DISSERTATION

PROGRESS TOWARD THE SYNTHESIS OF PROVIDENCIN

Submitted by
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ABSTRACT

PROGRESS TOWARD THE SYNTHESIS OF PROVIDENCIN

Providencin, a highly oxygenated diterpene, was isolated from the sea plume *Pseudopterogorgia kallos* in 2003 by Rodriguez and co-workers. Providencin was revealed to be a cembrane-based diterpene containing an unprecedented [12.2.0]hexadecane ring-system. Providencin was found to possess anti-cancer activity against human breast (MCF7), lung (NCI-H460) and CNS (SF-268) cancer cell lines. The unique structure and biological activity make providencin an attractive target for total synthesis and our work toward providencin began shortly after its isolation. The initial focus of each approach has centered on the unique trans-fused cyclobutanol moiety. A formal [2 + 2] cycloaddition is our chosen approach to the synthesis of the cyclobutane moiety. Further elaboration of our cyclobutane compounds has led to the synthesis of several highly functionalized intermediates. Our efforts toward the synthesis of providencin are discussed herein.
ACKNOWLEDGEMENTS

First and foremost, I must thank Professor John L. Wood for the opportunity to study organic chemistry in his group. It has been an honor and a privilege to work for John for the past 5 years. His knowledge of and passion for organic chemistry is a constant source of inspiration. I truly appreciated the time he spent with me discussing my chemistry.

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Finally, I wish to thank my family and friends for their love and support during my graduate career. Without their constant encouragement I could not have made it to this point. Thank you to Becca for being such a wonderful friend and carpool mate. Thank you to the Williams group women especially Jenni and T for always making me smile. An enormous thank you to my husband Greg for taking this arduous journey with me, I am forever grateful for your love and support.
ABOUT THE AUTHOR

Sarah was born on April 16th, 1983 to parents Philip and Laurie. Although they would divorce a few years later, Sarah always had the love and support of both parents and their new families. When Sarah was 8 she got a baby sister, Chelsea, who was of course the cutest baby in the whole world. Even though the family tree was now a bit complicated it provided a network of supportive people.

Beginning in her early elementary school years Sarah developed a love of math and science, which continued throughout her education. Sarah spent her 16th birthday at a chemistry competition for high school students. She would later graduate from Bear Creek High School, where she had spent several years in the band, had met her future husband and had pursued her love of math and science.

In the fall of 2001, Sarah began college at the Colorado School of Mines, with the hope of becoming a chemical engineer. As her schooling progressed it became apparent that Sarah’s love of research made her better suited to chemistry than chemical engineering and she switched majors. After doing research in the Voorhees lab, Sarah decided to go to graduate school and was accepted by Colorado State University.

Prior to beginning her graduate career, Sarah interned at Array Biopharma and worked in the process group under Dr. Paul Nichols. After her first semester of graduate school Sarah joined the Wood group and anxiously awaited the arrival of the graduate students and boxes from Yale University. After the unpacking Sarah began work on the providencin project, which continued until 2010. Upon completion of her Ph.D., Sarah will begin post doctoral studies with Dr. Robert Williams at Colorado State University.
To my wonderful husband Greg
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LIST OF ABBREVIATIONS

Å  angstrom
Ac  acetate
AcOH  acetic acid
AgClO4  silver perchlorate
AgNO3  silver nitrate
AIBN  azobisisobutyronitrile
app  apparent
Ar  aryl
AsPh3  triphenylarsine
9-BBN  9-borabicyclo[3.3.1]nonane
BF3•OEt2  boron trifluoride diethyl etherate
BH3•DMS  borane dimethylsulfide complex
Bn  benzyl
br  broad
BT  benzothiazole
Bz  benzoyl
C  carbon
C6H6  benzene
CAN  cerium(IV) ammonium nitrate
cat.  catalytic
CCl4  carbon tetrachloride
CH2Cl2  dichloromethane
CH3CN  acetonitrile
CO  carbon monoxide
Cp2ZrCl2  bis(cyclopentadienyl)zirconium dichloride
CrCl2  chromium(II) chloride
CSA  camphorsulfonic acid
CsF  cesium fluoride
CuCl  copper(I) chloride
CuI  copper(I) iodide
d  doublet
DCC  dicyclohexylcarbodiimide
DCE  1,2-dichloroethane
dd  doublet of doublets
ddd  doublet of doublet of doublets
dddd  doublet of doublet of doublet of doublets
DDQ  2,3-dichloro-5,6-dicyanobenzoquinone
DIBAL-H  diisobutylaluminum hydride
DMAP  4-(dimethylamino)pyridine
DME  dimethoxyethane
DMF  dimethylformamide
DMP  Dess-Martin periodinane
DMS  dimethylsulfide
DMSO  dimethylsulfoxide
dppf  
1,1'-bis(diphenylphosphino)ferrocene

dt  
doublet of triplet

DTBMP  
2,6-di-tert-butyl-4-methylpyridine

ent  
enantiomer

ESI–APCI  
electrospray ionization – atmospheric pressure chemical ionization

Et  
ethyl

Et₂AlCl  
diethylaluminum chloride

Et₃N  
triethylamine

EtOAc  
ethyl acetate

EtOH  
ethanol

g  
gram

GGPP  
geranylgeranyl pyrophosphate

h  
hour(s)

H  
hydrogen

H₂O  
water

H₂O₂  
hydrogen peroxide

H₂SO₄  
sulfuric acid

HFIP  
hexafluoroisopropanol

Hg(OAc)₂  
mercury(II) acetate

HMPA  
hexamethyolphosphoramide

HRMS  
high resolution mass spectrometry

HWE  
Horner-Wadsworth-Emmons

Hz  
hertz

hv  
light

i-Bu₂AlCl  
diisobutylaluminum chloride

IBX  
2-iodoxybenzoic acid

Im  
imidazole

i-Pr₂NEt  
N,N-Diisopropylethylamine, Hünig’s Base

i-PrMgCl  
isopropyl magnesium chloride

IR  
infrared

J  
coupling constant

K₂CO₃  
potassium carbonate

kg  
kilogram

KHMDS  
potassium bis(trimethylsilyl)amide

KOT-Bu  
potassium tert-butoxide

LAH  
lithium aluminum hydride

LDA  
lithium diisopropylamide

LiHMDS  
lithium bis(trimethylsilyl)amide

LiNₐc₂  
lithium dicyclohexylamide

m  
milli, multiplet (NMR), mid (IR)

mCPBA  
meta-chloroperoxybenzoic acid

Me  
methyl

Me₂CO  
acetone

Me₂SO₄  
dimethylsulfate

Me₃SI  
trimethylsulfonium iodide

MeO₂CCN  
methyl cyanoformate, Mander’s reagent
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<tr>
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</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>mL</td>
<td>milliliter</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole</td>
</tr>
<tr>
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<td>monomethoxytrityl</td>
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<td>molecular sieves</td>
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<td>mol</td>
<td>mole(s)</td>
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<tr>
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<td>methoxymethyl ether</td>
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<tr>
<td>MsCl</td>
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<td>sodium bis(trimethylsilyl)amide</td>
</tr>
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<td>sodium iodide</td>
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<tr>
<td>NaIO₄</td>
<td>sodium periodate</td>
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<tr>
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<td>n-butyllithium</td>
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<td>ammonium fluoride</td>
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<td>NHK</td>
<td>Nozaki-Hiyama-Kishi</td>
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<td>N,O-dimethylhydroxylamine</td>
</tr>
<tr>
<td>nm</td>
<td>nanometer</td>
</tr>
<tr>
<td>NMO</td>
<td>N-methylmorpholine-N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>O₃</td>
<td>ozone</td>
</tr>
<tr>
<td>ºC</td>
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<tr>
<td>OTf</td>
<td>triflate</td>
</tr>
<tr>
<td>Pd(OAc)₂</td>
<td>palladium(II) acetate</td>
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<tr>
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<td>tris(dibenzylideneacetone)dipalladium(0)</td>
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<tr>
<td>PdCl₂</td>
<td>palladium(II) chloride</td>
</tr>
<tr>
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<td>protecting group</td>
</tr>
<tr>
<td>Ph</td>
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</tr>
<tr>
<td>Ph₃P</td>
<td>triphenylphosphine</td>
</tr>
<tr>
<td>(PhSe)₂</td>
<td>diphenyl diselenide</td>
</tr>
<tr>
<td>PhSeCl</td>
<td>phenyl selenyl chloride</td>
</tr>
<tr>
<td>Piv</td>
<td>pivaloyl</td>
</tr>
<tr>
<td>PMB</td>
<td>paramethoxybenzyl</td>
</tr>
<tr>
<td>PPH₃</td>
<td>triphenylphosphine</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>PTAP</td>
<td>phenyltrimethyl ammonium tribromide</td>
</tr>
<tr>
<td>PTB</td>
<td>pyridinium tribromide</td>
</tr>
<tr>
<td>pTSA</td>
<td>p-toluenesulfonic acid</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
</tbody>
</table>
q  quartet
quint.  quintuplet
RCM  ring-closing metathesis
Rf  retention factor
RhCl(PPh$_3$)$_3$  chlorotris(triphenylphosphine)rhodium(I), Wilkinson's catalyst
rt  room temperature
RuCp(MeCN)$_3$PF$_6$  tris(acetonitrile)cyclopentadienylruthenium(II) hexafluorophosphate
RuO$_2$•XH$_2$O  ruthenium(IV) oxide hydrate
s  singlet (NMR), strong (IR)
SeO$_2$  selenium dioxide
SnCl$_2$  tin(II) chloride
SnMe$_3$  trimethyltin
SOCl$_2$  thionyl chloride
t  triplet
TBAF  tetrabutylammonium fluoride
TBAI  tetrabutylammonium iodide
TBDPS  tert-butylidiphenylsilyl
TBS  tert-butylmethydisilyl
$t$-Bu  tert-butyl
$t$-BuLi  tert-butyllithium
tert  tertiary
TES  triethylsilyl
Tf$_2$O  triflic anhydride
TFA  trifluoroacetate, trifluoroacetic acid
TFAA  trifluoroacetic anhydride
THF  tetrahydrofuran
THP  tetrahydropyrans
TIPS  triisopropylsilyl
TLC  thin layer chromatography
TMSCHN$_2$  trimethylsilyldiazomethane
TOF LCMS  time of flight liquid chromatography mass spectrometry
TPAP  tetrapropylammonium perruthenate
Tr  trityl
w  weak
$\delta$  chemical shift
$\Delta$  heat
Chapter 1

Providencin

1.1 Background

1.1.1 Isolation and Biological Activity

Providencin (1) was isolated in 2003 by Rodriguez and co-workers, from the Caribbean sea plume *Pseudopterogorgia kallos* (Figure 1.1.1.1). The gorgonians encompass approximately 500 species of sea fans, sea plumes and sea whips found in oceans throughout the world. *Pseudopterogorgia kallos* and related gorgonian octocorals have proven to be an abundant source of secondary metabolites that possess a diverse range of structural features and biological activities.

Figure 1.1.1.1 Providencin (1)

![Providencin (1)](image)

Providencin was isolated as a colorless amorphous solid in 0.0012% yield from over 1 kg of dried *Pseudopterogorgia kallos* and its structure and relative stereochemistry
were determined through a combination of NMR spectroscopy and X-ray crystallographic analysis. These studies revealed 1 to be a highly oxygenated diterpene containing an unprecedented [12.2.0]hexadecane ring system. Some of the more intriguing structural features include the trans-fused cyclobutanol moiety, the tri-substituted furan and the epoxidized butenolide.¹

Providencin was tested for biological activity and showed anti-cancer activity against human breast (MCF7), lung (NCI-H460) and CNS (SF-268) cancer cell lines. The growth inhibition of treated cells compared to untreated cells was 57, 39, and 94% respectively.¹ Unfortunately, the dearth of naturally occurring 1 has prevented further biological testing.

1.1.2 Related Compounds

Providencin is one of several structurally intriguing natural products to be isolated from Pseudopterogorgia kallos. Rodriguez et al. have proposed that the carbon skeletons represented by 1 and six other compounds or classes of compounds share a common biogenic precursor (Figure 1.1.2.1).¹ ⁴ Cembrane-based compounds arise from the cyclization of geranylgeranyl pyrophosphate (GGPP).⁴ It has been proposed that cyclization or ring contraction of a cembrane skeleton leads to seven novel carbon skeletons. The providenciane carbon skeleton found in 1 results from a C₂-C₁₇ cyclization of a cembrane-based compound.
Figure 1.1.2.1 Cembrane and related diterpene carbon skeletons

Providencin is closely related to a class of diterpenes with cembrane-based skeletons known as furanocembranoids. These compounds are typified by a polyoxygenated 14-membered macrocycle containing a furan ring and often a butenolide (Figure 1.1.2.2).
**Figure 1.1.2.2** Furanocembrane skeletal structure

It was discerned that providencin 1 most closely resembles some members of the bipinnatin family of natural products (Figure 1.1.2.3).5 These furanocembranes were first isolated from *Pseudopterogorgia bipinnata* but the bipinnatins and their derivatives have also been found in other gorgonian species including *Pseudopterogorgia kallos*, from which 1 was isolated.
Figure 1.1.2.3 Bipinnatin family of natural products

In addition to providencin 1, several other intriguing diterpene natural products have been isolated from Pseudopterogorgia kallos (Figure 1.1.2.4). These compounds show a wide variety of structural and biological characteristics and have therefore been the target of several synthetic studies. Kallolide A (13), the first and most abundant metabolite to be isolated from Pseudopterogorgia kallos, has potent anti-inflammatory activity and was synthesized in 1998 by Marshall and Liao. Beilschowskysin (17) was found to have anti-malarial and anti-cancer activity. Several studies towards the cyclobutane-containing core have been published but there has been no total synthesis to date. The study and synthesis of intricarene (18) and its proposed biogenic precursor,
bipinnatin J (11), have been accomplished by both the Trauner and Pattenden groups. However, no specific synthetic work has been reported for kallosin A (14), kallolide E (15), kallolide G (16) or ciereszkolide (19).

Figure 1.1.2.4 Related *Pseudopterogorgia kallos* isolates

![Structures](image)

1.2 Synthesis of Relevant Structures

The synthesis of furanocembrane-based diterpenes has been the aim of several research groups. These synthetic studies have shown that a variety of distinctive approaches can effectively produce the various moieties found in these molecules. The main distinction in these approaches is whether or not the furan and/or butenolide moieties are introduced prior or subsequent to the macrocyclization.

1.2.1 Introduction of Furans in the synthesis of Furanocembranes

Marshall recognized two possible approaches to the introduction of the furan moiety in furanocembrane natural products. The first method was to synthesize a furan substrate, which could then be homologated and undergo macrocyclization. This
approach has been successfully demonstrated with the total synthesis of (±)-bipinnatin J (11) (Scheme 1.2.1.1).11

**Scheme 1.2.1.1 Introduction of furan in the synthesis of Bipinnatin J (11)**

![Scheme 1.2.1.1](image)

The second method was to construct a macrocycle, containing the necessary functionalization in which to introduce the furan post-macrocyclization. Marshall has published two such approaches in the synthesis of (−)-deoxypukalide (25) and (ent)-rubifolide (28) (Scheme 1.2.1.2).10, 12 In the synthesis of (−)-deoxypukalide (25), the macrocyclic ynone 23 was treated with silica gel to furnish the tri-substituted furan 24. Alternatively, silver nitrate catalyzed the cyclization of allenone 26 to give furan 27 a precursor to (ent)-rubifolide (28).
Scheme 1.2.1.2 Furan formation in the synthesis of furanocembranes (25) and (28)

A third approach, proposed by Tokoroyama and co-workers, was to combine the furan formation and macrocyclization into a single step. A Feist-Bénary-type reaction of a tethered epoxy-aldehyde and β-ketoester 29 was shown to yield the macrocyclic furan 30 (Scheme 1.2.1.3). This particular approach has yet to be used in the total synthesis of a furanocembrane natural product.
**Scheme 1.2.1.3** Feist-Bénary approach to furan formation/macrocyclization

![Scheme 1.2.1.3](image)

1.2.2 Macrocyclization in the Synthesis of Furanocembranes

To date, reported approaches to the macrocyclic core of the furanocembranes involve either macrocyclization prior to formation of the furan or after the formation of the furan. As mentioned above, Marshall utilized the former approach in the syntheses of (−)-deoxypukalide (25) and (ent)-rubifolide (28) (Scheme 1.2.2.1).\textsuperscript{10, 12} In the synthesis of (ent)-rubifolide (28), treatment of allenylstannane aldehyde 31 with BF$_3$•OEt$_2$ resulted in a cyclized homopropargylic alcohol. Subsequent oxidation and in situ isomerization of the alkyne to the allene resulted in the furan precursor allenone 32. In the case of (−)-deoxypukalide (25) intramolecular alkylation of β-ketoester 33 furnished alkyne 34, the furan precursor.
**Scheme 1.2.2.1** Macrocyclization in the synthesis of (28) and (25)

![Scheme 1.2.2.1](image)

Furan formation followed by macrocyclization has been used in several syntheses. An intramolecular Stille coupling, between a vinyl iodide and stannylfuran in substance 35 furnished macrocycle 36, which was used by Pattenden and co-workers in the synthesis of bis-deoxylophotoxin (37) (Scheme 1.2.2.2).14

**Scheme 1.2.2.2** Macrocyclization in the synthesis of Bis-Deoxylophotoxin (37)

![Scheme 1.2.2.2](image)

Intramolecular cyclization of an allyl bromide and an aldehyde 38 under standard Nozaki-Hiyama-Kishi (NHK) conditions resulted in the desired homoallylic alcohols 39
(Scheme 1.2.2.3). The Pattenden group used this approach in the synthesis of (+)-Z-deoxypukalide (25).\textsuperscript{15}

Scheme 1.2.2.3 Macrocyclization in the synthesis of (+)-Z-Deoxypukalide (25)

1.2.3 Introduction of Butenolide Moiety in the Synthesis of Furanocembranes

There have been several approaches to the butenolide moiety found in some of the furanocembrane natural products. One approach, used in the synthesis of (±)-acerosolide (43), involves lactonization of a γ-hydroxy ester 40 to a γ-lactone 41. Conversion of the lactone to the selenide is followed by oxidation to the selenoxide, which subsequently undergoes elimination to yield the butenolide 42. This approach has generally been used to introduce the butenolide prior to macrocyclization. Paquette, Pattenden and Rawal have favored this approach in the synthesis of bis-deoxylophotoxin (37), (±)-acerosolide (43) and (±)-bipinnatin J (11), respectively (Scheme 1.2.3.1).\textsuperscript{11a, 14, 16}
Scheme 1.2.3.1 Butenolide formation in the synthesis of (±)-Acerosolide (43)

<table>
<thead>
<tr>
<th>Structure 40</th>
<th>Structure 41</th>
<th>Structure 42</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Trauner and co-workers utilized another approach towards the butenolide moiety, which was synthesized prior to macrocyclization, involving a Trost enyne reaction. Propargyl alcohol 44 was treated with allyl alcohol 45 and catalytic ruthenium (II) under acidic conditions to give butenolide 46 (Scheme 1.2.3.2). This reaction was used in the synthesis of (±)-bipinnatin J (11).

Scheme 1.2.3.2 Butenolide formation in the synthesis of Bipinnatin J (11)

Marshall took an independent approach and developed methodology to introduce the butenolide post macrocyclization. In this instance the macrocyclic alkyne 47 undergoes hydroxycarbonylation to give the allenoic acid 48, which is treated directly with silver nitrate on silica to yield the butenolide. Marshall and co-workers have used this method to install the butenolide in the syntheses of (−)-deoxypukalide (25), (ent)-rubifolide (28) and kallolide A (13) (Scheme 1.2.3.3).
Scheme 1.2.3.3 Butenolide formation in the synthesis of (–)-Deoxypukalide (25)

1.3 Previous Synthetic Work Towards Providencin

Three research groups have published work towards the synthesis of providencin (1). The Pattenden group from the University of Nottingham, the Mulzer group from the University of Vienna and the White group from Oregon State University have each taken different approaches toward the synthesis of this molecule.

1.3.1 Pattenden’s Synthetic Work

In 2006, Pattenden and co-workers published the first synthetic work towards the synthesis of 1. They proposed that a radical C-H insertion reaction could be utilized to access the cyclobutanol moiety of 1. They envisioned that 1 could be obtained by applying this reaction to bipinnatin E (6) (Scheme 1.3.1.1).

Scheme 1.3.1.1 Proposed biosynthesis of Providencin (1)
To test this hypothesis, Pattenden and co-workers utilized a model system (Scheme 1.3.1.2). Starting with 2-methyl-3-furoic acid 49, esterification and subsequent bromination gave furanmethyl bromide 50. Deprotonation of methyl 3-methylbut-2-enoate 51 with LDA and treatment with bromide 50 gave the desired β,γ-unsaturated ester 52. The radical cyclization precursor was obtained by oxidation of 52 with selenium dioxide. Irradiation of aldehyde 53 in benzene yielded the desired cyclobutanol 54 in 19% yield. Although the model study was successful, bipinnatin E (6) has not been synthesized and thus its conversion to 1 via the radical cyclization described above has yet to be demonstrated.

**Scheme 1.3.1.2** Pattenden’s synthesis of exo-methylene cyclobutanol 54

1.3.2 Mulzer’s Synthetic Work

Mulzer and co-workers have published several papers regarding their work towards the synthesis of 1.\(^1\) In their initial retrosynthetic analysis they proposed starting with commercially available, chiral bicyclo[3.2.0]cyclo-hept-6-en-2-one 55. Homologation of cyclobutanone 55 to cyclobutane 56 and subsequent combination with lactone 57 could provide diene 58. Subsequent RCM could furnish compound 59.
containing a [12.2.0]hexadecane ring system (Scheme 1.3.2.1). The [12.2.0]hexadecane ring system is unique to 1.

**Scheme 1.3.2.1** Mulzer’s original retrosynthesis of Providencin (1)

In the forward sense the synthesis began with the conversion of cyclobutanone 55 to the TBS-silyl enol ether 60 (Scheme 1.3.2.2). Hydroboration, silyl protection, ozonolysis and sodium borohydride reduction yielded bis-protected tetraol 61. Mono-protection of 61 and oxidation of the remaining alcohol to the aldehyde was followed by conversion to the alkyne 62 using the Bestmann-Ohira reagent. Deprotonation of the alkyne 62 and treatment with epoxide 63 furnished 64. Conversion to the protected allylic alcohol 56 was accomplished via formation of an epoxide and subsequent ring opening followed by benzoyl protection of the resultant alcohol. Deprotection and oxidation provided an aldehyde, which when exposed to deprotonated lactone 57 afforded the RCM-precursor. Unfortunately, all attempts to effect a ring closing metathesis were unsuccessful.
Scheme 1.3.2.2 Mulzer’s attempted synthesis of macrocycle 59

In a further attempt toward the synthesis of 1, Mulzer and co-workers envisioned combining trans-cyclobutanol 65 and propargyl iodide 66 fragments via an alkylation reaction (Scheme 1.3.2.3). Further elaboration of 67 and subsequent ring-closing metathesis would give macrocycle 68.
Synthesis of the trans-cyclobutanol 65 began with the commercially available racemic cyclobutanone 55 (Scheme 1.3.2.4). Reduction of the ketone and subsequent enzymatic resolution yielded enantiomerically pure alcohol 69. TIPS protection of alcohol 69 was followed by ozonolysis and treatment with sodium borohydride to furnish the triol 70. Mono-protectio with monomethoxytrityl chloride (MMTrCl), oxidation and successive epimerization gave aldehyde 71. A Reformatsky reaction and IBX oxidation provided the trans-cyclobutanol coupling partner 65.
Scheme 1.3.2.4 Mulzer’s synthesis of β-ketoester 65

Synthesis of the propargyl iodide coupling partner 66 commenced with reduction of (S)-maleic ester 73 and bis-TBS protection of the resultant diol (Scheme 1.3.2.5). Conversion of the ester 74 to the Weinreb amide and treatment with methylmagnesium bromide provided the methyl ketone 75. Addition of deprotonated alkyne 76 to methyl ketone 75 furnished the tertiary alcohol 77. Benzoylation, PMB-removal and conversion to the propargyl iodide yielded the desired coupling partner 66.

Scheme 1.3.2.5 Mulzer’s synthesis of propargyl iodide 66
The coupling of the two fragments was accomplished through the alkylation of \( \beta \)-ketoester 65 with propargyl iodide 66 (Scheme 1.3.2.6). Wipf cyclization followed by selenium-mediated equilibration to the E-olefin generated furan 78.\(^{19}\) Removal of the MMTr group and oxidation to the aldehyde was followed by addition of the phosphonate and a second oxidation to give keto phosphonate 79. The primary alcohol was deprotected and subsequently oxidized to the aldehyde followed by macrocyclization via an HWE reaction to give enone 68. To date no further elaboration of this substrate has been published.

**Scheme 1.3.2.6** Mulzer’s synthesis of macrocycle 68
A third approach that Mulzer and co-workers took toward the synthesis of providencin 1 also involved a RCM approach to the macrocyclic core (Scheme 1.3.2.7). However, in this approach the RCM was envisioned to occur on a substrate in which the butenolide and furan moieties were already present. The RCM precursor 81 would arise from an aldol reaction between lactone 57 and aldehyde 81. Cyclobutanone 55 would again be the starting point for the synthesis of the cyclobutyl furan.

**Scheme 1.3.2.7 Mulzer’s third retrosynthesis of Providencin (1)**

First, the lactone coupling partner 57 was synthesized in four steps from (R)-glycidyl tosylate 83 (Scheme 1.3.2.8). Cuprate addition to epoxide 83 provided the homoallyl alcohol that was then converted to the epoxide 86 upon treatment with sodium hydride. The epoxide was then treated with the dianion of (phenylseleno) acetic acid 87 to give the hydroxy acid 88 that underwent acid-catalyzed cyclization to the lactone 57 coupling partner.
Synthesis of the furan coupling partner 81 commenced with the alkylation of β-ketoester 65 was with propargyl iodide 89 (Scheme 1.3.2.9). Wipf cyclization furnished the alkenyl-furan 91. Removal of the MMTr group was followed by oxidation to provide aldehyde 81. Deprotonation of lactone 57 and treatment with aldehyde 84 gave the desired lactone, which upon treatment with hydrogen peroxide gave butenolide 82. Treatment with Grubbs II catalyst furnished the Z-isomer of macrocycle 92 as a 1:1 mixture of diastereomers. All attempts to convert the Z-olefin to the E-olefin were unsuccessful. Similarly attempts to invert the configuration of cis-epoxides synthesized from the Z-olefin were also unsuccessful.
Scheme 1.3.2.9 Mulzer’s synthesis of macrocycle 92

1.3.3 White’s Synthetic Work

Most recently, White and co-workers published their work on the cyclobutyl furan sector of 1. The key step involved a zirconium-mediated deoxygenative ring-contraction of a glucose-derived furanoside 94 to yield a tetra-substituted cyclobutanol 95 for further elaboration (Scheme 1.3.3.1).
Scheme 1.3.3.1 White’s retrosynthesis of Providencin (1)

Synthesis of the furanoside 94 commenced with the four-step synthesis of the known alcohol 97 (Scheme 1.3.3.2). This alcohol was PMB-protected and the exo-cyclic acetonide was selectively removed. Reaction of diol 98 with iodine, triphenylphosphine and imidazole furnished the 2-vinyltetrahydrofuran 99. Subsequent methanolysis of the acetonide and TBS-protection of remaining alcohol gave the desired furanoside 94.

Scheme 1.3.3.2 White’s synthesis of furanoside 94
Treatment of furanoside 94 with in situ generated dicyclopentadienylzirconium gave the desired cyclobutanol 95 in 86% yield with complete retention of stereochemistry (Scheme 1.3.3.3). The secondary alcohol was protected as its silyl-ether and subsequent Wacker-oxidation yielded methyl ketone 100. Deprotonation of 100 and treatment with methyl cyanoformate furnished β-ketoester 101. Treatment of 101 with glyceraldehyde acetonide 102 and PPTS resulted in Knoevenagel condensation, followed by deprotection and cyclization give cyclobutyl furan 103. Oxidation with TPAP gave an aldehyde, which was subjected to HWE-olefination and gave a 2.5:1 mixture of E:Z of olefins 105. White reported that work is currently underway to elaborate cyclobutyl furan 105 to 1.

Scheme 1.3.3.3 White’s synthesis of 3-fur-2-yl-cyclobutanone 105
1.4 Previous Wood Group Efforts

1.4.1 First Generation Efforts

The Wood group effort towards the synthesis of 1 began shortly after its isolation in 2003.\textsuperscript{21} The original retrosynthetic analysis calls for introduction of the exo-methylene and epoxides moieties at a late stage in the synthesis to avoid carrying these potentially sensitive moieties through many steps (Scheme 1.4.1.1). We anticipated that rigidity of macrocycle 110 would direct the epoxidations. The trisubstituted olefin was seen as arising from the methylation of a vinyl triflate generated from β-ketofuran 109. The cyclization of enol 108 via Marshall’s protocol would yield the desired β-ketofuran 109. Allylic oxidation of 107 followed by lactonization and enolization could generate the furan precursor 108. Homologation of cyclobutane 106 and RCM would furnish the macrocyclic core of 1.
Scheme 1.4.1.1 Our original retrosynthetic approach to Providencin (1)

Our first synthetic efforts focused on preparing cyclobutane 106 (Scheme 1.4.1.2). In addition to the trans-ring fusion, the cyclobutane moiety of 1 contains both alcohol and exo-methylene moieties. Accordingly the design of cyclobutane 106 accounts for the trans-stereochemistry at C1 and C2 and incorporation of functional groups poised for further elaboration. We chose to pursue a [2 + 2] cycloaddition for generating the cyclobutane after finding a patent that described the aluminum-promoted [2 + 2] cycloaddition of ethyl ketene acetal (111) and diethylfumarate (112). This reaction could be preformed on multigram scale and in good yield. Furthermore, Bisacchi and co-workers demonstrated that cyclobutane 113 could be resolved via the crystallization of the bis-amide derivatives 114.
Scheme 1.4.1.2 Lewis Acid promoted [2 + 2] cycloaddition

Reduction of diester 113 followed by diol protection and acetal removal furnished cyclobutanone 115 (Scheme 1.4.1.3). Advancement of 115 via formylation was accomplished using triethyl orthoformate in the presence of i-Pr₂NEt and BF₃•OEt₂, thus establishing the requisite trans-relationship at C1 and C2. Diastereoselective reduction of the ketone 116 from the least hindered side of the cyclobutanone followed by acylation of the resultant alcohol gave intermediate 117. The benzyl-protecting groups were oxidized to benzoyl-protecting groups to facilitate more facile removal and the diethylacetal was subsequently replaced with a dithiane yielding 119. The two benzoates and the acetate were concomitantly removed. The resultant triol was selectively protected by introduction of an acetonide on the 1,3-diol and protection of the remaining alcohol as its silyl ether. Dithiane 120 was converted to the corresponding aldehyde 106 by treatment with methyl iodide in aqueous base conditions. This sequence delivered a cyclobutane possessing an array of differentiable functional groups with the relative stereochemistry found in 1.
Scheme 1.4.1.3 Elaboration of cyclobutane 113

1. LAH, THF, 0 °C to rt
2. NaH, BnBr, DMF
3. H₂SO₄, CH₃CN
   (51% yield, three steps)

113 → 115

(EtO)₂CH, BF₃·OEt₂, i-Pr₂NEt, CH₂Cl₂, –78 °C
   (90% yield)

1. L-Selectride,
   THF, –78 °C to rt
2. Ac₂O, Py
   (85% yield, two steps)

116 → 117

RuO₂⋅H₂O, NaIO₄
2:3:2 CCl₄·H₂O·CH₃CN
   (66–90% yield)

118 → 119

1. NaOCH₂, CH₃OH, 65 °C
2. MeO·OMe, PPTS, CH₂Cl₂
3. TES-Cl, Et₃N,
   DMAP, CH₂Cl₂
   (45% yield, three steps)

120 → 106

Unfortunately, attempts to effect an aldol reaction between aldehyde 106 and methyl propionate 121 or a more functionalized ester 123 were ineffective (Scheme 1.4.1.4). A screen of various bases and conditions for quenching the reaction failed to produce any desired product. Starting material 106 was the only compound recovered after work-up of these reactions.
Scheme 1.4.1.4 Attempted aldol reactions

Our attention turned towards an approach emphasizing a Reformatsky reaction. A model system, utilizing α-bromo-methylpropionate 125, was used to test the feasibility of this reaction with aldehyde 106 (Scheme 1.4.1.5). Under standard Reformatsky conditions a small amount of desired product was obtained; however, no starting material was recovered. Application of milder reaction conditions failed to produce any desired product (Scheme 1.4.1.5, eq 2).

Scheme 1.4.1.5 Attempted Reformatsky reactions
In a final attempt to utilize aldehyde 106, we attempted a Roskamp reaction to produce the corresponding β-ketoester. Treatment of aldehyde 106 with ethyl diazoacetate and catalytic tin chloride yielded the desired β-ketoester 129 in modest yield (Scheme 1.4.1.6). However, attempts to alkylate β-ketoester 129 with propargyl iodide 130 or other electrophiles were unsuccessful under a variety of alkylation conditions. In most cases the β-ketoester 129 decomposed under the reaction conditions. Due to the difficulties encountered with the homologation of aldehyde 106, we elected to revise our retrosynthetic approach.

**Scheme 1.4.1.6 Attempted alkylation of β-ketoester 129**

1.4.2 Second Generation Efforts

Upon review of our previous work we decided to pursue a course that would involve the acylation of a cyclobutanone 115 with a malonyl chloride 132 (Scheme 1.4.2.1). The macrocycle 134 would result from the homologation of 133 and subsequent RCM. The trisubstituted olefin precursor 135 could be obtained after furan cyclization and introduction of the butenolide. This retrosynthesis would then intercept the previously outlined retrosynthetic approach (Scheme 1.4.1.1).
Scheme 1.4.2.1 Our second retrosynthetic approach to Providencin (1)

1. Epoxidation
2. Exo-methylene

1. Furan
2. Butenolide

1. Homologation
2. RCM

The synthesis of a malonyl chloride coupling partner 132 began with propargyl chloride 136 (Scheme 1.4.2.2). Deprotonation of propargyl chloride 136 was followed by treatment with 4-pentenal 137, and subsequent TBS-protection furnished propargyl silyl ether 138. Alkylation of dimethyl malonate 139 with propargyl chloride 138 followed by mono-hydrolysis yielded acid 140, which was readily converted to the corresponding acid chloride 141. Deprotonation of cyclobutanone 115 by LiHMDS followed by treatment with acid chloride 141 gave the functionalized cyclobutanone 142 in moderate yield. The relative trans-stereochemistry of the substituents on the C1 and C2 positions was achieved by approach of the electrophile from the opposite face of the substituent on C1.
Scheme 1.4.2.2 Acylation of cyclobutanone 115

With substrate 142 in hand, we next attempted furan cyclization using Marshall’s protocol. The TBS-protecting group was removed and the alcohol oxidized to give the alkynone 144 (Scheme 1.4.2.3). Unfortunately, all attempts to cyclize 144 to the furan under acidic conditions failed. Treatment of alkynone 144 under basic conditions resulted in cleavage to give cyclobutanone 115 and β-ketoester 146 fragments.
Scheme 1.4.2.3 Attempted furan cyclization

Concerned that the ester group was interfering with furan cyclization we prepared alkynone 147. Attempts to cyclize alkynone 147 were also unsuccessful. In contrast to 144, alkynone 147 proved stable but still unreactive to both acidic and basic conditions (Scheme 1.4.2.4). Despite these setbacks, we still hoped that the furan cyclization would be feasible on a substrate in which the macrocycle was already in place as demonstrated in the synthesis of (-)-deoxypukalide (20) (Scheme 1.2.1.2).

Scheme 1.4.2.4 Attempted furan cyclization

Given our success with the acylation of cyclobutane 115, we embarked upon the synthesis of a cyclobutane 149 and acid chloride 150 for use in the acylation
reaction (Scheme 1.4.2.5). Each was appended with an alkene and subsequent to acylation could undergo a RCM to furnish the macrocyclic core of 1.

**Scheme 1.4.2.5** Our third retrosynthetic approach to Providencin (1)

![Scheme Image]

The synthesis of the cyclobutane fragment 149 began with the previously synthesized diol 152 (Scheme 1.4.2.6). Mono-protection followed by oxidation gave aldehyde 153. A Wittig olefination and subsequent selective deprotection furnished aldehyde 154. The allylic alcohol 155 was obtained as a 1:1 mixture of diastereomers by treatment of 154 with propenyl magnesium bromide. Protection of the secondary alcohol and removal of the acetal provided the cyclobutanone coupling partner 149.
Scheme 1.4.2.6 Synthesis of cyclobutanone 149

Synthesis of the acid chloride coupling partner commenced with the PMB-protection of α-hydroxybutyrolactone 156 and subsequent reduction to the lactol 158 (Scheme 1.4.2.7). Methenylation of the lactol under Wittig conditions gave the primary alcohol that was subsequently oxidized to aldehyde 159.

Scheme 1.4.2.7 Synthesis of aldehyde 159

To complete the preparation of acid chloride coupling partner 150, aldehyde 159 was treated with deprotonated propargyl chloride 136 to yield a secondary alcohol that was subsequently protected as its silyl ether 160 (Scheme 1.4.2.8). Alkylation of dimethyl malonate 139 with propargyl chloride 160 and mono-hydrolysis of the resultant ester provided acid 161. Conversion to acid chloride 150 was accomplished through treatment of acid 161 with thionyl chloride. With both coupling partners in hand we set out to synthesize the macrocyclic core of 1.
Scheme 1.4.2.8 Synthesis of acid chloride 150

Our first attempt toward the coupling via acylation of cyclobutanolone 134 with the acid chloride 140 generated from 139 met with limited success under a wide variety of conditions (Scheme 1.4.2.9). As an alternative to the acylation we attempted to couple the dimethyl malonate intermediate 162 and the cyclobutanone 149 via cross-metathesis. We were unsuccessful, even when the alkyne was protected as its cobalt hexacarbonyl complex. Under the reaction conditions the malonate 162 began to decompose but cyclobutanone 149 was recovered unchanged.
Scheme 1.4.2.9 Attempted coupling of 149 and 150

Given our failed attempts at coupling fragments 149 and 150 through acylation or 149 and 162 via cross-metathesis, we considered a new approach. In this instance, two fragments acid 164 and alcohol 165 could be coupled through an esterification reaction and a subsequent RCM would provide butenolide 166 (Scheme 1.4.2.10).

Scheme 1.4.2.10 Our fourth retrosynthetic approach to Providencin (1)
This sequence of esterification and RCM was tested on a simplified system wherein the previously prepared malonate 162 was used as a starting point (Scheme 1.4.2.11). Removal of the PMB-protecting group and subsequent acylation with acryloyl chloride furnished diene 168. To prevent enyne-metathesis the alkyne was protected as its cobalt hexacarbonyl complex. Treatment with Grubbs 2nd generation catalyst in a sealed tube was followed by deprotection of the alkyne to give butenolide 169.

**Scheme 1.4.2.11 Esterification/RCM approach to butenolide 169**

Next we attempted to synthesize an appropriate coupling partner for the esterification and RCM sequence. Unfortunately, all attempts to elaborate aldehyde 155 using Baylis-Hillman, Nozaki-Hiyama-Kishi, and Grignard conditions were unsuccessful. Thus, without the necessary coupling partner 174 the esterification and RCM transformation could not be realized (Scheme 1.4.2.12).
1.5 Conclusions

This chapter describes the isolation and properties of the highly oxygenated diterpene providencin 1. Related compounds, synthesis of relevant moieties, and other groups’ synthetic work toward the synthesis of 1 have also been discussed. In addition, our initial efforts toward the synthesis of this novel natural product have been reviewed.

We have demonstrated that a [2 + 2] cycloaddition is a powerful way to access functionalized cyclobutanes. However, homologation of our initial cyclobutane substrates was less efficient than hoped. We also observed a difficulty with the generation of furans from keto-alkynones in our system. Additionally, we have shown that cyclobutanones can be acylated in some instances, although this transformation failed to yield the desired product when more elaborate substrates were employed. Our inability to effect the coupling of advanced intermediates through acylation and cross-metathesis led us to consider esterification as an alternative means of coupling advanced intermediates. While we have successfully synthesized some advanced intermediates towards the total synthesis of providencin 1, our failure to achieve the synthesis of the macrocyclic core of providencin caused us to review our approach to this molecule. Further efforts toward our goal will be outlined in the following chapters.
1.6 References


Chapter 2

Construction of the Cyclobutyl Furan

2.1 Synthesis of Cyclobutanes

The trans-fused cyclobutanol moiety of providencin (1) is the most distinctive feature of this unprecedented [12.2.0]hexadecane ring system. It is, therefore, unsurprising that the major focus of synthetic efforts, including our own, towards 1 have focused on this aspect of the molecule. In general there are five major approaches to cyclobutane synthesis: [3 + 1] annulation, ring expansion, ring contraction, acyclic cyclization and [2 + 2] cycloadditions. The relative merits of each approach will be briefly discussed, with particular emphasis on our chosen approach, [2 + 2] cycloaddition.

2.1.1 [3 + 1] Annulation Reactions

The condensation of diethyl malonate with 1,3-dibromopropane was one of the earliest examples of cyclobutane synthesis.¹ This method is sometimes still used to synthesize cyclobutanes, as demonstrated by Christie and Pritchard, et al. and Johnson, et al. in their syntheses of 1,1-diester-cyclobutanes (Scheme 2.1.1.1).² However, this approach suffers from several disadvantages, including: a lack of stereo-control, possible
Epimerization of stereocenters under basic reaction conditions, and the potential for oligomerization.

**Scheme 2.1.1.1** [3 + 1] Annulation reaction with 1,3-dibromo compounds

**Christie and Pritchard:**

\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
\text{Ph} & \quad \text{MeO} \quad \text{CO} \quad \text{OMe} \\
\end{align*}
\]

\[
\begin{align*}
175 & \quad + \quad 139 \\
\rightarrow & \quad \text{Ph} \quad \text{MeO} \quad \text{CO} \quad \text{OMe} \\
176 & \\
\text{i. NaH, THF, 0 °C, 1 h} \\
\text{ii. 65 °C, 6 h} \\
(74\% \text{ yield})
\end{align*}
\]

**Johnson:**

\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
\text{Ph} & \quad \text{MeO} \quad \text{CO} \quad \text{OMe} \\
\end{align*}
\]

\[
\begin{align*}
177 & \quad + \quad 139 \\
\rightarrow & \quad \text{MeO} \quad \text{CO} \quad \text{OMe} \\
178 & \\
\text{NaH, dioxane, 100 °C} \\
(54\% \text{ yield})
\end{align*}
\]

Recently, de Meijere and co-workers demonstrated the synthesis of cyclobutanones via a [3 + 1] cyclization of methylenecyclopropanes with carbon monoxide (Scheme 2.1.1.2).\(^3\) Treatment of an exo-methylene cyclopropane 179 with octacarbonyl dicobalt under an atmosphere of carbon monoxide provided a regioisomeric mixture of exo-methylene cyclobutanones 180. While this is a unique approach to the synthesis of substituted cyclobutanes the yields and regioselectivities were often modest, and we felt the reaction scope was too limiting prompting us to consider alternative methods for accessing cyclobutane substrates.

**Scheme 2.1.1.2** [3 + 1] Cyclization of methylenecyclopropanes and carbon monoxide

\[
\begin{align*}
179 & \quad \xrightarrow{[\text{Co}_2(\text{CO})_8]} \quad \text{Ph} \quad \text{MeO} \quad \text{CO} \quad \text{OMe} \\
\text{THF, 60 °C, 12 h} \\
(90\% \text{ yield}) & \quad \rightarrow \\
180 & \quad \downarrow \\
& \quad 180 \ a \quad 85 : 15 \\
& \quad 180 \ b
\end{align*}
\]
2.1.2 Ring Expansion Reactions

The ring expansion of cyclopropanes is a second approach for the synthesis of cyclobutanes. One example of this is the conversion of an alkylidene-cyclopropane to a cyclobutanone.\(^1\) Treatment of cyclopropane 181 with \(m\)CPBA generated an intermediate epoxide in situ which then underwent a ring expansion to give cyclobutanone 182 (Scheme 2.1.2.1).

**Scheme 2.1.2.1** Ring expansion of epoxidized alkylidene-cyclopropanes

\[
\text{HO-CH=CH-C=CH} \quad \xrightarrow{m\text{CPBA, CH}_2\text{Cl}_2 (52\% \text{ yield})} \quad \text{[Epoxide]} \quad \rightarrow \quad \text{HO-CH=CH-C=O}
\]

Chiral cyclobutanones can be accessed through the use of an enantioselective epoxidation method, such as the Sharpless method. Cyclopropane ring expansion reactions can also be diastereoselective when chiral cyclopropane starting materials are employed. Hussain et al. have shown that treatment of a cyclopropanol 183 with a Lewis acid furnished primarily the \(cis\)-isomer of cyclobutanone 184 a (Scheme 2.1.2.2).\(^4\) The \(trans\)-isomer 184 b was obtained by treating the same cyclopropanol with a Brönsted acid. The stereodivergence was proposed to arise from an epimerization of the product via enol formation under the protic acid conditions. While such methods can be useful in the synthesis of cyclobutanes, the nontrivial synthesis of hydroxy-cyclopropane substrates makes this approach less attractive.
2.1.3 Ring Contraction Reactions

A third approach to cyclobutane synthesis, the ring contraction reactions of cyclopentanes and tetrahydropyrans is less widely used than other methods. Ring contraction of cyclopentane substrates generally involves a Wolff rearrangement, a Favorskii rearrangement, a Wagner-Meerwein rearrangement or a photodecarbonylation. Such reactions are not generally useful for the synthesis of enantiomerically pure cyclobutanes unless the starting material is readily accessible from a chiral pool approach. The ring contraction of furanose-derived tetrahydrofurans allows for a more general approach toward the synthesis of chiral cyclobutanols and has the advantage of the retention of stereochemistry during the ring contraction reaction.

Taguchi et al. were among the first to show that ring contractions of tetrahydrofurans furnished cyclobutanols with good diastereoselectivity. As described vide supra, White and co-workers have used a zirconium-mediated ring contraction reaction to convert tetrahydrofuran 94 to cyclobutanol 95 in good yield and with retention of stereochemistry (Scheme 2.1.3.1). The enantiopure tetrahydrofuran was synthesized in eight steps from glucose.
Scheme 2.1.3.1 Ring contraction of tetrahydrofuran 94

\[
\begin{align*}
\text{Scheme 2.1.3.1 Ring contraction of tetrahydrofuran 94} \\
\text{Cp}_2\text{ZrCl}_2, n\text{-BuLi} \rightleftharpoons \text{BF}_3\text{OEt}_2, -78^\circ \text{C} (86\% \text{ yield}) \\
\end{align*}
\]

2.1.4 Cyclization of Acyclic Substrates

A fourth method to generate cyclobutanes utilizes ionic or radical cyclization of acyclic substrates. Unfortunately, such reactions generally result in the stereochemical equilibration of the reacting centers. However, the stereochemistry at the non-reacting centers of the cyclobutane is generally conserved. One variation of acyclic cyclization is the Norrish-Yang photocyclization. In this reaction a carbonyl with a γ-hydrogen can react to form a cyclobutanol. Abstraction of the γ-hydrogen by the excited carbonyl yields a diradical intermediate that can undergo either fragmentation or cyclization (Scheme 2.1.4.1).

Scheme 2.1.4.1 Norrish-Yang photocyclization

\[
\begin{align*}
\text{Scheme 2.1.4.1 Norrish-Yang photocyclization} \\
\end{align*}
\]

Pattenden and co-workers have utilized this radical cyclization reaction to generate an exo-methylene cyclobutanol such as the one found in 1 (Scheme 2.1.4.2). While it is possible to synthesize chiral cyclobutans from compounds that possess chiral centers at the 2- and/or 3-positions via this method it is not generally applicable. The potential for fragmentation products and other side reactions limits the general utility of this transformation.
2.1.5 [2 + 2] Cycloaddition Reactions

The [2 + 2] cycloaddition reaction is arguably the most widely employed method for the synthesis of cyclobutane substrates. The photochemical [2 + 2] cycloaddition is allowed based on orbital symmetry considerations; however, such reactions are generally not regio- or stereoselective. The thermal [2 + 2] cycloaddition of alkenes is forbidden by orbital symmetry considerations. Formal thermal [2 + 2] cycloadditions, generally referred to simply as [2 + 2] cycloadditions, proceed via intermediates which are sufficiently long lived to undergo stereochemical equilibration and are typically not regioselective. However, methods involving the [2 + 2] cycloaddition reaction of alkenes with ketenes and ketene equivalents circumvent both the regio- and stereochemical issues. While such reactions proceed via an asynchornous mechanism, the reactive intermediates are suitably short-lived, thus allowing the alkene-configuration to be retained in the cyclobutanone substrate. Ketene-alkene cycloaddition reactions proceed regioselectively with the more nucleophilic carbon of the alkene adding to the carbonyl carbon of the ketene. One widely used substituted-ketene is dichloroketene (191). Dichloroketene (191) is widely used as a ketene surrogate due to its higher reactivity compared to the parent ketene. Furthermore, reduction of the 2,2-dichlorocyclobutanone 192 provides the corresponding saturated cyclobutanone product 193 (Scheme 2.1.5.1).
Another alternative to a traditional [2 + 2] cycloaddition is a Lewis acid-promoted [2 + 2] cycloaddition reaction between an electron deficient alkene and an electron rich alkene (Scheme 2.1.5.2). One such example is the Lewis acid-promoted cycloaddition of diethyl fumarate (112) and ketene diethylacetal (111) that has been previously used by our group in earlier work towards the synthesis of 1 (Scheme 1.4.1.2).

Scheme 2.1.5.2 [2 + 2] cycloaddition of (111) and (112)

2.2 Ketene Cycloadditions Towards the Synthesis of Providencin

2.2.1 Methylene Ketene

The [2 + 2] cycloaddition reaction allows the rapid buildup of molecular complexity and is therefore an attractive strategy for cyclobutane synthesis. We postulated it might be possible to introduce both the exo-methylene and oxygen moieties of the cyclobutane in one step via a [2 + 2] cycloaddition; thus methylene ketene (195) would be an ideal coupling partner (Scheme 2.2.1.1). However, methylene ketene (195) is difficult to generate and is so reactive that only dimers and oligomers of it have ever
been observed. To date, no [2 + 2] cycloaddition between methylene ketene (195) and an alkene has been observed.

**Scheme 2.2.1.1** [2 + 2] cycloaddition of methylene ketene (195) and an alkene

\[
\begin{array}{c}
194 \quad R'R' \\
\text{methylene ketene} \\
(195) \\
\hline
R \quad H \quad H \\
\end{array}
\rightarrow
\begin{array}{c}
196 \\
\end{array}
\]

Paquette and co-workers reported chloro[(trimethylsilyl)methyl]ketene 198 as a substitute for the elusive methylene ketene (195).\(^{12}\) They demonstrated that chloro[(trimethylsilyl)methyl]ketene 198 could be generated via dehydrohalogenation of α-chloro acid chloride 197, which could then undergo the [2 + 2] cycloaddition with dihydropyran 199 to provide cyclobutanone 200. Subsequent TBAF-mediated elimination gave exomethylene cyclobutanone 201 in modest yield (Scheme 2.2.1.2).

**Scheme 2.2.1.2** Chloro[(trimethylsilyl)methyl]ketene as a methylene ketene equivalent

\[
\begin{array}{c}
\text{Cl} \quad \text{Cl} \\
197 \quad \text{Cl} \quad \text{TMS} \\
\text{Et}_3 \text{N} \\
pentane \\
\hline
\end{array}
\rightarrow
\begin{array}{c}
199 \\
\end{array}
\]

\[
\begin{array}{c}
\text{Cl} \quad \text{Cl} \\
198 \quad \text{TMS} \\
pentane \quad 0 \degree \text{C} \\
(93\% \text{ yield}) \\
\hline
200 \\
\text{Cl} \quad \text{TMS} \\
\text{TBAF} \quad \text{DMSO, } 20 \degree \text{C} \\
(30\% \text{ yield}) \\
\hline
201 \\
\end{array}
\]

We were intrigued by the potential of such a reaction toward the synthesis of providencin (1). The use of chloro[(trimethylsilyl)methyl]ketene 198 toward the synthesis of 1 could allow for the introduction of the cyclobutane on an advanced
intermediate, perhaps one with the furan and/or macrocycle already in place. To further investigate the [2 + 2] cycloaddition between a 2-vinylfuran and a ketene, we employed the more accessible dichloroketene (191) and hoped with this substrate to establish the regiochemical preference upon the reaction between a furyl alkene and a ketene (Scheme 2.2.1.3).

**Scheme 2.2.1.3** Regiochemical outcome of [2 + 2] cycloaddition of 202 and 198

![Chemical structure](image)

**2.2.2** **Dichloroketene**

Dichloroketene (191) is one of the most widely used ketenes and has proven particularly useful when applied in [2 + 2] cycloaddition reactions.\(^\text{10}\) Dichloroketene (191) must be generated in situ, and in the presence of the alkene with which it is to be reacted to prevent ketene dimerization. The two primary methods for generating 191 are dehydrohalogenation of dichloroacetyl chloride (205) using triethylamine or dehalogenation of trichloroacetyl chloride (206) using activated zinc (Scheme 2.2.1.1).\(^\text{13}\) We chose the latter method because the reagents are commercially available, relatively inexpensive and this method is more widely used.\(^\text{10}\)

**Scheme 2.2.1.1** Synthesis of dichloroketene (191)
First we prepared a test substrate vinylfuran 209. Wittig olefination of hexyltriphenylphosphonium bromide (207) with furfural (208) provided furyl alkene 209 (Scheme 2.2.1.2). Alkene 209 was treated with dichloroketene (191), generated in situ by reduction of trichloroacetyl chloride (206) with zinc. This indeed resulted in formation of a cyclobutanone 210. However, the cyclobutanone proved to be unstable and it underwent decomposition upon exposure to silica gel.

Scheme 2.2.1.2 [2 + 2] Cycloaddition of furyl alkene 209 and dichloroketene (191)

We postulated that reduction of the dichloride might furnish a more stable cyclobutanone. Thus, after completion of the [2 + 2] cycloaddition, 3% NH₄Cl in methanol was added the reaction mixture and the resultant solution brought to reflux for an additional 15 minutes (Scheme 2.2.1.3). Upon work-up, we were able to isolate a mono-chloro cyclobutanone product 211 that was more stable than the dichlorocyclobutanone 210, however its propensity toward decomposition on silica was problematic.
**Scheme 2.2.1.3** [2 + 2] Cycloaddition and in situ reduction

In spite of the instability of these compounds we were able to confirm the formation of a [2 + 2] product and the regiochemical outcome through NMR studies. This analysis confirmed the presence of 3-furylcyclobutanone 211 wherein the furan and ketone are 1,3-disposed (Scheme 2.2.1.3). Given that our plan for preparing 1 called for a [2 + 2] cycloaddition between a vinylfuran 202 and chloro[(trimethylsilyl)methyl]-ketene 198 to generate a 2-furylcyclobutanone 203 (Scheme 2.2.1.4), we were disappointed by the observed regiochemical outcome.

**Scheme 2.2.1.4** Regiochemical outcome of proposed [2 + 2] cycloaddition

However, the successful preparation of 3-furylcyclobutanone 211 inspired an alternative approach to the synthesis of the cyclobutyl furan portion of 1. Thus, we now envisioned that cycloaddition between vinylfuran 202 and dichloroketene (191) could yield 3-furylcyclobutanone 212 which could then undergo olefination to furnish an exo-methylene cyclobutane 213 (Scheme 2.2.2.5). Subsequent installation of the alcohol would provide the furyl cyclobutanol portion of 1.
**Scheme 2.2.2.5 Proposed synthesis of an exo-methylene cyclobutanol**

![Scheme 2.2.2.5 Proposed synthesis of an exo-methylene cyclobutanol](image)

**2.3 Functionalized Furans**

Having decided to utilize the [2 + 2] reaction with dichloroketene to synthesize the cyclobutyl furan moiety in providencin, we developed a new retrosynthetic approach (Scheme 2.3.1). As illustrated, the revised plan again calls for introduction of the epoxide moieties at a late stage in the synthesis. Macrolactonization and subsequent RCM would provide the butenolide-containing macrocyclic core 218 of 1. The macrolactonization precursor 217 would arise from elaboration of cyclobutyl furan 216. A [2 + 2] cycloaddition of dichloroketene (191) with alkenyl furan 215 would provide cyclobutanone 216. Thus, our primary efforts focused on constructing a vinyl furan substrate 215 on which to effect the [2 + 2] cycloaddition. This furan 215 would possess the appropriate ester functionality and a handle at C-5 of the furan for further elaboration.
Scheme 2.3.1 Retrosynthetic approach to Providencin (1) utilizing [2 + 2] cycloaddition

2.3.1 Alkynone Cyclization to Furnish Furans

We began by investigating the synthesis of 2,3,5-trisubstituted furans. We initially intended to use the cyclization of an alkynone 221 to access a fully functionalized furan 222. The alkynone 221 would be the result of an alkylation of a β-ketoester 220 (Scheme 2.3.1.1).

Scheme 2.3.1.1 Retrosynthetic approach to the synthesis of furan 222

Our synthesis of β-ketoester 220 began with the protection of 3-buten-1-ol 223 as its THP-ether (Scheme 2.3.1.2). Ozonolysis of the alkene, followed by olefination...
furnished α,β-unsaturated ester 225. A reduction/oxidation sequence provided aldehyde 226. Aldol reaction of methyl acetate and aldehyde 226 gave an allylic alcohol that was directly oxidized to yield β-ketoester 220.

**Scheme 2.3.1.2 Synthesis of β-ketoester 220**

![Scheme 2.3.1.2](image)

The propargyl iodide coupling partner was synthesized in three steps from 2-butyn-1,4-diol 227 (Scheme 2.3.1.3). The diol was mono-protected as its silyl ether 228 and the remaining alcohol was converted to the iodide via the mesylate 229 to provide propargyl iodide 219.

**Scheme 2.3.1.3 Synthesis of propargyl iodide 219**

![Scheme 2.3.1.3](image)

Attempts to mono-alkylate β-ketoester 220 with iodide 219 were unsuccessful. Initial attempts yielded primarily bis-alkylated product 230, along with recovered iodide and decomposition products (Scheme 2.3.1.4). Even when a substoichiometric amount of
iodide was used, the bis-alkylation product still predominated. Attempts to alkylate \( \beta \)-ketoester 220 with the iodide 219 derived from the mesylate 229 in situ, resulted in decomposition of 220. Attempts to utilize KO\( \text{t-Bu} \) instead of NaH or to change the order of addition also resulted in decomposition of \( \beta \)-ketoester 220. The difficulties with the alkylation reaction, coupled with our previous difficulties with alkynone cyclization (Scheme 1.4.2.3), led us to reevaluate our approach to the furyl alkene.

**Scheme 2.3.1.4 Alkylation of 220 with 219**

![Scheme 2.3.1.4 Alkylation of 220 with 219](image)

2.3.2 Paal–Knorr Synthesis of Furans

Our next attempt at the furyl alkene employed a more commonly used method for the synthesis of furans: the acid-catalyzed cyclization of 1,4-dicarbonyls, known as the Paal-Knorr furan synthesis.\(^{14}\) We envisioned converting the \( \beta \)-ketoester 220 (or a similar \( \beta \)-ketoester) to a 1,4-diketone 231. Subsequent cyclization of the 1,4-diketone 231 would provide the furan 232 (Scheme 2.3.2.1).

**Scheme 2.3.2.1 Revised retrosynthetic approach to furyl alkene**

![Scheme 2.3.2.1 Revised retrosynthetic approach to furyl alkene](image)
We began to investigate the synthesis of 1,4-diketones such as \textbf{231} and were most interested in methods that would utilize previously prepared \(\beta\)-ketoester \textbf{220} as substrate and provide products with the 5-position of the furan poised for further elaboration.

One such method is the addition of ketones to vinylic acetates in the presence of one-electron oxidants. Heiba and Dessau have demonstrated the synthesis of 1,4-diketones from the reaction of a ketone and isopropenyl acetate \textbf{234} in the presence of manganic acetate (Scheme 2.3.2.2).\textsuperscript{15} Unfortunately, these reactions showed low yields and poor selectivity when applied to 2-alkanones.

\textbf{Scheme 2.3.2.2} Heiba and Dessau synthesis of 1,4-diketones

\[
\begin{align*}
\text{Scheme 2.3.2.2} \quad & \quad \text{Heiba and Dessau synthesis of 1,4-diketones} \\
& \quad \text{Baciocchi and Ruzziconi et al. greatly expanded the scope and utility of this reaction by replacing the manganic acetate with cerium(IV) ammonium nitrate (CAN) (Scheme 2.3.2.3).}\textsuperscript{16} \quad \text{Yields and regioselectivity were significantly improved with the addition occurring primarily at the more substituted position of the 2-alkanone. Malonates were also successfully converted to 1,4-dicarbonyl compounds. They also demonstrated that vinyl acetate \textbf{240} could be used in place of isopropenyl acetate \textbf{234} to obtain 4-keto dimethylacetals such as \textbf{241}.}
\end{align*}
\]

\[
\begin{align*}
\text{Mn(OAc)}_{26} \quad \text{AcOH} \quad \text{(22\% yield)}
\end{align*}
\]
Scheme 2.3.2.3 Baciocchi and Ruzziconi synthesis of 1,4-dicarbonyls

\[
\begin{align*}
\text{O} & \quad \text{O} \\
236 & \quad + \quad 234 \\
\text{i. CAN, MeOH, rt} & \quad \text{ii. NaHCO}_3, \text{H}_2\text{O, 40 ºC} \\
\text{(78% yield)} & \\
\text{O} & \quad \text{O} \\
237 & \end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
139 & \quad + \quad 234 \\
\text{i. CAN, MeOH, rt} & \quad \text{ii. NaHCO}_3, \text{H}_2\text{O, 40 ºC} \\
\text{(82% yield)} & \\
\text{O} & \quad \text{O} \\
238 & \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
239 & \quad + \quad 240 \\
\text{i. CAN, MeOH, rt} & \quad \text{ii. NaHCO}_3, \text{CH}_3\text{OH, 40 ºC} \\
\text{(69% yield)} & \\
\text{O} & \quad \text{O} \\
241 & \\
\end{align*}
\]

In a further extension of this chemistry, Baciocchi and Ruzziconi have demonstrated the possibility of accessing furan substrates 243 from 1,3-dicarbonyls 242 and isopropenyl acetates 234 (Scheme 2.3.2.4).\(^{16b}\) The initial CAN reaction gave a dihydrofuran that subsequently underwent elimination to the furan upon heating with PPTS. By changing either the 1,3-dicarbonyl or the vinyl substrates they were able to access 3-substituted, 2,3-disubstitued, 2,3,4-trisubstitued or 2,3,5-trisubstitued furans.

Scheme 2.3.2.4 Synthesis of 2,3,5-trisubstituted furan 243

\[
\begin{align*}
\text{O} & \quad \text{O} \\
242 & \quad + \quad 234 \\
\text{1. CAN, CH}_3\text{CN} & \quad \text{2. NaHCO}_3, \text{CH}_3\text{CN} \\
\text{3. PPTS, toluene, 110 ºC} & \quad \text{(81% yield)} \\
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
243 & \\
\end{align*}
\]

Based on these precedents we envisioned accessing a 2,3,5-trisubstituted furan, with an ester at the 3-position, utilizing the oxidative coupling chemistry (Scheme 2.3.2.5). We sought to demonstrate that a β-ketoester 244 and a vinyl acetate 245 could
be reacted under conditions similar to those of Baciocchi and Ruzziconi to furnish a 2,3,5-trisubstituted furan 246.

**Scheme 2.3.2.5 Proposed synthesis of 2,3,5-trisubstituted furan 246**

Towards this end, CAN was added to a methanolic solution of methyl acetoacetate 247 and isopropenyl acetate 234 at room temperature (Scheme 2.3.2.6). This mixture was then treated with aqueous sodium bicarbonate and heated to 40 °C for two hours. Upon work-up and purification three products were identified: furan 248, dihydrofuran 249 and 1,4-diketone 250. To our satisfaction we also found that heating the reaction to reflux overnight provided furan 248 as the primary product.

**Scheme 2.3.2.6 Synthesis of 2,3,5-trisubstituted furan 248**

Having prepared a 2,3,5-trisubstituted furan using a β-ketoester 247 and isopropenyl acetate 234, we set out to investigate the reaction using more functionalized substrates. Unfortunately, attempts to effect the transformation on our previously synthesized β-ketoester 220 only resulted in a trace amount of furan lacking the THP-
protecting group 251 (Scheme 2.3.2.7). Attempting the reaction on the free alcohol 252 a or the TBS-protected alcohol 252 b resulted in no furan products and decomposition of the starting materials.

**Scheme 2.3.2.7** Attempted synthesis of furyl alkenes

As an alternative we attempted to incorporate vinyl carbonate and vinyl ether substrates into the oxidative coupling reaction. In the event, reaction of known compounds 254 and 256 with methyl acetoacetate 247 in the presence of CAN did not result in the formation of any addition or furan products.\(^\text{17}\) The vinyl substrates were found to decompose under the reaction conditions (Scheme 2.3.2.8).

**Scheme 2.3.2.8** Attempted synthesis of alternatively substituted furans
In summary, we have demonstrated the feasibility of the synthesis of 2,3,5-trisubstituted furans from simple substrates via the oxidative coupling between β-ketoester 247 and isopropenyl acetate 234. However, we were unable to effect the same transformation on more highly functionalized β-ketoesters and vinyl ethers. Thus we chose to investigate an alternative approach to access the alkenyl furan substrate 232.

2.3.3 A Feist-Bénary Approach to Synthesis of Functionalized Furans

Another classic method for the synthesis of poly-substituted furans is the Feist-Bénary reaction. A generic Feist-Bénary reaction involves the synthesis of furans through the reaction of β-ketoesters and α-halo carbonyl compounds. This approach would allow for access to a highly functionalized furan 246 from a β-ketoester 244 and α-halo aldehyde 258. Elaboration of furan substrate 246 could furnish alkenyl furan 215 (Scheme 2.3.3.1).

Scheme 2.3.3.1 A Feist-Bénary approach to the synthesis of a vinyl furan

Many modifications to the Feist-Bénary reaction have been reported. As mentioned previously (Scheme 1.2.1.3) the use of an epoxy aldehyde in lieu of an α-halo carbonyl results in a 2,3,5-trisubstituted furan with a handle at the 2-postion and a methyl alcohol moiety at the 5-position of the furan. Langer and co-workers have shown that (2,4-dioxobutylidene)-phosphoranes 259 and α-chloro aldehydes 260 will undergo the
Feist-Bénary reaction to give (2-furyl)-methylphosphonium chlorides \(261\) (Scheme 2.3.3.2).\(^{19}\)

**Scheme 2.3.3.2** Feist-Bénary approach to (2-furyl)-methylphosphonium chlorides

![Scheme 2.3.3.2](image)

The great versatility of the Feist-Bénary reaction, along with its many variations makes it well suited for our synthesis of the furan moiety. As such, furan \(264\) appeared to be a good starting point, wherein the sulfide could provide a handle for subsequent introduction of an olefin chain via a Julia-olefination. Paquette and co-workers have previously synthesized \(264\) in their synthesis of \((\pm)-11, O(3)\)-dihydropseudopterolide.\(^{20}\) In their variation, the reaction of glyceraldehyde acetonide \(263\) and \(\beta\)-ketoester \(262\), followed by acid-catalyzed cyclization, furnished tri-substituted furan \(264\) (Scheme 2.3.3.3).

We prepared furan \(264\) following Paquette’s protocol. Advancement of furan \(264\) commenced with protection of the alcohol as its silyl ether and subsequent oxidation gave sulfone \(265\) (Scheme 2.3.3.3). Deprotonation and treatment with hydrocinnamaldehyde \(266\) was followed by addition of acetic anhydride to furnish acetate \(267\). Reductive elimination with SmI\(_2\) allowed access to the fully functionalized alkenyl furan \(268\).
**Scheme 2.3.3.3** Synthesis of alkenyl furan 268

We were very pleased to have accessed a fully functionalized alkenyl furan 268. However, the irreproducibility of the reductive elimination coupled with the necessary use of stoichiometric amounts of samarium metal, prompted us to investigate a modified Julia-olefination. Julia and co-workers discovered that using heteroaryl sulfones in place of phenyl sulfones allows for one-pot olefination reactions.\(^{21}\) We elected to employ a benzothiazol-2-yl sulfone. We initially attempted to synthesize the sulfone in the same way we had previously synthesized phenyl sulfone 265 (Scheme 2.3.3.3). However, we found the furan forming reaction to be quite low yielding. We subsequently modified the procedure so that the benzothiazol-2-yl moiety was introduced following furan cyclization. In this case ethyl 4-chloroacetaldehyde 269 was condensed with glyceraldehyde acetonide 263 in the presence of a catalytic amount of piperidine (Scheme 2.3.3.4). Then pTSA was added directly to the reaction to induce cyclization and furnish...
The alcohol was protected as its silyl ether, and the chloride was displaced with benzothiazole. Oxidation of sulfide to sulfone was accomplished with mCPBA. Deprotonation of the sulfone and subsequent treatment with hydrocinnamaldehyde furnished alkene.

Scheme 2.3.4 Synthesis of alkenyl furan via modified Julia-olefination

To our surprise in this instance the olefination yielded the cis-alkene rather than the trans-alkene as the primary product. The outcome of the olefination depends on the stereochemistry of the initial addition into the aldehyde, with syn β-alkoxysulfoles leading to (Z)-olefins and anti β-alkoxysulfoles leading to (E)-olefins (Scheme 2.3.5). However, in the case of benzylic sulfoles the addition is reversible, and since the elimination of syn β-alkoxysulfoles to (Z)-olefins is faster, the product ratio heavily favors the (Z)-olefin product.
**Scheme 2.3.3.5** Stereochemistry of modified Julia-olefination

With both the *cis* and *trans*-alkenyl furans in hand we set out to attempt our *[2 + 2]* cycloaddition. Using the conditions developed on simplified substrate 209 (Section 2.2.2) we attempted the transformation using both *cis* and *trans*-olefin substrates (Scheme 2.4.1.1). Unfortunately, neither substrate underwent the desired *[2 + 2]* cycloaddition reaction. When the *trans*-alkene 268 was employed we recovered starting material and observed some decomposition. When the *cis*-alkene 275 was employed, only a small amount of *trans*-isomer 268 was recovered.
**Scheme 2.4.1.1** Attempted [2 + 2] cycloaddition of alkenyl furans 268/275

We employed alternative reaction conditions based on other literature precedent (Scheme 2.4.1.2). Heating the reaction to higher temperatures or using microwave conditions resulted in no reaction. The Zn–Cu couple conditions resulted in decomposition of the starting materials.

**Scheme 2.4.1.2** Additional [2 + 2] cycloaddition attempts

Given the success of our model [2 + 2] system (Section 2.2.2), we wondered what was preventing the [2 + 2] cycloaddition reaction of the fully functionalized furan 268/275 from taking place. One possible explanation was that the increase of steric bulk around the alkene is preventing the reaction. Another explanation was that the conjugated alkene was too electron deficient to undergo this transformation. It is known...
that ketenes react with isolated-alkenes, dienes and activated alkenes such as vinyl ethers readily, however ketenes do not react with deactivated alkenes.\textsuperscript{24}

Therefore, we elected to alter the electronics of the olefin by reducing the ester on both the \textit{cis}- and \textit{trans}-substrates. The ester \textbf{268/275} was reduced with LAH and the resultant alcohol subsequently protected as its silyl ether \textbf{285/286}. Attempts to effect the \([2 + 2]\) cycloaddition again failed, with cleavage of the silyl group being one of the competing pathways observed (Scheme 2.4.1.3).

**Scheme 2.4.1.3** [2 + 2] Cycloaddition attempts on reduced furyl alkenes \textbf{285/286}

We decided to exchange the TBDPS-protecting groups for less labile benzyl-protecting groups. Even though the \([2 + 2]\) cycloaddition did not occur with the \textit{trans}-alkene \textbf{288}, we were pleased to discover that the \([2 + 2]\) cycloaddition did occur when the \textit{cis}-alkene \textbf{290} was employed, to provide the desired product \textbf{291} as a mixture of diastereomers (Scheme 2.4.1.4).
While we had at last obtained a functionalized furyl cyclobutanone 291, we had several concerns about this approach. First, we noted the lack of stereocontrol in this approach. Second, there was the necessity to reduce the ester to the alcohol in order for the [2 + 2] cycloaddition to take place. Later in the synthesis the alcohol would need to be converted back to the ester, wherein oxidation of the furan was likely.

2.4.2 Ketene Equivalents in the [2 + 2] Cycloaddition

We postulated that it might be possible utilize an alkenyl furan with the ester intact, such as 268/275, in a [2 + 2] cycloaddition if we employed ketene equivalents in place of dichloroketene (Scheme 2.4.2.1). Ketene equivalents are known to sometimes undergo [2 + 2] cycloadditions in reactions where ketenes have failed to give the desired products. In a final attempt to convert a furyl alkene 292 into a furyl cyclobutanone 293 we investigated the use of ketene equivalents in the [2 + 2] cycloaddition.
Scheme 2.4.2.1 [2 + 2] Cycloaddition with ketene or ketene equivalents

2.4.3 Ketene Dimethylacetal

While ketenes do not react with deactivated alkenes, ketene acetals participate in a formal [2 + 2] reaction with electron-deficient olefins under Lewis acid-mediated conditions. Using the previously described conditions (Section 1.4.1), we attempted to effect the [2 + 2] transformation with alkenyl furan 275 and ketene dimethyl acetal 294 (Scheme 2.4.3.1). Unfortunately no reaction took place and we recovered only starting material. Attempts to vary the reaction conditions failed to produce any desired product and again starting material was recovered.

Scheme 2.4.3.1 Attempted [2 + 2] cycloaddition with ketene dimethyl acetal

2.4.4 Keteniminium [2 + 2] Cycloadditions

Keteniminium salts 296 have been used as ketene equivalents in the synthesis of cyclobutanones from alkene substrates. In contrast to ketenes, theses salts do not undergo dimerization, and they react with a wider range of alkenes because they are more
electrophilic than most ketenes. Importantly, keteniminium salts are readily prepared from amides 297 or α-halo enamines 298 (Scheme 2.4.4.1).

**Scheme 2.4.4.1 Synthesis of keteniminium salts**

Amide substrates with a wide variety of substitution, both on the nitrogen and alpha to the carbonyl, have been successfully employed in the generation of keteniminium salts and their subsequent [2 + 2] cycloaddition. Both inter- and intramolecular variants of this reaction are known. Literature precedent had shown that conjugated alkenes undergo [2 + 2] cycloaddition with keteniminium salts to yield cyclobutanones. Hartmann and Heine have shown that in situ generated tetramethylketeniminium ions 300 react with α,β-unsaturated ketones, esters, and amides 301 to give cyclobutanones 302 (Scheme 2.4.4.2). We were hopeful that such an approach would result in the desired [2 + 2] cycloaddition on one of our furyl alkene substrates.

**Scheme 2.4.4.2 [2 + 2] Cycloaddition of tetramethylketeniminium salts**
We first prepared a simple amide substrate to test an intermolecular version of this type of reaction on our previously synthesized alkenyl furan 275 (Scheme 2.4.4.3). The amide 304 was cooled in DCE and treated with triflic anhydride. Then the alkene and collidine were added, and the reaction was warmed to room temperature. We observed no desired product and decomposition of the starting material. We subsequently elected to attempt this reaction with the benzyl-protected substrate 303. The reaction failed to produce any cyclobutanone product, and no starting material was obtained, again due to decomposition under the reaction conditions. We also attempted the synthesis of other keteniminium precursors but were unsuccessful.

Scheme 2.4.4.3 Attempted intermolecular keteniminium [2 + 2] cycloaddition

As an alternative to the intermolecular approach, we attempted an intramolecular keteniminium cycloaddition reaction that we hoped would be more successful. A simplified alkenyl furan substrate 310 was prepared to test its reactivity in the proposed intramolecular keteniminium cycloaddition reaction (Scheme 2.4.4.4). Ethyl 4-chloroacetoacetate 269 and chloroacetaldehyde 306 underwent a Knoevenagal condensation aqueous, basic conditions to give an enone intermediate, which was directly treated with pTSA in dichloromethane overnight to induce cyclization to furan 307. The chloride was displaced with benzothiazole 272 and subsequent oxidation furnished
sulfone 309. Deprotonation followed by treatment with hydrocinnamaldehyde 266 provided furyl alkene 310.

**Scheme 2.4.4.4 Synthesis of alkenyl furan 310**

Our first attempt at intramolecular keteniminium cycloaddition was executed on ester substrate 313. Ester 310 was saponified to carboxylic acid 311 and alkylated with amide 312 (Scheme 2.4.4.5). Exposure of amide 313 to triflic anhydride at 0 °C, followed by treatment with DTBMP, and heating to 80 °C only resulted in decomposition of the starting material. Attempts to confirm the formation of the keteniminium intermediate by trapping with methanol and cyclohexene failed.
**Scheme 2.4.4.5** Attempted intramolecular keteniminium [2 + 2] cycloaddition

Concerned that the ester may be interfering with the formation of the iminium ketene we next attempted an intramolecular keteniminium cycloaddition on an ether substrate. Alkenyl furan 310 was reduced with lithium aluminum hydride to give alcohol 315 (Scheme 2.4.4.6). Alkylation of alcohol 315 with bromide 316, in aqueous 35% NaOH solution, in the presence of a phase transfer catalyst tetrabutylammonium hydrogensulfate, furnished ether 317. Unfortunately, treatment of the ether substrate 317 with triflic anhydride followed by either DTBMP or collidine failed to provide any cycloaddition products. We observed decomposition of the starting material under a variety of conditions. Using other common variations such as changing the solvent to benzene or adding 4Å molecular sieves did not improve the outcome of the reaction.
Scheme 2.4.4.6 Attempted intramolecular keteniminium [2 + 2] cycloaddition

Concurrently, we pursued an approach wherein the amide was tethered to the other side of the alkene. Deprotonation of sulfone 309 and subsequent treatment with aldehyde 319 furnished alkene 320 (Scheme 2.4.4.7). Deprotection and etherification with bromide 316 provided ether 322. However, we also observed significant quantities of the elimination product that resulted in a diene, but enough of the desired product was isolated to attempt the cycloaddition. The use of sodium hydride as a base did not reduce the amount of elimination product observed. Treatment of amide 322 with triflic anhydride and subsequently collidine failed to produce any desired product. Some starting material was recovered but the remainder was lost due to decomposition.
It became apparent that our substrates were ill disposed to undergo the keteniminium cycloaddition reactions. Even when the triflic anhydride was distilled before use, and excess of collidine or DTBMP and 4Å molecular sieves were used we still observed decomposition. Clearly a more effective approach would be needed.

2.5 Conclusions

This chapter covers the various approaches to the synthesis of cyclobutanes and our synthetic efforts towards the synthesis of a furyl cyclobutane en route to providencin (1). We have shown that it is possible to effect a [2 + 2] cycloaddition between an alkenyl furan and dichloroketene (Scheme 2.5.1). We have synthesized highly functionalized furan substrates 268/275/303 with appropriate functionalization for further elaboration. However, we found the [2 + 2] cycloaddition reaction does not proceed when there is an ester moiety at the 3-position of our furan substrates. The use of ketene equivalents on the ester substrates failed to produce any cyclobutanone products. The reaction was no more
successful when attempted intramolecularly. We have effected the [2 + 2] cycloaddition reaction on an alkenyl furan 290, where the ester at the 3-position of the furan had been reduced to an alcohol. However, the requisite oxidation state changes were a concern. We have since decided to reevaluate our retrosynthetic approach and further efforts toward the synthesis of providencin (1) will be discussed in the following chapter.

**Scheme 2.5.1 Chapter 2 summary**

\[
\begin{align*}
\text{Scheme 2.5.1 Chapter 2 summary} \\
\newcommand{\mymath}[1]{\text{\footnotesize #1}}
\end{align*}
\]
2.6 Experimental Procedures

2.6.1 General Information

Unless otherwise stated, reactions were mechanically stirred in flame-dried glassware under an atmosphere of nitrogen. Tetrahydrofuran, benzene, toluene, dichloromethane and diethyl ether were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. Commercially available reagents were obtained from Sigma-Aldrich, Strem, TCI-America or Alfa Aesar and were used as received. All known compounds were identified by comparison of NMR spectra to those reported in the literature.

Thin layer chromatography was performed using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 µm). Developed plates were visualized using a 254 nm UV lamp and/or with the appropriate dip followed by heating. Typical dip solutions were ethanolic anisaldehyde, ceric ammonium molybdate and potassium permanganate. Flash chromatography was generally performed with Silicycle SiliaFlash® P60 (230-400 mesh) silica gel as the stationary phase. Infrared spectra were recorded on a Nicolet Avatar 320 FT-IR. Samples were analyzed as thin films on NaCl plates (sample dissolved in CH₂Cl₂) and the spectra are presented as transmittance vs. wavenumber (cm⁻¹). High-resolution mass spectrometry was conducted on an Agilent 6210 TOF LCMS. Proton (¹H) and carbon (¹³C) NMR spectra were recorded on a Varian Inova 400 or 300 spectrometer. Spectra were obtained at 22 ºC in CDCl₃ unless otherwise noted. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants (J) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d =
doublet, t = triplet, q = quartet, quint. = quintuplet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, dt = doublet of triplets, br = broad, app = apparent.

2.6.2 Preparative Procedures

Hexyltriphenylphosphonium bromide 207 (0.618 g, 1.44 mmol) was dissolved in THF (10 mL) and cooled to 0 °C. 1M LiHMDS (1.8 mL, 1.8 mmol) was added dropwise and solution turned from pale yellow to bright orange. Furfural 208 (0.1 mL, 1.2 mmol) was added dropwise and the reaction was allowed to warm to room temperature. When TLC showed consumption of furfural the reaction was concentrated onto silica gel and purified by flash chromatography (hexanes). 209 was obtained as a mixture of olefin isomers in near quantitative yield.

209: Rf = 0.6, hexanes; 1H NMR (400 MHz, CDCl3) δ 7.37 (d, J=1.7 Hz, 0.2H), 7.30 (d, J=1.6 Hz, 0.8H), 6.39 (dd, J=3.3, 1.8 Hz, 0.2H), 6.34 (dd, J=3.3, 1.8 Hz, 0.8H), 6.25 (d, J=3.5 Hz, 0.2H), 6.20–6.17 (m, 1.8H), 6.12 (d, J=3.5 Hz, 0.8H), 5.56 (dt, J=11.8, 7.3 Hz, 0.2 H), 2.44 (app q, J=7.3 Hz, 0.4H), 2.17 (app q, J=7.2 Hz, 1.6H), 1.46–1.41 (m, 2H), 1.37–1.29 (m, 4H), 0.90 (app t, J=7.0 Hz, 3H); 13C NMR (100 MHz, CDCl3) cis–isomer δ 153.5, 141.3, 131.7, 117.3, 111.2, 108.8, 31.8, 29.4, 29.36, 22.7, 14.2 trans–isomer δ 153.61 141.1 130.5, 118.7, 11.3, 106.0, 33.0, 31.6, 29.1, 22.8, 14.3; IR (NaCl thin film): 2958(s), 2927(s), 2857(m), 1491(w), 1012(m), 959(m), 728(s); HRMS (ESI–APCI) m/z calcd. for C11H17O [M+H]+: 165.1274, found: 165.1275
To a solution of \( \text{209} \) (0.218 g, 1.33 mmol), zinc (0.435 g, 6.65 mmol) (activated by heating to 150 °C for 3–18 h), DME (0.15 mL, 1.46 mmol) in diethyl ether (5 mL) at reflux was added trichloroacetyl chloride (0.16 mL, 1.46 mmol) in diethyl ether (3 mL) dropwise via a syringe pump. When TLC showed consumption of \( \text{209} \) the reaction was cooled and filtered through celite. The filtrate was washed 5x with dilute sodium bicarbonate solutions then dried over MgSO\(_4\). Concentration in vacuo yielded a yellow oil, this product proved unstable to silica gel and alumina, resulting in a <10% yield, and was used without further purification.

\( \text{210} \): \( ^1 \text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.44 (s, 1H), 6.38 (m, 2H), 4.28 (d, \( J=11.25 \) Hz, 1H), 4.13 (dt, \( J=15.32, 11.25, 7.68 \) Hz, 1H), 1.91–1.82 (m, 1H), 1.6–1.5 (m, 1H), 1.36–1.13 (m, 6H), 0.83 (t, \( J=6.9 \) Hz, 3H); \( ^{13} \text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 195.8, 148.6, 143.5, 111.9, 110.6, 87.0, 59.7, 49.5, 31.6, 27.5, 26.1, 22.4, 14.1; IR (NaCl thin film): 2957(m), 2930(m), 2860(m), 1807(s), 1150(w), 921(w), 738(w); HRMS (ESI–APCI) \( m/z \) calcd. for \( \text{C}_{13}\text{H}_{15}\text{Cl}_2\text{O}_2 \) [M–H]\(^-\): 273.0455, found: 273.0451
To a solution of 210 (0.066 g, 0.4 mmol), zinc (0.262 g, 4 mmol) (activated by heating to 150 ºC for 3–18 h), DME (0.07 mL, 0.6 mmol) in diethyl ether (3 mL) at reflux was added trichloroacetyl chloride (0.07 mL, 0.6 mmol) in diethyl ether (1 mL) dropwise via a syringe pump. When TLC showed consumption of 211 a solution of 3% NH₄Cl in MeOH (0.5 mL) was added. After 20 min the reaction was cooled and filtered through celite. The filtrate was washed 5x with dilute sodium bicarbonate solutions then dried over MgSO₄. Concentration in vacuo yielded a crude yellow oil 211 in ~50% yield. This product proved unstable to silica gel and alumina and was used without further purification.

211: ¹H NMR (400 MHz, CDCl₃) δ 7.41–7.40 (m, 1H), 6.37 (dd, J=3.2, 1.9 Hz, 0.4H), 6.33 (dd, J=3.2, 1.9 Hz, 0.6H), 6.27–6.26 (m, 1H), 5.20 (dd, J=7.8, 2.8 Hz, 0.4H), 5.16 (dd, J=9.8, 2.8 Hz, 0.6H), 4.11 (t, J=10.0 Hz, 0.6H), 3.76 (dd, J=10.3, 7.8 Hz, 0.4H), 3.61–3.52 (m, 1H), 1.71–1.07 (m, 8H), 0.80 (t, J=6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 202.5/200.8, 150.2/149.6, 142.5/142.7, 110.6/110.1, 108.5/110.4, 63.6/61.5, 61.4/59.6, 39.4/35.7, 31.4, 26.9/27.2, 27.0/25.1, 22.2, 13.9 ; IR (NaCl thin film): 2956(s), 2930(s), 2860(m), 1795(s), 735(m); HRMS (ESI–APCI) m/z calcd. for C₁₃H₁₉O₂ [M+H]⁺: 207.138, found: 207.1384 (this is the mass for the over-reduced product)

3,4-dihydro–2H–pyran (50.4 mL, 556 mmol) in diethyl ether (250 mL) was cooled in an ice bath. Then p–toluenesulfonic acid (0.2 g, 1.1 mmol) and 3–butene–1–ol 223 (11.86 mL, 139 mmol) were added and reaction was allowed to warm to room
temperature and stir overnight. The reaction was quenched with NH₄OH (2 mL) in MeOH (20 mL) and concentrated. Ether was added to the residue and the ammonium p–toluenesulfate removed by filtration. The filtrate was concentrated and crude ¹H NMR of the alkene matched the published data. ²⁷

The crude alkene was dissolved in 1:1 MeOH:CH₂Cl₂ (1 L) with pyridine (1 mL) and the reaction cooled to –78 °C. Ozone was bubbled through the reaction for 3 h until solution turned blue. Air was bubbled through the reaction until blue color dissipated and then dimethylsulfide (45 mL) was added and reaction was allowed to warm to room temperature. Water (500 mL) was added and layers were separated. The aqueous layer was extracted twice with dichloromethane (250 mL) and combined organics were dried over MgSO₄ and concentrated. Crude ¹H NMR of the aldehyde matched the published data. ²⁸

The crude aldehyde and ethyl (triphenylphosphoranylidene)acetate ²²⁴ (48.4 g, 139 mmol) in THF (250 mL) were heated to reflux for 12 h. Reaction was cooled and concentrated onto silica gel. Material was purified by flash chromatography (4:1 hexanes:EtOAc) to yield ²²⁵ in 71% yield over three steps.

²²⁵: \( R_f = 0.33, 4:1 \) hexanes:EtOAc; ¹H NMR (400 MHz, CDCl₃) \( \delta 6.98 \) (dt, \( J=15.7, 8.8, 6.9 \) Hz, 1H), 5.90 (dt, \( J=15.7, 1.6 \) Hz, 1H), 4.59 (m, 1H), 4.18 (q, \( J=7.1 \) Hz, 2H), 3.88–3.81 (m, 2H), 3.54–3.48 (m, 2H), 2.49 (dddd, \( J=13.4, 6.7, 6.7, 1.6 \) Hz, 2H), 1.85–1.77 (m, 1H), 1.74–1.67 (m, 1H), 1.61–1.48 (m, 4H), 1.28 (t, \( J=7.1 \) Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) \( \delta 166.7, 145.9, 123.1, 99.0, 65.8, 62.5, 60.4, 32.8, 30.8, 25.6, 19.7, 14.5; \) IR (NaCl thin film): 2941(s), 2871(s), 1722(s), 1657(m), 1262(m), 1218(s), 1033(s),
Ethyl ester 225 (6.2 g, 27 mmol) was stirred in THF (150 mL) and cooled to in an ice bath. 1M DIBAL-H in THF (68 mL, 68 mmol) was added dropwise via addition funnel. After addition the reaction was warmed to room temperature and stirred for 1 hour. When TLC showed a complete conversion, the reaction was cooled in an ice bath and carefully quenched with 0.5M Rochelle’s salt solution. The layers were separated and the aqueous layer was extracted with three times with ether. The combined organics were washed with brine, dried over MgSO₄ and concentrated. Crude ¹H NMR of the alcohol matched the published data.²⁹

Oxalyl chloride (2 mL, 22.5 mmol) was added to dichloromethane (100 mL) cooled to −78 °C. Then dimethylsulfoxide (3.4 mL, 48 mmol) was added dropwise and the reaction was stirred at −78 °C for 30 minutes. Then alcohol (2.8 g, 15 mmol) in dichloromethane (100 mL) was added dropwise and the reaction was stirred for 30 minutes at −78 °C. Triethylamine (10.4 mL, 75 mmol) was added and the reaction was warmed to 0 °C. The reaction was quenched with sodium bicarbonate solution. The layers were separated and the aqueous was extracted three times with ether. The combined organics were washed with sodium hydrogensulfate solution 1x, sodium bicarbonate solution 1x, and brine 1x, dried over MgSO₄ and concentrated. The crude material was flashed in 2:1 hexanes:EtOAc and aldehyde 226 was obtained in 73% yield over two steps.
$\textbf{226}$: $R_f = 0.37$, 2:1 hexanes:EtOAc; $^1\text{H} \text{NMR}$ (400 MHz, CDCl$_3$) $\delta$ 9.50 (d, $J=7.9$ Hz, 1H), 6.87 (dt, $J=15.8$, 6.8 Hz, 1H), 6.18 (dd, $J=15.7$, 7.9 Hz, 1H), 4.59 (s, 1H), 3.92–3.79 (m, 2H), 3.58–3.47 (m, 2H), 2.61 (dddd, $J=13.0$, 6.6, 6.6, 1.3 Hz, 2H), 1.80–1.65 (m, 2H), 1.59–1.49 (m, 4H); $^{13}\text{C} \text{NMR}$ (100 MHz, CDCl$_3$) $\delta$ 194.2, 155.5, 134.4, 99.2, 65.4, 62.7, 33.3, 30.8, 25.6, 19.7; IR (NaCl thin film): 2943(m), 2870(w), 1692(s), 1134(m), 1033(m); HRMS (ESI–APCI) $m/z$ calcd. for $\text{C}_{10}\text{H}_{17}\text{O}_3 [\text{M+H}]^+$: 185.1172, found: 185.1167

The diisopropylamine (1.4 mL, 10.1 mmol) was stirred in THF (13 mL) at $-78 \, ^{\circ}\text{C}$. Then 1.6 M $n$-BuLi (6.3 mL, 10.1 mmol) was added dropwise and the reaction was stirred at $-78 \, ^{\circ}\text{C}$ for 30 minutes. Methyl acetate (0.68 mL, 8.5 mmol) was added dropwise and the reaction was stirred for a further 30 minutes. Then aldehyde $\textbf{226}$ (1.5g, 8.1 mmol) in THF was added and reaction was allowed to slowly warm to 0 $^{\circ}\text{C}$. TLC showed a complete reaction so reaction was quenched at 0 $^{\circ}\text{C}$ with NH$_4$Cl solution. The layers were separated and the aqueous layer was extracted three times with ether. Combined organics were washed with brine, dried over MgSO$_4$ and concentrated in vacuo. The crude material was dissolved in CH$_2$Cl$_2$ and MnO$_2$ was added portionwise. The reaction was stirred overnight. When starting material remained we added additional MnO$_2$ at intervals until all starting material was consumed. Reaction was filtered through celite and concentrated. The crude material was flashed in 4:1 hexanes:EtOAc and the $\beta$-ketoester $\textbf{220}$ was obtained in 25% yield over two steps. The enol form was also observed in the NMR.
**220**: R$_f$ = 0.22, 4:1 hexanes:EtOAc; $^1$H NMR (400 MHz, CDCl$_3$) δ 11.79 (d, J=1.3 Hz, 0.3H), 6.93 (dt, J=16.0, 6.9 Hz, 0.7H), 6.68 (dt, J=15.6, 7.1 Hz, 0.3H), 6.24 (dt, J=16.0, 1.4 Hz, 0.7H), 5.89 (app dd, J=15.6, 1.4 Hz, 0.3H), 5.00 (s, 0.3H), 4.59 (m, 1H), 3.90–3.81 (m, 2H), 3.74 (m, 2.1H), 3.60 (s, 0.9H), 3.56–3.48 (m, 2H), 2.57–2.47 (m, 2H), 1.60–1.50 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) keto-form δ 192.1, 168.0, 146.9, 131.1, 99.1, 65.6, 62.6, 52.6, 46.8, 33.2, 30.8, 25.6, 19.7, enol-form δ 173.5, 169.5, 137.7, 126.1, 90.6, 66.2, 62.6, 51.4, 46.8, 33.2, 30.8, 25.6, 19.7; IR (NaCl thin film): 2947(m), 2870(w), 1746(m), 1240(s), 1033(s); HRMS (ESI–APCI) $m/z$ calcd. for C$_{13}$H$_{20}$NaO$_5$ [M+Na]$^+$: 279.1203, found: 279.1205

Oxalyl chloride (0.72 mL, 8.25 mmol) was added to dichloromethane (30 mL) cooled to −78 °C. Then dimethylsulfoxide (1.25 mL, 17.6 mmol) in dichloromethane (30 mL) was added dropwise and the reaction was stirred at −78 °C for 30 minutes. Then known alcohol pp252$^{31}$ (1.2 g, 5.5 mmol) in dichloromethane (10 mL) was added dropwise and the reaction was stirred for 30 minutes at −78 °C. Triethylamine (3.8 mL, 27.5 mmol) was added and the reaction was warmed to 0 °C. The reaction was quenched with sodium bicarbonate solution. The layers were separated and the aqueous was extracted three times with ether. The combined organics were washed with sodium hydrogensulfate solution 1x, sodium bicarbonate solution 1x, brine 1x, were dried over MgSO$_4$ and concentrated. The crude aldehyde p252 was carried on directly.
p252: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.51 (d, $J=7.9$ Hz, 1H), 6.88 (dt, $J=15.7$, 6.9 Hz, 1H), 6.17 (ddt, $J=15.8$, 7.8 Hz, 1H), 3.78 (t, $J=6.2$ Hz, 2H), 2.54 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 194.2, 155.7, 134.5, 61.4, 36.3, 26.1, 18.5, –5.1; IR (NaCl thin film): 2955(s), 2930(s), 2866(m), 1697(s), 1257(m), 1101(s), 836(s), 777(m); HRMS (ESI–APCI) $m/z$ calcd. for C$_{11}$H$_{23}$O$_2$Si [M+H]$^+$: 215.1462, found: 215.1461

The diisopropylamine (0.97 mL, 6.89 mmol) was stirred in THF (10 mL) at –78 ºC. Then 1.6 M n-BuLi (4.9 mL, 6.89 mmol) was added dropwise and the reaction was stirred at –78 ºC for 30 minutes. Methyl acetate (0.46 mL, 5.78 mmol) was added dropwise and the reaction was stirred for a further 30 minutes. Then aldehyde p252 (5.5 mmol) in THF (2 mL) was added and reaction was allowed to slowly warm to 0 ºC. TLC showed a complete reaction so reaction was quenched at 0 ºC with NH$_4$Cl solution. The layers were separated and the aqueous layer was extracted three times with ether. Combined organics were washed with brine, dried over MgSO$_4$ and concentrated in vacuo. The crude material was dissolved in CH$_2$Cl$_2$ (125 mL) and MnO$_2$ (12 g, 137.5 mmol) was added portionwise. The reaction was stirred overnight. When starting material remained we added additional MnO$_2$ at intervals until all starting material was consumed. Reaction was filtered through celite and concentrated. The crude material was flashed in 10:1 hexanes:EtOAc and the $\beta$-ketoester 252 was obtained in 27% yield over three steps. The enol form was also observed in the NMR.

252: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 11.79 (d, $J=1.4$ Hz, 0.3H), 6.89 (dt, $J=16.0$, 7.0 Hz, 0.7H), 6.65 (dt, $J=15.5$, 6.6 Hz, 0.3H), 6.21 (dt, $J=16.0$, 1.5 Hz, 0.7H), 5.85 (app dd, $J=15.5$, 1.5 Hz, 0.3H), 5.00 (s, 0.3H), 3.76–3.70 (m, 5H), 3.59 (s, 1.4H), 2.48–2.37 (m,
Known alcohol 264\textsuperscript{20b} (0.5 g, 1.7 mmol) was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (10 mL) and a few crystals of DMAP were added followed by triethylamine (0.28 mL, 2.04 mmol) and TBDPSCl (0.49 mL, 1.9 mmol). The reaction was allowed to stir overnight. The reaction was diluted with ether and the organic layer was washed with H\textsubscript{2}O 1x, dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo}. The crude material was flashed in 4:1 hexanes:EtOAc and furan \textbf{p265} was obtained in 91% yield.

\textbf{p265}: R\textsubscript{f} = 0.55, 4:1 hexanes:EtOAc; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.75–7.73 (m, 4H), 7.51–7.40 (m, 8H), 7.30–7.22 (m, 3H), 6.43 (s, 1H), 4.62 (s, 2H), 4.44 (s, 2H), 4.25 (q, \(J=7.1\) Hz, 2H), 1.34 (t, \(J=7.1\) Hz, 3H), 1.11 (s, 9H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 163.5, 156.9, 153.4, 135.8, 135.1, 133.3, 131.8, 130.0, 129.0, 128.0, 127.3, 115.9, 108.5, 60.5, 58.8, 31.1, 27.0, 19.5, 14.5; IR (NaCl thin film): 2930(w), 2857(w), 1716(s), 1427(w), 1208(m), 1062(s), 701(m); HRMS (ESI–APCI) \(m/z\) calcd. for C\textsubscript{31}H\textsubscript{34}NaO\textsubscript{4}SSi [M+Na]\textsuperscript{+}: 553.1839, found: 553.1843
The sulfide \( p265 \) (0.168 g, 0.325 mmol) was dissolved in \( \text{CH}_2\text{Cl}_2 \) (2 mL) and the reaction was cooled to 0 ºC. Then \( m\text{CPBA} \) (0.142 g, 0.65 mmol) was added in one portion. The reaction was allowed to warm to room temperature and stir overnight. The reaction was concentrated and the residue was dissolved in EtOAc. The organic layer was washed with \( \text{Na}_2\text{S}_2\text{O}_3 \) 1x, \( \text{NaHCO}_3 \) 1x, dried over MgSO\(_4\) and concentrated in vacuo. The crude material was clean by \( ^1\text{H} \) NMR and material was used directly.

\( 265 \): R\text{f} = 0.27, 4:1 hexanes:EtOAc; \( ^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.71–7.67 (m, 6H), 7.56 (app t, \( J=7.5 \) Hz, 1H), 7.47–7.39 (m, 8H), 6.42 (s, 1H), 4.81 (s, 2H), 4.57 (s, 2H), 4.08 (q, \( J=7.1 \) Hz, 2H), 1.25 (t, \( J=7.1 \) Hz, 3H), 1.07 (s, 9H); \( ^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 162.5, 155.7, 147.1, 138.5, 135.8, 134.0, 133.1, 130.1, 129.0, 128.5, 128.0, 119.5, 108.7, 60.8, 58.8, 55.2, 27.0, 19.4, 14.4; IR (NaCl thin film): 2930(w), 2857(w), 1717(s), 1327(s), 1222(m), 1065(s), 747(s); HRMS (ESI–APCI) \( m/z \) calcd. for \( \text{C}_{31}\text{H}_{34}\text{NaO}_{6}\text{SSi}[\text{M}+\text{Na}]^+ \): 585.1738, found: 585.1737

Sulfone \( 265 \) (3.38 g, 6 mmol) was dissolved in THF (20 mL) and cooled to –78 ºC. Then \( n\text{-BuLi} \) (4.4 mL, 6.6 mmol) was added and the reaction was stirred for 30 minutes at –78 ºC. The aldehyde \( 266 \) (0.83 mL, 6.3 mmol) was added and the reaction stirred at –78 ºC for a further three hours. Acetic anhydride (1.13 mL, 12 mmol) was
added and the reaction was allowed to warm to room temperature. The reaction was quenched with saturated NH₄Cl solution and the layers were separated. The aqueous layer was extracted with ether 2x. Combined organics were dried over MgSO₄ and concentrated in vacuo to give 267. The crude material was carried on directly.

The acetate 267 was dissolved in THF (20 mL) and was then transferred to a flask containing SmI₂ (20 mmol) and HMPA (15 mL) in THF (200 mL) via syringe. When starting material was consumed by TLC the reaction was diluted with ether and washed with 1 M HCl 1x, NaHCO₃ 1x, H₂O 1x, and brine 1x. The organic layer was dried over MgSO₄ and concentrated in vacuo. The crude material was flashed in 4:1 hexanes:EtOAc. The furyl alkene was isolated in 12% yield for two steps.

268: Rₚ = 0.28, 4:1 hexanes:EtOAc; ¹H NMR (400 MHz, CDCl₃) δ 7.71–7.69 (m, 4H), 7.46–7.36 (m, 6H), 7.32–7.24 (m, 2H), 7.22–7.19 (m, 3H), 6.97 (app d, J=16.0 Hz, 1H), 6.49–6.41 (m, 2H), 4.61 (s, 2H), 4.28 (q, J=7.1 Hz, 2H), 2.83–2.79 (m, 2H), 2.61–2.53 (m, 2H), 1.35 (t, J=7.1 Hz, 3H), 1.07 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 163.7, 156.3, 152.4, 141.4, 135.6, 134.6, 133.2, 129.8, 128.4, 127.7, 126.0, 118.3, 113.3, 108.9, 60.2, 58.7, 35.4, 34.9, 26.8, 19.3, 14.4; IR (NaCl thin film): 3070(w), 3026(w), 2957(m), 2930(m), 2558(m), 1711(s), 1057(s), 701(s); HRMS (ESI–APCI) m/z calcd. for C₁₈H₁₅O₃ [M–OTBDPS]⁺: 283.1329, found: 283.1332

The bis-acetonide (5.25 g, 20 mmol) was stirred in (80 mL) of CH₂Cl₂ and cooled to 0 °C and then sodium bicarbonate solution (1 mL, 1 mmol) was added. When the cleavage appeared to be complete MgSO₄ was added and reaction was stirred for a further
15 min. The reaction was filtered. Then β-ketoester 269 (2.7 mL, 20 mmol) and piperidine (0.2 mL, 2 mmol) were added to filtrate, which was then heated to reflux overnight. Then pTSA (0.76 g, 4 mmol) was added and the reaction, which was refluxed until reaction appeared to be complete by TLC. The reaction was cooled and quenched with H₂O and the aqueous layer was extracted with CH₂Cl₂. The combined organics were washed with H₂O 1x, brine 1x, dried over MgSO₄ and concentrated in vacuo. The crude material was flashed in 2:1 hexanes:EtOAc and furan 270 was isolated in 60% yield.

270: Rᵣ = 0.09, 4:1 hexanes:EtOAc; ¹H NMR (400 MHz, CDCl₃) δ 6.59 (s, 1H), 4.88 (s, 2H), 4.59 (s, 2H), 4.30 (q, J=7.1 Hz , 2H), 1.35 (t, J=7.1 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 163.0, 155.0, 154.7, 117.3, 109.1, 61.1, 57.3, 35.8, 14.4; IR (NaCl thin film): 3425(w), 2983(w), 1717(s), 1228(m), 1077(s); HRMS (ESI–APCI) m/z calcd. for C₉H₁₁ClO₄ [M–H]⁻: 217.0273, found: 217.0278

**Alcohol 270** (85 mg, 0.39 mmol) was stirred in CH₂Cl₂ at room temperature. Then DMAP, Et₃N (0.065 mL, 0.47 mmol), and TBDPSCI (0.11 mL, 0.43 mmol) were added successively and the reaction was stirred overnight. The reaction was concentrated and the residue was dissolved in Et₂O and washed with H₂O 2x, dried over MgSO₄ and concentrated in vacuo. The crude material was flashed in 4:1 hexanes:EtOAc. The protected alcohol 271 was isolated in 80% yield.

271: Rᵣ = 0.59, 4:1 hexanes:EtOAc; ¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, J=6.9 Hz , 4H), 7.46–7.38 (m, 6H), 6.44 (s, 1H), 4.86 (s, 2H), 4.62 (s, 2H), 4.32 (q, J=7.5 Hz, 2H),

![Diagram of 271](image-url)
1.37 (t, $J$=7.5 Hz, 3H), 1.06 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 163.0, 154.7, 154.4, 135.8, 133.2, 130.1, 128.0, 117.2, 108.7, 60.9, 58.8, 35.9, 27.0, 19.5, 14.5; IR (NaCl thin film): 2932(w), 2858(w), 1718(s), 1270(m), 1069(s), 702(s); HRMS (ESI–APCI) $m/z$ calcd. for C$_{15}$H$_{14}$O$_3$ [M–OTBDPS]$^+$: 243.1016, found: 243.1022

Chloride 271 (2.19 g, 4.8 mmol) and 2-mercaptobenzothiazole (0.825 g, 4.9 mmol) were dissolved in CH$_2$Cl$_2$ (25 mL). Then Et$_3$N (0.7 mL, 5.0 mmol) was added and the reaction was heated to reflux overnight. The reaction was concentrated and the residue dissolved in EtOAc. The organic layer was washed with NaOH 1x, HCl 1x, and brine, dried over MgSO$_4$ and concentrated in vacuo. The crude material was flashed in 20:1 – 4:1 hexanes:EtOAc.

The sulfide 273 was isolated in >95% yield.

273: $R_f$ = 0.41, 4:1 hexanes:EtOAc; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.89 (d, $J$=8.1 Hz, 1H), 7.75 (d, $J$=8.5 Hz, 1H), 7.67–7.64 (m, 4H), 7.44–7.26 (m, 8H), 6.44 (s, 1H), 4.96 (s, 2H), 4.57 (s, 2H), 4.30 (q, $J$=7.1 Hz, 2H), 1.34 (t, $J$=7.1 Hz, 3H), 1.02 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.6, 163.4, 154.9, 154.0, 153.4, 135.8, 133.2, 130.0, 128.0, 126.3, 124.6, 122.0, 121.2, 117.0, 108.7, 60.8, 58.8, 29.5, 26.9, 19.4, 15.4; IR (NaCl thin film): 2958(m), 2931(m), 2857(m), 1717(s), 1428(s), 1065(s), 702(s); HRMS (ESI–APCI) $m/z$ calcd. for C$_{32}$H$_{34}$NO$_4$S$_2$Si [M+H]$^+$: 588.1693, found: 588.1693
The sulfide 273 (4.8 mmol) was dissolved in CH₂Cl₂ (25 mL) and mCPBA (2.1 g, 9.6 mmol) was added. Reaction was allowed to stir overnight. The reaction was concentrated. The residue was dissolved in EtOAc and was washed with Na₂S₂O₃ 3x, NaHCO₃ 3x, dried over Na₂SO₄ and concentrated in vacuo. The crude material was flashed in 20:1 – 4:1 hexanes:EtOAc. The sulfone 274 was isolated in about 70% yield.

274: Rᵣ = 0.30, 4:1 hexanes:EtOAc; ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, J=8.0 Hz, 1H), 7.86 (d, J=8.1 Hz, 1H), 7.64–7.52 (m, 6H), 7.46–7.37 (m, 6H), 6.48 (s, 1H), 5.19 (s, 2H), 4.47 (s, 2H), 4.03 (q, J=7.1 Hz, 2H), 1.22 (t, J=7.1 Hz, 3H), 1.04 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 164.7, 162.3, 156.0, 152.7, 145.2, 137.3, 135.6, 132.9, 129.0, 128.1, 127.8, 127.6, 125.6, 122.3, 120.3, 108.7, 60.8, 58.5, 54.0, 26.7, 19.2, 14.1; IR (NaCl thin film): 2931(w), 2858(w), 1718(s), 1344(s), 1066(s), 703(s); HRMS (ESI–APCI) m/z calcd. for C₃₂H₃₄NO₆S₂Si [M+H]⁺: 620.1591, found: 620.1593

LiHMDS (2.85 mL, 3.05 mmol) was stirred in THF (20 mL) and cooled to –78 °C. Then sulfone 274 (1.744 g, 2.9 mmol) in THF (25 mL) was added slowly and reaction was stirred for a further 30 min. Then aldehyde 266 (0.45 mL, 3.05 mmol) was added and reaction was allowed to slowly warm to room temperature. Reaction was quenched with H₂O and the aqueous layer was extracted with Et₂O 2x. The combined organics were washed with H₂O 2x, dried over MgSO₄ and concentrated in
After flashing the crude material in 20:1 hexanes:EtOAc \textbf{275} was isolated in around 80% yield.

\textbf{275}: \( R_f = 0.5 \), 4:1 hexanes:EtOAc; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.71–7.68 (m, 4H), 7.46–7.27 (m, 7H), 7.25–7.15 (m, 4H), 6.92 (dt, \( J = 12.0, 1.6 \) Hz, 1H), 6.48 (s, 1H), 5.85 (dt, \( J = 12.0, 7.3 \) Hz, 1H), 4.63 (s, 2H), 4.30 (q, \( J = 7.1 \) Hz, 2H), 2.95–2.89 (m, 2H), 2.80 (dd, \( J = 7.8 \) Hz, 2H), 1.36 (t, \( J = 7.1 \) Hz, 3H), 1.06 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 163.8, 157.1, 152.8, 141.8, 135.8, 133.3, 130.0, 128.7, 128.6, 128.0, 126.1, 116.6, 115.4, 109.1, 60.5, 59.0, 35.9, 31.6, 27.0, 19.5, 14.6; IR (NaCl thin film): 2958 (m), 2931 (m), 2858 (m), 1712 (s), 1427 (m), 1229 (m), 1208 (m), 1061 (s), 700 (s); HRMS (ESI–APCI) \( \text{m}/\text{z} \) calcd. for \( \text{C}_{34}\text{H}_{58}\text{NaO}_4\text{Si} [\text{M}+\text{Na}]^+ \): 561.2432, found: 561.2436

Ester \textbf{268} (0.63 g, 1.17 mmol) was dissolved in THF (24 mL) and cooled to 0 °C. Then LAH (0.093 g, 2.34 mmol) was added in one portion. When reaction appeared complete by TLC it was carefully quenched with saturated Na\(_2\)SO\(_4\). The mixture was filtered, dried with Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. The material was flashed in 2:1 hexanes:EtOAc. The purified alcohol \textbf{p285} was isolated in around 73% yield.

\textbf{p285}: \( R_f = 0.3 \), 2:1 hexanes:EtOAc; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.72–7.68 (m, 4H), 7.45–7.35 (m, 6H), 7.32–7.28 (m, 2H), 7.23–7.18 (m, 3H), 6.29–6.14 (m, 3H), 4.62 (s, 2H), 4.46 (d, \( J = 5.7 \) Hz, 2H), 2.79 (app t, \( J = 8.2, 7.4 \) Hz, 2H), 2.52 (app q, \( J = 7.7, 7.1 \) Hz, 2H), 1.22 (t, \( J = 5.7 \) Hz, 1H), 1.06 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 152.7, 149.1, 141.6, 135.6, 134.8, 133.4, 129.7, 129.5, 128.4, 127.7, 125.9, 120.6, 116.8, 109.5, 59.0,
56.3, 35.8, 34.9, 26.8, 19.3; IR (NaCl thin film): 3341(w), 3070(w), 3026(w), 2930(m), 2557(m), 1112(s), 1069(m), 701(s); HRMS (ESI–APCI) m/z calcd. for C_{16}H_{17}O_{2} [M–OTBDPS]^+: 241.1223, found: 241.122

Alcohol **p285** (60 mg, 0.12 mmol) was stirred in CH₂Cl₂ (8 mL) at room temperature. Then DMAP, Et₃N (0.02 mL, 0.144 mmol), and TBDPSCl (0.034 mL, 0.132 mmol) were added successively and the reaction was stirred overnight. The reaction was concentrated and the residue was dissolved in Et₂O and washed with H₂O 2x, dried over MgSO₄ and concentrated *in vacuo*. The crude material was flashed in 4:1 hexanes:EtOAc. The protected alcohol **285** was isolated in 85% yield.

**285**: Rₑ = 0.41, 20:1 hexanes:EtOAc; ¹H NMR (400 MHz, CDCl₃) δ 7.73–7.65 (m, 8H), 7.45–7.32 (m, 12H), 7.30–7.18 (m, 5H), 6.20–6.03 (m, 3H), 4.60 (s, 2H), 4.53 (s, 2H), 2.74–2.68 (m, 2H), 2.45–2.38 (m, 2H), 1.06 (s, 9H), 1.04 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 152.4, 148.2, 141.8, 135.4, 133.7, 133.6, 130.1, 130.0, 129.6, 128.5, 128.4, 127.8, 126.0, 121.0, 117.6, 109.7, 59.2, 57.9, 36.0, 35.0, 27.0, 19.4; IR (NaCl thin film): 3307(w), 2929(m), 2856(m), 1112(s), 1053(m), 701(s); HRMS (ESI–APCI) m/z calcd. for C₃₂H₅₅O₂Si [M–OTBDPS]^+: 479.2401, found: 479.2409

Ester **275** (0.119 g, 0.22 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. Then LAH (0.0175 g, 0.44 mmol) was added in one portion. When reaction appeared complete by TLC it was carefully quenched with saturated Na₂SO₄. The mixture was filtered, dried with Na₂SO₄ and concentrated *in vacuo*. The
material was flashed in 2:1 hexanes:EtOAc. The purified alcohol **p286** was isolated in around 90% yield.

**p286**: R_f = 0.3, 2:1 hexanes:EtOAc; ^1^H NMR (400 MHz, CDCl_3) δ 7.72–7.68 (m, 4H), 7.44–7.28 (m, 7H), 7.25–7.17 (m, 4H), 6.19–6.16 (m, 2H), 6.00 (dt, J=11.8, 7.4, 7.1 Hz, 1H), 4.64 (s, 2H), 4.48 (s, 2H), 2.92–2.86 (m, 2H), 2.80–2.76 (m, 2H), 1.29 (s, 1H), 1.06 (s, 9H); ^13^C NMR (100 MHz, CDCl_3) δ 153.3, 149.8, 142.0, 135.8, 133.5, 130.6, 129.9, 128.57, 128.5, 127.9, 126.0, 123.1, 114.9, 109.3, 59.2, 56.6, 36.1, 31.1, 26.9, 19.4; IR (NaCl thin film): 3307(w), 3026(w), 2929(m), 2856(m), 1427(m), 1112(s), 1053(m), 1090(s), 972(s); HRMS (ESI–APCI) m/z calcd. for C_{32}H_{36}NaO_3Si [M+Na]^+: 519.2326, found: 519.2327

Alcohol **p286** (49 mg, 0.1 mmol) was stirred in CH_2Cl_2 (2 mL) at room temperature. Then DMAP, Et_3N (0.02 mL, 0.17 mmol), and TBDPSCI (0.04 mL, 0.15 mmol) were added successively and the reaction was stirred overnight. The reaction was concentrated and the residue was dissolved in Et_2O and washed with H_2O 2x, dried over MgSO_4 and concentrated in vacuo. The crude material was flashed in 4:1 hexanes:EtOAc. The protected alcohol **286** was isolated in 67% yield.

**286**: R_f = 0.41, 20:1 hexanes:EtOAc; ^1^H NMR (400 MHz, CDCl_3) δ 7.73–7.67 (m, 8H), 7.44–7.33 (m, 12H), 7.24–7.14 (m, 5H), 6.20 (s, 1H), 5.95 (dt, J=11.8, 1.5, 1.3 Hz, 1H), 5.44 (dt, J=11.8, 7.3 Hz, 1H), 4.64 (s, 2H), 4.55 (s, 2H), 2.87–2.81 (m, 2H), 2.77–2.70 (m, 2H), 1.06 (s, 18H); ^13^C NMR (100 MHz, CDCl_3) δ 153.0, 148.8, 142.2, 135.8, 133.8, 133.6, 129.9, 129.4, 128.8, 128.5, 127.9, 125.9, 123.5, 115.5, 109.5, 59.3, 58.0, 36.2, 31.1, 26.9, 19.4; IR (NaCl thin film): 3307(w), 2929(m), 2856(m), 1112(s), 1053(m),
700(s); HRMS (ESI–APCI) m/z calcd. for C$_{32}$H$_{35}$O$_2$Si [M–OTBDPS]$^+$: 479.2401, found: 479.2409

The same method was used on both the cis- and trans-isomers. The alcohol p$_{285}$/p$_{286}$ (0.065 g, 0.13 mmol) and benzyl bromide (0.017 mL, 0.14 mmol) were dissolved in THF (6 mL) and cooled to 0 °C. NaH (0.006 g, 0.14 mmol) was added and reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with H$_2$O and the aqueous layer was extracted with Et$_2$O 2x. The combined organics were washed with H$_2$O, brine, dried over MgSO$_4$ and concentrated in vacuo. The material was flashed in 50:1 – 20:1 hexanes:EtOAc and p$_{288}$/p$_{290}$ were isolated in 70–80% yield.

pp$_{288}$: R$_f$ = 0.75, 4:1 hexanes:EtOAc; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.72–7.69 (m, 4H), 7.44–7.28 (m, 12H), 7.23–7.18 (m, 4H), 6.23–6.11 (m, 3H), 4.62 (s, 2H), 4.45 (s, 2H), 4.34 (s, 2H), 2.79–2.75 (m, 2H), 2.53–2.48 (m, 2H), 1.07 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 152.8, 150.1, 141.9, 138.5, 135.9, 133.6, 129.9, 129.5, 128.8, 128.6, 128.1, 127.9, 126.1, 118.1, 117.3, 110.3, 71.6, 63.0, 59.2, 36.0, 35.1, 27.0, 19.5; IR (NaCl thin film): 3068(w), 3027(w), 2926(m), 2855(m), 1452(s), 1428(m), 699(s); HRMS (ESI–APCI) m/z calcd. for C$_{23}$H$_{23}$O$_2$ [M–OTBDPS]$^+$: 331.1693, found: 331.1688

pp$_{290}$: R$_f$ = 0.75, 4:1 hexanes:EtOAc; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.70–7.68 (m, 4H), 7.43–7.28 (m, 12H), 7.23–7.15 (m, 4H), 6.20 (s, 1H), 6.11 (d, J=11.8 Hz, 1H), 5.55 (dt, J=11.8, 7.4, 7.2 Hz, 1H), 4.64 (s, 2H), 4.46 (s, 2H), 4.36 (s, 2H), 2.91–2.86 (m, 2H), 2.79–2.76 (m, 2H), 1.04 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 153.2, 150.6, 142.1,
138.4, 135.8, 133.5, 130.3, 130.0, 128.7, 128.6, 128.5, 128.1, 127.9, 127.8, 126.0, 120.5, 115.2, 109.9, 71.8, 63.2, 59.3, 36.2, 31.1, 26.9, 19.4; IR (NaCl thin film): 3027(w), 2927(m), 2856(m), 1112(m), 1064(m), 700(s); HRMS (ESI–APCI) m/z calcd. for C_{23}H_{23}O_2 [M–OTBDPS]^+: 331.1693, found: 331.1698

The same method was used on both the cis- and trans-isomers. Silyl ethers pp288/pp290 (0.525 g, 0.9 mmol) were dissolved in THF (24 mL) and cooled to 0 °C. Then TBAF (1.8 mL, 1.8 mmol) was added and reaction was allowed to stir for 30 min. Additional TBAF was added until all starting material was consumed by TLC. The reaction was quenched with H_2O and the aqueous layer was extracted with Et_2O 2x. The combined organics were washed with H_2O, brine, dried over MgSO_4 and concentrated in vacuo. The material was flashed in 2:1 – 1:1 hexanes:EtOAc and alcohols p288/p290 were obtained in 50–80% yield.

**p288**: R_f = 0.09, 4:1 hexanes:EtOAc; ^1H NMR (400 MHz, CDCl_3) δ 7.37–7.28 (m, 7H), 7.22–7.18 (m, 3H), 6.36–6.19 (m, 3H), 4.58 (d, J=5.4 Hz, 2H), 4.49 (s, 2H), 4.36 (s, 2H), 2.77 (app t, J=8.0, 7.6 Hz, 2H), 2.54–2.48 (m, 2H), 1.65 (t, J=6.0 Hz 1H); ^13C NMR (100 MHz, CDCl_3) δ 152.7, 150.6, 141.8, 138.4, 130.3, 128.6, 128.1, 127.9, 126.1, 118.3, 117.1, 110.8, 71.9, 63.0, 57.9, 35.9, 35.1; IR (NaCl thin film): 3420(w), 3026(w), 2923(m), 2853(m), 1066(m), 698(s); HRMS (ESI–APCI) m/z calcd. for C_{23}H_{28}NO_3 [M+NH_4]^+: 366.2064, found: 366.2058

**p290**: R_f = 0.09, 4:1 hexanes:EtOAc; ^1H NMR (400 MHz, CDCl_3) δ 7.37–7.27 (m, 8H), 7.24–7.17 (m, 2H), 6.35 (s, 1H), 6.12 (d, J=11.8 Hz, 1H), 5.61 (dt, J=11.8, 7.4, 7.1 Hz,
1H), 4.60 (s, 2H), 4.50 (s, 2H), 4.37 (s, 2H), 2.91–2.85 (m, 2H), 2.81–2.77 (m, 2H), 1.61 (t, \( J=5.4 \) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 153.0, 150.9, 142.1, 138.3, 130.9, 128.6, 128.5, 128.4, 128.0, 127.8, 126.0, 120.6, 115.1, 110.3, 71.9, 63.1, 57.9, 36.0, 31.2; IR (NaCl thin film): 3423(w), 3062(w), 2924(m), 2854(m), 1542(s), 1065(m), 698(s); HRMS (ESI–APCI) \( m/z \) calcd. for C\(_{23}\)H\(_{23}\)O\(_2\) \([M–OH]\)^+: 331.1695, found: 331.1695

The alcohol p\( ^{290} \) (78 mg, 0.22 mmol), BnBr (0.03 mL, 0.25 mmol), and NaI were stirred in THF (5 mL) and cooled to 0 °C. NaH (10 mg, 0.25 mmol) was added and reaction was allowed to warm to room temperature and stir overnight. The reaction was quenched with H\(_2\)O and the aqueous layer was extracted with Et\(_2\)O 2x. The combined organics were washed with H\(_2\)O, brine, dried over MgSO\(_4\) and concentrated \textit{in vacuo}. The material was flashed in 50:1 – 20:1 hexanes:EtOAc and \( ^{288/290} \) was isolated as a mixture in 70–80% yield.

\( ^{288/290} \): \( R_f = 0.6, \) hexanes; \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.38–7.27 (m, 11H), 7.26–7.16 (m, 4H), 6.40 (s, 0.4H), 6.36 (s, 0.6H), 6.33–6.20 (m, 1.2H), 6.14 (dt, \( J=11.8, 1.5 \) Hz, 0.4H), 5.62 (dt, \( J=11.8, 7.5, 7.3 \) Hz, 0.4 H), 4.58 (s, 0.8H), 4.58 (s, 1.2H), 4.50 (s, 0.8H), 4.49 (s, 2H), 4.46 (s, 1.2H), 4.39 (s, 0.8H), 4.38 (s, 1.2H), 2.95–2.89 (m, 0.8H), 2.82–2.76 (m, 2H), 2.54–2.49 (m, 1.2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \textit{cis}–isomer \( \delta \) 151.2, 150.5, 142.1, 138.1, 131.0, 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 126.0, 120.5, 115.1, 111.9, 72.1, 71.9, 64.2, 63.1, 36.0, 31.2 \textit{trans}–isomer \( \delta \) 151.0, 150.8, 141.8, 138.4, 130.3, 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 126.1, 118.2, 117.1, 112.4, 72.0,
71.7, 64.1, 62.9, 35.8, 35.0; IR (NaCl thin film): 3026(w), 2852(m), 1452(m), 1063(s), 734(m), 696(s); HRMS (ESI–APCI) m/z calcd. for C_{25}H_{25}O_{2} [M−OBn]^+: 331.1693, found: 331.1697

To a solution of 288/290 (0.037 g, 0.084 mmol), zinc (0.055 g, 0.84 mmol) (activated by heating to 150 °C for 3–18h), DME (0.03 mL, 0.25 mmol) in diethyl ether (3 mL) at reflux was added trichloroacetyl chloride (0.03 mL, 0.25 mmol) in diethyl ether (1 mL) dropwise via a syringe pump. When TLC showed consumption of 288/290 a solution of 3% NH_{4}Cl in MeOH (0.5 mL) was added. After 20 min the reaction was cooled and filtered through celite. The filtrate was washed repeatedly (5x) with dilute sodium bicarbonate solutions then dried over MgSO_{4}. Concentration in vacuo yielded 291 in 86% crude yield.

291: R_{f} = 0.6, hexanes; ^{1}H NMR (400 MHz, CDCl_{3}) δ diastereomers a, b: 7.36–7.28 (m, 10H), 7.22–7.12 (m, 3H), 7.07–6.97 (m, 2H), 6.39 (s, 0.7H), 6.37 (s, 0.3H), 5.40 (dd, J=10.4, 2.8 Hz, 0.7H), 5.05 (dd, J=9.2, 2.7 Hz, 0.3H), 4.57–4.35 (m, 8H), 3.33 (dd, J=9.2, 8.5 Hz, 0.3H), 2.68–2.60 (m, 0.6H), 2.55–2.42 (m, 1.4H), 2.15–1.69 (m, 2H); diastereomer c: 7.36–7.28 (m, 5H), 7.26 (s, 5H), 7.22–7.13 (m, 3H), 7.02 (d, J=7.8 Hz, 2H), 6.36 (s, 1H), 5.10 (d, J=9.7 Hz, 1H), 4.53 (s, 4H), 4.49–4.35 (m, 4H), 4.10–4.05 (m, 1H), 3.52–3.45 (m, 1H), 2.58–2.54 (m, 2H), 2.18–2.09 (m, 1H), 1.82–1.73 (m, 1H); ^{13}C NMR (100 MHz, CDCl_{3}) δ diastereomers a, b: 202.6, 151.5, 147.7, 140.5, 137.9, 128.5, 127.9, 126.2, 121.1, 111.9, 72.2, 72.1, 63.9, 63.5, 63.0, 60.6, 37.8, 33.1, 28.7; δ diastereomer c: 200.5, 152.5, 147.5, 140.8, 138.1, 128.5, 127.9, 126.2,
122.9, 110.9, 71.8, 63.7, 63.0, 61.9, 58.1, 33.7, 33.4, 27.1; IR (NaCl thin film): 3086(w), 3062(w), 3028(m), 2922(s), 2855(s), 1794(s), 1453(m), 1066(s), 697(s); HRMS (ESI–APCI) m/z calcd. for C_{32}H_{35}ClN_{4}[M+NH_{4}]^{+}: 532.2249, found: 532.2254

The β-ketoester 269 (16.1 mL, 100 mmol) was stirred in 250 mL of H_{2}O, K_{2}CO_{3} (15.2 g, 110 mmol) was added and reaction was stirred for 5 min before addition of chloroacetaldehyde 306 (25.8 mL, 200 mmol). The aqueous solution was extracted with CH_{2}Cl_{2} and pTSA (3.8 g, 20 mmol) was added and reaction was stirred overnight. The organic layer was washed with H_{2}O and dried over MgSO_{4}. Concentration in vacuo yielded 307 in 77% crude yield.

307: R_{f} = 0.48, 4:1 hexanes:EtOAc; ^{1}H NMR (400 MHz, CDCl_{3}) δ 7.38 (d, J=1.9 Hz, 1H), 6.70 (d, J=1.9 Hz, 1H), 4.91 (s, 2H), 4.32 (q, J=7.1 Hz, 2H), 1.36 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_{3}) δ 162.8, 155.0, 142.8, 116.6, 111.3, 60.9, 35.6, 14.3; IR (NaCl thin film): 2983(w), 1719(s), 1308(s), 1061(s), 750(m); HRMS (ESI–APCI) m/z calcd. for C_{8}H_{10}ClO_{3}[M+H]^{+}: 189.0313, found: 189.0312

Chloride 307 (0.988 g, 5.24 mmol), DMAP and 2-mercaptobenzothiazole (0.902 g, 5.4 mmol) were dissolved in CH_{2}Cl_{2} (25 mL). Then Et_{3}N (0.76 mL, 5.5 mmol) was added and the reaction was stirred overnight. The reaction was concentrated and the residue dissolved in EtOAc. The organic
layer was washed with NaOH 1x, HCl 1x, and brine, dried over MgSO₄ and concentrated in vacuo. The crude material was flashed in 10:1 hexanes:EtOAc. The sulfide 308 was isolated in 91% yield.

**308**: Rₜ = 0.37, 4:1 hexanes:EtOAc; ^¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, J=8.1 Hz, 1H), 7.77 (d, J=8.5 Hz, 1H), 7.46–7.41 (m, 1H), 7.33–7.27 (m, 1H), 6.71 (d, J=2.0 Hz, 1H), 5.01 (s, 2H), 4.32 (q, J=7.1 Hz, 2H), 1.36 (t, J=7.1 Hz, 3H); ^13C NMR (100 MHz, CDCl₃) δ 165.3, 163.2, 155.6, 153.2, 142.2, 135.7, 126.2, 124.5, 121.9, 121.1, 116.1, 111.2, 60.8, 29.2, 14.4; IR (NaCl thin film): 3126(w), 3060(w), 2979(w), 1712(s), 1601(w), 1427(s), 1304(s), 1174(m), 993(m), 726(m); HRMS (ESI–APCI) m/z calcd. for C₁₅H₁₄NO₃S₂ [M+H]^+: 320.0410, found: 320.0413

The sulfide 308 (2.34 g, 8.92 mmol) was dissolved in CH₂Cl₂ (50 mL) and mCPBA (3.89 g, 17.84 mmol) was added. Reaction was allowed to stir overnight. The reaction was concentrated. The residue was dissolved in EtOAc and was washed with Na₂S₂O₃ 3x, NaHCO₃ 3x, dried over Na₂SO₄ and concentrated in vacuo. The crude material was flashed in 20:1 – 4:1 hexanes:EtOAc. The sulfone 309 was isolated in about 76% yield.

**309**: Rₜ= 0.18, 4:1 hexanes:EtOAc; ^¹H NMR (400 MHz, CDCl₃) δ 8.23 (app d, J=8.8 Hz, 1H), 7.99 (d, J=8.8 Hz, 1H), 7.66–7.57 (m, 2H), 7.37 (d, J=1.9 Hz, 1H), 6.70 (d, J=1.9 Hz, 1H), 5.25 (s, 2H), 4.01 (q, J=7.1 Hz, 2H), 1.20 (t, J=7.1 Hz, 3H); ^13C NMR (100 MHz, CDCl₃) δ 164.7, 162.4, 152.8, 146.2, 144.3, 137.5, 128.3, 127.8, 125.8, 122.4, 119.9, 111.7, 61.0, 53.9, 14.2; IR (NaCl thin film): 3146(w), 3124(w), 2986(w), 2922(w),
LiHMDS (0.61 mL, 0.657 mmol) was stirred in THF (5 mL) and cooled to −78 ºC. Then sulfone 309 (0.22 g, 0.626 mmol) in THF (5 mL) was added slowly and reaction was stirred for a further 30 min. Then aldehyde 266 (0.1 mL, 0.657 mmol) was added and reaction was allowed to slowly warm to room temperature. Reaction was quenched with H₂O and the aqueous layer was extracted with Et₂O 2x. The combined organics were washed with H₂O 2x, dried over MgSO₄ and concentrated in vacuo. After flashing the crude material in 20:1 hexanes:EtOAc 275 was isolated in around 88% yield.

310: Rᶠ = 0.63, 4:1 hexanes:EtOAc; $^1$H NMR (400 MHz, CDCl₃) δ 7.33 (d, J=1.9 Hz, 1H), 7.32–7.28 (m, 2H), 7.26–7.18 (m, 3H), 6.94 (dt, J=12.0, 1.6 Hz, 1H), 6.73 (d, J=1.9 Hz, 1H), 5.88 (dt, J=12.0, 7.4, 7.3 Hz, 1H), 4.31 (q, J=7.1 Hz, 2H), 2.96–2.90 (m, 2H), 2.83–2.79 (m, 2H), 1.36 (t, J=7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl₃) δ 163.6, 157.4, 141.8, 141.0, 135.7, 128.5, 128.4, 126.0, 116.4, 114.8, 111.5, 60.4, 35.8, 31.5, 14.5; IR (NaCl thin film): 3085(w), 3027(w), 2987(w), 2931(w), 2858(w), 1712(s), 1298(s), 1276(s), 1182(s), 737(m); HRMS (ESI–APCI) m/z calcd. for C₁₇H₁₉O₃ [M+H]⁺: 271.1329, found: 271.1331
The ester **310** (0.055 g, 0.2 mmol) was refluxed in 5 mL of 20% NaOH solution for 2 h. The reaction was cooled and carefully quenched with 1M HCl until acidic. The aqueous layer was extracted with EtOAc 3x. The combined organics were dried over MgSO₄ and concentrated *in vacuo* to give **311** in <95% yield. The material was clean by ¹H NMR and was carried on crude.

**311**: ¹H NMR (400 MHz, CDCl₃) δ 7.36 (d, J=1.9 Hz, 1H), 7.33–7.28 (m, 2H), 7.25–7.18 (m, 3H), 6.95 (dt, J=12.0, 1.5 Hz, 1H), 6.77 (d, J=1.9 Hz, 1H), 5.93 (dt, J=12.0, 7.4, 7.3 Hz, 1H), 2.97–2.91 (m, 2H), 2.84–2.80 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 169.0, 158.8, 141.7, 141.3, 136.9, 128.5, 126.1, 116.3, 113.9 111.6, 35.8, 31.6; IR (NaCl thin film): 3156(w), 3061(w), 3026(w), 2923(w), 2665(w), 2567(w), 1677(s), 1560(m), 1303(m), 737(m); HRMS (ESI–APCI) m/z calcd. for C₁₁H₁₃O₃ [M–H]⁻: 241.0870, found: 241.0868

Mesylate **312** (0.28 g, 1.35 mmol), acid **311** (0.28 g, 1.17 mmol), and Cs₂CO₃ (0.42 g, 1.29 mmol), were stirred in DMF (5 mL) overnight. The reaction was diluted with CH₂Cl₂ and washed with H₂O. The combined organics were dried with MgSO₄ and concentrated *in vacuo*. The crude material was flashed in 1:1 hexanes:EtOAc and **313** was obtained in 14% yield.

**313**: Rₜ = 0.73, EtOAc; ¹H NMR (400 MHz, CDCl₃) δ 7.33 (d, J=1.8 Hz, 1H), 7.31–7.27 (m, 2H), 7.24–7.17 (m, 3H), 6.98 (app d, J=11.8 Hz, 1H), 6.79 (d, J=1.9 Hz, 1H), 5.88
(dt, J=12.0, 7.4, 7.2 Hz, 1H), 4.79 (s, 2H), 3.52 (t, J=6.9 Hz, 2H), 3.44 (t, J=6.8 Hz, 2H), 2.94–2.88 (m, 2H), 2.81–2.77 (m, 2H), 2.00 (quint., J=6.8, 6.7 Hz, 2H), (1.87 (quint., J=6.8, 6.7 Hz, 2H); 
13C NMR (100 MHz, CDCl3); δ 165.1, 163.0, 158.2, 141.8, 141.1, 136.2, 128.5, 128.4, 126.0, 116.5, 113.9, 111.6, 62.0, 46.1, 45.4, 35.8, 31.6, 26.3, 24.0; IR (NaCl thin film): 2924(w), 2874(w), 1716(m), 1668(s), 1447(m), 1297(m), 1275(m), 1169(m); HRMS (ESI–APCI) m/z calcd. for C21H24NO4 [M+H]+: 354.17, found: 354.1703

Ester 310 (0.709 g, 2.62 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. Then DIBAL-H (5.25 g, 5.25 mmol) was added until TLC showed consumption of 310. The reaction was carefully quenched with Rochelle's salt solution and the mixture was stirred overnight. The aqueous layer was extracted with Et2O 2x. The combined organics were washed with brine, dried over MgSO4 and concentrated in vacuo. The crude material was flashed in 4:1 – 2:1 – 1:1 hexanes:EtOAc and 315 was isolated in 91% yield.

315: Rf = 0.16, 4:1 hexanes:EtOAc; 1H NMR (400 MHz, CDCl3) δ 7.38 (d, J=1.7 Hz, 1H), 7.33–7.19 (m, 5H), 6.46 (d, J=1.7 Hz, 0.8H), 6.43 (d, J=1.7 Hz, 0.2H), 6.35–6.23 (m, 0.4H), 6.22 (app d, J=11.8 Hz, 0.8), 5.63 (dt, J=11.8, 7.4, 7.2 Hz, 0.8H), 4.54 (s, 2H), 3.69 (t, J=6.4 Hz, 0.2H), 2.94–2.87 (m, 1.6H), 2.82–2.75 (m, 1.6H), 2.75–2.71 (m, 0.2H), 2.58–2.52 (m, 0.4H), 1.95–1.88 (m, 0.2H); 13C NMR (100 MHz, CDCl3) δ cis-isomer: 150.2, 142.0, 141.6, 130.8, 128.6, 128.4, 125.9, 122.3, 114.8, 111.5, 56.5, 36.0, 31.1; trans–isomer: 149.7, 141.6, 141.3, 130.0, 128.6, 128.4, 126.0, 120.1, 117.0, 111.9, 56.3, 35.8, 35.0; IR (NaCl thin film): 3377(m), 3026(m), 2925(m), 2859(m), 1496(m),
Alcohol 315 (0.274 g, 1.2 mmol) and bromide 316 (0.192 g, 1 mmol) were stirred in toluene (10 mL). Then a 35% NaOH solution (10 mL) and tetrabutylammonium hydrogensulfate (0.068 g, 0.2 mmol) were added and reaction was stirred for 3–5 h. The reaction was diluted with H2O and the aqueous layer was extracted with Et2O 2x. The combined organics were washed with saturated NH4Cl solution 1x, dried over MgSO4 and concentrated. The crude material was flashed in 1:1 – 1:2 – 0:1 hexanes:EtOAc and 317 was obtained in >95% yield.

317: Rf = 0.58, EtOAc; 1H NMR (400 MHz, CDCl3) δ 7.38 (d, J=1.87 Hz, 1H), 7.32–7.18 (m, 5H), 6.46 (d, J=1.8 Hz, 1H), 6.24 (app d, J=11.8 Hz, 1H), 5.64 (dt, J=11.8, 7.4, 7.2 Hz, 1H), 4.53 (s, 2H), 4.04 (s, 2H), 3.51 (t, J=6.8 Hz, 2H), 3.35 (t, J=6.7 Hz, 2H), 2.94–2.88 (m, 2H), 2.81–2.77 (m, 2H), 1.92 (quint., J=6.6 Hz, 2H), 1.80 (quint., J=6.6 Hz, 2H); 13C NMR (100 MHz, CDCl3) δ 167.7, 151.3, 151.9, 141.9, 141.4, 130.7, 128.4, 128.3, 125.8, 118.9, 114.7, 112.1, 68.7, 63.8, 45.8, 45.6, 35.9, 30.9, 26.1, 23.9; IR (NaCl thin film): 3025(w), 2949(m), 2873(m), 1450(s), 1128(m), 735(m), 700(m); HRMS (ESI–APCI) m/z calcd. for C21H25NNaO3 [M+Na]+: 362.1727, found: 362.1725
Sulfone 309 (0.583 g, 1.66 mmol) was stirred in THF (15 mL) and cooled to −78 °C. Then LiHMDS (1.75 g, 1.75 mmol) was added slowly and reaction was stirred for a further 30 min. Then aldehyde 319 (0.39 g, 2.07 mmol) was added and reaction was allowed to slowly warm to room temperature. Reaction was quenched with H₂O and the aqueous layer was extracted with Et₂O 2x. The combined organics were dried over MgSO₄ and concentrated in vacuo. After flashing the crude material in 20:1 hexanes:EtOAc 320 was isolated in around 75% yield.

320: Rᵣ = 0.66, 4:1 hexanes:EtOAc; ¹H NMR (400 MHz, CDCl₃) δ 7.32 (d, J=1.9 Hz, 1H), 6.96 (dt, J=12.0, 1.7 Hz, 1H), 6.72 (d, J=1.9 Hz, 1H), 5.88 (dt, J=12.0, 7.5 Hz, 1H), 4.30 (q, J=7.1 Hz, 2H), 3.74 (t, J=7.1 Hz, 2H), 2.84–2.79 (m, 2H), 1.35 (t, J=7.1 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 163.6, 157.4, 140.9, 132.9, 117.2, 114.8, 111.4, 62.7, 60.4, 33.5, 26.0, 18.4, 14.4, −5.2; IR (NaCl thin film): 2956(m), 2930(m), 2857(m), 1716(s), 1297(m), 1100(m), 836(m), 776(m), 738(m); HRMS (ESI–APCI) m/z calcd. for C₁₇H₂₉O₄Si [M+H]⁺: 325.183, found: 325.183

Silyl ether 320 (0.408 g, 1.26 mmol) was dissolved in THF (10 mL) and cooled to 0 °C. Then TBAF (5 mL, 5.03 mmol) was added and reaction was allowed to stir for 30 min. Additional TBAF was added until all starting material was consumed by TLC. The reaction was quenched with H₂O and the aqueous layer was extracted with Et₂O 2x.
The combined organics were dried over MgSO₄ and concentrated in vacuo. The material was flashed in 2:1 – 1:1 hexanes:EtOAc and alcohol 321 was obtained in 93% yield.

321: Rᵣ = 0.1, 4:1 hexanes:EtOAc; ¹H NMR (400 MHz, CDCl₃) δ 7.33 (d, J=1.9 Hz, 1H), 7.01 (dt, J=12.0, 1.7 Hz, 1H), 6.72 (d, J=1.9 Hz, 1H), 5.86 (dt, J=12.0, 7.6 Hz, 1H), 4.29 (q, J=7.1 Hz, 2H), 3.78 (t, J=6.5 Hz, 2H), 2.89–2.84 (m, 2H), 1.84 (s, 1H), 1.34 (t, J=7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 163.6, 157.1, 141.1, 132.2, 118.1, 115.1, 111.5, 62.4, 60.5, 33.3, 14.4; IR (NaCl thin film): 3409(m), 2982(m), 2934(m), 1712(s), 1300(s), 1182(s), 1050(s), 1036(s), 740(m); HRMS (ESI–APCI) m/z calcd. for C₁₁H₁₅O₄ [M+H]⁺: 211.0965, found: 211.0967
Alcohol 321 (0.186 g, 0.88 mmol) and bromide 316 (0.142 g, 0.74 mmol) were stirred in toluene (10 mL). Then a 35% NaOH solution (10 mL) and tetrabutylammonium hydrogensulfate (0.061 g, 0.2 mmol) were added and reaction was stirred for 2 h. The reaction was diluted with H₂O and the aqueous layer was extracted with Et₂O 2x. The combined organics were washed with saturated NH₄Cl solution 1x, dried over MgSO₄ and concentrated. The crude material was flashed in 1:1 – 1:2 – 0:1 hexanes:EtOAc and 322 was obtained in 22% yield as a mixture of alkenes. There were also considerable amounts of the elimination product observed.

322: Rᵣ = 0.36, 4:1 hexanes:EtOAc; ¹H NMR (400 MHz, CDCl₃) δ 7.33 (d, J=1.8 Hz, 0.8H), 7.23 (d, J=1.8 Hz, 0.2H), 7.04–6.97 (m, 1H), 6.72 (d, J=1.8 Hz, 0.8H), 6.67 (d, J=1.8 Hz, 0.2H), 6.50 (dt, J=16.0, 8.6, 7.2 Hz, 0.2H), 5.89 (dt, J=12.0, 7.3 Hz, 0.8H), 4.29 (q, J=7.1 Hz, 2H), 4.10 (s, 2H), 3.68 (t, J=6.6 Hz, 2H), 3.49 (t, J=6.9 Hz, 2H), 3.43 (t, J=6.7 Hz, 2H), 2.96–2.90 (m, 2H), 2.61–2.56 (m, 2H), 1.97–1.87 (m, 2H), 1.82–1.81 (m, 2H), 1.35 (t, J=7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ cis-isomer: 167.9, 163.5, 157.2, 141.1, 132.4, 117.5, 115.0, 111.1, 71.0, 70.8, 60.4, 45.9, 45.8, 30.7, 26.3, 24.0; trans-isomer: 167.9, 163.5, 157.2, 140.9, 131.9, 119.6, 115.0, 111.6, 70.9, 70.6, 60.4, 45.9, 45.8, 33.5, 26.3, 24.0; IR (NaCl thin film): 3394(m), 2975(w), 2929(w), 2872(w), 1710(m), 1646(m), 1136(s); HRMS (ESI–APCI) m/z calcd. for C₁₇H₂₄NO₅ [M+H]⁺: 322.1649, found: 322.1651
2.7 References


16. (a) Baciocchi, E.; Civitarese, G.; Ruzziconi, R., Synthesis of 1,4-Dicarbonyl Compounds by the Ceric Ammonium Nitrate Promoted Reaction of Ketones with Vinyl and Isopropenyl Acetate. *Tetrahedron Letters* 1987, 28 (44), 5357-5360; (b) Baciocchi, E.; Ruzziconi, R., Synthesis of 3-Acyl and 3-Carboalkoxyfurans by the Ceric Ammonium-Nitrate Promoted Addition of 1,3-Dicarbonyl Compounds to Vinylic Acetates. *Synthetic Communications* 1988, 18 (15), 1841-1846.


22. (a) Blakemore, P. R., The Modified Julia Olefination: Alkene Synthesis Via the Condensation of Metallated Heteroarylalkylsulfones with Carbonyl Compounds. *Journal of the Chemical Society, Perkin Transactions I* **2002**, (23), 2563-2585; (b) Blakemore, P. R., The Modified Julia Olefination: Alkene Synthesis Via the


Appendix A2: Spectral Data Relevant to Chapter 2
Figure A2.1 1H NMR spectrum (400MHz, CDCl3) of compound 209
Figure A2.2 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 209

Figure A2.3 IR spectrum (thin film, NaCl) of compound 209
Figure A2.4 1H NMR spectrum (400MHz, CDCl3) of compound 210
Figure A2.5 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 210

Figure A2.6 IR spectrum (thin film, NaCl) of compound 210
Figure A2.7 1H NMR spectrum (400MHz, CDCl3) of compound 211
**Figure A2.8** $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 211

**Figure A2.9** IR spectrum (thin film, NaCl) of compound 211
Figure A2.10 1H NMR spectrum (400MHz, CDCl3) of compound 225
**Figure A2.11** $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 225

**Figure A2.12** IR spectrum (thin film, NaCl) of compound 225
Figure A2.13 1H NMR spectrum (400MHz, CDCl3) of compound 226
Figure A2.14 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 226

Figure A2.15 IR spectrum (thin film, NaCl) of compound 226
Figure A2.16 1H NMR spectrum (400MHz, CDCl3) of compound 220
Figure A2.17 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 220

Figure A2.18 IR spectrum (thin film, NaCl) of compound 220
Figure A2.19 1H NMR spectrum (400MHz, CDCl3) of compound p252
Figure A2.20 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound p252

Figure A2.21 IR spectrum (thin film, NaCl) of compound p252
Figure A2.23 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 252

Figure A2.24 IR spectrum (thin film, NaCl) of compound 252
Figure A2.25 1H NMR spectrum (400MHz, CDCl3) of compound p265
Figure A2.26 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound p265

Figure A2.27 IR spectrum (thin film, NaCl) of compound p265
Figure A2.28 1H NMR spectrum (400MHz, CDCl3) of compound 265
**Figure A2.29** $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 265

**Figure A2.30** IR spectrum (thin film, NaCl) of compound 265
Figure A2.31 1H NMR spectrum (400MHz, CDCl3) of compound 268
Figure A2.32 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 268

Figure A2.33 IR spectrum (thin film, NaCl) of compound 268
Figure A2.34 1H NMR spectrum (400MHz, CDCl3) of compound 270
Figure A2.35 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 270

Figure A2.36 IR spectrum (thin film, NaCl) of compound 270
Figure A2.37 1H NMR spectrum (400MHz, CDCl3) of compound 271
Figure A2.38 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 271

Figure A2.39 IR spectrum (thin film, NaCl) of compound 271
Figure A2.40 1H NMR spectrum (400MHz, CDCl3) of compound 273
Figure A2.41 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 273

Figure A2.42 IR spectrum (thin film, NaCl) of compound 273
Figure A2.43 1H NMR spectrum (400MHz, CDCl3) of compound 274
Figure A2.44 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 274

Figure A2.45 IR spectrum (thin film, NaCl) of compound 274
Figure A2.46 1H NMR spectrum (400MHz, CDCl3) of compound 275
Figure A2.47 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 275

Figure A2.48 IR spectrum (thin film, NaCl) of compound 275
Figure A2.49 1H NMR spectrum (400MHz, CDCl3) of compound p285
**Figure A2.50** $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound p285

**Figure A2.51** IR spectrum (thin film, NaCl) of compound p285
Figure A2.52 1H NMR spectrum (400MHz, CDCl3) of compound p286
Figure A2.53 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound p286

Figure A2.54 IR spectrum (thin film, NaCl) of compound p286
Figure A2.55 1H NMR spectrum (400MHz, CDCl3) of compound 285/286
Figure A2.56 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 285/286

Figure A2.57 IR spectrum (thin film, NaCl) of compound 285/286
Figure A2.59 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound pp288

Figure A2.60 IR spectrum (thin film, NaCl) of compound pp288
Figure A2.61 1H NMR spectrum (400MHz, CDCl3) of compound p288
Figure A2.62 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound p288

Figure A2.63 IR spectrum (thin film, NaCl) of compound p288
Figure A2.65 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 288/290

Figure A2.66 IR spectrum (thin film, NaCl) of compound 288/290
Figure A2.68 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound pp290

Figure A2.69 IR spectrum (thin film, NaCl) of compound pp290
Figure A2.70 1H NMR spectrum (400MHz, CDCl3) of compound **p290**
Figure A2.71 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound p290

Figure A2.72 IR spectrum (thin film, NaCl) of compound p290
Figure A2.73 1H NMR spectrum (400MHz, CDCl3) of compound 291
Figure A2.74 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 291

Figure A2.75 IR spectrum (thin film, NaCl) of compound 291
Figure A2.76 1H NMR spectrum (400MHz, CDCl3) of compound 307
Figure A2.77 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 307

Figure A2.78 IR spectrum (thin film, NaCl) of compound 307
Figure A2.79 1H NMR spectrum (400MHz, CDCl3) of compound 308
Figure A2.80 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 308

Figure A2.81 IR spectrum (thin film, NaCl) of compound 308
Figure A2.82 1H NMR spectrum (400MHz, CDCl3) of compound 309
**Figure A2.83** $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 309

**Figure A2.84** IR spectrum (thin film, NaCl) of compound 309
Figure A2.85 1H NMR spectrum (400MHz, CDCl3) of compound 310
Figure A2.86 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 310

Figure A2.87 IR spectrum (thin film, NaCl) of compound 310
Figure A2.88 1H NMR spectrum (400MHz, CDCl3) of compound 311
Figure A2.89 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 311

Figure A2.90 IR spectrum (thin film, NaCl) of compound 311
Figure A2.91 1H NMR spectrum (400MHz, CDCl3) of compound 313
Figure A2.92 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 313

Figure A2.93 IR spectrum (thin film, NaCl) of compound 313
Figure A2.94 1H NMR spectrum (400MHz, CDCl3) of compound 315
Figure A2.95 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 315

Figure A2.96 IR spectrum (thin film, NaCl) of compound 315
**Figure A2.97** 1H NMR spectrum (400MHz, CDCl3) of compound 317
Figure A2.98 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 317

Figure A2.99 IR spectrum (thin film, NaCl) of compound 317
Figure A2.100 1H NMR spectrum (400MHz, CDCl3) of compound 320
Figure A2.101 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 320

Figure A2.102 IR spectrum (thin film, NaCl) of compound 320
Figure A2.103 1H NMR spectrum (400MHz, CDCl3) of compound 321
Figure A2.104 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 321

Figure A2.105 IR spectrum (thin film, NaCl) of compound 321
Figure A2.106 1H NMR spectrum (400MHz, CDCl3) of compound 322
Figure A2.107 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 322

Figure A2.108 IR spectrum (thin film, NaCl) of compound 322
Chapter 3

A Revised Approach and Future Work Towards Providencin

3.1 A More Convergent Approach to the Furyl Cyclobutane

In our work towards providencin (1) thus far, we had encountered several pitfalls in our synthesis of the furyl cyclobutanone portion. The sequence employed to access the furyl cyclobutanone became lengthy and, due in part to its linear nature, low yielding. Therefore, a revised approach was needed, one in which a more convergent route was taken. To this end, we envisioned a retrosynthesis in which a late stage epoxidation and deprotection would provide 1 (Scheme 3.1.1). Butenolide 218 would arise from a macrolactonization/RCM sequence performed on diene 217, which in turn, would derive from furyl cyclobutanone 325. A coupling reaction between a functionalized furan 246 and a functionalized cyclobutane 324 would provide this furyl cyclobutanone 325 in a convergent fashion.
**Scheme 3.1.1** A new retrosynthetic approach to Providencin (1)

![Scheme 3.1.1](image)

### 3.1.1 Buchwald / Hartwig Type α-Arylation of Ketones

We elected to investigate Buchwald, Hartwig and Miura type α-arylations of ketones for the coupling of the two functionalized substrates.\(^1\) In particular, an α-arylation of a cyclobutanone 326 with a 2-bromofuran 327 would yield a highly functionalized furyl cyclobutanone 325 in short order (Scheme 3.1.1.1).

**Scheme 3.1.1.1** Buchwald/Hartwig retrosynthetic approach to furyl cyclobutanone

![Scheme 3.1.1.1](image)

These reactions are compatible with a wide variety of aryl halides (e.g., 328), including those with electron withdrawing groups.\(^1\) Hartwig et al. have demonstrated that
α,α-disubstituted esters (e.g., 332) undergo arylation with 2-bromofuran 331 (Scheme 3.1.1.2). Although the corresponding coupling of halo furans and ketones has not been reported, a number of cyclic ketones 329 do participate in the palladium-catalyzed coupling reaction. However, among the latter there are no examples of α-arylation of cyclobutanones; thus, addressing the synthesis of 1 via the coupling of a cyclobutanone and a halo furan advances the forefront of this powerful coupling method (Scheme 3.1.1.2).

**Scheme 3.1.1.2** Examples of α-arylations

Mechanistically these transformations begin with the oxidative addition of an aryl halide 335 to a Pd(0) complex 334 (Scheme 3.1.1.3). Ligand exchange with an enolate of ketone 337 gives a palladium enolate complex 338 that subsequently undergoes reductive elimination to provide an α-aryl ketone 339. In general these reactions proceed with good regioselectivity and functional group tolerance. However, complications involving uncatalyzed cross-coupling between ketone substrates 337 and β-hydride elimination of the palladium complex 338 have been observed.
Scheme 3.1.1.3 Mechanism for α-arylations

3.1.2 Investigations into the α-Arylation Chemistry

At the outset our efforts focused on identifying optimal reaction conditions for preparing a simple, known α-arylation product, 2-phenylcyclohexanone 342. The use of sodium tert-butoxide, palladium(II) acetate, and tri-(tert-butyl)phosphine provided effective cross-coupling of cyclohexanone 341 and bromobenzene 340 (Scheme 3.1.2.1). These conditions furnished the mono-arylation product (342) in 34% yield following separation from a small amount of the corresponding bis-arylation product. Subsequent efforts revealed that the tri-(tert-butyl)phosphine could be replaced with the air-stable tri-(tert-butyl)phosphonium tetrafluoroborate salt, allowing for the assembly of reactions outside a glovebox.4
Next, in an effort to establish whether 2-bromofurans would participate in the α-arylation of ketones, we subjected 2-bromofuran 331 and cyclohexanone 341 to our established conditions (Scheme 3.1.2.2). Although we were gratified to find that these conditions furnished the known 2-furan-2-ylcyclohexanone product 343, the yield was disappointing. We anticipated the yields could be improved with further optimization.

Having established the viability of a furan/ketone coupling, we next explored the α-arylation of cyclobutanone 344 with bromobenzene 340. Unfortunately, initial attempts using our established conditions were unsuccessful and a subsequent screen of additional reaction conditions was met with limited success (Scheme 3.1.2.3). When LiHMDS was utilized small amounts of a tentative product 345 were observed by NMR and GC/MS; however, the material proved unisolable. When KHMDS was employed and the reaction was allowed to stir at room temperature for two hours prior to heating, a
low yield of the known aryl tetralone 346 was obtained as the only isolable product. This compound presumably arises from an arylation/rearrangement sequence. 8

Scheme 3.1.2.3 α-Arylation of cyclobutanone

Concerned that low yields in the coupling of 345 may have been the result of cross-coupling of cyclobutanone with itself, we attempted to couple a more elaborate cyclobutanone 115 with bromobenzene 340. The attempted α-arylation of cyclobutanone 115 resulted only in decomposition of the ketone (Scheme 3.1.2.4). Further experimentation revealed that functionalized cyclobutanones like 115 are not stable to deprotonation at room temperature, let alone at elevated temperatures. Thus, decomposition of the deprotonated cyclobutanones superceded the desired cross-coupling reaction.
**Scheme 3.1.2.4** Attempted $\alpha$-arylation of cyclobutanone 115

![Scheme 3.1.2.4]

Concurrently, investigation into the use of the more elaborate methyl 2-bromofuran-3-carboxylate 350 was underway (Scheme 3.1.2.5). The furan 350 had been prepared by reacting the dianion of 3-furoic acid (348) with 1,2-dibromo-1,1,2,2-tetrachloroethane 349 followed by esterification of the resultant acid using dimethyl sulfate. Alternative brominating reagents were tested but proved inferior to 349.

**Scheme 3.1.2.5** Synthesis of bromo-cyclobutanone 350

![Scheme 3.1.2.5]

Unfortunately, the $\alpha$-arylation of cyclohexanone (341) with methyl 2-bromofuran-3-carboxylate (350) was unsuccessful (Scheme 3.1.2.6). The observation of starting material, debrominated furan and several cyclohexanone condensation products led us to conclude that the rate of the desired cross-coupling was not competitive.

**Scheme 3.1.2.6** Attempted $\alpha$-arylation of cyclohexanone with 350

![Scheme 3.1.2.6]
We have demonstrated the successful $\alpha$-arylation of cyclohexanone $341$ with 2-bromofuran $350$. However, the instability of substituted cyclobutanones $115$ under the reaction conditions and slow reactivity of methyl 2-bromofuran-3-carboxylate $350$ led us to conclude that this was not a viable approach toward the synthesis of $1$. Thus, we began to investigate alternative coupling chemistries.

### 3.1.3 Bromide Displacement on Cyclobutanone Substrates

Having successfully trapped the carbanion of 3-furoic acid $348$ with electrophilic bromine, we postulated that it might be possible to alkylate 3-furoic acid $348$ with a halo-cyclobutane. With this plan in mind we set out to prepare an $\alpha$-bromo cyclobutanone $352$ (Scheme 3.1.3.1).

**Scheme 3.1.3.1** A revised retrosynthesis for a furyl cyclobutanone $354$

![Scheme 3.1.3.1]

Zard and co-workers have shown that the silyl-enol ethers of cyclobutanones can be generated and subsequently treated with NBS to furnish the corresponding $\alpha$-bromo derivatives.$^{10}$ Initial attempts to utilize this reaction on cyclobutanone $115$ resulted in only recovery of starting material. Mulzer et al. have shown that silyl-enol ethers of cyclobutanones can be generated using LiHMDS as a base.$^{11}$ We were pleased to find that treatment of cyclobutanone $115$ with TBS-OTf followed by LiHMDS provided silyl-enol ether $355$ (Scheme 3.1.3.2). Treatment of silyl-enol ether $355$ with NBS
subsequently provided the desired mono-brominated cyclobutanone 356, albeit in modest yields.

**Scheme 3.1.3.2 Synthesis of α-bromocyclobutane 356**

The dianion of 3-furoic acid 348, generated by treatment with LDA, was exposed to cyclobutanone 356 at low temperature and allowed to slowly warm to room temperature before being quenched (Scheme 3.1.3.3). Direct conversion to the methyl ester provided a small amount of furyl cyclobutanone 357; however, the yield was low, multiple other products were present and some starting material 356 remained. In an effort to optimize the reaction, it was repeated but quenched at –78 °C. Under these conditions a new product was observed which, upon treatment with diazomethane, was converted to a methyl ester. Detailed spectroscopic analysis of this ester provided data that was consistent with cyclobutanol 359; thus, rather than undergoing nucleophilic displacement of the bromide, the dianion derived from 348 adds preferentially to the carbonyl and furnishes cyclobutanol 358.
Scheme 3.1.3.3 Coupling of 3-furoic acid (348) and bromocyclobutanone 356

Further investigations revealed that treatment of the 1,2-adduct, cyclobutanol 359, with LiHMDS at low temperature followed by warming induces a rearrangement reaction that furnishes the desired cyclobutanone 357. Optimization studies revealed that the best yields of cyclobutanone 357 are obtained when substrates 358 and 359 are carried forward without purification (Scheme 3.1.3.4). This approach successfully provides cyclobutanone 357 in 60% isolated yield over three steps. Cyclobutanone 357 was isolated as a single diastereomer, and 1D nOe experiments confirmed the illustrated \textit{trans-trans}-relationship between substituents.

Scheme 3.1.3.4 Synthesis of furyl cyclobutanone 357
With cyclobutanone 357 in hand we sought to access diol 360, via removal of the benzyl protecting groups (Scheme 3.1.3.5). Traditional conditions employing either hydrogenation or boron tribromide resulted in the degradation of starting material 357. Attempts to oxidize the benzyl groups to benzyloxy groups led to decomposition of the starting material 357. Given these difficulties we elected to use different protecting groups from the outset.

**Scheme 3.1.3.5** Attempted removal of benzyl protecting groups

In considering the nature of alternative protecting groups we noted the work of Poisson who has demonstrated that cyclobutanones such as 362 undergo silica-gel mediated elimination during purification to give exo-methylene cyclobutanones 363 (Scheme 3.1.3.6). Such a transformation would be ideal in the synthesis of the exo-methylene cyclobutanol moiety in 1. Thus synthesis of bis-benzoyl protected diol 361 began.
Scheme 3.1.3.6 Poisson’s synthesis of exo-methylene cyclobutanones

\[
\begin{array}{c}
\text{RO} \quad \text{Bz} \\
\text{362} \\
\end{array} \quad \xrightarrow{\text{silica gel}} \quad \begin{array}{c}
\text{RO} \quad \text{Bz} \\
\text{363} \\
\end{array}
\]

Treatment of known diol 364 with either benzoic anhydride or benzoyl chloride and triethylamine provided the bis-protected diol 365 (Scheme 3.1.3.7). Subsequent cleavage of the acetal provided cyclobutanone 366 in near quantitative yields.

Scheme 3.1.3.7 Synthesis of bis-benzoyl protected cyclobutanone 366

\[
\begin{array}{c}
\text{HO} \quad \text{OMe} \\
\text{364} \\
\end{array} \quad \xrightarrow{\text{Bz}_2\text{O}, \text{Et}_3\text{N}, \text{DMAP} \text{ EtOAc, rt or BzCl, Et}_3\text{N}, \text{DMAP } \text{EtOAc, rt} (>95\% \text{ yield})} \quad \begin{array}{c}
\text{OMe} \quad \text{OMe} \\
\text{365} \\
\end{array} \quad \xrightarrow{\text{H}_2\text{SO}_4, \text{CH}_3\text{CN, rt} (99\% \text{ yield})} \quad \begin{array}{c}
\text{O} \\
\text{366} \\
\end{array}
\]

Bromination alpha to the carbonyl in 366 resulted in the desired bromo-cyclobutanone 367. Unfortunately, attempted purification led to mixtures of the desired product 367 and the exo-methylene cyclobutanone 368 (Scheme 3.1.3.8). Pre-treating the silica with triethylamine or utilizing basic alumina resulted in decomposition of the products. Attempts to convert the mixture entirely to methylene cyclobutanone 368 by stirring with silica gel were not successful.

Scheme 3.1.3.8 Bromination of cyclobutanone 366

\[
\begin{array}{c}
\text{BzO} \quad \text{OBz} \\
\text{366} \\
\end{array} \quad \xrightarrow{\text{1. TBS-OTf, THF, } -78^\circ \text{C then LiHMDS} \text{ BzO} \quad \text{OBz} \quad \text{367} \text{ silica} \quad \begin{array}{c}
\text{Br} \quad \text{OBz} \\
\text{367} \\
\end{array} \quad + \quad \begin{array}{c}
\text{Br} \quad \text{BzO} \quad \text{OBz} \\
\text{368} \\
\end{array}
\]

In an effort to determine the utility of methylene cyclobutanone 368 we exposed this material to the dianion derived from 348 under conditions that had proven effective
in the coupling of 356 (vide supra, Scheme 3.1.3.4). Unfortunately, the addition was unsuccessful and only decomposition was observed (Scheme 3.1.3.9).

Scheme 3.1.3.9 Attempted coupling of 3-furoic acid (348) and 368

Although this initial negative result was discouraging we continued our investigations by attempting to develop a more robust approach to bromo-cyclobutanone 367. To this end, efforts to brominate acetal 365 via addition of pyridinium tribromide or phenyltrimethyl ammonium tribromide did provide some brominated material. Unfortunately, the latter reactions were not clean and attempts to separate the derived complex mixtures of four compounds were unsuccessful (Scheme 3.1.3.10).

Scheme 3.1.3.10 Bromination of cyclobutyl acetal 365

Given past success with the ruthenium oxide oxidation of benzyl groups to benzoyl groups on cyclobutanone substrate 117 (Scheme 1.4.1.3) we endeavored to effect this transformation on bromo-cyclobutanone 356. Although the benzyl-protected cyclobutanone 356 was smoothly converted to the benzoyl-protected cyclobutanone 367,
this material could not be purified due to a facile elimination that furnishes the corresponding exomethylene 368 (Scheme 3.1.3.11).

Scheme 3.1.3.11 RuO$_2$ oxidation of bis-benzyl protected cyclobutanone 356

![Scheme 3.1.3.11](image)

3.1.4 Future work on Furyl-Cyclobutanone Chemistry

We have alkylated 3-furoic acid with bromo-cyclobutanone 356 and this has provided us with a furyl cyclobutanone 357 which possesses a relative stereochemistry configuration appropriate for conversion to 1; however, to complete the synthesis, this intermediate (or one analogous to it) will have to undergo stereoselective reduction and conversion to the corresponding exomethylene. The feasibility and order of these latter two events remain to be addressed. In the event, we will first determine the stereochemical outcome upon reduction of cyclobutanone 357 using bulky hydride reagents; we anticipate steric will aid in delivering the desired cis-relationship between the alcohol and furan substituents. We will also determine if there is any advantage in carrying out this reduction subsequent to introduction of the exo-methylene 373 (cf., eq. 2 and 3 in Scheme 3.1.4.1).
Another major concern for synthesis of 1 is the preparation of a cyclobutanone coupling partner possessing the necessary absolute stereochemistry. We plan to address this issue by employing a method in which the stereochemistry at C1 is set early. Based on previous observation, setting the stereochemistry at C1 will provide the necessary stereocontrol to access the desired stereochemistry at C2 and C17 (Scheme 3.1.4.2).
Of particular use will be the method developed by Bisacchi and co-workers (vide supra, Section 1.4.1), where the bis-amide derivatives of cyclobutane 113 are separated via crystallization to provide enantiopure cyclobutaneone 114 (Scheme 3.1.4.3). A second approach would involve the use of chemistry developed by Poisson et al., which demonstrated that chiral enol ethers 380 can be used in the asymmetric synthesis of cyclobutanones 381 via a [2 + 2] cycloaddition with dichloroketene 191. Utilization of either method should allow access to a functionalized cyclobutane with the desired chemistry at the C1 position.

Scheme 3.1.4.3 Proposed synthesis of cyclobutanones with desired C1 stereochemistry

3.2 Consideration of the Western Portion of Providencin

3.2.1 A Functionalized Furan Coupling Partner

For a truly convergent approach it is necessary to prepare a furan coupling partner which contains all the functionality for conversion to 1. We postulated that the commercially available 5-bromo-3-furoic acid 382 would be an ideal starting point for
the synthesis of a functionalized furan.\textsuperscript{14} Several pathways for further elaboration from furan 382 seem plausible (Scheme 3.2.1.1). Lithium-halogen exchange and subsequent treatment with an electrophile could provide homologated furan 383. Conversion of bromide 382 to furylstannane 384, followed by a Stille cross-coupling would furnish furan 386. Alternatively, furan 386 could also be accessed through a Suzuki cross-coupling. Access to alkenyl furan 387 could be gained through either a Heck reaction or via a Negishi cross-coupling.

**Scheme 3.2.1.1 Proposed homologation of 3-furoic acid derivatives**

3.2.2 The C7–C8 Epoxide

Our current approach employs a late stage introduction of the two epoxides, however, this may prove problematic. To date no synthesis of an epoxide-containing
furanocembrane has been completed via a late stage epoxidation (Scheme 3.2.2.1). Indeed no synthesis of any C7–C8 epoxy furanocembrane has been achieved.

**Scheme 3.2.2.1** Proposed late stage epoxidation of furanocembranes

Pattenden and co-workers specifically discuss the need for further innovation in the synthesis of furanocembranes, especially when it comes to incorporating epoxides into these molecules. One issue with the synthesis of these epoxides may be their sensitivity to acidic conditions. Recently, Pattenden has reported that treatment of epoxyfuran 389 with either aqueous acid or pTSA in methanol results in the opening of the epoxide via intermediate 390 (Scheme 3.2.2.2). It is clear that epoxide opening is a potential issue in these substrates and due care must be taken when considering the purification and further elaboration of these epoxide substrates.
Scheme 3.2.2.2 Acid-promoted epoxide opening

\[
\begin{align*}
\text{Cl} \quad \text{H}_2\text{O}^+ & \quad \overset{\text{HCl (aq)}}{\leftrightarrow} \quad \text{Me} \quad \overset{\rho\text{TSA MeOH}}{\rightarrow} \\
\text{391} & \quad \text{390} & \quad \text{392}
\end{align*}
\]

3.2.3 Possible Methods of Epoxide Synthesis

An ideal scenario for access to an epoxy furan would involve the synthesis of halohydrin 393 wherein a masked epoxide exists prior to macrocyclization (Scheme 3.2.3.1). Thus the alcohol could remain protected until introduction of the epoxide 394 was desired. A similar approach would involve synthesis of diol 395 and subsequent conversion to the epoxide 394.

Scheme 3.2.3.1 Proposed introduction of furyl epoxides
3.3 Conclusions

Although we have found that the Buchwald–Hartwig type α-arylations of ketones is not an efficient method to couple bromofuran and cyclobutanone substrates, we did establish that ketones can undergo α-arylations with 2-bromofurans (Scheme 3.3.1). We established that enolates derived from our substituted cyclobutanone intermediates are unstable above −78 °C, which led us to pursue an alkylation approach. We have successfully demonstrated the coupling of 3-furoic acid and a functionalized α-bromocyclobutanone via addition of the furan to the cyclobutanone. Further elaboration should provide a substrate well suited for advancement towards providencin (1).

Scheme 3.3.1 Chapter 3 summary
3.4 Experimental Procedures

3.4.1 General Information

Unless otherwise stated, reactions were mechanically stirred in flame-dried glassware under an atmosphere of nitrogen. Tetrahydrofuran and diethyl ether were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. Commercially available reagents were obtained from Sigma-Aldrich, Strem, TCI-America or Alfa Aesar and were used as received. All known compounds were identified by comparison of NMR spectra to those reported in the literature.

Thin layer chromatography was performed using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 µm). Developed plates were visualized using a 254 nm UV lamp and/or with the appropriate dip followed by heating. Typical dip solutions were ethanolic anisaldehyde and potassium permanganate. Flash chromatography was generally performed with Silicycle SiliaFlash® P60 (230-400 mesh) silica gel as the stationary phase. Infrared spectra were recorded on a Nicolet Avatar 320 FT-IR. Samples were analyzed as thin films on NaCl plates (sample dissolved in CH₂Cl₂) and the spectra are presented as transmittance vs. wavenumber (cm⁻¹). High-resolution mass spectrometry was conducted on an Agilent 6210 TOF LCMS. Proton (¹H) and carbon (¹³C) NMR spectra were recorded on a Varian Inova 400 or 300 spectrometer. Spectra were obtained at 22 °C in CDCl₃ unless otherwise noted. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants (J) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets,
dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent.

### 3.4.2 Preparative Procedures

Cyclobutanone 115\(^{17}\) (0.134 g, 0.43 mmol) was dissolved in THF (10 mL) and cooled to –78 °C and TBS-OTf (0.29 mL, 1.29 mmol) was added slowly. Then 1M LiHMDS (2.2 mL, 2.15 mmol) was added rapidly down the side of the flask. After 1 h the reaction was carefully quenched with saturated NH\(_4\)Cl solution. The aqueous layer was extracted with Et\(_2\)O 2x. The combined organics were washed with H\(_2\)O and dried over MgSO\(_4\) and then concentrated \textit{in vacuo}. The crude material was dissolved in THF (10 mL) and cooled to 0 °C. NBS (0.084 g, 0.47 mmol) was added in one portion and reaction was allowed to warm to room temperature and stir for 1 h. The reaction was quenched with H\(_2\)O and the aqueous layer was extracted with Et\(_2\)O 2x. The combined organics were washed with brine, dried over MgSO\(_4\) and concentrated \textit{in vacuo}. The crude material was flashed in 10:1 hexanes:EtOAc. Bromocyclobutanone 356 was isolated in 40% yield for two steps. 356: R\(_f\) = 0.28, 4:1 hexanes:EtOAc; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.39–7.29 (m, 10H), 4.99 (dd, \(J=7.7, 2.4\) Hz, 1H), 4.64–4.56 (m, 2H), 4.56–4.50 (m, 2H), 3.83 (dt, \(J=9.9, 3.9\) Hz, 1H), 3.78–3.70 (m, 2H), 3.65–3.56 (m, 2H), 2.87–2.81 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 199.3, 137.9, 137.8, 128.6, 128.5, 128.0, 127.8, 127.7, 127.6, 73.3, 73.2, 67.9, 66.2, 58.4, 48.3, 41.0 IR (NaCl thin film): 3030(w), 2857(w), 1792(s), 1113(m), 737(m), 697(m); HRMS (ESI–APCI) \(m/z\) calcd. for C\(_{20}\)H\(_{25}\)BrNO\(_3\) [M+NH\(_4\)]\(^{+}\): 406.1012, found: 406.1011
To 3-furoic acid 348 (0.028 g, 0.249 mmol) in THF (3 mL) at –78 ºC, was added 0.5M LDA (1 mL, 0.497 mmol). The reaction was stirred for 30 min at –78 ºC and then bromocyclobutanone 356 (0.088 g, 0.226 mmol) in THF (1 mL) was added. When starting material was consumed by TLC the reaction was quenched with saturated NH₄Cl solution. The aqueous layer was extracted with Et₂O 2x. The combined organics were washed with H₂O and dried over MgSO₄ and then concentrated in vacuo. The crude material was stirred in Et₂O at room temperature and excess diazomethane was added. The reaction was filtered through MgSO₄ and then concentrated in vacuo. The crude material was flashed in 4:1 – 2:1 hexanes:EtOAc. Cyclobutanone 357 was isolated in 60% yield over 2 steps.

357: R₆ = 0.17, 4:1 hexanes:EtOAc; ¹H NMR (400 MHz, CDCl₃) δ 7.50 (d, J=0.9 Hz, 1H), 7.38–7.17 (m, 10H), 6.83 (d, J=0.9 Hz, 1H), 4.55 (s, 2H), 4.40 (s, 2H), 3.90 (s, 3H), 3.86 (dd, J=19.0, 5.5 Hz, 1H), 3.59 (dd, J=16.3, 5.8 Hz, 1H), 3.54–3.49 (m, 2H), 3.03 (dd, J=14.1, 5.1 Hz, 1H), 2.23 (quint., J=5.9 Hz, 1H), 2.04–1.96 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 186.5, 163.3, 152.2, 144.2, 138.4, 138.3, 128.5, 128.4, 127.8, 127.6, 121.7, 113.6, 72.9, 72.8, 70.8, 66.7, 52.5, 30.6, 28.3, 26.7; IR (NaCl thin film): 3030(w), 2924(m), 2857(m), 1732(s), 1485(m), 1306(m), 1049(s), 738(m), 698(m); HRMS (ESI–APCI) m/z calcd. for C₂₆H₂₆NaO₆ [M+Na]⁺: 457.1622, found: 457.1625

To 3-furoic acid 348 (0.123 g, 1.1 mmol) in THF (10 mL) at –78 ºC, was added 0.5M LDA (4.4 mL, 2.2 mmol). The reaction was stirred for 30 min at –78 ºC and then bromocyclobutanone 356
(0.383 g, 1 mmol) in THF (1 mL) was added and reaction was stirred at –78 ºC. When starting material was consumed by TLC the reaction was quenched with saturated NH₄Cl solution. The aqueous layer was extracted with Et₂O 2x. The combined organics were washed with H₂O and dried over MgSO₄ and then concentrated in vacuo. The crude material was dissolved in Et₂O and treated with excess diazomethane at room temperature. The reaction was concentrated in vacuo. The crude material was flashed in 20:1 – 10:1 – 4:1 hexanes:EtOAc and 359 was obtained in around 20% yield.

359: Rᵣ = 0.31, 4:1 hexanes:EtOAc; ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.21 (m, 8H), 7.10–7.08 (m, 2H), 6.66 (d, J=1.9 Hz, 1H), 6.13 (d, J=0.7 Hz, 1H), 5.49 (d, J=8.9 Hz, 1H), 4.58 (s, 2H), 4.14 (dd, J=11.7, 8.7 Hz, 2H), 3.89 (d, J=6.8 Hz, 2H), 3.78 (s, 3H), 3.35–3.28 (m, 2H), 2.95 (q, J=4.8 Hz, 1H), 2.83–2.76 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 165.7, 160.2, 140.9, 138.2, 138.0, 128.5, 128.3, 128.0, 127.7, 127.5, 114.6, 111.5, 75.2, 73.5, 73.2, 72.3, 68.8, 52.3, 51.0, 49.0, 38.7; IR (NaCl thin film): 3301(w), 3030(w), 2950(w), 2857(m), 1725(m), 1693(s), 1312(s), 1209(s), 1073(s), 740(s), 698(s); HRMS (ESI–APCI) m/z calcd. for C₂₆H₂₈BrO₆ [M+H]⁺: 515.1064, found: 515.105

Known cyclobutanone 366¹⁸ (0.108 g, 0.35 mmol) was dissolved in THF (5 mL) and cooled to –78 °C. and TBS-OTf (0.24 mL, 1.05 mmol) was added slowly. Then 1M LiHMDS (1.75 mL, 1.75 mmol) was added rapidly down the side of the flask. After 1 h the reaction was carefully quenched with saturated NH₄Cl solution. The aqueous layer was extracted with Et₂O 2x. The combined organics were washed with H₂O and dried over MgSO₄ and then concentrated in vacuo. The crude material was dissolved in THF (10 mL) and cooled to 0 °C. NBS (0.068 g, 0.38 mmol) was added in one portion and reaction was allowed to
warm to room temperature and stir for 1 h. The reaction was quenched with H₂O and the aqueous layer was extracted with Et₂O 2x. The combined organics were washed with brine, dried over MgSO₄ and concentrated in vacuo.

Attempts to flash the crude material resulted in mixtures of the desired product 367 and the elimination product 368.

367: \(^1\text{H NMR (400 MHz, CDCl}_3\) δ 8.05–7.97 (m, 4H), 7.63–7.57 (m, 2H), 7.51–7.43 (m, 4H), 5.01 (dd, \(J=10.1, 2.4\) Hz, 1H), 4.75–4.55 (m, 4H), 3.76–3.71 (m, 1H), 3.15–3.08 (m, 1H); \(^{13}\text{C NMR (100 MHz, CDCl}_3\) δ 196.7, 166.3, 166.2, 133.6, 133.5, 130.3, 129.8, 129.3, 128.6, 63.8, 60.6, 58.5, 48.8, 40.6; IR (NaCl thin film): 3064(w), 2952(w), 1797(m), 1722(s), 1270(s), 1115(m), 710(m); HRMS (ESI–APCI) \(m/z\) calcd. for C₂₀H₁₂BrNO₅ [M+NH₄]⁺: 434.0598, found: 434.0591

368: \(^1\text{H NMR (400 MHz, CDCl}_3\) δ 8.04–8.01 (m, 2H), 7.61–7.57 (m, 1H), 7.46 (app t, \(J=7.8, 7.5\) Hz, 2H), 6.09–6.06 (m, 1H), 5.48–5.46 (m, 1H), 5.15 (d, \(J=8.8\) Hz, 0.25H), 4.83 (d, \(J=5.8\) Hz, 0.75H), 4.75–4.55 (m, 2H), 3.74–3.69(m, 0.25H), 3.63–3.57 (m, 0.75H); \(^{13}\text{C NMR (100 MHz, CDCl}_3\) δ 190.6, 166.2, 150.7, 133.6, 129.7, 128.7, 128.6, 118.2, 64.2, 49.4, 47.4; IR (NaCl thin film): 3064(w), 2954(w), 2851(w), 1772(s), 1719(s), 1271(s), 710(m); HRMS (ESI–APCI) \(m/z\) calcd. for C₁₃H₁₂BrO₃ [M+H]⁺: 294.9964, found: 294.995
3.5 References


and Antiviral Activity of Enantiomeric Forms of Cyclobutyl Nucleoside Analogs.  


Appendix A3: Spectral Data Relevant to Chapter 3
Figure A3.2 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 356

![13C NMR spectrum of compound 356](image)

Figure A3.3 IR spectrum (thin film, NaCl) of compound 356

![IR spectrum of compound 356](image)
**Figure A3.4** $^1$H NMR spectrum (400MHz, CDCl3) of compound 357
Figure A3.5 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 357

Figure A3.6 IR spectrum (thin film, NaCl) of compound 357
Figure A3.7 $^1$H NMR spectrum (400MHz, CDCl3) of compound 359
Figure A3.8 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 359

Figure A3.9 IR spectrum (thin film, NaCl) of compound 359
Figure A3.10 $^1$H NMR spectrum (400MHz, CDCl3) of compound 367
Figure A3.11  $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 367

Figure A3.12 IR spectrum (thin film, NaCl) of compound 367
Figure A3.13 \(^1\)H NMR spectrum (400MHz, CDCl\(_3\)) of compound 368
Figure A3.14 $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 368

Figure A3.15 IR spectrum (thin film, NaCl) of compound 368
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