would have

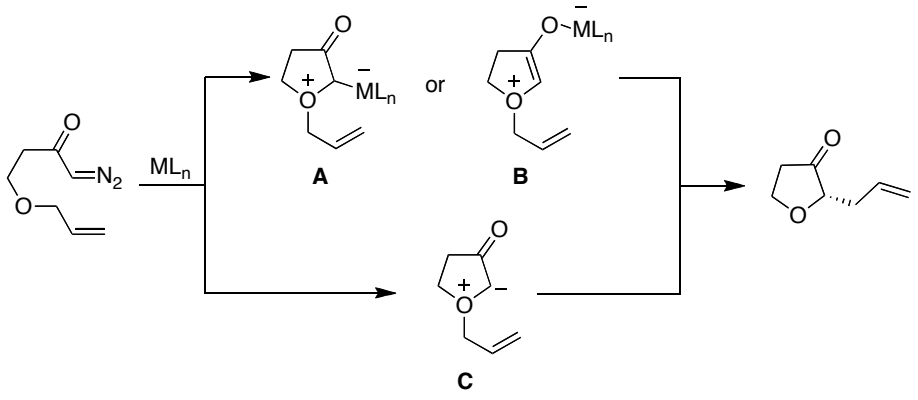


Figure 1.4 Proposed reaction pathways of [2,3]-sigmatropic rearrangement.

been the same regardless of metal catalyst used (Figure 1.4). This mechanism is still the subject of debate because an alternative pathway involving the transfer of

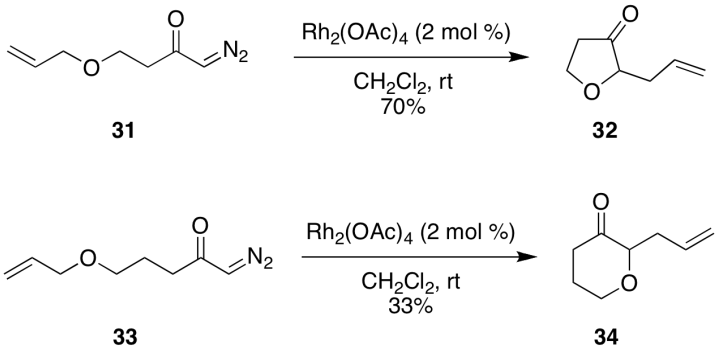
the allyl group to the metal and then reductive elimination to give the product, cannot be ruled out.

1.4 Factors Affecting Oxonium Ylide Rearrangements.

There are many factors that affect the generation and rearrangements of oxonium ylides. The key factors are oxonium ylide ring size, nature of the catalyst used, and substituent on the migrating group.

1.4.1 Oxonium Ylide Ring Size

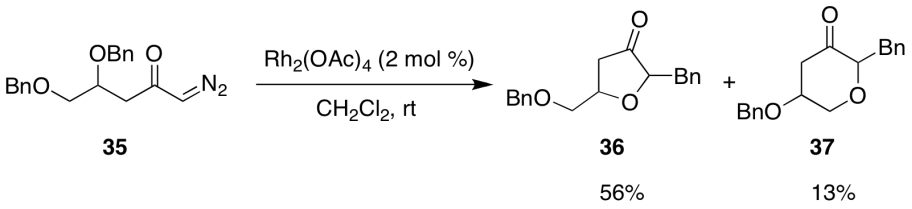
The catalytic generation of a metallocarbene intermediate from a diazoketone can be problematic because of the potential competing carbenoid pathways as described earlier in this chapter. An early example that illustrates this problem



Scheme 1.13 Importance of oxonium ylide ring size.

was detailed in a report by Pirrung[10] in which excellent conversion to desired rearrangement products was seen when the ethereal oxygen was located five atoms away from the carbenoid carbon. This was observed in the rearrangement of diazoketone **31** to 3-furanone **32** in good yield. However, when the ylide formed is part of a six-membered ring, competing C-H insertion products are

isolated and the yield of the desired product, **34**, was reduced (Scheme 1.13). This result was not surprising because C-H insertion generally favours the formation of five membered rings over six membered rings; activation of the C-H bond by the oxygen[18] facilitates the C-H insertion, explaining the poor yield of the desired [2,3]-shift product **34**. These two examples demonstrate that when the ylide ring size is greater than five, C-H insertion will start to compete. Another report supporting these findings resulted from competition studies reported by West[19] in 2004. Substrates were prepared that contained two benzyloxy groups able to participate in the Stevens rearrangement via 5- or 6-membered oxonium ylides. Diazoketone **35** produced a mixture of **36** and **37** when treated with $Rh_2(OAc)_4$ with a strong preference for **36**, which was formed via a five-membered oxonium ylide (Scheme 1.14).



35 **36** **37**

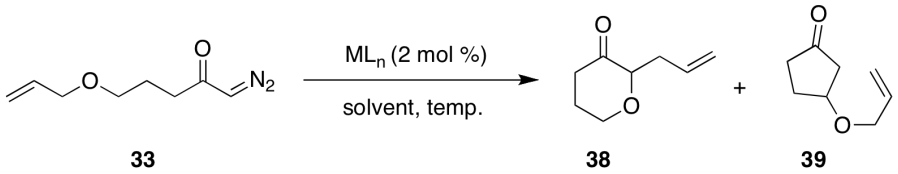
56% 13%

Scheme 1.14 Preference for five-membered oxonium ylide formation of diazoketone **35**.

1.4.2 The Role of the Catalyst.

As a direct result of the breakthrough reports of both Pirrung and Johnson, oxonium ylides are now almost exclusively generated from the decomposition of diazocarbonyl compounds using either rhodium or copper catalysts.[3,20] The choice of metal catalyst directly effect the outcome of the reaction. Over the past three decades, the importance of ligands on the metal center has been investigated.[3,20] Oxonium ylide rearrangements can be tuned to the appropriate reactivity by using rhodium versus copper or simply by altering the electronics of the metal center by

changing the associated ligands. This phenomenon was illustrated by Clark[21] in 1993 when he investigated catalyst effects on the [2,3]-rearrangement of diazoketone **33** (Table 1.3). Reaction of the diazoketone with a variety of metal catalysts showed that [2,3]-rearrangement with copper was superior to rhodium.

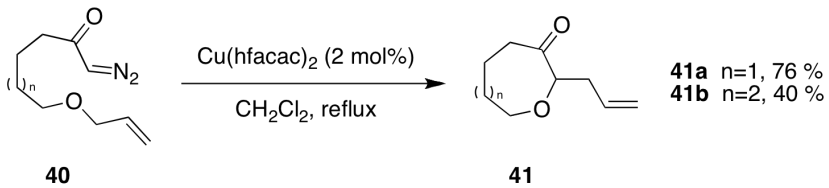


33 **38** **39**

ML_n	Solvent	Temperature	Yield of **38** (%)	Yield of **39** (%)
$Rh_2(OAc)_4$	CH_2Cl_2	rt	37	22
$Rh_2(OAc)_4$	CH_2Cl_2	reflux	41	18
$Rh_2(OAc)_4$	C_6H_6	rt	15	18
$Rh_2(OAc)_4$	THF	reflux	58	12
$Cu(acac)_2$	THF	reflux	60	12
$Cu(acac)_2$	CH_2Cl_2	reflux	61	12
$Cu(tfacac)_2$	CH_2Cl_2	reflux	78	0
$Cu(hfacac)_2$	CH_2Cl_2	reflux	83	0

Table 1.3 Catalyst effects for the [2,3]-rearrangement of diazoketone **33**.

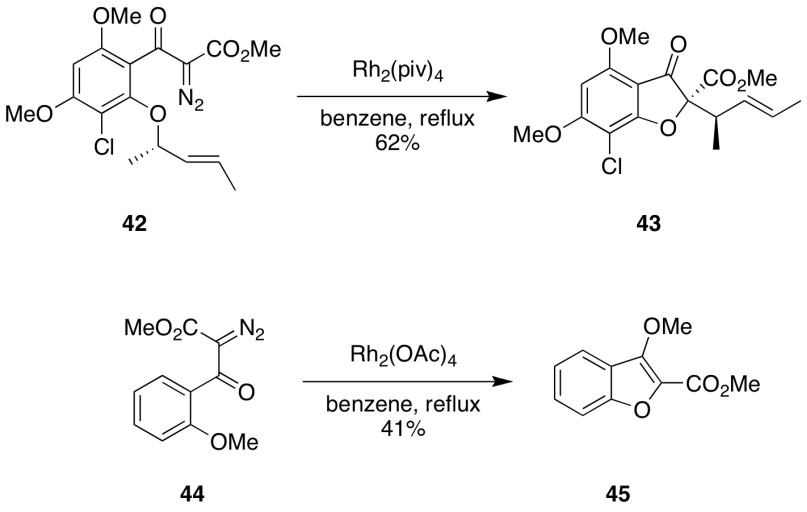
Clark also found that increasing the electrophilicity of the copper catalyst increased the yield of the reaction and suppressed C-H insertion. This was also observed in the formation of larger heterocycles, as diazoketones **40a,b** were



40 **41**

Scheme 1.15 Formation of seven and eight-membered heterocycles **41a,b**.

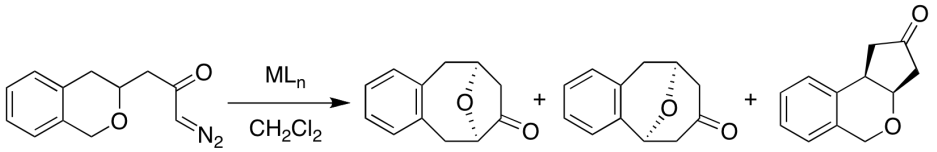
found to give a good yield of the seven-membered ether **41a** and a moderate yield of the eight-membered ether **41b** (Scheme 1.15). Clark proposed that increasing the electron demand of the catalyst could enhance the electrophilicity of the metallocarbene intermediate and essentially eliminate the possibility for C-H insertion in favour of the faster oxygen insertion process. He also speculated that high yields obtained from the $Cu(hfacac)_2$-catalysed reactions resulted from stabilization of the metal-bound ylide intermediates, which suppresses reformation of the original species by ring-opening of the cyclic ylide. Another argument suggests that this stabilization leads to a reduction in the energy difference between the metal-bound ylide-species and the transition states for rearrangement, thereby improving the reaction efficiency. This argument is supported by two independent reports by Pirrung and West where evidence for reversible ylide formation is discussed. Pirrung's key step in the synthesis of (+)-griseofulvin[22] utilized a sigmatropic rearrangement of an oxonium ylide generated from the decomposition of diazoketoester **42** in the presence of catalytic $Rh_2(piv)_4$ generating **43** in good yield as a single diastereomer (Scheme 1.16). This rearrangement raised the



Scheme 1.16 [2,3] versus [1,4] shift in (+)-griseofulvin synthesis.

important issue of reaction selectivity because there was a potential for ylide formation to occur from attack of the metallocarbene by the methyl ether oxygen at the other ortho position. If ylide formation occurred irreversibly, a mixture of products derived from the two ylides would be expected. For example, diazoketone **44** was prepared from o-anisic acid and it was treated with $Rh_2(OAc)_4$. Oxonium ylide formation did occur between the metallocarbene and aromatic OMe to produce **45** via a 1,4-migration. Because no analogous products were isolated in the conversion of **42** to **43**, Pirrung proposed that the O-methyl ylide was formed reversibly allowing for interconversion with the O-allyl ether and exclusive rearrangement through the lower energy [2,3]-shift.

West[13,15] reported similar findings comparing copper and rhodium catalyzed intramolecular generation and subsequent [1,2]-shift of an oxonium ylide. When diazoketone **46** was subjected to decomposition by $Rh_2(OAc)_4$, only products **48** and **49** were formed from intramolecular C-H insertion (Scheme 1.17). Interestingly, when $Cu(hfacac)_2$ was used in place of $Rh_2(OAc)_4$, only the



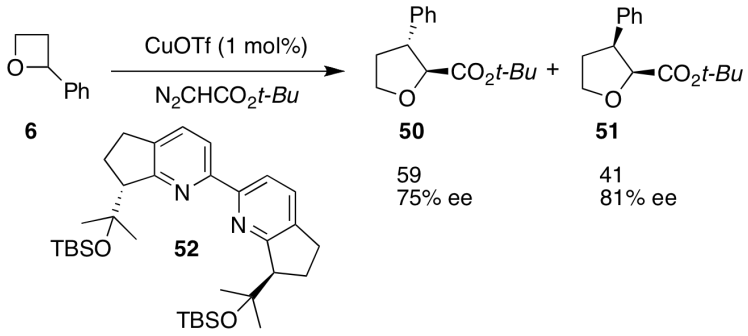
46 **47** **48** **49**

$Rh_2(OAc)_4$	0	10%	40%
$Cu(hfacac)_2$	95%		

Scheme 1.17 Catalyst effects in the ring expansion of **46**.

benzocycloctenone **47** was observed due to a [1,2]-shift of the oxonium ylide intermediate. These differences in reactivity were rationalized by the proposed equilibration between oxonium ylide and Rh-carbenoid and the greater electrophilicity of copper carbenoids[23,24] to favor ylide formation over C-H

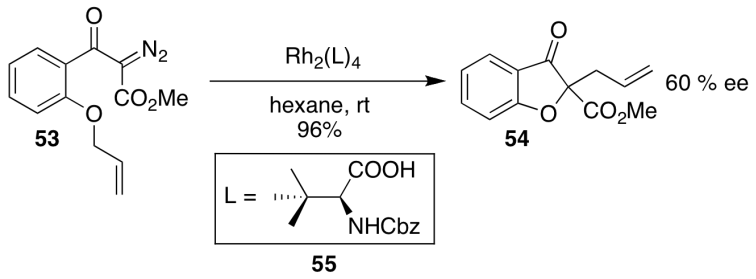
insertion. The difference in reactivity between catalytically generated metallocarbenes from rhodium and copper as observed by Clark, Pirrung and West illustrates that the electrophilicity of the metallocarbene as well as ylide reversibility are two important factors in oxonium ylide rearrangements. The role of the metal is still unclear, but these findings support the concept that the metal centre may remain associated during the bond cleavage/bond formation steps. Additional evidence for metal associated rearrangement can be found in several studies using chiral copper and rhodium catalysts.



Scheme 1.18 Enantioselective ring expansion of 2-phenyloxetane **6**.

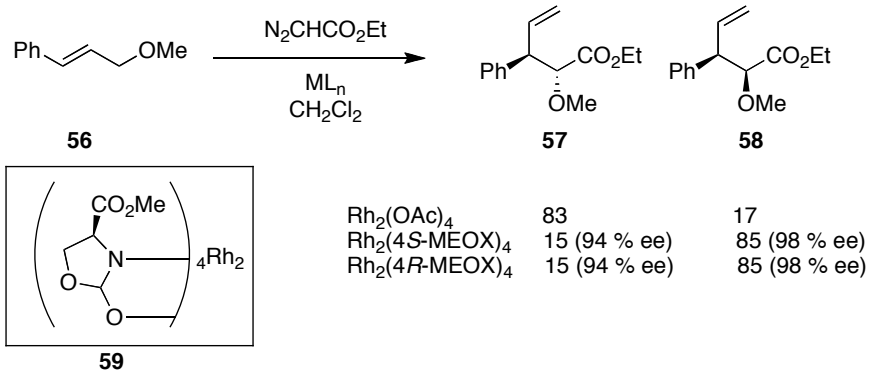
In 1968, Nozaki[25] reported the earliest asymmetric Stevens rearrangement. 2-Phenyloxetane was reacted with a chiral copper carbenoid generated from the decomposition of ethyl diazoacetate by a chiral copper chelate. This reaction furnished optically active products, suggesting that a chiral copper species is involved in the bond forming process. An improvement to this initial result was reported by Katsuki.[26] The enantiospecific ring expansion of 2-phenyloxetane **6** was realized by reacting it with *t*-butyldiazoacetate, CuOTf and chiral ligand **52** to yield **50** and **51** (Scheme 1.18). The resulting ring expansion had good levels of enantioselectivity but poor diastereoselectivity yielding essentially a 1:1 mixture of products **50** and **51**. Because the enantiopure products were formed from a racemic starting material, it suggests that the catalyst must be closely associated in the bond-forming step. Additional evidence for a metal associated mechanism

was provided by McKervey[27] in 1997 when he demonstrated the first use of a chiral rhodium (II) carboxylate catalyst in the [2,3]-sigmatropic rearrangement of an oxonium ylide by treatment of diazoketone **53** with chiral rhodium catalyst **55** to furnish **54** in excellent yield and modest enantioselectivity (Scheme 1.19). Although the results described above do suggest a metal bound mechanism, the asymmetric transformations could have arisen from the free ylide after dissociation of the metal but before inversion at the onium center.[16]



Scheme 1.19 Enantioselective [2,3]-sigmatropic shift of allylic ether **53**.

In 1998 Doyle[28] observed an interesting inversion of diastereoselectivity in the [2,3]-rearrangement of an allylic ether **56** (Scheme 1.19). A $Rh_2(OAc)_4$ catalyzed reaction primarily produced **57** as the major isomer; however, when chiral rhodium catalyst **59** was used, complete reversal of diastereoselectivity was



Scheme 1.20 Inversion of diastereoselectivity when using chiral catalysis.

observed with the formation of **58** as the major product. The author proposed that this catalyst-dependent diastereoselectivity indicates that during the bond-forming step the metal must be closely associated. The examples discussed in this section show the importance of ring size for oxonium ylide formation and the importance of the metal catalyst. Strong evidence for a metal associated/bound mechanism has been put forth by various groups and should lead to the development of more efficient catalysts for the generation and enantioselective rearrangement of oxonium ylides.

1.5 Rearrangements of Oxonium Ylides

The rearrangement of an oxonium ylide, resulting from the catalytic decomposition of a diazo compound in the presence of a metal, is a powerful reaction and is useful in the formation of a variety of interesting heterocycles and carbocycles. Potential reaction pathways are dependent on where the migrating group is located because in these rearrangements, the migrating group directs the reaction (Figure 1.5). If the migrating group (X) is exocyclic, once the oxonium

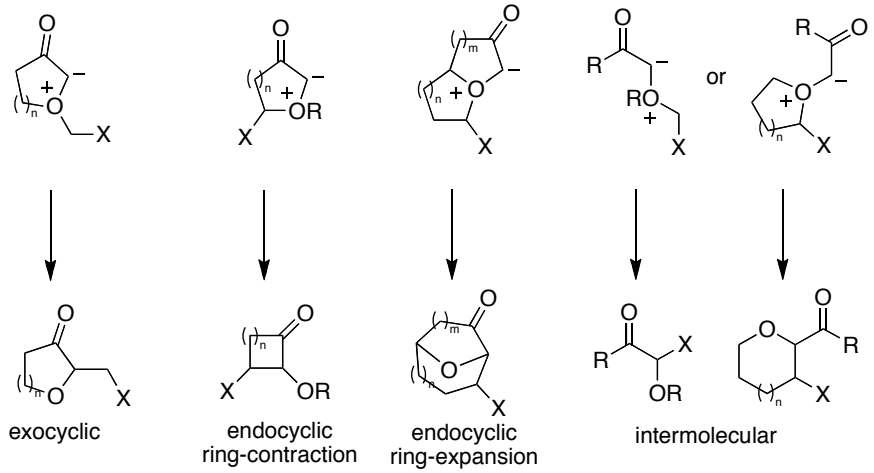
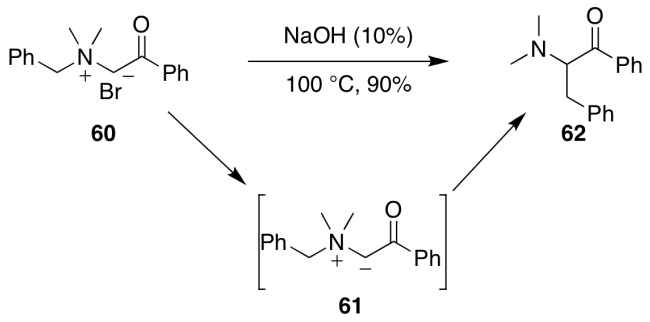


Figure 1.5 Possibilities in rearrangements of oxonium ylides.

ylide is formed, then the products obtained will be heterocyclic. On the other hand, when the migrating group is endocyclic either ring-contraction or ring-expansion can occur. Finally, intermolecular ylide generation can lead to ring expansion of an oxygen heterocycle or simple ether insertion followed by rearrangement. This section focuses on the intramolecular generation and rearrangement of oxonium ylides and the application of these reactions in synthesis.

1.5.1 [1,2]-shifts of Oxonium Ylides - The Stevens Rearrangement

In 1928 Stevens[29] observed an interesting rearrangement during attempts to find new nitrogen protecting groups. When ammonium salt **60** was reacted with NaOH at elevated temperature they found that the benzyl group migrated to the carbon α to the ketone providing **62** in excellent yield (Scheme 1.21). It was proposed that this rearrangement proceeded through an initial ylide **61** followed by [1,2]-migration of the benzyl group attached to the nitrogen. This reaction is now called the Stevens rearrangement and since this initial report it has enjoyed considerable attention in the generation and [1,2]-shift of onium ylides.[3,20] The Stevens rearrangement of oxonium ylides has been the least studied of the



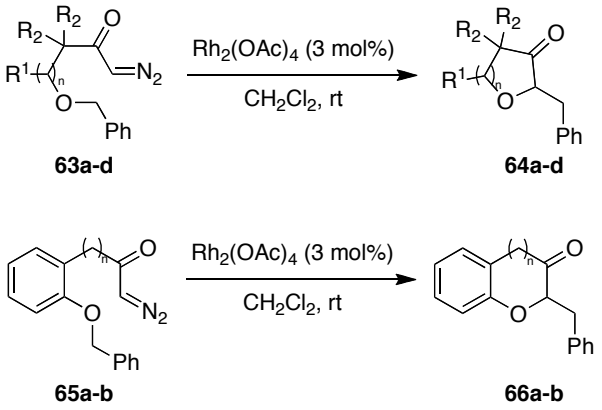
Scheme 1.21 The first reported Stevens Rearrangement.

onium ylide rearrangements. Since the development of mild catalytic methods for generating oxonium ylides from diazo compounds, the Stevens rearrangement of

oxonium ylides has been explored with considerable success. The early investigation by Johnson[11] demonstrated that the Stevens [1,2]-shift of catalytically generated oxonium ylides was an efficient and selective reaction and has inspired chemists to further investigate this class of reactive intermediates.

1.5.2. Synthesis of Heterocycles from the Stevens [1,2]-shift of Oxonium Ylides

Until 1992, the tandem oxonium ylide generation/Stevens [1,2]-shift protocol had received little attention in terms of synthetic utility beyond the initial report by Johnson.[11] At this time, West[12] published a route to substituted tetrahydrofuranones using this elegant chemistry. When a variety of diazoketones

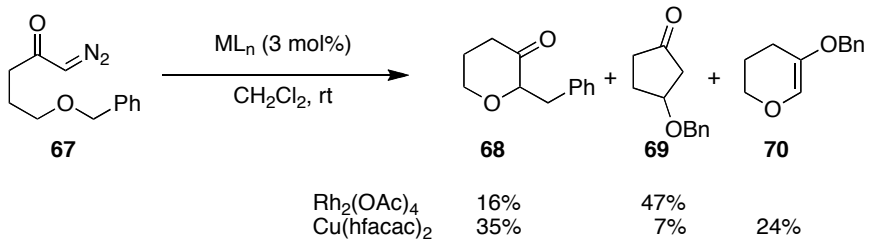


substrate	R^1	R^2	n	Product	Yield (%)
63a	H	H	1	**64a**	64
63b	H	Me	1	**64b**	65
63c	H	H	2	**64c**	16
63d	Me	H	1	**65d**	52
65a	-	-	0	**66a**	70
65b	-	-	1	**66b**	67

Table 1.4 Synthesis of 3-tetrahydrofuranones **64a-d** from a Stevens [1,2]-shift.

63a-d and **65a-b** were reacted with catalytic $Rh_2(OAc)_4$, products **64a-d** and **65a-b**, resulting from a Stevens rearrangement of an oxonium ylide, were isolated (Table 1.4). These products were isolated in moderate to good yield from the corresponding diazoketones, thus providing access to substituted tetrahydrofuranones.

Two years later, West[13] demonstrated that the choice of catalyst affected the product distribution of the Stevens rearrangement. When diazoketone **67** was subject to decomposition by rhodium or copper catalysis, products **68**, **69**, and **70** were formed in varying yields (Scheme 1.22). Using $Rh_2(OAc)_4$ as a catalyst primarily furnished the C-H insertion product **69** in 47% yield. Copper catalysis yielded the desired product **68** as the major component with **69** and [1,4]-shift product **70** as the minor components. Interestingly, the [1,4]-product was not isolated or detected in the rhodium-catalyzed reaction, suggesting that different mechanisms are at work when the catalyst is changed

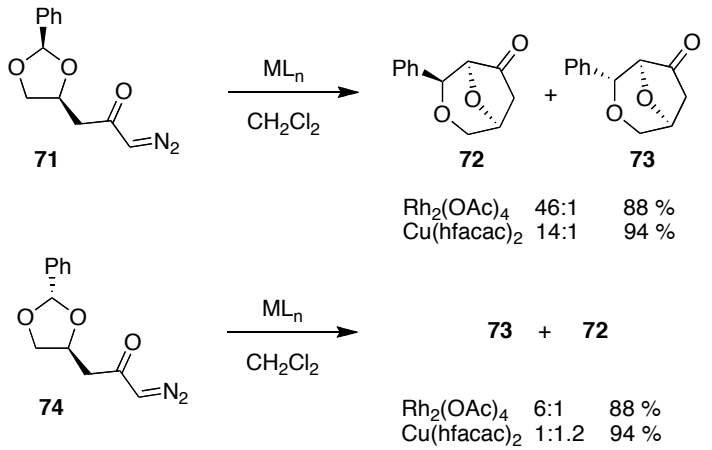


Scheme 1.22 Catalyst effects in the rearrangement of benzyl ether **67**.

from rhodium to copper. Another interesting observation is that no homodimers were isolated from any of the copper-catalyzed cases suggesting once again that the role of the metal is important during the rearrangement step.

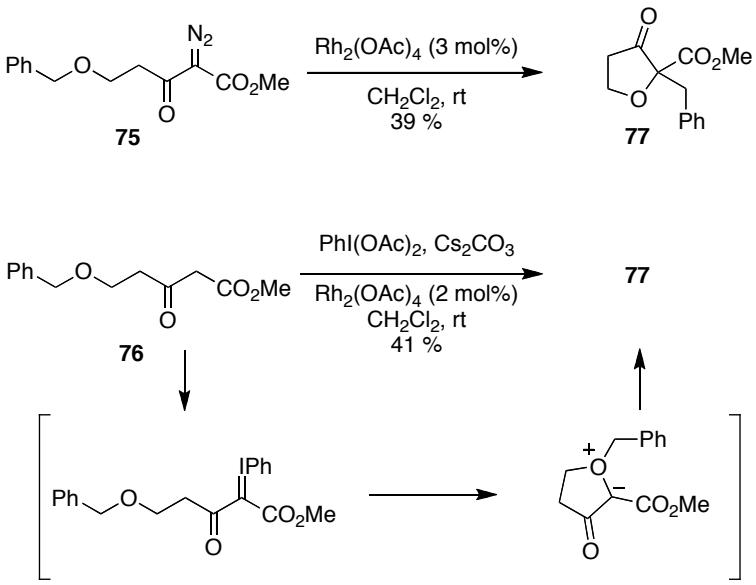
The synthesis of medium-sized heterocycles can also be achieved using this chemistry as reported by West.[30] In this report, a variety of cyclic acetals with pendent diazoketones were subjected to catalytic metal conditions to produce

ring-expanded products in good to excellent yields (Scheme 1.23). Interestingly, one acetal isomer **71** rearranged with substantial or complete retention of stereochemistry. On the other hand anomer **73** rearranged with inversion of stereochemistry, in the presence of $Rh_2(OAc)_4$, which was attributed to fast bond rotation in comparison to carbon-carbon bond formation in the presumed biradical intermediate. The analogous copper catalyzed reaction produced essentially a 1:1 mixture of diastereomers suggesting, as discussed previously, that rhodium and copper catalyzed reactions may operate by different mechanisms. This reaction proved to be an excellent entry into medium-sized cyclic ethers containing an oxygen bridge.



Scheme 1.23 Synthesis of cyclic ethers **72** and **73** by a Stevens rearrangement.

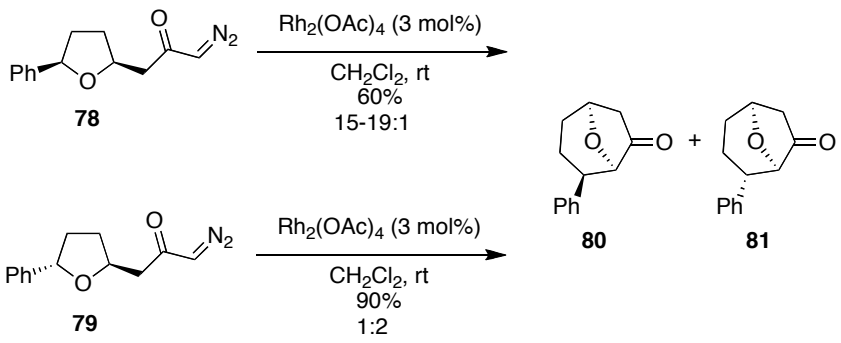
A recent example to come out of the West[31] group explored the direct conversion of active methylene-containing compounds to oxonium ylides via *in situ* generated iodonium ylides. It was found that in the presence of a metal catalyst [1,2]-shift products were produced in comparable yields to the method using of the diazoketones to access the same oxonium ylide intermediates (Scheme 1.24). Diazoketoester **75** was found to undergo the Stevens rearrangement to yield furanone **77** in 39% yield. The new one-pot procedure proved to be more efficient and afforded **77** in a 41% yield over two steps from **76**.



Scheme 1.24 In situ generation of oxonium ylide.

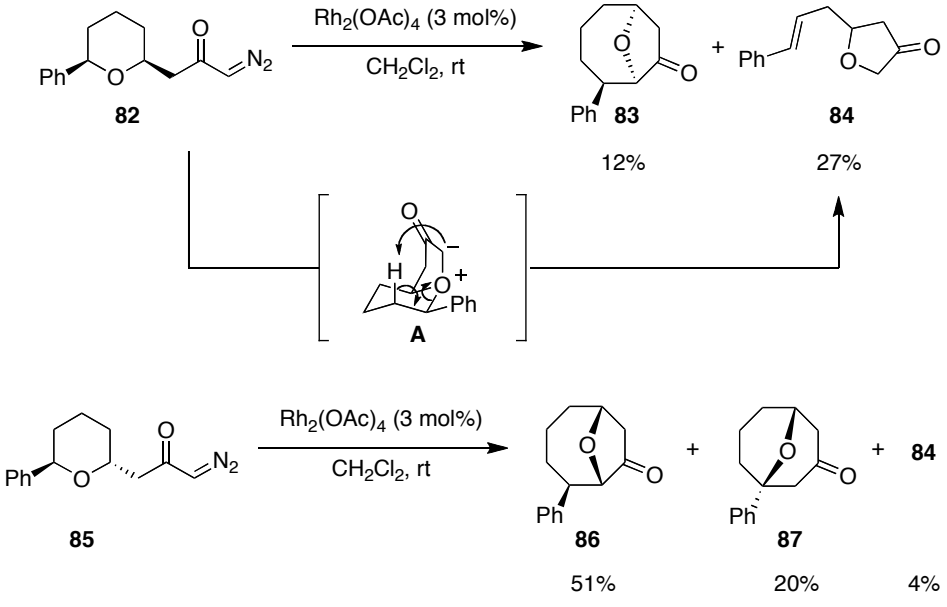
1.5.3 Synthesis of Carbocycles via an Oxonium Ylide Stevens Rearrangement

The synthesis of a variety of carbocyclic molecules can be achieved by using a migrating group that is in the ring. This allows for the selective synthesis of ring sizes varying from as small as four to as large as eight. Work by Johnson[11] provided the earliest example of this selective synthesis. In this work, detailed earlier in this chapter, various diazoketones efficiently furnished cyclobutanones in good yields (Scheme 1.4). In 1994 West[15] extended this chemistry to demonstrate that if the migrating group was part of a fused bicyclic oxonium ylide intermediate, the resulting rearrangement would lead to an ether-bridged medium-sized ring. For example, when diazoketone **78** was reacted with catalytic rhodium acetate, it afforded a moderate yield of ring-expanded products **80** and **81** with excellent diastereoselectivity and retention of stereochemistry (Scheme 1.25).



Scheme 1.25 Stevens rearrangement furnishing ether bridged seven-membered ring **80** and **81**.

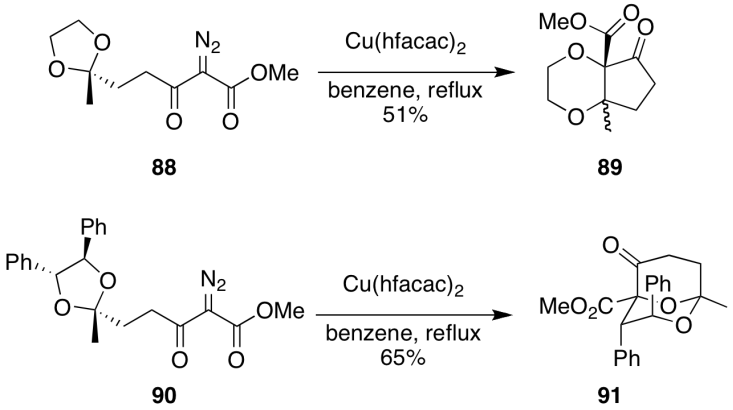
The *trans* compound **79** successfully rearranged under identical reaction conditions in excellent yield but with poor diastereoselectivity; however, overall retention of stereochemistry was observed. The decrease in stereoselectivity was rationalized as the result of slow carbon-carbon bond formation allowing for



Scheme 1.26 Stevens rearrangement of tetrahydropyran diazoketones

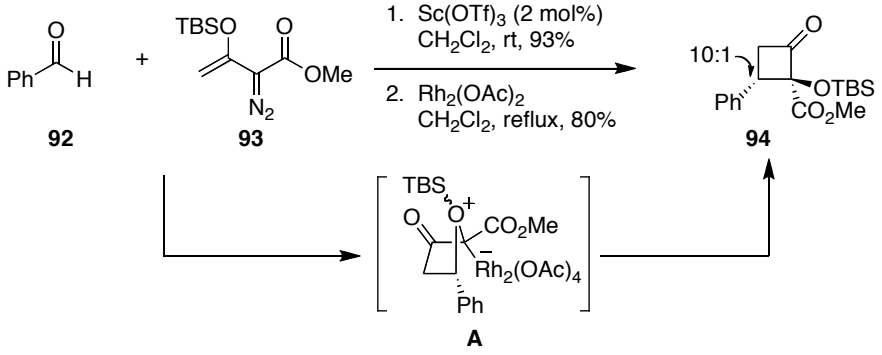
randomization of the biradical intermediates to occur. Interestingly when the starting heterocycle was changed from the five to the six-membered ring **82**, a poor yield of the *cis*-product **83** was obtained, as a single diastereomer, with an additional product **84** arising from α',β-fragmentation of the bicyclic oxonium ylide (Scheme 1.26). The *trans*-tetrahydropyran **85** efficiently produced the cyclooctanone **86** as a single diastereomer in 50% yield with retention of stereochemistry along with 20% of the C-H insertion product **87** and only a minor amount of product **84**. The α',β-fragmentation product **84** was thought to come from deprotonation of the axial hydrogen atom by the basic ylide **A** leading to internal elimination.

Zercher described the use of cyclic acetals as the directing group for the Stevens rearrangement of oxonium ylides. The first report[32] showed that diazoketone **88** could be reacted with $Cu(hfacac)_2$ to generate the oxonium ylide intermediate, which rearranged to give **89** in moderate yield. Zercher commented that the catalyst had to be pre-dried or the water present would facilitate formation of the α',β-fragmentation product. A year later[33] he demonstrated that diazoketone **90** did not furnish analogous products, but gave rise to **91** as a single diastereomer in good yield. In this example migration occurred on the benzylic carbon of the acetal and not the ketal carbon observed in the previous case. The presence of the phenyl radical stabilizing group promotes the exocyclic shift instead of the endocyclic shift.



Scheme 1.27 Zercher Stevens rearrangements directed by ketals.

In 2005, Doyle[34] illustrated the efficient construction of highly substituted cyclobutanones using oxonium ylide rearrangement. In this report diazoacetoacetate **93** was found to undergo a $Sc(OTf)_3$ catalyzed Mukaiyama aldol addition with aromatic and aliphatic aldehydes. These products then

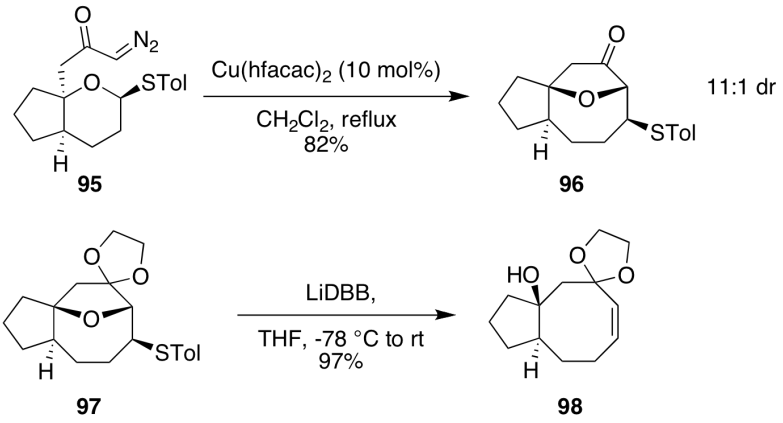


Scheme 1.28 Cyclobutanone **94** formation via oxonium ylide [1,2]-shift.

underwent $Rh_2(OAc)_4$ catalyzed ring closure to form cyclobutanones with high diastereocontrol. This is seen in the example of benzaldehyde **92** and diazoacetoacetate **93** wherein Mukaiyama aldol addition and subsequent reaction with catalytic $Rh_2(OAc)_4$ led to the formation of the cyclobutanone **94** in an excellent yield and as a 10:1 mixture of diastereomers (Scheme 1.28). The efficiency of this reaction was surprising because desilylation of intermediate **A** could potentially be a competing process. This Stevens rearrangement was believed to proceed through intermediate **A**, which accounts for the high stereoselectivity in this reaction.

A similarity among the examples discussed in this section is the presence of an aryl group or an oxygen atom attached to the migrating carbon. Although these groups are effective, development of other stabilizing groups for the Stevens rearrangement needed to be investigated. In 2003 West[35] reported an alternative to phenyl or oxygen stabilizing groups in the ring expansion to form medium sized rings by using a mixed monothioacetal, in which an aryl sulfide serves as

the directing group for this rearrangement. Construction of cyclooctanoid **96** was achieved in excellent yield and diastereoselectivity by reacting diazoketone **95** with $Cu(hfacac)_2$ in CH_2Cl_2 at reflux (Scheme 1.29). The product **96** was obtained with predominant retention of configuration, suggesting rapid recombination of the presumed biradical intermediate with very little randomization through bond rotation. After protection of the ketone, ketal **97** could be subjected to reductive desulfurization conditions, resulting in eliminative opening of the bridging ether to give **98**. Thus, the aryl sulfide serves two important functions: first as a highly effective directing group for the [1,2]-shift, then as a trigger for the cleavage of the ether bridge to install a bridgehead alcohol and an alkene.



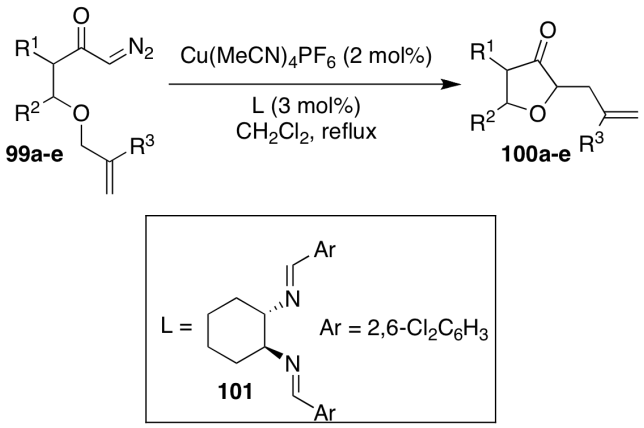
Scheme 1.29 Sulfur-directed Stevens rearrangement and ether bridge opening.

1.6 Oxonium Ylide [2,3]-Sigmatropic Rearrangements

The [2,3]-sigmatropic shift of a catalytically generated oxonium ylide has enjoyed considerable attention since its discovery by Pirrung[10] and Johnson.[11] This section will illustrate the synthetic utility of this process in the synthesis of hetero- and carbocycles with regio-, diastereo- and enantioselectivity.

1.6.1 Applications of Oxonium Ylide [2,3]-shifts: Heterocycle formation

Pirrung first showed that a variety of heterocycles could be constructed by the [2,3]-rearrangement of an oxonium ylide intermediate. Since this report many chemists have showcased the utility of this reaction in the synthesis of a variety of interesting heterocycles. Clark[36] demonstrated that this transformation could be achieved asymmetrically using chiral copper carbenoids. Reacting a series of diazoketones **99a-e**



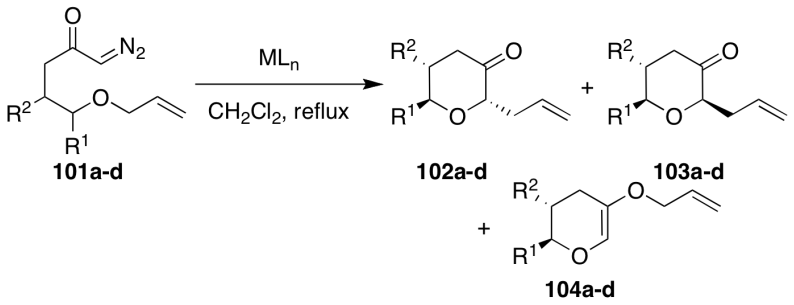
Substrate	R^1	R^2	R^3	Yield (%)	ee (%)
99a	H	H	H	62	57
99b	Me	H	H	57	56
99c	H	Me	H	54	23
99d	H	H	Me	62	6
99e	Me	H	Me	92	42

Table 1.5 Enantioselective [2,3]-shift of diazoketones **99a-e**.

with $Cu(MeCN)_4PF_6$ in the presence of chiral ligand **101** affords furanones **100a-e** in good to excellent yields with moderate enantioselectivity (Table 1.5). The substituent pattern of the starting diazoketones **99a-e** had an overwhelming effect on the level of enantiocontrol. Substitution adjacent to the ether-oxygen of **99c** or on the 2-position of the allyl group **99d**, dramatically reduced the enantiocontrol.

Substitution next to the ketone appeared to have no effect on the enantioselectivity at all. The preparation of five-membered cyclic ethers was could be achieved enantioselectively via oxonium ylide [2,3]-rearrangement.

Clark[37] has also shown that excellent diastereoselectivities can be obtained during the synthesis of tetrahydropyran-3-ones. In these reactions the thermodynamically less favorable *trans*-isomer **102a-d** predominated in all of



Subst.	R^1	R^2	ML_n	Yield **102** + **103** (%)	Ratio **102:103**	Yield (%) **104**
101a	Me	H	$Cu(acac)_2$	28	92:8	4
101a	Me	H	$Cu(tfacac)_2$	65	91:9	5
101a	Me	H	$Cu(hfacac)_2$	68	78:22	10
101b	i-Pr	H	$Cu(acac)_2$	40	96:4	7
101b	i-Pr	H	$Cu(tfacac)_2$	64	94:6	9
101b	i-Pr	H	$Cu(hfacac)_2$	65	76:24	13
101b	i-Pr	H	$Rh_2(OAc)_4$	17	21:79	0
101c	H	i-Pr	$Cu(acac)_2$	80	81:19	0
101c	H	i-Pr	$Cu(tfacac)_2$	71	70:30	0
101c	H	i-Pr	$Cu(hfacac)_2$	72	69:31	0
101d	H	Ph	$Cu(acac)_2$	61	86:14	0

Table 1.6 Diastereoselective [2,3]-shift of diazoketones **101a-d**.

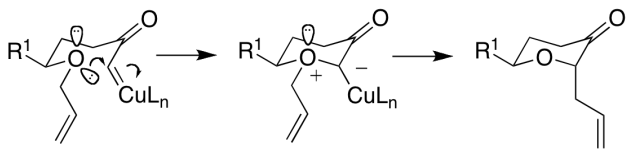
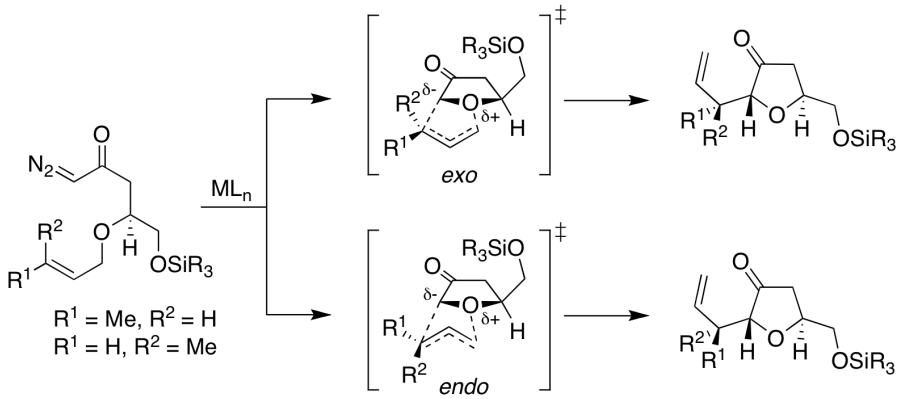


Figure 1.6 Rationalization for diastereoselectivity in the [2,3]-shift.

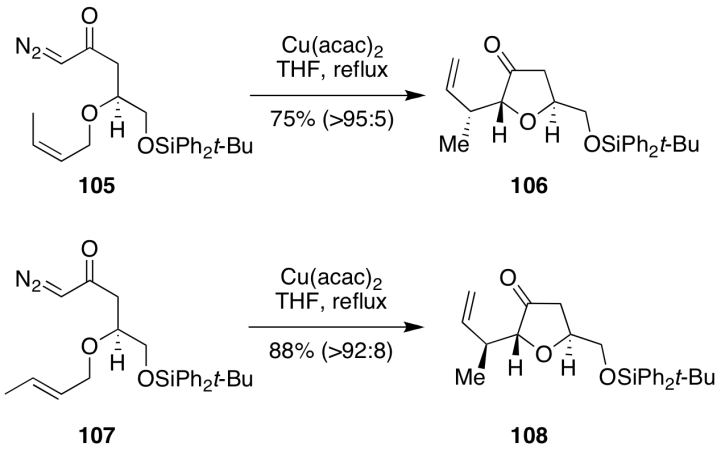
the copper catalyzed examples (Table 1.6). However, when rhodium was used there was a reversal in diastereoselectivity observed, yielding the favored *cis*-isomer **103a-d** albeit in poor yield. Clark proposed that these observations support a metal associated mechanism because the rearrangement of the free ylide would afford the same product ratios regardless of the catalyst used. From these results it was apparent that better yields were observed for products **101c,d** but the level of diastereocontrol was inferior to the products **102** and **103**. Clark rationalized the diastereoselectivity by explaining that the lone pairs on the ether-oxygen are diastereotopic, and attack of the lone pair will be dictated by the six-membered intermediate where the allyl group and the substituent are in equatorial positions (Figure 1.6).

These two reports from the Clark group demonstrate the efficiency and stereoselectivity of the [2,3]-rearrangement of an oxonium ylides and recently this



Scheme 1.30 Potential reaction pathways for the [2,3]-shift towards the synthesis of the gambieric acids.

chemistry was used in their synthesis of the A-ring fragment of the gambieric acids.[38] This key reaction was pivotal in closing the heterocyclic ring and in the creation of two stereogenic centers. The rearrangement could potentially proceed through the *exo* or *endo* transition state, so it was important to examine the geometry of the double bond in the allylic ether starting material (Scheme 1.31). To determine which isomer would provide the desired furanone, (*Z*)- and (*E*)-isomers **105** and **107** were both prepared and treated with $Cu(acac)_2$ in THF at reflux to furnish the furanones **106** and **108** in good yields and excellent

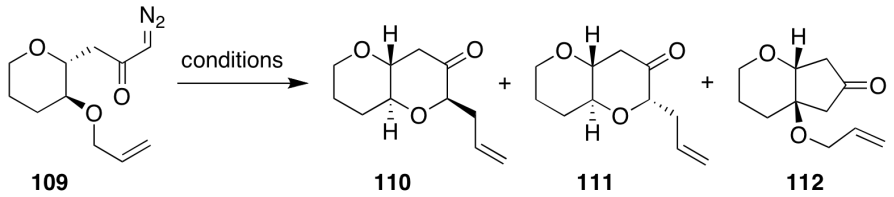


Scheme 1.31 Importance of double bond geometry in the [2,3]-shift of **105** and **107**.

diastereoselectivities (Scheme 1.31). Only two of the four possible diastereoisomers were obtained, and no *cis*-isomers were formed. Confirmation from X-ray analysis confirmed that the [2,3]-shift occurred via the *endo* transition state; therefore the *E*-crotyl ether **107** was used to provide the proper relative stereochemistry for the natural product. This work showed that the A-ring fragment could be constructed in an efficient 12-step route highlighted by the diastereoselective [2,3]-rearrangement of an oxonium ylide.

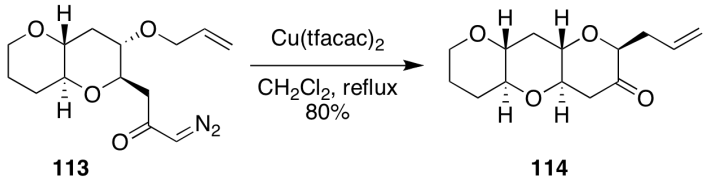
West[39] applied the stereoselective oxonium ylide [2,3]-shift in an iterative synthesis of polycyclic ethers. $Cu(hfacac)_2$ and $Cu(tfacac)_2$ were chosen as catalysts to favor six-membered oxonium ylide formation from allylic ether **109**

over the potential five-membered C-H insertion product **112**. The optimal copper catalyst was found to be $Cu(tfacac)_2$ furnishing the desired products **110** and **111** in good yield and excellent diastereoselectivity (entry 4, Table 1.7). Interestingly when $Rh_2(OAc)_4$ was used the diastereoselectivity was reversed and the C-H insertion product, cyclopentanone **112**, was now a prominent product.



Entry	Catalyst/mol%	Addn time	Solvent	Ratio **110:111:112**	Yield (%) **110,111**	Yield (%) **112**
1	$Cu(hfacac)_2$/10	3 h	CH_2Cl_2	1:5:1	36	5
2	$Cu(tfacac)_2$/10	3 h	CH_2Cl_2	1:40:2	66	-
3	$Cu(tfacac)_2$/5	3 h	CH_2Cl_2	1:30:2	72	-
4	$Cu(tfacac)_2$/5	5 min	CH_2Cl_2	1:30:2	80	-
5	$Cu(tfacac)_2$/10	3 h	$PhCH_3$	1:15:6	-	-
6	$Rh_2(OAc)_4$/3	3 h	CH_2Cl_2	4:1:5	32	27

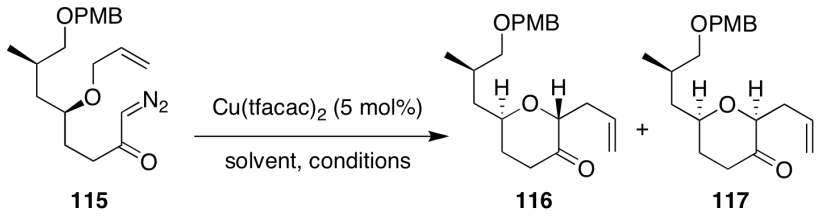
Table 1.7 Catalyst optimization for the iterative synthesis of polycyclic ethers.



Scheme 1.32 Second iteration in the synthesis of polycyclic ethers.

Compound **110** was subjected to the reaction conditions ($Rh_2(OAc)_4$, CH_2Cl_2, reflux) for the formation of **111** and no epimerization was observed. West suggested that a metal-associated ylide in the product-forming step is the origin of the catalyst dependent diastereoselectivity but this phenomenon is not fully understood. Compound **111** could be converted to **110** in three steps with an epimerization/reduction/oxidation protocol. Compound **110** was converted to diazoketone **113** and was found to undergo the second iteration in an 80% yield affording a single detectable diastereomer **114** (Scheme 1.32). This isomer could be epimerized to a 10:1 mixture of the desired stereoisomer proving that an iterative process using the [2,3]-shift of an appropriate oxonium ylide is an effective approach to poly(pyran) scaffolds.

Yakura[40] reported a route to the dihydropyran portion of laulimalide using a copper-catalyzed oxonium ylide [2,3]-shift. Diazoketone **115** was prepared by a short synthetic sequence and, under catalytic copper conditions, was found to

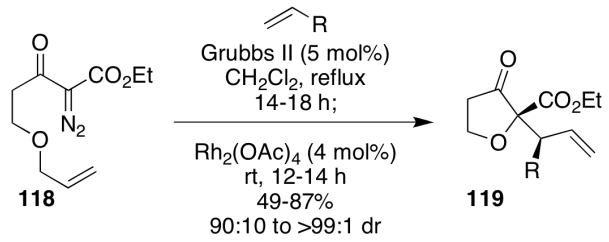


Entry	Solvent	Conditions	Yield (%)	*trans:cis*
1	CH_2Cl_2	rt, 7 h	Quant.	80:20
2	THF	rt, 19 h	56	>99:1
3	THF:CH_2Cl_2 (1:1)	rt, 7 h	98	86:14
4	THF:CH_2Cl_2 (4:1)	rt, 15 h	59	95:5
5	THF:CH_2Cl_2 (4:1)	reflux, 4 h	82	97:3

Table 1.8 Copper-catalyzed [2,3]-rearrangement towards the synthesis of laulimalide.

form the desired pyranone unit **116** in good yield and excellent stereoselectivity (Table 1.8). The key to this rearrangement was the solvent and was found to proceed best with $Cu(tfacac)_2$ in a 4:1 mixture of CH_2Cl_2 to THF. This unusual solvent mixture was used because CH_2Cl_2 produced consistently better yields and THF produced better stereoselectivity. Pyranone **116** could be converted to a known intermediate in the total synthesis of laulimalide.

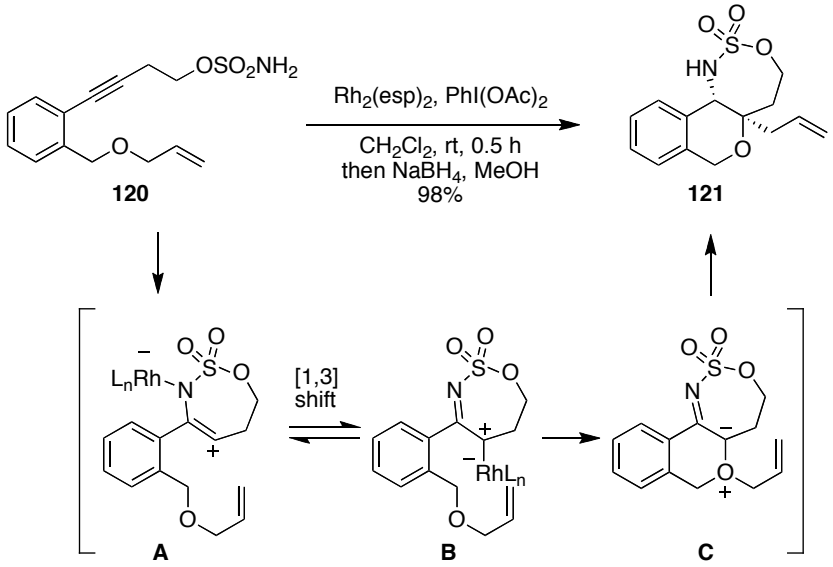
Hodgson[41] has recently developed a general method for manipulation of the allyl migrating group in a one-pot cross-metathesis/oxonium ylide formation-rearrangement sequence (Scheme 1.33). This reaction was first conducted in a two-step fashion but Hodgson was encouraged by the ability of **118** to undergo stereoselective cross-metathesis in the presence of diazo and allylic ether functionalities; therefore, a one-pot protocol was adopted and **118** was found to yield a variety of different furanones **119** in good yields and diastereoselectivities. The rearrangement was found to proceed through an *endo* transition state, yielding high diastereoselectivity for the *E*-isomers. This is not surprising because in Clark's approach to the gambieric acids, seen earlier in this section, similar substrates rearranged through an *endo* transition state.



Scheme 1.33 One-pot cross-metathesis oxonium ylide formation-rearrangement.

Recently Blakey[42] has reported a tandem metallonitrene alkyne metathesis/oxonium ylide rearrangement process yielding a variety of heterocycles in good to excellent yields. In this work sulfamate ester **120** is

converted to the metallonitrene using $PhI(OAc)_2$ and 2 mol% $Rh_2(esp)_2$ followed by attack by the alkyne to form intermediate **A**, a transient vinyl cation (Scheme 1.34). This cation is either directly trapped by attack from the ether oxygen or proceeds through a [1,3]-rhodium transfer **B** but once the oxonium ylide **C** is formed the [2,3]-rearrangement occurs to produce an N-sulfonyl imine and subsequent stereoselective reduction with $NaBH_4$ occurs to give bicyclic product **121** in excellent yield.

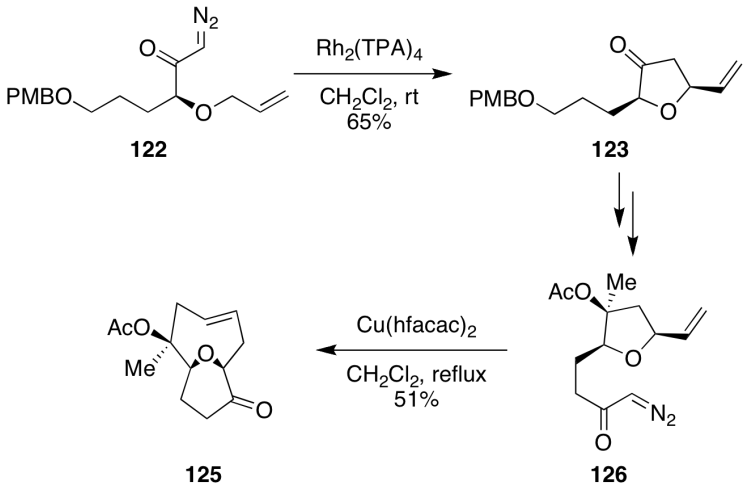


Scheme 1.34 Tandem metallonitrene alkyne metathesis/oxonium ylide rearrangement.

1.6.2 Applications of Oxonium Ylide [2,3]-shifts: Synthesis of Carbocycles.

The Clark group has had an interest in the synthesis of a variety of highly oxidized sesquiterpene lactones. Their approach to these structures utilizes an oxonium ylide [2,3]-rearrangement that results in ring expansion to give a medium-sized carbocycle containing an ether bridge. This strategy also utilizes another powerful carbenoid reaction, C-H insertion, for the construction of the

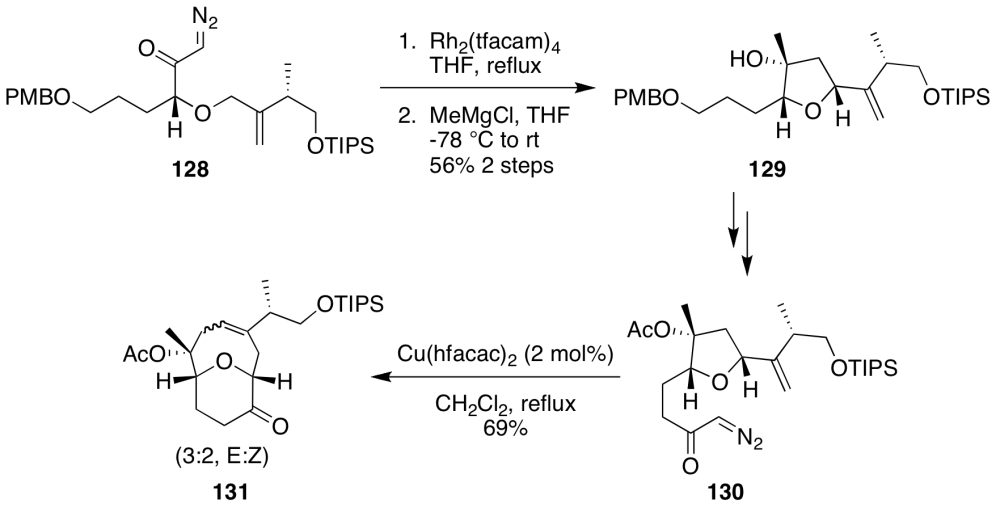
furanone precursor. In 1996 Clark[43] first reported an approach to these types of molecules in the stereoselective synthesis of the bicyclic core of neoliacinic acid. The synthesis of furanone **123** was achieved by reacting diazoketone **122** with catalytic $Rh_2(O_2CCPh_3)_4$ affording the C-H insertion product **123** in good yield, although significant levels of the product of a competing cyclopropanation process were seen. The furanone **123** was elaborated to the desired diazoketone in five steps and the key ring expansion was realized by reacting diazoketone **126** with $Cu(hfacac)_2$ in CH_2Cl_2 at reflux to furnish **125** in moderate yield (Scheme 1.35). When this reaction was conducted with catalytic $Rh_2(OAc)_4$ a 1:1 mixture of *cis* and *trans* double bond isomers was formed in a moderate combined yield.



Scheme 1.35 First generation approach to neoliacinic acid.

Clark rationalized the poor stereoselectivity by suggesting that the rhodium catalyst was isomerizing the double bond under these conditions. This was confirmed when compound **125** was shown to isomerize in the presence of $Rh_2(OAc)_4$ in a 90% yield. A second-generation approach was reported by Clark[44] in 2008 where the synthesis of the tricyclic core of neoliacinic acid was realized using the same strategy seen above. After extensive optimization of the C-H insertion reaction, $Rh_2(tfacam)_4$ was found to be the optimal catalyst for this

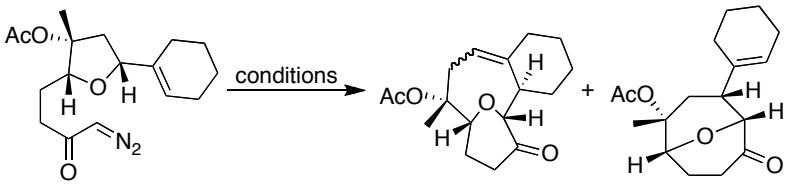
transformation. This was apparent when diazoketone **128** underwent efficient C-H insertion affording the desired furanone, which was directly subjected to MeMgCl without isolation to yield alcohol **129** in good yield over two steps (Scheme 1.36). Alcohol **129** was then converted to the diazoketone **130**, which, was smoothly converted to the ring expanded product **131** in good yield as a 3:2 mixture of *E:Z* isomers. The thermodynamically favored *Z*-alkene was obtained in quantitative yield by exposure of the alkene



Scheme 1.36 Second-generation approach to the bicyclic core of neoliacinic acid.

mixture **131** to ethanethiol and AIBN in benzene at reflux. Clark has also applied this strategy towards a related natural product, labiatin A.[45] The diazoketone **132** was made using a C-H insertion protocol similar to the one described above and was found to rearrange smoothly, affording the tricyclic structure **133** in poor to good yield depending on the reaction conditions used (Table 1.9). The major by-product observed was the [1,2]-shift product **134**, the formation of which could be suppressed upon changing the solvent to benzene albeit with a dramatic decrease in the overall yield. The mixture of double bond isomers in the desired product **133** could be isomerized under the same reaction conditions described above. These three reports by Clark have shown that the intramolecular C-H insertion

and oxonium ylide formation/rearrangement sequence is an efficient way to construct these interesting molecules.

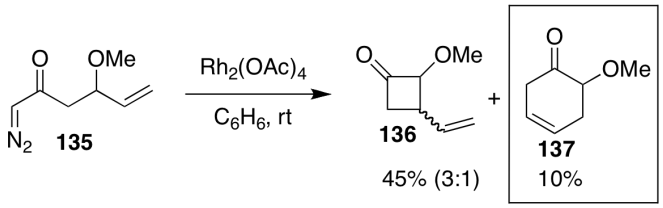


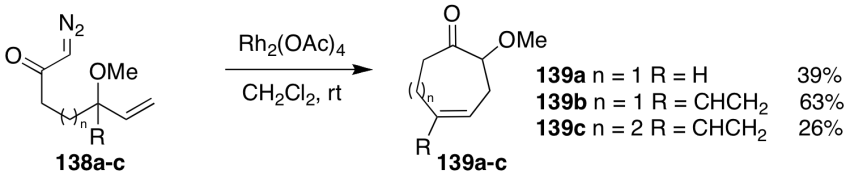
132 **133** **134**

Entry	ML_n	Solvent	Yield **133** + **134** (%), Ratio **133**:**134**	Ratio **133** (*E*:*Z*)
1	$Cu(hfacac)_2$	CH_2Cl_2	83, 2:1	3:2
2	$Cu(hfacac)_2$	C_6H_6	52, 6:1	4:1
3	$Cu(acac)_2$	CH_2Cl_2	35, 2:1	1:1
4	$Rh_2(OAc)_4$	CH_2Cl_2	22, 3:1	1:6

Table 1.9 Synthesis of tricyclic core of liabiatin A.

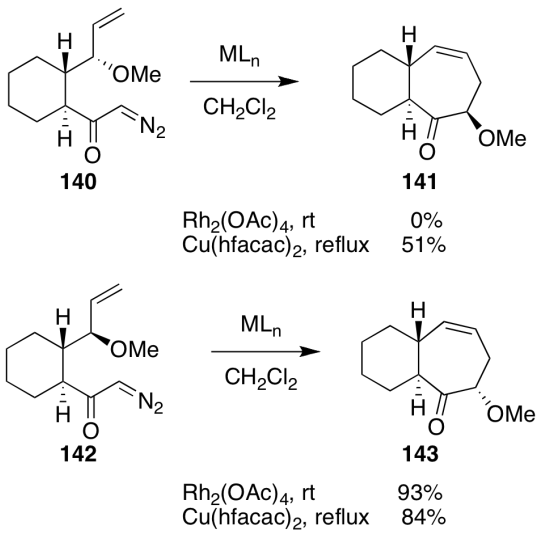
Recently, Clark[46] has also used [2,3]-rearrangements of oxonium ylides in the construction of medium-sized carbocycles. This chemistry was inspired by Johnson's[11] original report where in treatment of the diazoketone **135** with $Rh_2(OAc)_4$ afforded cyclobutanone **136** as the major product accompanied by only minor amounts of [2,3]-shift product **137**. Clark wondered if this strategy could





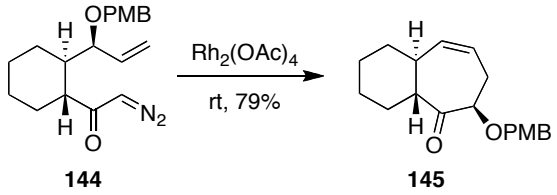
Scheme 1.37 Medium-sized ring synthesis by a [2,3]-rearrangement of allylic ethers.

be modified to yield larger rings via a [2,3]-rearrangement instead of ring-contraction via a vinyl stabilized [1,2]-shift pathway. Acyclic diazoketones **138a-c** were found to undergo ring expansion to furnish medium-sized carbocycles **139a-c** in poor to good yields (Scheme 1.37). The reason that diazoketones **138a-c** are able to undergo the [2,3]-rearrangement was due to the vinyl group being suitably orientated for rearrangement while in Johnson's case, it was not. Success with this transformation prompted Clark[47] to investigate polycyclic systems. Cyclic diastereoisomeric diazoketones **140** and **142** were prepared and underwent ylide formation and rearrangement when treated with either $Cu(hfacac)_2$ or $Rh_2(OAc)_4$ to furnish the [2,3]-shift products **141** and **143** respectively (Scheme 1.38). Interestingly, the configuration at the methoxy-substituted centre had a strong effect on the outcome: while **142** underwent clean rearrangement to **143** in excellent yield with either catalyst, diastereomer **140** gave diminished yields of **141** with $Cu(hfacac)_2$ and none at all with $Rh_2(OAc)_4$. Clark suggests that, in the case of the ylide derived from substrate **142**, the relative configurations of the stereogenic centers deliver a favorable low energy conformation, facilitating [2,3]-rearrangement, whereas in the other case they do not. In these bicyclic cases



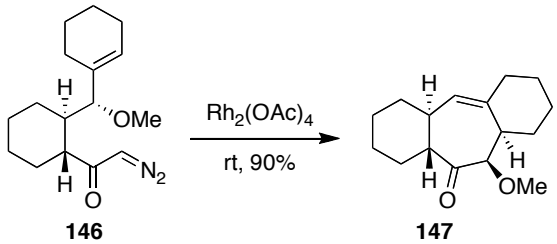
Scheme 1.38 Construction of fused medium-ring carbocycles **141** and **143**.

the only isolable products are derived from the [2,3]-rearrangement pathway while no products arising from [1,2]-shift or cyclopropanation are observed. However, the $Rh_2(OAc)_4$ catalyzed reaction of diazoketone **140** instead produces a diastereomeric mixture of [1,2]-shift products along with a minor amount of C-H insertion products. Clark[48] broadened the scope of this reaction by using an ether substituent other than a methyl group to allow for further functional group manipulation after deprotection. Towards this end the PMB ether **144** was investigated, and was found to undergo smooth conversion to the desired bicyclic product **145** (Scheme 1.39). Bicyclic diazoketone **146** was also prepared and gave the [2,3]-rearrangement product **147** in an excellent yield as a single diastereomer (Scheme 1.40). Clark's findings show that monocyclic, bicyclic and



Scheme 1.39 Alternative protecting group strategy.

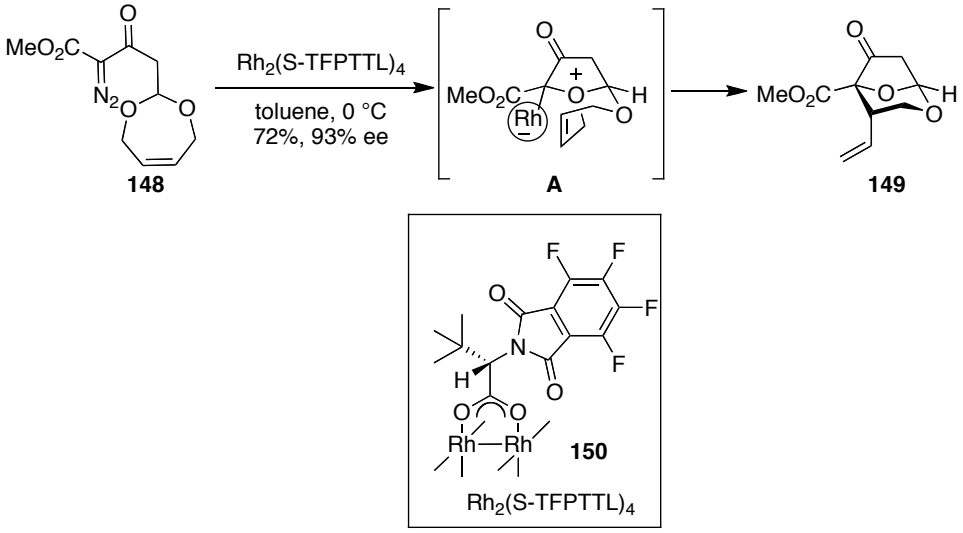
tricyclic systems containing a seven-membered ring can be efficiently constructed via carbenoid generation, ylide formation, and [2,3]-sigmatropic rearrangement. However, Clark explains that the success of this transformation is highly



Scheme 1.40 Synthesis of tricyclic system.

dependent on the relative configuration of the stereocentres in the starting diazoketone substrates.

Recently Hashimoto[49] reported a concise and enantioselective synthesis of the zaragozic acid core by way of [2,3]-sigmatropic rearrangement of an oxonium ylide using chiral dirhodium(II) carboxylates. In this work, diazoketone **148** was

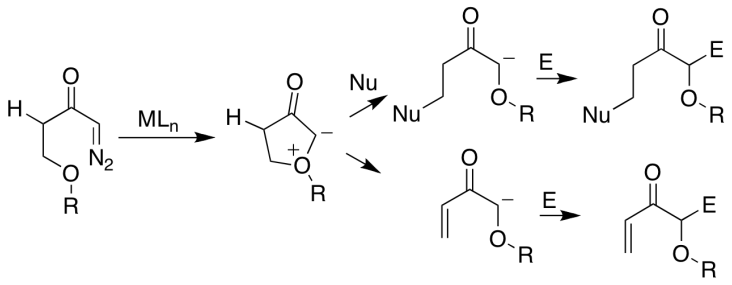


Scheme 1.41 Enantioselective [2,3]-rearrangement towards the synthesis of zaragozic acid .

treated with rhodium catalyst **150** in toluene generating the zaragozic acid core structure **149** in 72% yield and 93% ee (Scheme 1.41). The enantioselectivity is the highest ever reported for [2,3]-sigmatropic rearrangement of a cyclic oxonium ylide and was proposed to proceed through the relatively long-lived catalyst-bound oxonium ylide **A**.

1.7 Fragmentation, Nucleophilic Addition and Multicomponent Reactions

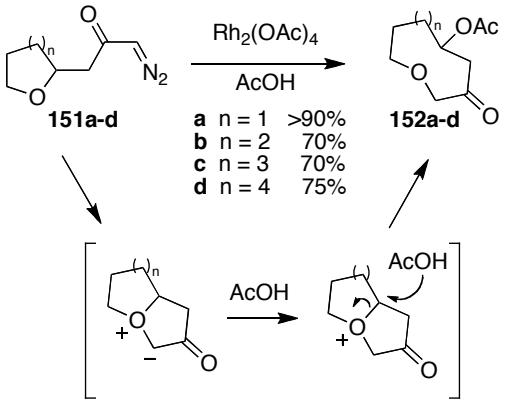
Intermolecular trapping of a metal enolate derived from an oxonium ylide is an attractive process involving multiple bond-forming events that may occur in a one-pot reaction. The generation of an oxonium ylide without a competent



Scheme 1.42 Potential fragmentation and nucleophilic trapping pathways.

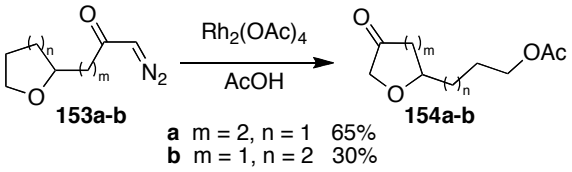
migrating group usually results in fragmentation of the oxonium ylide intermediate to provide an enolate, which can either be protonated or used as a nucleophile. If an external nucleophile is present in the reaction mixture, S_N2 displacement at one of the neutral carbons attached to the oxonium oxygen can occur leaving a metal enolate, which can undergo protonation or treated with an added electrophile (Scheme 1.42).

One of the earliest examples of this process was reported by Oku[50] wherein diazoketones **151a-d** were reacted with catalytic $Rh_2(OAc)_4$ in the presence of excess acetic acid furnishing the macrocyclic ethers **152a-d** in good to



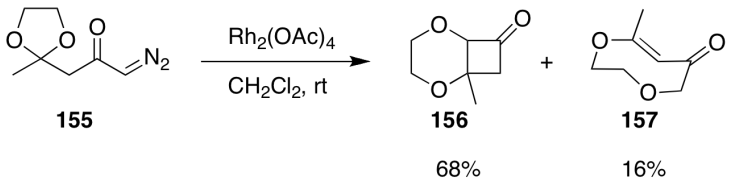
Scheme 1.43 Synthesis of macrocyclic ethers **152a-d**.

excellent yields (Scheme 1.43). Interestingly when oxonium ylide ring size was increased preferential attack was observed at the less substituted oxonium carbon giving rise to a ring-switching reaction (Scheme 1.44). Other nucleophiles were investigated and a trend was observed. Oku suggested that pKa and nucleophilicity played an important role in the reaction because methanol gave little or no ring-expanded product while acetic acid produced moderate to excellent yields of products.

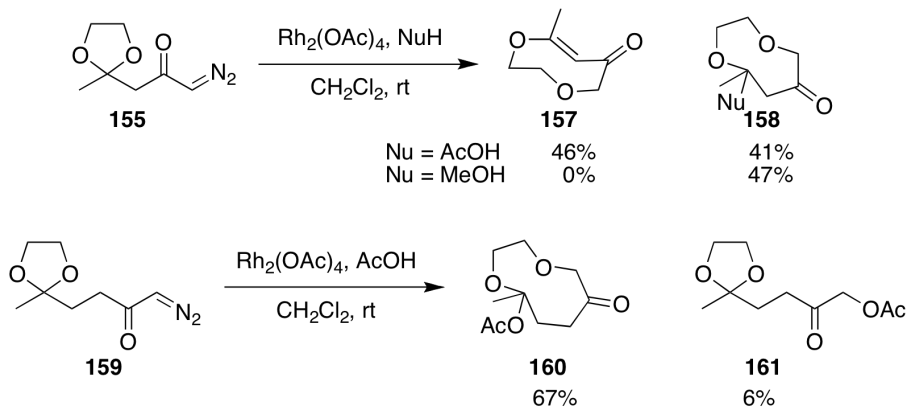


Scheme 1.44 Ring-switching reaction.

Next Oku[51] turned his attention to the ring expansion of cyclic acetals instead of the cyclic ethers previously described. This ring-enlargement was more difficult to predict because now there was potential for the [1,2]-shift pathway to operate with a competent oxygen-stabilizing group on the migrating carbon. The first substrate examined, **155**, had been previously shown by Johnson[11] to undergo ring contraction via [1,2]-shift to give **156**, along with minor amounts of fragmentation product **157** (Scheme 1.45). However, when the reaction was carried out in the presence of acetic acid, only **157** and nucleophilic displacement product **158** were obtained (Scheme 1.46). In the case of substrate **159**, bearing a

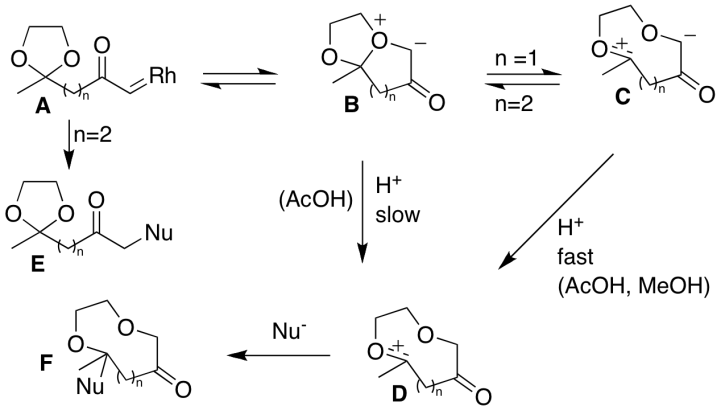


Scheme 1.45 Synthesis of cyclobutanone **156** by a Stevens rearrangement.



Scheme 1.46 Acetal ring expansion of diazoketones **155** and **159**.

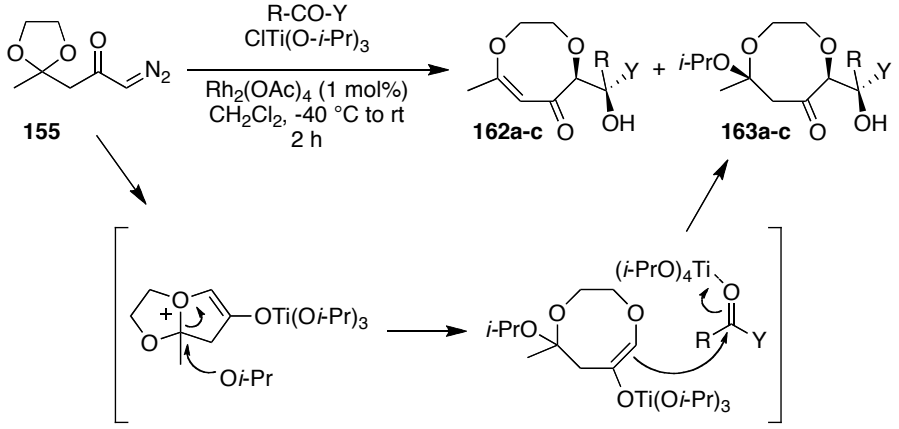
longer side-chain, only ring expansion product **160** and the simple metallocarbene-acetic acid adduct **161** were isolated. Oku rationalized his observations by suggesting the size of the oxonium ylide ring directly affects the products ratio. The formation of strained oxonium ylide intermediate **B** and the stabilities of both the ylides and their ring-opened monocyclic zwitterion **C** appear to be the dominant factors influencing the ring-enlargement products (Scheme 1.47). When AcOH is present the product ratios can be explained by the equilibrium between oxonium ylide **B** and metal carbenoid **A**. In the reactions where rearrangement must occur via a six-membered ylide the equilibrium may favor the metal carbenoid, which would allow formation of the product **E**. Exclusive formation of carbene trapping product **E** with MeOH when n = 2 was rationalized in terms of ineffective protonation of **B** by the weakly acidic MeOH, allowing the material to drain off via metallocarbene **A**. In the case of AcOH, cyclization can occur with subsequent slow protonation of the ylide intermediate **B** or formation of zwitterion structure **C** followed by fast protonation to lead to product **F** after nucleophilic attack. In the five-membered case MeOH can successfully aid in ring-expansion because the formation of five-membered oxonium ylide **B** will be fast and the strain of bicyclic oxonium ylide **B** will allow favorable fragmentation to monocyclic zwitterion **C**. Once intermediate **C** is generated, fast protonation will occur followed by trapping of the oxonium ion



Scheme 1.47 Possible mechanism for ring-expansion.

intermediate **D** by MeOH.

Recently Oku[52] has extended this methodology to carbon-carbon bond-forming reactions of acetal-derived oxonium ylides via metal-enolate intermediates. Oku found that treatment of diazoketone **155** with a catalytic

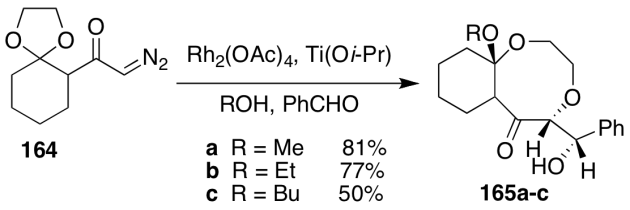


Substrate	R	Y	Yield of **162** (%)	Yield of **163** (%)
1	Styryl	H	66	28
2	Isopropyl	H	35	20
3	Phenyl	Me	37	5

Table 1.10 Carbon-carbon bond formation between oxonium ylides and aldehydes.

amount of $Rh_2(OAc)_4$ in the presence of $ClTi(O\textit{i}\text{-}Pr)_4$ resulted in C-C bond formation with a variety of aldehydes to provide good yields of aldol adducts **162** and **163** (Table 1.10)**.**

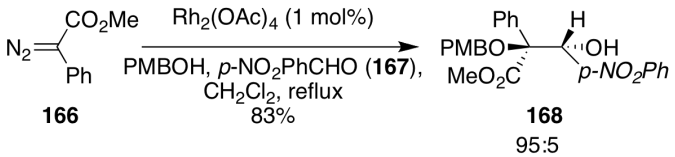
Muthusamy[53] reported similar findings in a highly diastereoselective tandem ring-enlargement and aldol-type process. In this work diazoketone **164**



Scheme 1.48 Three-component reaction.

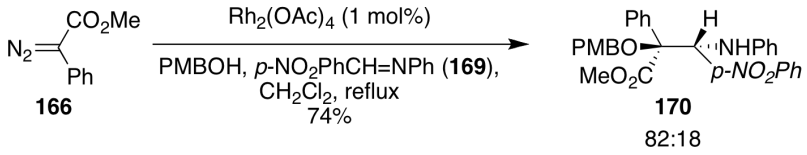
was found to undergo a three-component reaction in good yields furnishing **165a-c** as single diastereomers. Interestingly, trapping by the isopropyl group from the titanium can be suppressed by the addition of another alcohol nucleophile (Scheme 1.48).

In 2005 Hu[54] reported the first three-component reaction of aryl diazoacetates, alcohols, and aldehydes/imines. Previous work had postulated that OH-insertion reactions of metallocarbenes proceeded through a concerted, 3-centre transition state, rather than stepwise formation of an oxonium ylide followed by proton-transfer. However, these results clearly implicated the intermediacy of the ylide. For example, Hu found that reaction of phenyldiazoacetate **166** with PMBOH in the presence of $Rh_2(OAc)_4$ efficiently afforded an intermediate that could attack aldehyde **167** to give alcohol **168** in



Scheme 1.49 Trapping oxonium ylide with an aldehyde.

good yield and diastereoselectivity (Scheme 1.49). This approach also worked with imine **169** to afford amine **170** with the same efficiency and similar stereoselectivity (Scheme 1.50). Hu found that electron-rich alcohols were required for this reaction to be successful, as well as electron-deficient aldehydes or imines. In order to carry out the process with electron-rich aldehyde partners, it was necessary to include Lewis acid in the reaction mixture to avoid significant amounts of metallocarbene O-H insertion product. This work provides a convenient route to α,β-dihydroxy acid and α-hydroxy-β-amino acid derivatives via this interesting three-component reaction.



Scheme 1.50 Trapping oxonium ylide with an imine.

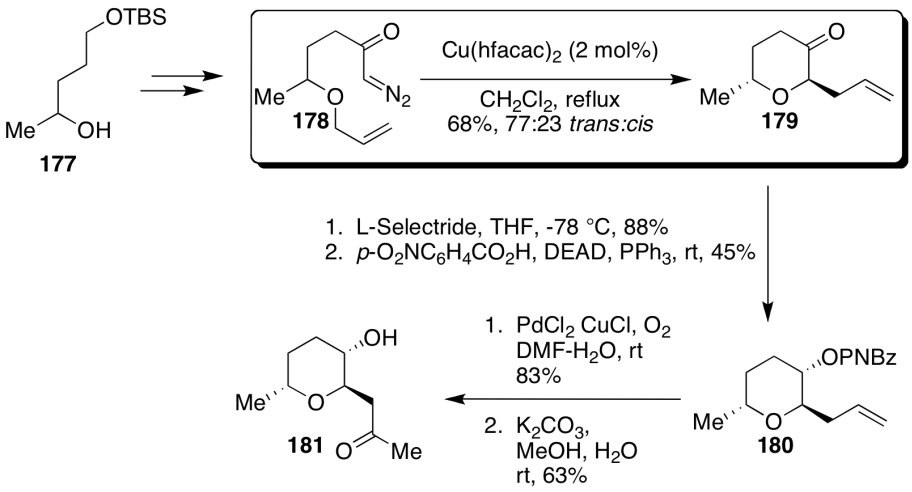
1.8 Applications in Total Synthesis

Pirrung[22] illustrated that the use of an oxonium ylide generation/rearrangement protocol is an efficient way to synthesize interesting molecules like (+)-griseofulvin (Scheme 1.16). This section will highlight oxonium ylide rearrangements in the synthesis of natural products.

1.8.1 Synthesis of Decarestrictine L

In 1994 Clark[55] embarked on the total synthesis of a of a monocyclic pyran-containing natural product decarestrictine L. Clark's earlier work on oxonium ylide generation and [2,3]-rearrangements in the synthesis of a variety of heterocycles seemed especially applicable to this molecule. The synthesis began

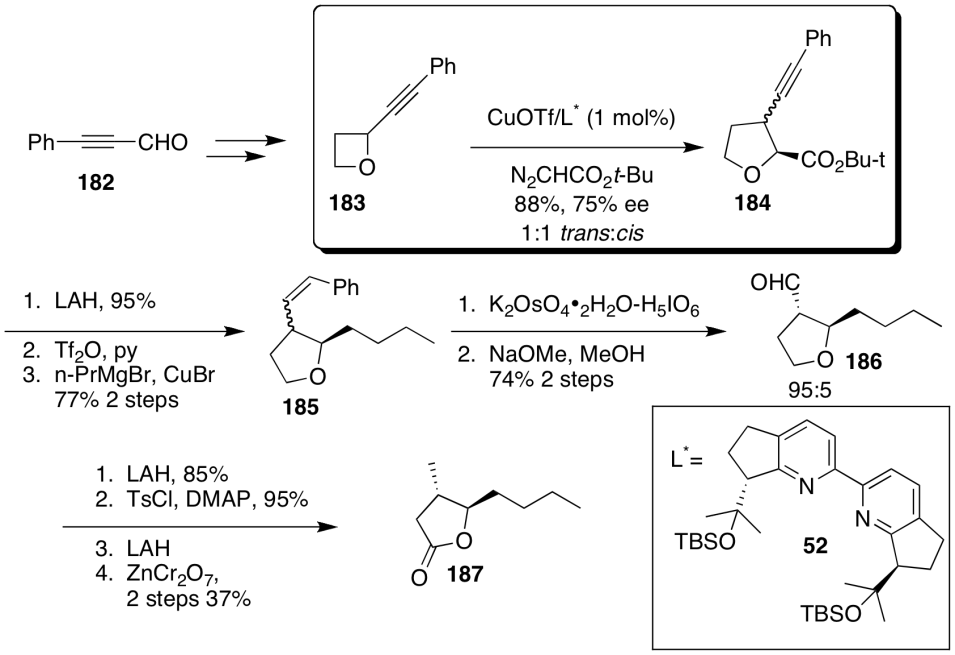
with alcohol **177**, which was elaborated to diazoketone **178** in four steps to set the stage for the key rearrangement reaction. Diazoketone **178** was found to undergo oxonium ylide formation derived from the attack of the ethereal oxygen on the electrophilic carbenoid followed by a concerted [2,3]-shift to furnish tetrahydrofuran-3-one **179** in good yield and diastereoselectivity (Scheme 1.51). The synthesis was then completed in four steps by first stereoselective reduction of the lactone producing the undesired stereochemistry, and subsequent inversion under Mitsunobu conditions to give **180**. Methyl ketone formation was achieved by a Wacker oxidation of the terminal alkene and finally deprotection under standard conditions afforded decarestrictine L **181** in nine steps from alcohol **177**.



Scheme 1.51 Total synthesis of decarestrictine L.

1.8.2 *Synthesis of trans*-Whiskey Lactone

Katsuki[56] used an enantioselective Stevens rearrangement as the key step in his synthesis of *trans*-whiskey lactone. The synthesis began with alkyne **182**,

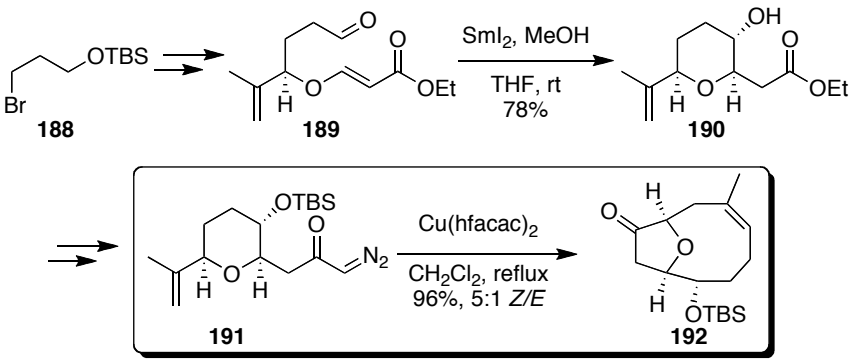


Scheme 1.52 Total Synthesis of *trans*-whiskey lactone.

which was converted to oxetane **183** in six steps in a conventional manner. The key Stevens rearrangement was realized by reacting oxetane **183** with *t*-butyl diazoacetate in the presence of catalytic chiral copper catalyst, formed in situ from CuOTf and ligand **52**, furnishing the desired tetrahydrofuran **184** in 88% yield, 75% ee and as a 1:1 mixture of *cis:trans* isomers (Scheme 1.52). The mixture of *trans*- and *cis*-tetrahydrofurans was converted to compound **185** in three steps before oxidative cleavage under modified Lemieux-Johnson conditions. The mixture was then subjected to epimerization at the C-3 carbon with NaOMe converting the 1:1 mixture to a 95:5 mixture of *trans*:*cis* **186**. The total synthesis was completed in four steps to furnish *trans*-whiskey lactone **187**, showcasing the enantioselective Stevens rearrangement of an oxonium ylide as the key transformation.

1.8.3 Synthesis of Vigulariol

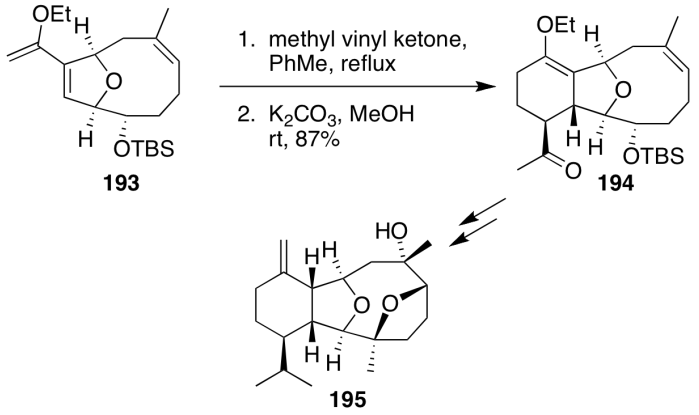
Vigulariol is a member of the cladiellin family of ether-bridged 2,11-cyclized cembranoid marine natural products. Clark's synthetic strategy to assemble this molecule involved the [2,3]-rearrangement of an oxonium ylide to furnish the desired core ring structure of vigulariol.[57] The synthesis began with bromide **188**, which was converted to aldehyde **189** in four steps. Reductive cyclization was accomplished by treatment with SmI_2 in the presence of methanol



Scheme 1.53 Synthesis of the core ring structure of vigulariol.

to deliver tetrahydropyranol **190** as a single diastereomer in good yield. After several synthetic steps, treatment of diazoketone **191** with $Cu(hfacac)_2$ produced an oxonium ylide intermediate, which subsequently underwent a [2,3]-rearrangement to produce the three-carbon ring expansion product **192** in excellent yield as a 5:1 mixture of double bond isomers (Scheme 1.53). The strained *trans*-isomer was converted into the desired **192** upon treatment with AIBN and ethanethiol in benzene at reflux. Next, synthesis of the six-membered ring was achieved using an intermolecular Diels-Alder reaction between diene **193** and methyl vinyl ketone in toluene at reflux. This reaction was highly regioselective and exhibited high facial diastereoselectivity on the diene, yielding a 2:1 mixture of *exo* and *endo* diastereoisomers (Scheme 1.54). This mixture could be epimerized to the *exo* adduct **194** with potassium carbonate in methanol.

Adduct **194** could be converted to vigulariol **195** in eight steps using standard synthetic methods. This synthesis illustrates that the core of vigulariol can be constructed via a highly efficient oxonium ylide rearrangement generated from an electrophilic copper carbenoid species.

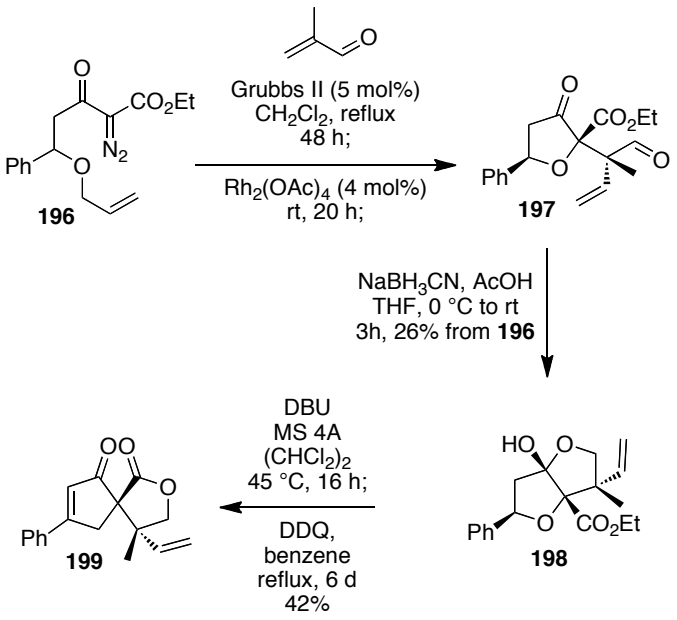


Scheme 1.54 Synthesis of the six-membered ring.

1.8.4 Synthesis of Hyperolactone C

Hodgson[41] recently published an efficient route to hyperolactone C using a one-pot alkene cross-metathesis/oxonium ylide formation-rearrangement. Diazoketone **196**, which is available in two steps from ethyl diazoacetate, was subjected to cross-metathesis with methacrolein yielding an *E*-enal. Subsequent addition of catalytic $Rh_2(OAc)_4$ allowed ylide formation and rearrangement to furnish the desired aldehyde **197** which was unstable; it was therefore immediately reduced with $NaBH_3CN$ providing hemiketal **198** in a 26% yield over three steps (Scheme 1.55). Hemiketal **198** was converted to a spirolactone using DBU which was directly dehydrogenated using DDQ to afford hyperolactone C **199** in 42% over two steps. This total synthesis demonstrates that oxonium ylide formation-rearrangement can be compatible with cross-

metathesis, which enables the manipulation of the allyl migrating group during the rearrangement process.



1.55 Synthesis of hyperolactone C.

1.9 Conclusions

Oxonium ylides are reactive intermediates that can undergo a variety of different reactions ranging from rearrangements to nucleophilic addition. The catalytic generation of oxonium ylides from diazoketones and ethers using either copper or rhodium metal catalyst provides a mild and efficient method of generating these reactive intermediates either intra- or intermolecularly.

This chapter has highlighted the power of the mild and selective generation of oxonium ylides and subsequent rearrangements to furnish a variety of hetero- and carbocyclic frameworks. Intelligent substrate design in addition to informed catalyst choice can allow for the selective formation of oxonium ylides or other potential carbenoids while efficiently and stereoselectively delivering the desired rearrangement products.

In the following chapters further development of the oxygen and sulfur directed Stevens rearrangement of an oxonium ylide will be discussed and will be highlighted as the key step in a Stevens [1,2]-shift approach to phorbol.

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Chapter 2

Sulfur-Directed Stevens Rearrangement of Oxonium Ylides For the Synthesis of Medium-Sized Ether Bridged Ring Systems

2.1 Introduction

Carbon frameworks that contain a seven- or eight-membered ring fused to a smaller ring are found in a variety of natural products. In the West group we are focused on terpenoid compounds like dactylol **1** and phorbol **2** possessing a hydroxyl group at the bridgehead position (Figure 2.1). There has been a number of synthetic approaches[1-7] to these compounds that utilize an ether-bridged intermediate, which upon cleavage could unveil the angular hydroxyl group. The limitation of using this strategy is that cleavage of the ether-bridge was often found to be difficult without a suitable trigger for efficient and selective ring opening.

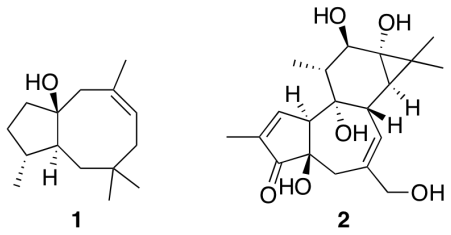
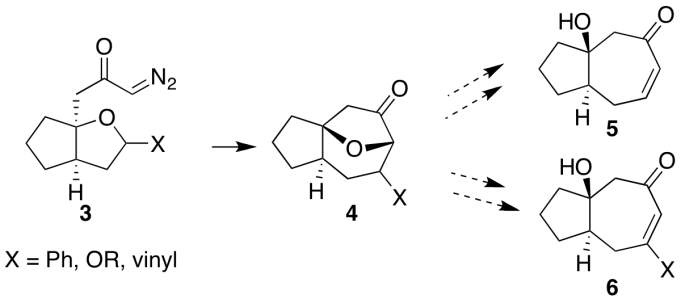


Figure 2.1 Terpenoid natural products.

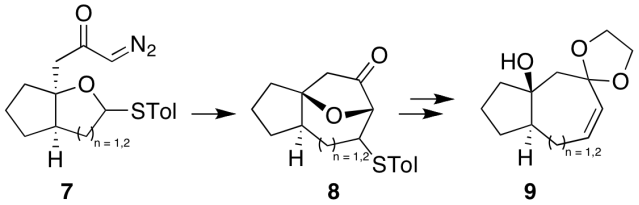
The West group has previously demonstrated that ring expansion of smaller oxygen heterocycles to ether-bridged medium-sized ring using the intramolecular rearrangement of an oxonium ylide is an efficient and stereoselective reaction, discussed in detail in chapter one.[8] This rearrangement

typically required a stabilizing substituent on the migrating carbon such as oxygen, vinyl and aryl groups **3**, which were found to be excellent for the Stevens rearrangement (Scheme 2.1). Unfortunately, while these functionalities are useful for facilitating the rearrangement, subsequent cleavage of the ether bridge in products **4** is not easily achieved with these types of functional groups and would require a number of synthetic manipulations to furnish products like **5** or **6**. Another potential problem associated with these directing groups is further synthetic manipulation or removal of the directing group could prove to be difficult. The development of a Stevens rearrangement that utilizes a directing



Scheme 2.1 Phenyl, vinyl and OR stabilized Stevens rearrangements.

group that could be easily removed or used for further synthetic manipulations would be attractive methodology allowing for a versatile approach to a variety of carbocyclic frameworks. Towards this end, the West group has developed a sulfur-directed intramolecular Stevens rearrangement of diazoketones **7** providing



Scheme 2.2 Sulfur-directed Stevens rearrangement.

efficient construction of bicyclic ether-bridged medium-sized rings such as **8** (Figure 2.3).[9] Using an aryl sulfide as a directing group allows for the cleavage of the ether bridge using a reductive desulfurization protocol to reveal angular hydroxyl groups like **9** (Scheme 2.2).

2.2 Sulfur-Directed Stevens Rearrangement

The success of the bicyclic sulfur-directed Stevens rearrangement toward the synthesis of eight- and seven-membered rings fused to a five-membered ring prompted us to investigate the corresponding series bearing a fused cyclohexane ring. There are a variety of natural products that have a six-membered ring fused to a seven- or eight-membered ring (Figure 2.2). Expanding the scope of the sulfur-directed Stevens rearrangement to include a six-membered ring series would allow us to determine whether this methodology could prove useful towards the synthesis of these types of natural products.

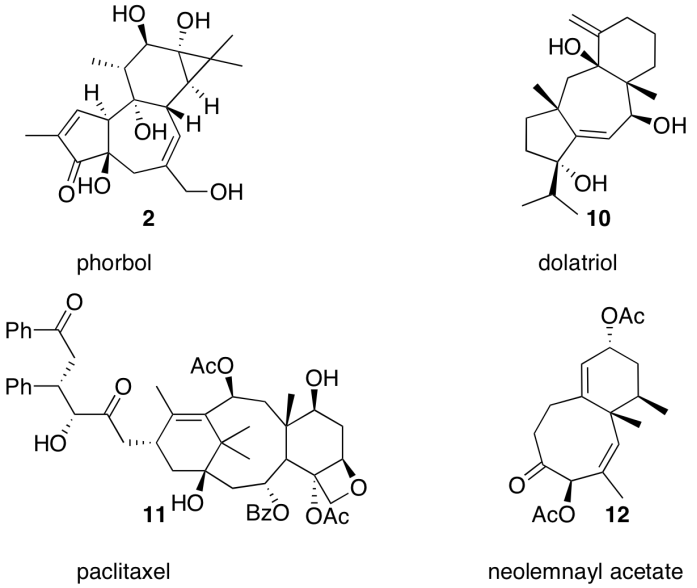
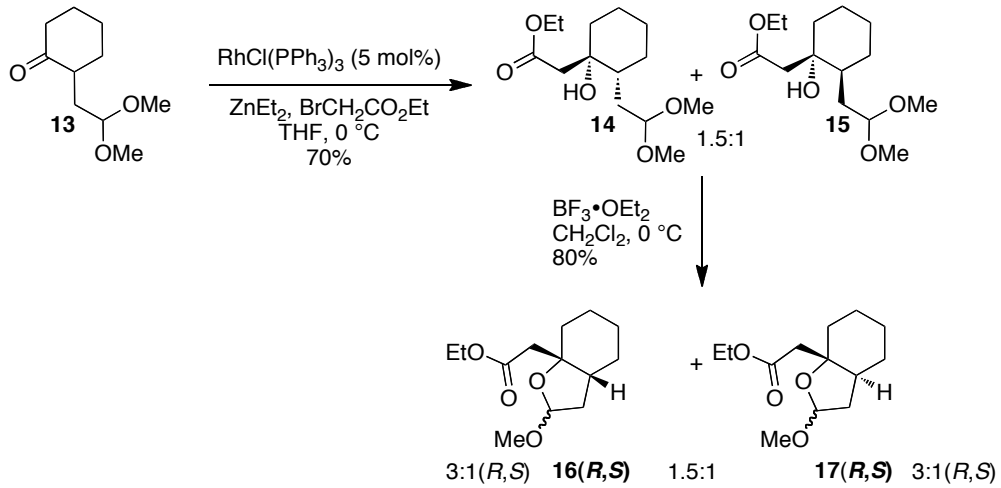


Figure 2.2 Natural products containing a medium-sized ring.

While application of the Stevens rearrangement as the key step towards the synthesis of these complex targets is the ultimate goal, our first objective was to design an efficient synthesis of a variety of model bicyclic diazoketones containing a six-membered carbocyclic ring fused to a five- or six-membered cyclic mixed acetal. Using relatively simple model substrates would allow for efficient access to the key diazoketones in few synthetic steps. This chapter discusses the synthesis of the diazoketone substrates and subsequent rearrangement.

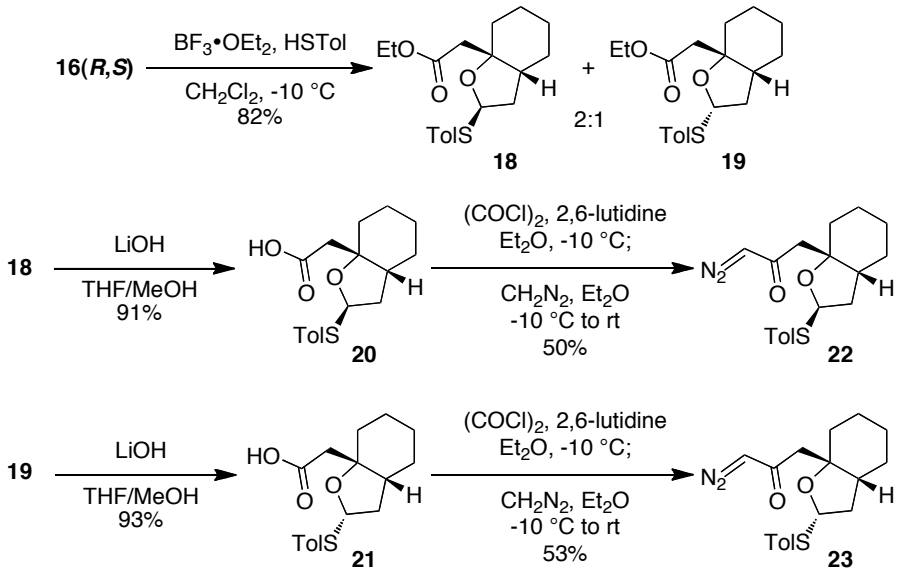
2.2.1 Synthesis of Six-Five Bicyclic Diazoketones.

To investigate the synthesis of the six-seven ring systems we required substrates like **16** and **17** (Scheme 2.3). The first objective was installation of the ester side chain, which needed considerable optimization. In previous studies[9] the addition of either the lithium enolate of ethyl acetate or a Reformatsky reagent



Scheme 2.3 Synthesis of mixed-acetal substrates.

derived from ethyl bromoacetate was successful, but in this case no reaction was seen, leading to recovery of ketone **13**.[10] Failure to observe any addition under these conditions may be due to an unusually facile proton transfer process, quenching the ester anion and preventing consumption of the cyclohexanone. Honda[11] has reported a rhodium catalyzed Reformatsky addition as a mild alternative for the addition of ester enolates to ketones. Gratifyingly, when this protocol was adopted, a 1.5:1 mixture of alcohols **14** and **15** respectively was obtained in a 70% combined yield (Scheme 2.3). These adducts were difficult to separate so they were taken on as a mixture to the next step. The alcohols **14** and **15** could be easily cyclized to mixed acetals **16(*R*,*S*)** and **17(*R*,*S*)** using BF_3•OEt_2 at -10 °C resulting in a 1.5:1 mixture of *cis:trans* ring junction isomers (Scheme 2.3). If this reaction was allowed to proceed for more than ten minutes, decomposition of the mixed acetals was found to occur and if the temperature was raised, a decrease in yield was also seen. With mixed acetals in hand the next step was to install the aryl sulfide-directing group, which was achieved using

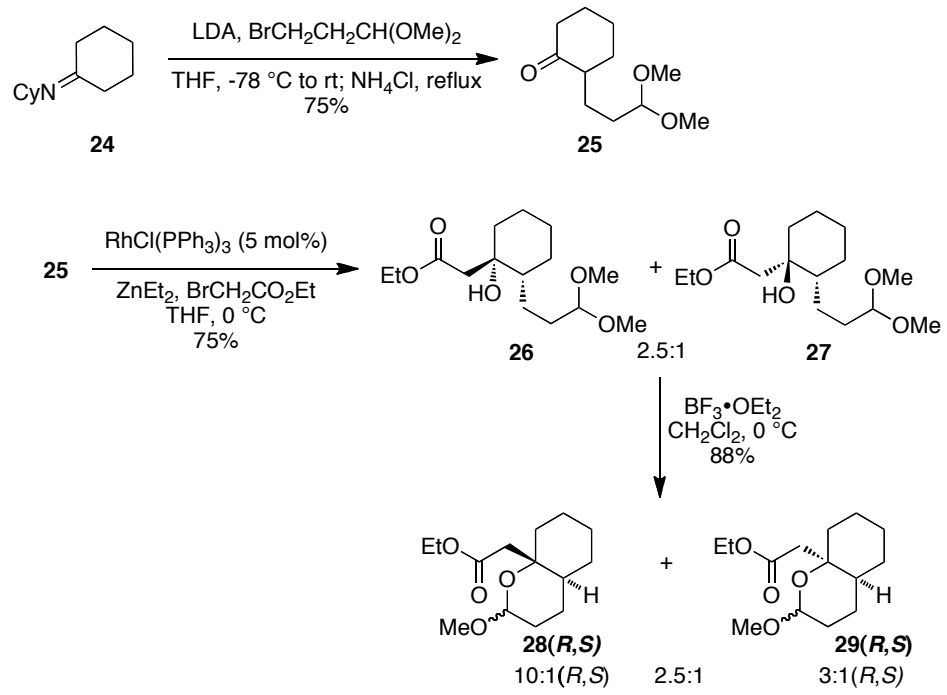


Scheme 2.4 Diazoketone formation from *cis* isomer **16**.

BF_3•OEt_2 and one equivalent of *p*-thiocresol (Scheme 2.4). The *cis* isomer **16** was carried on and was found to produce an 82% yield of thioacetals **18** and **19** as a 2:1 mixture of α,β anomers. The anomers were readily separable at this point and were independently subjected to saponification of the ethyl ester. Carboxylic acids **20** and **21** were obtained in near quantitative yields by treatment of ethyl esters **18** and **19** with LiOH in MeOH/THF. Synthesis of diazoketones **22** and **23** was found to be problematic using standard *in situ* formation of the acid chloride followed by immediate reaction with freshly prepared diazomethane, due to the acid sensitivity of the acetal moiety. Unfortunately using the mixed anhydride protocol, involving stepwise formation and isolation of a mixed anhydride prior to treatment with diazomethane, produced only trace amounts of diazoketones **22** and **23**. Previous studies[2] have observed that the addition of 2,6-lutidine during the acid chloride formation preserved the acetal by scavenging the acid generated during the reaction. Diazoketones **22** and **23** were obtained in moderate yields under these modified conditions.

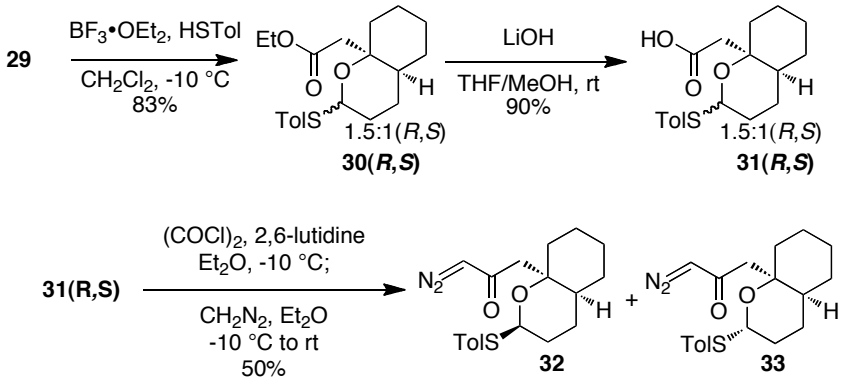
2.2.2 Synthesis of Six-Six Bicyclic Diazoketones

Synthesis of a higher homologue of the previously described diazoketone was achieved by using a similar sequence of reactions. Kinetic alkylation of imine **24**[5] with $Br(CH_2)_2CH(OMe)_2$[6] followed by hydrolysis of the imine under standard conditions provided ketone **25** in good yield (Scheme 2.5). Following the procedure outlined in the previous section, addition of the ester side-chain was achieved in 75% yield as a 2.5:1 mixture of alcohols **26** and **27** with the *trans* diastereomer as the major product. Cyclization occurred smoothly with BF_3•OEt_2 catalyzed conditions generating acetals **28(*R*,*S*)** and **29(*R*,*S*)**. The *trans* and *cis* ring fusion isomers were isolated and taken on separately through the remainder of the route. Synthesis of the *cis* ring fused diazoketone was accomplished using an analogous sequence of steps to the one described above. Formation of the mixed acetal from anomers **29** was achieved using BF_3•OEt_2 and *p*-thiocresol at



Scheme 2.5 Six-membered mixed-acetal synthesis.

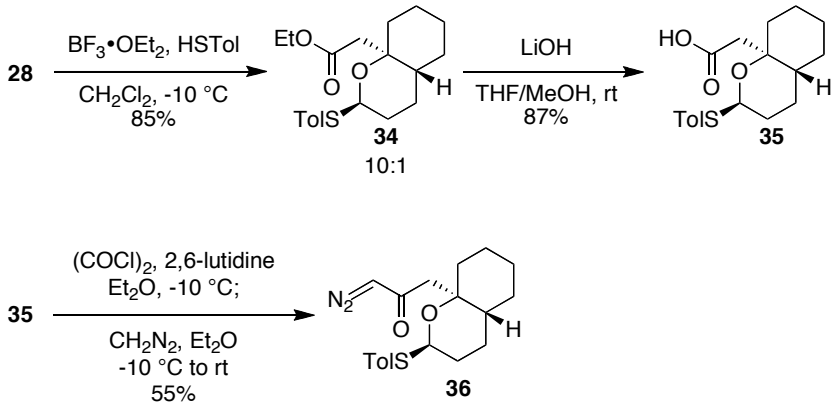
low temperature furnishing a 1.5:1 ratio of inseparable thioacetals **30(*R*,*S*)** (Scheme 2.6). This mixture was taken on to the next step wherein the ester moiety was converted to the carboxylic acids **31(*R*,*S*)** in excellent yield under standard conditions. Conversion of acids **31(*R*,*S*)** to diazoketones **32** and **33** was



Scheme 2.6 Synthesis of *cis*-fused 6-6 ring system diazoketones.

accomplished using the optimized conditions adopted in the six-seven series. At this point the diazoketones were readily separable that effectively sets the stage to investigate the key transformation.

Synthesis of the *trans* diazoketone was conducted in the same manner with similar yields (Scheme 2.7). Notably, formation of the thioglycoside proceeded with an overwhelming preference for one anomer over the other, which was not observed in the *cis* ring series. In this case only the major anomer was further elaborated to the key diazoketone substrate.



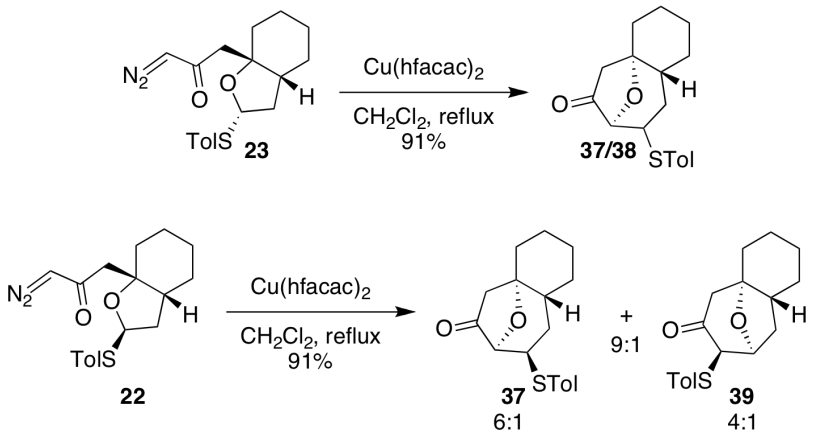
Scheme 2.7 Synthesis of *trans*-fused system diazoketone **36**.

2.3 Stevens Rearrangements of Bicyclic Diazoketones

With five diazoketones available varying in the size of the heterocyclic ring and/or the configuration at the acetal centre, the key oxonium ylide Stevens rearrangement was examined. Both copper and rhodium catalysts have been found to efficiently catalyze the Stevens rearrangement.[12-15] In related studies[9] the optimal catalyst for the sulfur-directed Stevens rearrangement was found to be $Cu(hfacac)_2$ so this catalyst was initially chosen to investigate this transformation.

2.3.1 Rearrangement of Tetrahydrofuran Substrates

Beginning with the tetrahydrofuran series, diazoketone **23** was stirred with $Cu(hfacac)_2$ in CH_2Cl_2 at reflux and gratifyingly produced the desired ether-bridged seven-six ring expansion product **37/38** in excellent yield as a 1:1 mixture of diastereomers, epimeric at the sulfur-substituted centre (Scheme 2.8). Interestingly, subjection of the other anomer **22** to identical reaction conditions yielded a 9:1 ratio of rearrangement products favoring the desired six-seven product **37**. Elucidation of the structure was determined by careful analysis of the NMR data, IR spectral data, and comparison to previous studies.[9] The carbonyl



Scheme 2.8 Stevens rearrangements of diazoketones **22** and **23**.

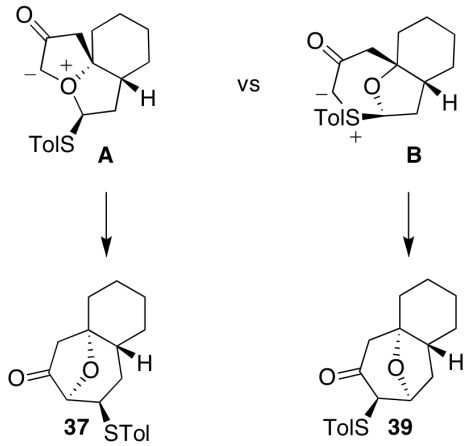
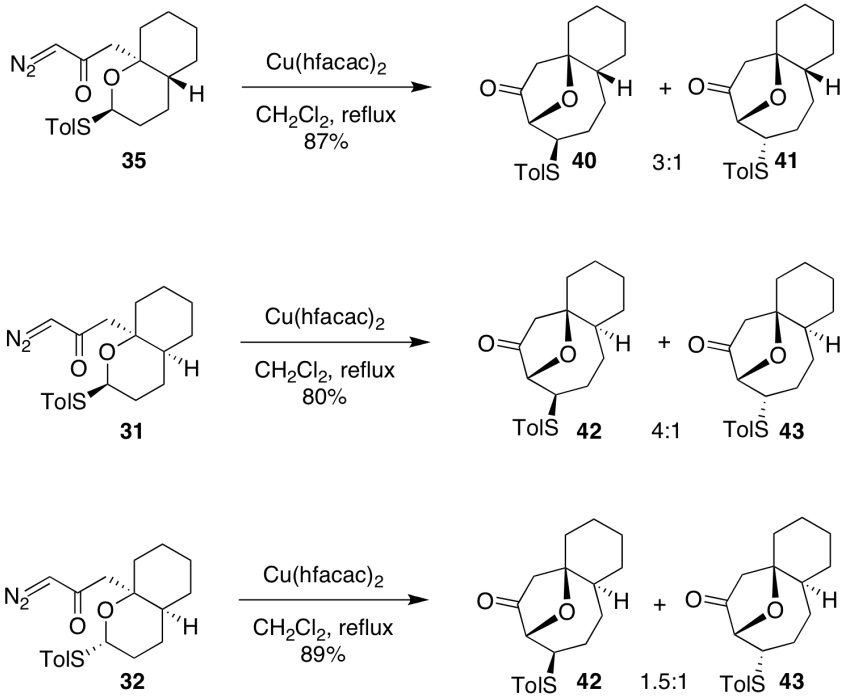


Figure 2.3 Oxonium Ylide vs. Sulfonium Ylide.

signal of major product **37** was 213 ppm in the ^{13}C NMR spectrum, consistent with a carbonyl in a five-membered ring. The IR spectrum displayed a carbonyl stretch at 1762 cm^{-1}, also consistent with a cyclopentanone substructure.[16] The minor product **39** showed an IR carbonyl stretch at 1712 cm^{-1} and a ^{13}C carbonyl signal at 205 ppm suggesting inclusion of the ketone carbonyl in a larger ring, as seen in isomer **39**.[16] The proton NMR spectrum for major product **37** shows a doublet for the oxygen bridge proton and a ddd for the proton attached sulfur substituted carbon, also supporting the formation of the oxonium ylide product. We envision formation of this minor product via competing generation of sulfonium ylide **B**, which can then undergo oxygen-stabilized [1,2]-shift to afford **39** (Figure 2.3). This does not occur in the rearrangement of anomer **23** because the aryl sulfide is *trans* to the diazoketone side-chain, effectively preventing formation of the sulfonium ylide due to prohibitive ring-strain.

2.3.2 Rearrangement of Tetrahydropyran Substrates

The tetrahydropyran series behaved similarly to those seen in the previous section. Treatment of diazoketone **35** with $Cu(hfacac)_2$ provided ring expanded

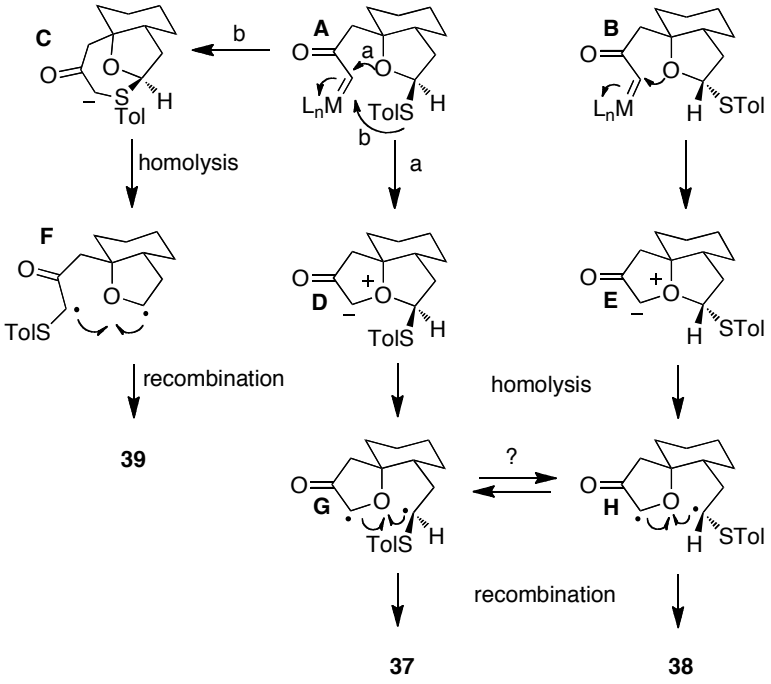


Scheme 2.9 Synthesis of 6-8 oxa-bridged medium-sized rings.

products **40** and **41** in combined yield of 87% (Scheme 2.9). Diazoketones **31** and **32** were subjected to identical reaction conditions and both furnished the desired ring expansion products in good yields. Diazoketone **31,** possessing a *trans* relationship between the diazoketone and the aryl sulfide, rearranged with similar diastereoselectivity as seen in the previous case. Compounds **40** and **42** are products of rearrangement with retention of stereochemistry at the sulfide-substituted centre, confirmed by analysis of the X-ray structure of **40**. It is notable that substrate **32**, in which the diazoketone side-chain is *cis* to the aryl sulfide, underwent rearrangement with poor diastereoselectivity slightly favouring the inversion product **43**. Also, only trace amounts of a compound believed to be analogous to sulfonium ylide product **39** were obtained.

2.4 Discussion

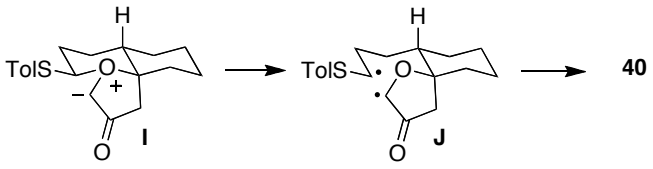
The tetrahydrofuran substrates efficiently afford the desired ring expanded products in similar yields but different diastereoselectivities. When the diazoketone moiety and the aryl sulfide group are in a *trans* relationship a good yield of the desired ring expanded products was obtained but as a 1:1 mixture of isomers. Anomer **22** furnishes the same two diastereomeric products, but with much higher degree of stereochemical retention. To explain these results, the conformations of reactive intermediates can be analyzed. Both anomers should easily form their respective metallocarbene species **A** and **B** (Scheme 2.10). For metallocarbene intermediate **A** where the aryl sulfide group and the diazoketone are *cis* to one another, sulfonium ylide formation can occur. The cyclic seven-membered sulfonium ylide **C** can undergo homolysis producing biradical intermediate **F** which, upon recombination, forms ring-expanded product **39**. As suggested earlier metallocarbene species **B** cannot undergo sulfonium ylide formation explaining why only products **37** and **38**, derived from oxonium ylide formation, are isolated. The differences in stereoselectivity observed in the oxonium ylide rearrangement of the two different anomers can be explained by intermediates **G** and **H** (Scheme 2.10). Attack of the ring oxygen on to the



Scheme 2.10 Possible mechanism for the formation of **37**, **38** and **39**.

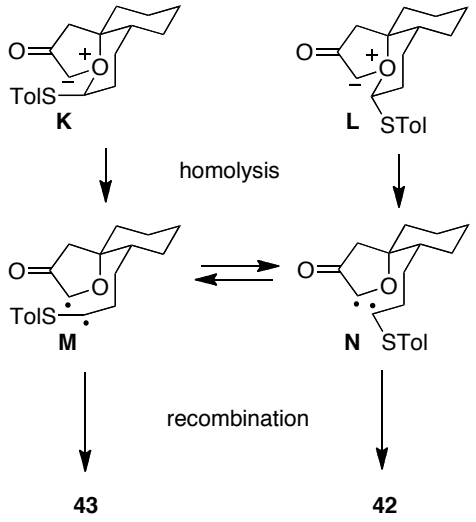
metallocarbene leads to the formation of oxonium ylides **D** and **E** which, upon homolysis of the carbon-oxygen bond provides biradical intermediates **G** and **H**. Since **37** and **38** are formed in a 1:1 ratio from oxonium ylide intermediate **E**, it seems apparent that the initially formed biradical **H** persists long enough to randomize its conformation, as rapid recombination would produce mainly **38**. Slow recombination of this intermediate allows for bond rotation producing biradical intermediate **G**. The Stevens rearrangement of oxonium ylide **D** furnishes the desired ring-expanded product **37** in a 6:1 ratio with retention of stereochemistry, suggesting that biradical intermediate **G** is faster to recombine than **H**.

In the six-eight membered ring series, similar results were observed. The configuration at the migrating center appears to be crucial for the diastereoselectivity. Examination of the *trans* ring fusion oxonium ylide **I** the aryl sulfide is in an equatorial orientation (Scheme 2.11). Homolysis of the oxygen carbon bond generates biradical species **J** and upon bond formation provides the



Scheme 2.11 Trans tetrahydropyran analysis.

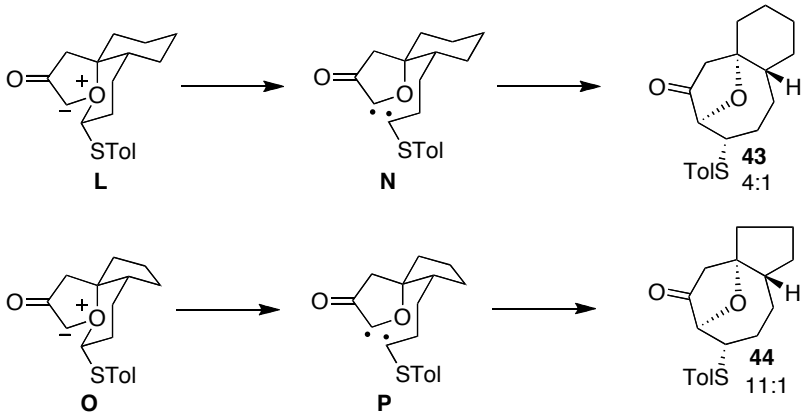
major product **40**. This phenomenon is also observed in the *cis*–ring system, **L** where the aryl sulfide is in an equatorial orientation and *trans* relationship to the diazoketone side-chain (Scheme 2.12). Homolysis generates biradical **N** that efficiently recombines to furnish the major product **42**. On the other hand, oxonium ylide **K**, where the aryl sulfide is in an axial orientation, upon homolysis generates biradical **M**, which is slow to recombine and can undergo bond rotation to form biradical **N**. It appears that when the aryl sulfide is oriented in a *cis* relationship to the diazoketone side-chain the rearrangement is not selective and furnishes approximately a 1:1 mixture of diastereomers.



Scheme 2.12 Cis tetrahydropyran analysis.

Comparison of the 6-8 systems formed in this work with the previously studied 5-8 systems[9] is also informative (Scheme 2.13). In that case, oxonium

ylide **O** furnished the product **44** in good diastereoselectivity, indicating rapid recombination of the presumed biradical intermediate **P**. In contrast, ylide **I** provided **40** in only moderate diastereoselectivity indicating a greater degree of randomization by biradical **J**. The reasons for this apparent dependence of recombination rate on the size of the distal ring is unclear, and merits further examination in future studies.



Scheme 2.13 Comparing ring size in the Stevens rearrangement.

2.5 Conclusions

In summary, an efficient synthesis of bicyclic medium-sized carbocycles has been realized. The diazoketone precursors are available in a few synthetic steps from readily available starting materials. The key rearrangement provides the ether-bridged compounds in high yields with reasonable stereoselectivity. The diastereoselectivity of the Stevens rearrangement of bicyclic diazoketones with a carbocyclic ring fused to an oxygen heterocycle is dependant on the size of the carbocyclic ring as well as the size of the heterocyclic ring. Increasing the size of the carbocyclic ring will reduce the stereoselectivity but an increase in the size of the heterocyclic ring increases the stereoselectivity. Another important observation is that the relative configuration at the migrating carbon directly affects the diastereoselectivity of the Stevens rearrangement.

The chemistry described in this chapter could potentially be used towards the synthesis of a variety of biologically interesting molecules possessing a six membered ring fused to a medium sized ring. Successful extension of the sulfur-directed Stevens rearrangement has been achieved and will be highlighted as the key transformation in our approach to (+)-phorbol, which will be described in Chapter 4.

2.6 Experimental

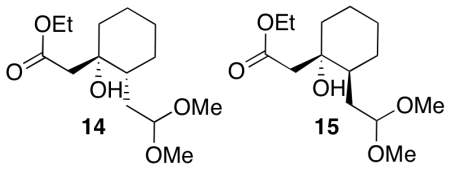
2.6.1 General Information

Reactions were carried out in flame-dried glassware under a positive argon atmosphere unless otherwise stated. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannulae. Solvents were distilled before use: methylene chloride (CH_2Cl_2) from calcium hydride, diethyl ether (Et_2O) and tetrahydrofuran (THF) from sodium/benzophenone ketyl, and toluene from sodium metal. Ethereal diazomethane was prepared from Diazald according to literature procedures.[17] Thin layer chromatography (T.L.C.) was performed on plates of silica precoated with 0.25 mm Kieselgel 60 F_{254}. Flash chromatography columns were packed with 230-400 mesh silica gel. Radial chromatography was performed on plates of silica pre-coated with 2, or 4 mm silica gel 60 PF_{254} containing gypsum.

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz or 500 MHz on Varian Inova 400 and 500, Mercury 400, or Unity 500 spectrometers, and the chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane (0 ppm). Coupling constants (*J*) are reported in Hz. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets, etc. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 125 MHz or 100 MHz and are reported (ppm) relative to the center line of a triplet at 77.23 ppm for deuterochloroform. Infrared (IR) spectra were measured with 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).

2.6.2 Characterization

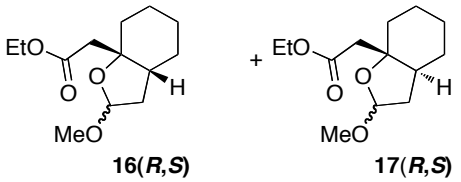


Alcohols (14/15). To a stirred solution of $RhCl(PPh_3)_3$ (129 mg, 0.140 mmol) in THF (34 mL) at 0 °C, was added ethyl-α-bromoacetate (750 μL, 6.73 mmol), ketone[10] **13** (1.04 g, 5.61 mmol), and a 1.00 M hexane solution of Et_2Zn (11.2 mL, 11.2 mmol). After stirring overnight, saturated aqueous $NaHCO_3$ (30 mL) was added. The reaction mixture was filtered, and the filtrate partitioned between Et_2O and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated. The residue was purified by gradient column chromatography (silica gel; 5%, 10%, 15% EtOAc/hexanes until the products were recovered) to provide a 1.3:1 mixture of alcohols **14/15** (1.15 g) as a colourless oil in a combined overall yield of 75%. A small amount of each diastereomer was isolated for characterization purposes.

Major 14: R_f 0.29 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3514, 2934, 2863, 2831, 1714, 1454, 1454, 1371, 1326, 1193, 1126, 1059, 975 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.49 (dd, J = 7.0, 4.5 Hz, 1H), 4.16 (m, 2H), 3.73 (s, OH, 1H), 3.33 (s, 3H), 3.31 (s, 3H), 2.59 (d, J_{AB} = 15.5 Hz, 1H), 2.39 (d, J_{AB} = 15.5 Hz, 1H), 2.08 (ddd, J = 14.0, 7.5, 3.0 Hz, 1H), 1.87-1.79 (m, 1H), 1.69-1.58 (m, 3H), 1.45-1.39 (m, 1H), 1.38-1.24 (m, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.19 (ddd, J = 14.0, 9.5, 6.0 Hz, 1H), 1.13-1.04 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3,

103.3, 72.7, 60.7, 53.1, 51.5, 42.4, 38.0, 37.4, 32.4, 28.7, 24.8, 23.4, 14.2; HRMS (ESI, $[M+Na]^+$) calcd for $C_{14}H_{26}O_5Na$ 297.1672, found 297.1673.

Minor 15: R_f 0.30 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3510, 2935, 2860, 2831, 1713. 1446, 1372, 1327, 1189, 1126, 1057, 971 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.43 (dd, J = 7.0, 4.0 Hz, 1H), 4.16 (q, J = 7.0 Hz, 2H), 3.35 (s, OH, 1H), 3.32 (s, 3H), 3.31 (s, 3H), 2.72 (d, J_{AB} = 15.0 Hz, 1H), 2.34 (d, J_{AB} = 15.0 Hz, 1H), 1.90 (ddd, J = 14.0, 7.5, 2.5 Hz, 1H), 1.75-1.70 (m, 1H), 1.66-1.59 (m, 3H), 1.55-1.42 (m, 4H), 1.42-1.36 (m, 1H), 1.30-1.22 (m, 1H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 103.7, 71.8, 60.6, 53.0, 52.6, 44.1, 40.7, 36.8, 32.5, 27.7, 24.8, 21.6, 14.2; HRMS (ESI, $[M+Na]^+$) calcd for $C_{14}H_{26}O_5Na$ 297.1672, found 297.1669.



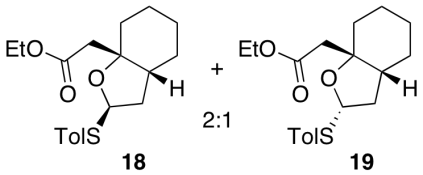
16(*R,S*) **17(*R,S*)**

Mixed Acetals 16(*R,S*)/17(*R,S*). To a solution of **14** and **15** (1.01 g, 3.69 mmol) in CH_2Cl_2 (185 mL) at -15 °C was added BF_3•OEt_2 (468 μL, 3.69 mmol). The reaction was stirred for 10 min at which time TLC showed consumption of starting material. The reaction was quenched with Et_3N (1 mL) and water (100 mL) and the resulting phases separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts washed with water and brine, then dried ($MgSO_4$), filtered and concentrated. The crude product was purified by gradient column chromatography (silica gel; 5%, 10%, 15% EtOAc/hexanes until the products were recovered) to afford **16(*R,S*)** (3:1 mixture of anomers, 327 mg) and **17(*R,S*)** (3:1 mixture of anomers, 383 mg) as yellow oils in an 82% combined yield. (Ratio was determined by integration of OMe singlets in the ^1H NMR sprectra.) A small amount of **17(*R*)** and **17(*S*)** were isolated for characterization purposes.

***Cis* Ring Fusion Anomer Mixture 16(*R*,*S*):** R_f 0.67 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2932, 2860, 1732, 1448, 1370, 1235, 1178, 1101, 1029, 976 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.03-5.02 (m, 1.3H), 4.17-4.12 (m, 3H), 3.37 (s, 1H), 3.36 (s, 3H), 2.68 (d, J_{AB} = 13.5 Hz, 1H), 2.58 (d, J_{AB} = 13.5 Hz, 1H), 2.58 (d, J_{AB} = 14.0 Hz, 0.3H), 2.48 (d, J_{AB} = 14.0 Hz, 0.3H), 2.35 (app quintet, J = 7.0 Hz, 1H), 2.29-2.21 (m, 1H), 2.05-1.94 (m, 2H), 1.94-1.84 (m, 1H), 1.81-1.58 (m, 4H), 1.58-1.43 (m, 3H), 1.43-1.29 (m, 4H), 1.29-1.24 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) Major δ 170.9, 104.5, 82.6, 60.2, 55.1, 44.6, 39.7, 38.4, 33.6, 27.5, 22.8, 22.1, 14.3; Minor δ 170.9, 105.1, 82.3, 60.2, 55.6, 43.1, 40.6, 37.1, 33.3, 25.8, 21.8, 21.0, 14.3; HRMS (ESI, $[M+Na]^+$) calcd for $C_{13}H_{22}O_4Na$ 265.1410, found 265.1413.

***Trans* Ring Fusion Anomer Major 17(*R*):** R_f 0.53 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2935, 2877, 1737, 1459, 1373, 1174, 1048, 1007, 965 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.07 (dd, J = 6.0, 5.0 Hz, 1H), 4.20-4.13 (m, 2H), 3.41 (s, 3H), 2.60 (dd, J_{AB} = 14.5, 2.0 Hz, 1H), 2.56 (d, J_{AB} = 14.5 Hz, 1H), 2.51 (dt, J = 12.0, 3.0 Hz, 1H), 2.27-2.23 (m, 1H), 1.80-1.70 (m, 3H), 1.70-1.60 (m, 2H), 1.56-1.47 (m, 1H), 1.37-1.16 (m, 3H), 1.29 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 105.5, 81.9, 60.1, 56.1, 49.2, 36.0, 35.7, 35.1, 25.6, 25.2, 22.7, 14.3; HRMS (ESI, $[M+Na]^+$) calcd for $C_{13}H_{22}O_4Na$ 265.1410, found 265.1411.

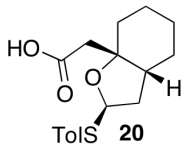
***Trans* Ring Fusion Anomer Minor 17(*S*):** R_f 0.62 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2934, 1735, 1456, 1275, 1192, 1168, 1109, 1004, 966 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.03-5.02 (m, 1H), 4.20-4.12 (m, 2H), 3.35, (s, 3H), 2.40, (d, J_{AB} = 13.0 Hz, 1H), 2.18 (d, J_{AB} = 13.0 Hz, 1H), 1.92-1.73 (m, 5H), 1.50-1.43 (m, 2H), 1.38-1.25 (m, 3H), 1.27 (t, J = 7.5 Hz, 3H), 1.15-1.05 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 103.9, 83.4, 60.2, 55.1, 46.3, 36.7, 35.6, 35.5, 25.6, 24.9, 23.0, 14.2; HRMS (ESI, $[M+Na]^+$) calcd for $C_{13}H_{22}O_4Na$ 265.1410, found 265.1404.



Mixed Thioacetals 18,19. To a solution of **16α,β** (3:1 mixture of anomers, 264 mg, 1.09 mmol) and *p*-thiocresol (135 mg, 1.09 mmol) in CH_2Cl_2 (109 mL) at –15 °C was added BF_3•OEt_2 (138 μL, 1.09 mmol) and the reaction was stirred until deemed complete by TLC. The reaction was quenched with Et_3N (1 mL) and water (30 mL) and the resulting bi-layer was separated. The aqueous phase was extracted with CH_2Cl_2 (30 mL) and the combined organic extracts were washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was first passed through a pad of silica gel eluted with Et_2O, and purified by radial chromatography (silica gel, 4 mm plate, solvent ramp: 100 mL each of 3%, 6% then 9% EtOAc/hexanes until the product was recovered) to afford products **18** (200 mg) as a colourless oil and **19** (100 mg) as a white solid in a 82% combined yield.

***Cis* Ring Fusion Major Thioacetal 18:** R_f 0.72 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2931, 2858, 1731, 1494, 1448, 1234, 1161, 1059, 1003, 951 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 5.56 (t, J = 6.5 Hz, 1H), 4.14 (m, 2H), 2.80 (d, J_{AB} = 14.0 Hz, 1H), 2.60 (d, J_{AB} = 14.0 Hz, 1H), 2.40 (app quintet, J = 6.5 Hz, 1H), 2.33 (s, 3H), 2.28 (ddd, J = 13.0, 7.5, 5.5 Hz, 1H), 2.20 (app quintet, J = 6.0 Hz, 1H), 1.82-1.64 (m, 3H), 1.54-1.44 (m, 2H), 1.42-1.24 (m, 3H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 137.0, 132.0, 132.0, 129.5, 85.9, 84.1, 60.3, 44.2, 40.0, 38.8, 33.1, 27.4, 22.6, 21.9, 21.1, 14.2; HRMS (ESI, $[M+Na]^+$) calcd for $C_{19}H_{26}O_3SNa$ 357.1495, found 357.1502.

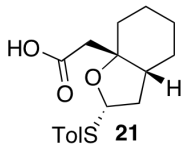
***Cis* Ring Fusion Minor Thioacetal 19:** m.p. 44-46 °C; R_f 0.68 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2932, 2861, 1731, 1494, 1447, 1369, 1282, 1177, 1157, 1033, 951 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 5.48 (app t, *J* = 7.5 Hz, 1H), 4.14 (m, 2H), 2.61-2.44 (m, 1H), 2.58 (d, J_{AB} = 13.5 Hz, 1H), 2.53 (d, J_{AB} = 13.5 Hz, 1H), 2.49 (app dt, *J* = 13.2, 7.3 Hz, 1H), 2.40-2.33 (m, 1H), 2.31 (s, 3H), 2.03 (dt, *J* = 13.5, 8.0 Hz, 1H), 1.92 (ddd, *J* = 14.0, 10.5, 4.0 Hz, 1H), 1.80-1.69 (m, 2H), 1.67-1.58 (m, 2H), 1.51-1.37 (m, 1H), 1.34-1.23 (m, 1H), 1.26 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 136.5, 132.6, 130.9, 129.5, 84.9, 83.7, 60.2, 42.8, 40.8, 37.5, 33.7, 26.1, 22.8, 21.3, 21.0, 14.3; HRMS (ESI, $[M+Na]^+$) calcd for $C_{19}H_{26}O_3SNa$ 357.1495, found 357.1499.



20

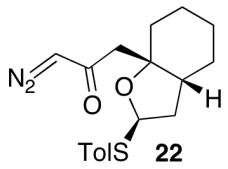
Carboxylic Acid 20. To a solution of thioacetal **18** (115 mg, 0.344 mmol) in THF (1 mL) and methanol (1 mL) was added a 2.00 M solution of LiOH (344 μL, 0.688 mmol). The reaction mixture was stirred for 24 h at room temperature, during which time the reaction mixture turned slightly yellow. The reaction was diluted with water (5 mL) and Et_2O (5 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was washed with Et_2O (5 mL). The aqueous layer was then acidified with 0.5 M HCl to pH ~3, resulting in a cloudy suspension. To this aqueous phase was then added ethyl acetate (10 mL) and the resulting layers separated. The aqueous layer was washed with 3 portions of ethyl acetate (5 mL) and the combined organic extracts were washed with water (5 mL), then brine (5 mL), dried ($MgSO_4$), filtered and concentrated to give the acid **20** as a yellow oil (95 mg, 90%): IR (CH_2Cl_2 cast) 3600-2500, 3021, 2932, 2859, 1706, 1494, 1448, 1409, 1301, 1281, 1112, 1003, 951, 923 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.25, (br s, OH, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.64 (t, *J* = 7.0 Hz, 1H), 2.81 (d, J_{AB} = 15.0 Hz, 1H), 2.63 (d,

J_{AB} = 15.0 Hz, 1H), 2.36-2.31 (m, 1H), 2.34 (s, 3H), 2.26-2.16 (m, 2H), 1.85 (app dq, J = 14.5, 4.0 Hz, 1H), 1.72-1.69 (m, 1H), 1.61 (ddd, J = 14.0, 9.5, 4.5 Hz, 1H), 1.57-1.50 (m, 1H), 1.48-1.25 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 137.9, 132.3, 130.5, 129.9, 86.5, 84.0, 44.5, 41.1, 38.4, 32.7, 27.3, 22.5, 21.6, 21.1; HRMS (EI, M^+) calcd for $C_{17}H_{22}O_3S$ 306.1289, found 306.1281.



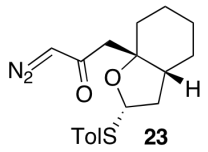
21

Carboxylic Acid 21. To a solution of thioacetal **19** (197 mg, 0.589 mmol) in THF (2 mL) and methanol (2 mL) was added a 2.00 M solution of LiOH (589 μL, 1.18 mmol). The reaction was stirred for 24 h at room temperature, during which time the reaction mixture turned slightly yellow. The reaction was diluted with water (10 mL) and Et_2O (10 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was washed with Et_2O (10 mL). The aqueous layer was then acidified with 0.5 M HCl to pH ~3, resulting in a cloudy suspension. To this aqueous phase was then added ethyl acetate (20 mL) and the resulting layers separated. The aqueous layer was washed with 3 portions of ethyl acetate (10 mL) and the combined organic extracts were washed with water (10 mL), then brine (10 mL), dried ($MgSO_4$), filtered and concentrated to give the acid **21** as a yellow oil (178 mg, 99%): IR (CH_2Cl_2 cast) 3600-2500, 2929, 2670, 1704, 1493, 1449, 1278, 1227, 1032, 996 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55, (br s, OH, 1H), 7.40 (d, J = 8.0, 2H), 7.15 (d, J = 8.0 Hz, 2H), 5.49 (app t, J = 8.5 Hz, 1H), 2.76 (d, J_{AB} = 15.0 Hz, 1H), 2.61 (d, J_{AB} = 15.0 Hz, 1H), 2.46 (app dt, J = 12.5, 6.0 Hz, 1H), 2.25-2.12 (m, 2H), 2.01-1.93 (m, 1H), 1.84-1.78 (m, 1H), 1.77-1.66 (m, 2H), 1.65-1.40 (m, 5H), 1.30-1.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 137.9, 132.3, 130.8, 129.8, 85.9, 83.6, 42.6, 42.0, 36.6, 33.1, 25.2, 23.0, 21.1, 20.4; HRMS (EI, M^+) calcd for $C_{17}H_{22}O_3S$ 306.1289, found 306.1292.



22

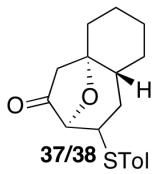
Diazoketone 22. To a solution of carboxylic acid **20** (62 mg, 0.20 mmol) in CH_2Cl_2 (8 mL) at –15 °C was added 2,6-lutidine (26 μL, 0.31 mmol) followed by oxalyl chloride (27 μL, 0.31 mmol) and catalytic DMF (ca. 5 μL). The reaction was stirred for 2 h before solvent was removed by rotary evaporation to give a yellow oil and a white precipitate. This material was redissolved in dry Et_2O and the suspension filtered through a flame-dried fritted filter (D), and the residue was washed several times with dry Et_2O (3 x 5 mL). The ethereal solution of the acid chloride was added via cannula to a solution of freshly prepared diazomethane (~2 mmol) in Et_2O at –15 °C. The resulting mixture was stirred for 20 h as the cooling bath expired. A gentle stream of Ar(g) was applied to the system to allow for slow evaporation of both excess diazomethane and Et_2O, and the resulting yellow oil diluted with Et_2O, passed through a short pad of silica gel in a fritted filter and eluted with Et_2O. The filtrate was concentrated and the resulting oil was purified by radial chromatography (silica gel, 2 mm plate, solvent ramp: 50 mL each of 3%, 6%, 9% then 12% EtOAc/hexanes until the products were recovered) to give **22** (32 mg, 48%) as a yellow oil: R_f 0.47 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3104, 2931, 2101, 1638, 1494, 1356, 1162, 1001, 950 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 5.68 (m, 2H), 2.80 (d, J_{AB} = 14.0 Hz, 1H), 2.49 (d, J_{AB} = 14.0 Hz, 1H), 2.38-2.30 (m, 1H), 2.32 (s, 3H), 2.22-2.16 (m, 1H), 1.78-1.58 (m, 3H), 1.52-1.24 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.6, 136.9, 132.2, 130.0, 129.8, 86.3, 85.3, 53.2, 48.4, 41.2, 36.5, 34.0, 25.0, 24.1, 22.0, 20.5; HRMS (ESI, $[M+Na]^+$) calcd for $C_{18}H_{22}O_2N_2SNa$ 353.1300, found 353.1301.



23

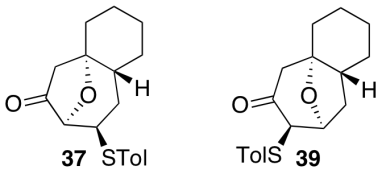
Diazoketone 23. To a solution of carboxylic acid **21** (21 mg, 0.069 mmol) in CH_2Cl_2 (8 mL) at –15 °C was added 2,6-lutidine (13 μL, 0.11 mmol) followed by oxalyl chloride (11 μL, 0.11 mmol) and catalytic DMF (ca. 2 μL). The reaction was stirred for 2 h before solvent was removed by rotary evaporation to give a yellow oil and a white precipitate. This material was redissolved in dry Et_2O and the suspension filtered through a flame-dried fritted filter (D), the residue was washed several times with dry Et_2O (3 x 5 mL). The ethereal solution of the acid chloride was added via cannula to a solution of freshly prepared diazomethane (~ 2 mmol) in Et_2O at –15 °C. The resulting mixture was stirred for 20 h as the cooling bath expired. A gentle stream of Ar(g) was applied to the system to allow for slow evaporation of both excess diazomethane and Et_2O, and the resulting yellow oil diluted in Et_2O, passed through a short pad of silica gel in a fritted filter, eluting with Et_2O. The filtrate was concentrated and the resulting oil was purified by radial chromatography (silica gel, 2 mm plate, solvent ramp: 50 mL each of 3%, 6%, 9% then 12% EtOAc/hexanes until the products were recovered) to give **23** (12 mg, 53%) as a yellow oil: R_f 0.35 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3114, 2929, 2861, 2102, 1635, 1493, 1458, 1353, 1150, 1037, 990 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 7.5 Hz, 2H), 7.11 (d, J = 7.5 Hz, 2H), 5.52 (br s, 1H), 5.44 (dd, J = 8.5, 7.0 Hz, 1H), 2.66 (d, J_{AB} = 13.5 Hz, 1H), 2.37 (d, J_{AB} = 13.5 Hz, 1H), 3.37 (app dt, J = 13.0, 7.0 Hz, 1H), 2.33 (s, 3H), 2.21 (br s, 1H), 2.12 (ddd, J = 12.5, 12.0, 8.5 Hz, 1H), 1.86 (app t, J = 12.0 Hz, 1H), 1.80-1.60 (m, 4H), 1.50-1.36 (m, 2H), 1.30-1.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.5, 137.1, 132.4, 130.4, 130.0, 85.2, 84.2, 57.2, 48.7, 41.5, 36.1, 33.5, 24.6, 23.7, 21.6, 20.2; HRMS (ESI, $[M+Na]^+$) calcd for $C_{18}H_{22}O_2N_2SNa$ 353.1300, found 353.1300.

Carbene Transfer Reaction of 23: Preparation of 37/38



To a solution of $Cu(hfacac)_2$ (1 mg, 3 x 10^{-3} mmol) in CH_2Cl_2 (2 mL) at reflux was added a solution of **23** (9 mg, 0.03 mmol) in CH_2Cl_2 (1 mL), and the resulting mixture was monitored by TLC. Upon consumption of diazoketone (30 min) the reaction mixture was cooled to room temperature and quenched by the addition of saturated $NaHCO_3$ solution (3 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 5 mL). The organic extracts were combined and washed with water (2 mL), brine (2 mL), dried ($MgSO_4$), filtered and concentrated. The resulting oil was purified by column chromatography (silica gel; 15% EtOAc / hexanes until the product was recovered) to yield **37/38** (7.5 mg) as an inseparable mixture of white solids, in a combined overall yield of 91%.

Carbene Transfer Reaction of 22: Preparation of 37 and 39[18]

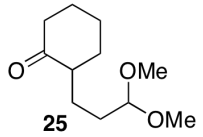


To a solution of $Cu(hfacac)_2$ (8 mg, 0.02 mmol) in CH_2Cl_2 (15 mL) at reflux was added a solution of **22** (55 mg, 0.17 mmol) in CH_2Cl_2 (2 mL), and the resulting mixture was monitored by TLC. Upon consumption of diazoketone (30 min) the reaction mixture was cooled to room temperature and quenched by the addition of saturated $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous

phase extracted with CH_2Cl_2 (2 x 10 mL). The organic extracts were combined and washed with water (5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated. The resulting oil was purified by column chromatography (silica gel; 15 % EtOAc / hexanes until the product was recovered) to yield **37** (40 mg) and **39** (5 mg) as white solids, in a combined overall yield of 90%.

Major 37: m.p. 81-83 °C; R_f 0.31 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3019, 2932, 2857, 1762, 1597, 1493, 1493, 1458, 1400, 1178, 1032, 942 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 3.93 (d, J = 4.0 Hz, 1H), 3.54 (app td, J = 9.0, 4.5 Hz, 1H), 2.37-2.30 (m, 1H), 2.33 (s, 3H), 2.24 (d, J_{AB} = 18.0 Hz, 1H), 1.95-1.75 (m, 5H), 1.70-1.55 (m, 4H), 1.52-1.44 (m, 1H), 1.32-1.21 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.7, 137.8, 133.2, 129.8, 129.5, 80.6, 80.3, 49.1, 43.2, 40.2, 36.4, 31.6, 28.0, 25.7, 21.5, 21.1; HRMS (EI, M^+) calcd for $C_{18}H_{22}O_2S$ 302.1341, found 302.1340.

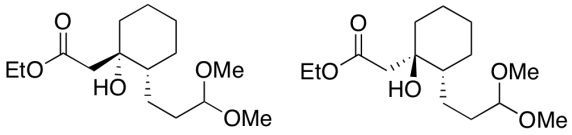
Minor 39: R_f 0.34 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3019, 2930, 2855, 1712, 1494, 1448, 1400, 1218, 1116, 1017, 986 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 4.79 (ddd, J = 6.0, 3.6, 1.6 Hz, 1H), 3.33 (br s, 1H), 2.96 (d, J_{AB} = 16.0 Hz, 1H), 2.34 (s, 3H), 2.21-2.14 (m, 1H), 2.13 (d, J_{ABX} = 16.0, 1.2 Hz, 1H), 1.98-1.87 (m, 1H), 1.86-1.81 (m, 2H), 1.74-1.60 (m, 2H), 1.59-1.51 (m, 2H), 1.51-1.41 (m, 1H), 1.20-1.09 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 137.8 132.2, 130.3, 129.7, 82.2, 77.1, 76.8, 61.5, 50.8, 40.7, 37.9, 33.7, 32.1, 24.1, 21.0; HRMS (EI, M^+) calcd for $C_{18}H_{22}O_2S$ 302.1341, found 302.1338



25

Ketone 25. To a stirring solution of diisopropylamine (3.90 mL, 27.0 mmol) in THF (75 mL) at –78 °C was added *n*BuLi (12.3 mL, 2.20 M solution in hexane,

27.0 mmol) and the resulting mixture was stirred for –78 °C for 45 min. A solution of imine **24**[5] (4.62 g, 25.8 mmol) in THF (2 mL) was added via cannula and the reaction mixture turned bright yellow. This reaction mixture was stirred for 15 min and then warmed to 0 °C and stirred for 2 h. The reaction was cooled to –78 °C and a solution of $BrCH_2CH_2CH(OMe)_2$[6] (5.19 g, 28.3 mmol) in THF (1 mL) was added dropwise. The reaction mixture was allowed to stir overnight while the cooling bath expired. Saturated aqueous NH_4Cl was added and the reaction was then heated to reflux for 5 h. The reaction was cooled to room temperature and Et_2O (100 mL) was added. After separation of the phases, the aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by gradient column chromatography (silica gel; 5 %, 10 %, 15 % EtOAc/hexanes until the products were recovered) to yield **25** (3.8 g, 74%) as a yellow oil: R_f 0.43 (30 % EtOAc/hexanes); IR (CH_2Cl_2 cast) 2936, 2862, 2831, 1710, 1449, 1386, 1208, 1128, 1060, 964 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.31 (t, *J* = 6.0 Hz, 1H), 3.28 (s, 6H), 2.38-2.32 (m, 1H), 2.30-2.22 (m, 2H), 2.10-1.96 (m, 2H), 1.86-1.72 (m, 2H), 1.71-1.50 (m, 5H), 1.36 (app qd, *J* = 12.0, 4.0 Hz, 1H), 1.27-1.19 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.8, 104.6, 52.8, 52.5, 50.4, 42.0, 34.0, 30.1, 28.0, 24.9, 24.5; HRMS (EI, M^+) calcd for $C_{11}H_{20}O_3$ 200.1413, found 200.1408.



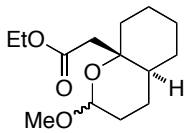
26 **27**

Alcohols 26/27. To a stirred solution of $RhCl(PPh_3)_3$ (219 mg, 0.237 mmol) in THF (72 mL) at 0 °C were added α-bromoacetate (1.58 mL, 14.2 mmol), ketone **25** (1.90 g, 9.48 mmol), and a 1.00 M hexane solution of Et_2Zn (20.9 mL, 20.9 mmol). After stirring overnight, saturated aqueous $NaHCO_3$ (60 mL) was added. The reaction was filtered, and the filtrate partitioned between Et_2O and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated. The residue was

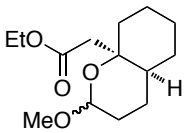
purified by gradient column chromatography (silica gel; 5%, 10%, 15% EtOAc/hexanes until the products were recovered) to yield a 2.5:1 mixture of alcohols **26/27** (2.11 g) as a colourless oil in a combined overall yield of 77%. A small amount of each diastereomer was isolated for characterization purposes.

Major 26: R_f 0.26 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3512, 2933, 2860, 2831, 1730, 1446, 1371, 1330, 1188, 1128, 1067, 989 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.33 (t, J = 6.0 Hz, 1H), 4.16 (q, J = 7.0 Hz, 2H), 3.31 (s, 3H), 3.30 (s, 3H), 3.14 (br s, OH, 1H), 2.77 (d, J_{AB} = 15.0 Hz, 1H), 2.32 (d, J_{AB} = 15.0 Hz, 1H), 1.76-1.57 (m, 6H), 1.50-1.41 (m, 2H), 1.41-1.32 (m, 2H), 1.30-1.15 (3H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 104.8, 72.1, 60.8, 52.9, 52.4, 44.6, 44.1, 37.0, 30.7, 26.7, 25.0, 24.0, 21.6 14.2; HRMS (EI, M^+) calcd for $C_{15}H_{28}O_5$ 288.1937, found 288.1939.

Minor 27: R_f 0.28 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3512, 2933, 2860, 2831, 1730, 1446, 1371, 1330, 1188, 1128, 1067, 989 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.35 (t, J = 6.0 Hz, 1H), 4.17 (q, J = 7.0 Hz, 2H), 3.71 (br s, OH, 1H), 3.32 (s, 6H), 2.57 (d, J_{AB} = 15.0 Hz, 1H), 2.43 (d, J_{AB} = 15.0 Hz, 1H), 1.86-1.58 (m, 7H), 1.54-1.46 (m, 1H), 1.46-1.36 (m, 2H), 1.36-1.22 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H), 1.10-0.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 104.8, 73.0, 60.7, 52.7, 52.4, 44.5, 44.1, 37.8, 31.0, 27.4, 24.6, 23.9, 21.6 14.2; HRMS (EI, M^+) calcd for $C_{15}H_{28}O_5$ 288.1937, found 288.1939.



28(*R*,*S*)



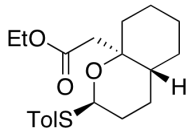
29(*R*,*S*)

Mixed Acetals 28/29(*R*,*S*). To a solution of **26** and **27** (2.96 g, 10.3 mmol) in CH_2Cl_2 (513 mL) at –15 °C was added BF_3•OEt_2 (1.27 mL, 10.3 mmol). The reaction was stirred for 10 min, at which time TLC showed consumption of starting material. The reaction was quenched with Et_3N (5 mL) and water (200

mL) and the resulting phases were separated. The aqueous layer was extracted with CH_2Cl_2 (200 mL) and the combined organic extracts were washed with water and brine, then dried ($MgSO_4$), filtered and concentrated. The crude product was purified by gradient column chromatography (silica gel; 5%, 10%, 15% EtOAc/hexanes until the products were recovered) to afford **28(*R*,*S*)** (743 mg) and **29(*R*,*S*)** (1.49 g) (as a mixture of anomers; ratio based on integration of OMe singlets) as yellow oils in 85% combined yield.

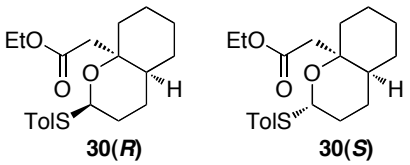
***Trans* Fused 28(*R*,*S*):** 10:1 mixture of anomers; R_f 0.63 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2932, 2869, 1732, 1446, 1221, 1076, 997 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.89 (dd, J = 8.0, 2.5 Hz, 1H), 4.71 (t, J = 2.5 Hz, 0.1H), 4.24-4.14 (m, 1H), 4.13-4.04 (m, 1H), 3.42 (s, 3H), 3.40 (s, 0.3H), 2.26 (m, 0.1), 2.73 (dd, J_{ABX} = 13.5, 1.5 Hz, 1H), 2.52 (d, J_{AB} = 13.5 Hz, 1H), 2.52 (m, 0.1), 2.18 (app dt, J = 13.0, 3.5 Hz, 1H), 1.90-1.80 (m, 1H), 1.75-1.67 (m, 3H), 1.60-1.41 (m, 7H), 1.41-1.21 (m, 4H), 1.26 (t, J = 7.0 Hz, 3H), 0.96 (app qd, J = 13.0, 4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 171.7, 100.0, 97.5, 75.5, 60.3, 59.8, 56.4, 56.0, 46.5, 36.8, 36.4, 32.1, 31.6 29.9, 28.9, 25.9, 25.8, 24.9, 22.8, 22.7, 20.9, 14.3, 14.2 (some carbons from the minor anomer were not observed); HRMS (EI, M^+) calcd for $C_{14}H_{24}O_4$ 256.1675, found 256.1664.

***Cis* Fused 29(*R*,*S*):** 3:1 mixture of anomers; R_f 0.54 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2034, 2865, 1732, 1447, 1369, 1224, 1129, 1034, 1005, 992 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.78 (dd, J = 5.5, 3.5 Hz, 1H), 4.66 (dd, J = 5.0, 3.5 Hz, 0.3H), 4.21-4.09 (m, 2.6H), 3.40 (s, 3H), 3.38 (s, 0.9H), 3.08 (d, J_{AB} = 13.5 Hz, 0.3H), 2.81 (d, J_{AB} = 13.5 Hz, 1H), 2.55 (d, J_{AB} = 13.5 Hz, 0.3H), 2.48 (d, J_{AB} = 13.5 Hz, 1H), 2.20-2.10 (m, 1H), 1.93-1.79 (m, 1H), 1.74-1.54 (m, 11H), 1.54-1.36 (m, 3H), 1.34-1.23 (m, 2H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 171.0, 98.4, 98.3, 75.9, 75.7, 60.2, 60.0, 55.3, 55.2, 44.1, 42.7, 37.1, 36.6, 34.9 (2C), 28.2, 27.7 (2C), 27.6, 23.4, 22.7, 22.6, 22.5, 22.4, 22.1, 14.4, 14.3; HRMS (EI, M^+) calcd for $C_{14}H_{24}O_4$ 256.1675, found 256.1668.



34

***Trans* Fused Thioacetal 34.** To a solution of **28** (340 mg, 1.35 mmol) and *p*-thiocresol (166 mg, 1.35 mmol) in CH_2Cl_2 (68 mL) at –15°C was added BF_3•OEt_2 (169 μL, 1.35 mmol) and the reaction was stirred until deemed complete by TLC. The reaction was quenched with Et_3N (1 mL) and water (30 mL) and the resulting bi-layer was separated. The aqueous phase was extracted with CH_2Cl_2 (20 mL) and the combined organic extracts were washed with water (20 mL), brine (20 mL), dried with ($MgSO_4$), filtered and concentrated. The crude product was first passed through a pad of silica gel in a fritted filter, eluted with Et_2O, and then purified by radial chromatography (silica gel, 4 mm plate, solvent ramp: 100 mL each of 3%, 6% then 9% EtOAc/hexanes until the product was recovered) to afford product **34** (380 mg, 81%) as a colourless solid: m.p. 70-73 °C; R_f (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3021, 2937, 2873, 1729, 1490, 1320, 1240, 1052, 966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.5 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 5.23 (dd, J =12.1, 2.9 Hz, 1H), 3.96 (dq, J_{AMX3} = 10.9, 7.3 Hz, 1H), 3.71 (dq, J_{AMX3} = 10.7, 7.2 Hz, 1H), 2.81 (dd, J_{ABX} = 13.6, 1.7 Hz, 1H), 2.48 (d, J_{AB} = 13.6 Hz, 1H), 2.32 (s, 3H), 2.34-2.27 (m, 1H), 1.99 (app dq, J = 13.2, 3.1 Hz, 1H), 1.80 (m, 3H), 1.58-1.21 (m, 7H), 1.27 (t, J = 7.3 Hz, 3H), 0.97 (app qd, J = 13.2, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 137.3, 133.5, 129.7, 129.1, 78.9, 78.2, 60.1, 44.9, 36.2, 32.5, 31.5, 29.2, 25.9, 25.7, 22.9, 21.0, 14.0; HRMS (ESI, $[M+Na]^+$) calcd for $C_{20}H_{28}O_3S$ 371.1651, found 371.1652.



30(*R*) **30(*S*)**

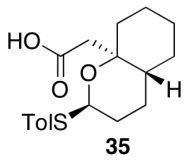
***Cis* Fused Thioacetals 30(*R*,*S*).** To a solution of **29(*R*,*S*)** (639 mg, 2.49 mmol)

and *p*-thiocresol (310 mg, 2.49 mmol) in CH_2Cl_2 (250 mL) at –15°C was added BF_3•OEt_2 (316 μL, 2.49 mmol) and the reaction was stirred until deemed complete by TLC. The reaction was quenched with Et_3N (2 mL) and water (60 mL) and the resulting bi-layer was separated. The aqueous phase was extracted with CH_2Cl_2 (40 mL) and the combined organic extracts were washed with water (40 mL), brine (40 mL), dried with ($MgSO_4$), filtered and concentrated. The crude product was first passed through a pad of silica gel in a fritted filter, eluted with Et_2O, and then purified by radial chromatography (silica gel, 4 mm plate, solvent ramp: 100 mL each of 3%, 6% then 9% EtOAc/hexanes until the product was recovered) to yield the product, a colourless oil, as a 1.5:1 mixture of inseparable anomers **30α,β** (720 mg, 83%). A small amount of each diastereomer was isolated for characterization purposes.

Major 30α: R_f 0.80 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2931, 2866, 1729, 1493, 1461, 1344, 1217, 1178, 1038, 907 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H), 4.99 (dd, *J* = 11.6, 2.2 Hz, 1H), 4.18-4.06 (m, 2H), 2.82 (d, J_{AB} = 13.3 Hz, 1H), 2.61 (d, J_{AB} = 13.3 Hz, 1H), 2.31 (s, 3H), 2.05 (app dt, *J* = 13.0, 4.4 Hz, 1H), 1.98-1.83 (m, 3H), 1.75-1.57 (m, 4H), 1.55-1.30 (m, 5H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 136.8, 131.8, 131.1, 129.2, 78.7, 78.7, 60.2, 43.6, 37.8, 31.7, 28.9, 26.8, 25.3, 23.7, 21.1, 20.0, 14.2; HRMS (EI, M^+) calcd for $C_{20}H_{28}O_3S$ 348.1759, found 348.1758.

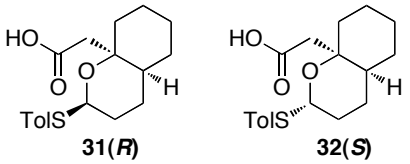
Minor 30β: R_f 0.80 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2934, 2862, 1727, 1493, 1445, 1368, 1227, 1101, 1030, 941 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 5.11 (dd, *J* = 11.7, 3.3 Hz, 1H), 4.12-3.96 (m, 2H), 2.75 (d, J_{AB} = 13.4 Hz, 1H), 2.65 (d, J_{AB} = 13.4 Hz, 1H), 2.34 (s, 3H), 2.07 (app tt, *J* = 13.8, 4.8 Hz, 1H), 2.04-1.98 (m, 1H), 1.78 (app qd, *J* = 13.4, 5.1 Hz, 1H), 1.71-1.56 (m, 4H), 1.56-1.40 (m, 4H), 1.30-1.15 (m, 2H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 137.5, 133.5, 129.6,

129.2, 79.2, 76.6, 60.3, 41.3, 37.0, 35.0, 26.8, 25.9, 25.5, 25.3, 21.5, 21.1, 14.2; HRMS (EI, M^+) calcd for $C_{20}H_{28}O_3S$ 348.1759, found 348.1767.



35

Acid 35. To a solution of thioacetal **34** (117 mg, 0.336 mmol) in THF (1 mL) and methanol (1 mL) was added a 2.00 M solution of LiOH (336 μL, 0.672 mmol). The reaction was stirred for 24 hours at room temperature, during which time the reaction mixture turned slightly yellow. The reaction was then diluted with water (5 mL) and Et_2O (5 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was washed with Et_2O (5 mL). The aqueous layer was then acidified with 0.5 M HCl to pH ~3, resulting in a cloudy suspension. To this aqueous phase was added ethyl acetate (15 mL) and the resulting layers separated. The aqueous layer was washed with 3 portions of ethyl acetate (5 mL) and the combined organic extracts washed with water (5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated to give the acid as a yellow oil (94 mg, 88%): IR (CH_2Cl_2 cast) 3400-2500, 2931, 2864, 1704, 1492, 1450, 1403, 1227, 1058, 972 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.01 (br s, OH, 1H), 7.45 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 5.11 (dd, J = 12.3, 2.9 Hz, 1H), 2.86 (d, J_{AB} = 15.0 Hz, 1H), 2.57 (d, J_{AB} = 15.0 Hz, 1H), 2.33 (s, 3H), 2.17-2.12 (m, 1H), 2.06 (app qd, J = 13.5, 3.3 Hz, 1H), 1.79-1.64 (m, 3H), 1.62-1.42 (m, 5H), 1.41-1.24 (m, 2H), 1.04 (qd, J = 13.0, 4.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 137.8, 133.7, 129.7, 129.2, 79.6, 78.7 44.8, 36.4, 32.5, 31.5, 29.2, 26.0, 25.7, 23.0, 20.9; HRMS (EI, M^+) calcd for $C_{18}H_{24}O_3S$ 320.1446, found 320.1445.



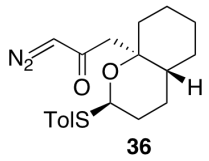
31(*R*) **32(*S*)**

Acid 31(*R*,*S*): To a solution of acids **30(*R*,*S*)** (1.11 g, 3.19 mmol) in THF (5 mL) and methanol (5 mL) was added a 2.00 M solution of LiOH (3.19 mL, 6.40 mmol). The reaction was stirred for 24 h at room temperature, during which time the reaction mixture turned slightly yellow. The reaction was then diluted with water (20 mL) and Et_2O (20 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was washed with Et_2O (20 mL). The aqueous layer was then acidified with 0.5 M HCl to pH ~3, resulting in a cloudy suspension. To this aqueous phase was then added ethyl acetate (40 mL) and the resulting layers separated. The aqueous layer was washed with 3 portions of ethyl acetate (20 mL) and the combined organic extracts washed with water (20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated to give the acids (1.5:1 mixture) as a yellow oils (1.01 g, 93%):

31(*R*): IR (CH_2Cl_2 cast) 3400-2500, 2934, 2861, 1706, 1493, 1446, 1262, 1237, 1030, 977 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.01 (br s, OH, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 5.08 (dd, J = 11.6, 2.4 Hz, 1H), 2.80 (d, J_{AB} = 16.2 Hz, 1H), 2.77 (d, J_{AB} = 15.2 Hz, 1H), 2.34 (s, 3H), 2.13-2.07 (m, 1H), 2.01-1.97 (m, 1H), 1.84-1.78 (m, 1H), 1.75-1.57 (m, 4H), 1.57-1.46 (m, 4H), 1.35-1.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 138.0, 133.9, 129.4, 129.0, 79.8, 41.1, 36.5, 35.5, 26.9, 26.7, 26.1, 25.1, 24.9, 21.6, 21.2; HRMS (EI, M^+) calcd for $C_{18}H_{24}O_3S$ 320.1446, found 320.1431.

31(*S*): IR (CH_2Cl_2 cast) 3400-2500, 2934, 2861, 1706, 1493, 1446, 1262, 1237, 1030, 977 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.01 (br s, OH, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 5.09 (dd, J = 11.3, 3.5 Hz, 1H), 2.91 (d, J_{AB} = 14.2 Hz, 1H), 2.57 (d, J_{AB} = 14.2 Hz, 1H), 2.34 (s, 3H), 2.13-2.07 (m, 1H), 2.01 (app tt, J = 13.2, 4.5 Hz, 1H), 1.82 (app qd, J = 13.2, 4.8 Hz, 1H), 1.75-1.57 (m, 4H), 1.57-1.46 (m, 4H), 1.35-1.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4,

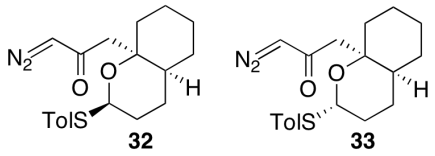
138.0, 133.9, 129.4, 129.0, 79.8, 41.1, 36.5, 35.5, 26.9, 26.7, 26.1, 25.1, 24.9, 21.6, 21.2; HRMS (EI, M^+) calcd for $C_{18}H_{24}O_3S$ 320.1446, found 320.1431.



36

Diazoketone 36. To a solution of carboxylic acid **35** (189 mg, 0.590 mmol) in CH_2Cl_2 (24 mL) at –15 °C was added 2,6-lutidine (103 μL, 0.885 mmol) followed by oxalyl chloride (77.0 μL, 0.885 mmol) and catalytic DMF (~10 μL). The reaction was stirred for 2 h, and solvent was removed by rotary evaporation to give a yellow oil and a white precipitate. This material was redissolved in dry Et_2O and the suspension filtered through a flame-dried fritted filter (D), and the filter pad was washed several times with dry Et_2O (3 x 5 mL). The ethereal solution of the acid chloride was added via cannula to a solution of freshly prepared diazomethane (4 mmol) in Et_2O (12 mL) at –15 °C. The resulting mixture was stirred for 20 h as the cooling bath expired. A gentle stream of Ar was applied to the system to allow for slow evaporation of both excess diazomethane and Et_2O. The resulting yellow oil was diluted in ether, passed through a short pad of silica gel in a fritted filter and eluted with Et_2O. The filtrate was concentrated and the resulting oil purified by radial chromatography (silica gel, 2 mm plate, solvent ramp: 50 mL each of 3%, 6%, 9% then 12% EtOAc/hexanes until the products were recovered) to yield **36** (105 mg, 52%): R_f 0.47 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3108, 2930, 2866, 2100, 1684, 1635, 1492, 1361, 1241, 1166, 1073, 985 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 5.00 (dd, J = 12.2, 2.8 Hz, 1H), 4.54 (s, 1H), 2.76 (dd, J_{ABX} = 15.2, 1.2 Hz, 1H), 2.39 (d, J_{AB} = 15.2 Hz, 1H), 2.31 (s, 3H), 2.09 (dddd, J = 13.4, 4.2, 2.7, 2.7 Hz, 1H), 1.93 (d, J = 10.8 Hz, 1H), 1.76-1.60 (m, 3H), 1.60-1.46 (m, 2H), 1.46-1.36 (m, 3H), 1.36-1.25 (m, 2H), 1.09 (dq, J = 13.0, 4.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 138.9, 135.8,

129.6, 129.3, 80.4, 78.7, 54.8, 45.3, 37.2, 36.7, 32.4, 29.2, 26.0, 25.7, 22.7, 21.0
HRMS (ESI, $[M+Na]^+$) calcd for $C_{19}H_{24}O_2N_2SNa$ 367.1451, found 367.1452.



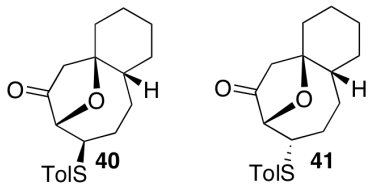
Diazoketones 32 and 33. To a solution of **31(*R*)** and **31(*S*)** (1.5:1 mixture, 774 mg, 2.42 mmol) in CH_2Cl_2 (96 mL) at –15 °C was added 2,6-lutidine (564 μL, 4.84 mmol) followed by oxalyl chloride (422 μl, 4.84 mmol) and catalytic DMF (~20 μl). The reaction was stirred for 2 h, and solvent was removed by rotary evaporation to give a yellow oil and a white precipitate. This material was redissolved in dry Et_2O and the suspension filtered through a flame-dried fritted filter (D), washed several times with dry Et_2O (3 x 5 mL). The ethereal solution of the acid chloride was added via cannula to a solution of freshly prepared diazomethane (24 mmol) in Et_2O (72 mL) at –15 °C. The resulting mixture was stirred for 20 h as the cooling bath expired. A gentle stream of Ar was applied to the system to allow for slow evaporation of both excess diazomethane and Et_2O, and the resulting yellow oil was diluted in ether, passed through a short pad of silica gel in a fritted filter, and eluted with Et_2O. The filtrate was concentrated and the resulting oil was purified by radial chromatography (silica gel, 2 mm plate, solvent ramp: 50 mL each of 3%, 6%, 9% then 12% EtOAc/hexanes until the products were recovered) to yield **32** (214 mg) and **33** (199 mg) as yellow oils in a combined 50% yield.

Diazoketone 33: R_f 0.54 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3112, 2932, 2867, 2099, 1633, 1492, 1353, 1151, 1074, 1035, 1001, 973 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 5.39 (br s, 1H), 5.13 (dd, J = 11.5, 1.8 Hz, 1H), 2.75 (d, J_{AB} = 13.5 Hz, 1H), 2.60 (d, J_{AB} = 13.5 Hz, 1H), 2.31 (s, 3H), 2.10-1.86 (m, 3H), 1.80-1.6 (m, 4H), 1.59-1.47 (m, 2H), 1.47-1.26 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.7, 137.1, 131.3, 129.7,

129.5, 79.2, 78.1, 55.9, 50.6, 31.7, 31.8, 28.8, 26.7, 25.4, 23.5, 21.0, 19.8; HRMS (ESI, $[M+Na]^+$) calcd for $C_{19}H_{24}O_3N_2SNa$ 367.1451, found 367.1451.

Diazoketone 32: R_f 0.38 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3108, 2934, 2861, 2102, 1634, 1493, 1493, 1358, 1266, 1160, 1030, 973 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 5.01 (dd, J = 11.5, 3.3 Hz, 1H), 4.80 (br s, 1H), 2.99 (d, J_{AB} = 14.4 Hz, 1H), 2.32 (s, 3H), 2.23 (d, J_{AB} = 14.4 Hz, 1H), 2.00-1.88 (m, 2H), 1.87-1.77 (m, 1H), 1.77-1.60 (m, 4H), 1.53-1.34 (m, 4H), 1.34-1.27 (m, 1H), 1.25-1.15 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 138.5, 135.3, 129.5, 129.2, 80.1, 80.1, 55.1, 47.2, 36.8, 36.1, 27.0, 26.0, 25.2, 25.0, 21.4, 21.1; HRMS (ESI, $[M+Na]^+$) calcd for $C_{19}H_{24}O_3N_2SNa$ 367.1451, found 367.1455.

Carbene Transfer Reaction of 35: Preparation of 40[19] and 41

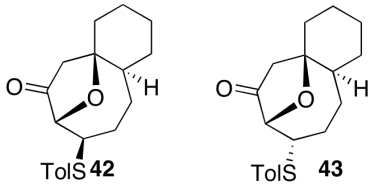


To a solution of $Cu(hfacac)_2$ (10 mg, 0.017 mmol) in CH_2Cl_2 (18 mL) at reflux was added a solution of **35** (68 mg, 0.20 mmol) in CH_2Cl_2 (2 mL), and the resulting mixture monitored by TLC. Upon consumption of diazoketone (30 min) the reaction mixture was cooled to room temperature and quenched by the addition of saturated $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The organic extracts were combined and washed with water (5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated. The resulting oil was purified by column chromatography (silica gel; 15% EtOAc / hexanes until the product was recovered) to yield **40** (40 mg) and **41** (15 mg) as white solids, in a combined overall yield of 87%. The relative stereochemistry was determined by analysis of the X-ray structure of **40**.

Major 40: m.p. 79-81 °C; R_f 0.56 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3018, 2919, 2861, 1742, 1494, 1449, 1402, 1259, 1183, 1098, 969 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 4.25 (s, 1H), 3.59 (dd, J = 11.4, 6.8 Hz, 1H), 2.54 (d, J_{AB} = 18.0 Hz, 1H), 2.31 (s, 3H), 2.20 (d, J_{AB} = 18.0 Hz, 1H), 2.19-2.12 (m, 1H), 1.91-1.72 (m, 3H), 1.70-1.57 (m, 4H), 1.48 (dd, 15.9, 7.5 Hz, 1H), 1.32-1.24 (m, 2H), 1.04-0.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.6, 137.1, 131.8, 131.1, 129.9, 85.6, 82.7, 51.4, 50.4, 42.8, 39.8, 31.4, 31.3, 30.0, 25.5, 24.4, 21.1; HRMS (EI, M^+) calcd for $C_{19}H_{24}O_2S$ 316.1497, found 316.1492.

Minor 41: m.p. 85-86 °C R_f 0.49 (30 % EtOAc/hexanes); IR (CH_2Cl_2 cast) 2927, 2857, 1753, 1492, 1454, 1170, 1170, 1061, 904 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 8.5 Hz, 2H), 7.11-7.10 (m, 2H), 4.41 (app dt, J = 8.0, 1.0 Hz, 1H), 3.86 (t, J = 7.0 Hz, 1H), 2.65 (dd, J_{ABX} = 18.5, 0.5 Hz, 1H), 2.32 (s, 3H), 2.19 (d, J_{ABX} = 18.5, 1.0 Hz, 1H), 2.12-2.03 (m, 1H), 1.95 (dddd, J = 15.5, 3.5, 2.0, 2.0 Hz, 1H), 1.89-1.78 (m, 2H), 1.72-1.54 (m, 4H), 1.42-1.16 (m, 4H), 1.11-1.0 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.3, 137.1, 132.1, 132.0, 129.8, 86.0, 79.3, 50.5, 50.3, 43.0, 39.8, 31.8, 31.4, 27.5, 25.5, 24.4, 21.1; HRMS (ESI, $[M+Na]^+$) calcd for $C_{19}H_{24}O_2SNa$ 339.1389, found 339.1388.

Carbene Transfer Reaction of 31: Preparation of 42 and 43[18]



To a solution of $Cu(hfacac)_2$ (6 mg, 0.01 mmol) in CH_2Cl_2 (11 mL) at reflux was added a solution of **31** (40 mg, 0.12 mmol) in CH_2Cl_2 (2 mL), and the resulting mixture was monitored by TLC. Upon consumption of diazoketone (30 min) the

reaction mixture was cooled to room temperature and quenched by the addition of saturated $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The organic extracts were combined and washed with water (5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated. The resulting oil was purified by column chromatography (silica gel; 25% CH_2Cl_2/hexanes until the product was recovered) to yield **42** (25 mg) and **43** (5 mg) as white solids, in a combined overall yield of 87%.

Carbene Transfer Reaction of 32, Preparation of 42 and 43

To a solution of $Cu(hfacac)_2$ (15 mg, 0.031 mmol) in CH_2Cl_2 (28 mL) at reflux was added a solution of **32** (104 mg, 0.311 mmol) in CH_2Cl_2 (2 mL), and the resulting mixture was monitored by TLC. Upon consumption of diazoketone (30 min) the reaction mixture was cooled to room temperature and quenched by the addition of saturated $NaHCO_3$ solution (20 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 15 mL). The organic extracts were combined and washed with water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated. The resulting oil was purified by column chromatography (silica gel; 25% CH_2Cl_2/hexanes until the product was recovered) to yield **42** (50 mg) and **43** (33 mg) as white solids, in a combined overall yield of 91%.

Major 42: m.p. 105-107 °C; R_f 0.38 (50% CH_2Cl_2/hexanes); IR (CH_2Cl_2 cast) 3016, 2918, 2859, 2845, 1740, 1495, 1443, 1399, 1297, 1186, 1087, 1022, 941 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 4.28 (s, 1H), 3.58 (dd, J = 10.5, 7.5 Hz, 1H), 2.34 (s, 2H), 2.31 (s, 3H), 1.96-1.78 (m, 5H), 1.76-1.40 (m, 6H), 1.32-1.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.1, 137.0, 131.8, 131.2, 129.8, 84.2, 83.2, 51.7, 49.4, 44.9, 38.9, 28.1, 26.8, 25.8, 25.4, 22.1, 21.1; HRMS (EI, M^+) calcd for $C_{19}H_{24}O_2S$ 316.1497, found 316.1497.

Minor 43: m.p. 100-102 °C; R_f 0.21 (50% CH_2Cl_2/hexanes); IR (CH_2Cl_2 cast) 2930, 2859, 1755, 1493, 1448, 1401, 1258, 1162, 1071, 1053, 937 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 4.35 (dt, J = 7.5, 1.0 Hz, 1H), 3.82 (dt, J = 7.5, 2.0 Hz, 1H), 2.48 (dd, J_{ABX} = 18.5 Hz, 1.0 H), 2.35 (dd, J_{ABX} = 18.5 Hz, 1.0 H), 2.32 (s, 3H), 2.26 (dddd, J = 15.0, 13.0, 7.5, 2.0 Hz, 1H), 1.93-1.87 (m, 1H), 1.84-1.75 (m, 2H), 1.75-1.56 (m, 5H), 1.46-1.40 (m, 1H), 1.34-1.22 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.7, 137.1, 132.2, 132.1, 129.8, 83.2, 80.1, 50.2, 50.0, 45.0, 38.8, 27.1, 26.1, 26.0, 25.7, 22.1, 21.0; HRMS (ESI, $[M+Na]^+$) calcd for $C_{19}H_{24}O_2SNa$ 339.1389, 309.1387 found.

2.7 References

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18. Structure and relative stereochemistry was assigned analogous to compound **40**.
19. Structure was confirmed by X-ray crystallography.

Chapter 3

Approach to the Tigliane and Daphnane Diterpene Family

3.1 Introduction

Tigliane and daphnane diterpenes are a family of terpenoids possessing a congested tetracyclic framework with a seven-membered central ring fused to a five and six-membered ring (Figure 3.1). These natural products contain a variety of stereocentres and feature two hydroxyl groups at bridgehead positions that possess a *trans* relationship. Many research groups have published routes towards the synthesis of these interesting molecules, and some of these approaches will be highlighted in the next section.

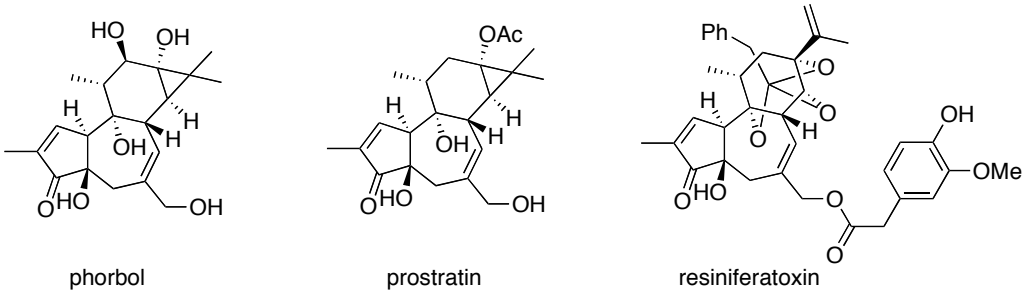


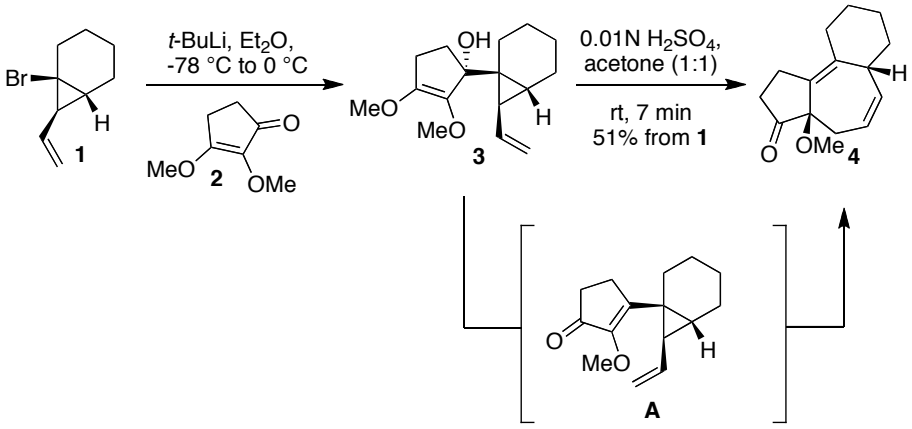
Figure 3.1 Tigliane and daphnane diterpenes.

The West group has had a particular interest in the synthesis of phorbol due to its unique biological activity as well as its structural complexity. This chapter will demonstrate that our oxygen-directed Stevens rearrangement of an oxonium ylide is an efficient methodology for the construction of the five-seven-six ring system found in this family of diterpenes.

3.2 Approaches to the Tigliane and Daphnane Diterpenes

3.2.1 Wender Approaches: Rearrangements and Cycloadditions

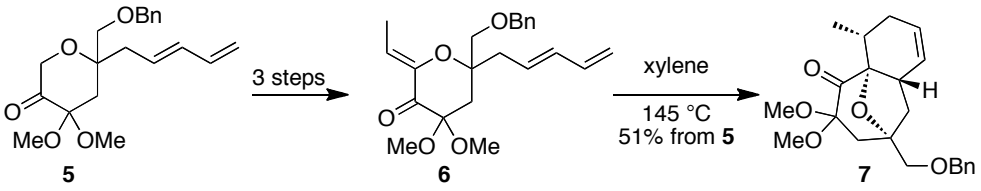
A number of groups have embarked upon the synthesis of the interesting scaffold that these diterpenes possess. Wender has published three attractive routes to this carbon framework over the last thirty years. Wender's[1] earliest report utilized a divinylcyclopropane rearrangement affording the tricyclic system in a concise manner. Preparation of the desired rearrangement substrate **3** was achieved by treatment of 1-bromo-2-vinylcyclopropane **1** with *t*-BuLi then with cyclopentenone **2** (Scheme 3.1). Compound **3** was treated with dilute acid generating divinylcyclopropane intermediate **A**, which subsequently rearranged furnishing the tricyclic product **4** in 51% yield from **1**. Although this methodology allows for efficient construction of the tricyclic core, additional manipulation of the six and seven-membered rings was found to be difficult.



Scheme 3.1 Divinylcyclopropane rearrangement.

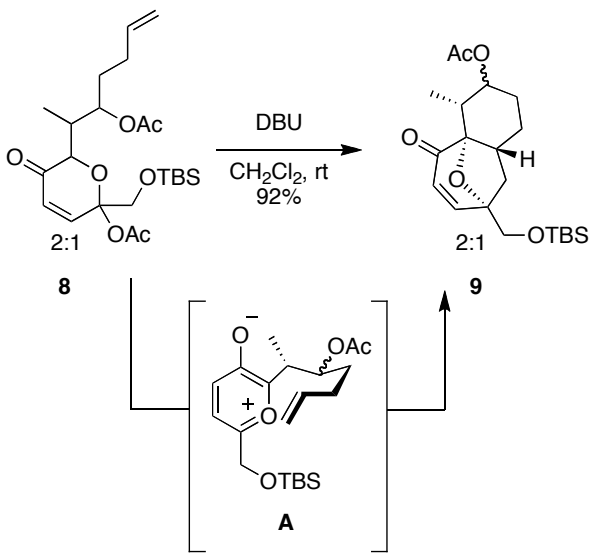
Wender's[2] second approach utilized an intramolecular Diels-Alder reaction to construct the six-seven bicyclic ring system. In this work ketone **5** is readily available from 2-methoxybutadiene and ethyl glyoxalate. Subsequent synthesis of the desired Diels-Alder precursor **6** was achieved in three steps by a

cross-aldol condensation reaction (Scheme 3.2). With **6** in hand heating in xylenes afforded the Diels-Alder adduct **7** as a single isomer in 51% yield from **5** (Scheme 3.2). The Diels-Alder product is an attractive intermediate because it allows for facile formation of the three-membered ring, by a cyclopropanation protocol, and also allows for formation of the five-membered ring through a series of functional group manipulations. Also, the oxygen bridge in **7** provides internal protection of the angular hydroxyl group and converts the flexible six-seven-membered ring into a conformationally and facially biased system.



Scheme 3.2 Intramolecular Diels-Alder reaction.

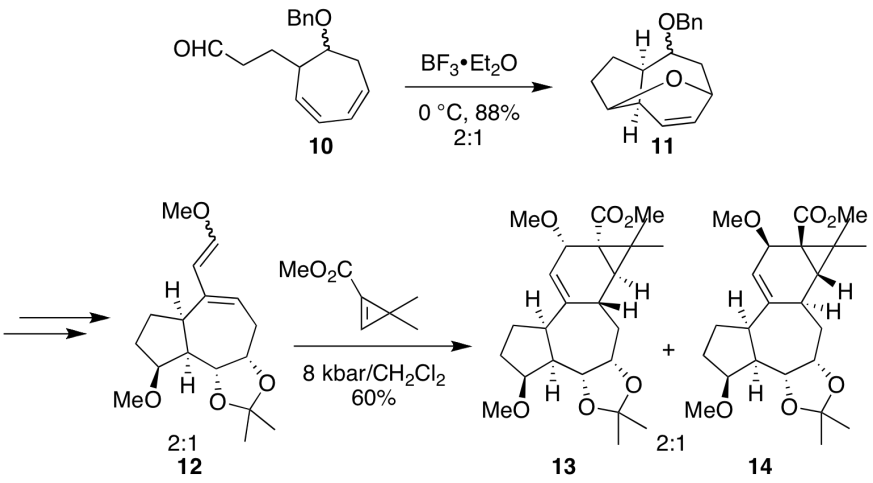
Wender[3] developed another elegant route to these molecules using an oxidopyrylium-alkene cycloaddition strategy delivering the six-seven-ring system in a very efficient manner. Treatment of this intermediate **8** with DBU at room temperature afforded **9** in excellent yield as a 2:1 mixture of diastereomers (Scheme 3.3). This reaction occurred with complete selectivity resulting from a chair-like transition state **A** placing the methyl group in an equatorial position to minimize steric interactions. All three of these strategies allow for efficient construction of the core ring structure of these natural products.



Scheme 3.3 Oxidopyrylium-alkene cycloaddition.

3.2.2 Rigby Diels-Alder Approach

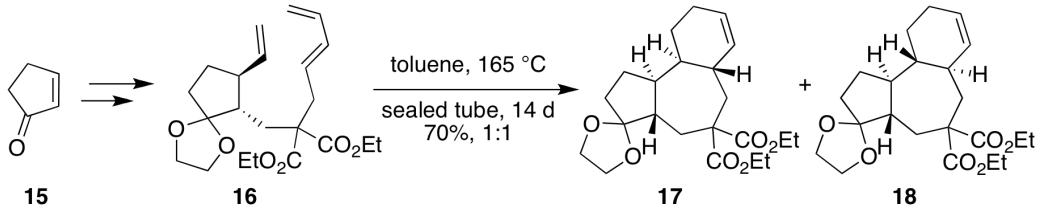
Rigby[4] has also reported an approach to the tigliane skeleton using a stereocontrolled Lewis acid mediated cyclization followed by a Diels-Alder cycloaddition, which simultaneously forms the six-membered C-ring while introducing the three-membered D-ring. In this work, aldehyde **10** was treated with two equivalents of BF_3•Et_2O at room temperature to afford ether **11** in excellent yield (Scheme 3.4). Ether **11** could be transformed into diene **12** in ten steps, which upon reaction with *gem*-dimethylcyclopropenecarboxylate, provided the tigliane tetracycles **13** and **14** in moderate yield as a 2:1 mixture of diastereomers.



Scheme 3.4 Rigby's intermolecular Diels-Alder approach.

3.2.3 Bulman Page Diels-Alder Approach

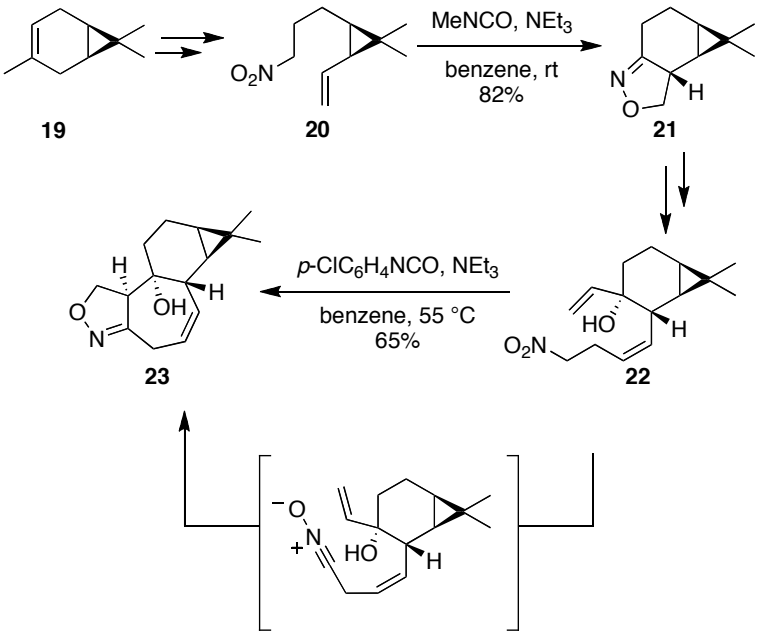
Another example of a Diels-Alder approach was published by Bulman Page[5] in 1997 in which an intramolecular Diels-Alder cycloaddition led directly to the tricyclic core. Diels-Alder precursor **16** was available in four steps from cyclopentenone **15** utilizing conjugate addition and alkylation chemistry (Scheme 3.5). Triene **16** was then heated in a sealed tube for fourteen days providing the product as a 1:1 mixture of *exo* isomers **17** and **18** (Scheme 3.5). Even though the Diels-Alder reaction was sluggish and not stereoselective, the construction of the tricyclic core was successfully achieved in a few synthetic steps.



Scheme 3.5 Bulman Page's IMDA approach.

3.2.4 Shibasaki Nitrile Oxide Cycloaddition Approach

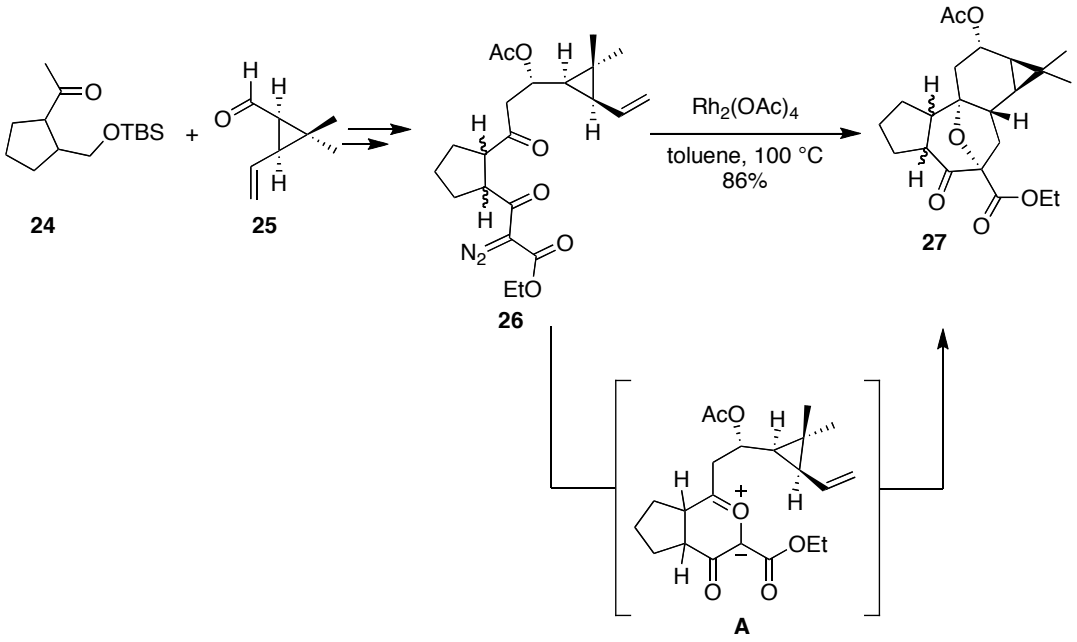
Shibasaki[6] has demonstrated that an intramolecular nitrile oxide cycloaddition is an excellent strategy for the synthesis of the carbon skeleton of the tiglianes. The synthesis of the six-three ring system was accomplished by converting (+)-carene **19** into the nitro compound **20** in nine steps (Scheme 3.6). Compound **20** was then treated with methyl isocyanate in the presence of triethylamine to furnish isoxazoline **21** in excellent yield as a single diastereomer. Isoxazoline **21** could be converted to **22** in ten steps and the crucial cycloaddition, as second nitrile oxide [3+2]-cycloaddition, was performed with treatment of **22** with *p*-chlorophenyl isocyanate and triethylamine. This reaction successfully delivered the desired isoxazoline **23** in moderate yield as a single diastereomer.



Scheme 3.6 Shibasaki's 1,3-dipolar cycloaddition approach.

3.2.5 Dauben Carbonyl Ylide Approach

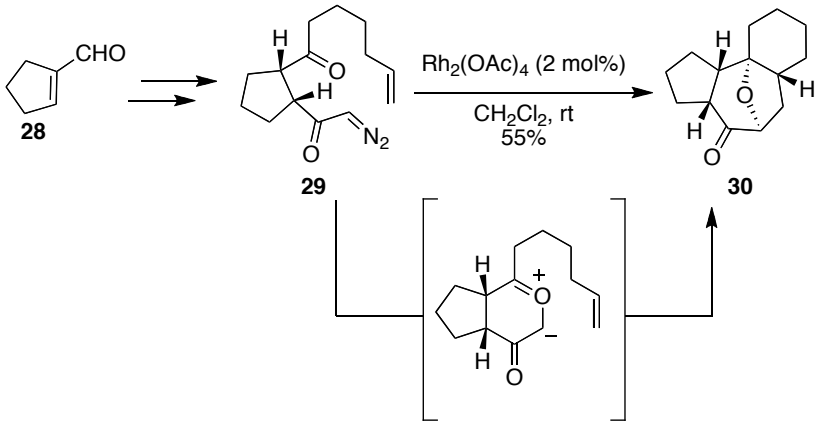
Dauben[7] has explored a different approach to these structures by using a rhodium(II)-catalyzed intramolecular cycloaddition to form the seven and six-membered rings simultaneously with the five and the three-membered rings already in place. Diazoketoester **26** was synthesized from simple building blocks **24** and **25** in six steps in an efficient manner (Scheme 3.7). The diazoketoester, as a 1:1 mixture of *trans* isomers were treated with catalytic $Rh_2(OAc)_4$ to generate the electrophilic metallocarbene, which was attacked by the pendent ketone to form the carbonyl ylide **A**. This ylide intermediate underwent [3+2]-cycloaddition with the remote vinyl group in excellent yield providing the correct relative stereochemistry at the six-seven ring junctions.



Scheme 3.7 Dauben's $Rh_2(OAc)_4$ catalyzed carbonyl ylide cycloaddition.

3.2.6 McMills Carbonyl Ylide Approach

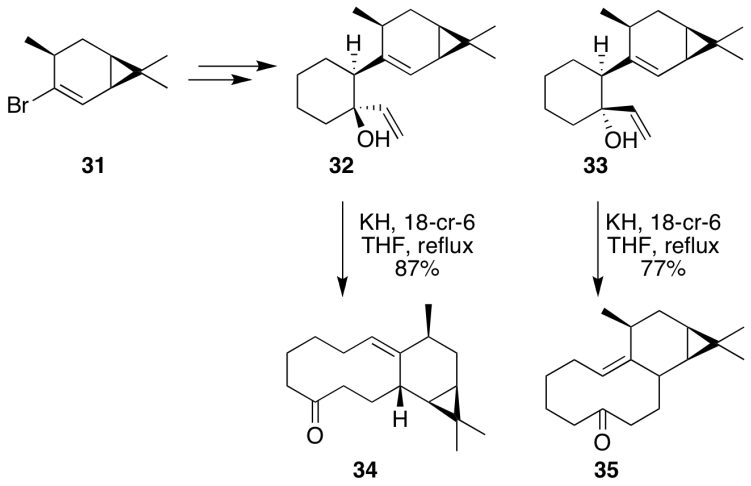
Shortly after this report McMills[8] published a similar strategy using an analogous cycloaddition protocol but instead of using a diazoketoester, a diazoketone was used as the carbonyl ylide precursor. Diazoketone **29** could be easily prepared from unsaturated aldehyde **28** (Scheme 3.8). Cycloadduct **30** was obtained in moderate yield by treatment of diazoketone **29** with $Rh_2(OAc)_4$ at room temperature (Scheme 3.8). Cycloadduct **30** was obtained as a single detectable diastereomer demonstrating the stereoselectivity of this 1,3-dipoar cycloaddition.



Scheme 3.8 1,3-dipolar cycloaddition approach.

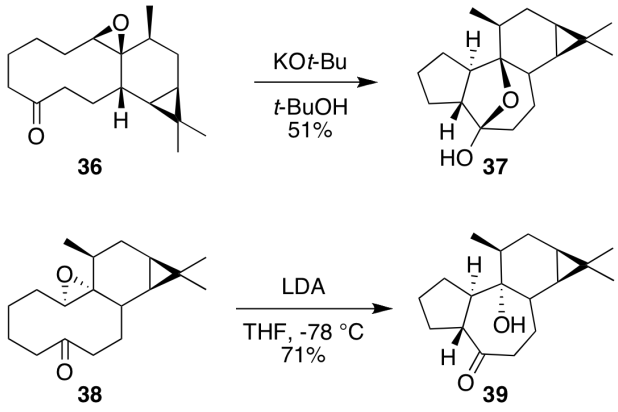
3.2.7 Paquette Oxy-Cope Rearrangement Approach

Paquette's[9] approach to this challenging framework used an anionic oxy-Cope rearrangement/base-promoted cyclization. Diastereomeric alcohols **32** and **33** were prepared in a few steps starting with cyclopropane **31** (Scheme 3.9). These alcohols were treated with KH in THF at reflux to afford macrocyclic ketones **34** and **35** in good yields and as single isomers resulting from an anionic



Scheme 3.9 Paquette's anionic oxy-Cope strategy.

oxy-Cope rearrangement. Ketones **34** and **35** were easily transformed into the desired epoxides **36** and **38** by treatment with *m*-CPBA and subsequent intramolecular cyclization to hemiketal **37** and ketone **39** was achieved using basic conditions in moderate to good yield (Scheme 3.10). Epoxide **36**, when subjected to kinetically controlled conditions (LDA, -78 °C) did not lead to cyclization but under thermodynamic control hemiketal **37** was formed in moderate yield.

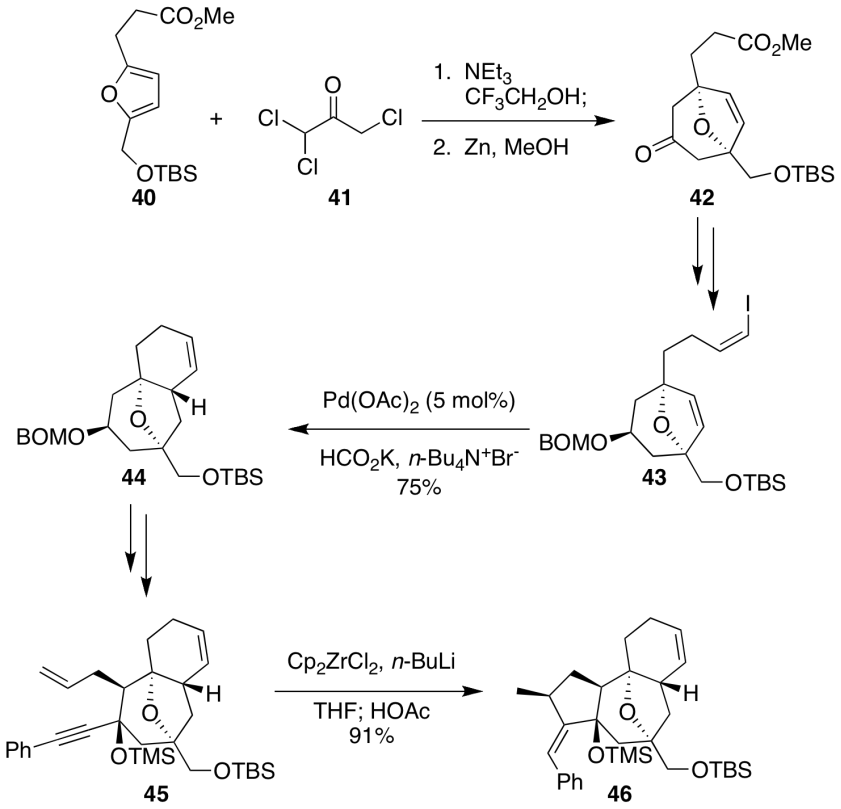


Scheme 3.10 Intramolecular base-promoted cyclization.

Conversely epoxide **38** was found to undergo efficient cyclization, under kinetic conditions, yielding the desired tricyclic compound **39** in good yield and as a single regioisomer.

3.2.7 Cha [4 + 3] Oxyallyl Cycloaddition Approach

Another elegant approach was reported by Cha[10] in 1999 wherein the seven-membered ring was made by treatment of furan **40** with 1,1,3-trichloroacetone **41** in a [4 + 3] oxyallyl cycloaddition (Scheme 3.11). The cycloadduct **42** was generated in good yield based on recovered starting material. Cycloadduct **42** was elaborated to Heck precursor **43** in six steps and when **43**

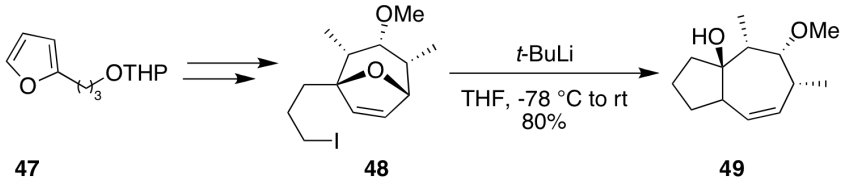


Scheme 3.11 Cha's [4 + 3] oxyally cycloaddition approach.

was treated with $Pd(OAc)_2$ and HCO_2K it furnished **44** in 75% yield as a single stereoisomer. With the six-membered ring in place, installation of the five-membered ring was accomplished using a zirconocene-mediated enyne cyclization, under Negishi's conditions, affording **46** in excellent yield as a single stereoisomer.

3.2.9 Lautens [4 +3] Oxyallyl Cycloaddition Approach

Lautens[11] used a similar approach by using a [4 + 3] oxyallyl cycloaddition reaction to furnish the desired oxabicyclo[3.2.1] compound bearing a three-atom tether, which was then used to open the bridged bicyclic ether regio- and stereoselectively. Iodo compound **48** could be easily prepared from furan **47** and 2,4-dibromopentane-3-one (Scheme 3.12). Treating **48** with *t*-BuLi at low temperature allowed for lithium-halogen exchange followed by S_N2' ring opening to give **49** in good yield as a single detectable regio- and stereoisomer (Scheme 3.11).

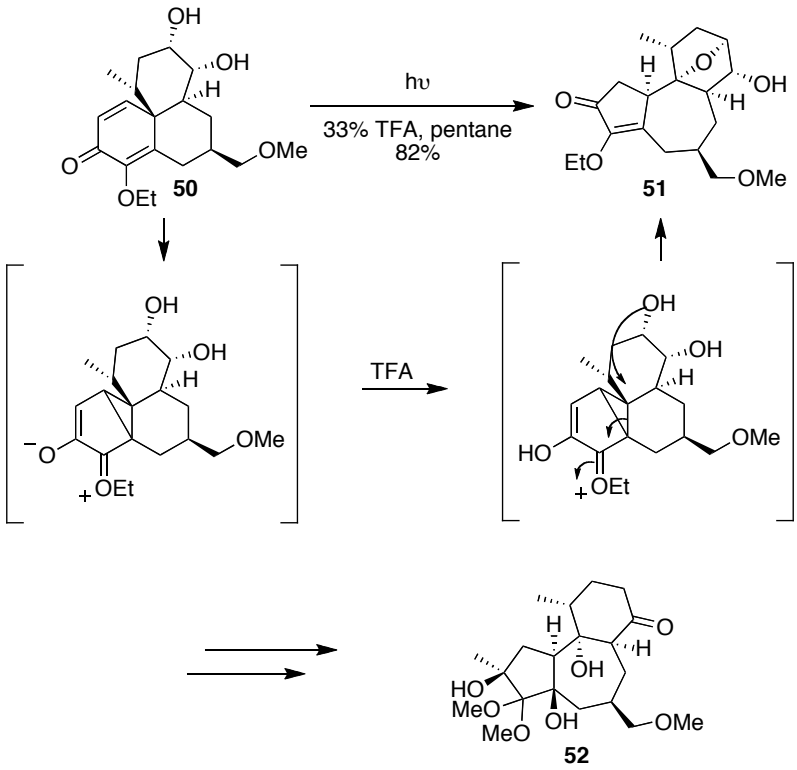


Scheme 3.12 Lauten's anionic ring-opening.

3.2.10 Carreira Photorearrangement Approach

Carreira[12] has developed an elegant photorearrangement for the construction of the daphnanes. Complex tricycle **50** was irradiated in the presence of TFA to afford the desired tricycle **51** in 82% yield as a single isomer (Scheme 3.13). This reaction is thought to proceed through a photo-Nazarov cyclization followed by cyclopropane opening to produce the ether-bridged product **51**. This

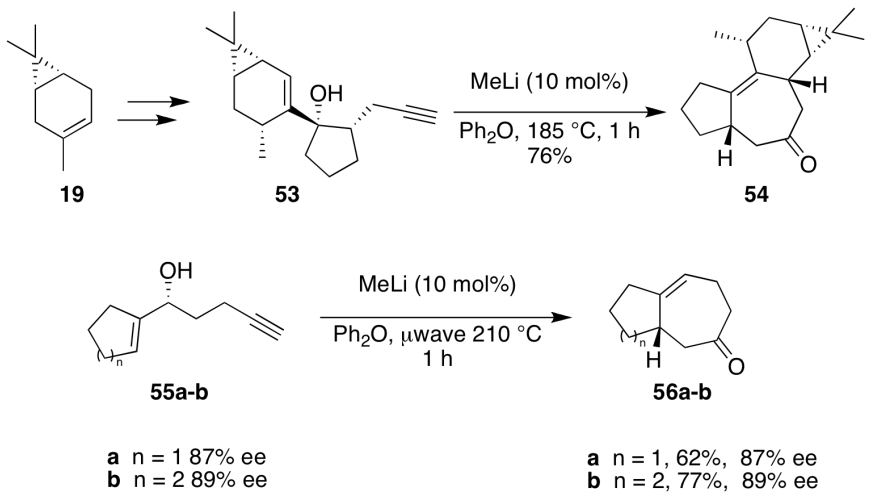
intermediate could be further elaborated to the highly functionalized tricyclic compound **52** using standard functional group manipulation.



Scheme 3.13 Carreira's photorearrangement approach.

3.2.11 Ovaska 5-*exo*-dig Cyclization/Claisen Rearrangement Approach

Ovaska[13] has developed an enantioselective tandem 5-*exo*-dig cyclization/Claisen rearrangement process for the construction of the complicated tetracyclic core of the tiglianes. Alcohol **53**, which is available from (+)-carene **19**, was treated with catalytic MeLi in Ph_2O and heated to 185 °C to furnish the tetracyclic product in good yield and as a single isomer (Scheme 3.14). In 2009 he demonstrated that chirality could be transferred in the rearrangement step by preparing alcohols **55a-b**, which were found to undergo this domino process in good yields and with essentially no loss of enantiopurity.



Scheme 3.14 5-*exo*-dig cyclization/Claisen rearrangement.

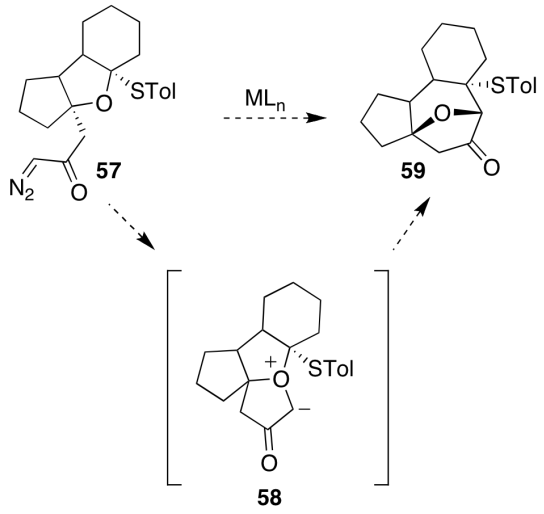
3.3 An Oxonium Ylide Approach to the Tigliane and Daphnane Skeletons

In previous chapters it has been shown that heteroatom directed Stevens rearrangement of an oxonium ylide is an efficient way to build seven- and eight-membered rings. Our approach to these natural products involves the use of a tricyclic diazoketone as the precursor to the construction of the inherent five-seven-six ring system. The Stevens rearrangement would allow for the synthesis of the core seven-membered ring as well as introduce the required angular oxygenation as a protected bridging ether. This diazoketone was thought to come from readily available starting materials making this an attractive and convergent approach to these molecules.

3.3.1 First Approach: Sulfur-Directed Stevens Rearrangement

Our first approach began as an extension of the chemistry discussed in Chapter 2 wherein an additional ring would allow for efficient assembly of the

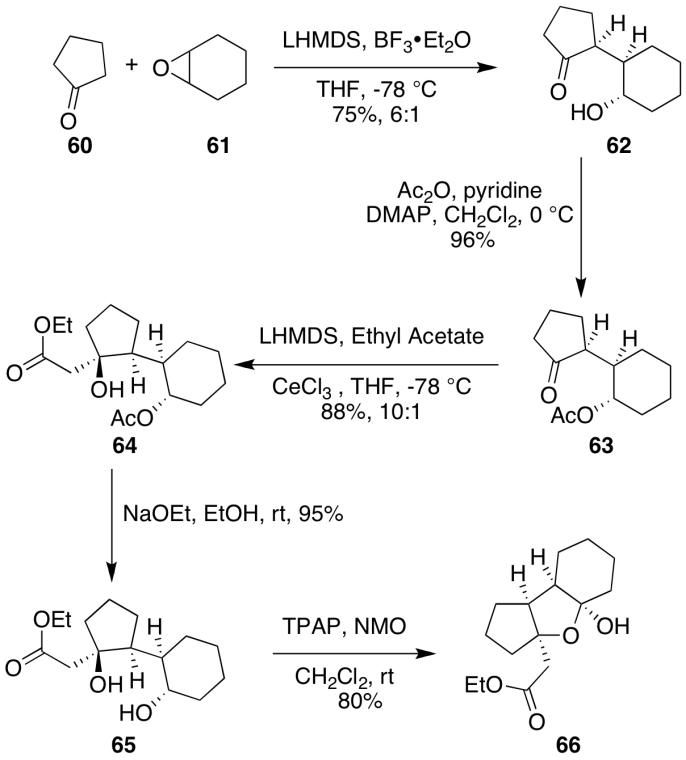
tricyclic core seen in many of the examples at the beginning of this chapter. The key to the success of this methodology would be a concise and stereoselective synthesis of diazoketone **57** and subsequent reaction with a metal catalyst to form ylide intermediate **58**, which could undergo the Stevens rearrangement to yield the desired tricyclic compound **59** (Scheme 3.15).



Scheme 3.15 Proposed sulfur-directed Stevens rearrangement.

3.3.2 Synthesis of Substrates

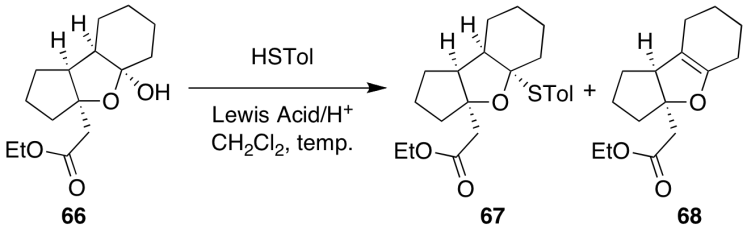
The synthesis began by generating alcohol **62** from cyclopentanone **60** and cyclohexene oxide **61** following a known procedure.[14] This epoxide opening was achieved by making the enolate of cyclopentanone **60** at low temperature followed by the addition of cyclohexene oxide **61** and two equivalents of BF_3•Et_2O (Scheme 3.16). This reaction produced a 6:1 mixture of diastereomers in good yield with the *syn* isomer being the major one. This inseparable mixture was then protected using standard acetylation conditions providing a separable mixture of acetates in excellent yield. The next step was installation of the ester side chain that would ultimately become the key diazoketone. Lithium enolate addition as



Scheme 3.16 Synthesis of hemiacetal **66**.

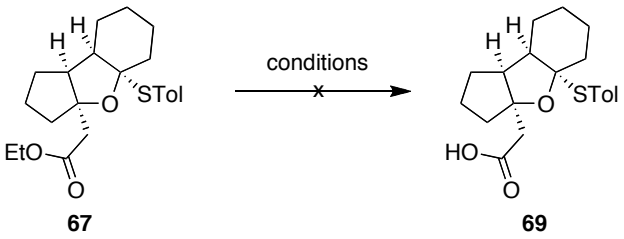
well as Reformatsky addition failed to deliver the desired alcohol **64**. In the end, this transformation was achieved by adding the cerium enolate[15] of ethyl acetate into ketone **63** to furnish the desired tertiary alcohol **64** as a 10:1 mixture of diastereomers in excellent yield. Diol **65** was obtained under standard NaOEt/EtOH deprotection conditions and was subsequently oxidized with TPAP/NMO to give unstable hemiacetal **66** in good yield as a single isomer. With hemiacetal **66** in hand the next step was to prepare thioacetal **67**, which was found to be a difficult transformation. A variety of Lewis acids as well as protic acid conditions led to a mixture of desired thioacetal **67** and dihydrofuran elimination product **68** (Table 3.1). Conversion of the enol ether **68** to the desired thioacetal was met with limited success, never isolating more than a 2:1 mixture of thioacetal to enol ether. After a difficult separation of these products attempts were made to access carboxylic acid **69,** but under standard

saponification conditions (LiOH, NaOH, KOH, TMSOK) a complex mixture was observed and carboxylic acid **69** could not be detected or isolated (Scheme 3.17). Failure to obtain carboxylic acid **69** brought about a change in our approach to the tricyclic core, which led to the utilization of dihydrofuran **68**.



Entry	Lewis Acid/H^+	Temperature (°C)	Ratio **67:68**
1	BF_3•Et_2O	-78	0:100
2	TMSOTf	-78	1:2
3	$ZnCl_2$	-10	1:2
4	TsOH	-10	1:2
5	PPTS	-10	2:1

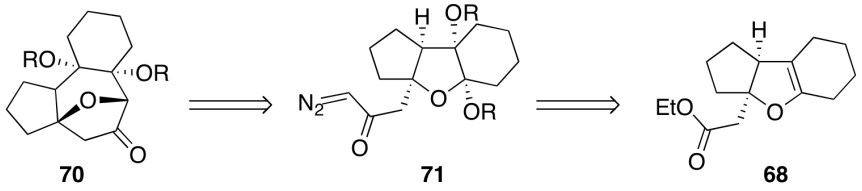
Table 3.1 Synthesis of thioacetal **67**.



Scheme 3.17 Attempted acid formation.

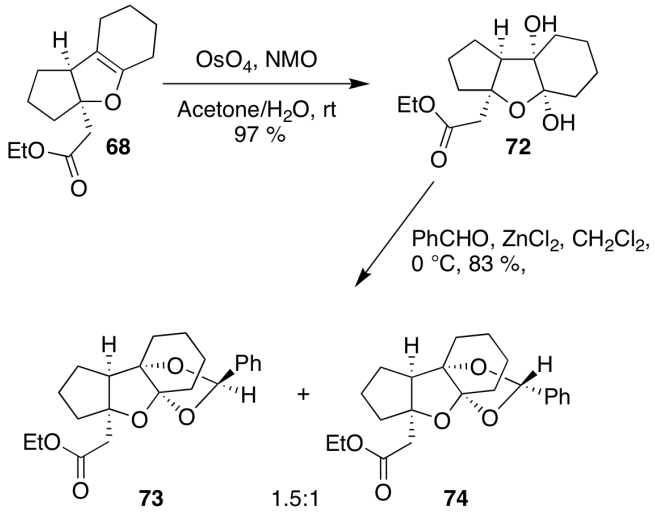
3.3.3 Second-Generation Approach: Oxygen-Directed Stevens Rearrangement

The second-generation approach was to utilize an oxygen-directed Stevens rearrangement of a diazoketone **71** to construct the tricyclic core **70** (Scheme 3.18). Dihydrofuran **68** had potential for allowing access to oxygenation at the migrating carbon and would give an opportunity to install the bridgehead hydroxyl group found at the six-seven ring junction through dihydroxylation (Scheme 3.18).



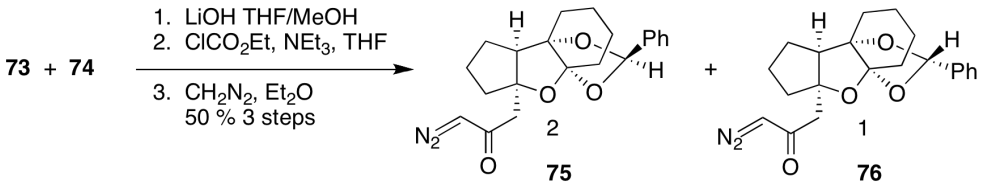
Scheme 3.18 Oxygen-directed Stevens rearrangement.

Dihydrofuran **68** was dihydroxylated using standard conditions providing diol **72** as a single diastereomer in an excellent yield (Scheme 3.19). The next step was to protect the diol, which was achieved by treatment of **72** with benzaldehyde in the presence of $ZnCl_2$. This reaction provided benzylidenes **73** and **74** in 83% yield as a 1.5:1 mixture of diastereomers after considerable optimization. A reaction temperature of 0 °C was critical: at -10 °C the reaction became sluggish, while at room temperature a complex mixture of products was formed. Benzaldehyde had to be distilled before use and ten equivalents of aldehyde gave the best yields. Finally, zinc chloride was the only Lewis acid that furnished the benzylidene products, and 1.5 equivalents was found to be optimal. The two diastereomers were difficult to separate and could be taken on as a mixture and easily separated after diazoketone formation.



Scheme 3.19 Protection of diol **72** as benzylidenes **73** and **74**.

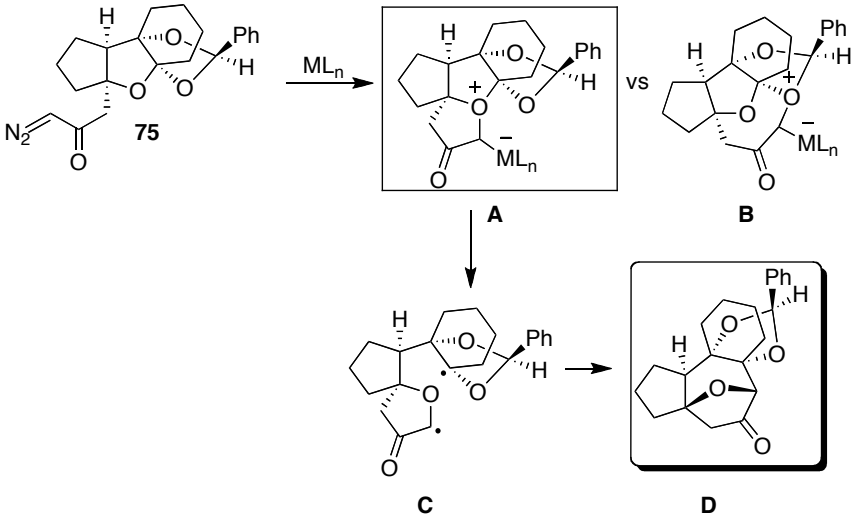
Our first approach to diazoketones **75** and **76** was to make the acid under standard conditions (LiOH) and, without purification, make the acid chloride in situ followed by the addition of an Et_2O/CH_2N_2 solution. Although this protocol worked well in the synthesis of the diazoketones in chapter two, in this case it produced only trace amounts of the desired diazoketones. An alternative carboxyl activation procedure using PPh_3 and NBS also failed to furnish the diazoketones. Gratifyingly the synthesis of diazoketones **75** and **76** was accomplished in 50% yield by saponification of the mixture using LiOH followed by mixed anhydride formation with ethyl chloroformate and NEt_3 and treatment with CH_2N_2 in Et_2O (Scheme 3.20).



Scheme 3.20 Synthesis of diazoketones **75** and **76**.

3.3.4 Oxonium Ylide Generation and Stevens Rearrangement.

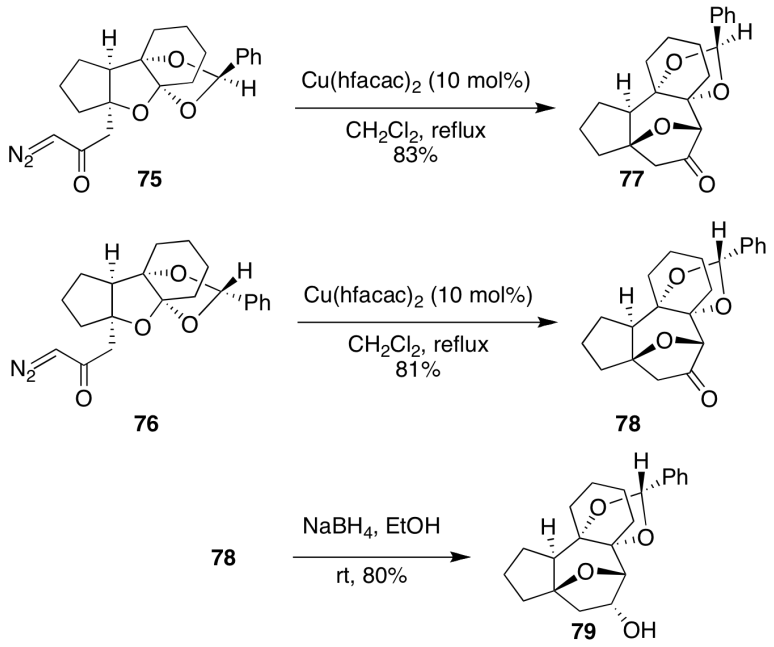
With the key diazoketones **75** and **76** in hand the stage was set to examine the oxygen-directed Stevens rearrangement. The outcome of this rearrangement was slightly worrisome because at least two oxygen atoms were considered available to react with the metallocarbene intermediate form different ylides **A** and **B** (Scheme 3.21). The undesired ylide **B** could undergo [1,2]-shift to give an isomeric product to the desired one, or suffer ionic fragmentation since the oxonium oxygen is part of two separate acetals. However, formation of five-membered ylide **A** was deemed to be more likely for kinetic reasons. If the five-membered ylide is formed and homolysis occurs[16] the resulting biradical **C**, could undergo radical forming product **D**. The catalyst chosen for this rearrangement



Scheme 3.21 Potential reaction pathways of diazoketone **75**.

was $Cu(hfacac)_2$ because of its success in the sulfur-directed Stevens rearrangement, demonstrated in Chapter two. When diazoketones **75** and **76** were treated with catalytic $Cu(hfacac)_2$ the ring-expanded products **77** and **78** were

isolated in good yields and as single diastereomers (Scheme 3.22). No other rearrangement products were observed, demonstrating the selectivity and efficiency of this reaction. Attempts to grow suitable crystals for X-ray crystallographic analysis failed, but selective reduction of ketone **78** to secondary alcohol **79** furnished a product suitable for X-ray analysis confirming the oxa-bridged tricyclic structure (Figure 3.2).



Scheme 3.22 Stevens rearrangement of diazoketones **75** and **76**.

The selectivity observed in this rearrangement can be attributed to the benzylidene protecting group. In this reaction the directing group is part of a ring adding increased rigidity to the system, allowing for stereoselective and efficient recombination of the biradical intermediate. This approach addresses two major problems in the synthesis of these natural products; the formation of the seven-membered ring as well as stereoselective introduction of the two sites of

bridgehead oxygenation in a *trans* fashion. The tricyclic core can be synthesized in eleven steps starting from commercially available starting materials.

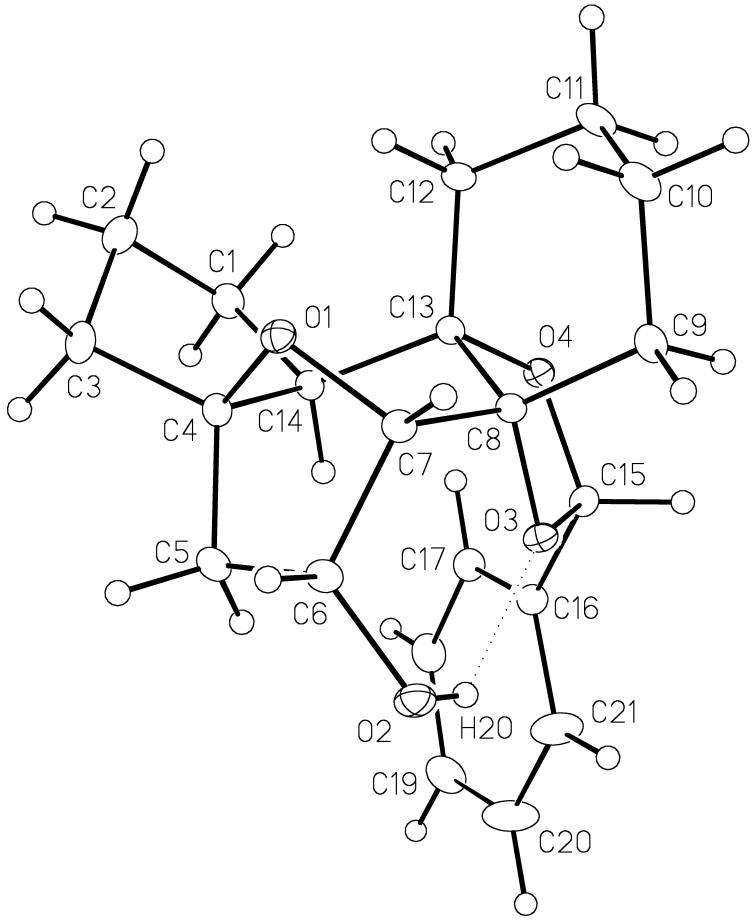
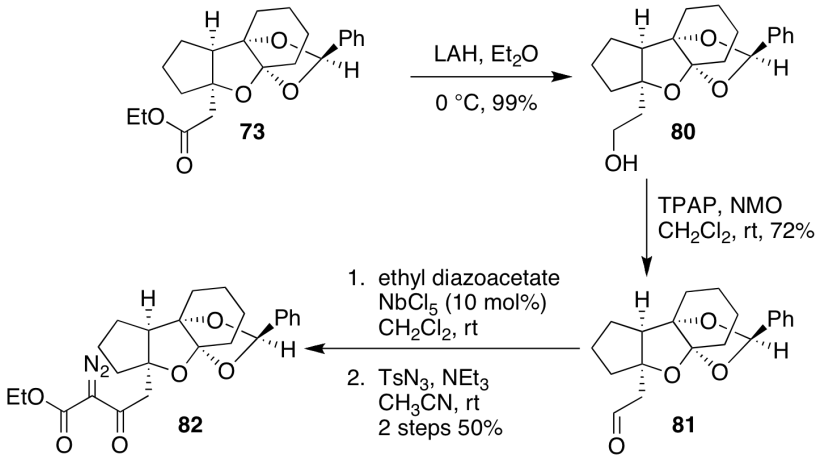


Figure 3.2 ORTEP structure from X-ray diffraction analysis of alcohol **79**.

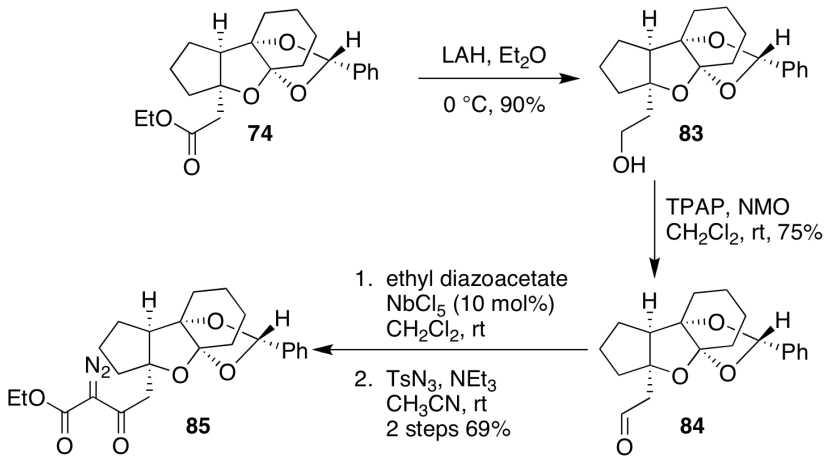
3.3.5 Synthesis of Diazoketoester Substrates

Success of the diazoketone rearrangement prompted us to investigate the analogous diazoketoester rearrangement, which would introduce another functionality handle for further manipulation. The synthesis of the diazoketoesters was achieved by using one of the intermediates in the diazoketone synthesis. An attempt to carry out a cross-Claisen reaction with ester **73** failed to



Scheme 3.23 Synthesis of diazoketoester **82**.

afford the desired ketoester in good yield, furnishing mostly dimerized ethyl acetate. An alternative approach was adopted which involved reduction of the ester to afford the primary alcohol **80** in excellent yield followed by TPAP oxidation to aldehyde **81** in 72% yield (Scheme 3.23). Other oxidation protocols furnished **81** in consistently lower yields than were obtained using TPAP. Synthesis of diazoketoester **82** was accomplished in two steps by formation of the ketoester using a modified[18] Roskamp procedure followed by Regitz[19] diazotransfer protocol providing the diazoketoester **82** in 50% yield over two

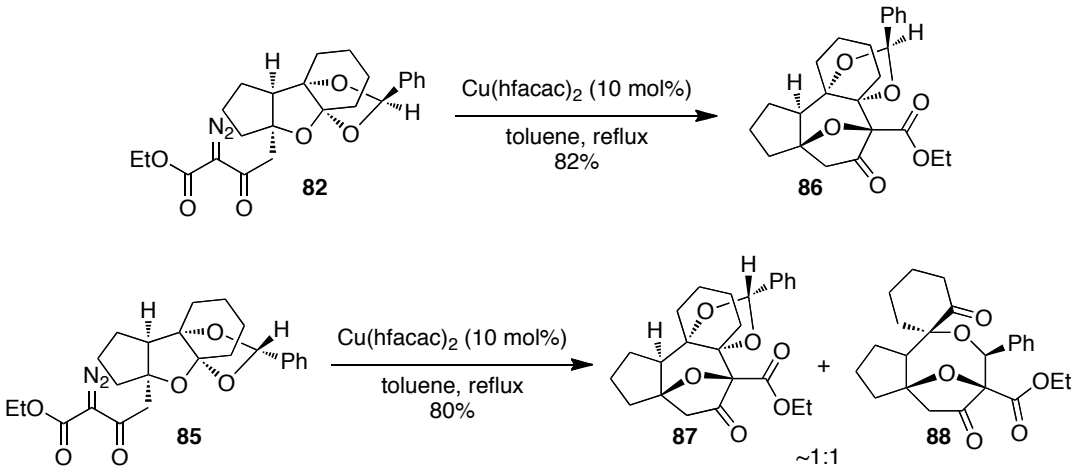


Scheme 3.24 Synthesis of diazoketoester **85**.

steps. Diazoketoester **85** was obtained using the same reaction sequence with slightly better yields (Scheme 3.24). Fortunately, both diazoketoesters **82** and **85** could be obtained in a four-step sequence using the known esters **73** and **74** from the diazoketone series.

3.3.6 Stevens Rearrangement of Diazoketoesters

With diazoketoesters in hand the Stevens rearrangement was attempted with the identical reaction conditions ($Cu(hfacac)_2$, CH_2Cl_2) used for the formation of tricyclic compounds **77** and **78** but no reaction occurred. This was not entirely surprising because it is known that doubly stabilized diazoketoesters, similar to **82** and **85** require higher temperatures[20] to undergo efficient undergo metallocarbene formation. Subsequent treatment of **82** with $Cu(hfacac)_2$ in toluene at reflux afforded the ring expansion product **86** in good yield as a single diastereomer (Scheme 3.25). With the optimized conditions established, rearrangement of diazoketoester **85** was attempted and surprisingly furnished a 1:1 mixture of the desired ring expansion product **87** and an unidentified product. Fortunately X-ray crystallography both confirmed the structure of Stevens rearrangement product **87** and identified the other product as the eight-membered cyclic ether **88**.



Scheme 3.25 Stevens rearrangement of diazoketoesters **82** and **83**.

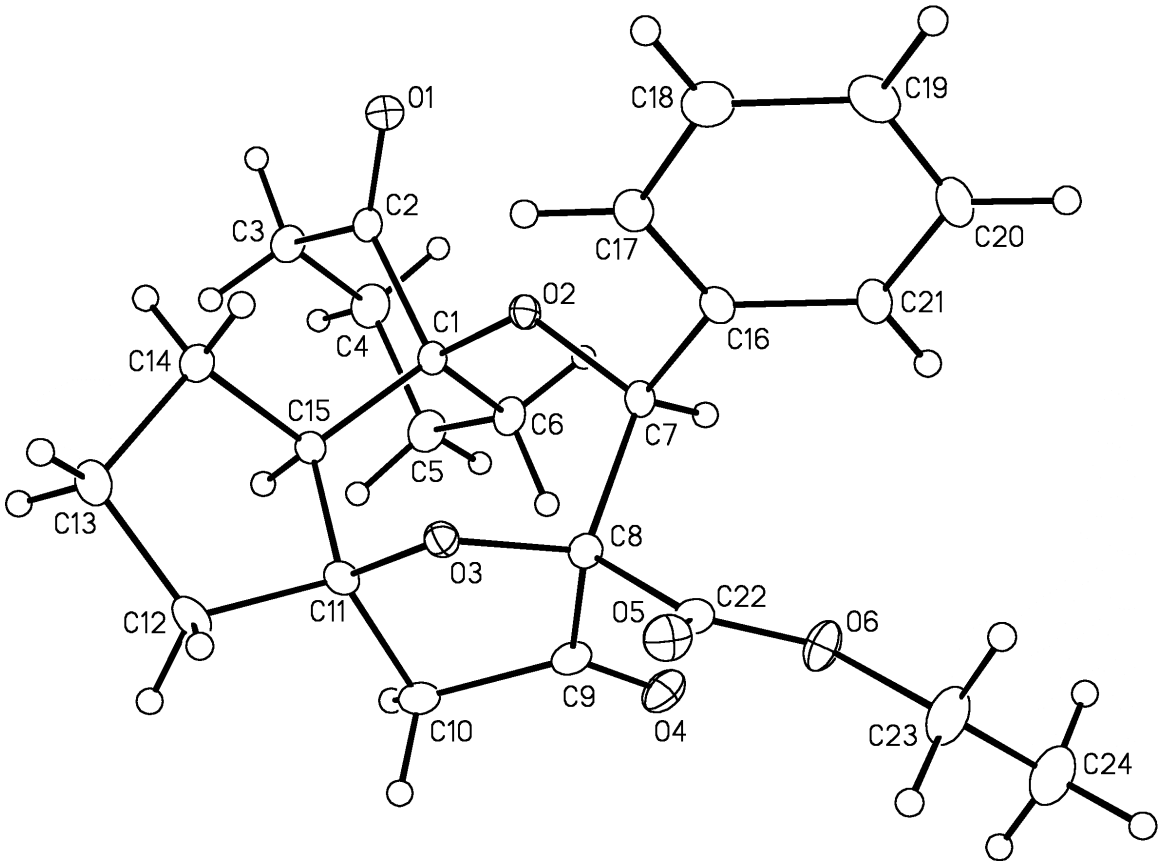
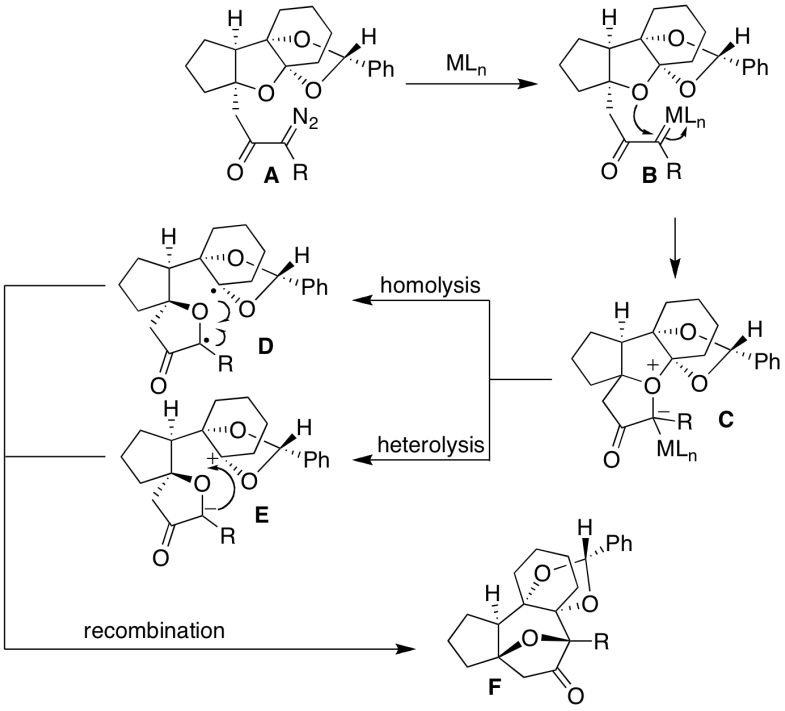


Figure 3.3 ORTEP structure from X-ray diffraction analysis of **88**.

3.3.7 Mechanism of the Oxygen-Directed Stevens Rearrangement

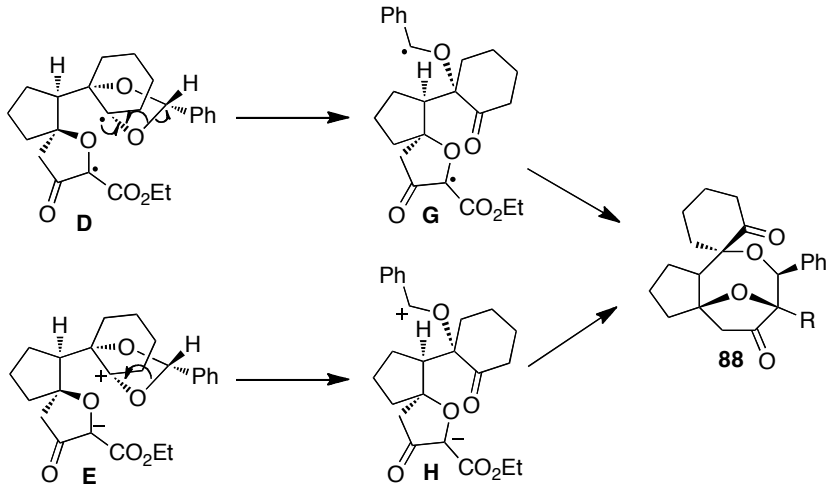
Although the mechanism of the Stevens rearrangement has been discussed in some detail in chapter one, the unexpected isolation of ether **88** as a major product requires some explanation in the context of the presumed mechanistic pathway of these reactions. The first step of the reaction is complexation of the diazoketone with extrusion of dinitrogen gas to give metallocarbene **B**, which is attacked by the lone-pair of the cyclic ether to form an oxonium ylide **C** (Scheme 3.26). The presence of the oxygen-atom on the migrating carbon suggests that two possible mechanisms could proceed to give the Stevens rearrangement products. Homolysis of the carbon oxygen bond to give biradical **D** and rapid



Scheme 3.26 Proposed mechanism for ring expansion.

recombination would explain formation of Stevens products **F**. An alternative mechanism involving heterolysis to give ion pair **E** followed by ring closure could also furnish Stevens products **F**. Ether **88** is believed to arise from further fragmentation of intermediates **D** or **E** leading to the formation of intermediates **G** (a highly stable benzylic ether radical) and **H** (a highly stabilized benzylic ether carbocation (Scheme 3.27). Carbon-carbon bond formation could then occur providing ether **88**. A possible reason that this product is formed in this rearrangement and not with the other diazoketoester **82** could be a steric issue. Repulsion between the phenyl and ester groups could promote further fragmentation to generate a stabilized intermediate **G** or **H**.[20] It may be possible to distinguish between **G** and **H** by incorporating a radical trap into the molecule to compete with the radical recombination of the biradical intermediate, ruling out the ion pair mechanism. There are two possible reasons that the same type of ether side product is not observed in the analogous diazoketone **76**. Firstly, the phenyl group is less likely to hinder bond formation because steric repulsion is minimal

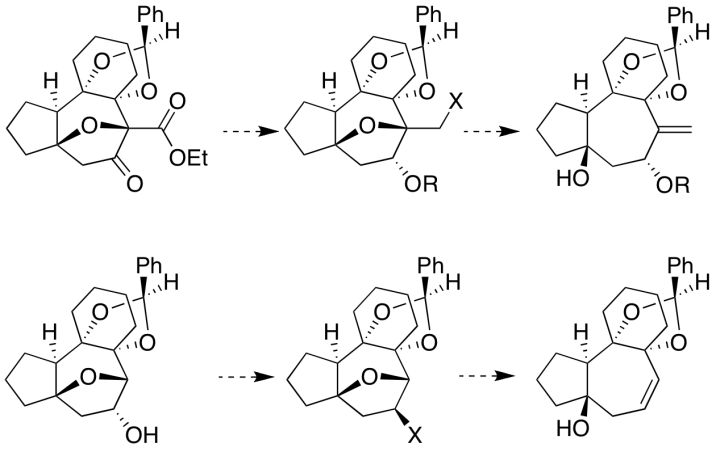
due to the hydrogen atom in place of an ester side chain. Also, the temperature is considerably lower (CH_2Cl_2 at reflux) so even if bond formation is slow, secondary fragmentation to the other reactive intermediate might not be possible.



Scheme 3.27 Proposed mechanism for the formation of eight-membered ether **88**.

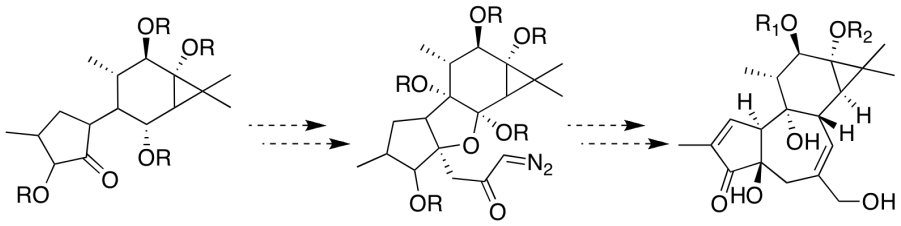
3.4 Conclusions and Future Work

We have discovered that oxonium ylide generation and subsequent Stevens rearrangement is an efficient and stereoselective way to construct the tricyclic core of the tigliane and daphnane diterpenes. Diazoketones and diazoketoesters are both suitable substrates for the oxonium ylide Stevens



Scheme 3.28 Possible ether-bridge cleavage strategies.

rearrangement and can be prepared from simple, readily available starting materials. A weakness of this methodology is that the oxygen-directed Stevens rearrangement does not posses a suitable trigger for ether-cleavage to occur like the one observed in the sulfur-directed Stevens rearrangement.[17] A possible solution to this problem could involve manipulation of the ketone or ester to generate a functionality that could open the ether bridge, like a halogen or sulfide (Scheme 3.28). If a suitable ether cleavage approach were developed, the methodology outlined in this chapter could potentially be used towards the synthesis of one or more of these natural products by using more functionalized starting materials. This would allow for a convergent synthesis of these natural products in an efficient and stereoselective manner (Scheme 3.29).



Scheme 3.29 Potential application to phorbol skeleton using more functionalized substrates.

3.5 Experimental

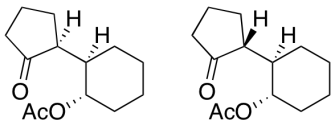
3.5.1 General Information

Reactions were carried out in flame-dried glassware under a positive argon atmosphere unless otherwise stated. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannulae. Solvents were distilled before use: methylene chloride (CH_2Cl_2) from calcium hydride, diethyl ether (Et_2O) and tetrahydrofuran (THF) from sodium/benzophenone ketyl, and toluene from sodium metal. Ethereal diazomethane was prepared from Diazald according to literature procedures.[21] Cerium trichloride ($CeCl_3 \bullet 7H_2O$) and zinc chloride

($ZnCl_2$) were dried in vacuo at 150°C for 2 hours. Thin layer chromatography (T.L.C.) was performed on plates of silica precoated with 0.25 mm Kieselgel 60 F_{254}. Flash chromatography columns were packed with 230-400 mesh silica gel. Radial chromatography was performed on plates of silica pre-coated with 2, or 4 mm silica gel 60 PF_{254} containing gypsum.

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz or 500 MHz on Varian Inova 400 and 500, Mercury 400, or Unity 500 spectrometers, and the chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane (0 ppm). Coupling constants (*J*) are reported in Hz. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets, etc. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 125 MHz or 100 MHz and are reported (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).

3.5.2 Characterization



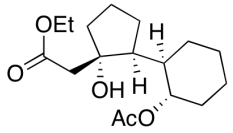
63a **63b**

Ketone 63a/b. A 5:1 mixture of alcohols **62**[14] (4.63 g, 25.4 mmol) was dissolved in CH_2Cl_2 (25 mL). Pyridine (4.10 mL, 50.8 mmol), DMAP (310 mg, 2.54 mmol) and acetic anhydride (3.60 mL, 38.1 mmol) were added at 0 ºC. The reaction mixture was allowed to warm to room temperature and stirred overnight. The

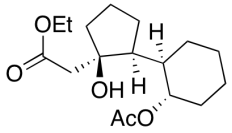
reaction was quenched with the addition of 1 N HCl (100 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL). The organic extracts were combined and washed with water (50 mL), pre-dried with brine (50 mL), dried ($MgSO_4$), filtered and concentrated. The resulting oil was purified by gradient column chromatography (silica gel; 5%, 10%, 15% EtOAc/hexanes until the products were recovered) to yield **63a** (4.36 g) and **63b** (1.09 g) as colourless oils in a combined overall yield of 96%.

Major 63a: R_f 0.34 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2936, 2860, 1737, 1451, 1407, 1311, 1239, 1153, 1134, 1119, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.65 (ddd, J = 10.4, 10.4, 4.6 Hz, 1H), 2.32 -2.24 (m, 1H), 2.23-2.17 (m, 1H), 2.07-1.89 (m, 5H), 1.93 (s, 3H), 1.76-1.60 (m, 5H), 1.32-1.20 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.1, 170.3, 74.1, 52.1, 41.5, 38.7, 31.8, 30.8, 25.5, 24.4 (2C), 21.2, 21.0; HRMS (ESI, $[M+Na]^+$) calcd for $C_{13}H_{20}O_3Na$ 247.1305, found: m/z 247.1304.

Minor 63b: R_f 0.41 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2937, 2861, 1737, 1451, 1407, 1375, 1317, 1243, 1212, 1162, 1114, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.65 (ddd, *J* = 15.0, 15.0, 4.3 Hz, 1H), 2.36 -2.26 (m, 2H), 2.18-2.11 (app tt, *J* = 11.6, 3.4, Hz, 1H), 2.05-1.94 (m, 4H), 2.02 (s, 3H), 1.76-1.60 (m, 4H), 1.42-1.47 (m, 1H), 1.34-1.2 (m, 3H), 1.06-1.14 (app qd, *J* = 12.5, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.0, 170.6, 74.3, 49.7, 41.1, 39.3, 32.2, 26.0, 25.2, 24.7, 23.9, 21.2, 20.7; (ESI, $[M+Na]^+$) calcd for $C_{13}H_{20}O_3Na$ 247.1305, found: m/z 247.1306.



64a



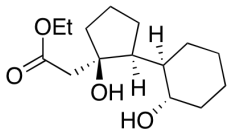
64b

Alcohol 64a/b. To a stirred solution of hexamethyldisilazane (1.58 mL, 7.59 mmol) in THF (20 mL) at –78 °C was added *n*BuLi (3.96 mL of 1.60M solution, 6.33 mmol) and the resulting mixture was stirred at –78 ºC for 30 min. The reaction was then warmed to 0 ºC and stirred for 15 min before being cooled once again to –78 ºC. Ethyl acetate (528 μL, 5.27 mmol) was added dropwise, and the mixture was stirred for 45 min. Dry cerium trichloride powder (1.29 g, 5.27 mmol) was added, and the heterogeneous solution was stirred for an additional 2 h at the same temperature. A THF solution (3 mL) of ketone **63a** (977 mg, 4.36 mmol) was added dropwise to the above mixture and the reaction mixture was stirred for 2 h at –78 ºC. The reaction was then diluted with Et_2O (50 mL) and quenched by the addition of saturated ammonium chloride solution (25 mL) and allowed to warm to room temperature. After separation of the phases, the aqueous layer was extracted with Et_2O (3 x 25 mL) and the combined organic extracts were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (silica gel; 5%, 10%, 15% EtOAc/hexanes until the products were recovered) to yield **64a** (1.09 g) as a colourless oil and **64b** (113 mg) as a white solid, in a combined overall yield of 88%.

Major 64a: R_f 0.38 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3532, 2939, 2863, 1729, 1449, 1371, 1336, 1300, 1246, 1187, 1128, 1097, 1075, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.66 (ddd, J = 9.0, 9.0, 3.9 Hz, 1H), 4.20-4.11 (m, 2H), 3.40 (s, OH, 1H), 2.72 (d, J_{AB} = 14.6 Hz, 1H) 2.42 (d, J_{AB} = 14.6 Hz, 1H), 2.20 (s, 3H), 2.00-1.94 (m, 1H), 1.92-1.8 (m, 3H), 1.79-1.59 (m, 6H), 1.58-1.49 (m, 1H), 1.49-1.37 (m, 2H), 1.37-1.30 (m, 2H), 1.29-1.24 (m, 1H), 1.29-1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 169.9, 79.6, 75.4, 60.5, 51.5, 45.3, 40.5, 39.9, 31.3, 31.2, 37.2, 24.9, 23.7 21.7, 21.5, 14.2; HRMS (ESI, $[M+Na]^+$) calcd for $C_{17}H_{28}O_5Na$ 335.1829, found: m/z 335.1829.

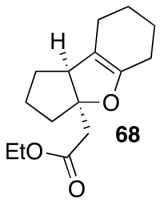
Minor 64b: m.p. 68-69 °C; R_f 0.38 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3517, 2937, 2867, 1733, 1450, 1371, 1331, 1244, 1203, 1095, 1028 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$) δ 4.72 (ddd, J = 9.0, 9.0, 3.9 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.82 (s, OH, 1H), 2.63 (d, J_{AB} = 15.7 Hz, 1H) 2.4 (d, J_{AB} = 15.7 Hz, 1H), 2.20 (s, 3H), 2.00-1.94 (m, 1H), 1.93-1.82 (m, 3H), 1.81-1.67 (m, 3H), 1.66-1.56 (m, 4H), 1.55-1.46 (m, 1H), 1.45-1.25 (m, 4H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 170.3, 80.7, 74.2, 60.7, 49.8, 39.9, 39.8, 39.0, 29.0, 27.6, 27.1, 22.7, 22.3, 21.5, 20.5, 14.1; HRMS (ESI, $[M+Na]^+$) calcd for $C_{17}H_{28}O_5Na$ 335.1829, found: m/z 335.1829.



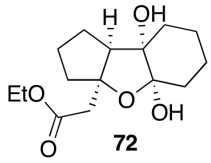
65

Diol 65. NaOEt (2.0 mL, 0.50M, in anhydrous EtOH, 0.42 mmol) was added via syringe to a stirred solution of **64a** (358 mg, 1.05 mmol) in EtOH (3 mL). The reaction was stirred for 30 min. To the reaction was then added EtOAc (20 mL) and 1 N HCl (10 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with EtOAc (20 mL). The combined extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography (silica gel; 30% EtOAc / hexanes) to give **65** (270 mg, 95%) as a colourless oil: R_f 0.16 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3249, 2930, 2859, 1732, 1449, 1369, 1321, 1299, 1242, 1191, 1120, 1065, 1047 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60, (br s, 2OH, 2H), 4.18 (q, J = 7.5 Hz, 2H), 3.34 (ddd, J = 9.5, 9.5, 4.5 Hz, 1H), 2.82 (d, J_{AB} = 15.5 Hz, 1H), 2.37 (d, J_{AB} = 15.5 Hz, 1H), 2.05-2.00 (m, 1H), 1.93-1.80 (m, 3H), 1.78-1.66 (m, 3H), 1.65-1.61 (m, 1H), 1.60-1.49 (m, 3H), 1.46 (dd, J = 11.5, 7.0 Hz, 1H), 1.28 (t, J = 7 Hz, 3H), 1.32-1.26 (m, 1H), 1.23-1.16 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 78.6, 70.2, 60.8, 55.9, 43.0, 42.4, 39.3, 35.7, 34.3, 26.2, 24.6, 23.7, 20.6, 14.2; HRMS (ESI, $[M+Na]^+$) calcd for $C_{15}H_{26}O_4Na$ 293.1723, found: m/z 293.1724.



68

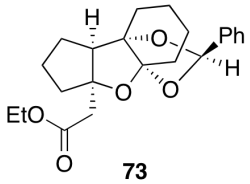
Enol Ether 68. A solution of alcohol **65** (1.0 g, 3.7 mmol), NMO (650 mg, 5.55 mmol), and 4Å molecular sieves (500 mg) in CH_2Cl_2 (37 mL) was stirred at room temperature for 20 min. To this was added TPAP (65 mg, 0.185 mmol) and the resulting mixture was stirred for 2 h. The reaction mixture was passed through a short plug of silica gel, and concentrated. The crude product was then dissolved in dichloromethane (74 mL) and cooled to –78 ºC. To this solution was added BF_3•OEt_2 (680 μl, 5.55 mmol) dropwise and the resulting mixture was stirred for 30 min. The reaction was then quenched by the addition water (20 mL) and NEt_3 (1 mL), and the aqueous phase was back-extracted with CH_2Cl_2 (50 mL). The combined organic extracts were washed with water (30 mL), brine (30mL), dried ($MgSO_4$), and concentrated to give the crude product as a yellow oil. This material was then purified by column chromatography (silica gel; 5% EtOAc / hexanes) to give **68** (705 mg, 76%) as a colourless oil: R_f 0.64 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2934, 2860, 1737, 1447, 1369, 1333, 1289, 1239, 1203, 1178, 1155, 1117, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.12 (q, J = 7.1 Hz, 2H), 3.04 (br s, 1H), 2.70 (d, J_{AB} = 14.1 Hz, 1H), 2.68 (d, J_{AB} = 14.1 Hz, 1H), 2.06-1.96 (m, 3H), 1.94-1.88 (m, 2H), 1.76-1.55 (m, 9H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 150.1, 107.2, 93.4, 60.2, 53.9, 43.6, 39.9, 30.9, 24.3, 23.1, 23.0, 22.9, 22.3, 14.2; HRMS (ESI, $[M+Na]^+$) calcd for $C_{15}H_{22}O_3Na$ 273.1461, found: m/z 273.1462.



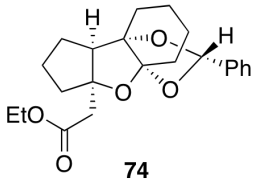
72

Diol 72. To a stirred solution of **68** (656 mg, 2.62 mmol) in acetone (17 mL) and

water (2 mL) was added NMO (614 mg, 5.24 mmol) and 4 wt. % OsO_4 solution in water (832 μL, 0.131 mmol). The mixture was allowed to stir for 24 h at room temperature and then quenched by the addition of saturated $Na_2S_2O_3$ solution (15 mL). After separation of the phases, the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic extracts washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography (silica gel; 30% EtOAc/hexanes until the products were recovered) to yield **72** (724 mg, 97%) as colourless oil: R_f 0.15 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3420, 2939, 2868, 1730, 1450, 1370, 1301, 1196, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.15 (m, 2H), 3.58 (s, OH, 1H), 2.85 (d, J_{AB} = 14.5 Hz, 1H), 2.84 (d, J = 1.5 Hz, 1H), 2.77 (d, J_{AB} = 14.5 Hz, 1H), 2.69 (dd, J = 9.0, 3.5 Hz, 1H), 2.20-1.74 (m, 7H), 1.70-1.43 (m, 6H), 1.38-1.30 (m, 1H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 106.0, 90.8, 78.9, 60.5, 58.8, 46.6, 38.2, 33.9, 31.6, 25.8, 23.1, 22.2, 21.0, 14.2; HRMS (ESI, $[M+Na]^+$) calcd for $C_{15}H_{24}O_5Na$ 307.1516, found: m/z 307.1515.



73



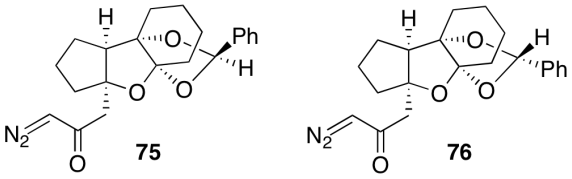
74

Benzylidienes 73/74. To a stirred solution of **72** (330 mg, 1.16 mmol) in CH_2Cl_2 (12 mL) at 0 °C was added benzaldehyde (1.18 mL, 11.6 mmol). The reaction was stirred for 10 min. To this solution was added dry $ZnCl_2$ (237 mg, 1.74 mmol) and the resulting mixture was stirred for 3 h at 0 °C. The reaction was quenched by the addition of water (10 mL) and the aqueous phase was back-extracted with CH_2Cl_2 (20 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was purified by gradient column chromatography (1%, 3%, 5%, 8% EtOAc / hexanes) to give **73** and **74** (360 mg, 83%) as colourless oils in a 1.5:1 mixture of anomers.

A small amount of each diastereomer was isolated, by careful chromatography, for characterization purposes.

Major Anomer 73: R_f 0.59 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2952, 2871, 1733, 1457, 1392, 1338, 1195, 1058, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53-7.51 (m, 2H), 7.41-7.35 (m, 3H), 6.12 (s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.06 (d, J_{AB} = 14.7 Hz, 1H), 2.95 (d, J_{AB} = 14.7 Hz, 1H), 2.95 (dd, J = 10.1, 3.7 Hz, 1H), 2.27 (app dt, J = 14.0, 4.2 Hz, 1H), 1.92-1.78 (m, 4H), 1.76-1.62 (m, 4H), 1.60-1.51 (m, 4H), 1.42 (dddd, J = 20.5, 7.3, 7.3, 5.6 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 138.0, 129.1, 128.4, 126.5, 113.1, 101.4, 92.3, 90.1, 60.4, 56.4, 44.0, 39.8, 32.3, 30.1, 28.1, 25.6, 19.9, 19.1, 14.2; HRMS (ESI, $[M+Na]^+$) calcd for $C_{22}H_{28}O_5Na$ 395.1829, found: m/z 395.1830.

Minor Anomer 74: R_f 0.59 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2940, 2867, 1730, 1451, 1392, 1369, 1197, 1045, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61-7.58 (m, 2H), 7.40-7.33 (m, 3H), 6.05 (s, 1H), 4.08 (m, 2H), 2.90 (d, J_{AB} = 15.0 Hz, 1H), 2.88 (dd, J = 8.8, 6.8 Hz, 1H) 2.76 (d, J_{AB} = 15 Hz, 1H), 2.51-2.46 (m, 1H), 2.28-2.22 (m, 1H), 1.98-1.80 (m, 6H), 1.78-1.66 (m, 3H), 1.66-1.58 (m, 1H), 1.53-1.36 (m, 2H), 1.24 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 137.4, 129.0, 128.2, 126.7, 112.8, 102.5, 93.4, 91.0, 60.0, 56.2, 44.1, 39.9, 34.9, 29.9, 26.7, 25.3, 23.3, 21.0, 14.2; HRMS (ESI, $[M+Na]^+$)calcd for $C_{22}H_{28}O_5$ (Na) 395.1829, found: m/z 395.1830.



Diazoketones 75 and 76. To a solution of **73/74** (1.5:1 mixture of anomers, 810 mg, 2.17 mmol) in THF (4 mL) and MeOH (4 mL) was added 2.00 N LiOH (2.17

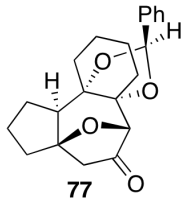
mL, 4.35 mmol). The reaction mixture was stirred for 24 h during which time the reaction turned slightly yellow and the starting material was consumed. To this reaction was then added Et_2O (50 mL) and H_2O (50 mL). After the layers were separated EtOAc (50 mL) was added to the aqueous phase followed by the dropwise addition of 1 N HCl until the pH reached ~3. The cloudy aqueous phase was then extracted with EtOAc (3 x 30 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated to yield the desired acid. The crude product was dissolved in THF (22 mL) and cooled to 0 °C. To this solution was added NEt_3 (692 μL, 4.97 mmol) and ethyl chloroformate (396 μL, 4.14 mmol). The reaction was stirred at this temperature for 1 h before being warmed to room temperature. At this time the reaction mixture was directly transferred via cannula to a freshly prepared solution of diazomethane (~20 mmol) in Et_2O (~60 mL) and the resulting mixture stirred for 16 h. A gentle stream of Ar(g) was applied to the system to allow for slow evaporation of both excess diazomethane and solvent. The crude yellow oil was purified by column chromatography (silica gel; 5%, 10%, 15% EtOAc/hexanes until the products were recovered) to yield **75** (210 mg) and **76** (190 mg) as yellow oils in a combined overall yield of 50% over 3 steps.

Major Anomer 75: R_f 0.26 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3104, 3067, 2943, 2867, 2102, 1639, 1452, 1360, 1045, 952 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57-7.55 (m, 2H), 7.42-7.37 (m, 3H), 6.09 (s, 1H), 5.02 (br s, 1H), 2.96 (d, J_{AB} = 13.5 Hz, 1H), 2.68 (t, J = 7.5 Hz, 1H), 2.49 (d, J_{AB} = 13.5 Hz, 1H), 2.52-2.40 (m, 1H), 2.29-2.23 (m, 1H), 1.91-1.78 (m, 5H), 1.75-1.58 (m, 4H), 1.53-1.36 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.3, 137.9, 128.9, 128.3, 126.0, 113.0, 101.9, 93.8, 90.7, 57.3, 55.4, 50.6, 39.5, 34.8, 30.0, 26.6, 25.0, 23.2, 20.8; HRMS (ESI, $[M+Na]^+$) calcd for $C_{21}H_{24}O_4N_2Na$ 391.1628, found: m/z 391.1631.

Minor Anomer 76: R_f 0.36 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3094, 2953, 2870, 2104, 1744, 1637, 1361, 1055, 959 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53-7.50 (m, 2H), 7.43-7.35 (m, 3H), 6.13 (s, 1H), 5.64 (br s, 1H), 3.16 (d, J_{AB} =

13.6 Hz, 1H), 2.82 (dd, J = 10.0, 3.6 Hz, 1H), 2.69 (d, J_{AB} = 13.6 Hz, 1H), 2.26 (app dt, J = 14.0, 4.0 Hz, 1H), 1.92-1.78 (m, 5H), 1.82-1.63 (m, 4H), 1.62-1.45 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 137.8, 129.2, 128.4, 126.4, 113.4, 101.4, 92.6, 90.0, 57.5, 56.0, 51.0, 39.2, 32.3, 29.5, 27.8, 25.6, 19.5, 18.9; HRMS (ESI, $[M+Na]^+$) calcd for $C_{21}H_{24}O_4N_2Na$ 391.1628, found: m/z 391.1629.

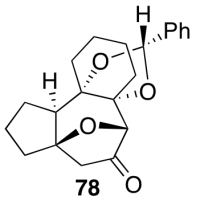
Carbene Transfer Reaction of 75: Preparation of 77[23]



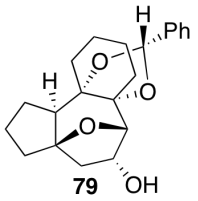
77

To a solution of $Cu(hfacac)_2$ (2 mg, 5 x 10^{-3} mmol) in CH_2Cl_2 (4 mL) at reflux was added a solution of **75** (17 mg, 0.046 mmol) in CH_2Cl_2 (1 mL), and the resulting mixture monitored by TLC. Upon consumption of diazoketone (30 min) the reaction mixture was cooled to room temperature and quenched by the addition of saturated $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The organic extracts were combined and washed with water (5 mL), pre-dried with brine (5 mL), dried ($MgSO_4$), filtered and concentrated. The resulting oil was purified by column chromatography (silica gel; 15 % EtOAc/hexanes until the product was recovered) to yield **77** (13 mg, 81%) as a white solid: m.p. 144-145 °C; R_f 0.43 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3063, 3035, 2944, 2872, 2248, 1767, 1451, 1275, 1069, 917 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.31 (m, 5H), 6.14 (s, 1H), 3.56 (s, 1H), 2.60 (d, J_{AB} = 17.5 Hz, 1H), 2.40 (dd, J = 13.0, 6.5 Hz, 1H), 2.30 (d, J_{AB} = 17.5 Hz, 1H), 2.22-2.14 (m, 1H), 2.10-1.84 (m, 8H), 1.82-1.75 (m, 1H), 1.72-1.56 (m, 3H), 1.50 (dddd, J = 21.5, 13.0, 4.0, 4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.9, 137.7, 128.1, 127.8, 125.2, 99.3, 88.0, 84.3, 81.5, 81.4, 53.8, 44.0, 35.0, 33.3, 32.0, 28.1, 22.7, 21.4, 20.1; HRMS (EI, M^+) calcd for $C_{21}H_{24}O_4$ 340.1675, found: m/z 340.1672.

Carbene Transfer Reaction of 76, Preparation of 78[23]

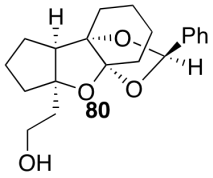


To a solution of $Cu(hfacac)_2$ (3 mg, 6 x 10^{-3} mmol) in CH_2Cl_2 (5 mL) at reflux was added a solution of **76** (23 mg, 0.062 mmol) in CH_2Cl_2 (1 mL), and the resulting mixture monitored by TLC. Upon consumption of diazoketone (30 min) the reaction mixture was cooled to room temperature and quenched by the addition of saturated $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The organic extracts were combined and washed with water (5 mL), pre-dried with brine (5 mL), dried ($MgSO_4$), filtered and concentrated. The resulting oil was purified by column chromatography (silica gel; 15% EtOAc/hexanes until the product was recovered) to yield **78** (18 mg, 85%) as a white solid: m.p. 148-150 °C; R_f 0.43 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2941, 2873, 1760, 1449, 1221, 1075, 1006 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.31 (m, 5H), 6.14 (s, 1H), 3.56 (s, 1H), 2.89 (dd, J_{ABX} = 17.4, 0.9 Hz, 1H), 2.52 (dd, J_{ABX} = 17.4, 0.9 Hz, 1H), 2.29 (dd, J = 13.4, 6.5 Hz, 1H), 2.18-2.00 (m, 5H), 1.92 (dddd, J = 13.0, 9.5, 4.5, 1.0 Hz, 1H), 1.94 (dt, J = 13.5, 7.5 Hz, 1H), 1.67-1.50 (m, 4H), 1.41-1.27 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.6, 142.0, 128.1, 127.6, 125.0, 100.5, 88.7, 84.0, 83.8, 80.6, 53.7, 45.0, 34.8, 33.9, 32.2, 28.2, 22.9, 21.7, 19.8; HRMS (EI, M^+) calcd for $C_{21}H_{24}O_4$ 340.1675, found: m/z 340.1675.



79

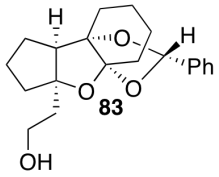
Alcohol 79.[22] A solution of **78** (25 mg, 0.073 mmol) in 95 % ethanol (500 μL) was treated with sodium borohydride (4 mg, 0.1 mmol) at room temperature. The reaction was stirred for 30 min, and quenched with saturated NH_4Cl solution (1 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The organic extracts were combined and washed with water (5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated. The resulting crude material was purified by column chromatography (silica gel; 15% EtOAc / hexanes until the product was recovered) to yield **79** (20 mg, 80%) as a white solid: m.p. 100-102 °C; R_f 0.35 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3528, 3086, 3062, 3031, 2957, 2941, 2929, 2890, 2853, 1427, 1122, 1109, 1056 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.42-7.33 (m, 3H), 6.24 (s, 1H), 4.44 (ddd, *J* = 11.6, 11.6, 6.0 Hz, 1H), 4.10 (d, *J* = 6.0 Hz, 1H), 3.95 (d, *J* = 11.6 Hz, 1H), 2.27 (dd, *J* = 12.8, 10.8 Hz, 1H), 2.14 (dt, *J* = 13.6, 4.4 Hz, 1H), 2.08 (t, *J* = 8 Hz, 1H), 2.04-1.8 (m, 3H), 1.79-1.55 (m, 9H), 1.51-1.39 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 128.5, 128.4, 125.3, 100.4, 89.2, 84.9, 81.2, 79.9, 75.1, 54.7, 45.6, 38.9, 34.7, 30.9, 26.7, 24.3, 21.4, 20.9; HRMS (ESI, $[M+Na]^+$) calcd for $C_{21}H_{26}O_5Na$ 365.1723, found: m/z 365.1722.



80

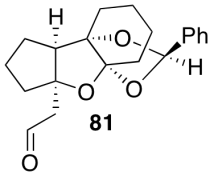
Alcohol 80. A solution of **73** (96 mg, 0.26 mmol) in dry Et_2O (2 mL) was added by cannula to a stirred solution of LAH (15 mg, 0.39 mmol) in dry Et_2O (1 mL) at 0 °C. The solution was stirred under Ar(g) and allowed to warm to room

temperature. The reaction was quenched with solid Na_2SO_4•10 H_2O (500 mg) and stirred overnight. The solution was filtered through a pad of Celite/magnesium sulfate and the filtrate concentrated to obtain a crude colourless oil. The resulting crude oil was purified by column chromatography (silica gel; 30% EtOAc / hexanes until the product was recovered) to yield **80** (83 mg, 99%) as a colourless oil: R_f 0.14 (30 % EtOAc/hexanes); IR (CH_2Cl_2 cast) 3454, 3066, 3035, 2945, 2867, 1453, 1395, 1344, 1326, 2305, 2332, 1194, 1047, 952 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52-7.50 (m, 2H), 7.41-7.34 (m, 3H), 6.25 (s, 1H), 4.02 (ddd, *J* = 11.2, 9.6, 3.6 Hz, 1H), 3.83 (app dt, *J* = 9.5, 4.8 Hz, 1H), 2.90 (br s, OH, 1H), 2.69 (dd, *J* = 9.4, 4.2 Hz, 1H), 2.53 (ddd, *J* = 14.4, 9.5, 4.8 Hz, 1H), 2.32 (app dt, *J* = 14.4, 3.7 Hz, 1H), 2.02-1.92 (m, 2H), 1.90-1.80 (m, 2H), 1.80-1.68 (m, 4H), 1.68-1.54 (m, 5H), 1.50-1.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 129.1, 128.4, 126.5, 113.6, 101.6, 95.6, 90.0, 60.6, 58.7, 41.7, 39.6, 32.2, 30.6, 27.9, 25.6, 19.8, 19.1; HRMS (ESI, $[M+Na]^+$) calcd for $C_{20}H_{26}O_4Na$ 353.1723, found: m/z 353.1722.



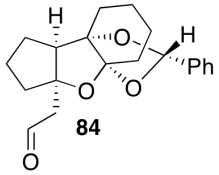
Alcohol 83. A solution of **74** (79 mg, 0.21 mmol) in dry Et_2O (2 mL) was added by cannula to a stirred solution of LAH (12 mg, 0.32 mmol) in dry Et_2O (1 mL) at 0 °C. The solution was stirred under Ar and allowed to warm to room temperature. The reaction was quenched with solid Na_2SO_4•10 H_2O (500 mg) and stirred overnight. The reaction was filtered through a pad of Celite/magnesium sulfate and the filtrate concentrated to obtain the crude colourless oil. The resulting oil was purified by column chromatography (silica gel; 30% EtOAc / hexanes until the product was recovered) to yield **83** (63 mg, 90%) as a colourless oil: R_f 0.16 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3434, 3092, 3066, 3036,

2952, 2869, 1458, 1395, 1220, 1053, 1025, 957 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65-7.62 (m, 2H), 7.43-7.35 (m, 3H), 6.05 (s, 1H), 3.85 (ddd, *J* = 11.5, 9.5, 4.5 Hz, 1H), 3.67 (app dt, *J* = 10.5, 5.0 Hz, 1H), 2.59 (dd, *J* = 10.0, 5.5 Hz, 1H), 2.50-2.37 (m, 3H), 2.29-2.23 (m, 1H), 2.00-1.94 (m, 1H) 1.93-1.75 (m, 4H), 1.75-1.65 (m, 3H), 1.65-1.55 (m, 2H), 1.53 (app dt, *J* = 14.5, 4.5 Hz, 1H), 1.50-1.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 129.1, 128.4, 126.5, 113.6, 101.6, 96.7, 90.8, 60.6, 57.9, 41.5, 39.6, 35.1, 30.1, 26.7, 25.2, 23.4, 20.9; HRMS (ESI, $[M+Na]^+$) calcd for $C_{20}H_{26}O_4Na$ 353.1723; found: m/z 353.1722.

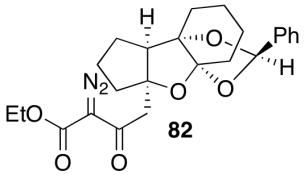


81

Aldehyde 81. A solution of alcohol **80** (83 mg, 0.25 mmol), NMO (44 mg, 0.38 mmol), and 4Å molecular sieves (500 mg) in CH_2Cl_2 (2.5 mL) was stirred at room temperature for 20 min. To this solution was added TPAP (7 mg, 0.019 mmol) and the resulting mixture was stirred for 2 h. The reaction mixture was passed through a short plug of silica gel and concentrated. The resulting crude oil was purified by column chromatography (silica gel; 15% EtOAc / hexanes until the product was recovered) to yield **81** (60 mg, 72%) as a colourless oil: R_f 0.40 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3036, 2953, 2870, 1722, 1458, 1196, 1064, 958 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.93 (dd, *J* = 3.0, 2.5 Hz, 1H), 7.53-7.50 (m, 2H), 7.42-7.35 (m, 3H), 6.13 (s, 1H), 3.24 (dd, *J* = 15.5, 2.5 Hz, 1H), 2.78 (dd, *J* = 9.5, 4.0 Hz, 1H), 2.76 (dd, *J* = 15.5, 3 Hz, 1H), 2.30 (dddd, *J* = 13.5, 4.0, 4.0, 1.0 Hz, 1H), 2.30-1.80 (m, 5H), 1.80-1.64 (m, 5H), 1.63-1.54 (m, 2H), 1.52-1.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.7, 137.8, 129.2, 128.4, 126.4, 113.5, 101.6, 91.7, 89.8, 57.7, 53.5, 40.3, 32.5, 30.3, 27.6, 25.7, 20.2, 19.3; HRMS (ESI, $[M+Na]^+$) calcd for $C_{20}H_{24}O_4Na$ 351.1567, found: m/z 351.1563.

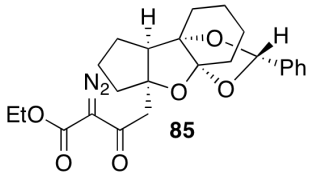


Aldehyde 84. A solution of alcohol **83** (60 mg, 0.18 mmol), NMO (33 mg, 0.38 mmol), and 4Å molecular sieves (500 mg) in CH_2Cl_2 (2.5 mL) was stirred at room temperature for 20 min. To this solution was added TPAP (3 mg, 9 x 10^{-3} mmol) and the resulting mixture was stirred for 2 h. The reaction mixture was passed through a short plug of silica gel and concentrated. The resulting crude oil was purified by column chromatography (silica gel; 15% EtOAc / hexanes until the product was recovered) to yield **84** (45 mg, 75%) as a colourless oil: R_f 0.44 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3036, 2944, 2867, 1721, 1496, 1452, 1045, 952 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.72 (dd, *J* = 3.5, 2.0 Hz, 1H), 7.53-7.51 (m, 2H), 7.41-7.36 (m, 3H), 6.09 (s, 1H), 3.11 (dd, *J* = 16.0, 2.0 Hz, 1H), 2.66 (dd, *J* = 8.5, 7.0 Hz, 1H), 2.54-2.48 (m, 1H), 2.47 (dd, *J* = 16.0, 3.0 Hz, 1H), 2.26 (dddd, *J* = 14.5, 3.0, 3.0, 1.0 Hz, 1H), 2.00-1.81 (m, 5H), 1.78-1.60 (m, 5H), 1.54-1.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 137.5, 129.1, 128.3, 126.3, 113.2, 102.4, 92.7, 90.7, 57.2, 53.6, 40.3, 34.8, 29.9, 26.5, 25.3, 23.4, 21.0; HRMS (ESI, $[M+Na]^+$) calcd for $C_{20}H_{24}O_4Na$ 351.1567, found: m/z 351.1566.



Diazoketoester 82. To a solution of aldehyde **81** (164 mg, 0.499 mmol) in CH_2Cl_2 (5 mL) was added ethyl diazoacetate (77 μL, 0.75 mmol) and $NbCl_5$ (13 mg, 0.050 mmol). The reaction was stirred at room temperature for 5 h before being quenched with the addition of brine (10 mL). After separation of the

organic and aqueous layers, the aqueous layer was extracted with CH_2Cl_2 (20 mL). The organic extracts were combined and washed with water (10 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated. The crude oil was then dissolved in CH_3CN (5 mL) and TsN_3 (197 mg, 0.998 mmol) and Et_3N (167 μl, 1.20 mmol) were added sequentially. The reaction was stirred overnight and then concentrated and purified by column chromatography (silica gel; 5%, 10%, 15% EtOAc/hexanes until the products were recovered) to yield **82** (110 mg, 50% over two steps) as a yellow oil: R_f 0.42 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2950, 2870, 2134, 1716, 1652, 1458, 1372, 1301, 1093, 1027, 959 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.51 (m, 2H), 7.40-7.33 (m, 3H), 6.18 (s, 1H), 4.29 (q, J = 7.2 Hz, 2H), 3.87 (d, J_{AB} = 16.7 Hz, 1H), 3.34 (d, J_{AB} = 16.7 Hz, 1H), 2.90 (dd, J = 9.3, 3.4 Hz, 1H), 2.26 (app tt, J = 13.5, 3.7 Hz, 1H), 2.06-1.98 (m, 1H), 1.94-1.78 (m, 5H), 1.78-1.63 (m, 3H), 1.63-1.52 (m, 3H), 1.52-1.40 (m, 1H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 161.2, 138.1, 129.0, 128.3, 126.5, 113.1, 101.2, 93.2, 90.1, 61.4, 57.1, 47.7, 40.1, 32.1, 29.8, 27.8, 25.6, 19.5, 18.9, 14.3 (diazo carbon not detected); HRMS (ESI, $[M+Na]^+$) calcd for $C_{24}H_{28}O_6N_2Na$ 463.1839, found: m/z 463.1835.

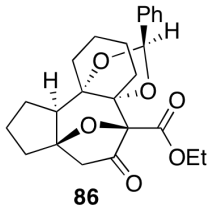


85

Diazoketoester 85. To a solution of aldehyde **84** (42 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) was added ethyl diazoacetate (20 μL, 0.19 mmol) and $NbCl_5$ (3 mg, 0.01 mmol). The reaction was stirred at room temperature for 5 h before being quenched by the addition brine (5 mL) and after separation of the organic and aqueous layers, the aqueous layer was extracted with CH_2Cl_2 (10 mL). The organic extracts were combined and washed with water (5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated. The crude oil was then dissolved in

CH_3CN (1 mL) and TsN_3 (50 mg, 0.26 mmol) and Et_3N (43 μL, 0.31 mmol) were added sequentially. The reaction was stirred overnight and then concentrated and purified by column chromatography (silica gel; 5%, 10%, 15% EtOAc/hexanes until the products were recovered) to yield **85** (38 mg, 67% over two steps) as a yellow oil: R_f 0.41 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2942, 2868, 2132, 1720, 1654, 1452, 1345, 1300, 1210, 1062, 952 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57-7.53 (m, 2H), 7.36-7.27 (m, 3H), 6.04 (s, 1H), 4.20-4.09 (m, 2H), 3.59 (d, J_{AB} = 18.2 Hz, 1H), 3.16 (d, J_{AB} = 18.2 Hz, 1H), 2.85 (dd, J = 9.7, 5.7 Hz, 1H), 2.54-2.46 (m, 1H), 2.28-2.20 (m, 1H), 2.00 (dt, J = 11.7, 5.9 Hz, 1H), 1.92-1.60 (m, 9H), 1.52-1.34 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 160.9, 137.7, 128.6, 128.1, 126.6, 112.3, 102.3, 93.6, 90.8, 61.2, 56.7, 49.3, 40.0, 34.8, 29.9, 26.6, 25.4, 23.3, 21.0, 14.2 (diazo carbon not detected); HRMS (ESI, $[M+Na]^+$) calcd for $C_{24}H_{28}O_6N_2Na$ 463.1839, found: m/z 463.1837.

Carbene Transfer Reaction of 82, Preparation of 86

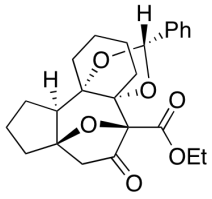


86

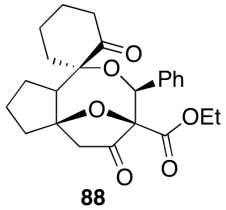
To a solution of $Cu(hfacac)_2$ (3 mg, 6 x 10^{-3} mmol) in toluene (4 mL) at reflux was added a solution of **82** (25 mg, 0.057 mmol) in toluene (1 mL), and the resulting mixture monitored by TLC. Upon consumption of diazoketone (30 min) the reaction mixture was cooled to room temperature and quenched by the addition of saturated $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The organic extracts were combined and washed with water (5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated. The resulting oil was purified by column chromatography

(silica gel; 15% EtOAc / hexanes until the product was recovered) to yield **86** (19 mg, 82%) as a white solid: m.p. 150-151 °C; R_f 0.35 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2931, 2872, 1769, 1739, 1449, 1254, 1097, 1083, 1027, 854 cm^{-1}; ^1H NMR; (500 MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.35-7.31 (m, 2H), 7.28-7.25 (m, 1H), 6.09 (s, 1H), 4.41-4.31 (m, 2H), 3.01 (d, J_{AB} = 17.4 Hz, 1H), 2.67 (d, J_{AB} = 17.4 Hz, 1H), 2.31 (dd, J = 13.3, 6.3 Hz, 1H), 2.26-2.06 (m, 4H), 1.99-1.91 (m, 2H), 1.88-1.82 (dt, J = 12.7, 6.7 Hz, 1H), 1.66-1.56 (m, 2H), 1.56-1.48 (m, 3H), 1.45-1.22 (m, 2H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6, 165.2, 141.7, 128.0, 127.6, 125.1, 100.7, 88.0, 87.0, 86.7, 82.0, 61.9, 53.9, 45.2, 34.7, 34.1, 29.2, 28.5, 22.6, 21.8, 19.8, 14.3; HRMS (ESI, $[M+Na]^+$) calcd for $C_{24}H_{28}O_6Na$ 435.1778, found: m/z 435.1778.

Carbene Transfer Reaction of 85, Preparation of 87 and 88[22]



87



88

To a solution of $Cu(hfacac)_2$ (8 mg, 0.02 mmol) in toluene (13 mL) at reflux was added a solution of **85** (68 mg, 0.15 mmol) in toluene (2 mL). The resulting reaction mixture was monitored by TLC. Upon consumption of diazoketone (30 min) the reaction mixture was cooled to room temperature and quenched by the addition of saturated $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The organic extracts were combined and washed with water (5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated. The resulting oil was purified by column chromatography (silica gel; 15% EtOAc / hexanes until the product was recovered) to yield **87** (25 mg) and **88** (28 mg) as white solids in an overall combined yield of 83%.

Carbocycle 87: m.p. 152-154 °C; R_f 0.29 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2971, 2942, 2927, 2874, 1764, 1733, 1466, 1099, 1069, 1028, 863 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48-7.55 (m, 2H), 7.39-7.32 (m, 3H), 6.18 (s, 1H), 4.35-4.25 (m, 2H), 2.65 (d, J_{AB} = 17.5 Hz, 1H), 2.39 (d, J_{AB} = 17.5 Hz, 1H), 2.34 (dd, J = 13.3, 6.0 Hz, 1H), 2.27-2.15 (m, 3H), 2.05-1.85 (m, 5H), 1.80-1.72 (m, 1H), 1.71-1.63 (m, 2H), 1.60 (dt, J = 13.5, 3.5 Hz, 1H), 1.57-1.44 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 165.8, 137.6, 128.0, 127.6, 125.5, 99.7, 88.8, 86.3, 83.8, 82.9, 61.7, 54.0, 44.1, 34.8, 32.0, 29.9, 28.5, 22.4, 21.5, 20.1, 14.2; HRMS (ESI, $[M+Na]^+$) calcd for $C_{24}H_{28}O_6Na$ 435.1778, found: m/z 435.1778.

Ether 88: m.p. 155-157 °C; R_f 0.13 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2942, 2870, 1769, 1746, 1742, 1456, 1250, 1134, 1097, 914 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50-7.46 (m, 2H), 7.31-7.24 (m, 3H), 5.30 (s, 1H), 3.81-3.68 (m, 2H), 2.88 (d, J_{AB} = 17.4 Hz, 1H), 2.60 (d, J_{AB} = 17.4 Hz, 1H), 2.51 (td, J = 14.2, 7.6 Hz, 1H), 2.19-2.10 (m, 4H), 2.10-1.88 (m, 4H), 1.88-1.78 (m, 2H), 1.78-1.56 (m, 4H), 0.81 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.2, 208.4, 164.7, 138.5, 129.0, 128.4, 128.2, 91.0, 89.1, 85.3, 80.8, 61.9, 54.0, 47.1, 40.0, 38.7, 37.4, 28.5, 27.2, 21.9, 21.1, 13.4; HRMS (ESI, $[M+Na]^+$) calcd for $C_{24}H_{28}O_6Na$ 435.1778, found: m/z 435.1775.

3.6 References

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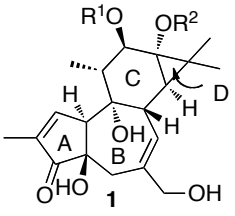
22. Structures were confirmed by X-ray crystallography.
23. Structures were assigned analogous to products confirmed by X-ray crystallography.

Chapter 4

Progress Towards the Total Synthesis of Phorbol

4.1 Introduction

Phorbol esters are known as potent tumor promoters that amplify the effect of carcinogenesis in animals (Figure 4.1).[1] These phorbol derivatives are thought to activate protein kinase C (PKC)[2,3], a key enzyme that mediates cellular signal transduction pathways, by acting as tight-binding mimics of the endogeneous ligand diacyl gylcerol (DAG). While DAG is metabolized immediately through phosphorylation or hydrolysis, phorbol esters activate PKC and induce malignant cell growth. RasGRP is a protein that initiates the MAP kinase signal transduction pathway and is also activated by phorbol esters via a similar interaction.[4] RasGRP mediates T cell activation making the development of phorbol analogues that lack tumor-promoting properties and inhibit this protein interesting targets for the treatment of diseases of the immune system.[4]



phorbol: $R^1 = R^2 = H$
phorbol myristate acetate (PMA): $R^1 = C(=O)C_{13}H_{27}$, $R^2 = C(=O)CH_3$
phorbol dibutyrate (PDB): $R^1 = R^2 = C(=O)C_3H_7$

Figure 4.1 Structure of phorbol and phorbol esters.

Structurally, phorbol has a congested tetracyclic carbocyclic framework consisting of fused five, seven, six and three membered rings. Phorbol possesses an extensive array of stereocentres, which has posed a great challenge to its chemical synthesis. Modification of the phorbol core system has also been problematic due to its degradation in the presence of acid, base, heat and light and

also its hazardous nature.[1] An efficient route to phorbol would also allow construction of analogues of potential therapeutic use that are not accessible via modification of the natural compound.

4.2 Phorbol Mode of Activation

Phorbol esters are thought to activate PKC in a bifunctional manner. The hydrophobic ester side-chains are believed to anchor the molecule to the cell-membrane while the hydrophilic part is thought to bind to PKC through hydrogen bonding of the primary alcohol at C20, tertiary alcohol at C4, and the ketone at C3 (Figure 4.2).[5] The C20 alcohol forms a hydrogen bond with the main-chain amide of Thr-242 and donates a hydrogen bond to the backbone carbonyls of Thr-242 and Leu-251. The C3 oxygen forms a hydrogen bond with the amide nitrogen of Gly-253 and the C4 hydroxyl forms a hydrogen bond with the carbonyl of Gly-253. The C12 hydroxyl is not involved in binding to PKC and neither is the C9 hydroxyl group, which instead forms an intramolecular bond with the C13 acetyl moiety.

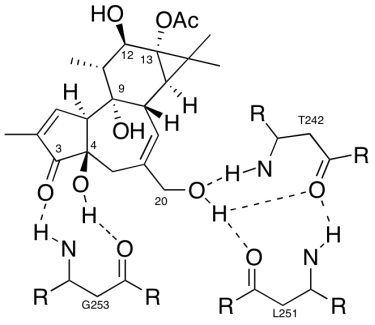
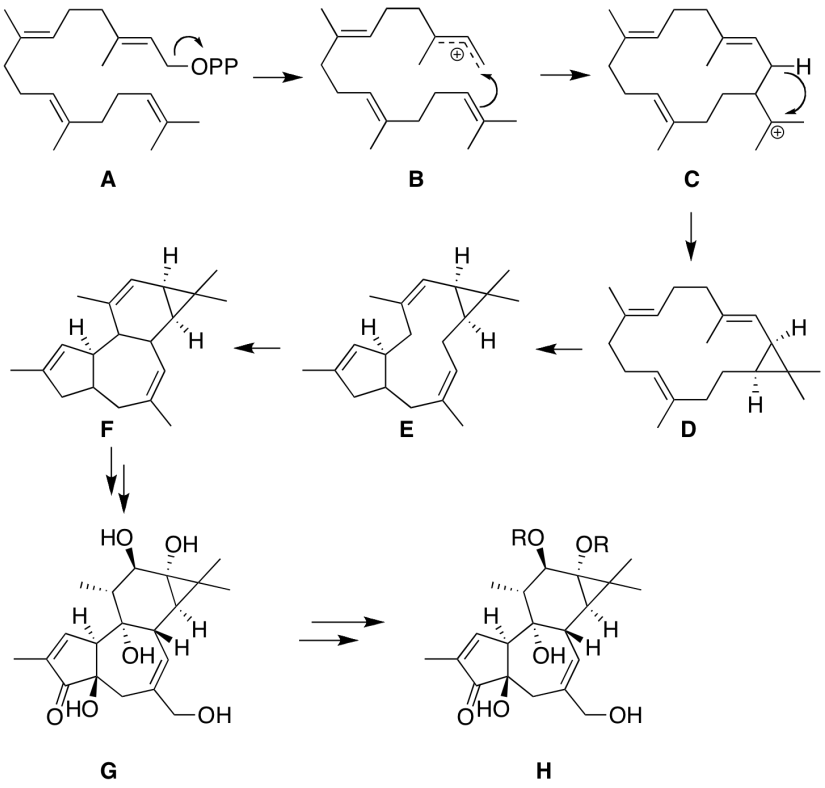


Figure 4.2 Proposed Phorbol Ester binding.

4.3 Biosynthesis of Phorbol and Phorbol esters.

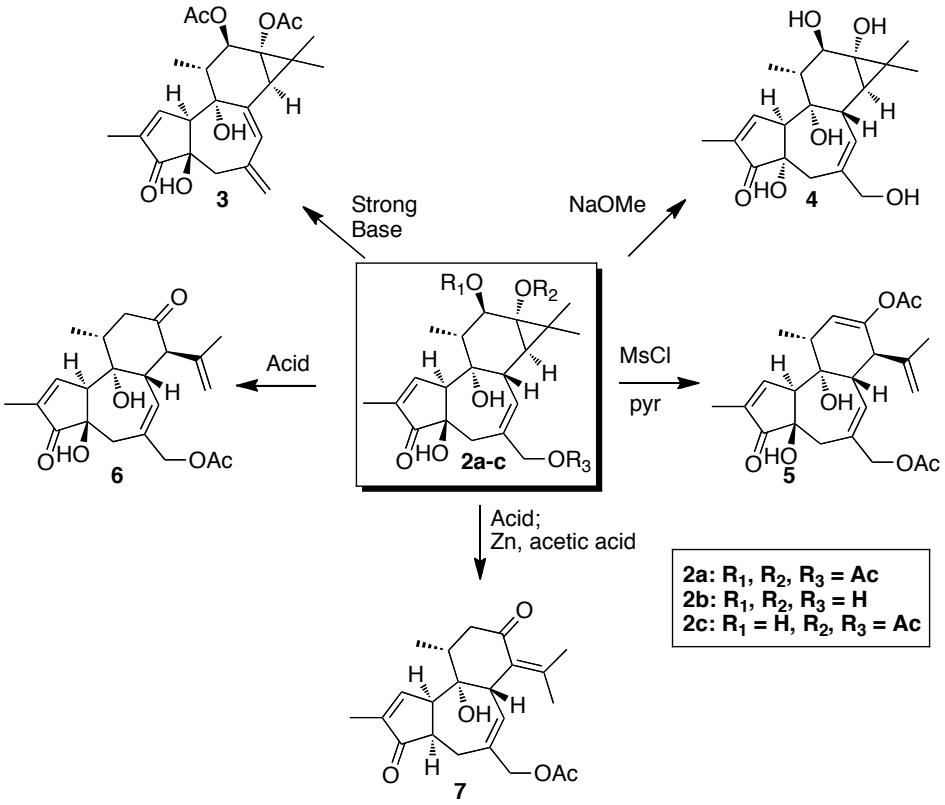
The biosynthesis of phorbol and phorbol esters is still not completely understood but they are thought to arise from geranylgeranyl diphosphate (GGPP) **A** (Scheme 4.1).[6] Generation of carbocation **B** initiates a macrocyclization by cation-olefin cyclization to afford 14-membered ring **C** which, upon loss of a proton results in cyclopropanation leading to casbene **D**. Casbene is an antifungal metabolite produced by the castor oil plant, *Ricinus communis* (Euphorbiaceae). Casbene is postulated to undergo five-membered ring closure to generate intermediate **E**, followed by another ring closure to furnish the tigliane skeleton **F**. The manner in which these cyclizations occur has yet to be elucidated. Various enzymatic oxygenations could then occur to provide lead to phorbol **G** and further esterfications of **G** could lead to different phorbol esters **H**.



Scheme 4.1 Proposed biosynthesis of phorbol and phorbol esters.

4.4 Reactivity of the Phorbol Skeleton

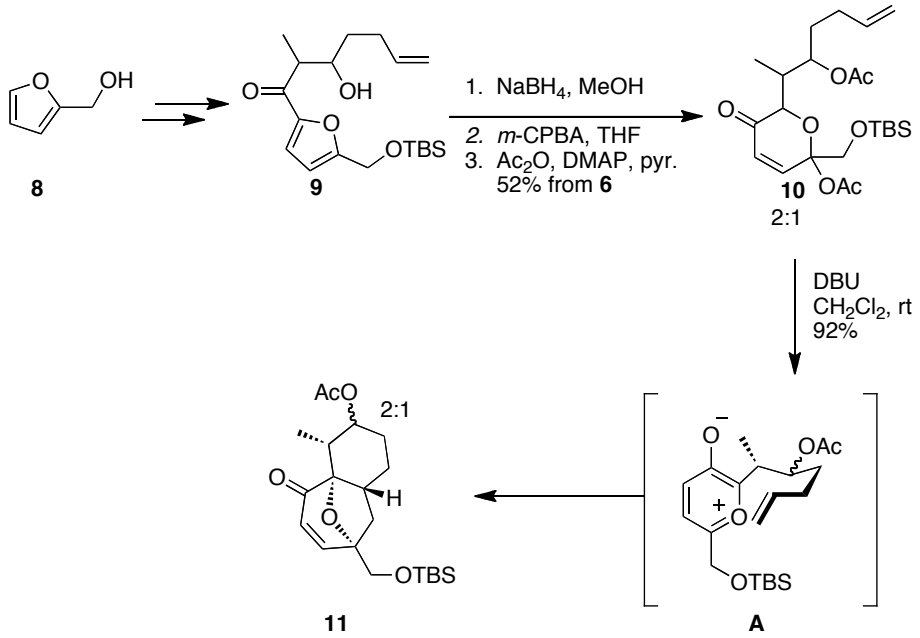
Phorbol and phorbol esters are sensitive to acids, bases, heat and light which makes these compounds difficult to handle and manipulate.[1] Under strongly basic conditions, phorbol-12,13,20-triacetate **2a** can be converted to compound **3** through via a conjugate elimination (Scheme 4.2). Treatment of phorbol **2b** with sodium methoxide provides compound **4** by a vinylogous retroaldol followed by realdolization to isomerize the stereochemistry at the five-seven ring junction. The cyclopropane is affected when phorbol-13,20-diacetate **2c** is treated with MsCl and pyridine, affording the ring opened product **5**. Phorbol **2b** is also acid sensitive, which is observed upon treatment with H_2SO_4 yields compound **6**. Subsequent treatment with Zn in AcOH can lead to the formation of enone **7**.



Scheme 4.2 Phorbol and phorbol ester reactivity.

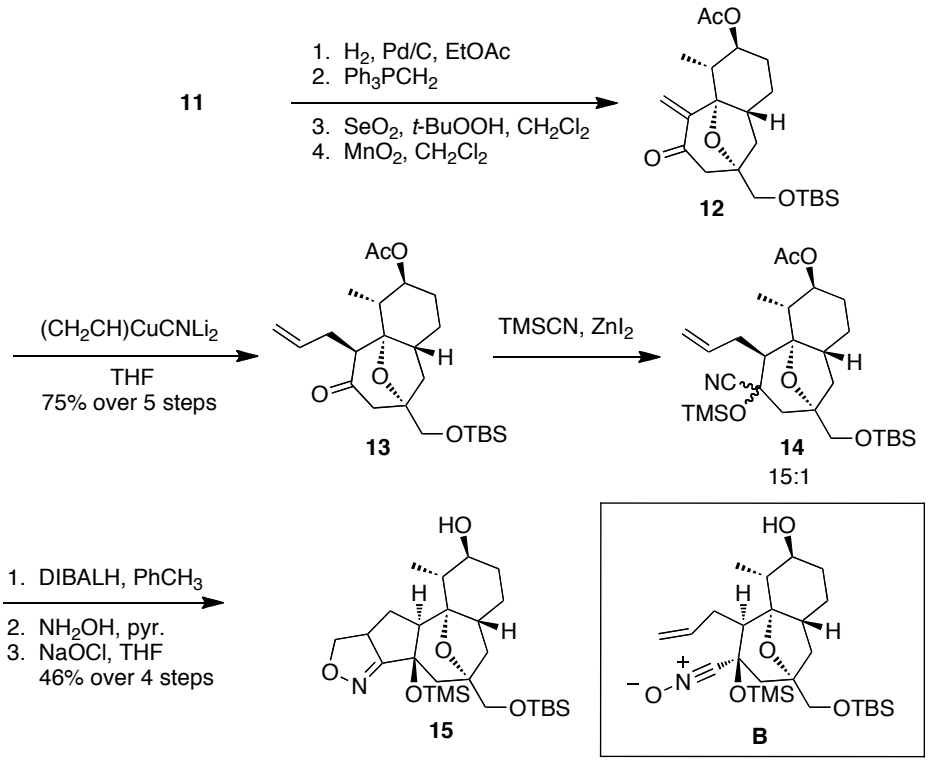
4.5 First Total Synthesis of Phorbol

Wender[7,8] achieved the first total synthesis of phorbol in 1989 using the [5 + 2] strategy discussed in chapter three. Furan **9** was available in a few steps starting from furfuryl alcohol **8** and was oxidized to pyranone **10** in a three-step process (Scheme 4.3). Reduction of the ketone with $NaBH_4$ followed by oxygen-directed epoxidation yielded the unprotected pyranone, which was acetylated using standard conditions to generate the cycloaddition precursor **10**. Efficient conversion of pyranone to cycloaddition product **11** was achieved in a 92% yield as a 2:1 mixture of diastereomers. Cycloaddition proceeded with complete diastereoselectivity with each diastereomer of pyranone **10** yielding only one diastereomer of the product. The rationale for the diastereoselectivity was suggested to arise from a chair-like conformation **A** assumed by the tether during cycloaddition. Both of the epimers were independently carried through the synthesis, with comparable efficiency to the point of convergence, but for clarity only one epimer is shown.



Scheme 4.3 Formation of the BC ring system by a [5+2]-cycloaddition.

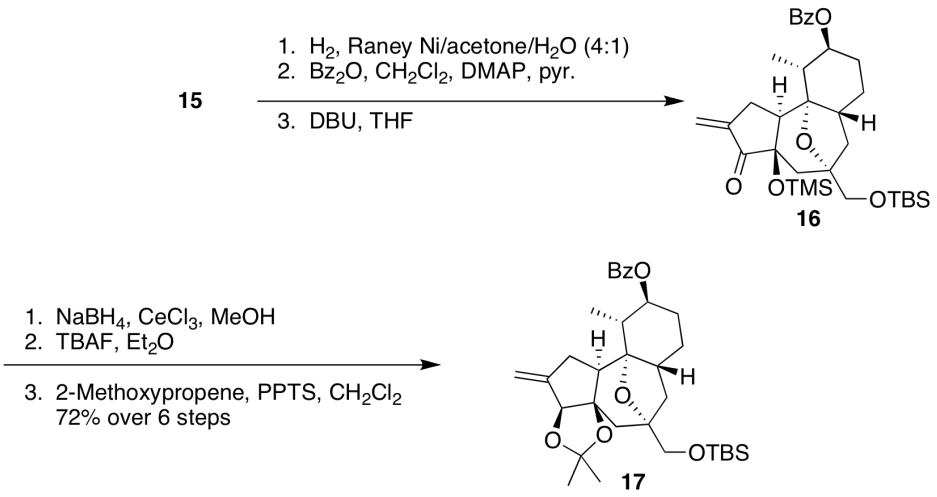
Synthesis of the A-ring required conversion of cycloadduct **11** to enone **12,** which was accomplished in a four-step sequence (Scheme 4.4). Phorbol possesses a *trans*-fused five-seven ring junction so it was essential for the protonation to occur from the top face. This key step was accomplished by the addition of a vinyl cuprate reagent to enone **12**, which gave the desired ketone **13** as a single isomer in 75% yield over five steps (Scheme 4.2). The desired stereochemical outcome was achieved due to the influence of the oxygen bridge, which sterically and stereoelectronically controlled protonation of the enolate.



Scheme 4.4 A-ring formation by a nitrile oxide cycloaddition.

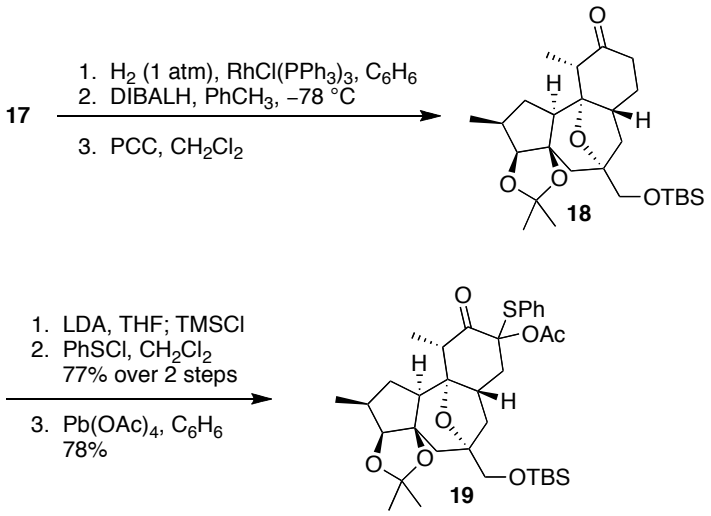
Wender utilized an intramolecular nitrile oxide cycloaddition for the construction of the A-ring. Towards this end, introduction of the nitrile functionality was achieved with TMSCN and ZnI_2 producing a 15:1 mixture of isomers **14**. The major isomer resulted from kinetic addition of cyanide to the less sterically encumbered bottom face and delivery of the nitrile in the correct *trans* orientation

to the allyl group. This reaction set the stage for A-ring formation and provided the tertiary alcohol as the protected TMS ether. Nitrile **14** was reduced to the aldehyde using DIBALH and the aldehyde was directly converted to the oxime using standard conditions. The A-ring was then formed in excellent yield by oxidation to the nitrile oxide intermediate **B** and subsequent 1,3-dipolar cycloaddition to afford isoxazoline **15**. Isoxazoline was reduced to the hydroxy ketone, which was then dehydrated, by benzoylation and DBU-catalyzed elimination producing enone **16** (Scheme 4.5). As discussed earlier, the A-ring in phorbol is highly sensitive towards acids, bases, heat and light, so Wender decided to proceed with the synthesis using a protected version of the A-ring. As a result the methylene ketone was reduced using Luche conditions and the tertiary alcohol was deprotected using TBAF. The resulting diol was protected as the acetonide using PPTS and 2-methoxypropene furnishing compound **17** in excellent yield over six steps. The synthesis of this advanced intermediate was achieved in 23 steps and an overall 10% yield, which set the stage for opening of the ether bridge as well as installation of the D-ring.

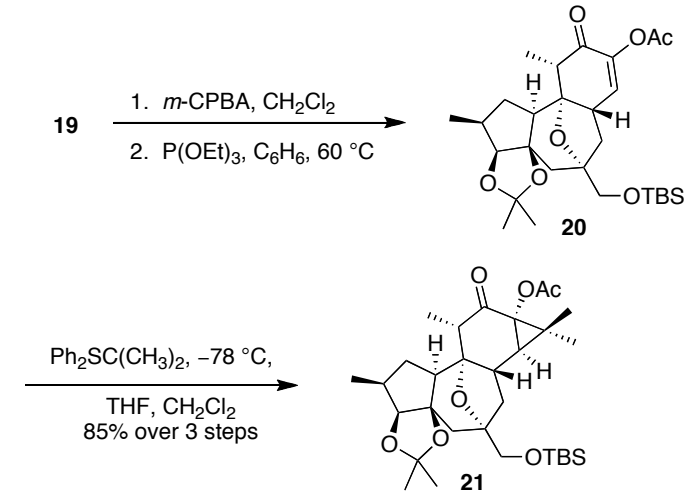


Scheme 4.5 A-ring elaboration.

Manipulation of compound **17** to ketone **18** was accomplished in three steps by reduction, deprotection and oxidation protocol (Scheme 4.6). Kinetic deprotonation of ketone **18** was achieved without epimerization of the methyl substituted carbon and the resulting enolate trapped as the silyl-enol ether. Subsequently, the silyl-enol ether was treated with phenylsulfenyl chloride yielding the desired ketone intermediate. α-Oxidation of the ketone with $Pb(OAc)_4$ provided the compound **19** as an inconsequential mixture of stereoisomers. Oxidation of the sulfide with m-CPBA to the sulfoxide followed

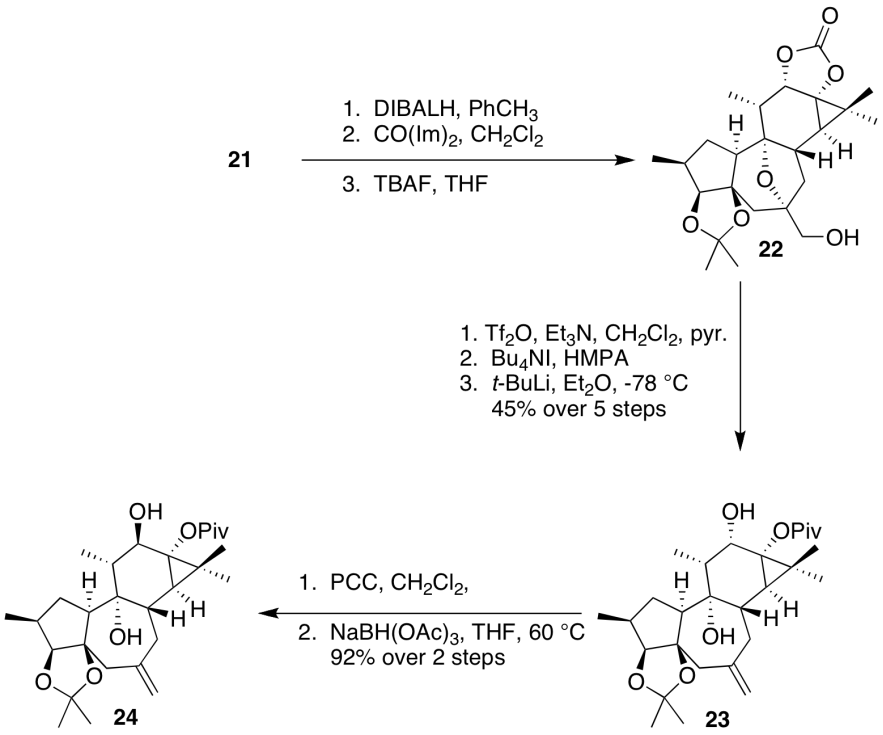


Scheme 4.6 D-ring precursor synthesis.

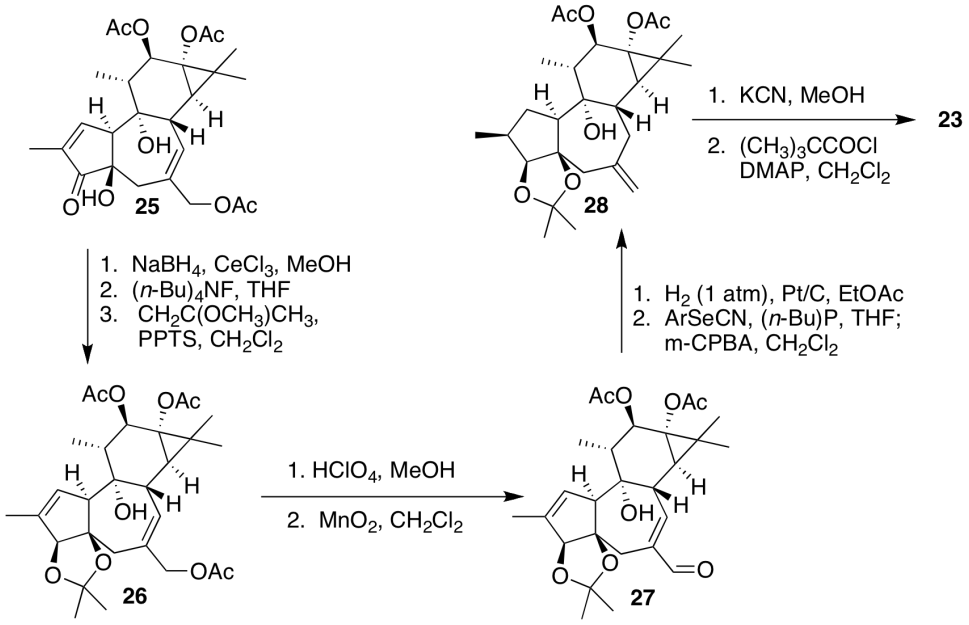


Scheme 4.7 Synthesis of the D-ring by sulfur-ylide addition.

by elimination afforded the acetoxy enone **20**, which was then treated with sulfur ylide to provide compound **21 (**Scheme 4.7). In this reaction cyclopropanation occurred exclusively from the top face to give the desired product in excellent yield. Reduction of ketone **21** was problematic when DIBALH or LAH was used, predominantly producing the undesired isomer, therefore internal delivery of the hydride was necessary (Scheme 4.8). This was achieved by reducing both the ketone and the ester to a diol, which was then protected as the cyclic carbonate followed by removal of the silyl group to generate the primary alcohol **22**. The primary alcohol was converted to the triflate, which was subsequently displaced with iodide affording the primary iodide. Treatment of iodide with *t*-BuLi resulted in selective removal of the cyclic carbonate as well as ether bridge cleavage, yielding a diol **23** that was immediately oxidized to the ketone using PCC. Gratifyingly, $NaBH(OAc)_3$ exclusively delivered the hydride from the bottom face of the ketone producing alcohol **24** in excellent yield. The structure of alcohol **21** was confirmed by chemical degradation of phorbol triacetate **25** to the enantiomerically pure alcohol **24** in nine synthetic steps (Scheme 4.9).

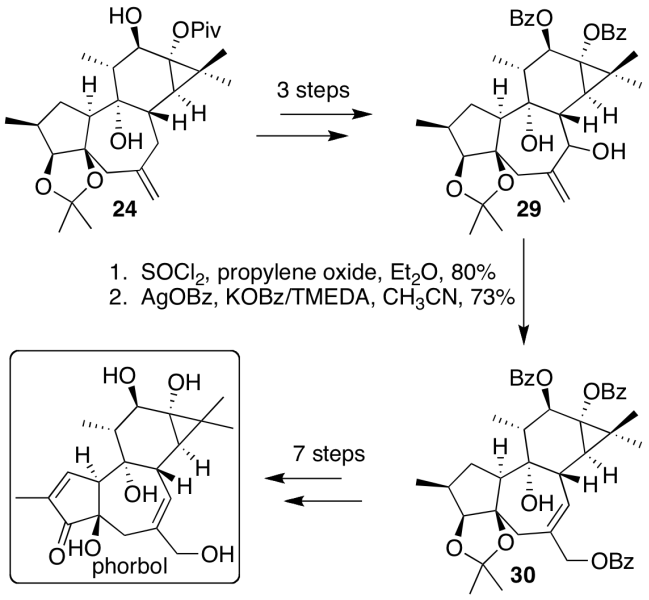


Scheme 4.8 Ether-bridge opening and stereoselective reduction.



Scheme 4.9 Conversion of phorbol triacetate **24** to compound **23**.

At this point B-ring functionalization was required and the A-ring needed to be unveiled. The desired oxidation of the exocyclic double bond was achieved by converting alcohol **24** to allylic alcohol **29** in three steps (Scheme 4.10). Treatment of the allylic alcohol with $SOCl_2$ afforded the secondary chloride in 80% yield. Subsequently, benzoate displacement in the presence of silver(I)benzoate furnished compound **30** in good yield which proceeds through a S_N1 like mechanism. The synthesis of phorbol was accomplished in seven steps from intermediate **30** involving a series of deprotections and oxidation of the A-ring to the enone. Wender's first total synthesis of phorbol was completed in a total of 55 linear steps.

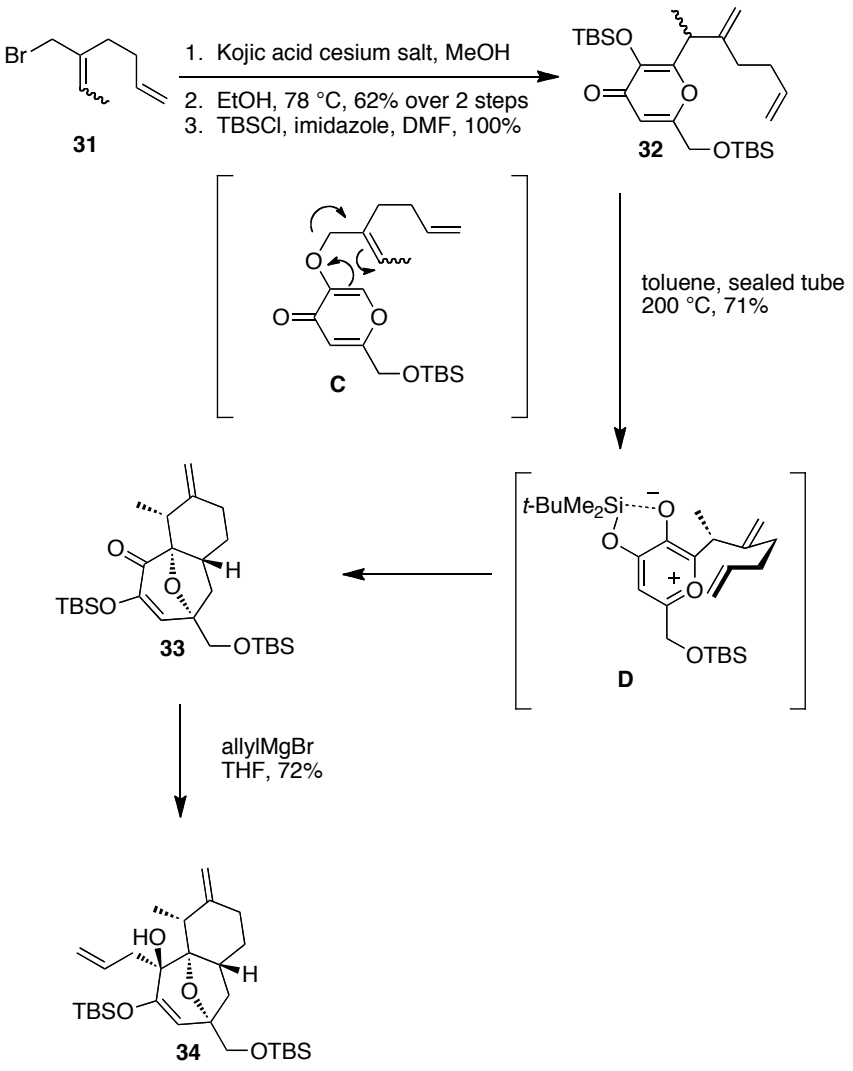


Scheme 4.10 Completion of the synthesis.

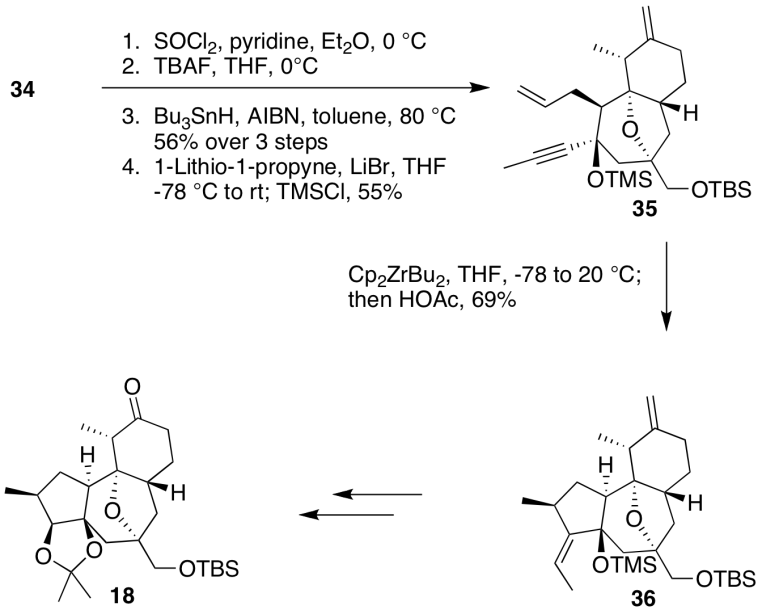
4.6 Second-Generation Synthesis of Phorbol

A year after the first total synthesis was published, Wender[9] reported a second-generation approach using a more direct route to intermediate **18**. Wender thought that a more functionalized substrate could be used in the [5 + 2] cycloaddition step to allow for easier A-ring formation. The synthesis began with treatment of allylic bromide **31** with the cesium salt of kojic acid providing intermediate **C**, which after heating led to smooth rearrangement (Scheme 4.11). The resulting free secondary alcohol was protected affording cycloaddition precursor **32** in good yield. There are a few differences between this [5 +2] cycloaddition and the [5 +2] cycloaddition used in the first total synthesis of phorbol. Instead of a DBU initiated cycloaddition, the cycloadduct **33** was obtained in good yield and as a single diastereomer upon heating in a sealed tube. Interestingly, the reaction resulted from an unprecedented silicon transfer-induced oxidopyrylium cycloaddition. The Si-transfer was shown to be essential to this cycloaddition by replacement of the OTBS with OMe to give an unreactive

substrate. The construction of the A-ring was envisioned by a transition metal mediated ring closure. Installation of the desired allyl side chain was accomplished by reacting cycloadduct **33** with allylmagnesium bromide, providing allylic alcohol **34** in good yield as a single diastereomer.



Scheme 4.11 Second generation synthesis [5+2]-cycloaddition.



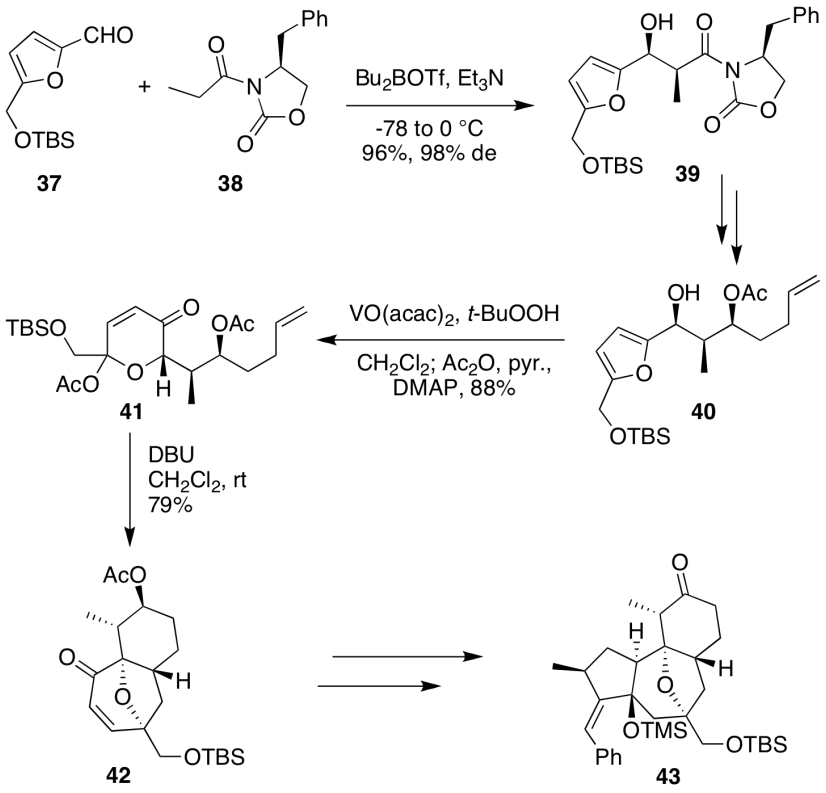
Scheme 4.12 A-ring synthesis by cyclization of enyne **35**.

Alcohol **34** was converted to the allylic chloride under standard conditions and the enol ether subsequently protonated to give a chloro ketone. The chloro ketone was then reduced with Bu_3SnH and AIBN to give the ketone in 56% over 3 steps. Addition of 1-lithio-1-propyne to the ketone with immediate silylation afforded protected alcohol **35** in 55% yield and 88% isomeric purity (Scheme 4.12). Cyclization of the enyne with dibutylzirconocene followed by acetic acid quench of the zirconacyclopentene intermediate gave of diene **36** in 69% yield as a single diastereomer. This diene was converted to ketone **18** in three steps, completing a formal synthesis of phorbol utilizing a shorter 16-step sequence to ketone **18**.

4.7 First Formal Asymmetric Synthesis of Phorbol

In 1997 Wender[10] reported the first formal asymmetric synthesis of phorbol utilizing an oxidopyrylium-alkene [5 + 2] cycloaddition as the key step in

the synthesis of the core BC ring structure. Aldehyde **37** was found to participate in a highly diastereoselective aldol reaction with *N*-propionyl oxazolidinone **38** providing alcohol **39** in 96% yield and 98% diastereoselectivity (Scheme 4.13). The alcohol was manipulated to furan **40** in four steps. This substrate was found to undergo oxidative ring expansion with $VO(acac)_2$/*t*-BuOOH and the crude hydroxy pyranones were acetylated to afford **41** in an 88% yield as an inconsequential 2:1 mixture of isomers. The key reaction was then realized by reacting pyranones **41** with DBU, producing **42** as a single diastereomer in 79%



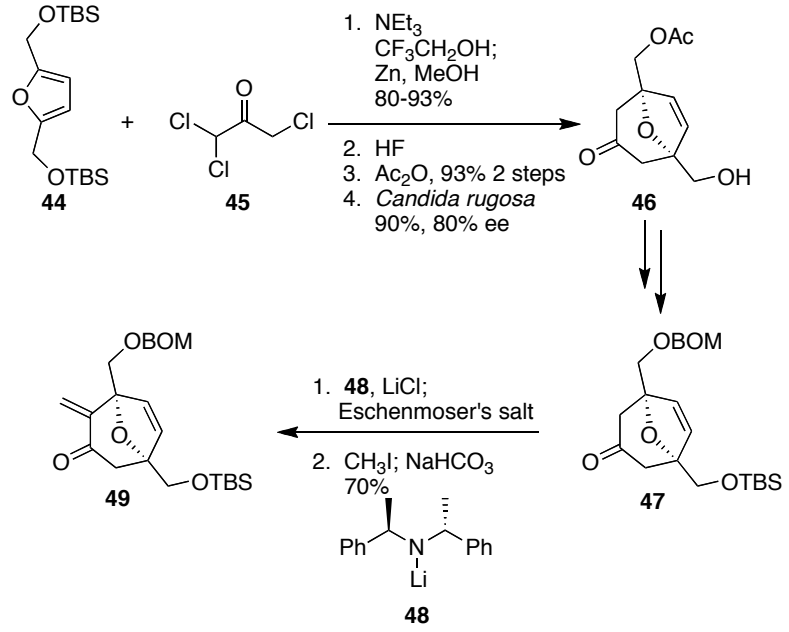
Scheme 4.13 Wender's asymmetric synthesis.

yield. This [5 + 2]cycloaddition was suggested to proceed through a chair-like conformation with the methyl group equatorially disposed to minimize steric interactions with the pyranone carbonyl, described earlier in this chapter. Compound **42** could be elaborated to ketone **37** in seven steps utilizing chemistry

developed in the earlier syntheses. The remainder of the asymmetric was completed in an analogous route to those used in the first two syntheses. The asymmetric synthesis allows for efficient conversion of furfuryl alcohol to phorbol in 33 steps, improving the first total synthesis by eliminating the need for 20 steps.

4.8 Cha's Formal Total Synthesis

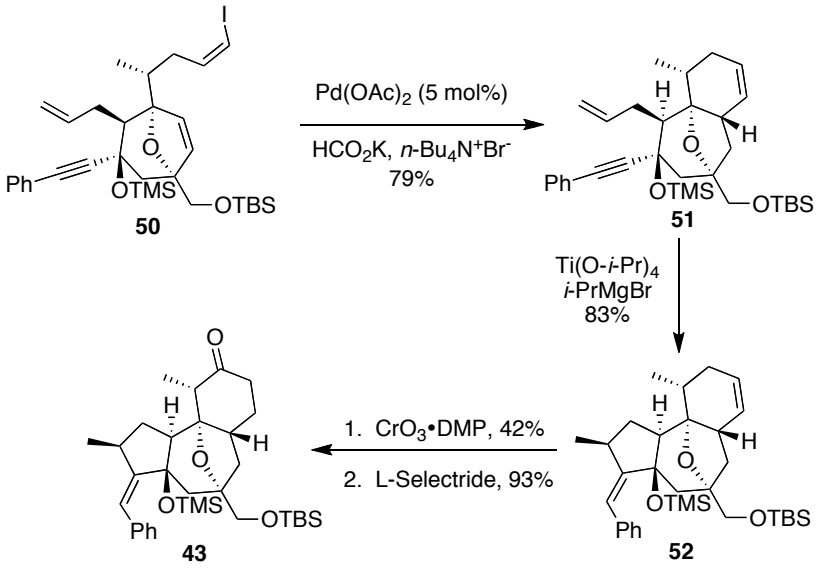
In chapter three Cha's [4+3] cycloaddition strategy was shown to be an efficient way to construct the seven-membered ring of the tigliane and daphnane diterpenes including appropriate handles for the construction of the five and six-membered rings. Cha[11] showcased this methodology in his formal asymmetric



Scheme 4.14 Cha's formal total synthesis.

synthesis of phorbol wherein the [4+3] cycloaddition reaction was used to construct the core seven-membered ring and an intramolecular Heck cyclization for the formation of the six-membered ring. Assembly of the seven-membered

ring was achieved in the first step of the synthesis by treatment of the readily available furan **44** with 1,1,3-trichloroacetone **45** to furnish cycloadduct in yields between 80-93% based on recovered starting material (Scheme 4.14). At this point both TBS groups were exchanged for acetates and the meso cycloadduct was subjected desymmetrization using lipase *Candida rugosa* to afford the enantiomerically pure alcohol **46** in good yield with 90% ee. Installation of the A-ring required regio- and stereoselective introduction of the allyl fragment, which was achieved by asymmetric deprotonation of **47** using Simpkins' base **48** in the presence of LiCl. Mannich condensation with Eschenmoser's salt followed by elimination provided the enone **49** in 70% overall yield. This intermediate was converted to vinyl iodide **50** in eight steps in a straightforward manner.



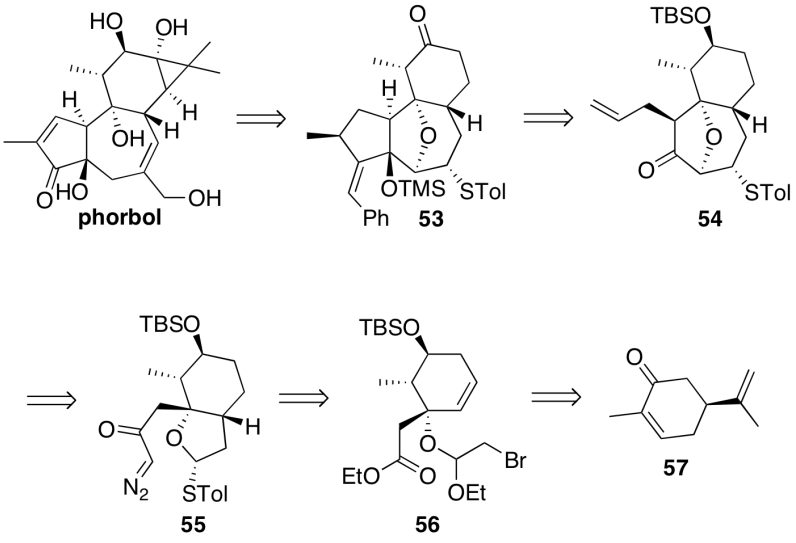
Scheme 4.15 Synthesis of Wender's intermediate **43**.

Cyclization was found occur under Heck conditions to produce the bicyclic 6-7 intermediate **51** in good yield and as a single isomer (Scheme 4.15). Formation of the five-membered ring was achieved by cyclization of enyne **51** under Negishi's zirconocene-mediated cyclization conditions, affording an inseparable 4:1 mixture of the tetracycle **52**. Gratifyingly, an improved yield of 83% of **52** could be realized by using Sato's enyne cyclization protocol with

Ti(O*i*Pr)$_4$/*i*PrMgBr, and provided the tetracycle as a single isomer. This tetracyclic compound could be converted to Wender's key intermediate **43** through a two-step sequence involving an allylic oxidation with CrO_3•DMP followed by L-Selectride reduction of the enone.

4.9 West Group Approach to Phorbol: Sulfur-Directed Stevens Rearrangement

Our approach to the synthesis of phorbol follows a similar approach to that used by Wender[7-10] in his total synthesis. Construction of the core BC ring system was our first objective and we envisioned that this could be accomplished by a sulfur-directed Stevens rearrangement of a tricyclic oxonium ylide (Chapter 2). We believe that phorbol could result from the manipulation of ketone **53**, which is very similar to Wender's key

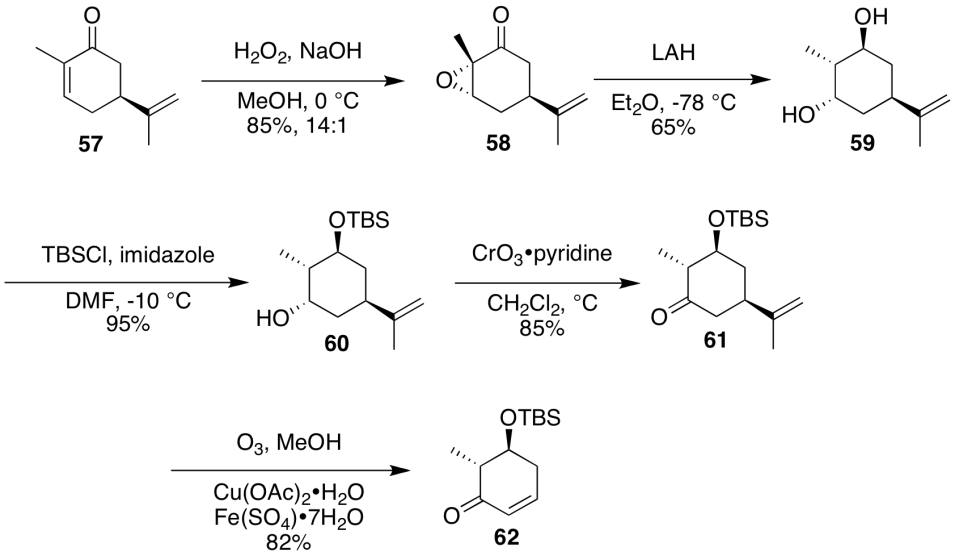


Scheme 4.16 First Approach to phorbol.

intermediate **43** (Scheme 4.16). Our ketone **53** could come from functionalization of bicycle **54**, followed by enyne metathesis. Intermediate **54** could arise from the Stevens rearrangement of diazoketone **55**, which is available in a few steps from radical cyclization of bromoacetal **56**. The bromoacetal was envisioned to come from (*S*)-carvone **57** via a short sequence.

4.9.1 Towards the Synthesis of Bromoacetal

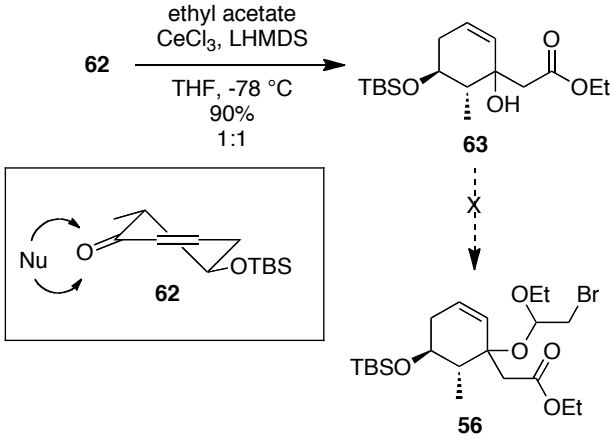
This approach to the synthesis of phorbol required an efficient construction of bromoacetal **56**. A regio- and stereoselective epoxidation of (*S*)-carvone[12] **57** was achieved using H_2O_2 in the presence of NaOH, affording epoxy-ketone **58** in good yield and diastereoselectivity (Scheme 4.17). Reduction of the ketone and subsequent opening of the epoxide with LAH furnished the desired



Scheme 4.17 Synthesis of enone **62**.

diol[12] **59** in good yield. Differentiation of the diols was accomplished by selective protection of the equatorial alcohol with a TBS group, which provided the desired alcohol[12] **60** in excellent yield. The next step was oxidation of the secondary

alcohol, which was done by reacting the alcohol with Collins' reagent to produce the ketone **61** in good yield. At this point we decided that formation of the enone would provide the requisite olefin for radical cyclization. Therefore, oxidation of the ketone to enone **62** was performed in one step by oxidative cleavage of the isopropenyl group in MeOH followed by treatment with $Cu(OAc)_2 \bullet H_2O$ and $Fe(SO_4) \bullet 7H_2O$.[13] This five step sequence allows for efficient and stereoselective synthesis of the necessary enone and could be carried out on a 50 gram scale. With enone **62** in hand the next step was installation of the ester side chain. Towards this end the enone **62** was subjected to Rh-catalyzed Reformatsky conditions. Unfortunately, no reaction occurred under these conditions; however, addition of the cerium enolate[14] of ethyl acetate was somewhat successful and provided tertiary alcohols **63** as a dreadful 1:1 inseparable mixture of diastereomers (Scheme 4.18). A variety of other nucleophiles were examined with no improvement of stereoselectivity, suggesting that selective equatorial attack on the carbonyl was not possible in this system. Another problem associated with this route was that any attempt to form the bromoacetal **56** failed.

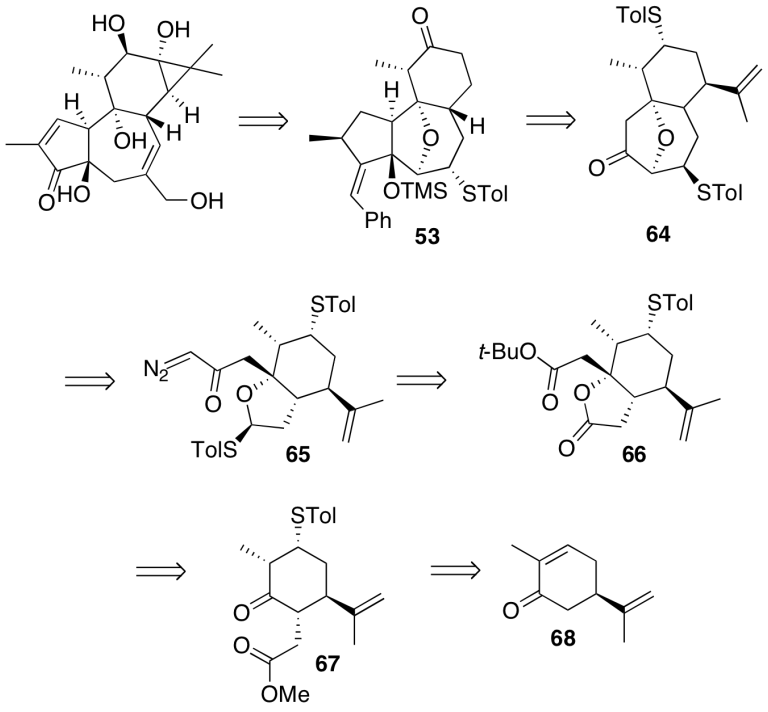


Scheme 4.18 Attempted bromoacetal formation.

In most cases, only recovered starting material was isolated. Otherwise, complete degradation of the starting material was observed with no evidence of formation of the bromoacetal **56**.

4.9.2 Second Generation Synthesis

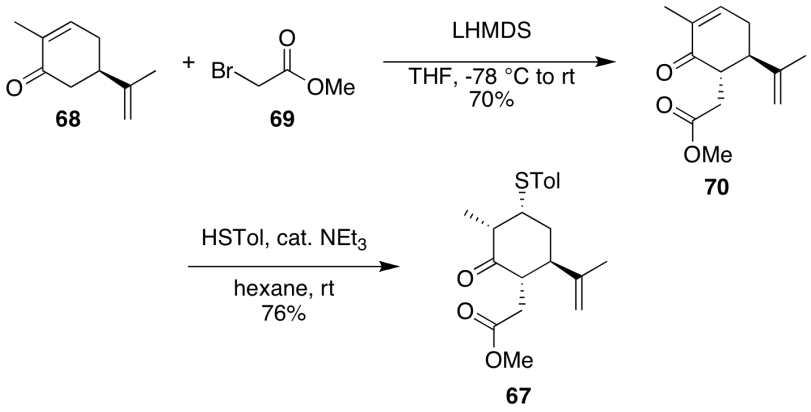
Failure to introduce the ester side chain in a stereoselective manner and difficulties installing the bromoacetal moiety led to our development of an alternate route. Towards this end a new retrosynthesis was envisioned where we would still hope to intercept ketone **53** by manipulation of ketone **64** (Scheme 4.19). This ketone could arise from the Stevens rearrangement of diazoketone **65**, which could be derived from manipulation of lactone **66**. The key lactone intermediate was envisioned to come from stereoselective addition of *t*-butyl acetate into ketone **67** directed by the axial aryl sulfide, and subsequent lactonization. This ketone could be synthesized in two steps from readily available (R)-carvone **68**.



Scheme 4.19 Second generation approach.

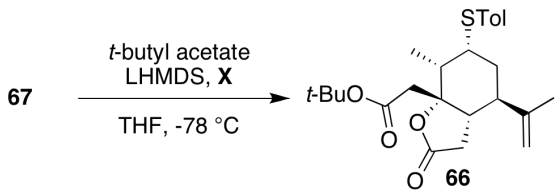
4.9.3 Synthesis of the BC ring System Phorbol

Synthesis of ketoester **70** by kinetic enolate formation at low temperature followed by the addition of methyl bromoacetate **69** yielded the ketoester in 70% yield as a single diastereomer (Scheme 4.20).[15] The ketoester was treated with thiocresol and a catalytic amount of Et_3N to furnish ketone **67** as a single diastereomer in 76% yield (95% yield based on recovered starting material). The absolute stereochemistry was proven by analysis of the X-ray crystal structure.



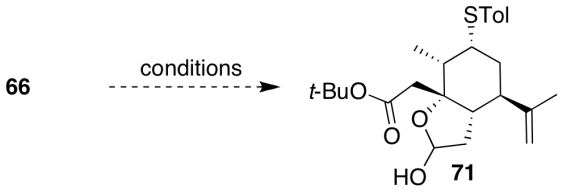
Scheme 4.20 Alkylation and conjugate addition.

Introduction of the key ester side-chain was next examined with the hope that the bottom face would be too sterically congested, disfavouring axial addition into the ketone **67**. Addition of the lithium enolate of *t*-butyl acetate was attempted and yielded little or no product. Successful addition of the cerium enolate in Chapter three led to examination of CeF_3 and $CeCl_3$ in this reaction. Fortunately, both cerium enolates[14] provided the desired lactone **66** in excellent yields with different diastereoselectivities (Table 4.1). Interestingly, CeF_3 produced a 10:1 mixture while $CeCl_3$ produced a >20:1 ratio. It should be noted that the quality of the $CeCl_3$ is important, lower grade $CeCl_3$ provided a 10:1 mixture analogous to the CeF_3 case.



X	Yield (%)	Diastereoselectivity
N/A	trace	N/A
CeF_3	90	10:1
$CeCl_3$	85	>20:1

Table 4.1 Cerium enolate addition.

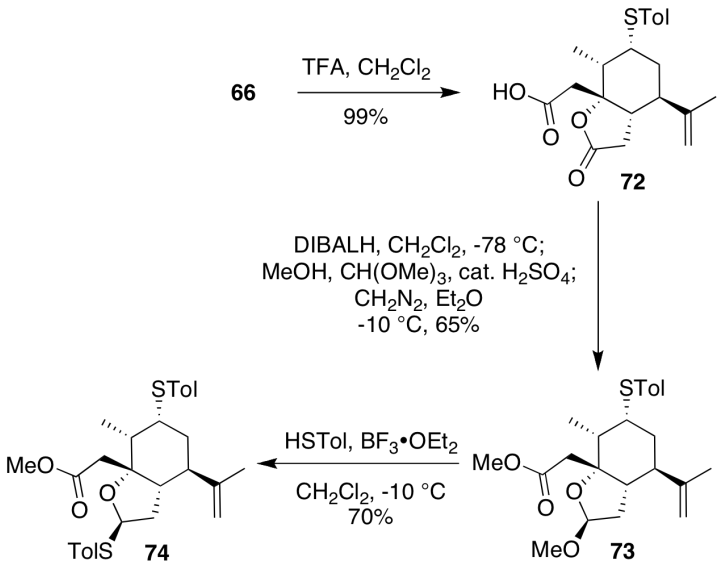


R-H (equiv)	Solvent	Temperature (°C)
DIBALH (1.0)	DME	–60
DIBALH (1.0)	CH_2Cl_2	–78
DIBALH (2.0)	CH_2Cl_2	–78
DIBALH (1.0)	Toluene	–78
Red-Al (1.5)	THF	–78
Red-Al (1.5)	Toluene	–15
Red-Al (2.0)	THF	–78

Table 4.2 Attempted reduction of Lactone **66**.

Reduction of lactone **66** to the hemiacetal **71** proved to be extremely difficult as a variety of different reducing agents at different temperatures failed to produce the lactol (Table 4.2). These reductions produced a complex mixture, which led us to

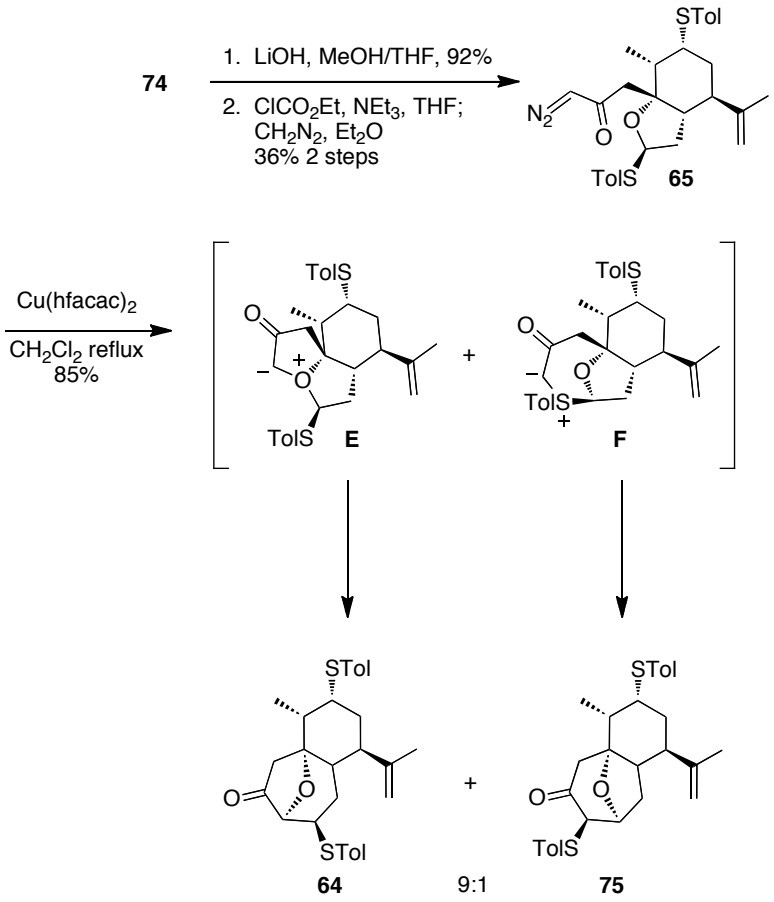
investigate the conversion of *t*-butyl ester to the acid before reduction of the lactone. Conversion of the acid would allow for 2 equivalents of DIBALH to be used. The first equivalent would deprotonate the acid rendering the acid less reactive towards reduction by DIBALH. The second equivalent could then selectively reduce the lactone to the lactol, solving the problem of over reduction. Hydrolysis



Scheme 4.21 Synthesis of thioacetal **74**.

of the *t*-butyl ester was achieved using TFA in CH_2Cl_2, affording acid **72** in excellent yield (Scheme 4.21). With the acid in hand, reduction of the lactone was successful when 2.5 equivalents of DIBALH were used at -78 °C followed by treatment with acidic methanol provided the mixed acetal. The crude acid was then converted to the methyl ester upon reaction with a freshly prepared solution of diazomethane, providing acetal **73** in a 65% yield over three steps. Conversion of the mixed acetal to thioacetal **74** was accomplished using thiocresol and BF_3•OEt_2 affording the product as a single diastereomer. The methyl ester of thioacetal **74** was then converted to the acid in excellent yield by treatment with a 2N solution of LiOH in THF/MeOH. Conversion of the acid to the mixed

anhydride followed by addition of diazomethane furnished the key diazoketone **65** intermediate in 36% yield over two steps. With the diazoketone in hand, the stage was set for the construction of the core BC ring structure via a Stevens rearrangement of an oxonium ylide. Gratifyingly, treatment of diazoketone **65** with catalytic $Cu(hfacac)_2$ in CH_2Cl_2 at reflux provided a 9:1 mixture of regioisomers **64** and **75** in 85% combined yield (Scheme 4.22). These products were each isolated as single diastereomers instead



Scheme 4.22 Stevens rearrangement of diazoketone **65**.

of a mixture of four possible diastereomers. The chemoselectivity is similar to that observed in the model study. When the diazoketone moiety is *cis* to the sulfide,

rearrangement via sulfonium ylide **F** can operate as a minor pathway, while the bulk of the material is converted via oxonium ylide **E**. Interestingly complete diastereoselectivity is observed with this highly functionalized substrate, suggesting that greater conformational rigidity through substitution on the C-ring may lead to slower rates of randomization of biradical intermediate **H** relative to recombination compared to biradical intermediate **G** seen in Chapter two (Figure 4.3). This result suggests that the Stevens rearrangement is an excellent method for the formation of the seven-membered ring found in phorbol.

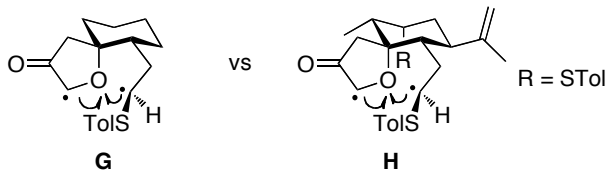
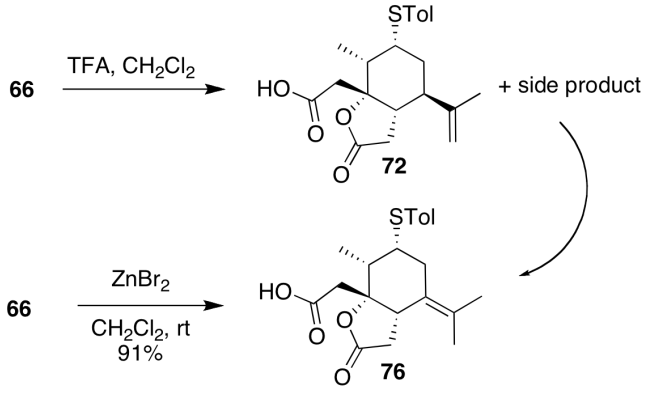


Figure 4.3 Comparison of biradical intermediates **G** and **H**.

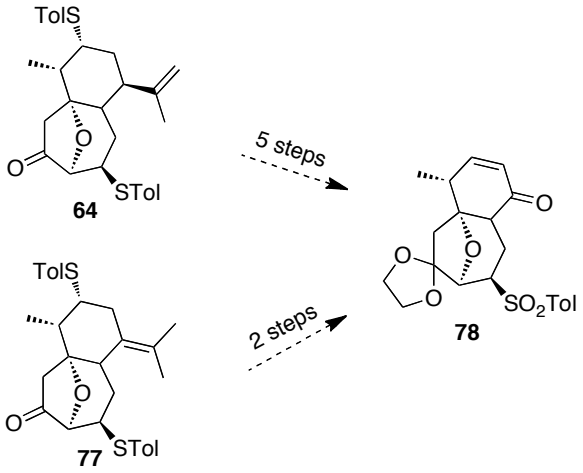
4.9.4 Third Generation Synthesis

Unfortunately, during the scale up of this synthesis a problem with the hydrolysis of the *t*-butyl ester **66** arose, producing an unknown side product that was inseparable from the desired carboxylic acid **72** (Scheme 4.23). Other



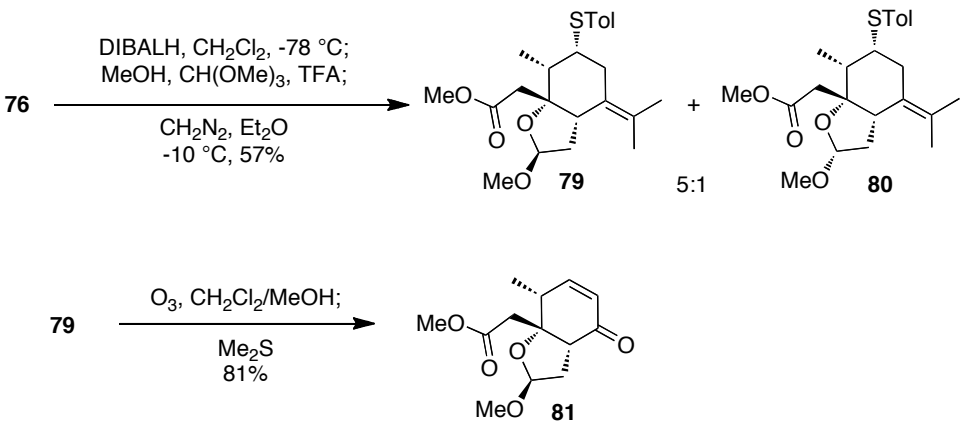
Scheme 4.23 Hydrolysis of *t*-butyl ester **66**.

hydrolysis conditions were examined in an effort to eliminate the side-product formation. During this survey, $ZnBr_2$ was found to produce the side-product as the only detectable product. With large quantities of this material in hand, it was possible to elucidate its structure as **76**, resulting from isomerization of the isopropenyl double bond to the tetrasubstituted isopropylidene. The ultimate role of the isopropenyl group was to provide a handle for functionalization to a ketone and subsequent elimination to afford a double bond where di-oxygenation is required (Scheme 4.24). This original sequence would require approximately 4 synthetic manipulations to construct enone **78**. However, the opportune double-bond migration under hydrolysis conditions afforded a product that could potentially be converted to the enone in two steps.



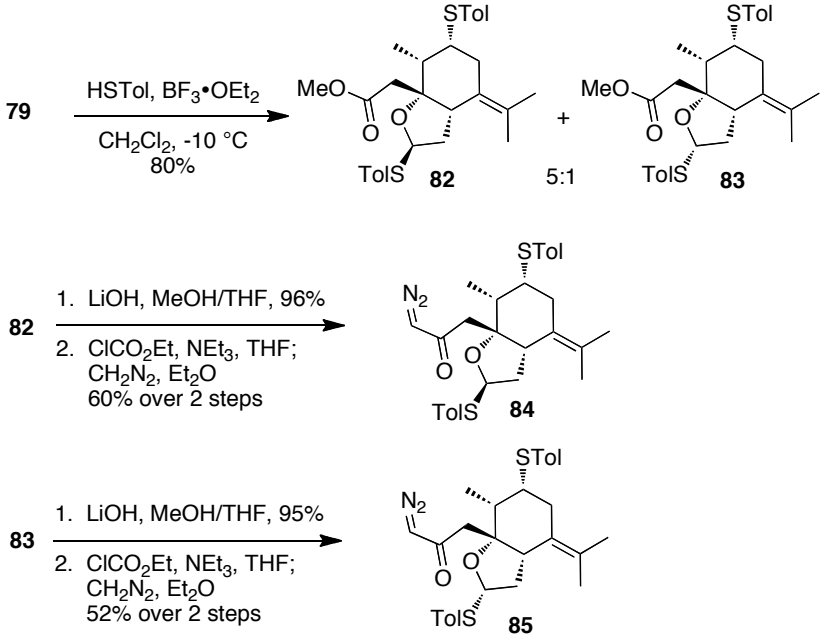
Scheme 4.24 Potential enone formation.

Consequently, carboxylic acid **76** was reacted with DIBALH, the reaction was quenched with acidic MeOH, and then treated with diazomethane to generate mixed acetals **79** and **80** in good yield over three steps. At this point mixed, acetal **79** was subjected to ozonolysis to examine the possibility of a one-pot



Scheme 4.25 Formation of enone **81**.

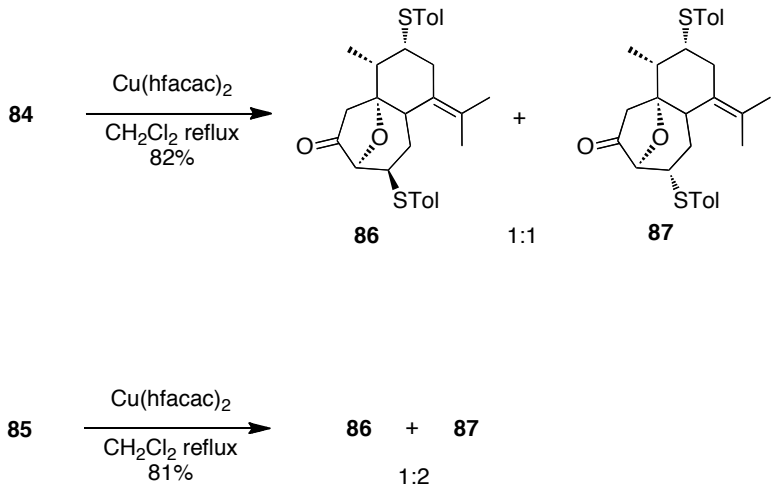
oxidation and elimination sequence. Enone **81** was produced by ozonolysis of **79**, demonstrating that this transformation could deliver the desired enone (Scheme 4.25). In order to perform the sulfur-directed Stevens rearrangement, acetals **79** and **80** were transformed to the mixed thioacetal before oxidation to avoid conjugate addition to the enone by thiocresol.



Scheme 4.26 Synthesis of diazoketones **84** and **85**.

Thioexchange was accomplished using thiocresol and BF_3•Et_2O, furnishing thioacetals **82** and **83** in good yield as a separable mixture of anomers (Scheme 4.26). Saponification of the methyl esters provided the carboxylic acid followed by in situ formation of the mixed anhydride and treatment with diazomethane to generate diazoketones **84** and **85** in moderate yield over three steps.

Diazoketone **84** was treated with catalytic amount of $Cu(hfacac)_2$ in CH_2Cl_2 at reflux, which afforded a mixture of ring-expanded products **86** and **87** (Scheme 4.27). Diazoketone **85** was found to generate the same products under identical reaction conditions slightly favouring product **87**. Efficient conversion of diazoketone **84** to ring expanded products **86** and **87** was slightly surprising because in all previous studies showed that when the diazoketone side-chain and the STol group are *cis* to one another, reaction via the sulfonium ylide is a



Scheme 4.27 Stevens rearrangement of diazoketones **84** and **85**.

competing process. A possible explanation for the absence of sulfonium ylide formation is the diazoketone side-chain has adopted an axial orientation (**A** and **B**) and now the STol group is not close enough in space to undergo sulfonium ylide formation (Figure 4.4). The previous Stevens rearrangement of diazoketone **65**, discussed earlier in the chapter, can undergo competing sulfonium ylide

rearrangement since the diazoketone is in an equatorial orientation **C**, which allows for the STol group to attack the metallocarbene intermediate.

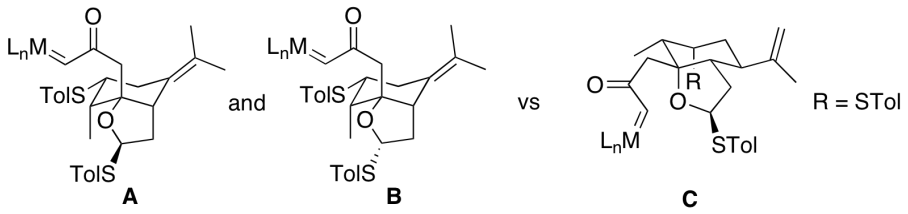
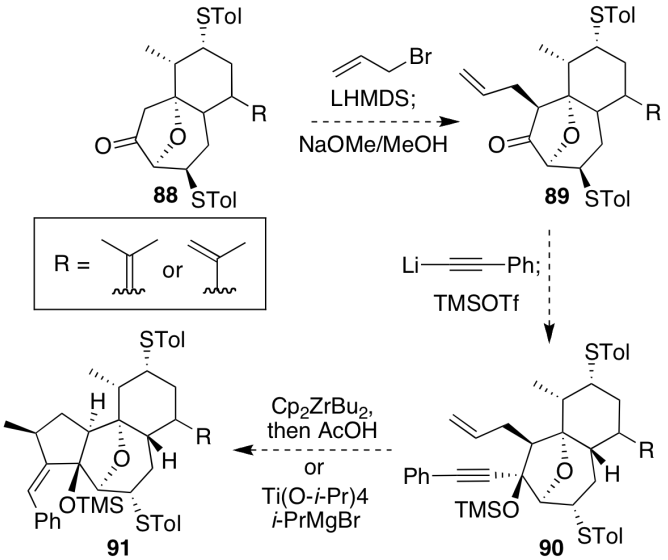


Figure 4.4 Possible conformations of metallocarbene intermediates.

4.10 Future Work and Conclusion

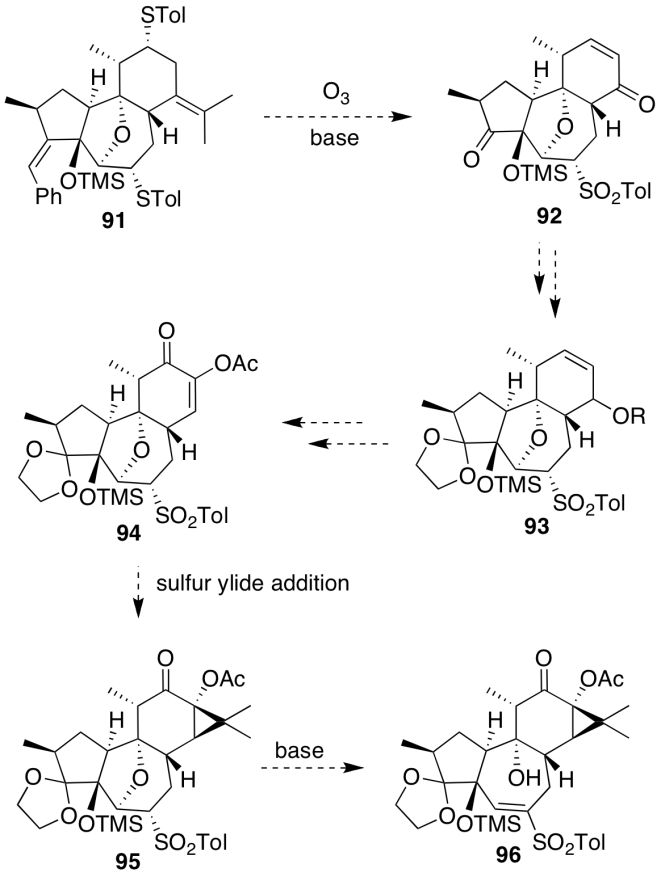
4.10.1 Future Work

In analogy to Wender's approach synthesis of the A-ring would be the next challenge. Alkylation of ketone **88** could potentially proceed on either face (Scheme 4.28). Cha has shown that alkylation of a similar ketone was unselective



Scheme 4.28 Proposed A-ring synthesis.

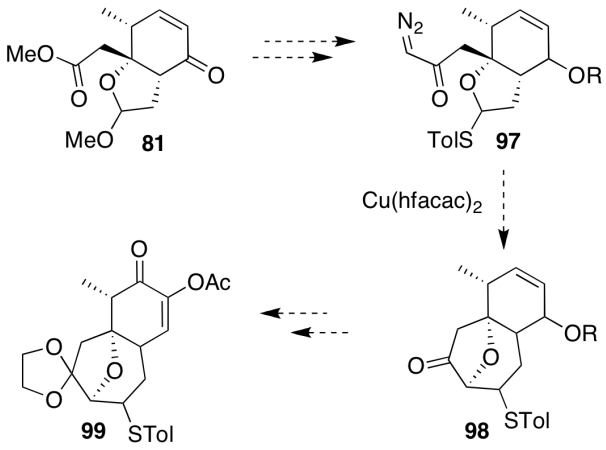
but the product could be epimerized with NaOMe to furnish the desired stereochemistry in ketone **89**.[16] The next two steps would be identical to those used in Wender's synthesis. Phenylacetylene addition to the ketone would be followed by protection to furnish compound **90**. Either the Zr or Ti mediated cyclization protocols, similar to those employed in Wender's and Cha's routes, could be used to form the A-ring in **91**. After the A-ring is in place, installation of the D-ring could be accomplished in a few synthetic manipulations. Ozonolysis of both double bonds would furnish a ketone on the five-membered ring and an enone on the six-membered ring in compound **92** (Scheme 4.29). Selective protection of the ketone followed by enone reduction/protection could provide compound **93**. At this point a few options are available for manipulation to



Scheme 4.29 Proposed D-ring synthesis.

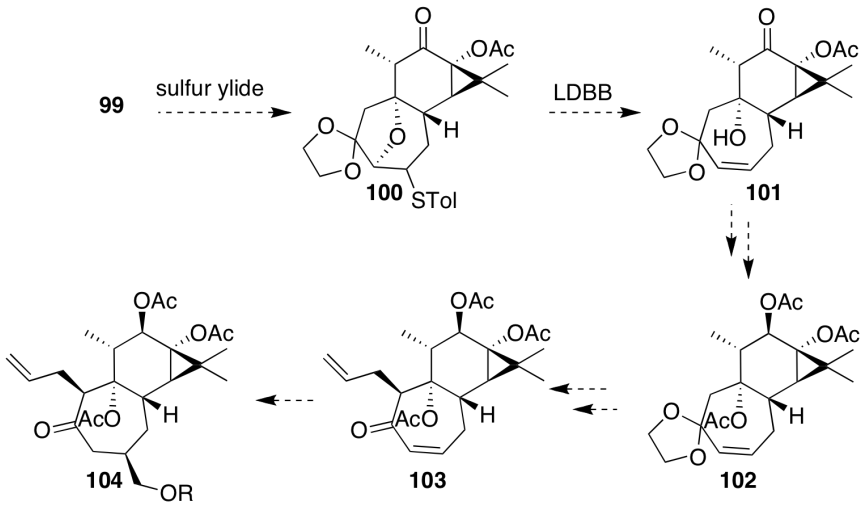
ketone **93**. Dihydroxylation, hydroboration or an epoxidation/ring-opening protocol could potentially be used to install oxygenation and subsequent oxidation/elimination could furnish enone **94**. This intermediate could be subjected to Wender's protocol for synthesis of the D-ring using a sulfur ylide addition to furnish compound **95**. Opening of the ether-bridge could then be achieved using base catalysis to generate vinyl sulfone **96**.

An alternative route utilizing mixed acetal **81** could also be envisioned. Diazoketone **97** could potentially be made in five steps by reduction of the enone, protection of the resulting alcohol, thioacetal formation, saponification to the acid and finally diazoketone installation using chemistry described earlier in this chapter. Under catalytic $Cu(hfacac)_2$ conditions ketone **98** could be obtained and,



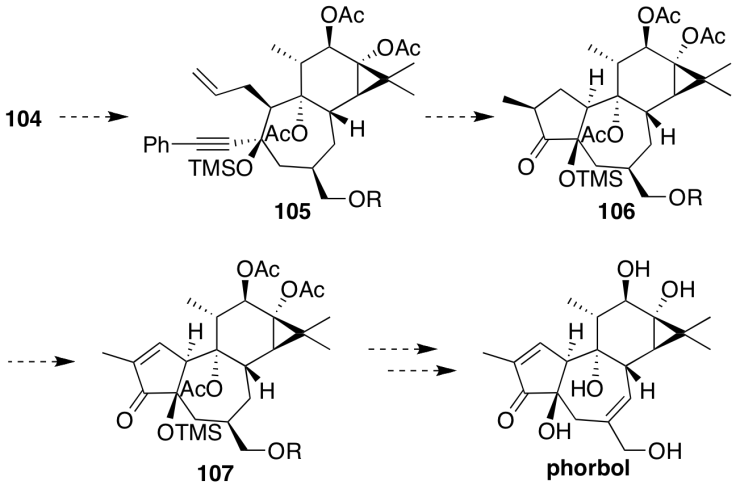
Scheme 4.30 Alternative B-ring synthesis.

with further manipulation of the double bond and elimination of the OR group could generate the D-ring precursor **99**. Sulfur ylide addition to this ketone would allow for construction of the D-ring in compound **100** (Scheme 4.31). Opening of the ether bridge could be achieved using reductive desulfurization, which would provide tertiary alcohol **101**. A directed hydride reduction would afford the secondary alcohol in the correct orientation and protection of both the secondary and tertiary alcohols could generate intermediate **102**. Removal of the acetal



Scheme 4.31 Proposed route to compound **92**.

followed by alkylation would lead to enone **103**, which would provide the opportunity to install the necessary carbon side-chain required on the seven-membered ring by conjugate addition. Addition of phenylacetylene to intermediate **104** followed by protection could provide compound **105** (Scheme 4.32). The final steps of this synthesis would utilize chemistry described in the previous approach. Annulation followed by ozonolysis would generate ketone



Scheme 4.32 End game proposal.

106, which could be converted to enone **107** using Wender's approach.[10] The last steps would involve introduction of the double bond in the seven-membered ring and global deprotection to complete the synthesis of phorbol.

4.10.2 Conclusion

A stereoselective route to the BC ring system of phorbol has been realized using the sulfur-directed Stevens rearrangement of an oxonium ylide as the key step. This rearrangement furnished the seven-membered ring efficiently and has all the functional group handles needed to construct the final two rings. Starting from the readily available carvone our key intermediate can be prepared in 11 steps with excellent stereoselectivity and efficiency.

Chapters 2-4 have demonstrated that the heteroatom directed Stevens rearrangement is an excellent strategy for the synthesis of medium-sized rings fused to smaller carbocyclic rings bearing oxygenation at the bridgehead carbon. Many factors have been shown to affect the chemo- and stereoselectivity of this rearrangement. The configuration at the acetal centre directly affects the stereoselectivity of the rearrangement. Also, it has been observed that in most cases when the STol group is *cis* to the diazoketone side-chain, competing sulfonium ylide rearrangement occurs. Finally, the Stevens rearrangements used towards the synthesis of phorbol have shown that the conformation of the six-membered carbocyclic ring plays an important role not only on the stereoselectivity but also the chemoselectivity. Further studies examining different substitution on the cyclohexane ring may lead to a better understanding of this complex rearrangement.

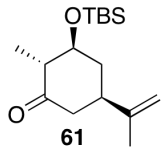
4.11 Experimental

4.11.1 General Information

Reactions were carried out in flame-dried glassware under a positive argon atmosphere unless otherwise stated. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannulae. Solvents were distilled before use: methylene chloride (CH_2Cl_2) from calcium hydride, diethyl ether (Et_2O) and tetrahydrofuran (THF) from sodium/benzophenone ketyl, and toluene from sodium metal. Ethereal diazomethane was prepared from Diazald according to literature procedures.[17] Cerium trichloride ($CeCl_3 \bullet 7H_2O$) and zinc chloride ($ZnCl_2$) were dried in vacuo at 150°C for 2 hours. Thin layer chromatography (T.L.C.) was performed on plates of silica precoated with 0.25 mm Kieselgel 60 F_{254}. Flash chromatography columns were packed with 230-400 mesh silica gel. Radial chromatography was performed on plates of silica pre-coated with 2, or 4 mm silica gel 60 PF_{254} containing gypsum.

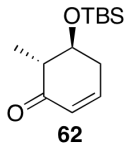
Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz or 500 MHz on Varian Inova 400 and 500, Mercury 400, or Unity 500 spectrometers, and the chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane (0 ppm). Coupling constants (*J*) are reported in Hz. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets, etc. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 125 MHz or 100 MHz and are reported (ppm) relative to the centerline of a triplet at 77.23 ppm for deuterochloroform. Infrared (IR) spectra were measured with 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).

4.11.2 Characterization



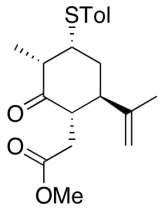
61

Ketone 61. To a solution of pyridine (4.0 mL, 50 mmol) in CH_2Cl_2 (40 mL) was added CrO_3 (2.5 g, 25 mmol) and the reaction was stirred at 0 °C for 15 min. Alcohol **60**[12] (1.41 g, 4.93 mmol) in CH_2Cl_2 (2 mL) was added and the resulting mixture was stirred for 20 h. The reaction was quenched by addition of Et_2O (50 mL) and allowed to stir for an additional hour. Then, the reaction mixture was filtered through a neutral Al_2O_2 column, and washed with Et_2O (50 mL). The combined organic layers were concentrated and the residue purified by column chromatography (silica gel; 5% EtOAc/hexanes until the products were recovered) to give ketone **61** (1.11 g, 80%) as a white solid: m.p. 49-50 °C; R_f 0.44 (15% EtOAc/hexanes); $[\alpha]_D$ 57.32 (c (0.0860, CH_2Cl_2); IR (CH_2Cl_2 cast) 3084, 2954, 2890, 2859, 1714, 1645, 1452, 1361, 1255, 1068, 1055, 1006, 939 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.79 (app quintet, *J* = 1.5 Hz, 1H), 4.76 (m, 1H), 3.44 (app td, *J* = 10.5, 4.1 Hz, 1H), 2.44-2.37 (m, 2H), 2.28 (app td, *J* = 13.5, 1.5 Hz, 1H), 2.20 (app tt, *J* = 12.5, 3.0 Hz, 1H), 2.10 (dddd, *J* = 12.5, 4.0, 3.0, 2.0 Hz, 1H), 1.78-1.69 (m, 1H), 1.75 (br s, 3H), 1.09 (d, *J* = 6.5 Hz, 3H), 0.97 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 146.7, 110.3, 75.6, 53.9, 46.2, 40.6, 39.9, 25.8, 20.2, 18.0, 10.9, -4.2, -4.8; HRMS (ESI, $[M+Na]^+$) calcd for $C_{16}H_{30}O_2SiNa$ 305.1907, found m/z 305.1907.



62

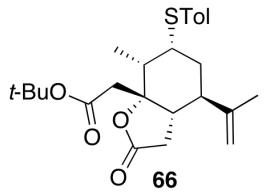
Enone 62. Ozone was bubbled into a solution of **61** (1.68 g, 5.93 mmol) in MeOH (17 mL) at –78 °C until the solution turned a persistent blue colour. The solution was then allowed to stir for 30 min. Oxygen was bubbled into the solution until it was colourless, after which the cooling bath was removed and $Cu(OAc)_2 \bullet H_2O$ (2.37 g, 11.9 mmol) was added in one portion. The resulting suspension was stirred for 15 min, and $FeSO_4 \bullet 7H_2O$ (1.98 g, 7.12 mmol) was then added in two portions over 10 min. The dark green suspension was stirred for 20 h at which time water (50 mL) was added and the resulting mixture extracted with Et_2O (6 x 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (50 mL), dried ($MgSO_4$), filtered and concentrated. The resulting oil was purified by column chromatography (silica gel; 5 % EtOAc / hexanes until the product was recovered) to afford **62** (1.18 g, 83%) as a colourless oil: R_f 0.33 (15% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2954, 2890, 2859, 1695, 1452, 1361, 1255, 1055, 1006, 939 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.81 (ddd, J = 8.0, 4.5, 3.0 Hz, 1H), 6.05 (ddd, J = 8.0, 2.5, 1.5 Hz, 1H), 3.79 (ddd, J = 9.0, 7.5, 5.0 Hz, 1H), 2.61 (dddd, J = 19.0, 5.0, 5.0, 1.5 Hz, 1H), 2.42-2.38 (m, 2H), 1.19 (d, J = 7.0 Hz, 3H), 0.95 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 145.5, 129.5, 72.6, 51.1, 35.5, 25.6, 17.9, 11.2, -4.4, -4.9; HRMS (ESI, $[M+Na]^+$) calcd for $C_{13}H_{24}O_2SiNa$ 263.1443, found 263.1440.



67

Ketone 67. A solution of **70**[15] (13.5 g, 60.6 mmol) in hexane (60 mL) was treated with *p*-thiocresol (8.29 g, 66.6 mmol) and NEt_3 (1.69 mL, 1.21 mmol). The

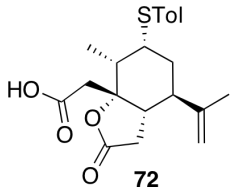
suspension was stirred at room temperature for 20 h before the solid was filtered to yield **67** (16.0 g, 76%) as a white solid: m.p. 120-122 °C; R_f 0.29 (15% EtOAc/hexanes); $[\alpha]_D$ -182.6 (c 0.980, CH_2Cl_2); IR (CH_2Cl_2 cast) 3074, 3007, 2957, 2933, 2913, 1725, 1715, 1647, 1495, 1437, 1375, 1226, 1193, 987 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 4.83 (app t, *J* = 1.5 Hz, 1H), 4.82 (br s, 1H), 3.81 (ddd, *J* = 5.5, 3.5, 3.5 Hz, 1H), 3.68 (s, 3H), 3.03 (app quintet, *J* = 6.5 Hz, 1H), 2.96-2.85 (m, 2H), 2.67 (dd, *J* = 16.5, 9.0 Hz, 1H), 2.33 (s, 3H), 2.23 (dd, *J* = 17.0, 3.0 Hz, 1H), 2.08 (ddd, *J* = 14.0, 11.5, 3.0 Hz, 1H), 1.88 (app dt, *J* = 14.5, 3.5 Hz, 1H), 1.68 (s, 3H), 1.22 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.8, 173.4, 144.9, 137.7, 133.2, 130.6, 129.9, 113.5, 54.6, 51.6, 49.3, 48.3, 46.6, 36.0, 31.8, 21.1, 18.8, 12.9; HRMS (ESI, $[M+Na]^+$) calcd for $C_{20}H_{26}NaO_3S$ 369.1495, found m/z 369.1495.



66

Lactone 66. To a stirred solution of hexamethyldisilazane (1.32 mL, 6.32 mmol) in THF (12 mL) at –78 °C was added *n*-BuLi (3.29 mL of 1.60M solution, 5.27 mmol) and the resulting mixture was stirred for 30 min. This mixture was then warmed to 0 °C over several minutes and stirred for 15 min before being cooled once again to –78 °C. *t*-Butyl acetate (707 μL, 5.27 mmol) was added dropwise, and the mixture was stirred for 45 min. Dry cerium trichloride powder (1.29 g, 5.27 mmol) was then added and the heterogeneous mixture stirred for an additional 2 h at the same temperature. A THF solution (2 mL) of ketone **67** (913 mg, 2.64 mmol) was added dropwise to the above mixture and the reaction mixture was stirred for 2 h. The reaction mixture was then diluted with Et_2O (30 mL) and quenched by the addition of saturated ammonium chloride solution (25 mL). After separation of the phases, the aqueous layer was extracted with Et_2O (3 x 25 mL) and the combined organic extracts were washed with water (50 mL),

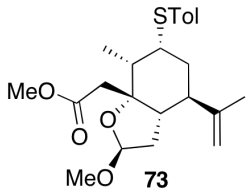
brine (50 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (silica gel; 5%, 10%, 15% EtOAc/hexanes until the products were recovered) to yield **66** (966 mg, 85%) as a white solid: R_f 0.23 (15% EtOAc/hexanes); m.p. 84-86 °C; $[\alpha]_D$ -74.2 (c 2.20, CH_2Cl_2); IR (CH_2Cl_2 cast) 3071, 2976, 2937, 1783, 1723, 1644, 1493, 1456, 1393, 1235, 1168, 1117, 1053, 953 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.1 Hz, 2H), 4.86-4.83 (m, 2H), 3.44 (app q, J = 3.3 Hz, 1H), 2.85 (d, J_{AB} = 14.6 Hz, 1H), 2.81-2.69 (m, 2H), 2.75 (d, J_{AB} = 17.6 Hz, 1H), 2.49 (d, J_{AB} = 14.6 Hz, 1H), 2.44-2.37 (m, 1H), 2.38 (d, J_{AB} = 17.6 Hz, 1H), 2.31 (s, 3H), 1.78 (app dt, J = 13.7, 3.4 Hz, 1H), 1.66 (s, 3H), 1.54-1.50 (m, 1H), 1.47 (s, 9H), 1.42 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 168.7, 145.4, 137.0, 132.8, 132.7, 129.7, 113.1, 86.8, 81.7, 52.0, 42.2, 41.8, 39.6, 38.4, 35.2, 33.9, 28.0, 21.1, 19.5, 14.9; HRMS (ESI, $[M+Na]^+$) calcd for $C_{25}H_{34}O_4SNa$ 453.2070, found m/z 453.2065.



72

Acid 72. To a solution of lactone **66** (406 mg, 0.943 mmol) in CH_2Cl_2 (9 mL) was added TFA (2.18 mL, 28.3 mmol). The reaction was stirred for 2 hours at room temperature after which time the mixture was concentrated and filtered through a short pad of silica gel and eluted with 50% ethyl acetate/hexane (30 mL). This solution was then concentrated to yield acid **72** (353 mg, 99%) as a colourless viscous oil: $[\alpha]_D$ -73.7 (c 1.08, CH_2Cl_2); IR (CH_2Cl_2 cast) 3500-2900, 3071, 2974, 2939, 1779, 1738, 1644, 1493, 1441, 1382, 1183, 1051, 961 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.25, (br s, OH, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 4.88-4.86 (m, 2H), 3.44 (app q, J = 3.6 Hz, 1H), 3.02 (d, J_{AB} = 15.2 Hz, 1H), 2.86-2.70 (m, 2H), 2.78 (d, J_{AB} = 18.0 Hz, 1H) 2.66 (d, J_{AB} = 15.2 Hz, 1H), 2.52-2.44 (m, 1H), 2.45 (d, J_{AB} = 18.0 Hz, 1H), 2.34 (s, 3H), 1.81-1.77 (m, 1H), 1.67 (s, 3H), 1.64-1.58 (m, 1H), 1.45 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

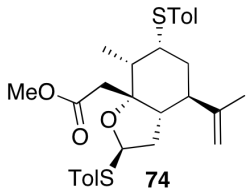
175.8, 174.1, 145.1, 137.1, 132.6, 132.3, 129.8, 113.2, 86.5, 60.5, 51.8, 41.6, 40.3, 38.3, 35.2, 33.5, 21.0, 19.4, 14.8; HRMS (ESI, $[M+Na]^+$) calcd for $C_{21}H_{26}O_4SNa$ 397.1444, found m/z 397.1449.



73

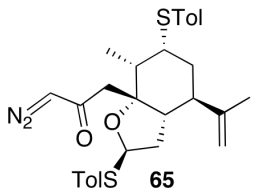
Mixed Acetal 73. To a solution of acid **72** (590 mg, 1.58 mmol) in CH_2Cl_2 (16 mL) was added DIBALH (3.94 mL, 1.00 M solution in CH_2Cl_2, 3.94 mmol) dropwise at –78 °C. After being stirred for 1 hour, the reaction mixture was quenched with MeOH (20 mL) and allowed to warm to room temperature. To this mixture was added trimethyl orthoformate (219 μL, 2.01 mmol) and 2 drops of H_2SO_4. The resulting mixture was stirred for 12 h at room temperature, quenched with brine (10 mL) and diluted with CH_2Cl_2 (10 mL). The layers were separated, and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude oil was redissolved in THF (2 mL) and added via cannula to a freshly prepared solution of diazomethane (~8 mmol) in Et_2O (~24 mL). The resulting mixture was stirred for 2 hours at which time a gentle stream of Ar(g) was applied to the system to allow for slow evaporation of both excess diazomethane and Et_2O. The resulting oil was purified by column chromatography (silica gel; 5%, 10%, 15% EtOAc/hexanes until the products were recovered) to yield **73** (390 mg, 61%) as a colourless oil: R_f 0.47 (30% EtOAc/hexanes); $[\alpha]_D$ -69.41 (c 2.50, CH_2Cl_2); IR (CH_2Cl_2 cast) 2952, 2935, 1735, 1643, 1493, 1439, 1333, 1201, 1105, 983 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 5.17 (app t, J = 5.5 Hz, 1H), 4.84-4.81 (m, 2H), 3.68 (s, 3H), 3.39 (s, 3H), 3.32-3.28 (m, 1H), 2.87 (d, J_{AB} = 15.5 Hz, 1H), 2.74 (d, J_{AB} = 15.5 Hz, 1H), 2.63 (app td, J = 12.5, 3.5 Hz, 1H), 2.50 (dd, J = 11.5, 6.5 Hz, 1H), 2.35-2.27 (m, 1H), 2.32 (s, 3H), 2.17 (dd, J = 13.5, 6.0 Hz, 1H), 2.03 (ddd, J = 12.0, 6.5,

5.0 Hz, 1H), 1.75 (app dt, J = 13.5, 3.5 Hz, 1H), 1.67 (s, 3H), 1.62-1.50 (m, 1H), 1.37 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 147.0, 136.5, 134.5, 132.3, 129.6, 112.2, 104.7, 84.8, 55.9, 53.5, 51.5, 43.0, 42.3, 41.2, 38.6, 36.6, 35.0, 21.0, 19.6, 15.4; HRMS (ESI, $[M+Na]^+$) calcd for $C_{23}H_{32}O_4SNa$ 427.1914, found m/z 427.1916.



74

Thioacetal 74. To a solution of **73** (245 mg, 0.606 mmol) and *p*-thiocresol (90 mg, 0.73 mmol) in CH_2Cl_2 (6 mL) was added BF_3•OEt_2 (90 μL, 0.73 mmol) at –15 °C. The reaction was stirred until deemed complete by TLC (30 min). The reaction was then quenched with Et_3N (0.5 mL) and water (10 mL) and the resulting bi-layer was separated. The aqueous phase was extracted with CH_2Cl_2 (20 mL) and the combined organic extracts were washed with water (5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (silica gel; 2%, 5% then 10% EtOAc/hexanes until the product was recovered) to afford **74** (210 mg, 70%) as a yellow oil: R_f 0.41 (15% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2974, 2920, 1733, 1491, 1437, 1288, 108, 1157, 1099, 1053, 1018, 917 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 5.71 (dd, J = 9.5, 6.5 Hz, 1H), 4.83 (br s, 1H), 4.82 (app t, J = 1.5 Hz, 1H), 3.68 (s, 3H), 3.32 (app q, J = 3.0 Hz, 1H), 2.85 (d, J_{AB} = 15.0 Hz, 1H), 2.79-2.73 (m, 1H), 2.74 (d, J_{AB} = 15.0 Hz, 1H), 2.55 (dd, J = 11.0, 6.5 Hz, 1H), 2.37-2.27 (m, 2H), 2.32 (s, 6H), 2.21 (ddd, J = 13.5, 9.5, 6.5 Hz, 1H), 1.74 (app dt, J = 13.5, 3.5 Hz, 1H), 1.68 (s, 3H), 1.54 (app td, J = 13.5, 2.5 Hz, 1H), 1.40 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 147.0, 136.7, 136.2, 134.1, 132.9, 132.5, 129.9, 129.6, 129.6, 112.4, 86.4, 83.9, 53.3, 51.6, 42.5, 41.5, 41.3, 38.8, 37.1, 34.5, 21.1, 21.0, 19.5, 15.6; HRMS (ESI, $[M+Na]^+$) calcd for $C_{29}H_{36}O_3S_2$ Na 519.1998, found m/z 519.1992.

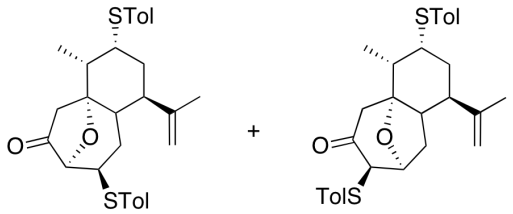


65

Diazoketone 65. To a solution of thioacetal **74** (93 mg, 0.19 mmol) in THF (1 mL) and methanol (1 mL) was added a 2.0 M solution of LiOH (234 μL, 0.468 mmol). The reaction was stirred for 24 h at room temperature, during which time the reaction mixture turned slightly yellow. The reaction was diluted with water (5 mL) and Et_2O (5 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was washed with Et_2O (5 mL). The aqueous layer was then acidified with 0.5 M HCl to pH ~3, resulting in a cloudy suspension. This aqueous phase was then diluted with ethyl acetate (10 mL) and the resulting layers separated. The aqueous layer was washed with 3 portions of ethyl acetate (5 mL) and the combined organic extracts were washed with water (5 mL), then brine (5 mL), dried ($MgSO_4$), filtered and concentrated to give the acid as a yellow oil (82 mg, 91%): IR (CH_2Cl_2 cast) 3350-2900, 2978, 2924, 1707, 1493, 1429, 1295, 1179, 1009, 942 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.00 (br s, OH, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 5.73 (dd, *J* = 9.5, 6.5 Hz, 1H), 4.83 (br s, 2H), 3.31 (app q, *J* = 3.5 Hz, 1H), 2.86 (d, J_{AB} = 15.5 Hz, 1H), 2.80-2.74 (m, 1H), 2.76 (d, J_{AB} = 15.5 Hz, 1H), 2.50 (dd, *J* = 11.5, 6.5 Hz, 1H), 2.40-2.30 (m, 2H), 2.32 (s, 6H), 2.21 (ddd, *J* = 14.0, 10.0, 6.5 Hz, 1H), 1.75 (app dt, *J* = 13.5, 3.5 Hz, 1H), 1.67 (s, 3H), 1.53 (app td, *J* = 13.5, 3.0 Hz, 1H), 1.41 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 146.8, 136.8, 136.4, 133.9, 132.8, 132.6, 132.5, 130.0, 129.7, 112.6, 86.3, 84.1, 53.2, 42.9, 42.1, 41.3, 39.2, 37.0, 34.4, 21.1, 21.0, 19.6, 15.6; HRMS (ESI, $[M+Na]^+$) calcd for $C_{28}H_{34}O_2S_2Na$ 505.1842, found m/z 505.1846: The acid (68 mg, 0.14 mmol) was dissolved in THF (1 mL) and cooled to 0 °C. To this solution was added NEt_3 (22 μL, 0.16 mmol) and ethyl chloroformate (15 μl, 0.16 mmol). The reaction was stirred at this temperature for 1 h and then warmed to room temperature. At this time the reaction was directly

transferred to a freshly prepared solution of diazomethane (~4 mmol) in Et_2O (~12 mL) and the resulting mixture stirred for 16 h. A gentle stream of Ar(g) was applied to the system to allow for slow evaporation of both excess diazomethane and solvent. The crude yellow oil was purified by column chromatography (silica gel; 5%, 10%, 15% EtOAc/hexanes until the products were recovered) to yield **65** (26 mg, 36%) and **74** (27 mg, 39%) as yellow oils: **65:** R_f 0.22 (15% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3017, 2974, 2924, 2865, 2105, 1732, 1636, 1493, 1457, 1493, 1356, 1019, 958 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 5.71 (dd, *J* = 9.5, 6.5 Hz, 1H), 5.34 (br s, 1H), 4.84 (br s, 1H), 4.81 (app t, *J* = 1.5 Hz, 1H), 3.31 (app q, *J* = 3.5 Hz, 1H), 2.82-2.65 (m, 3H), 2.43 (app qd, *J* = 11.5, 6.5 Hz, 1H), 2.38-2.30 (m, 1H), 2.32 (s, 6H), 2.17 (ddd, *J* = 13.5, 9.5, 6.5 Hz, 1H), 1.73 (app dt, *J* = 13.5, 3.5 Hz, 1H), 1.69 (s, 3H), 1.62-1.55 (m, 2H), 1.37 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.1, 147.0, 136.7, 136.2, 134.1, 132.9, 132.5, 129.9, 129.6, 129.6, 112.4, 86.4, 83.9, 60.0, 55.6, 53.3, 42.5, 41.3, 38.8, 37.1, 36.3, 34.5, 21.0, 19.5, 17.1; HRMS (ESI, $[M+Na]^+$) calcd for $C_{29}H_{34}O_2N_2S_2Na$ 529.1954, found m/z 529.1950.

Carbene Transfer Reaction of 65: Preparation of 64 and 75



64 **75**

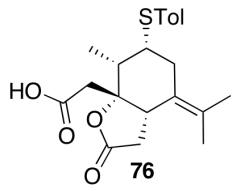
To a refluxing solution of $Cu(hfacac)_2$ (9 mg, 0.02 mmol) in CH_2Cl_2 (3 mL) was added a solution of **65** (55 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) and the resulting reaction was monitored by TLC. Upon consumption of diazoketone (30 min), the

reaction mixture was cooled to room temperature and quenched with saturated $NaHCO_3$ solution (5 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 5 mL). The organic extracts were combined and washed with water (2 mL), brine (2 mL), dried ($MgSO_4$), filtered and concentrated. The resulting oil was purified by column chromatography (silica gel; 5 % EtOAc / hexanes until the product was recovered) to yield **64** (18 mg) as a colourless and **75** (2 mg) as a colourless oil in a combined overall yield of 85%.

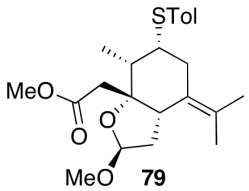
Major 64. R_f 0.50 (30% EtOAc/hexanes); $[\alpha]_D$ -35.3 (c 0.860, CH_2Cl_2); IR (CH_2Cl_2 cast) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 2966, 2933, 1760, 1644, 1493, 1457, 1164, 1031, 895 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 4.90 (br s, 1H), 4.85 (app t, *J* = 1.5 Hz, 1H), 4.08 (br s, 1H), 3.52 (dt, *J* = 13.5, 5.0 Hz, 1H), 3.35 (ddd, *J* = 4.5, 3.5, 3.5 Hz, 1H), 3.28 (app td, *J* = 12.0, 2.5 Hz, 1H), 2.72 (dd, J_{ABX} = 18.5, 1.0 Hz, 1H), 2.34 (s, 3H), 2.32 (s, 3H), 2.21-2.14 (m, 3H), 1.93 (app dt, *J* = 13.5, 2.5 Hz, 1H), 1.72 (app td, *J* = 13.5, 3.5 Hz, 1H), 1.65-1.55 (m, 2H), 1.62 (s, 3H), 1.30 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0, 146.6, 137.9, 136.8, 134.2, 133.5, 132.2, 129.8, 129.7, 129.3, 113.1, 82.8, 80.2, 54.0, 44.7, 43.6, 40.0, 39.3, 37.7, 36.6, 27.6, 21.1, 21.0, 20.3 14.3; HRMS (ESI, $[M+Na]^+$) calcd for $C_{29}H_{34}O_2S_2Na$ 501.1898, m/z 501.1892 found.

Minor 75. R_f 0.58 (30% EtOAc/hexanes); $[\alpha]_D$ -147.30 (c 0.240, CH_2Cl_2); IR (CH_2Cl_2 cast) 3019, 2964, 2923, 2850, 1712, 1643, 1493, 1455, 1320, 1210, 1062, 1019, 894 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.32 (m, 4H), 7.10 (d, *J* = 8.0 Hz, 4H), 4.84 (dt, *J* = 8.0, 2.0 Hz, 1H), 4.78-4.77 (m, 2H), 3.41-3.34 (m, 2H), 3.31 (t, *J* = 1.5 Hz, 1H), 2.64 (dt, *J* = 11.5, 3.5 Hz, 1H), 2.34 (s, 3H), 2.32 (s, 3H), 2.02-1.93 (m, 4H), 1.81 (app dt, *J* = 13.5, 3.5 Hz, 1H), 1.75 (app qd, *J* = 9.0, 2.0 Hz, 1H), 1.62 (s, 3H), 1.58-1.47 (m, 1H), 1.46 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 146.1, 137.7, 136.9, 132.4, 132.0, 129.8, 129.7, 129.6, 121.3, 112.2, 84.8, 82.3, 61.2, 52.3, 48.4, 44.5, 44.4, 40.6, 35.9, 35.0, 29.7, 21.0,

19.8, 14.8; HRMS (ESI, $[M+Na]^+$) calcd for $C_{29}H_{34}O_2S_2Na$ 501.1898, m/z 501.1894 found.

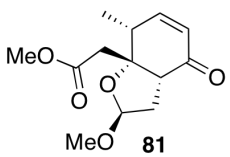


Acid 76. To a solution of lactone **66** (710 mg, 1.65 mmol) in CH_2Cl_2 (3 mL) was added $ZnBr_2$ (1.85 g, 8.24 mmol) and the reaction was stirred for 24 h at room temperature. The reaction was then diluted with water (40 mL) and CH_2Cl_2 (40 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer washed with CH_2Cl_2 (20 mL). The combined organic extracts were washed brine (15 mL), dried ($MgSO_4$), filtered and concentrated to yield acid **76** (560 mg, 91%) as a colourless viscous oil: $[\alpha]_D$ -60.63 (c 0.500, CH_2Cl_2); IR (CH_2Cl_2 cast) 3400-2900, 2979, 2922, 1778, 1747, 1493, 1429, 1295, 1209, 1177, 1010, 942 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.0 Hz, 2H), 7.13-7.11 (m, 2H), 3.84 (app t, *J* = 11.2 Hz, 1H), 3.18 (app dt, *J* = 10.8, 4.4 Hz, 1H), 2.80-2.68 (m, 4H), 2.47 (dd, *J* = 18.0, 11.2 Hz, 1H), 2.38-2.21 (m, 2H), 2.34 (s, 3H), 1.67 (d, *J* = 2.0 Hz, 3H), 1.63 (d, *J* = 1.0 Hz, 3H), 1.21 (d, *J* = 7.2 Hz, 3H), (COOH proton not detected); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 173.5, 137.5, 132.4, 130.8, 130.4, 129.9, 124.3, 86.4, 48.1, 43.3, 41.1, 40.6, 35.5, 27.7, 21.1, 20.7, 20.4, 10.6; HRMS (ESI, $[M+Na]^+$) calcd for $C_{21}H_{26}O_4SNa$ 373.1479, found m/z 373.1476.



Mixed Acetal 79. To a solution of acid **76** (1.46 g, 3.90 mmol) in CH_2Cl_2 (8 mL) was added dropwise DIBALH (9.73 mL, 1.00M solution in CH_2Cl_2, 9.73 mmol)

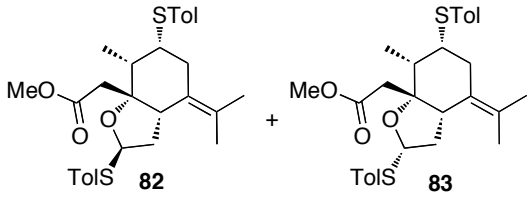
at –78 °C. After being stirred for 1 h, the reaction mixture was quenched with MeOH (20 mL) and allowed to warm to room temperature. To this mixture was added trimethyl orthoformate (2.13 mL, 19.5 mmol) and TFA (450 μl, 5.84 mmol). The resulting mixture was stirred for 12 h at room temperature, quenched with brine (50 mL) and diluted with CH_2Cl_2 (50 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude oil was redissolved in THF (2 mL) and added to a freshly prepared solution of diazomethane (~12 mmol) in Et_2O (~40 mL). The resulting mixture was stirred for 2 hours at which time a gentle stream of Ar(g) was applied to the system to allow for slow evaporation of both excess diazomethane and Et_2O. The resulting oil was purified by column chromatography (silica gel; 5%, 10%, 15% EtOAc/hexanes until the products were recovered) to yield **79** (900 mg, 57%) as a colourless oil: R_f 0.26 (30% EtOAc/hexanes); $[\alpha]_D$ 28.13 (c 0.860, CH_2Cl_2); IR (CH_2Cl_2 cast) 2979, 2950, 2916, 2831, 1737, 1493, 1438, 1376, 1331, 1268, 1217, 1099, 1029, 992, 964 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 5.01 (d, J = 5.0 Hz, 1H), 3.65-3.58 (m, 1H), 3.63 (s, 3H), 3.35 (s, 3H), 3.16 (app dt, J = 11.5, 4.5 Hz, 1H), 2.70 (dd, J = 15.5, 4.5 Hz, 1H), 2.65 (s, 3H), 2.60 (d, J_{AB} = 14.5 Hz, 1H), 2.51 (d, J_{AB} = 14.5 Hz, 1H), 2.27-2.17 (m, 2H), 2.06-1.93 (m, 2H), 1.72 (d, J = 2.5 Hz, 3H), 1.63 (br s, 3H), 1.14 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 136.8, 132.0, 131.9, 129.7, 128.2, 125.7, 104.8, 86.2, 54.6, 51.6, 48.9, 46.0, 42.5, 40.9, 38.9, 27.8, 21.1, 20.7, 20.2, 11.3; HRMS (ESI, $[M+Na]^+$) calcd for $C_{23}H_{32}O_4SNa$ 427.1914, found m/z 427.1912.



81

Enone 81. Ozone was bubbled into a solution of **79** (71 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) and MeOH (175 μl) at –78 °C until the solution turned a persistent

blue colour. The solution was then allowed to stir for 30 min. Oxygen was bubbled into the solution until it was colourless, after which the cooling bath was removed and Me_2S (52 μL, 0.70 mmol) was added. The resulting mixture was stirred for 20 hours and quenched by the addition of $NaHCO_3$ (5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by column chromatography (silica gel; 10 % EtOAc / hexanes until the product was recovered) to afford **81** (35 mg, 80%) as a colourless oil: R_f 0.23 (15% EtOAc/hexanes); $[\alpha]_D$ 10.87 (c 0.860, CH_2Cl_2); IR (CH_2Cl_2 cast) 3034, 2990, 2953, 2834, 1734, 1674, 1440, 1458, 1351, 1307, 1214, 1170, 1104, 1024, 991 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.78 (dd, *J* = 10.0, 3.0 Hz, 1H), 6.03 (dd, *J* = 10.0, 2.5 Hz, 1H), 4.94 (ddd, *J* = 5.5, 3.5, 0.5 Hz, 1H), 3.67 (s, 3H), 3.35 (s, 3H), 3.26 (ddd, *J* = 8.5, 4.5, 1.0 Hz, 1H), 2.99-2.93 (m, 1H), 2.93 (d, J_{AB} = 15.0 Hz, 1H), 2.80 (d, J_{AB} = 15.0 Hz, 1H), 2.66 (ddd, *J* = 14.0, 6.0, 4.5 Hz, 1H), 2.36 (ddd, *J* = 13.5, 8.5, 3.5 Hz, 1H), 1.27 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 171.0, 153.1, 127.0, 104.4, 84.3, 55.6, 51.8, 51.4, 43.0, 37.2, 35.7, 15.7; HRMS (ESI, $[M+Na]^+$) calcd for $C_{13}H_{18}O_5Na$ 277.1046, found m/z 277.1047.

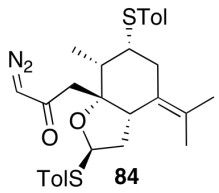


Thioacetals 82 and 83. To a solution of **79** (5:1 mixture of anomers) (233 mg, 0.576 mmol) and *p*-thiocresol (86 mg, 0.69 mmol) in CH_2Cl_2 (6 mL) was added BF_3•OEt_2 (84 μL, 0.69 mmol) at –15 °C. The reaction was stirred until deemed complete by TLC (30 min). The reaction was quenched with Et_3N (0.5 mL) and water (10 mL) and the resulting bi-layer separated. The aqueous phase was extracted with CH_2Cl_2 (20 mL) and the combined organic extracts were washed

with water (5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (silica gel; 2%, 5% then 10% EtOAc/hexanes until the product was recovered) to afford **82** (191 mg) and **83** (38 mg) as colourless oils in a combined yield of 80%:

Major Anomer 82: R_f 0.29 (15% EtOAc/hexanes); $[\alpha]_D$ 99.93 (c 0.820, CH_2Cl_2); IR (CH_2Cl_2 cast) 3019, 2950, 2922, 2862, 1734, 1493, 1437, 1287, 1212, 1179, 1092, 1017, 955 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.13-7.09 (m, 4H), 5.63 (dd, *J* = 8.0, 1.5 Hz, 1H), 3.62-3.58 (m, 1H), 3.61 (s, 3H), 3.14 (app dt, *J* = 12.0, 4.0 Hz, 1H), 2.73 (d, J_{AB} = 13.5 Hz, 1H), 2.72-2.66 (m, 1H), 2.70 (d, J_{AB} = 13.5 Hz, 1H), 2.41 (app td, *J* =13.0, 8.0 Hz, 1H), 2.33 (s, 6H), 2.27 (app qd, *J* = 7.5, 4.5, 1H), 2.14 (ddd, *J* = 13.5, 8.5, 1.5 Hz, 1H), 1.72 (d, *J* = 2.0 Hz, 3H), 1.63 (d, *J* = 1.0 Hz, 3H), 1.46-1.26 (m, 1H), 1.25 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 137.3, 136.9, 132.5, 132.0, 131.6, 131.3, 129.8, 129.7, 128.8, 125.3, 87.7, 86.6, 51.7, 48.7, 45.6, 44.2, 41.1, 39.4, 27.2, 21.1, 21.0, 20.7, 20.2, 11.0; HRMS (ESI, $[M+Na]^+$) calcd for $C_{29}H_{36}O_3S_2Na$ 519.1998, found m/z 519.2007.

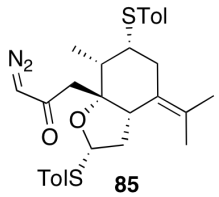
Minor Anomer 83: R_f 0.27 (15% EtOAc/hexanes); $[\alpha]_D$ -30.79 (c 0.300, CH_2Cl_2); IR (CH_2Cl_2 cast) 2974, 2920, 1735, 1493, 1438, 1288, 108, 1157, 1053, 1018, 917 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.11-7.07 (m, 4H), 5.45 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.75 (dd, *J* = 13.0, 7.0 Hz, 1H), 3.66 (d, *J* = 6.5 Hz, 1H), 3.64 (s, 3H), 3.08 (app dt, *J* = 13.0, 4.0 Hz, 1H), 2.71-2.63 (m, 1H), 2.65 (d, J_{AB} = 13.5 Hz, 1H), 2.53 (d, J_{AB} = 13.5 Hz, 1H), 2.33 (s, 3H), 2.32 (s, 3H), 2.24 (t, *J* = 13.5 Hz, 1H), 2.11 (app qd, *J* = 7.5, 4.0 Hz, 1H), 1.94 (app td, *J* = 13.0, 11.0 Hz, 1H), 1.71 (d, *J* = 2.0 Hz, 3H), 1.65 (d, *J* = 1.0 Hz, 3H), 1.28 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 137.1, 136.1, 132.9, 132.1, 131.3, 129.7, 129.6, 129.5, 129.1, 125.4, 87.0, 86.5, 51.5, 48.9, 45.0, 43.8, 42.6, 38.9, 26.8, 21.1, 21.0, 20.8, 20.3, 11.9; HRMS (ESI, $[M+Na]^+$) calcd for $C_{29}H_{36}O_3S_2Na$ 519.1998, found m/z 519.2008.



84

Diazoketone 84: To a solution of thioacetal **82** (85 mg, 0.17 mmol) in THF (1 mL) and methanol (1 mL) was added a 2.0 M solution of LiOH (260 μL, 0.513 mmol). The reaction was stirred for 48 hours at room temperature, during which time the reaction mixture turned slightly yellow. The reaction was diluted with water (5 mL) and Et_2O (5 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was washed with Et_2O (5 mL). The aqueous layer was then acidified with 0.5 M HCl to pH ~3, resulting in a cloudy suspension. This aqueous phase was then diluted with ethyl acetate (10 mL) and the resulting layers separated. The aqueous layer was washed with 3 portions of ethyl acetate (5 mL) and the combined organic extracts washed with water (5 mL) then brine (5 mL), dried ($MgSO_4$), filtered and concentrated to give the acid **76** as a colourless oil (80 mg, 96%): $[\alpha]_D$ 144.75 (c (0.230), CH_2Cl_2); IR (CH_2Cl_2 cast) 3400-2500, 3019, 2921, 1707, 1493, 1444, 1301, 1227, 1061, 1018, 953 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 5.68 (dd, *J* = 7.5, 1.0 Hz, 1H), 3.32 (dd, *J* = 12.5, 8.5 Hz, 1H), 3.14 (app dt, *J* = 12.5, 4.0 Hz, 1H), 2.82 (d, J_{AB} = 14.5 Hz, 1H), 2.71-2.65 (m, 1H), 2.68 (d, J_{AB} = 14.5 Hz, 1H), 2.41 (app dt, *J* = 13.5, 8.0 Hz, 1H), 2.34 (s, 3H), 2.33 (s, 3H), 2.28-2.24 (m, 1H), 2.22-2.14 (m, 2H), 1.66 (d, *J* = 2.0 Hz, 3H), 1.62 (d, *J* = 1.0 Hz, 3H), 1.12 (d, *J* = 7.5 Hz, 3H), (COOH proton not detected); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 138.1, 137.0, 133.4, 131.7, 131.2, 130.0, 129.9, 129.8, 129.2, 124.7, 87.8, 87.3, 48.3, 46.2, 45.6, 40.1, 39.0, 27.0, 21.2, 21.1, 20.7, 20.2, 10.8; HRMS (ESI, $[M+Na]^+$) calcd for $C_{28}H_{34}O_3S_2Na$ 505.1842, found m/z 505.1850. The acid (72 mg, 0.15 mmol) was dissolved in THF (1 mL) and cooled to 0 °C. To this solution was added NEt_3 (50

μL, 0.36 mmol) and ethyl chloroformate (29 μL, 0.30 mmol). The reaction was stirred at this temperature for 1 hour before being warmed to room temperature. At this time the reaction was then directly transferred via cannula to a freshly prepared solution of diazomethane (~2 mmol) in Et_2O (~12 mL) and the resulting mixture stirred for 16 hours. A gentle stream of Ar(g) was applied to the system to allow for slow evaporation of both excess diazomethane and solvent. The crude yellow oil was purified by column chromatography (silica gel; 5%, 10%, 15% EtOAc/hexanes until the products were recovered) to yield **84** (45 mg, 60%) as a yellow oil: R_f (30% EtOAc/hexanes); $[\alpha]_D$ 94.98 (c 0.340, CH_2Cl_2); IR (CH_2Cl_2 cast) 3018, 2974, 2922, 2865, 2103, 1734, 1636, 1493, 1457, 1492, 1356, 1104, 1017, 958 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 5.73 (d, *J* = 8.0 Hz, 1H), 5.34 (br s, 1H), 3.26 (dd, *J* = 13.0, 8.0 Hz, 1H), 3.18 (app dt, *J* = 12.5, 3.5 Hz, 1H), 2.70-2.56 (m, 3H), 2.33 (s, 3H), 2.32 (s, 3H), 2.33-2.32 (m, 1H), 2.25-2.18 (m, 1H), 2.14-2.08 (m, 1H), 2.12 (ddd, *J* = 13.5, 8.5, 1.0 Hz, 1H), 1.67 (d, *J* =1.5 Hz, 3H), 1.62 (d, *J* = 1.0 Hz, 3H), 1.09 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 137.2, 136.9, 131.9, 131.8, 131.2, 131.1, 129.8, 129.7, 129.2, 124.8, 88.0, 86.8, 56.0, 52.5, 48.0, 45.4, 39.9, 38.8, 26.6, 21.1, 21.0, 20.8, 20.2, 10.7; HRMS (ESI, $[M+Na]^+$) calcd for $C_{29}H_{34}O_2N_2S_2Na$ 529.1954, found m/z 529.1954.



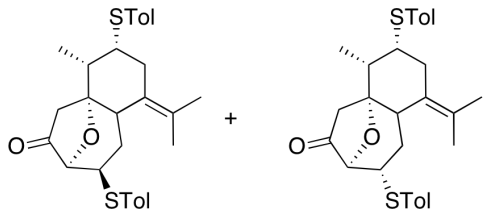
85

Diazoketone 85: To a solution of thioacetal **83** (43 mg, 0.086 mmol) in THF (1 mL) and methanol (1 mL) was added a 2.0 M solution of LiOH (130 μL, 0.257 mmol). The reaction was stirred for 48 hours at room temperature, during which time the reaction mixture turned slightly yellow. The reaction was diluted with water (5 mL) and Et_2O (5 mL) and transferred to a separatory funnel. The layers

were separated and the aqueous layer was washed with Et_2O (5 mL). The aqueous layer was then acidified with 0.5 M HCl to pH ~3, resulting in a cloudy suspension. This aqueous phase was then diluted with ethyl acetate (10 mL) and the resulting layers separated. The aqueous layer was washed with 3 portions of ethyl acetate (5 mL) and the combined organic extracts washed with water (5 mL), then brine (5 mL), dried ($MgSO_4$), filtered and concentrated to give the acid **76** as a colourless oil (39 mg, 95%): $[\alpha]_D$ 144.75 (c (0.230), CH_2Cl_2); IR (CH_2Cl_2 cast) 3400-2500, 3019, 2921, 1707, 1493, 1444, 1301, 1227, 1061, 1018, 953 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 5.68 (dd, *J* = 7.5, 1.0 Hz, 1H), 3.32 (12.5, 8.5 Hz, 1H), 3.14 (dt, *J* = 12.5, 4.0 Hz, 1H), 2.82 (d, J_{AB} = 14.5 Hz, 1H), 2.71-2.65 (m, 1H), 2.68 (d, J_{AB} = 14.5 Hz, 1H), 2.41 (app dt, *J* = 13.5, 8.0 Hz, 1H), 2.34 (s, 3H), 2.33 (s, 3H), 2.26 (m, 1H), 2.22-2.14 (m, 2H), 1.66 (d, *J* = 2.0 Hz, 3H), 1.62 (d, *J* = 1.0 Hz, 3H), 1.22 (d, *J* = 7.5 Hz, 3H), (COOH proton not detected); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 138.1, 137.0, 133.4, 131.7, 131.2, 130.0, 129.9, 129.8, 129.2, 124.7, 87.8, 87.3, 48.3, 46.2, 45.6, 40.1, 39.0, 27.0, 21.2, 21.1, 20.7, 20.2, 10.8; HRMS (ESI, $[M+Na]^+$) calcd for $C_{28}H_{34}O_3S_2Na$ 505.1842, found m/z 505.1850. The acid (30 mg, 0.062 mmol) was dissolved in THF (1 mL) and cooled to 0 °C. To this solution was added NEt_3 (21 μL, 0.15 mmol) and ethyl chloroformate (14 μL, 0.12 mmol). The reaction was stirred at this temperature for 1 hour then warmed to room temperature. At this the reaction was directly transferred to a freshly prepared solution of diazomethane (~2 mmol) in Et_2O (~12 mL) and the resulting mixture stirred for 16 hours. A gentle stream of Ar(g) was applied to the system to allow for slow evaporation of both excess diazomethane and solvent. The crude yellow oil was purified by column chromatography (silica gel; 5%, 10%, 15% EtOAc/hexanes until the products were recovered) to yield **85** (16 mg, 52%) as a yellow oil: R_f (30% EtOAc/hexanes); $[\alpha]_D$ -6.61 (c 0.130, CH_2Cl_2); IR (CH_2Cl_2 cast) 3018, 2973, 2921, 2101, 1634, 1493, 1356, 1147, 1052, 809 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.11-7.09 (m, 4H), 5.42 (dd, *J* = 6.0, 4.5 Hz, 1H), 5.40 (br s, 1H), 3.15 (app dt, *J* =13.0, 3.5 Hz, 1H), 2.65 (dd, *J*

= 15.5, 3.5 Hz, 1H), 2.57-2.50 (m, 1H), 2.34-2.25 (m, 2H), 2.34 (s, 6H), 2.23-2.15 (m, 3H), 1.92 (app q, *J* = 13.0 Hz, 1H), 1.69 (d, *J* = 2.0 Hz, 3H), 1.63 (br s, 3H), 1.28 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 137.0, 136.8, 132.1, 132.0, 130.8, 129.8, 129.7, 129.6, 129.2, 124.0, 87.7, 86.8, 63.2, 56.1, 51.6, 48.6, 44.8, 41.6, 41.5, 38.5, 26.5, 21.8, 20.2, 12.1; HRMS (ESI, $[M+Na]^+$) calcd for $C_{29}H_{34}O_2N_2S_2Na$ 529.1954, found m/z 529.1952.

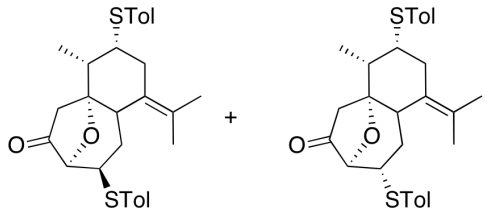
Carbene Transfer Reaction of 84: Preparation of 86 and 87



86 **87**

To a refluxing solution of $Cu(hfacac)_2$ (3 mg, 6 x 10^{-3} mmol) in CH_2Cl_2 (5 mL) was added a solution of **84** (30 mg, 0.062 mmol) in CH_2Cl_2 (1 mL), and the resulting mixture was monitored by TLC. Upon consumption of diazoketone (30 min) the reaction mixture was cooled to room temperature and quenched with saturated $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The organic extracts were combined and washed with water (5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated. The resulting oil was purified by column chromatography (silica gel; 15 % EtOAc / hexanes until the product was recovered) to yield an inseparable 1:1 mixture **86**/**87** (23 mg, 82%) as colourless oils.

Carbene Transfer Reaction of 84: Preparation of 86 and 87



86 **87**

To a refluxing solution of $Cu(hfacac)_2$ (1 mg, 2 x 10^{-3} mmol) in CH_2Cl_2 (1 mL) was added a solution of **85** (12 mg, 0.024 mmol) in CH_2Cl_2 (1 mL), and the resulting mixture was monitored by TLC. Upon consumption of diazoketone (30 min) the reaction mixture was cooled to room temperature and quenched with saturated $NaHCO_3$ solution (5 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 5mL). The organic extracts were combined and washed with water (2 mL), brine (2 mL), dried ($MgSO_4$), filtered and concentrated. The resulting oil was purified by column chromatography (silica gel; 15 % EtOAc / hexanes until the product was recovered) to yield an inseparable 1:2 mixture **86**/**87** (9 mg, 81%) as colourless oils (characterized as a 1:2 mixture): IR (CH_2Cl_2 cast) 3018, 2968, 2922, 1759, 1492, 1452, 1377, 1289, 1180, 1067, 1017, 909 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44-7.30 (m, 6H), 7.29 (m, 6H), 4.18 (br s, 1H), 4.04 (br s, 0.5H), 3.82 (d, *J* = 4.5 Hz, 0.5H), 3.56-3.50 (m, 1H), 3.48-3.39 (m, 2H), 3.39-3.34 (m, 1H), 3.20-3.12 (m, 2H), 3.10-3.04 (m, 0.5H), 2.82-2.79 (m, 1H), 2.72-2.67 (m, 2H), 2.35-2.30 (m, 8H), 2.18-2.10 (m, 4H), 2.00-1.93 (m, 2H), 1.70 (br s, 3H), 1.60 (br s, 1.5H), 1.56 (br s, 3H), 1.30-1.18 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.1, 213.0, 138.1, 137.8, 136.2, 136.1, 135.3, 134.9, 133.8, 133.2, 132.1, 131.0, 129.8, 129.7, 129.6, 129.5 129.4, 129.0, 128.5, 126.9, 126.3, 84.8, 84.7, 80.0, 78.3, 50.7, 46.7, 45.8, 45.6, 45.5, 43.2, 42.4, 38.0, 37.7, 35.2, 34.2, 31.4, 29.7, 29.1, 21.2, 21.1, 21.0, 20.5, 20.4, 20.2, 13.6, 13.5 (some carbons from the minor isomer were not observed); HRMS (ESI, $[M+Na]^+$) calcd for $C_{29}H_{34}O_2S_2Na$ 501.1898, found m/z 501.1897.

4.12 References

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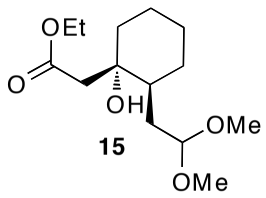
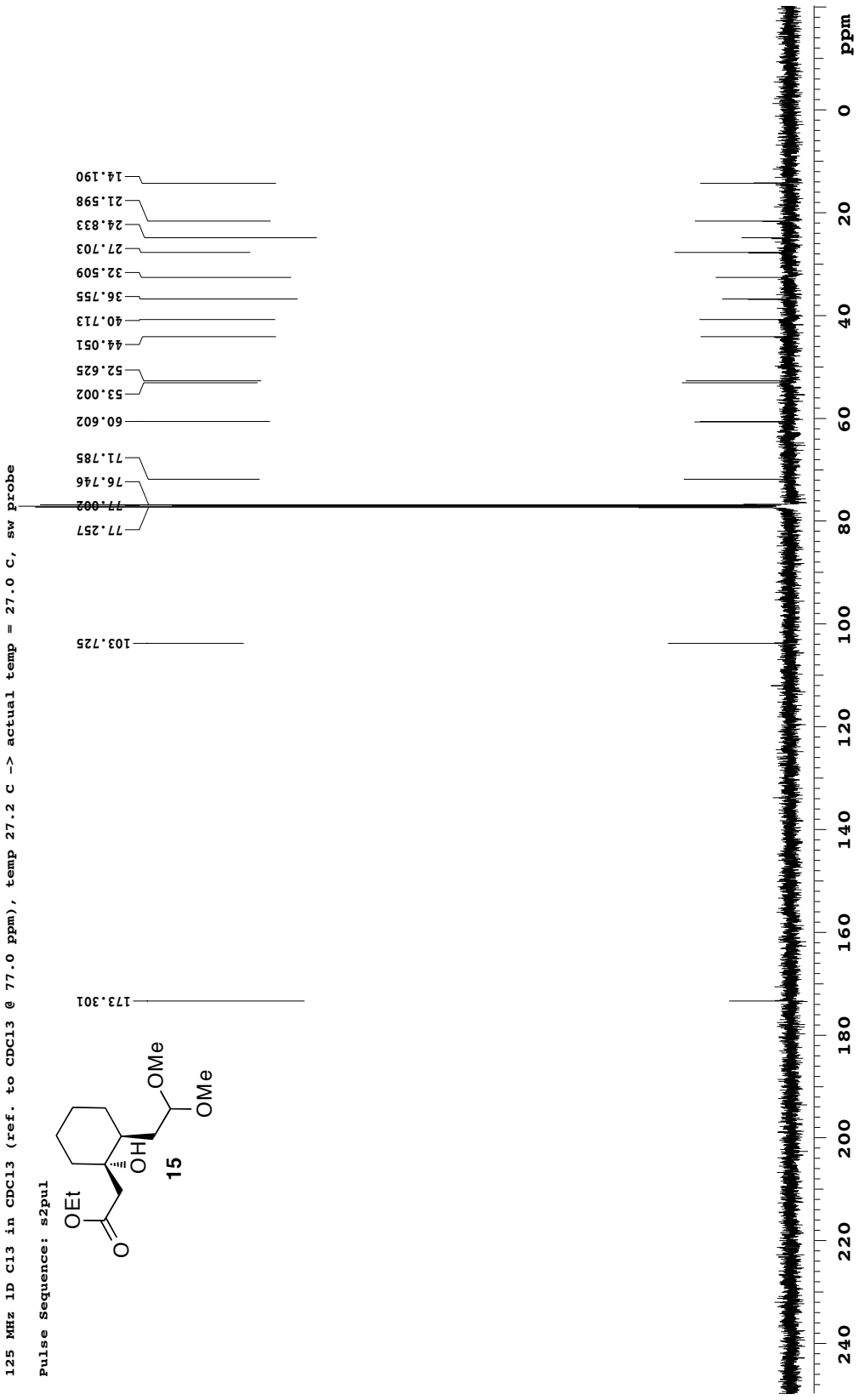
Appendix I: Selected NMR Spectra
(Chapter 2)

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

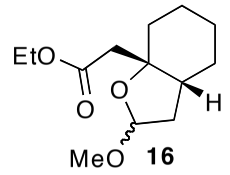


15

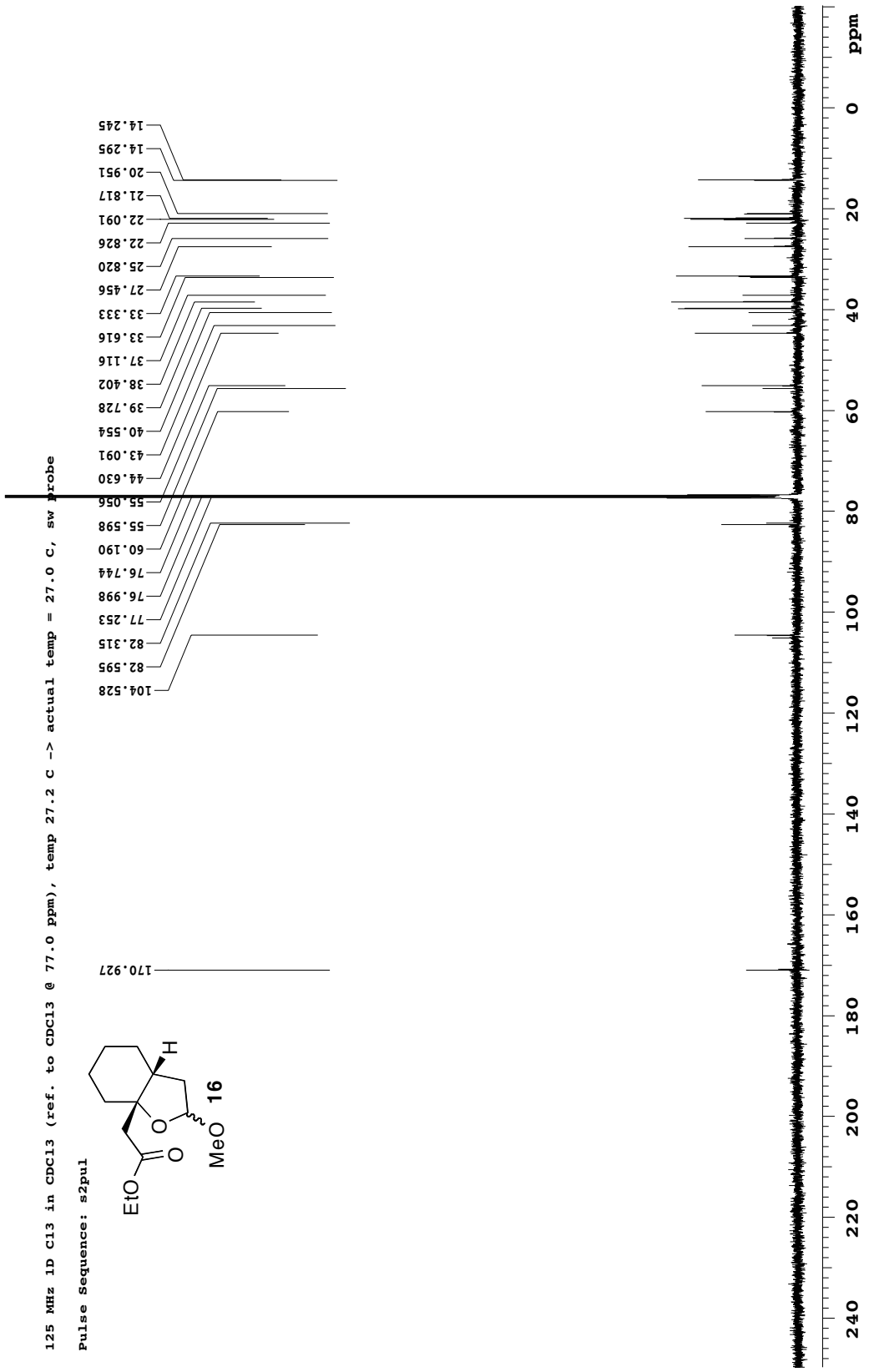

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
Pulse Sequence: s2pul
173.301
103.725
77.257
77.002
76.746
71.785
60.602
53.002
52.625
44.051
40.713
36.755
32.509
27.703
24.833
21.598
14.190
OEt
O
OH
OMe
OMe
15
ppm

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

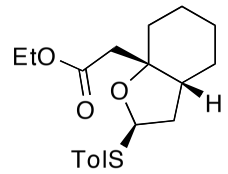


16


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
170.927
104.528
82.595
82.315
77.253
76.998
76.744
60.190
55.598
55.056
44.630
43.091
40.554
39.728
38.402
37.116
33.616
33.333
27.456
25.820
22.826
22.091
21.817
20.951
14.295
14.245
EtO
O
O
MeO
16
H
ppm
240
220
200
180
160
140
120
100
80
60
40
20
0

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

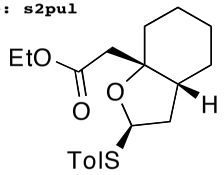
Pulse Sequence: s2pul



18

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

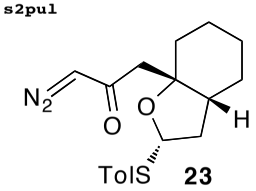
Pulse Sequence: s2pul



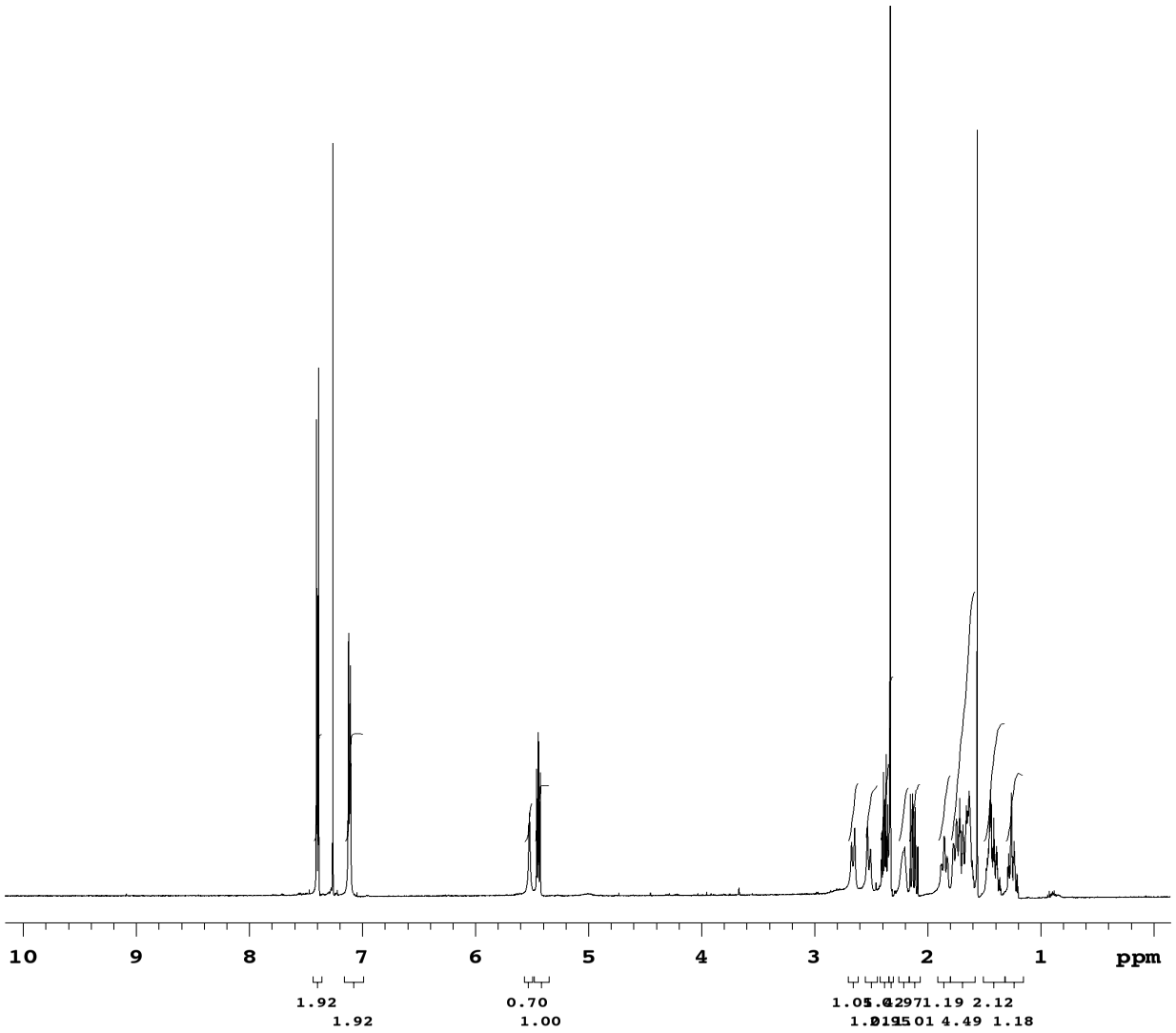
18

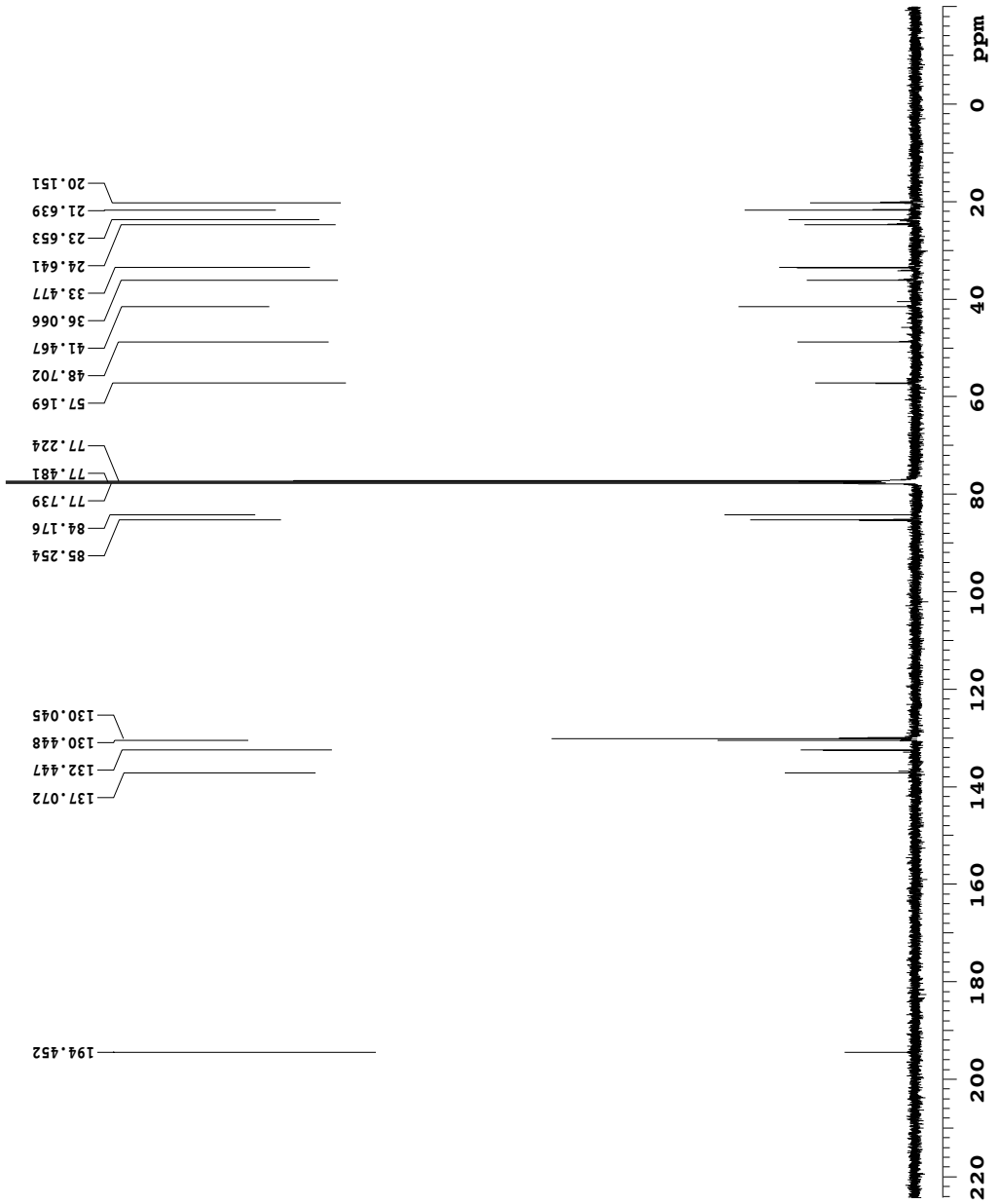
498.1 MHz 1H in CDCl3

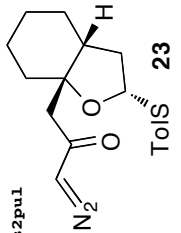
Pulse Sequence: s2pul



23





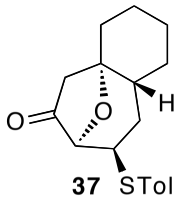


125.3 MHz 13C[1H] in CDCl3

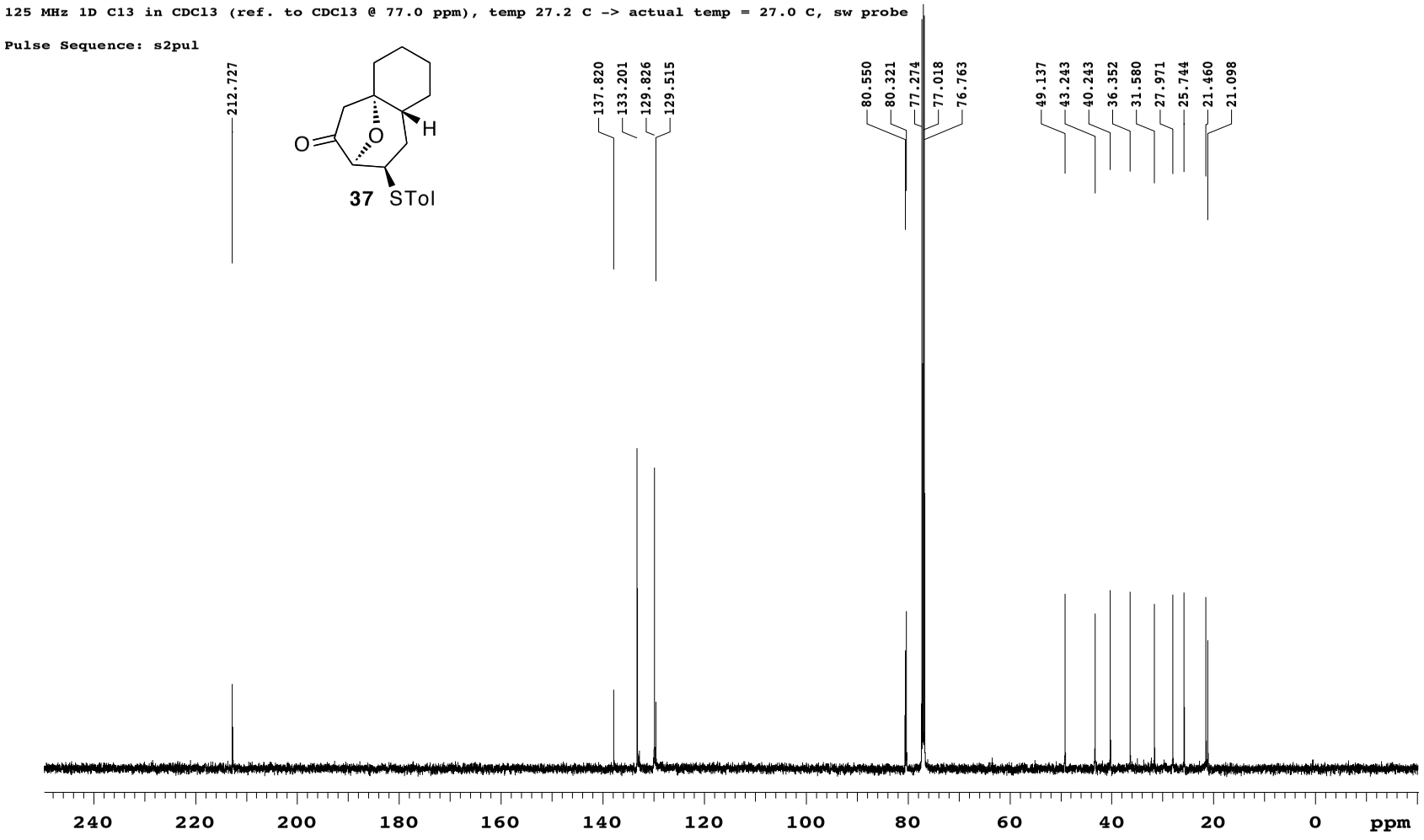
Pulse Sequence: s2pul

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

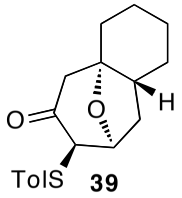


37 STol

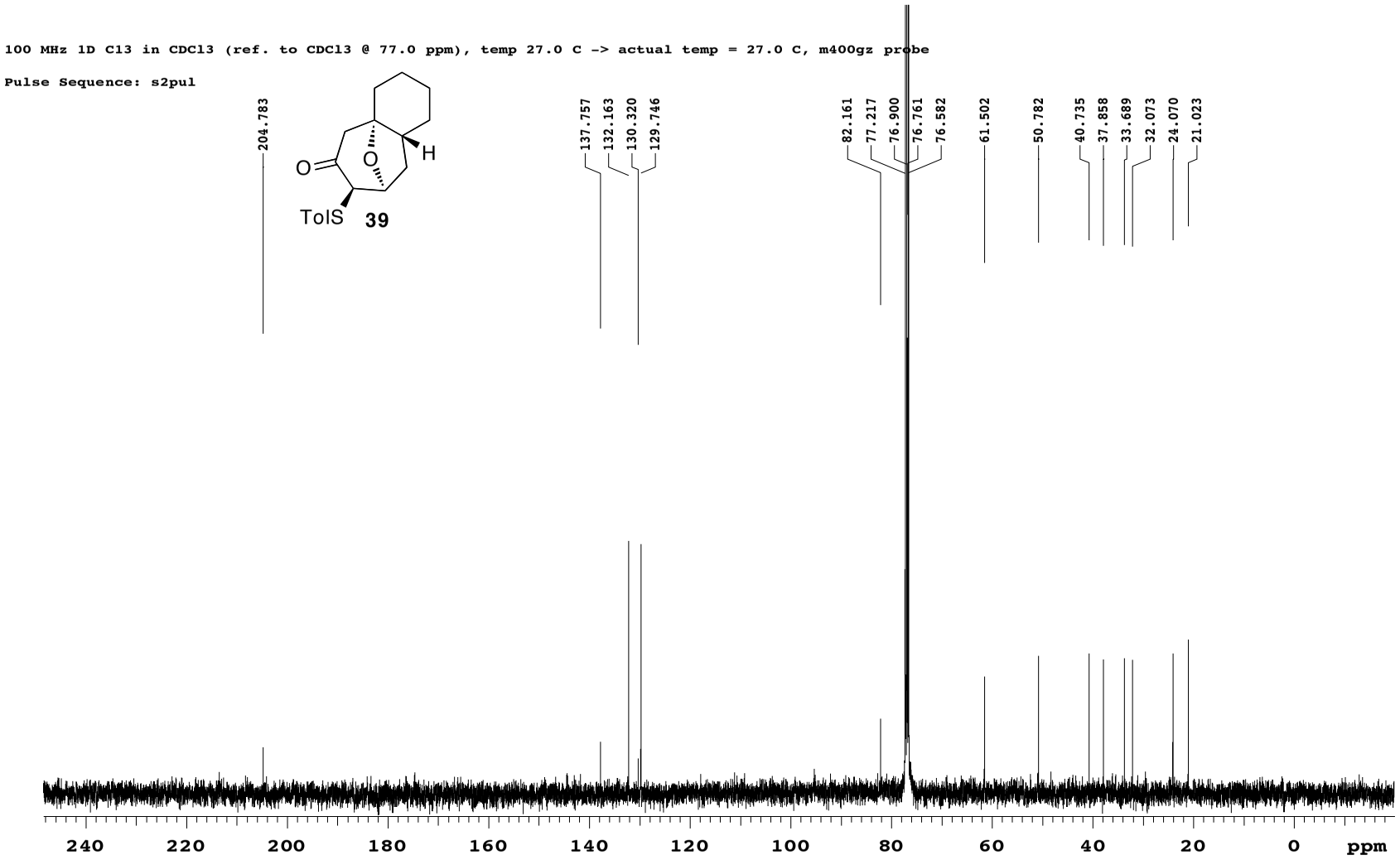

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
Pulse Sequence: s2pul
212.727
137.820
133.201
129.826
129.515
80.550
80.321
77.274
77.018
76.763
49.137
43.243
40.243
36.352
31.580
27.971
25.744
21.460
21.098
O
O
H
37 STol
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe

Pulse Sequence: s2pul

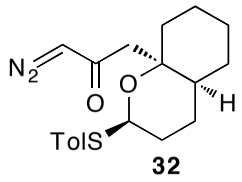


39

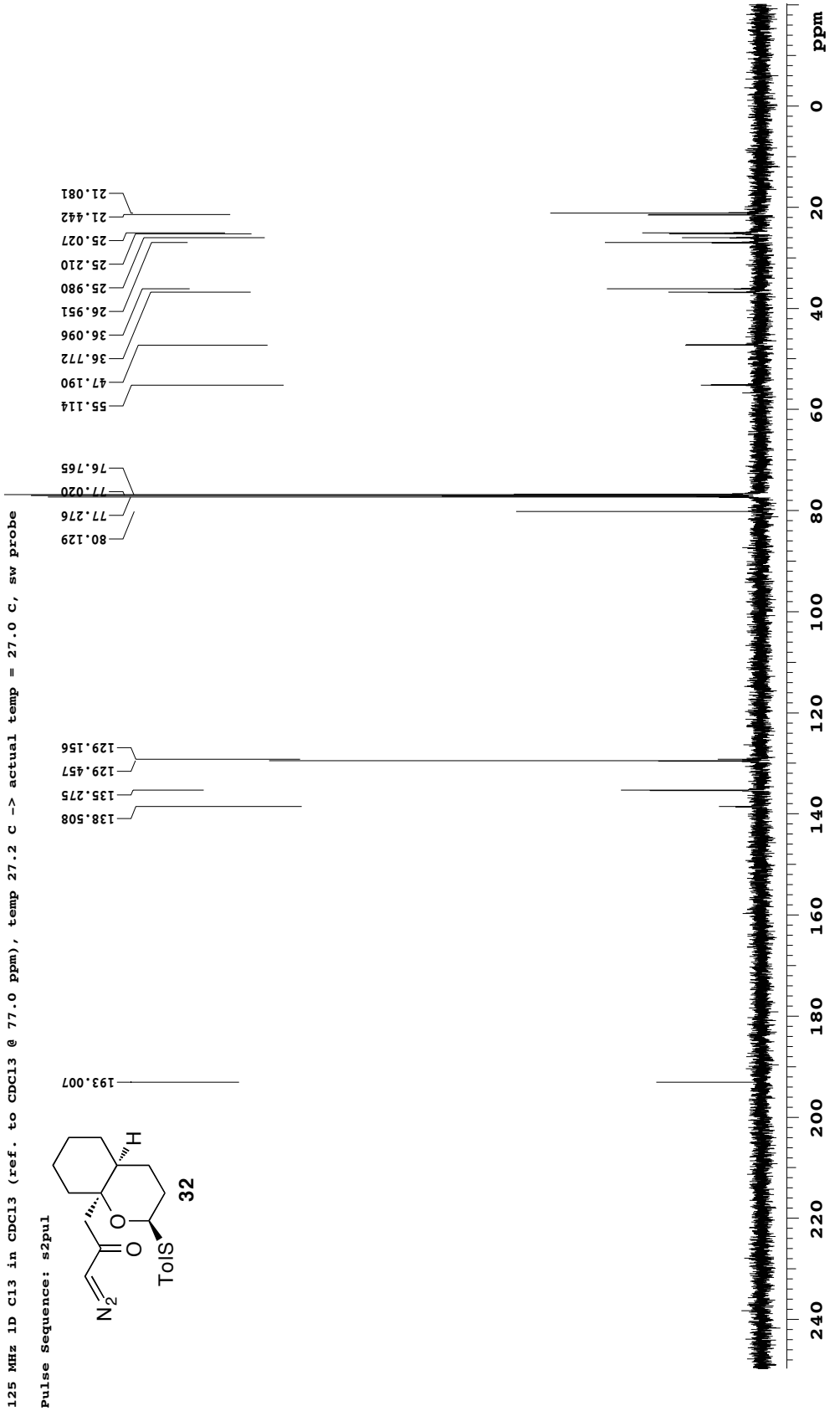

100 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Pulse Sequence: s2pul
204.783
137.757
132.163
130.320
129.746
82.161
77.217
76.900
76.761
76.582
61.502
50.782
40.735
37.858
33.689
32.073
24.070
21.023
O
O
H
TolS
39
240
220
200
180
160
140
120
100
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

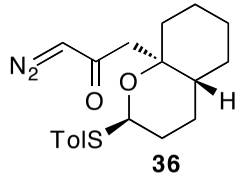


32

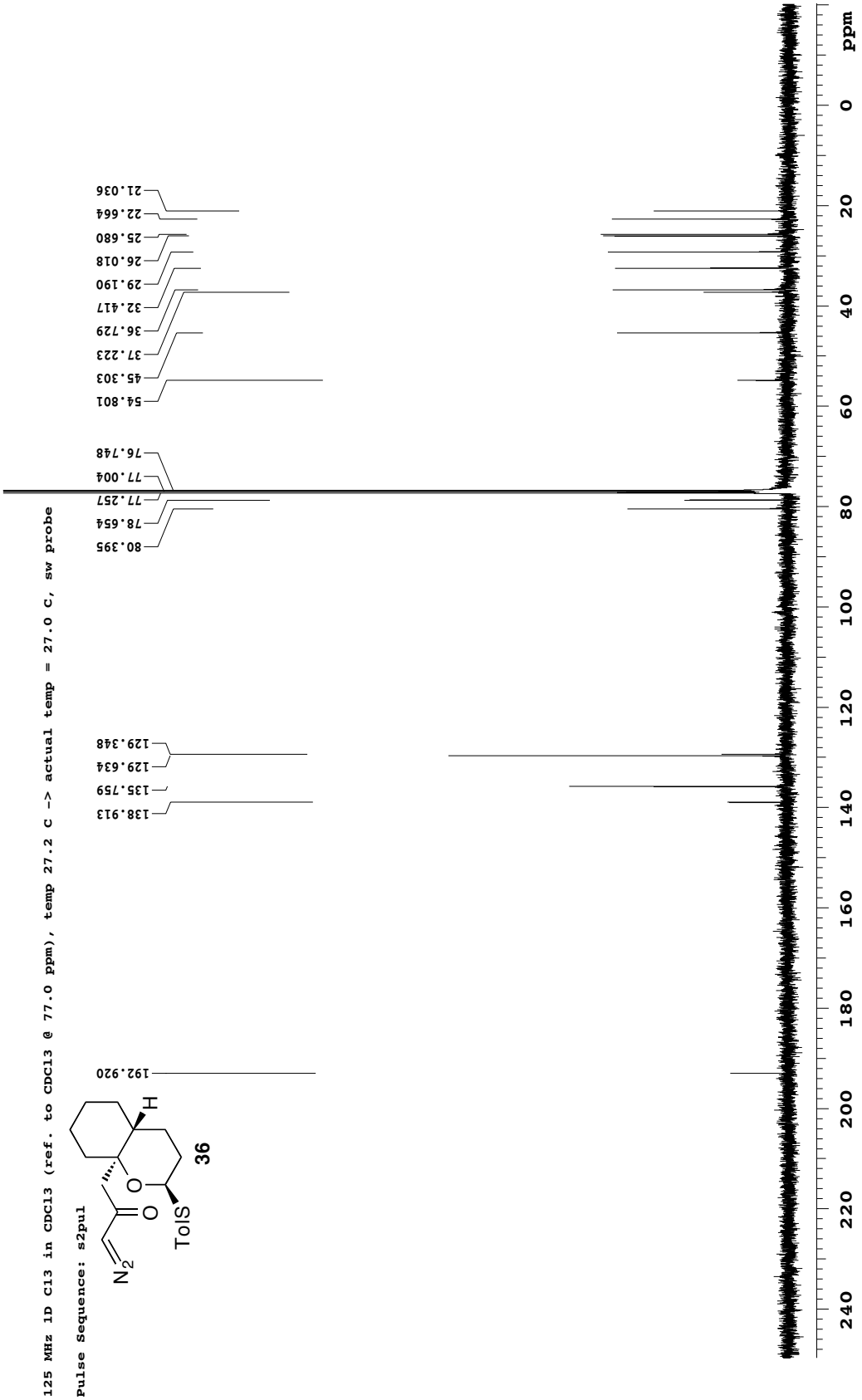

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
Pulse Sequence: s2pul
193.007
138.508
135.275
129.457
129.156
80.129
77.276
77.020
76.765
55.114
47.190
36.772
36.096
26.951
25.980
25.210
25.027
21.442
21.081
32
TolS
O
O
H
N2
ppm
0
20
40
60
80
100
120
140
160
180
200
220
240

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

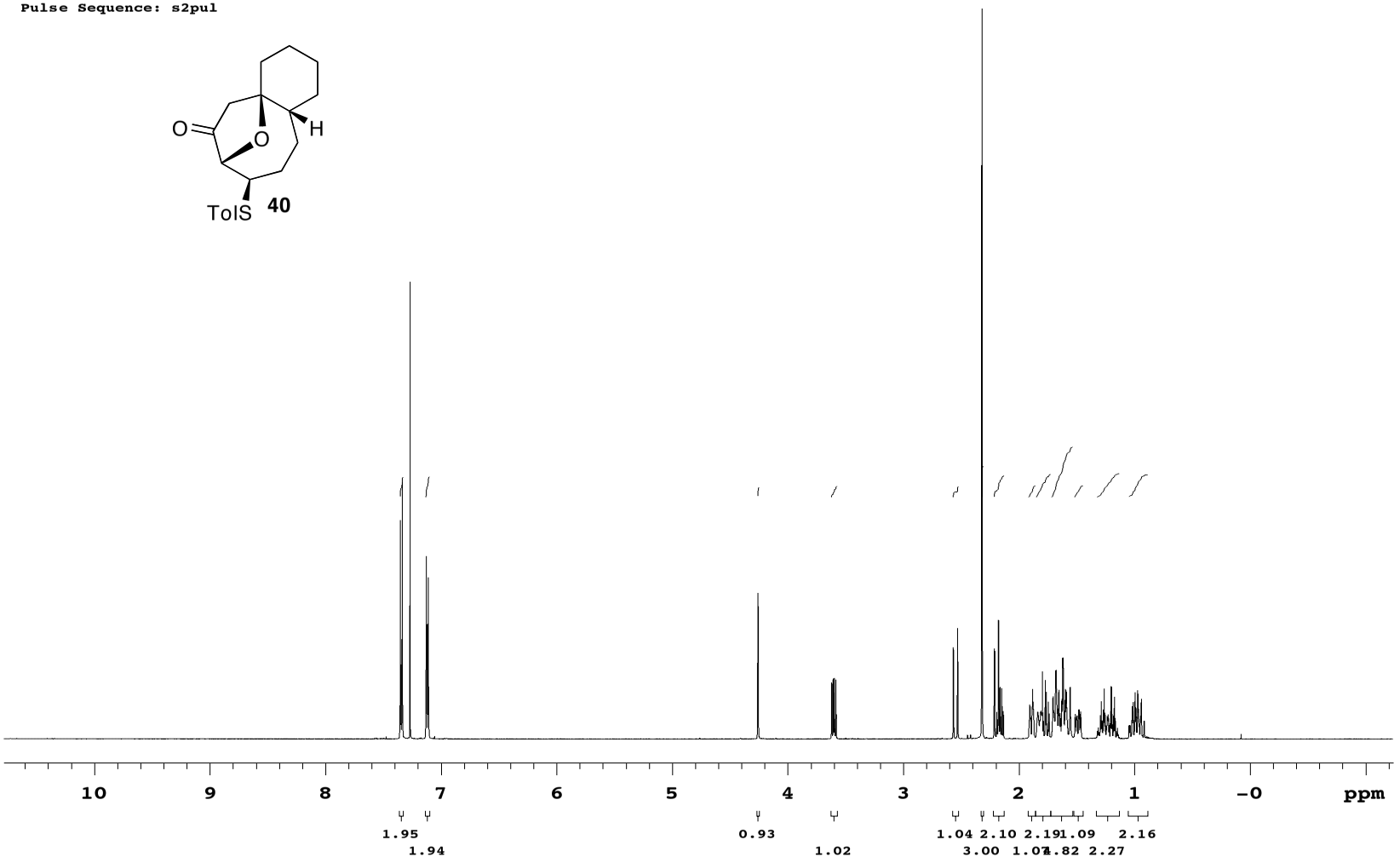


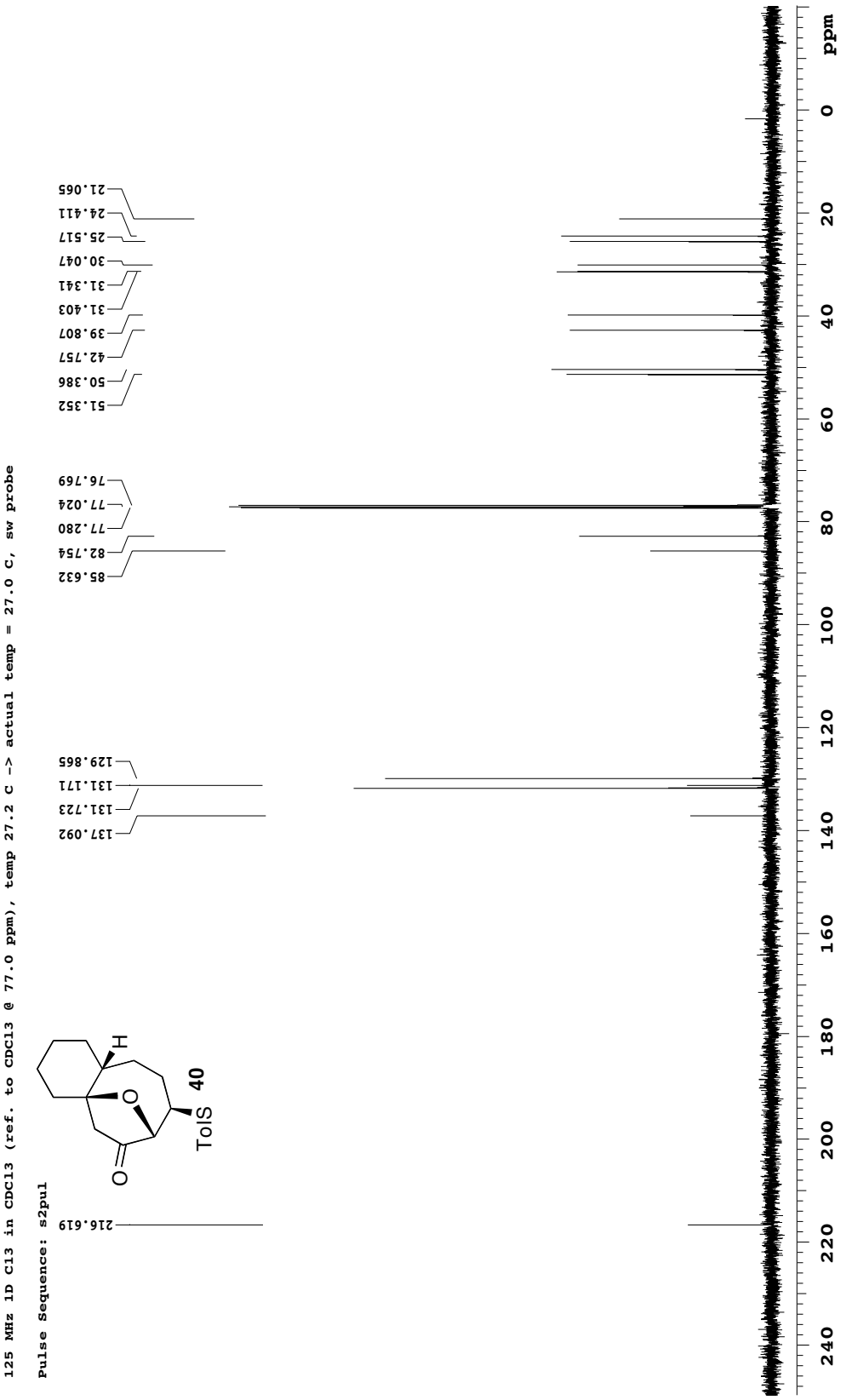
36


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
192.920
138.913
135.759
129.634
129.348
80.395
78.654
77.257
77.004
76.748
54.801
45.303
37.223
36.729
32.417
29.190
26.018
25.680
22.664
21.036
TolS
36
ppm

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, sw500u probe

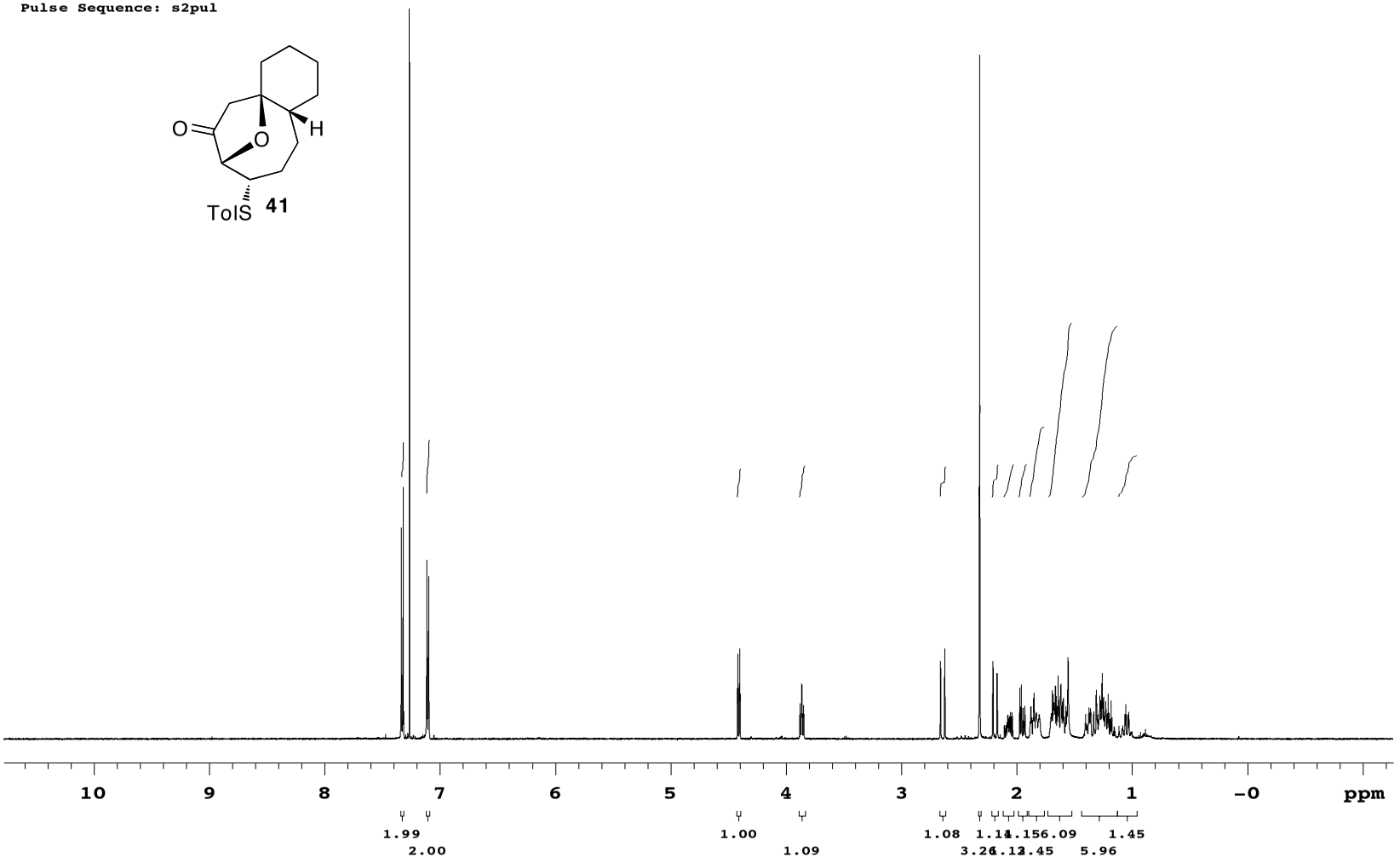
Pulse Sequence: s2pul

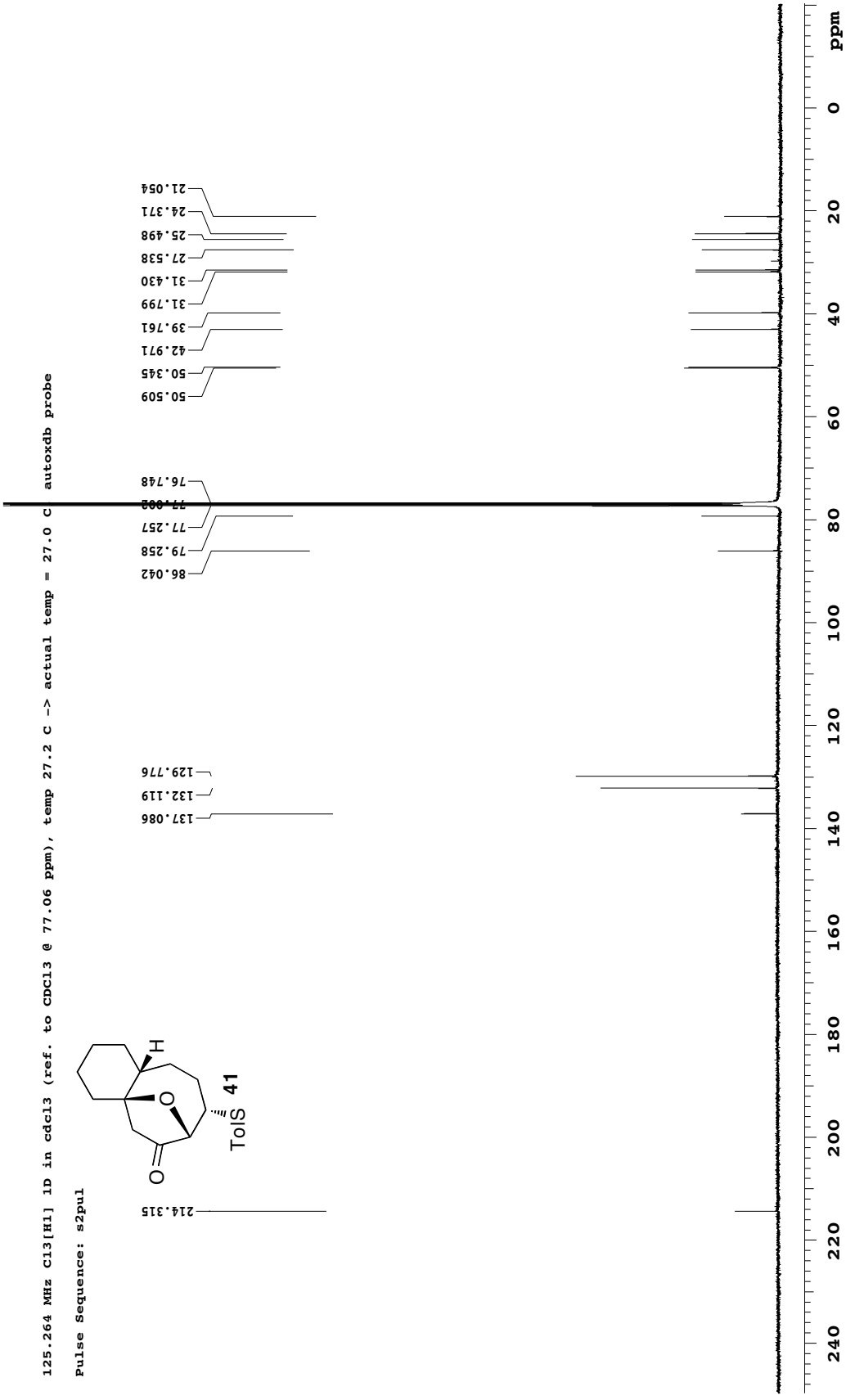



125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
Pulse Sequence: s2pul
216.619
137.092
131.723
131.171
129.865
85.632
82.754
77.280
77.024
76.769
51.352
50.386
42.757
39.807
31.403
31.341
30.047
25.517
24.411
21.065
H
O
O
TolS
40
ppm
0
20
40
60
80
100
120
140
160
180
200
220
240

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

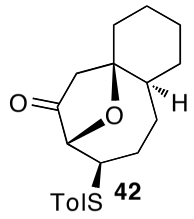
Pulse Sequence: s2pul



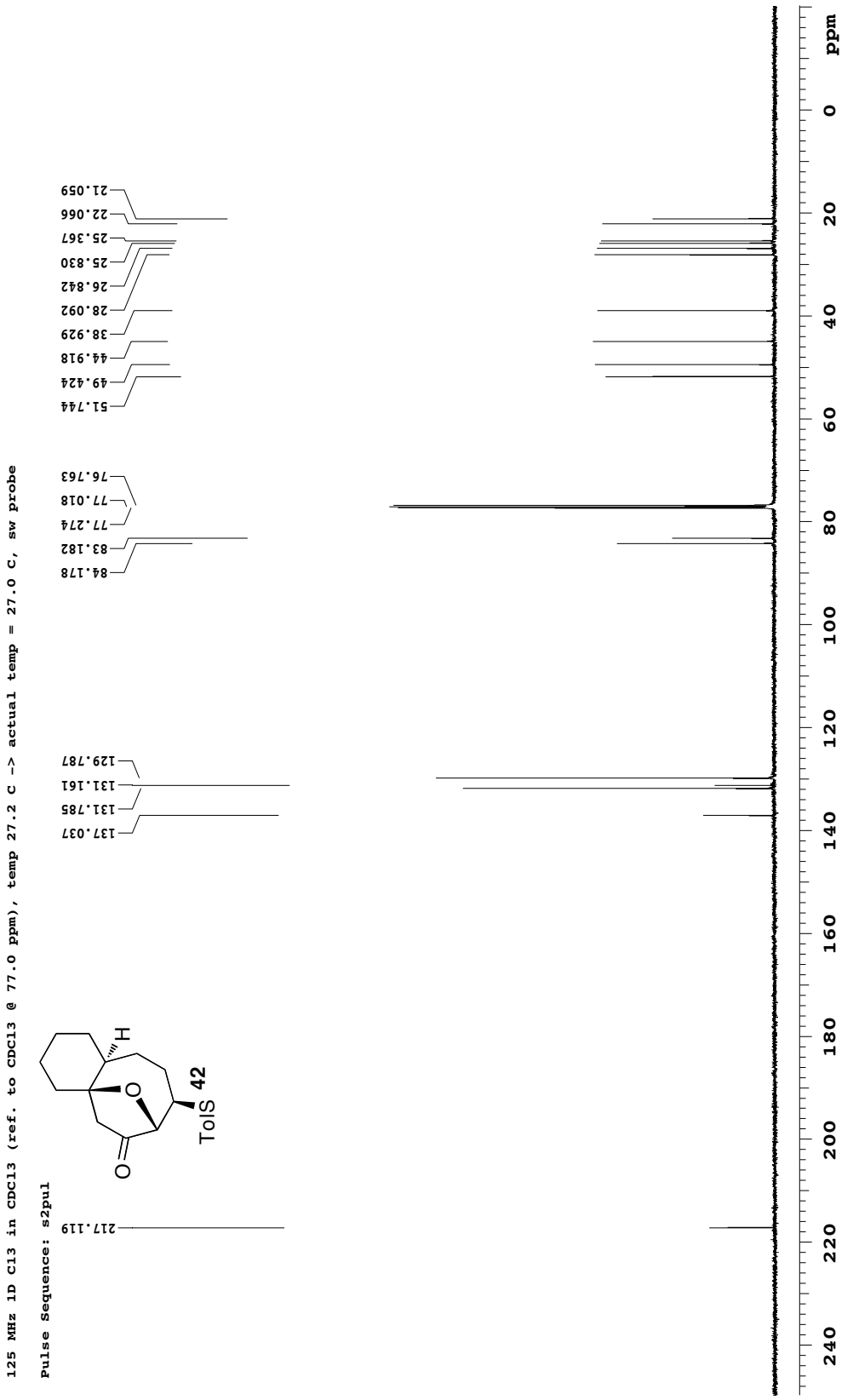

125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C autoxdb probe
Pulse Sequence: s2pul
214.315
137.086
132.119
129.776
86.042
79.258
77.257
77.008
76.748
50.509
50.345
42.971
39.761
31.799
31.430
27.538
25.498
24.371
21.054
TolS
41
ppm

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

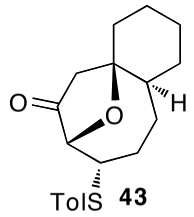


42

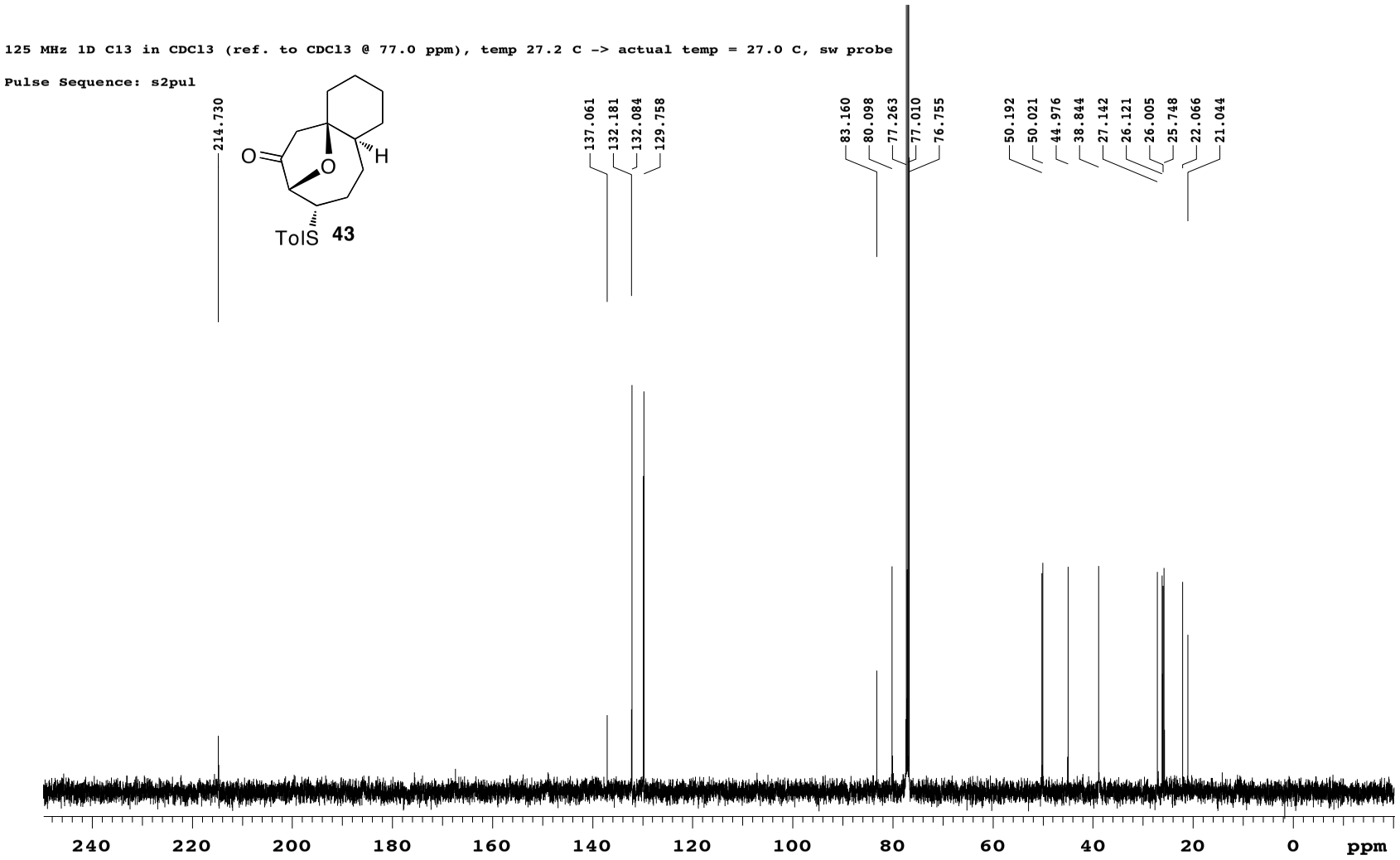

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
Pulse Sequence: s2pul
217.119
137.037
131.785
131.161
129.787
84.178
83.182
77.274
77.018
76.763
51.744
49.424
44.918
38.929
28.092
26.842
25.830
25.367
22.066
21.059
H
O
O
TolS
42
240
220
200
180
160
140
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



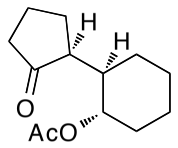
43


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
214.730
137.061
132.181
132.084
129.758
83.160
80.098
77.263
77.010
76.755
50.192
50.021
44.976
38.844
27.142
26.121
26.005
25.748
22.066
21.044
O
O
H
TolS
43
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Appendix II: Selected NMR Spectra
(Chapter 3)

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

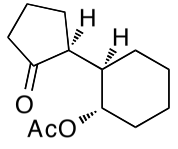
Pulse Sequence: s2pul



63a

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

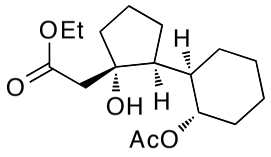
Pulse Sequence: s2pul



63a

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

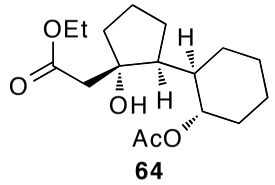
Pulse Sequence: s2pul



64

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

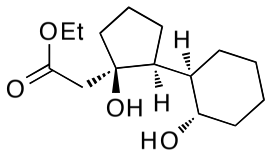
Pulse Sequence: s2pul



64

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

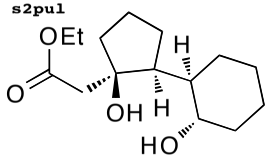
Pulse Sequence: s2pul



65

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

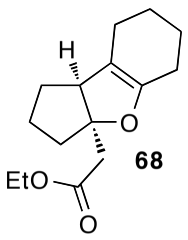
Pulse Sequence: s2pul



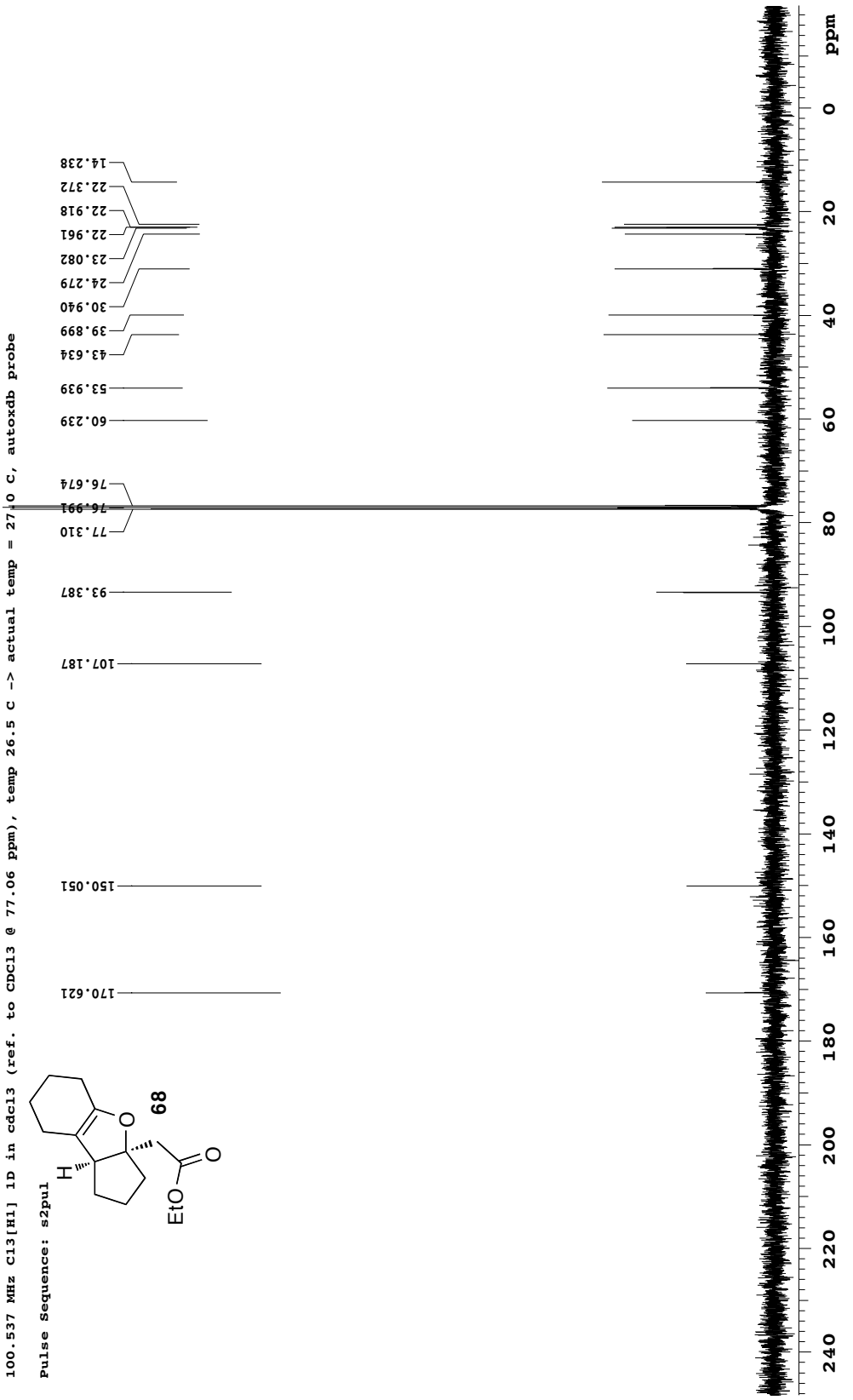
65

399.794 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.5 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul

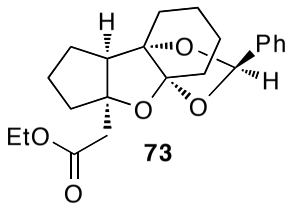


68


100.537 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.5 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
68
H
O
O
EtO
14.238
22.372
22.918
22.961
23.082
24.279
30.940
39.899
43.634
53.939
60.239
76.674
76.991
77.310
93.387
107.187
150.051
170.621
ppm
0
20
40
60
80
100
120
140
160
180
200
220
240

499.821 MHz H1 1D in c6d6 (ref. to C6D6 @ 7.15 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

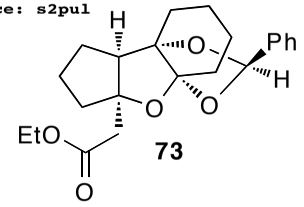
Pulse Sequence: s2pul



73

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

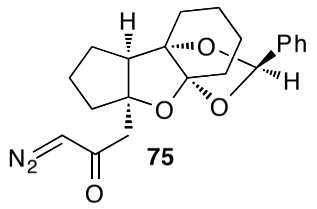
Pulse Sequence: s2pul



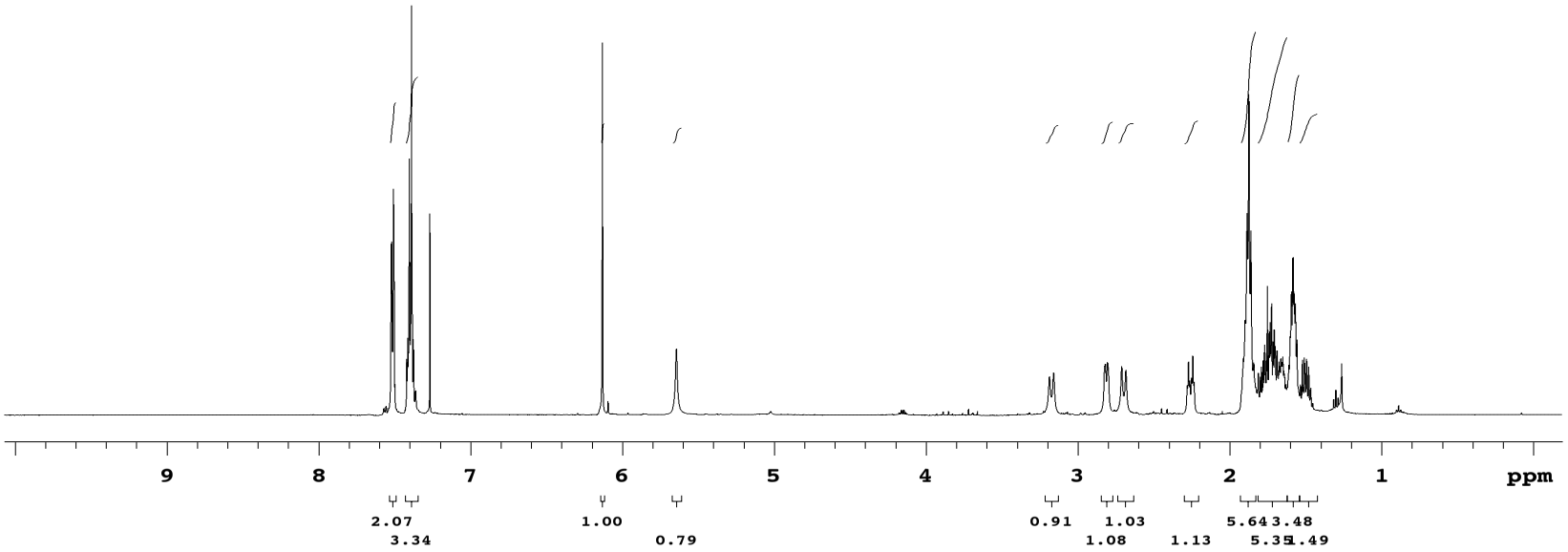
73

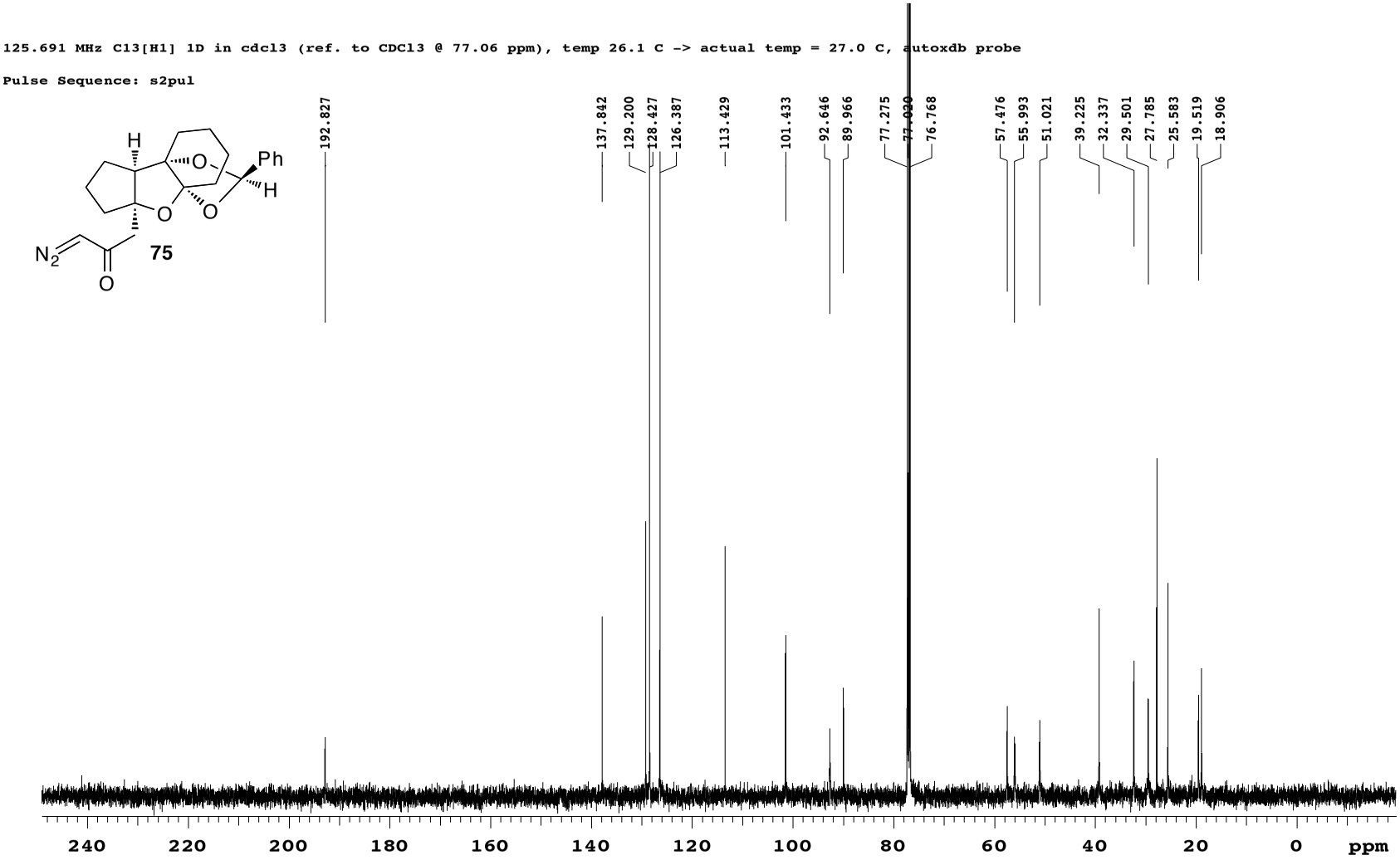
499.821 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul



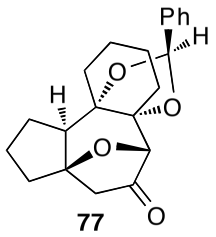
75



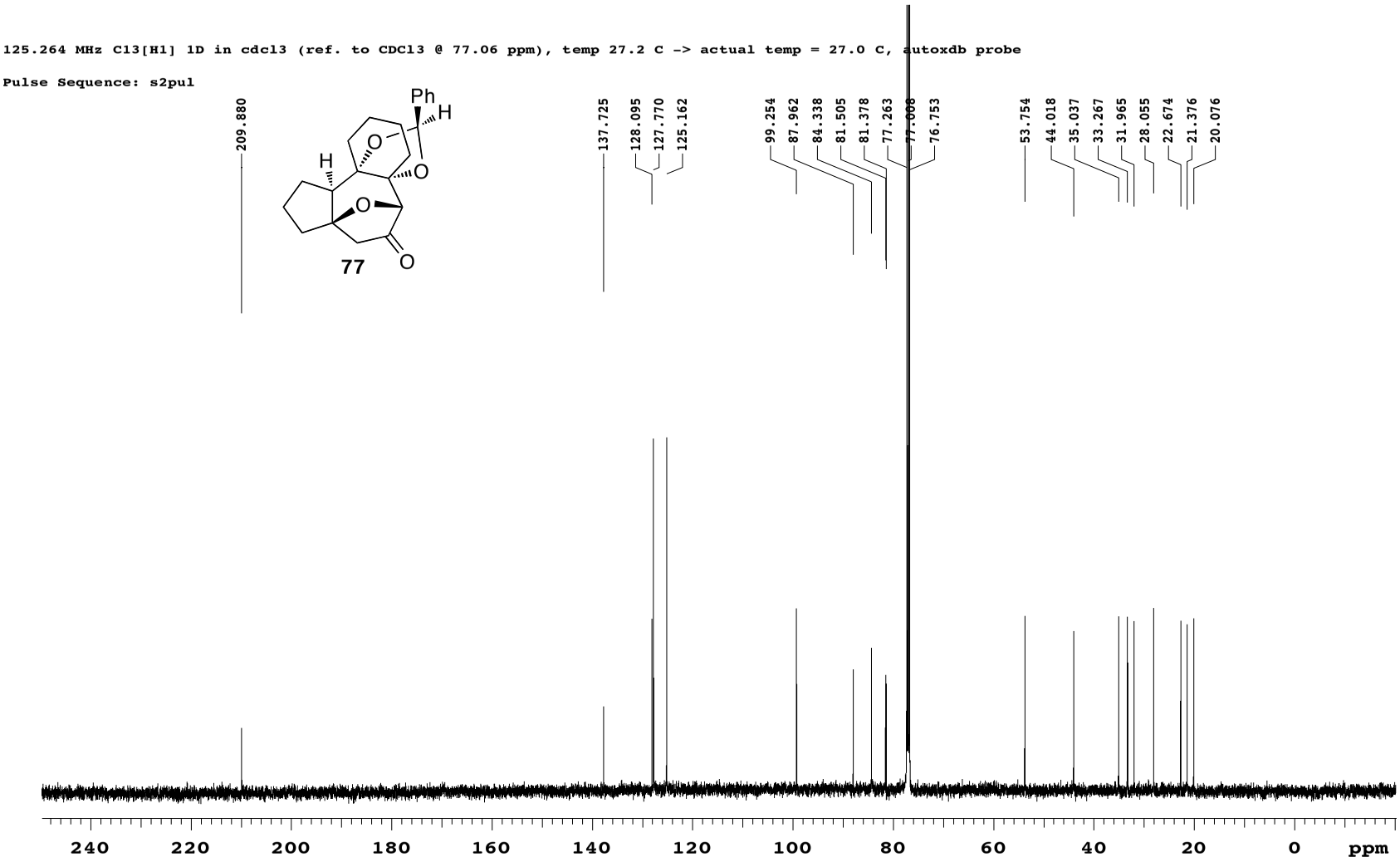

125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
H
O
Ph
H
O
O
N2
O
75
192.827
137.842
129.200
128.427
126.387
113.429
101.433
92.646
89.966
77.275
77.030
76.768
57.476
55.993
51.021
39.225
32.337
29.501
27.785
25.583
19.519
18.906
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

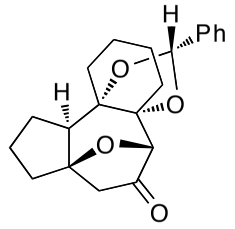


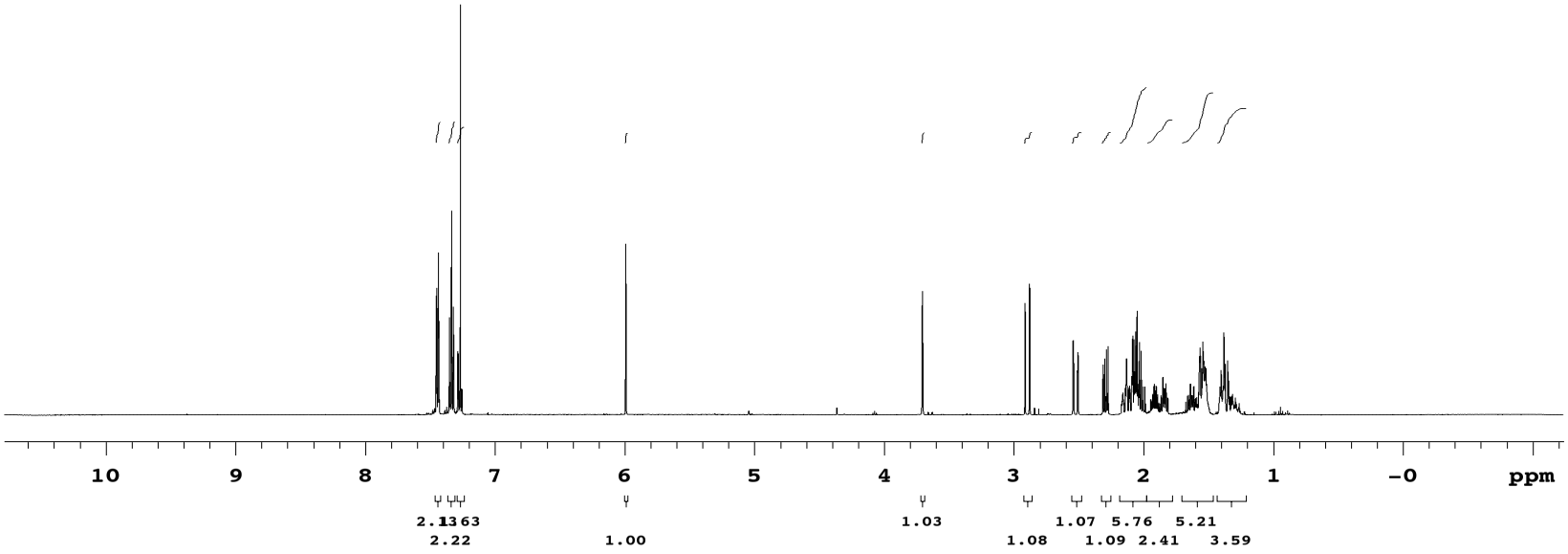
77

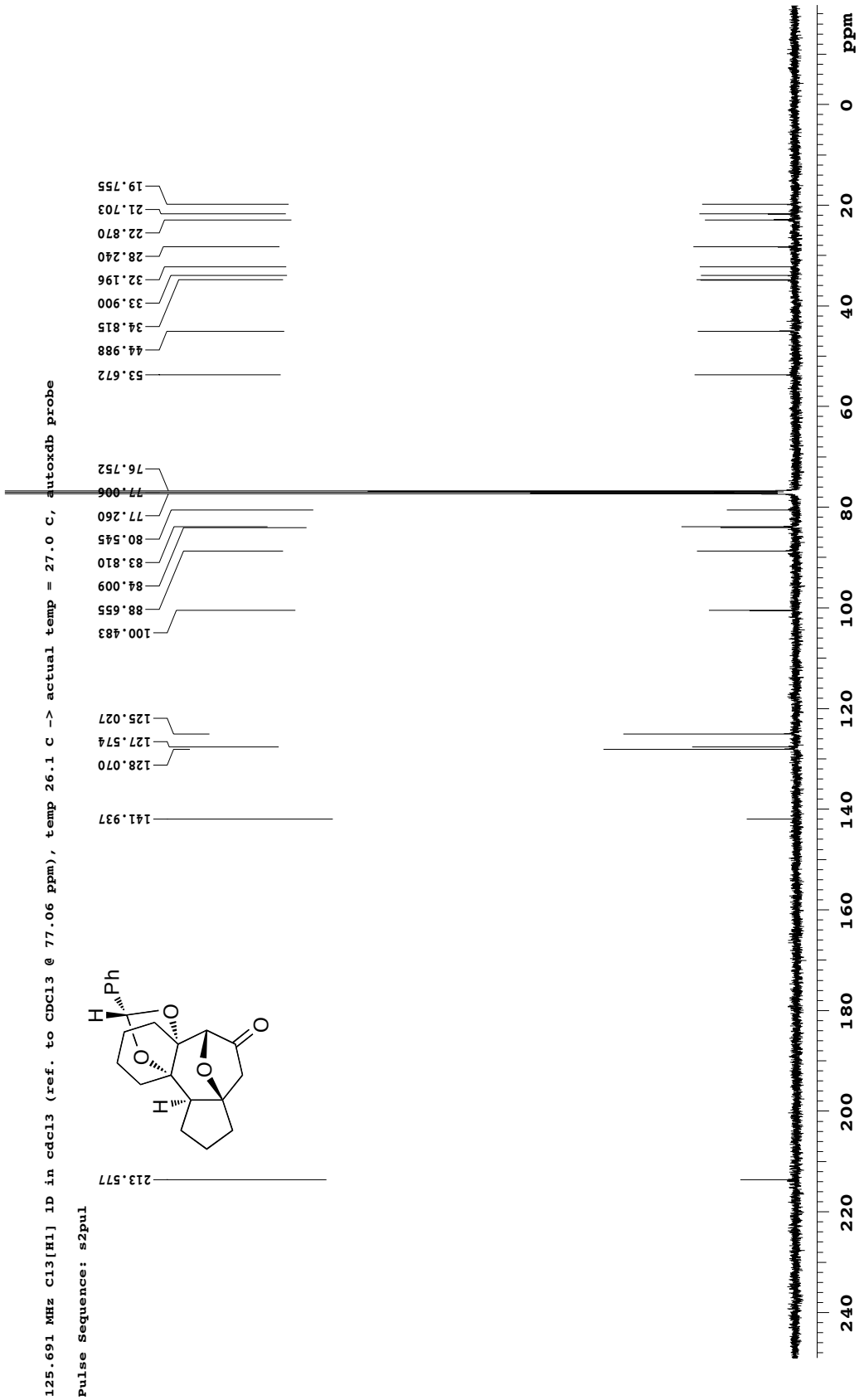

125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
209.880
137.725
128.095
127.770
125.162
99.254
87.962
84.338
81.505
81.378
77.263
77.008
76.753
53.754
44.018
35.037
33.267
31.965
28.055
22.674
21.376
20.076
Ph
H
O
O
H
O
O
77
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

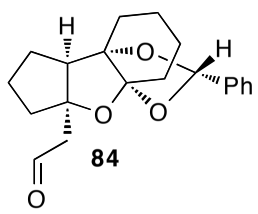





125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
213.577
141.937
128.070
127.574
125.027
100.483
88.655
84.009
83.810
80.545
77.260
77.006
76.752
53.672
44.988
34.815
33.900
32.196
28.240
22.870
21.703
19.755
ppm

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

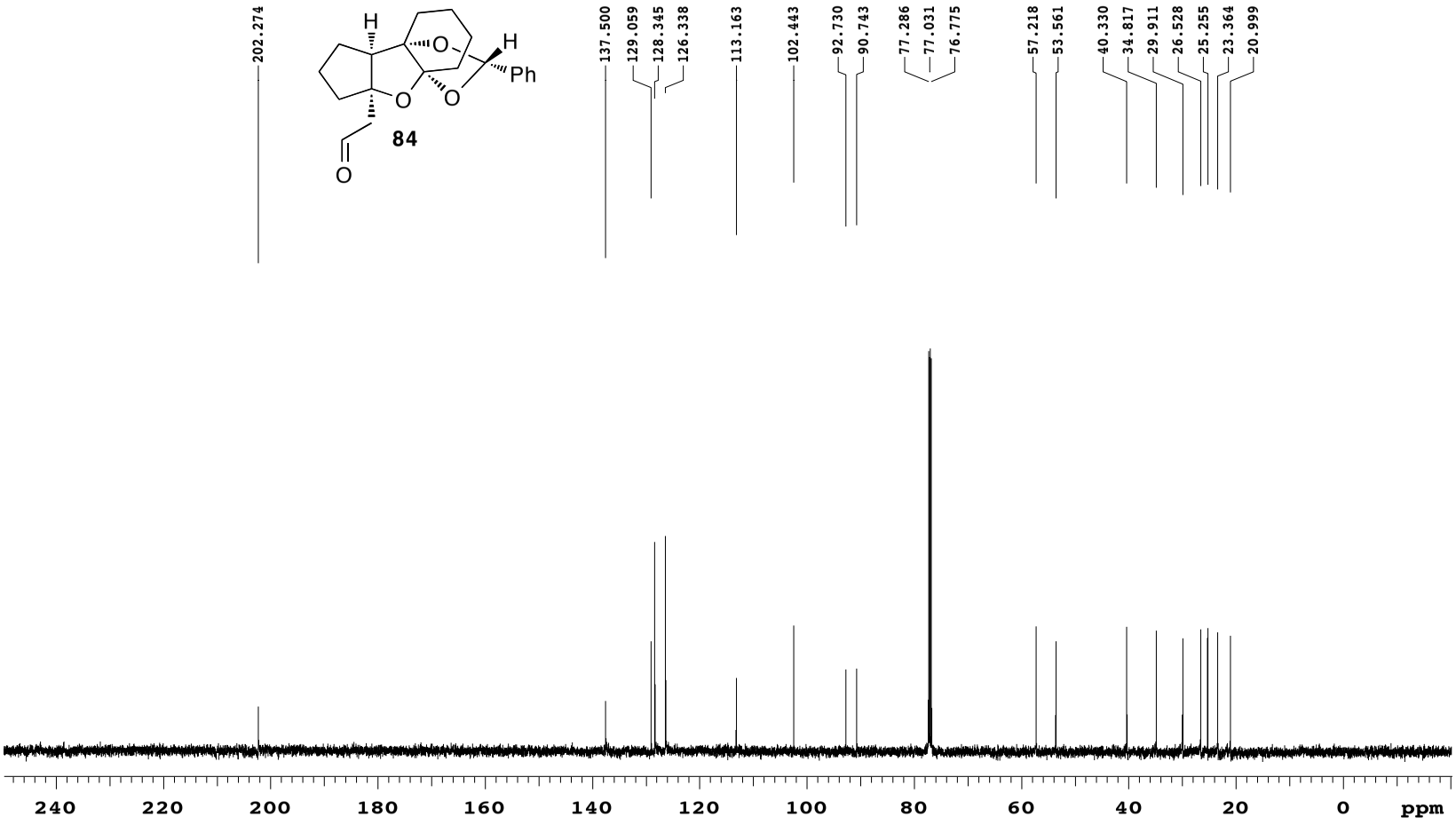
Pulse Sequence: s2pul



84

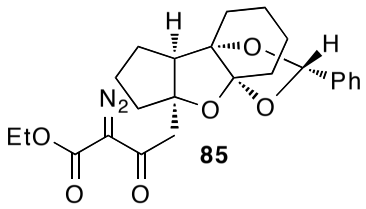
125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul

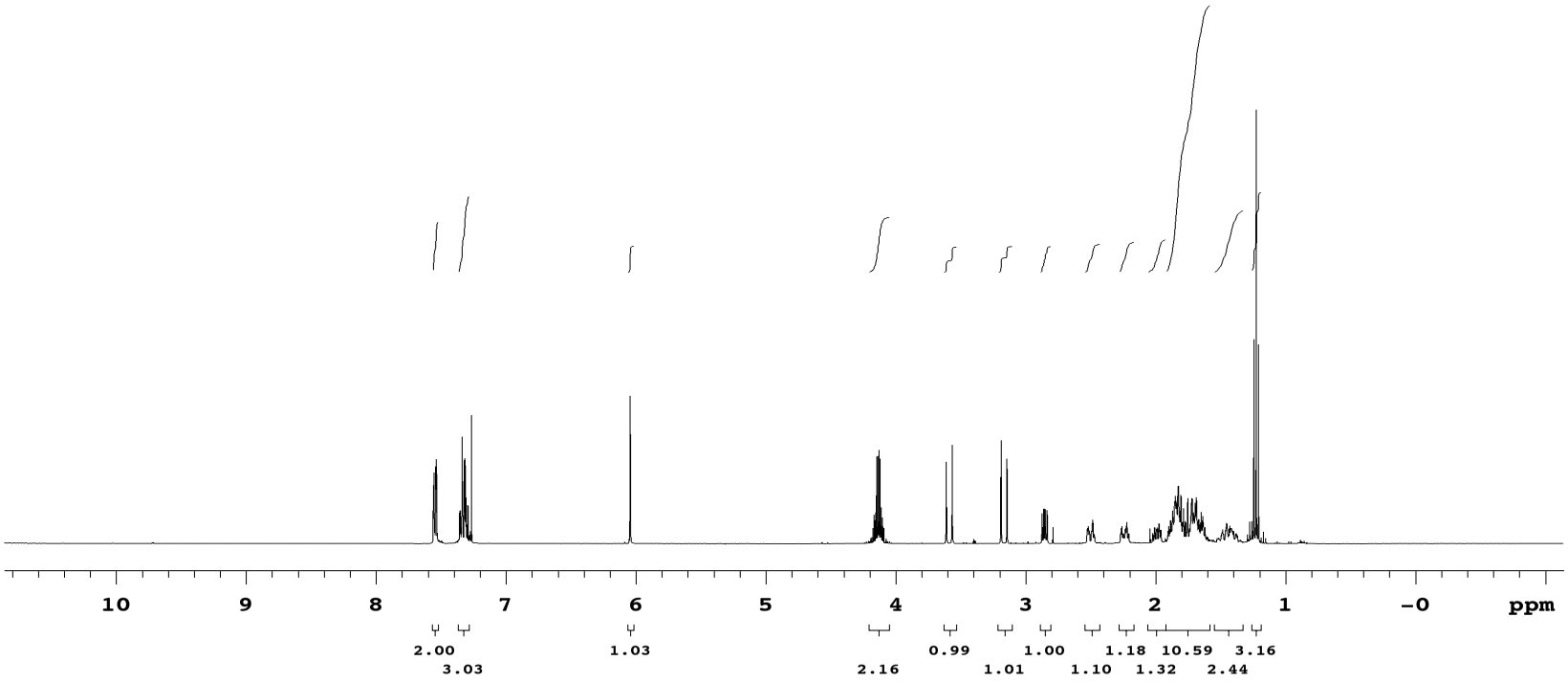


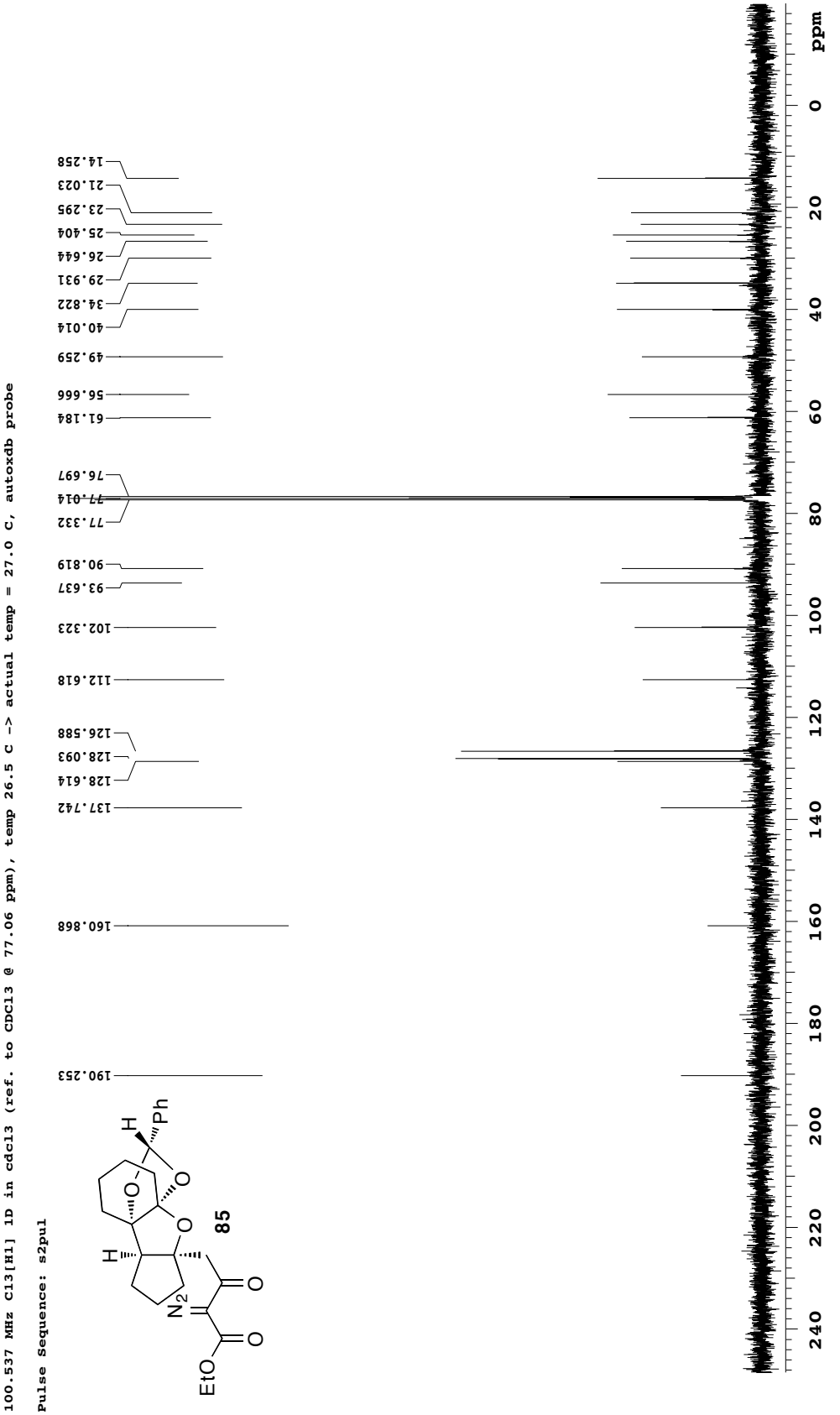
399.794 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.5 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul



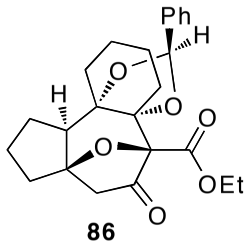
85



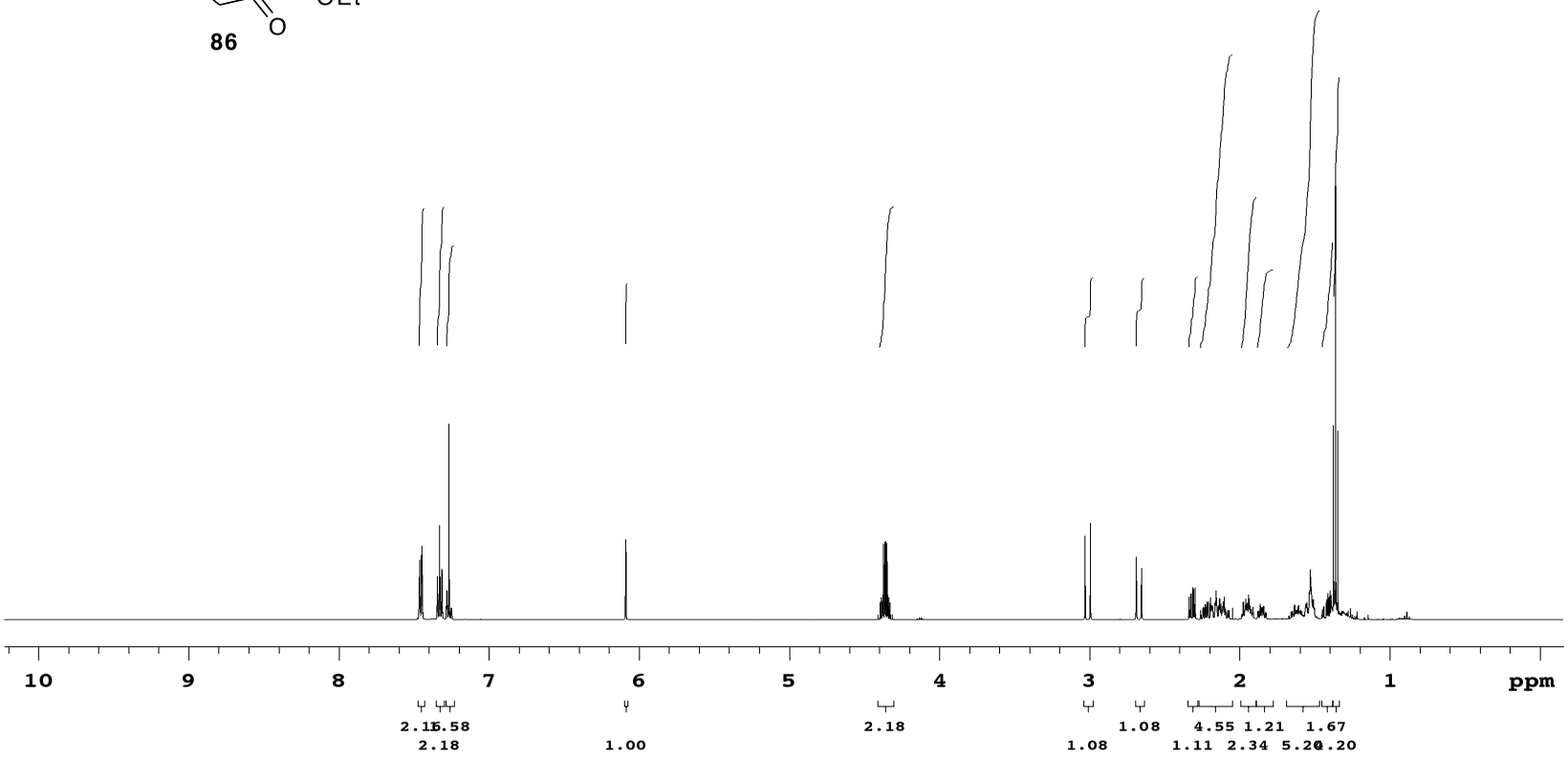

100.537 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.5 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
190.253
160.868
137.742
128.614
128.093
126.588
112.618
102.323
93.637
90.819
77.332
77.014
76.697
61.184
56.666
49.259
40.014
34.822
29.931
26.644
25.404
23.295
21.023
14.258
85
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

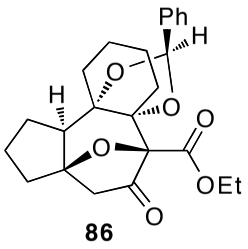


86



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

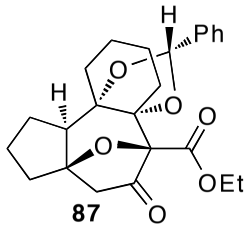
Pulse Sequence: s2pul



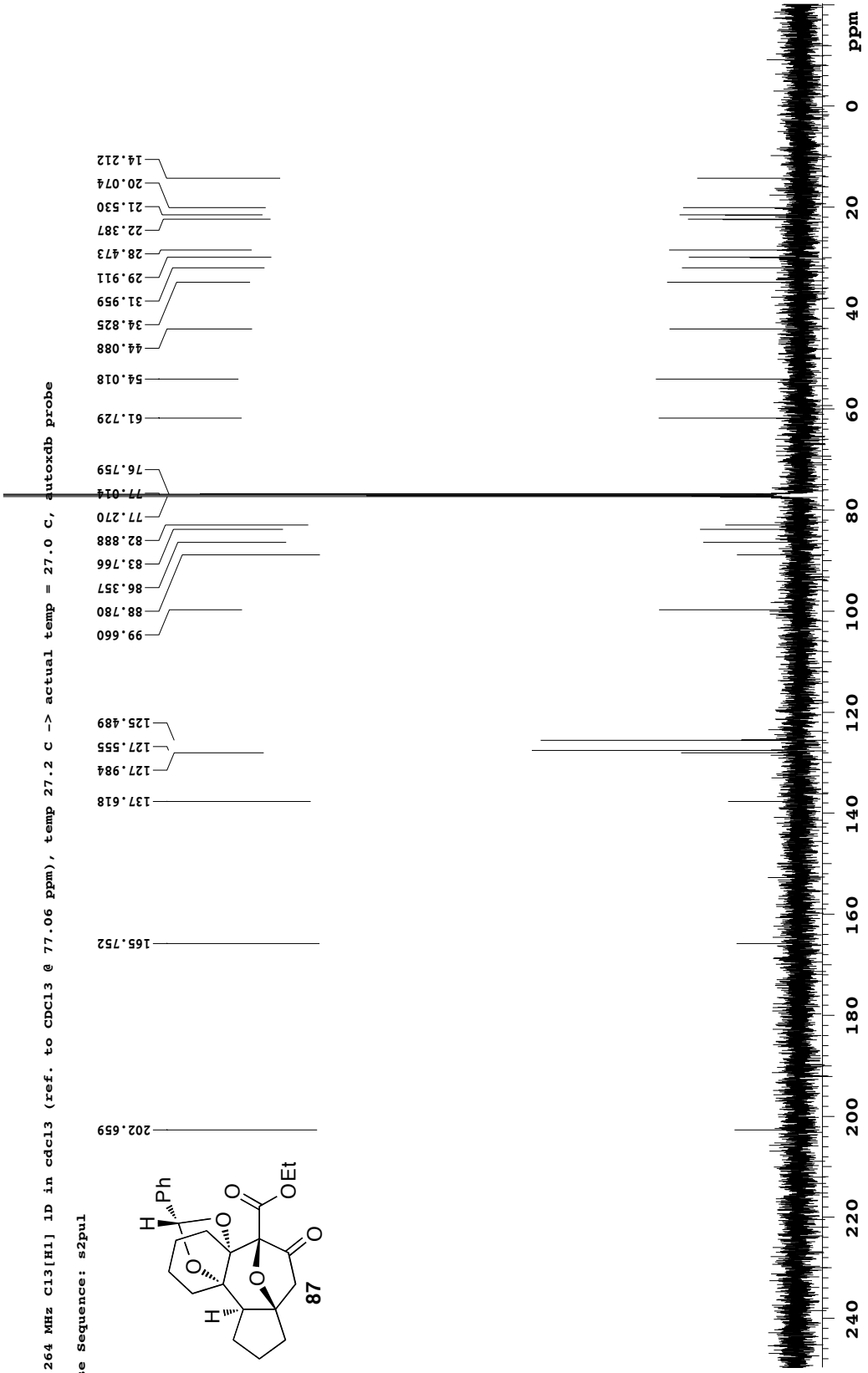
86

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

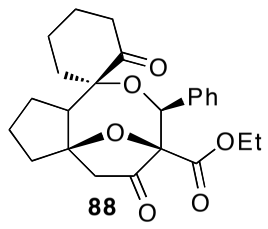


87

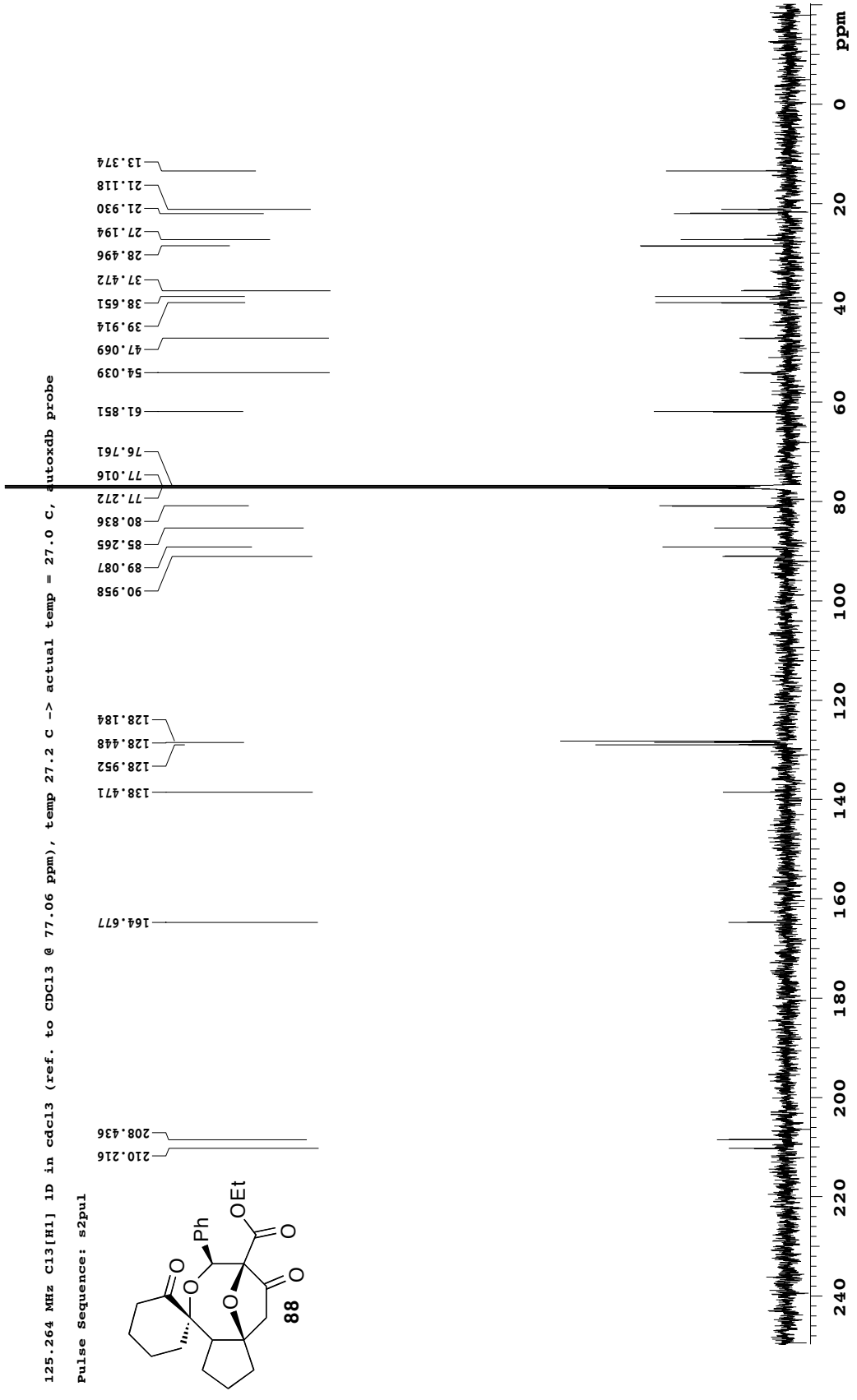

125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
202.659
165.752
137.618
127.984
127.555
125.489
99.660
88.780
86.357
83.766
82.888
77.270
77.014
76.759
61.729
54.018
44.088
34.825
31.959
29.911
28.473
22.387
21.530
20.074
14.212
Ph
OEt
87
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



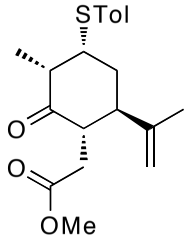
88


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
210.216
208.436
164.677
138.471
128.952
128.448
128.184
90.958
89.087
85.265
80.836
77.272
77.016
76.761
61.851
54.039
47.069
39.914
38.651
37.472
28.496
27.194
21.930
21.118
13.374
Ph
OEt
O
88
ppm

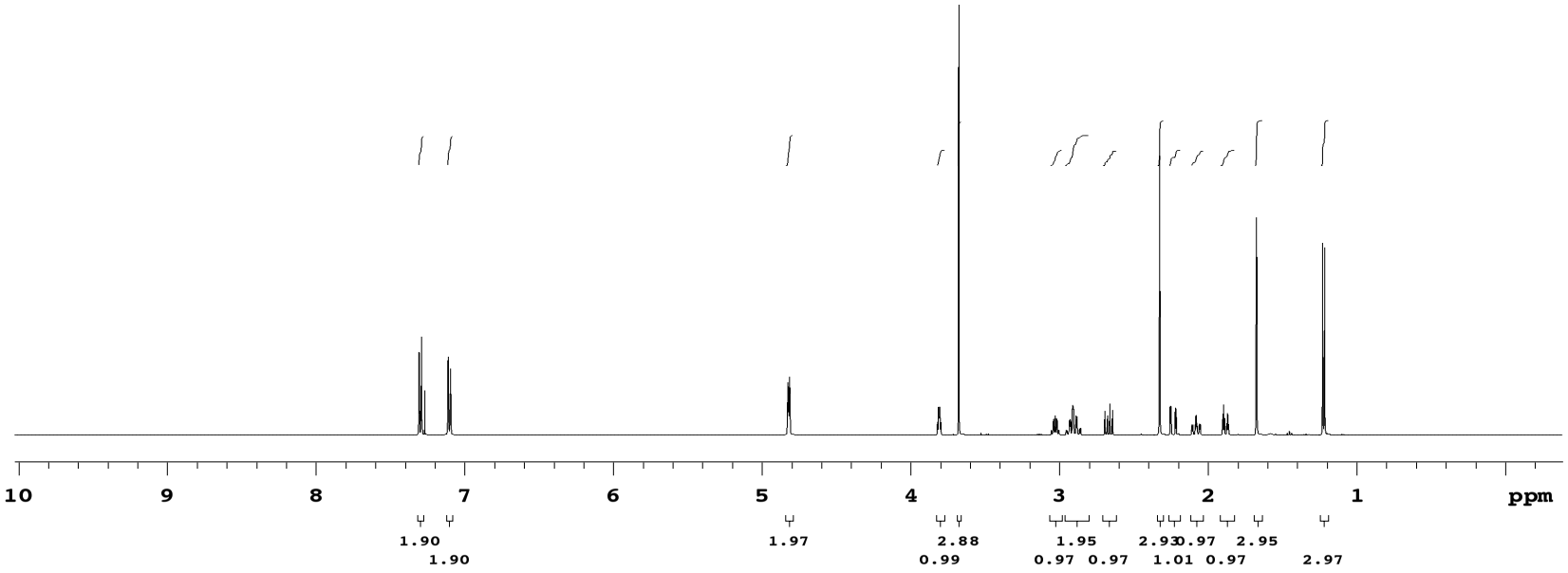
Appendix III: Selected NMR Spectra
(Chapter 4)

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

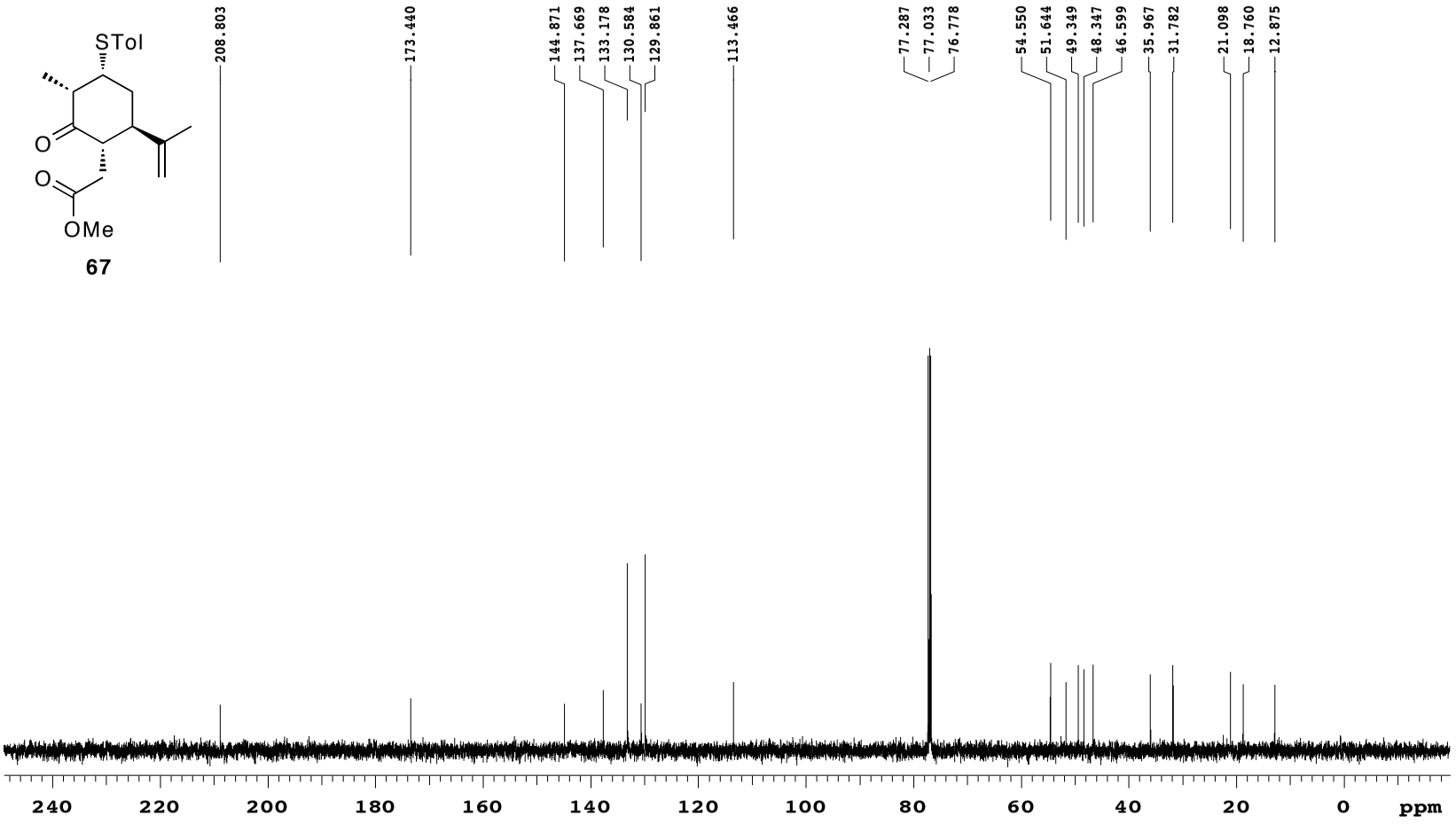


67



cs8-ketone
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

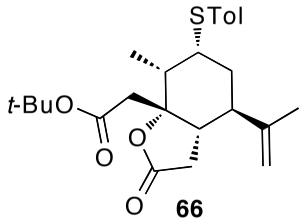
Pulse Sequence: s2pul



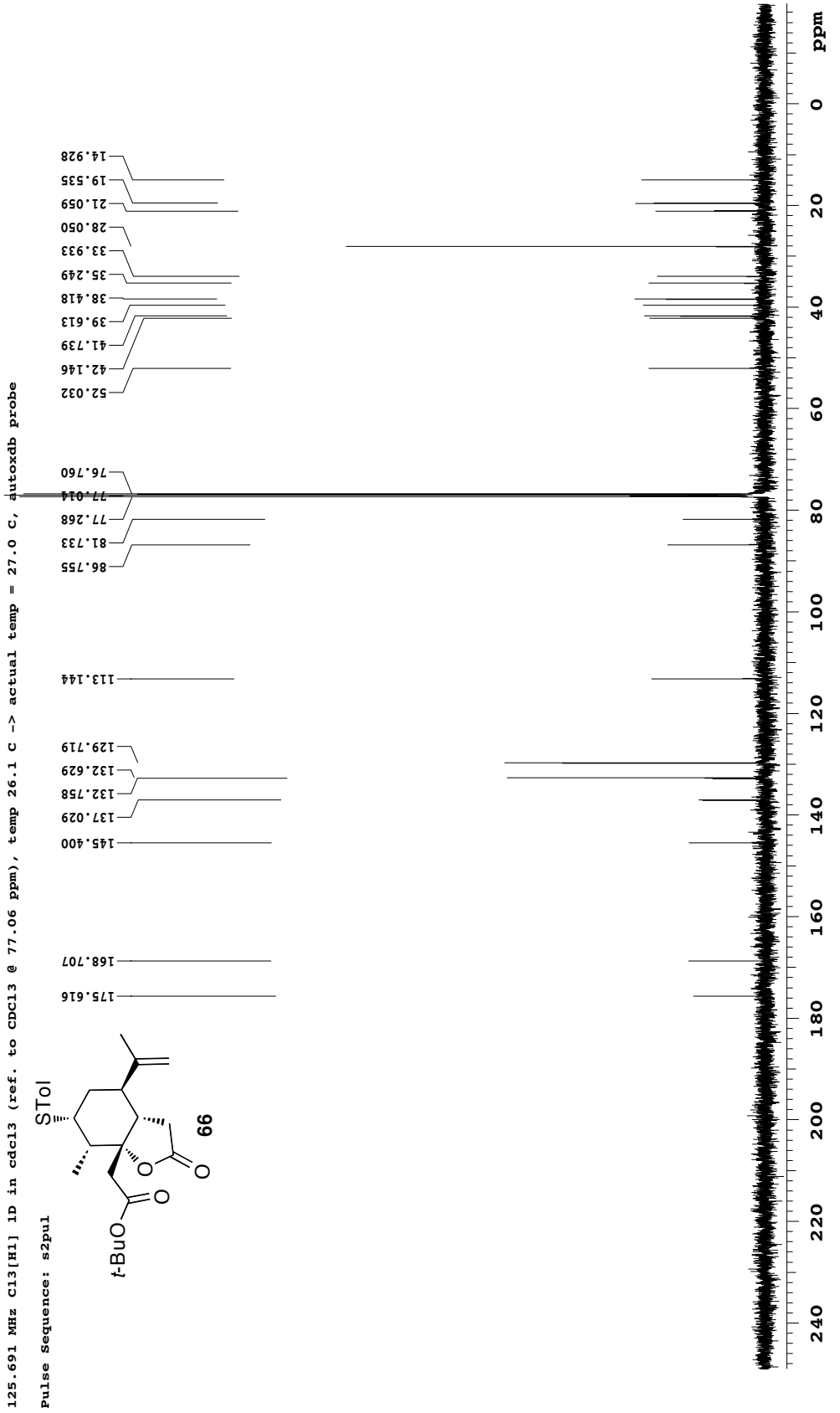
67

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

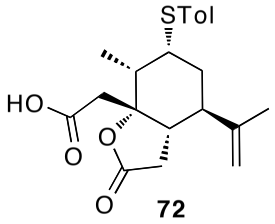


66


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
STol
t-BuO
O
O
O
O
99
175.616
168.707
145.400
137.029
132.758
132.629
129.719
113.144
86.755
81.733
77.268
77.014
76.760
52.032
42.146
41.739
39.613
38.418
35.249
33.933
28.050
21.059
19.535
14.928
ppm
0
20
40
60
80
100
120
140
160
180
200
220
240

400.392 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe

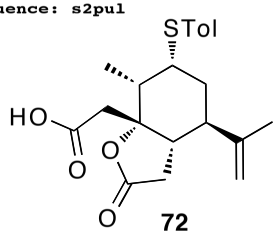
Pulse Sequence: s2pul



72

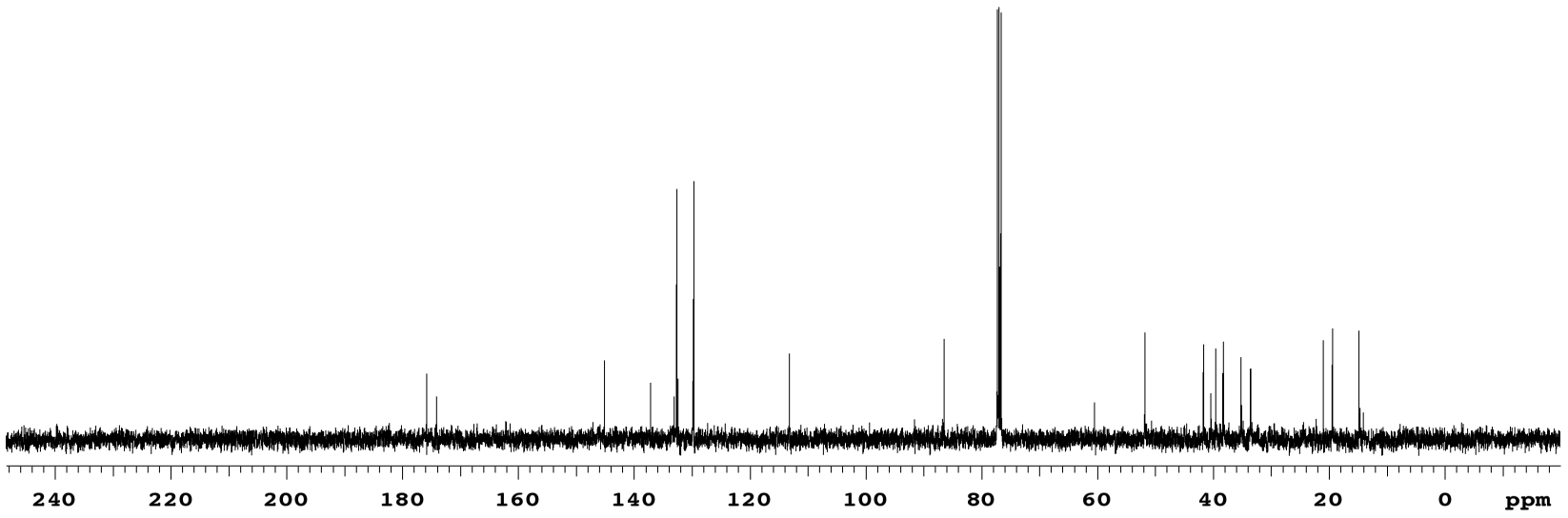
100.688 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe

Pulse Sequence: s2pul



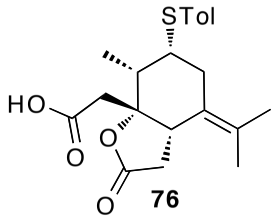
72

175.812
174.108
145.117
137.132
133.046
132.641
132.377
129.833
129.702
113.172
86.480
77.273
76.955
76.638
60.523
51.807
41.685
40.396
39.571
38.273
35.168
33.542
20.985
19.420
14.810

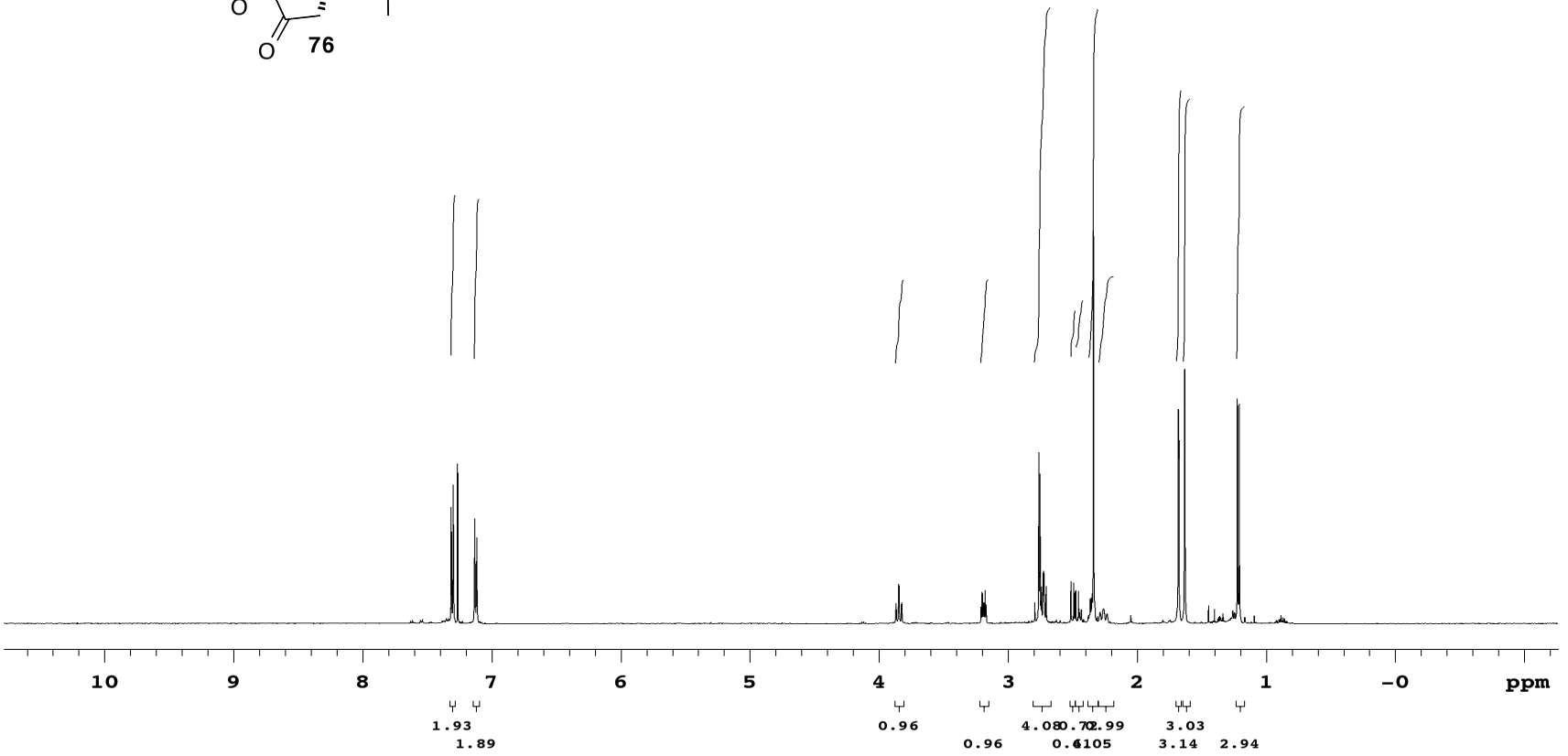


cs11-39-Acid
498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul

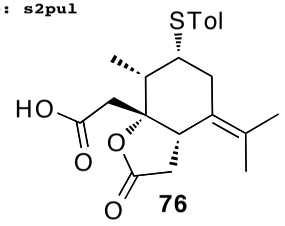


76



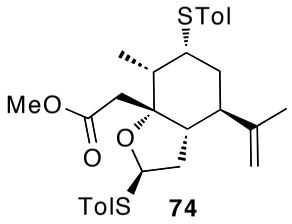
125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul

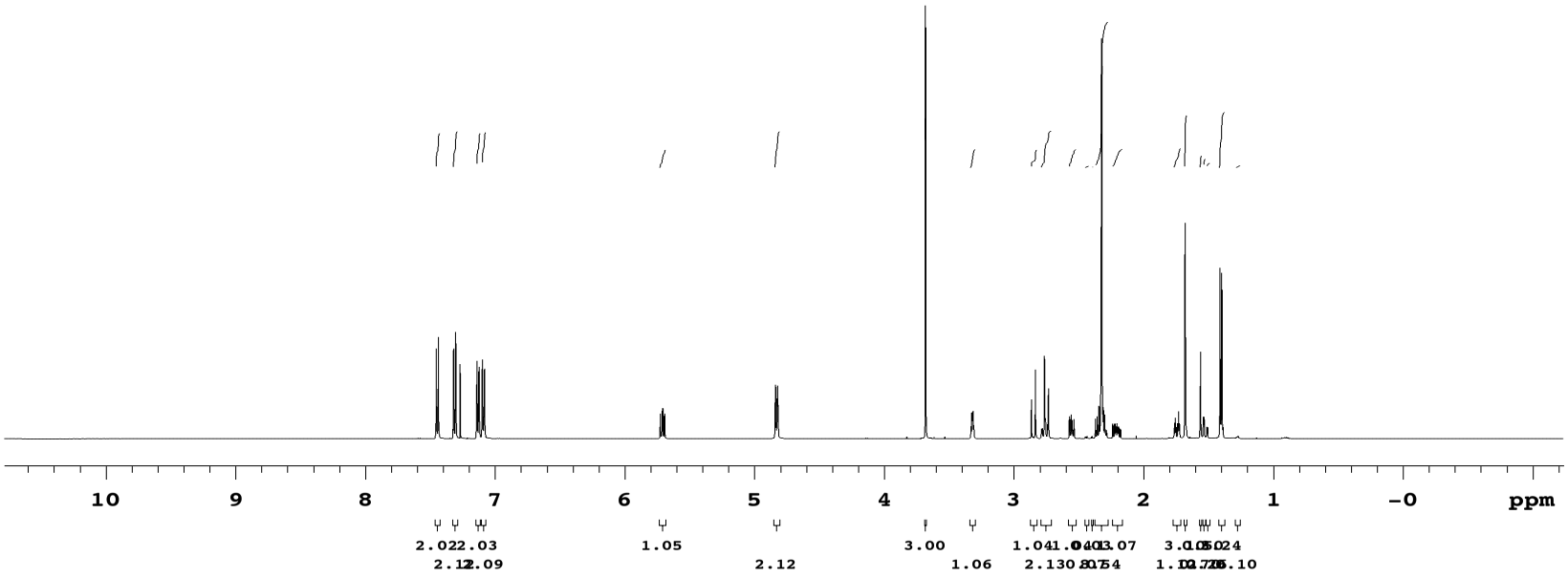


499.821 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul

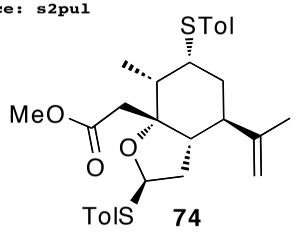


74



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

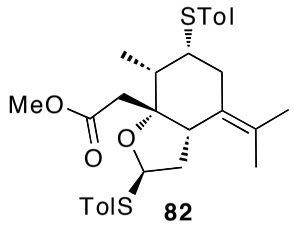
Pulse Sequence: s2pul



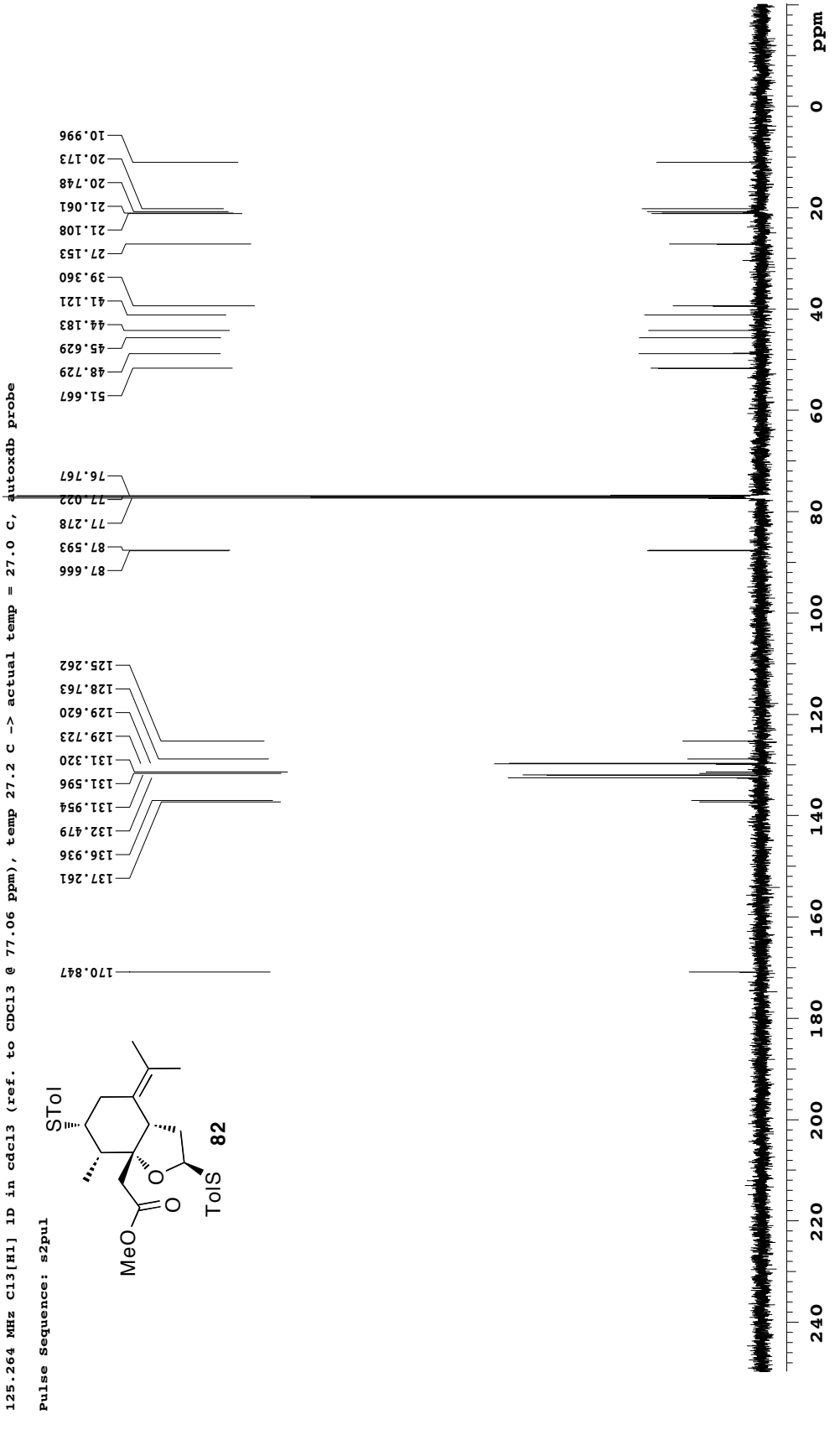
74

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

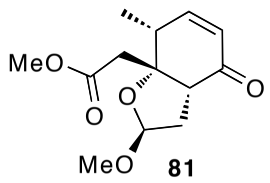


82

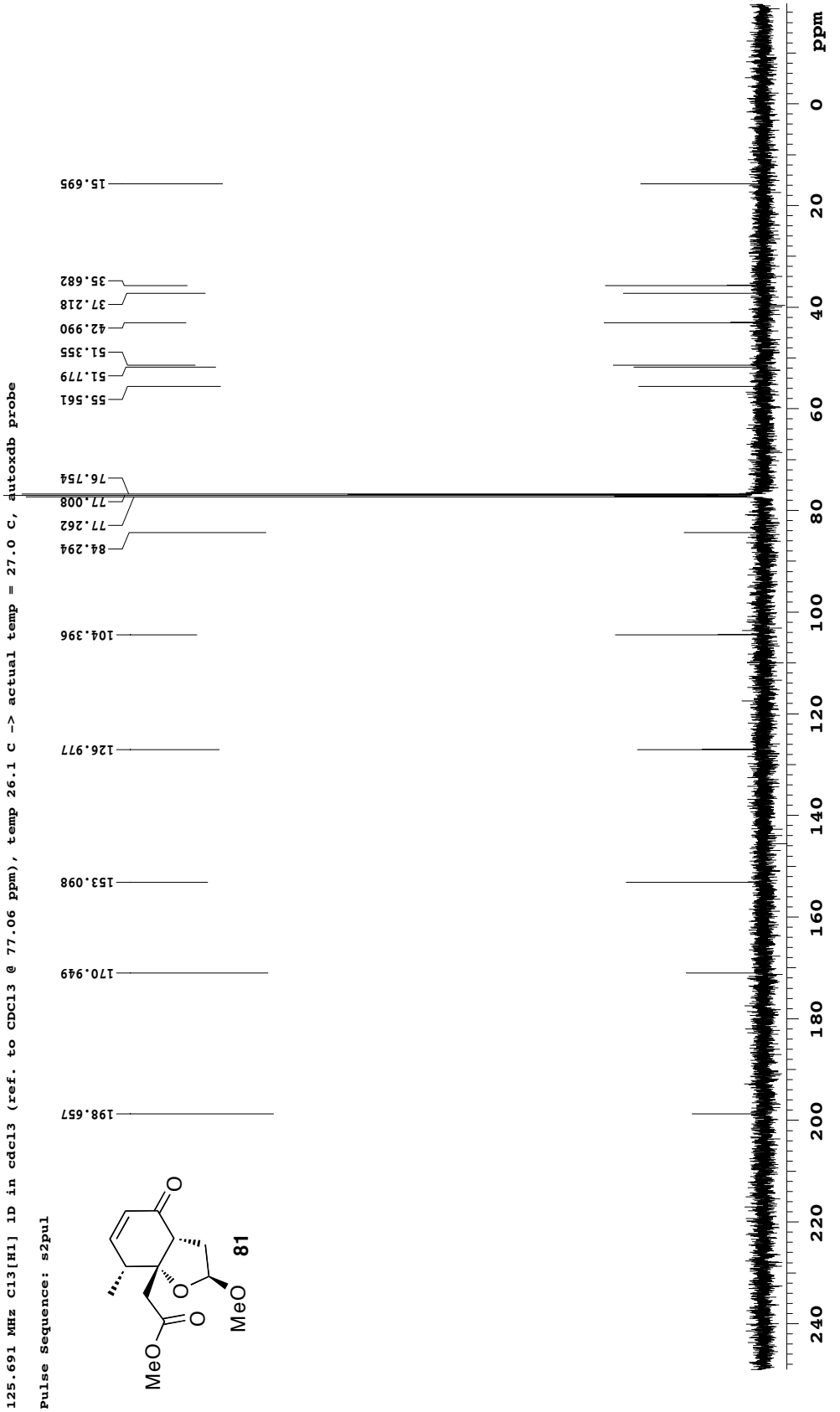

125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
170.847
137.261
136.936
132.479
131.954
131.596
131.320
129.723
129.620
128.763
125.262
87.666
87.593
77.278
77.022
76.767
51.667
48.729
45.629
44.183
41.121
39.360
27.153
21.108
21.061
20.748
20.173
10.996
STol
MeO
O
O
TolS
82
ppm
0
20
40
60
80
100
120
140
160
180
200
220
240

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

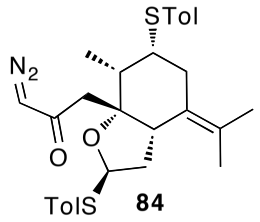


81

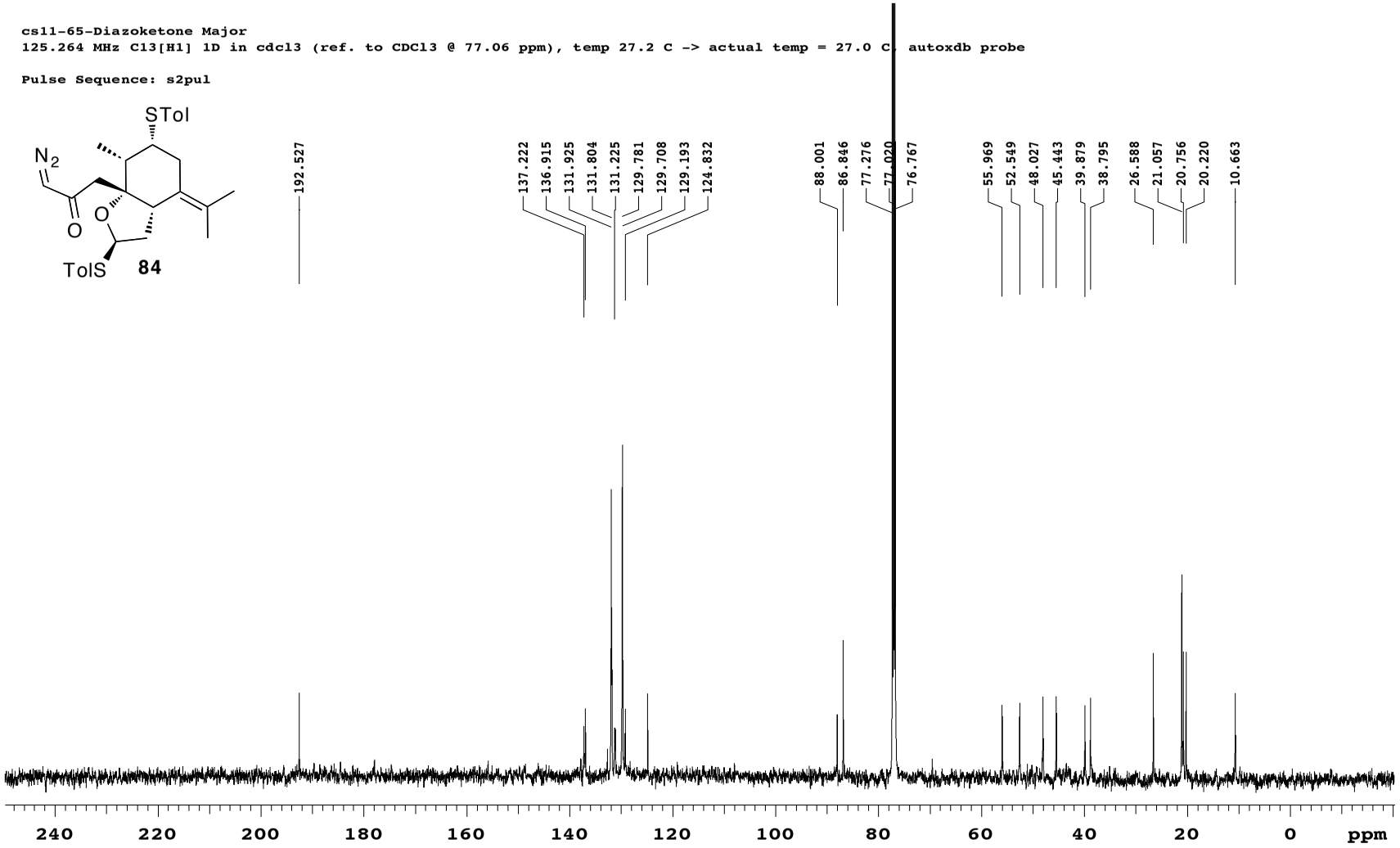

125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
198.657
170.949
153.098
126.977
104.396
84.294
77.262
77.008
76.754
55.561
51.779
51.355
42.990
37.218
35.682
15.695
MeO
MeO
81
ppm

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

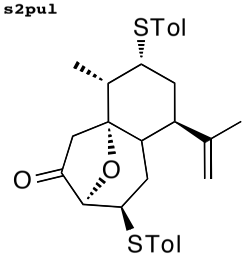


84


cs11-65-Diazoketone Major
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
STol
N2
O
O
TolS
84
192.527
137.222
136.915
131.925
131.804
131.225
129.781
129.708
129.193
124.832
88.001
86.846
77.276
77.020
76.767
55.969
52.549
48.027
45.443
39.879
38.795
26.588
21.057
20.756
20.220
10.663
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

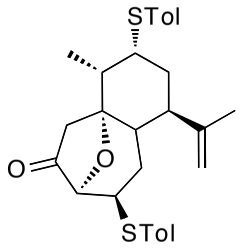
Pulse Sequence: s2pul



64

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



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Appendix IV: X-ray Crystallographic Data for Compounds 34, and 40 (Chapter 2)

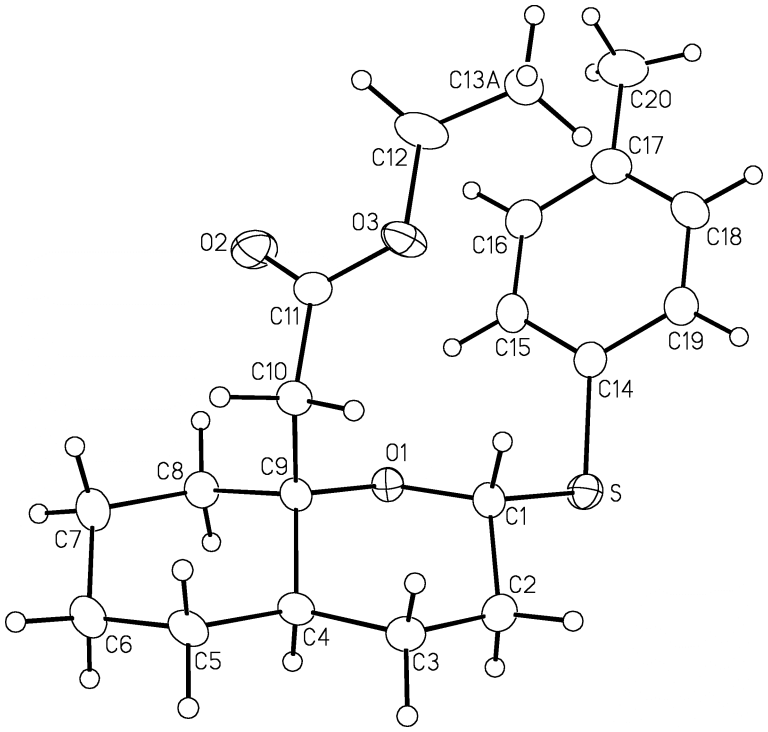
STRUCTURE REPORT

XCL Code: FGW0705 **Date:** 16 May 2007

Compound: Ethyl {2-[(4-methylphenyl)thio]octahydro-8a*H*-chromen-8a-yl}acetate

Formula: $C_{20}H_{28}O_3S$

Supervisor: F. G. West **Crystallographer:** M. J. Ferguson

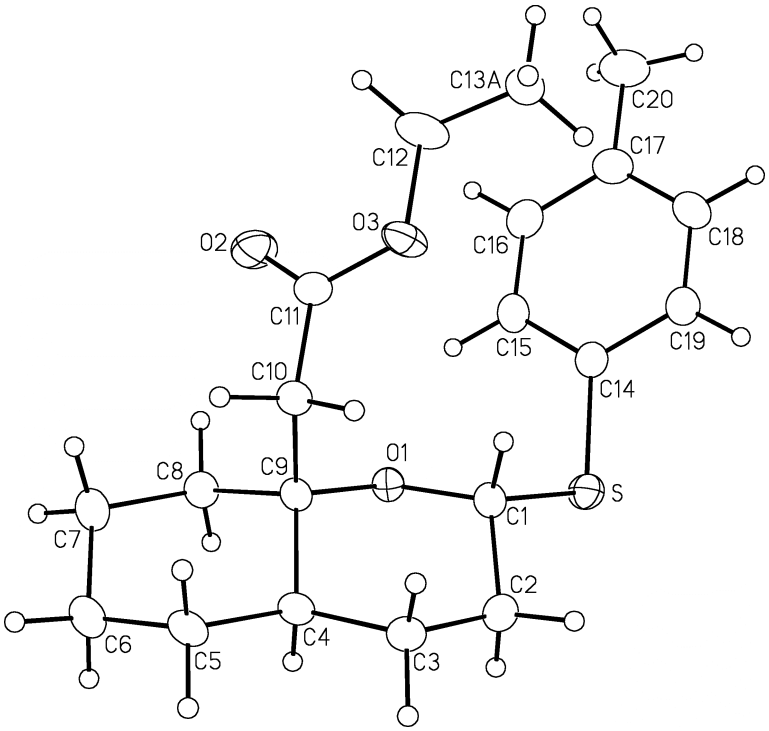


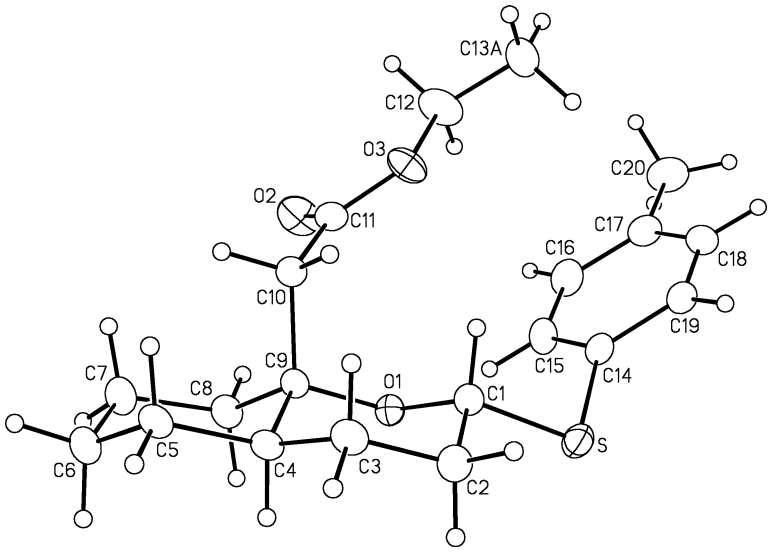
Compound 34

Figure Legends

Figure 1. Perspective view of the ethyl {2-[(4-methylphenyl)thio]octahydro-8a*H*-chromen-8a-yl}acetate molecule showing the atom labelling scheme. Only the major orientation of the disordered ethyl group is shown. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

Figure 2. Alternate view showing the stereochemistry at carbon atoms C1, C4 and C9.




C13A
C12
O3
O2
C11
C10
C20
C17
C16
C18
C19
C15
C14
C9
C7
C8
O1
C1
S
C5
C6
C4
C3
C2

List of Tables

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{20}H_{28}O_3S$
formula weight	348.48
crystal dimensions (mm)	0.43 ´ 0.25 ´ 0.12
crystal system	monoclinic
space group	$P2_1/n$ (an alternate setting of $P2_1/c$ [No. 14])
unit cell parameters[a]	
a (Å)	8.6522 (11)
b (Å)	23.914 (3)
c (Å)	9.4023 (12)
b (deg)	102.611 (2)
V (Å^3)	1898.5 (4)
Z	4
r_{calcd} (g cm^{-3})	1.219
μ (mm^{-1})	0.185
B. Data Collection and Refinement Conditions	
diffractometer	Bruker PLATFORM/SMART 1000 CCD[b]
radiation (*l* [Å])	graphite-monochromated Mo K*a* (0.71073)
temperature (°C)	–80
scan type	*w* scans (0.3°) (20 s exposures)
data collection 2*q* limit (deg)	52.78
total data collected	14457 (-10 ≤ *h* ≤ 10, -29 ≤ *k* ≤ 29, -11 ≤ *l* ≤ 11)
independent reflections	3885 (R_{int} = 0.0379)
number of observed reflections (*NO*)	2781 [$F_o^2 \geq 2s(F_o^2)$]
structure solution method	direct methods (*SIR*97[c])
refinement method (*SHELXL–97*[d])	full-matrix least-squares on F^2
absorption correction method	multi-scan (*SADABS*)
range of transmission factors	0.9782–.9248
data/restraints/parameters	3885 [$F_o^2 \geq -3s(F_o^2)$] / 0 / 227
goodness-of-fit (*S*)[e]	1.041 [$F_o^2 \geq -3s(F_o^2)$]
final *R* indices[f]	

R_1 [$F_o^2 \geq 2s(F_o^2)$]	0.0518
wR_2 [$F_o^2 \geq -3s(F_o^2)$]	0.1359
largest difference peak and hole	0.507 and –0.268 e Å^{-3}

[a]Obtained from least-squares refinement of 4411 reflections with $4.76° < 2q < 47.38°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

(continued)

Table 1. Crystallographic Experimental Details (continued)

[c]Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Cryst.* **1999**, *32*, 115–119.

[d]Sheldrick, G. M. *SHELXL-97*. Program for crystal structure determination. University of Göttingen, Germany, 1997.

[e]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [s^2(F_o^2) + (0.0572P)^2 + 0.6989P]^{-1}$ where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$).

[f]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

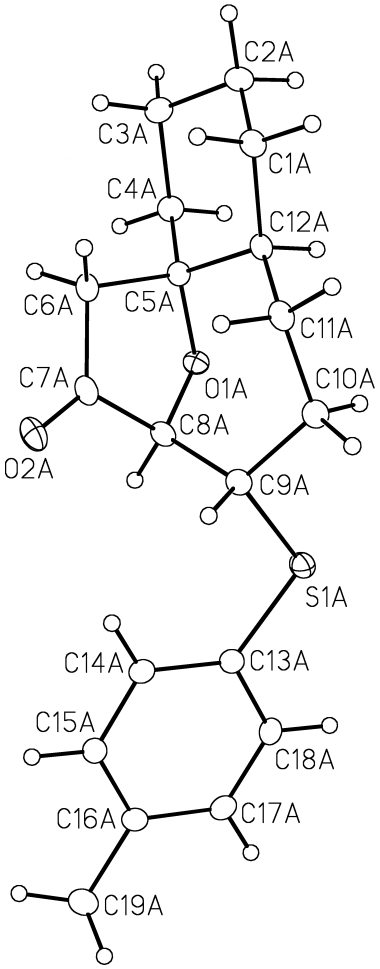
STRUCTURE REPORT

XCL Code: FGW0905 **Date:** 25 November 2009

Compound: 8-{(*p*-Tolyl)thio}octahydro-2*H*-4a,7-epoxybenzo[8]annulen-6(5*H*)-one

Formula: $C_{19}H_{24}O_2S$

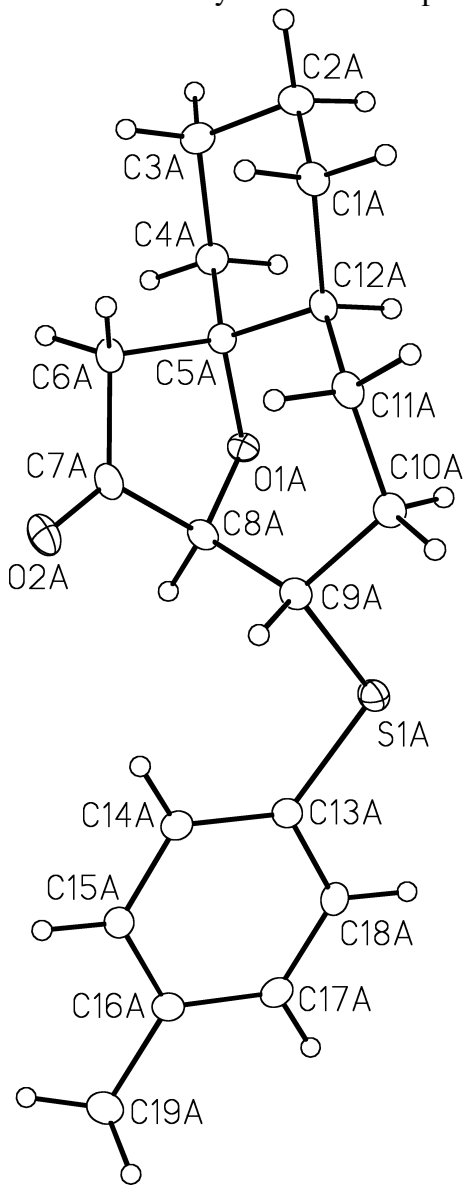
Supervisor: F. G. West **Crystallographer:** R. McDonald



Compound 40

Figure Legends

Figure 1. Perspective view of one of the two crystallographically-independent molecules of 8-{(*p*-tolyl)thio}octahydro-2*H*-4a,7-epoxybenzo[8]annulen-6(5*H*)-one (molecule A) showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.



List of Tables

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{19}H_{24}O_2S$
formula weight	316.44
crystal dimensions (mm)	0.54 ´ 0.35 ´ 0.06
crystal system	monoclinic
space group	$P2_1/n$ (an alternate setting of $P2_1/c$ [No. 14])
unit cell parameters[a]	
a (Å)	13.0212 (6)
b (Å)	10.9190 (5)
c (Å)	24.1384 (11)
b (deg)	105.4497 (6)
V (Å^3)	3307.9 (3)
Z	8
r_{calcd} (g cm^{-3})	1.271
μ (mm^{-1})	0.201
B. Data Collection and Refinement Conditions	
diffractometer	Bruker D8/APEX II CCD[b]
radiation (*l* [Å])	graphite-monochromated Mo K*a* (0.71073)
temperature (°C)	–100
scan type	*w* scans (0.3°) (20 s exposures)
data collection 2*q* limit (deg)	52.66
total data collected	25625 (-16 ≤ *h* ≤ 16, -13 ≤ *k* ≤ 13, -30 ≤ *l* ≤ 30)
independent reflections	6724 (R_{int} = 0.0378)
number of observed reflections (*NO*)	4912 [$F_o^2 \geq 2s(F_o^2)$]
structure solution method	direct methods (*SHELXD*[c])
refinement method (*SHELXL–97*[d])	full-matrix least-squares on F^2
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9873–0.8993
data/restraints/parameters	6724 [$F_o^2 \geq -3s(F_o^2)$] / 0 / 399
goodness-of-fit (*S*)[e]	1.019 [$F_o^2 \geq -3s(F_o^2)$]
final *R* indices[f]	
R_1 [$F_o^2 \geq 2s(F_o^2)$]	0.0369

wR_2 [$F_o^2 \geq -3s(F_o^2)$]	0.1016
largest difference peak and hole	0.217 and –0.244 e Å^{-3}

[a]Obtained from least-squares refinement of 8335 reflections with 4.94° < 2q < 50.42°.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

(continued)

Table 1. Crystallographic Experimental Details (continued)

[c]Schneider, T. R.; Sheldrick, G. M. *Acta Crystallogr*. **2002**, *D58*, 1772–1779.

[d]Sheldrick, G. M. *Acta Crystallogr*. **2008**, *A64*, 112–122.

[e]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [s^2(F_o^2) + (0.0476P)^2 + 0.7489P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[f]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Appendix V: X-ray Crystallographic Data for Compounds 87 and 88. (Chapter 3)

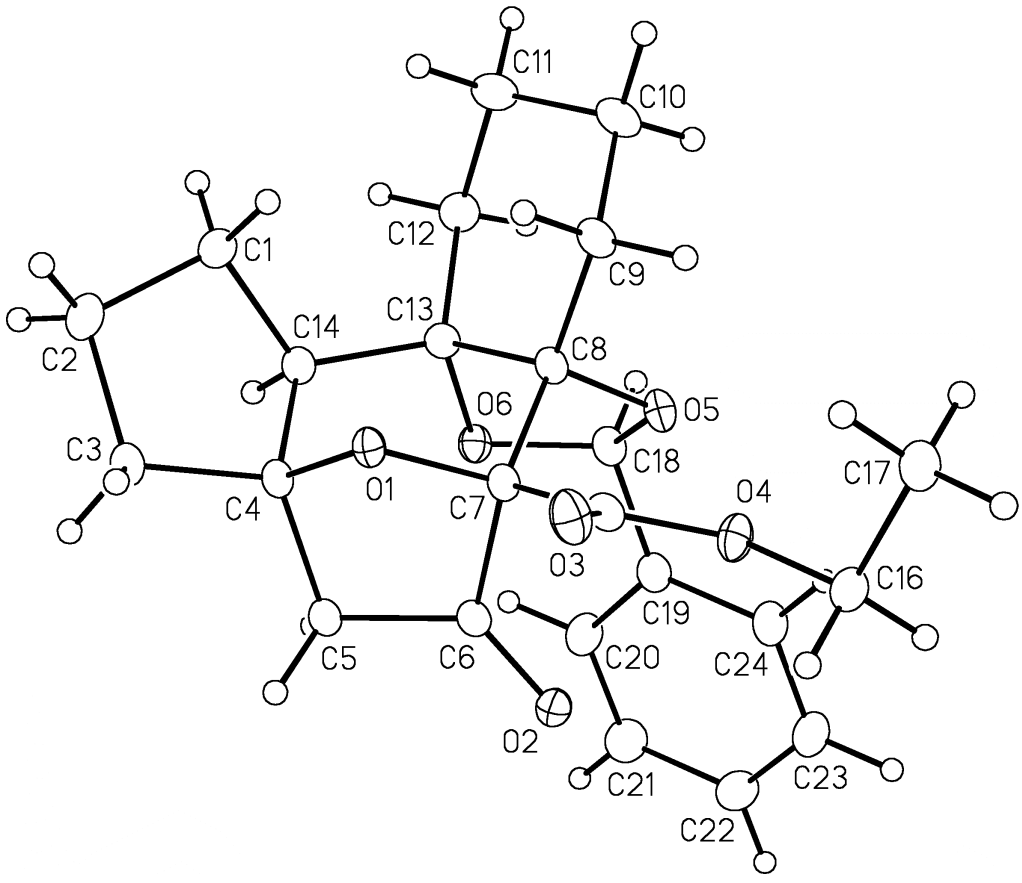
STRUCTURE REPORT

XCL Code: FGW0902 **Date:** 29 May 2009

Compound: Ethyl 5-oxo-12-phenyldecahydro-6*H*-3a,6-epoxy-6a,10a-(epoxymethanooxy)benzo[*e*]azulene-6-carboxylate

Formula: $C_{24}H_{28}O_6$

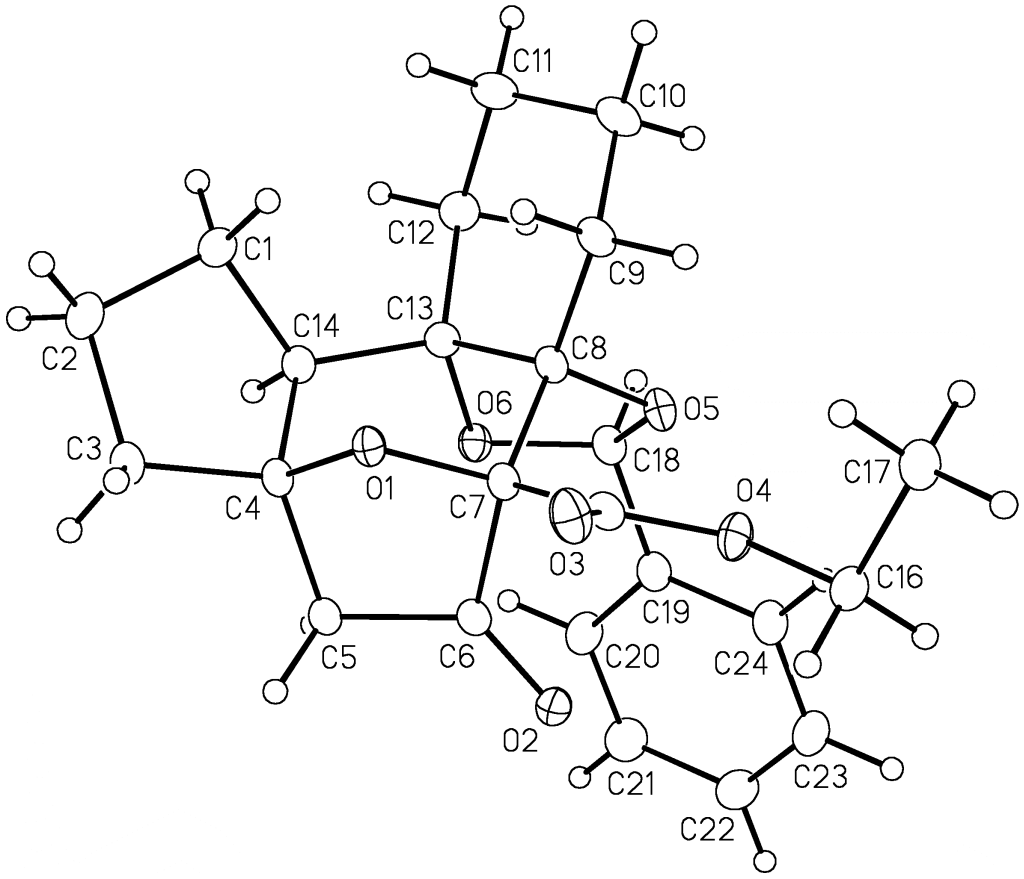
Supervisor: F. G. West **Crystallographer:** R. McDonald



Compound 87

Figure Legends

Figure 1. Perspective view of the ethyl 5-oxo-12-phenyldecahydro-6*H*-3a,6-epoxy-6a,10a-(epoxymethanooxy)benzo[*e*]azulene-6-carboxylate molecule showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.



List of Tables

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{24}H_{28}O_6$
formula weight	412.46
crystal dimensions (mm)	0.67 ´ 0.23 ´ 0.18
crystal system	monoclinic
space group	$P2_1/c$ (No. 14)
unit cell parameters[a]	
a (Å)	12.2754 (13)
b (Å)	17.8152 (18)
c (Å)	9.4850 (10)
b (deg)	100.2038 (12)
V (Å^3)	2041.5 (4)
Z	4
r_{calcd} (g cm^{-3})	1.342
μ (mm^{-1})	0.096
B. Data Collection and Refinement Conditions	
diffractometer	Bruker PLATFORM/SMART 1000 CCD[b]
radiation (*l* [Å])	graphite-monochromated Mo K*a* (0.71073)
temperature (°C)	–100
scan type	*w* scans (0.3°) (15 s exposures)
data collection 2*q* limit (deg)	55.04
total data collected	16984 (-15 ≤ *h* ≤ 15, -23 ≤ *k* ≤ 23, -12 ≤ *l* ≤ 12)
independent reflections	4683 (R_{int} = 0.0290)
number of observed reflections (*NO*)	3508 [$F_o^2 \geq 2s(F_o^2)$]
structure solution method	direct methods (*SHELXS–97*[c])
refinement method (*SHELXL–97*[c])	full-matrix least-squares on F^2
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9829–0.9383
data/restraints/parameters	4683 [$F_o^2 \geq -3s(F_o^2)$] / 0 / 271
goodness-of-fit (*S*)[d]	1.034 [$F_o^2 \geq -3s(F_o^2)$]

final R indices[e]	
R_1 [$F_o^2 \geq 2s(F_o^2)$]	0.0485
wR_2 [$F_o^2 \geq -3s(F_o^2)$]	0.1291
largest difference peak and hole	0.355 and –0.198 e Å^{-3}

[a]Obtained from least-squares refinement of 7118 reflections with $4.92° < 2q < 55.00°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

(continued)

Table 1. Crystallographic Experimental Details (continued)

[c]Sheldrick, G. M. *Acta Crystallogr*. **2008**, *A64*, 112–122.

[d]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [s^2(F_o^2) + (0.0640P)^2 + 0.6509P]^{-1}$ where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$).

[e]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

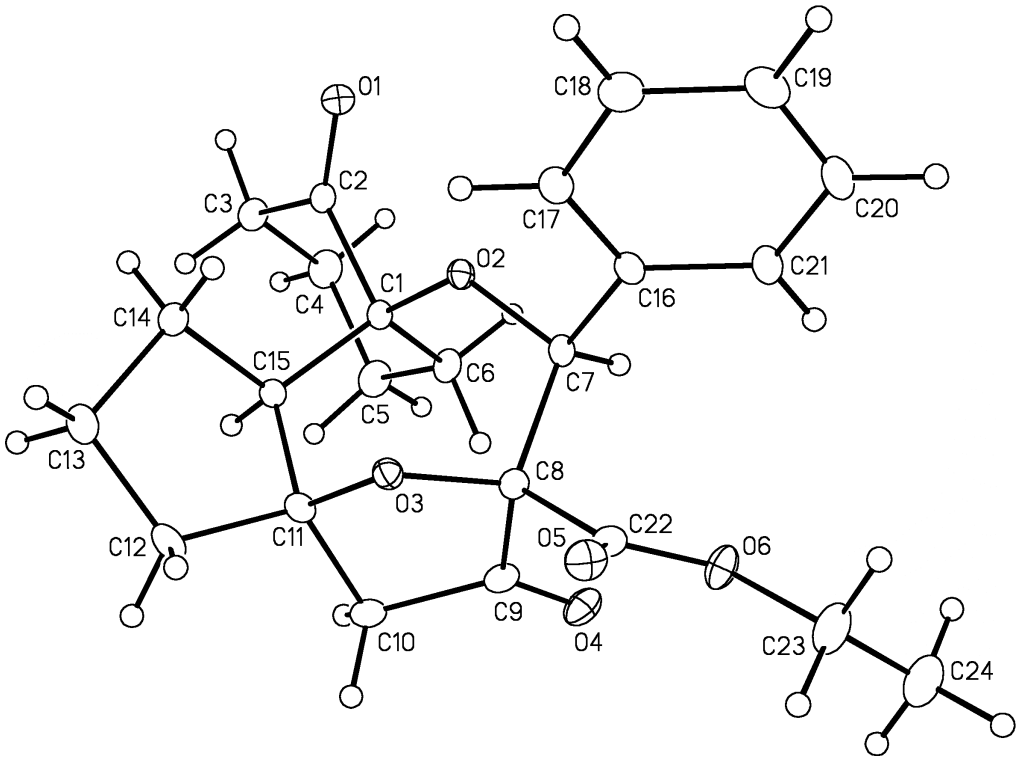
STRUCTURE REPORT

XCL Code: FGW0903 **Date:** 18 June 2009

Compound: Ethyl 2,5'-dioxo-3'-phenylhexahydrospiro(cyclohexane-1,1'-[2,10]dioxa[4,6a]epoxycyclopenta[*c*]oxocine)-4'(3'*H*)-carboxylate

Formula: $C_{24}H_{28}O_6$

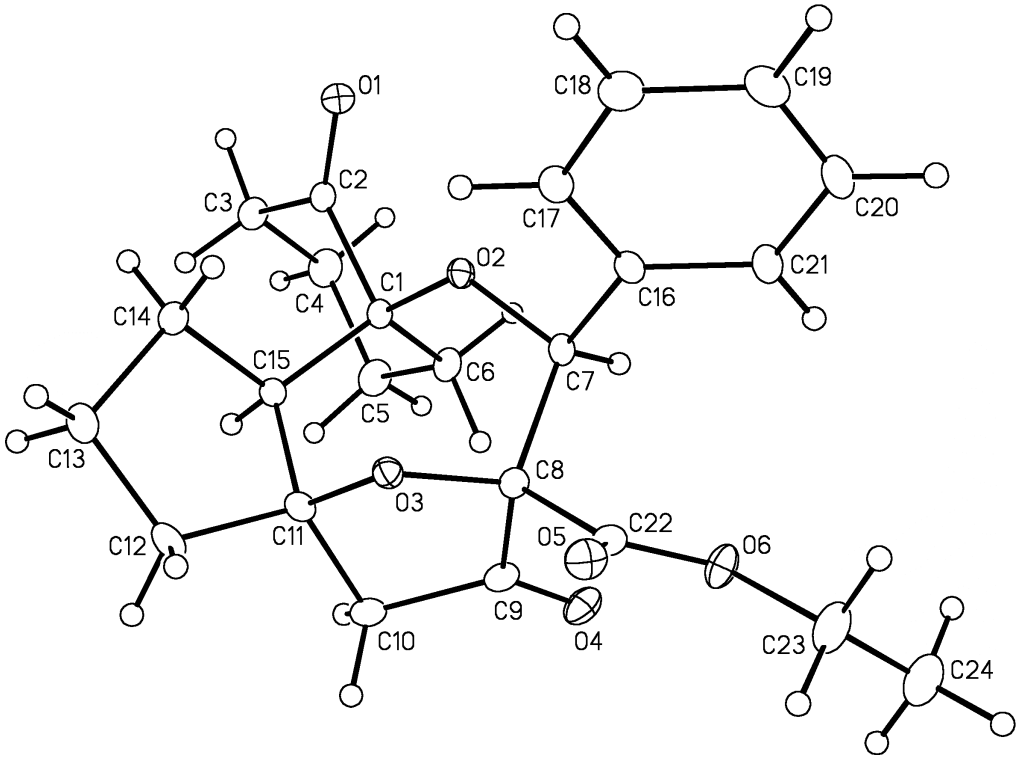
Supervisor: F. G. West **Crystallographer:** R. McDonald



Compound 88

Figure Legends

Figure 1. Perspective view of the ethyl 2,5'-dioxo-3'-phenylhexahydrospiro(cyclohexane-1,1'-[2,10]dioxa[4,6a]epoxycyclopenta[*c*]oxocine)-4'(3'*H*)-carboxylate molecule showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.



List of Tables

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{24}H_{28}O_6$
formula weight	412.46
crystal dimensions (mm)	0.46 ´ 0.41 ´ 0.40
crystal system	orthorhombic
space group	$Pna2_1$ (No. 33)
unit cell parameters[a]	
a (Å)	12.6475 (5)
b (Å)	11.3248 (4)
c (Å)	14.4129 (5)
V (Å^3)	2064.37 (13)
Z	4
r_{calcd} (g cm^{-3})	1.327
μ (mm^{-1})	0.095
B. Data Collection and Refinement Conditions	
diffractometer	Bruker D8/APEX II CCD[b]
radiation (*l* [Å])	graphite-monochromated Mo K*a* (0.71073)
temperature (°C)	–100
scan type	*w* scans (0.3°) (15 s exposures)
data collection 2*q* limit (deg)	54.96
total data collected	28043 (-16 ≤ *h* ≤ 16, -14 ≤ *k* ≤ 14, -18 ≤ *l* ≤ 18)
independent reflections	4715 (R_{int} = 0.0208)
number of observed reflections (*NO*)	4619 [$F_o^2 \geq 2s(F_o^2)$]
structure solution method	direct methods (*SHELXD*[c])
refinement method (*SHELXL–97*[d])	full-matrix least-squares on F^2
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9629–0.9578
data/restraints/parameters	4715 [$F_o^2 \geq -3s(F_o^2)$] / 0 / 271
Flack absolute structure parameter[e]	0.3(6)

goodness-of-fit (S)[f]	1.054 [$F_o^2 \geq -3s(F_o^2)$]
final R indices[g]	
R_1 [$F_o^2 \geq 2s(F_o^2)$]	0.0353
wR_2 [$F_o^2 \geq -3s(F_o^2)$]	0.1002
largest difference peak and hole	0.647 and –0.205 e Å^{-3}

[a]Obtained from least-squares refinement of 9824 reflections with 4.58° < 2q < 54.96°.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

(continued)

Table 1. Crystallographic Experimental Details (continued)

[c]Schneider, T. R.; Sheldrick, G. M. *Acta Crystallogr*. **2002**, *D58*, 1772-1779.

[d]Sheldrick, G. M. *Acta Crystallogr*. **2008**, *A64*, 112–122.

[e]Flack, H. D. *Acta Crystallogr*. **1983**, *A39*, 876–881; Flack, H. D.; Bernardinelli, G. *Acta Crystallogr*. **1999**, *A55*, 908–915; Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst*. **2000**, *33*, 1143–1148. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration. For this structure the Flack parameter is meaningless due to the low anomalous scattering power of the atoms in this structure (none heavier than oxygen). We make no claims regarding absolute structure since both enantomers are present in the crystal (the space group is achiral).

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [s^2(F_o^2) + (0.0702P)^2 + 0.2821P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Appendix VI: X-ray Crystallographic Data for Compound 67 (Chapter 4)

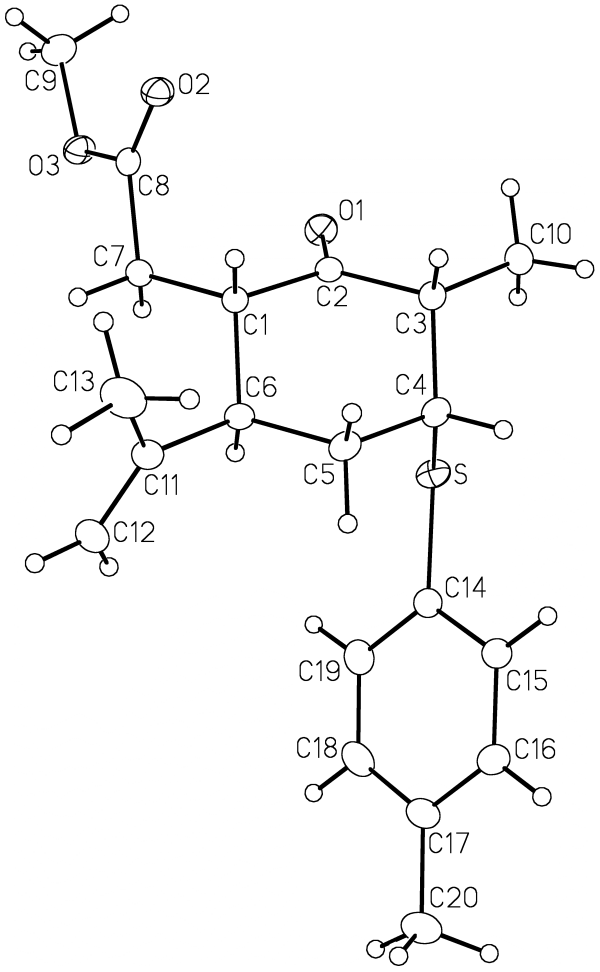
STRUCTURE REPORT

XCL Code: FGW0805 **Date:** 12 June 2008

Compound: methyl {3-methyl-4-[(4-methylphenyl)sulfanyl]-2-oxo-6-(prop-1-en-2-yl)cyclohexyl}acetate

Formula: $C_{20}H_{26}O_3S$

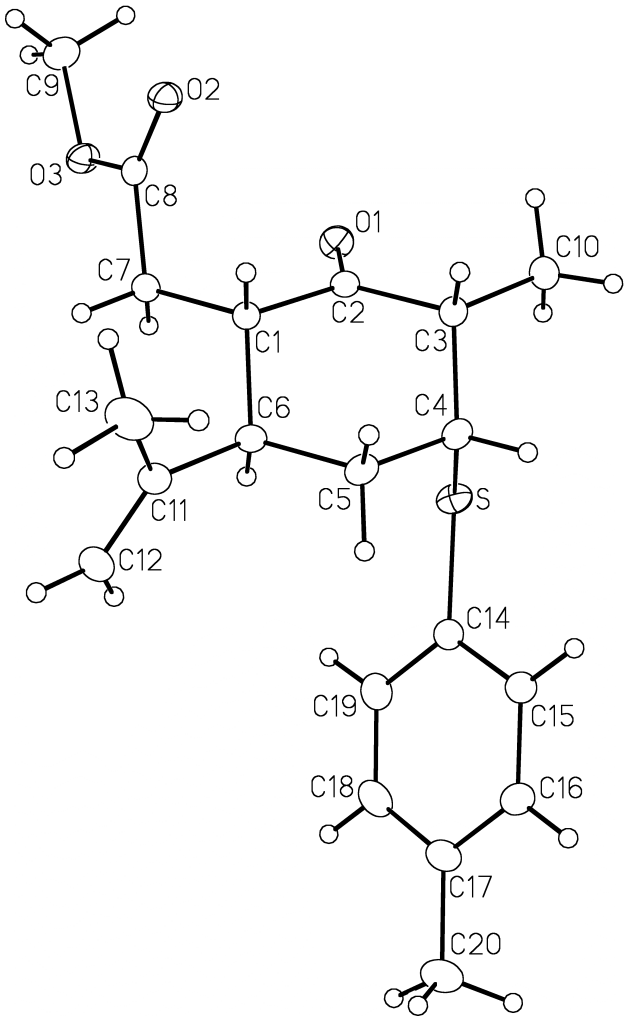
Supervisor: F. G. West **Crystallographer:** M. J. Ferguson



Compound 67

Figure Legends

Figure 1. Perspective view of the methyl {3-methyl-4-[(4-methylphenyl)sulfanyl]-2-oxo-6-(prop-1-en-2-yl)cyclohexyl}acetate molecule showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.



List of Tables

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{20}H_{26}O_3S$
formula weight	346.47
crystal dimensions (mm)	0.51 ´ 0.45 ´ 0.33
crystal system	orthorhombic
space group	$P2_12_12_1$ (No. 19)
unit cell parameters[a]	
a (Å)	10.0409 (9)
b (Å)	12.1742 (10)
c (Å)	15.6460 (13)
V (Å^3)	1912.6 (3)
Z	4
r_{calcd} (g cm^{-3})	1.203
μ (mm^{-1})	0.183
B. Data Collection and Refinement Conditions	
diffractometer	Bruker PLATFORM/SMART 1000 CCD[b]
radiation (*l* [Å])	graphite-monochromated Mo K*a* (0.71073)
temperature (°C)	–80
scan type	*w* scans (0.3°) (20 s exposures)
data collection 2*q* limit (deg)	54.94
total data collected	16673 (–12 ≤ *h* ≤ 12, –15 ≤ *k* ≤ 15, –20 ≤ *l* ≤ 20)
independent reflections	4382 (R_{int} = 0.0165)
number of observed reflections (*NO*)	4235 [$F_o^2 \geq 2s(F_o^2)$]
structure solution method	direct methods (*SHELXS–97*[c])
refinement method (*SHELXL–97*[c])	full-matrix least-squares on F^2
absorption correction method	multi-scan (*SADABS*)
range of transmission factors	0.9420–0.9124
data/restraints/parameters	4382 [$F_o^2 \geq -3s(F_o^2)$] / 0 / 220
Flack absolute structure parameter[d]	0.05(5)
goodness-of-fit (*S*)[e]	1.075 [$F_o^2 \geq -3s(F_o^2)$]
final *R* indices[f]	
R_1 [$F_o^2 \geq 2s(F_o^2)$]	0.0319

wR_2 [$F_o^2 \geq -3s(F_o^2)$]	0.0862
largest difference peak and hole	0.260 and –0.154 e Å^{-3}

[a]Obtained from least-squares refinement of 7020 reflections with 4.82° < 2q < 54.90°.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

(continued)

Table 1. Crystallographic Experimental Details (continued)

[c]Sheldrick, G. M. *Acta Crystallogr*. **2008**, *A64*, 112–122.

[d]Flack, H. D. *Acta Crystallogr*. **1983**, *A39*, 876–881; Flack, H. D.; Bernardinelli, G. *Acta Crystallogr*. **1999**, *A55*, 908–915; Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst*. **2000**, *33*, 1143–1148. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration

[e]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [s^2(F_o^2) + (0.0578P)^2 + 0.1400P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[f]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.