University of Alberta

Synthetic Studies Towards (+)-Dactylol Utilizing an Oxonium Ylide Rearrangement and Related Studies.

by

Jeffrey Robert Johnston

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For my wife Yee Chee and my daughter Jocelyn

Abstract

Dactylol is a structurally interesting sesquiterpene natural product. One of its key structural features is an the eight-membered ring. The challenges of synthesizing an eight membered ring are discussed in Chapter 1. In addition, various methods for generating an eight-membered ring are highlighted within the several discussed total syntheses of dactylol.

The West group has developed methodologies for generating eight membered rings that have utilized the rearrangement of an oxonium ylide. This method has been applied towards the total synthesis of dactylol. In Chapter 2, the previous synthetic routes as well as extensions to these routes are discussed. In addition, an advanced route towards the natural product has been developed and is examined in detail.

In our approach towards the total synthesis of dactylol, we discovered a side product during a dicyclohexylcarbodiimide esterification reaction. This side product was determined to be an imino-oxazinone. The synthesis of these heterocycles has been developed using an *in situ* generated acyl ketene, which undergoes a formal [4+2] cycloaddition with a carbodiimide. This convergent approach has been applied to several different acyl ketenes and carbodiimides and is discussed in Chapter 3.

During our studies of dactylol we became interested in the Stevens rearrangement of an oxonium ylide with an adjacent cyclopropylcarbinyl group. This rearrangement substrate has not been previously investigated and is interesting as it would give valuable mechanistic information on the Stevens rearrangement. The preliminary investigations into these compounds are discussed in Chapter 4.

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Standard List of Abbreviations

$[\alpha]_D^{20}$	specific rotation at 20 degrees Celsius and 589nm [expressed without units; the units, (deg·mL)/(g·dm), are understood]
Å	angstrom(s)
Ac	acetyl
acac	acetylacetonate
Ar	aryl
app	apparent (spectral)
aq	aqueous
Bn	benzyl
Boc	tert-butyloxycarbonyl
br	broad (spectral)
i-Bu	*iso*-butyl
n-Bu, Bu	butyl
t-Bu	tert-butyl
c	concentration (g/100 mL) for optical rotation
°C	degrees Celsius
calcd	calculated
cat	catalytic
COD	cycloocta-1,5-diene
COSY	homonuclear correlation spectroscopy
Cp	cyclopentadienyl
Cy	cyclohexyl
δ	chemical shift in parts per million downfield from tetramethylsilane
Δ	heat; difference
d	day(s); doublet (spectral)
dd	doublet-of-doublets
dba	dibenzylideneacetone

DBU	1,8-diazabicyclo[5.4.0.]undec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCU	dicyclohexylurea
DIBAL-H	diisobutylaluminum hydride
DIC	diisopropyl carbodiimide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-Dimethyltetrahydropyrimidin-2(1H)-one
DMSO	dimethyl sulfoxide
DMS	dimethyl sulfide
dppb	1,4-Bis(diphenylphosphino)butane
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact (mass spectrometry)
ESI	electrospray ionization (mass spectrometry)
Et	ethyl
eq	equation
equiv	equivalents
FT	Fourier transform
g	gram(s)
h	hour(s)
hfacac	hexafluoroacetylacetonate
HMBC	heteronuclear multiple bond coherence
HMDS	hexamethylsilazane
HMPA	hexamethyl phosphoramide
HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectrum
hν	electromagnetic irradiation
Hz	hertz

IR	infrared spectroscopy
J	coupling constant (in NMR)
kcal	kilocalorie
L	litre(s)
LiDBB	lithium 4,4’-di-*tert*-butylbiphenylide
LDA	lithium diisopropylamide
M	moles per litre
m	multiplet (spectral)
M	molar (moles per liter); mega
μ	micro
μw	microwave irradiation
M+	parent molecular ion
mCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MHz	megahertz
min	minute(s)
mmol	millimole(s)
MMPP	magnesium monoperoxyphthalate
mol	mole(s)
m.p.	melting point
Ms	mesyl; methanesulfonyl
MS	molecular sieves; mass spectrometry
m/z	mass to charge ratio (mass spectrometry)
N	normal (equivalents per liter)
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
nm	nanometers
NMO	N-methylmorpholine-N-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
Nu	nucleophile

PCC	pyridinium chlorochromate
pent	*n*-pentyl
Ph	phenyl
Piv	pivaloyl
PMB	*para*-methoxybenzyl
ppm	parts per million (spectral)
Pr	*n*-propyl
c-Pr	cyclopropyl
i-Pr	isopropyl
py	pyridine
q	quartet (spectral)
quant	quantitative yield
RaNi	Raney nickel
RCM	ring closing metathesis
R_f	retention factor (chromatography)
rt	room temperature
s	singlet (spectral); second (s)
SEM	2-(trimethylsilyl)ethoxymethyl-
t	triplet (spectral)
temp	temperature
TES	triethylsilyl
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenyl silyl
TBS	*tert*-butyldimethyl silyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl

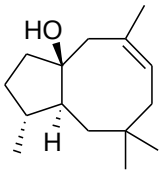
Tol	tolyl
TPAP	tetra-n-propylammonium perruthenate
Tr	trityl
TROESY	Transverse Rotating-frame Overhauser Enhancement Spectroscopy (NMR spectroscopy)
Ts, tosyl;	*p*-toluenesulfonyl

Chapter 1

Introduction

1.1 Background

Dactylol **1** is a sesquiterpene isolated from the red seaweed *Laurencia poitei*,[1] and from the Caribbean sea hare *Aplysia dactylomela*,[2] as reported in 1978 (Figure 1-1). More specifically, this small molecule was isolated from the digestive glands of the sea hare, which suggests that the sea hare obtained dactylol from consumed *Laurencia poitei,* which is most likely the actual source.[1]

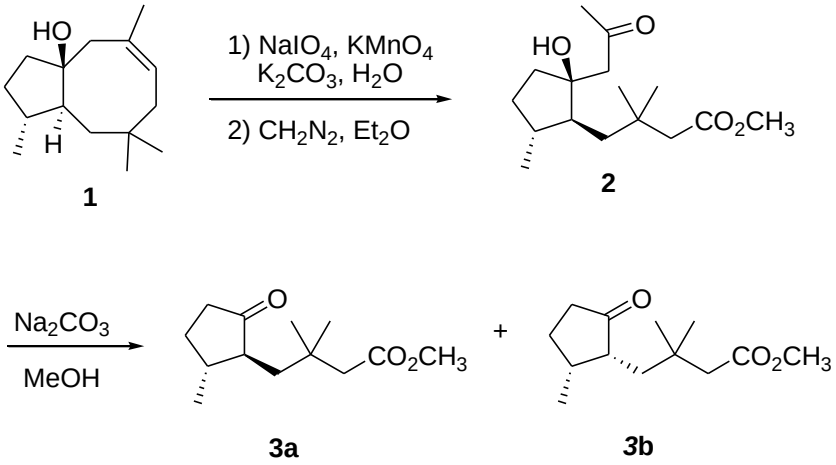


(+)-dactylol
1

Figure 1-1: The elucidated structure for (+)-dactylol.

The Schmitz group derived a partial structure for the natural product based on spectral data; however, to get the complete structure, and confirm the partial structure, they performed chemical degradation experiments (Scheme 1-1).[2] They identified an alkene within an alkyl chain so they performed an oxidative cleavage with sodium periodate and potassium permanganate. This

generated a ketoacid, which was methylated with diazomethane to form the ketoester **2**. In the presence of base, the ketoester underwent a retro-aldol reaction, resulting in an 85:15 ratio of the *trans* (**3a**) to *cis* (**3b**) cyclopentanone isomers. The structures of the products from the aforementioned reactions were elucidated and the structure of dactylol **1** was inferred based upon these degradation products.



1 **2** **3a** ***3b***

Scheme 1-1: Degradation of dactylol for structure elucidation.

To establish the absolute configuration, the circular dichroism curve was analyzed for both cyclopentanone isomers (**3a** and **3b**) and compared to those of similar structures (Figure 1-2). (*R*)-2-Methylcyclopentanone **4** and (2*R*, 3*S*)-*trans*-dimethylcyclopentanone **5** display a strong negative Cotton effect in their CD spectra, in contrast to the strong positive Cotton effect of *trans* cyclopentanone **3a**, which suggested the absolute stereochemistry as that shown in **1**. In addition, the authors mentioned that the *cis*-cyclopentanone **3b** had a

negative Cotton effect, consistent with other known compounds, also supporting their proposal. Interestingly, in 1999, the other enantiomer, (-)-dactylol, was isolated from the liverwort *Conocephalum conicum*.[3]

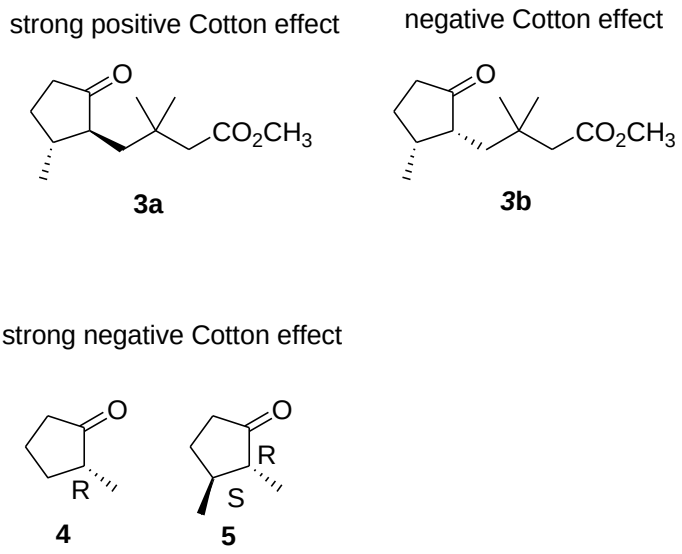


Figure 1-2: Comparison of the CD spectra results for dactylol degradation products and known cyclopentanones for absolute configuration evidence.

Currently there is only one report of biological testing for the natural product dactylol.[4] The authors reported biological studies of brown algae extracts, two of which contained (+)-dactylol. They reported that the (+)-dactylol-containing extracts inhibited the growth of several Gram-positive and Gram-negative bacteria. Also they reported that an extract containing (+)-dactylol had 94 % β-carotene bleaching inhibition. Their studies, however, did not include the testing of isolated components of the mixtures, so conclusions to the activity of (+)-dactylol cannot be established. Furthermore, neither dactylol

nor extracts containing this compound have been subjected to the extensive biological screening that is now commonplace for all newly isolated natural compounds.

1.2 Biosynthesis

Dactylol has been suggested to be biosynthetically derived from the monocyclic sesquiterpene humulene **6** (Figure 1-3).[5] There are two major conformers of humulene in equilibrium, **6** and **6'**.[6, 7] Protonation of the second

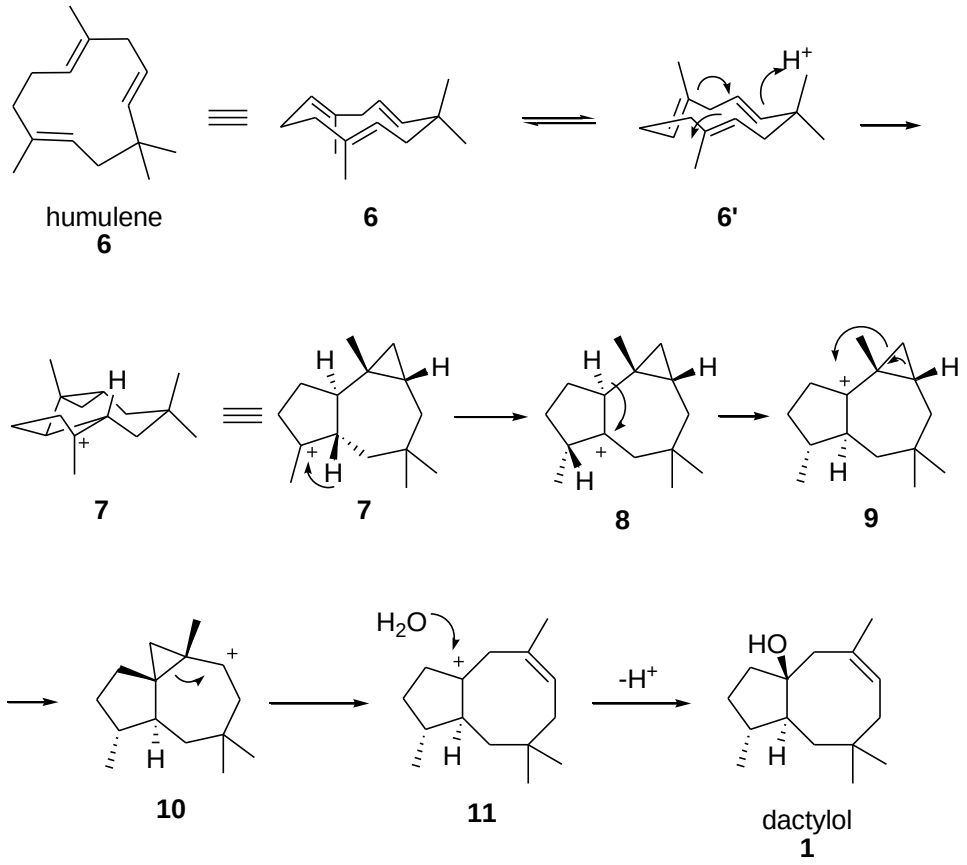


Figure 1-3: Proposed biosynthetic pathway for dactylol **1.**

conformer **6'**, followed by two olefin cyclizations, would form the 5-7-3 fused ring system **7**. Two subsequent [1,2]-hydride shifts would put the methyl and the bridgehead protons in the correct configuration in **9**. A "cyclopropane sliding reaction" followed by a ring-opening and addition of water/hydroxide ion would form the olefin and place the methyl in the correct position to form dactylol **1**.

1.3 Synthetic Challenges

Dactylol contains several structural features that pose significant synthetic challenges. The molecule contains a bicyclo[6.3.0]undecene ring system, with 3 contiguous stereogenic centers all contained within the five-membered ring (C-1, C-3a, C-9a) (Figure 1-4). Two of the stereogenic centers occur at the ring fusion, and are in a *trans* relationship (C-3a and C-9a), while one of those centers is a quaternary oxygenated carbon (C-3a). Finally, there is also a *cis* trisubstituted alkene (C-5 and C-6), and a geminal dimethyl group (C-8) found on the eight-membered ring.

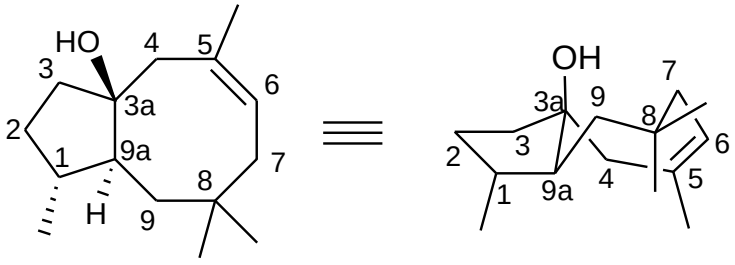


Figure 1-4: Two and three dimensional representation for dactylol.

While there are several synthetic challenges within the structure of dactylol, the most significant is the eight-membered ring. A comparison of the relative energies of the conformations of six-membered and eight-membered rings can provide a better gauge of the difficulty of eight-membered ring synthesis. The total strain energy has been calculated for several alicyclic conformers (Figure 1-5).[8, 9] Comparing that of cyclohexane to cyclooctane clearly demonstrates the additional strain of an eight-membered ring. There are three major conformers of cyclohexane with the chair (**C**) being the most stable, while the second most stable conformer, the twist boat (**TB**), is 5.6 kcal/mol higher in energy. Comparatively, the lowest energy conformation of cyclooctane is 11.1 kcal/mol, which is 10 kcal/mol higher than the chair conformer of cyclohexane. Of the six major conformers of cyclooctane, the four most stable are within 1.9 kcal/mol of each other. This small energy difference makes it

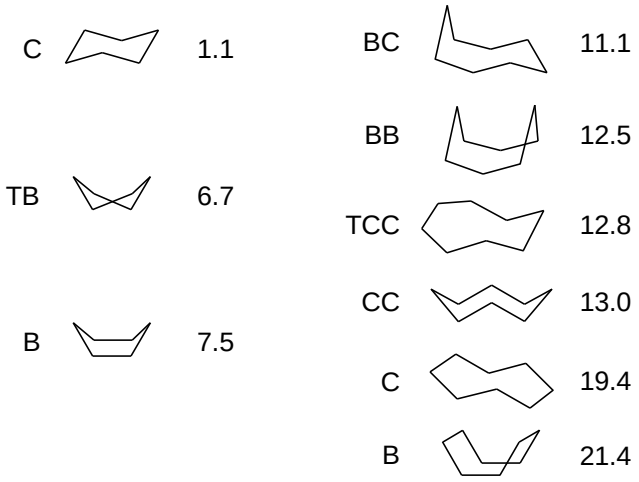
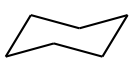
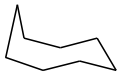


Figure 1-5: Low energy conformations and energy (kcal/mol) for cyclohexane (left) and cyclooctane (right).

difficult to predict the conformation of a cyclooctane intermediate in any given reaction, which is why it has been called the "conformationally most complex cycloalkane".[9] The difficulty associated with predicting cyclooctane conformations consequently makes it difficult to predict the stereochemical outcome of various reactions.

Comparing the components of the strain energy between the most stable conformer of cyclooctane and cyclohexane can provide specific reasons for the large energy difference. The calculated most stable conformer of cyclooctane, the boat chair conformation (**BC**), was found to have angle strain 3 kcal/mol higher than the chair conformer of cyclohexane (Table 1-1). The torsional strain was found to be almost 5 kcal/mol higher, while the sum of nonbonding interactions, which include carbon-carbon, carbon-hydrogen and hydrogen-

Table 1-1: Conformational energy contributors (kcal/mol) for the chair conformation of cyclohexane and the boat-chair conformation of cyclooctane.

			Difference in Energy (kcal/mol)
angle strain	0.02	3.36	3.34
torsional strain	0.34	5.22	4.88
nonbonding interactions	0.71	2.52	1.81
sum of strain energy	1.08	11.10	10.02

hydrogen interactions, was found to be 1.8 kcal/mol higher in energy than cyclohexane. The sum of the strain energies was therefore found to be 10 kcal/mol higher than cyclohexane, as mentioned previously.

The calculations mentioned above have been supported by synthetic studies that monitored the ring closure rates of several malonate derivatives.[10, 11] The rate for the eight-membered ring formation of **15** was more than three orders of magnitude slower than that for the six-membered ring **13** at 25 °C (Figure 1-6). Additionally, the yield of the reaction forming the eight-membered ring **15** was only 13 % compared to a quantitative yield for that of the six-membered ring **13**. These data clearly demonstrate the unique difficulties associated with forming eight-membered rings by conventional closure of acyclic 1,8-bifunctional precursors.

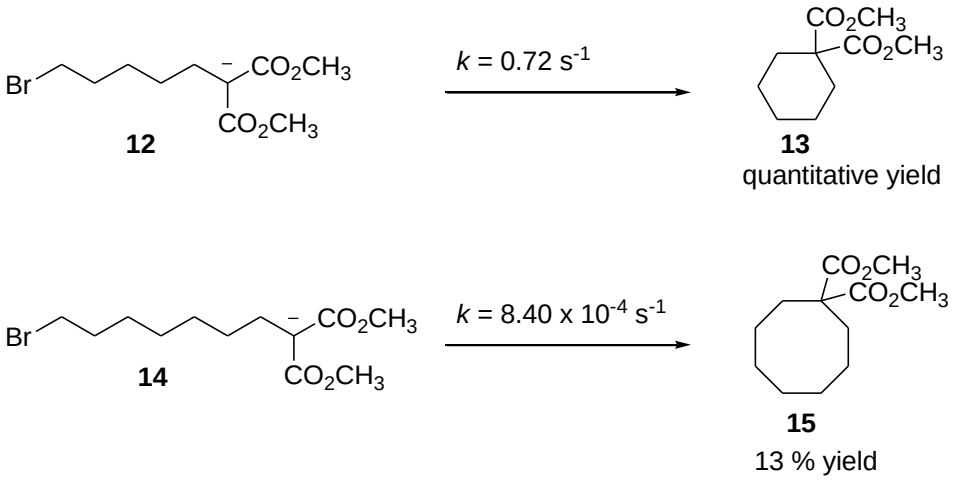


Figure 1-6: Example of cyclization rates for a ring-closing reaction forming a six- and an eight-membered ring.

Transannular reactivity is also a major problem with the synthesis of functionalized eight-membered rings. Cyclooctanoids have been shown to have significant transannular interactions, which can be seen in comparing the carbon chemical shifts of several cyclooctanones to those of analogous cyclohexanones (Figure 1-7).[12] Substitution of a methylene in **16** with an amine (**17**) in a cyclohexanone ring system had very little effect on the chemical shift (3 ppm) of the carbonyl carbon, suggesting little or no interaction of the nitrogen lone pair electrons with the π* orbitals of the ketone. Looking at the cyclooctanone case, however, the authors observed a much more significant chemical shift difference of 9 ppm between **18** and **19,** attributed to the shielding of the ketone in **19** by the interaction with the amine. It should be noted that this experiment does not rule out the possibility that a different geometry, imposed by the substitution of the amine for the methylene, affecting the various strain energies of the eight-membered ring causing a change in the ^{13}C chemical shifts in **19**.

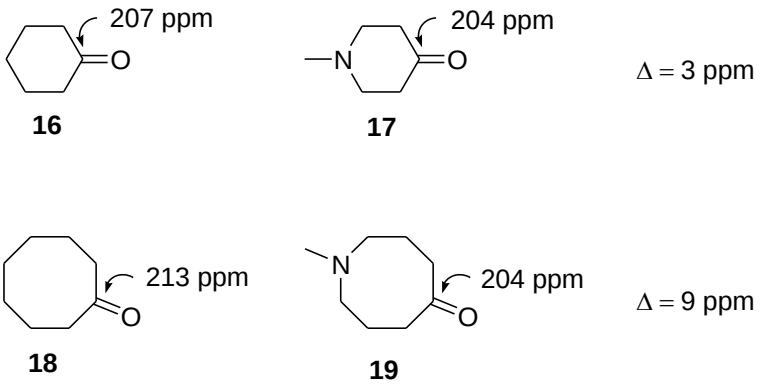


Figure 1-7: The chemical shift differences of similar ketones.

Another ^{13}C-NMR observation was reported that compared differently substituted cyclooctanes, in particular the chemical shifts of exocyclic alkenes and ketones located on opposite sides of cyclooctane.[13] Bishop observed that the diketone **22** had a chemical shift difference of 5 ppm compared to the monoketone **18,** although this could be partly due to a difference in the ring geometry. The geometry of the diketone **22** and the methylene ketone **21** should be more comparable and this had a chemical shift difference of 3 ppm. Because the ketone is remote from the methylene the change in chemical shift is attributed to through space interactions from across the ring. More specifically the chemical shift difference might be the effect of anisotropy or orbital overlap from the methylene interacting with the ketone.

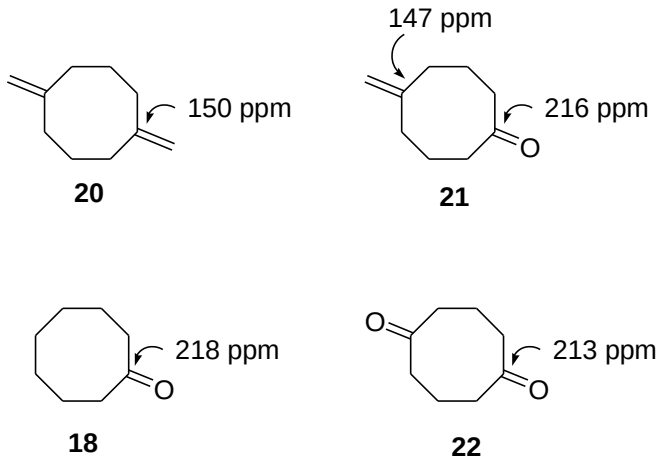
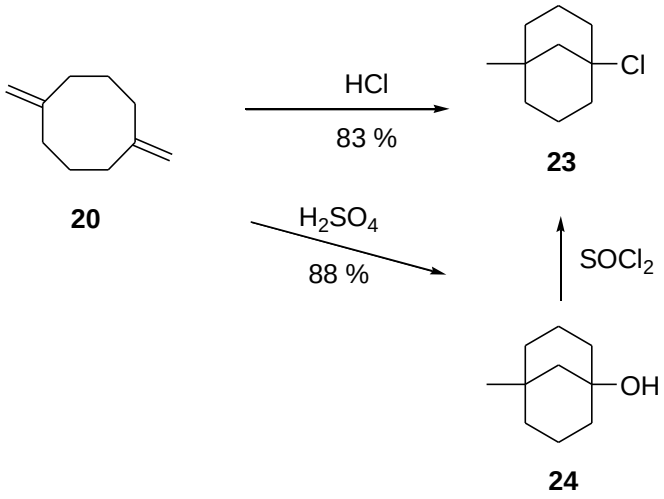


Figure 1-8: ^{13}C NMR chemical shifts of functional groups in cyclooctanes.

1,5-Methylidenecyclooctane **20** also underwent processes that demonstrated a strong propensity for transannular reactivity (Scheme 1-2).[14, 15] In the presence of hydrochloric acid one of the methylenes of **20** was protonated,

followed by attack of the remote methylene, forming a cation that was trapped by chloride to form **23**. The same reaction occurred in the presence of sulfuric acid, with the exception of water trapping the final carbocation to form **24**. Both of the products were formed in very good yields of 83 and 88 % for the respective hydrochloric acid and sufuric acid reactions. To provide additional confirmation of the structure, the bicyclic alcohol **24** was converted to the bicyclic chloride **23** with thionyl chloride. Efficient transannular cyclization in these cases nicely demonstrated the favorability of such processes; however, these observations indicate the potential pitfalls that might be encountered in a synthetic sequence employing intermediates with reactive functionality exposed across an eight-membered ring.



Scheme 1-2: Transannular reactions of cyclooctane **20**.

Dactylol is a structurally interesting sesquiterpene natural product. The relatively small size of the natural product makes it an excellent proving ground for testing interesting, unconventional methodologies that form cyclooctanes. A

synthetic strategy must also encompass the various structural features attached to the cyclooctane. As an added challenge, once the eight-membered ring is made, the multiple conformations make selective functionalization difficult to predict. And lastly, because of the propensity for transannular reactions, one must be careful of their choice of functional groups and reaction conditions utilized.

1.4 Shirahama and Matsumoto Synthesis (1985)

Shirahama and Matsumoto undertook the synthesis of dactylol to provide evidence for their proposed biosynthetic pathway. They decided to intercept the biosynthetic pathway with africanol **25,** which closely resembles the cation **9,**

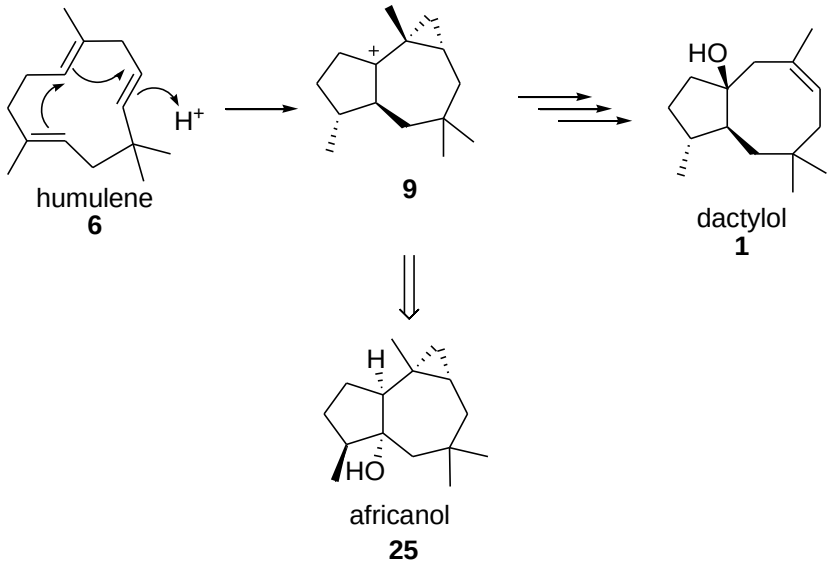
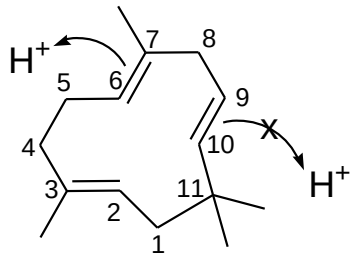


Figure 1-9: Similarities between the dactylol biosynthetic intermediate **9** and africanol **25**.

and synthesize africanol **25** from humulene **6** (Figure 1-9).[5] The biosynthetic route begins with the protonation of the humulene C-9, C-10 alkene (Figure 1-10). This could not be directly probed because protonation of **6** occurs exclusively at the C-6, C-7 olefin.[16-21]

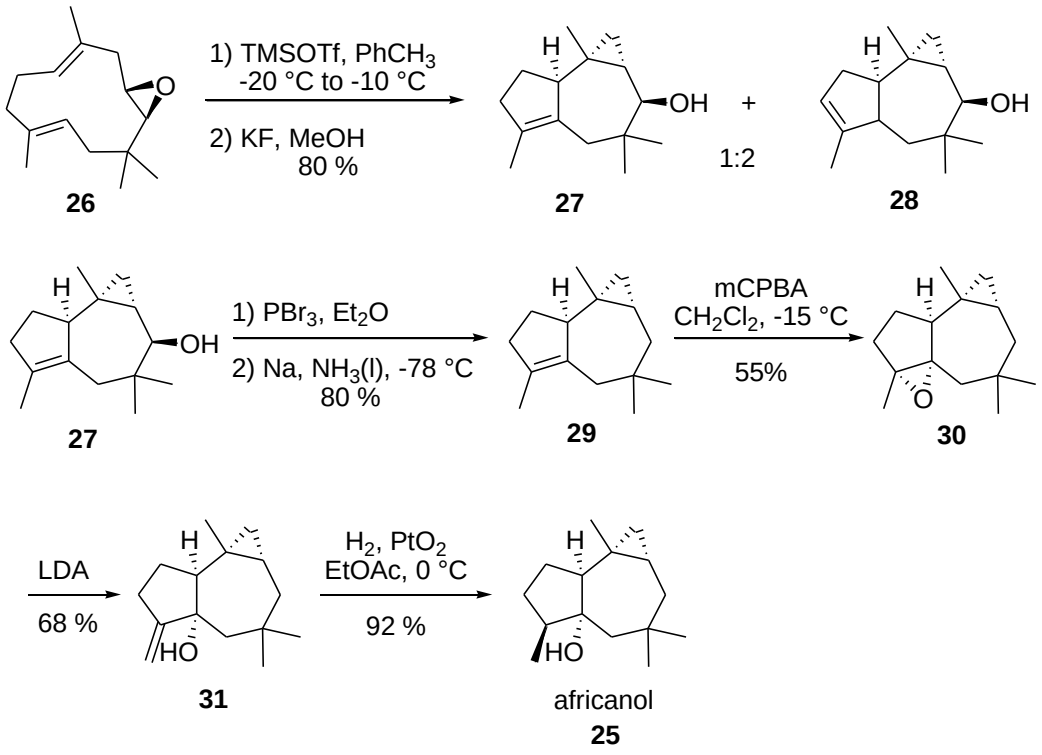


humulene
6

Figure 1-10: The required protonation initiation for biosynthetic cascade at C10 and experimentally observed protonation at C6.

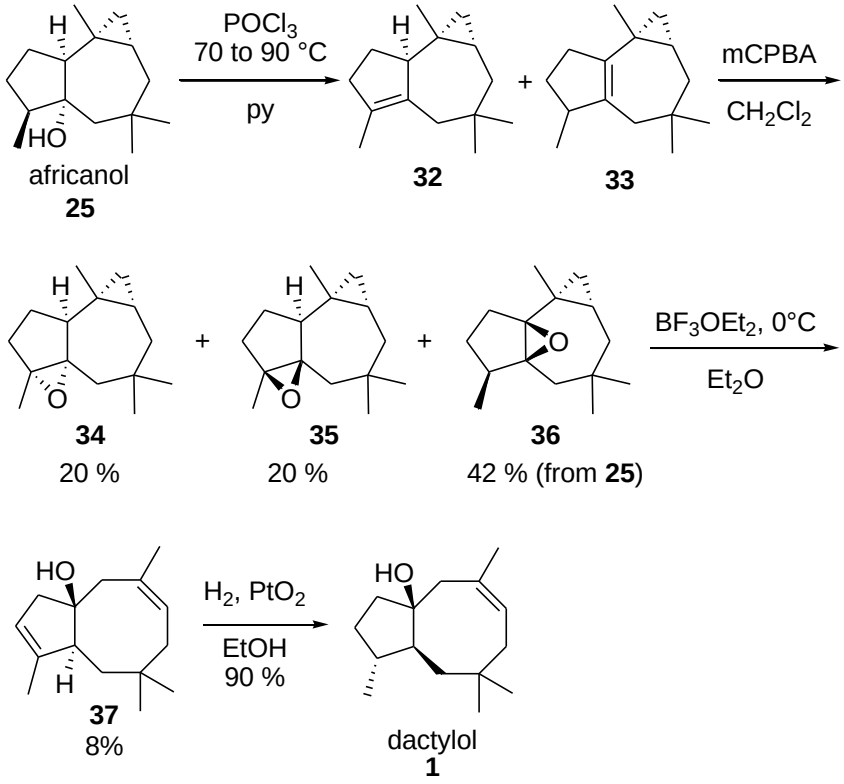
Because of the difficulty to achieve the required protonation they decided to begin their synthesis with epoxide **26**, a compound whose principal conformers mimic those of humulene (Scheme 1-3).[16] Treatment of epoxide **26** with trimethylsilyl triflate initiated an epoxide ring-opening/cationic cyclization leading to the requisite 5-7-3 ring system in **27**. This fascinating cascade process furnished two challenging rings, a cycloheptane and a cyclopropane, in a single transformation. Unfortunately, elimination α to the intermediate tricyclic carbocation occured in two directions generating a product mixture of 1:2 in favor of the undesired product. The silyl group was removed with potassium

fluoride to give the free alcohols **27** and **28** in an 80 % yield over two steps. Removal of the alcohol in **27** was accomplished by conversion to the bromide and subsequent dehalogenation by dissolving metal reduction, forming **29** in an overall yield of 80 %. Upon treatment of **29** with mCPBA, a mixture of epoxides was formed from which the desired epoxide **30** could be isolated in 55% yield. Eliminative opening of the epoxide with LDA furnished exocyclic olefin **31** in 68% yield. Stereoselective hydrogenation with Adams' catalyst introduced the methyl branch in the correct configuration to generate africanol **25** in 92% yield.



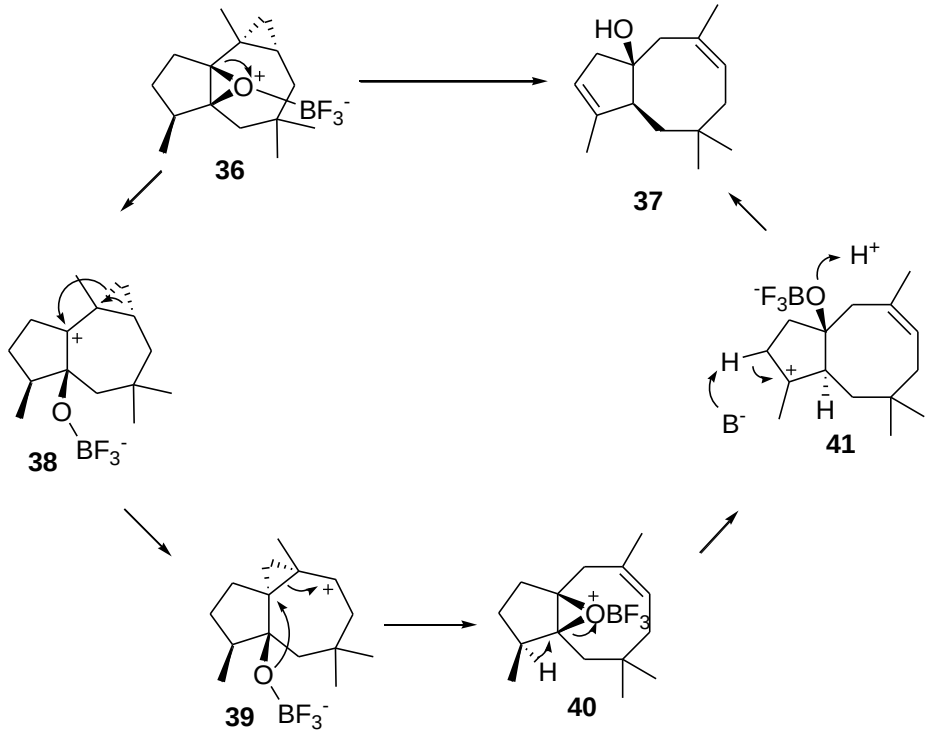
Scheme 1-3: Shirahama and Matsumoto synthesis of africanol **25.**

Dehydration of africanol **25** with phosphorus oxychloride formed a mixture of the two tetrasubstituted olefins **32** and **33**, which was subsequently epoxidized to generate a mixture of isomers **34**, **35**, and **36** in 82 % yield from **25** (Scheme 1-4).[5] The product **36**, isolated in 42 % yield, was then subjected to boron trifluoride. In an outstanding cascade of events the eight-membered ring was formed with the correct relative configuration at the 5-8 ring junction. Selective hydrogenation of **37** gave a compound with identical spectral data to the natural product dactylol **1**.



Scheme 1-4: Synthetic conversion of africanol **25** to dactylol **1.**

The mechanism of the rearrangement cascade warrants discussion. After the Lewis acid opens the epoxide to generate **38** the biosynthetically inspired cyclopropane sliding reaction can occur, effectively moving the cyclopropane to the bridgehead position to form **39** (Scheme 1-5). Cyclopropylcarbinyl–homoallyl rearrangement would then result in a ring-expansion, followed by subsequent closure of the nearby alcohol to reform the epoxide in **40**. The ring-expansion process installs the methyl group and cyclooctene olefin in the correct positions needed for dactylol. Epoxide opening of **40** in the opposite sense would then form a new bridgehead carbocation that is neutralized by a [1,2]



Scheme 1-5: Proposed mechanism of the rearrangement cascade generating dactylol **1.**

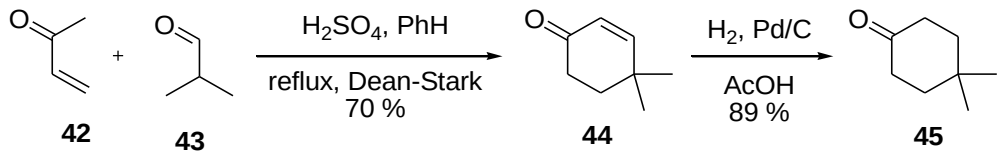
hydride shift to generate **41**. Finally, elimination and protonation would generate **37.** Importantly, although the configuration at the secondary methyl branch of africanol is lost during this process, the stereochemical information is relayed to the adjacent bridgehead carbon through a stereoselective 1,2-hydride shift.

Overall, this total synthesis may not have been the most efficient route to dactylol due to several low yielding steps and a number of selectivity issues. It does, however, provide support for the authors' biosynthetic proposal by demonstrating that humulene and africanol may serve as chemical precursors to dactylol. Most importantly it gives evidence for the proposed and unique cyclopropane sliding reaction.

1.4.1 Paquette Formal Synthesis (1985)

Paquette and coworkers reported a formal synthesis of dactylol,[22, 23] utilizing the final steps performed by Shirahama, Matsumoto and coworkers.[5] Rather than using the biosynthetic precursor humulene, the Paquette group set out to prepare the key tricyclic intermediate using a de novo route starting from 4,4-dimethylcyclohexanone.

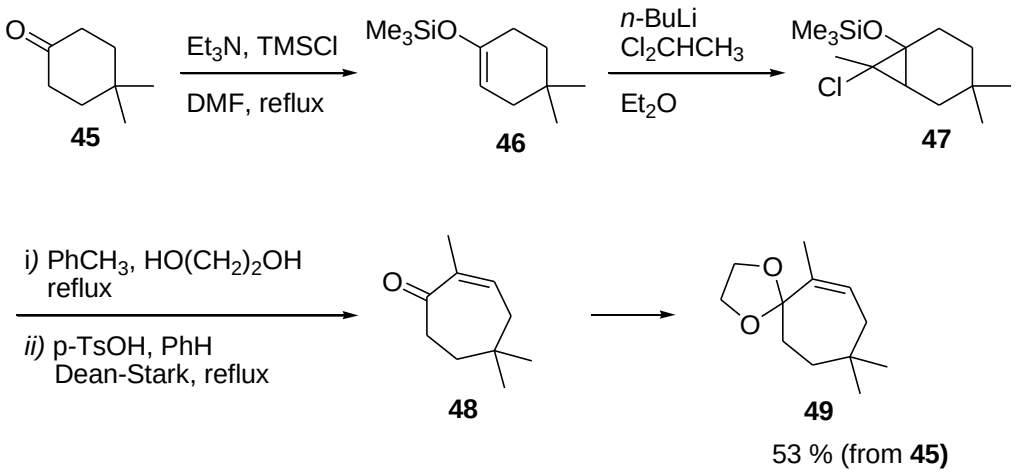
Dimethyl cyclohexanone **45**, while currently commercially available, is a rather expensive starting material when considering a multi-step synthesis (Scheme 1-6). Alternatively, this material can be synthesized in good yield over two steps by coupling inexpensive isobutyraldehyde **43** and methyl vinyl ketone **42** in refluxing benzene and sulfuric acid, followed by hydrogenation of the resulting enone.[24, 25] This synthesis allowed the Paquette group to obtain the desired dimethyl cyclohexanone in large quantities.



42 **43** **44** **45**

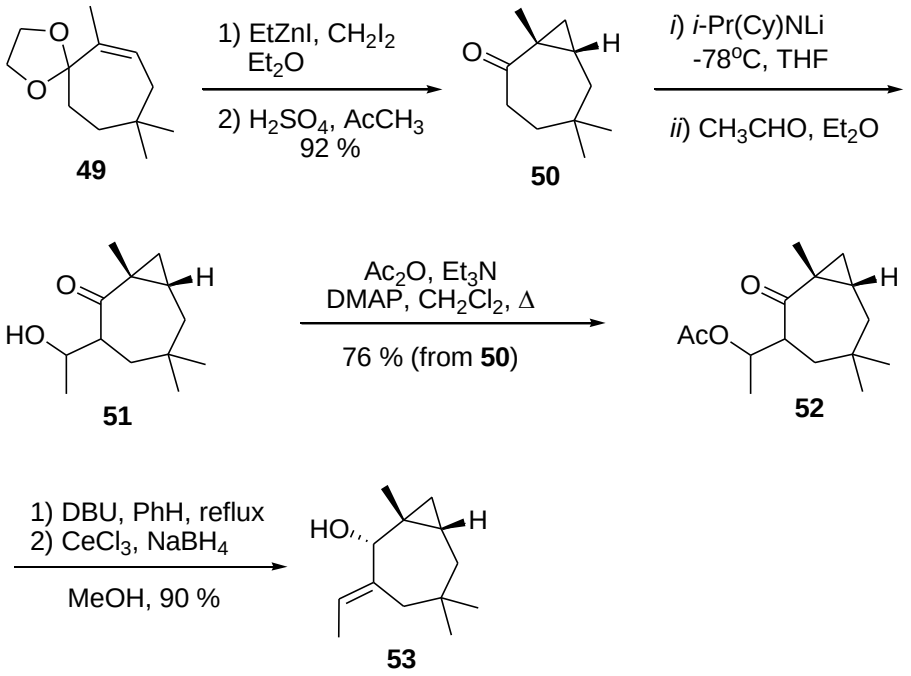
Scheme 1-6: Synthetic route for starting material **45.**

With cyclohexanone **45** in hand, the Ohio State team converted it to the trimethylsilyl enol ether **46**, which was then cyclopropanated with chloromethyl carbene, generated in situ by treatment of 1,1-dichloroethane with butyllithium, to give **47** (Scheme 1-7). Heating of this halocyclopropane **47** effected a ring-expansion to afford cycloheptenone **48**, which was then protected as the acetal to generate **49** in 53% yield overall from **45**.



Scheme 1-7: Synthesis of cycloheptenone ketal **49.**

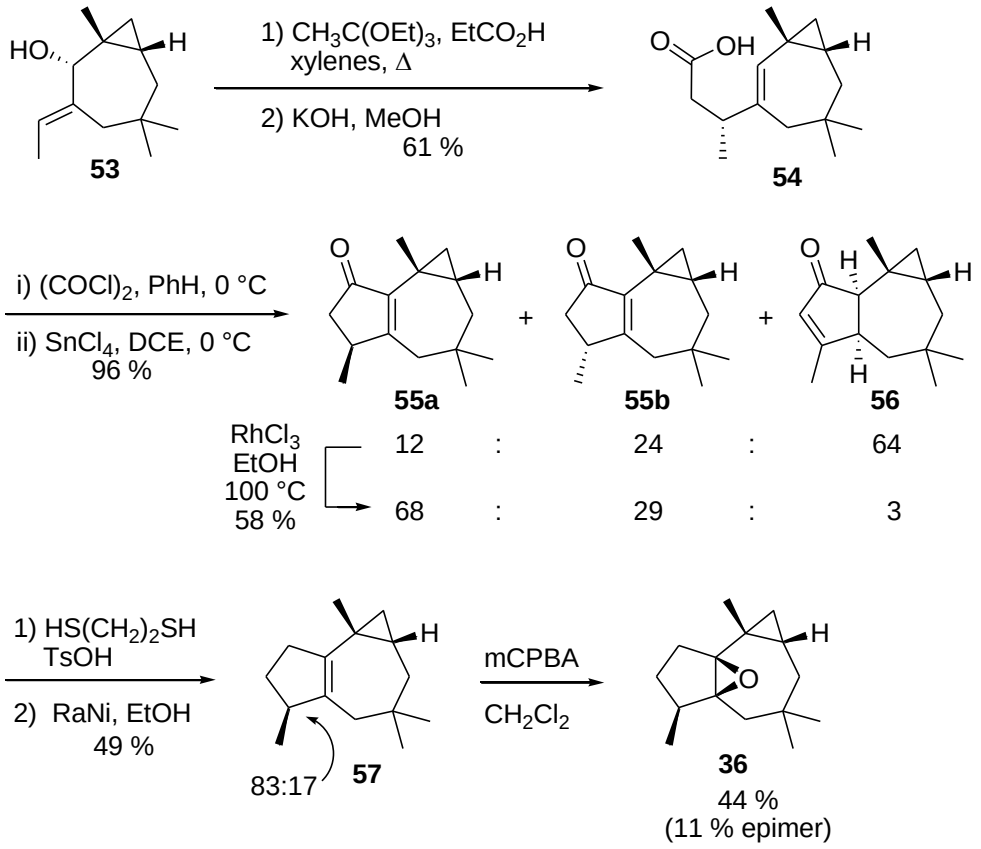
Cyclopropanation of the alkene **49** via Simmons-Smith reaction, followed by deprotection of the ketal with sulfuric acid, generated the desired cyclopropyl ketone **50** in 92 % yield (Scheme 1-8). An aldol reaction produced an isomeric mixture of alcohols **51** that were acetylated with acetic anhydride to afford **52** in 76 % yield over two steps. The acetate was then eliminated with DBU in refluxing benzene to afford the exocyclic ethylidene group as a single geometrical isomer, and the ketone was then stereoselectively reduced under Luche conditions to the allylic alcohol to generate **53** in 90 % yield over two steps. Dehydration of the initial aldol adduct **51** under acidic conditions without resorting to the acetate was also possible, but did not prove to be scalable.



Scheme 1-8: The Paquette group's synthesis of alcohol **53.**

The stereochemistry of the alcohol in **53** was important as it would be transferred by a Johnson-Claisen rearrangement (Scheme 1-9). In the event, the allylic alcohol **53** was treated with triethyl orthoacetate with a trace of propionic acid in refluxing xylenes, effecting stereospecific C–C bond formation via a [3,3]-shift. The ester was saponified to afford the carboxylic acid **54** in a two-step yield of 61%. While the stereochemistry of the cyclopentyl methyl group was in the correct configuration for dactylol, it was opposite of that found in the Shirahama and Masumoto synthetic intermediate. Although it would theoretically be possible to obtain the opposite configuration by inverting the allylic alcohol stereochemistry, this proved to be unnecessary based on subsequent steps. The carboxylic acid **54** was converted to the acyl chloride

which, after subjection to tin chloride, underwent Friedel–Crafts acylation. Although the yield for the acylation was excellent, at 96 %, three different products, **55a**, **55b**, and **56**, were formed in a ratio of 12:24:64, respectively, in which the desired enone **55a** was the minor product. The authors mentioned that this ratio could be improved by heating with rhodium(III) chloride in ethanol, which improved the ratio to 68:29:3 in favour of the desired epimer **55a**; however, they did not use this improved mixture in the synthetic sequence towards dactylol. They instead carried forward the mixture containing the enone **55a** as the minor product. The ketones were reduced to a methylene by a thioketalization/Raney-Nickel reduction sequence. Surprisingly the outcome was the isolation of a 83:17 ratio of methyl epimers in 49 % yield with the major component being the desired epimer **57**. Epoxidation of the alkene generated the intermediate **36** utilized in the Shirahama and Matsumoto synthesis. This intermediate can be converted into dactylol in two steps, thus completing the formal synthesis by the Paquette group.

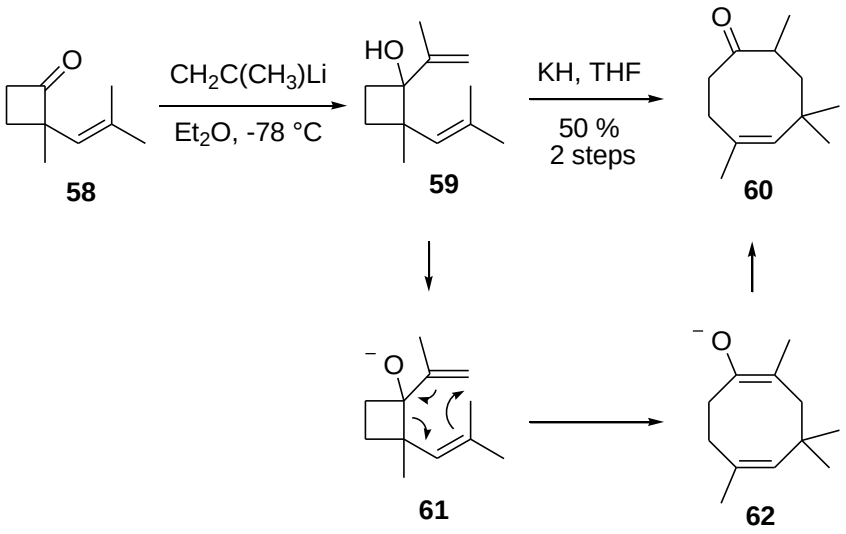


Scheme 1-9: The conclusion of the Paquette group's formal synthesis of dactylol with the synthesis of **36.**

1.4.2 Gadwood Total Synthesis (1985)

The Cope rearrangement has been found to proceed at lower temperatures when combined with a cyclobutane ring opening.[26-31] Gadwood and Lett advanced this method by applying it to an analogous oxy-Cope rearrangement for the synthesis of cyclooctanoids.[32] Addition of an alkenyl Grignard reagent into the cyclobutyl ketone **58** generated the desired

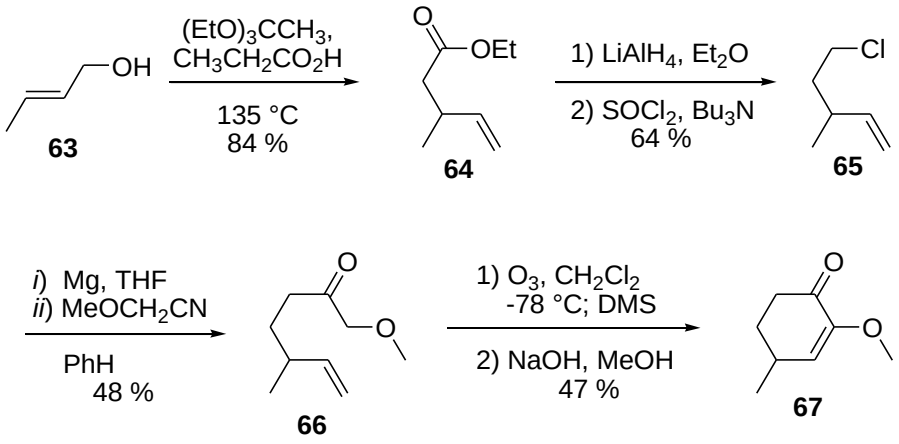
divinylcyclobutane **59** which, when deprotonated at room temperature to form **61**, underwent rapid ring-expansion by [3,3]-shift to form cyclooctenone product **60** after tautomerization. The advantage of this route was that several different alkenyl Grignard reagents could be added into the ketone, providing diverse products. This method takes advantage of a strained cyclobutane to reduce the activation barrier for the oxy-Cope rearrangement by raising the ground-state energy of the starting material.



Scheme 1-10: A methodology developed by the Gadwood group employed in the synthesis of cyclooctane **60.**

The total synthesis by the Gadwood group began with crotyl alcohol **63** (Scheme 1-11). Treatment with triethyl orthoacetate and catalytic propionic acid at 135 °C generated the desired Johnson-Claisen rearrangement product **64** in 84 % yield. Reduction of the ester and treatment of the resulting alcohol with

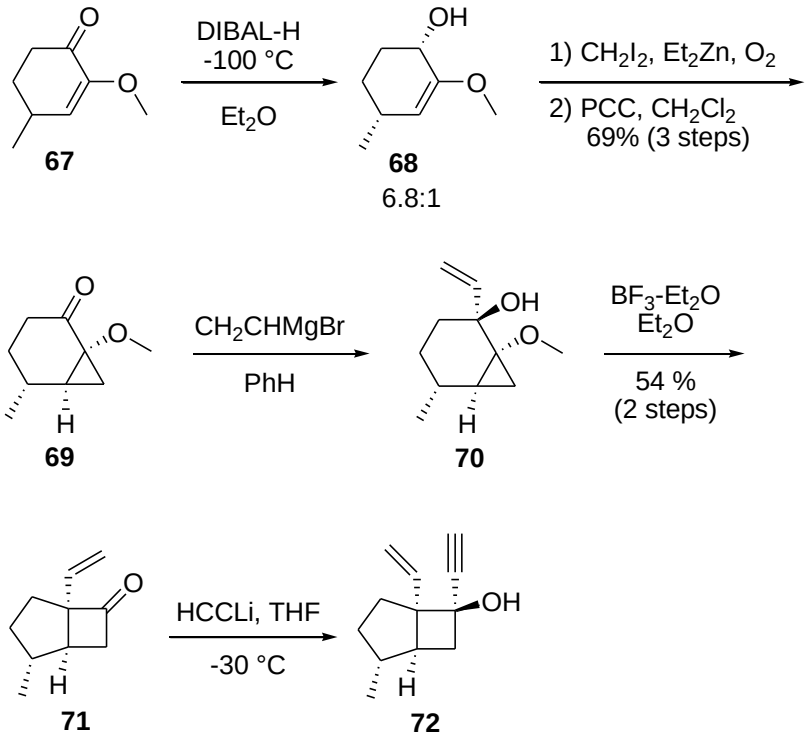
thionyl chloride afforded the corresponding primary chloride **65** in an overall yield of 64%. The chloride was converted into a Grignard reagent and subsequently added into methoxyacetonitrile which, after hydrolysis, formed the desired ketone **66** in 48 % yield. The terminal olefin was oxidatively cleaved to give an aldehyde which, in the presence of base, formed the cyclohexenone **67** in 47 % yield.



Scheme 1-11: Synthesis of enone **67** from crotyl alcohol **63.**

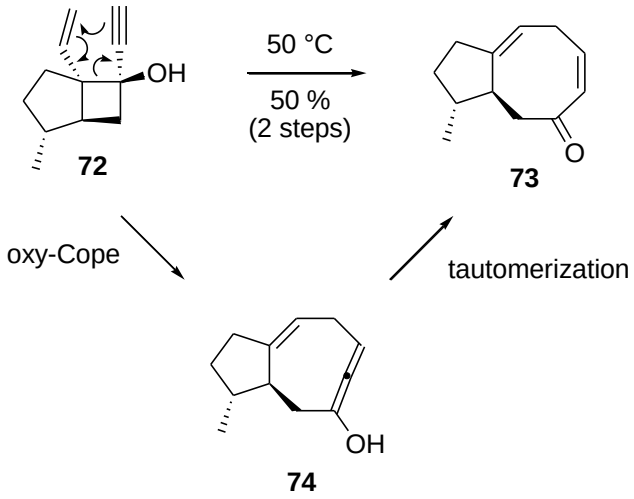
Next, a stereoselective cyclopropanation was required. To achieve this, the Gadwood group decided to perform a hydroxyl-directed cyclopropanation. The ketone in **67** was temporarily reduced to an inseparable mixture of alcohols **68** which, after Simmons-Smith cyclopropanation, generated a 6.8:1 ratio of products epimeric at the methyl group (Scheme 1-12). The major isomer was oxidized with PCC to produce the cyclopropyl ketone **69** in a 69 % yield over three steps. Addition of vinylmagnesium bromide into the ketone (**69**) generated

the allylic alcohol **70** that, in the presence of boron trifluoride etherate, rearranged to the desired 5-4 bicyclic ketone **71** in an overall yield of 54 % over two steps. Subsequent addition of lithium acetylide into the ketone generated the alcohol **72** which was the key substrate for the formation of the cyclooctane ring.



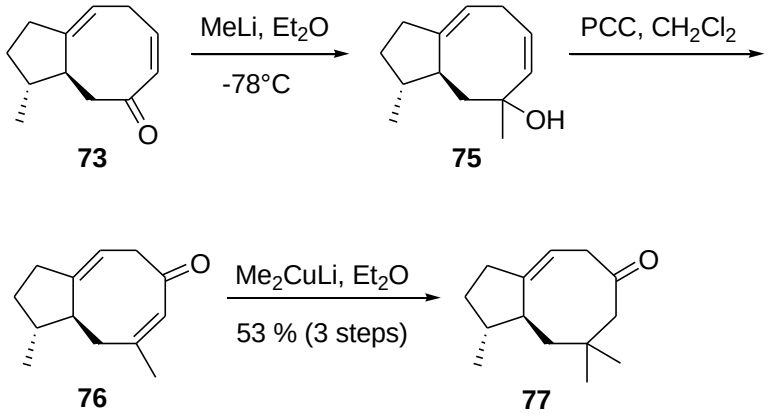
Scheme 1-12: The synthesis of key substrate **72.**

Enyne **72** was heated to 50 °C, initiating the oxy-Cope rearrangement which, after tautomerization of **74**, produced cyclooctadienone **73** in 50 % yield over two steps (Scheme 1-13). Next, the 1,2-addition of methyllithium to enone intermediate **73** afforded tertiary allylic alcohol **75**, which after oxidation with allylic inversion furnished dienone **76** (Scheme 1-14). Conjugate addition of



Scheme 1-13: Key rearrangement mechanism for cyclooctane **73.**

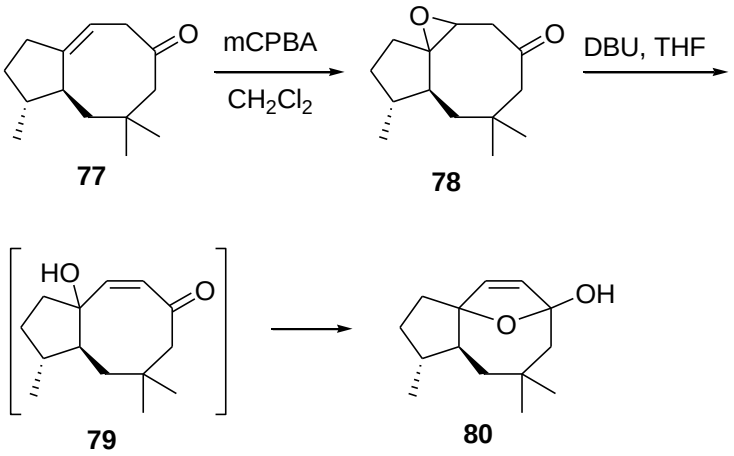
lithium dimethylcuprate into the enone gave the desired geminal dimethyl product in 53 % yield over three steps.



Scheme 1-14: The introduction of geminal dimethyl group into **73.**

At this stage in the route, the bridgehead oxygenation needed for the angular hydroxyl group in dactylol needed to be introduced. After several

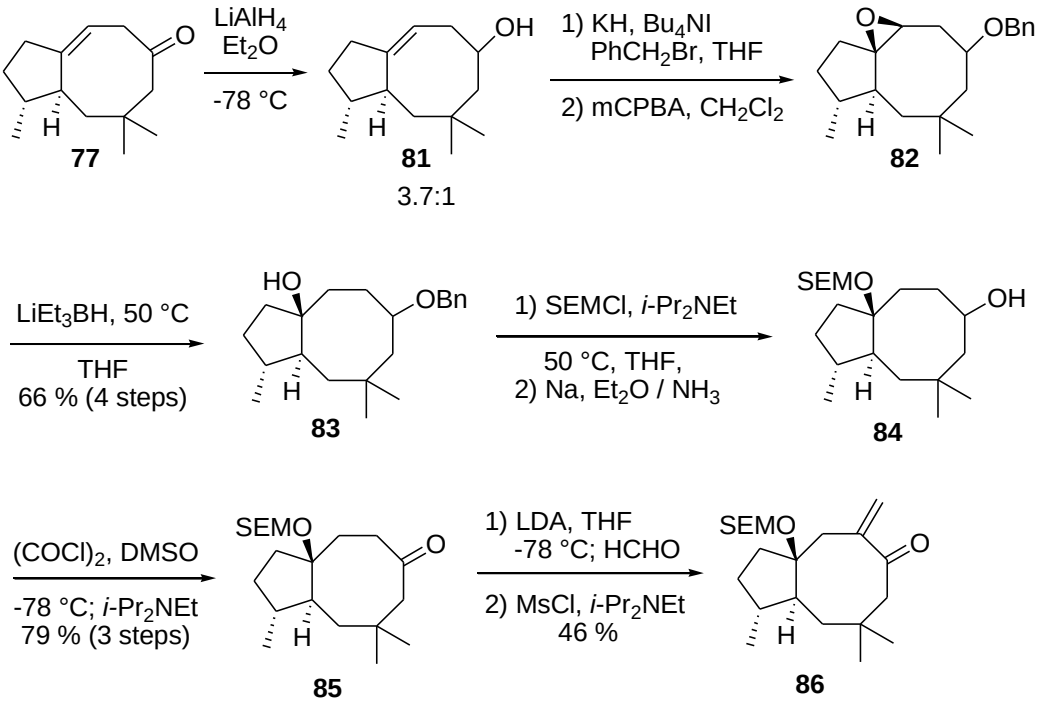
unsuccessful attempts to hydrate the alkene **77**, the authors found that epoxidation to generate **78** was an effective way to introduce oxygenation (Scheme 1-15). Eliminative opening of the epoxide could be achieved with DBU; however, the only product isolated was the hemiketal **80**. Attempts to revert the hemiketal to its isomeric hydroxyketone **79** with concomitant protection proved to be ineffective. The formation of this intractable intermediate was an unfortunate consequence of the transannular reactivity commonly observed with eight-membered rings.



Scheme 1-15: A transannular reaction forming terminal side product **80.**

Due to the difficulties encountered with the undesired reactivity involving the angular hydroxyl group the authors were forced to approach dactylol from a different angle. To avoid a ketone and an alcohol in the cyclooctene ring protecting groups were needed. The ketone **77** was reduced with lithium aluminum hydride, forming a mixture of isomers **81** in a 3.7:1 ratio (Scheme 1-16). This reduction was found to be less selective with DIBAL-H,

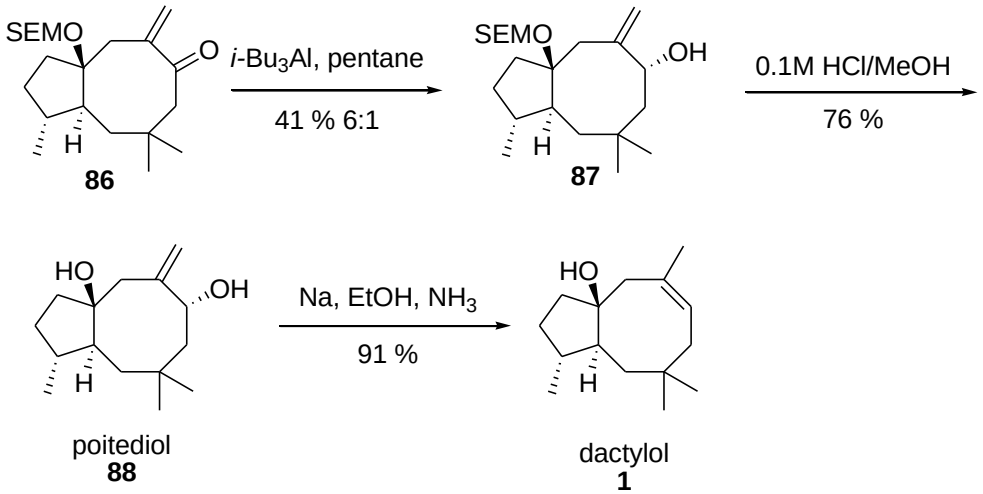
and gave the opposite selectivity with reduction by lithium in ammonia. Attempts to epoxidize the homoallylic alcohol **81** using several different sets of conditions was found to either be ineffective or produced the wrong stereoisomer. By first protecting the alcohol as its benzyl ether, the essential epoxide **82** could be formed. The epoxide was then reductively opened with Super-Hydride® to generate the required alcohol **83** in an excellent yield of 66 % over 4 steps. After protection of the bridghead alcohol the benzyl protecting group was removed using sodium in ammonia to generate **84**. Oxidation of the secondary alcohol under Swern oxidation conditions generated the ketone **85** in 79 % yield over three steps. In this case, having the alcohol protected allowed the free ketone to



Scheme 1-16: The synthesis of enone **86** from cyclooctenone **77.**

be formed without the occurrence of transannular hemiketalization. Next, an exocyclic methylene group was installed by regioselective aldolization using formaldehyde, followed by conversion of the alcohol to a mesylate and elimination to form **86**.

Reduction of the ketone **86** with tri-*i*-butylaluminum generated the alcohol in a 6:1 ratio of epimers **87** in favour of the geometry found in the natural product poitediol **88 (**Scheme 1-17**)**. Deprotection of the SEM ether was carried out with hydrochloric acid to generate poitediol **88** in 76 % yield. Notably poitediol **88** differs from dactylol **1** only by an additional alcoholic stereogenic center and an isomeric alkene. Otherwise poitediol contains all the correct stereogenic centers and rings found in dactylol. Finally, deoxygenation



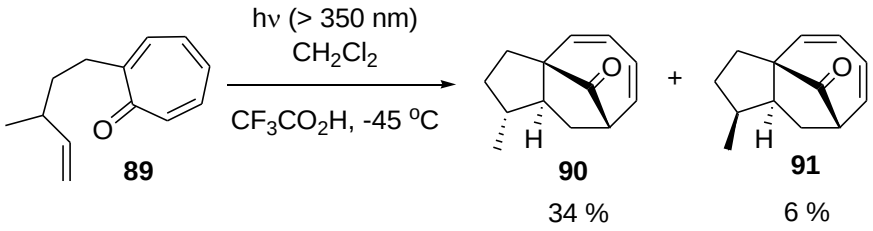
Scheme 1-17: The final step to synthesize natural products poitediol **88** and dactylol **1.**

of the allylic alcohol under Birch conditions generated the trisubstituted alkene to afford the natural product dactylol **1** in 91 % yield.

After being plagued by multiple selectivity and transannular reactivity issues during their original route, the Gadwood group had to resort to a multistep detour involving several protection schemes in order to ultimately produce dactylol. In addition, the Gadwood group faced a lengthy synthesis of the intermediates early in the synthesis. Despite these difficulties, the Gadwood group was the first to report the total syntheses of the natural products dactylol and poitediol. Gadwood's report on the synthesis of dactylol was received only the month before the total synthesis reported by Shirahama and Matsumoto.

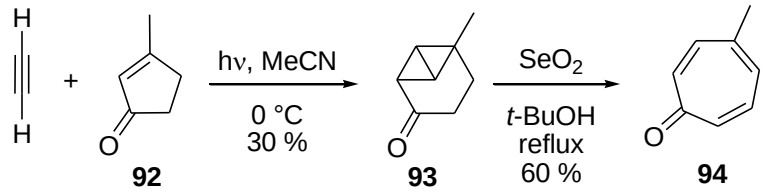
1.4.3 Feldman Total Synthesis (1990)

The Feldman group had previously reported new methodology involving the intramolecular [6+2]-photocycloaddition of a tropone and a pendent alkene.[33] Remarkably, when a methyl group was included in the tether (**89**) the major product **90** of this cycloaddition contained the correct relative stereochemistry of all three stereogenic centers in dactylol (Scheme 1-18). With the ability to form the skeleton for dactylol they set to synthesize the natural product.



Scheme 1-18: The Feldman methodology for making the bicyclo[6.3.0]undecene skeleton.

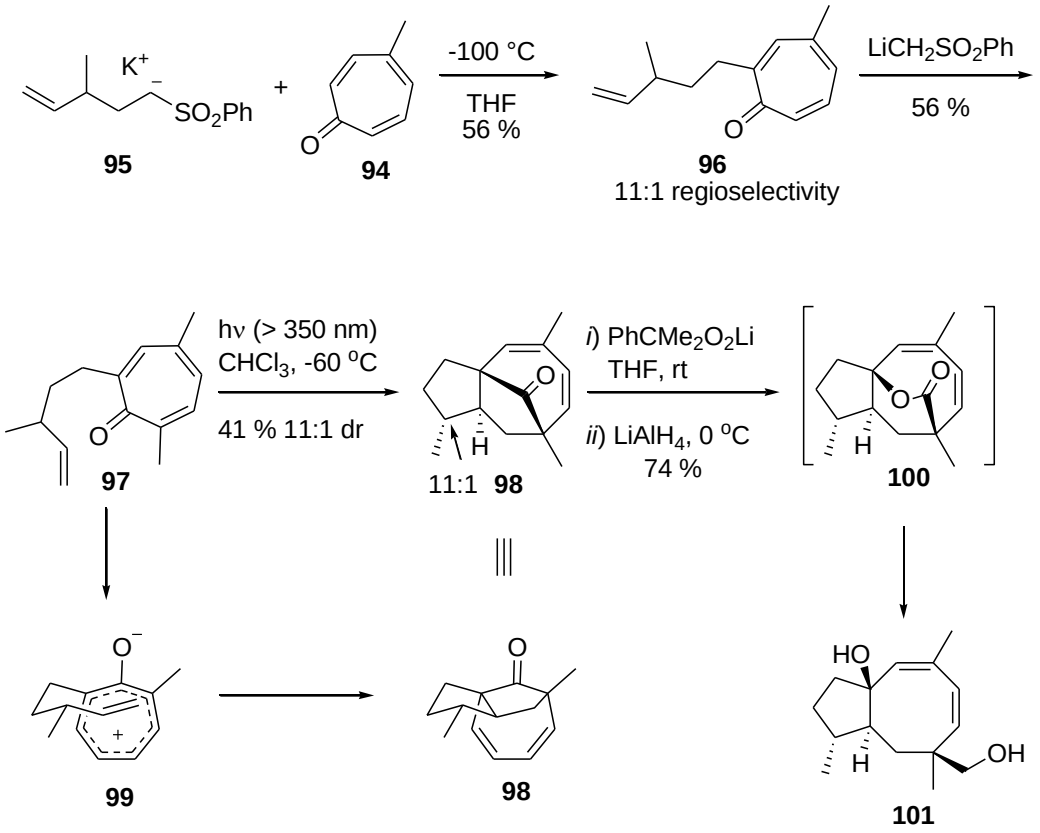
A convenient route to 4-methyltropone **94** using readily available starting materials provided a suitable starting point for the Feldman synthesis (Scheme 1-19).[34] Irradiation of a solution of acetylene and cyclopentenone **92** in acetonitrile produced the tricyclic bis(cyclopropane) intermediate **93** in 30 % yield. Treatment of **93** with SeO_2 in *t*-butanol at reflux generated 4-methyltropone **94** in 60 % yield. This methodology offered the Feldman group an efficient and scalable route to the key tropone building block for their total synthesis.



Scheme 1-19: Synthetic route for starting material tropone **94.**

Alkylation of synthetic 4-methyltropone with the sulfone stabilized carbanion **95** produced an 11:1 mixture in favour of the desired isomer **96**

(Scheme 1-20).[35, 36] (The minor isomer resulted from attack at the 7-position rather than the 2-position). Subsequent methylation, using the same methodology, introduced the 7-methyl substituent (**97**) in 56 % yield.



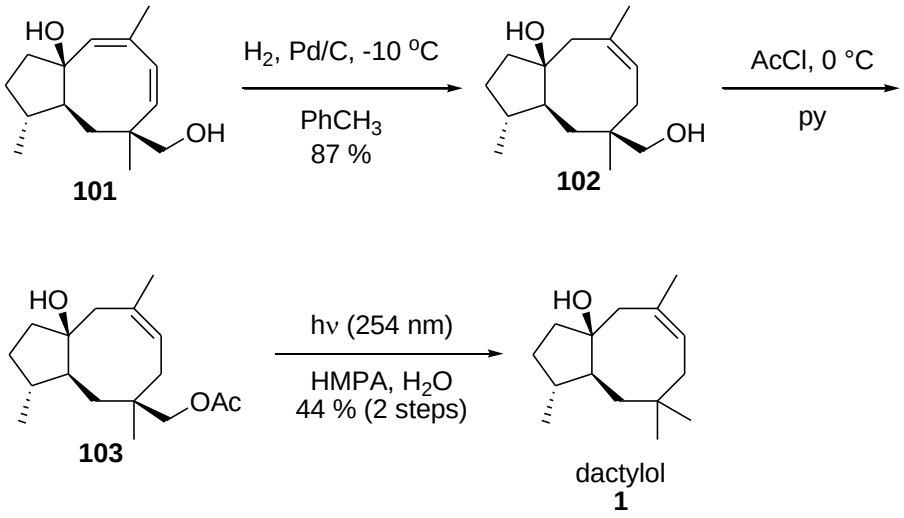
Scheme 1-20: The Feldman synthesis of advanced intermediate **101** towards dactylol.

Next, the key substrate **97** was irradiated at -60 °C, generating the desired [6+2] adduct **98** along with the methyl epimer in 41 % yield as an 11:1 ratio. The reaction is believed to proceed through the an excited state structure resembling **99** (or related hydroxytropylium ion) after the initial irradiation. The

alkene, which is in close proximity to the tropylium was proposed to adopt two major conformers. The conformer in which the side-chain methyl group occupied a pseudoequatorial position (shown) was expected to predominate and would lead to the major diastereromeric cycloadduct **98**. The pseudoaxial methyl conformer would give rise to the minor product. Finally, the authors propose that a stepwise cycloaddition occurred, resulting in the desired 5-8 ring system **98**.[35] Regioselective oxidation of the bridging ketone in **98** to produce the lactone **100** was accomplished via a Baeyer–Villiger reaction. Reduction of the lactone with lithium aluminum hydride resulted in the formation of the desired diol in 74 % over 2 steps. The authors reported that while it was possible to isolate **100,** the reduction of the crude mixture and isolation of the diol **101** was more convenient. It is notable that the regioselectivity of the Baeyer-Villiger oxidation was quite fortuitous, resulting in oxygenation at the bridgehead position where the eventual angular hydroxyl would reside.

Numerous attempts at regioselective partial reduction of the 1,3-diene in **101** to the required trisubstituted olefin in **102** using either radical or dissolving metal reduction conditions were met with poor results (Scheme 1-21).[37] Alternatively, the diene **101** was reduced with palladium on carbon, which fortuitously generated the desired monoolefin **102** without the observation of other isomers or over-reduction products. To complete the synthesis, the primary alcohol needed to be converted to a hydrogen to obtain the desired geminal dimethyl moiety. Removal of this alcohol proved to be quite difficult

but after trying numerous methods the authors were able to successfully obtain the natural product by using a acetylation-irradiation strategy.[38] The last step yielded dactylol **1** in 44 % yield over two steps.



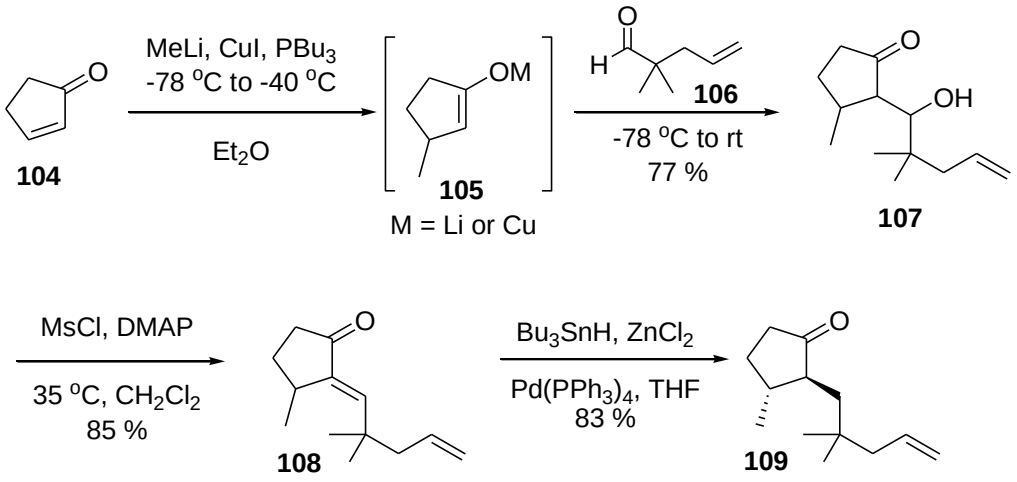
Scheme 1-21: The final steps for Feldman's total synthesis of dactylol **1.**

Although some unanticipated difficulties arose in the later steps of the synthesis, the Feldman route is remarkably short and direct. Furthermore, it serves as an excellent demonstration of the strategic value of this unusual [6+2]-photocycloaddition method for the rapid assembly of polycyclic products containing a cyclooctane ring.

1.4.4 Fürstner Total Synthesis (1996)

The Fürstner group envisioned that dactylol could be efficiently made by using ring-closing metathesis for the eight-membered ring.[39] Their synthesis

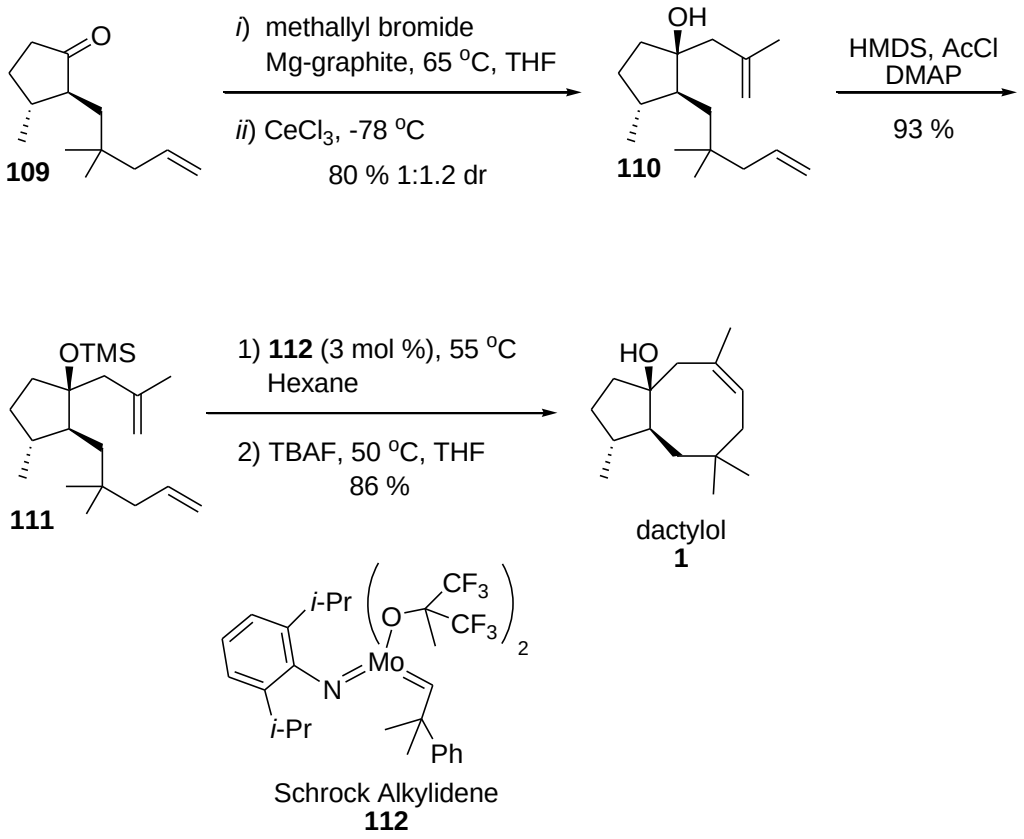
began with conjugate addition of methyllithium to cyclopentenone **104** followed by aldol addition of the resulting enolate **105** to 2,2-dimethylpent-4-enal **106** (Scheme 1-22). This procedure gave the desired disubstituted cyclopentanone **107** in 77 % yield. Dehydration of the secondary alcohol was accomplished by treatment with mesyl chloride and DMAP in methylene chloride. The resulting enone **108**, formed in 85 % yield, was reduced to give the desired *trans* cyclopentanone **109** in 83 % yield.



Scheme 1-22: The synthesis of cyclopentanone **109.**

An organocerium reagent was prepared and subsequently added into the ketone, generating a 1:1.2 ratio of diastereoisomers **110** in 80 % yield (Scheme 1-23). At this point attempts to close the eight-membered ring using ring closing metathesis (RCM) were unsuccessful, and the authors inferred that the problem may have resulted from the presence of a free hydroxyl group in the substrate. The alcohol was protected with a TMS group generating **111** in 93 % yield, and

subsequent ring closing metathesis with Schrock's alkylidene catalyst **112** and deprotection successfully generated dactylol **1** in 86 % yield over the two steps. The synthesis was racemic and suffered from a low diastereomeric ratio in the ketone methallylation step. Nonetheless, this synthesis is very concise, arriving at dactylol **1** in only seven steps from cyclopentenone **104**.

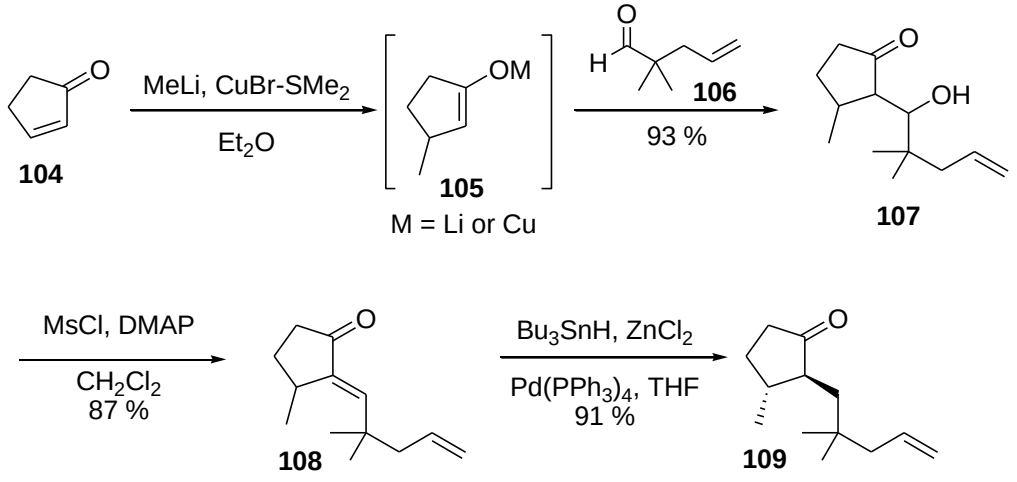


Scheme 1-23: The final steps of Fürstners total synthesis converting cyclopentanone **109** into dactylol **1.**

1.4.5 Vanderwal Total Synthesis (2010)

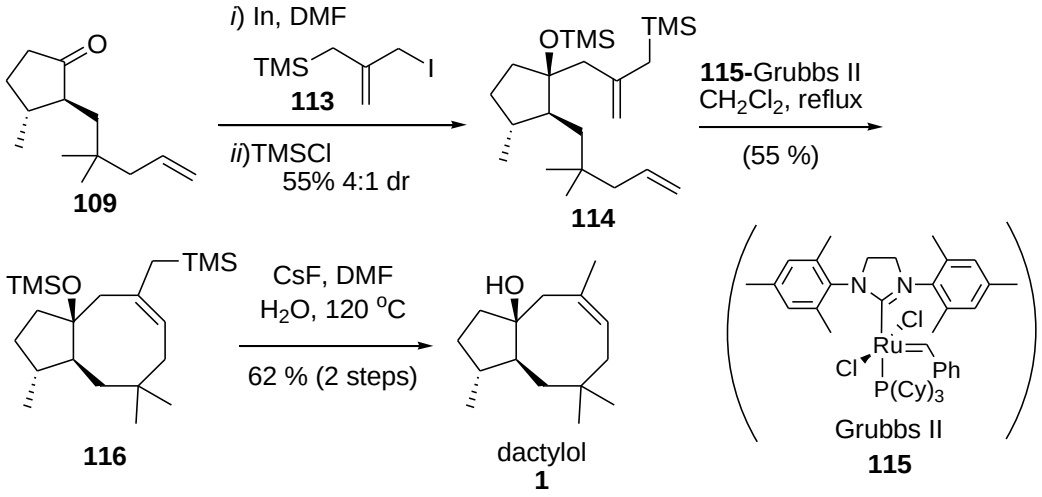
The most recent total synthesis of dactylol was reported by Vanderwal's group in 2010.[40] This approach employed a very similar strategy to the Fürstner group's,[39] including use of the same early intermediates and a key ring closing metathesis step, so it is discussed out of chronological order.

Beginning with cyclopentenone **104**, the Vanderwal group used slightly different conditions from those used by Fürstner and was able to increase the yield of the tandem conjugate addition/aldol reaction from 77 % to 93 % (Scheme 1-24). Dehydration was accomplished as in the Fürstner route, by elimination of the mesylate, generating the alkene **108** in 87 % yield. Palladium-catalyzed conjugate reduction with tributyltin hydride afforded the *trans*-cyclopentanone **109** in 91% yield, a significant improvement over the previous route.



Scheme 1-24: The synthesis of cyclopentanone **109.**

At this point, the synthetic route diverged slightly from the earlier Fürstner strategy, utilizing a different nucleophile in the ketone addition step. Trimethysilylmethallyl iodide **113**, indium metal and ketone **109** were combined, and the resulting tertiary alcohol was protected *in situ* with trimethylsilyl chloride to furnish silyl ether **114** in 55% yield over two steps and as a 4:1 ratio of diastereomers (Scheme 1-25). The product **114** differed from the one used in the Fürstner synthesis by the presence of an allylic silyl group and, fortunately, under the different conditions it was formed in a higher diastereomeric ratio. At this point, the authors carried out the RCM step using the second generation Grubbs catalyst. Subsequent treatment with CsF effected desilylation of both the silyl ether and the allylic silane, furnishing dactylol **1** in 62% over two steps.

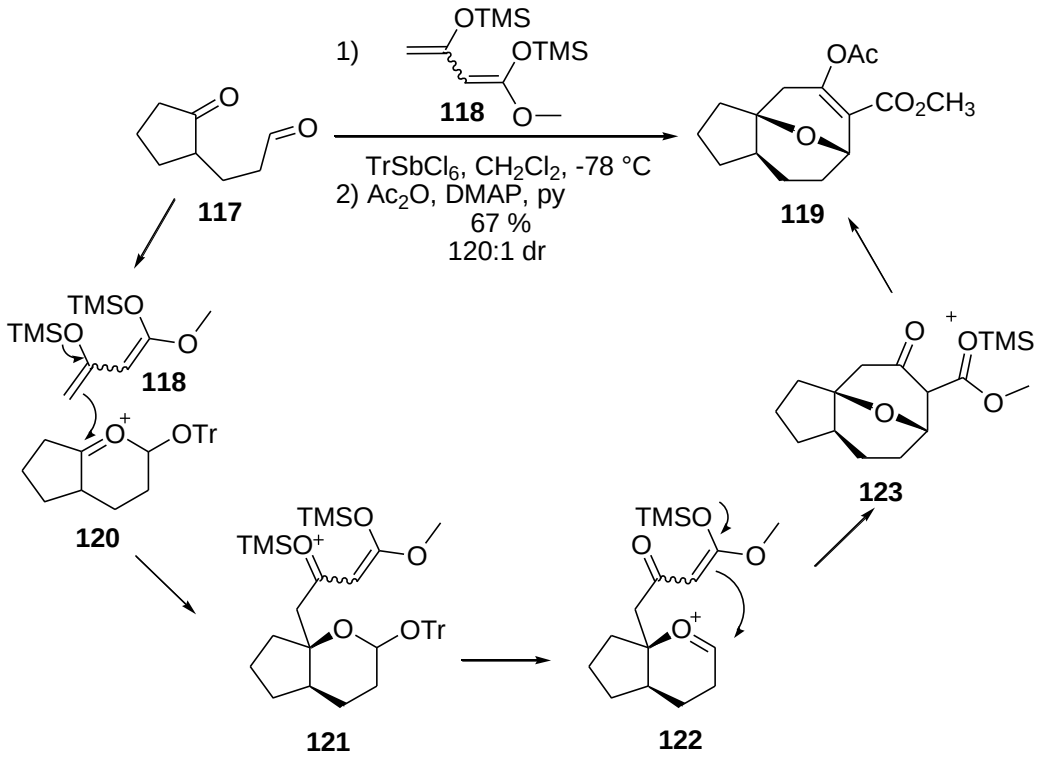


Scheme 1-25: The Vanderwal group synthesis of dactylol **1** from cyclopentanone **109.**

Although the Vanderwal approach closely mimicked the earlier Fürstner route, it did introduce some innovations. In particular, use of an allylic silane partner in the RCM step installed a functionalized olefin in the newly formed eight-membered ring. In the case of dactylol, this was subjected to simple desilylation, but the authors also utilized this intermediate in an oxidative process to form the related natural product poitediol **88**, demonstrating the versatility of this class of intermediates.

1.4.6 Molander Total Synthesis (1995)

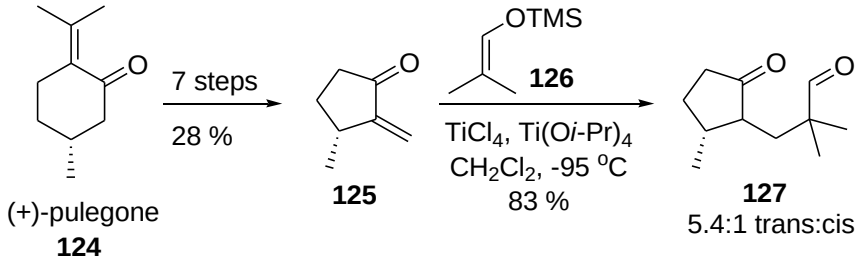
The Molander group developed a 5+3 annulation reaction applicable to the bicyclo[6.3.0]undecene skeleton found in dactylol.[41] Dienolate equivalent **118** and dicarbonyl **117** were combined in the presence of trityl hexachloroantimonate catalyst, and after acetylation, 5-8 fused ring system **119** was generated in 67 % yield in a diastereomeric ratio of 120:1 in favour of the ring-fusion stereochemistry found in dactylol (Scheme 1-26).



Scheme 1-26: The mechanism for the [5+3] annulation reaction.

The mechanism involves the initial formation of the oxocarbenium ion **120** from the closure of the ketone oxygen on to the activated aldehyde. Then the more nucleophilic terminus of enol ether **118** reacts with the oxocarbenium ion. This is followed by ionization to form a second oxocarbenium ion **122**, which is attacked by the remaining silyl ketene acetal, resulting in ether-bridged cyclooctanone ring **119**. This methodology demonstrates a convergent intermolecular reaction that effectively generates an eight-membered ring while affording the requisite stereochemistry found in dactylol.

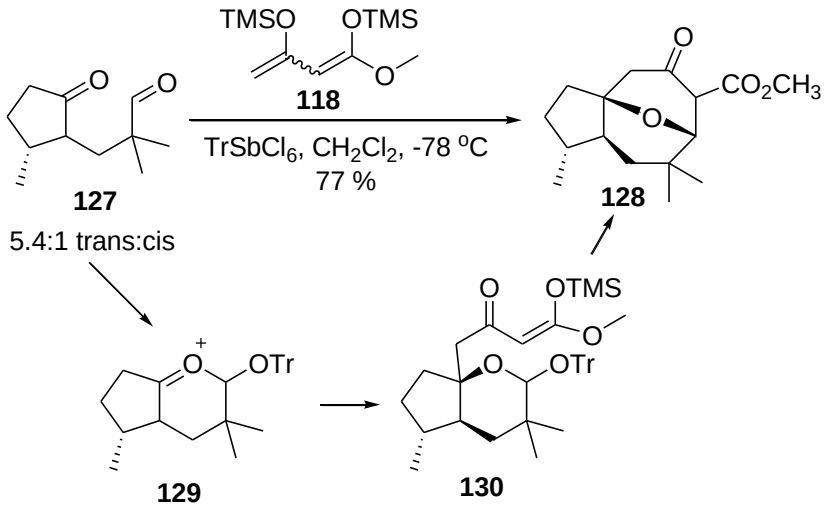
As a demonstration of their 5+3 annulation methodology, the Molander group set out to synthesize dactylol, and began the synthesis with the known optically pure α-methylene-β-methylcyclopentanone **125** (Scheme 1-27).[42] This material was produced in seven steps from pulegone **125** following the procedure by Marx and Norman.[43] The enone **125** underwent Mukaiyama Michael addition with dimethyl-substituted silyl enol ether **126** to generate the dicarbonyl in 83 % yield. Unfortunately the 5.4:1 *trans* to *cis* ratio could not be improved under epimerization conditions and so the inseparable mixture was carried forward.



Scheme 1-27: The synthesis of key substrate **127.**

With the ketoaldehyde **127** in hand, the key [5+3] annulation protocol was attempted (Scheme 1-28). Subjecting the mixture of dicarbonyl compounds **127** to the bis(silyloxy)-1,3-diene **128** and trityl hexachloroantimonate complex produced the desired 5-8 system **128** in 77 % yield as a mixture of keto-enol tautomers. Surprisingly, only one stereoisomer was isolated; the authors were unsure as to the fate of the minor *cis* diastereomer in the initial ketoaldehyde

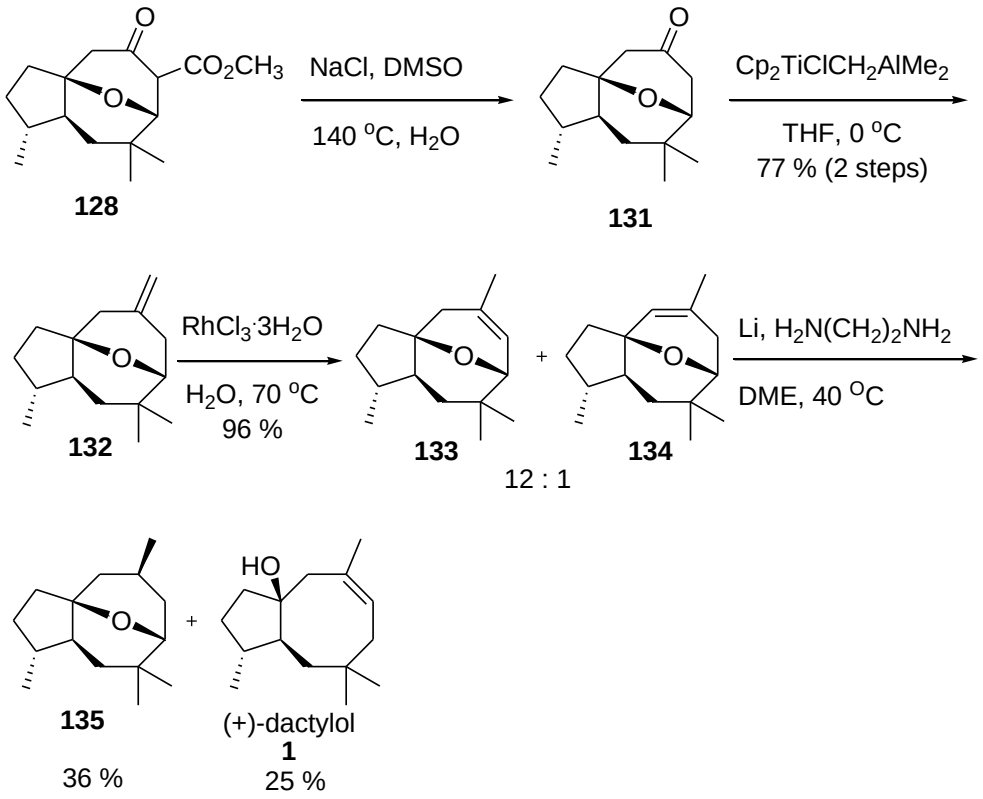
mixture. Under these reaction conditions epimerization has been shown to not occur.[41]



Scheme 1-28: The mechanism for generating the eight-membered ring in **128**.

Next, the ester **128** was decarboxylated under Krapcho conditions and the resulting ketone **131** was subsequently olefinated under Tebbe conditions to afford the exo-methylene compound **132** in a yield of 77 % over two steps. Rhodium(III)-catalyzed alkene isomerisation was accomplished in an excellent yield of 96%, resulting in a mixture of internal alkenes **133** and **134** as a 12:1 ratio in favour of the desired alkene **133**. The mixture of alkenes was then subjected to dissolving metal reduction conditions to open the bridging ether and generate enantiopure dactylol **1** in 25 % yield. Unfortunately, undesired product **135** resulting from competing reduction of the trisubstituted olefin was also formed, in 36% yield; this final step detracted from an otherwise concise and efficient route. This synthesis validated the 5+3 annulation protocol, which is

the only method used for the synthesis of dactylol that forms the eight-membered ring convergently. This synthesis was also the first enantioselective synthesis of dactylol.

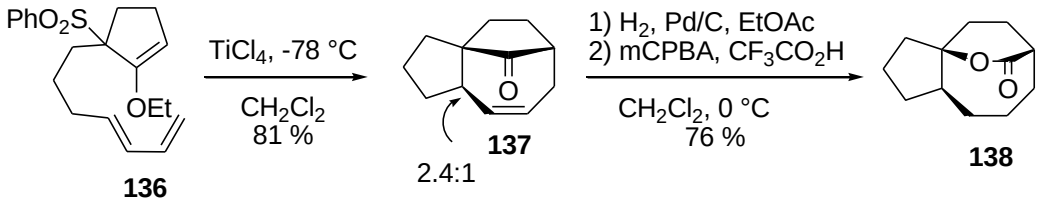


Scheme 1-29: The final steps of Molander's synthesis of (+)-dactylol.

1.4.7 Harmata Total Synthesis (2000)

Prior to their synthesis of dactylol the Harmata group had developed a [4+3]-cycloaddition reaction using Lewis acid activation of oxygen-substituted allylic sulfones.[44] This methodology involved tethering a suitable cyclopentene

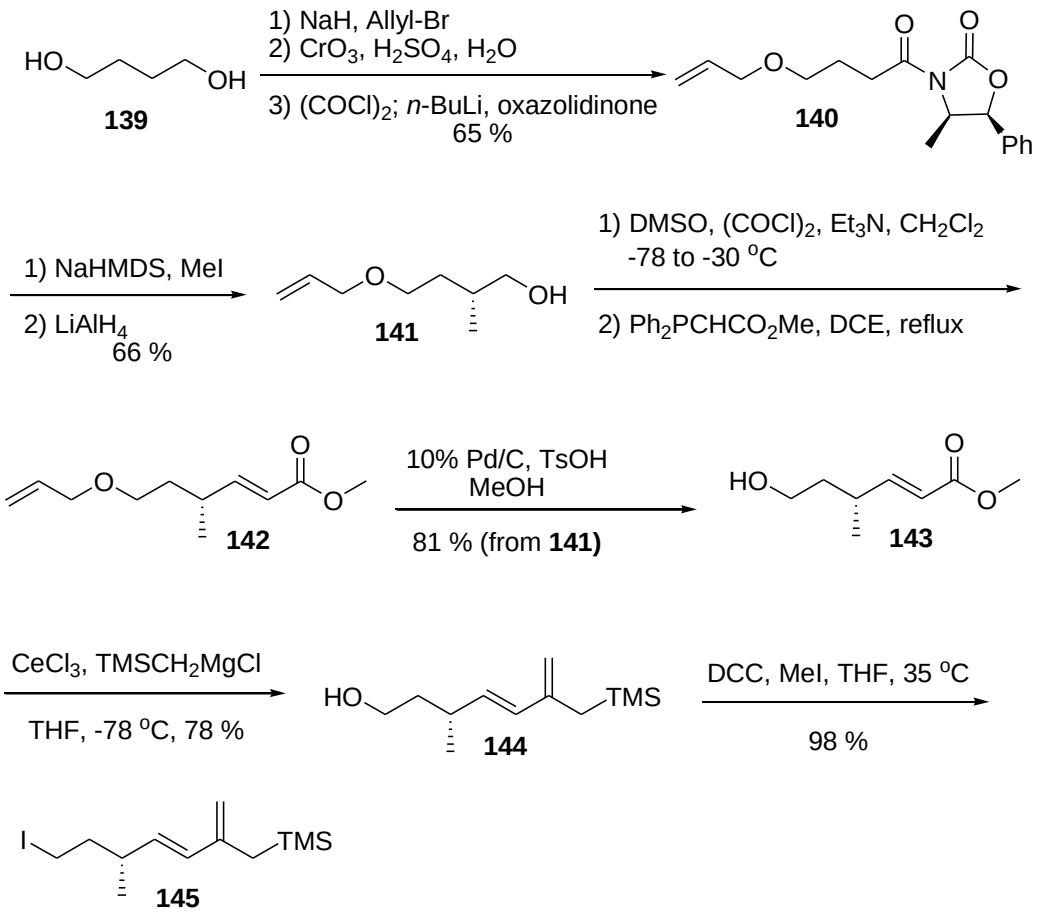
substrate to a 1,3 diene (**136**) and treating it with titanium tetrachloride to generate the [4+3] adduct **137** (Scheme 1-30). The major product was the *trans* fused 5-8 ring system. Hydrogenation of the olefin **137** with palladium on carbon followed by a Baeyer-Villager reaction generated a *trans*-fused 5-8 ring system **138** with bridgehead oxygenation, possessing much of the functionality and stereochemical relationships of dactylol. In order to apply this methodology to the natural product, certain modifications would be necessary, including improved stereoselectivity and incorporation of the necessary methyl branch in the tether that would become the cyclopentane ring, as well as functionality that could permit the eventual introduction of the required *gem*-dimethyl substitution. Also, an alternative method for generation of the cyclopentenyl anion was applied.



Scheme 1-30: The methodology of the Harmata group to synthesize the bicyclo[6.3.0]undecene ring system .

The first target in the Harmata synthesis was the diene side chain **145**, which would be tethered to the cyclopentene later in the synthesis (Scheme 1-31). Starting from 1,4-butanediol **139**, monoprotection of one of the alcohols with an allyl group and subsequent oxidation of the other alcohol under Jones

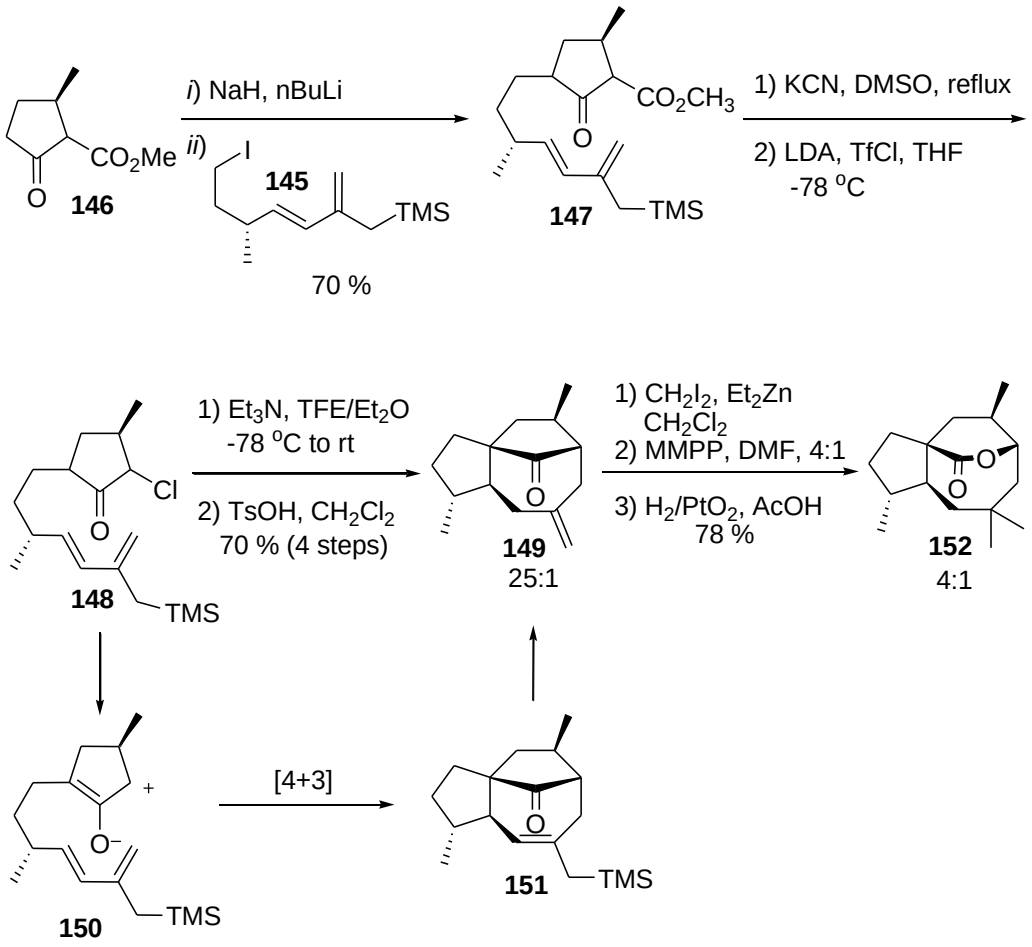
conditions generated the carboxylic acid.[45] This acid was converted to a chiral oxazolidinone **140** in 65 % yield over 3 steps. Asymmetric alkylation under the standard Evans conditions introduced the necessary methylated stereogenic center in the tether, after which the chiral auxiliary was removed with lithium aluminum hydride to give the free alcohol **141** in a 66 % yield over two steps. The alcohol was oxidized to an aldehyde which was then subjected to a Wittig



Scheme 1-31: The synthesis of diene **145** from diol **140.**

reaction to generate conjugated ester **142**. Finally, deprotection produced the free alcohol **143** in an overall 81 % yield over 3 steps from **141**. The ester was converted to the diene **144** in 78 % yield by treating it with an excess of trimethylsilylmethyl magnesium chloride and cerium chloride. The alcohol was then converted to the iodide **145** in 98 % yield with dicyclohexyl carbodiimide and methyl iodide, completing the preparation of one major fragment.

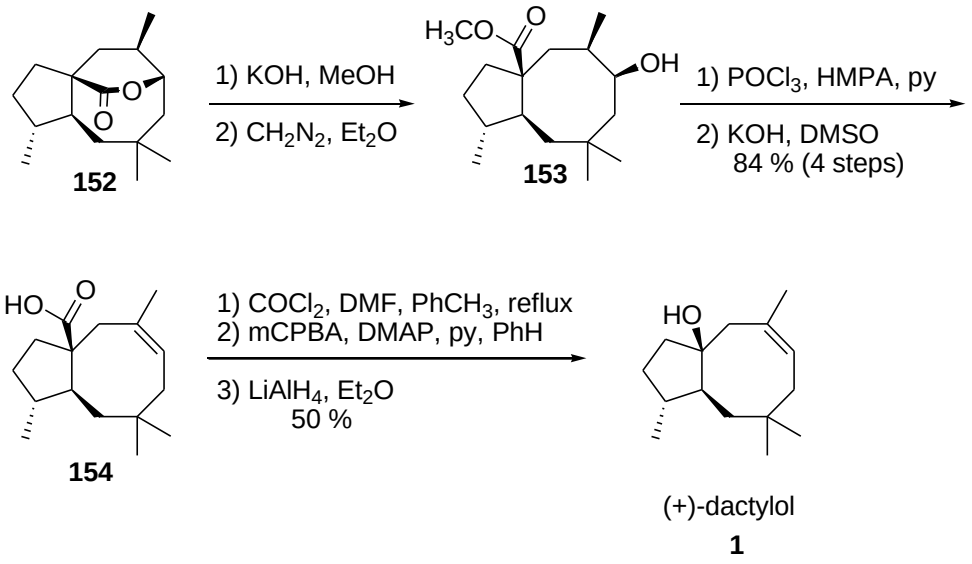
Similar to the Molander synthesis, enantiopure cyclopentanone **146** is available from pulegone (Scheme 1-32).[43] This compound could be doubly deprotonated and the resulting dienolate selectively alkylated with the previously described primary iodide **145** to produce the desired adduct **147** in 70 % yield.[46] Krapcho decarboxylation followed by chlorination produced the desired α-chloroketone **148**, which was the substrate required for the key [4+3] reaction. The substrate was stirred with triethylamine in a mixture of diethyl ether and trifluoroethanol (the latter a highly ionizing but non-nucleophilic solvent), resulting in efficient [4+3]-cycloaddition. The resultant allylic silane adduct **151** was then subjected to protodesilylation with TsOH to afford the exocyclic methylene compound **149** in 70% yield overall. Notably, this product was obtained as a 25:1 ratio of diastereomers, a ratio much higher than those found in the less-substituted model study. The authors speculate that the two methyl-substituted stereogenic centers work in synergy to enhance the stereoselectivity.



Scheme 1-32: The synthetic route of ester **152** from nonracemic **146**

A Simmons-Smith reaction generated a cyclopropane from the olefin **149**, and then the ketone was subjected to a Baeyer-Villiger reaction to generate the corresponding lactone. Surprisingly, and unfortunately, the Baeyer-Villiger reaction generated the unexpected regioisomer as the major product, with oxygen insertion occurring *away* from the bridgehead position.[47] Hydrogenolysis with platinum oxide converted the cyclopropane to the desired geminal dimethyl group (**152**), with a yield of 78 % over three steps.

Saponification of the bridging ester in **152** generated the carboxylic acid and the free alcohol (Scheme 1-33). The acid was converted to its methyl ester (**153)** using diazomethane, and then dehydration of the alcohol with phosphorus oxychloride formed the desired trisubstituted alkene. Saponification reformed the carboxylic acid (**154**) in an overall yield was 84 % over 4 steps. Conversion of the acid **154** to the acid chloride followed by treatment with m-CPBA



Scheme 1-33: Harmata's synthesis of (+)-dactylol from intermediate **152.**

produced a mixed carbonate by way of the "carboxy inversion reaction"[48], which was reduced to generate the alcohol **1** in a 50 % yield over 3 steps. This completed Harmata's synthesis of (+)-dactylol. The highlight of this route was the highly stereoselective intramolecular [4+3] cycloaddition that formed both the five- and the eight-membered rings found in the natural product.

1.5 Conclusions

Dactylol is a seemingly simple target; numerous synthetic approaches have been devised for this natural product and a number of successful total syntheses have been reported. Specifically, there has been one racemic formal synthesis, five racemic total syntheses, and two non-racemic total syntheses. The most interesting aspect of these syntheses is the use of inventive methods for generating the eight-membered ring. As mentioned earlier, eight-membered rings suffer entropic and enthalpic barriers that complicate the use of conventional ring closing techniques, such as those commonly applied to make six-membered rings. Also apparent from these syntheses are problems with transannular reactivity and selectivity issues. The problems that arose and the solutions to those problems from the execution of synthetic plans towards dactylol gave valuable information in the area of cyclooctanoid natural product syntheses that can be used for more complex products. Dactylol remains a synthetic challenge that can continue to validate synthetic methods, and can help to provide a better understanding of the reactivity and selectivity of reactions surrounding eight-membered rings.

In addition, there are more reasons to explore the total synthesis of dactylol, despite its ambiguous biomedical relevance. Specifically, it serves as an ideal proving ground for new methodology and new synthetic strategies

designed to address the main challenging structural features found in dactylol including the eight-membered ring, the angular hydroxyl and the three contiguous stereocenters. Similar features are found in other more structurally complex, biologically active natural products such as phorbol,[49] kalmanol,[50] and variecolin,[51] and solutions to the dactylol problem may be applicable to these targets as well.

1.6 References

1. Fenical, W.; Schulte, G. R.; Finer, J.; Clardy, J. *J. Org. Chem.* **1978,** *43*, 3628-3630.
2. Schmitz, F. J.; Hollenbeak, K. H.; Vanderah, D. J. *Tetrahedron* **1978,** *34*, 2719-2722.
3. Melching, S.; König, W. A. *Phytochemistry* **1999,** *51*, 517-523.
4. Demirel, Z.; Yilmaz-Koz, F. F.; Karabay-Yavasoglu, U. N.; Ozdemir, G.; Sukatar, A. *J. Serb. Chem. Soc*. **2009,** *74*, 619-628.
5. Hayasaka, K.; Ohtsuka, T.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1985,** *26*, 873-876.
6. Shirahama, H.; Osawa, E.; Matsumoto, T. *Tetrahedron Lett.* **1978,** 23, 1987-1990.
7. Shirahama, H.; Osawa, E.; Matsumoto, T. *J. Am. Chem. Soc.* **1980,** *102*, 3208-3213.
8. Hendrickson, J. B. *J. Am. Chem. Soc.* **1964,** *86*, 4854-4866.

9. Hendrickson, J. B. *J. Am. Chem. Soc.* **1967,** *89*, 7036-7043.

10. Casadei, M. A.; Galli, C.; Mandolini, L. *J. Org. Chem.* **1981,** *46*, 3127-3128.

11. Casadei, M. A.; Galli, C.; Mandolini, L. *J. Am. Chem. Soc.* **1984,** *106*, 1051-1056.

12. Spanka, G.; Rademacher, P.; Duddeck, H. *J. Chem. Soc., Perkin Trans. 2* **1988,** 2119-2121.

13. Bishop, R., *Aust. J. Chem.* **1984,** *37*, 319-325.

14. Bishop, R. *J. Chem. Soc., Perkin Trans. 1,* **1974**, 2364-2367.

15. Baggaley, K. H.; Evans, W. H.; Graham, S. H.; Jonas, D. A.; Jones, D. H. *Tetrahedron* **1968,** *24*, 3445-3452.

16. Shirahama, H.; Hayano, K.; Kanemoto, Y.; Misumi, S.; Ohtsuka, T.; Hashiba, N.; Furusaki, A.; Murata, S.; Noyori, R.; Matsumoto, T. *Tetrahedron Lett.* **1980,** *21*, 4835-4838.

17. Naya, Y.; Hirose, Y. *Chem. Lett.* **1973**, 133-136.

18. Naya, Y.; Hirose, Y. *Chem. Lett.* **1973**, 727-732.

19. Baines, D.; Forreste.J; Parker, W. *J. Chem. Soc., Perkin Trans. 1,* **1974**, 1598-1603.

20. Dauben, W. G.; Hubbell, J. P.; Vietmeyer, N. D. *J. Org. Chem.* **1975,** *40*, 479-485.

21. Mehta, G.; Singh, B. P. *Tetrahedron Lett.* **1975**, 3961-3962.

22. Paquette, L. A.; Hun Ham, W.; Dime, D. S., *Tetrahedron Lett.* **1985,** *26*, 4983-4986.

23. Paquette, L. A.; Ham, W. H. *J. Am. Chem. Soc.* **1987,** *109*, 3025-3036.

24. Flaugh, M. E.; Crowell, T. A.; Farlow, D. S. *J. Org. Chem.* **1980,** *45*, 5399-5400.

25. Bordwell, F. G.; Wellman, K. M. *J. Org. Chem.* **1963,** *28*, 1347-1352.

26. Grimme, W. *J. Am. Chem. Soc.* **1972,** *94*, 2525-2526.

27. Berson, J. A.; Dervan, P. B. *J. Am. Chem. Soc.* **1972,** *94*, 8949-8950.

28. Berson, J. A.; Dervan, P. B.; Jenkins, J. A. *J. Am. Chem. Soc.* **1972,** *94*, 7598-7599.

29. Berson, J. A.; Dervan, P. B. *J. Am. Chem. Soc.* **1973,** *95*, 269-270.

30. Hammond, G. S.; Deboer, C. D. *J. Am. Chem. Soc.* **1964,** *86*, 899-902.

31. Vogel, E. *Justus Liebigs Ann. Chem.* **1958,** *615*, 1.

32. Gadwood, R. C.; Lett, R. M. *J. Org. Chem.* **1982,** *47*, 2268-2275.

33. Feldman, K. S.; Come, J. H.; Kosmider, B. J.; Smith, P. M.; Rotella, D. P.; Wu, M. J. *J. Org. Chem.* **1989,** *54*, 592-601.

34. Cavazza, M.; Guerriero, A.; Pietra, F. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2005-2008.

35. Feldman, K. S.; Wu, M. J.; Rotella, D. P. *J. Am. Chem. Soc.* **1989,** *111*, 6457-6458.

36. Funk, R. L.; Bolton, G. L. *J. Am. Chem. Soc.* **1986,** *108*, 4655-4657.

37. Feldman, K. S.; Wu, M. J.; Rotella, D. P. *J. Am. Chem. Soc.* **1990,** *112*, 8490-8496.

38. Pete, J.-P.; Portella, C.; Monneret, C.; Florent, J.-C.; Khuong-Huu, Q. *Synthesis* **1977,** 11, 774-776.

39. Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996,** *61*, 8746-8749.

40. Dowling, M. S.; Vanderwal, C. D. *J. Org. Chem.* **2010,** *75*, 6908-6922.

41. Molander, G. A.; Cameron, K. O. *J. Org. Chem.* **1993,** *58*, 5931-5943.

42. Molander, G. A.; Eastwood, P. R. *J. Org. Chem.* **1995,** *60*, 4559-4565.

43. Marx, J. N.; Norman, L. R. *J. Org. Chem.* **1975,** *40*, 1602-1606.

44. Harmata, M.; Elomari, S.; Barnes, C. L. *J. Am. Chem. Soc.* **1996,** *118*, 2860-2871.

45. Harmata, M.; Rashatasakhon, P.; Barnes, C. L. *Can. J. Chem.* **2006,** *84*, 1456-1469.

46. Harmata, M.; Rashatasakhon, P. *Org. Lett.* **2000,** *2*, 2913-2915.

47. Harmata, M.; Rashatasakhon, P. *Tetrahedron Lett.* **2002,** *43*, 3641-3644.

48. Denney, D. B.; Sherman, N. *J. Org. Chem.* **1965,** *30*, 3760-3761.

49. Irie, K.; Ishii, T.; Ohigashi, H.; Wender, P. A.; Miller, B. L.; Takeda, N. *J. Org. Chem.* **1996,** *61*, 2164-2173.

50. Burke, J. W.; Doskotch, R. W.; Ni, C. Z.; Clardy, J. *J. Am. chem. Soc.* **1989,** *111*, 5831-5833.

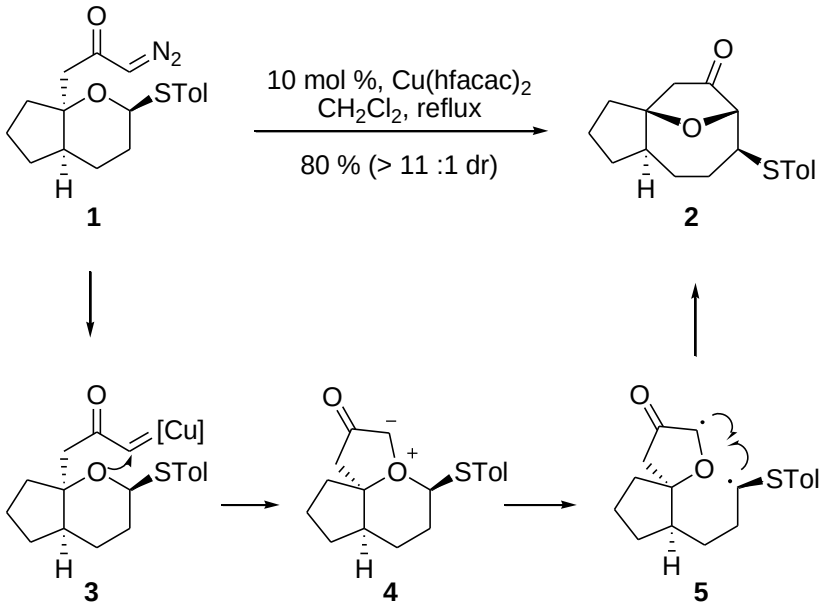
51. Molander, G. A.; Quirmbach, M. S.; Silva, L. F.; Spencer, K. C.; Balsells, J. *Org. Lett.* **2001,** *3*, 2257-2260.

Chapter 2

Synthetic Studies Towards the Total Synthesis of (+)-Dactylol

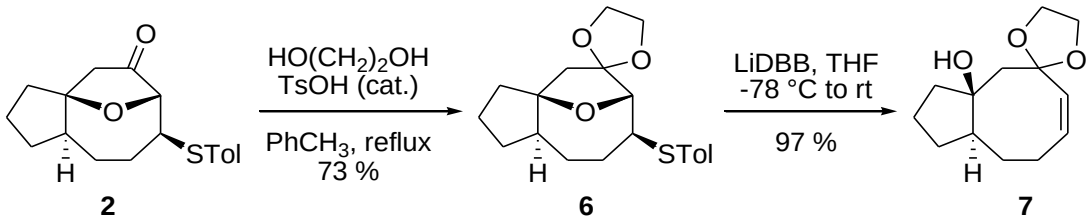
2.1 Background: Synthesis of a 5-8 Ring System

An intriguing route to bicyclo[6.3.0]undecane ring systems with oxygenation at one of the bridgehead carbons was reported by the West group. [1] This approach utilized easily prepared mixed monothioacetals with pendent diazoketone chains such as **1** (Scheme 2-1). When this substrate was stirred in the presence of copper (II) hexafluoroacetylacetonate in dichloromethane at reflux, the cyclooctanoid product **2** was obtained in good yield (80 %) with a diastereomeric ratio of greater than 11:1. In the presence of $Cu(hfacac)_2$, the diazoketone **1** decomposes to generate metallocarbene **3**. The oxygen, strategically positioned five atoms away, attacks the carbene to form oxonium ylide **4** (note that this intermediate may remain associated with the copper catalyst). This placement of oxygen helps to avoid alternate C-H insertion pathways.[2] Homolytic cleavage of the C-O bond generates the diradical **5**, which is facilitated by the radical stabilizing thioether.[1] The diradical can then recombine to form product **2**.



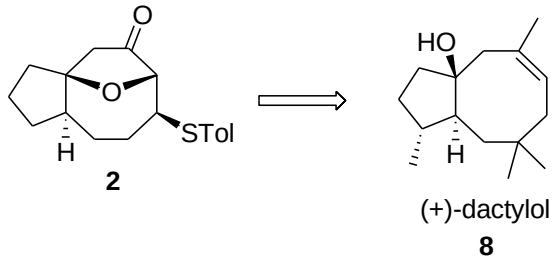
Scheme 2-1: Stevens rearrangement of a diazoketone to generate an eight-membered ring.

In addition to the aforementioned benefit, the thioether also facilitates the opening of the bridging ether. To illustrate this, the West group first protected ketone **2** to generate the acetal **6** in 73 % yield (Scheme 2-2).[1] Reductive desulfurization opened the ether to form the tertiary alcohol **7** in 97 % yield.



Scheme 2-2: Reductive desulfurization to cleave bridging ether.

This approach effectively created the 5-8 fused system **2** with a bridgehead hydroxyl that is very similar to the natural product dactylol **8** (Figure 2-1). The stereochemistry of the fused ring system is nicely set by first creating a *cis*-fused 5-6 bicyclic mixed acetal, a relatively easily formed ring system in comparison to the eventual 5-8 bicyclic target. The ring opening process establishes the bridgehead alcohol in the correct *trans* relationship to the other bridgehead centre as is found in dactylol. Still missing are the four methyl groups, one of which resides at a stereogenic center on the cyclopentane ring, and the trisubstituted olefin.



2 (+)-dactylol **8**

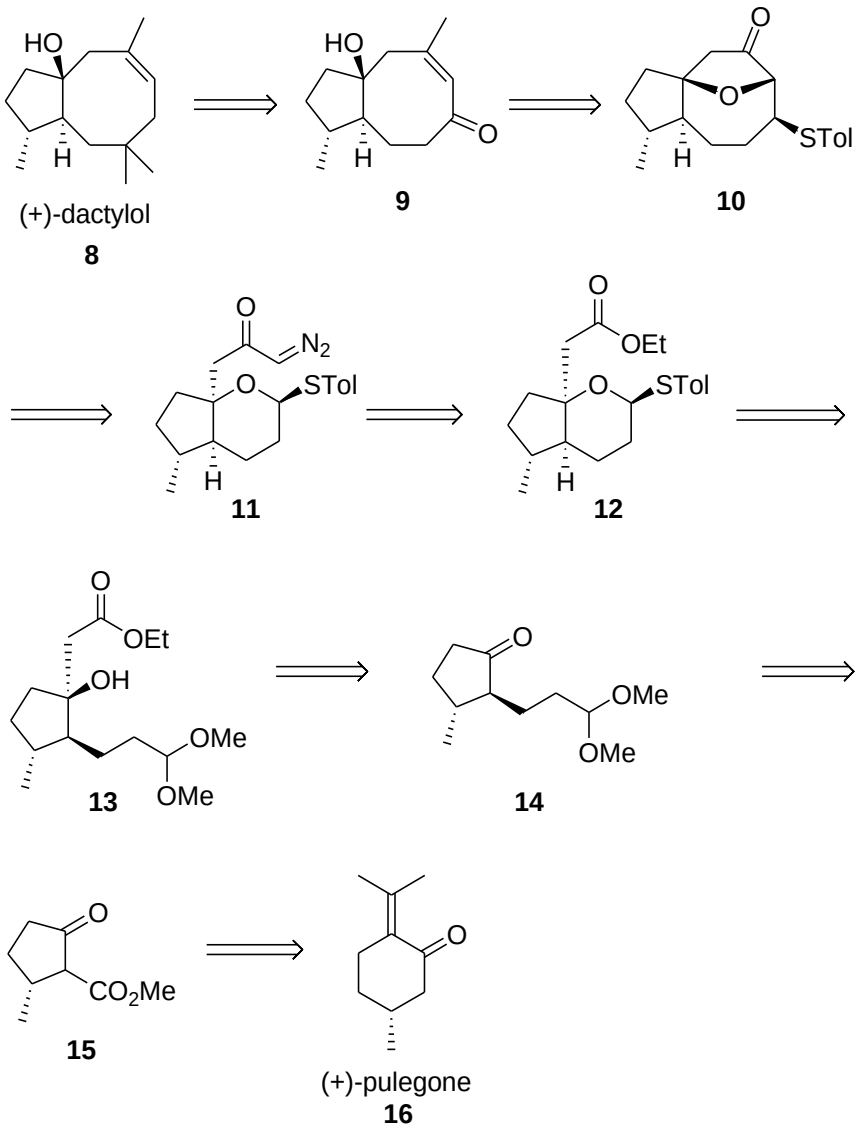
Figure 2-1: Structural comparison of products from oxonium ylide methodology and dactylol.

2.1.1 First Generation Route Towards (+)-Dactylol

2.1.1.1 Retrosynthetic Analysis

In light of the promising results from the model study, Dr. Graham Murphy undertook a synthesis of (+)-dactylol **8**, utilizing the oxonium ylide

methodology to make the requisite 5-8 system.[3] The proposed route would use the ketone functionality in **9** to install the geminal dimethyl substitution late in the synthesis by enolate alkylation, and subsequent deoxygenation of the ketone would generate the natural product **8** (Scheme 2-3). The alcohol would be formed from the reductive desulfurization of **10,** which differs from **2** by the

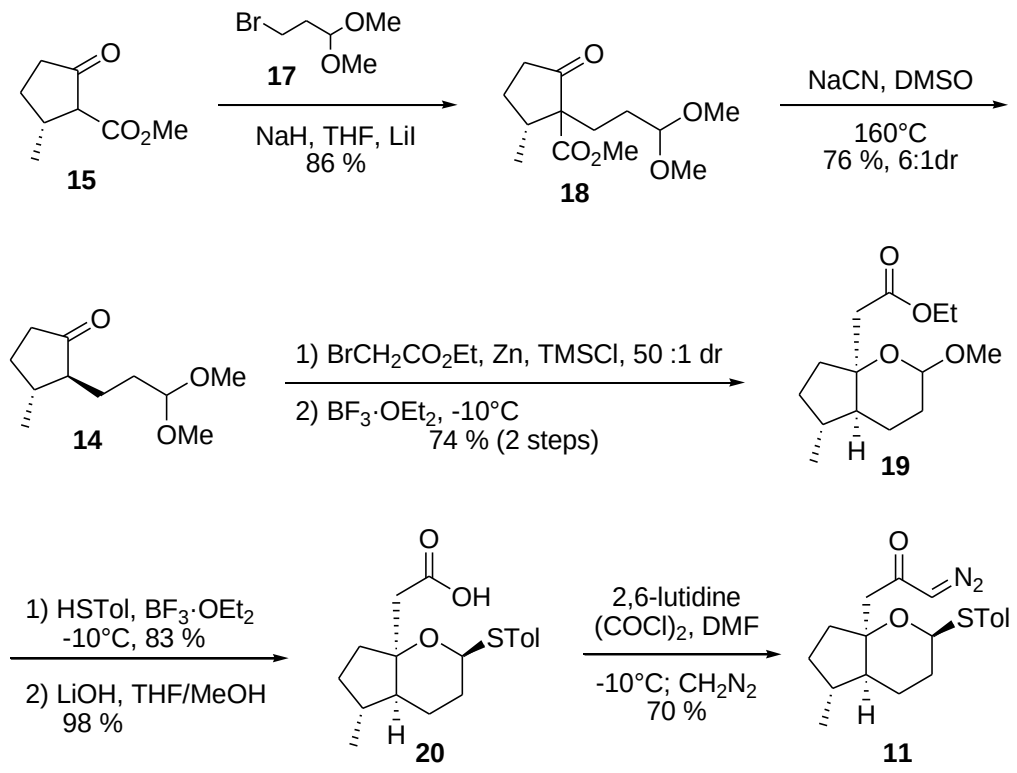


Scheme 2-3: Retrosynthetic analysis of dactylol by West and Murphy.

presence of the branching methyl on the cyclopentane ring and by being enantiomerically pure. The rearrangement precursor **11** could be generated from the corresponding ester **12**, subsequent to the formation of a six-membered thioacetal derived from a acyclic acetal **13**. The tertiary alcohol could be made from an anionic addition into ketone **14**, which should proceed selectively as the anion would be added to the less hindered side of the carbonyl group, thus setting the stereochemistry for the alcohol in the natural product. Ketone **14** could ultimately be made from the ketoester **15**, a compound shown to be accessible by a short route from the cheap, enantiopure and readily available *R*-(+)-pulegone **16**.[4]

2.1.1.2 Execution of the Original Route

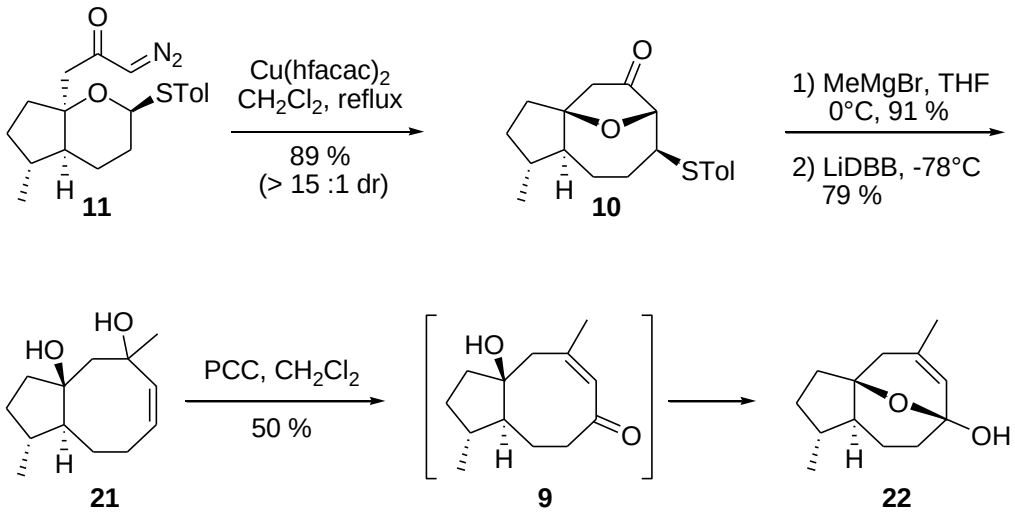
Following the preparation of ketoester **15** by the known route,[4] alkylation with known bromoacetal **17**[5] followed by Krapcho decarboxylation of **18** generated the 2,3-*trans*-disubstituted cyclopentanone **14** in an overall yield of 65 % (Scheme 2-4). Reformatsky addition to **14** and mixed acetal formation were successfully achieved, furnishing the desired *cis* 5-6 fused bicycle **19** in 83 % and 89 % yields, respectively. The cyclic acetal **19** was converted to mixed thioacetal in 83 % yield and the ester was saponified in 98 % yield to generate **20**. The carboxylic acid was activated by conversion *in situ* to a transient acid chloride, followed by treatment with diazomethane to produce the key intermediate diazoketone **11** in 70 % yield.



Scheme 2-4: Synthesis of diazoketone **11** from β-ketoester **15.**

The key intermediate **11**, differing from the model substrate by a methyl group on the cyclopentyl ring, was subjected to copper catalysis in dichloromethane at reflux and produced the desired 5-8 ring system **10** in 89 % yield (*Scheme 2-5*). When compared to the model substrate, the yield fortuitously increased and the ratio of thioether epimers, which is ultimately inconsequential, increased to 15:1. Methylmagnesium bromide was added into the ketone in 91 % yield. This was a clever method as it added a necessary methyl group while removing the ketone prior to the thioether reductive elimination. Next, the alcohol was subjected to LiDBB at -78 °C and the desired ring-opened product **21** was obtained in 79 % yield. This reaction opened the

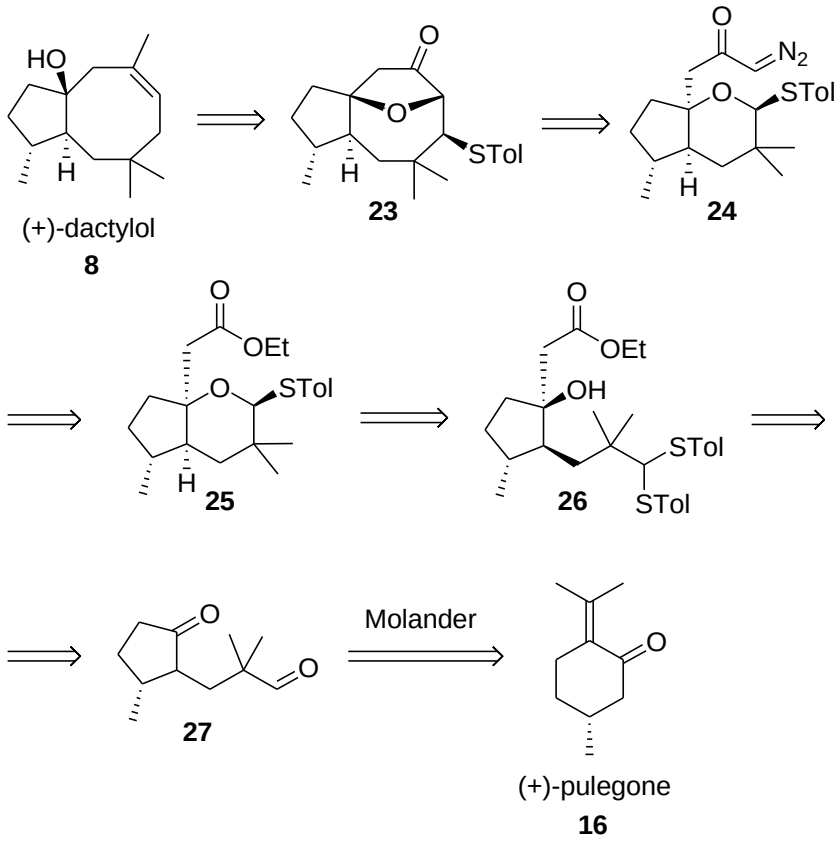
bridging ether to reveal the bridgehead alcohol with the correct configuration found in the natural product **8**. Dr. Murphy then attempted to oxidatively transpose the allylic alcohol by reacting the diol **21** with pyridinium chlorochromate; however, rather than isolating the desired conjugated ketone **9,** hemiacetal **22** was isolated. Unfortunately, it appears that the conformation of the cyclooctene ring placed the angular hydroxyl group in close proximity to the newly formed ketone, leading to a highly favourable transannular hemiketalization. All efforts to further modify the hemiketal or to circumvent its formation by selective protection of the bridgehead alcohol were unsuccessful.



Scheme 2-5: Rearrangement of diazoketone **11** and formation of undesired hemiacetal **22**

2.1.2 Second Generation Approach to Dactylol

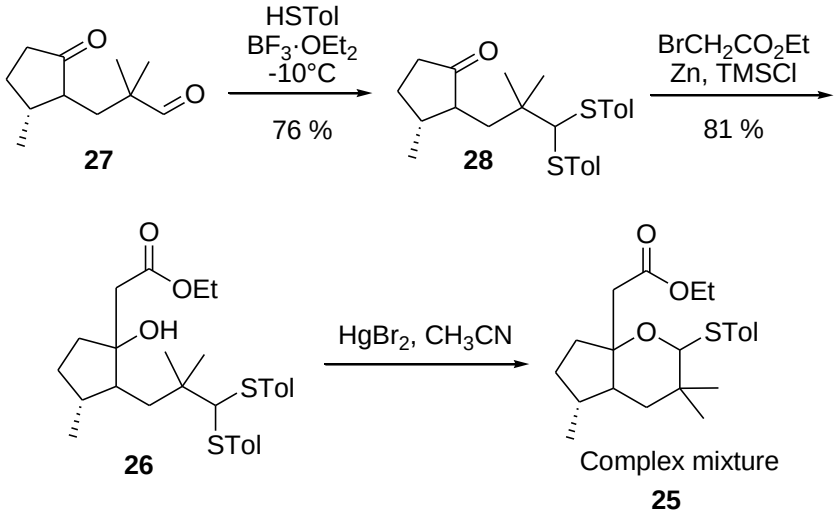
The strategy with the late stage introduction of the geminal methyl group proved to be problematic due to the inability to achieve enolate character at that position as a result of irreversible transannular hemiketalization. To avoid this problem, the route was modified, while retaining the same overall strategy. Formation of dactylol from intermediate **23** containing three of the necessary methyl groups could be envisioned (Scheme 2-6). Once again the 5-8 system of



Scheme 2-6: Modified retrosynthetic analysis with early introduction of geminal dimethyl group.

23 could be formed from the corresponding diazoketone **24** through a Stevens rearrangement of an oxonium ylide. Through a similar strategy to the last route (following an acetalization Reformatsky sequence) a trimethyl ketoaldehyde **27** would need to be made. Fortunately, this intermediate had been made previously by Molander's group from enantiopure pulegone **16**.[4]

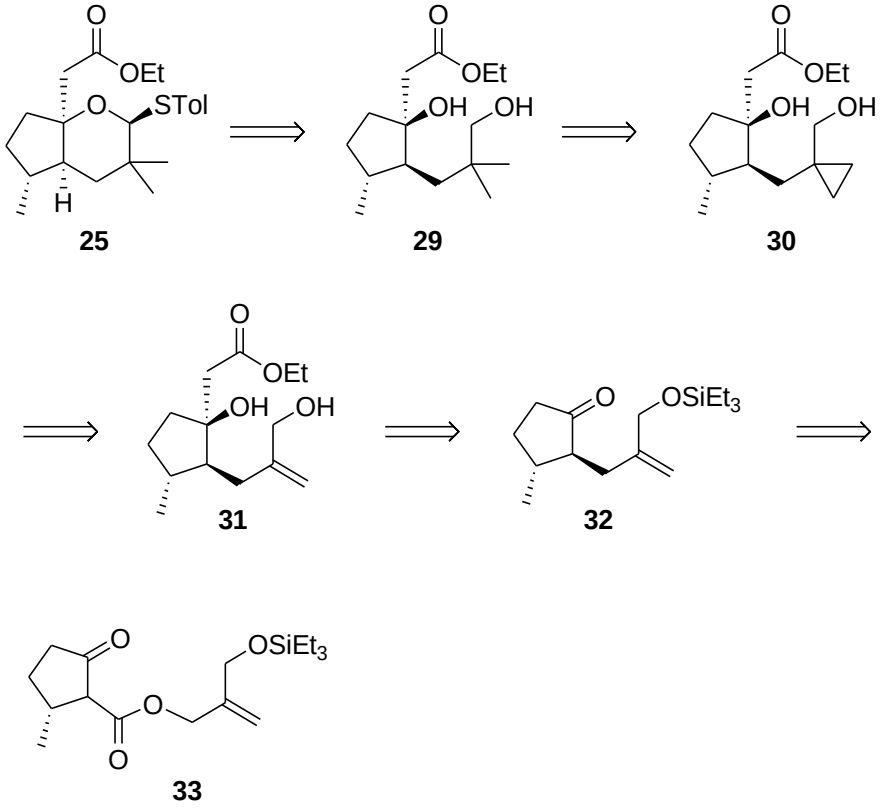
Aldehyde **27** was synthesized as a mixture of diastereomers (Scheme 2-7). Numerous attempts at protecting the aldehyde as an acetal were unsuccessful; however, thioacetalization proved to be successful, generating **28** in 76 % yield. Reformatsky addition into the ketone **28** was accomplished in 81 % yield; unfortunately this resulted in a mixture of diastereomers of alcohol **26** whose exact composition could not be determined. The mixture was carried



Scheme 2-7: The Synthesis of the geminal dimethyl containing mixed thioacetal **25**.

forward to the cyclization step. Unfortunately, **25** was isolated as a mixture of diastereomers, indicating that this approach would not be suitable. Accordingly, the strategy was once again modified.

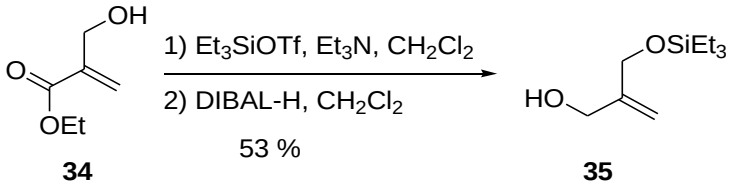
As an alternative to Molander's strategy, our group probed a slighly modified sequence. Rather than beginning with a geminal dimethyl group, a cyclopropanation/hydrogenolysis sequence on an alkene could be utilized to introduce the geminal dimethyl at a later stage (*Scheme 2-8*). If allyl alcohol **31**



Scheme 2-8: Modified retrosynthetic analysis with cylopropanation to introduce geminal dimethyl group.

were accessible, cyclopropanation followed by hydrogenolysis would form the dimethyl compound **29**. This could then be converted into the desired thioacetal **25,** which could then be carried forward through the remainder of the previously outlined synthesis.

The new route required an allylic side-chain containing a protected allylic alcohol moiety. The necessary fragment was prepared by first protection of unsaturated hydroxy ester **34** as its triethylsilyl ether (Scheme 2-9). The ester was then reduced with DIBAL-H, forming the allyl alcohol **35** in 53 % yield over two steps.

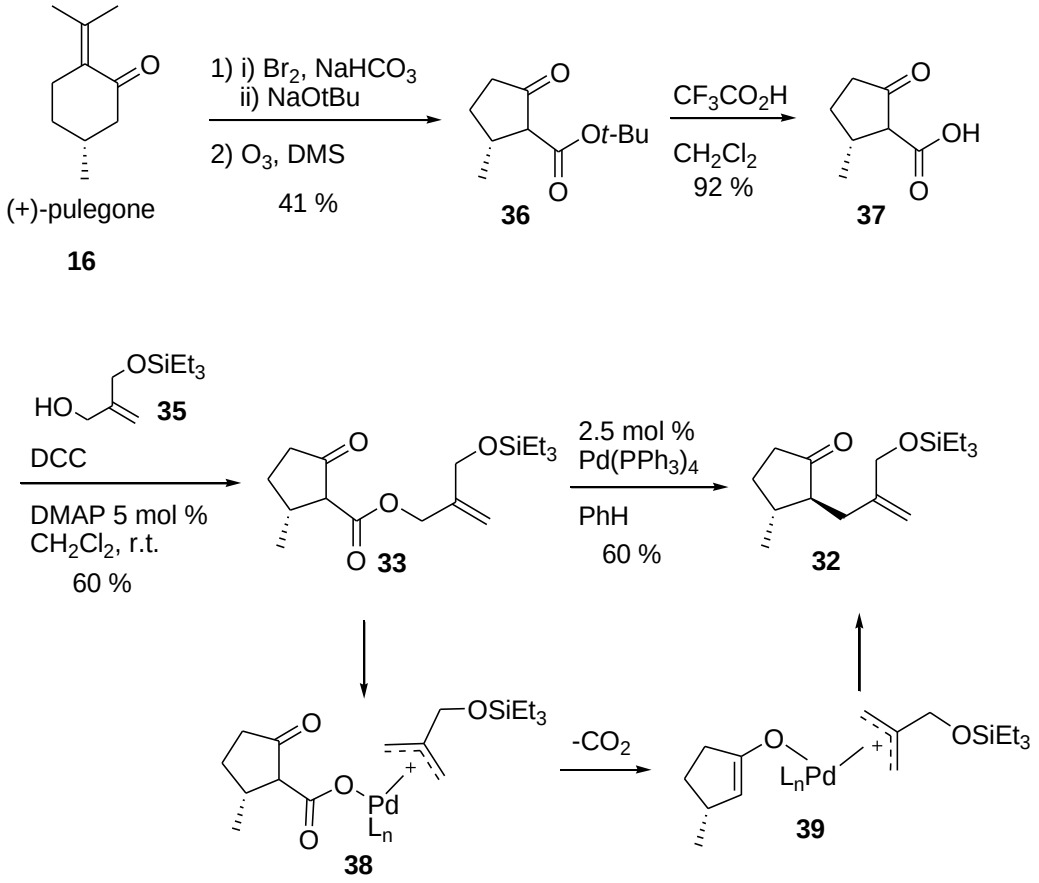


34 **35**

Scheme 2-9: The synthesis of allyl alcohol **35**.

Carboxylic acid **37** was required to couple to the aforementioned alcohol **35** (Scheme 2-10)**.** The β-ketoester **36** was once again made from pulegone, except in this case the *t*-butyl ester was formed by substituting *t*-BuOH for MeOH, allowing for eventual access to the desired acid **37** under acidic conditions (to avoid undesired decarboxylation). The procedure from Marx and Norman[6] was replicated and the ester **36** was obtained in 41% yield. The *t*-butyl

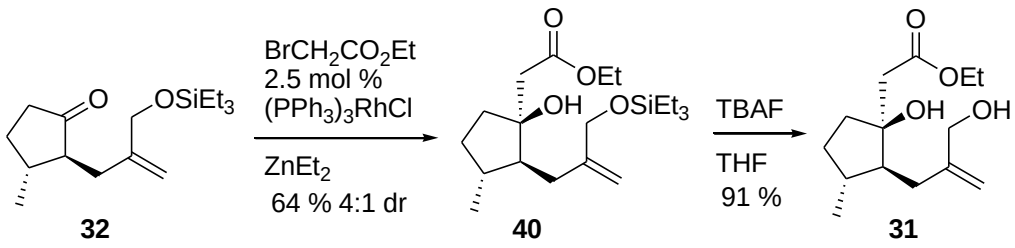
ester **36** was cleaved using trifluoroacetic acid to afford **37** in 92 % yield and the resulting acid was coupled to alcohol **35** with DCC, generating the desired ester **33** in 60 % yield. In the presence of palladium(0), a decarboxylative allylation formed the desired allyl cyclopentanone **32** in 60 % yield.



Scheme 2-10: Synthesis of allyl cyclopentanone **32**.

Next, a rhodium-catalyzed Reformatsky addition to the ketone **32** formed the tertiary alcohol **40** in 64 % yield as a 4:1 mixture of diastereomers (Scheme 2-11). Deprotection of the silyl group generated the diol **31** in 91 %

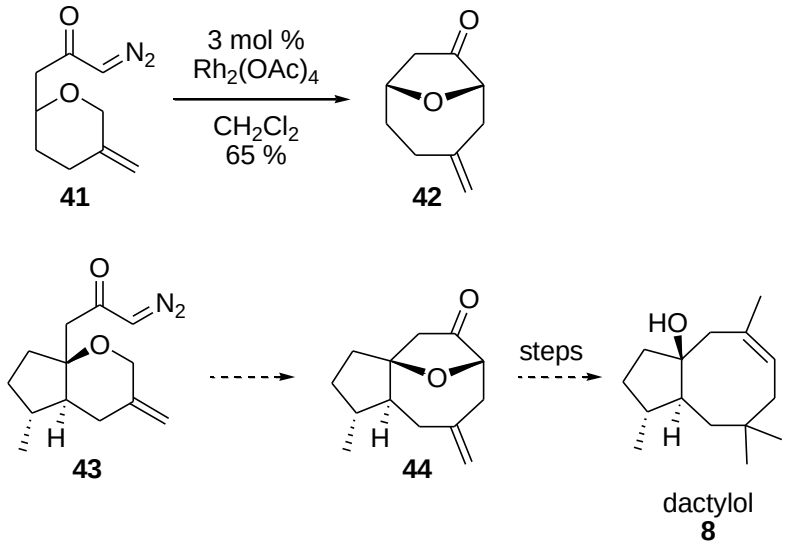
yield. With the alkene diol in hand a cyclopropanation/ hydrogenolysis sequence would generate the geminal dimethyl group; however, cyclopropanation of **31** or any of its precursors was not successful.



Scheme 2-11: Reformatsky addition and deprotection to form diol **31**.

2.1.3 Third Generation Approach to Dactylol

Previously, the West group had found that when the diazoketone **41** was subjected to a rhodium catalyst, the ring expanded product **42** was generated (Scheme 2-12). An analogous tricyclic rearrangement product **44** looks remarkably similar to the natural product dactylol **8**. The exocyclic methylene group in **44** is in the correct location for the required geminal dimethyl group, which could be potentially be introduced by a cyclopropanation/ hydrogenolysis sequence. An important challenge faced with this route is the opening of the bridging ether, a problem that was previously solved by reductive elimination triggered by a thioether moiety, which is not present in the proposed intermediate **44**.



Scheme 2-12: Eight-membered ring synthesis from an allylic ether and its potential application to the dactylol problem.

The presence of an olefin and the absence of the radical-stabilizing ArS- group implicate a different rearrangement mechanism in the key step. Once again the pendant ether would attack the transient metallocarbene **45,** leading to the formation of fused bicyclic oxonium ylide **46** (Figure 2-2). Ylide **46** could then undergo a [2,3]-sigmatropic rearrangement to form ether-bridged cyclooctanone **42**. Although **42** could also arise via a [1,2]-Stevens rearrangement mechanism, exclusive rearrangement via the [2,3] pathway is assumed based upon observation of complete allylic inversion in a substrate bearing a substituent on the exocyclic alkene carbon.

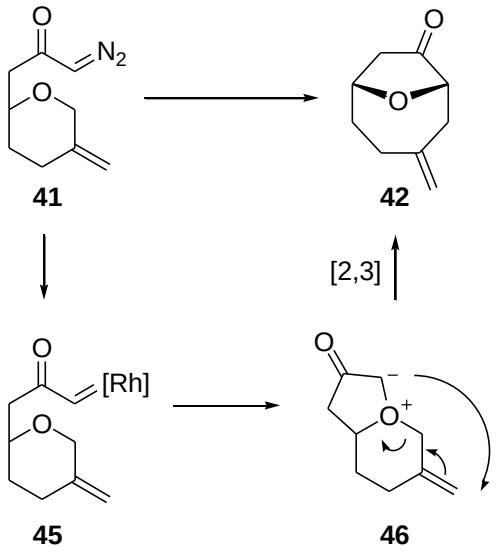


Figure 2-2: Proposed mechanism for rearrangement of allyl ether **41**.

2.1.3.1 Retrosynthetic analysis

The synthetic route utilizing a [2,3]-sigmatropic rearrangement was a promising alternative for the synthesis of dactylol, so a synthetic plan was devised (Figure 2-3). The natural product dactylol **8** could be made from the corresponding allyl ether **47**. The terminal olefin in **47** could be made from ketone **48** by a Wittig reaction while the geminal dimethyl group could be introduced through a cyclopropanation/ hydrogenolysis sequence of **44**. This 5-8 bicyclic molecule **44** is the key intermediate that potentially could arise from the [2,3]-sigmatropic rearrangement of the diazoketone **43,** which could be obtained from the previously prepared diol **31**.

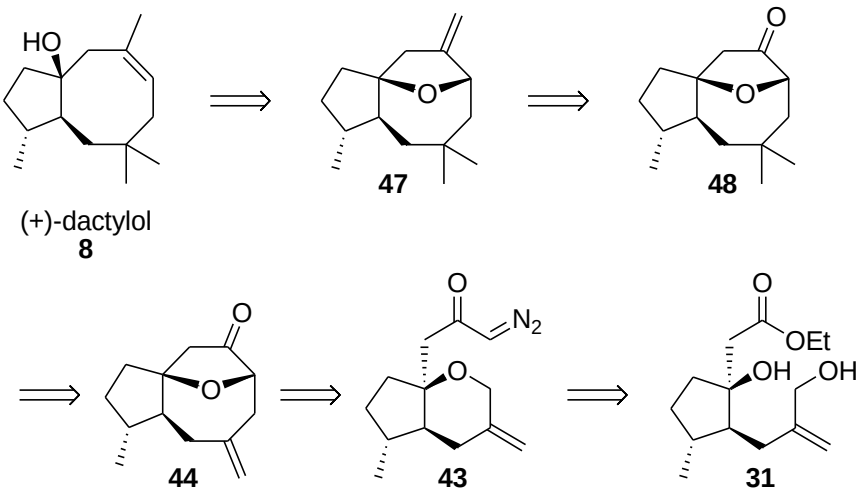
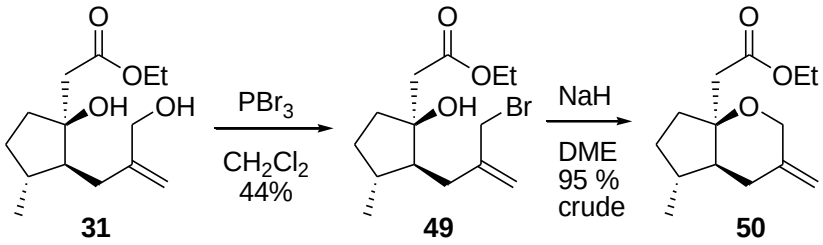


Figure 2-3: Retrosynthetic analysis including [2, 3] rearrangement protocol.

The previously synthesized diol **31** was subjected to phosphorus tribromide to generate the allyl bromide **49** in 44 % yield (Scheme 2-13). This was then cyclized to the cyclic ether **50** by subjection to sodium hydride, and it was isolated in a 95% crude yield. Unfortunately, Murphy was not able to carry this route beyond this stage due to graduation.

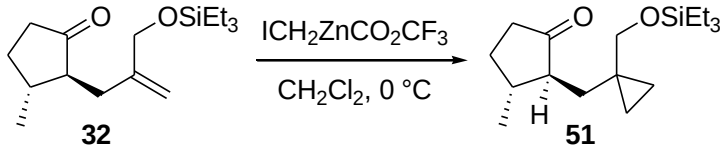


Scheme 2-13: Conversion of diol **31** to tetrahydropyran **50**.

2.2 Results and Discussion

2.2.1 Second Generation Revisited

The second generation approach was revisited to see if a geminal dimethyl containing side-chain could be introduced with control of stereochemistry. The cyclopentanone **32** was subjected to Simmons-Smith cyclopropanation conditions (Scheme 2-14). With $Zn(CH_2I)_2$ as the cyclopropanation reagent there was no reaction. The more reactive $ICH_2ZnO_2CCF_3$ was used as an alternative and the starting material was completely consumed; however, after an extended time the reaction mixture formed a complex mixture. The crude product was purified and the resulting proton NMR spectra revealed cyclopropane peaks with an absence of alkene peaks; however, it was apparent that more than one component was present. With careful control this reaction might be a method for obtaining the geminal dimethyl group, but for the time being it was abandoned.

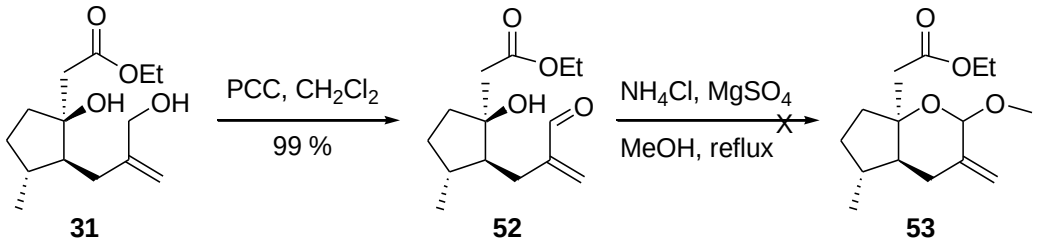


32 **51**

Scheme 2-14: Attempted cyclopropanation of allyl ether **32**.

The diol **31** was prepared as before and oxidized with PCC to the aldehyde **52** in near quantitative yield (Scheme 2-15). An acetalization of the

aldehyde to form **53** was attempted, but none of the desired mixed acetal was isolated. The major product from this reaction seemed to contain a trisubstituted alkene, indicating isomerisation of the olefin under the reaction conditions. Given its lack of applicability to the dactylol route, this compound was not fully characterized.



Scheme 2-15: Attempted formation of acetal **53** from diol **31**.

Another common approach to cyclopropanation is Corey's sulfoxonium ylide method.[7] This method cyclopropanates the alkene of an unsaturated carbonyl and, while **52** fits that requirement, we wanted to avoid the epoxidation of the aldehyde. Alternatively a substrate such as **55** would suffice (Figure 2-4). This substrate could be made by first esterifying the acid **37** with the corresponding allyl alcohol to form **54.** The ester **54** could then undergo a decarboxylative allylation reaction to generate **55**. A more streamlined approach was also considered that could afford the product in one step instead of two. A decarboxylative coupling reaction had been developed that could couple β-

ketoacid **37** to an allyl acetate to generate **55** in one step.[8] This method would be an effective way to make the desired compound.

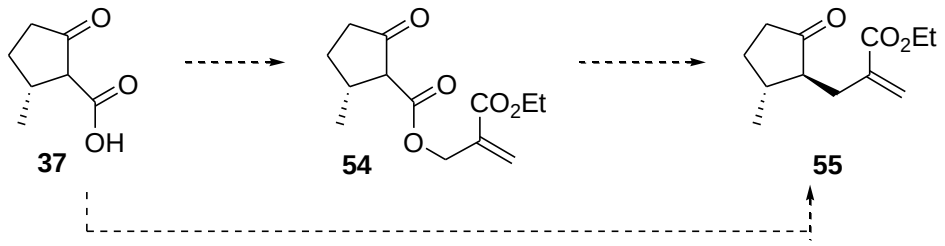
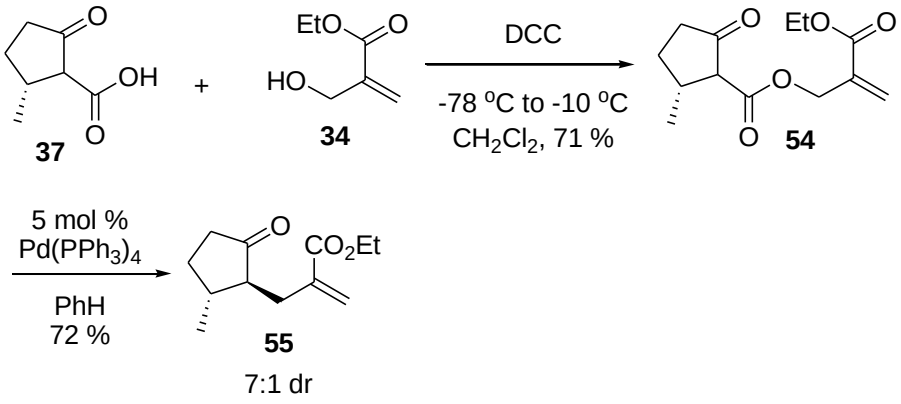


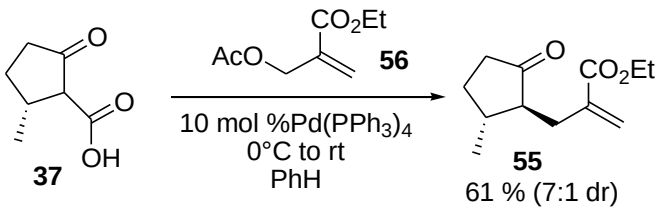
Figure 2-4: Potential routes to unsaturated ester **55**.

First the two step method was probed. The β-ketoacid **37**, prepared via the route previously devised by our group, was coupled with the alcohol **34** (Scheme 2-16). Using the optimized conditions discussed in the next section, the ester was obtained in 71 % yield using DCC as the coupling reagent. Then, ester **54** was subjected to 10 mol % of $Pd(PPh_3)_4$ in benzene and the desired decarboxylative allylation product **55** was obtained in a 72 % yield.



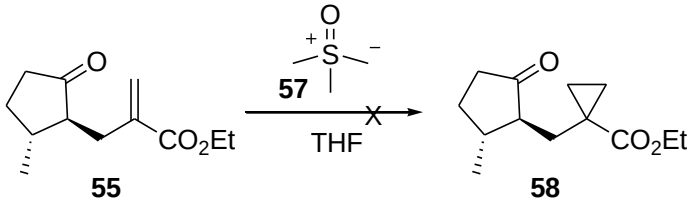
Scheme 2-16: Synthesis of conjugated ester **55**.

For the alternative 1-step decarboxylative coupling approach, first the corresponding allyl acetate **56** was required, which was available via a published procedure (Scheme 2-17).[9] The acetate **56** and the β-ketoacid **37** were combined with catalytic $Pd(PPh_3)_4$, and we were pleased to note that this process proceeded in a reasonable yield of 61 %. Various conditions were probed including temperature, time, catalyst loading and solvent; however, there was little variation in the outcome.



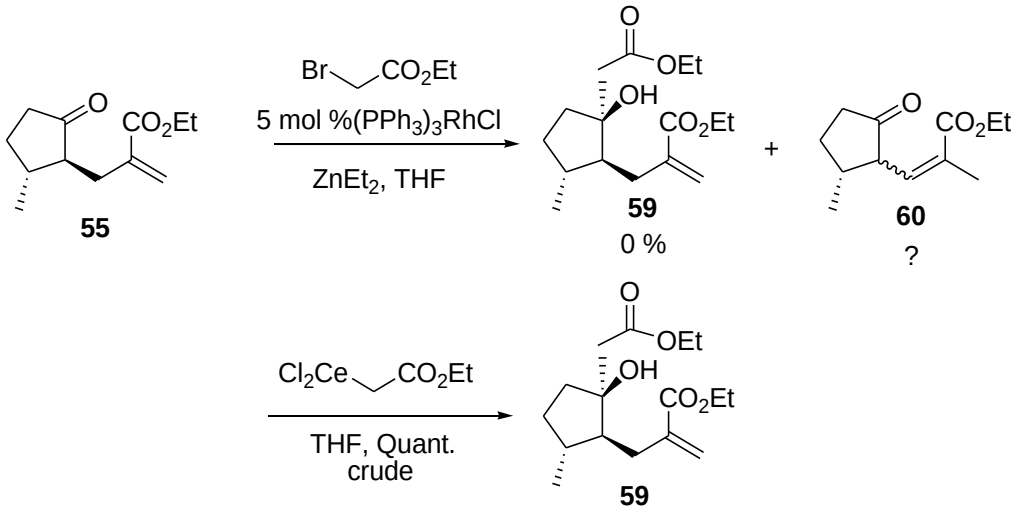
Scheme 2-17: One-step protocol for preparation of **55** from **37.**

After the desired alkylation product **55** was obtained the cyclopropanation was attempted with methylide **57**, but unfortunately there was no reaction (Scheme 2-18). This was only a minor setback as this cyclopropanation could also be attempted at a later stage, so the synthetic sequence was carried further.



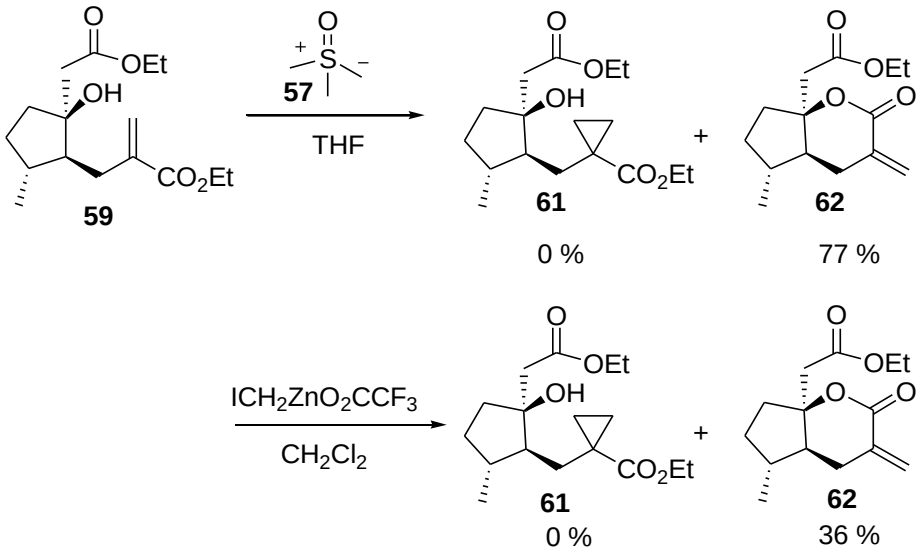
Scheme 2-18: Attempted cyclopropanation of conjugated ester **55**.

Addition of the ester side chain to **55** was attempted using a rhodium catalyzed Reformatsky reaction; however, none of the desired adduct **59** was observed. Instead an apparent olefin isomerisation product tentatively assigned as **60** was obtained (Scheme 2-19). As an alternative, addition of the cerium enolate was examined, and this process afforded **59** in quantitative yield as a single diastereomer.



Scheme 2-19: Reformatsky type addition on ketone **55**.

With the diester **59** in hand, a cyclopropanation was attempted. First, the sulfonium methylide method was investigated; however, this produced none of the desired product (Scheme 2-20). Instead, the major product isolated was the δ-lactone in a 77 % yield. Using Simmons-Smith conditions also failed to afford any of the desired **61**, and only the δ-lactone was isolated in 36 % yield.



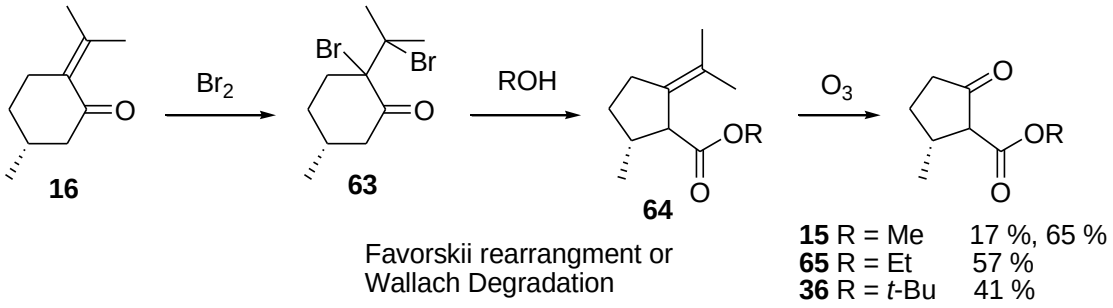
Scheme 2-20: Attempted cyclopropanation on **59** with formation of lactone **62.**

Despite the lack of a successful cyclopropanation this route still showed promise. The lactone product **62** offered an additional substrate to test the cyclopropanation. In addition, the mixed thioacetal was still accessible. However, this was not investigated further because an alternate route (next section) that was concurrently investigated was at a more advanced stage.

2.2.2 Optimization and Continuation of the Third Generation Route Towards Dactylol

The third generation route established by Murphy was an effective method to obtain the desired precursors for the [2,3] rearrangement; however, the results in this sequence were preliminary, with none of the optimization that

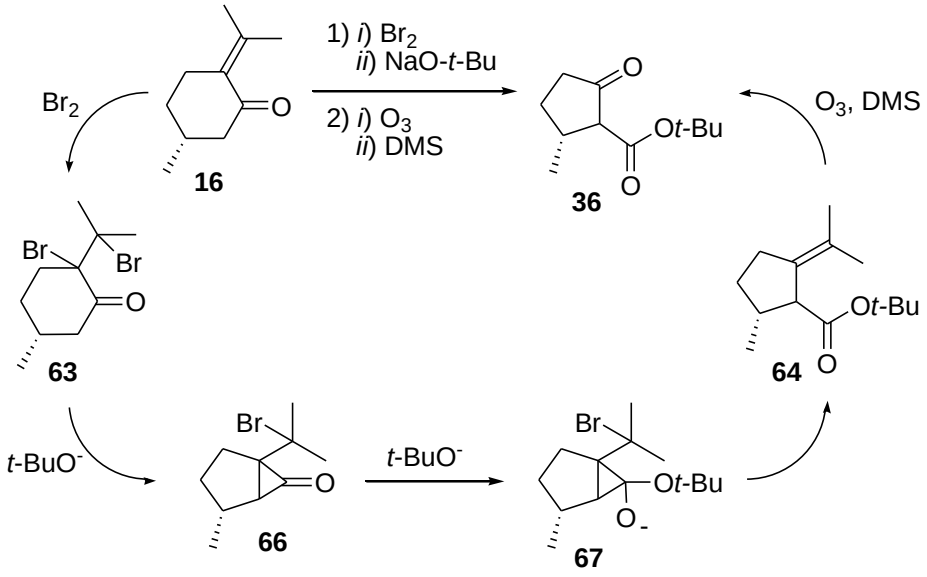
would be necessary for a successful multistep synthesis. The first part of the route to be optimized was the sequence to generate the β-ketoester **65** (Scheme 2-21). The key ring-contraction step is a variant on the Favorskii rearrangement utilizing dibromide **63**, sometimes referred to as the Wallach degradation.[10] The syntheses of the esters (**15, 65,** and **36**) from pulegone **16** has been reported several times. The methyl ester **15** has been reported by Yates with an overall yield of 17 %,[11] and by Hudlicky with significantly higher yield of 65 %.[12] In addition, Marx described the synthesis of ethyl ester **65** with a yield of 57 %.[6] We were interested in the *t*-butyl ester **36,** which has been reported; however, the yield and procedural details were not included.[13] Murphy used the procedure reported by Marx and synthesized the *t*-butyl ester with an overall yield of 41 %. This yield was comparatively lower than the reported examples and so we wished to optimize this procedure.



Scheme 2-21: Conversion of pulegone to methyl, ethyl and *t*-butyl β-ketoesters.

The mechanism for the reaction is as follows. Addition of bromine to the alkene double bond furnishes dibromide **63** (Scheme 2-22). Sodium *t*-butoxide

next generates the ketone enolate, which undergoes intramolecular S_N2 displacement of the α-bromide to form cyclopropanone **66**. This cyclopropanone is attacked by another equivalent of *t*-butoxide anion, and the resulting tetrahedral intermediate undergoes fragmentation with elimination of the remaining bromide to give ester **64**. Finally, ozonolysis of the reformed olefin provides β-ketoester **36**.



Scheme 2-22: Mechanism of Favorskii rearrangement of **16.**

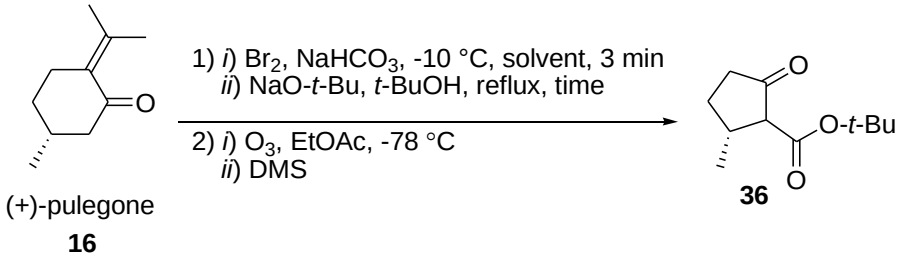
Initially our focus was on the bromination step. Excess reagent, longer bromination time or higher bromination temperature led to decreased yields so the bromination time was kept short and at -10 °C using near stoichiometric quantities of bromine. Monitoring by TLC indicated the formation of increasing amounts of undesired by-products as the reaction time was increased, and poor overall yields were obtained. To minimize decomposition, the reaction times

were shortened and the crude dibromide was not isolated but was carried on directly to the next step.

Next, the Favorskii rearrangement step was examined. Since intermediate *t*-butyl pulegonate **64** could not be obtained in pure form, the yields given are for the entire sequence from pulegone to the β-ketoester **36.** The previous procedure utilized a derivatization step entailing the formation of the semicarbazone of the unreacted pulegone to separate it from **64.** This was found useful when purification was to be achieved by distillation. However, removal of unreacted **16** during chromatographic purification was effective, allowing the omission of the semicarbazide step.

Diethyl ether was found to be a more effective solvent than THF (*Table 2-1*). The use of potassium *t*-butoxide as base was expected to simplify the procedure; however, when it was used in place of sodium *t*-butoxide it resulted in slightly lower yields and was not scalable. In addition, excess *t*-BuOH was found to improve the yield, whereas excess sodium decreased the yield.

Table 2-1: Optimization of reaction sequence forming **36**.



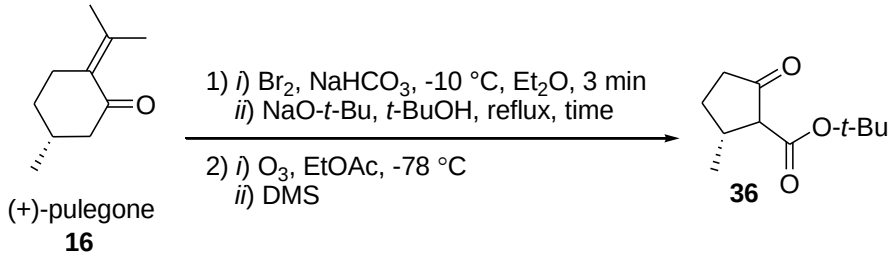
(+)-pulegone **16** **36**

Trial	Solvent	Base, equiv.	*t*-BuOH equiv.	Time (h)	Yield
1	Et_2O	NaO*t*-Bu, 2	14	20	23 %
2	THF	NaO*t*-Bu, 2	14	20	8 %
3	Et_2O	NaO*t*-Bu, 4	14	10	14 %
4	Et_2O	NaO*t*-Bu, 2	30	20	34 %
5[a]	Et_2O	NaO*t*-Bu, 2	30	20	35 %
6	Et_2O	KO*t*-Bu, 2	30	20	26 %
7	Et_2O	NaO*t*-Bu, 2	30	20	44 %

See experimental for detailed conditions [a]CH_2Cl_2/MeOH used instead of EtOAc in O_3 step.

Having selected the optimal conditions the scalability of this process was investigated. The bromination/Favorskii/ozonolysis sequence was carried out using 41 mmol, 83 mmol, 166 mmol and 416 mmol of pulegone (Table 2-2). Notably, while very little variation of yield was seen, at the largest scale an overall yield of 64 % was achieved. This represents an average of 86 % yield per step over the entire process.

Table 2-2: Optimization and scale up for **36.**[a]

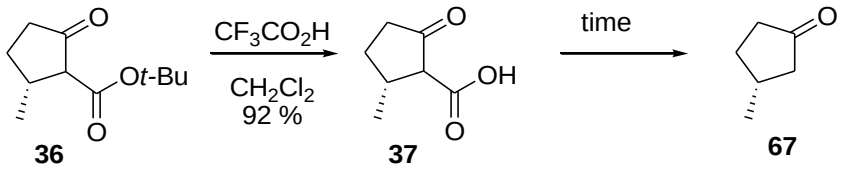


(+)-pulegone **16** → **36**

Trial	Pulegone (mmol)	Na (equiv)	*t*-BuOH	Temp	Time	Yield
1	10	4	14	rt	24 h	28 %
2	10	2	28	reflux	24 h	40 %
3	10	2	28	rt	24 h	32 %
4	10	2	28	reflux	1 h	37 %
5	41	2	28	reflux	24 h	37 %
6	83	2	28	reflux	17 h	36 %
7	116	2	28	reflux	22 h	40 %
8	416	2	28	reflux	20 h	64 %

[a]See experimental for detailed conditions.

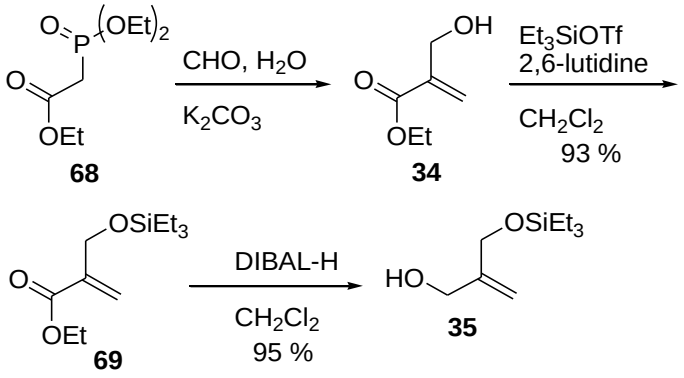
With **36** now available in large quantities, removal of the *t*-butyl group was examined in detail. The ester **36** was converted into carboxylic acid **37** using trifluoroacetic acid (Scheme 2-23). Optimal conversion took place with high concentrations of acid. More dilute conditions led to longer reaction times,



Scheme 2-23: Generation of carboxylic acid **37**.

and no product was formed with catalytic amounts of acid. Notably the product would also decarboxylate to generate **67** after extended periods, so the acid was used immediately in the next step.

An alcohol was synthesised to combine with the carboxylic acid; starting with a known procedure,[14] triethyl phosphonoacetate **68** was converted to the conjugated ester (Scheme 2-24). Then the primary allylic alcohol of **34** was protected as a triethylsilyl ether in 93 % yield and then the ester was reduced with diisobutyl aluminum hydride in 95 % yield. For this two step process the overall yield of **35** was improved to 88 % from the previous 53 %.



Scheme 2-24: Alcohol side chain synthesis.

After the carboxylic acid and the alcohol were synthesized the coupling could be performed; however, initial attempts at the esterification using DCC resulted in low yields of product. During our investigations into the reaction several discoveries were made. Longer reaction times were found to be

detrimental, and 1 min reactions were found to be best. Having more DCC than acid was also observed to give poor results. The exclusion of DMAP dropped the yield as well. In our initial tests we were forced to used an excess (3 equivalents) of carboxylic acid **37** to get yields as high as 86 %. Slightly more favorable conditions using 1.6 equivalents of acid gave a slightly lower yield (75 %).

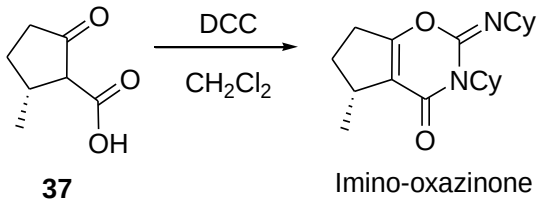
Table 2-3: Optimization of DCC esterification.[a]

#	**37** (equiv)	**35** (equiv)	DCC (equiv)	DMAP (equiv)	Temp	Reaction Time	yield
1	1	1.3	1.3	0.10	0 °C to rt	9 h	31%
2	1	1.5	2.2	0.6	0 °C	30 min	10 %
3	1	1.6	1.5	0.3	-10 °C	1 h	23 %
4	1	1.2	1.2	0.06	0 °C	30 min	69 %
5	1.2	1	1.2	0.06	0 °C	30 min	40 %
6	1	1.2	1	0	0 °C	30 min	18 %
7	1	1.2	1	0.10	0 °C	1 min	35 %
8	1	1.2	1.3	0.10	-78 °C	5 min	30 %
9	3	1	1.6	0.05	0 °C	1 min	86 %
10	1.6	1	1.3	0.03	0 °C	1 min	75 %

[a]See experimental for detailed conditions.

A 75 % yield was acceptable for producing material despite the excess acid; however, when the reaction was repeated on a larger scale the yield dropped and on occasion no product was obtained. Lack of reproducibility combined with a procedure that required excess of the valuable acid resulted in a procedure that was not amenable to a total synthesis so, unfortunately, the reaction needed to be investigated further.

It was observed that when only the carboxylic acid **37** and DCC were combined an exothermic reaction occurred forming an unreactive side product. This product was determined to be an imino-oxazinone (Scheme 2-25, see chapter 3 for more details) and it was also observed that some deprotection occurred over the course of the reaction. In addition, with careful observation

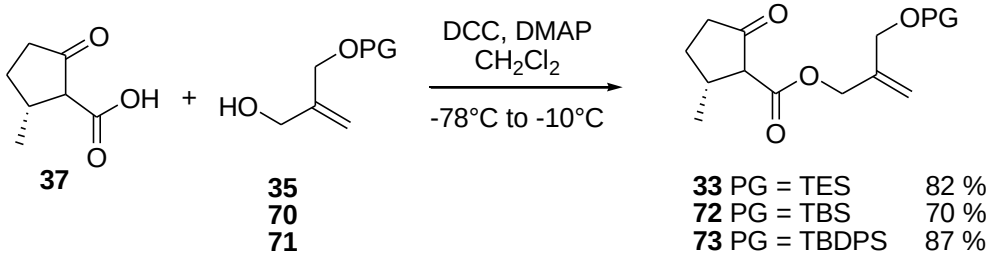


37 Imino-oxazinone

Scheme 2-25: Side product formed in DCC esterification reaction.

and a gradual increase in temperature it was observed that the reaction does not proceed until the temperature is raised to -10 °C. Also, it was observed that the materials are not soluble in cold dichloromethane. With all of these factors in mind, the following conditions were probed with a stoichiometric amount of the reagents and a catalytic amount of DMAP. The alcohol **35** and the acid **37** were

separately dissolved in dichloromethane, cooled to -78 °C and then combined. This assured that no deprotection would occur. Then DCC and DMAP were added to the solution after which the temperature was increased to -10 °C. With these conditions the ester was generated in 82 % yield and the reaction was consistent and scalable (Scheme 2-26). Additional alcohol side chains were prepared with different silyl protecting groups (**70** and **71**) to see if improvements could be made in the synthesis. With protection as a TBDPS ether, the ester **73** was generated in 87 % yield. The TBS ester **72** was generated in a slightly lower yield but was still useful as it was much cheaper and so was used for larger scale reactions.

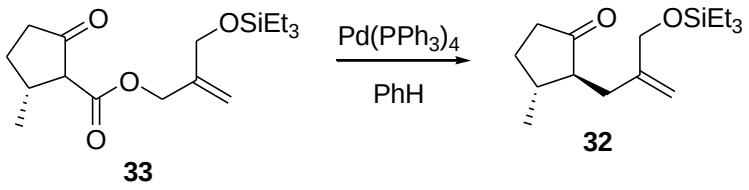


Scheme 2-26: Optimized esterification performed with different side chains.

The next step was the palladium catalyzed allylation reaction.[15] Initially with 7.8 mol % of catalyst a 68 % yield of product was obtained after 5 hours. An increased reaction time and less catalyst dropped the yield slightly to 64 % (Table 2-4). The reaction was performed for five hours with half the amount of catalyst and the yield dropped to 58 % (entry 3). Benzene was replaced with the less hazardous toluene and unfortunately the yield decreased substantially,

regardless of reaction temperature. Ultimately, the source of catalyst proved to be the critical factor. Changing to a newer source of $Pd(PPh_3)_4$ resulted in a much higher yield of **32,** even at 1.8 % loading. Moreover, the reaction was scalable.

Table 2-4: Optimization of palladium-catalyzed allylation reaction.

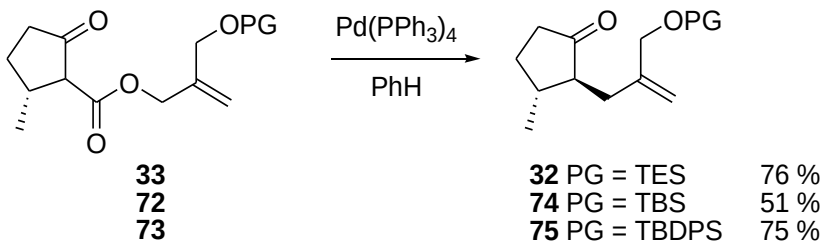


33 **32**

Trial	Catalyst (mol %)	Solvent	Time (h)	Temp	Yield
1	8	Benzene	5	rt	68 %
2	3	Benzene	32	rt	64 %
3	4	Benzene	5	rt	58 %
4	3	Toluene	5	rt	35 %
5	3	Toluene	5	0 °C	26 %
6[a]	2	Benzene	4	rt	76 %

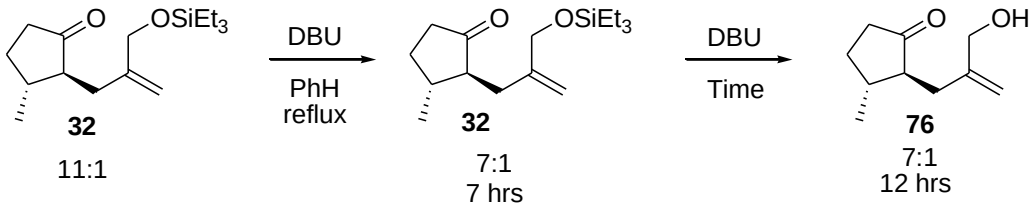
[a] A better quality catalyst was utilized.

The best conditions were applied to the differentially protected substrates. The yield of the TBDPS-protected substrate **74** was 75 %, comparable to the yield of the TES-protected substrate **33.** The TBS protected product **74** was generated in a much lower yield of 51 % (Scheme 2-27).



Scheme 2-27: Decarboxylative allylation reaction on different substrates.

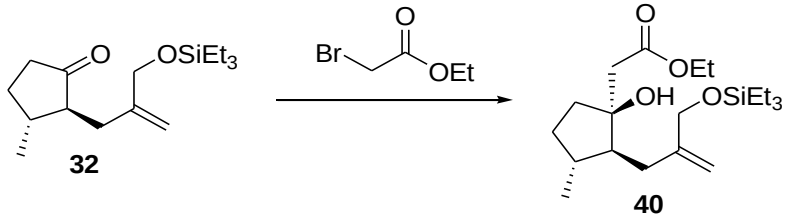
Throughout all of the conditions tested the diastereoselectivity was consistently 11:1 in favour of the desired *trans* diastereoisomer. In the ^{1}H NMR spectrum, the methyl group of the major isomer appeared downfield of the methyl group of the minor isomer. This observation is consistent with other 2,3-*trans*-cyclopentanones.[16, 17] To epimerize the minor diastereomer the product mixture was subjected to DBU in benzene for 7 hours; however, the product ratio was found to decrease to 7:1 (Scheme 2-28). This unfortunate result was also reported by Molander with a similar substrate.[4] No further stereochemical change was seen with extended reaction time, indicating that this is the thermodynamic ratio. However, loss of the triethylsilyl ether was observed.



Scheme 2-28: Epimerization of cyclopentanone **32.**

Addition of the ester side-chain to the cyclopentanone was examined next (Table *2-5*). Standard conditions using Zn metal[18, 19] were ineffective (entries 1-3). Use of Wilkinson's catalyst with diethylzinc[20] afforded moderate amounts of the desired product in an acceptable dr of 8:1 (entry 4). Longer reaction times were counterproductive, but carrying out the reaction at room temperature provided the product in good yield (entry 6), and even better yield on a larger scale. This improvement may be due to an increased likelyhood of

Table 2-5: Optimization of Reformatsky type reaction.



32 **40**

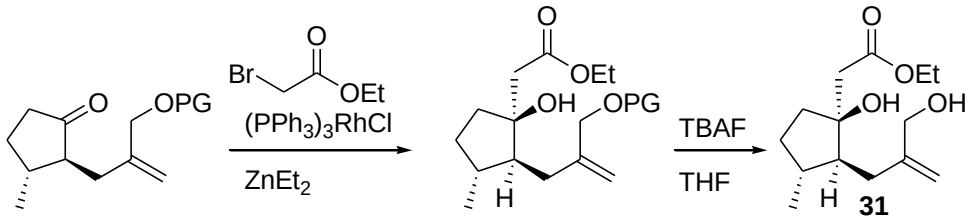
Trial	Activator/ Catalyst	Reductant	Temp	Time	dr	Yield
1	TMSCl	Zn	0°C to rt	17 d	-	0
2	TMSCl	Zn	reflux	2 h	-	0
3	$ZnCl_2$	K	0°C to rt	9 d	-	0
4	$(PPh_3)_3RhCl$	$ZnEt_2$	-78 °C to rt	4 d	8:1	34 %
5[a]	$(PPh_3)_3RhCl$	$ZnEt_2$	-78 °C to rt	21 d	4:1	24 %
6[b]	$(PPh_3)_3RhCl$	$ZnEt_2$	rt	32 h	2:1	68 %
7[c]	$(PPh_3)_3$ RhCl	$ZnEt_2$	rt	30 min	4:1	80 %

[a] Product and starting material from entry 4 re-subjected to the reaction conditions.

[b]Reaction performed at 18 mg scale. [c]Reaction performed at 770 mg scale.

of interference by adventitious oxygen.[21] While the yield was acceptable under the optimal conditions, it was not possible to achieve a dr of greater than 4:1.

The optimized rhodium-catalyzed Reformatsky reaction was performed with the three different silyl-protected alcohols and the protecting groups were removed with TBAF in Et_2O (Scheme 2-29). Deprotection of the triethylsilyl group worked well, affording diol **31** in 88 % yield (70 % over two steps). The TBS-protected substrate was converted to **31** in a comparable yield of 69 % over two steps; however, the Reformatsky addition generated a slightly lower diastereomeric ratio of 2.2:1. The TBDPS-protected substrate **74** reacted with a higher diastereomeric ratio of 6.4:1; however, in that case the overall yield over two steps was only 53 %. It was observed that the minor isomer from the Reformatsky reaction was a solid and could be isolated from the mixture.

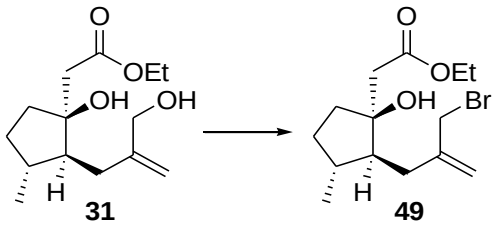


Scheme 2-29: Reformatsky reaction on silyl-protected substrates.

The next reaction step in the sequence is the conversion of allylic alcohol **31** to allylic halide **49** so that tetrahydropyran **50** could be formed. The first

attempts with phosphorus tribromide resulted in a low yield of 23 % (entry 1, Table *2-6*). Bromination with N-bromosuccinimide and dimethyl sulfide generated a side product (**82** see below).[22] Changing to triphenylphosphine and carbon tetrabromide proved to be much more effective, generating the product in 92 % yield.[23]

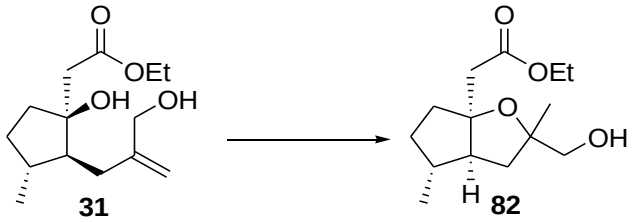
Table 2-6: Optimization of allyl bromide formation reaction.



31 **49**

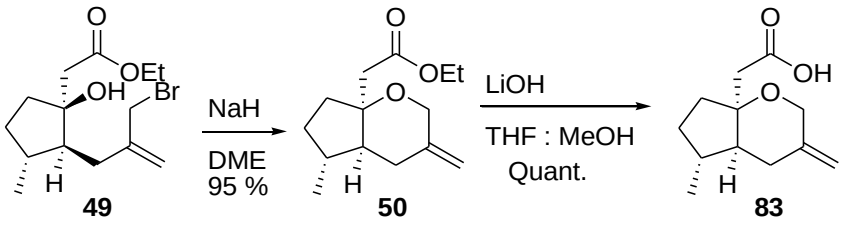
Trial	Reagent	Solvent	Temp	Yield
1	PBr_3	CH_2Cl_2	0 °C	23 %
2	NBS/DMS	CH_2Cl_2	0 °C	0 %
3	CBr_4, PPh_3	CH_3CN	rt	92 %

On occasion a significant side product was formed during the halogenation step, especially at larger scales. This product, lacking an olefin, was assigned structure **82** (Scheme 2-30). We surmise that this compound results from acid-catalyzed cyclization.



Scheme 2-30: Side product occasionally observed during the bromination of **31**.

Tetrahydropyran **50** was then formed by adding sodium hydride to the allyl bromide **49** (Scheme 2-31). With THF or diethyl ether as the solvent the reaction was found to be slow, but in dimethoxyethane the reaction was much faster. This result was essentially the same as the previously reported method.[3] Ester **50** was saponified with lithium hydroxide and carboxylic acid **83** was obtained in quantitative yield.



Scheme 2-31: Cyclization and saponification of **49.**

To confirm the relative stereochemsitry of the major isomer, a TROESY experiment was performed on ester **50** (Figure 2-5). Both protons α to the ester were correlated to the bridgehead proton and one of the protons next to the alkene. The methyl group had a correlation to a proton next to the alkene as

well. These correlations provide good evidence for the proposed stereochemistry.

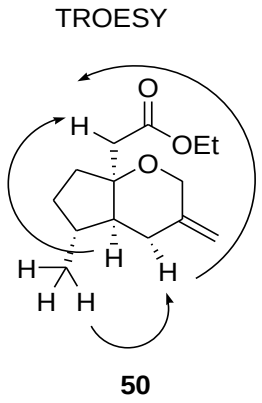


Figure 2-5: TROESY experiment on **50.**

The stereogenic center next to the ether was formed in only a 4:1 ratio (**31,** Figure 2-6**)**. This ratio could be increased by forming that stereogenic center intramolecularly rather than intermolecularly. Performing a Horner-

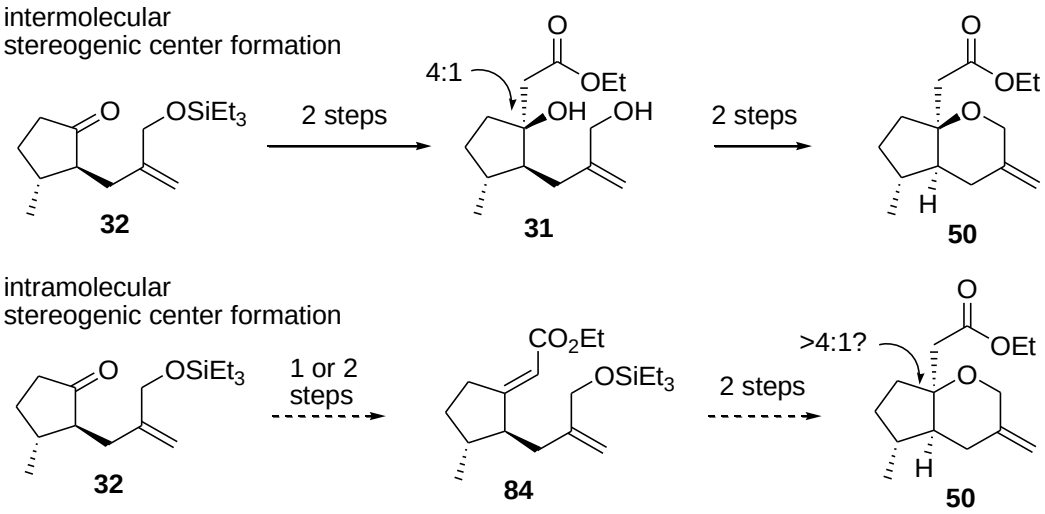
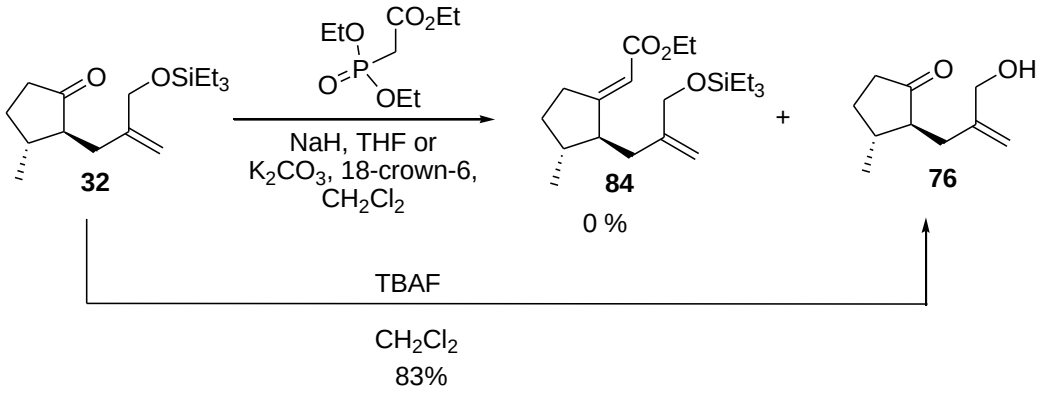


Figure 2-6: Potential intramolecular cyclization to increase stereoselectivity.

Wadsworth-Emmons reaction on ketone **32** could form the conjugated ester **84** in one step. After deprotection the tethered alcohol in **84** could then undergo a conjugate addition into the alkene, thus forming the stereogenic center intramolecularly, and possibly increasing the stereoselectivity. This sequence could also decrease the number of synthetic steps, making a more efficient synthesis.

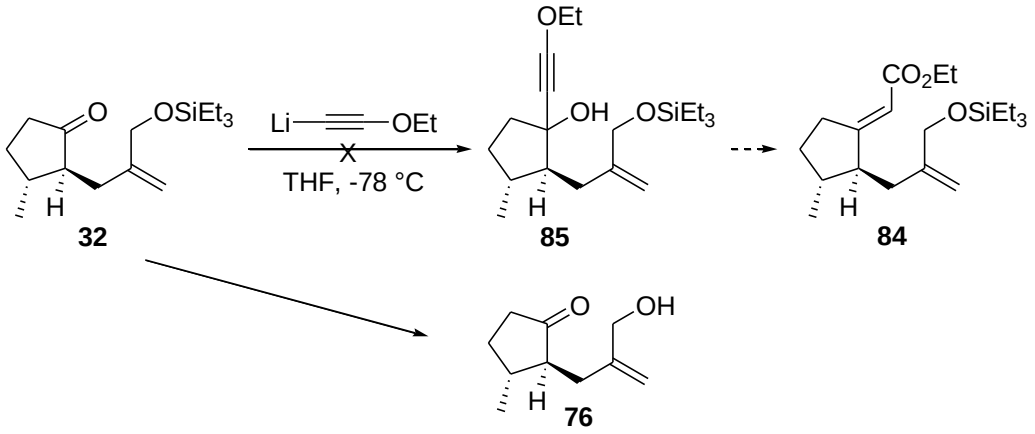
The ketone **32** was subjected to Horner-Wadsworth-Emmons conditions, using triethyl phosphonoacetate and base (Scheme 2-32). Different conditions were used; however, the only product obtained was the deprotected alcohol **76**. The product was confirmed by deprotection of the starting ketone using TBAF in dichloromethane.



Scheme 2-32: Attempted Horner-Wadsworth-Emmons reaction.

An alternative to the Horner-Wadsworth-Emmons reaction is an addition of a lithium acetylide to form **85** followed by a Meyer-Schuster rearrangement to

generate **84** (Scheme 2-33).[24] Adding the lithium acetylide to ketone **32** only resulted in deprotected alcohol with no sign of the desired acetylide adduct **85** in the crude NMR spectra. This alternate pathway may be viable using a different protecting group on the primary alcohol; however, this route was not investigated any further.

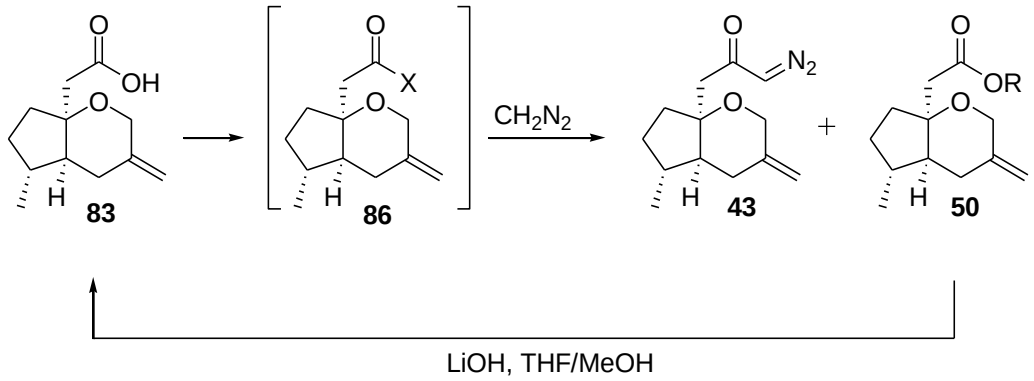


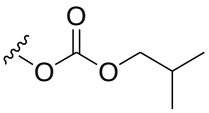
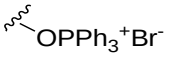
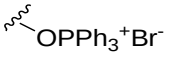
Scheme 2-33: Attempted synthesis of Meyer-Schuster substrate **85**.

The next transformation in the sequence is the conversion of the acid **83** into the key reactive intermediate diazoketone **43** (Table 2-7). For this process the carboxylic acid **83** was activated (**86**) and then combined with diazomethane. Under these conditions unreacted carboxylic acid is transformed into the methyl ester. In addition, ethanol or water may be present from the diazomethane generation. These would ultimately introduce ester by-products (**50**) in addition to the diazoketone **43**. These esters were isolated as a mixture with impurities and so were hard to quantify. So instead the esters **50** were saponified and quantified as the carboxylic acid **83**. Several acyl activators were investigated. *i*-Butyl carbonate and the mixed sulfonic anhydride[25] were found to be

ineffective as acyl activators (entries 1 and 2). The acyl chloride was formed using oxalyl chloride, and was found to give

Table 2-7: Diazoacetylation optimization results.



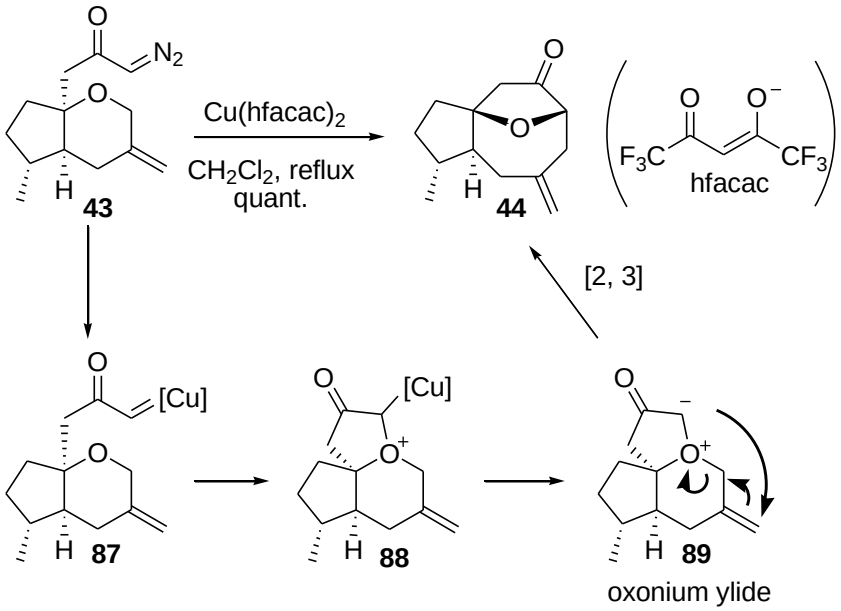
Trial	Order of addition[a]	-X	Yield of recovered **83**	Yield of **43**
1	inverse		-	traces
2	inverse		-	0 %
3	normal		4 %	75 %
4	inverse		27 %	28 %
5	normal		-	41 %
6	inverse		9 %	74 %

[a]"normal" addition refers to the addition of substrate to the CH_2N_2 solution; "inverse" refers the addition of CH_2N_2 solution to the substrate.

43 in 75 % yield. The mixture of esters was saponified and 4 % of the carboxylic acid was recovered (entry 3). When the order of addition was changed, adding diazomethane to the reaction, the yield was considerably lower

at 28 % product and 27 % acid (entry 4). On occasion, it was also found that when the acyl chloride method was utilized the product could not be obtained pure. An alternative method was investigated: utilizing triphenylphosphine and *N*-bromosuccinimide afforded **43** in 74 % yield. However, the overall conversion was better, since an additional 9 % of carboxylic acid **83** could be recovered (entry 6).[26] Converse to the oxalyl chloride method, adding the activated acyl to diazomethane worked considerably worse giving 41 % yield (entry 5).

With the diazoketone in hand the key rearrangement could then be performed (Scheme 2-34). The substrate **43** was treated with copper(II) hexafluoroacetylacetonate in dichloromethane at reflux and the product **44** was obtained in a quantitative yield. The crude NMR spectrum obtained after workup was exceptionally clean with no observable side products. The reaction is believed to occur as follows: first complexation of the diazoketone to the metal complex with loss of N_2 affords the metallocarbene **87.** This is followed by attachment of the electron-deficient metallocarbene to the ether oxygen to furnish oxonium ylide **89.** The ylide can then undergo a [2, 3]-sigmatropic rearrangement to form the ether-bridged cyclooctanone **44**.



Scheme 2-34: Key rearrangement and mechanism to form **44**.

2.2.3 End-Game Strategy

With the requisite 5-8 ring system obtained, the final steps towards the natural product dactylol could be performed (Figure 2-7). The required steps include the conversion of the exocyclic methylene into a geminal dimethyl group, the opening of the bridging ether and the introduction of another methyl

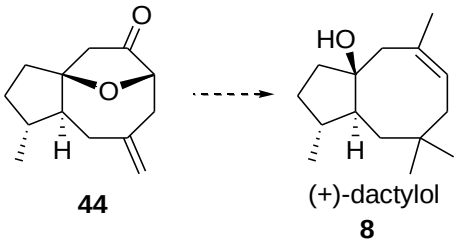
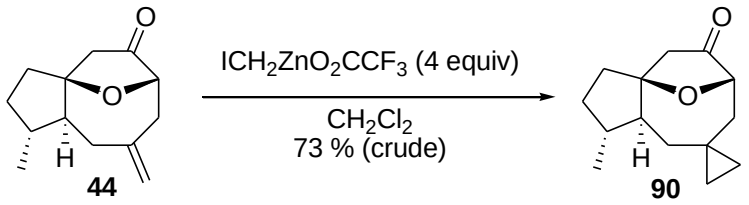


Figure 2-7: Advance intermediate **44** and dactylol **8.**

group. We decided that the formation of the geminal dimethyl group would be explored first, using the previously discussed cyclopropanation/hydrogenolysis approach.

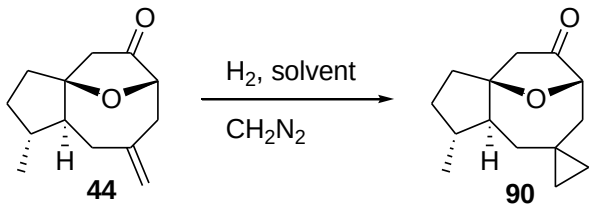
A Simmons-Smith cyclopropanation was attempted on substrate **44.** Numerous attempts resulted in low conversion and inseparable product/starting material mixtures. On a couple of occasions it was possible to isolate the desired product, but the yield was only as high as 73 % (crude) and the procedure was not reproducible.



Scheme 2-35: Simmons-Smith cyclopropanation study on **44**.

Given the disappointing results in the attempted Simmons-Smith cyclopropanation of **44**, alternative methods were explored (Scheme 2-36). Metal-catalyzed cyclopropanations with diazomethane have been shown to be an effective strategy.[27] Rhodium(II) acetate and copper(II) acetylacetonate were largely ineffective, but palladium(II) acetate (5 mol %) afforded the desired cyclopropane in a moderate 36 % conversion. Increasing amounts of catalyst led to higher conversion, but under essentially non-catalytic conditions. These

results suggested that it might be preferable to carry out the cyclopropanation at a later point in the sequence.



	conversion
$Rh_2(OAc)_4$ (20 mol %)	5%
$Cu(acac)_2$ (30 mol %)	0%
$Pd(OAc)_2$ (5 mol %)	36%
$Pd(OAc)_2$ (50 mol %)	50%

Scheme 2-36: Metal-catalyzed cyclopropanation study on **44.**

Rather than trying to cyclopropanate at the stage of **44,** we chose to investigate prior addition of a methyl group into the ketone, whose presence we suspected might be contributing to the low reactivity of that substrate. Moreover, the known propensity of nearby hydroxyl groups to direct Simmons-Smith cyclopropanations[28] suggested that the resulting tertiary alcohol might be a superior substrate. Thus, methylated substrate **91** would be subjected to cyclopropanation/hydrogenolysis to afford geminal dimethyl-containing intermediate **92** (Figure 2-8). Conversion of the alcohol to a suitable carbanion precursor (e.g., chloride, as in **93**) would permit the regioselective opening of the bridging ether under reductive conditions, leading directly to dactylol **8.**

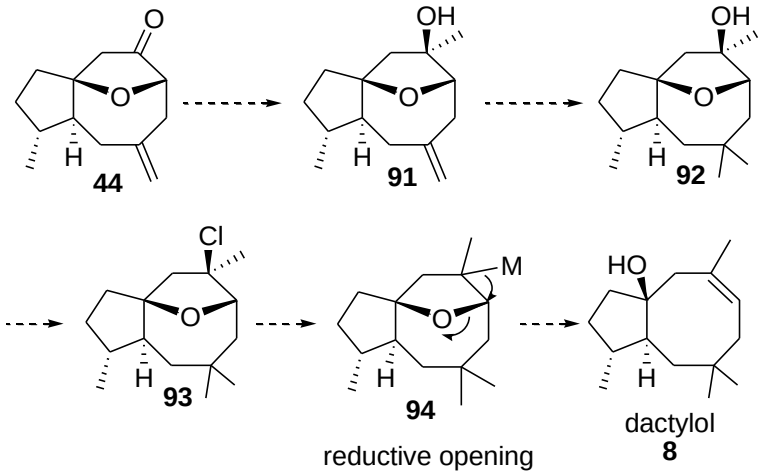
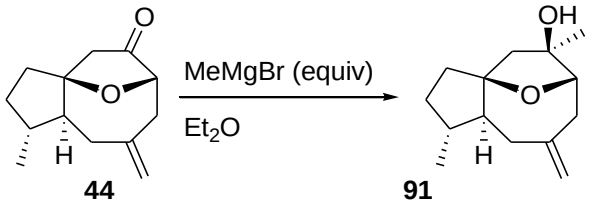


Figure 2-8: Approach for introduction of geminal dimethyl and opening bridging ether.

The methylmagnesium bromide addition into ketone **44** was initially found to proceed in low yield (Scheme 2-37). Adding additional equivalents of reagent led to a decreased yield so the temperature was dropped. Finally, we

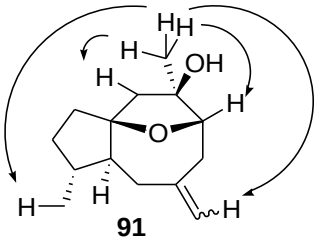


equiv.	Temp.	Time	Yield
2	0 °C	2.5 h	54 %
7	0 °C	1.5 h	17 %
6	-78 °C to rt	2.0 h	63 %
6	-78 °C to 0 °C	2.0 h	81 %

Scheme 2-37: Optimization of methyl Grignard addition to ketone **44**.

found that carrying out the addition at -78 °C followed by warming to 0 °C afforded the tertiary alcohol in a very acceptable yield of 81 %.

To our surprise alcohol **91** was formed as a single diastereomer. This stereocenter would ultimately become an sp^2 carbon, so its configuration may well be of no consequence. Nonetheless, we carried out a TROESY experiment to clarify the question (Figure 2-9). Irradiation of the newly added methyl group led to enhancements of signals for the neighbouring protons, as expected. However, the protons of the exocyclic methylene and the remote methyl on the cyclopentane ring also showed an enhancement, providing strong evidence for the indicated configuration. This stereochemical outcome was surprising, as greater steric hindrance was expected on the bottom face of **44.**

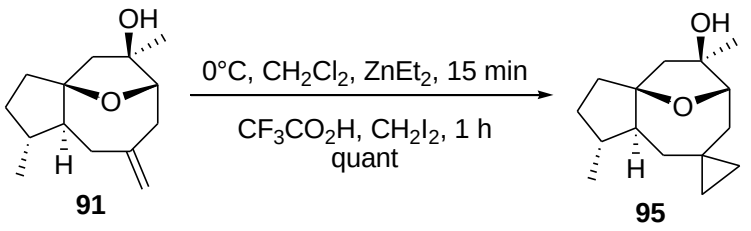


91

Figure 2-9: NOE correlations observed for tertiary alcohol methyl group of **91.**

Simmons-Smith cyclopropanation was once again examined, now using alcohol **91** (Scheme 2-38). A 69 % yield of cyclopropane **95** was realized from pretreatment of **91** for 5 minutes with $ZnEt_2$, followed by trifluoroacetic acid and

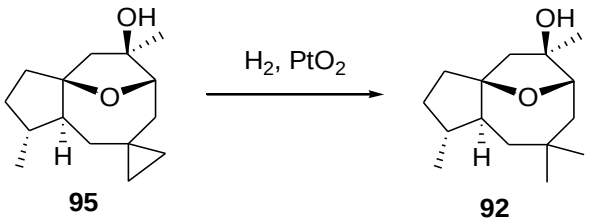
diiodomethane. The yield of the desired product could be improved to quantitative by increasing the stirring time with $ZnEt_2$.



Scheme 2-38: Optimized conditions for cyclopropanation of **91**.

After the successful synthesis of the cyclopropane, hydrogenolysis was needed to introduce the geminal dimethyl moiety. Initially, the hydrogenolysis was investigated with PtO_2 in ethyl acetate; however, no product was observed and when the pressure was increased to 60 psi, decomposition of the solvent was observed (*Table 2-8*). The solvent was changed to acetic acid and full conversion was obtained with a large excess of metal (entries 4 and 5). Increasing the temperature resulted in full conversion; however, the only product obtained was a side product (Scheme 2-39). To avoid the side product the temperature was kept at room temperature and the pressure was incrementally increased; this resulted in no improvements in the conversion. Instead, the pressure was dropped to atmospheric and the time was increased. After 14 days we observed full conversion. Unfortunately at this point the material quality was too poor to quantify (entry 12). The successful reaction at low pressures and relatively low loading was insightful. A possible reason for this trend is due to

Table 2-8: Variation of cyclopropane hydrogenolysis conditions.



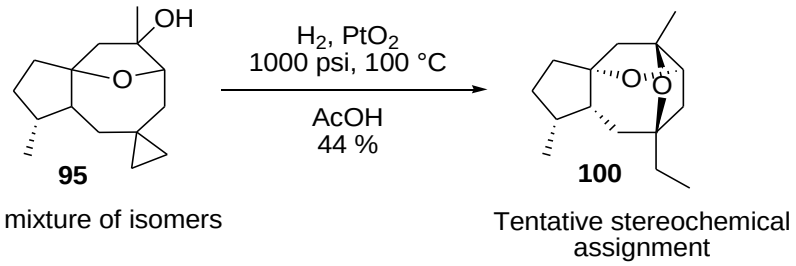
Trial	PtO_2 equiv	Solvent	Pressure (psi)	Temp. (°C)	Time	Conversion[a]	Yield
1	0.7	EtOAc	30	rt	30 min	0 %	
2	0.8	EtOAc	60	rt	30 min	0 %	
3[b]	1.0	EtOAc	60	rt	9 h	0 %	
4	1.0	AcOH	60	rt	6 h	low	
5	9.0	AcOH	60	rt	67 h	100 %	61 %
6	0.2	AcOH	1000	100	22 h	100 %	44 % [c]
7	1.2	AcOH	1800	rt	8 h	low	
8	0.5	AcOH	6900	rt	20 h	low	
9	0.6	AcOH	38	rt	48 h	increase	
10	0.4	AcOH	60	rt	29 h	low	
11	0.9	AcOH	10	rt	100 h	increase	
12	1.1	AcOH	balloon	rt	14 d	100 %	

[a] Determined by ^{1}H NMR analysis by disappearance of cyclopropane signals. [b]EtOAc decomposed. [c] Side product.

the competitive binding of cyclopropane to the metal surface; when extra pressure is added hydrogen could be populating all of the available sites on platinum not allowing the cyclopropane to adsorb, thus not letting the reaction

proceed. The lower pressure could allow an equilibrium of binding allowing the cyclopropane to react. This may also be why excess catalyst is required with higher pressure, as excess platinum can adsorb all of the cyclopropane allowing the reaction to take place. During our studies we observed that the catalyst was reusable after each reaction. This suggested that a catalytic reaction might be possible.

When optimizing the cyclopropane hydrogenolysis reaction, using a minor isomer mixture of **95,** the interesting diether side product **100** was obtained (Scheme 2-39). This product was a result of a cyclopropane protonation with concomitant transannular nucleophilic attack by the tertiary alcohol.



Scheme 2-39: Diether side product from the attempted hydrogenolysis of **95.**

Having solved the geminal dimethyl challenge, the final issue to be addressed was the bridging ether, whose regioselective opening would simultaneously install the trisubstituted olefin and the angular hydroxyl. We envisioned several possible strategies to accomplish this objective (Figure 2-10).

Dehydration of the tertiary alcohol towards the methyl group (path A) would afford exocyclic olefin **47**. This same intermediate could arise via a derivative **96** with an improved leaving group (path B). This allylic ether could then undergo S_N2'-type hydride addition to furnish dactylol **8**.[29] Intermediate **96** could also be used in a reductive elimination to provide **8** via the corresponding organometallic intermediate.[30]

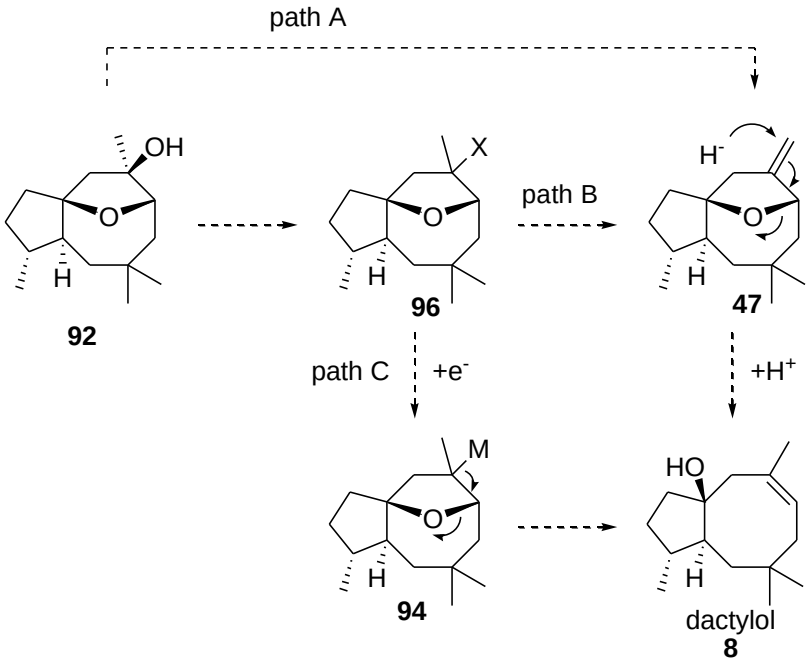
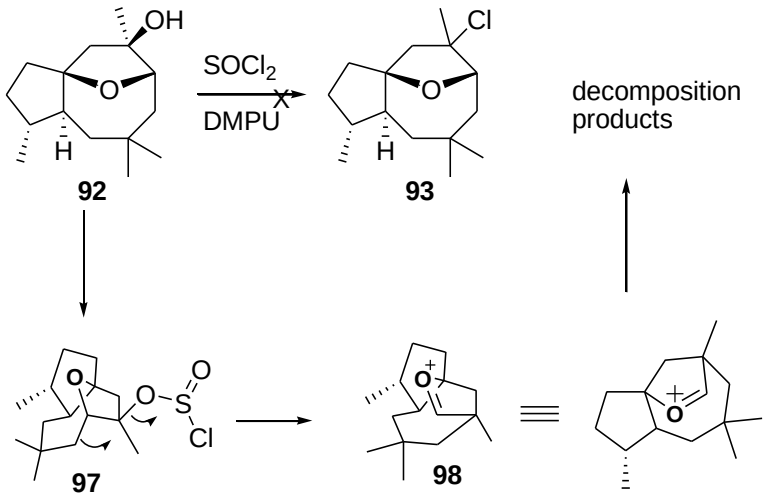


Figure 2-10: Proposed strategy for opening the bridging ether from alcohol **92.**

Initial efforts focused on the formation of olefin **47.** Direct elimination with the Burgess reagent (freshly prepared) afforded no reaction and complete recovery of starting material. Since intermediate **96** could potentially be used in either path B or C, we turned our attention to formation of chloride **93** (Scheme

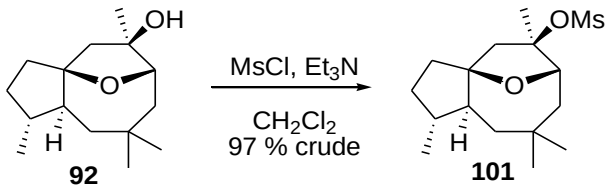
2-40). Upon treatment with thionyl chloride in DMPU,[30] the starting material underwent a rapid decomposition.

A possible rearrangement pathway is shown in the scheme. Because of the stereoselective addition of methyl to ketone **44**, the activated chlorosulfinate **97** is well aligned for 1,2-alkyl shift with loss of SO_2 and chloride to form oxocarbenium ion **98.** This intermediate could then decompose further or undergo hydrolysis on work-up. A close analogy to this process has been observed in a related 5,7-fused bicyclic carbon skeleton possessing a bridging ether.[31] Notably, the same pathway does not occur in the other alcohol epimer of that system. Although it may be possible to overcome this problem, we chose not to use additional quantities of the precious intermediate **92** on a route that caused its complete destruction, and instead focused on other approaches for activating the alcohol.



Scheme 2-40: Possible rearrangement pathway in attempted chlorination of **92**.

The likely skeletal rearrangement with thionyl chloride suggested avoidance of cationic pathways. As an alternative, we sought to convert **92** to the corresponding mesylate **101** (Scheme 2-41), with a goal of exploring possible base-mediated eliminations. In the event, treatment with MsCl and Et_3N afforded **101** in 97 % yield (crude). Treatment of the mesylated product with a variety of bases (DBU, LDA, NaH) at room temperature or 100 °C afforded only recovered starting material or alcohol **92**.



Scheme 2-41: The mesylation of alcohol **92.**

2.3 Conclusions and Future Work

In the first generation approach, to dactylol, the lactone **62** was made in a acceptable yield and number of steps (Figure 2-11). This approach towards dactylol could be advanced further by a cyclopropanation/hydrogenolysis sequence to form **126**, which has a germinal dimethyl group**.** A reduction of the lactone (and subsequent reformation of the ester) followed by mixed thioacetal formation would result in the precursor for the Stevens rearrangement. Because

this route introduces the mixed thioacetal, the established reductive-desulfurization ether-opening protocol can be utilized.

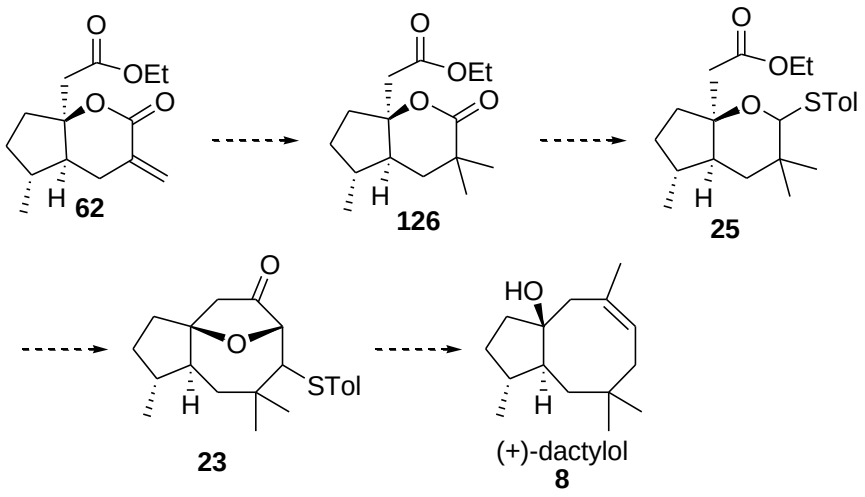


Figure 2-11: An approach towards dactylol using Stevens rearrangement.

In regards to the third generation approach an advanced synthetic route towards the natural product dacylol has been established. The opening steps were initially problematic and unoptimized, but after extensive experimentation they now can be performed consistently at large scales with very good yields. The synthesis of the key cyclooctane has been shown to be feasible with a [2,3] rearrangement of an oxonium ylide. And finally an advanced intermediate towards the total synthesis of dactylol has been made. This intermediate contains the required geminal dimethyl group that has previously been elusive.

The next required step in this route is the formation of the exocyclic olefin **47** (Figure 2-12). The dehydration of the alcohol has not been

exhaustively pursued, and it could be revisited with a method such as the dehydration with Martin's sulfurane.[32] Alternatively the alkene could be made from the ketone, via Wittig reaction; however, this method would require protection (or temporary reduction) of the ketone so that the geminal dimethyl can be first installed.

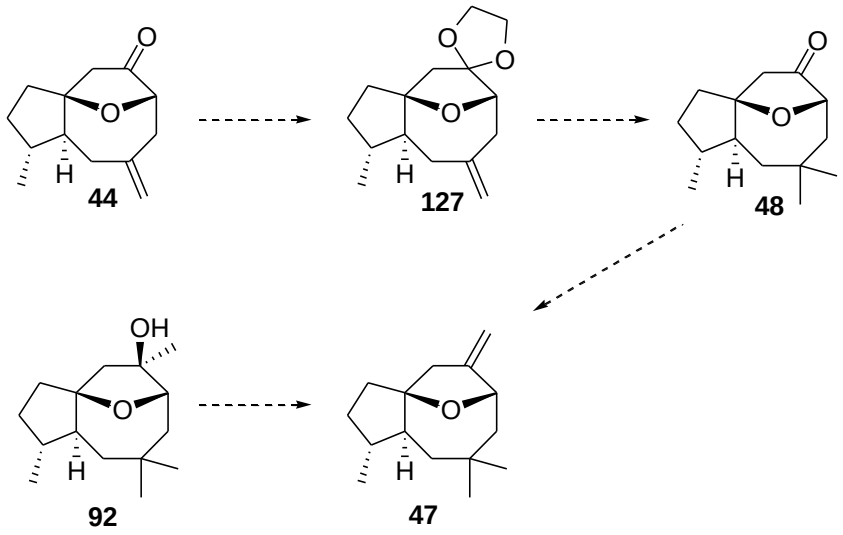


Figure 2-12: Synthetic approach towards dactylol using [2, 3] rearrangement product **44.**

With the alkene installed the conversion to dactylol is analogous to an allyl deprotection. There are methods that use metals such as zirconium[33] or titanium[34] that may result in the formation of dactylol (Figure 2-13). The method using zirconium is believed to proceed through a zirconacyclopropane **128.** Opening to the allylic zirconium **129** and then protonolysis would generate dactylol **8**. Allylic ethers have also been cleaved by borane generated *in situ*.[29]

This method is believed to reduce the allyl group after coordination to the ether in **47** and could also lead to the formation of dactylol **8**.

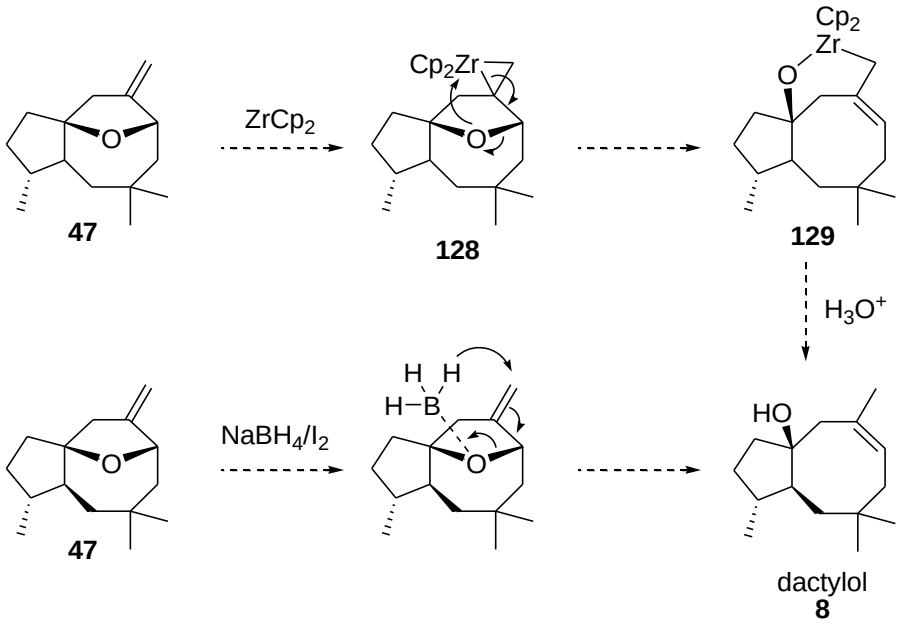


Figure 2-13: Methods for the reduction of an allyl ether.

Another method also suitable for this ether cleavage, has been reported by the Lautens group.[35] DIBAL-H in the presence of nickel catalyst would

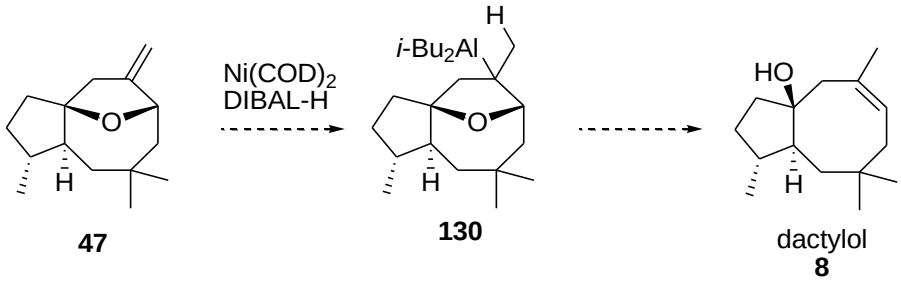


Figure 2-14: The use of DIBAL-H to open bridging ether.

generate the hydroaluminated product **130** (Figure 2-14). β-Elimination would afford the alkene and tertiary alcohol.

If the ether opening proves to be problematic there is another approach one can take. SmI_2 has been shown to reduce α-hetero-ketones including ethers. Reduction of **48** could open the ether to the alcohol **131** (Figure 2-15).[36, 37] The ketone would then need to be converted to the trisubstituted alkene to complete the synthesis.

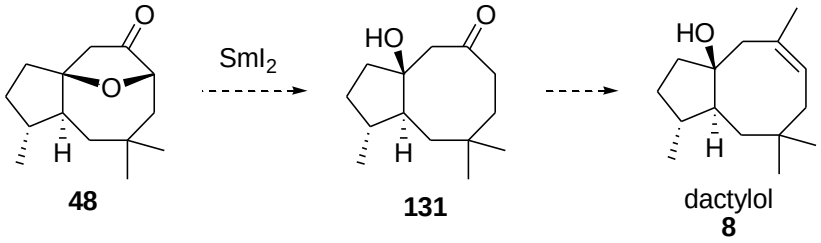


Figure 2-15: The potential use of SmI_2 to open bridging ether.

2.4 Experimental

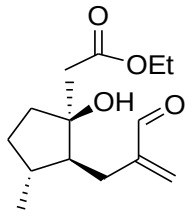
2.4.1 General Information

The reactions were carried out in oven (120 °C) or flame-dried glassware under a positive argon atmosphere unless otherwise stated. The transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannulae. Solvents were distilled before use: dichloromethane and dichloroethane from calcium hydride, toluene from sodium metal. Solutions that

were "dried over $MgSO_4$", were vacuum filtered through a plug of anhydrous $MgSO_4$. Thin layer chromatography was performed on glass plates precoated with 0.25 mm silica gel with fluorescent indicator UV_{254} (Rose Scientific). Flash chromatography columns were packed with 230-400 mesh silica gel (Merck).

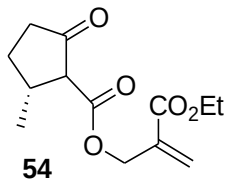
Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz or 500 MHz on Varian Inova 400 and 500, Mercury 400, or Unity 500 spectrometers, and the chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane (0 ppm) and referenced to the deuterochloroform peak at 7.26 ppm. Chemical shifts are reported to 3 decimal places where distinctions could be made but they are reproducible only to 2 decimal places. Coupling constants (*J*) are reported in Hz to 1 decimal place. The multiplicity of signals observed in the ^{1}H NMR are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets, etc. The carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 126 MHz or 101 MHz and are reported (ppm) relative to the center line of a triplet at 77.23 ppm for deuterochloroform. Chemical shifts are reported to 2 decimal places where distinctions could be made but they are reproducible only to 1 decimal place. Infrared (IR) spectra were measured with a Nicolet Magna 750 FT-IR spectrophotometer and Nic-Plan FTIR Microscope. Mass spectra were determined on a Kratos Analytical MS-50 (EI) or Applied Biosystems Mariner Biospectrometry Workstation (ESI). Optical rotation was measured on a Perkin Elmer 241 Polarimeter.

2.4.2 Procedures and Characterizations



52

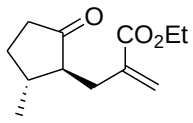
Aldehyde 52. Dichloromethane (1 mL) was added to alcohol **31** (10.3 mg, 0.0402 mmol) under an argon atmosphere. PCC (12.6 mg, 0.0585 mmol) was added and stirred for 4 h. TLC analysis indicated an incomplete reaction so additional PCC (6.2 mg, 0.029 mmol) was added, and the reaction was stirred for an additional 2 h. Diethyl ether (10 mL) was added and the solution was filtered through cotton, then eluted through a short silica gel plug to yield 10.1 mg of **52** (99 %) as a colourless oil (99 % yield). $[\alpha]_D^{20}$ = -31.0 (*c* 0.23, $CHCl_3$); IR (cast film) 3514 (br), 1716, 1692 cm $^{-1}$; ^{1}H NMR (498 MHz, $CDCl_3$) δ 9.55 (s, 1H), 6.46 (s, 1H), 6.09 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.81 (br s, 1H), 2.58 (d, *J* = 15.7 Hz, 1H), 2.43 (d, *J* = 15.8 Hz, 1H), 2.30 (dd, *J* = 6.9, 15.1 Hz, 1H), 2.14 (dd, *J* = 7.8, 14.9 Hz, 1H), 1.83-1.75 (m, 3H), 1.68-1.55 (m, 2H), 1.46-1.38 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.00 (d , *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.7, 173.6, 149.0, 135.4, 81.2, 60.8, 54.8, 40.4, 38.7, 38.6, 30.9, 28.0, 21.3, 14.2.; MS (ESI) *m/z* calcd for $C_{14}H_{22}O_4Na$ ($M+Na^+$) 277.1710 found 277.1408.



54

Allylic β-ketoester 54. Acid **37** (102.5 mg 0.721 mmol), alcohol **34** (148.3 mg, 1.14 mmol) and DCC (0.686) were separately dissolved in CH_2Cl_2 (1 mL each) under an argon atmosphere and then cooled to -78 °C. The alcohol solution was then added to the acid solution via cannula. After approximately 7 min, the DCC solution was added to the mixture with the aid of CH_2Cl_2 (0.5 mL) via cannula. After 1.5 h the solution was warmed to -10 °C and stirred for 21 h while gradually warming to room temperature. The reaction was filtered through cotton. The filtrate was washed with 1M NH_4Cl (9 mL) and brine (5 mL), and then dried over $MgSO_4$ and concentrated. After purification by column chromatography (15 % EtOAc/hexanes) a clear oil (130.3 mg, 75 % yield) was obtained in a 9.2:1 dr (ratio determined by integration of methyl group at 1.20 ppm for the major and 1.13 ppm for the minor in the ^{1}H NMR spectrum): R_f = 0.33 (15 % EtOAc/hexanes); $[\alpha]_D^{20}$ = +38.5 (*c* 0.63, $CHCl_3$); IR (cast film) 1757, 1730 cm $^{-1}$; ^{1}H NMR (498 MHz, $CDCl_3$) δ 6.37 (br s, 1H), 5.91 (br s, 1H), 4.94 (d, J_{AB} = 14.3 Hz, 1H), 4.87 (d, J_{AB} = 14.3 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.82 (d, *J* = 11.4 Hz, 1H), 2.62 (qddd, *J* = 6.1, 6.1, 11.6, 11.6, 1H), 2.43 (br dd,

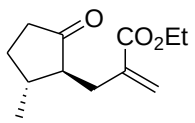
J= 8.5, 18.9 Hz, 1H) 2.33 (ddd, *J* = 8.7, 10.6, 19.5 Hz, 1H), 2.21 (br ddd, *J* = 7.1, 7.1, 13.5 Hz, 1H), 1.49 (dddd, *J* = 8.5, 11.5, 11.5, 11.5 Hz, 1H) 1.31 (t, *J* = 7.1 Hz, 3H), 1.20 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.4, 168.5, 165.1, 135.0, 127.2, 63.1, 63.0, 61.0, 38.7, 36.4, 29.4, 19.3, 14.1; MS (ESI) *m/z* calcd for $C_{13}H_{18}O_5Na$ ($M+Na^+$) 277.1046 found 277.1048.



55

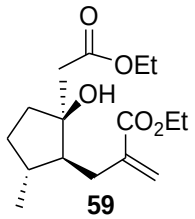
Allyl Cyclopentanone 55. Benzene (5 mL) was added to the ester **54** (0.993 g, 0.391 mmol) under argon. $Pd(PPh_3)_4$ (44 mg, 0.038 mmol) was added and then the reaction was stirred for 4 days . Et_2O (5 mL) was added, and the reaction was filtered through cotton and concentrated. Gradient column chromatography (hexane, 7 % EtOAc/hexanes, and then 10 % EtOAc/hexanes) afforded 59.2 mg (72 %) of product **55** (6:1 dr; ratio determined by integration of methyl group at 1.12 ppm for the major and 0.87 ppm for the minor in the ^{1}H NMR spectrum) as a colourless oil: R_f = 0.51 (20 % EtOAc/hexanes); $[\alpha]_D^{20}$ = +56.6 (*c* = 1.64, CH_2Cl_2); IR (cast film) 1741, 1719 cm $^{-1}$; ^{1}H NMR (498 MHz, $CDCl_3$) δ 6.20 (br s, 1H), 5.62 (br s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.72 (dd, *J* = 6.1, 14.5 Hz, 1H), 2.39 (dd, *J* = 6.4, 14.5 Hz, 1H), 2.32 (dd, *J* = 8.6, 16.6 Hz, 1H), 2.12-2.04 (m, 2H), 1.95-1.90 (m, 1H), 1.90-1.80 (m, 1H), 1.44-1.35 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.8, 167.0,

138.6, 126.9, 60.7, 55.5, 37.7, 37.3, 30.7, 29.5, 19.8, 14.2; MS (ESI) *m/z* calcd for $C_{12}H_{18}O_3Na$ ($M+Na^+$) 233.1148 found 233.1148.



55

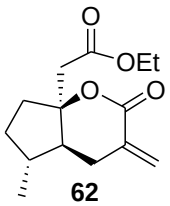
Cyclopentanone 55 via Direct coupling. Carboxylic acid **37** (93.8 mg, 0.660 mmol) and acetate **56**[9] (156.4 mg, 0.908 mmol) were combined under argon and cooled to 0 °C. PhH (5 mL) and then $Pd(PPh_3)_4$ (78.6 mg, 0.0680 mmol) were added. The reaction was warmed to rt after 10 min. After 2 h the reaction mixture was concentrated and then Et_2O was added. The mixture was then filtered through cotton and washed with 2M NaOH (10 mL), H_2O (10 mL) and brine (10 mL). The organic layer was vacuum filtered through Celite and anhydrous $MgSO_4$. The crude product was purified by gradient column chromatography (0 %, 7 %, and 10 % EtOAc/hexanes) to provide 85.3 mg (61 % yield) of **55** (7:1 dr; ratio determined by integration of methyl group at 1.12 ppm for the major and 0.87 ppm for the minor in the ^1H NMR spectrum) as a colourless oil. Spectra data were consistent with those reported above.



59

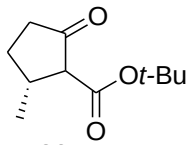
Aldol Adduct 59. Hexamethyldisilazane (80 µL, 0.38 mmol) was added to THF (0.4 mL) under an argon atmosphere, and then cooled to -78 °C. *n*-Butylithium

(220 µL, 1.6 M, 0.352 mmol) was added. After 1.7 h at -78 °C solution of EtOAc (40 µL, 0.41 mmol in 0.4 mL of THF) was added via cannula. The reaction mixture was transferred via cannula into a flask containing $CeCl_3$ (112.5 mg, 0.456 mmol; dried under high vacuum at 100 °C for 1 h). After 2.5 h a cold -78 °C solution of **55** in THF (0.4 mL) was added to the mixture via cannula. The flask was rinsed with additional THF (0.4 mL) before being cooled to -78 °C and added to the reaction. NH_4Cl (1M, 2 mL) was added to the reaction after 1.75 h. The phases were separated and the aqueous layer was extracted with Et_2O (2 mL), then the combined organic layers were washed with brine (2 mL) and dried over $MgSO_4$. The solution was concentrated to yield 38.4 mg as a colourless oil that was carried on to the next step without purification: $[\alpha]_D^{20}$ = -6.9 (*c* = 1.64, $CHCl_3$); IR (cast film) 3511 (br), 1731 cm $^{-1}$; ^{1}H NMR (498 MHz, $CDCl_3$) δ 6.15 (d, *J* = 1.7 Hz, 1H), 5.65 (br d, *J* = 1.7 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.17 (br q, *J* = 7.1 Hz, 2H), 2.78 (d, *J* = 15.8 Hz, 1H), 2.67-2.60 (m, 1H), 2.36-2.30 (m, 1H), 2.32 (d, *J* = 15.8 Hz, 1H), 2.04-1.98 (m, 1H), 1.96-1.89 (m, 1H), 1.83-1.70 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.36-1.24 (m, 2H), 1.14 (dddd, *J* = 5.1, 6.8, 9.4, 12.6 Hz, 1H), 0.96 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 167.4, 140.5, 126.2, 114.7, 80.5, 60.6, 54.5, 44.0, 38.7, 38.3, 31.5, 31.0, 20.9, 14.24, 14.17; MS (ESI) *m/z* calcd for $C_{16}H_{26}O_5Na$ ($M+Na^+$) 321.1672 found 321.1673.



62

Lactone 62. NaH (8.3 mg, 60 % in mineral oil, 0.21 mmol) was added to $Me_3S(O)I$ (19 mg, 0.087 mmol) in THF (1 mL) under an argon atmosphere. The reaction was heated at reflux for 3 h and then cooled to -78 °C. Compound **59** (11 mg, 0.037 mmol) was added as a THF solution (3 portions of 1 mL each) via cannula. After 1.5 h H_2O (2 mL) and Et_2O (2 mL) were added and the phases were separated. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. Purification by gradient column chromatography (hexanes, 10 % EtOAc and 17 % EtOAc/hexanes), afforded 7.2 mg (77 %) of **62** as a colourless oil; R_f = 0.33 (20 % EtOAc/hexanes); $[\alpha]_D^{20}$ = -3.3 (*c* = 0.72, $CHCl_3$); IR (cast film) 1730 cm $^{-1}$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.41 (br s, 1H), 5.58 (br s, 1H), 4.20-4.10 (m, 2H), 2.84-2.77 (m, 1H), 2.81 (d, J_{AB} = 14.6 Hz, 1H), 2.71 (d, J_{AB} = 14.5 Hz, 1H), 2.57 (br d, *J* = 15.0 Hz, 1H), 2.14 (ddd, *J* = 5.7, 9.7, 15.2 Hz, 1H), 2.06 (ddd, *J* = 6.4, 8.1, 14.4 Hz, 1H), 2.01-1.94 (m, 1H), 1.91-1.82 (m, 1H), 1.64-1.48 (m, 1H), 1.31-1.20 (m, 3H), 1.27 (t, *J* = 7.2 Hz, 1H), 1.03 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 165.3, 131.7, 128.6, 91.5, 60.9, 47.1, 43.3, 38.1, 36.2, 30.5, 27.4, 18.8, 14.1; MS (ESI) *m/z* calcd for $C_{14}H_{20}O_4Na$ ($M+Na^+$) 275.1254 found 274.1254.

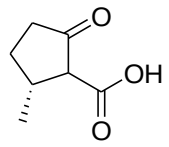


36

***t*-Butyl β-ketoester 36.** A solution of *t*-BuONa was prepared by adding cut, flattened Na metal (23 g, 1.0 mol) to *t*-BuOH (840 mL) under argon gas. The mixture was heated at reflux for 4 days then cooled to rt. (+)-Pulegone **16** (85 %

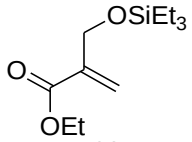
technical grade, 80 mL, 420 mmol) and $NaHCO_3$ (12 g, 130 mmol) were added to Et_2O (500 mL) under argon. Bromine (23 mL, 460 mmol) was added quickly via syringe. After the orange colour of the solution became faint (less than one min) it was added to the *t*-butoxide solution via cannula. (An ice bath should be kept on hand to cool the reaction if it becomes too vigorous and the stirring of the *t*-butoxide solution needs to be ensured during addition of bromine solution, as eruption will occur). After the addition was complete the reaction was stirred at reflux for 20 h. The reaction was cooled to 0 °C, acidified with 1M HCl (500 mL), and the phases were separated. The organic layer was washed with H_2O (500 mL) and brine (500 mL). The solution was then dried over $MgSO_4$ and concentrated. The product was split into three equal parts and each batch subjected to ozonolysis via the following procedure: ethyl acetate (500 mL) was added to starting material and the resulting solution was cooled to -78°C. Ozone (produced by a Welsbach model T-816 ozone generator) was bubbled into the solution until it became green. Oxygen gas was bubbled through the solution for 30 min, during which the colour changed to yellow. Dimethyl sulfide (75 mL) was added and the reaction was allowed to warm up overnight. The three batches were combined and the remaining DMS removed by distillation. 1M HCl (500 mL) was added, and then the solution was extracted four times with Et_2O (500 mL × 2 and 250 mL × 2). Each 500 mL organic layer was washed with H_2O (250 mL) and brine (250 mL). The product mixture was dried over $MgSO_4$ and concentrated *in vacuo*. The reaction was purified via column chromatography (7 % EtOAc / hexane) to give 52.5 g (64 %) of **36** as a brown

oil: $[\alpha]_D^{20}$ = +68.6 (*c* 1.35, $CHCl_3$). The remaining spectroscopic data were consistent with previously reported values.[3]



37

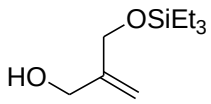
β-Ketoacid 37. A dichloromethane/trifluoroacetic acid solution (1:1, 60 mL) was added to β-ketoester **36** (5.0 g, 35mmol). After 40 min the reaction was concentrated *in vacuo* and purified by column chromatography (30 % EtOAc, Hexanes) to give 3.4 g of a black oil (95 % yield) that became a semi-solid in a freezer: $[\alpha]_D^{20}$ = 60.3 (*c* 1.92, CH_2Cl_2). The remaining spectral data were consistent with the previously reported values.[3]



69

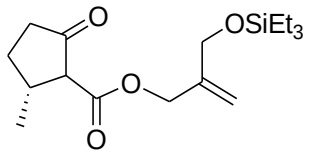
Allyl ether 69. Dichloromethane (0.65 mL) was added to compound **34** (85 mg, 0.65 mmol) under argon. The solution was cooled to 0°C and then 2,6-lutidine (150 µL, 1.30 mmol) was added. TESOTf (0.16 mL, 0.72 mmol) was then added. After 1 h NH_4Cl (saturated, 6 mL) was added. The mixture was then extracted with Et_2O (2 x 6 mL). The combined organic layers were washed with brine (6 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Compound **69** was obtained as a colourless, clear oil in 93 % yield (148 mg) after column

chromatography (30 % EtOAc/hexanes). Spectroscopic data were consistent with previously reported values.[3]



35

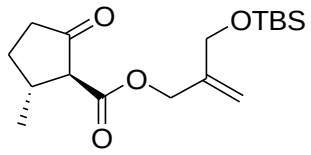
Allyl alcohol 35. Dichloromethane (2.1 mL) was added to compound **69** (101 mg, 0.411 mmol) under argon. The solution was cooled to -78°C and then DIBALH (1 mL, 1M solution in CH_2Cl_2) was added dropwise. After 2 h H_2O (70 mL) and Et_2O (50 mL) were added. A portion of NH_4Cl (saturated) was added to break up the emulsion. The organic layer washed with brine, dried over $MgSO_4$ and concentrated *in vacuo.* ^{1}H NMR analysis indicated pure product **35**, that matched the reported data.[3]



33

β-Ketoester 33. Dichloromethane (10 mL) was added to carboxylic acid **37** (2.1 g, 15 mmol) under argon, and then cooled to -78 °C. Dichloromethane (10 mL) was added to alcohol **35** (3.1 g, 15 mmol) under argon and then cooled to -78 °C. Then the carboxylic acid solution was added to the alcohol solution via cannula. DCC (3.1 g, 15 mmol) and DMAP (0.18 g, 1.5 mmol) in CH_2Cl_2 (10 mL) were

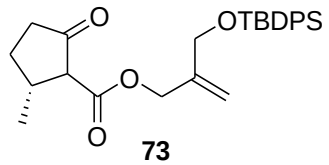
added to the above solution via addition funnel over 10 min. The reaction was stirred for 15 min and then warmed to -10 °C. After 1 h H_2O (100 mL), and Et_2O (100 mL) were added and the mixture was filtered through Celite®. After separation of the phases the aqueous layer was extracted with Et_2O (100 mL). The combined organic layers were washed with H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated. After purification of crude product by column chromatography (7% EtOAc/hexanes), 4.0 g (82 % yield) of a colourless oil was obtained: $[\alpha]_D^{20}$ = 26.8 (*c* 0.21, CH_2Cl_2). The remaining spectral data for the product were consistent with the previously reported values.[3]



22

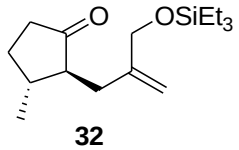
β-Ketoester 72. The procedure for compound **33** was repeated at a larger scale using alcohol **70**. The procedure produced 27 g of product (70 % yield) as colourless oil: R_f = 0.75 (30% EtOAc, 1% AcOH, in hexanes); $[\alpha]_D^{20}$ = 36.1 (*c* 2.07, $CHCl_3$); IR 1757, 1731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.24 (m, 1H), 5.16 (m, 1H), 4.70 (br d, J_{AB} = 13.0 Hz, 1H), 4.66 (br d, J_{AB} = 13.0 Hz, 1H), 4.19 (br d, J_{AB} = 13.6 Hz, 1H), 4.16 (br d, J_{AB} = 13.9 Hz, 1H), 2.79 (br d, *J* = 11.4 Hz, 1H), 2.61 (qddd, *J* = 6.4, 6.4, 11.3, 11.3 Hz, 1H), 2.44 (br dd, *J* = 8.4, 19.0 Hz, 1H), 2.32 (ddd, *J* = 8.6, 11.4, 18.9 Hz, 1H), 2.20 (dddd, *J* = 2.1, 6.3, 8.5, 12.7 Hz, 1H), 1.48 (dddd, *J* = 8.4, 11.3, 11.3, 12.7 Hz, 1H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.4, 168.8, 142.9, 113.0, 65.3,

63.7, 63.1, 38.7, 36.4, 29.4, 25.9, 19.3, 18.3, -5.5; MS (EI) *m/z* calcd for $C_{17}H_{29}SiO_4$ ($M\text{-}H^+$) 325.1835 found 325.1831.



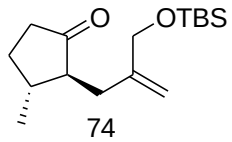
73

Ester with TBDPS protected alcohol 73. The procedure for compound **32** was replicated except at a different scale, different chromatographic eluent and using alcohol **71**. The crude product was purified by column chromatography (10 % EtOAc/hexanes) to give 1.3 g (87 % yield) of product **73** as colourless oil: The spectra data were consistent with the reported values.[3]



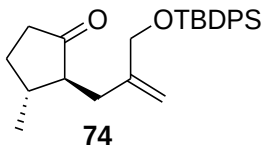
32

TES containing Cyclopentanone 32. Benzene (8 mL) and $Pd(PPh_3)_4$ (0.27g, 0.23 mmol) were added to ketoester **33** (4.17 g, 12.8 mmol) under argon gas. After 4 h, Et_2O (5 mL) was added, and the mixture was filtered through Celite®, and concentrated. Crude product was purified by column chromatography (5% EtOAc, hexanes) to afford 2.7 g (76% yield) as a colourless oil: $[\alpha]_D^{20} = 58.5$ (*c* 1.47, CH_2Cl_2). The remaining spectral data for the product were consistent with the previously reported values.[3]



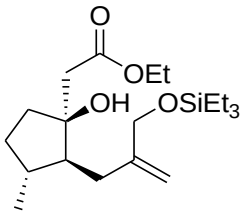
74

TBS Containing Cyclopentanone 74. The procedure for compound **32** was replicated except at a different scale. 12 g of product **74** was obtained as a colourless oil in 51% yield: R_f = 0.31 (5% EtOAc/hexanes). $[\alpha]_D^{20}$ = 66.4 (*c* 2.47, $CHCl_3$); IR 1742 cm $^{-1}$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.10 (br s, 1H), 4.86 (br s, 1H), 4.07 (br d, J_{AB} = 14.3Hz, 1H), 4.01 (br d, J_{AB} = 14.4Hz, 1H), 2.41 (dd, *J* = 5.6, 14.8Hz, 1H), 2.37-2.30 (m, 1H), 2.16 (dd, *J* = 6.8, 14.9Hz, 1H), 2.14-2.06 (m, 2H), 1.91 (qddd, *J* = 6.2, 6.2, 10.4, 10.4Hz, 1H), 1.82 (ddd, *J* = 1.4, 5.4, 6.7Hz, 1H), 1.47-1.37 (m, 1H), 1.14 (d, J = 6.4Hz, 3H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 220.4, 146.2, 110.6, 65.8, 55.0, 37.6, 37.4, 31.8, 29.4, 25.9, 19.9, 18.4, -5.4; MS (EI) *m/z* calcd for $C_{16}H_{30}SiO_2$ (M^+) 282.2015 found 282.1999.



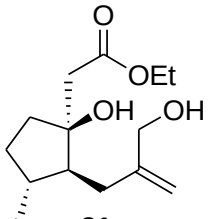
74

TBDPS Protected Ketone 74. The procedure for compound **32** was replicated except at a different scale and with a different chromatographic eluent. The crude product was purified by column chromatography (7 % EtOAc/hexanes) to furnish 680 mg (75 % yield) of product **74** as a colourless oil: The spectra data of the product were consistent with the reported values.[3]



40

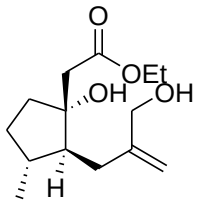
Aldol adduct 40. Ketone **32** (0.77g, 2.7 mmol) was placed under an argon atmosphere. Tetrahydrofuran (30 mL) was added followed by ethyl bromoacetate (1.2 mL, 11 mmol). $(PPh_3)_3RhCl$ (0.13 g, 0.14 mmol) was added followed by the rapid addition of $ZnEt_2$ (16 mL, of 1M solution in hexanes, 16 mmol). Gas and heat was evolved from the reaction. After 30 min the reaction was cooled to 0 °C and then HCl (1M, 50 mL) was added slowly. The mixture was extracted with Et_2O (2x 30 mL) and the phases were separated. The organic layer was washed with a saturated $NaHCO_3$ / H_2O (1:1, 50 mL) mixture and brine (50 mL). After drying over $MgSO_4$ and concentration the crude product was purified via flash column chromatography (5% EtOAc/ hexanes) to furnish 1.0 g (80 % yield) of a clear colourless oil as a 4:1 (^{1}H NMR) mixture of diastereomers: R_f = 0.43 (15% EtOAc/hexanes). The spectral data for the product were consistent with the previously reported values.[3]



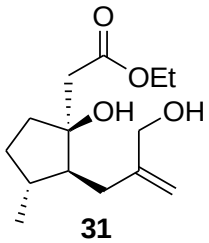
31

Alcohol 31 from TES protected 40. The TES protected alcohol **32** (0.80 g, 2.2 mmol) was added to Et_2O (54 mL) under argon. TBAF (2.4mL of 1M, 2.4

mmol) was added and then stirred for 4 h. The reaction was washed with NH_4Cl (1M, 30 mL) and then the aqueous layer extracted with Et_2O (30 mL). The organic layer was dried over $MgSO_4$ and concentrated. Crude product **31** was purified by column chromatography (30 % EtOAc/hexanes) to furnish 0.49 g (88 % yield) of a clear oil: Major alcohol epimer of **31**: $[\alpha]_D^{20}$ = -31.5 (*c* 2.81, $CHCl_3$). The remaining spectral data for the product were consistent with the previously reported values.[3]



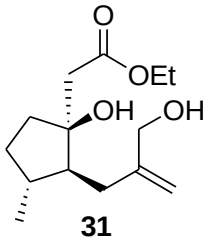
Minor alcohol epimer of 31. $[\alpha]_D^{20}$ = -42.4 (*c* 0.92, CH_2Cl_2); IR (cast film) 3424 (br), 1714 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (br s, 1H), 4.98 (br s, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.12 (s, 2H), 3.05 (br s, 2H), 2.72 (d, J_{AB} = 15.8Hz, 1H), 2.42 (d, J_{AB} = 15.8Hz, 1H), 2.18 (dd, *J* = 7.9, 14.5 Hz, 1H), 2.08 (dd, *J*= 6.8, 14.4 Hz, 1H), 1.85-1.74 (m, 3H), 1.68-1.52 (m, 2H), 1.46-1.36 (m, 1H), 1.29 (br t, *J* = 7.1Hz, 3H), 1.05 (d, *J* = 6.5Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 147.6, 113.1, 81.3, 65.8, 60.9, 53.8, 40.0, 38.7, 38.4, 35.0, 30.7, 20.8, 12.2; MS (ESI) *m/z* calcd for $C_{14}H_{24}O_4Na$ ($M+Na^+$) 279.1567 found 279.1567.



31

Compound 31 from TBS protected cyclopentanone 74. Tetrahydrofuran (450 mL) was added to ketone **74** (12.2g, 43.2 mmol) under argon. Ethyl bromoacetate (19 mL, 173 mmol) and $(PPh_3)_3RhCl$ (2.0 g, 2.2 mmol) were added and then the reaction was cooled to 0°C. $ZnEt_2$ (188 g of 1M solution in hexanes, 188 mmol) was added via cannula over 40 min. After 10 min the reaction was warmed to rt and stirred for 16 h. The reaction was cooled to 0 °C, and then HCl (1M, 500 mL) was added slowly (gas evolved). The solution was extracted with Et_2O (500 mL) and then the phases were separated. The organic layer was washed with saturated $NaHCO_3$ / H_2O (1:1, 500 mL) and brine (500 mL) and then the solution was dried over $MgSO_4$ and concentrated. The mixture was purified via flash column chromatography (5, 7 then 15% EtOAc/hexanes) to give 14.5 g of impure **80** as a clear oil obtained in a 2.6:1 (ratio determined by integration of methyl group at 1.01 ppm for the major and 1.05 ppm for the minor in the ^1H NMR spectrum) mixture of diastereomers. The product was deprotected as follows: Et_2O (90 mL) was added to compound **80** (14.5 g, crude), followed by TBAF (15 mL, 1M in THF). After 24 h NH_4Cl (1M, 100 mL) was added and the phases were separated. The aqueous layer was extracted with Et_2O (100 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by column

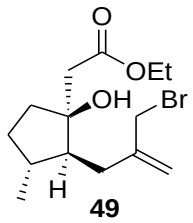
chromatography (30 % EtOAc/hexanes) to furnish 7.7 g (69 % yield over two steps, mixture of diastereomers) of product **31** as a colourless oil. The spectral data matched those reported above.



31

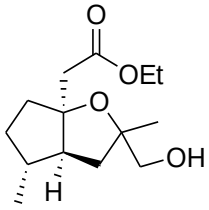
Compound 31 from TBDPS protected cyclopentanone 74. Tetrahydrofuran (69 mL) was added to ketone **75** (2.8 g, 6.9 mmol) under argon. Ethyl bromoacetate (3.0 mL, 27.4 mmol) and $(PPh_3)_3RhCl$ (0.31 g, 0.34 mmol) were added. $ZnEt_2$ (41 mL of 1M solution in hexanes, 41 mmol) was then added portion-wise. After 3 h the the reaction was cooled to 0 °C, and then HCl (1M, 100 mL). The solution was extracted with Et_2O (100 mL) and then the phases were separated the phases were separated. The organic layer was washed with saturated $NaHCO_3$ / H_2O (1:1, 100 mL) and brine (100 mL) and then the solution was dried over $MgSO_4$ and concentrated. A crude brown oil was obtained as a 6.4:1 (^{1}H NMR) mixture of diastereomers that was carried forward. The product was deprotected as follows: Et_2O (10 mL) was added to compound the crude mixture (2.9 g, 5.9 mmol), followed by TBAF (6.5 mL, 1M in THF, 6.5 mmol). After 24 h NH_4Cl (1M, 50 mL) was added and the phases were separated. The aqueous layer was extracted with Et_2O (2 x 30 mL) and the combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (30 %

EtOAc/hexanes) to furnish 0.94 g (53 % yield over two steps, as a mixture of diastereomers) of product **31** as a colourless oil. The spectral data matched those reported above.



49

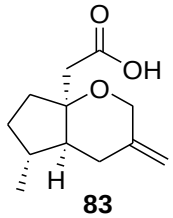
Allyl bromide 49. Acetonitrile (20 mL) was added to **31** (0.93 g, 3.6 mmol) under argon in a foil-covered flask. Triphenylphosphine (1.14 g, 4.31 mmol) was added followed by CBr_4 (1.48 g, 4.46 mmol). The reaction was stirred overnight and then purified by column chromatography (7 % EtOAc/Hexanes) to give 1.06 g (92 % yield) of product **49** as a clear oil. The spectral data for the product were consistent with the reported values.[3]



82

Alcohol 82. The compound **82** was occasionally isolated from the reaction producing compound **49.** $[\alpha]_D^{20}$ = -9.7 (*c* 1.93, $CHCl_3$); IR (cast film) 3463 (br), 1733 cm $^{-1}$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18 (qd, *J* = 7.2, 10.9Hz, 2H), 4.15

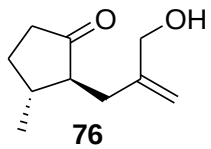
(qd, J = 7.1, 10.9 Hz, 2H), 3.45 (s, 2H), 2.71 (d, J_{AB} = 13.8 Hz, 1H), 2.63 (d, J_{AB} = 13.8 Hz, 1H), 2.28 (ddd, J = 4.9, 4.9, 9.6, 1H), 2.10-1.84 (m, 6H), 1.29 (t, J = 7.2 Hz, 1H), 1.31-1.28 (m, 1H), 1.24 (s, 3H), 0.99 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 93.8, 85.9, 68.8, 60.2, 56.9, 46.7, 41.2, 40.4, 38.7, 33.2, 25.4, 20.0, 14.3; MS (ESI) *m/z* calcd for $C_{14}H_{24}O_4Na$ ($M+Na^+$) 279.1567 found 279.1565.



83

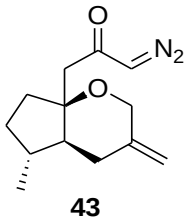
Compound 83. A solution of THF:MeOH (1:1, 1 mL) and LiOH (2M, 0.4 mL) were added to compound **50**[3] (73.5 mg, 0.308 mmol)**.** After 5 h the mixture was washed with Et_2O (6 mL) and the phases were separated. The organic layer was then extracted with H_2O (6 mL) and the phases were separated. The aqueous layer was acidified with HCl (1M, 3 mL, pH<1) and extracted with Et_2O (2 x 6 mL). The combined extracted organic layers were washed with H_2O (6 mL) and brine (6 mL), and was dried over $MgSO_4$ and concentrated *in vacuo.* 64.0 mg (99 % yield) of product **83** was obtained as a white solid and was used without purification in the next step: $[\alpha]_D^{20}$ = -24.5 (*c* 0.78, $CHCl_3$); IR (cast film) 3700-2400, 1708 cm $^{-1}$;^{1}H NMR (500 MHz, $CDCl_3$) δ 9.92 (br s, 1H), 4.91 (s, 1H), 4.87 (br s, 1H), 4.26 (br d, J_{AB} = 13.6 Hz, 1H), 4.13 (d, J_{AB} = 13.6 Hz, 1H), 3.13 (d, J = 15.5 Hz, 1H), 2.52-2.45 (m, 1H), 2.41 (d, J = 15.6 Hz, 1H), 2.28 (br dd, J = 2.6, 14.3 Hz, 1H), 2.05-1.80 (m, 4H), 1.36 (ddd, J = 2.8, 5.3, 10.0 Hz, 1H),

1.25-1.16 (m, 1H), 0.98 (d, J = 6.3 Hz, 3H); MS (EI) *m/z* calcd for $C_{12}H_{18}O_3$ (M+) 210.1256 found 210.1251.



76

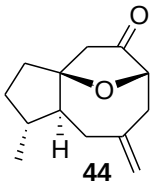
Allyl alcohol 76. Diethyl ether (1 mL) and TBAF (1M in CH_2Cl_2, 130 µL, 0.13mmol) were added to ketone **32** (35 mg, 0.12 mmol) under argon. The reaction was stirred over night and then saturated NH_4Cl (2 mL) was added. The mixture was extracted with Et_2O (4 mL), and then the separated organic layer was concentrated. The compound was purified by column chromatography (30 % EtOAc/hexanes) and 17 mg of a colourless oil (83 % yield) was obtained. The spectral data were consistent with the with previously reported values.[3]



43

Diazoketone 43. Dichloromethane (1 mL) was added to carboxylic acid **83** (32 mg, 0.15 mmol) under argon, and the reaction was cooled to 0 °C. Triphenyl phosphine (44 mg, 0.17 mmol) was added followed by *N*-bromosuccinimide (36 mg, 0.18 mmol). After 25 min, freshly prepared CH_2N_2 in Et_2O (0.40 mmol in 1.5 mL Et_2O) was added via pipette. After 15 h (gradually warmed to room

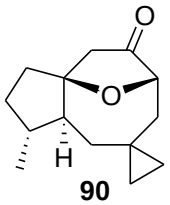
temperature) the reaction was concentrated and H_2O (10 mL) was added, and extracted with Et_2O (3 x 10 mL). The separated organic layer was washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL) and then was dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (20% EtOAc/ hexanes). A mixture of esters was obtained (R_f = 0.50 in 15 % EtOAc / hexanes) and saponified under the conditions given above for preparation of **83** from **50** to give 2.9 mg (9 % yield over two steps) of carboxylic acid **83**. Diazoketone **43** was isolated as a yellow oil (36 mg, 74 %) that was used immediately in the next step: R_f = 0.14 (15 % EtOAc / hexanes). $[\alpha]_D^{20}$ = -56.7 (*c* 0.49, $CHCl_3$); IR (cast film) 2103, 1633 cm $^{-1}$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.48 (br s, 1H), 4.85 (br s, 1H), 4.79 (br s, 1H), 4.19 (d, *J* = 13.5 Hz, 1H), 4.02 (d, *J* = 13.4 Hz, 1H), 3.01 (d, *J* = 13.9 Hz, 1H), 2.48 (br dd, *J* = 4.4, 14.6 Hz, 1H), 2.40 (br d, *J* = 13.9 Hz, 1H), 2.25 (d, *J* = 14.3 Hz, 1H), 2.01-1.86 (m, 3H), 1.82-1.77 (m, 1H), 1.43 (br s, 1H), 1.22-1.14 (m, 1H), 0.96 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 141.2, 110.1, 82.5, 65.7, 55.7, 51.6, 45.8, 36.4, 35.2, 31.0, 29.7, 18.8; MS (ESI) *m/z* calcd for $C_{13}H_{18}N_2O_2Na$ ($M+Na^+$) 257.1260 found 257.1260.



44

Cyclooctanone 44. $Cu(hfacac)_2$ (6.8 mg, 0.014 mmol) was added to CH_2Cl_2 (3 mL) at reflux under argon. A solution of diazoketone **43** (21 mg, 0.090 mmol) in

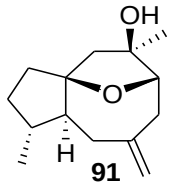
CH_2Cl_2 (6 mL) was added and the reaction was stirred at reflux for 30 min. The reaction was cooled and washed with K_2CO_3 (0.5 M, 6 mL). The separated aqueous layer was back extracted with CH_2Cl_2 (12 mL). The combined organic layers were washed with brine (9 mL) dried over $MgSO_4$, and concentrated. The crude compound passed through silica plug with EtOAc/hexane (20 %) and concentrated to reveal 19 mg (quantitative yield) of a white semi-solid: $[\alpha]_D^{20}$ = 18.8 (*c* 0.40, CH_2Cl_2); IR (cast film) 1758 cm $^{-1}$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (s, 2H), 4.26 (s, 1H), 2.67 (d, *J* = 17.9 Hz, 1H), 2.60-2.62 (m, 1H), 2.36 (d, *J* = 17.9Hz, 1H), 2.26 (dd, *J*= 5.0, 13.0 Hz, 1H), 2.20 (dd, *J* = 8.9, 13.0 Hz, 1H), 2.09-2.04 (m, 2H), 1.97-1.90 (m, 1H), 1.90-1.83 (m, 1H), 1.21 (dddd, *J* = 9.3, 12.0, 12.0, 12.0 Hz, 1H), 1.23-1.11 (m, 1H), 1.02 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.9, 143.0, 114.8, 91.0, 79.8, 59.0, 50.3, 41.3, 39.7, 39.6, 36.2, 32.4, 18.6; MS (EI) *m/z* calcd for $C_{13}H_{18}O_2$ (M+) 206.1307 found 206.1312.



90

Cyclopropyl ketone 90. Dichloromethane (1 mL) and alkene **44** (11 mg, 0.051 mmol) were combined under an argon atmosphere. Diethylzinc (0.10 mL of 1M in hexanes, 0.10 mmol), CF_3CO_2H (7.6 μL, 0.10 mmol), CH_2I_2 (10 μL, 0.12 mmol) and CH_2Cl_2 (1 mL) were combined and added dropwise to the solution of **44**. After 2 h the reaction was incomplete, so diethylzinc (0.10 mL of 1M in

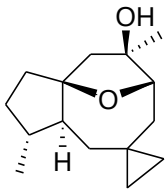
hexanes, 0.10 mmol), CH_2I_2 (10 μL, 0.12 mmol) and CH_2Cl_2 (1 mL) were combined and added dropwise to the reaction mixture. After 2 d CH_2Cl_2 (2 mL), and NH_4Cl (2 mL) were added. The layers were separated and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to furnish 8.2 mg (73 % yield) of product **90** as a colourless oil**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21-4.19 (m, 1H), 2.67 (br d, J_{AB} = 18.0 Hz, 1H), 2.62 (br d, J_{AB} = 18.4 Hz, 1H), 2.35 (ddd, *J* = 1.1, 5.2, 14.2 Hz, 1H), 2.16-2.04 (m, 2H), 1.90-1.83 (m, 1H), 1.72-1.64 (m, 1H), 1.31-1.24 (m, 3H), 1.15 (dddd, *J* = 7.3, 10.9, 12.0, 12.0 Hz, 1H), 0.93-0.88 (m, 1H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.30-0.24 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.0, 90.8, 81.0, 58.5, 53.0, 42.2, 41.7, 41.5, 39.5, 33.7, 10.9, 17.2, 15.0, 11.7.



91

Alcohol 91. Ketone **44** (3.9 mg, 0.019 mmol) was dissolved in Et_2O (1 mL) under argon. The solution was cooled to -78 °C and then MeMgBr (80 μL of 1.5M solution in Et_2O, 0.12 mmol) was added and the mixture was stirred for 30 min. The reaction was warmed to 0 °C and after 1.5 h NH_4Cl (1M, 1 mL) was added. The aqueous layer was extracted with Et_2O (1 mL) and the phases were separated. The organic layer was washed with brine (2 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (17 % EtOAc/ hexanes) to give 4.2 mg of **91** (81 % yield) as a single isomer: R_f = 0.39 (20 % EtOAc/hexanes) $[\alpha]_D^{20}$ = 24.1 (*c* 1.17, $CHCl_3$);

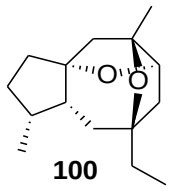
IR (cast film) 3432 (br) cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 4.87-4.90 (m, 2H), 3.91 (d, *J* = 6.0 Hz, 1H), 2.74 (d, *J* = 4.0 Hz, 1H), 2.49 (dd, *J* = 6.1, 12.3 Hz, 1H), 2.40 (dd, *J* = 6.05, 14.1 Hz, 1H), 2.16 (d, J_{AB} = 13.3 Hz, 1H), 2.09 (d, J_{AB} = 13.3 Hz, 1H), 2.07 (dd, 11.5, 11.5 Hz, 1H), 1.97-1.79 (m, 4H), 1.66-1.57 (m, 1H), 1.38 (s, 3H), 1.21 (ddd, *J* = 6.2, 10.3, 10.3 Hz, 1H), 1.14-1.04 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ147.8, 113.1, 91.6, 84.6, 79.2, 29.7, 55.7, 41.7, 41.5, 40.3, 38.1, 33.1, 29.7, 18.6; MS (EI) *m/z* calcd for $C_{14}H_{22}O_2$ ($M+Na^+$) 222.1620 found 222.1620.



95

Cyclopropane 95. Dichloromethane (0.4 mL) was added to alkene **91** (4.8 mg, 21.6 µmol) under argon. The reaction was cooled to 0 °C, and then diethylzinc (220 µL, 1M solution in hexanes) was added and the mixture was stirred for 5 min. Trifluoroacetic acid (8 µL, 110 µmol) was added and stirred for 12 min. Diiodomethane (20 µL, 250 µmol) was then added while the ice bath gradually warmed. After 15.5 h NH_4Cl (1 M, 2 mL) was added and the phases were separated. The aqueous layer was extracted with Et_2O (2 x 3 mL), and separated. The organic layer was washed with brine (3 mL), dried over $MgSO_4$ and concentrated. After purification by flash column chromatography (17 % EtOAc/hexanes) product **95** was obtained in 90 % yield (4.6 mg) as a colourless oil: R_f = 0.31 (17 % EtOAc/hexanes), ^1H NMR (400 MHz, $CDCl_3$) δ 3.82 (app.

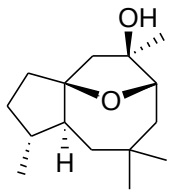
d, *J* = 5.9 Hz, 1H), 2.56 (d, *J* = 12.8 Hz, 1H), 2.23 (ddd, *J* = 1.7, 6.0, 14.7 Hz, 1H), 2.08_8 (d, *J* = 12.5 Hz, 1H), 2.08_7 (ddd, *J* = 1.8, 11.0, 11.4 Hz, 1H), 1.96-1.86 (m, 2H), 1.85-1.78 (m, 1H), 1.60-1.50 (m, 1H), 1.50 (br s, 1H), 1.43 (s, 3H), 1.30-1.24 (m, 2H), 1.14-1.03 (m, 1H), 0.95 (ddd, *J* = 1.6, 5.5, 13.7 Hz, 1H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.69-0.62 (m, 1H), 0.52-0.47 (m, 1H), 0.34-0.27 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 91.2, 85.7, 77.8, 58.8, 54.7, 41.9, 41.2, 39.2, 39.0, 33.8, 30.4, 18.6, 16.6, 16.3, 13.5.



100

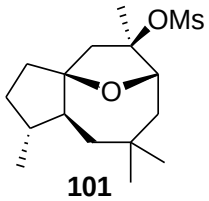
Diether 100. Acetic acid (0.4 mL) and PtO_2 (0.7 mg, 3 μmol) were added to compound **95** (6.3 mg, 0.027 mmol). After 1000 psi of H_2 was introduced the mixture was heated to 100 °C. After 22 h the reaction was cooled and concentrated *in vacuo*. Et_2O (3 mL) was added and the solution was washed with NaOH (1M, 3mL x 2), H_2O (3 mL) and brine (3 mL). The organic layer was dried over $MgSO_4$, concentrated and purified via column chromatography (7% EtOAc/hexanes) to give 2.8 mg (44 % yield) of **100** as a clear oil: $[\alpha]_D^{20}$ = -12.8 (*c* 0.28, $CHCl_3$); IR (cast film) 2929 cm $^{-1}$; ^{1}H NMR (498 MHz, $CDCl_3$) δ 4.25 (d, *J* = 2.9 Hz, 1H), 2.08 (d, *J* = 12.2 Hz, 1H), 2.00 (d, *J* = 12.2 Hz, 1H), 2.01-1.81 (m, 6H), 1.74-1.56 (m, 3H), 1.51-1.40 (m, 2H), 1.34 (s, 3H), 1.14-1.06 (m, 1H), 0.93 (d, *J* = 6.3 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 93.6, 91.0, 87.2, 86.1, 53.5, 52.3, 44.9, 42.3, 41.0, 36.3, 34.6, 33.3,

23.3, 18.3, 8.9; MS (EI) *m/z* calcd for $C_{15}H_{24}O_2$ (M+) 236.1776 found 239.1778.



92

Geminal dimethyl alcohol 92. Cyclopropane **95** (18 mg, 74 μmol), PtO_2 (151 mg, 666 μmol) and glacial AcOH (2 mL) were hydrogenated at 60 psi of H_2 for a total of 67 h. Two times during the reaction (at 3.5 h, and at 20 h), the reaction progress was observed by ^{1}H NMR analysis with the following procedure: the reaction was concentrated *in vacuo* and filtered, an ^{1}H NMR spectrum was obtained; the crude product mixture, the recovered PtO_2 and AcOH (2 mL) were then combined and placed under 60 psi of H_2. The reaction mixture was filtered through cotton and concentrated. Diethyl ether (1 mL) and $NaHCO_3$ (1M, 1 mL) were added. After separation of the layers, the aqueous layer was extracted with Et_2O (1 mL). The combined organic layers were washed with brine (2 mL) dried over $MgSO_4$ and concentrated *in vacuo*. After purification by column chromatography (17 % EtOAc/hexanes) 10.5 mg (60 % yield) of pure **92** (white solid) and 7.3 mg (41 %) of crude product **92** (oil) was obtained: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (dd, J = 7.2, 7.2 Hz, 1H), 2.16 (d, J_{AB} = 12.8 Hz, 1H), 1.98 (d, J_{AB} = 12.9 Hz, 1H), 1.82-1.66 (m, 5H), 1.56-1.24 (m, 5H), 1.43 (s, 3H), 1.07 (s, 3H), 1.06-0.83 (m, 1H), 0.98 (s, 3H), 0.97 (d, J = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 89.8, 82.3, 80.5, 58.1, 55.8, 43.7, 41.6, 40.9, 40.5, 32.8, 32.5, 32.1, 30.9, 30.2, 19.8.



101

Mesylate 101. Dichloromethane (1 mL) was added to **92** (4.2 mg, 18 μmol) under an argon atmosphere. After cooling to -10 °C, Et_3N (5 μL, 40 μmol) and MsCl (3 μL, 40 μmol) were added. After 1 h, CH_2Cl_2 (1 mL) and cold H_2O (1 mL) were added and the phases were separated. The organic layer was washed with cold HCl (1M, 1 mL), and cold brine (1 mL). The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo* to furnish 5.6 mg (97 %) of product **101**; R_f = 0.45 (20 % EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (dd, *J* = 7.6, 7.6 Hz, 1H), 3.01 (s, 3H), 2.56 (d, *J* = 13.3 Hz, 1H), 2.18 (d, *J* = 13.5 Hz, 1H), 1.82-1.64 (m, 4H), 1.76 (m, 3H), 1.52-1.25 (m, 5H), 1.07 (s, 3H), 1.05-0.92 (m, 1H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.96 (s, 3H).

2.5 References

1. Marmsater, F. P.; Murphy, G. K.; West, F. G. *J. Am. Chem. Soc.* **2003**, *125*, 14724-14725.
2. Eberlein, T. H.; West, F. G.; Tester, R. W. *J. Org. Chem.* **1992**, *57*, 3479-3482.
3. Murphy, G. K. Ph. D. Thesis. University of Alberta, **2007**.
4. Molander, G. A.; Eastwood, P. R. *J. Org. Chem.* **1995**, *60*, 4559-4565.

5. Hu, X.-G.; Jia, Y.-M.; Xiang, J.; Yu, C.-Y. *Synlett* **2010**, 982-986.

6. Marx, J. N.; Norman, L. R. *J. Org. Chem.* **1975**, *40*, 1602-1606.

7. Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353-1364.

8. Tsuda, T.; Okada, M.; Nishi, S.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 421-426.

9. Leue, S.; Miao, W.; Kanazawa, A.; Genisson, Y.; Garcon, S.; Greene, A. E., *J. Chem. Soc., Perkin Trans. 1* **2001**, 2903-2905.

10. Wallach, O. *Justus Liebigs Ann. Chem.* **1896**, *289*, 337-361.

11. Yates, P.; Jorgenson, M. J.; Singh, P. *J. Am. Chem. Soc.* **1969**, *91*, 4739-4748.

12. Hudlicky, T.; Short, R. P. *J. Org. Chem.* 1982, *47*, 1522-1527.

13. Ouvrard, N.; Rodriguez, J.; Santelli, M., *Angew. Chem. Int. Ed.* **1992**, *31*, 1651-1653.

14. Villieras, J.; Rambaud, M., *Synthesis.* **1982**, 924-926.

15. Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381-6384.

16. Pfeffer, P. E.; Osman, S. F. *J. Org. Chem.* **1972**, *37*, 2425-2428.

17. Smith, A. B.; Wexler, B. A.; Slade, J. S. *Tetrahedron Lett.* **1980**, *21*, 3237-3240.

18. Picotin, G.; Miginiac, P. *J. Org. Chem.* 1987, *52*, 4796-4798.

19. Rieke, R. D.; Uhm, S. J., *Synthesis* **1975**, 452-453.

20. Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549-2551.

21. Fernández-Ibáñez, M. Á.; Maciá, B.; Minnaard, A. J.; Feringa, B. L.

Angew. Chem. Int. Ed. **2008**, *47*, 1317-1319.

22. Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, *13*, 4339-4342.

23. Trost, B. M.; Dong, G.; Vance, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 4540-4541.

24. Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027-4029.

25. Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Choi, H.-S.; Fong, K. C.; He, Y.; Yoon, W. H. *Org. Lett.* **1999**, *1*, 883-886.

26. Cuevas-Yañez, E.; GarcIa, M. A.; de la Mora, M. A.; Muchowski, J. M.; Cruz-Almanza, R. *Tetrahedron Lett.* **2003**, *44*, 4815-4817.

27. Tomilov, Y. V.; Dokichev, V. A.; Dzhemilev, U. M.; Nefedov, O. M. *Russ. Chem. Rev.* **1993**, *62*, 799-838.

28. Lee, J. A.; Kim, H. O.; Tosh, D. K.; Moon, H. R.; Kim, S.; Jeong, L. S. *Org. Lett.* **2006**, *8*, 5081-5083.

29. Thomas, R. M.; Mohan, G. H.; Iyengar, D. S. *Tetrahedron Lett.* **1997**, *38*, 4721-4724.

30. Geng, Z.; Chen, B.; Chiu, P. *Angew. Chem. Int. Ed* **2006**, *45*, 6197-6201.

31. Sammes, P. G.; Street, L. J. *J. Chem. Soc., Chem. Commun.* **1983**, 666-668.

32. Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003-5010.

33. Ito, H.; Taguchi, T.; Hanzawa, Y. *J. Org. Chem.* **1993**, *58*, 774-775.

34. Kadam, S. M.; Nayak, S. K.; Banerji, A. *Tetrahedron Lett.* **1992**, *33*, 5129-5132.

35. Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem. Soc* **1995**, *117*, 532-533.

36. Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135-1138.

37. Castro, J.; Sorensen, H.; Riera, A.; Morin, C.; Moyano, A.; Pericas, M. A.; Greene, A. E. *J. Am. Chem. Soc.* **1990**, *112*, 9388-9389.

Chapter 3

Synthesis of Imino-Oxazinones From Carbodiimides and Acyl Ketenes

3.1 Biological Activity of Oxazinones

Globally in 2009, the top three selling drugs contained nitrogen heterocycles, a fact that reflects the enormous impact of these compounds on the pharmaceutical industry.[1] Oxazinones, more specifically imino- and amino-oxazinones (**1** and **2** respectively**)** are a class of heteroatom-rich heterocycles that have been the topic of bioactivity patents (Figure 3-1). In the last 15 years amino-oxazinones have been found to have analgesic,[2] tranquilizing,[3]

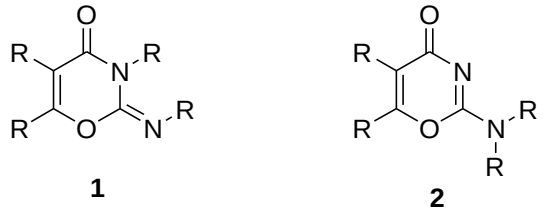


Figure 3-1: The structurally similar imino- and amino-oxazinones.

insecticidal,[4] and anticancer activities,[5] and have also been found to inhibit type 1, 11-β hydroxysteroid dehydrogenase.[6] The structurally similar imino-oxazinones, first reported by Deck and Dains,[7] were found to have significant fungicidal activity that has sparked several patents in the last 10 years. For

example, compounds **3**, **4** and **5** (Figure 3-2) were found to have substantial activity against the fungal agents *Erysiphe* [syn. Blumeria] *graminis* f. sp. *tritici* (causal agent of wheat powdery mildew), *Puccinia recondita* (causal agent of wheat leaf rust), *Phytophthora infestans* (causal agent of potato and tomato late blight), and/or *Sphaerotheca fuliginea* (causal agent of cucumber mildew).[8-11]

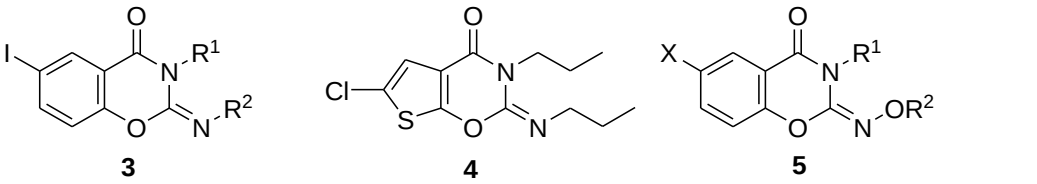


Figure 3-2: Examples of biologically active oxazinones

3.1.1 Diversification of Imino-oxazinones

In addition to their biological activity, imino-oxazinones are also versatile substrates suitable for conversion to other heterocycles. For example, in one step the imino-oxazinone **1** can be converted into a derivatized uracil **9**, while retaining all four substituents (Figure 3-3).[12] Imino-oxazinone **1** can also be selectively converted to an oxo-oxazinone in a single transformation with complete control over the three substituents. Additionally, different primary amines can be utilized to convert the oxo-oxazinone **7** to uracil derivatives **10** with a different substituent on one of the ring nitrogens. Finally, an oxazine **6**

can be formed by the reduction of an imino-oxazinone **1**. In general, the synthesis of imino-oxazinones allows for a divergent approach for the synthesis of heteroatom-rich heterocycles with excellent control of the substituents.

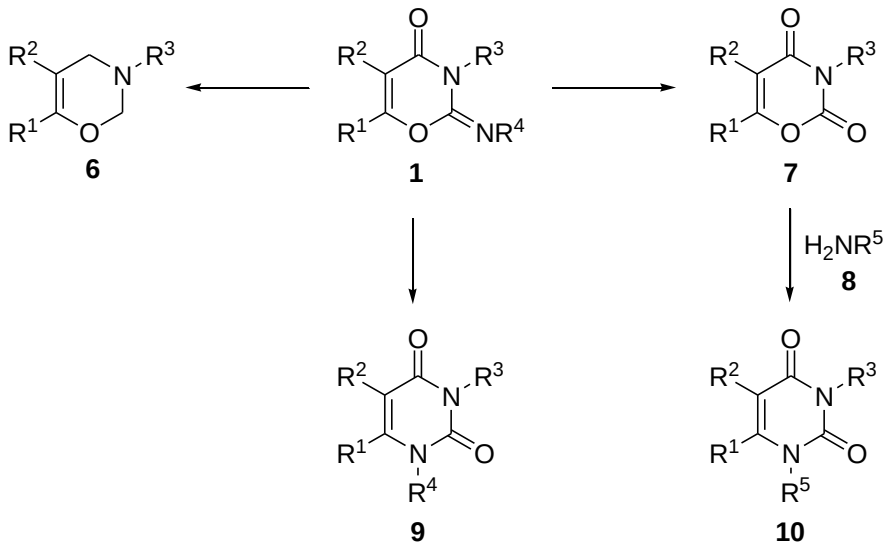
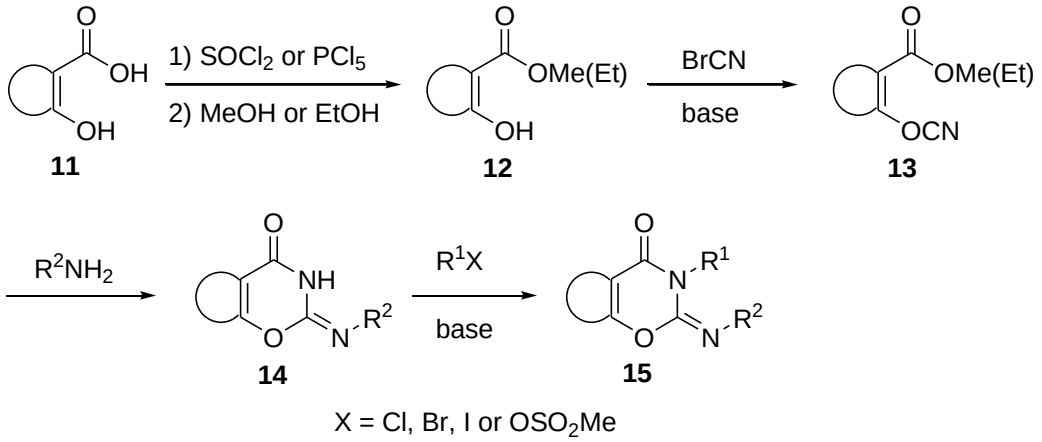


Figure 3-3: Divergent synthesis of heterocycles from imino-oxazinone derivatization.

3.1.2 Multistep Syntheses of Imino-Oxazinones

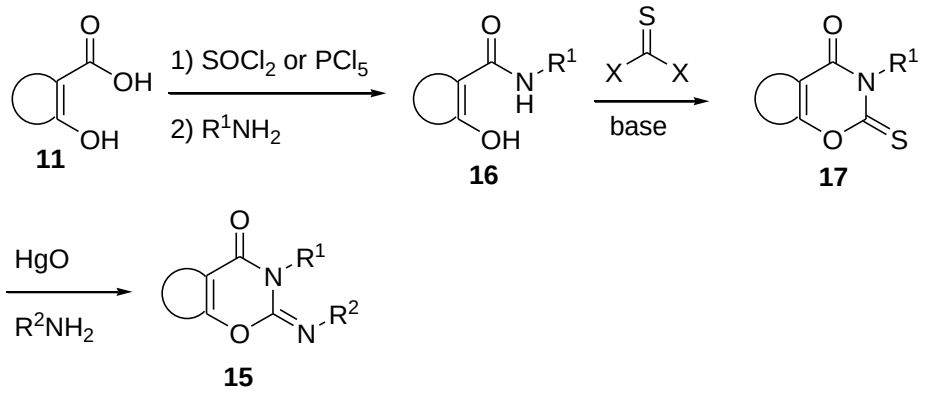
Imino-oxazinones can be synthesized from the tautomeric β-keto acids **11** in two different ways (Scheme 3-1).[8] The first approach begins with esterification of the acid **11**, forming either the methyl or the ethyl ester **12**, followed by reaction with cyanogen bromide to form the cyanate **13**. Treatment of intermediate **13** with a primary amine leads to the formation of the unsubstituted imino-oxazinone **14** (tautomeric to the amino-oxazinone). Finally, alkylation of the ring nitrogen generates the desired substituted imino-oxazinone.



11 **12** **13** **14** **15**

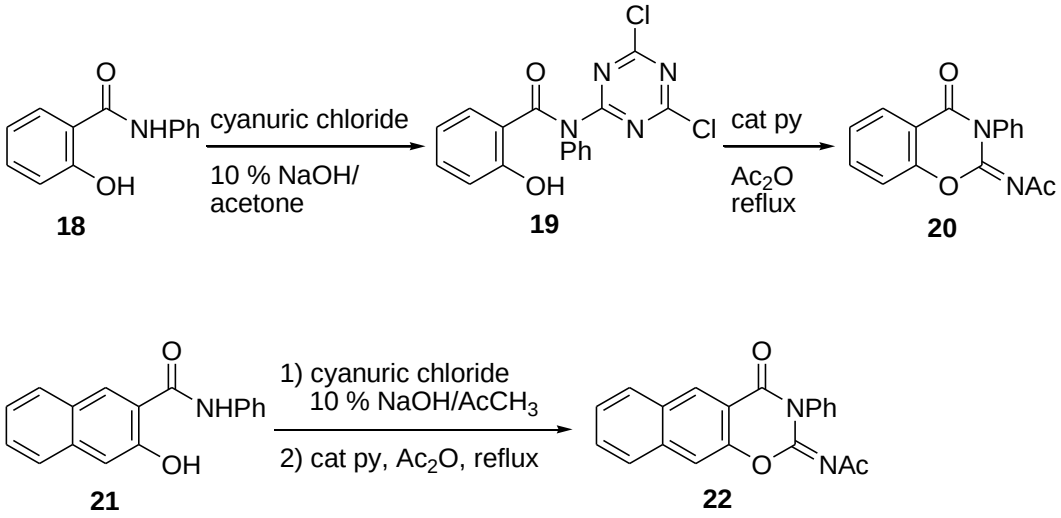
Scheme 3-1: The formation of imino-oxazines **15** from a cyanate **13.**

A second method for making imino-oxazinones, also utilizing the β-keto-acid **11** (again shown in enol form), begins with formation of amide **16**, by activation of the acid and addition of the desired primary amine (Scheme 3-2). The amide **16** is then converted to an *O*-alkyl-thiocarbamate **17** by reacting the β-keto amide **16** with a thiophosgene equivalent. Finally, treatment with a primary amine and mercury oxide forms the desired imino-oxazinone. It should be noted that both of these methods allow for the incorporation of different alkyl groups on either nitrogen of the product, allowing the facile construction of a variety of imino-oxazinone analogues. Numerous examples were provided wherein various substituted aromatic or heteroaromatic fused rings and alkyl groups were used.



Scheme 3-2: Imino-oxazinone from thioxo-oxazinone

o-Hydroxybenzamides **18** and **21**, structurally similar to the enolized β-ketoamides described above, can be used to make imino-oxazinones **20** and **22** via a somewhat different approach (Scheme 3-3).[14] In one example, salicylanilide **18** was reacted with cyanuric chloride, followed by treatment with

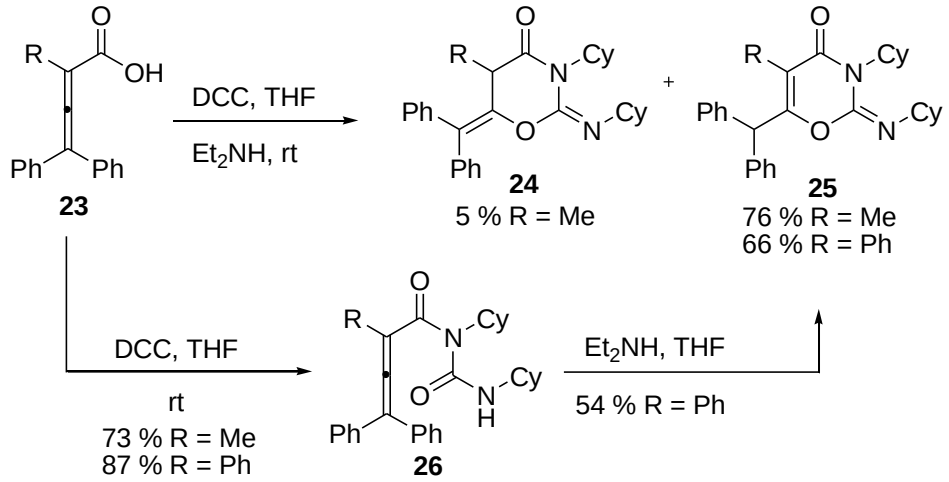


Scheme 3-3: Cyanuric chloride utilization for oxazinone formation.

a drop of pyridine in refluxing acetic anhydride to form the imino-oxazinone **20**.This method was repeated to also make the fused naphthyl imino-oxazinone.

3.1.3 One-step Syntheses of Imino-Oxazinones

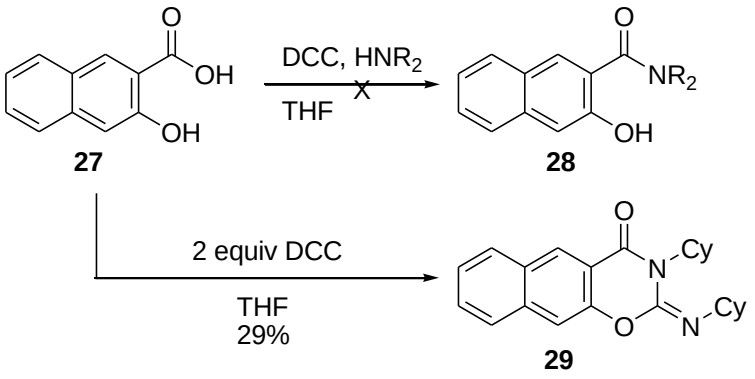
A convenient one-step method to make imino-oxazinones has been reported by Orahovats and Trifonov (Scheme 3-4).[15] The reaction of allene **23** with DCC in the presence of diethylamine produces the imino-oxazinone **25** in only one step. Substituting either a methyl or a phenyl on the allene affected the yields only marginally as the products were formed in 76 % and 66 % yield, respectively. Excluding base in this reaction allowed for the isolation of the presumed intermediate in the cyclization process, the *N*-acylurea **26**, in 73 and 87 % yield, respectively, for the methyl- and phenyl-substituted products.



Scheme 3-4: Carbodiimide reaction with allene **23**.

By addition of base, the phenyl substituted *N*-acylurea **26** underwent conversion to the imino-oxazinone **25** in 54 % yield. This last transformation was also mentioned to be possible with only heat, but notably the exocyclic double bond product **24** forms exclusively unless heating is prolonged.

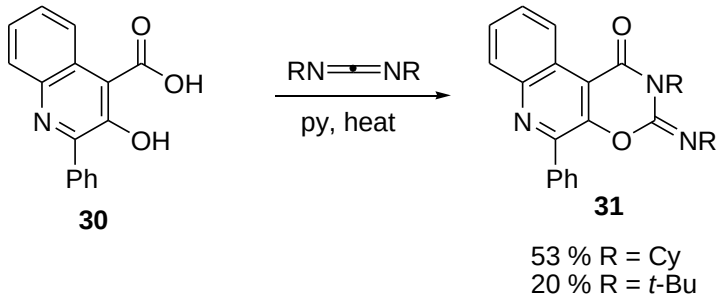
In 1967, a highly concise synthesis of an imino-oxazinone was reported by the May group (Scheme 3-5).[13] The May group attempted to form the naphthalene amide **28** from the carboxylic acid **27** using DCC; however, the only observed product was the imino-oxazinone **29**. This product was generated in 29 % yield from two



Scheme 3-5: A concise synthesis of imino-oxazinone **29.**

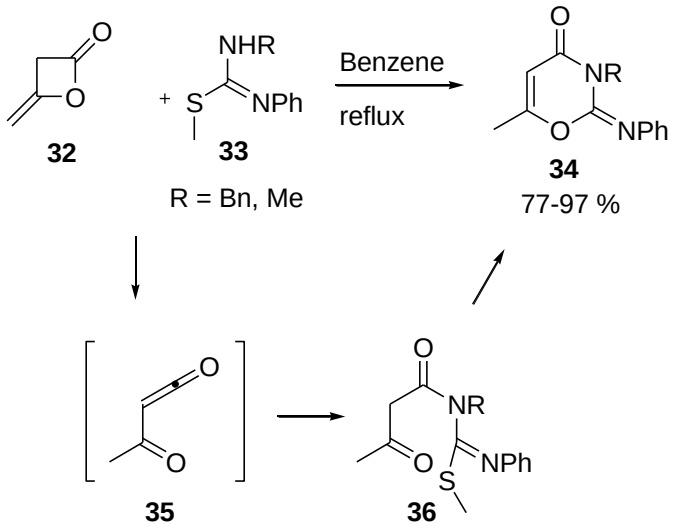
equivalents of DCC. Later, in a similar reaction, Joullié and coworkers made oxazinoquinolinones to test for antimalarial activity against *Plasmodium berghei* and *Plasmodium gallinaceum*.[16] In this work, cyclohexyl and *t*-butyl carbodiimides were used to generate products **31** in reported yields of 53 % and

20 %, respectively (Scheme 3-6). These examples demonstrate a highly streamlined route to form imino-oxazinones from the corresponding phenolic acids in a one-step process that is significantly simplified relative to the previously discussed routes.



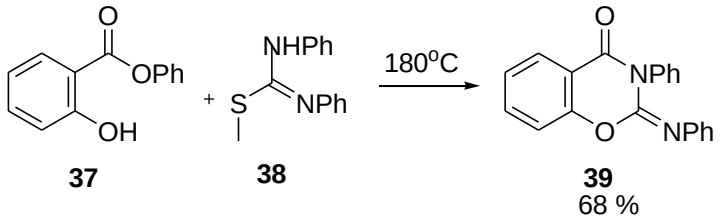
Scheme 3-6: The synthesis of oxazinone **31.**

A method was reported by Lacey that also formed the imino-oxazinone in one step (Scheme 3-7).[17] Diketene **32**, upon heating, formed the acyl ketene **35**, which reacted with the isothiourea **33** through nitrogen to form the intermediate **36**, which after loss of methanethiol formed the imino-oxazinone **34**. Notably, this method formed the product regioselectively, with the more basic alkyl-substituted nitrogen contained within the ring and the aryl-substituted nitrogen as part of the exocyclic imino group.



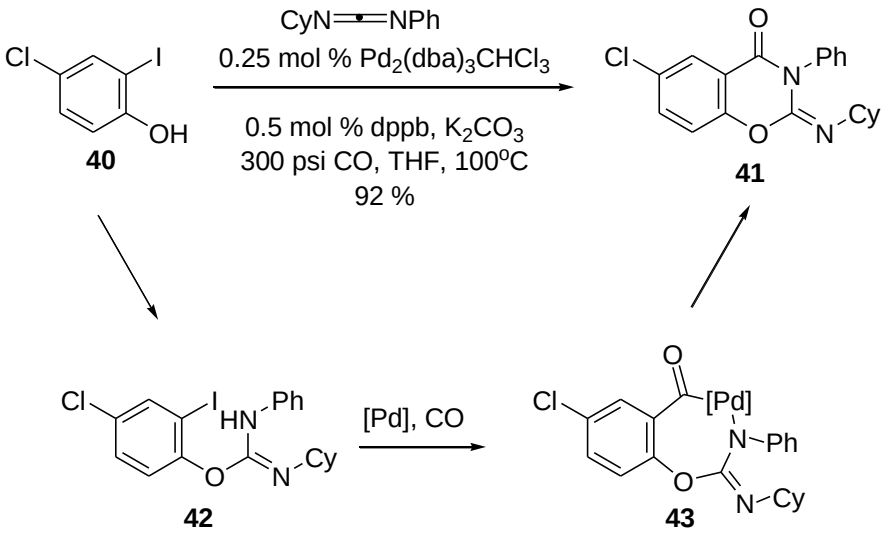
Scheme 3-7: The synthesis of of imino-oxazinone using diketene.

An equally concise but less atom economical method, also utilizing an *S*-methyl thiourea, has been carried out using phenyl salicylate **37** and isothiourea **38** (Scheme 3-8).[7] Heating these compounds created the desired oxazinone **39** in 68 % yield. The authors did not propose a mechanism; however, compound **37** likely loses phenoxide (or phenol) from the ester to generate an acyl ketene that reacts like the acylketene in the aforementioned reaction.



Scheme 3-8: The synthesis of **39** from phenyl salicylate **37.**

Alper and Larksarp reported an entirely different route that convergently produces imino-oxazinones **41** from *o*-iodo phenols **40** and carbodiimides under CO via palladium catalysis (Scheme 3-9).[18] This work demonstrated that several carbodiimides could be utilized, including unsymmetrical examples in order to produce one regioisomer containing the alkyl group on the imine nitrogen and the aryl group on the ring nitrogen. The advantages of this reaction are the highly convergent use of three components, high yields, and catalytic efficiency.



Scheme 3-9: The convergent synthesis of imino-oxazinone **41** using catalysis.

3.1.3.1 Coupling Acyl Ketenes With Carbodiimides

A highly convergent method for synthesizing imino-oxazinones utilizes a carbodiimide and an acyl ketene **44** generated from diketene **45**, dioxinone **46**,

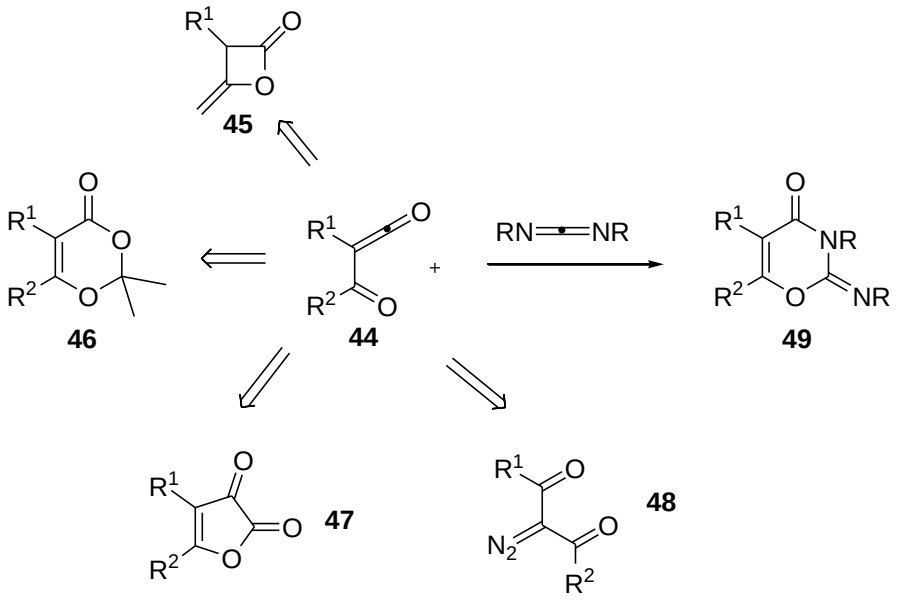
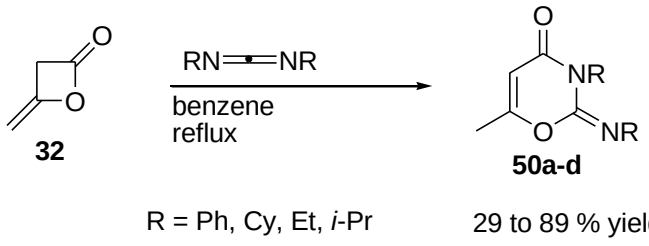


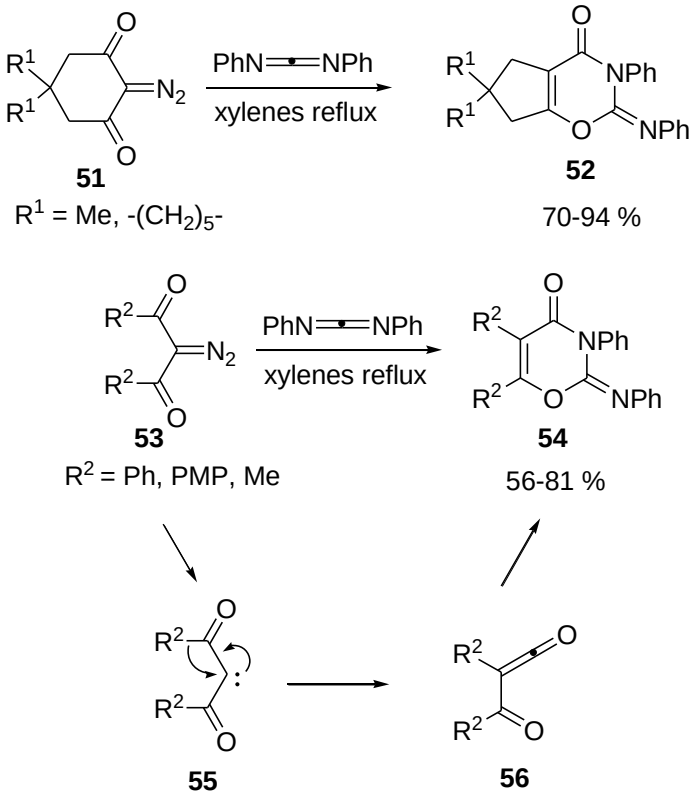
Figure 3-4: Different methods for acyl ketene generation for imino-oxazinone formation

furandione **47** or diazodiketone **48** (Figure 3-4).[19-23] Lacey has demonstrated the use of diketene **32** for this process to form four different imino-oxazinones **50a-d** in yields ranging from 29 to 89 % (Scheme 3-10).[24] This method works well and boasts the only method with complete atom economy; however, its scope is limited by accessibility of substituted diketenes.



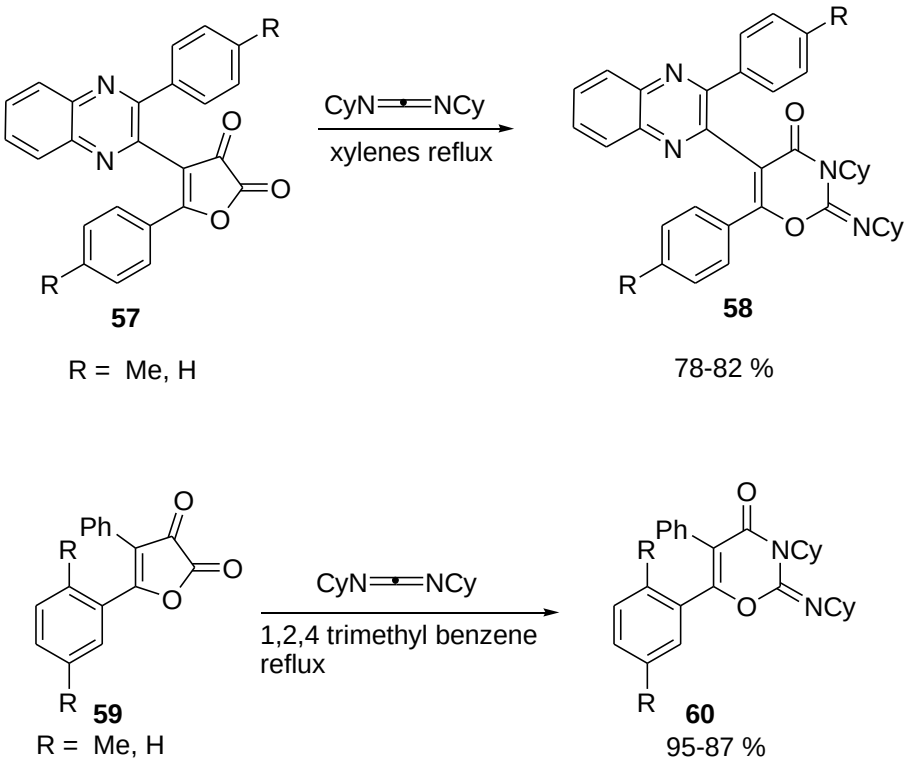
Scheme 3-10: The synthesis of imino-oxazinones **50a-d** from diketene **32.**

Capuano and coworkers utilized the Wolff rearrangement[25] to form an acyl ketene from diazodiketone precursors for the synthesis of imino-oxazinones. In xylenes at reflux the diazodiketone **53** expels nitrogen gas, resulting in a carbene **55,** which can undergo a [1,2] shift to form an acyl ketene **56** (Scheme 3-11). Various diketones were used to couple with diphenylcarbodiimide to provide several oxazinones in moderate to good yields, including fused bicyclic examples **52**.[26]



Scheme 3-11: The Wolff rearrangement used for imino-oxazinone syntheses.

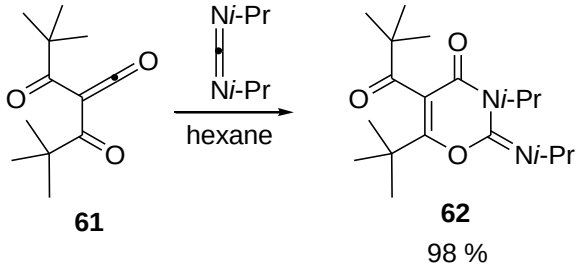
Maslivets and coworkers demonstrated a different method that also utilized the loss of carbon monoxide to produce a reactive acyl ketene intermediate en route to imino-oxazinones.[19-21] This methodology involved the loss of carbon monoxide gas from furandione starting materials **57** and **59** under thermal conditions (Scheme 3-12). The desired oxazinones **58** and **60** were subsequently formed in very good yields after the addition of DCC.



Scheme 3-12: The use of furandione for oxazinone syntheses.

There is one example in the literature that utilizes a stable acyl ketene to synthesize imino-oxazinones.[22] Bis(*t*-butyl)acyl ketene **61**, whose steric bulk impedes dimerization, undergoes efficient reaction in the presence of

carbodiimide to furnish the imino-oxazinone **62** in an excellent 98 % yield (Scheme 3-13). In previous examples, heat was needed to generate the acyl ketene, thus leaving the reactivity of the acyl ketene to speculation. The successful performance of this reaction at room temperature suggests that the acyl ketene is a reactive substrate.

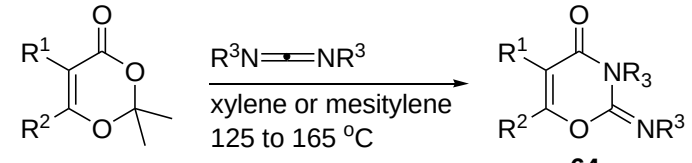


61 **62**

98 %

Scheme 3-13: The reaction of stable acyl ketene **61** with carbodiimide.

Dioxinones have also been utilized in the synthesis of imino-oxazinones. Upon heating, acetone is expelled from the dioxinone **63** to afford the reactive acyl ketene (Scheme 3-14). Several dioxinones **63** have been treated with symmetrical phenyl and cyclohexyl carbodiimide resulting in yields ranging from 35 to 86 %.[27]



63

R^1 = H, Me, Ph

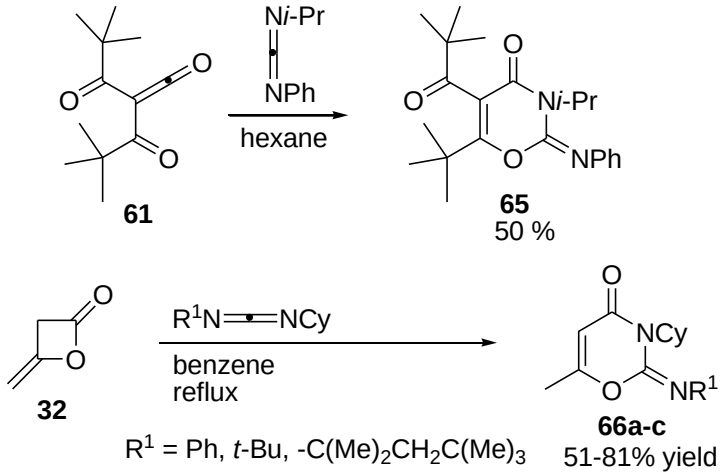
R^2 = Me, Ph

64

35-86 % yield

Scheme 3-14: The synthesis of imino-oxazinones from dioxinones **63.**

For the most part the acyl ketene approach to imino-oxazinones has utilized symmetrical carbodiimides, but there are a few examples employing unsymmetrical reactants, such as with diketene **32**[24] and also with the stable bis(*t*-butyl)acyl ketene **61** (Scheme 3-15).[22] In the first example, the more nucleophilic nitrogen of the carbodiimide reacted with the central ketene carbon; the less nucleophilic phenyl substituted amine was exocyclic in the product **65**. This selectivity was also observed with the second example when a phenyl substituted carbodiimide was utilized. Alternatively, when *t*-butyl carbodiimide was utilized, the sterically bulky *t*-butyl amine ended up at the less sterically congested exocyclic imino position on **66.**



Scheme 3-15: The syntheses of imino-oxazinones with unsymmetrical carbodiimides.

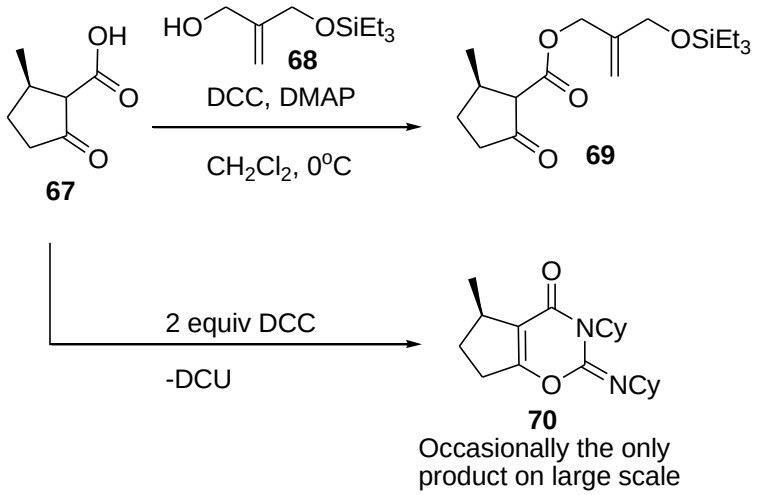
While all of the aforementioned methods proceeded regioselectively and in acceptable yield, they lacked generality from the standpoint of the acyl ketene;

the acylketenes were not readily derivitized. In this respect, dioxinone precursors are attractive, due to the commercial availability of the parent compound 2,2,6-trimethyl-1,3-dioxin-4-one, and straightforward methods for its structural modification, thus allowing the installation of different substituents on the acyl ketene. The reaction of substituted dioxinones with unsymmetrical carbodiimides could potentially lead to the formation of imino-oxazinones with control over all four substituents. We were interested in this proposal from a mechanistic standpoint and also from a synthetic standpoint. This process would be valuable because it would allow for the convergent synthesis of a variety of highly functionalized heterocycles for biological testing.

3.2 Results and Discussion

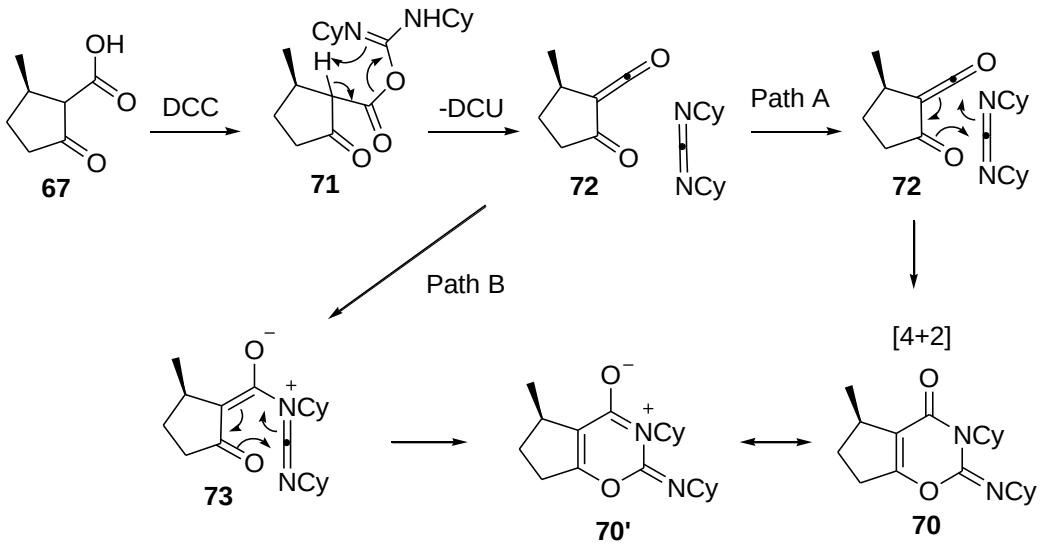
3.2.1 Background

In the early steps of our synthetic approach to dactylol, it was necessary to generate **69** with an esterification reaction on large scale (Scheme 3-16). Unfortunately, this esterification proved to be quite capricious, and in some cases yielded *none* of the desired ester. In these cases, a different product was obtained, which proved to be imino-oxazinone **70**. At room temperature, when the alcohol **68** was excluded from the reaction, the imino-oxazinone was obtained in an unoptimized yield of 56 %. These types of products have been isolated in similar cases by other groups attempting typical DCC coupling reactions.[13, 28]



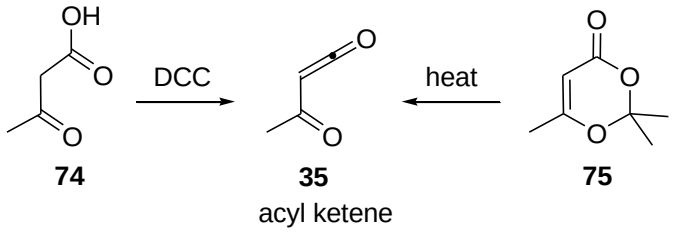
Scheme 3-16: The unsuspected product **70** of a DCC esterification.

The mechanism for this reaction is believed to proceed through capture of DCC by the acid **67** to first form the *O*-acylurea **71**, which could then undergo a retro-ene reaction to generate the acyl ketene **72** and an equivalent of dicyclohexylurea (Scheme 3-17). This ketene intermediate has been suggested in esterification reactions using β-ketoacids or diethylphosphonoacetic acid.[28] Next, this ketene **72** could react with an alcohol to form a β-keto ester; however, in the absence of an alcohol another equivalent of carbodiimide can react with the acyl ketene **72** in one of two potential pathways. Path A describes a possible [4+2] cycloaddition process that would lead directly to the imino-oxazinone product **70**, while Path B depicts a stepwise pathway involving nucleophilic addition of the carbodiimide nitrogen to the ketene to generate **73,** and subsequent 6π-electrocyclization to form the product **70**.



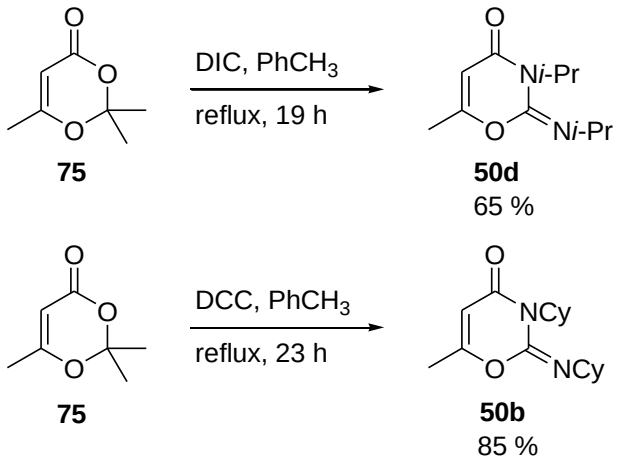
Scheme 3-17: The proposed mechanism for imino-oxazinone formation from β-keto-acid and DCC.

This interesting result served as the inspiration for the study of the generality of the acyl ketene + carbodiimide approach to imino-oxazinones. However, given the difficulties associated with handling β-keto acids, we opted to focus on dioxinone **75** precursors to access the reactive acyl ketene intermediate **35** (Scheme 3-18). Initially, the commercially available



Scheme 3-18: The generation of an acyl ketene from two potential pathways.

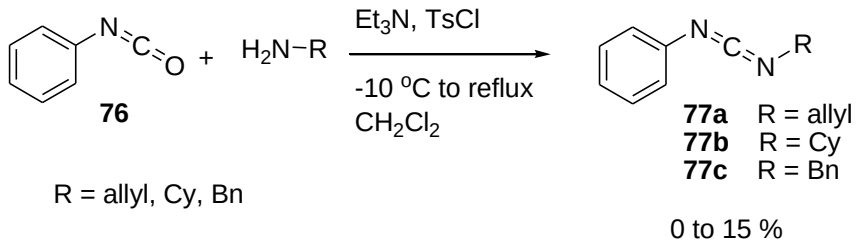
carbodiimides diisopropyl carbodiimide (DIC) and DCC were coupled with the simplest 6-methyldioxinone **75**, to form the respective diisopropyl and dicyclohexyl methyl imino-oxazinones **50d** and **50b** (Scheme 3-19).[24] The reaction with DIC, under ordinary thermal conditions (toluene at reflux), was found to be slow, requiring 19 hours to afford the product **50d** in an un-optimized 65% yield. The cyclohexyl oxazinone **50b** was formed in a higher yield of 85 %, but also required a long reaction time of 22 hours. To circumvent the long reaction times, microwave irradiation was investigated as a useful alternative. Moreover, in conjunction with the alternative heating regime, we proposed to examine the use of unsymmetrical carbodiimides in this process, with a goal of developing a procedurally simple and general route to a diverse set of imino-oxazinones.



Scheme 3-19 Initial Acyl ketene Carbodiimide Coupling

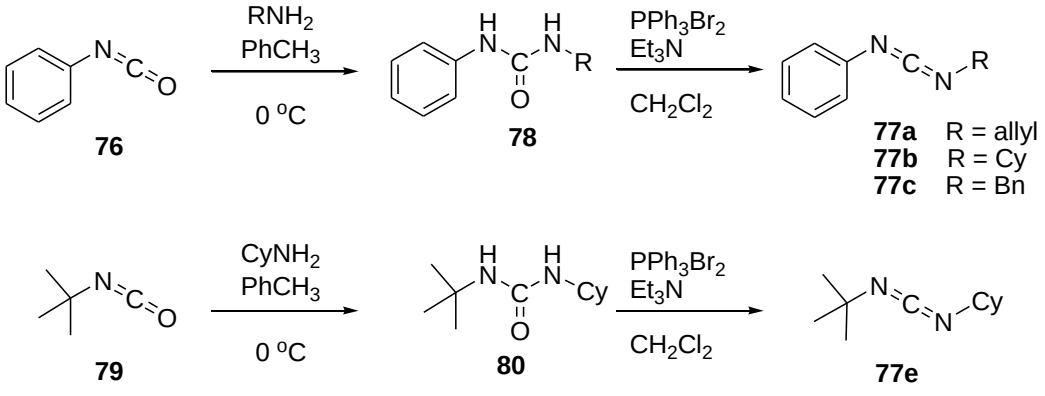
3.2.2 Substrate Synthesis: Preparation of Unsymmetric Carbodiimides

Several unsymmetrical carbodiimides have previously been made.[24, 29, 30] We initially focused on a method employing isocyanates and primary amines in the presence of tosyl chloride as a dehydrating agent. The advantages of this approach were the cheap and readily available reactants and the one-step procedure.[31] Phenyl isocyanate **76** was found to undergo successful reaction with alkyl amines, but purification of the product was found to be problematic (Scheme 3-20), with neither distillation nor column chromatography furnishing the desired products in pure form or acceptable yields. For example the cyclohexyl phenylcarbodiimide **77b** was only obtained in only 15 % yield, while the pentyl phenylcarbodiimide **77d** was formed in higher yields but could not be obtained pure. The major impurity observed by NMR analysis of the crude product appeared to contain a tosyl moiety. With this in mind, acetyl chloride was evaluated as an alternative dehydration reagent, but also gave unsatisfactory results. In light of these difficulties, another procedure was explored.



Scheme 3-20: Initial attempts at synthesizing carbodiimides in one step.

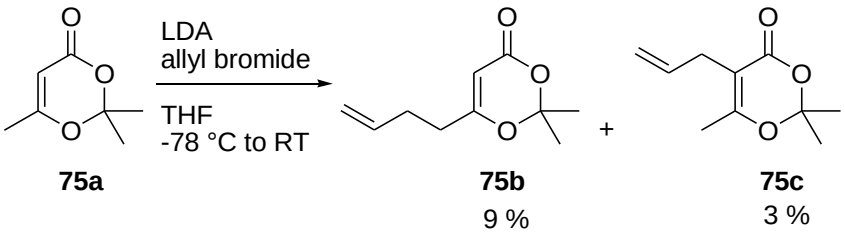
To avoid the isolation and purification problems described above, we examined a variation on the isocyanate procedure employing two separate steps (Scheme 3-21). First the urea was prepared by mixing phenyl (**76**) or *t*-butyl (**79**) isocyanate with different amines, affording several ureas (**78** and **80**) that were readily purified by recrystallization. For the dehydration step, triphenylphosphine dibromide was utilized in place of tosyl chloride.[32] Bulb-to-bulb (Kugelrohr) distillation proved to be necessary for the effective purification of the carbodiimides; standard distillation procedures resulted in extensive loss of the product due to decomposition. This method was found to be effective for the construction of various unsymmetrical carbodiimides with the exception of allyl *t*-butyl carbodiimide, which decomposed upon distillation. The carbodiimides were used immediately after distillation to avoid possible decomposition.



Scheme 3-21: A two step method for the synthesis of carbodiimides.

3.2.3 Synthesis of Dioxinones

The synthesis of 6-butenyl dioxinone **75b** has been reported in the literature (Scheme 3-22).[33] A terminal olefin on the side-chain would be a useful moiety, given its ability to participate in a wide range of functionalization steps later in a synthetic sequence.[34] When this method was roughly followed (with the substitution of allyl bromide for allyl iodide) a mixture of two monosubstituted products, **75b** and **75c,** was obtained. The low yield obtained is likely due to the presence of acetone in the dioxinone starting material. Despite the yield was low in comparison to the literature value (50 %), the reaction afforded two differentially substituted dioxinone substrates in one step.[33, 35] and since it could be easily scaled up, no effort was made to optimize the procedure.

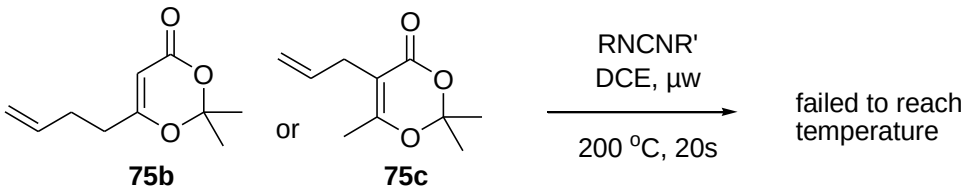


Scheme 3-22: Allylation of the 6-methyl dioxinone.

3.2.4 Preliminary Investigation of Unsymmetrical Carbodiimides

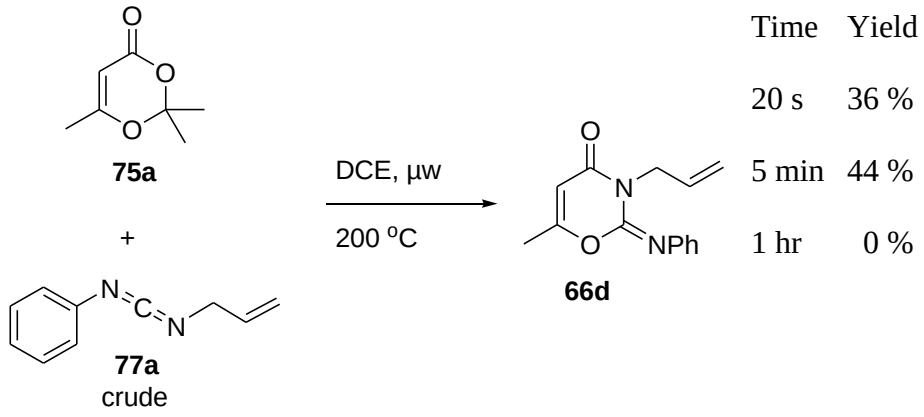
Initially, the coupling reaction was attempted with carbodiimides obtained from the TsCl conditions, and dioxinones **75b** and **75c** at 0.1 molar

concentration in the microwave reactor (Scheme 3-23). Unfortunately, an insufficient rate of temperature increase caused an automatic shut-down of the reactor in each case.



Scheme 3-23: The attempted reaction of dioxinones with carbodiimides using microwave irradiation.

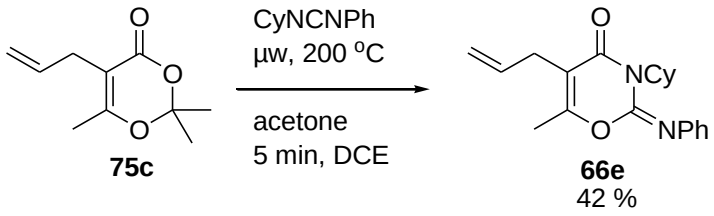
Increased polarity or concentration of the reaction solution can enhance the rate of microwave heating. In fact quadrupling the concentration of 6-methyl dioxinone **75a** did sufficiently increase the rate of heating, allowing the reaction to proceed without automatic shut-down (Scheme 3-24). The 6-methyl dioxinone **75a** was then heated in the presence of crude allyl phenylcarbodiimide **77a** for different lengths of time. A slight increase in yield was observed when the reaction time was increased from 20 seconds to 5 minutes. However, no product was obtained on extended heating, indicating that thermal decomposition of the product was probably occurring.



Scheme 3-24: The initial study of different reaction times for imino-oxazinone formation.

Cyclohexyl phenylcarbodiimide was examined with the more highly substituted 5-allyl dioxinone **75c** (Scheme 3-25). However, even at the higher concentration this reaction was hampered by automatic shut-down of the reactor due to slow heating. An important difference between this case and the earlier example using 6-methyl dioxinone **75a** was the fact that the commercially available **75a** was packaged as a 95:5 mixture of dioxinone and acetone. The presence of free acetone might enhance the rate of microwave heating, and to test this hypothesis 0.3 equivalents acetone was added to the reaction of dioxinone **75c**. In the event, we found that the rate of temperature increase was sufficient to avoid automatic shut-down. However, although this problem was solved, it became clear that the presence of an additional ring substituent resulted in slower consumption of the dioxinone. In was necessary to heat this

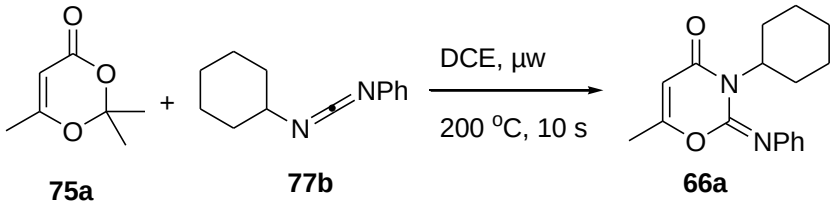
reaction at 200 °C for 5 minutes to ensure consumption of **75c**. Notably, while the yield was modest (42 %), the product was isolated as a single regioisomer.



75c **66e** 42 %

Scheme 3-25: The reaction of dioxinone **75c** and the addition of acetone to increase the rate of heating.

Next, the cyclohexyl phenylcarbodiimide **77b** was heated with the simple 6-methyldioxinone **75a** (Scheme 3-26). At 200 °C, this reaction was complete in only 10 seconds, affording the dioxinone product **66a** as a single regioisomer in 75 % yield.

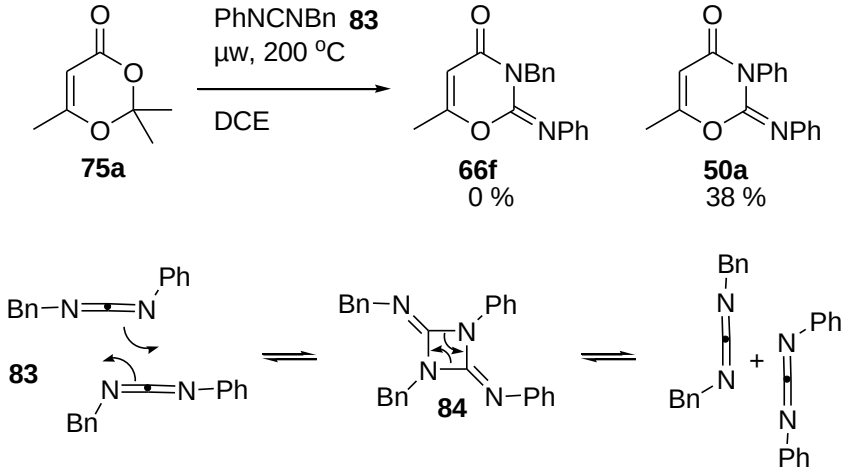


75a **77b** **66a** 75 %

Scheme 3-26: The rapid reaction of dioxinone **75a** with diimide **77b.**

Finally, the simple 6-methyl dioxinone **75a** was heated with benzyl phenyl carbodiimide using microwave irradiation at 200 °C (Scheme 3-27). Surprisingly, after purification, the only product isolated was the *N, N'*-diphenyl

imino-oxazinone **50a**. Careful examination of the starting material revealed that the "benzyl phenylcarbodiimide" was in fact diphenyl carbodiimide. It seems likely that the unexpected formation of diphenyl carbodiimide occurred during the first, unsuccessful distillation of the crude benzyl phenyl carbodiimide; at the



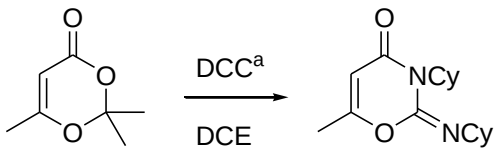
Scheme 3-27: The inadvertent synthesis of imino-oxazinone **50a** because of a carbodiimide thermal rearrangement.

high temperatures experienced during this process, a [2+2]/retro-[2+2] sequence may occur, forming the two symmetrical carbodiimides. Subsequent bulb-to-bulb distillation furnished the more volatile diphenyl carbodiimide, which was inadvertently used in the next step.

3.2.5 Optimization of Imino-Oxazinone Synthesis Via Microwave Heating

Having shown in the preliminary studies discussed above that this process was feasible, we then set out to optimize the microwave heating conditions through systematic variation of time and temperature. Using DCC and trimethydioxinone, conversion of the starting material was measured at temperatures ranging from 100-170°C and times ranging from 10 seconds to 60 minutes (Table 3-1). At lower temperatures, the reaction was incomplete even

Table 3-1: The optimization of temperature and time for dioxinone reaction.



75a **50b**

Time	Conversion (^{1}H NMR)				
	100 °C	110 °C	130 °C	150 °C	170 °C
10 s	0 %	9 %	12 %	61 %	97 %
5 min	3 %	11 %	56 %	100 %	NA
30 min	19 %	52 %	100 %	100 %	NA
60 min	37 %	72 %	100 %	100 %	NA

[a] Refer to experimental for procedure.

after 1 hour. On the other hand, at 150 °C the reaction was complete after only 5 minutes. At temperatures above 150 °C, 10 seconds was sufficient for full conversion.

3.2.6 Regioisomer Determination

The regiochemistry of imino-oxazinones has previously been confirmed by first hydrolysis of the imine and then structure identification to confirm the remaining amine substitution.[12] Alternatively the regiochemistry can be confirmed with nOe and HMBC correlations (Figure 3-5). For example an nOe correlation was observed between the alkene hydrogen and the cyclohexane methylene protons of oxazinone **66a**. Additionally, the methyl group was found to have an nOe correlation with the phenyl protons, and we also observed an HMBC correlation between the cyclohexyl methine proton and both the imine

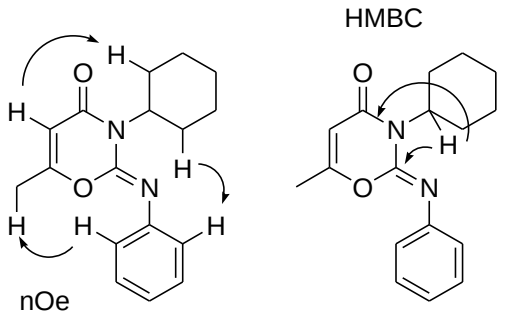


Figure 3-5: HMBC and nOe correlations for oxazinone **66a.**

and the carbonyl carbons; both of these observations would not have been observed with the other regioisomer. Another clue regarding regiochemistry utilizes chemical shift data in the 1D ^{1}H NMR spectrum. The chemical shift of the cyclohexyl proton in **66a** is 4.83 ppm (Figure 3-6). The comparable proton in the dicyclohexyl compound **50b** occurs at a similar chemical shift of 4.68 ppm whereas the cyclohexyl methine proton on the imine nitrogen appears upfield at 3.60 ppm. If the other isomer of **50b** had been formed (**85**) the cyclohexyl methine proton should be observed at around 3.6 ppm. This difference in chemical shift allows for the easy identification of regiochemistry in subsequent cases.

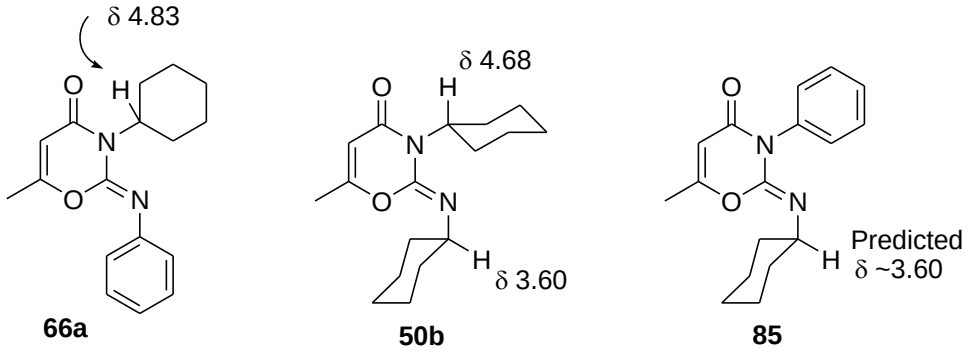


Figure 3-6: The ^{1}H NMR chemical shift as an indication of regiochemistry.

In one case, X-ray crystallographic analysis allowed for an unequivocal assignment of imine geometry, which was helpful since we considered the nOe data to be inconclusive. The known diphenyl imino-oxazine **50a**[17, 24, 27] was recrystallized (Figure 3-7) and the X-ray crystal structure (obtained by M. J. Ferguson, University of Alberta) confirmed the (*Z*)-geometry of the imine.[20]

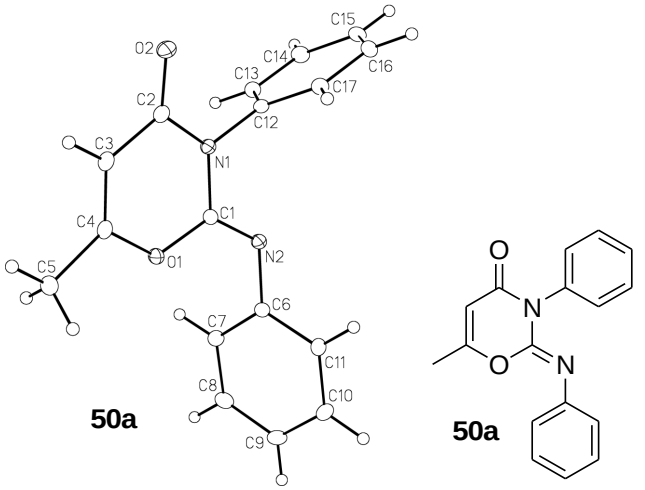


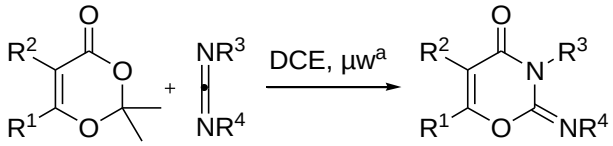
Figure 3-7: The crystal structure of diphenyl imino-oxazinone **50a**.

3.2.7 Reaction Scope

Several pairs of reactants were heated at both 150 and 200 °C for 5 min in an effort to determine the scope of this reaction (*Table 3-2*). When heating the parent dioxinone with cyclohexylphenylcarbodiimide, the reaction was found to be very fast at 200 °C, affording a 75 % yield after only 10 seconds (entry 1); however, increasing the time to 5 minutes dropped the yield to 64 %. This result is likely due to decomposition during the prolonged reaction time at high temperature, since once the temperature was lowered to 150 °C the yield increased to 71 % (entry 2). Notably, on a separate occasion longer reaction times were tested and a drop in yield was observed. Allylphenylcarbodiimide worked very well at both 200 and 150 °C, with yields of 93 and 89 %, respectively. The higher temperatures were favorable for the 6-butenyl dioxinone substrate, which could be due to the additional steric bulk of the butenyl group requiring higher temperatures for the reaction (entries 5 to 7);

these substrates may benefit from longer reaction times. The reaction with 5-allyl-6-methyl dioxinone (R^2 = allyl, entry 8) was observed to be slow when monitored by TLC, so this reaction was only performed at 200 °C and afforded the desired product in a low yield of 42 %. In all of the reactions, only one regioisomer was isolated.

Table 3-2: Imino-oxazinone reaction scope.



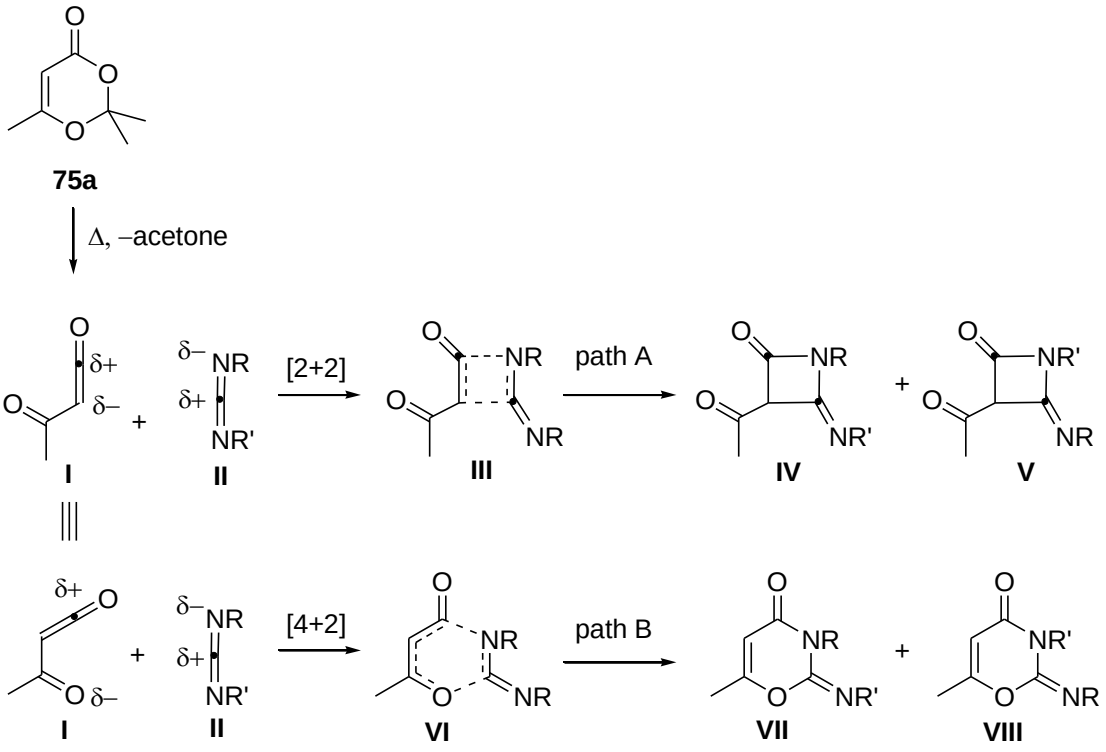
75a-c **77a,d,e** **66a-d,f-g**

entry	R^1	R^2	R^3	R^4	product	acetone	yield [b]	yield [c]
1[d]	Me	H	Cy	Ph	**66a**	0	75 %	NA
2	Me	H	Cy	Ph	**66a**	0	64 %	71 %
3	Me	H	Allyl	Ph	**66d**	0	93 %	89 %
4	Me	H	Cy	*t*-Bu	**66b**	0	70 %	82 %
5	Butenyl	H	Cy	Ph	**66g**	4 mM	75 %	51 %
6	Butenyl	H	Allyl	Ph	**66h**	4 mM	68 %	65 %
7	Butenyl	H	Cy	*t*-Bu	**66i**	4 mM	71 %	60 %
8	Me	Allyl	Cy	Ph	**66e**	4 mM	42 %	NA

[a] 1,2 - Dichloroethane (0.5 mL), acetone (0 or 5 μL), dioxinone (0.2 mmol) and carbodiimide (0.3 mmol) were combined and irradiated (150 °C or 200 °C) for 5 min. [b] Isolated yield after column chromatography, reaction performed at 200 °C. [c] Isolated yield after column chromatography, reaction performed at 150 °C. [d] Reaction performed for 10 s.

3.2.8 Regioselectivity Discussion

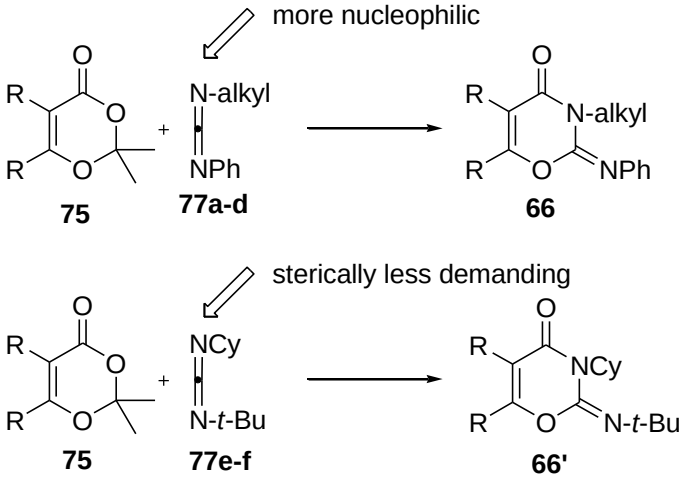
Several cycloaddition products could be imagined when considering the reaction between an acyl ketene and an unsymmetrical carbodiimide. Narrowing the number of products by consideration of the partial charges on the reaction partners (**I** and **II)** reduces the number of possible adducts to four (Scheme 3-28). One reaction pathway involves a [2+2] cycloaddition (path A) that would potentially give rise to two different regioisomeric β-lactams (**IV** and **V**). These products have been previously observed by another group studying the reaction of a ketene with a carbodiimide;[36] however, this pathway was not observed in



Scheme 3-28: The potential products of dioxinone **75a** and a carbodiimide.

any of the cases examined in this study. Alternatively, a [4+2] cycloaddition could give two different isomers (**VII** and **VIII**) depending on which imine (C=NR) moiety of the carbodiimide reacts as the dienophile (path B).

When a carbodiimide substituted with two alkyl groups was used, the only product isolated had the larger group (*t*-butyl) on the exocyclic imino nitrogen **66'**, indicating a preference for reaction with the sterically less demanding C=NR group (Scheme 3-29). Thus, it appears that the products obtained under these reaction conditions are formed based on steric considerations. Alternatively, electronic factors may come into play in cases involving a carbodiimide substituted with one aryl and one alkyl group **77a-d**. In these cases, the alkyl-substituted nitrogen was always incorporated into the oxazinone ring, indicating preferential participation of the alkyl imino group in



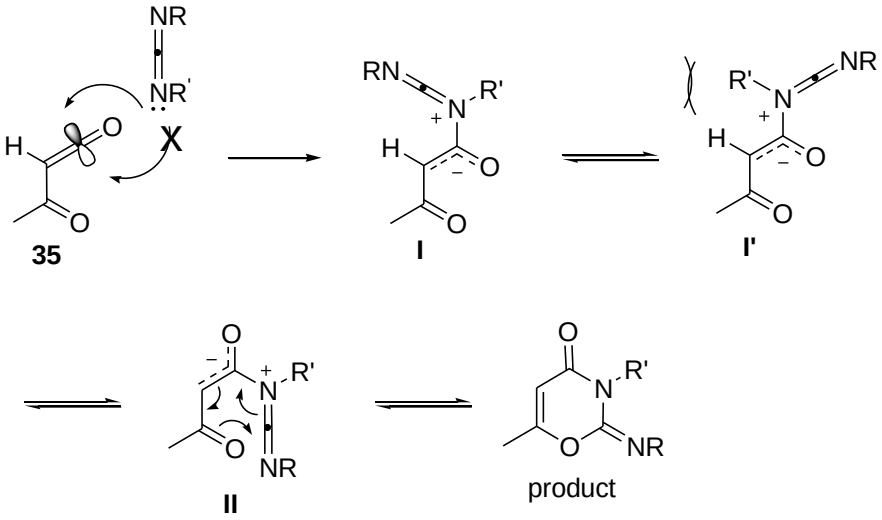
Scheme 3-29: An explanation for the regioselectivity of imino-oxazinone formation.

the cycloaddition. That is, the more nucleophilic nitrogen,[24] which is attached to the alkyl group participates in the reaction with the electrophilic ketene.

3.2.9 Mechanism

Our results show that the regioselectivity is determined by steric or electronic factors. The fact that the most basic nitrogen of the carbodiimide bonds with the ketene C=O carbon suggests the possible involvement of a stepwise mechanism (or at least a highly asynchronous mechanism). Formally this process is a [4+2] cycloaddition; however, the largest orbital coefficient in the LUMO of an acyl ketene **35** is in-plane with the molecule (Scheme 3-30) and thus perpendicular to the acyl π system (i.e., the LUMO is not a 4 atom conjugated system required for a concerted [4+2]-cycloaddition).[37, 38] The atom bearing the largest LUMO coefficient is likely first attacked by the most basic nitrogen. Since this central orbital is in-plane, the carbodiimide is expected to approach from the less sterically encumbered side, which is on the same side as the hydrogen and the opposite side of the acyl group in **35.** Two different rotamers **I** and **I'**, can be formed as a result of this process. In the case of the intermediate substituted with a large group (such as R' = cyclohexyl), there should be more preference for the R' group to be away from the indicated hydrogen (**I**' rotamer) forcing the nitrogen out of planarity towards the reactive conformer **II**. After rotation about the C-C bond (of the former ketene) to **II**, the

conformation would be correct to allow the final cyclization to the product. Alternatively, when the substituent is smaller (such as R' = allyl) there should be less steric congestion (in rotamer **I'**), decreasing the tendency for the rotation to **II**. In terms of the simple 6-methyl dioxinone **75a** and cyclohexyl phenylcarbodiimide**,** the yield was higher at shorter times (or lower temperatures), which could be attributed to the large cyclohexyl group promoting facile rotation from **I'** to **II**. On the other hand, the allyl carbodiimide generated the oxazinone with a higher yield when the temperature was higher; the substrate may have required higher temperatures to ultimately achieve the correct rotamer.



Scheme 3-30: Proposed mechanism of Imino-Oxazinone formation.

The low yield and reactivity of the 5-allyl dioxinone might be due to the additional steric constraints involved in the initial attack of the carbodiimide

nitrogen onto the acyl ketene **86** since the allyl group is much larger than a hydrogen (Figure 3-8). Also, the larger allyl group may cause the molecule to adopt a different conformer that does not lead to product formation.

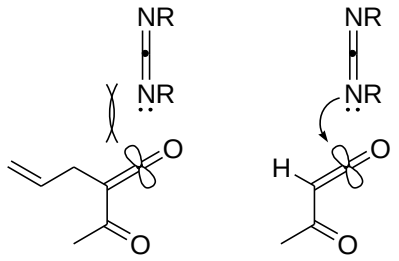
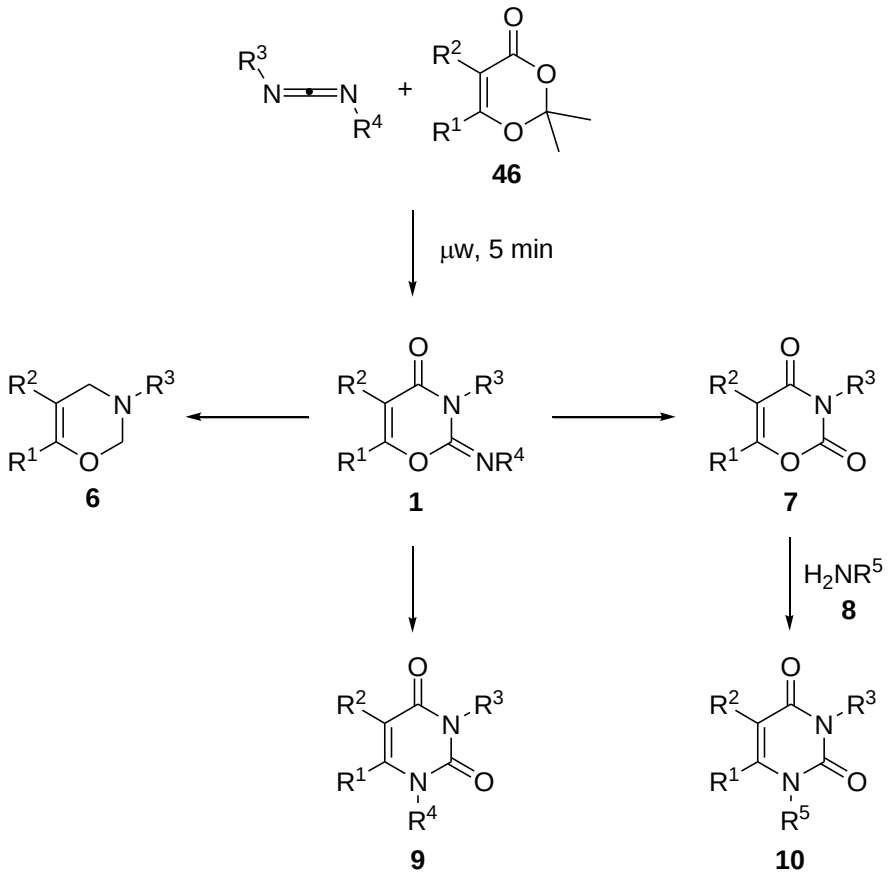


Figure 3-8: Comparison of the sterically encumbered **86** to the less substituted **35.**

3.3 Conclusions and Future Work

This study has shown that variously substituted dioxinones **46** and carbodiimides, both of which are readily available, undergo efficient coupling to afford the biologically relevant imino-oxazinone skeleton with complete regioselectivity (Scheme 3-31). In this process, the substitution pattern at all four possible variable positions can be controlled. In addition, distilled solvents and an inert atmosphere were not required, and the reaction conditions are simple and short with microwave heating. Previous studies have shown that the imino-oxazinone products can be converted to other heterocyclic ring systems (**6**, **7**, **9** and **10**). The rapid and convergent assembly of simple building blocks should allow this process to be used in the construction of larger libraries, while

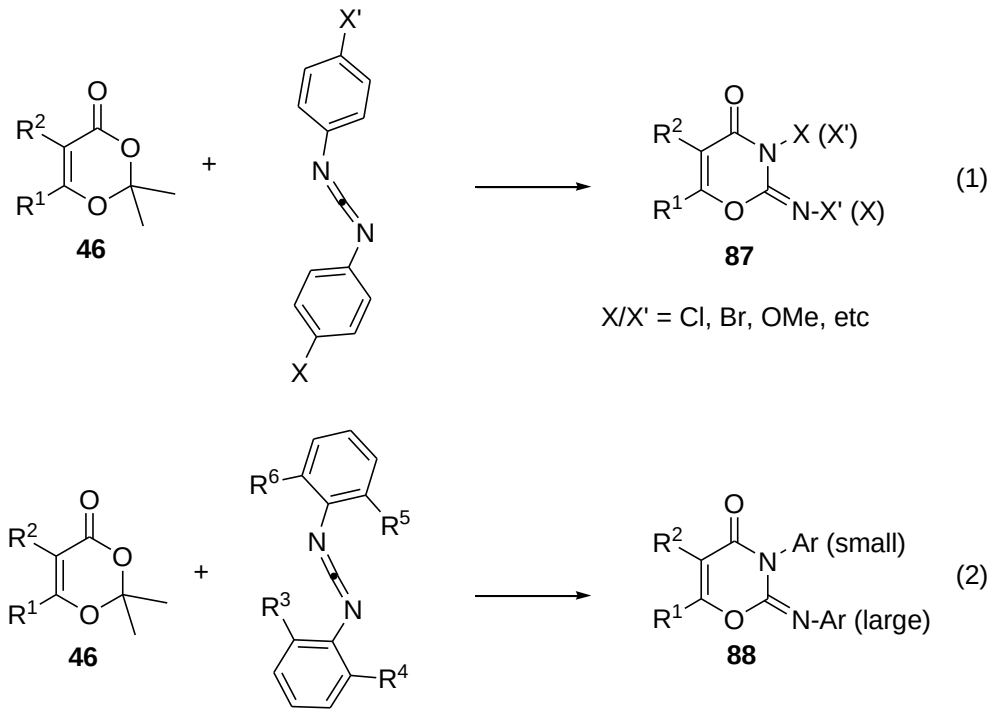
the option of divergent functionalization of the imino-oxazinone products would allow for the formation of an even larger number of ultimate products via an overall sequence that is quite short.



Scheme 3-31: The convergent synthesis of imino-oxazinones and their divergent syntheses of other heterocycles.

Differentially substituted diaryl carbodiimides could be useful substrates to evaluate the role of electronic effects in the regiochemical outcome (eq 1, Scheme 3-32). An example would be inclusion of remote electron-withdrawing

and –releasing groups on the aryl groups, which should lead to a reaction controlled only by electronic effects. Alternatively, ortho substitution may allow further evaluation of steric effects on the process (eq 2).



Scheme 3-32: Two possible methods for probing regioselectivity by either sterics or electronics.

3.4 Experimental

3.4.1 General Information

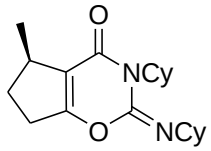
The reactions were carried out in oven (120 °C) or flame-dried glassware under a positive argon atmosphere unless otherwise stated. The transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannulae. Solvents were distilled before use: dichloromethane and

dichloroethane from calcium hydride, toluene from sodium metal. Microwave heating was carried out in a Biotage Initiator microwave reactor, using 2-5 mL vials. Reaction temperature was determined through measurement of the vial surface temperature using an infrared sensor, then corrected for internal temperature by the unit's processor using a proprietary algorithm. 2,2,6-Trimethyl-4H-1,3-dioxin-4-one **75a** (Aldrich) was obtained with 5 % (by weight) acetone and used directly. Thin layer chromatography was performed on glass plates precoated with 0.25 mm silica gel with fluorescent indicator UV_{254} (Rose Scientific). Flash chromatography columns were packed with 230-400 mesh silica gel (Merck).

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) and referenced to the chloroform peak at 7.26 ppm. Chemical shifts are reported to 3 decimal places where distinctions could be made but they are reproducible only to 2 decimal places. Coupling constants (*J*) are reported in Hz to 1 decimal place. The multiplicity of signals observed in the ^{1}H NMR are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets, etc. The carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 126 MHz or 101 MHz and are reported (ppm) relative to the center line of a triplet at 77.23 ppm for chloroform. Infrared (IR) spectra were measured with a Nicolet Magna 750 FT-

IR spectrophotometer and Nic-Plan FTIR Microscope. Mass spectra were determined on a Kratos Analytical MS-50 (EI) or Applied Biosystems Mariner Biospectrometry Workstation (ESI). Optical rotation was measured on a Perkin Elmer 241 Polarimeter.

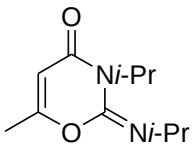
3.4.2 Procedures and Characterizations



70

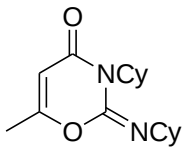
***N, N'*-Dicyclohexyl iminooxazinone 70.** Dicyclohexylcarbodiimide (111 mg, 0.539 mmol) and dichloromethane (2 ml) were added to ketoacid **67** (57 mg, 0.40 mmol) under argon and stirred for 24 h. The reaction was filtered through cotton wool and concentrated *in vacuo*. The product was purified by flash column chromatography using 7 % EtOAc in hexanes and was isolated as a white semi-solid in 56 % yield (50 mg). $[\alpha]_D^{20}$ = -15.7 (*c* 0.67, $CHCl_3$); IR (cast film) 1693, 1654 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.71 (tt, *J* = 3.8, 12.0Hz, 1H), 3.65-3.58 (m, 1H), 3.11-3.03 (m, 1H), 2.65 (dddd, *J* = 2.2, 5.6, 9.5, 17.6 Hz, 1H), 2.58-2.48 (m, 3H), 2.23 (dddd, *J* = 5.6, 8.4, 9.6, 13.1 Hz, 1H), 1.80-1.73 (m, 4H), 1.68-1.60 (m, 3H), 1.57-1.50 (m, 4H), 1.39-1.28 (m, 7H), 1.27-1.11 (m, 1H), 1.23 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.5, 160.8, 140.1, 113.7, 54.1, 53.0, 34.7, 34.0, 33.9, 29.5, 29.0, 28.1, 27.9, 26.5, 26.5, 26.1,

25.6, 24.3 (2C), 20.3; MS (ESI) *m/z* calcd for $C_{20}H_{31}N_2O_2$ ($M+H^+$) 331.2380 found 331.2375.



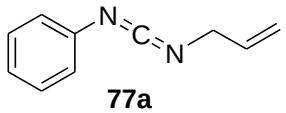
50d

Diisopropyl oxazinone 50d. Trimethyl dioxinone **75a** (25 g, 0.17 mmol), diisopropylcarbodiimide (28 mg, 0.18 mmol) and $PhCH_3$ (2 mL) were refluxed for 19 h under an argon atmosphere. The reaction mixture was cooled and then directly purified by column chromatography (15 % EtOAc/Hexanes) to furnish 25 mg (68 % yield) of compound **50d** as a white solid whose spectroscopic data were consistent with previously reported values.[24]



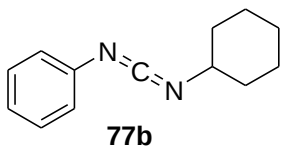
50b

Dicyclohexyl oxazinone 50b. Trimethyl dioxinone **75a** (200 µL, 1.5 mmol), dicyclohexylcarbodiimide (DCC; 0.31 g, 1.5 mmol) and $PhCH_3$ (5 mL) were heated at reflux for 23 h under an argon atmosphere. Reaction was cooled and then directly purified by column chromatography (15 % EtOAc/hexanes) to furnish 352 mg (85 % yield) of compound **50b** as a white solid whose spectroscopic data were consistent with previously reported values.[24, 27]



77a

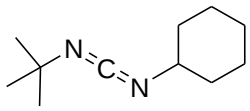
***N*-Phenyl, *N*'-allylcarbodiimide 77a:** Phenyl isocyanate (2.0 mL, 18 mmol) was added to toluene (20 mL) under an argon atmosphere and the solution was cooled to 0 °C. Allyl amine (1.4 mL, 18 mmol) was added and the reaction was stirred for 40 min. The reaction was concentrated *in vacuo* and then was washed with a 1:1 solution of MeOH and H_2O (75 mL x 2). After recrystallization using EtOH, 2.3 g (71 %) of *N*-phenyl, *N*'-allylurea was obtained as a white solid. Triphenylphosphine (3.4 g, 13 mmol) and CH_2Cl_2 (15 mL) were placed under an argon atmosphere and cooled to 0 °C. Bromine (0.67 mL, 13 mmol) was added followed by Et_3N (5.5 mL, 39 mmol). After 15 min the urea (2.3 g, 13 mmol) was added. After 2 hours the reaction was washed with H_2O (10 mL), dried over $MgSO_4$ and concentrated *in vacuo.* The resulting mixture was mixed with hexanes (15 mL x 2) and filtered. The hexane solution was concentrated *in vacuo.* The resulting oil was purified by bulb-to-bulb distillation and 163 mg (8 % yield) of carbodiimide **77a** was obtained as a clear oil whose spectroscopic data were consistent with previously reported values.[39]



77b

***N*-Phenyl, *N*'-cyclohexylcarbodiimide 77b:** Phenyl isocyanate (2.0 mL, 18 mmol) was added to toluene (20 mL) under an argon atmosphere and the

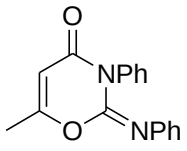
solution was cooled to 0 °C. Cyclohexylamine (2.0 mL, 18 mmol) was added and the reaction was stirred for 40 min. The reaction was concentrated *in vacuo* and then was washed with a 1:1 solution of MeOH and H_2O (75 mL x 2). After recrystallization using EtOH, 2.6 g (66 %) of *N*-phenyl, *N*'-cyclohexylurea was obtained as a white solid. Triphenylphosphine (3.5g, 13 mmol) and CH_2Cl_2 (15 mL) were placed under an argon atmosphere and cooled to 0 °C. Bromine (0.62 mL, 12 mmol) was added followed by Et_3N (5.1 mL, 36 mmol). After 15 min the urea (2.6 g, 12 mmol) was added. After 2 hours the reaction was washed with H_2O (10 mL) dried over $MgSO_4$ and concentrated *in vacuo.* The resulting mixture was mixed with hexanes (15 mL x 2) and filtered. The hexane solution was concentrated *in vacuo.* The resulting oil was purified by bulb-to-bulb distillation and 390 mg (16 % yield) of carbodiimide **77b** was obtained as a clear oil whose spectroscopic data were consistent with previously reported values.[39]



77e

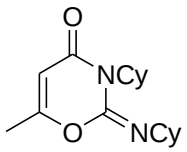
***N*-*t*-Butyl, *N*'-cyclohexylcarbodiimide 77e:** Phenyl isocyanate (5.0 mL, 18 mmol) was added to toluene (40 mL) under an argon atmosphere and the solution was cooled to 0 °C. Cyclohexylamine (5.0 mL, 44 mmol) was added dropwise via addition funnel and the reaction was stirred for 40 min. The reaction was concentrated *in vacuo* and then was washed with a 1:1 solution of MeOH and H_2O (150 mL x 2). After recrystallization using EtOH, 5.4 g (64 %) of *N*-*t*-butyl, *N*'-cyclohexylurea was obtained as a white solid.

Triphenylphosphine (7.2 g, 32 mmol) and CH_2Cl_2 (70 mL) were placed under an argon atmosphere and cooled to 0 °C. Bromine (1.4 mL, 27 mmol) was added followed by Et_3N (11 mL, 82 mmol). After 40 min the urea (5.4 g, 27.2 mmol) was added. After 3 hours the reaction was washed with H_2O (100 mL) dried over $MgSO_4$ and concentrated *in vacuo.* The resulting mixture was mixed with hexanes (150 mL x 2) and filtered. The hexane solution was concentrated *in vacuo.* The resulting oil was purified by bulb-to-bulb distillation and 241 mg (5 % yield) of carbodiimide **77e** was obtained as a clear oil whose spectroscopic data were consistent with previously reported values.[39]



50a

Diphenylimino-oxazinone 50a: Trimethyl dioxinone **75a** (34 mg, 0.23 mmol), diphenylcarbodiimide (52 mg, 0.25 mmol) and DCE (0.5 mL) were combined in a microwave vial (0.5-2 mL). After microwave irradiation (200 °C) for 20 s the reaction was purified directly by column chromatography (30 % EtOAc/Hexanes) and 24 mg (38 % yield) of compound **50a** was obtained as a white solid and was recrystallized from Et_2O, EtOAc and hexanes whose spectroscopic data were consistent with previously reported values.[24, 27]



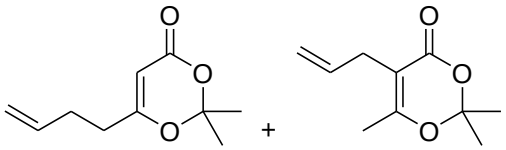
50b

NMR study for imino-oxazinone 50b. A 15 mL standard solution containing

dioxinone **75a** (0.910 g, 6.08 mmol, 0.405 mM) and DCC (1.49 g, 7.22 mmol, 0.48 mM) in DCE was prepared. A portion of the standard solution (0.5 mL) was added to each microwave vial (0.5-2 mL) and irradiated at the temperature indicated below. After the time indicated below the solutions were dried with a stream of air overnight and then analyzed by ^{1}H NMR. The imino-oxazinone H-C=C signal at 5.404_4-5.39_5 ppm and the dioxinone H-C=C signal at 5.24-5.23 ppm were integrated and recorded below. The time and temperature are indicated below. The conversion was calculated and recorded in the table. Entries 20, 21, 23 and 25 failed to reach the temperature and an auto-shutdown of the microwave occurred.

entry	ratio				
1	product	dioxinone	temp	time(sec)	conv (%)
2	0	1	100	10	0%
3	0.03	1	100	300	3%
4	0.24	1	100	1800	19%
5	0.58	1	100	3600	37%
6	0.1	1	110	10	9%
7	0.12	1	110	300	11%
8	1.1	1	110	1800	52%
9	2.56	1	110	3600	72%
10	0.13	1	130	10	12%
12	1.27	1	130	300	56%
13	1	0	130	1800	100%

14	1	0	130	3600	100%
15	1.59	1	150	10	61%
16	1	0	150	300	100%
17	1	0	150	1800	100%
18	1	0	150	3600	100%
19	36.97	1	170	10	97%
20			170	300	auto-shutdown
21			170	1800	auto-shutdown
22	1	0	170	3600	100%
23			200	10	auto-shutdown
24	1	0	200	300	100%
25			200	1800	auto-shutdown
26	1	0	200	3600	100%

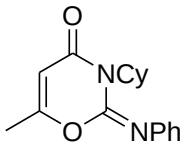


75b **75c**

5-Allyl-6-methyl dioxinone 75c and 6-butenyl dioxinone 75b. Trimethyl dioxinone **75a** (95 % containing 5 % acetone, 1.0 mL, 7.2 mmol) was added to THF under an atmosphere of argon. The solution was then cooled to -78 °C and then LDA (4.7 mL, of a 1.8M solution in heptanes/THF/ethylbenzene, 8.6 mmol) was added. After 1 h allyl bromide (0.74 mL, 8.6 mmol) was added. The reaction was stirred for 1.5 h and then quenched with NH_4Cl (1M, 40 mL). The

aqueous layer was separated and extracted with Et_2O (40 mL). The combined organic layers were washed with brine (40 mL) dried over $MgSO_4$ and concentrated *in vacuo*. After purification by column chromatography (15 % EtOAc/hexanes) 45 mg (3.4 % yield) of **75c** and 122 mg (9.3 % yield) of **75b** were obtained both as clear colorless oils whose spectroscopic data were consistent with previously reported values.[33, 35]

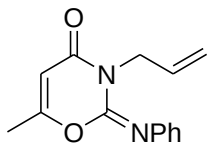
General Procedure for imino-oxazinones 66a, b, d, e, g, h: 1,2-Dichloroethane (0.5 mL) and acetone (0 or 5.0 μL, 0.068 mmol), were added to the dioxinone (0.2 mmol) and carbodiimide (0.3 mmol) in a microwave vial (0.5-2 mL). The reaction mixture was then subjected to microwave irradiation (150 or 200 °C) for 5 min unless otherwise indicated. The reaction mixture was then purified by flash column chromatography. The yields, temperature, time and amount of acetone are also given in Table *3-2*.



66a

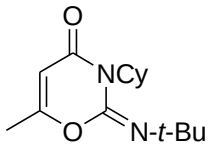
Imino-oxazinone 66a. The general procedure above was followed with 6-methyldioxinone **75a (**32 mg, 0.21 mmol) and *N*-cyclohexyl, *N'*-phenylcarbodiimide (51 mg, 0.26 mmol). The reaction was performed at 150 °C or 200 °C and then was directly purified by column chromatography (15 %

EtOAc / Hexanes) to furnish 39 mg (64 % yield; 200 °C), 43 mg (71 % yield; 150 °C) or 45 mg (75 % yield; 200 °C for 10 s) of product **66a** as a white solid whose spectroscopic data were consistent with previously reported values.[24]



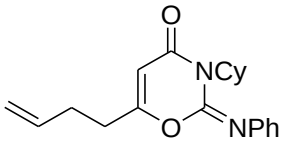
66d

Imino-oxazinone 66d. The general procedure above was followed with 6-methyl-dioxinone **75a (**33 mg, 0.22 mmol) and *N*-allyl, *N'*-phenylcarbodiimide (42 mg, 0.27 mmol). The reaction was performed at 150 °C or 200 °C and then was directly purified by column chromatography (10 % EtOAc / hexanes) to furnish 49 mg (93 % yield; 200 °C), 47 mg (89 % yield; 150 °C) of product **66d** as a clear, colorless oil: R_f = 0.20 (15 % EtOAc / hexanes); IR (cast film) 1690, 1648, 1594 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.29 (m, 2H), 7.09-7.06 (m, 1H), 7.02-7.00 (m, 2H), 5.99 (tdd, *J* = 5.8, 10.2, 17.2 Hz, 1H), 5.62 (br d, 1.0 Hz, 1H), 5.35 (tdd, *J* = 1.5, 1.5, 17.2 Hz, 1H), 5.24 (tdd, *J* = 1.3, 1.3, 10.2 Hz, 1H), 4.65 (ddd, 1.3, 1.3, 5.8 Hz, 2H), 2.03 (d, *J* = 1.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2, 160.2, 144.7, 141.6, 131.3, 128.7, 123.4, 122.7, 118.1, 100.5, 44.0, 18.8; MS (ESI) *m/z* calcd for $C_{14}H_{15}N_2O_2$ ($M+H^+$) 243.1128 found 243.1127.



66b

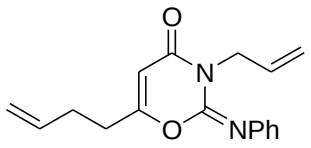
Imino-oxazinone 66b. The general procedure above was followed with 6-methyldioxinone **75a (**34 mg, 0.22 mmol) and *N*-*t*-butyl, *N'*-cyclohexylcarbodiimide (46 mg, 0.25 mmol). The reaction was performed at 150 °C or 200 °C and then was directly purified by column chromatography (7 % EtOAc / hexanes) to furnish 41 mg (70 % yield; 200 °C) or 48 mg (82 % yield; 150 °C) of product **66b** as a white solid whose spectroscopic data were consistent with previously reported values.[24]



66g

Imino-oxazinone 66g. The general procedure above was followed with 6-butenyldioxinone **75b (**40 mg, 0.22 mmol), acetone (5.0 μL, 0.068 mmol) and *N*-cyclohexyl, *N'*-phenylcarbodiimide (54 mg, 0.27 mmol). The reaction was performed at 150 °C or 200 °C and then was directly purified by column chromatography (5 % EtOAc / hexanes) to furnish 54 mg (75 % yield; 200 °C) or 36 mg (51 % yield; 150 °C) of product **66g** as a white/clear semi-solid: R_f = 0.57 (22 % EtOAc / hexanes). IR (neat film) 1687, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.28 (m, 2H), 7.08-7.04 (m, 1H), 7.00-6.96 (m, 2H), 5.70 (tdd, *J* = 6.4, 9.7, 17.6 Hz, 1H), 5.53 (br s, 1H), 5.05-5.00 (m, 2H), 4.82 (tt, *J* =

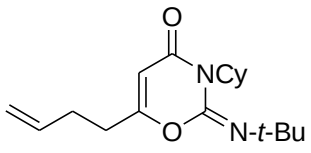
3.7, 12.2 Hz, 1H), 2.56 (dddd, *J* = 3.5, 12.5, 12.5, 12.5 Hz, 2H), 2.35-2.30 (m, 2H), 2.25-2.18 (m, 2H), 1.87-1.80 (m, 2H), 1.75-1.61 (m, 3H), 1.45-1.33 (m, 2H), 1.29-1.26 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 161.2, 145.1, 141.5, 135.6, 128.6, 123.2, 122.4, 116.4, 100.5, 55.3, 31.6, 29.4, 28.1, 26.3, 25.3; MS (ESI) *m/z* calcd for $C_{20}H_{25}N_2O_2$ ($M+H^+$) 325.1911 found 325.1910.



66h

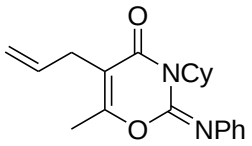
Imino-oxazinone 66h. The general procedure above was followed with 6-butenyl-dioxinone **75b (**43 mg, 0.24 mmol), acetone (5.0 µL, 0.068 mmol) and *N*-allyl, *N'*-phenylcarbodiimide (46 mg, 0.29 mmol). The reaction was performed at 150 °C or 200 °C and then was directly purified by column chromatography (5 % EtOAc / hexanes) to furnish 45 mg (68 % yield; 200 °C) or 43 mg (65 % yield; 150 °C) of product **66h** a clear, colorless oil: R_f = 0.33 (15 % EtOAc / hexanes) IR (neat film) 1685, 1642 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.27 (m, 2H), 7.10-7.04 (m, 1H), 7.01-6.97 (m, 2H), 5.99 (tdd, *J* = 5.8, 10.3, 17.2 Hz, 1H), 5.71 (tdd, *J* = 6.5, 9.8, 17.5 Hz, 1H), 5.61 (s, 1H), 5.34, (tdd, *J* = 1.4, 1.4, 17.2 Hz, 1H), 5.24 (tdd, *J* = 1.2, 1.2, 10.2 Hz, 1H), 5.07-5.00 (m, 2H) , 4.64 (ddd, *J* = 1.3, 1.3, 5.8 Hz, 2H), 2.41-2.35 (m, 2H), 2.29-2.21 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 160.2, 144.7, 141.6, 135.4, 131.2, 128.7, 123.4, 122.6, 118.1, 116.6, 100.0, 44.0, 31.8, 29.5; MS *m/z* calcd

for $C_{17}H_{19}N_2O_2$ ($M+H^+$) 283.1441 found 283.1439.



66i

Imino-oxazinone 66i. The general procedure above was followed with 6-butenyldioxinone **75b (**39 mg, 0.22 mmol), acetone (5.0 µL, 0.068 mmol) and *N*-*t*-butyl, *N'*-cyclohexylcarbodiimide (47 mg, 0.26 mmol). The reaction was performed at 150 °C or 200 °C and then was directly purified by column chromatography (5 % EtOAc / hexanes) to furnish 47 mg (71 % yield; 200 °C) or 39 mg (60 % yield; 150 °C) of product **66i** as a clear, colorless oil: R_f = 0.28 (7 % EtOAc / hexanes); IR (neat film) 1690, 1646 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 5.80 (tdd, *J* = 6.3, 10.6, 16.8 Hz, 1H), 5.42 (s, 1H), 5.12-5.05 (m, 2H), 4.65 (tt, *J* = 3.7, 12.0 Hz, 1H), 2.47 (dddd, *J* = 3.7, 12.5, 12.5, 12.5 Hz, 2H), 2.42-2.34 (m, 4H), 1.78 (app. d, *J* = 13.2 Hz, 2H), 1.64-1.52 (m, 3H), 1.37-1.26 (m, 2H), 1.29 (s, 9H), 1.15 (ttd, *J* = 3.6, 13.0, 13.0, 1H); ^{13}C NMR (60 °C, 126 MHz, $CDCl_3$) δ 164.6, 161.7, 138.0 (br), 135.9, 116.5, 100.2, 55.0, 53.1, 32.2, 30.5, 29.9, 28.3, 26.5, 25.7; MS *m/z* calcd for $C_{18}H_{29}N_2O_2$ ($M+H^+$) 305.2224 found 305.2225.



66e

Imino-oxazinone 66e. The general procedure above was followed with 5-allyl-6-methyldioxinone **75c (**42 mg, 0.23 mmol), acetone (5.0 μL, 0.068 mmol) and *N*-cyclohexyl, *N'*-phenylcarbodiimide (58 mg, 0.29 mmol). The reaction was performed at 200 °C and then was directly purified by column chromatography (2.5 % EtOAc / hexanes) to furnish 31 mg (42 % yield; 200 °C) of product **66e** white semi-solid: IR (neat film) 1685, 1649 cm^{-1}; ^{1}H NMR (500 MHz $CDCl_3$) δ 7.32-7.28 (m, 2H), 7.07-7.03 (m, 1H), 7.02-6.99 (m, 2H), 5.81 (tdd, *J* = 6.2, 10.1, 17.1 Hz, 1H), 5.07 (tdd, *J* = 1.6, 1.6, 12.8 Hz, 1H), 5.03 (tdd, *J* = 1.6, 1.6, 5.8 Hz, 1H), 4.85 (tt, *J* = 3.9, 12.1 Hz, 1H), 3.06 (d, *J* = 6.2 Hz, 2H), 2.57 (dddd, *J* = 3.4, 12.5, 12.5, 12.5 Hz, 2H), 1.98 (s, 3H), 1.83 (br d, *J* = 13.2 Hz, 2H), 1.74-1.61 (m, 3H), 1.45-1.32 (m, 2H), 1.22 (tdt, *J* = 3.4, 12.9, 13.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.2, 161.6, 158.9, 145.3, 134.5, 128.7, 123.0, 122.6, 115.5, 109.1, 55.7, 28.8, 28.1, 26.4, 25.4, 16.2; MS (ESI) *m/z* calcd for $C_{20}H_{25}N_2O_2$ ($M+H^+$) 325.1911 found 325.1913.

3.5 References

1. IMS Health Midas, 2009. http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Static

File/Top_Line_Data/Top%2015%20Global%20Products_2009.pdf (Accessed May 22, 2011.)

2. Andrejchikov, Y. S.; Nekrasov, D. D.; Semyakina, N. V.; Zalesov, V. S. Soviet Union Patent SU 1 112 747 A1, 1996.
3. Andrejchikov, Y. S.; Nekrasov, D. D.; Bergtejl, B. A.; Zalesov, V. S. Soviet Union Patent SU 1 088 317 A1, 1996.
4. Zhang, W.; McCann, S. F. International Patent WO 2010/005692 A2, 2010.
5. Theodorescu, D.; Lee, J. K. International Patent WO 2008/027912 A3, 2008.
6. Itai, A.; Muto, S.; Tokuyama, R.; Fukasawa, H.; Yanase, T. United States Patent US 2010/0113448 A1, 2010.
7. Deck, J. F.; Dains, F. B. *J. Am. Chem. Soc.* **1933,** *55*, 4986-4991.
8. Bereznak, J. F.; Marshall, E. A. International Patent WO 00/51992, 2000.
9. Blasco, J. T. I.; Grote, T.; Scherer, M.; Stieri, R.; Strathmann, S.; Schofl, U.; Rheinheimer, J. United States Patent US 2007/0197557 A1, 2007.
10. Rheinheimer, J.; Gypser, A.; Rose, I.; Grote, T.; Schafer, P.; Schieweck, F.; Ammermann, E.; Speakman, J.-B.; Strathmann, S.; Lorenz, G. United States Patent US 2004/0181061 A1, 2005.
11. Hong, W.; Selby, T. P. United States Patent US 2010/0105670 A1, 2008.
12. Lacey, R. N. United Kingdom Patent GB 738,581, 1955.
13. May, E. L. *J. Med. Chem.* **1967,** *10*, 505-506.
14. Joshi, B. S.; Srinivasan, R.; Talavdekar, R. V.; Venkataraman, K.

Tetrahedron **1960,** *11*, 133-139.

15. Trifonov, L. S.; Orahovats, A. S. *Helv. Chim. Acta* **1986,** *69*, 1585-1587.
16. March, L. C.; Romanchi.Wa; Bajwa, G. S.; Joullie, M. M. *J. Med. Chem.* **1973,** *16*, 337-342.
17. Lacey, R. N. *J. Chem. Soc.* **1954**, 845-849.
18. Larksarp, C.; Alper, H. *J. Org. Chem.* **1999,** *64*, 9194-9200.
19. Lisovenko, N. Y.; Maslivets, A. N. *Chem. Heterocycl. Compd.* **2004,** *40*, 247-248.
20. Lisovenko, N. Y.; Maslivets, A. N.; Aliev, Z. G. *Russ. J. Org. Chem.* **2007,** *43*, 117-120.
21. Vostrov, E. S.; Leont'eva, E. V.; Tarasova, O. P.; Maslivets, A. N. *Russ. J. Org. Chem.* **2004,** *40*, 1058-1061.
22. Kappe, C. O.; Farber, G.; Wentrup, C.; Kollenz, G. *J. Org. Chem.* **1992,** *57*, 7078-7083.
23. Sakaki, J. I.; Sugita, Y.; Sato, M.; Kaneko, C. *Tetrahedron* **1991,** *47*, 6197-6214.
24. Lacey, R. N.; Ward, W. R. *J. Chem. Soc.* **1958**, 2134-2141.
25. Wolff, L. *Liebigs Ann. Chem.* **1902,** *325*, 129-195.
26. Capuano, L.; Kirn, H. R.; Zander, R. *Chem. Ber. Recl.* **1976,** *109*, 2456-2461.
27. Sato, M.; Ogasawara, H.; Kato, T. *Chem. Pharm. Bull.* **1984,** *32*, 2602-2608.
28. Shelkov, R.; Nahmany, M.; Melman, A. *J. Org. Chem.* **2002,** *67*, 8975-

8982.

29. Palomo, C.; Mestres, R. *Synthesis* **1981**, 373-374.

30. Alder, A. United States Patent 4,990,232, 1991.

31. Sheehan, J.; Cruickshank, P.; Boshart, G. *J. Org. Chem.* **1961,** *26*, 2525-2528.

32. Bestmann, H. J.; Lienert, J.; Mott, L. *Justus Liebigs Ann. Chem.* **1968,** *718*, 24-32.

33. Cramer, N.; Laschat, S.; Baro, A.; Schwalbe, H.; Richter, C. *Angew. Chem., Int. Ed.* **2005,** *44*, 820-822.

34. Patai, S., *The Chemistry of Alkenes*. Interscience: New York, 1964.

35. Vu, V. A.; Berillon, L.; Knochel, P. *Tetrahedron Lett.* **2001,** *42*, 6847-6850.

36. Moore, H. W.; Chow, K.; Nguyen, N. V. *J. Org. Chem.* **1987,** *52*, 2530-2537.

37. Wong, M. W.; Wentrup, C. *J. Org. Chem.* **1994,** *59*, 5279-5285.

38. Tidwell, T. T., *Ketenes*. Wiley-Interscience: New York, 1995.

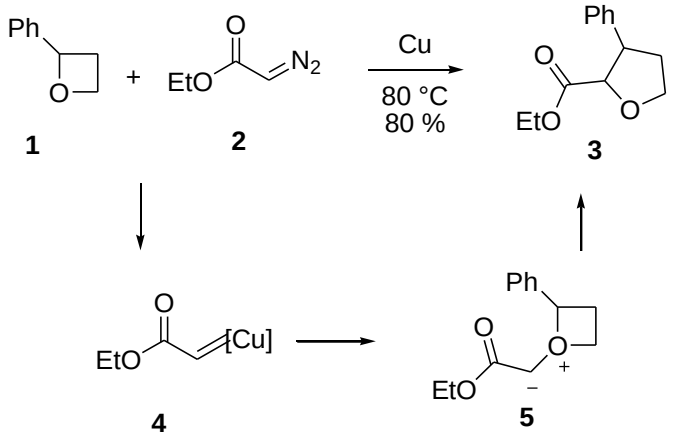
39. Alder, A. European Patent EP307361A2, 1989.

Chapter 4

Preliminary Studies on Cyclopropyl Substituted Migrating Groups in Oxonium Ylide Rearrangements

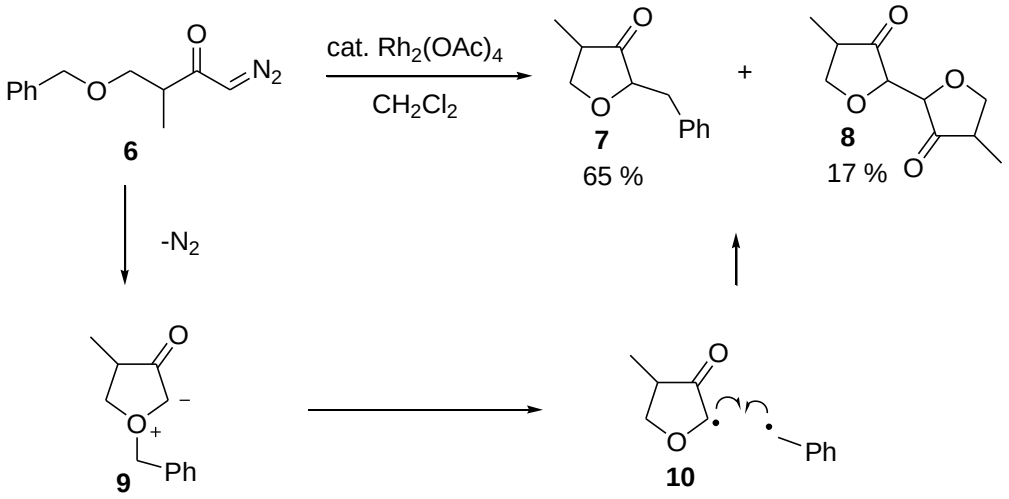
4.1 Introduction: Stevens [1 , 2] Rearrangement of an Oxonium Ylide

In 1966 Nozaki and coworkers reported the formation of tetrahydrofuran **3** from the intermolecular reaction of ethyl diazoacetate **2** and oxetane **1** (Scheme 4-1).[1] The authors found that using copper to generate carbene **4,** rather than conventional methods such as heat or photolysis, was more effective, producing cleaner reactions with higher yields. The oxygen in **1** was believed to react with the generated metallocarbene **4** to produce the oxonium ylide **5**, which would then rearrange by [1,2]-migration of the benzylic carbon to form the tetrahydrofuran **3**.



Scheme 4-1: Mechanism for a Stevens rearrangement of an oxonium ylide.

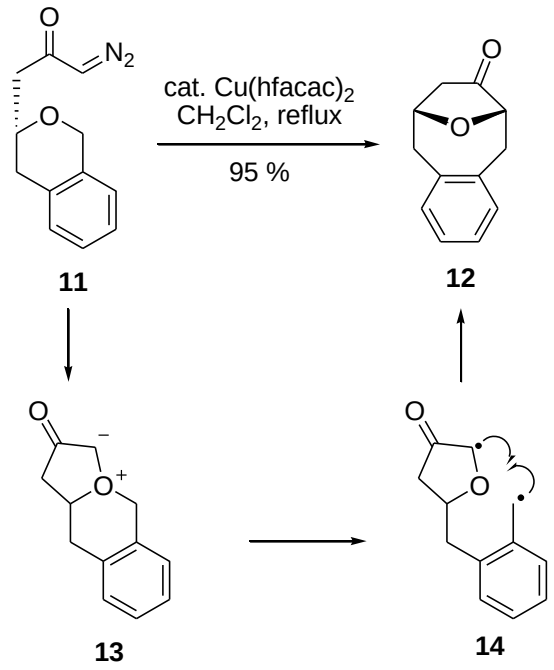
In 1992, West reported an intramolecular variant of the aforementioned reaction that gave additional insight into the mechanism.[2] They found that compound **6** rearranged in the presence of rhodium catalyst to generate the tetrahydrofuran **7** in 65 % yield and the dimer product **8** in 17 % yield (Scheme 4-2). Similar to Nozaki, they proposed oxonium ylide formation, which in this case involves intramolecular addition of the metallocarbene to the ether oxygen, to form **9.** They then proposed C-C bond homolysis to generate benzyl radical and the radical **10.** The radical **10** could then recombine with the benzyl radical to form **7,** or dimerize to form product **8.**



Scheme 4-2: Stevens rearrangement of a cyclic oxonium ylide.

In 1994 West reported an extension of this methodology that can generate an eight-membered ring in a high yield.[3] Diazoketone **11** was subjected to copper catalyst and furnished the ring expansion product **12** via a [1,2]-shift of

the presumed oxonium ylide intermediate **13** (Scheme 4-3)**.** This method was highly successful with a yield of 95 %.



Scheme 4-3: Stevens rearrangement of an oxonium ylide forming an eight-membered ring.

4.2 Background

In Chapter 2, the synthesis of advanced intermediate **16** was reported, towards the total synthesis of dactylol **17** (Figure 4-1)**.** Ultimately the geminal dimethyl group in dactylol **17** was to arise from a cyclopropanation /hydrogenolysis sequence on the exocyclic methylene group in **16.** As an alternative we considered the cyclopropane **18** and its rearrangement into **19.** If

successful, this sequence could be a viable alternative route to **17** from the one used, and would also allow us to explore some interesting mechanistic questions.

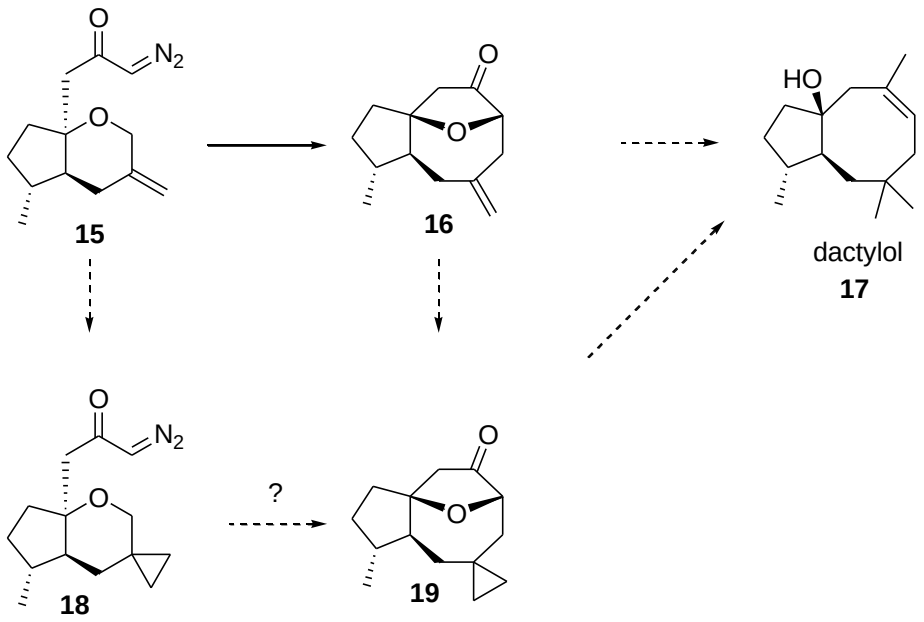


Figure 4-1: Alternative route towards dactylol utilizing cylopropane **18**.

While this may look feasible, mechanistic considerations need to be taken into account. After diazodecomposition, intramolecular attack of oxygen would generate oxonium ylide **20** (Figure 4-2)**.** Homolytic cleavage of the C-O bond would generate diradical **21,** which after recombination would form the desired product **19.** This sequence entails certain assumptions. First, there are two possible C-O bonds in **20** that could undergo homolysis: the indicated ring opening to **21**, and an alternative cleavage of the ring-fusing C-O bond to the bridgehead carbon. The latter pathway is unlikely as it has not been seen in

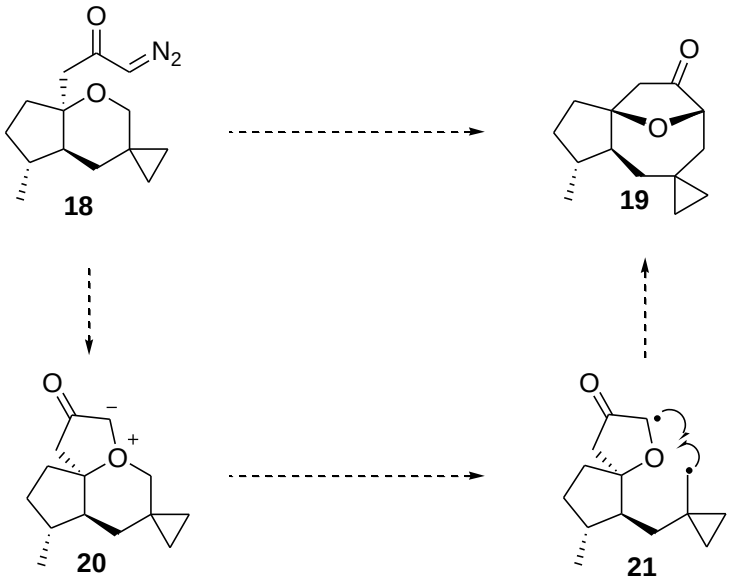


Figure 4-2: Mechanism for the hypothetical rearrangement of **18** to **19**.

related systems. However, the indicated cyclopropylcarbinylradical intermediate merits further discussion. Simple cyclopropylcarbinyl radical **22** has been studied and the authors found that rapid scission of the cyclopropane occurred to form butenyl radical **23** (Figure 4-3).[4] If an analogous ring opening occurred in the case of **21**, recombination of the tetrahydrofuranone radical with the homoallyl radical would give either-bridged cyclononanone **25.** While this rearrangement would be detrimental to the synthesis of dactylol, the resulting reaction sequence is definitely an interesting outcome. This result would provide additional evidence for the proposed radical pair mechanism of the Stevens [1,2]-shift. Although there has been convincing data in support of a stepwise homolytic pathway,[5] it remains

controversial. Also, if this reaction proceeded in high yield, it would provide access to new classes of medium-sized carbocyclic targets.

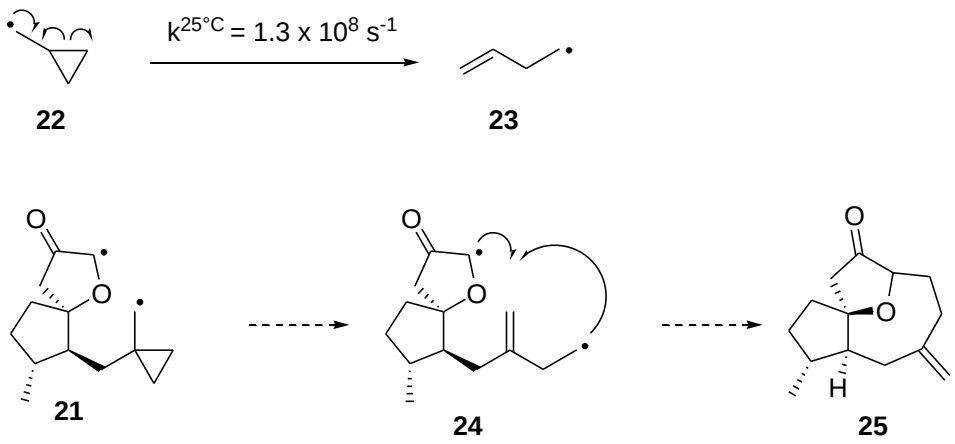


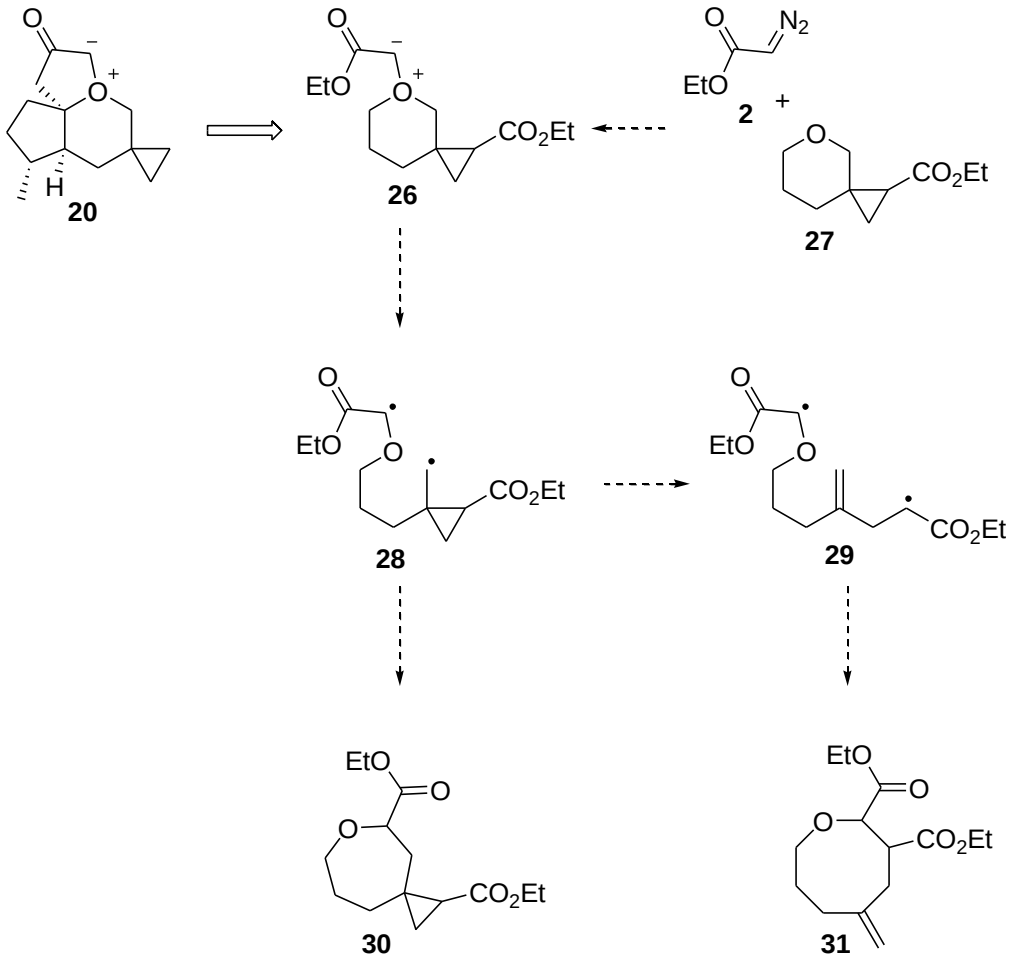
Figure 4-3: Cyclopropylcarbinyl-homoallyl rearrangement and its possible impact on the fate of **21**.

4.3 Results and Discussion

To explore this new reactivity, we chose to focus on simple model substrates rather than sacrificing precious intermediates in the dactylol sequence. Ideally, these would include examples of the favourable intramolecular ylide formation such as that mentioned above but also the analogous intermolecular ylide formation.

4.3.1 Intermolecular Cyclopropylcarbinyl Ylide Formation

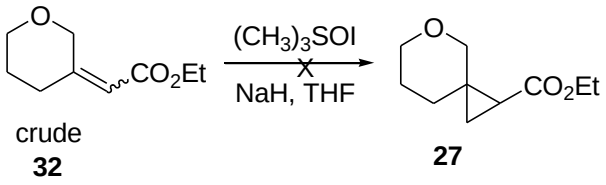
When analysing **20** we considered a simpler intermediate such as **26** (Scheme 4-4). This ylide **26** could form from ethyl diazoacetate and the cyclopropane **27.** The homolytic cleavage of the ylide would generate **28.** There are two pathways that we would be interested in. One pathway would afford the



Scheme 4-4: Intermolecular ylide formation of **26** to generate medium sized rings **30** and **31.**

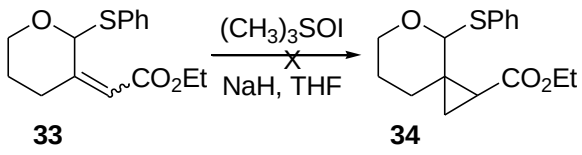
simple radical recombination product **30** while the other would involve the opening of the radical to form butenyl radical **29**, followed by recombination to generate **31**. The generation of **30** or **31** is an interesting process as they both form medium sized rings.

The known cyclic ether **32** was synthesized by the reported procedure,[6] and unfortunately it was obtained impure (Scheme 4-5). Product **32** was nonetheless subjected to cyclopropanation conditions; however, no cyclopropane was isolated, and only **32** was recovered**.**



Scheme 4-5: Attempted cyclopropanation of **32**.

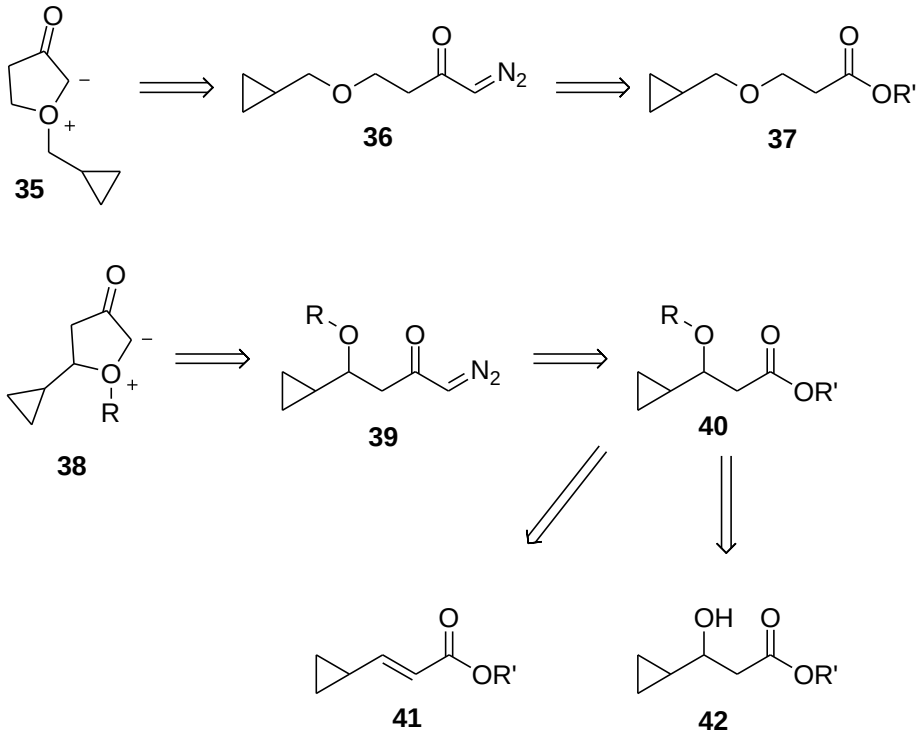
Mixed thioacetal **33** was obtained in the same manner as **32** (Scheme 4-6).[6] Unfortunately, the cyclopropanation of this compound was also unsuccessful, with no generated cyclopropane being isolated.



Scheme 4-6: Attempted cyclopropanation of mixed thioacetal **26.**

4.3.2 Approaches to Cyclic Oxonium Ylides with Endocyclic Cyclopropylcarbinyl Carbons

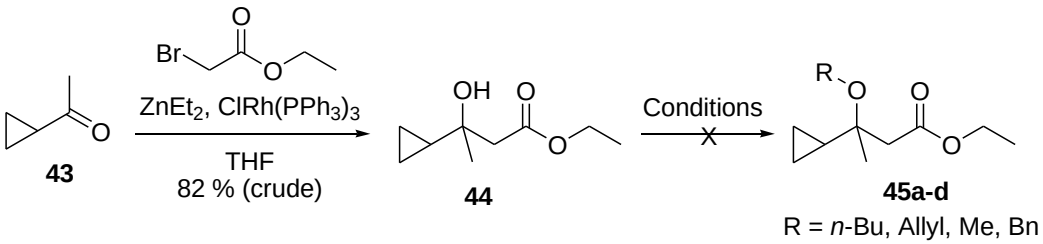
Two plans for cyclic ylides bearing cyclopropylcarbinyl groups were devised in which one route would allow for more variation in the substrates. We imagined two different ylides: one with the cyclopropylcarbinyl group attached in an exocyclic fashion to the oxonium oxygen, as in **35**, and another cyclopropylcarbinyl carbon held within the ring of the cyclic oxonium ylide, as in **38** (Scheme 4-7)**.** Compound **35** could be formed from linear diazoketone **36,** which could come from ester **37.** The branched ylide **38** could be generated



Scheme 4-7: Retrosyntheses of ylides **35** and **38.**

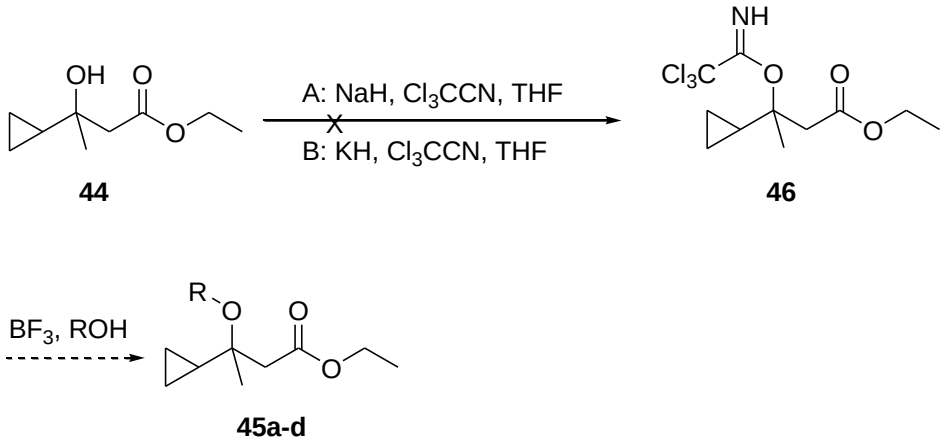
from the diazoketone **39,** which could be formed from ester **40.** We thought that the R group in **40** could be varied by a conjugate addition of several different alcohols into the conjugated ester **41.** Alternatively, alkylation of the alcohol in **42** could also give various examples of **40** for experimentation. Given the greater flexibility possible in substrates such as **39**, we initially focused on the preparation of these compounds.

We began the synthesis of the branched cyclopropane by synthesizing known **44** from a rhodium-catalyzed Reformatsky addition into ketone **43** (Scheme 4-8).[7] An alkylation of the alcohol was attempted using many different conditions; however, under all the conditions attempted little to no product was obtained and mostly starting material was observed.



Scheme 4-8: Synthesis of **44** and attempted alcohol alkylation.

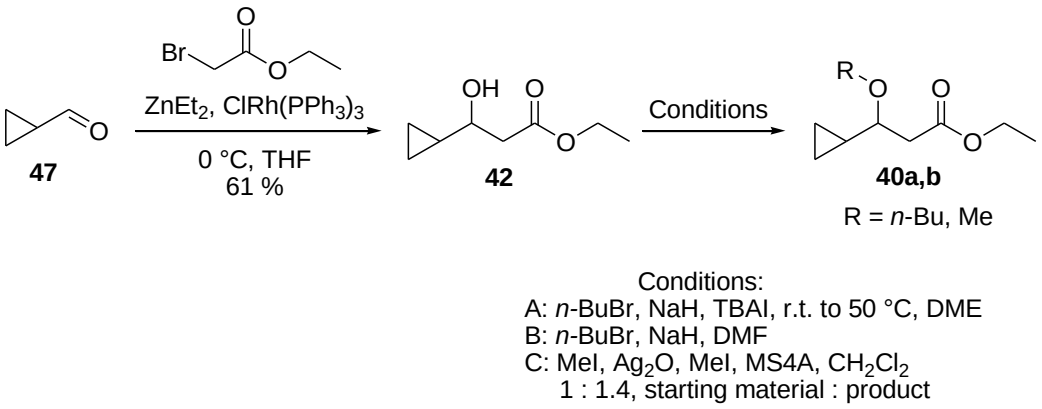
The steric hindrance of the alcohol in **44** may have been the cause for the lack of reactivity. To circumvent that problem, a method using trichloroacetimidate was attempted that was advertized to effectively substitute tertiary alcohols[8] (Scheme 4-9); this method has also been used to activate a cyclopropylcarbinol.[9] However, under the conditions acetimidate **46** was not isolated and only recovered starting material or a complex mixture was obtained.



Scheme 4-9: Attempted alkylation of **44** using trichloroacetimidate.

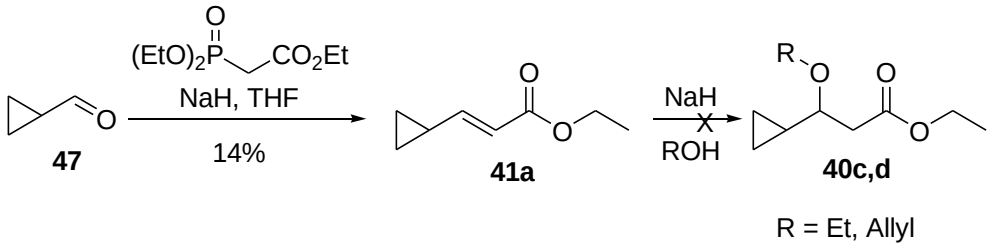
On the assumption that an alkylation of a secondary alcohol might proceed more successfully, we next set out to make a new substrate. Starting with cyclopropyl carboxyaldehyde **47,** the rhodium-catalyzed Reformatsky reaction was performed (Scheme 4-10). The desired adduct **42** was obtained in 61 % yield.[10] Next, conditions were applied for alkylation of the secondary alcohol. Alkylation with butyl bromide was unsuccessful under all the conditions attempted. Methylation was performed with silver oxide in dichloromethane; this reaction was only marginally successful, as it produced

only a 1:1.4 ratio of starting material to product. This method was proving to not be general, so other methods were probed.



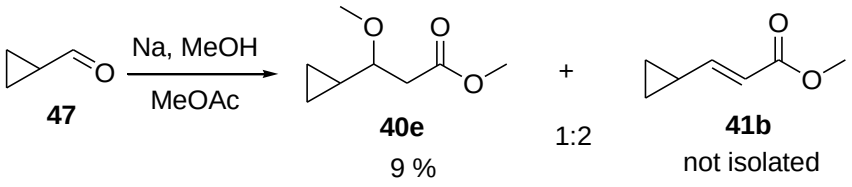
Scheme 4-10: Synthesis of alcohol **42** and attempted alkylation.

Because of the poor results trying to alkylate the alcohol, a different approach was taken. Starting again from aldehyde **47**, a Horner-Wadsworth-Emmons reaction was performed and the desired conjugated ester **41a** was obtained in a low 14 % yield (Scheme 4-11).[11] With more care this reaction could have proceeded in a higher yield; however, the material obtained was sufficient for further experimentation. The ester was subjected to sodium hydride in either allyl alcohol or ethanol, but unfortunately little of the conjugate adduct was seen.



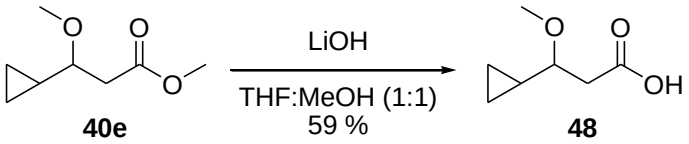
Scheme 4-11: Horner-Wadsworth-Emmons reaction to synthesize **41a** and the attempted conjugate addition of alkoxide.

The aforementioned methods would have provided a divergent method that would provide several substrates; however, due to the problems associated with their syntheses a less convergent approach was adopted. Cyclopropane carboxaldehyde **47** was combined with, methyl acetate, methanol and sodium (Scheme 4-12) and after stirring overnight the desired product **40e** was obtained in a low yield of 9 %.[12] The conjugated ester **41b** was also observed, but was not needed, so it was discarded. Although the yield of **40e** was poor, there was



Scheme 4-12: Synthesis of the cyclopropane **40e.**

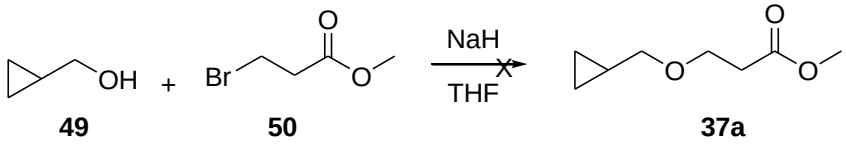
sufficient material to proceed. Next, ester **40e** was saponified with lithium hydroxide and after purification the carboxylic acid **48** was obtained in 59 % yield (Scheme 4-13).



Scheme 4-13: Saponification of ester **40e**.

4.3.3 Linear Ether Synthesis

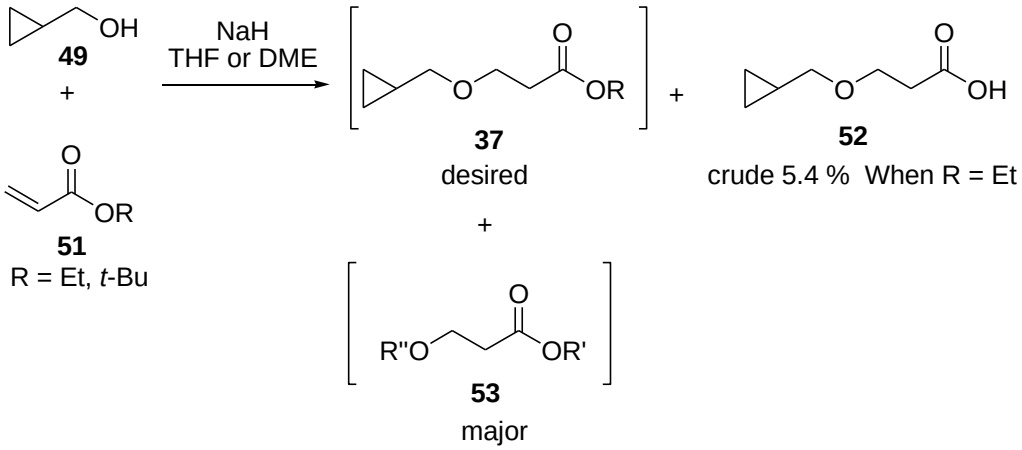
The unbranched substrate (**36** in Scheme 4-7) was also attractive, although the required linear route would not permit divergent synthesis of multiple substrates. Nonetheless, such a substrate would be desirable to test the overall notion of cyclopropylcarbinyl migration. The first attempted method was a simple alkylation of cyclopropane methanol **49** with alkyl halide **50**; this method appeared to generate only a small amount of product and so it was abandoned for other potentially more fruitful methods (Scheme 4-14)**.**



Scheme 4-14: The attempted alkylation of alcohol **49.**

As an alternative, acrylates were used as Michael acceptors with cyclopropanemethanol **49** (Scheme 4-15). Ethyl or *t*-butyl acrylate **51** was combined with cyclopropane methanol **49** and sodium hydride. Unfortunately, the reaction produced a complex mixture. It appeared that transesterification in

addition to Michael addition was occurring producing a combination of esters and/or ethers. Material **52** was also formed and fortunately it could be isolated. The yield was low, but this was the necessary intermediate for diazoketone formation, and so it was carried forward.

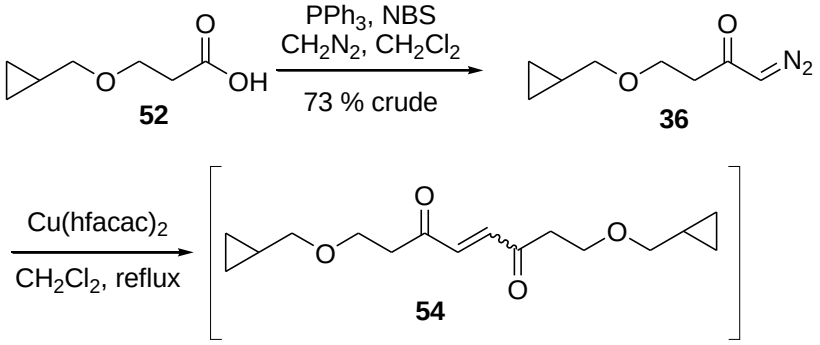


Scheme 4-15: The conjugate addition of alcohol **49** to *t*-butyl and ethyl acrylate.

4.3.4 Syntheses and Reaction of Cyclopropylcarbinyl Diazoketones

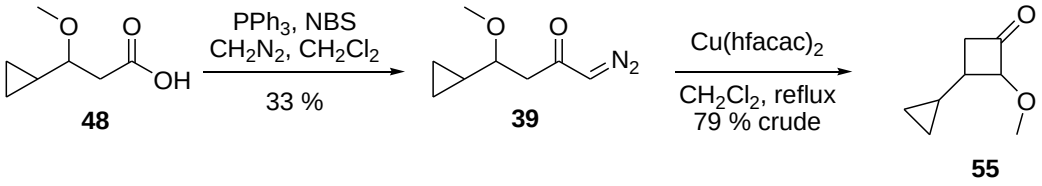
Next, acid **52** was converted into the diazoketone **36** (Scheme 4-16). The carboxylic acid was activated with triphenylphosphine and *N*-bromosuccinimide, and, after addition of diazomethane, the diazoketone **36** was obtained in a crude yield of 73 %; after column chromatography the compound was still impure but was carried forward nonetheless. Under the standard reaction conditions (catalytic $Cu(hfacac)_2$, CH_2Cl_2 at reflux) the diazoketone was consumed. The

crude NMR spectrum indicated that the cyclopropane was intact and suggested that dimer **54** was the major product formed.



Scheme 4-16: Synthesis of diazoketone **36** and subsequent rearrangement conditions.

In the same manner as above, the branched carboxylic acid **48** was converted to the diazoketone **39** and was obtained in a crude unoptimized yield of 33 %. Compound **39** was then subjected to the aforementioned rearrangement conditions and interestingly cyclobutanone **55** was obtained in a 79 % crude yield as a 5:1 mixture of diastereomers.



Scheme 4-17: Synthesis of diazoketone **39**and its conversion into cyclobutanone **55.**

The formation of cyclobutanone has interesting implications and warrants discussion of the mechanism. After diazodecomposition, generating metallocarbene **56**, attack of the pendant oxygen produces the intermediate **57**. The metal may dissociate to form ylide **57**. The heterolytic cleavage of this product would generate **58**, which, after recombination would for the product. Alternatively the formation of diradical **59** would also form the product after recombination. Interestingly, the opening of the cyclopropane to generate **60** was not observed. If the diradical is formed then the radical recombination would have to be faster than the formation of the ring opened **60**. Alternatively, this cyclobutanone product could be suggestive of either the heterolytic cleavage product **58**, as the reactive intermediate, or a metal associated product that precludes the formation of a cyclopropylcarbinyl radical.

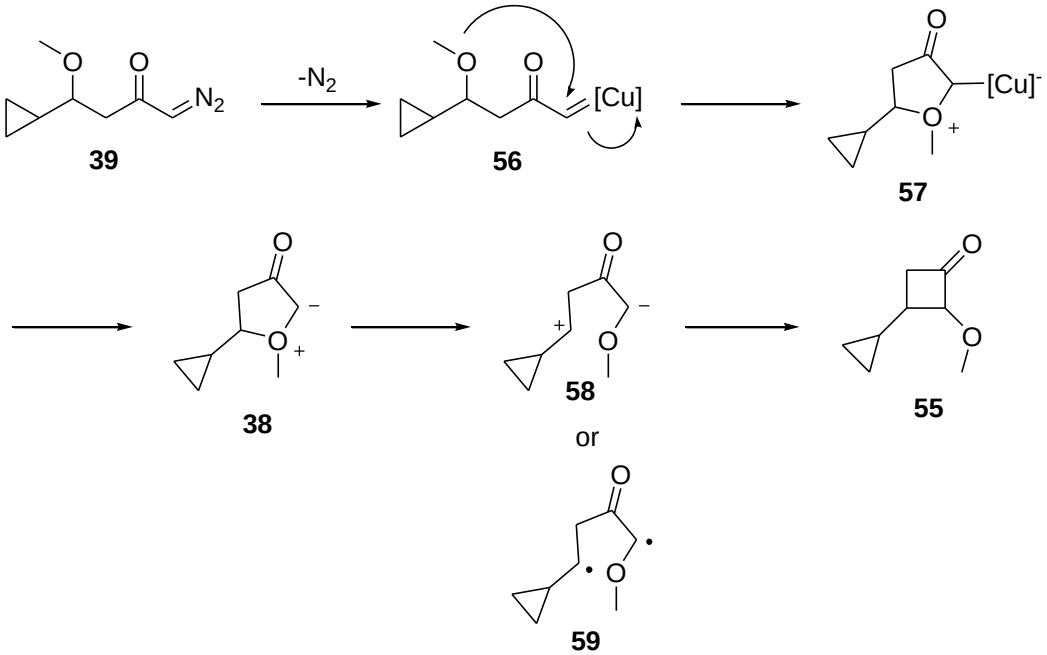
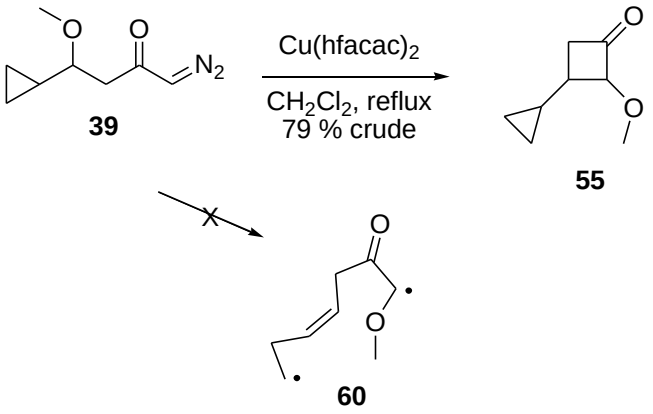


Figure 4-4: Proposed mechanism for generation of cyclobutanone **55**.

4.4 Conclusions and Future Work

The diazoketone **39** has been made and interestingly the generation of products derived from the cyclopropane opened **60** have not been observed. This observation suggests that either a diradical is not formed or the generation of the cyclobutanone is faster than the cyclopropane opening to generate **60**. The reaction of diazoketone **39** with different catalysts may produce different products if the formation of the diradical could be facilitated.



Scheme 4-18: Rearrangement to generate cyclobutanone **55.**

The formation of a mixed thioacetal, such as **61**, would be an interesting substrate to study. If homolytic cleavage takes place to generate **62** and **63**, the cyclopropylcarbinyl radical **63** should be more stable and less reactive than the aforementioned intermediate **59**. Recombination would be slower and it may be possible to observe products derived from the ring-opened **65**.

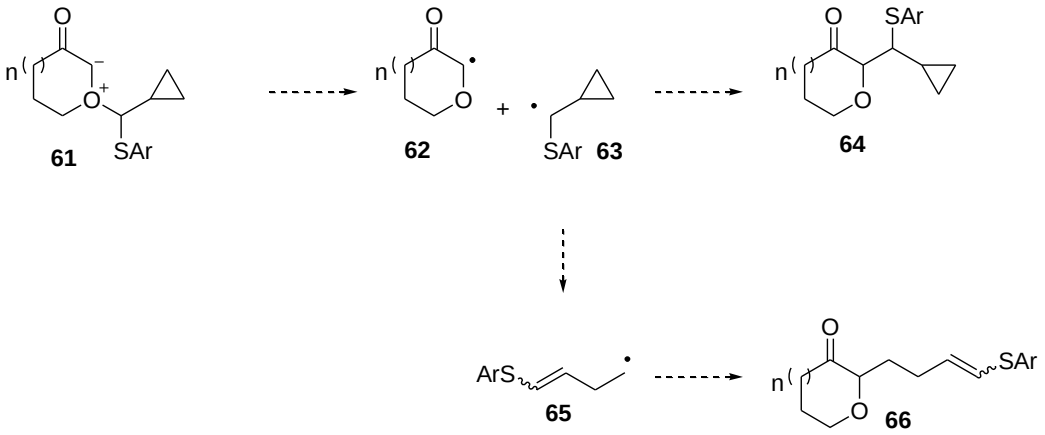


Figure 4-5: Thioether stabilized radical and possible products.

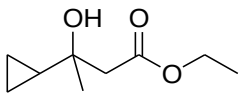
4.5 Experimental

4.5.1 General Information

The reactions were carried out in oven (120 °C) or flame-dried glassware under a positive argon atmosphere unless otherwise stated. The transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannulae. Solvents were distilled before use: dichloromethane and dichloroethane from calcium hydride, toluene from sodium metal. Solutions that were "dried over $MgSO_4$", were vacuum filtered through a plug of anhydrous $MgSO_4$. Thin layer chromatography was performed on glass plates precoated with 0.25 mm silica gel with fluorescent indicator UV_{254} (Rose Scientific). Flash chromatography columns were packed with 230-400 mesh silica gel (Merck).

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) and referenced to the deuterochloroform peak at 7.26 ppm. Chemical shifts are reported to 3 decimal places where distinctions could be made but they are reproducible only to 2 decimal places. Coupling constants (*J*) are reported in Hz to 1 decimal place. The multiplicity of signals observed in the ^{1}H NMR are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets, etc. The carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 126 MHz or 101 MHz and are reported (ppm) relative to the center line of a triplet at 77.23 ppm for deuterochloroform. Chemical shifts are reported to 2 decimal places where distinctions could be made but they are reproducible only to 1 decimal place. Infrared (IR) spectra were measured with a Nicolet Magna 750 FT-IR spectrophotometer and Nic-Plan FTIR Microscope. Mass spectra were determined on a Kratos Analytical MS-50 (EI) or Applied Biosystems Mariner Biospectrometry Workstation (ESI).

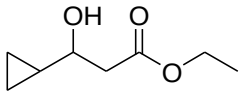
4.5.2 Procedures and Characterizations



44

Ethyl 3-cyclopropyl-3-hydroxybutanoate 44. Tetrahydrofuran (20 mL) was

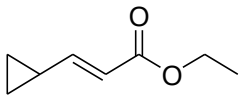
added to cyclpropyl methyl ketone (1.0 mL, 10 mmol) under argon. Ethyl bromoacetate (4.5 mL, 40 mmol) was added followed by $ClRh(PPh)_3$ (270 mg, 0.29 mmol). The reaction was fitted with a long Vigreux column and then $ZnEt_2$ (60 mL, 1M in hexanes, 60 mmol) was added portion-wise via syringe over 10 min. The solution was occasionally cooled with an ice bath when the reaction became vigorous. After 2.5 h the reaction was cooled to 0 °C, and then H_2O (30 mL) and HCl (5 mL, 1M) were added. The mixture was then filtered through cotton and the cotton was rinsed with Et_2O (5 mL). The organic layer was separated, washed with $NaHCO_3$ (30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (7 % EtOAc/hexanes) afforded 1.4 g (82 %) of a clear colorless oil. The spectroscopic data were consistent with previously reported values.[7]



42

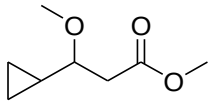
Ethyl 3-cyclopropyl-3-hydroxypropanoate 42. THF (6 mL) was added to cyclopropanecarboxaldehyde (200 μL, 2.7 mmol) under argon. Ethyl bromoacetate (1.2 mL, 11 mmol) was added followed by $ClRh(PPh)_3$ (250 mg, 0.27 mmol). The solution was cooled to 0 °C, and then diethyl zinc (16 mL, 1M in hexanes, 16 mmol) was added. The ice bath was removed after 10 min, and the reaction was stirred at rt for 1h. The reaction was cooled to 0 °C, and then H_2O (5 mL) and HCl (5 mL, 1M) were added. The mixture was then filtered through cotton and rinsed with Et_2O. The organic layer was separated, washed

with $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated. Purification by column chromatography (20 % EtOAc/hexanes) afforded 260 mg (61 %) of **42** as a colorless oil. The spectroscopic data were consistent with previously reported values.[10]



41a

(E)-Ethyl 3-cyclopropylacrylate 41a. NaH (120 mg, 60 % in mineral oil, 3 mmol) was added to THF (4 mL) under an argon atmosphere. Triethyl phosphonoacetate (690 µL, 3.5 mmol) was added drop-wise. After 2 h cyclopropanecarboxaldehyde (200 µL, 2.7 mmol) was added. After 2 h the mixture was purified by column chromatography (7 % EtOAc/hexanes) and 52 mg (14 % yield) of product **41a** was obtained as a clear colourless oil. The spectroscopic data were consistent with previously reported values.[11]

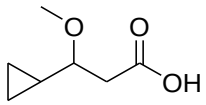


40e

Methyl 3-cyclopropyl-3-methoxypropanoate 40e.

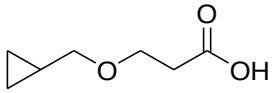
Cyclopropanecarboxaldehyde (100 µL, 1.3 mmol), MeOAc (0.5 mL) and MeOH (6.0 µL, 0.15 mmol) were combined under an argon atmosphere. Na (25 mg, 1.1 mmol) was then added. After 24 h MeOH (2 mL) was added. The reaction was stirred for 30 min and then concentrated *in vacuo*. Diethyl ether (2 mL), H_2O (2 mL) and 1M HCl (2 mL) were then added. After separation of the layers the organic layer was washed with brine (2 mL), dried over $MgSO_4$ and concentrated

in vacuo. ^{1}H NMR indicated a 2:1 ratio of **41b**:**40e**. The mixture was purified by column chromatography (10 % EtOAc/ hexanes) and 18 mg (9.0 %) of **40e** was obtained as a clear, colourless oil. The spectroscopic data were consistent with previously reported values.[12]



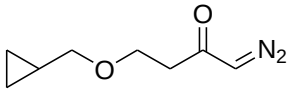
48

3-Cyclopropyl-3-methoxypropanoic acid 48. A lithium hydroxide solution (2M, 10 mL) and THF:MeOH (1:1, 10 mL) were added to **40e**. After 15 h the mixture was washed with Et_2O (10 mL). After separation of the layers, the organic layer was extracted with NaOH (1M, 10 mL). The separated aqueous layers were combined, acidified with 1N HCl to pH = 1, and extracted with Et_2O (3 x 60 mL). The combined organic layers were washed with brine (30 mL) dried over $MgSO_4$ and concentrated *in vacuo*. The mixture was purified by column chromatography (20 % EtOAc/hexanes, with 1 % AcOH) and 430 mg of product **48** (59 %) was obtained: R_f = 0.27 (20 % EtOAc, 1 % AcOH /hexanes) IR (cast film) 3600-2400, 1712 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.46 (s, 3H), 2.99-2.95 (m, 1H), 2.70-2.62 (m, 2H), 0.90-0.85 (m, 1H), 0.73-0.67 (m, 2H), 0.53-0.45 (m, 1H), 0.15-0.10 (m, 1H), (carboxylic acid proton not detected); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 81.8, 56.0, 40.5, 14.2, 5.3, 0.6; MS (ESI) m/z calcd for $C_7H_{11}O_3$ (M-H+) 143.0714 found 143.0712.



52

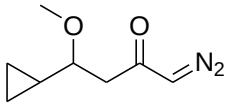
3-(Cyclopropylmethoxy)propanoic acid 52. Sodium hydride (60 % in mineral oil, 147 mg, 3.67 mmol) was added to THF (10 mL) under an argon atmosphere. Cyclopropanemethanol (315 µL, 3.89 mmol) was then added. After 23 min ethyl acrylate (200 µL, 1.83 mmol) was added. The reaction was heated to 40 °C overnight and then Et_2O (15 mL) and H_2O (10 mL) were added. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. ^1H NMR indicated cyclopropane methanol as the major component. The aqueous layer was acidified with 1M HCl (until pH =1) and then extracted with Et_2O (15 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo.* After purification by column chromatography (30 % EtOAc/hexanes) ^1H NMR indicated that compound **52** was obtained in crude 5.4 % yield (14 mg): IR (cast film) 3700-2400, 1715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.74 (t, *J* = 6.4 Hz, 2H), 3.32 (d, *J* = 7.0 Hz, 2H), 2.65 (t, *J* = 6.4 Hz, 2H), 1.10-1.02 (m, 1H), 0.56-0.52 (m, 2H), 0.22-0.19 (m, 2H), (carboxylic acid proton not detected); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.1, 75.9, 65.4, 34.9, 10.4, 3.0; MS (ESI) m/z calcd for $C_7H_{12}O_3Na$ ($M+Na^+$) 167.0679 found 167.0678.



36

Diazoketone 36. Dichloromethane (2 mL) was added to compound **52** (14 mg, 0.099 mmol) under an argon atmosphere and the reaction was cooled to 0 °C. Triphenylphosphine (37 mg, 0.14 mmol) and NBS (24 mg, 0.14 mmol) were

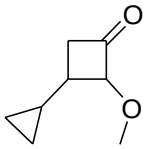
added. After 20 minutes the reaction was cooled to -78 °C and then was added via cannula to freshly prepared CH_2N_2 in Et_2O (5.8 mmol in 20 mL Et_2O). The reaction was gradually warmed to rt. After 22.5 h the reaction was concentrated *in vacuo* and then H_2O (10 mL) was added. The mixture was extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with $NaHCO_3$ (10 mL) and brine (10 mL), and then dried over $MgSO_4$ and concentrated *in vacuo*. After purification by column chromatography (30 % EtOAc/ hexanes) 12.8 mg (73 %) of **36** as an impure clear yellow oil was obtained: 0.32 R_f (30 % EtOAc/hexanes); IR (cast film) 2106, 1640 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.38 (br s, 1H), 3.72 (t, *J* = 6.2 Hz, 2H), 3.28 (d, *J* = 6.9 Hz, 2H), 2.58 (br s, 2H), 1.07-0.99 (m, 1H), 0.54-0.51 (m, 2H), 0.21-0.18 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.1, 75.9, 66.0, 55.1, 41.4, 10.5, 3.0; MS (ESI) m/z calcd for $C_8H_{12}N_2\ NaO_2$ ($M+Na^+$) 191.0791 found 191.0791.



39

Branched diazoketone 39. Dichloromethane (15 mL) was added to compound **48** (210 mg, 1.47 mmol) under an argon atmosphere and the mixture was cooled to 0 °C. Triphenylphosphine (409 mg, 1.56 mmol) and NBS (280 mg, 1.58 mmol) were added to the mixture. After 30 minutes freshly prepared CH_2N_2 in Et_2O (4 mmol in 5 mL Et_2O). The reaction was gradually warmed to rt. After 24 h the reaction was concentrated *in vacuo* and purified by column chromatography (30 % EtOAc/ hexanes). 82.5 mg (33 % yield) of **39** as an impure clear yellow oil was obtained: 0.54 R_f (50 % EtOAc/hexanes); IR (neat)

2108, 1637 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (br s, 1H), 3.41 (s, 3H), 3.03-2.96 (m, 1H), 2.64-2.50 (m, 2H), 0.87-0.78 (m, 1H), 0.71-0.62 (m, 1H), 0.50-0.42 (m, 2H), 0.15-0.07 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.1, 82.2, 57.1, 55.4, 47.0, 14.6, 5.3, 0.6; MS (ESI) m/z calcd for $C_8H_{12}N_2$ NaO_2 ($M+Na^+$) 191.0791 found 191.0790.



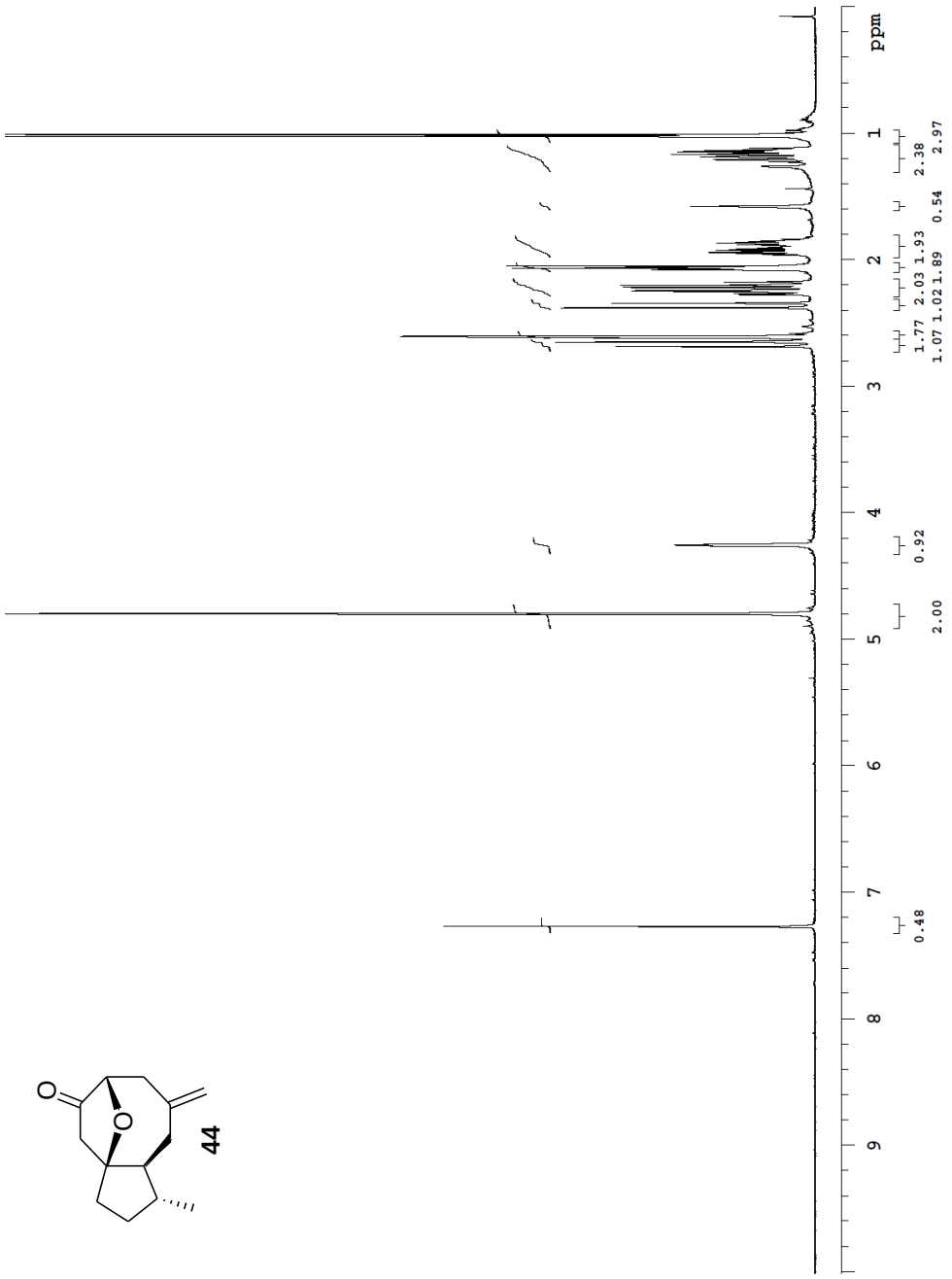
Cyclobutanone 55. Dichloromethane (2 mL) and $Cu(hfacac)_2$ (42 mg, 0.088 mmol) were placed under an argon atmosphere and heated to reflux. The diazoketone **39** (45 mg, 0.27 mmol) in CH_2Cl_2 (1 mL) was added via cannula to the reaction. The reaction mixture was cooled to room temperature after 30 min. The mixture was washed with 0.5M K_2CO_2 (3 mL) and then the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL) and then the phases were separated. The combined organic layers were washed with H_2O (2 mL) and dried over $MgSO_4$. After concentration *in vacuo*, 45 mg (79 % crude) of compound **55** (5:1 dr; ratio determined by integration of methine protone at 4.57 ppm for the major and 4.27 ppm for the minor in the ^{1}H NMR spectrum) was obtained as a colourless oil: IR (neat) 1787 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.57 (d, *J* = 1.7 Hz, 1H), 3.54 (s, 3H), 2.94 (br dd, *J* = 1.9, 3.4 Hz, 1H), 2.45 (br d, *J* = 3.4 Hz, 1H), 2.16-2.08 (m, 1H), 0.91-0.83 (m, 1H), 0.72-0.65 (m, 1H), 0.55-0.48 (m, 1H), 0.32-0.16 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.0, 89.7, 58.9, 44.7, 35.3, 9.8, 7.9, 2.1; MS (EI) m/z calcd for $C_8H_{12}O_2$ (M+) 140.0837 found 140.0831.

4.6 References

1. Nozaki, H.; Takaya, H.; Noyori, R. *Tetrahedron* **1966,** *22*, 3393-3401.
2. Eberlein, T. H.; West, F. G.; Tester, R. W. *J. Org. Chem.* **1992,** *57*, 3479-3482.
3. West, F. G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.* **1994,** *59*, 6892-6894.
4. Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1976,** *98*, 7024-7026.
5. Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1009-1027.
6. Ghosh, A. K.; Kawahama, R. *Tetrahedron Lett.* **1999,** *40*, 4751-4754.
7. Cozzi, P. G. *Angew. Chem. Int. Ed.* **2006,** *45*, 2951-2954.
8. Bourgeois, M.-J.; Montaudon, E.; Maillard, B. *Tetrahedron* **1993,** *49*, 2477-2484.
9. Eichler, E.; Yan, F.; Sealy, J.; Whitfield, D. M. *Tetrahedron* **2001,** *57*, 6679-6693.
10. Wolf, H.; Mätzel, U. *Tetrahedron Lett.* **1979,** *20*, 2339-2342.
11. Arai, S.; Koike, Y.; Hada, H.; Nishida, A. *J. Org. Chem.* **2010,** *75*, 7573-7579.
12. Nakazawa, M.; Mitani, T.; Satake, Y.; Ohzono, S.; Asanuma, G.; Shiono, M. Process for the preparation of cyclopropylacetylenes. European patent EP847974A1, 1998.

Appendix I: Selected NMR Spectra

(Chapter 2)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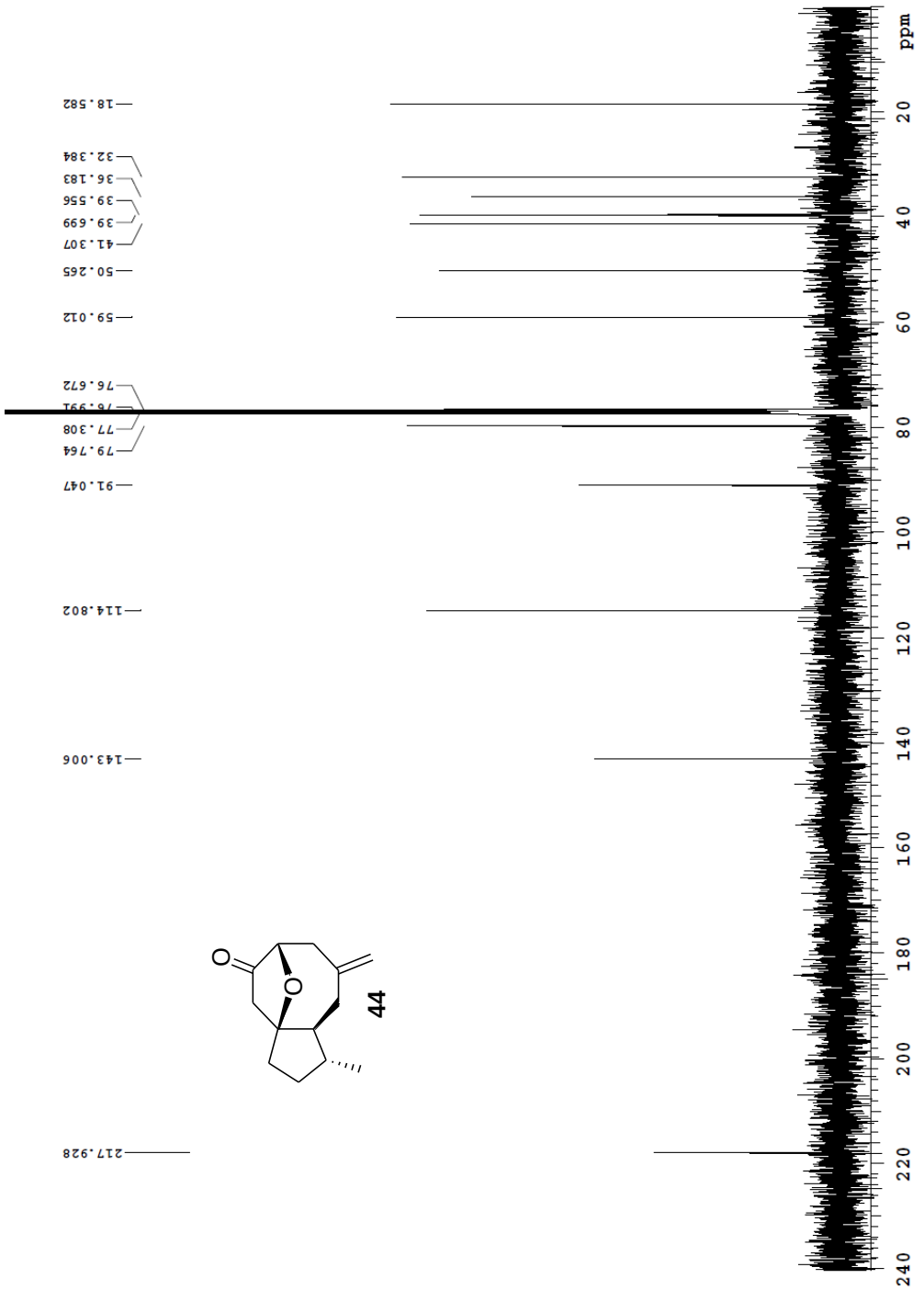
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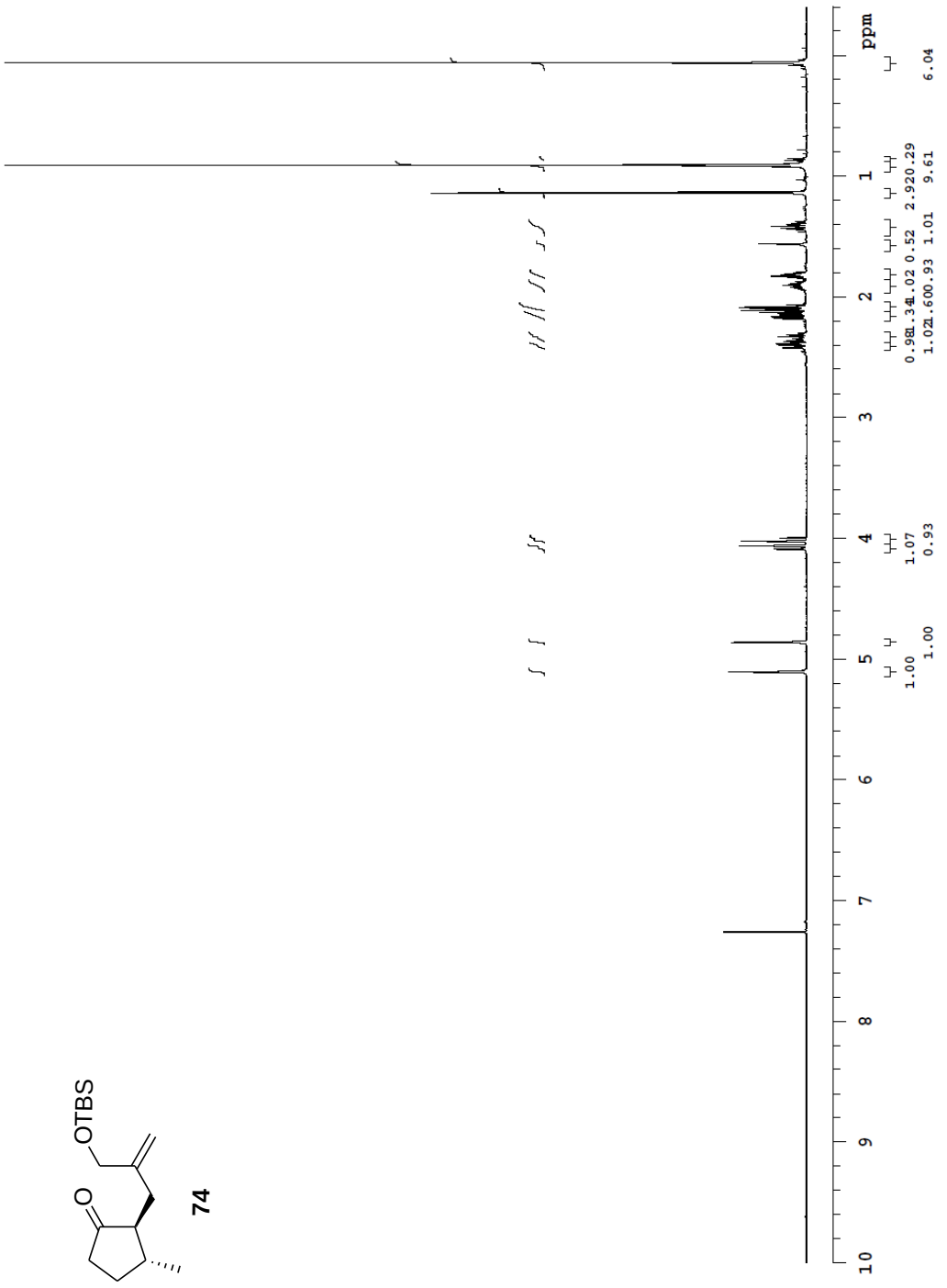
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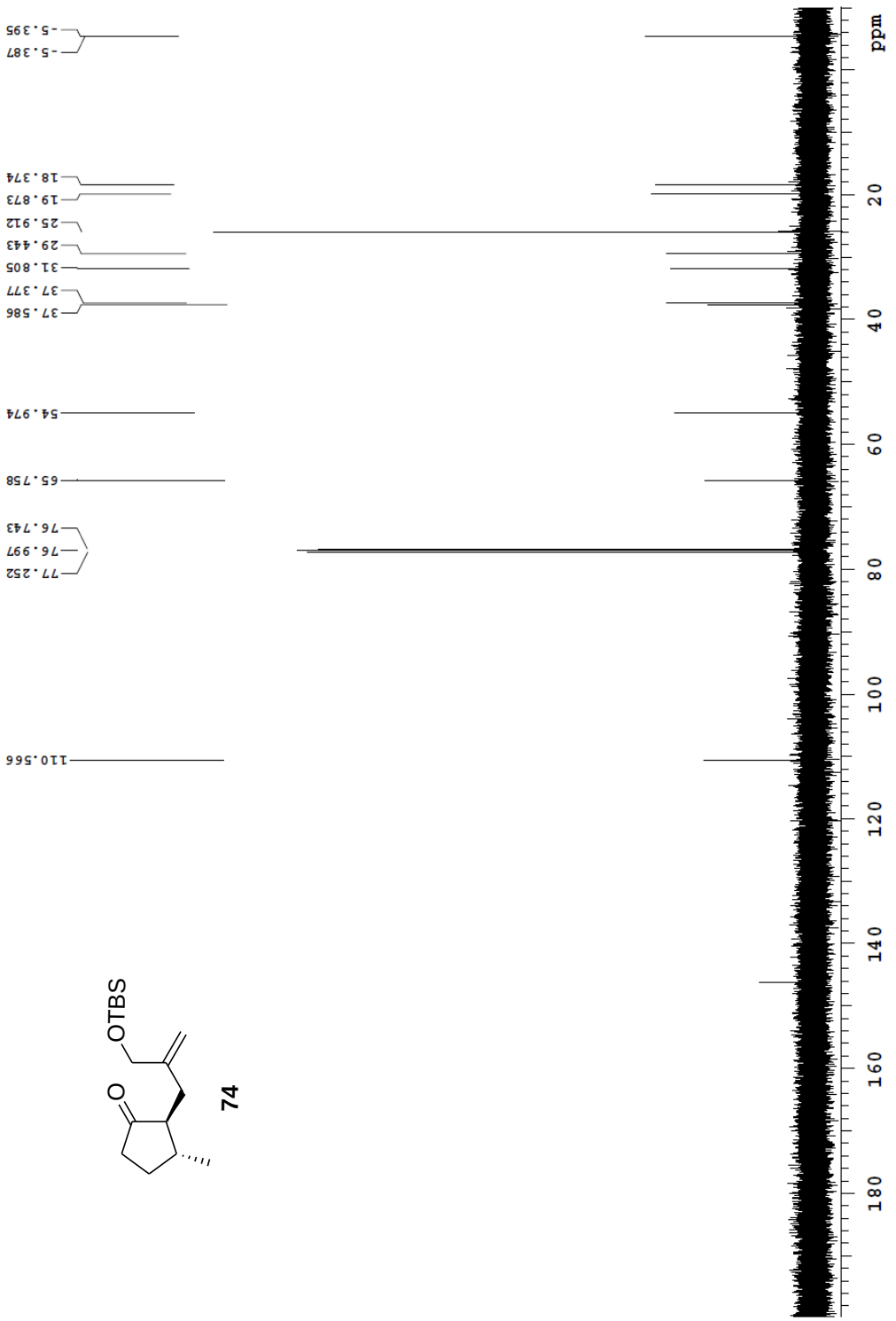
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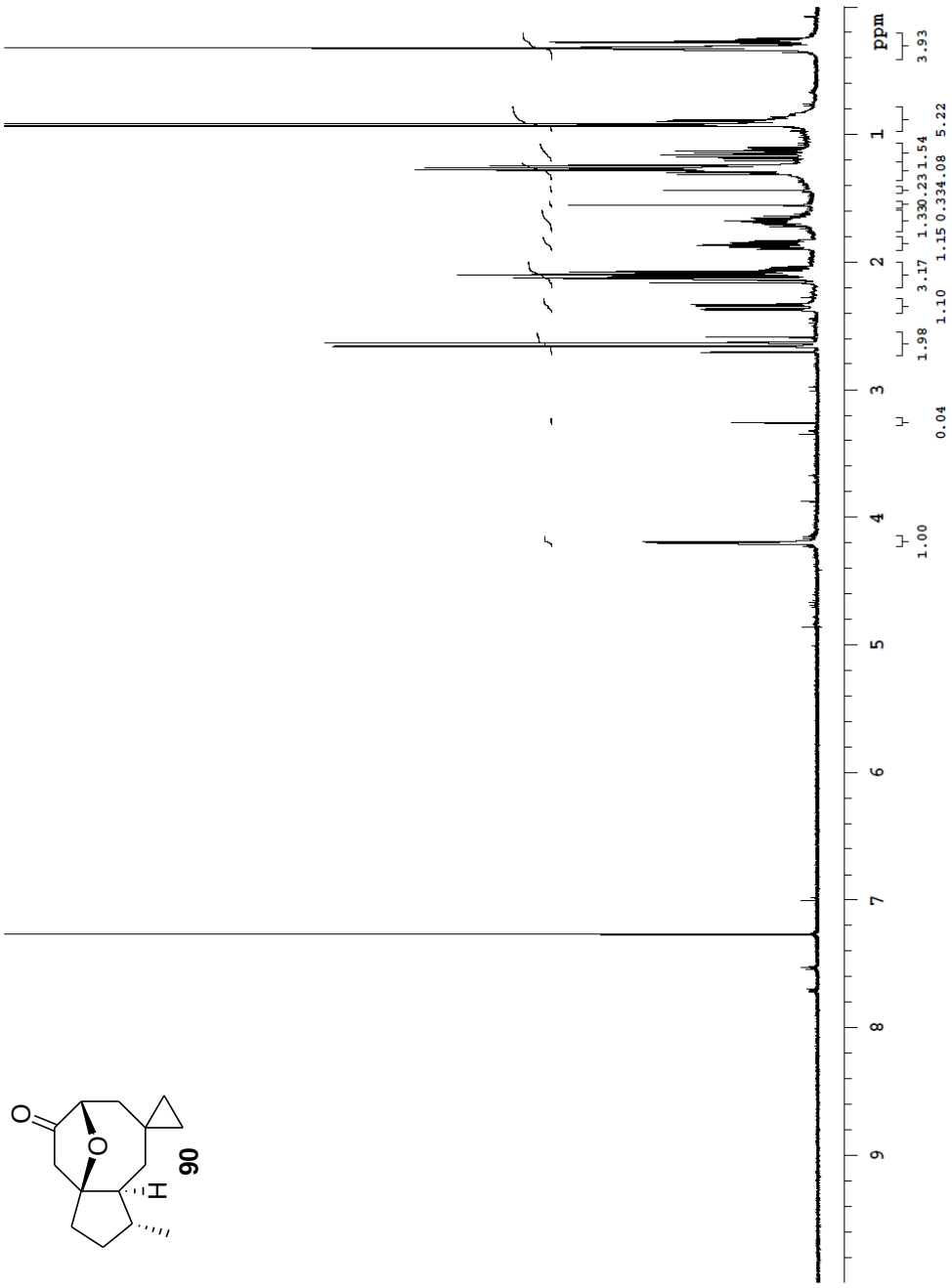
80
100
120
140
160
180
OTBS
O
74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O
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3.17
1.33
0.23
1.15
0.33
4.08
1.10
0.04
1.00

11.701
15.003
17.187
18.875
33.710
39.525
41.525
41.728
42.219
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58.515
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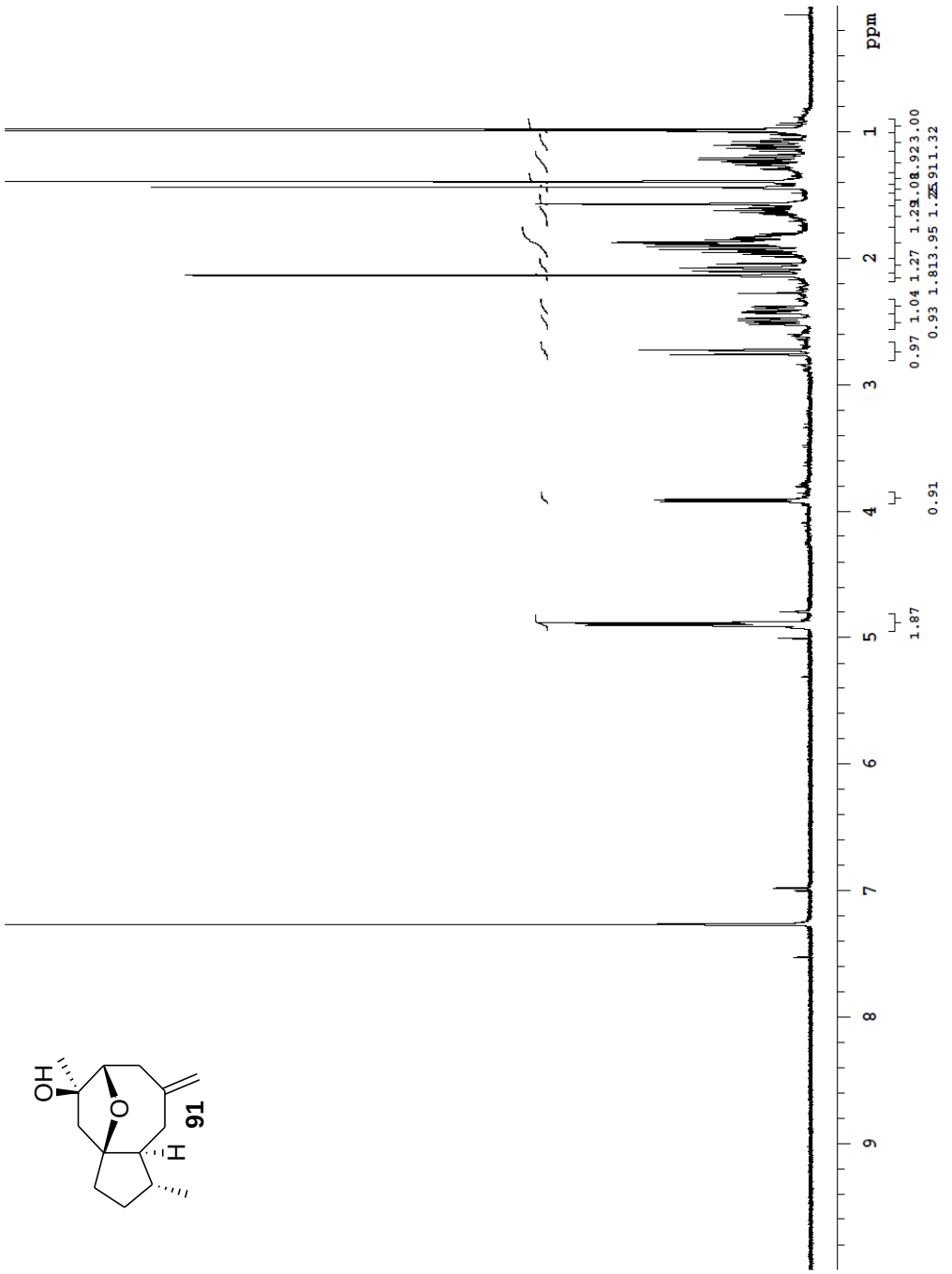
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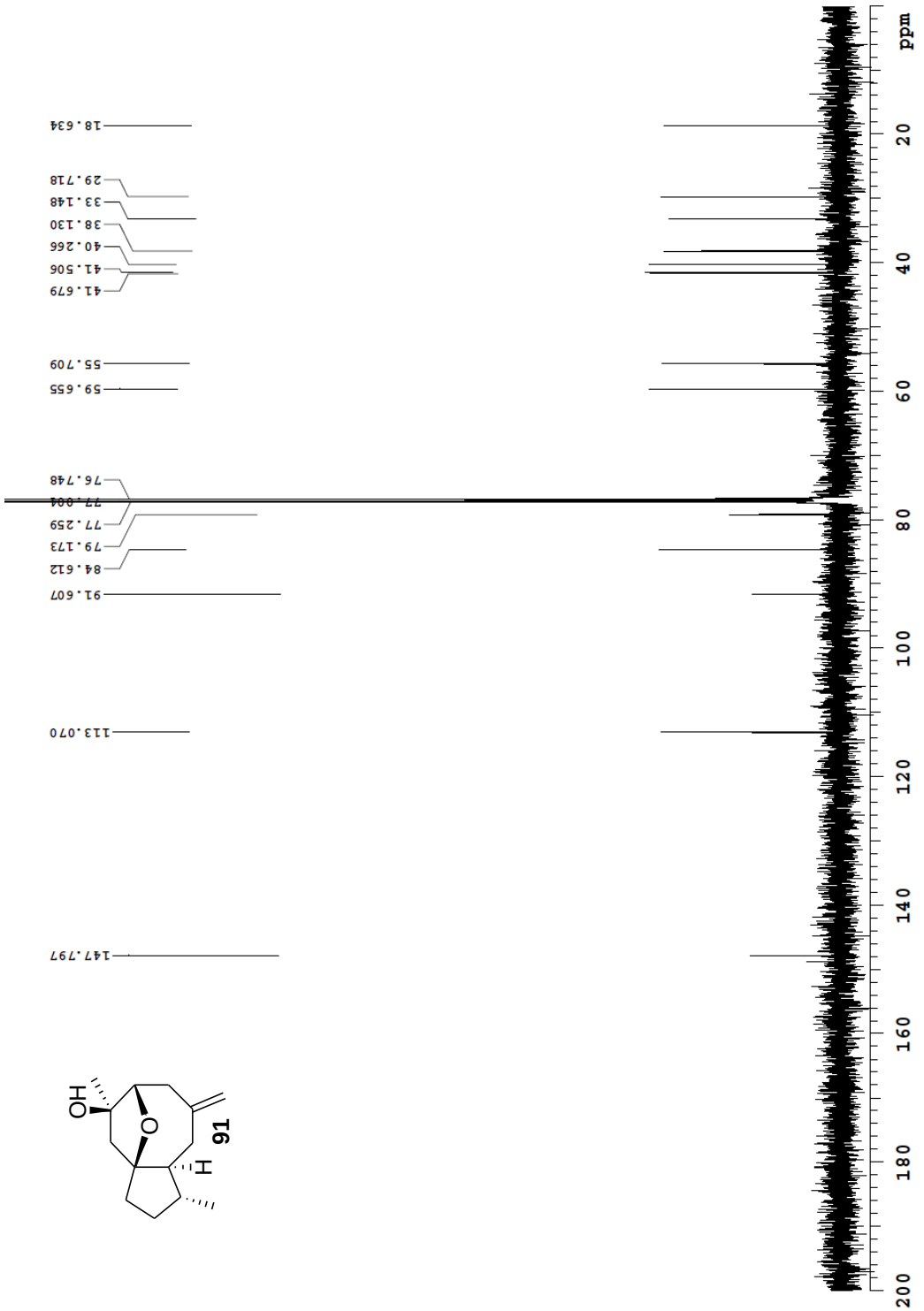
1.87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84.612
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H
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ppm
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60
80
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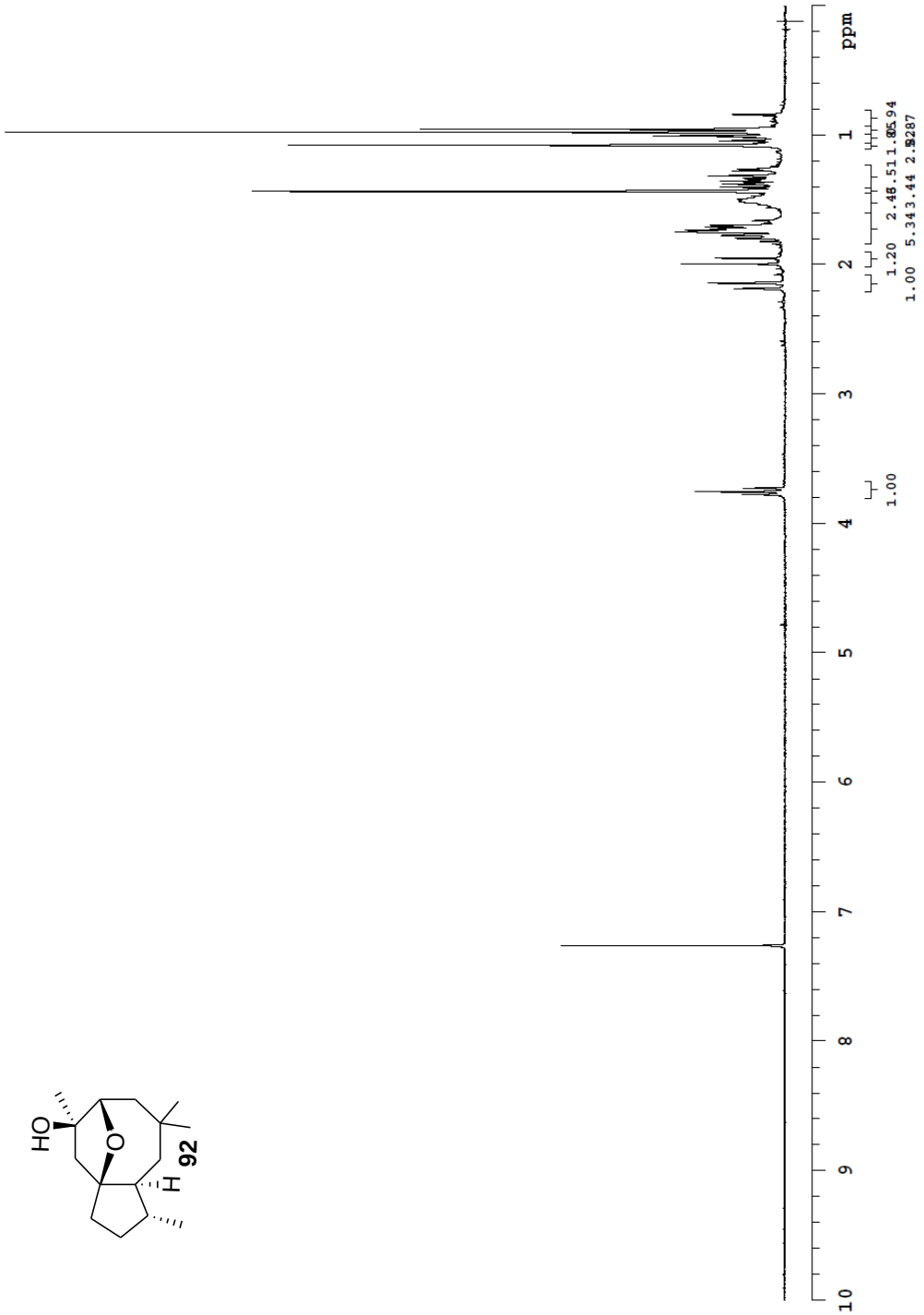
120
140
160
180
200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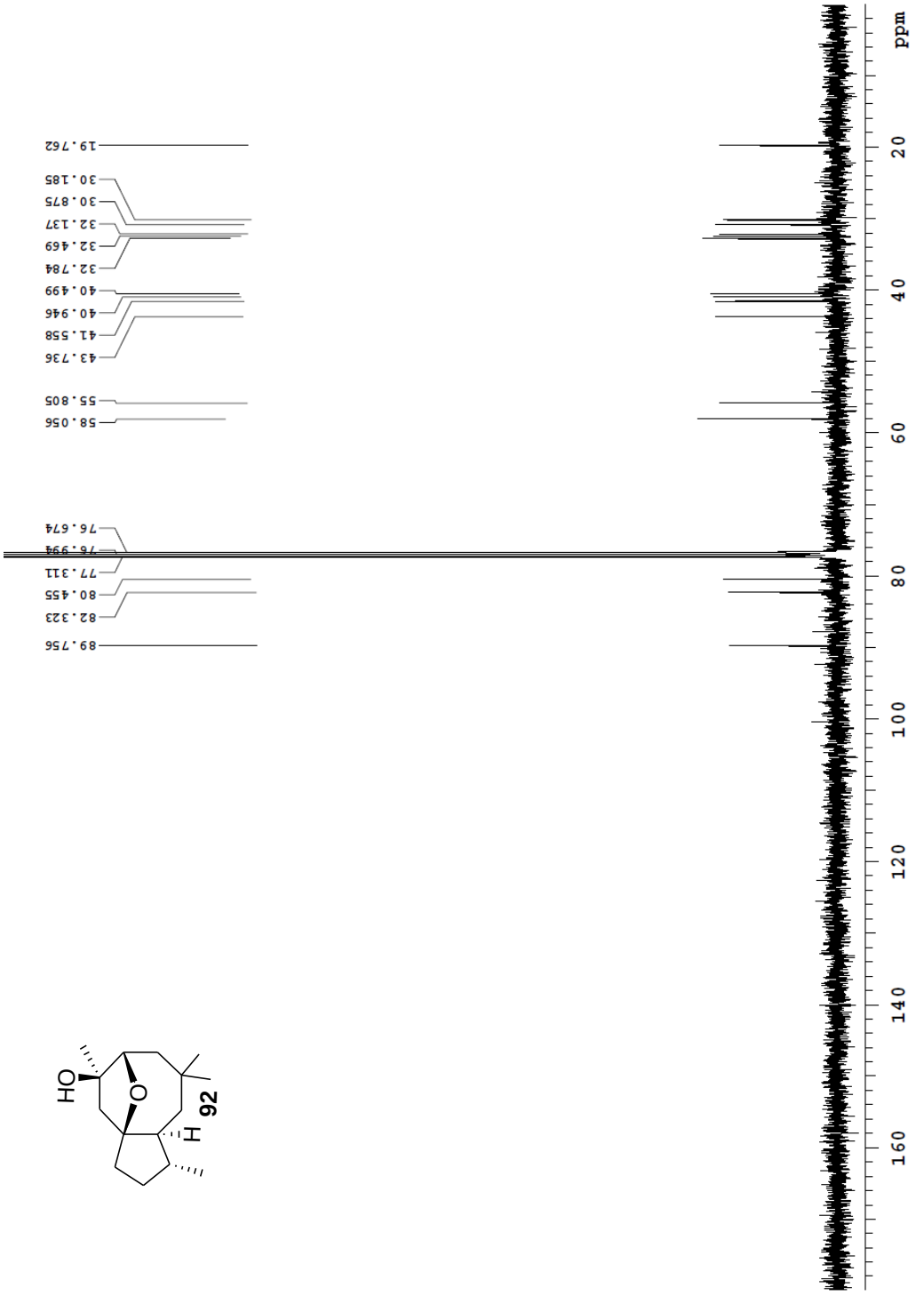
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40.499
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43.736
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76.674
76.994
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100
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HO
O
H
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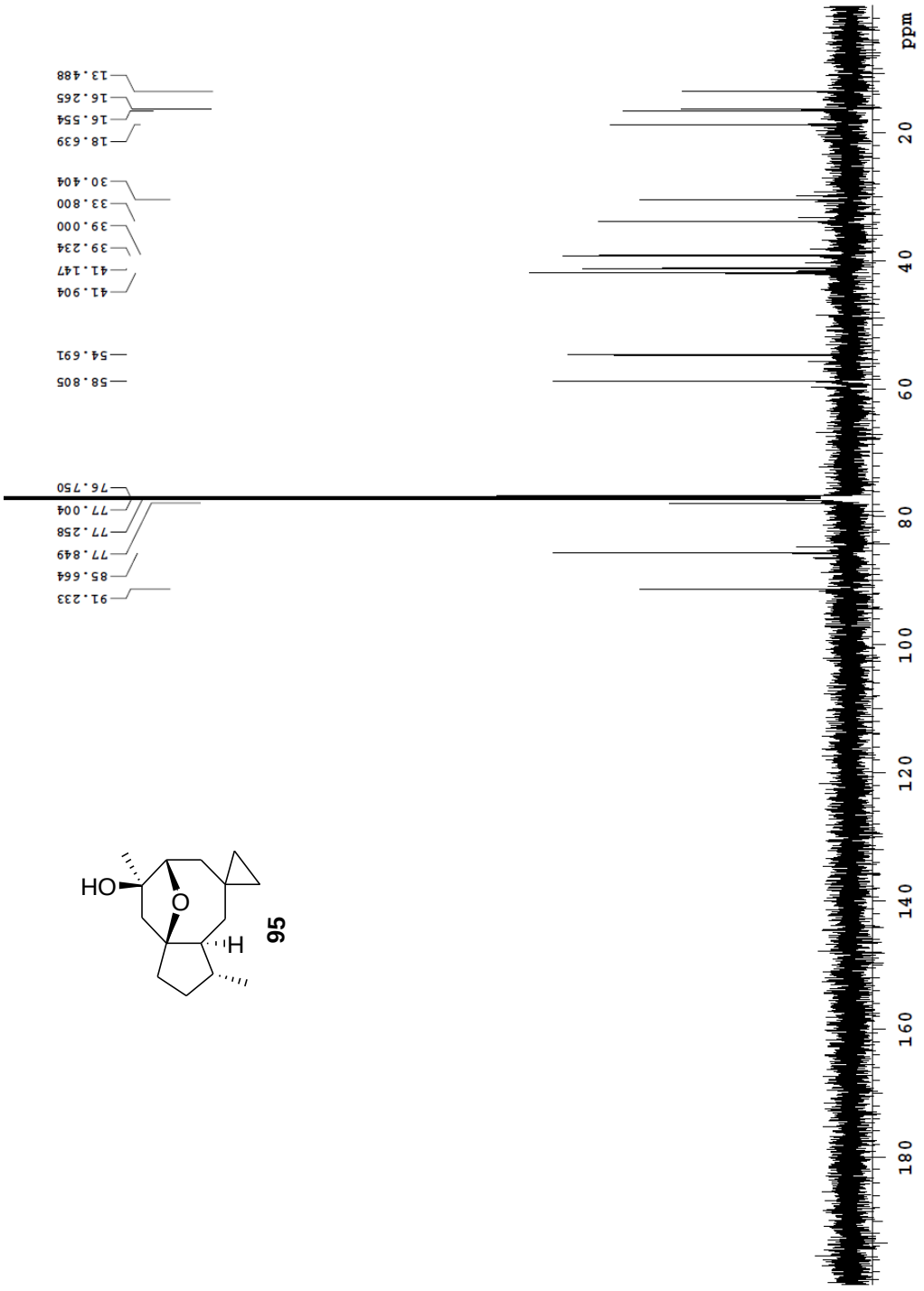
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77.004
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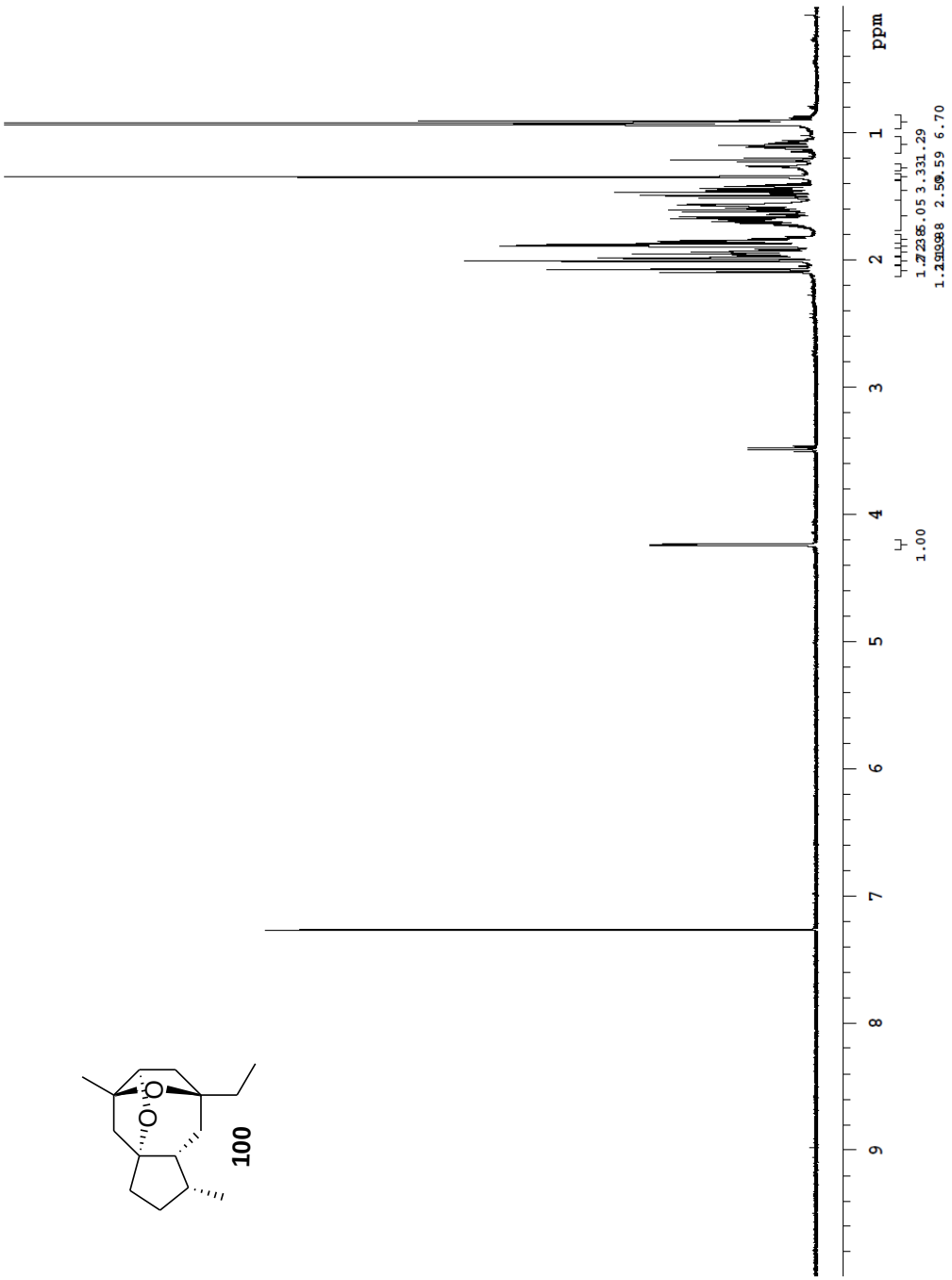
120
140
160
180

HO
O
H

95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O

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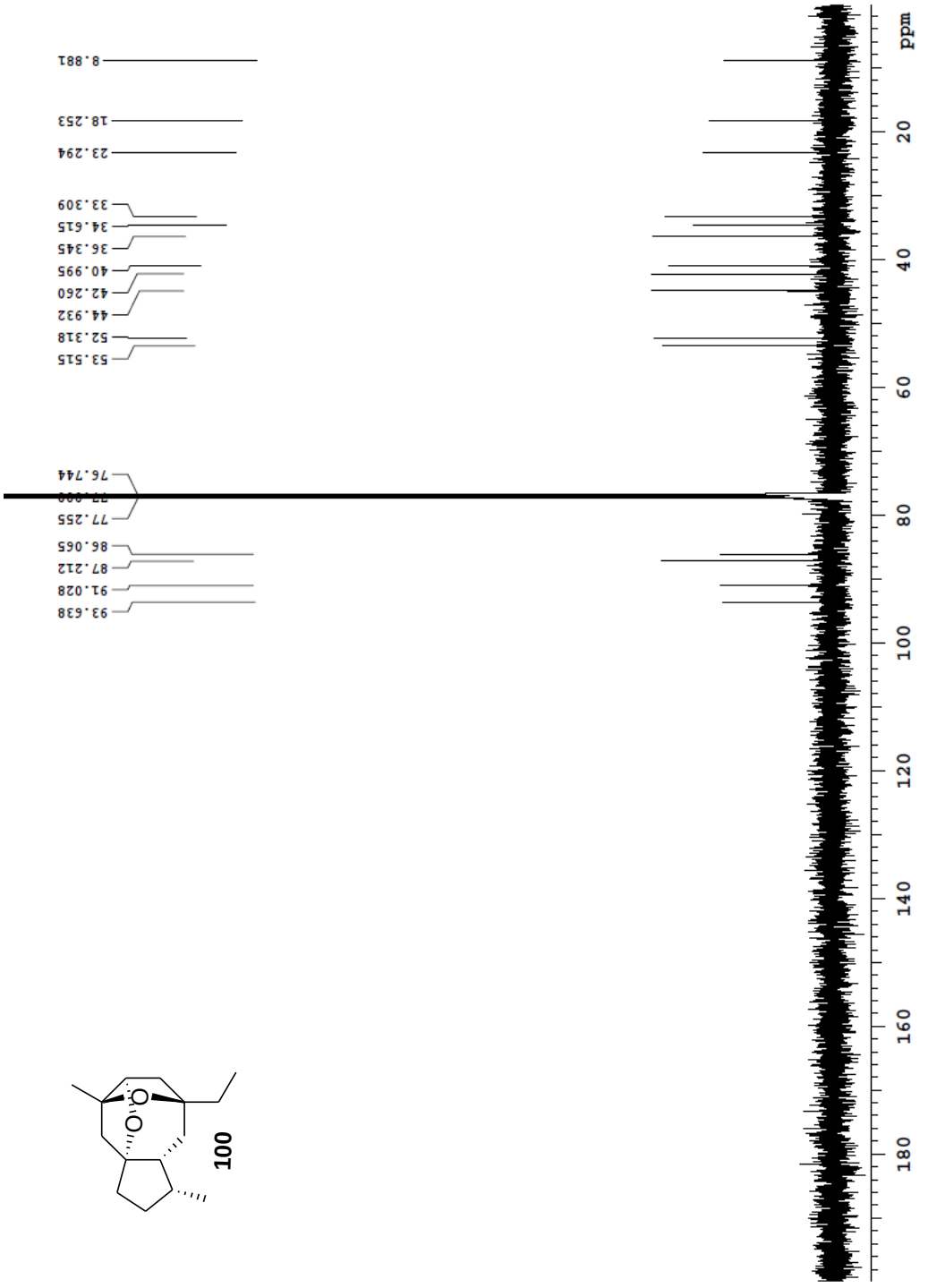
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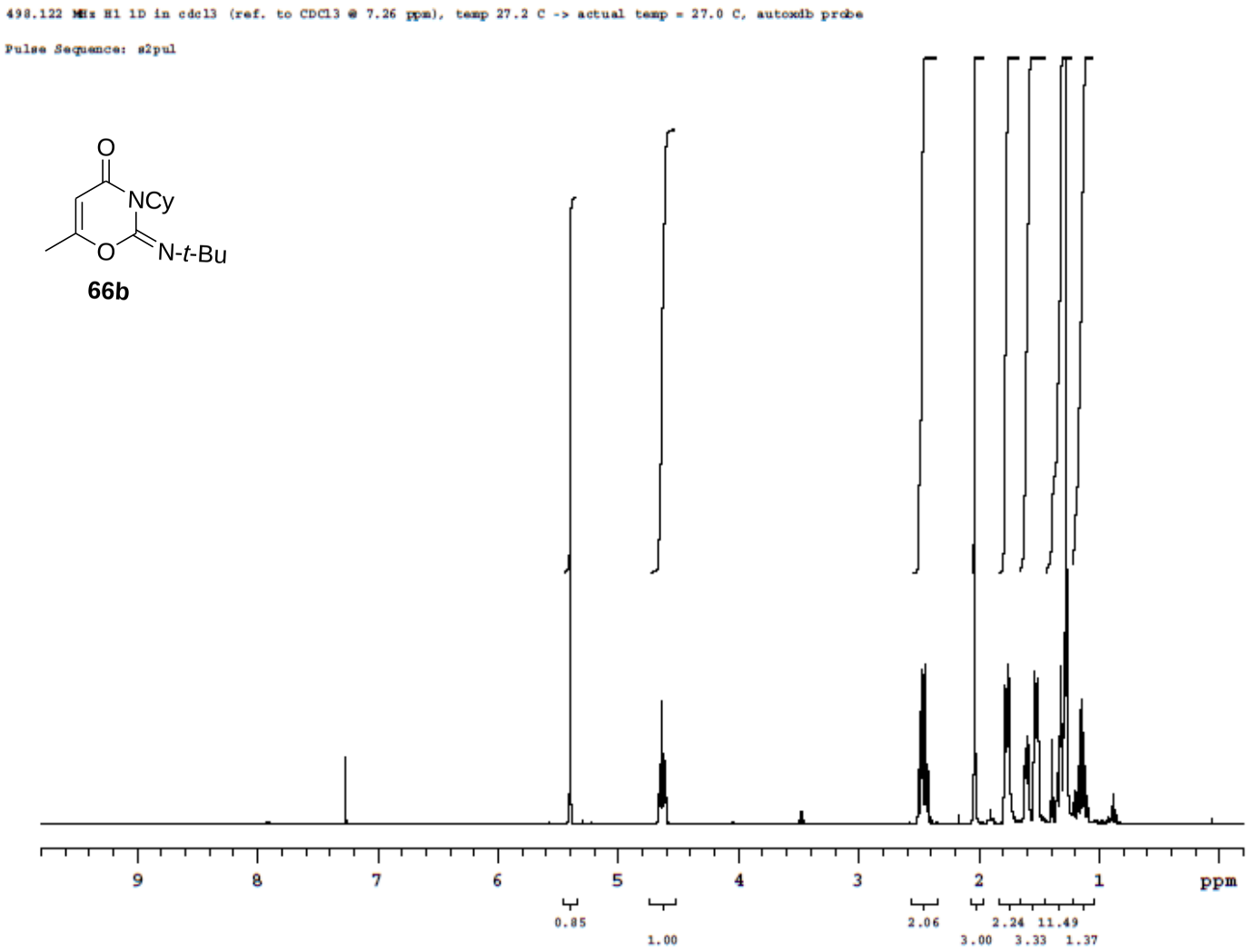
Appendix II: Selected NMR Spectra

(Chapter 3)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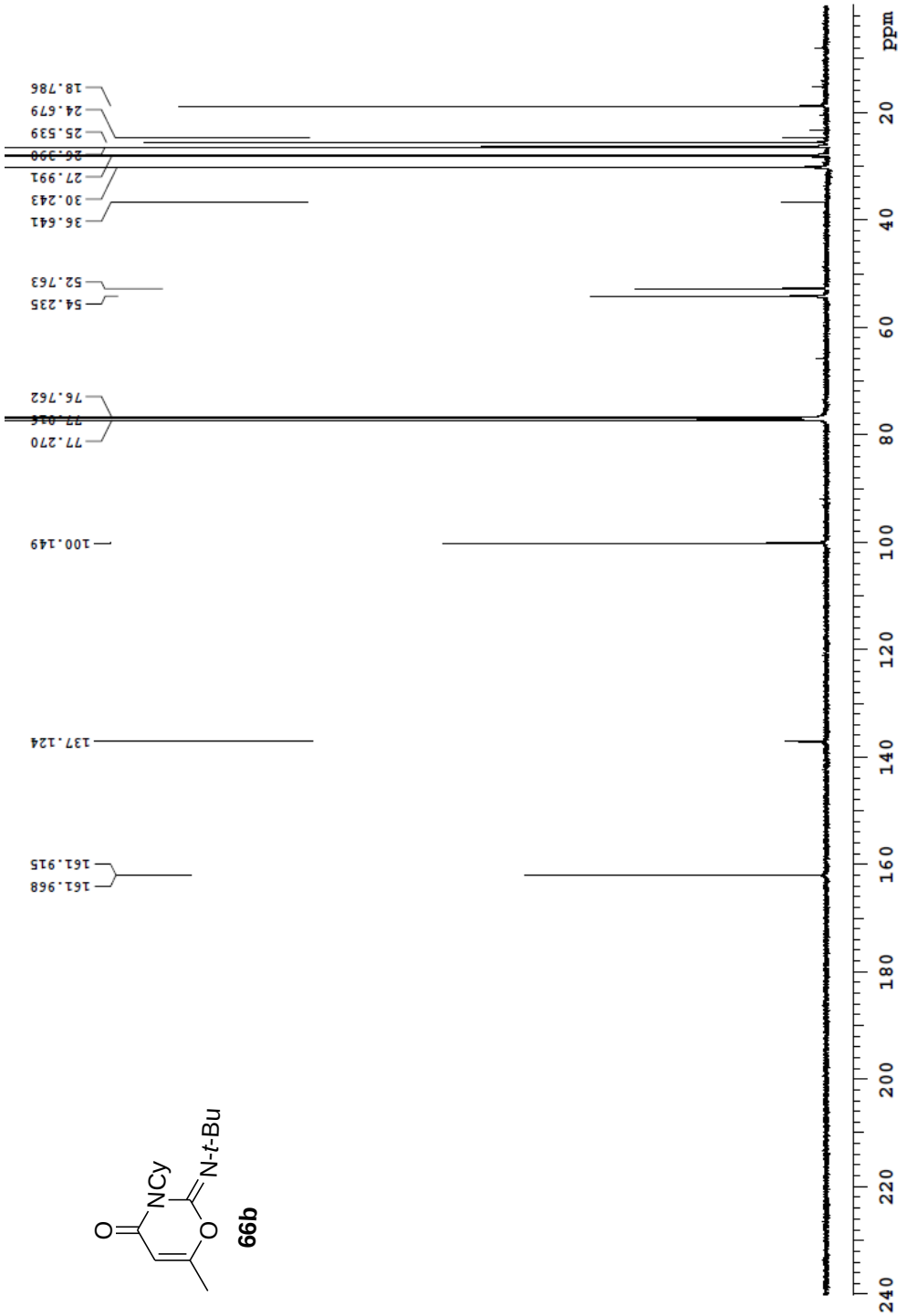
NCy
O
N-t-Bu
66b
9
8
7
6
5
4
3
2
1
ppm
0.85
1.00
2.06
3.00
2.24
3.33
11.49
1.37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25.539
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76.762
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137.124
161.915
161.968
ppm
20
40
60
80
100
120
140
160
180
200
220
240
O
NCy
N-t-Bu
O

66b

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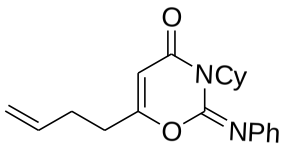
Pulse Sequence: s2pul



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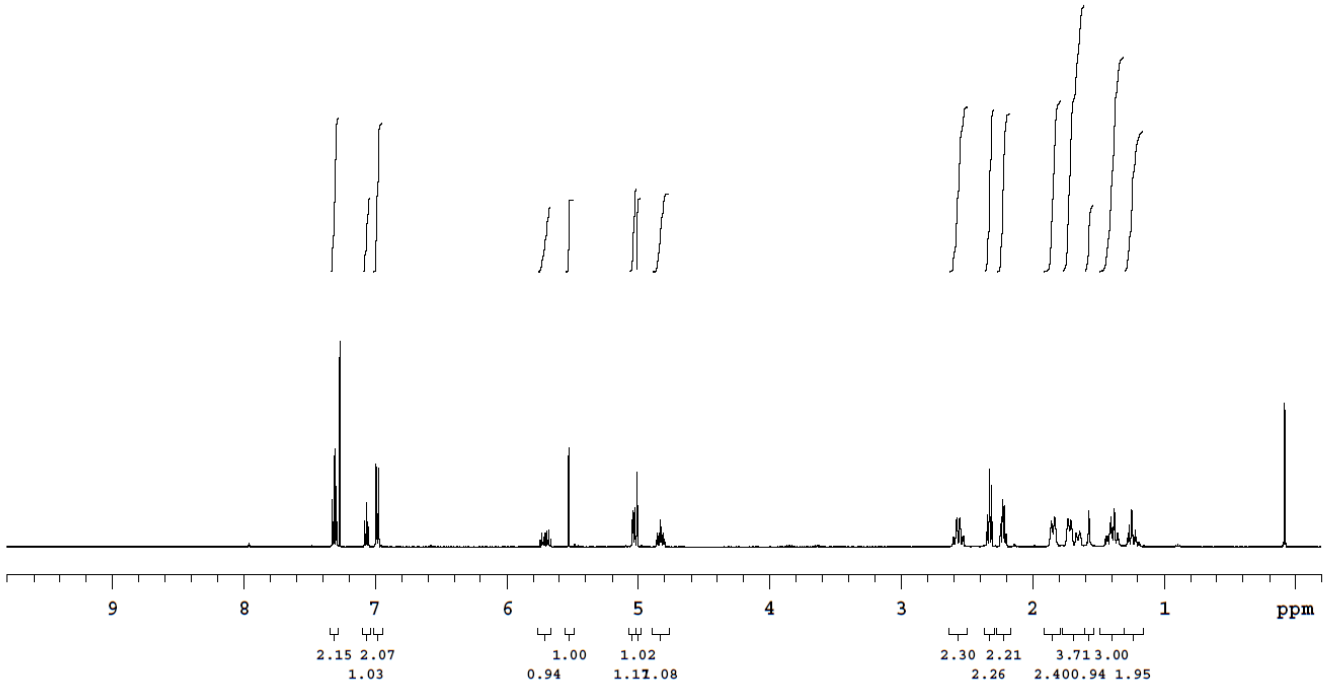

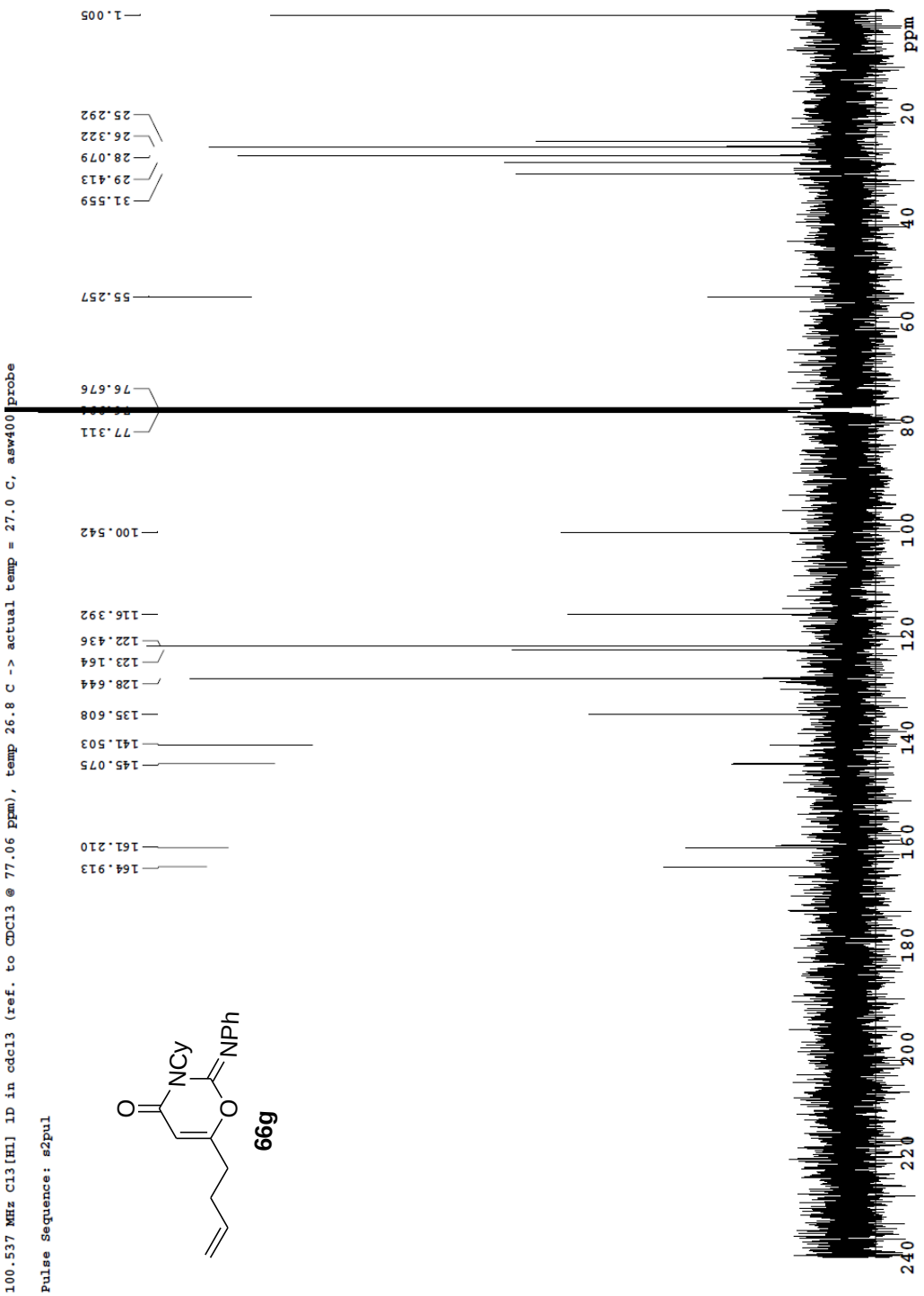
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Pulse Sequence: s2pul
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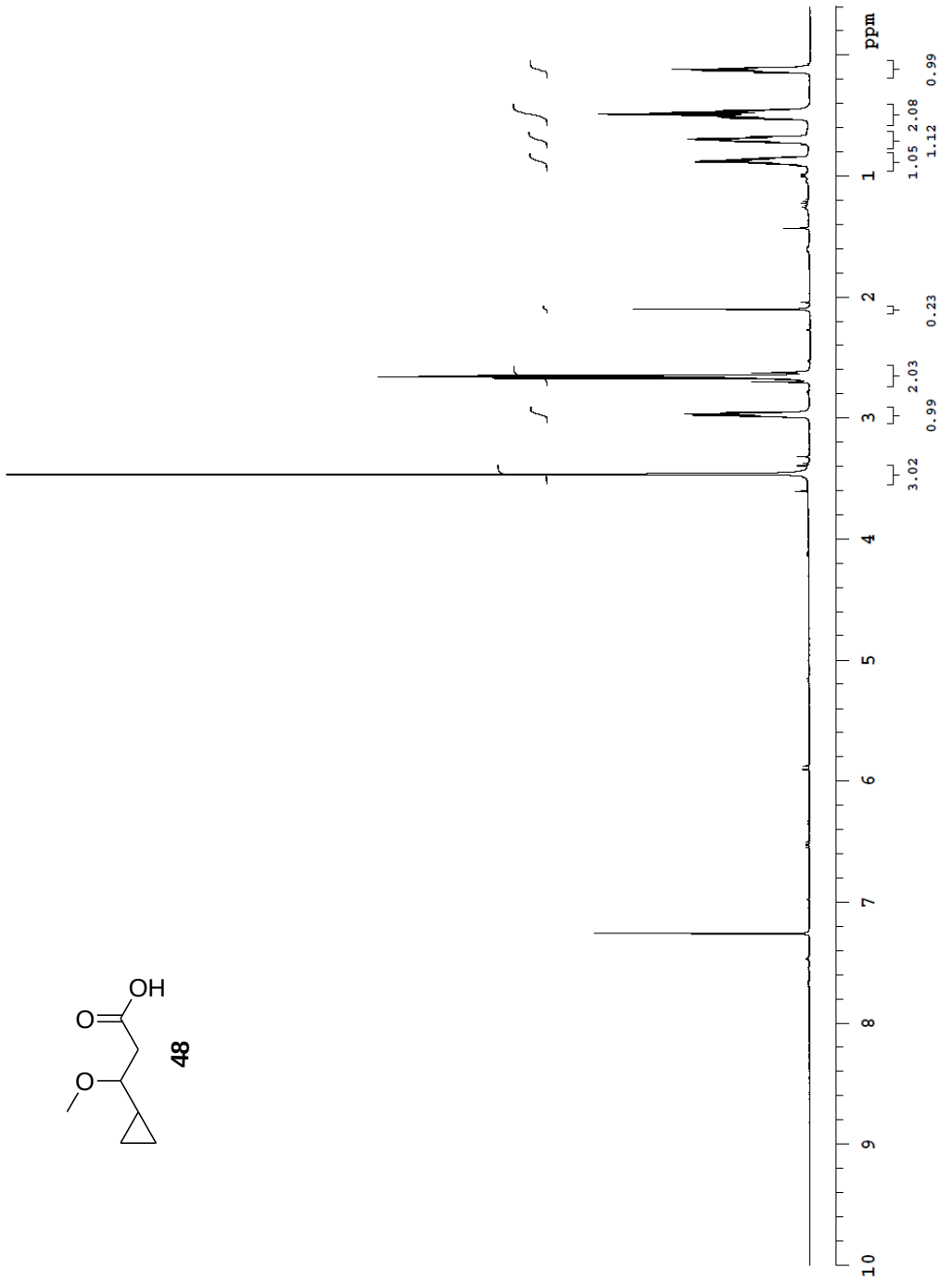
26.322
28.079
29.413
31.559
55.257
76.676
77.311
100.542
116.392
122.436
123.164
128.644
135.608
141.503
145.075
161.210
164.913
NCy
NPh
O
O
66g
ppm
20
40
60
80
100
120
140
160
180
200
220
240

Appendix III: Selected NMR Spectra

(Chapter 4)



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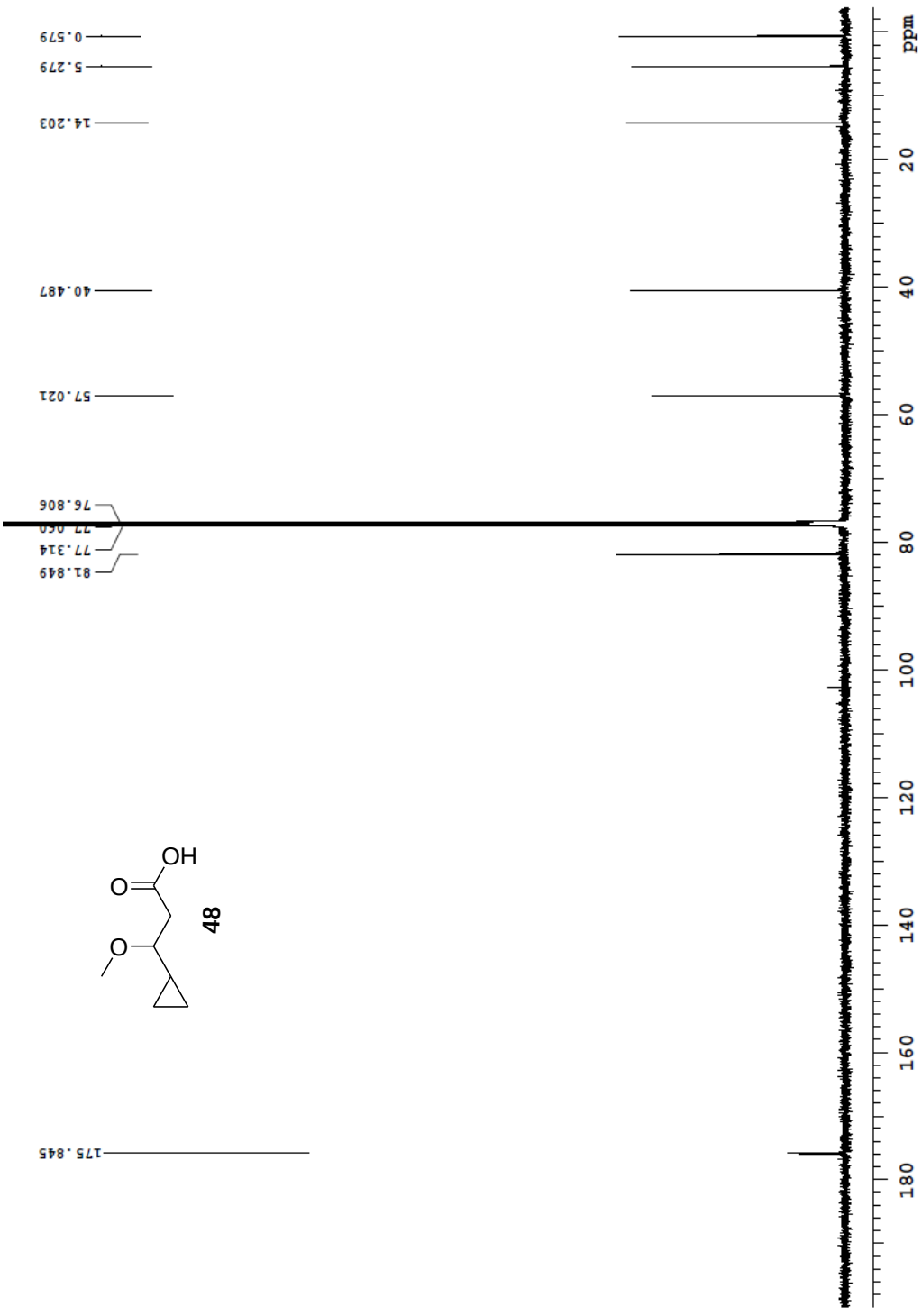
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77.060
77.314
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175.845
ppm
20
40
60
80
100
120
140
160
180
OH
O
O
48

Appendix IV: X-ray Crystallographic Data for Compound 50a

(Chapter 3)

Compound 50a

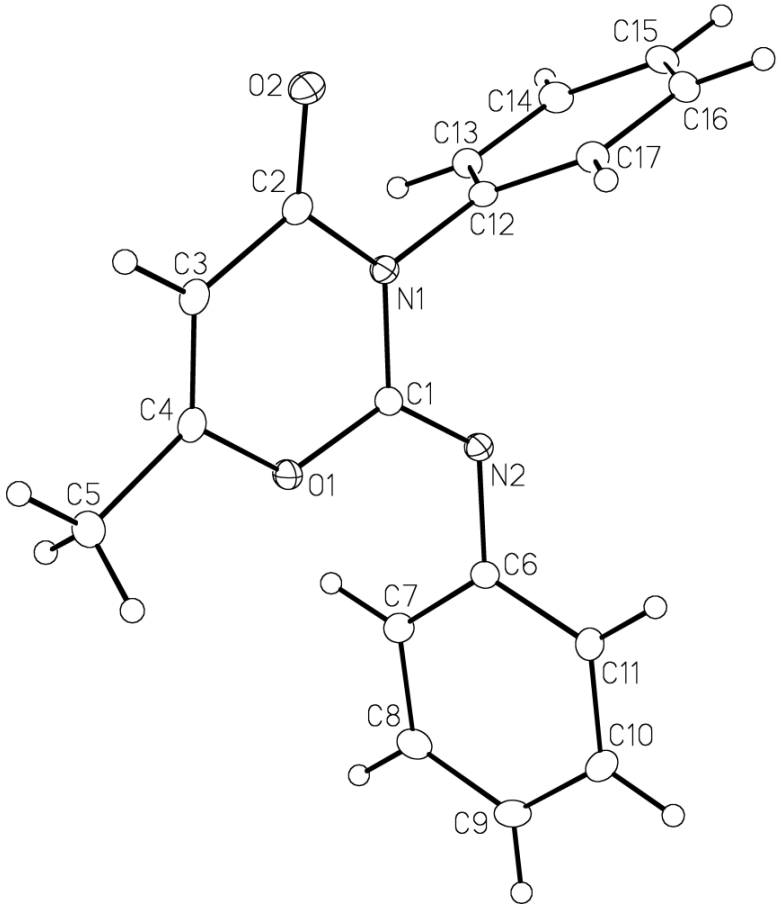

Figure 1. Perspective view of the 3-phenyl-6-methyl-2-(phenylimino)-2,3-dihydro-4*H*-1,3-oxazin-4-one molecule showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

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STRUCTURE REPORT

XCL Code: FGW1007 **Date:** 15 April 2010

Compound: 3-phenyl-6-methyl-2-(phenylimino)-2,3-dihydro-4*H*-1,3-oxazin-4-one

Formula: $C_{17}H_{14}N_2O_2$

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

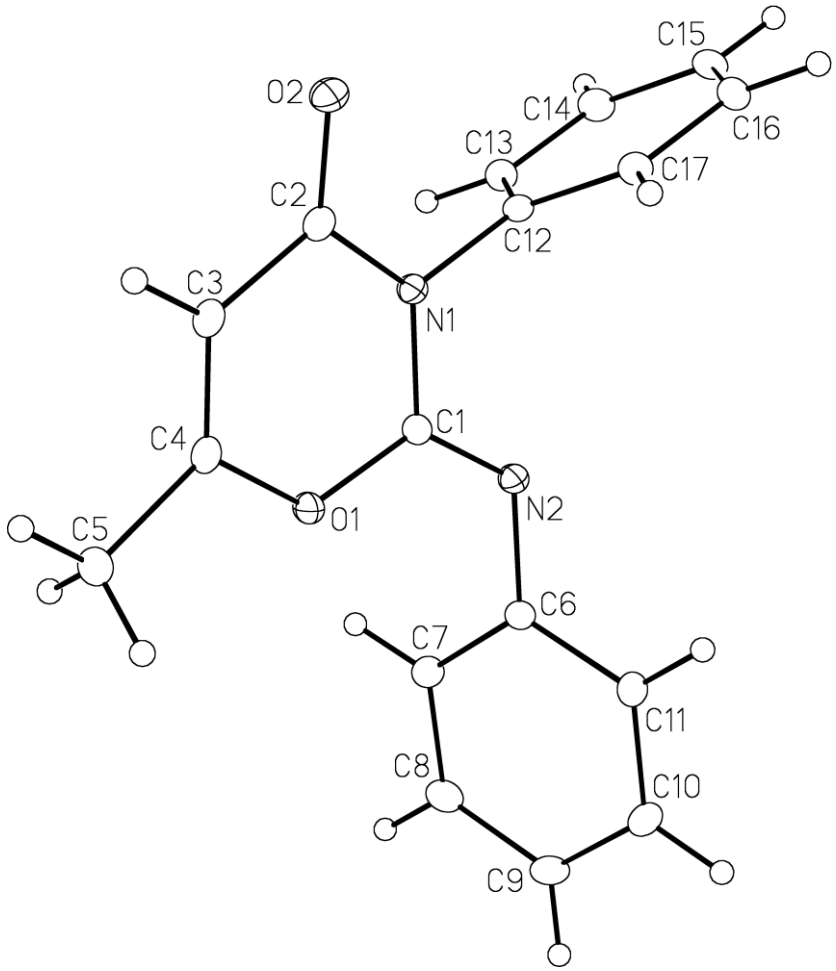

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{17}H_{14}N_2O_2$
formula weight	278.30
crystal dimensions (mm)	0.81 × 0.69 × 0.60
crystal system	monoclinic
space group	$P2_1/c$ (No. 14)
unit cell parameters[a]	
a (Å)	5.4826 (2)
b (Å)	27.6858 (9)
c (Å)	9.4334 (3)
β (deg)	99.0295 (3)
V (Å^3)	1414.15 (8)
Z	4
ρ_{calcd} (g cm^{-3})	1.307
μ (mm^{-1})	0.087
B. Data Collection and Refinement Conditions	
diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–100
scan type	ω scans (0.3°) (15 s exposures)
data collection 2θ limit (deg)	55.02
total data collected	12404 (-7 ≤ h ≤ 7, -35 ≤ k ≤ 35, -12 ≤ l ≤ 12)
independent reflections	3242 (R_{int} = 0.0126)
number of observed reflections (*NO*)	3120 [$F_o^2 \geq 2\sigma(F_o^2)$]
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	0.9495–0.9325
data/restraints/parameters	3242 / 0 / 192
extinction coefficient (x)[d]	0.0251(19)
goodness-of-fit (S)[d] [all data]	1.049
final R indices[f]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0345
wR_2 [all data]	0.0897
largest difference peak and hole	0.258 and –0.166 e Å^{-3}

[a]Obtained from least-squares refinement of 9663 reflections with $4.62° < 2\theta < 54.98°$.

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

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

[d]$F_c^* = kF_c[1 + x\{0.001F_c^2\lambda^3/\sin(2\theta)\}]^{-1/4}$ where k is the overall scale factor.

[e]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0405P)^2 + 0.4417P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

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

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	*x*	*y*	*z*	U_{eq}, Å^2
O1	0.06283(14)	0.40715(2)	-0.15304(7)	0.02753(17)*
O2	-0.30375(15)	0.46164(3)	0.14771(8)	0.03396(19)*
N1	-0.02483(15)	0.40844(3)	0.08330(8)	0.02347(18)*
N2	0.19931(15)	0.34595(3)	0.00594(9)	0.02462(19)*
C1	0.08619(17)	0.38518(3)	-0.02108(10)	0.02221(19)*
C2	-0.19453(18)	0.44616(3)	0.05415(11)	0.0255(2)*
C3	-0.22319(19)	0.46436(4)	-0.09186(11)	0.0281(2)*
C4	-0.09422(19)	0.44577(3)	-0.18680(11)	0.0272(2)*
C5	-0.0938(3)	0.46184(4)	-0.33727(12)	0.0388(3)*
C6	0.31273(17)	0.32133(3)	-0.09848(10)	0.0220(2)*
C7	0.50799(18)	0.34106(4)	-0.15685(10)	0.0264(2)*
C8	0.62572(19)	0.31409(4)	-0.24991(11)	0.0306(2)*
C9	0.5471(2)	0.26771(4)	-0.28822(11)	0.0324(2)*
C10	0.3510(2)	0.24794(4)	-0.23106(12)	0.0324(2)*
C11	0.23671(19)	0.27432(4)	-0.13502(11)	0.0275(2)*
C12	0.01480(18)	0.38757(3)	0.22578(10)	0.0226(2)*
C13	0.23074(18)	0.39841(4)	0.31718(11)	0.0267(2)*
C14	0.26998(19)	0.37799(4)	0.45339(11)	0.0303(2)*
C15	0.0953(2)	0.34725(4)	0.49638(11)	0.0291(2)*
C16	-0.12034(19)	0.33699(4)	0.40340(11)	0.0285(2)*
C17	-0.16198(18)	0.35719(4)	0.26670(11)	0.0263(2)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table 3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2	Distance
O1	C1	1.3733(11)	C6	C11	1.3933(14)
O1	C4	1.3784(12)	C7	C8	1.3866(14)
O2	C2	1.2194(12)	C8	C9	1.3844(16)
N1	C1	1.3939(12)	C9	C10	1.3884(16)
N1	C2	1.3969(12)	C10	C11	1.3877(14)
N1	C12	1.4478(12)	C12	C13	1.3837(14)
N2	C1	1.2569(12)	C12	C17	1.3833(14)
N2	C6	1.4190(12)	C13	C14	1.3893(14)
C2	C3	1.4518(14)	C14	C15	1.3884(15)
C3	C4	1.3288(15)	C15	C16	1.3865(15)
C4	C5	1.4879(14)	C16	C17	1.3911(14)
C6	C7	1.3902(13)			

Table 4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C1	O1	C4	121.27(8)				
C1	N1	C2	123.89(8)				
C1	N1	C12	116.92(7)				
C2	N1	C12	118.65(8)	N2	C6	C11	118.27(9)
C1	N2	C6	122.03(8)	C7	C6	C11	119.21(9)
O1	C1	N1	116.53(8)	C6	C7	C8	120.21(9)
O1	C1	N2	122.65(8)	C7	C8	C9	120.53(10)
N1	C1	N2	120.82(8)	C8	C9	C10	119.51(9)
O2	C2	N1	120.52(9)	C9	C10	C11	120.18(10)
O2	C2	C3	124.91(9)	C6	C11	C10	120.33(10)
N1	C2	C3	114.56(8)	N1	C12	C13	118.75(9)
C2	C3	C4	121.02(9)	N1	C12	C17	119.48(9)
O1	C4	C3	121.59(9)	C13	C12	C17	121.76(9)
O1	C4	C5	110.97(9)	C12	C13	C14	118.77(9)
C3	C4	C5	127.44(10)	C13	C14	C15	120.38(10)
N2	C6	C7	122.33(9)	C14	C15	C16	119.97(9)
				C15	C16	C17	120.25(10)
				C12	C17	C16	118.87(9)

Table 5. Torsional Angles (deg)

Atom1	Atom2	Atom3	Atom4	Angle
C4	O1	C1	N1	-9.94(13)
C4	O1	C1	N2	169.50(9)
C1	O1	C4	C3	2.25(15)
C1	O1	C4	C5	-177.79(9)
C2	N1	C1	O1	13.21(14)
C2	N1	C1	N2	-166.24(9)
C12	N1	C1	O1	-175.38(8)
C12	N1	C1	N2	5.17(14)
C1	N1	C2	O2	172.47(9)
C1	N1	C2	C3	-8.15(14)
C12	N1	C2	O2	1.20(14)
C12	N1	C2	C3	-179.43(8)
C1	N1	C12	C13	82.42(11)
C1	N1	C12	C17	-97.11(11)
C2	N1	C12	C13	-105.70(10)
C2	N1	C12	C17	74.77(12)
C6	N2	C1	O1	0.19(15)
C6	N2	C1	N1	179.61(9)
C1	N2	C6	C7	63.71(13)
C1	N2	C6	C11	-121.22(10)
O2	C2	C3	C4	179.10(10)
N1	C2	C3	C4	-0.24(15)
C2	C3	C4	O1	3.07(16)
C2	C3	C4	C5	-176.87(11)
N2	C6	C7	C8	174.82(9)
C11	C6	C7	C8	-0.21(14)
N2	C6	C11	C10	-176.68(9)
C7	C6	C11	C10	-1.45(14)
C6	C7	C8	C9	1.41(15)
C7	C8	C9	C10	-0.94(16)
C8	C9	C10	C11	-0.72(16)
C9	C10	C11	C6	1.92(16)
N1	C12	C13	C14	-179.35(8)
C17	C12	C13	C14	0.17(15)
N1	C12	C17	C16	179.35(8)
C13	C12	C17	C16	-0.17(14)
C12	C13	C14	C15	0.09(15)
C13	C14	C15	C16	-0.35(15)

C14	C15	C16	C17	0.36(15)
C15	C16	C17	C12	-0.10(15)

Table 6. Anisotropic Displacement Parameters (U_{ij}, Å^2)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.0357(4)	0.0247(3)	0.0230(3)	0.0043(3)	0.0072(3)	0.0081(3)
O2	0.0375(4)	0.0312(4)	0.0355(4)	0.0018(3)	0.0132(3)	0.0118(3)
N1	0.0269(4)	0.0220(4)	0.0222(4)	0.0016(3)	0.0058(3)	0.0047(3)
N2	0.0285(4)	0.0233(4)	0.0228(4)	0.0013(3)	0.0064(3)	0.0042(3)
C1	0.0237(4)	0.0219(4)	0.0212(4)	0.0008(3)	0.0040(3)	-0.0001(3)
C2	0.0258(5)	0.0207(4)	0.0304(5)	0.0000(4)	0.0053(4)	0.0022(4)
C3	0.0316(5)	0.0211(4)	0.0308(5)	0.0033(4)	0.0025(4)	0.0052(4)
C4	0.0332(5)	0.0198(4)	0.0273(5)	0.0028(4)	0.0009(4)	0.0021(4)
C5	0.0586(7)	0.0307(5)	0.0268(5)	0.0058(4)	0.0058(5)	0.0095(5)
C6	0.0237(4)	0.0229(4)	0.0189(4)	0.0016(3)	0.0013(3)	0.0051(3)
C7	0.0255(5)	0.0272(5)	0.0260(5)	-0.0018(4)	0.0021(4)	-0.0019(4)
C8	0.0243(5)	0.0408(6)	0.0271(5)	0.0005(4)	0.0057(4)	0.0023(4)
C9	0.0356(6)	0.0361(6)	0.0258(5)	-0.0037(4)	0.0059(4)	0.0118(4)
C10	0.0410(6)	0.0232(5)	0.0323(5)	-0.0033(4)	0.0037(4)	0.0040(4)
C11	0.0298(5)	0.0231(5)	0.0300(5)	0.0029(4)	0.0063(4)	0.0014(4)
C12	0.0265(5)	0.0209(4)	0.0215(4)	0.0000(3)	0.0067(3)	0.0057(3)
C13	0.0254(5)	0.0266(5)	0.0289(5)	0.0000(4)	0.0066(4)	0.0006(4)
C14	0.0266(5)	0.0363(5)	0.0268(5)	-0.0010(4)	0.0011(4)	0.0030(4)
C15	0.0327(5)	0.0329(5)	0.0225(5)	0.0029(4)	0.0073(4)	0.0077(4)
C16	0.0299(5)	0.0291(5)	0.0283(5)	0.0023(4)	0.0103(4)	0.0005(4)
C17	0.0254(5)	0.0276(5)	0.0259(5)	-0.0011(4)	0.0045(4)	0.0008(4)

The form of the anisotropic displacement parameter is:
$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$

Table 7. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H3	-0.3359	0.4899	-0.1200	0.034
H5A	-0.2161	0.4876	-0.3612	0.047
H5B	-0.1354	0.4345	-0.4026	0.047

H5C	0.0705	0.4741	-0.3472	0.047
H7	0.5609	0.3731	-0.1329	0.032
H8	0.7614	0.3276	-0.2877	0.037
H9	0.6267	0.2495	-0.3531	0.039
H10	0.2950	0.2163	-0.2578	0.039
H11	0.1060	0.2603	-0.0940	0.033
H13	0.3499	0.4194	0.2874	0.032
H14	0.4172	0.3851	0.5175	0.036
H15	0.1236	0.3332	0.5895	0.035
H16	-0.2401	0.3161	0.4332	0.034
H17	-0.3093	0.3502	0.2025	0.032